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Supporting Information

Development of Tetramethylenedisulfotetramine (TETS) Hapten Library: Synthesis, Electrophysiological Studies, and Immune Response in Rabbits.

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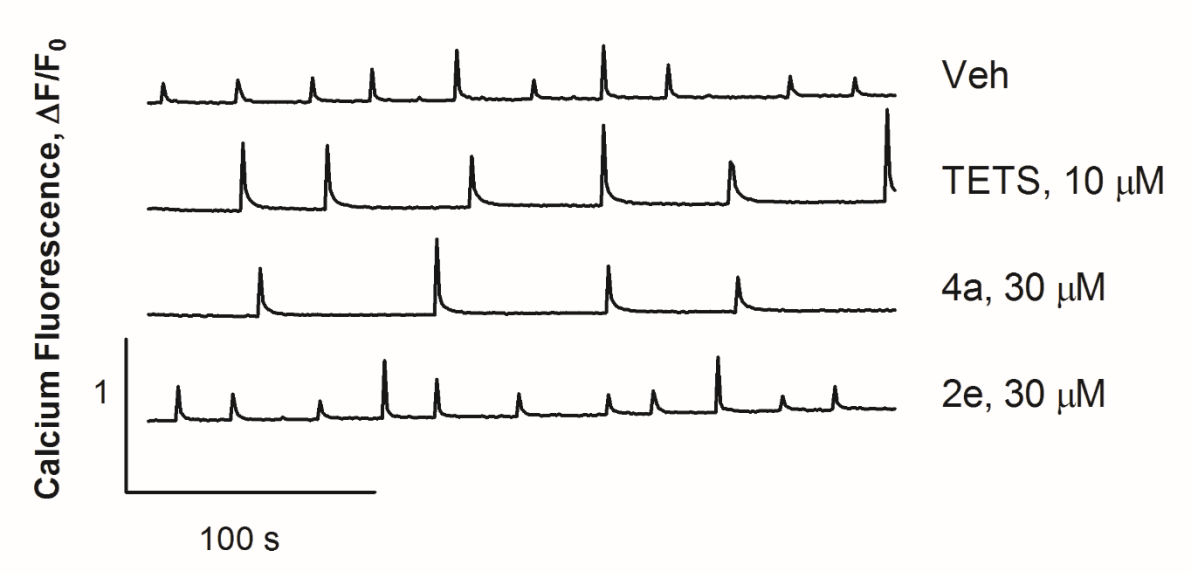


Figure S1. SCOs after TETS analog **7k** are similar to TETS. Raw fluorescent traces showing SCOs after the addition of vehicle, TETS (10 μM), TETS analog **7k** (30 μM) and TETS analog **7e** (30 μM).

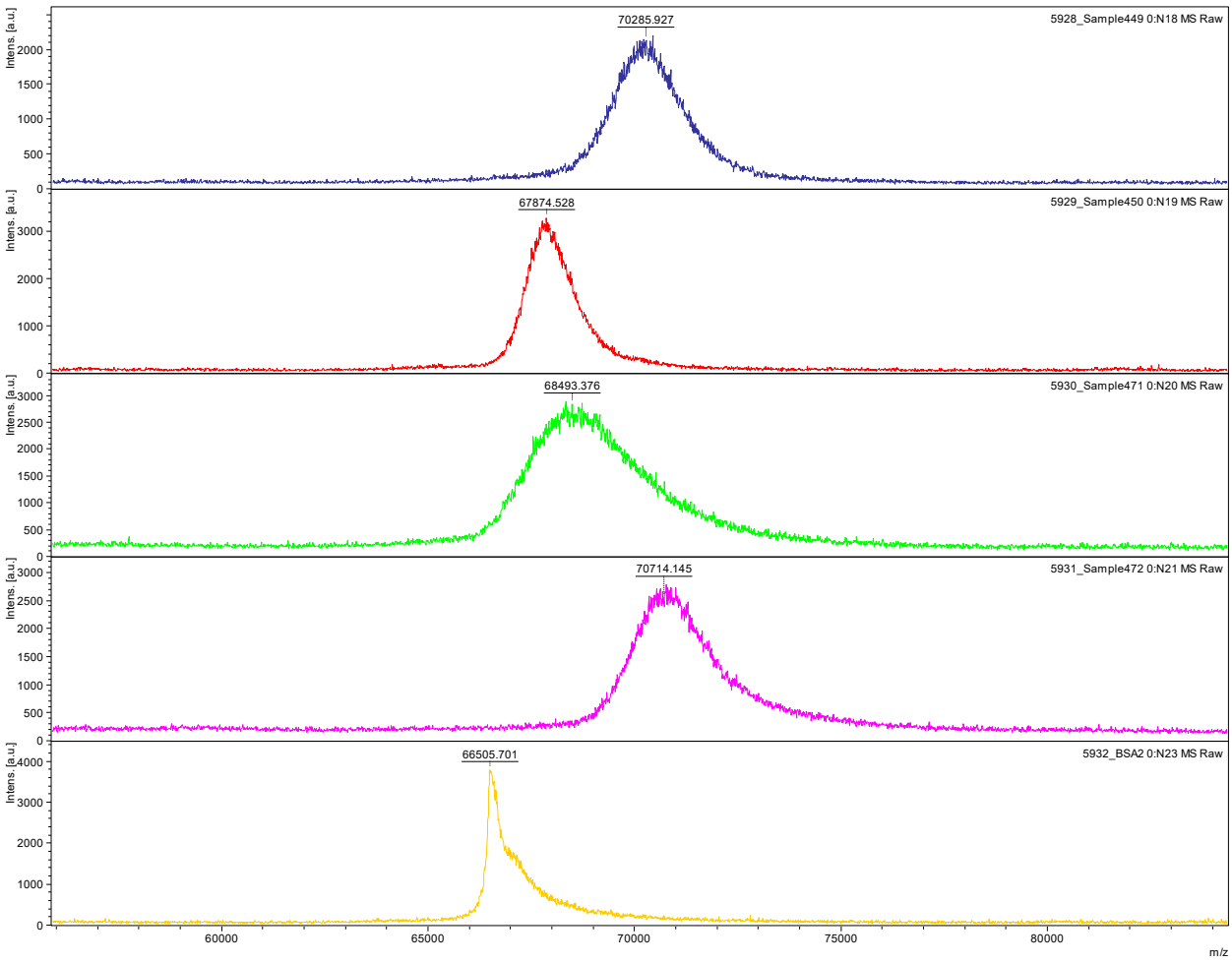


Figure S2. Representative MALDI MS spectra for BSA conjugates of haptens **2j** (blue, n = 11.5), **2c** (red, n = 4.9), **2k** conjugated through azo linker (green, n = 5.4) **2d** (purple, n = 12.5) and BSA (yellow). MALDI spectra were acquired on a Bruker UltraFlextreme (Billerica, MA) operated in linear mode from 20-100 kDa. Samples were spotted using dihydroxyacetophenone (DHAP) matrix using the standard Bruker matrix protocol. Laser fluence was typically around 50-55% of maximum and spectra were summed from 3-4,000 shots.

Reagents and instruments

All reactions were carried out under an atmosphere of dry nitrogen. All chemicals purchased from commercial sources were used as received without further purification unless indicated. Compounds **9**-**11** were synthesized according to published procedures.[1] Analytical thin-layer chromatography (TLC) was performed on Merck TLC silica gel 60 F_{254} plates. Flash chromatography was performed on silica gel (230–400 mesh) from Macherey Nagel. NMR spectra were recorded on Varian VNMRS 600, Inova 400, Mercury 300 or Bruker Avance III 800 MHz instruments. Multiplicity is described by the abbreviations b = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet. Chemical shifts are given

in ppm. ^{1}H NMR spectra were referenced to the residual solvent peak. HRMS spectra were recorded on Thermo Electron LTQ-Orbitrap XL Hybrid MS in ESI and on Agilent GC–MS system with Q/TOFMS 7200 in EI. Melting points were determined on an OptiMelt melting point apparatus.

Goat anti-rabbit IgG-horseradish peroxidase (HRP) conjugate was purchased from Abcam (Boston. MA). ELISA absorbances were spectrophotometrically read with a microplate reader (Molecular Devices, Sunnyvale, CA) at wavelength 450 nm.

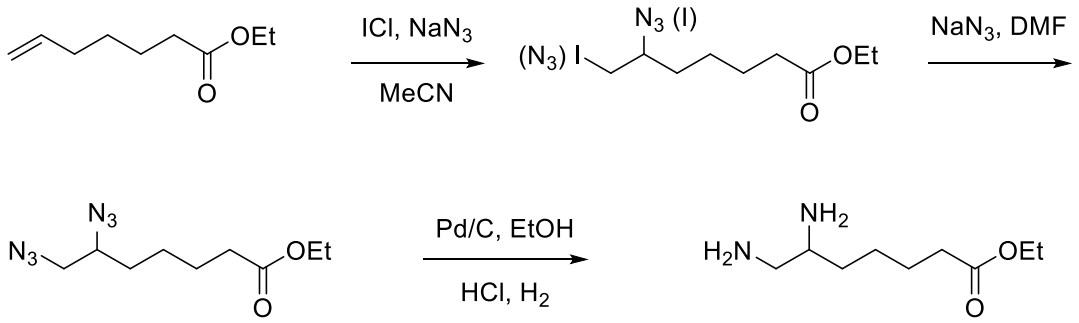
GS-21 was from MTI-GlobalStem (Gaithersburg, MD). The Ca^{2+} sensitive fluorescence dye Fluo-4-AM, and Neurobasal medium were purchased from Life Technology (Grand Island, NY). Tetramethylenedisulfotetramine (TETS) was synthesized as described previously.[2]

Buffers for ELISA. All buffers and aqueous solutions were prepared with ultrapure deionized water; phosphate-buffered saline (PBS, 10 mM, pH 7.5); wash buffer PBST (PBS containing 0.05% Tween 20); coating buffer (14 mM Na_2CO_3, 35 mM $NaHCO_3$, pH 9.8); blocking buffer (1% BSA in PBST); substrate buffer (0.1 M sodium citrate/acetate buffer, pH 5.5). Substrate solution contained 0.2 mL of 0.6% TMB (in dimethyl sulfoxide, DMSO w/v), 0.05 mL of 1% H_2O_2 in 12.5 mL of substrate buffer. Stop solution was 2 M H_2SO_4.

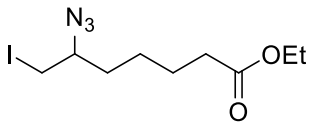
Synthetic procedures

CAUTION! Low molecular weight azides and polyazides are potentially-explosive substances. Face-shield and blast-shield should be used at all times while manipulating these compounds.

Synthesis of ethyl 6,7-diaminoheptanoate



Scheme S1. Synthesis of ethyl 6-azido-7-iodoheptanoate.

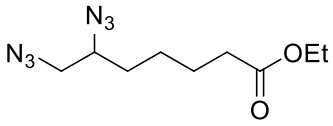


Ethyl 6-azido-7-iodoheptanoate. A solution of ICl (3.24 g, 20 mmol, 2 equiv) in MeCN (20 mL) was added dropwise to a suspension of NaN_3 (2.6 g, 40 mmol, 4 equiv) in MeCN (20 mL) at 0 °C over 20 min.

The reaction mixture was allowed to warm up to room temperature (RT) and a solution of ethyl hept-6-enoate (1.56 g, 10 mmol, 1 equiv) was added dropwise. The resulting mixture was stirred overnight, quenched with water and extracted with Et_2O (3×20 mL). Combined organics were washed with 5 % aqueous $Na_2S_2O_3$ solution, dried over $MgSO_4$, filtered and evaporated. Crude product was dissolved in Et_2O and filtered through a short pad of silica gel to give pure ethyl 6-azido-7-iodoheptanoate containing ~20 % of ethyl 7-azido-6-iodoheptanoate as a yellow liquid (3.257 g, quant). The product was used in the next step without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.10 (q, *J* = 7.1 Hz, 2H), 4.07 – 4.03 (m, 0.2H), 3.72 (dd, *J* = 12.9, 6.0 Hz, 0.2H), 3.60 (dd, *J* = 12.9, 6.9 Hz, 0.2H), 3.39 (dq, *J* = 8.3, 5.5 Hz, 0.8H), 3.24 (m, 1.6H), 2.29 (t, *J* = 7.4 Hz, 2H), 1.79 – 1.51 (m, 4H), 1.50 – 1.35 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H).

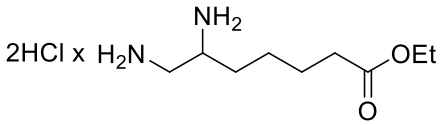
^{13}C NMR (151 MHz, $CDCl_3$) δ 173.3, 62.5, 60.4, 59.0, 36.8, 34.2, 34.04, 34.03, 31.7, 28.8, 25.4, 24.5, 24.1, 14.32, 14.31, 8.4.



Ethyl 6,7-diazidoheptanoate. A mixture of ethyl 6-azido-7-iodoheptanoate (3.257 g, 10 mmol, 1 equiv), NaN_3 (1.3 g, 20 mmol, 2 equiv) and DMF (30 mL) was heated at 55 °C overnight, quenched with water (90 mL) and extracted with Et_2O (4×40 mL). Combined extracts were washed with water, dried over $MgSO_4$, filtered and evaporated to give light-yellow liquid (1.88 g, 78 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (q, *J* = 7.1 Hz, 2H), 3.44 (tdd, *J* = 7.2, 5.8, 4.0 Hz, 1H), 3.37 (dd, *J* = 12.7, 4.0 Hz, 1H), 3.29 (dd, *J* = 12.6, 7.3 Hz, 1H), 2.29 (t, *J* = 7.3 Hz, 2H), 1.67 – 1.33 (m, 6H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 61.9, 60.4, 54.8, 34.0, 31.5, 25.4, 24.6, 14.3.

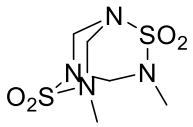


Ethyl 6,7-diaminoheptanoate. A mixture of ethyl 6,7-diazidoheptanoate (1.88 g, 7.83 mmol, 1 equiv), Pd/C (10 %, 1.66 g), concentrated aqueous hydrochloric acid (11 M, 1.42 mL, 15.7 mmol, 2 equiv) and EtOH (50 mL) was stirred under hydrogen atmosphere for 30 h. The reaction mixture was filtered through a short pad of Celite and evaporated to give crude product containing up to 1.9 equiv of ethanol as impurity (by NMR). The product was used in the next step without further purification. Yield 2.401 g (quant).

^{1}H NMR (600 MHz, CD_3OD) δ 4.12 (q, *J* = 7.1 Hz, 2H), 3.65 (m, 1H), 3.33 (m, 2H), 2.39 (t, *J* = 7.4 Hz, 2H), 1.89 – 1.75 (m, 2H), 1.73 – 1.61 (m, 2H), 1.59 – 1.44 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, CD_3OD) δ 175.1, 61.5, 50.8, 42.1, 34.5, 31.3, 25.4, 14.6.

General procedure for the synthesis of TETS analogues 2 and 4. A solution of disulfamide **8** (0.75 mmol) and dimethoxymethane (0.171 g, 2.25 mmol, 3 equiv) in trifluoroacetic acid (7.5 mL) was stirred at RT for 3 h and evaporated. The residue was triturated in a small amount of dichloromethane or methanol and filtered. For **2e** and **2h** filtration of the reaction mixture through a short column of silica gel and elution with EtOAc was performed prior to the trituration step in order to remove polar side products.

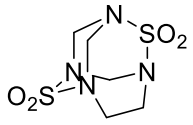


(±)-(1*R*,5*R*)-3,7-Dimethyl-2,6-dithia-1,3,5,7-tetraazabicyclo[3.3.1]nonane 2,2,6,6-tetraoxide 4a. Yield 0.143 g, 73 %. Mp 246 °C.

^{1}H NMR (800 MHz, $CDCl_3$) δ 5.31 (t, *J* = 1.6 Hz, 2H), 4.66 (dt, *J* = 13.3, 1.6 Hz, 2H), 4.59 (d, *J* = 13.4 Hz, 2H), 2.91 (d, *J* = 1.6 Hz, 6H).

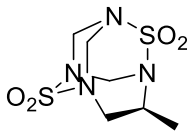
^{13}C NMR (201 MHz, $CDCl_3$) δ 69.7, 67.5, 35.6.

IR (neat/cm^{-1}) 3023, 2974, 2949, 2884, 1680.



(±)-(1*R*,3*S*,8*R*)-2,7-Dithia-1,3,6,8-tetraazatricyclo[4.3.1.1^{3,8}]undecane 2,2,7,7-tetraoxide 2a. Yield 92 %. Mp 283 °C.

^{1}H NMR (800 MHz, CD_3COCD_3) δ 5.50 (t, *J* = 1.9 Hz, 2H), 5.24 (d, *J* = 14.9 Hz, 2H), 4.73 (dt, *J* = 14.9, 1.9 Hz, 2H), 3.83 (m, 2H), 3.70 (m, 2H).
^{13}C NMR (201 MHz, CD_3COCD_3) δ 71.4, 67.4, 51.2.
IR (neat/cm^{-1}) 3028, 2975, 1674.
HRMS (EI), calculated for $C_5H_{10}N_4O_4S_2$ ($[M]^{+\bullet}$) *m/z* 254.0143, found *m/z* 254.0152.



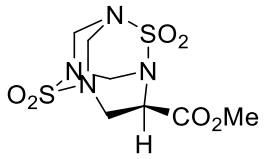
(±)-(1*R*,4*S*,6*S*,8*R*)-4-Methyl-2,7-dithia-1,3,6,8-tetraazatricyclo[4.3.1.1^{3,8}]undecane 2,2,7,7-tetraoxide 2b. Yield 87 % (mixture of diastereomers). Multiple trituration and recrystallization from methanol provided major isomer contaminated with up to 9 % of minor isomer.

^{1}H NMR (800 MHz, CD_3COCD_3) δ 5.47 (t, *J* = 1.9 Hz, 2H), 5.26 (d, *J* = 14.9 Hz, 1H), 5.23 (d, *J* = 14.9 Hz, 1H), 4.79 (dt, *J* = 14.9, 1.9 Hz, 1H), 4.75 (dt, *J* = 14.9, 1.9 Hz, 1H), 4.11 (ddq, *J* = 10.1, 6.9, 6.9 Hz, 1H), 3.93 (dd, *J* = 14.9, 7.1 Hz, 1H), 3.46 (dd, *J* = 14.9, 10.1 Hz, 1H), 1.40 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (201 MHz, CD_3COCD_3) δ 72.5, 70.3, 69.0, 61.6, 58.7, 19.3.

IR (neat/cm^{-1}, mixture of diastereomers) 3038, 2978, 1781.

HRMS (EI), calculated for $C_6H_{12}N_4O_4S_2$ ([M]$^{+\bullet}$) *m/z* 268.0300, found *m/z* 268.0314.



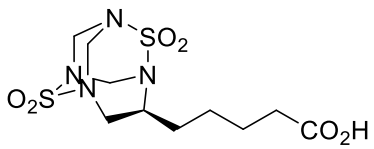
(±)-Methyl (1*R*,4*R*,6*S*,8*R*)-2,7-dithia-1,3,6,8-tetraazatricyclo[4.3.1.1^{3,8}]undecane-4-carboxylate 2,2,7,7-tetraoxide 2c. Yield 53 % (mixture of isomers). Recrystallization of the mixture from MeOH provided almost pure major isomer.

^{1}H NMR (800 MHz, $CDCl_3$) δ 5.42 (m, 2H), 5.28 (d, *J* = 14.9 Hz, 1H), 5.15 (d, *J* = 14.9 Hz, 1H), 4.68 (m, 2H), 4.48 (t, *J* = 8.5 Hz, 1H), 4.22 (dd, *J* = 15.4, 8.3 Hz, 1H), 4.03 (dd, *J* = 15.3, 8.7 Hz, 1H), 3.83 (s, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) δ 168.1, 71.8, 69.0, 68.3, 63.7, 54.2, 53.4.

IR (neat/cm^{-1}, mixture of diastereomers) 3038, 2962, 1746.

HRMS (EI), calculated for $C_7H_{12}N_4O_6S_2$ ([M]$^{+\bullet}$) *m/z* 312.0198, found *m/z* 312.0212.



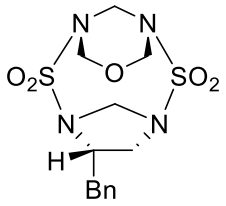
(±)-5-((1*R*,4*S*,6*S*,8*R*)-2,2,7,7-tetraoxido-2,7-dithia-1,3,6,8-tetraazatricyclo[4.3.1.1^{3,8}]undecan-4-yl)pentanoic acid 2d. After evaporation of the trifluoroacetic acid, water was added and the resulting

mixture was allowed to stay at RT overnight. The residual trifluoroacetic acid caused hydrolysis of the ester function. Yield 2.355 g, 85 % (mixture of isomers). Crude product was used for protein conjugation without further purification. Small amount of the crude product was partially purified by flash column chromatography with CH_2Cl_2/MeOH/AcOH = 95:4.5:0.5 as a solvent.

^{1}H NMR (800 MHz, $CDCl_3$) δ 5.39 (s, 2H), 5.20 (d, *J* = 14.8 Hz, 1H), 5.13 (d, *J* = 14.8 Hz, 1H), 4.63 (d, *J* = 14.8 Hz, 1H), 4.56 (d, *J* = 14.9 Hz, 1H), 3.96 (dd, *J* = 14.8, 7.1 Hz, 1H), 3.80 (m, 1H), 3.34 (dd, *J* = 14.7, 10.1 Hz, 1H), 2.38 (m, 2H), 1.98 (m, 1H), 1.70 – 1.51 (m, 3H), 1.42 – 1.32 (m, 2H).

^{13}C NMR (201 MHz, $CDCl_3$) δ 179.0, 71.92, 70.2, 68.5, 65.9, 57.7, 33.7, 32.6, 26.1, 24.2.

HRMS (ESI), calculated for $C_{10}H_{17}N_4O_6S_2$ ($[M–H]^–$) *m/z* 353.0595, found *m/z* 353.0594.

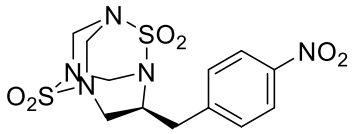


(1*R*,3*R*,4*S*,6*R*,8*S*)-4-benzyl-10-oxa-2,7-dithia-1,3,6,8-tetraazatricyclo[6.3.1.1^{3,6}]tridecane 2,2,7,7-tetraoxide 2e. Yield 9.4 %.

^{1}H NMR (800 MHz, CD_3COCD_3) δ 7.33 (m, 4H), 7.26 (m, 1H), 5.51 (d, *J* = 11.7 Hz, 1H), 5.45 (m, 3H), 5.09 (m, 3H), 4.70 (td, *J* = 8.8, 4.4 Hz, 1H), 4.40 (d, *J* = 13.6 Hz, 1H), 4.07 (dd, *J* = 13.4, 8.4 Hz, 1H), 3.31 (dd, *J* = 13.3, 5.8 Hz, 1H), 3.08 (dd, *J* = 13.7, 5.4 Hz, 1H), 2.96 (dd, *J* = 13.7, 8.8 Hz, 1H).

^{13}C NMR (201 MHz, CD_3COCD_3) δ 137.3, 130.5, 129.5, 127.7, 80.1, 80.0, 67.1, 60.9, 59.4, 51.9, 40.7.

HRMS (EI), calculated for $C_{13}H_{18}N_4O_5S_2$ ($[M]^{+\bullet}$) *m/z* 374.0719, found *m/z* 374.0709.



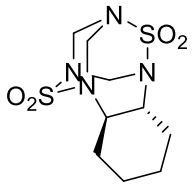
(1*R*,4*S*,6*S*,8*R*)-4-(4-Nitrobenzyl)-2,7-dithia-1,3,6,8-tetraazatricyclo[4.3.1.1^{3,8}]undecane 2,2,7,7-tetraoxide 2f. Yield 30 %.

^{1}H NMR (800 MHz, CD_3COCD_3) δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 5.50 (dd, *J* = 14.5, 3.0 Hz, 1H), 5.47 (dd, *J* = 14.3, 2.6 Hz, 1H), 5.28 (d, *J* = 14.8 Hz, 1H), 5.17 (d, *J* = 15.0 Hz, 1H), 4.88 (dd, *J* = 14.8, 2.9 Hz, 1H), 4.60 (dd, *J* = 15.1, 2.8 Hz, 1H), 4.30 (tdd, *J* = 10.0, 7.0, 5.5 Hz, 1H), 4.04 (dd, *J* = 15.0, 7.1 Hz, 1H), 3.70 (dd, *J* = 15.1, 9.9 Hz, 1H), 3.35 (dd, *J* = 14.0, 10.0 Hz, 1H), 3.20 (dd, *J* = 14.0, 5.5 Hz, 1H).

^{13}C NMR (201 MHz, CD_3COCD_3) δ 147.8, 147.0, 131.4, 124.3, 72.4, 70.5, 69.0, 66.8, 57.7, 39.2.

IR (neat/cm^{-1}) 1603, 1514.

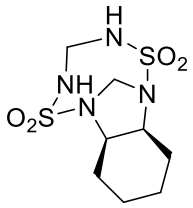
HRMS (EI), calculated for $C_{12}H_{15}N_5O_6S_2$ ($[M]^{+\bullet}$) *m/z* 389.0464, found *m/z* 389.0527.



(1*S*,3*R*,5*R*,7a*R*,11a*R*)-Hexahydro-2*H*,4*H*,6*H*-1,5:3,7-diepithiobenzo[*h*][1,3,5,7]tetrazonine 12,12,13,13-tetraoxide 2g. Yield 55 %. Mp 306 °C.

^{1}H NMR (600 MHz, CD_3COCD_3) δ 5.45 (t, *J* = 1.9 Hz, 2H), 5.26 (d, *J* = 14.8 Hz, 2H), 4.80 (dt, *J* = 14.8, 2.0 Hz, 2H), 3.65 (m, 2H), 2.12 (m, 2H), 1.78 (m, 4H), 1.31 (m, 2H).
^{13}C NMR (151 MHz, CD_3COCD_3) δ 72.8, 70.7, 69.5, 34.8, 26.4.

IR (neat/cm^{-1}) 3047, 2947, 2863.
HRMS (EI), calculated for $C_9H_{16}N_4O_4S_2$ ($[M]^{+\bullet}$) *m/z* 308.0613, found *m/z* 308.0629.

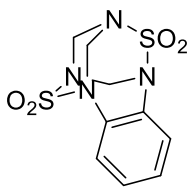


(7a*R*,11a*S*)-Octahydro-3*H*-1,7-methanobenzo[*g*][1,5,2,4,6,9]dithiatetrazonine 2,2,6,6-tetraoxide 2h. Yield 5.2 %. Mp 199 °C.

^{1}H NMR (600 MHz, CD_3COCD_3) δ 7.38 (d, *J* = 7.6 Hz, 2H), 5.47 (d, *J* = 13.3 Hz, 1H), 4.67 (m, 1H), 4.64 (d, *J* = 13.5 Hz, 1H), 4.51 (m, 1H), 4.23 (m, 2H), 1.78 (m, 4H), 1.60 (m, 2H), 1.41 (m, 2H).

^{13}C NMR (151 MHz, CD_3COCD_3) δ 66.4, 58.6, 53.4, 53.3, 26.9, 20.3.

IR (neat/cm^{-1}) 3324, 3280, 2940, 2923, 2858.
HRMS (ESI), calculated for $C_8H_{15}N_4O_4S_2$ ($[M–H]^{-}$) *m/z* 295.0540, found *m/z* 295.0539.

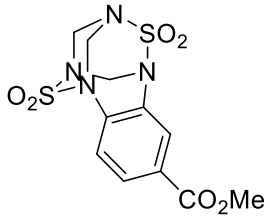


(±)-(1*S*,3*R*,5*R*)-2*H*,4*H*,6*H*-1,5:3,7-Diepithiobenzo[*h*][1,3,5,7]tetrazonine 12,12,13,13-tetraoxide 2i. Yield 79 %. Mp 249 °C.

^{1}H NMR (600 MHz, CD_3COCD_3) δ 7.51 (m, 2H), 7.43 (m, 2H), 5.89 (s, 2H), 5.62 (d, *J* = 14.8 Hz, 2H), 5.42 (d, *J* = 14.9 Hz, 2H).

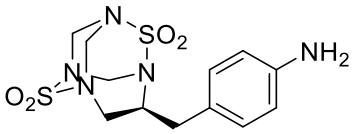
^{13}C NMR (151 MHz, CD_3COCD_3) δ 141.6, 131.8, 131.7, 72.5, 69.9, 29.8.

IR (neat/cm^{-1}) 3058, 3020, 1730.
HRMS (EI), calculated for $C_9H_{10}N_4O_4S_2$ ([M]$^{+\bullet}$) *m/z* 302.0143, found *m/z* 302.0192.



(±)-Methyl (1*S*,3*R*,5*R*)-2*H*,4*H*,6*H*-1,5:3,7-diepithiobenzo[*h*][1,3,5,7]tetrazonine-9-carboxylate 12,12,13,13-tetraoxide 2j. Yield 61 %. Mp 236 °C.

^{1}H NMR (600 MHz, CD_3COCD_3) δ 8.10 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.95 (d, *J* = 1.9 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 5.92 (s, 2H), 5.66 (dd, *J* = 15.0, 5.7 Hz, 2H), 5.50 (m, 2H), 3.93 (s, 3H).
^{13}C NMR (151 MHz, CD_3COCD_3) δ 165.4, 145.5, 142.0, 133.6, 132.64, 132.57, 132.4, 72.5, 69.9, 69.8, 53.0.
IR (neat/cm^{-1}) 2954, 2922, 2853, 1719.
HRMS (EI), calculated for $C_{11}H_{12}N_4O_6S_2$ ([M]$^{+\bullet}$) *m/z* 360.0198, found *m/z* 360.0204.

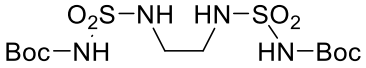


(±)-(1*R*,4*S*,6*S*,8*R*)-4-(4-Aminobenzyl)-2,7-dithia-1,3,6,8-tetraazatricyclo[4.3.1.13,8]undecane 2,2,7,7-tetraoxide 2k. A mixture of (1*R*,4*S*,6*S*,8*R*)-4-(4-nitrobenzyl)-2,7-dithia-1,3,6,8-tetraazatricyclo[4.3.1.1^{3,8}]undecane 2,2,7,7-tetraoxide **2f** (20 mg, 51.4 µmol, 1 equiv), Zn (33 mg, 514 µmol, 10 equiv) and AcOH/MeOH = 1:1 (2 mL) was stirred at RT overnight, filtered through a short pad of Celite and evaporated. The resulting product was used in the next step without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.03 (d, *J* = 7.7 Hz, 2H), 6.73 (d, *J* = 7.8 Hz, 2H), 5.37 (s, 2H), 5.14 (d, *J* = 14.7 Hz, 1H), 5.08 (d, *J* = 14.9 Hz, 1H), 4.68 (d, *J* = 14.8 Hz, 1H), 4.43 (d, *J* = 14.8 Hz, 1H), 3.95 (m, 2H), 3.44 (m, 1H), 3.16 (dd, *J* = 13.9, 8.4 Hz, 1H), 2.81 (m, 1H).

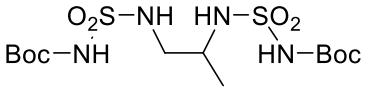
^{13}C NMR (151 MHz, $CDCl_3$) δ 130.1, 130.1, 116.9, 71.9, 70.1, 68.6, 67.5, 57.6, 38.6.

General procedure for the synthesis of sulfamides 8. To a cooled (0 °C) solution of chlorosulfonyl isocyanate (1.415 g, 10 mmol, 1 equiv) in CH_2Cl_2 (17 mL) was added *tert*-butanol (0.74 g, 10 mmol, 1 equiv). The resulting solution was stirred for 30 min prior to the addition of Et_3N (3.23 g, 32 mmol, 3.2 equiv) and diamine (5 mmol, 0.5 equiv) in CH_2Cl_2 (17 mL). The reaction mixture was stirred at RT for 1 hour, quenched with water (40 mL) and $HCl_{conc.}$ to pH 3, and extracted with EtOAc (3×50 mL). Combined organic fractions were dried over $MgSO_4$, filtered and evaporated.



Di-*tert*-butyl ((ethane-1,2-diylbis(azanediyl))bis(sulfonyl))dicarbamate 8a. Yield 85 %. Mp 148 °C.

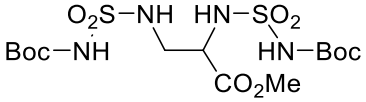
^{1}H NMR (600 MHz, CD_3OD) δ 3.18 (s, 4H), 1.50 (s, 18H).
^{13}C NMR (151 MHz, CD_3OD) δ 152.8, 83.3, 43.9, 28.4.
IR (neat/cm^{-1}) 3311, 3287, 2995, 2942, 2879, 1711.
HRMS (ESI), calculated for $C_{12}H_{25}N_4O_8S_2$ ($[M-H]^-$) *m/z* 417.1119, found *m/z* 417.1116.



***tert*-Butyl (*N*-(2-((*N*-(*tert*-butoxycarbonyl)sulfamoyl)amino)propyl)sulfamoyl)carbamate 8b**. Yield 94%. Mp 244 °C.

^{1}H NMR (600 MHz, CD_3COCD_3) δ 9.64 (br s, 2H), 6.54 (d, *J* = 7.8 Hz, 1H), 6.48 (t, *J* = 6.4 Hz, 1H), 3.68 (p, *J* = 6.7 Hz, 1H), 3.22 (m, 1H), 3.14 (m, 1H), 1.474 (s, 9H), 1.469 (s, 9H), 1.30 (d, *J* = 6.6 Hz, 3H).
^{13}C NMR (151 MHz, CD_3COCD_3) δ 151.6, 151.5, 82.8, 82.7, 50.7, 49.5, 28.21, 28.17, 18.5.

IR (neat/cm^{-1}) 3038, 2978, 1781.
HRMS (ESI), calculated for $C_{13}H_{27}N_4O_8S_2$ ($[M-H]^-$) *m/z* 431.1276, found *m/z* 431.1280.

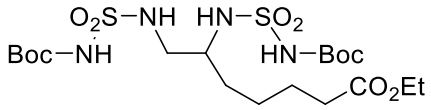


Methyl 2,3-bis((*N*-(*tert*-butoxycarbonyl)sulfamoyl)amino)propanoate 8c. Starting material, (*DL*)-2,3-diaminopropionic acid methyl ester dihydrochloride was prepared according to the literature procedure.[3] Yield 79 %.

^{1}H NMR (800 MHz, CD_3COCD_3) δ 9.73 (br s, 2H), 6.94 (s, 1H), 6.67 (t, *J* = 6.8 Hz, 1H), 4.44 (t, *J* = 5.5 Hz, 1H), 3.75 (s, 3H), 3.52 (m, 2H), 1.47 (s, 9H), 1.47 (s, 9H).

^{13}C NMR (201 MHz, CD_3COCD_3) δ 170.5, 151.40, 151.36, 82.94, 82.89, 57.4, 53.0, 46.5, 46.4, 28.18, 28.16.

HRMS (ESI), calculated for $C_{14}H_{27}N_4O_{10}S_2$ ([M–H]$^-$) *m/z* 475.1174, found *m/z* 475.1174.

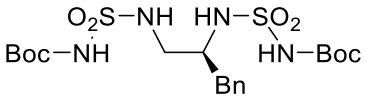


Ethyl 6,7-bis((*N*-(*tert*-butoxycarbonyl)sulfamoyl)amino)heptanoate 8d. Obtained product contained some impurities and was used in the next step without purification. White sticky solid. Yield quantitative.

^{1}H NMR (600 MHz, CD_3COCD_3) δ 9.65 (s, 1H), 9.63 (s, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 6.44 (t, *J* = 6.3 Hz, 1H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.56 (m, 1H), 3.27 (dt, *J* = 13.0, 5.8 Hz, 1H), 3.19 (dt, *J* = 12.9, 6.4 Hz, 1H), 2.29 (t, *J* = 7.5 Hz, 2H), 1.78 (m, 1H), 1.62 (m, 3H), 1.43-1.55 (m, 2H), 1.48 (s, 9H), 1.47 (s, 9H), 1.20 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, CD_3COCD_3) δ 173.5, 151.6, 151.5, 82.8, 82.7, 60.5, 54.7, 47.9, 34.4, 32.3, 28.3, 28.2, 25.6, 25.4, 14.6.

HRMS (ESI), calculated for $C_{19}H_{37}N_4O_{10}S_2$ ([M–H]$^-$) *m/z* 545.1957, found *m/z* 545.1954.

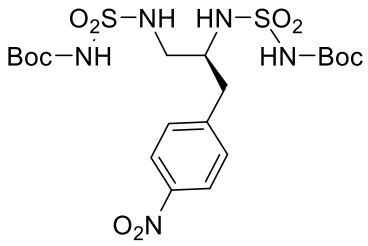


***tert*-Butyl (*S*)-(*N*-(2-((*N*-(*tert*-butoxycarbonyl)sulfamoyl)amino)-3-phenylpropyl)sulfamoyl)carbamate 8e**.

^{1}H NMR (800 MHz, CD_3COCD_3) δ 7.35 – 7.21 (m, 5H), 3.86 (dq, *J* = 8.3, 5.6 Hz, 1H), 3.16 (m, 1H), 3.05 (dd, *J* = 13.8, 5.5 Hz, 1H), 3.00 (dd, *J* = 13.9, 8.4 Hz, 1H), 1.47 (s, 9H), 1.45 (s, 9H).

^{13}C NMR (201 MHz, CD_3COCD_3) δ 151.7, 151.4, 138.4, 130.3, 129.3, 127.5, 82.9, 82.9, 56.3, 46.6, 39.2, 28.3, 28.2.

IR (neat/cm^{-1}) 3282, 2982, 2934, 1718.
HRMS (ESI), calculated for $C_{19}H_{31}N_4O_8S_2$ ([M–H]$^-$) *m/z* 507.1589, found *m/z* 507.1586.

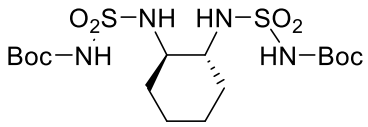


***tert*-Butyl (*S*)-(*N*-(2-((*N*-(*tert*-butoxycarbonyl)sulfamoyl)amino)-3-(4-nitrophenyl)propyl)sulfamoyl)carbamate 8f**. Yield 82 %.

^{1}H NMR (800 MHz, CD_3COCD_3) δ 9.68 (br s, 1H), 9.66 (br s, 1H), 8.18 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.60 (t, *J* = 6.4 Hz, 1H), 3.98 (m, 1H), 3.27 (m, 2H), 3.11 (dd, *J* = 13.9, 7.2 Hz, 1H), 1.45 (s, 9H), 1.44 (s, 9H).

^{13}C NMR (201 MHz, CD_3COCD_3) δ 151.6, 151.5, 147.7, 146.9, 131.7, 124.2, 82.9, 82.8, 55.9, 47.1, 38.8, 28.2, 28.2.

IR (neat/cm^{-1}) 3297, 2918, 2850, 1712.
HRMS (ESI), calculated for $C_{19}H_{30}N_5O_{10}S_2$ ([M–H]$^-$) *m/z* 552.1440, found *m/z* 552.1439.

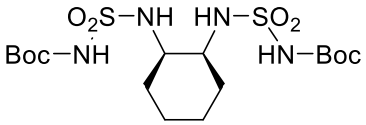


Di-*tert*-butyl ((((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(azanediyl))bis(sulfonyl))dicarbamate 8g. Yield 87%. Mp 163 °C.

^{1}H NMR (600 MHz, CD_3COCD_3) δ 9.61 (s, 2H), 6.42 (d, *J* = 3.8 Hz, 2H), 3.25 (m, 2H), 2.23 (d, *J* = 13.5 Hz, 2H), 1.71 (m, 2H), 1.47 (s, 18H).

^{13}C NMR (151 MHz, CD_3COCD_3) δ 151.7, 82.8, 57.6, 32.9, 28.2, 24.7.

IR (neat/cm^{-1}) 3331, 3289, 3178, 2974, 2936, 2858, 1741.
HRMS (ESI), calculated for $C_{16}H_{31}N_4O_8S_2$ ([M-H]$^-$) *m/z* 471.1589, found *m/z* 471.1587.



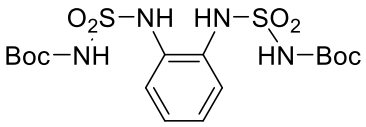
Di-*tert*-butyl ((((1*R*,2*S*)-cyclohexane-1,2-diyl)bis(azanediyl))bis(sulfonyl))dicarbamate 8h. Yield 85%. Mp 168 °C.

^{1}H NMR (600 MHz, CD_3COCD_3) δ 9.63 (s, 2H), 6.29 (d, *J* = 7.1 Hz, 2H), 3.64 (m, 2H), 1.92 (m, 2H), 1.71 (m, 4H), 1.47 (s, 18H), 1.40 (m, 2H).

^{1}H NMR (800 MHz, CD_3OD) δ 3.57 (d, *J* = 7.2 Hz, 2H), 1.76 (m, 2H), 1.64 (m, 4H), 1.50 (s, 18H), 1.40 (m, 2H).

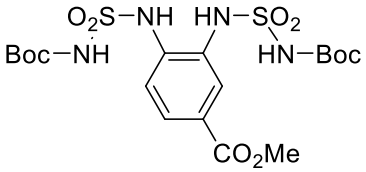
^{13}C NMR (201 MHz, CD_3OD) δ 152.7, 83.5, 55.8, 49.0, 29.6, 28.4.

IR (neat/cm^{-1}) 3321, 3264, 2992, 2976, 2939, 2864, 1733, 1713.
HRMS (ESI), calculated for $C_{16}H_{31}N_4O_8S_2$ ($[M–H]^–$) *m/z* 471.1589, found *m/z* 471.1588.



Di-*tert*-butyl ((1,2-phenylenebis(azanediyl))bis(sulfonyl))dicarbamate 8i. Yield quantitative. Mp 127 °C.

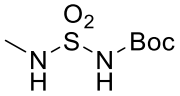
^{1}H NMR (800 MHz, CD_3COCD_3) δ 7.90 (s, 2H), 7.53 (m, 2H), 7.32 (m, 2H), 7.21 (m, 1H), 6.38 (m, 1H), 1.46 (s, 18H).
^{13}C NMR (201 MHz, CD_3COCD_3) δ 152.00, 131.02, 127.96, 126.32, 84.02, 28.07.
IR (neat/cm^{-1}) 3381, 3282, 3246, 2985, 2933, 1745, 1730.
HRMS (ESI), calculated for $C_{16}H_{25}N_4O_8S_2$ ($[M–H]^–$) *m/z* 465.1119, found *m/z* 465.1118.



Methyl 3,4-bis((*N*-(*tert*-butoxycarbonyl)sulfamoyl)amino)benzoate 8j. Yield 74 %. Mp 136 °C.

^{1}H NMR (800 MHz, CD_3COCD_3) δ 8.10 (d, *J* = 2.0 Hz, 1H), 7.96 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 3.88 (s, 3H), 1.49 (s, 9H), 1.43 (s, 9H).
^{13}C NMR (201 MHz, CD_3COCD_3) δ 166.0, 152.0, 151.5, 137.4, 129.6, 128.8, 128.4, 123.4, 84.1, 84.0, 52.6, 28.1, 28.0.

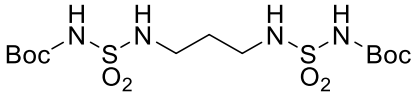
IR (neat/cm^{-1}) 3359, 3327, 3141, 3060, 2982, 2848, 1740, 1701, 1610.
HRMS (ESI), calculated for $C_{18}H_{27}N_4O_{10}S_2$ ([M–H]$^-$) *m/z* 523.1174, found *m/z* 523.1172.



***tert*-Butyl (*N*-methylsulfamoyl)carbamate 8k**. Yield quantitative.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.76 (s, 1H), 7.31 (q, *J* = 5.0 Hz, 1H), 2.48 (s, 3H), 1.42 (s, 9H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 150.7, 81.3, 28.9, 27.8.

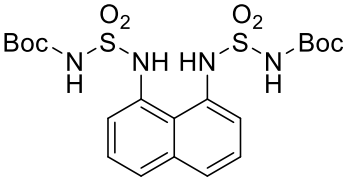


Di-*tert*-butyl ((propane-1,3-diylbis(azanediyl))bis(sulfonyl))dicarbamate 8l. Yield 72 %.

^{1}H NMR (600 MHz, CD_3COCD_3) δ 9.59 (br s, 2H), 6.47 (t, *J* = 6.2 Hz, 2H), 3.19 (q, *J* = 6.7 Hz, 4H), 1.89 (p, *J* = 6.9 Hz, 4H), 1.46 (s, 18H).

^{13}C NMR (151 MHz, CD_3COCD_3) δ 151.6, 82.6, 41.6, 28.2.

IR (neat/cm^{-1}) 3263, 3205, 2972, 1696.
HRMS (ESI), calculated for $C_{13}H_{27}N_4O_8S_2$ ([M–H]$^-$) *m/z* 431.1276, found *m/z* 431.1273.

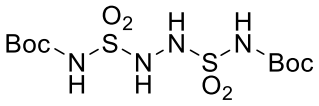


Di-*tert*-butyl ((naphthalene-1,8-diylbis(azanediyl))bis(sulfonyl))dicarbamate 8m. Yield quantitative.

^{1}H NMR (800 MHz, CD_3COCD_3) δ 9.92 (br s, 2H), 9.82 (s, 2H), 7.88 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.67 (d, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 7.8 Hz, 2H), 1.28 (s, 18H).

^{13}C NMR (201 MHz, CD_3COCD_3) δ 151.3, 137.1, 133.1, 128.4, 126.8, 124.0, 123.7, 83.4, 27.9.

IR (neat/cm^{-1}) 3232, 2981, 2934, 1719, 1603, 1582.
HRMS (ESI), calculated for $C_{20}H_{27}N_4O_8S_2$ ([M–H]$^-$) *m/z* 515.1276, found *m/z* 515.1273.

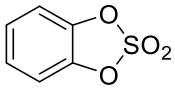


Di-*tert*-butyl (hydrazinedisulfonyl)dicarbamate 8n. Yield quantitative.

^{1}H NMR (800 MHz, CD_3COCD_3) δ 9.98 (br s, 2H), 8.90 (s, 2H), 1.46 (s, 18H).

^{13}C NMR (201 MHz, CD_3COCD_3) δ 150.8, 83.1, 28.2.

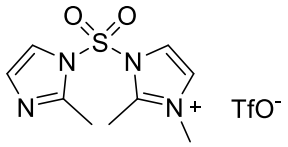
IR (neat/cm^{-1}) 3443, 3256, 2980, 2936, 1717, 1679, 1606.
HRMS (ESI), calculated for $C_{10}H_{21}N_4O_8S_2$ ([M–H]$^-$) *m/z* 389.0806, found *m/z* 389.0805.



Catechol sulfate 12 was synthesized according to the literature procedure.[4]

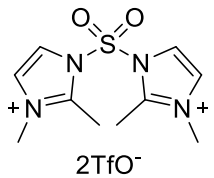
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 125.5, 111.9.



2,3-Dimethyl-1-((2-methyl-1*H*-imidazol-1-yl)sulfonyl)-1*H*-imidazol-3-ium trifluoromethanesulfonate 13 was synthesized by modified literature procedure.[5] Briefly, a solution of methyl trifluoromethansulfonate (0.87 mL, 7.7 mmol, 1 equiv) in CH_2Cl_2 (27 mL) was added dropwise over 2 hours to a cooled to -15 °C solution of 1,1'-sulfonylbis(2-methyl-1H-imidazole) [5] (2.26 g, 10 mmol, 1.3 equiv). The reaction mixture was stirred at -5 °C for 1.5 h and the precipitate was filtered under atmosphere of dry nitrogen. Drying of the precipitate under vacuum provided pure product as a white crystalline solid (2.454 g, 82 %). Mp 95 °C.

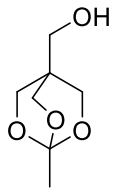
^{1}H NMR (600 MHz, CD_3OD) δ 8.30 (d, *J* = 2.5 Hz, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.77 (d, *J* = 2.5 Hz, 1H), 7.11 (d, *J* = 2.0 Hz, 1H), 3.89 (s, 3H), 2.88 (s, 3H), 2.64 (s, 3H).



1,1'-Sulfonylbis(2,3-dimethyl-1H-imidazol-3-ium) trifluoromethanesulfonate 14. To a cooled to 0 °C solution of 1,1'-sulfonylbis(2-methyl-1H-imidazole) (0.67 g, 2.97 mmol, 1 equiv) in CH_2Cl_2 (16 mL) was added a solution of methyl trifluoromethansulfonate (0.7 mL, 6.23 mmol, 2.1 equiv) in CH_2Cl_2 (12 mL). The reaction mixture was stirred for 1 h at 0 °C and then 1 h at RT. Filtration of the precipitate under an atmosphere of dry nitrogen provided pure precipitate as a white crystalline solid (1.508 g, 92 %).

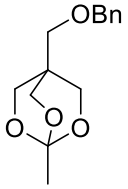
^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (d, *J* = 2.6 Hz, 1H), 7.85 (d, *J* = 2.6 Hz, 1H), 3.91 (s, 4H), 2.93 (s, 4H).
^{13}C NMR (151 MHz, CD_3CN) δ 151.5, 125.7, 122.3, 37.6, 13.2.
IR (neat/cm^{-1}) 3157, 3136, 1718, 1601.

HRMS (ESI), calculated for $C_{10}H_{16}N_4O_2S$ ($[M]^{2+}$) *m/z* 128.0491, found *m/z* 128.0494.



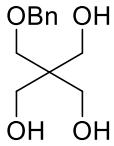
(1-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-4-yl)methanol was synthesized according to the literature procedure.[6] Briefly, triethyl orthoacetate (18.3 mL, 100 mmol, 1 equiv) and *p*TSA·H_2O (50 mg, 0.26 mmol, 0.0026 equiv) were added to a suspension of pentaerythritol (13.6 g, 100 mmol, 1 equiv) in toluene (10 mL). The resulting mixture was heated to reflux and the ethanol was distilled off over a period of 10 h. Toluene was then distilled off and the residue was sublimed at 130 °C to give pure product as a white crystalline solid (14.742 g, 92 %).

^{1}H NMR (400 MHz, CD_3OD) δ 3.94 (s, 6H), 3.32 (s, 2H), 1.32 (s, 3H).
^{13}C NMR (101 MHz, CD_3OD) δ 109.6, 70.4, 61.3, 36.8, 23.8.



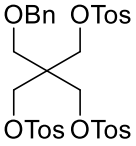
4-((Benzyloxy)methyl)-1-methyl-2,6,7-trioxabicyclo[2.2.2]octane was synthesized according to the literature procedure.[6] Briefly, (1-methyl-2,6,7-trioxabicyclo[2.2.2]octan-4-yl)methanol (14.7 g, 91.9 mmol, 1 equiv) and benzyl bromide (13.12 mL, 110.3 mmol, 1.2 equiv) were sequentially added to a suspension of KOH (24.18 g, 432 mmol, 4.7 equiv) in DMSO (150 mL). The reaction mixture was stirred for 1 h, quenched with water (1.5 L) and extracted with Et_2O (2×150 mL). Combined extracts were washed with brine, water, dried over $MgSO_4$, filtered and evaporated. Crude product (23.635 g, quant) was used in the next step without any further purification.

^{1}H NMR (300 MHz, CD_3OD) δ 7.30 (m, 5H), 4.44 (s, 2H), 4.00 (s, 6H), 3.18 (s, 2H), 1.45 (s, 3H).
^{13}C NMR (75 MHz, CD_3OD) δ 137.6, 128.6, 128.0, 127.5, 108.6, 73.6, 69.6, 68.4, 35.0, 23.6.



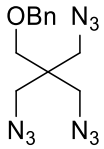
2-((Benzyloxy)methyl)-2-(hydroxymethyl)propane-1,3-diol 15 was synthesized according to the literature procedure. [6] Briefly, to a solution of 4-((benzyloxy)methyl)-1-methyl-2,6,7-trioxabicyclo[2.2.2]octane (91.9 mmol, 1 equiv) in MeOH (60 mL) was added an aqueous solution of hydrochloric acid (0.01 M, 235 mL) and the resulting mixture was stirred at RT for 1 h. $NaHCO_3$ (8.57g, 102 mmol, 1.11 equiv) was added and the resulting mixture was stirred for 1 h and evaporated. The residue was triturated with MeOH, filtered and evaporated. Crude product (20.59 g, quant) was used in the next step without any further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.46 (s, 2H), 3.64 (s, 6H), 3.43 (s, 2H).



2-((Benzyloxy)methyl)-2-((tosyloxy)methyl)propane-1,3-diyl bis(4-methylbenzenesulfonate) was synthesized according to the literature procedure.[6] Briefly, to a cooled to -5 °C solution of 2-((benzyloxy)methyl)-2-(hydroxymethyl)propane-1,3-diol **15** (20.59 g, 91 mmol, 1 equiv) in pyridine was added *p*-toluenesulfonyl chloride (69.414g, 364 mmol, 4 equiv) slowly. The reaction mixture was stirred at 0 °C for 2 h and then at RT for 24 h. It was then poured onto ice/water mixture and the resulting precipitate was filtered and dried under vacuum. Crude product (50.5 g, 80.5 %) was used in the next step without any further purification.

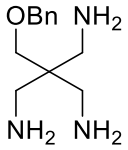
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 6H), 7.31 (d, *J* = 8.0 Hz, 6H), 7.28 (m, 3H), 7.08 (m, 2H), 4.26 (s, 2H), 3.91 (s, 6H), 3.31 (s, 2H), 2.43 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 137.3, 131.9, 130.2, 128.4, 128.0, 127.9, 127.4, 73.4, 66.8, 66.4, 43.9, 21.8.



((3-Azido-2,2-bis(azidomethyl)propoxy)methyl)benzene was synthesized according to the literature procedure. [6] Briefly, a mixture of 2-((benzyloxy)methyl)-2-((tosyloxy)methyl)propane-1,3-diyl bis(4-methylbenzenesulfonate) (6.53 g, 9.48 mmol, 1 equiv), sodium azide (3.08 g, 47.4 mmol, 5 equiv) and

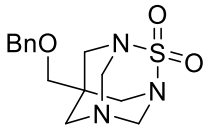
DMF (20 mL) was stirred at 100 °C for 18 h. Another portion of sodium azide (1 g) was added and the resulting mixture was stirred at 100 °C for 2 days, quenched with water and extracted with Et_2O (3×30 mL). Combined organics were dried over Na_2SO_4, filtered and evaporated. Purification of the residue by flash column chromatography (EtOAc/hexanes = 10:90) provided pure product as a colorless oil (2.908 g, quant).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H), 4.53 (s, 2H), 3.37 (s, 6H), 3.34 (s, 2H).



2-(Aminomethyl)-2-((benzyloxy)methyl)propane-1,3-diamine 16 was synthesized according to the literature procedure. [6] Briefly, a mixture of ((3-azido-2,2-bis(azidomethyl)propoxy)methyl)benzene (2.33 g, 7.74 mmol, 1 equiv), Pd/C (10 % wt, 1.64 g, 1.55 mmol, 0.2 equiv) and MeOH (18 mL) was stirred under an atmosphere of hydrogen for 20 h and filtered through a short pad of Celite. The Celite pad was washed with a small amount of MeOH. Evaporation of the solvent gave the desired product as a colorless oil (containing ~50 mol % of MeOH based on NMR, 1.879 g, quant).

^{1}H NMR (300 MHz, CD_3OD) δ 7.35 (m, 5H), 4.77 (s, 6H), 4.49 (s, 2H), 3.37 (s, 2H), 2.60 (s, 6H).
^{13}C NMR (75 MHz, CD_3OD) δ 139.8, 129.5, 128.8, 128.8, 74.4, 72.9, 44.6, 43.5.



(1*R*,3*S*,5*r*,7*r*)-7-((Benzyloxy)methyl)-2-thia-1,3,5-triazaadamantane 2,2-dioxide 17.

Method A. A solution of catechol sulfate **12** (40 mg, 0.237 mmol, 1 equiv) in dioxane (1 mL) was added dropwise to a solution of 2-(aminomethyl)-2-((benzyloxy)methyl)propane-1,3-diamine **16** (53 mg, 0.237 mmol, 1 equiv) in dioxane (4 mL). The resulting mixture was refluxed for 3 h and then stirred at RT overnight. An aqueous solution of formaldehyde (37 % wt, 53 µL, 0.712 mmol, 3 equiv) was added dropwise and the reaction mixture was stirred at 40 °C for 4 h. The reaction mixture was loaded onto the short silica gel column and eluted with CH_2Cl_2/MeOH = 98:2 solvent mixture. All fractions were analyzed for presence of desired product by mass spectrometry. Fractions containing desired product were combined and evaporated. Trituration of the residue with a small amount of dichloromethane provided pure product as a colorless crystals (33 mg, 45 %).

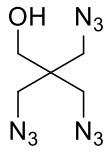
Method B. A mixture of 2-(aminomethyl)-2-((benzyloxy)methyl)propane-1,3-diamine **16** (45 mg, 0.199 mmol, 1 equiv), sulfamide (19 mg, 0.199 mmol, 1 equiv) and pyridine (1 mL) was refluxed for 5 h. An aqueous solution of formaldehyde (37 % wt, 60 µL, 0.796 mmol, 4 equiv) was added at once. The

resulting mixture was left to slowly cool to RT. The reaction mixture was loaded onto a short silica gel column and eluted with CH_2Cl_2/MeOH = 98:2. All fractions were analyzed for presence of the desired product by mass spectrometry. Fractions containing the desired product were combined and evaporated. Trituration of the residue with a small amount of dichloromethane provided pure product as a colorless crystals (15 mg, 24 %). Mp 110 °C.

^{1}H NMR (800 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.34 (m, 1H), 7.30 (m, 2H), 5.03 (d, *J* = 13.2 Hz, 2H), 4.47 (m, 4H), 4.15 (d, *J* = 14.0 Hz, 2H), 3.59 (dt, *J* = 14.2, 1.9 Hz, 2H), 3.34 (s, 2H), 3.00 (s, 2H).

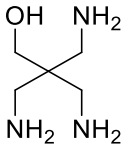
^{13}C NMR (201 MHz, $CDCl_3$) δ 137.5, 128.6, 128.0, 127.6, 73.5, 72.9, 72.1, 59.4, 58.2, 25.7.

IR (neat/cm^{-1}) 2957, 1718.
HRMS (ESI), calculated for $C_{14}H_{20}N_3O_3S$ (MH^+) *m/z* 310.1220, found *m/z* 310.1233.



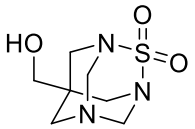
3-Azido-2,2-bis(azidomethyl)propan-1-ol. A mixture of pentaerythritol tribromide (3.25 g, 10 mmol, 1 equiv), NaN_3 (3.9 g, 60 mmol, 6 equiv) and DMF (25 mL) was heated at 100 °C for 2 days. The reaction mixture was cooled down to RT, quenched with water (80 mL) and extracted with Et_2O (4×20 mL). Combined organics were dried over $MgSO_4$, filtered and evaporated. Product contaminated with small amount of DMF was used in the next step without purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.52 (s, 2H), 3.36 (s, 6H), 2.15 (s, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 62.1, 51.6, 44.6.



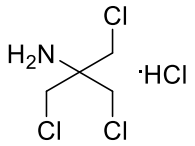
3-Amino-2,2-bis(aminomethyl)propan-1-ol 18. A mixture of 3-Azido-2,2-bis(azidomethyl)propan-1-ol (10 mmol, 1 equiv), Pd/C (10 % wt, 2.12 g, 2 mmol, 0.2 equiv) and EtOH (100 mL) was stirred under an atmosphere of hydrogen for 2 days and filtered through a short pad of Celite. The Celite pad was washed with a small amount of EtOH. Evaporation of the solvent gave the desired product as a colorless oil (1.4 g, quant).

^{1}H NMR (300 MHz, CD_3OD) δ 4.63 (s, 6H), 3.51 (s, 2H), 2.64 (s, 6H).
^{13}C NMR (75 MHz, CD_3OD) δ 64.8, 44.2, 43.5.



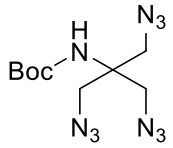
(1*R*,3*S*,5*r*,7*r*)-7-(Hydroxymethyl)-2-thia-1,3,5-triazaadamantane 2,2-dioxide 6a. A solution of catechol sulfate **12** (1.634 g, 9.5 mmol, 1 equiv) in dioxane (10 mL) was added dropwise to a refluxed solution of 3-amino-2,2-bis(aminomethyl)propan-1-ol **18** (1.3 g, 9.5 mmol, 1 equiv) in dioxane (90 mL). The resulting mixture was refluxed for 12 h. An aqueous solution of formaldehyde (37 % wt, 2.83 mL, 38 mmol, 4 equiv) was added dropwise and the reaction mixture was stirred at reflux for 30 min, cooled down to RT and evaporated. The residue was triturated with hot CH_2Cl_2/MeOH = 95:5 loaded onto the short silica gel column and eluted with CH_2Cl_2/MeOH = 95:5. All fractions were analyzed for the presence of the desired product by mass-spectrometry. Fractions containing the desired product were combined and evaporated. Trituration of the residue with a small amount of dichloromethane provided pure product as a colorless crystals (310 mg, 15 %). Mp 280 °C.

^{1}H NMR (800 MHz, CD_3COCD_3) δ 4.88 (d, *J* = 13.0 Hz, 2H), 4.59 (d, *J* = 12.5 Hz, 2H), 4.07 (d, *J* = 13.1 Hz, 2H), 3.92 (s, 1H), 3.66 (d, *J* = 13.7 Hz, 2H), 3.33 (s, 2H), 3.18 (s, 2H).
^{13}C NMR (201 MHz, CD_3COCD_3) δ 73.4, 65.0, 59.2, 58.6.
IR (neat/cm^{-1}) 3233, 3032, 2968, 1708.
HRMS (ESI), calculated for $C_7H_{14}N_3O_3S$ (MH^+) *m/z* 220.0750, found *m/z* 220.0758.



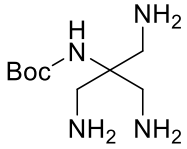
1,3-Dichloro-2-(chloromethyl)propan-2-aminium chloride was synthesized according to the literature procedure.[7] Briefly, $SOCl_2$ (60.95 mL, 840 mmol, 4.2 equiv) and pyridine (8.08 mL, 100 mmol, 0.5 equiv) were sequentially added to a flask containing TRIS base cooled to 0 °C (24.2 g, 200 mmol, 1 equiv). The reaction mixture was allowed to warm up to RT and stirred until gas evolution ceased. Then it was gradually heated up to 120 °C over the 5 h period. The resulting mixture was cooled to 20 °C and quenched by slowly adding 8 mL of water. An additional 42 mL of water was added followed by the addition of sulfuric acid solution (11 mL of $H_2SO_{4conc.}$ in 48 mL of water) over period of 10 min. The resulting mixture was refluxed until gas evolution ceased, then cooled to 10 °C, basified with NaOH to pH 10 and extracted with CH_2Cl_2 (5×150 mL). Combined organics were dried over $MgSO_4$, filtered and evaporated. The residue was redissolved in Et_2O (150 mL) and HCl (2M in Et_2O, 100 mL) was added. Crystalline product was removed by filtration (19.04 g, 45 %).

^{1}H NMR (300 MHz, D_2O) δ 4.01 (s, 6H).



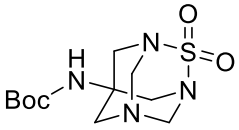
***tert*-Butyl (1,3-diazido-2-(azidomethyl)propan-2-yl)carbamate** was synthesized according to the literature procedure.[8] Briefly, a solution of 1,3-dichloro-2-(chloromethyl)propan-2-aminium chloride (2.13 g, 10 mmol, 1 equiv) and NaN_3 (3.25 g, 50 mmol, 5 equiv) in water (50 mL) was heated to 100 °C for 18 h. The resulting mixture was cooled to RT, basified to pH 10–11 with 1 M NaOH solution and extracted with Et_2O (3×20 mL). Combined organics were dried over $MgSO_4$, filtered and concentrated to ~5 mL. The residue was dissolved in EtOH (25 mL) and was added to a solution of Boc_2O (2.18 g, 10 mmol, 1 equiv) in EtOH (25 mL). The reaction mixture was stirred at RT overnight and concentrated to dryness. Trituration of the crude product with water gave pure product as a pale-yellow solid (2.6 g, 88 %).

^{1}H NMR (400 MHz, CD_3OD) δ 3.54 (s, 6H), 1.45 (s, 9H).



***tert*-Butyl (1,3-diamino-2-(aminomethyl)propan-2-yl)carbamate 19** was synthesized according to the literature procedure.[8b] Briefly, a mixture of *tert*-butyl (1,3-diazido-2-(azidomethyl)propan-2-yl)carbamate (10 mmol, 1 equiv), Pd/C (10 % wt, 2.12 g, 2 mmol, 0.2 equiv) and EtOH (100 mL) was stirred under an atmosphere of hydrogen for 16 h and filtered through a short pad of Celite. The Celite pad was washed with a small amount of EtOH. Evaporation of the solvent gave the desired product as a colorless oil (94 mg, 82 %).

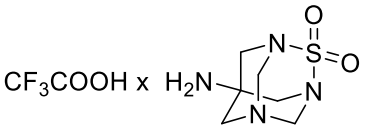
^{1}H NMR (300 MHz, CD_3OD) δ 2.79 (s, 6H), 1.44 (s, 9H).



***tert*-Butyl ((1*R*,3*S*,5*r*,7*r*)-2,2-dioxido-2-thia-1,3,5-triazaadamantan-7-yl)carbamate 20**. A solution of catechol sulfate **12** (1.39 g, 8.07 mmol, 1 equiv) in dioxane (5 mL) was added dropwise to a refluxing solution of *tert*-butyl (1,3-diamino-2-(aminomethyl)propan-2-yl)carbamate **19** (1.759 g, 8.07 mmol, 1 equiv) in dioxane (80 mL). The resulting mixture was refluxed overnight. An aqueous solution of formaldehyde (37 % wt, 2.4 mL, 32.3 mmol, 4 equiv) was added dropwise and the reaction mixture was allowed to slowly cool to RT over 3 h. The resulting mixture was concentrated under reduced pressure and the residue was chromatographed (EtOAc). All fractions were analyzed for presence of desired product by mass spectrometry. Fractions containing the desired product were combined and evaporated.

Trituration of the residue with a small amount of methanol provided pure product as colorless crystals (646 mg, 26 %). Mp 230 °C.

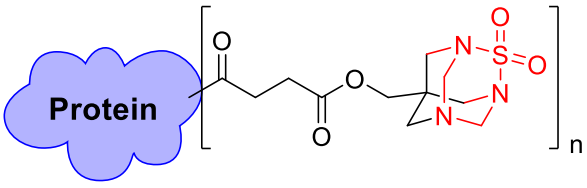
^{1}H NMR (800 MHz, CD_3SOCD_3) δ 6.91 (br s, 1H), 4.72 (d, *J* = 13.1 Hz, 2H), 4.61 (d, *J* = 12.8 Hz, 2H), 4.24 (d, *J* = 13.1 Hz, 2H), 3.68 (d, *J* = 13.1 Hz, 2H), 3.44 (s, 2H), 1.37 (s, 9H).
^{13}C NMR (201 MHz, CD_3SOCD_3) δ 154.1, 71.7, 58.7, 57.0, 38.0, 28.1.
IR (neat/cm^{-1}) 3230, 3035, 2968, 2363, 1707.
HRMS (ESI), calculated for $C_{11}H_{21}N_4O_4S$ (MH^+) *m/z* 305.1278, found *m/z* 305.1290.



(1*R*,3*S*,5*r*,7*r*)-7-Amino-2-thia-1,3,5-triazaadamantane 2,2-dioxide 6b. *tert*-Butyl ((1*R*,3*S*,5*r*,7*r*)-2,2-dioxido-2-thia-1,3,5-triazaadamantan-7-yl)carbamate (324 mg, 1.07 mmol) was suspended in CH_2Cl_2 (4 mL) and CF_3COOH (4 mL) was added dropwise at 0 °C. The reaction mixture was stirred at RT for 3 h and evaporated to give product as a pale-yellow powder (quant).

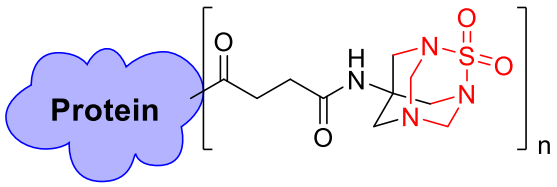
^{1}H NMR (800 MHz, CD_3OD) δ 4.98 (d, *J* = 13.3 Hz, 2H), 4.62 (dm, *J* = 13.4 Hz, 2H), 4.32 (dm, *J* = 13.8, 2H), 3.81 (dt, *J* = 13.9, 2.2 Hz, 2H), 3.57 (s, 2H).
^{13}C NMR (201 MHz, CD_3OD) δ 73.0, 59.0, 57.5, 40.1.
IR (neat/cm^{-1}) 2917, 2847, 1746, 1660.
HRMS (ESI), calculated for $C_6H_{13}N_4O_2S$ (MH^+) *m/z* 205.0754, found *m/z* 205.0760.

Preparation of immunogens and coating antigens

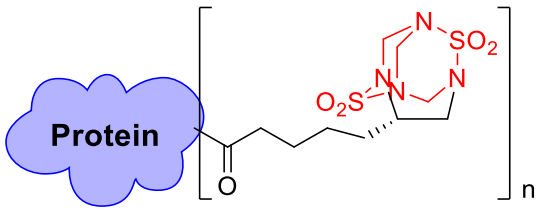


Preparation of the coating/immunizing antigen based on hapten 6a. A mixture of (1*R*,3*S*,5*r*,7*r*)-7-(hydroxymethyl)-2-thia-1,3,5-triazaadamantane 2,2-dioxide **6a** (150 mg, 685 µmol, 1 equiv), succinic anhydride (137 mg, 1.37 mmol, 2 equiv), DMAP (8.4 mg, 68 µmol, 0.1 equiv) and Et_3N (138 mg, 1.37 mmol, 2 equiv) in DMF (5 mL) was heated to 70 °C for 5 h. After cooling the reaction mixture to RT, NHS (158 mg, 1.37 mmol, 2 equiv) and EDC (263 mg, 1.37 mmol, 2 equiv) were added and the resulting

mixture was stirred for 16 h, quenched with water and extracted with CH_2Cl_2 (5×10 mL). Combined organics were dried over Na_2SO_4, filtered and evaporated. The residue was dissolved in dry DMF (5.37 mL) to give ~0.096 M solution of the activated hapten (based on ~80 % yield). A solution of the appropriate protein (25 mg of BSA, CONA or THY) in PBS buffer (10 mM, 4 mL) was then treated with the DMF solution of the activated hapten (25, 50 or 100 equiv). The resulting solution was stirred at RT for 1 h and then at 4 °C overnight. Antigens were purified with a Zeba™ Spin Desalting Column (7K MWCO, 10 mL) as per the manufacturer's procedure.

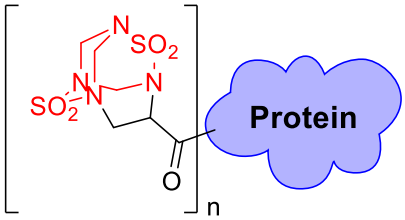


Preparation of the coating/immunizing antigen based on the hapten 6b. Et_3N (565 mg, 5.59 mmol, 10 equiv) was added dropwise to the solution of (1*R*,3*S*,5*r*,7*r*)-7-amino-2-thia-1,3,5-triazaadamantane 2,2-dioxide **6b** (5.6 mmol, 1 equiv) and succinic anhydride (112 mg, 1.12 mmol, 2 equiv) in CH_2Cl_2 (5 mL). The reaction mixture was stirred overnight. NHS (129 mg, 1.12 mmol, 2 equiv) and EDC (215 mg, 1.12 mmol, 2 equiv) were added and the resulting mixture was stirred for 16 h, evaporated and the residue was dissolved in dry DMF (5 mL) to give ~0.083 M solution of the activated hapten (based on ~80% yield). A solution of the appropriate protein (25 mg of BSA, CONA or THY) in PBS buffer (10 mM, 4 mL) was then treated with the DMF solution of the activated hapten (25, 50 or 100 equiv). The resulting solution was stirred at RT for 1 h and then at 4 °C overnight. Antigens were purified with a Zeba™ Spin Desalting Column (7K MWCO, 10 mL) as per the manufacturer's procedure.

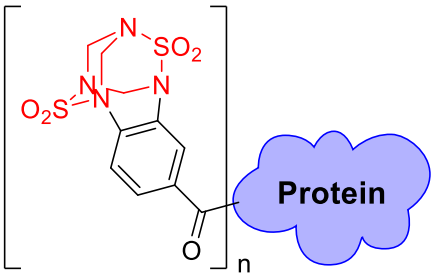


Preparation of the coating/immunizing antigen based on the hapten 2d. EDC (100 mg, 523 µmol, 2 equiv) was added to a solution of **2d** (262 µmol, 1 equiv) and NHS (39 mg, 340 µmol, 1.3 equiv) in CH_2Cl_2 (4 mL). The reaction mixture was stirred at RT overnight, evaporated and the residue was dissolved in dry DMF (1.65 mL) to give a ~0.155 M solution of the activated hapten (based on quantitative yield). A solution of the appropriate protein (20 mg of BSA or THY) in PBS buffer (10 mM, 4 mL) was then treated with the DMF solution of the activated hapten (50 and 400 equiv for BSA and THY respectively).

The resulting solution was stirred at RT for 1 h and then at 4 °C overnight. Antigens were purified with a Zeba™ Spin Desalting Column (7K MWCO, 5 mL) as per the manufacturer's procedure.

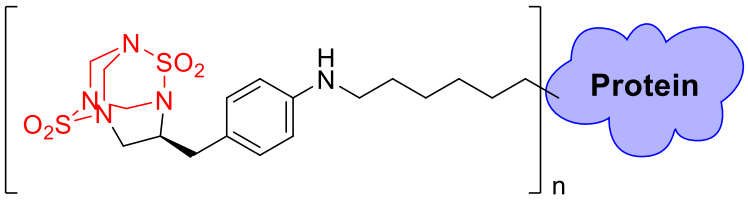


Preparation of the coating/immunizing antigen based on the hapten 2c. A solution of **2c** (63 mg, 202 µmol, 1 equiv) and NaOH (10 M, 30 µL, 303 µmol) in THF/MeOH = 3:1 mixture (4 mL) was stirred overnight, neutralized with aq. sol. of HCl (3 M) and evaporated. The residue was dissolved in DMSO-d_6 (1.5 mL), disuccinimidyl carbonate (78 mg, 303 µmol, 1.5 equiv) and Et_3N (20 mg, 202 µmol, 1 equiv) were added and the resulting mixture was stirred at RT overnight. The reaction was monitored by NMR. Water (4 mL) was added and the resulting mixture was extracted with EtOAc (4×3 mL). Combined organics were dried over $MgSO_4$, filtered and evaporated. Product was dissolved in 2 mL of dry DMF to give ~0.122 M solution of the activated hapten (based on quantitative yield). A solution of the appropriate protein (10 mg of BSA, CONA or THY) in PBS buffer (10 mM, 2 mL) was then treated with DMF solution of the activated hapten (25 or 100 equiv for BSA and CONA, and 300 equiv for THY). The resulting solution was stirred at RT for 1 h and then at 4 °C overnight. Antigens were purified with a Zeba™ Spin Desalting Column (7K MWCO, 5 mL) as per the manufacturer's procedure.



Preparation of the coating/immunizing antigen based on the hapten 2j. A solution of **2j** (54 mg, 150 µmol, 1 equiv) and NaOH (10 M, 26 µL, 254 µmol, 1.7 equiv) in THF/MeOH = 3:1 mixture (4 mL) was stirred overnight, neutralized with aq. sol. of HCl (3 M) and evaporated. The residue was dissolved in DMSO-d_6 (1.5 mL), disuccinimidyl carbonate (58 mg, 225 µmol, 1.5 equiv) and Et_3N (15 mg, 150 µmol, 1 equiv) were added and the resulting mixture was stirred at RT overnight. The reaction was monitored by NMR. Water (4 mL) was added and the resulting mixture was extracted with EtOAc (4×3 mL). Combined organics were dried over $MgSO_4$, filtered and evaporated. Product was dissolved in 2 mL of dry DMF to give ~0.09 M solution of the activated hapten (based on quantitative yield). A solution of the appropriate

protein (10 mg of BSA, CONA or THY) in PBS buffer (10 mM, 2 mL) was then treated with the DMF solution of the activated hapten (25 or 100 equiv for BSA and CONA, and 300 equiv for THY). The resulting solution was stirred at RT for 1 h and then at 4 °C overnight. Antigens were purified with a Zeba™ Spin Desalting Column (7K MWCO, 5 mL) as per the manufacturer's procedure.



Preparation of the coating/immunizing antigen based on the hapten 2k. A solution of **2k** (4.3 mg, 11.9 µmol, 400 equiv) in DMF (0.3 mL) was added dropwise to a solution of THY (20 mg, 29.9 nmol, 1 equiv) and glutaraldehyde (25 %, 30 µL) in PBS buffer. After stirring for 15 min $NaBH_3CN$ (~1 mg) was added in one portion and the resulting mixture was stirred overnight at 4 °C. Antigens were purified with a Zeba™ Spin Desalting Column (7K MWCO, 10 mL) as per the manufacturer's procedure.

Immunization and antiserum preparation

The immunization procedure followed the protocol reported previously[9]. In brief, two to three female New Zealand white rabbits were immunized for each immunogen. The final bleed was collected after about 3 months of booster injections every 2 weeks following the first immunization. Blood was collected in test tubes and allowed to clot. Serum was obtained by centrifugation, stored at -20 °C, and used without purification.

Primary cultures of hippocampal neurons

Animals were treated according to protocols approved by the Institutional Animal Care and Use Committee of the University of California, Davis. Hippocampal neuron cultures were dissociated from hippocampi dissected from C57Bl/6J mouse pups at postnatal day 0 as described previously[10], with the substitution of commercially available GS21 for the supplement NS21, and GlutaMAX for l-glutamine in the maintenance media. For Ca^{2+} imaging studies using FLIPR, dissociated hippocampal cells were plated onto poly-L-lysine-coated 96-well imaging plates (BD, Franklin Lakes, NJ) at a density of 0.75×10^5 cell/well. The medium was changed twice a week by replacing half the volume of culture medium in the well with serum-free Neurobasal complete medium. The neurons were maintained at 37 °C with 5% CO_2 and 95% humidity.

Measurement of synchronous intracellular Ca^{2+} oscillations

Hippocampal neurons at 14 days *in vitro* (DIV) were used to investigate how TETS or the TETS analogs alter synchronous Ca^{2+} oscillations that normally occur in healthy hippocampal neurons at this developmental stage. Acquisition temporal resolution was 1 Hz. Baseline recordings were acquired in Locke's buffer (8.6 mM HEPES, 5.6 mM KCl, 154 mM NaCl, 5.6 mM glucose, 1.0 mM $MgCl_2$, 2.3 mM $CaCl_2$, and 0.0001 mM glycine, pH 7.4) for 10 min followed by addition of TETS or TETS analogs using a programmable 96-channel pipetting robotic system in the FLIPR Tetra, while recording the fluorescence signal from intracellular Ca^{2+} concentration ($[Ca^{2+}]i$) for an additional 15 min.

Data analysis. Baseline and peak intensities were determined and delta F over F_0 calculated using Origin software (version 9.1, OriginLab Corporation, Northampton, MA). The values of mean peak amplitude and frequency were normalized to the basal period for each well, yielding a value of mean amplitude or frequency as a percent of basal. The measurements were repeated in 7-8 wells and the mean and SEM were determined. The graphing and statistical analysis were performed using GraphPad Prism software (Version 5.0, GraphPad Software Inc., San Diego, CA). Statistical significance between different groups was calculated in Prism using an ANOVA with Tukey's multiple comparison test; *p* values below 0.05 were considered statistically significant.

Preparation of cells expressing the α1β2γ2L $GABA_A$ receptors

cDNA for the human $GABA_A$ receptors α1, β2 and γ2L (a gift from Dr. Robert L. Macdonald from Vanderbilt University, Tennessee) were cloned in pcDNA3.1 expression vectors. Fibroblast L929 cells were cultured in Dulbecco's modified Eagle's medium (Lonza) supplemented with 10% fetal bovine serum, 100 U/mL penicillin and 100 mg/mL streptomycin (Invitrogen) and maintained in humidified 95% O_2 and 5% CO_2 air at 37 °C. Cells were transfected using FuGENE 6 (Roche) transfection reagent with an equal amount of each of the subunits in combination with pEGFP-C1. The transfection ratio of total cDNA to transfection reagent was 3:1. 36 h post-transfection, cells were plated on glass coverslips and transfected cells were identified using an epifluorescence microscope for electrophysiological whole-cell voltage-clamp studies.

Electrophysiological recordings

Whole-cell voltage-clamp recordings were performed at RT with an EPC-10 HEKA amplifier. Cells were bathed in an external Ringer solution that consisted of 160 mM NaCl, 4.5 mM KCl, 1 mM $MgCl_2$, 2 mM $CaCl_2$, 10 mM HEPES, pH 7.4, 311 mOsm. Recording electrodes were pulled and fire-polished to resistances of 1.4–1.8 MΩ and filled with an internal solution consisting of (in mM) 154 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 10 HEPES and 10 EGTA with pH 7.3 and 308 mOsm. Cells were voltage clamped at –80 mV and control currents were recorded under the application of 25 µM GABA, using a gravity-fed fast perfusion system, for 5–6 s followed by a 30–40 s wash with external solution. Inhibition of currents were

determined by the reduction in current level elicited by the same amount of GABA after the pre-application of TETS or its analogs for 3 min. TETS and its analogs were prepared in DMSO at 10 mM stocks from which test dilutions were freshly prepared immediately before each application onto cells. Data analysis was performed using Excel (Microsoft) and Origin 7.0 (OriginLab Corp.) software. Data fitting to the Hill equation to obtain IC_{50} values are performed with Origin 7.0. Data are presented as mean ± S.D.

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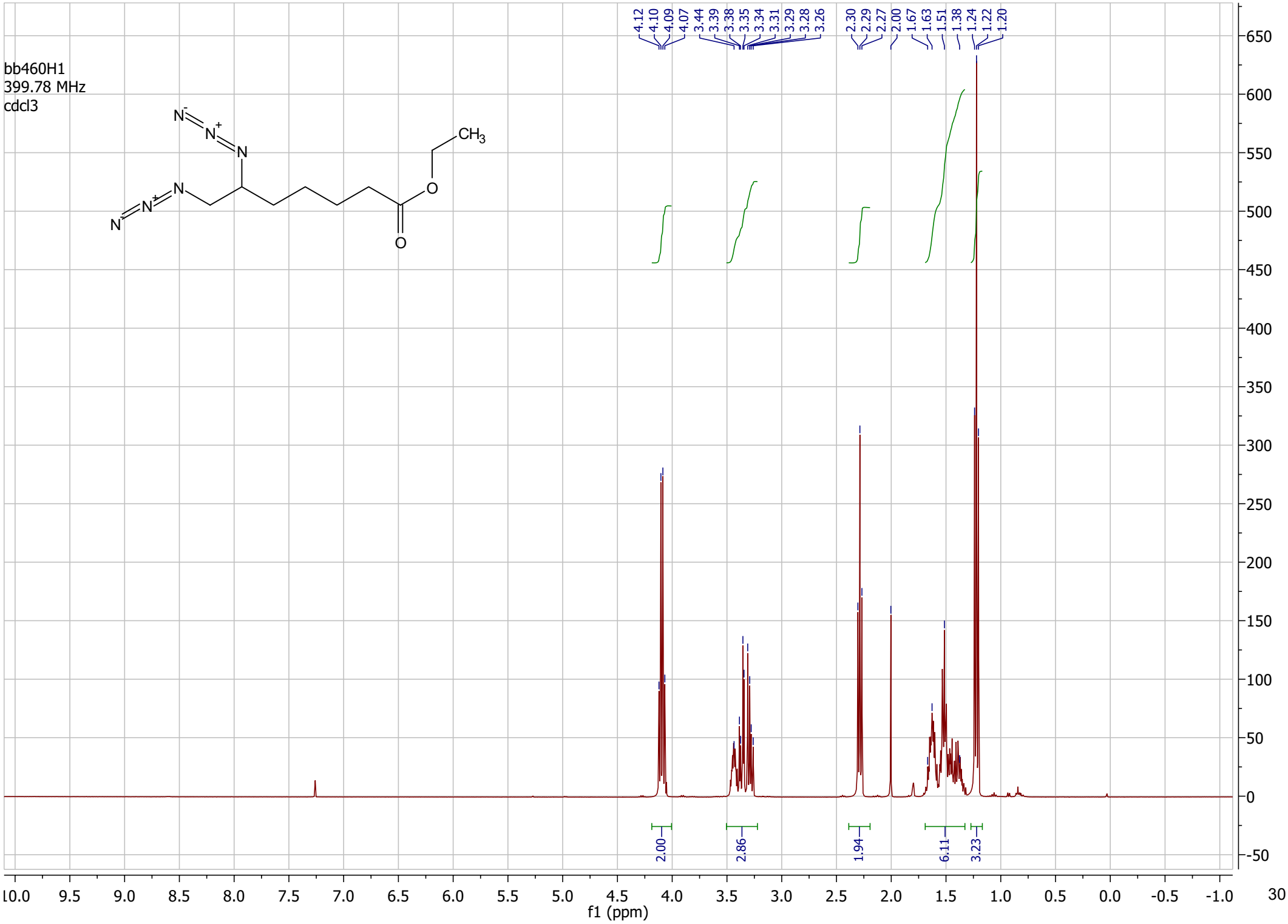
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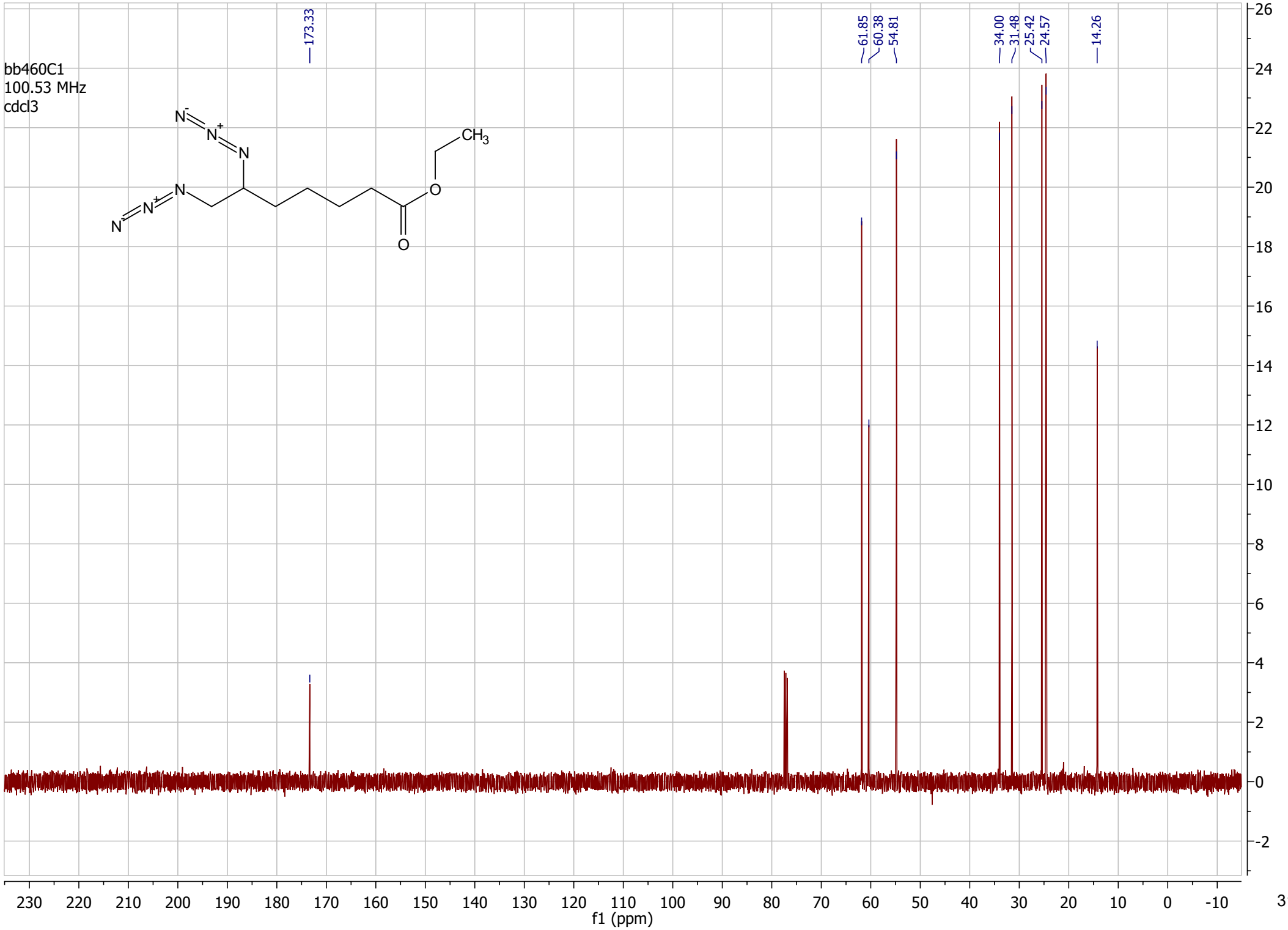
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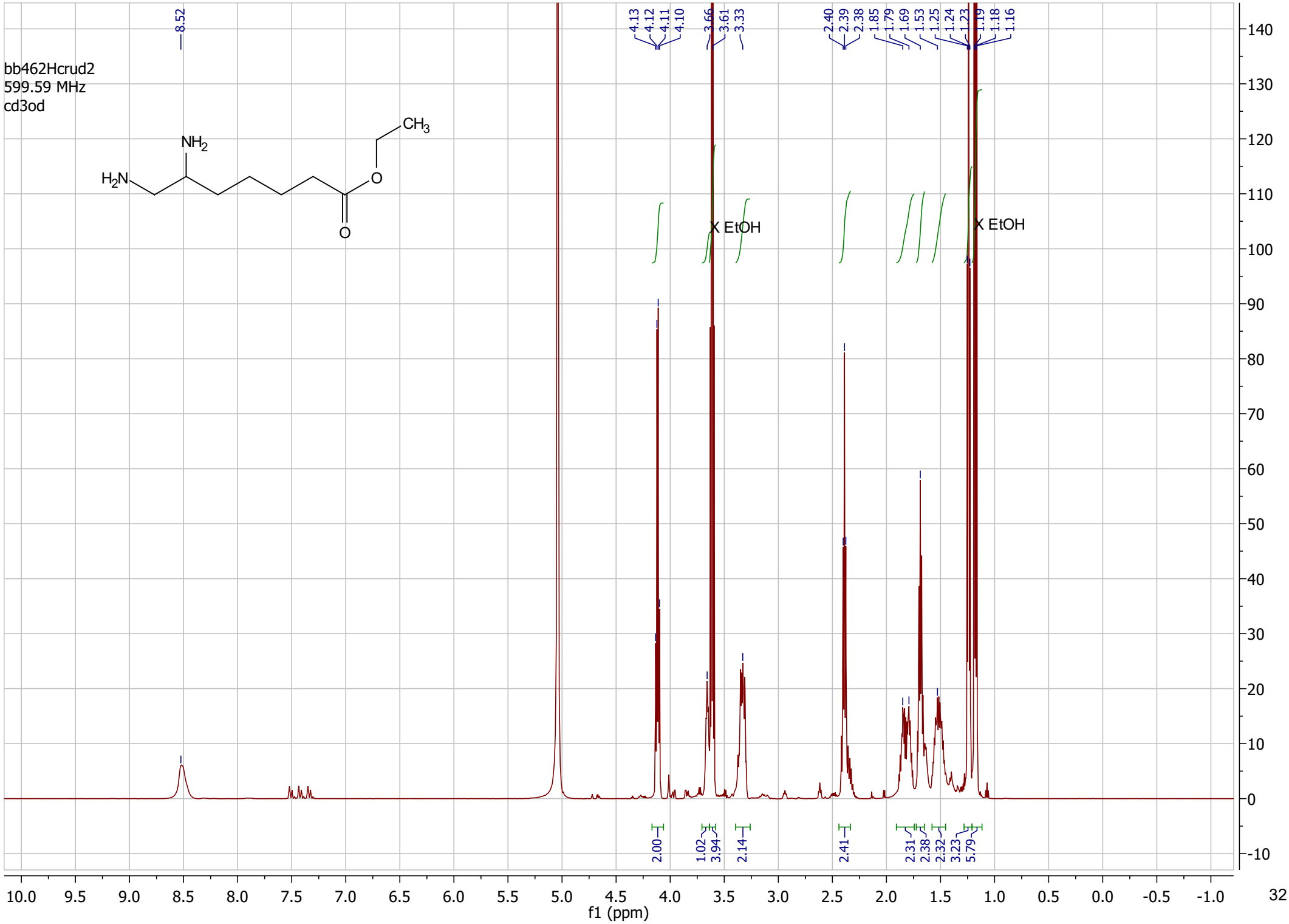
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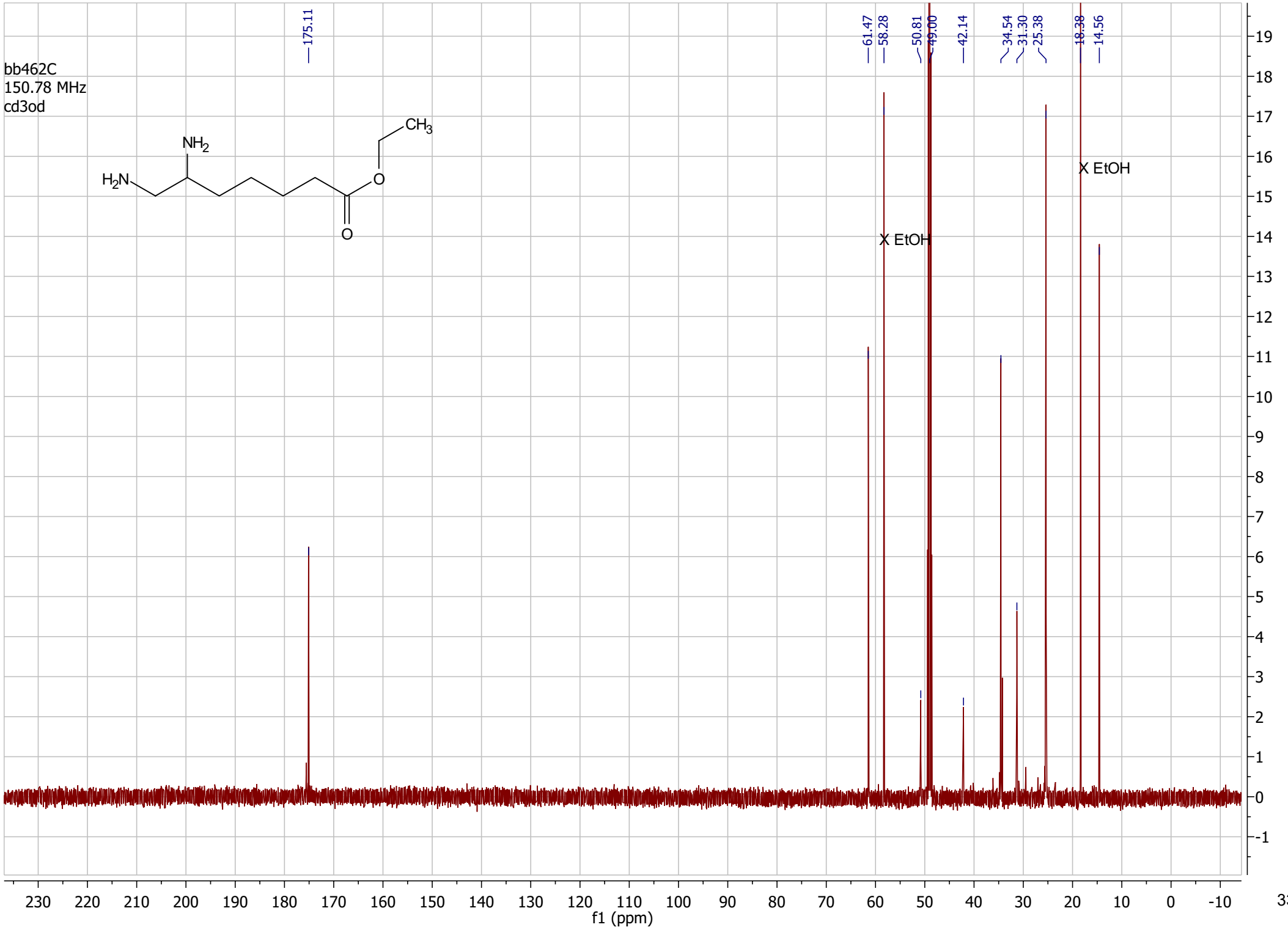
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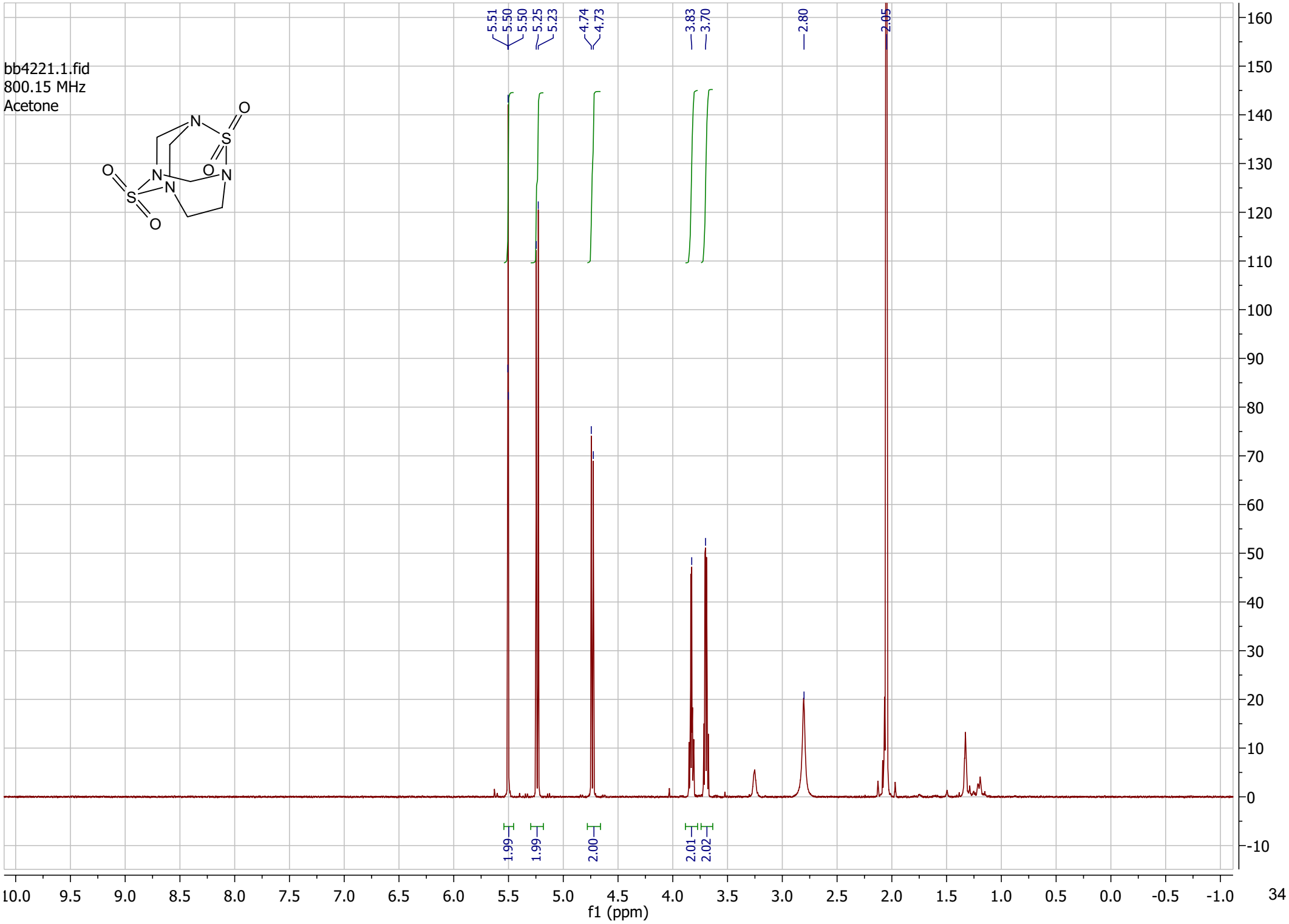
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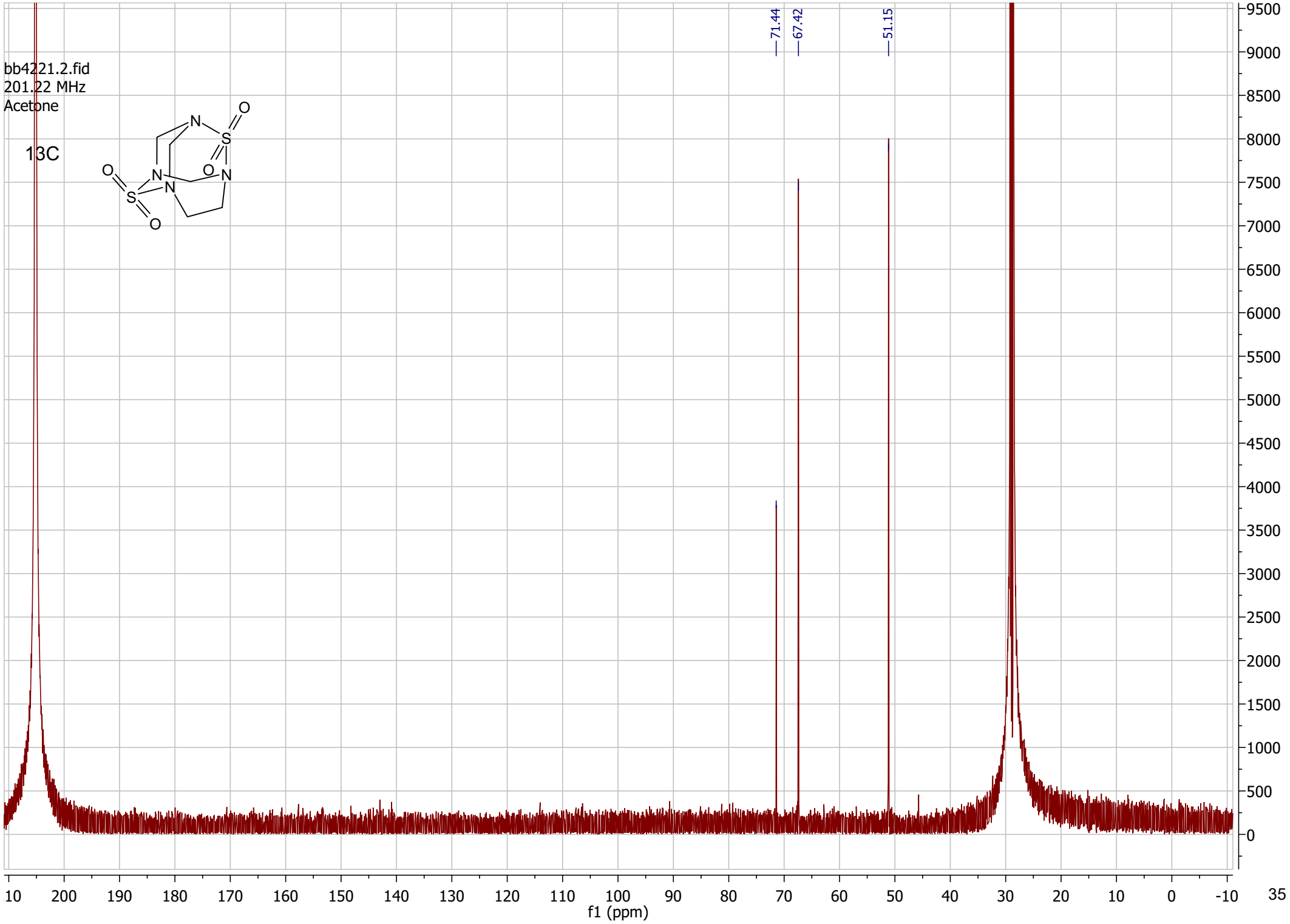
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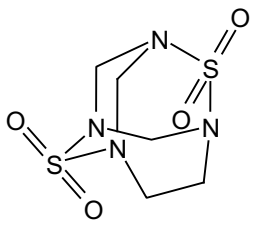

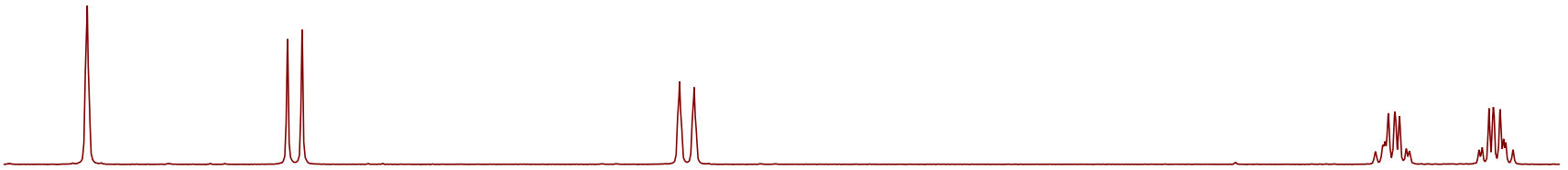

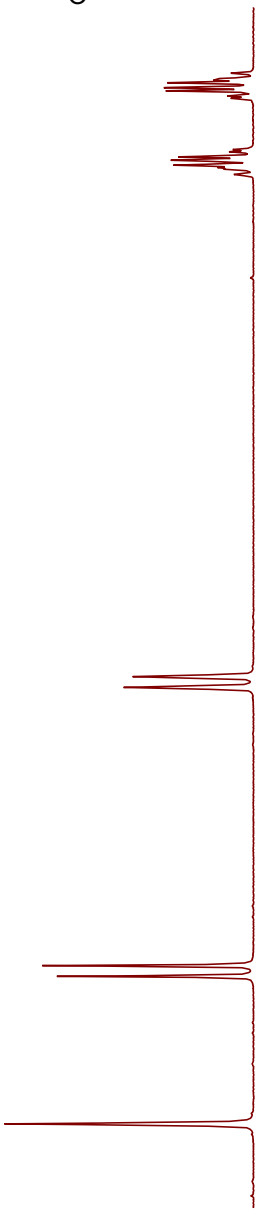

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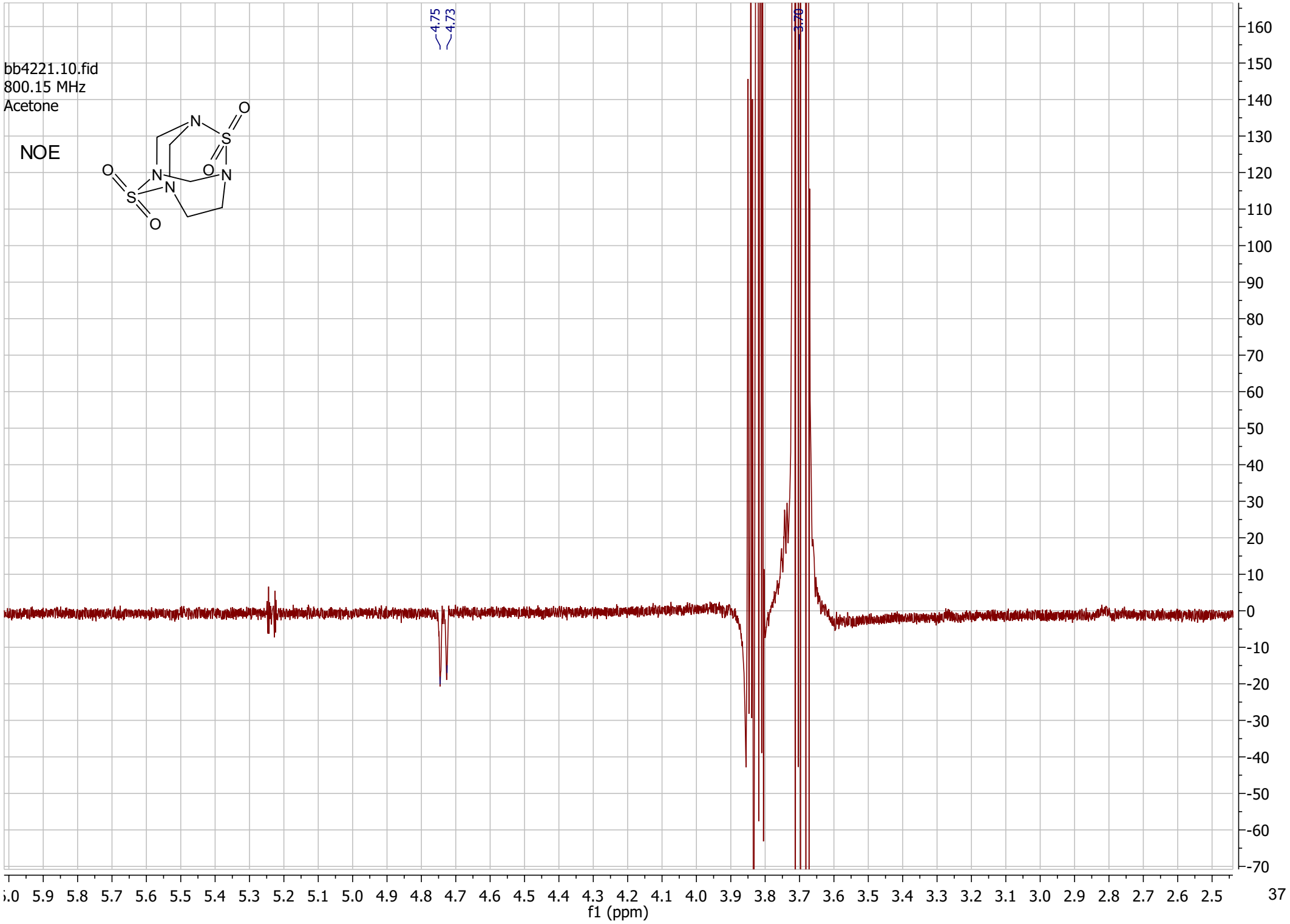
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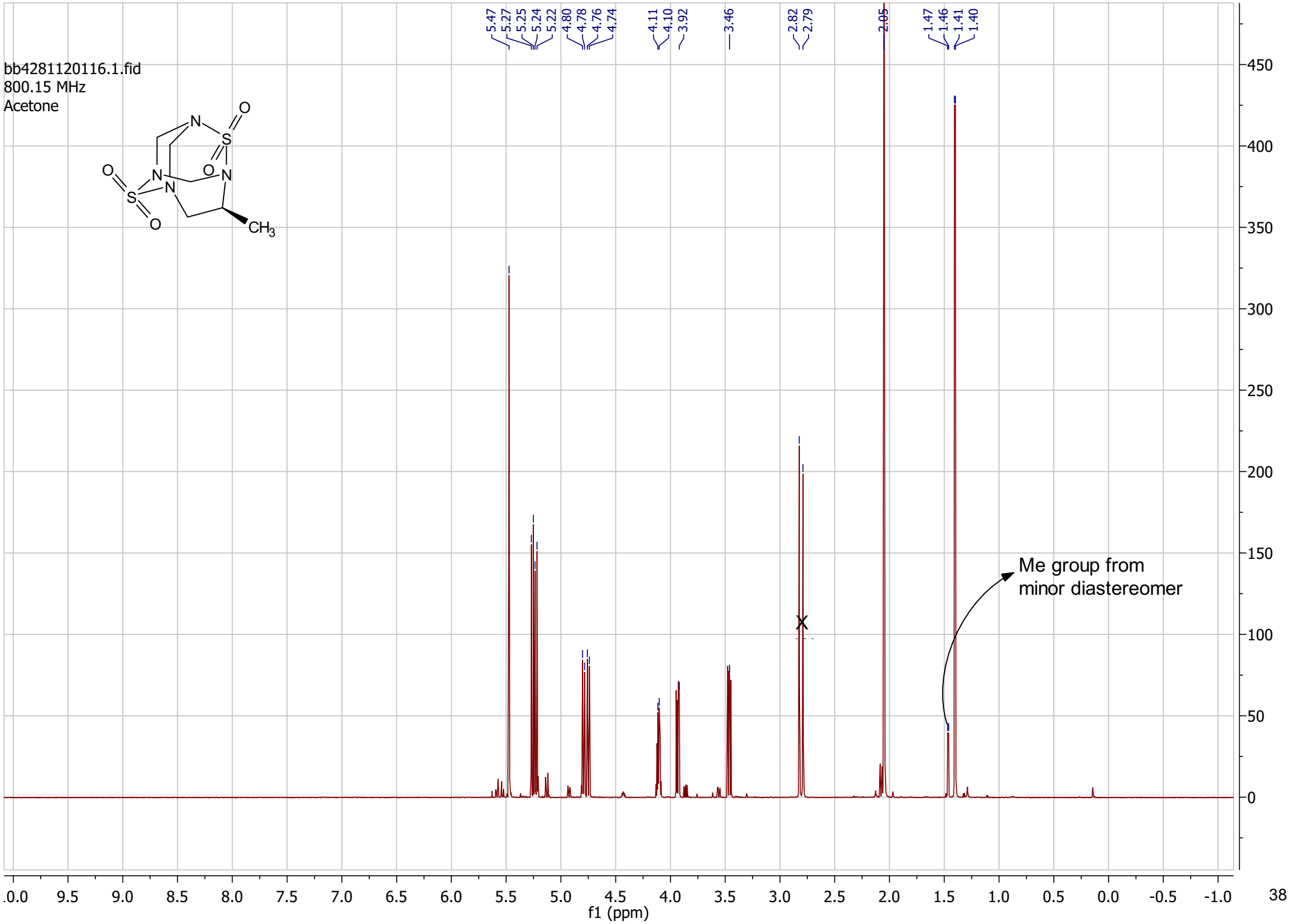
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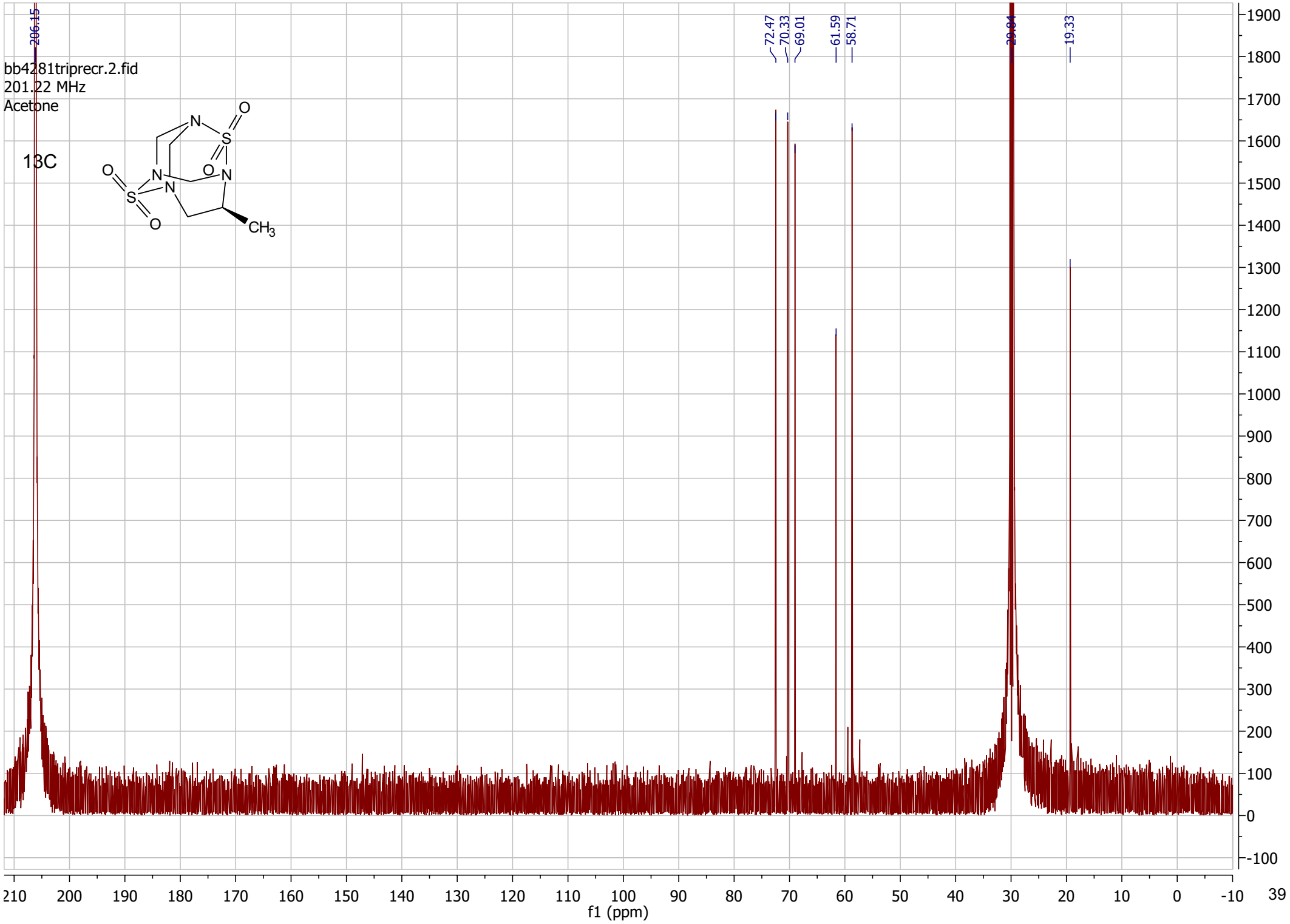
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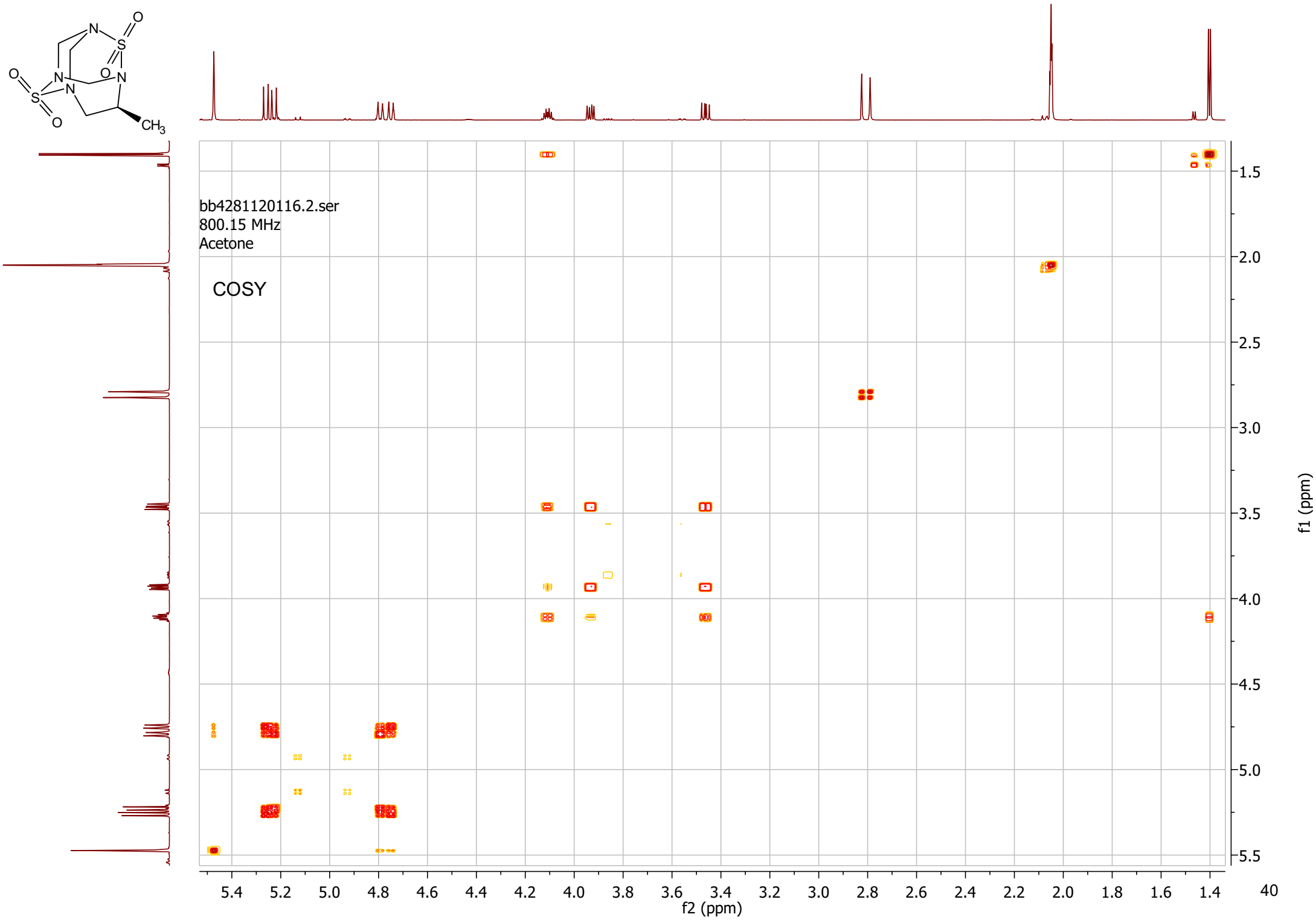
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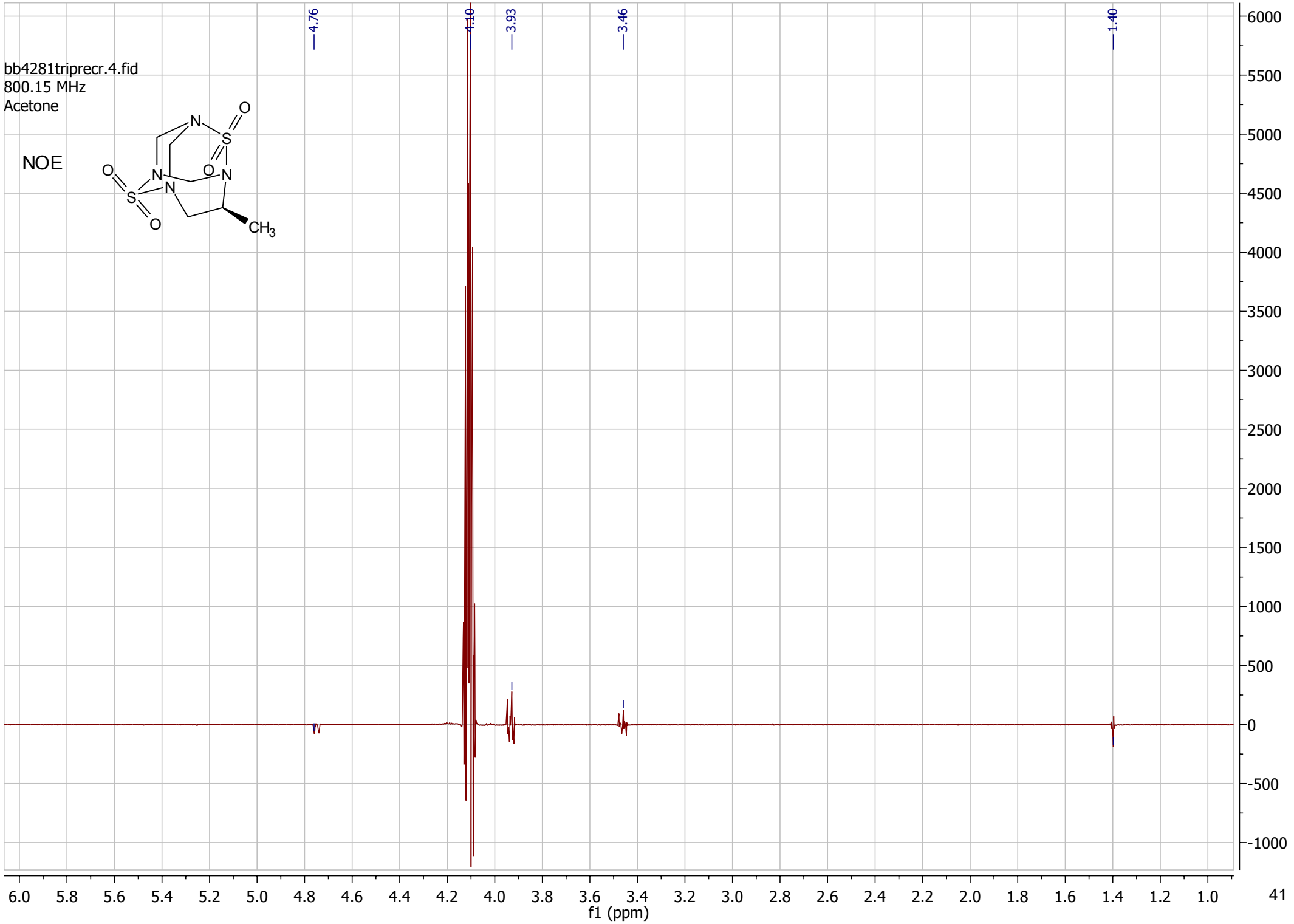
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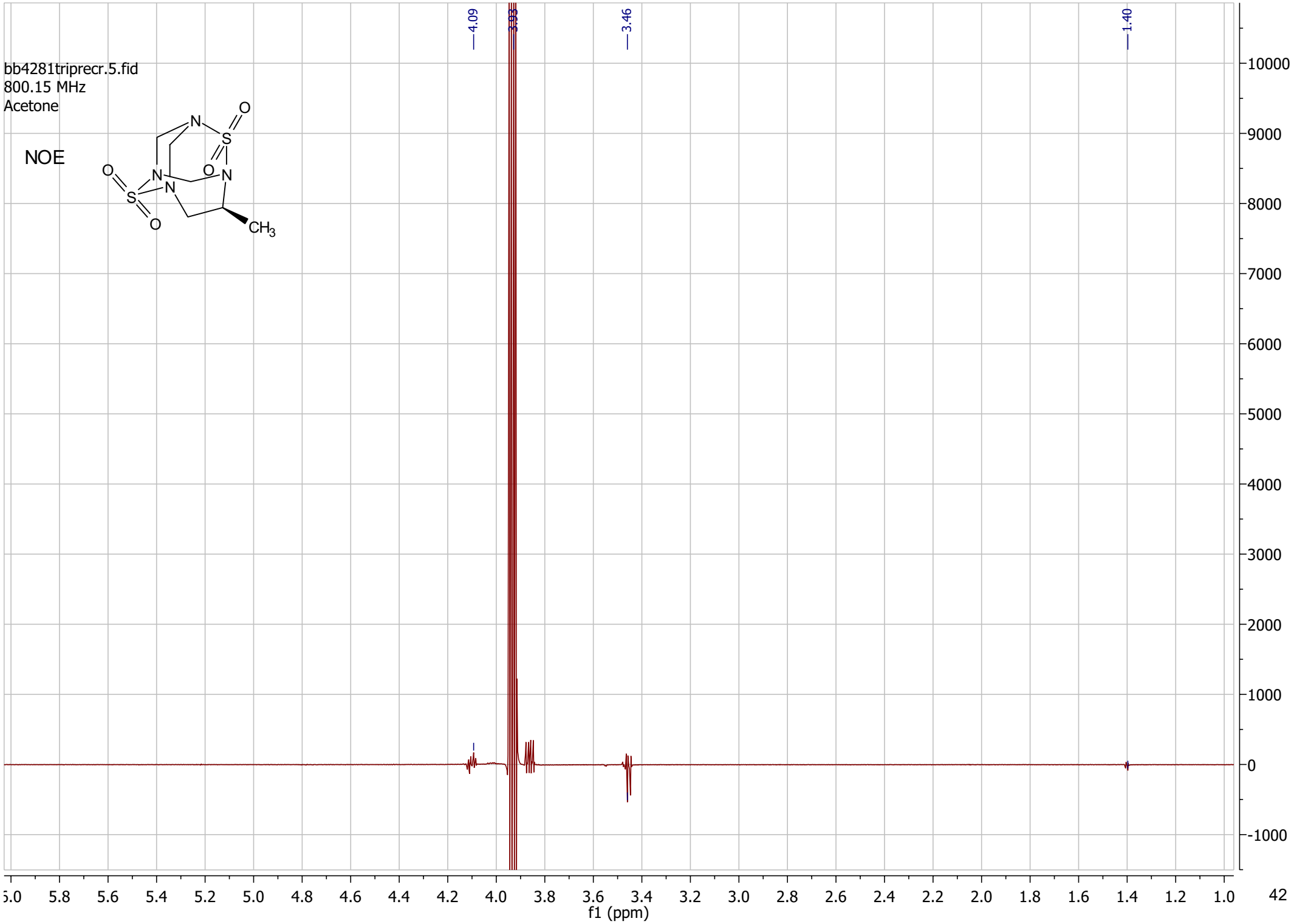
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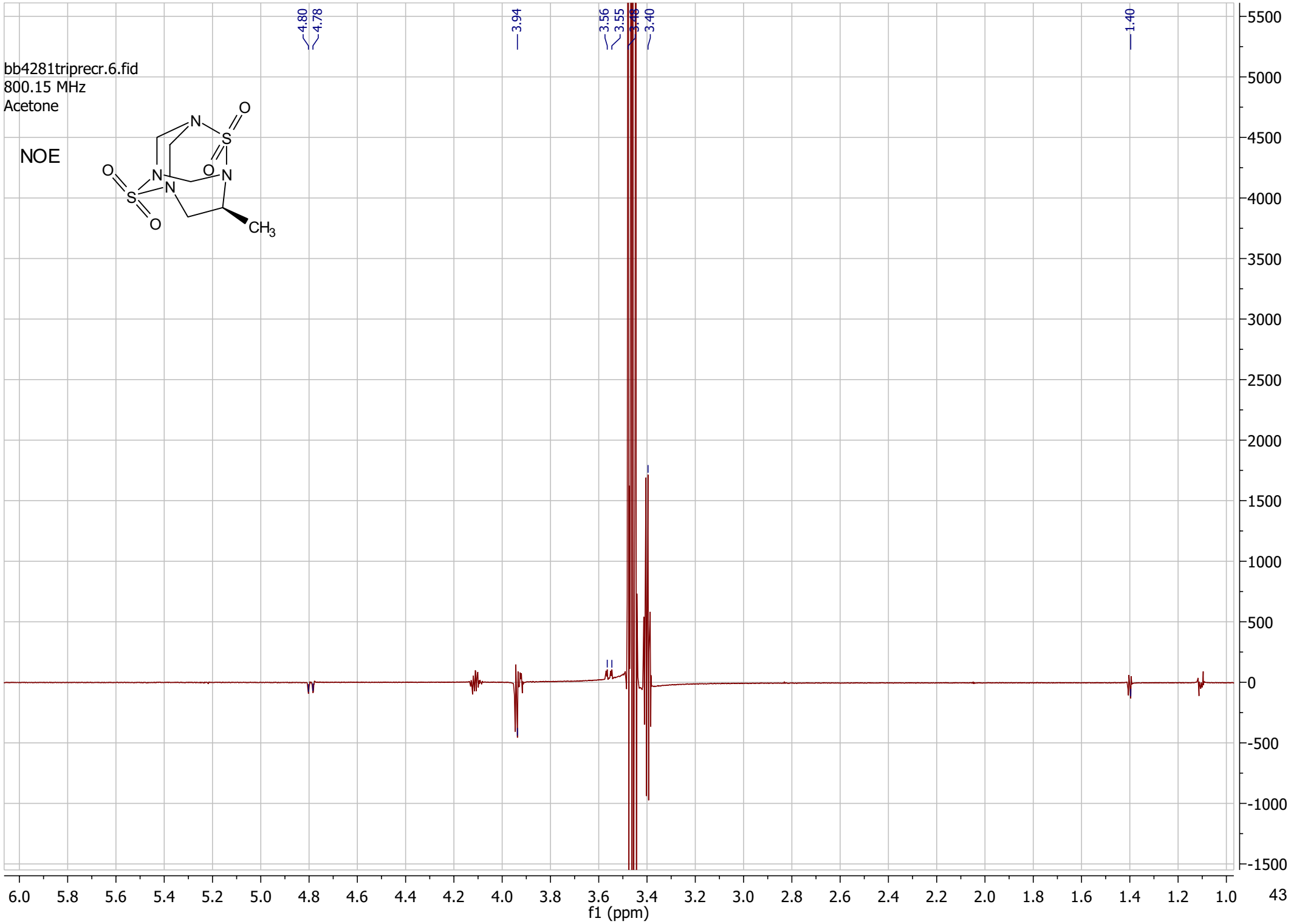
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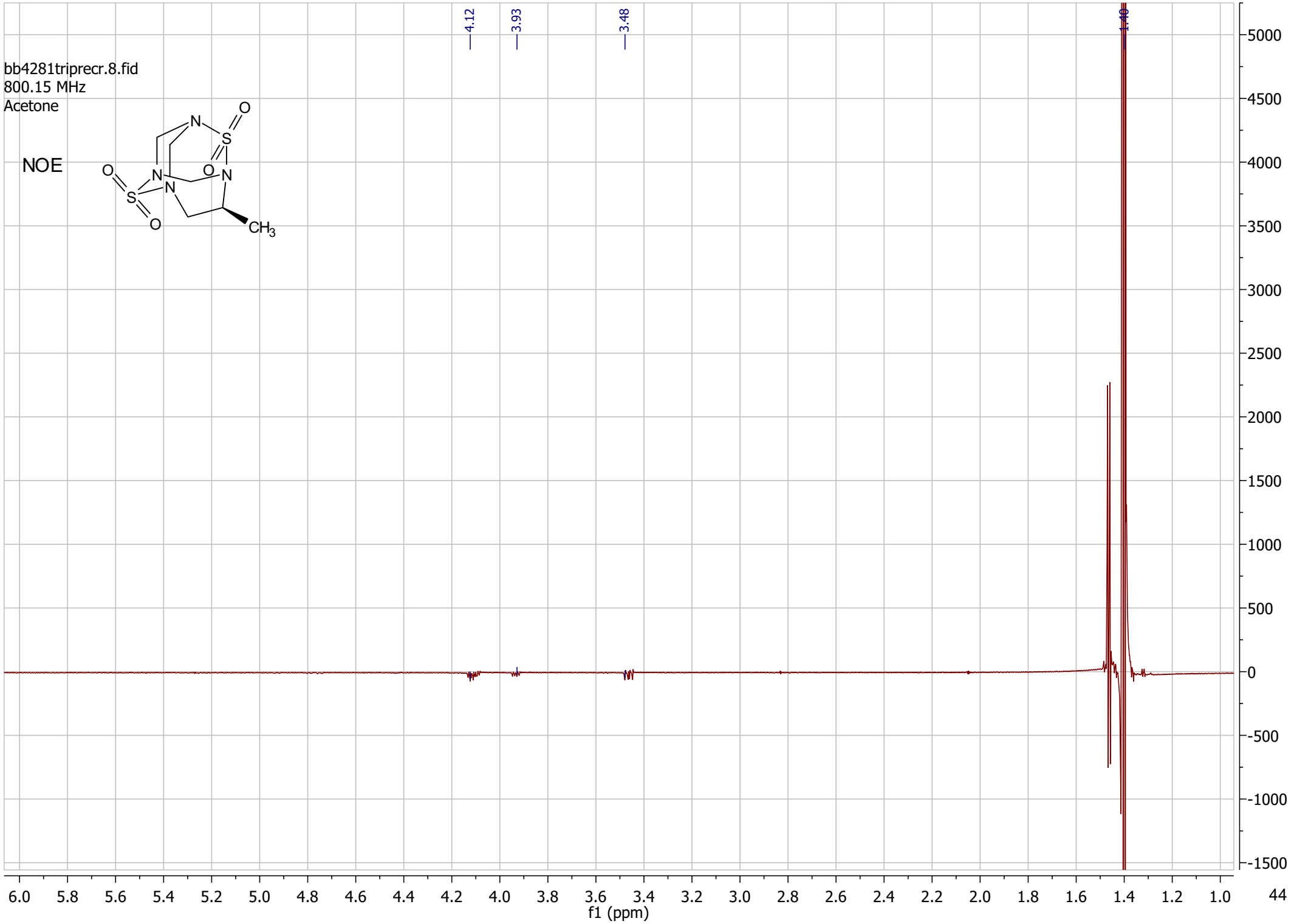
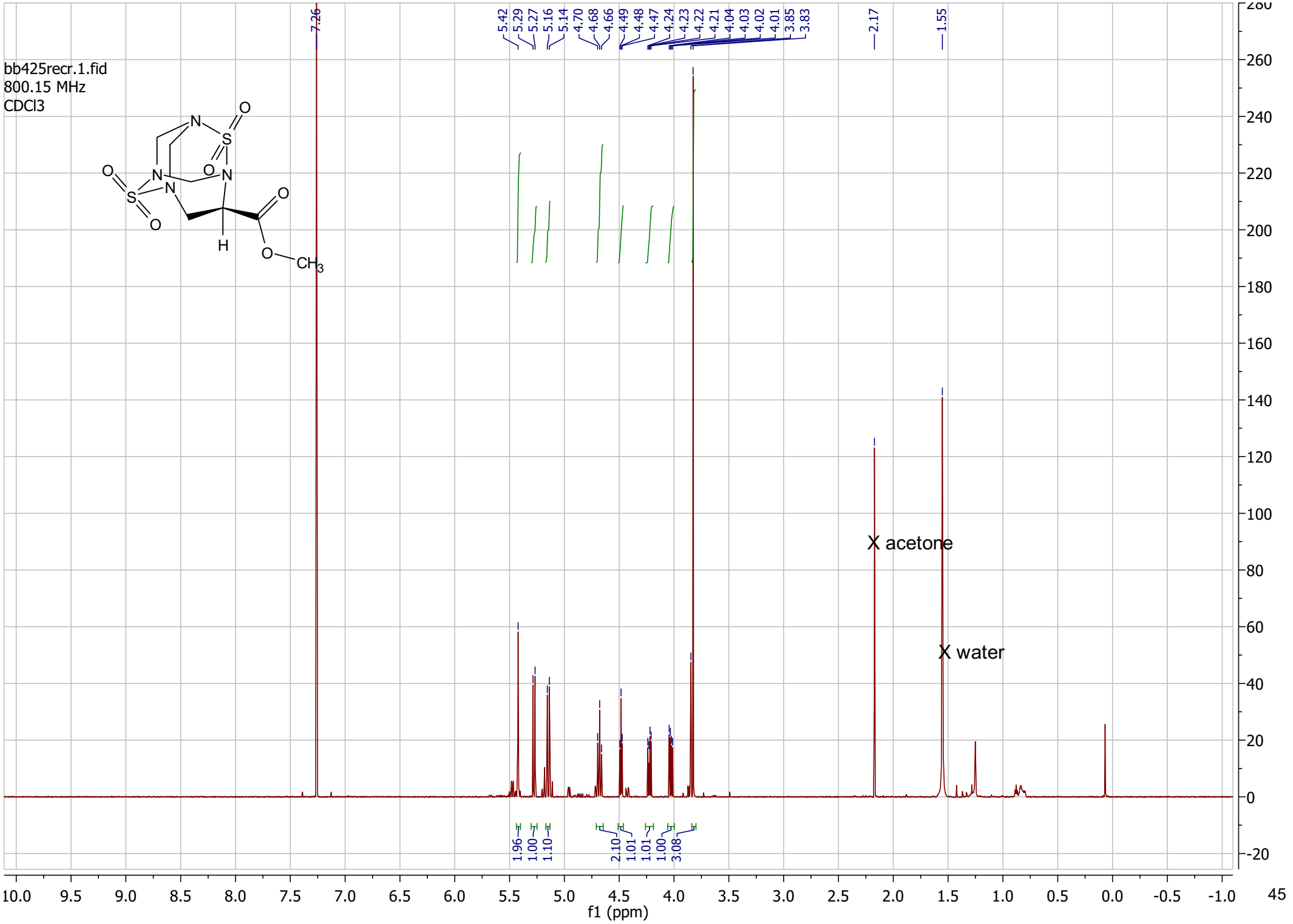
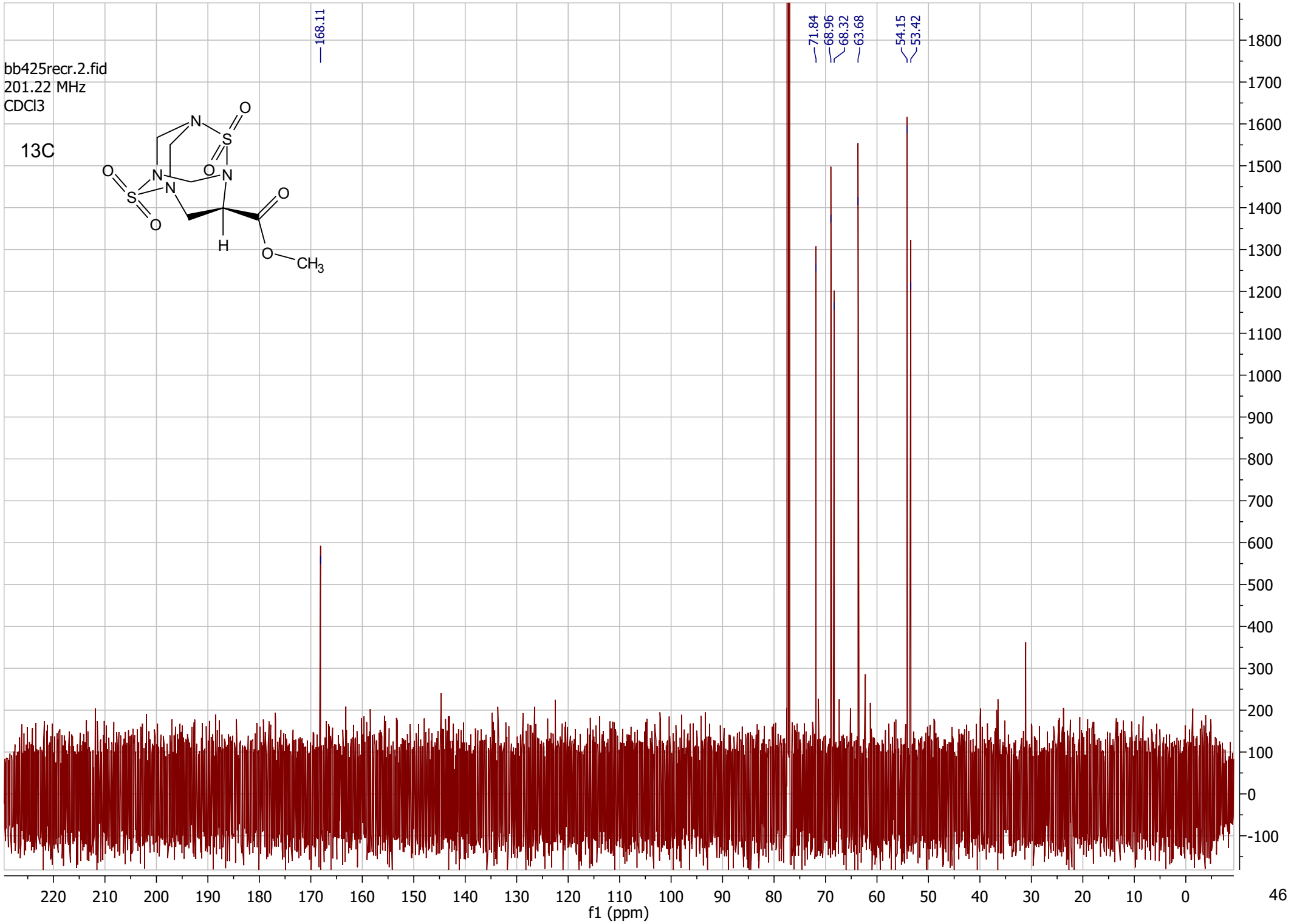
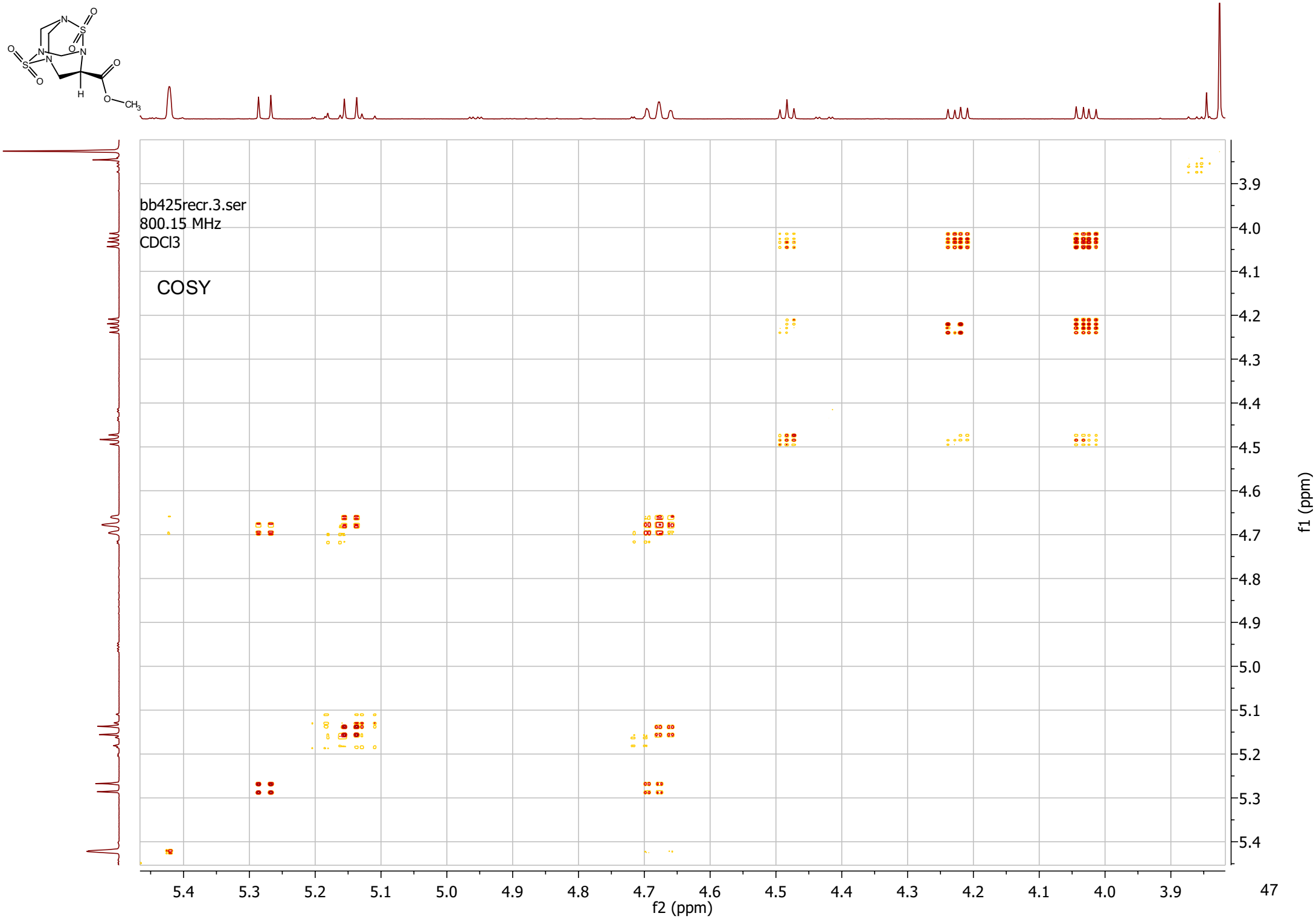
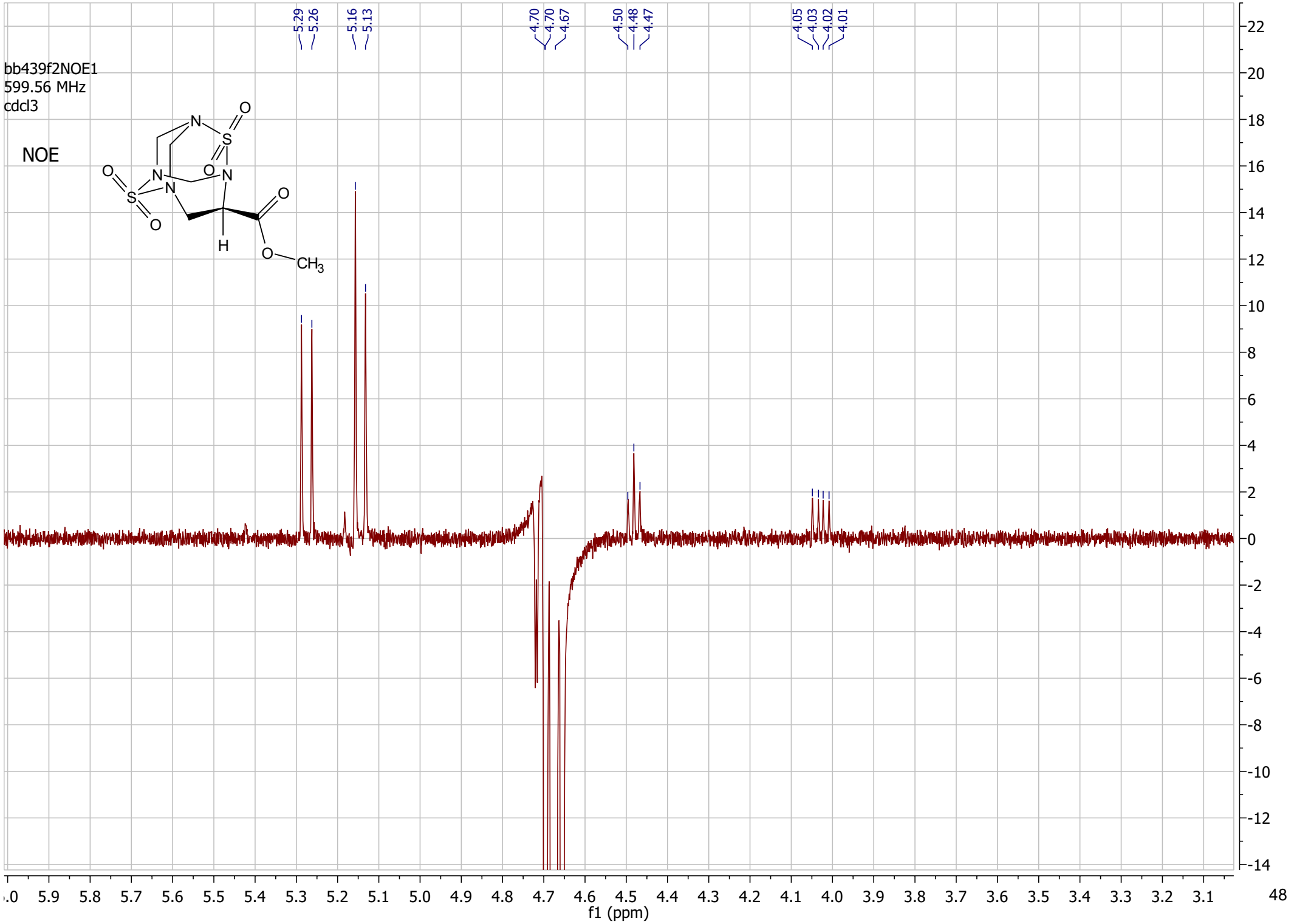
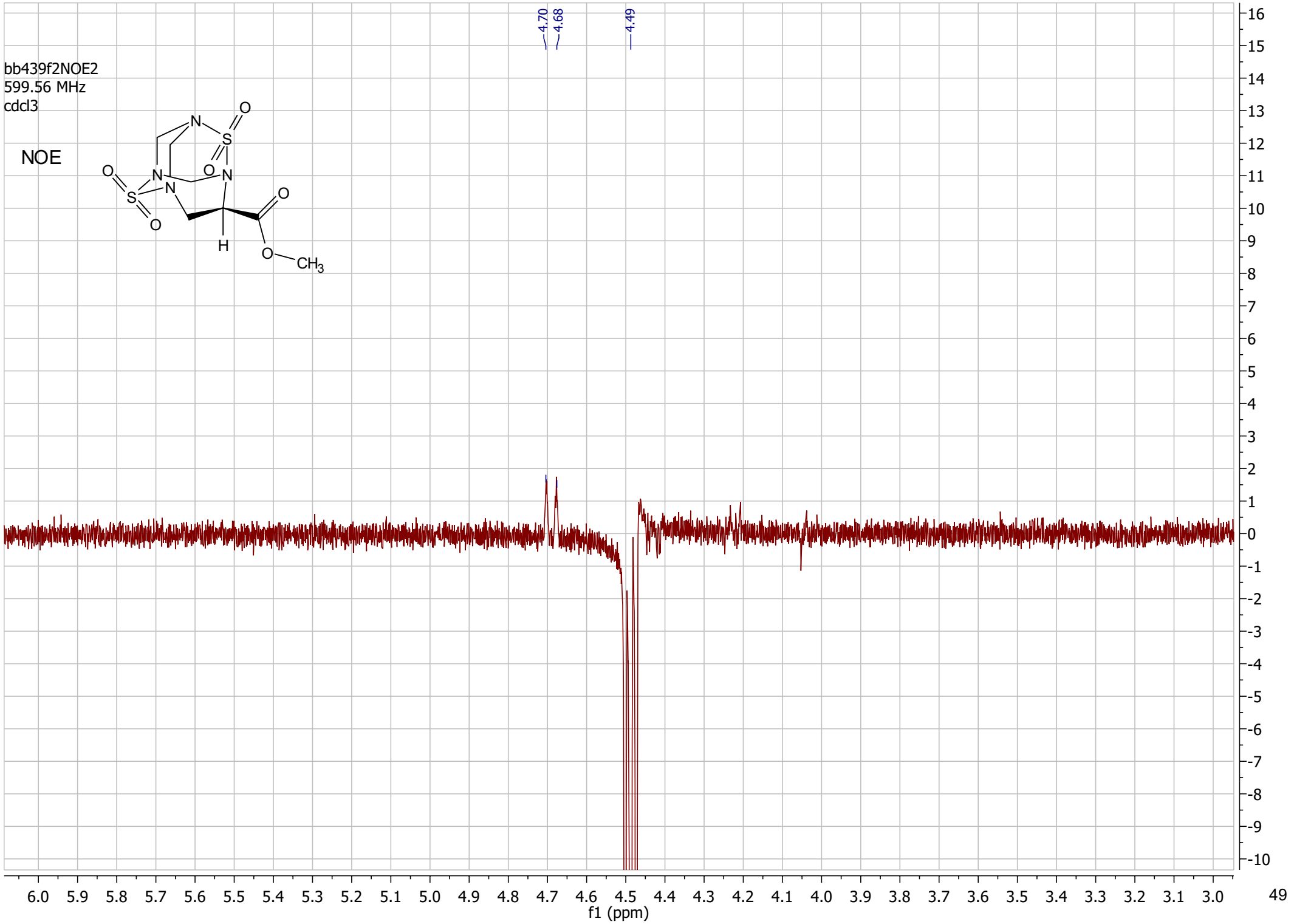

bb4281triprecr.8.fid
800.15 MHz
Acetone
NOE
4.12
3.93
3.48
1.40
f1 (ppm)


bb425recr.1.fid
800.15 MHz
CDCl3
7.26
5.42
5.29
5.27
5.16
5.14
4.70
4.68
4.66
4.49
4.48
4.47
4.24
4.23
4.22
4.21
4.04
4.03
4.02
4.01
3.85
3.83
2.17
1.55
X acetone
X water
1.96
1.00
1.10
2.10
1.01
1.01
1.00
3.08
f1 (ppm)

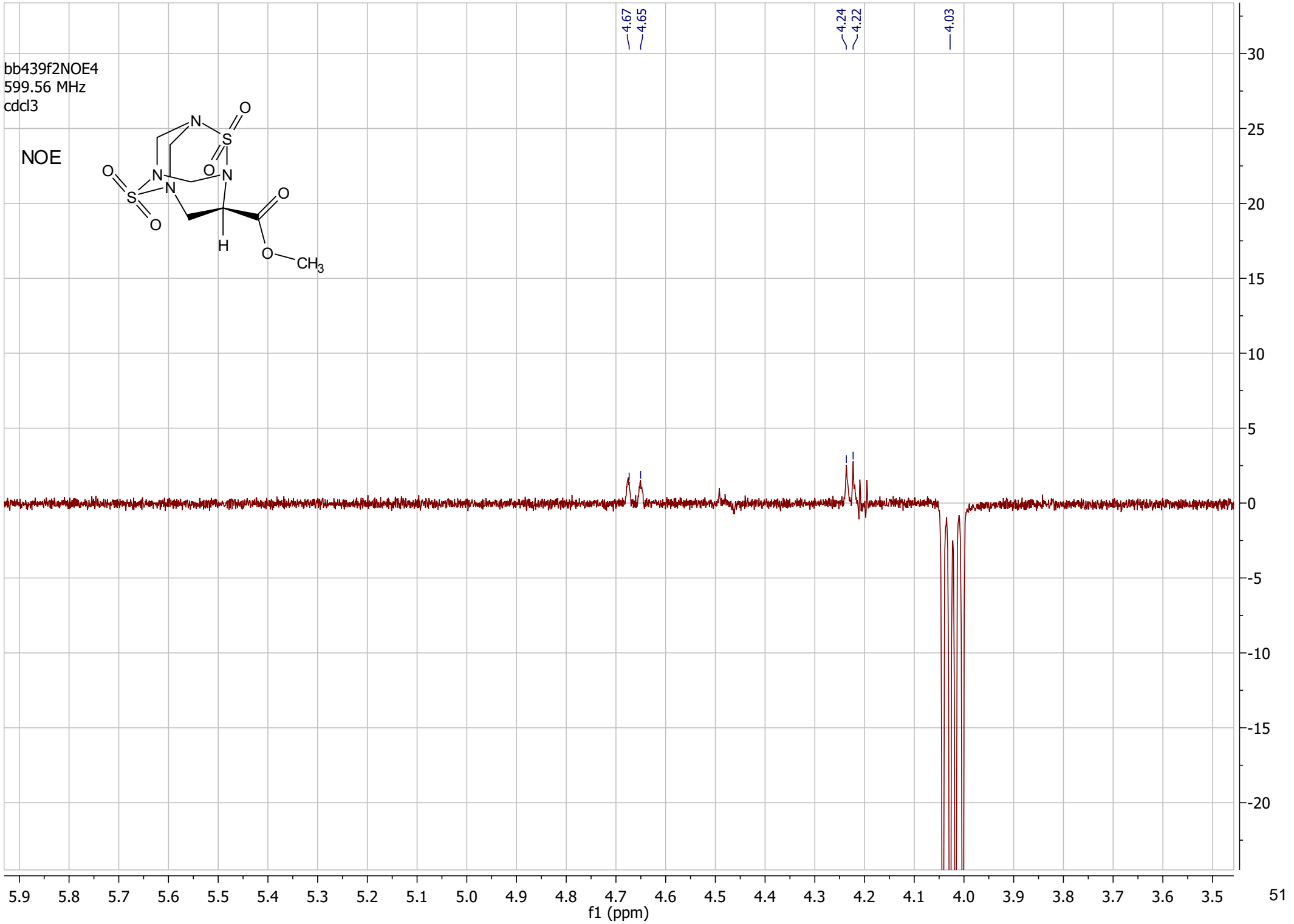

bb425recr.2.fid
201.22 MHz
CDCl3
13C
168.11
71.84
68.96
68.32
63.68
54.15
53.42
f1 (ppm)

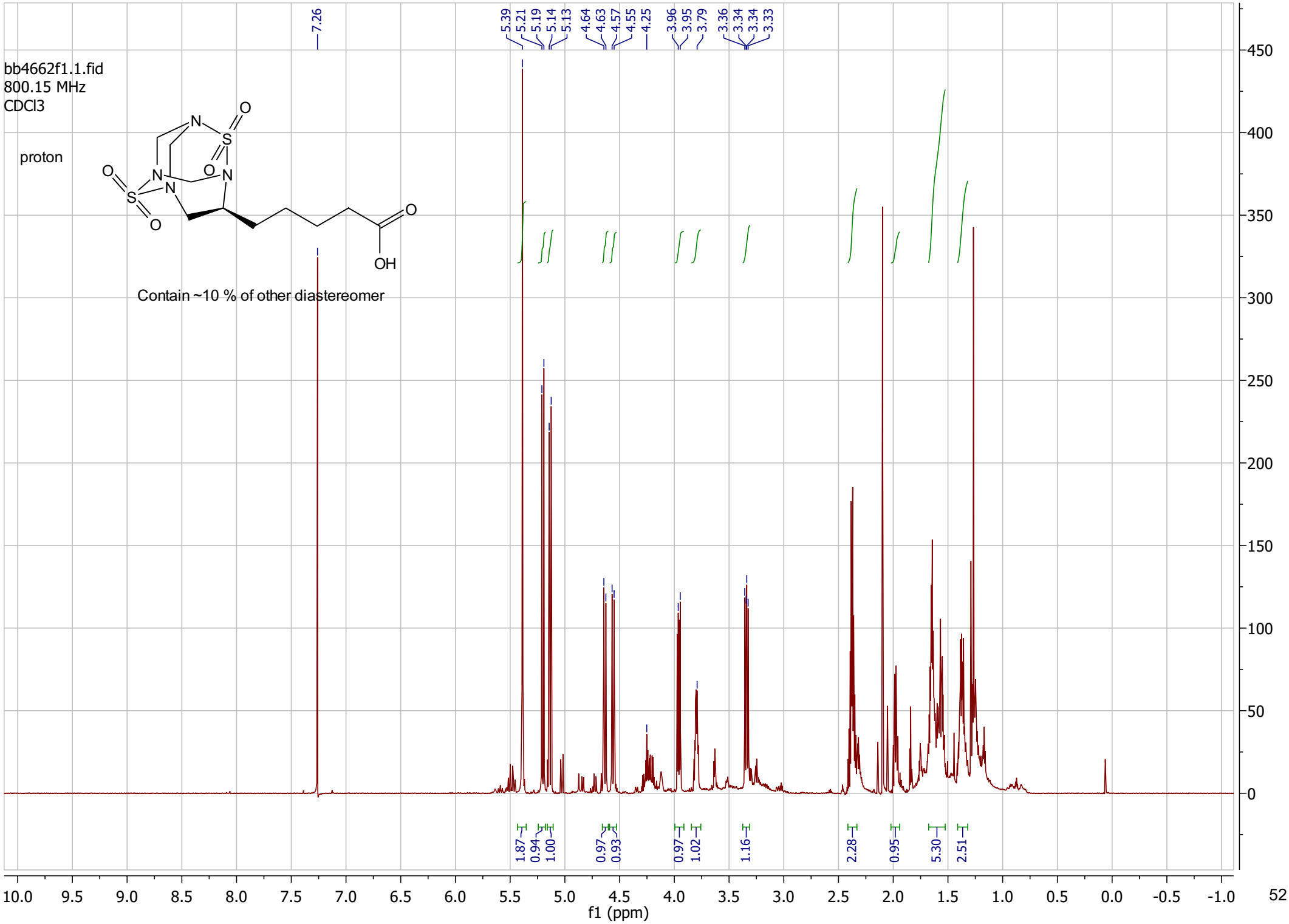

bb425recr.3.ser
800.15 MHz
CDCl3
COSY
f2 (ppm)
f1 (ppm)
5.4
5.3
5.2
5.1
5.0
4.9
4.8
4.7
4.6
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.9
4.0
4.1
4.2
4.3
4.4
4.5
4.6
4.7
4.8
4.9
5.0
5.1
5.2
5.3
5.4

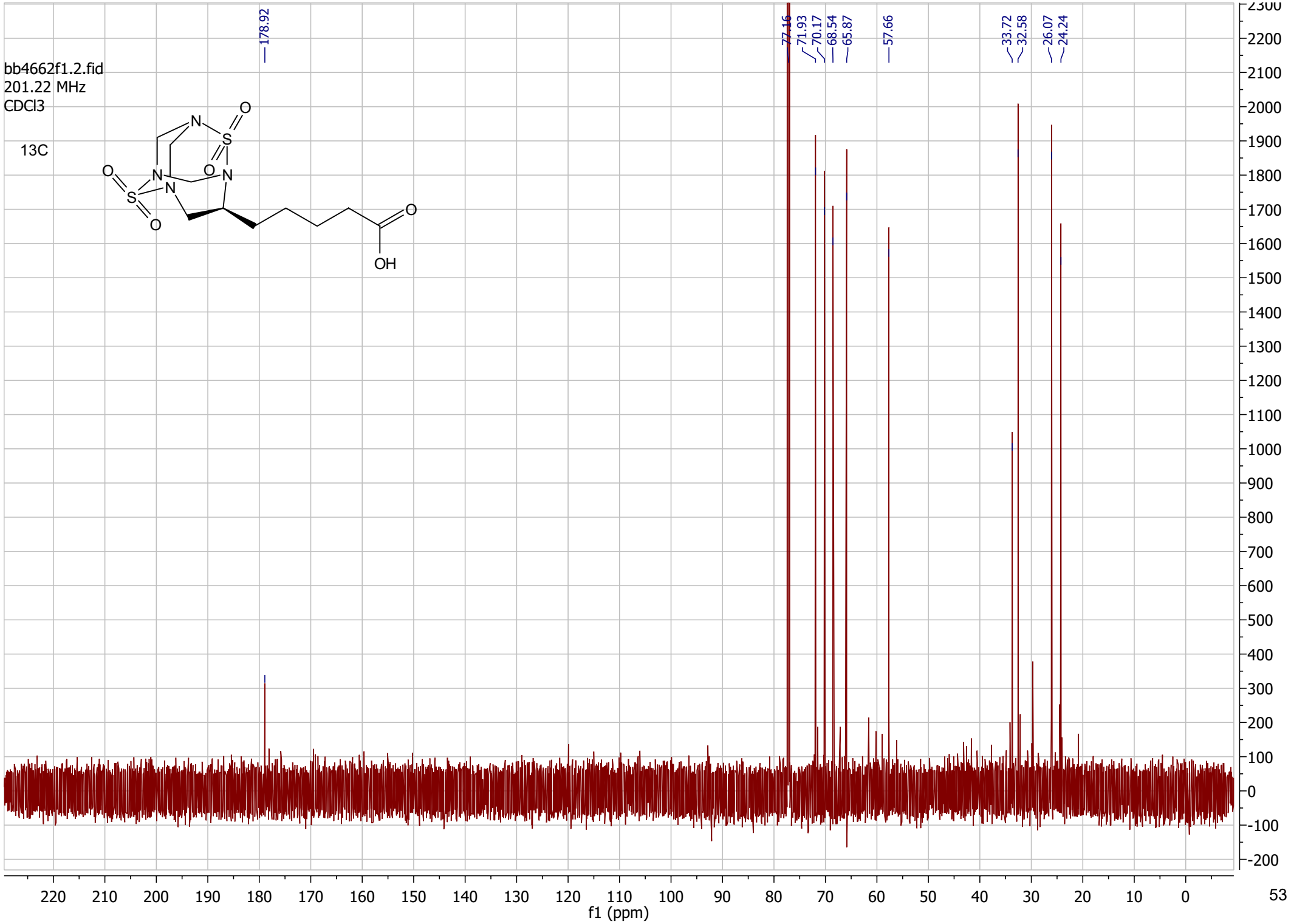

bb439f2NOE1
599.56 MHz
cdcl3
NOE
5.29
5.26
5.16
5.13
4.70
4.70
4.67
4.50
4.48
4.47
4.05
4.03
4.02
4.01
f1 (ppm)

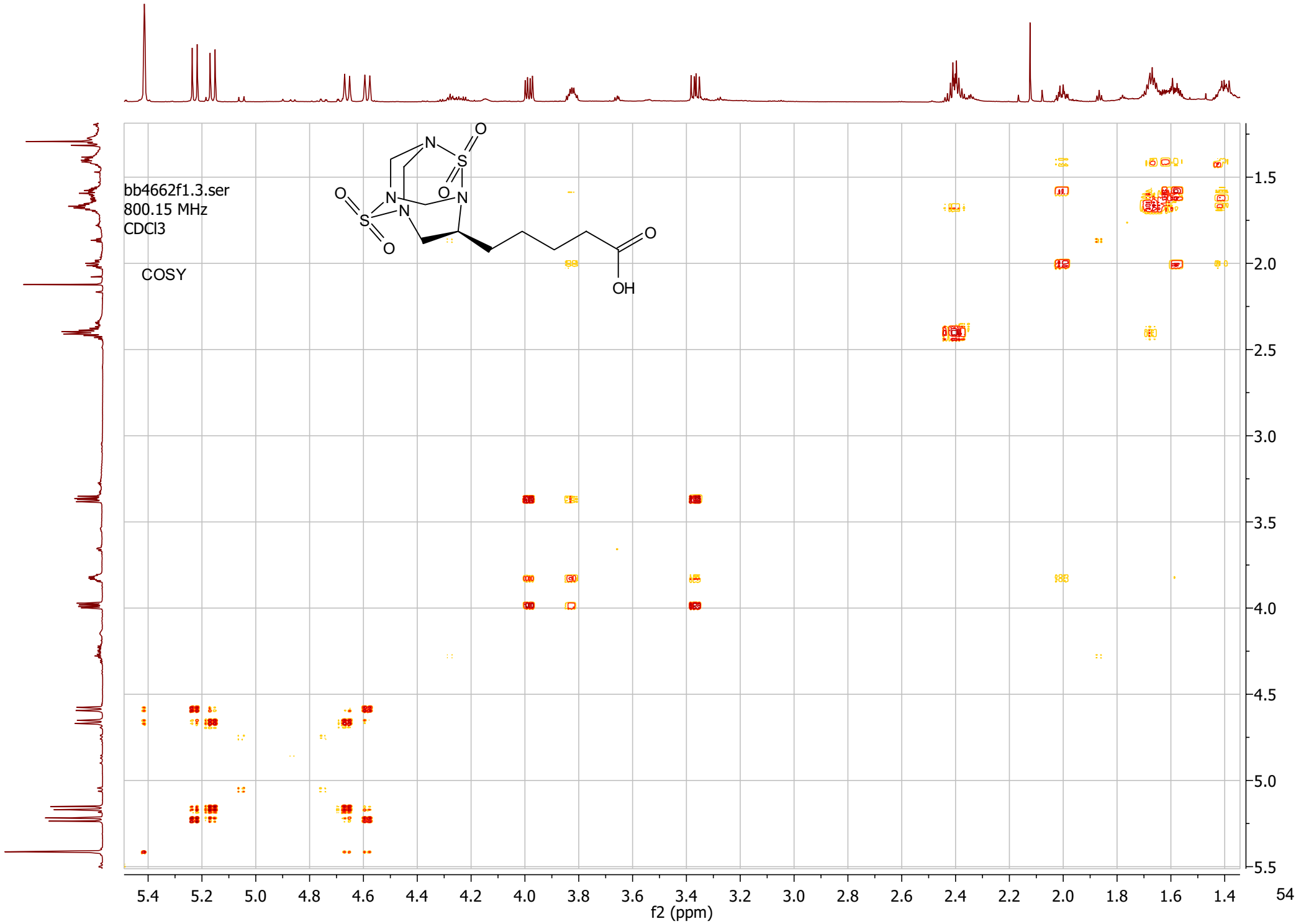

bb439f2NOE2
599.56 MHz
cdcl3
NOE
4.70
4.68
4.49
f1 (ppm)

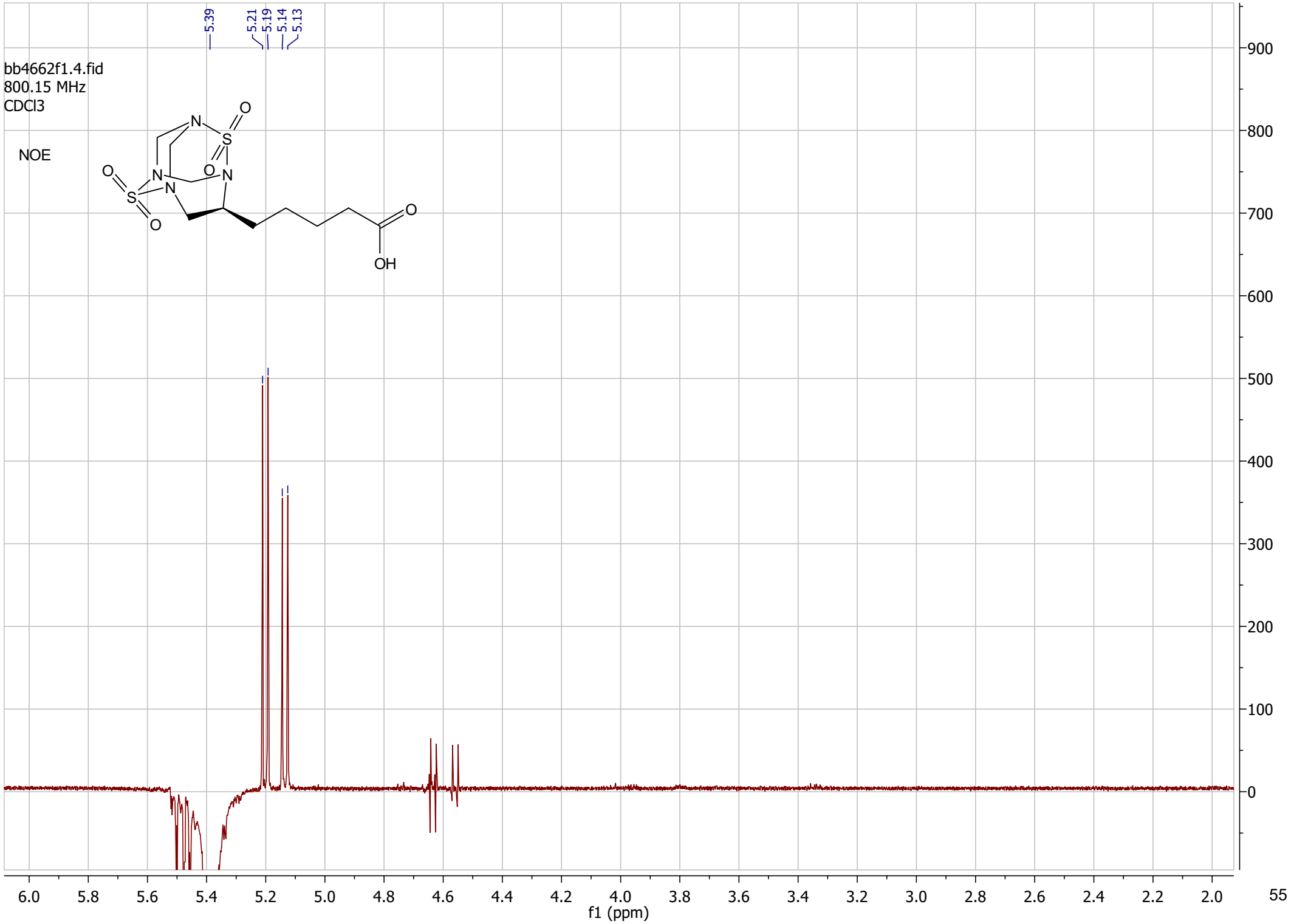

bb439f2NOE3
599.56 MHz
cdcl3
NOE
4.50
4.48
4.21
4.02
4.01
f1 (ppm)

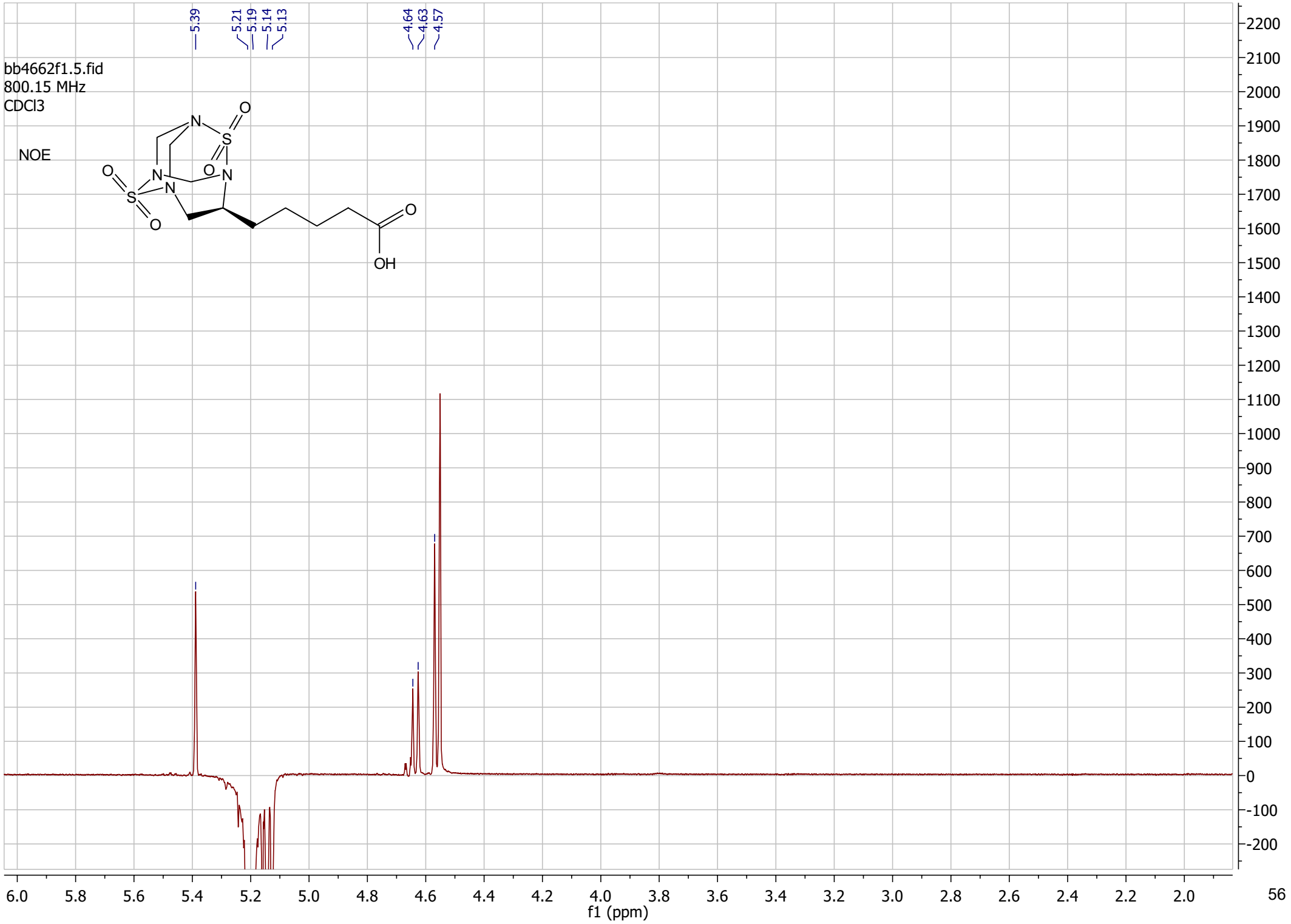

bb439f2NOE4
599.56 MHz
cdcl3
NOE
4.67
4.65
4.24
4.22
4.03
f1 (ppm)

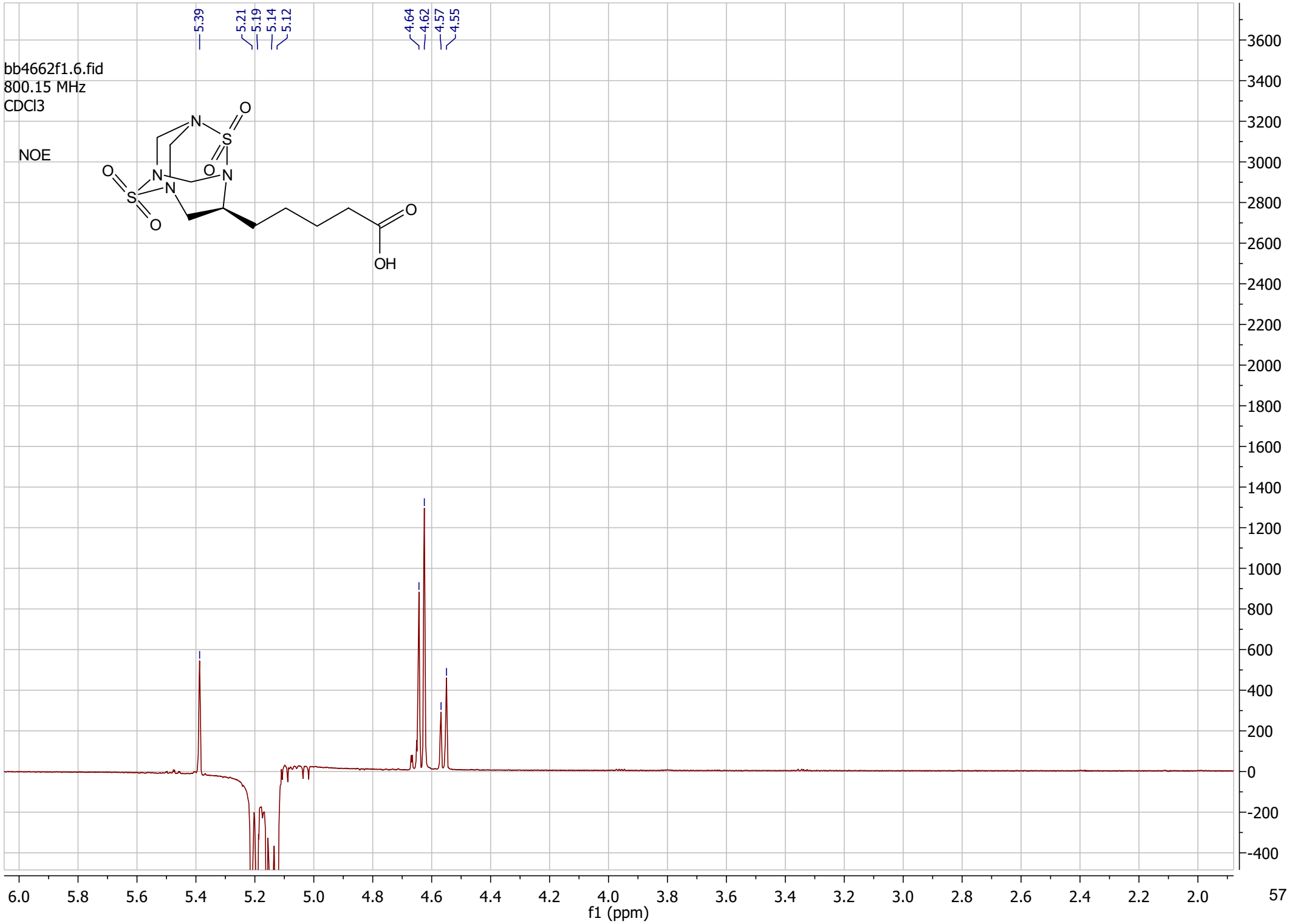

bb4662f1.1.fid
800.15 MHz
CDCl3
proton
Contain ~10 % of other diastereomer
7.26
5.39
5.21
5.19
5.14
5.13
4.64
4.63
4.57
4.55
4.25
3.96
3.95
3.79
3.36
3.34
3.34
3.33
1.87
0.94
1.00
0.97
0.93
0.97
1.02
1.16
2.28
0.95
5.30
2.51
f1 (ppm)

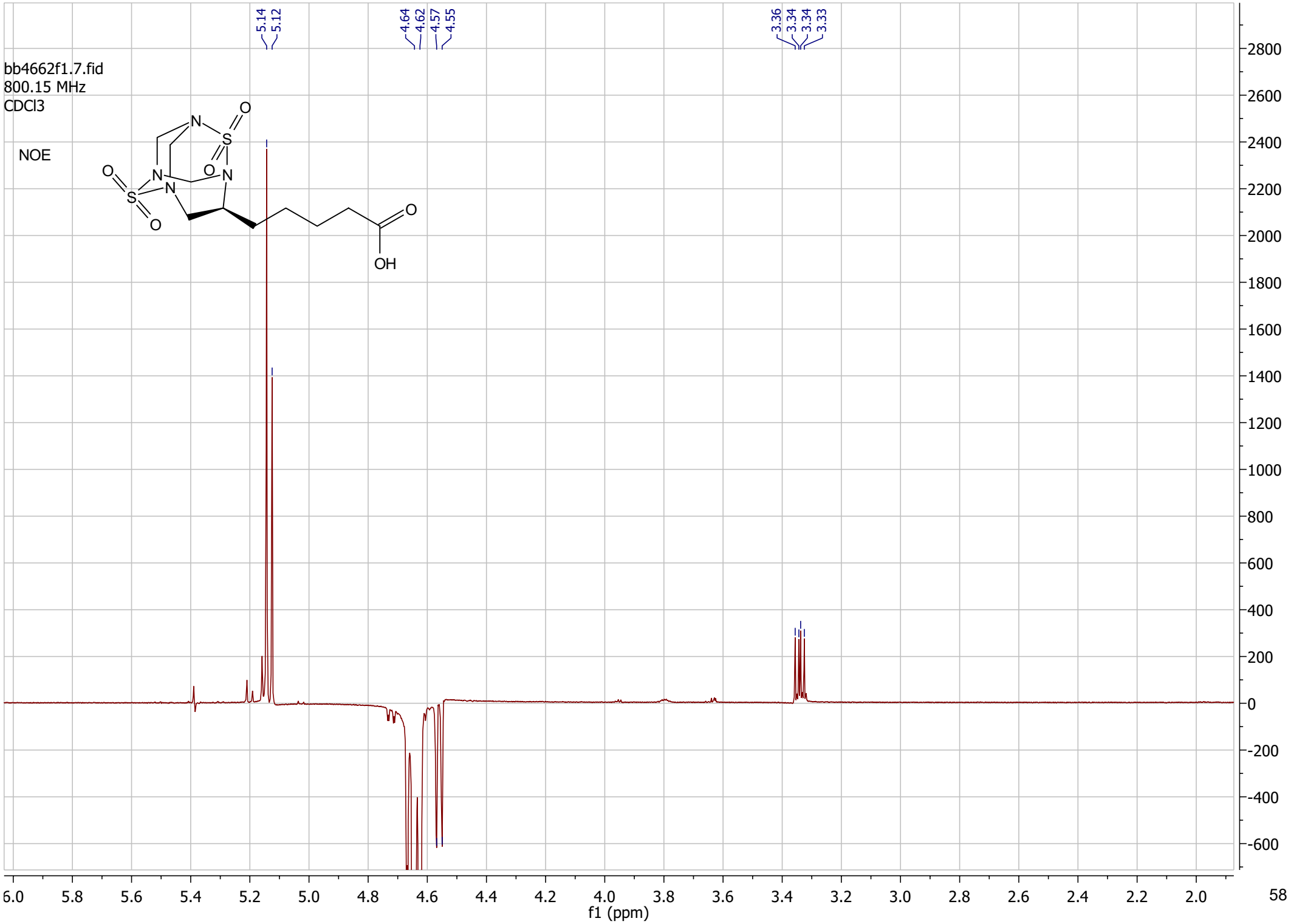

bb4662f1.2.fid
201.22 MHz
CDCl3
13C
178.92
77.16
71.93
70.17
68.54
65.87
57.66
33.72
32.58
26.07
24.24
OH
f1 (ppm)

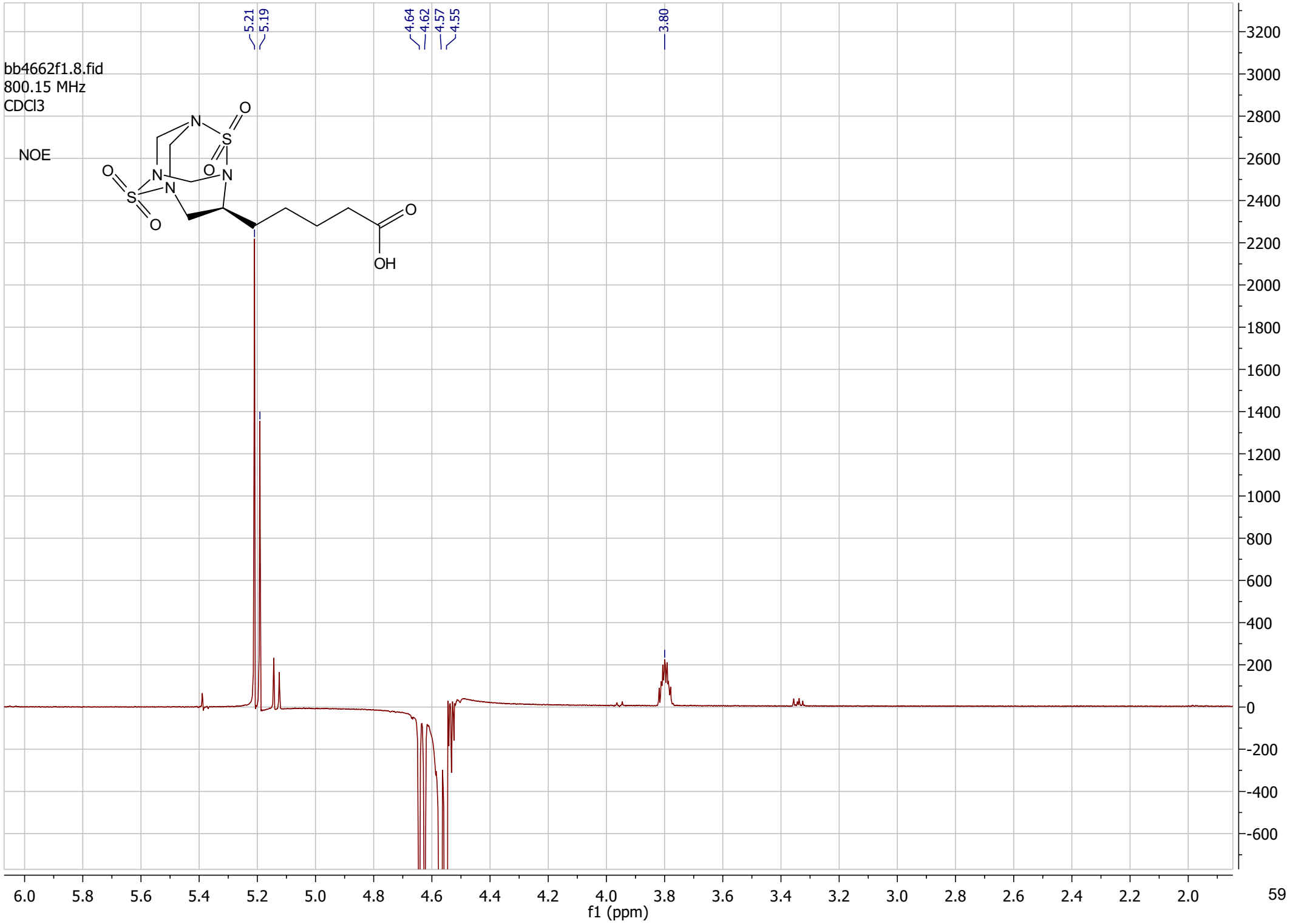

bb4662f1.3.ser
800.15 MHz
CDCl3
COSY
N
S
O
N
O
N
S
O
O
O
OH
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
f2 (ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
f1 (ppm)

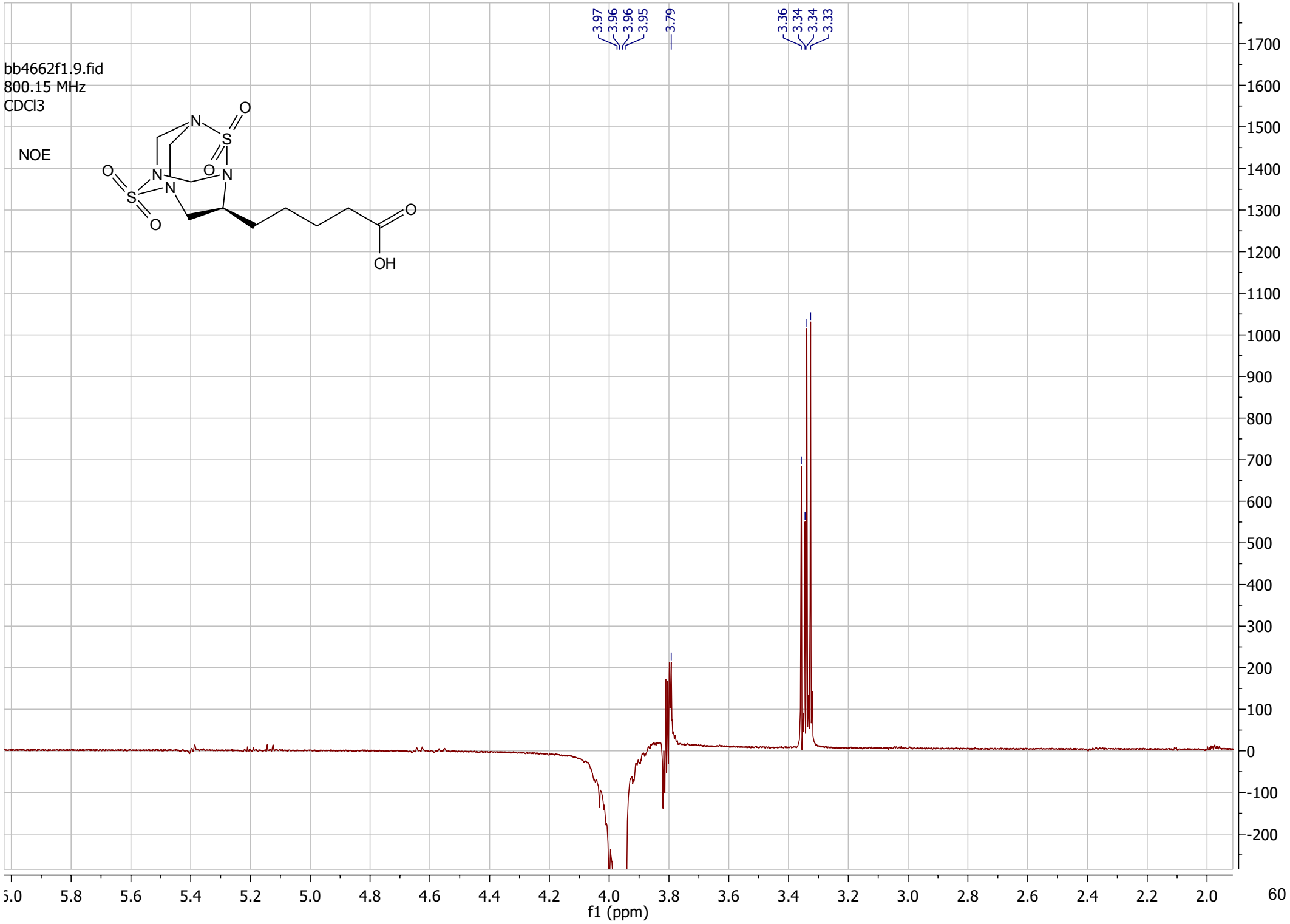

5.39
5.21
5.19
5.14
5.13
bb4662f1.4.fid
800.15 MHz
CDCl3
NOE
O
N
S
O
O
N
O
N
N
S
O
O
O
OH
900
800
700
600
500
400
300
200
100
0
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
f1 (ppm)

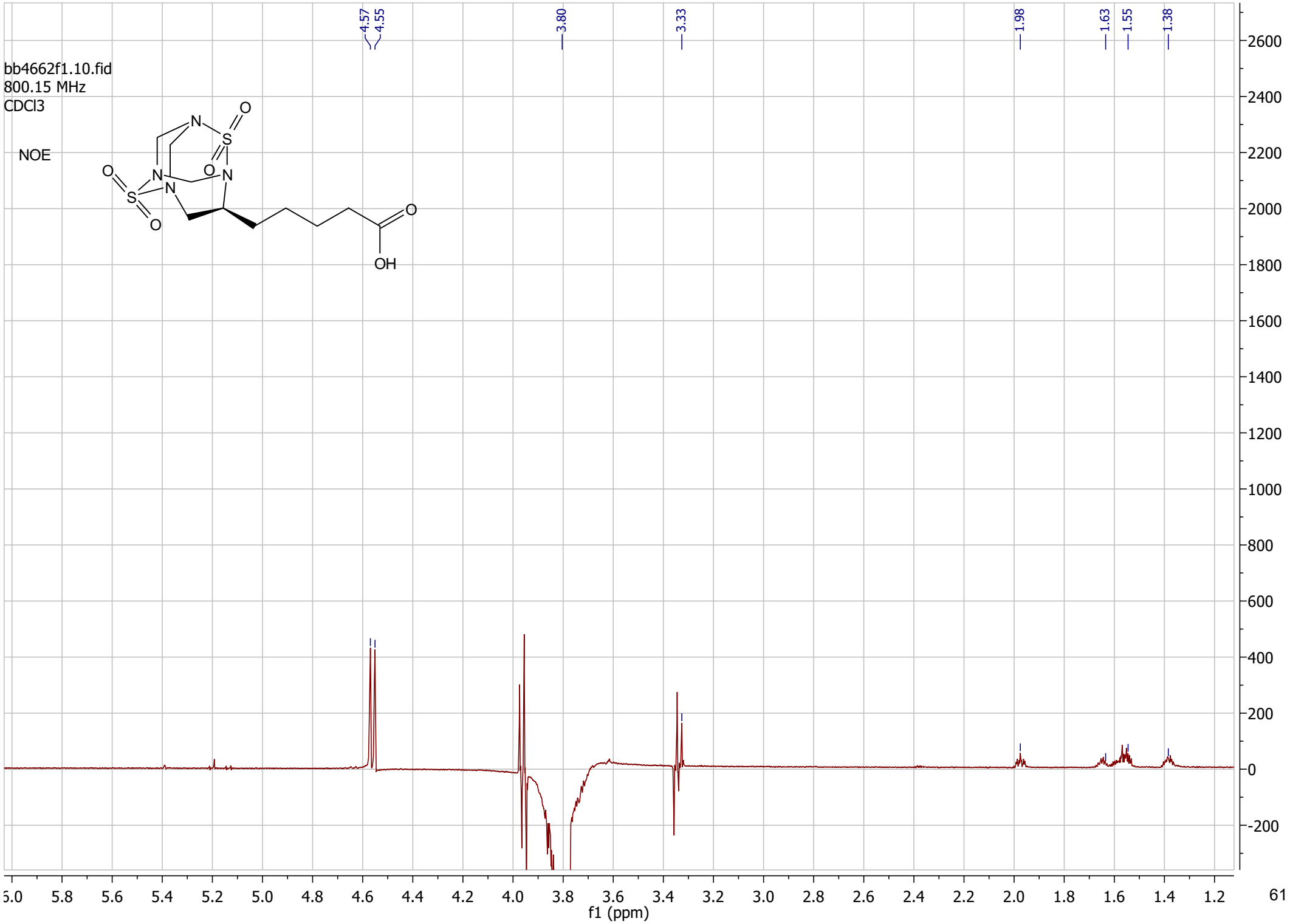

5.39
5.21
5.19
5.14
5.13
4.64
4.63
4.57
bb4662f1.5.fid
800.15 MHz
CDCl3
NOE
N
O
S
O
N
O
N
S
N
O
O
OH
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
f1 (ppm)

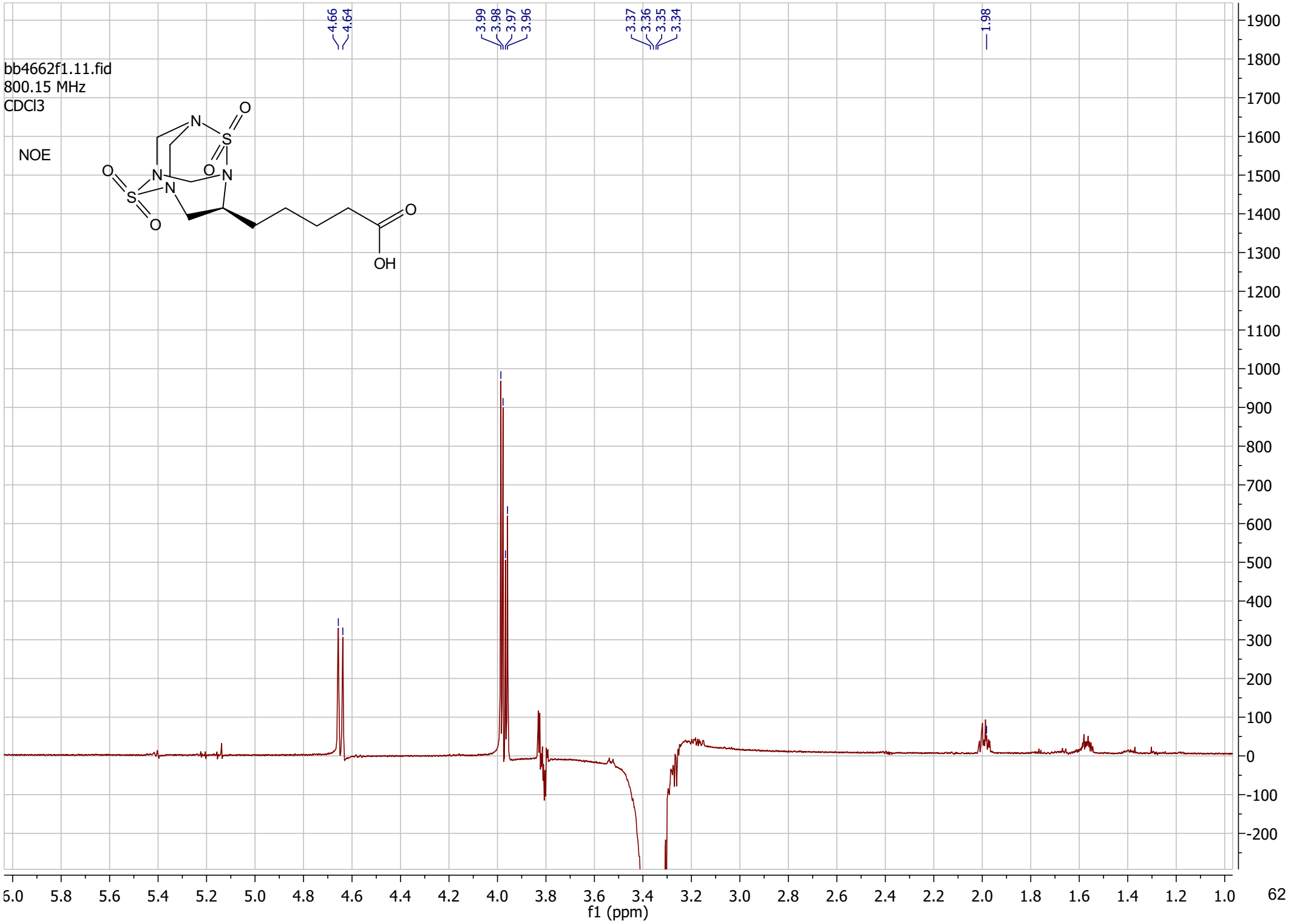

5.39
5.21
5.19
5.14
5.12
4.64
4.62
4.57
4.55
bb4662f1.6.fid
800.15 MHz
CDCl3
NOE
O
N
S
O
O
N
O
N
N
S
O
O
O
OH
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
-400
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
f1 (ppm)

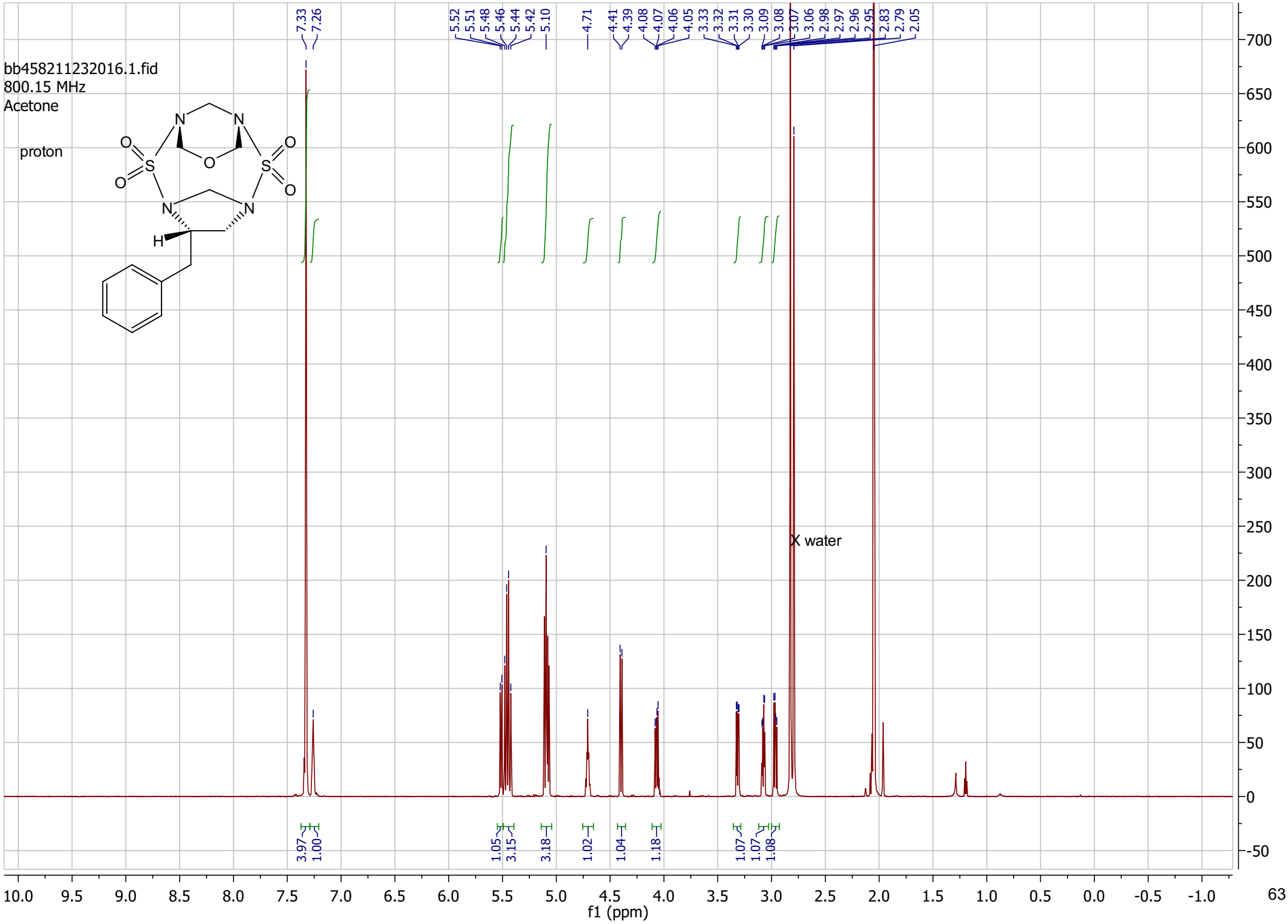

bb4662f1.7.fid
800.15 MHz
CDCl3
NOE
5.14
5.12
4.64
4.62
4.57
4.55
3.36
3.34
3.34
3.33
OH
f1 (ppm)

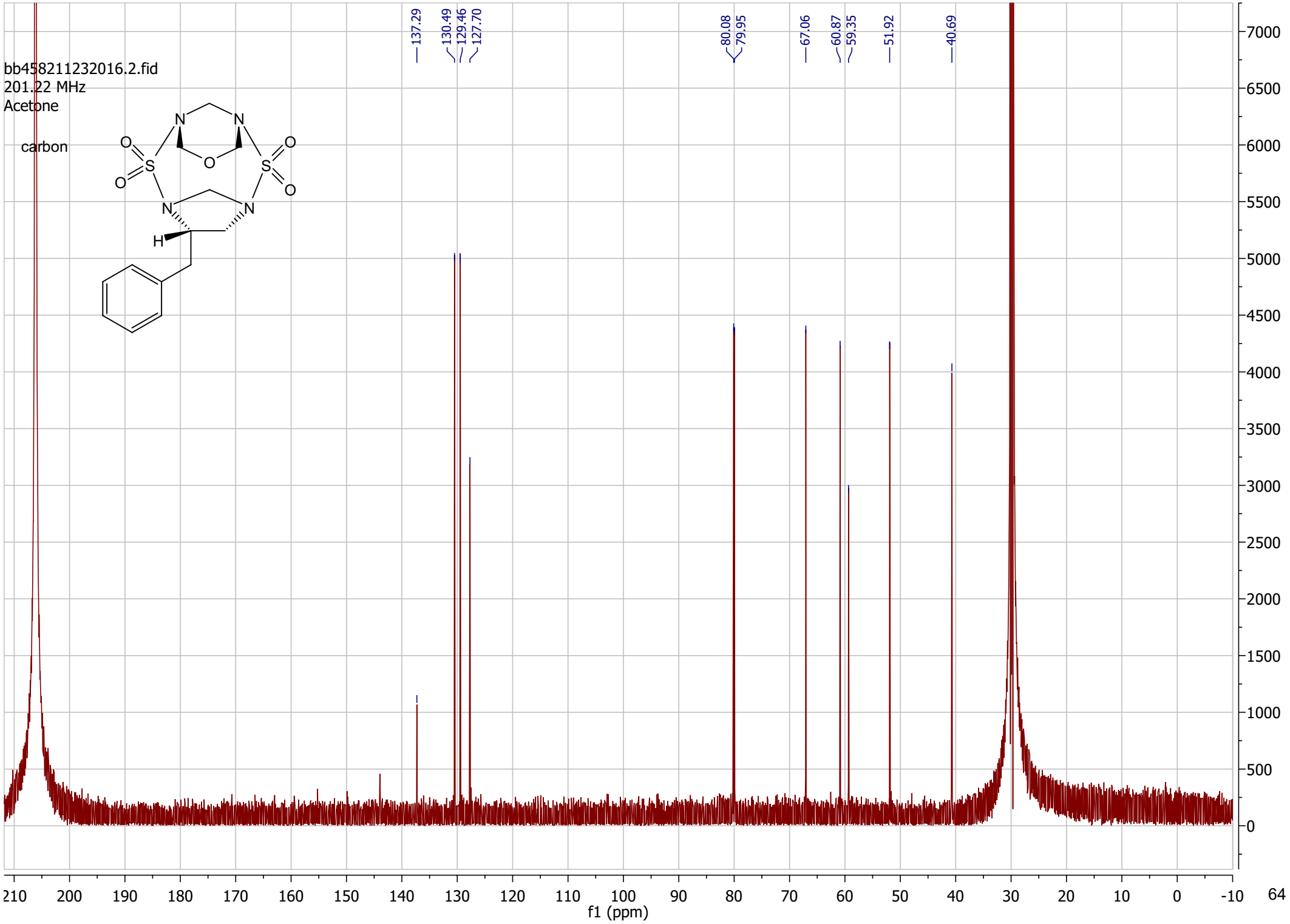

5.21
5.19
4.64
4.62
4.57
4.55
3.80
bb4662f1.8.fid
800.15 MHz
CDCl3
NOE
O
N
S
O
O
N
O
N
N
S
O
O
OH
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
-400
-600
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
f1 (ppm)

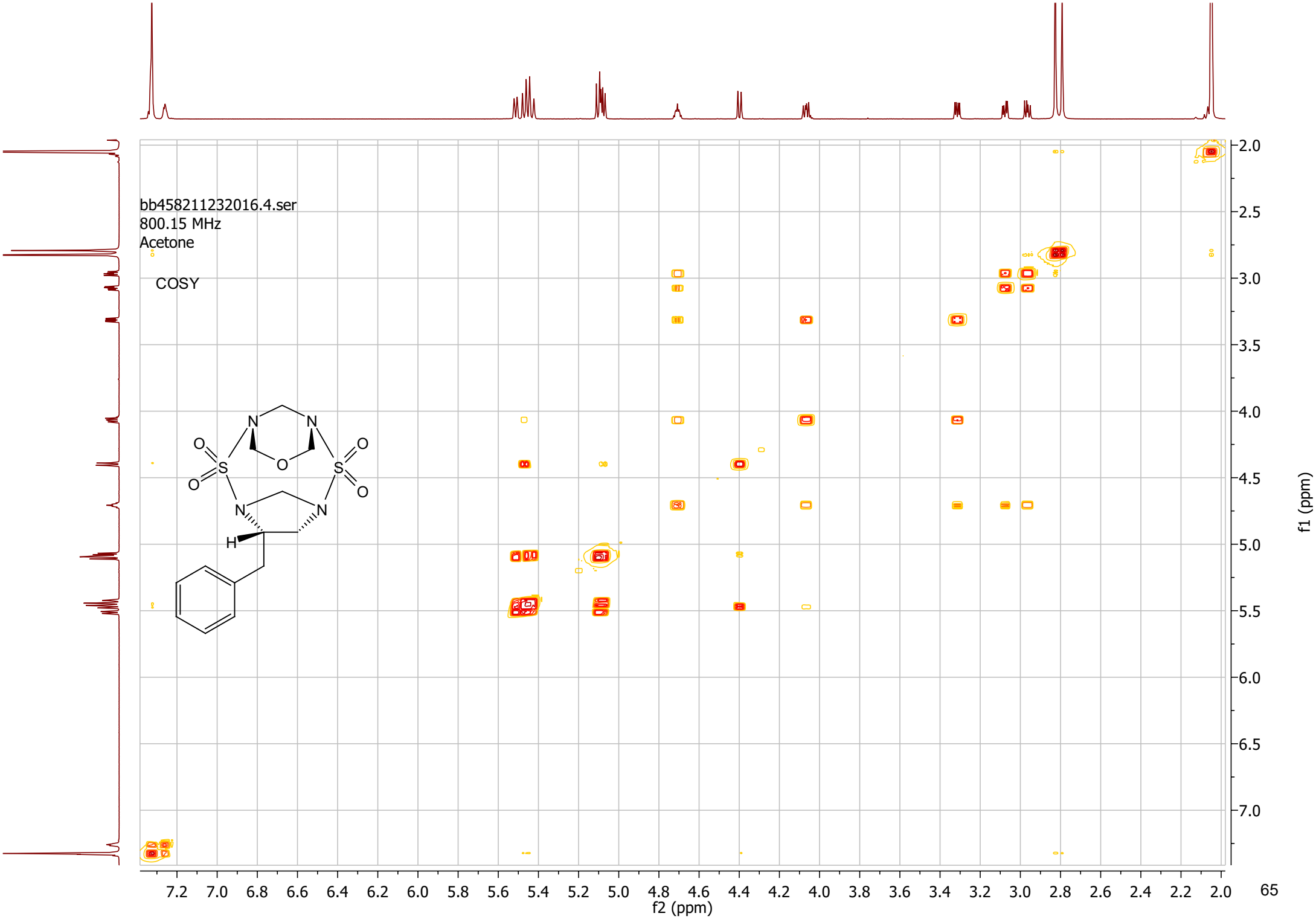

bb4662f1.9.fid
800.15 MHz
CDCl3
NOE
3.97
3.96
3.96
3.95
3.79
3.36
3.34
3.34
3.33
OH
f1 (ppm)

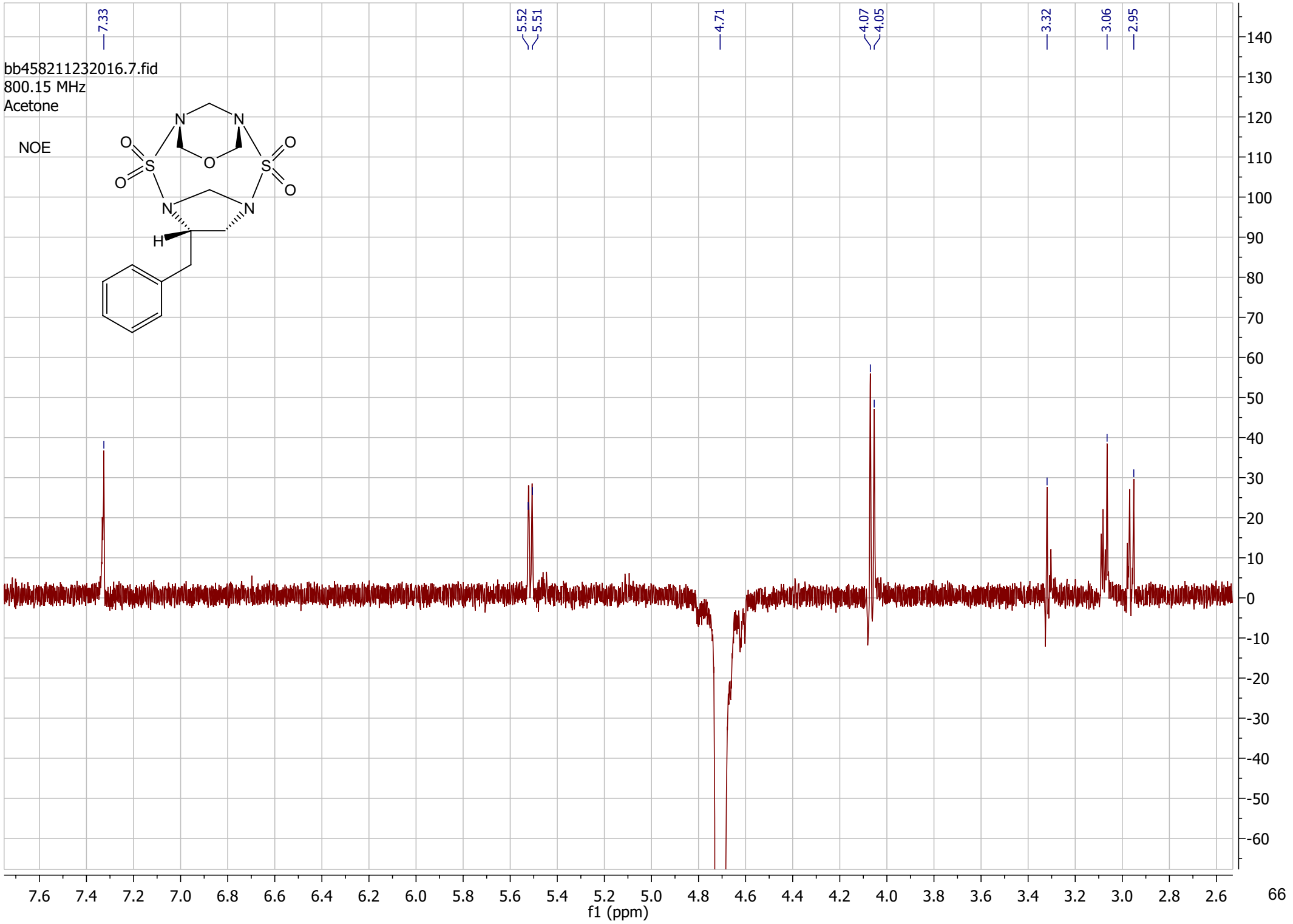

bb4662f1.10.fid
800.15 MHz
CDCl3
NOE
4.57
4.55
3.80
3.33
1.98
1.63
1.55
1.38
OH
f1 (ppm)

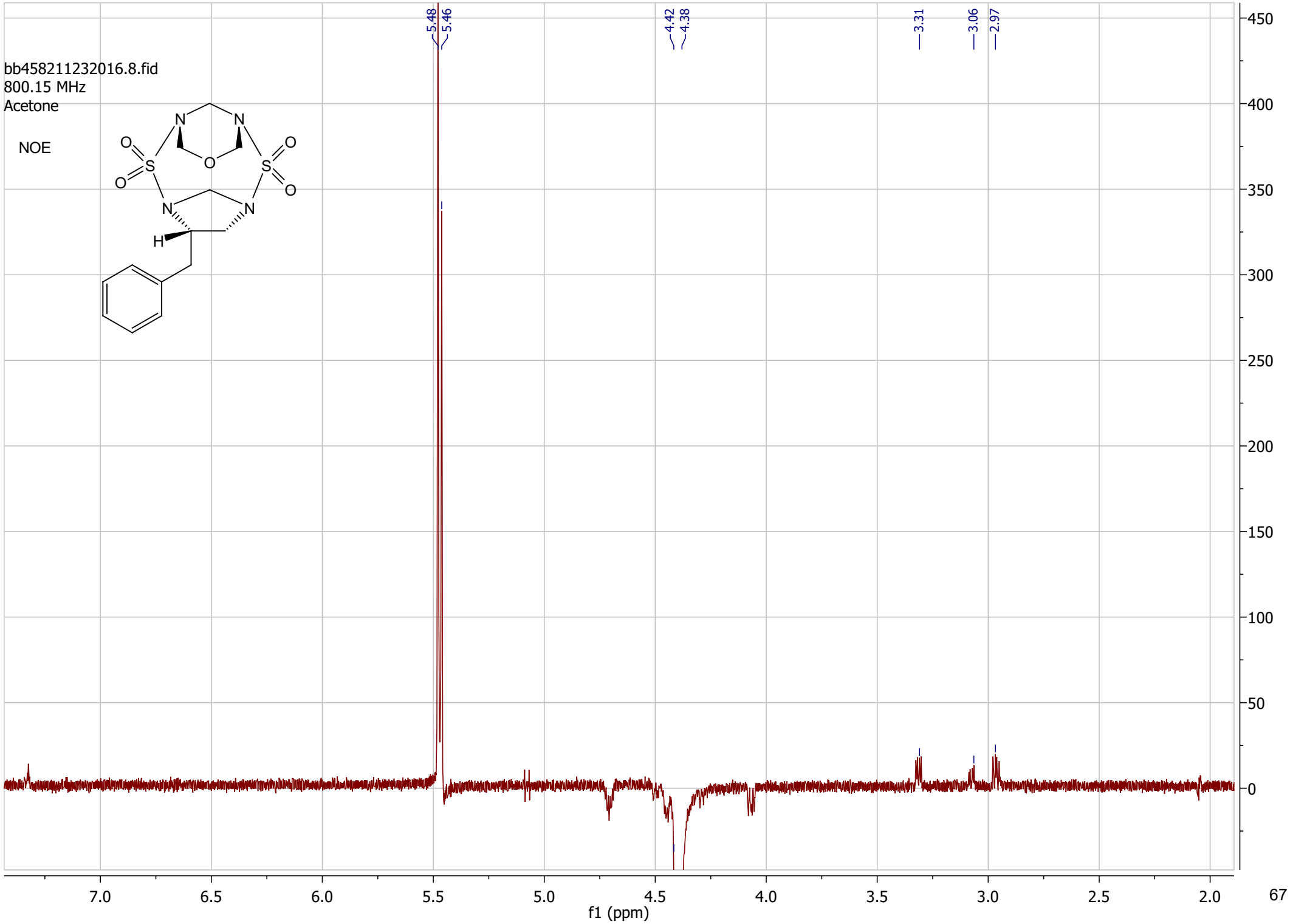

4.66
4.64
3.99
3.98
3.97
3.96
3.37
3.36
3.35
3.34
1.98
bb4662f1.11.fid
800.15 MHz
CDCl3
NOE
N
S
O
N
O
N
N
O
S
O
O
OH
f1 (ppm)

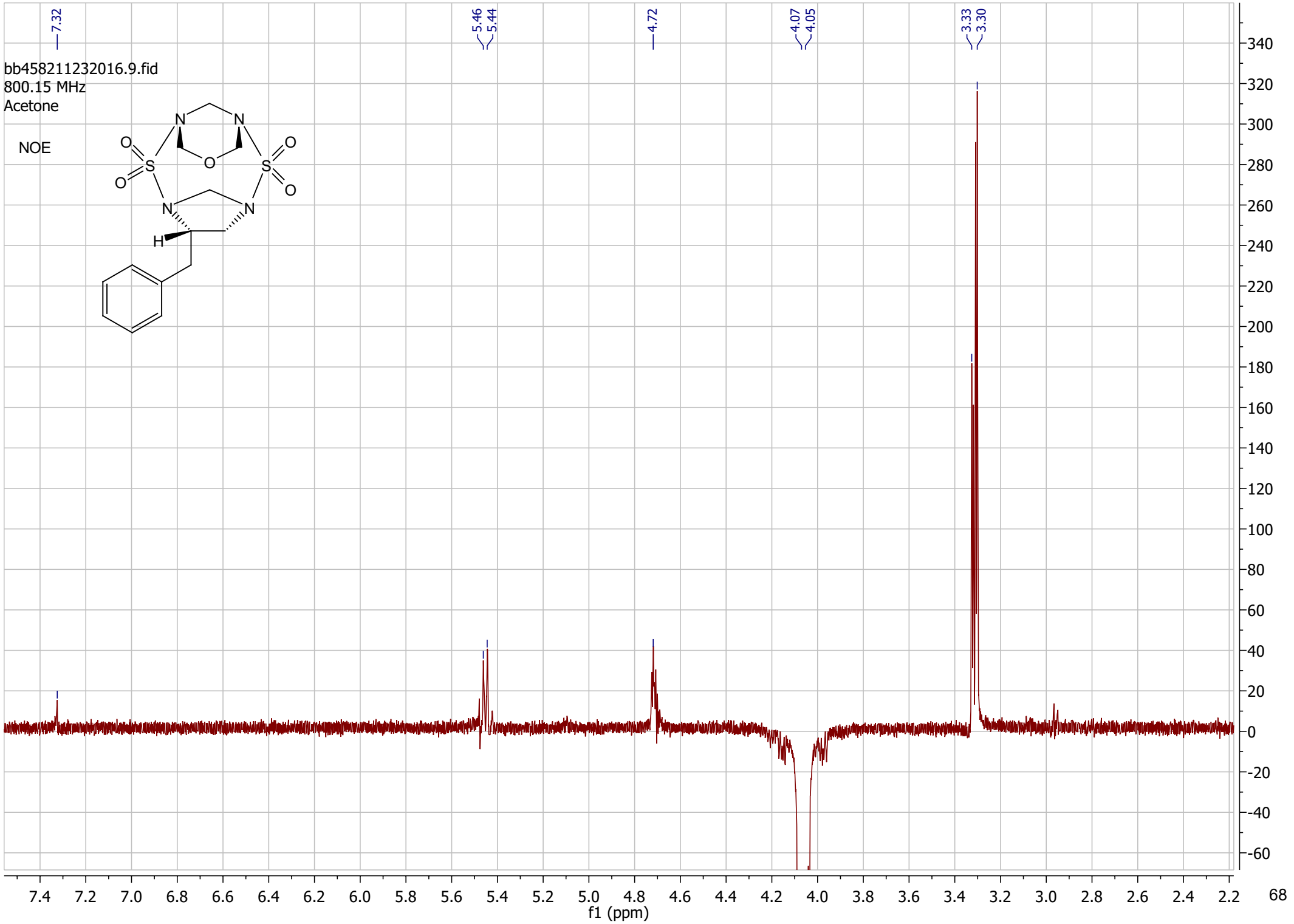

bb458211232016.1.fid
800.15 MHz
Acetone
proton
7.33
7.26
5.52
5.51
5.48
5.46
5.44
5.42
5.10
4.71
4.41
4.39
4.08
4.07
4.06
4.05
3.33
3.32
3.31
3.30
3.09
3.08
3.07
3.06
2.98
2.97
2.96
2.95
2.83
2.79
2.05
X water
3.97
1.00
1.05
3.15
3.18
1.02
1.04
1.18
1.07
1.07
1.08
f1 (ppm)

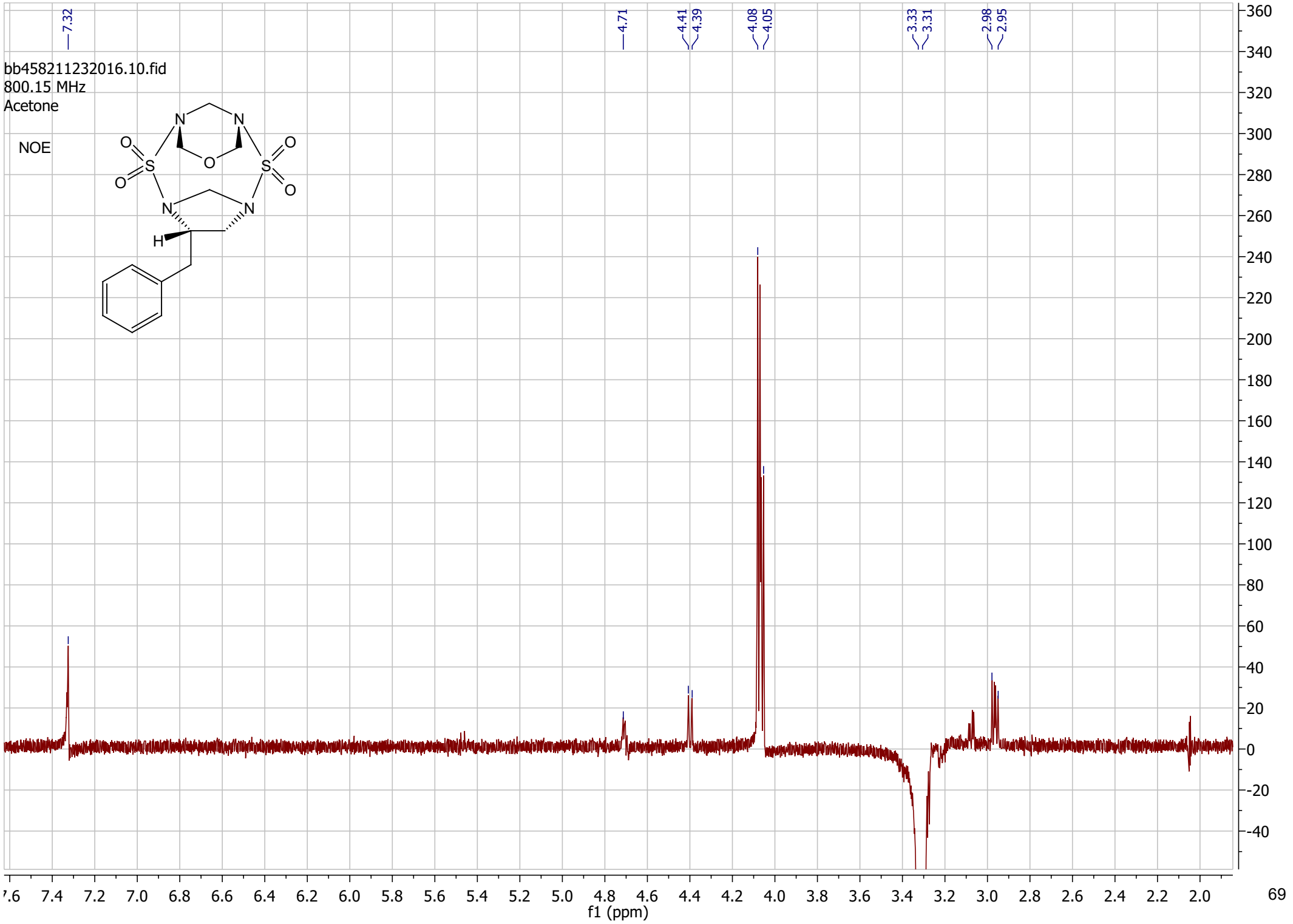

bb458211232016.2.fid
201.22 MHz
Acetone
carbon
137.29
130.49
129.46
127.70
80.08
79.95
67.06
60.87
59.35
51.92
40.69
f1 (ppm)

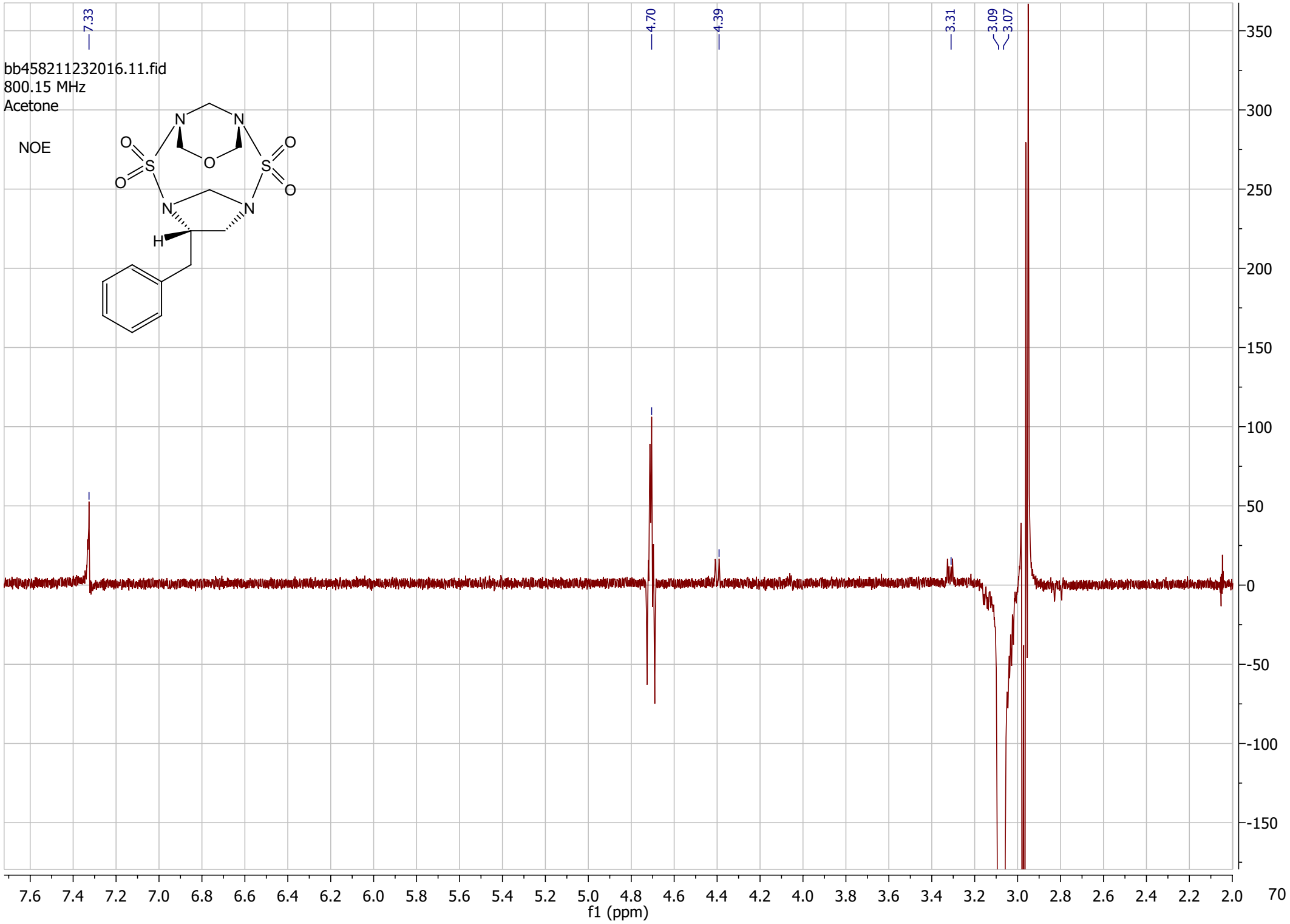

bb458211232016.4.ser
800.15 MHz
Acetone
COSY
f2 (ppm)
f1 (ppm)
7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0
2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0
N N O S S O O O O N N H

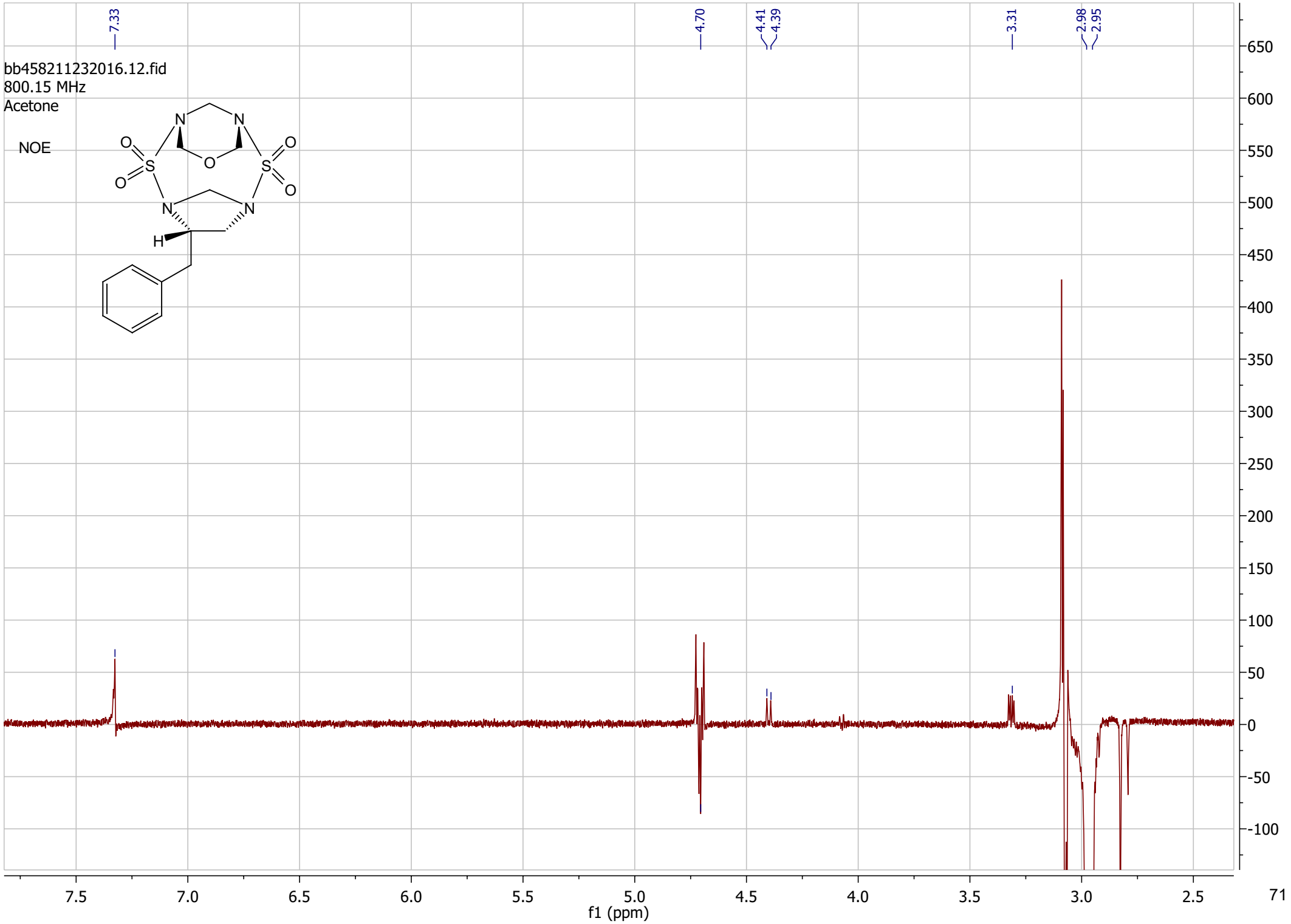

7.33
5.52
5.51
4.71
4.07
4.05
3.32
3.06
2.95
bb458211232016.7.fid
800.15 MHz
Acetone
NOE
f1 (ppm)

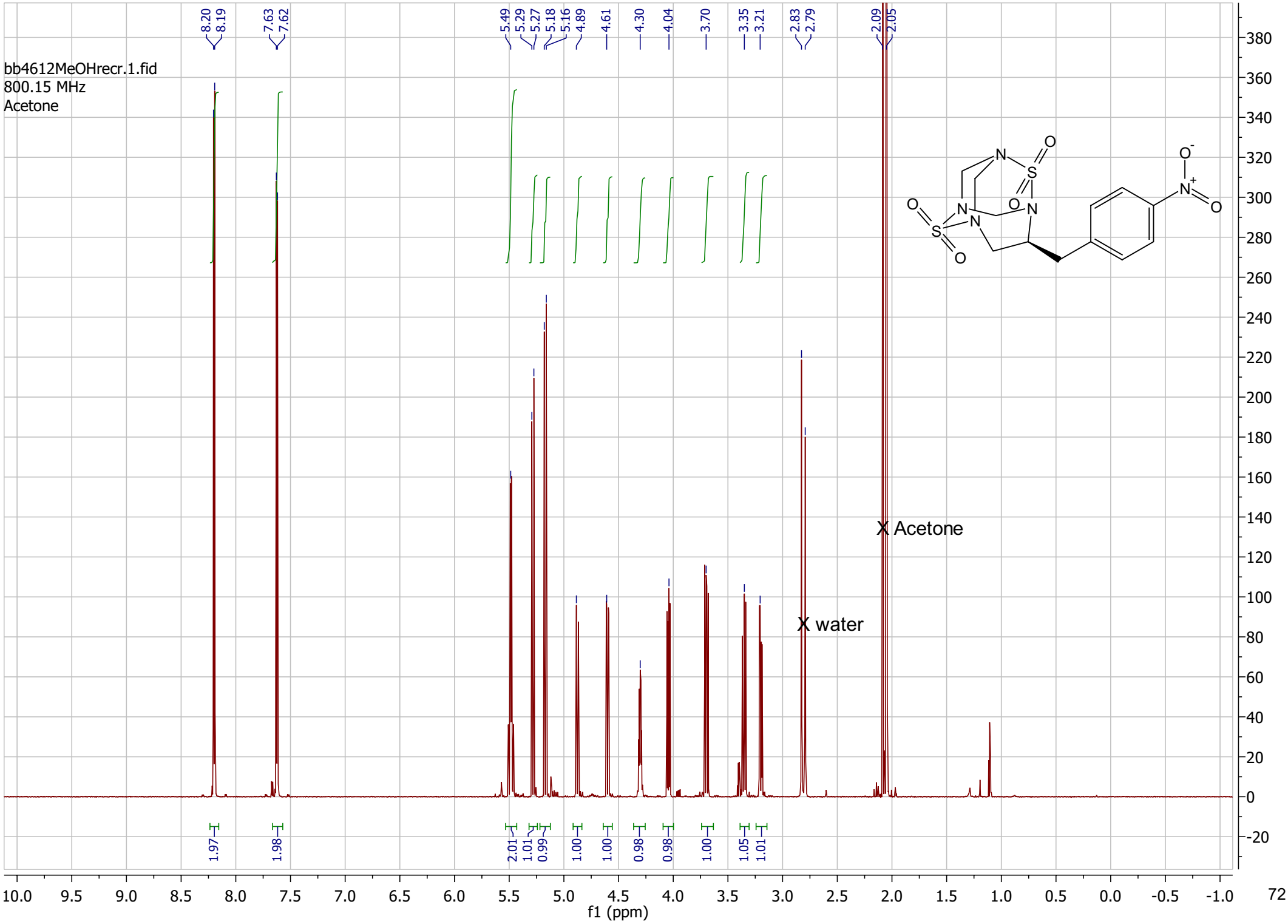

bb458211232016.8.fid
800.15 MHz
Acetone
NOE
5.48
5.46
4.42
4.38
3.31
3.06
2.97
f1 (ppm)

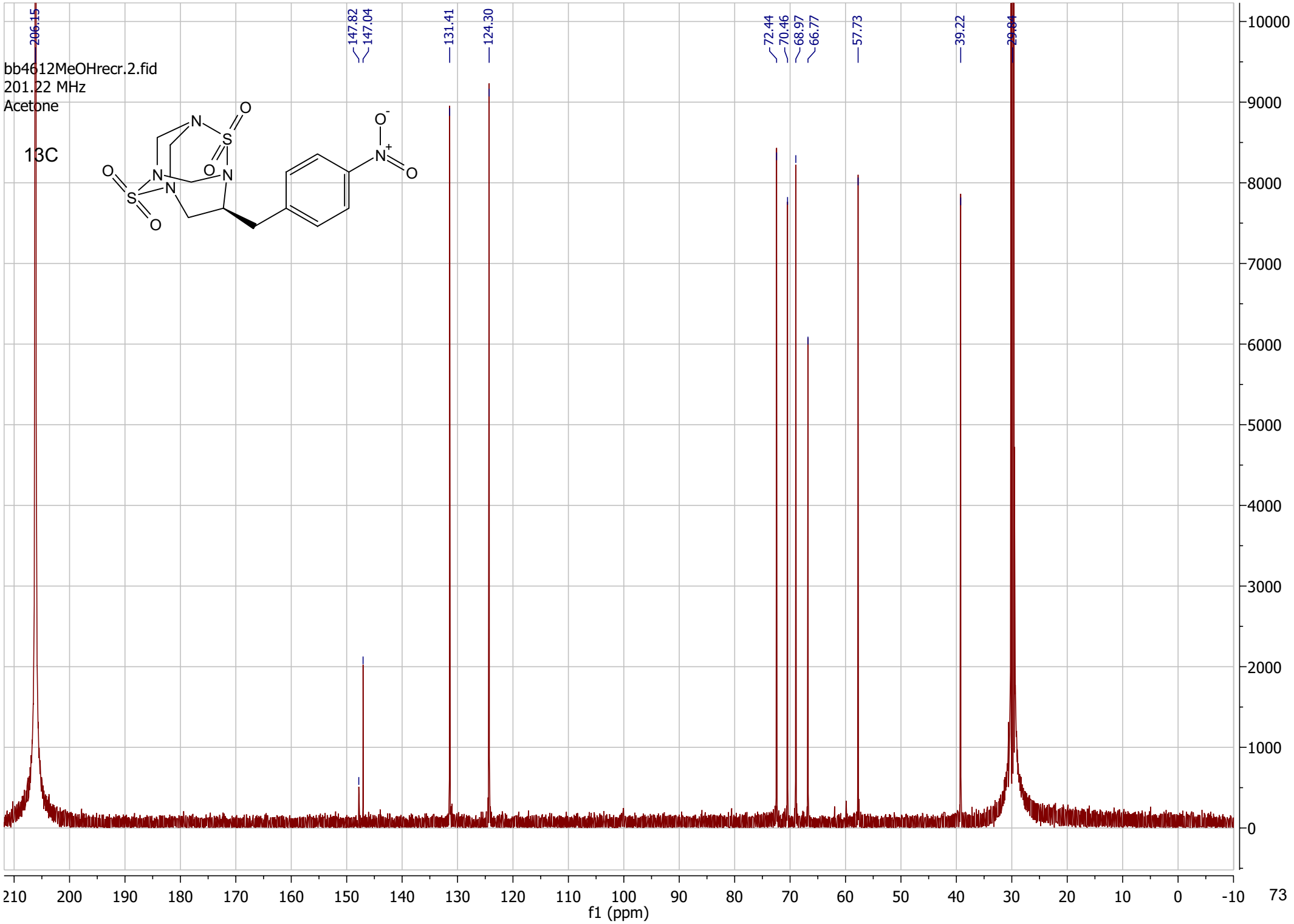

7.32
5.46
5.44
4.72
4.07
4.05
3.33
3.30
bb458211232016.9.fid
800.15 MHz
Acetone
NOE
N
N
O
S
S
O
O
O
O
N
N
H
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
-60
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
f1 (ppm)

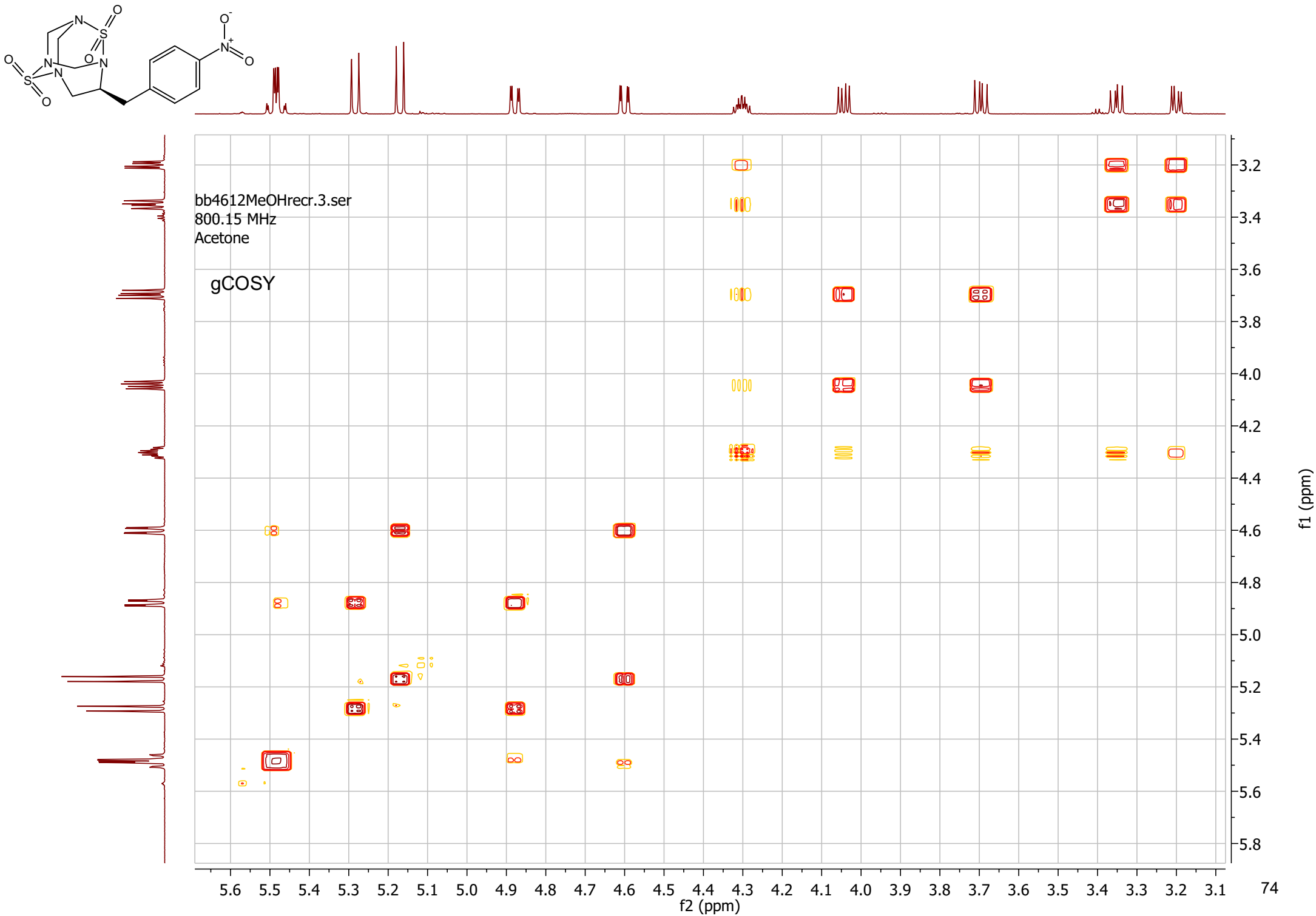

7.32
4.71
4.41
4.39
4.08
4.05
3.33
3.31
2.98
2.95
bb458211232016.10.fid
800.15 MHz
Acetone
NOE
f1 (ppm)

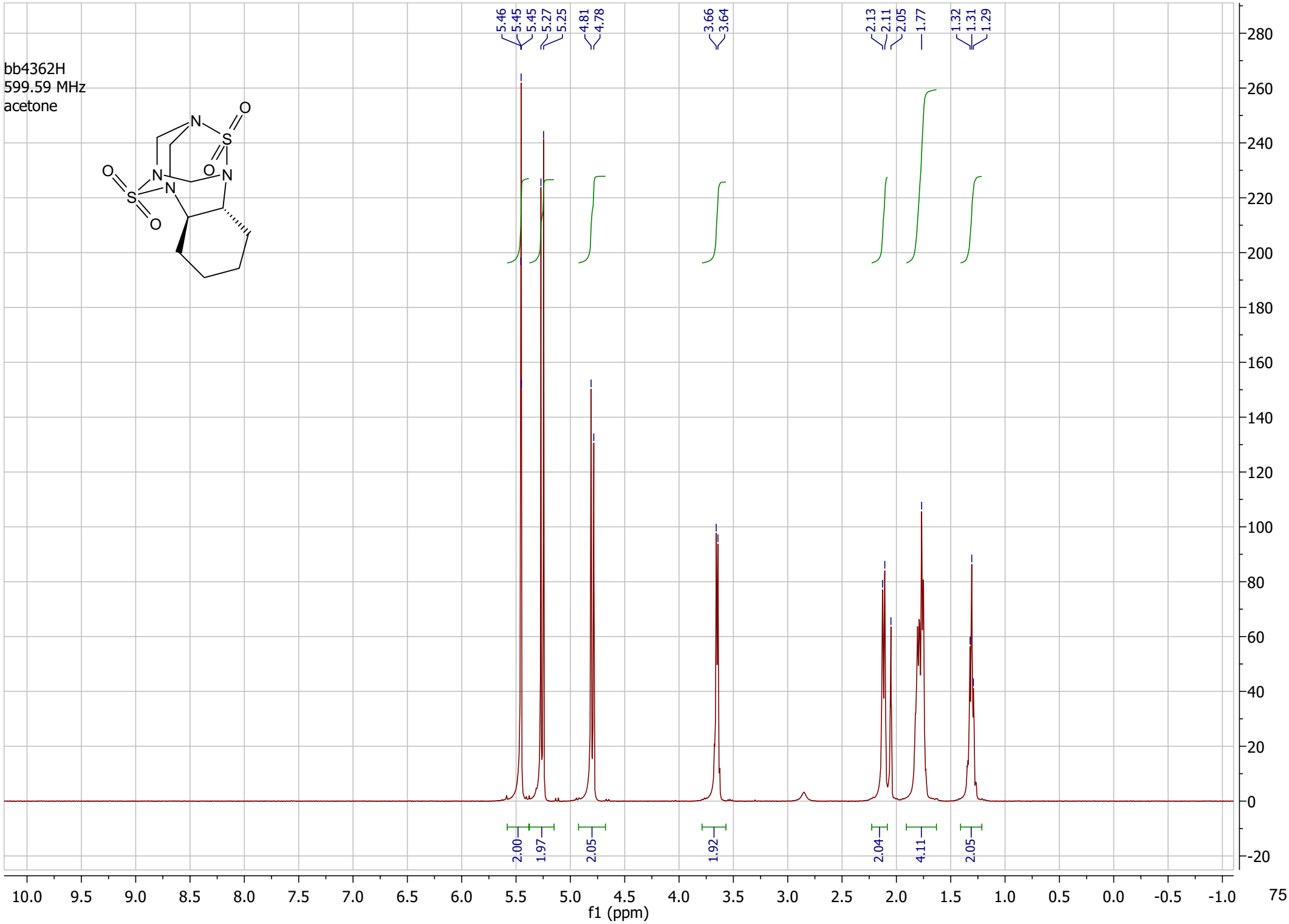

7.33
4.70
4.39
3.31
3.09
3.07
bb458211232016.11.fid
800.15 MHz
Acetone
NOE
N
N
O
S
S
O
O
O
O
N
N
H
350
300
250
200
150
100
50
0
-50
-100
-150
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
f1 (ppm)
70

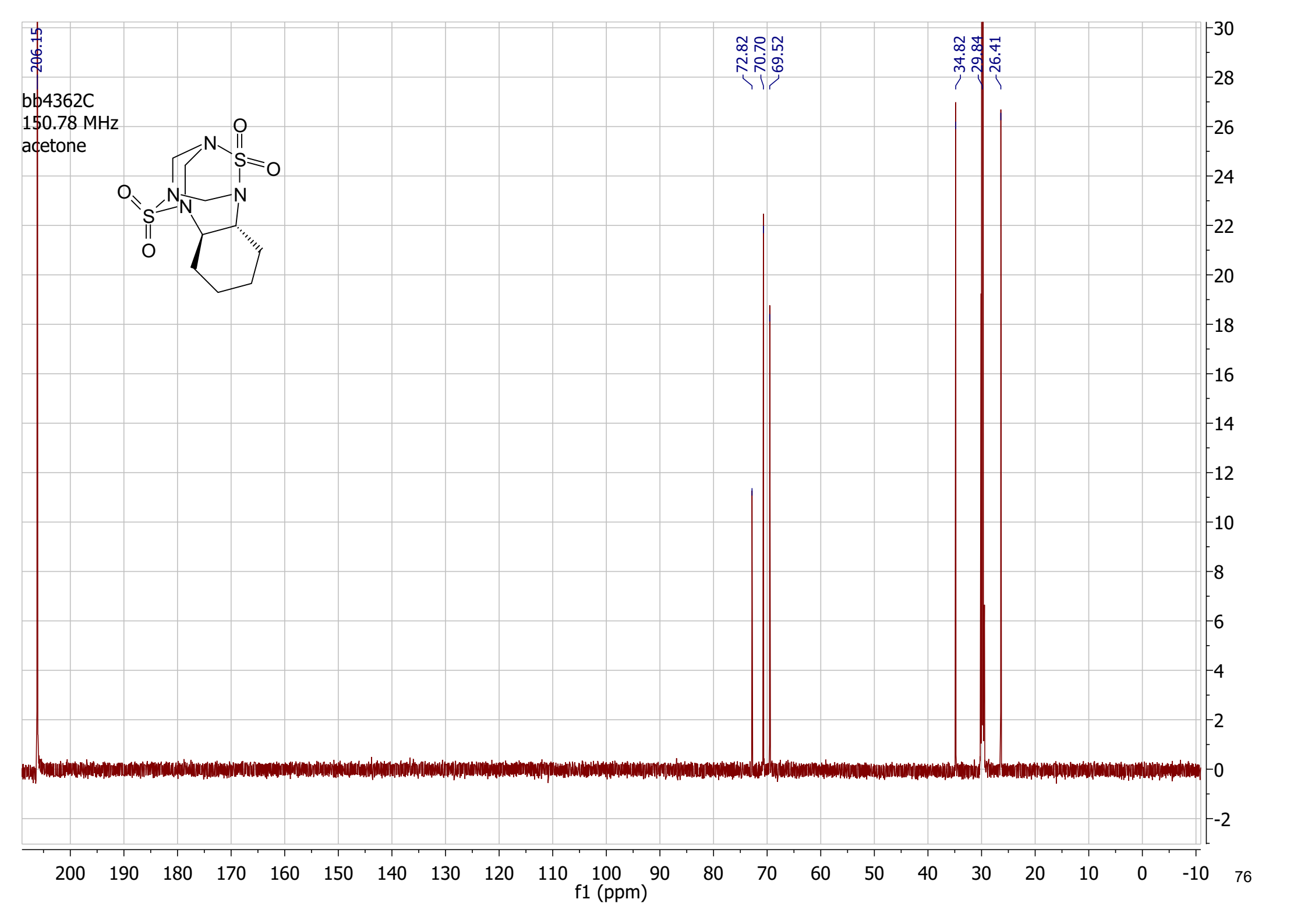

7.33
4.70
4.41
4.39
3.31
2.98
2.95
bb458211232016.12.fid
800.15 MHz
Acetone
NOE
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
-100
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
f1 (ppm)

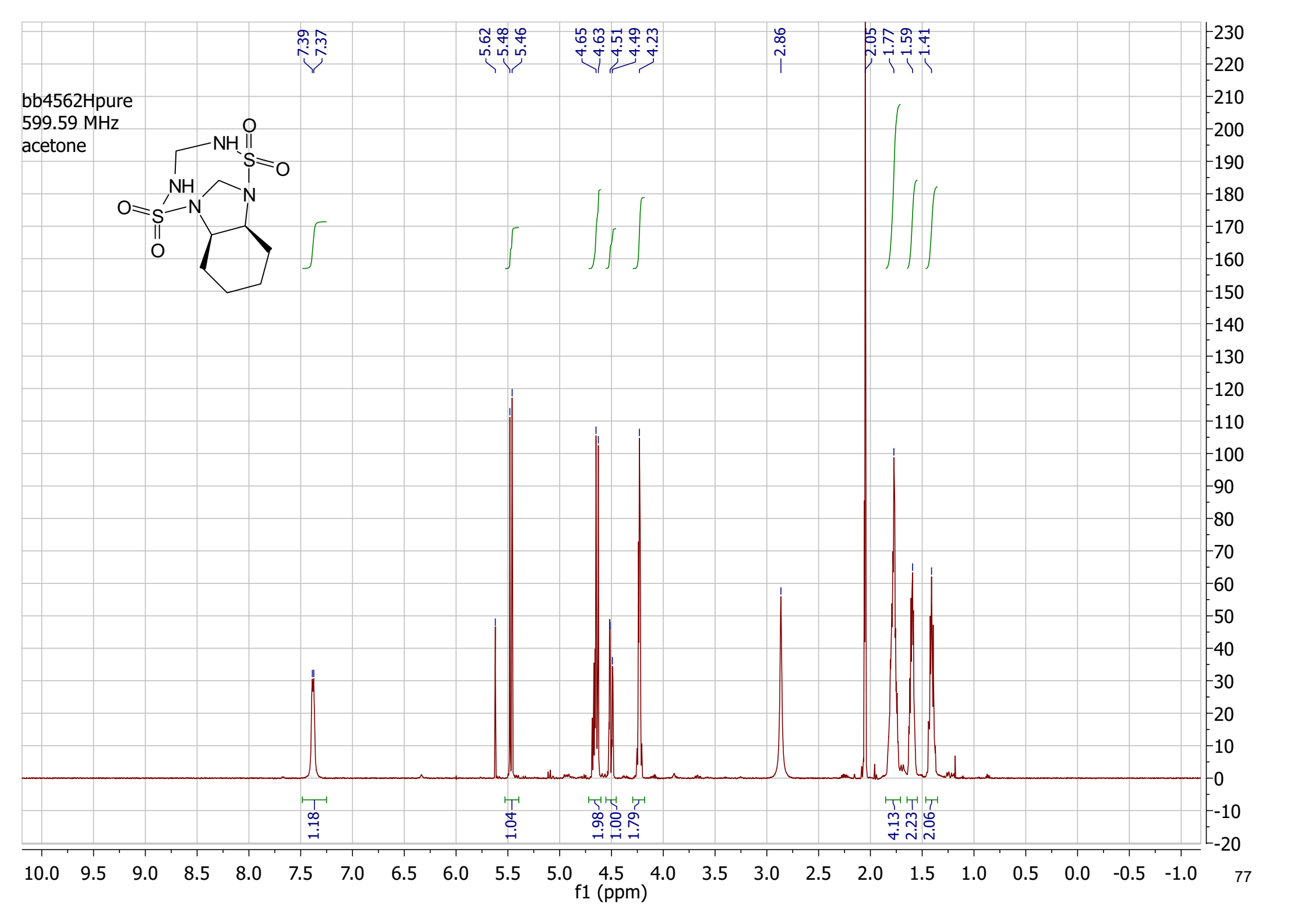

bb4612MeOHrecr.1.fid
800.15 MHz
Acetone
8.20
8.19
7.63
7.62
5.49
5.29
5.27
5.18
5.16
4.89
4.61
4.30
4.04
3.70
3.35
3.21
2.83
2.79
2.09
2.05
X Acetone
X water
1.97
1.98
2.01
1.01
0.99
1.00
1.00
0.98
0.98
1.00
1.05
1.01
f1 (ppm)

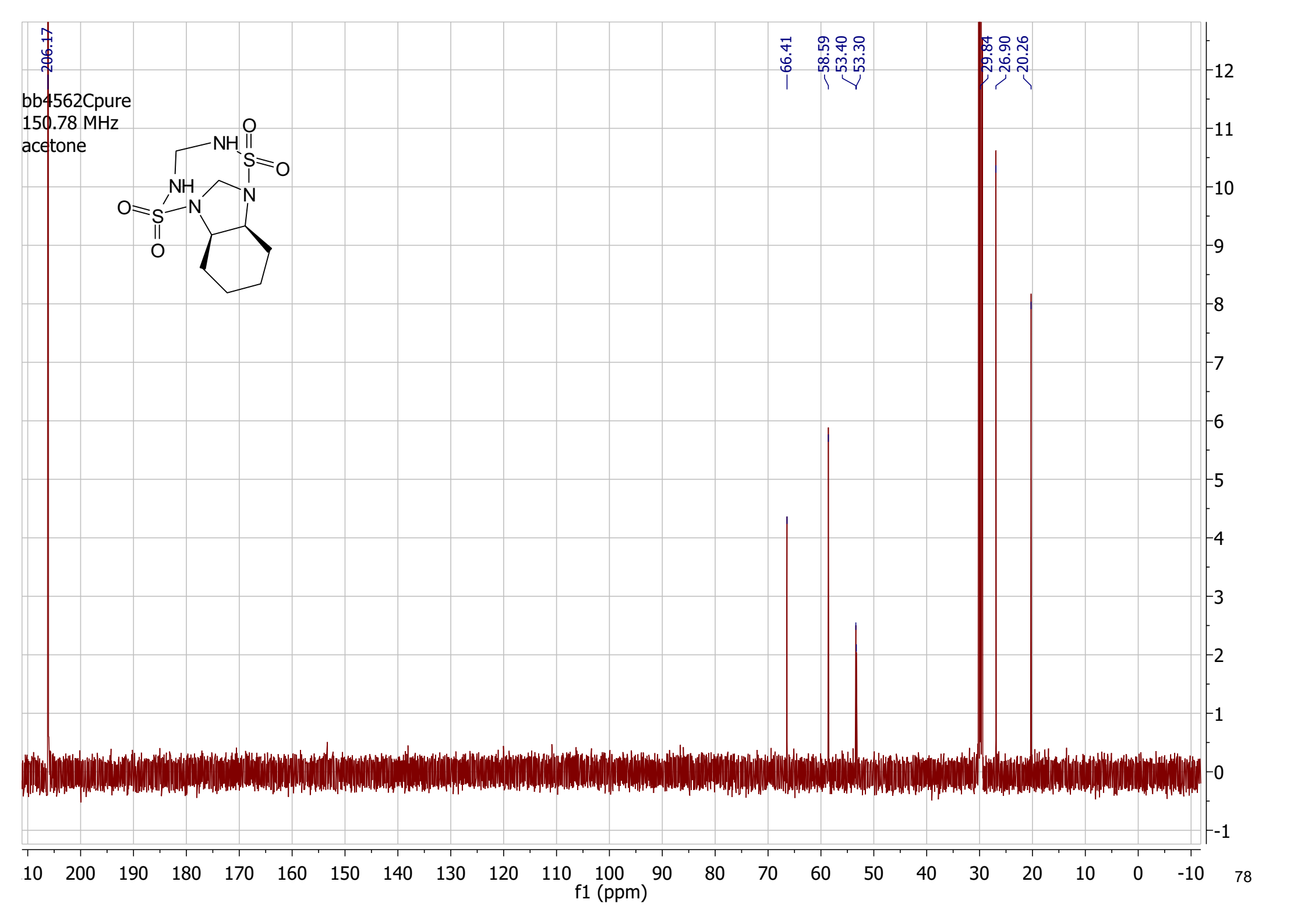

bb4612MeOHrecr.2.fid
201.22 MHz
Acetone
13C
206.15
147.82
147.04
131.41
124.30
72.44
70.46
68.97
66.77
57.73
39.22
29.84
f1 (ppm)

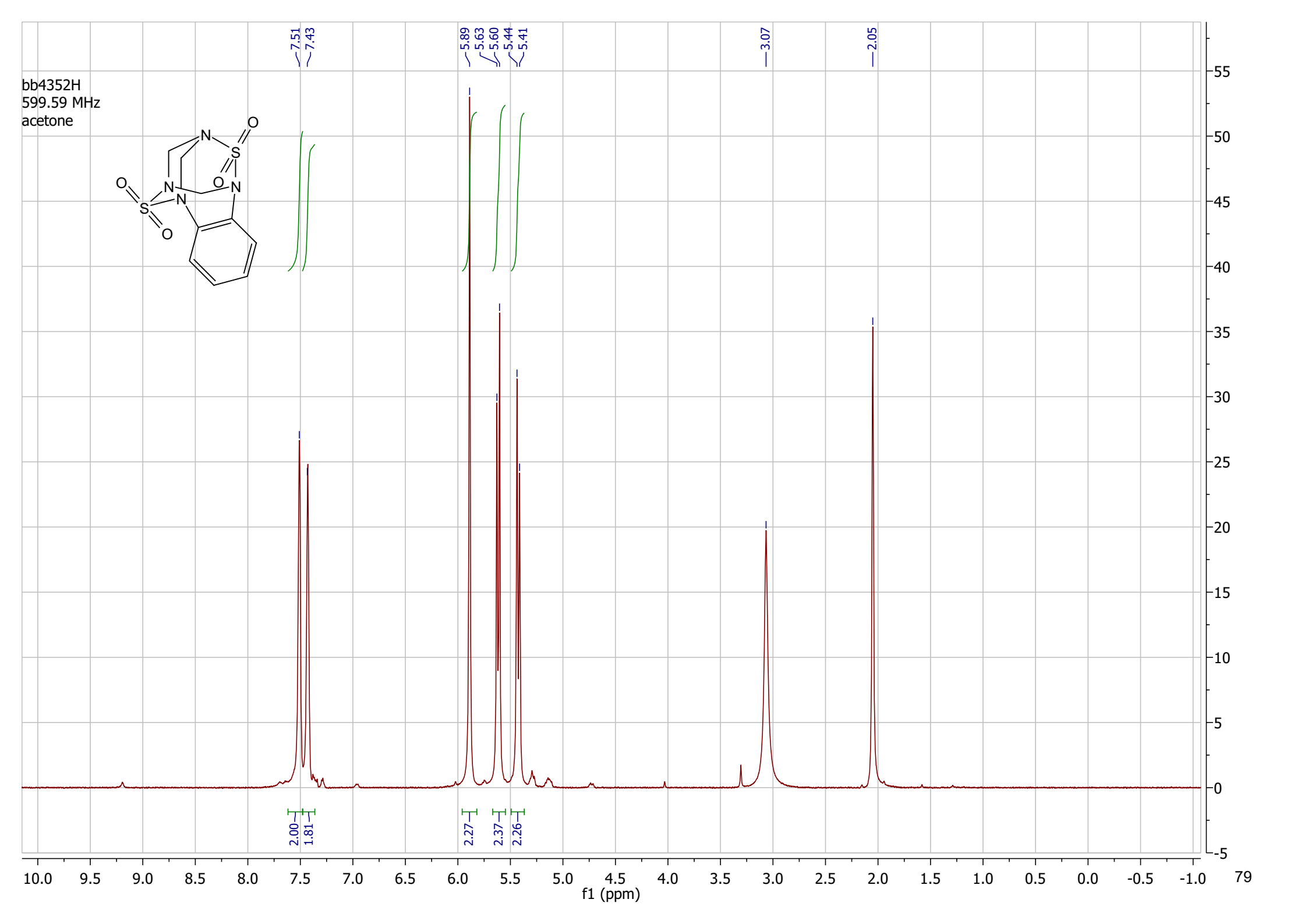

bb4612MeOHrecr.3.ser
800.15 MHz
Acetone
gCOSY
f2 (ppm)
f1 (ppm)
5.6 5.5 5.4 5.3 5.2 5.1 5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1
3.2 3.4 3.6 3.8 4.0 4.2 4.4 4.6 4.8 5.0 5.2 5.4 5.6 5.8

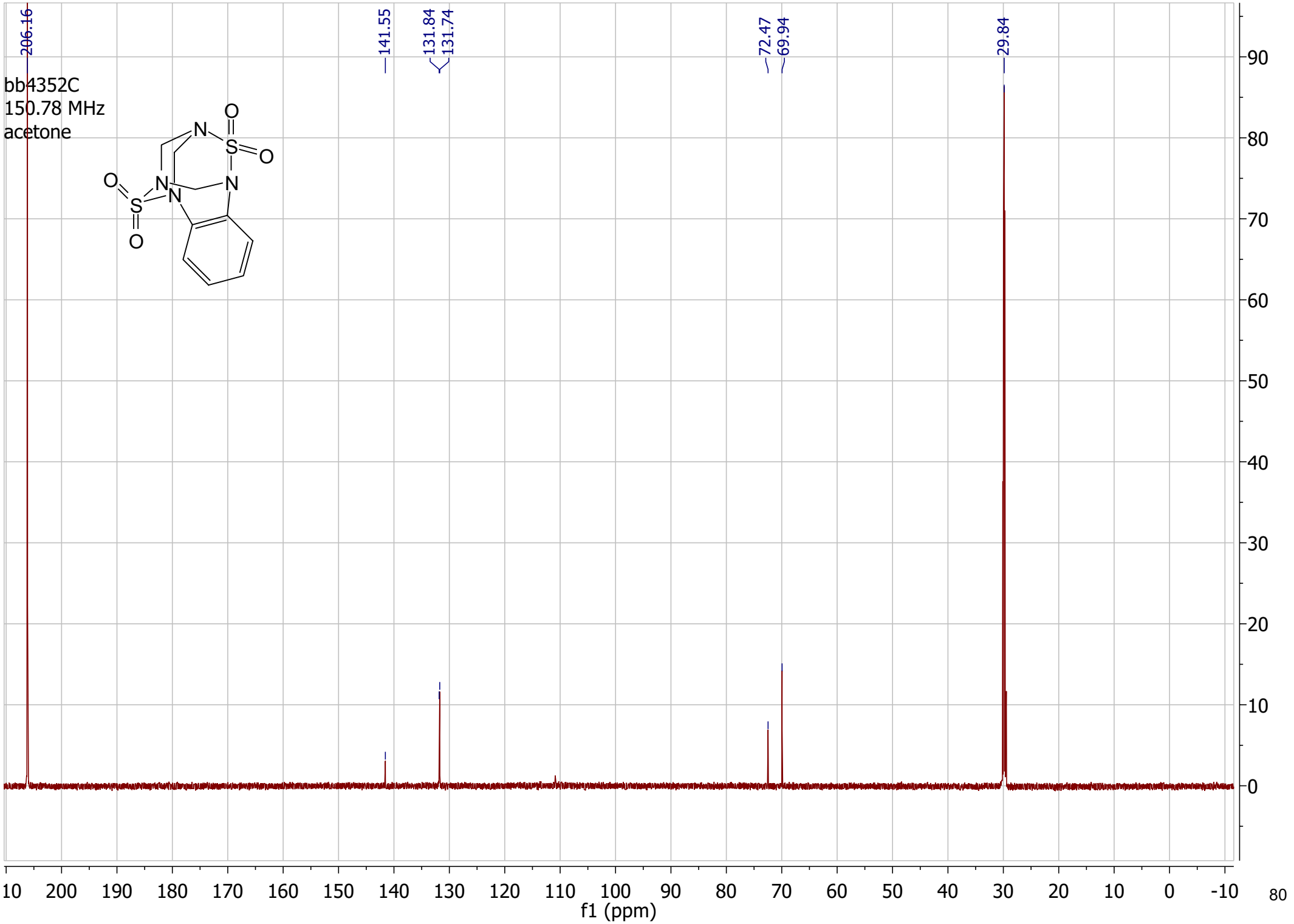

bb4362H
599.59 MHz
acetone
5.46
5.45
5.45
5.27
5.25
4.81
4.78
3.66
3.64
2.13
2.11
2.05
1.77
1.32
1.31
1.29
2.00
1.97
2.05
1.92
2.04
4.11
2.05
f1 (ppm)

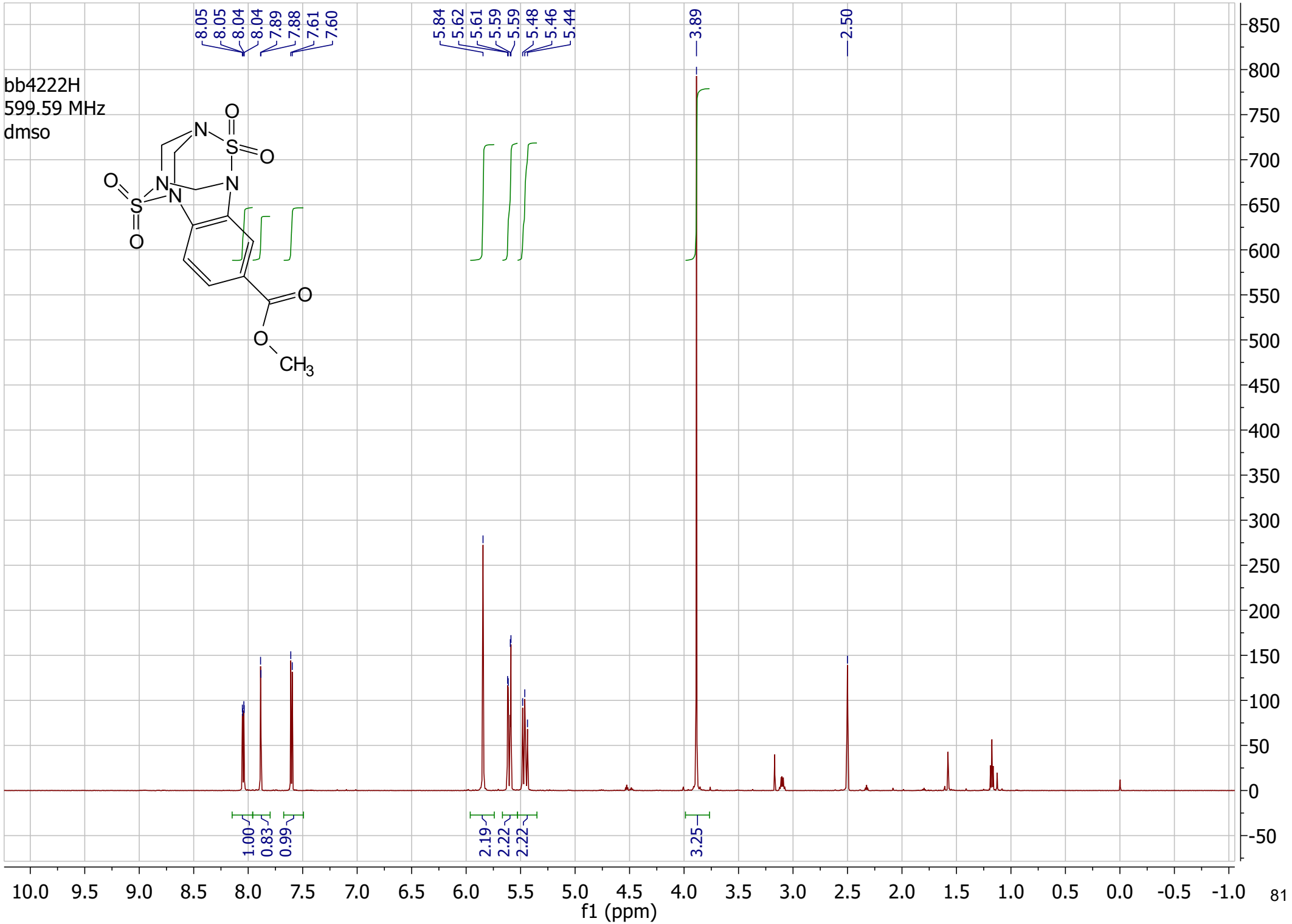

206.15
72.82
70.70
69.52
34.82
29.84
26.41
bb4362C
150.78 MHz
acetone
O
N
S
O
O
N
N
N
S
O
f1 (ppm)
76

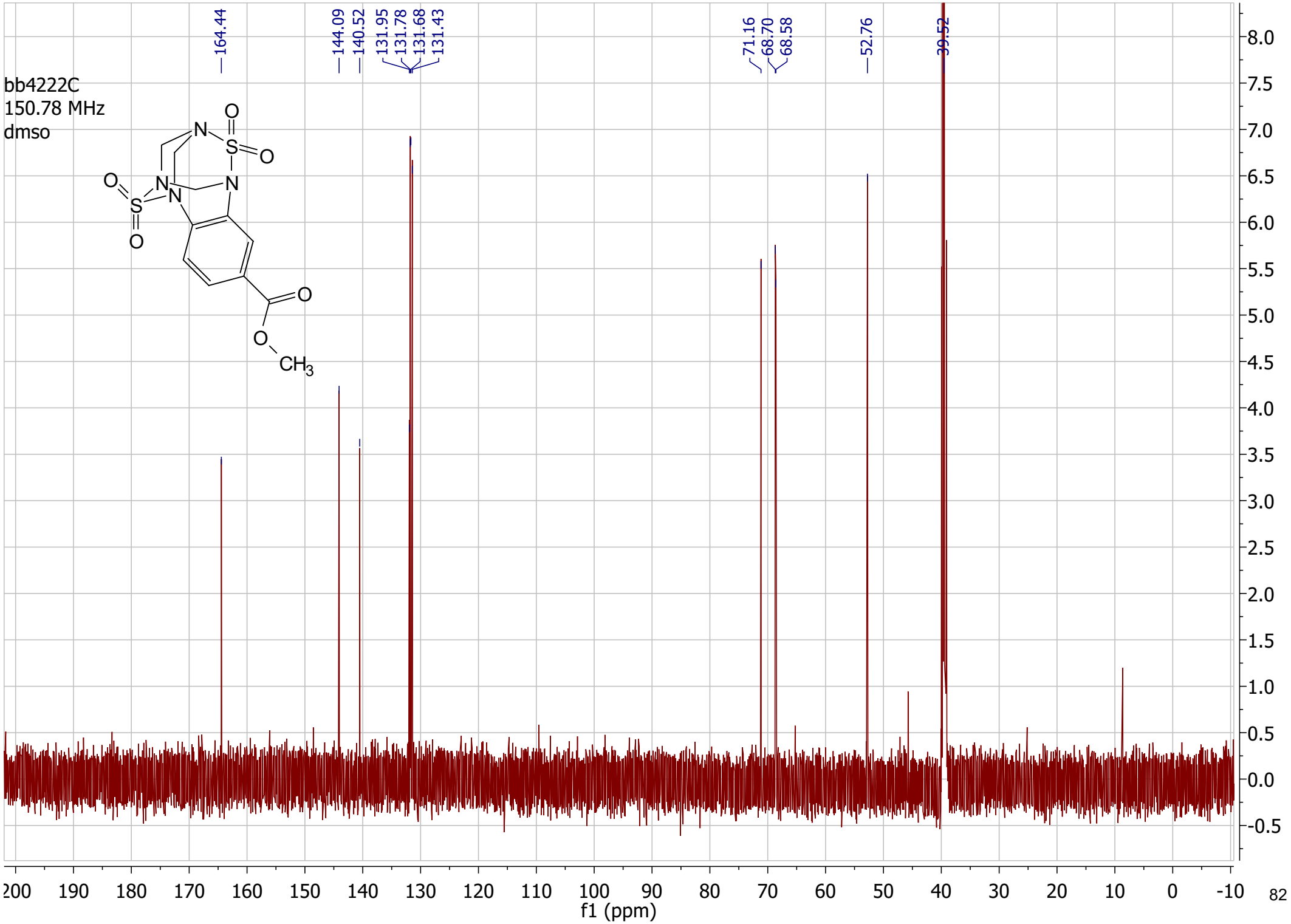

bb4562Hpure
599.59 MHz
acetone
7.39
7.37
5.62
5.48
5.46
4.65
4.63
4.51
4.49
4.23
2.86
2.05
1.77
1.59
1.41
1.18
1.04
1.98
1.00
1.79
4.13
2.23
2.06
f1 (ppm)
77

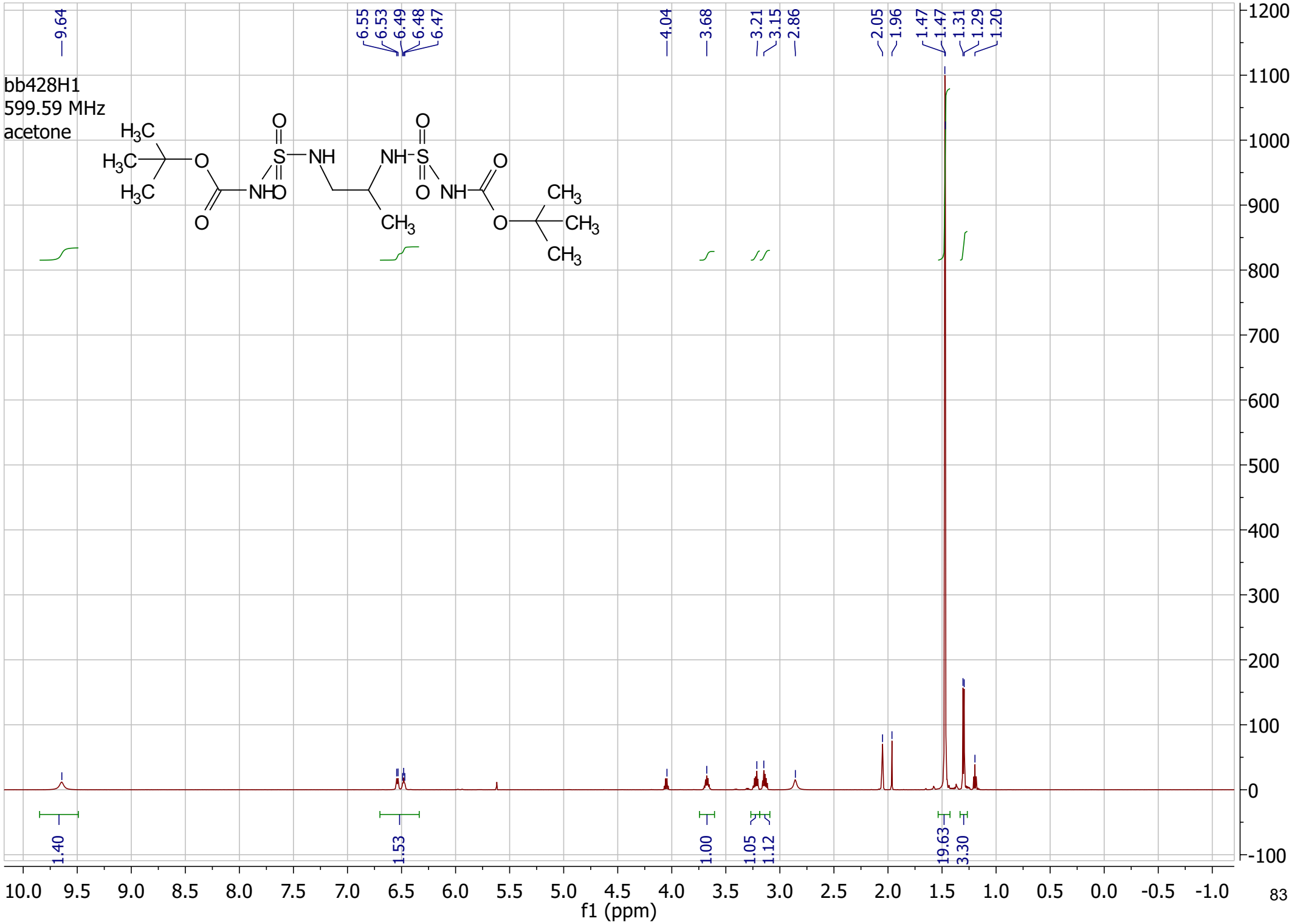

206.17
66.41
58.59
53.40
53.30
29.84
26.90
20.26
bb4562Cpure
150.78 MHz
acetone
NH
O
S
O
NH
N
N
O
S
O
f1 (ppm)

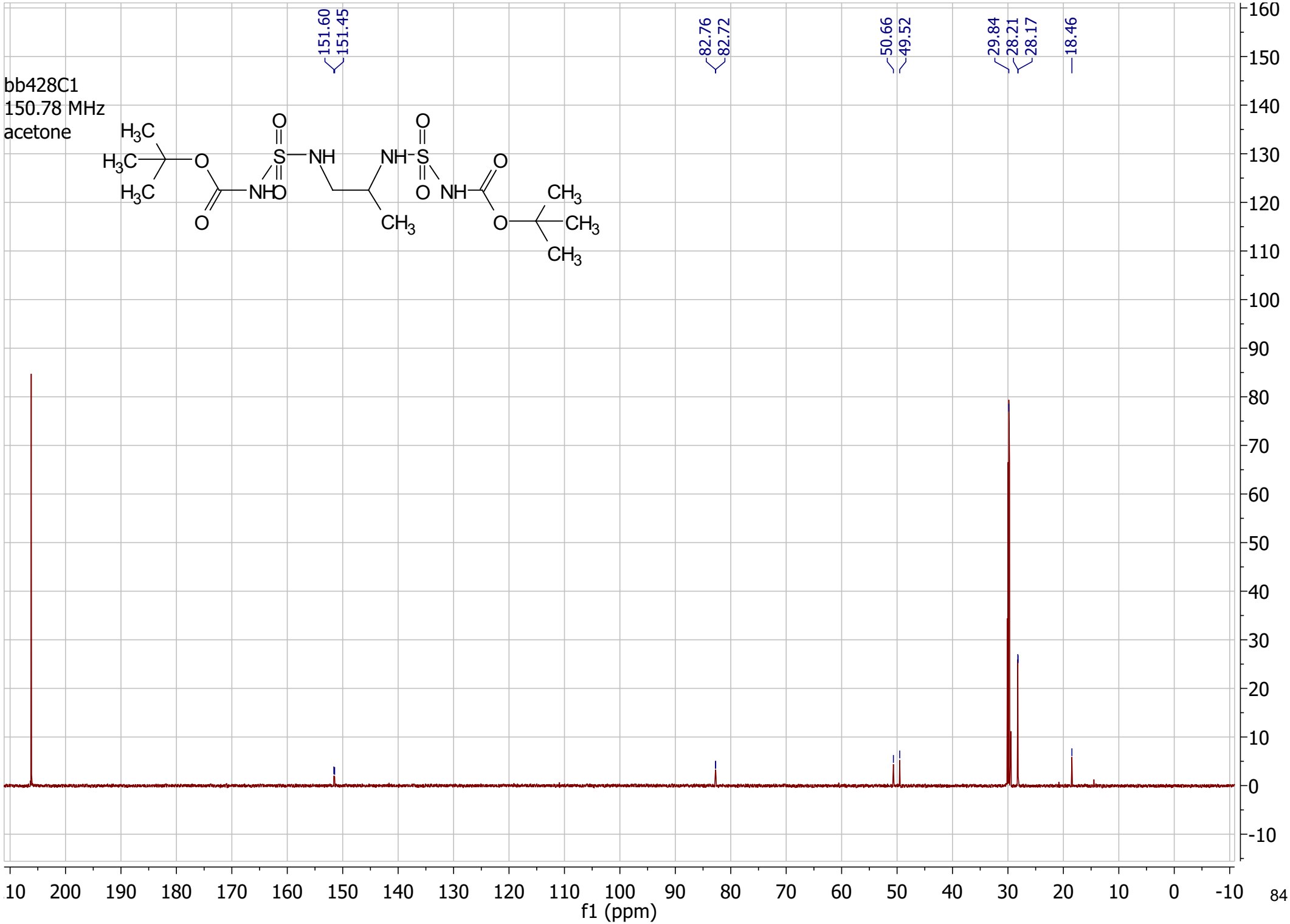

bb4352H
599.59 MHz
acetone
7.51
7.43
5.89
5.63
5.60
5.44
5.41
3.07
2.05
2.00
1.81
2.27
2.37
2.26
f1 (ppm)

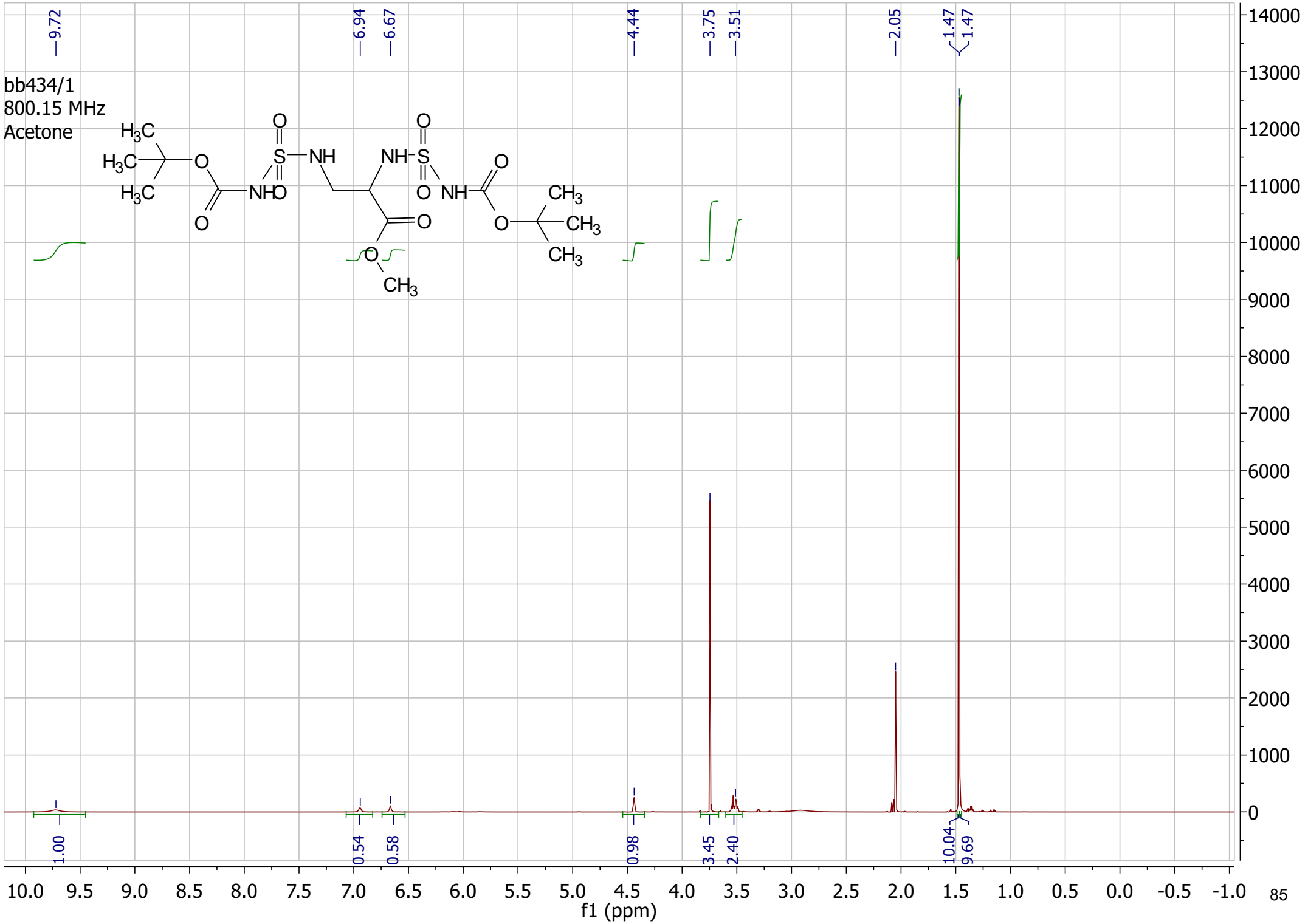

206.16
141.55
131.84
131.74
72.47
69.94
29.84
bb4352C
150.78 MHz
acetone
O
N
S
O
O
N
N
N
S
O
O
f1 (ppm)

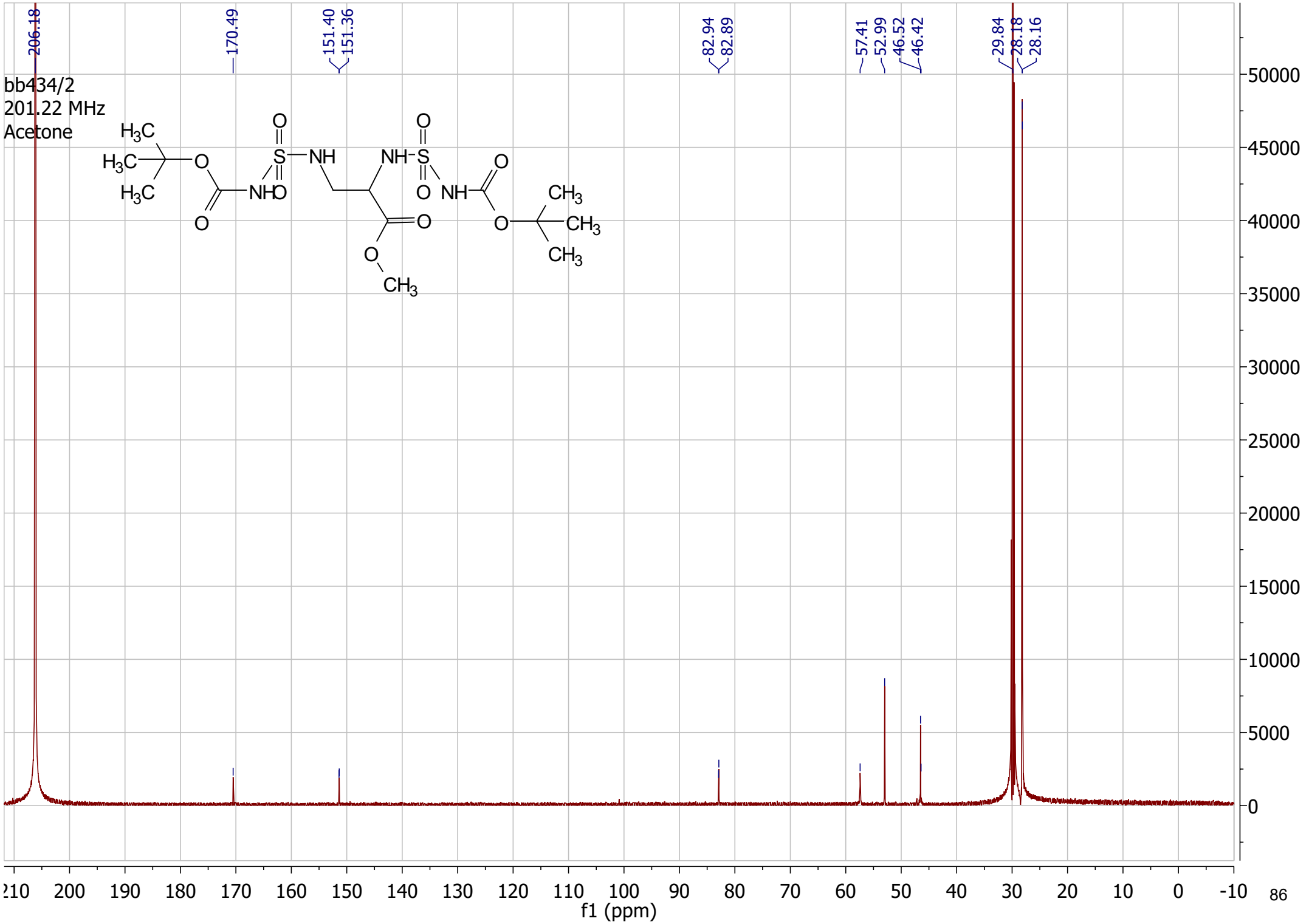

bb4222H
599.59 MHz
dmso
8.05
8.05
8.04
8.04
7.89
7.88
7.61
7.60
5.84
5.62
5.61
5.59
5.59
5.48
5.46
5.44
3.89
2.50
1.00
0.83
0.99
2.19
2.22
2.22
3.25
f1 (ppm)

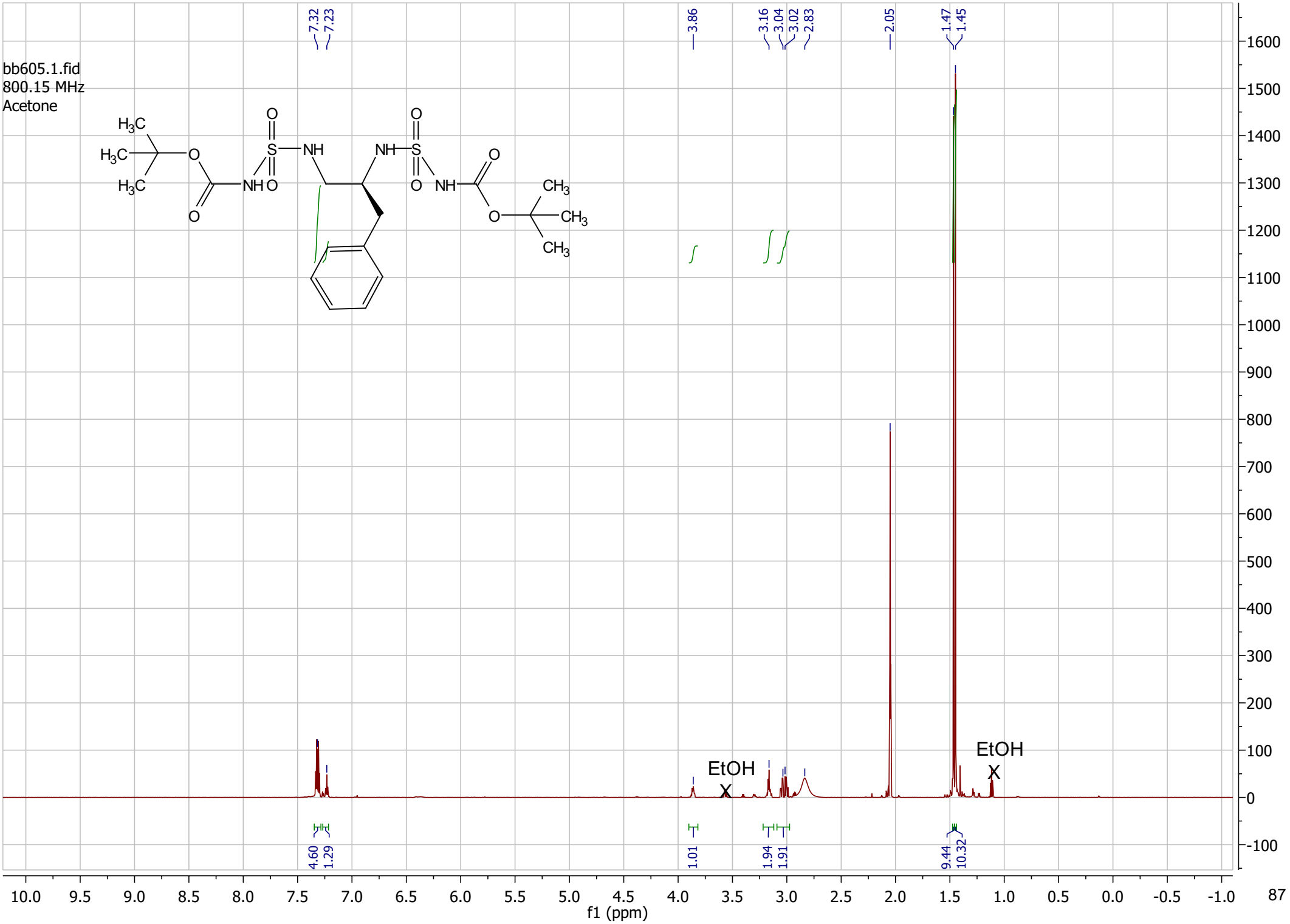

bb4222C
150.78 MHz
dmso
164.44
144.09
140.52
131.95
131.78
131.68
131.43
71.16
68.70
68.58
52.76
39.52
f1 (ppm)

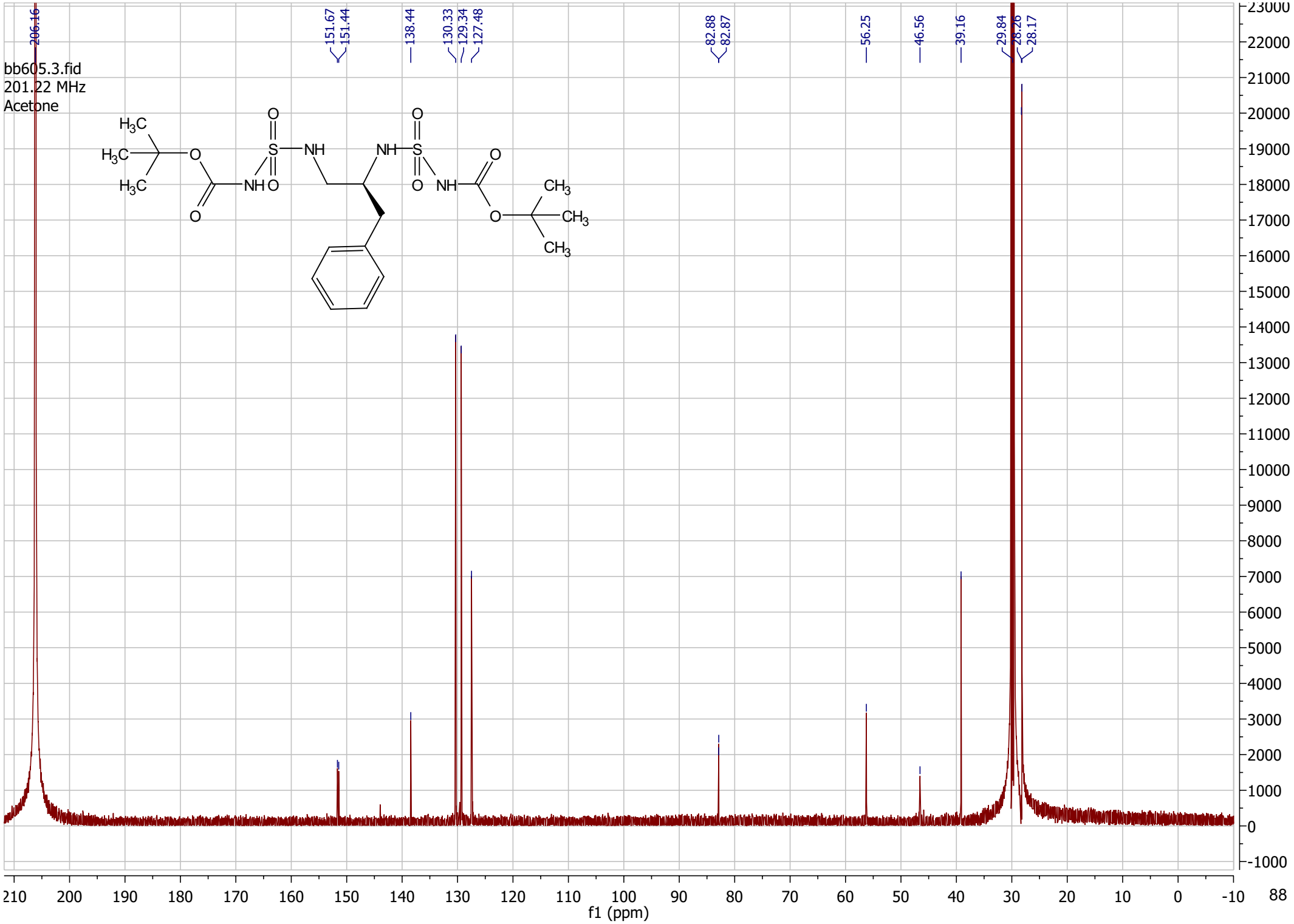

bb428H1
599.59 MHz
acetone
9.64
6.55
6.53
6.49
6.48
6.47
4.04
3.68
3.21
3.15
2.86
2.05
1.96
1.47
1.47
1.31
1.29
1.20
1.40
1.53
1.00
1.05
1.12
19.63
3.30
f1 (ppm)

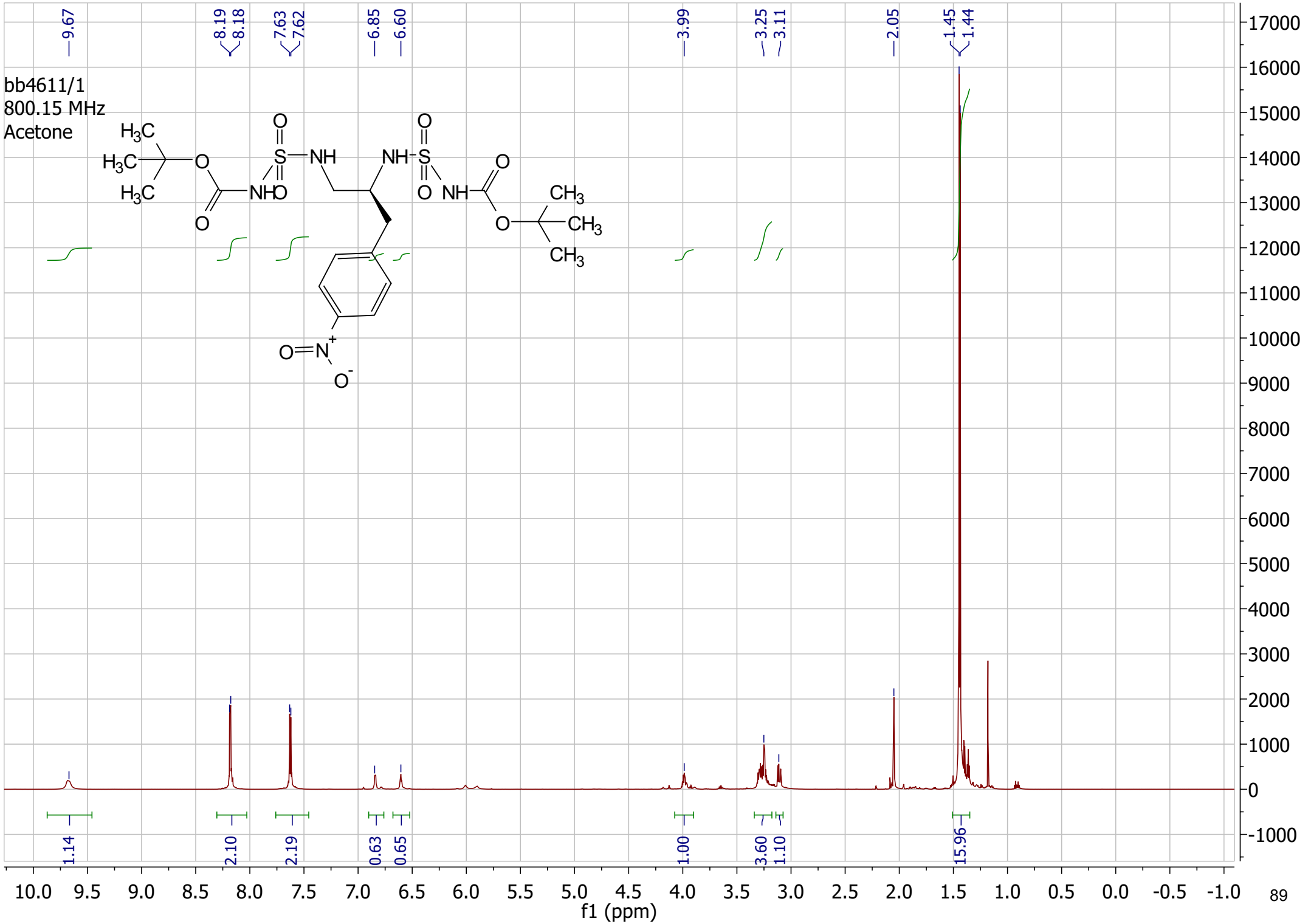

bb428C1
150.78 MHz
acetone
151.60
151.45
82.76
82.72
50.66
49.52
29.84
28.21
28.17
18.46
f1 (ppm)

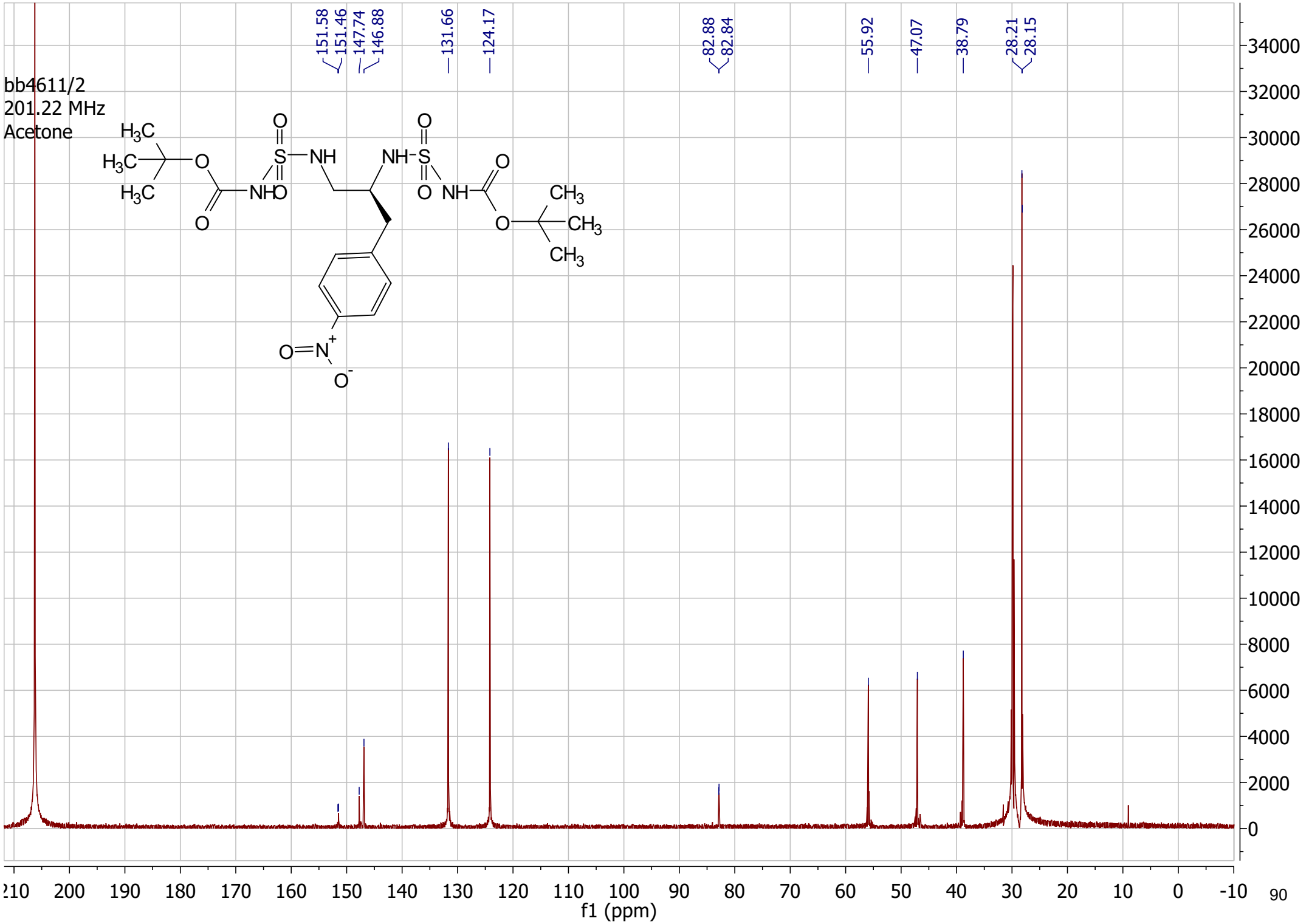

bb434/1
800.15 MHz
Acetone
9.72
6.94
6.67
4.44
3.75
3.51
2.05
1.47
1.47
1.00
0.54
0.58
0.98
3.45
2.40
10.04
9.69
f1 (ppm)

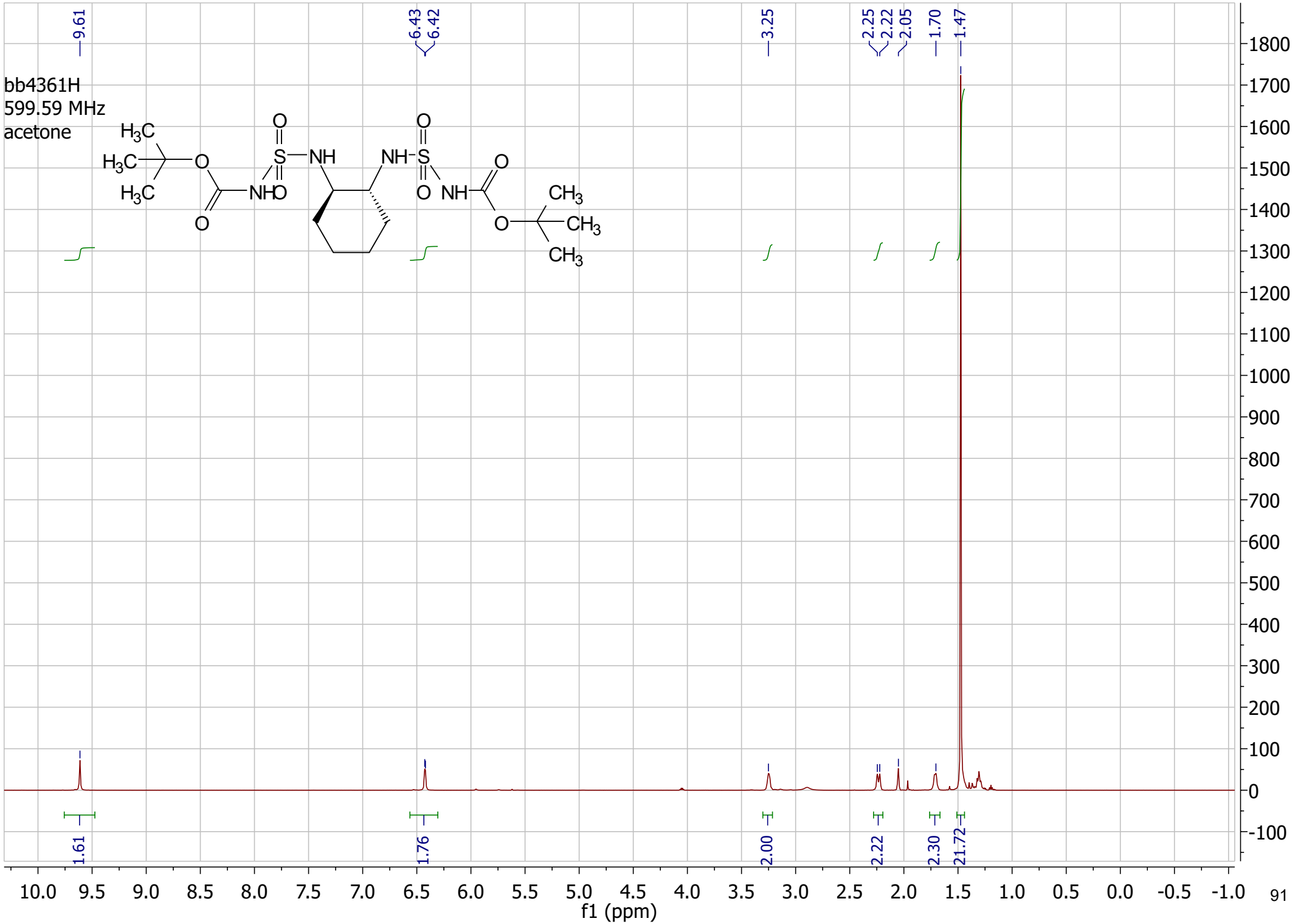

206.18
170.49
151.40
151.36
82.94
82.89
57.41
52.99
46.52
46.42
29.84
28.18
28.16
bb434/2
201.22 MHz
Acetone
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

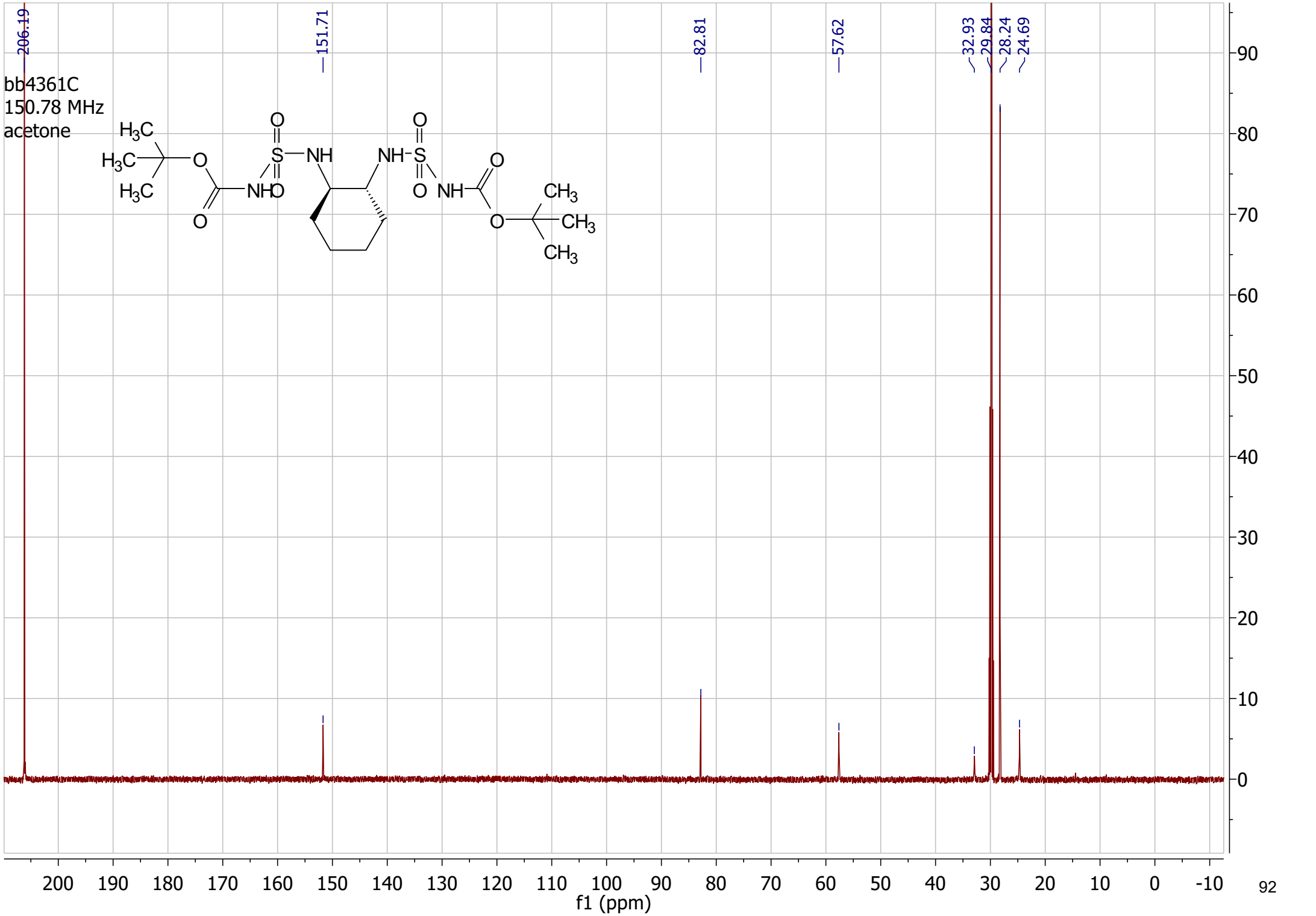

bb605.1.fid
800.15 MHz
Acetone
7.32
7.23
3.86
3.16
3.04
3.02
2.83
2.05
1.47
1.45
EtOH
X
EtOH
X
4.60
1.29
1.01
1.94
1.91
9.44
10.32
f1 (ppm)

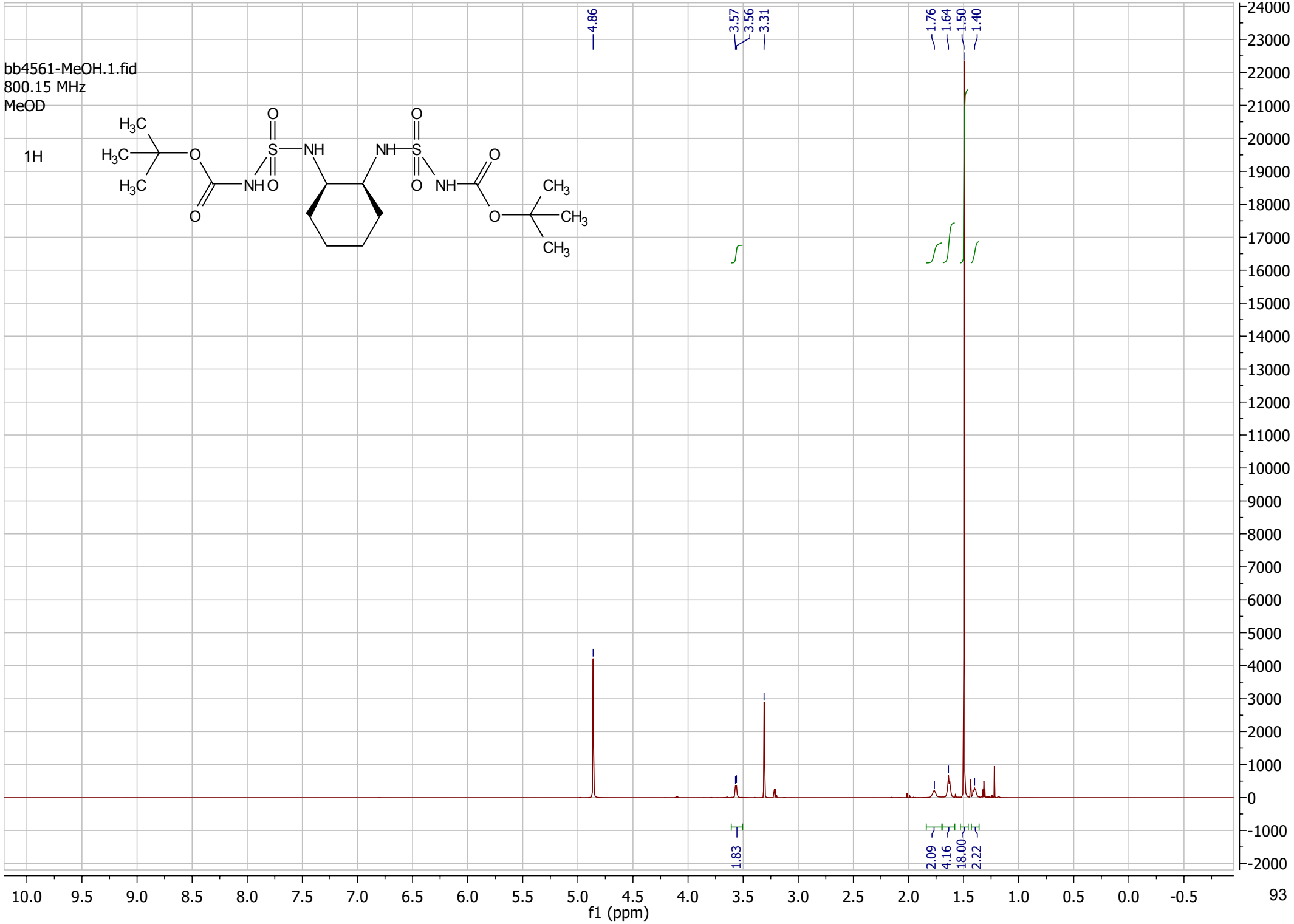

bb605.3.fid
201.22 MHz
Acetone
206.16
151.67
151.44
138.44
130.33
129.34
127.48
82.88
82.87
56.25
46.56
39.16
29.84
28.26
28.17
f1 (ppm)

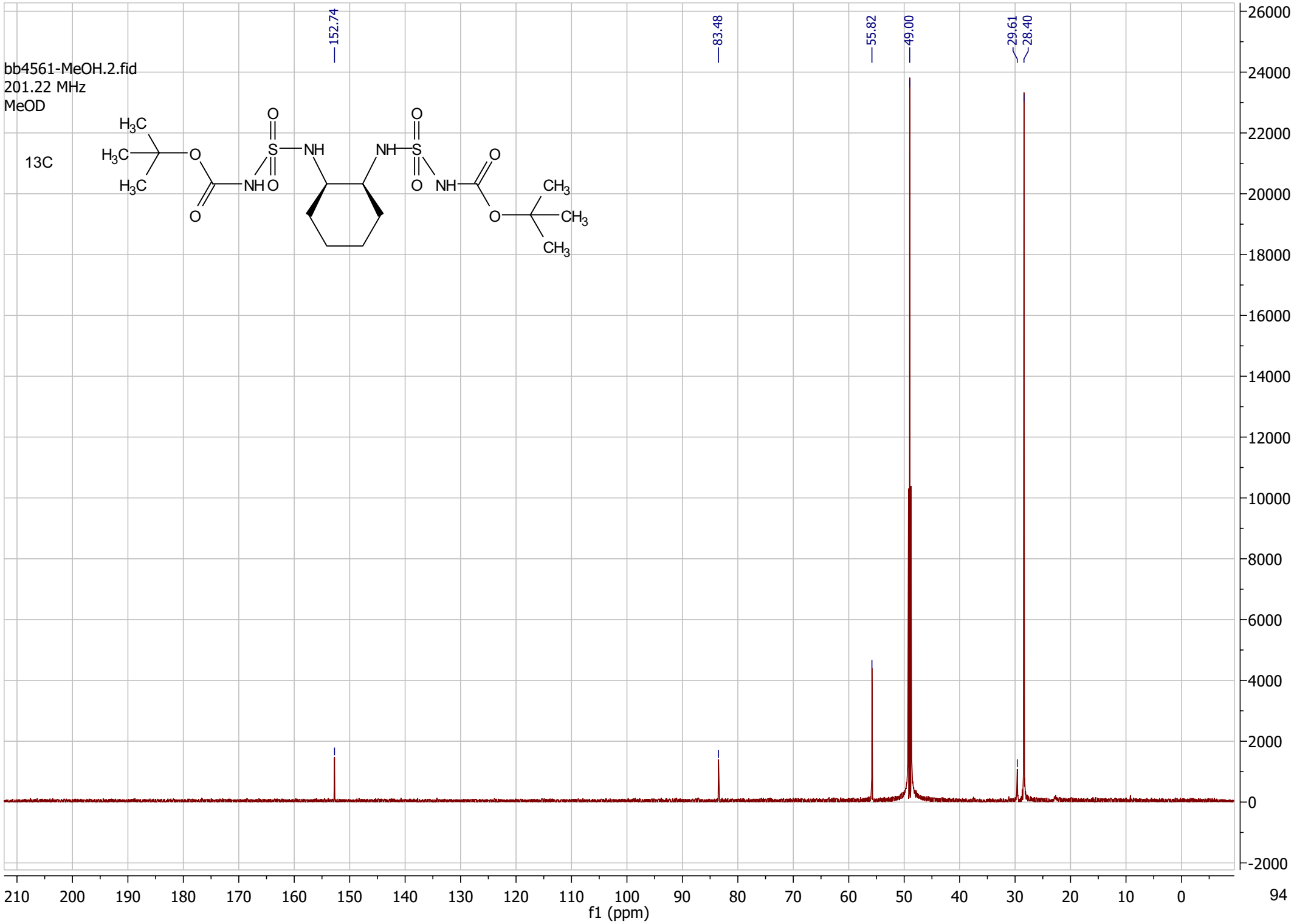

bb4611/1
800.15 MHz
Acetone
9.67
8.19
8.18
7.63
7.62
6.85
6.60
3.99
3.25
3.11
2.05
1.45
1.44
1.14
2.10
2.19
0.63
0.65
1.00
3.60
1.10
15.96
f1 (ppm)

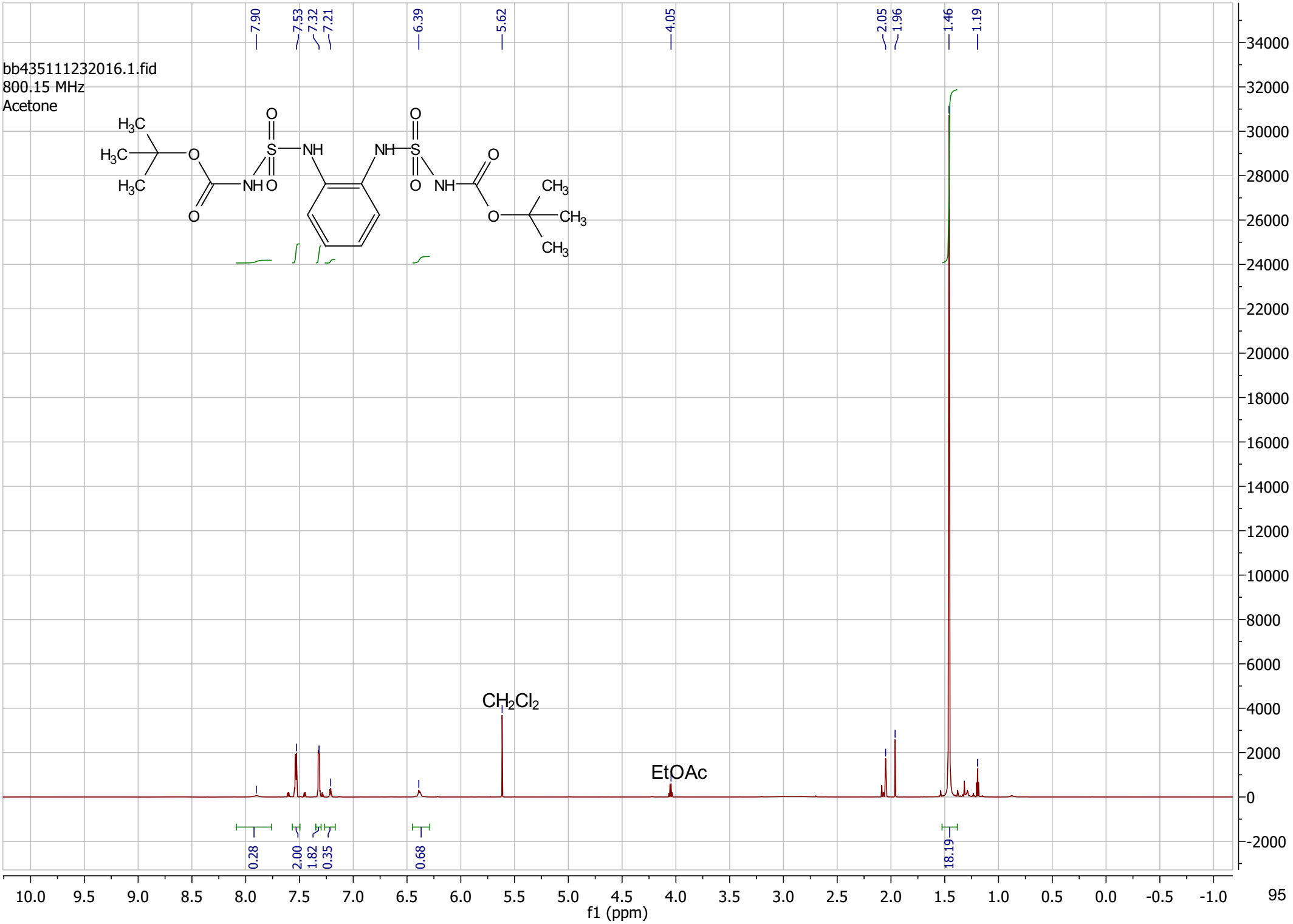

bb4611/2
201.22 MHz
Acetone
151.58
151.46
147.74
146.88
131.66
124.17
82.88
82.84
55.92
47.07
38.79
28.21
28.15
f1 (ppm)

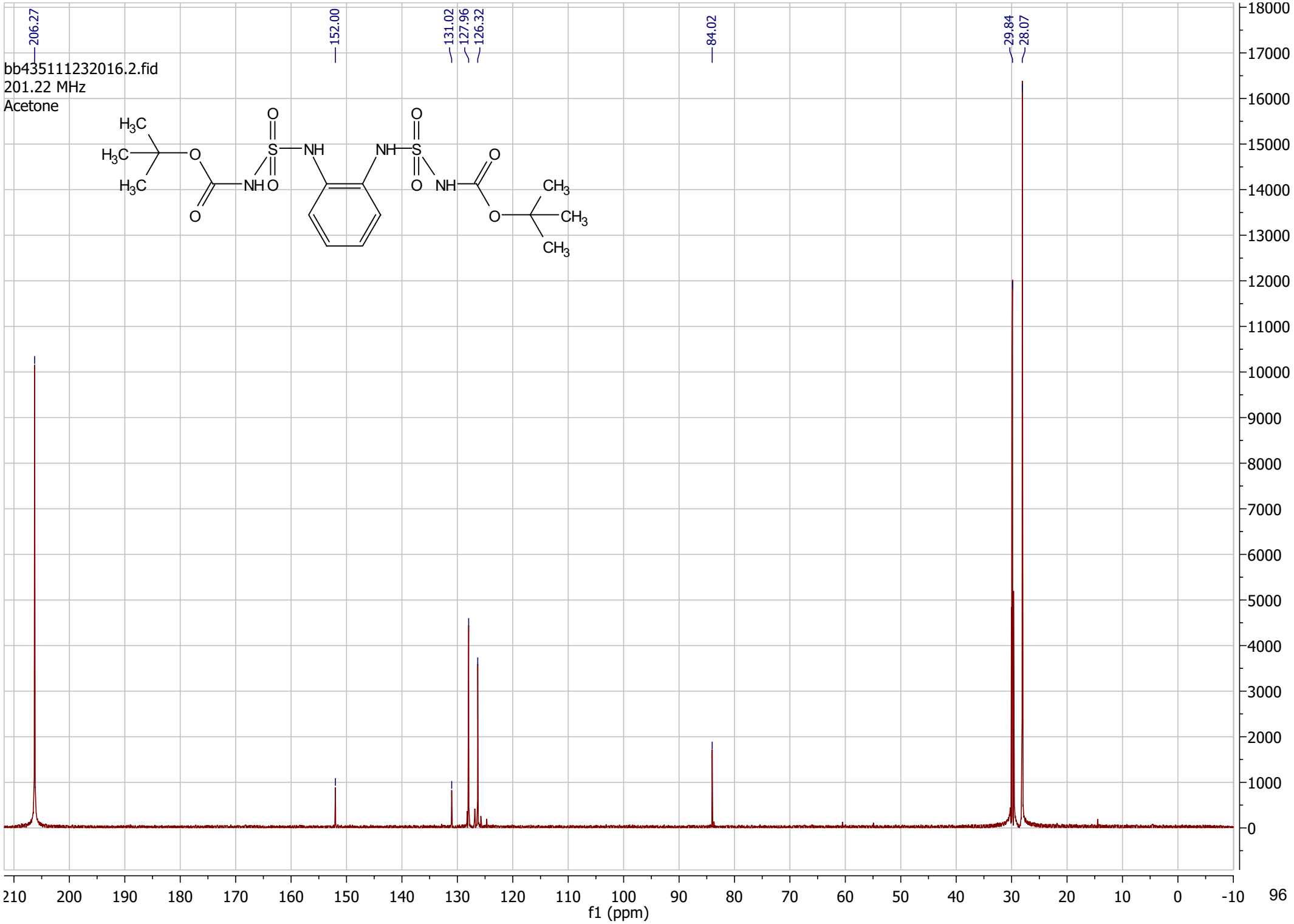

bb4361H
599.59 MHz
acetone
9.61
6.43
6.42
3.25
2.25
2.22
2.05
1.70
1.47
1.61
1.76
2.00
2.22
2.30
21.72
f1 (ppm)

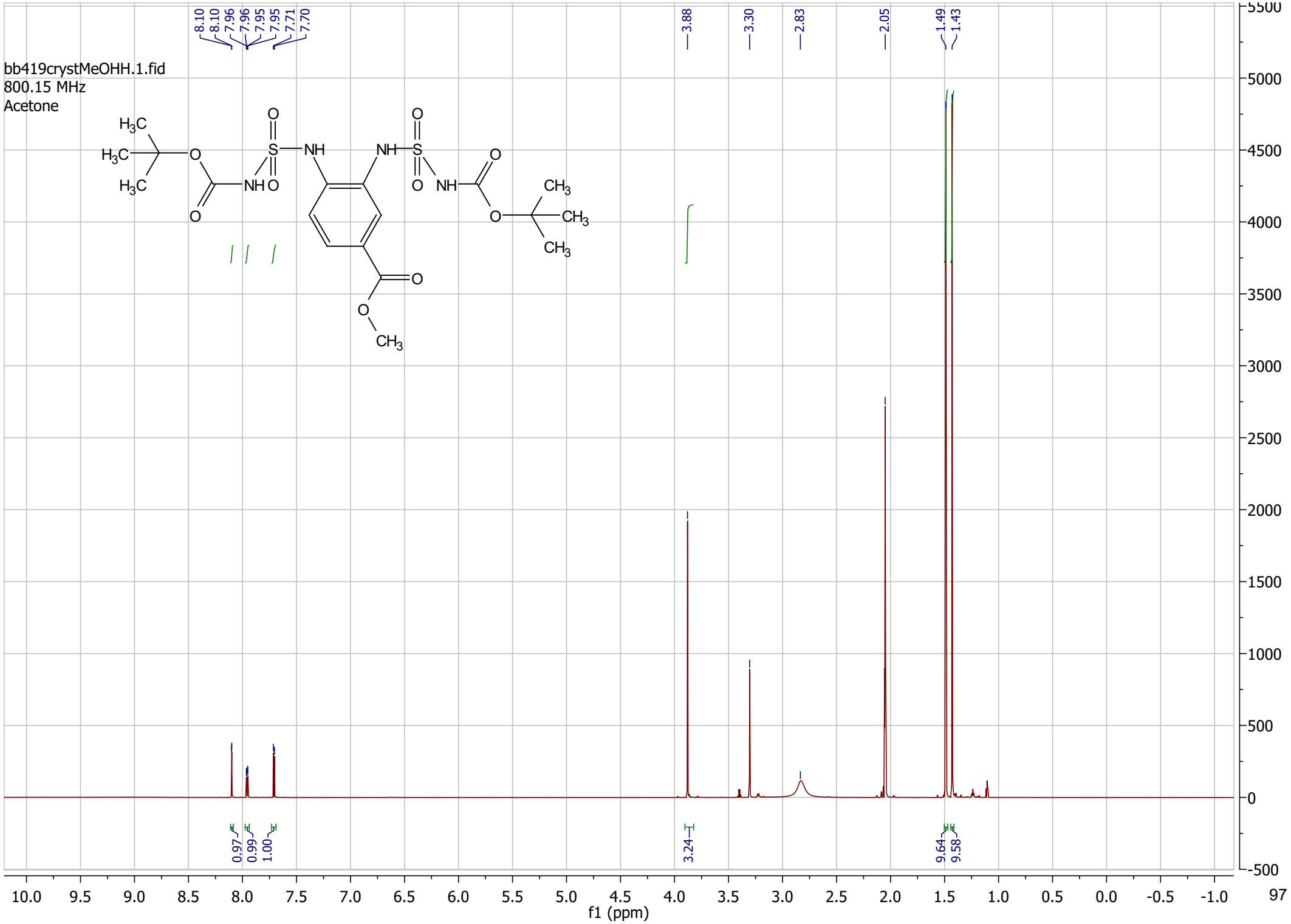

206.19
151.71
82.81
57.62
32.93
29.84
28.24
24.69
bb4361C
150.78 MHz
acetone
f1 (ppm)

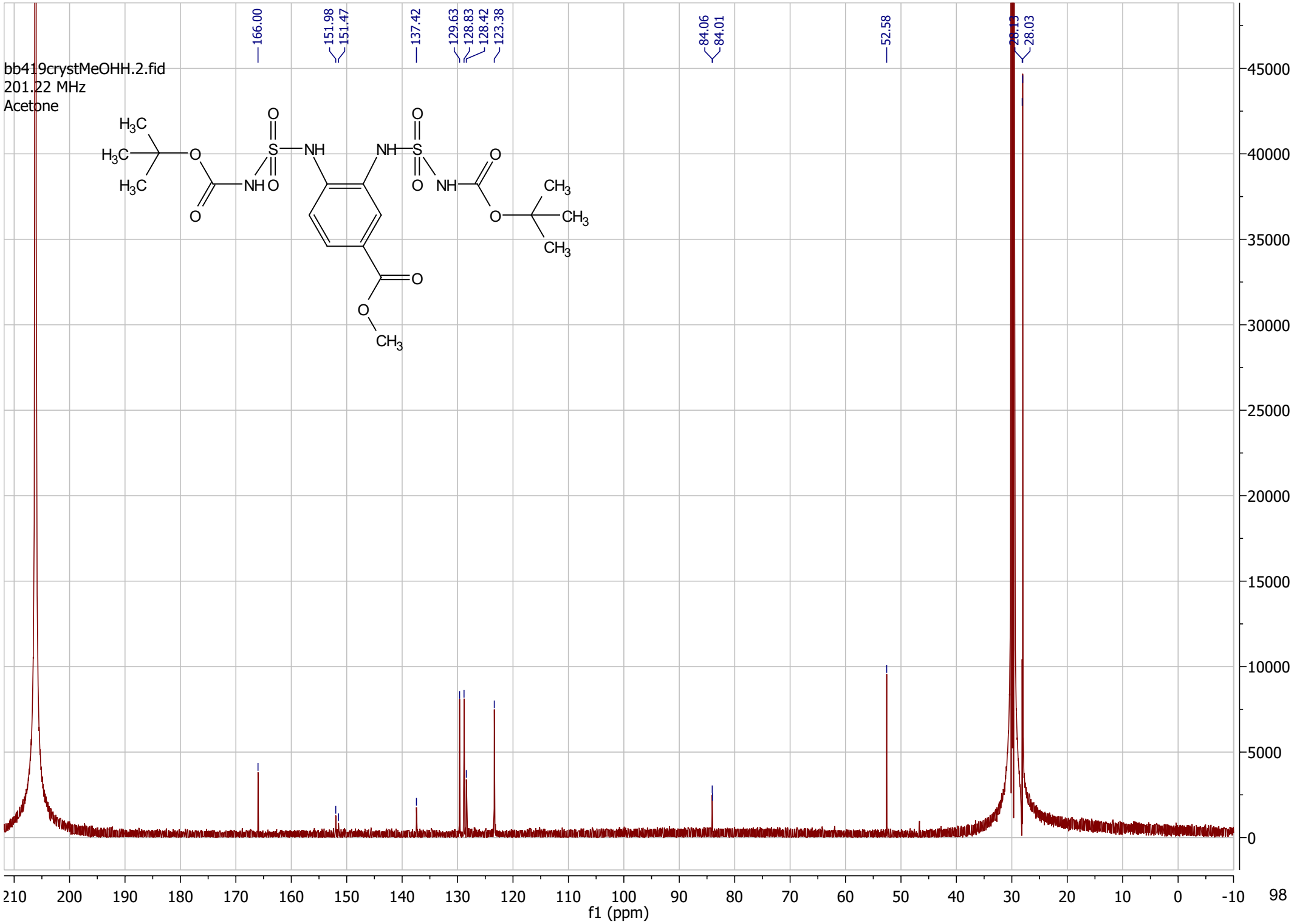

bb4561-MeOH.1.fid
800.15 MHz
MeOD
1H
4.86
3.57
3.56
3.31
1.76
1.64
1.50
1.40
1.83
2.09
4.16
18.00
2.22
f1 (ppm)
93

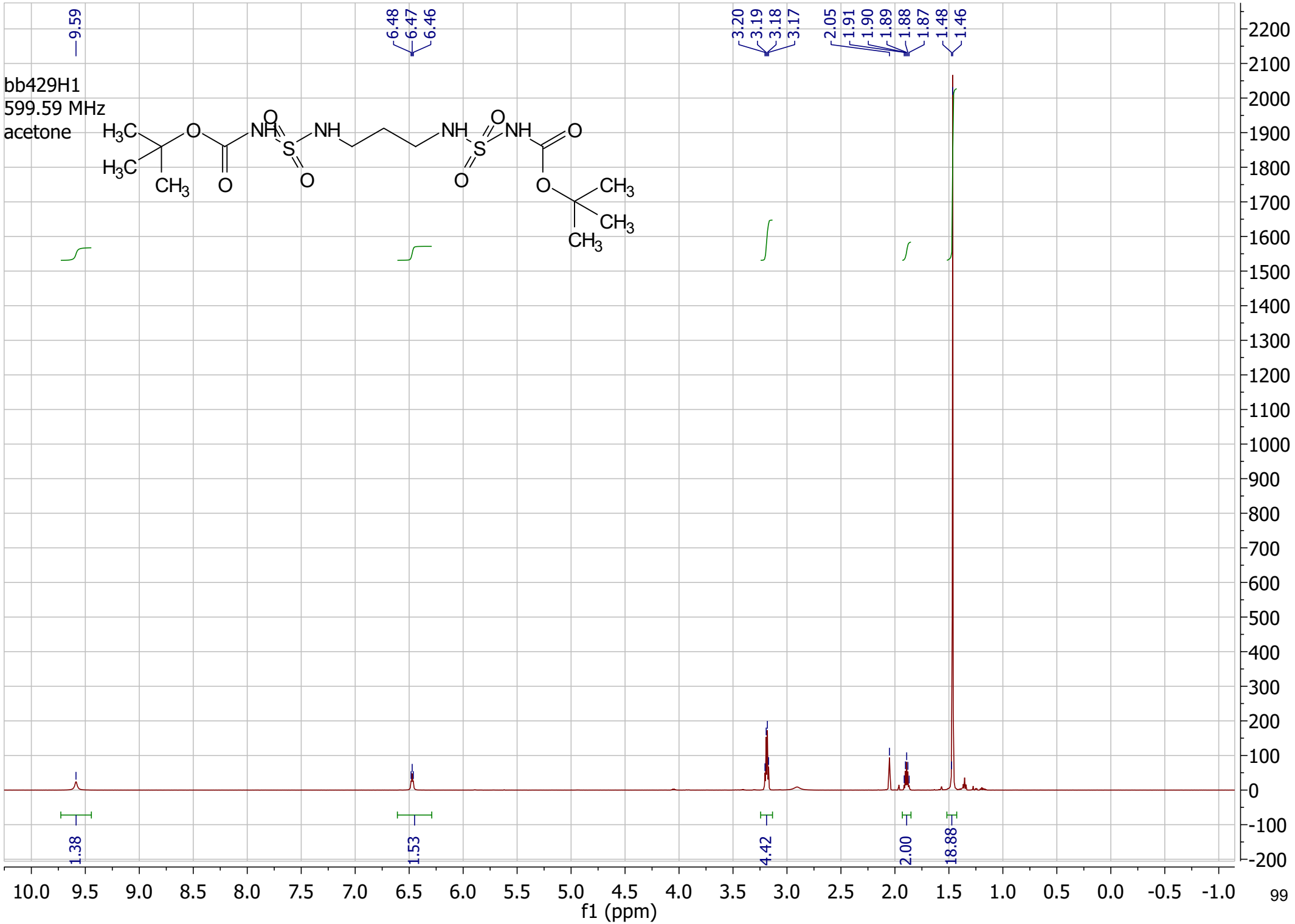

bb4561-MeOH.2.fid
201.22 MHz
MeOD
13C
152.74
83.48
55.82
49.00
29.61
28.40
f1 (ppm)

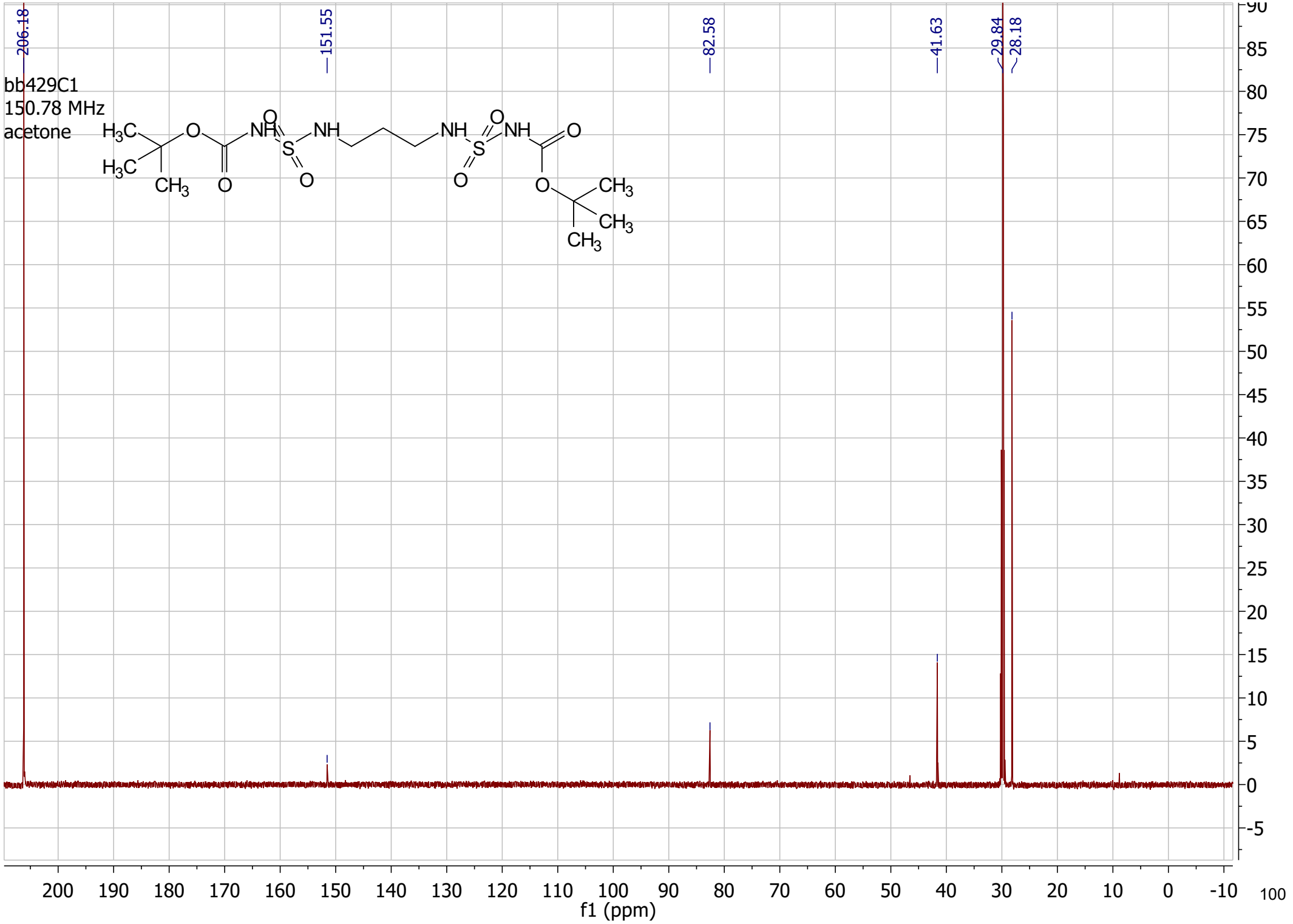

bb435111232016.1.fid
800.15 MHz
Acetone
7.90
7.53
7.32
7.21
6.39
5.62
4.05
2.05
1.96
1.46
1.19
CH2Cl2
EtOAc
0.28
2.00
1.82
0.35
0.68
18.19
f1 (ppm)

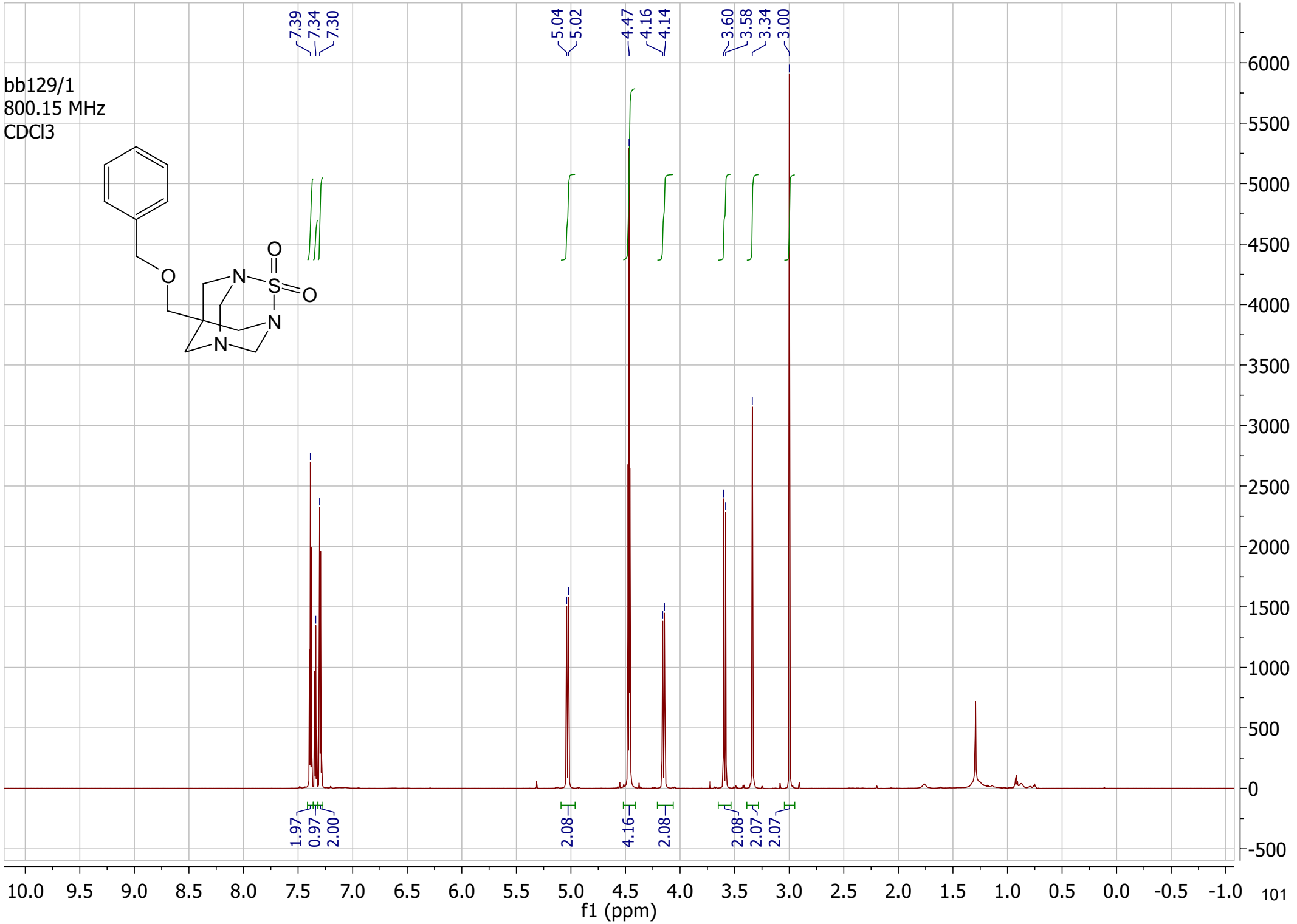

206.27
152.00
131.02
127.96
126.32
84.02
29.84
28.07
bb435111232016.2.fid
201.22 MHz
Acetone
f1 (ppm)

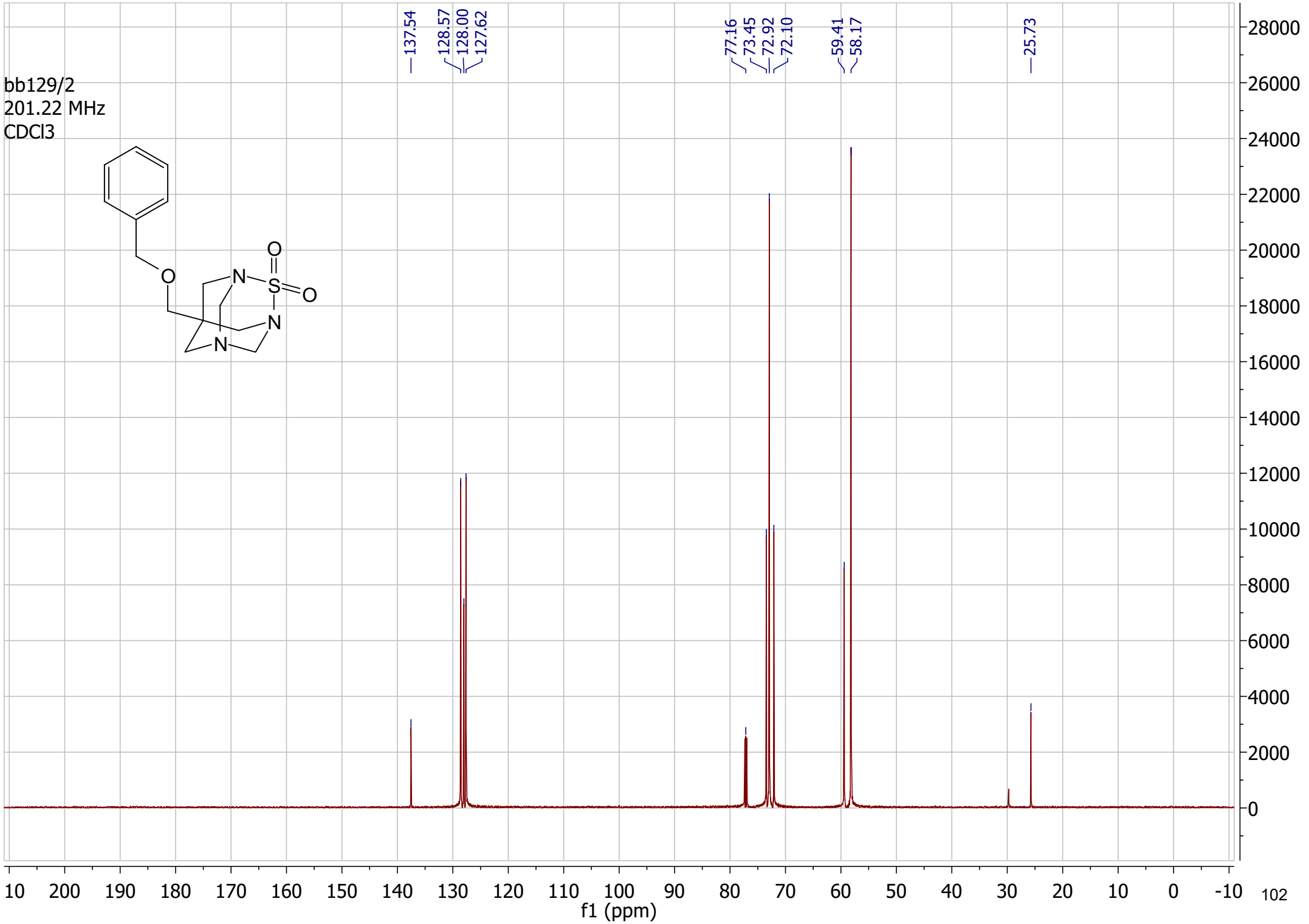

bb419crystMeOHH.1.fid
800.15 MHz
Acetone
8.10
8.10
7.96
7.96
7.95
7.95
7.71
7.70
3.88
3.30
2.83
2.05
1.49
1.43
0.97
0.99
1.00
3.24
9.64
9.58
f1 (ppm)

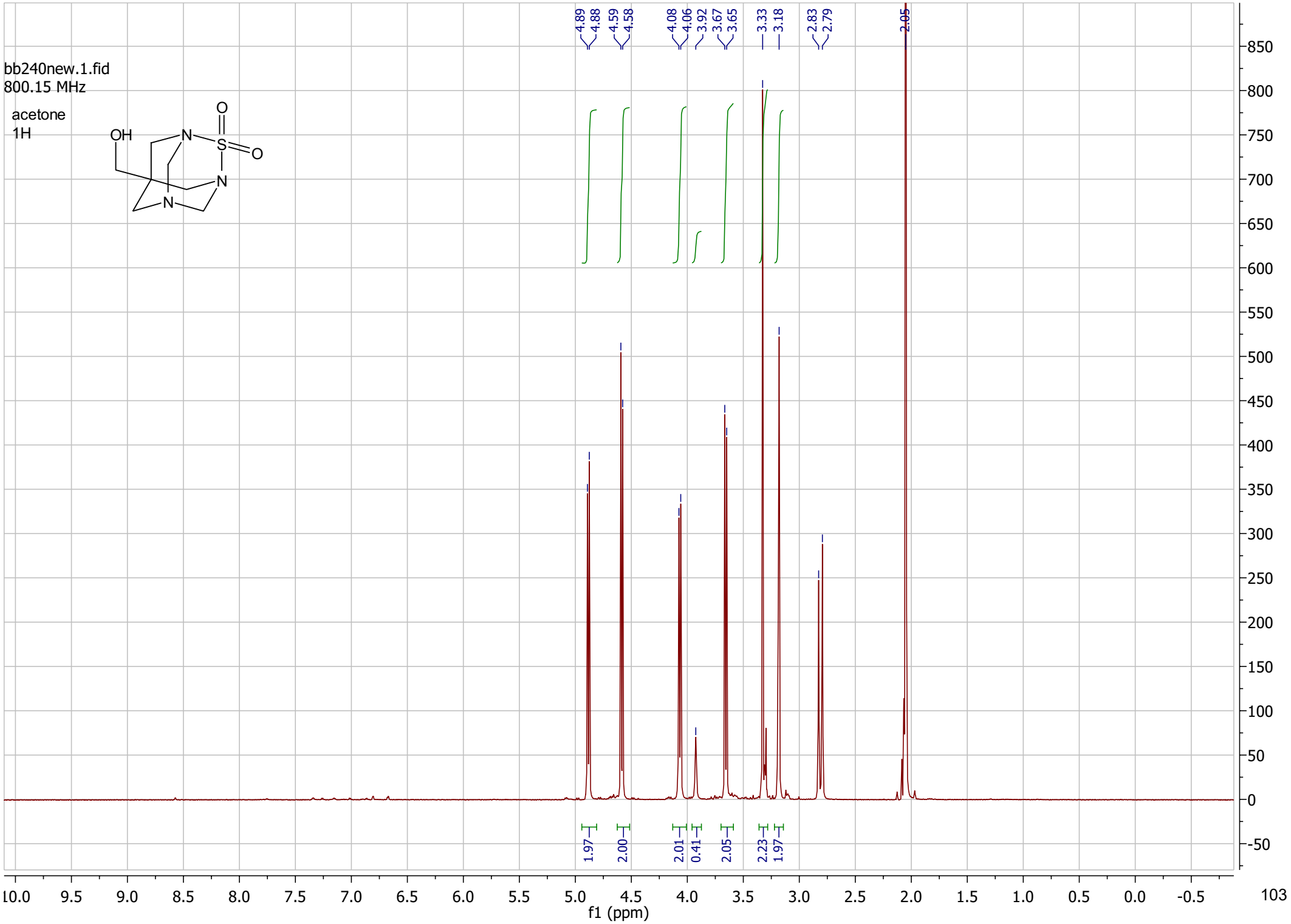

bb419crystMeOHH.2.fid
201.22 MHz
Acetone
166.00
151.98
151.47
137.42
129.63
128.83
128.42
123.38
84.06
84.01
52.58
28.13
28.03
f1 (ppm)

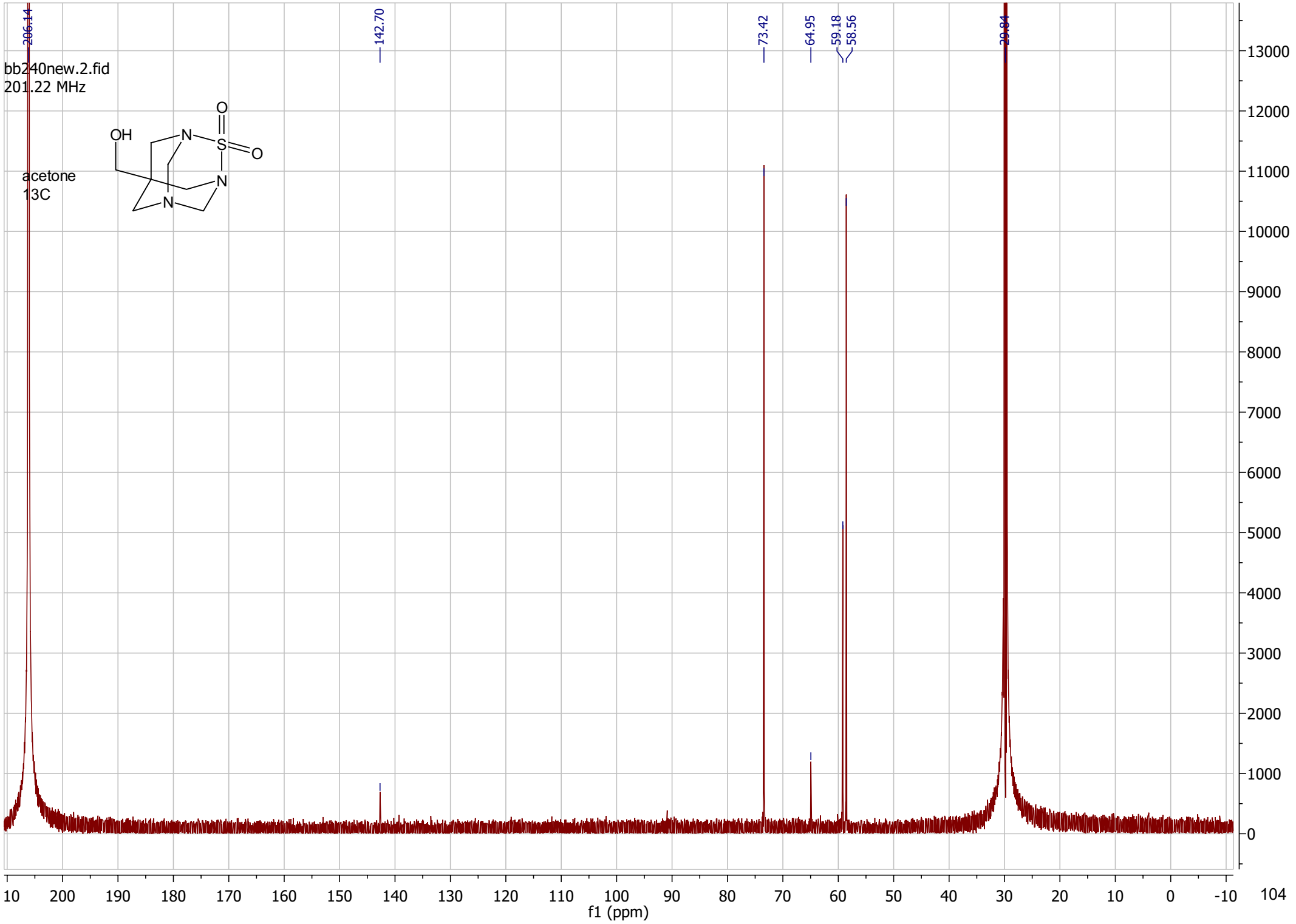

bb429H1
599.59 MHz
acetone
9.59
6.48
6.47
6.46
3.20
3.19
3.18
3.17
2.05
1.91
1.90
1.89
1.88
1.87
1.48
1.46
1.38
1.53
4.42
2.00
18.88
f1 (ppm)
99

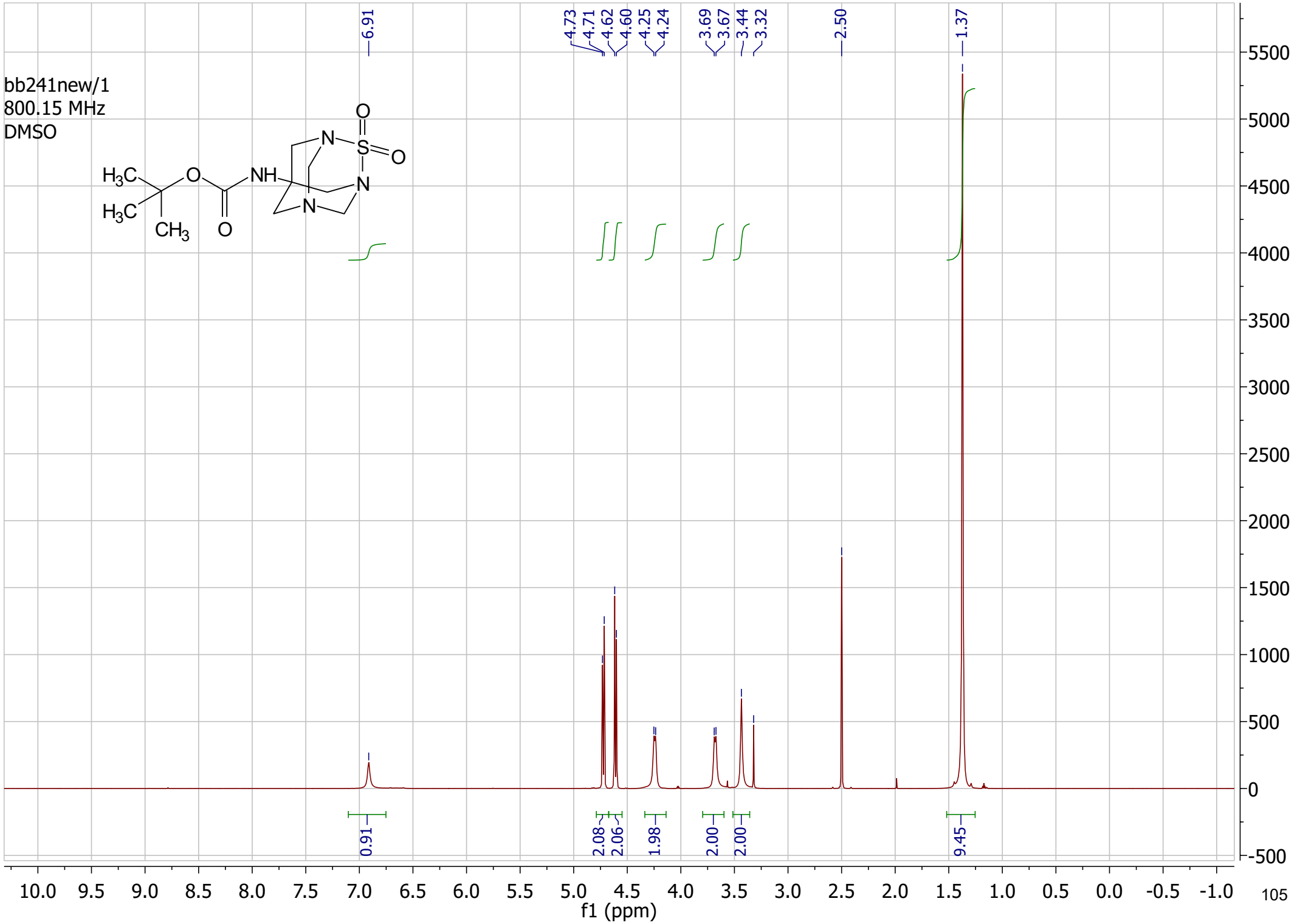

206.18
151.55
82.58
41.63
29.84
28.18
bb429C1
150.78 MHz
acetone
f1 (ppm)

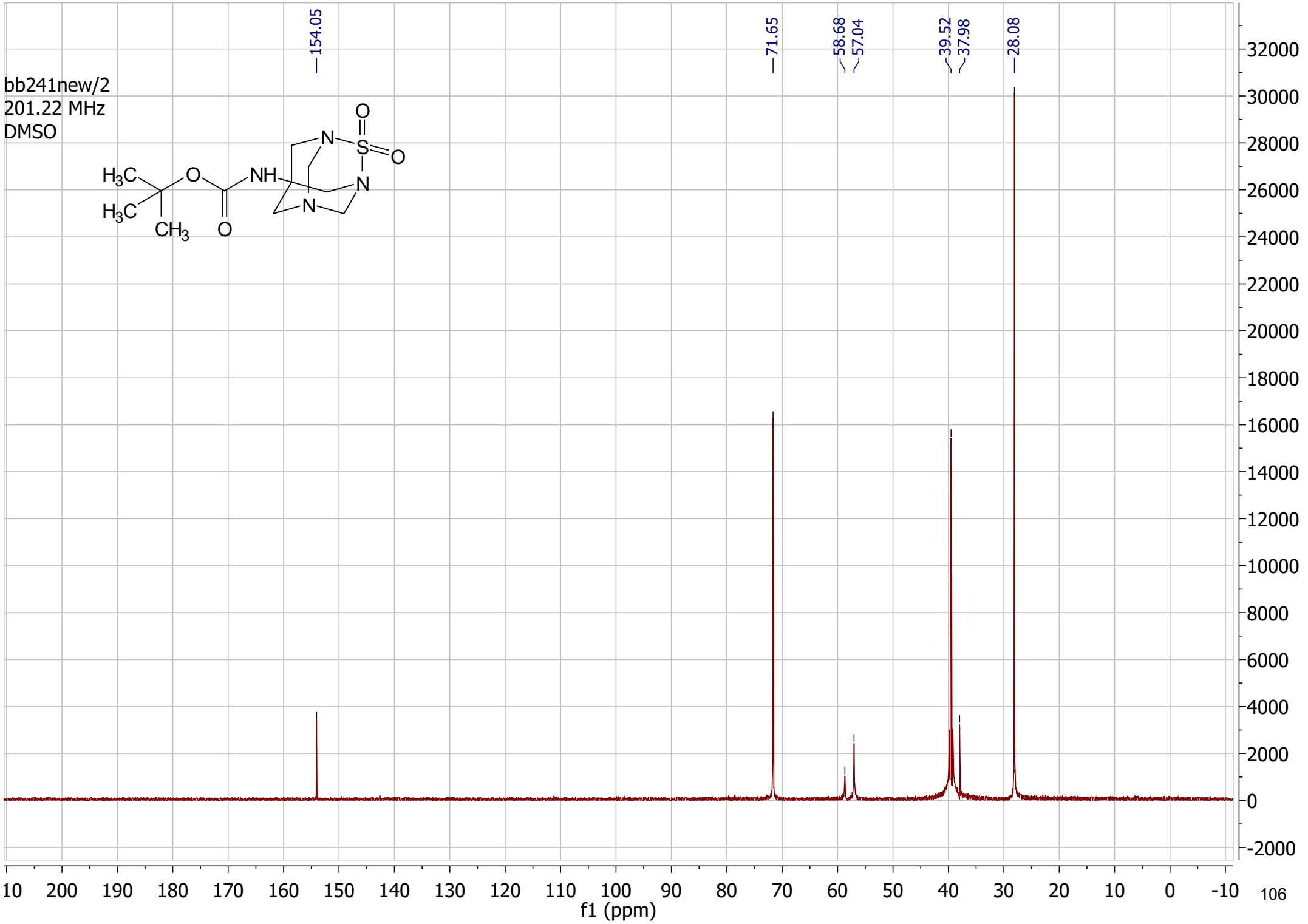

bb129/1
800.15 MHz
CDCl3
7.39
7.34
7.30
5.04
5.02
4.47
4.16
4.14
3.60
3.58
3.34
3.00
1.97
0.97
2.00
2.08
4.16
2.08
2.08
2.07
2.07
f1 (ppm)

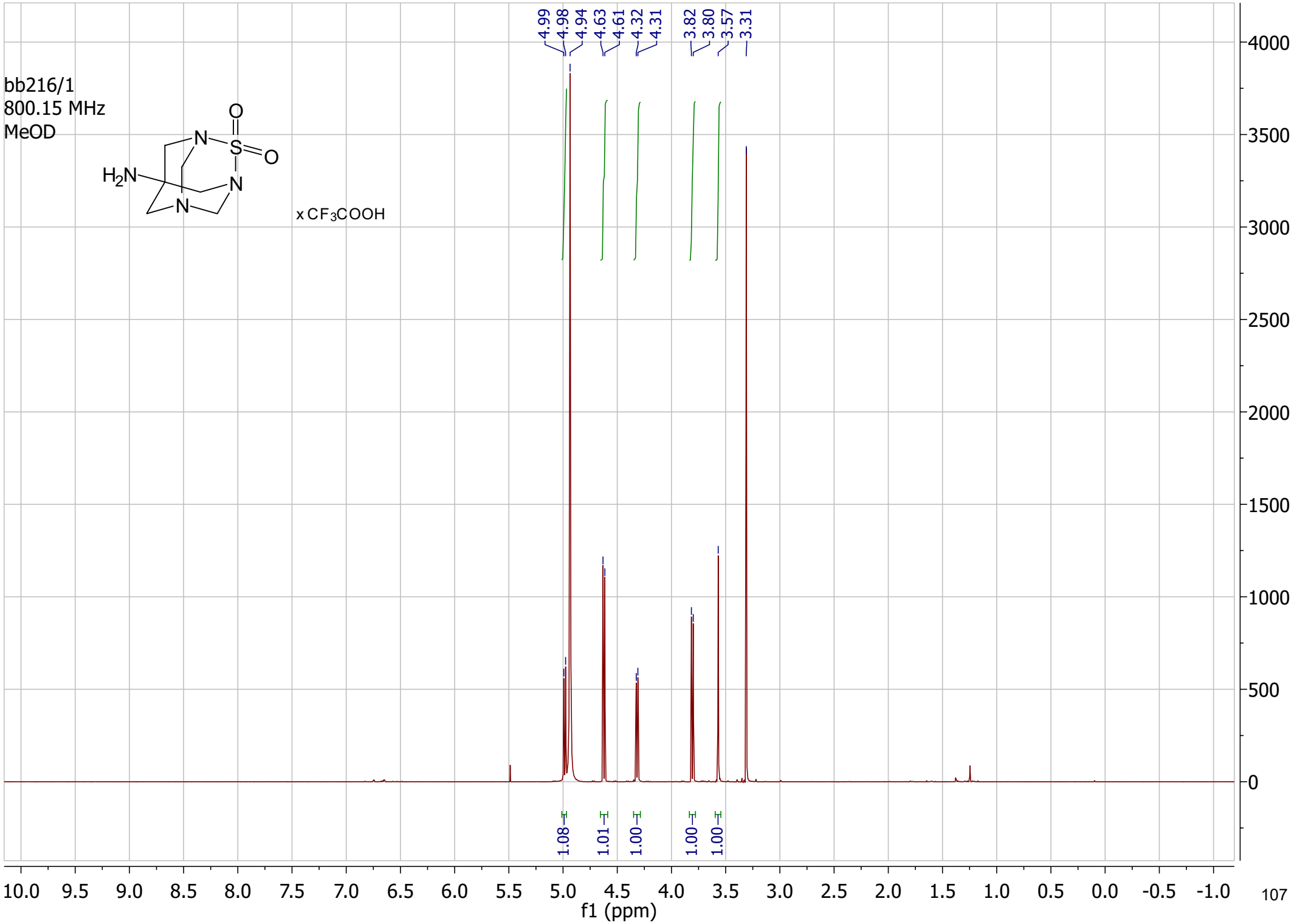

bb129/2
201.22 MHz
CDCl3
137.54
128.57
128.00
127.62
77.16
73.45
72.92
72.10
59.41
58.17
25.73
O
N
S
O
O
N
N
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

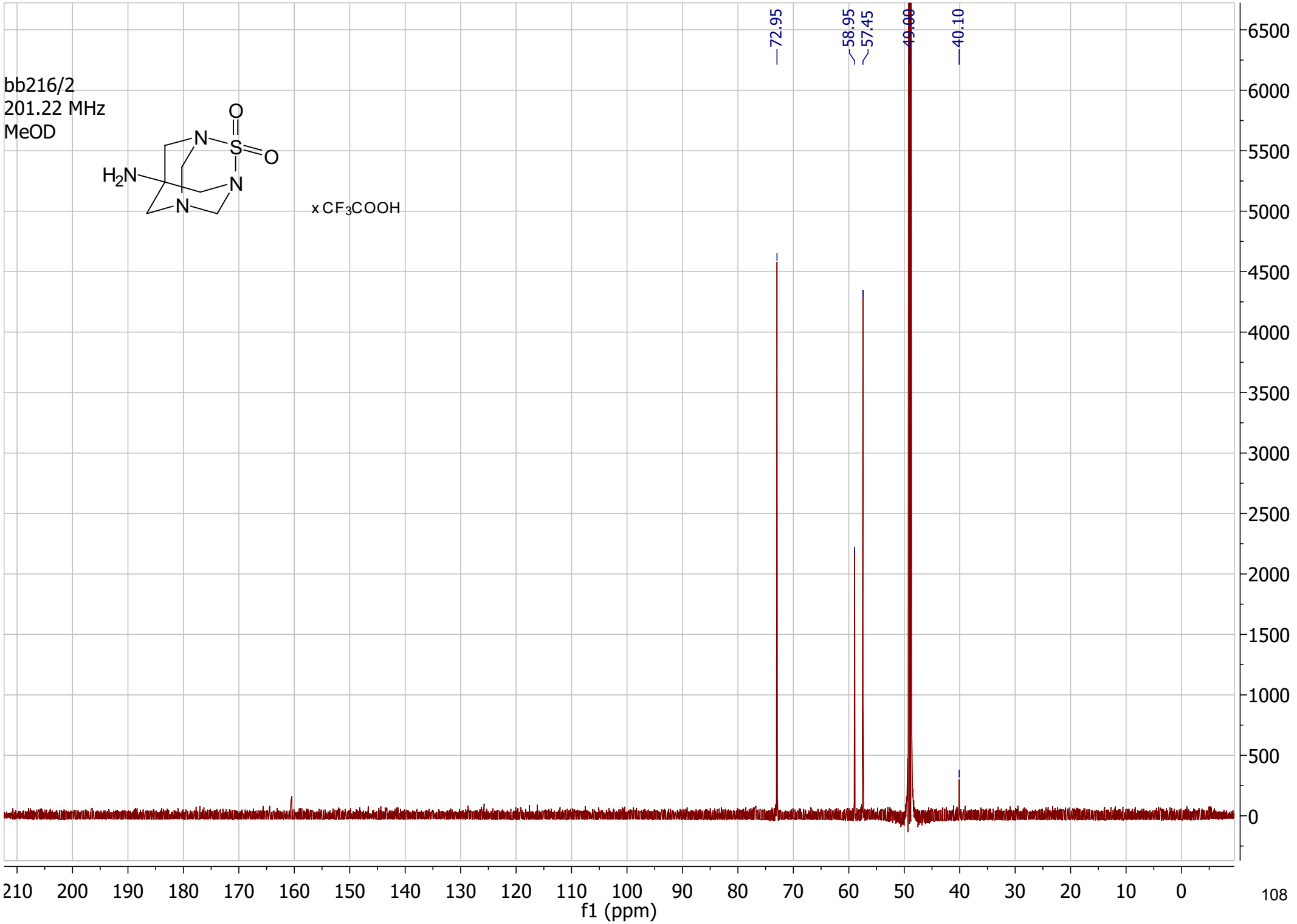

bb240new.1.fid
800.15 MHz
acetone
1H
OH
N
S
O
O
N
N
4.89
4.88
4.59
4.58
4.08
4.06
3.92
3.67
3.65
3.33
3.18
2.83
2.79
2.05
1.97
2.00
2.01
0.41
2.05
2.23
1.97
f1 (ppm)


206.14
142.70
73.42
64.95
59.18
58.56
29.84
bb240new.2.fid
201.22 MHz
acetone
13C
OH
N
S
O
O
N
N
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
104


bb241new/1
800.15 MHz
DMSO
6.91
4.73
4.71
4.62
4.60
4.25
4.24
3.69
3.67
3.44
3.32
2.50
1.37
0.91
2.08
2.06
1.98
2.00
2.00
9.45
f1 (ppm)


bb241new/2
201.22 MHz
DMSO
154.05
71.65
58.68
57.04
39.52
37.98
28.08
f1 (ppm)


bb216/1
800.15 MHz
MeOD
xCF3COOH
4.99
4.98
4.94
4.63
4.61
4.32
4.31
3.82
3.80
3.57
3.31
1.08
1.01
1.00
1.00
1.00
f1 (ppm)


bb216/2
201.22 MHz
MeOD
xCF3COOH
72.95
58.95
57.45
49.00
40.10
f1 (ppm)