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Supporting Information

# A Scaffold-Diversity Synthesis of Biologically Intriguing Cyclic Sulfonamides

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**Supporting Information**

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## 1. General Information

All commercially available compounds were used as provided without further purification unless otherwise noted. Solvents were purchased from Fisher, VWR and Acros in laboratory, reagent and anhydrous grade, as labelled by corresponding companies. If no additional information regarding treatment is given, the solvents were used directly from the container. Reagents were purchased from Alfa Aesar, Sigma Aldrich and VWR respectively. If it is stated, that a reaction was carried out under an Argon atmosphere, standard Schlenk techniques were used. Column chromatography was performed using silica gel (Acros, particle size 0.035-0.070 mm).

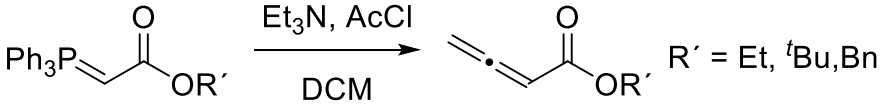
$^{1}$H, $^{13}$C and $^{19}$F-NMR were recorded on a Bruker DRX400 (400 MHz), Bruker DRX500 (500 MHz), INOVA500 (500 MHz) or Bruker Biospin AVANCE HDX-III (700 MHz) using Chloroform-*d* ($CDCl_3$), $CD_2Cl_2$, $(CD_3)_2CO$, or $(CD_3)_2SO$ as solvent at room temperature. $^{1}$H and $^{13}$C-NMR spectra were calibrated to the solvent signals of Chloroform-*d* (7.26 and 77.16 ppm), $CD_2Cl_2$ (5.32 and 53.84 ppm), $CD_3CN$ (1.94 and 1.32/118.26 ppm) or $(CD_3)_2SO$ (2.50 and 39.52 ppm).[1] The abbreviations *s*, *d*, *t*, *q* and *m* stand for singlet, doublet, triplet, quartet and multiplet in that order. High resolution mass spectra (HRMS) were recorded on a *LTQ Orbitrap* mass spectrometer coupled to an *Accela HPLC*-System (HPLC column: Hypersyl GOLD, 50 mm x 1 mm, particle size 1.9 µm; Ionization method: electron spray ionization). Preparative HPLC was performed using a 1260 Infinity II system by Agilent Technologies and Nucleodur C18 Gravity VP10/125 5 µm or Nucleodur C18 gravity VP21/125 5 µm columns by Macherey-Nagel.

## 2. Experimental section - Synthesis

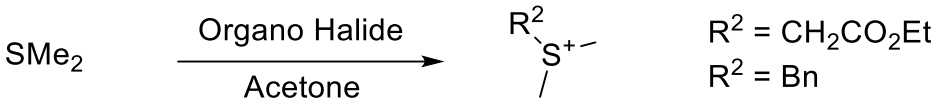
### 2.1. Branching Pathway

#### 2.1.1 Synthesis of Ketimines (1), Allenes (3) and Sulfonium Salts

$CO_2$Et-**1**,[1] H-**1**,[2] Me-**1**[3], 2-Pyr-**1**[4] were synthesized according to procedures previously reported in literature. Spectral data were in accordance with reported ones.

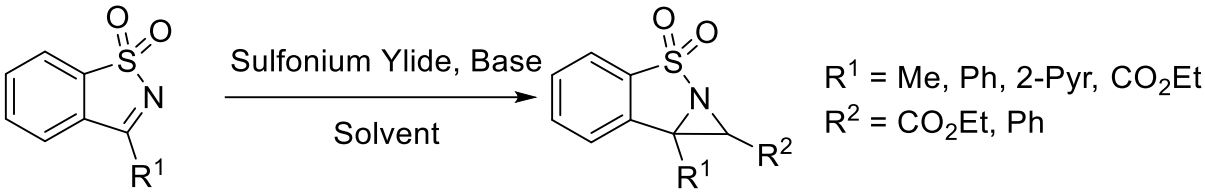



Allenes **3-OEt**, **3-OtBu** and **3-OBn** were synthesized according to reported literature procedures;[5][6] with recorded spectral data matching previously reported ones.



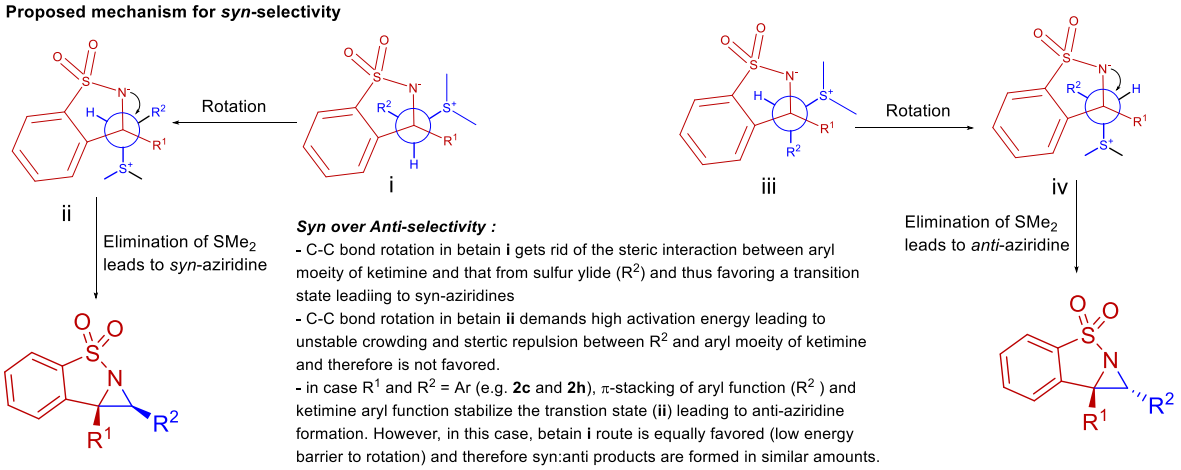

Sulfonium salts (carbethoxy)methyl dimethylsulfonium bromide and benzyl dimethylsulfonium bromide were synthesized and handled according to reported literature procedures; with recorded spectral data matching previously reported ones.[7][8]

### 2.1.2 Synthesis of Aziridines 2a-2h




*General Reaction Scheme*

Aziridines were synthesized according to general scheme depicted above. Observed diastereoselectivity (*syn* in most examples) or lack of it in cases of **2c** and **2h** can be described and established by the procedure shown in Scheme S1, referring to general considerations of sulfur ylide mediated aziridination.[9]

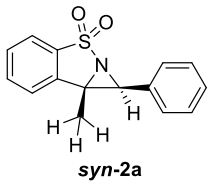



**Scheme S1: Model for diastereoselectivity of aziridination reaction.**

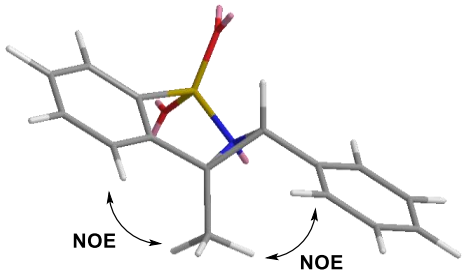
**(±)-7b-methyl-1-phenyl-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole 3,3-dioxide (2a)**

Benzyl dimethylsulfonium bromide (1.4 eq., 100.0 mg, 0.43 mmol), Potassium carbonate (2.0 eq., 32.8 mg, 0.24 mmol ) and 3-methylbenzo[d]isothiazole 1,1-dioxide **1-Me** (1.0 eq., 21.0 mg, 0.12 mmol) were combined in Acetonitrile (970 µl). The reaction was stirred for 10 h at ambient temperature. Then, an additional 2.2 eq (157 mg, 0.68 mmol) of sulfonium salt were added to the mixture and the reaction stirred for 30 additional hours at ambient temperature. The reaction was concentrated and objected to silica gel column chromatography (7% to 14% EA/CyH) to yield 22 mg (0.08 mmol, 68%) of ***syn*-2a** and 3 mg (0.01 mmol, 9%) of ***anti*-2a**.

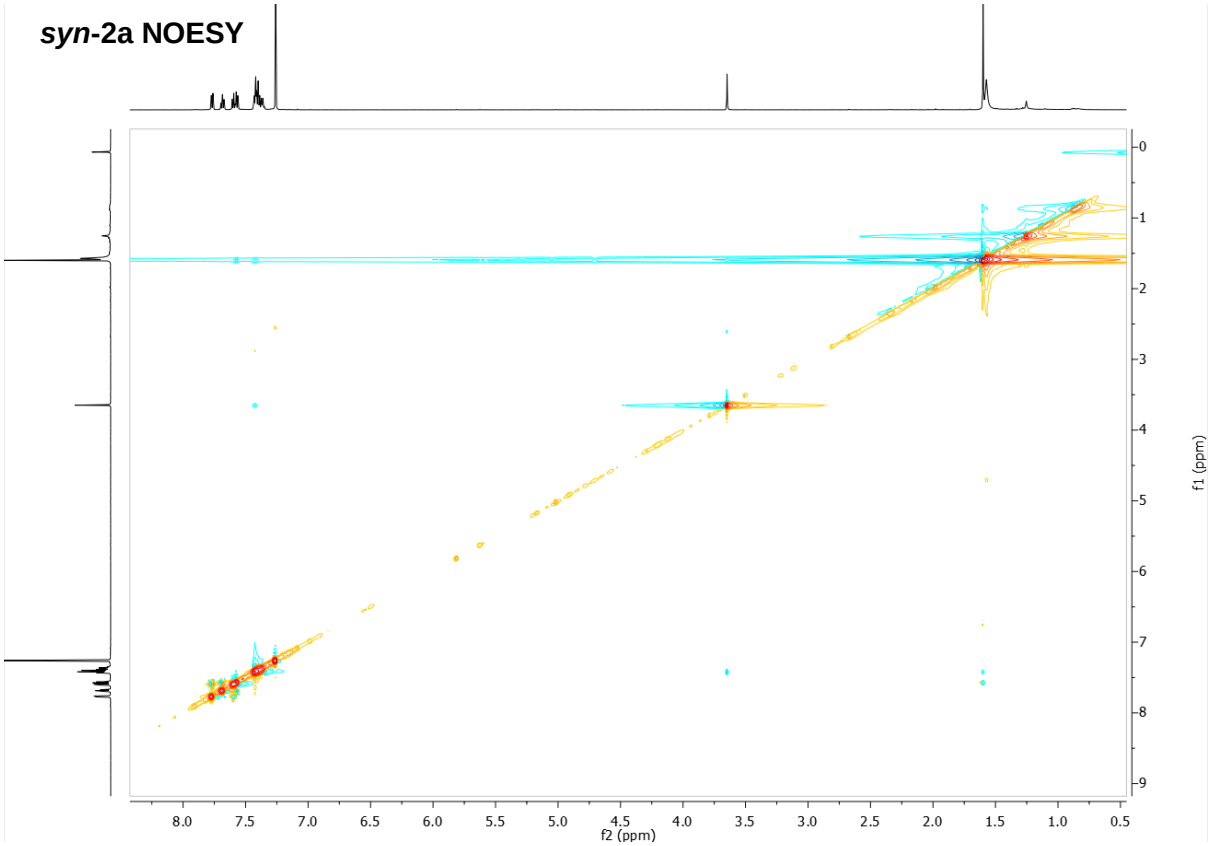
***syn*-2a**



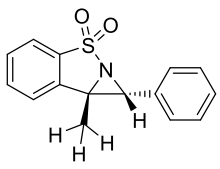

*syn*-2a

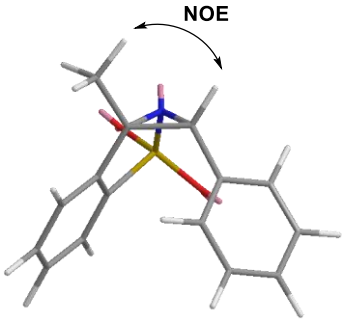



**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 7.77 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.69 (td, *J* = 7.6, 1.2 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.45 – 7.34 (m, 5H), 3.65 (s, 1H), 1.60 (s, 3H); **$^{13}$C NMR** (126 MHz, Chloroform-d) δ 141.2, 133.8, 133.7, 132.6, 130.3, 128.8, 128.7, 127.7, 124.3, 123.66, 61.6, 56.9, 13.1; **HMRS (ESI):** Calculated for $C_{15}$ $H_{14}$ $O_2$ N S = $[M+H]^+$: 272.07398, found: 272.07328



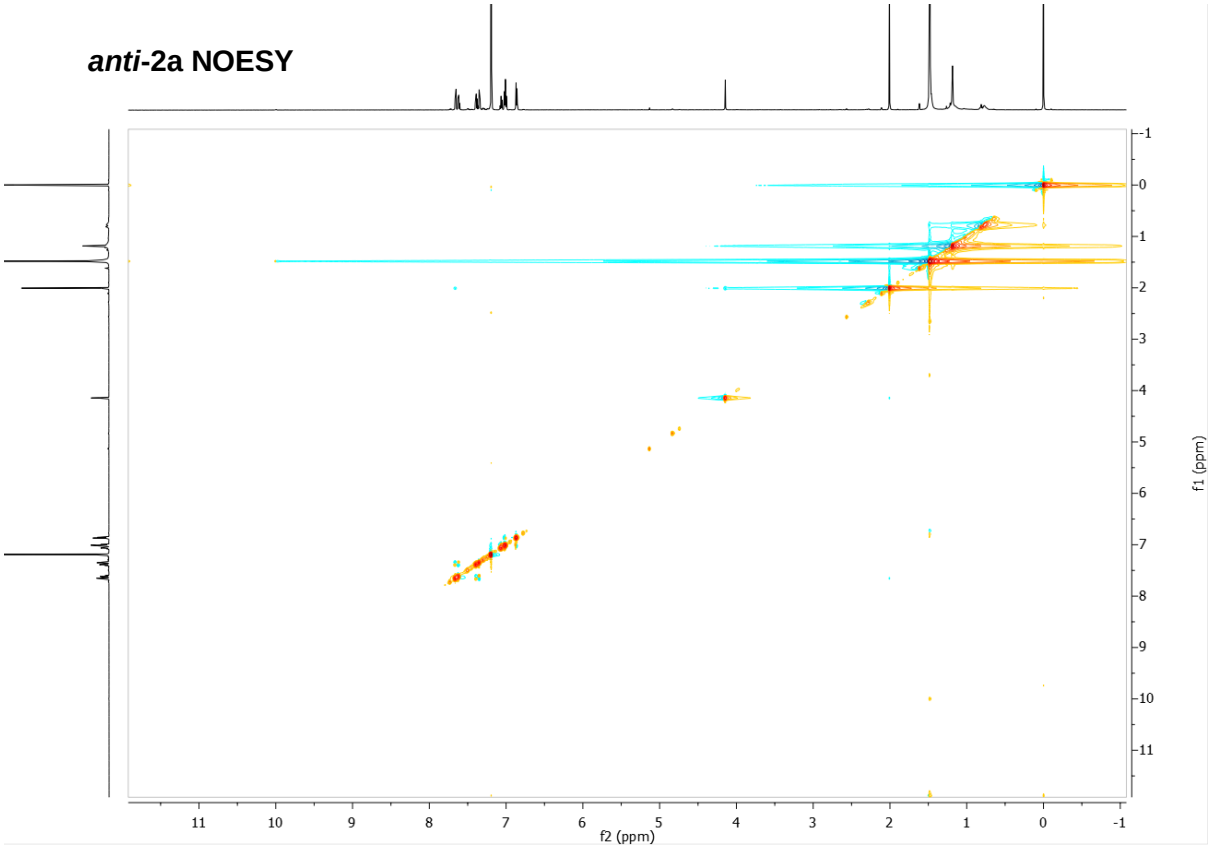

***anti*-2a**



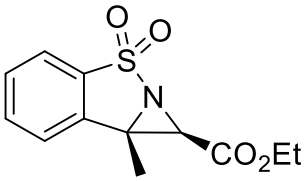




**$^{1}$H NMR** (600 MHz, Chloroform-*d*) δ 7.73 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.68 (ddd, *J* = 7.8, 7.1, 1.2 Hz, 1H), 7.46 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.41 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.15 – 7.12 (m, 1H), 7.10 – 7.06 (m, 2H), 6.93 (dq, *J* = 7.3, 1.2 Hz, 2H), 4.21 (s, 1H), 2.07 (s, 3H); **$^{13}$C NMR** (151 MHz, Chloroform-d) δ 137.7, 137.4, 133.4, 131.0, 130.4, 128.5, 128.3, 127.9, 125.6, 122.6, 62.2, 55.1, 19.7; **HMRS (ESI):** Calculated for $C_{15}$ $H_{14}$ $O_2$ N S = $[M+H]^+$: 272.07398, found: 272.07359

***anti*-2a NOESY**



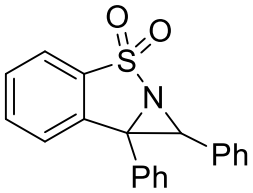

**(±)-7b-methyl-1-carbethoxy-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole 3,3-dioxide (2b)**




(Carbethoxymethyl)dimethylsulfonium bromide (1.2 eq., 99 mg, 0.43 mmol, Potassium carbonate (2.0 eq., 99.0 mg, 0.72 mmol ) and 3-methylbenzo[d]isothiazole 1,1-dioxide **1-Me** (1.0 eq., 65.0 mg, 0.36 mmol) were combined in Acetonitrile (1.3 ml). The reaction was concentrated and objected to silica gel column chromatography (15% to 21% EA/CyH) to yield 81.0 mg (0.30 mmol, 84%) of product aziridine.

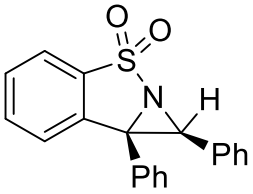
$R_f$ (30% EA/CyH) = 0.55; **$^1$H NMR** (400 MHz, Chloroform-d) δ 7.74 – 7.64 (m, 2H), 7.61 – 7.54 (m, 2H), 4.28 (m, 2H), 3.15 (s, 1H), 1.91 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 164.0, 139.2, 134.0, 133.2, 130.7, 124.9, 123.3, 62.4, 55.5, 53.9, 14.1, 13.3.
**HMRS (ESI):** Calculated for $C_{12}$ $H_{14}$ $O_4$ N S = $[M+H]^+$: 268.06381, found: 268.06385

**(±)-1,7b-diphenyl-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole 3,3-dioxide(2c)**




Benzyl dimethylsulfonium bromide (2.25 eq., 112.0 mg, 0.48 mmol was combined with Potassium carbonate (2.50., 74.0 mg, 0.53 mmol) in an oven-dried schlenk tube with a magnetic stirring bar and solved in 2.28 ml DMF. After 10 min. Ketimine (1.0 eq., 52.0 mg, 0.21 mmol mg) was added to the mixture. The reaction was stirred at ambient temperature overnight. After completion of conversion (TLC analysis), the reaction was quenched by adding saturated aqueous ammonium chloride solution (4 ml). 2 ml Ethyl Acetate were added and layers were separated. The aqueous layer was extracted twice more with 2 ml each. Combined organic layers were washed with water three times (10 ml each) and brine once. Concentration delivered crude material, which was objected to silica gel column chromatography (3:2 Ethyl acetate / Cyclohexane (v/v)) to deliver 67 mg (0.20 mmol, 94%) of aziridine.

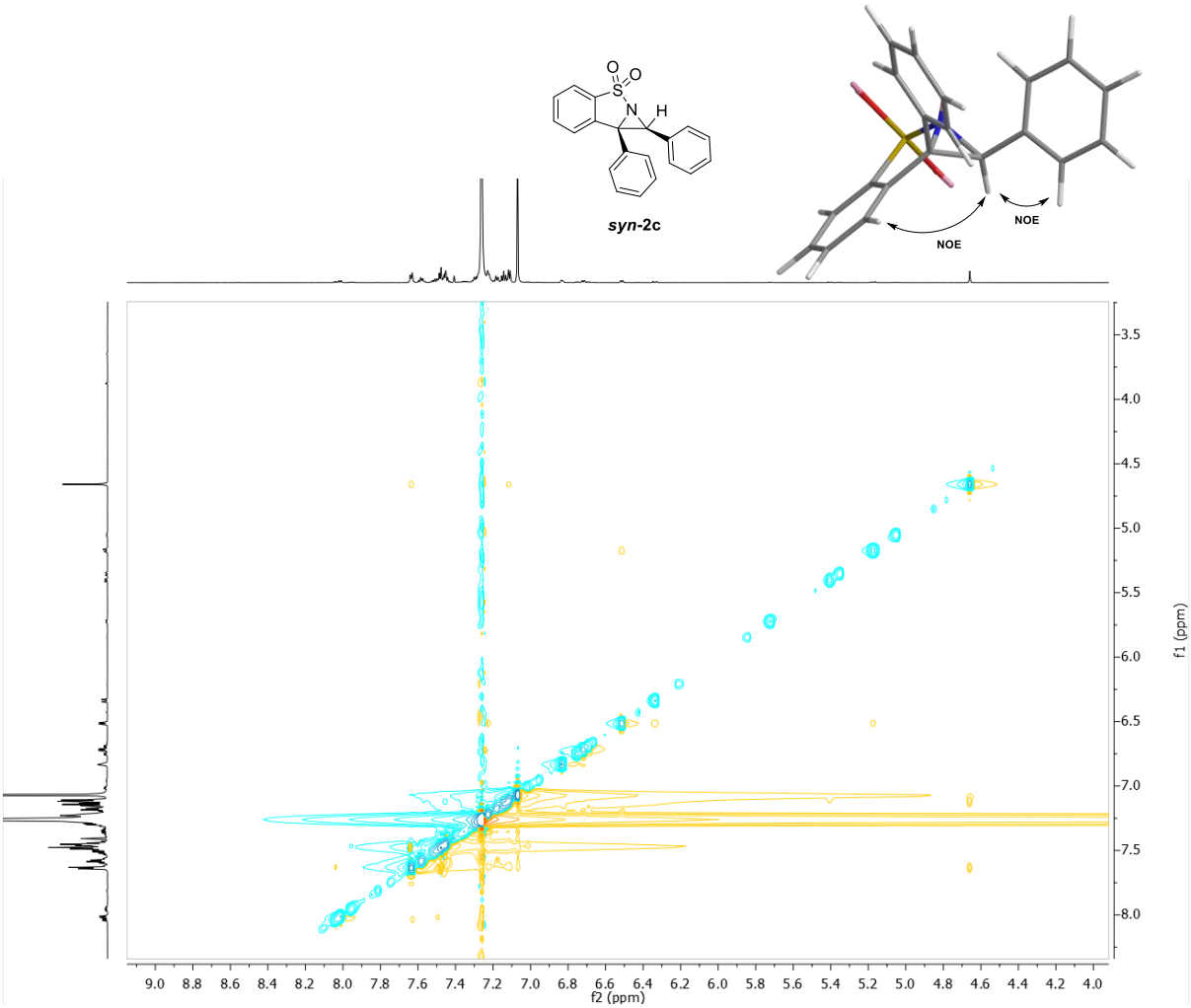
***Syn*-2c**



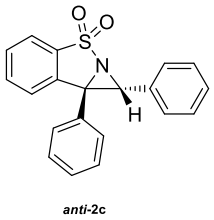

**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 7.66 – 7.61 (m, 2H), 7.61 – 7.56 (m, 1H), 7.52 – 7.41 (m, 6H), 7.20 – 7.09 (m, 5H), 4.65 (s, 1H).

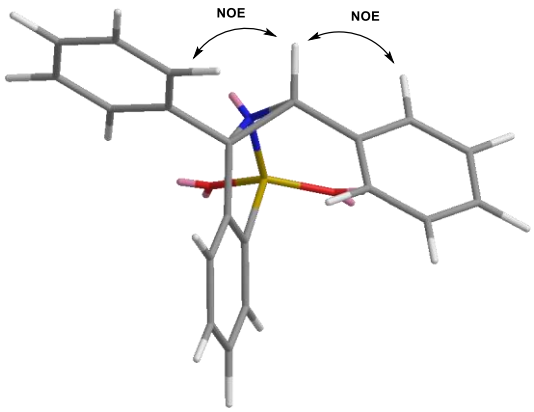
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 137.3, 136.7, 135.1, 133.2, 131.0, 130.4, 129.5, 129.1, 128.5, 128.5, 128.0, 127.9, 127.1, 122.2, 60.7, 60.2.

**HMRS (ESI):** Calculated for $C_{20}$ $H_{16}$ $O_2$ N S = $[M+H]^+$: 334.08963, found: 334.09003




***anti*-2c**

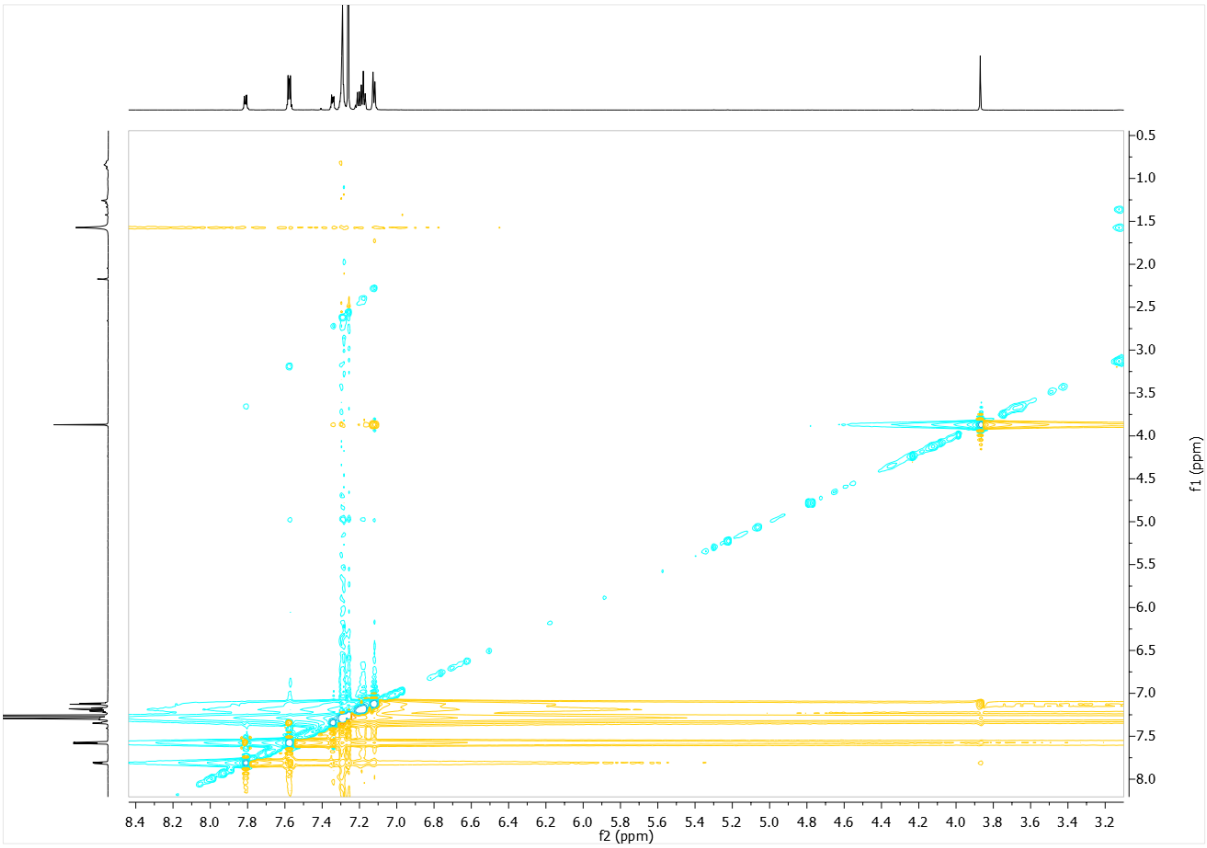


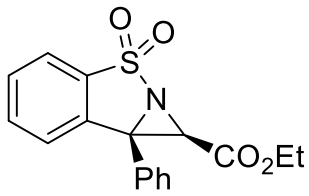

**$^{1}$H NMR** (700 MHz, Chloroform-*d*) δ 7.83 – 7.80 (m, 1H), 7.59 – 7.56 (m, 2H), 7.36 – 7.33 (m, 1H), 7.31 – 7.27 (m, 5H), 7.23 – 7.16 (m, 3H), 7.12 (d, *J* = 7.7 Hz, 2H), 3.87 (s, 1H).

**$^{13}$C NMR** (176 MHz, Chloroform-d) δ 140.6, 133.6, 133.2, 132.6, 130.9, 130.3, 129.3, 129.0, 128.8, 128.7, 128.3, 127.8, 125.6, 123.5, 62.4, 62.3.

**HMRS (ESI):** Calculated for $C_{20}$ $H_{16}$ $O_2$ N S = $[M+H]^+$: 334.08963, found: 334.09043




**(±)-Ethyl 7b-phenyl-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole-1-carboxylate 3,3-dioxide (2d)**



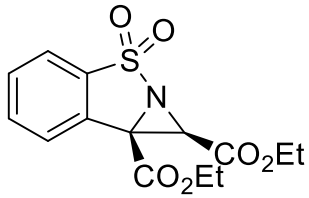

To (Carbethoxymethyl)dimethylsulfonium bromide (121 mg, 0.53 mmol, 1.35 eq.) was added sodium hydride (24 mg ,60 wt.% in paraffin oil, 1.55 eq.) in 3.8 ml *N*,*N*-DMF. The mixture was stirred for 5 min at ambient temperature and 3-(phenyl)- 1,2 benzothiazole 1,1-dioxide **1-Ph** (1.0 eq., 95 mg, 0.39 mmol) was added in one portion. The reaction was stirred for 10 h at ambient temperature. The reaction mixture was poured into 50 ml of saturated aqueous ammonium chloride solution and extracted with 10 ml Ethyl acetate (3 times). Combined organic layers were washed with water and brine (each 15 ml), dried over anhydrous sodium sulfate and concentrated. Objection to silica gel column chromatography (Ethyl Acetate/Cyclohexane 15-25%) furnished 32 mg (0.10 mmol, 25%) of desired aziridine.

**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 7.80 – 7.72 (m, 1H), 7.61 – 7.58 (m, 2H), 7.53 (dq, *J* = 5.1, 2.9 Hz, 2H), 7.46 – 7.40 (m, 4H), 4.10 – 3.96 (m, 2H), 3.50 (s, 1H), 0.96 (t, *J* = 7.2 Hz, 3H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 163.4, 138.4, 133.8, 132.7, 130.8, 130., 129.5, 129.0, 128.1, 126.0, 123.3, 62.1, 58.7, 56.6, 13.7.

**HMRS (ESI):** Calculated for $C_{17}$ $H_{16}$ $O_4$ N S = $[M+H]^+$: 330.07946, found: 330.07993

**(±)-Diethyl azirino[1,2-b]benzo[d]isothiazole-1,7b(1H)-dicarboxylate 3,3-dioxide(2e)**




(Carbethoxymethyl)dimethylsulfonium bromide (2.0 eq., 105 mg, 0.46 mmol) and Potassium carbonate (3.0 eq., 95.3 mg, 0.69 mmol) were combined in dry DMSO (2.3 ml) in a flame-dried 10 ml schlenk tubed equipped with a magnetic stirring bar under an Argon atmosphere. The mixture was stirred for 10 min and Ketimine **1-$CO_2$Et** (1.0 eq., 55 mg, 230.0 µmol) was added as a solid. The reaction was then monitored via TLC.

After 3 h, starting material had been consumed and the reaction mixture was quenched with 2 ml saturated aqueous ammonium chloride solution and the resulting mixture was poured into 40 ml water in a separation funnel.

The mixture was extracted with Ethyl acetate (5 times with 9 ml each). Combined organic layers were washed with water and brine and dried over anhydrous sodium sulfate. Concentration delivered crude product. Objection to silica gel column chromatography (16 to 30% EA/CyH) furnished 28 mg aziridine (0.09 mmol, 37% yield).

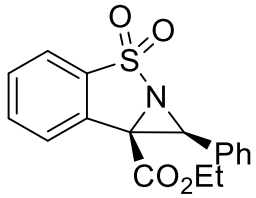
$R_f$ = 0.31 (30%EA/CyH); **$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 7.93 – 7.89 (m, 1H), 7.73 – 7.67 (m, 2H), 7.66 – 7.60 (m, 1H), 4.33 (qd, *J* = 7.1, 5.9 Hz, 2H), 4.24 (qd, *J* = 7.2, 0.6 Hz, 2H), 3.26 (s, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 162.8, 162.7, 134.1, 132.9, 132.8, 131.6, 126.4, 123.4, 63.3, 62.8, 55.3, 53.8, 13.9, 13.9.

**HMRS (ESI):** Calculated for $C_{14}$ $H_{16}$ $O_6$ N S = $[M+H]^+$: 326.06928, found: 326.06938

Calculated for $C_{14}$ $H_{15}$ $O_6$ N Na S = $[M+Na]^+$: 348.05123, found: 348.05129

**Ethyl 1-phenylazirino[1,2-b]benzo[d]isothiazole-7b(1H)-carboxylate 3,3-dioxide (2f)**




To 3-carbethoxy 1,2 benzothiazole 1,1-dioxide **1-$CO_2$Et** (1.0 eq., 24 mg, 0.10 mmol) in 0.8 ml Acetonitrile was added 2.1 eq. (benzyl)dimethylsulfonium bromide (49.1 mg, 0.21 mmol) and Potassium carbonate (2.05 eq., 28.4 mg, 0.21 mmol). The reaction was stirred for 14 h at ambient temperature.

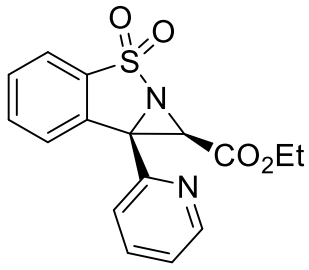
The reaction mixture was poured into 10 ml of saturated aqueous ammonium chloride solution and extracted with 5 ml Ethyl acetate (3 times). Combined organic layers were washed with water and brine (each 15 ml), dried over anhydrous sodium sulfate and concentrated. Objection to silica gel column chromatography (11% to 29% EA/CyH) furnished 18 mg (0.05 mmol, 54%) aziridine.

**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 8.17 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.78 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.73 (td, *J* = 7.7, 1.2 Hz, 10H), 7.65 (td, *J* = 7.6, 1.1 Hz, 1H), 7.51 – 7.48 (m, 2H), 7.39 – 7.35 (m, 3H), 4.16 – 4.01 (m, 2H), 3.80 (s, 1H), 1.02 (t, *J* = 7.1 Hz, 3H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 163.4, 134.7, 133.8, 133.2, 131.0, 130.9, 129.3, 128.4, 127.6, 126.5, 123.4, 62.5, 61.7, 57.7, 13.8.

**HMRS (ESI):** Calculated for $C_{17}$ $H_{16}$ $O_4$ N S = $[M+H]^+$: 330.07946, found: 330.07982

**(±)-Ethyl 7b-(pyridin-2-yl)-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole-1-carboxylate 3,3-dioxide (2g)**




(Carbethoxymethyl)dimethylsulfonium bromide (1.37 eq., 108 mg, 0.47 mmol), Potassium carbonate (2.0 eq., 95 mg ,0.69 mmol ) and 3-methylbenzo[*d*]isothiazole 1,1-dioxide **1-Me** (1.0 eq., 84.0 mg, 0.34 mmol) were combined in Acetonitrile (1.275 ml). The reaction was concentrated and objected to silica gel column chromatography (18% to 36% EA/CyH) to yield 103 mg (0.31 mmol, 91%) of product aziridine.

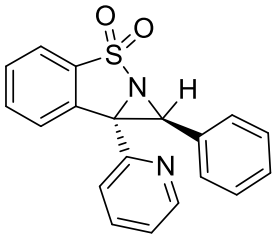
**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 8.63 (ddd, *J* = 4.9, 1.7, 1.0 Hz, 1H), 8.04 – 7.98 (m, 1H), 7.77 – 7.67 (m, 3H), 7.59 (pd, *J* = 7.4, 1.4 Hz, 1H), 7.31 (ddd, *J* = 7.2, 4.9, 1.6 Hz, 1H), 4.10 – 3.92 (m, 1H), 3.48 (s, 1H), 1.00 (t, *J* = 7.1 Hz, 2H).

**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 163.2, 151.7, 149.5, 137.8, 137.3, 134.0, 133.0, 131.1, 127.3, 124.2, 124.1, 123.3, 62.3, 56.8, 27.1, 14.0.

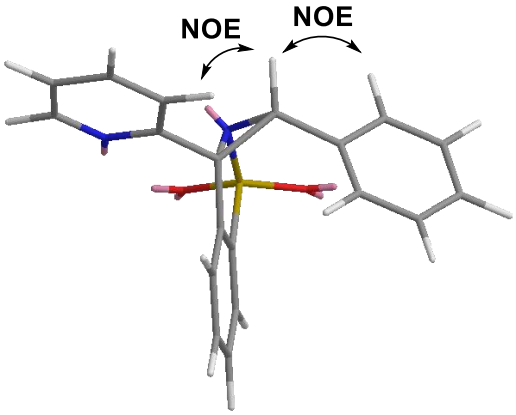
**HMRS (ESI):** Calculated for $C_{16}$ $H_{15}$ $O_4$ $N_2$ S = $[M+H]^+$: 331.07470, found: 331.07463

**(±)-1-Phenyl-7b-(pyridin-2-yl)-1,7b-dihydroazirino[1,2-*b*]benzo[*d*]isothiazole 3,3-dioxide (2h)**

Benzyldimethylsulfonium bromide (1.4 eq., 100.0 mg, 0.43 mmol), Potassium carbonate (2.0 eq., 32.8 mg, 0.24 mmol ) and 2-Pyridinyl Ketimine **2-Pyr-1** (1.0 eq., 29.0 mg, 0.12 mmol) were combined in Acetonitrile (970 µl). The reaction was stirred for 10 hours at ambient temperature. Then, additional 2.2 eq (157 mg, 0.68 mmol) of sulfonium salt were added to the mixture and the reaction stirred for 30 additional hours at ambient temperature. The reaction was stopped by concentration using a rotary evaporator and objected to silica gel column chromatography to yield 29 mg (0.09 mmol, 73%) of a 1:1 mixture of diastereomers.




***anti*-2h**

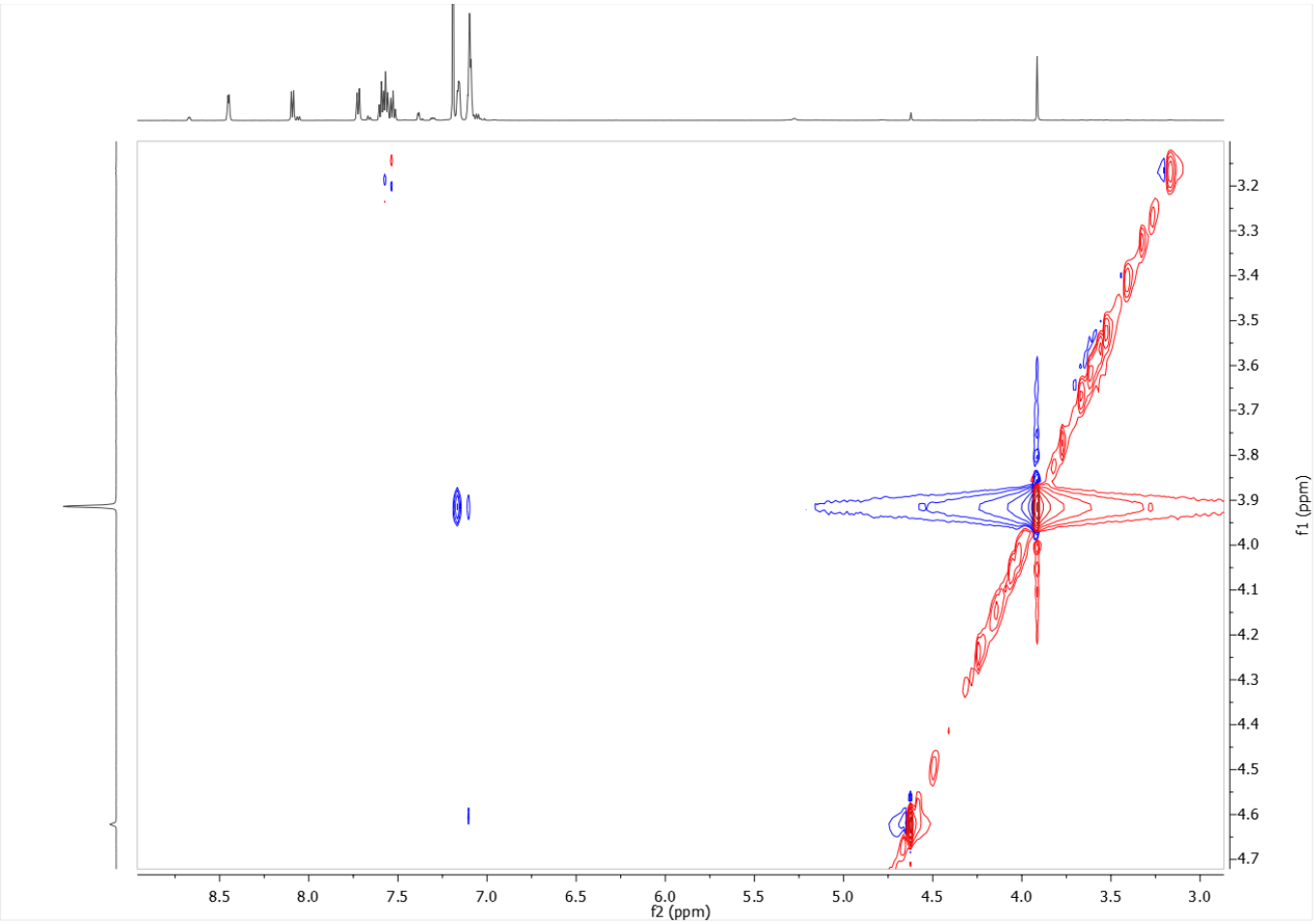



***anti*-2h**

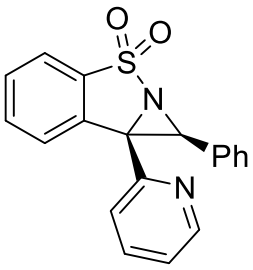
**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 8.53 – 8.50 (m, 1H), 8.15 (d, *J* = 7.7 Hz, 1H), 7.81 – 7.77 (m, 1H), 7.69 – 7.55 (m, 5H), 7.23 (dd, *J* = 6.8, 3.0 Hz, 2H), 7.16 (tt, *J* = 4.8, 2.7 Hz, 5H), 3.98 (s, 1H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 151.5, 149.5, 138.7, 136.7, 133.5, 133.1, 131.9, 130.3, 128.5, 128.2, 127.4, 126.7, 123.8, 123.7, 123.2, 62.9, 61.3.

**HMRS (ESI):** Calculated for $C_{19}$ $H_{15}$ $O_2$ $N_2$ S = $[M+H]^+$: 335.08487 found: 335.08570 Calculated for $C_{19}$ $H_{15}$ $O_2$ $N_2$ Na S = $[M+Na]^+$: 357.06682 found: 357.06777



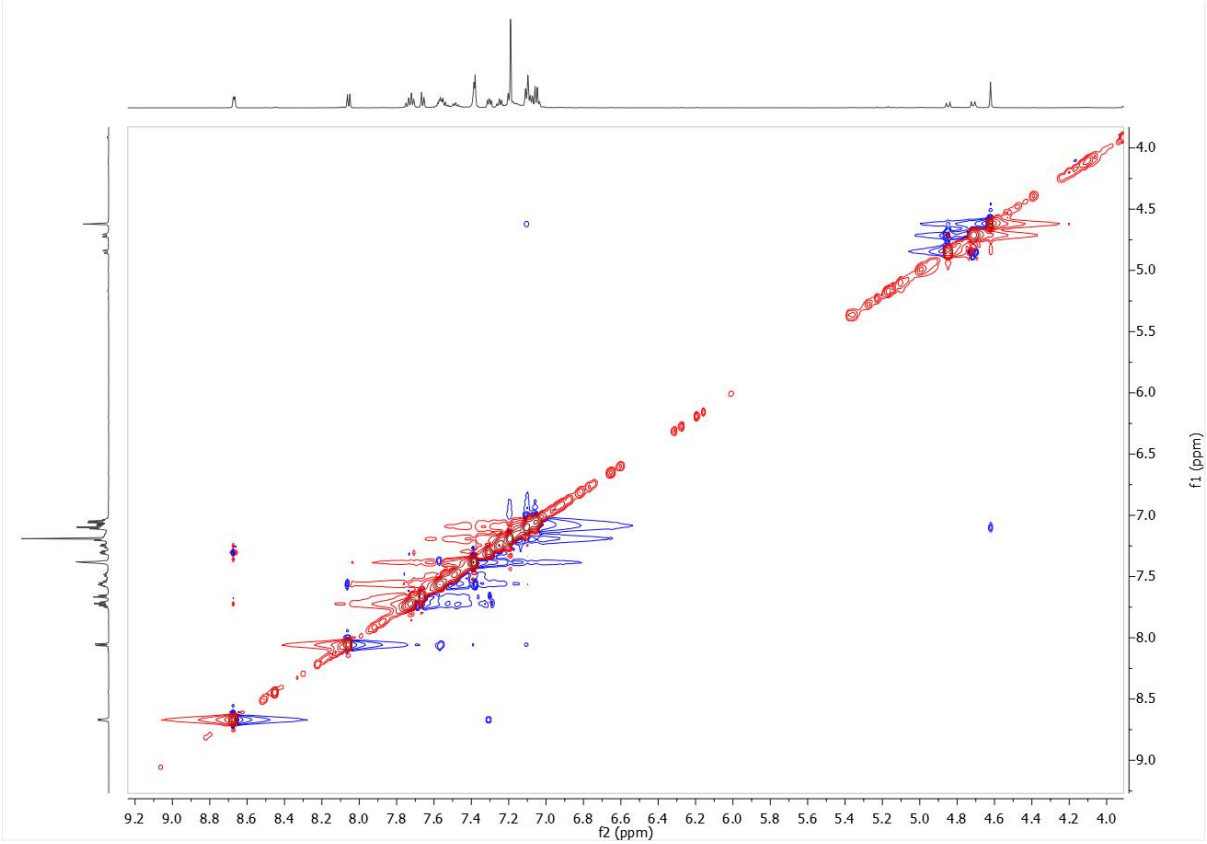

***syn*-2h**



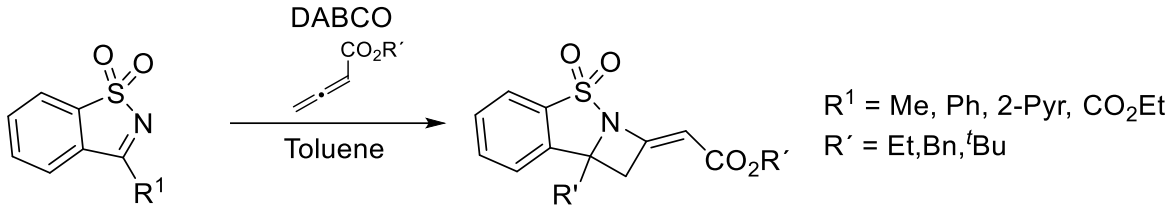

**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 8.74 (dt, *J* = 5.0, 1.3 Hz, 1H), 8.12 (d, *J* = 7.9 Hz, 1H), 7.79 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.76 – 7.72 (m, 1H), 7.64 (td, *J* = 4.9, 2.6 Hz, 1H), 7.38 (ddd, *J* = 7.6, 4.9, 1.3 Hz, 1H), 7.20 – 7.07 (m, 5H), 4.70 (s, 1H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 154.8, 149.8, 137.6, 137.1, 135.7, 133.3, 131.1, 130.5, 128.6, 128.1, 127.9, 124.1, 122.6, 122.3, 61.9, 59.4.

**HMRS (ESI):** Calculated for $C_{19}H_{15}O_2N_2S = [M+H]^+$: 335.08487, found: 335.08470


f1 (ppm)
f2 (ppm)

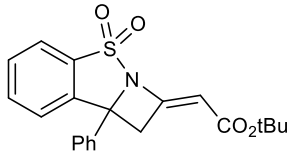
### 2.1.3 Synthesis of Azetidines




*General Reaction Scheme*

Azetidines **4a and 4b** were synthesized according to the procedure of Ye *et al.*[10] and results were in accordance with the reported yields and spectral data. For azetidines **4c-e**, same conditions with corresponding substrates and allenes were used.

**(±)-tert-butyl (*E*)-2-(4,4-dioxido-8b-phenyl-1,8b-dihydro-2H-azeto[1,2-b]benzo[d]-isothiazol-2-ylidene)acetate (4b)**



Yield: 742 mg, 52% (3.7 mmol scale)

**$^{1}$H NMR** (400 MHz, Chloroform-d) δ 7.80 (ddd, *J* = 7.8, 1.3, 0.7 Hz, 1H), 7.66 – 7.61 (m, 1H), 7.60 – 7.54 (m, 3H), 7.46 – 7.38 (m, 3H), 7.37 – 7.31 (m, 1H), 5.85 (t, *J* = 2.4 Hz, 1H), 4.01 (dd, *J* = 17.0, 2.4 Hz, 1H), 3.73 (dd, *J* = 17.0, 2.4 Hz, 1H), 1.42 (s, 9H).

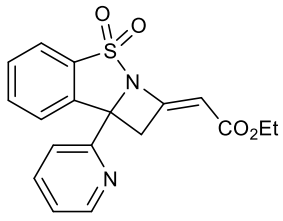
**$^{13}$C NMR** (176 MHz, Chloroform-d) δ 165.7, 154.9, 143.3, 139.4, 136.5, 134.3, 130.2, 129.1, 128.8, 125.8, 125.0, 122.4, 106.8, 80.7, 77.1, 43.3, 28.4.

**HMRS (ESI):** Calculated for $C_{21}$ $H_{22}$ $O_4$ N S = $[M+H]^+$: = 384.12641, found: 384.12632

Calculated for $C_{21}$ $H_{22}$ $O_4$ N Na S = $[M+Na]^+$: = 406.10835, found: 406.10802

Calculated for $C_{21}$ $H_{22}$ $O_4$ N K S = $[M+K]^+$: = 422.08229, found: 422.08188

**(±)-Ethyl (*E*)-2-(4,4-dioxido-8b-(pyridin-2-yl)-1,8b-dihydro-2H-azeto[1,2-b]benzo[d]-isothiazol-2-ylidene)acetate (4c)**[10]



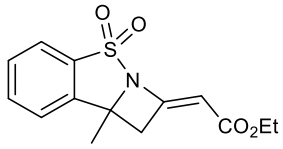
**$^{1}$H NMR** (400 MHz, Chloroform-d) δ 8.66 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H), 7.87 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.78 – 7.75 (m, 1H), 7.75 – 7.72 (m, 1H), 7.72 – 7.69 (m, 1H), 7.66 (ddd, *J* = 7.8, 4.7, 1.1 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.26 (ddd, *J* = 7.2, 4.9, 1.5 Hz, 1H), 5.96 (t, *J* = 2.3 Hz,

1H), 4.09 (ddd, *J* = 17.7, 8.9, 2.9 Hz, 3H), 3.74 (dd, *J* = 17.4, 2.4 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 166.0, 157.6, 156.1, 149.5, 141.6, 137.4, 136.2, 134.3, 130.3, 125.9, 123.3, 121.8, 120.3, 105.1, 76.0, 60.2, 42.9, 14.3.

**HMRS (ESI):** Calculated for $C_{18}$ $H_{17}$ $O_4$ $N_2$ S = $[M+H]^+$: = 357.09035, found: 357.09011

**(±)-ethyl (*E*)-2-(8b-methyl-4,4-dioxido-1,8b-dihydro-2H-azeto[1,2-b]benzo[d]isothiazol-2-ylidene)acetate** (**4d**)



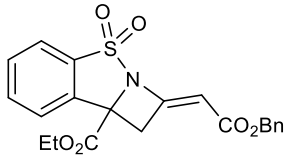

Yield: 28% (0.12 mmol scale, 10 mg)

**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 7.9 Hz, 1H), 7.72 – 7.67 (m, 1H), 7.58 (t, *J* = 7.6 Hz, 0H), 7.44 (d, *J* = 7.8 Hz, 1H), 5.87 (t, *J* = 2.3 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.53 (dd, *J* = 17.1, 2.3 Hz, 1H), 3.35 (dd, *J* = 17.1, 2.3 Hz, 1H), 1.90 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 4H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 166.4, 156.0, 143.9, 137.2, 134.3, 130.1, 123.8, 122.3, 104.4, 73.6, 60.2, 42.6, 25.7, 14.4

**HMRS (ESI):** Calculated for $C_{14}$ $H_{16}$ $O_4$ N S = $[M+H]^+$: = 294.07946, found: 294.07974

**(±)-Ethyl (*E*)-2-(2-(benzyloxy)-2-oxoethylidene)-1,2-dihydro-8bH-azeto[1,2-b]benzo[d]-isothiazole-8b-carboxylate 4,4-dioxide** (**4e**)




Yield: 90% (0.34 mmol scale, 140 mg)

**$^{1}$H NMR** (500 MHz, Chloroform-d) δ 7.80 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.77 – 7.62 (m, 3H), 7.35 – 7.30 (m, 5H), 5.96 (t, *J* = 2.3 Hz, 1H), 5.09 (d, *J* = 2.0 Hz, 2H), 4.36 – 4.23 (m, 2H), 4.02 – 3.95 (m, 1H), 3.50 (dd, *J* = 17.3, 2.3 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 9H).

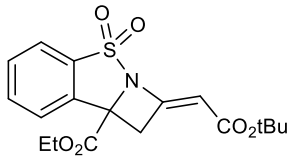
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 167.5, 165.8, 155.5, 137.2, 137.2, 135.8, 134.5, 131.2, 128.7, 128.4, 128.4, 125.3, 122.4, 104.9, 72.4, 66.3, 63.4, 40.9, 14.1.

**HMRS (ESI):** Calculated for $C_{21}$ $H_{20}$ $O_6$ N S = $[M+H]^+$: = 414.10058, found: 414.09967

Calculated for $C_{21}$ $H_{19}$ $O_6$ N Na S = $[M+Na]^+$: = 436.08253, found: 436.08153

Calculated for $C_{21}$ $H_{19}$ $O_6$ N K S = $[M+K]^+$: = 452.05647, found: 452.05550

**(±)-Ethyl (*E*)-2-(2-(tert-butoxy)-2-oxoethylidene)-1,2-dihydro-8bH-azeto[1,2-b]benzo[d]-isothiazole-8b-carboxylate 4,4-dioxide** (**4f**)



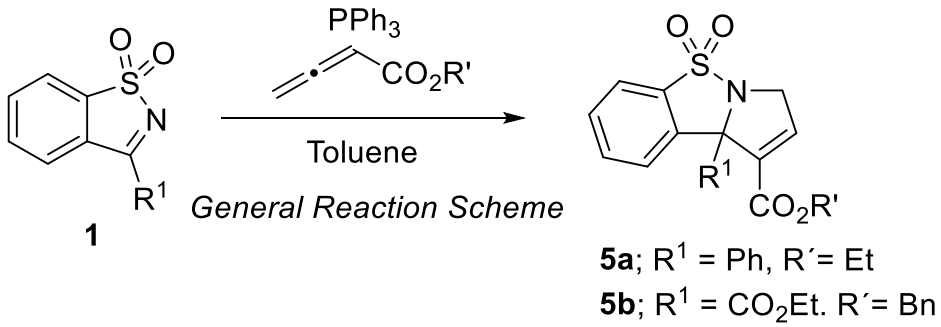
Yield: 85% (70 µmol scale, 27 mg)

**$^{1}$H NMR** (500 MHz, Chloroform-d) δ 7.81 (d, *J* = 7.8 Hz, 1H), 7.77 – 7.64 (m, 3H), 5.82 (t, *J* = 2.2 Hz, 1H), 4.37 – 4.23 (m, 2H), 3.96 (dd, *J* = 17.2, 2.2 Hz, 1H), 3.46 (dd, *J* = 17.2, 2.2 Hz, 1H), 1.41 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 3H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 167.6, 165.1, 153.6, 137.3, 137.2, 134.3, 131.1, 125.1, 122.3, 107.1, 80.8, 72.4, 63.2, 40.7, 28.2, 14.0.

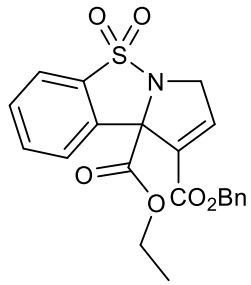
**HMRS (ESI):** Calculated for $C_{14}$ $H_{13}$ $O_6$ N S = $[M-^{t}Bu+H]^{+}$: = 324.05636, found: 324.05687

**2.1.4 Synthesis of fused Pyrrolines by Phosphine Catalysis**




Pyrroline **5a** was synthesized according to the procedure reported by Chen *et al*.[10]

**(±)-1-Benzyl 9b-ethyl benzo[d]pyrrolo[1,2-b]isothiazole-1,9b(3H)-dicarboxylate 5,5-dioxide(5b)**



Ketimine substrate **1-$CO_2$Et** (1.0 eq., 90 mg, 0.38 mmol) and $PPh_3$ (0.35 eq., 34.5 mg, 0.13 mmol) were combined in dry Toluene (6 ml) in an oven-dried Schlenk tube under an Argon atmosphere. Benzyloxyallene (1.70 eq., 93.5 mg, 0.64 mmol) was added and the reaction was

stirred at same temperature and monitored by TLC. After completion of conversion (5 h), the reaction mixture was concentrated under reduced pressure.

Crude reaction mixtures was subjected to silica gel column chromatography (12% to 16% EA/CyH) to give [3+2] product in 82% yield (0.31 mmol, 128 mg).

**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 8.03 – 7.93 (m, 1H), 7.81 – 7.74 (m, 1H), 7.64 – 7.53 (m, 2H), 7.43 – 7.31 (m, 5H), 7.01 (t, *J* = 2.3 Hz, 1H), 5.29 (d, *J* = 12.2 Hz, 1H), 5.24 (d, *J* = 12.2 Hz, 1H), 4.87 (d, *J* = 18.2 Hz, 1H), 4.38 (d, *J* = 18.2 Hz, 1H), 4.21 (qd, *J* = 7.1, 4.2 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H).

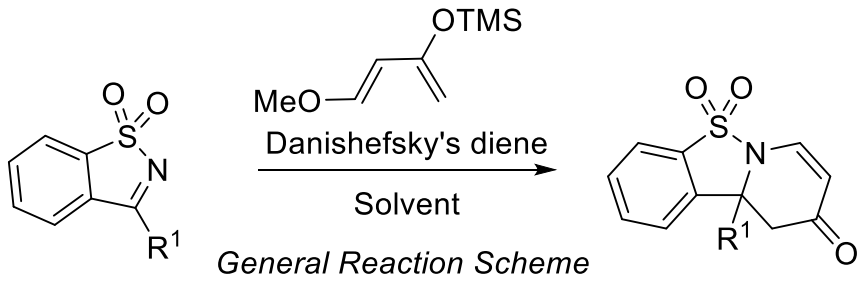
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 167.9, 161.8, 141.7, 136.5, 135.2, 135.1, 133.6, 133.4, 130.6, 128.8, 128.8, 128.5, 127.5, 121.4, 80.9, 67.3, 63.0, 54.8, 13.9.

**HMRS (ESI):** Calculated for $C_{21}H_{20}O_6NS = [M+H]^+$: = 414.10058, found: 414.10013

Calculated for $C_{21}H_{19}O_6NNaS = [M+H]^+$: = 436.08253, found: 436.08184

Calculated for $C_{21}H_{19}O_6NKS = [M+H]^+$: = 452.05593, found: 452.05647

### 2.1.5 Diels-Alder reaction of Ketimines with Danishefsky's diene

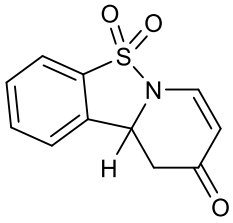



*General Reaction Scheme*

***General procedure:***

To a solution of Ketimine **1** (1.0 eq) in Toluene or *N*,*N*-DMF in a 35 ml microwave tube equipped with a magnetic stirring bar, Danishefsky's diene was added, the vessel was flushed with Argon, closed and heated in a microwave at corresponding maximum temperature at 250 W for 45 min. After reaction, 8 ml of saturated aqueous $NH_4Cl$ solution was added and the mixture was extracted with Ethyl acetate (three times 5 ml). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated using a rotary evaporator. The crude material was objected to silica gel flash chromatography.

**(±)-10,10a-dihydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (6a)**



***Conditions:***

Ketimine (1.0 eq., 148 mg, 0.89 mmol) in 3 ml *Toluene* (to give 0.30 M solution)

Danishefsky's diene (1.4 eq., 240 µl, 1.24 mmol)

Conditions: 140 °C (250 W) for 30 min

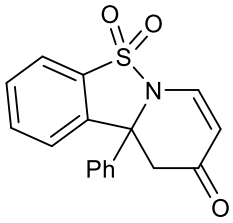
Silica gel flash chromatography (EA/ CyH 18%-26%) to furnish 200 mg of Sulfonamide (96%, 0.85 mmol).

**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 7.89 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.76 (td, *J* = 7.6, 1.1 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 5.58 (dd, *J* = 8.0, 1.1 Hz, 1H), 5.35 (dd, *J* = 15.2, 4.3 Hz, 1H), 3.06 (ddd, *J* = 16.0, 4.3, 1.1 Hz, 1H), 2.72 (dd, *J* = 16.0, 15.2 Hz, 1H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 190.8, 138.1, 134.8, 134.4, 134.2, 130.6, 123.7, 122.1, 108.4, 57.3, 41.1.

**HMRS (ESI)**: Calculated for $C_{11}H_{10}O_3NS = [M+H]^+$: = 236.03759 found: 236.03744

**(±)-10a-phenyl-10,10a-dihydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (6b)**



***Conditions:***

Ketimine (1.0 eq., 400 mg, 1.64 mmol) in 3.5 ml Toluene (to give a 0.45 M solution),

Danishefsky's diene (1.25 eq., 398 µl, 2.06 mmol),

Conditions: 180 °C (250 W) for 45 min,

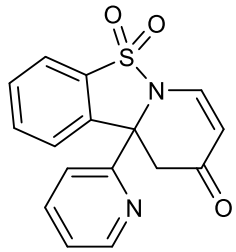
Silica gel flash chromatography (EA/ CyH 20%-34%) to furnish 315 mg of sulfonamide (62%, 1.01 mmol).

**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 7.91 – 7.88 (m, 1H), 7.66 (td, *J* = 7.6, 1.4 Hz, 1H), 7.61 (td, *J* = 7.6, 1.2 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.52 – 7.48 (m, 3H), 7.39 – 7.28 (m, 7H), 5.53 (dd, *J* = 7.8, 1.1 Hz, 2H), 3.66 (dd, *J* = 16.1, 1.1 Hz, 1H), 3.05 (d, *J* = 16.1 Hz, 1H).

**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 190.4, 140.5, 137.9, 136.8, 134.8, 132.2, 130.4, 129.5, 129.3, 126.3, 124.2, 122.1, 109.9, 69.3, 46.4.

**HMRS (ESI): Calculated for** $C_{17}H_{14}O_3NS = [M+H]^+$: = 312.06889, found: 312.06872

**(±)-10a-(pyridin-2-yl)-10,10a-dihydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (6c)**



***Conditions:***

Ketimine (1.0 eq., 240 mg, 0.98 mmol) in 4 ml Toluene:N,N DMF 7:1 (v/v, as Ketimine is not soluble in neat toluene, to give 0.25 M solution)

Danishefsky's diene (1.5 eq., 285 µl, 1.47 mmol)

Conditions: 140 °C (250 W) for 45 min

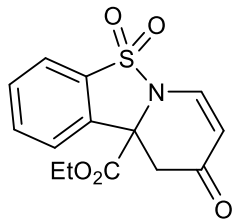
Silica gel flash chromatography (EA/ CyH 20%-32%) to furnish 238 mg of Sulfonamide (78%, 0.76 mmol).

**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 8.62 (d, *J* = 4.8 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.70 – 7.58 (m, 4H), 7.53 (d, *J* = 8.1 Hz, 1H), 5.52 (dd, *J* = 7.9, 1.0 Hz, 1H), 4.23 (dd, *J* = 15.7, 1.1 Hz, 1H), 2.93 (d, *J* = 15.7 Hz, 1H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 190.6, 156.6, 150.0, 139.0, 137.7, 136.5, 134.7, 132.1, 130.5, 125.0, 123.6, 121.7, 119.8, 109.7, 69.8, 46.1.

**HMRS (ESI)**: Calculated for $C_{17}H_{16}O_3N_2S = [M+H]^+$: = 313.06414 found: 316.06401

**(±)-10a-ethyl-10,10a-dihydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide--carbon dioxide (6d)**



***Conditions:***

Ketimine **1-$CO_2$Et** (1.0 eq., 248 mg, 1.00 mmol) in 3.4 ml Toluene (0.29 M),

Danishefsky's diene (1.4 eq., 271 µl, 1.40 mmol),

Conditions: 140 °C (250 W) for 45 min,

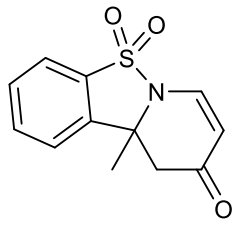
Silica gel flash chromatography (EA/ CyH 20%-34%) to furnish 290 mg of desired sulfonamide (94%, 0.94 mmol)

**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 7.6 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.74 – 7.62 (m, 3H), 5.58 (d, *J* = 8.0 Hz, 1H), 4.28 – 4.12 (m, 2H), 3.61 (d, *J* = 16.1 Hz, 1H), 2.83 (d, *J* = 16.1 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H).

**$^{13}$C NMR** (176 MHz, Chloroform-d) δ 194.8, 169.8, 164.2, 137.1, 135.7, 133.7, 130.8, 124.3, 122.0, 104.9, 65.6, 63.5, 58.0, 14.1.

**HMRS (ESI)**: Calculated for $C_{14}H_{14}O_5NS$ = $[M+H]^+$: = 308.05872, found: 308.05897

**(±)-10a-methyl-10,10a-dihydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (6e)**




***Conditions:***

Ketimine (1.0 eq., 200.0 mg, 1.10 mmol) in 5 ml *Toluene* (to give 0.22 M solution)

Danishefsky's diene (1.25 eq., 267 µl, 1.38 mmol)

Conditions: 140 °C (250 W) for 30 min

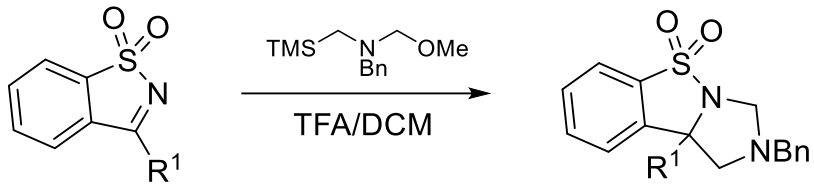
Silica gel flash chromatography (EA/ CyH 22%-34%) to furnish 19 mg of Sulfonamide (7% yield, 0.08 mmol)

**$^{1}$H NMR** (700 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 7.8 Hz, 1H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 5.58 (d, *J* = 7.9 Hz, 1H), 2.88 (d, *J* = 15.7 Hz, 1H), 2.81 (d, *J* = 15.7 Hz, 1H), 1.71 (s, 3H).

**$^{13}$C NMR** (176 MHz, Chloroform-d) δ 190.7, 141.3, 136.7, 134.6, 133.2, 130.4, 130.3, 122.8, 122.1, 106.9, 64.1, 47.3, 24.3.

**HMRS (ESI)**: Calculated for $C_{12}H_{12}O_3NS$ = $[M+H]^+$: = 250.05324 found: 250.05298

### 2.1.6 [3+2] Cycloaddition of Ketimines with Azomethine ylides

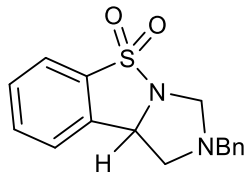



*General Reaction Scheme*

**General procedure for synthesis of fused imidazolidines 8a-e**

*N*-(Methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (82.0 µl, 0.30 mmol) and corresponding imine (0.10 mmol) were combined in $CH_2Cl_2$ (0.7 mL) in an oven-dried Schlenk tube and a mixture of TFA and $CH_2Cl_2$ (10% v/v in 36 µl DCM, 0.5 eq.) was added *via* syringe. The resultant mixture was stirred at 0° C (ice-water bath) for 1 h. The crude reaction mixture was purified by flash chromatography on silica gel (EtOAc/Petroleum Ether) to afford corresponding tricyclic sulfonamides.

**(±)-2-benzyl-1,2,3,9b-tetrahydrobenzo[d]imidazo[1,5-b]isothiazole 5,5-dioxide (8a)**



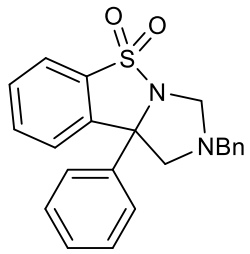

Yield: 37%, 11 mg, 0.04 mmol

**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 7.6 Hz, 1H), 7.63 (td, *J* = 7.6, 1.1 Hz, 1H), 7.57 – 7.52 (m, 1H), 7.33 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.30 – 7.22 (m, 4H), 7.18 (d, *J* = 7.2 Hz, 1H), 5.07 (dd, *J* = 7.0, 2.8 Hz, 1H), 4.74 (d, *J* = 8.6 Hz, 1H), 3.87 (d, *J* = 8.6 Hz, 1H), 3.60 (d, *J* = 13.2 Hz, 1H), 3.52 (d, *J* = 13.2 Hz, 1H), 3.22 (dd, *J* = 10.5, 2.8 Hz, 1H), 3.17 (dd, *J* = 10.5, 7.0 Hz, 1H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 139.9, 137.3, 136.2, 133.4, 129.6, 128.5, 128.5, 127.5, 123.8, 121.6, 71.0, 63.2, 58.0, 57.2.

**HMRS (ESI**): Calculated for $C_{16}H_{17}O_2N_2S = [M+H]^+$: = 301.10053, found: 301.10053

**(±)-2-benzyl-9b-phenyl-1,2,3,9b-tetrahydrobenzo[d]imidazo[1,5-b]isothiazole 5,5-dioxide (8b)**



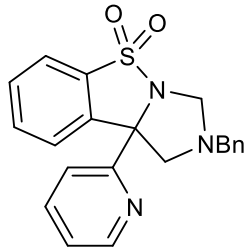

Yield: 83%, 73 mg, 0.19 mmol

**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 7.7 Hz 1H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 7.4 Hz, 1H), 7.45 (d, *J* = 8.5, 1H), 7.36 (t, *J* = 7.3 Hz, 2H), 7.32 – 7.22 (m, 4H), 7.14 (d, *J* = 6.8 Hz, 2H), 4.98 (d, *J* = 9.0 Hz, 1H), 3.92 (d, *J* = 8.9 Hz, 1H), 3.84 (d, *J* = 10.1 Hz, 1H), 3.59 (d, *J* = 13.2 Hz, 2H), 3.50 (d, *J* = 13.2 Hz, 2H), 3.30 (d, *J* = 10.2 Hz, 2H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 144.0, 142.7, 137.7, 135.4, 133.8, 129.7, 129.0, 128.7, 128.6, 128.2, 127.7, 125.9, 124.3, 121.3, 77.4, 71.6, 66.4, 56.7

**HMRS (ESI): Calculated for** $C_{22}H_{21}O_2N_2S = [M+H]^+$: = 377.13183, found: 377.13178

**(±)-2-benzyl-9b-(pyridin-2-yl)-1,2,3,9b-tetrahydrobenzo[d]imidazo[1,5-b]isothiazole 5,5-dioxide (8c)**



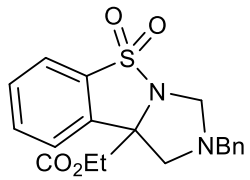

Yield: 67%, 28 mg, 74 µmol

**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 8.57 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.95 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.85 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.72 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.65 (td, *J* = 7.8, 1.8 Hz, 1H), 7.57 (td, *J* = 7.6, 1.2 Hz, 1H), 7.50 (td, *J* = 7.5, 1.1 Hz, 1H), 7.28 – 7.21 (m, 3H), 7.18 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.14 – 7.09 (m, 2H), 4.96 (dd, *J* = 9.0, 1.3 Hz, 1H), 3.97 (d, *J* = 9.0 Hz, 1H), 3.88 (dd, *J* = 11.0, 1.3 Hz, 1H), 3.58 (d, *J* = 13.3 Hz, 1H), 3.46 (d, *J* = 13.3 Hz, 1H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 161.0, 149.5, 142.8, 137.5, 137.4, 134.7, 133.6, 129.7, 128.7, 128.5, 127.5, 125.3, 122.8, 121.1, 120.2, 77.4, 72.0, 65.7, 57.1.

**HMRS (ESI)**: Calculated for $C_{21}H_{20}O_2N_3S = [M+H]^+$: = 378.12707, found: 378.12685

**(±)-2-benzyl-9b-methyl-1,2,3,9b-tetrahydrobenzo[d]imidazo[1,5-b]isothiazole 5,5-dioxide (8d)**




Yield: 48%, 18 mg, 0.05 mmol

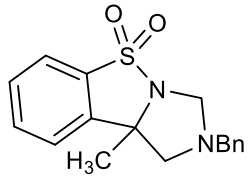
**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 7.74 – 7.70 (m, 1H), 7.63 – 7.51 (m, 3H), 7.24 – 7.16 (m, 3H), 7.08 – 7.04 (m, 2H), 4.76 (dd, *J* = 9.1, 0.5 Hz, 1H), 4.18 (tq, *J* = 7.1, 3.6 Hz, 2H), 4.01 (d, *J* = 9.1 Hz, 1H), 3.52 (d, *J* = 13.1 Hz, 1H), 3.41 (d, *J* = 0.7 Hz, 2H), 3.39 (s, 1H), 1.20 (t, *J* = 7.1 Hz, 3H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 169.7, 138.2, 137.1, 135.7, 133.7, 130.6, 128.6, 128.6, 127.7, 124.7, 121.7, 75.2, 72.1, 63.0, 62.7, 57.2, 14.0.

**HMRS (ESI)**: Calculated for $C_{19}H_{21}O_4N_2S$ = $[M+H]^+$: = 373.12165, found: 373.12118

**Calculated for** $C_{19}H_{20}O_4N_2NaS$ = $[M+H]^+$: = 395.10360, found: 395.10346

**(±)-2-benzyl-9b-methyl-1,2,3,9b-tetrahydrobenzo[d]imidazo[1,5-b]isothiazole 5,5-dioxide (8e)**



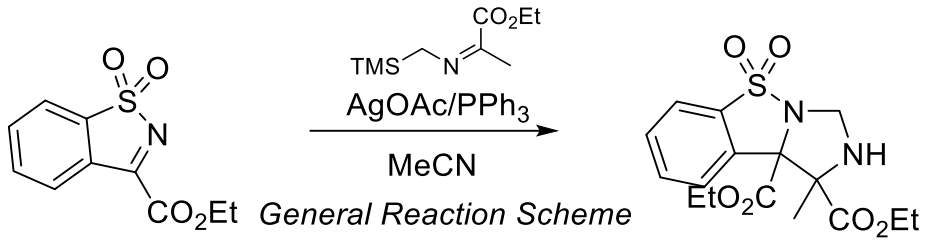

Yield: 73%, 23 mg, 0.07 mmol

**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 7.75 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.62 (td, *J* = 7.5, 1.2 Hz, 1H), 7.52 (td, *J* = 7.6, 1.0 Hz, 1H), 7.31 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.27 – 7.21 (m, 3H), 7.11 (dd, *J* = 7.9, 1.7 Hz, 2H), 4.75 (dd, *J* = 8.6, 1.1 Hz, 1H), 3.83 (d, *J* = 8.6 Hz, 1H), 3.57 – 3.44 (m, 2H), 3.38 (dd, *J* = 10.0, 1.2 Hz, 1H), 2.78 (d, *J* = 10.0 Hz, 1H), 1.71 (s, 3H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 145.0, 137.3, 136.0, 133.6, 129.3, 128.5, 128.5, 127.5, 122.9, 121.4, 72.1, 71.1. 65.3, 56.7, 27.3.

**HMRS (ESI)**: Calculated for $C_{17}H_{19}O_2N_2S$ = $[M+H]^+$: = 315.11618, found: 315.11605

### 2.1.7 Reaction of Pyruvate derived α-silyl imines with Ketimines




*General Reaction Scheme*

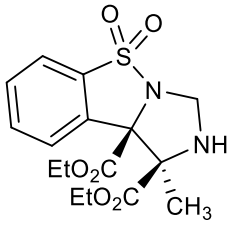
**(±)-diethyl-1-methyl-2,3-dihydrobenzo[d]imidazo[1,5-b]isothiazole-1,9b(1H)-dicarboxylate 5,5-dioxide (10)**

***Condition A*** *(affording ~ 1:1 d.r.)*

To a solution of ketimine **1-$CO_2$Et** (19 mg, 80 µmol, 1.0 equiv.) in 500 µl dry $Et_2O$ was added silylimine (365.470 µl, 90 mg per ml in diethyl ether solution, 158.83 µmol, 2.0 equiv.) followed by the addition of AgOAc (30mol%, 4.0 mg, 23.82 µmol) and $PPh_3$ (30mol%, 6.3 mg, 23.82 µmol). The reaction was stirred at 21° C and monitored *via* TLC for completion. The reaction mixture was then quenched by the addition of brine and transferred to a separation funnel. EA was added and layers were separated. The aqueous layer was extracted twice more with EA. Combined organic layers were washed with water and brine once more each and dried over $Na_2SO_4$. The solvent was removed *in vacuo* and the residue was objected to silica gel column chromatography (25% to 27% to 29% to 32% to 39% EA/CyH, 1 CV each) to elute two products ***syn*-10** and ***anti*-10** in 38% (11 mg, 0.03 mmol) and 31% (9 mg, 0.02 mmol) yield, respectively.

***Optimized Condition B*** *(affording 100:15 d.r.)*

$AgNO_3$ (20mol%, 9.9 mg, 58.5 µmol) and tri(4-trifluoromethylphenyl)phosphine (20mol% 27 mg, 58.5 µmol, ) were combined in 1.84 ml dry MeCN at 0 °C. Ketimine **1-$CO_2$Et** (70 mg, 293 µmol, 1.0 equiv.) and silylimine (2.0 eq., 585.16 µl, 585.16 µmol, 1 mM in diethyl ether) were subsequently added. The reaction was stirred at 0° C for 2 h and monitored *via* TLC for completion. HCl (20 µl) was added to the reaction mixture and stirred for 20 more minutes. The reaction mixture was then quenched by the addition of 50 µl 1 M aq. HCl. The mixture was concentrated and redissolved in Chloroform/Ethanol (9:1) and passed through a short pad of silica gel. The crude material was then analyzed by proton NMR to show a diastereomeric ratio of 100:15 in favor of ***syn*-10**. Objection to silica gel column chromatography (using gradient 25% to 27% to 29% to 32% to 39% EA/CyH) then furnished 57 mg (154.7 µmol, 53% combined yield) of fused imidazoline.




***syn*-10**

**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 7.96 (d, J= 7.8 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.69 (td, *J* = 7.6 Hz, 1H), 7.64 (td, *J* = 7.6 Hz, 1H), 4.75 (d, *J* = 8.5 Hz, 1H), 4.59 (d, *J* = 8.5 Hz, 1H), 4.33 (qd, *J* = 7.2, 3.2 Hz, 2H), 4.18 (tq, *J* = 7.1, 3.6 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.23 (d, *J* = 7.1 Hz, 3H), 0.95 (s, 3H).

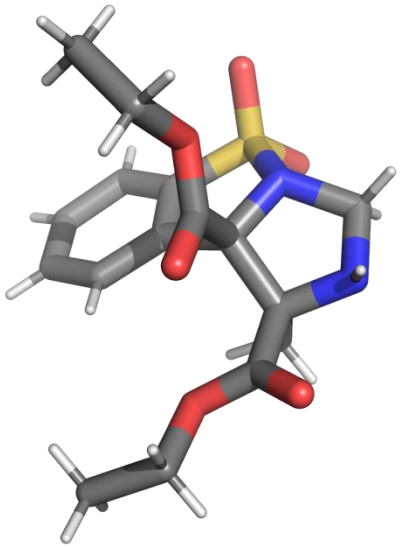
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 171.3, 136.6, 133.3, 133.3, 131.1, 127.4, 121.4, 80.4, 72.0, 63.2, 62.8, 62.7, 20.2, 14.2, 14.0.

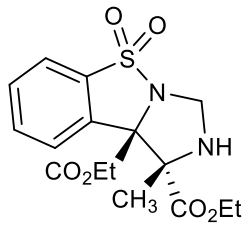
**HMRS (ESI)**: Calculated for $C_{16}H_{21}O_6N_2S$ = $[M+H]^+$: = 369.11148, found: 369.11103

Calculated for $C_{16}H_{20}O_6N_2NaS$ = $[M+H]^+$: = 391.09343, found: 391.09237

Calculated for $C_{16}H_{20}O_6N_2KS$ = $[M+H]^+$: = 407.06737, found: 407.06662

**Xray Deposition number at the Cambridge Crystallographic Data Centre: CCDC 1910465**





***anti-10***

**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 7.3 Hz, 1H), 7.63 – 7.56 (m, 2H), 5.14 (d, *J* = 9.8 Hz, 1H), 4.43 (d, *J* = 9.8 Hz, 1H), 4.30 (qd, *J* = 7.2, 1.6 Hz, 2H), 3.83 – 3.74 (m, 1H), 3.72 – 3.63 (m, 1H), 1.63 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 169.4, 168.1, 135.6, 133.2, 132.6, 130.8, 127.4, 120.9, 80.4, 74.7, 65.2, 62.9, 62.1, 20.2, 14.1, 13.5.

**HMRS (ESI)**: Calculated for $C_{16}H_{21}O_6N_2S = [M+H]^+$: = 369.11148, found: 369.11134

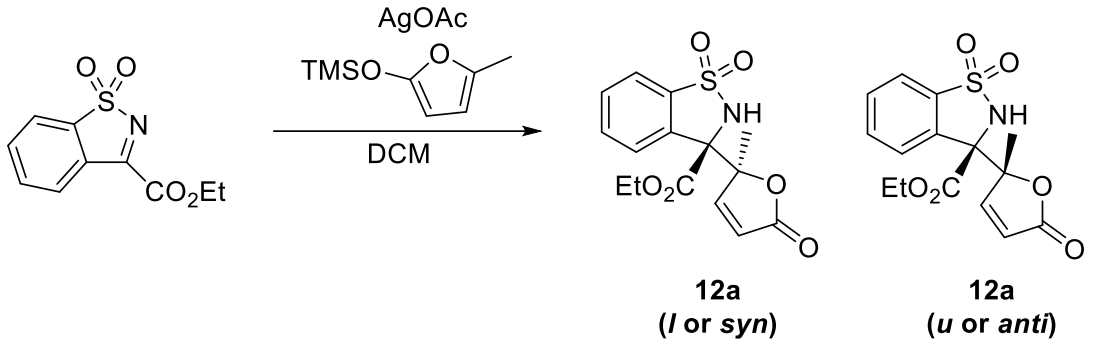
Calculated for $C_{16}H_{20}O_6N_2NaS = [M+H]^+$: = 391.09343, found: 391.09284

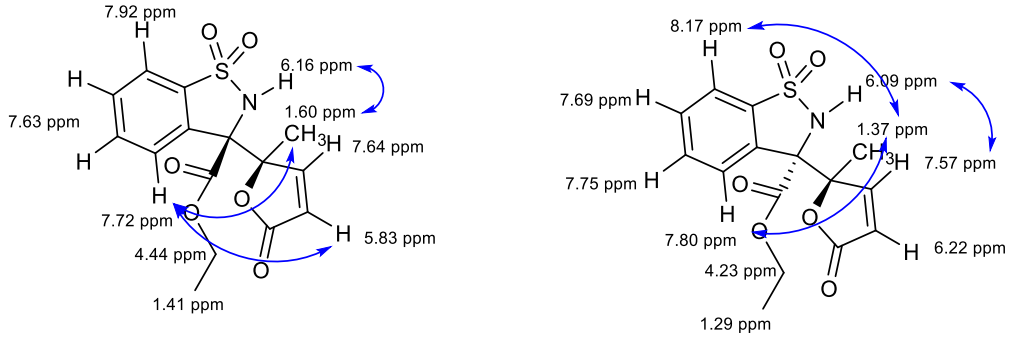
Calculated for $C_{16}H_{20}O_6N_2KS = [M+H]^+$: = 407.06737, found: 407.06702

**Table S1**: Conditions for optimizations of diastereoselectivity in 3+2 cyclization of *N*-sulfonyl ketimines (**1**) with α-silyl imines (**9**). Diastereoselectivity was determined by integration of peaks in $^{1}$H-NMR spectra of crude reaction mixtures

| Condition # | Phosphine | Solvent | T/°C | Scale / mmol | d.r. |
|---|---|---|---|---|---|
| 1 | Triphenylphosphine | DCM | -40 to 21 | 0.09 | n.d. |
| 2 | Tri-o-tolylphosphine | $Et_2O$ | 21 | 0.08 | 24:10 |
| 3 | Triphenylphosphine | $Et_2O$ | 21 | 0.08 | 19:10 |
| 4 | Tricyclohexylphosphine | $Et_2O$ | 21 | 0.08 | 10:9.2 |
| 5 | Tri(4-$CF_3$)-phenylphosphine | $Et_2O$ | 21 | 0.08 | 22:10 |
| 6 | XPhos | $Et_2O$ | 21 | 0.08 | 11:10 |
| 7 | Tri-o-tolylphosphine | MeCN | 21 | 0.08 | 5:1 |
| 8 | iPhox | MeCN | 21 | 0.08 | 100:17 |
| 9 | (*Sa*,*S*)-DTB-Bn-SIPHOX | MeCN | 21 | 0.08 | 100:23 |
| 10 | Tri(4-$CF_3$)-phenylphosphine | MeCN | 0 | 0.08 | 100:16 |
| 11 | Tri(4-$CF_3$)-phenylphosphine | MeCN | 0 | 0.3 | 100:15 |

## 2.2. Vinylogous Addition of Silyl Enol Ether to Ketimines (12a)




The proposed structures were based on evaluation of 1D –NOE NMR experiments (see below).

To 239 mg (1.0 eq, 1.00 mmol) of 3-carbethoxy 1,2 benzothiazole 1,1 dioxide (**1-$CO_2$Et**) and AgOAc in dry DCM (3.7 ml) under an Argon atmosphere in an oven-dried Schlenk flask, Silyl Enol Ether (1.6 eq, 312 µl, 1.60 mmol) was added at -78°C (Acetone-dry ice bath). The reaction was stirred at same temperature and monitored by TLC. After completion of reaction (10 min), sat. aqueous $NaHCO_3$ solution was added and stirred for 5 min at 0 °C, then transferred to a separation funnel and 8 ml of Ethyl acetate were added. Layers were separated and the aqueous layer was extracted two more times (8 ml Ethyl Acetate each). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After removal of solvent, the residue was purified using silica gel flash column chromatography (22% EA/CyH to 35% EA/CyH) to yield product in 89% yield (300 mg, 0.89 mmol) and 86:14 d.r.

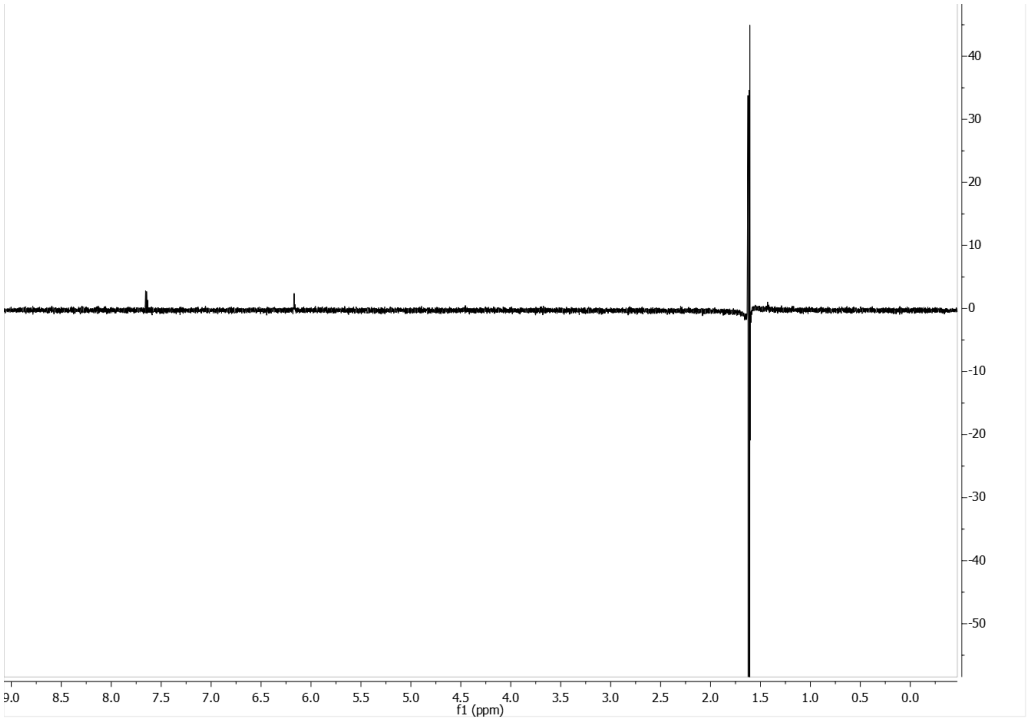
**(±)Ethyl 3-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (*l* or *syn* 12a)**

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.95 – 7.91 (m, 1H), 7.74 – 7.71 (m, 1H), 7.67 – 7.61 (m, 3H), 6.15 (s, 1H), 5.84 (d, *J* = 5.7 Hz, 1H), 4.52 – 4.39 (m, 2H), 1.61 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H); **$^{13}$C NMR** (126 MHz, Chloroform-d) δ 171.8, 167.9, 157.6, 135.8, 133.9, 132.2, 131.6,

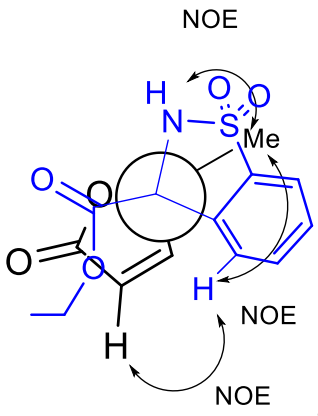
127.5, 123.1, 121.7, 89.6, 71.6, 64.9, 20.8, 14.2; **HMRS (ESI)**: Calculated for $C_{15}H_{16}O_6\,N\,S$ = $[M+H]^+$: = 338.06928, found: 338.06994

Calculated for $C_{15}\,H_{15}\,O_6\,N\,Na\,S$ = $[M+H]^+$: = 360.05123, found: 360.05266

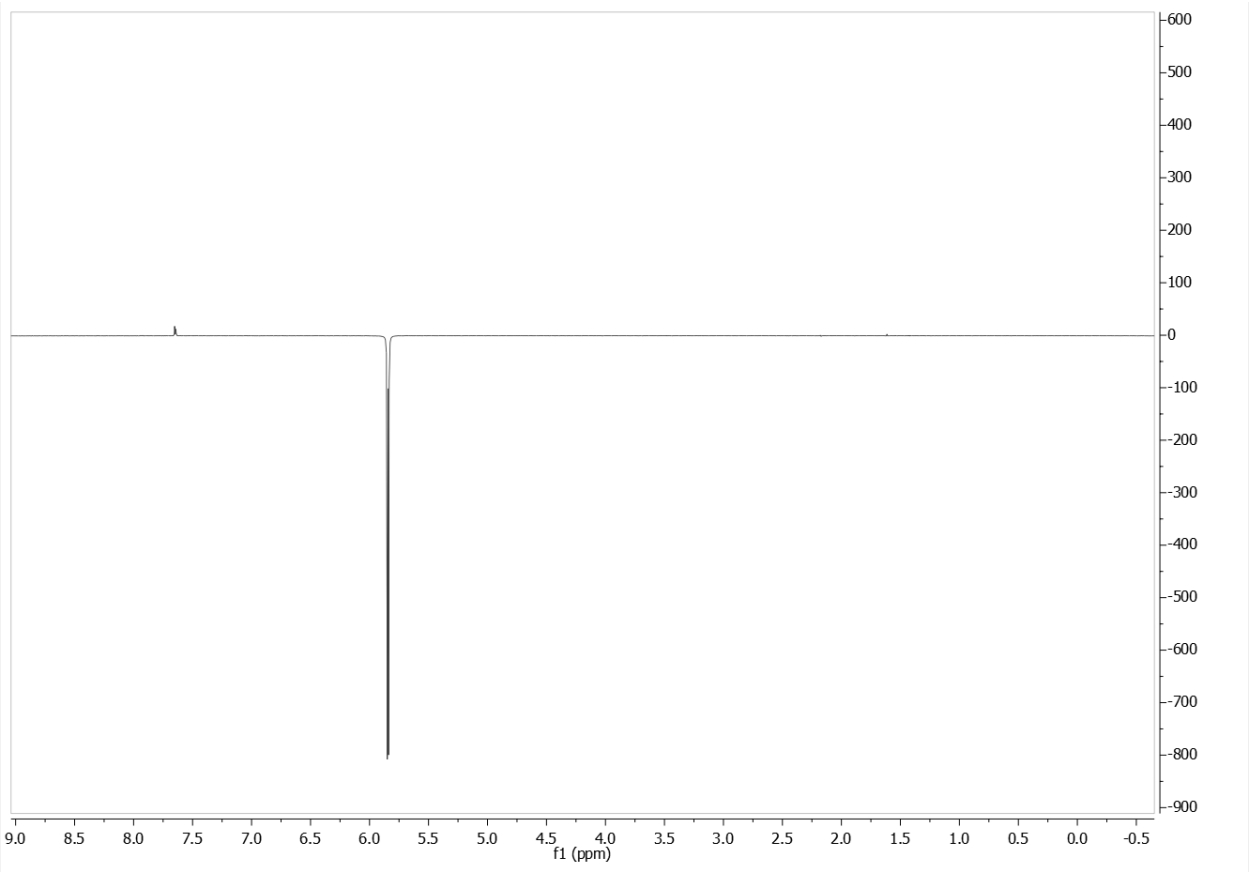
***l*-12a 1D NOE-experiments**




Irradiation of methyl group (1.6 ppm) shows NOE with sulfonamide amine N-H (6.15 ppm) and aromatic proton at ~7.6 ppm.




***syn*-12a or *l*-12a**




Irradiation of lactone proton in α carbonyl position (5.8 ppm) shows NOE to aromatic proton at roughly 7.6 ppm. Both observations lead us to conclude that we this is in fact diastereomer in conformation depicted in structure below.

**(±)-Ethyl 3-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (*anti or l*-12a)**

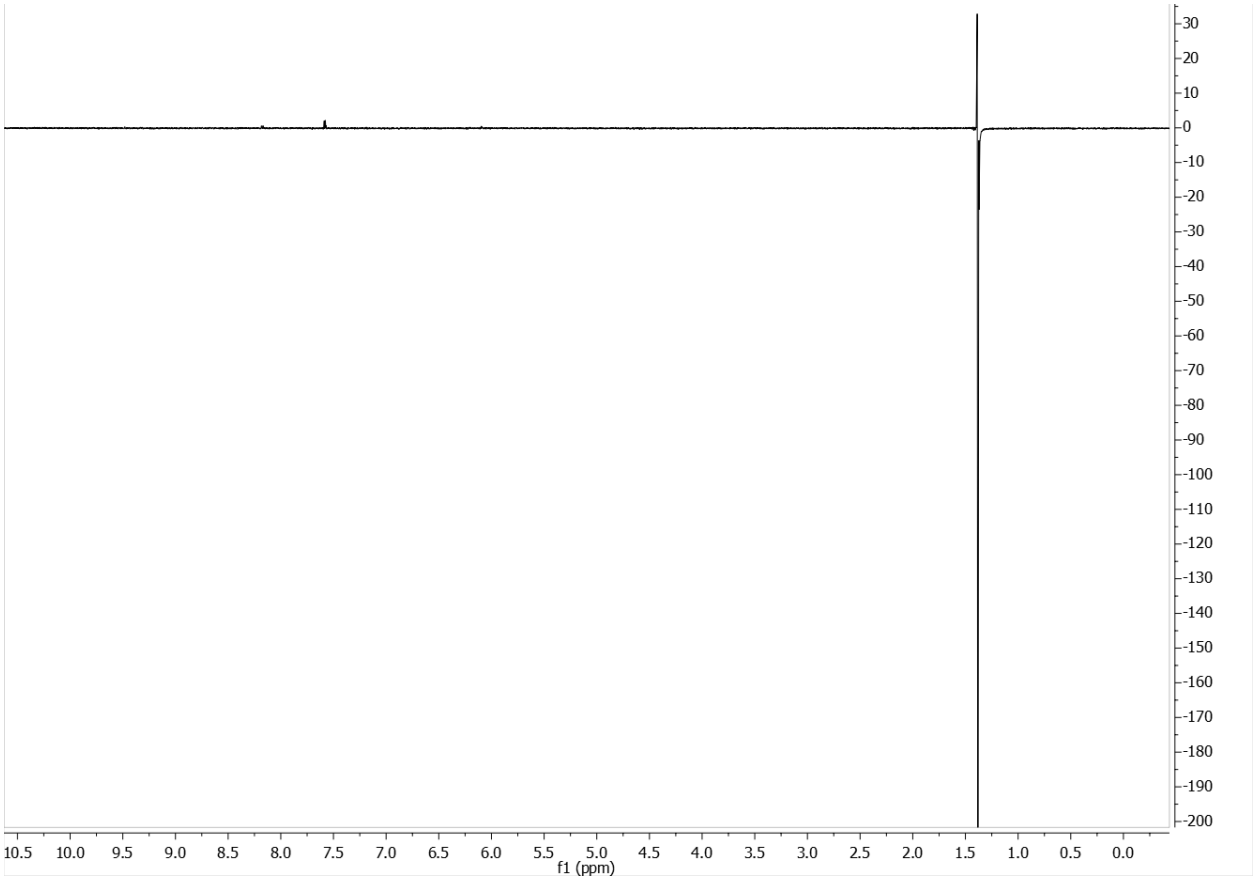
**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 8.17 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.82 – 7.79 (m, 1H), 7.75 (td, *J* = 7.6, 1.3 Hz, 1H), 7.69 (td, *J* = 7.6, 1.1 Hz, 1H), 7.57 (d, *J* = 5.7 Hz, 1H), 6.20 (d, *J* = 5.6 Hz, 1H), 6.09 (s, 1H), 4.29 – 4.16 (m, 2H), 1.37 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 171.1, 167.7, 157.7, 136.3, 133.9, 132.4, 131.6, 128.7, 123.3, 121.6, 90.4, 72.0, 60.5, 19.6, 13.9.

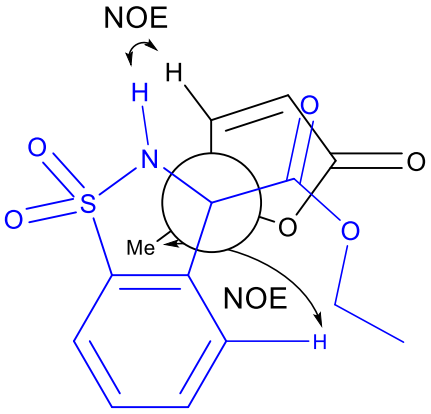
**HMRS (ESI)**: Calculated for $C_{15}H_{16}O_6NS = [M+H]^+$: = 338.06928, found: 338.06966

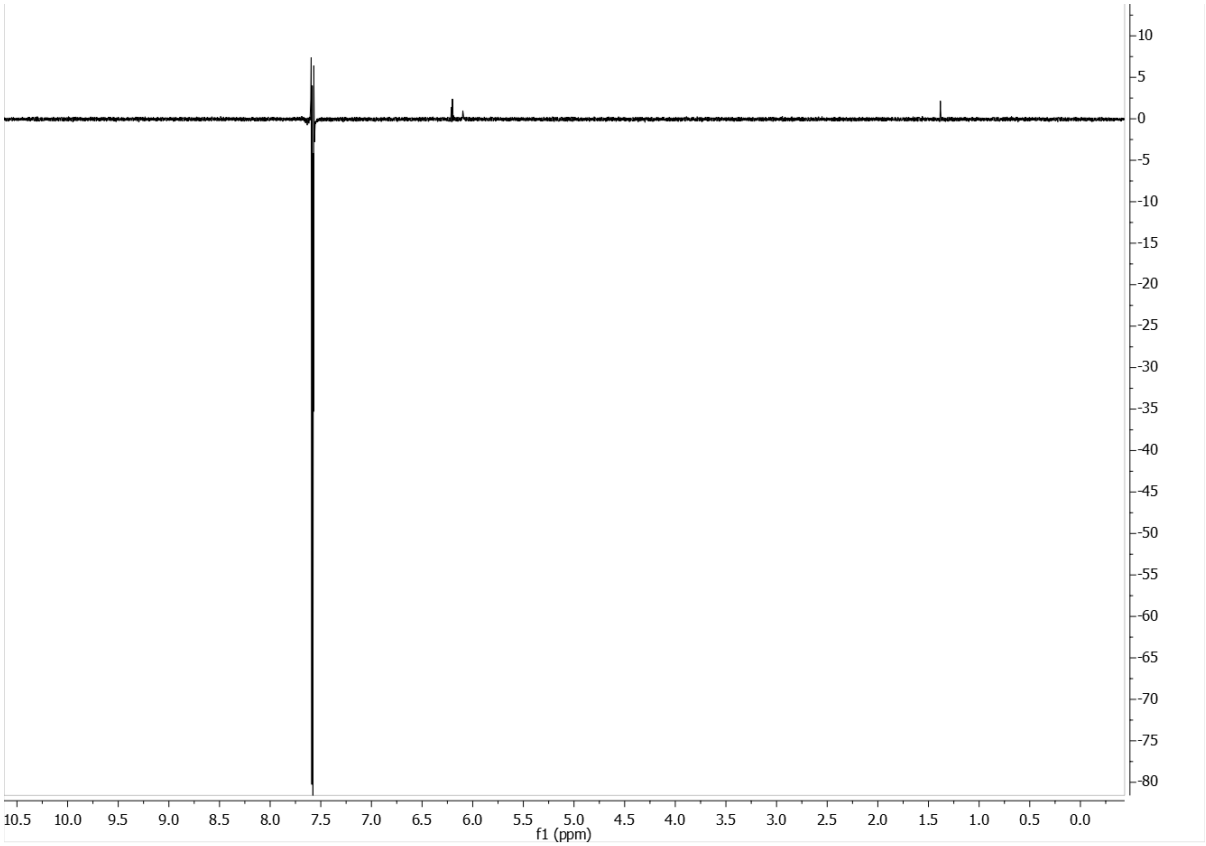
Calculated for $C_{15}H_{15}O_6NNaS = [M+H]^+$: = 360.05123, found: 360.05123

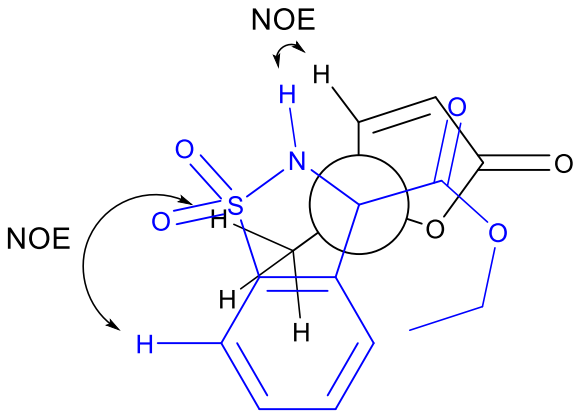
***anti*- or *l*-12a 1D NOE-experiments**

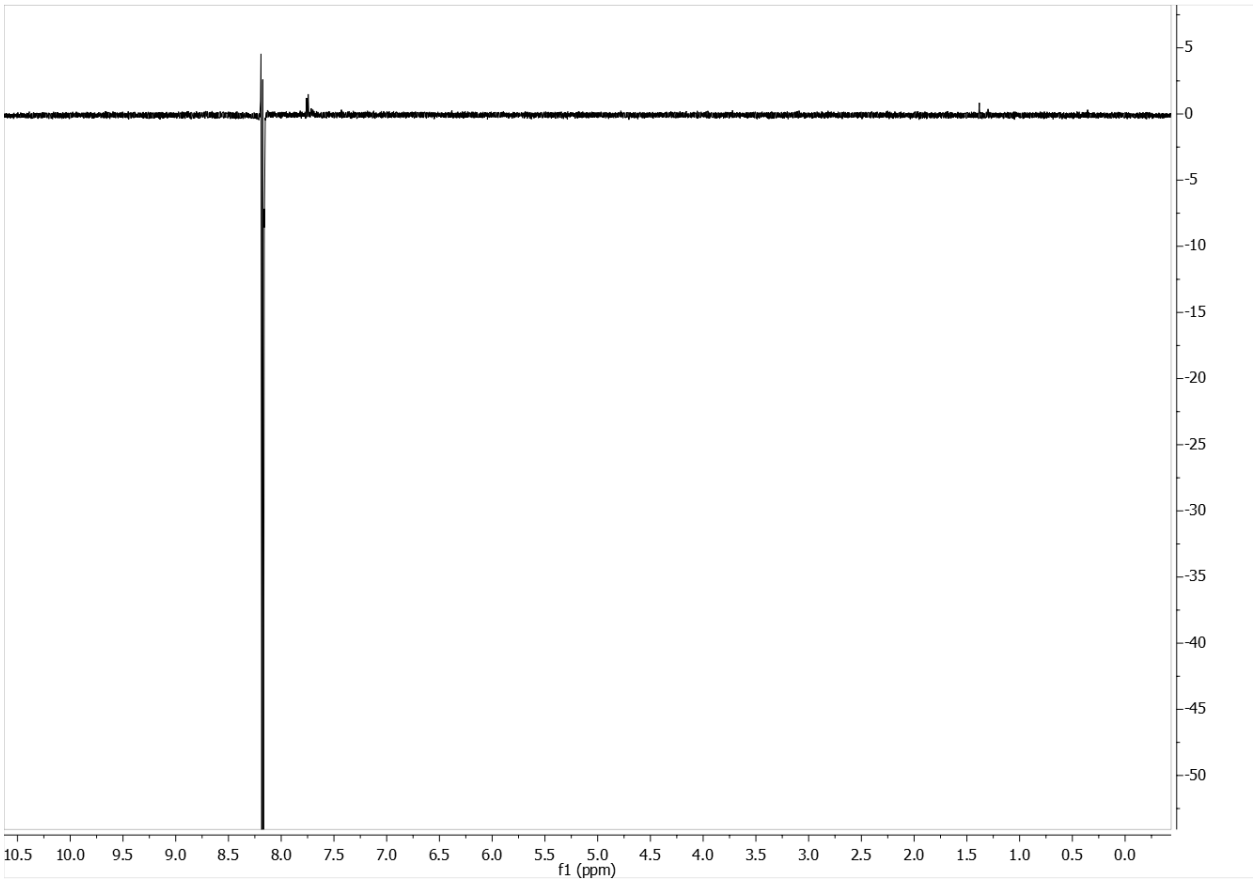



Aromatic proton shows weak NOE of methyl group (1.4 ppm) with aromatic proton at 7.8 ppm, hinting towards conformation depicted below.

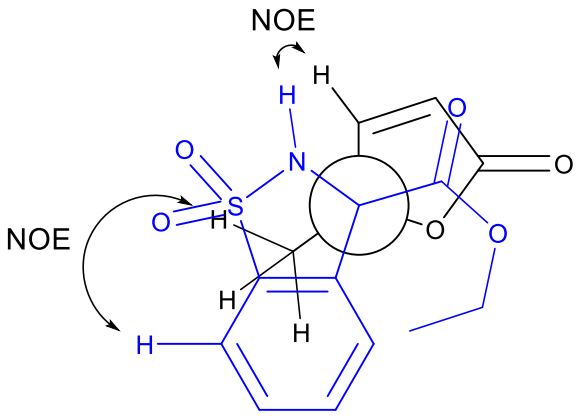



10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


NOE
H
H
O
O
N
O
S
O
H
O
O
NOE
H
H
H




Irradiation of 7‘ (8.15 ppm) shows NOE with not only neighbouring aromatic proton (~7.6 ppm) but also weak effect with methyl group (1.37 ppm).

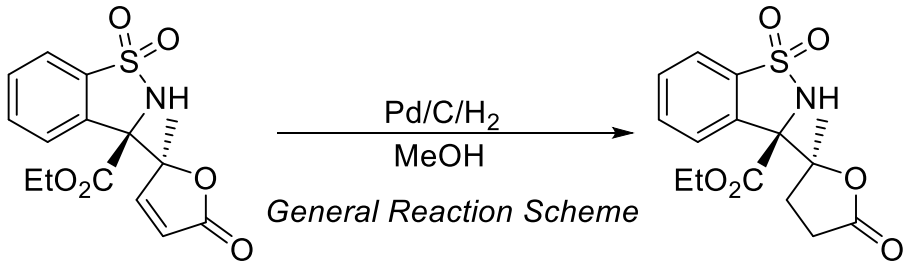


### 2.2.1 Screening conditions for improvement of 12a diastereomeric ratio

**Table S1:** Screening conditions to improve d.r. of vinylogous addition to ketimines.

| Condition # | Catalyst | Solvent | d.r. |
|---|---|---|---|
| 1 | $Ti(O^iPr)_4$ | DCM | 1:2 |
| 2 | $Zn(OTf)_2$ | DCM | n.d. Complex mixture |
| 3 | $Cu(OTf)_2$ | DCM | 3:1 |
| 4 | $Dy(OTf)_3$ | DCM | n.d. – Complex mixture |
| 5 | AgOAc | $Et_2O$ | 2:1 (f2:f1) |
| 6 | AgOAc | THF | 10:13 |
| 7 | AgOAc | DCM +TMEDA | 10:6.8 |
| 8 | AgOAc | DCM | 93:7 |

**(±)-3-ethyl-1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-3-yl)-5-methyldihydrofuran-2(3H)-one-carbon dioxide (*syn or I*-12b)**




Sulfonamide ***syn*-12a** (62 mg, 183.8 µmol) and Pd on Carbon (10 wt.%, 22.5 mg, 21.14 µmol) were dissolved in EtOH (1.4 ml) in a 10 ml Schlenk tube and stirred at ambient temperature (21 °C). The vessel was evacuated and refilled with hydrogen. This was repeated two times. The mixture was allowed to come to ambient temperature and stirred under an hydrogen atmosphere for 3 h. Then, reaction mixture was filtered over celite, concentrated and objected to silica gel column chromatography (25% to 35% EA/CyH) to yield 39 mg (0.11 mmol, 63%) of product sulfonamide and recover 28 mg (0.07 mmol, 37%) of starting material.

**$^1$H NMR** (700 MHz, Chloroform-*d*) δ 8.02 – 7.99 (m, 1H), 7.81 – 7.78 (m, 1H), 7.69 – 7.65 (m, 2H), 6.05 (s, 1H), 4.44 – 4.32 (m, 2H), 2.51 – 2.45 (m, 1H), 2.16 – 2.11 (m, 1H), 2.07 – 1.98 (m, 2H), 1.52 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H).

**$^{13}$C NMR** (176 MHz, Chloroform-d) δ 175.9, 168.4, 136.4, 133.7, 132.4, 131.4, 128.3, 121.7, 87.4, 72.7, 64.4, 29.8, 28.0, 23.8, 14.0.

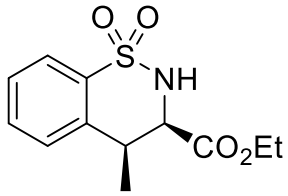
**HMRS (ESI)**: Calculated for $C_{15}H_{18}O_6NS = [M+H]^+$: = 340.08493, found: 340.08524

Calculated for $C_{15}H_{17}O_6NNaS = [M+H]^+$: = 362.06688, found: 362.06717

## 2.3 Folding Pathway

### 2.3.1 Hydrogenolysis of Aziridines

**(±)- 4-methyl-3-carbethoxy-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide (13a)**

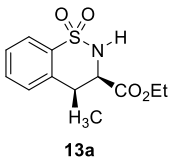



Sulfonamide **2b** (1.0 eq., 40 mg, 0.15 mmol) and Palladium on carbon (10 wt.%, 0.1 eq., 8.0 mg, 0.05 mmol) were dissolved in 1 ml Ethanol in a 10 ml tube equipped with a stirring bar. The vessel was evacuated and refilled with hydrogen using a balloon. This was repeated twice and the reaction was left stirring at 21 °C under an hydrogen atmosphere for 4 h. Then, it was filtered using a syringe filter and concentrated under reduced pressure to give 24 mg (0.09 mmol, 60% yield) product.

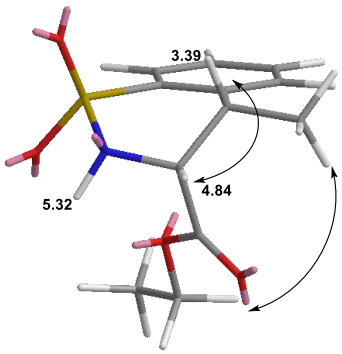
**$^{1}$H NMR** (700 MHz, Chloroform-*d*) δ 7.81 (dq, *J* = 7.9, 1.4 Hz, 1H), 7.50 (tt, *J* = 7.6, 1.3 Hz, 1H), 7.41 (tq, *J* = 7.6, 1.2 Hz, 1H), 7.28 (dd, *J* = 8.0, 1.2 Hz, 1H), 5.36 – 5.27 (m, 1H), 4.84 (ddd, *J* = 10.4, 3.7, 1.0 Hz, 1H), 4.32 (qt, *J* = 7.2, 1.2 Hz, 2H), 3.39 (qd, *J* = 7.2, 3.7 Hz, 1H), 1.35 (td, *J* = 7.2, 1.2 Hz, 3H), 1.23 (d, *J* = 7.2 Hz, 3H).

**$^{13}$C NMR** (176 MHz, Chloroform-d) δ 168.3, 139.2, 136.4, 132.6, 129.4, 128.2, 124.1, 62.4, 57.8, 34.7, 17.5, 14.2.

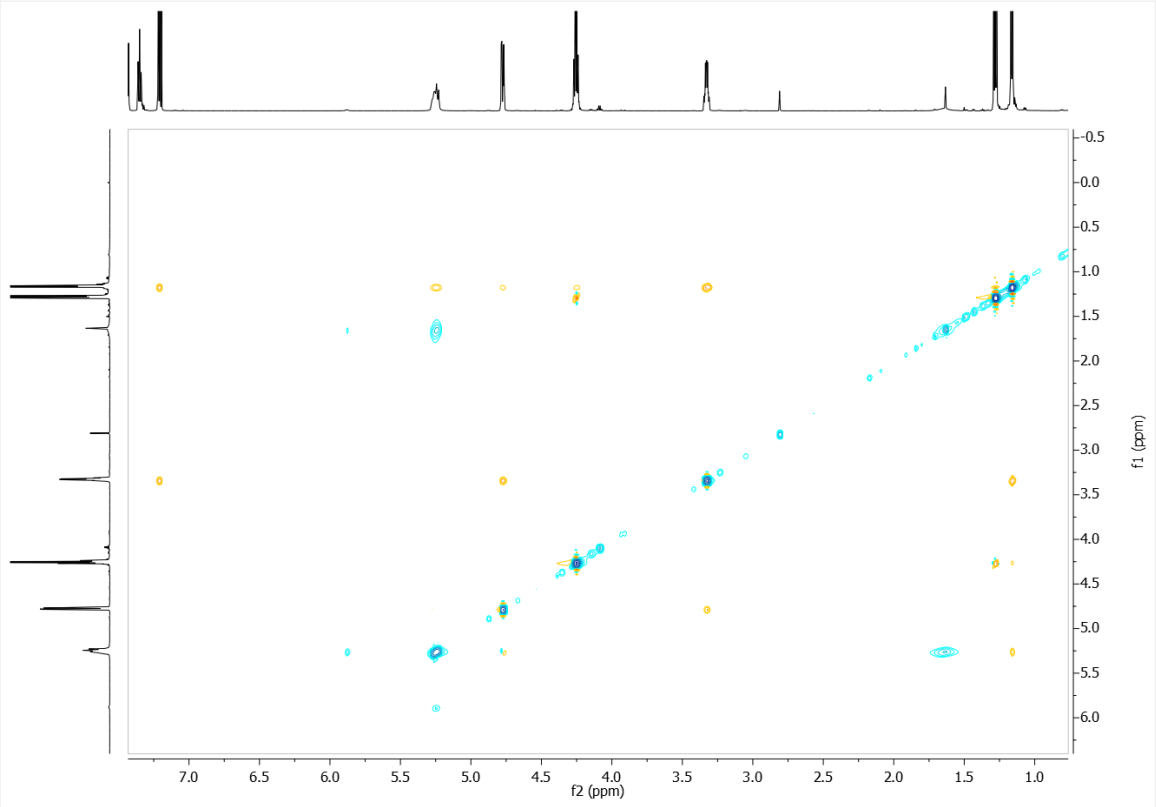
**HMRS (ESI)**: Calculated for $C_{12}$ $H_{16}$ $O_4$ N S $[M+H]^+$: = 270.07946, found: 270.07923



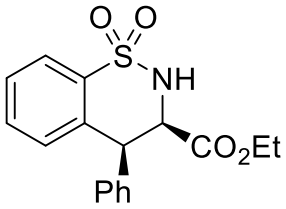

**13a**



**NOESY**




**(±)-*syn*- 4-Phenyl-3-carbethoxy-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide (13b)**



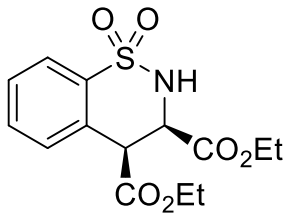

Sulfonamide **2d** (1.0 eq., 17 mg, 51.61 µmol) was combined with Pd/C (10 wt.%, 4.4 mg, 4.13 µmol ) in a 10 ml Schlenk tube and dissolved in 500 µl of a Ethanol/Ethyl acetate mixture (2:1 v/v). The reaction vessel was carefully evacuated under stirring and refilled with hydrogen. This was repeated twice and the reaction was allowed to stir at 21 °C under an hydrogen atmosphere. After completion of conversion, the reaction mixture was filtered using a syringe filter and concentrated to give 16 mg (0.05 mmol, quantitative) of desired product.

**$^{1}$H NMR** (700 MHz, Chloroform-*d*) δ 7.95 – 7.90 (m, 1H), 7.49 – 7.41 (m, 2H), 7.31 – 7.22 (m, 3H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.96 (dd, *J* = 7.3, 2.2 Hz, 2H), 5.11 (d, *J* = 11.7 Hz, 1H), 5.04 (dd, *J* = 11.7, 3.8 Hz [syn], 1H), 4.58 (d, *J* = 3.8 Hz [syn], 1H), 4.15 – 4.03 (m, 2H), 1.16 (t, *J* = 7.1 Hz, 3H).

**$^{13}$C NMR** (176 MHz, Chloroform-d) δ 167.1, 137.4, 137.2, 136.7, 132.9, 130.9, 129.2, 129.0, 128.9, 128.4, 124.3, 62.3, 58.8, 46.0, 14.1.

**HMRS (ESI)**: Calculated for $C_{17}$ $H_{18}$ $O_4$ N S = $[M+H]^+$: = 332.09511, found: 332.09556

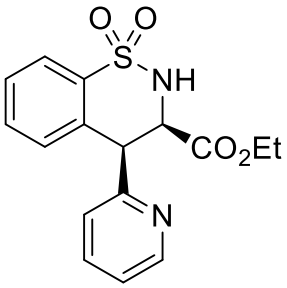
**(±)-*syn*- Diethyl 3,4-dihydro-2H-benzo[e][1,2]thiazine-3,4-dicarboxylate 1,1-dioxide (13c)**




Sulfonamide **2e** (1.0 eq., 20 mg, 61.47 µmol ) and Palladium on carbon (10 wt.%, 0.1 eq., 6.5 mg, 0.01 mmol) were dissolved in 650 µl of a 3:1 Ethanol/Ethyl Acetate (v/v) mixture in a 10 ml Schlenk tube equipped with a stirring bar. The vessel was evacuated and refilled with hydrogen using a balloon. This was repeated twice and the reeaction was left stirring at 21 °C under an hydrogen atmosphere. After completion of conversion, filtration using a syringe filter and concentration delivered desired 8 mg (0.02 mmol, 40% yield) of desired sulfonamide as one diastereomer.

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.91 – 7.87 (m, 1H), 7.60 – 7.48 (m, 3H), 5.84 (d, *J* = 12.4 Hz, 1H), 4.85 (dd, *J* = 12.4, 3.9 Hz [syn], 1H), 4.31 (qd, *J* = 7.1, 1.1 Hz, 2H), 4.27 (d, *J* = 3.9 Hz [syn], 1H), 4.17 (qd, *J* = 7.1, 3.3 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 170.8, 168.1, 137.3, 132.8, 130.8, 130.7, 129.9, 125.1, 63.0, 62.8, 56.5, 44.8, 14.4, 14.3.
**HMRS (ESI)**: Calculated for $C_{14}$ $H_{18}$ $O_6$ N S = $[M+H]^+$: = 328.08493, found: 328.08529

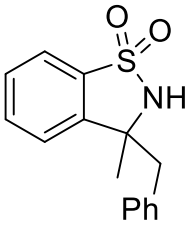
**(±)-Ethyl (*syn*)-C4-(pyridin-2-yl)phenylalaninate 1,1-dioxide (13d)**




Palladium on carbon (0.1 eq., 6.4 mg, 6.05 µmol) and Sulfonamide **2g** (1.0 eq., 20 mg, 60.54 µmol) were combined in 600 µl Ethanol/Ethyl Acetate (3:1 v/v) in a 10 ml Schlenk tube equipped with a magnetic stirring bar. The vessel was evacuated and refilled with hydrogen. This procedure was repeated 2 times. The mixture was kept stirring for 4 h. Then, it was filtered using a syringe filter and concentrated to give product 6 mg sulfonamide (0.02 mmol, 30%).

**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 8.43 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.95 – 7.89 (m, 1H), 7.68 (td, *J* = 7.7, 1.8 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.33 – 7.28 (m, 1H), 7.25 – 7.21 (m, 1H), 7.18 (ddd, *J* = 7.7, 4.9, 1.1 Hz, 1H), 5.12 (dd, *J* = 12.2, 4.1 Hz, 1H), 4.56 (d, *J* = 4.1 Hz, 1H), 4.06 (qd, *J* = 7.1, 2.5 Hz, 2H), 1.08 (t, *J* = 7.1 Hz, 3H).
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 168.0, 159.2, 149.9, 137.7, 137.1, 136.1, 132.4, 130.0, 128.8, 124.9, 123.3, 123.2, 62.0, 58.9, 45.6, 14.1.
**HMRS (ESI)**: Calculated for $C_{16}$ $H_{17}$ $O_4$ $N_2$ S = $[M+H]^+$: = 333.09035, found: 333.09018

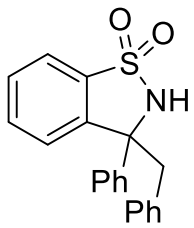
**(±)-4-methyl-3-phenyl-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide (14a)**




Sulfonamide **2a** (1.0 eq., 20 mg, 73.71 µmol) and Palladium on carbon (10 wt.%, 0.1 eq., 7.8 mg, 0.01 mmol) were dissolved in 750 µl of a 3:1 (v/v) Ethanol/Ethyl Acetate Mixture in a 10 ml tube equipped with a stirring bar. The vessel was evacuated and refilled with hydrogen using a balloon. This was repeated twice and the reaction was left stirring at 21 °C under an hydrogen atmosphere for 16 h. Then it was filtered using a syringe filter and concentrated under reduced pressure to give 22 mg (0.08 mmol, 69%) of sulfonamide.

**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 7.76 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.65 (td, *J* = 7.6, 1.1 Hz, 1H), 7.54 (td, *J* = 7.6, 1.0 Hz, 1H), 7.36 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.35 – 7.27 (m, 3H), 7.23 – 7.18 (m, 2H), 4.69 (s, 1H), 3.18 (d, *J* = 13.6 Hz, 1H), 3.03 (d, *J* = 13.6 Hz, 1H), 1.57 (s, 3H).
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 144.9, 135.5, 135.3, 133.3, 130.9, 129.5, 128.6, 127.5, 123.5, 121.6, 63.6, 47.8, 26.7.
**HMRS (ESI)**: Calculated for $C_{15}$ $H_{15}$ $O_2$ N S = $[M+H]^+$: $C_{15}$ $H_{16}$ $O_2$ N S = 274.08963, found: 274.08965

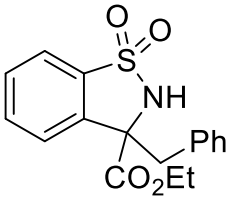
**(±)-3-benzyl-3-methyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (14b)**




Sulfonamide **2c** (1.0 eq., 20 mg, 0.06 mmol) and Palladium on carbon (10 wt.%, 0.1 eq., 6.4 mg, 0.01 mmol) were dissolved in 600 µl Ethanol/Ethyl Acetate (3:1 v/v) in a 10 ml tube equipped with a stirring bar. The vessel was evacuated and refilled with hydrogen using a balloon. This was repeated twice and the reaction was left stirring at 21 °C under an hydrogen atmosphere for 4 h. Then, it was filtered using a syringe filter and concentrated under reduced pressure to give 6 mg (0.02 mmol, 30% yield) product.

**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 7.74 – 7.66 (m, 3H), 7.63 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 7.52 (ddd, *J* = 8.5, 7.7, 1.2 Hz, 2H), 7.42 – 7.37 (m, 2H), 7.35 – 7.30 (m, 1H), 7.24 – 7.15 (m, 3H), 6.94 (dt, *J* = 6.6, 1.6 Hz, 2H), 4.88 (s, 1H), 3.77 (d, *J* = 14.0 Hz, 1H), 3.59 (d, *J* = 14.0 Hz, 1H).
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 143.2, 141.8, 134.7, 134.5, 133.3, 130.6, 129.6, 129.1, 128.8, 128.4, 127.8, 126.4, 125.0, 121.7, 68.8, 46.6
**HMRS (ESI)**: Calculated for $C_{20}$ $H_{18}$ $O_2$ N S = $[M+H]^+$: $C_{15}$ $H_{16}$ $O_2$ N S = 336.10528, found: 336.10549

**(±)-Ethyl 3-benzyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (14c)**




Ethyl 1-phenylazirino[1,2-b]benzo[d]isothiazole-7b(1H)-carboxylate 3,3-dioxide **2f** (1.0 eq., 23 mg, 69.83 µmol) was combined with Palladium on Carbon(10 wt.%, 0.1 eq., 7.4 mg, 0.01 mmol) in a 10 ml Schlenk tube and dissolved in 700 µl of a Ethanol/Ethyl acetate mixture (5:1 v/v). The reaction vessel was carefully evacuated under stirring and refilled with hydrogen. This was repeated twice and the reaction was allowed to stir at 21 °C under an hydrogen atmosphere. The reaction was monitored via TLC. After completion of conversion, reaction mixture was filtered using a syringe filter and concentrated to give 12 mg sulfonamide product (0.04 mmol, 66%).

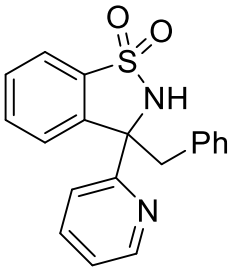
**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 7.74 – 7.66 (m, 3H), 7.63 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 7.52 (ddd, *J* = 8.5, 7.7, 1.2 Hz, 2H), 7.42 – 7.37 (m, 2H), 7.35 – 7.30 (m, 1H), 7.24 – 7.15 (m, 3H), 6.94 (dt, *J* = 6.6, 1.6 Hz, 2H), 4.88 (s, 1H), 3.77 (d, *J* = 14.0 Hz, 1H), 3.59 (d, *J* = 14.0 Hz, 1H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 143.6, 141.8, 134.7, 134.5, 133.3, 130.6, 129.6, 129.1, 128.8, 128.4, 127.8, 126.4, 125.0, 121.7, 68.8, 46.6,

**HMRS (ESI)**: Calculated for $C_{17}$ $H_{18}$ $O_4$ N S = $[M+H]^+$: = 332.09511, found: 332.09535

Calculated for $C_{17}$ $H_{17}$ $O_4$ N Na S = $[M+H]^+$: = 354.07705, found: 354.07723

**(±)-3-benzyl-3-(pyridin-2-yl)-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide(14d)**

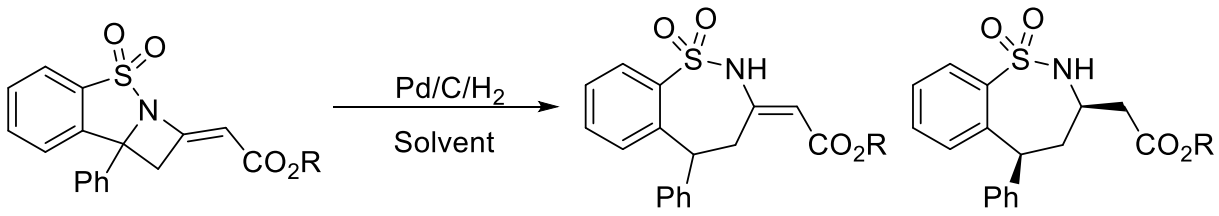



1-phenyl-7b-(pyridin-2-yl)-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole 3,3-dioxide **2h** (1.0 eq., 10 mg, 29.90 µmoll) was combined with Pd/C (10 wt.%; 0.15 eq., 4.7 mg, 4.49 µmol) and dissolved in 500 µl Ethanol/Ethyl Acetate (2:1) in a 10 ml round bottom flask equipped with a magnetic stirring bar and a septum. The mixture was carefully evacuated and refilled with hydrogen (using a hydrogen-filled balloon). This procedure was repeated twice and the reaction was stirred under an hydrogen atmosphere at 21 °C and monitored by TLC. After 15

h, the reaction mixture was filtered. Concentration delivered crude reaction mixture. Silica gel column chromatography yielded 5 mg (0.01 mmol, 50%) of product sulfonamide.

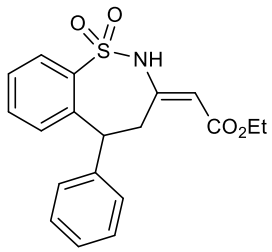
**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 8.63 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.97 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.73 (d, *J* = 7.76 Hz), 7.70 –7.61 (m, 2H), 7.53 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.22 (ddd, *J* = 7.3, 4.8, 1.2 Hz, 1H), 7.20 – 7.13 (m, 3H), 6.99 – 6.94 (m, 2H), 5.83 (s, 1H), 4.10 (d, *J* = 13.8 Hz, 1H), 3.44 (d, *J* = 13.8 Hz, 1H).
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 158.9, 148.9, 142.5, 137.5, 135.2, 134.5, 133.4, 130.5, 129.8, 128.7, 127.6, 125.5, 123.1, 121.4, 121.0, 69.5, 46.9.
**HMRS (ESI)**: Calculated for $C_{19}$ $H_{17}$ $O_2$ N2 S = $[M+H]^+$: = 337.10053, found: 337.10054

### 2.3.2 Hydrogenolysis of Azetidines 15




*General Reaction Scheme*

**(±)-Ethyl (E)-2-(1,1-dioxido-5-phenyl-4,5-dihydrobenzo[f][1,2]thiazepin-3(2H)-ylidene)-acetate (15a')**

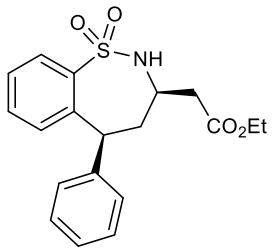



Sulfonamide **4a** (1.0 eq., 350 mg, 0.98 mmol) was dissolved in 10 ml Ethyl acetate and 83 mg (10wt.% Pd/C, 8 mol%., 78 µmol) and charged with 8 atm hydrogen in a high pressure cylinder and was stirred for 60 h at 21 °C. Eight drops of glacial AcOH were added and the reaction was placed again under 7.5 atm of hydrogen and stirred at that temperature. After 20 h, almost no conversion could be determined and another 6 mol% of Pd/C were added (by that time, it contained 141 mg, 0.14 eq.,0.13 mmol of Pd/C in total). It was stirred for 18 additional hours. As no further conversion (TLC, U-HPLC-MS analysis) could be observed, reaction mixture was filtered over celite and concentrated. Silica gel column chromatography

(12% to 15% EA/CyH) yielded Products **15a'** and **15a** in 49% (173mg, 0.48 mmol) and 51% (179 mg, 0.50 mmol) yield.

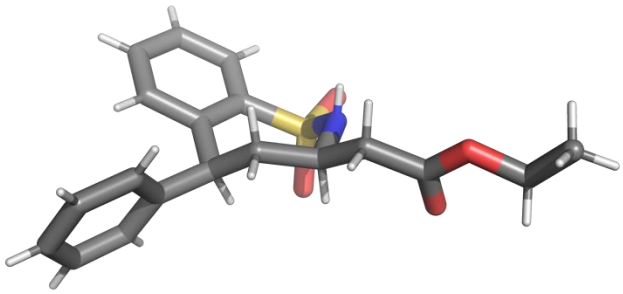
**$^1$H NMR** (700 MHz, Chloroform-*d*) δ 11.02 (s, 1H), 7.38 (td, *J* = 7.5, 1.6 Hz, 1H), 7.34 (td, *J* = 7.6, 1.4 Hz, 1H), 7.29 (td, *J* = 7.3, 6.6, 1.2 Hz, 2H), 7.24 – 7.21 (m, 1H), 7.18 – 7.15 (m, 2H), 7.14 (dt, *J* = 7.6, 1.0 Hz, 1H), 4.93 (s, 1H), 4.59 (dd, *J* = 10.0, 5.2 Hz, 1H), 4.12 (qd, *J* = 7.1, 1.9 Hz, 2H), 3.73 (t, *J* = 12.6 Hz, 1H), 3.24 – 3.17 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H).
**$^{13}$C NMR** (176 MHz, Chloroform-d) δ 168.9, 152.2, 144.4, 139.4, 139.3, 134.1, 132.7, 129.1, 128.3, 127.3, 127.0, 125.8, 96.4, 60.3, 50.8, 38.4, 14.3.
**HMRS (ESI)**: Calculated for $C_{19}H_{20}O_4NS$ = $[M+H]^+$: = 358.11076, found: 358.11134
Calculated for $C_{19}H_{19}O_4NNaS$ = $[M+H]^+$: = 380.09270, found: 380.09279

**(±)-Ethyl 2-((*syn*)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-3-yl)acetate (15a)**

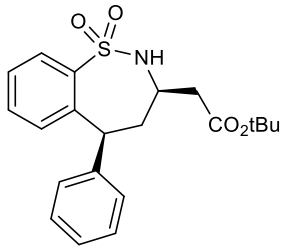



**$^1$H NMR** (400 MHz, Chloroform-d) δ 8.09 – 8.04 (m, 1H), 7.45 – 7.37 (m, 2H), 7.34-7.27 (m, 3H), 7.25 – 7.22 (m, 2H), 6.66 – 6.61 (m, 1H), 6.67 – 6.59 (m, 1H), 5.40 (d, *J* = 9.6 Hz, 1H), 5.11 (dd, *J* = 5.8, 2.5 Hz, 1H), 4.41 – 4.31 (m, 1H), 4.21 – 4.08 (m, 2H), 2.79 (dd, *J* = 16.6, 4.9 Hz, 1H), 2.59 (dd, *J* = 16.6, 4.9 Hz, 1H), 2.31-2.25 (m, 2H), 1.28 – 1.24 (t, *J* = 7.04 Hz, 3H).
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 171.7, 143.4, 142.8, 141.2, 132.8, 129.7, 129.2, 129.1, 127.8, 127.4, 126.8, 61.4, 53.3, 46.6, 39.7, 39.1, 14.3.
**HMRS (ESI)**: Calculated for $C_{19}H_{22}O_4NS$ = $[M+H]^+$: = 360.12641, found: 360.12695

**Xray Deposition number at the Cambridge Crystallographic Data Centre: CCDC 1910510**



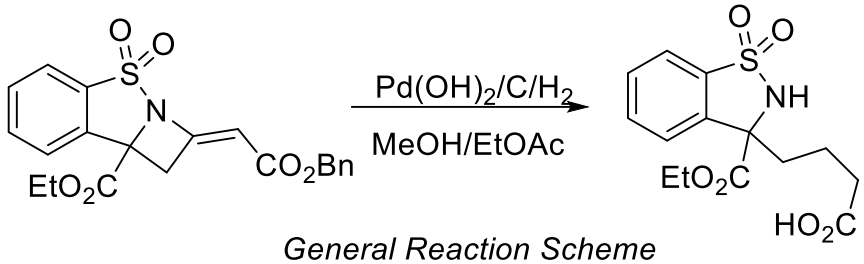
**(±)-Tert-butyl 2-((*syn*)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-3-yl)acetate (15b)**




59% yield (0.64 mmol, 274 mg)

**$^{1}$H NMR** (600 MHz, Chloroform-d) δ 8.10 – 8.06 (m, 1H), 7.45 – 7.42 (m, 2H), 7.37 – 7.34 (m, 1H), 7.33 – 7.30 (m, 2H), 7.28 – 7.26 (m, 2H), 6.67 – 6.64 (m, 1H), 5.50 (d, *J* = 9.5 Hz, 1H), 5.13 (d, *J* = 9.9 Hz, 1H), 4.37 – 4.30 (m, 1H), 2.76 (dd, *J* = 16.7, 4.7 Hz, 1H), 2.51 (dd, *J* = 16.7, 4.9 Hz, 1H), 2.36 – 2.25 (m, 2H), 1.46 (s, 9H).
**$^{13}$C NMR** (151 MHz, Chloroform-d) δ 171.0, 143.3, 142.7, 141.0, 132.5, 129.4, 129.0, 128.9, 127.6, 127.1, 126.6, 53.3, 46.5, 40.4, 38.8, 28.1, 26.9.
**HMRS (ESI)**: Calculated for $C_{21}H_{26}O_4NNaS$ = $[M+Na]^+$: = 411.14748, found: 411.14993

**(±)-4-(3-(ethoxycarbonyl)-1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-3-yl)butanoic acid (16)**




*General Reaction Scheme*

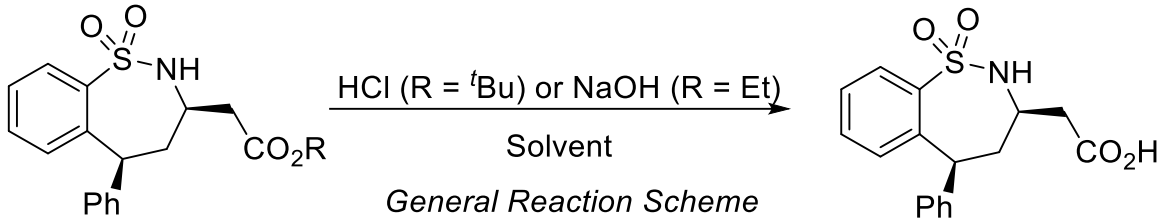
Pearlman's catalyst (20wt%., 9mol%, 7.2 mg, 0.01 mmol) and **4d** (1.0 eq.,50 mg, 0.12 mmol) were dissolved in a 3:1 (v/v) Methanol/Ethyl Acetate Mixture (1.250) in a 10 ml tube equipped with a stirring bar. The vessel was placed in a high-pressure reactor, which was then sealed and charged with Hydrogen (9 atm). The reactor was placed on a stirring plate and left there for 2 h. Then, reaction mixture was filtered to furnish 37 mg (0.11 mmol, 93% yield) of (+)-4-(3-(ethoxycarbonyl)-1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-3-yl)butanoic acid **16**.

**$^{1}$H NMR** (700 MHz, Chloroform-d) δ 7.76 (d, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.66 (t, *J* = 7.7 Hz), 7.60 (dd, *J* = 11.1, 3.9 Hz, 1H), 5.83 (s, 1H), 4.37 – 4.28 (m, 2H), 2.43 (dt, *J* = 16.7, 7.0 Hz, 1H), 2.36 (dt, *J* = 16.7, 7.3 Hz, 1H), 2.29 (ddd, *J* = 13.7, 11.5, 4.8 Hz, 1H), 2.05 (ddd, *J* = 13.7, 11.7, 4.8 Hz, 1H), 1.76 – 1.64 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).

**$^{13}$C NMR** (176 MHz, Chloroform-d) δ 178.3, 169.9, 137.9, 135.4, 133.6, 130.6, 124.9, 121.5, 69.0, 63.8, 39.3, 33.1, 19.7, 14.1.

**HMRS (ESI)**: Calculated for $C_{14}H_{18}O_6NS$ = $[M+H]^+$: = 328.08493, found: 328.08477

### 2.3.2.1 Hydrolysis of Esters 15




*General Reaction Scheme*

**(±)-2-((*syn*)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-3-yl)acetic acid (17)**

**By hydrolysis from Ethyl Ester 15a**

Sulfonamide **15a** (1.0 eq. 252 mg, 701.09 µmol) was dissolved in 9.16 ml THF/MeCN 4:1 v/v mixture. Then, 2.92 ml water and aqueous 2 M NaOH (974 µl) was added to the solution. The resulting mixture was stirred at ambient temperature stirred for 19 hours. The reaction was quenched by addition of 1 M HCl (2.103 ml, 2.10 mmol) and concentrated under reduced pressure. Silica gel column chromatography (20% to 40% EA/CyH to 10% EtOH/EA) delivered 217 mg (0.65 mmol, 93%) free acid as a white solid.

**By hydrolysis of tert-butyl ester 15b**

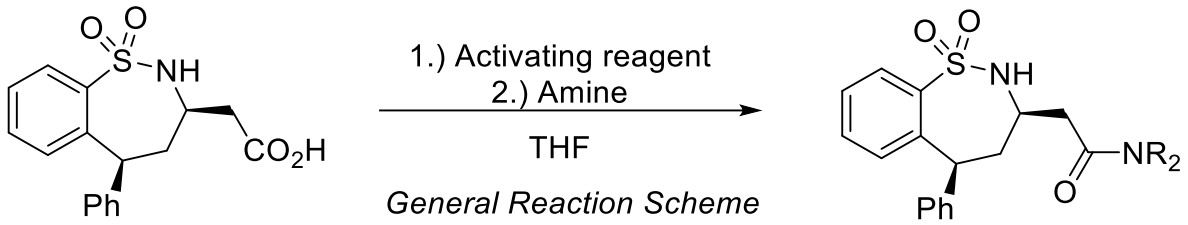
Tert-butyl Ester **15b** (1.0 eq., 145 mg, 374.20 µmol) was dissolved in 3.2 ml THF/1 M aq. HCl (3:1 v/v) in a 30 ml microwave tube. The vessel was sealed and irradiated at 100 °C/250 W for 45 min using a microwave synthesizer. The reaction was quenched by addition of aqueous 2 M NaOH and extracted using Ethyl acetate ( 3 x 5 ml). Concentration and silica gel column chromatography (20% to 40% to 10% EtOH/EA) delivered free acid (24 mg, 0.07 mmol, 19%) delivered free acid (24 mg, 0.07 mmol, 19%) and allowed recovery of unreacted starting material (81 mg, 0.21 mmol, 56%).

**$^{1}$H NMR** (500 MHz, Acetonitrile-$d_3$) δ 7.99 – 7.95 (m, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.38 – 7.32 (m, 2H), 7.29 – 7.25 (m, 2H), 6.63 – 6.59 (m, 1H), 5.51 (d, *J* = 9.9 Hz, 1H), 5.05 (d, *J* = 10.6 Hz, 1H), 4.36-4.27 (m, 1H), 2.59 (dd, *J* = 16.1, 5.6 Hz, 1H), 2.51 (dd, *J* = 16.1, 7.8 Hz, 1H), 2.32 (d, *J* = 14.0, 1.5 Hz,1H), 2.08 (dd, *J* = 14.0, 2.4 Hz, 1H).

**$^{13}$C NMR** (126 MHz, $CD_3CN$) δ 172.3, 144.5, 143.9, 142.3, 133.5, 130.1, 129.8, 129.8, 128.1, 127.9, 127.5, 54.4, 47.3, 40.2, 40.1.

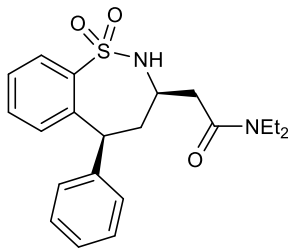
**HMRS (ESI)**: Calculated for $C_{17}H_{18}O_4NS = [M+H]^+$: = 332.09511, found: 332.09543

**2.3.2.2 Synthesis of Amides 18a-c**




*General Reaction Scheme*

**(±)-2-((*syn*)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-3-yl)-N,N-diethylacetamide (18a)**



To a solution of 40 mg of carboxylic acid **17** (1.0 eq.,120.70 µmol) in chloroform (0.9 ml) was added oxalyl chloride (1.15 eq., 238 µl, 5% solution in DCM). The vial was heated gently and dissolved after a few minutes. It was then heated at 60 °C overnight. The reaction was allowed to cool to room temperature and then concentrated under reduced pressure to remove any excess oxalyl chloride. Then, the reaction mixture was redissolved in THF (0.9 ml) and diethylamine (4.0 eq., 50 µl, 483 µmol) was added dropwise at 0 °C. After completion of conversion, reaction mixture was concentrated under reduced pressure, dried *in vacuo* and purified by preparative HPLC (C18, 25% to 80% MeCN/$H_2O$ (+0.1% v/v HCOOH)) to yield 27 mg (0.07 mmol, 58%).

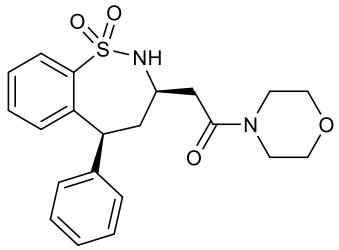
**$^1$H NMR** (600 MHz, Chloroform-*d*) δ 8.08 – 8.02 (m, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.34 – 7.31 (m, 1H), 7.27 – 7.23 (m, 4H), 6.64 – 6.59 (m, 1H), 5.09 (d, *J* = 10.8 Hz, 1H), 4.36 – 4.29 (m, 1H), 3.38 (dt, *J* = 14.1, 7.0 Hz, 1H), 3.32-3.20 (m, 3H), 2.80 (dd, *J* = 16.7, 4.5 Hz, 1H), 2.68 – 2.58 (m, 2H), 2.14 (ddd, *J* = 13.9, 2.3, 1.0 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H).

**$^{13}$C NMR** (151 MHz, Chloroform-d) δ 170.0, 143.8, 142.8, 141.3, 132.5, 129.5, 129.1, 129.0, 127.9, 127.2, 126.6, 54.0, 46.9, 42.3, 40.5, 38.7, 37.3, 14.3, 13.1.

**HMRS (ESI)**: Calculated for $C_{21}H_{27}O_3NS$ = $[M+H]^+$: = 387.17369, found: 387.17375

Calculated for $C_{21}H_{26}O_3NNaS$ = $[M+H]^+$: = 409.15563, found: 409.15560

**(±)-2-((*syn*)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-3-yl)-1-morpholinoethan-1-one (18b)**



To a solution of Acid **17** (1.0 eq., 25 mg, 76 µmol) in chloroform (1 ml) was added thionyl chloride (1.20 eq., 7.5 µl, 90 µmol, as 5% solution in $CHCl_3$). The vial was heated gently and dissolved after a few minutes. It was then heated at 40° C for 16 h. The reaction was allowed to cool to room temperature and then concentrated under reduced pressure to remove any excess thionyl chloride. Crude acyl chloride was then dissolved in 500 µl THF in an oven-dried Schlenk tube equipped with a magnetic stirring bar under Argon atmosphere. Then, 5.0 eq. morpholine (29 µl, 0.34 mmol) was added and the reaction was kept stirring overnight. Then, it was concentrated, dried and purified by preparative HPLC to deliver 14 mg (7.49 µmol, 10% yield) of product sulfonamide.

Purification by preparative HPLC (C18, 35% to 90% MeCN/$H_2O$ (+0.1% v/v TFA))

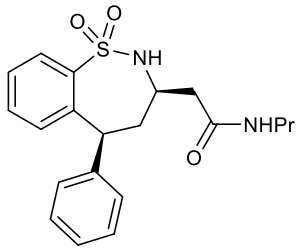
**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 8.08 – 8.02 (m, 1H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.29 – 7.23 (m, 4H), 6.65 – 6.61 (m, 1H), 6.17 (d, *J* = 9.6 Hz, 1H), 5.07 (d, *J* = 10.8 Hz, 1H), 4.37 (m, 1H), 3.77 – 3.61 (m, 5H), 3.53 – 3.40 (m, 3H), 2.79 (dd, *J* = 16.7, 4.8 Hz, 1H), 2.70 – 2.55 (m, 2H), 2.16 (d, *J* = 12.7 Hz, 1H).

**$^{13}$C NMR** (176 MHz, Chloroform-d) δ 167.3, 141.6, 140.7, 139.2, 130.5, 127.5, 127.1, 127.0, 125.8, 125.2, 124.6, 64.8, 64.5, 51.7, 45.0, 44.0, 39.8, 36.9, 35.4.

**HMRS (ESI)**: Calculated for $C_{21}H_{25}O_4N_2S = [M+H]^+$: = 401.15218, found: 401.15295

Calculated for $C_{21}H_{24}O_4N_2NaS = [M+H]^+$: = 423.13490 found: 423.13396

**(±)-2-((syn)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-3-yl)-N-propylacetamide (18c)**

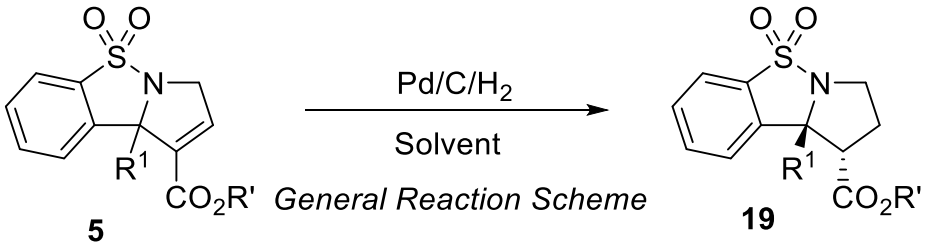


To a solution of Acid **17** (1.0 eq., 25 mg, 76 µmol) in chloroform (1 ml) was added thionyl chloride (1.20 eq., 7.5 µl, 90 µmol, as 5% solution in $CHCl_3$). The vial was heated gently and dissolved after a few minutes. It was then heated at 40° C for 16 h . The reaction was allowed to cool to room temperature and then concentrated under reduced pressure to remove any excess thionyl chloride. Crude acyl chloride was then dissolved in 500 µl THF in an oven-dried

Schlenk tube equipped with a magnetic stirring bar under Argon atmosphere. Then, 5.0 eq. n-propylamine (28 µl, 0.34 mmol) was added and the reaction was kept stirring overnight. Then, it was concentrated, dried and purified by preparative HPLC to deliver 14 mg (0.04 mmol, 50% yield) of product sulfonamide.

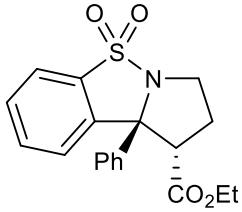
Purification by preparative HPLC (C18, 35% to 90% MeCN/$H_2O$ (+0.1% v/v TFA))
**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 8.04 (dd, *J* = 5.5, 2.0 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.29 – 7.27 (m, 1H), 7.24 (ddd, *J* = 8.0, 3.5, 2.0 Hz, 3H), 6.63 – 6.58 (m, 1H), 6.31 (s, 1H), 5.59 (d, *J* = 6.0 Hz, 1H), 5.09 (d, *J* = 10.6 Hz, 1H), 4.30 (s, 1H), 3.23 – 3.13 (m, 2H), 2.76 (dd, *J* = 15.6, 4.3 Hz, 1H), 2.41 – 2.32 (m, 2H), 2.23 – 2.17 (m, 1H), 1.52 (h, *J* = 7.1 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H).
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 170.8, 143.6, 142.6, 141.2, 132.5, 129.5, 129.1, 127.8, 127.2, 126.7, 53.7, 46.5, 41.4, 40.5, 38.7, 22.9, 11.5
**HMRS (ESI)**: Calculated for $C_{20}H_{25}O_3N_2S$ = $[M+H]^+$: = 373.15804, found: 373.15774
Calculated for $C_{20}H_{24}O_3N_2NaS$ = $[M+H]^+$: = 395.13998 found: 395.13907

### 2.3.3 Synthesis of fused Pyrrolines by Reduction



*General Reaction Scheme*

**(±)-Ethyl 9b-phenyl-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-1-carboxylate 5,5-dioxide** (**19a**)




To 23 mg Pyrroline **5a** (1.0 eq., 0.06 mmol) in 1.5 ml of a Methanol/Ethyl Acetate Mixture (5:1) was added 3.2 mg Pearlman's Catalyst (20wt.%, 4mol%, 2.26 µmol,) in a Schlenk tube. The mixture was cooled to 0°C, degassed and refilled with hydrogen, again degassed, once more refilled with hydrogen using a balloon and stirred at rt.
After 40 min, TLC (Ethyl Acetate/CyH 1:3) showed complete conversion of starting material (r*f*= 0.33) to a product (r*f* = 0.24). The mixture was filtered through a syringe filter and the

solvent was removed under reduced pressure to obtain crude product, which was purified using silica gel column chromatography (14%-20% EA/CH) to yield **12a** in 95% yield (22 mg, 0.06 mmol).

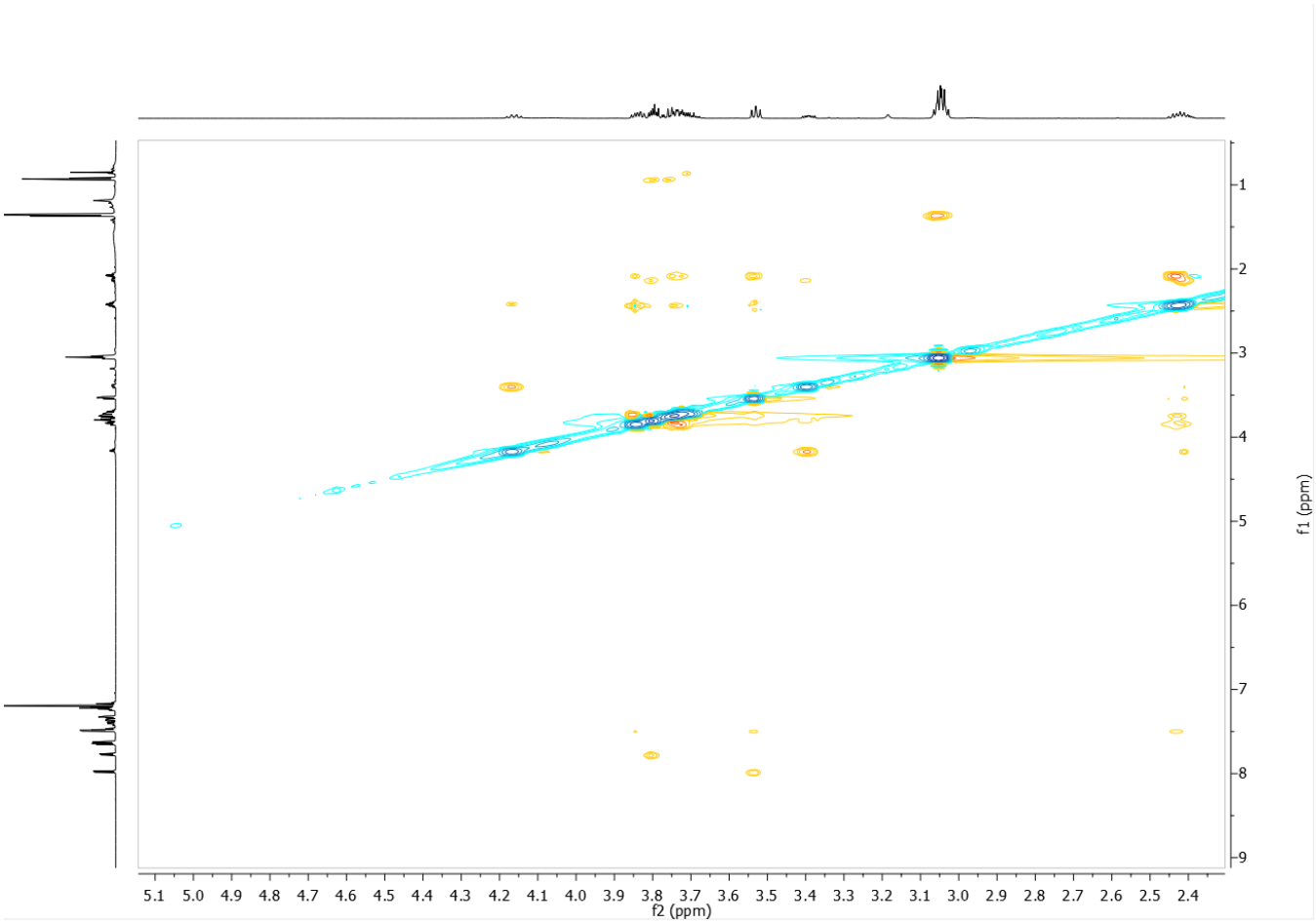
**$^{1}$H NMR** (600 MHz, Chloroform-*d*) δ 8.05 (d, *J* = 7.9 Hz, 1H), 7.73 – 7.67 (m, 2H), 7.59 – 7.53 (m, 3H), 7.33– 7.27 (m, 2H), 7.27 – 7.21 (m, 1H), 3.94-3.73 (m, 4H), 3.60 (t, *J* =7.6 Hz, 1H), 2.49 (m, 1H), 2.15 (m, 1H), 1.0 (t, *J* = 7.1 Hz, 3H).

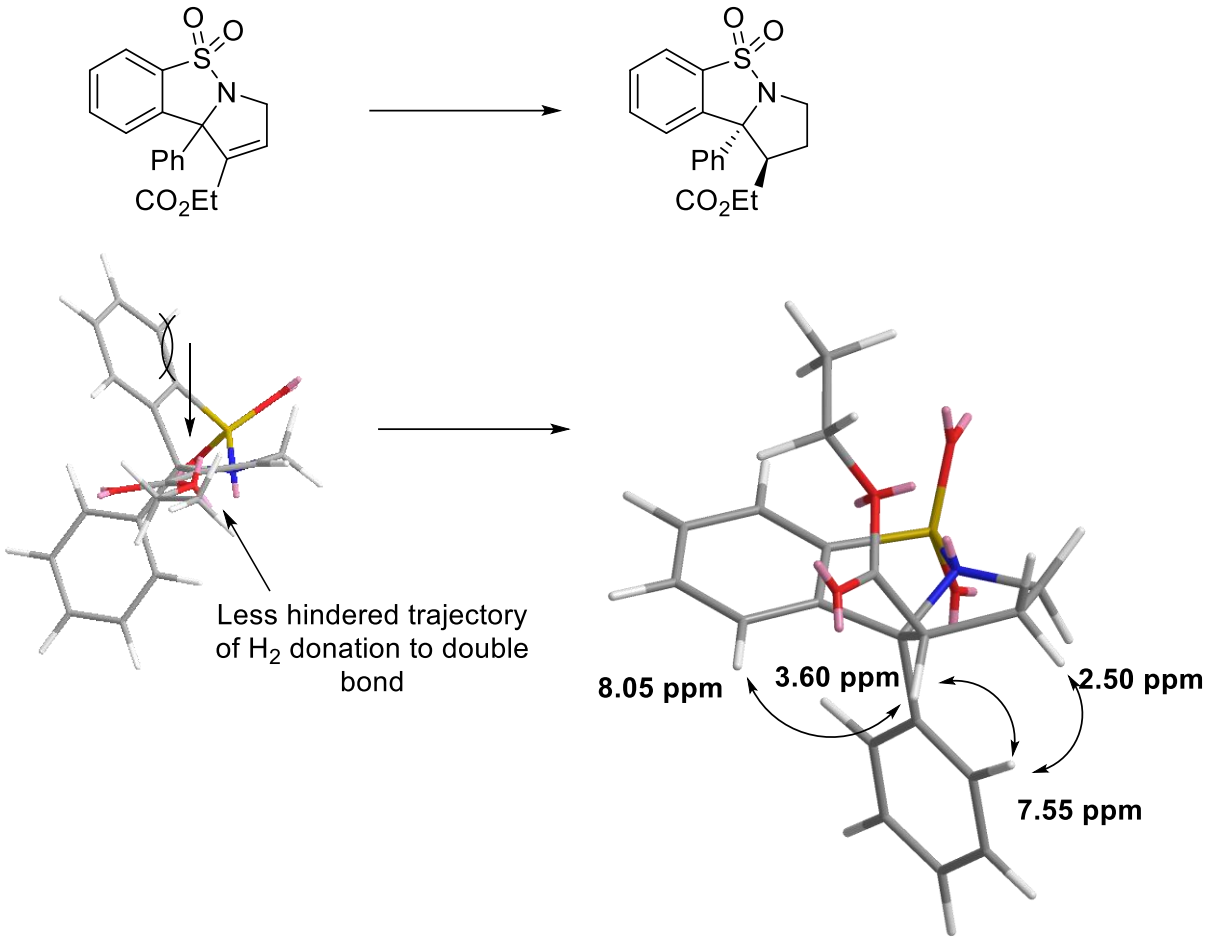
**$^{13}$C NMR** (151 MHz, Chloroform-d) δ 170.2, 143.6, 139.1, 135.9, 133.1, 129.7, 128.2, 128.1, 126.8, 125.6, 121.7, 78.2, 61.3, 56.7, 48.4, 28.9, 13.7

**HMRS (ESI)**: Calculated for $C_{19}H_{20}O_4NS$ = $[M+H]^+$: = 358.11076, found: 358.11092

Calculated for $C_{19}H_{19}O_4NNaS$ = $[M+H]^+$: = 380.09270, found: 380.09282

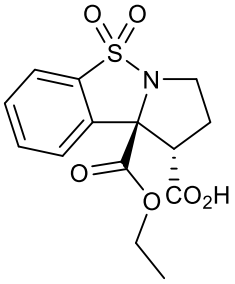
**19a NOESY**






Structure of lowest energy conformation of substrate hints that addition leading to anti-pyrrolidine may be preferred, as the most probable structure (deduced via NOE interactions) suggests.

**(±)-9b-(ethoxycarbonyl)-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-1-carboxylic acid 5,5-dioxide (19b)**



*Structure assigned in analogy to* **19a***.*

Pearlman's catalyst (10mol%, 8.4 mg, 0,01 mmol) and **5b** (1.0 eq., 50.0 mg, 0.12 mmol) were dissolved in a 3:1 Methanol/Ethyl Acetate (3:1 v/v) mixture in a 10 ml glass tube equipped with a stirring bar. The open vessel was placed in a high-pressure reactor, which was then sealed and charged with Hydrogen (9 atm). The reactor was placed on a stirring plate and left there for 3 h. Then, reaction mixture was filtered using a syringe filter. Concentration of filtrate delivered **19b** in 92% yield (36 mg, 0.11 mmol).

**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 7.94 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 7.65 Hz, 1H), 7.68 (td, *J* = 7.6, 1.3 Hz, 1H), 7.63 (dd, *J* = 7.6, 1.1 Hz, 1H), 4.21 (m, 2H), 3.89 (dt, *J* = 10.7, 7.6 Hz, 1H), 3.68 (ddd, *J* = 10.7, 7.6, 4.6 Hz, 1H), 3.27 (t, *J* = 8.4 Hz, 1H), 2.67 (m, 1H), 2.42 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 2H).

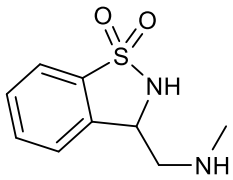
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 175.7, 168.7, 136.7, 135.1, 133.7, 130.9, 126.4, 121.5, 63.0, 60.6, 53.7, 46.5, 30.1, 13.9.

**HMRS (ESI)**: Calculated for $C_{14}H_{16}O_6NS = [M+H]^+$: = 326.06928, found: 326.06963

Calculated for $C_{14}H_{15}O_6NNaS = [M+H]^+$: = 348.05123, found: 348.05164

### 2.3.4 Ring modulation reaction of cycloadduct 8a

**(±)-3-(aminomethyl)-2-methyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (20)**



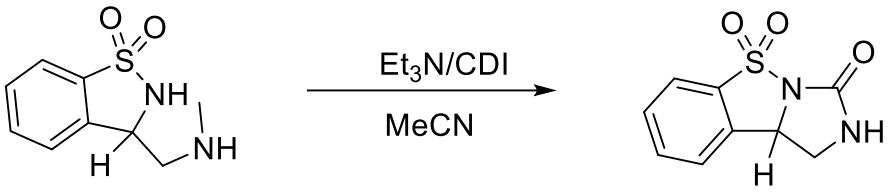
Sulfonamide **8a** (1.0 eq., 55 mg, 0.18 mmol) was dissolved in 1.8 ml in a 10 ml glass vial equipped with a magnetic stirring bar. Pd/C (10 wt.% , 0.1 eq., 19.5 mg, 0.02 mmol) was added and the open vial was placed in a high-pressure reactor, whichw as charged with 7 atm of hydrogen. The reactor was placed on a stirring plate and the reaction was stirred at ambient temperature for 16 h. Then, it was filtered over celite and concentrated. Purification by preparative HPLC (C18, 10% to 50% MeCN/$H_2O$ (+0.1% v/v TFA))) delivered unstable Product **20** in 87% yield (34 mg, 0.16 mmol).

**$^1$H NMR** (500 MHz, Acetonitrile-$d_3$) δ 7.75 – 7.73 (d, *J* = 8.1 Hz, 1H), 7.67 – 7.65 (m, 1H), 7.57 (t, *J* = 7.9 Hz, 2H), 4.77 (dd, *J* = 8.8, 4.9 Hz, 1H), 2.70 (dd, *J* = 12.6, 4.9 Hz, 1H), 2.54 (dd, *J* = 12.6, 8.8 Hz, 1H), 2.28 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CD_3CN$) δ 139.8, 136.6, 133.6, 130.2, 125.7, 121.3, 118.0, 64.1, 55.8, 45.4.

**HMRS (ESI)**: Calculated for $C_9H_{13}O_2N_2S$ = $[M+H]^+$: = 213.06922, found: 213.06943

**(±)-2-methyl-1,9b-dihydrobenzo[d]imidazo[1,5-b]isothiazol-3(2H)-one 5,5-dioxide (21)**



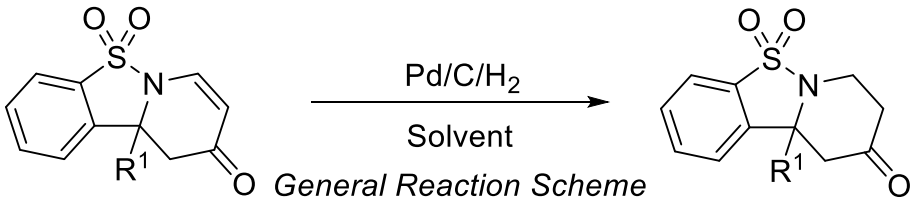

**20** (crude) **21**

Crude sulfonamide **20** (1.0 eq.,33 mg, 109.86 µmol) was dissolved in 1.0 ml MeOH in a 10 ml glass vial equipped with a magnetic stirring bar. Pd/C (10 wt.% , 0.1 eq., 19.5 mg, 0.02 mmol) was added and the open vial was placed in a high-pressure reactor, which was charged with 7 atm of hydrogen. The reactor was placed on a stirring plate and the reaction was stirred at ambient temperature for 16 h. Then, it was filtered over celite and concentrated. It was dissolved in 2 ml dry acetonitrile and triethylamine (2.30 eq., 35 µl, 252.7 µmol) and CDI (1.15 eq., 20.5 mg, 0.13 mmol) were added and the reaction stirred at 21° C for 16 h. Then, it was

stopped by addition of 1 M aqueous HCl (50 µl) and concentrated. The residue was purified by preparative HPLC (C18, 10% to 60% MeCN/$H_2O$ (+0.1% v/v TFA)) to yield 6 mg (23%, 0.03 mmol) of **21**.

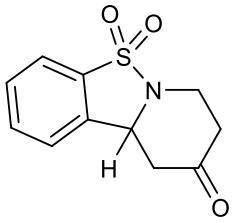
**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 7.8, 1H), 7.71 (td, *J* = 7.6, 1.0 Hz, 1H), 7.62 (t, *J* = 7.7, 1H), 7.42 (dq, *J* = 7.8, 0.7 Hz, 1H), 5.40 (dd, *J* = 9.3, 4.5 Hz, 1H), 4.01 (t, *J* = 9.3 Hz, 1H), 3.67 (dd, *J* = 9.1, 4.5 Hz, 1H), 2.89 (s, 3H).
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 152.5, 136.9, 135.3, 132.9, 129.5, 122.5, 121.2, 53.9, 49.3, 29.9.
**HMRS (ESI)**: Calculated for $C_{10}H_{11}O_3N_2S$ = $[M+H]^+$: = 239.04849, found: 239.04863
Calculated for $C_{10}H_{11}O_3N_2NaS$ = $[M+Na]^+$: = 261.03043, found: 261.03012

### 2.3.5 Synthesis of tetrahydropyridones 22a-d



*General Reaction Scheme*

**(±)-7,8,10,10a-tetrahydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (22a)**

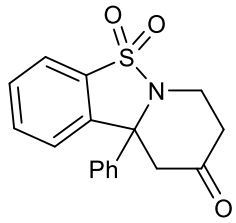



Enamide **6a** (1.0 eq., 195 mg, 0.83 mmol) was combined with Pd/C (10wt% , 0.1 eq., 88 mg, 82.89 µmol) and dissolved in 16 ml EtOH/Ethyl Acetate 1:1 (v/v). The mixture was stirred in a high-pressure reactor 18 h under 8 atm of hydrogen pressure. Then, reaction mixture was filtered over celite and concentrated. The main component of reaction mixture was alcohol. Crude reaction mixture was dissolved in 22 ml DCM and solid sodium bicarbonate (6.25 eq., 435 mg, 0.01 mol) was added. The reaction mixture was cooled down to 0° C (ice-water bath) and DMP (2.5 eq., 879 mg, 2.07 mmol) was carefully added portionwise over 10 min under a stream of Argon. The reaction was monitored via TLC. After completion of conversion (3 h) 50 ml of aqueous sodium thiosulfate solution was added and the reaction mixture was transferred to a separation funnel. Layers were separated and the aqueous layer was extracted twice

more with 40 ml DCM each. Combined organic layers were washed with brine (25 ml each) and dried over anhydrous sodium sulfate. Concentration delivered crude product ,which was objected to silica gel flash column chromatography (29% to 35% EA/CyH) to yield tetrahydropyridin-4one **22a** in 59% yield (117 mg, 0.49 mmol).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.89 – 7.85 (m, 1H), 7.67 (td, *J* = 7.6, 1.3 Hz, 1H), 7.63 – 7.58 (m, 1H), 7.41 – 7.34 (m, 1H), 4.66 (dd, *J* = 12.0, 3.7 Hz, 1H), 4.19 (ddd, *J* = 13.3, 7.3, 2.1 Hz, 1H), 3.40 (ddd, *J* = 13.2, 12.0, 3.7 Hz, 1H), 2.97 (ddd, *J* = 14.1, 3.7, 1.7 Hz, 1H), 2.83 (dddd, *J* = 14.8, 12.0, 7.3, 0.8 Hz, 1H), 2.63 – 2.54 (m, 2H).
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 204.4, 136.6, 134.5, 133.3, 129.9, 123.3, 121.6, 58.1, 45.9, 39.4, 38.4.
**HMRS (ESI)**: Calculated for $C_{11}H_{12}O_3NS$ = $[M+H]^+$: = 238.05324 found: 238.05324

**(±)-10a-phenyl-7,8,10,10a-tetrahydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (22b)**

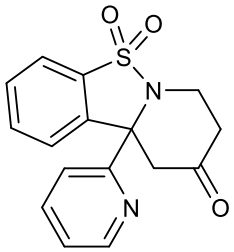



Tricyclic sulfonamide **6b** (307 mg, 986.01 µmol) and Pd on Carbon (10 wt%,74 mg, 69.02 µmol) were dissolved in Ethanol (18 ml) in a 100 ml Schlenk flask equipped with a magnetic stirring bar. The mixture stirred at ambient temperature with a balloon filled with hydrogen attached. The reaction was monitored by TLC. After 3 h, TLC analysis had implicated complete conversion of starting material and the mixture was filtered over celite and solvent was evaporated under reduced pressure to give crude reaction product, which was purified by silica gel column chromatography (18% to 32% EA/CyH) to give product sulfonamide **22b** in 90% yield (278 mg, 0.89 mmol).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.92 – 7.89 (m, 1H), 7.59 – 7.51 (m, 2H), 7.44 – 7.29 (m, 6H), 7.03 – 6.98 (m, 1H), 4.18 (ddd, *J* = 14.7, 7.6, 1.5 Hz, 1H), 3.55 (dd, *J* = 14.4, 1.6 Hz, 1H), 3.13 (ddd, *J* = 14.7, 12.3, 3.8 Hz, 1H), 2.96 – 2.84 (m, 3H), 2.34 – 2.25 (m, 1H).

**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 204.5, 142.8, 137.8, 133.8, 132.7, 129.8, 129.5, 129.1, 127.5, 124.0, 121.8, 69.1, 49.6, 39.1, 36.1.
**HMRS (ESI)**: Calculated for $C_{17}H_{16}O_3N_2S$ = $[M+H]^+$: = 314.08454, found: 314.08470

**(±)-10a-(pyridin-2-yl)-7,8,10,10a-tetrahydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (22c)**



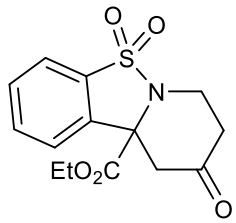
Sulfonamide **6c** (1.0 eq., 220 mg, 704.35 µmol) and Pd/C (0.12 eq., 90 mg, 84.52 µmol) were combined in a 35 ml reaction tube equipped with a magnetic stirring bar. 7 ml of Ethyl Acetate/EtOH (15:7 v/v) were added and the vessel was placed in a high-pressure reactor. The reactor was charged with 7 atm of hydrogen pressure and stirred for 16 h at 22 °C. Then reaction mixture was filtered over celite and concentrated. Silica gel column chromatography (19 to 23% EA/CyH) delivered desired product in 24% yield (54 mg, 0.17 mmol) and recovered starting material. Corresponding alcohol or other side products could not be detected.

**$^{1}$H NMR** (700 MHz, Chloroform-*d*) δ 8.67 – 8.62 (m, 1H), 7.92 – 7.88 (m, 1H), 7.65 (td, *J* = 7.7, 1.8 Hz, 1H), 7.60 – 7.59 (m, 2H), 7.31 (ddt, *J* = 10.2, 8.0, 0.8 Hz, 2H), 7.26 – 7.24 (m, 1H), 4.20 (ddd, *J* = 14.3, 7.4, 2.4 Hz, 1H), 4.00 (dd, *J* = 14.5, 1.6 Hz, 1H), 3.25 (ddd, *J* = 14.3, 11.4, 4.1 Hz, 1H), 2.80 (dddd, *J* = 15.4, 11.4, 7.4, 0.8 Hz, 1H), 2.70 (dd, *J* = 14.4, 0.8 Hz, 1H), 2.38 (dddd, *J* = 15.4, 4.0, 2.4, 1.5 Hz, 1H).

**$^{13}$C NMR** (176 MHz, Chloroform-d) δ 201.8, 155.4, 147.3, 138.8, 135.9, 131.8, 130.9, 128.1, 122.1, 121.6, 119.7, 119.3, 67.7, 47.2, 36.6, 34.3.

**HMRS (ESI)**: Calculated for $C_{16}H_{15}O_3N_2S$ = $[M+H]^+$: = 315.07979 found: 315.07962

**(±)-ethyl 9-oxo-7,8,9,10-tetrahydro-10aH-benzo[4,5]isothiazolo[2,3-a]pyridine-10a-carboxylate 5,5-dioxide (22d)**




Sulfonyl enamide **6d** (1.0 eq., 150 mg, 0.49 mmol) was dissolved in 9ml EtOH and 26 mg (5mol%, 10wt.%content ,24.40 µmol) of Pd/C was added to the mixture. The reaction vessel (35 ml tube containing magnetic stirring bar) was placed in a high-pressure reactor that was charged with 7 bars of hydrogen and placed on a stirring plate. The reaction was stirred at 20° C and monitored by TLC.

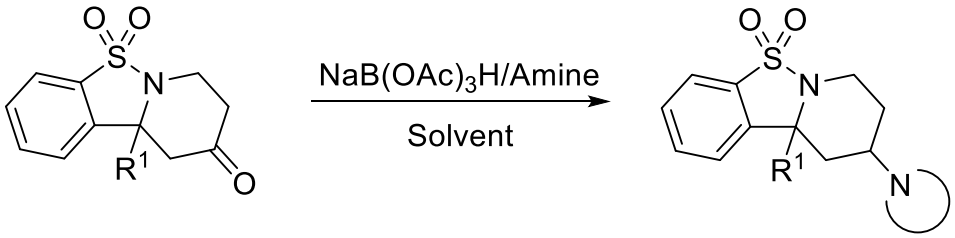
The crude reaction mixture was filtered over celite, concentrated and the residue objected to silica gel flash column chromatography (25 to 28 to 32 % EA/CyH) to yield tetrahydropyridin-4one **22c** in 97% yield (146 mg 0.47 mmol).

**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 7.91 – 7.85 (m, 1H), 7.73 – 7.63 (m, 2H), 7.58 – 7.53 (m, 1H), 4.30 – 4.17 (m, 3H), 3.62 (ddd, *J* = 14.0, 11.6, 4.1 Hz, 1H), 3.36 (dd, *J* = 14.4, 1.6 Hz, 1H), 2.76 (dddd, *J* = 15.0, 11.6, 7.6, 0.7 Hz, 1H), 2.62 (dd, *J* = 14.5, 0.7 Hz, 1H), 2.51 (ddt, *J* = 15.0, 4.0, 1.9 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H).

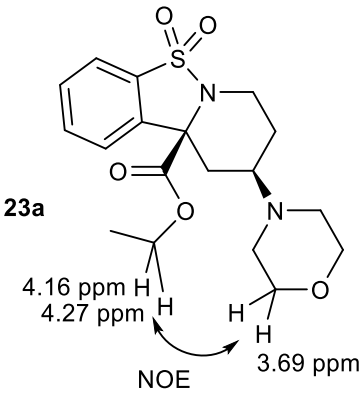
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 202.7, 168.1, 135.9, 133.7, 133.5, 130.8, 123.8, 121.9, 68.3, 63.5, 48.9, 38.8, 37.1, 14.1.

**HMRS (ESI)**: Calculated for $C_{14}H_{16}O_5NS = [M+H]^+$: = 310.07437 found: 310.07468

### 2.3.6 Synthesis of tricyclic sulfonamides 23a-e via reductive amination




**(±)-Ethyl 9-morpholino-7,8,9,10-tetrahydro-10aH-benzo[4,5]isothiazolo[2,3-a]pyridine-10a-carboxylate 5,5-dioxide (23a)**




Morpholine (1.2 eq., 6.7 µl, 0.08 mmol) was added dropwise via syringe to a solution of **22d** (1.0 eq., 20 mg, 64.7 µmol) with 2-Ethylhexanoic acid (1.25 eq., 12.9 µl, 0.08 mmol) in DCM (0.6 ml) and stirred for 20 min. Then, in situ generated $NaBH(OEh)_3$ (1.25 eq., 12.9 µl, 0.08 mmol) was added and the reaction stirred overnight. Then, solvents were removed and the residue purified by silica gel column chromatography (30% to 45% EA/CyH) to yield 16 mg (0.04 mmol, 65%) of amine product.

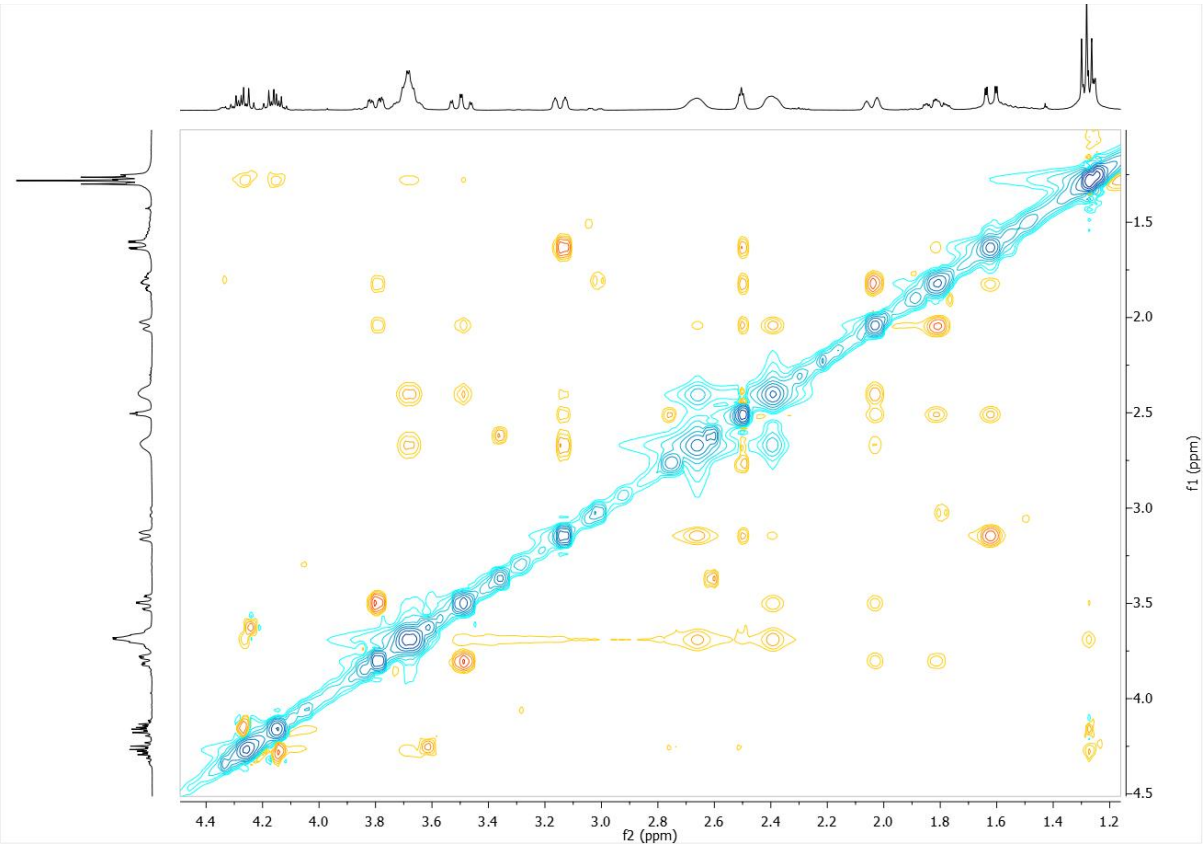
**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 7.7 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.66 – 7.54 (m, 2H), 4.27 (dq, *J* = 10.8, 7.3 Hz, 1H), 4.16 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.80 (ddd, *J* = 14.0, 4.9, 2.0 Hz, 1H), 3.75 – 3.62 (m, 4H), 3.50 (td, *J* = 13.7, 2.6 Hz, 1H), 3.15 (ddd, *J* = 14.2, 3.3, 2.0 Hz, 1H), 2.66 (s, 2H), 2.50 (p, *J* = 3.1 Hz, 1H), 2.40 (s, 2H), 2.04 (dt, *J* = 15.1, 2.6 Hz, 1H), 1.88 – 1.75 (m, 1H), 1.65 – 1.58 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H).

**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 170.4, 137.5, 133.3, 133.2, 130.2, 124.4, 121.5, 67.1, 64.2, 62.5, 56.7, 51.4, 36.6, 33.9, 25.5, 14.1.

**HMRS (ESI)**: Calculated for $C_{18}H_{25}O_5N_2S = [M+H]^+$: = 381.14787 found: 381.14779

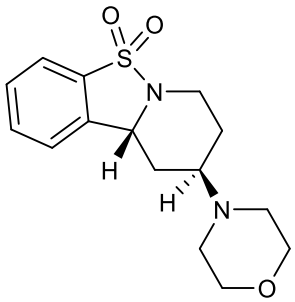
Calculated for $C_{18}H_{24}O_5N_2NaS = [M+H]^+$: = 403.12981 found: 403.12960

Calculated for $C_{18}H_{24}O_5N_2KS = [M+H]^+$: = 419.10375 found: 419.10375




NOE experiment shows NOE between Morpholine H and $CH_2$-group of ethyl ester.

**(±)-9-morpholino-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridine 5,5-dioxide (23b)**

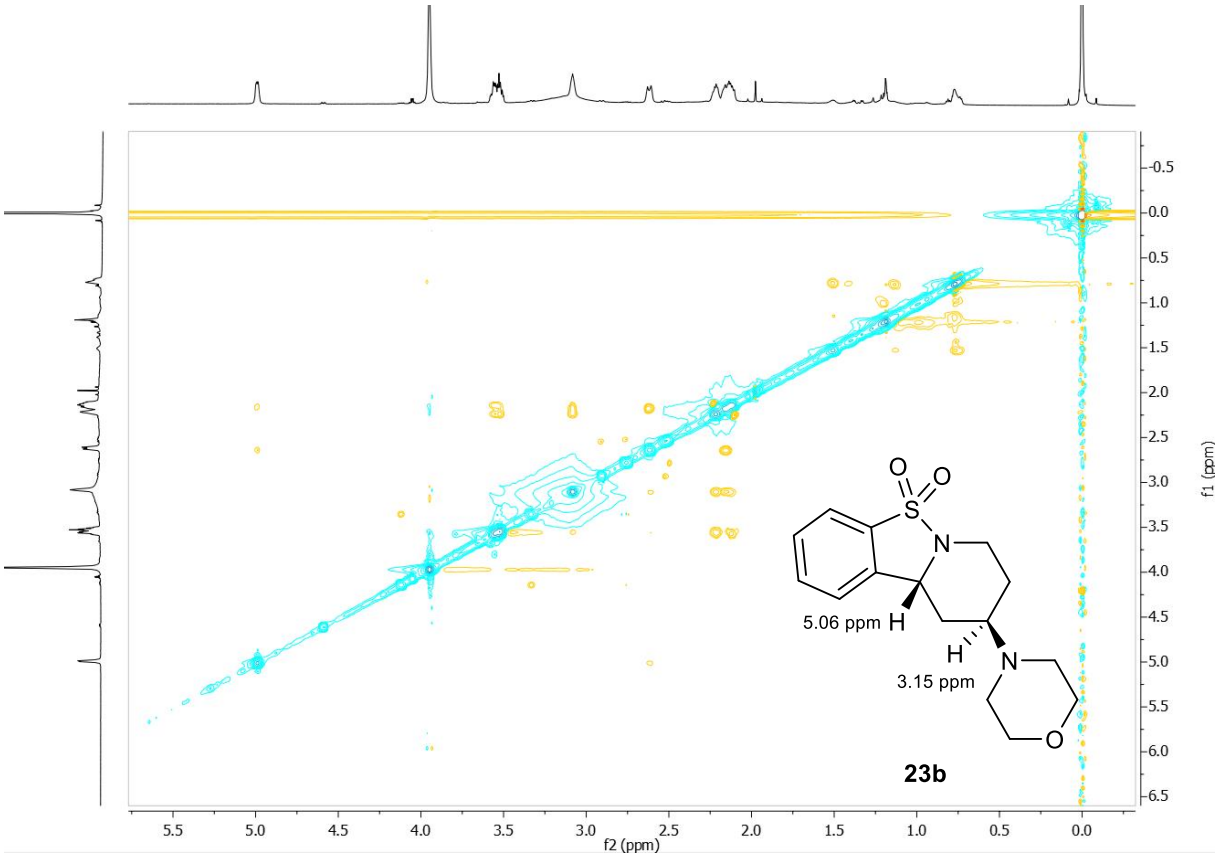


**22a** (1.0 eq., 16 mg, 67.43 µmol), morpholine (1.25 eq., 145 µl, 84.3 µmol, as 5% v/v solution in 1,2-DCE) and powdered 4 A molecular sieves were combined in dry 1,2 DCE (800 µl) in a two-necked round bottom flask under an Argon atmosphere and stirred for 12 h at ambient temperature. Then, sodium triacetoxyborohydride (1.4 eq., 20 mg, 94.40 µmol) and glacial acetic acid (1.05 eq., 4 µl, 70.80 µmol) were added and the reaction stirred at ambient temperature overnight. Then, it was concentrated in vacuo and the residue purified (C18, 10% to 38% MeCN/$H_2O$ (+0.1% v/v TFA)) yield 7.0 mg (0.02 mmol, 34%) of product sulfonamide.

**$^{1}$H NMR** (700 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 7.7 Hz, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 5.06 (dd, *J* = 9.4, 4.1 Hz, 1H), 4.02 (d, *J* = 4.7 Hz, 4H), 3.61 (ddt, *J* = 25.0, 13.2, 7.3 Hz, 2H), 3.33 – 2.99 (m, 6H), 2.69 (dt, *J* = 14.2, 5.3 Hz, 1H), 2.28 (h, *J* = 5.6, 4.3 Hz, 1H), 2.25 – 2.15 (m, 3H).

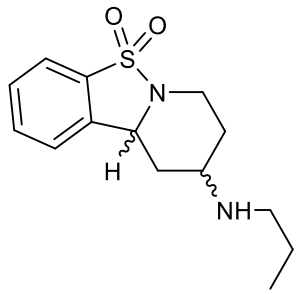
**$^{13}$C NMR** (176 MHz, Chloroform-d) δ 137.5, 134.8, 133.6, 130.0, 124.2, 122.1, 64.3, 60.1, 54.5, 50.4, 36.9, 29.6, 23.3.

**HMRS (ESI)**: Calculated for $C_{15}H_{21}O_3N_2S$ = $[M+H]^+$: = 381.12674 found: 381.12676




In NOESY experiment, no NOE between benzylic proton and the other tertiary proton can be established. For the other amines, in contrast, such an NOE could be found. Consequently, we suggest that we isolated above depicted stereoisomer.

**(±)-9-(propylamino)-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridine 5,5-dioxide (23c)**



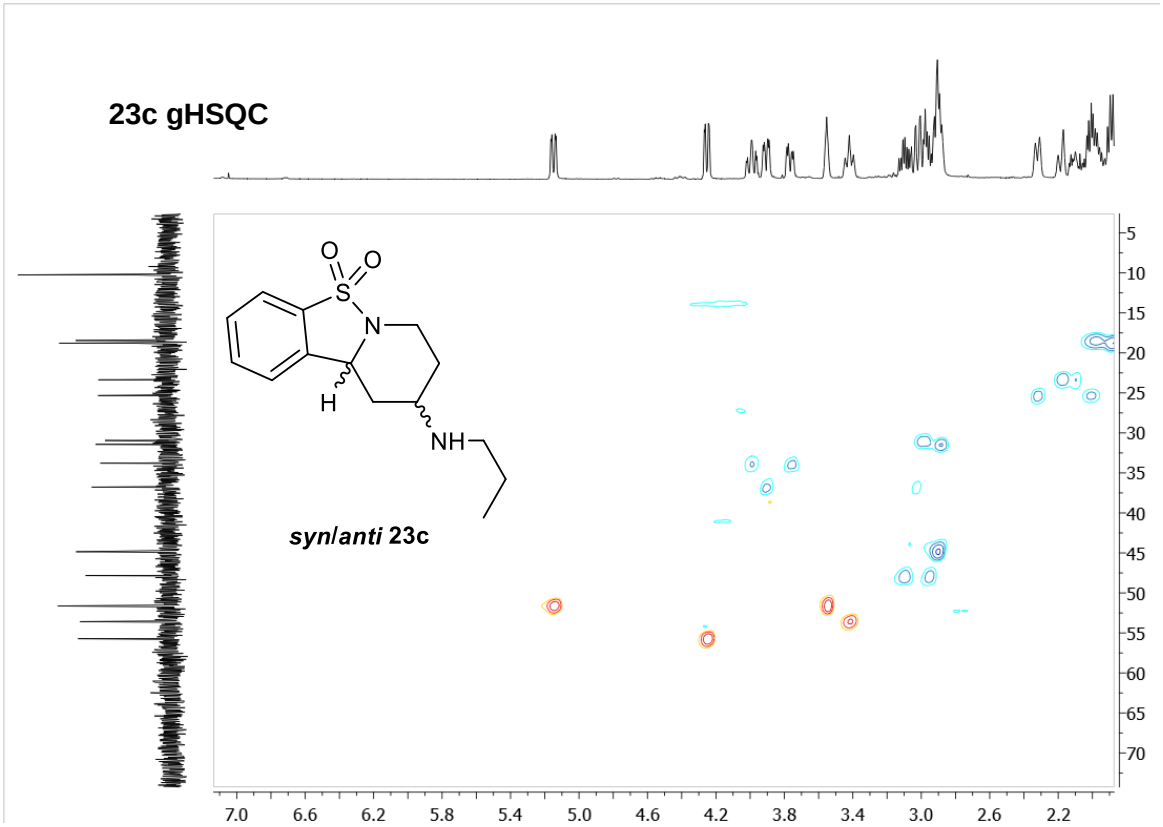
**22a** (1.0 eq., 28 mg, 110.93 µmol), n-propylamine (1.25 eq., 11 µl, 138.66 µmol) and powdered 4 A molecular sieves were combined in dry 1,2 DCE (800 µl) in a 10 ml oven-dried Schlenk tube under an Argon atmosphere and sodium triacetoxyborohydride (1.4 eq., 33 mg, 155.30 µmol) and glacial acetic acid (1.05 eq., 6.6 µl, 116.47 µmol) were added and the reaction stirred at ambient temperature overnight. The reaction was concentrated and the crude reaction material was purified by preparative HPLC (C18, 3% to 7% MeCN/$H_2O$ (+0.1% v/v TFA)) Lyophilization then delivered product amine **23c** (9.4 mg, 0.03 mmol, 30%) and alcohol side product **24** (11 mg, 0.05 mmol, 41%).

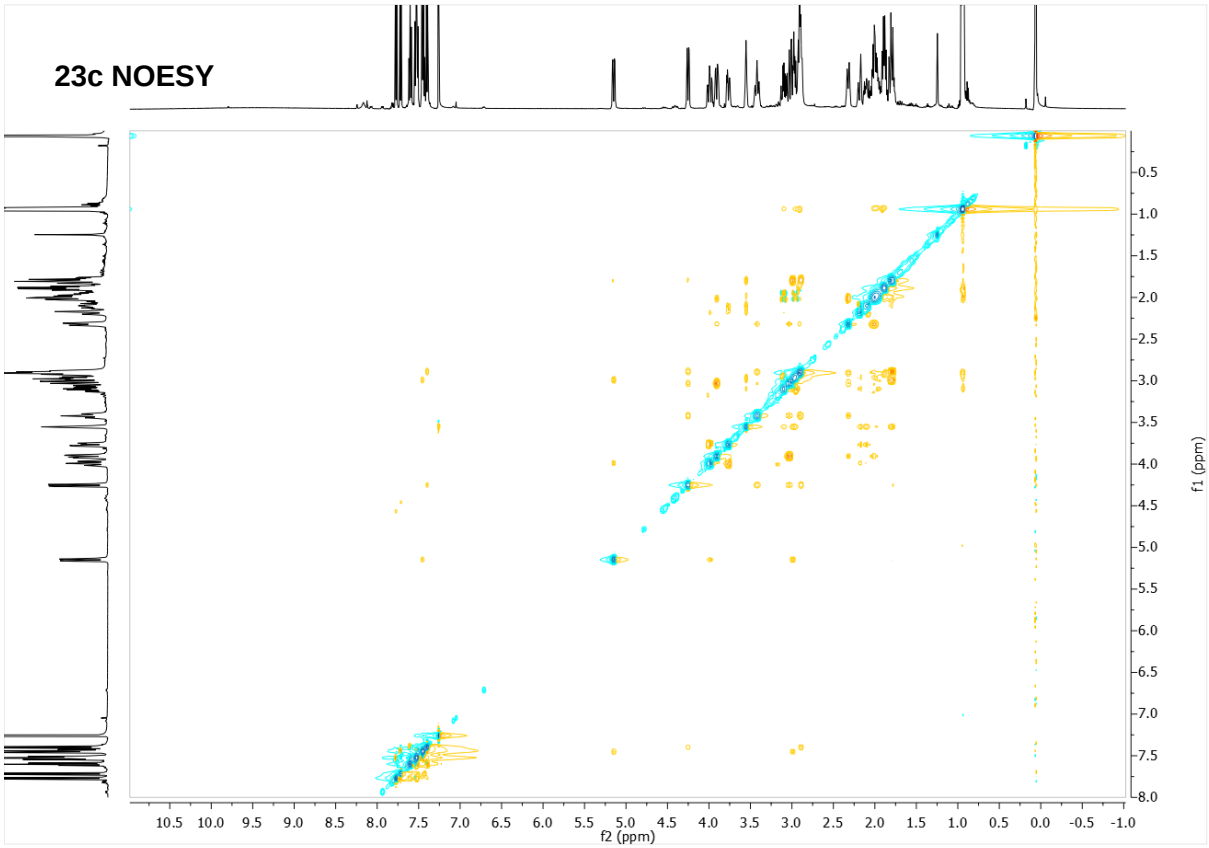
**Mixture of diastereomers, ~10:9 syn:anti (see NOESY)**

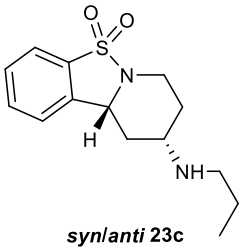
**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 7.7 Hz, 1H, *major*), 7.72 (d, *J* = 7.7 Hz, 1H, *minor*), 7.60 (td, *J* = 7.6, 1.1 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.47 – 7.38 (m, 3H), 5.15 (dd, *J* = 12.2, 3.1 Hz, 1H, minor), 4.25 (dd, *J* = 11.7, 2.9 Hz, 1H, major), 3.99 (ddd, *J* = 14.4, 12.8, 3.4 Hz, 1H), 3.91 (ddd, *J* = 13.5, 4.9, 2.0 Hz, 1H), 3.77 (ddd, *J* = 14.2, 5.6, 2.2 Hz, 1H), 3.55 (t, *J* = 3.5 Hz, 1H, minor), 3.42 (tt, *J* = 12.1, 3.6 Hz, 1H, major), 3.14 – 2.86 (m, 7H), 2.32 (d, *J* = 12.5 Hz, 1H, major), 2.19 (d, *J* = 14.9 Hz, 1H), 2.10 (ddd, *J* = 18.7, 9.2, 4.2 Hz, 1H), 2.06 (s, 0H), 1.89 (q, *J* = 7.8 Hz, 2H), 1.81 (dd, *J* = 13.5, 10.0 Hz, 1H), 0.94 (td, *J* = 7.4, 3.5 Hz, 6H).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 137.3, 136.4, 134.9, 134.6, 133.3, 133.2, 129.9, 129.6, 123.9, 123.4, 121.6, 121.4, 56.9, 54.8, 52.8, 49.0, 46.0, 37.9, 35.0, 32.6, 32.1, 26.5, 24.5, 20.0, 19.6, 11.4, 11.4.

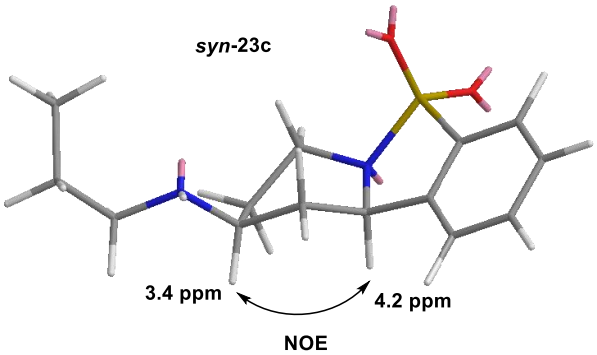
**HMRS (ESI**): Calculated for $C_{14}H_{21}O_2N_2S = [M+H]^+$: = 281.13183 found: 281.13189


23c gHSQC
O
O
S
N
H
NH
syn/anti 23c
5
10
15
20
25
30
35
40
45
50
55
60
65
70
7.0
6.6
6.2
5.8
5.4
5.0
4.6
4.2
3.8
3.4
3.0
2.6
2.2


23c NOESY
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f2 (ppm)

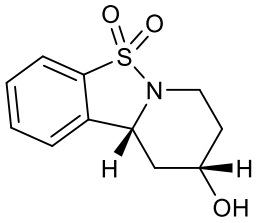



*syn/anti* 23c




*syn*-23c

**(±)-9-hydroxy-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridine 5,5-dioxide (24)**



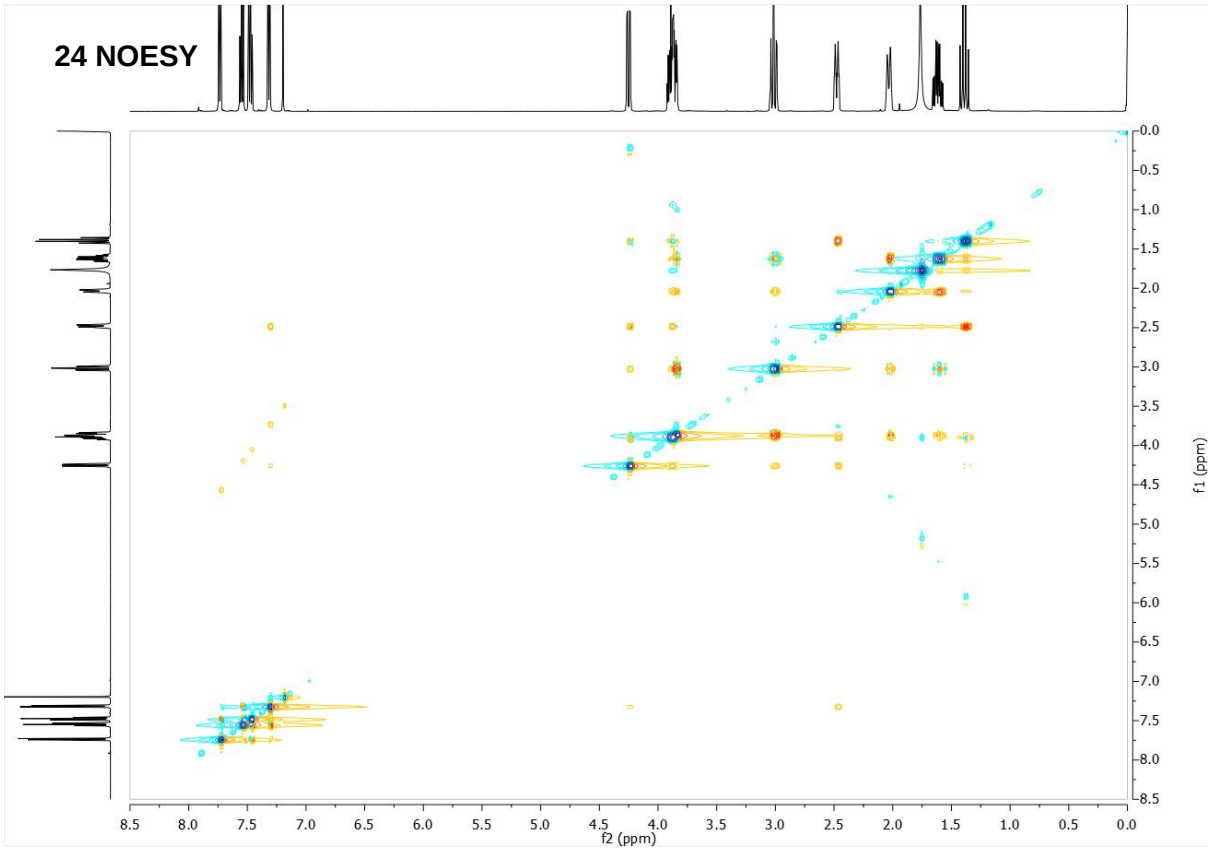

rel. stereochemistry

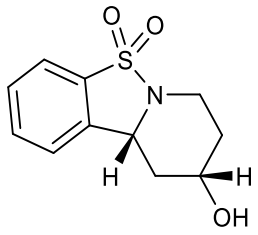
This product was isolated from reductive amination reaction towards **23c** in significant amount (see procedure above). Only by preparative HPLC, the product mixture could be purified and we found quite some amount of alcohol **24**.

**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 7.80 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.61 (td, *J* = 7.6, 1.2 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.38 (dd, *J* = 7.6, 1.0 Hz, 1H), 4.31 (dd, *J* = 11.9, 3.1 Hz, 1H), 4.00 – 3.88 (m, 2H), 3.08 (td, *J* = 13.1, 3.0 Hz, 1H), 2.54 (dddd, *J* = 12.2, 4.6, 3.2, 1.8 Hz, 1H), 2.10 (dq, *J* = 12.5, 2.4 Hz, 1H), 1.68 (tdd, *J* = 12.7, 11.2, 5.1 Hz, 1H), 1.45 (q, *J* = 11.8 Hz, 1H).

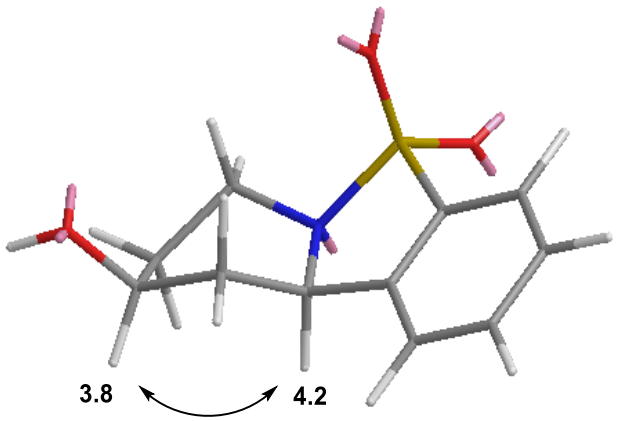
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 137.5, 135.2, 132.9, 129.5, 123.1, 121.6, 68.4, 57.5, 39.2, 37.9, 33.4.

**HMRS (ESI)**: Calculated for $C_{11}H_{14}O_3NS$ = $[M+H]^+$: = 240.06889 found: 240.06871



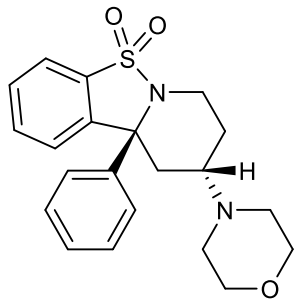




24




NOE

**(±)-9-morpholino-10a-phenyl-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridine 5,5-dioxide (23d)**

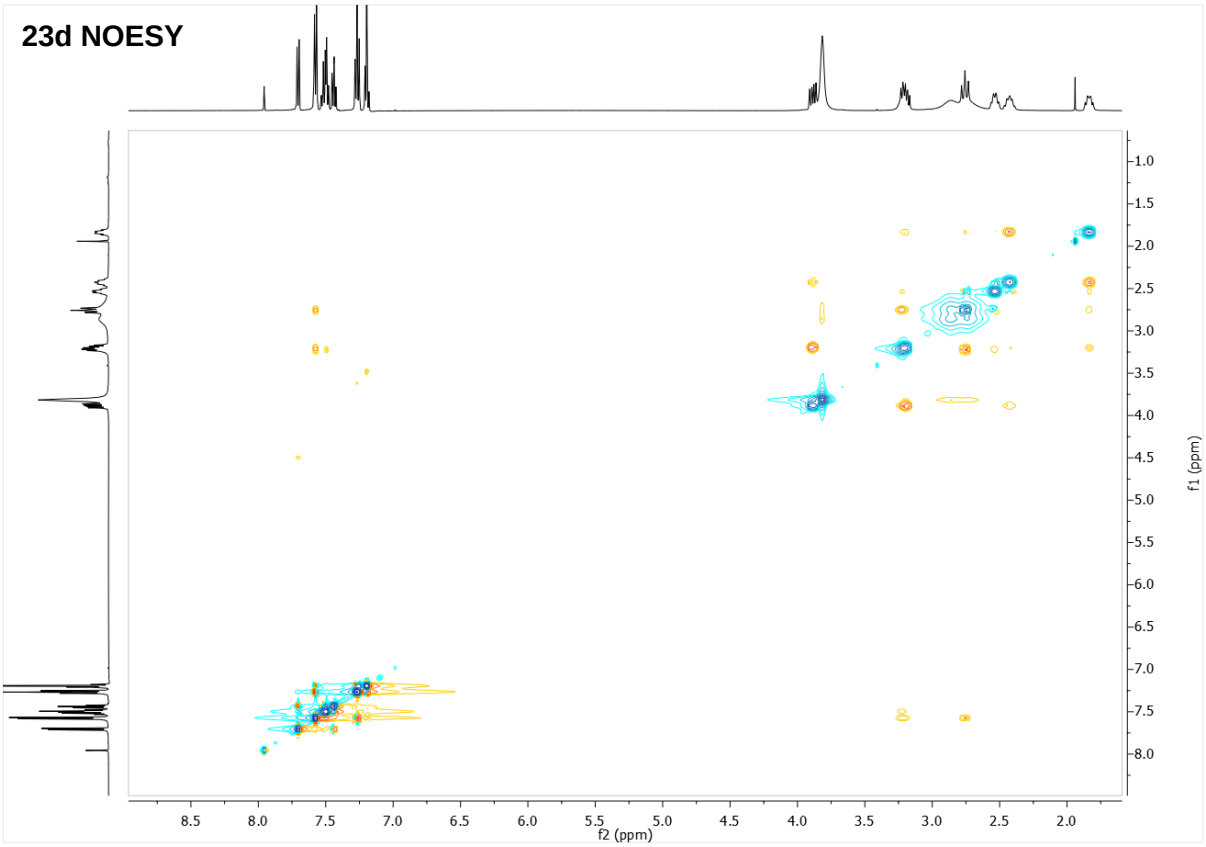


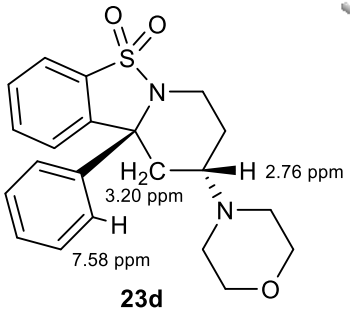
**22b** (1.0 eq., 25 mg, 71.8 µmol), morpholine (1.25 eq., 8 µl, 89.8 µmol) and powdered 4 A molecular sieves were combined in dry 1,2 DCE (600 µl) in a two-necked round bottom flask under an Argon atmosphere and sodium triacetoxyborohydride (1.4 eq., 21 mg, 100.5 µmol) and glacial acetic acid (1.05 eq., 4.3 µl, 75.4 µmol) were added and the reaction stirred at ambient temperature. After 16 h additional 2.3 eq. of morpholine (14 µl, 165.14 µmol) and an additional 1.4 eq. of sodium acetoxyborohydride (21 mg, 100.52 µmol) were added to the mixture. After 6 h of additional stirring, the reaction was quenched by addition of 3 ml sat. aq. ammonium chloride solution. The mixture was transferred to a separation funnel, diluted with water (15 ml) and extracted with 3 x 4 ml ethyl acetate. Combined organic layers were washed with brine and dried over anhydrous sodium sulfate. Concentration yielded crude product which was purified by preparative HPLC (10 to 38% Acetonitrile/water (+0.1 % HCOOH).) Lyophilization then delivered product (7.7 mg, 0.02 mmol, 28%).

**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 7.8 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.54 – 7.47 (m, 2H), 7.44 (ddd, *J* = 8.1, 6.8, 1.5 Hz, 1H), 7.27 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.20 (d, *J* = 6.2 Hz, 2H), 3.89 (ddd, *J* = 15.4, 8.6, 1.4 Hz, 1H), 3.82 (s, 4H), 3.20 (ddd, *J* = 15.3, 9.9, 7.3 Hz, 1H), 2.97 – 2.59 (m, 2H), 2.54 (tdd, *J* = 12.0, 8.4, 2.5 Hz, 1H), 2.43 (dq, *J* = 16.6, 8.5, 7.8 Hz, 1H), 1.84 (dt, *J* = 12.5, 8.3 Hz, 1H).

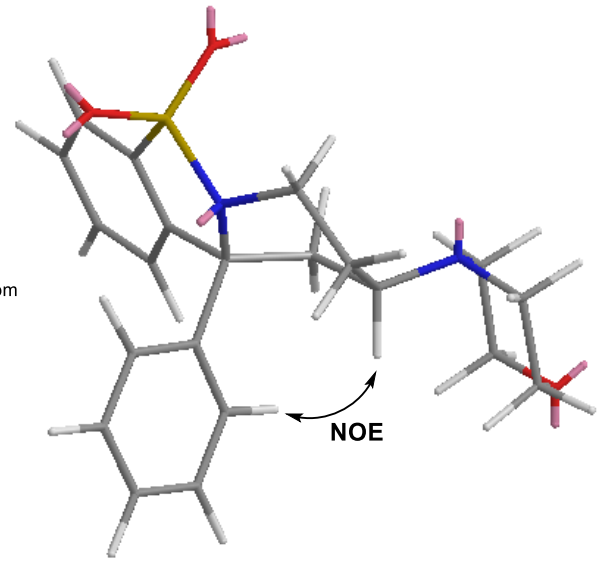
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 142.7, 141.4, 134.1, 132.6, 129.9, 129.1, 128.3, 125.3, 124.6, 121.4, 69.0, 64.6, 57.9, 49.6, 35.3, 35.2, 23.4.

**HMRS (ESI)**: Calculated for $C_{21}H_{25}O_3N_2S = [M+H]^+$: = 385.15804 found: 385.15842

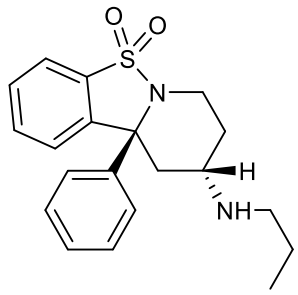

23d NOESY
f2 (ppm)
f1 (ppm)


O
O
S
N
H2C
H 2.76 ppm
3.20 ppm
N
H
7.58 ppm
O

**23d**

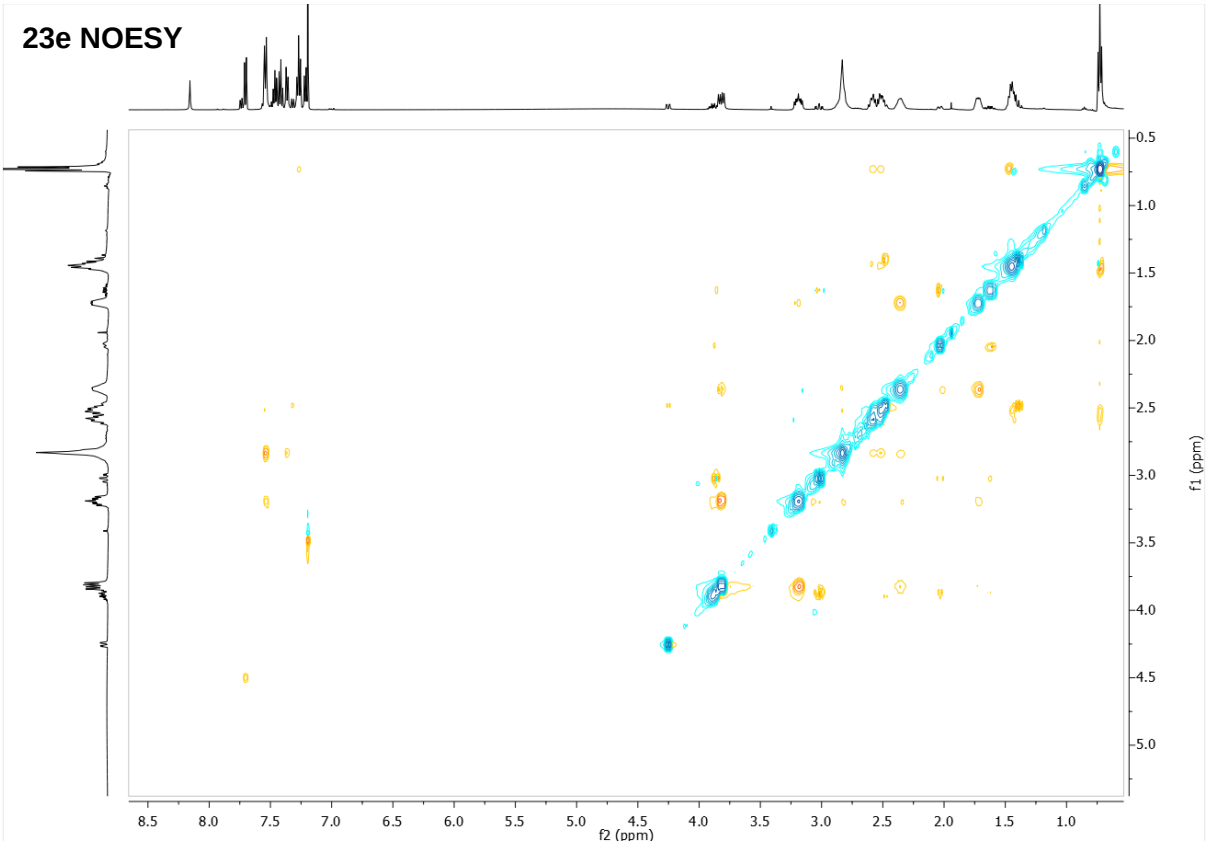

NOE

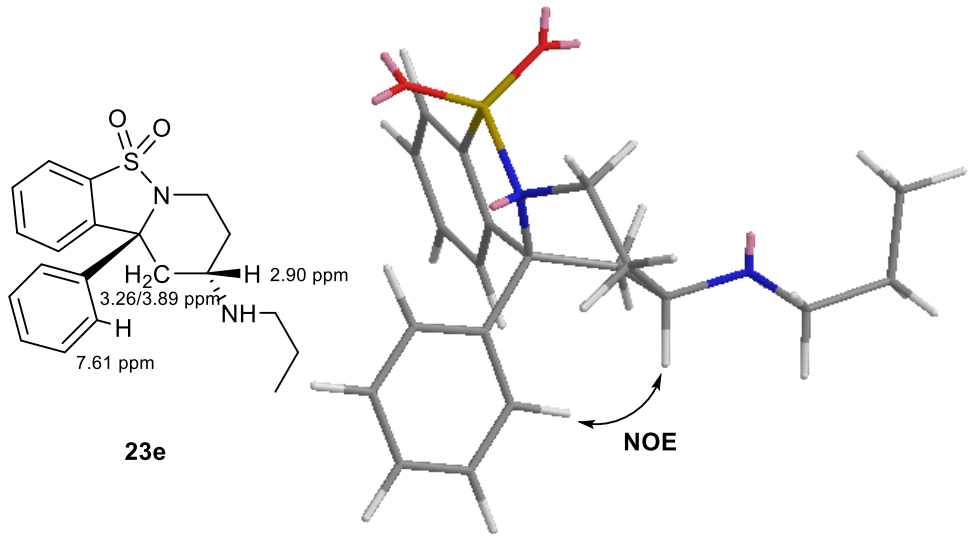
**(±)-10a-phenyl-9-(propylamino)-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridine 5,5-dioxide (23e)**



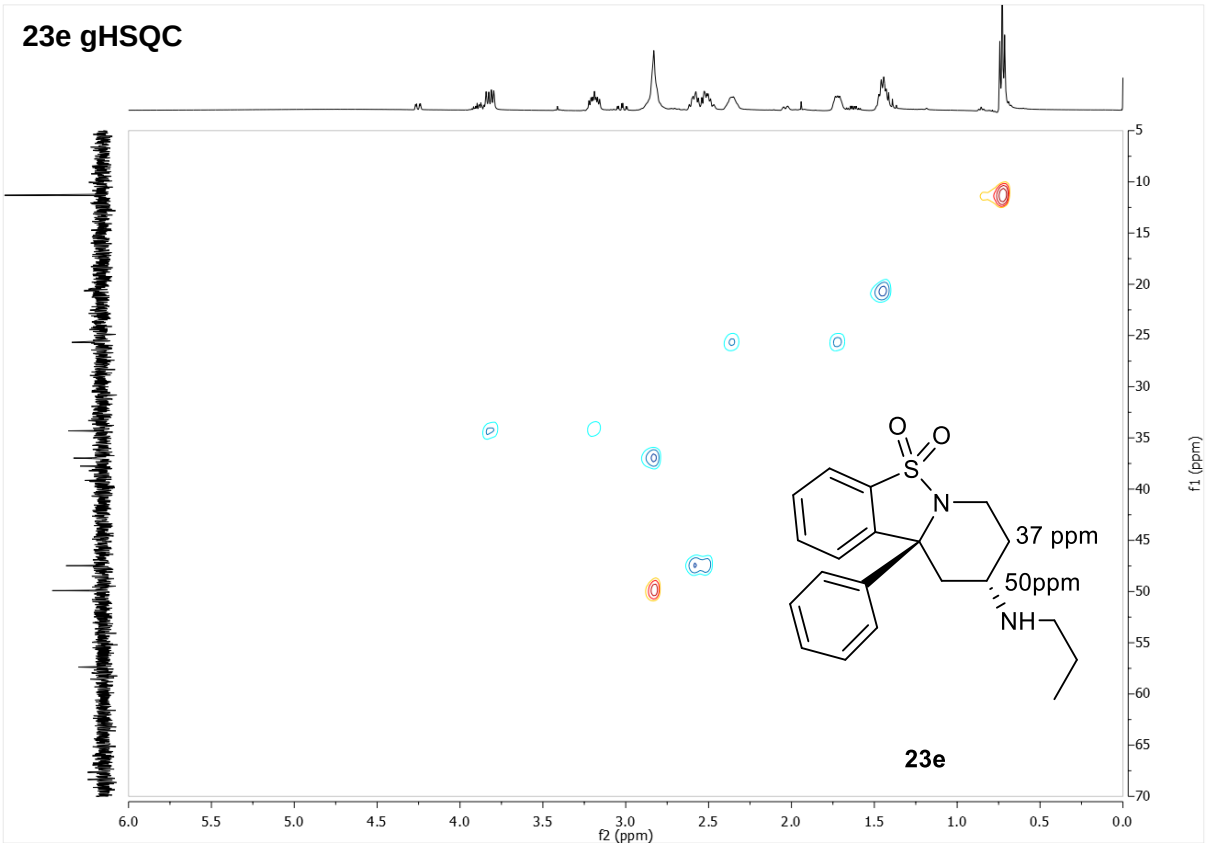

**22b** (1.0 eq., 25 mg, 71.80 µmol), n-propylamine (1.25 eq., 7.43 µl, 89.75 µmol) and powdered 4 A molecular sieves were combined in dry 1,2 DCE (600 µl) in a two-necked round bottom flask under an Argon atmosphere and sodium triacetoxyborohydride (1.4 eq., 21 mg, 100.52 µmol) and glacial acetic acid (1.05 eq., 4.312 µl, 75.39 µmol) were added and the reaction stirred at ambient temperature. After 16 h, additional 2.5 eq. of n-propylamine (15 µl, 179.50 µmol) and an additional 1.4 eq. of sodium acetoxyborohydride (21 mg, 100.52 µmol) were added to the mixture. After 1 d of additional stirring, reaction was concentrated under reduced pressure and the residue was purified by preparative HPLC (C18, 10% to 38% MeCN/$H_2O$ (+0.1% v/v TFA)) to yield 5 mg (20%, 14.03 µmol) of product amine.

**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 7.77 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.61 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.53 (td, *J* = 7.6, 1.5 Hz, 1H), 7.48 (td, *J* = 7.5, 1.0 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 3.92 – 3.85 (m, 1H), 3.30 – 3.21 (m, 1H), 2.90 (q, *J* = 9.7, 8.2 Hz, 3H), 2.70 – 2.51 (m, 2H), 2.48 – 2.36 (m, 1H), 1.78 (dd, *J* = 13.3, 6.6 Hz, 1H), 1.56 – 1.43 (m, 2H), 0.79 (t, *J* = 7.4 Hz, 3H).
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 142.1, 133.8, 132.5, 129.8, 129.3 (3 C), 128.5, 125.4, 124.5, 121.5, 57.5, 50.0, 47.6, 37.9, 37.1, 34.4, 25.8, 11.4.
**HMRS (ESI)**: Calculated for $C_{20}H_{25}O_2N_2S = [M+H]^+$: = 357.16313 found: 357.16270


23e NOESY
f2 (ppm)
f1 (ppm)


O
O
S
N
H2C
H 2.90 ppm
3.26/3.89 ppm
NH
H
7.61 ppm
NOE

**23e**




## 3. Cheminformatic Evaluation of compound Collection

### 3.1 Distribution of compound collection over chemical space (PMI)

Nelson's group developed the LLAMA platform which allows scientists to evaluate compounds according to their suitability for medicinal chemistry research after different parameters.[11] They also offer a principal moment of inertia (PMI) plot. Making use of this feature we could generate Supp. Figure 1 by overlay of different compounds. Position of different members of compound collection displays, in how far its three-dimensional structure resembles either rod (top left), sphere (top right) or disk (bottom).

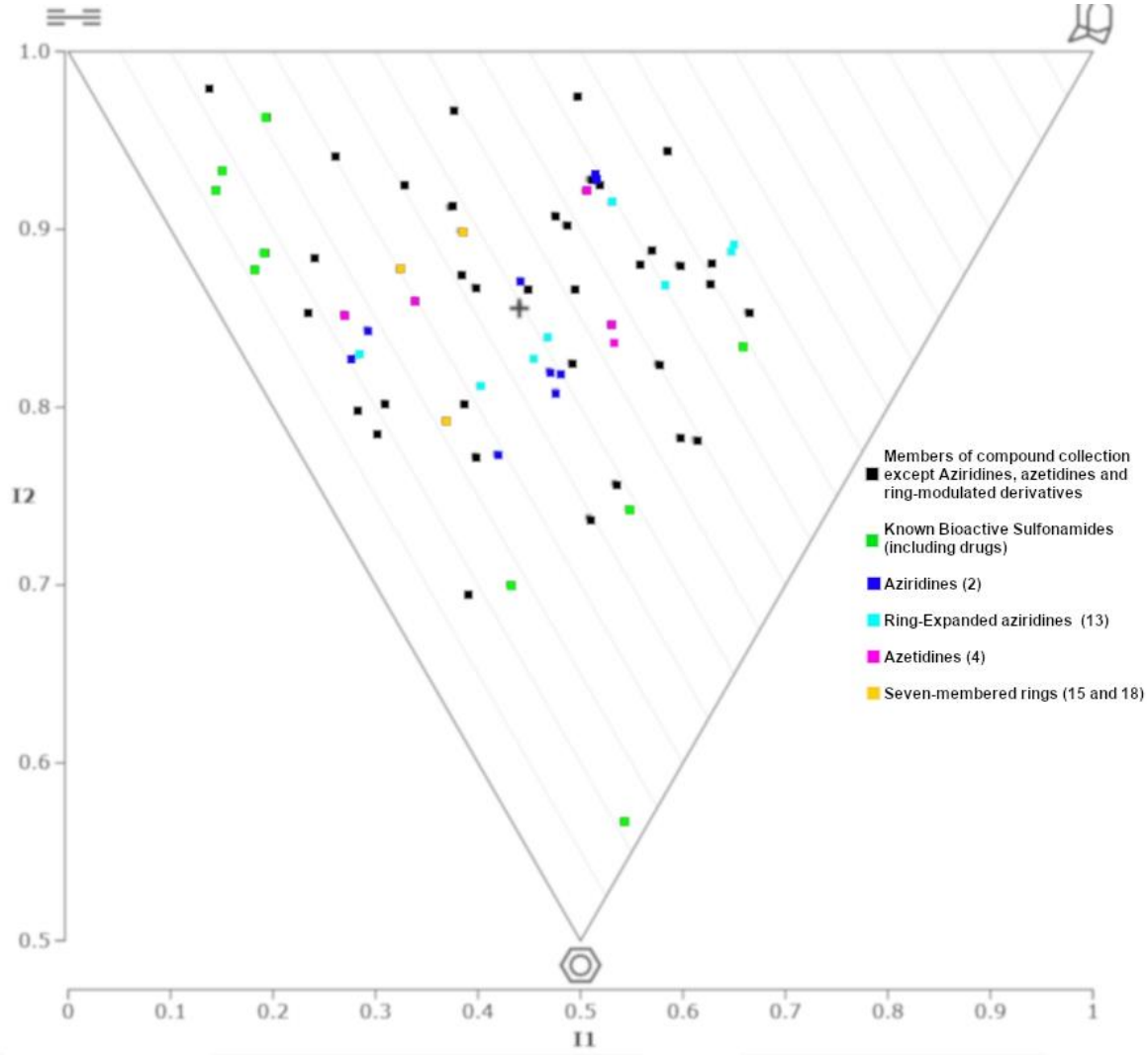



**Figure S1:**PMI plot of Compound collection. "+" denotes averaged center position in PMI plot.[11] Black squares show relative positions of compounds in comparison to commonly known bioactive sulfonamides (green, see also examples in Figure 1 of paper). Aziridines and azetidines, in particular are denoted by blue and light-blue squares, respectively. Azetidines are highlighted in margenta while their ring-expansion and derivatization products are depicted as orange squares.

### 3.2 Predicted molecular properties of compounds

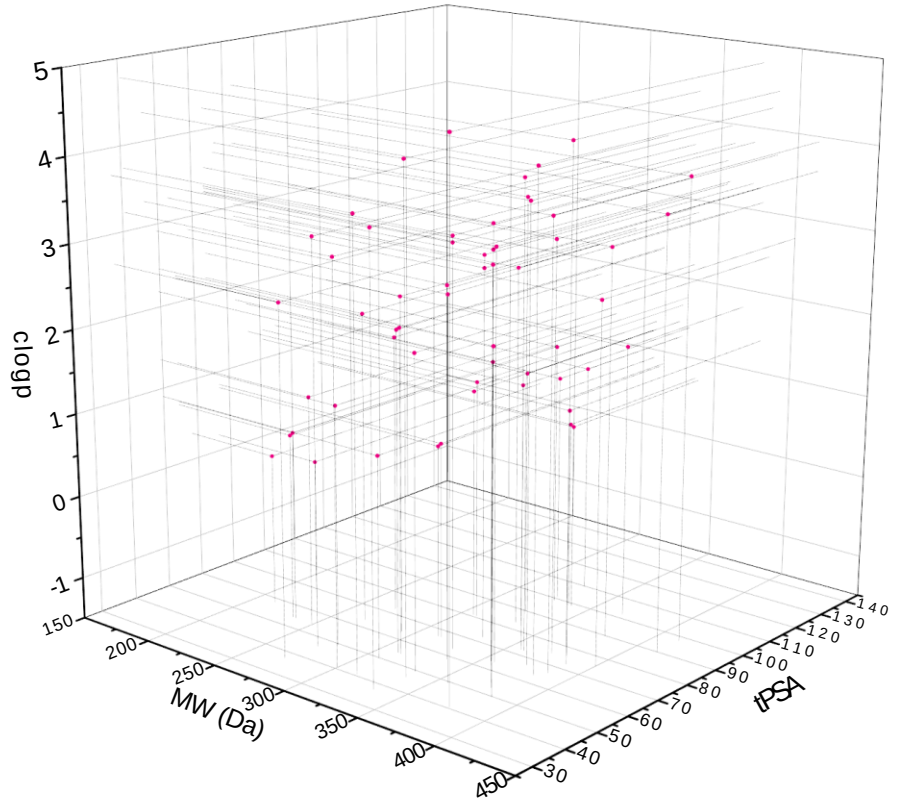



**Figure S2:** 3D Scatter Plot of clogp, tPSA and molweight as parameters that may be beneficial for bioavailability.

The figure shows synthesized compounds as dots according to their projective molecular properties: topological polar surface area ($^{t}$PSA, should be less than 140 or 90, if availability to central nervous system is required), clogp (should be roughly between -1 and 4), both displaying a degree of how well compounds pass through plasma membrane and molecular weight, which should be generally less than 500 Da. All of compounds fit these requirements.

## 4. Biological Evaluation

### 4.1 Supporting Figures

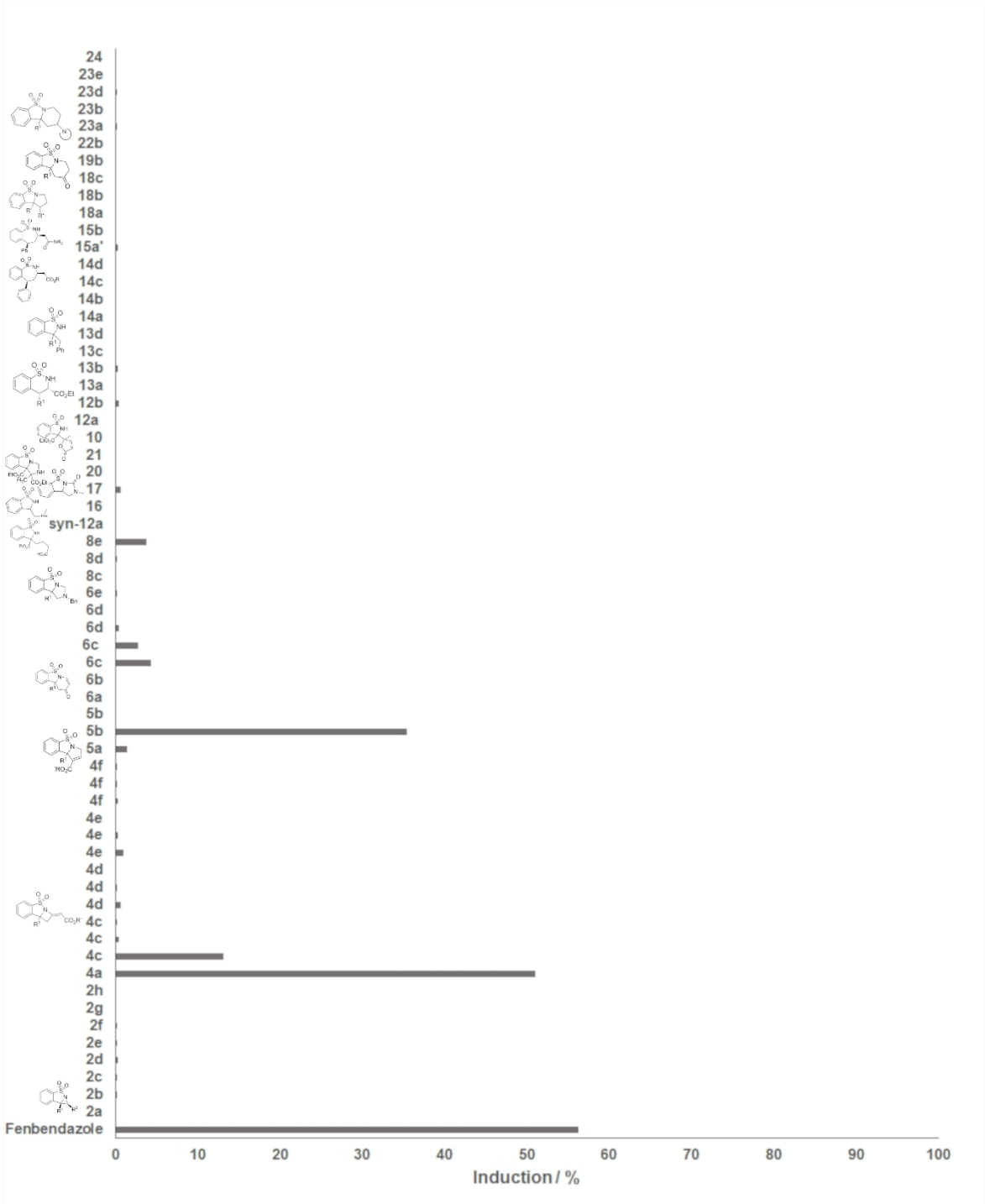



**Figure S3:** Activity (induction) of benzosulfonamides in the cell painting assay. Compounds were subjected to Cell painting assay performed in U2OS cells at a concentration of 10 µM. The induction is a measure of biological activity and is determined as the ratio of the number of parameters significantly different from the control vs. the total number of parameters.

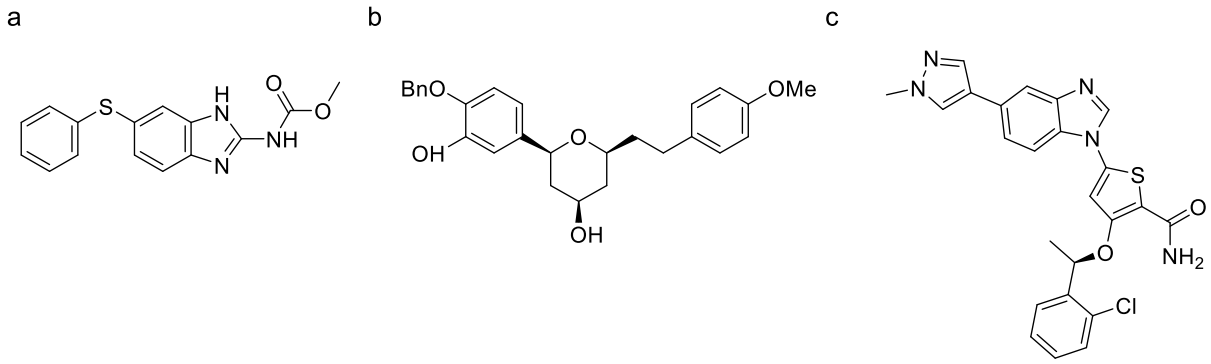



**Figure S4.** Structures of fenbendazole[13] (a), tubulexin A[14] (b) and the PLK1 inhibitor[15] (c).

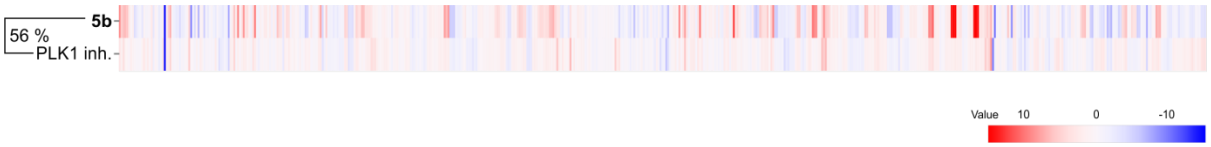



**Figure S5.** Fingerprint comparison for 5b (10 µM) with the fingerprint for a PLK1 inhibitor (PLK1 inh. 2 µM).

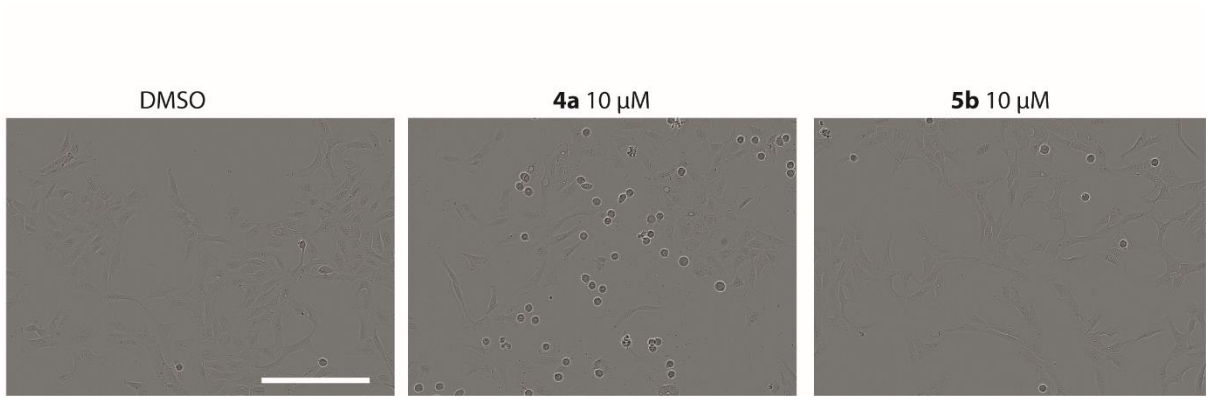



**Figure S6.** Benzosulfonamides 4a and 5b lead to accumulation of round cells. U2OS cells were treated with the compounds or DMSO followed by live-cell imaging. Images of cell after 24 h of treatment with 4a, 5b or DMSO as a control are shown. Scale bar: 300 µm.

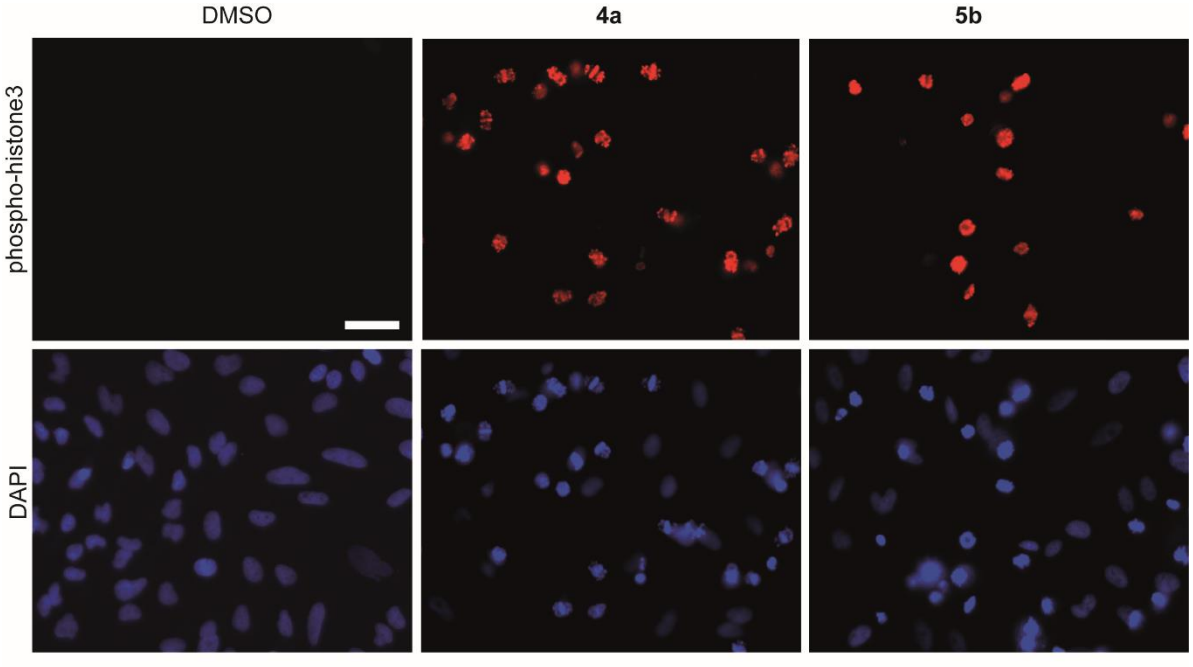



**Figure S7. Benzosulfonamides 4a and 5b lead to accumulation of phospho-histone 3-positive cells.** U2OS cells were treated with the compounds or DMSO for 24 h prior to staining for phospho-histone 3 as a marker for mitotic arrest and DNA using DAPI. Scale bar: 50 µm.

## 4.2 Experimental section - Biology

### Reagents

DAPI (4′,6-Diamidin-2-phenylindol, #10236276001), anti-tubulin FITC (Cat# F2168;) and Hoechst 33342 (Cat. No. B2261-25mg) were purchased from Sigma Aldrich. Anti-phospho-histone3 antibody was obtained from Abcam (Cat# ab5176). Tubulin purified from porcine brain was purchased from Cytoskeleton, Inc **(**#T240). Human bone osteosarcoma epithelial c*ells* U2OS were obtained from CLS (Cat# 300364; RRID: CVCL_0042). DMEM, sodium pyruvate and non-essential amino acid obtained from PAN Biotech, and fetal bovine serum (FBS) was purchased from Gibco. Mito Tracker Deep Red (Cat. No. M22426), Phalloidin (A12381), Concanavalin A (Cat. No. C11252), WGA-Alexa594 conjugate (Cat. No. W11262) and µl/ml SYTO 14 solution (Cat. No. S7576) were obtained from Thermo Fisher Scientific.

### Cell culture

U2OS cells were maintained in DMEM medium supplemented with 10 % fetal bovine serum (FBS) at 37 °C and 5% $CO_2$ in a humidified atmosphere. Cells were regularly assayed for mycoplasma contamination and were always confirmed to be free of mycoplasma.

### Cell painting assay

The cell painting assay[12] was carried out as described by and Bray *et al*.[17] with some modifications[18]. Initially, 5 µl U2OS medium were added to each well of a 384-well plate (PerkinElmer CellCarrier-384 Ultra). Subsequently, 1600 U2OS cells were seeded per well in 20 µl medium. The plate was incubated for 10 min at the room temperature prior to incubation for 4 h at 37 °C. Compounds were then added with the Echo 520 acoustic dispenser (Labcyte) and cells were incubation for 20 h at 37 °C. Subsequently, mitochondria were stained with Mito Tracker Deep Red for 30 min in the dark at 37 °C. Cells were fixed using 3.7 % formaldehyde (in PBS) for 20 min in the dark at 37 °C prior to permeabilization Triton X-100

for 15 min 37 °C in the dark. After three washing steps, cells were stained with Alexa Fluor 594 Phalloidin, Concanavalin A Alexa Fluor 488, Hoechst 33342, WGA-Alexa594 conjugate and SYTO 14. The plate was incubated for 30 min at 37 °C in the dark and washed three times with PBS. After the final washing step, the PBS was not aspirated. The plates were sealed and centrifuged for 1 min at 500 rpm.

The plates were prepared in triplicates with shifted layouts to reduce plate effects and imaged using a Micro XL High-Content Screening System (Molecular Devices) in 5 channels (DAPI: Ex350-400/ Em410-480; FITC: Ex470-500/ Em510-540; Spectrum Gold: Ex520-545/ Em560-585; TxRed: Ex535-585/ Em600-650; Cy5: Ex605-650/ Em670-715) with 9 sites per well and 20x magnification (binning 2).

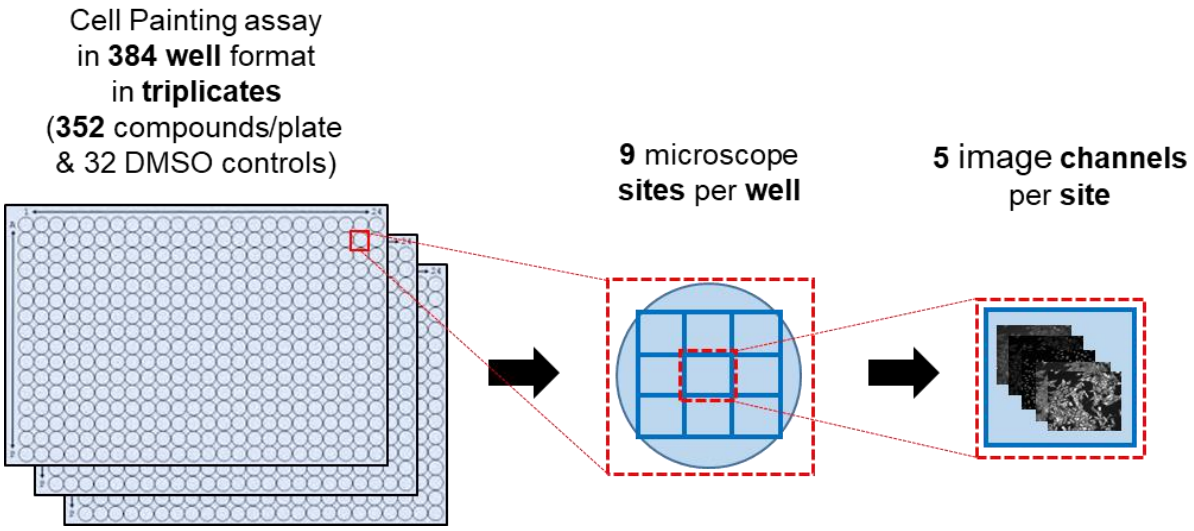



**Figure S8:** Image generation from Cell painting Assay.

The generated images were processed with the CellProfiler package (https://cellprofiler.org/) on a computing cluster of the Max Planck Society to extract 1716 cell features (parameters). The data was then further aggregated as medians per well (9 sites -> 1 well), then over the three replicates.

Further analysis was performed with custom Python (https://www.python.org/) scripts using the Pandas (https://pandas.pydata.org/) and Dask (https://dask.org/) data processing libraries (separate publication to follow).

From the total set of 1716 parameters a subset of highly reproducible and robust parameters was determined using the procedure described by Woehrmann et al.[19] in the following way: Two biological repeats of one plate containing reference compounds were analysed. For every parameter, its full profile over each whole plate was calculated. If the profiles from the two repeats showed a similarity >= 0.8 (see below), the parameter was added to the set.

This procedure was only performed once and resulted in a set of 579 robust parameters out of the total of 1716 that was used for all further analyses.

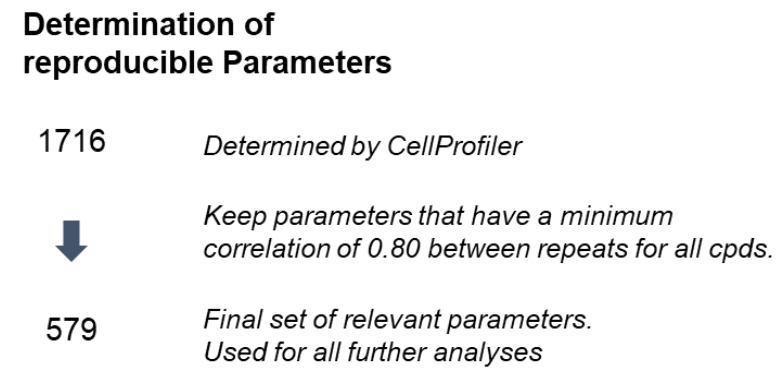



**Figure S9:** Determination of reproducible parameters in cell painting assay.

To determine the phenotypic profiles for each test compound Z-scores were then calculated for each parameter as how many times the Median Absolute Deviation (MAD) of the controls the measured parameter value of a test compound deviates from the Median of the controls:

$$z - score = \frac{value_{meas.} - Median_{Controls}}{MAD_{Controls}}$$

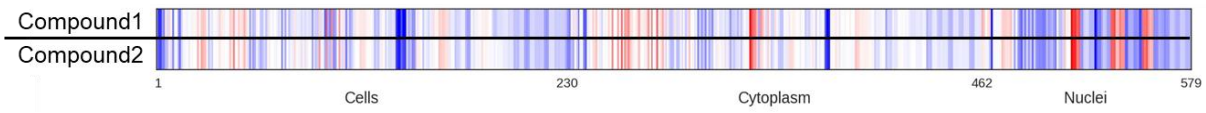
The phenotypic compound profile is then determined as the list of z-scores of all parameters for one compound.

In addition to the phenotypic profile, an induction value was determined for each compound as the fraction of significantly changed parameters, in percent:

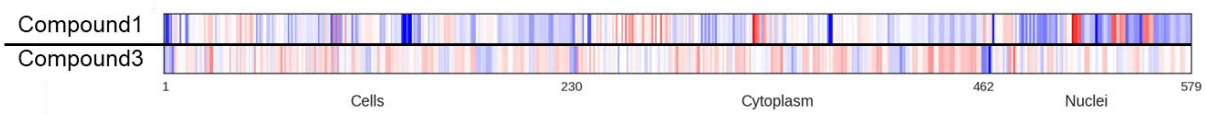
$$Induction\ [\%] = \frac{number\ of\ parameters\ with\ abs.\ values > 3}{total\ number\ of\ parameters}$$

Similarities of phenotypic profiles were calculated from the correlation distances between two profiles (https://docs.scipy.org/doc/scipy/reference/generated/scipy.spatial.distance.correlation.html; Similarity = 1 - Correlation Distance) and the compounds with the most similar profiles were determined from a set of 3000 reference compounds that was also measured in the assay.

An example for two compounds with highly similar profiles (96% similarity):




An example for two compounds with low similarity profiles (0% similarity):




Each colored band represents one Z-score of a parameter.

**Immunocytochemistry**

U2OS cells were seeded per well in a 96-well plate and incubated overnight. Cells were treated with compounds or DMSO as a control for 24 hours. Cells were then fixed using 3.7% paraformaldehyde in phosphate-buffered saline. PBS and permeabilized with 0.1% Triton X-100 (in PBS) prior to staining with DAPI to visualize DNA and anti-tubulin-FITC antibody or anti-phosphor-Histone3 antibody antibodies overnight at 4 C°. Images were acquired using Observer Z1 (Carl Zeiss, Germany) using 20X and 40 X objectives (LD Plan-Neofluar). Automated image analysis to quantify the percentage of phospho-histone3-positive cells was performed using the DAPI stain to assess the total number of cells and the software MetaMorph. Using GraphPad Prism 5, one-way analysis of variance (ANOVA) plus T-test were performed to check the significance of data represented in Figure 1f (***, P-value < 0.0001).

***In vitro* tubulin polymerization assay:**

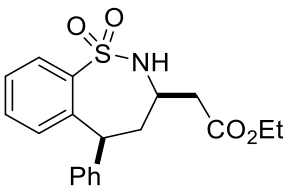
*In vitro* tubulin polymerization assay was performed as described previously.[14] Briefly, porcine α/β-tubulin was diluted in a general buffer containing 80 mM PIPES (pH 6.9), 2 mM $MgCl_2$ and 0.5 mM EGTA. Next, 10 µM of α/β-tubulin was added to a solution containing $MgCl_2$ and glutamate with a final concentration of 0.88 µM and 0.8 mM, respectively, and added to a 96-well plate. Afterwards, compounds at a final concentration 20 µM were added to the tubulin solution and incubated at room temperature for 20 min. The plate was then incubated on ice for another 20 min prior to addition of GTP to a final concentration of 500 µM. Tubulin polymerization was monitored for 60 min by means of turbidity measurements at 340 nm.

**Real-time live-cell analysis**

Cell growth was monitored by means of real-time live-cell analysis using the IncuCyte S3 (Essen Bioscience). For this, 4000 U2OS cells were seeded per well in 96-well plate and incubated overnight. The medium was then exchanged for fresh medium that contained the compounds or DMSO as a control. Cells were incubated for 48 h and cell growth were imaged

every two hours using in the bright-field mode. Cell confluence was quantified as a measure of cell growth using the IncuCyte S3 2019A software.

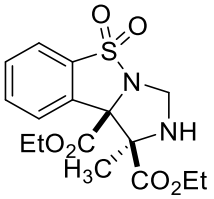
## 5. X-Ray Structures of Compounds 15a and *syn*-10




**15a**

***Crystal data and structure refinement for 15a.***

| | |
|---|---|
| Identification code | pbca |
| Empirical formula | $C_{19}H_{21}NO_4S$ |
| Formula weight | 359.43 |
| Temperature/K | 100 |
| Crystal system | orthorhombic |
| Space group | Pbca |
| a/Å | 16.4445(14) |
| b/Å | 9.7793(8) |
| c/Å | 21.9616(18) |
| α/° | 90 |
| β/° | 90 |
| γ/° | 90 |
| Volume/Å$^3$ | 3531.8(5) |
| Z | 8 |
| $\rho_{calc}$g/cm$^3$ | 1.352 |
| μ/mm$^{-1}$ | 0.207 |
| F(000) | 1520.0 |
| Crystal size/mm$^3$ | 0.277 × 0.116 × 0.059 |
| Radiation | MoKα (λ = 0.71073) |
| 2Θ range for data collection/° | 6.104 to 53.998 |
| Index ranges | $-21 \le h \le 21$, $-12 \le k \le 12$, $-28 \le l \le 28$ |
| Reflections collected | 82730 |
| Independent reflections | 3852 [$R_{int}$ = 0.0453, $R_{sigma}$ = 0.0160] |
| Data/restraints/parameters | 3852/0/251 |
| Goodness-of-fit on $F^2$ | 1.075 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0417, $wR_2$ = 0.0946 |
| Final R indexes [all data] | $R_1$ = 0.0493, $wR_2$ = 0.0985 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.49/-0.50 |



**syn-10**

***Crystal data and structure refinement for syn-10a.***

| | |
|---|---|
| Identification code | C0076_0m |
| Empirical formula | $C_{16}H_{20}N_2O_6S$ |
| Formula weight | 368.40 |
| Temperature/K | 100.0 |
| Crystal system | monoclinic |
| Space group | $P2_1/n$ |
| a/Å | 7.7558(3) |
| b/Å | 10.0904(4) |
| c/Å | 22.1316(10) |
| α/° | 90 |
| β/° | 98.937(2) |
| γ/° | 90 |
| Volume/Å$^3$ | 1710.97(12) |
| Z | 4 |
| $\rho_{calc}$g/cm$^3$ | 1.430 |
| μ/mm$^{-1}$ | 0.225 |
| F(000) | 776.0 |
| Crystal size/mm$^3$ | 0.937 × 0.388 × 0.274 |
| Radiation | MoKα (λ = 0.71073) |
| 2Θ range for data collection/° | 5.494 to 77.996 |
| Index ranges | $-13 \leq h \leq 13$, $-17 \leq k \leq 17$, $-39 \leq l \leq 39$ |
| Reflections collected | 83416 |
| Independent reflections | 9831 [$R_{int}$ = 0.0298, $R_{sigma}$ = 0.0188] |
| Data/restraints/parameters | 9831/0/234 |
| Goodness-of-fit on $F^2$ | 1.094 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0294, $wR_2$ = 0.0828 |
| Final R indexes [all data] | $R_1$ = 0.0317, $wR_2$ = 0.0848 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.68/-0.43 |

## 6. References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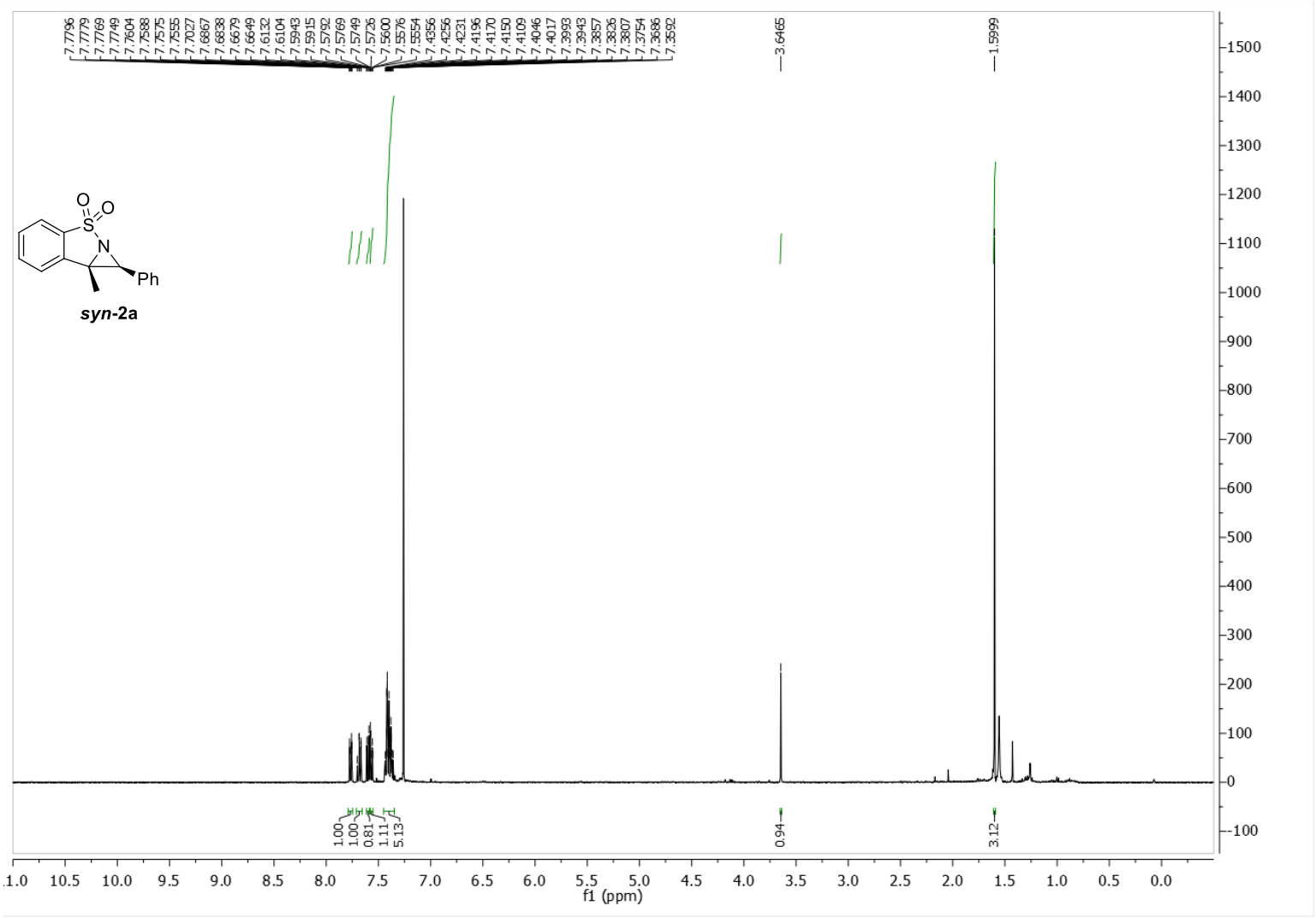
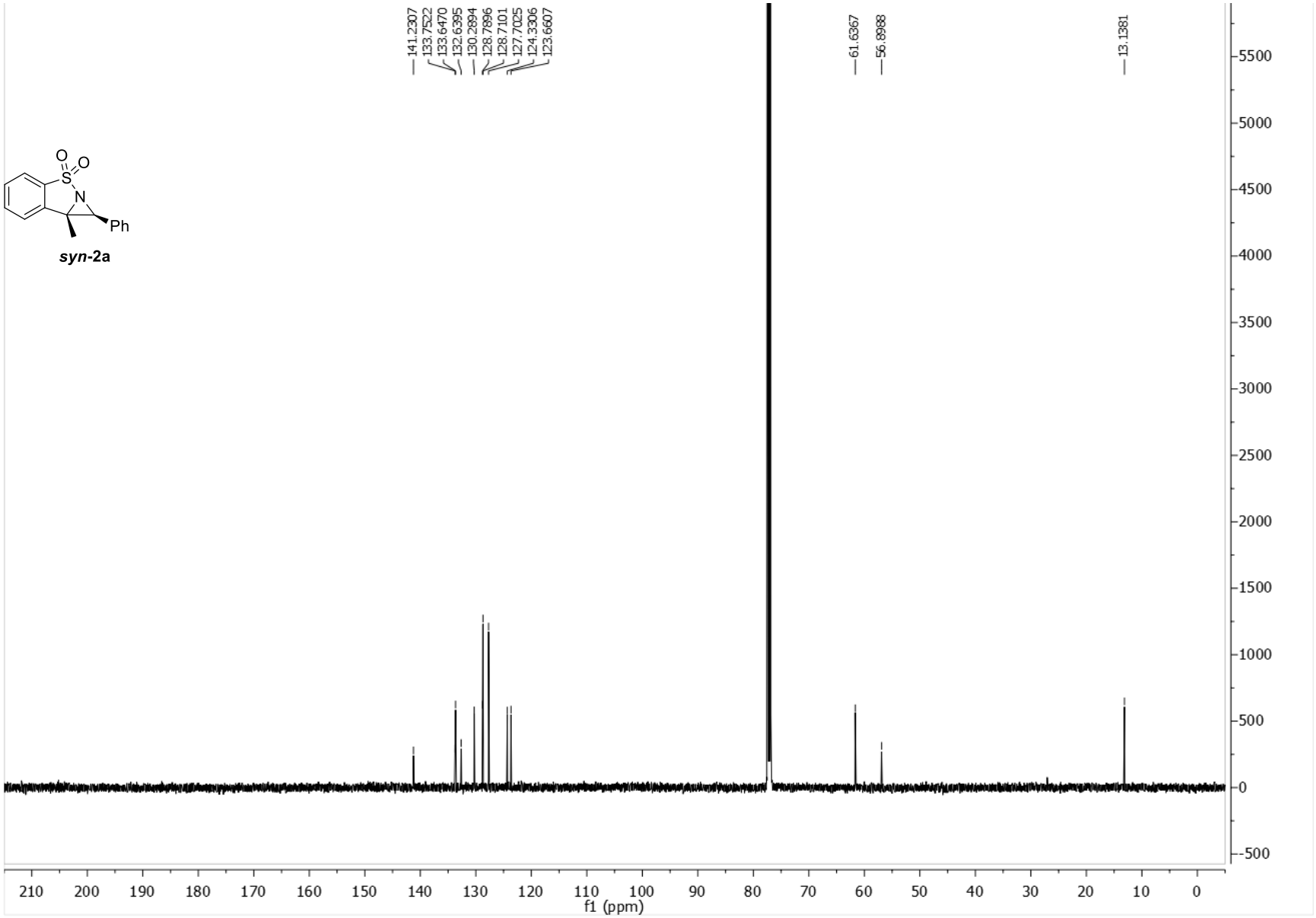
## 5. Copies of NMR Spectra

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13.1381
O
O
S
N
Ph
syn-2a
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
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200
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180
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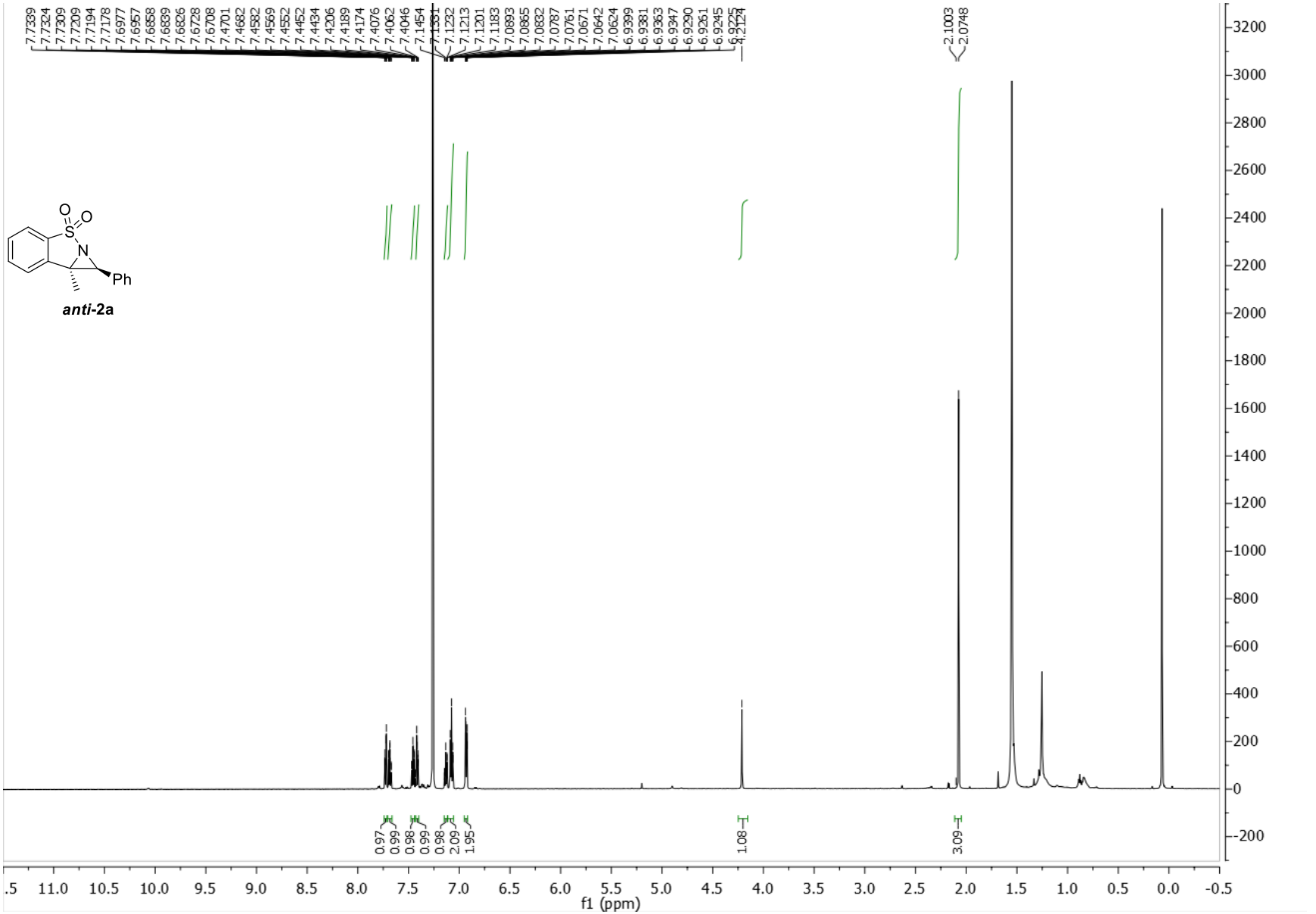
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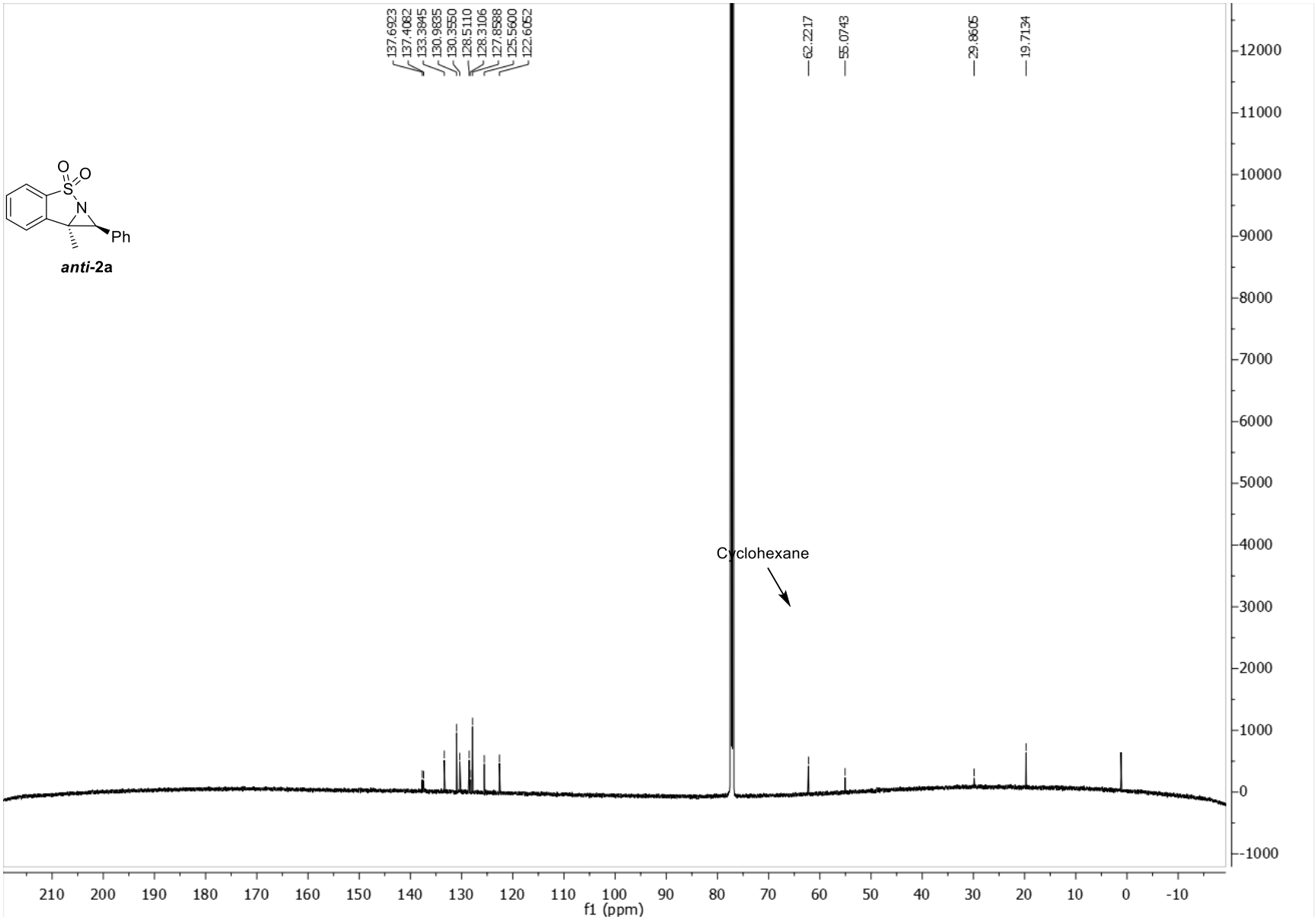
f1 (ppm)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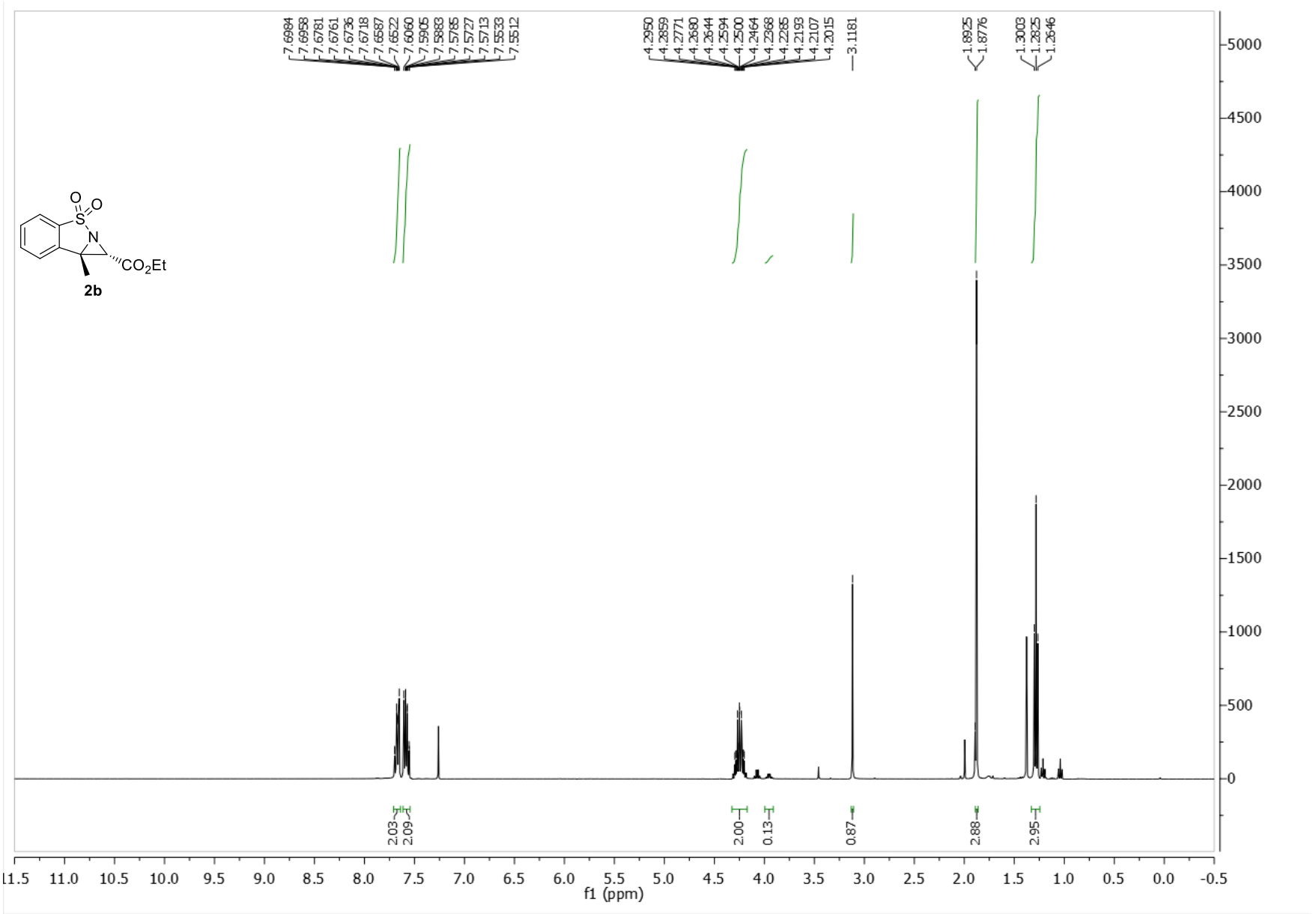
Ph
anti-2a
Cyclohexane
f1 (ppm)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1.8776
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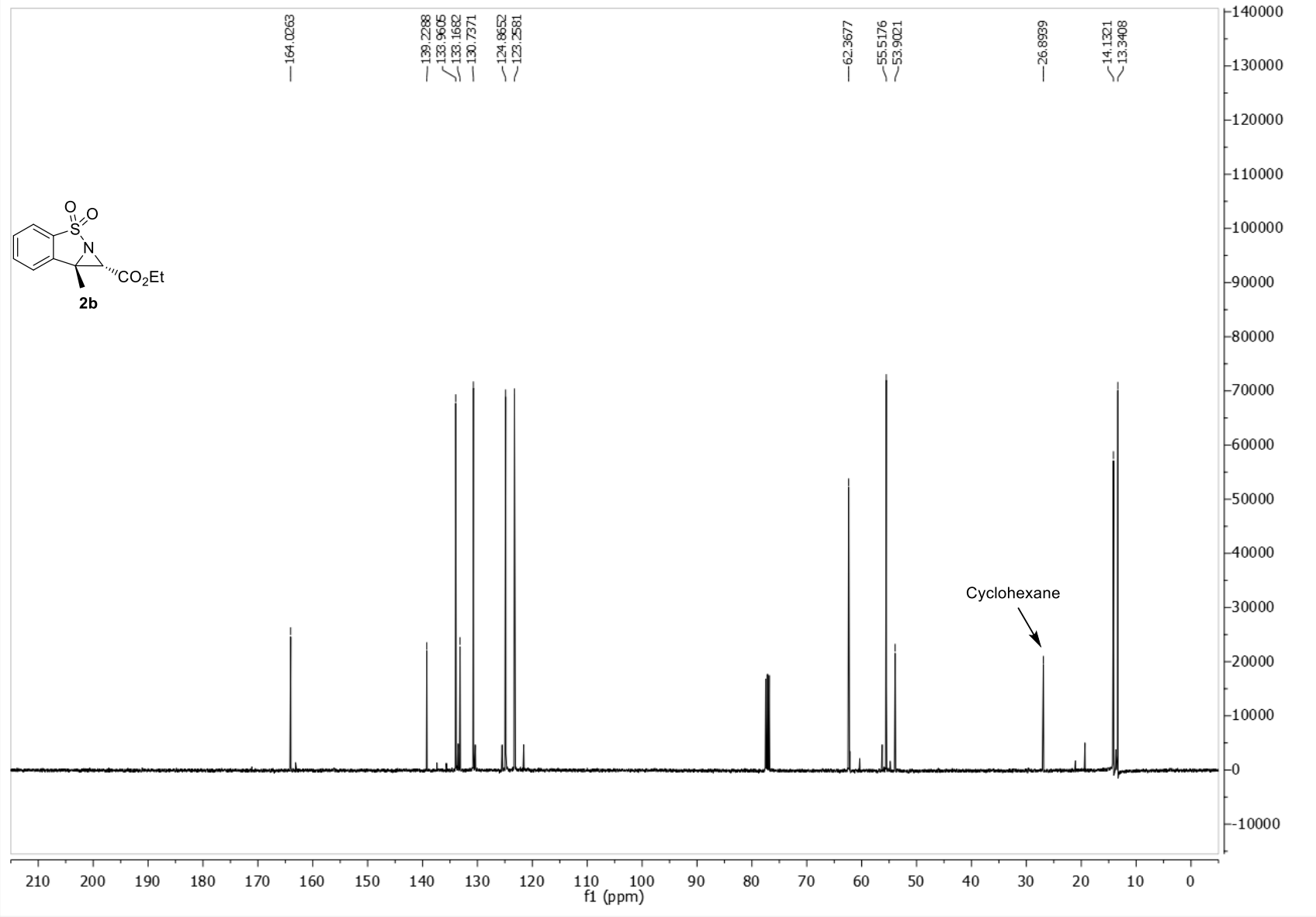
f1 (ppm)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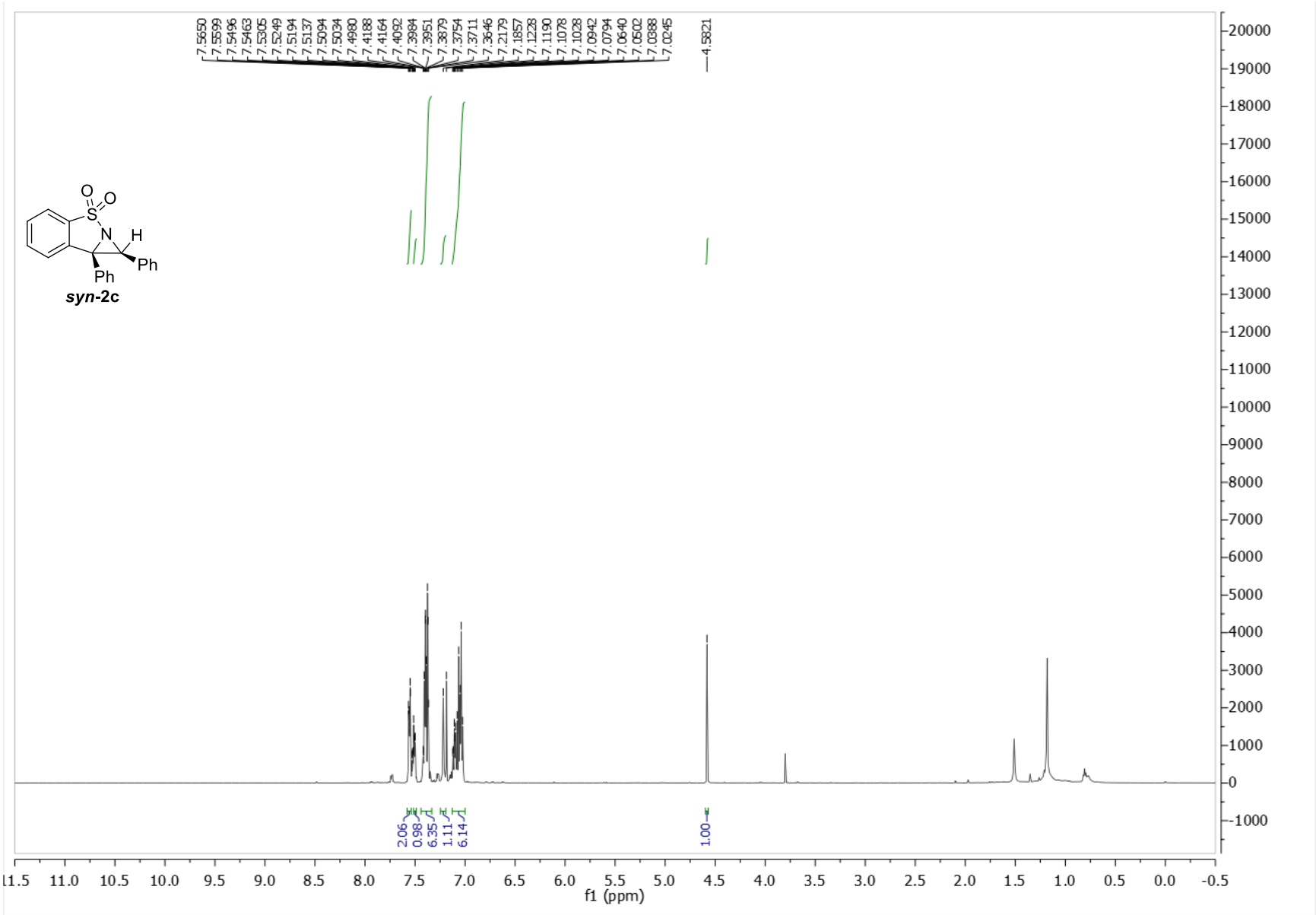
2b
f1 (ppm)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7.1857
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7.0245
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Ph
Ph
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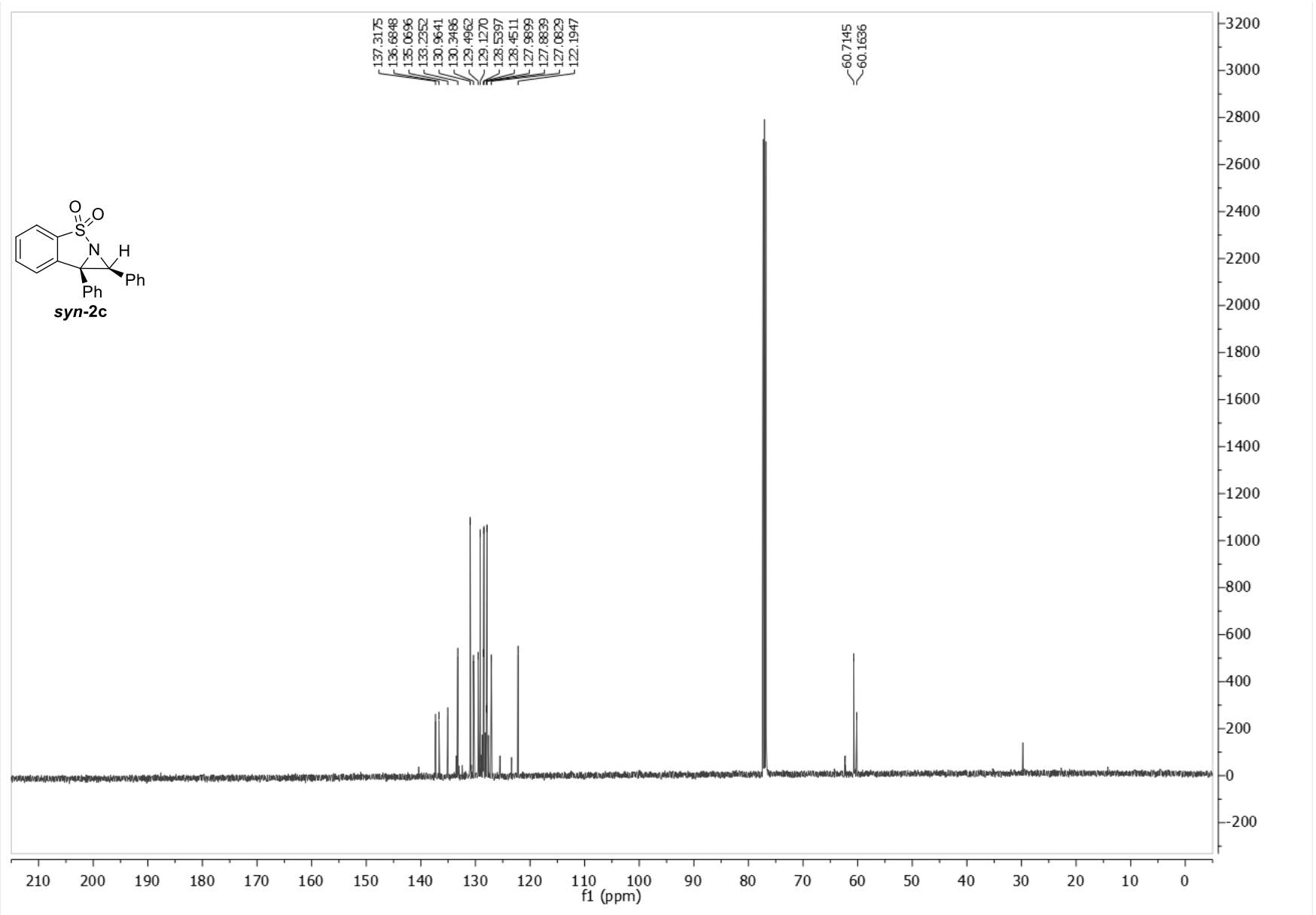
f1 (ppm)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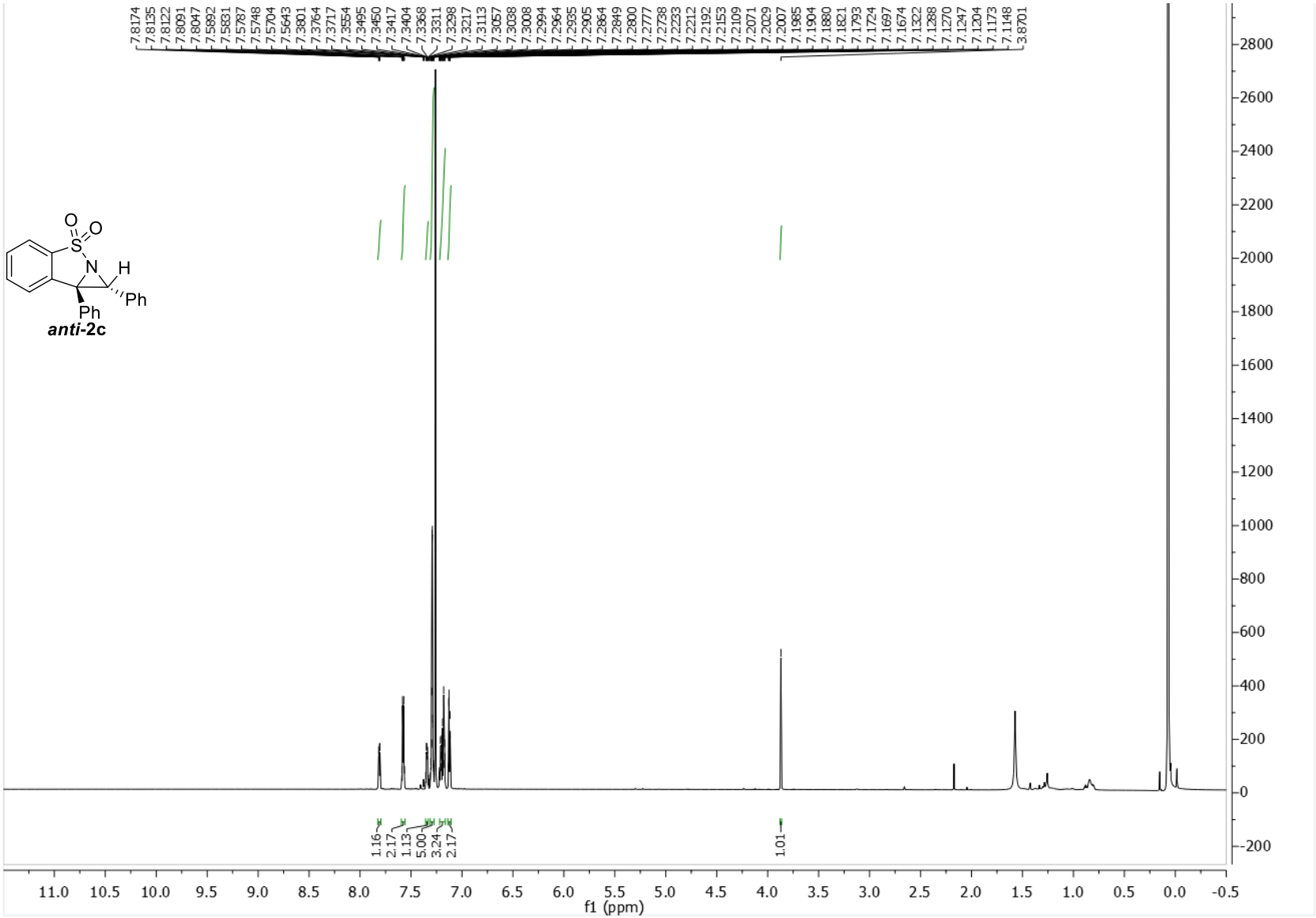
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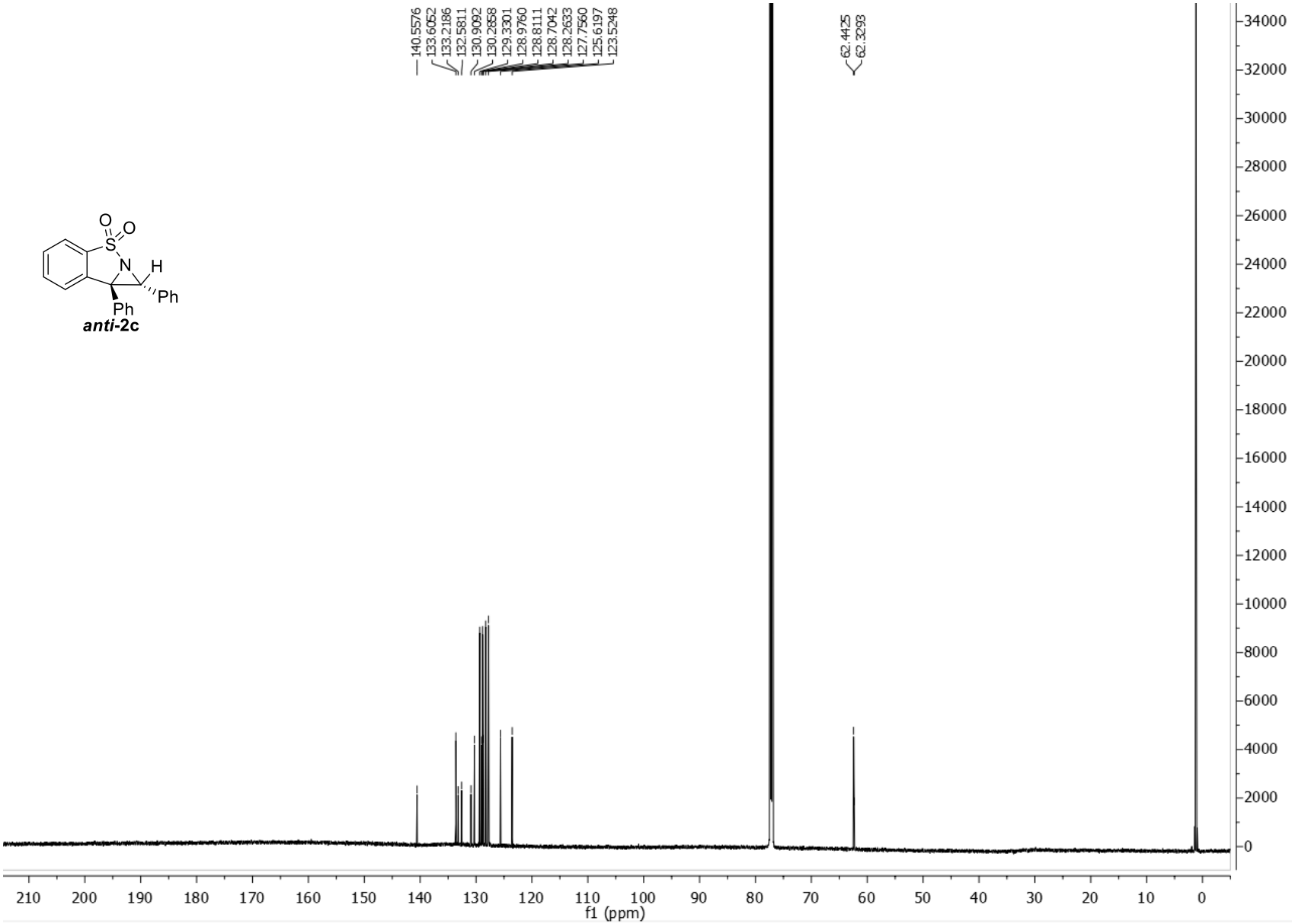
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anti-2c
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32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
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4000
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200
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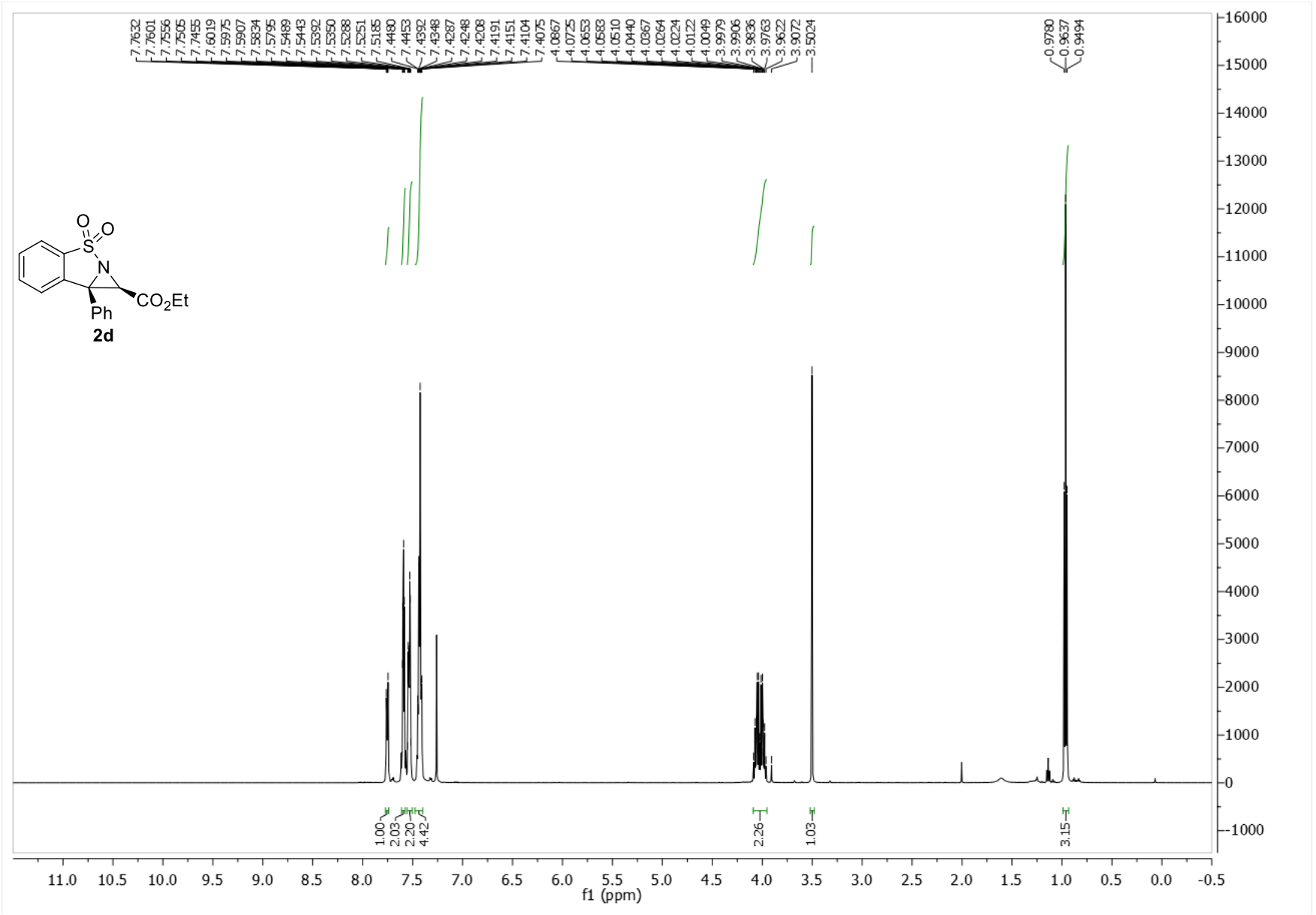
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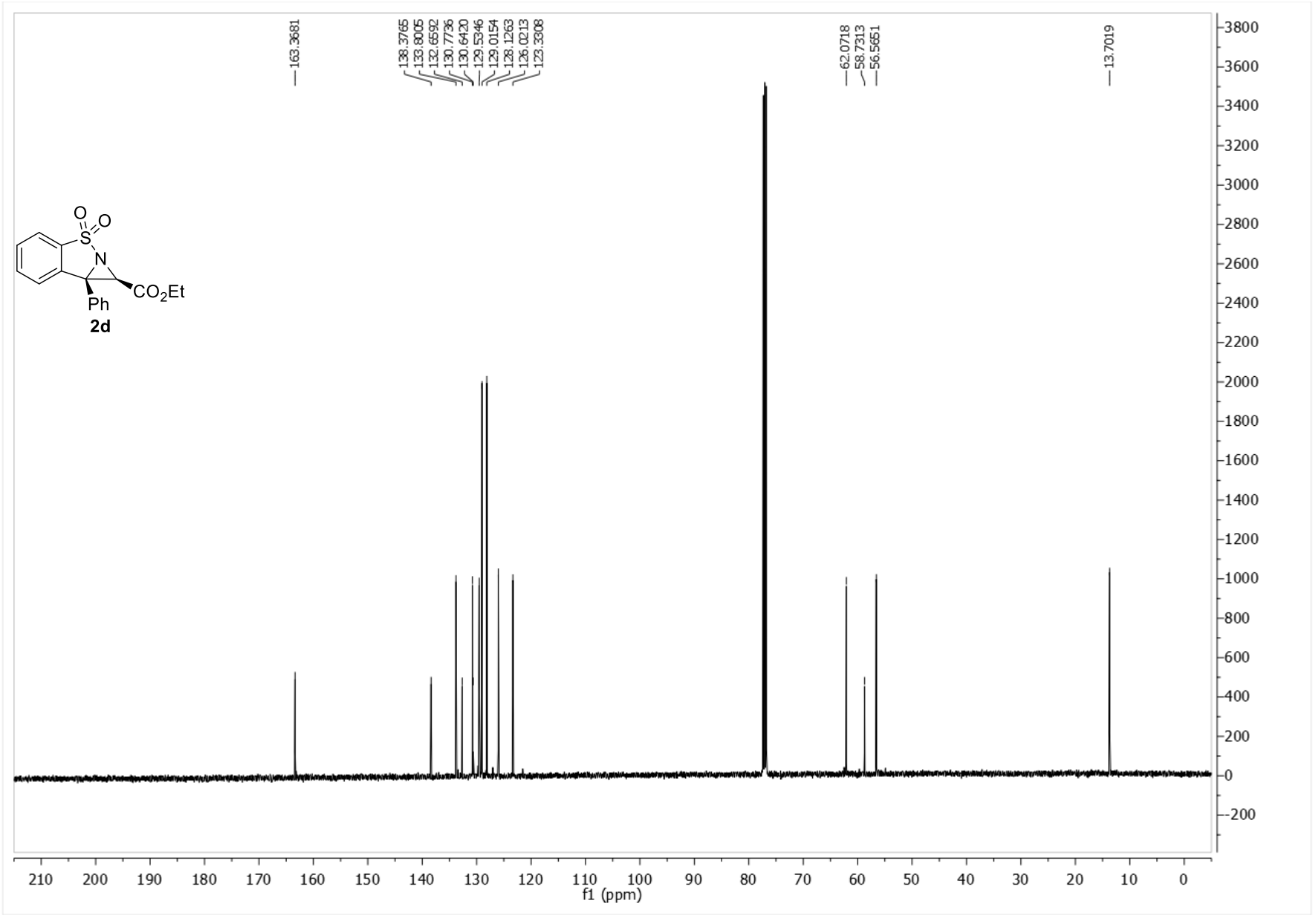
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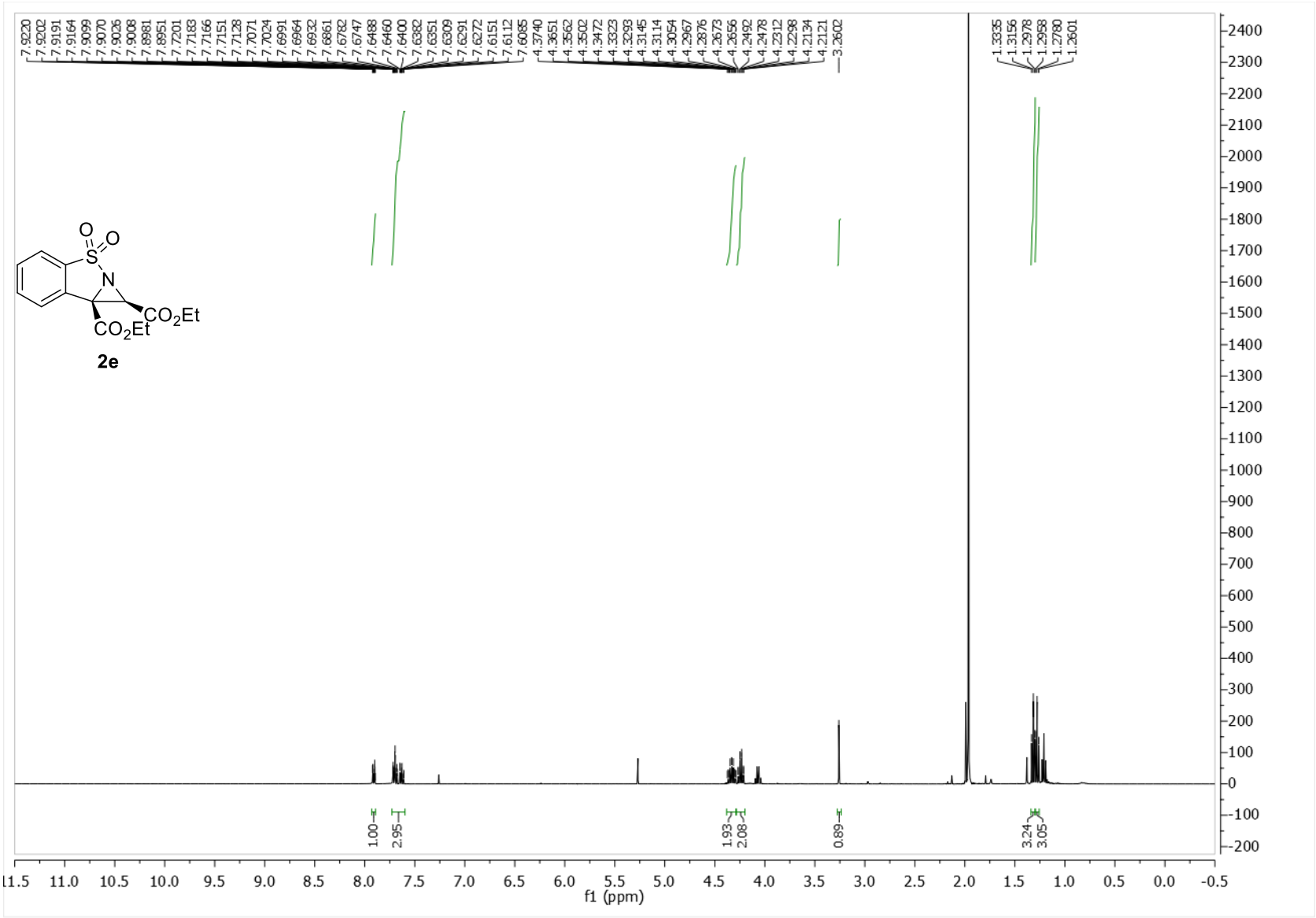
O
S
N
CO2Et
Ph
2d
f1 (ppm)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CO2Et
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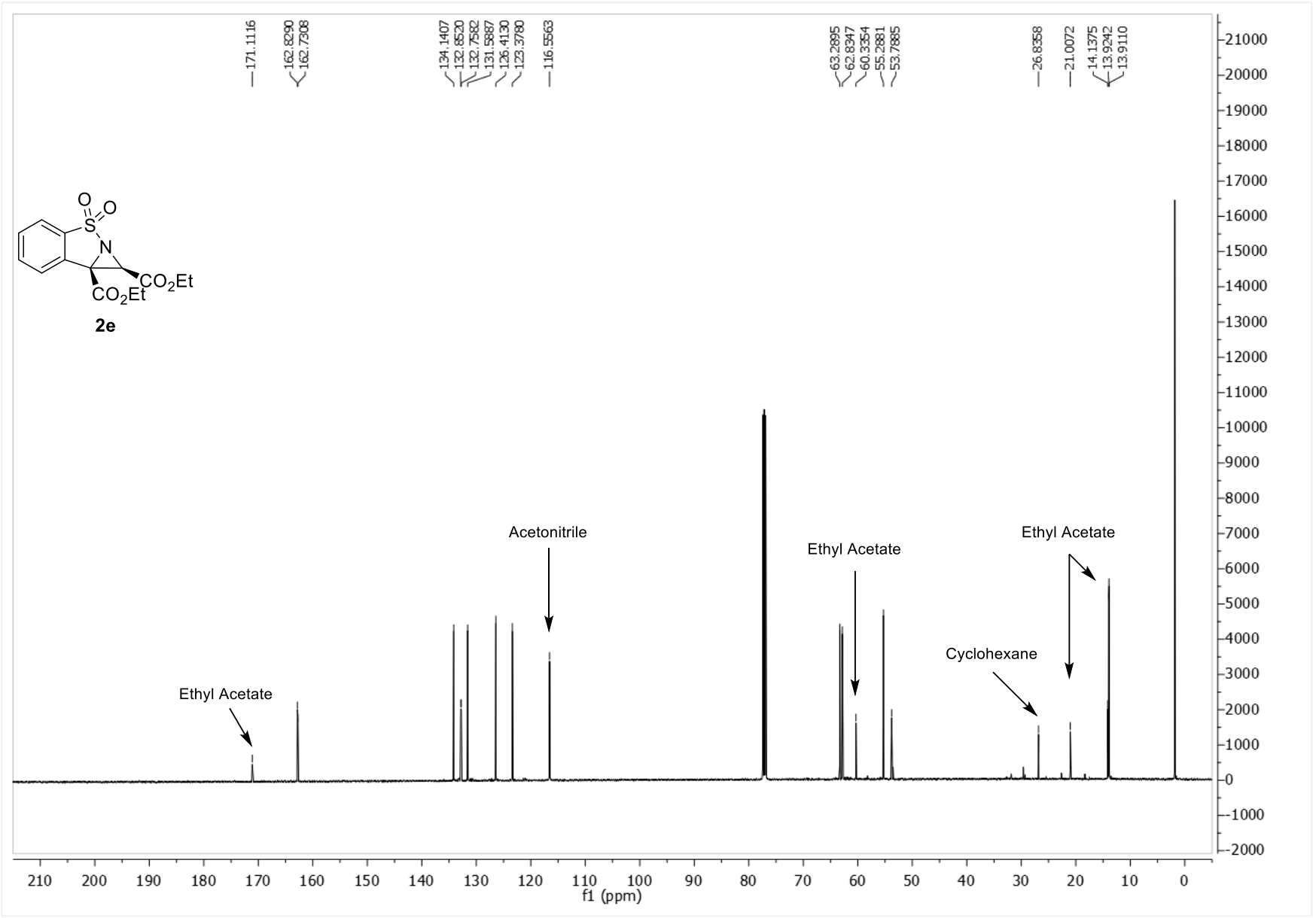
2.95
1.93
2.08
0.89
3.24
3.05
f1 (ppm)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131.5887
126.4130
123.3780
116.5563
63.2895
62.8347
60.3354
55.2881
53.7885
26.8358
21.0072
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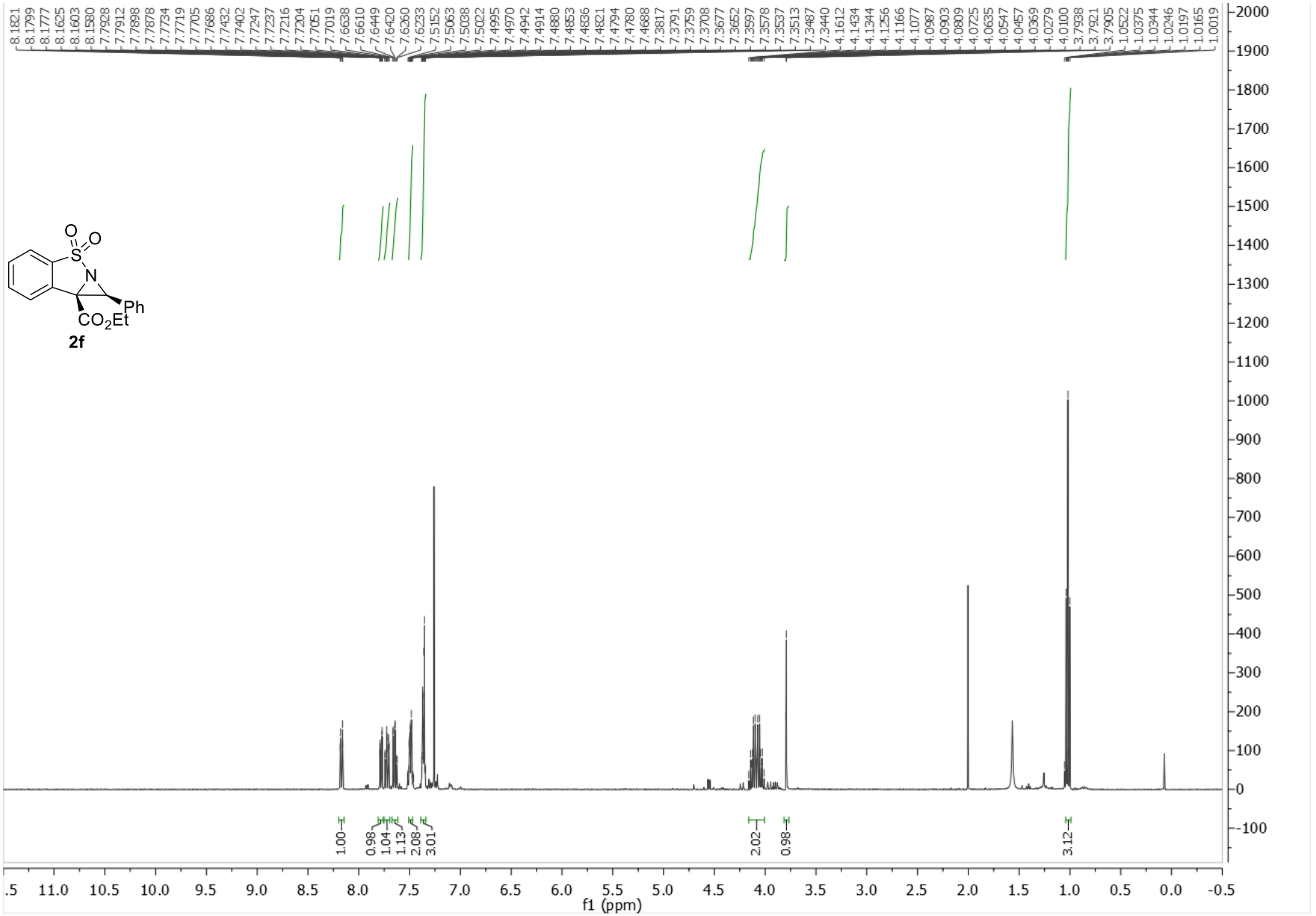
13.9242
13.9110
2e
Ethyl Acetate
Acetonitrile
Ethyl Acetate
Cyclohexane
Ethyl Acetate
f1 (ppm)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7.7719
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7.7686
7.7432
7.7402
7.7247
7.7237
7.7216
7.7204
7.7051
7.7019
7.6638
7.6610
7.6449
7.6420
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7.6233
7.5152
7.5063
7.5038
7.5022
7.4995
7.4970
7.4942
7.4914
7.4880
7.4853
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7.4821
7.4794
7.4780
7.4688
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7.3791
7.3759
7.3708
7.3677
7.3652
7.3597
7.3578
7.3537
7.3513
7.3487
7.3440
4.1612
4.1434
4.1344
4.1256
4.1166
4.1077
4.0987
4.0903
4.0809
4.0725
4.0635
4.0547
4.0457
4.0369
4.0279
4.0100
3.7938
3.7921
3.7905
1.0522
1.0375
1.0344
1.0246
1.0197
1.0165
1.0019
O
O
S
N
Ph
CO2Et
2f
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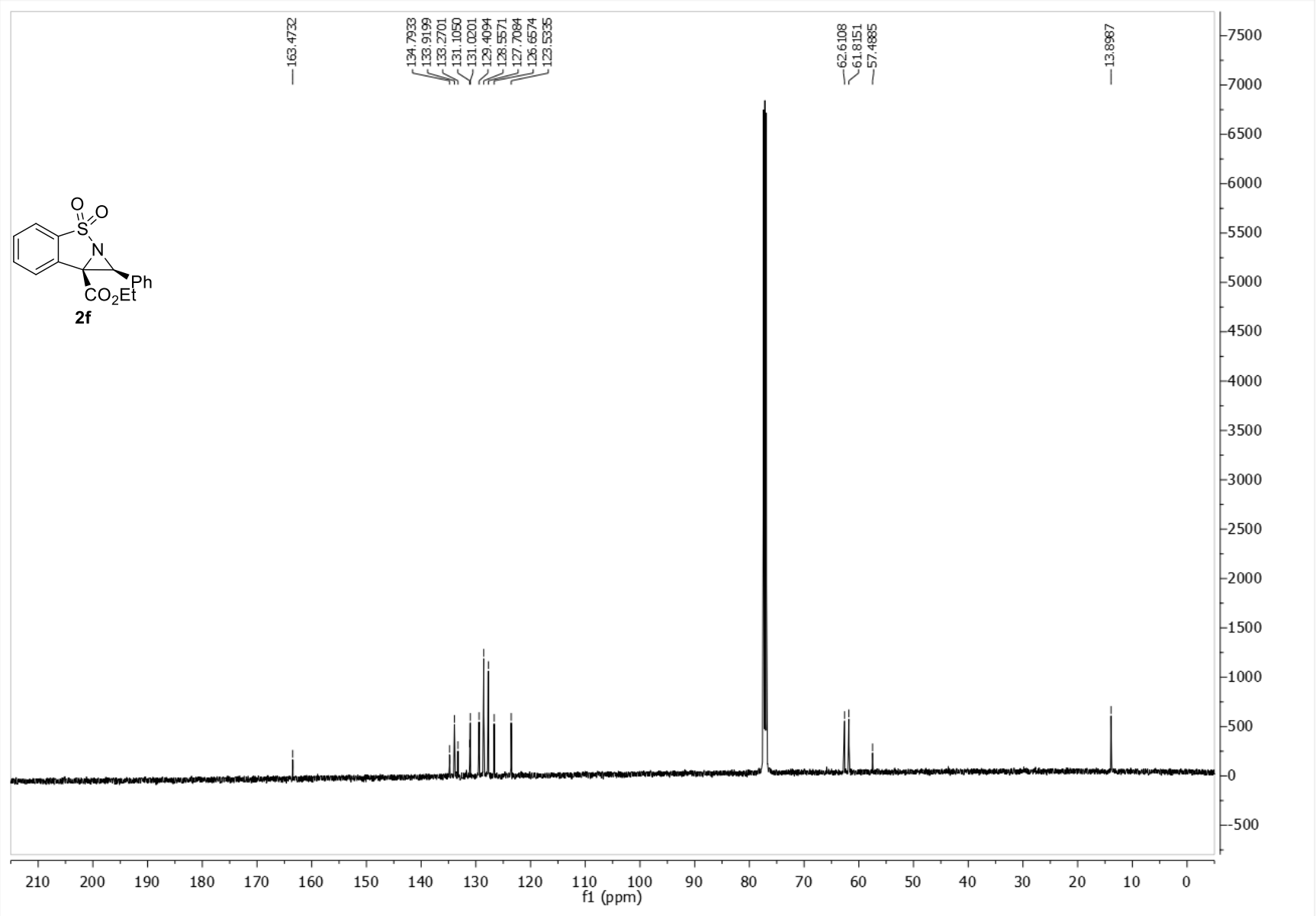
0.98
1.04
1.13
2.08
3.01
2.02
0.98
3.12
f1 (ppm)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129.4094
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127.7084
126.6574
123.5335
62.6108
61.8151
57.4885
13.8987
O
O
S
N
Ph
CO2Et
2f
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
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130
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110
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90
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70
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50
40
30
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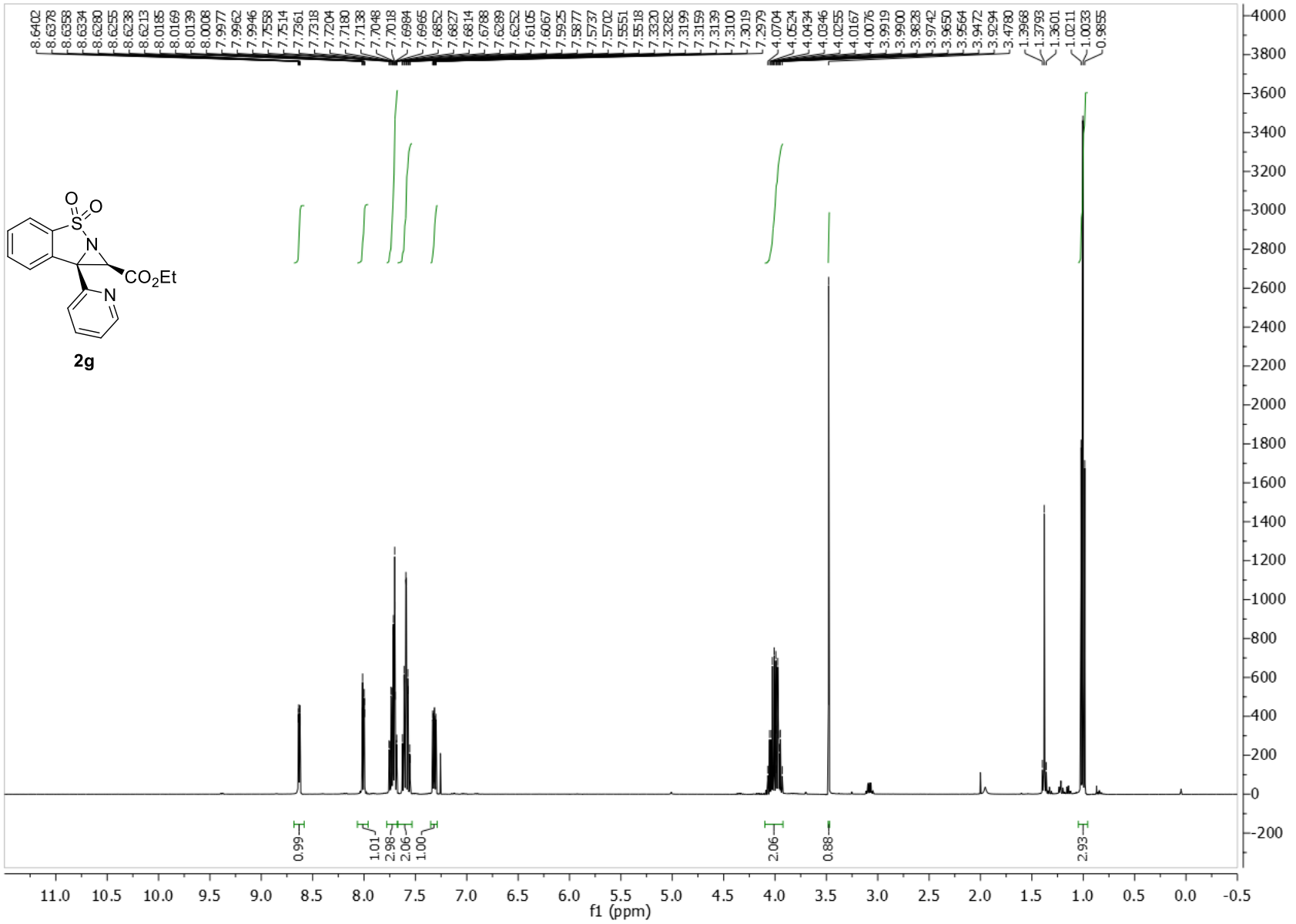
10
0
f1 (ppm)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8.0185
8.0169
8.0139
8.0008
7.9977
7.9962
7.9946
7.7558
7.7514
7.7361
7.7318
7.7204
7.7180
7.7138
7.7048
7.7018
7.6984
7.6965
7.6852
7.6827
7.6814
7.6788
7.6289
7.6252
7.6105
7.6067
7.5925
7.5877
7.5737
7.5702
7.5551
7.5518
7.3320
7.3282
7.3199
7.3159
7.3139
7.3100
7.3019
7.2979
4.0704
4.0524
4.0434
4.0346
4.0255
4.0167
4.0076
3.9919
3.9900
3.9828
3.9742
3.9650
3.9564
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3.9294
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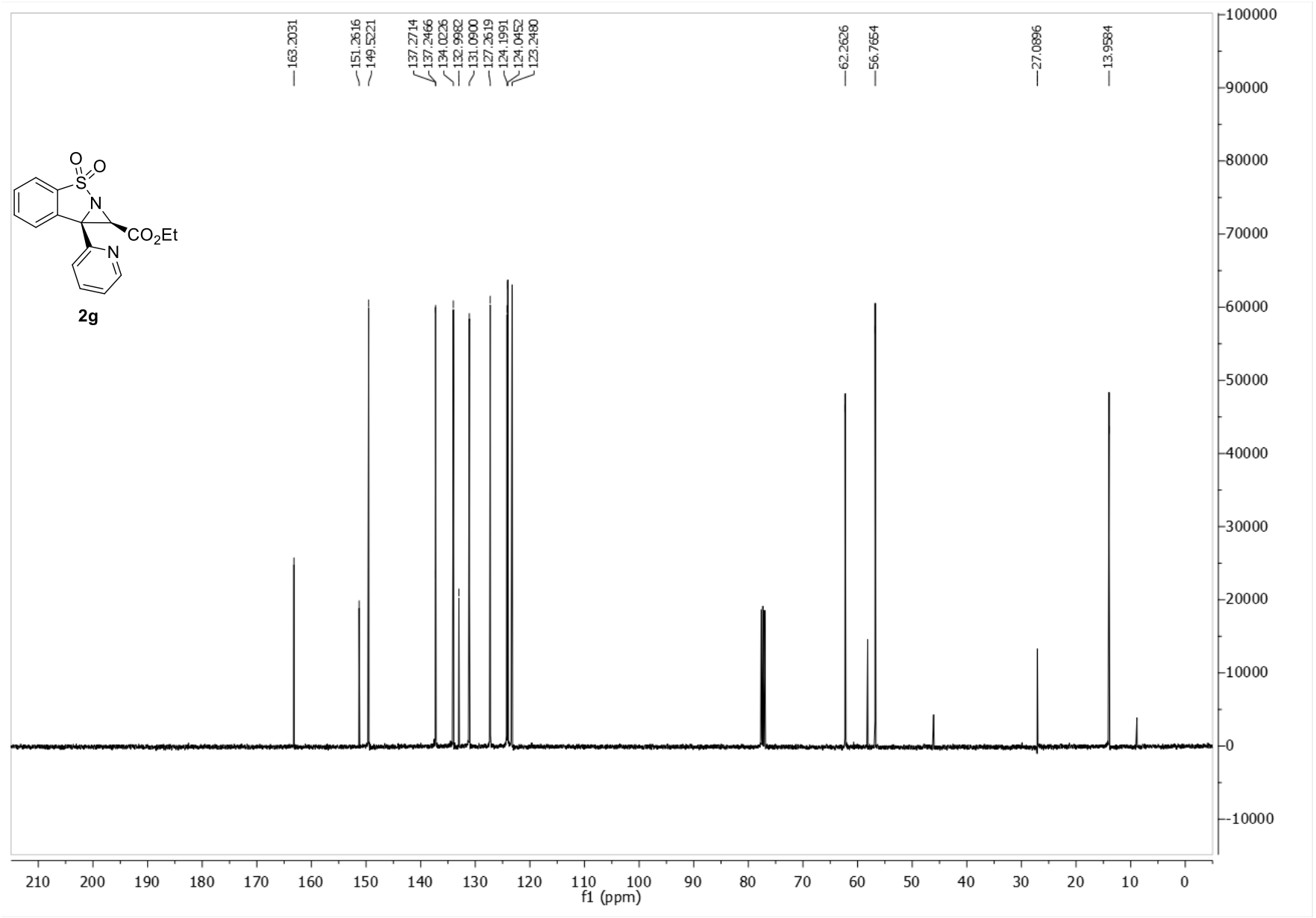
1.3968
1.3793
1.3601
1.0211
1.0033
0.9855
O
O
S
N
CO2Et
N
2g
0.99
1.01
2.98
2.06
1.00
2.06
0.88
2.93
f1 (ppm)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132.9982
131.0900
127.2619
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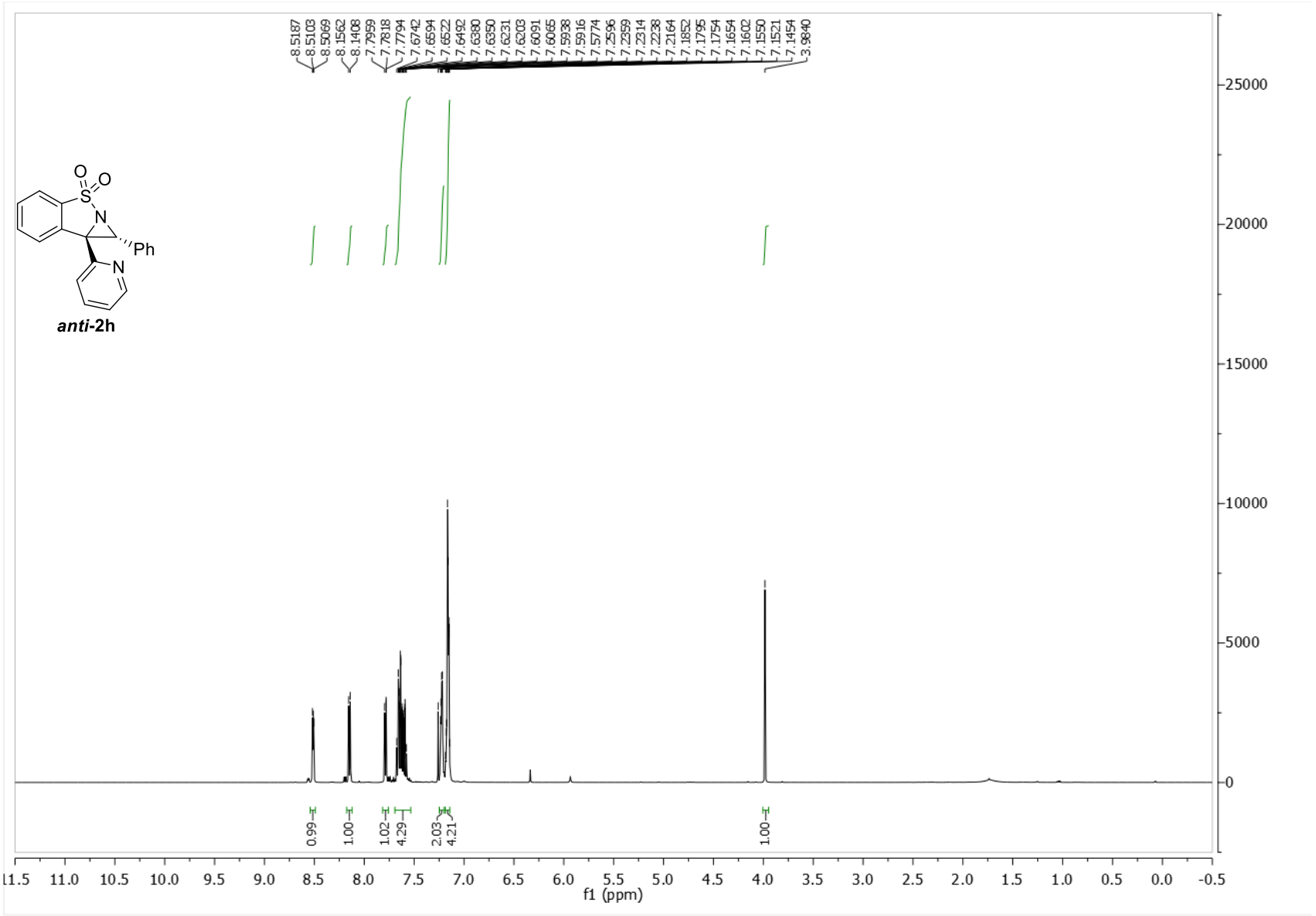
124.0452
123.2480
62.2626
56.7654
27.0896
13.9584
O
O
S
N
CO2Et
N
2g
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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8.5103
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8.1408
7.7959
7.7818
7.7794
7.6742
7.6594
7.6522
7.6492
7.6380
7.6350
7.6231
7.6203
7.6091
7.6065
7.5938
7.5916
7.5774
7.2596
7.2359
7.2314
7.2238
7.2164
7.1852
7.1795
7.1754
7.1654
7.1602
7.1550
7.1521
7.1454
3.9840
O
O
S
N
Ph
N
anti-2h
25000
20000
15000
10000
5000
0
0.99
1.00
1.02
4.29
2.03
4.21
1.00
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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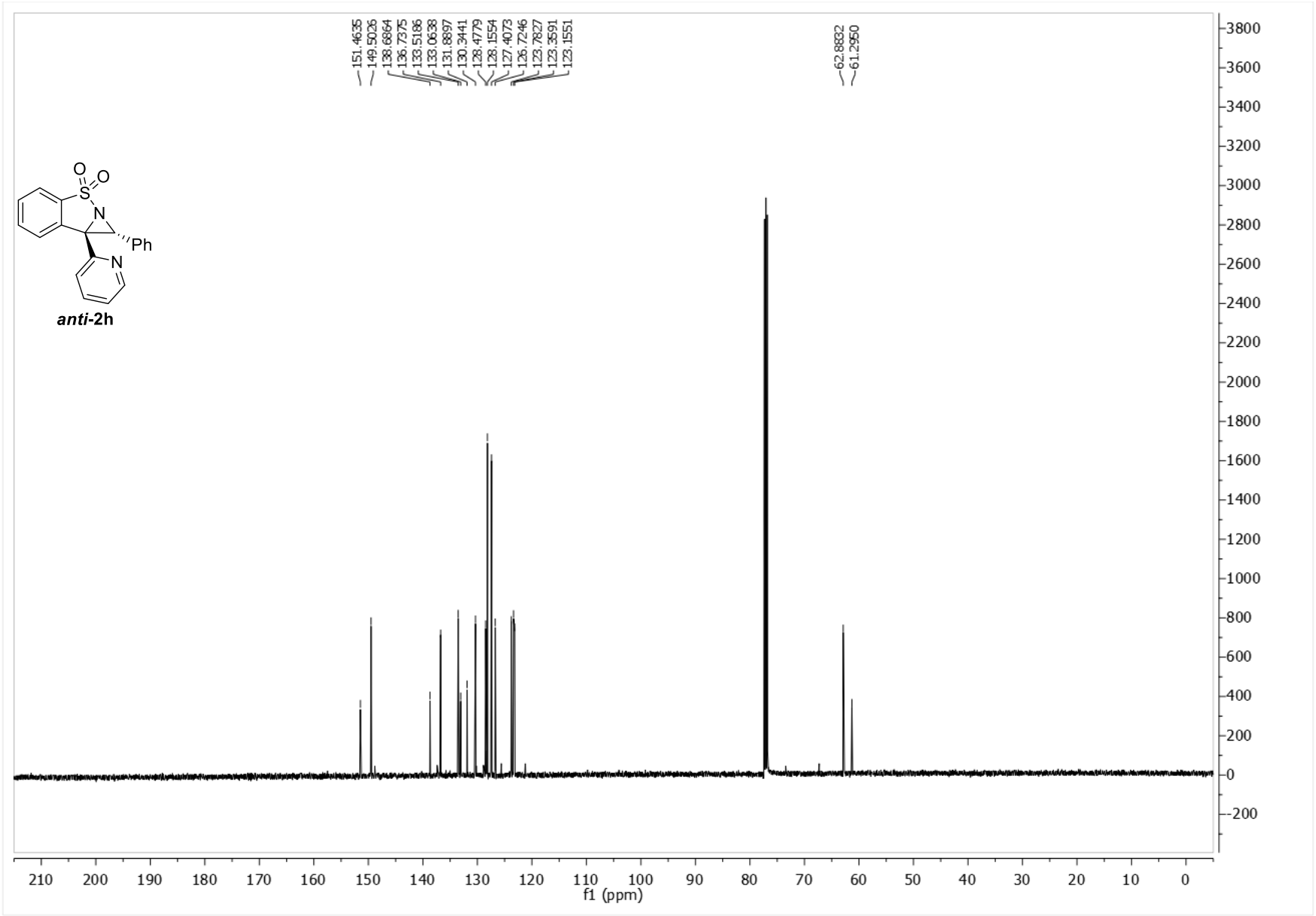
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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130.3441
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127.4073
126.7246
123.7827
123.3591
123.1551
62.8832
61.2950
O
O
S
N
Ph
N
anti-2h
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
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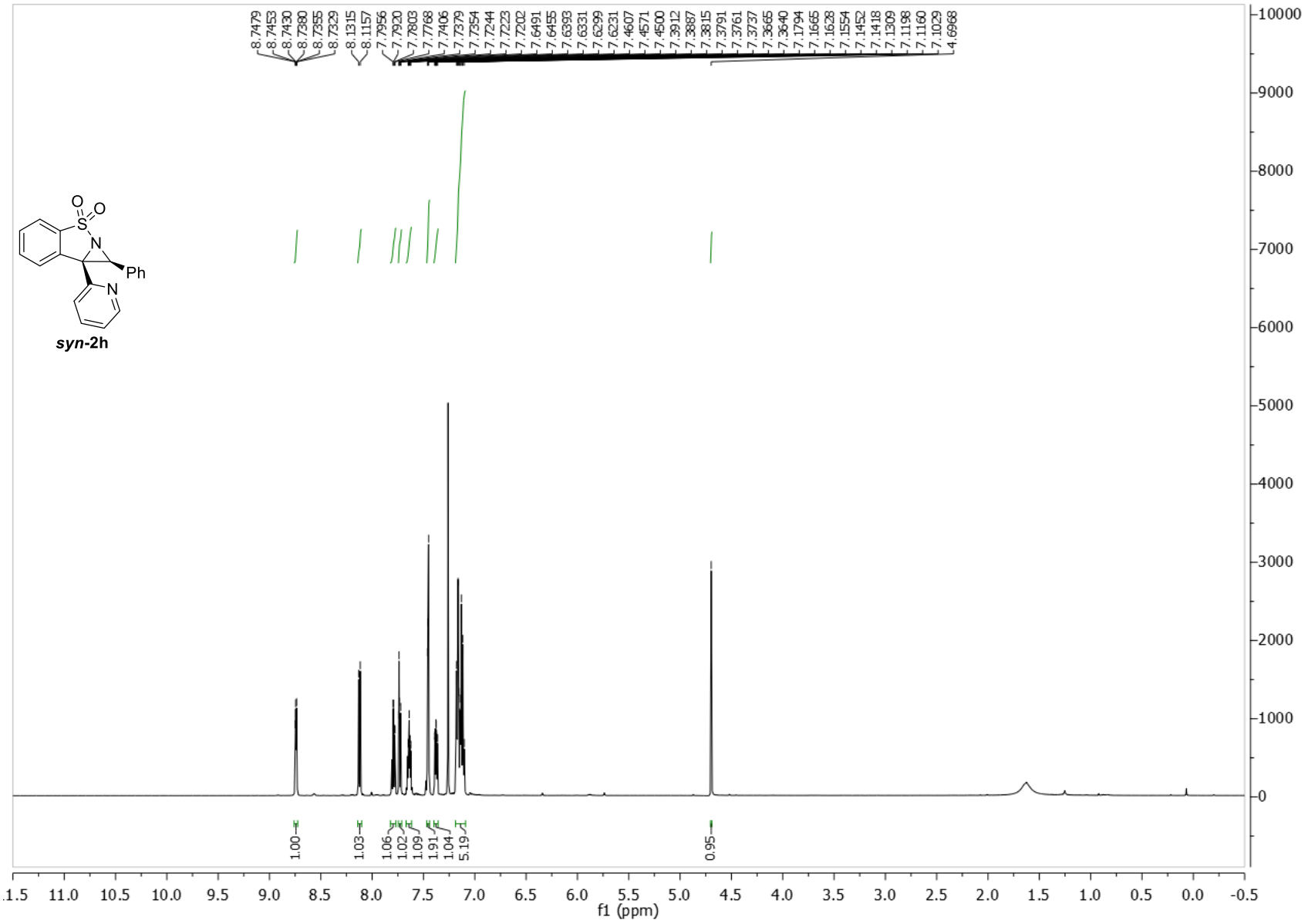
f1 (ppm)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7.7803
7.7768
7.7406
7.7379
7.7354
7.7244
7.7223
7.7202
7.6491
7.6455
7.6393
7.6331
7.6299
7.6231
7.4607
7.4571
7.4500
7.3912
7.3887
7.3815
7.3791
7.3761
7.3737
7.3665
7.3640
7.1794
7.1665
7.1628
7.1554
7.1452
7.1418
7.1309
7.1198
7.1160
7.1029
4.6968
O
O
S
N
Ph
N
syn-2h
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
1.00
1.03
1.06
1.02
1.09
1.91
1.04
5.19
0.95
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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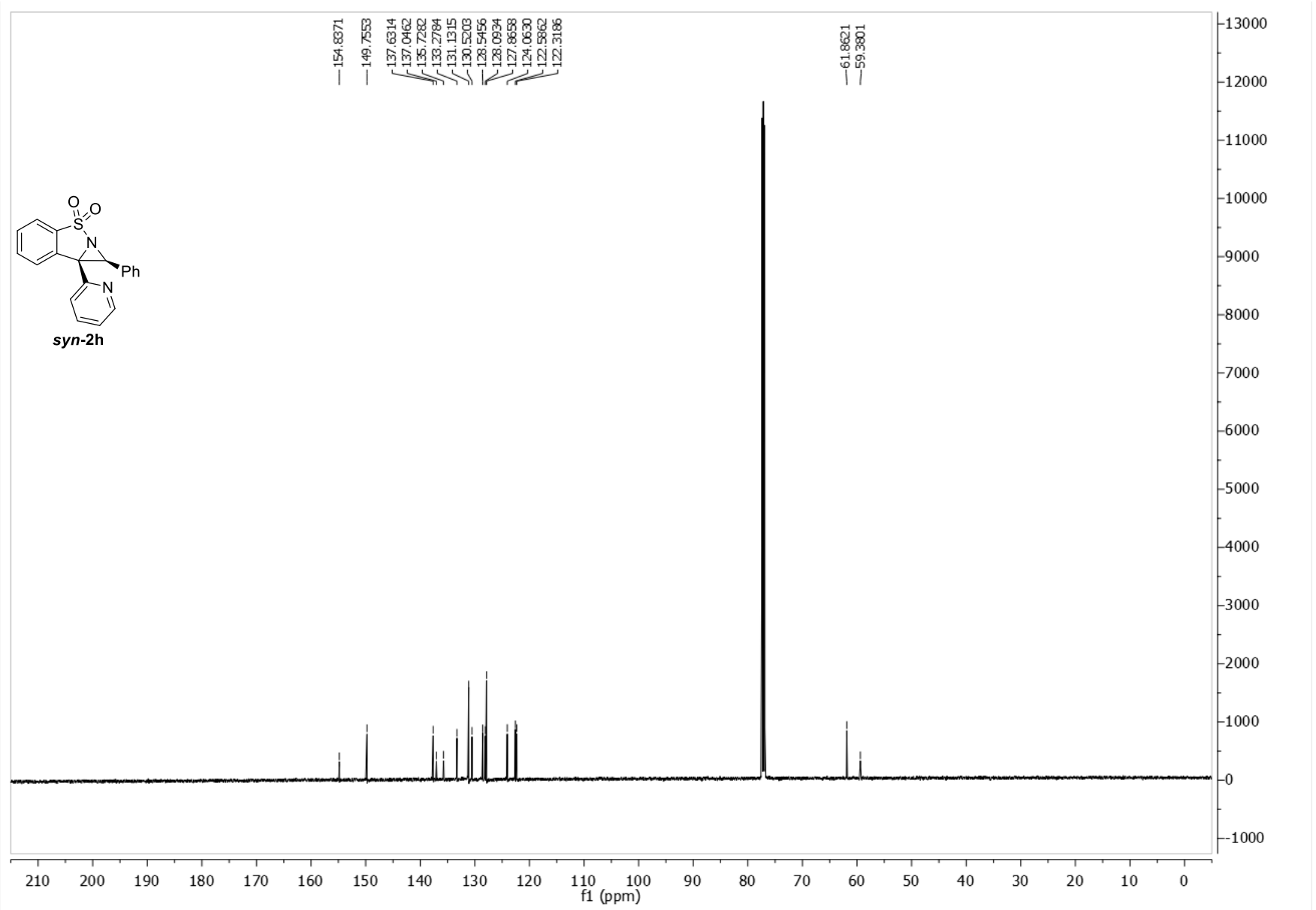
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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131.1315
130.5203
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128.0934
127.8658
124.0630
122.5862
122.3186
61.8621
59.3801
Ph
N
O
O
S
N
syn-2h
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
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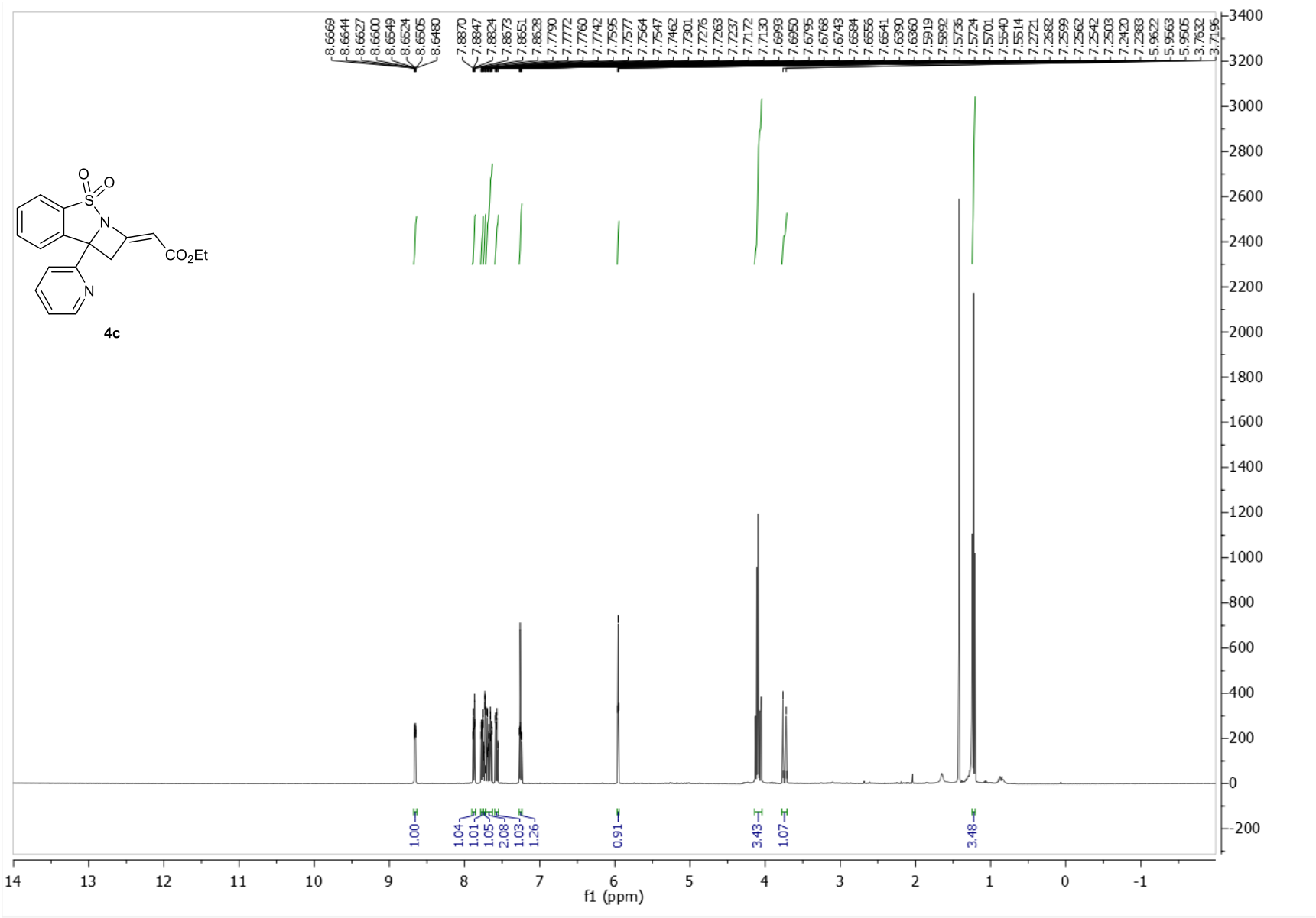
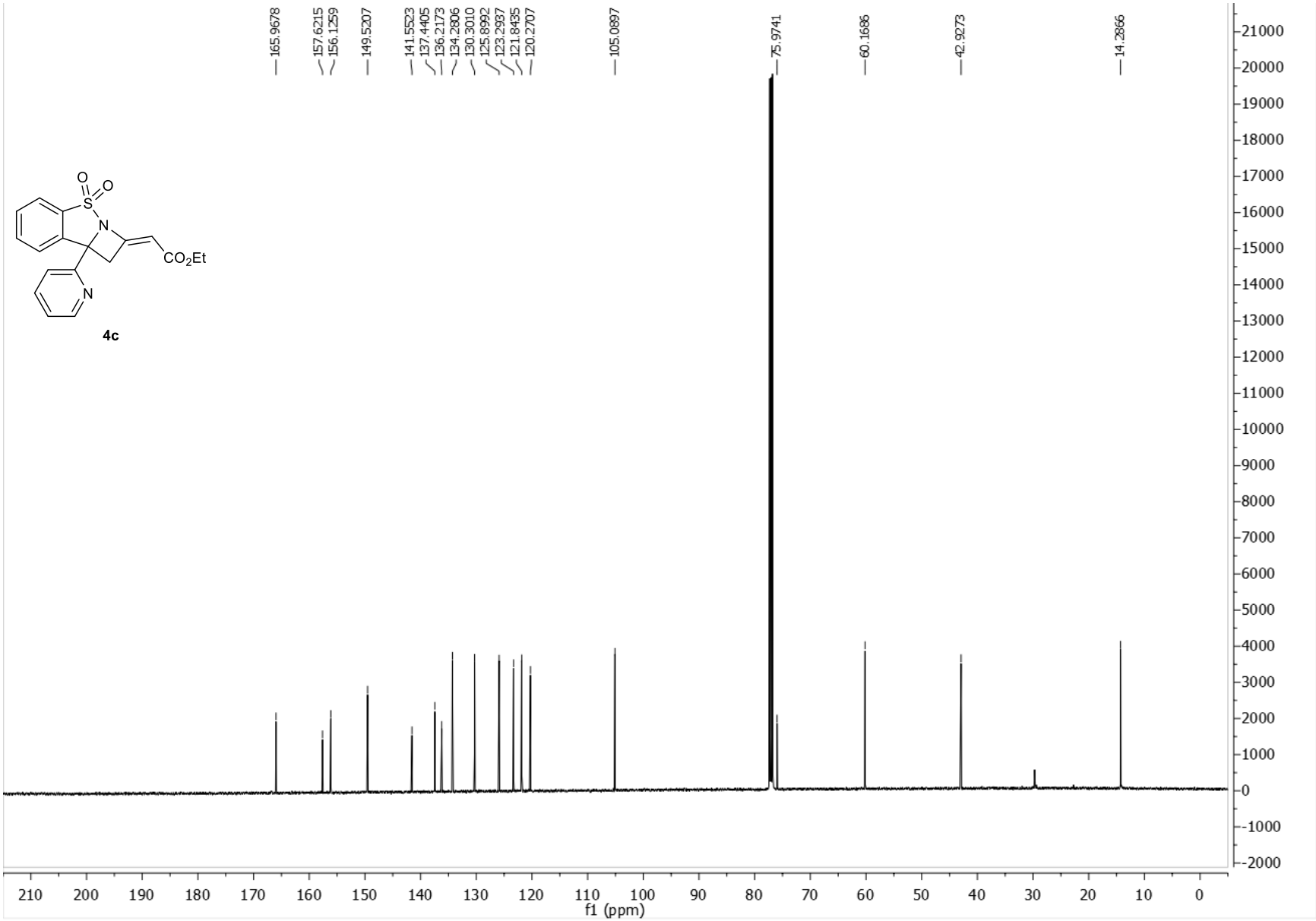
f1 (ppm)


4c
f1 (ppm)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130.3010
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123.2937
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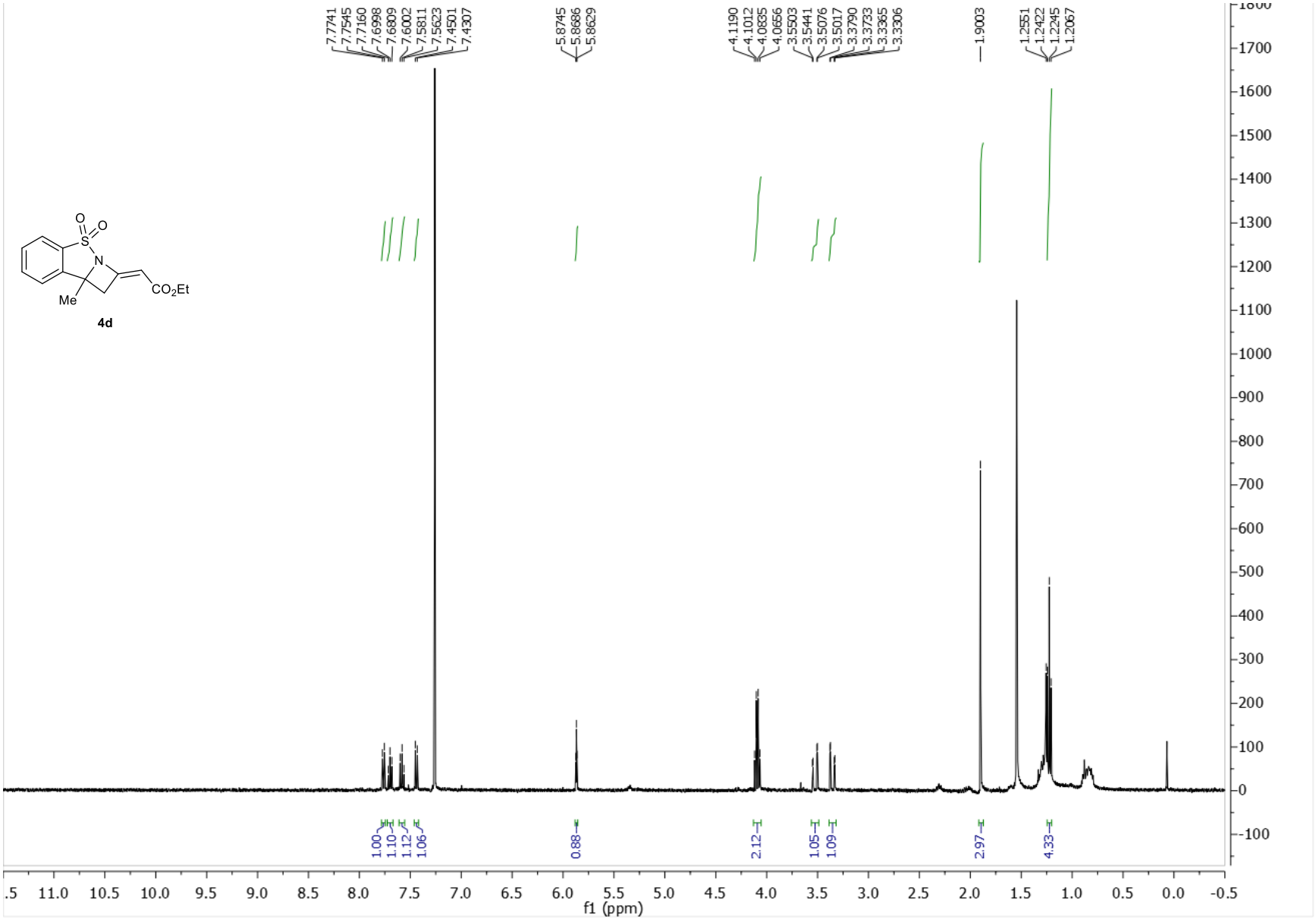
105.0897
75.9741
60.1686
42.9273
14.2866
CO2Et
4c
f1 (ppm)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5.8745
5.8686
5.8629
4.1190
4.1012
4.0835
4.0656
3.5503
3.5441
3.5076
3.5017
3.3790
3.3733
3.3365
3.3306
1.9003
1.2551
1.2422
1.2245
1.2067
O
O
S
N
Me
CO2Et
4d
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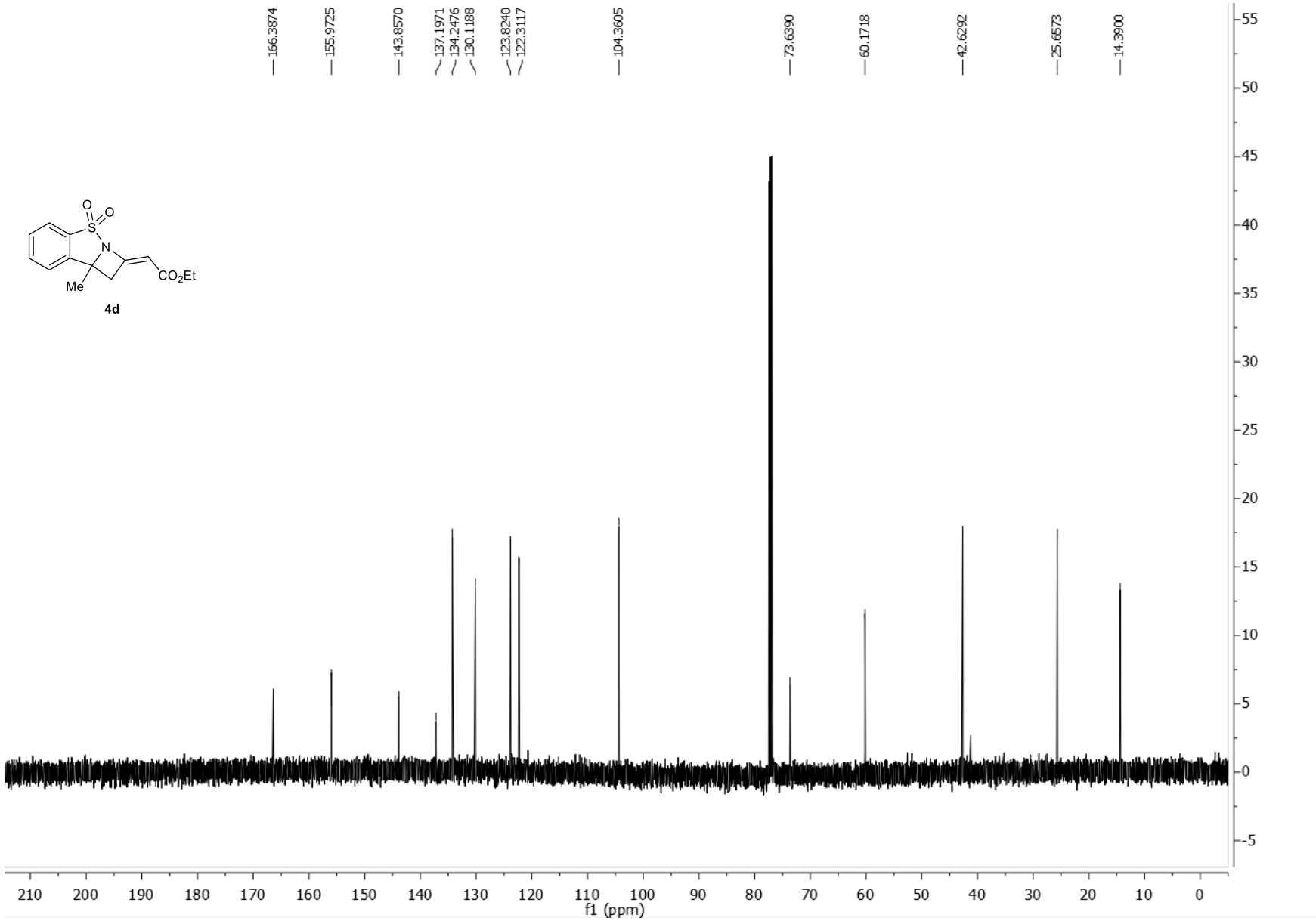
1.12
1.06
0.88
2.12
1.05
1.09
2.97
4.33
f1 (ppm)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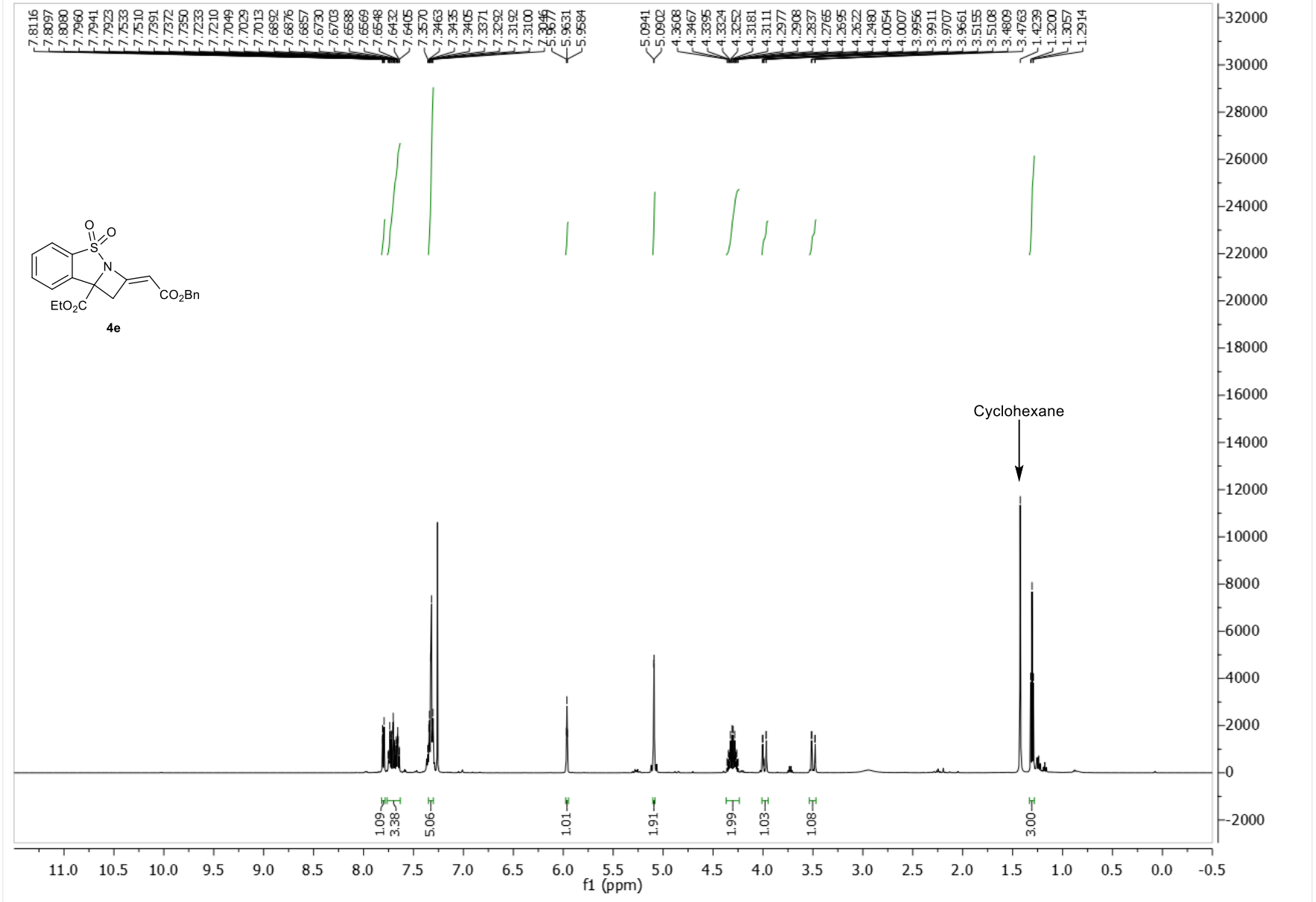
25.6573
14.3900
O
O
S
N
Me
CO2Et
4d
f1 (ppm)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7.7233
7.7210
7.7049
7.7029
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7.6548
7.6432
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3.9661
3.5155
3.5108
3.4809
3.4763
1.4239
1.3200
1.3057
1.2914
O
O
S
N
CO2Bn
EtO2C
4e
Cyclohexane
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5.06
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1.99
1.03
1.08
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32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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2.5
2.0
1.5
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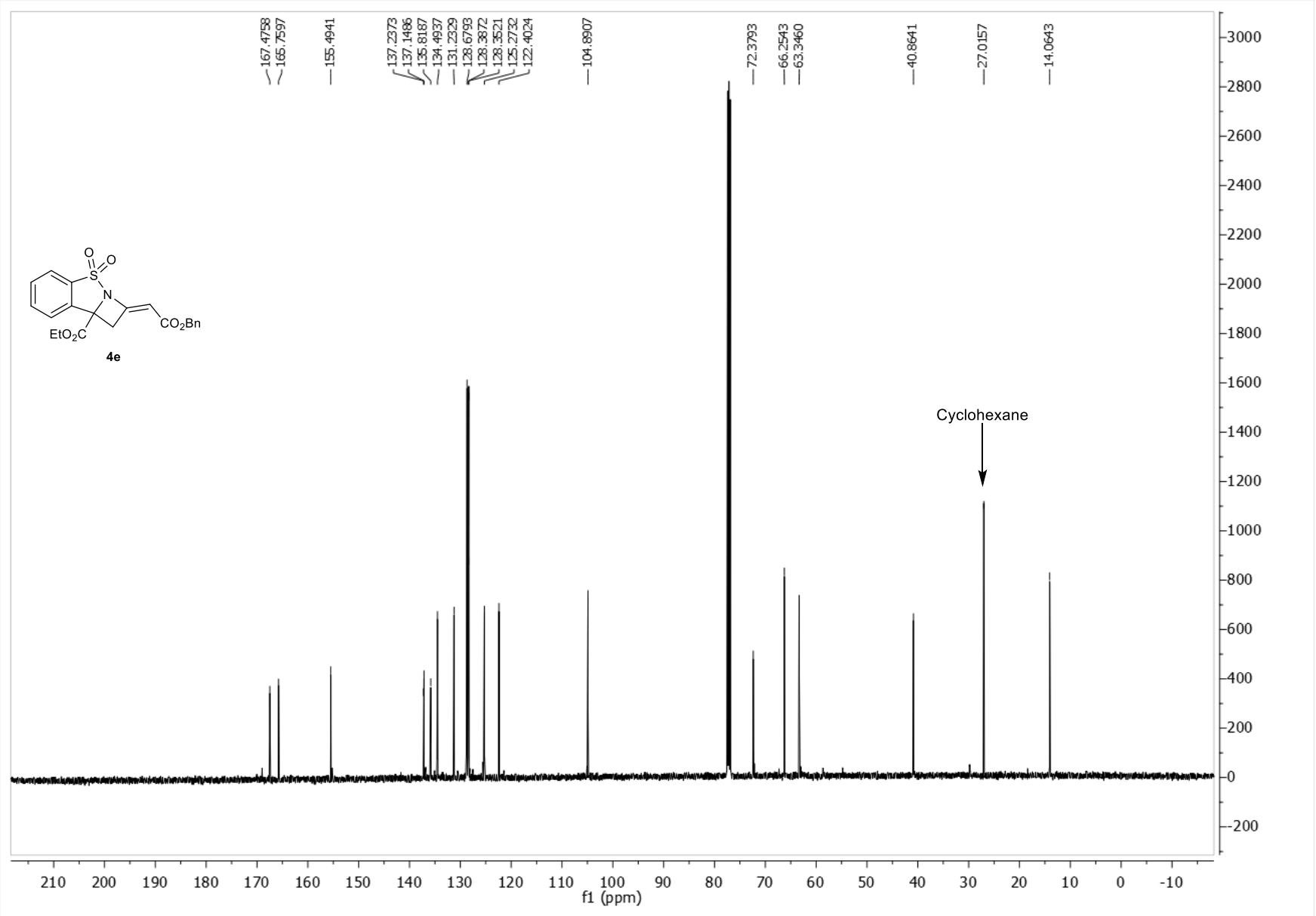
0.5
0.0
-0.5
f1 (ppm)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122.4024
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40.8641
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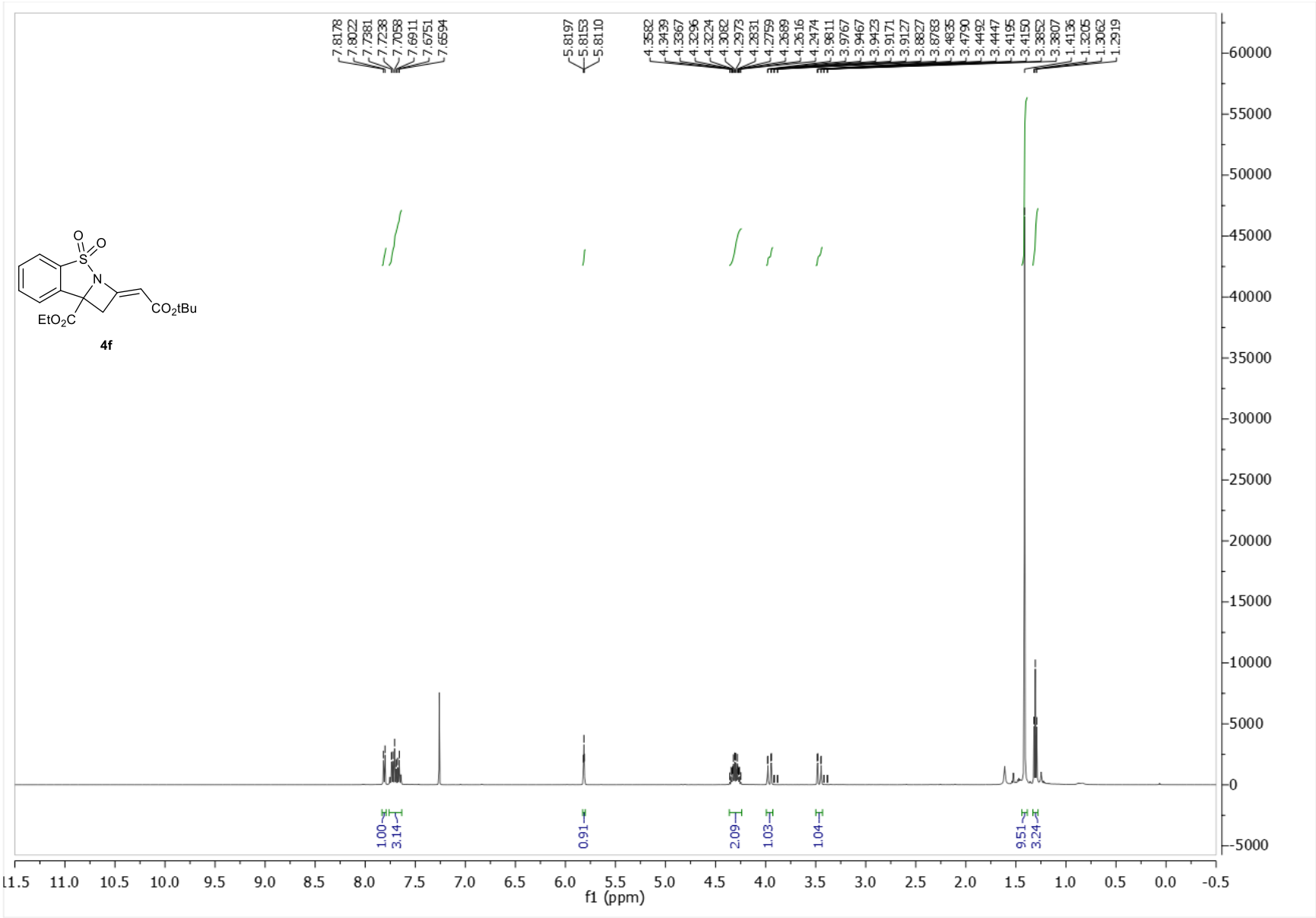
14.0643
Cyclohexane
4e
f1 (ppm)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4.3224
4.3082
4.2973
4.2831
4.2759
4.2689
4.2616
4.2474
3.9811
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3.4790
3.4492
3.4447
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3.4150
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1.4136
1.3205
1.3062
1.2919
EtO2C
CO2tBu
4f
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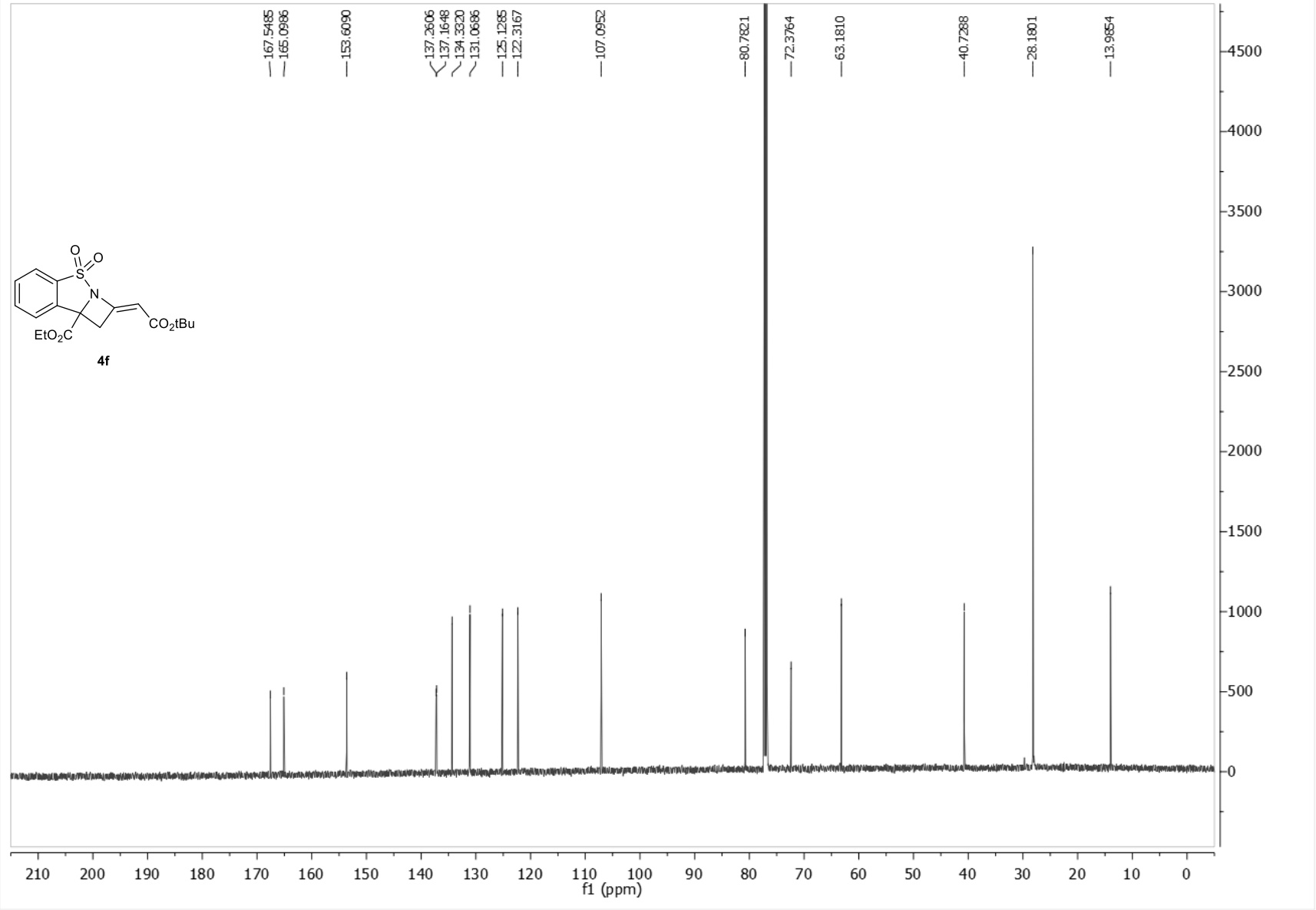
0.91
2.09
1.03
1.04
9.51
3.24
f1 (ppm)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72.3764
63.1810
40.7288
28.1801
13.9854
4500
4000
3500
3000
2500
2000
1500
1000
500
0
O
O
S
N
CO2tBu
EtO2C
4f
210
200
190
180
170
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150
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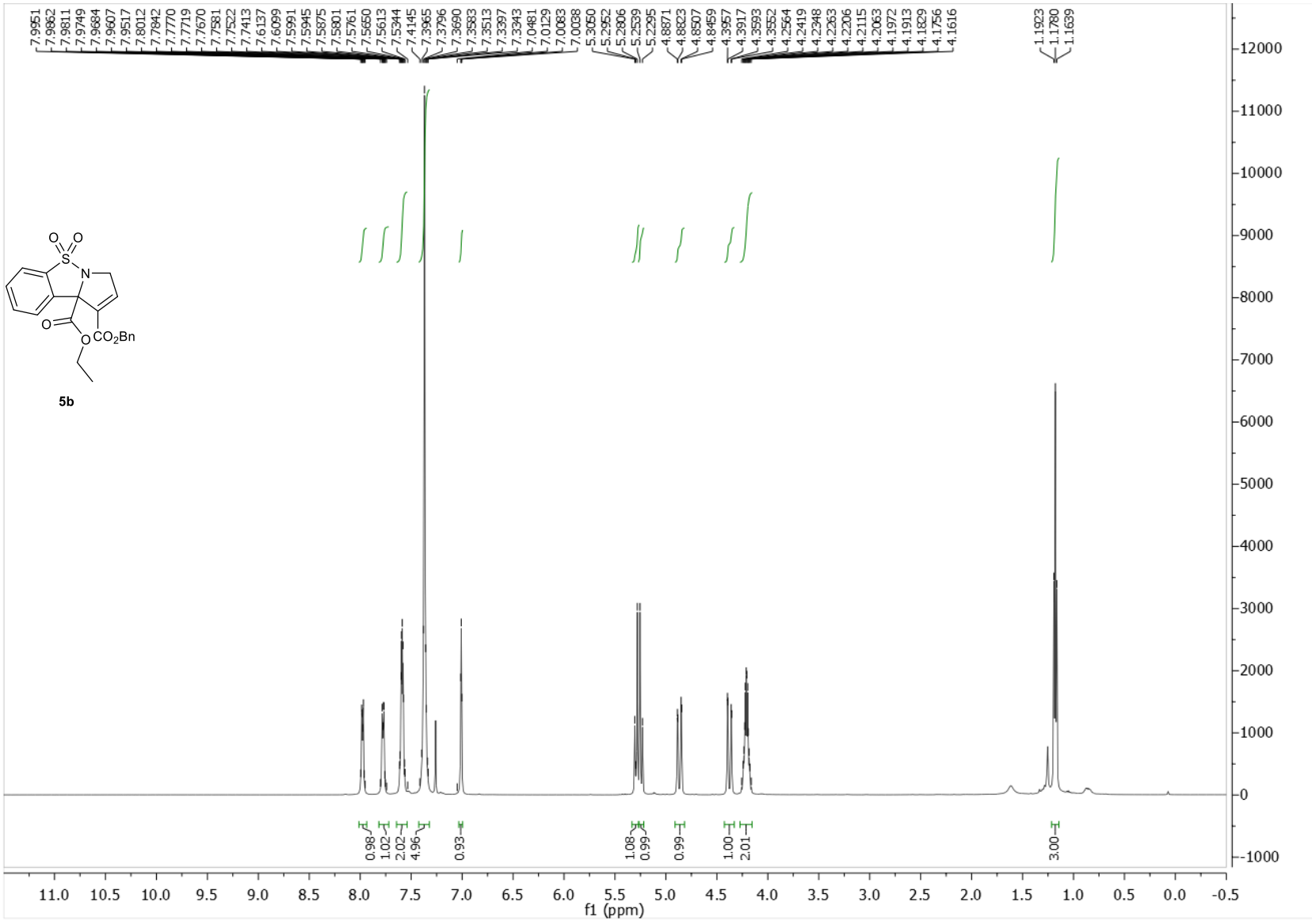
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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O
O
S
N
O
O
CO2Bn
5b
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2.02
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1.00
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9000
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6000
5000
4000
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2000
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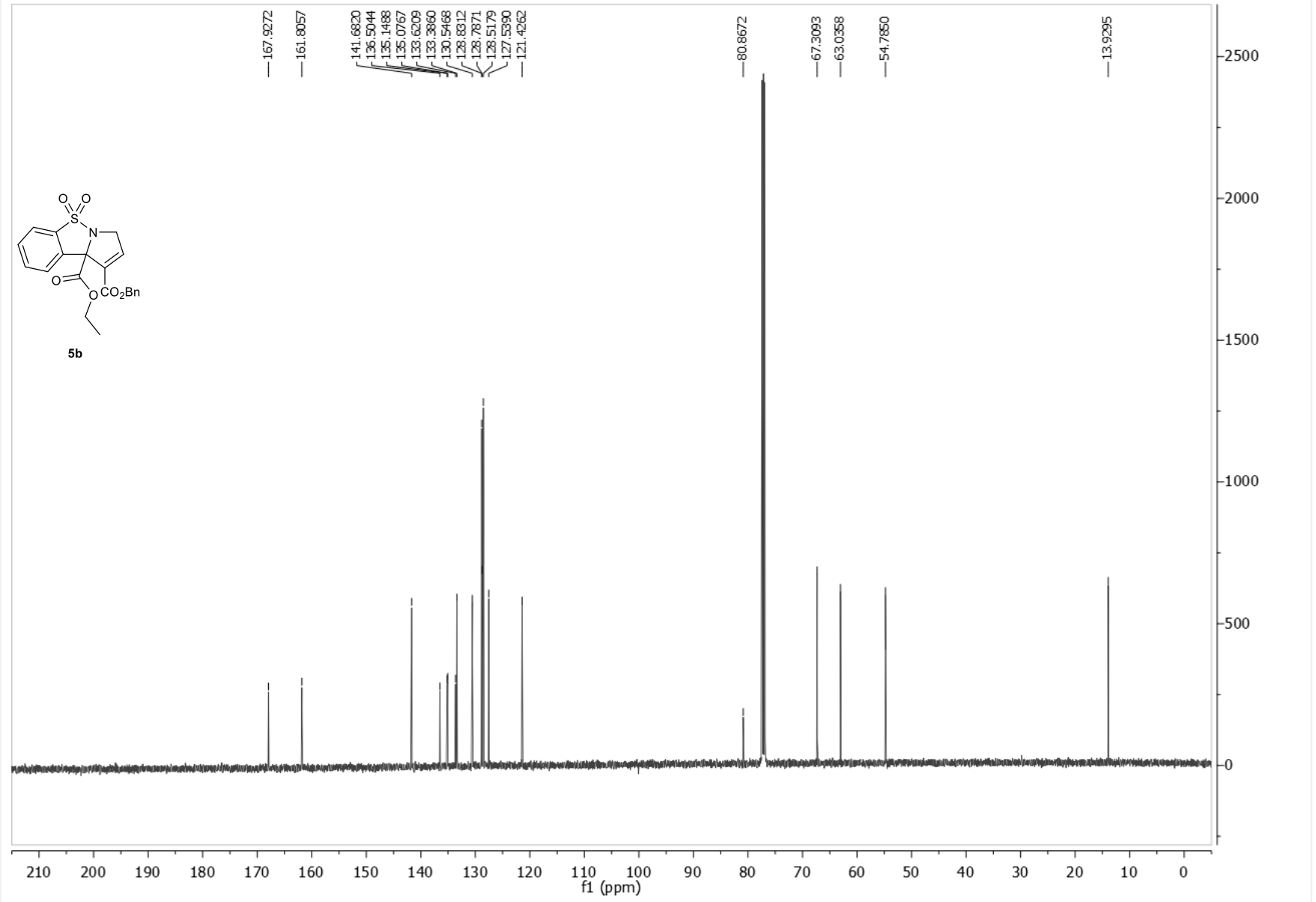
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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133.3860
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128.7871
128.5179
127.5390
121.4262
80.8672
67.3093
63.0358
54.7850
13.9295
2500
2000
1500
1000
500
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
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20
10
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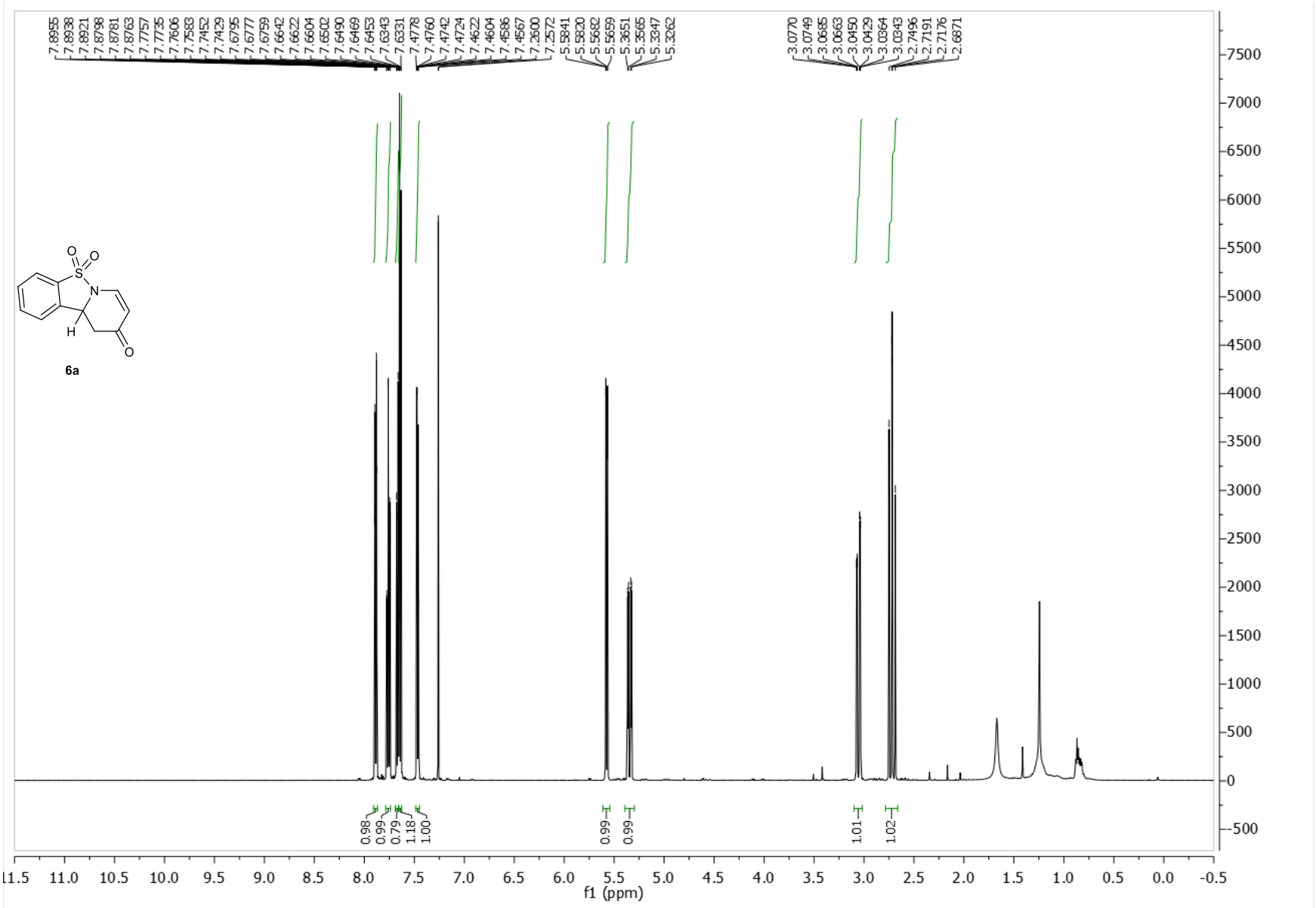
O
S
N
O
O
O
CO2Bn

5b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7.7583
7.7452
7.7429
7.6795
7.6777
7.6759
7.6642
7.6622
7.6604
7.6502
7.6490
7.6469
7.6453
7.6343
7.6331
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7.4760
7.4742
7.4724
7.4622
7.4604
7.4586
7.4567
7.2600
7.2572
5.5841
5.5820
5.5682
5.5659
5.3651
5.3565
5.3347
5.3262
3.0770
3.0749
3.0685
3.0663
3.0450
3.0429
3.0364
3.0343
2.7496
2.7191
2.7176
2.6871
O
O
S
N
H
O
6a
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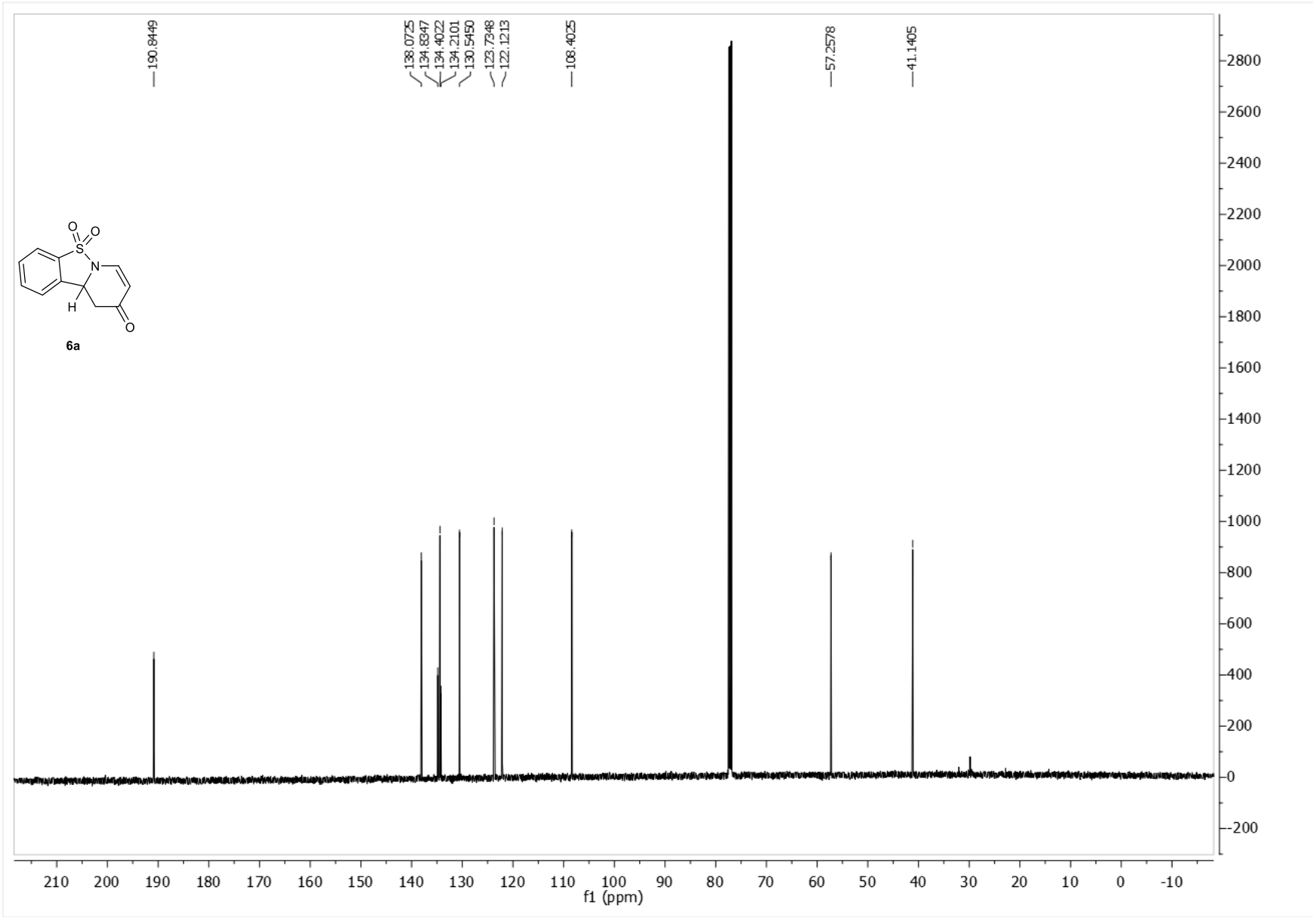
0.99
0.79
1.18
1.00
0.99
0.99
1.01
1.02
f1 (ppm)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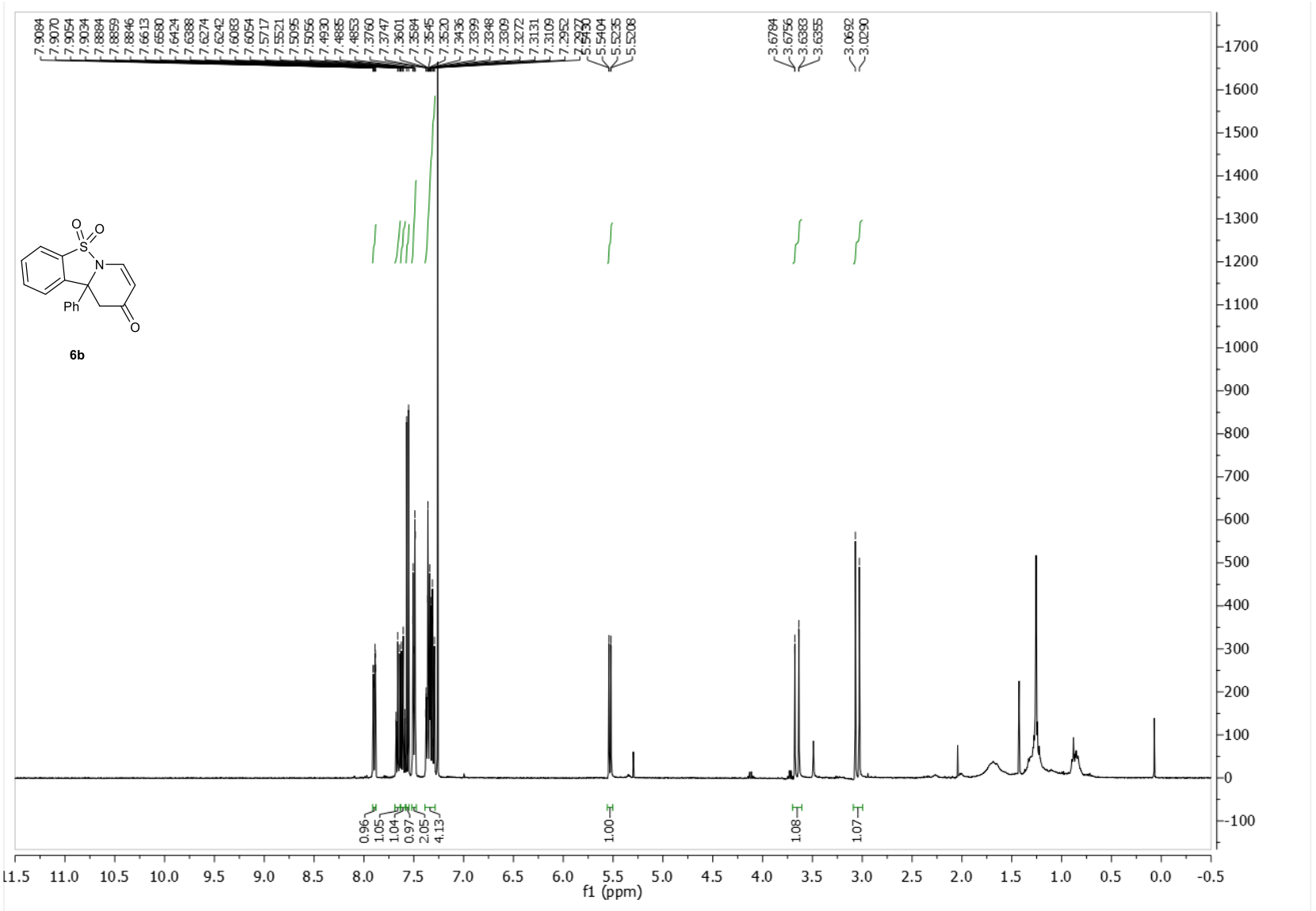
123.7348
122.1213
108.4025
57.2578
41.1405
6a
f1 (ppm)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7.8846
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7.6274
7.6242
7.6083
7.6054
7.5717
7.5521
7.5095
7.5056
7.4930
7.4885
7.4853
7.3760
7.3747
7.3601
7.3584
7.3545
7.3520
7.3436
7.3399
7.3348
7.3309
7.3272
7.3131
7.3109
7.2952
5.5404
5.5235
5.5208
3.6784
3.6756
3.6383
3.6355
3.0692
3.0290
O
O
S
N
Ph
O
6b
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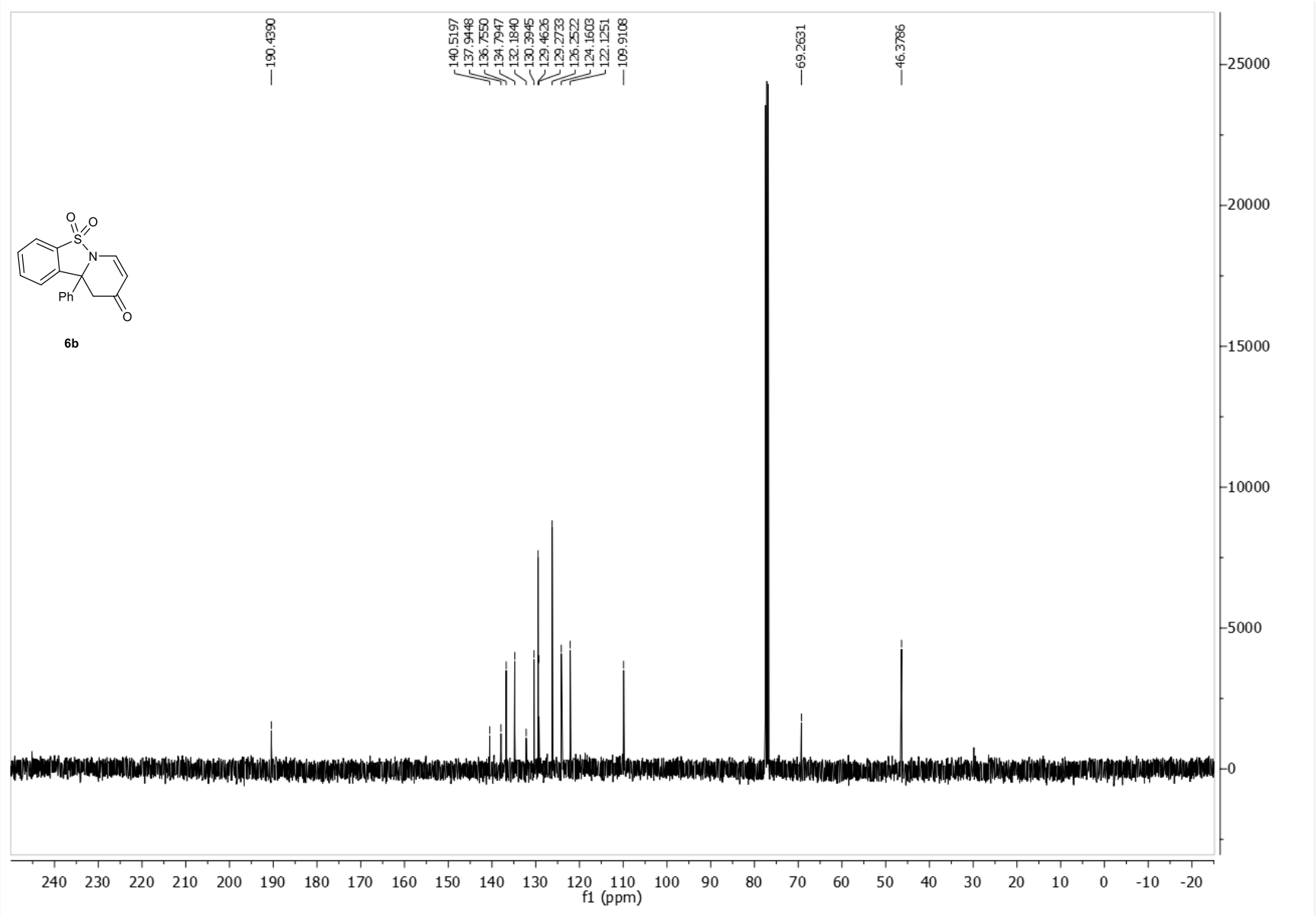
1.05
1.04
0.97
2.05
4.13
1.00
1.08
1.07
f1 (ppm)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132.1840
130.3945
129.4626
129.2733
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124.1603
122.1251
109.9108
69.2631
46.3786
O
O
S
N
Ph
O
6b
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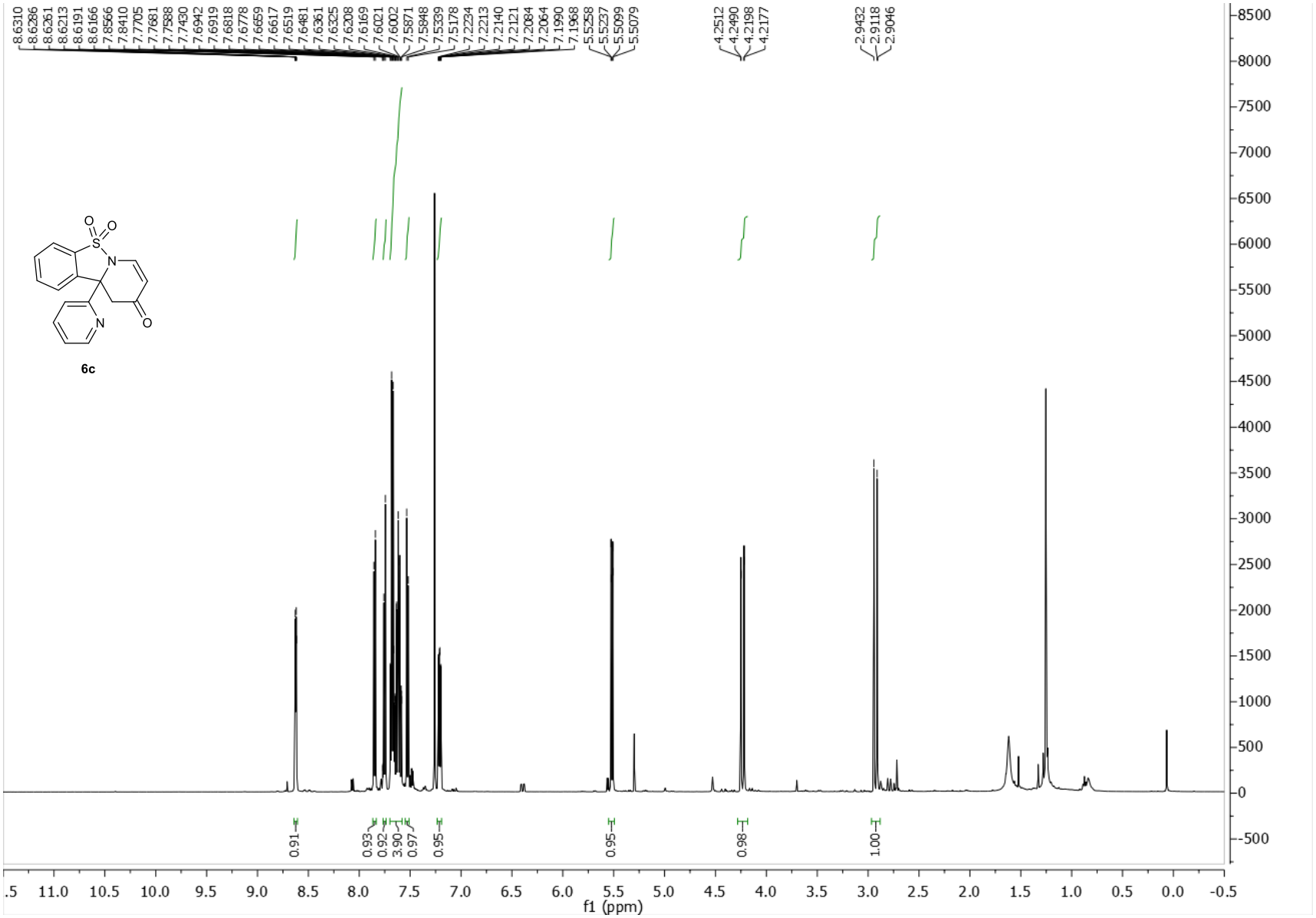
20000
15000
10000
5000
0
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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8.6261
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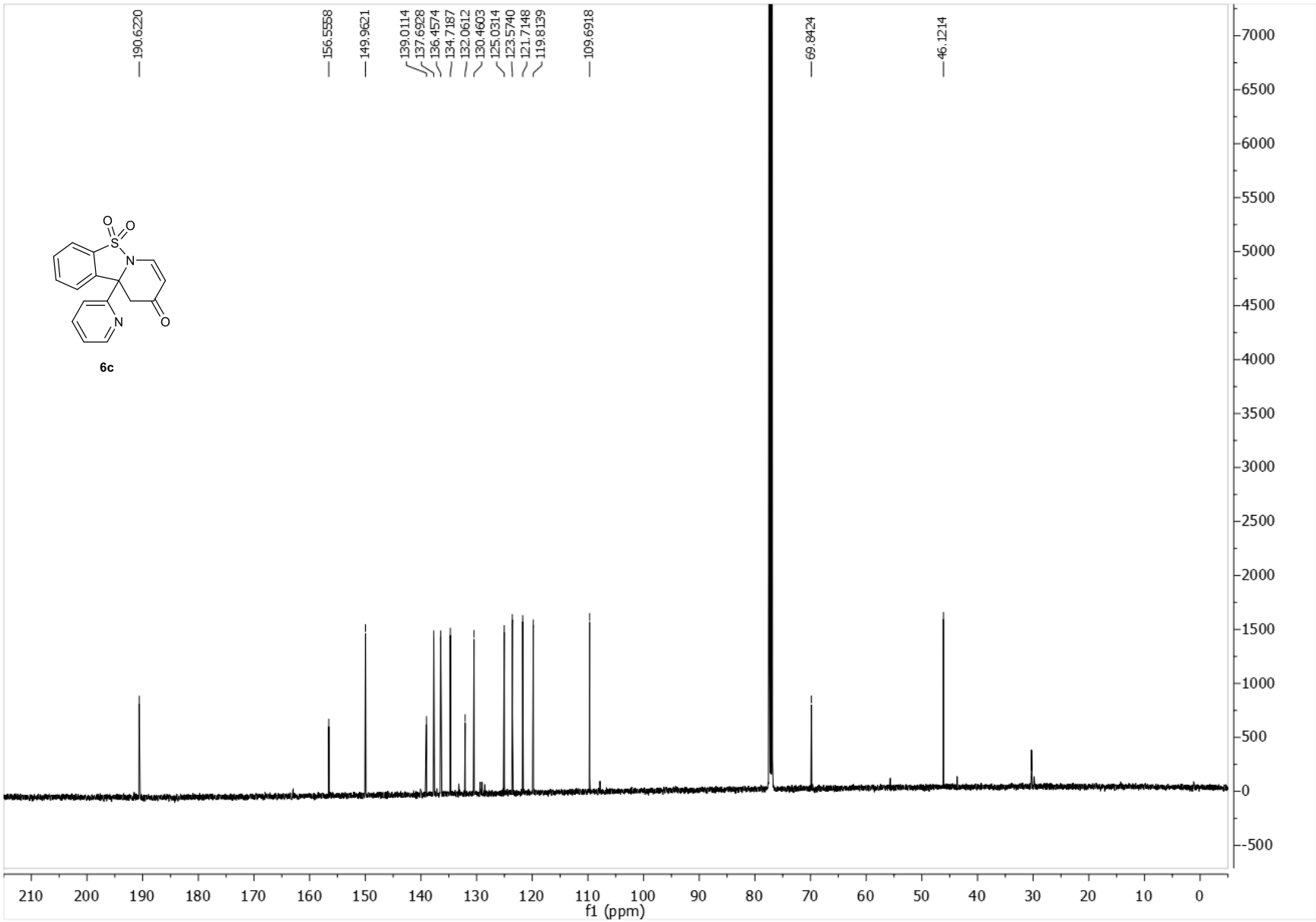
8.6166
7.8566
7.8410
7.7705
7.7681
7.7588
7.7430
7.6942
7.6919
7.6818
7.6778
7.6659
7.6617
7.6519
7.6481
7.6361
7.6325
7.6208
7.6169
7.6021
7.6002
7.5871
7.5848
7.5339
7.5178
7.2234
7.2213
7.2140
7.2121
7.2084
7.2064
7.1990
7.1968
5.5258
5.5237
5.5099
5.5079
4.2512
4.2490
4.2198
4.2177
2.9432
2.9118
2.9046
6c
0.91
0.93
0.92
3.90
0.97
0.95
0.95
0.98
1.00
f1 (ppm)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149.9621
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137.6928
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134.7187
132.0612
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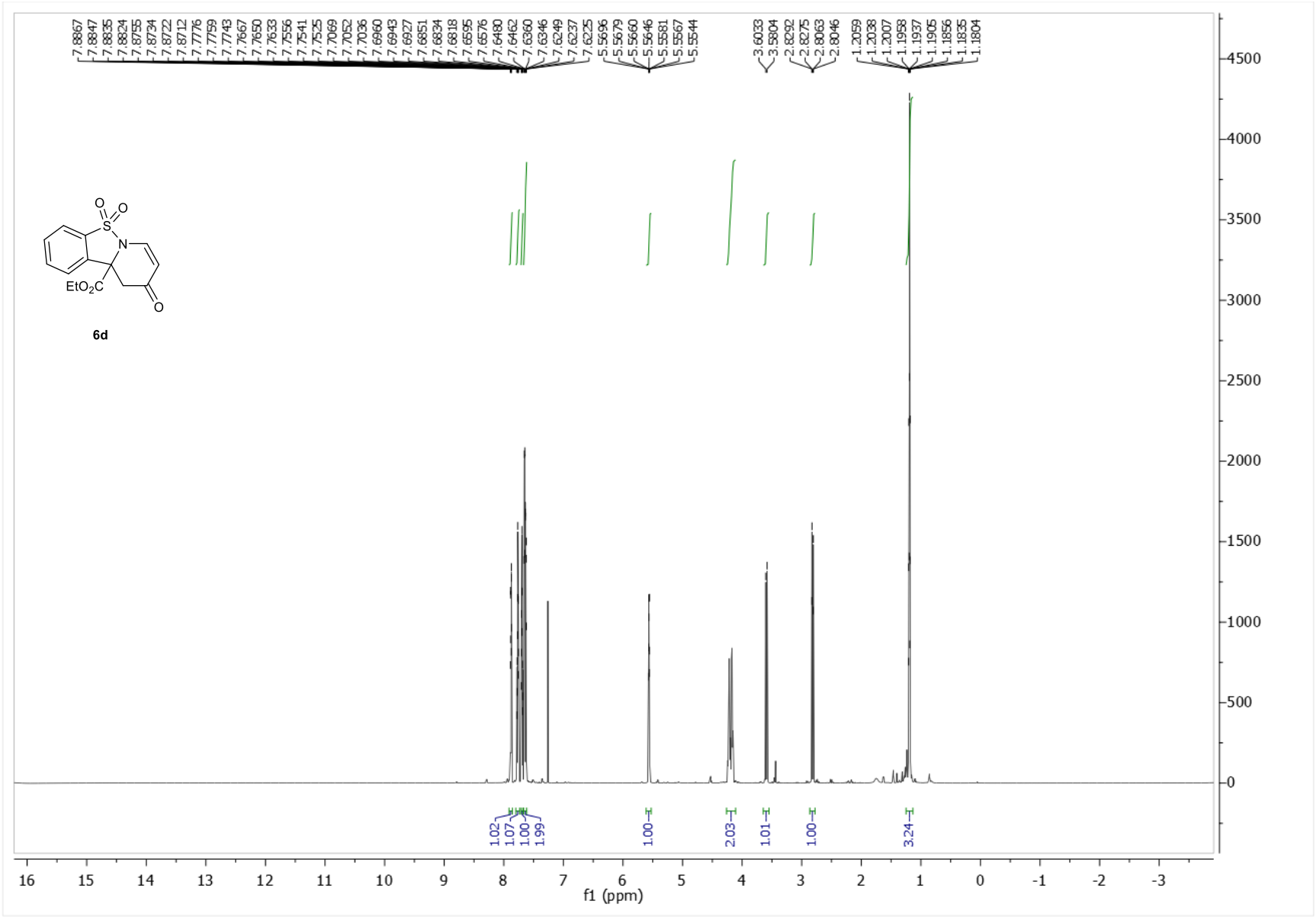
123.5740
121.7148
119.8139
109.6918
69.8424
46.1214
6c
f1 (ppm)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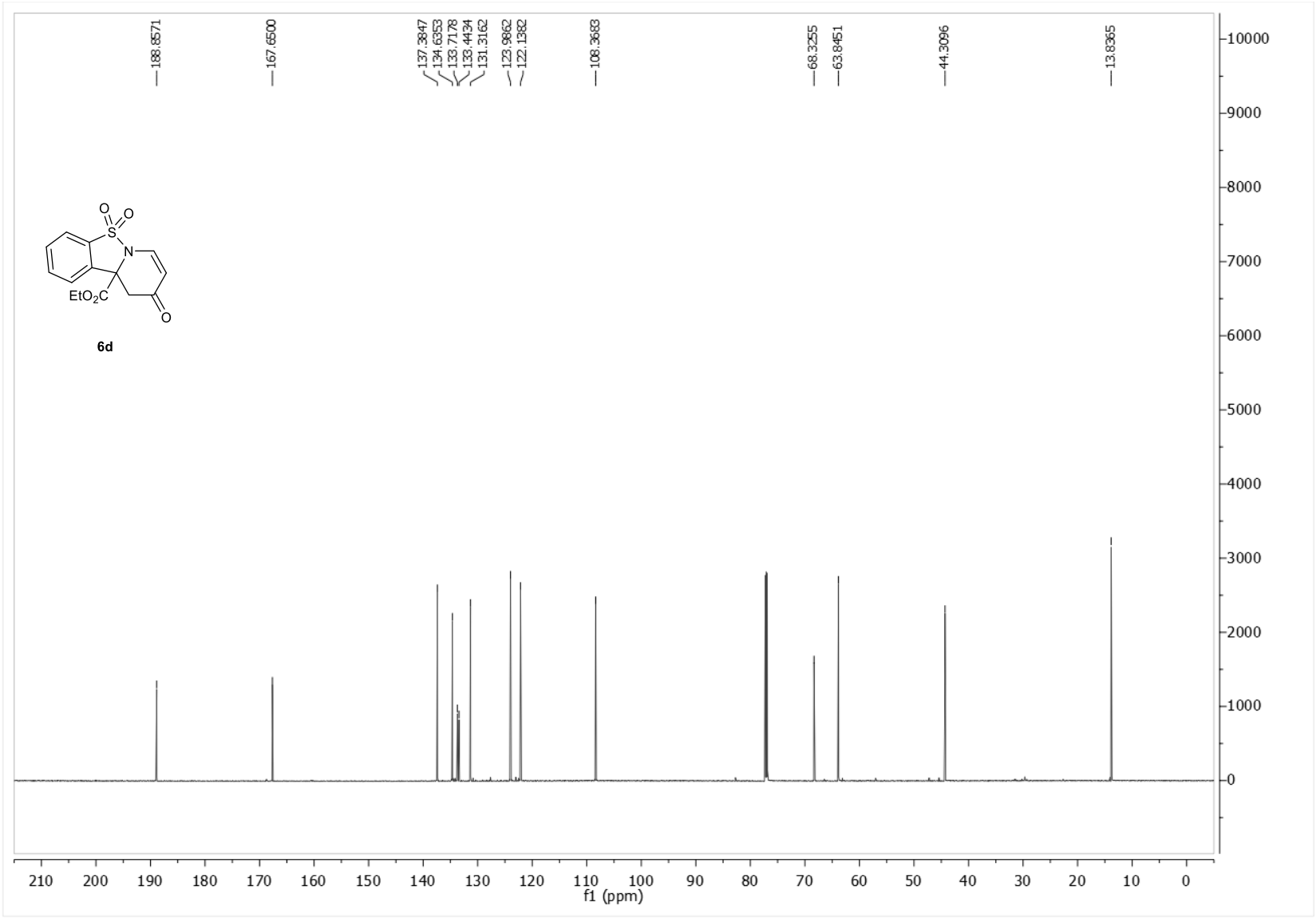
7.8734
7.8722
7.8712
7.7776
7.7759
7.7743
7.7667
7.7650
7.7633
7.7556
7.7541
7.7525
7.7069
7.7052
7.7036
7.6960
7.6943
7.6927
7.6851
7.6834
7.6818
7.6595
7.6576
7.6480
7.6462
7.6360
7.6346
7.6249
7.6237
7.6225
5.5696
5.5679
5.5660
5.5646
5.5581
5.5567
5.5544
3.6033
3.5804
2.8292
2.8275
2.8063
2.8046
1.2059
1.2038
1.2007
1.1958
1.1937
1.1905
1.1856
1.1835
1.1804
O
O
S
N
EtO2C
O
6d
4500
4000
3500
3000
2500
2000
1500
1000
500
0
1.02
1.07
1.00
1.99
1.00
2.03
1.01
1.00
3.24
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
f1 (ppm)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131.3162
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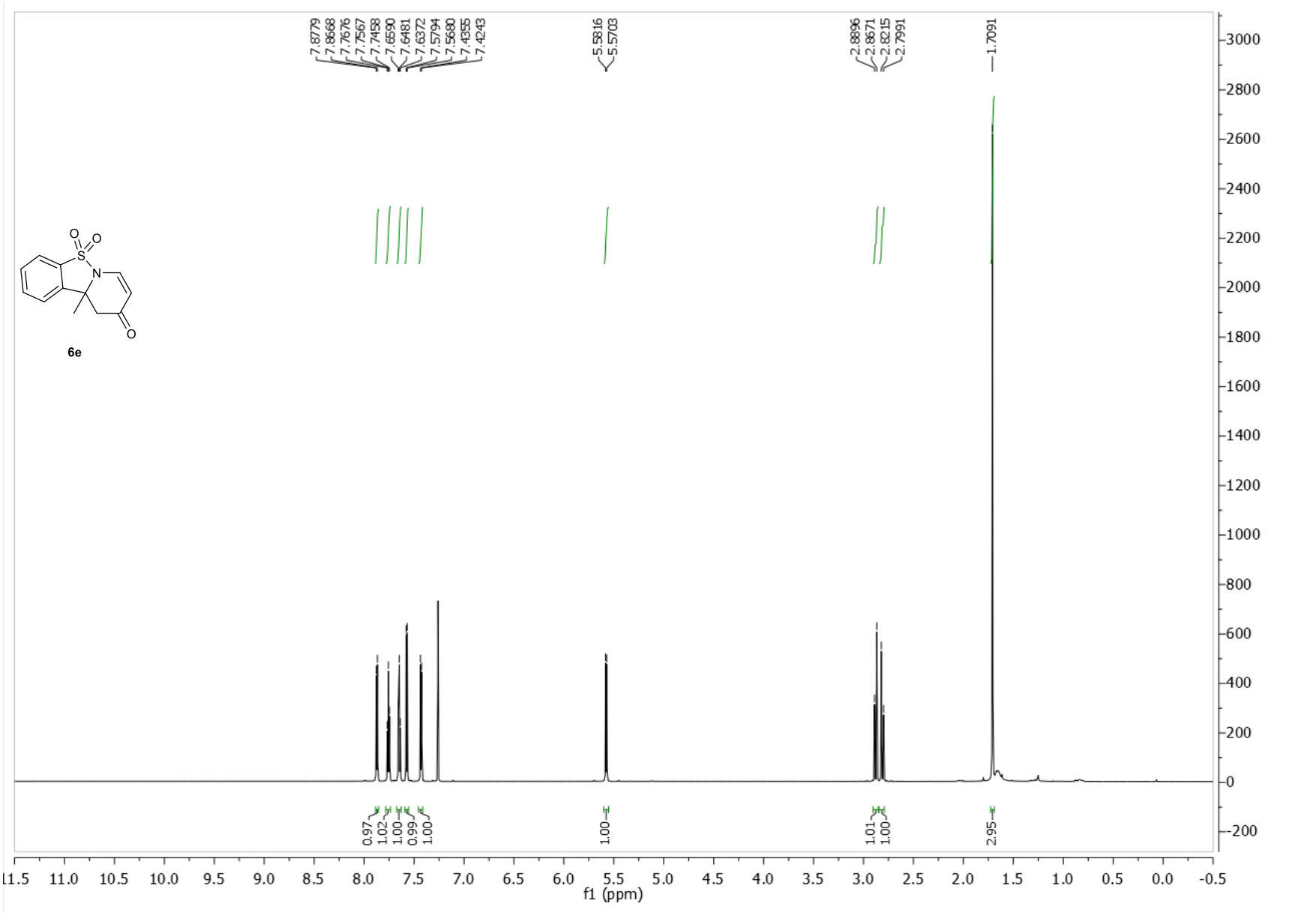
122.1382
108.3683
68.3255
63.8451
44.3096
13.8365
O
O
S
N
EtO2C
O
6d
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.6481
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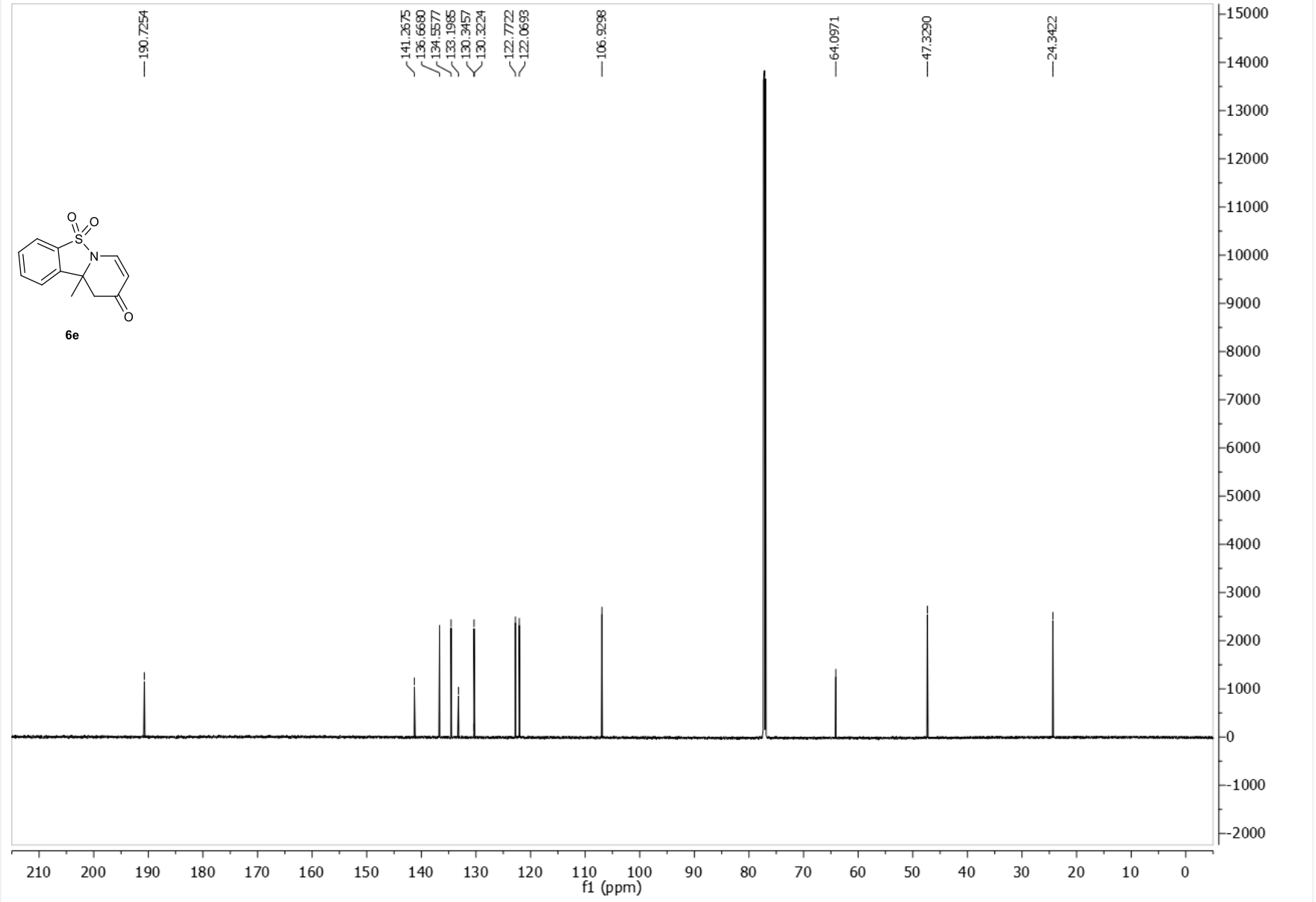
7.5794
7.5680
7.4355
7.4243
5.5816
5.5703
2.8896
2.8671
2.8215
2.7991
1.7091
6e
0.97
1.02
1.00
0.99
1.00
1.00
1.01
1.00
2.95
f1 (ppm)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133.1985
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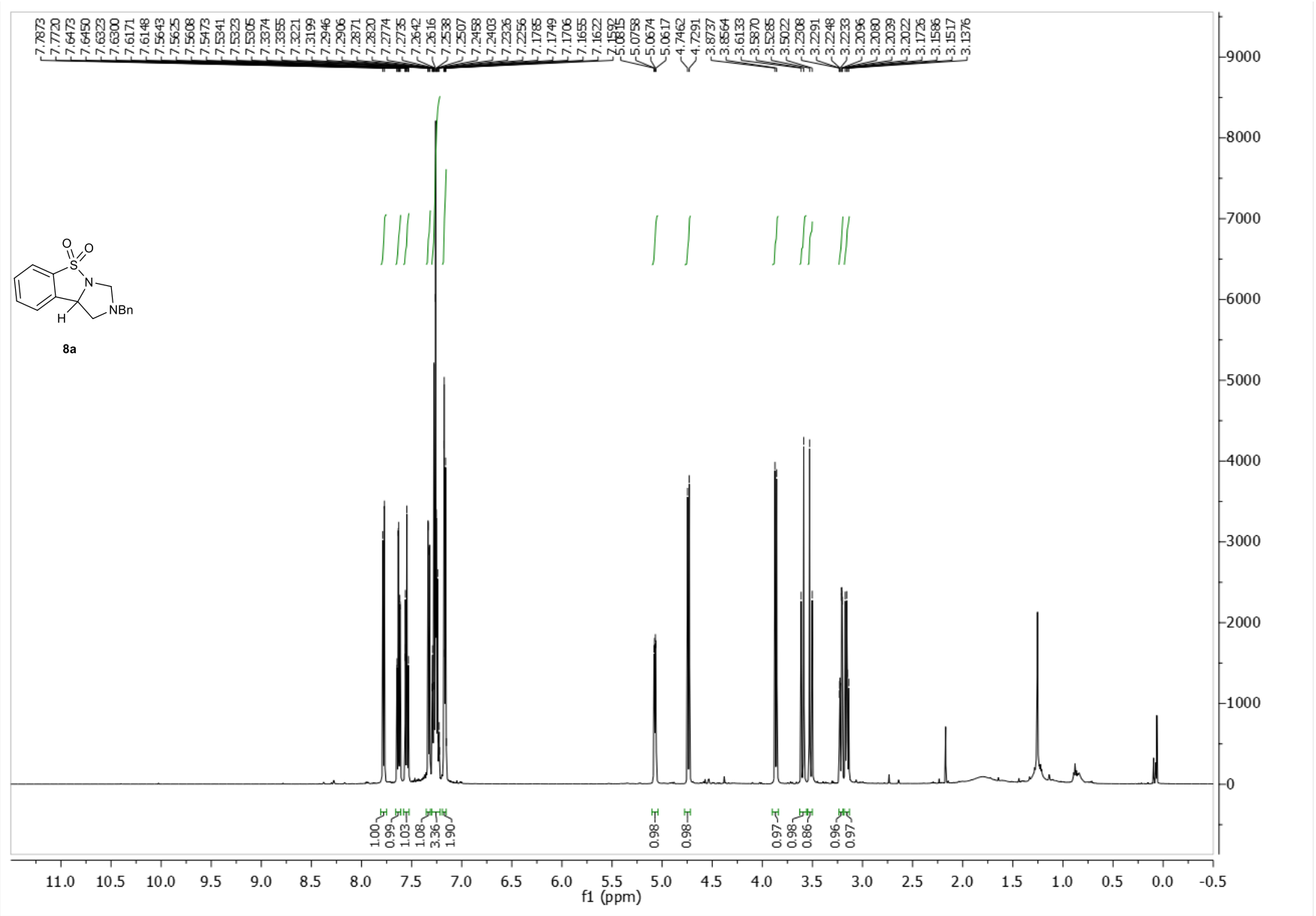
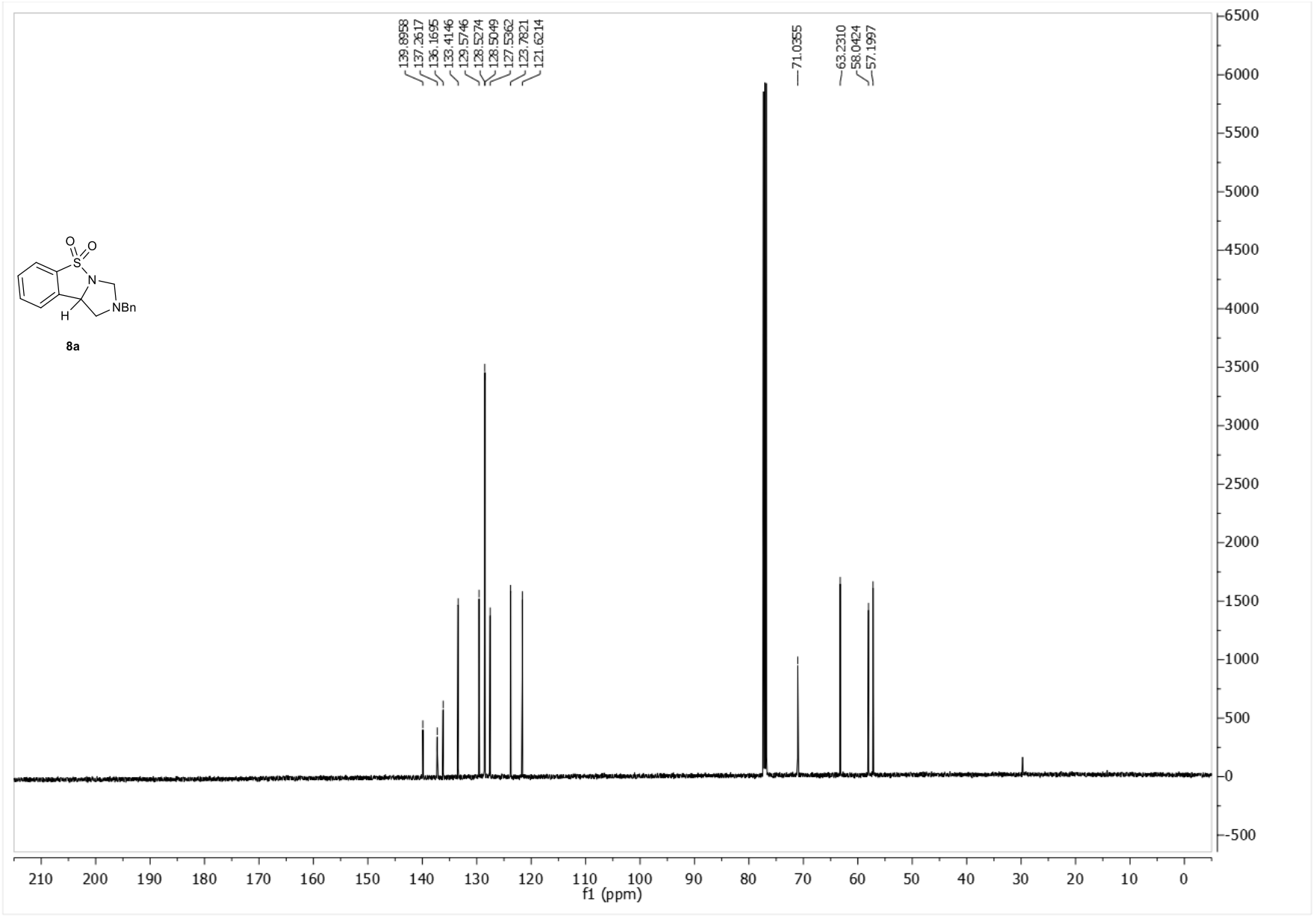
122.0693
106.9298
64.0971
47.3290
24.3422
6e
f1 (ppm)


8a
f1 (ppm)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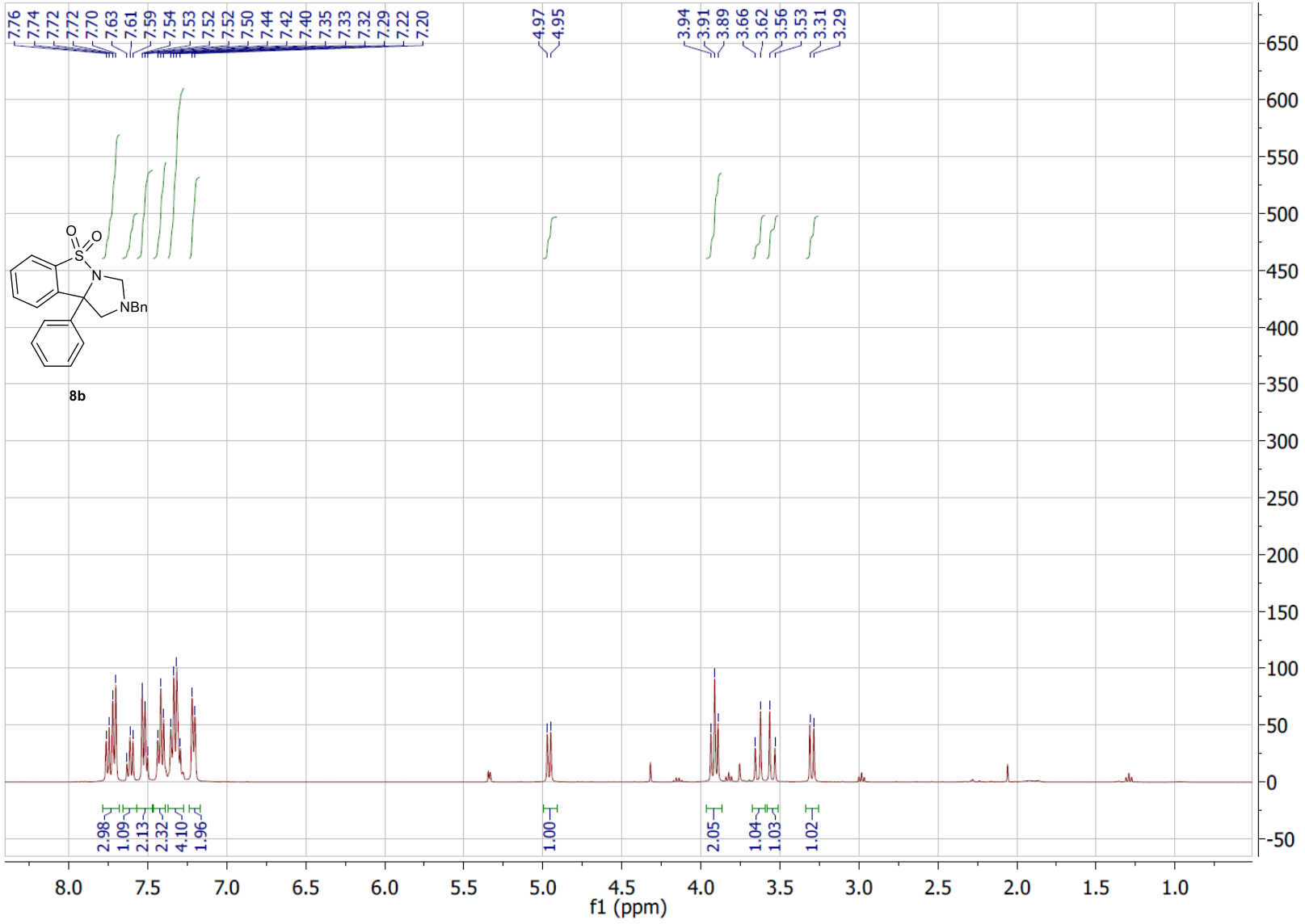
128.5049
127.5362
123.7821
121.6214
71.0355
63.2310
58.0424
57.1997
O
O
S
N
NBn
H
8a
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.61
7.59
7.54
7.53
7.52
7.52
7.50
7.44
7.42
7.40
7.35
7.33
7.32
7.29
7.22
7.20
4.97
4.95
3.94
3.91
3.89
3.66
3.62
3.56
3.53
3.31
3.29
O
O
S
N
NBn
8b
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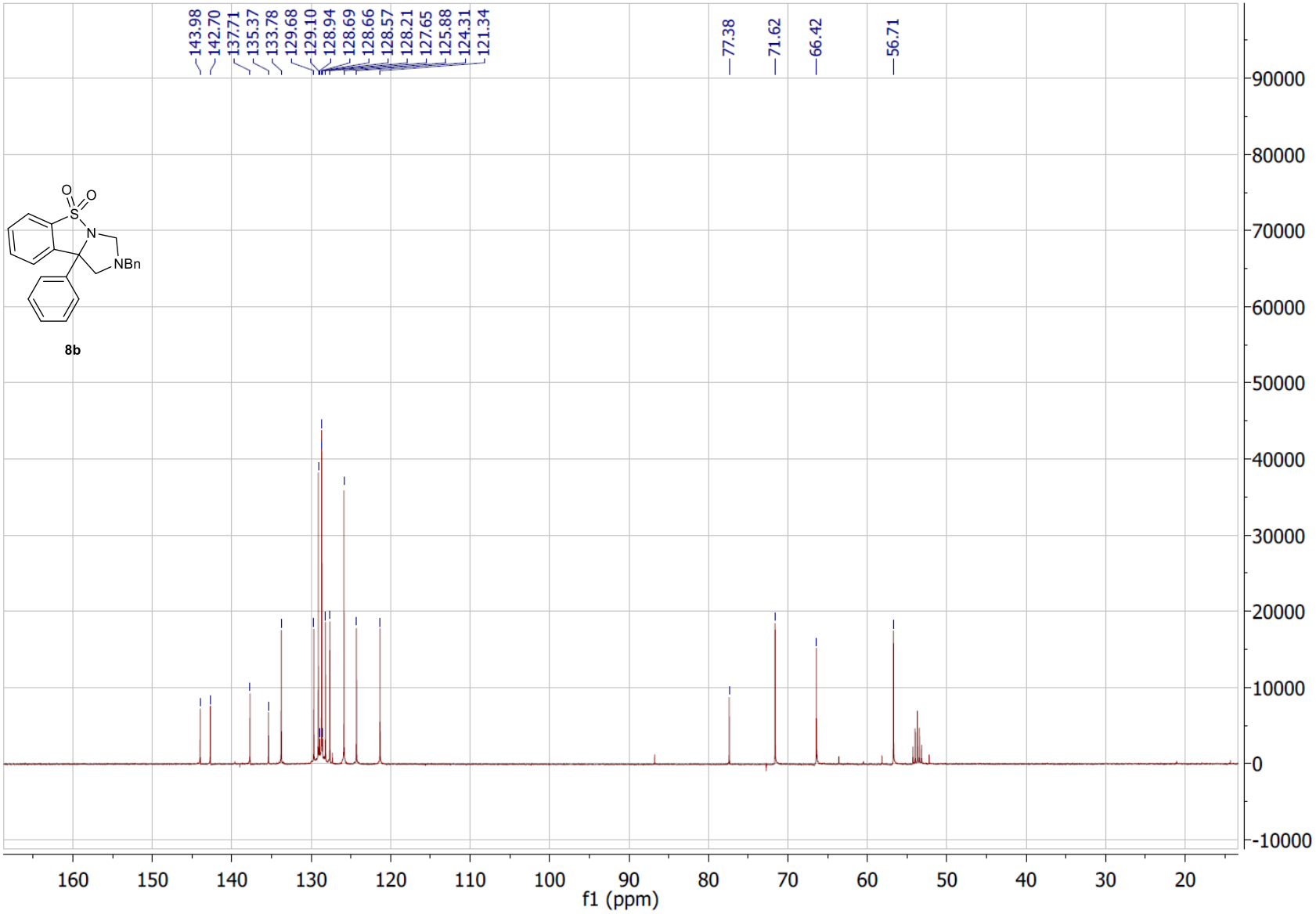
2.13
2.32
4.10
1.96
1.00
2.05
1.04
1.03
1.02
f1 (ppm)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129.10
128.94
128.69
128.66
128.57
128.21
127.65
125.88
124.31
121.34
77.38
71.62
66.42
56.71
O
O
S
N
NBn
8b
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
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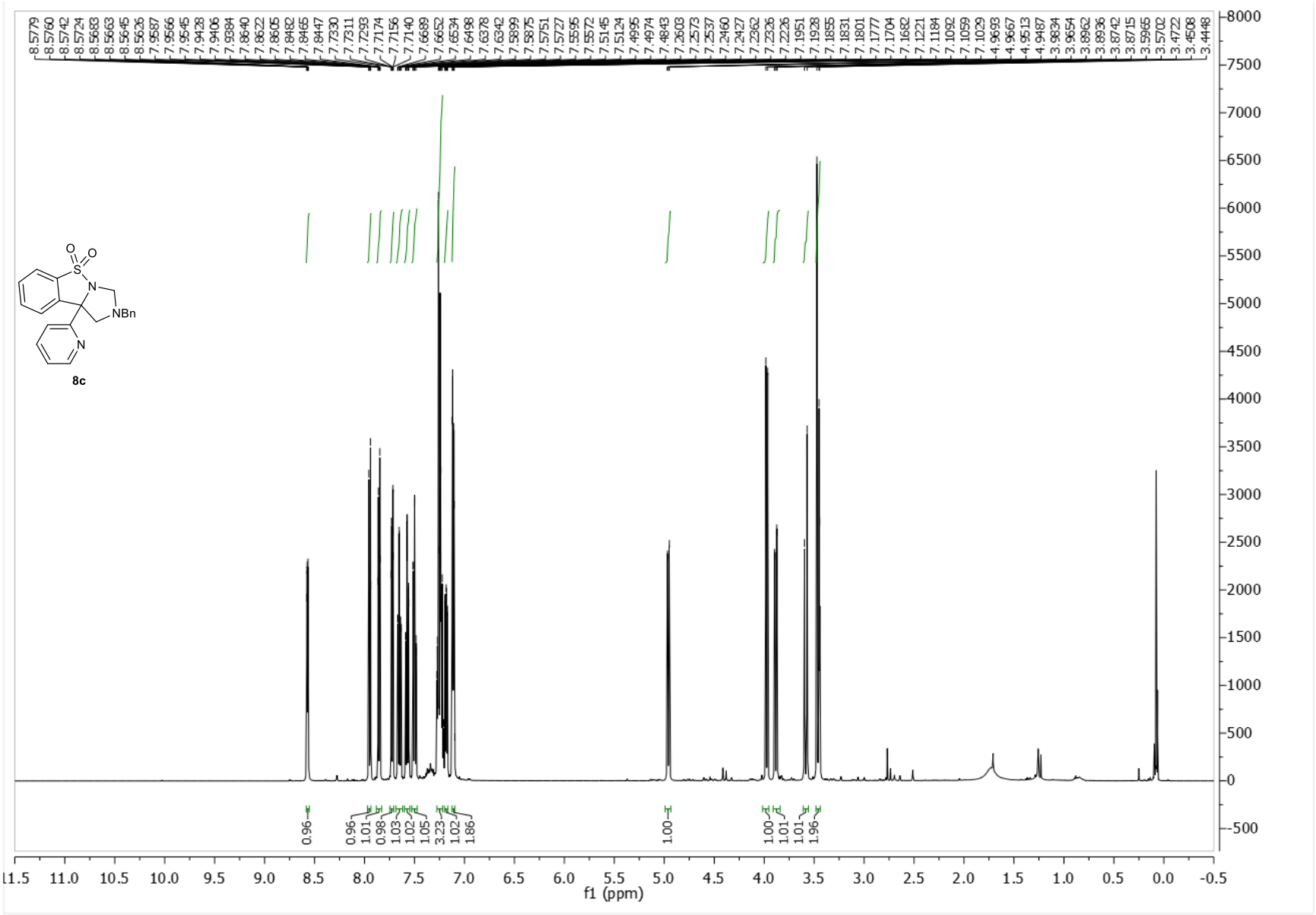
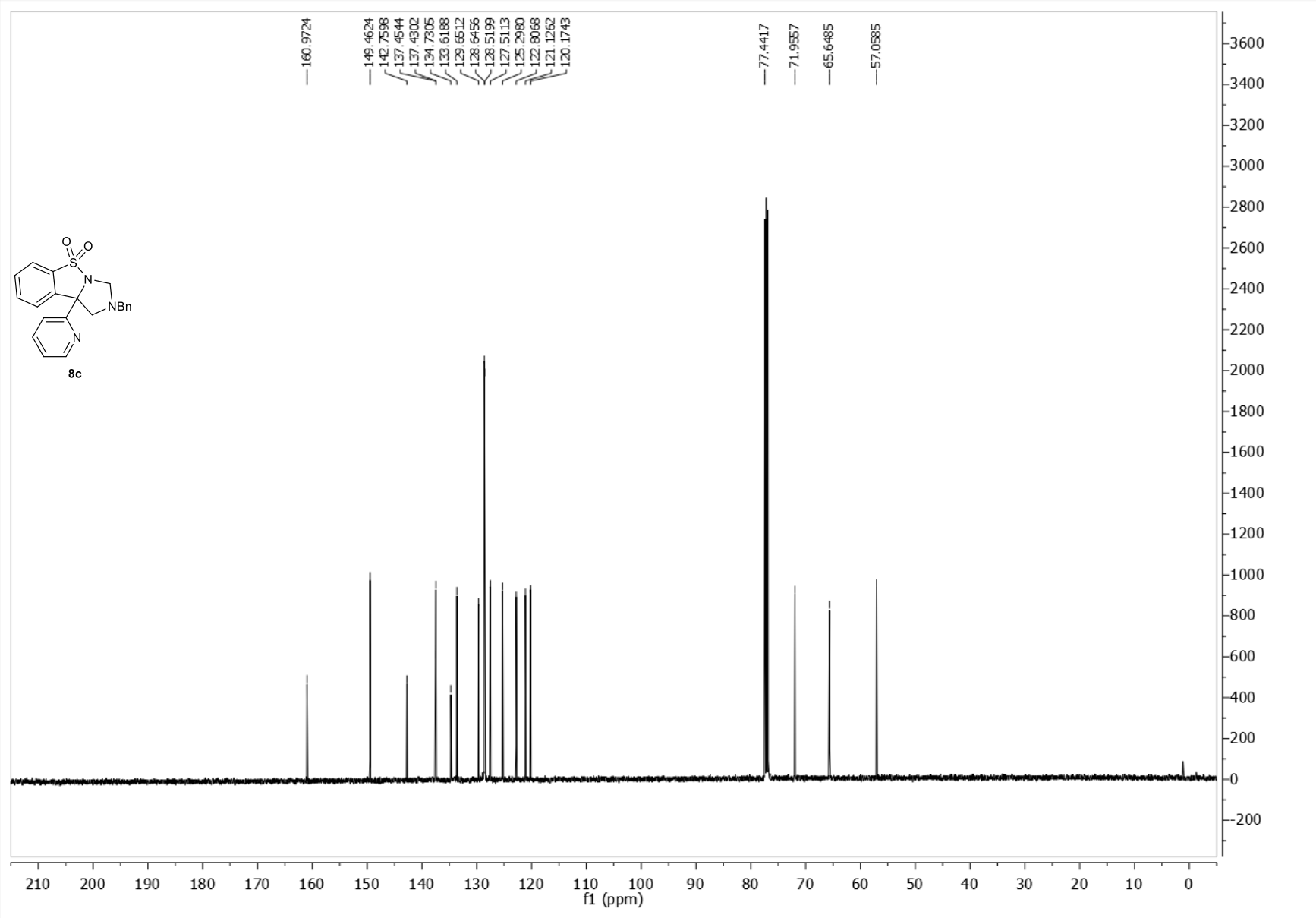
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)


8c
f1 (ppm)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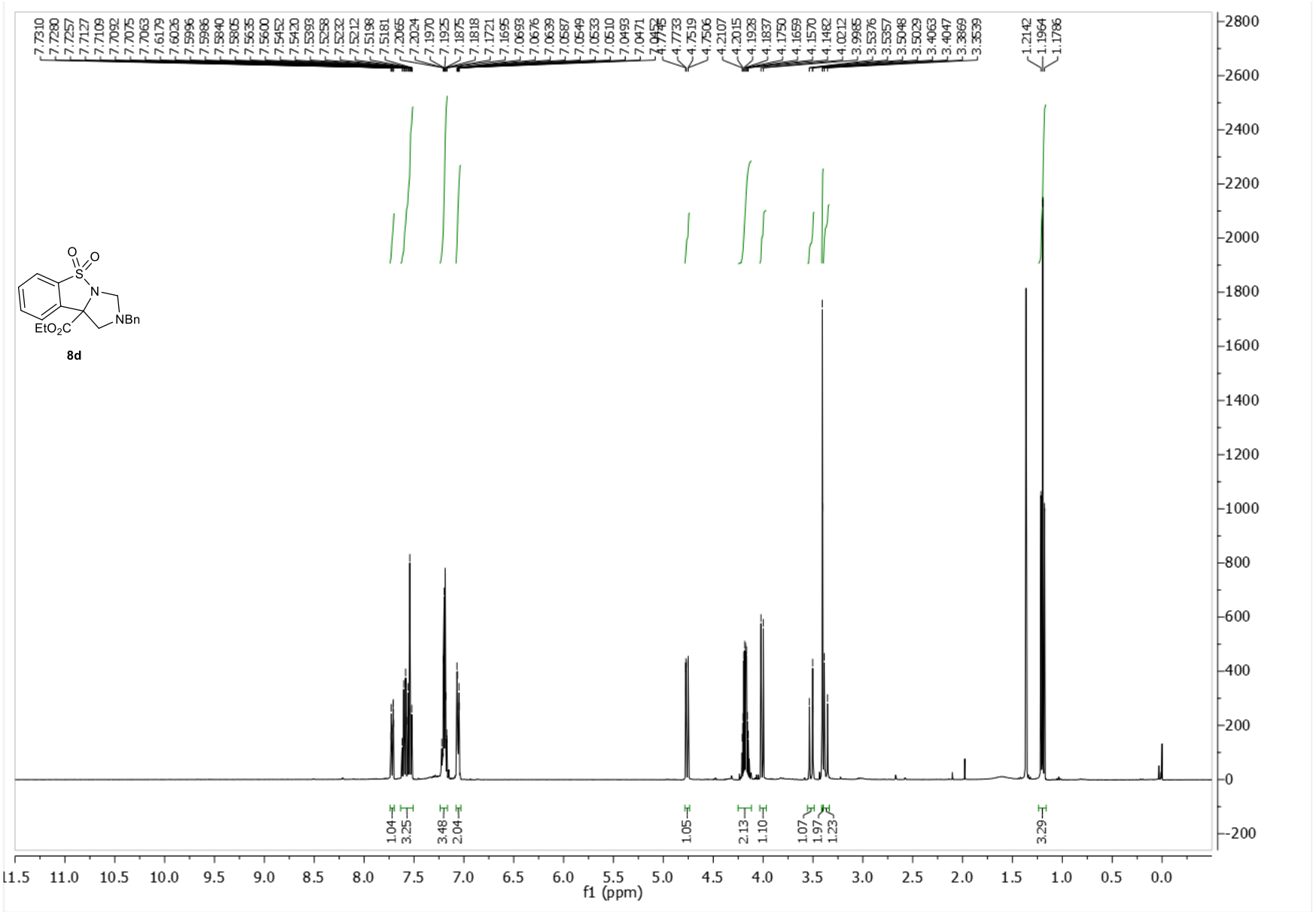
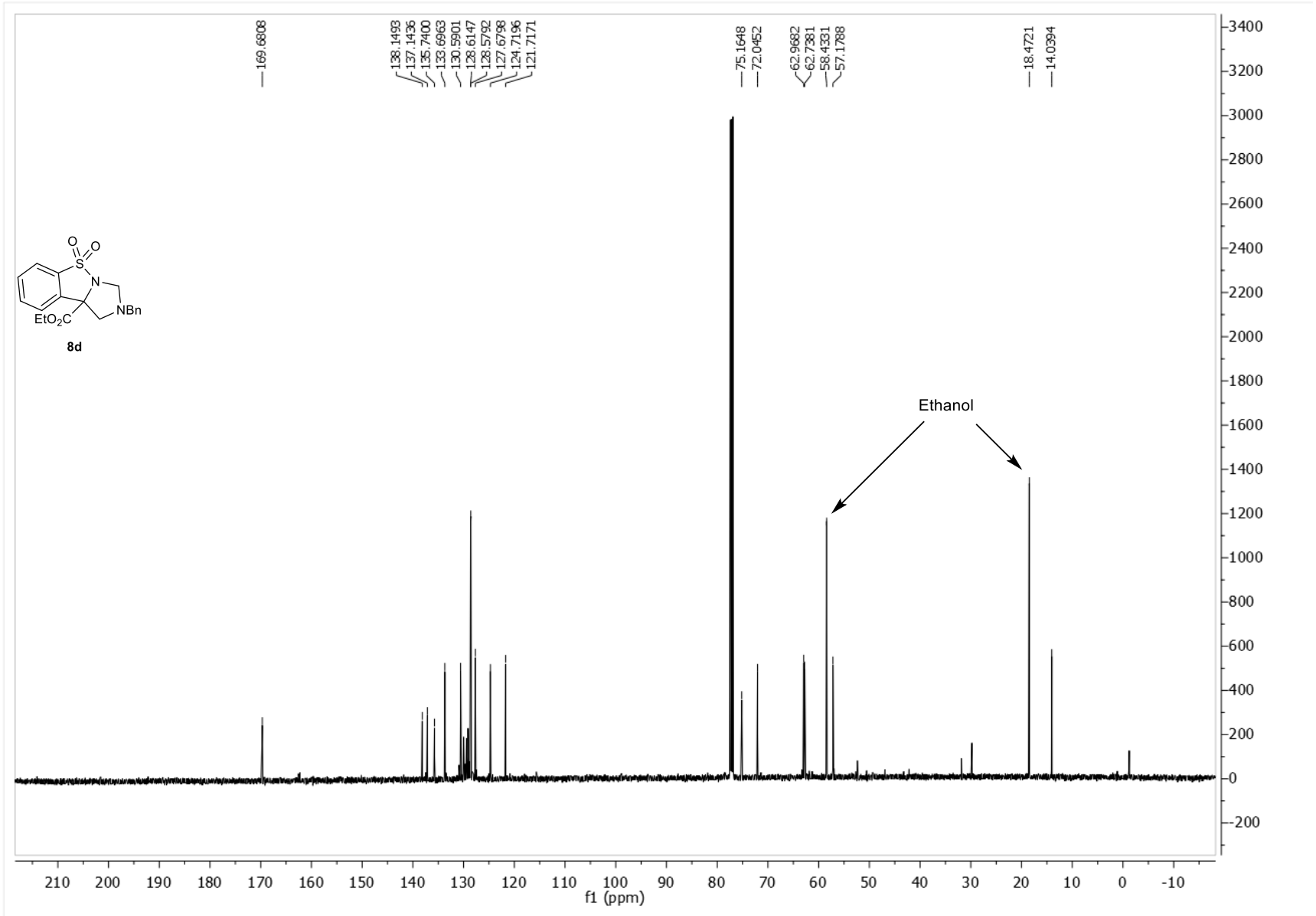
127.5113
125.2980
122.8068
121.1262
120.1743
77.4417
71.9557
65.6485
57.0585
O
O
S
N
NBn
N
8c
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8d
f1 (ppm)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124.7196
121.7171
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72.0452
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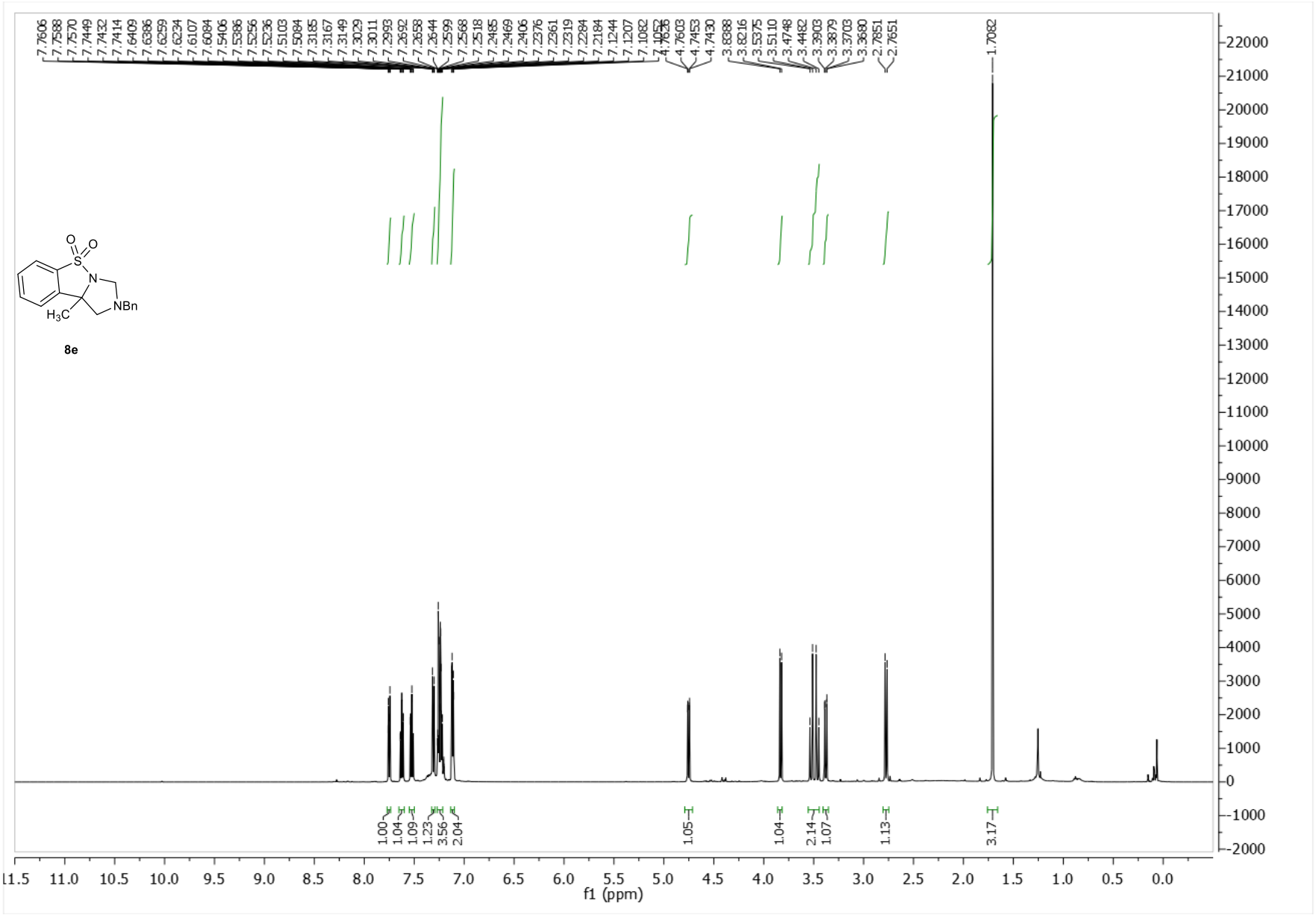
62.7381
58.4331
57.1788
18.4721
14.0394
Ethanol
8d
f1 (ppm)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7.5406
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7.5236
7.5103
7.5084
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7.3149
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7.2993
7.2692
7.2658
7.2644
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7.2568
7.2518
7.2485
7.2469
7.2406
7.2376
7.2361
7.2319
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4.7636
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4.7453
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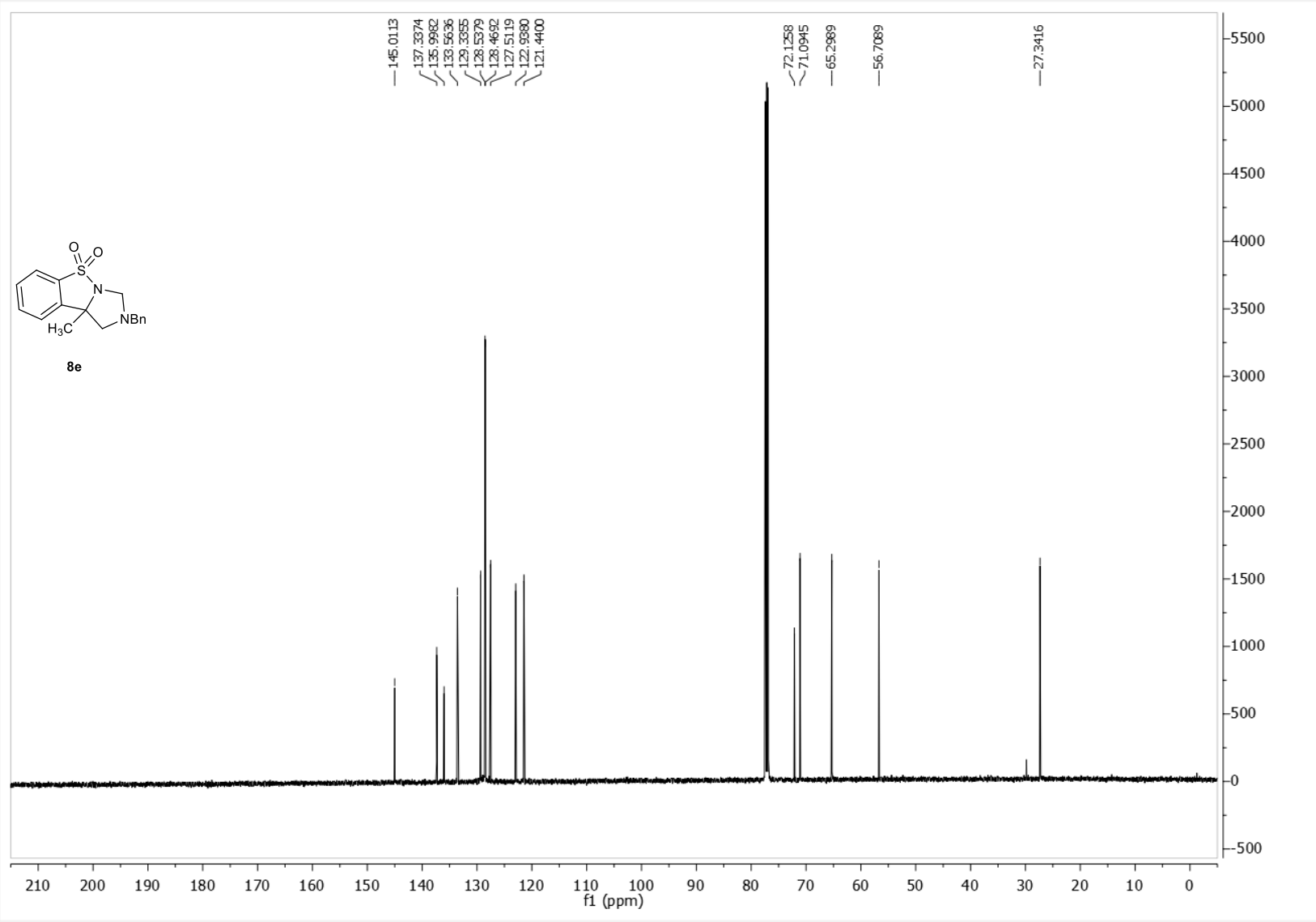
3.8216
3.5375
3.5110
3.4748
3.4482
3.3903
3.3879
3.3703
3.3680
2.7851
2.7651
1.7082
O
O
S
N
NBn
H3C
8e
1.00
1.04
1.09
1.23
3.56
2.04
1.05
1.04
2.14
1.07
1.13
3.17
f1 (ppm)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121.4400
72.1258
71.0945
65.2989
56.7089
27.3416
O
O
S
N
NBn
H3C
8e
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
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120
110
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90
80
70
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50
40
30
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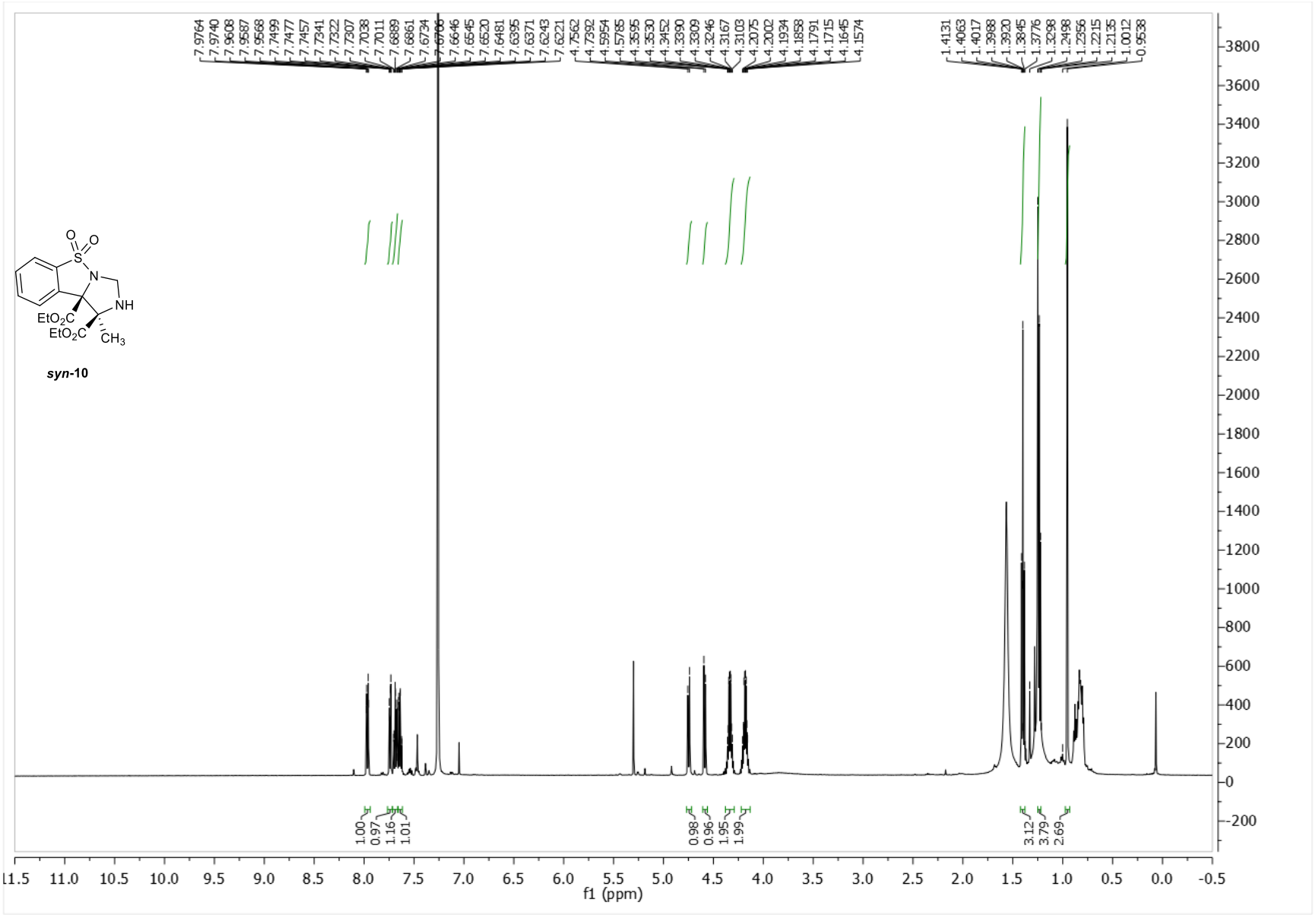
10
0
f1 (ppm)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7.7038
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4.7562
4.7392
4.5954
4.5785
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4.3452
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4.3309
4.3246
4.3167
4.3103
4.2075
4.2002
4.1934
4.1858
4.1791
4.1715
4.1645
4.1574
1.4131
1.4063
1.4017
1.3988
1.3920
1.3845
1.3776
1.3298
1.2498
1.2356
1.2215
1.2135
1.0012
0.9538
1.00
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1.16
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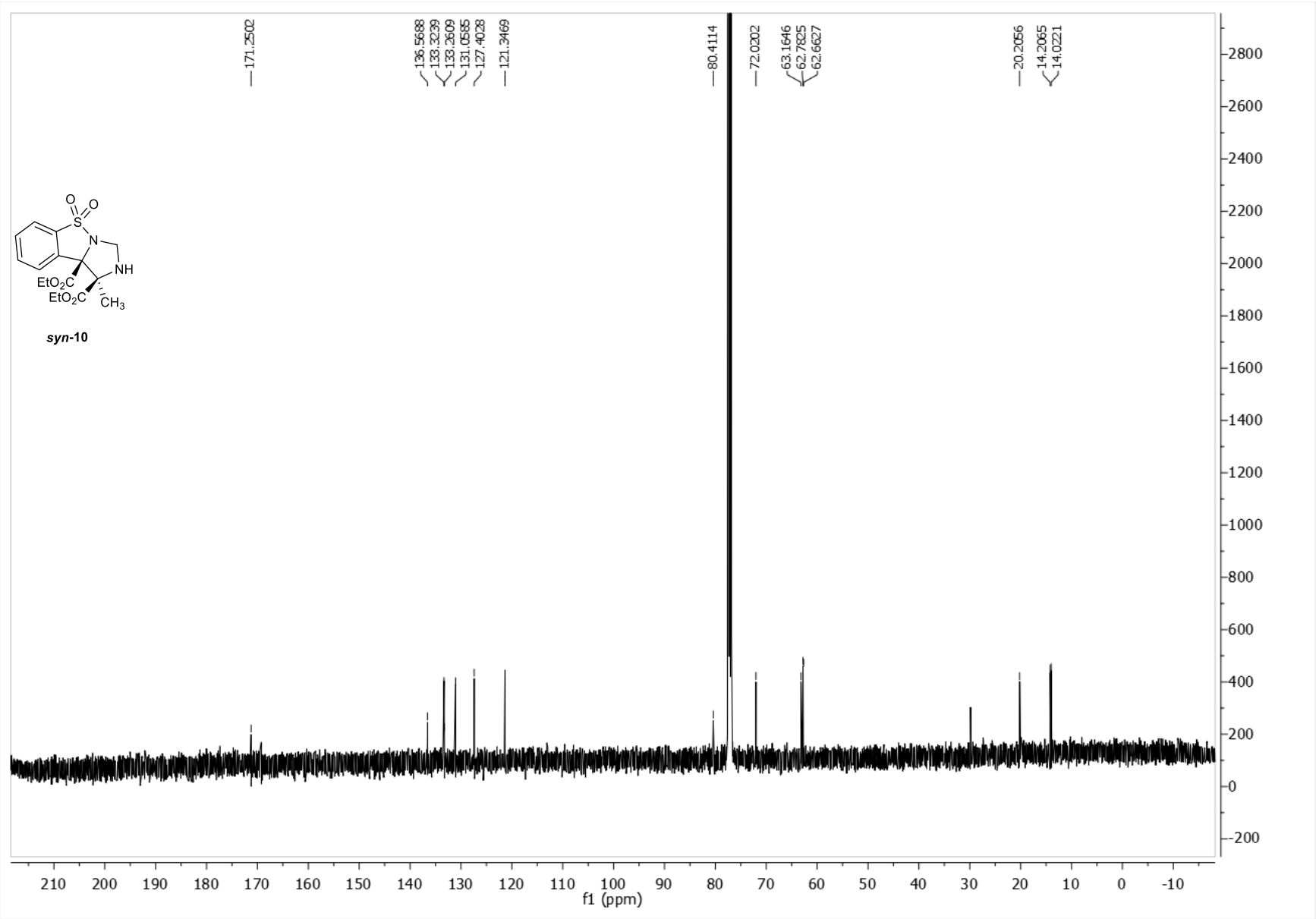
0.98
0.96
1.95
1.99
3.12
3.79
2.69
f1 (ppm)
syn-10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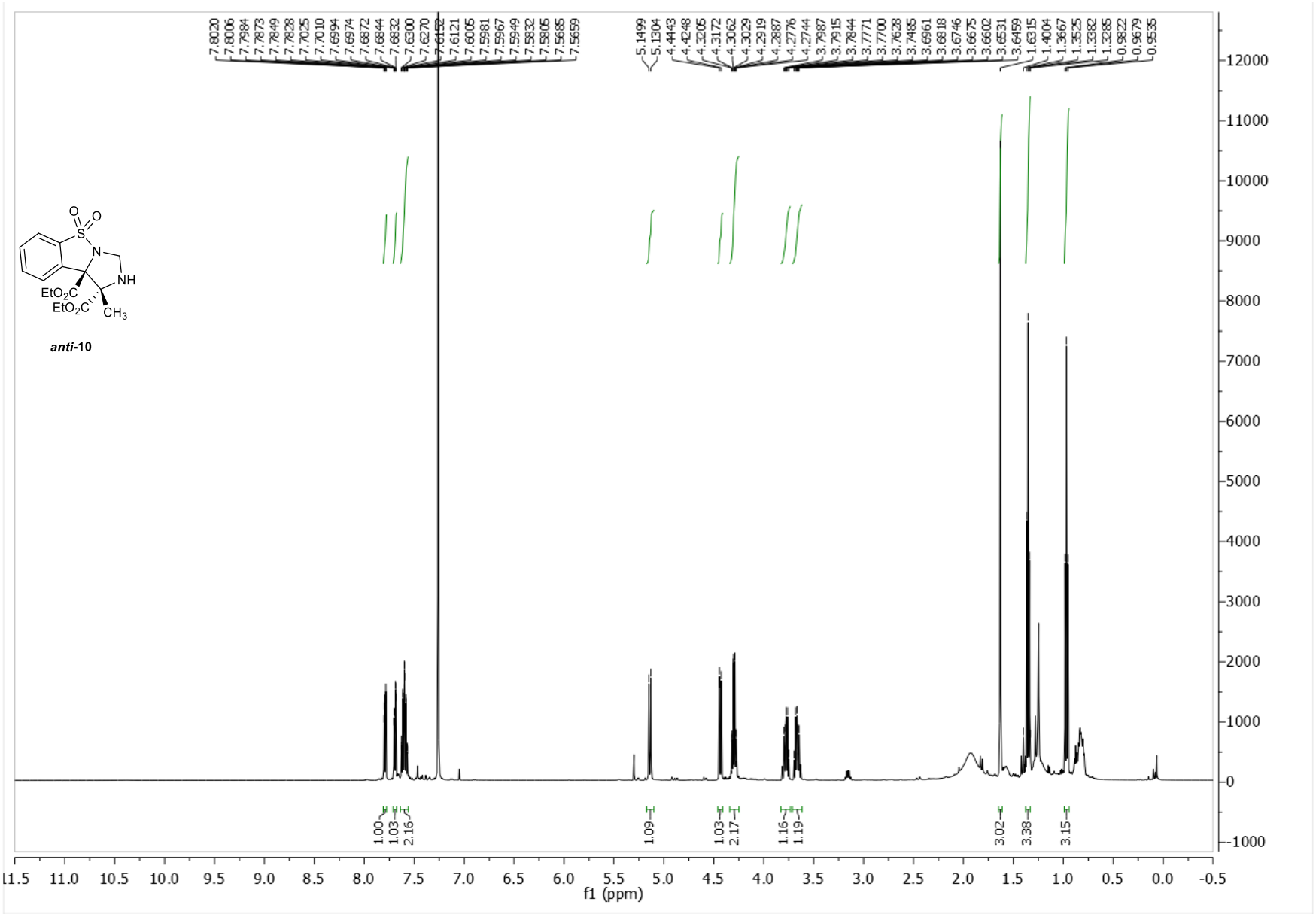
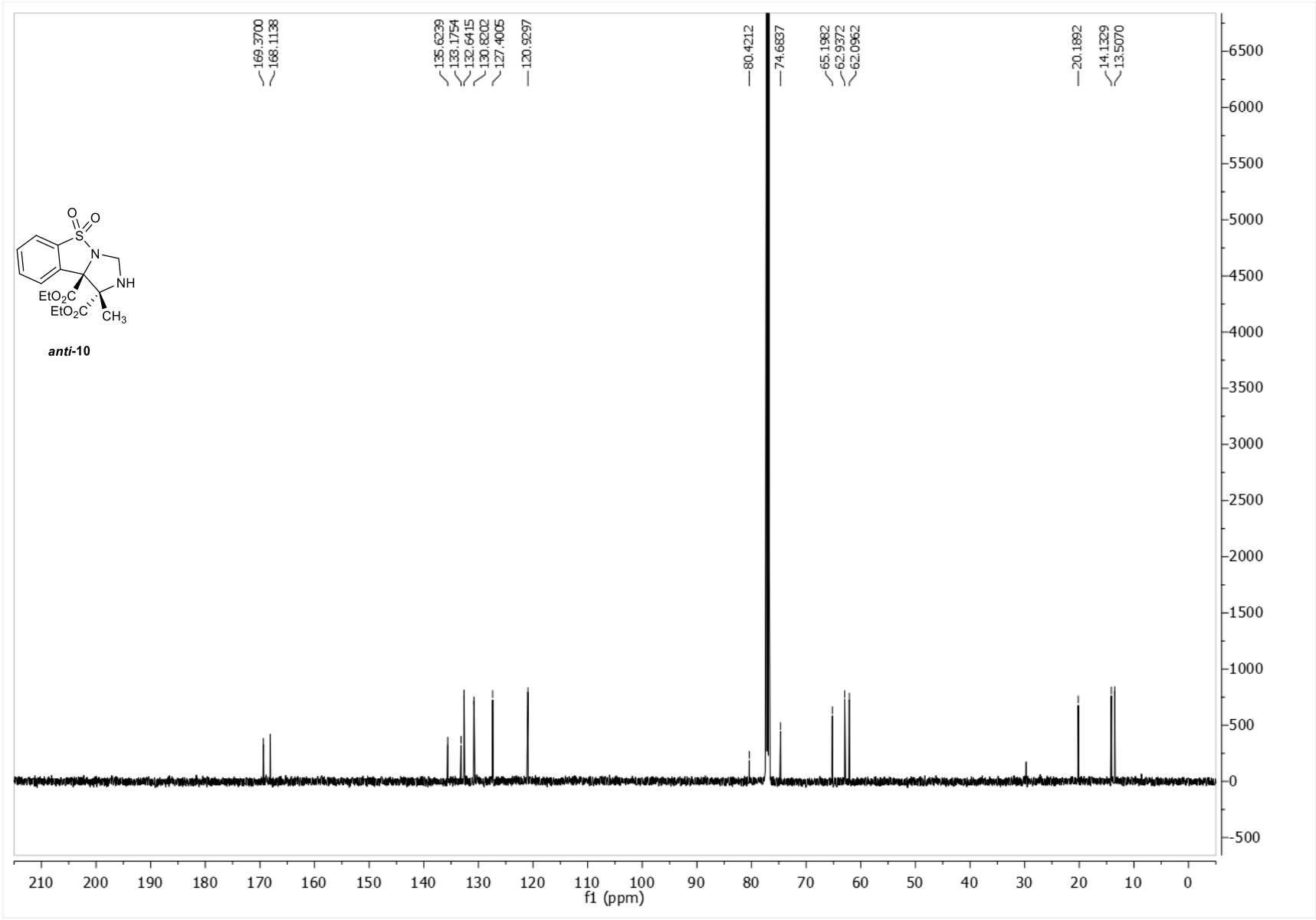
127.4028
121.3469
80.4114
72.0202
63.1646
62.7825
62.6627
20.2056
14.2065
14.0221
O
O
S
N
NH
EtO2C
EtO2C
CH3
syn-10
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


anti-10
f1 (ppm)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135.6239
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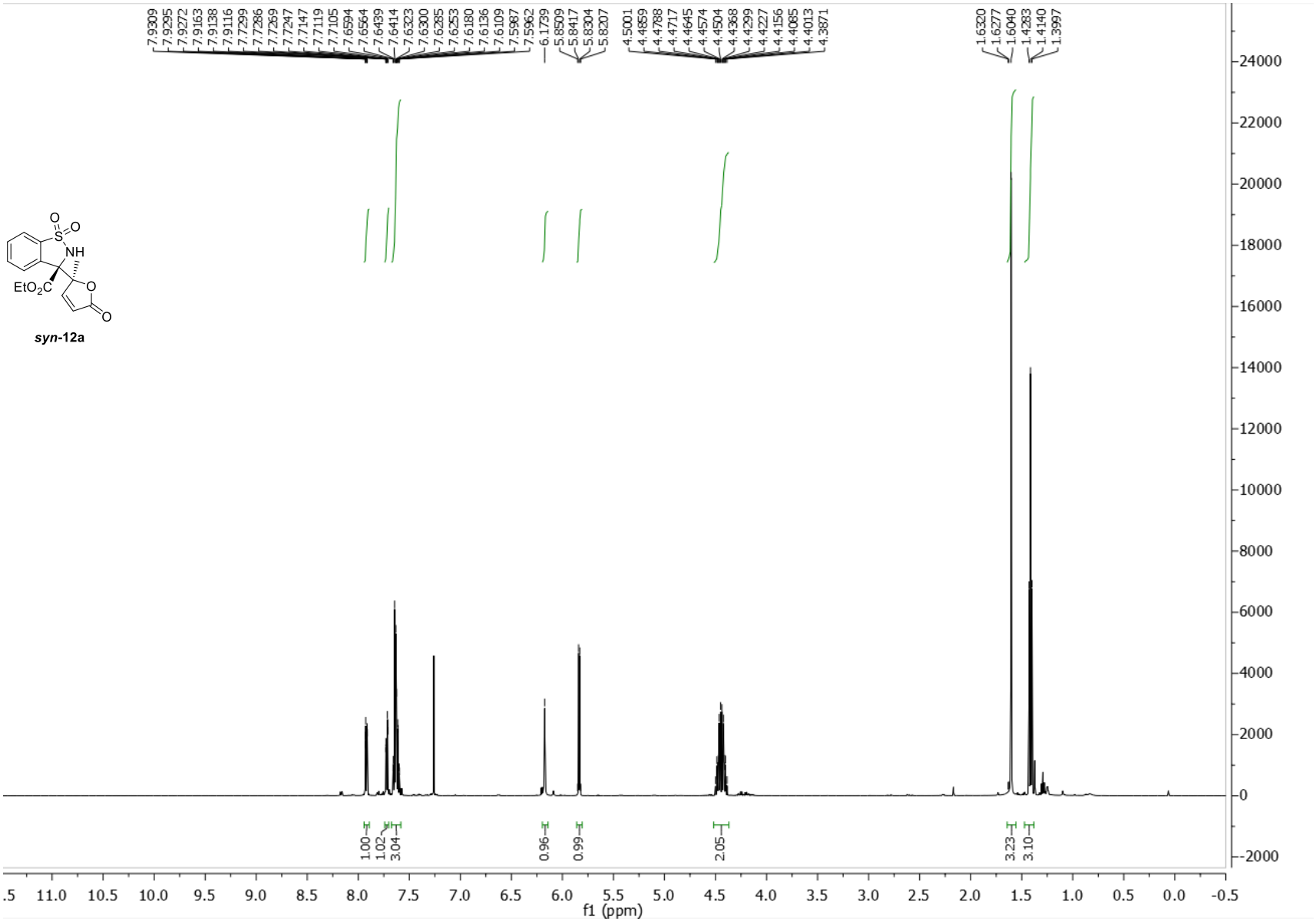
132.6415
130.8202
127.4005
120.9297
80.4212
74.6837
65.1982
62.9372
62.0962
20.1892
14.1329
13.5070
anti-10
f1 (ppm)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7.7299
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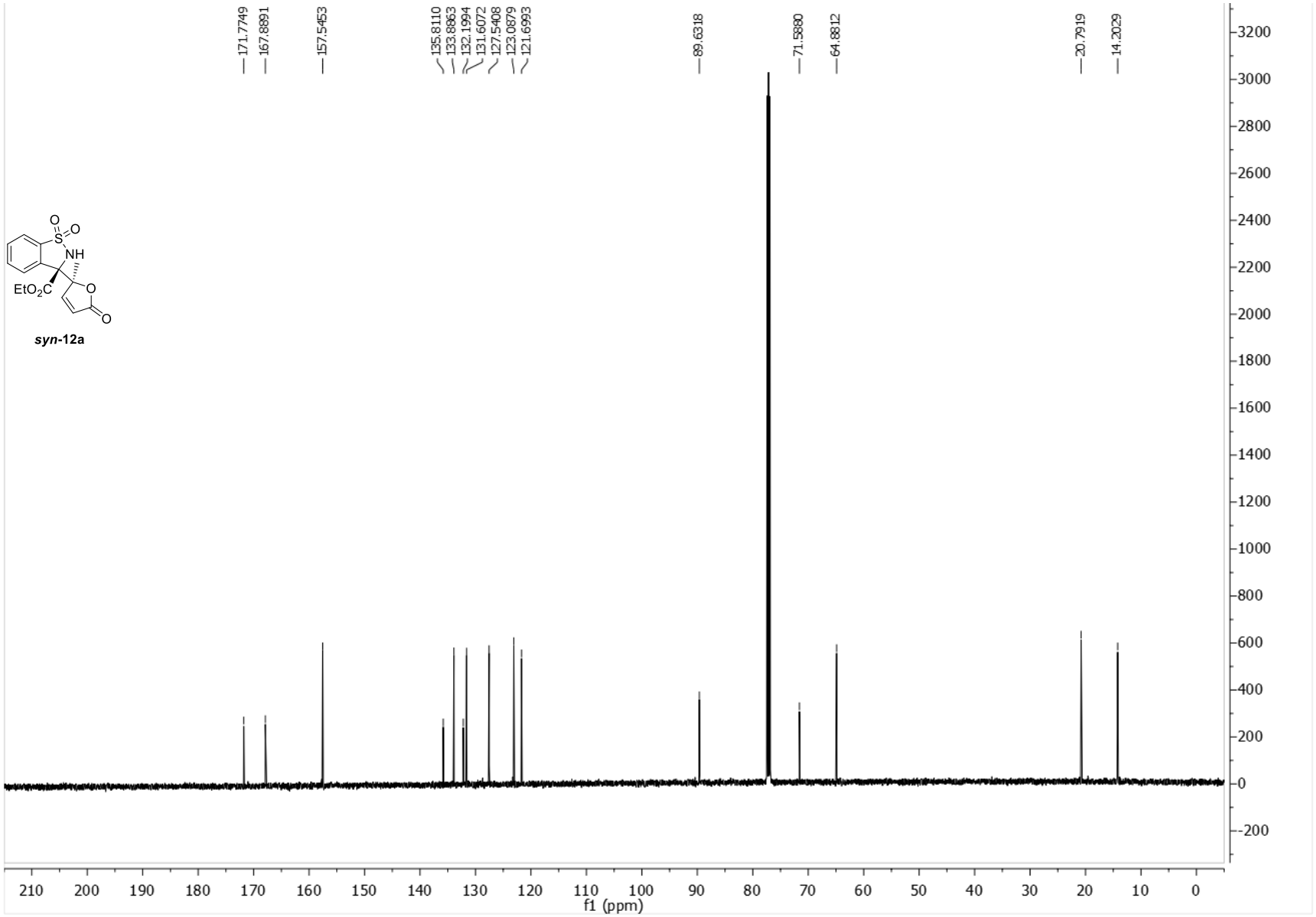
7.7269
7.7247
7.7147
7.7119
7.7105
7.6594
7.6564
7.6439
7.6414
7.6323
7.6300
7.6285
7.6253
7.6180
7.6136
7.6109
7.5987
7.5962
6.1739
5.8509
5.8417
5.8304
5.8207
4.5001
4.4859
4.4788
4.4717
4.4645
4.4574
4.4504
4.4368
4.4299
4.4227
4.4156
4.4085
4.4013
4.3871
1.6320
1.6277
1.6040
1.4283
1.4140
1.3997
1.00
1.02
3.04
0.96
0.99
2.05
3.23
3.10
f1 (ppm)

*syn*-12a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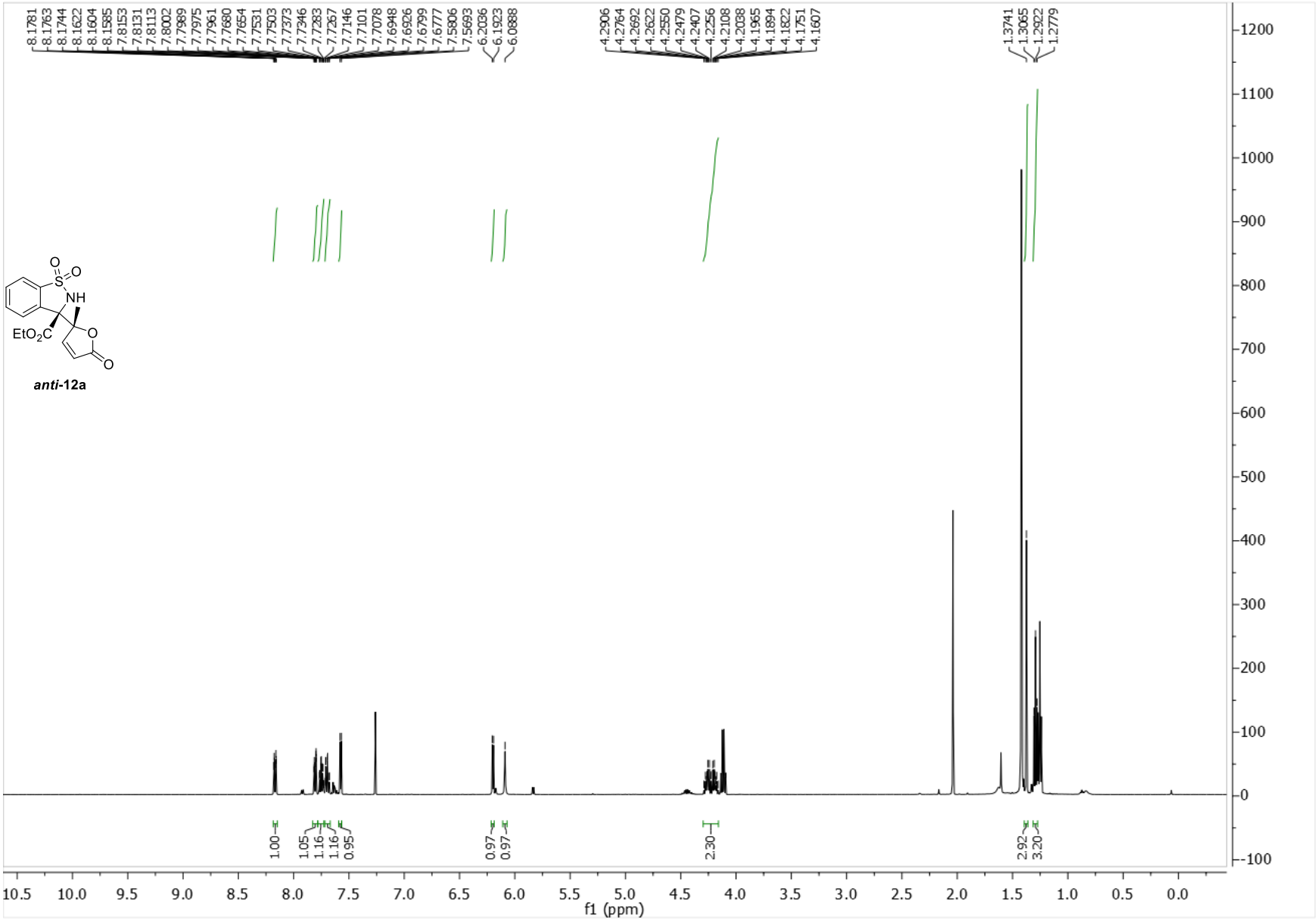
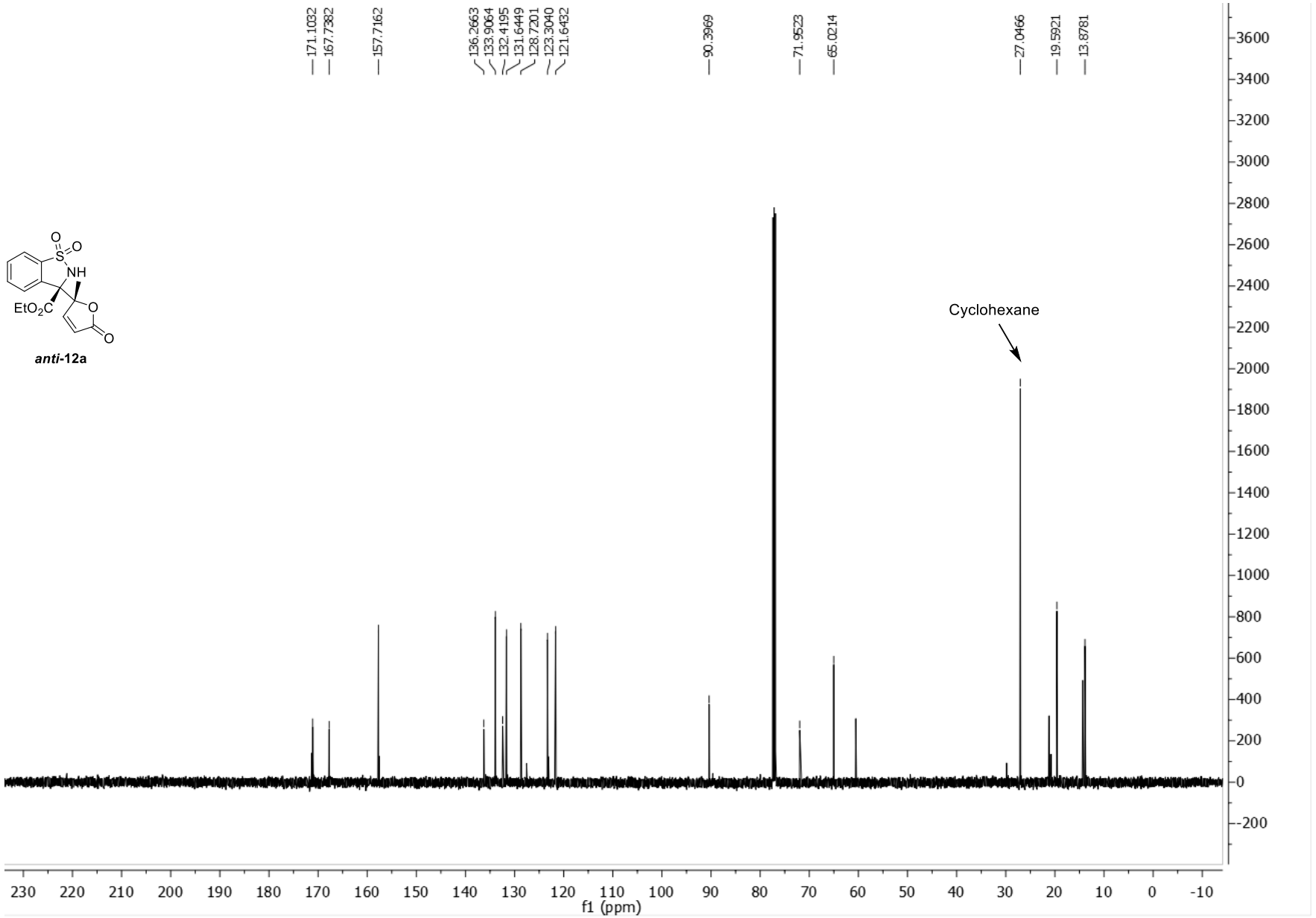
157.5453
135.8110
133.8863
132.1994
131.6072
127.5408
123.0879
121.6993
89.6318
71.5880
64.8812
20.7919
14.2029
syn-12a
f1 (ppm)


8.1781
8.1763
8.1744
8.1622
8.1604
8.1585
8.1153
7.8131
7.8113
7.8002
7.7989
7.7975
7.7961
7.7680
7.7654
7.7531
7.7503
7.7373
7.7346
7.7283
7.7267
7.7146
7.7101
7.7078
7.6948
7.6926
7.6799
7.6777
7.5806
7.5693
6.2036
6.1923
6.0888
4.2906
4.2764
4.2692
4.2622
4.2550
4.2479
4.2407
4.2256
4.2108
4.2038
4.1965
4.1894
4.1822
4.1751
4.1607
1.3741
1.3065
1.2922
1.2779
NH
EtO2C
anti-12a
1.00
1.05
1.16
1.16
0.95
0.97
0.97
2.30
2.92
3.20
f1 (ppm)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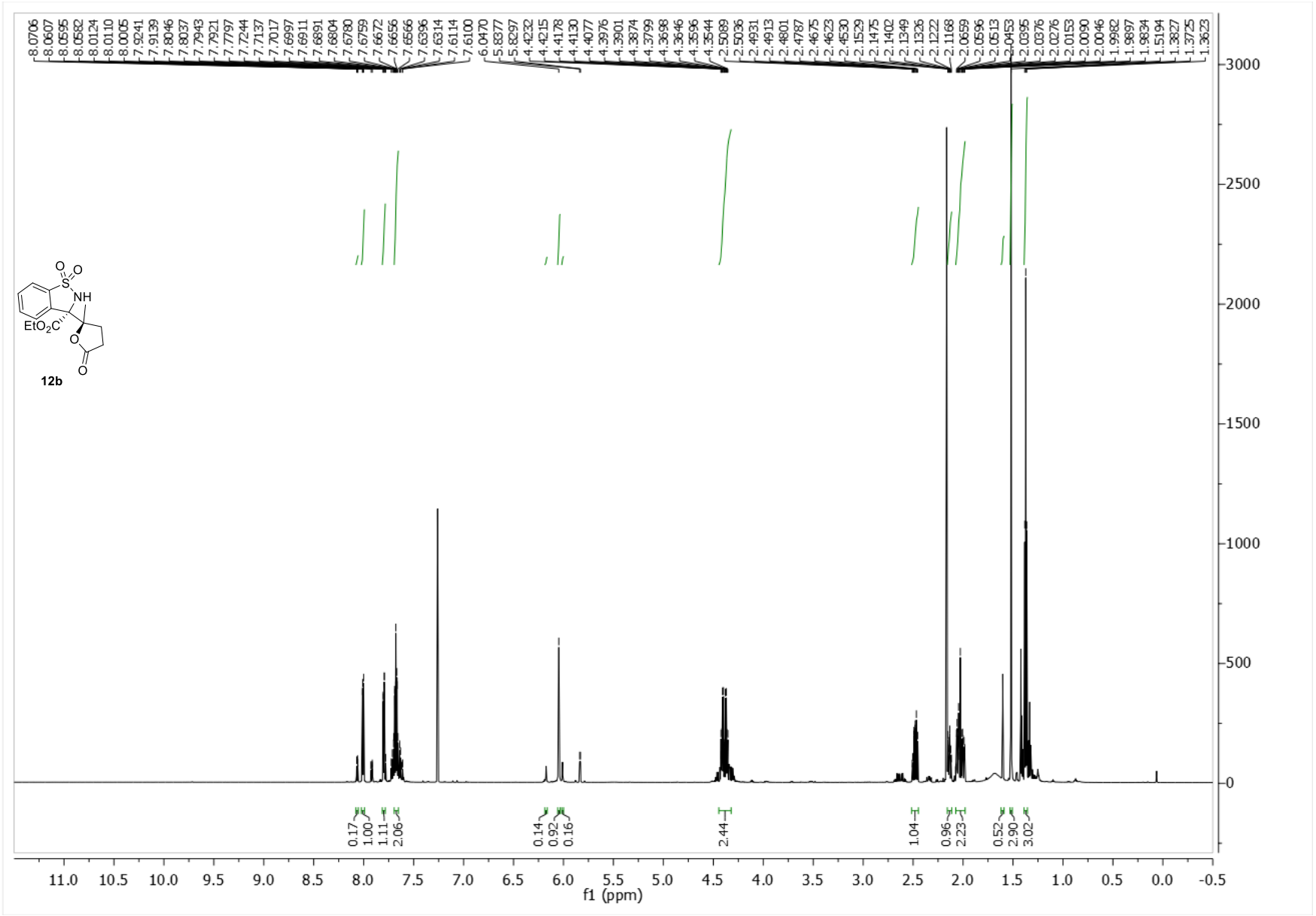
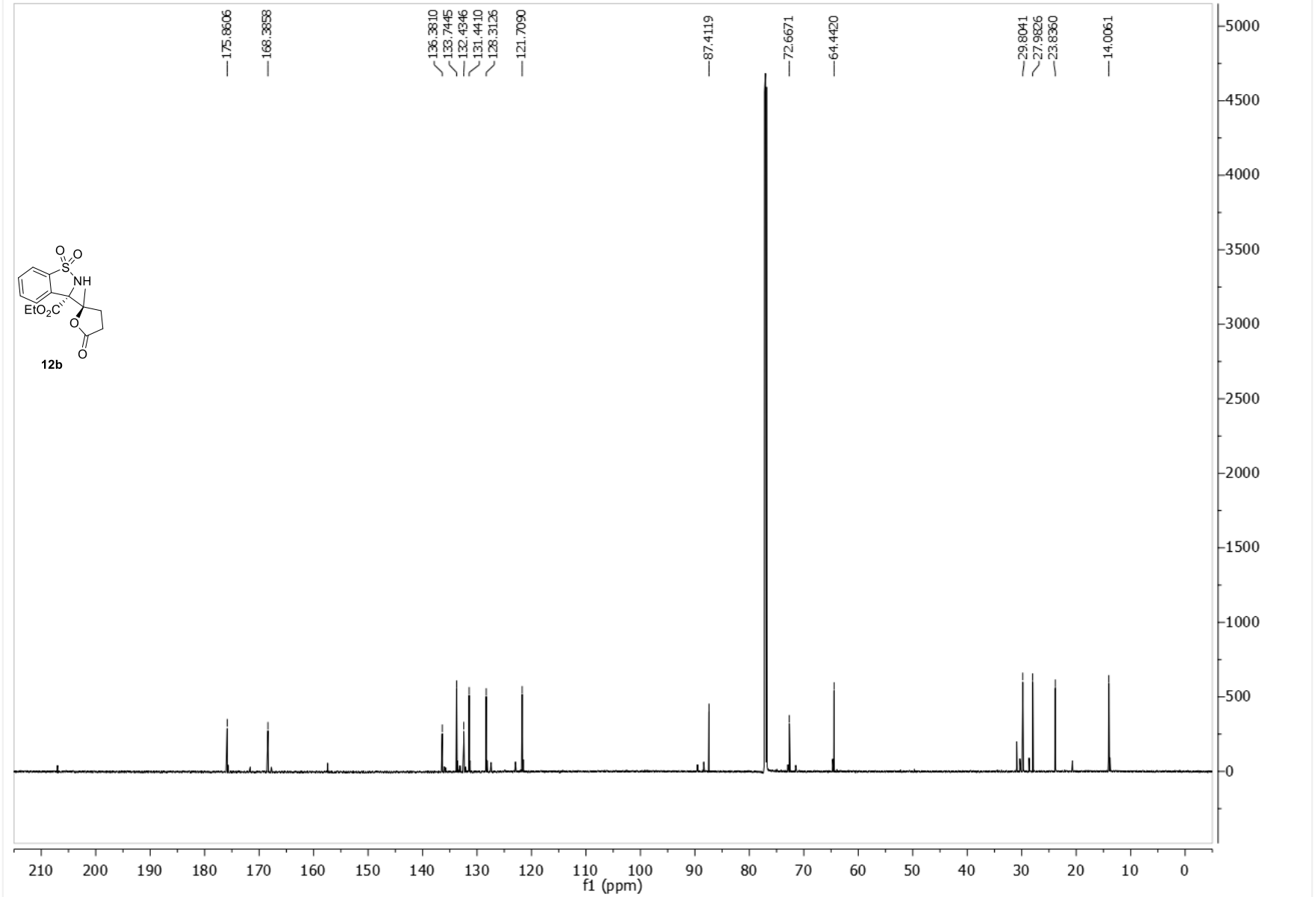
157.7162
136.2663
133.9064
132.4195
131.6449
128.7201
123.3040
121.6432
90.3969
71.9523
65.0214
27.0466
19.5921
13.8781
Cyclohexane
anti-12a
f1 (ppm)


12b
f1 (ppm)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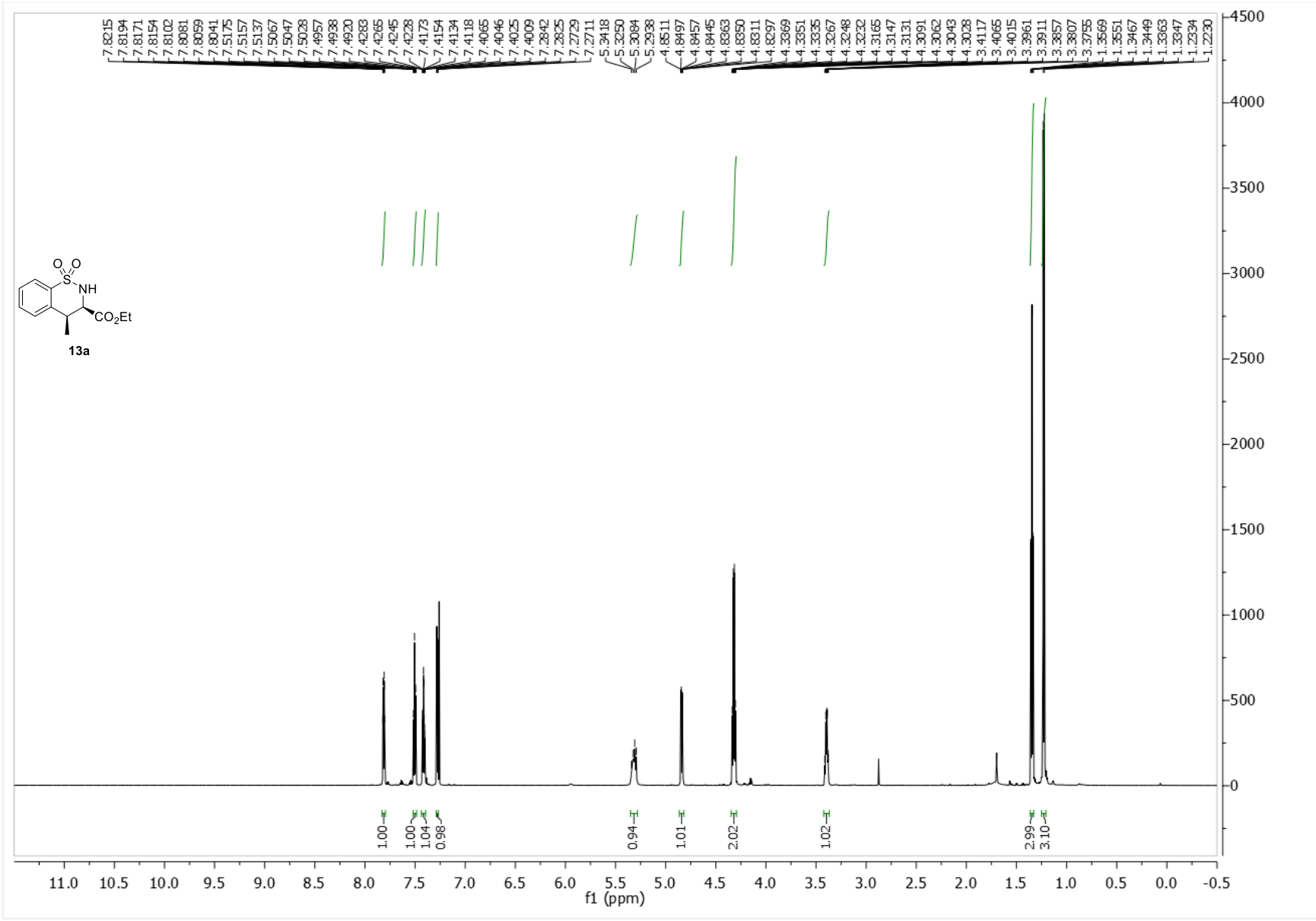
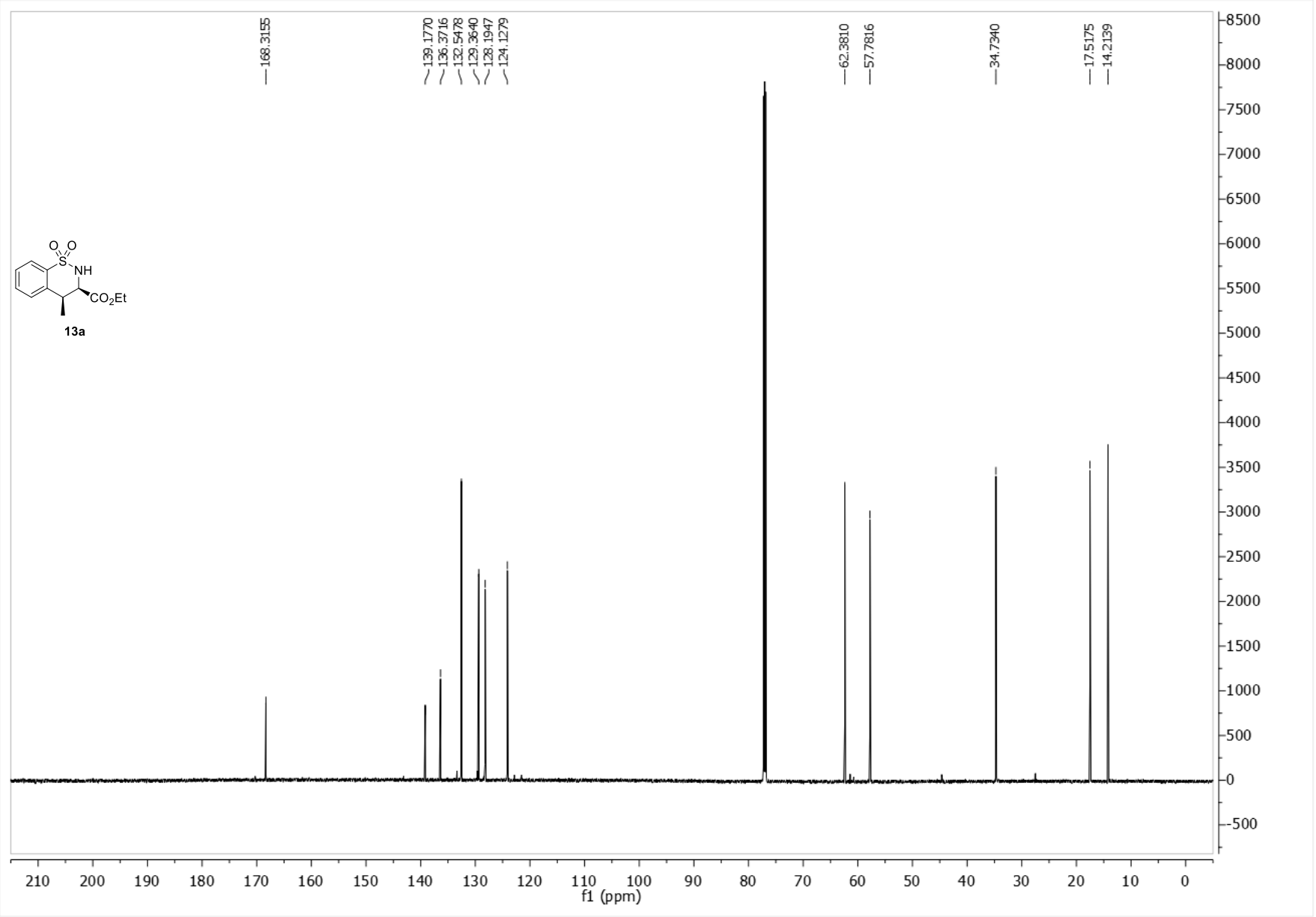
136.3810
133.7445
132.4346
131.4410
128.3126
121.7090
87.4119
72.6671
64.4420
29.8041
27.9826
23.8360
14.0061
12b
f1 (ppm)


13a
f1 (ppm)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139.1770
136.3716
132.5478
129.3640
128.1947
124.1279
62.3810
57.7816
34.7340
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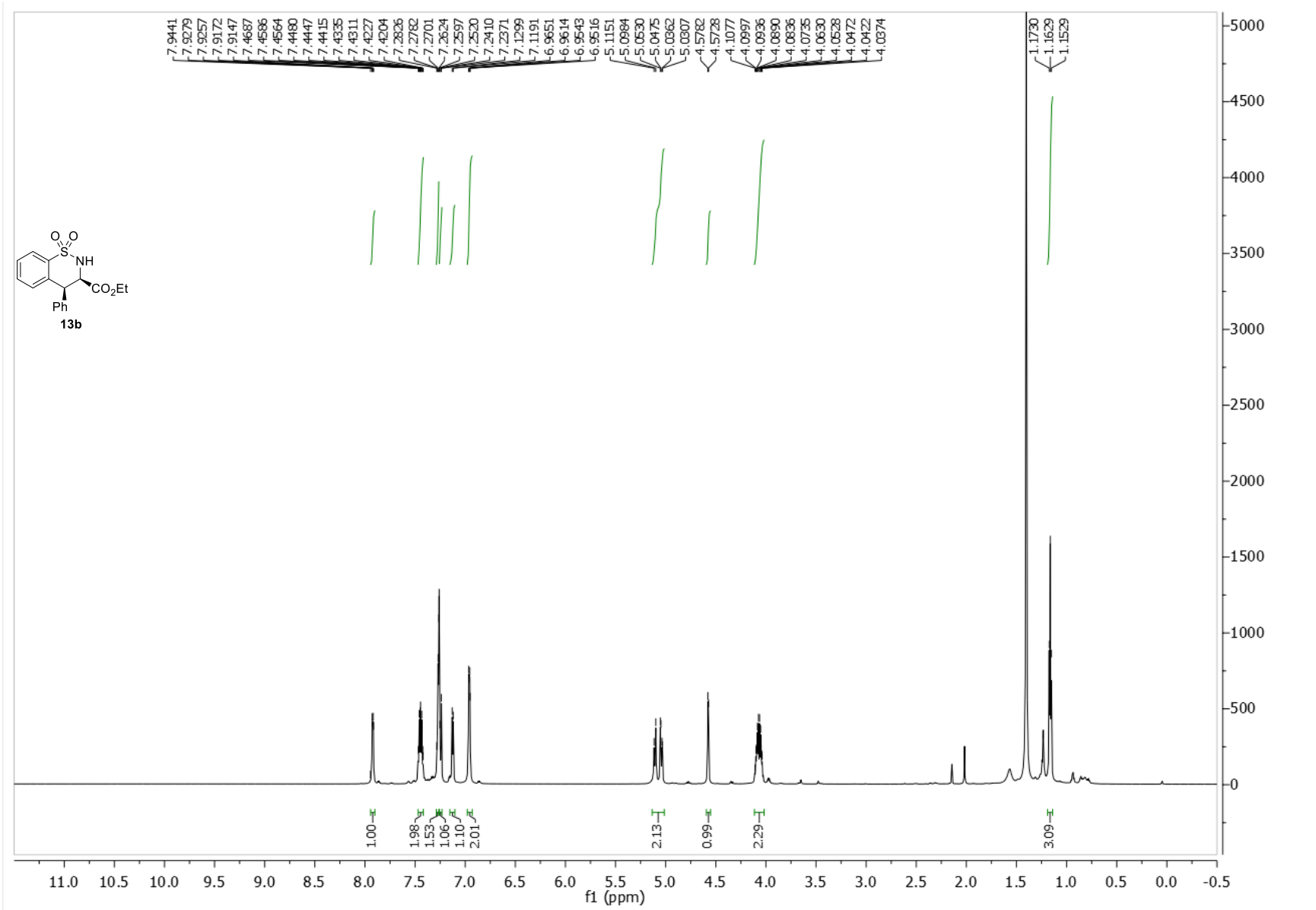
14.2139
NH
CO2Et
13a
f1 (ppm)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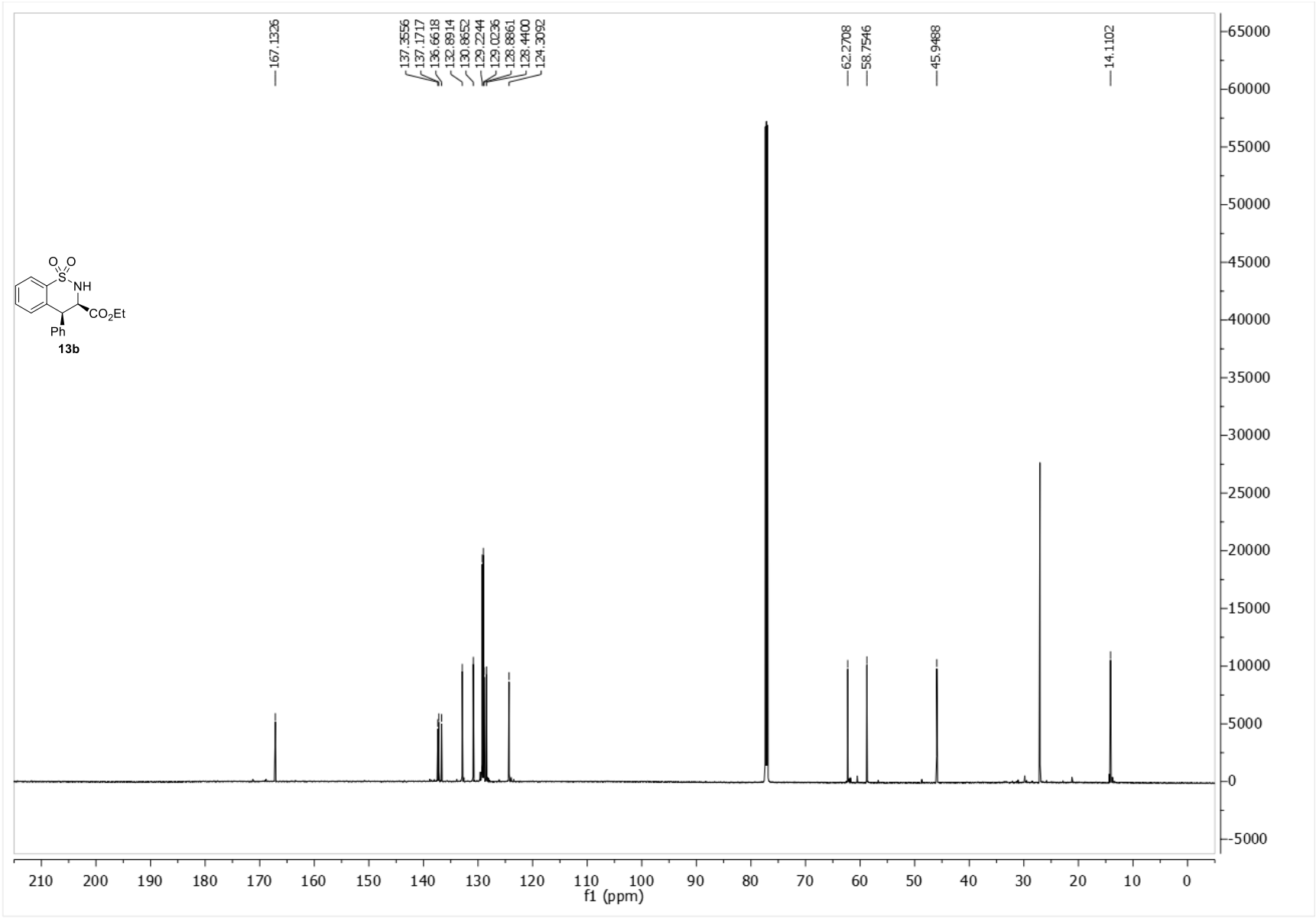
7.9279
7.9257
7.9172
7.9147
7.4687
7.4586
7.4564
7.4480
7.4447
7.4415
7.4335
7.4311
7.4227
7.4204
7.2826
7.2782
7.2701
7.2624
7.2597
7.2520
7.2410
7.2371
7.1299
7.1191
6.9651
6.9614
6.9543
6.9516
5.1151
5.0984
5.0530
5.0475
5.0362
5.0307
4.5782
4.5728
4.1077
4.0997
4.0936
4.0890
4.0836
4.0735
4.0630
4.0528
4.0472
4.0422
4.0374
1.1730
1.1629
1.1529
O
O
S
NH
CO2Et
Ph
13b
1.00
1.98
1.53
1.06
1.10
2.01
2.13
0.99
2.29
3.09
f1 (ppm)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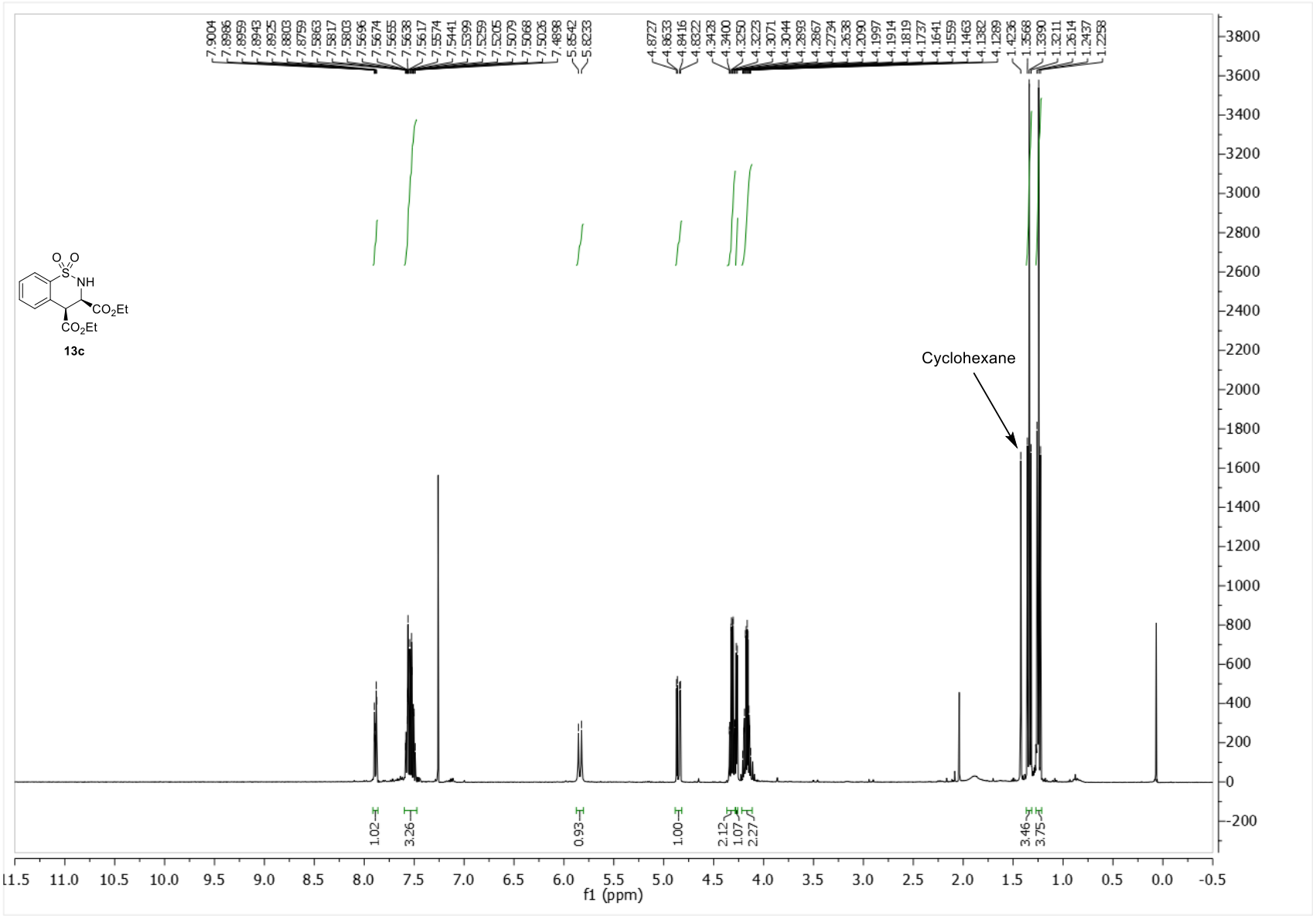
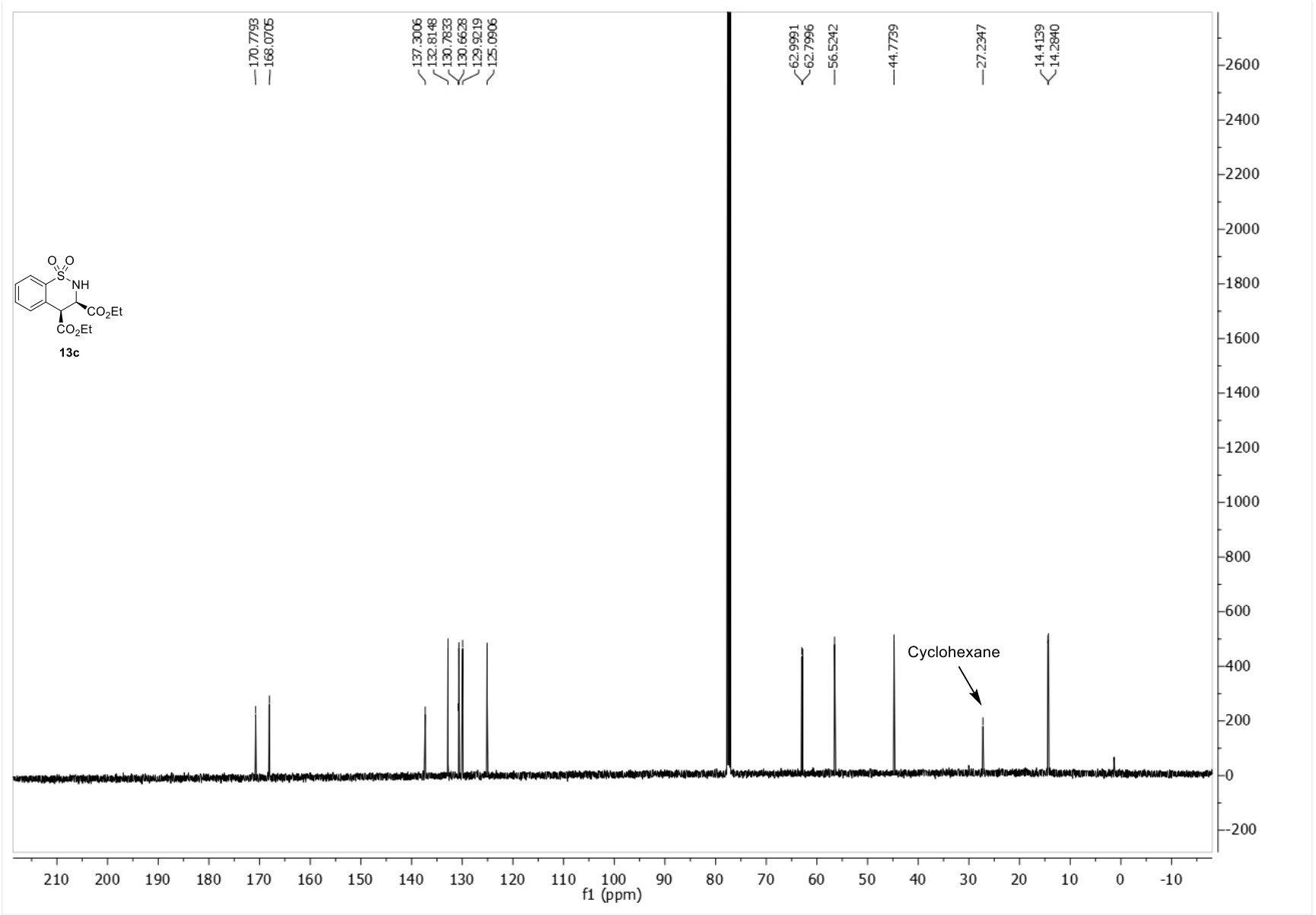
137.1717
136.6618
132.8914
130.8652
129.2244
129.0236
128.8861
128.4400
124.3092
62.2708
58.7546
45.9488
14.1102
NH
CO2Et
Ph
13b
f1 (ppm)


13c
Cyclohexane
f1 (ppm)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132.8148
130.7833
130.6628
129.9219
125.0906
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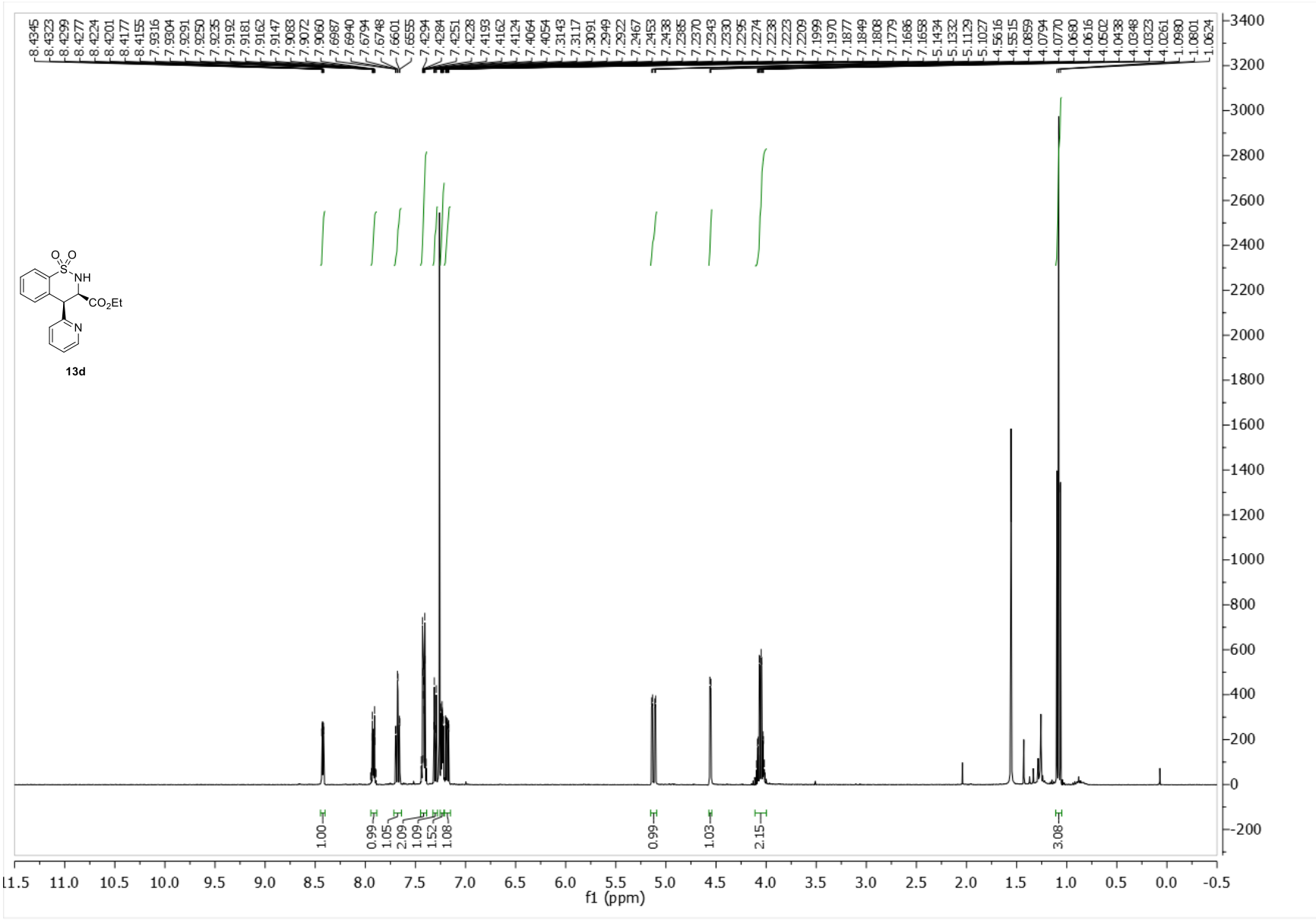
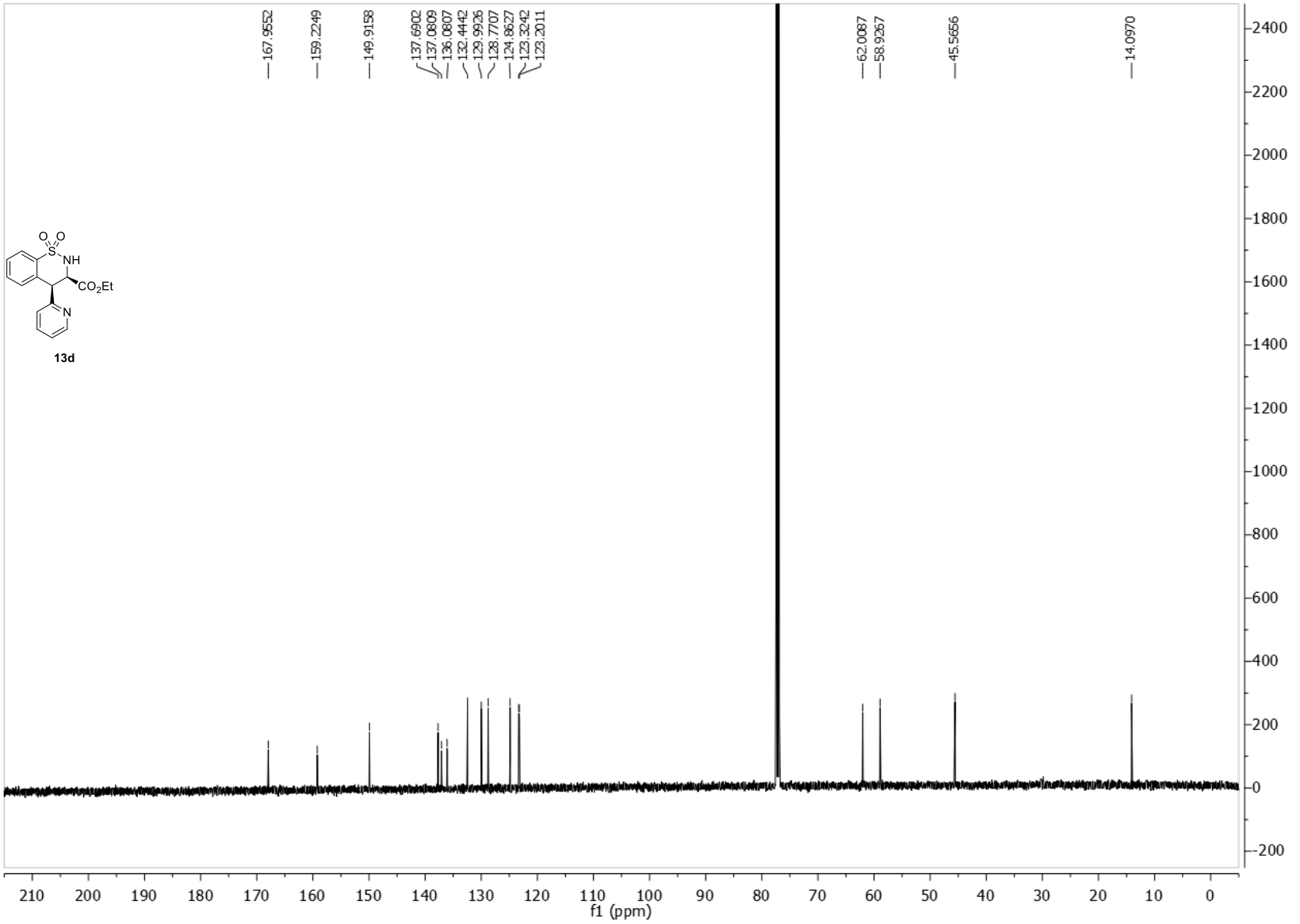
56.5242
44.7739
27.2347
14.4139
14.2840
Cyclohexane
13c
f1 (ppm)


13d
f1 (ppm)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149.9158
137.6902
137.0809
136.0807
132.4442
129.9926
128.7707
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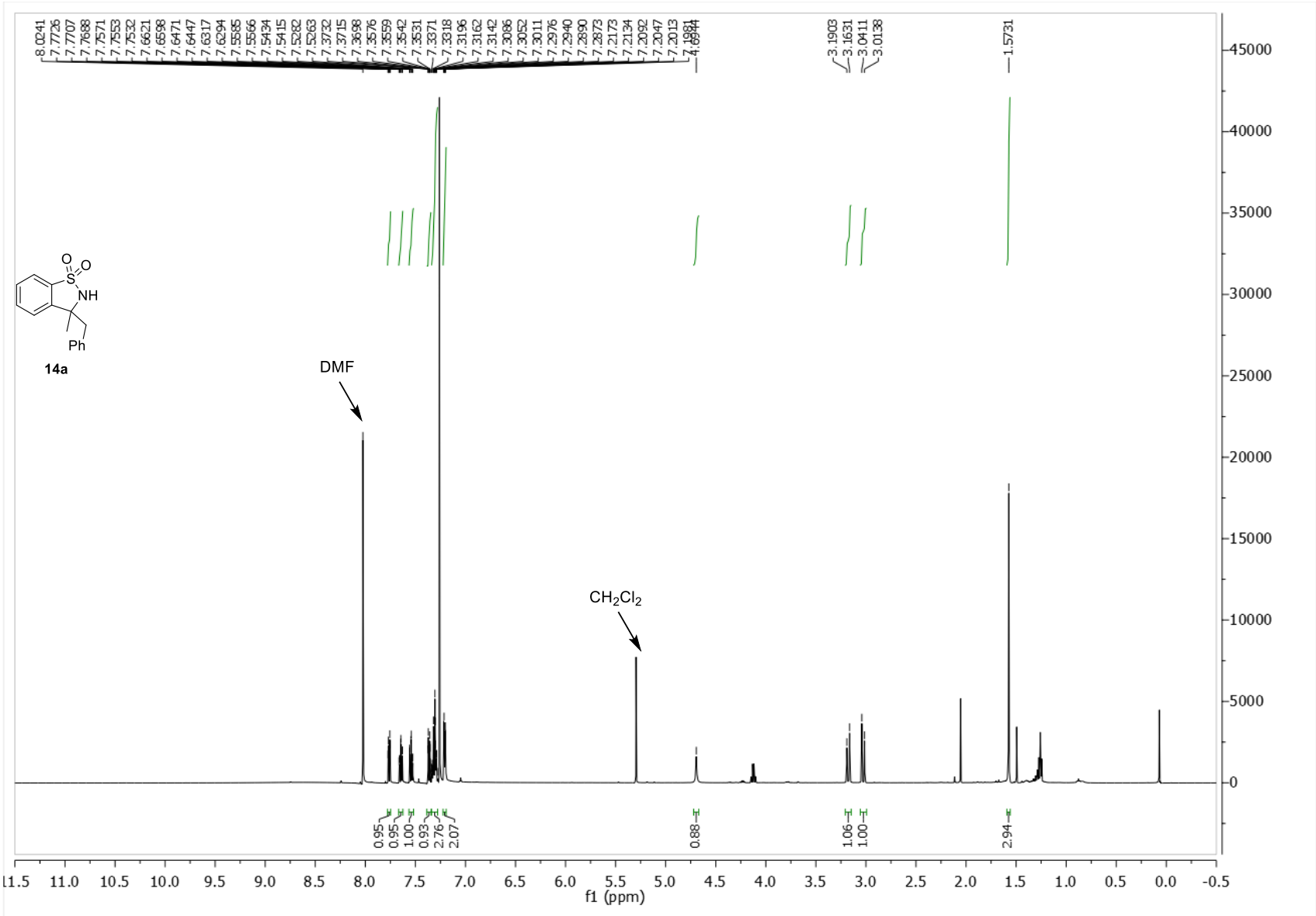
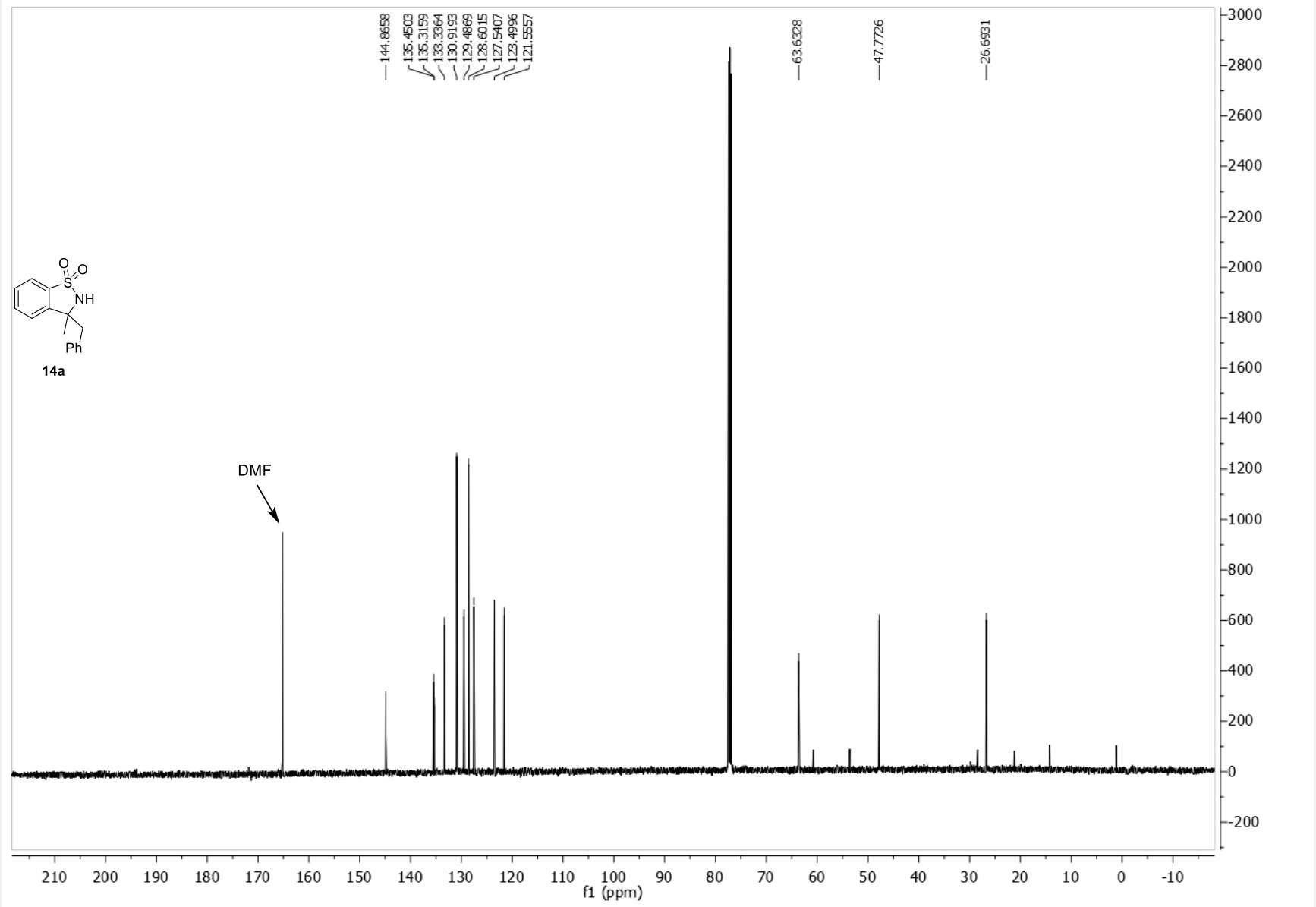
123.3242
123.2011
62.0087
58.9267
45.5656
14.0970
13d
f1 (ppm)


14a
DMF
$CH_2Cl_2$
f1 (ppm)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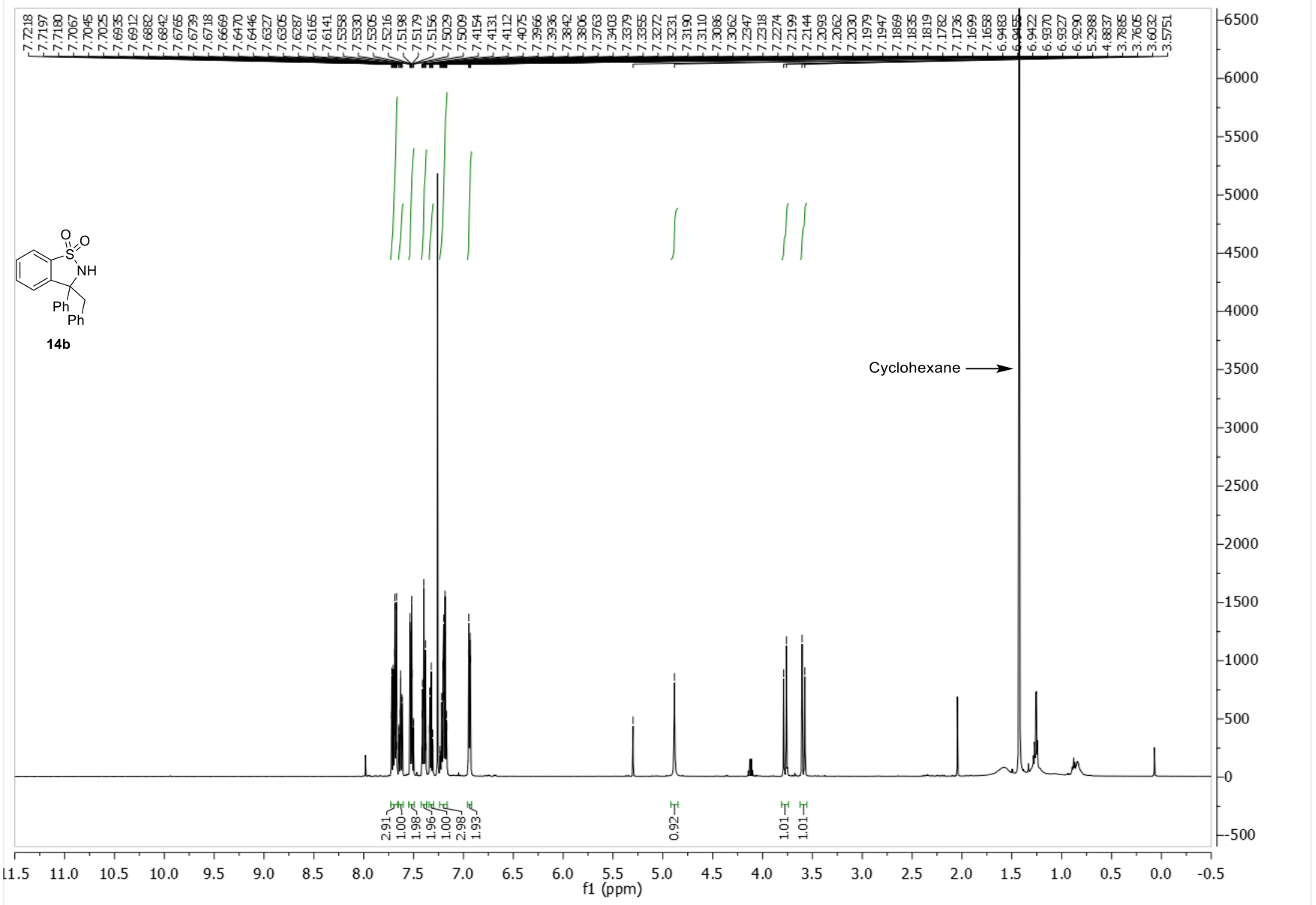
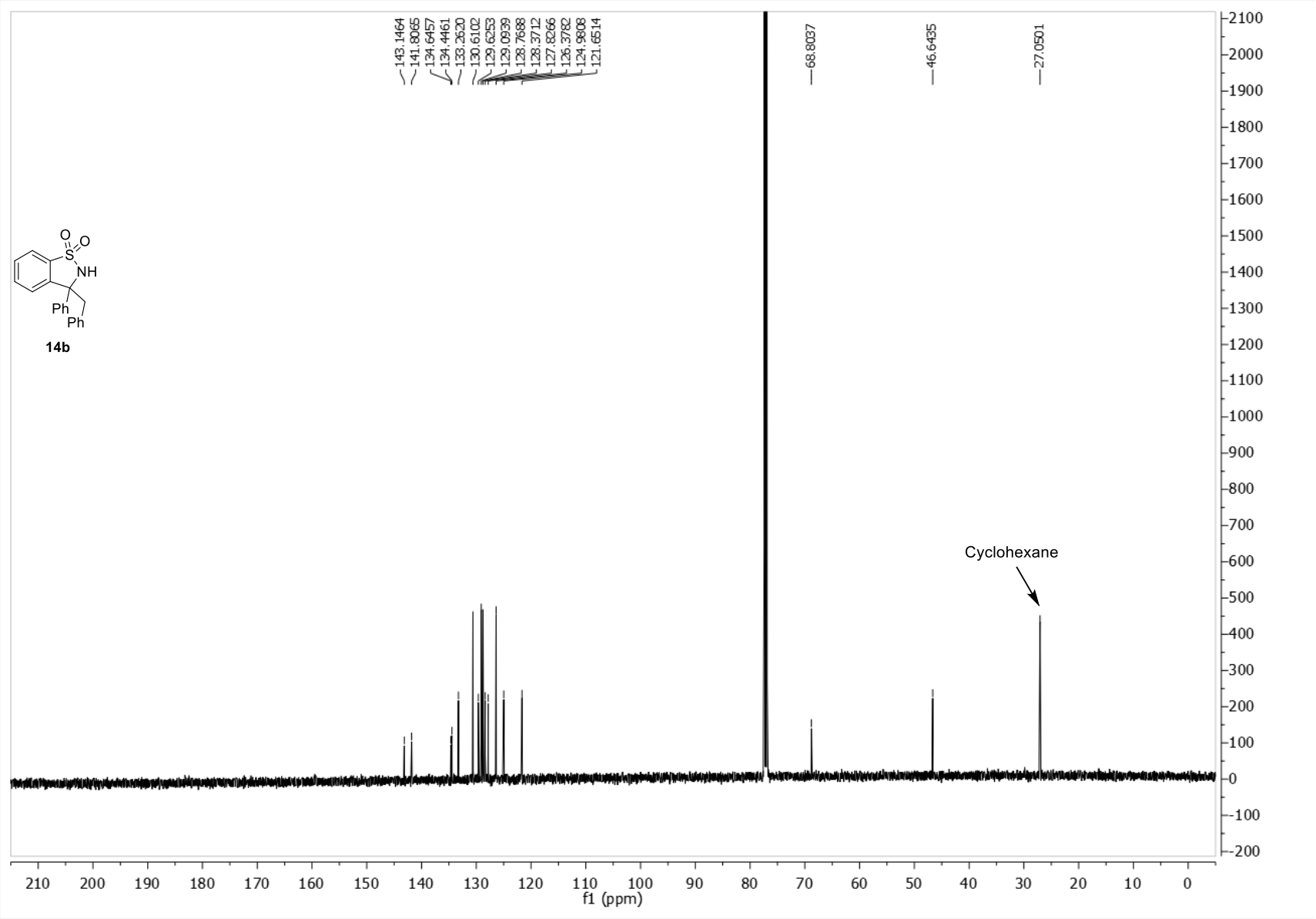
135.3159
133.3364
130.9193
129.4869
128.6015
127.5407
123.4996
121.5557
63.6328
47.7726
26.6931
DMF
O
O
S
NH
Ph
14a
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


14b
Cyclohexane
f1 (ppm)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134.4461
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130.6102
129.6253
129.0939
128.7688
128.3712
127.8266
126.3782
124.9808
121.6514
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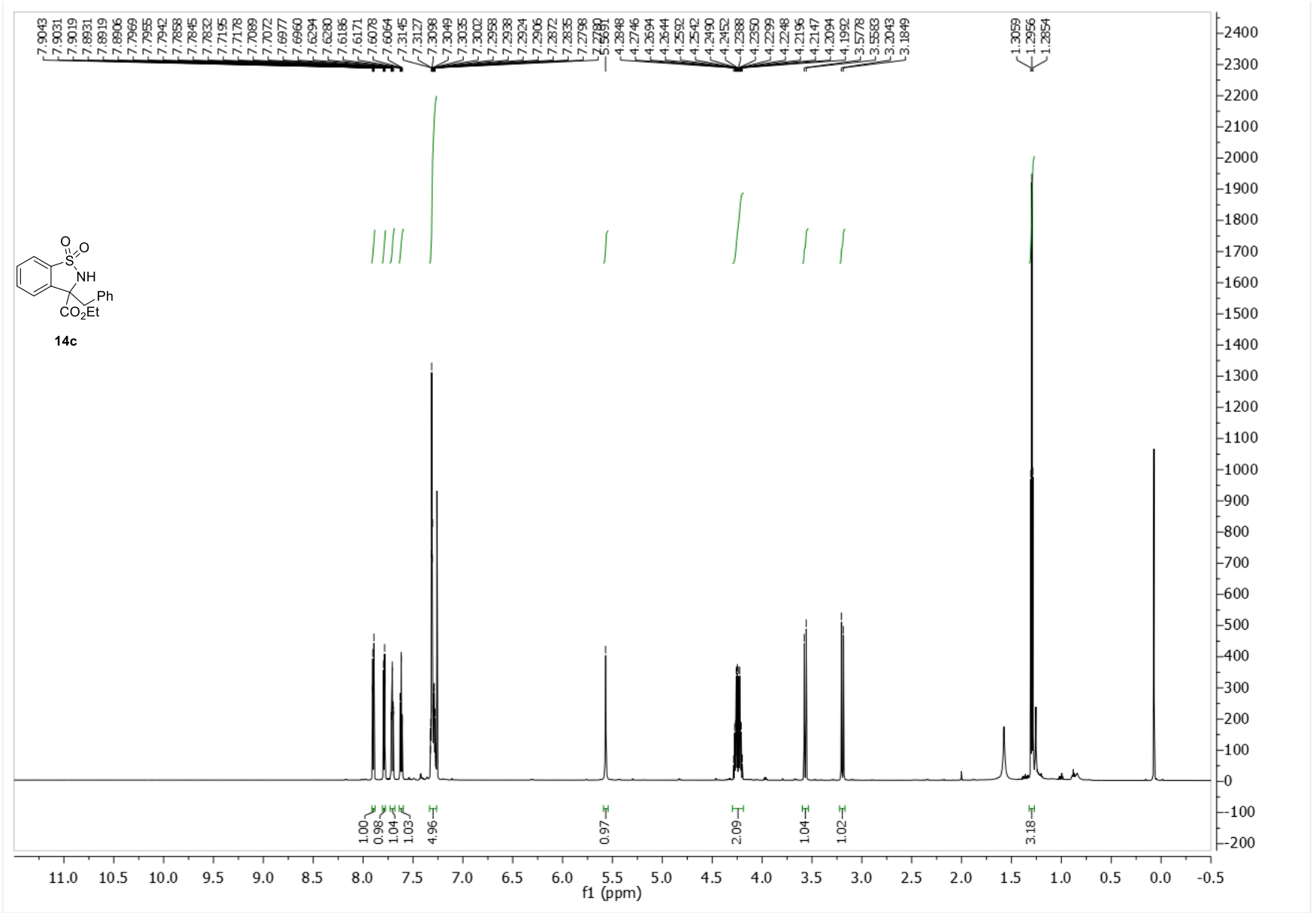
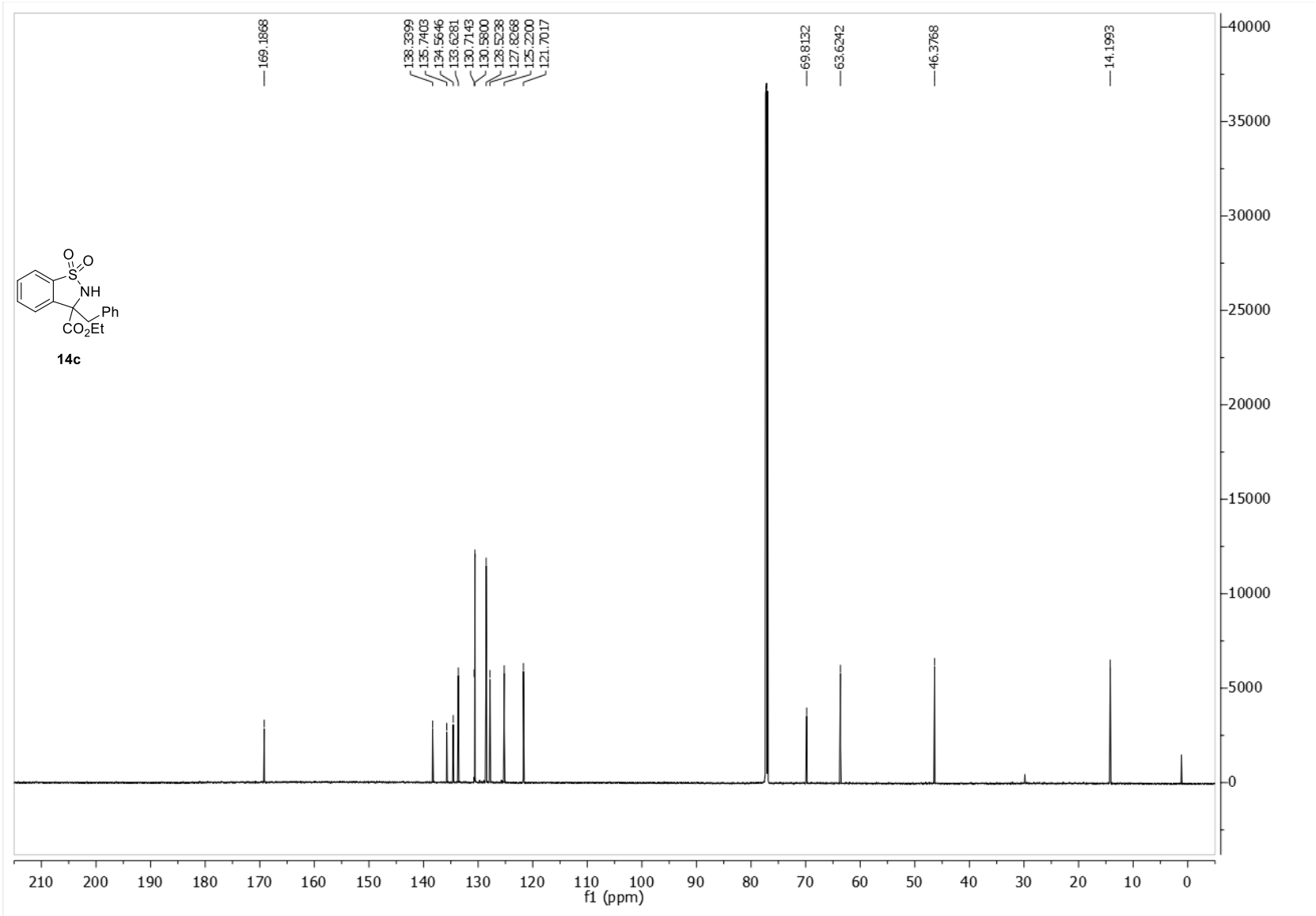
46.6435
27.0501
Cyclohexane
O
O
S
NH
Ph
Ph
14b
f1 (ppm)


14c
f1 (ppm)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134.5646
133.6281
130.7143
130.5800
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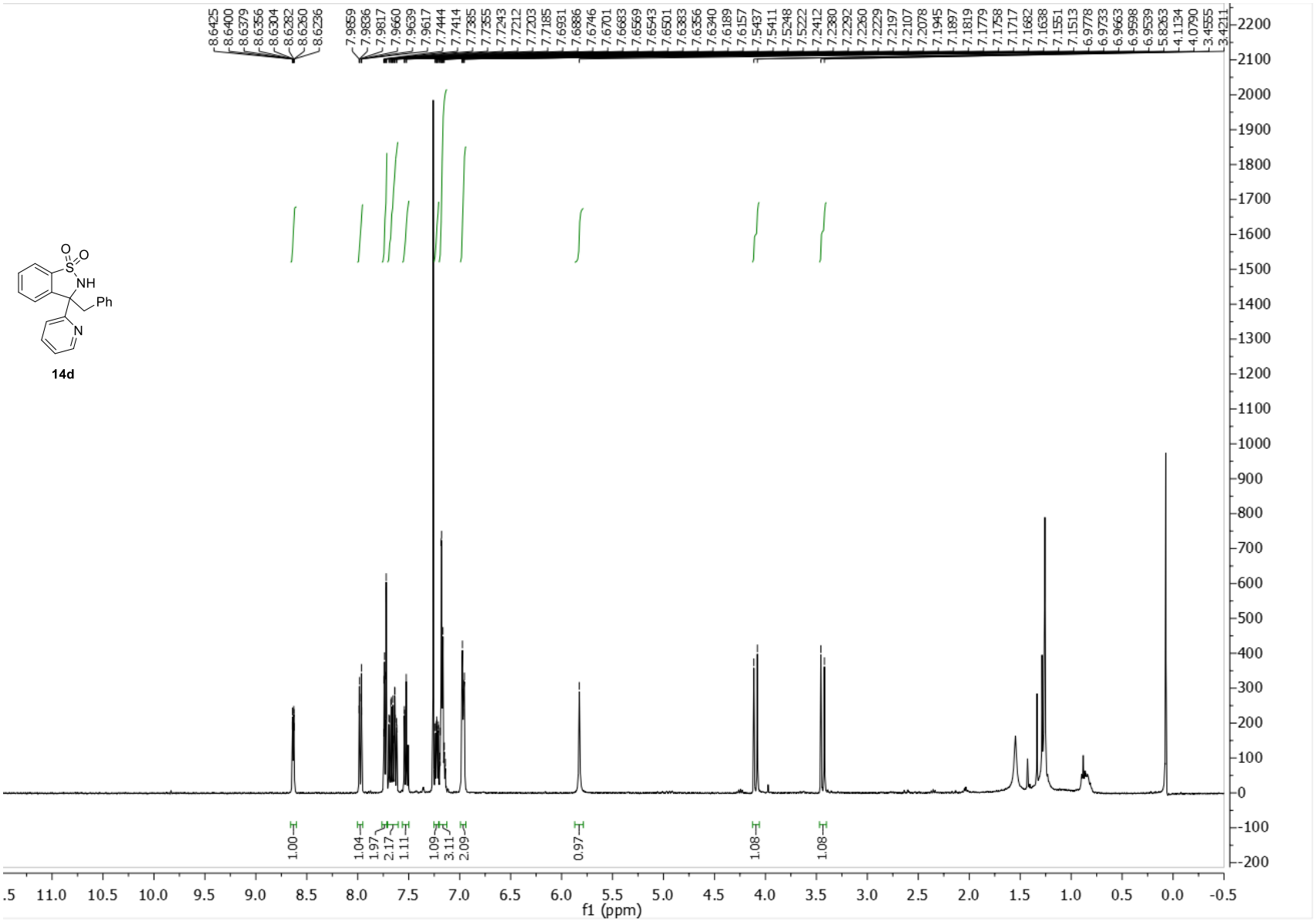
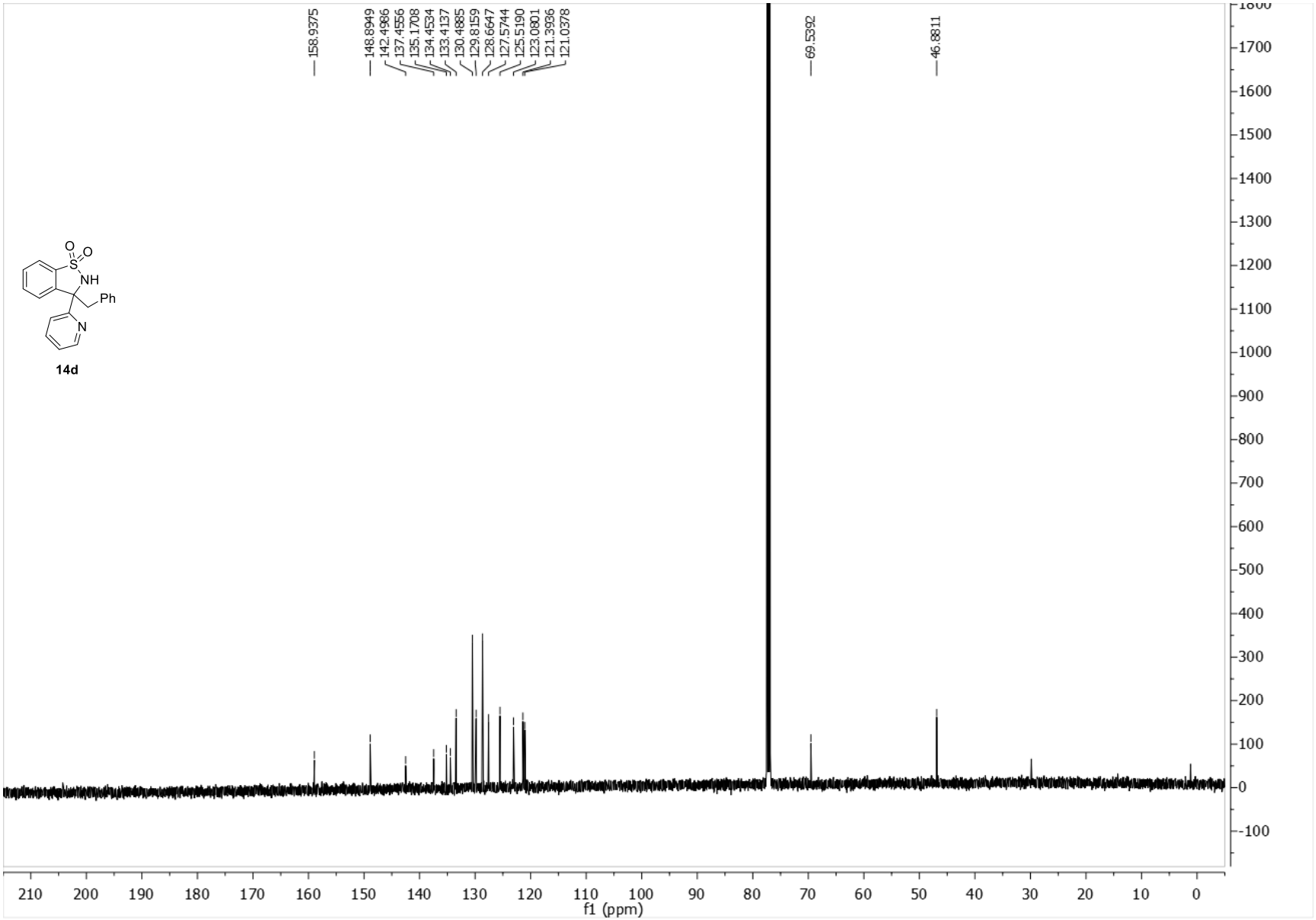
125.2200
121.7017
69.8132
63.6242
46.3768
14.1993
14c
f1 (ppm)


14d
f1 (ppm)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135.1708
134.4534
133.4137
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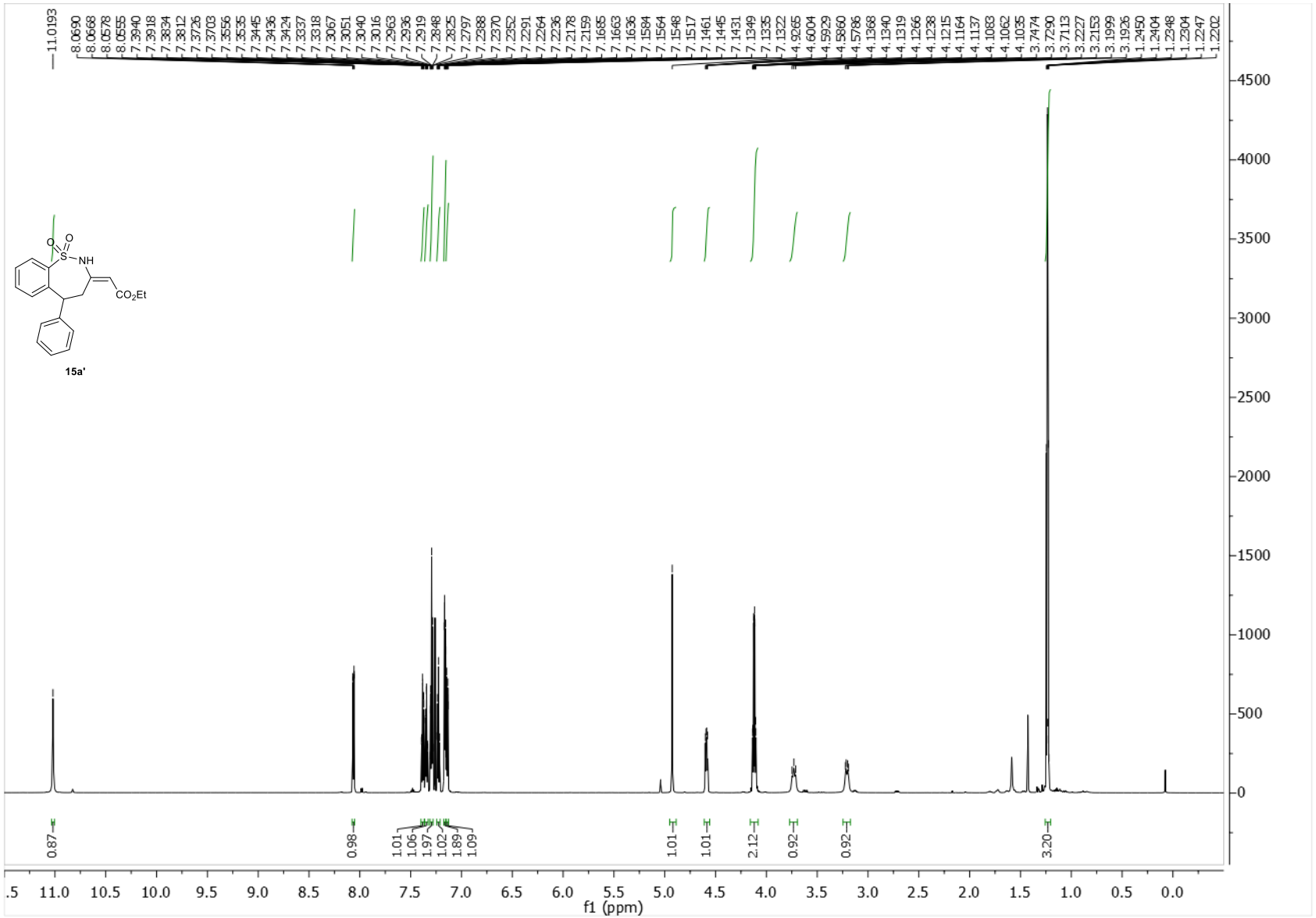
129.8159
128.6647
127.5744
125.5190
123.0801
121.3996
121.0378
69.5392
46.8811
O
O
S
NH
Ph
N
14d
f1 (ppm)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8.0668
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8.0555
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7.3918
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7.3812
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7.3703
7.3556
7.3535
7.3445
7.3436
7.3424
7.3337
7.3318
7.3067
7.3051
7.3040
7.3016
7.2963
7.2936
7.2919
7.2848
7.2825
7.2797
7.2388
7.2370
7.2352
7.2291
7.2264
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7.1663
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7.1564
7.1548
7.1517
7.1461
7.1445
7.1431
7.1349
7.1335
7.1322
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4.6004
4.5929
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4.1368
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4.1215
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4.1137
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4.1062
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3.7290
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3.2227
3.2153
3.1999
3.1926
1.2450
1.2404
1.2348
1.2304
1.2247
1.2202
O
O
S
NH
CO2Et
15a'
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0.87
0.98
1.01
1.06
1.97
1.02
1.89
1.09
1.01
1.01
2.12
0.92
0.92
3.20
.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
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1.0
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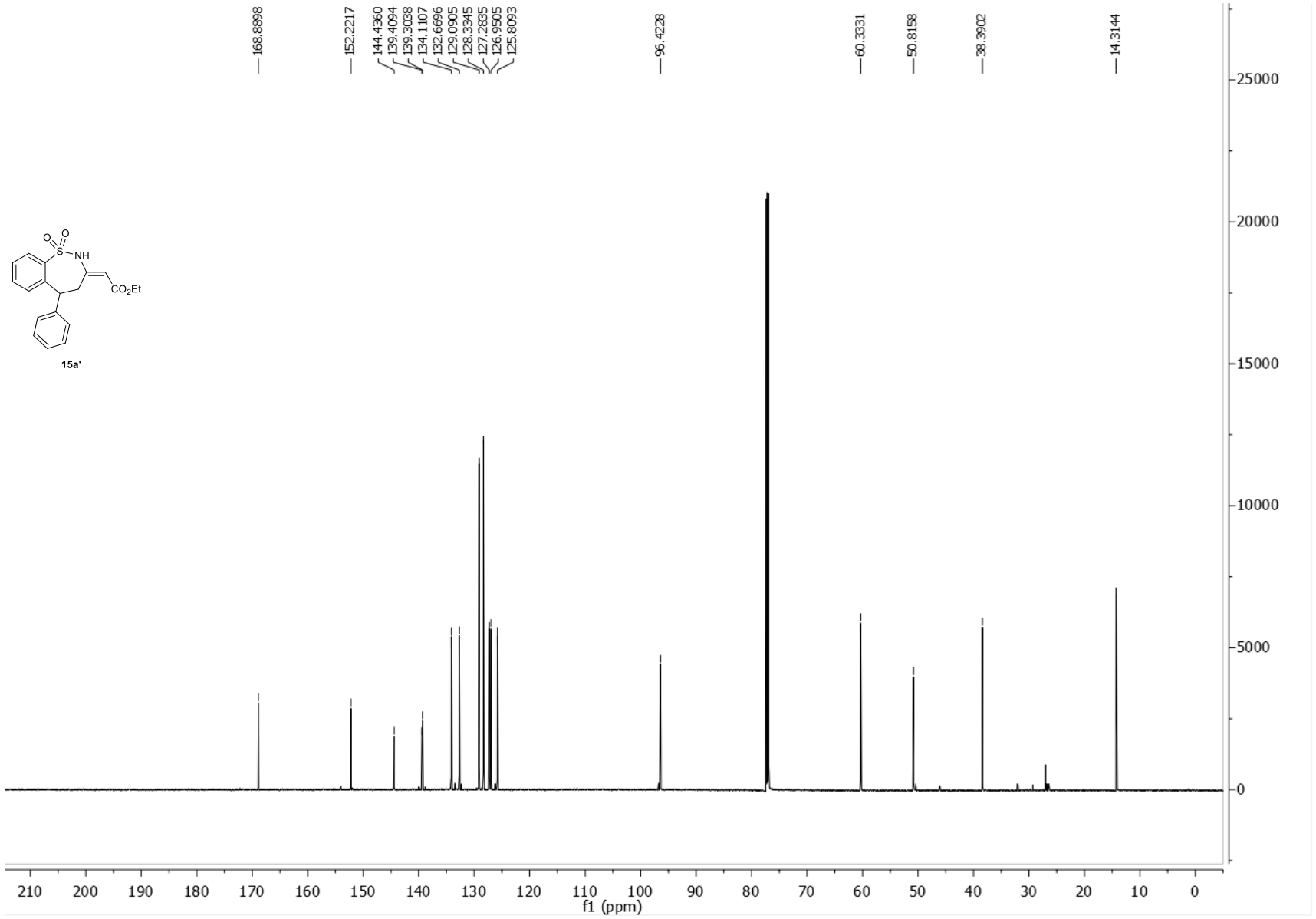
0.0
f1 (ppm)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126.9505
125.8093
96.4228
60.3331
50.8158
38.3902
14.3144
NH
CO2Et
15a'
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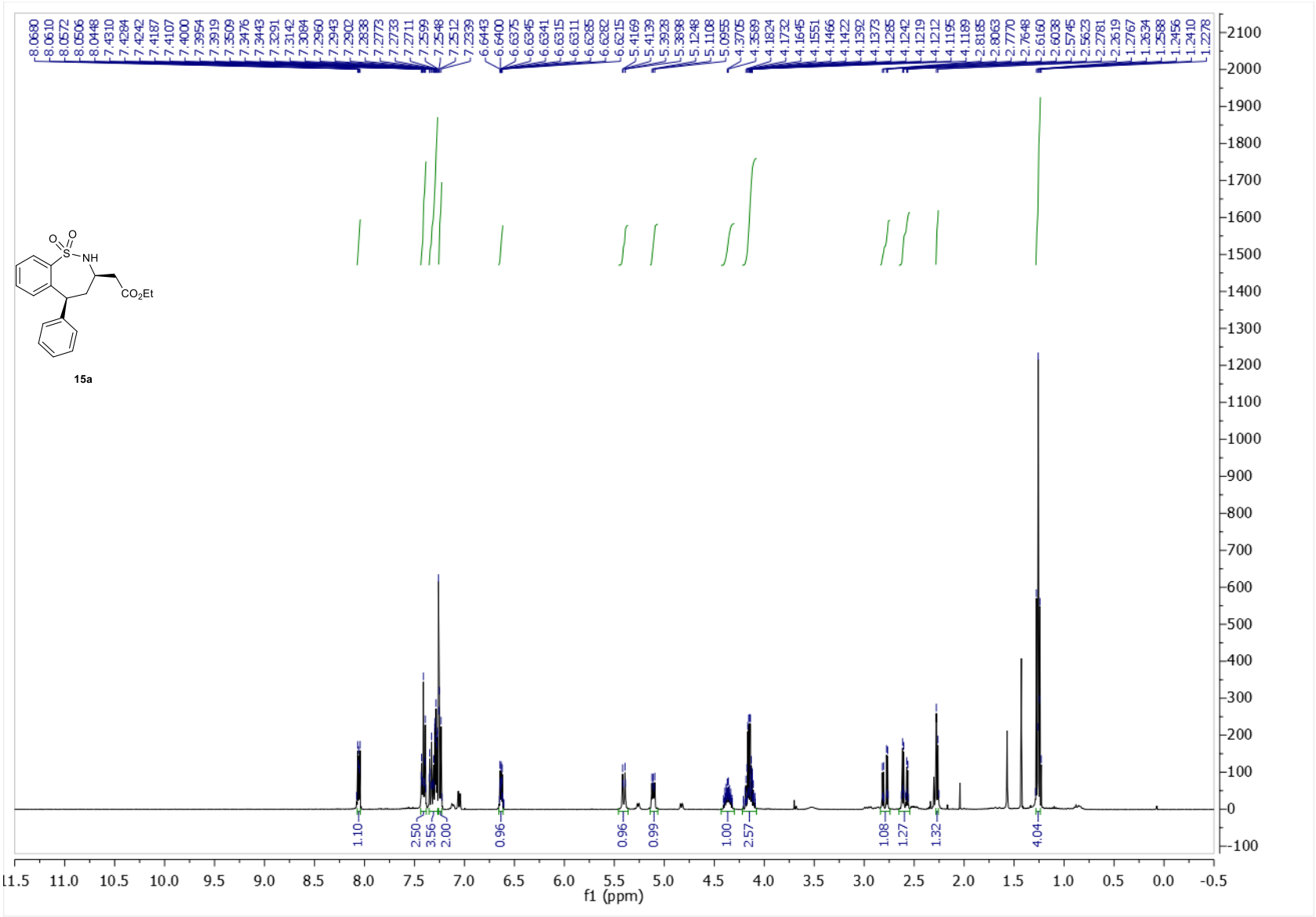
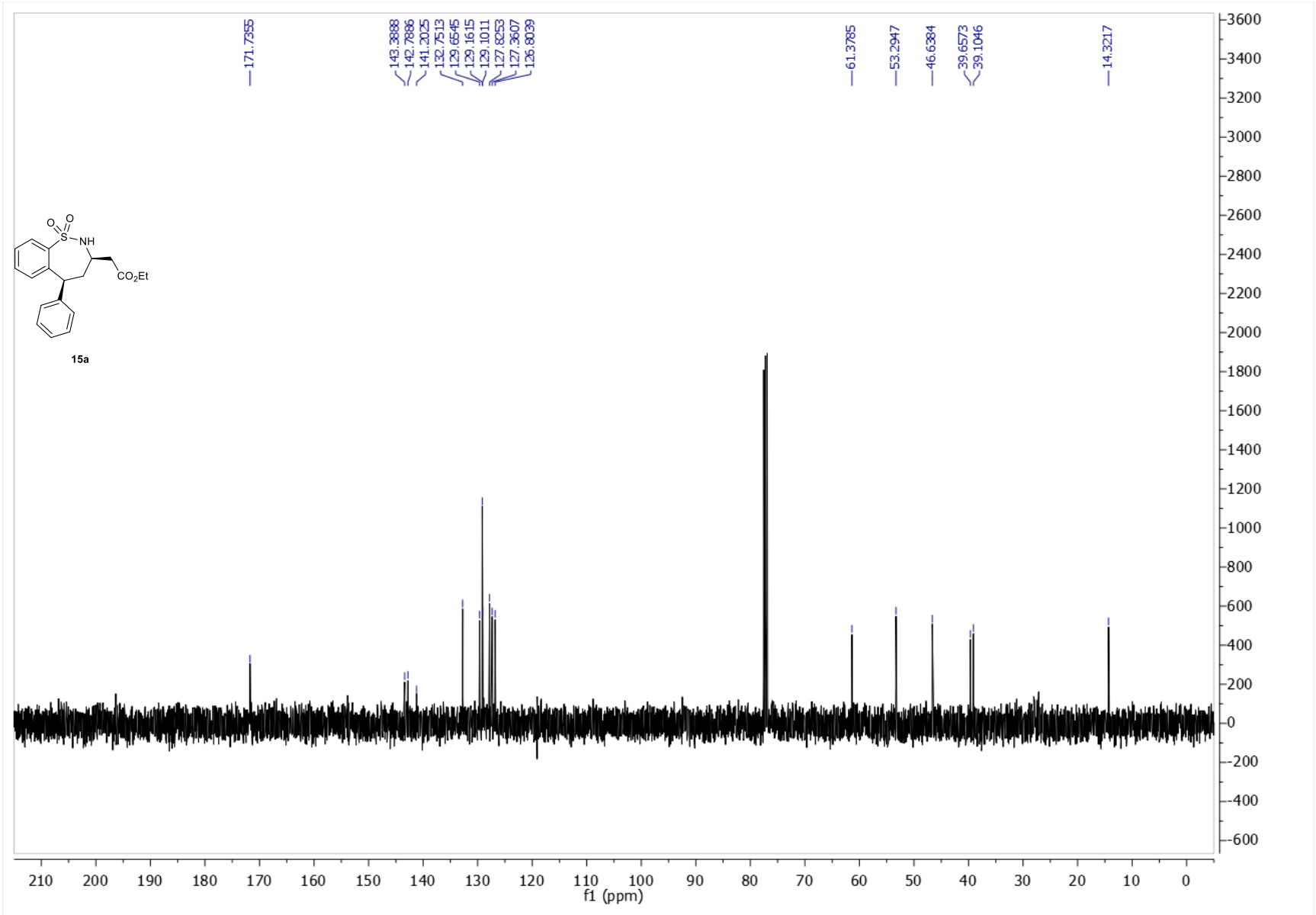
20000
15000
10000
5000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


15a
f1 (ppm)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141.2025
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129.1615
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127.8253
127.3607
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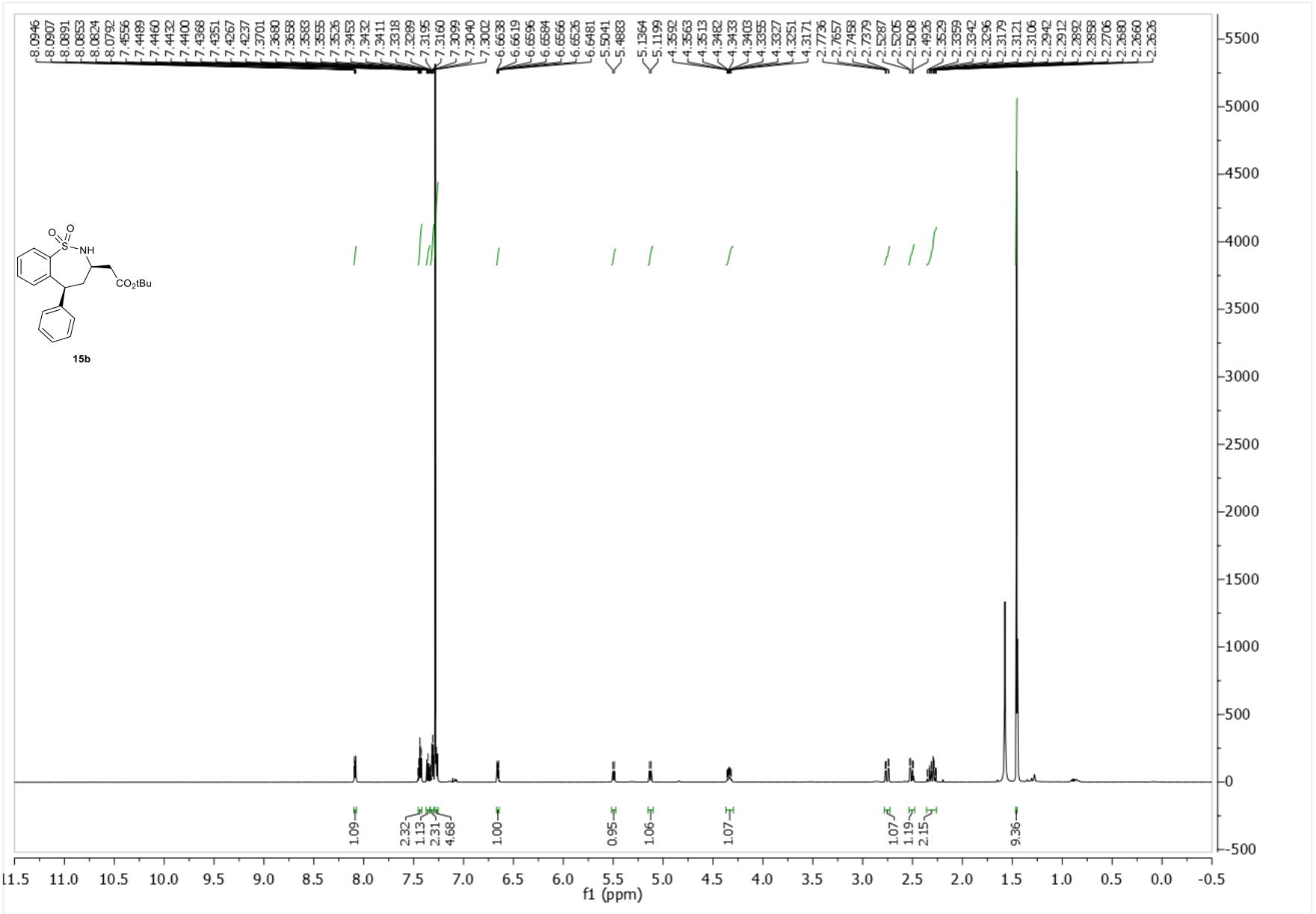
53.2947
46.6384
39.6573
39.1046
14.3217
NH
CO2Et
15a
f1 (ppm)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8.0891
8.0853
8.0824
8.0792
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7.4460
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7.4351
7.4267
7.4237
7.3701
7.3680
7.3658
7.3583
7.3555
7.3526
7.3453
7.3432
7.3411
7.3318
7.3289
7.3195
7.3160
7.3099
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7.3002
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6.6619
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6.6584
6.6566
6.6526
6.6481
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5.4983
5.1364
5.1199
4.3592
4.3563
4.3513
4.3482
4.3433
4.3403
4.3355
4.3327
4.3251
4.3171
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2.3179
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2.3106
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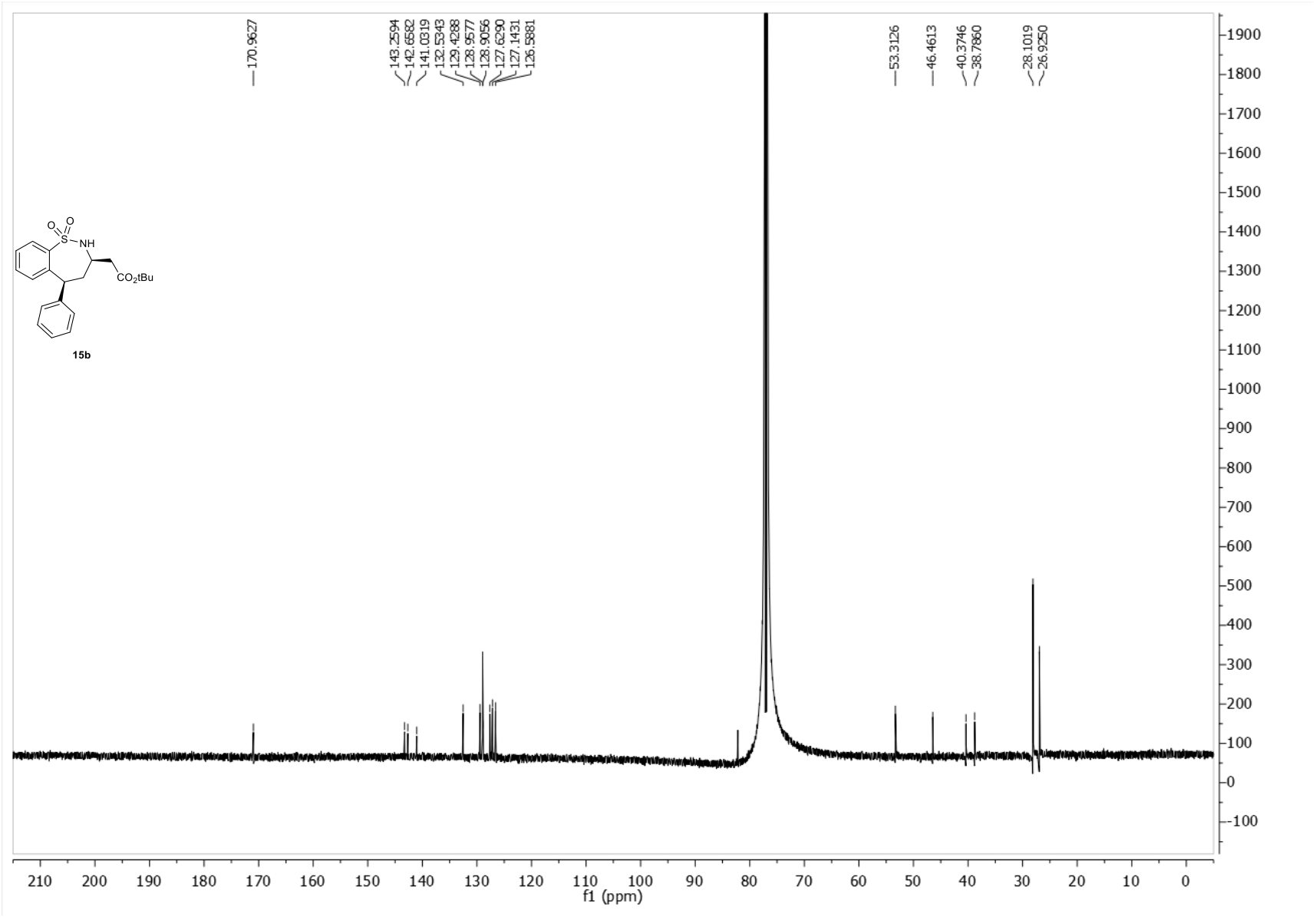
2.2912
2.2892
2.2858
2.2706
2.2680
2.2660
2.2626
O
O
S
NH
CO2tBu
15b
1.09
2.32
1.13
2.31
4.68
1.00
0.95
1.06
1.07
1.07
1.19
2.15
9.36
f1 (ppm)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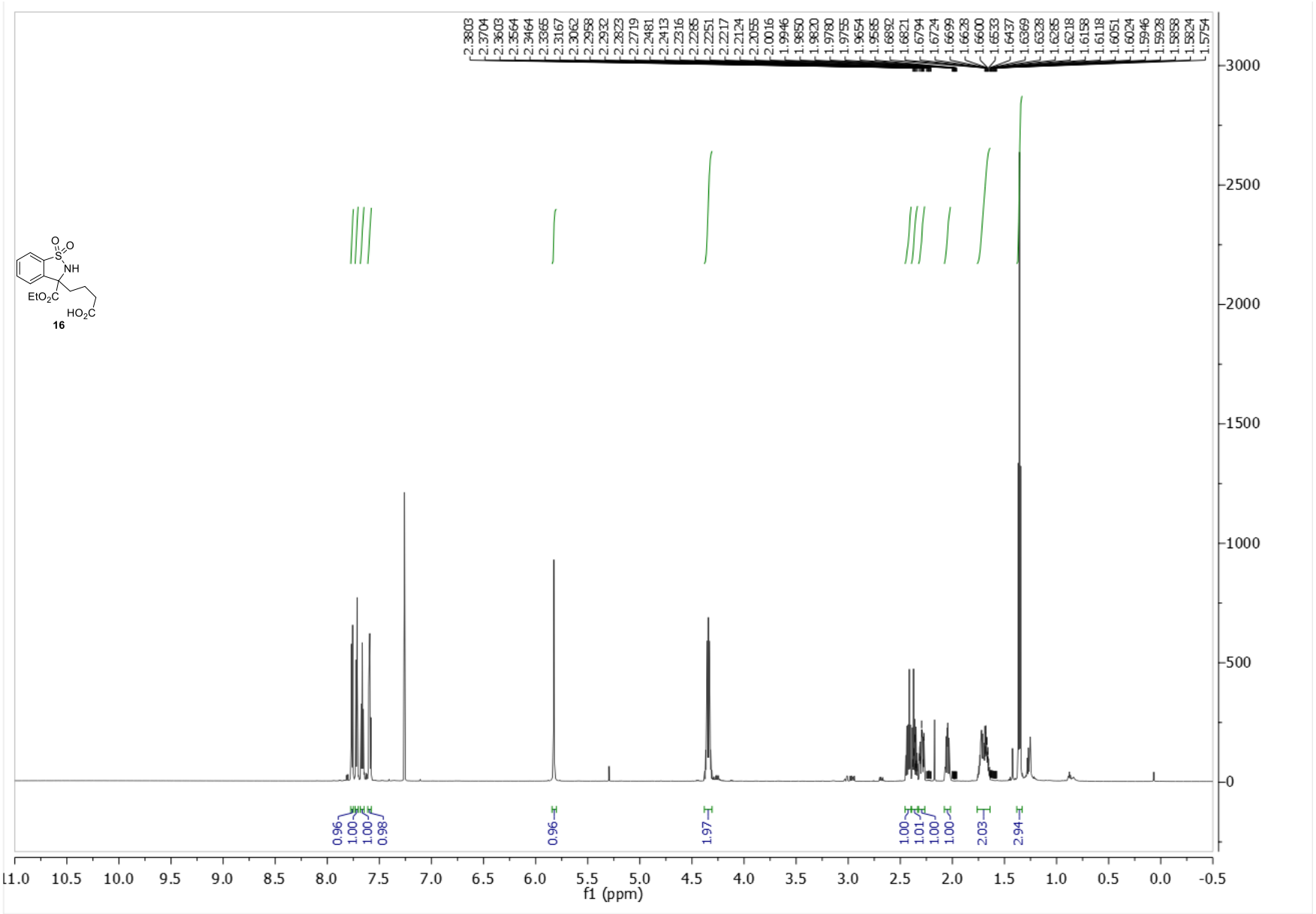
132.5343
129.4288
128.9577
128.9056
127.6290
127.1431
126.5881
53.3126
46.4613
40.3746
38.7860
28.1019
26.9250
NH
CO2tBu
15b
f1 (ppm)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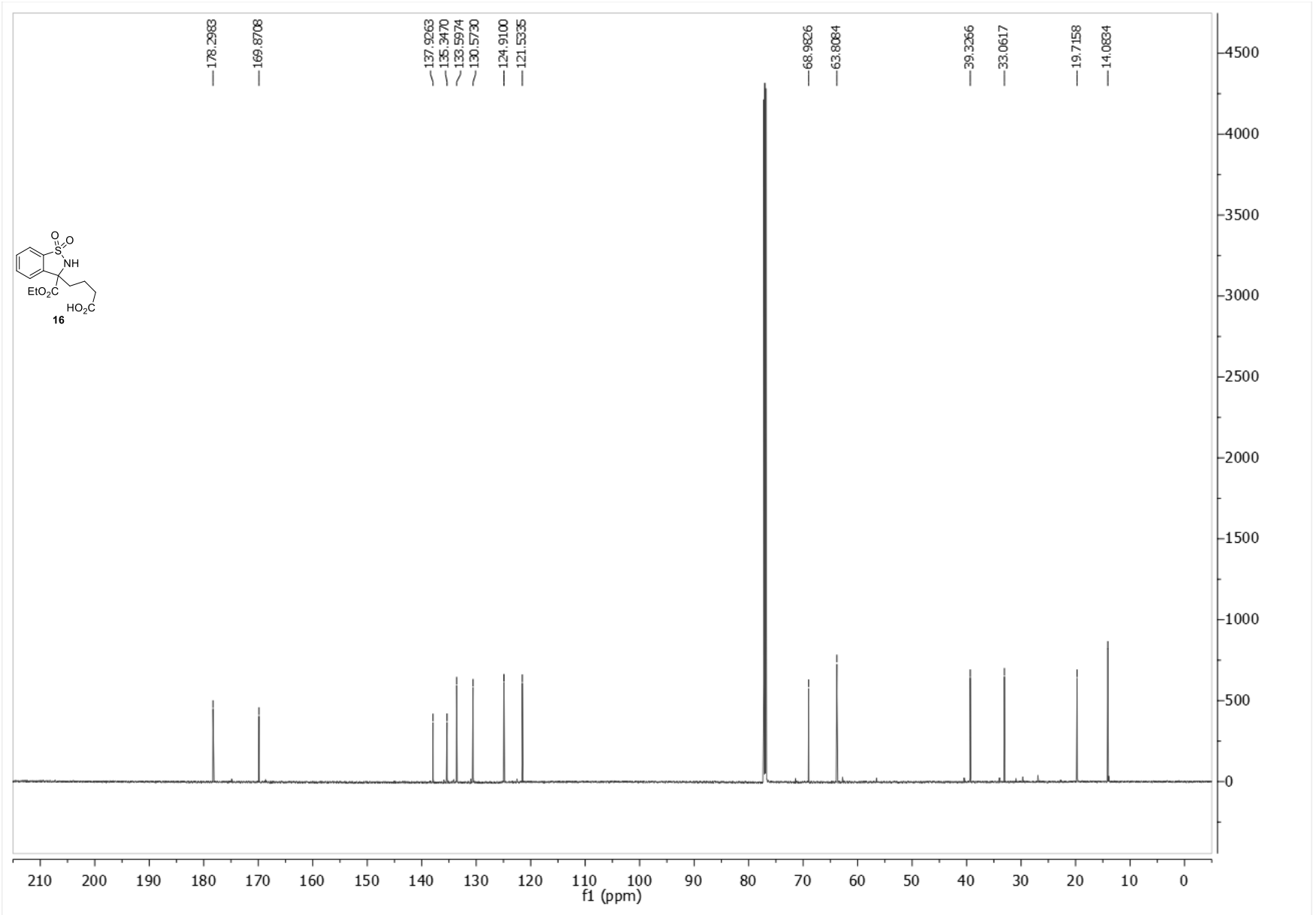
2.3365
2.3167
2.3062
2.2958
2.2932
2.2823
2.2719
2.2481
2.2413
2.2316
2.2285
2.2251
2.2217
2.2124
2.2055
2.0016
1.9946
1.9850
1.9820
1.9780
1.9755
1.9654
1.9585
1.6892
1.6821
1.6794
1.6724
1.6699
1.6628
1.6600
1.6533
1.6437
1.6369
1.6328
1.6285
1.6218
1.6158
1.6118
1.6051
1.6024
1.5946
1.5928
1.5858
1.5824
1.5754
NH
EtO2C
HO2C
16
0.96
1.00
1.00
0.98
0.96
1.97
1.00
1.01
1.00
1.00
2.03
2.94
f1 (ppm)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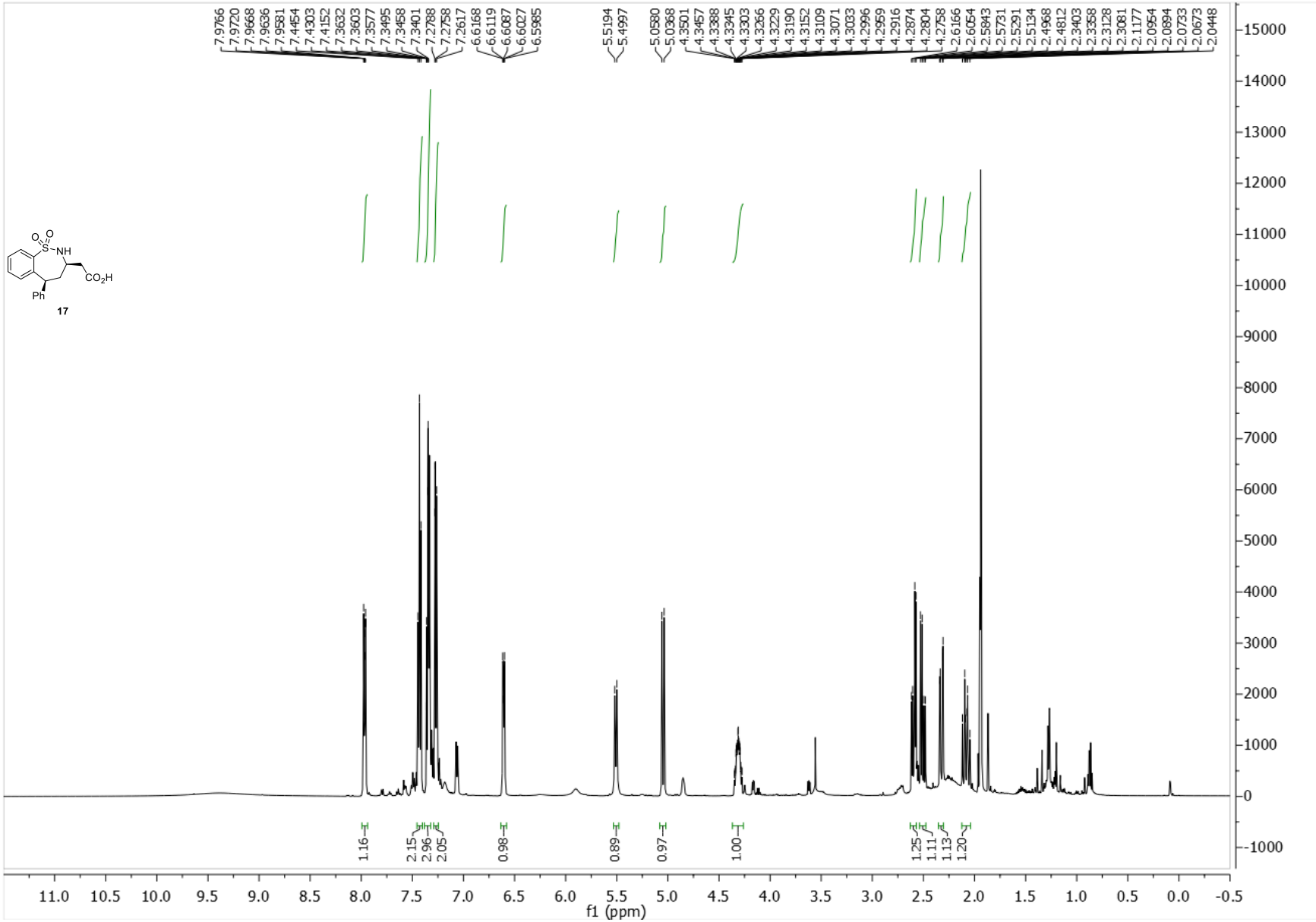
39.3266
33.0617
19.7158
14.0834
O
O
S
NH
EtO2C
HO2C
16
4500
4000
3500
3000
2500
2000
1500
1000
500
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.3577
7.3495
7.3458
7.3401
7.2788
7.2758
7.2617
6.6168
6.6119
6.6087
6.6027
6.5985
5.5194
5.4997
5.0580
5.0368
4.3501
4.3457
4.3388
4.3345
4.3303
4.3266
4.3229
4.3190
4.3152
4.3109
4.3071
4.3033
4.2996
4.2959
4.2916
4.2874
4.2804
4.2758
2.6166
2.6054
2.5843
2.5731
2.5291
2.5134
2.4968
2.4812
2.3403
2.3358
2.3128
2.3081
2.1177
2.0954
2.0894
2.0733
2.0673
2.0448
O
O
S
NH
CO2H
Ph
17
1.16
2.15
2.96
2.05
0.98
0.89
0.97
1.00
1.25
1.11
1.13
1.20
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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3.0
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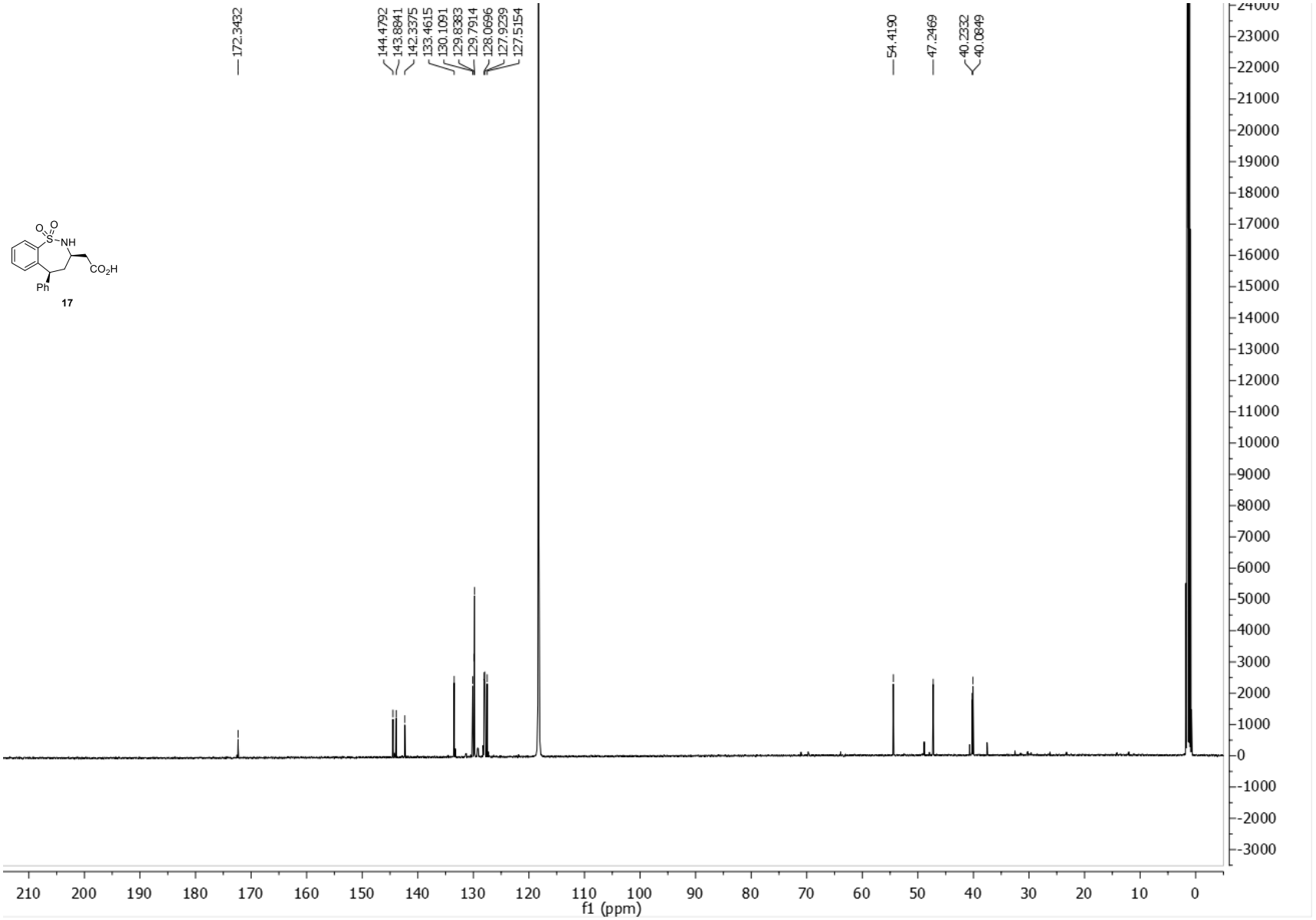
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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143.8841
142.3375
133.4615
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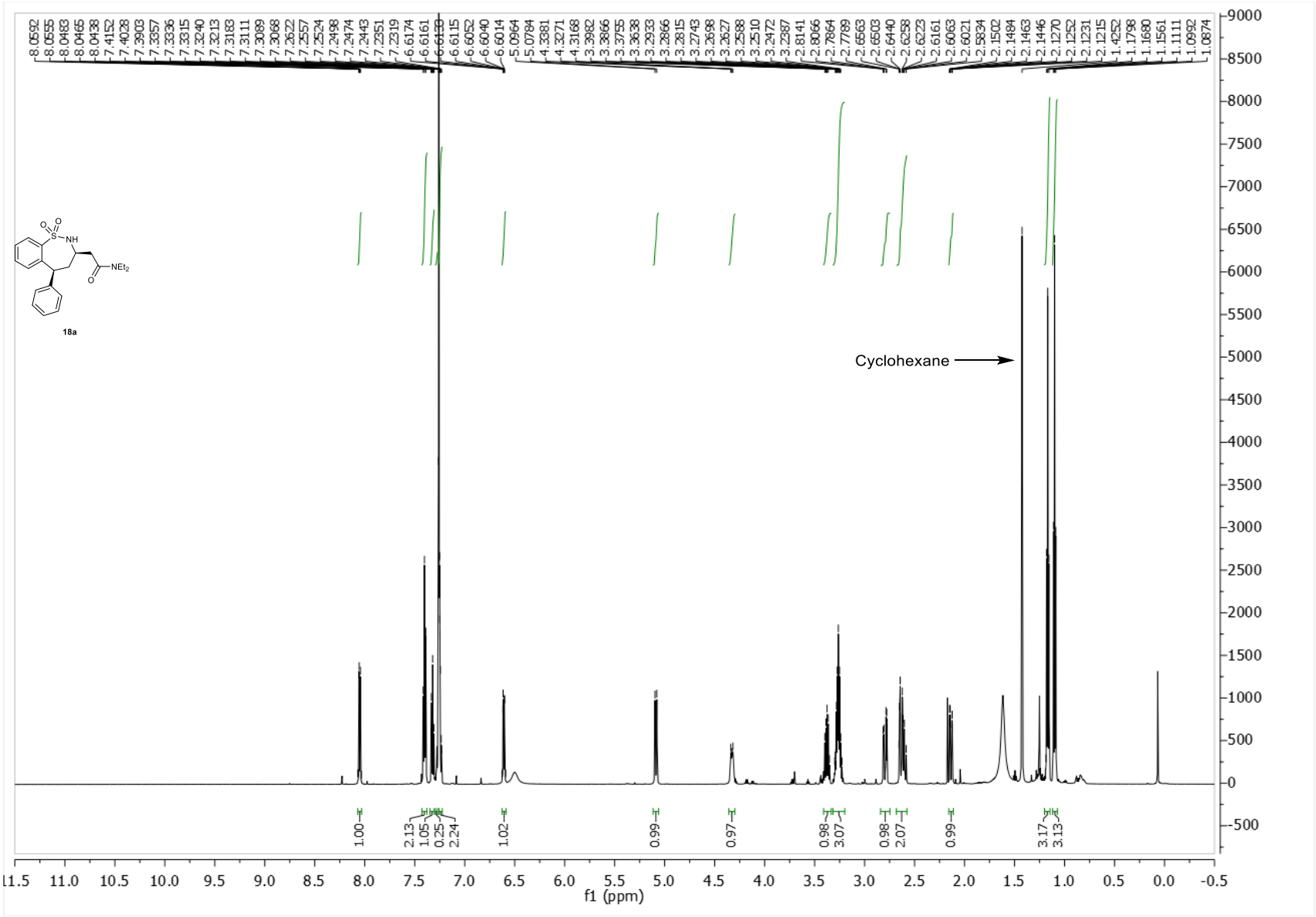
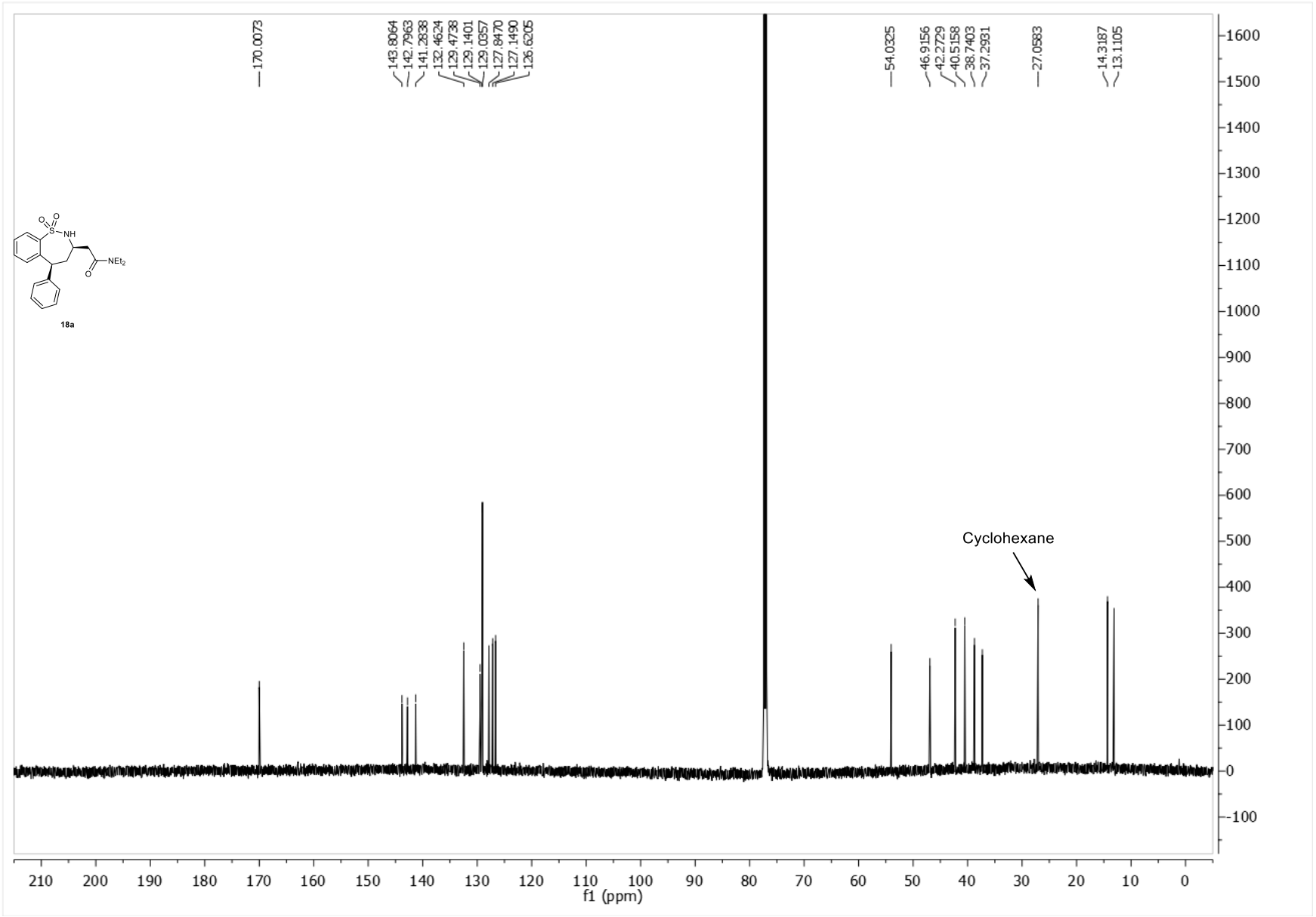
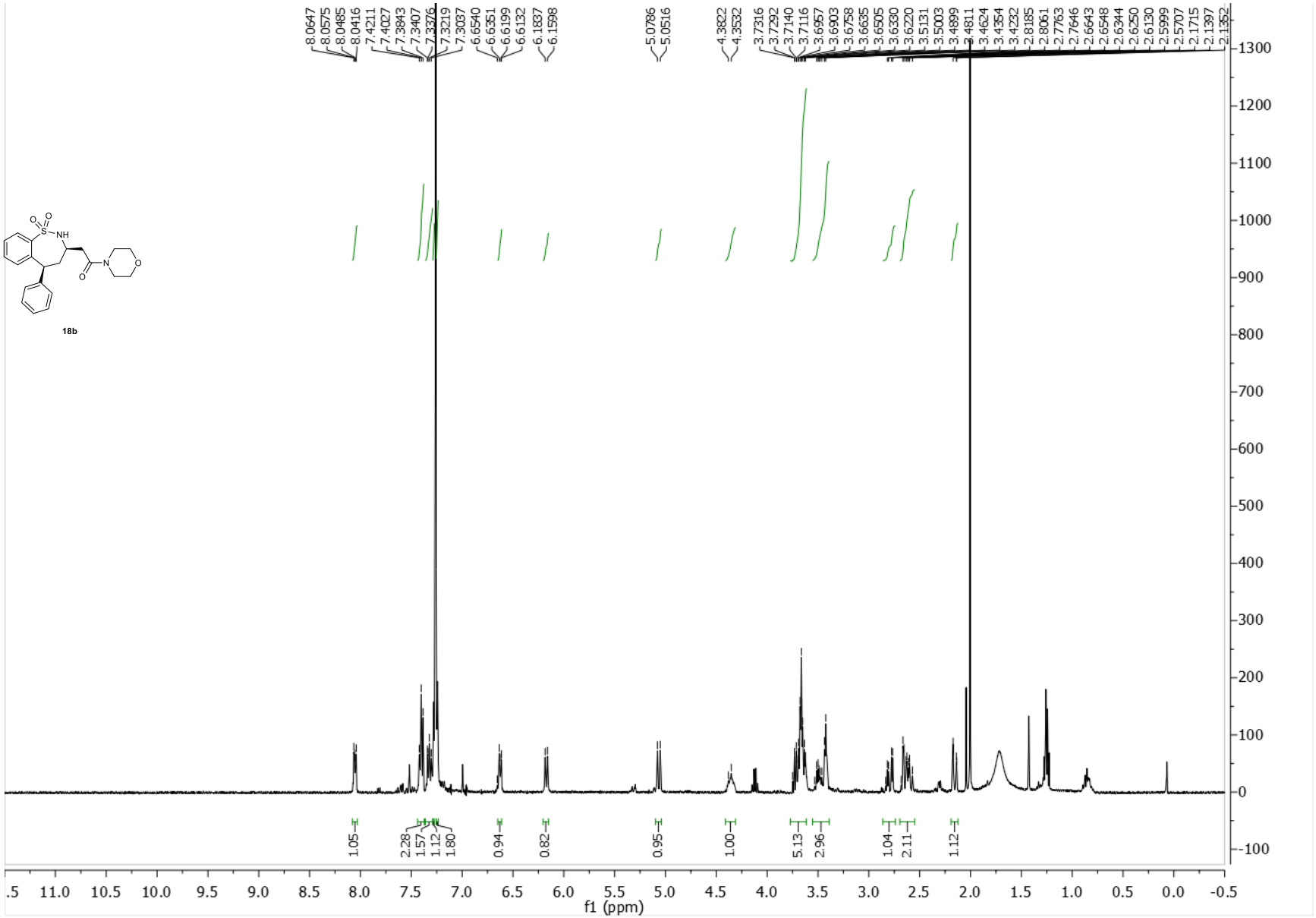
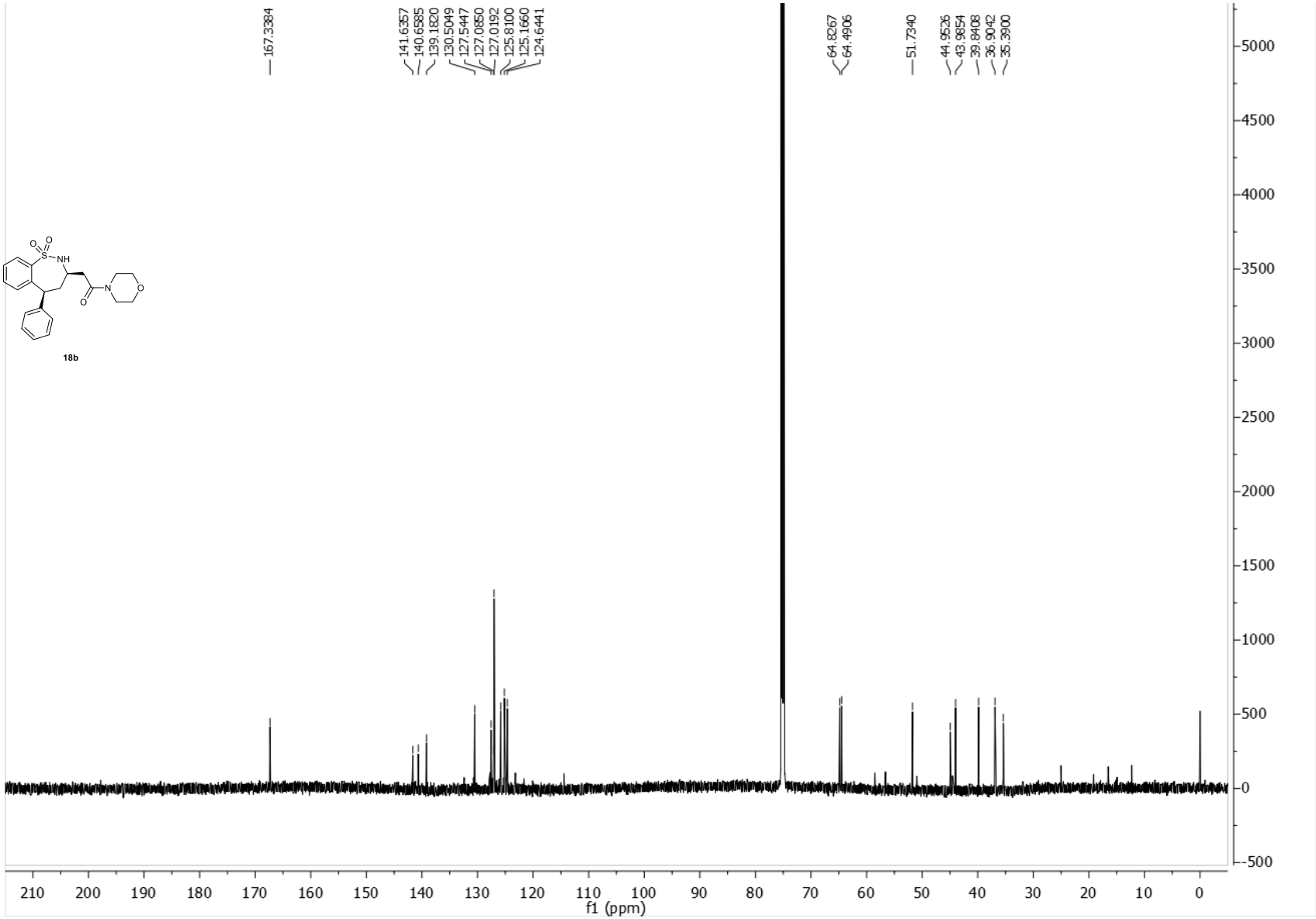
129.8383
129.7914
128.0696
127.9239
127.5154
54.4190
47.2469
40.2332
40.0849
O
O
S
NH
CO2H
Ph
17
f1 (ppm)


18a
Cyclohexane
f1 (ppm)


170.0073
143.8064
142.7963
141.2838
132.4624
129.4738
129.1401
129.0357
127.8470
127.1490
126.6205
54.0325
46.9156
42.2729
40.5158
38.7403
37.2931
27.0583
14.3187
13.1105
Cyclohexane
18a
f1 (ppm)


18b
f1 (ppm)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140.6585
139.1820
130.5049
127.5447
127.0850
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125.8100
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124.6441
64.8267
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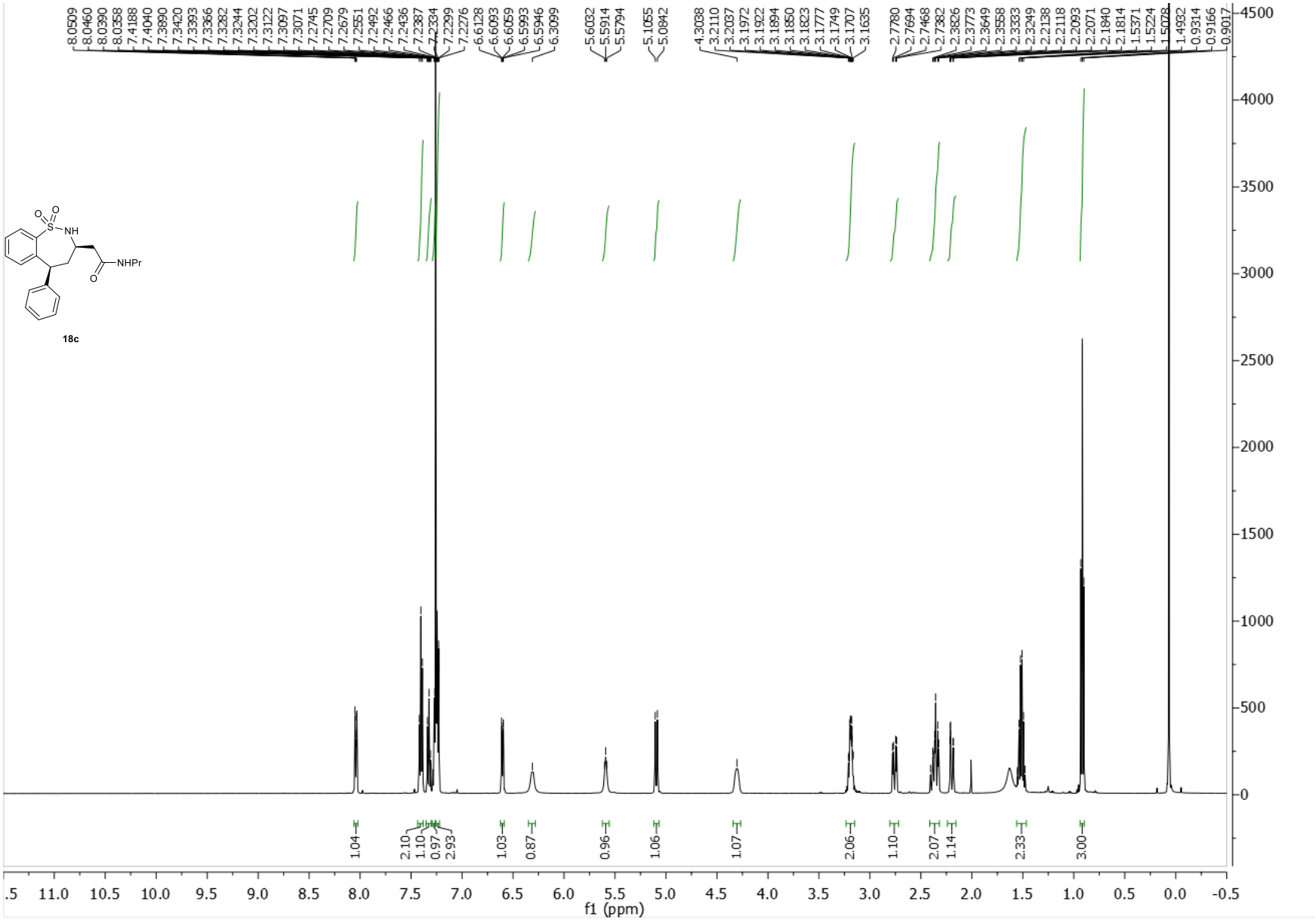
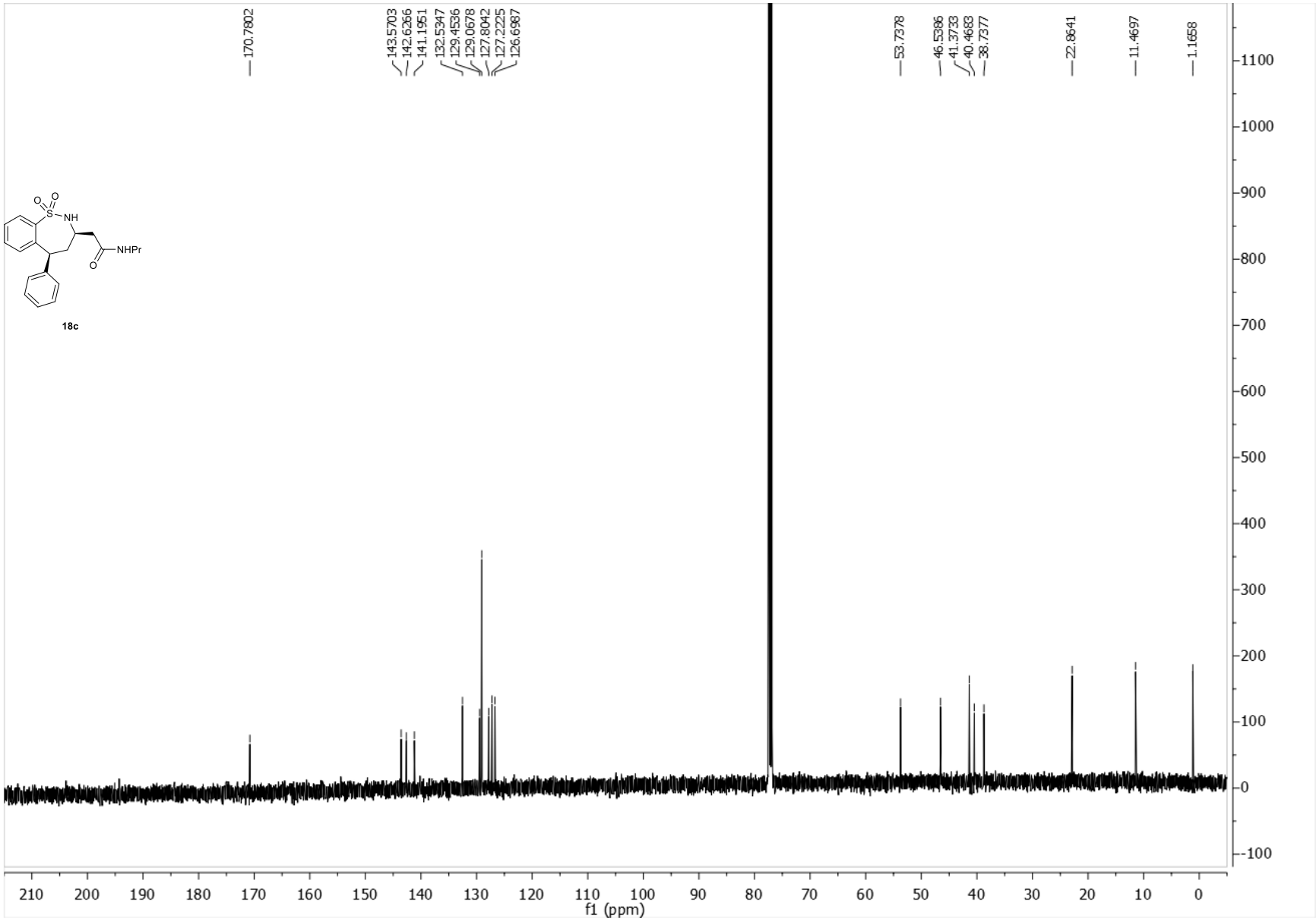
51.7340
44.9526
43.9854
39.8408
36.9042
35.3900
18b
f1 (ppm)


18c
f1 (ppm)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141.1951
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129.4536
129.0678
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127.2225
126.6987
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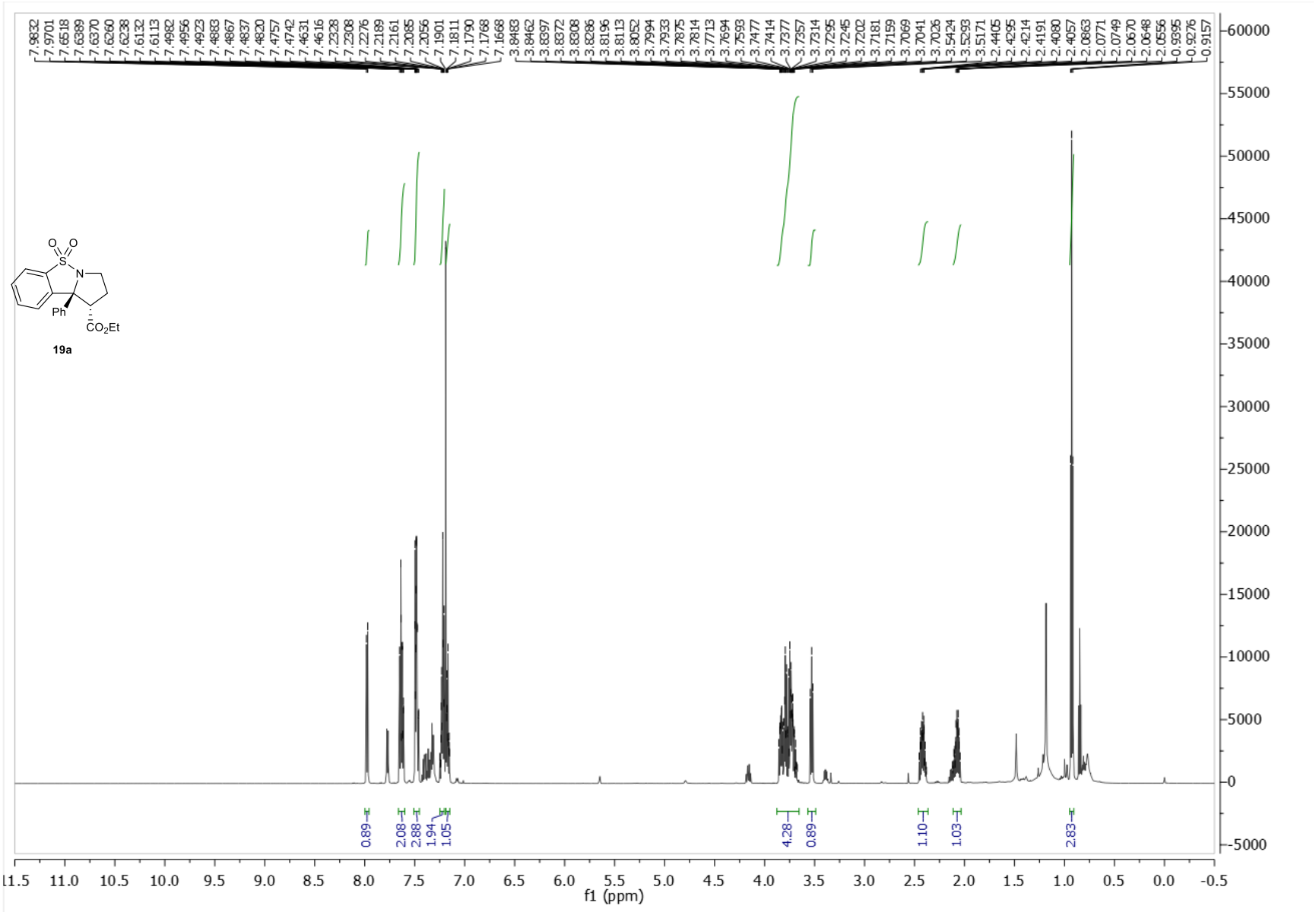
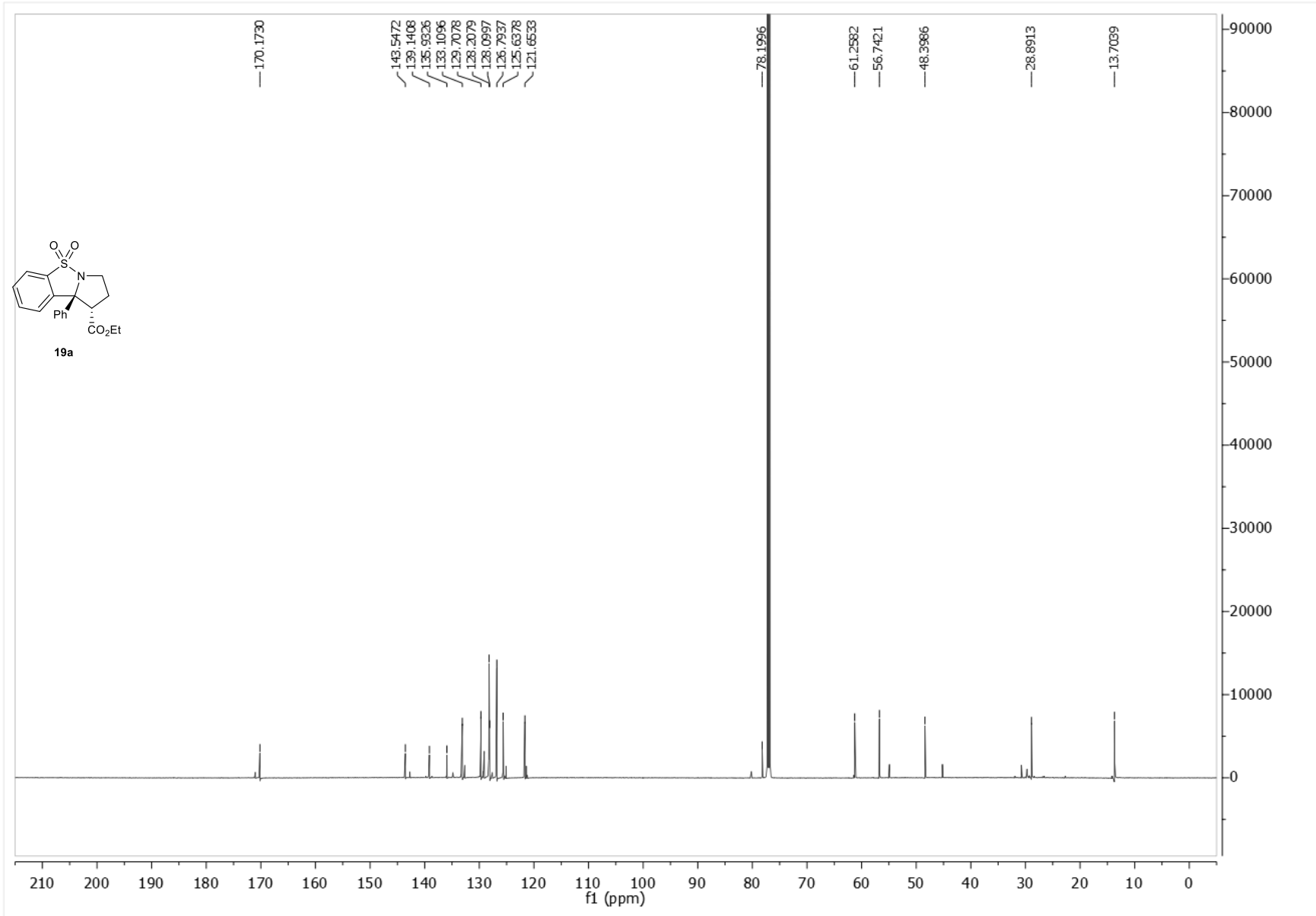
11.4697
1.1658
NHPr
18c
f1 (ppm)


19a
f1 (ppm)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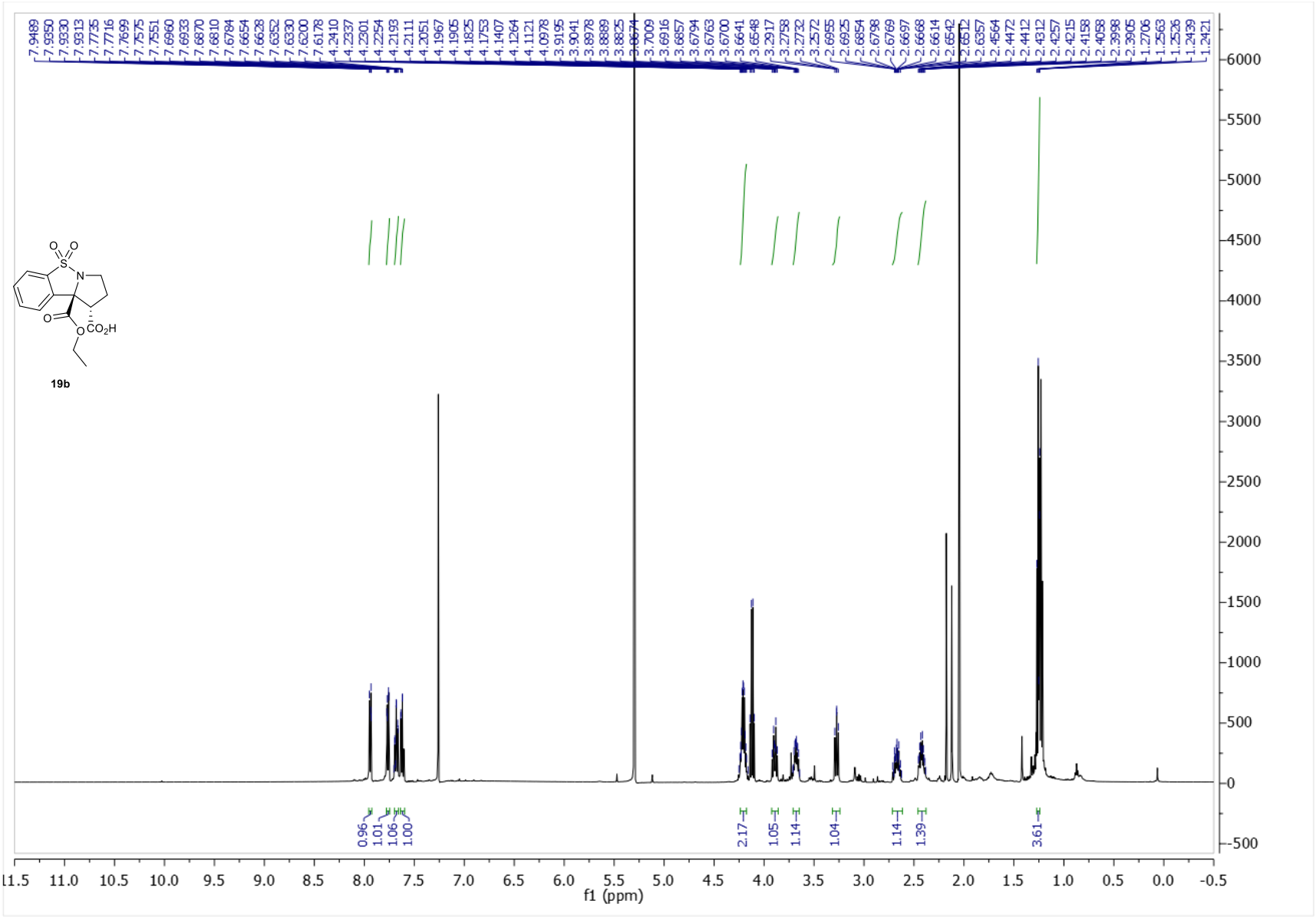
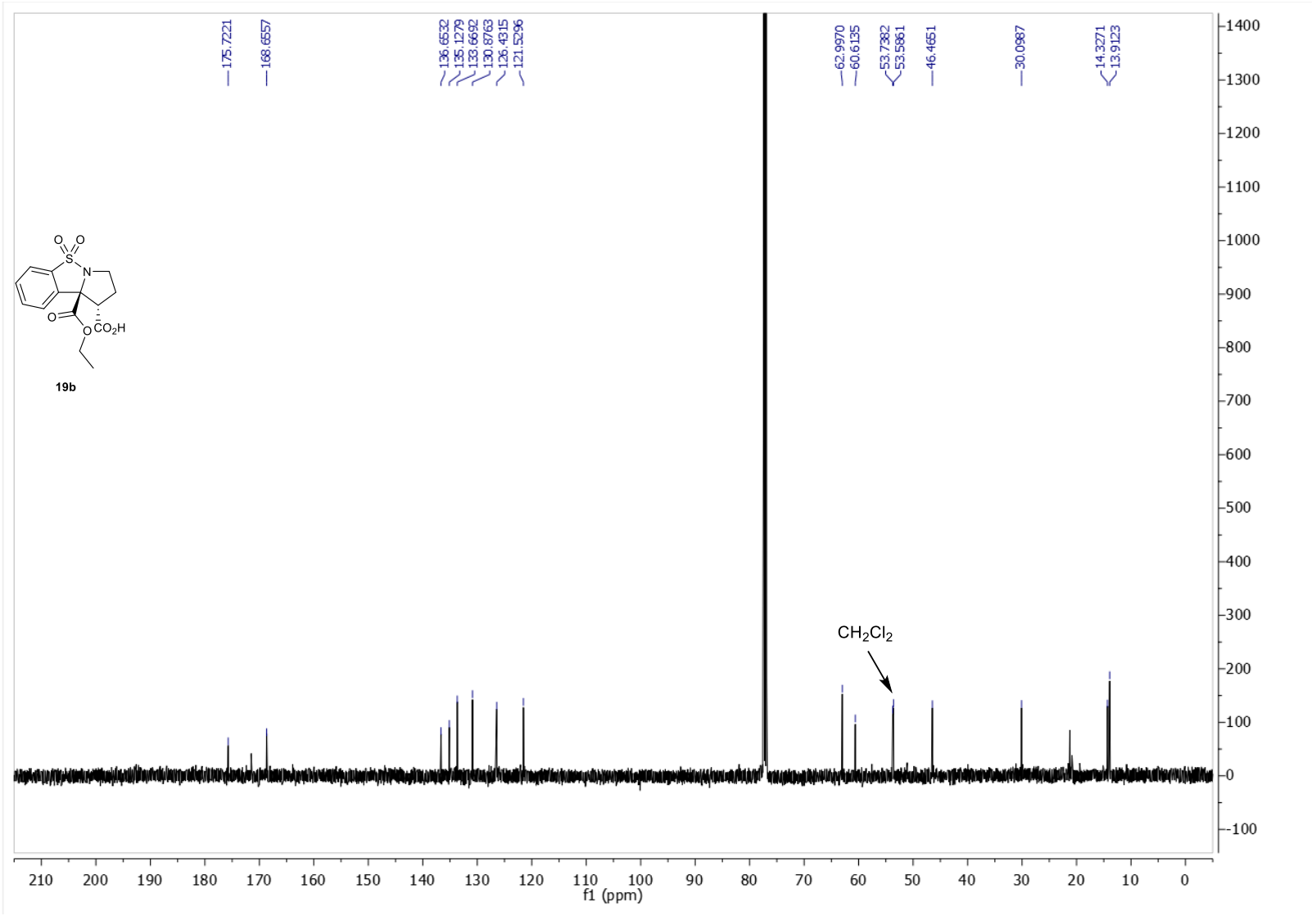
125.6378
121.6533
78.1996
61.2582
56.7421
48.3986
28.8913
13.7039
O
O
S
N
Ph
CO2Et
19a
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


19b
f1 (ppm)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126.4315
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62.9970
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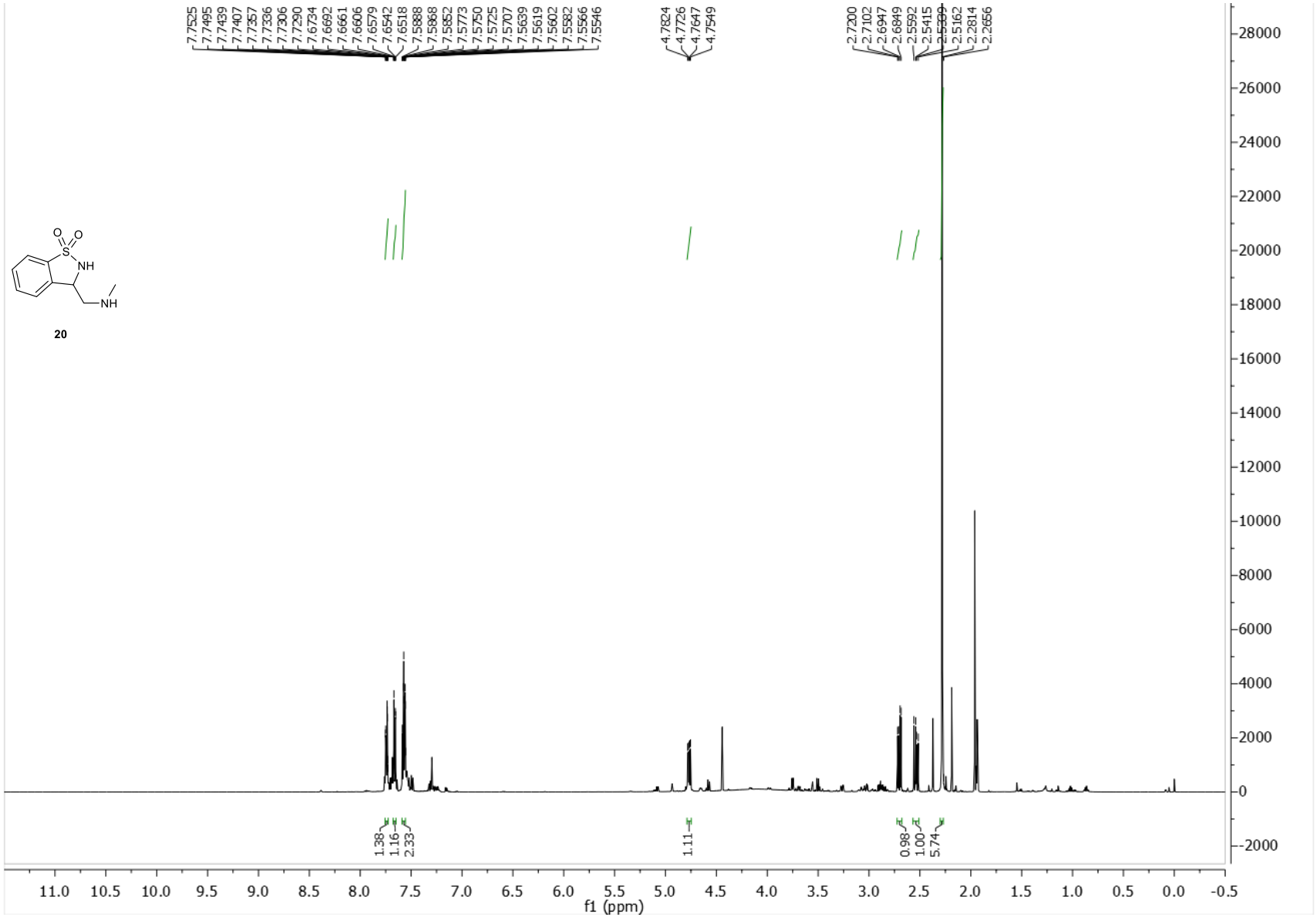
53.5861
46.4651
30.0987
14.3271
13.9123
CH2Cl2
19b
f1 (ppm)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7.6579
7.6542
7.6518
7.5888
7.5858
7.5852
7.5773
7.5750
7.5725
7.5707
7.5639
7.5619
7.5602
7.5582
7.5566
7.5546
4.7824
4.7726
4.7647
4.7549
2.7200
2.7102
2.6947
2.6849
2.5592
2.5415
2.5399
2.5162
2.2814
2.2656
O
O
S
NH
NH
20
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
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1.16
2.33
1.11
0.98
1.00
5.74
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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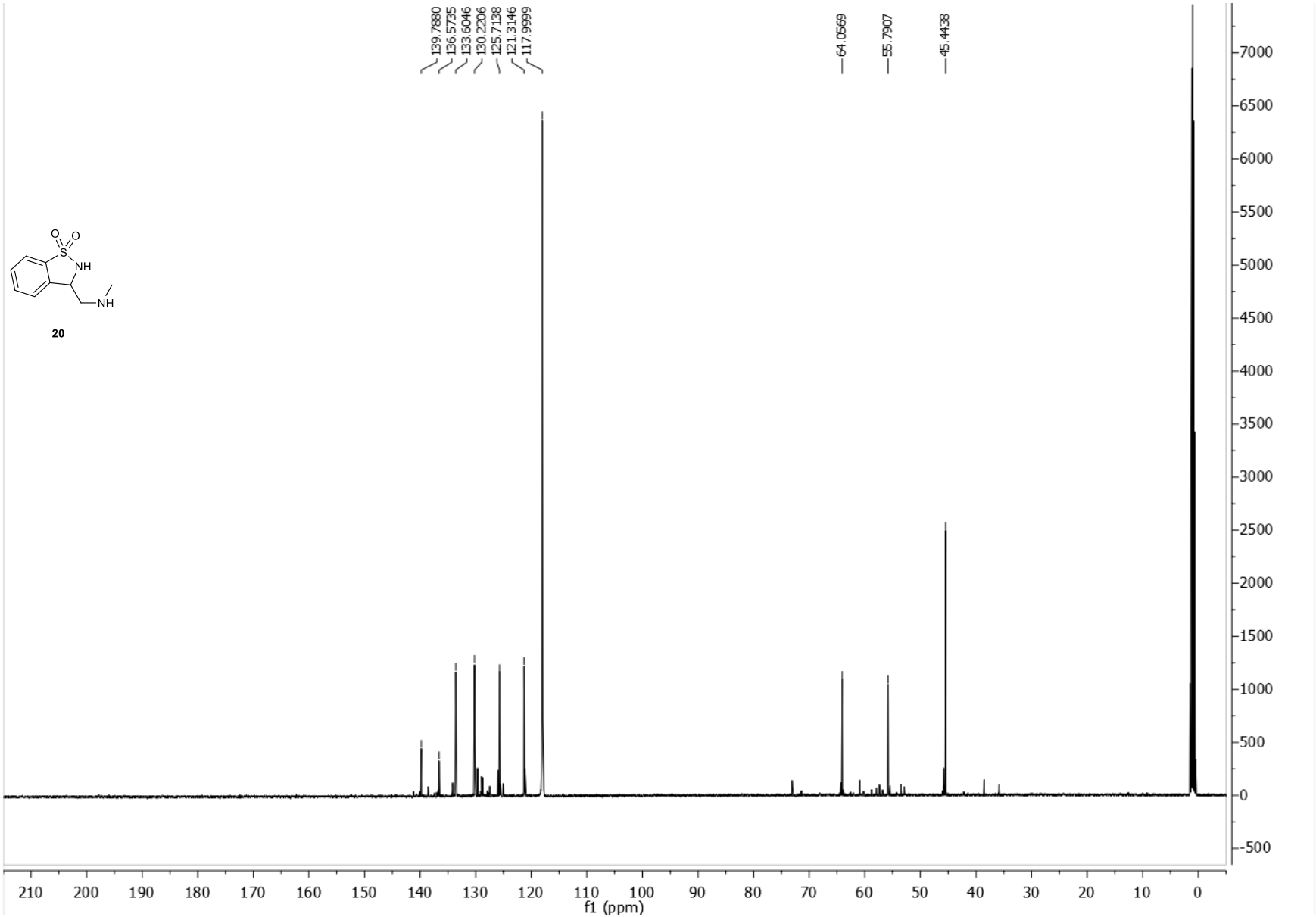
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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55.7907
45.4438
O
O
S
NH
NH
20
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
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160
150
140
130
120
110
100
90
80
70
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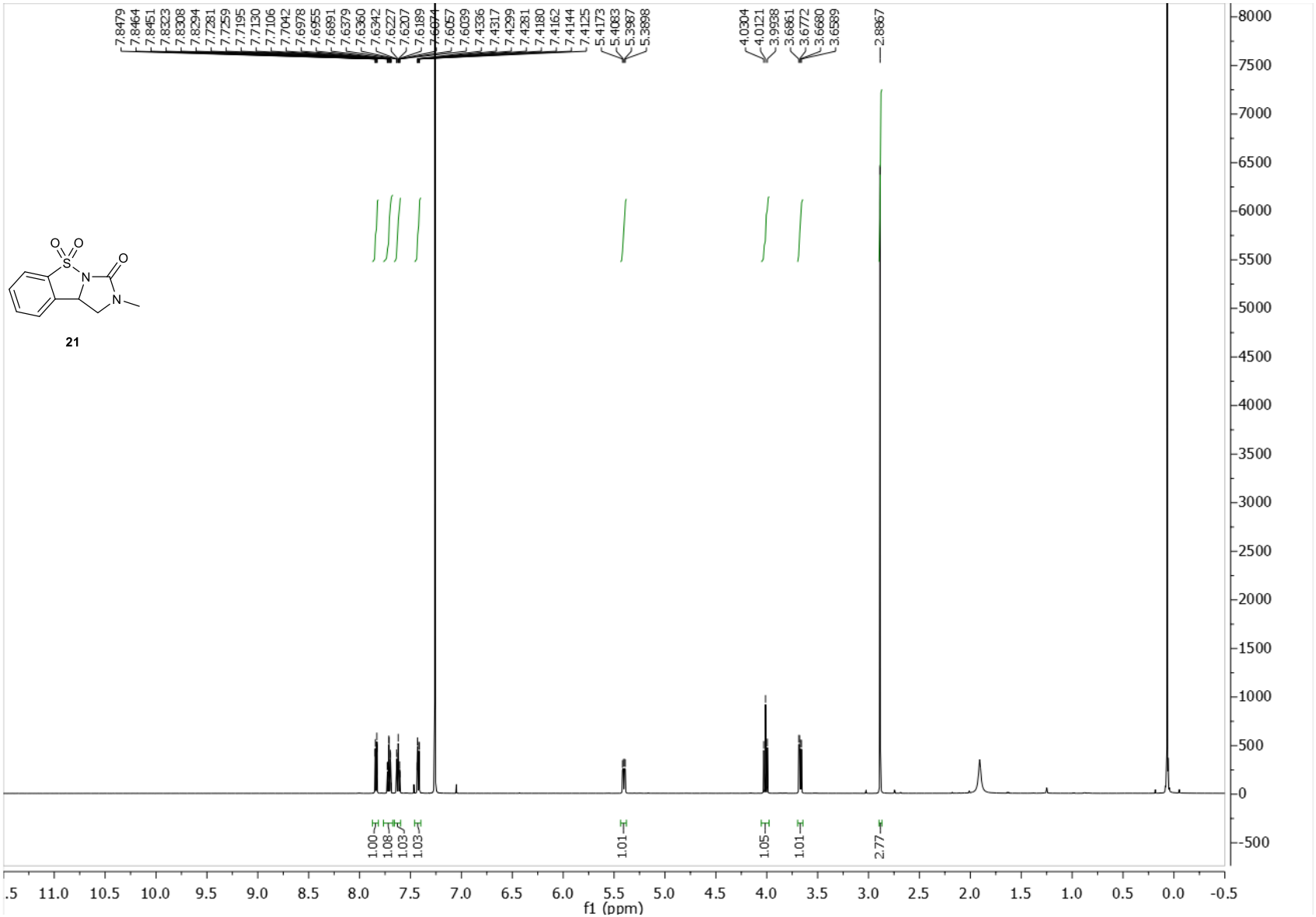
50
40
30
20
10
0
f1 (ppm)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7.7259
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7.7106
7.7042
7.6978
7.6955
7.6891
7.6379
7.6360
7.6342
7.6227
7.6207
7.6189
7.6074
7.6057
7.6039
7.4336
7.4317
7.4299
7.4281
7.4180
7.4162
7.4144
7.4125
5.4173
5.4083
5.3987
5.3898
4.0304
4.0121
3.9938
3.6861
3.6772
3.6680
3.6589
2.8867
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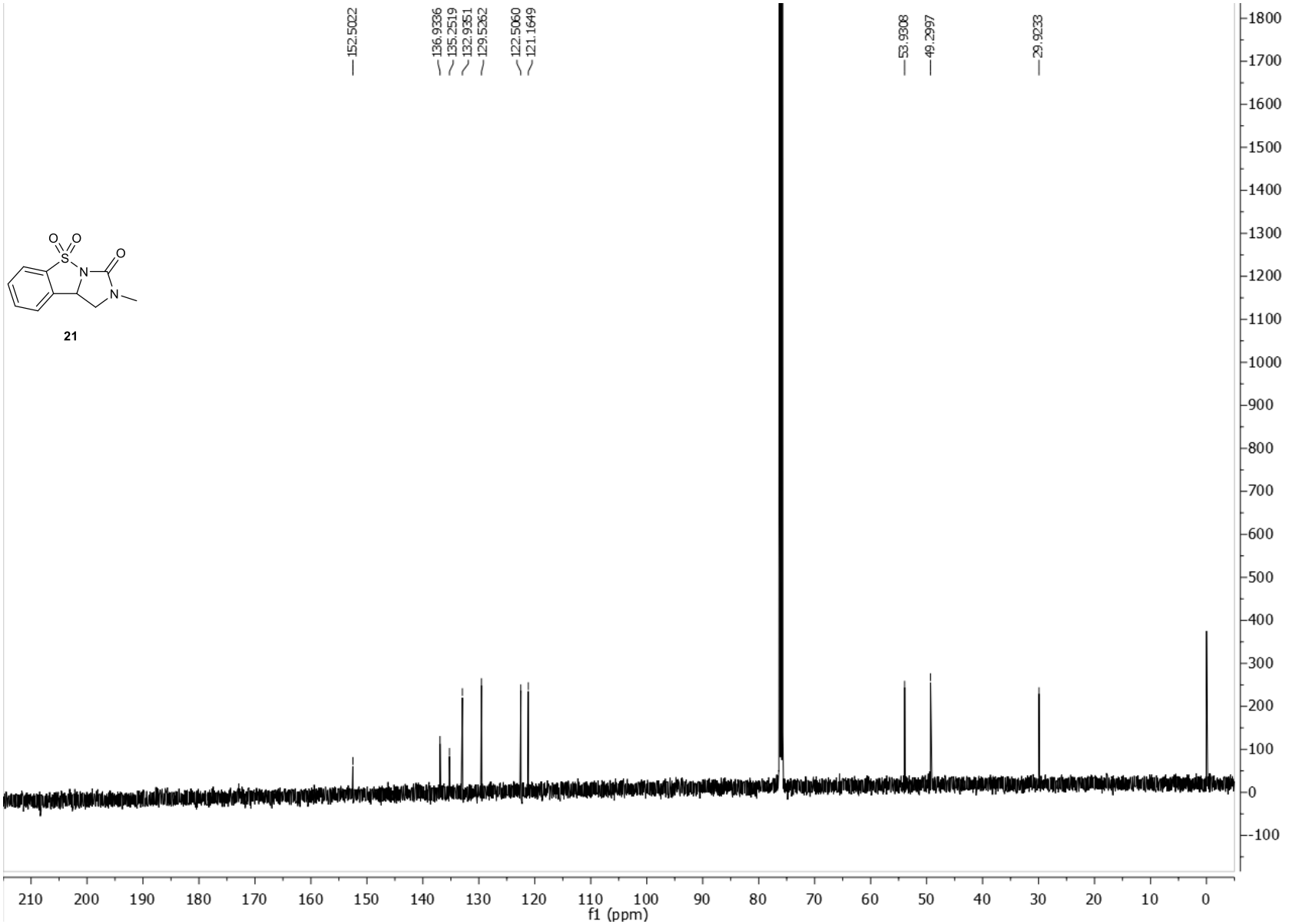
1.08
1.03
1.03
1.01
1.05
1.01
2.77
f1 (ppm)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136.9336
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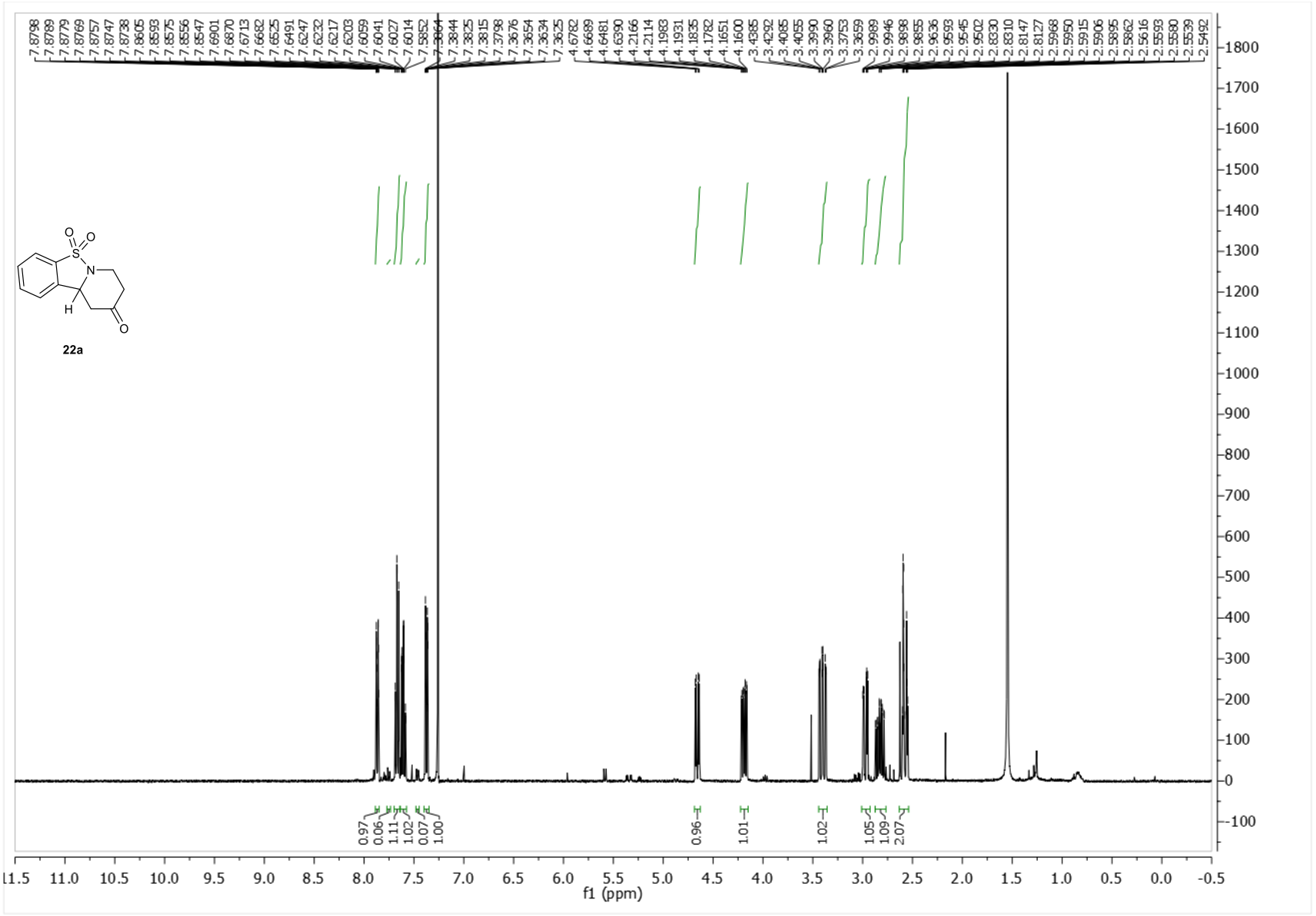
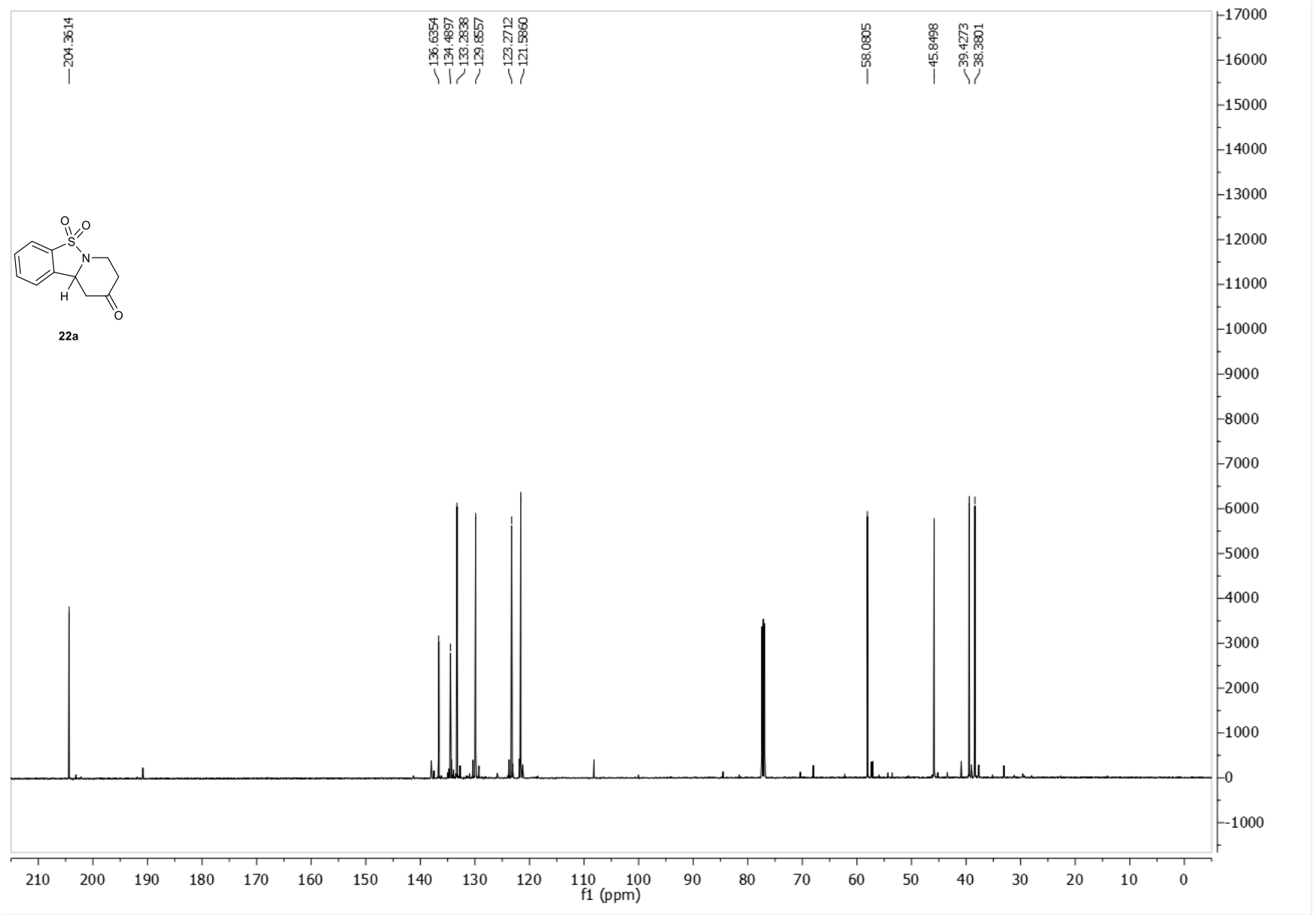
132.9351
129.5262
122.5060
121.1649
53.9308
49.2997
29.9233
21
f1 (ppm)


22a
f1 (ppm)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129.8557
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121.5860
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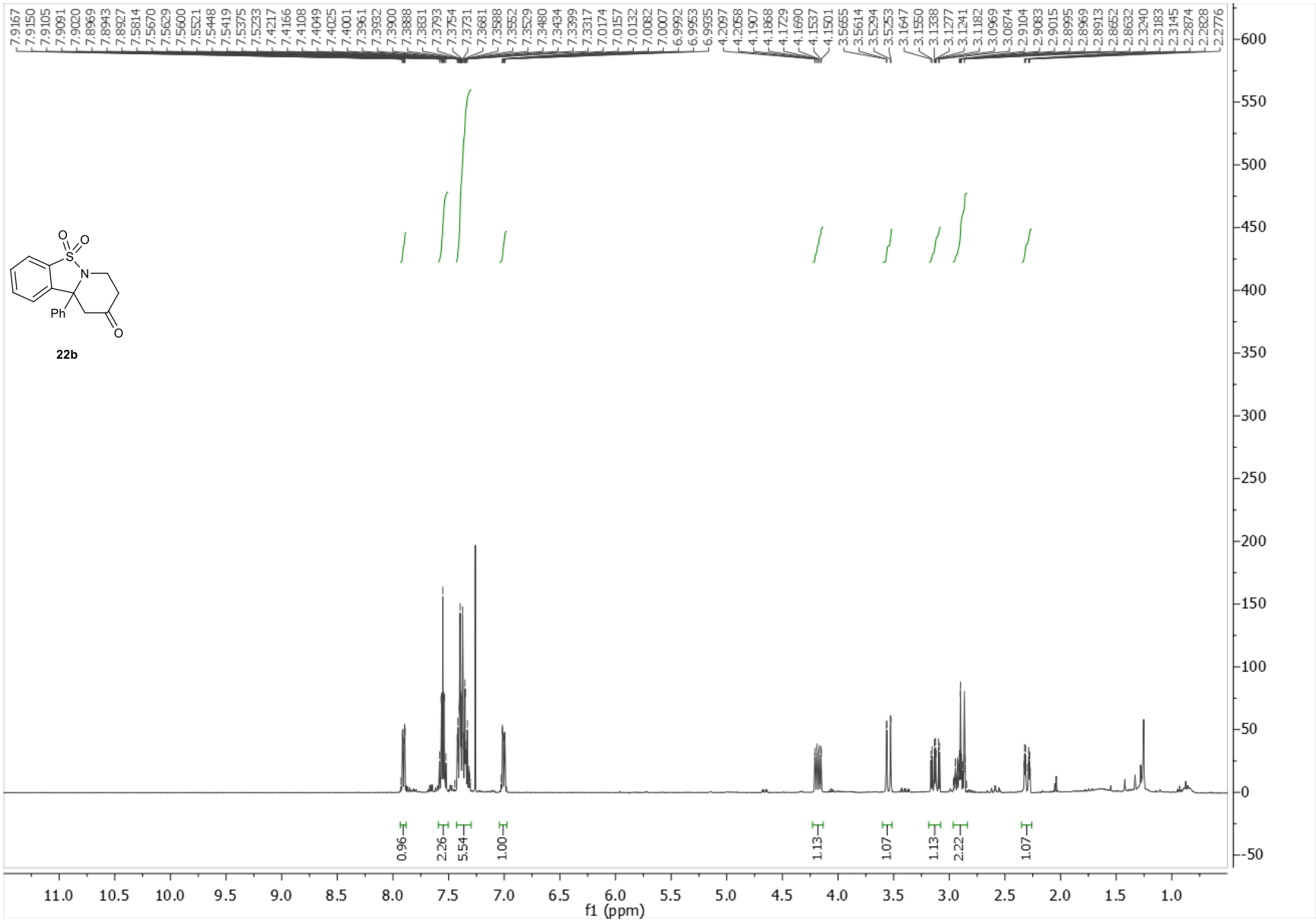
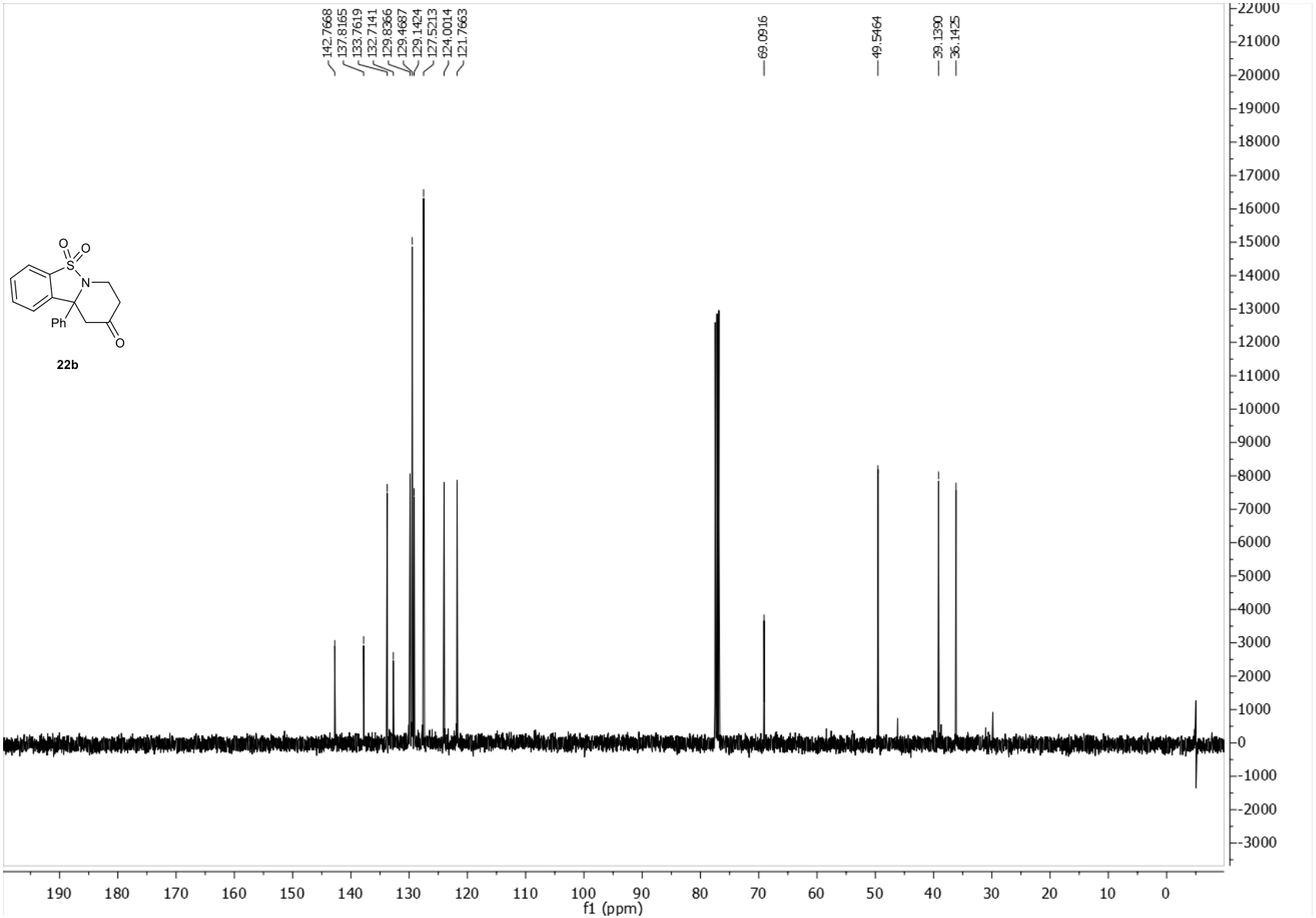
45.8498
39.4273
38.3801
22a
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


22b
f1 (ppm)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129.1424
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124.0014
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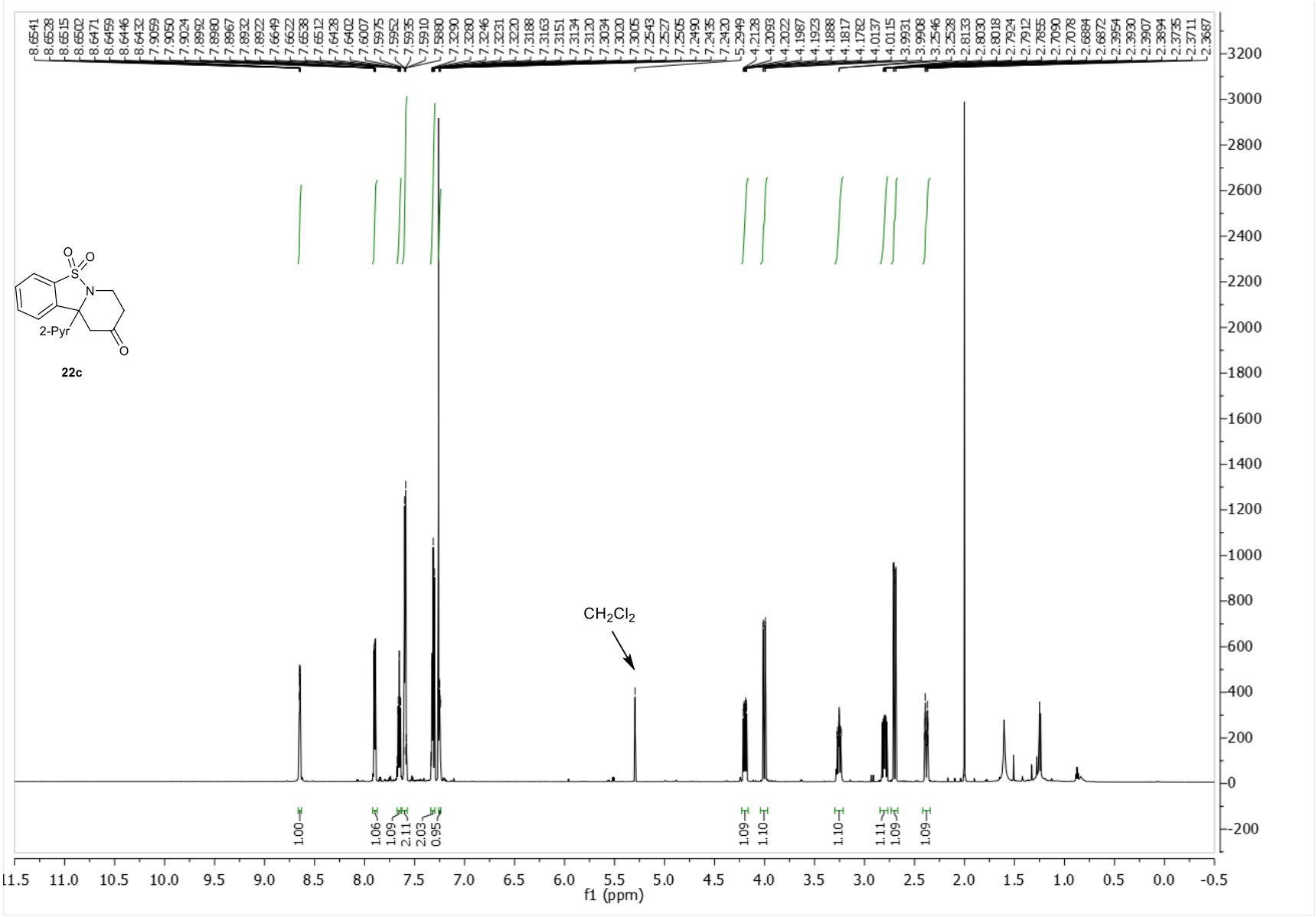
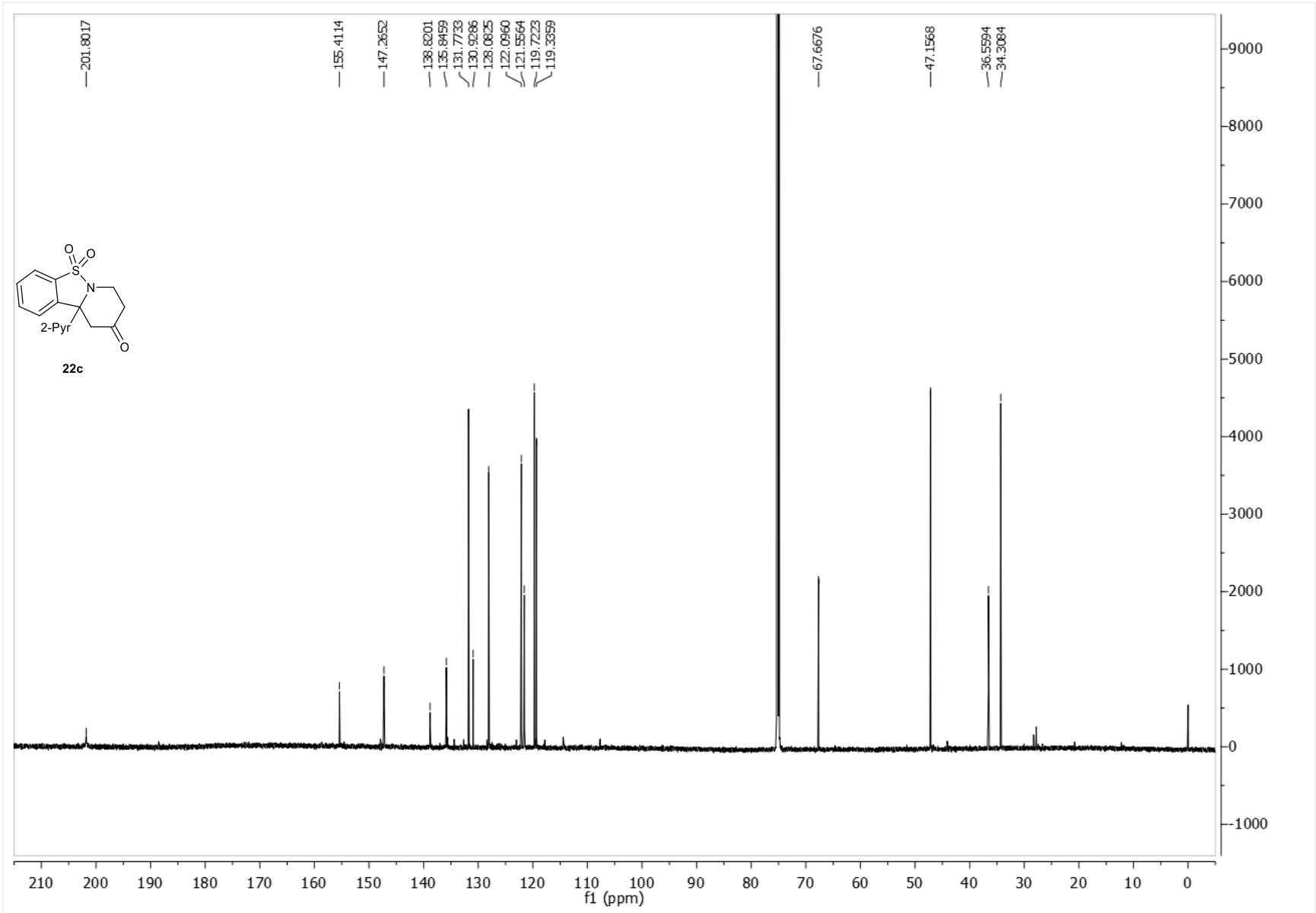
49.5464
39.1390
36.1425
O
O
S
N
Ph
O
22b
f1 (ppm)


22c
2-Pyr
$CH_2Cl_2$
f1 (ppm)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131.7733
130.9286
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122.0960
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119.3359
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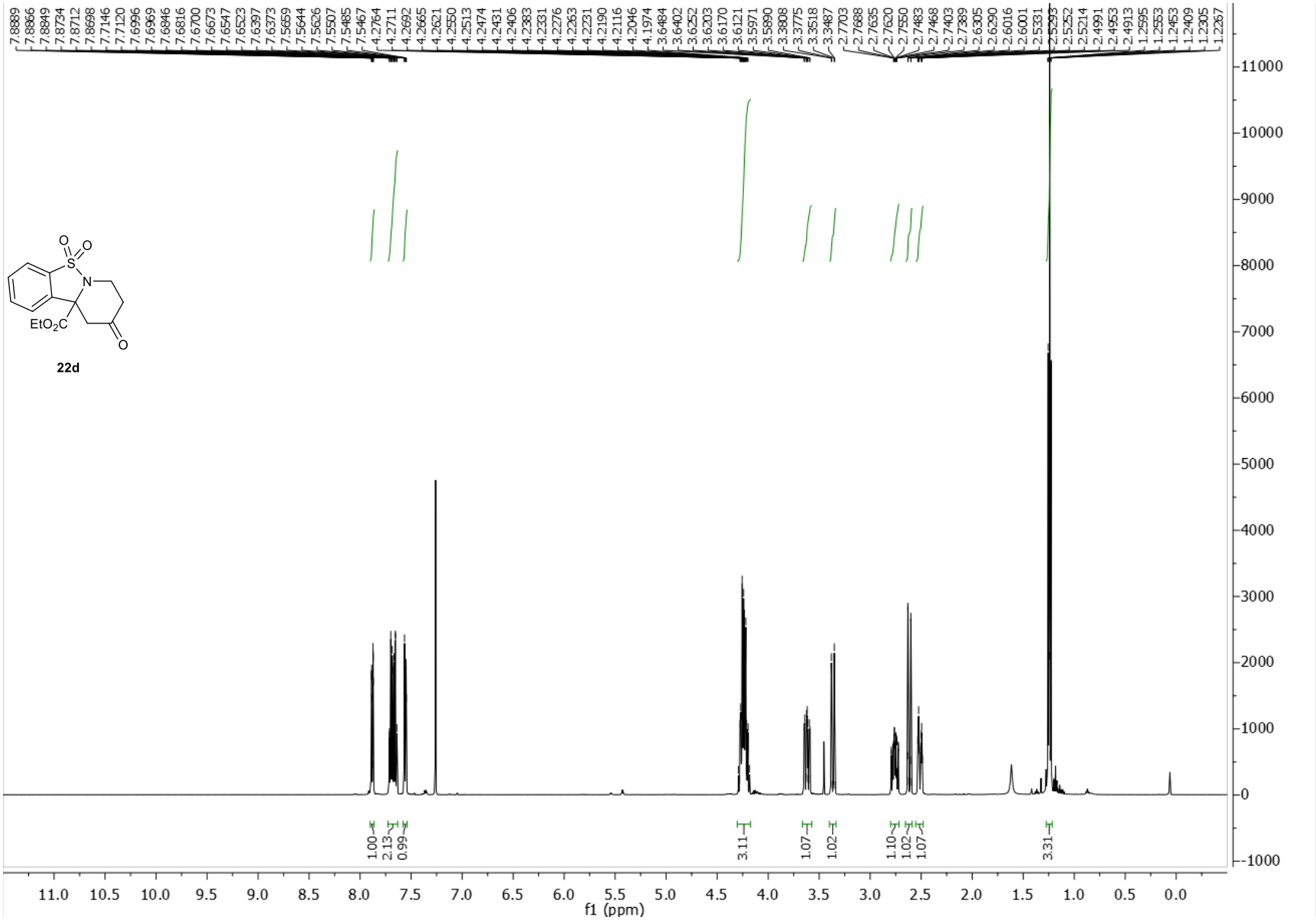
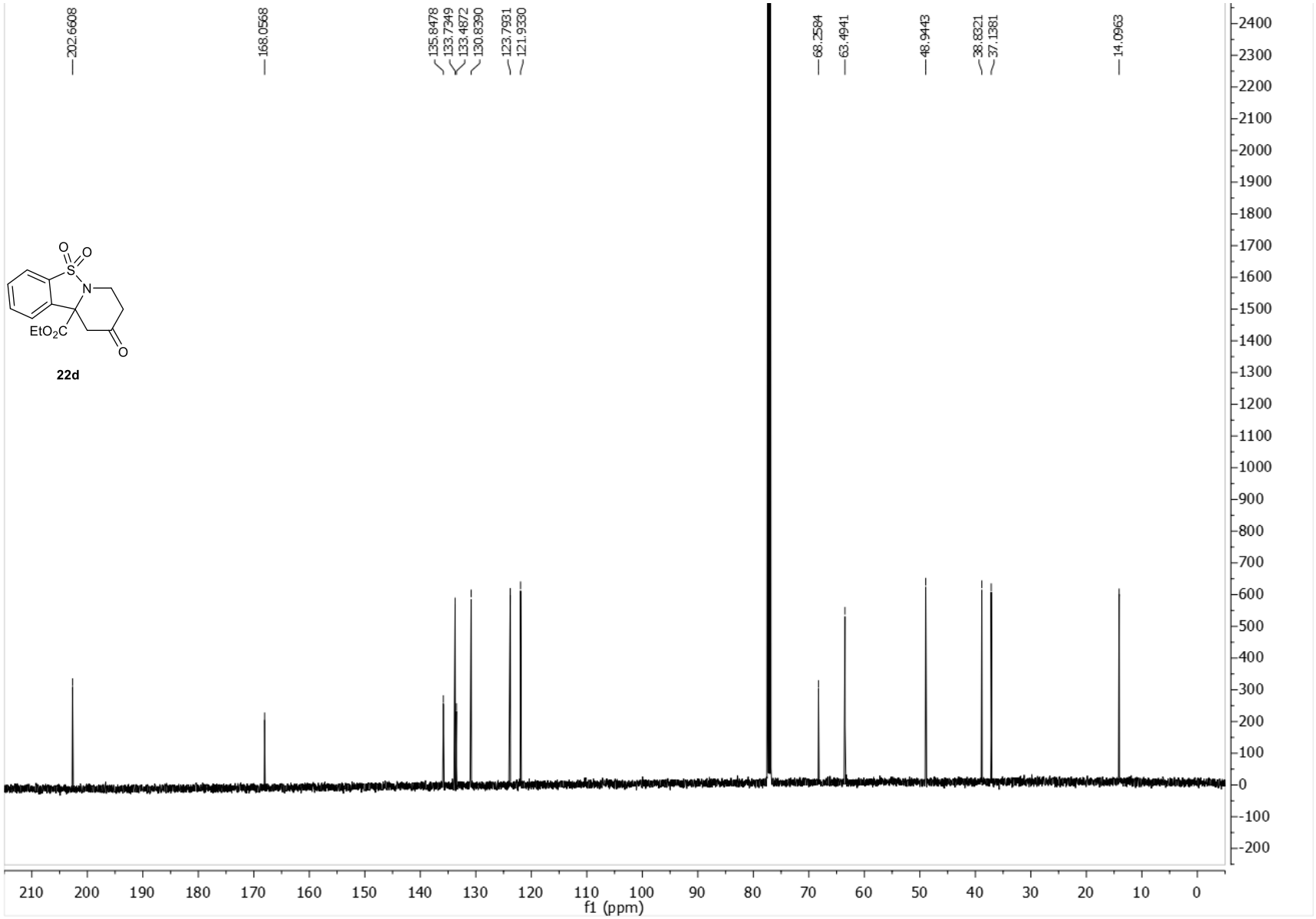
47.1568
36.5594
34.3084
2-Pyr
22c
f1 (ppm)


22d
f1 (ppm)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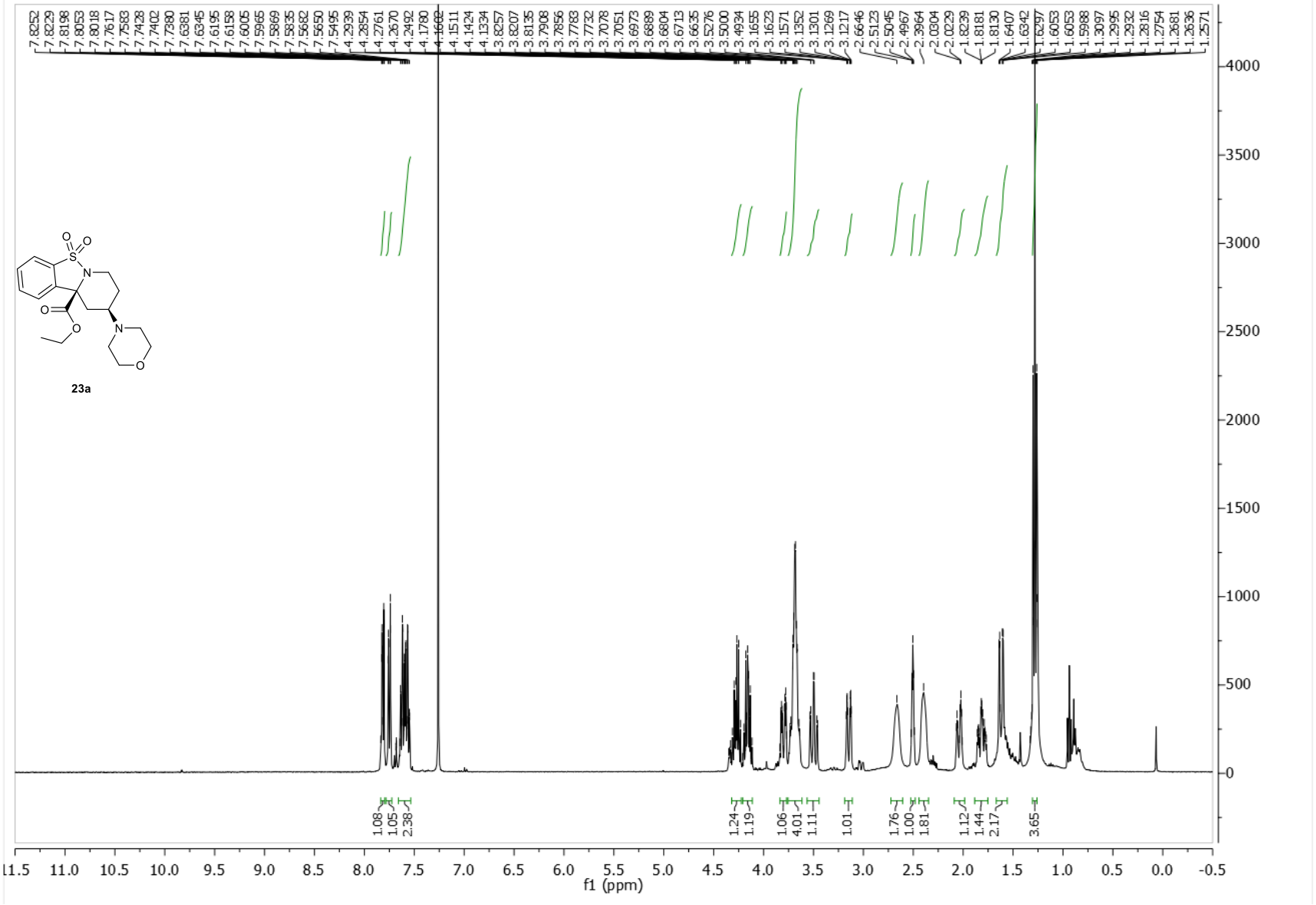
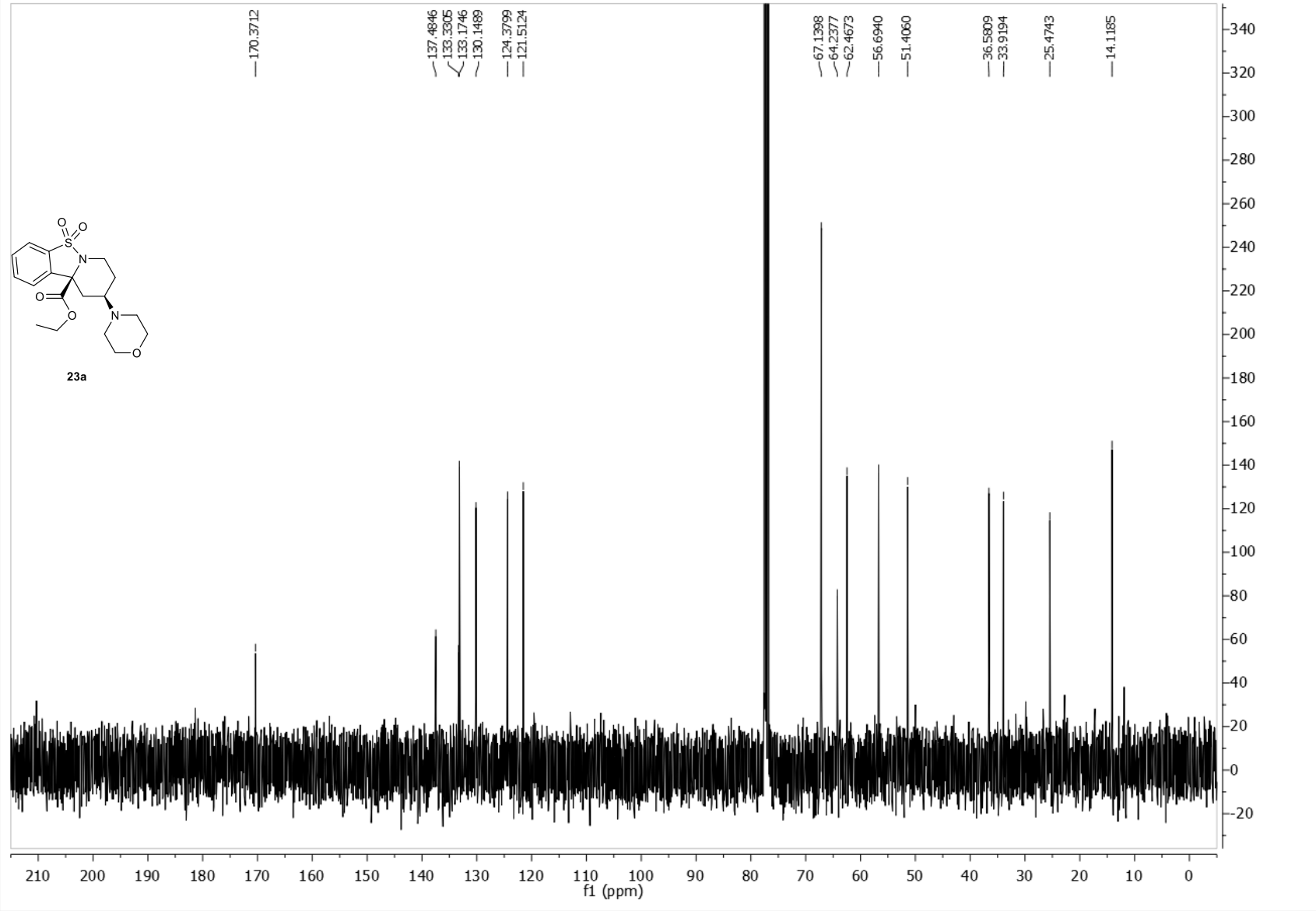
63.4941
48.9443
38.8321
37.1381
14.0963
22d
f1 (ppm)


23a
f1 (ppm)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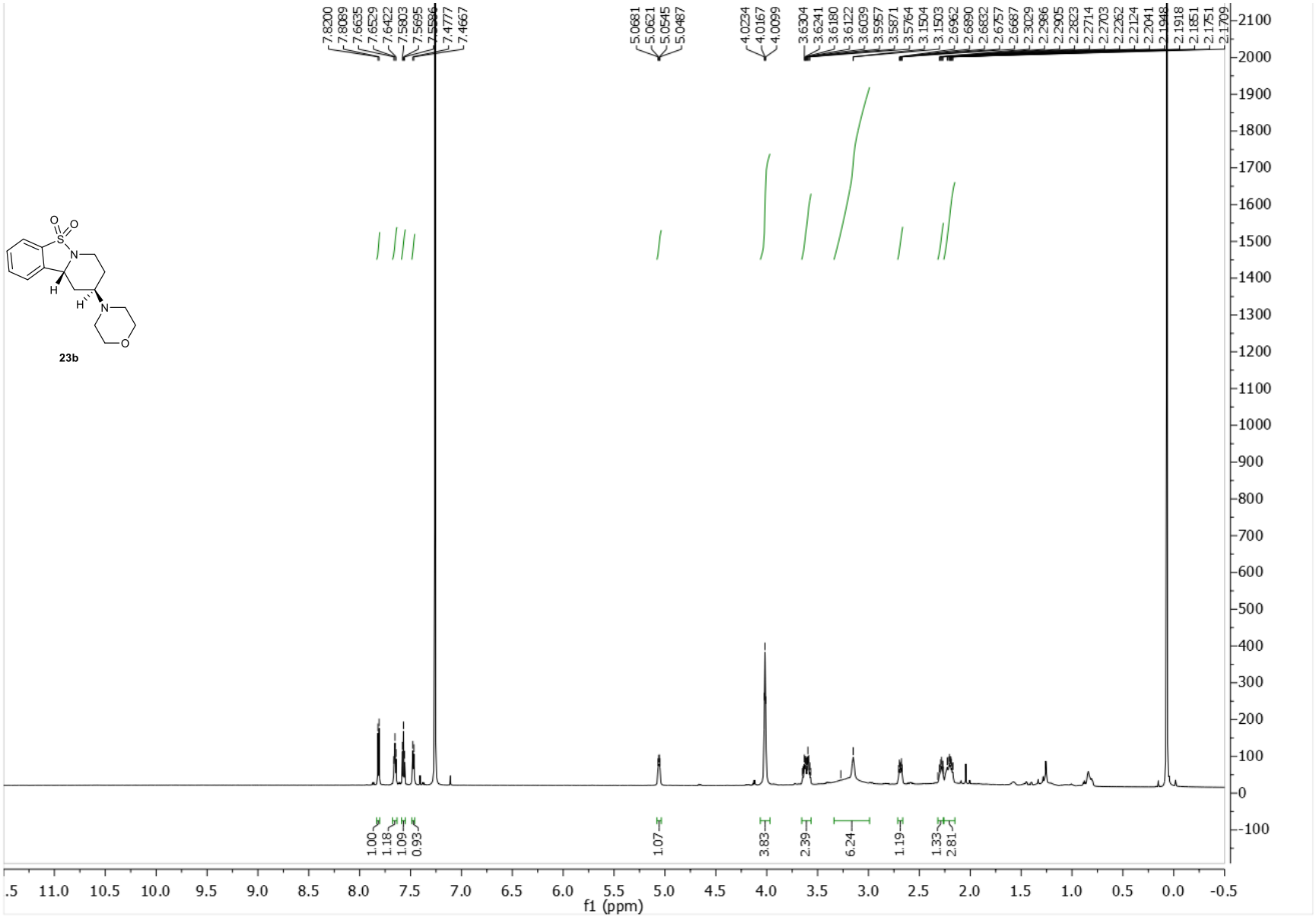
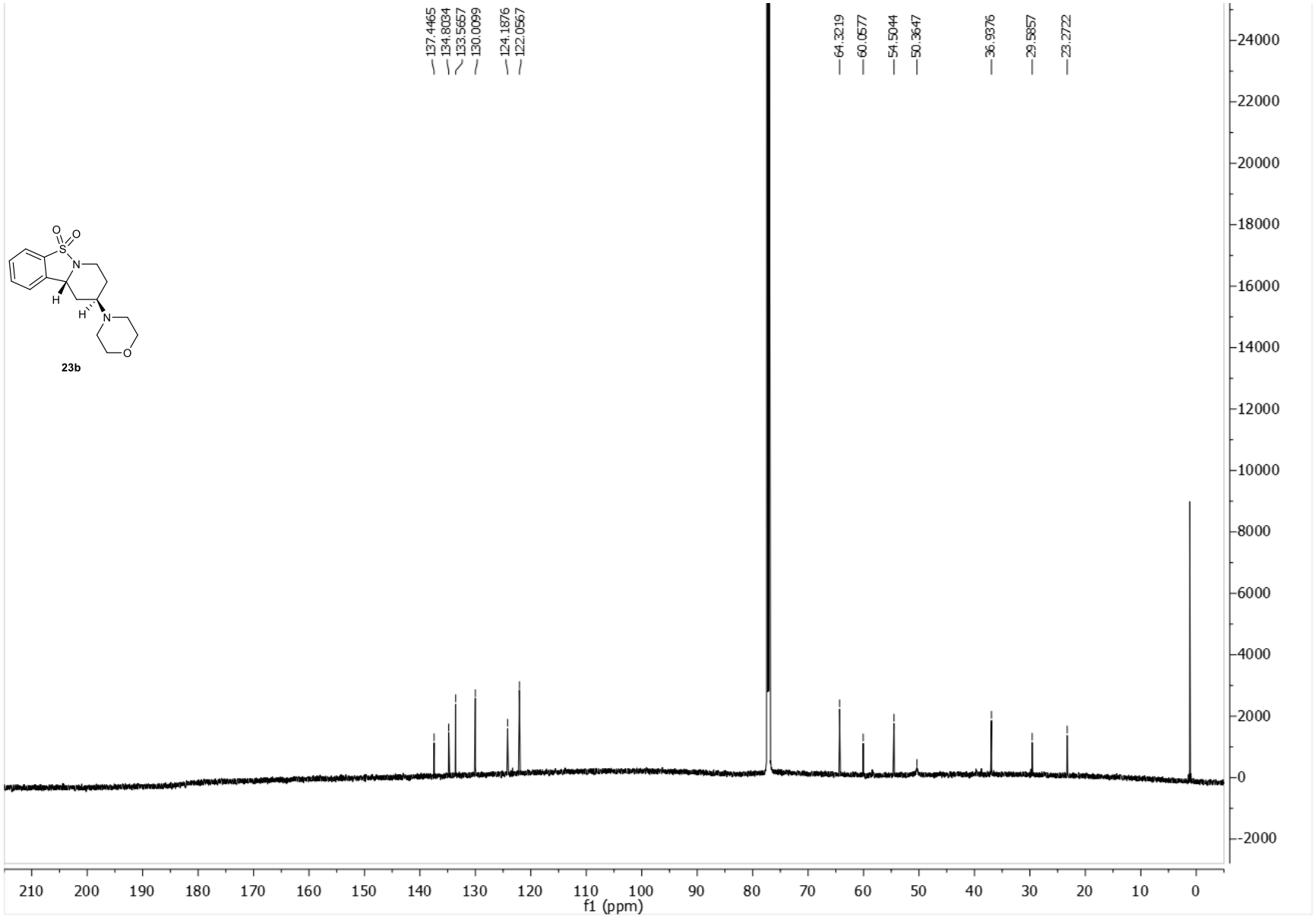
33.9194
25.4743
14.1185
23a
f1 (ppm)


23b
f1 (ppm)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133.5657
130.0099
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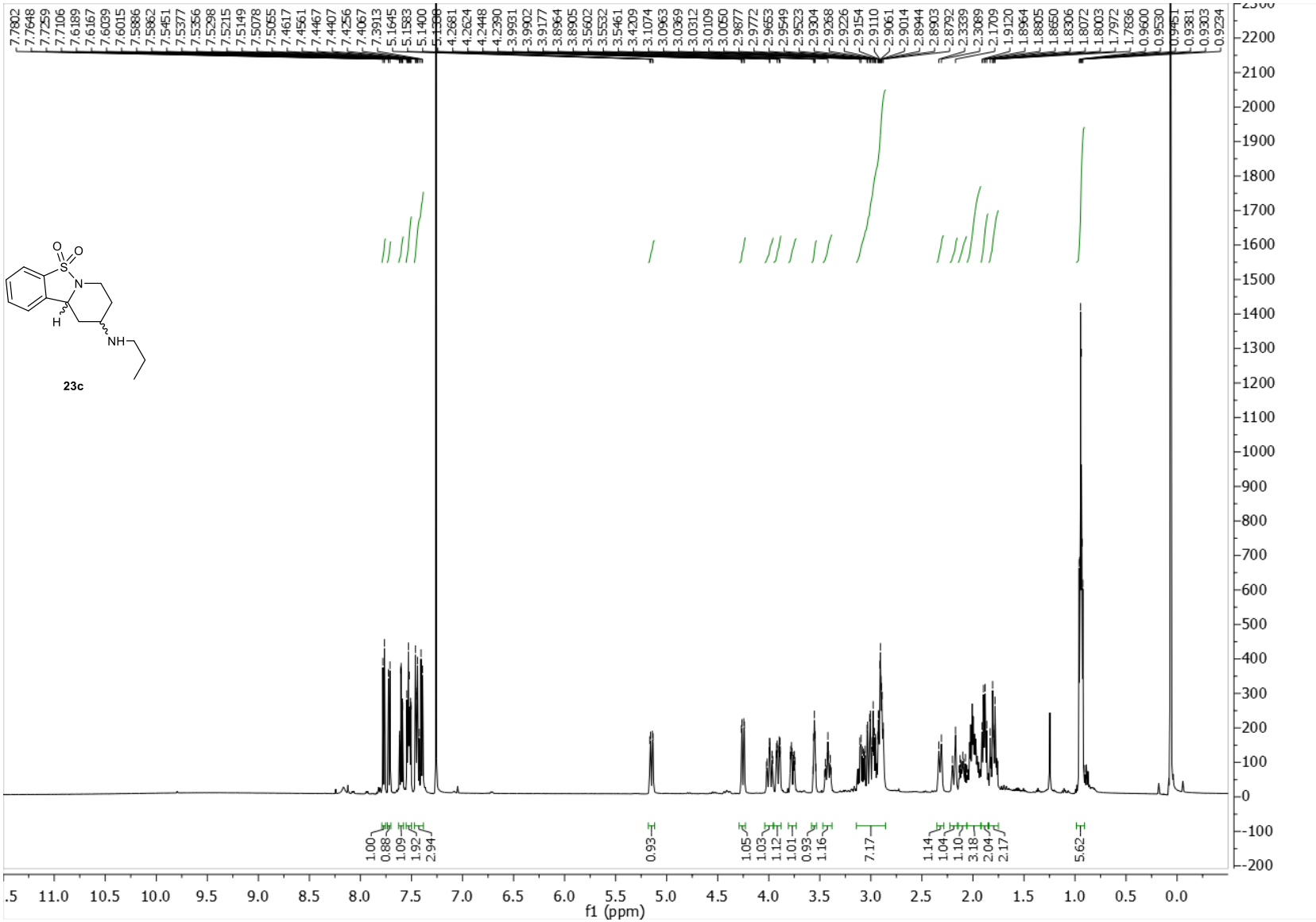
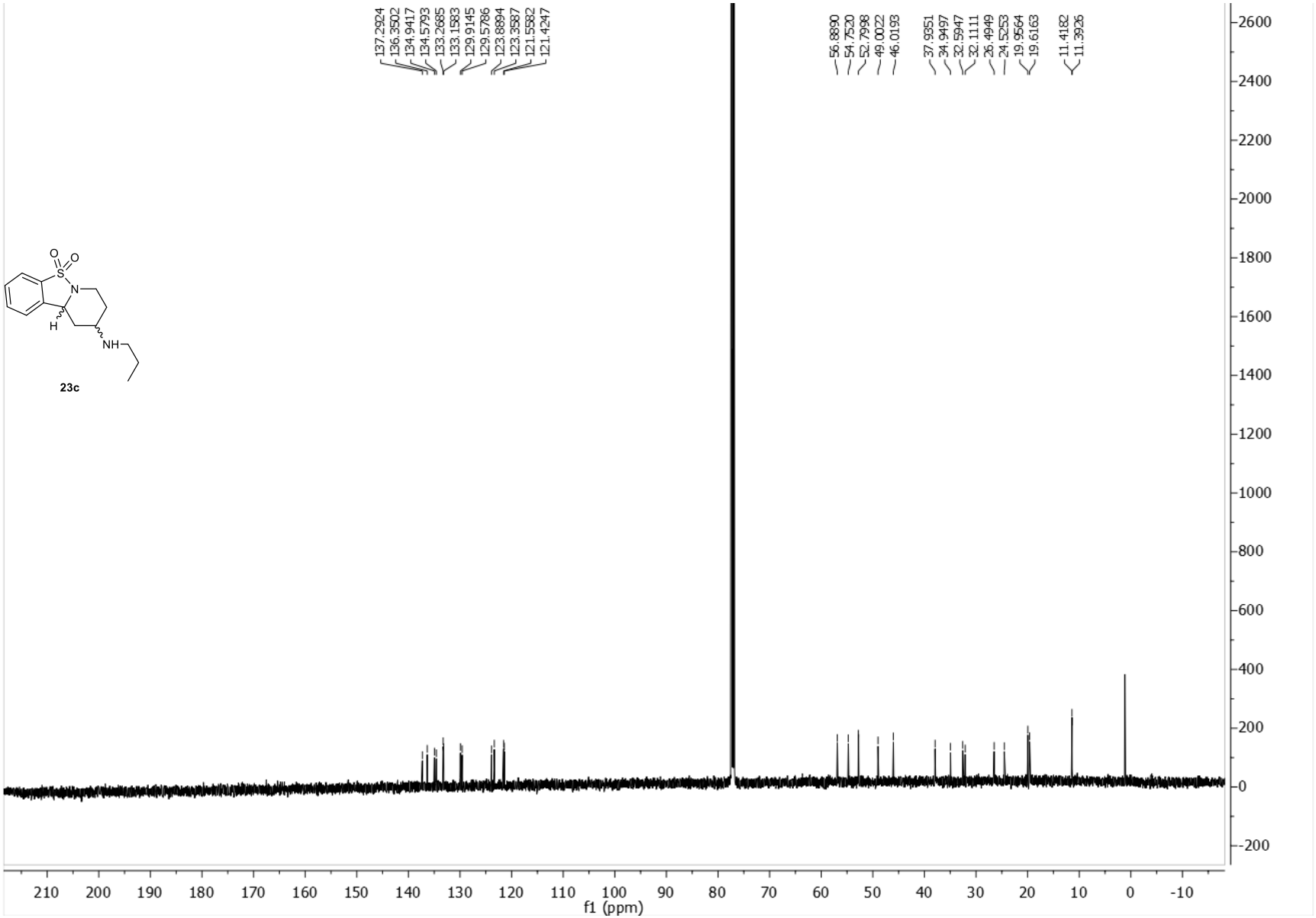
36.9376
29.5857
23.2722
23b
f1 (ppm)


23c
f1 (ppm)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133.1583
129.9145
129.5786
123.8894
123.3587
121.5582
121.4247
56.8890
54.7520
52.7998
49.0022
46.0193
37.9351
34.9497
32.5947
32.1111
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24.5253
19.9564
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11.3926
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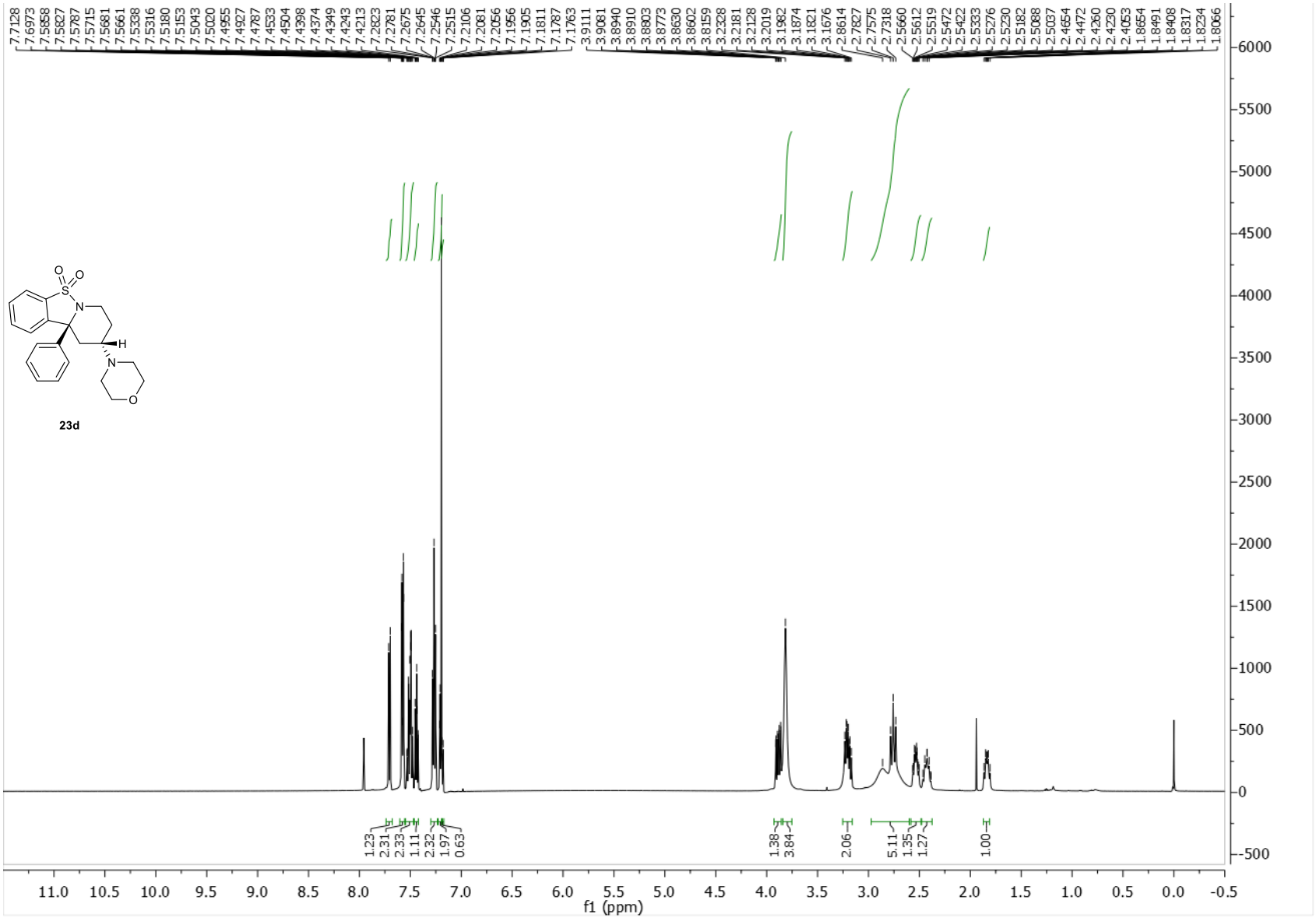
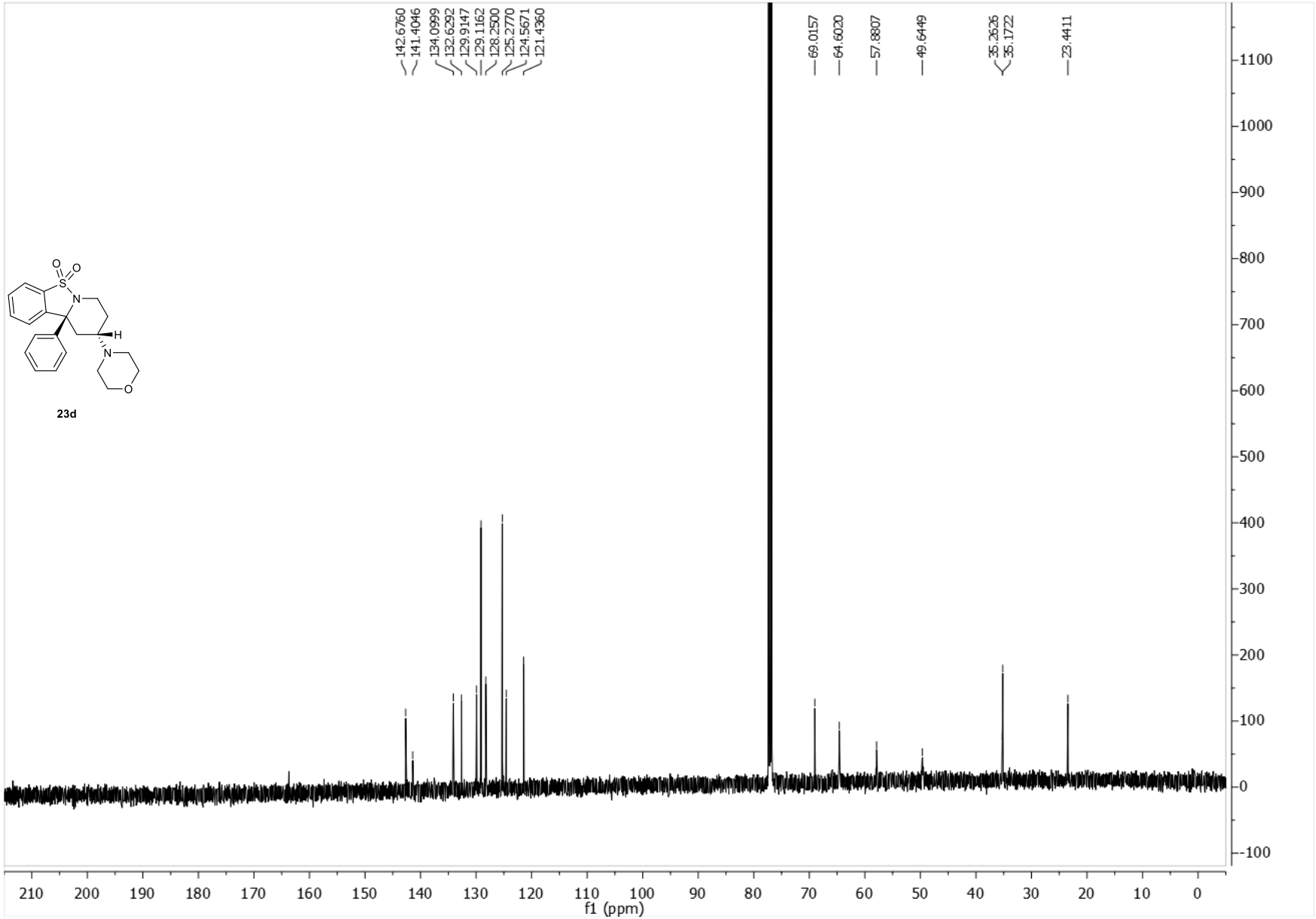
f1 (ppm)


23d
f1 (ppm)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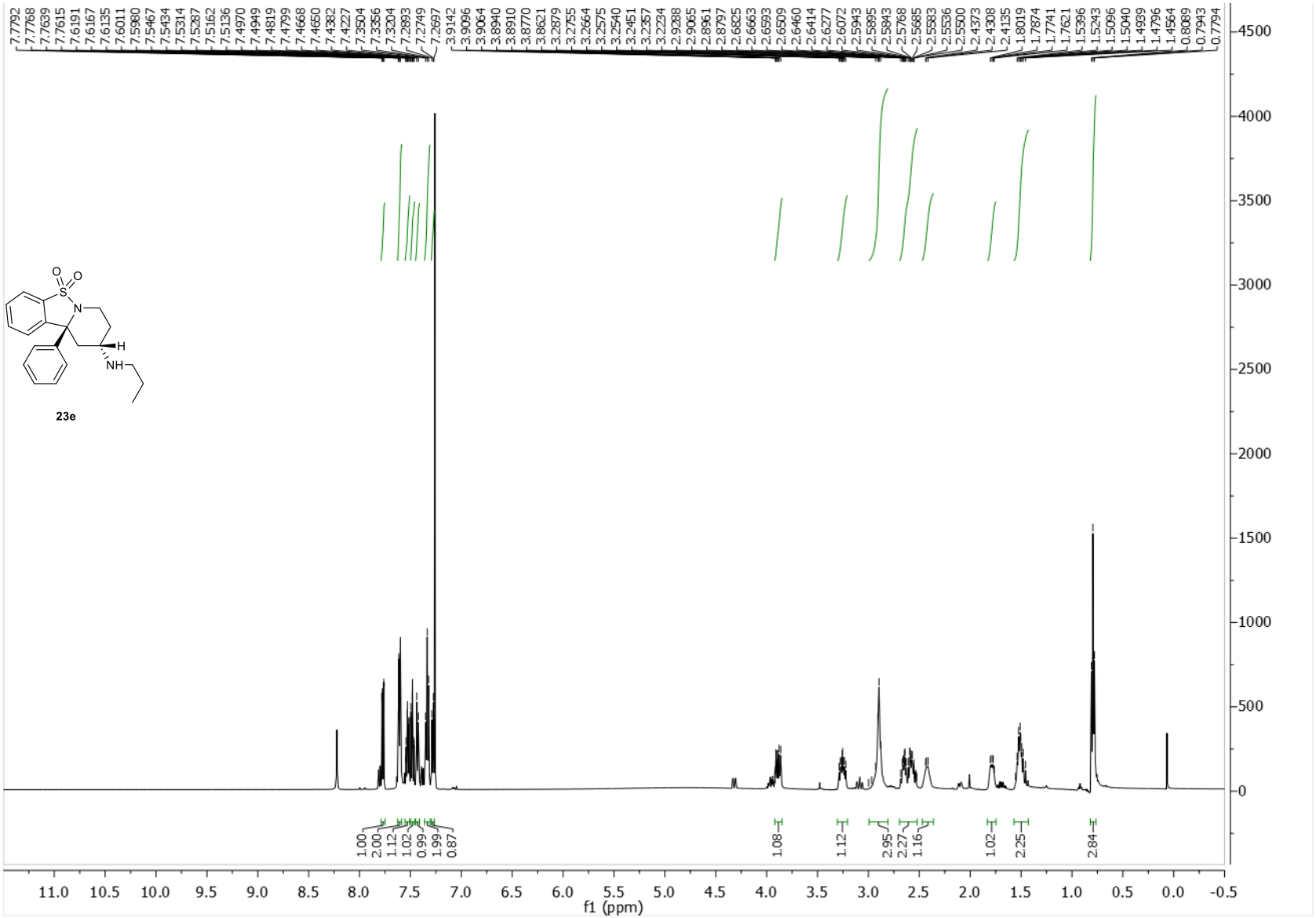
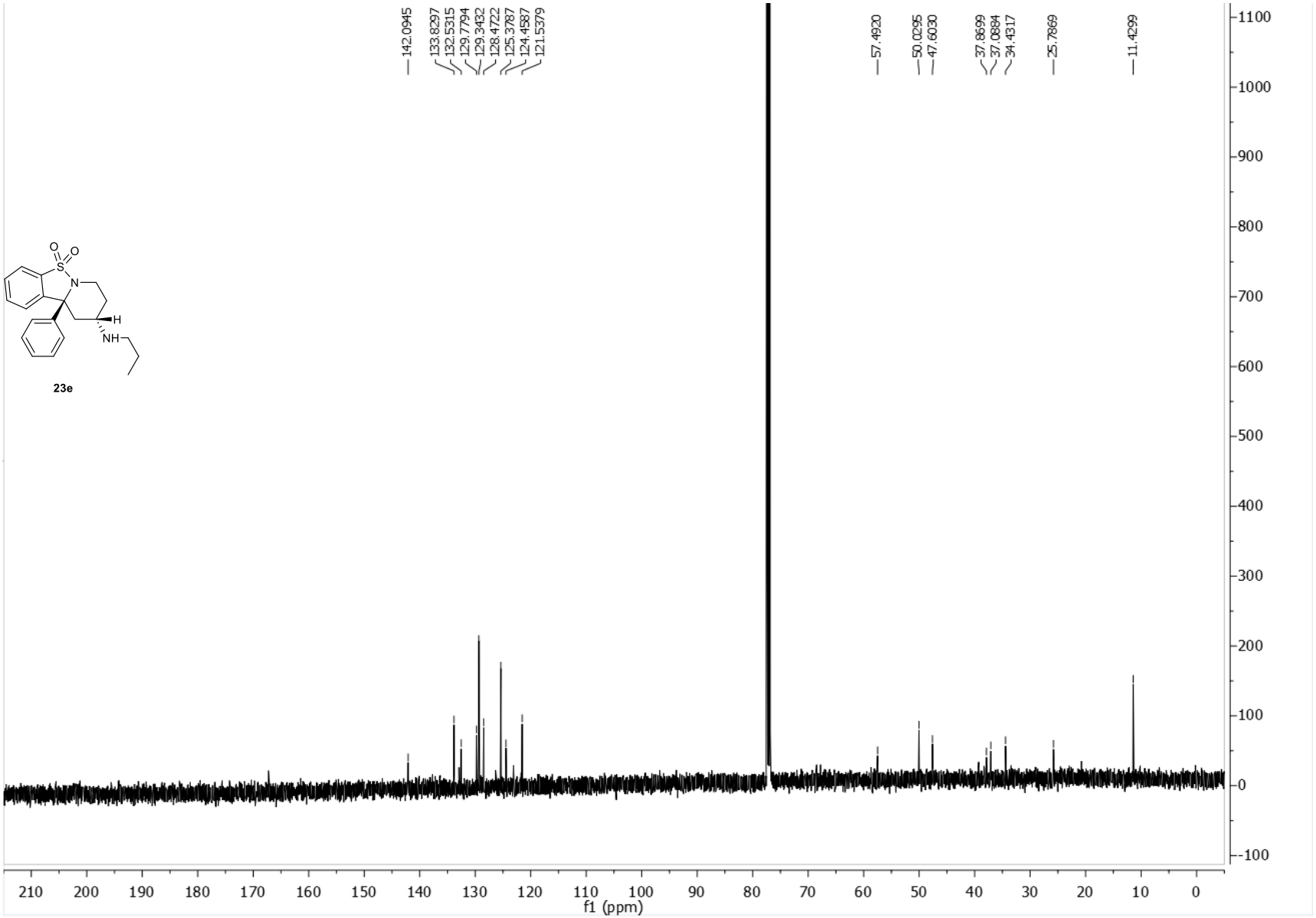
141.4046
134.0999
132.6292
129.9147
129.1162
128.2500
125.2770
124.5671
121.4360
69.0157
64.6020
57.8807
49.6449
35.2626
35.1722
23.4411
23d
f1 (ppm)


23e
f1 (ppm)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132.5315
129.7794
129.3432
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125.3787
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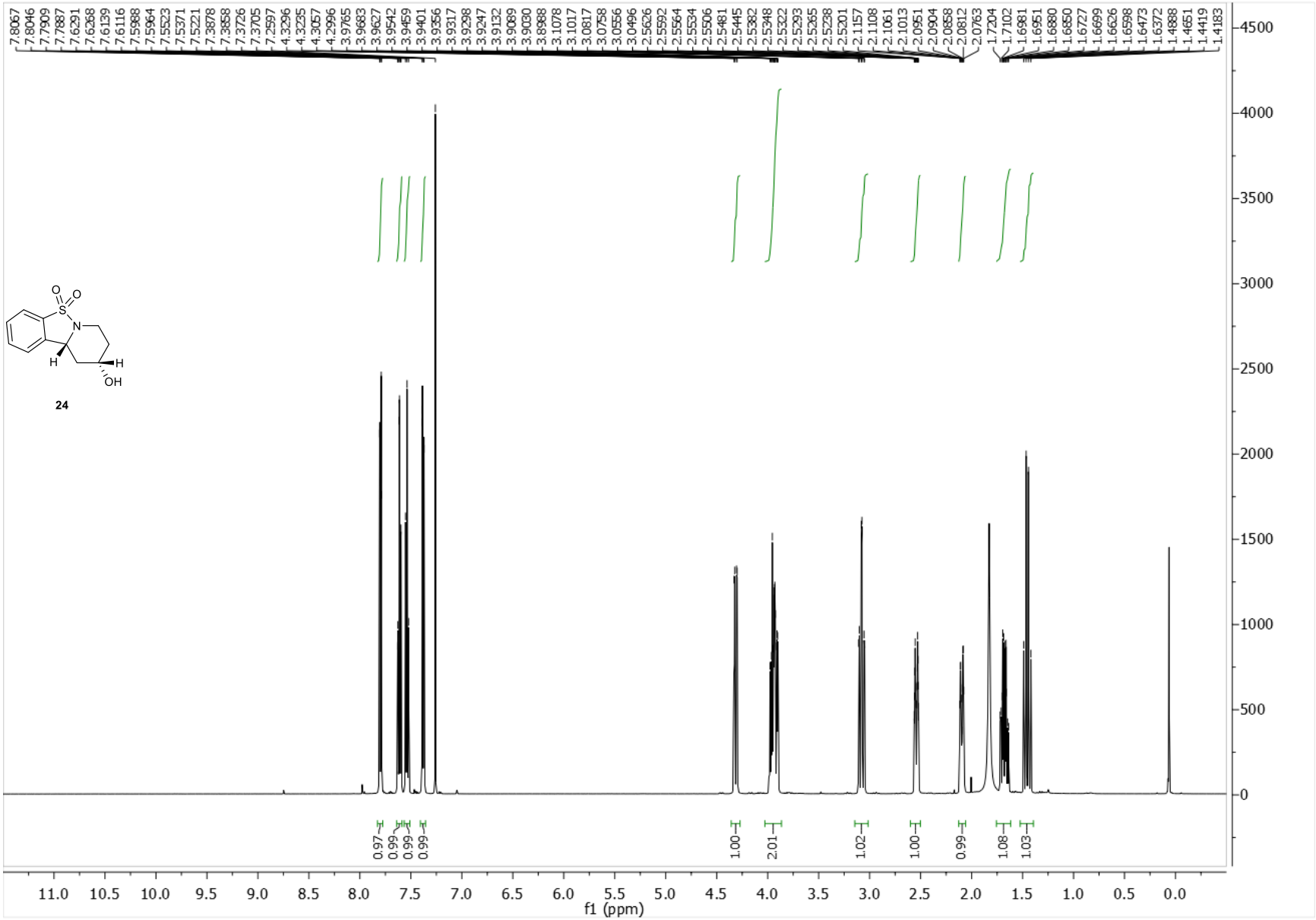
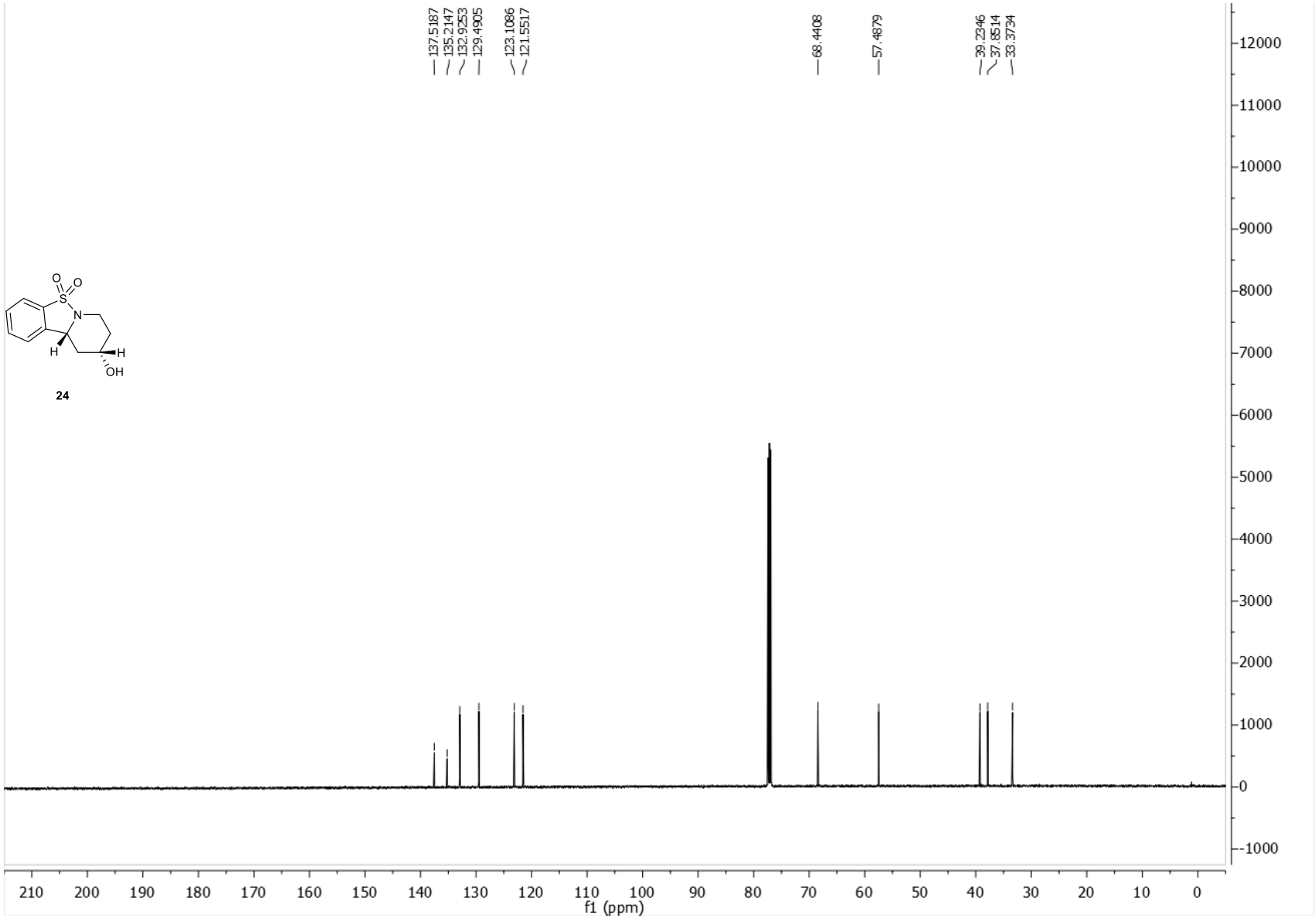
37.8699
37.0884
34.4317
25.7869
11.4299
23e
f1 (ppm)


24
f1 (ppm)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132.9253
129.4905
123.1086
121.5517
68.4408
57.4879
39.2346
37.8514
33.3734
O
O
S
N
H
H
OH
24
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)