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Synthesis of 1-(2-aminoethylsulfonyl)-2-phosphorylpyrrolidines *via* consecutive Arbuzov and aza-Michael reactions and their antitumor activity

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Contents

General

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 600 (working frequency 600.1 MHz for ^{1}H, 150.9 for ^{13}C) spectrometers in $(CD_3)_2SO$ and $CDCl_3$ relative to the residual solvent protons. ^{31}P NMR spectra were recorded on Bruker MSL 400 spectrometer (working frequency 161.94 MHz). IR spectra were obtained with a Bruker Vector 22 spectrometer. ESI-TOF mass spectra were recorded on a AmazonX (Bruker Daltonik GmbH) instrument. Elemental analysis was performed on Carlo Erba EA 1108 instrument. Melting points were determined in glass capillaries with a Stuart SMP 10 apparatus. All solvents were purified and dried according to standard procedures. 2-Ethoxy-1-(vinylsulfonyl)pyrrolidine **1** was obtained as described previously (A. V. Smolobochkin et al., *Chem. Biodivers.* **2019**, *16* (1), e1800490. https://doi.org/10.1002/cbdv.201800490.).

Synthetic procedures and compound characterization data

Diethyl (1-(vinylsulfonyl)pyrrolidin-2-yl)phosphonate **2**. To a mixture of 1-sulfonylpyrrolidine **1** (1.00 g, 5.00 mmol) and triethyl phosphite (1.62 g, 10 mmol) in dry benzene (30 ml), boron trifluoride etherate (1.38 g, 10 mmol) was added in inert atmosphere (Ar). The mixture was kept at room temperature for 10 days. Brine (50 ml) was then added, and the mixture was stirred vigorously for 15 min. The water layer was extracted with dichloromethane (3x50 ml). The organic extracts were combined, dried over $MgSO_4$ and the solvent was evaporated in vacuum. The residue was chromatographed on 230-400 mesh silica with hexane / ethyl acetate (1 : 2) to give the target compound **2** as yellowish oil. Yield 0.5 g (34%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ, ppm: 1.26 (td, *J* = 7.1 Hz, 4.3 Hz, 6H), 1.74 – 1.90 (m, 1H), 2.07 – 2.22 (m, 3H), 3.24 – 3.34 (m, 1H), 3.36 – 3.44 (m, 1H), 3.95 – 4.02 (m, 1H), 4.04 – 4.21 (m, 4H), 5.93 (d, 1H, *J* = 9.9 Hz), 6.20 (d, 1H, *J* = 16.6 Hz), 6.50 (dd, 1H, *J* = 16.5 Hz, 9.9 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 16.3 (d, *J* = 5.9 Hz), 16.4 (d, *J* = 5.7 Hz), 24.9 (d, *J* = 1.3 Hz), 27.3, 48.8 (d, *J* = 1.3 Hz), 55.2 (d, *J* = 169.5 Hz), 62.4 (d, *J* = 6.9 Hz), 63.2 (d, *J* = 7.2 Hz), 127.8, 133.2. **^{31}P NMR** (160 MHz, $CDCl_3$) δ: 23.3. ESI: m/z calcd for $C_{10}H_{20}NO_5PS$ $[M+Na]^+$ 320, found 320.

General method of synthesis of pyrrolidines 3a-c

To a solution of 1-(vinylsulfonyl)pyrrolidin-2-yl)phosphonate **2** (0.15 g, 0.5 mmol) in dry dichloromethane (5 ml), an appropriate amine (0.5 mmol) was added dropwise. The mixture was stirred at room temperature for 2 days. The solvent was evaporated in vacuum, the residue was washed with diethyl ether and dried in vacuum (room temperature, 0.1 Torr, 2 h) to give the target compounds **3a-c**.

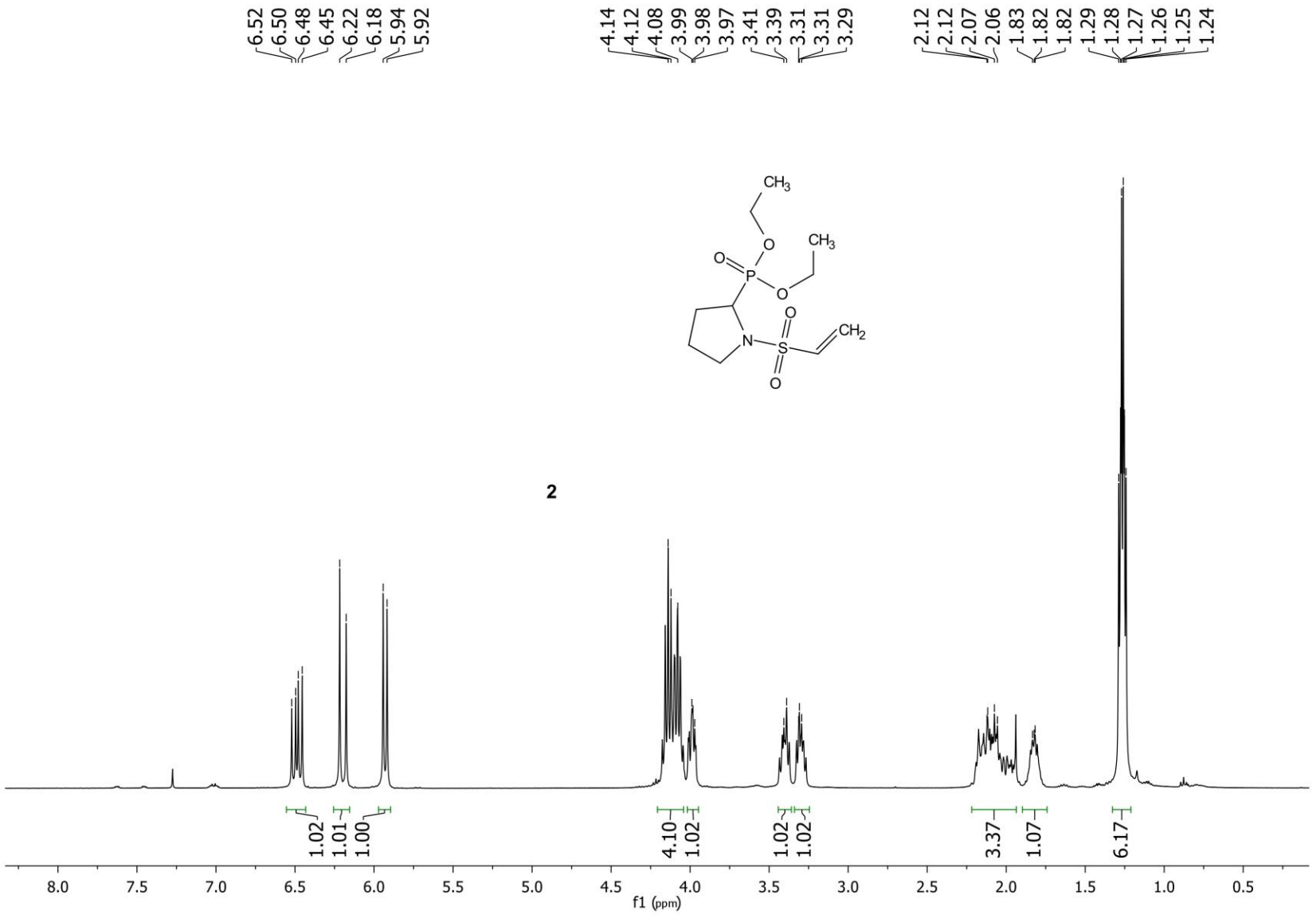
Diethyl [1-((2-diethylaminoethylsulfonyl)pyrrolidin-2-yl]phosphonate **3a**. Yield 0.18 g (95%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ, ppm: 0.91 – 1.15 (m, 6H), 1.29 – 1.43 (m, 6H), 1.86 – 1.96 (m, 1H), 2.08 – 2.27 (m, 3H), 2.47 – 2.64 (m, 4H), 2.97 – 3.06 (m, 2H), 3.24 – 3.38 (m, 3H), 3.65 – 3.77 (m, 1H), 4.13 – 4.22 (m, 4H), 4.25 – 4.35 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 11.9, 16.4, 25.5, 27.5, 46.2, 46.9, 49.2, 49.9, 54.6 (d, *J* = 168.8 Hz), 62.6. **^{31}P NMR** (160 MHz, $CDCl_3$) δ: 24.4. ESI: m/z calcd for $C_{14}H_{31}N_2O_5PS$ $[M+H]^+$ 371, found 371.

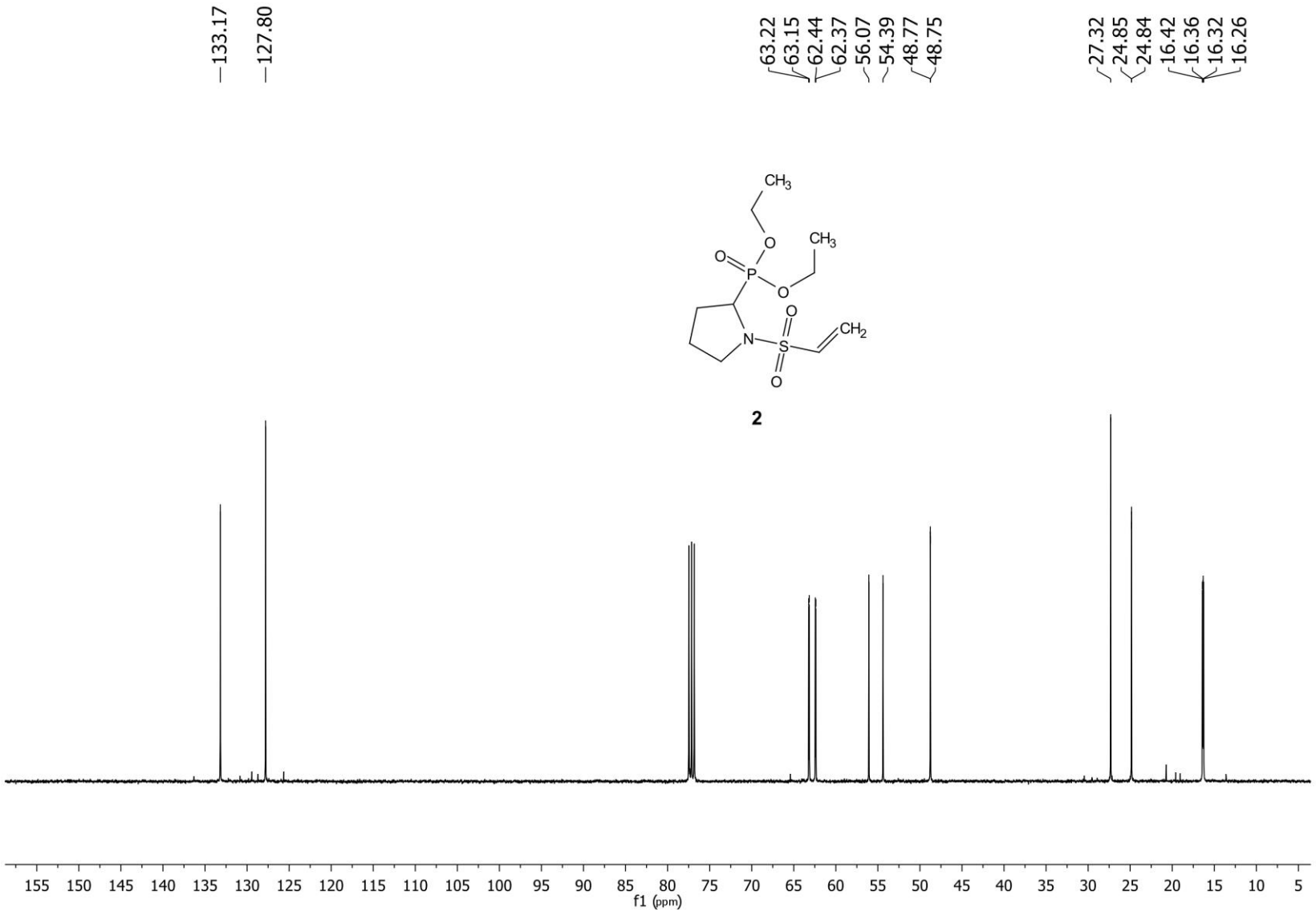
Diethyl [1-(2-morpholinoethylsulfonyl)pyrrolidin-2-yl]phosphonate **3b**. Yield 0.17 g (85%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ, ppm: 1.04 – 1.09 (t, *J* = 7.1 Hz, 6H), 1.86 – 1.96 (m, 1H), 2.04 – 2.14 (m, 1H), 2.15 – 2.25 (m, 2H), 2.47 – 2.55 (m, 4H), 2.86 (t, *J* = 7.6 Hz, 2H), 3.26 – 3.33 (m, 1H), 3.33 – 3.42 (m, 1H), 3.44 – 3.50 (m, 1H), 3.70 (t, *J* = 4.7 Hz, 4H), 3.73 – 3.83 (m, 1H), 4.12 – 4.22 (m, 4H), 4.29 – 4.34 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 16.5 (d, *J* = 5.7 Hz), 25.5, 27.6, 49.2, 50.5, 52.3, 53.4, 54.8 (d, *J* = 168.7 Hz), 62.6, 66.8. **^{31}P NMR** (160 MHz, $CDCl_3$) δ: 24.35. ESI: m/z calcd for $C_{14}H_{29}N_2O_6PS$ $[M+H]^+$ 385, found 385.

Diethyl {1-[2-(4-methylpiperazin-1-yl)ethylsulfonyl]pyrrolidin-2-yl}phosphonate **3c**. Yield 0.17 g (89%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ, ppm: 1.30 (t, *J* = 7.1 Hz, 6H), 1.80 –1.93 (m, 1H), 1.99 – 2.19 (m, 3H), 2.25 (s, 3H), 2.32 – 2.61 (m, 8H), 2.83 (t, *J* = 7.6, 2H), 3.21 –3.34 (m, 2H), 3.36 – 3.47 (m, 1H), 3.64 – 3.73 (m, 1H), 4.03 – 4.20 (m, 4H), 4.22 – 4.29 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 16.4 (d, *J* = 5.7 Hz), 25.5 (d, *J* = 1.7 Hz), 27.5, 45.8, 49.2 (d, *J* = 2.0 Hz), 50.5, 51.7, 52.7, 54.7 (d, *J* = 168.9 Hz), 54.9, 62.5. **^{31}P NMR** (160 MHz, $CDCl_3$) δ: 24.34. ESI: m/z calcd for $C_{15}H_{32}N_3O_5PS$ $[M+H]^+$ 398, found 398.

2-[(2-Ethoxypyrrolidin-1-yl)sulfonyl]-N,N-diethylethan-1-amine **4**. To a suspension of 1-sulfonylpyrrolidine **1** (1.2 g, 6 mmol) in dry acetonitrile (10 ml), diethylamine (0.5 g, 6 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated in vacuum, the residue was washed with diethyl ether and dried in vacuum (room temperature, 0.1 Torr, 2 h) to give the title compound **4**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ, ppm: 0.86-0.99 (m, 6H), 1.07 – 1.13 (m, 3H), 1.74 – 1.83 (m, 1H), 1.85 – 1.95 (m, 2H), 1.95 – 2.08 (m, 1H), 2.40 – 2.49 (m, 4H), 2.86 – 2.97 (m, 2H), 3.06 – 3.14 (m, 2H), 3.25 – 3.34 (m, 1H), 3.36 – 3.44 (m, 2H), 3.48 – 3.57 (m, 1H), 5.01 – 5.08 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 11.9,15.1, 23.1, 32.5, 46.0, 46.9, 47.2, 49.6, 63.1, 89.5. ESI: m/z calcd for $C_{12}H_{26}N_2O_3S$ $[M+H]^+$ 279, found 279.

Copies of NMR spectra

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16.42
16.36
16.32
16.26
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O
CH3
O
P
O
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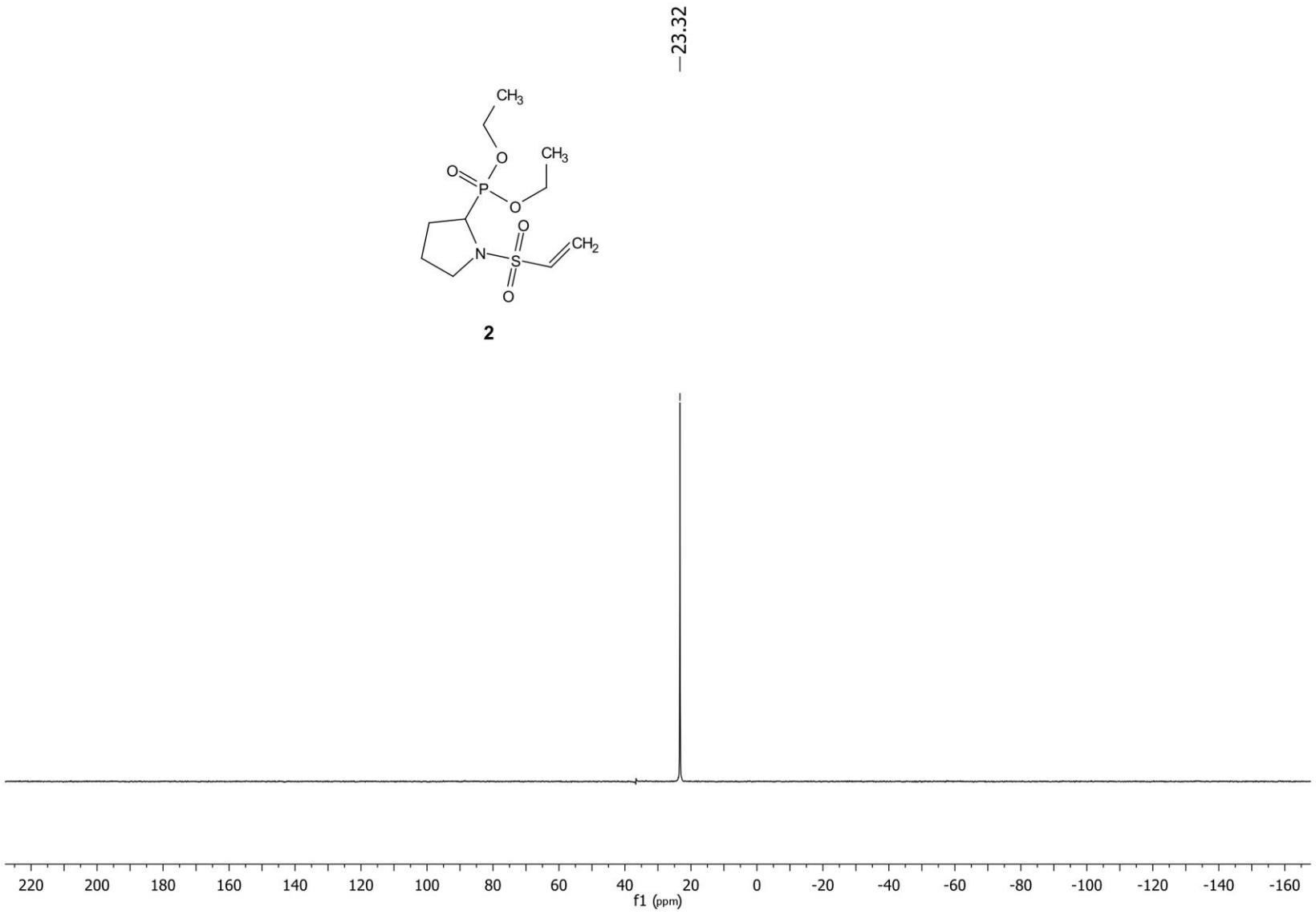
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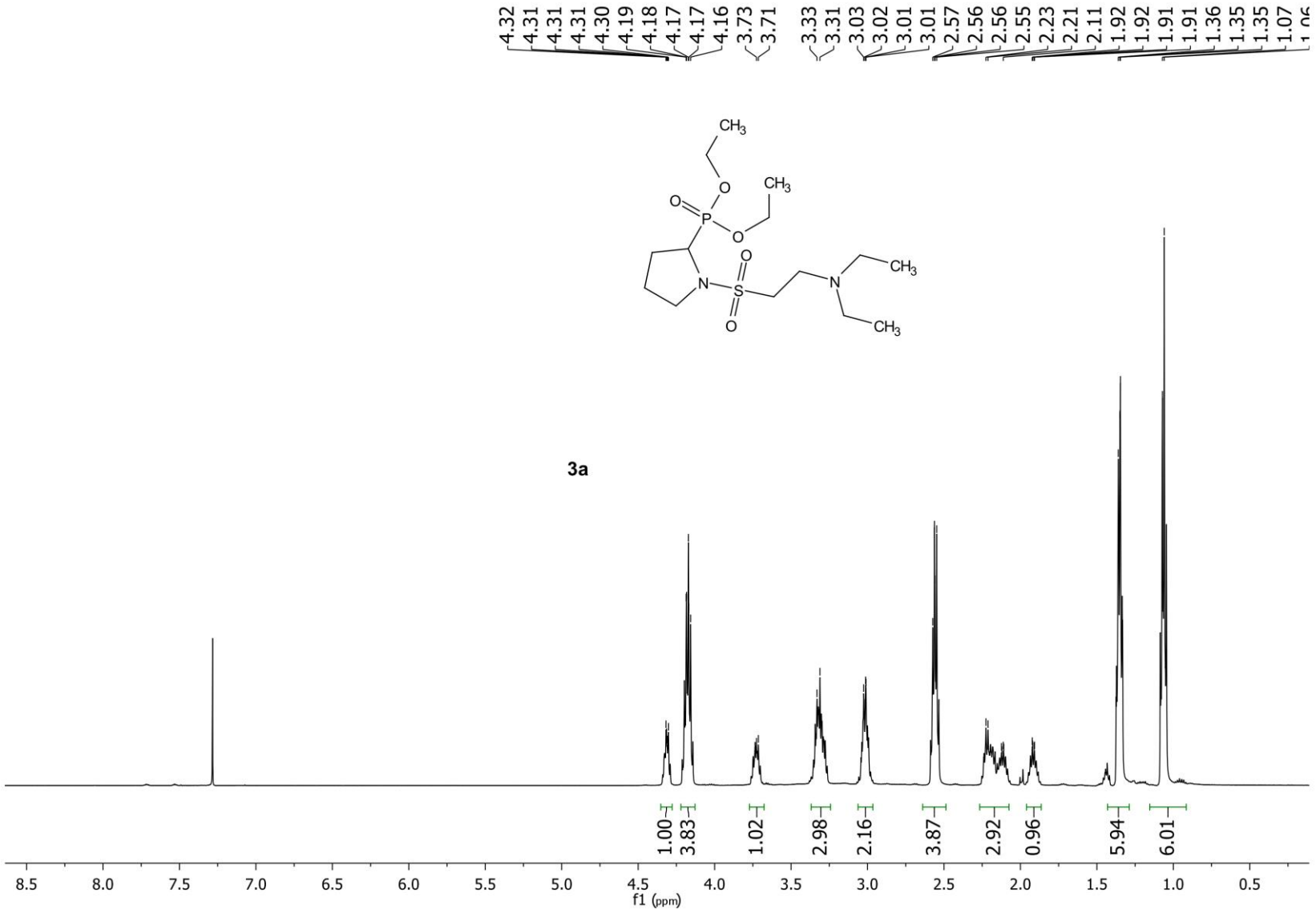
-160
f1 (ppm)

2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3.31
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3.02
3.01
3.01
2.57
2.56
2.56
2.55
2.23
2.21
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1.92
1.91
1.91
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1.35
1.35
1.07
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O
CH3
O
P
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O
O
N
S
N
CH3
CH3
3a
1.00
3.83
1.02
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2.16
3.87
2.92
0.96
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6.01
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6.0
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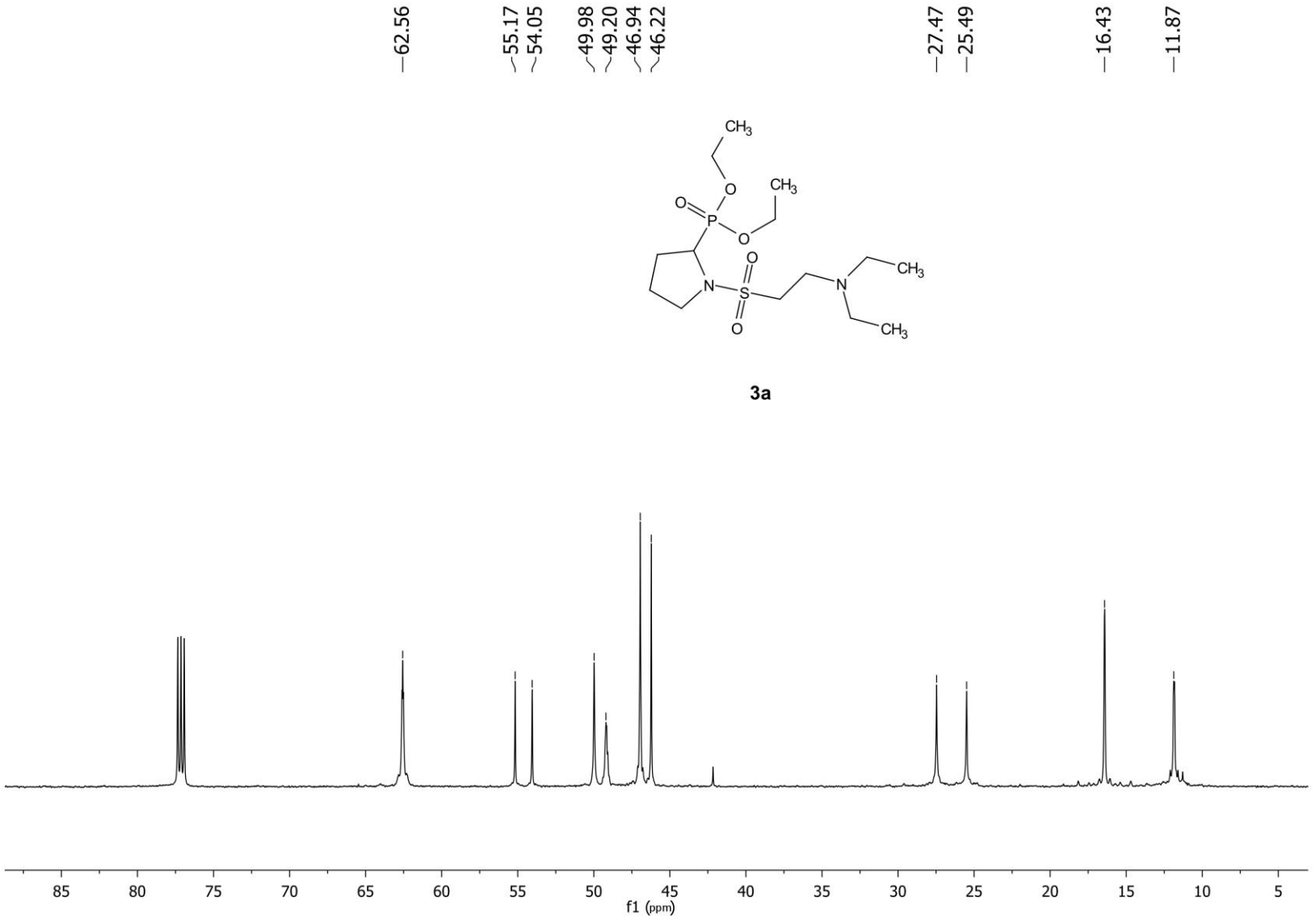
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N
S
O
O
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CH3
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10
5
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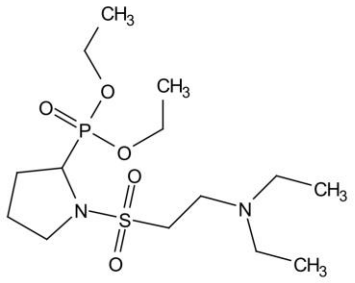
3a



3a

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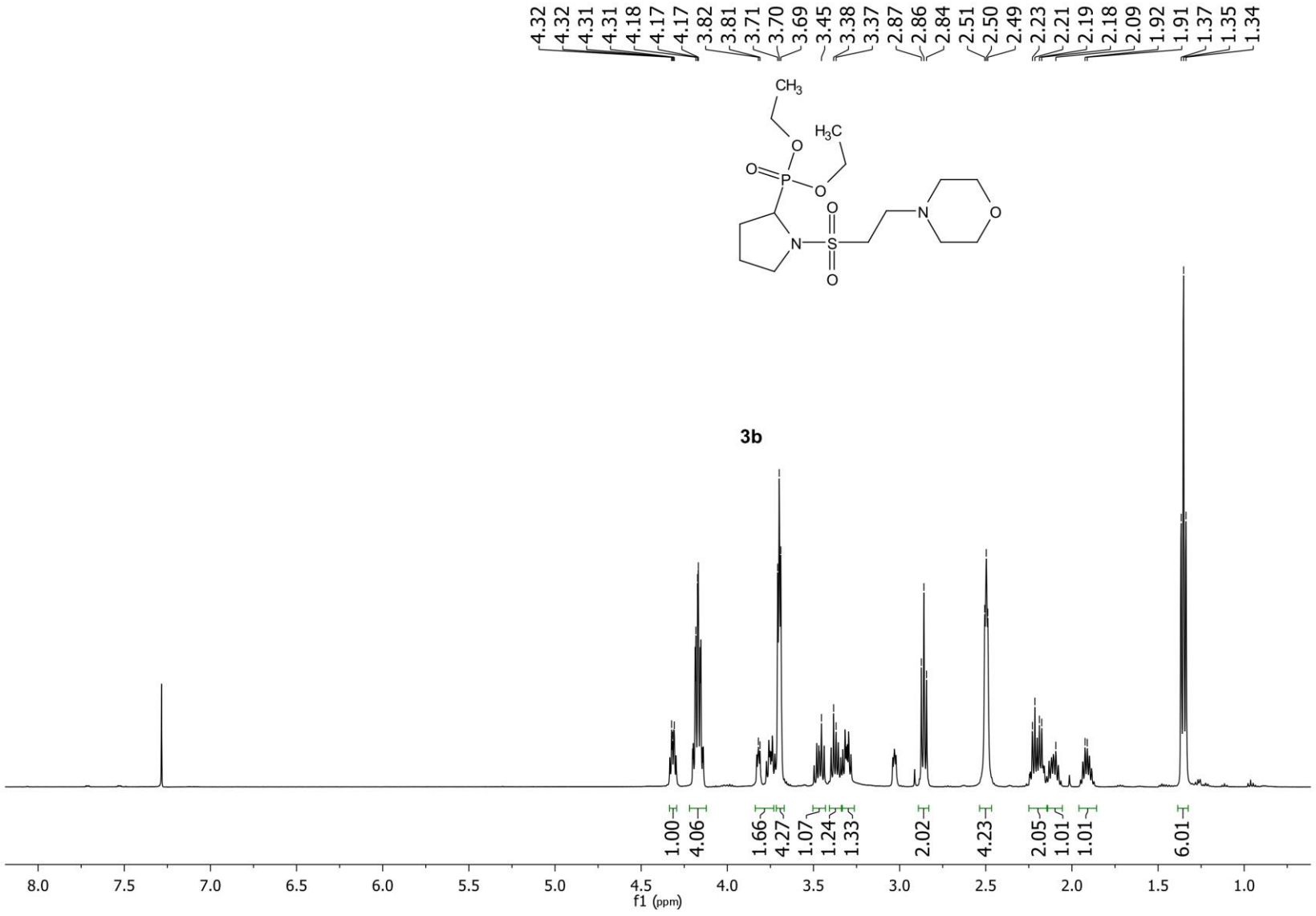
f1 (ppm)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2.18
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1.37
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1.34
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H3C
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O
N
O
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1.33
2.02
4.23
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1.01
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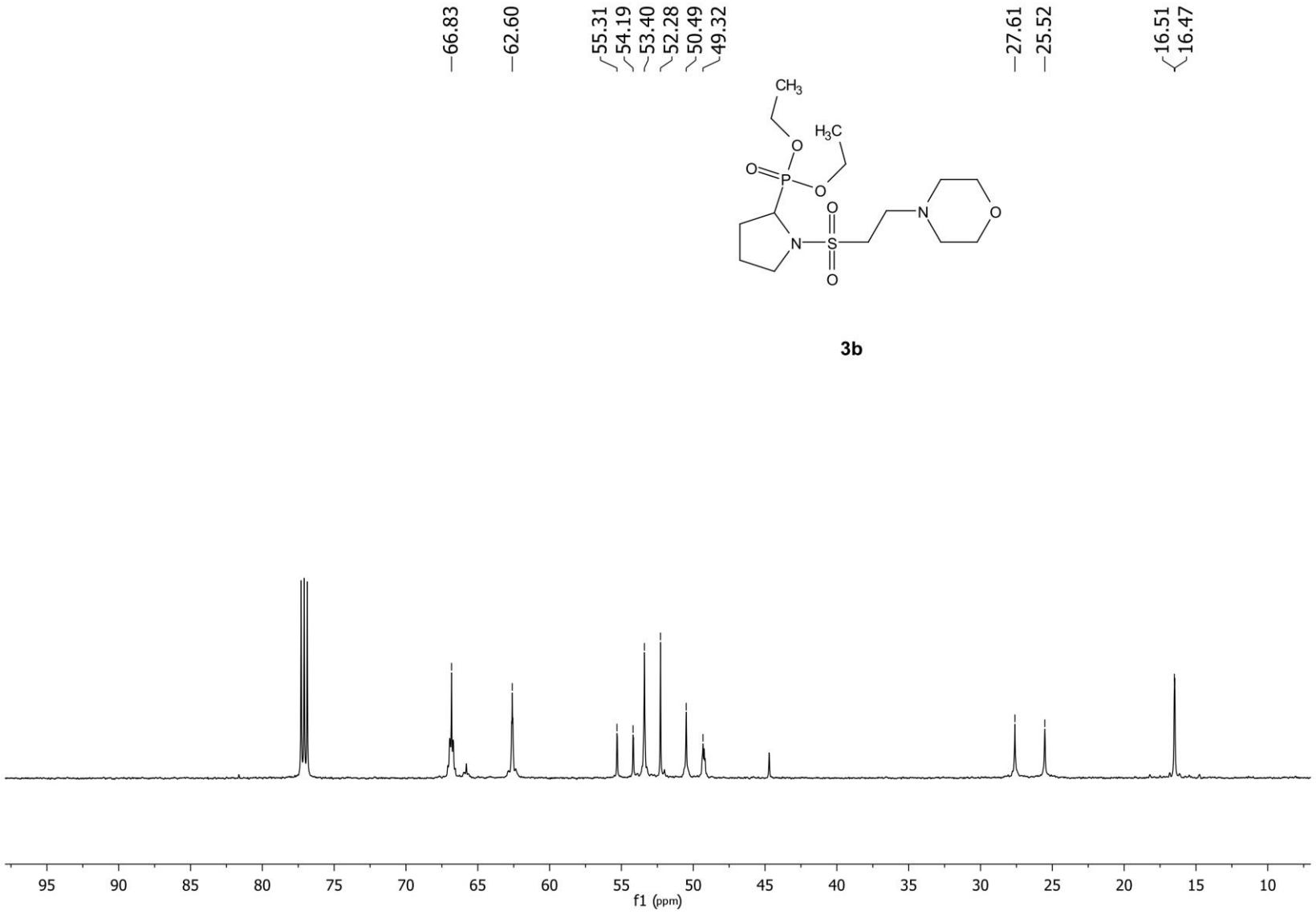
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P
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O
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N
S
O
N
O
O
95
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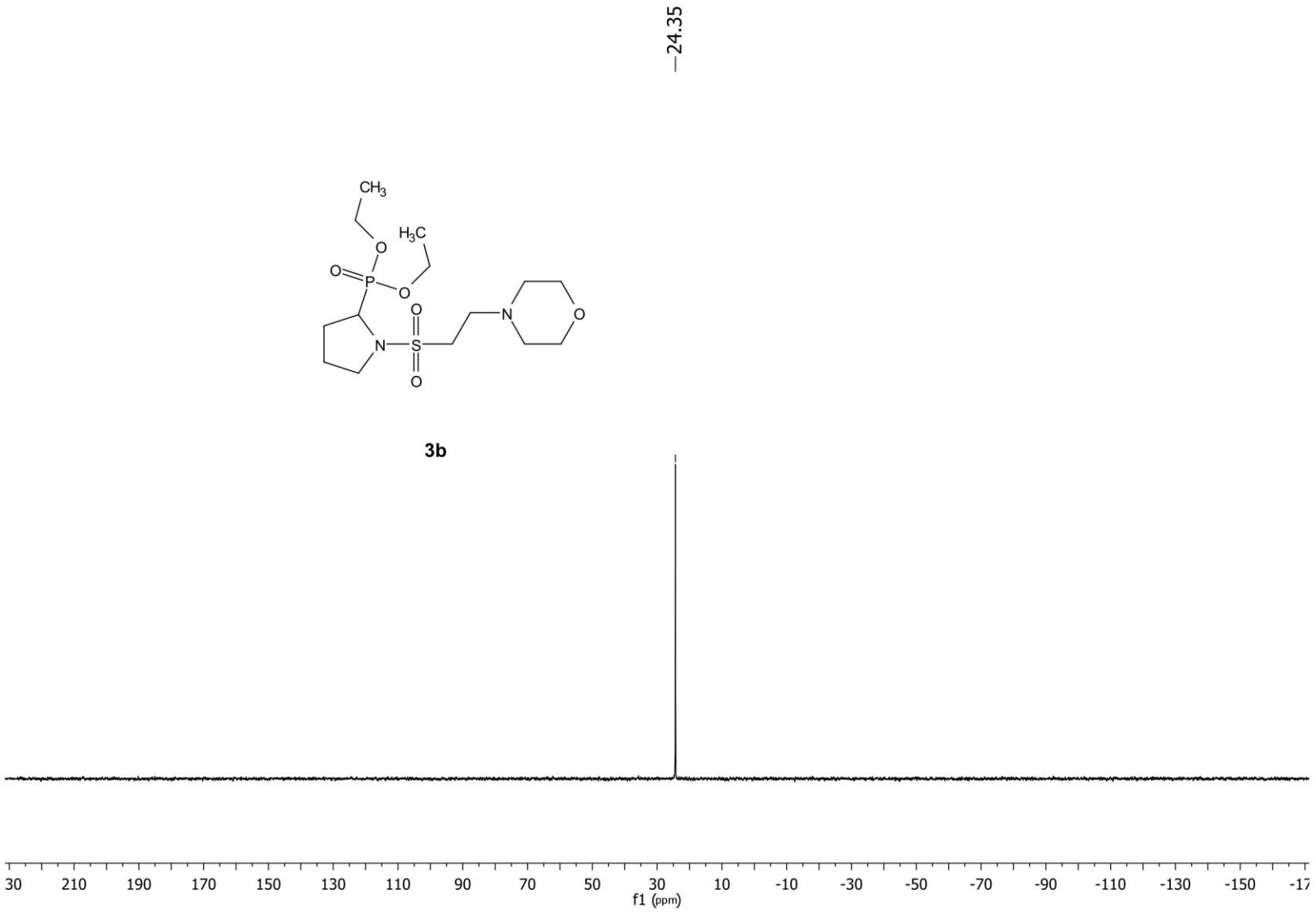
3b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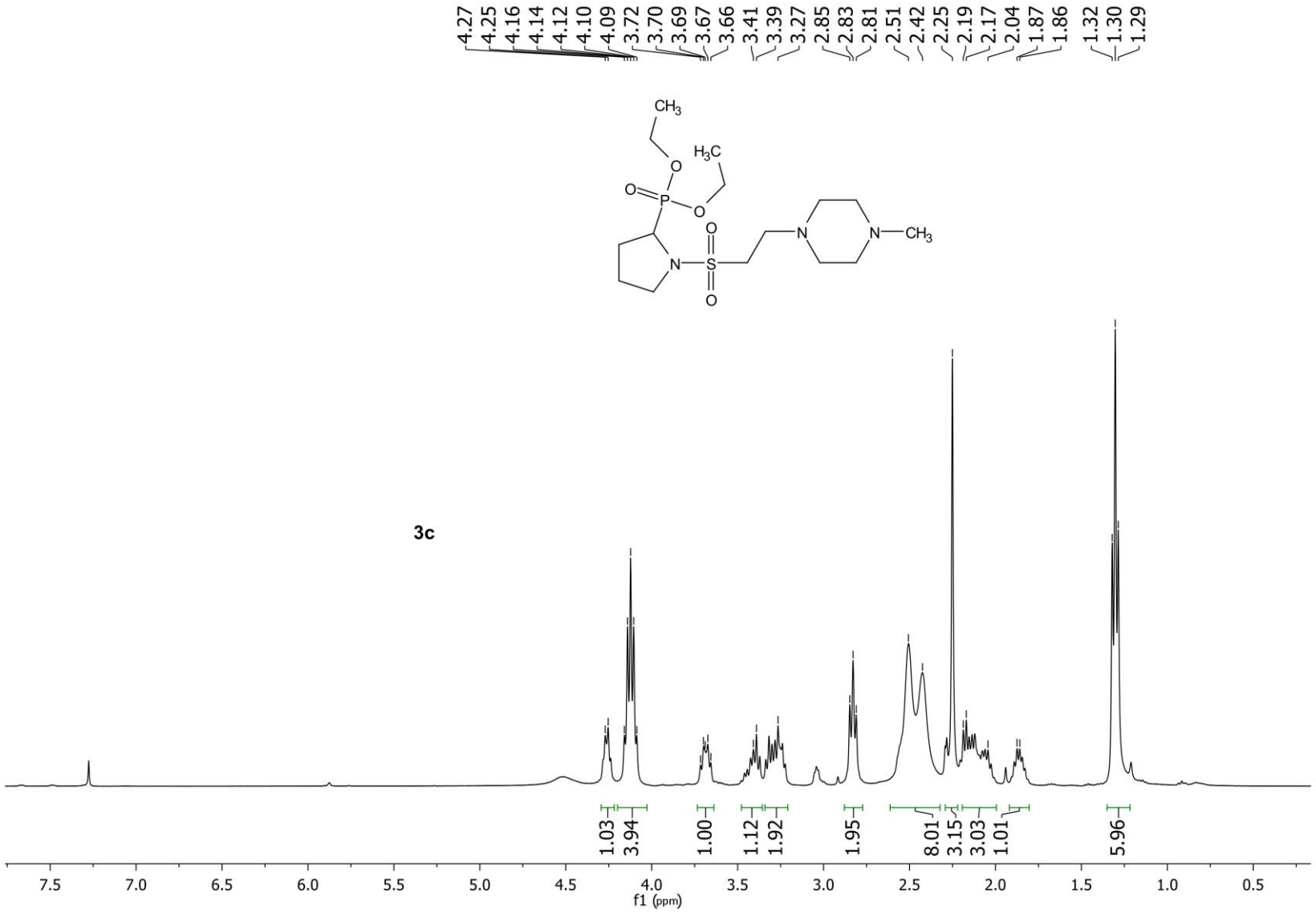
3b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2.83
2.81
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2.19
2.17
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1.86
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1.30
1.29
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H3C
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P
O
O
N
S
O
O
N
N
CH3
3c
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3.94
1.00
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1.92
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8.01
3.15
3.03
1.01
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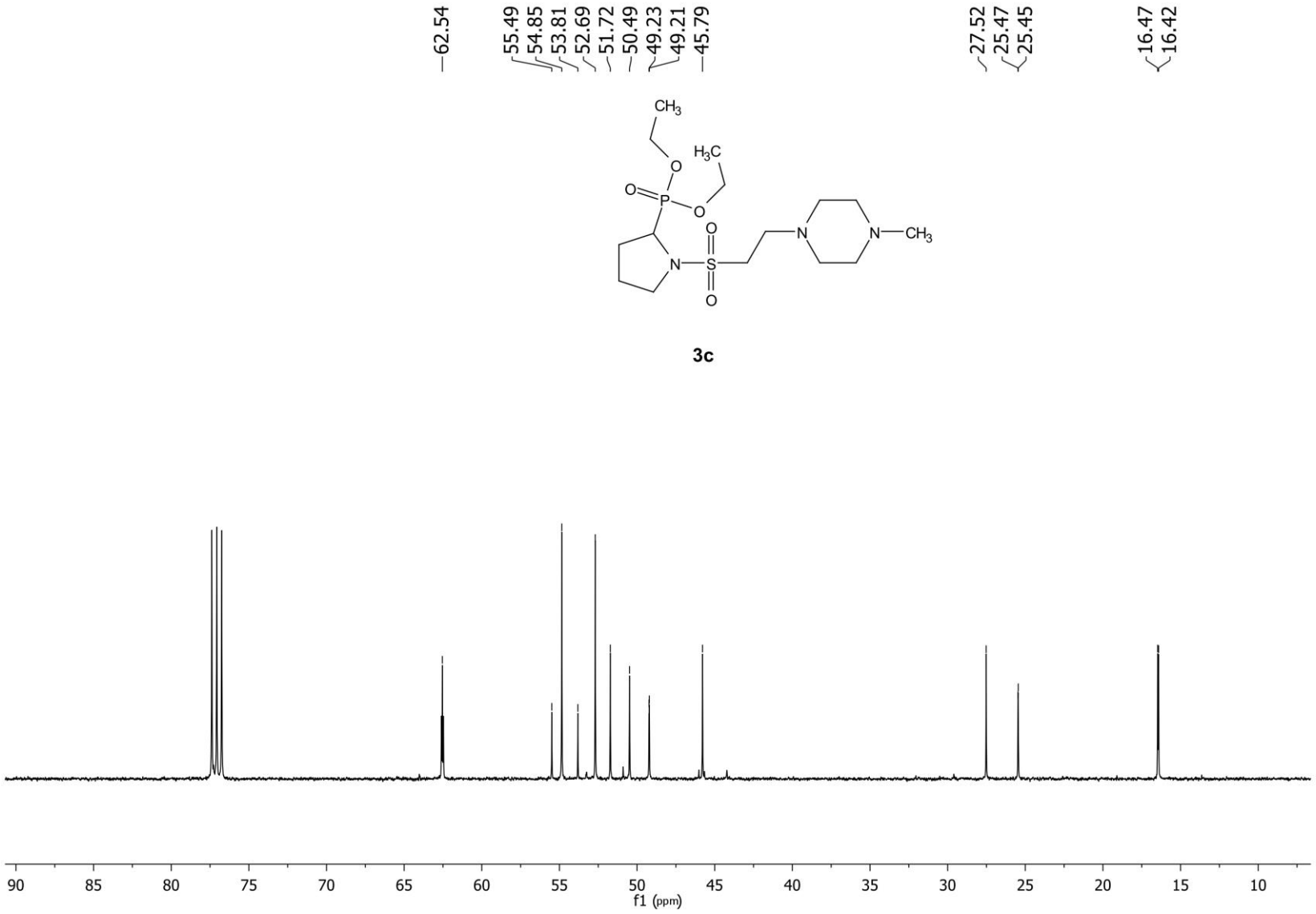
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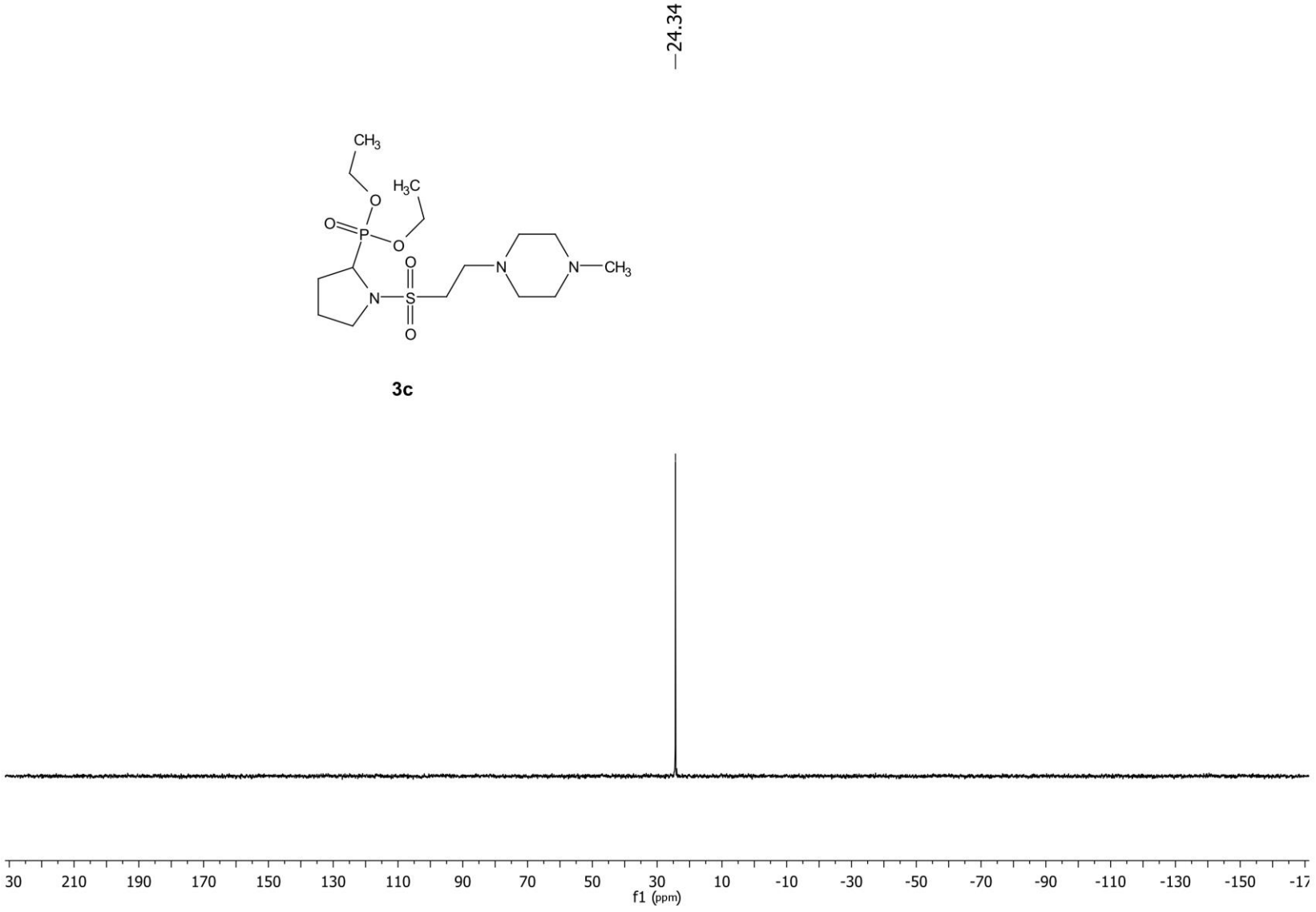
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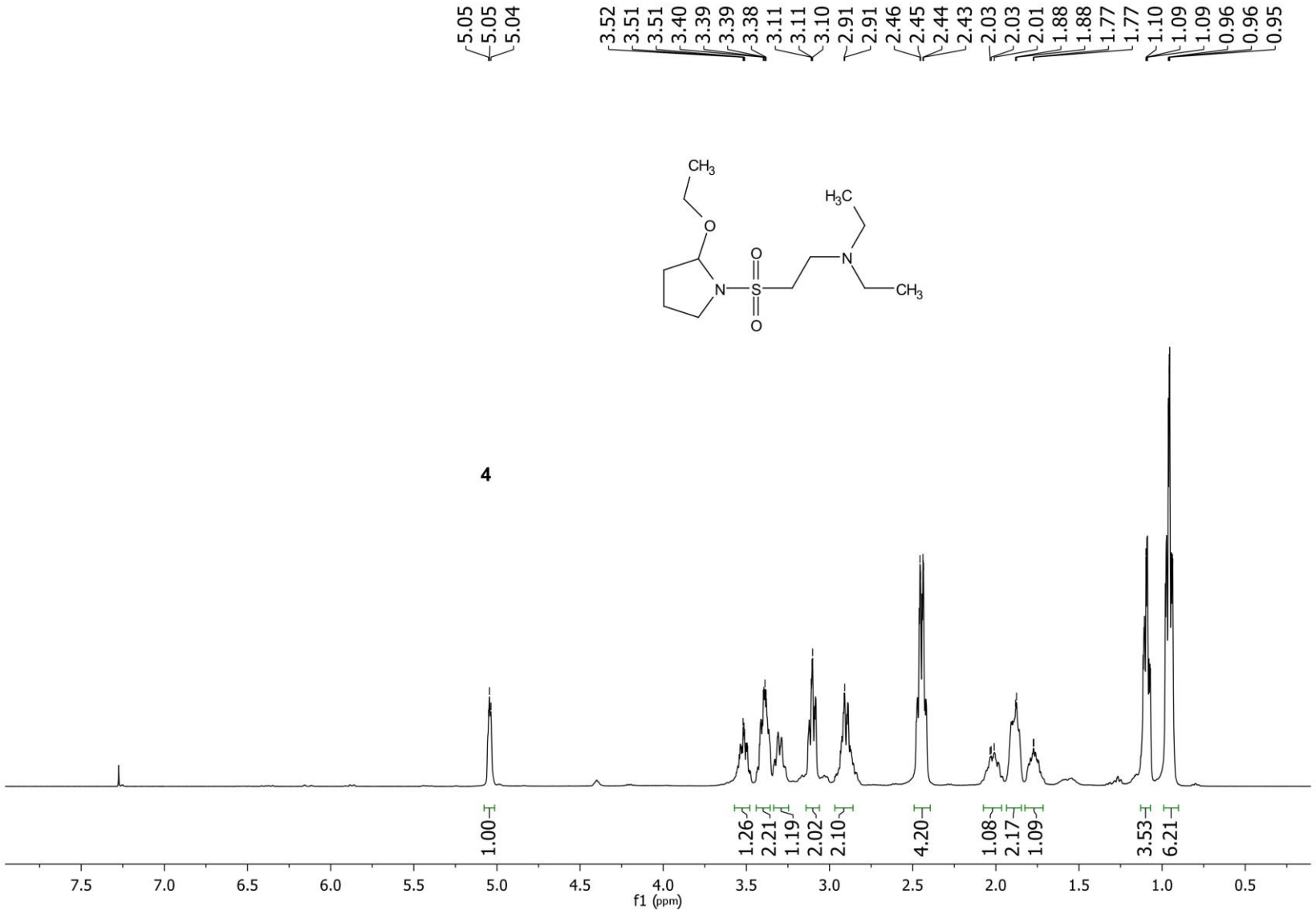
3c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2.01
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1.10
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H3C
O
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O
O
N
CH3
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1.26
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2.10
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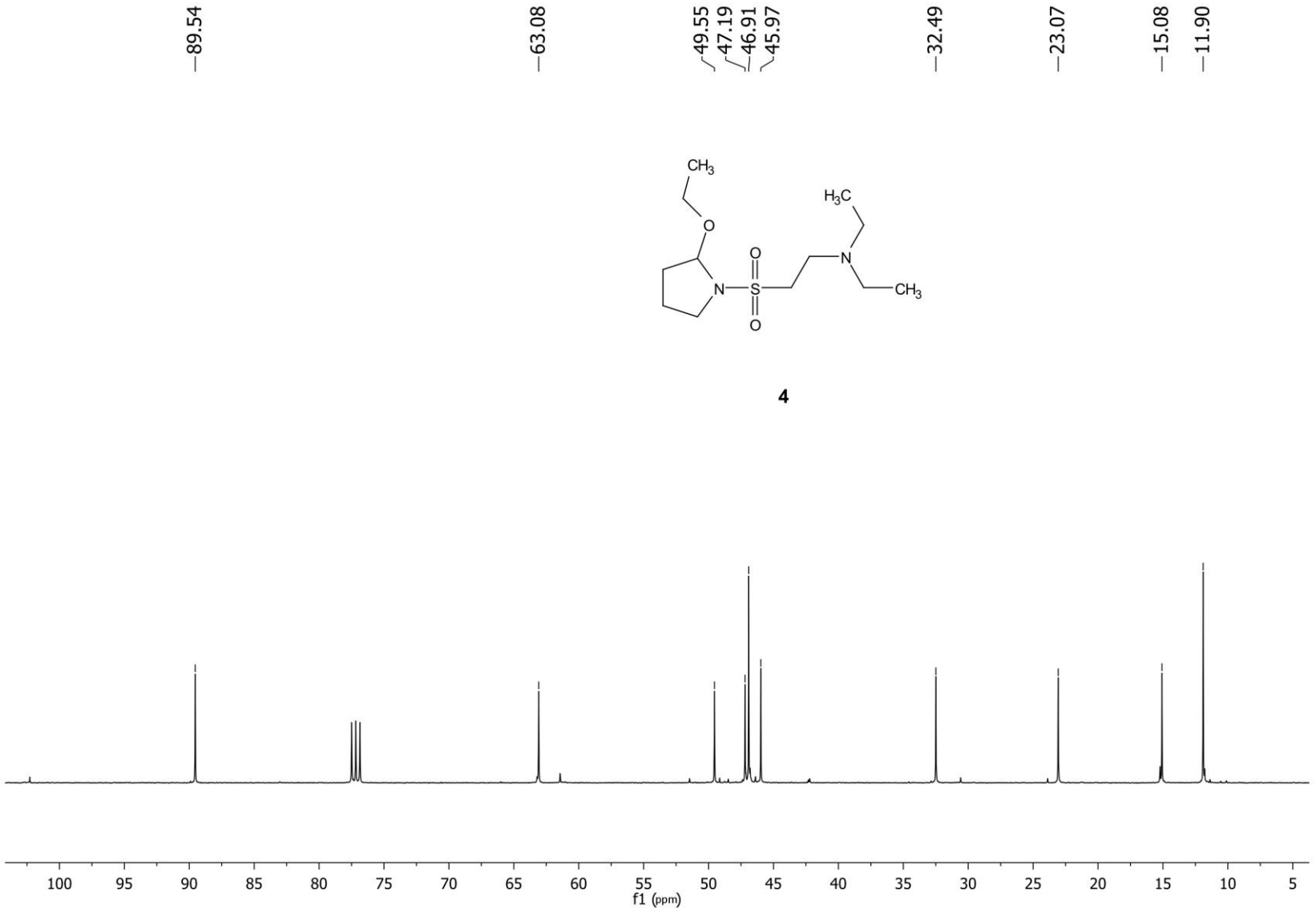
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O
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S
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CH3
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75
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65
60
55
50
45
40
35
30
25
20
15
10
5
f1 (ppm)

4