

Supplementary Material A

1. Chemical synthesis and analysis data

1.1. Compounds 8a,b and 4a,b

General procedure for the preparation of compounds 8a,b.

To a well stirred mixture of 2-iodophenol (4.54 mmol), palladium acetate (0.22 mmol), CuI (0.22 mmol) and triphenylphosphine (0.22 mmol) in dry triethylamine (10.0 ml) 3-butyne-1-ol or 4-pentyne-1-ol (5.0 mmol) was added under argon atmosphere. The reaction mixture was then stirred overnight at room temperature. The reaction mixture was concentrated, diluted with EtOAc (30 mL), and the organic layer was washed with H₂O (2 x 20 mL) and brine (30 mL). The organic layer was dried over MgSO₄ and filtered. The solvent was evaporated and the residue was purified by silica gel flash-column chromatography to yield a yellow oil:

2-(1-benzofuran-2-yl)ethanol 8a: [Yield: 87.0%]⁴⁴ (570 mg, 78.0%): R_f=0.39 (chloroform/EtOAc 7:3); ¹H NMR (600 MHz, CDCl₃): δ=3.04 (t, J=6.1 Hz, 2H, H-1), 3.99 (t, J=6.1 Hz, 2H, H-2), 6.51 (s, 1H, CH^{furan}), 7.17-7.23 (m, 2H, C₆H₄), 7.41 (d, J=7.8 Hz, 1H, C₆H₄), 7.49 ppm (d, J=7.8 Hz, 1H, C₆H₄); ¹³C NMR (150 MHz, CDCl₃): δ=32.33 (CH₂CH₂OH), 61.00 (CH₂CH₂OH), 103.91 (C^{furan}), 111.08, 120.65, 122.87, 123.77, 128.93, 155.09 (C₆H₄), 156.19 ppm (C^{furan}).

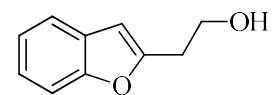
3-(1-benzofuran-2-yl)propan-1-ol 8b: (580 mg, 73.0%): R_f=0.40 (chloroform/EtOAc 7:3); ¹H NMR (600 MHz, CDCl₃): δ=1.97-2.03 (m, 2H, H-2), 2.87 (t, J=7.3 Hz, 2H, H-1), 3.72 (t, J=6.3 Hz, 2H, H-3), 6.40 (s, 1H, CH^{furan}), 7.15-7.21 (m, 2H, C₆H₄), 7.39 (d, J=7.4 Hz, 1H, C₆H₄), 7.46 ppm (d, J=7.2 Hz, 1H, C₆H₄); ¹³C NMR (150 MHz, CDCl₃): δ=25.03 (CH₂CH₂CH₂OH), 30.90 (CH₂CH₂CH₂OH), 62.21 (CH₂CH₂CH₂OH), 102.44 (C^{furan}), 110.96, 120.47, 122.70, 123.45, 129.12, 154.95 (C₆H₄), 157.20 ppm (C^{furan}).

General procedure for the preparation of compounds 4a,b.

To a solution of the appropriate alcohol **8a,b** in pyridine (6.91 mmol) at 0 °C methane sulfonyl chloride (1.72 mmol) was added dropwise. The reaction mixture was stirred at room temperature overnight and then poured into ice-cold water. The reaction mixture was quenched with hydrochloric acid until slightly acidic pH was noted. The water layer was extracted with diethyl ether (3x20mL). The organic layers were combined, dried over MgSO₄, and filtered. The solvent was evaporated and the residue was purified by silica gel flash-column chromatography to give the desired compound as a sticky oil:

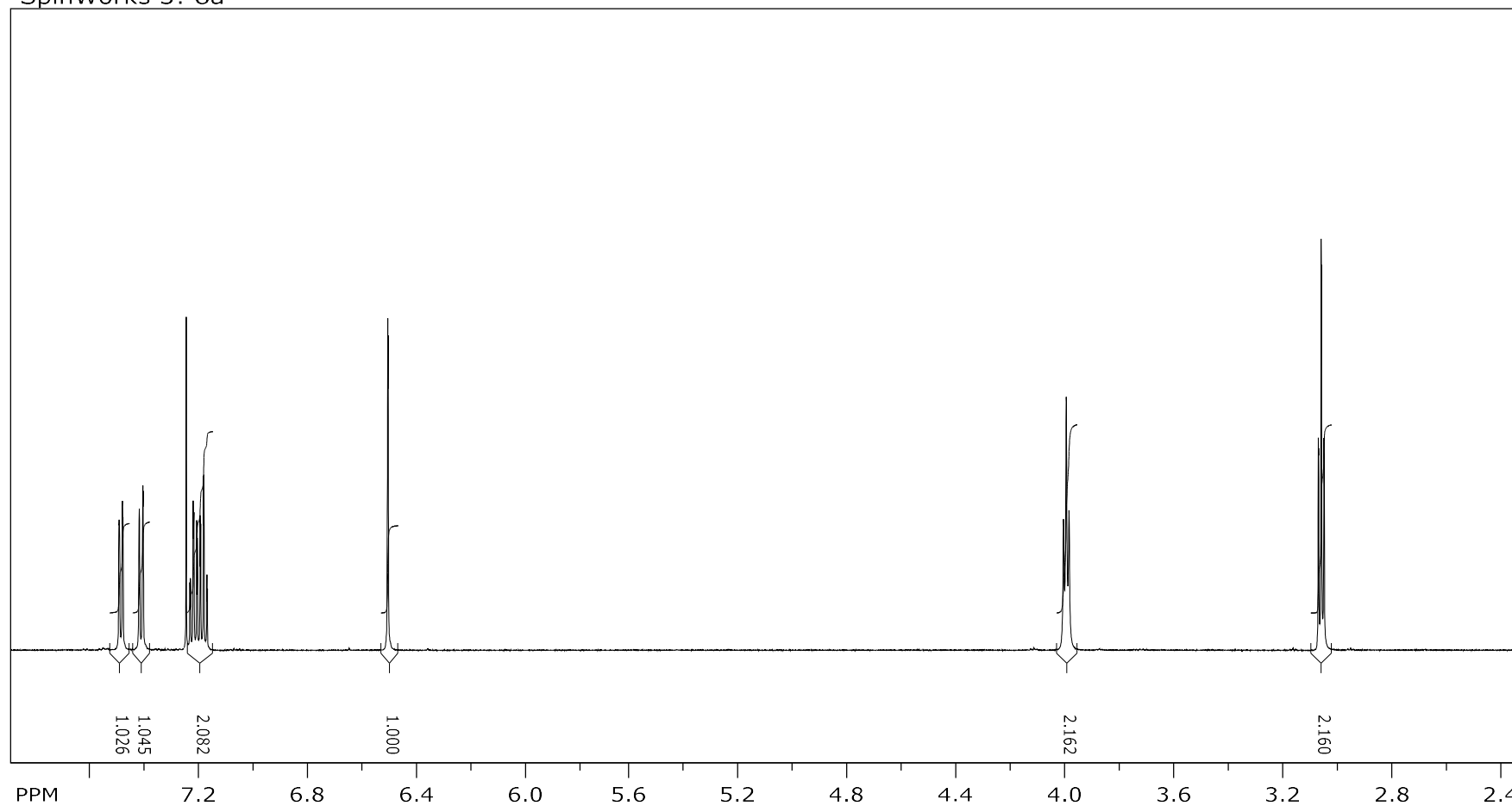
2-(1-benzofuran-2-yl)ethyl methanesulfonate 4a: (370 mg, 90.0%): R_f =0.81 (chloroform/EtOAc 7:1); ¹H NMR (600 MHz, CDCl₃): δ =2.94 (s, 3H, CH₃), 3.24 (t, J =6.6 Hz, 2H, CH₂CH₂OSO₂CH₃), 4.57 (t, J =6.6 Hz, 2H, CH₂CH₂OSO₂CH₃), 6.55 (s, 1H, CH^{furan}), 7.18-7.28 (m, 2H, C₆H₄), 7.40-7.42 (m, 1H, C₆H₄), 7.49-7.52 ppm (m, 1H, C₆H₄); ¹³C NMR (150 MHz, CDCl₃): δ =29.11 (CH₂CH₂OSO₂CH₂), 37.73 (CH₂CH₂OSO₂CH₃), 67.04 (CH₃), 104.67 (C^{furan}), 111.12, 120.91, 123.06, 124.18, 128.67, 153.36 (C₆H₄), 155.04 ppm (C^{furan}).

3-(1-benzofuran-2-yl)propyl methanesulfonate 4b: (390 mg, 89.0%): R_f =0.79 (chloroform/EtOAc 7:1); ¹H NMR (600 MHz, CDCl₃): δ =2.21 (m, 2H, CH₂CH₂CH₂OSO₂CH₃), 2.94 (t, J =7.3 Hz, 2H, CH₂CH₂CH₂OSO₂CH₃), 2.99 (s, 3H, CH₃), 4.30 (t, J =6.2 Hz, 2H, CH₂CH₂CH₂OSO₂CH₃), 6.45 (s, 1H, CH^{furan}), 7.17-7.23 (m, 2H, C₆H₄), 7.39 (d, J =7.9 Hz, 1H, C₆H₄), 7.48 ppm (d, J =7.5 Hz, 1H, C₆H₄); ¹³C NMR (150 MHz, CDCl₃): δ =24.65 (CH₂CH₂CH₂OSO₂CH₃), 27.57 (CH₂CH₂CH₂OSO₂CH₃), 37.53 (CH₃), 68.93 (CH₂CH₂CH₂OSO₂CH₃), 103.14 (C^{furan}), 110.96, 120.62, 122.82, 123.72, 128.86, 154.95 (C₆H₄), 157.20 ppm (C^{furan}).



1.2 ^1H and ^{13}C NMR spectral data of compounds 4a,b and 8a,b

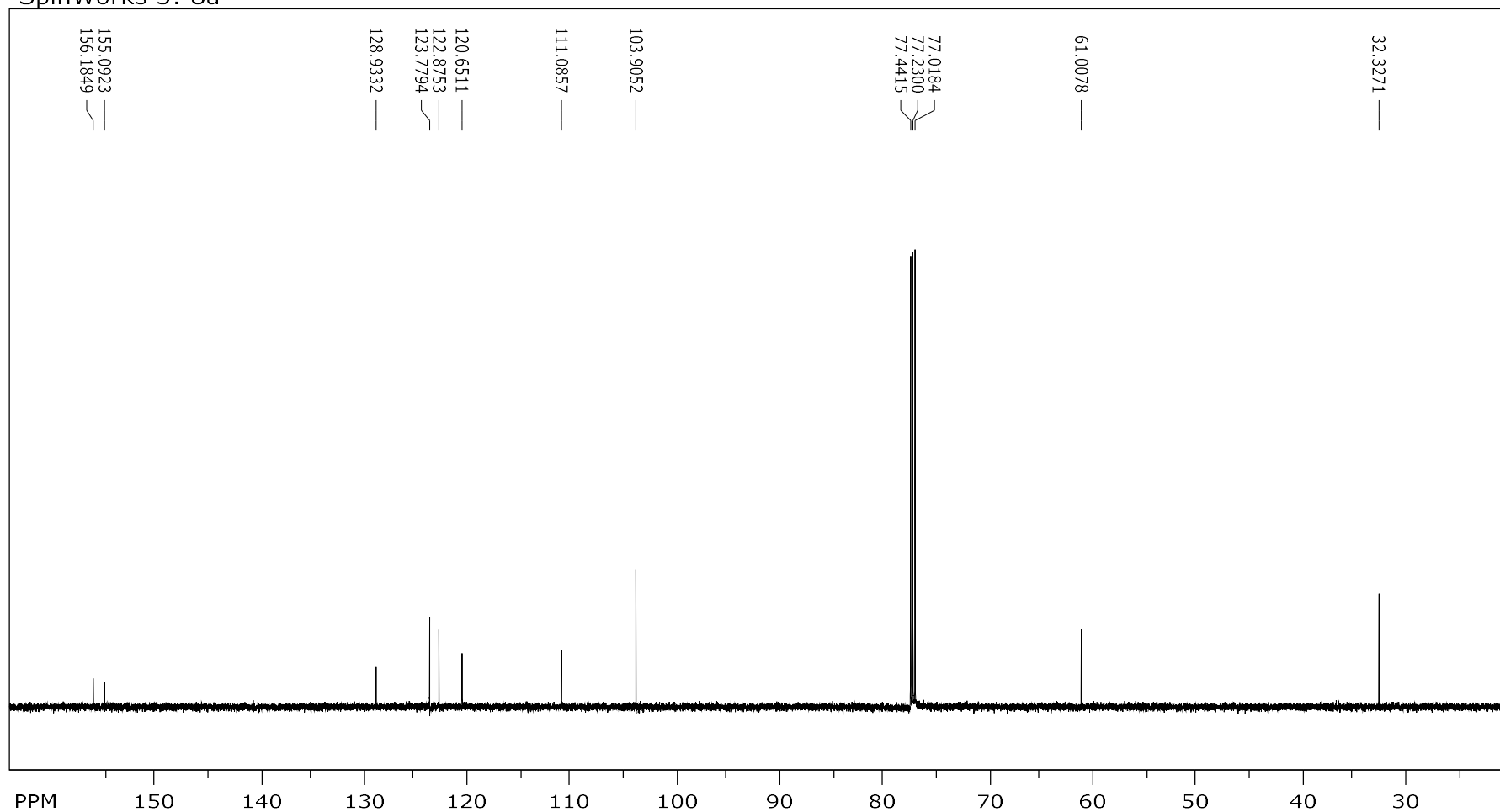
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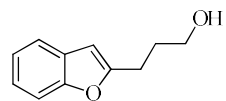
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SpinWorks 3: 8a

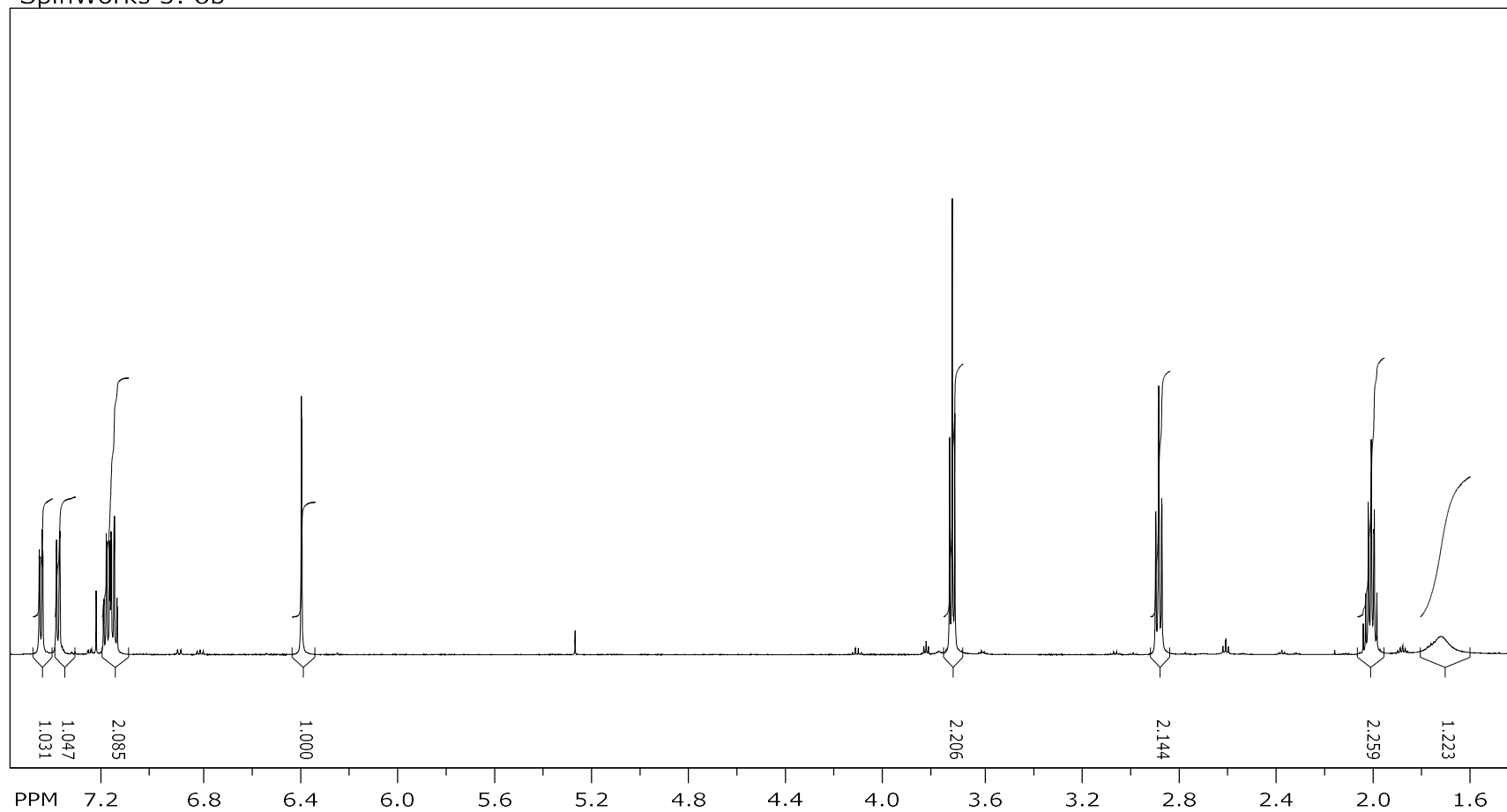


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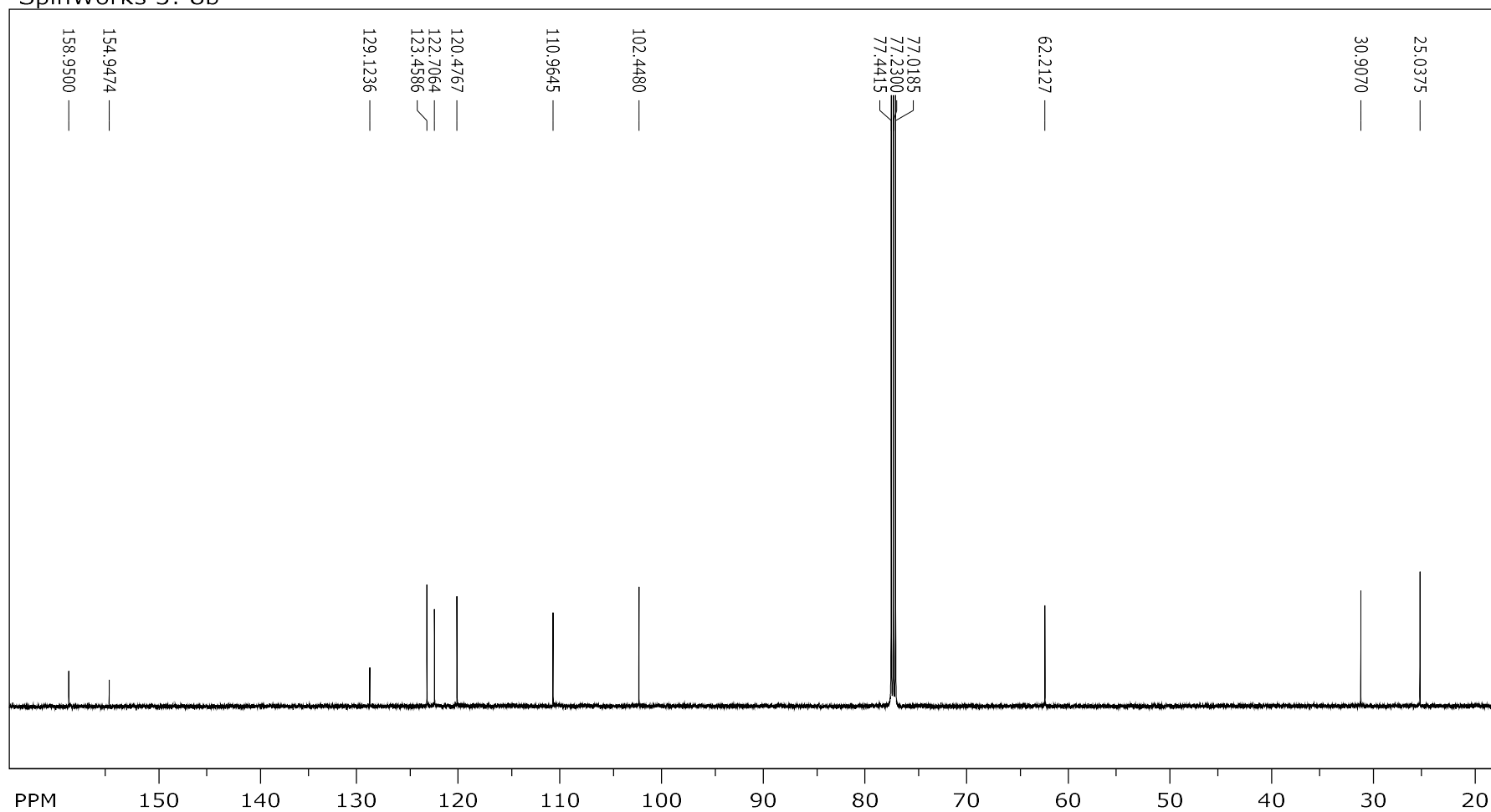
SpinWorks 3: 8b



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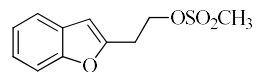
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SpinWorks 3: 8b

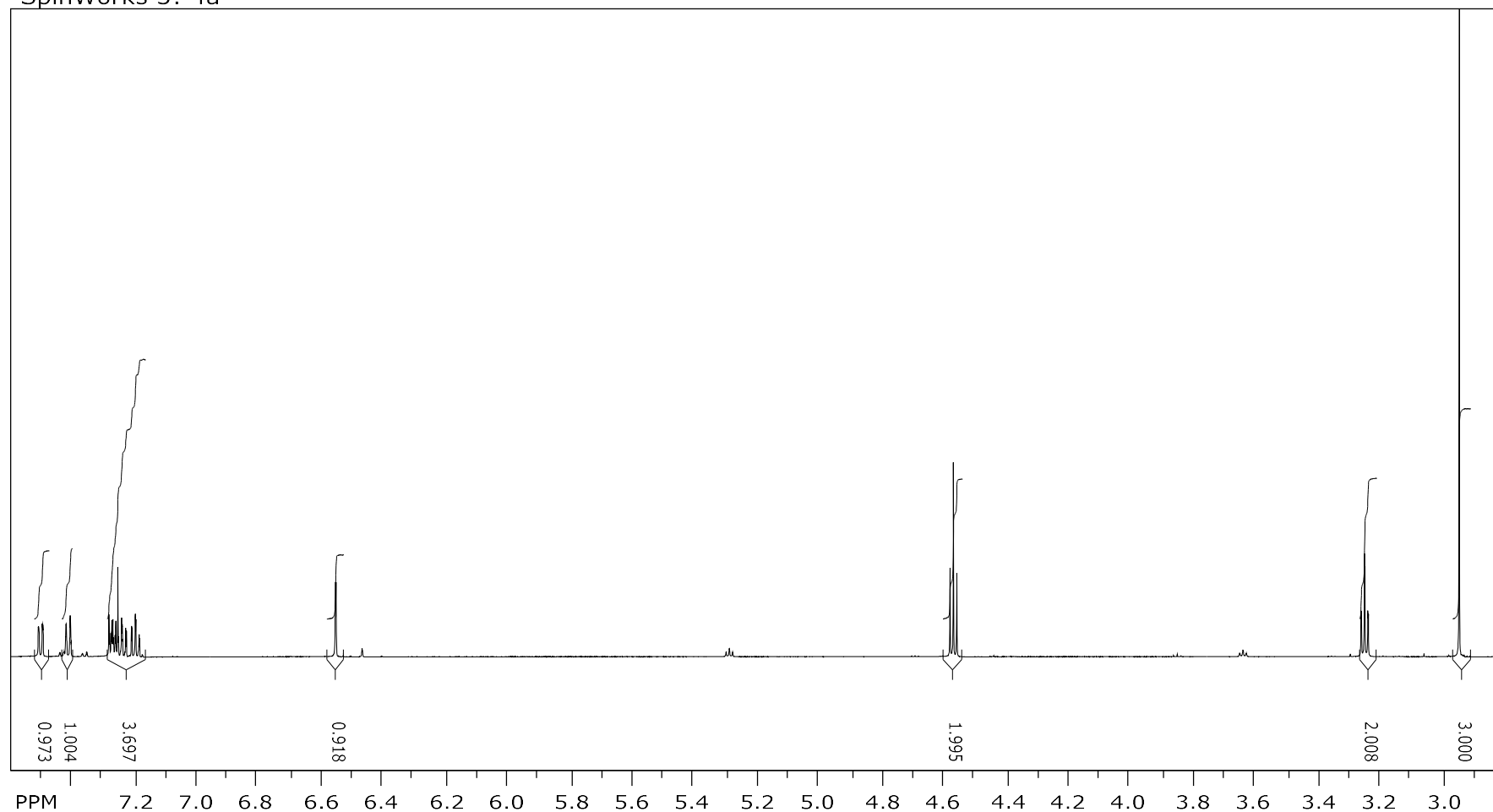


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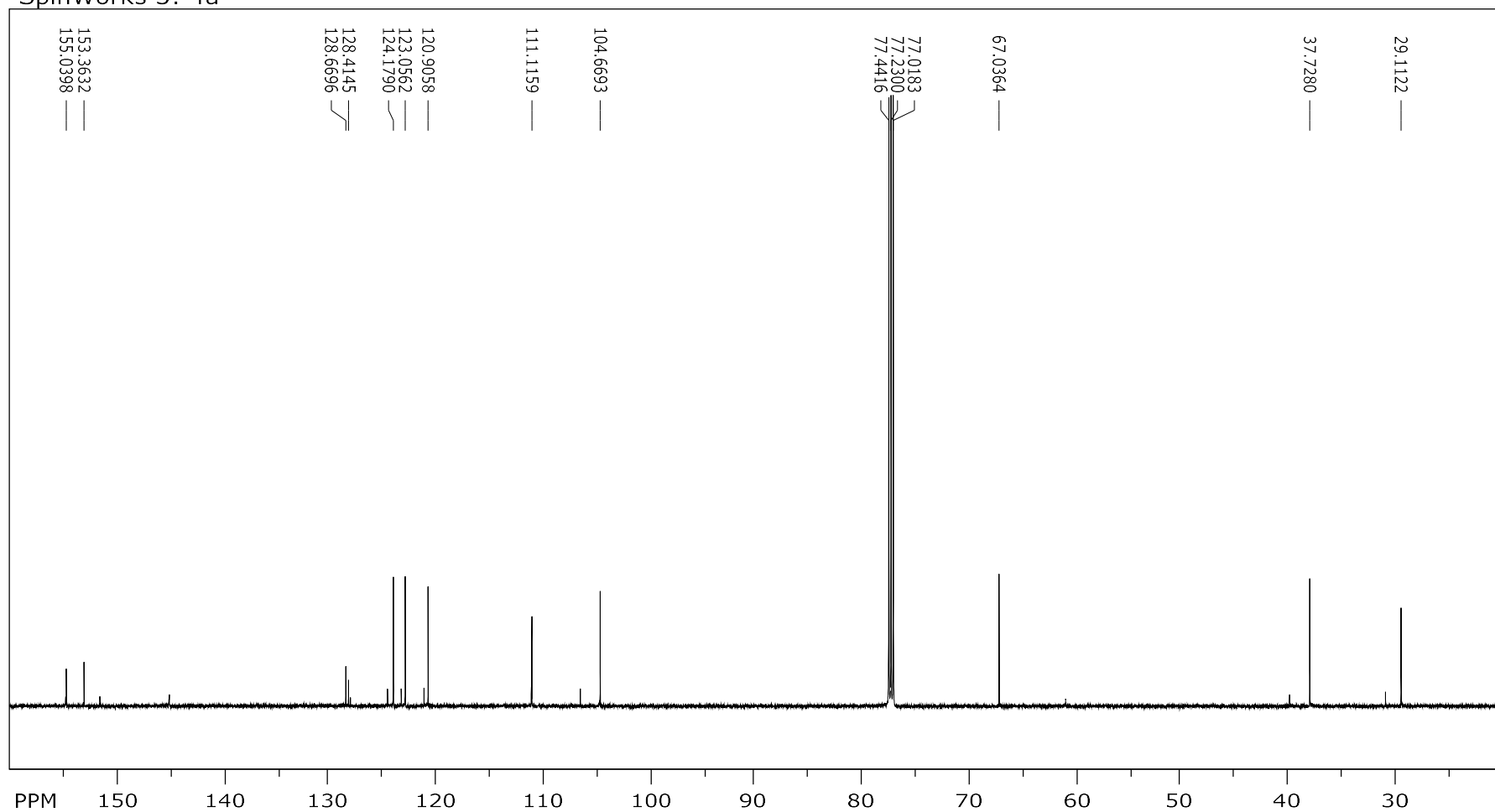
SpinWorks 3: 4a



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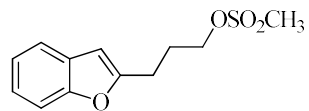
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SpinWorks 3: 4a

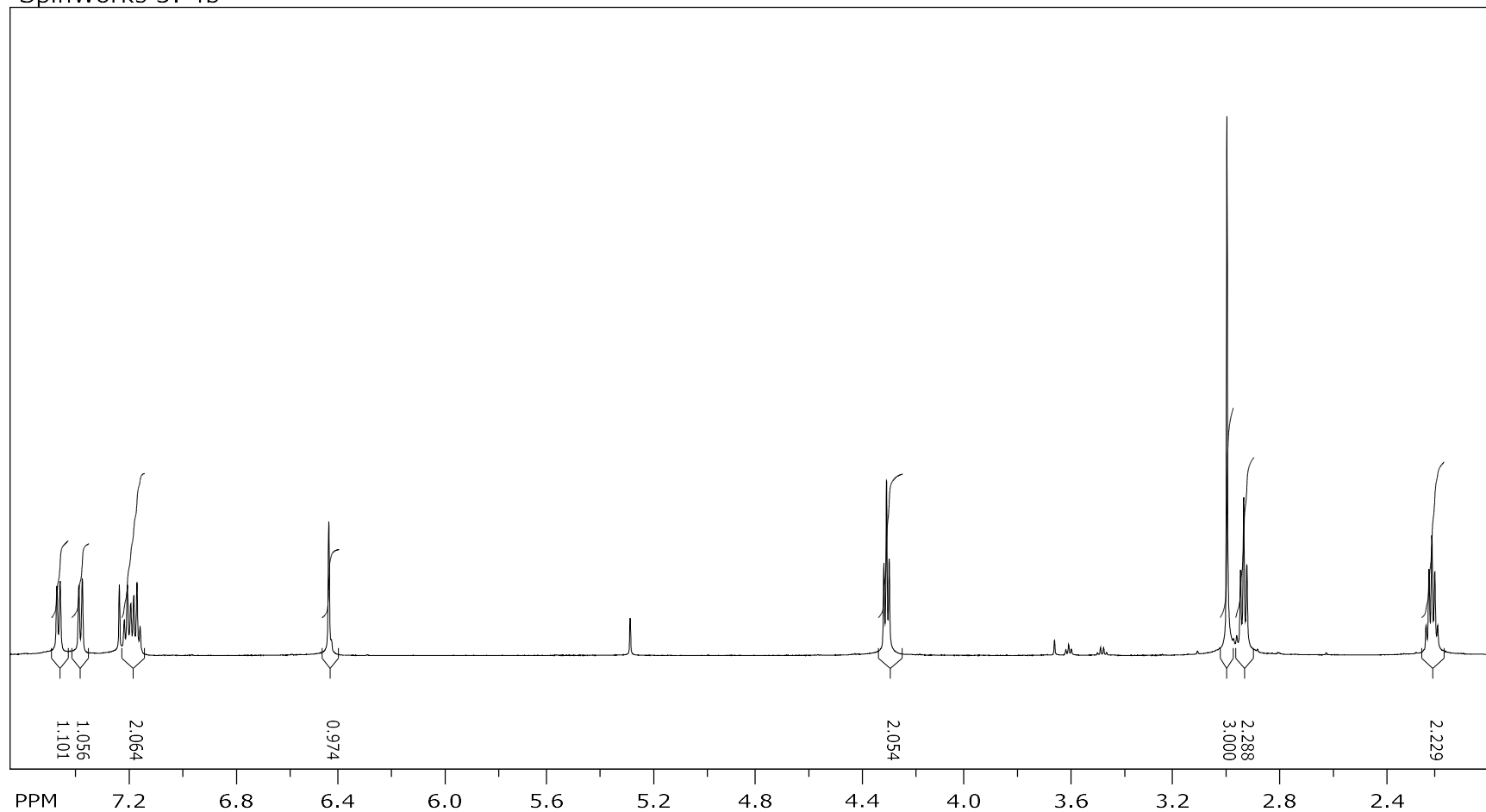


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Hz/cm: 850.799 ppm/cm: 5.63628



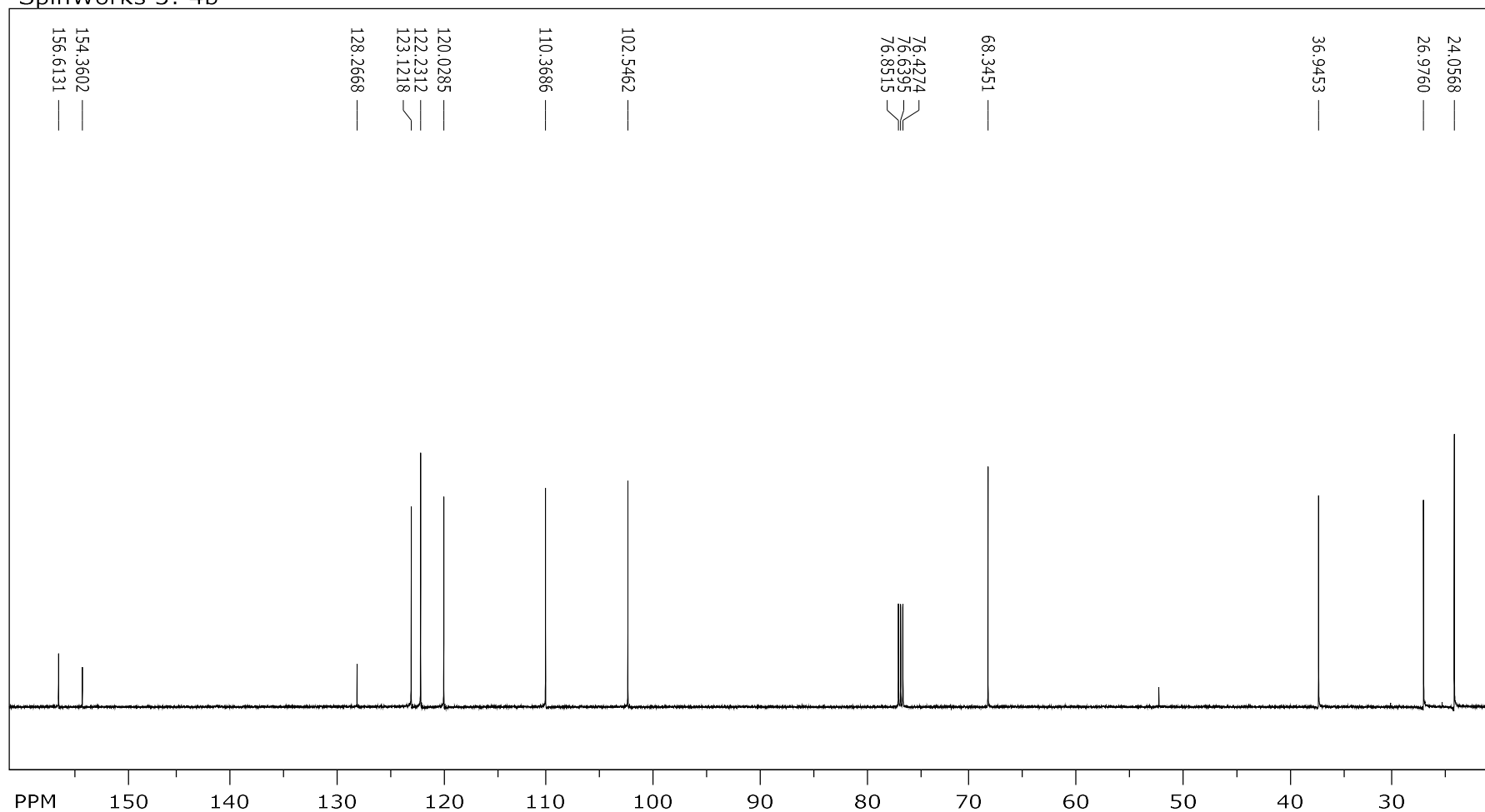
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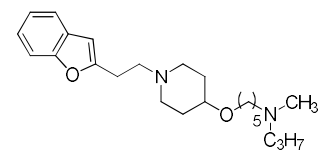
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SpinWorks 3: 4b



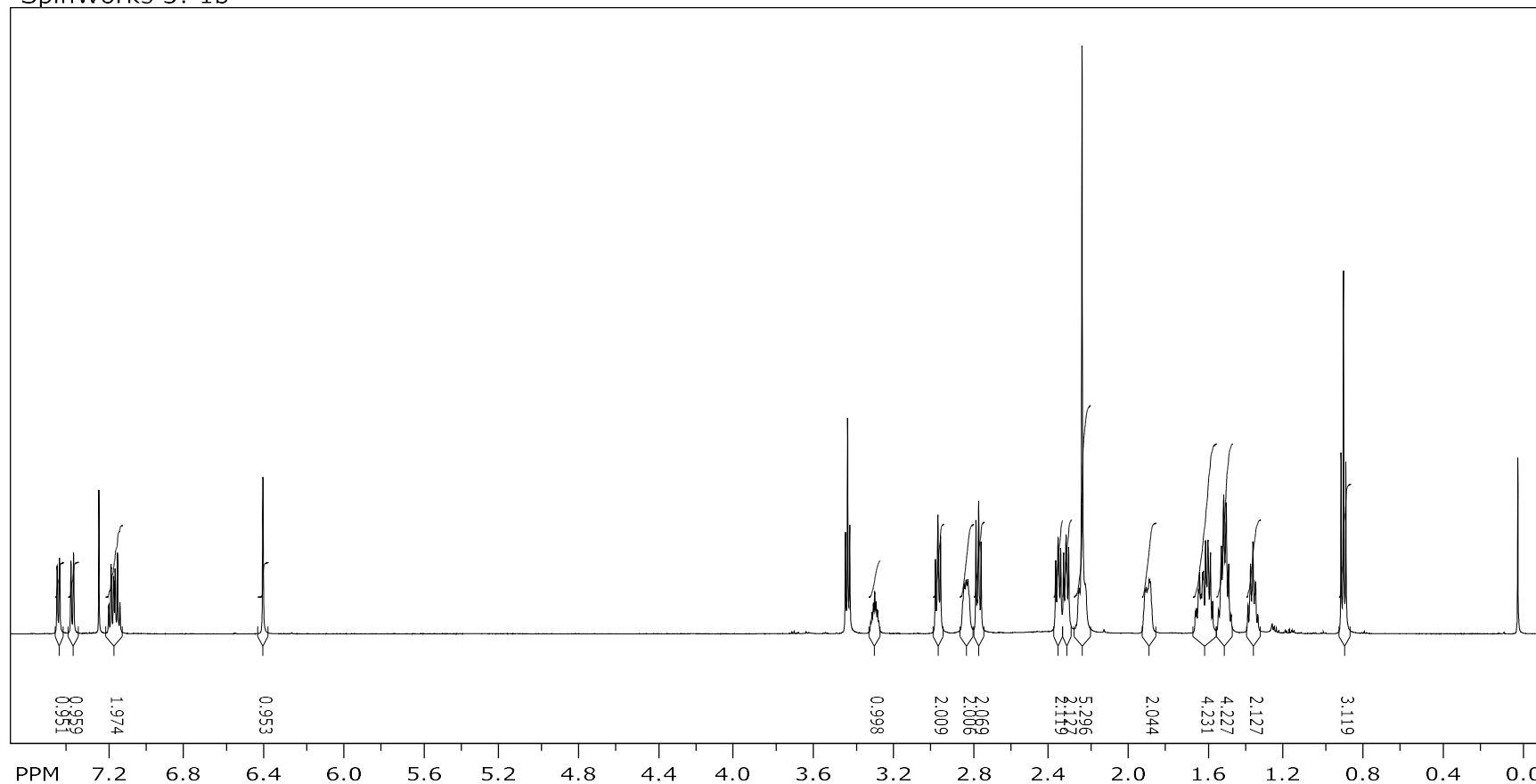
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3. ^1H and ^{13}C NMR spectral data of final compounds 1b,c,e,f and 2b,c,e,f

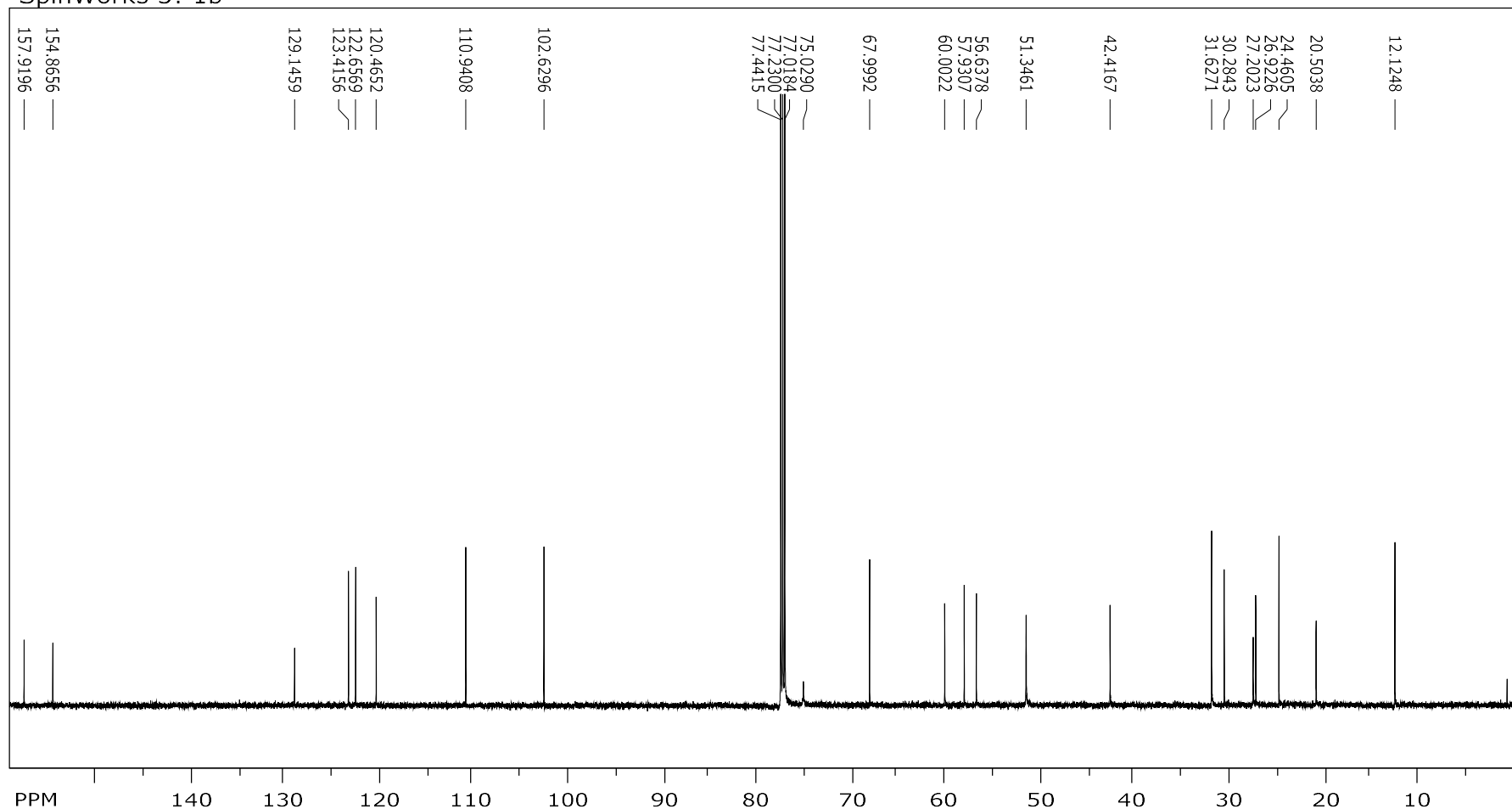
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 number of scans: 16

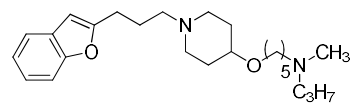
freq. of 0 ppm: 600.260018 MHz
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SpinWorks 3: 1b

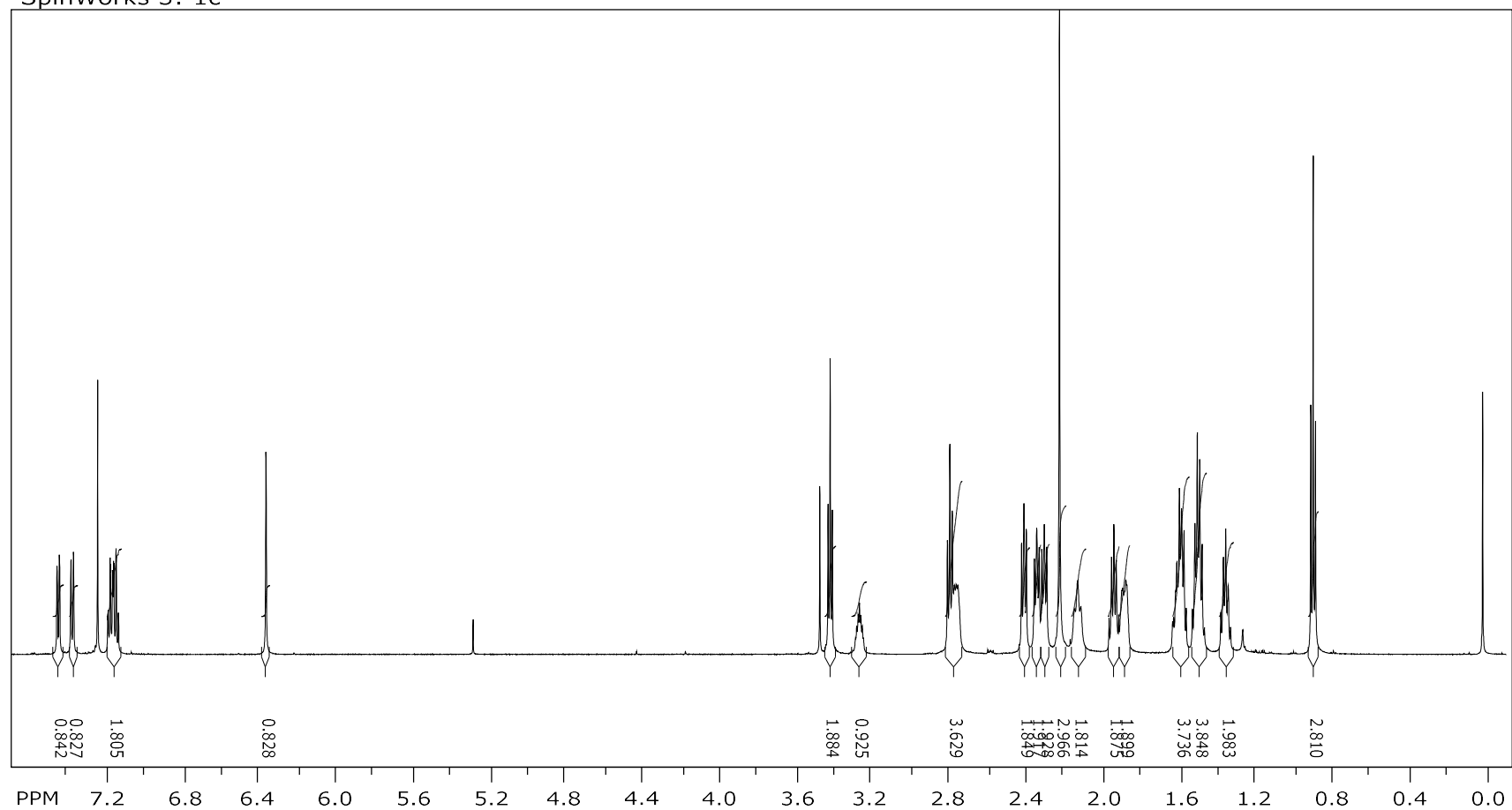


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freq. of 0 ppm: 150.935462 MHz
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 LB: 0.000 GF: 0.0000
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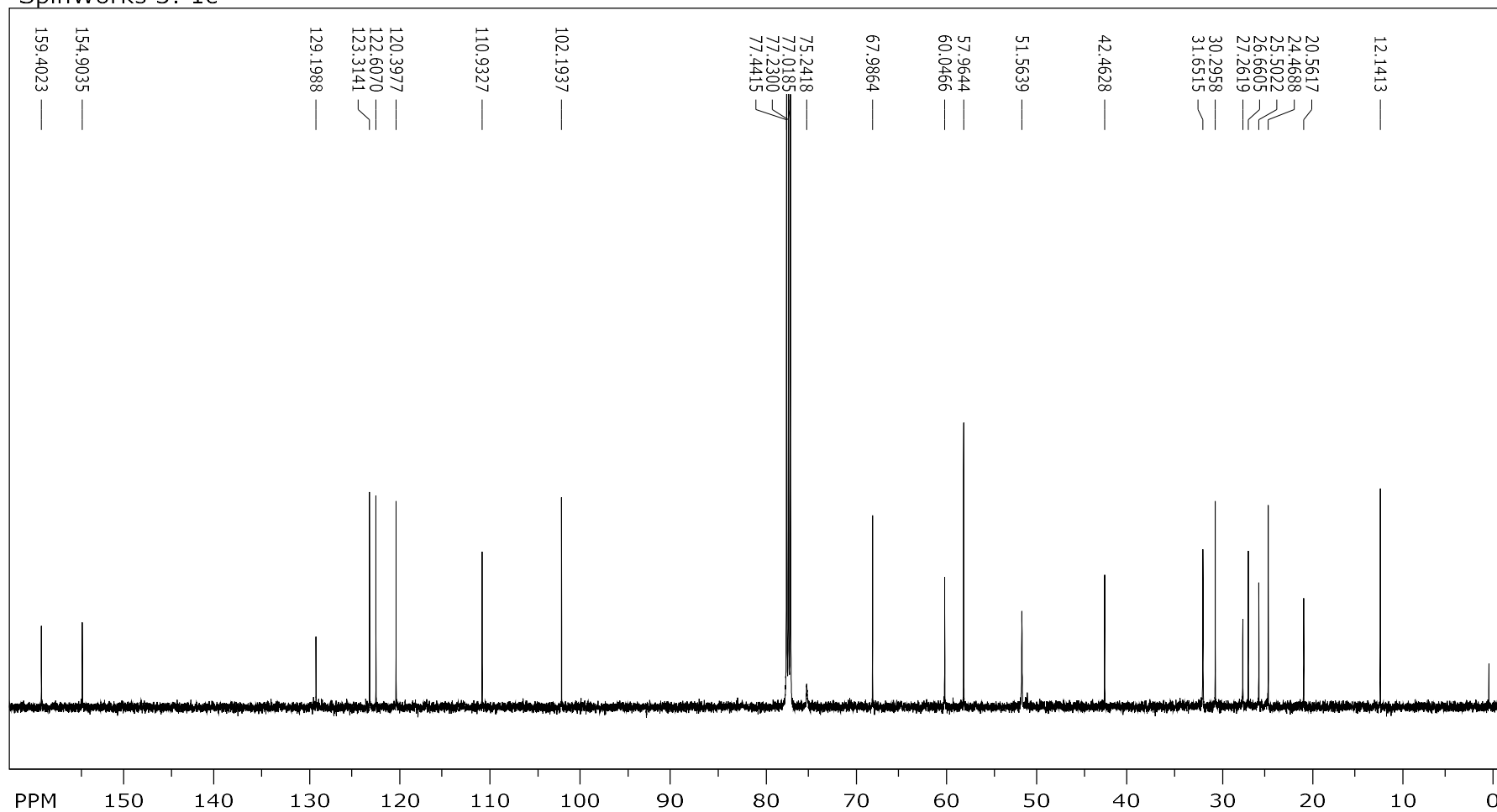
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 number of scans: 16

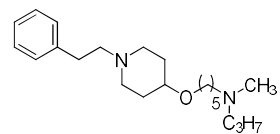
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SpinWorks 3: 1c

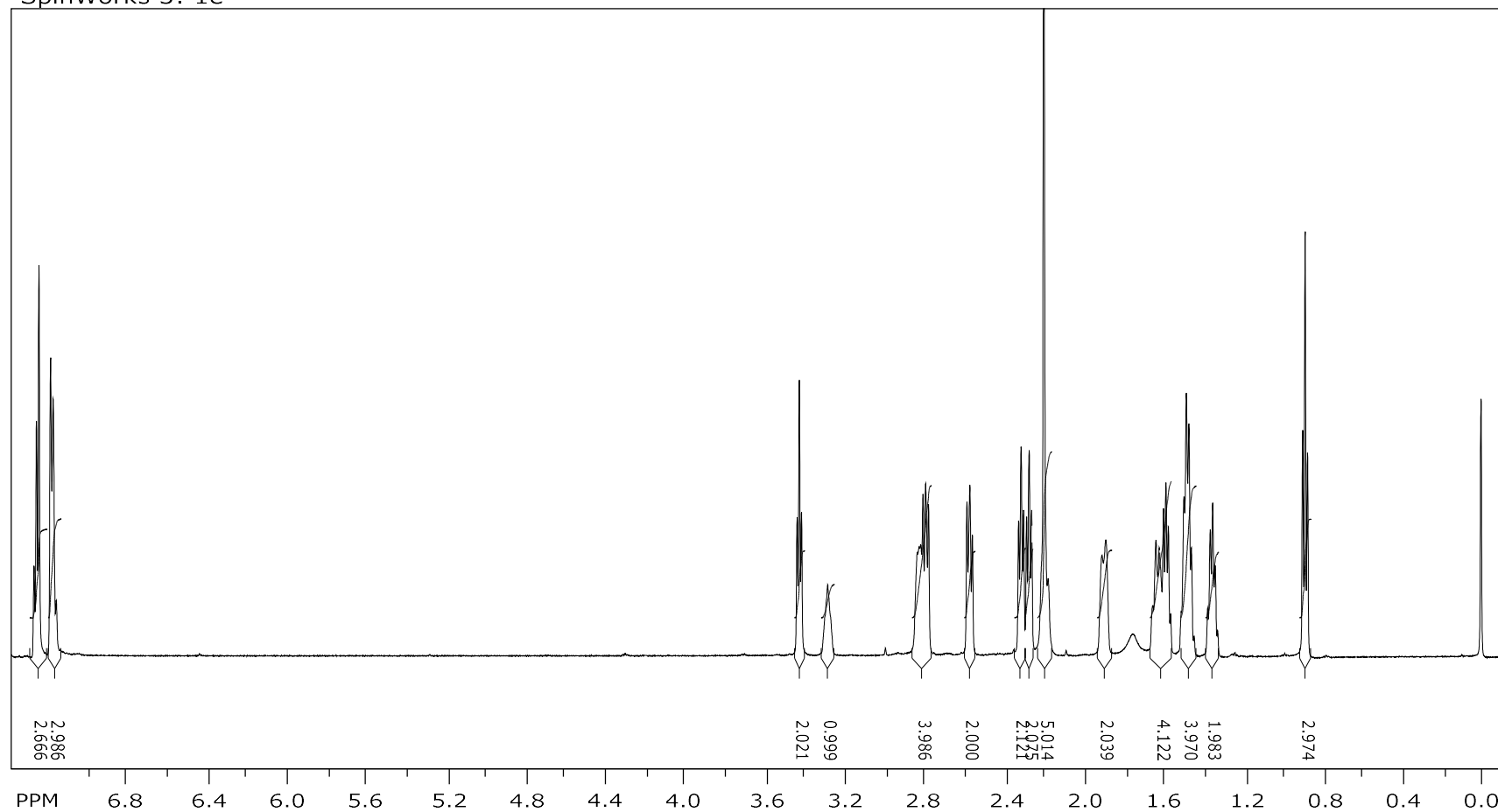


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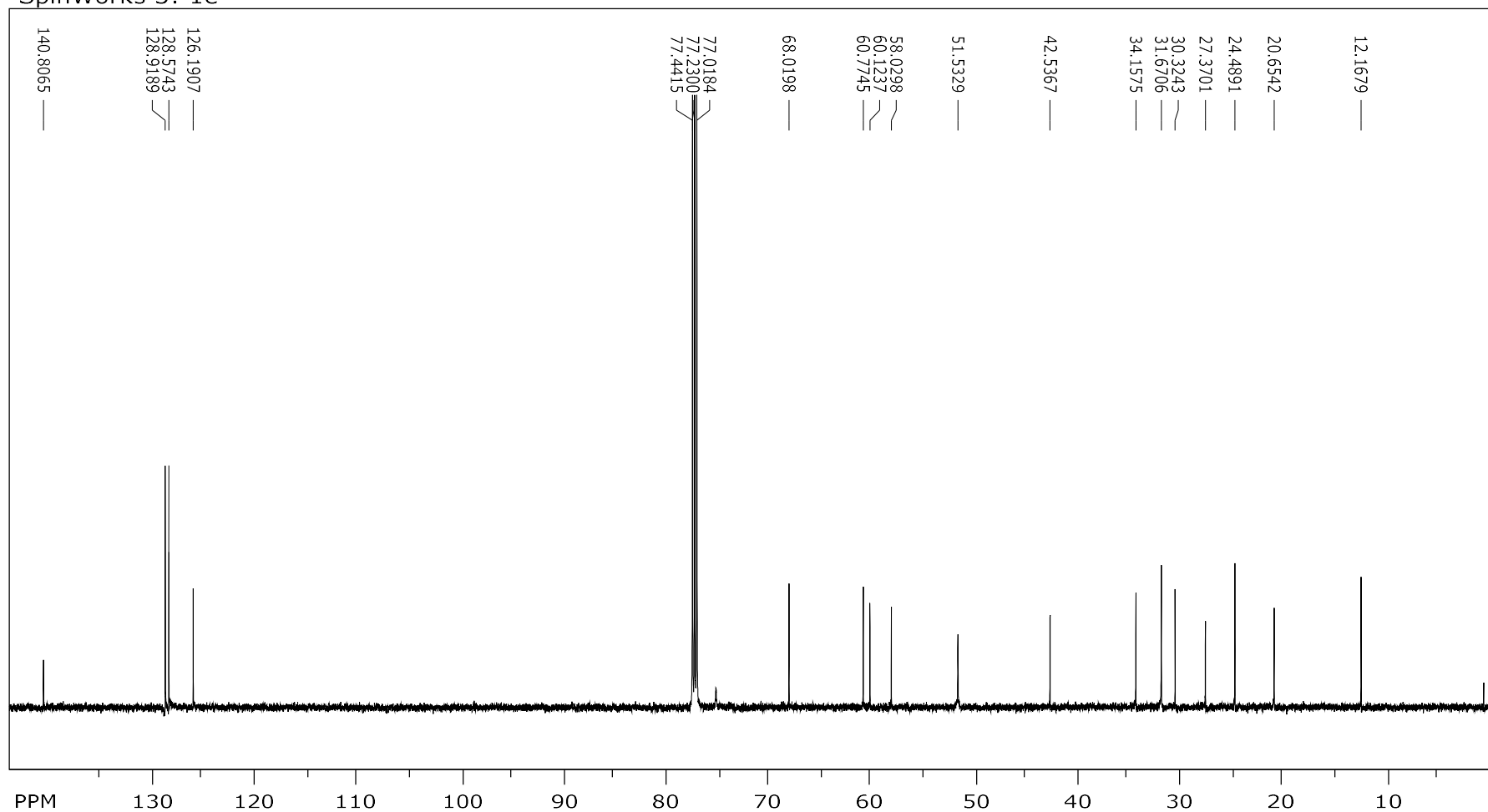
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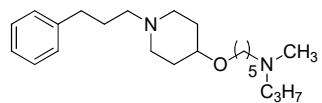
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SpinWorks 3: 1e

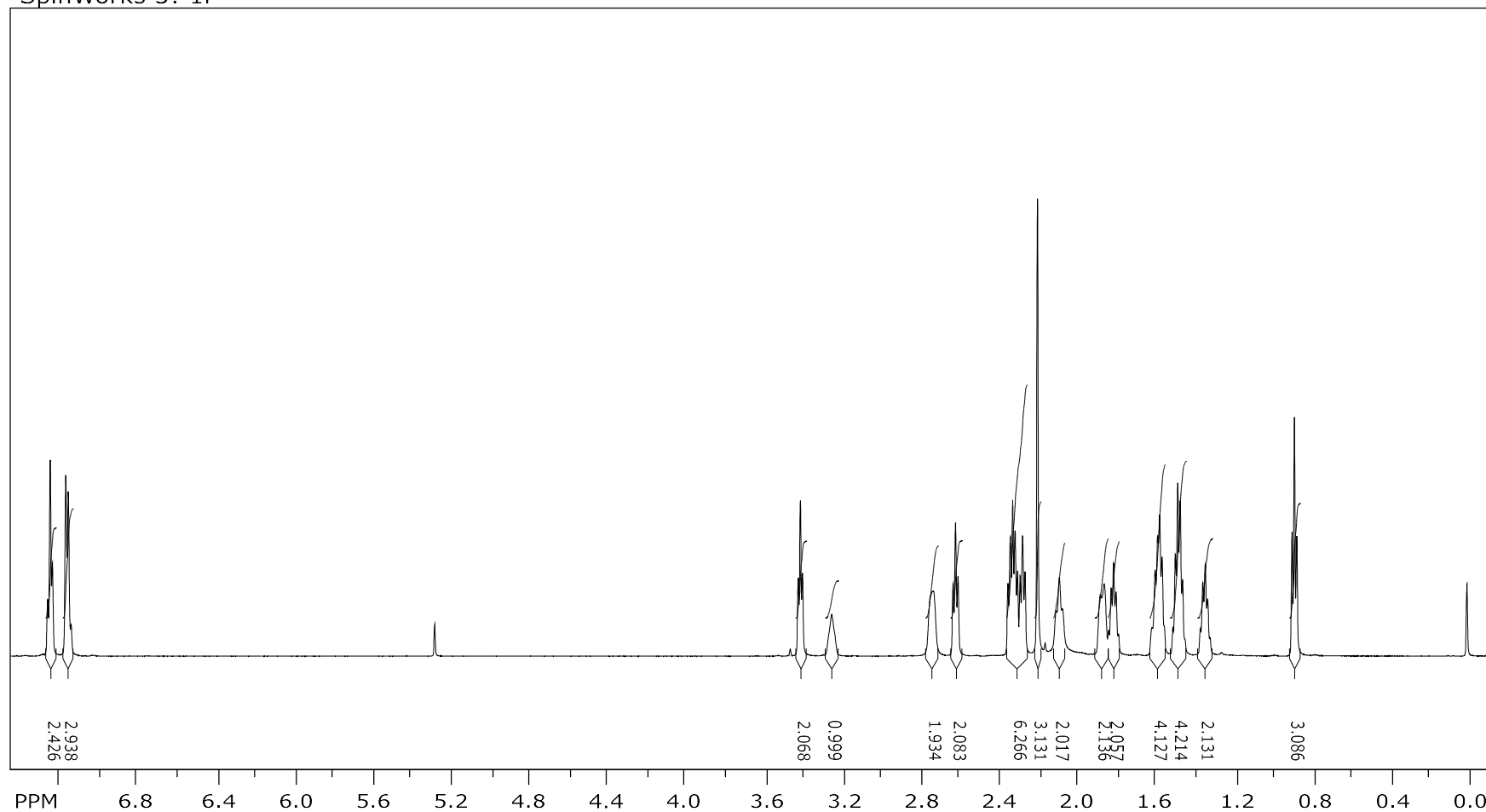


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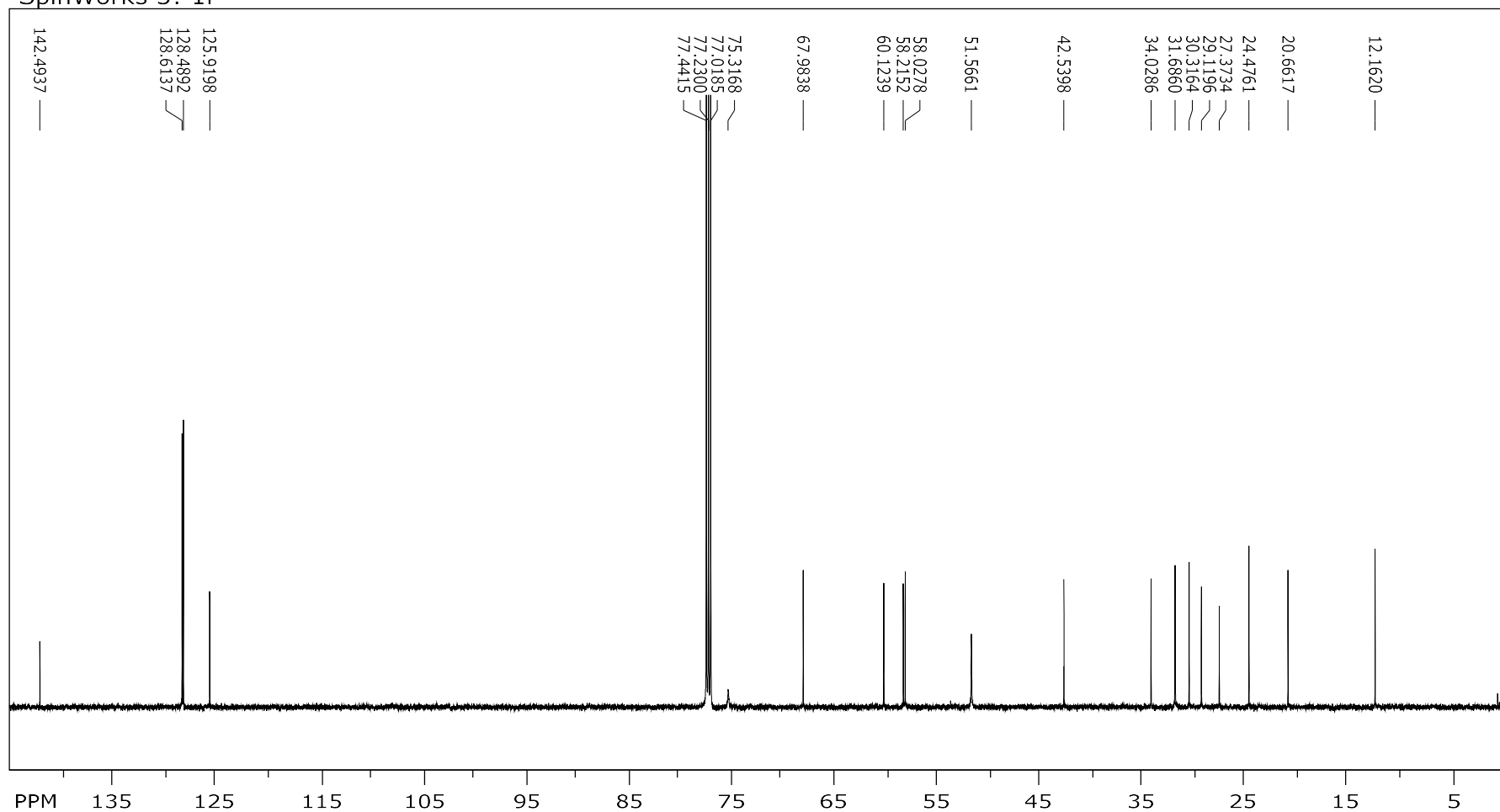
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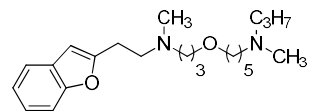
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SpinWorks 3: 1f

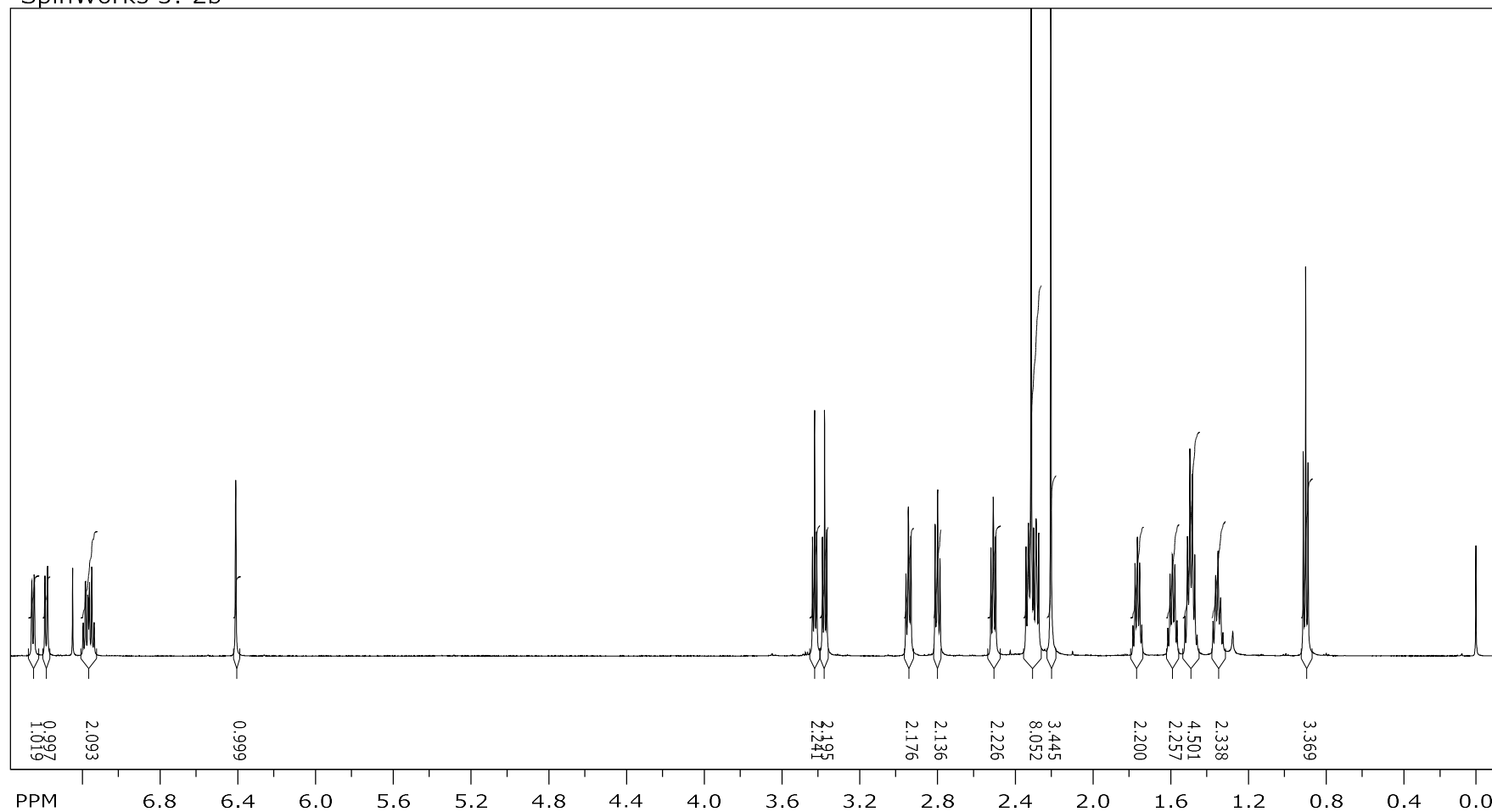


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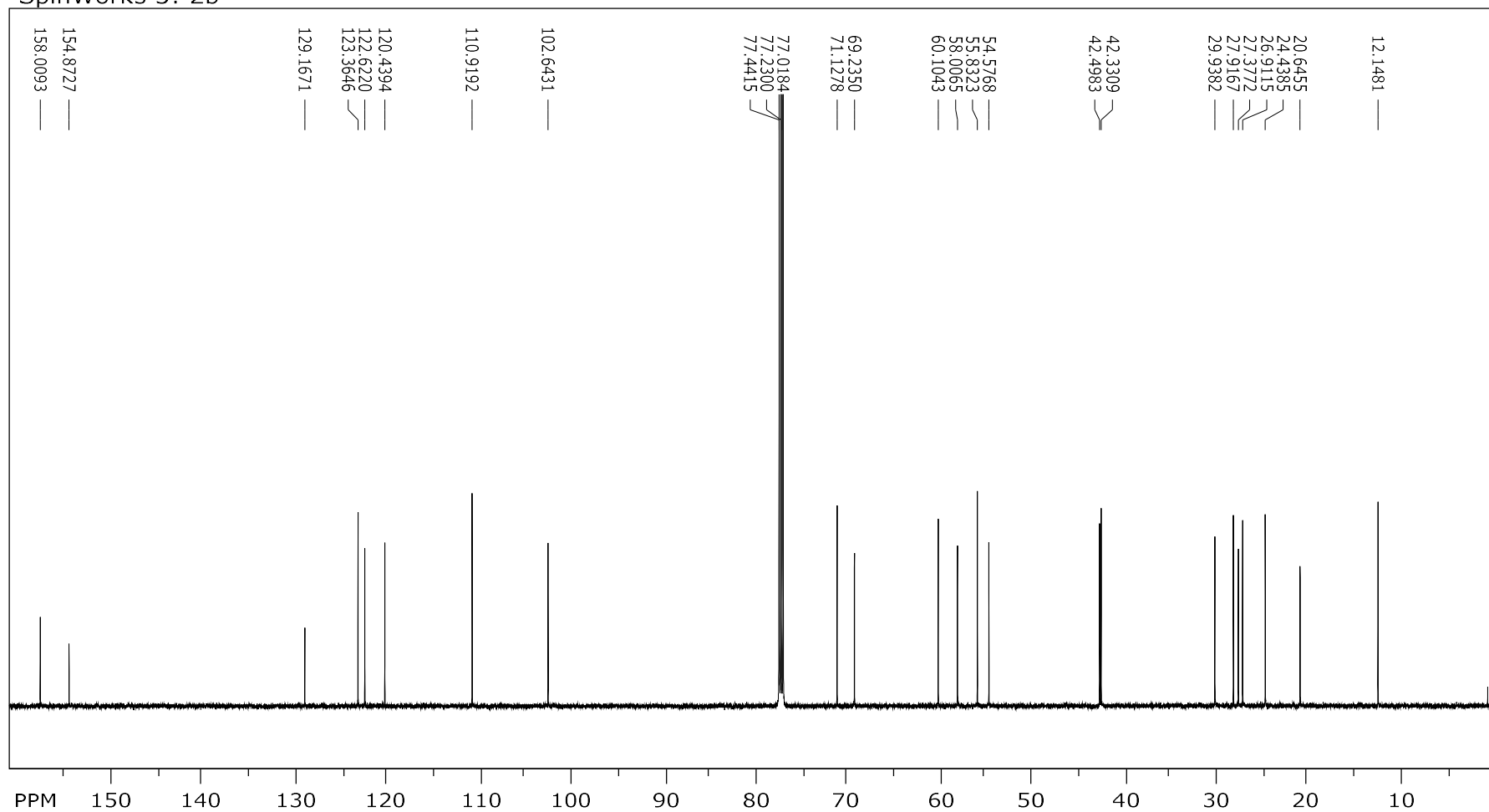
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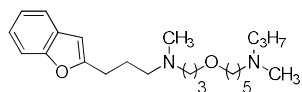
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SpinWorks 3: 2b

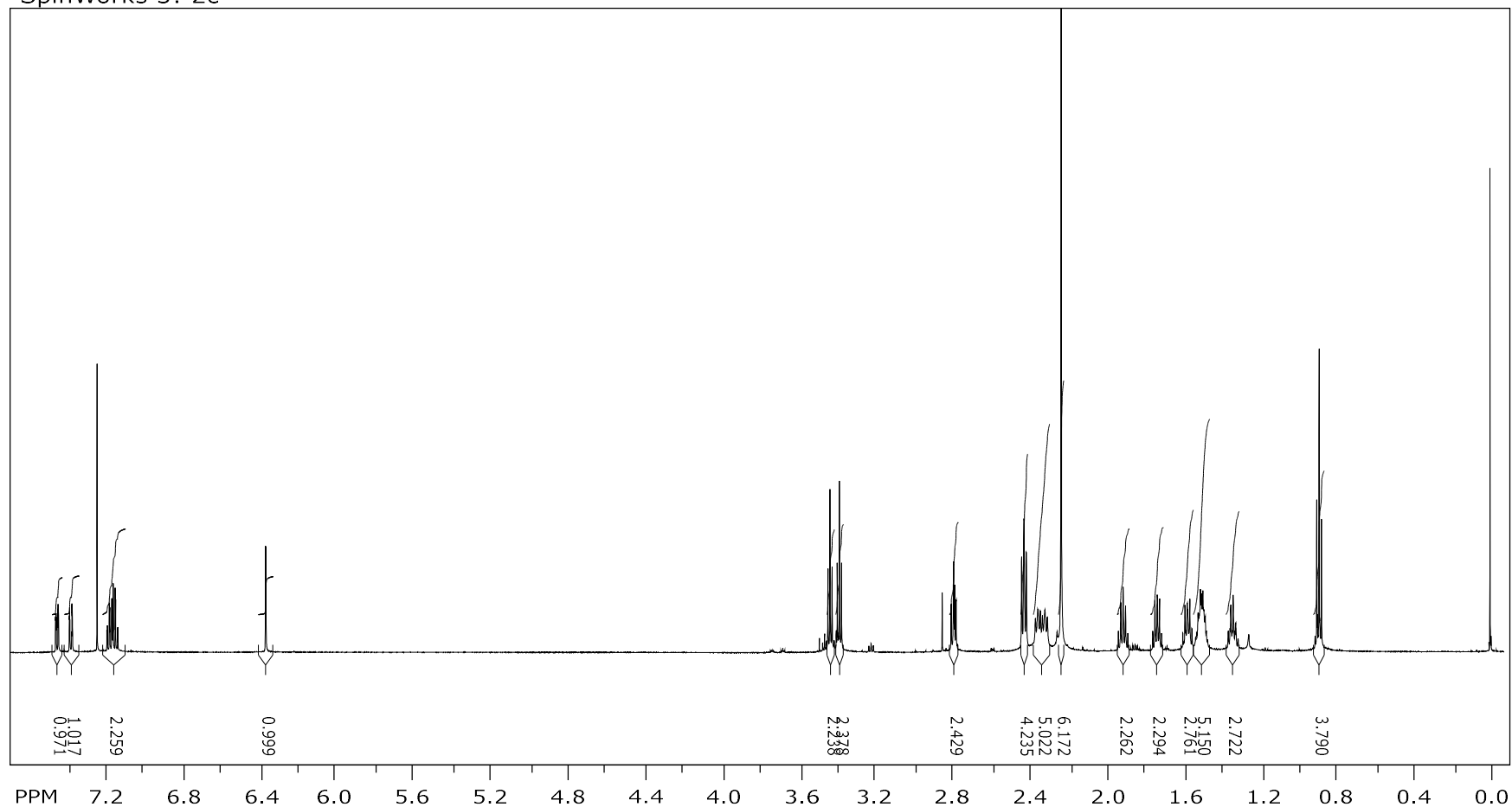


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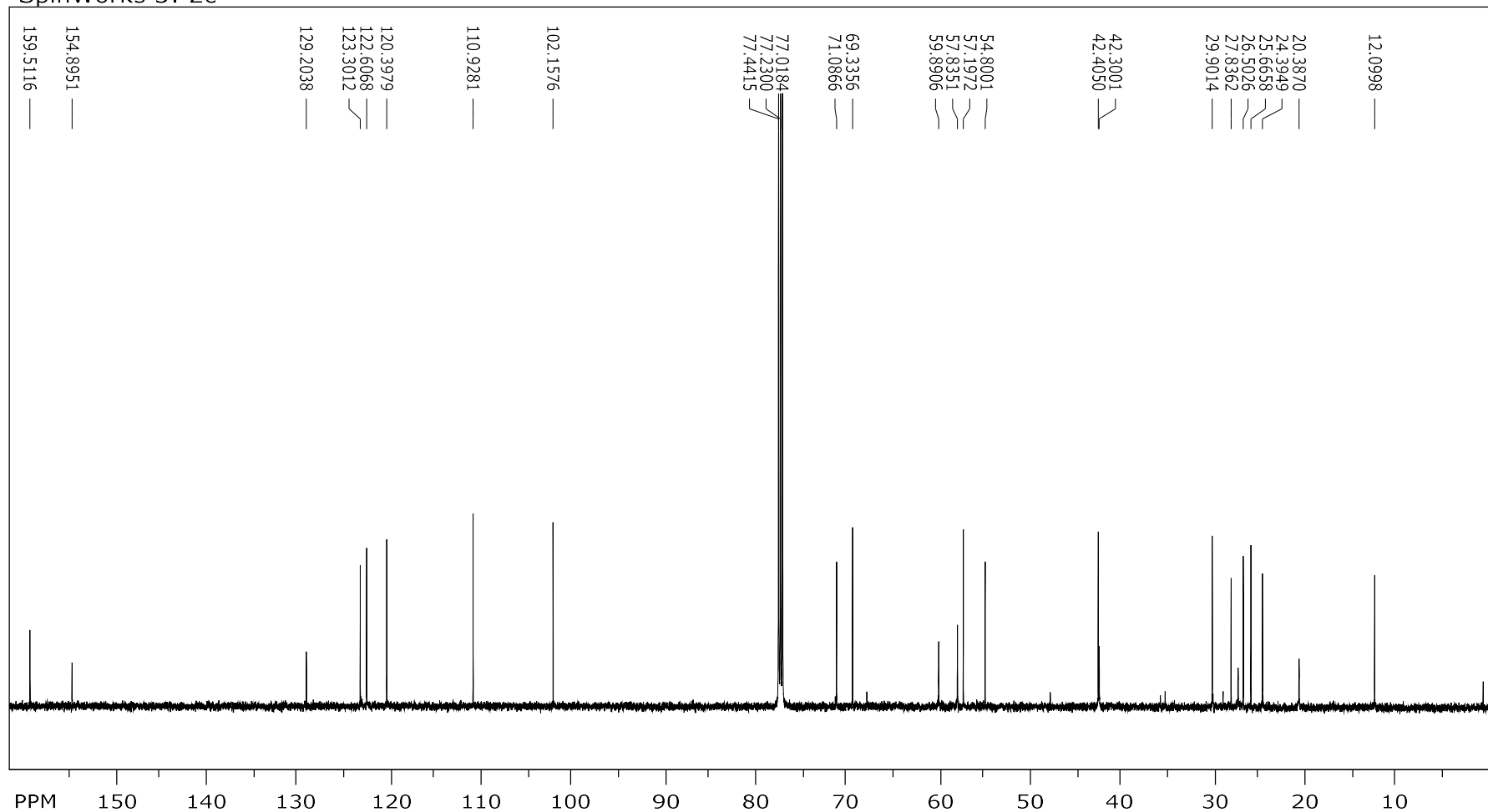
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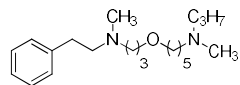
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SpinWorks 3: 2c

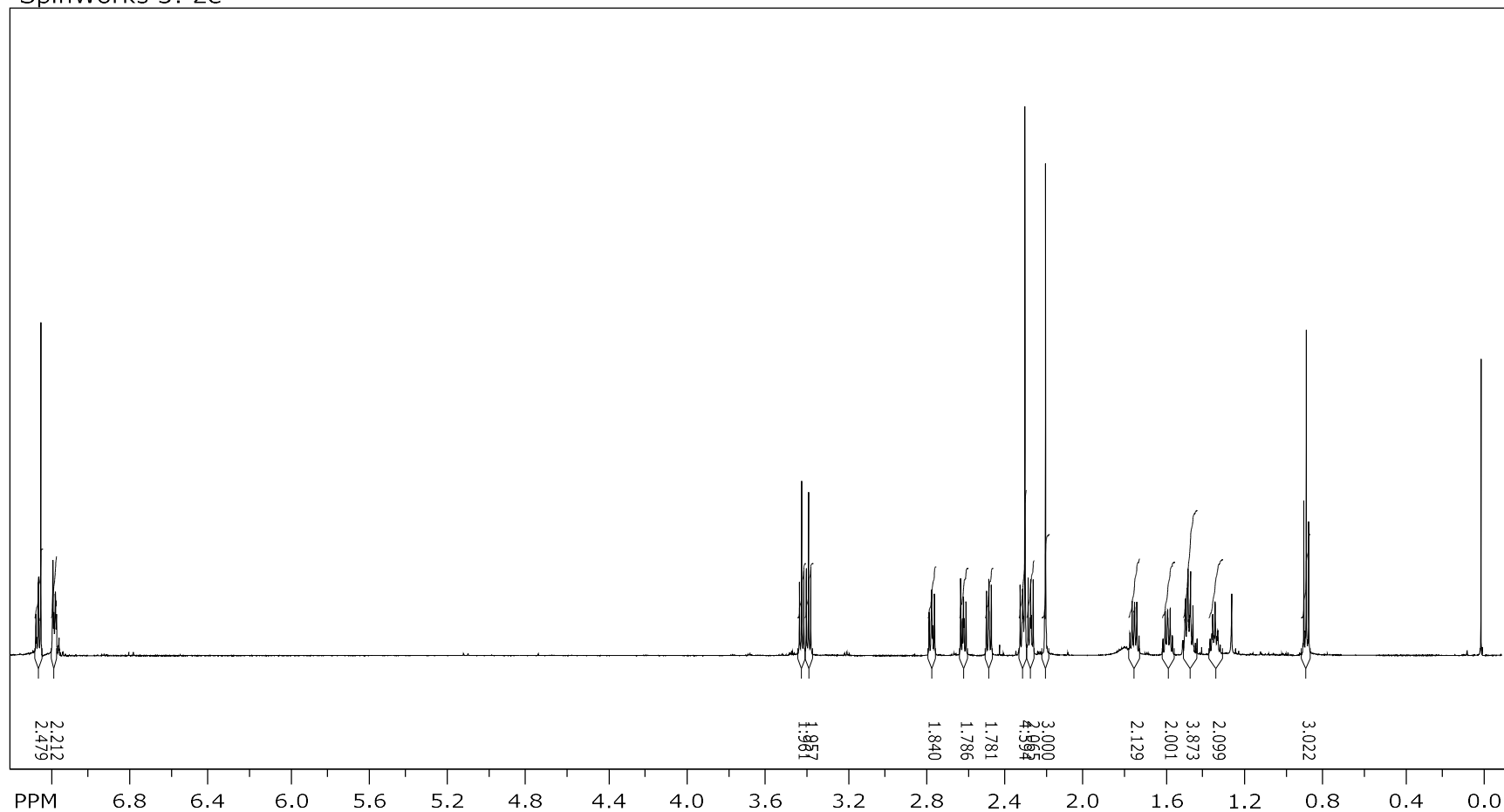


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 number of scans: 3072

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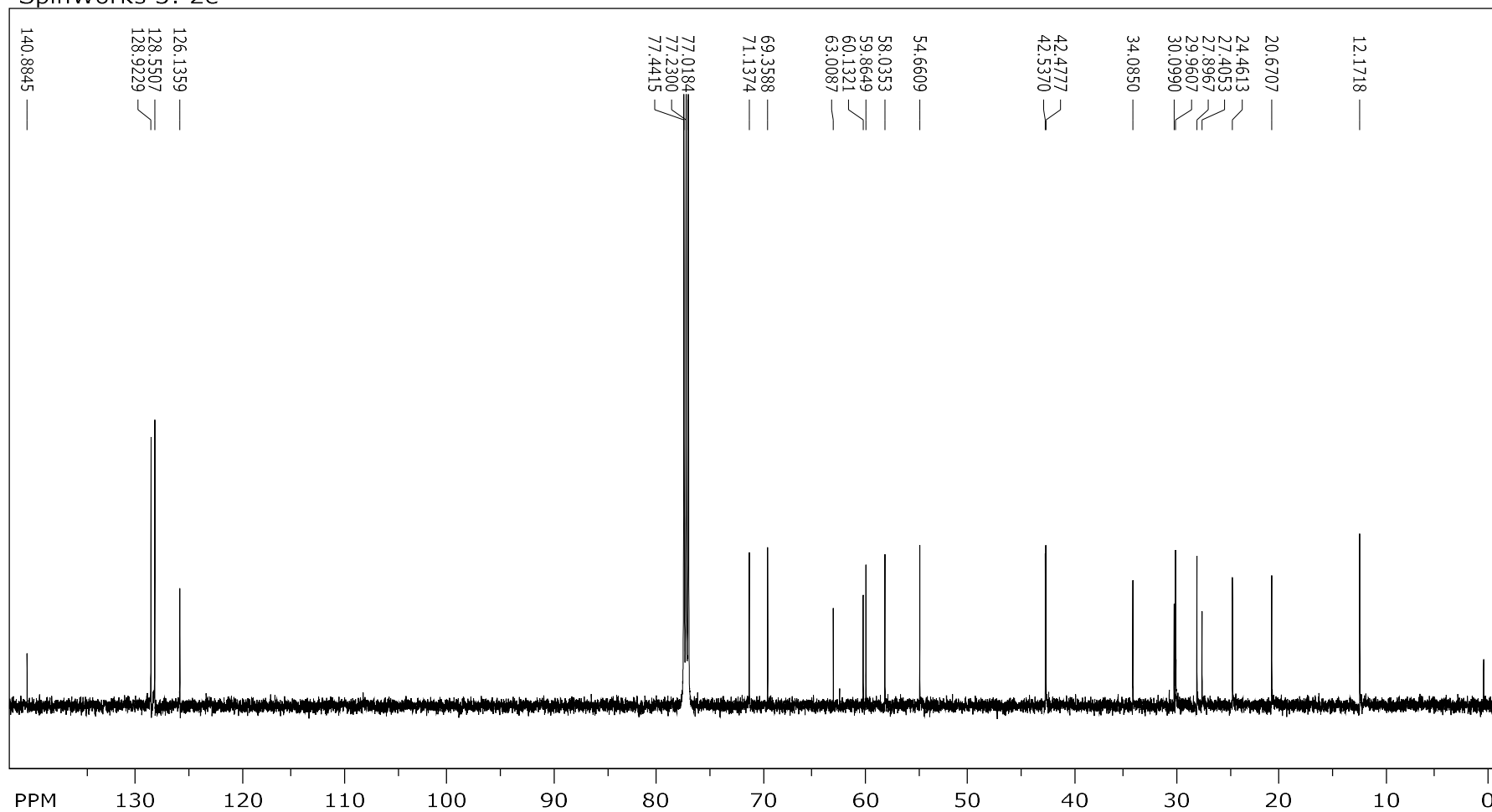
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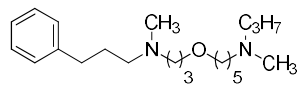
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 Hz/cm: 180.578 ppm/cm: 0.30083

SpinWorks 3: 2e

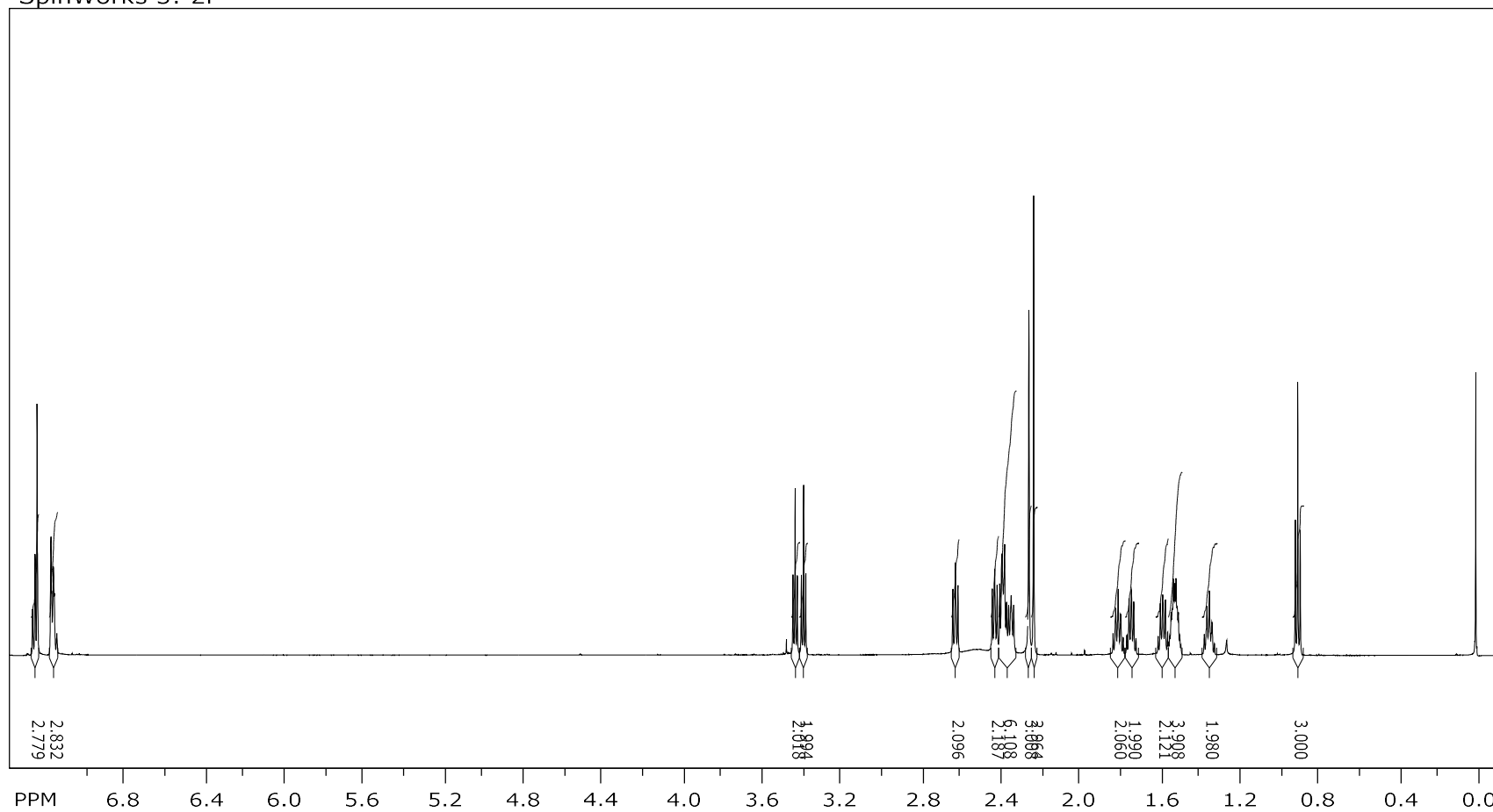


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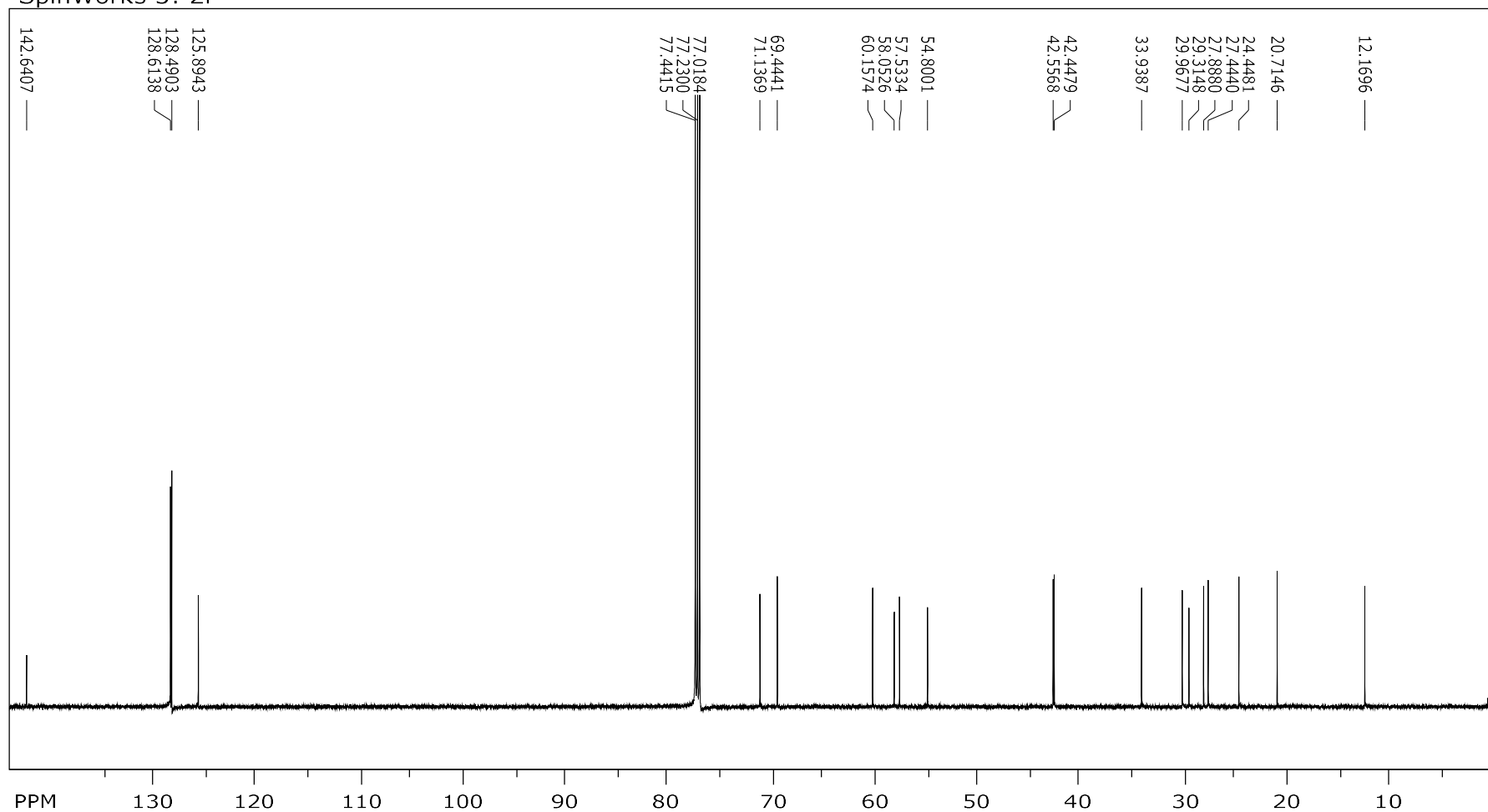
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 processed size: 32768 complex points
 LB: 0.000 GF: 0.0000
 Hz/cm: 180.182 ppm/cm: 0.30017

SpinWorks 3: 2f



file: ...FID UMED\bo-53-2-08.05.2015\11\fid expt: <zgpg30>
 transmitter freq.: 150.950591 MHz
 time domain size: 65536 points
 width: 36057.69 Hz = 238.8708 ppm = 0.550197 Hz/pt
 number of scans: 1024

freq. of 0 ppm: 150.935461 MHz
 processed size: 32768 complex points
 LB: 0.000 GF: 0.0000
 Hz/cm: 875.108 ppm/cm: 5.79731

Supplementary Material B

2.2. Pharmacology

2.2.1. Antagonism by ADS-003 (1a) and thioperamide of the inhibitory effect of R-(-)- α -methylhistamine (R- α -MH) on the electrically induced contraction of guinea-pig ileum strips

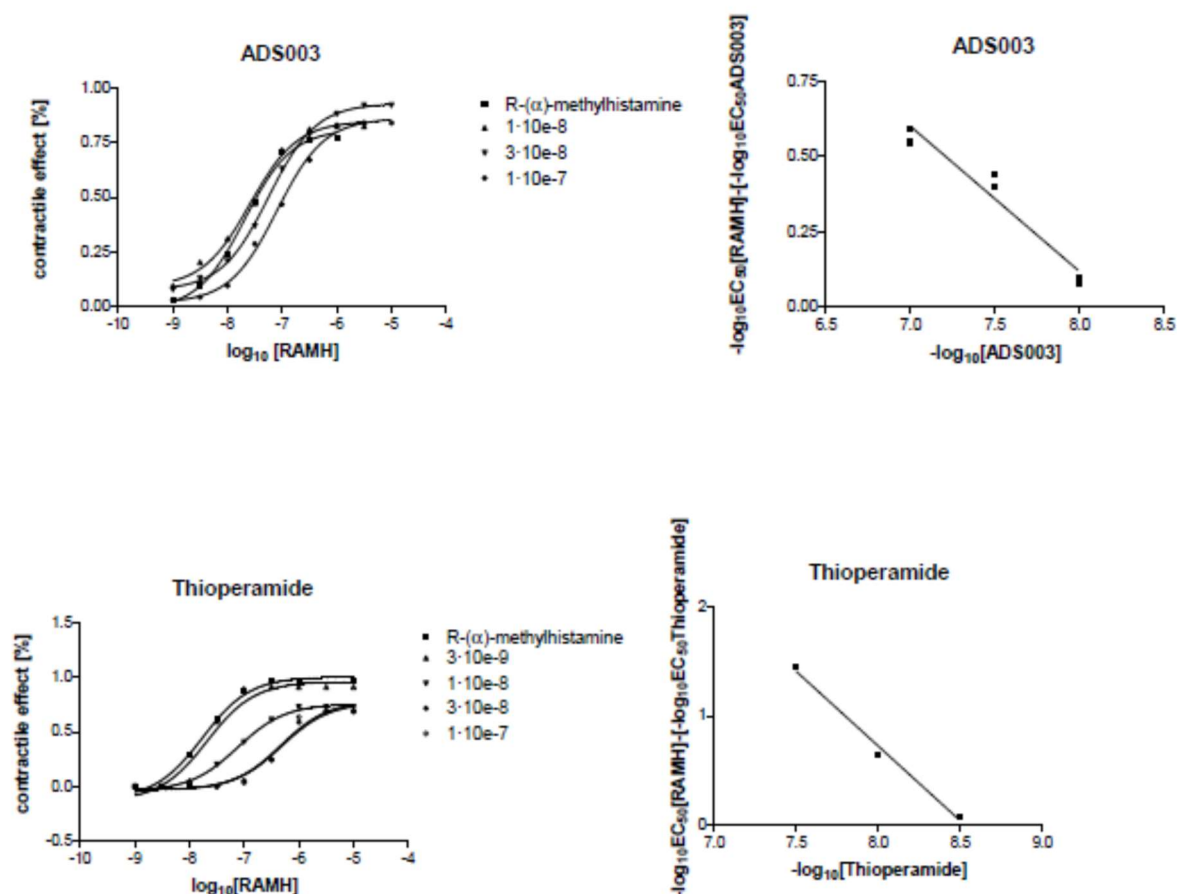


Figure 2 Antagonism by ADS-003 (1a) and thioperamide of the inhibitory effect of R-(-)- α -methylhistamine (R- α -MH) on the electrically induced contraction of guinea-pig ileum strips

2.2.2 Histamine H_3 receptor affinity

Saturation of rat and human H_3 receptors

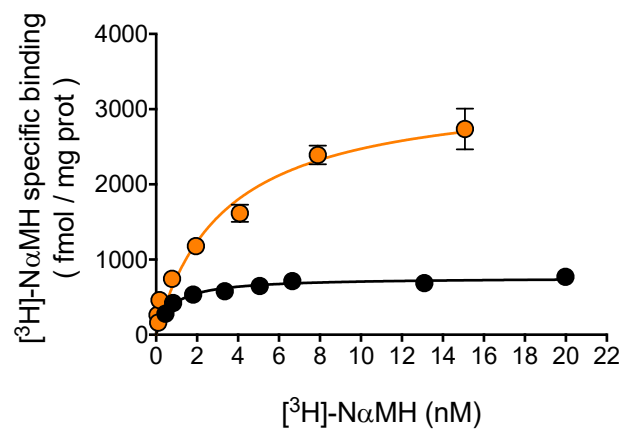


Figure 3. Saturation of rat and human H_3 R.

Competition binding of H_3 receptor ligands

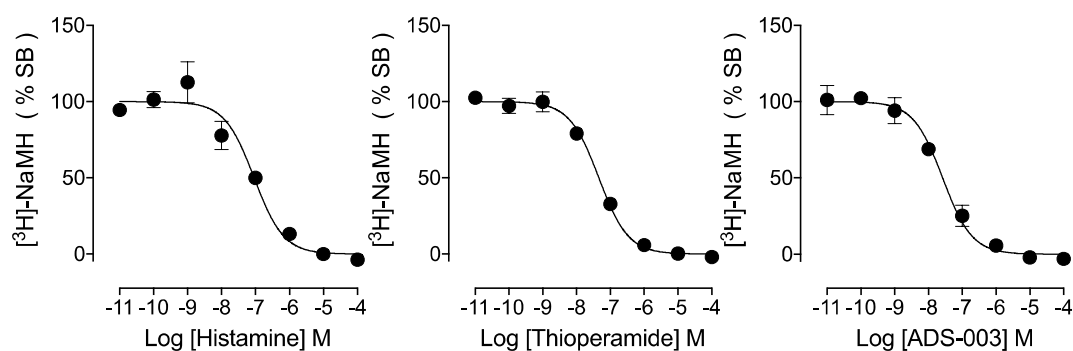


Figure 4 Competition binding of H_3 R ligands on rat H_3 receptor.

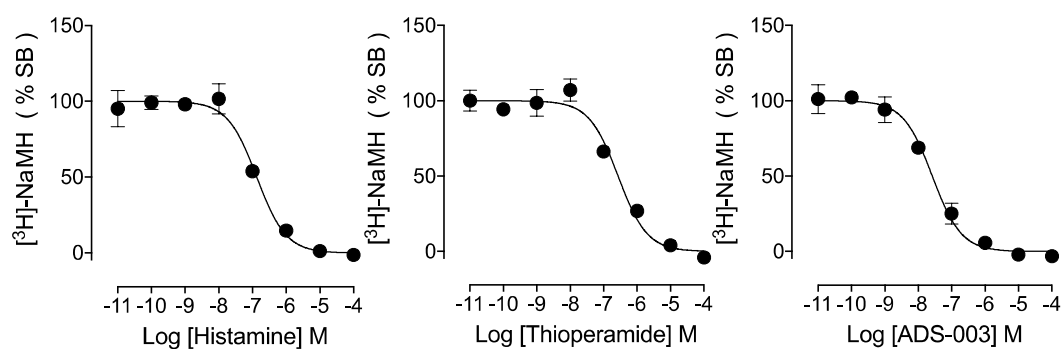


Figure 5: Competition binding of H_3 R ligands on human H_3 receptor.