

**Supporting Information**  
**for**  
**Poly(ethylene glycol)s as grinding additives in the  
mechanochemical preparation of highly  
functionalized 3,5-disubstituted hydantoins**

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**Experimental procedures, characterization of new compounds and  
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### General remarks and experimental procedures

All reagents were commercially available and used without any further purification. *L*- $\alpha$ -amino esters were used, except when otherwise specified. NMR spectra were recorded at room temperature with the appropriate deuterated solvent (CDCl<sub>3</sub> or DMSO-*d*<sub>6</sub>). Chemical shifts ( $\delta$ ) of <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra are reported in ppm relative to residual solvent signals (CHCl<sub>3</sub> in CDCl<sub>3</sub>:  $\delta$  = 7.27 ppm for <sup>1</sup>H and CDCl<sub>3</sub>:  $\delta$  = 77.04 ppm for <sup>13</sup>C NMR; DMSO in *d*<sub>6</sub>-DMSO:  $\delta$  = 2.54 ppm for <sup>1</sup>H and *d*<sub>6</sub>-DMSO:  $\delta$  = 40.45 ppm for <sup>13</sup>C NMR); values for the coupling constants *J* are given in Hz. <sup>1</sup>H NMR spectra were registered at 300 MHz and 400 MHz. <sup>13</sup>C NMR spectra were registered at 75 MHz and 100 MHz. HRMS measurements were performed on a TOF mass analyser. LC–MS analyses were performed with HPLC, column Onyx C18, (25 x 4.6 mm), flow 3 mL/min linear gradient CH<sub>3</sub>CN in water 0–100% (+ 0.1% HCO<sub>2</sub>H) in 2.5 min. Optical rotation measurements were performed at  $\lambda$  = 589 nm (Na lamp), the compounds were solubilized in CHCl<sub>3</sub>. The ball-milling experiments were performed in a planetary mill, 12 mL steel jar (50 stainless steel balls, 5 mm  $\varnothing$ ). The synthesis of compounds **2a–c**, **3a**, **4**, **5a** and **6** (Table 3) was performed according to previously reported procedures [1]. Their identity was assessed by comparison with the spectral data previously published [1]. The optical power was also measured: **2a** [ $\alpha$ ]<sub>D</sub><sup>20</sup> – 4.11 (*c* = 1.02, CHCl<sub>3</sub>); **2b** [ $\alpha$ ]<sub>D</sub><sup>20</sup> - 3.33 (*c* = 1.02, CHCl<sub>3</sub>); **2c** [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 4.66 (*c* = 1.05, CHCl<sub>3</sub>); **3a** [ $\alpha$ ]<sub>D</sub><sup>20</sup> - 4.60 (*c* = 1.00, CHCl<sub>3</sub>); **4** [ $\alpha$ ]<sub>D</sub><sup>20</sup> - 7.33 (*c* = 1.01, CHCl<sub>3</sub>); **5a** [ $\alpha$ ]<sub>D</sub><sup>20</sup> - 3.36 (*c* = 1.01, CHCl<sub>3</sub>); **6** [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 8.48 (*c* = 1.05, CHCl<sub>3</sub>).

**General procedure for the synthesis of 3,5-disubstituted hydantoins (Table 3).**

**Conditions A, dry grinding.** (Step 1) The  $\alpha$ -amino methyl ester hydrochloride (1.0 equiv.) and 1,1'-carbonylimidazole (CDI) (1.3 equiv.) were ground in a 12 mL stainless steel milling jar in a planetary ball-mill at 450 rpm for 40 minutes. (Step 2) The amine (1.6 equiv) and  $K_2CO_3$  (3.6 equiv) were added and the mixture was ground at 450 rpm for two hours. Distilled water was added to the crude and the desired compound was either precipitated and filtered over sintered glass, or extracted with ethyl acetate. The organic layer was washed with a 10% aq. citric acid solution ( $\times 3$ ) and brine ( $\times 1$ ), dried over  $MgSO_4$  and concentrated in vacuo. Only for compounds **3b** and **5b** a purification by flash chromatography was performed on the crude sample, respectively.

**Conditions B (with MeO-PEG-OMe, compounds 2a,b, 3a, 4, 4b and 6) and C (with HO-PEG-3400-OH, compounds 2a,b, 4, 4b and 6), wet grinding (Table 3).** In the case of PEG-assisted grinding the reaction was performed by a modification of conditions A: the suitable PEG polymer (450 mg/mmol substrate) was added in Step 2. The compound was recovered by extraction with ethyl acetate after addition of distilled water to the reaction mixture. The organic layer was washed with a 10% aq. citric acid and brine, dried over  $MgSO_4$  and concentrated in vacuo. When necessary, the compound was purified by flash chromatography.

**(S)-3-[4'-(4-Methyl-1H-pyrazol-1-yl)-phenylmethyl]-5-benzyl-2,4-**

**imidazolidinedione (3b, Table 3, entry 5).** The reaction scale was 1 mmol (conditions A). The compound was obtained by precipitation in water and purified by flash chromatography (linear gradient of AcOEt in  $Et_2O$ : 0–10%). White solid (108

mg, 30% isolated yield);  $[\alpha]_D^{20}$  - 66.6 ( $c = 1.04$ ,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  (ppm): 7.68 (s, 1H, ImH), 7.58 (s, 1H, ImH), 7.54 (d,  $J = 6.2$  Hz, 2H), 7.32 (d,  $J = 8.5$  Hz, 2H), 7.32-7.23 (m, 3H, ArH), 7.20-7.12 (m, 2H), 5.38 (s, 1H, NH), 4.60 (m, 2H,  $\text{NCH}_2$ ), 4.28 (dd,  $J = 8.4$  and  $J = 3.7$  Hz, 1H, NCH), 3.27 (dd,  $J = 8.6$  and  $J = 3.7$  Hz, 1H  $\text{CH}_2/\text{H}_a$ ), 2.86 (dd,  $J = 8.6$  and  $J = 5.4$  Hz, 1H  $\text{CH}_2/\text{H}_b$ ), 2.16 (s, 3H  $\text{CH}_3$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  (ppm): 172.8, 156.7, 142.1, 139.9, 135.1, 133.6, 129.7, 129.4, 129.1, 127.6, 125.4, 118.9, 118.5, 58.5, 41.7, 37.9, 29.8, 9.1; ESI-(+)  $m/z$ : 402.1  $[\text{M} + \text{CH}_3\text{CN} + \text{H}]^+$ , 361.2  $[\text{M} + \text{H}]^+$ , 268.4  $[\text{M} - \text{PhCH}_3]^+$ , 228.4, 184.4, 151.9, 130.3, 100.6  $[\text{M} - \text{CH}_2\text{PhPyr}-\text{CH}_2\text{Ph}]^+$ . HRMS ESI-(+): calcd for  $\text{C}_{21}\text{H}_{21}\text{N}_4\text{O}_2$   $[\text{M} + \text{H}]^+$  361.1665, found 361.1665

**(S)-3-(Furan-2-ylmethyl)-5-benzyl-2,4-imidazolidinedione (3c, Table 3, entry 6).**

The reaction scale was 1.0 mmol (conditions A). The compound was obtained by precipitation in water. White solid (190.0 mg, 70% isolated yield);  $[\alpha]_D^{20}$  - 3.4 ( $c = 1.03$ ,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ , 400 MHz)  $\delta$  (ppm): 8.31 (s, 1H, FuH), 7.48 (s, 1H, FuH), 7.26-7.19 (m, 3H, ArH), 7.15-7.10 (m, 2H, ArH), 6.29 (dd,  $J = 3.1$  and  $J = 1.9$  Hz, 1H, FuH), 5.83 (d,  $J = 3.2$  Hz, 1H, NH), 4.45 (t,  $J = 5.0$  Hz, 1H, NCH), 4.35 (q,  $J = 9.4$  Hz, 2H,  $\text{NCH}_2$ ), 2.97-2.95 (m, 2H,  $\text{CH}_2$ );  $^{13}\text{C NMR}$  ( $\text{DMSO}-d_6$ , 100 MHz)  $\delta$  (ppm): 173.1, 155.9, 149.5, 142.6, 135.4, 129.9, 128.3, 126.9, 110.6, 107.6, 57.3, 36.5, 34.5; ESI-(+)  $m/z$ : 271.2  $[\text{M} + \text{H}]^+$ , 203.0  $[\text{M} - \text{Fu}]^+$ , 186.3, 102.0  $[\text{M} - \text{CHF}_2 - \text{CPh}]^+$ . HRMS ESI-(+): calcd for  $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_3$   $[\text{M} + \text{H}]^+$  271.1087, found 271.1083.

**(S)-3-[4'-(4-Methyl-1H-pyrazol-1-yl)-phenylmethyl]-5-**

**((carboxybenzylamino)butyl)-2,4-imidazolidinedione (5b, Table 3, entry 9).** The reaction scale was 0.7557 mmol. The crude was precipitated by AcOEt (conditions A) or purified by column chromatography (37%  $^1\text{H NMR}$  yield, conditions C, linear

gradient of EtOH in Et<sub>2</sub>O: 0-10%). White solid (223.0 mg, 62% isolated yield for Conditions A);  $[\alpha]_D^{20}$  - 5.4 (*c* = 1.00, CHCl<sub>3</sub>); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz)  $\delta$  (ppm): 8.36 (s, 1H, PyrH), 8.21 (s, 1H, PyrH), 7.74 (d, *J* = 8.4 Hz, 2H, ArH), 7.53 (s, 1H, ), 7.41-7.18 (m, 8H, ArH + NH), 4.99 (s, 2H, CH<sub>2</sub>O), 4.53 (s, 2H, NCH<sub>2</sub>), 4.12 (t, *J* = 6.6 Hz, 1H, NCH), 2.96 (m, 2H, NCH<sub>2</sub>) 2.09 (s, 3H CH<sub>3</sub>), 1.80-1.18 (m, 6H, (CH<sub>2</sub>)<sub>3</sub>); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 75 MHz)  $\delta$  (ppm): 174.2, 156.6, 156.1, 141.6, 139.0, 137.3, 134.2, 128.5, 128.3, 127.7, 126.0, 117.9, 117.7, 65.1, 56.3, 30.9, 28.9, 21.5, 8.71; ESI-(+) *m/z*: 476.0 [M + H]<sup>+</sup>. HRMS ESI-(+): calcd for C<sub>26</sub>H<sub>30</sub>N<sub>5</sub>O<sub>4</sub> [M + H]<sup>+</sup> 476.2298, found 476.2294.

**(S)-3-(Furan-2-ylmethyl)-5-((carboxybenzylamino)butyl)-2,4-imidazolidinedione (5c, Table 3, entry 10).** The reaction scale was 0.7557 mmol (conditions A). NaCl (250 mg) was added during Step 1 [2]. The crude was precipitated by Et<sub>2</sub>O then purified by column chromatography (linear gradient of MeOH in CH<sub>2</sub>Cl<sub>2</sub>: 0-1%). White solid (107 mg, 37% isolated yield);  $[\alpha]_D^{20}$  -26.5 (*c* = 1.00, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  (ppm): 7.36-7.32 (m, 6H), 6.31 (m, 2H), 6.16 (m, 1H), 5.09 (s, 2H), 4.69 (sl, 1H), 4.65 (s, 2H), 4.02-3.97 (m, 1H), 3.17 (m, 2H), 1.91-1.86 (m, 1H), 1.52-1.28 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm): 173.5, 157.0, 156.8, 156.7, 149.0, 142.6, 136.6, 128.7, 128.3, 128.2, 110.6, 108.9, 66.9, 57.1, 40.5, 40.4, 35.0, 31.1, 29.5, 21.5; ESI-(+) *m/z* 408.2 [M+Na]<sup>+</sup>, 171.0 [(M-ZNH-Fu) + H]<sup>+</sup>; HRMS ESI-(+) calcd for C<sub>20</sub>H<sub>24</sub>N<sub>3</sub>O<sub>5</sub> [M+H]<sup>+</sup> 386.1716 found 386.1714.

**(S)-3-(1'-Methyl-1*H*-pyrazol-3'-methyl)5-((carboxybenzylamino)butyl)-2,4-imidazolidinedione (5d, Table 3, entry 11):** The reaction scale was 0.7557 mmol (Conditions A). The compound was recovered after liquid-liquid extraction with ethyl acetate and water. White solid (140.0 mg, 47% isolated yield);  $[\alpha]_D^{20}$  - 7.64 (*c* = 1.02,

CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ (ppm): 7.38-7.30 (m, 5H, ArH), 7.22 (d, *J* = 2.2 Hz, 1H, ImH), 6.16 (d, *J* = 2.2 Hz, 1H), 5.84 (s, 1H, NH), 5.09 (s, 2H, CH<sub>2</sub>O), 4.84 (m, 1H, NH), 4.67 (s, 2H, NCH<sub>2</sub>), 4.03 (t, *J* = 5.1 Hz, 1H, NCH), 3.81 (s, 3H, CH<sub>3</sub>), 3.25-3.11 (m, 2H, NCH<sub>2</sub>), 1.98-1.82 (m, 1H, CH<sub>2</sub>/H<sub>a</sub>), 1.81-1.66 (m, 1H, CH<sub>2</sub>/H<sub>b</sub>), 1.56-1.30 (m, 4H, (CH<sub>2</sub>)<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ (ppm): 173.7, 157.3, 156.7, 147.2, 136.7, 131.2, 128.7, 128.3, 104.9, 66.9, 57.1, 40.5, 39.9, 36.1, 31.1, 29.6, 21.6; ESI-(+) *m/z*: 422.1 [M+Na]<sup>+</sup>, 400.2 [M + H]<sup>+</sup>, 338.4, 292.1 [M – PhCH<sub>2</sub>O]<sup>+</sup>; HRMS ESI-(+): calcd for C<sub>20</sub>H<sub>26</sub>N<sub>5</sub>O<sub>4</sub> [M + H]<sup>+</sup> 400.1985, found 400.1983.

## References

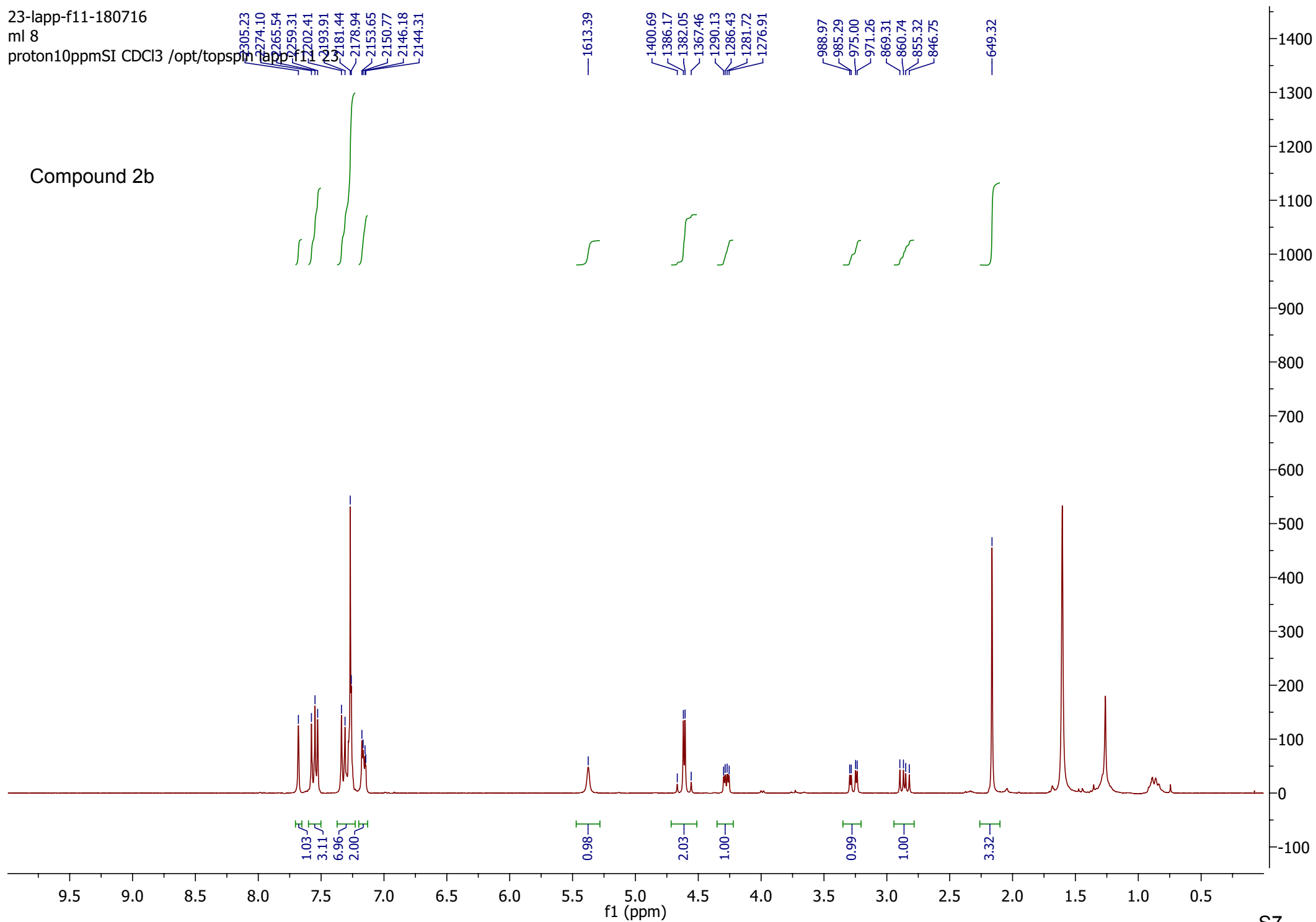
- [1] Konnert, L.; Dimassi, M.; Gonnet, L.; Lamaty, F.; Martinez, J.; Colacino, E., *RSC Advances* **2016**, *6*, 36978–36986.
- [2] Konnert, L.; Gaudiard, A.; Lamaty, F.; Martinez, J.; Colacino, E., *ACS Sustainable Chem. Eng.* **2013**, *1*, 1186–1191.

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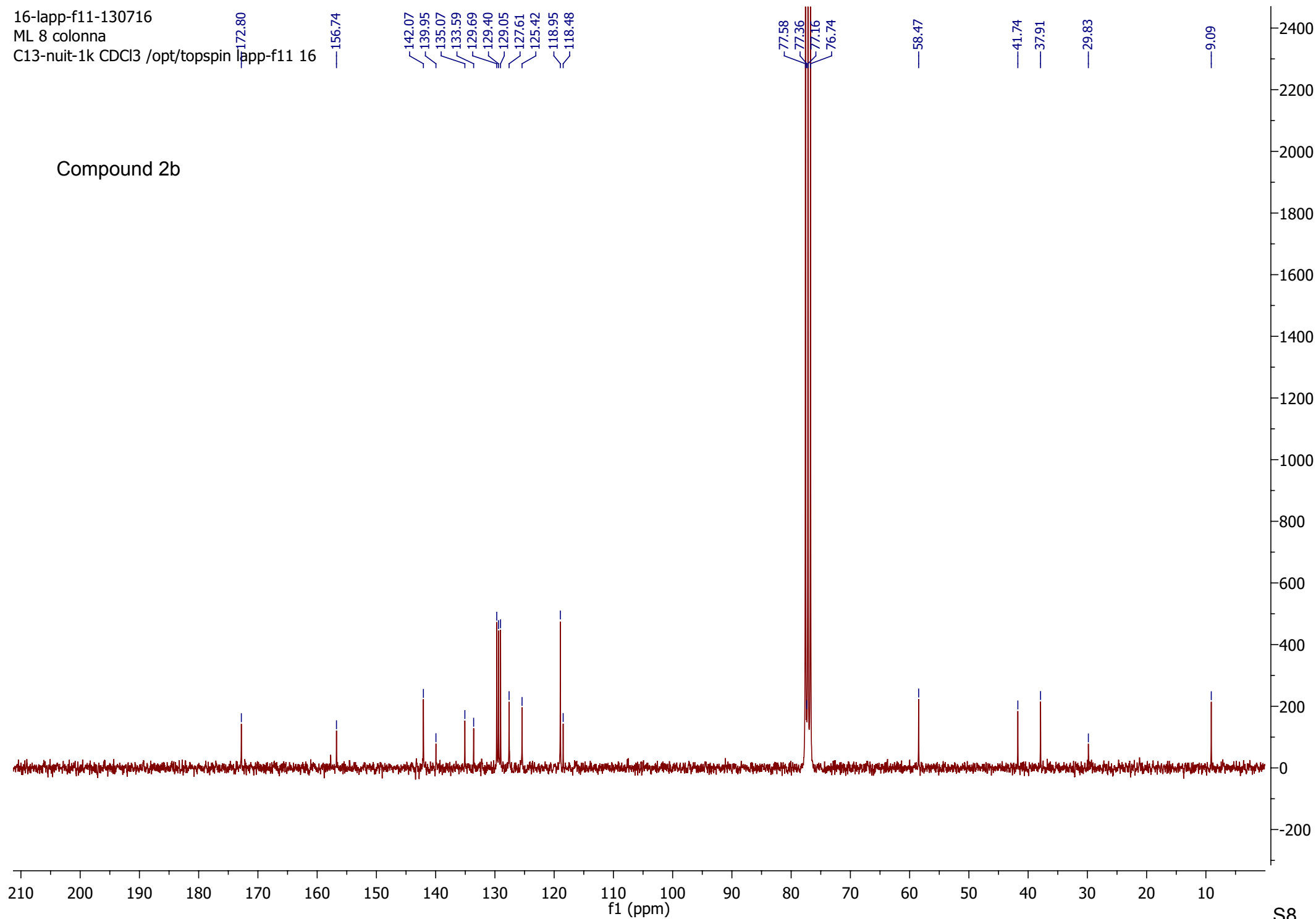
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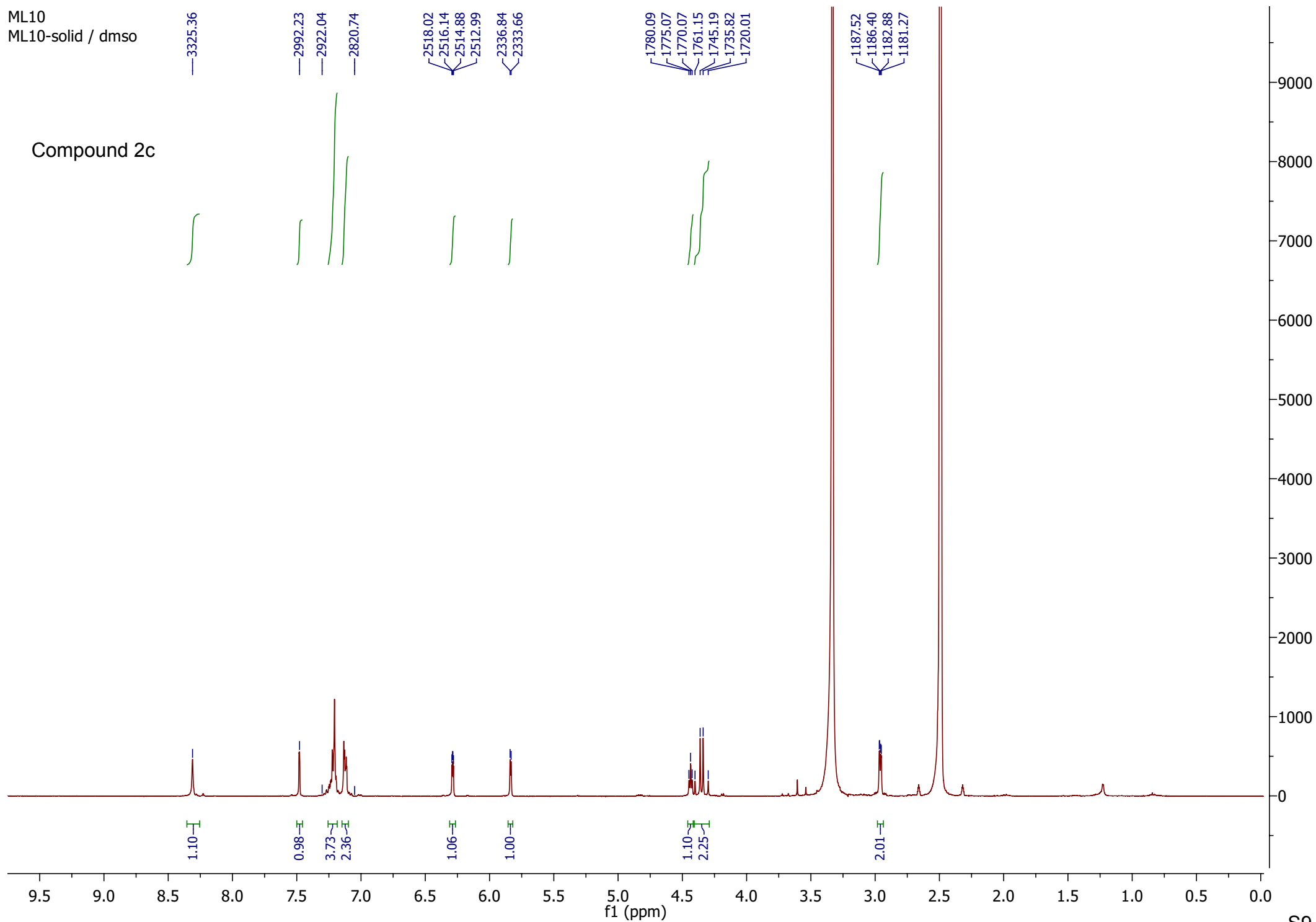
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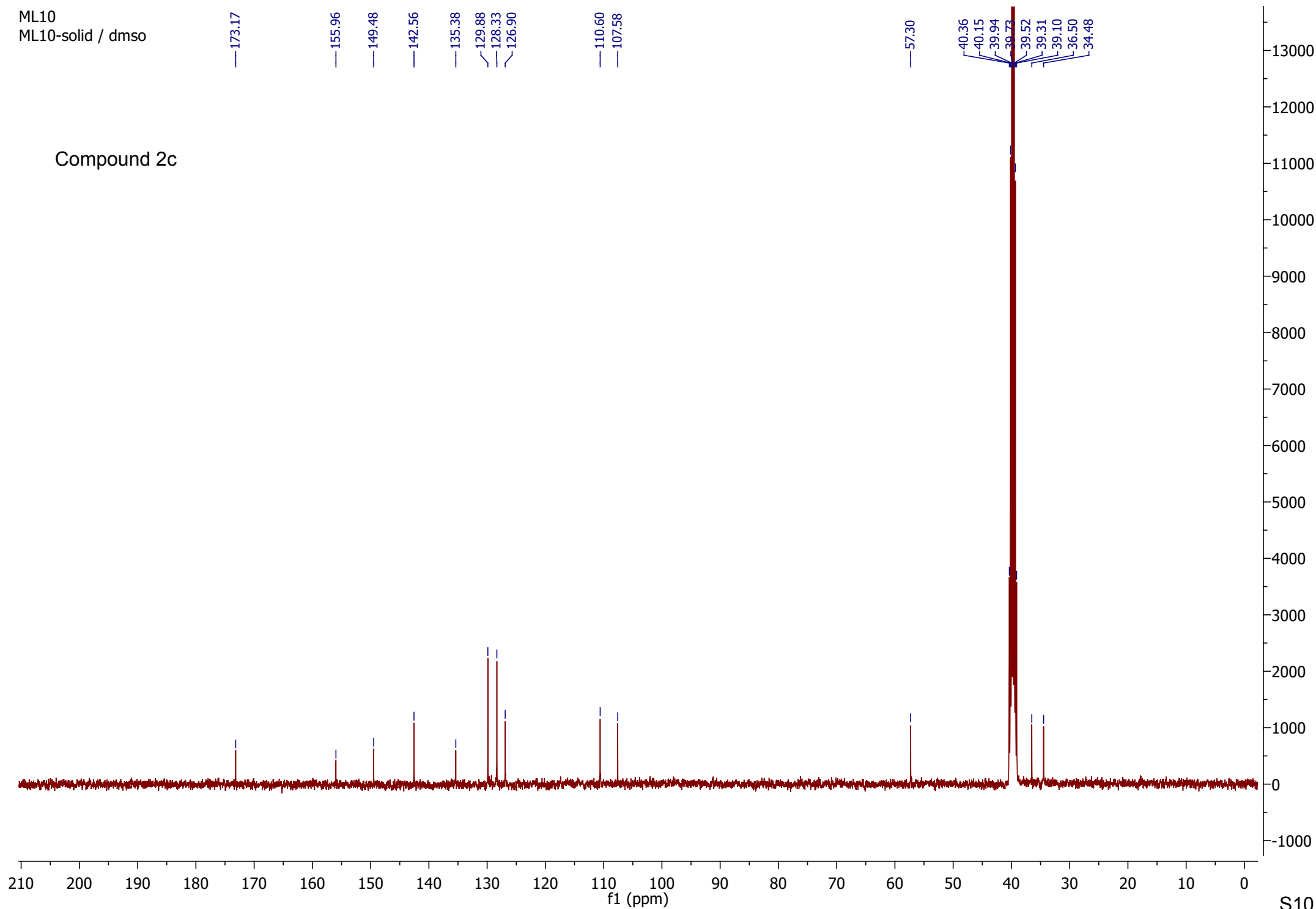
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Compound 2c



ML10  
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Compound 2c

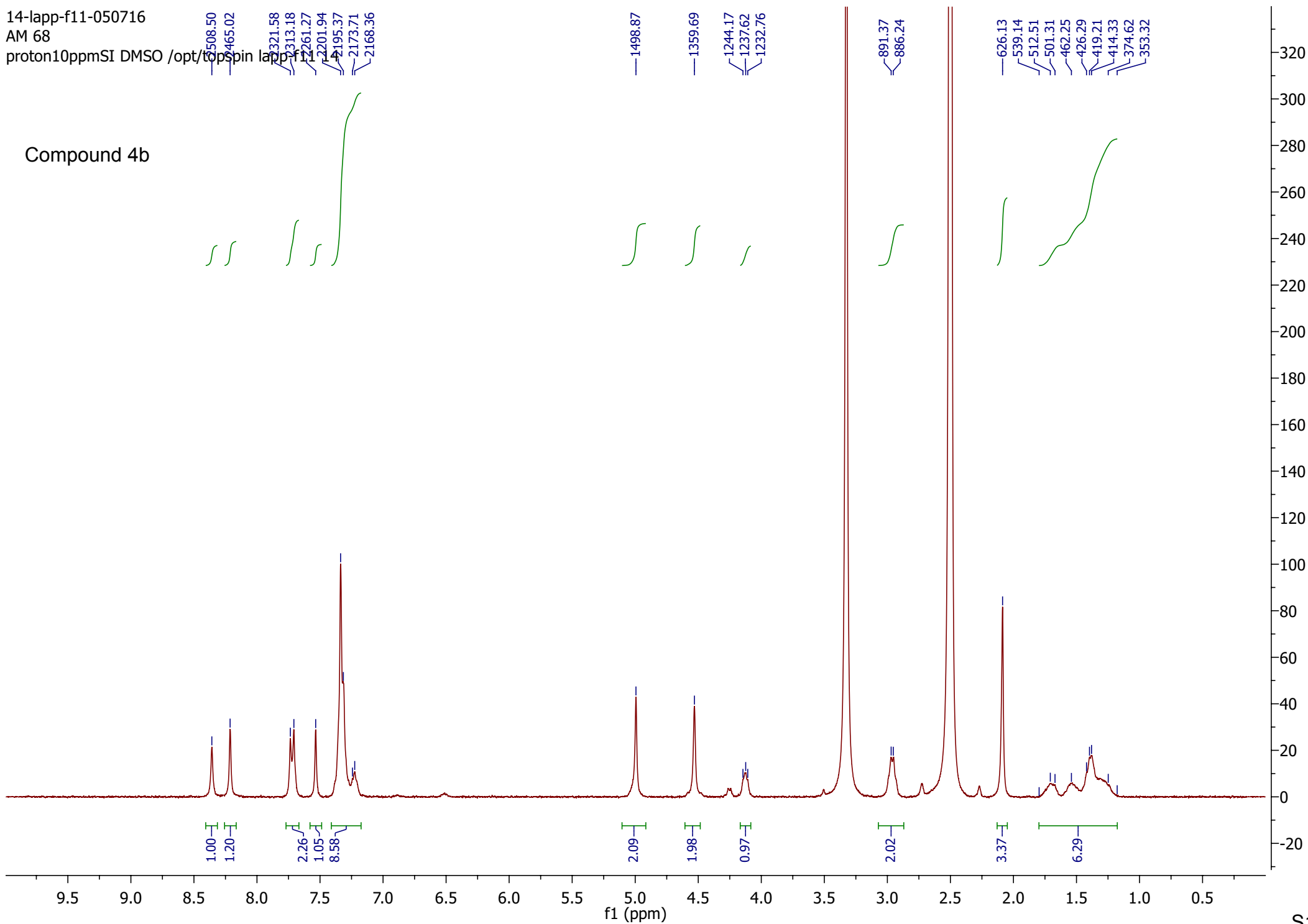


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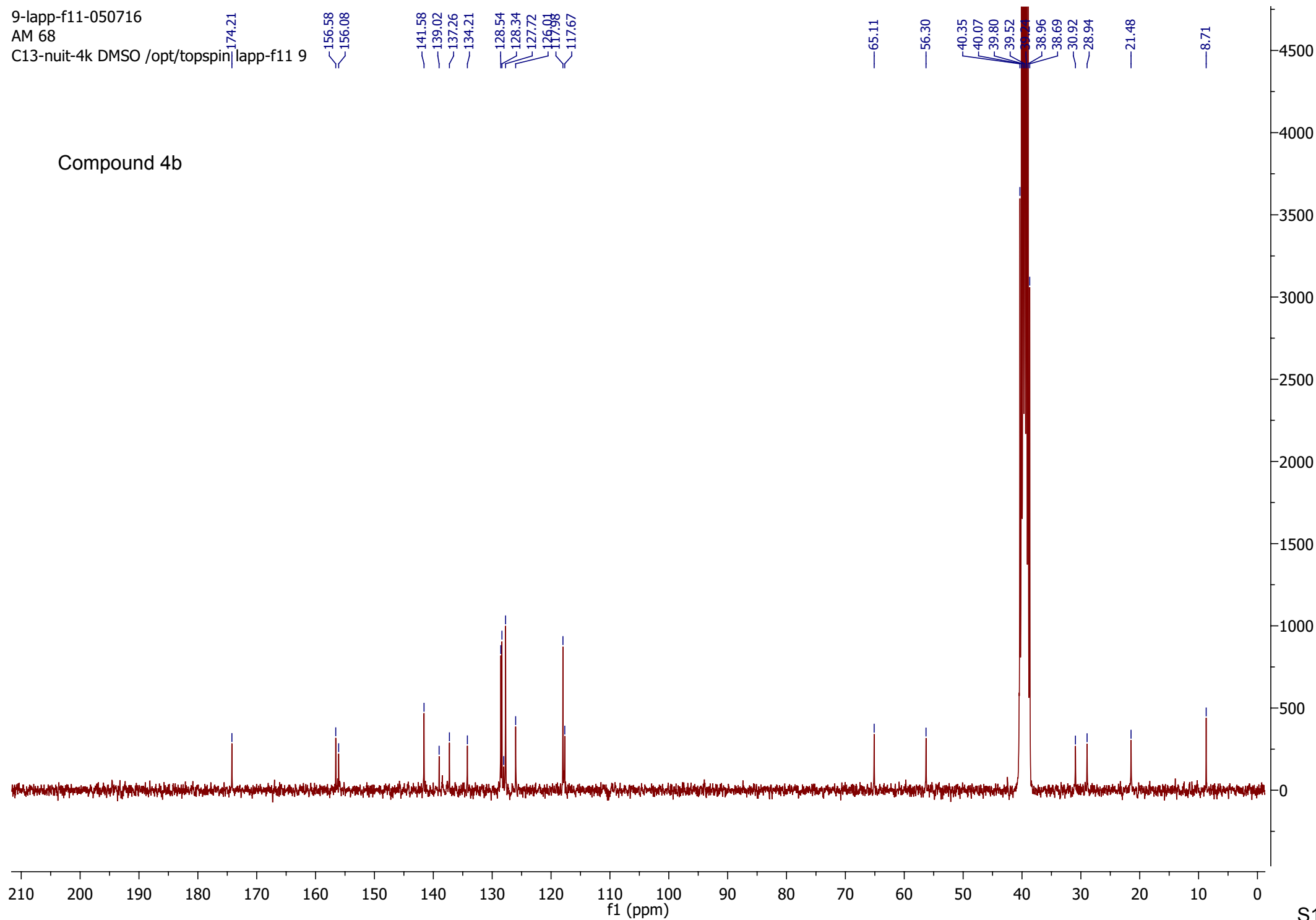
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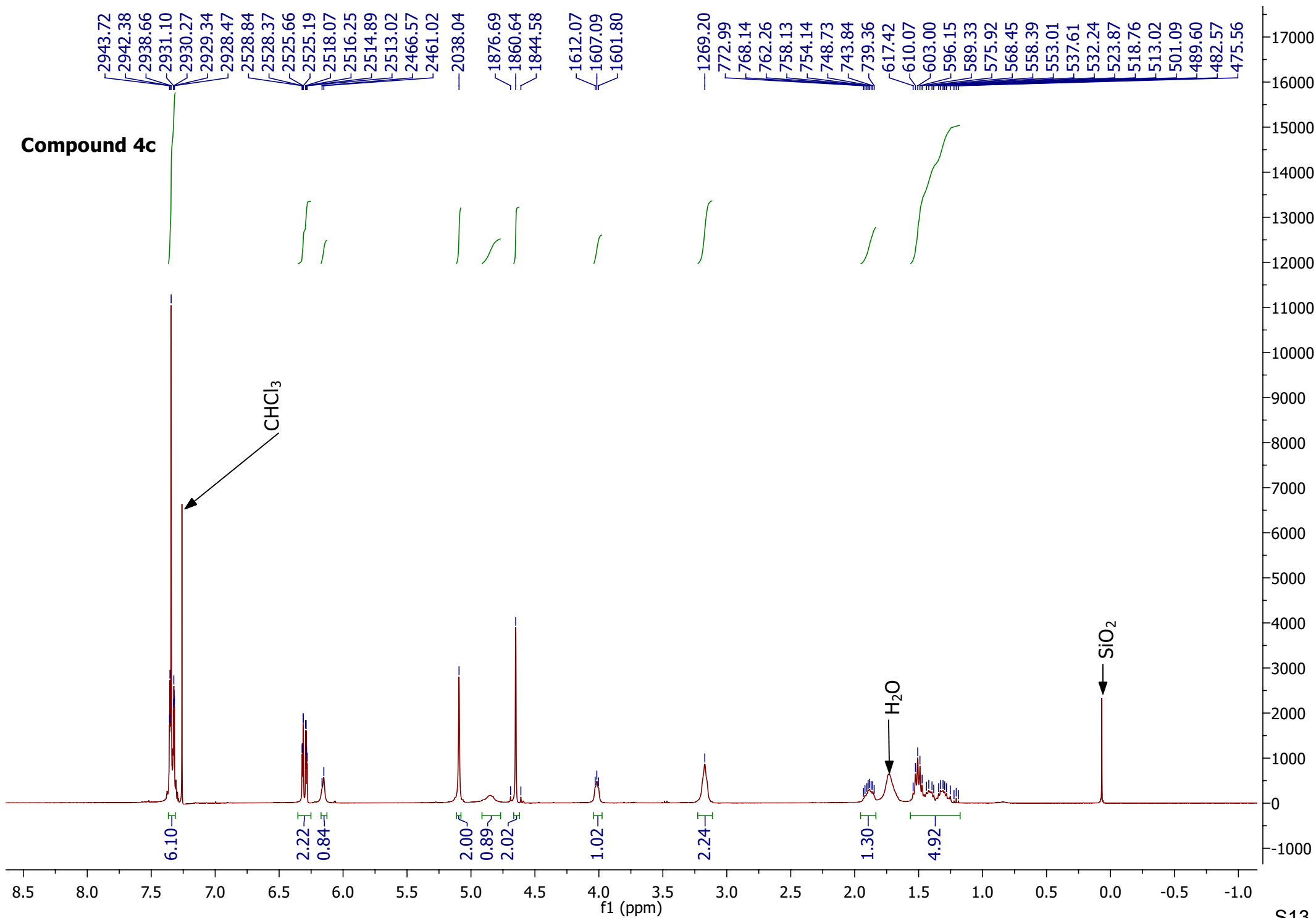
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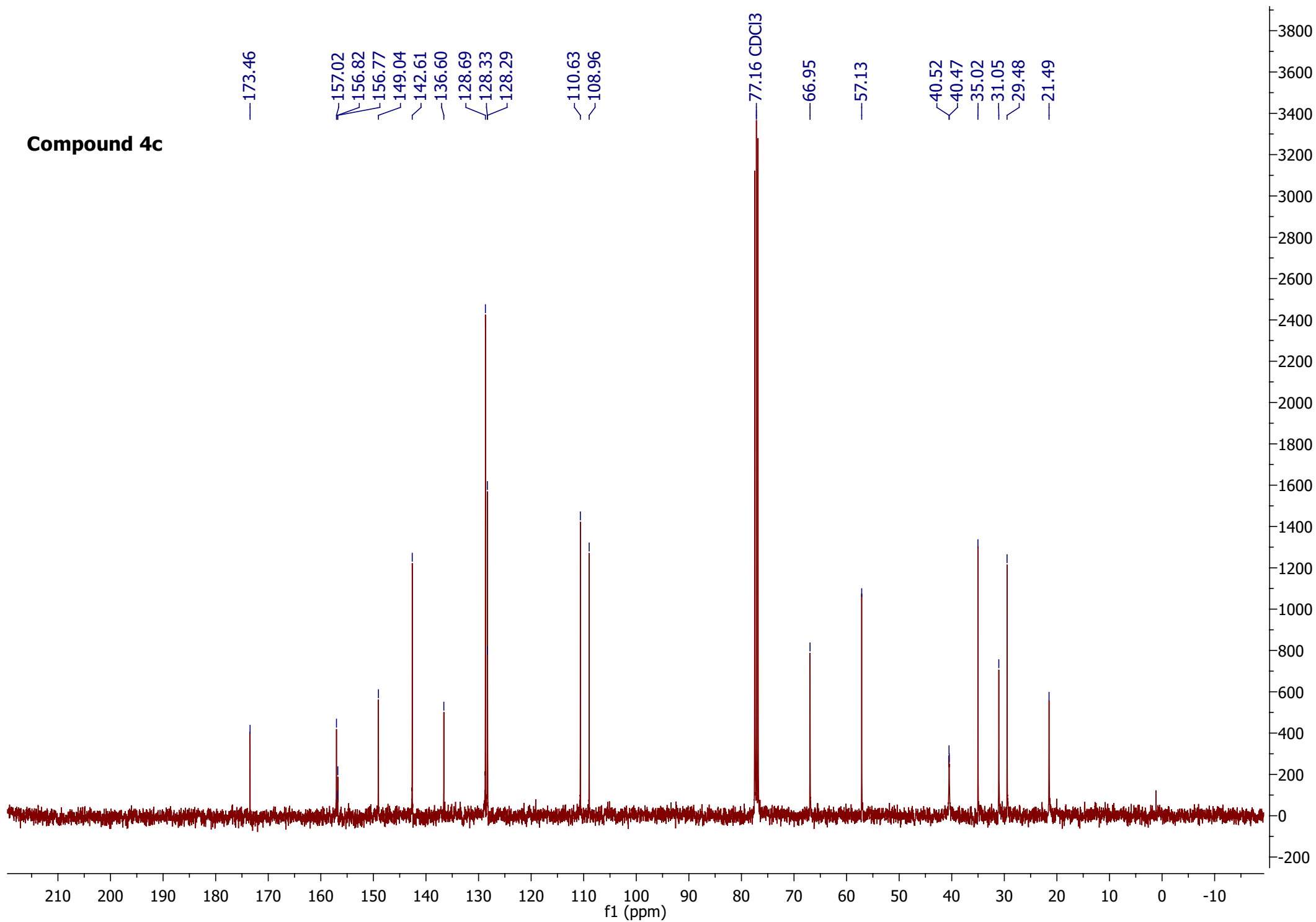
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AM 68  
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Compound 4b



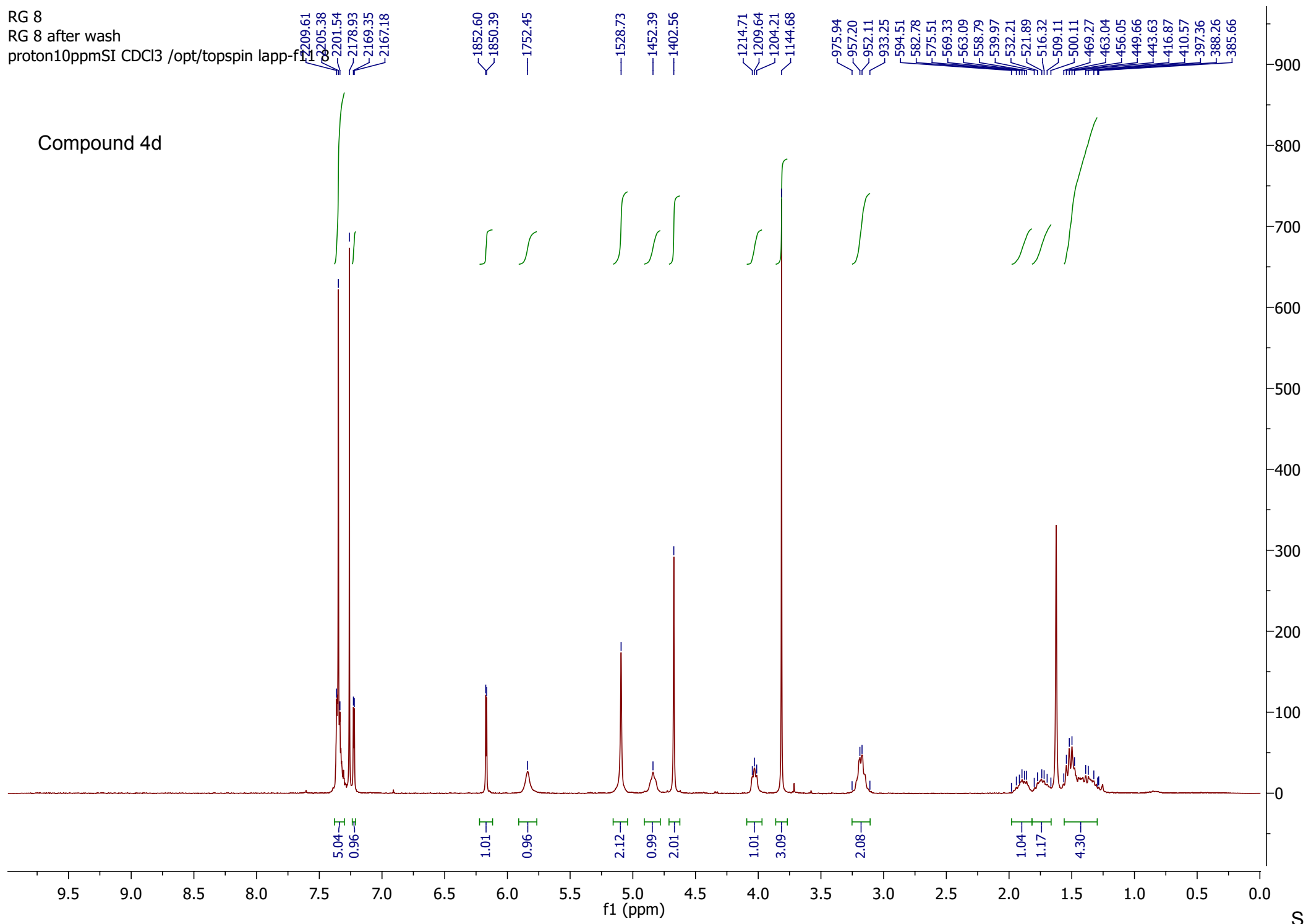


**Compound 4c**



RG 8  
RG 8 after wash  
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Compound 4d



8-lapp-f11-230616

RG8

C13-nuit-4k CDCl3 /opt/topspin/lapp-f11 8

Compound 4d

