Electronic Supplementary Information

Facile synthesis of 5-(alkylidene)thiophen-2(5*H*)-ones. A new class of biofilm inhibitors.

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Contents:

Experimental procedures:

2-Formyl-4-isopropyl-5-methoxythiophene 4b.

2-Chloropropane (62 mg, 0.80 mmol) and 2-formyl-5-methoxythiophene **4a** (108 mg, 0.76 mmol) in carbon disulfide (1 mL), were added dropwise at 0 ^{o}C to a suspension of aluminium chloride (100 mg, 0.76 mmol in carbon disulfide (1 mL). The mixture was stirred at 0 ^{o}C for 24h before it was poured into ice in 1M HCl. The product was extracted into ether, washed

with bicarbonate and brine before it was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography using hexane/EtOAc 6:1 for elution. Yield 33 mg (24%); δ_H (200 MHz, $CDCl_3$) 1.17 (6H, d, *J* 7.0, *i*-Pr), 2.98 (1H, septet, *J* 7.0, *i*-Pr), 3.98 (3H, s, MeO), 7.47 (1H, s, H4), 9.58 (1H, s, CHO).

4-tert-Butyl-2-formyl-5-methoxythiophene 4c.

2-Chloro-2-methylpropane (74 mg, 0.80 mmol) and 2-formyl-5-methoxythiophene **4a** (86 mg, 0.61 mmol) in carbon disulfide (1 mL), were added dropwise at 0 ^oC to a suspension of aluminium chloride (80 mg, 0.60 mmol in carbon disulfide (1 mL). The mixture was stirred at 0 ^oC for 4h before it was poured into ice in 1M HCl. The product was extracted into ether, washed with bicarbonate and brine before it was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography using hexane/EtOAc 6.5:1 for elution. Yield 70 mg (58%); δ_H (200 MHz, $CDCl_3$) 1.29 (9H, s, *t*-Bu), 4.00 (3H, s, MeO), 7.49 (1H, s, H4), 9.58 (1H, s, CHO); *m/z* (EI) 198 (M^+, 31%), 183 (100), 155 (6) 153 (12), 111 (6).

4-Bromo-2-formyl-5-methoxythiophene 4d.

N-Bromosuccinimide (1.42 g, 7.9 mmol) was added to a solution of 2-formyl-5-methoxythiophene **4a** (0.94 g, 6.6 mmol) in dichloromethane (10 mL) at room temperature. The mixture was stirred over night, diluted with ether (50 mL) and washed with water (2x25mL). The organic phase was dried ($MgSO_4$), filtered through a short silica-pad and the solvents were removed *in vacuo*. Yield 1.40 g (96%); mp 110 – 113 ^oC ; δ_H (200 MHz, $CDCl_3$) 4.06 (3H, s, MeO) 7.53 (1H, s, H4), 9.62 (1H, s, CHO); δ_C (75 MHz, $CDCl_3$) 61.9, 92.6, 128.3, 138.9, 168.7, 181.2; *m/z* (EI) 222 (M^++2-100%), 220 (M^+-97%), 207 (49), 205 (48), 179 (28), 177 (27), 151 (26), 149 (27), 69 (42); HRMS (EI). Calculated for $C_6H_5BrO_2S$: 219.9194. Found 219.9194.

4-Ethenyl-2-formyl-5-methoxythiophene 4e.

Compound **4j** (1.20 g, 5.40 mmol, 1.0 equiv.) and $PdCl_2(PPh_3)_2$ (0.378 g, 0.54 mmol, 0.1 equiv.) was stirred in degassed dry toluene (14.0 mL). Vinyl tributylstannane (1.9 mL, 6.48 mmol, 1.2 equiv.) was added and the reaction mixture was heated at 90 °C under an argon

atmosphere for 24 h. ^{1}H-NMR showed full conversion of the starting material. Toluene was removed *in vacuo*. Tetrahydrofuran and KF were added and the mixture was stirred on. Tetrahydrofuran was removed *in vacuo* before dichloromethane was added and the crude product was filtered trough a short column of silica. The product was purified by flash chromatography (ethyl acetate:hexane, gradient 5-20%). Yield 0.689g (76 %) ; δ_H (300 MHz, $CDCl_3$) 4.03 (3H, s, OMe), 5.19 (1H, dd, *J* 1.2, 11.2 Hz, CH=C**H**$_2$), 5.57 (1H, dd, *J* 1.2, 17.8 Hz, CH=C**H**$_2$), 6.59 (1H, dd, *J* 11.2, 17.8, C**H**=CH$_2$), 7.66 (1H, s, H3), 9.64 (1H, s, CHO); δ_C (75 MHz, $CDCl_3$) 61.5, 113.6 , 121.4, 126.4, 128.3, 135.6, 170.9, 182.1; *m/z* (EI) 168 (M^+, 100), 153 (24), 125 (36), 97 (56), 45 (22). HRMS (EI). Calculated for $C_8H_8O_2S$ 168.0245. Found 168.0250

4-(Chloromethyl)-2-formyl-5-methoxythiophene 4f.

Titanium tetrachloride (4.9 mL, 44 mmol) was added dropwise to a solution of 2-formyl-5-methoxythiophene **4a** (5.21g, 36.6 mmol) and chloromethyl ethyl ether (4.2 mL, 44.0 mmol) in dichloromethane (25 mL) at 0 ºC. The reaction mixture was heated to room temperature and stirred for 2 h. The reaction mixture was diluted with ether (100 mL) and washed with sodium chloride (aq, sat., 2x25 mL) and water (25 mL). The combined aqueous phases were extracted with dichloromethane (2x25 mL), and the combined organic phases were dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash column chromatography on silica (0 – 35% EtOAc in hexanes). Yield 5.10g (73%); mp 64 – 66 ºC; δ_H (200 MHz, $CDCl_3$) 4.06 (3H, s, MeO), 4.50 (2H, s, CH_2Cl), 7.59 (1H, s, H4), 9.64 (1H, CHO); δ_C (75 MHz, $CDCl_3$) 36.5, 61.8, 119.0, 128.7, 138.2, 172.3, 181.9; *m/z* (EI) 192 (M^++2, 11%), 190 (M^+, 29), 155 (100), 83 (19); HRMS (EI). Calculated for $C_7H_7ClO_2S$ 189.9855. Found 189.9855.

4-(1-Chloroethyl)-2-formyl-5-methoxythiophene 4g.

Compound **4k** (0.200, 1.20 mmol, 1.0 equiv.) was dissolved in chloroform (5.0 mL). $HCl_{(g)}$ was bubbled through the solution at 0 °C for 10 min. ^{1}H-NMR showed full conversion of the starting material and formation of the desired product **4e**. The crude product was used in the synthesis of **3e** without further purification. δ_H (200 MHz, $CDCl_3$) 1.80 (3H, d, *J* 6.9, *i*-Pr), 4.05 (3H, s, MeO), 5.21 (1H, q, *J* 6.9, *i*-Pr), 7.67 (1H, s, H3), 9.65 (s, 1H, CHO),

2-Formyl-5-methoxy-4-(2-thienyl)thiophene 4h.

4-Bromo-2-formyl-5-methoxythiophene **4h** (0.22 g, 1.0 mmol), tributyl(thiophen-2-yl)stannane (0.75 g, 2.0 mmol), $PdCl_2(PhCN)_2$ (38 mg, 0.1 mmol) and triphenylphosphine (79 mg, 0.3 mmol) were dissolved in *N*,*N*-dimethylformamide (3 mL) and stirred at 50 ºC for 24h. The reaction mixture was cooled to room temperature, diluted with ether (25 mL) and washed with water. The combined aqueous phases was extracted with ether (10 mL), and the combined organic phases were dried over $MgSO_4$, filtered and the solvents removed *in vacuo*. The product was purified by flash column chromatography on silica (0 – 20% EtOAc in hexanes).Yield 187 mg (83%); mp 73 – 74 ºC**;** δ_H (200 MHz, $CDCl_3$) 4.13 (3H, s, MeO), 7.05 (1H, dd, *J* 3.6, 5.1), 7.24 (1H, dd, *J* 5.1, 1.1), 7.33 (1H, dd, *J* 3.6, 1.1), 7.79 (1H, s, H4), 9.70 (1H, s, CHO); δ_C (75 MHz, $CDCl_3$) 61.9, 117.3, 123.9, 124.1, 127.2, 128.4, 134.8, 136.2, 168.8, 182.1; *m/z* (EI) 224 (M^+, 100%), 209 (68), 153 (66); HRMS (EI). Calculated for $C_{10}H_8O_2S$ 223.9966. Found 223.9968.

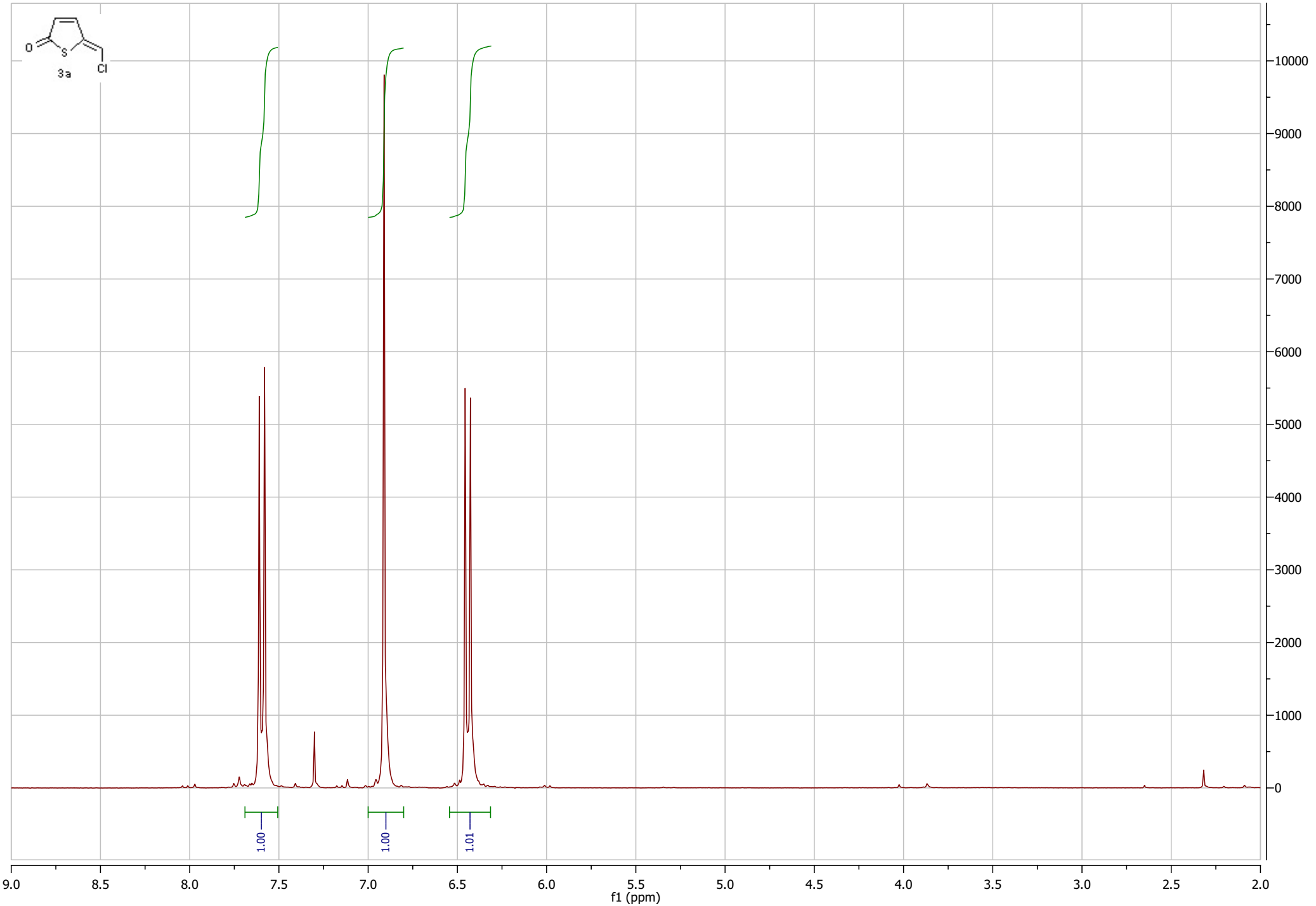
4-Ethyl-2-formyl-5-methoxythiophene 4i. Compound **4d** (0.0502 g, 0.299 mmol, 1.0 equiv.) was dissolved in MeOH (2.0 mL) and added to Pd/C (10 mg) in MeOH (3.0 mL). $H_{2(g)}$ was added (balloon of $H_{2(g)}$ over the reaction) to the reaction mixture at rt for 2.5 h. ^{1}H-NMR showed full conversion of the starting material. The reaction mixture was filtered through celite and MeOH removed *in vacuo*. The crude product was purified by flash chromatography (ethyl acetate: hexane, gradient 5-25 %). Yield 0.033 g (65 %); δ_H (300 MHz, $CDCl_3$) 1.15 (3H, t, *J* 7.6, C**H**$_3$), 2.48 (2H, q, *J* 7.6, C**H**$_2$), 3.97 (3H, s, 3H, MeO), 7.43 (1H, s, H3), 9.58 (1H, s, 1H, CHO); δ_C (75 MHz, $CDCl_3$) 13.9, 19.1, 61.2, 125.3, 127.6, 138.6, 170.3, 181.8; *m/z* (EI) 170 (82), 155 (100), 97 (33), 65 (24), 45 (19); HRMS (EI). Calculated for $C_8H_{10}O_2S$ 170.0402. Found 170.0398.

***N*-((5-Methoxythiophen-2-yl)methylene)aniline 7.** One drop acetyl chloride was added to a mixture of 2-formyl-5-methoxythiophene **4a** (114 mg, 0.8 mmol) and aniline (78 mg, 0.80 mmol) in ethanol (2 mL). The mixture was stirred for 24 h before the solvent was evaporated and the crude product purified by was purified by flash chromatography using hexane/EtOAc 5:1 for elution. Yield 77 mg (44%); δ_H (200 MHz; $CDCl_3$) 3.10 (3H, s, MeO), 6.20 (1H, d, *J*

4.2), 7.1-7.2 (4H, m, Ar), 7.3 – 7.4 (2H, m, Ar), 8.32 (1H, s, CHO); *m/z* (EI) 217 (M+, 100%), 202 (23), 174 (29), 104 (18), 77 (33).

2-(2,2-Dibromovinyl)-5-methoxythiophene 8. Tetrabromomethane (700 mg, 2.1 mmol), followed by triphenylphosphine (1.20 g, 4.8 mmol) were added to a solution of 2-formyl-5-methoxythiophene **4a** (282 mg, 2.0 mmol) in dichloromethane (10 mL) a 0 ^{o}C. The mixture was stirred for 30 min before it was filtered and evaporated. The crude product was purified by flash chromatography using hexane/EtOAc 10:1 for elution. Yield 230 mg (39%); δ_H (200 MHz; $CDCl_3$) 3.90 (3H, s, MeO), 6.12 (1H, d, *J* 4.0), 6.84 (1H, d, *J* 4.0), 7.41 (1H, s, H'); *m/z* (EI) 300 (M^++4, 45%), 298 (M^++2, 85), 296 (M^+, 43), 285 (53), 283 (100), 281 (51), 176 (9), 174 (9), 138 (16), 123 (32); HRMS (EI) Calculated for $C_7H_6Br_2O_1S_1$ 295.8506. Found 285.8502.

^{1}H NMR and ^{13}C NMR spectra of 3a-3o, 5, 6a-c, 6h, 9a, 9b, 10a, 10c, 10d, 10e, 11a and 11c:



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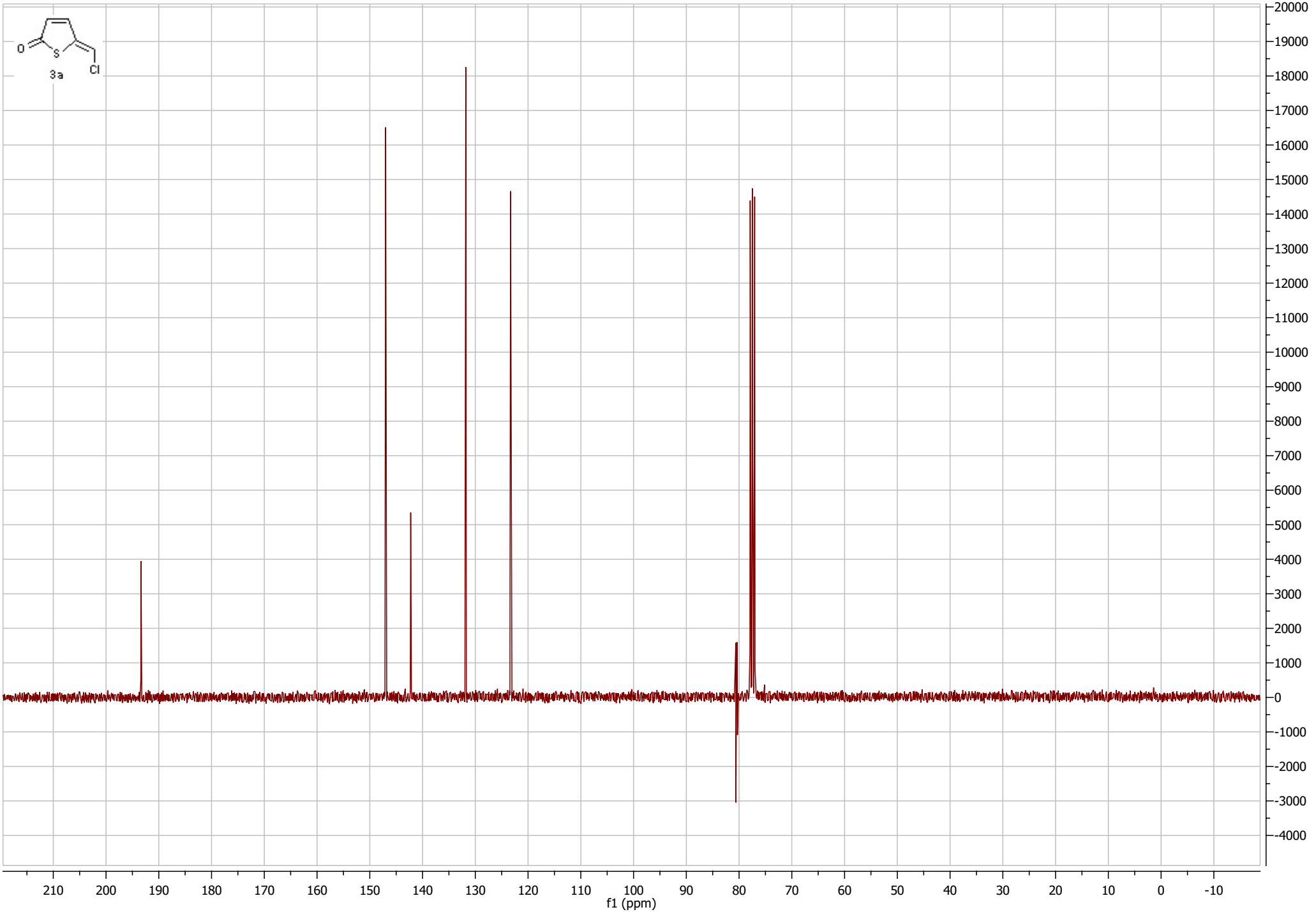

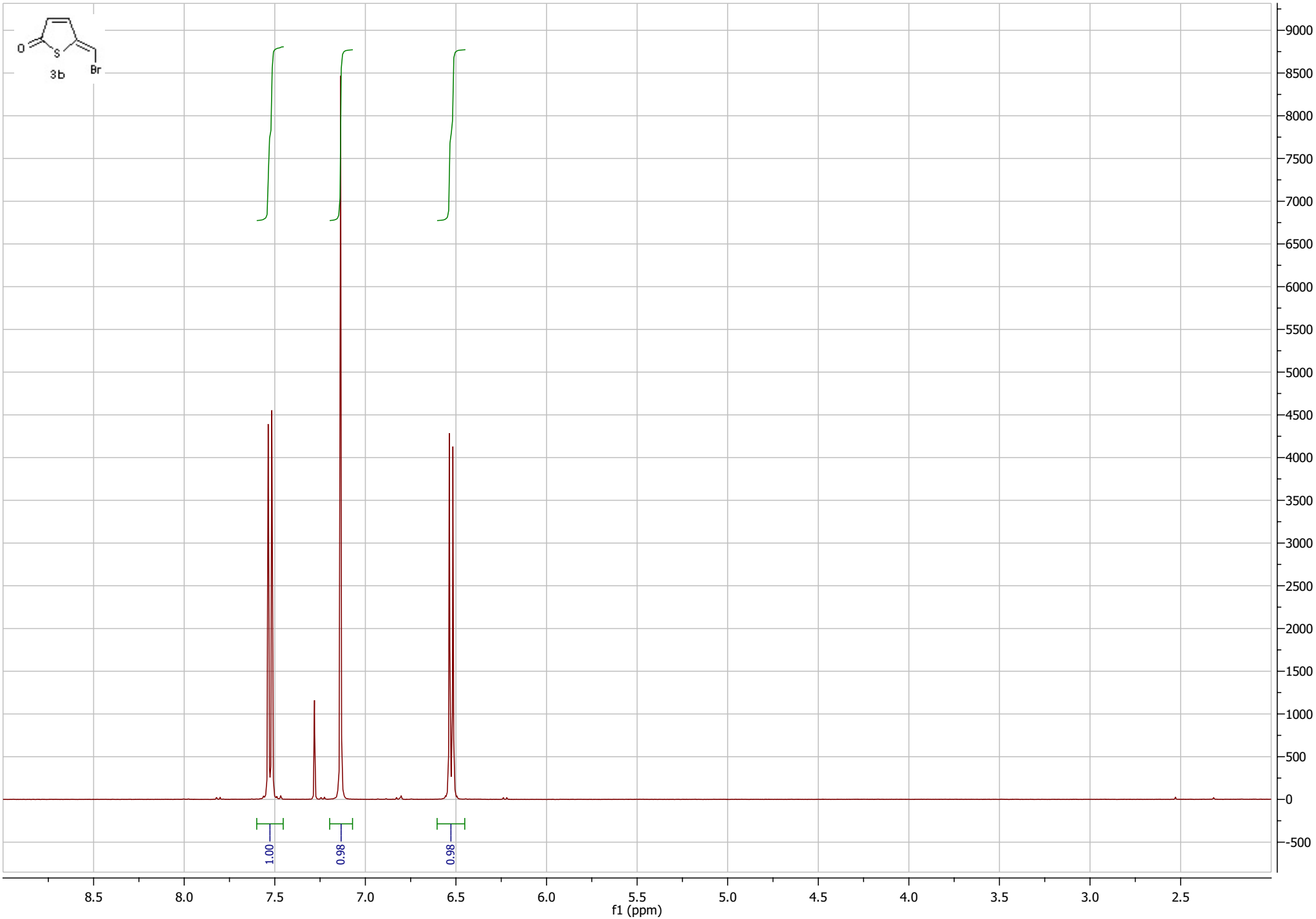

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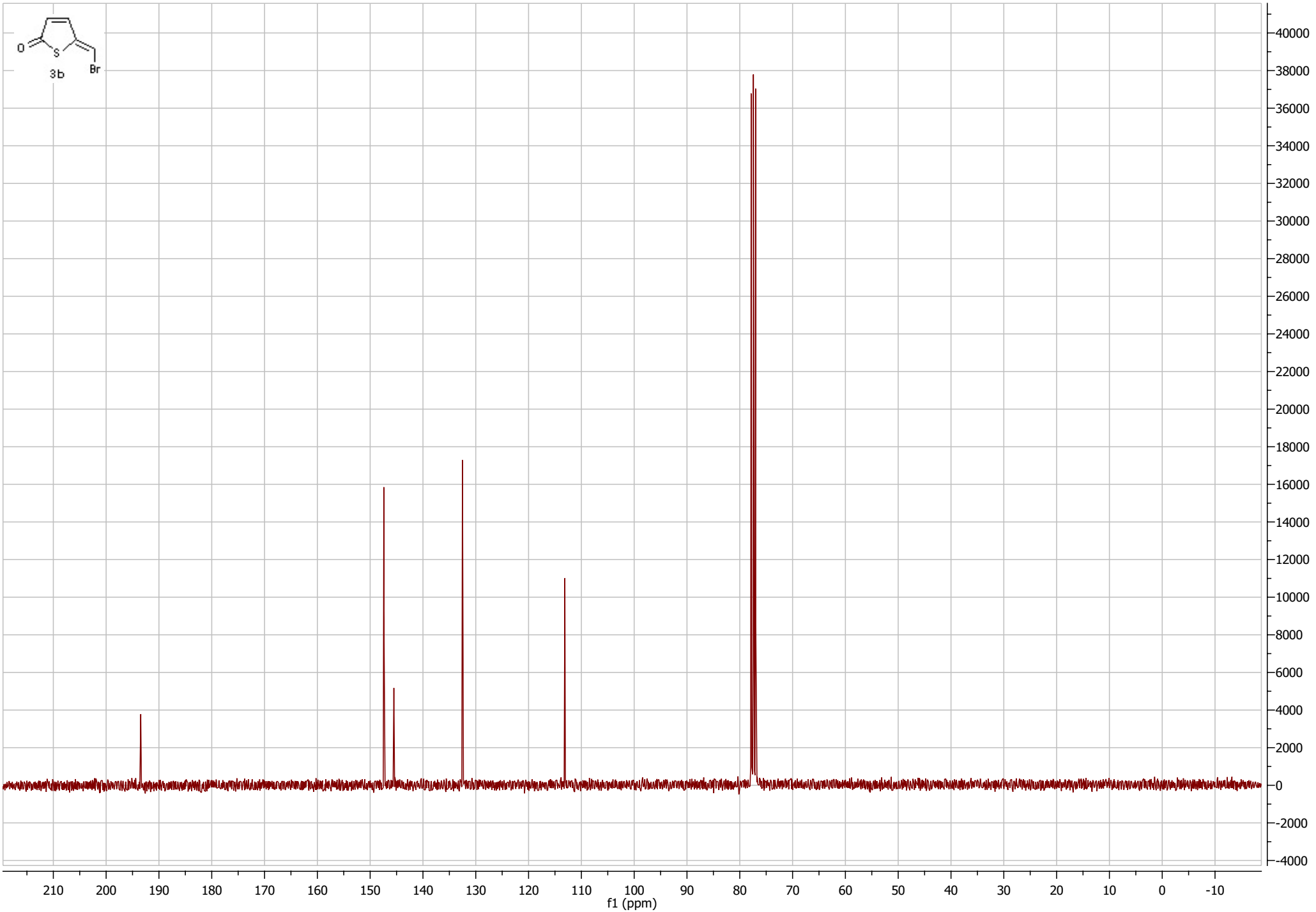

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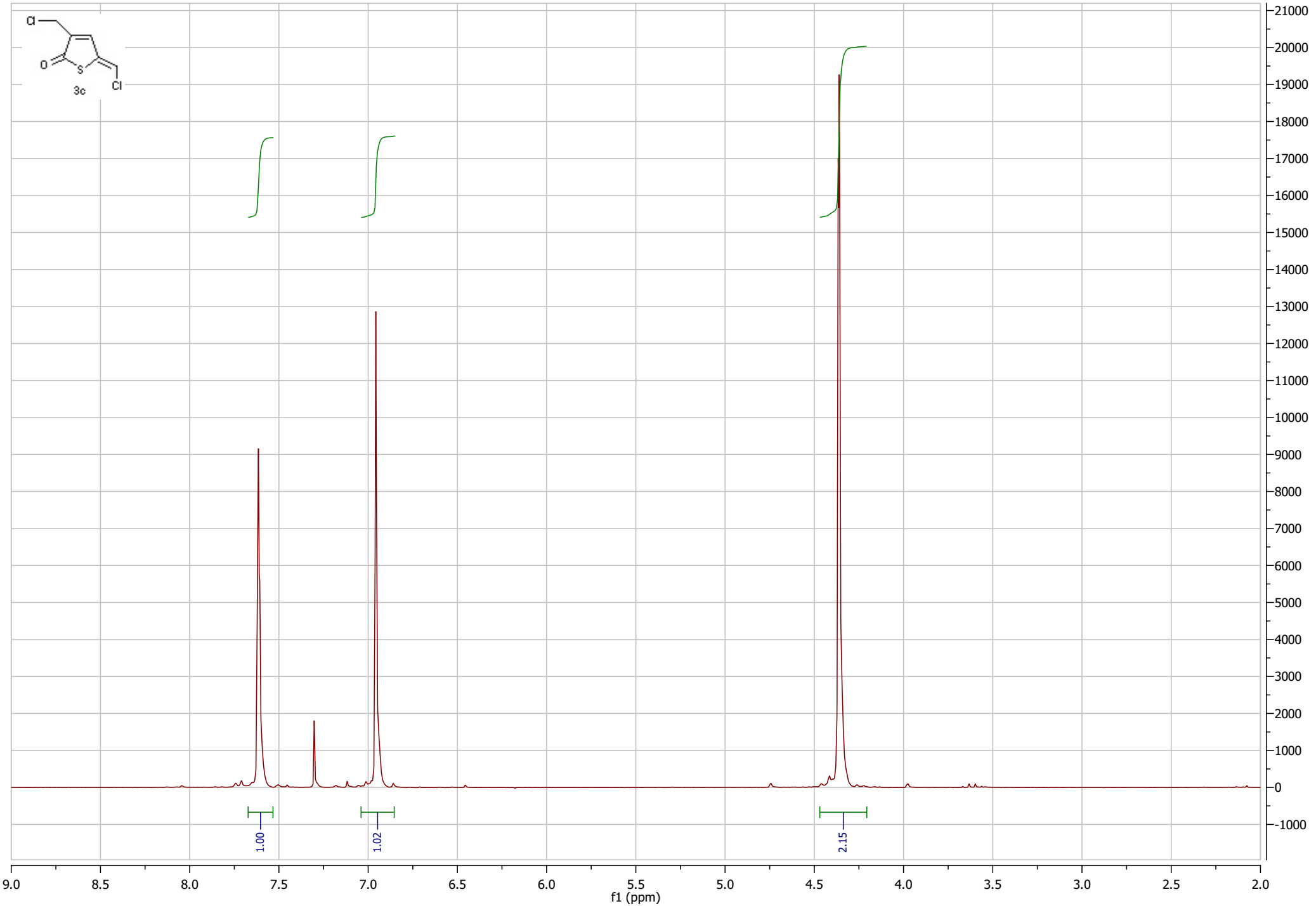

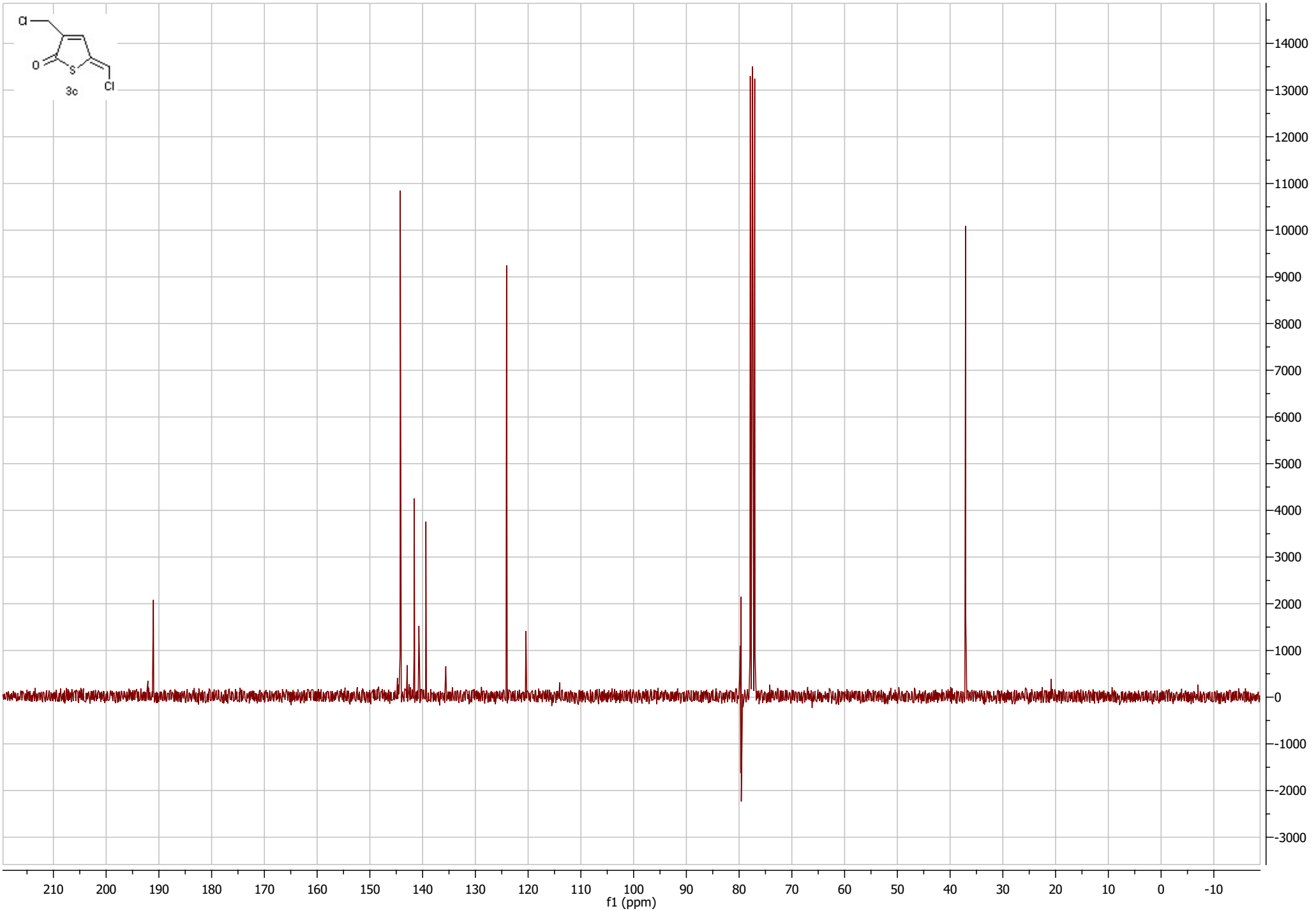

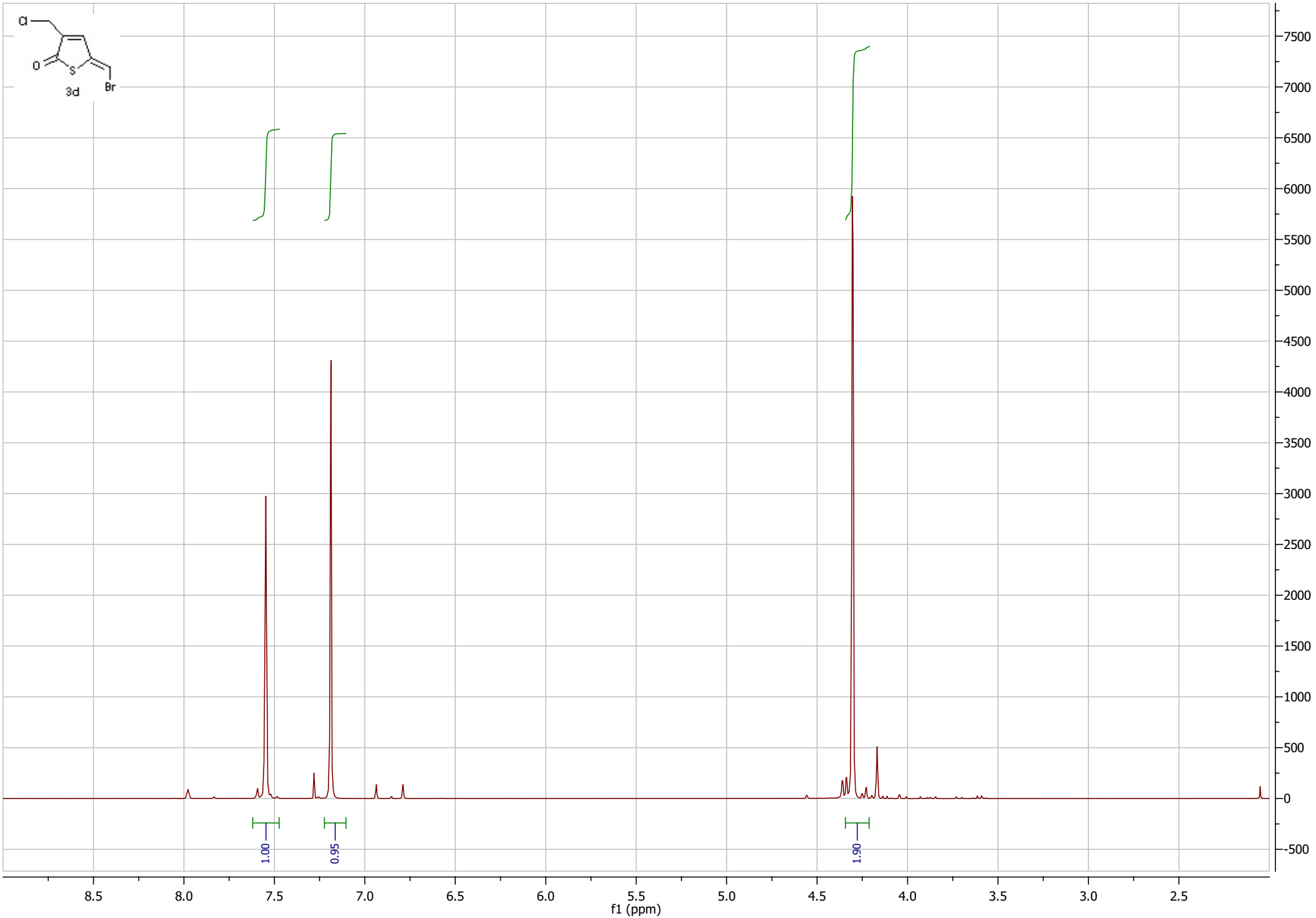

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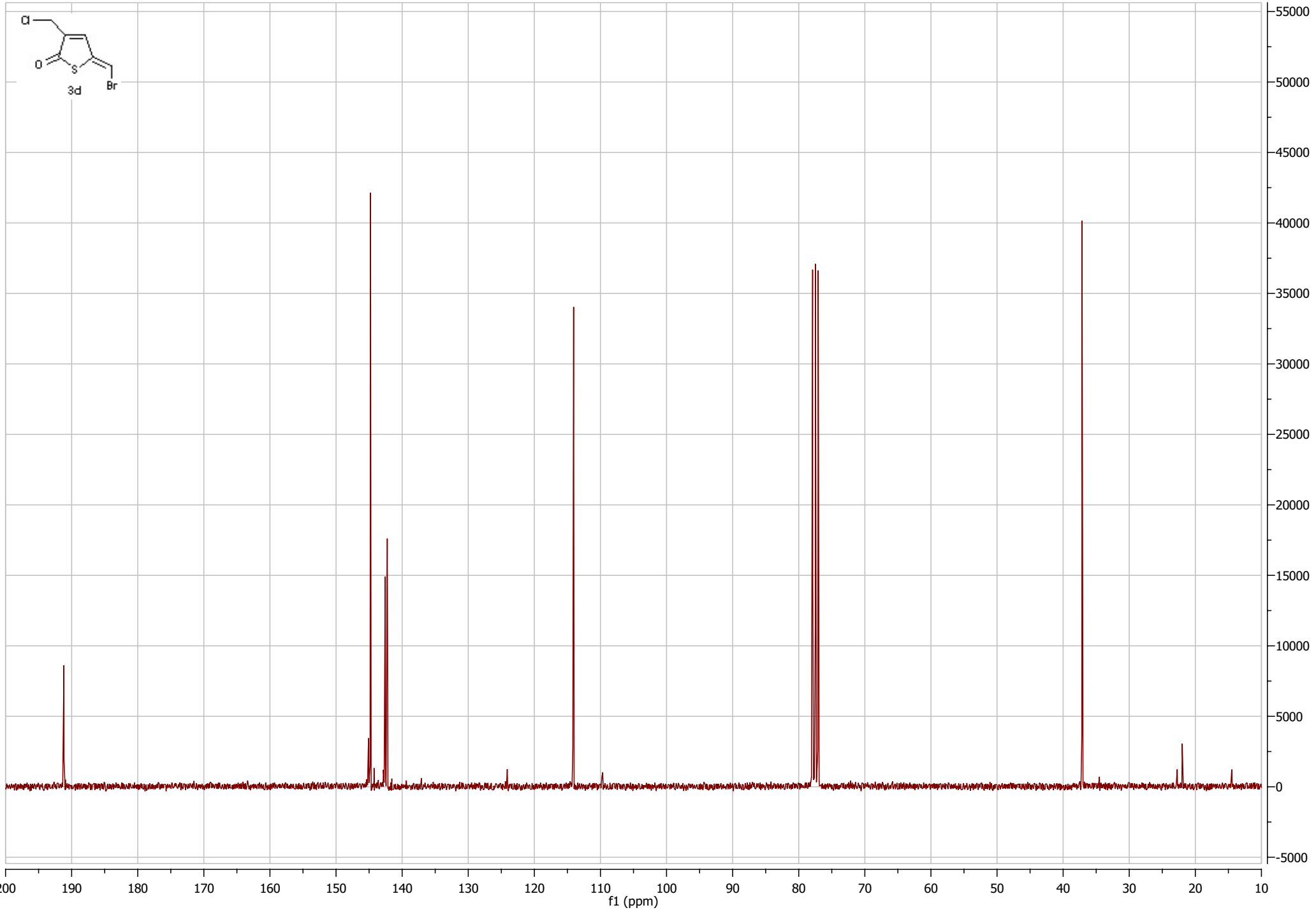

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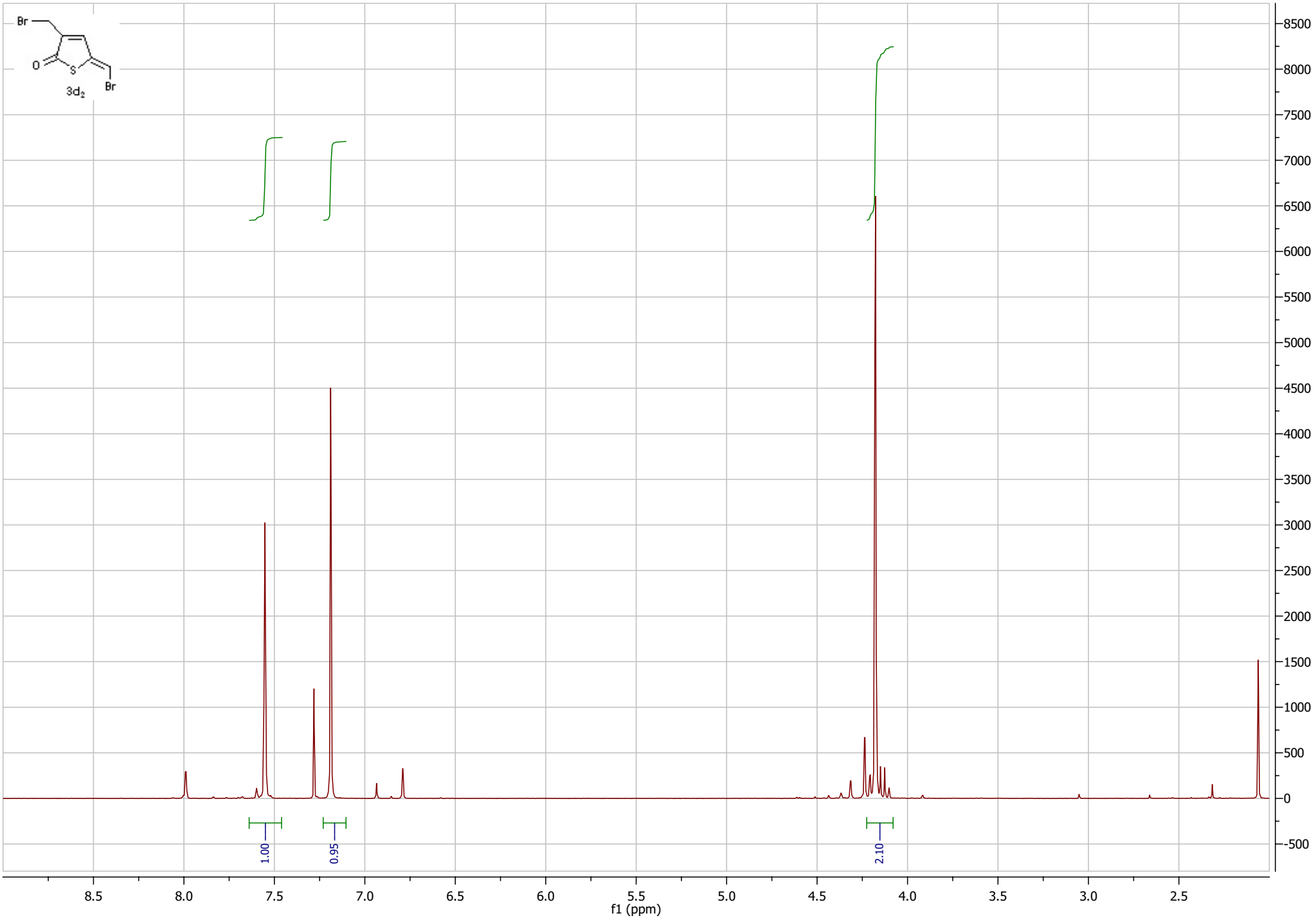

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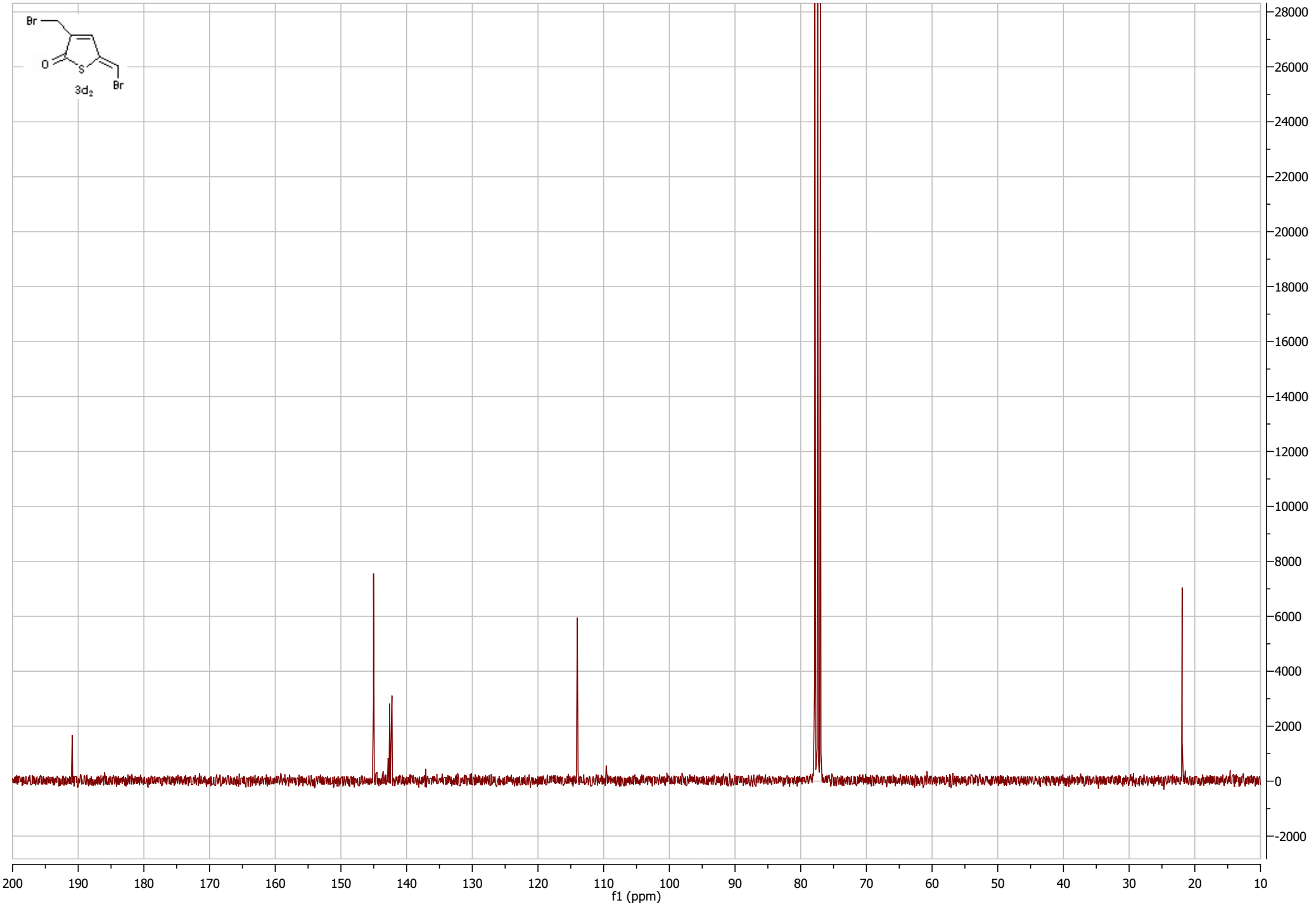

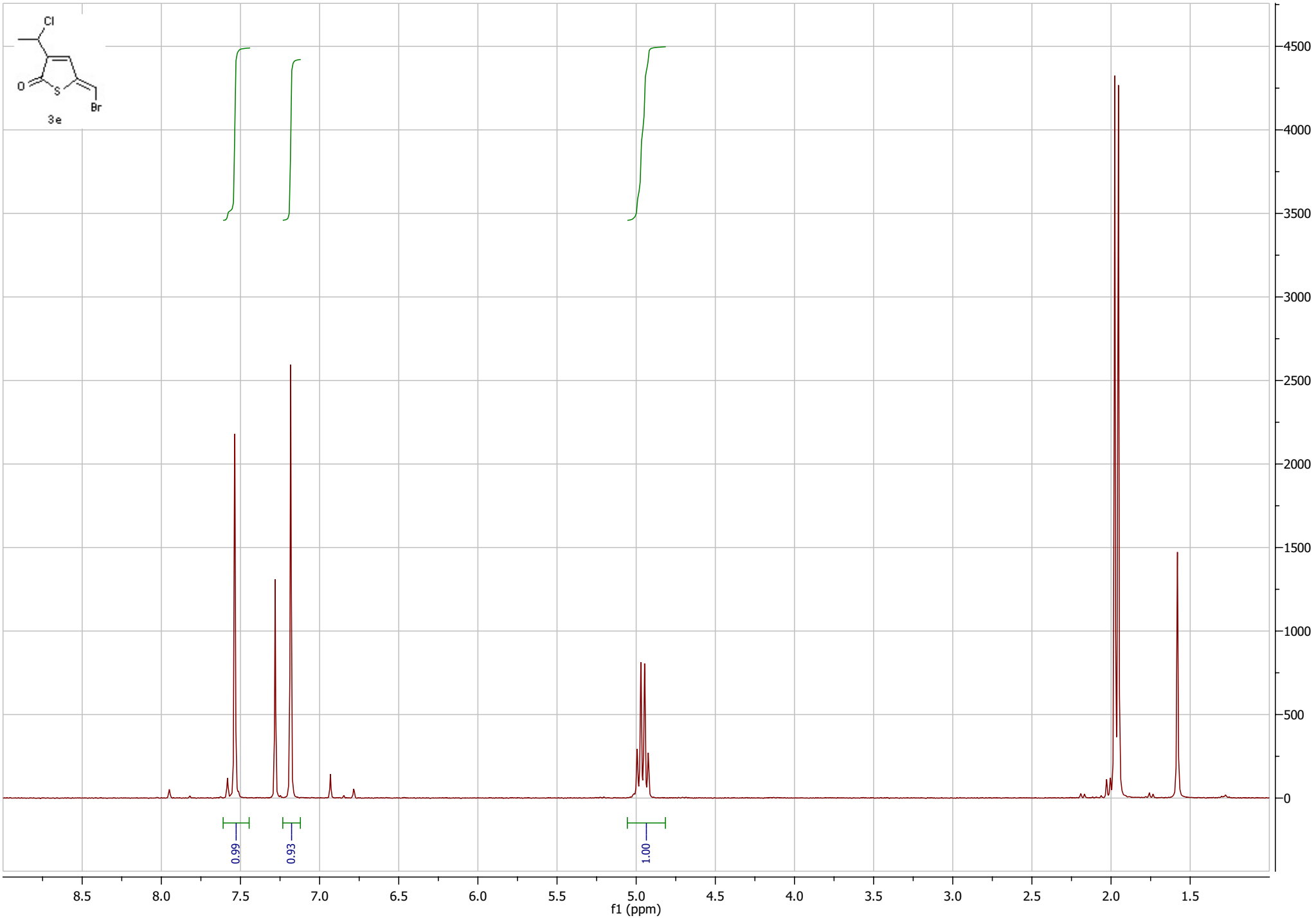

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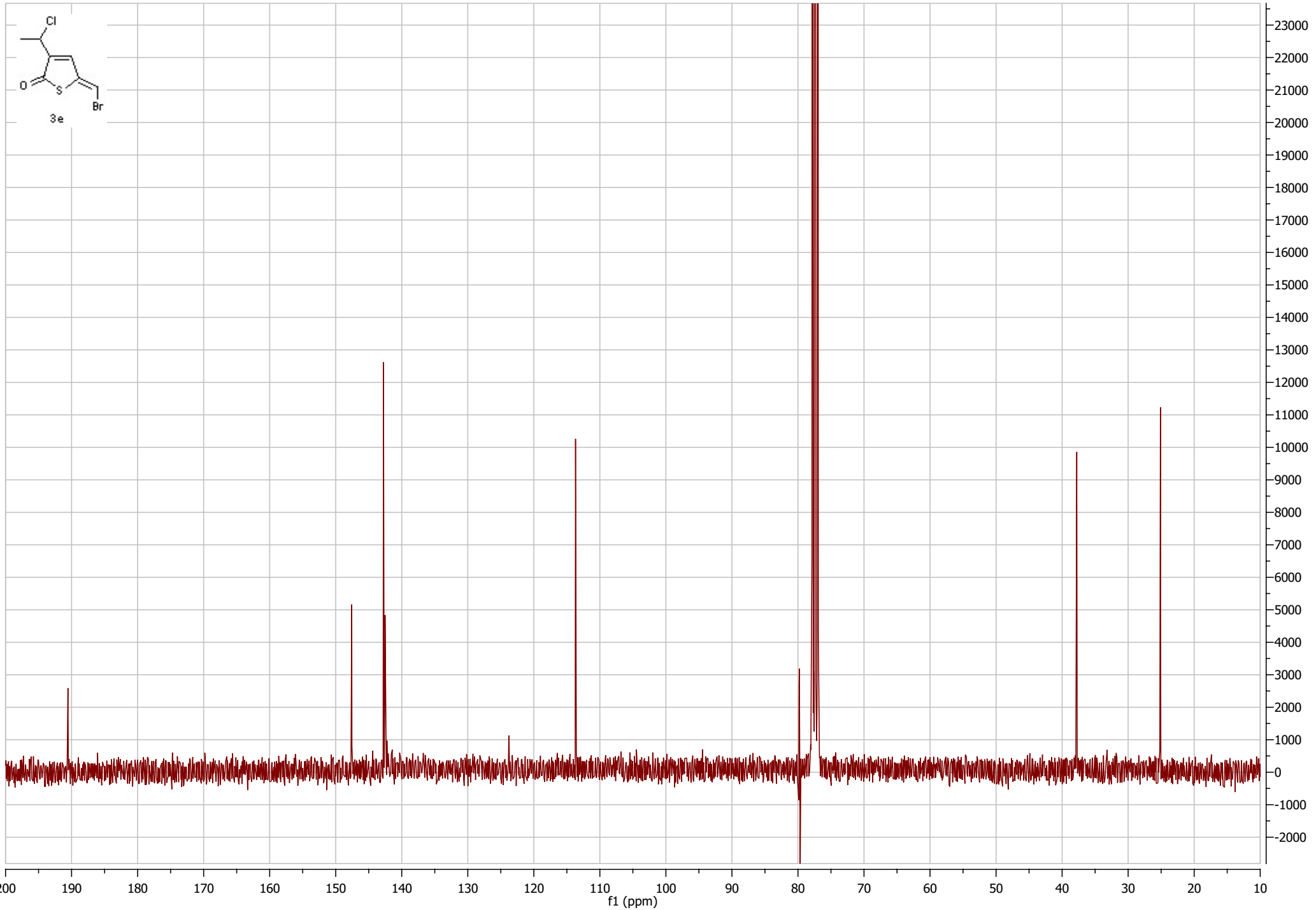

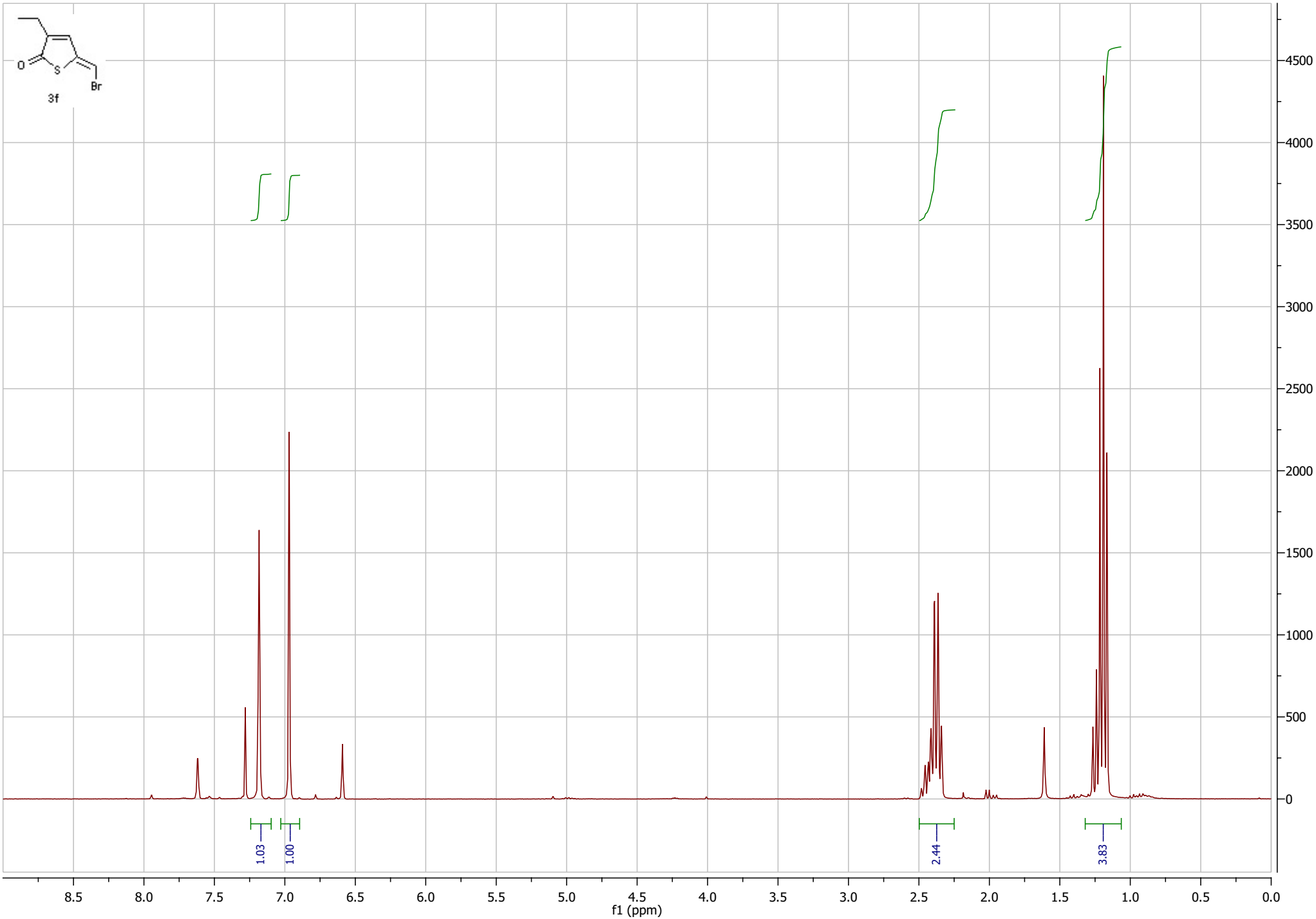

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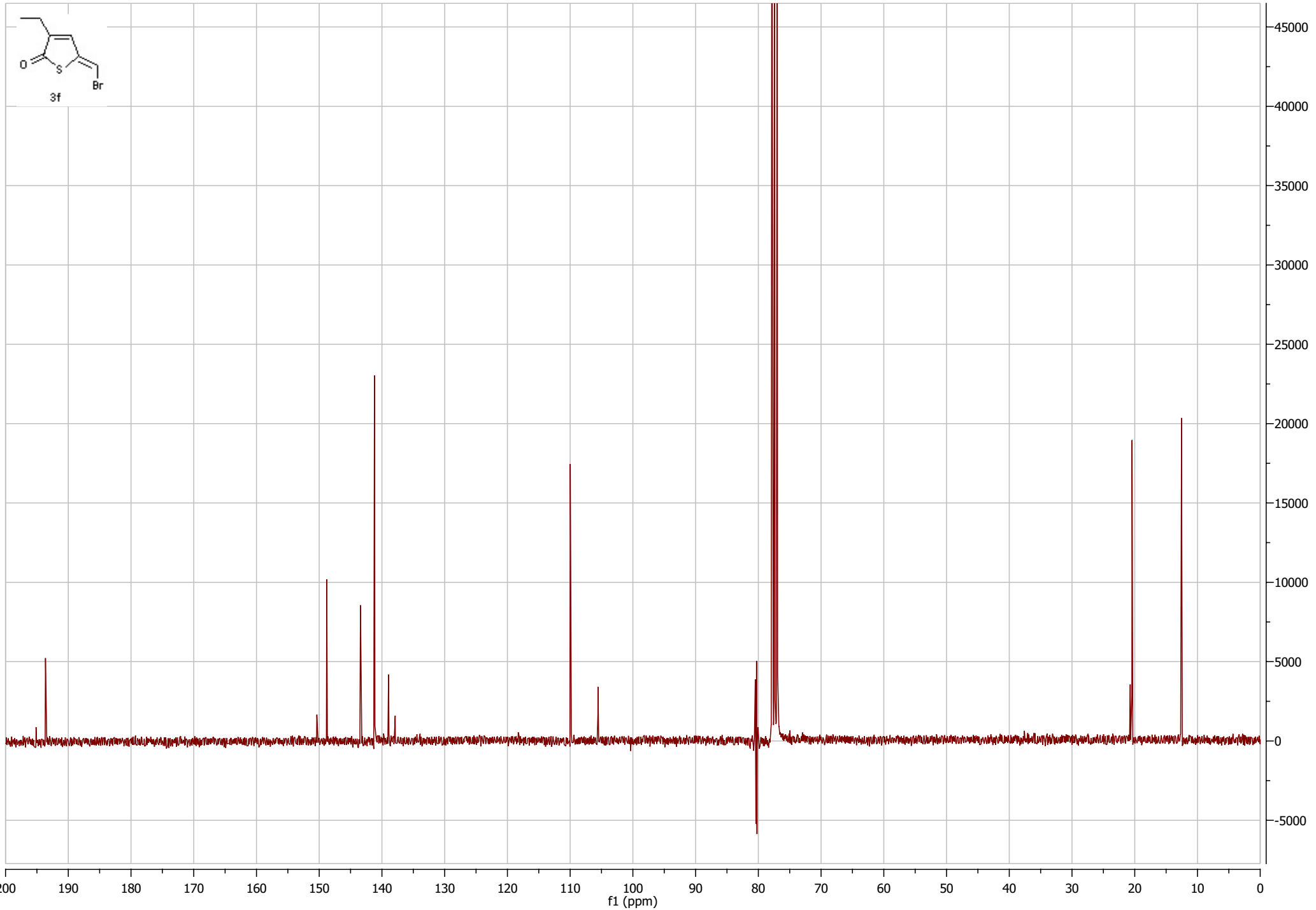

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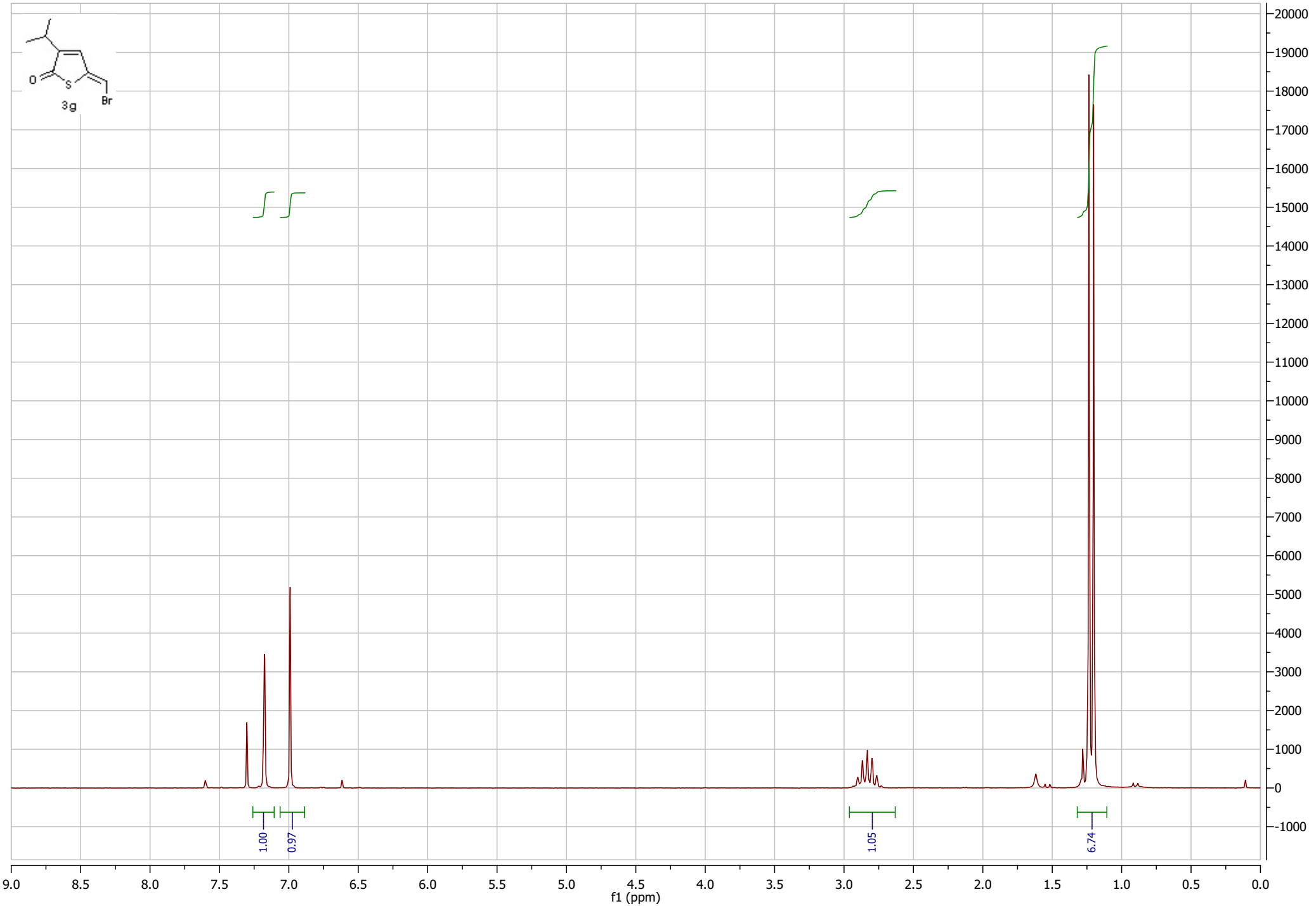

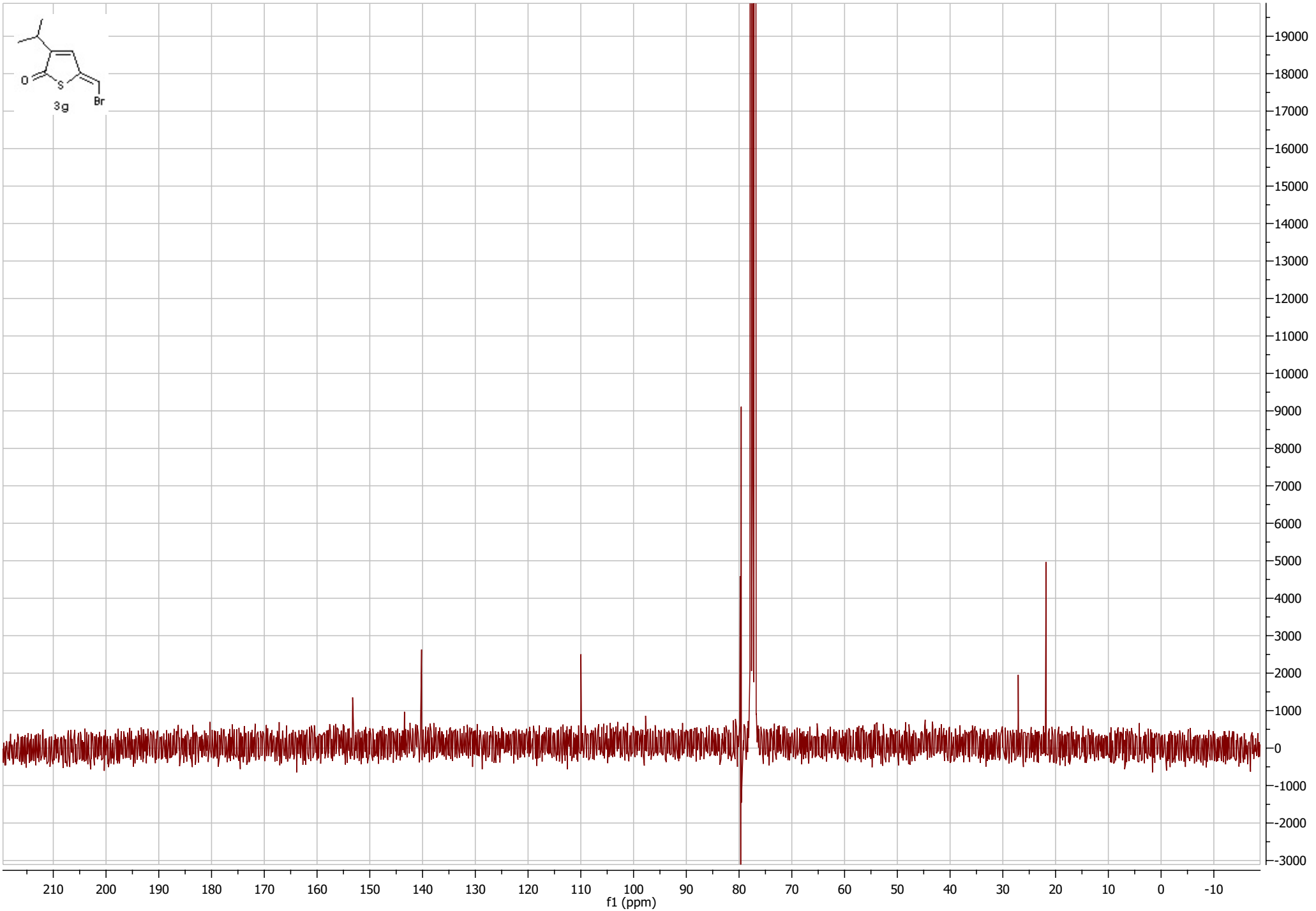

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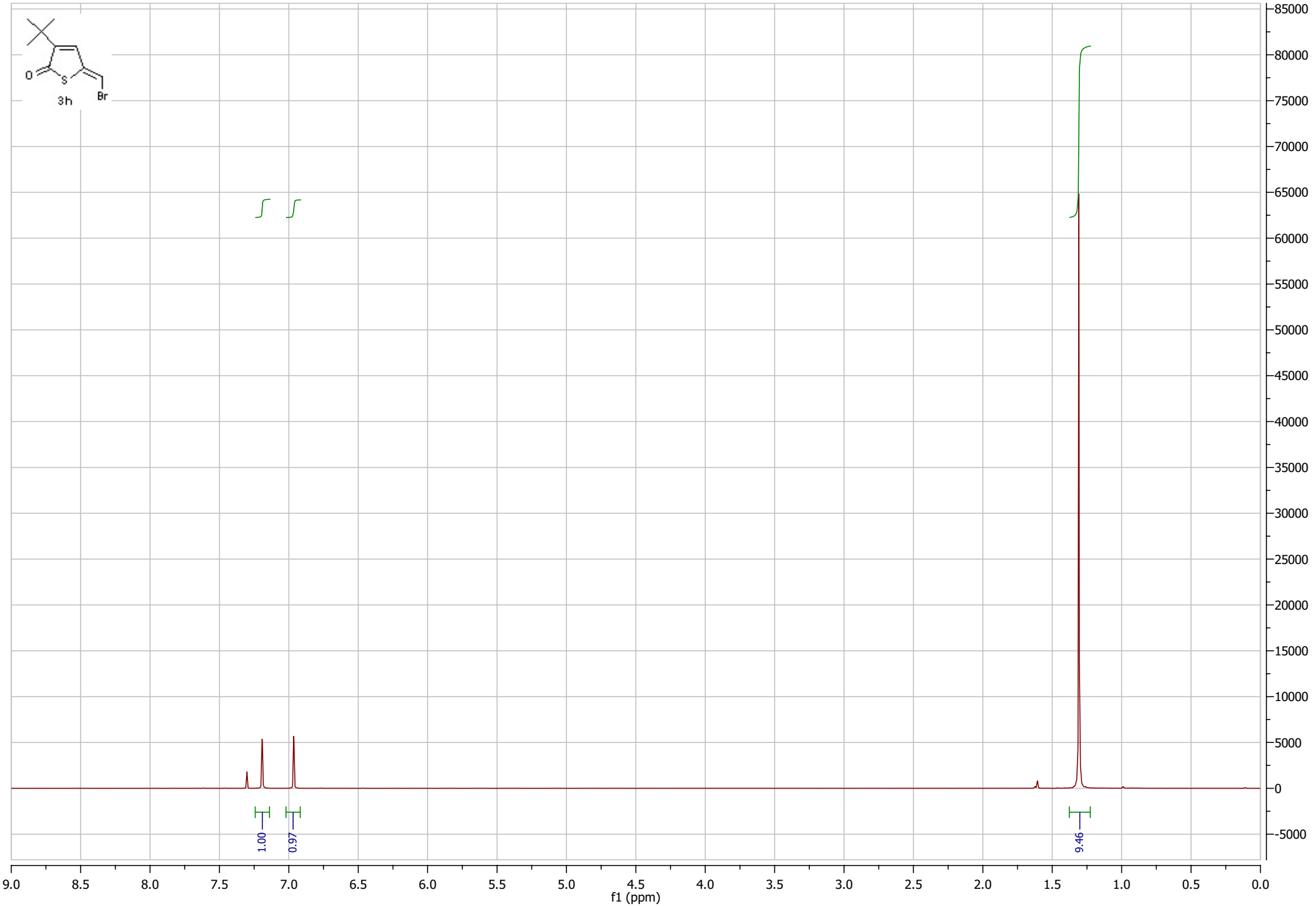

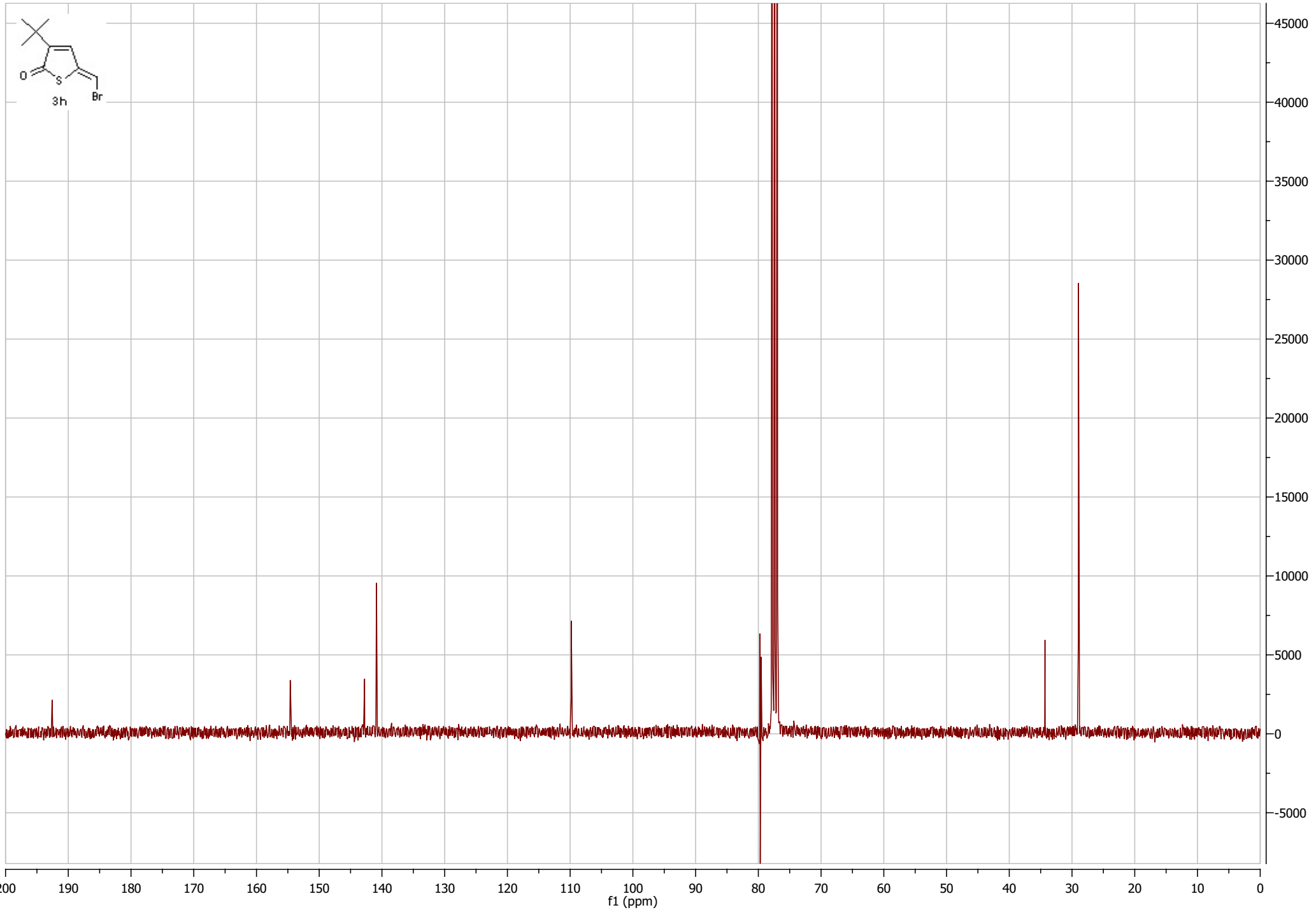

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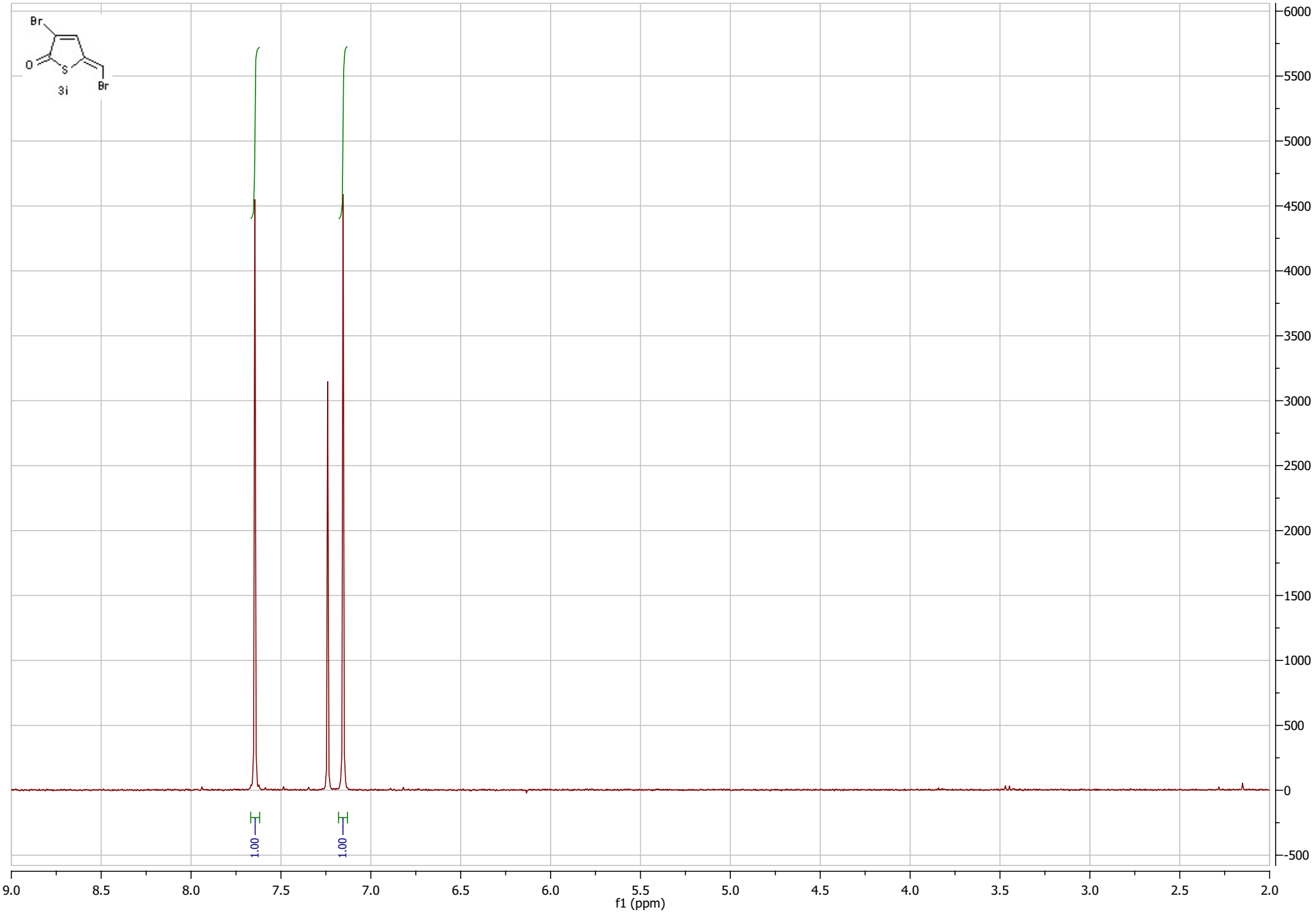

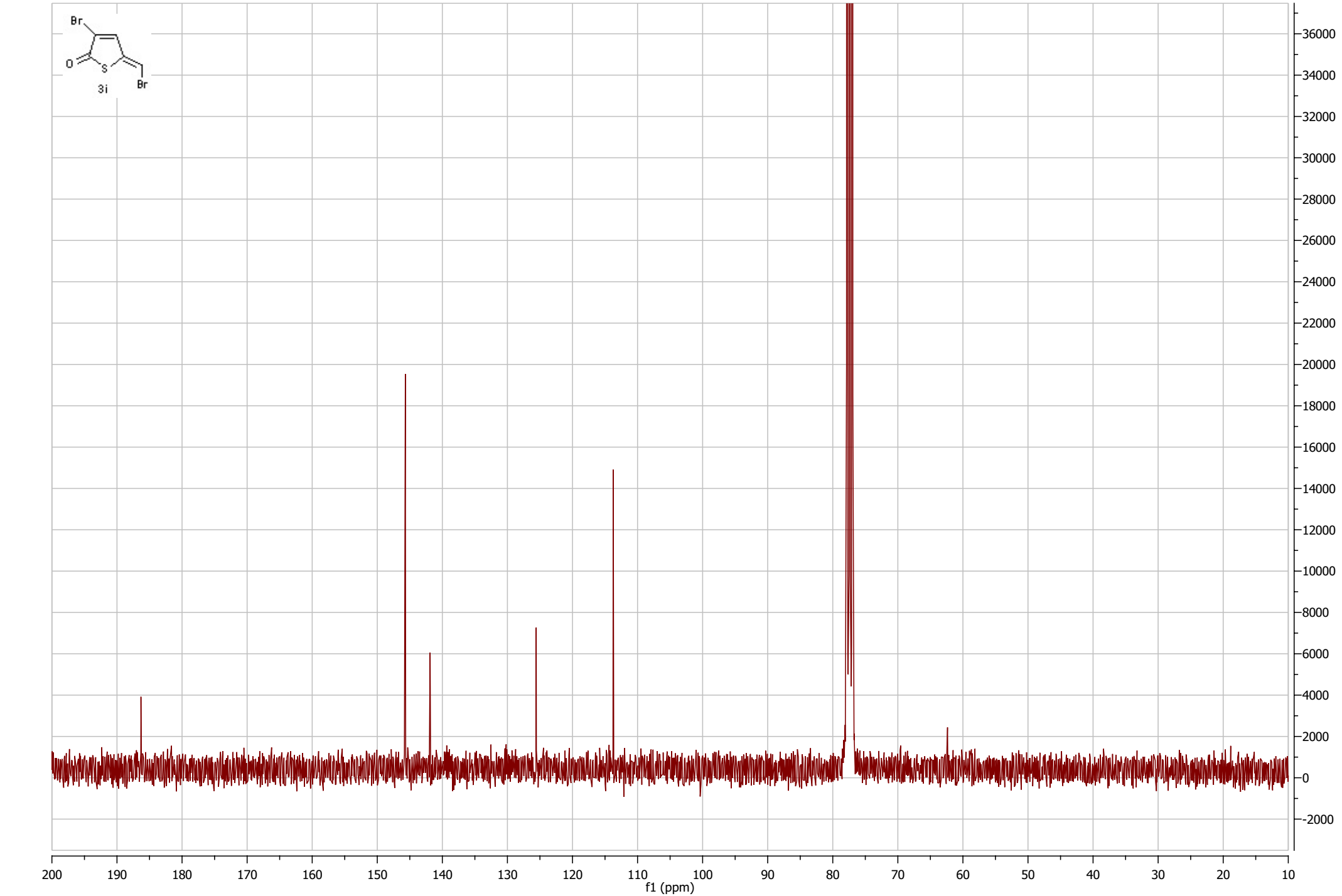

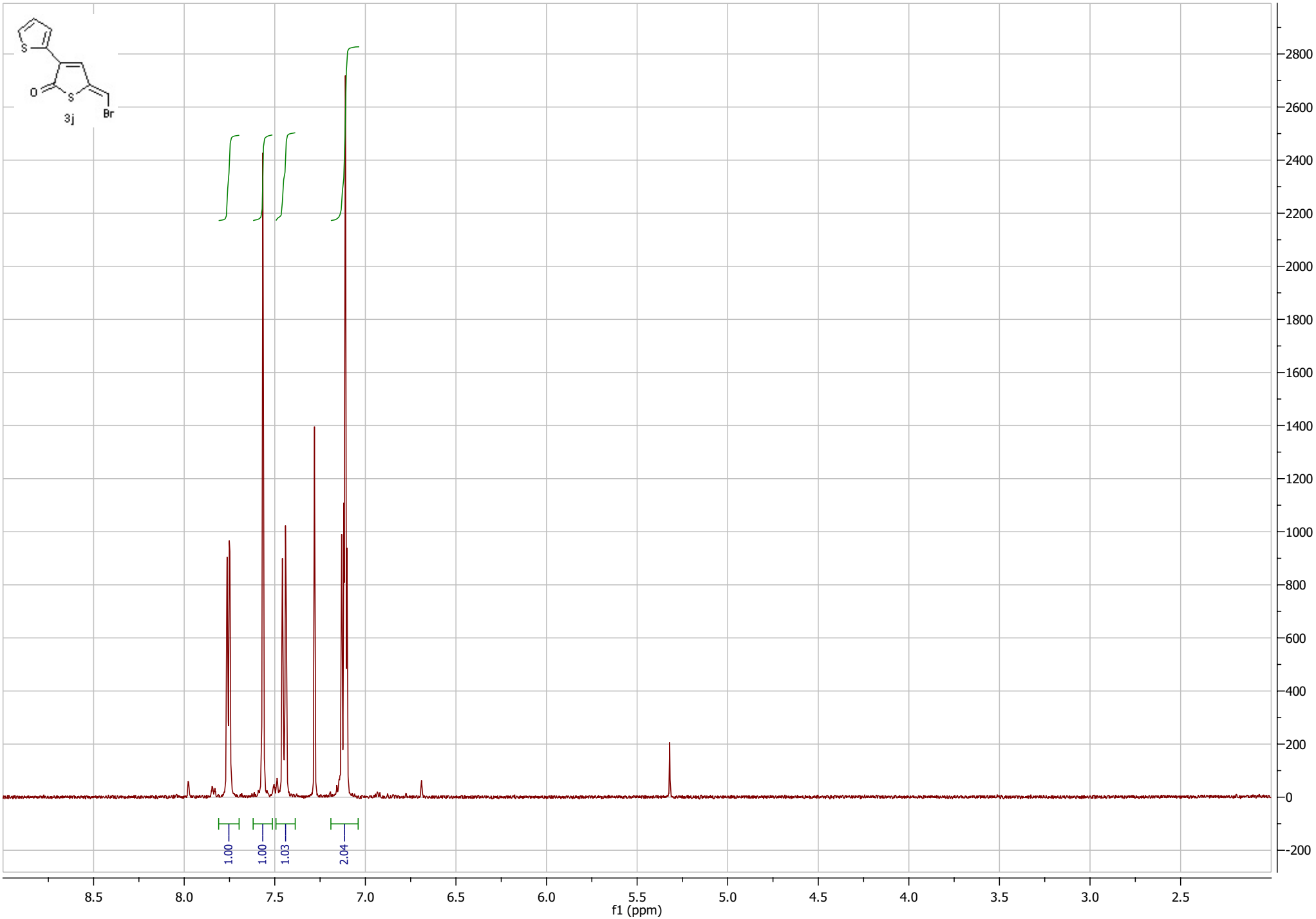

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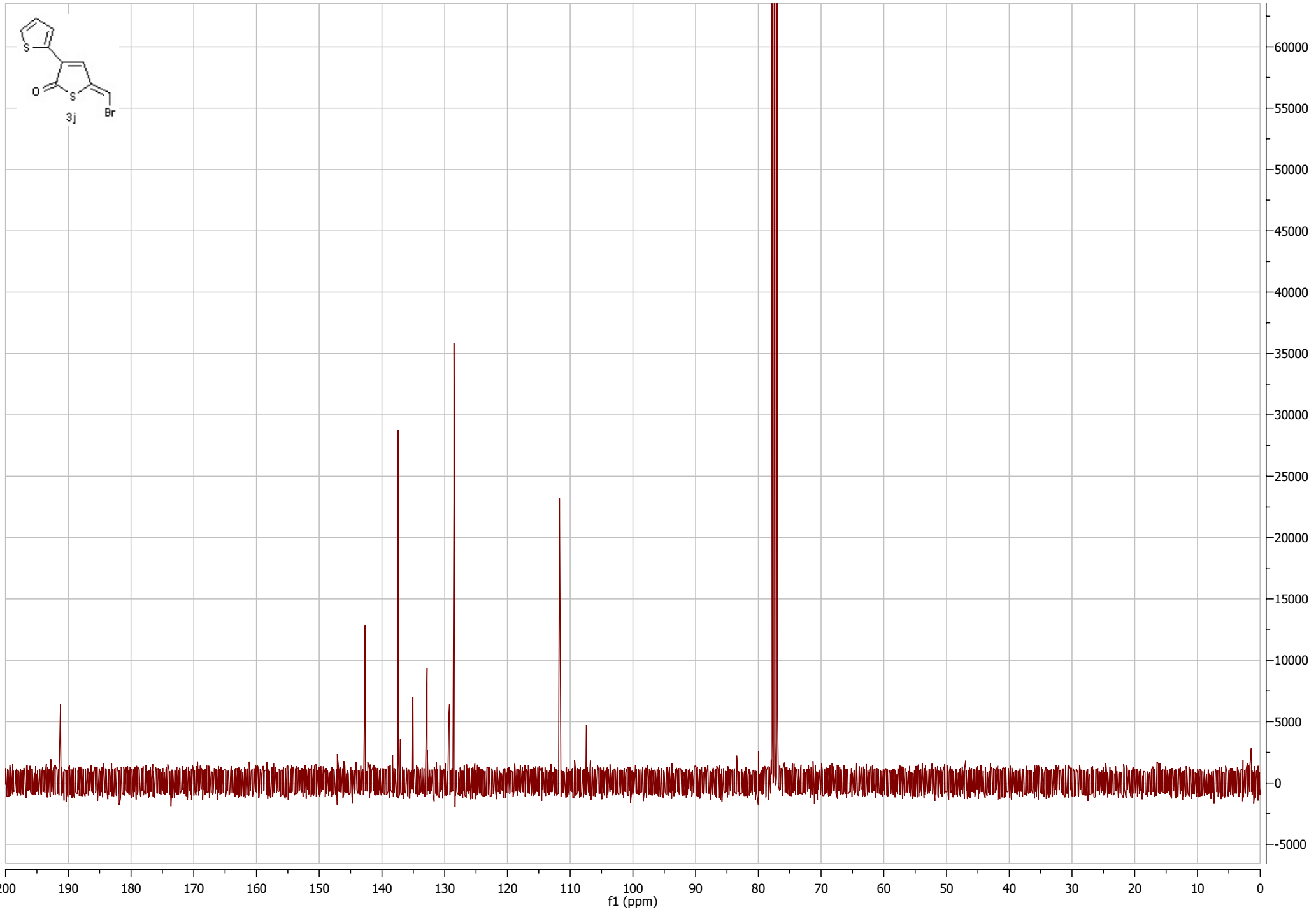

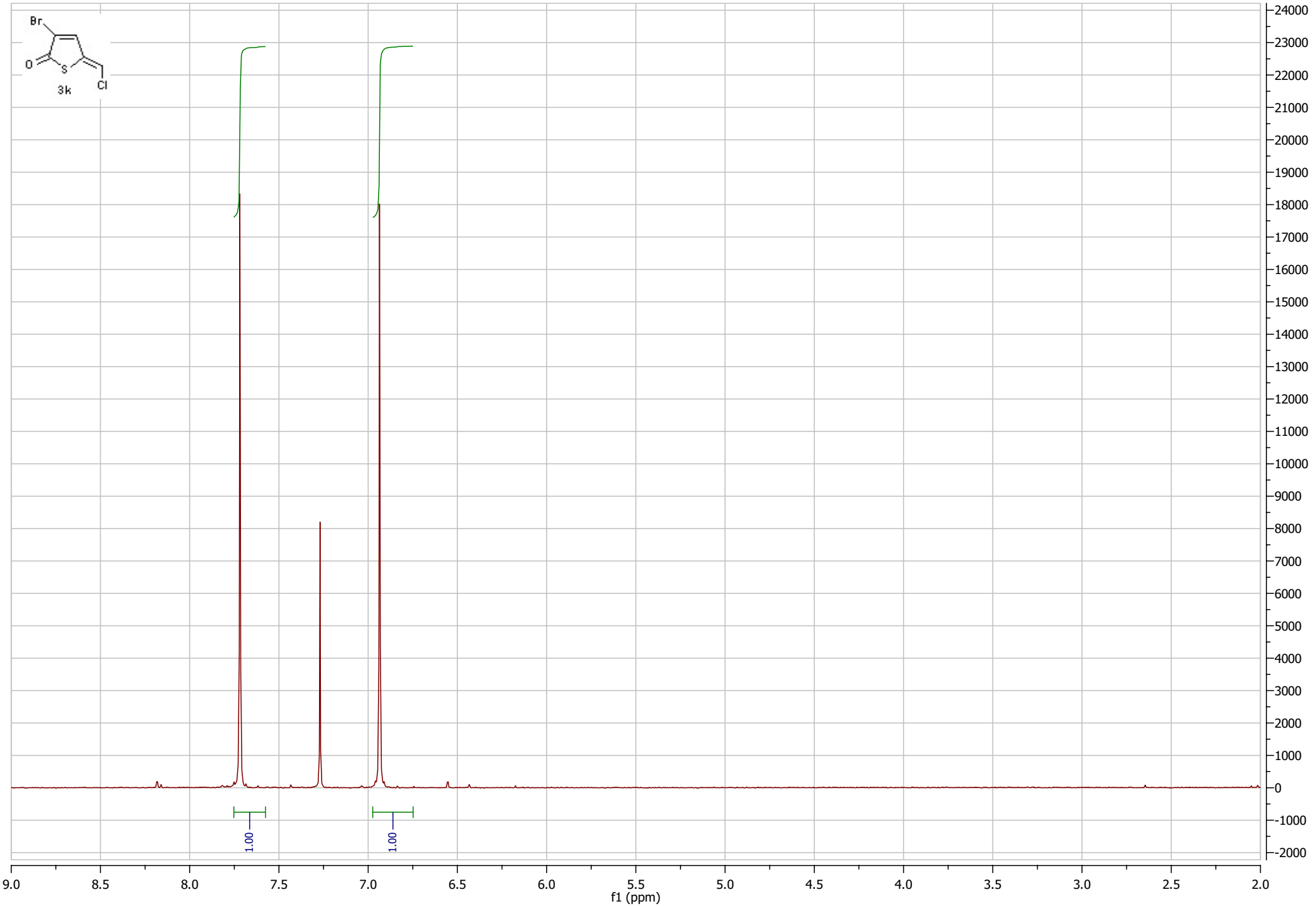

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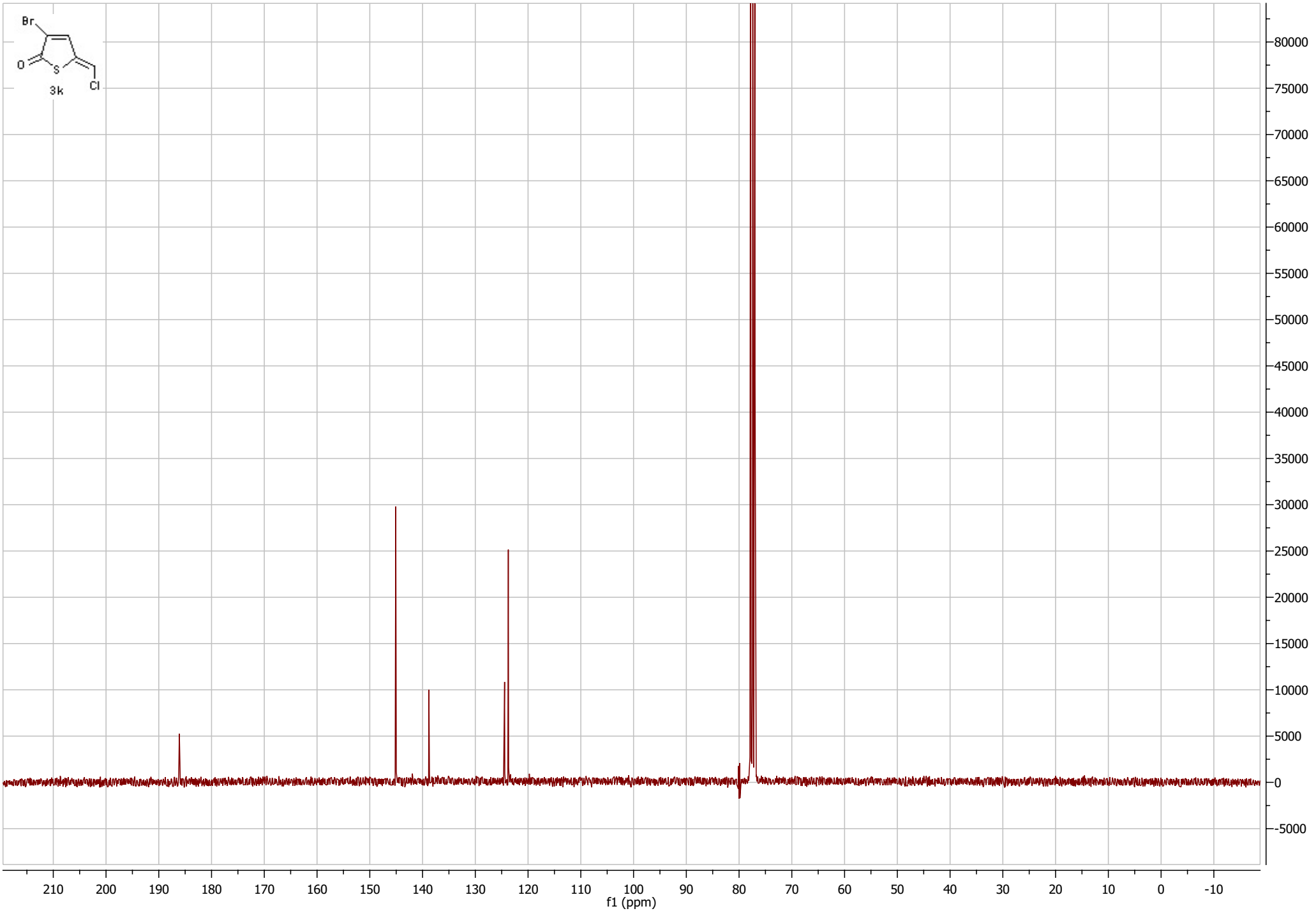

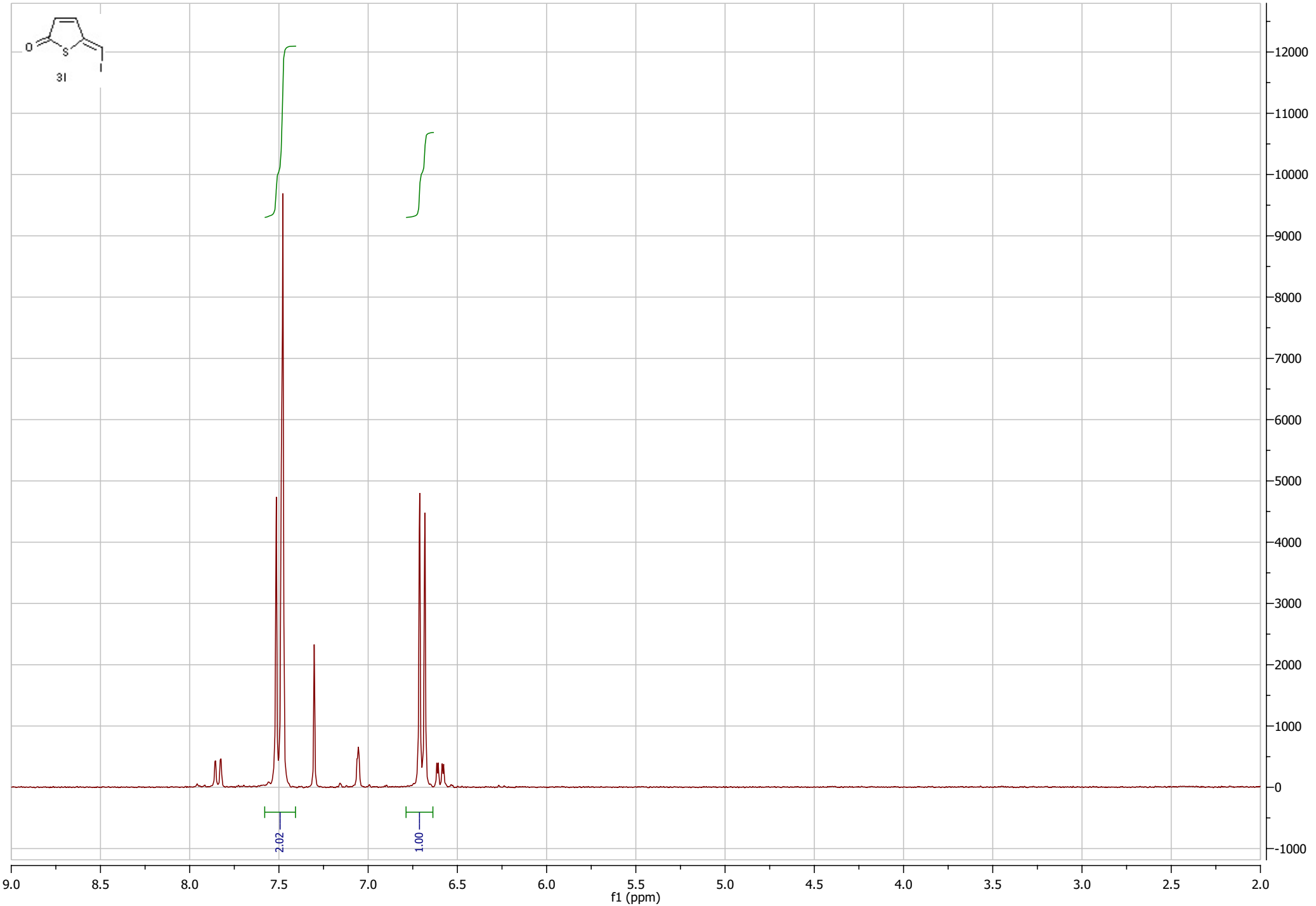

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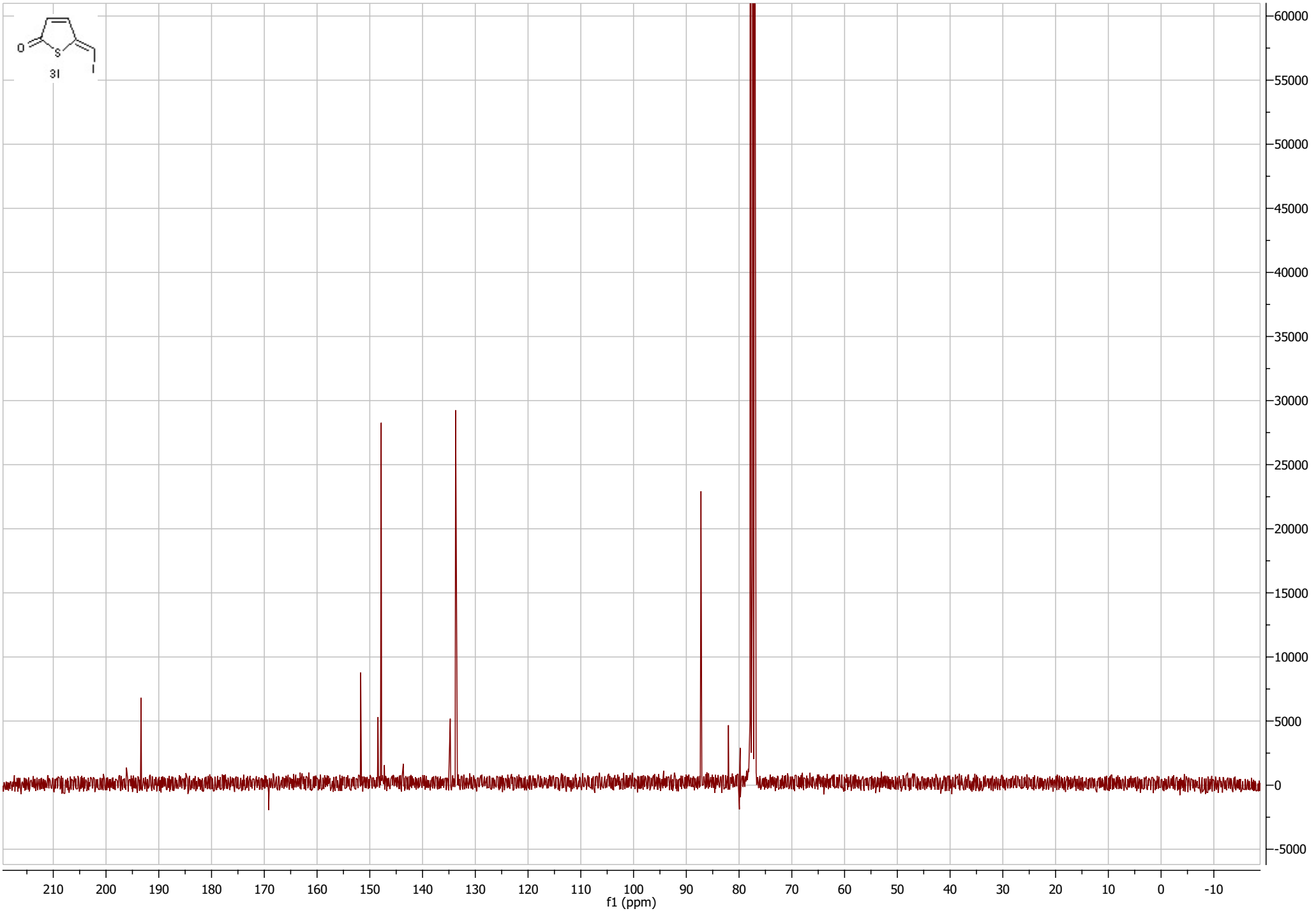

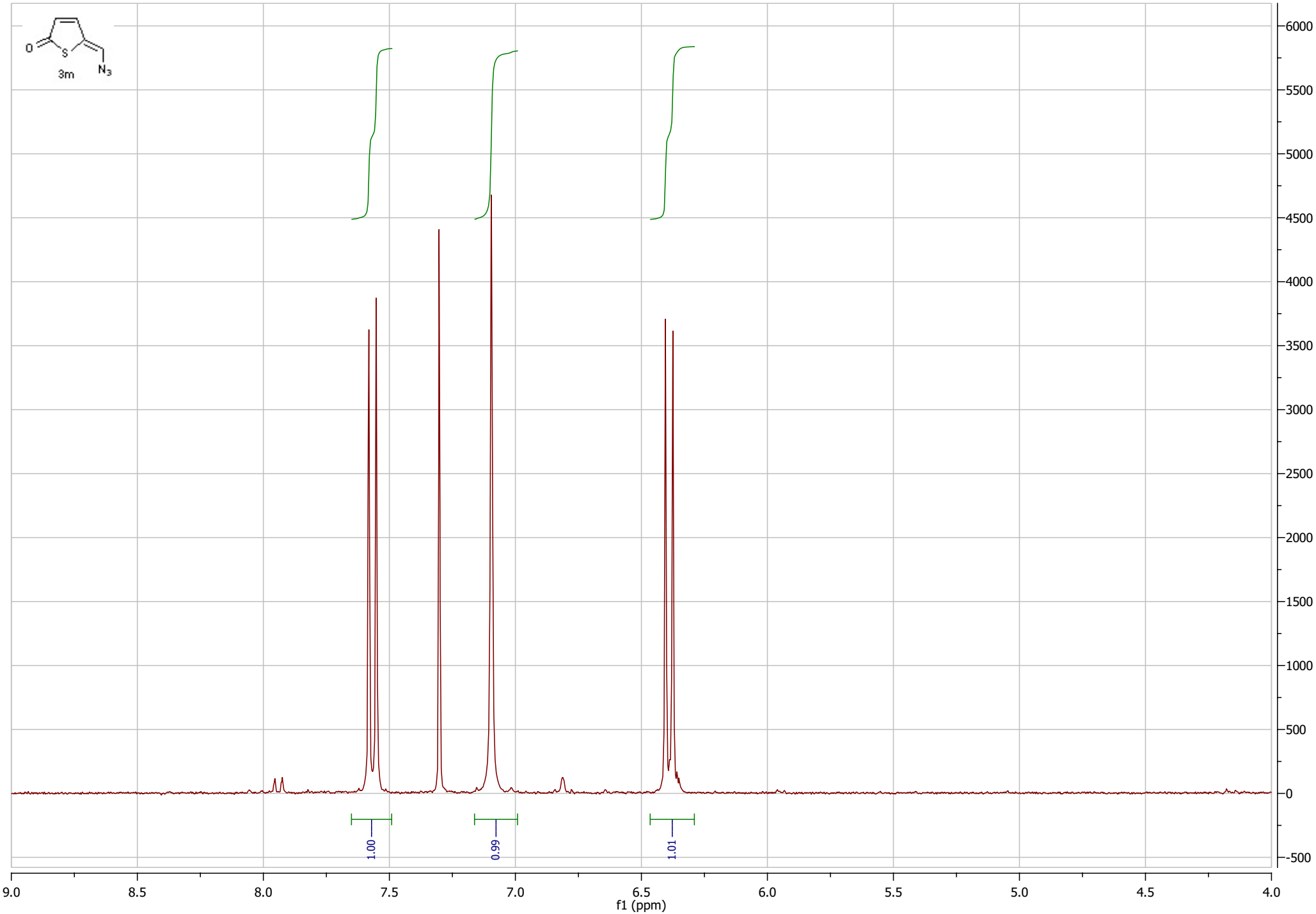

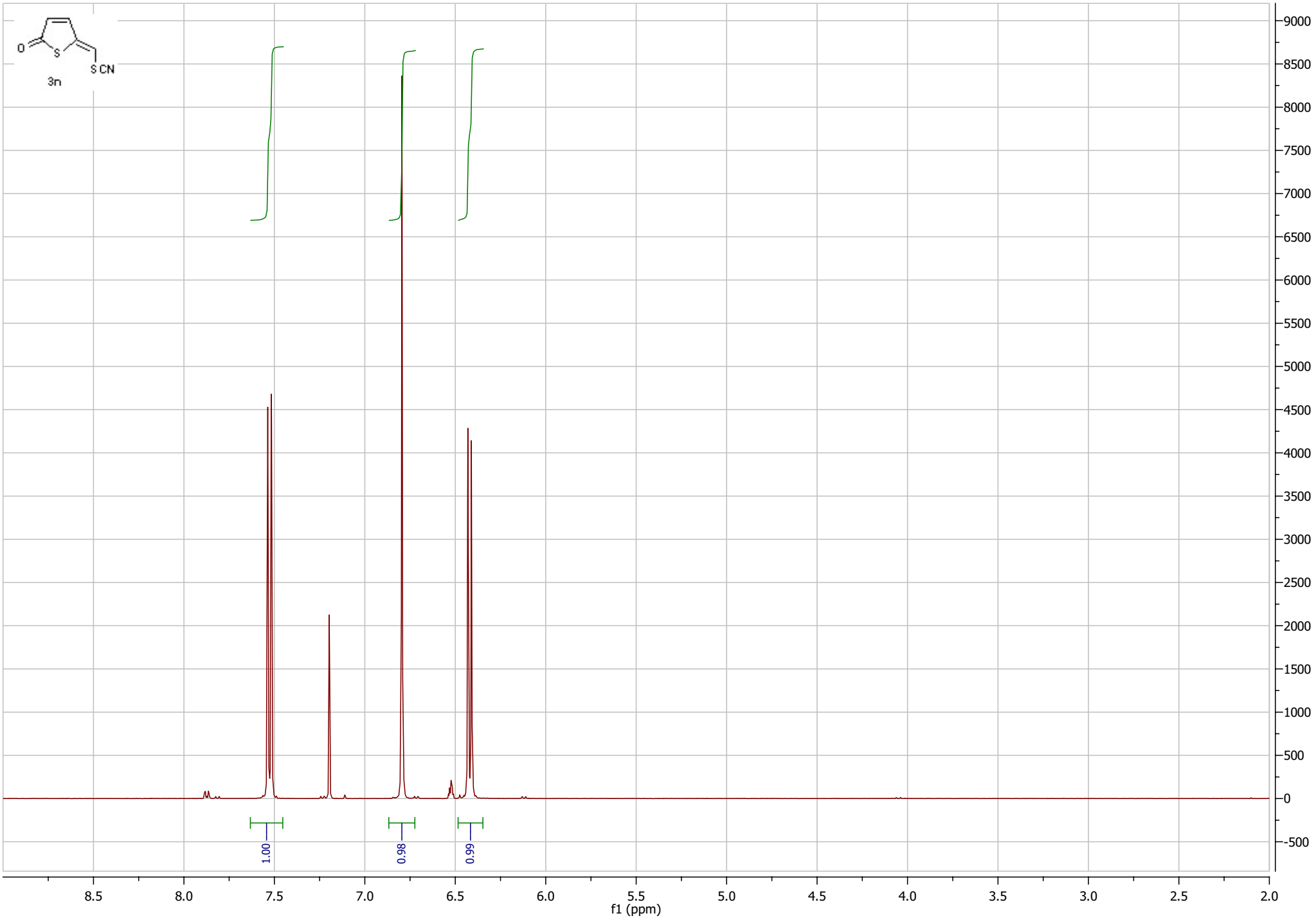

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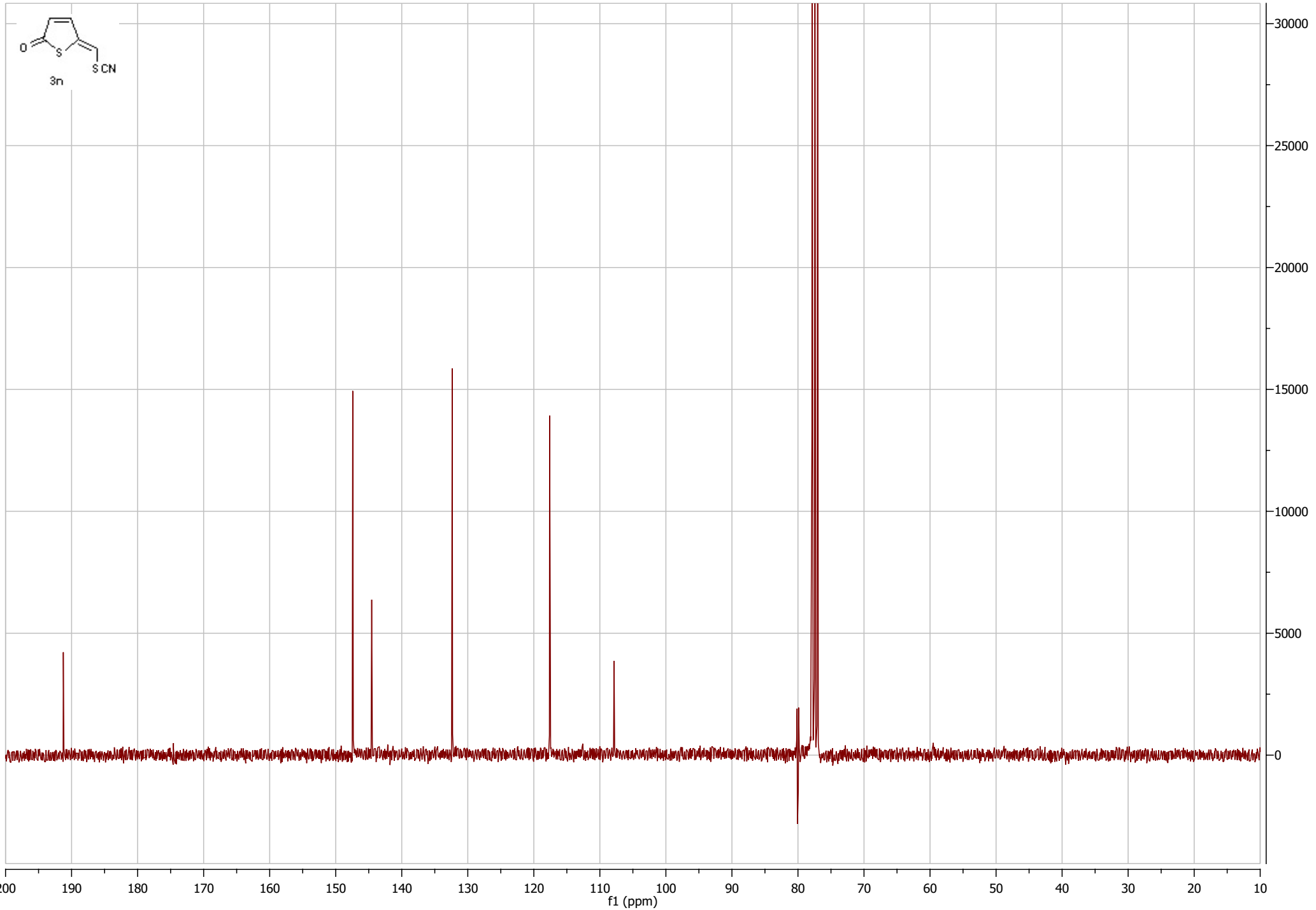

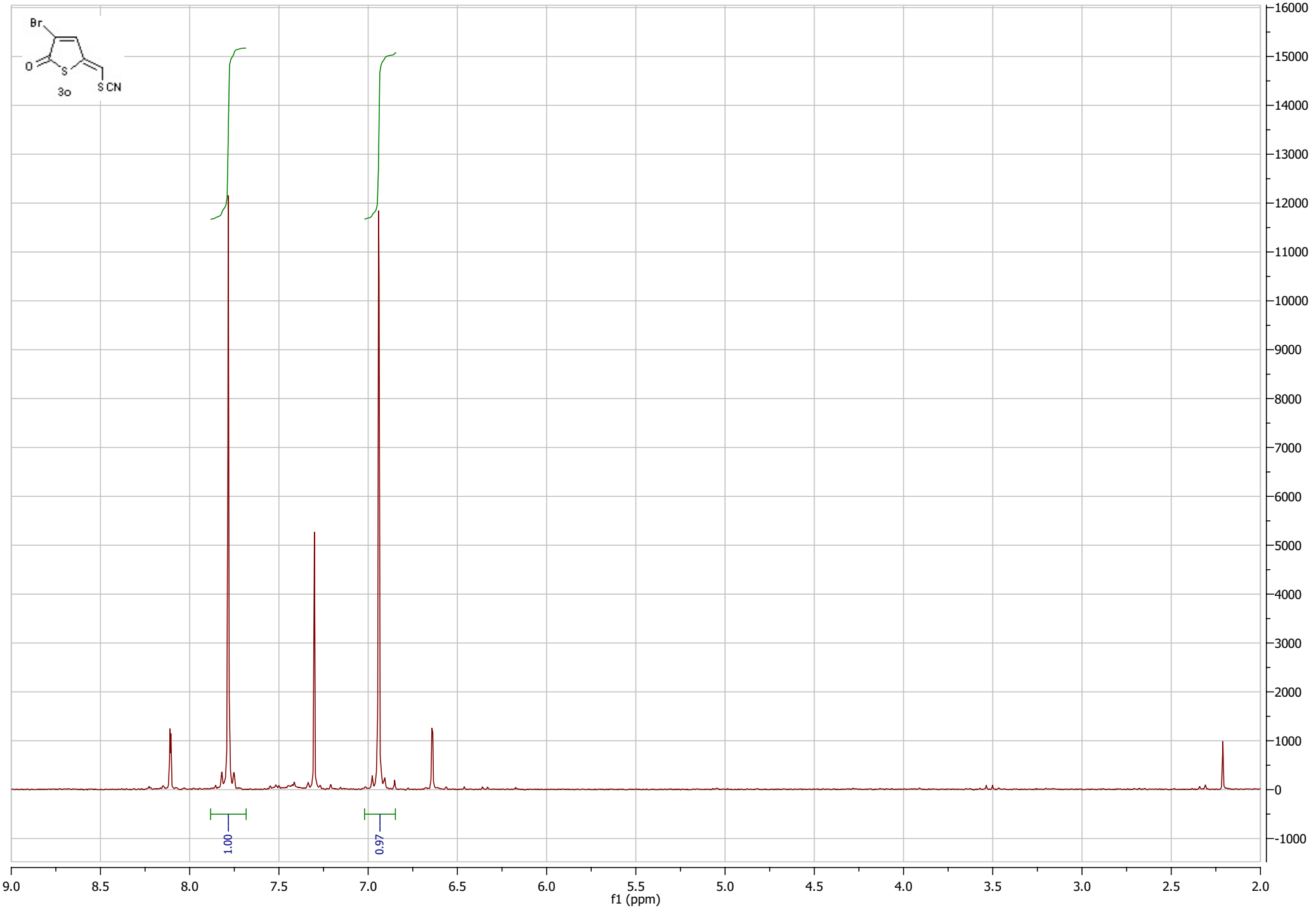

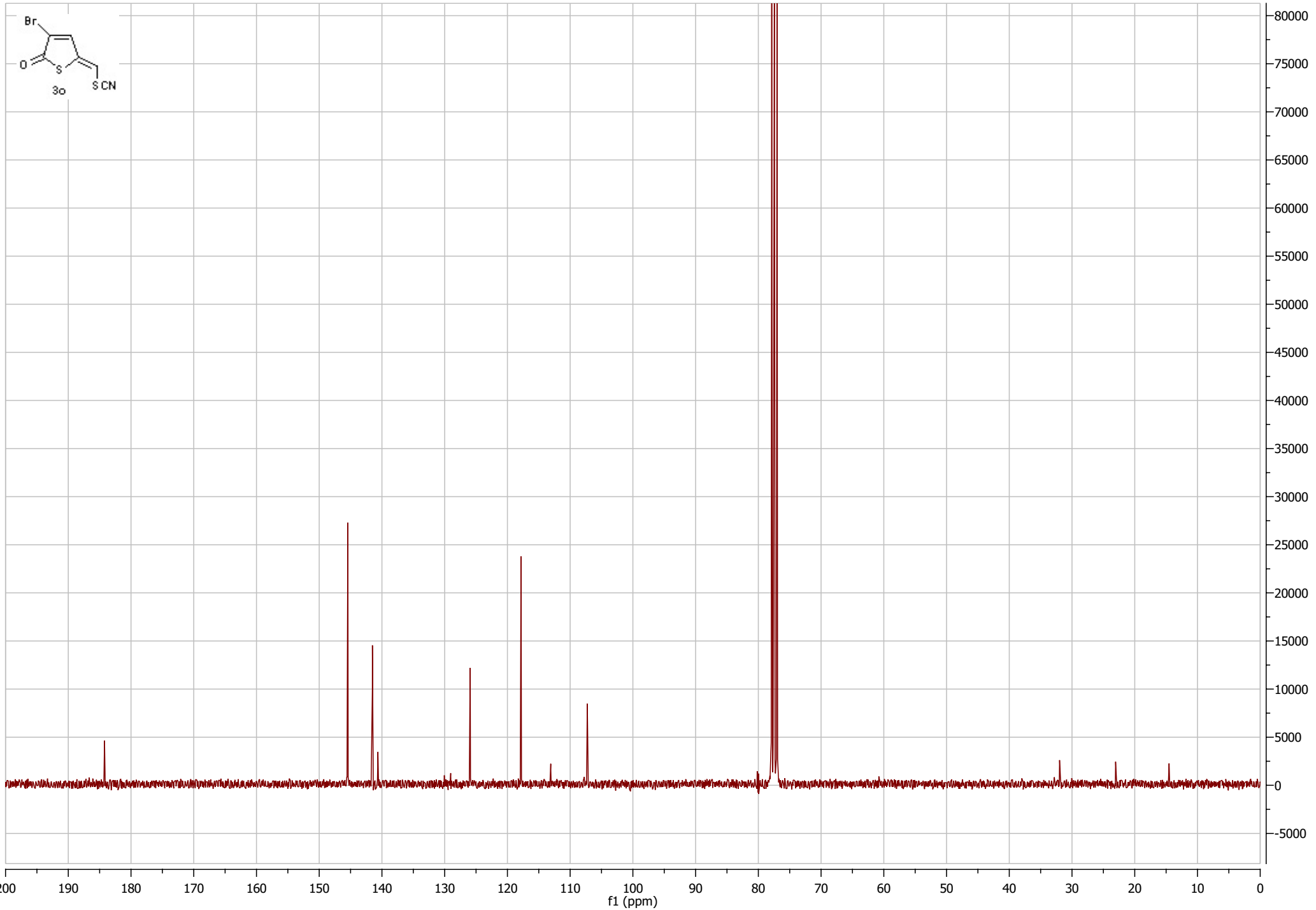

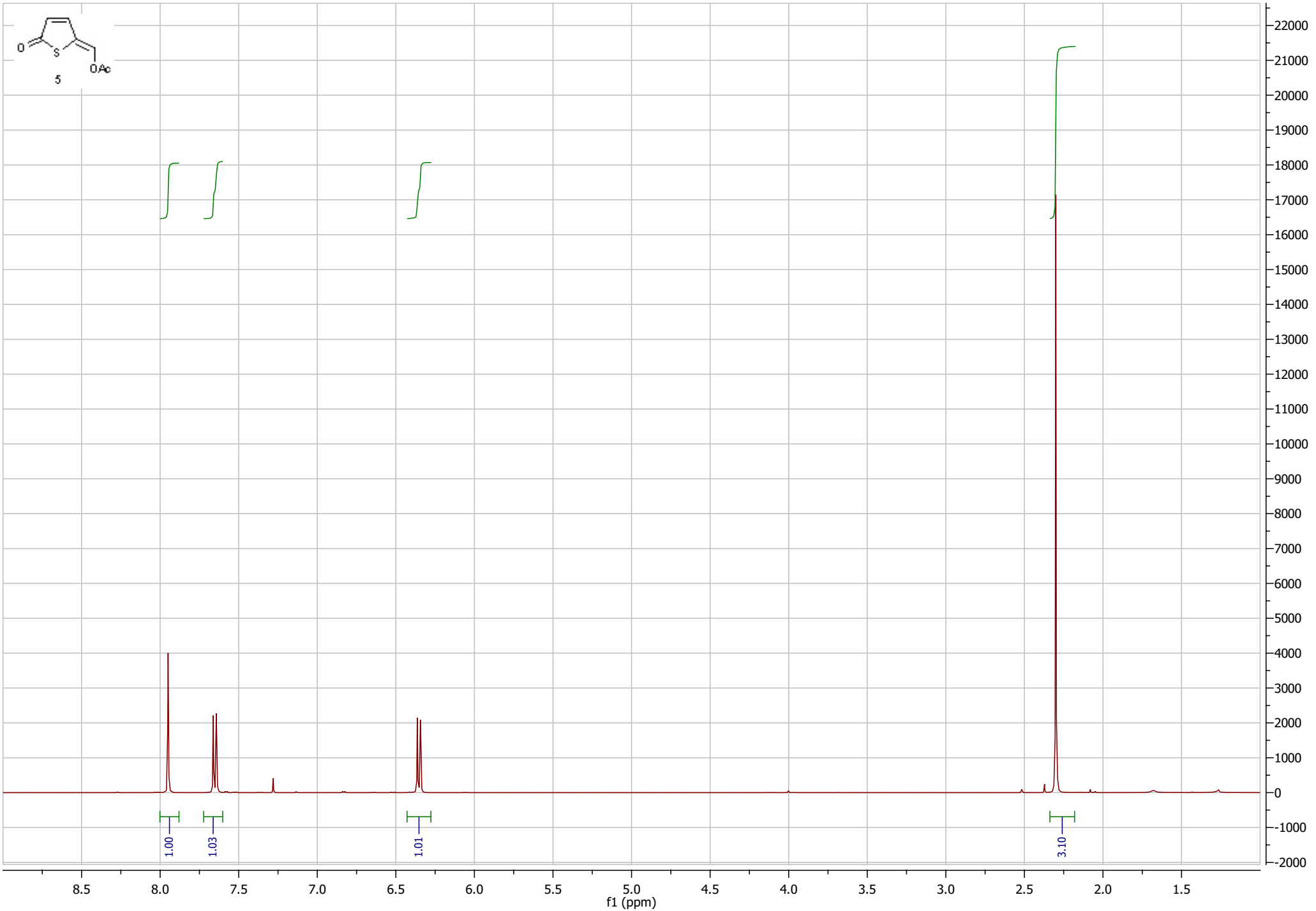

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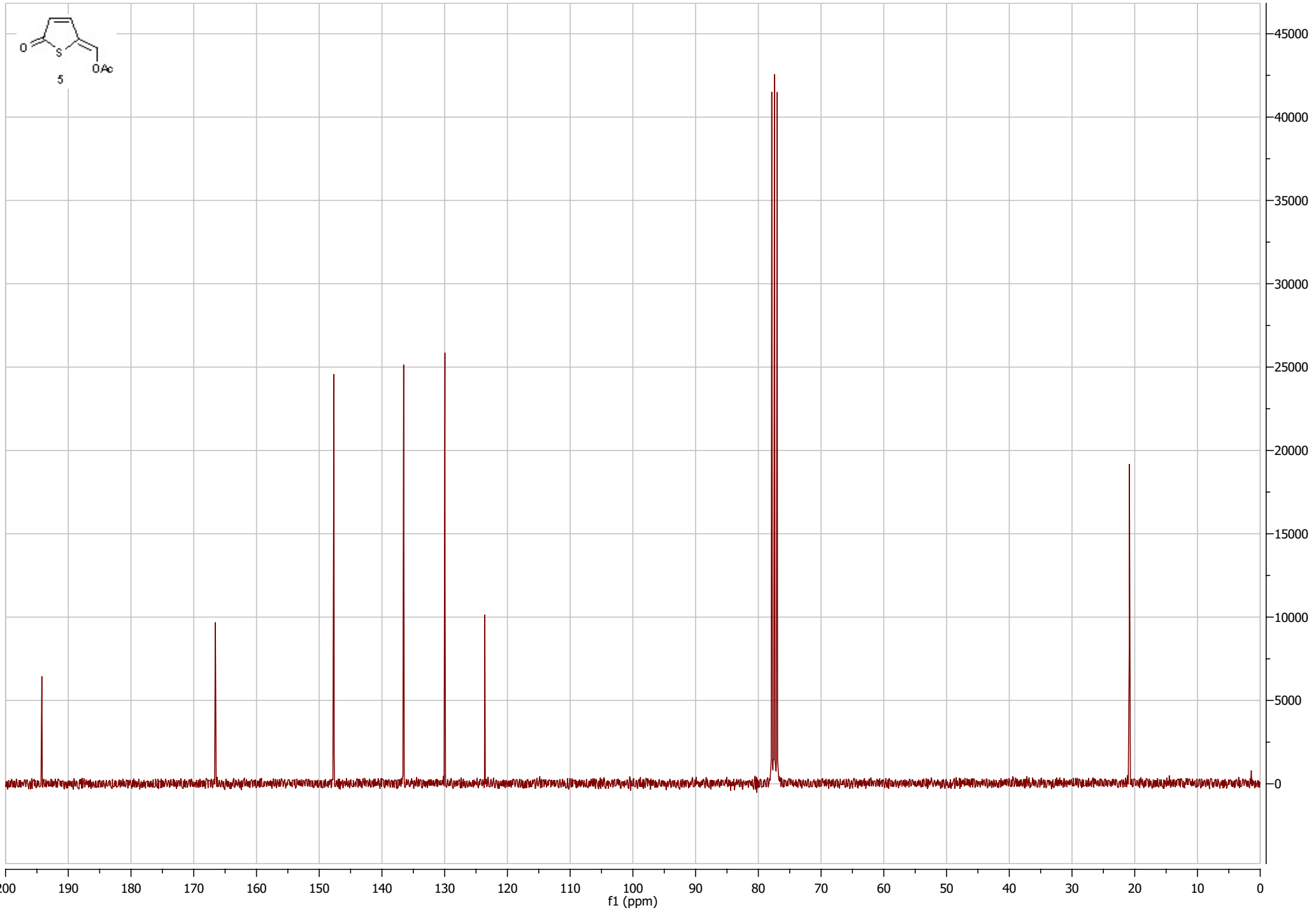

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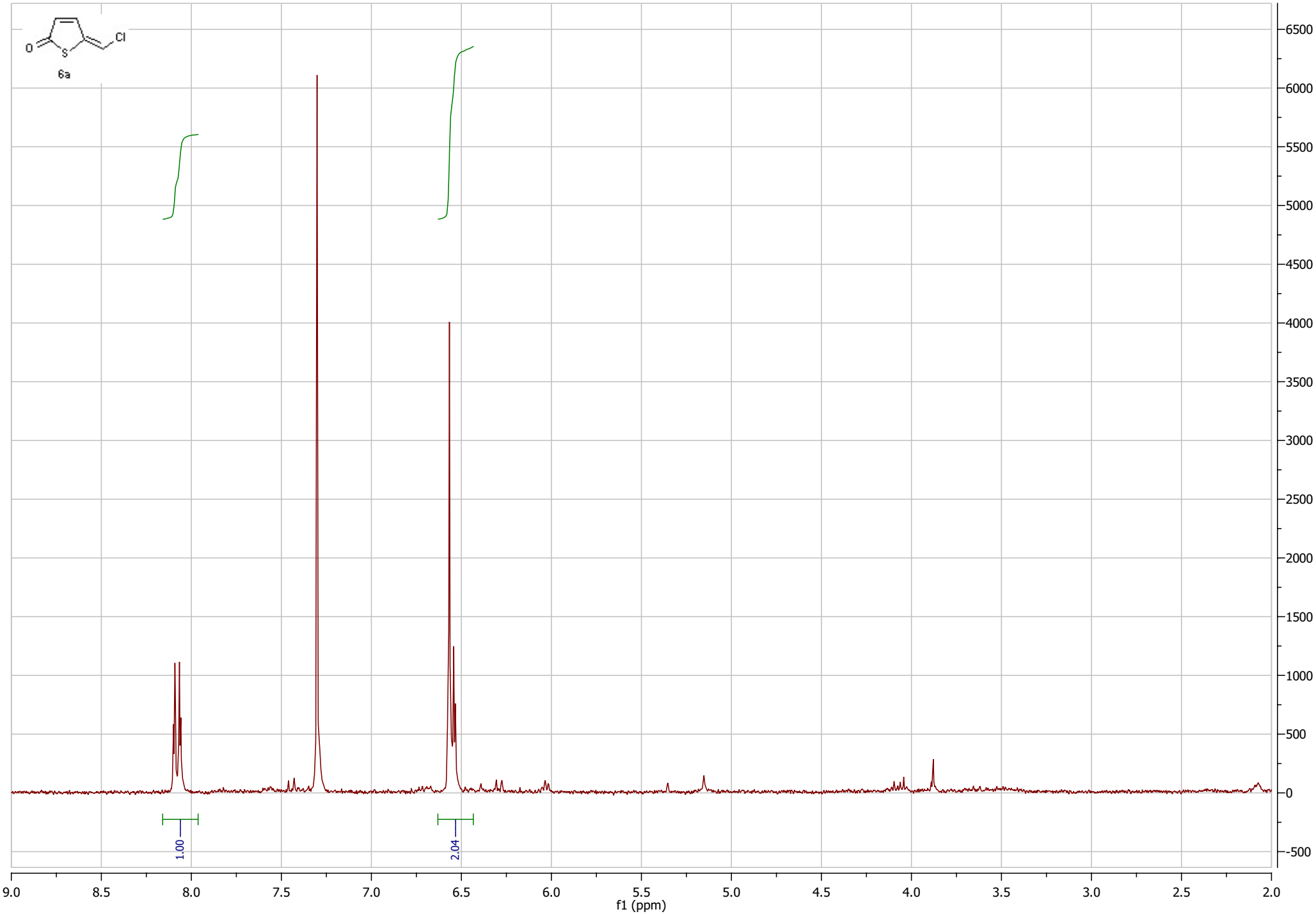

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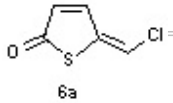

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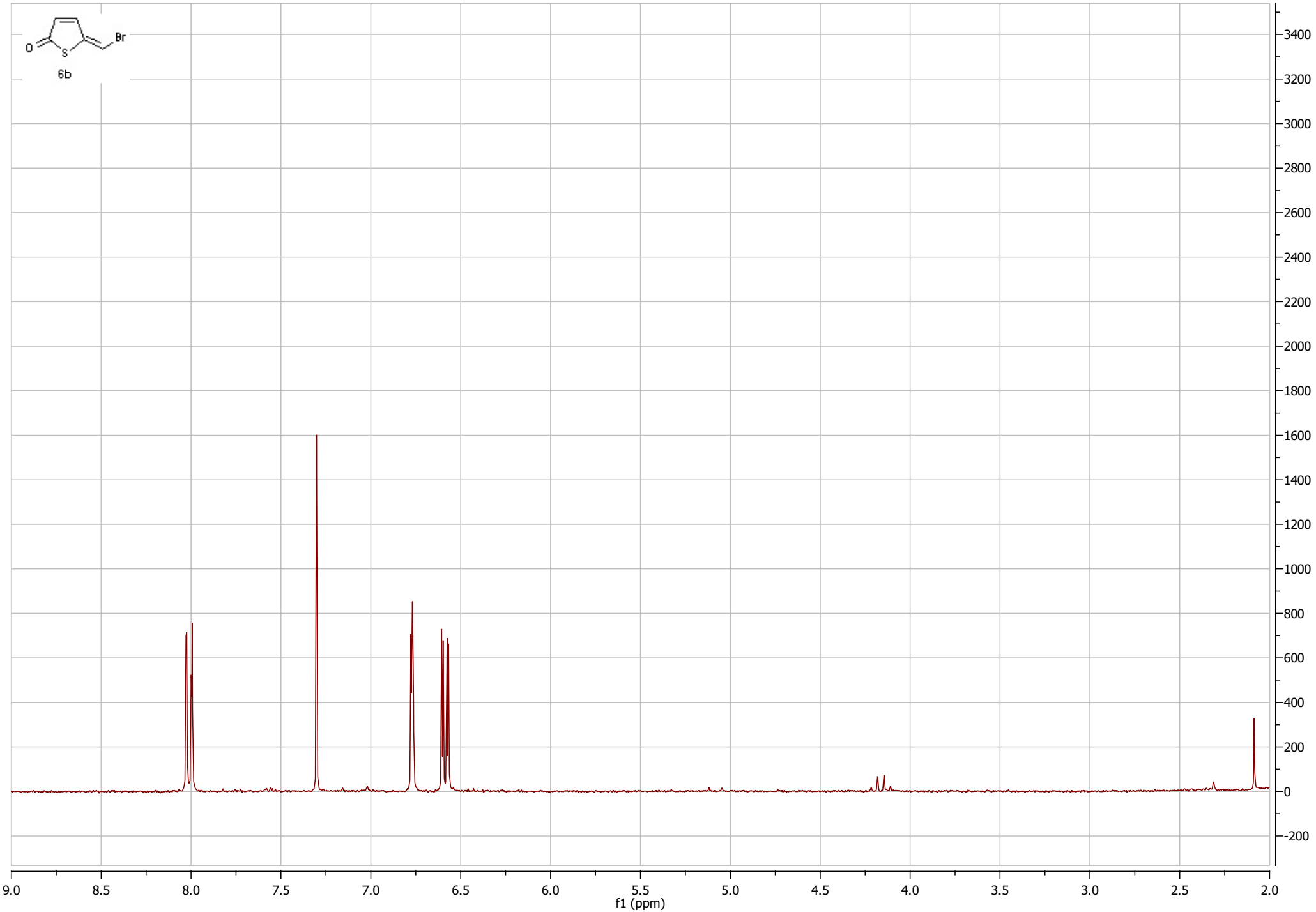

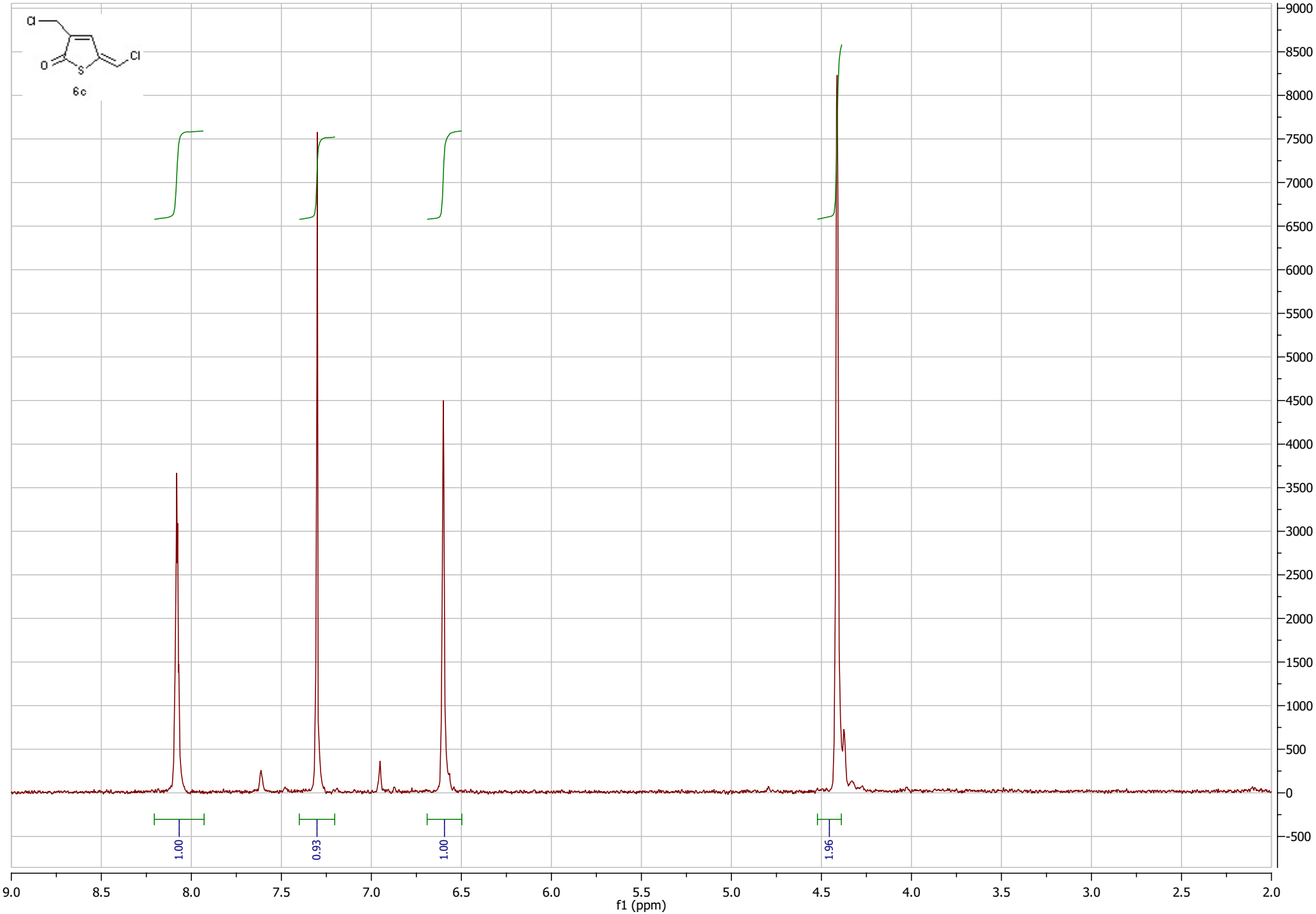

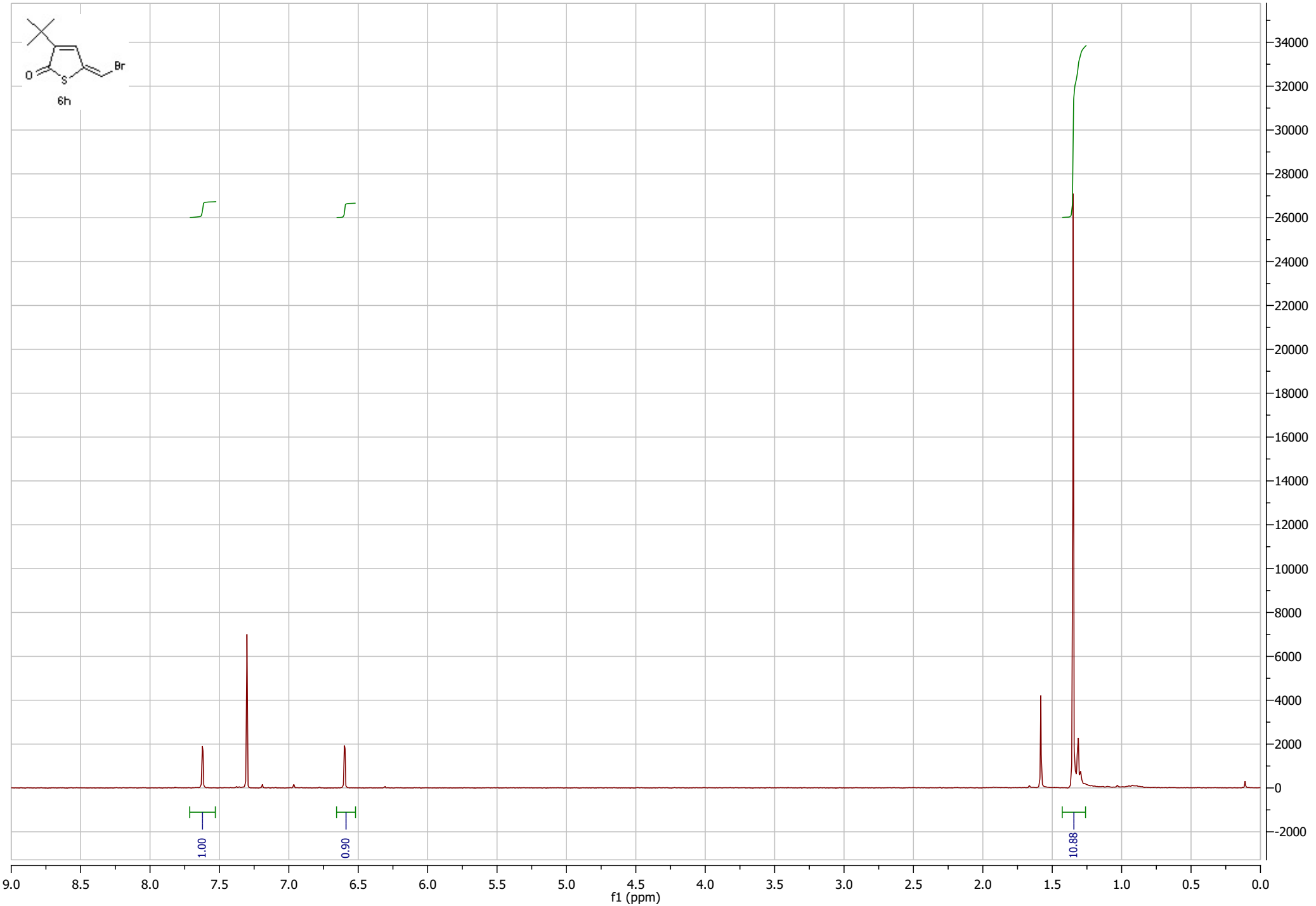

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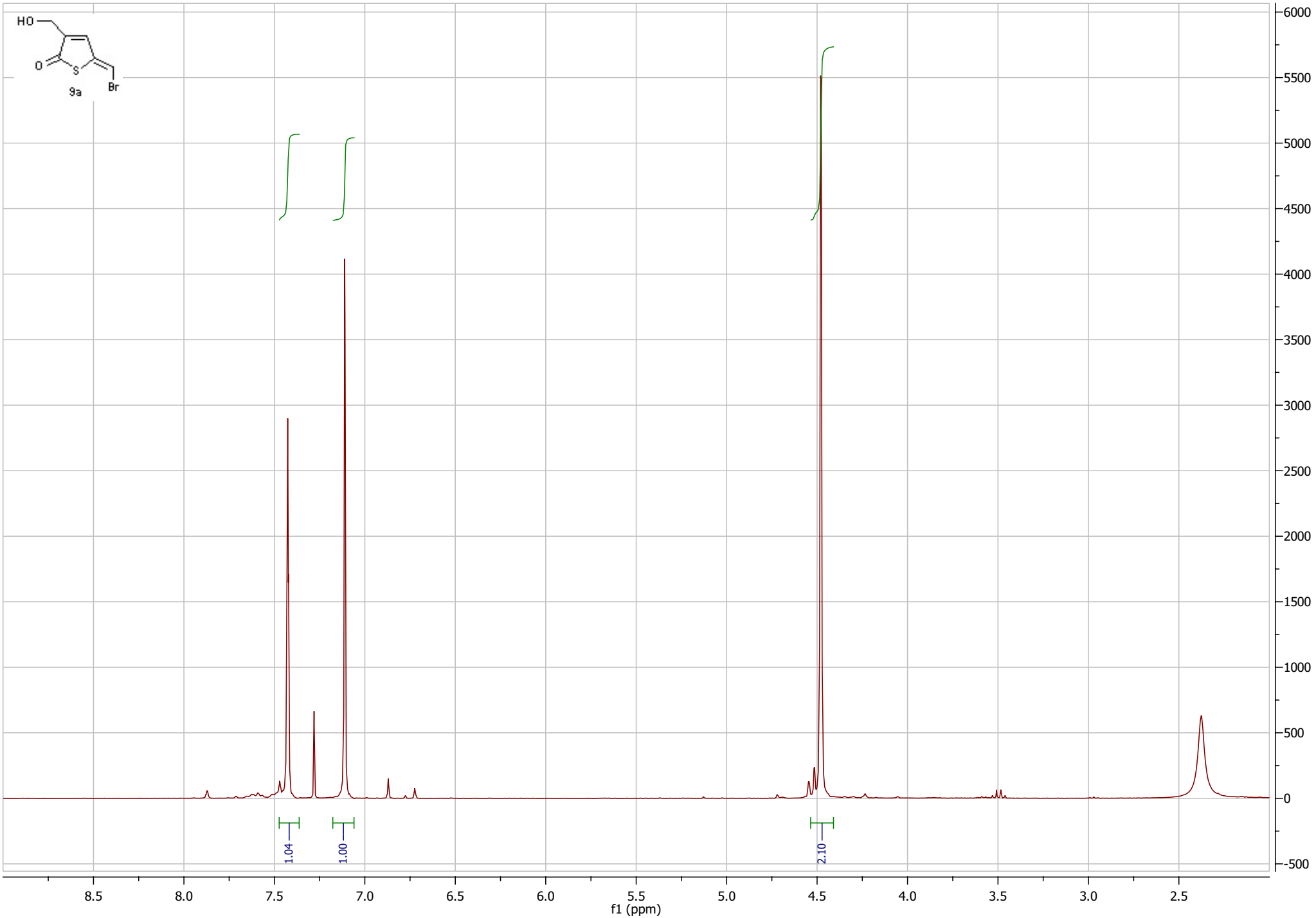

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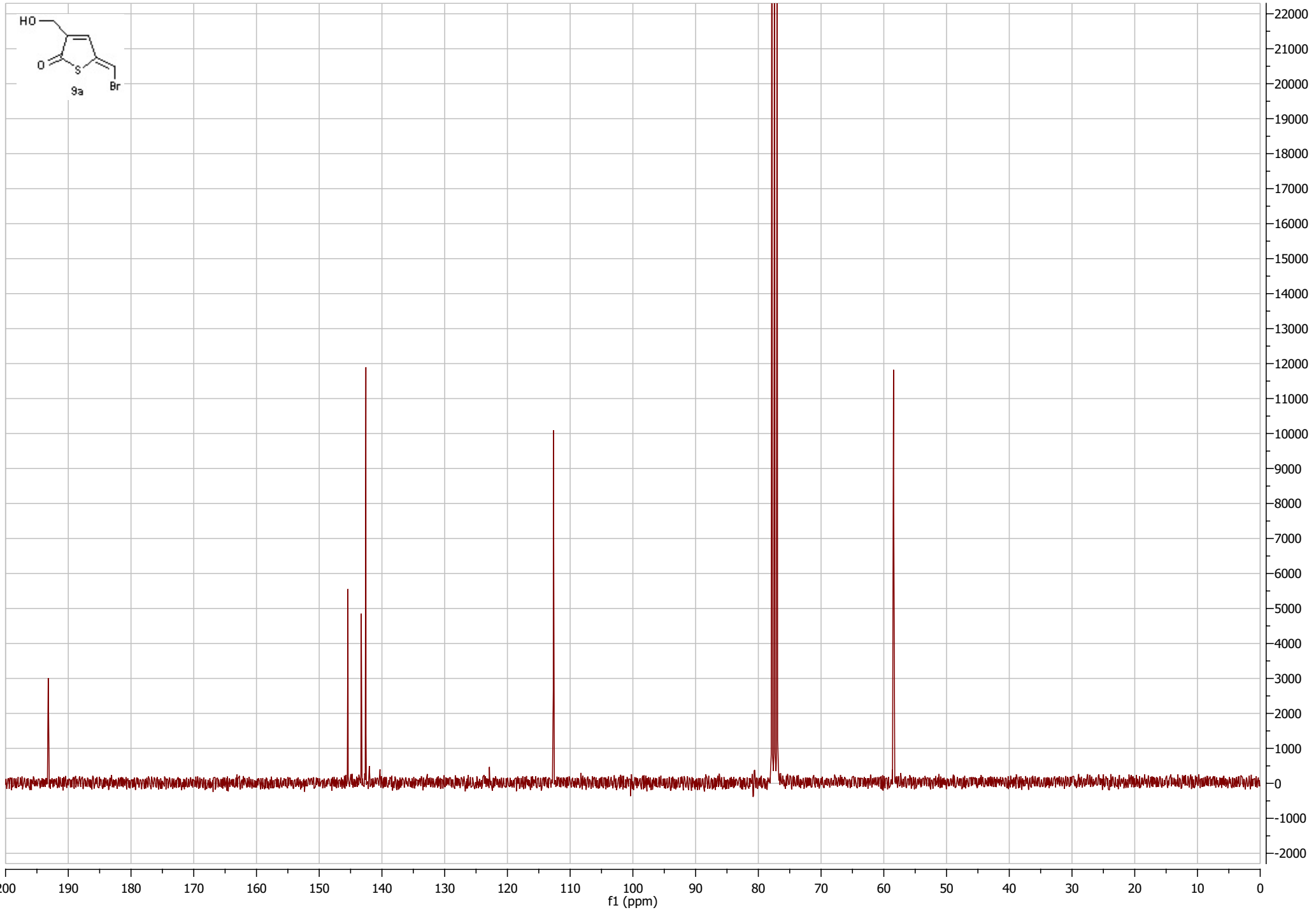

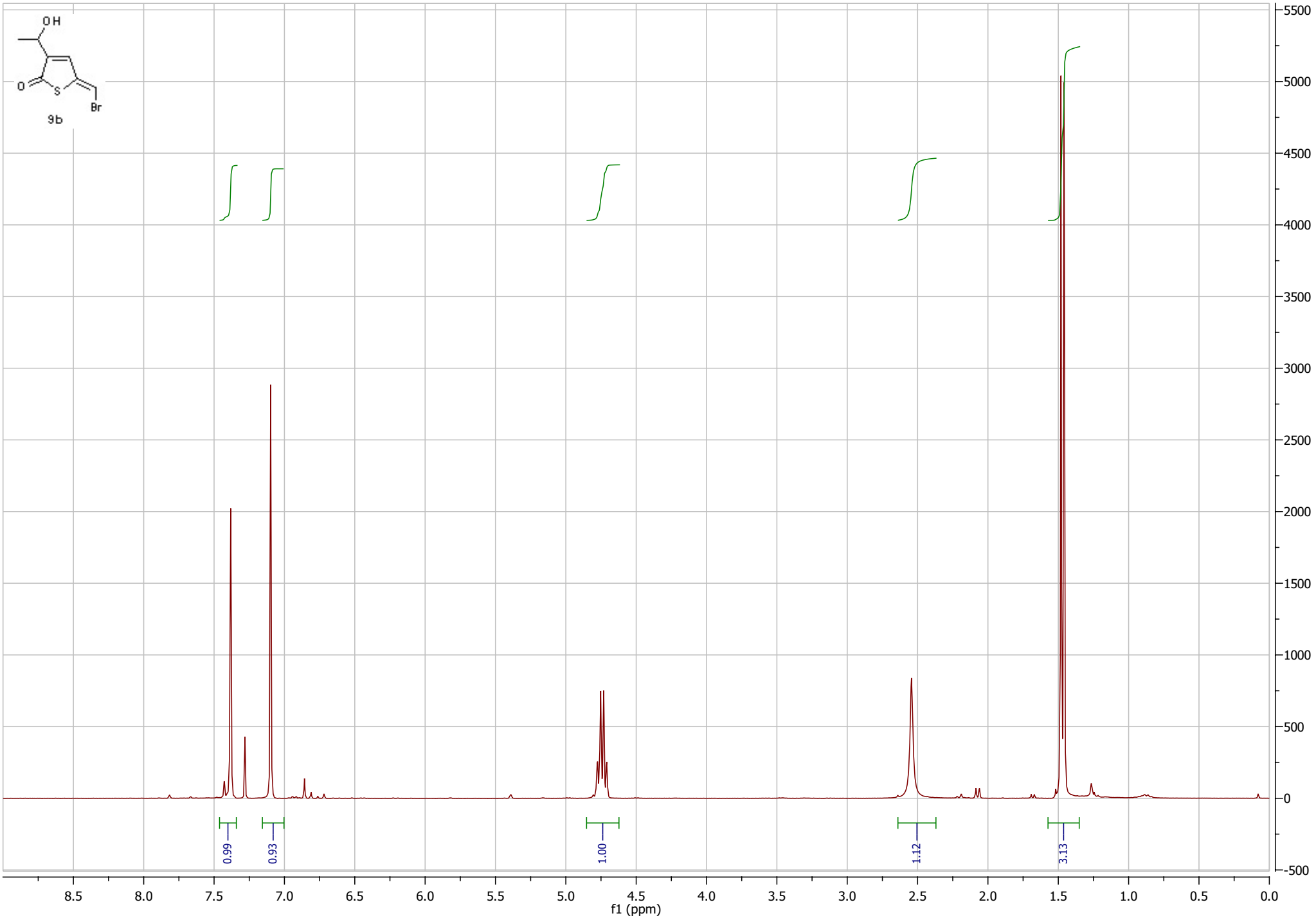

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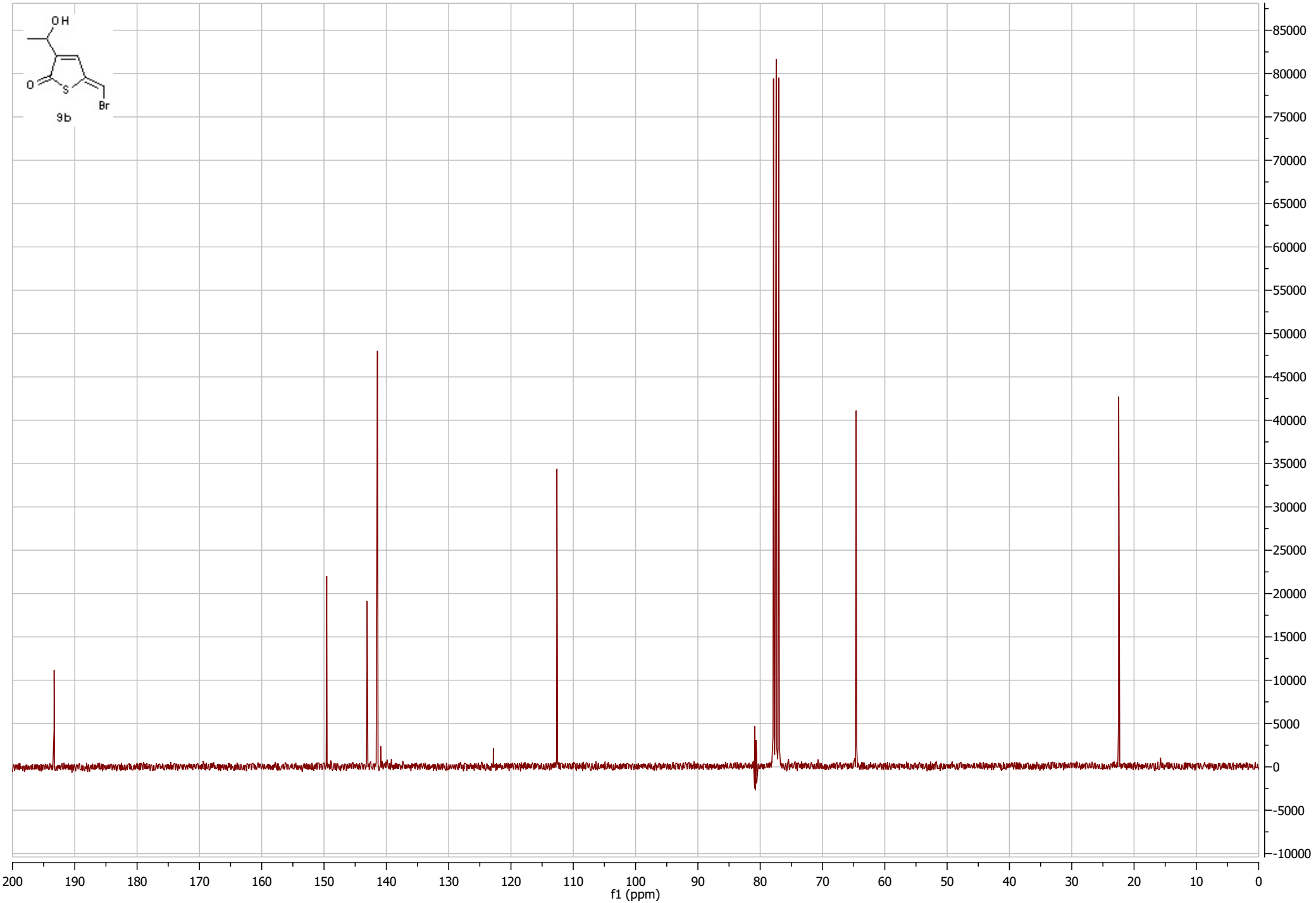

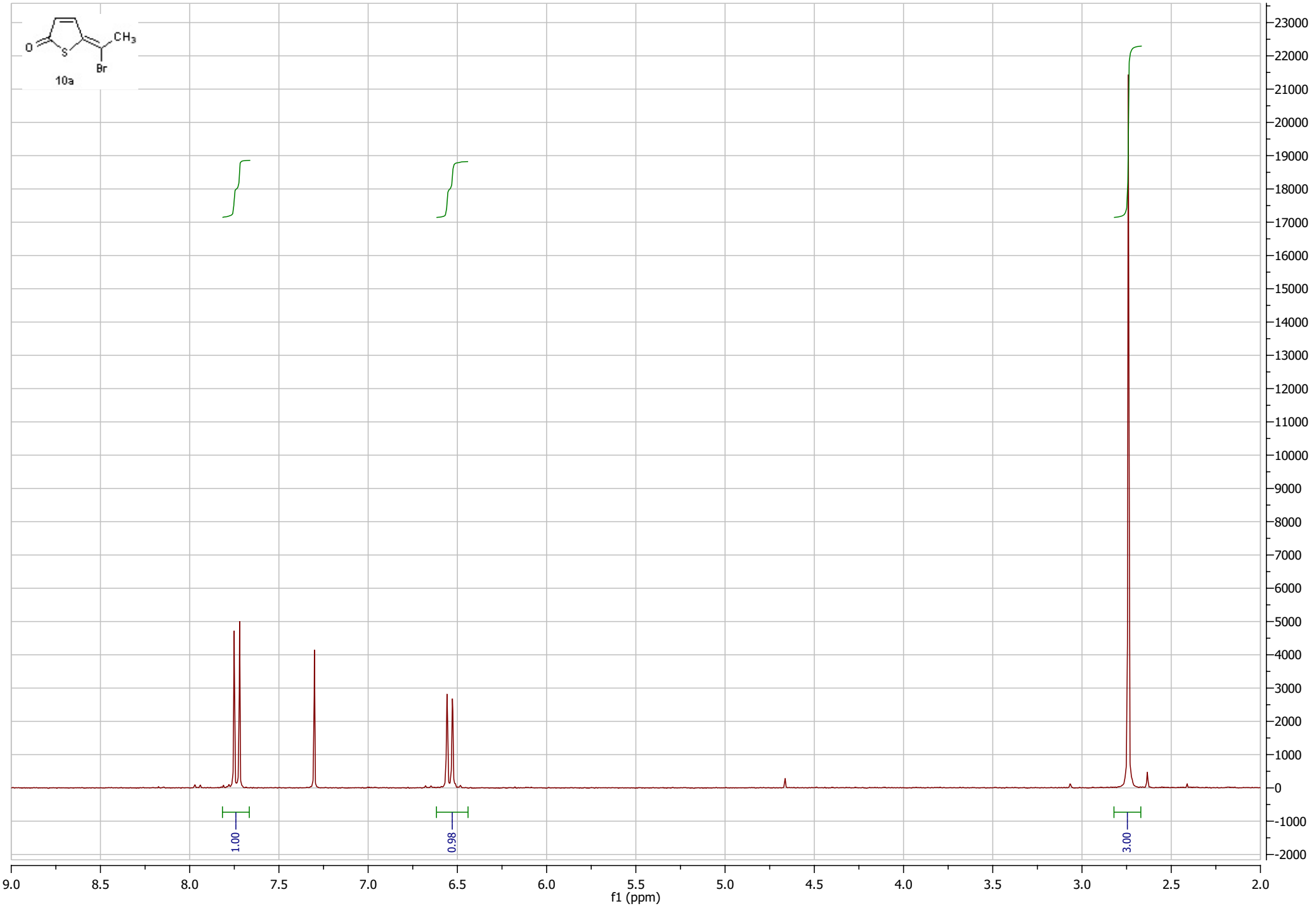

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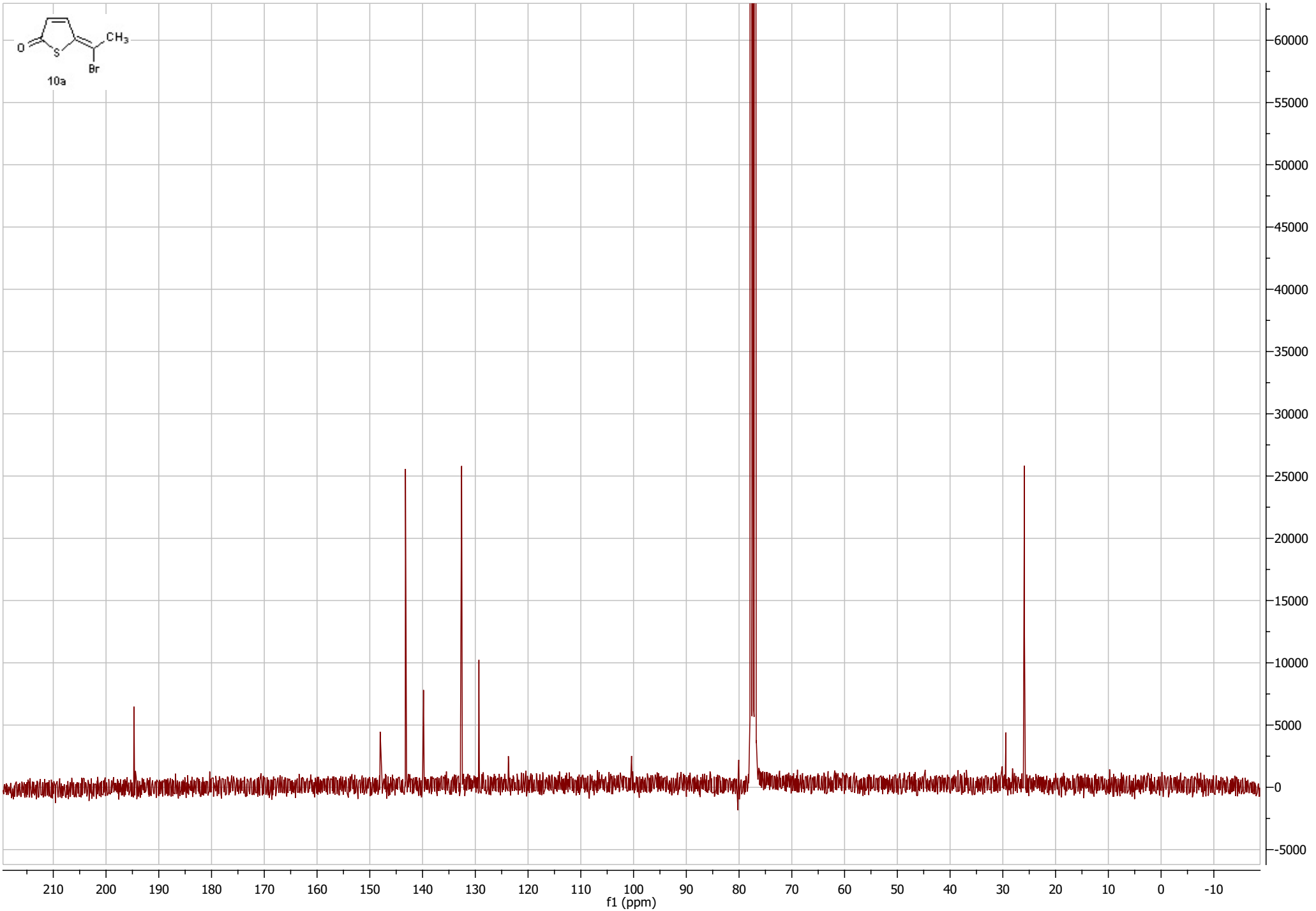

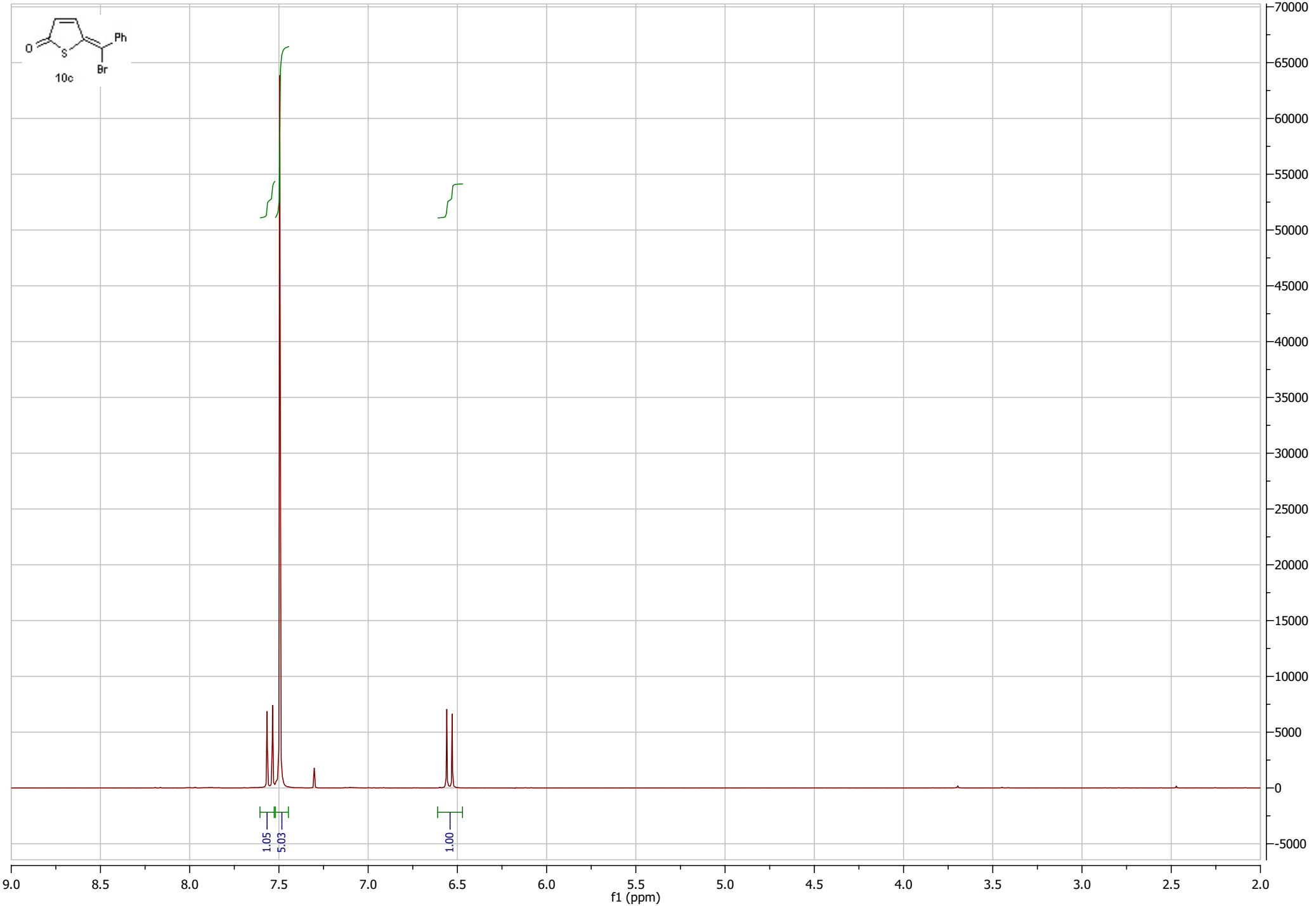

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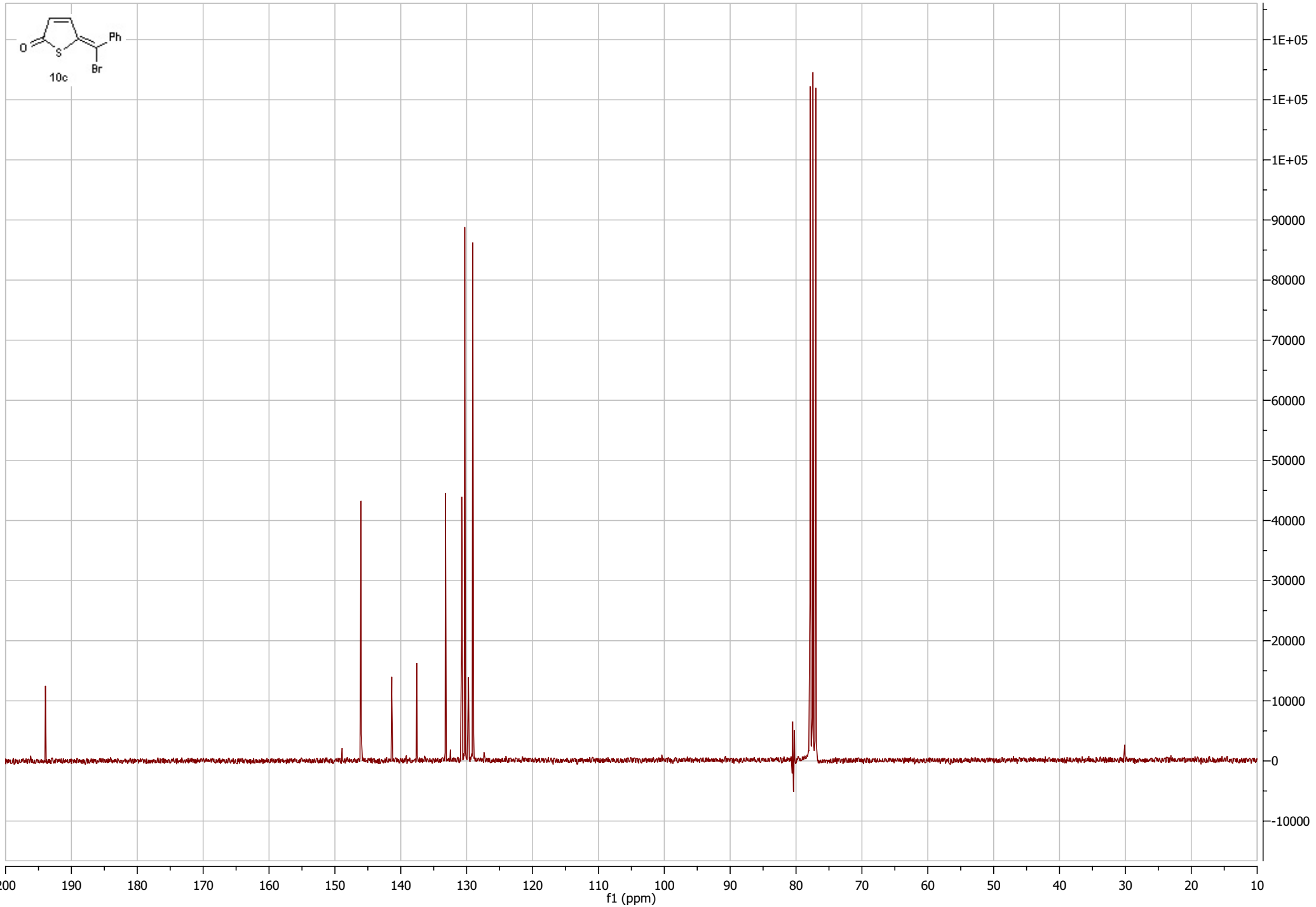

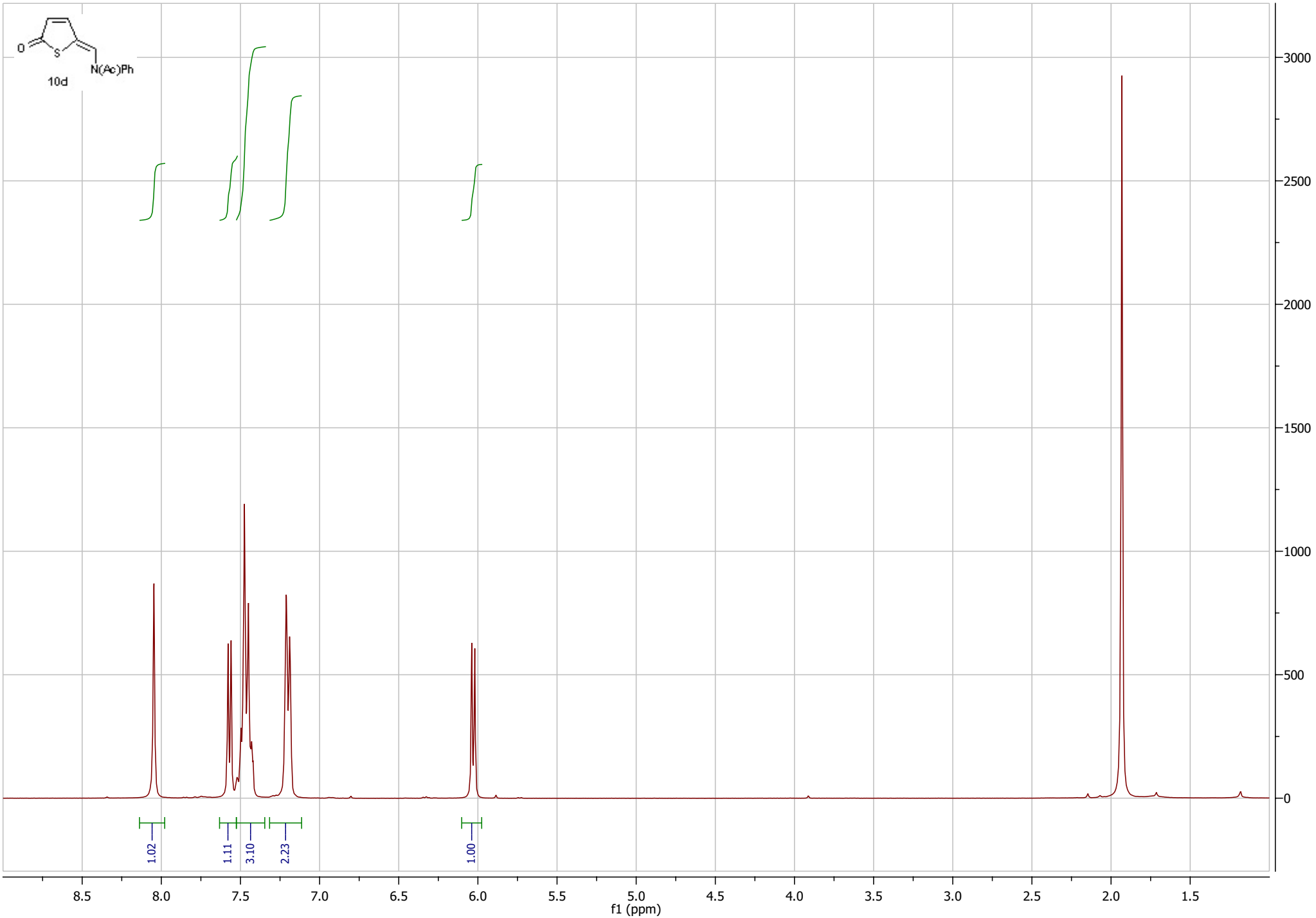

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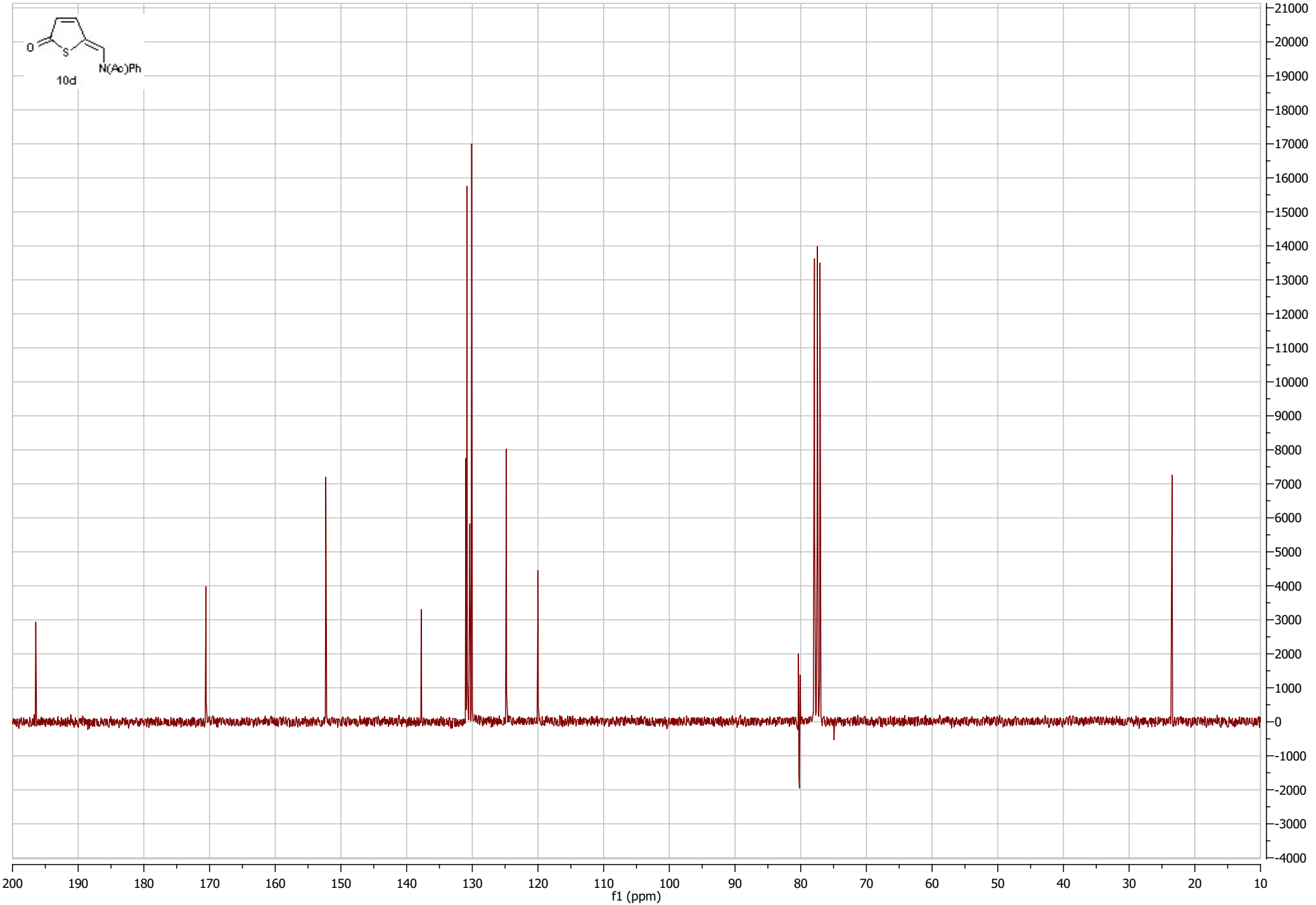

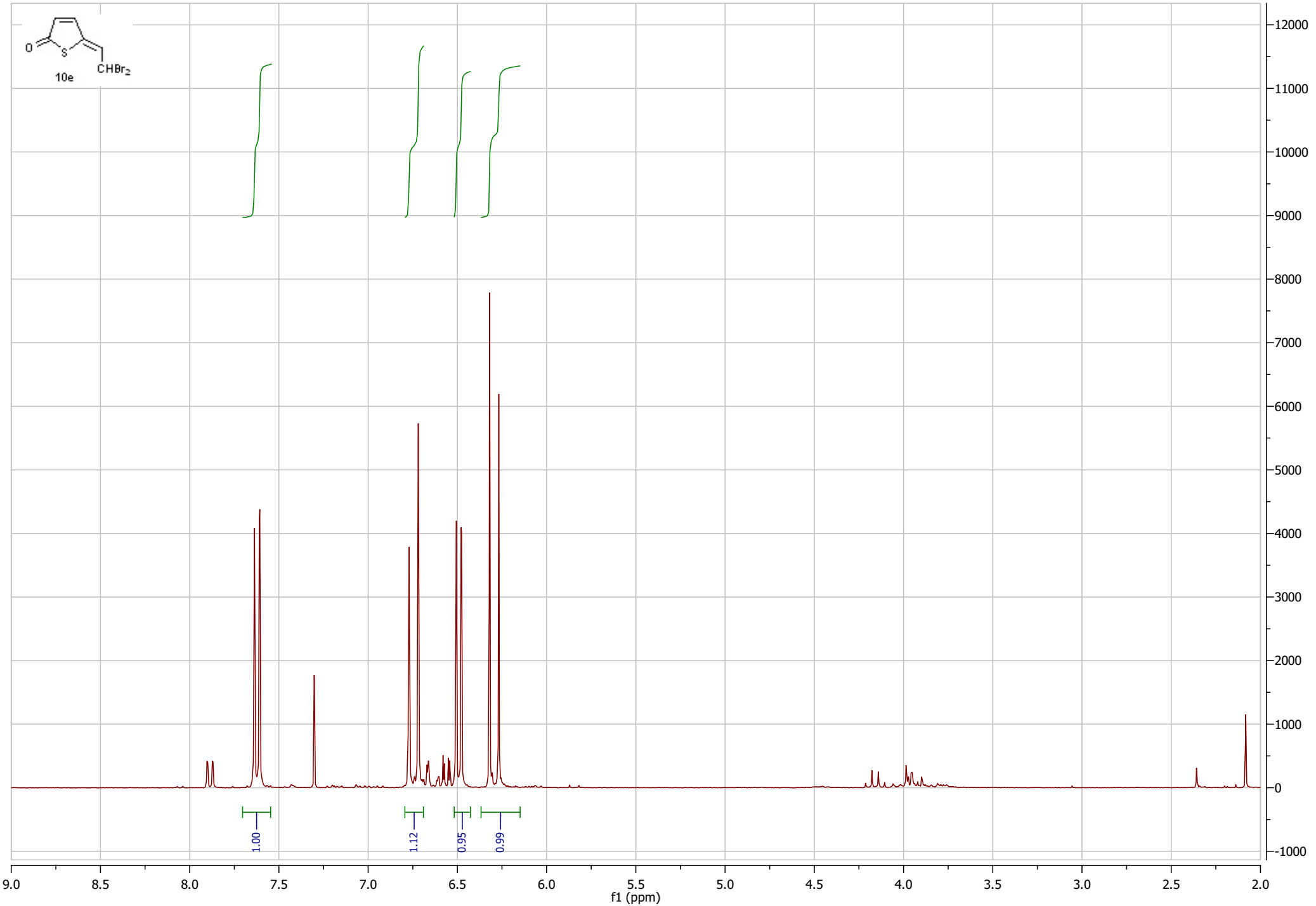

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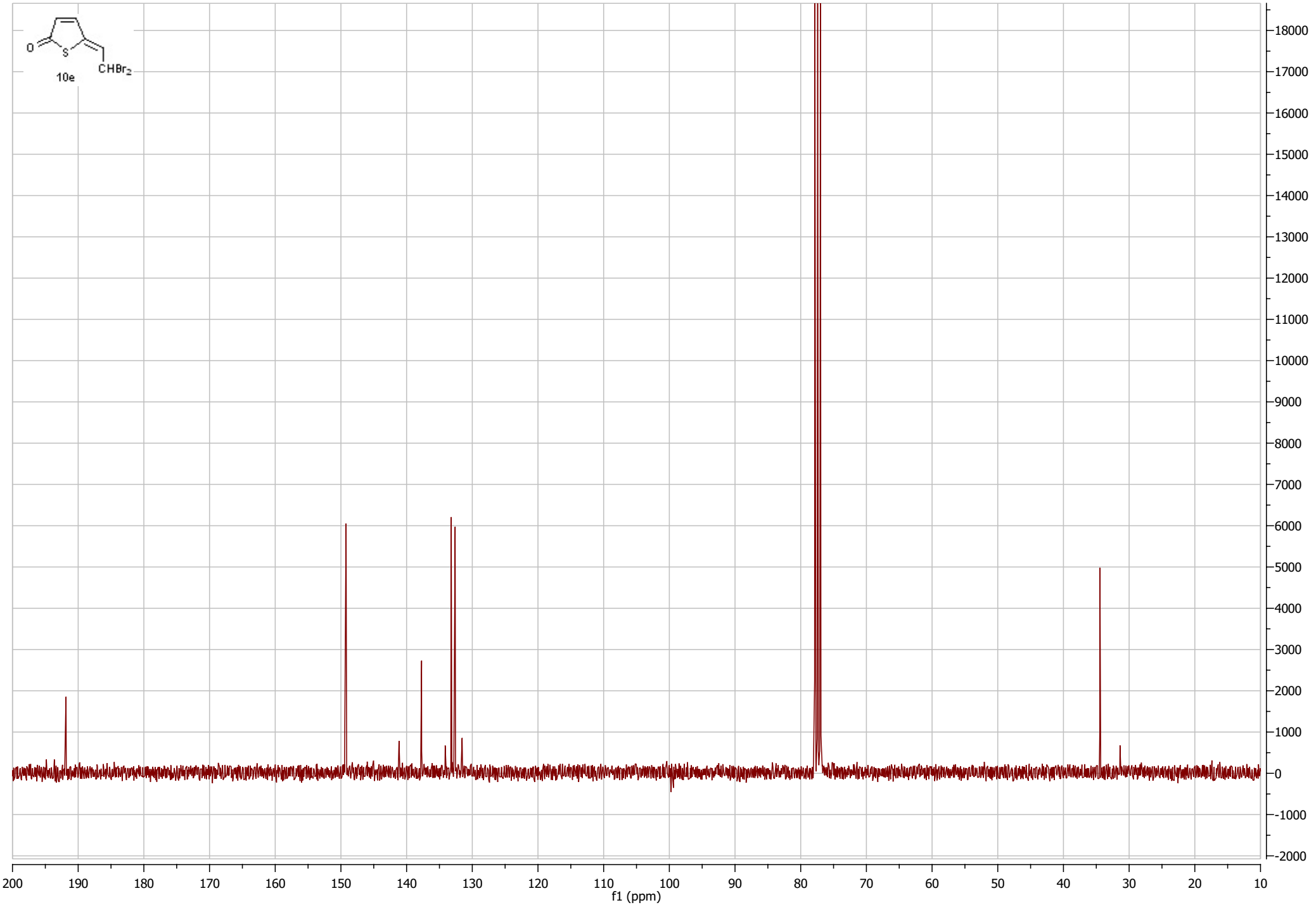

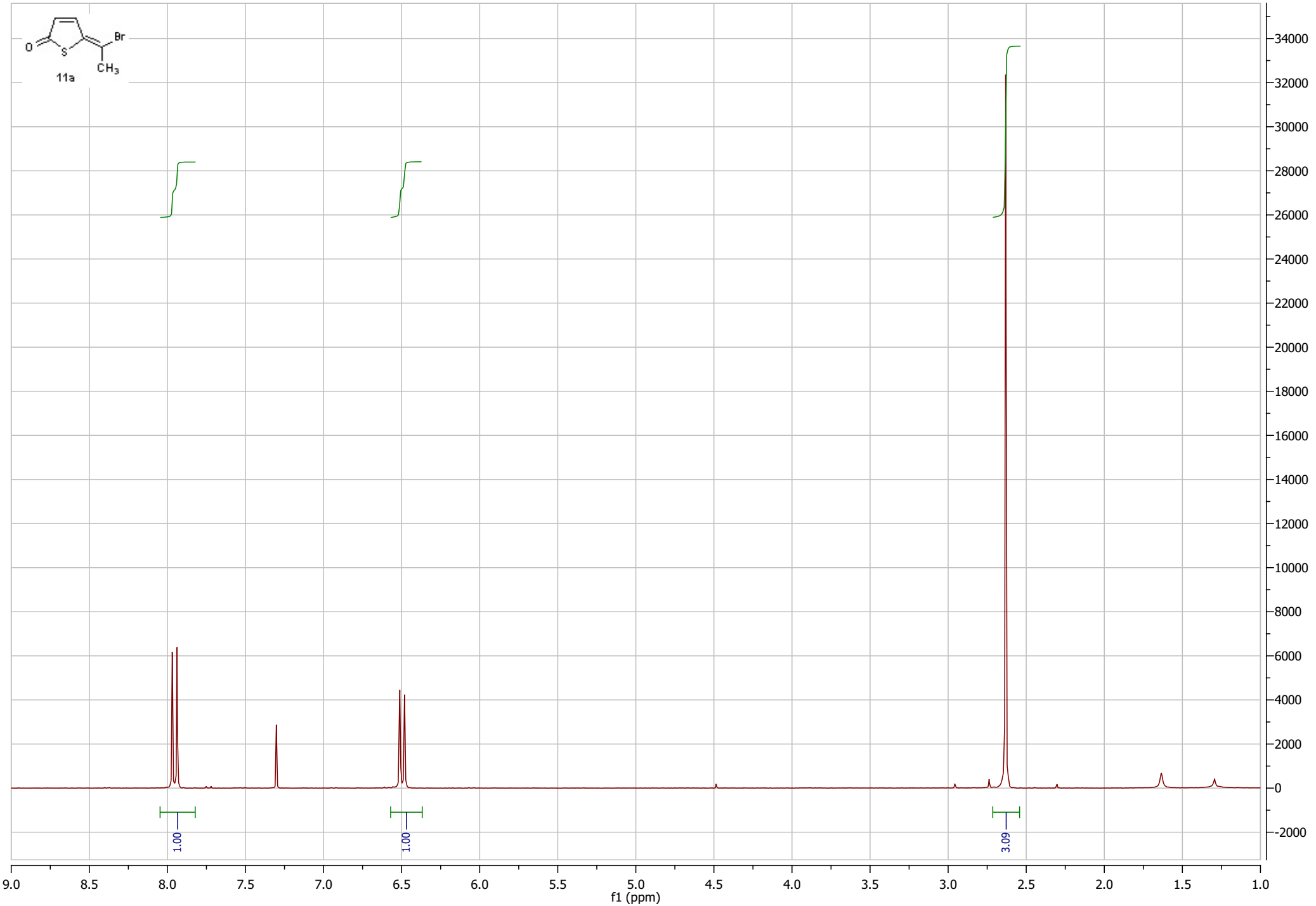

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