Synthesis of uniflorol B, a chromanone metabolite of *Calea uniflora*, and investigation of novel analogues as anti-leishmanial agents

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I - General information

Reagents were obtained from commercial suppliers and used without further purification. TLC analyses were performed using precoated Merck TLC Silica Gel 60 F254 plates. Purifications by column chromatography on silica gel were performed using Merck Silica Gel 60 (0,060-0,200 mm). NMR spectra were recorded on a Bruker Avance 300 or a Bruker DMX 500 instruments. Chemical shifts (δ) are reported in parts per million (ppm), relative to residual solvent as internal standard. The following abbreviations are used for multiplicities: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; td, triplet of doublets; m, multiplet; br, broad. Coupling constants (*J*) are reported in Hertz (Hz). HRMS analyses were obtained using a Bruker MaXis 4G instrument for ESI.

II – Synthetic procedures & characterization data

1-(2,2-dimethyl-4-oxochroman-6-yl)ethyl 2-(hydroxymethyl)but-2-enoate (1)

N-Bromosuccinimide (NBS) (046 mg, 0.26 mmol, 1.5 equiv.) was dissolved in DCM (1 mL) and the solution was cooled to 0°C. Dimethylsulfide (Me_2S) (38 µL, 0.52 mmol, 3.0 equiv.) was added dropwise and the reaction mixture was stirred for 1 hour at 0°C. 1-(2,2-dimethyl-4-oxochroman-6-yl)ethyl 3-hydroxy-2-methylenebutanoate **2** (0.050 g, 0.16 mmol, 1.0 equiv.) was added and the temperature was gradually increased to room temperature. The reaction was left under stirring overnight. Saturated $NaHCO_3$ (3 mL) was added and the intermediate **14** was extracted with DCM (3 x 2 mL). The organic phase was washed with water (2 x 5 mL), brine (5 mL), dried over magnesium sulfate and concentrated under reduced pressure. Compound **14** was dissolved in a mix of water (0.15 mL) and DMPU (0.3 mL). Na_2HPO_4 (49 mg, 0.346 mmol, 2.15 equiv.) and NaH_2PO_4 (41 mg, 0.346 mmol, 2.15 equiv.) were added and the mixture was left to reflux for 8 hours. Water (2 mL) was then added at room temperature and the final compound **1** was extracted with diethyl ether (3 x 2 mL). The combined organic phases were washed with water (5 mL), brine (5 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (DCM/EA: 90/10). Yield 46%. Light yellow oil.

^1H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, *J* = 2.3 Hz, 1H), 7.48 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.02 (q, *J* = 7.3 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 5.93 (q, *J* = 6.6 Hz, 1H), 4.35 (d, *J* = 6.6 Hz, 2H), 2.72 (s, 2H), 1,90 (d, *J* = 11.2 Hz, 3H), 1.60 (d, *J* = 6.6 Hz, 3H), 1.46 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.5, 166.8, 159.8, 141.0, 134.5, 134.1, 132.0, 124.1, 120.0, 118.8, 79.5, 72.1, 57.2, 48.9, 26.8, 26.7, 22.1, 14.4. HRMS (ESI) m/z calculated for $[M+Na]^+$ ($C_{18}H_{22}O_5Na$) 341.1359, found 341.1357.

1-(2,2-Dimethyl-4-oxochroman-6-yl)ethyl 3-hydroxy-2-methylenebutanoate (2)

A mixture of 1-(2,2-dimethyl-4-oxochroman-6-yl)ethyl acrylate **3** (390 mg, 1.42 mmol, 1.0 equiv.), acetaldehyde (80 µL, 1.42 mmol, 1.0 equiv.) and DABCO (159 mg, 1.42 mmol, 1 equiv.) in MeOH (0.1 mL) was left at room temperature for 3 days. Water (5 mL) was added and the compound was extracted with ethyl acetate (3 x 5 mL). The combined organic phases were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (dichloromethane: ethyl acetate 95:5). Yield: 40%. Colorless viscous oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, *J* = 2.3 Hz, 1H), 7.48 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.25 (s, 1H), 5.93 (q, *J* = 13.0 Hz, 1H), 5.83 (m, 1H), 4.64-4.58 (m, 1H), 2.71 (s, 2H), 2.65 (bs, OH), 1.57 (d, 3H), 1.49 (s, 6H), 1.37 e 1.35 (d, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 192.2, 165.8, 159.7, 143.9, 134.3, 133.8, 124.2, 124.0, 119.9, 118.7, 79.4, 72.1, 66.8, 48.7, 26.6, 22.3, 22.2, 21.9. HRMS (ESI) *m/z* calculated for $[M+Na]^+$ ($C_{18}H_{22}O_5Na$) 341.1359, found 341.1364.

1-(2,2-Dimethyl-4-oxochroman-6-yl)ethyl acrylate (3)

To a mixture of 6-(1-Hydroxyethyl)-2,2-dimethylchroman-4-one **4** (732 mg, 3.32 mmol, 1.0 equiv.), DMAP (10 mg, cat.) and triethylamine (895 µL, 6.40 mmol, 1.9 equiv.) in dry DCM (10 mL), was added acryloyl chloride (474.5 µL, 5.84 mmol, 1.8 equiv.) dropwise at 0°C. After complete addition, the reaction mixture was stirred at room temperature for 3 hours. The reaction was quenched by addition of ice water (20 mL). Extraction was carried out with DCM (3 x 10 mL). The organic phase was washed with 1 M HCl (40 mL), saturated $NaHCO_3$ (40 mL) and brine (40 mL), then dried over magnesium sulfate, filtered, and the solvent removed under vacuum. The crude residue was used in the next step without further purification. Yield: 100%; colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, *J* = 2.3 Hz, 1H), 7.48 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 6.42 (dd, *J* =17.3, 1.5 Hz, 1H), 6.13 (dd, *J* =17.3 Hz, 10.4 Hz, 1H), 5.91 (q, *J* = 6.7 Hz, 1H), 5.82 (dd, *J* = 10.4 Hz, 1.5 Hz, 1H), 2.71 (s, 2H), 1.56 (d, *J* = 6.7 Hz, 3H), 1.55 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.5, 165.6, 159.7, 134.6, 134.1, 131.1, 128.7, 124.2, 120.0, 118.7, 79.5, 71.8, 48.9, 26.8, 26.7, 22.05. HRMS (ESI) m/z calculated for $[M+Na]^+$ ($C_{16}H_{18}O_4Na$) 297.1097, found 297.1098.

6-(1-Hydroxyethyl)-2,2-dimethylchroman-4-one (4)

Method A: 6-acetyl-2,2-dimethylchroman-4-one **5** (200 mg, 0.9 mmol, 1.0 equiv.), dissolved in dimethylformamide (1.5 mL) was added to water (500 mL) containing *D. carota* slices (150 g). The reaction mixture was stirred vigorously for 7 days at room temperature. The reaction mixture was then extracted with ethyl acetate (6 × 50 mL), and the organic phases dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (PE: EtOAc) to afford (S)-4 (57.5 mg, 29%) as a yellow oil. [α]$_D$ (20 °C) −18.3 (c = 0.95, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 2.26 Hz, 1H), 7.47 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 4.79 (q, *J* = 6.5 Hz, 1H), 2.63 (s, 2H), 1.41 (d, *J* = 6.5 Hz, 3H), 1.37 (s, 6H).

Method B: 6-acetyl-2,2-dimethylchroman-4-one **5** (327 mg, 1.5 mmol, 1.0 equiv.) was dissolved in MeOH (4 mL) and the solution was cooled to -5°C. $NaBH_4$ (18 mg, 0.5 mmol, 0.33 equiv.) was added and the mixture was allowed to react for 45 minutes at the same temperature. The reaction mixture was quenched by addition of acetone (1 mL) followed by addition of water (10 mL) and extracted with DCM (3 x 5 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried over magnesium sulfate, filtered, and the solvent removed under vacuum. The crude residue was purified by column chromatography on silica gel (DCM/EA: 95/5) to afford alcohol **4** (178.5 mg, 54%) and **13** (43 mg, 13%).

1-(4-Hydroxy-2,2-dimethylchroman-6-yl)-ethanone (**13**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 2.3 Hz, 1H), 7.73 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 4.82 (dd, *J* = 8.5, 6.2 Hz, 1H), 2.47 (s, 3H), 2.15 (dd, *J* = 12.0, 6.2 Hz, 1H), 1.83 (dd, *J* = 12.0, 8.5 Hz, 1H), 1.40 (s, 3H), 1.25 (s, 3H).

Method C: 6-acetyl-2,2-dimethylchroman-4-one **5** (2.18 g, 10.0 mmol, 1.0 equiv.) was dissolved in EtOH (40 mL) under an argon atmosphere. Palladium (5% w/w on carbon powder) (220 mg, 10%) was added and the flask was evacuated and purged with H_2 gas (~ 1 atm, balloon). The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was filtered through a pad of celite ad concentrated. The crude material was purified by column chromatography on silica gel (DCM/EA: 95/5) to afford alcohol **4** (1.50 g, 68%) with **12** (531 mg, 26%) as a by-product.

6-Ethyl-2,2-dimethylchroman-4-one (**12**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.60 (m, 1H), 7.31 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 2.70 (s, 2H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.45 (s, 6H), 1.22 (t, *J* = 7.6 Hz, 3H).

6-Acetyl-2,2-dimethylchroman-4-one (5)

Method A: 5’-Acetyl-2’-hydroxyacephenone **6** (0.9 g, 5.2 mmol, 1.0 equiv.) was mixed with the ionic liquid ([bmim]Br) (1.48 g, 6.76 mmol, 1.3 equiv.). Acetone (7.7 mL, 104 mmol, 20.0 equiv.) and morpholine (0.9 mL, 10.4 mmol, 2.0 equiv.) were added. The mixture was refluxed at 95°C for 8 hours. Saturated NaCl solution (50 mL) was added to the cooled reaction mixture, and the product was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (DCM: cyclohexane 7:3) to afford **5** (0.760 g, 67%) as a pale yellow solid.

^{1}H NMR (300 MHz, CDCl$_3$) δ 8.44 (d, *J* = 2.3 Hz, 1H), 8.13 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 1H), 2.77 (s, 2H), 2.59 (s, 3H), 1.49 (s, 7H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 196.4, 191.7, 163.5, 135.4, 130.2, 128.2, 119.2, 119.0, 80.4, 48.6, 26.6, 26.4.

Method B: 6-Ethyl-2,2-dimethylchroman-4-one **12** (204 mg, 1.0 mmol, 1.0 equiv.) was dissolved in ACN (7 mL). A solution of potassium persulfate (541 mg, 2.0 mmol, 2.0 equiv.) in water (7 mL) and copper sulfate ($CuSO_4$.$5H_2O$) (50 mg, 0.2 mmol, 0.2 equiv.) were added. The resulting solution was stirred at 80°C for 2 h. After 2 h, $K_2S_2O_8$ (135 mg, 0.5 mmol, 0.5 equiv.) was added and heating was continued for 2 h. After cooling, the reaction mixture was diluted with H_2O (15 mL) and the product was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with saturated $NaHCO_3$ (3x 20 mL), brine (20 mL), dried over magnesium sulfate then filtered. The filtrate was concentrated to afford the desired compound (177 mg, 81%) as a pale yellow solid after purification by column chromatography on silica gel.

^{1}H NMR (300 MHz, CDCl$_3$) δ 8.44 (d, *J* = 2.3 Hz, 1H), 8.13 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 1H), 2.77 (s, 2H), 2.59 (s, 3H), 1.49 (s, 7H).

5’-Acetyl-2’-hydroxyacetophenone (6)

4-acetylphenyl acetate **8** (13 g, 73 mmol, 1 equiv.) was triturated with anhydrous aluminum chloride (39 g, 292 mmol, 4 equiv.). The reaction mixture was kept at 140°C for 2 hours. The medium was then cooled to 50°C. The reaction mixture was quenched by slow addition of a mixture of130 mL of conc. HCl and 270 mL of iced water. After addition of the HCl and H_2O, the reaction was stirred for 15 minutes at 50°C. The reaction mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (DCM 100%). Yield 77%; yellow solid.
^{1}H NMR (300 MHz, CDCl$_3$): δ 12.59 (s, 1H), 8.34 (d, *J* = 2.3 Hz, 1H), 7.98 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 2.63 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 204.8, 195.65, 166.0, 136.3, 131.8, 128.6, 119.2, 118.5, 26.7, 26.2.

4-Acetylphenyl acetate (8)

4-Hydroxyacetophenone **7** (10 g, 73.4 mmol, 1.0 equiv.) was dissolved in dichloromethane (50 mL). After cooling to 0°C (ice bath), acetic anhydride (10.5 mL, 110.2 mmol, 1.5 equiv.) and triethylamine (11.2 mL, 80.35 mmol, 1.1 equiv.) were then added dropwise. The reaction mixture was stirred at room temperature for 3 h. After total conversion of the starting material, saturated NaCl solution (50 mL) was added and the reaction mixture was extracted with dichloromethane (3 x 40 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel. Yield 99%; white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92-7.89 (m, 2H), 7.13-7.09 (m, 2H), 2.51 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.8, 168.8, 154.4, 134.7, 129.9, 121.8, 26.6, 21.1.

4-Ethylphenyl acetate (10)

4-Ethylphenol **9** (10 g, 82.0 mmol, 1.0 equiv.) was dissolved in dichloromethane (200 mL). Triethylamine (13.7 mL, 98.0 mmol, 1.2 equiv.) was added at 0°C, followed by the dropwise addition of acetyl chloride (7.0 mL, 98.0 mmol, 1.2 equiv.). The resulting mixture was stirred at room temperature overnight, then quenched with water (200 mL). The organic phase was separated, washed with 1 M NaOH solution (2 x 200 mL), brine (2 x 200 mL) and dried over magnesium sulfate. Solvent was removed under reduced pressure to afford the target compound (13.15 g, yield 99%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.14 (m, 2H), 6.99 (d, J = 8.5 Hz, 2H), 2.65 (q, J = 7.6 Hz, 2H), 2.29 (s, 3H), 1.24 (t, J = 7.6 Hz, 3H).

5’-Ethyl-2’-hydroxyacetophenone (11)

4-Ethylphenyl acetate **10** (1.6 g, 10 mmol, 1 equiv.) was dissolved in triflic acid (10 mL) at 0°C. The reaction mixture was stirred at room temperature for 6 hours, then poured into ice water. The reaction mixture was extracted with ethyl acetate (3x of 20 mL) and the combined organic layers were sequentially washed with 1 M HCl (50 mL), saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried over magnesium sulfate then filtered. The filtrate was concentrated to afford the desired compound (1.49 g, 92%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.10 (s, 1H), 7.52 (d, J = 2.2 Hz, 1H), 7.33 (dd, J = 8.5, 2.2 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 2.62 (d, J = 8.9 Hz, 5H), 1.24 (t, J = 7.6 Hz, 3H).

6-Ethyl-2,2-dimethylchroman-4-one (12)

5’-Ethyl-2’-hydroxyacephenone **11** (1.62 g, 10.0 mmol, 1.0 equiv.) was dissolved in EtOH (10 mL). Acetone (0.88 mL, 12.0 mmol, 1.2 equiv.) and pyrrolidine (1.5 mL, 20.0 mmol, 2.0 equiv.) were added. The mixture was stirred under reflux for 5 hours. After removal of the solvent, the crude material was dissolved in Et_2O (30 mL). The organic phase was washed successively with 2 M HCl (20 mL), 1 M NaOH (2 x 20 mL) and brine (30 mL), then dried over magnesium sulfate and concentrated under reduced pressure affording **12** (1. 6 g, 79%) as clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.60 (m, 1H), 7.31 (dd, J = 8.5, 2.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 2.70 (s, 2H), 2.60 (q, J = 7.6 Hz, 2H), 1.45 (s, 6H), 1.22 (t, J = 7.6 Hz, 3H).

Synthesis of compounds 17-20

General procedure: A mixture of 1-(2,2-dimethyl-4-oxochroman-6-yl)ethyl acrylate **3** (137 mg, 0.5 mmol, 1.0 equiv.), aldehyde (0.5 mmol, 1.0 equiv.) and DABCO (56 mg, 0.5 mmol, 1 equiv.) in MeOH (0.05 mL) was left at room temperature for 3 days. Water (2 mL) was added and the reaction was extracted with ethyl acetate (3 x 2 mL). The combined organic phases were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel.

1-(2,2-dimethyl-4-oxochroman-6-yl)ethyl 2-(hydroxy(phenyl)methyl)acrylate (17)

Obtained from benzaldehyde as a clear viscous oil (28%). This compound was obtained as a 1:1 mixture of diastereoisomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 2.4 Hz, 1H), 7.77 (d, *J* = 2.4 Hz, 1H),7.41 – 7.19 (m, both diastereroisomers, 14H), 6.86 (d, *J* = 8.6 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 6.43-6.40 (m, 1H), 6.40-6.37 (m, 1H), 5.92 – 5.78 (m, both diastereroisomers, 4H), 5.58-5.51 (m, both diastereroisomers, 2H), 3.00-2.94 (m, OH), 2.87-2.80 (m, OH), 2.71 (s, 2H), 2.70 (s, 2H), 1.49 (d, *J* = 6.7 Hz, 3H), 1.46 (d, *J* = 6.7 Hz, 3H), 1.45 (s, both diastereroisomers, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.5 and 192.4, 165.6 and 165.5, 159.75 and 159.7, 142.2, 141.4, 134.4 and 134.35, 133.7, 128.6, 128.0 and 127.9, 126.8 and 128.7, 126.6 and 126.3, 124.1, 119.9, 118.7, 79.5, 73.4 and 73.3, 72.4, 48.9, 26.8, 26.7, 21.9 and 21.8. HRMS (ESI) m/z calculated for $[M+Na]^+$ ($C_{23}H_{24}O_5Na$) 403.1516, found 403.1514.

1-(2,2-dimethyl-4-oxochroman-6-yl)ethyl 2-(hydroxy(4-nitrophenyl)methyl)acrylate (18)

Obtained from *p*-nitrobenzaldehyde as a clear viscous oil (19%). This compound was obtained as a 1:1 mixture of diastereoisomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.7 Hz, 2H), 8.15 (d, *J* = 8.7 Hz, 2H), 7.76 (d, *J* = 2.4 Hz, 1H), 7.75 (d, *J* = 2.4 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.52 (d, *J* = 8.7 Hz, 2H), 7.36 (dd, *J* = 8.7, 2.4 Hz, 2H), 7.33 (dd, *J* = 8.7, 2.4 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 6.45 (d, *J* = 4.6 Hz, both diastereroisomers, 2H), 5.94 – 5.78 (m, both diastereroisomers, 4H), 5.61 (d, *J* = 6.2 Hz, both diastereroisomers, 2H), 3.28-3.22 (m, OH), 3.19-3.13 (m, OH), 2.71 (s, both diastereroisomers, 4H), 1.52 (d, *J* = 6.6 Hz, 3H), 1.50 (d, *J* = 6.6 Hz, 3H), 1.45 (s, 6H), 1.44 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 165.2, 159.9 and 159.8, 148.7 and 148.7, 147.5, 141.3, 141.2, 134.40 and 134.4, 133.4 and 133.35, 127.65 and 127.4, 127.5 and 127.4, 124.1 and 124.0, 123.7, 120.0 and 119.95, 118.8 and 118.8, 79.6, 72.9 and 72.9, 72.75, 48.8, 26.7, 26.7 and26.6, 21.8. HRMS (ESI) m/z calculated for $[M+Na]^+$ ($C_{23}H_{23}NO_7Na$) 448.1367, found 448.1371.

1-(2,2-dimethyl-4-oxochroman-6-yl)ethyl 2-(hydroxy(3-nitrophenyl)methyl)acrylate (19)

Obtained from *m*-nitrobenzaldehyde as a clear viscous oil (34%). This compound was obtained as a 1:1 mixture of diastereoisomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (t, *J* = 2.1 Hz, 2H), 8.20 (t, *J* = 2.1 Hz, 2H), 8.16 – 8.09 (m, both diastereroisomers, 2H), 7.78 (d, *J* = 2.4 Hz, 1H), 7.75 (d, *J* = 2.4 Hz, 1H), 7.75 – 7.68 (m, both diastereroisomers, 2H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.37 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.33 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 1H), 6.48-6.46 (m, 1H), 6.46-6.44 (m, 1H), 5.95-5.92 (m, 1H), 5.95-5.92 (m, 1H), 5.90 – 5.88 (m, 1H), 5.85(q, *J* = 6.8 Hz, 1H), 5.84(q, *J* = 6.8 Hz, 1H), 5.63 (d, *J* = 3.0 Hz, 1H), 5.60 (d, *J* = 3.0 Hz, 1H), 3.30-3.23 (m, OH), 3.18-3.12 (m, OH), 2.71 (s, 2H), 2.71 (s, 2H), 1.53 (d, *J* = 6.6 Hz, 3H), 1.50 (d, *J* = 6.6 Hz, 3H), 1.45 (s, 6H), 1.44 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5 and 192.5, 165.2 and 165.15, 159.85 and 159.8, 148.3, 143.8 and 143.8, 141.4 and 141.3, 134.4 and 134.35, 133.35, 132.9 and 132.8, 129.4, 127.5 and 127.3, 124.1 and 124.0, 122.8 and 122.8, 121.8 and 121.6, 119.9 and 119.9, 118.8 and 118.8, 79.55 and 79.5, 72.85 and 72.8, 72.6 and 72.5, 48.8, 26.7 and 26.65, 21.75. HRMS (ESI) m/z calculated for $[M+K]^+$ ($C_{23}H_{23}NO_7K$) 464.1106, found 464.1106.

1-(2,2-dimethyl-4-oxochroman-6-yl)ethyl 3-hydroxy-2-methylene-5-phenylpentanoate (20)

Obtained from 3-phenylpropionaldehyde as a clear viscous oil (27%). This compound was obtained as a 1:1 mixture of diastereoisomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, 2.3 Hz, 1H), 7.85 (d, 2.3 Hz, 1H), 7.46 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.43 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.32 – 7.14 (m, 10H), 6.92 (d, *J* = 8.6 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 6.30-6.23 (m, both diastereroisomers, 2H), 5.92 (q, *J* = 6.6 Hz, both diastereroisomers, 2H), 5.85 – 5.77 (m, both diastereroisomers, 2H), 4.47-4.36 (m, both diastereroisomers, 2H), 3.78 (s, both diastereroisomers, OH), 2.88-2.50 (m, both diastereroisomers, 4H), 2.71 (s, both diastereroisomers, 4H), 2.04 – 1.88 (m, 4H), 1.56 (d, *J* = 6.6 Hz, both diastereroisomers, 6H), 1.45 (s, 6H), 1.45 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 167.1 and 165.8, 159.8, 142.65 and 142.6, 142.3, 141.8, 134.5, 133.9 and 133.8, 128.6 and 128.6, 128.5, 126.0, 125.5 and 125.4, 124.2, 120.0, 118.8, 79.5, 72.4, 71.3 and 71.1, 52.1, 48.9, 37.9 and 37.8, 32.2 and 32.2, 26.8 and 26.7, 22.0 and 22.0. HRMS (ESI) m/z calculated for $[M+Na]^+$ ($C_{25}H_{28}NO_5Na$) 431.1829, found 431.1831.

Synthetic approach to analogues 21-22 and 26-27

Representative procedure: Tiglic acid (150 mg, 1.5 mmol, 3.0 equiv), DIC (234 µL, 1.5 mmol, 3.0 equiv) and DMAP (18 mg, 0.15 mmol, 0.3 equiv) were subsequently added to a stirred solution of alcohol **4** (89 mg, 0.5 mmol, 1.0 equiv.) in anhydrous dichloromethane (5 mL) at 0°C. The resulting mixture was stirred at room temperature overnight. After completion of reaction, water (15 mL) was added and the compound was extracted with DCM (3 x 10 mL). The combined organic phases were washed with brine (2 x 20 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography on silica gel to afford **26** as a clear oil (89%).

(*E*)-1-(2,2-dimethyl-4-oxochroman-6-yl)ethyl 2-methylbut-2-enoate (21)

Obtained from tiglic acid and alcohol **4** as a clear oil (51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 2.4 Hz, 1H), 7.48 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.88 (q, *J* = 6.6 Hz, 1H), 2.71 (s, 2H), 1.88 – 1.81 (m, 3H), 1.78 (dd, *J* = 7.1, 1.1 Hz, 3H), 1.54 (d, *J* = 6.6 Hz, 3H), 1.45 (d, *J* = 1.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6, 167.4, 159.6, 137.6, 134.8, 134.6, 128.9, 124.0, 120.0, 118.6, 79.4, 71.6, 49.0, 26.8, 26.7, 22.2, 14.5, 12.2.

(*E*)-6-acetyl-2,2-dimethylchroman-4-yl 4-phenylbut-3-enoate (22)

Obtained from 4-phenylbut-3-noic acid and alcohol **13** as a pale yellow oil (91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 – 7.76 (m, 2H), 7.42 – 7.09 (m, 5H), 6.87 (d, *J* = 8.6 Hz, 1H), 6.62 – 6.45 (m, 1H), 6.32 (dt, *J* = 15.8, 7.1 Hz, 1H), 6.04 (t, *J* = 6.2 Hz, 1H), 3.64 – 3.22 (m, 2H), 2.48 (s, 3H), 2.29 (dd, *J* = 14.1, 5.8 Hz, 1H), 2.02 (dd, *J* = 14.1, 6.6 Hz, 1H), 1.43 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 171.4, 158.4, 136.8, 134.1, 130.5, 130.3, 130.2, 128.7, 127.8, 126.4, 121.3, 119.5, 117.9, 76.1, 66.0, 38.8, 38.6, 27.8, 27.3, 26.3. HRMS (ESI) m/z calculated for $[M+Na]^+$ ($C_{23}H_{24}O_4Na$) 387.1567, found 387.1566.

2,2-dimethylchroman-4-yl (*E*)-2-methylbut-2-enoate (26)

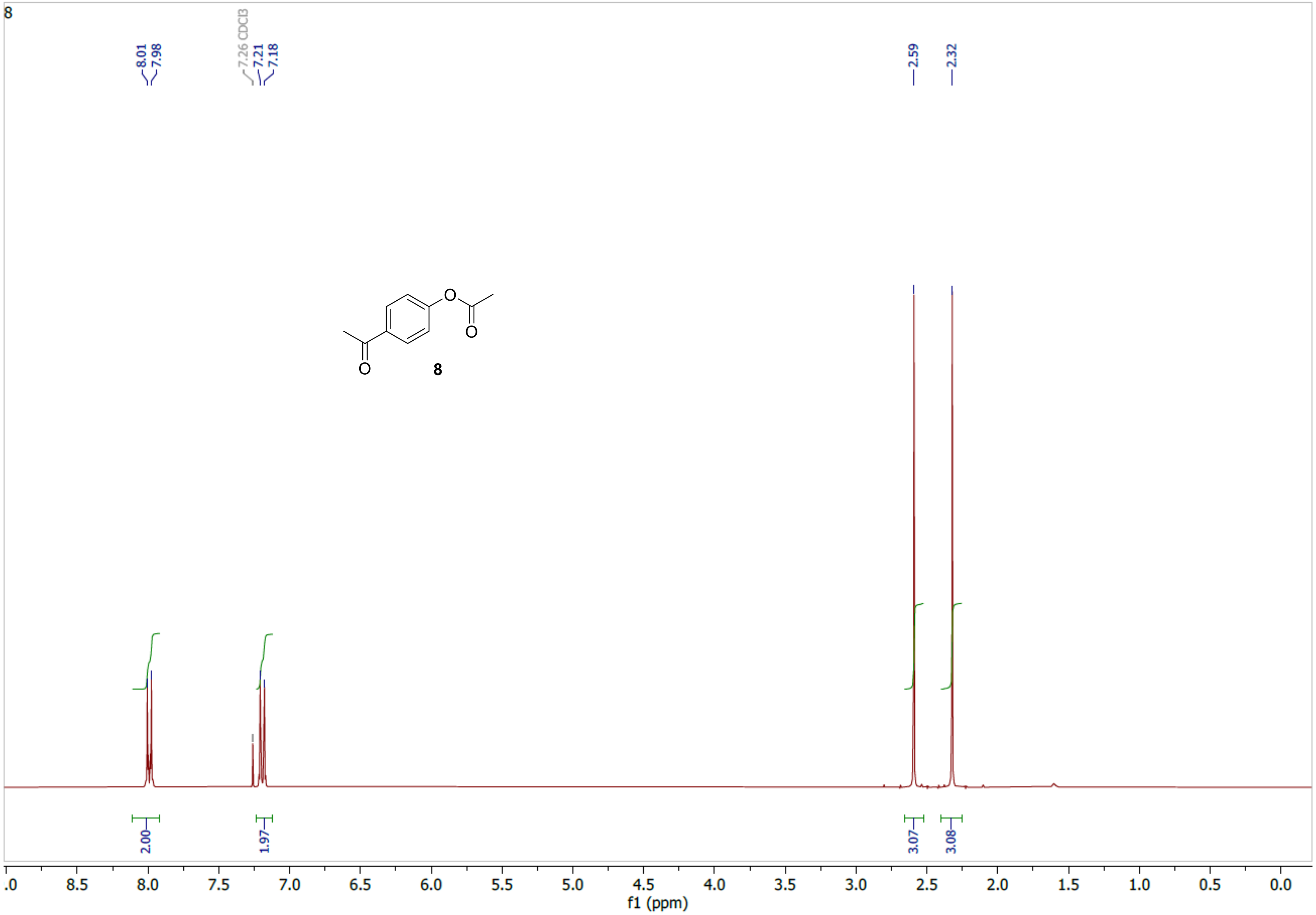
Obtained from tiglic acid and alcohol **25** as a clear oil (89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.13 (m, 2H), 6.96 – 6.77 (m, 3H), 6.07 (t, *J* = 6.0 Hz, 1H), 2.26 (dd, *J* = 14.1, 5.9 Hz, 1H), 2.01 (dd, *J* = 14.1, 6.2 Hz, 1H), 1.86 (t, *J* = 1.3 Hz, 3H), 1.79 (dd, *J* = 7.1, 1.2 Hz, 3H), 1.44 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 154.1, 138.0, 129.8, 129.2, 128.8, 120.4, 120.3, 117.6, 74.7, 65.8, 39.1, 27.6, 27.5, 14.6, 12.2. HRMS (ESI) m/z calculated for $[M+Na]^+$ ($C_{16}H_{20}O_3Na$) 283.1305, found 283.1304.

2,2-dimethylchroman-4-yl (*E*)-but-2-enoate (27)

Obtained from crotonic acid and alcohol **25** as a clear oil (65%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 – 7.15 (m, 2H), 7.02 (dq, *J* = 15.5, 6.9 Hz, 1H), 6.94 – 6.78 (m, 2H), 6.06 (t, *J* = 6.2 Hz, 1H), 5.88 (dq, *J* = 15.6, 1.7 Hz, 1H), 2.25 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.01 (dd, *J* = 14.0, 6.5 Hz, 1H), 1.89 (dd, *J* = 6.9, 1.7 Hz, 3H), 1.43 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 154.1, 145.4, 129.8, 129.0, 122.9, 120.4, 120.1, 117.7, 74.8, 65.6, 39.0, 27.7, 27.3, 18.2. HRMS (ESI) m/z calculated for $[M+Na]^+$ ($C_{15}H_{18}O_3Na$) 269.1148, found 269.1147.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8.0
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7.0
6.5
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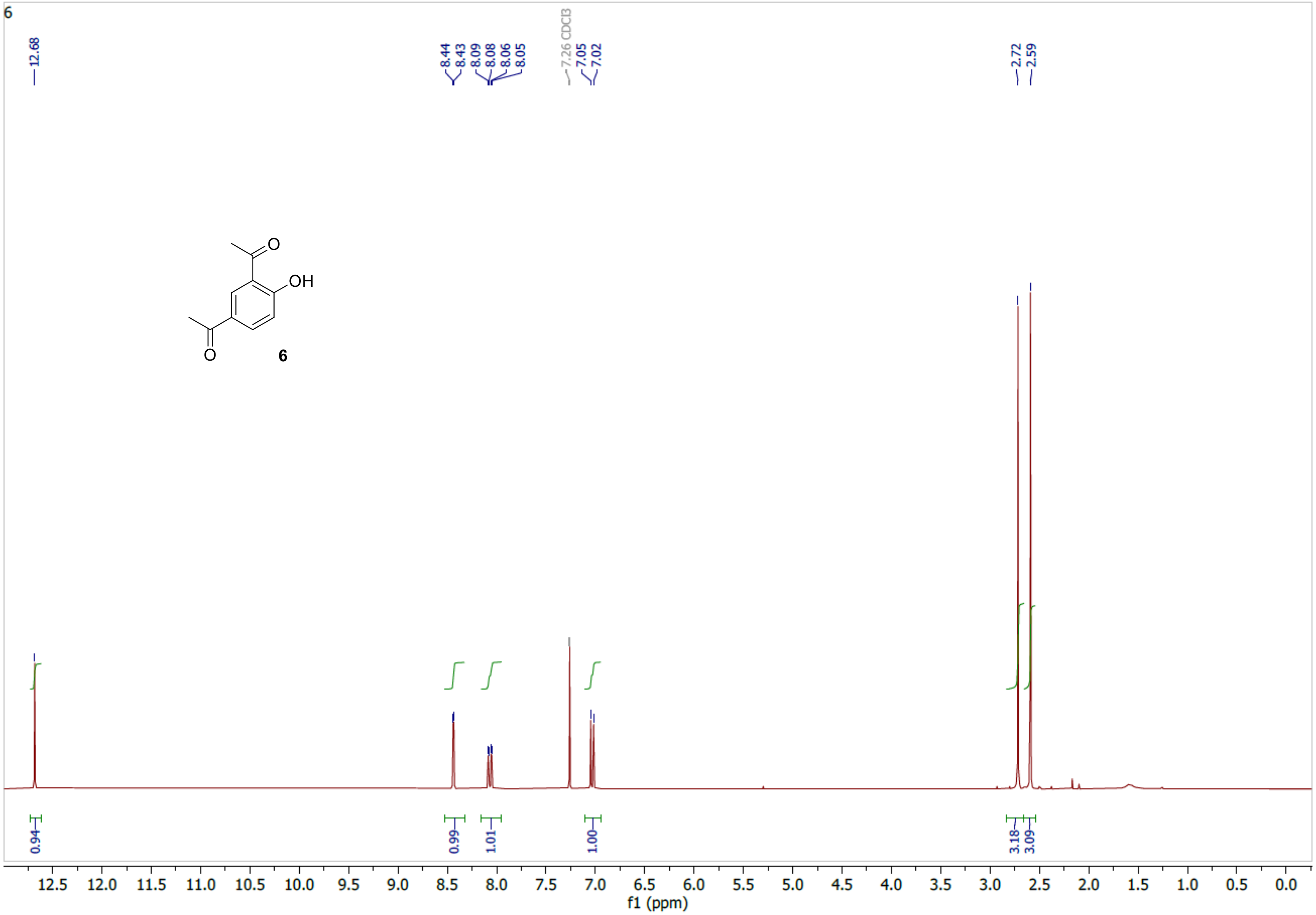
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2.59
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OH
O
6
0.94
0.99
1.01
1.00
3.18
3.09
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
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7.0
6.5
6.0
5.5
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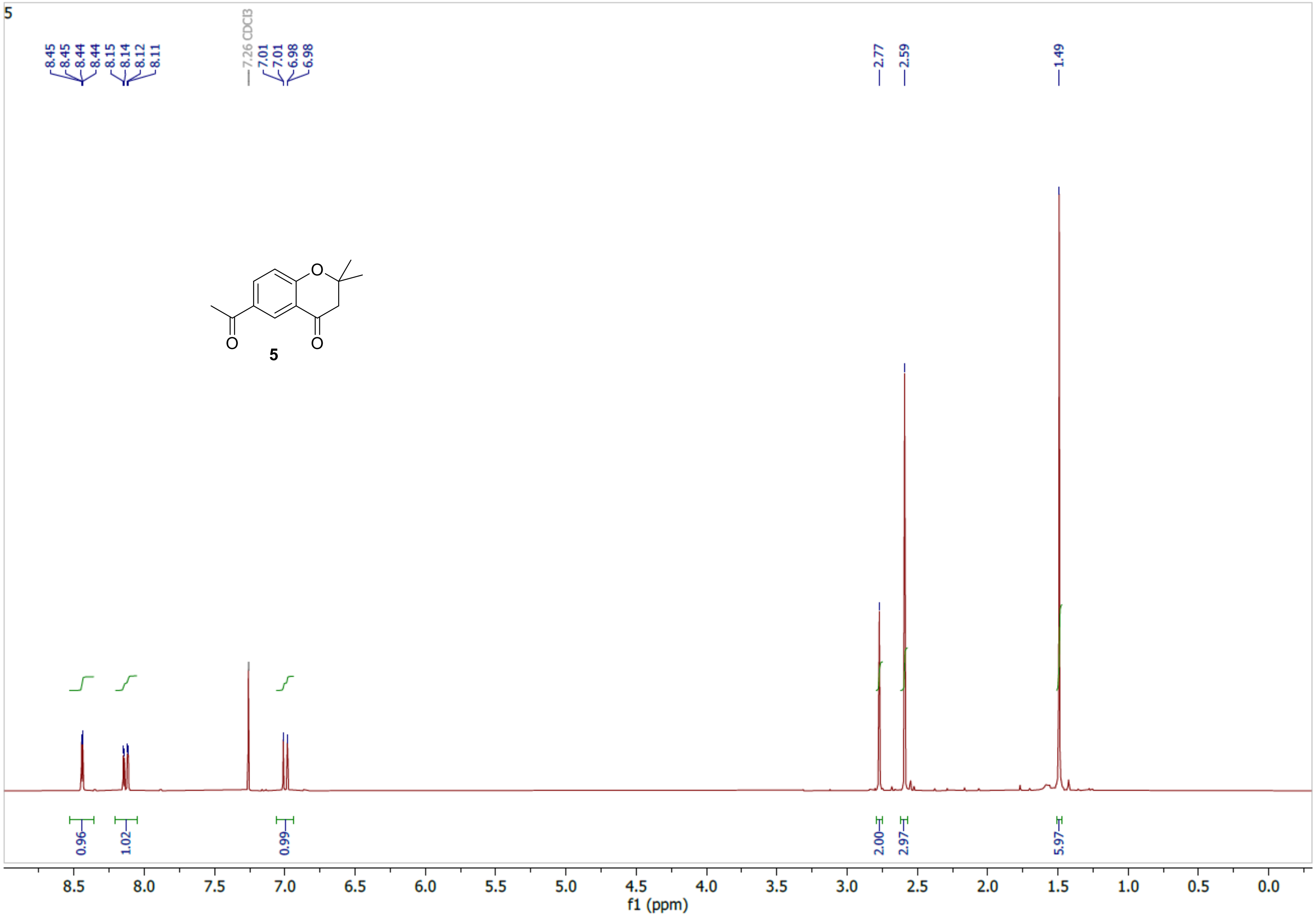
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7.01
6.98
6.98
2.77
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1.49
O
O
O
5
0.96
1.02
0.99
2.00
2.97
5.97
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7.0
6.5
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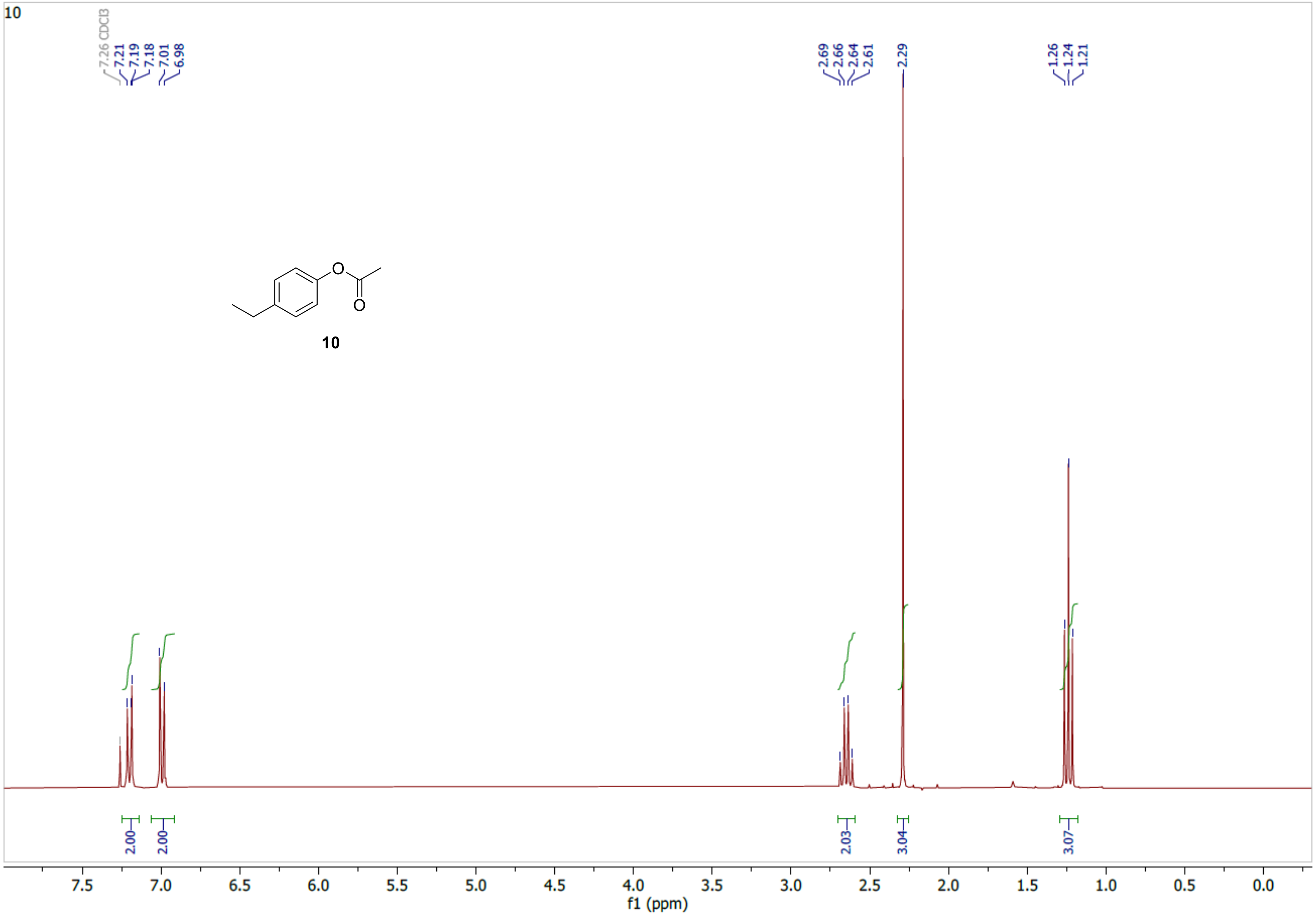
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2.64
2.61
2.29
1.26
1.24
1.21
O
O
10
2.00
2.00
2.03
3.04
3.07
7.5
7.0
6.5
6.0
5.5
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1.0
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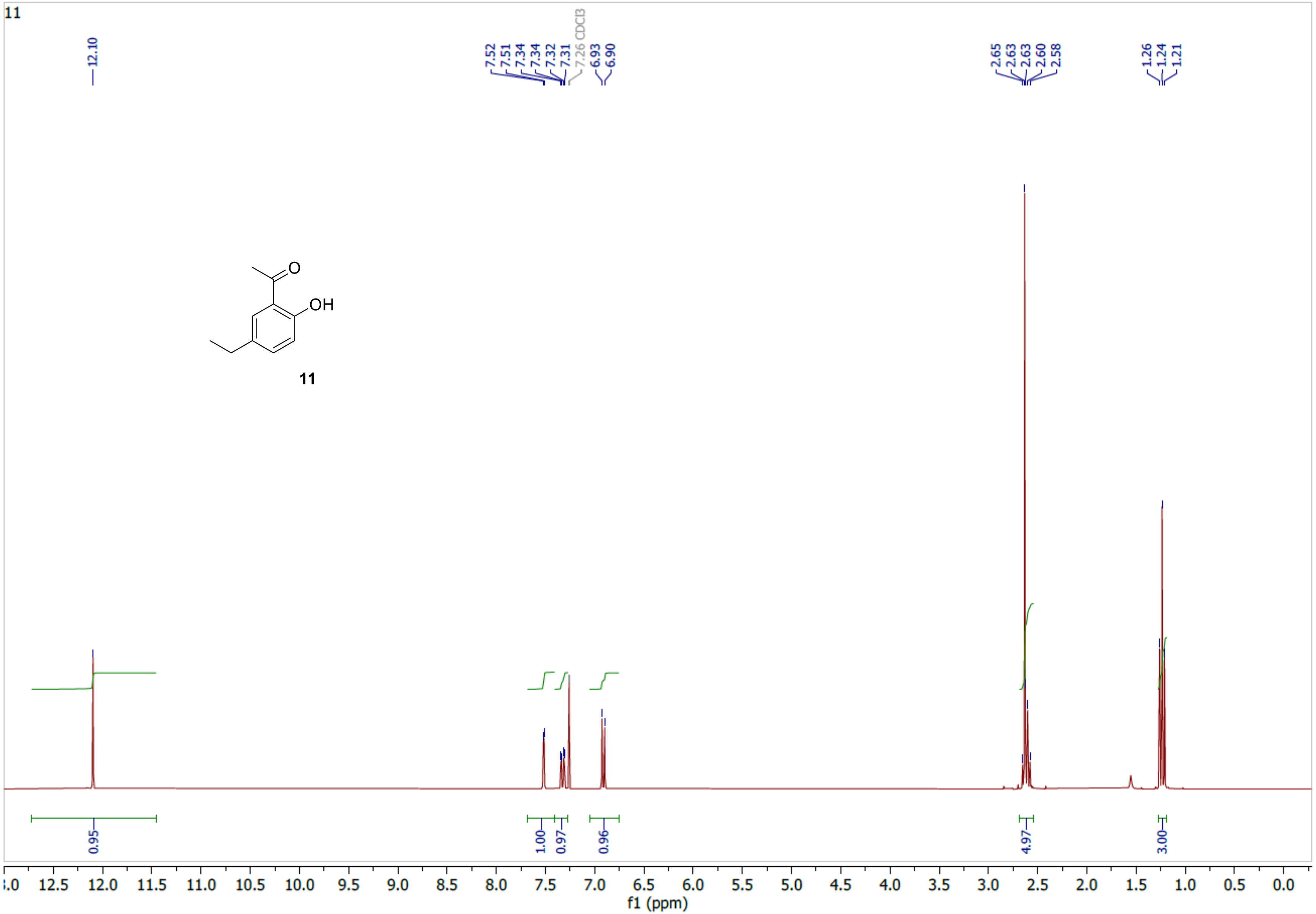
f1 (ppm)

11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2.63
2.60
2.58
1.26
1.24
1.21
O
OH
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0.97
0.96
4.97
3.00
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12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
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6.5
6.0
5.5
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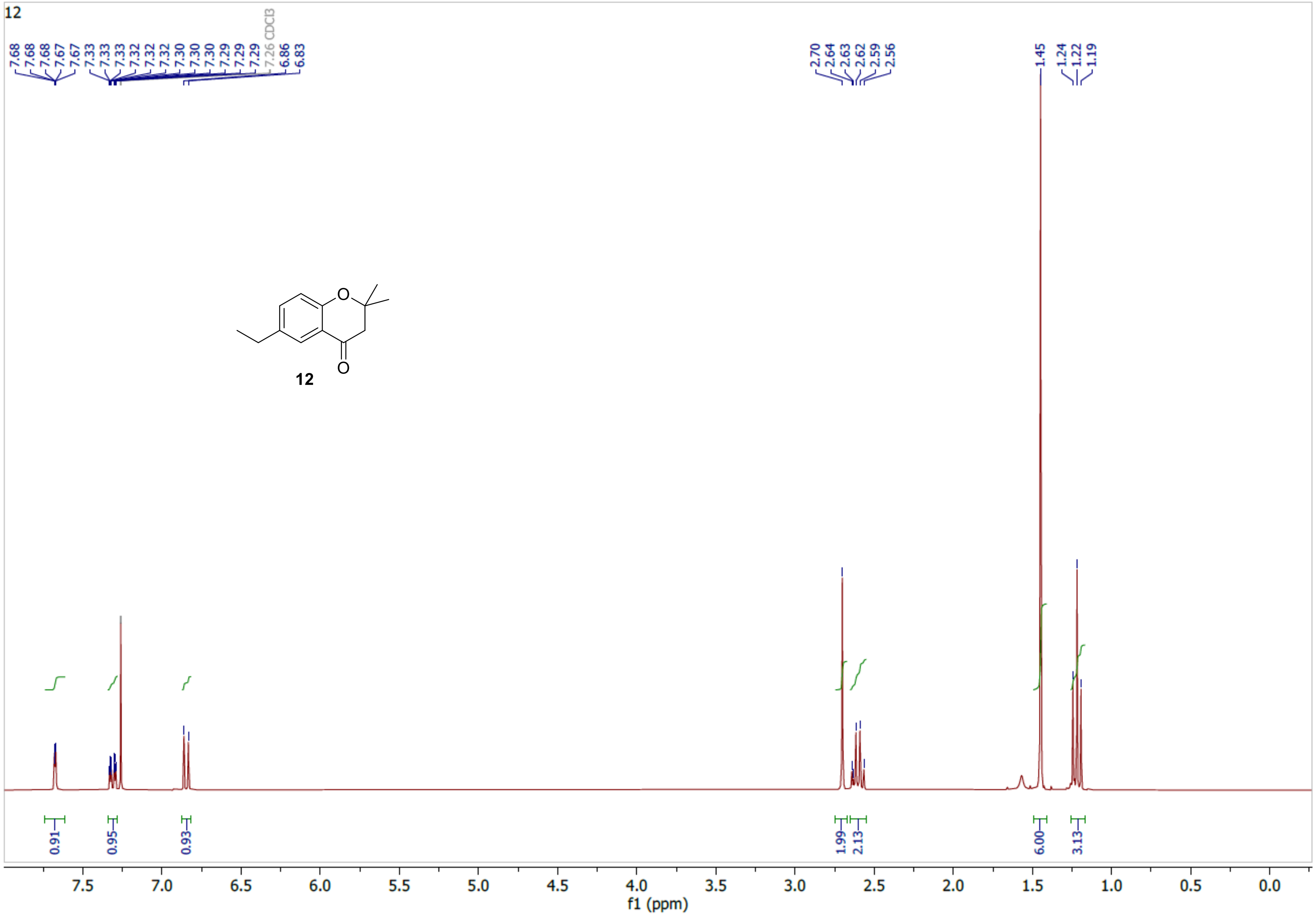
f1 (ppm)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7.30
7.30
7.29
7.29
7.29
7.26 CDCl3
6.86
6.83
2.70
2.64
2.63
2.62
2.59
2.56
1.45
1.24
1.22
1.19
O
O
12
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0.95
0.93
1.99
2.13
6.00
3.13
7.5
7.0
6.5
6.0
5.5
5.0
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4.0
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2.5
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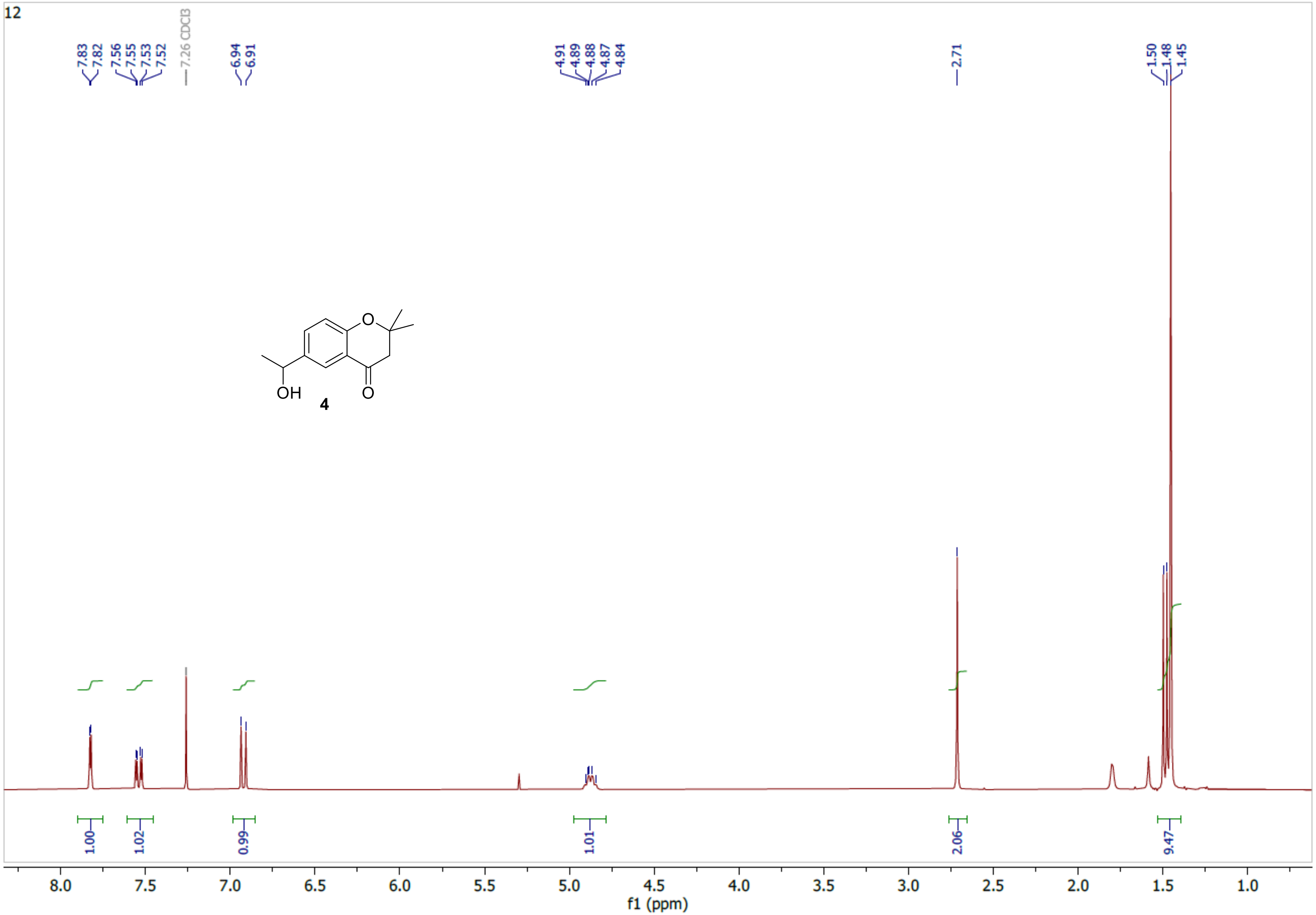
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1.48
1.45
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OH
O
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1.01
2.06
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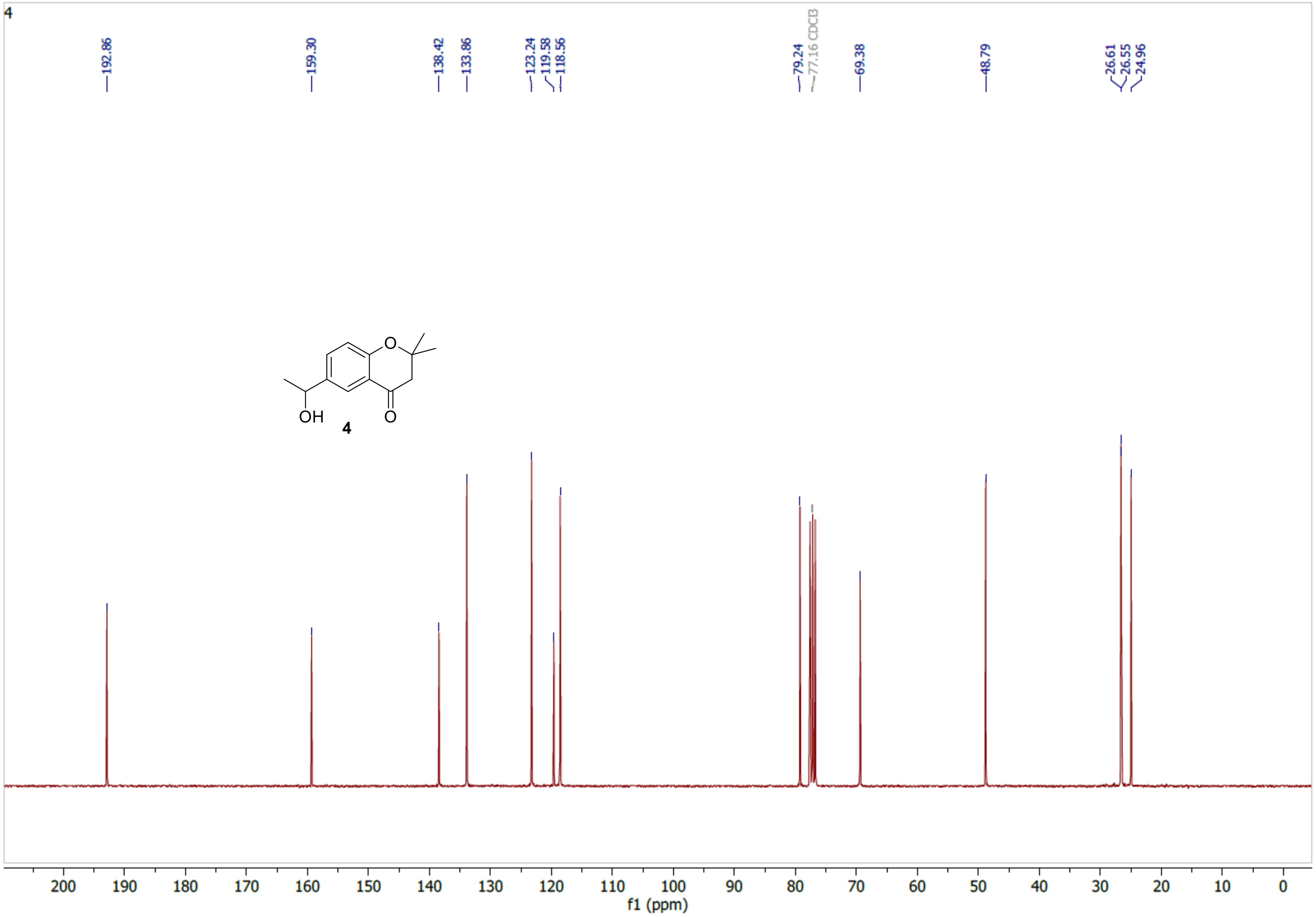
1.0
f1 (ppm)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26.55
24.96
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OH
O
4
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180
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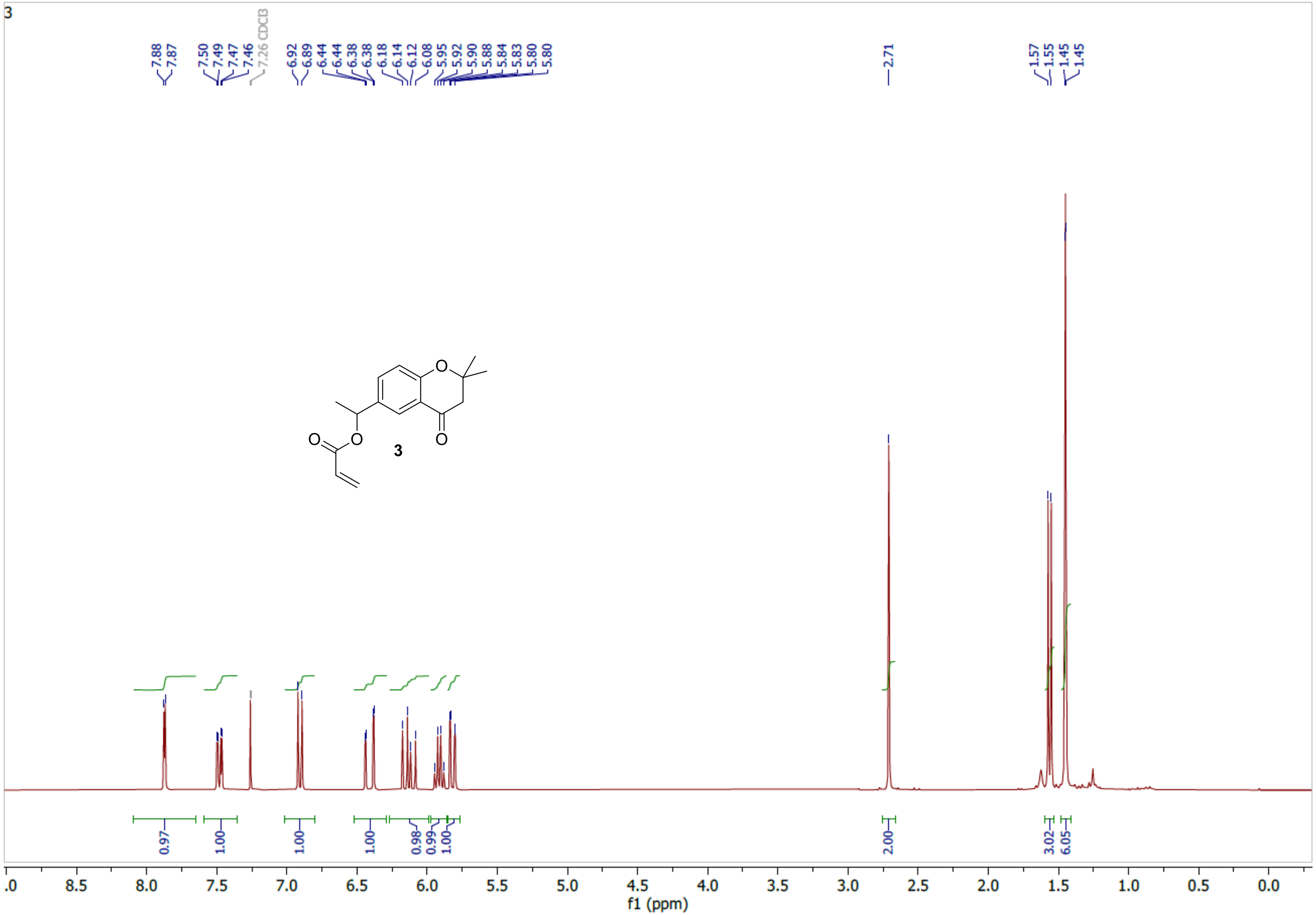
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5.80
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1.55
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1.45
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O
O
O
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1.00
1.00
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0.99
1.00
2.00
3.02
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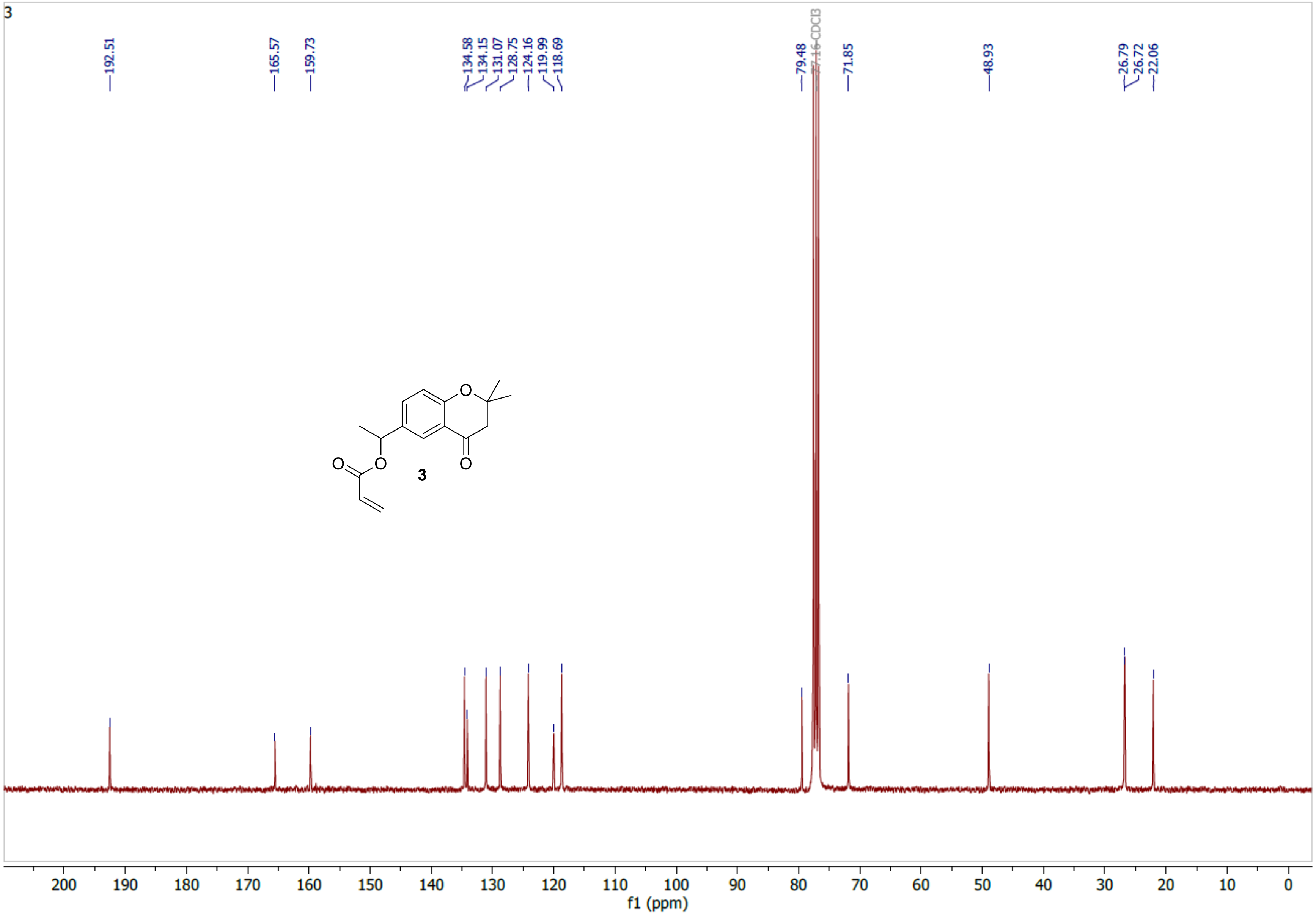
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48.93
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26.72
22.06
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O
O
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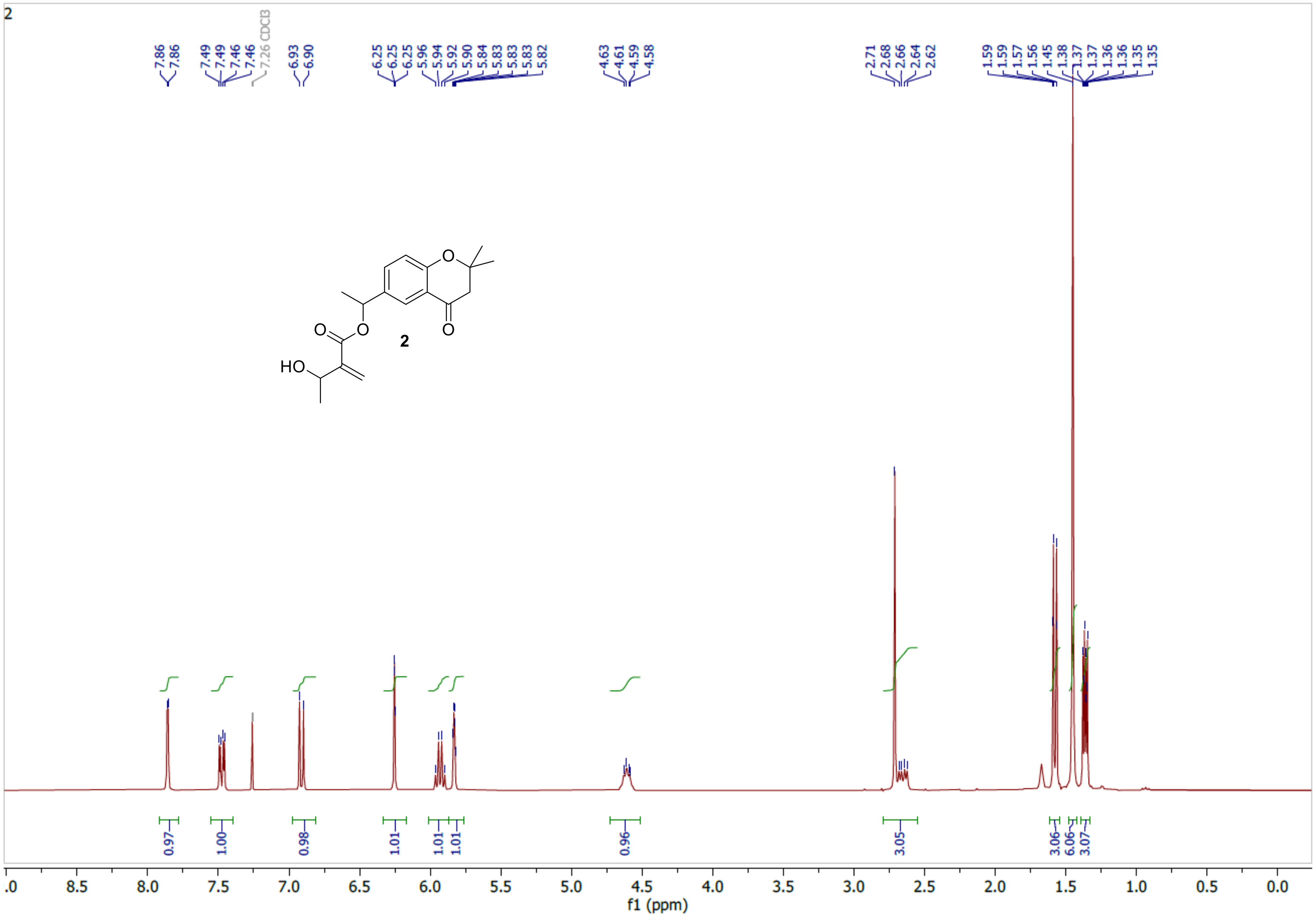
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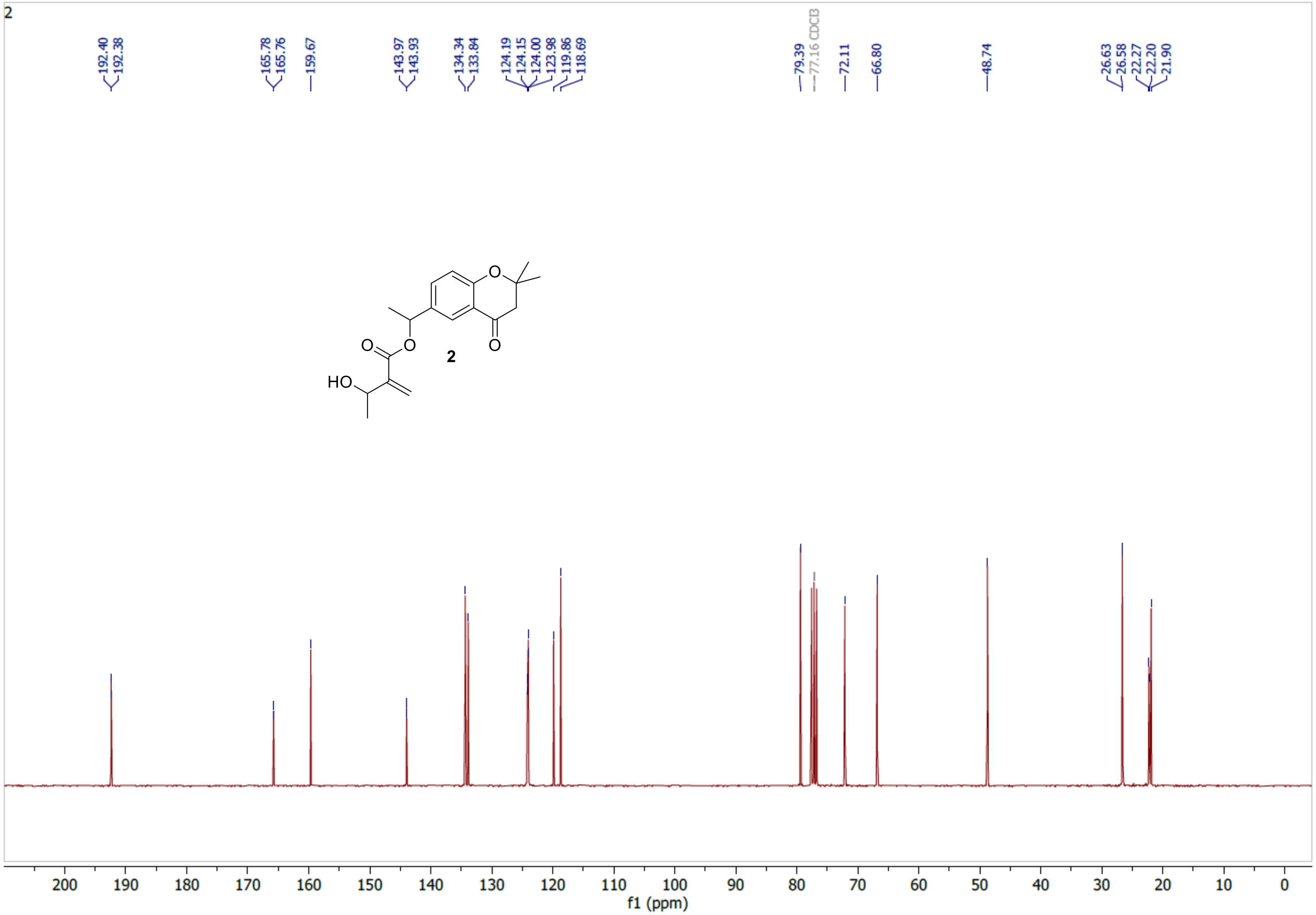
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26.58
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21.90
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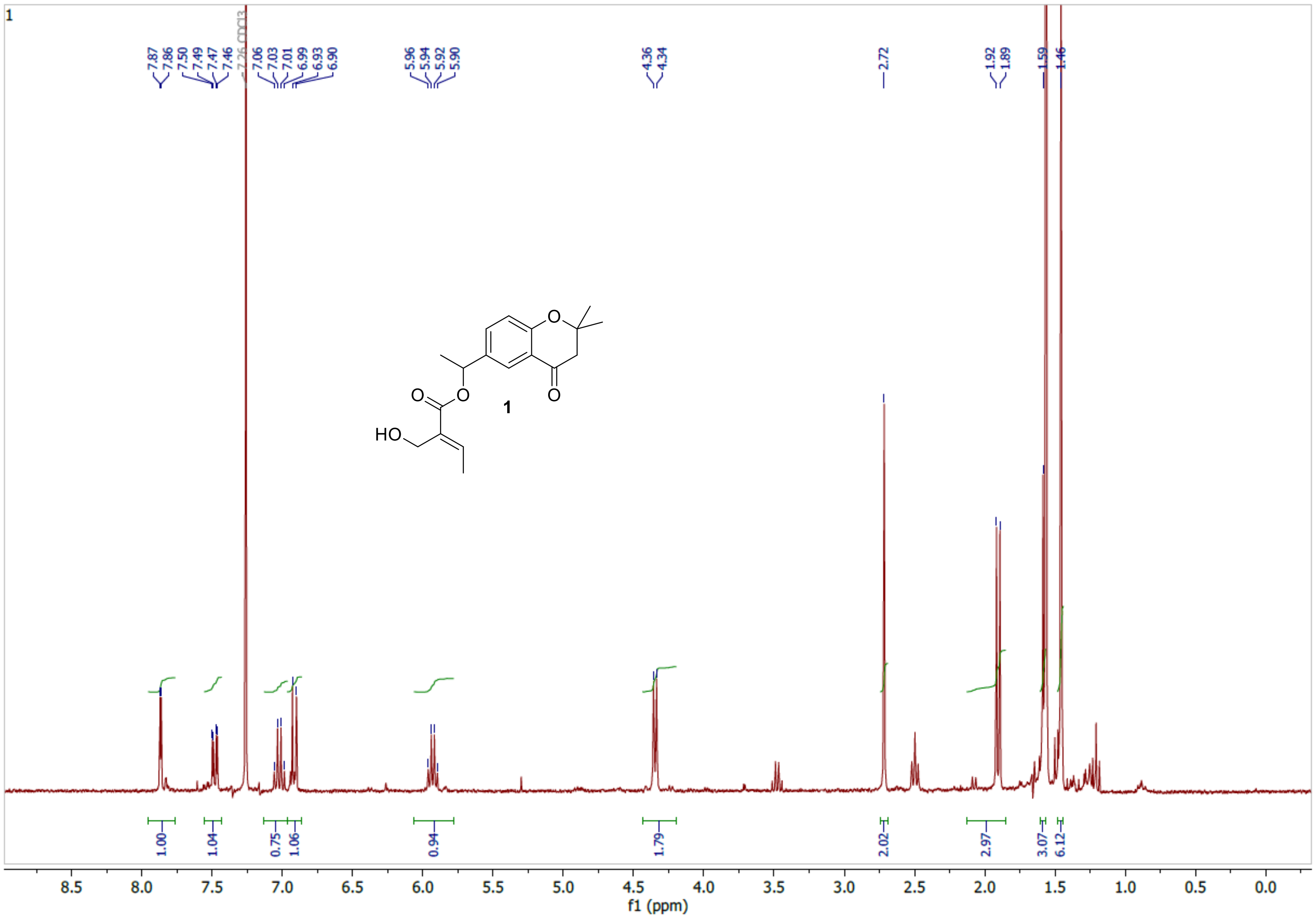
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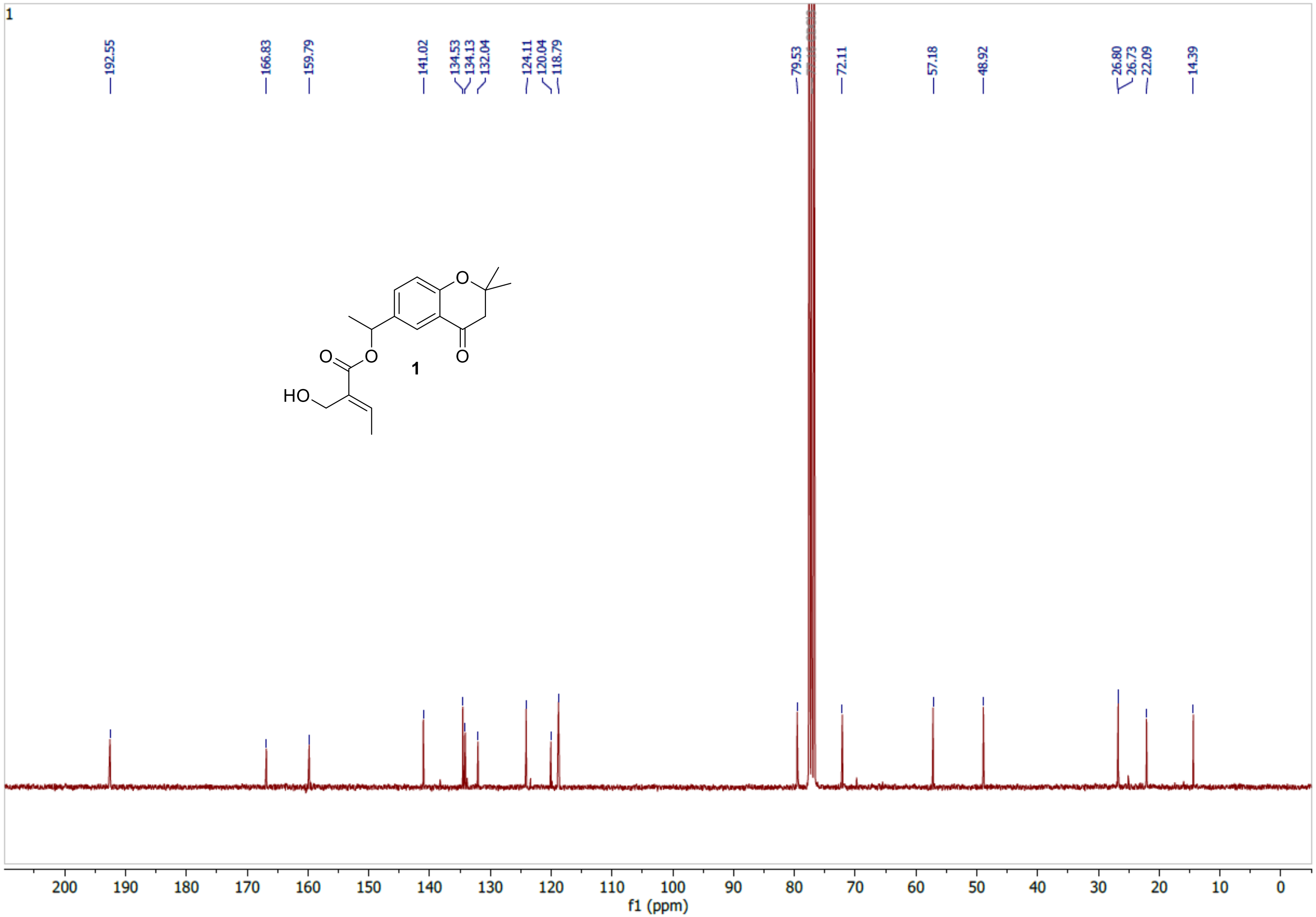
f1 (ppm)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O
O
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200
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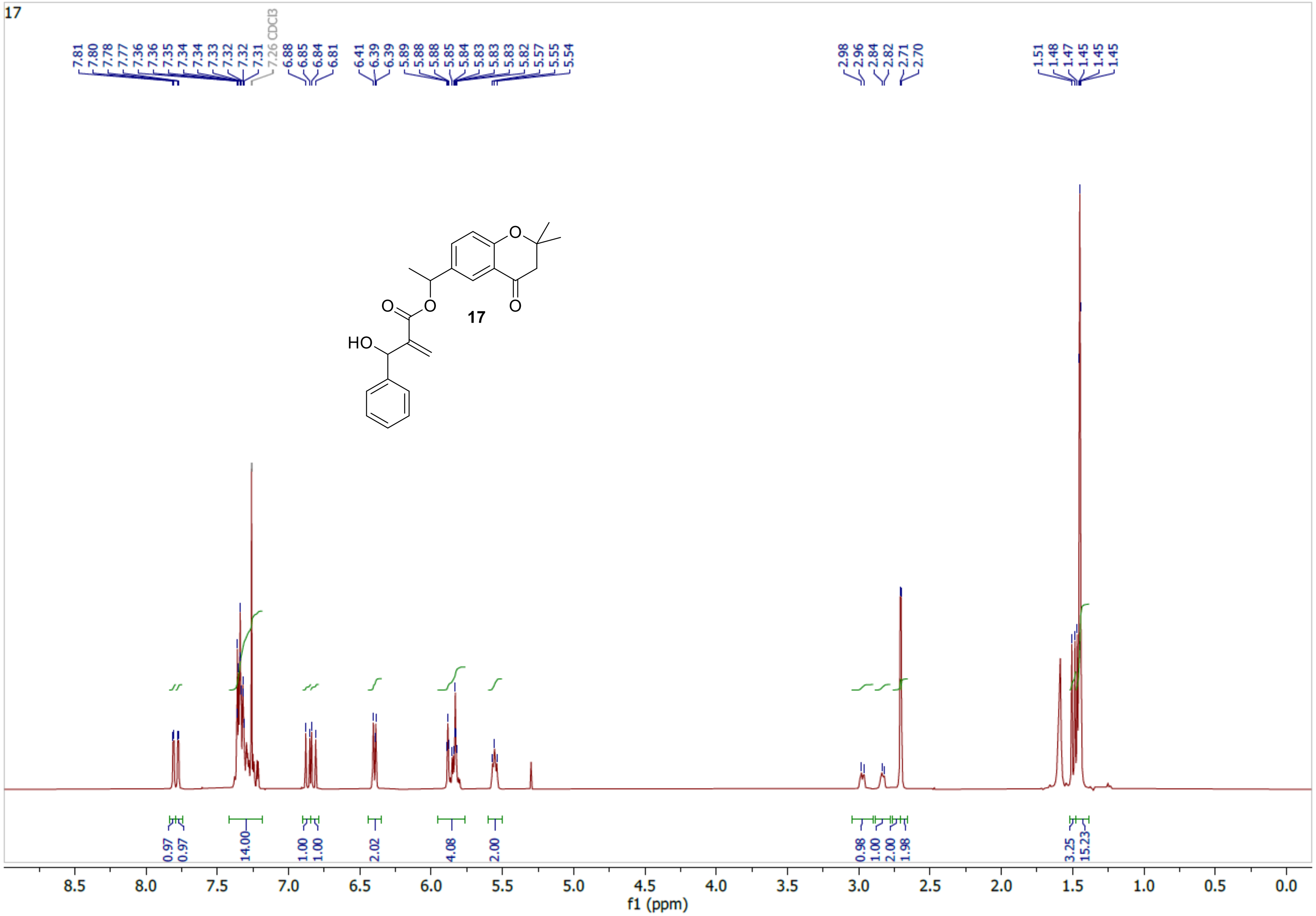
17



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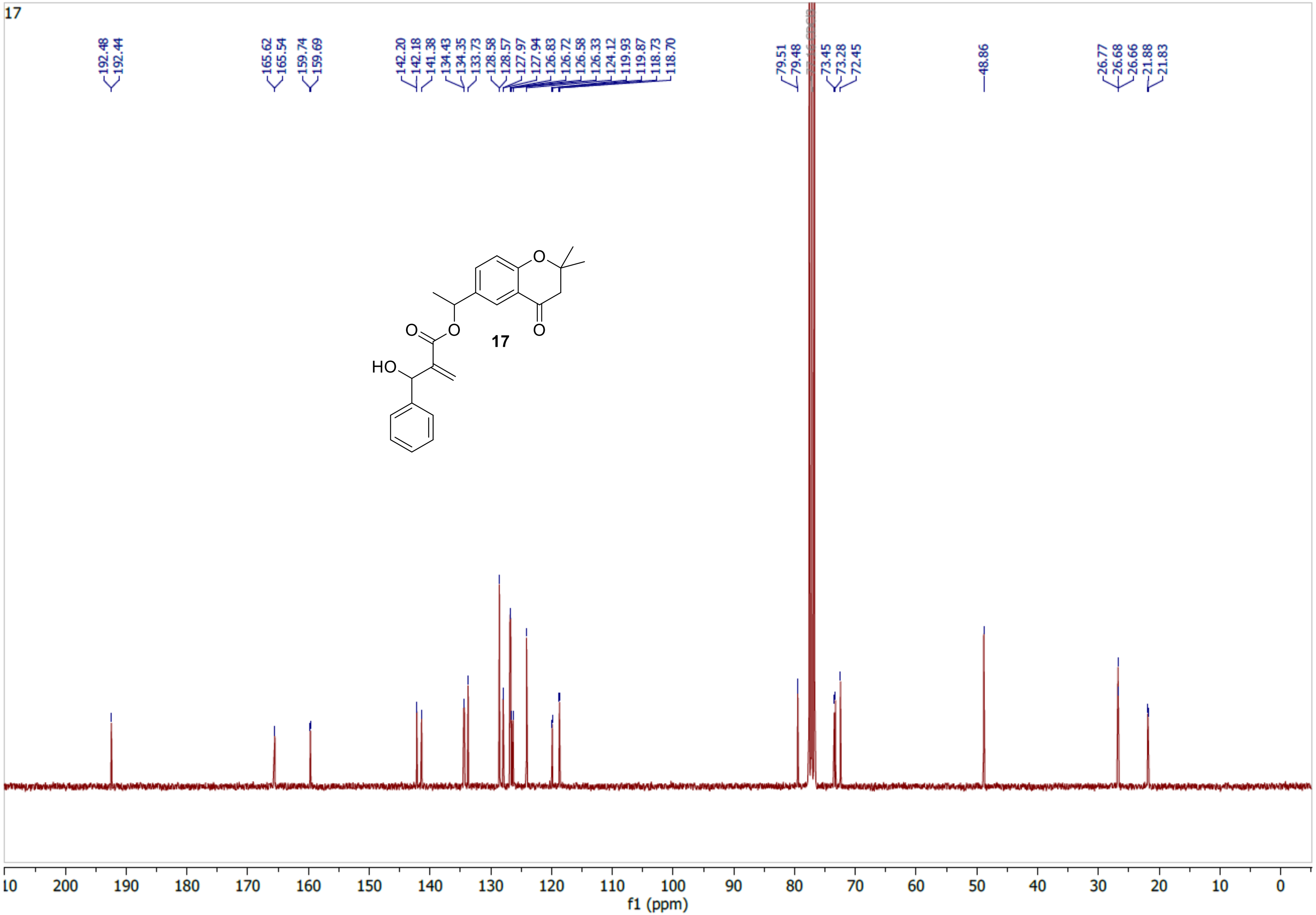
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128.57
127.97
127.94
126.83
126.72
126.58
126.33
124.12
119.93
119.87
118.73
118.70
79.51
79.48
77.16 CDCl3
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73.28
72.45
48.86
26.77
26.68
26.66
21.88
21.83
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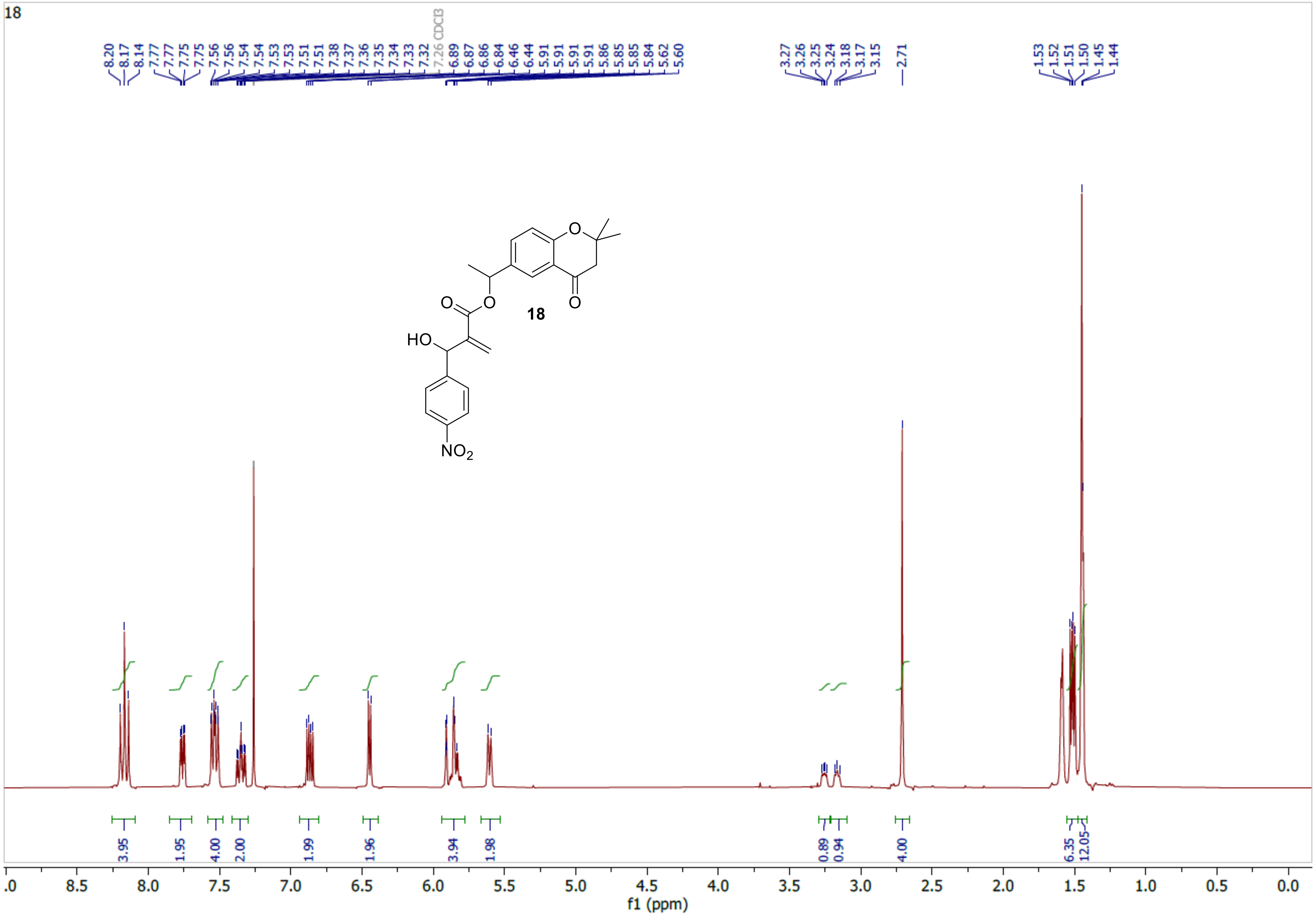
18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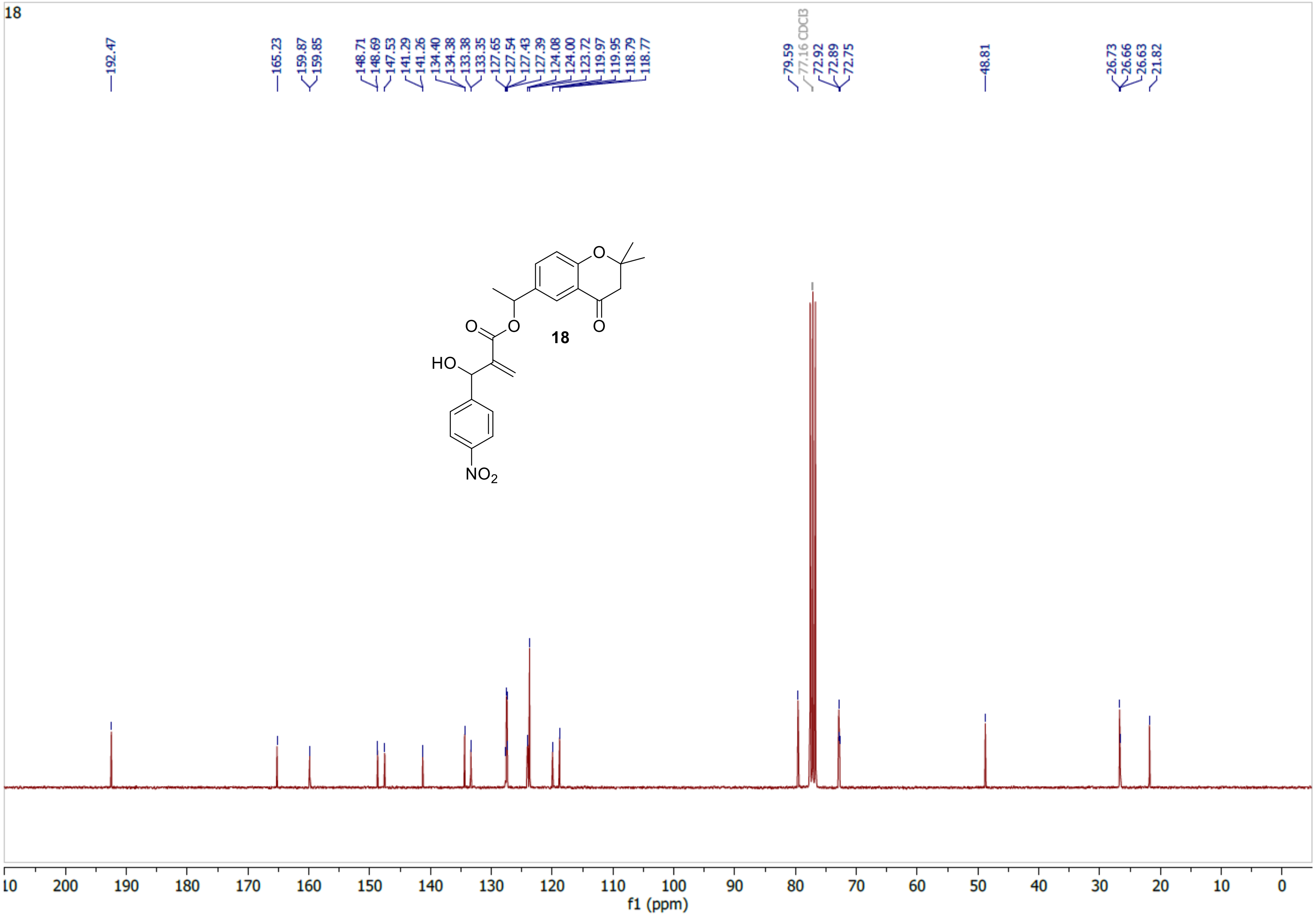
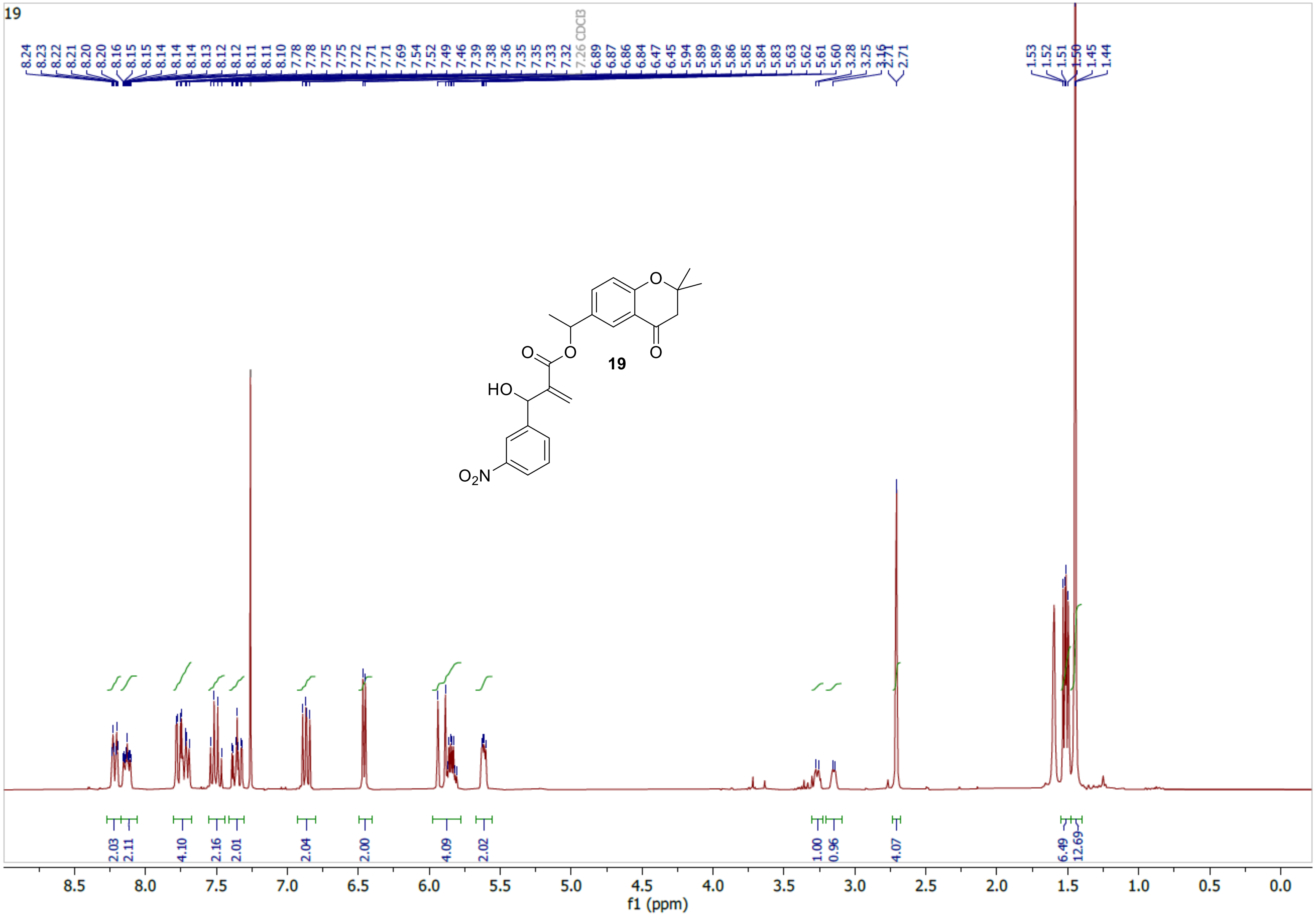
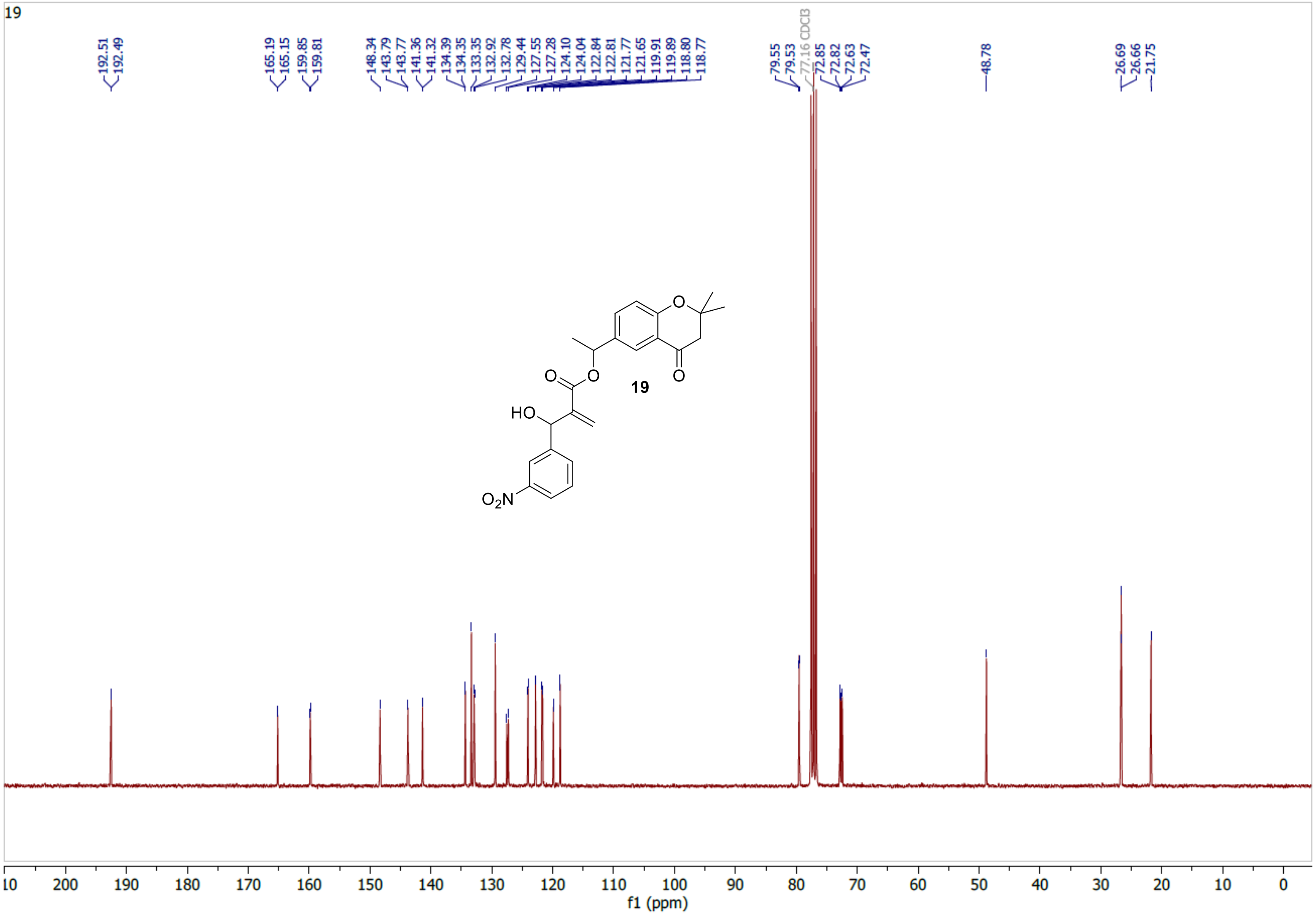
7.33
7.32
7.26 CDCl3
6.89
6.87
6.86
6.84
6.46
6.44
5.91
5.91
5.91
5.91
5.86
5.85
5.85
5.84
5.62
5.60
3.27
3.26
3.25
3.24
3.18
3.17
3.15
2.71
1.53
1.52
1.51
1.50
1.45
1.44
HO
O
O
O
O
NO2
18
3.95
1.95
4.00
2.00
1.99
1.96
3.94
1.98
0.89
0.94
4.00
6.35
12.05
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

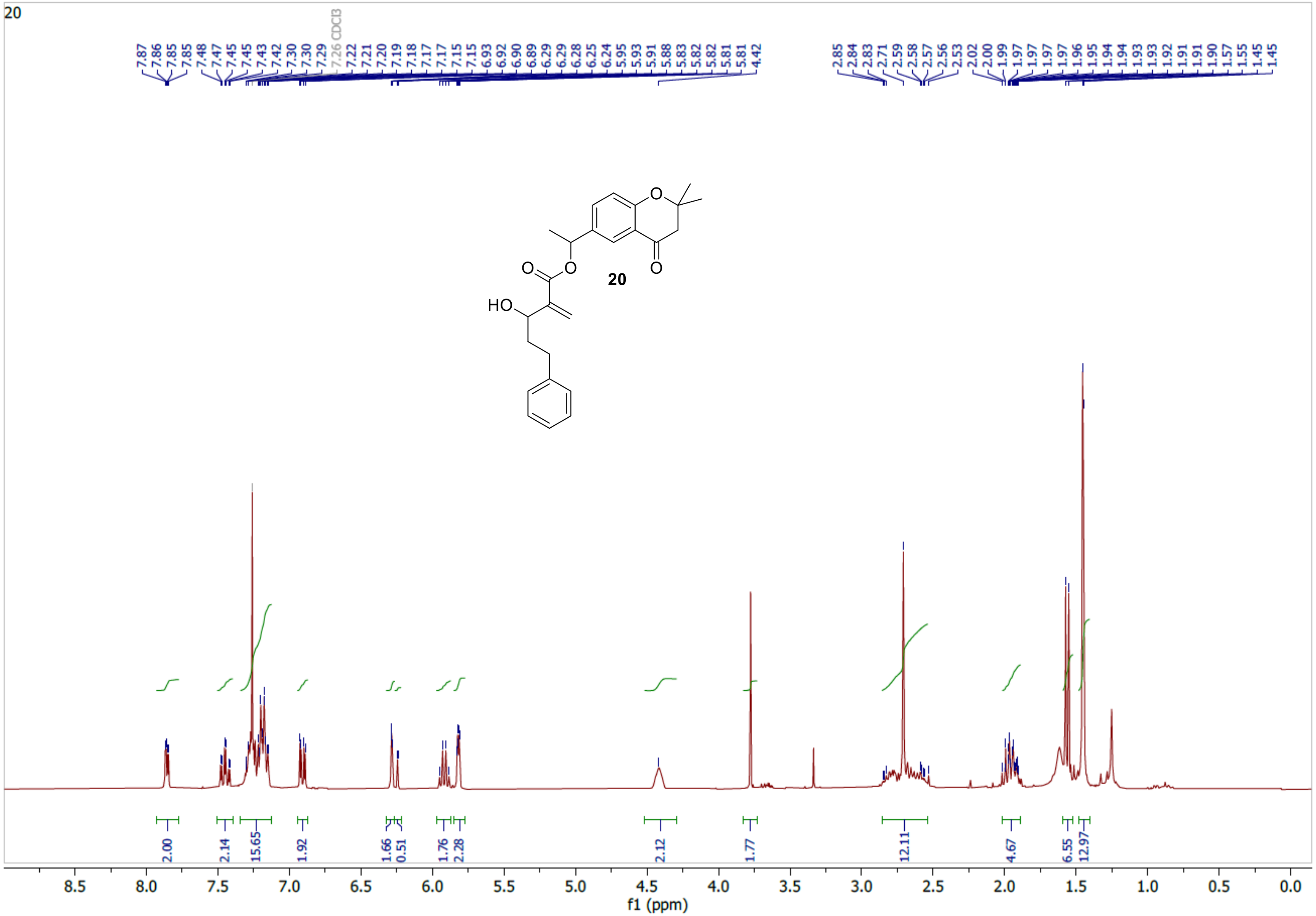

18
192.47
165.23
159.87
159.85
148.71
148.69
147.53
141.29
141.26
134.40
134.38
133.38
133.35
127.65
127.54
127.43
127.39
124.08
124.00
123.72
119.97
119.95
118.79
118.77
79.59
77.16 CDCl3
72.92
72.89
72.75
48.81
26.73
26.66
26.63
21.82
HO
O
O
O
O
NO2
18
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

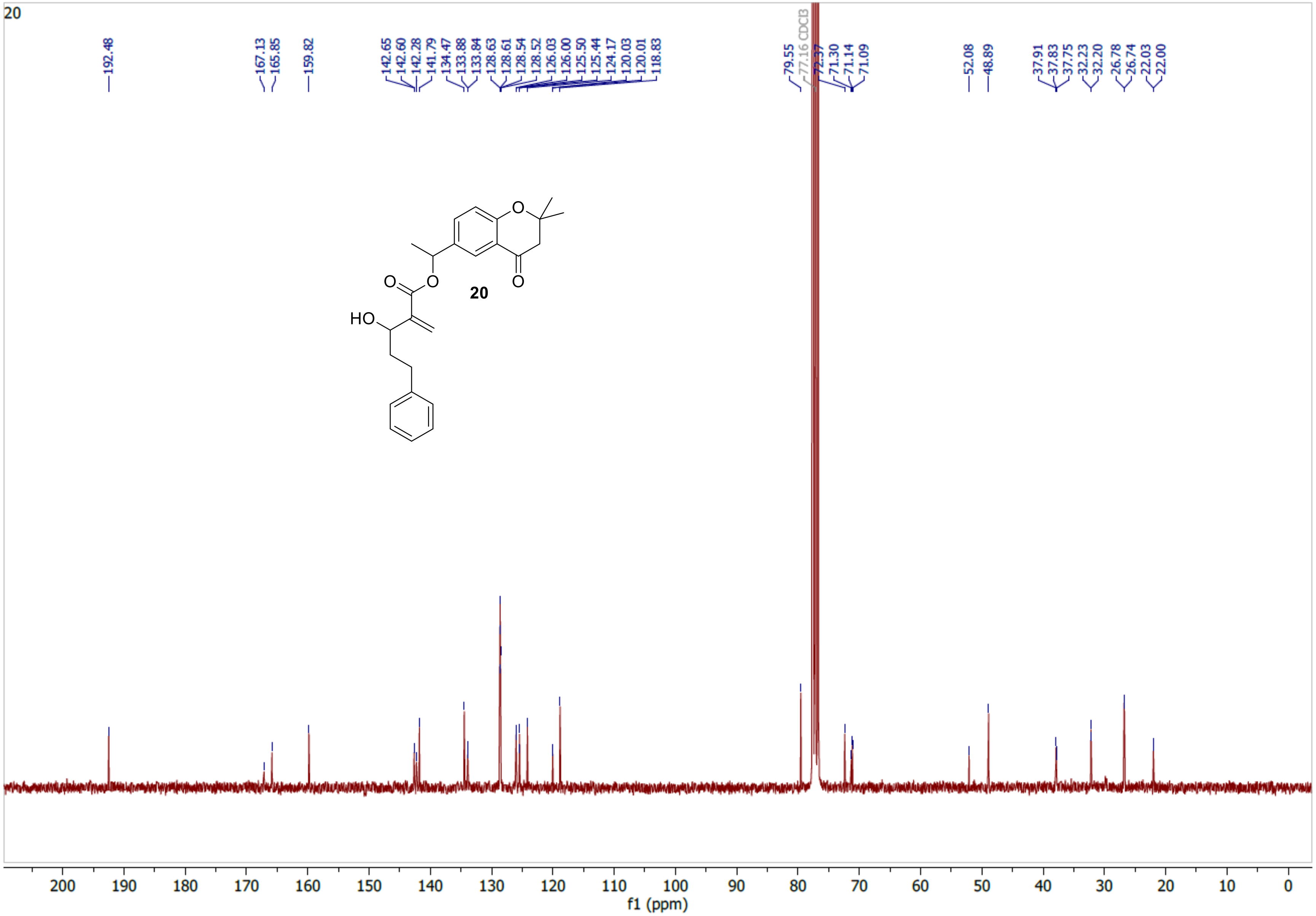
19

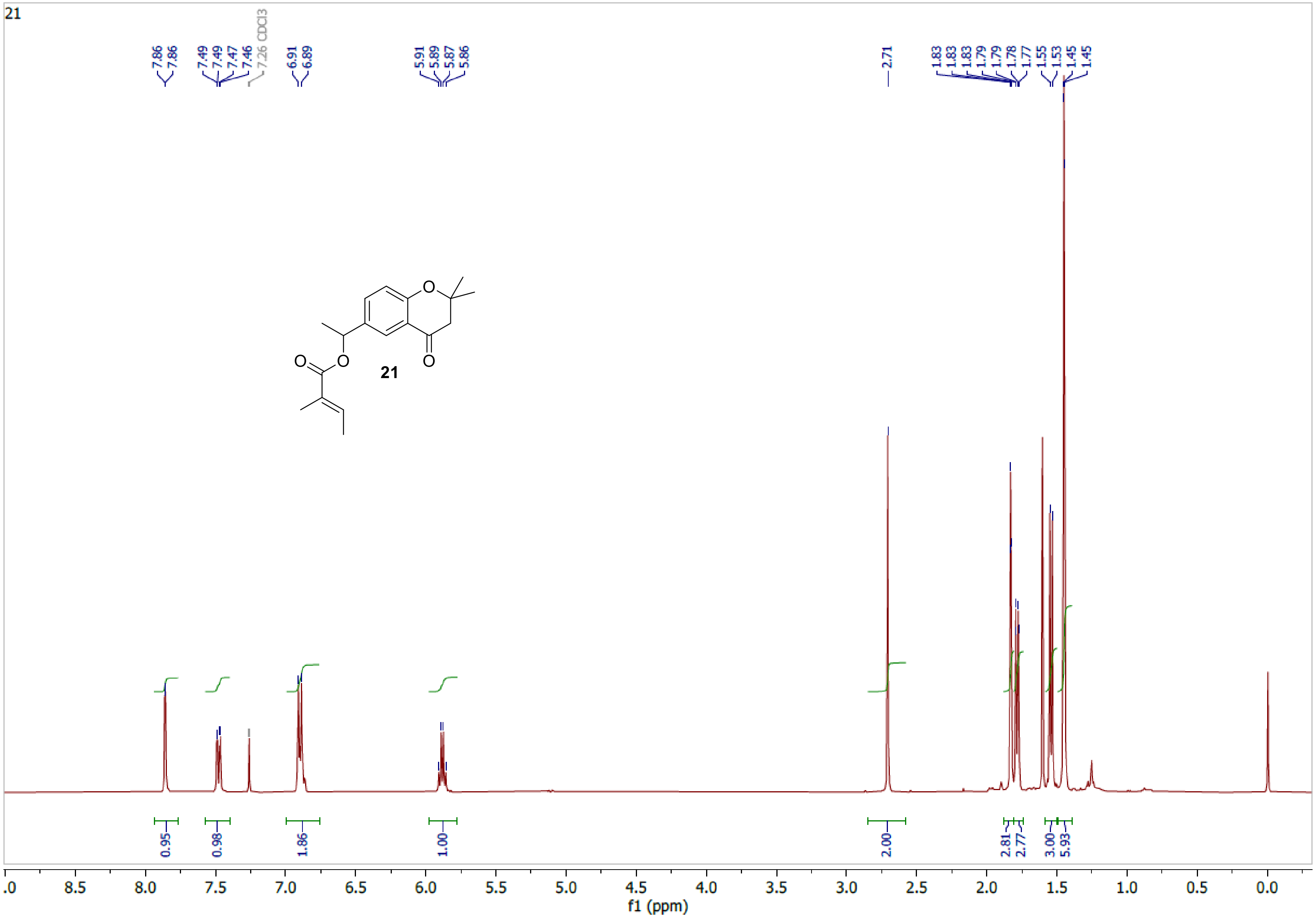

8.24
8.23
8.22
8.21
8.20
8.16
8.15
8.14
8.14
8.14
8.13
8.12
8.12
8.11
8.11
8.10
7.78
7.78
7.75
7.75
7.72
7.71
7.71
7.69
7.54
7.52
7.49
7.46
7.39
7.38
7.36
7.35
7.35
7.33
7.32
7.26 CDCl3
6.89
6.87
6.86
6.84
6.47
6.45
5.94
5.89
5.89
5.86
5.85
5.84
5.83
5.63
5.62
5.61
5.60
3.28
3.25
3.16
2.71
2.71
1.53
1.52
1.51
1.50
1.45
1.44
HO
O
O
O
O
O_2N
19
2.03
2.11
4.10
2.16
2.01
2.04
2.00
4.09
2.02
1.00
0.96
4.07
6.49
12.69
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)


19
192.51
192.49
165.19
165.15
159.85
159.81
148.34
143.79
143.77
141.36
141.32
134.39
134.35
133.35
132.92
132.78
129.44
127.55
127.28
124.10
124.04
122.84
122.81
121.77
121.65
119.91
119.89
118.80
118.77
79.55
79.53
77.16 CDCl3
72.85
72.82
72.63
72.47
48.78
26.69
26.66
21.75
HO
O
O
O
O
O_2N
19
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

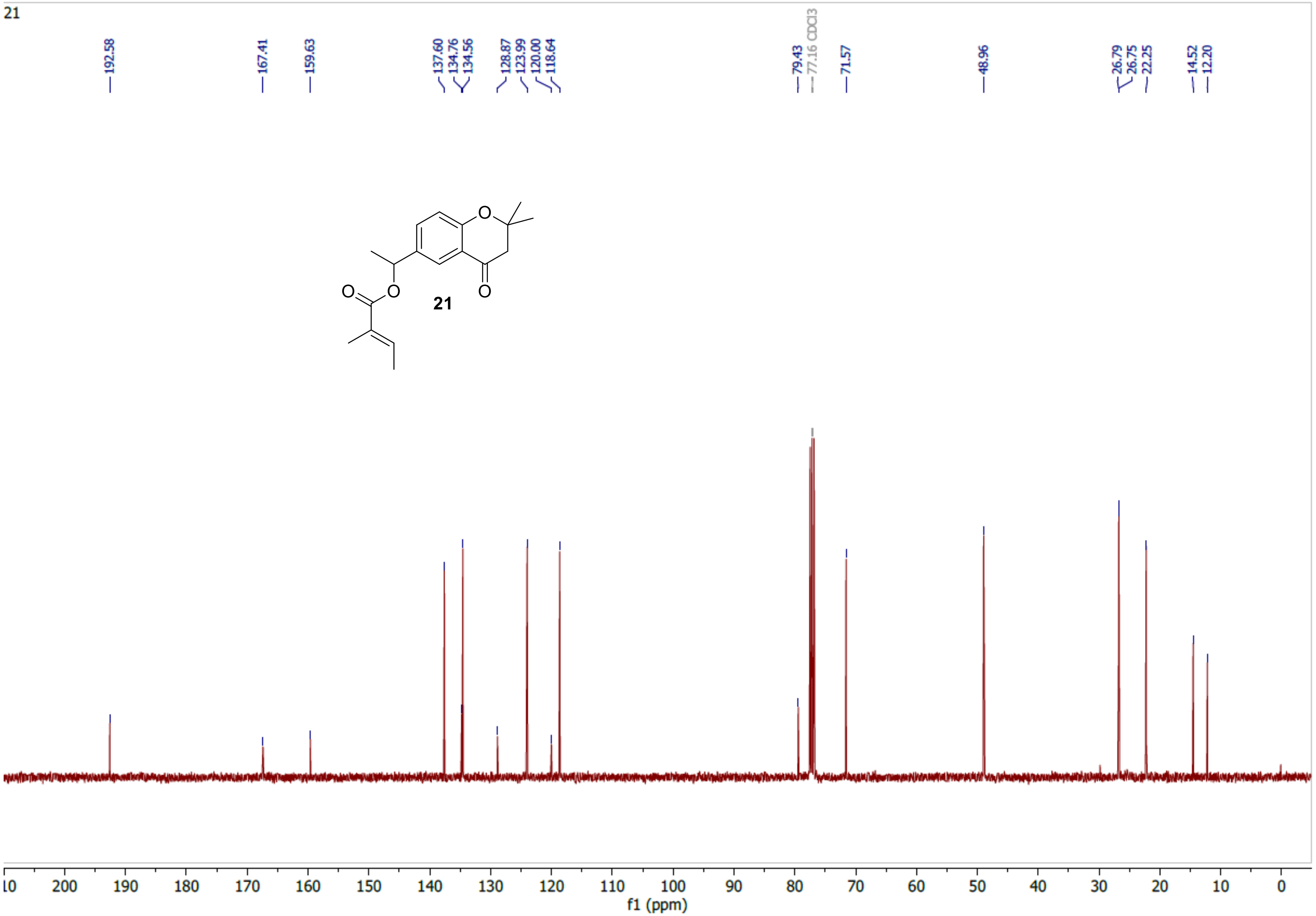
20


7.87
7.86
7.85
7.85
7.48
7.47
7.45
7.45
7.43
7.42
7.30
7.30
7.29
7.26 CDCl3
7.22
7.21
7.20
7.19
7.18
7.17
7.17
7.15
7.15
6.93
6.92
6.90
6.89
6.29
6.29
6.28
6.25
6.24
5.95
5.93
5.91
5.88
5.83
5.82
5.82
5.81
5.81
4.42
2.85
2.84
2.83
2.71
2.59
2.58
2.57
2.56
2.53
2.02
2.00
1.99
1.97
1.97
1.97
1.97
1.96
1.95
1.94
1.94
1.93
1.93
1.92
1.91
1.91
1.90
1.57
1.55
1.45
1.45
HO
O
O
O
O
O
20
2.00
2.14
15.65
1.92
1.66
0.51
1.76
2.28
2.12
1.77
12.11
4.67
6.55
12.97
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)


20
192.48
167.13
165.85
159.82
142.65
142.60
142.28
141.79
134.47
133.88
133.84
128.63
128.61
128.54
128.52
126.03
126.00
125.50
125.44
124.17
120.03
120.01
118.83
79.55
77.16 CDCl3
72.37
71.30
71.14
71.09
52.08
48.89
37.91
37.83
37.75
32.23
32.20
26.78
26.74
22.03
22.00
O
O
O
O
HO
20
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


21
7.86
7.86
7.49
7.49
7.47
7.46
7.26 CDCl3
6.91
6.89
5.91
5.89
5.87
5.86
2.71
1.83
1.83
1.83
1.79
1.79
1.78
1.77
1.55
1.53
1.45
1.45
O
O
O
O
21
0.95
0.98
1.86
1.00
2.00
2.81
2.77
3.00
5.93
.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)

21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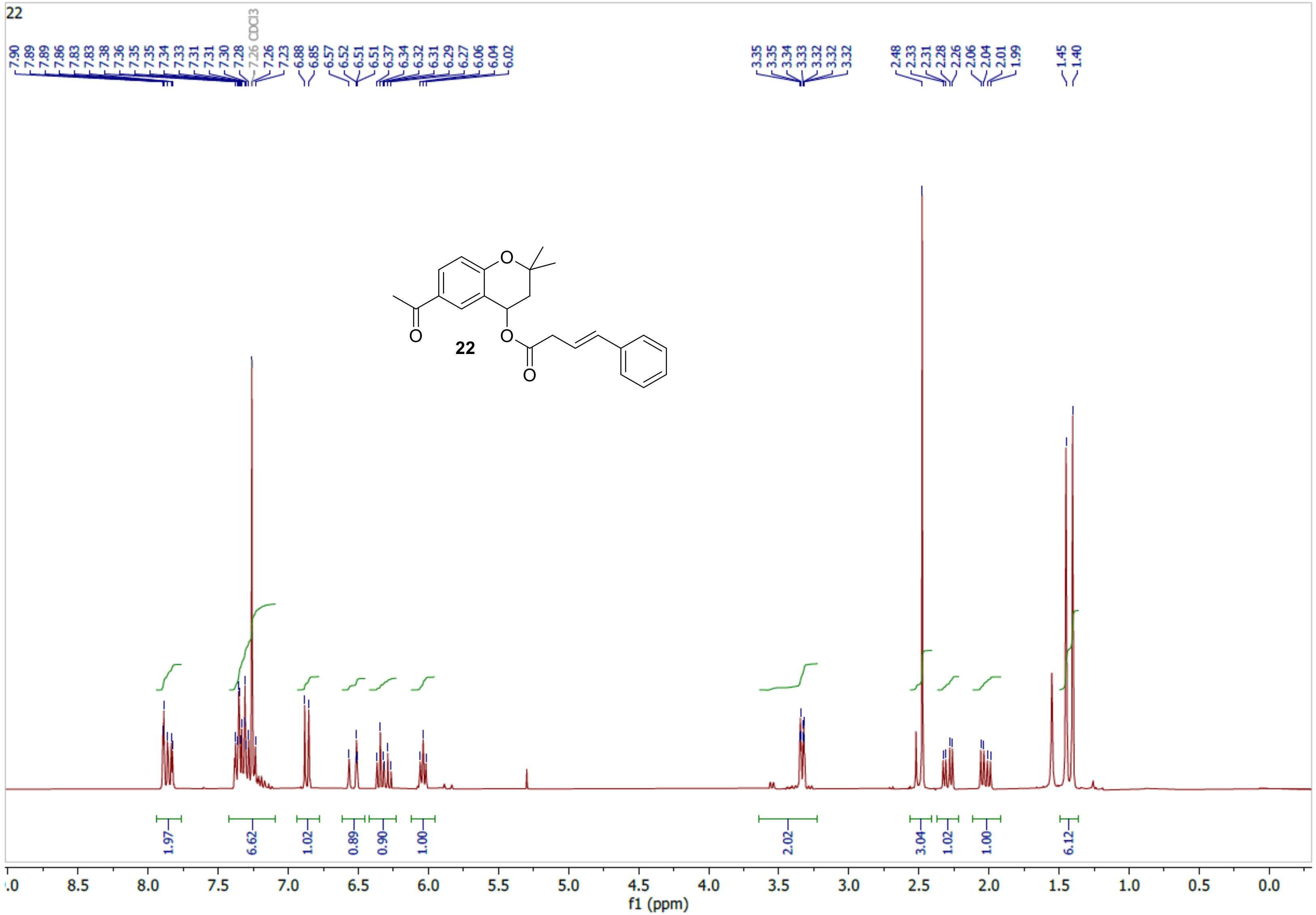
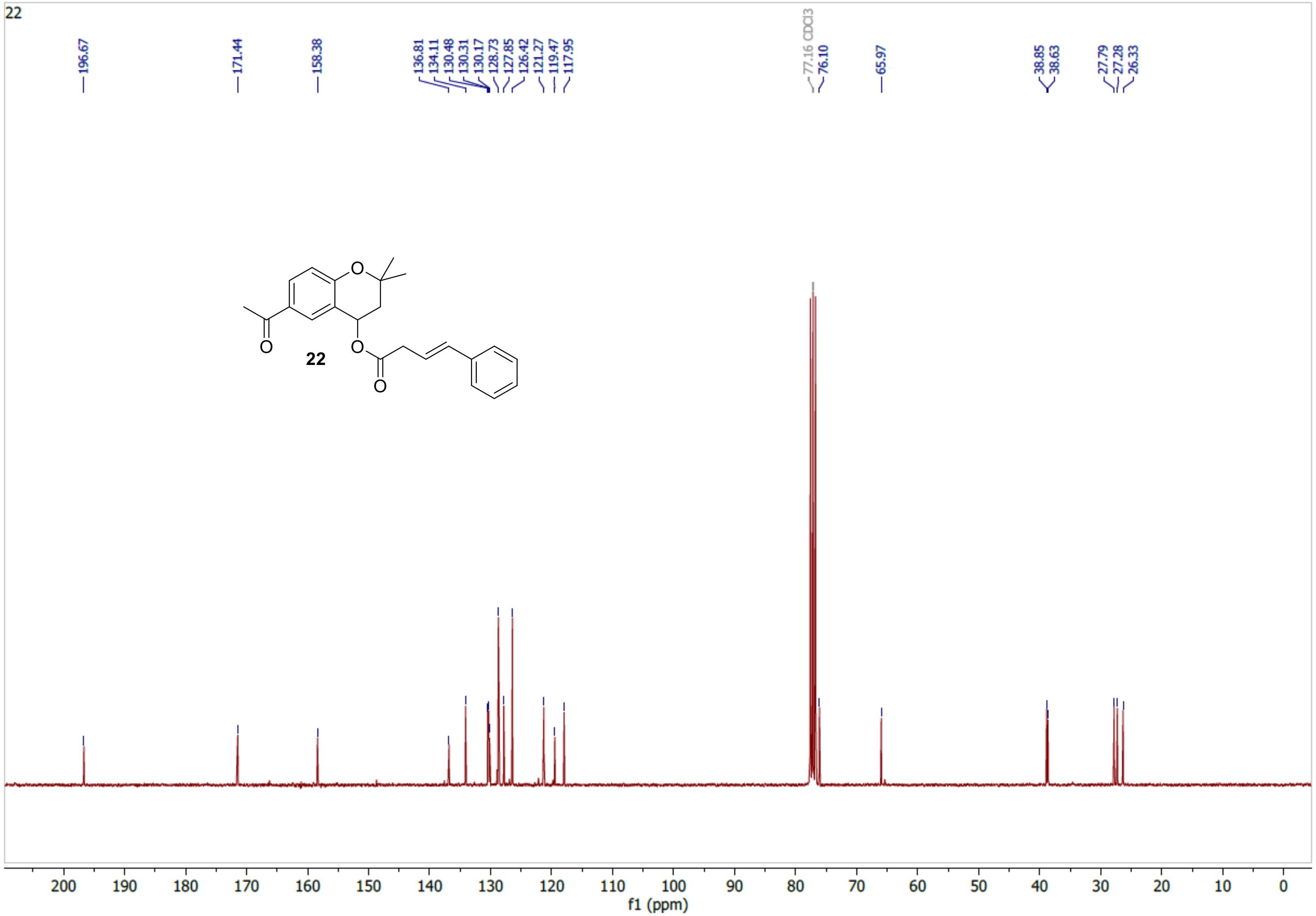
167.41
159.63
137.60
134.76
134.56
128.87
123.99
120.00
118.64
79.43
77.16 CDCl3
71.57
48.96
26.79
26.75
22.25
14.52
12.20
O
O
O
O
21
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


22
7.90
7.89
7.89
7.86
7.83
7.83
7.38
7.36
7.35
7.35
7.34
7.33
7.31
7.31
7.30
7.28
7.26 CDCl3
7.26
7.23
6.88
6.85
6.57
6.52
6.51
6.51
6.37
6.34
6.32
6.31
6.29
6.27
6.06
6.04
6.02
3.35
3.35
3.34
3.33
3.32
3.32
3.32
2.48
2.33
2.31
2.28
2.26
2.06
2.04
2.01
1.99
1.45
1.40
O
O
O
O
22
1.97
6.62
1.02
0.89
0.90
1.00
2.02
3.04
1.02
1.00
6.12
.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)


22
196.67
171.44
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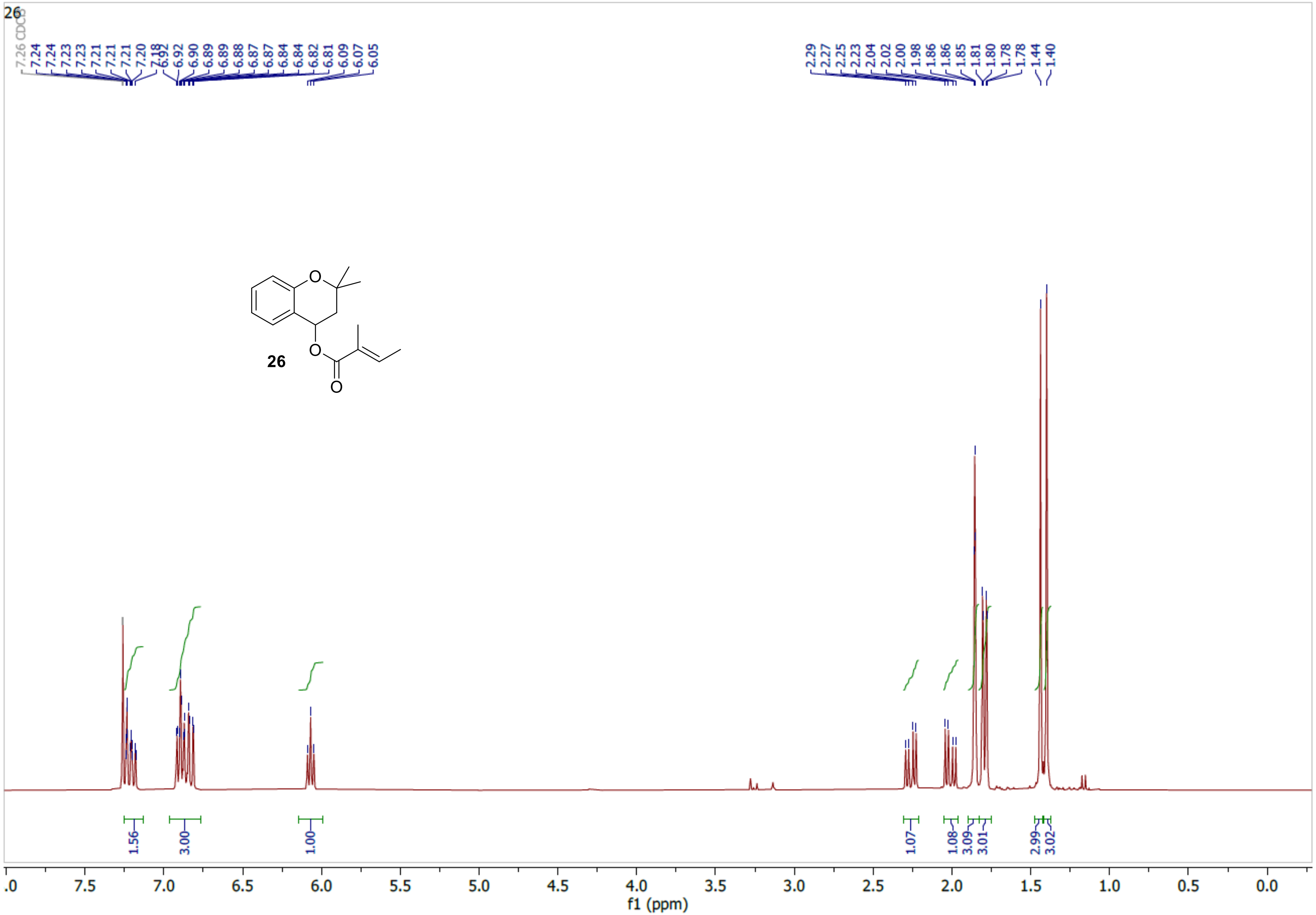
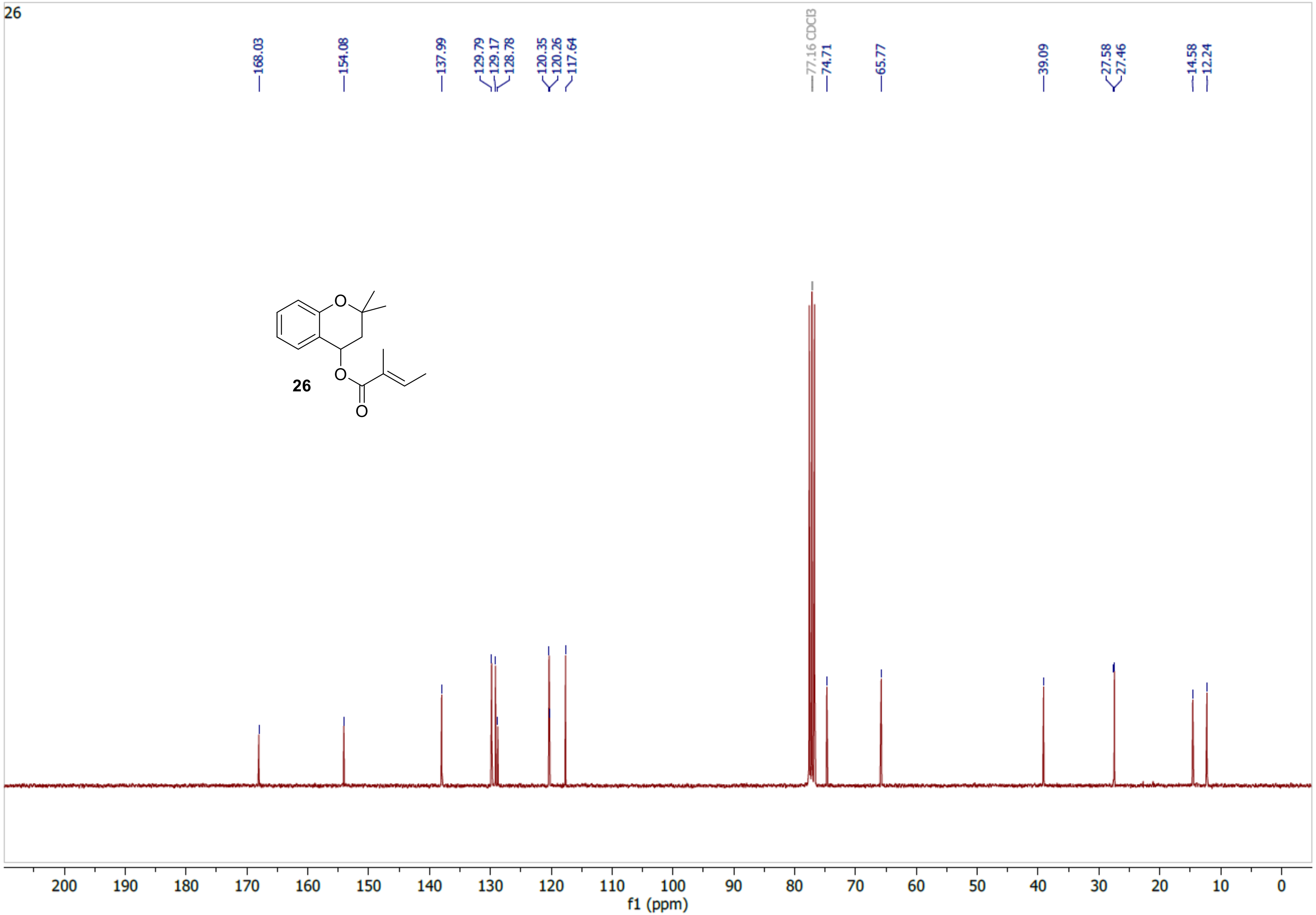
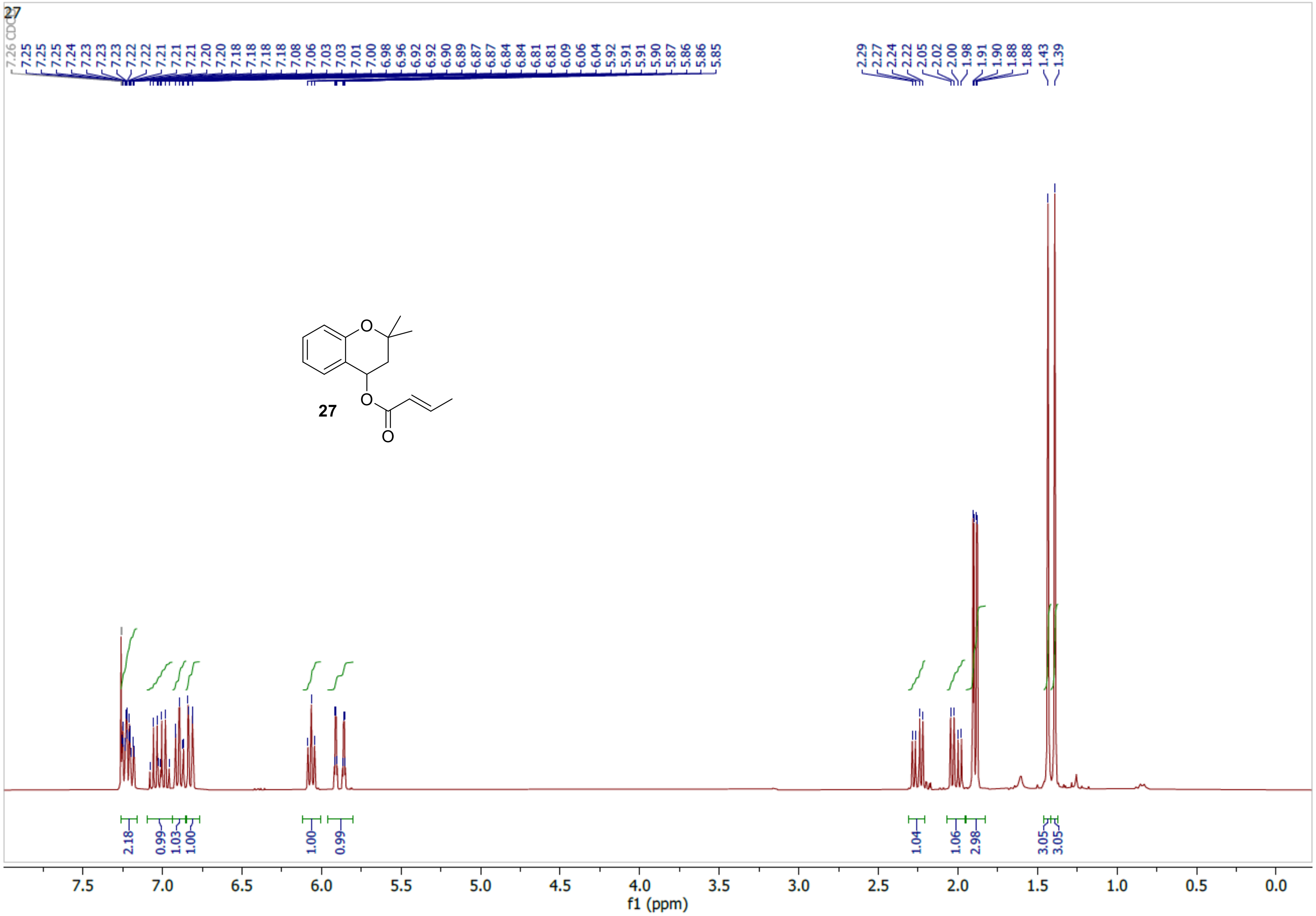
134.11
130.48
130.31
130.17
128.73
127.85
126.42
121.27
119.47
117.95
77.16 CDCl3
76.10
65.97
38.85
38.63
27.79
27.28
26.33
O
O
O
O
22
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


26
7.26 CDCl3
7.24
7.24
7.23
7.23
7.21
7.21
7.21
7.20
7.18
6.92
6.92
6.90
6.89
6.89
6.88
6.87
6.87
6.84
6.84
6.82
6.81
6.09
6.07
6.05
2.29
2.27
2.25
2.23
2.04
2.02
2.00
1.98
1.86
1.86
1.85
1.81
1.80
1.78
1.44
1.40
O
O
O
26
1.56
3.00
1.00
1.07
1.08
3.09
3.01
2.99
3.02
.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)


26
168.03
154.08
137.99
129.79
129.17
128.78
120.35
120.26
117.64
77.16 CDCl3
74.71
65.77
39.09
27.58
27.46
14.58
12.24
O
O
O
26
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


27
7.26 CDCl3
7.25
7.25
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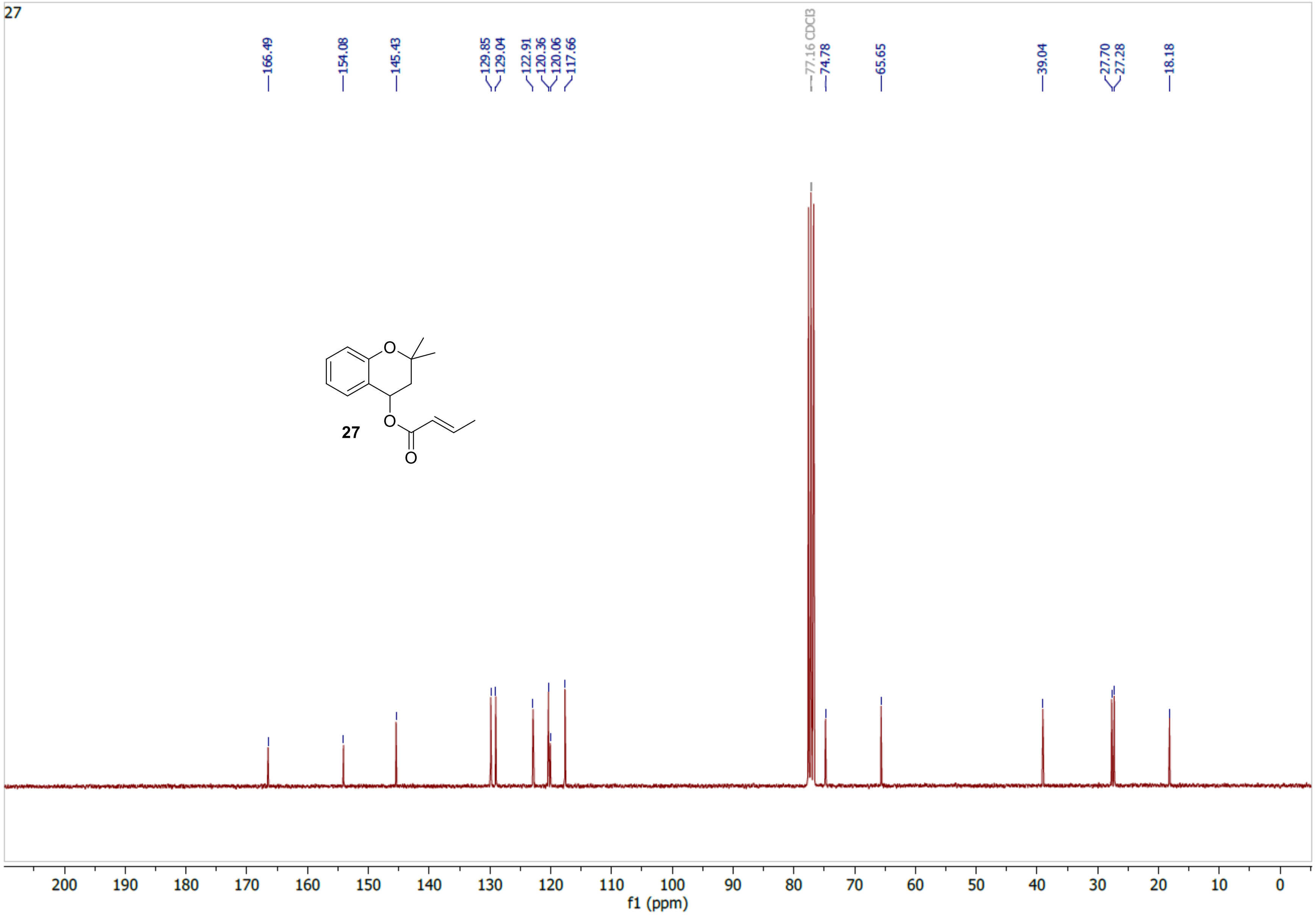
7.24
7.23
7.23
7.23
7.22
7.22
7.21
7.21
7.21
7.20
7.20
7.18
7.18
7.18
7.08
7.06
7.03
7.03
7.01
7.00
6.98
6.96
6.92
6.92
6.90
6.89
6.87
6.87
6.84
6.84
6.81
6.81
6.09
6.06
6.04
5.92
5.91
5.91
5.90
5.87
5.86
5.86
5.85
2.29
2.27
2.24
2.22
2.05
2.02
2.00
1.98
1.91
1.90
1.88
1.88
1.43
1.39
O
O
O
27
2.18
0.99
1.03
1.00
1.00
0.99
1.04
1.06
2.98
3.05
3.05
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)


27
166.49
154.08
145.43
129.85
129.04
122.91
120.36
120.06
117.66
77.16 CDCl3
74.78
65.65
39.04
27.70
27.28
18.18
O
O
O
27
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)