

Supplementary Materials

Synthesis and Biological Evaluation of α -Tocopherol Derivatives as Potential Anticancer Agents

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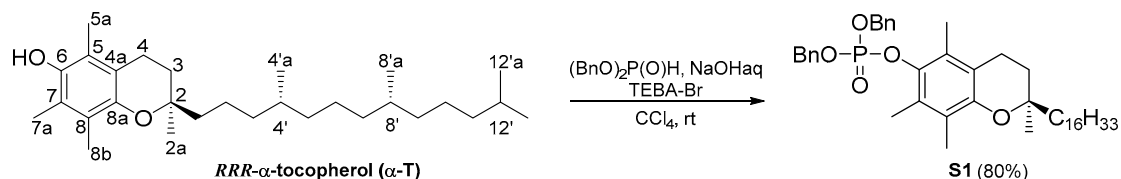
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1. Experimental procedures for the preparation of α -tocopheryl phosphate (α -TP)

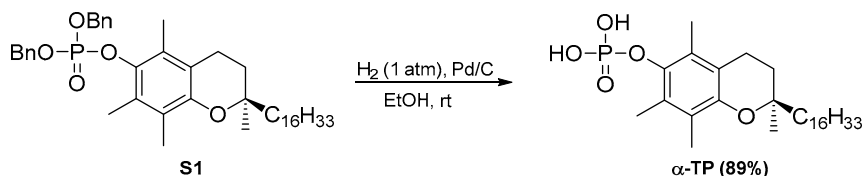
1.1. Synthesis of compound **S1**



TEBA-Br (28 mg) and 50% aqueous NaOH solution (0.9 mL) were added to a stirred solution of α -T (1.29 g, 3 mmol) in CCl_4 (6 mL) at room temperature. After 10 min the solution of dibenzyl phosphite (1.069 g, 4.08 mmol, 1.36 eq) in CCl_4 (7.5 mL) was added dropwise, and stirring was continued for 36 hours. Next, to the reaction mixture was added dichloromethane (20 mL) and it was washed with 2% hydrochloric acid, and water, dried over anhydrous Na_2SO_4 , and concentrated under vacuum. The crude product was purified using FC (hexane/ethyl acetate, 7:1, v/v) to give product **S1** as a colorless oil (1.655 g, 80% yield).

S1: $^{31}\text{P}\{^1\text{H}\}$ NMR (160 MHz, CDCl_3) δ -4.51 ppm; ^1H NMR (200 MHz, CDCl_3) δ 7.34–7.30 (m, 10H, H-Ar), 5.10 (d, J = 8.0 Hz, 4H, CH_2Ph), 2.56 (t, J = 6.8 Hz, 2H, H-4), 2.20 (s, 3H, H-8b), 2.17 (s, 3H, H-7a), 2.08 (s, 3H, H-5a), 1.83–1.72 (m, 2H, H-3), 1.30–1.02 (m, 24H, H-2a, H-1'–H-12'), 0.91–0.85 (m, 12H, H-4'a, H-8'a, H-12'a, H-13') ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 148.8 (C-8a), 140.7 (C-6), 135.9 (C_{Ar}), 135.8 (C_{Ar}), 128.42, 128.35, 127.8 (10 x CH_{Ar}), 127.1 (C-7), 125.3 (C-5), 123.2 (C-8), 117.6 (C-4a), 74.9 (C-2), 69.7 (CH_2Ph), 69.6 (CH_2Ph), 40.0 (C-1'), 39.3 (C-11'), 37.4 (C-3'), 37.4 (C-9'), 37.3 (C-5', C-7'), 32.8 (C-8'), 32.7 (C-4'), 31.2 (C-3), 27.9 (C-12'), 24.8 (C-10'), 24.4 (C-6'), 23.8 (C-2a), 22.7 (C-12'a), 22.6 (C-13'), 21.0 (C-2'), 20.7 (C-4), 19.7 (C-8'a), 19.6 (C-4'a), 13.8 (C-7a), 13.0 (C-8b), 11.8 (C-5a) ppm; IR (KBr) ν_{max} 3051, 3029, 2923, ~2000–1600 (aromatic overtones), 1457, 1278, 964, 741 cm^{-1} ; HRMS (ESI) m/z 713.4309 (calcd for $\text{C}_{43}\text{H}_{63}\text{NaO}_5\text{P}^+$ [$\text{M}+\text{Na}$] $^+$ 713.4305).

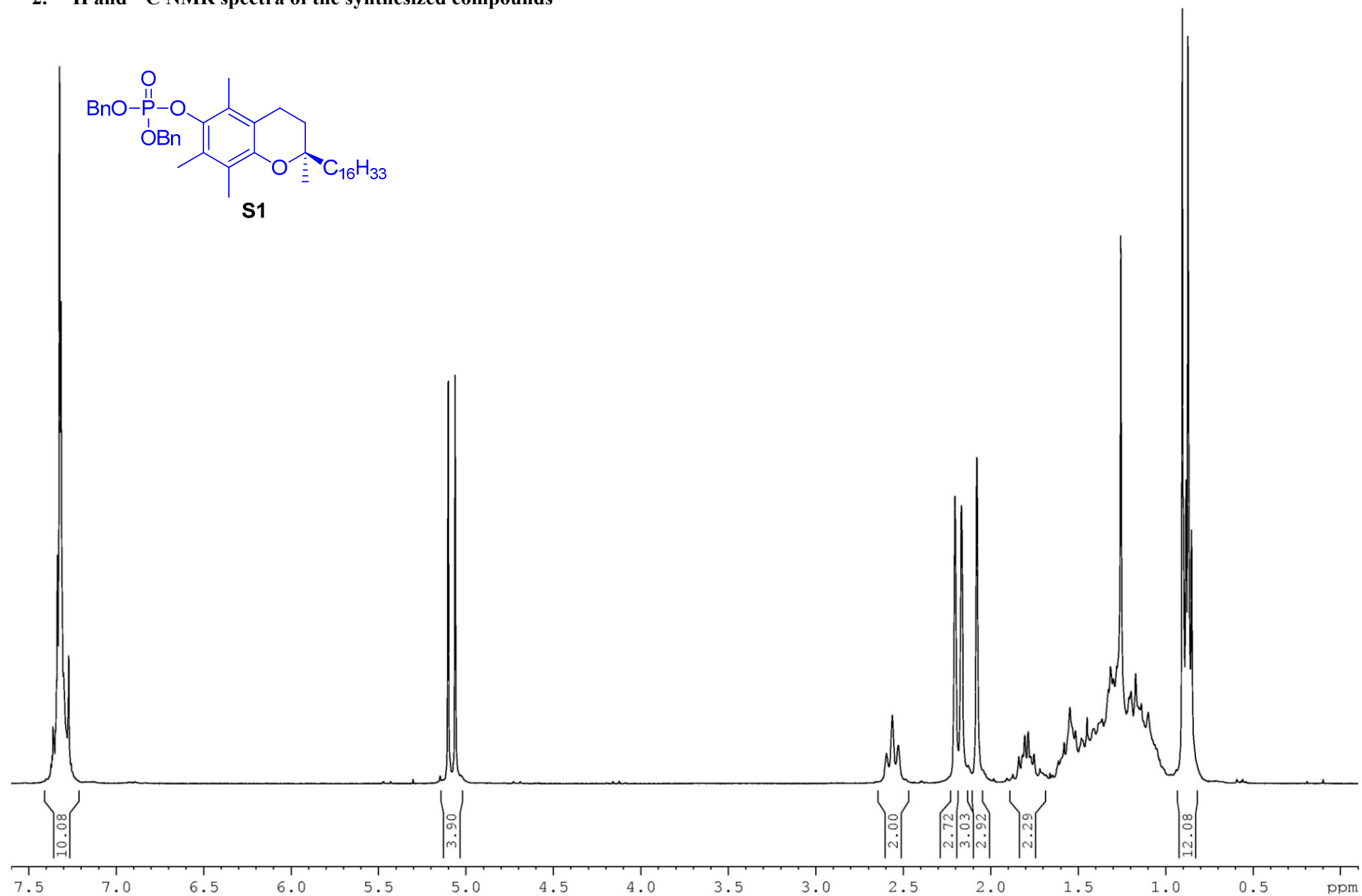
1.2. Synthesis of *RRR*- α -tocopheryl phosphate (α -TP)

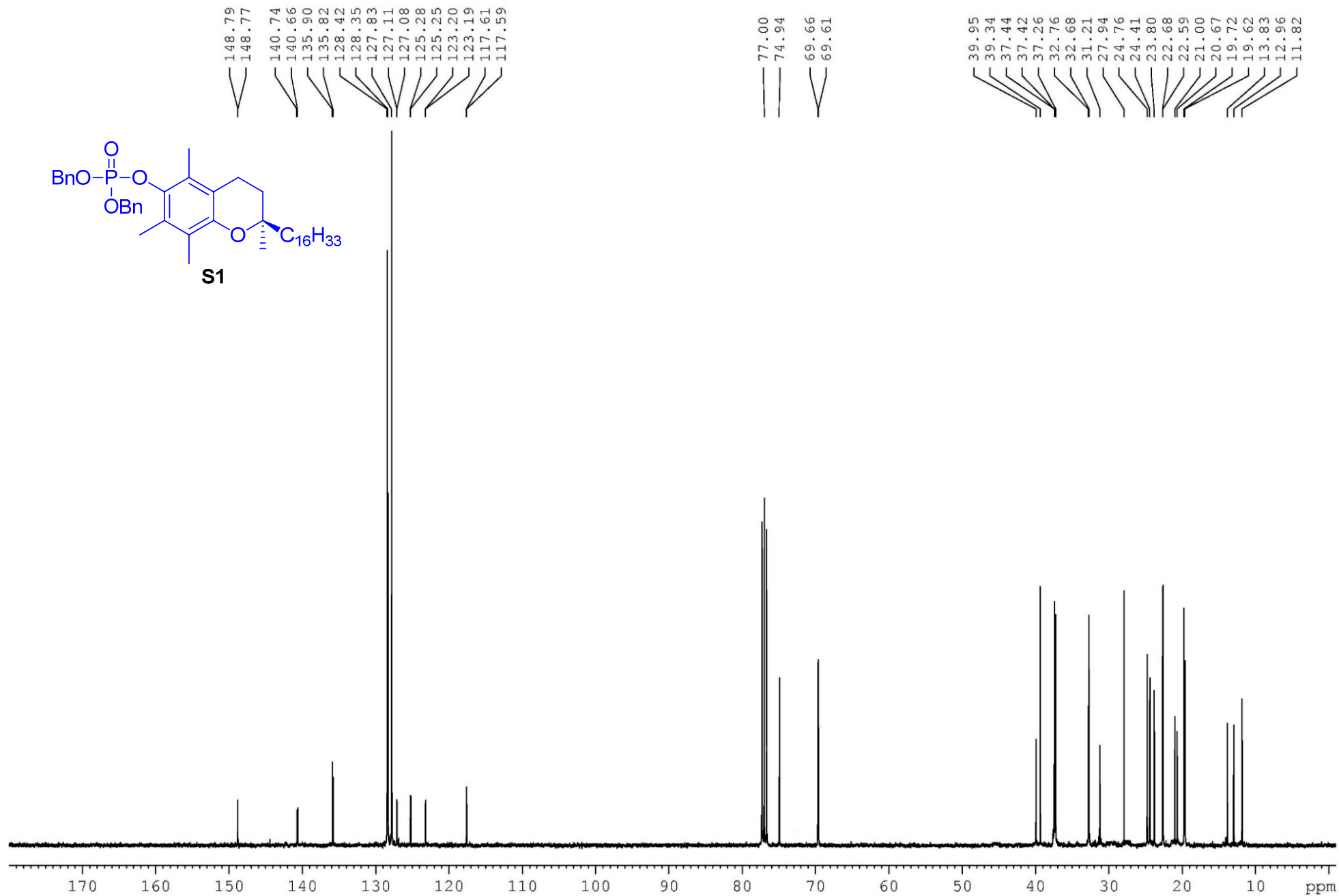
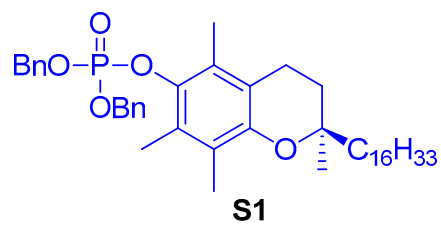


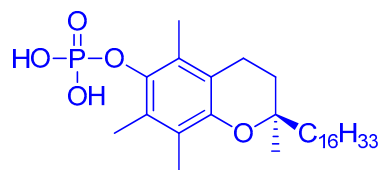
The mixture of compound **S1** (0.36 g, 0.52 mmol) and 10% Pd/C (80 mg) in EtOH (30 mL) was hydrogenated under atmospheric pressure at room temperature. After total conversion (TLC control) the reaction mixture was filtered through a pad of Celite and the filtrate was evaporated under reduced pressure to give α -TP as a white solid (236 mg, 89% yield).

α -TP: mp. 120.8–122.7°C; $^{31}\text{P}\{^1\text{H}\}$ NMR (160 MHz): δ -4.02 (CD_3OD), -1.51 (CDCl_3) ppm; ^1H NMR (400 MHz, CD_3OD): δ 2.61 (t, J = 6.7 Hz, 2H, H-4), 2.22 (s, 3H, H-8b), 2.18 (s, 3H, H-7a), 2.07 (s, 3H, H-5a), 1.821.77 (m, 2H, H-3), 1.59–1.02 (m, 24H, H-2a, H-1'–H-12'), 0.89–0.87 (m, 12H, H-4'a, H-8'a, H-12'a, H-13') ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CD_3OD): δ 149.5 (C-8a), 143.0 (C-6), 128.4 (C-7), 126.7 (C-5), 123.8 (C-8), 118.8 (C-4a), 75.9 (C-2), 40.6 (C-1'), 40.5 (C-11'), 38.5 (C-3'), 38.5 (C-9'), 38.4 (C-5', C-7'), 33.9 (C-8'), 33.8 (C-4'), 32.7 (C-3), 29.2 (C-12'), 25.9 (C-10'), 25.4 (C-6'), 24.2 (C-2a), 23.1 (C-12'a), 23.0 (C-13'), 22.0 (C-2'), 21.7 (C-4), 20.20 (8'a), 20.17 (C-4'a), 14.2 (C-7a), 13.3 (C-8b), 12.1 (C-5a) ppm; IR (KBr) ν_{max} 2930 (br), 1465, 1225, 1092, 988, 490 cm^{-1} ; HRMS m/z 511.3551 (calcd for $\text{C}_{29}\text{H}_{52}\text{O}_5\text{P}^+$ [$\text{M}+\text{H}$] $^+$ 511.3547). ^1H and ^{13}C NMR data were consistent with those reported in the literature [Harper, R.A.; Saleh, M.M.; Carpenter, G.; Abbate, V.; Proctor, G.; Harvey, R.D.; Gambogi, R.J.; Geonnotti, A.; Hider, R.; Jones, S.A. Soft, Adhesive (+) Alpha Tocopherol Phosphate Planar Bilayers That Control Oral Biofilm Growth through a Substantive Antimicrobial Effect. *Nanomedicine Nanotechnol. Biol. Med.* **2018**, *14*, 2307–2316, doi:10.1016/j.nano.2017.12.024].

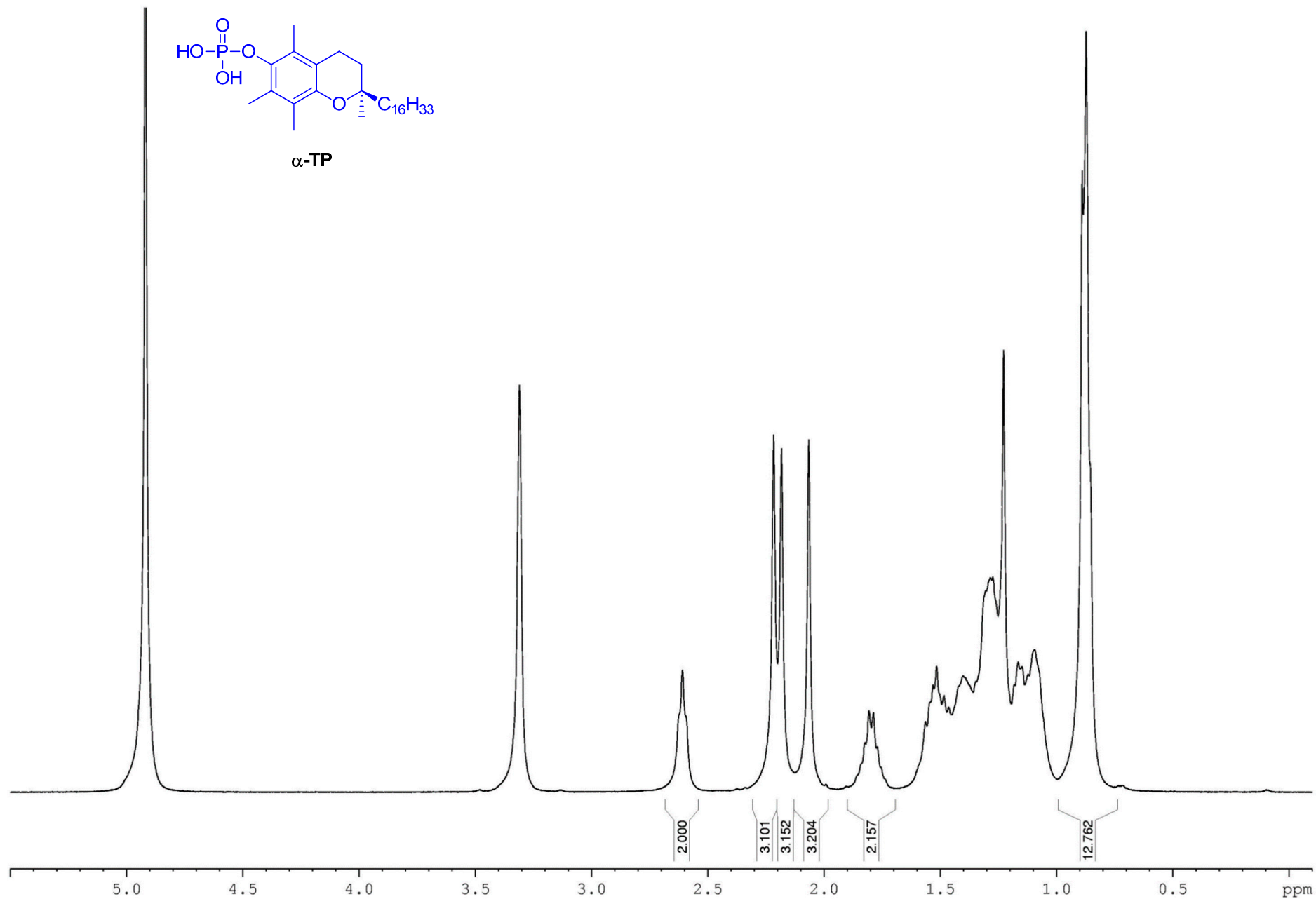
2. ^1H and ^{13}C NMR spectra of the synthesized compounds

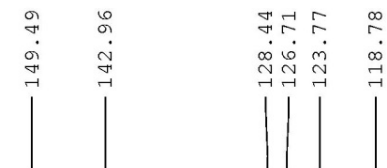


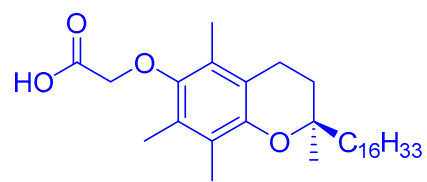




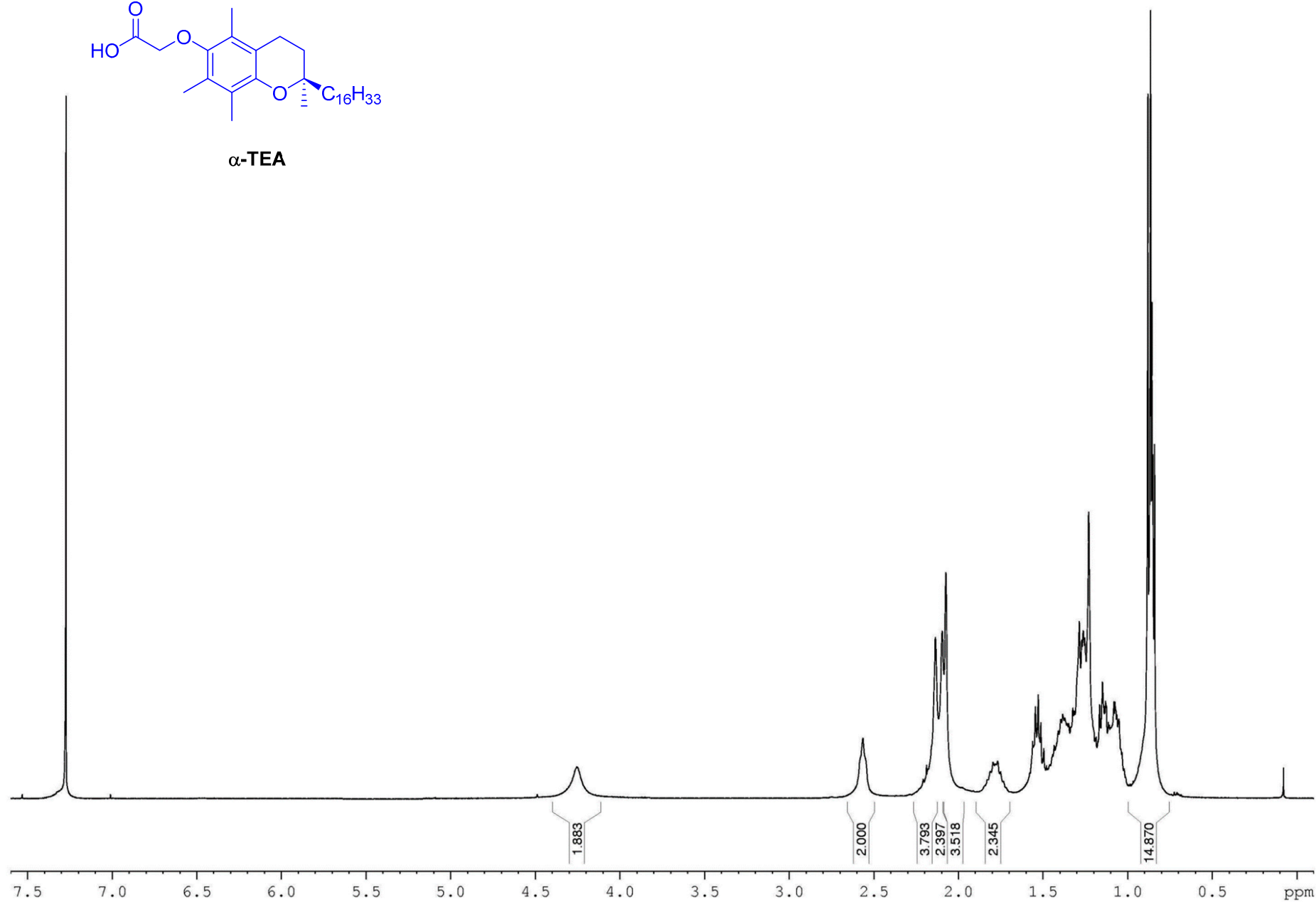
α -TP

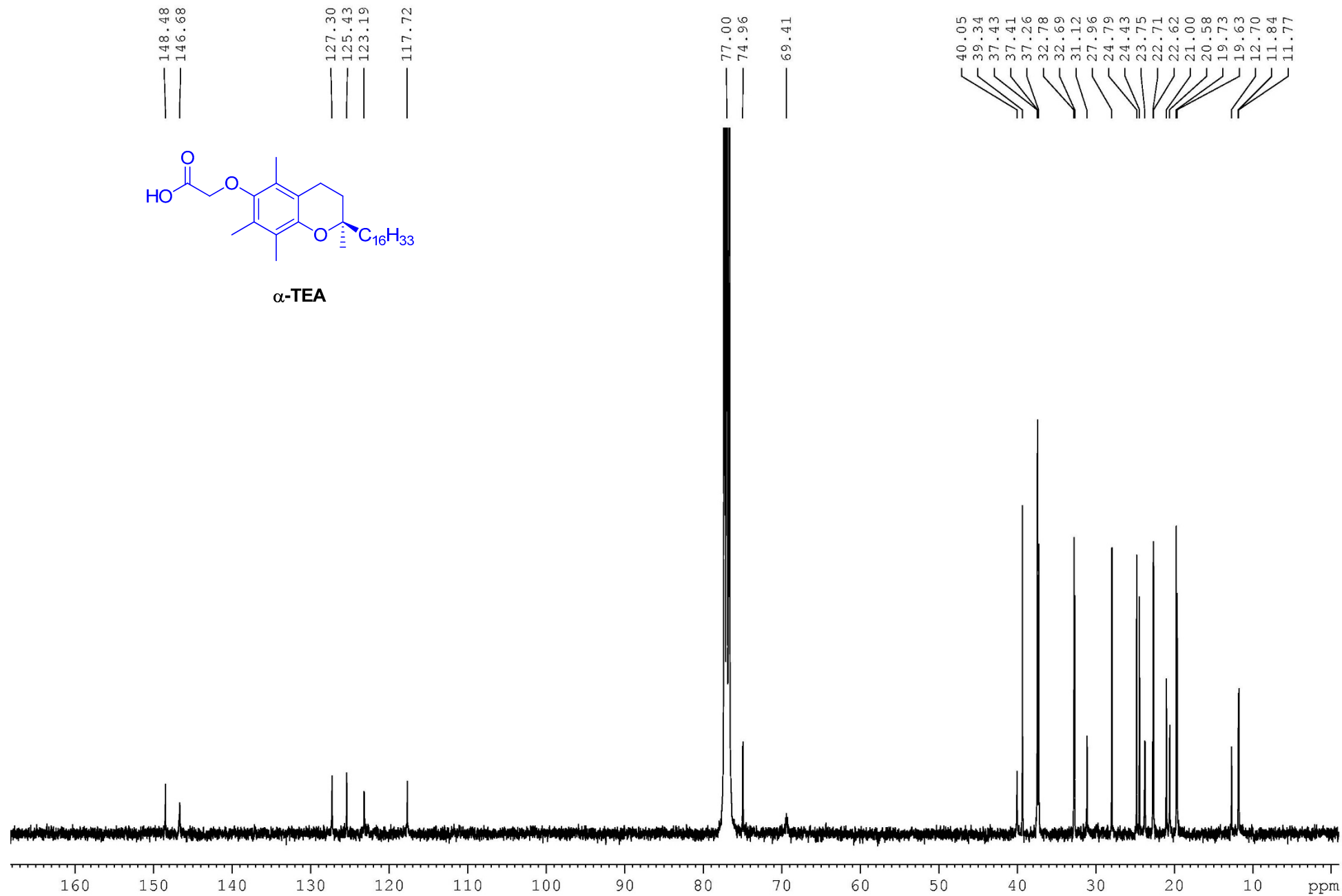


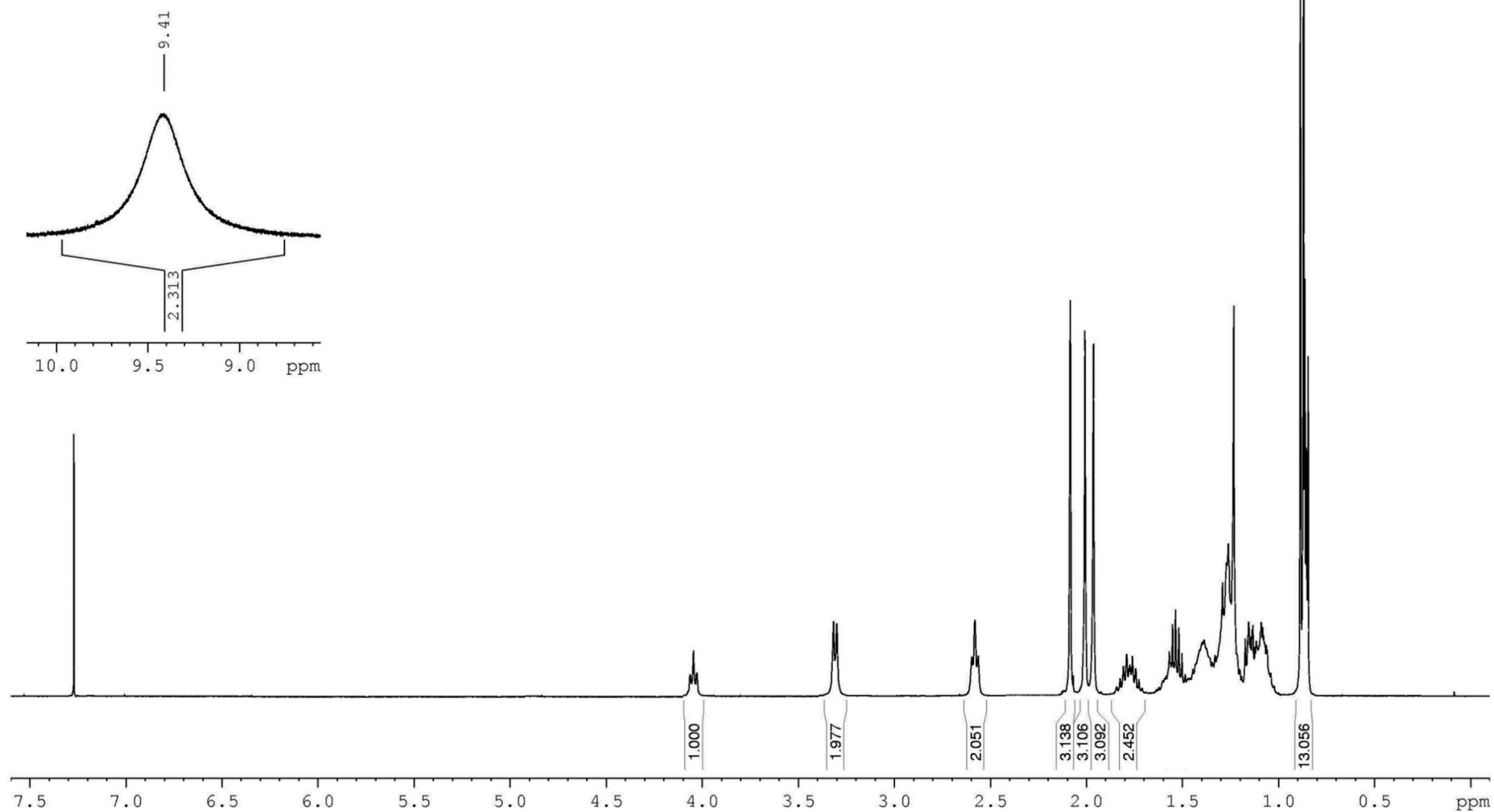
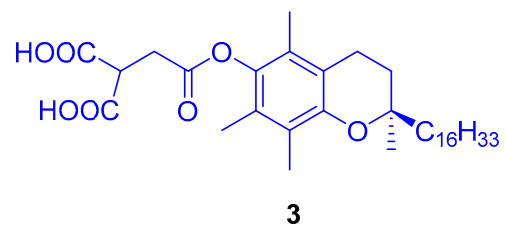


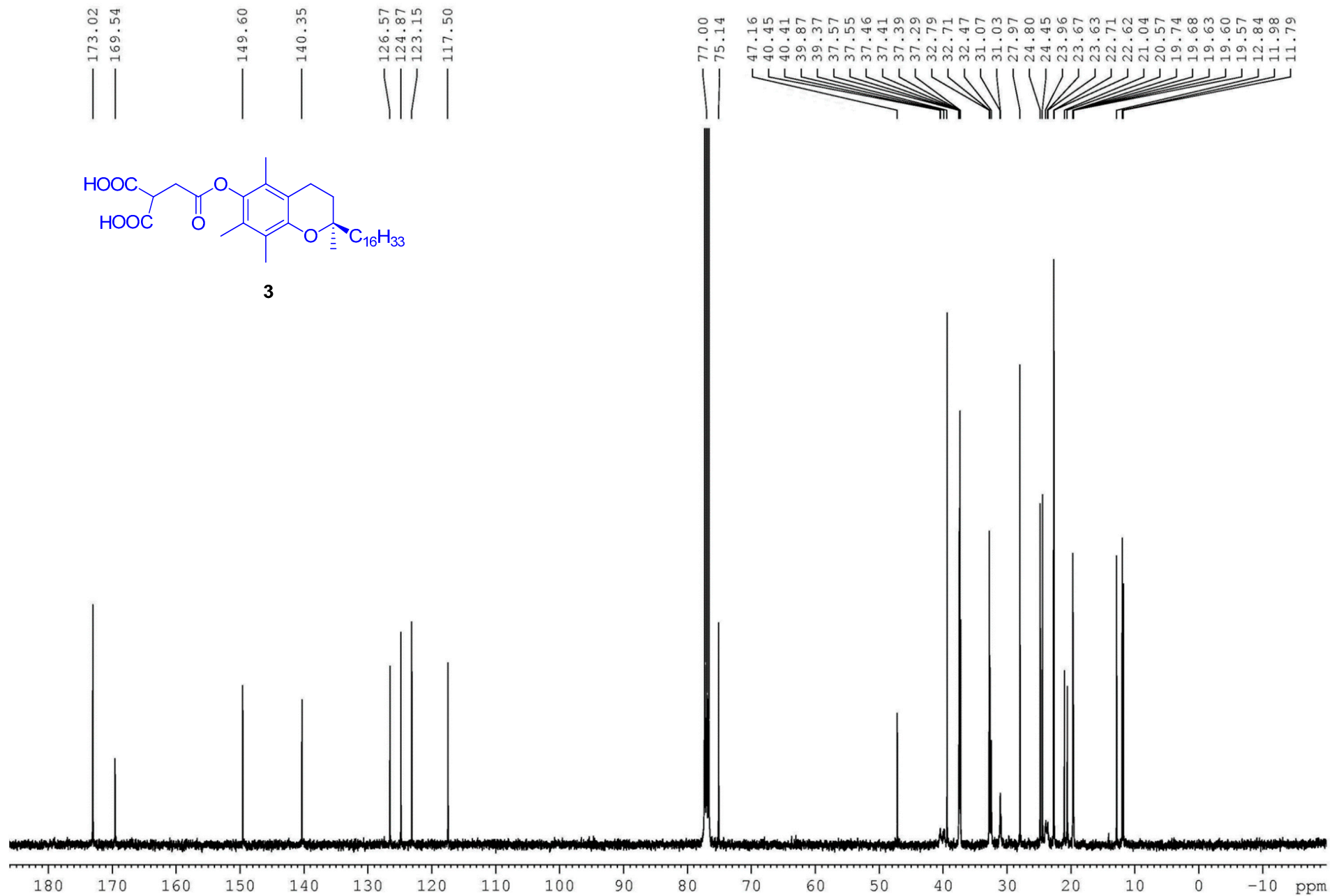


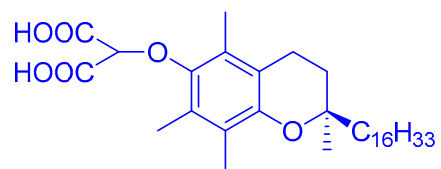
α -TEA



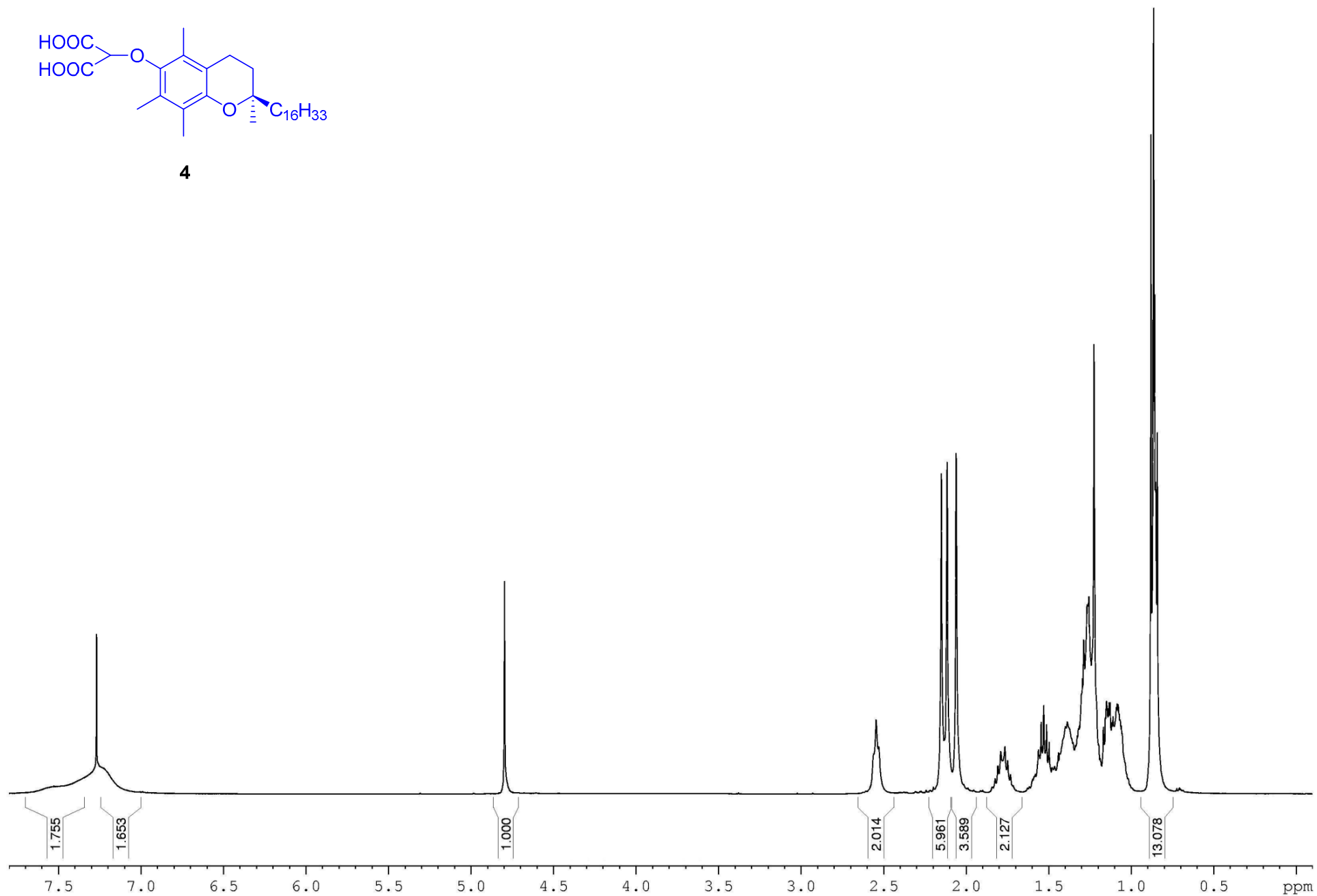


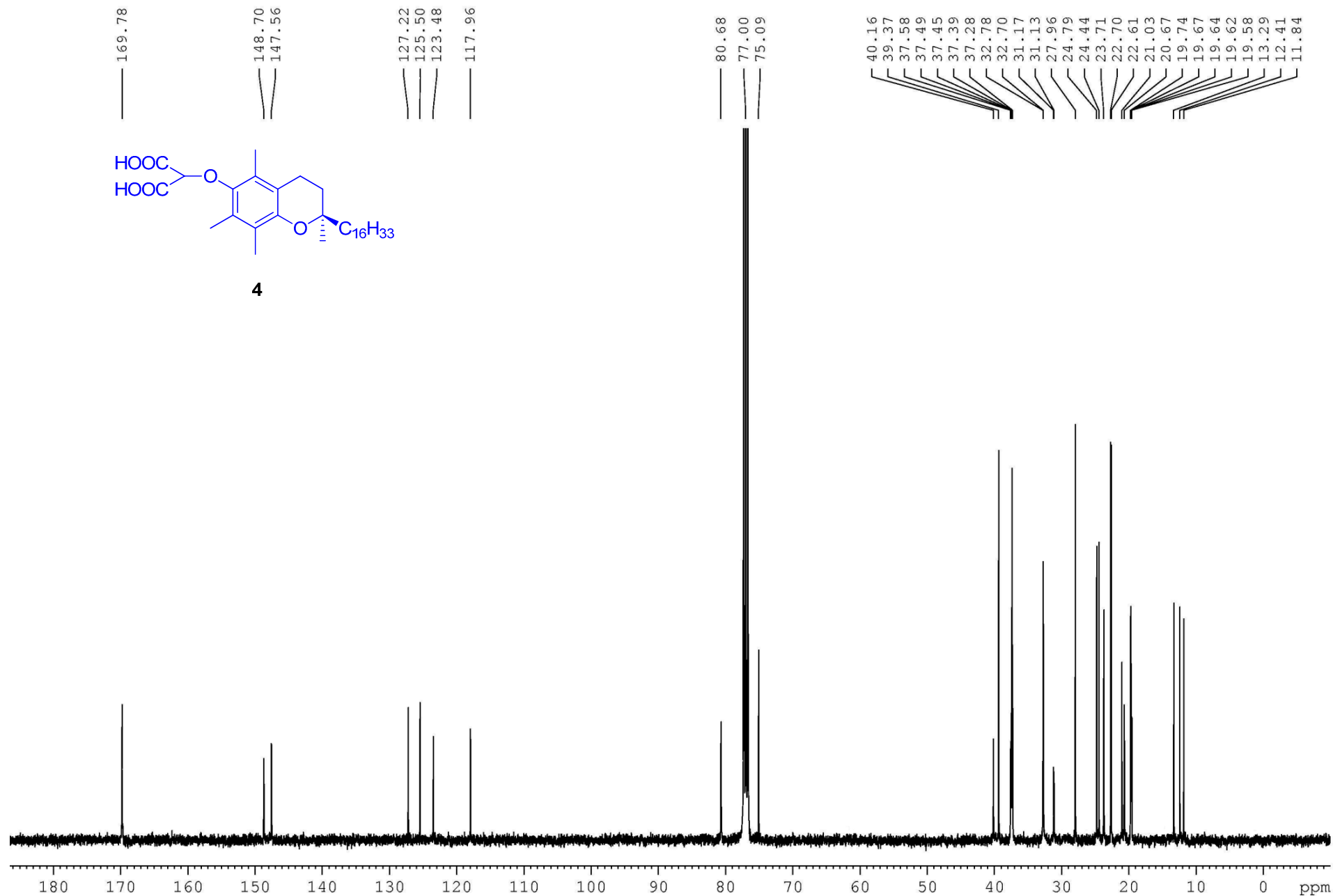


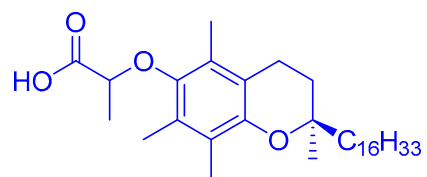




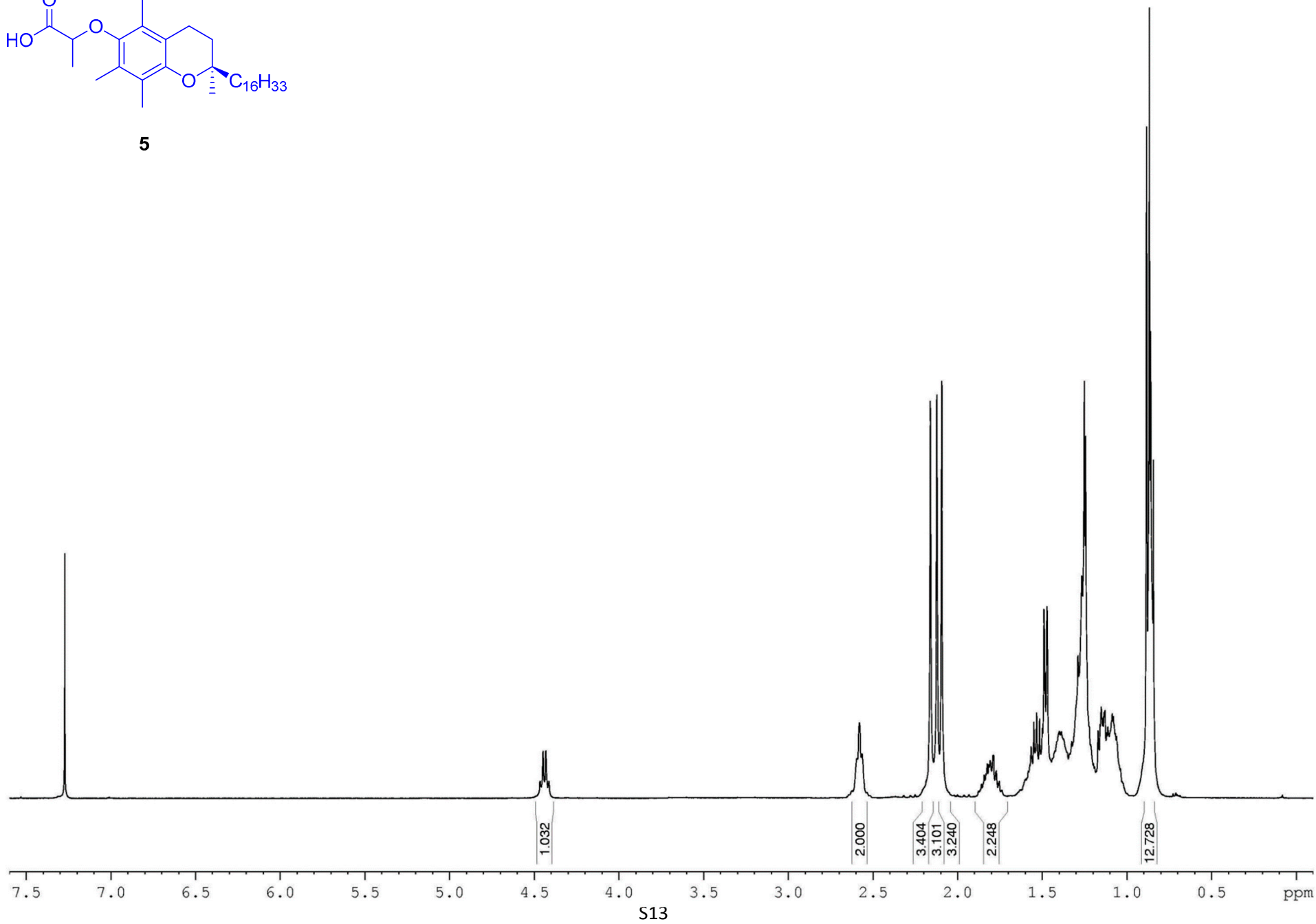
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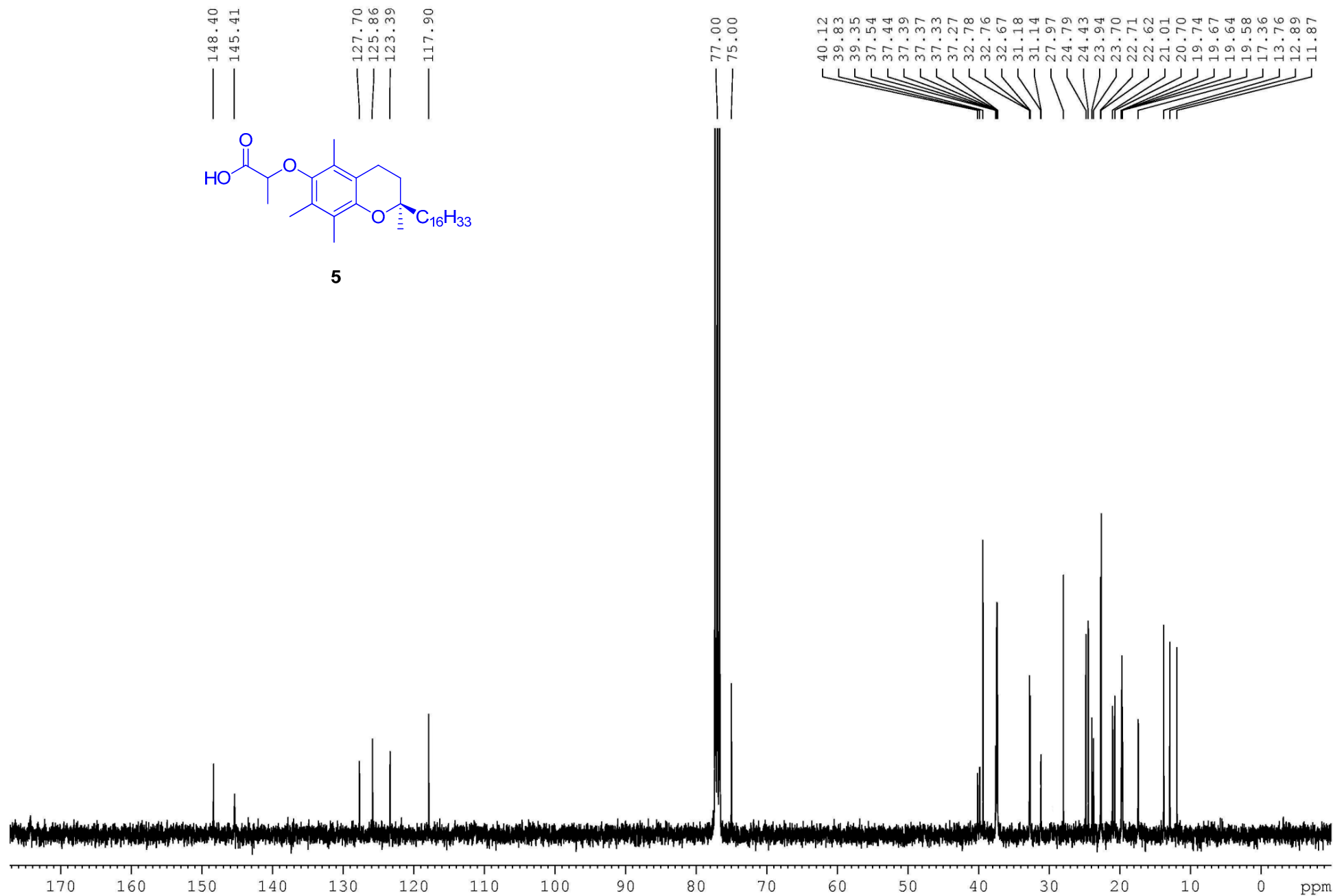


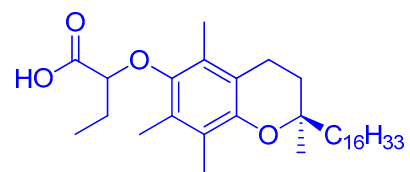




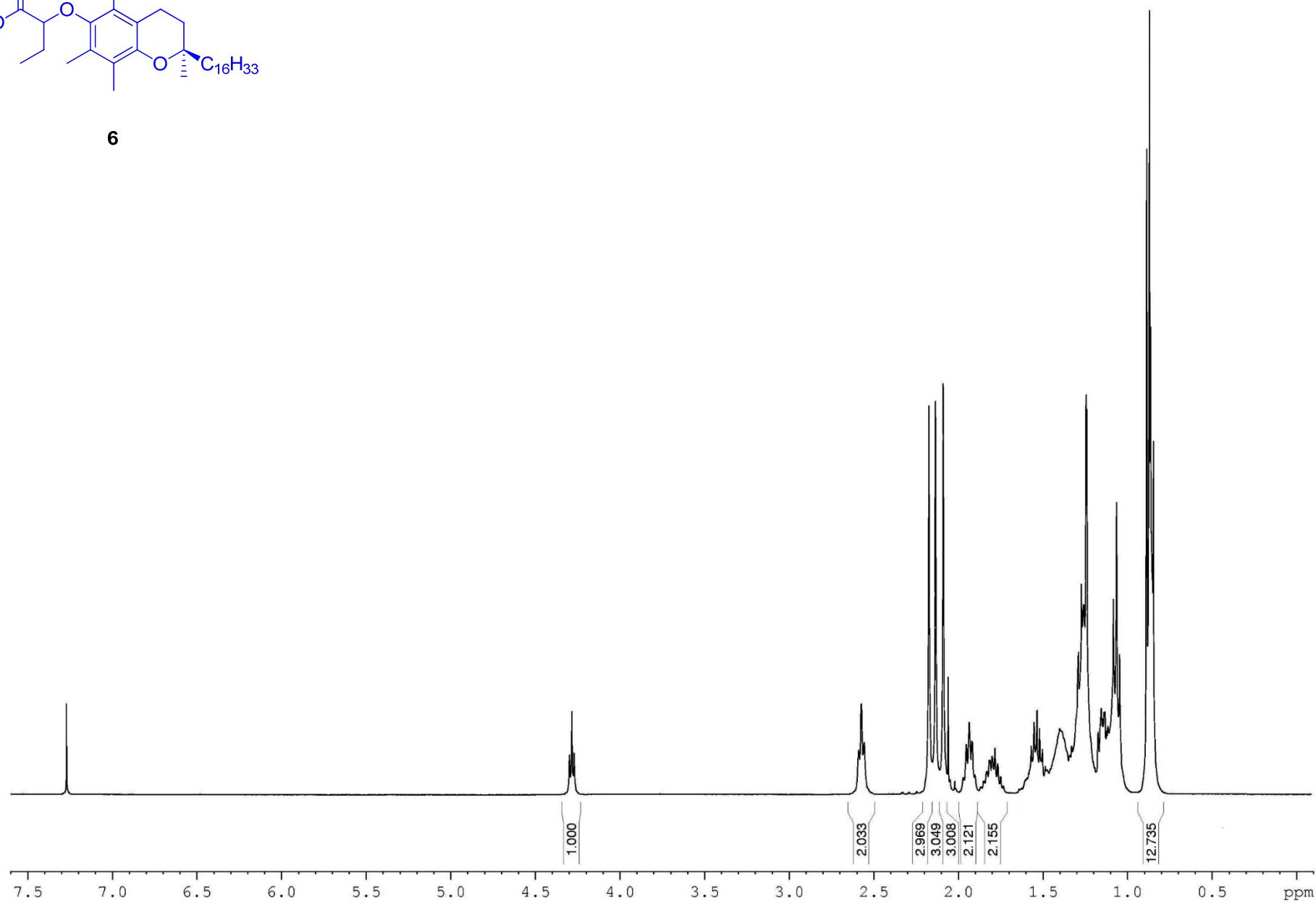
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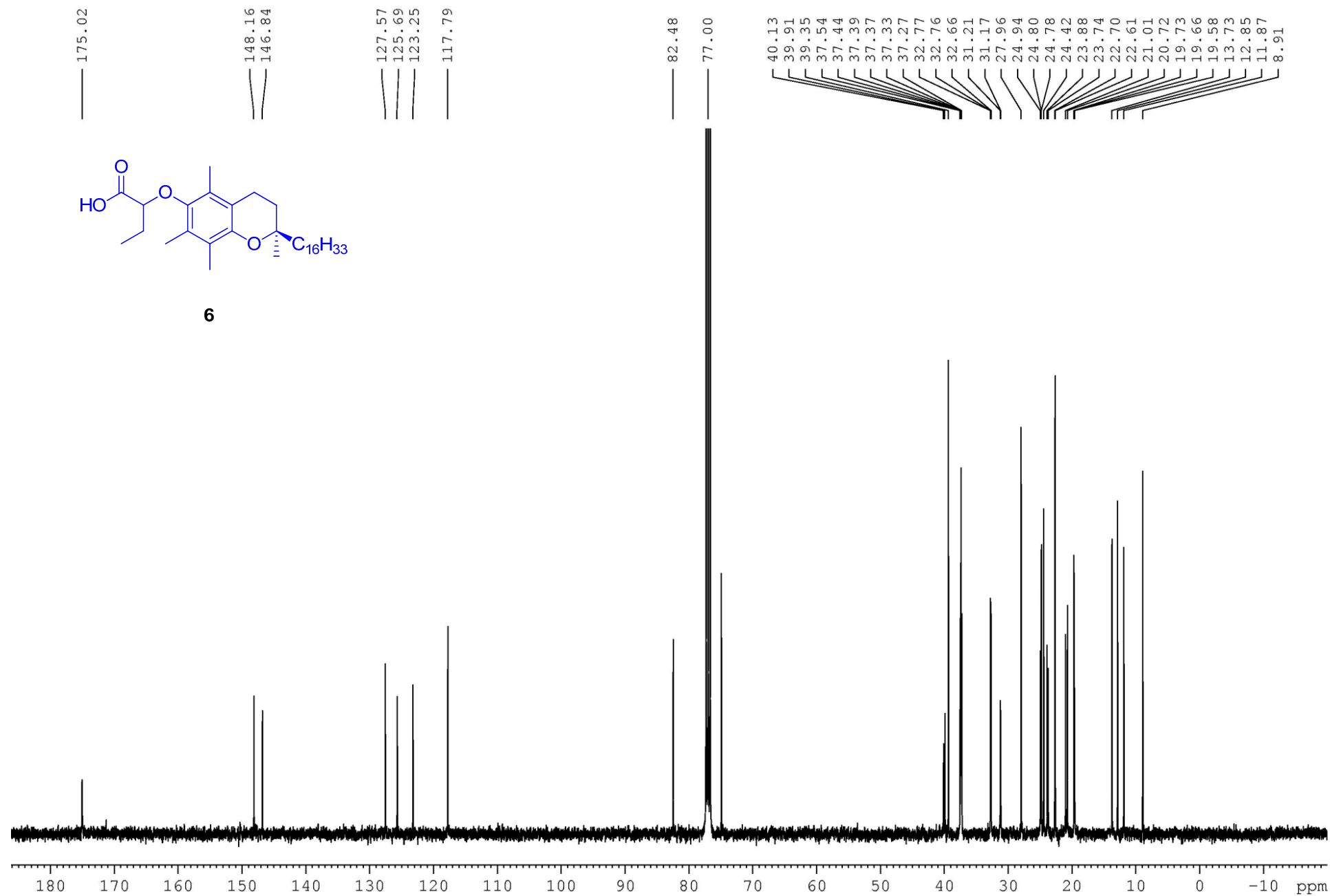


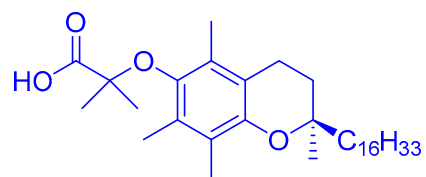




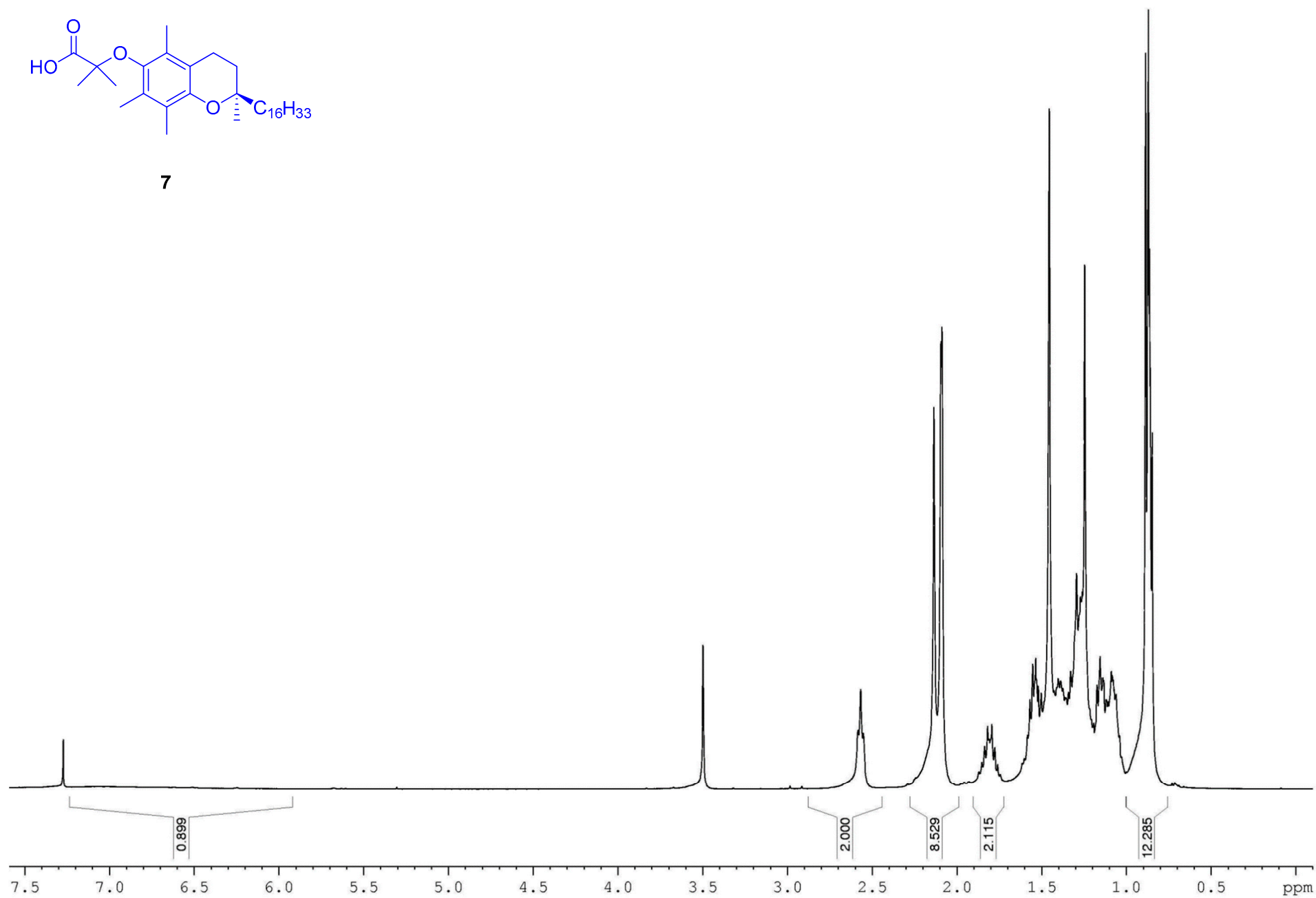
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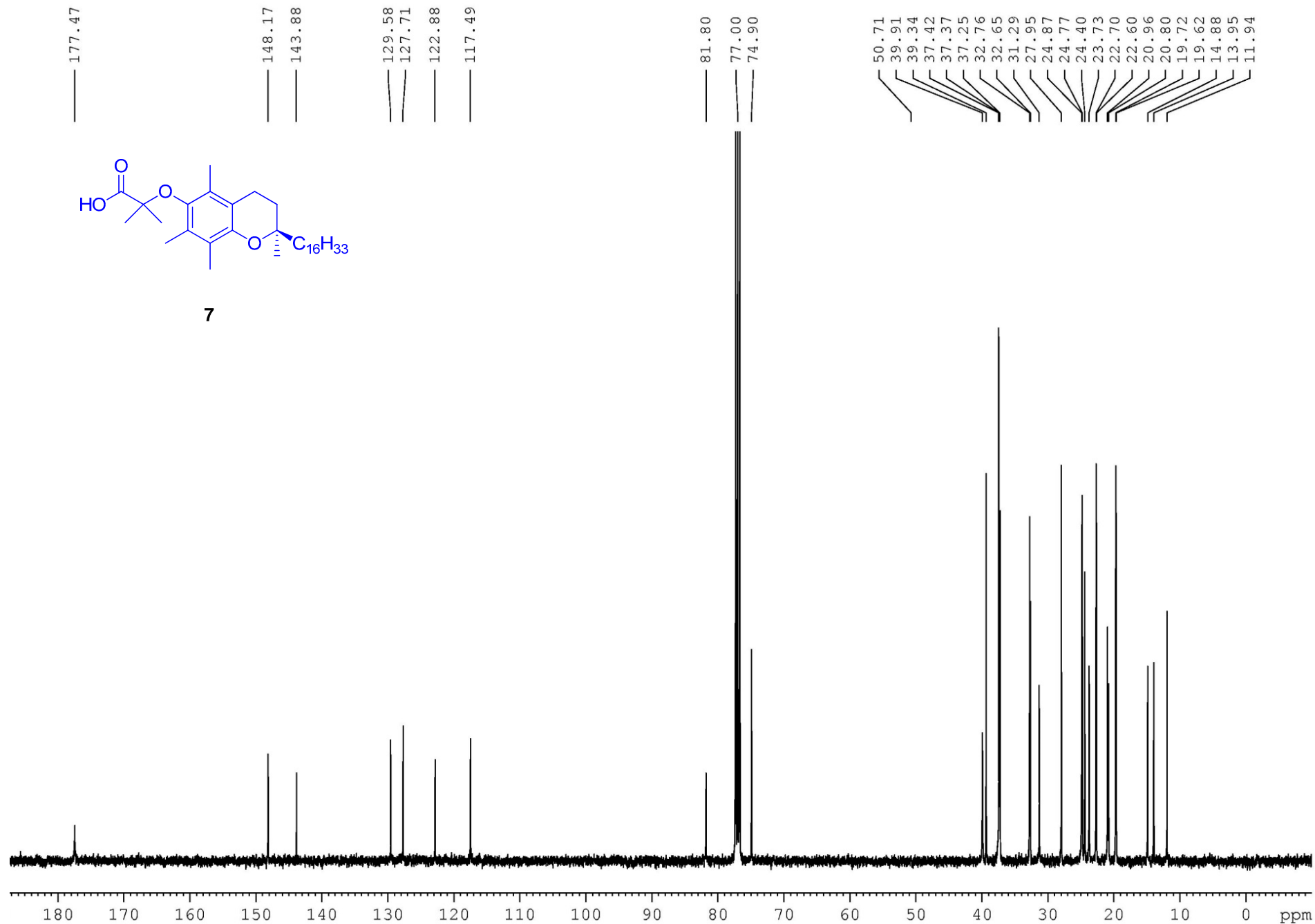


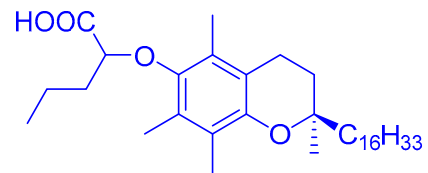




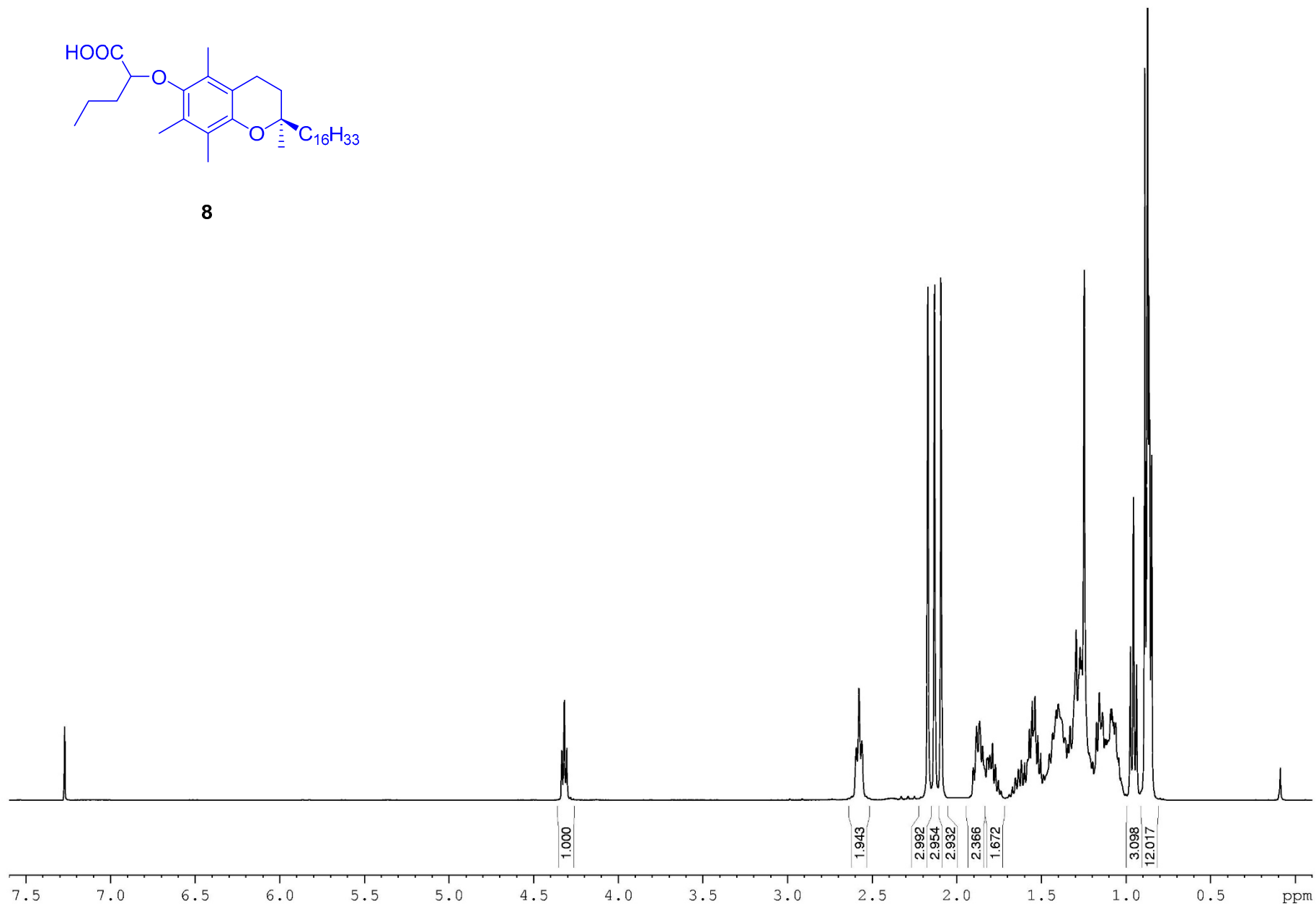
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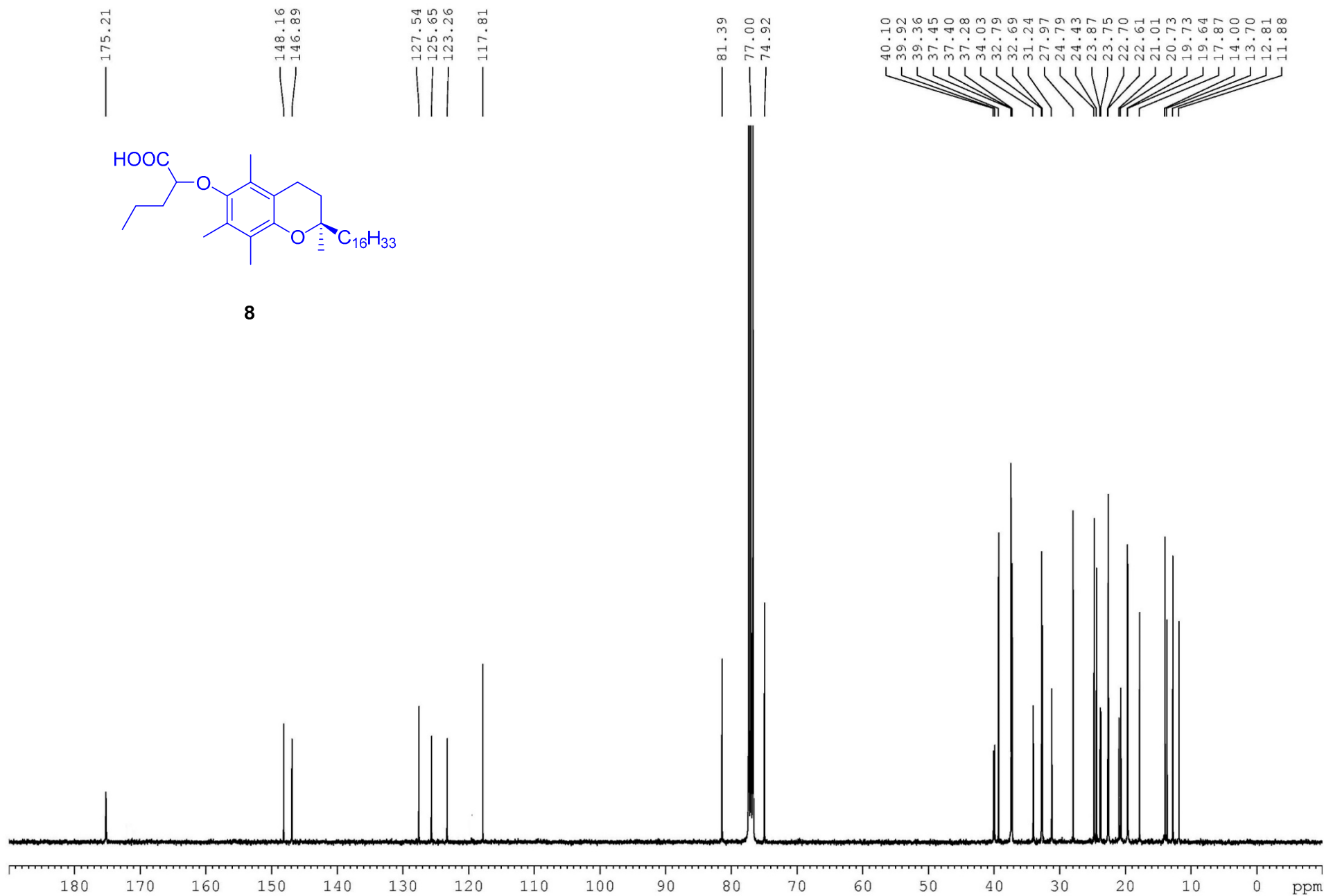


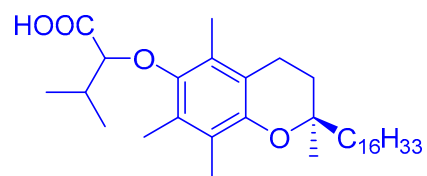




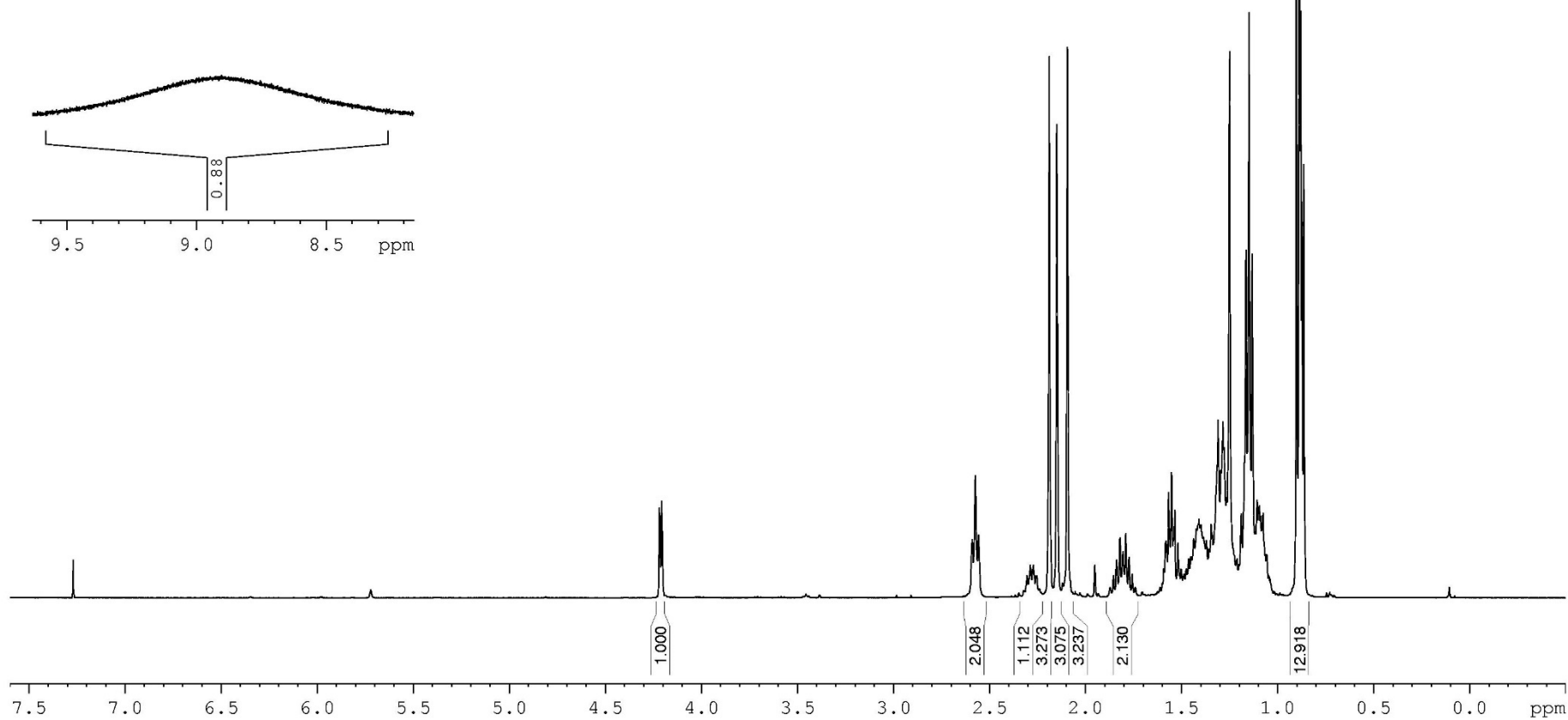
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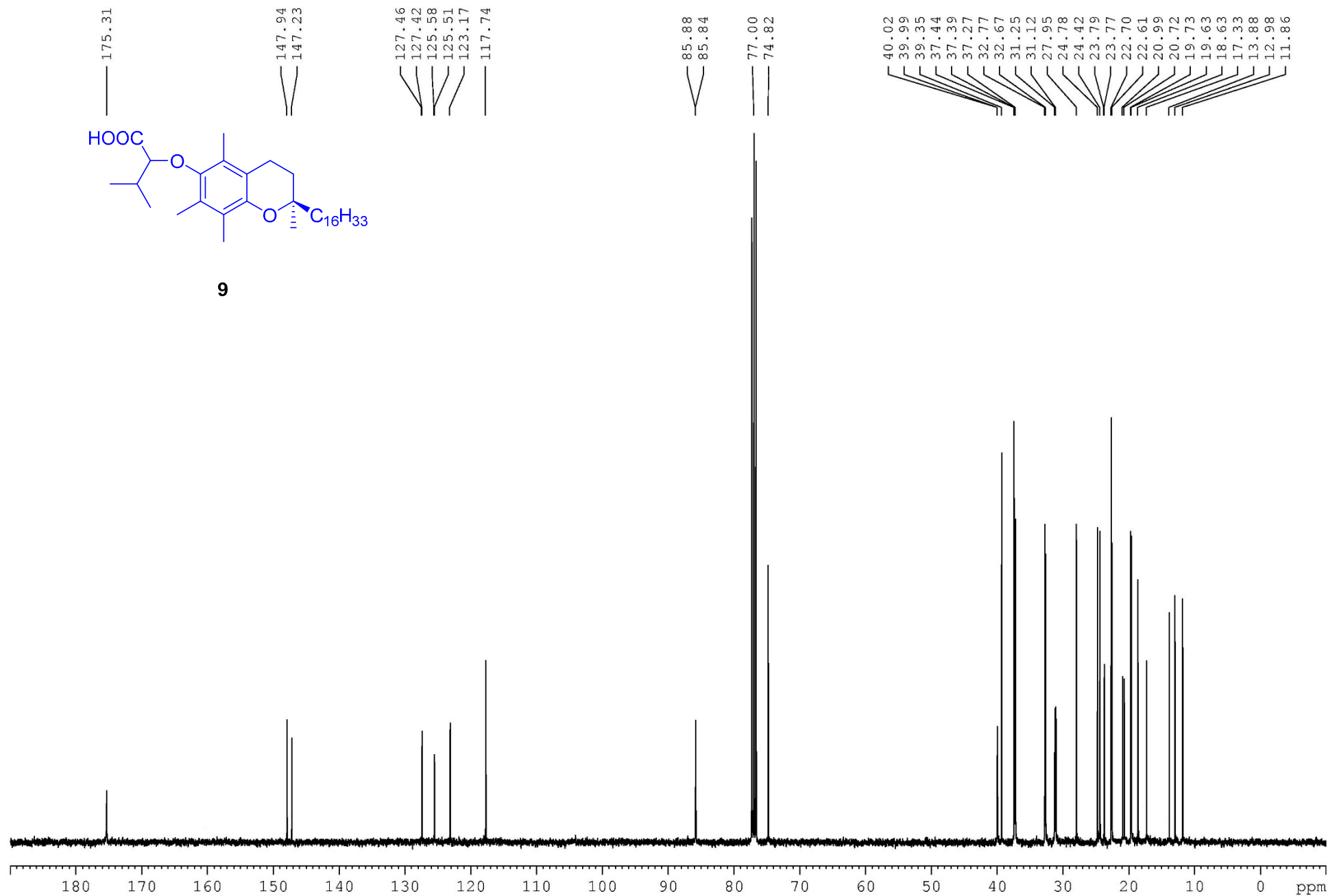


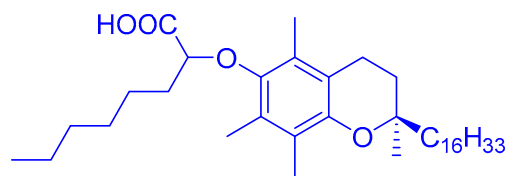




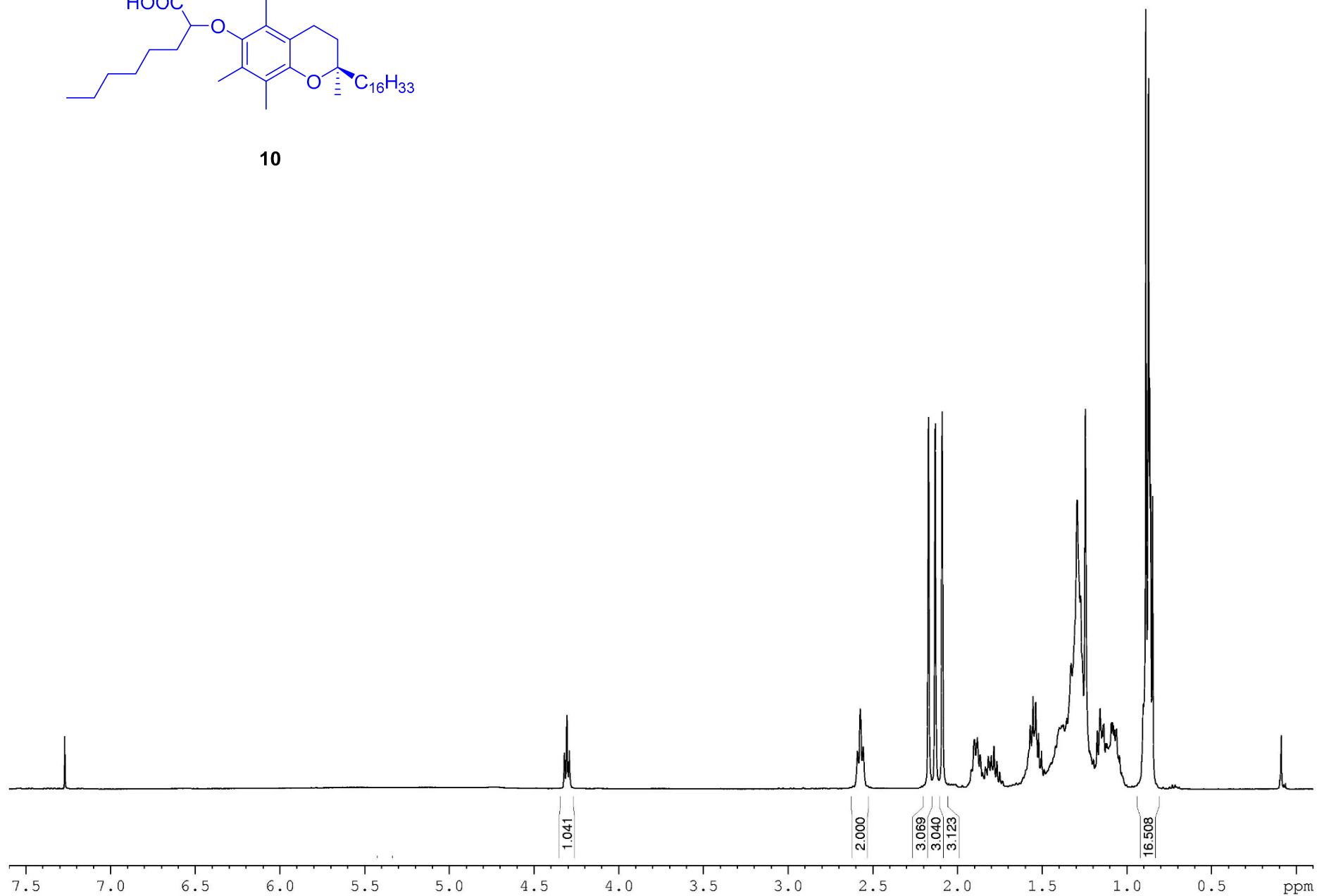
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S23

