Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supplementary data for

Spiralisones A–D: Acylphloroglucinol hemiketals from an Australian marine brown alga, *Zonaria spiralis*

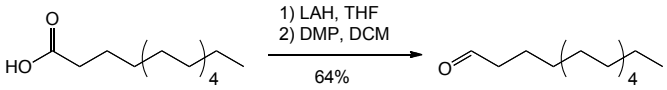
Hua Zhang [‡], Xue Xiao[‡], Melissa M. Conte, Zeinab Khalil and Robert J. Capon[*]

Division of Chemistry and Structural Biology, Institute for Molecular Bioscience, The University of Queensland, St. Lucia, Queensland 4072, Australia

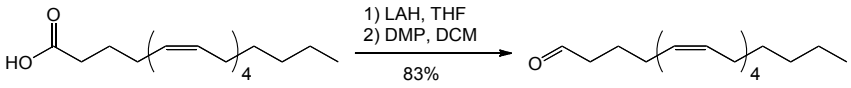
[‡] These authors contribute equally to this paper.

[*] Corresponding author. Tel.: +61 7 3346 2979, Fax: +61 7 3346 2090, E-mail: r.capon@uq.edu.au

Synthetic Procedures



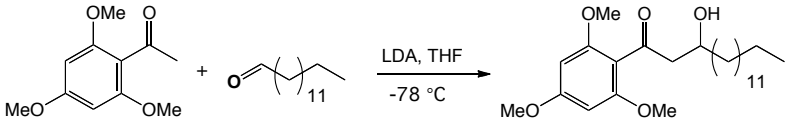
tetradecanal[1a]**:** LAH (1.05 g, 30 mmol) was added to dry THF (100 mL) at 0 ˚C, and then myristic acid (2.28 g, 10 mmol) was added to the suspension slowly. After stirring for 3 h at 0 ˚C, the reaction was quenched by addition of Na_2SO_4•$10H_2O$. The suspension was filtered and the filter cake was washed with THF and was evaporated to afford an alcohol residue without further purification. Dess–Martin periodinane (DMP) (4.24 g, 10 mmol) was added to a solution of the residue in DCM (100 mL) at 0 ˚C, and then the reaction was quenched by addition of sat. Na_2SO_3 and sat. $NaHCO_3$ successively. The mixture was extracted with DCM (3×50 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated. Then the resulting residue was purified by silica gel chromatography (EtOAc/hexane = 1:8) to afford tetradecanal (1.28 g, 64%) as colourless oil with spectral data in accord with published data. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.76 (s, 1H), 2.41 (t, *J* = 3.8 Hz, 2H), 1.62 (t, *J* = 7.2 Hz, 2H), 1.25-1.29 (m, 22H), 0.87 (t, *J* = 6.6 Hz, 3H).



arachidonal**:** LAH (19 mg, 0.49 mmol) was added to dry THF (15 mL) at 0 ˚C, and then arachidonic acid (50 mg, 0.16 mmol) was added to the suspension slowly. After stirring for 3 h at 0 ˚C, the reaction was quenched by addition of Na_2SO_4•$10H_2O$. The suspension was filtered and the filter cake was washed with THF and was evaporated to afford an alcohol residue without further purification. DMP (139 mg, 0.33 mmol) was added to a solution of the residue in DCM (15 mL) at 0 ˚C, and then the reaction was quenched by addition of sat. Na_2SO_3 and sat. $NaHCO_3$ successively. The mixture

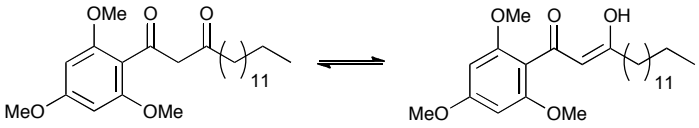
[1] a) Milite, C.; Castellano, S.; Benedetti, R.; Tosco, A.; Ciliberti, C.; Vicidomini, C.; Boully, L.; Franci, G.; Altucci, L.; Mai, A.; Sbardella, G. *Bioorg. Med. Chem.* **2011**, *19*, 3690–3701. b) Maharvi, G. M.; Edward, A. O.; Fauq, A.H. *Tetrahedron Letters* **2010**, *51*, 6426–6428.

was extracted with DCM (3×10 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated. Then the resulting residue was purified by silica gel chromatography (EtOAc/hexane = 1:8) to afford arachidonal (40 mg, 83%) as colourless oil.[1b] ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.78 (s, 1H), 5.35-5.42 (m, 8H), 2.80-2.84 (m, 6H), 2.10-2.14 (q, *J* = 7.1 Hz, 2H), 2.04-2.07 (q, *J* = 7.3 Hz, 2H), 1.69-1.74 (m, 2H), 1.25-1.37 (m, 8H), 0.89 (t, *J* = 7.1 Hz, 3H).



10a tetradecanal **11a**

11a: ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 6.10 (s, 1H), 4.11-4.15 (m, 1H), 3.82 (s, 3H), 3.78 (s, 6H), 2.96-3.00 (dd, *J* = 17.4, 2.4 Hz, 1H), 2.77-2.81 (dd, *J* = 17.4, 9.6 Hz, 1 H), 1.43-1.44 (m, 2H), 1.27-1.42 (m, 22H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 205.5, 162.6, 158.3, 113.2, 90.6, 68.2, 55.8, 55.4, 51.5, 36.4, 31.9, 29.7, 29.7, 29.65, 29.64, 29.63, 29.58, 29.56, 29.4, 25.5, 22.7, 14.1; UV (MeOH) λ_{max} (log ε) 213 (4.28) and 265 (3.95) nm; HR-ESI(+)MS *m/z* 423.3107 $[M + H]^+$ (calcd for $C_{25}H_{43}O_5$, 423.3107).



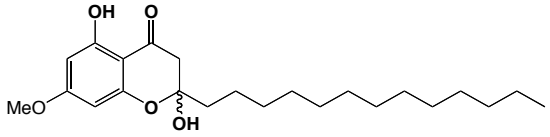
12a **12a'**

12a : 12a' = 1: 2 in $CDCl_3$

12a: ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 6.09 (s, 2H), 3.85 (s, 2H), 3.83 (s, 3H), 3.79 (s, 6H), 2.54 (t, *J* = 7.5, 2 H), 1.56-1.60 (m, 2H), 1.25-1.35 (m, 20H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 204.6, 196.0, 163.2, 159.0, 112.5, 90.6, 59.7, 55.8, 55.4, 43.0, 31.9, 29.14-29.67 (C×8), 23.5, 22.7, 14.1; HR-ESI(+)MS *m/z* 421.2948 $[M + H]^+$ (calcd for $C_{25}H_{41}O_5$, 421.2949).

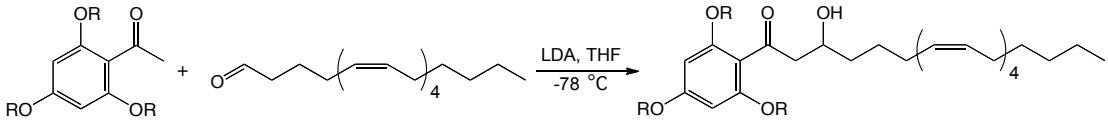
12a': ^{1}H NMR (600 MHz, $CDCl_3$): δ_H= 6.12 (s, 2H), 5.70 (s, 1H), 3.83 (s, 3H), 3.79 (s, 6H), 2.32 (t, *J* = 7.5, 2 H), 1.60-1.66 (m, 2H), 1.25-1.35 (m, 20H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 192.6, 186.1, 162.5, 159.1, 109.7, 103.6,

90.7, 56.0, 55.4, 38.2, 31.9, 29.14-29.67 (C×8), 25.8, 22.7, 14.1; HR-ESI(+)MS *m/z* 421.2948 $[M + H]^+$ (calcd for $C_{25}H_{41}O_5$, 421.2949).



8

8: ^{1}H NMR (600 MHz, $CDCl_3$): δ_H= 11.94 (s, 1H), 6.06 (s, 1H), 5.97 (s, 1H), 3.81 (s, 3H), 2.91 (d, *J* = 16.8, 1H), 2.77 (d, *J* = 16.8, 1H), 1.88-1.91 (m 2H), 1.49-1.53 (m, 2H), 1.25-1.37 (m, 20H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 194.9, 167.9, 163.8, 159.6, 102.6, 102.3, 95.0, 94.9, 55.7, 44.9, 41.2, 31.9, 29.69, 29.67, 29.64, 29.61, 29.50, 29.47, 29.45, 25.4, 23.2, 22.7, 14.1; UV (MeOH) λ_{max} (log ε) 201 (4.29), 218 (4.14) and 278 (4.17) nm; HR-ESI(+)MS *m/z* 393.2636 $[M + H]^+$ (calcd for $C_{23}H_{37}O_5$, 393.2636).



10a: R = Me
10b: R = MOM

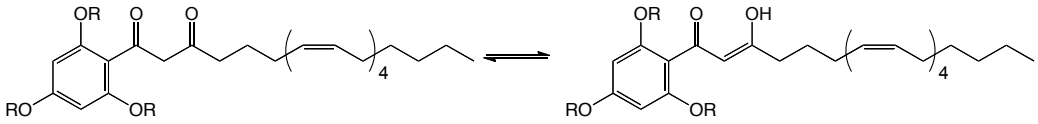
arachidonal

11b: R = Me
11c: R = MOM

Following the general procedure **11b** and **11c** were prepared from **10a** and **10b**, respectively.

11b: ^{1}H NMR (600 MHz, $CDCl_3$): δ_H= 6.10 (s, 2H), 5.32-5.42 (m, 8H), 4.11-4.17 (m, 1H), 3.82 (s, 3H), 3.78 (s, 6H), 2.98 (dd, *J* = 17.2, 2.4 1H), 2.78-2.84 (m, 7H), 2.09 (q, *J* = 7.0, 2H), 2.05 (q, *J* = 7.2, 2H), 1.52-1.56 (m, 2H), 1.42-1.48 (m, 2H), 1.33-1.36 (m, 2H), 1.25-1.30 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 205.4, 162.6, 158.3, 130.5, 130.0, 128.5, 128.4, 128.1, 128.0, 127.9, 127.6, 113.1, 90.6, 68.1, 55.9, 55.5, 51.5, 36.0, 31.5, 29.7, 29.3, 27.2, 27.15, 25.64, 25.62, 25.5, 22.6, 14.1; UV (MeOH) λ_{max} (log ε) 215 (4.02) and 266 (3.68) nm; HR-ESI(+)MS *m/z* 521.3245 $[M + Na]^+$ (calcd for $C_{31}H_{46}O_5Na$, 521.3245).

11c: ^{1}H NMR (600 MHz, CD_3OD): δ_H= 6.51 (s, 2H), 5.30-5.37 (m, 8H), 5.14 (s, 2H), 5.12 (s, 4H), 4.06-4.09 (m, 1H), 3.43 (s, 3H), 3.42 (s, 6H), 2.93 (d, *J* = 6.24 2H), 2.78-2.83 (m, 6H), 2.03-2.09 (m, 4H), 1.51-1.56 (m, 2H), 1.40-1.48 (m, 2H), 1.33-1.35 (m, 2H), 1.25-1.31 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD): δ_C = 203.3, 159.8, 155.3, 129.8, 129.5, 128.0, 127.9, 127.7, 127.6, 127.5, 127.3, 115.8, 96.6, 94.5, 94.1, 67.2, 55.3, 55.0, 52.3, 36.4, 31.2, 29.0, 26.8, 26.7, 25.6, 25.2, 25.17, 25.15, 22.2, 13.0; UV (MeOH) λ_{max} (log ε) 215 (3.86) and 253 (3.42) nm; HR-ESI(+)MS *m/z* 611.3563 $[M + Na]^+$ (calcd for $C_{34}H_{52}O_8Na$, 611.3554).



12b: R = Me
12c: R = MOM

12b : 12b' = 1: 2.2 in $CDCl_3$
12c : 12c' = 1: 2.6 in $CDCl_3$

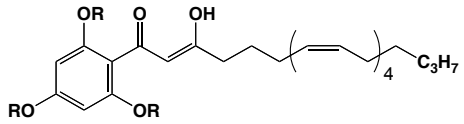
12b': R = Me
12c': R = MOM

12b: ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 6.09 (s, 2H), 5.34-5.40 (m, 8H), 3.85 (s, 2H), 3.83 (s, 3H), 3.79 (s, 6H), 2.79-2.83 (m, 6H), 2.57 (t, *J* = 7.8 Hz, 2H), 2.06-2.09 (m 2H), 2.04-2.06 (m, 2H), 1.64-1.70 (m, 2H), 1.24-1.37(m, 6H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 204.3, 196.0, 163.1, 159.1, 130.5, 129.3, 128.7, 128.6, 128.21, 128.19, 127.9, 127.6, 112.4, 90.6, 59.7, 55.8, 55.4, 42.3, 31.5, 29.7, 27.2, 26.5, 25.6 (C×3), 23.3, 22.6, 14.2; HR-ESI(+)MS *m/z* 519.3090 $[M + Na]^+$ (calcd for $C_{31}H_{44}O_5Na$, 519.3081).

12b': ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 6.11 (s, 2H), 5.71 (s, 1H), 5.34-5.40 (m, 8H), 3.83 (s, 3H), 3.79 (s, 6H), 2.79-2.83 (m, 6H), 2.35 (t, *J* = 7.8 Hz, 2H), 2.13-2.16 (m 2H), 2.04-2.06 (m, 2H), 1.71-1.75 (m, 2H), 1.24-1.37(m, 6H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 192.2, 186.1, 162.6, 159.0, 130.5, 129.2, 128.7, 128.6, 128.21, 128.19, 127.9, 127.5, 109.7, 103.7, 90.7, 56.0, 55.4, 37.6, 31.5, 29.3, 27.2, 26.7, 25.62 (C×4), 22.6, 14.2; HR-ESI(+)MS *m/z* 519.3090 $[M + Na]^+$ (calcd for $C_{31}H_{44}O_5Na$, 519.3081).

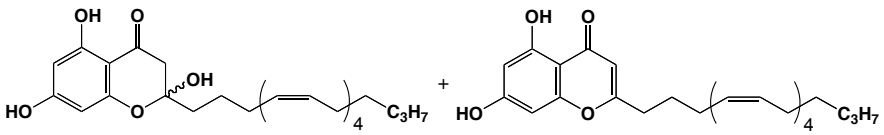
12c: ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 6.51 (s, 2H), 5.34-5.40 (m, 8H), 5.15 (s, 2H), 5.13 (s, 4H), 3.89 (s, 2H), 3.47 (s, 3H), 3.46 (s, 6H), 2.79-2.84 (m, 6H), 2.60 (t, *J* = 7.4 Hz, 2H), 2.05-2.09 (m 2H), 2.04-2.07 (m, 2H), 1.65-1.70 (m, 2H), 1.33-1.37 (m, 2H), 1.25-1.30 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 203.8, 196.2, 159.8, 156.0, 130.5, 129.1, 128.8, 128.6, 128.3, 128.1, 127.8, 127.5, 115.5, 96.9, 94.8, 94.4, 59.6, 56.5, 56.3, 42.5, 31.5, 29.7, 27.2, 26.5, 25.63 (C×3), 23.4, 22.6, 14.1; HR-ESI(+)MS *m/z* 609.3408 $[M + Na]^+$ (calcd for $C_{34}H_{50}O_8Na$, 609.3398).

12c': ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 6.53 (s, 2H), 5.71 (s, 1H), 5.30-5.37 (m, 8H), 5.15 (s, 2H), 5.13 (s, 4H), 3.47 (s, 3H), 3.45 (s, 6H), 2.79-2.84 (m, 6H), 2.36 (t, *J* = 7.7 Hz, 2H), 2.12-2.15 (m, 2H), 2.04-2.07 (m, 2H), 1.70-1.75 (m, 2H), 1.33-1.37 (m, 2H), 1.25-1.30 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 192.8, 185.6, 159.8, 156.0, 130.5, 129.1, 128.8, 128.6, 128.3, 128.1, 127.8, 127.5, 113.2, 103.6, 97.5, 95.0, 94.4, 56.3, 56.2, 37.8, 31.5, 29.3, 27.2, 26.7, 25.63 (C×4), 22.6, 14.1; HR-ESI(+)MS *m/z* 609.3408 $[M + Na]^+$ (calcd for $C_{34}H_{50}O_8Na$, 609.3398).



12c and **12c'**: R = MOM

1) HCl/MeOH, MeOH **1** = 16.1%, **9** = 33.3%
2) TFA, DCM **9** = 85%



1 **9**

9: ^{1}H NMR (600 MHz, DMSO-d_6): δ_H = 12.77 (s, 1H), 10.77 (br, 1H), 6.28 (d, *J* = 2.0 Hz 1H), 6.13 (d, *J* = 2.0 Hz 1H), 6.11 (s, 1H), 5.31-5.38 (m, 2H), 5.23-5.30 (m, 6H), 2.70-2.75 (m, 6H), 2.57 (t, *J* = 7.6 Hz 2H), 2.08 (q, *J* = 6.9 Hz 2H), 1.95 (q, *J* =

7.2 Hz 2H), 1.65-1.70 (m, 2H), 1.22-1.27 (m, 2H), 1.16-1.21 (m, 4H), 0.79 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 182.2, 170.8, 164.6, 162.0, 158.2, 130.4, 129.3, 128.9, 128.5, 128.31, 128.27, 128.1, 127.9, 107.9, 104.0, 99.2, 94.1, 33.2, 31.3, 29.14, 29.14, 27.0, 26.5, 26.3, 25.7, 25.6, 22.4, 14.3; UV (MeOH) λ_{max} (log ε) 215 (3.76), 218 (3.76), 239 (3.78), 246 (3.77) and 285 (3.38) nm; HR-ESI(+)MS m/z 437.2689 $[M + H]^+$ (calcd for $C_{28}H_{37}O_4$, 437.2686).

Bioassays

BACE1 inhibitory assay

The TruPoint Beta-Secretase Assay was conducted according to manufacturer's instructions (Perkin Elmer, AD0258). Briefly, compounds of interest were dispensed in duplicate into a 384 well plate at the desired concentrations (7% DMSO). BACE (0.3 mU/μL; Invitrogen, P2947) was added before incubating the plate at room temperature for 30 minutes. The reaction was started by the addition of substrate (200 nmol/L) to a final assay volume of 30 μL. The assay plate was incubated for 24 hours at room temperature, protected from light and covered with parafilm to prevent evaporation. The assay was read at 340/615nm using an Envision plate reader. Concentrations given are for final assay conditions.

CDK5 (Cyclin-dependent kinase 5)/p25 inhibitory assay

Assay buffer: 6.25 mM MOPS, pH 7.2, 6.25 mM $MgCl_2$, 1.25 mM EGTA, 1.25 mM EDTA, 0.25% glycerol. Assay components were sourced as follows: CDK5/p25 (Sigma Aldrich, C0745), ATP (Sigma Aldrich, A7699), Histone (Sigma Aldrich, H4524), Kinase-Glo (Promega, V6712), 384 well plates (Perkin Elmer, 6007290).

CDK5/p25 (0.8 ng/μL) was added to a 384 well plate containing compounds of interest (1% DMSO) that had been dispensed in duplicate. Following a 10 minutes' incubation at room temperature, ATP (4 μM) and Histone (300 μg/mL) were added to a final assay volume of 25 μL. The assay plate was covered with parafilm to prevent evaporation and incubated at 27 °C for 60 minutes. The plate was equilibrated at room temperature for 10 minutes before the addition of Kinase-Glo reagent (20 μL). After a further 10 minutes luminescence was measured with a Polarstar plate reader. Concentrations given are for final assay conditions. Controls included a 'No Kinase' control (ATP, Histone only), 'Kinase' control (Kinase, ATP and Histone) and a 'Vehicle' control (Kinase, ATP, Histone and DMSO). Percent inhibition was calculated as follows: Percent inhibition = ((Test sample – Kinase control) / (No Kinase control – Kinase control)) × 100. IC_{50} values were calculated using Prism.

GSK3β (Glycogen synthase kinase 3β) inhibitory assay

Assay buffer: 50 mM HEPES, pH 7.5, 1 mM EDTA, 1 mM EGTA, 15 mM $Mg(CH_3CO_2)_2$. Assay components were sourced as follows: GSK3β (Millipore, 14-306), GSK3β substrate C-terminal fragment of GS-2 peptide [His-Ser-Ser-Pro-His-Gln-Ser(PO_3H_2)-Glu-Asp-Glu-Glu-Glu] (Auspep), ATP (Sigma Aldrich, A7699), Kinase-Glo (Promega, V6712), 384 well plates (Perkin Elmer, 6007290).

GSK3β (0.4 ng/μL) was added to a 384 well plate containing compounds of interest (1% DMSO) that had been dispensed in duplicate. Following a 10 minutes' incubation at room temperature, ATP (0.4 μM) and GSK3β substrate (15 μM) were added to a final assay volume of 25 μL. The assay plate was covered with parafilm to prevent evaporation and incubated at room temperature for 60 minutes. Kinase-Glo reagent (20 μL) was added and incubated for a further 10 minutes before measuring luminescence with a Polarstar plate reader. Concentrations given are for final assay conditions. Controls included a 'No Kinase' control (ATP, GSK3β substrate only), 'Kinase' control (Kinase, ATP and GSK3β substrate) and a 'Vehicle' control (Kinase, ATP, GSK3β substrate and DMSO). Percent inhibition was calculated as follows Percent inhibition = ((Test sample – Kinase control) / (No Kinase control – Kinase control)) × 100. IC_{50} values were calculated using Prism.

CK1δ (Casein kinase 1δ) inhibitory assay

Assay buffer: 7.5 mM MOPS, pH 7.0, 0.25 mM EDTA, 0.003% Brij-35, 1% Glycerol, 0.03% BME, 0.5 mg/mL BSA, 12.5 mM $Mg(CH_3CO_2)_2$. Assay components were sourced as follows: CK1 delta (Millipore, 14-520), CK1tide (Millipore, 12-529), ATP (Sigma Aldrich, A7699), Kinase-Glo (Promega, V6712), 384 well plates (Perkin Elmer, 6007290).

CK1δ (0.4 ng/μL) was added to a 384 well plate containing compounds of interest (1% DMSO) that had been dispensed in duplicate. Following a 10 minutes' incubation at room temperature, ATP (6 μM) and CK1tide (125 μM) were added to a final assay volume of 25 μL. The assay plate was covered with parafilm to prevent evaporation, and incubated at 27 °C for 60 minutes. The plate was then equilibrated at room temperature for 10 minutes before the addition of Kinase-Glo reagent (20 μL). After a further 10 minutes luminescence was measured with a Polarstar plate reader.

Concentrations given are for final assay conditions. Controls included a 'No Kinase' control (ATP, CK1tide only), 'Kinase' control (Kinase, ATP and CK1tide) and a 'Vehicle' control (Kinase, ATP, CK1tide and DMSO). Percent inhibition was calculated as follows: Percent inhibition = ((Test sample – Kinase control) / (No Kinase control – Kinase control)) × 100. IC_{50} values were calculated using Prism.

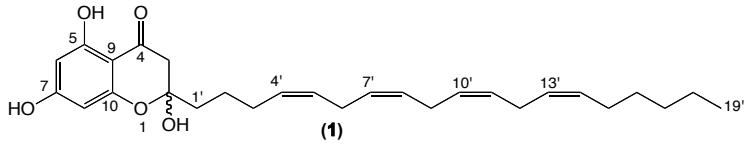
Antibacterial Assay

The bacterium to be tested was streaked onto a tryptic soy agar plate and was incubated at 37 °C for 24 h. One colony was then transferred to fresh tryptic soy broth (15 mL) and the cell density was adjusted to 10^4–10^5 cfu/mL. Test compounds were dissolved in DMSO and diluted with H_2O to give a 300 μM stock solution (10% DMSO). The stock solution was then serially diluted with 10% DMSO to give final concentrations of 30 μM to 0.01 μM in 1% DMSO. An aliquot (20 μL) of each dilution was transferred to a 96-well microtitre plate and freshly prepared microbial broth (180 μL) was added to each well. The plates were incubated at 37 °C for 24 h and the optical density of each well was measured spectrophotometrically at 600 nm. Each test compound was screened against the Gram-negative bacterium *Escherichia coli* (ATCC 11775), and the Gram-positive bacteria *Staphylococcus aureus* (ATCC 9144 and ATCC 25923) and *Bacillus subtilis* (ATCC 6633 and ATCC 6051).

Antifungal Assay

The fungus to be tested was streaked onto a Sabouraud agar plate and was incubated at 26.5 °C for 48 h. One colony was then transferred to fresh Sabouraud broth (15 mL) and the cell density was adjusted to 10^4–10^5 cfu/mL. Test compounds were dissolved in DMSO and diluted with H_2O to give a 300 μM stock solution (10% DMSO). The stock solution was then serially diluted with 10% DMSO to give final concentrations of 30 μM to 0.01 μM in 1% DMSO. An aliquot (20 μL) of each dilution was transferred to a 96-well microtitre plate and freshly prepared microbial broth (180 μL) was added to each well. The plates were incubated at 26.5 °C for 48 h and the optical density of each well was measured spectrophotometrically at 600 nm. Each test compound was screened against the fungus *Candida albicans* (ATCC 90028).

Assay buffer: 6.25 mM MOPS, pH 7.2, 6.25 mM $MgCl_2$, 1.25 mM EGTA, 1.25 mM EDTA, 0.25% glycerol. Assay components were sourced as follows: CDK5/p25 (Sigma Aldrich, C0745), ATP (Sigma Aldrich, A7699), Histone (Sigma Aldrich, H4524), Kinase-Glo (Promega, V6712), 384 well plates (Perkin Elmer, 6007290).

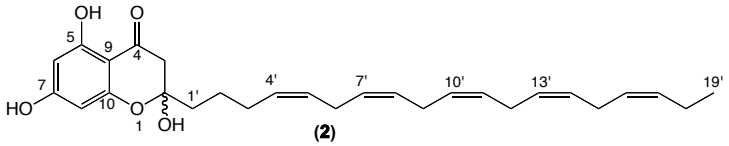


(**1**)

Table S1. NMR data ($CDCl_3$, 600 MHz) for spiralisone A (**1**)

No.	δ_C [A]	δ_H (multi., *J* (Hz))	COSY	HMBC (^1H to ^{13}C)
2	102.5			
3	45.1	a 2.88 (d, 16.9)	H-3′b	C-2′, C-4′
		b 2.74 (d, 16.9)	H-3′a	C-2′, C-4′
4	195.0			
5	164.2			
6	97.0	5.96 (br s)		C-5′, C-8′, C-9′
7	164.7			
8	96.2	5.89 (br s)		C-6′, C-7′, C-9′, C-10′
9	102.9			
10	160.2			
1′	40.8	1.89 (br t, 8.1)	H-2	C-2, C-3, C-2′, C-3′
2′	23.4	1.58 (m)	H-1, H-3	
3′	27.0	2.15 (m)	H-2, H-4	C-1, C-2, C-4, C-5
4′	129.2	5.30–5.43 (m)		
5′	129.2[B]	5.30–5.43 (m)		
6′	25.9	2.77–2.85 (m)		
7′	128.9[B]	5.30–5.43 (m)		
8′	128.5[B]	5.30–5.43 (m)		
9′	25.9	2.77–2.85 (m)		
10′	128.3[B]	5.30–5.43 (m)		
11′	128.1[B]	5.30–5.43 (m)		
12′	25.9	2.77–2.85 (m)		
13′	127.7	5.31 (m)		C-15
14′	130.8	5.38 (m)	H-15	C-12
15′	27.5	2.03 (m)	H-14, H-16	C-13, C-14, C-16, C-17
16′	29.5	1.34 (m)	H-15, H-17	C-14, C-15, C-17, C-18
17′	31.7	1.26 (m)	H-16	C-18
18′	22.8	1.29 (m)	H-19	C-17
19′	14.3	0.87 (t, 7.0)	H-18	C-17, C-18
5′-OH		11.92 (s)		C-5′, C-6′, C-9′
7′-OH		5.70 (br s)		

[A] ^{13}C NMR assignments were supported by HSQC experiment; [B] Interchangeable signals within the column.

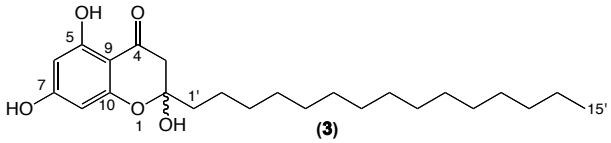


(**2**)

Table S2. NMR data ($CDCl_3$, 600 MHz) for spiralisone B (**2**)

No.	δ_C[A]	δ_H (multi., *J* (Hz))	COSY	HMBC (^1H to ^{13}C)
2	102.5			
3	45.1	a 2.88 (d, 17.2)	H-3′b	C-1, C-2′, C-4′
		b 2.74 (d, 17.2)	H-3′a	C-2′, C-4′
4	195.1			
5	164.1			
6	97.0	5.95 (d, 1.7)		C-5′, C-7′, C-8′, C-9′
7	164.9			
8	96.3	5.89 (d, 1.7)		C-6′, C-7′, C-9′, C-10′
9	102.8			
10	160.2			
1′	40.8	1.89 (br t, 8.2)	H-2	C-2, C-3, C-2′, C-3′
2′	23.4	1.58 (m)	H-1, H-3	C-1, C-3, C-4
3′	27.0	2.14 (m)	H-2, H-4	C-1, C-2, C-4, C-5
4′	129.2	5.32–5.44 (m)		
5′	129.2[B]	5.32–5.44 (m)		
6′	25.9[C]	2.77–2.85 (m)		
7′	128.8[B]	5.32–5.44 (m)		
8′	128.5[B]	5.32–5.44 (m)		
9′	25.9[C]	2.77–2.85 (m)		
10′	128.4[B]	5.32–5.44 (m)		
11′	128.3[B]	5.32–5.44 (m)		
12′	25.9[C]	2.77–2.85 (m)		
13′	128.3[B]	5.32–5.44 (m)		
14′	128.1[B]	5.32–5.44 (m)		
15′	25.8[C]	2.77–2.85 (m)		
16′	127.2	5.30 (m)		C-15, C-18
17′	132.3	5.38 (m)	H-18	C-18, C-19
18′	20.8	2.05 (m)	H-17, H-19	C-16, C-17, C-19
19′	14.5	0.95 (t, 7.5)	H-18	C-17, C-18
5′-OH		11.91 (s)		C-5′, C-6′, C-9′
7′-OH		5.99 (br s)		

[A] ^{13}C NMR assignments were supported by HSQC experiment; [B,C] Interchangeable signals within the column.

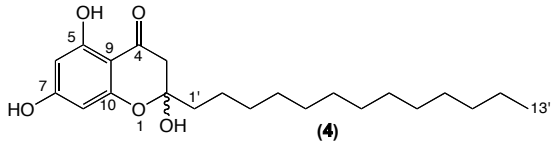


(3)

Table S3. NMR data ($CDCl_3$, 600 MHz) for spiralisone C (**3**)

No.	δ_C [A]	δ_H (multi., *J* (Hz))	COSY	HMBC (^1H to ^{13}C)
2	102.6			
3	45.1	2.88 (d, 16.9)	H-3′b	C-2′, C-4′
		2.75 (d, 16.9)	H-3′a	C-2′, C-4′
4	195.1			
5	164.2			
6	96.9	5.96 (d, 1.6)		C-5′, C-8′, C-9′
7	164.7			
8	96.1	5.89 (d, 1.6)		C-6′, C-7′, C-9′, C-10′
9	103.0			
10	160.2			
1′	41.4	1.87 (br t, 7.6)	H-2	C-2, C-3, C-2′, C-3′
2′	23.4	1.48 (m)	H-1, H-3	C-1, C-3
3′	29.7	1.34 (m)	H-2, H-4	
4′	29.9[B]	1.20–1.30		
5′	29.9[B]	1.20–1.30		
6′	29.9[B]	1.20–1.30		
7′	29.9[B]	1.20–1.30		
8′	29.9[B]	1.20–1.30		
9′	29.8[B]	1.20–1.30		
10′	29.7[B]	1.20–1.30		
11′	29.7[B]	1.20–1.30		
12′	29.6[B]	1.20–1.30		
13′	32.2	1.24 (m)		C-15
14′	22.9	1.27 (m)	H-15	C-13
15′	14.3	0.86 (t, 7.0)	H-14	C-13, C-14
5′-OH		11.93 (s)		C-5′, C-6′, C-9′
7′-OH		5.52 (br s)		

[A] ^{13}C NMR assignments were supported by HSQC experiment; [B] Interchangeable signals within the column.

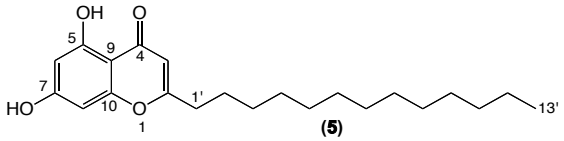


(**4**)

Table S4. NMR data ($CDCl_3$, 600 MHz) for spiralisone D (**4**)

No.	δ_C [A]	δ_H (multi., *J* (Hz))	COSY	HMBC (^1H to ^{13}C)
2	102.6			
3	45.1	a 2.88 (d, 16.9)	H-3′b	C-1, C-2′, C-4′
		b 2.74 (d, 16.9)	H-3′a	C-2′, C-4′
4	195.1			
5	164.2			
6	96.9	5.96 (br s)		C-5′, C-8′, C-9′
7	164.6			
8	96.2	5.89 (br s)		C-6′, C-7′, C-9′, C-10′
9	102.9			
10	160.3			
1′	41.4	1.87 (br t, 7.6)	H-2	C-2, C-3, C-2′, C-3′
2′	23.4	1.48 (m)	H-1, H-3	C-1, C-3
3′	29.7	1.34 (m)	H-2, H-4	C-1, C-2
4′	29.9[B]	1.21–1.30 (m)		
5′	29.9[B]	1.21–1.30 (m)		
6′	29.9[B]	1.21–1.30 (m)		
7′	29.8[B]	1.21–1.30 (m)		
8′	29.7[B]	1.21–1.30 (m)		
9′	29.7[B]	1.21–1.30 (m)		
10′	29.6[B]	1.21–1.30 (m)		
11′	32.1	1.24 (m)		
12′	22.9	1.28 (m)	H-13	C-11, C-13
13′	14.3	0.86 (t, 7.0)	H-12	C-11, C-12
5′-OH		11.93 (s)		C-5′, C-6′, C-9′
7′-OH		5.63 (br s)		

[A] ^{13}C NMR assignments were supported by HSQC experiment; [B] Interchangeable signals within the column.

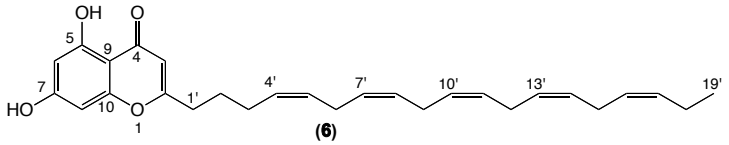


(5)

Table S5. NMR data ($CDCl_3$ with 2% CD_3OD, 600 MHz) for 5,7-Dihydroxy-2-tridecanyl chromone (**5**)

No.	δ_C [A]	δ_H (multi., *J* (Hz))	COSY	HMBC (^1H to ^{13}C)
2	170.7			
3	107.9	5.96 (s)		C-1, C-2′, C-9′
4	182.8			
5	158.8			
6	94.3	6.27 (d, 2.0)		C-8′, C-9′
7	163.8			
8	99.2	6.20 (d, 2.0)		C-6′, C-7′, C-9′, C-10′
9	104.9			
10	161.9			
1′	34.4	2.52 (br t, 7.6),	H-2	C-2, C-3, C-2′, C-3′
2′	26.9	1.65 (m)	H-1, H-3	C-1, C-3, C-2′
3′	29.2	1.33 (m)	H-2, H-4	
4′	29.8[B]	1.19–1.29 (m)		
5′	29.8[B]	1.19–1.29 (m)		
6′	29.8[B]	1.19–1.29 (m)		
7′	29.8[B]	1.19–1.29 (m)		
8′	29.6[B]	1.19–1.29 (m)		
9′	29.5[B]	1.19–1.29 (m)		
10′	29.4[B]	1.19–1.29 (m)		
11′	32.1	1.22 (m)		
12′	22.9	1.25 (m)	H-13	C-13, C-11
13′	14.3	0.84 (t, 7.0)	H-12	C-11, C-12

[A] ^{13}C NMR assignments were supported by HSQC experiment; [B] Interchangeable signals within the column.

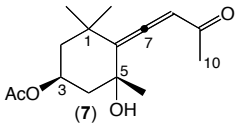


(**6**)

Table S6. NMR data ($CDCl_3$) comparison with literature data for 5,7-dihydroxy-2-(4*Z*,7*Z*,10*Z*,13*Z*,16*Z*-nonadecapentaenyl) chromone (**6**)

	1		**Literature data***	
No.	δ_C[A] (150 MHz)	δ_H[A] (600 MHz)	δ_C[A] (20 MHz)	δ_H[B] (270 MHz)
2	170.5		171.4	
3	108.2	6.02 (s)	107.7	6.21 (s)
4	182.8		183.2	
5	158.5		158.9	
6	94.3	6.31 (br s)	94.7	6.74 (d, 2)
7	162.6		163.9	
8	99.6	6.25 (br s)	100.0	6.68 (d, 2)
9	105.5		105.1	
10	162.6		162.5	
1′	33.9	2.56 (t, 7.7)	33.8	
2′	26.9	1.77 (m)	26.8	
3′	26.7	2.16 (m)	26.5	
4′	128.7	5.36 (m)	128.9	
5′	129.5	5.42 (m)	129.7	
6′	25.9[C]	2.77–2.84 (m)	25.7[E]	
7′	128.8[D]	5.32–5.39 (m)	128.7[F]	
8′	128.5[D]	5.32–5.39 (m)	128.6[F]	
9′	25.9[C]	2.77–2.84 (m)	25.7[E]	
10′	128.5[D]	5.32–5.39 (m)	128.6[F]	
11′	128.2[D]	5.32–5.39 (m)	128.3[F]	
12′	25.9[C]	2.77–2.84 (m)	25.7[E]	
13′	128.2[D]	5.32–5.39 (m)	128.3[F]	
14′	128.1[D]	5.32–5.39 (m)	128.3[F]	5.45
15′	25.8[C]	2.77–2.84 (m)	25.6[E]	2.94
16′	127.2	5.29 (m)	127.3	
17′	132.3	5.37 (m)	132.3	
18′	20.8	2.05 (m)	20.6	
19′	14.5	0.95 (t, 7.5)	14.3	
5′-OH		6.40 (br s)		
7′-OH		12.68 (br s)		

[A] measure in $CDCl_3$, [B] measured in pyridine-d_5;
[C–F] Interchangeable signals within the column.
* *Tetrahedron Lett.* **1982**, *23*, 1509–1512. *Org. Lett.* **2009**, *11*, 587–588.



(**7**)

Table S7. NMR data comparison with literature data for apo-9′-fucoxanthinone (**7**) in CD_3OD

	7		**Literature data***	
No.	δ_C (150 MHz)	δ_H (600 MHz)	δ_C	δ_H
1	37.1		37.2	
2	46.3	a. 1.48 (dd, 12.4, 11.5) b. 2.00 (ddd, 12.4, 4.2, 2.2)	46.4	a 1.60 (dd, 12.7, 11.5) b. 2.04 (ddd, 12.7, 4.1, 2.2)
3	69.1	5.38 (tt, 11.5, 4.2)	69.2	5.42 (tt, 11.5, 4.1)
4	46.2	a. 1.56 (dd, 12.9, 11.5) b. 2.23 (ddd, 12.9, 4.2, 2.2)	46.3	a. 1.49 (dd, 12.7, 11.5) b. 2.27 (ddd, 12.7, 4.1, 2.2)
5	72.4		72.4	
6	119.8		119.9	
7	211.6		211.6	
8	101.4	5.86 (s)	101.5	5.90 (s)
9	200.9		200.9	
10	26.8	2.20 (s)	26.9	2.24 (s)
11	29.4	1.43 (s)	29.5	1.46 (s)
12	32.2	1.17 (s)	32.3	1.20 (s)
13	30.7	1.39 (s)	30.8	1.43 (s)
MeCO	172.4		172.5	
MeCO	21.3	2.03 (s)	21.4	2.07 (s)

* *J. Nat. Prod., 1995, **58**, 1097–1099.*

Table S8. Kinase inhibitory and antimicrobial assay results (IC_{50} in μM)

	1	**2**	**3**	**4**	**5**	**6**	**7**
CDK5/p25	10	3.0	>30	>30	>30	10	>30
CK1δ	<10	5.0	*NT*	*NT*	*NT*	<10	*NT*
GSK3β	<10	5.4	*NT*	*NT*	*NT*	<10	*NT*
B. subtilis[a]	6.4	*NA*	8.7	2.5	*NA*	10	*NA*
B. subtilis[b]	8.1	*NA*	5.0	3.3	*NA*	5.3	*NA*
S. aureus[c]	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
S. aureus[d]	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
E. coli[e]	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
P. aeruginosa[f]	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
C. albicans[g]	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*

Microbial strains are: [a] ATCC 6051, [b] ATCC 6633, [c] ATCC 9144, [d] ATCC 25923, [e] ATCC 11775, [f] ATCC 10145, [g] ATCC 90028.

NT: Not tested; *NA*: Not active.

Figure S1 ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum for spiralisone A (**1**)

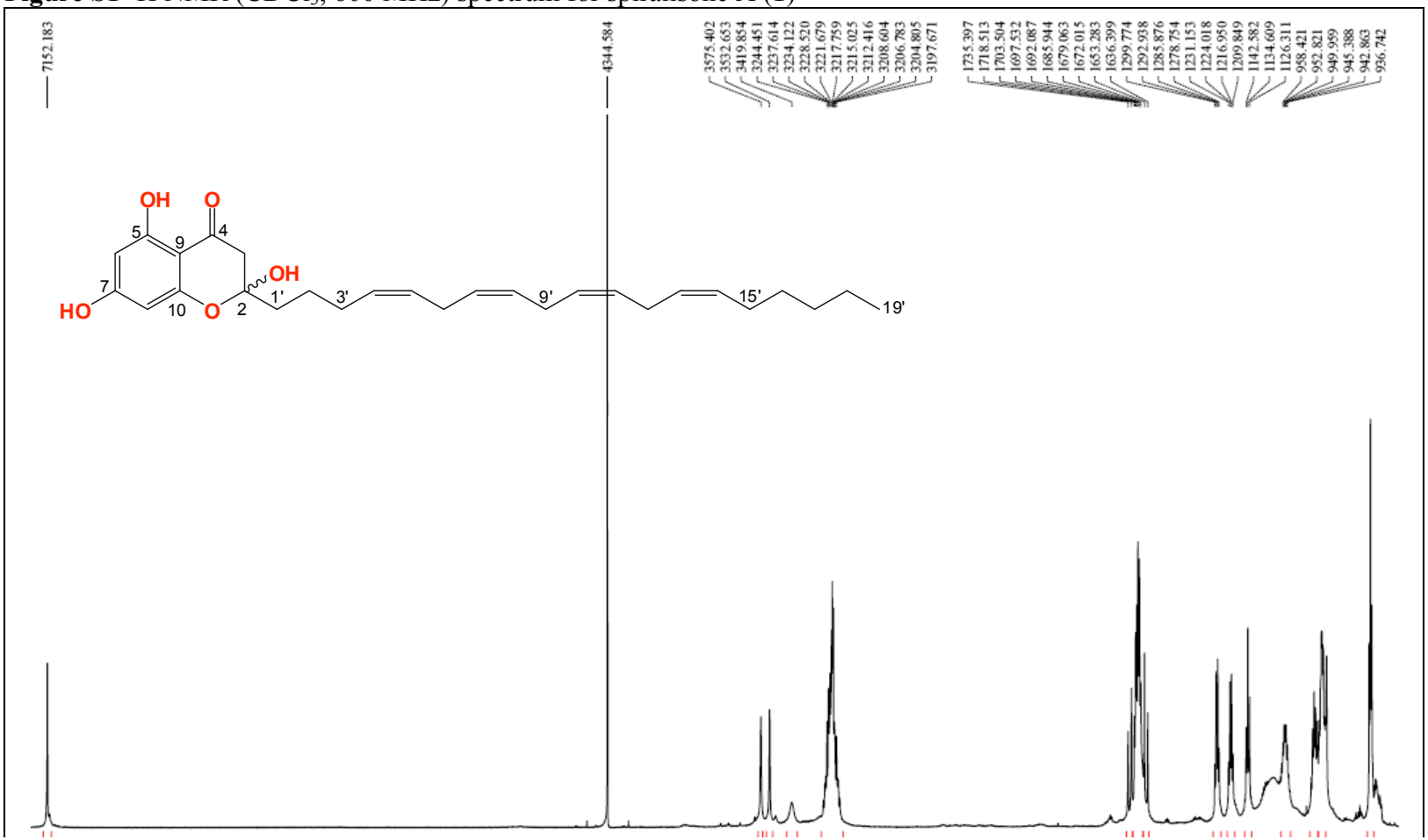


Figure S2 ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum for spiralisone B (**2**)

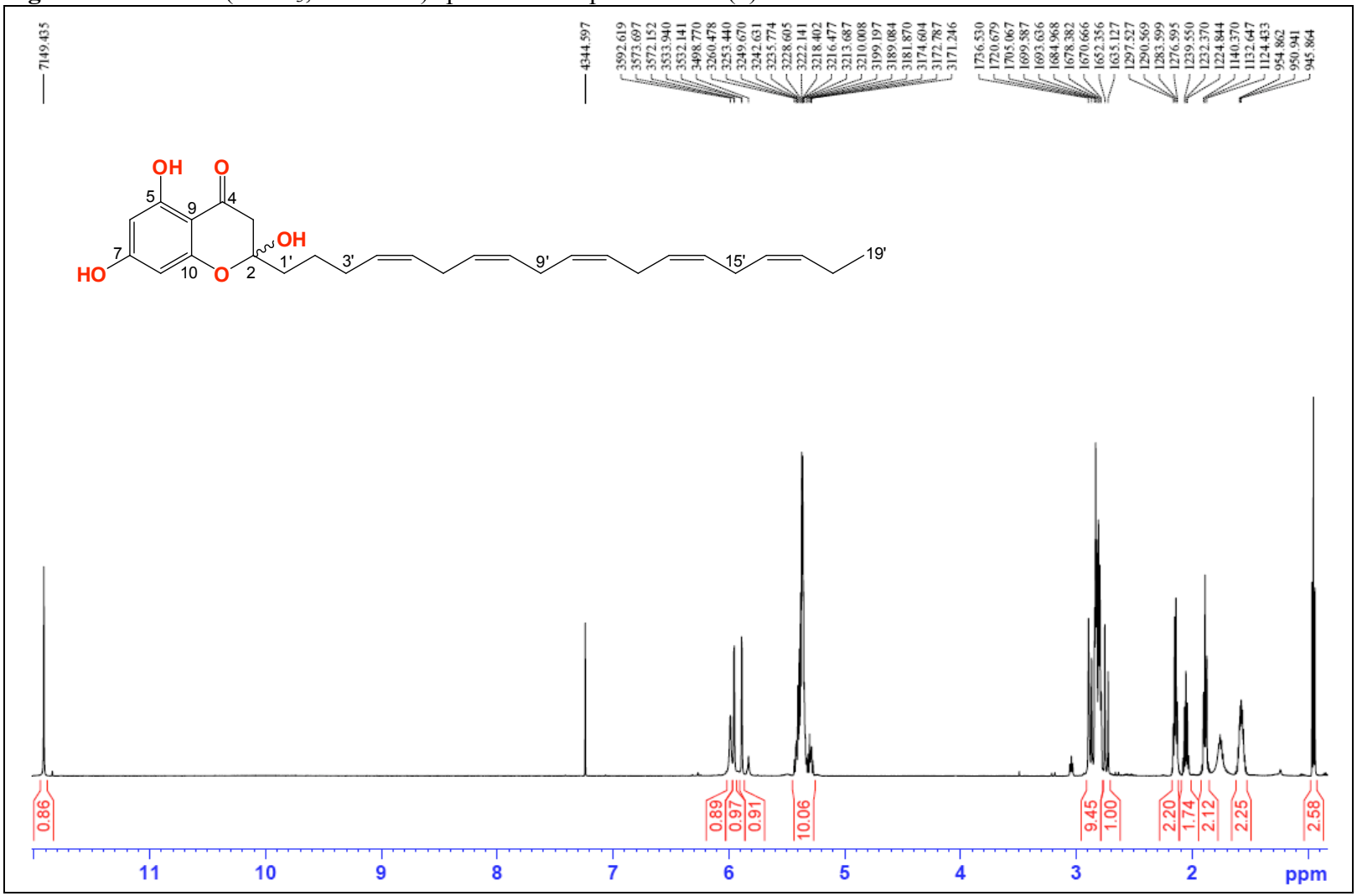


Figure S3 ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum for spiralisone C (**3**)

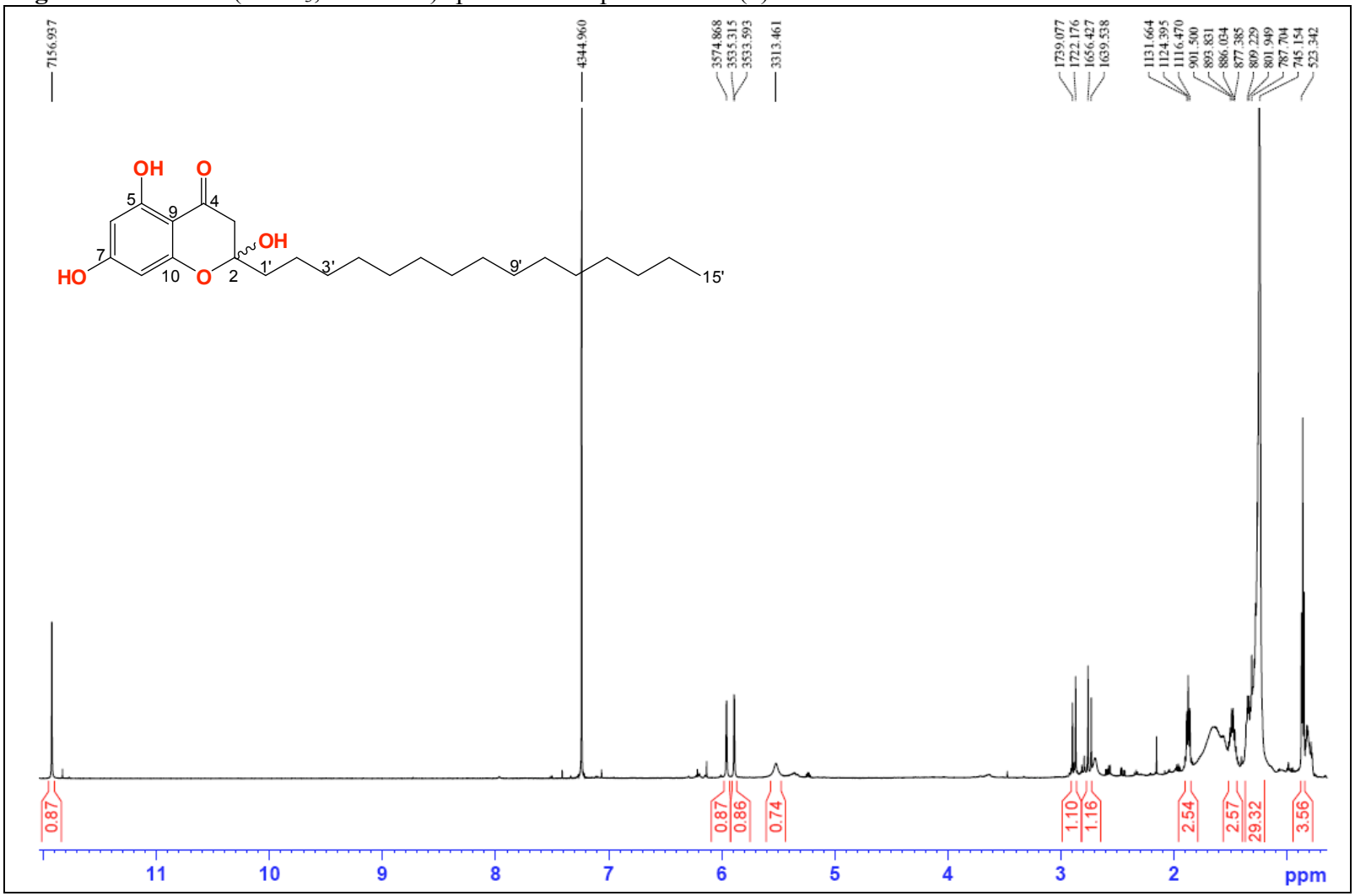


Figure S4 ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum for spiralisone D (**4**)

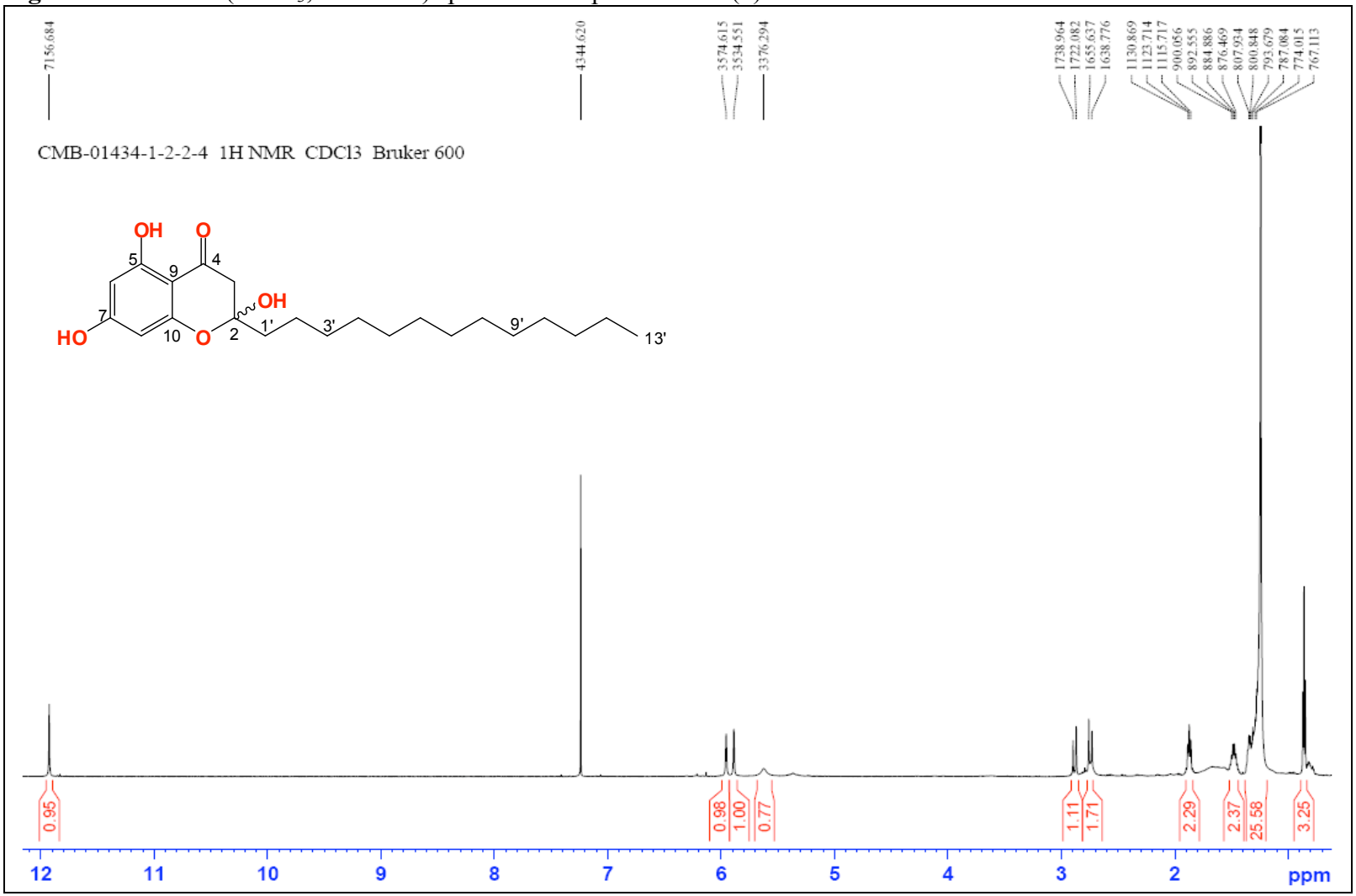


Figure S5 ^{1}H NMR ($CDCl_3$ with 2% CD_3OD, 600 MHz) for 5,7-Dihydroxy-2-tridecanyl chromone (**5**)

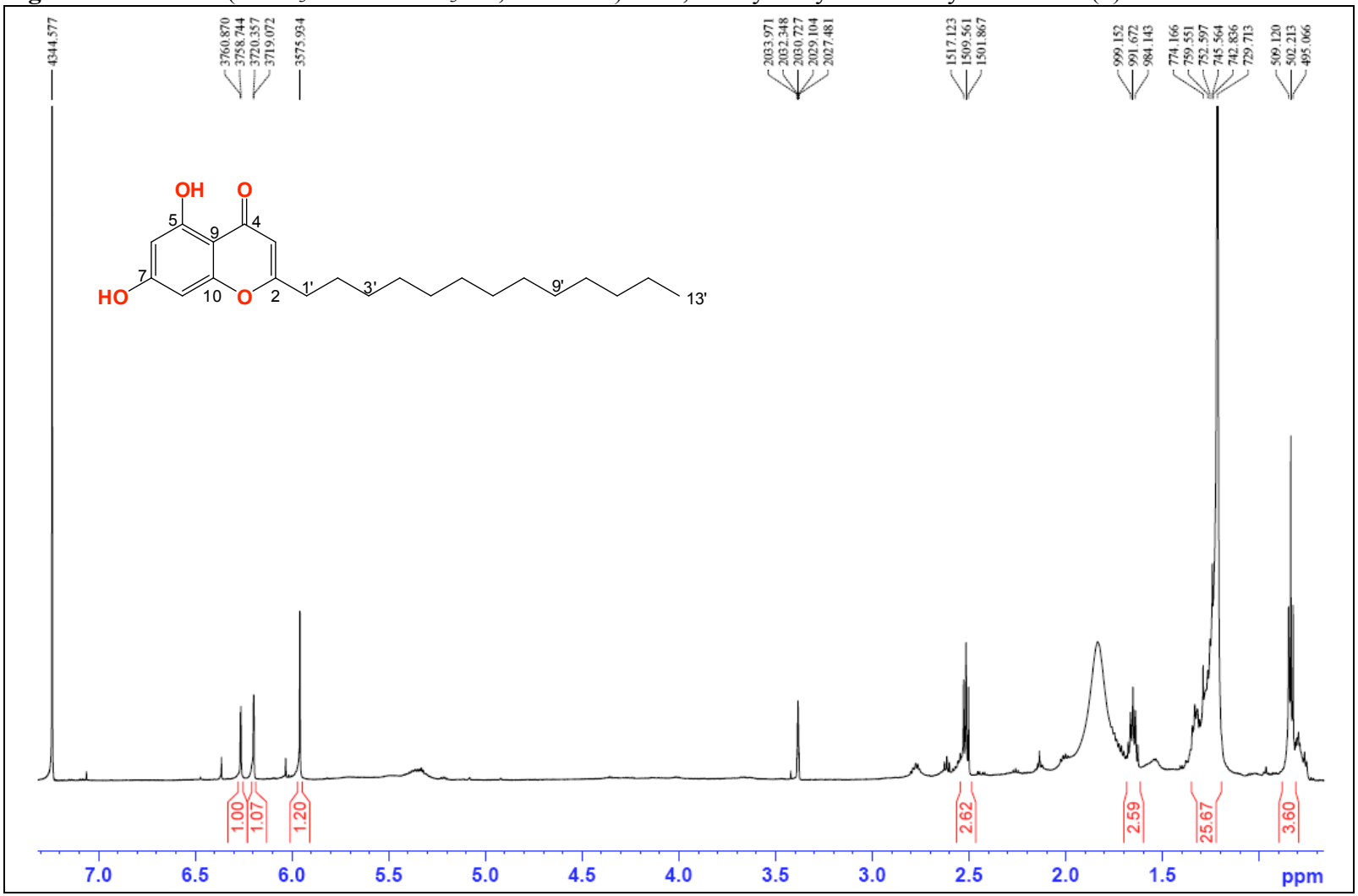


Figure S6 ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum for 5,7-dihydroxy-2-(4*Z*,7*Z*,10*Z*,13*Z*,16*Z*-nonadecapentaenyl) chromone (**6**)

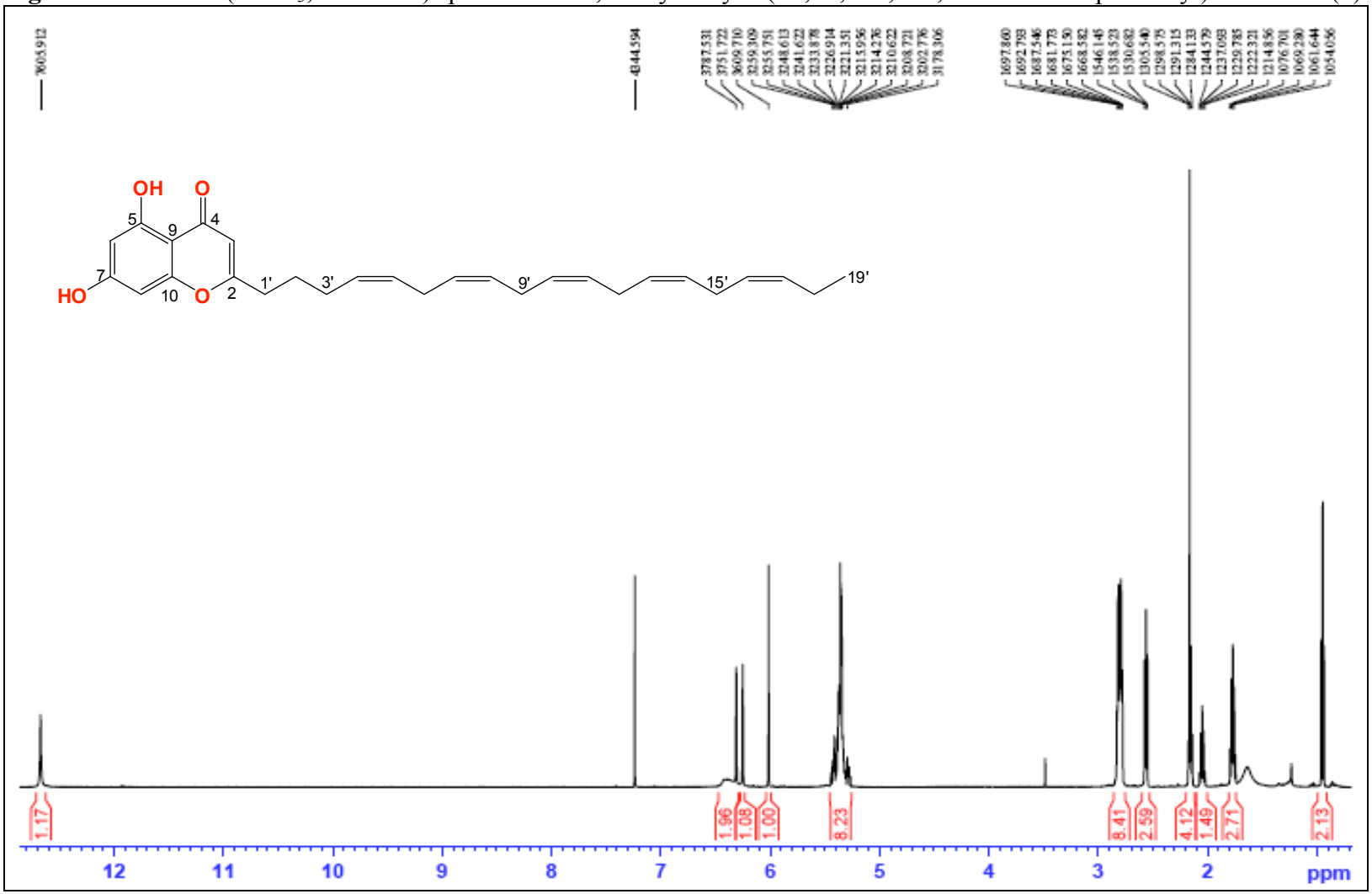


Figure S7 ^{1}H NMR (CD_3OD, 600 MHz) spectrum for compound apo-9′-fucoxanthinone (**7**)

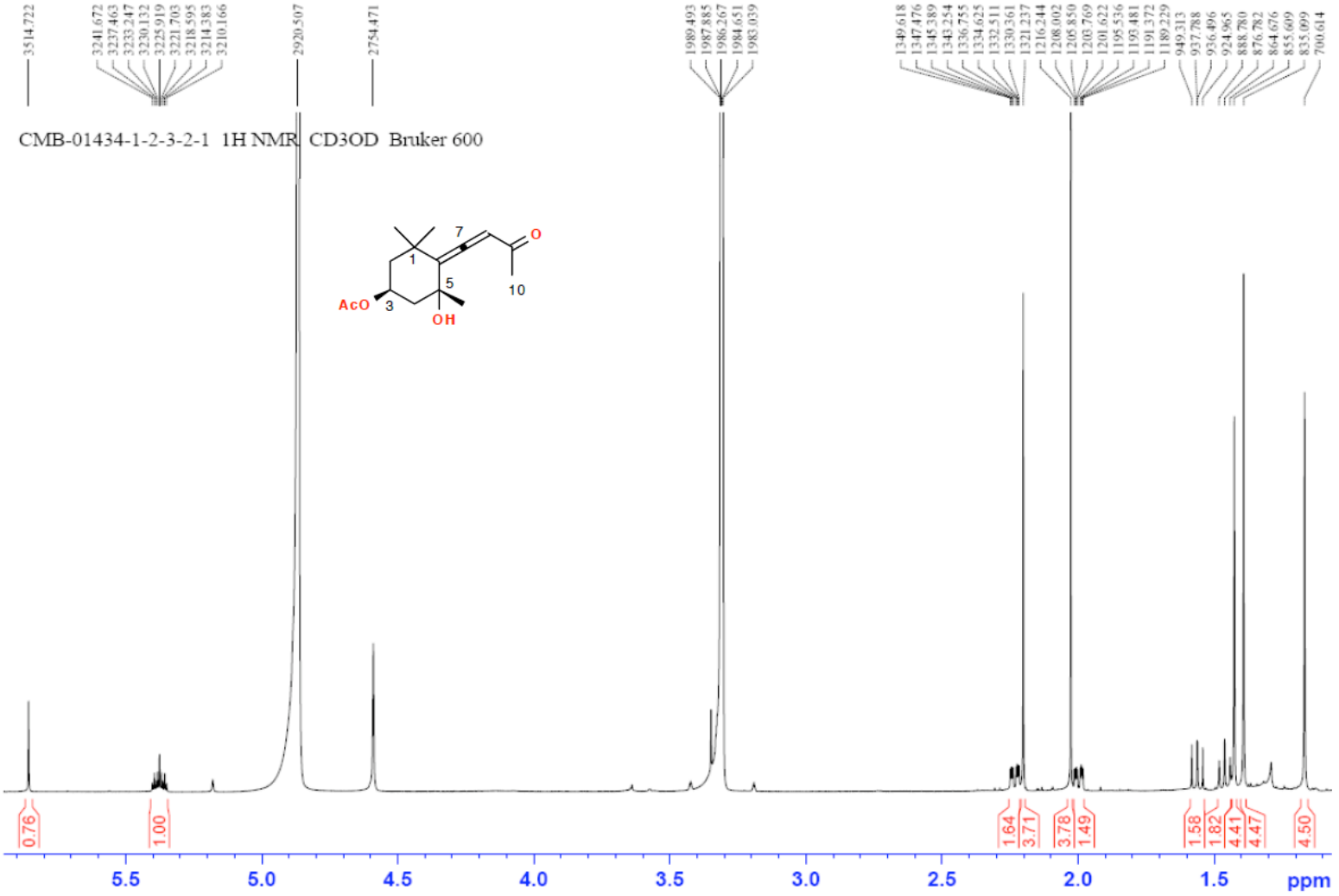


Figure S8 ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum for 8

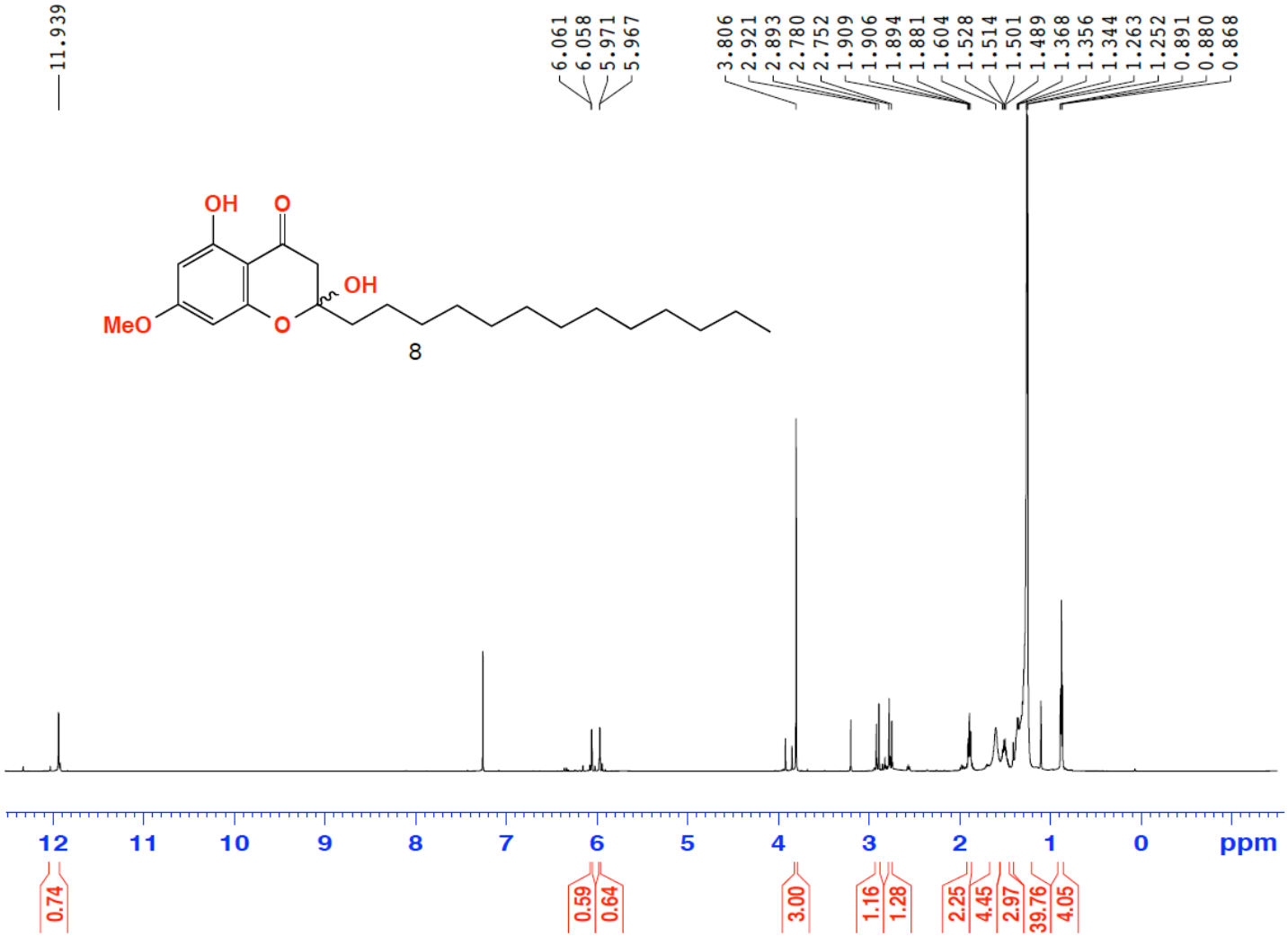


Figure S9 ^{13}C NMR ($CDCl_3$, 150 MHz) spectrum for **8**

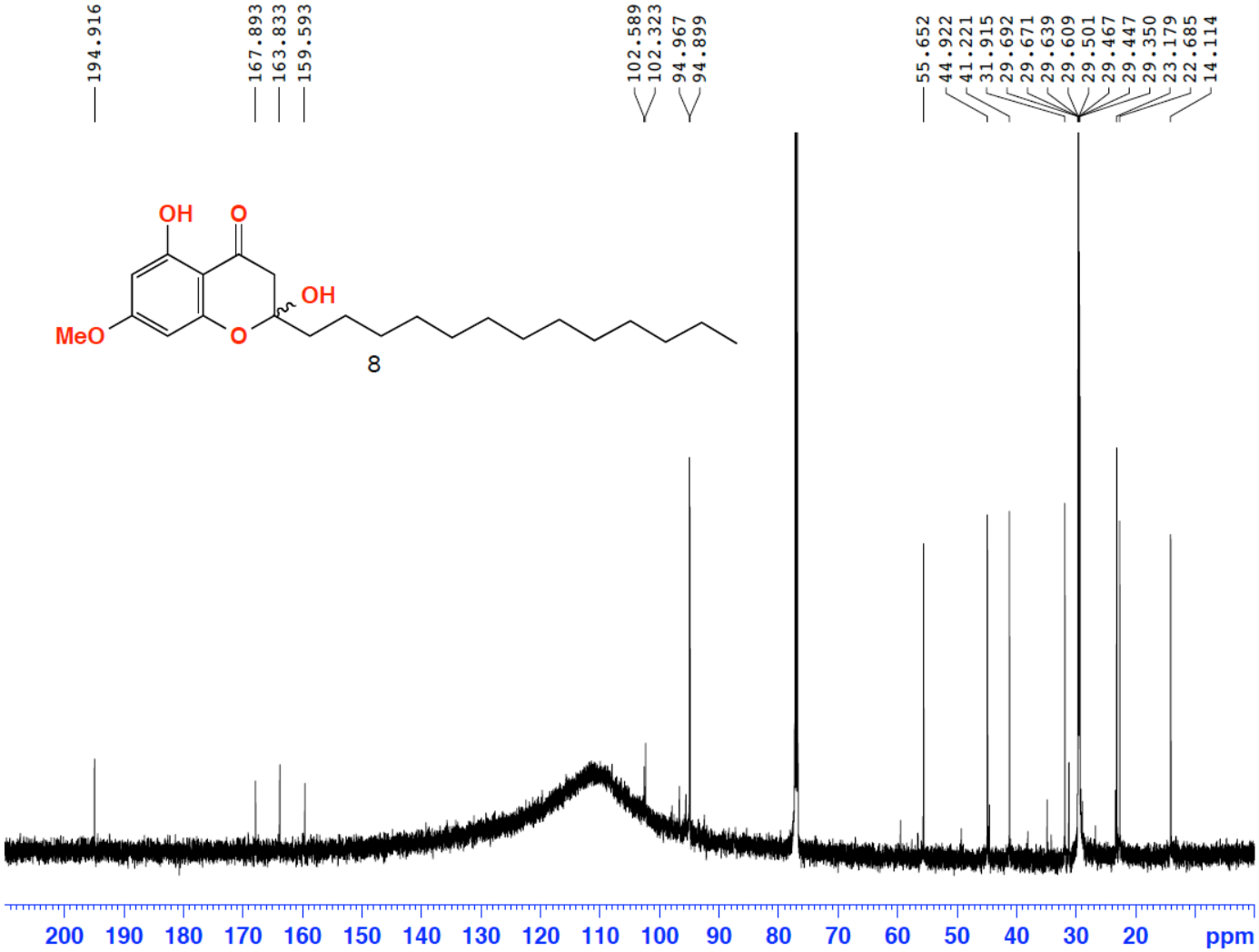


Figure S10 ^{1}H NMR (DMSO-d_6, 600 MHz) spectrum for **9**

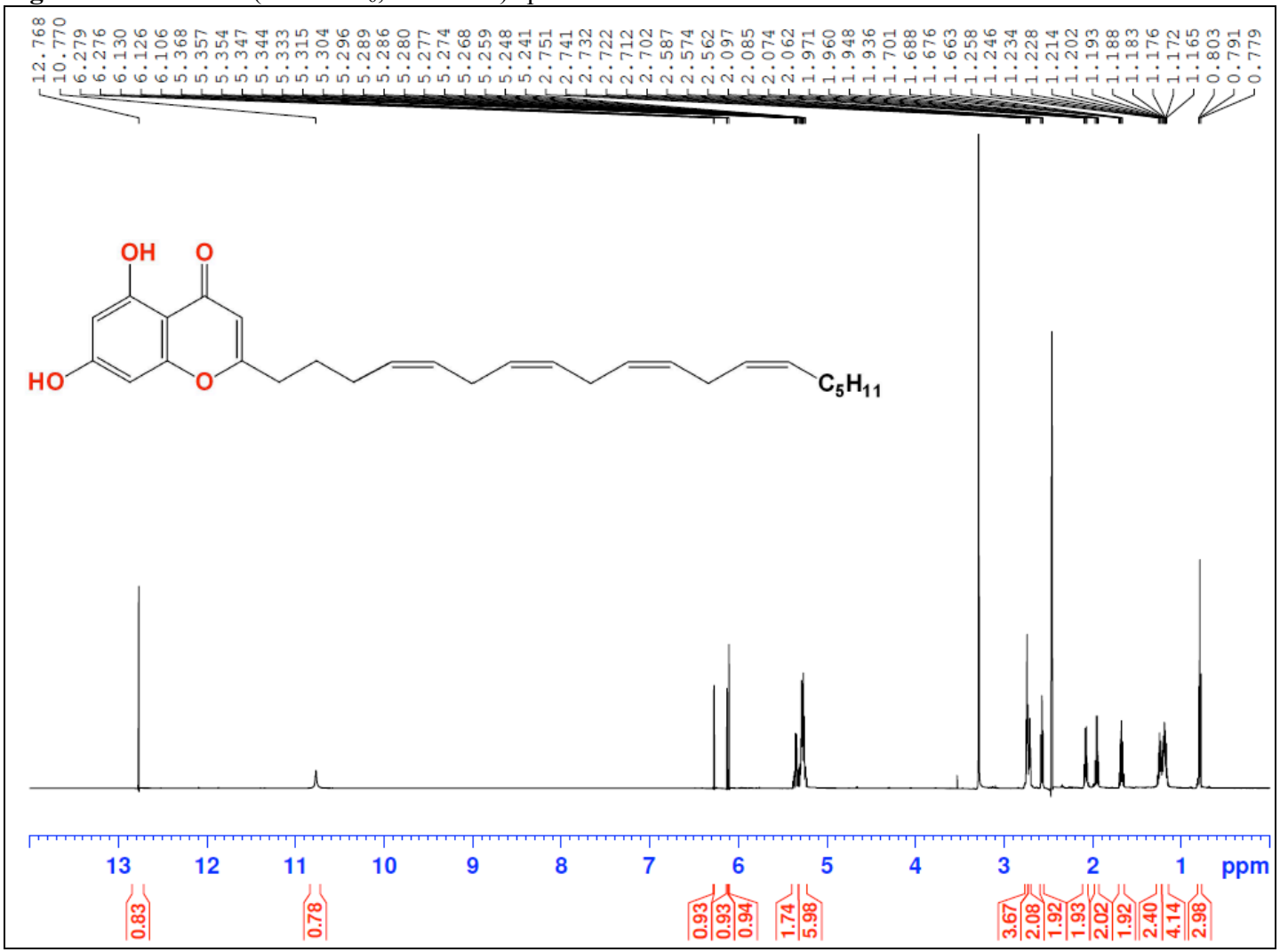


Figure S11 ^{13}C NMR (DMSO-d_6, 150 MHz) spectrum for **9**

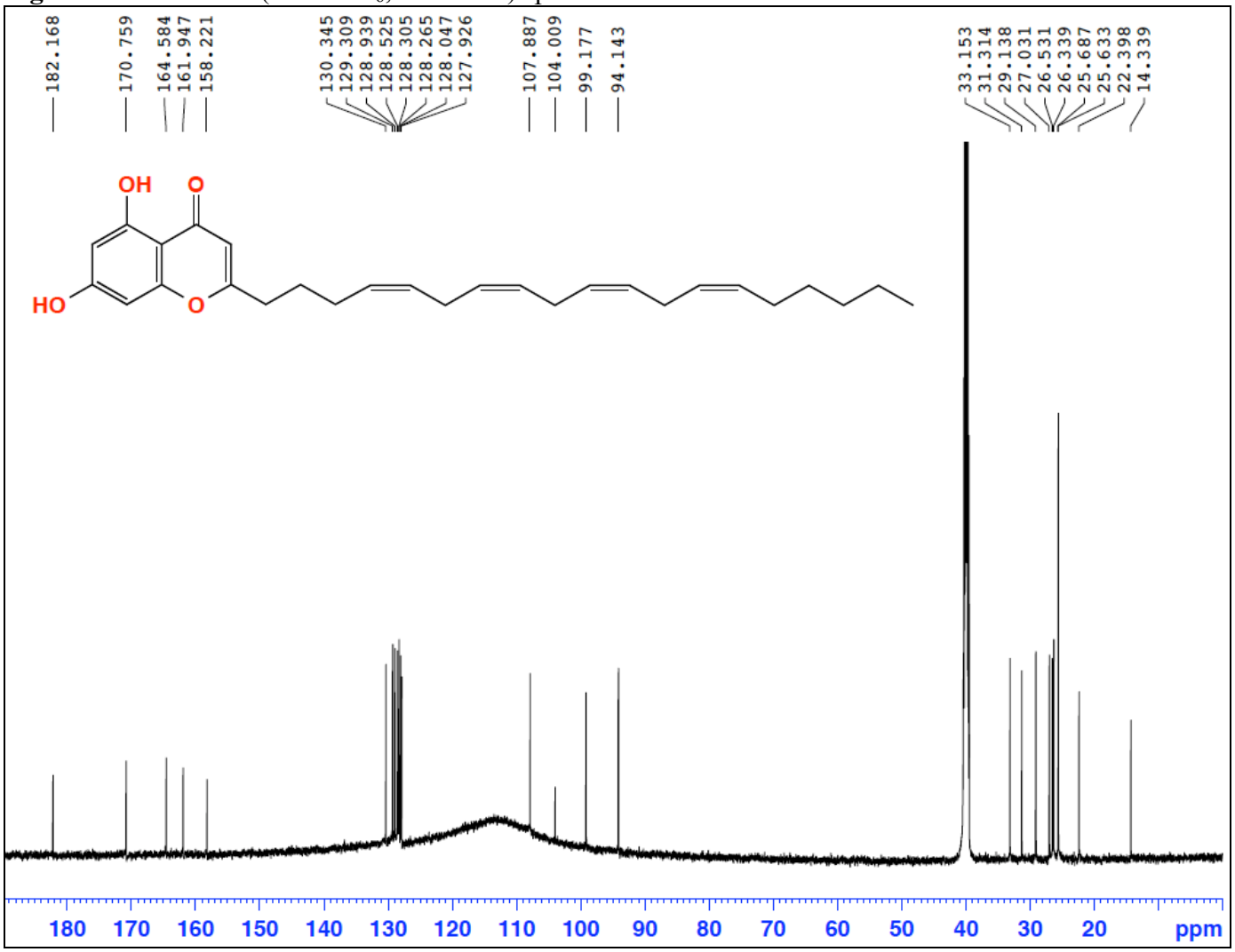


Figure S12 ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum for compound tetradecanal

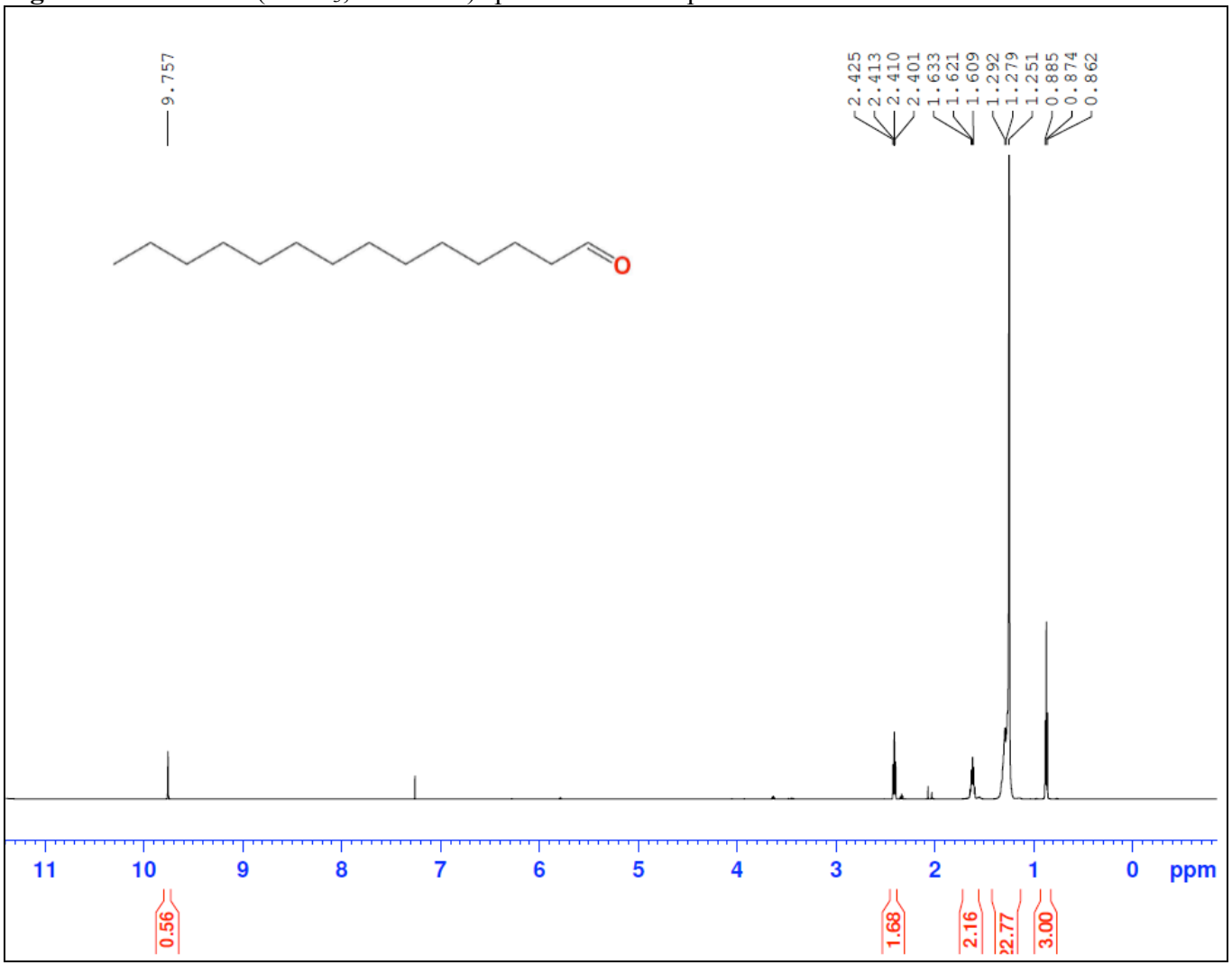


Figure S13 ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum for compound arachidonal

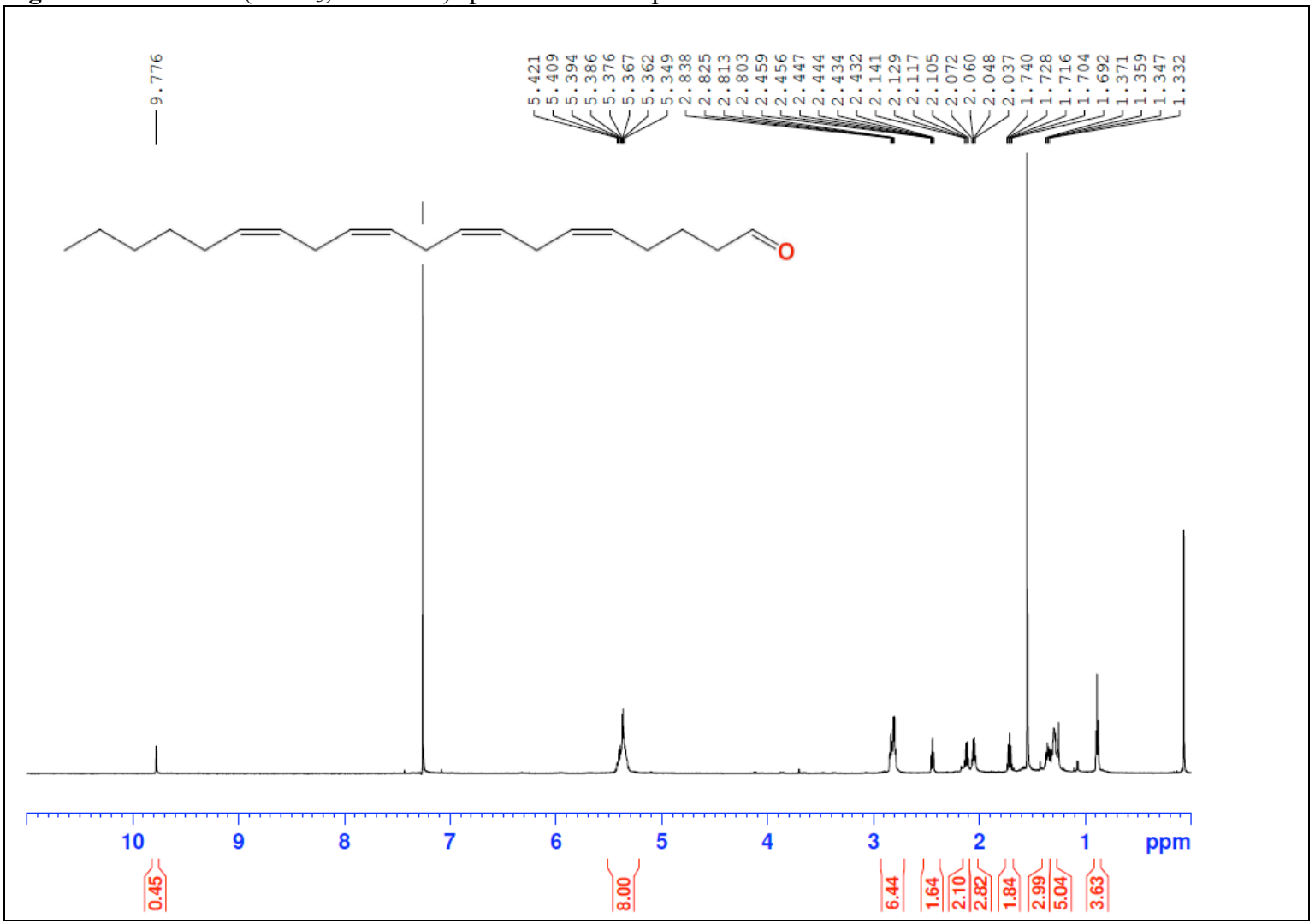


Figure S14 ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum for **11a**

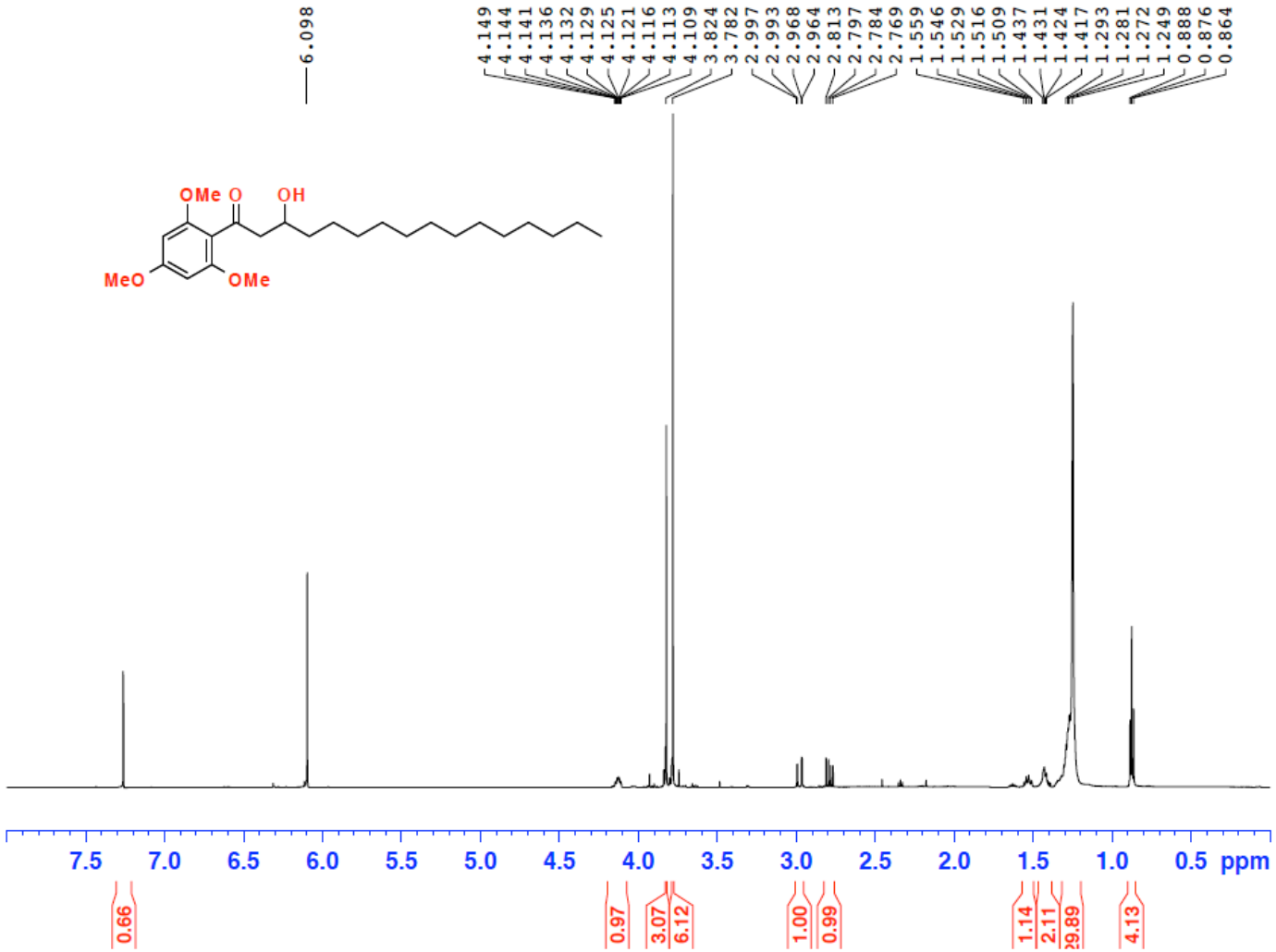


Figure S15 ^{13}C NMR ($CDCl_3$, 150 MHz) spectrum for **11a**

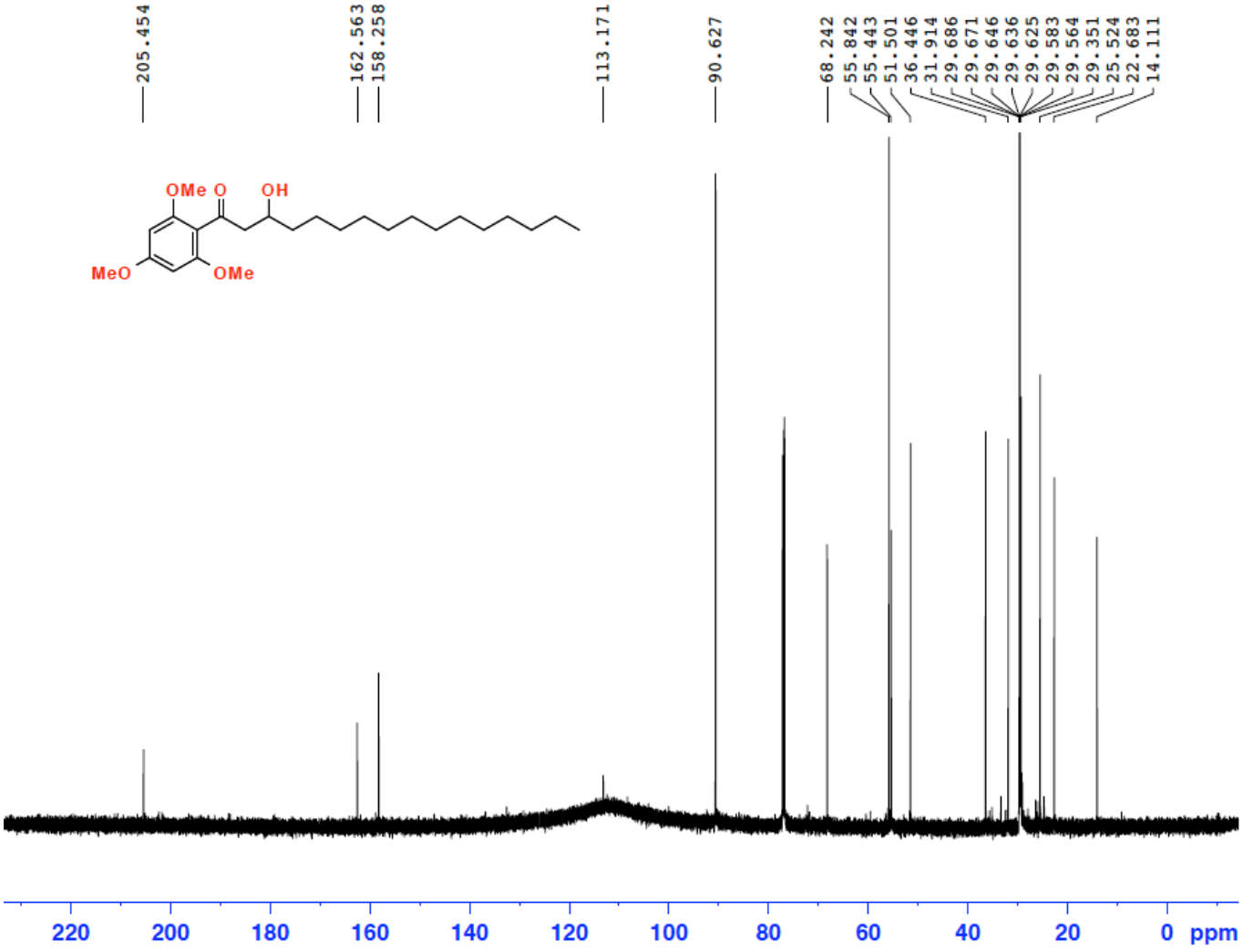


Figure S16 ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum for keto-enol (**12a, 12a'**)

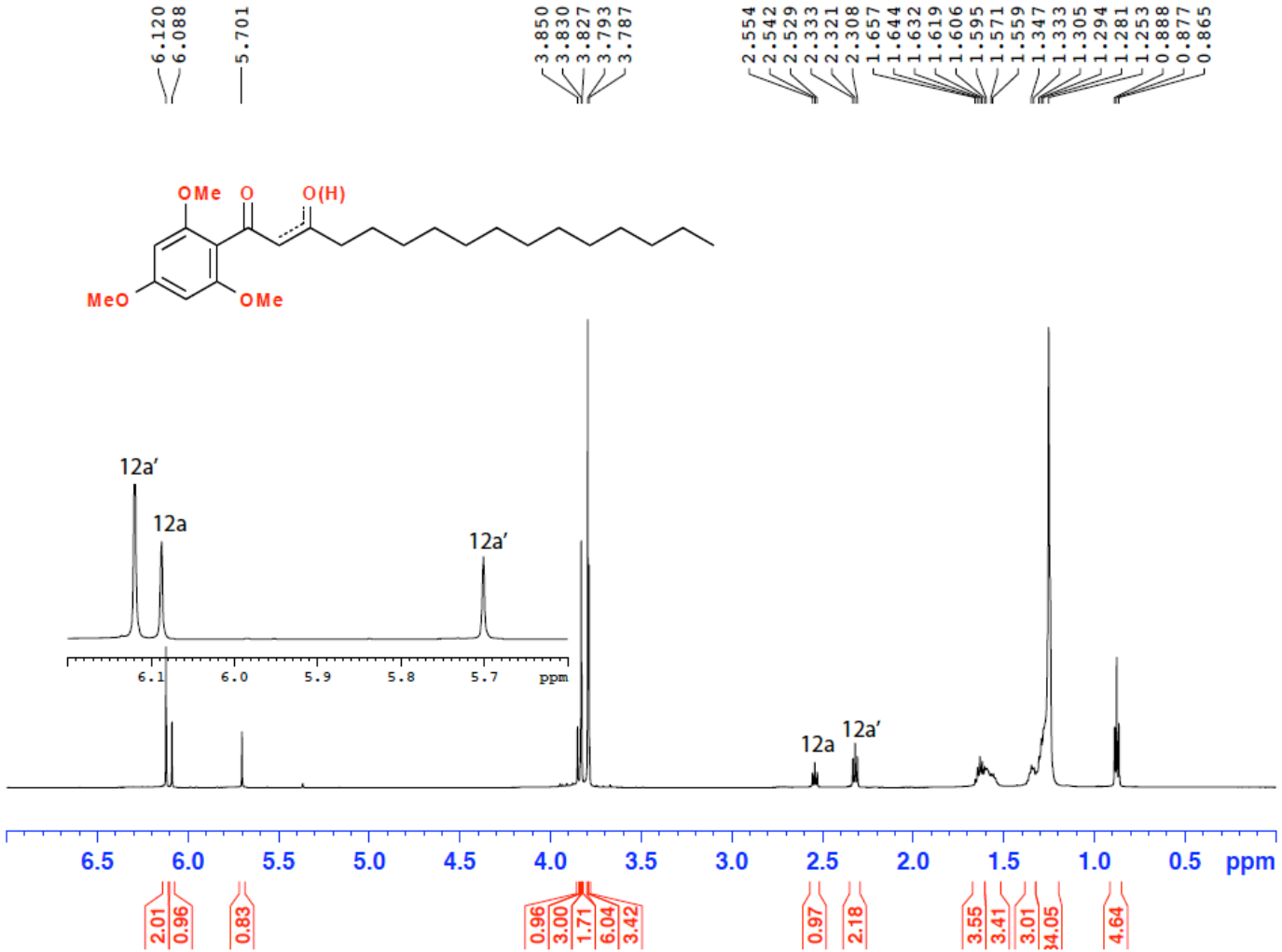


Figure S17 ^{13}C NMR ($CDCl_3$, 150 MHz) spectrum for keto-enol (**12a, 12a'**)

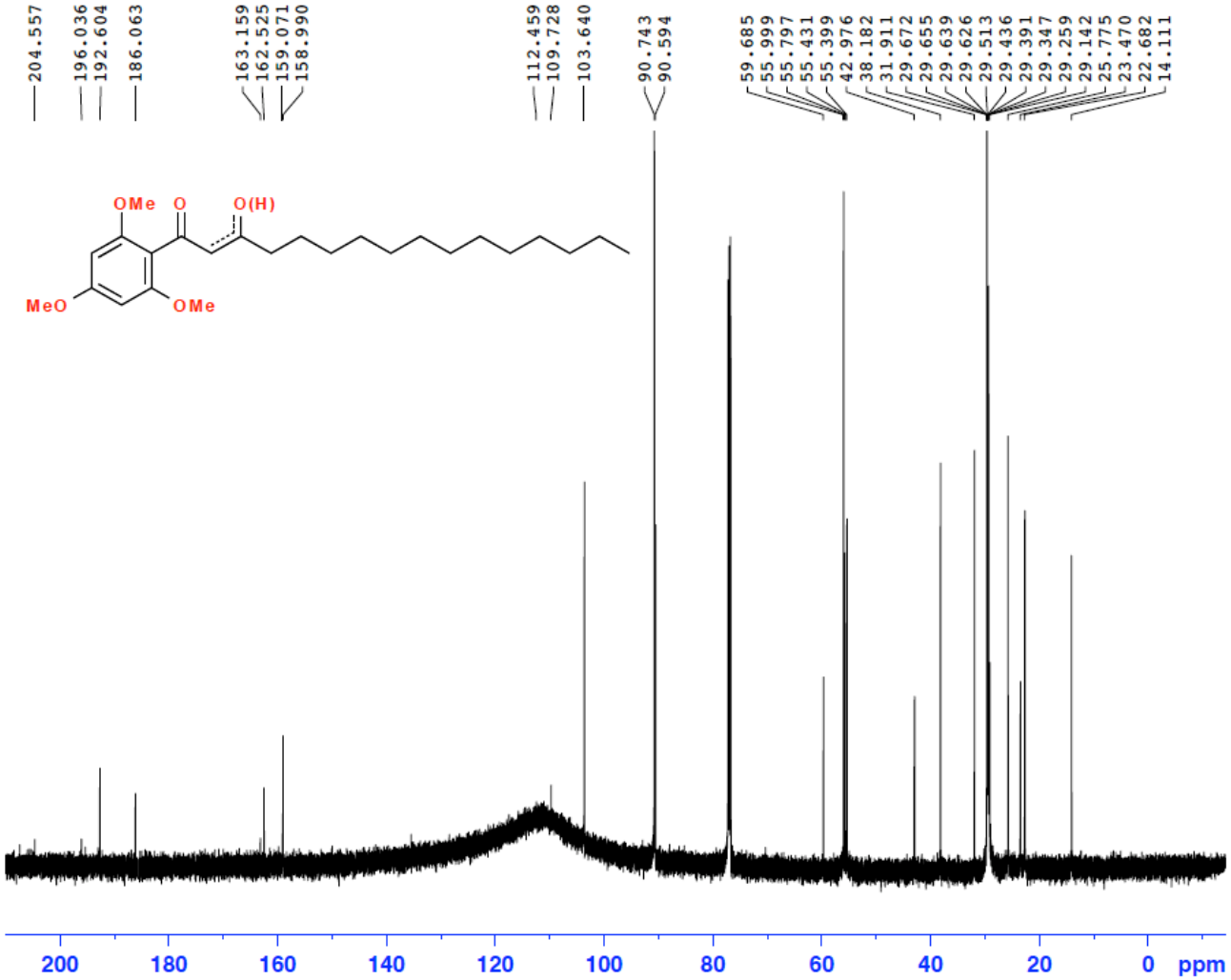


Figure S18 ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum for **11b**

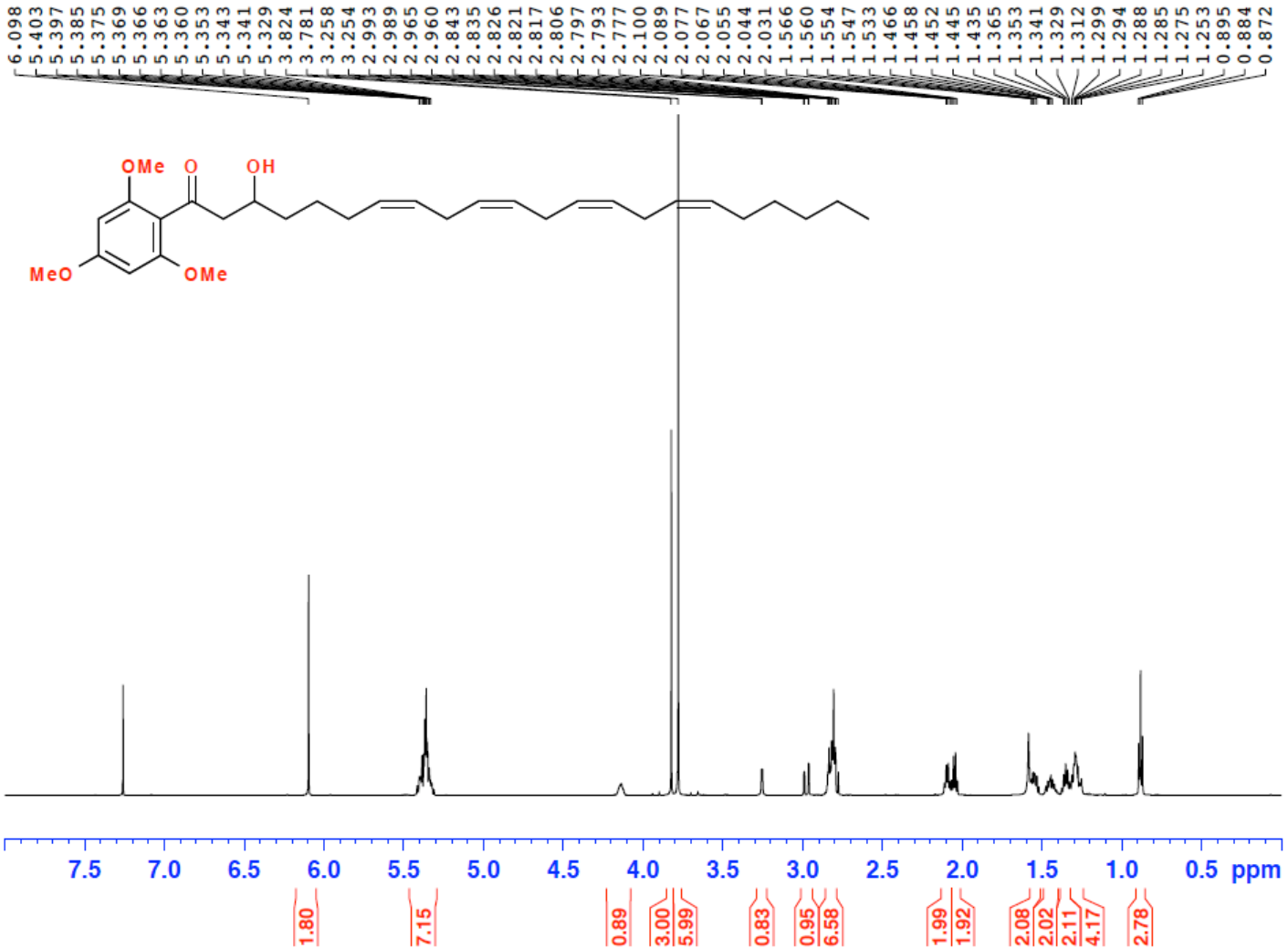


Figure S19 ^{13}C NMR ($CDCl_3$, 150MHz) spectrum for **11b**

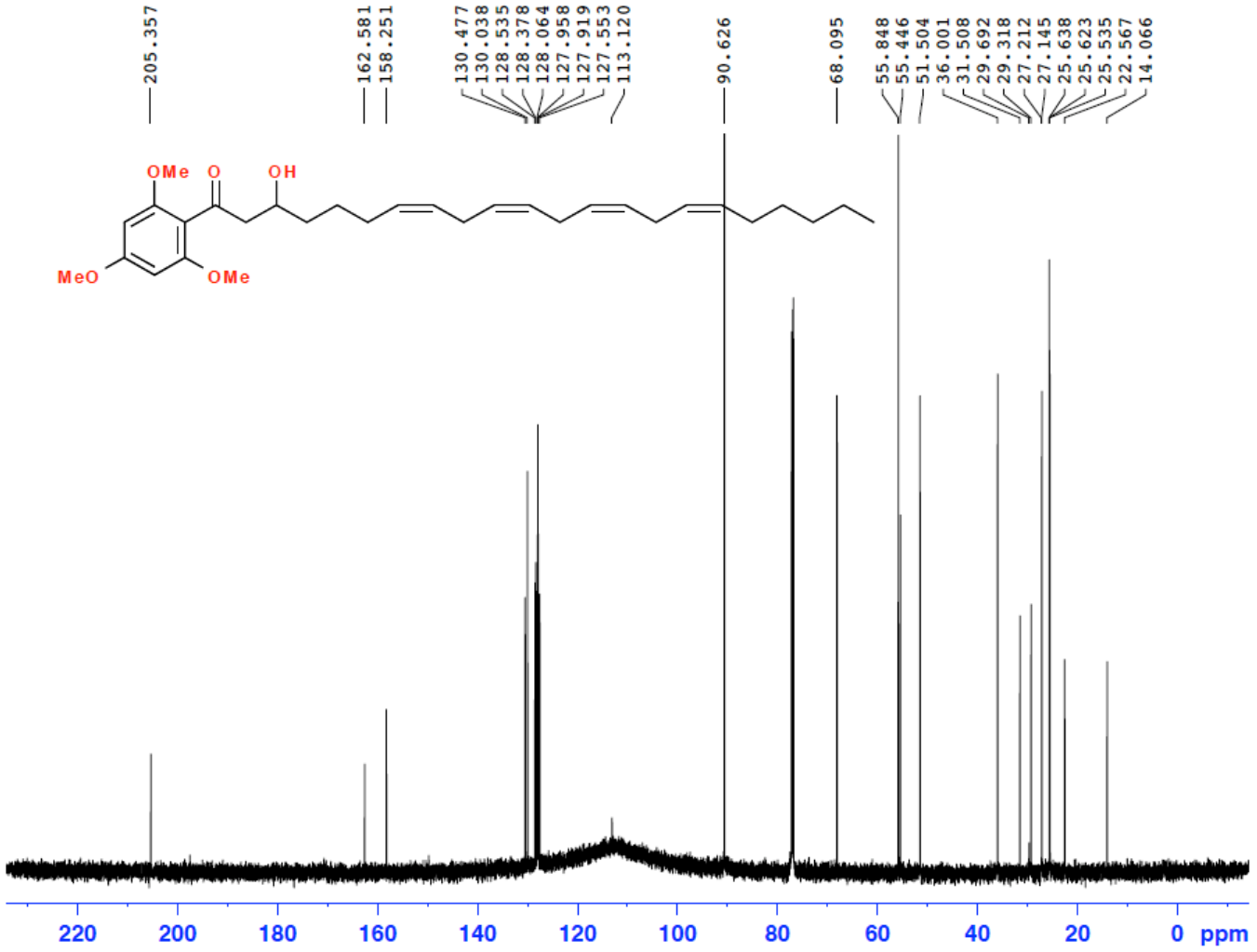


Figure S20 ^{1}H NMR (CD_3OD, 600 MHz) spectrum for **11c**

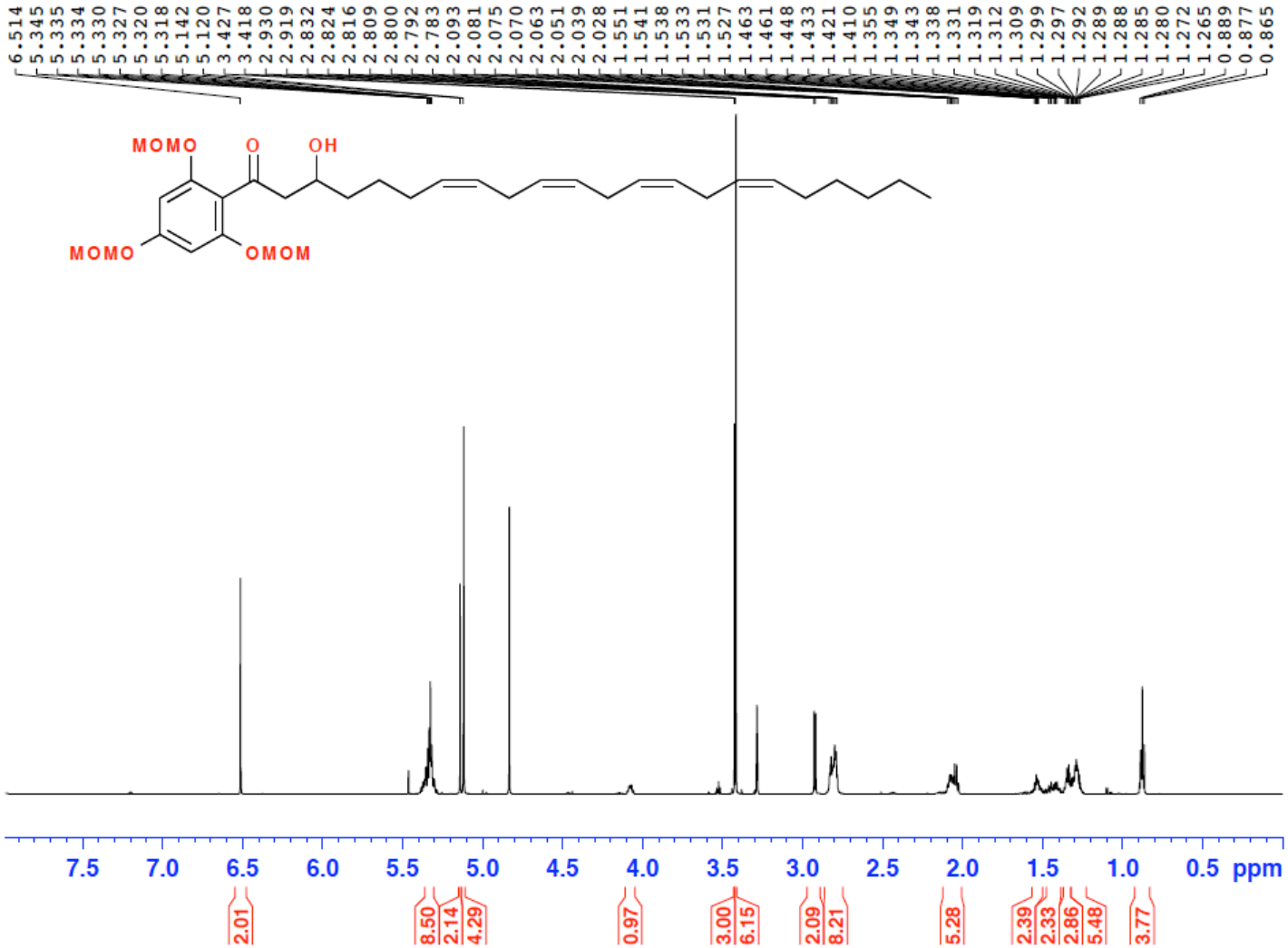


Figure S21 ^{13}C NMR (CD_3OD, 150 MHz) spectrum for **11c**

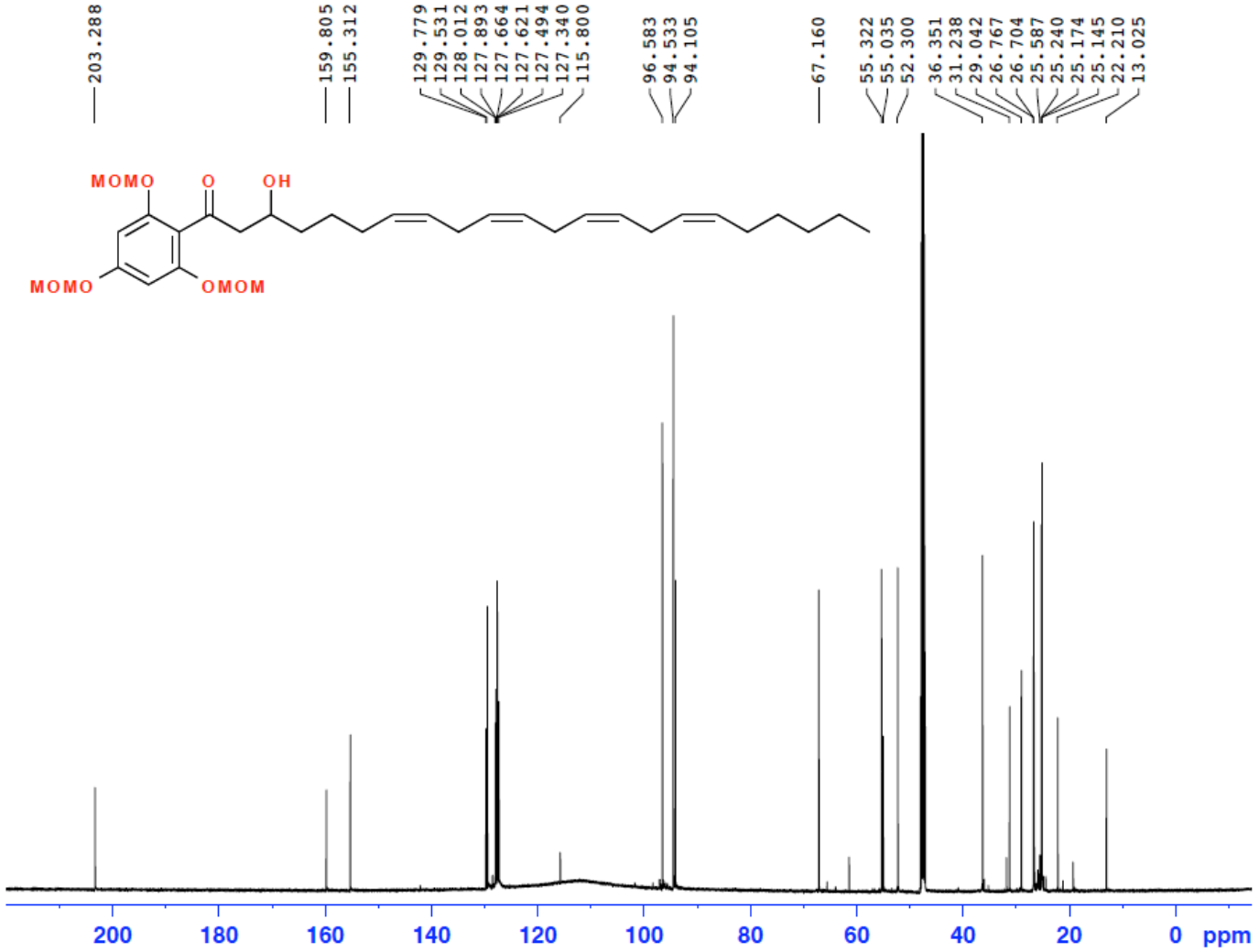


Figure S22 ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum for keto-enol (**12b, 12b'**)

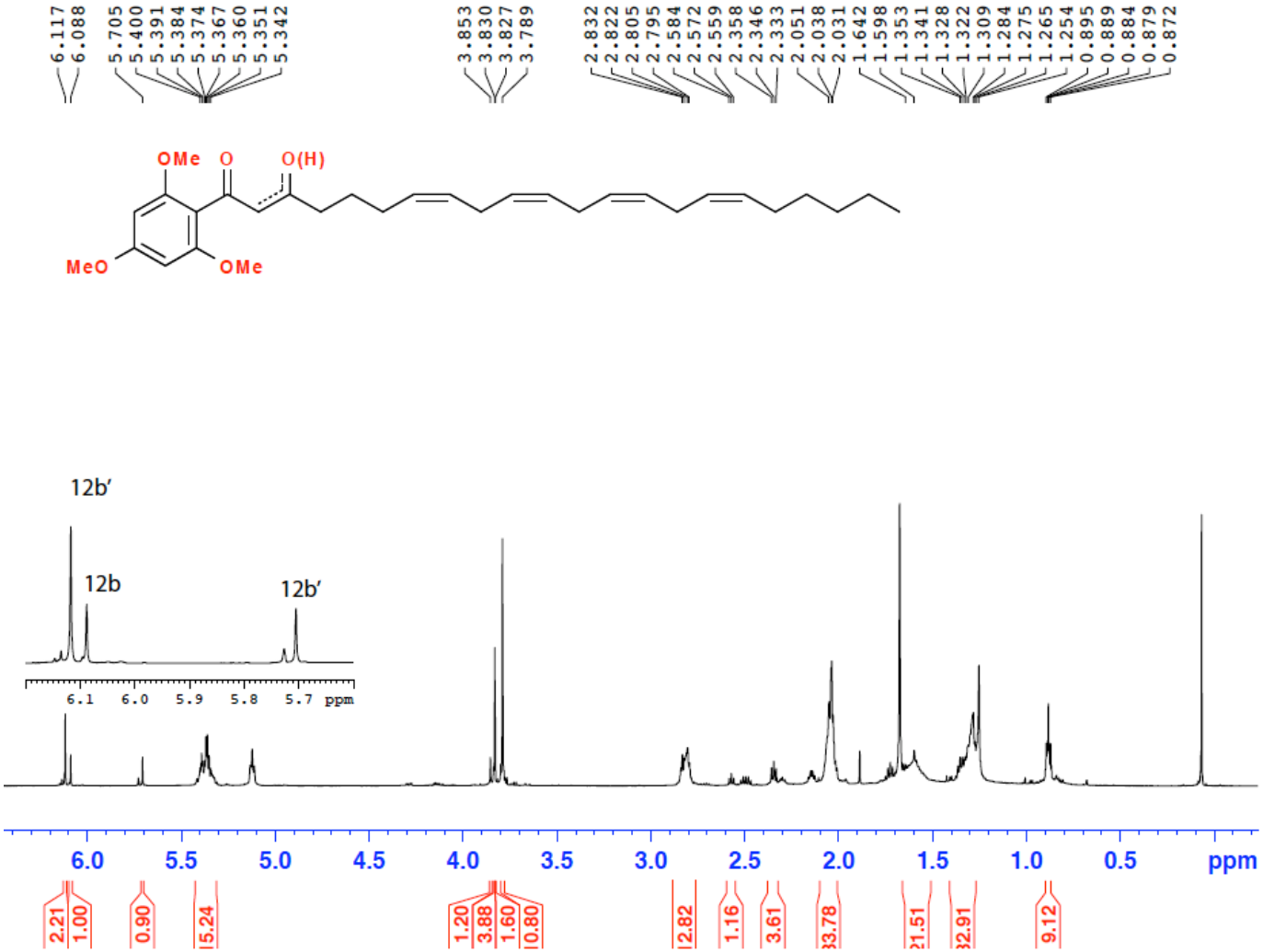


Figure S23 ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum for keto-enol (**12c, 12c'**)

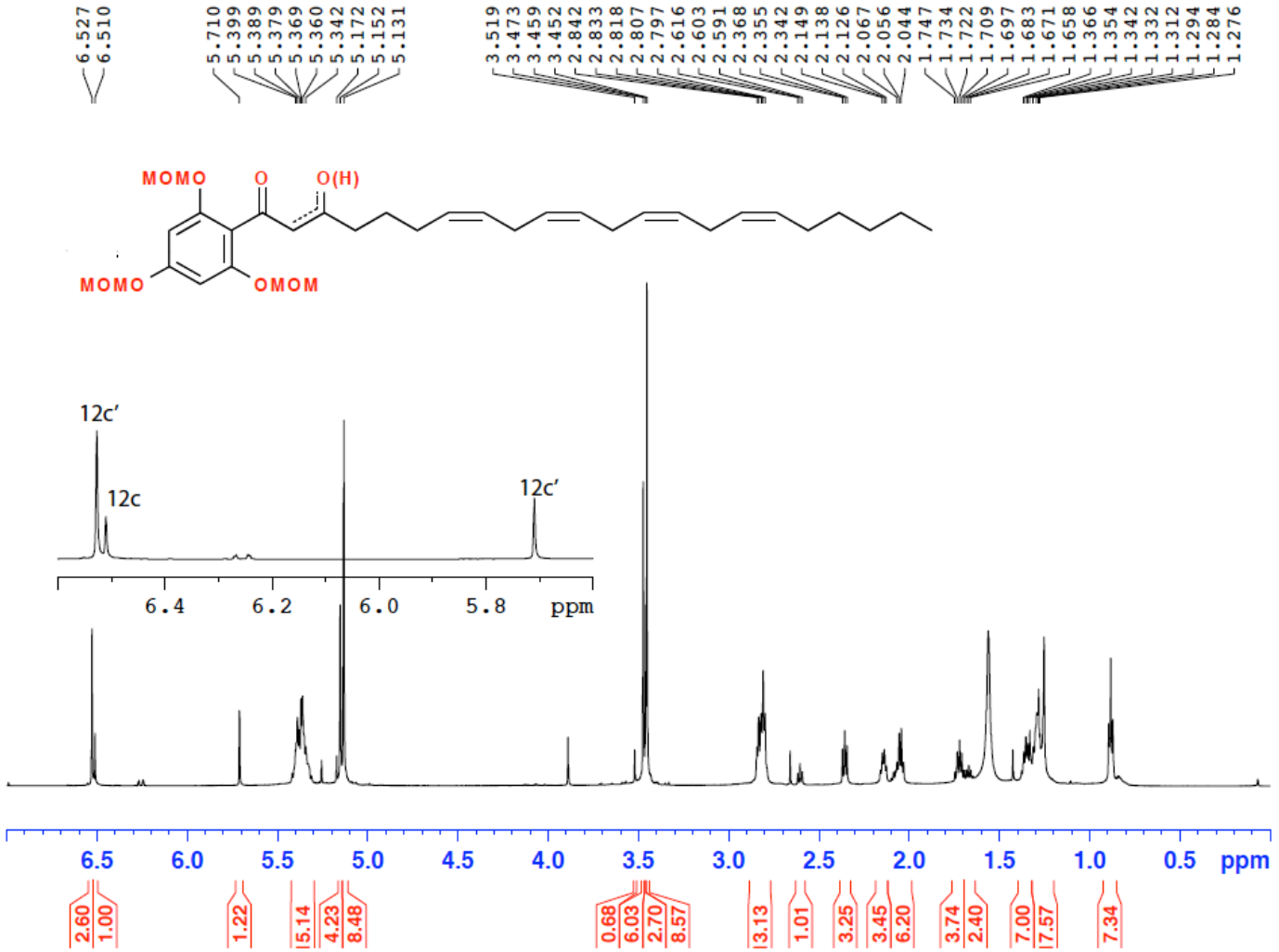


Figure S24 ^{13}C NMR ($CDCl_3$, 150 MHz) spectrum for keto-enol (**12c, 12c'**)

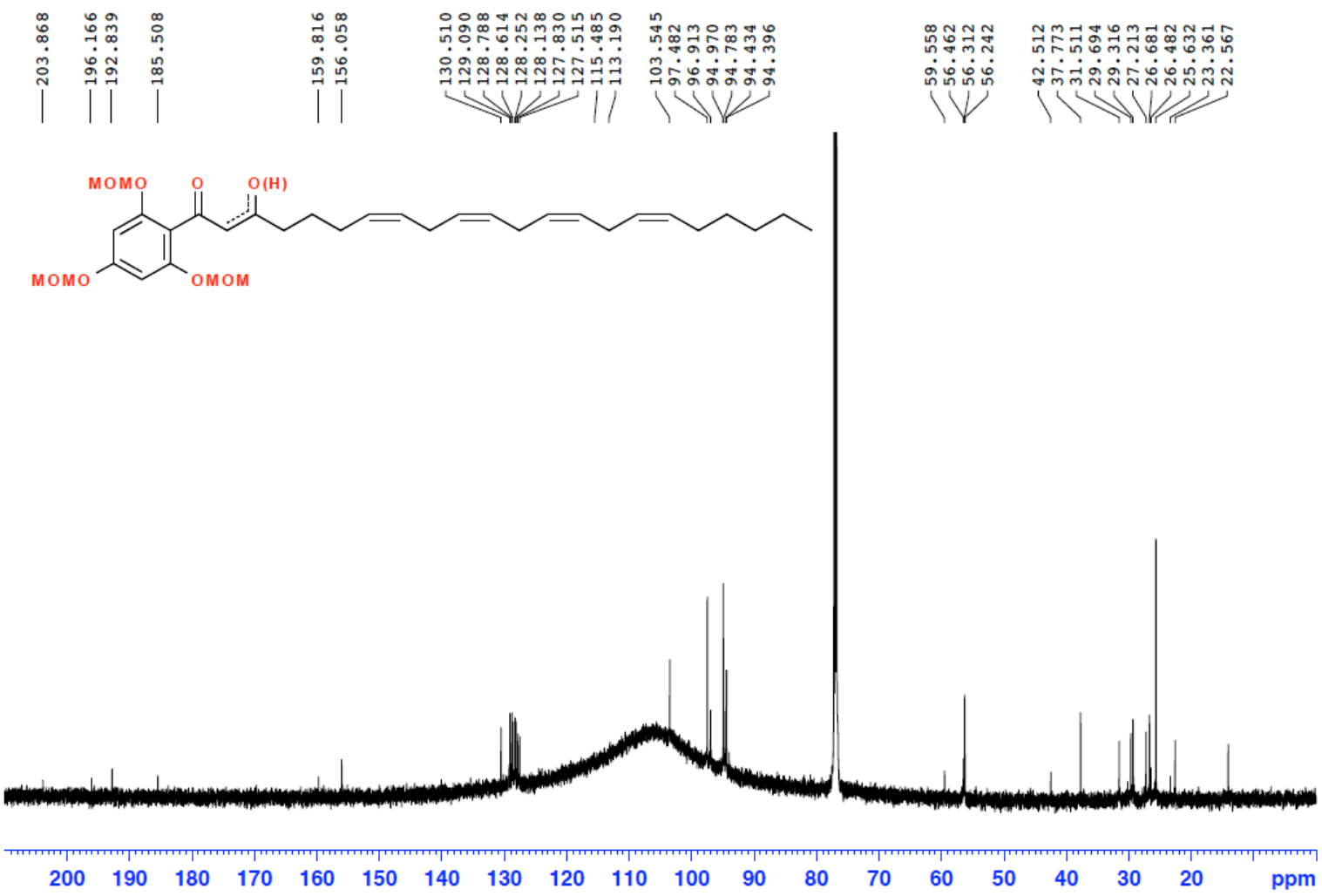


Figure S25 ^{1}H NMR ($CDCl_3$, 600 MHz) comparison of synthetic **4** with natural **4**

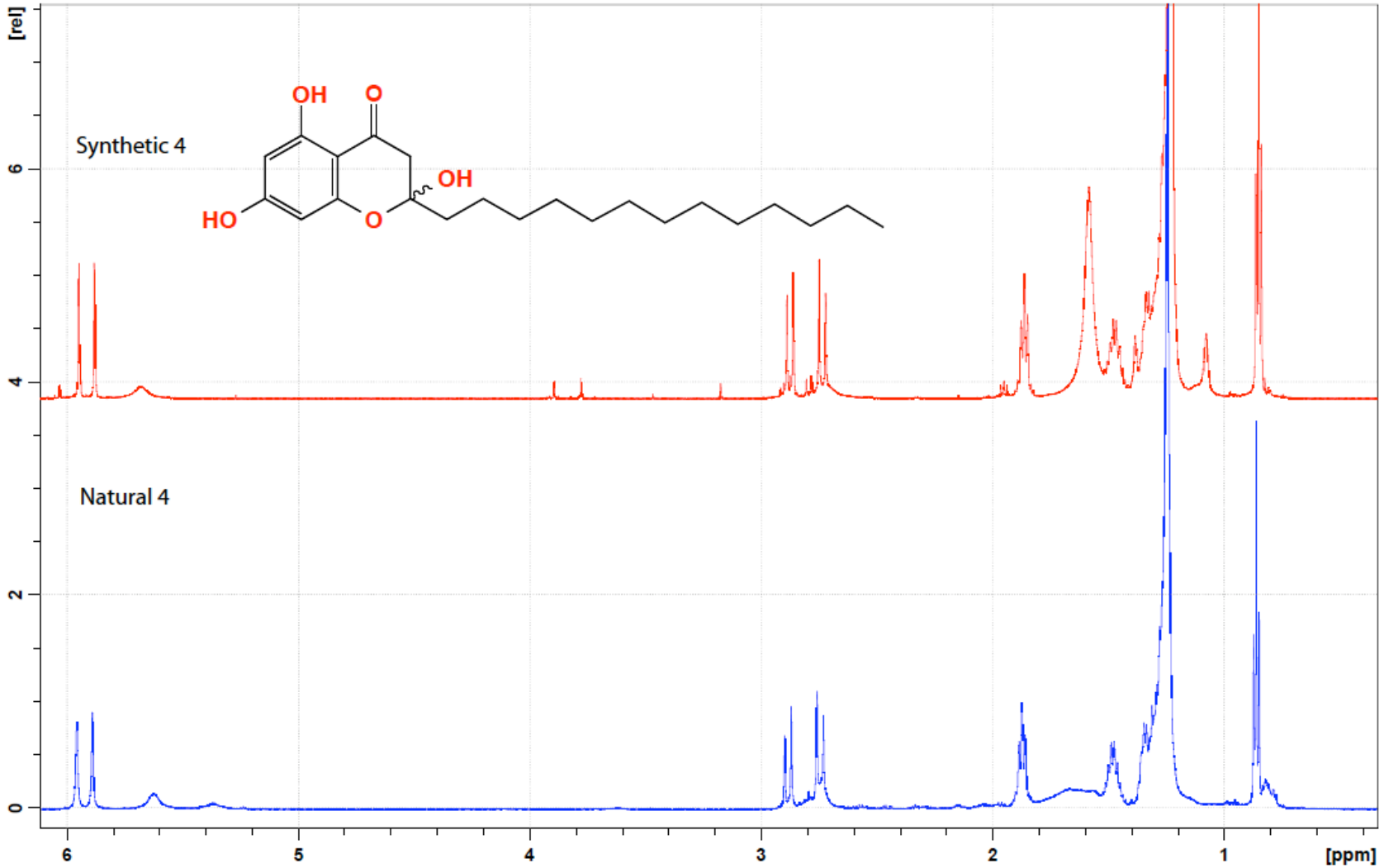


Figure S26 ^{1}H NMR ($CDCl_3$, 600 MHz) comparison of synthetic **5** with natural **5**

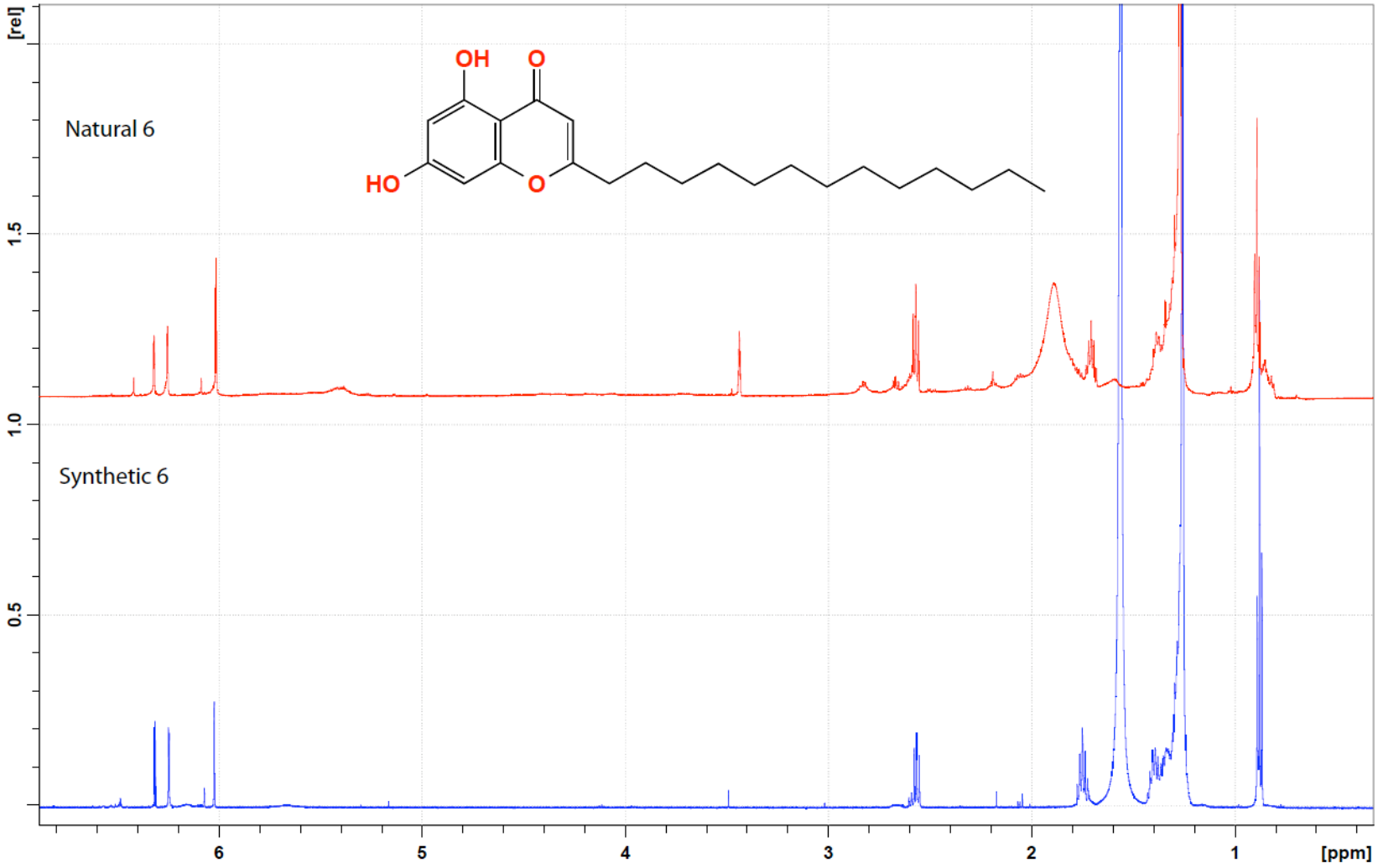


Figure S27 ^{1}H NMR ($CDCl_3$, 600 MHz) comparison of synthetic **1** with natural **1**

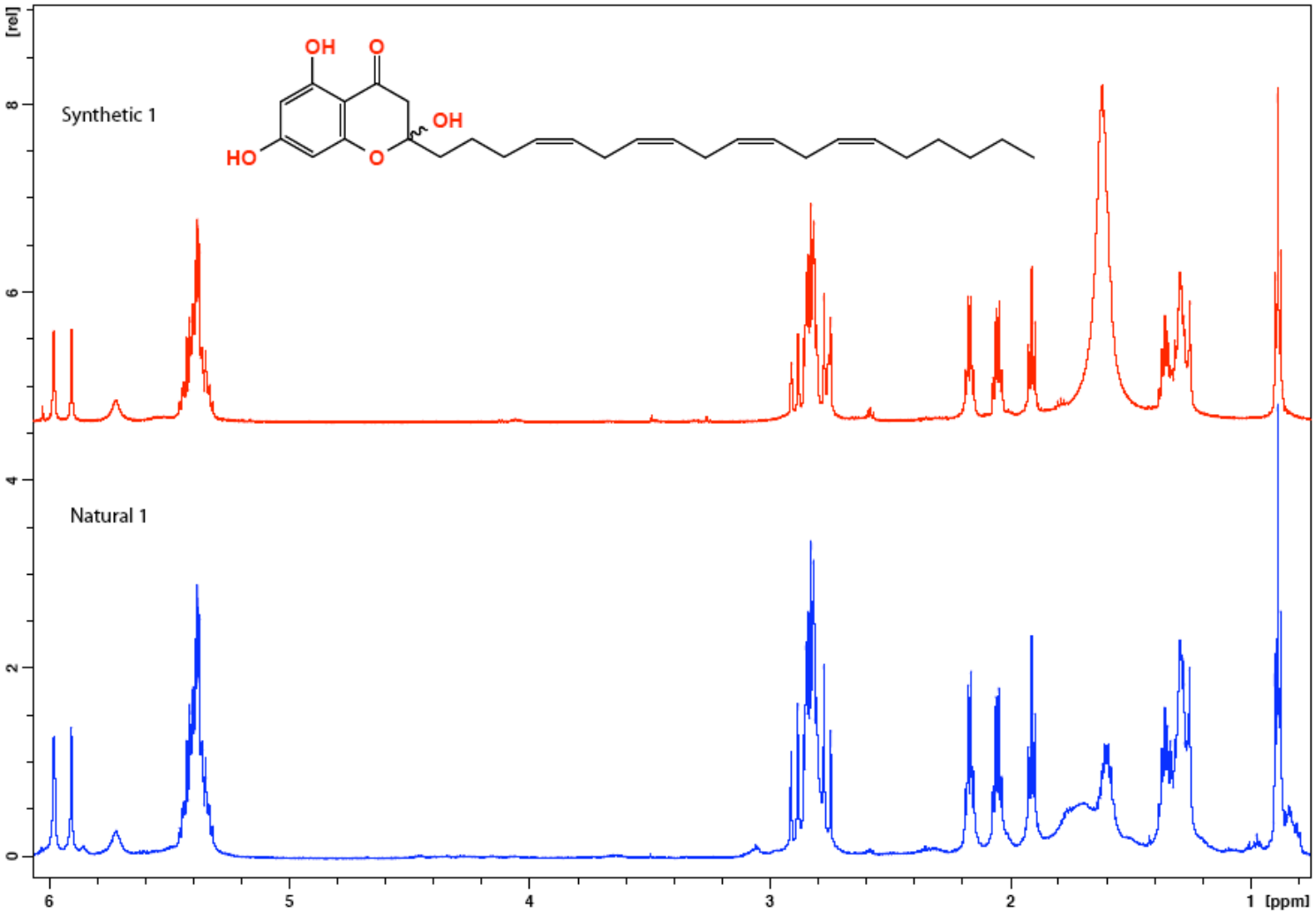
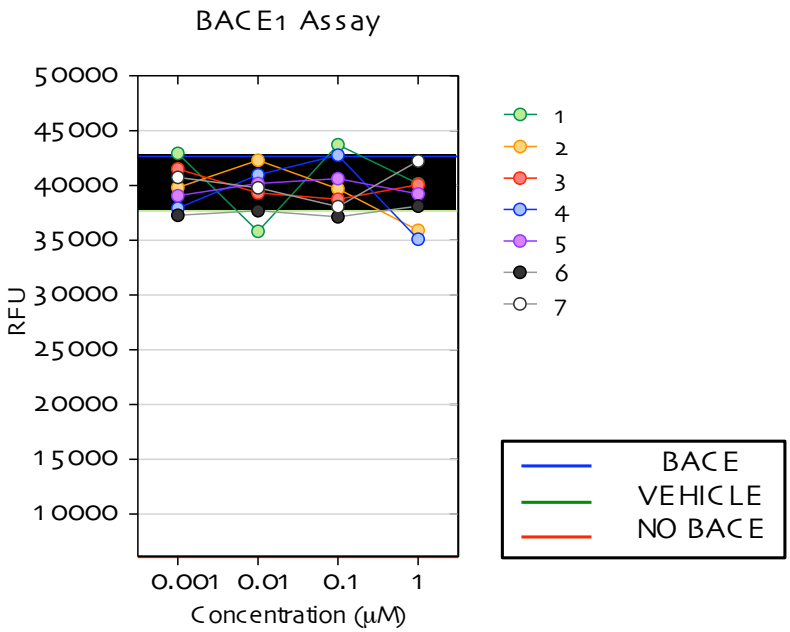


Figure S28 BACE1 inhibitory assay results for **1**–**7**



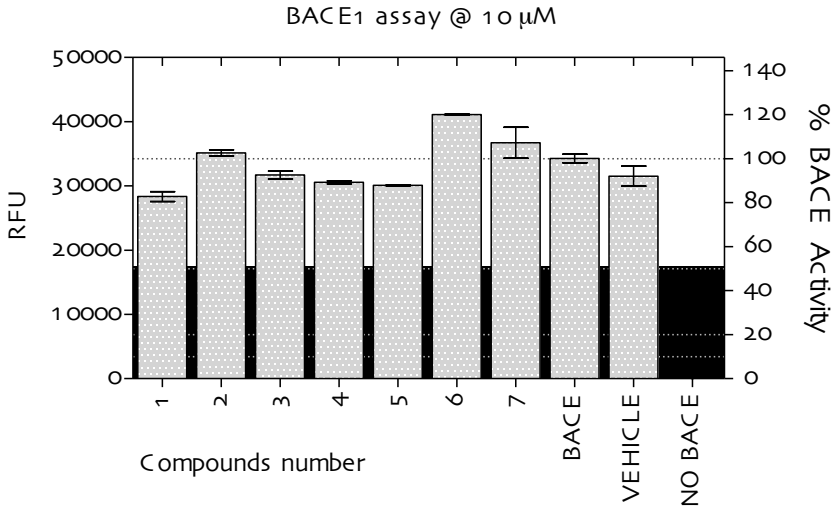


Figure S29 CDK5/p25 inhibitory assay results for **1**–**7**

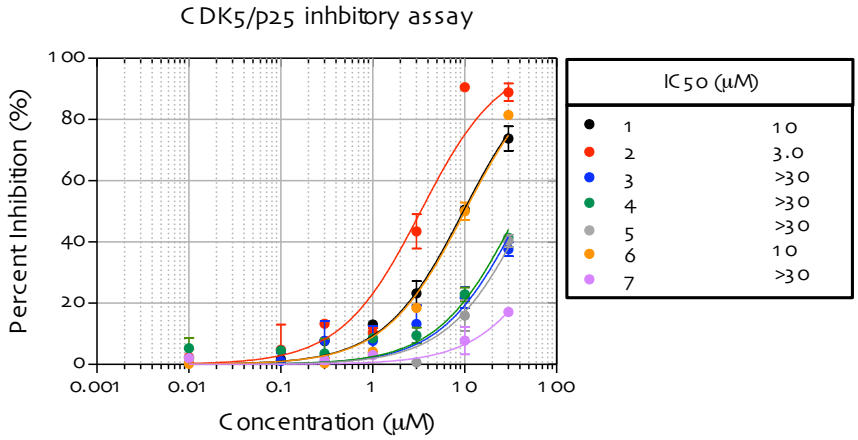


Figure S30 CK1δ inhibitory assay results for **1**, **2** and **6**

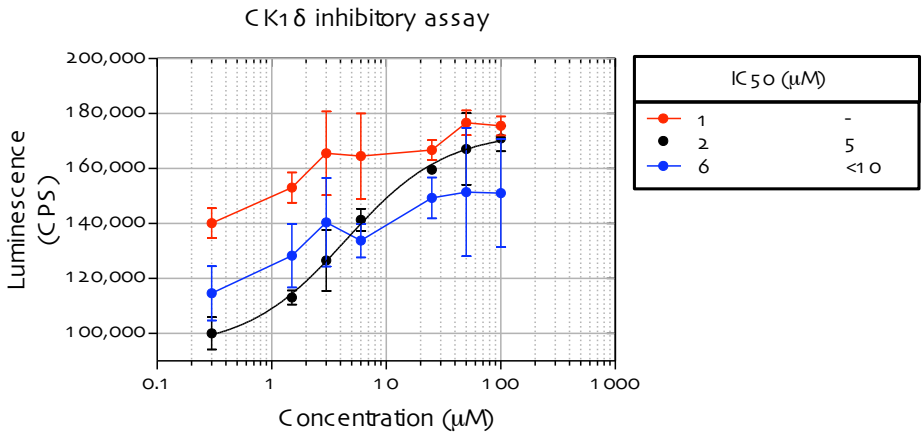


Figure S31 GSK3β inhibitory assay results for **1**, **2** and **6**

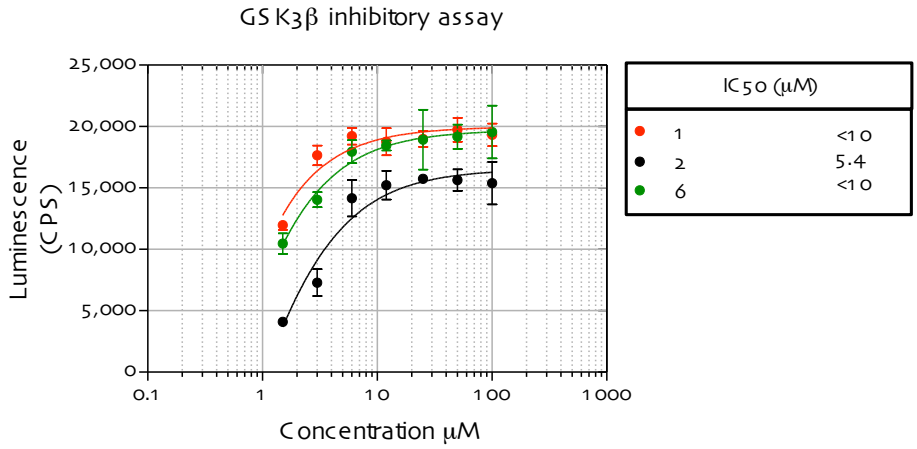
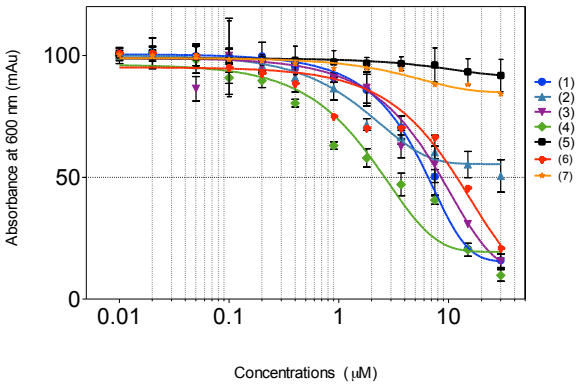
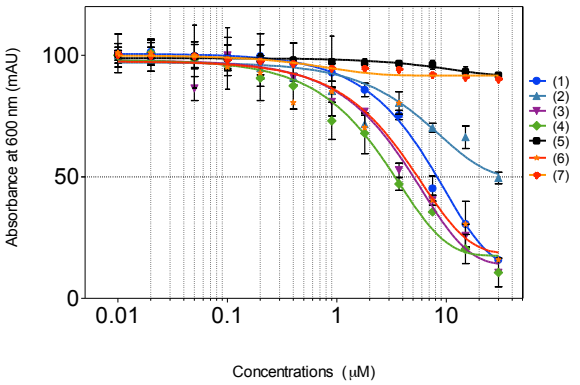


Figure S32 Antimicrobial assays results for **1**–**7**

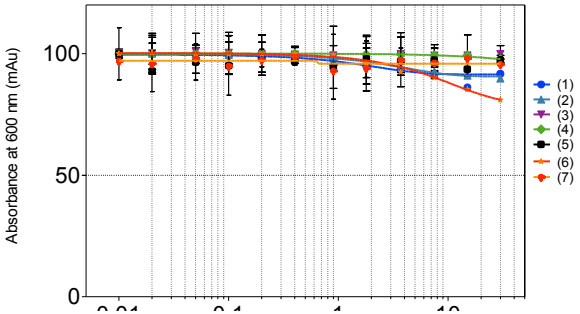
Bacillus subtilis ATCC 6051



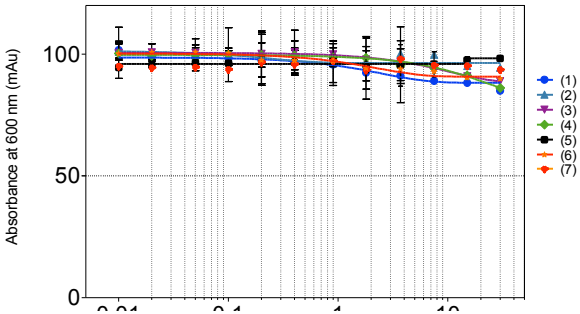
Bacillus subtilis ATCC 6633



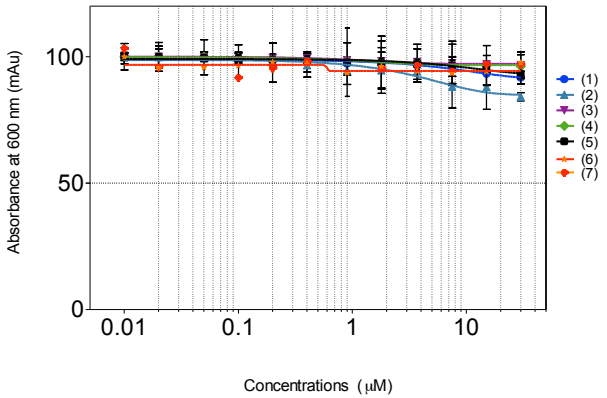
Staphylococcus aureus ATCC 9144



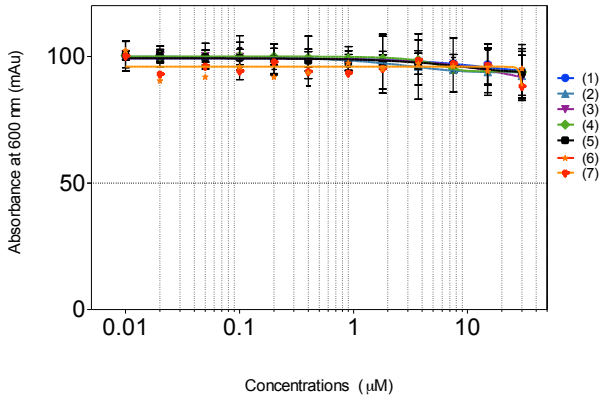
Staphylococcus aureus ATCC 25923



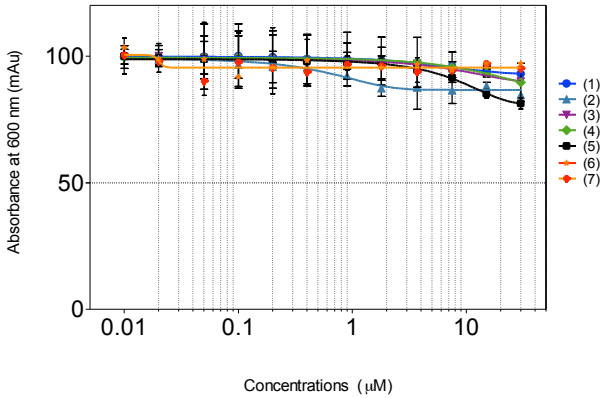
Escherichia coli ATCC 11775



Pseudomonas aeruginosa ATCC 10145



Candida albicans ATCC 90028



Antimicrobial assays results for **1**–**7**

	Escherichia coli **ATCC 11775**		***Pseudomonas aeruginosa*** **ATCC 10145**		***Staphylococcus aureus*** **ATCC 25923**		***Staphylococcus aureus*** **ATCC 9144**		***Bacillus subtilis*** **ATCC 6051**		***Bacillus subtilis*** **ATCC 6633**		***Candida albicans*** **ATCC 90028**	
No.	**MIC/μM**	**IC_{50}/μM**	**MIC/μM**	**IC_{50}/μM**	**MIC/μM**	**IC_{50}/μM**	**MIC/μM**	**IC_{50}/μM**	**MIC/μM**	**IC_{50}/μM**	**MIC/μM**	**IC_{50}/μM**	**MIC/μM**	**IC_{50}/μM**
1	--		--	--	--	--	--	--	15	6.4	15	8.1	--	--
2	--		--	--	--	--	--	--	--	--	--	--	--	--
3	--	--	--	--	--	--	--	--	15	8.7	15	5.0	--	--
4	--	--	--	--	--	--	--	--	15	2.5	7.5	3.3	--	--
5	--	--	--	--	--	--	--	--	--	--	--	--	--	--
6	--	--	--	--	--	--	--	--	30	10.2	15	5.3	--	--
7	--	--	--	--	--	--	--	--	--	--	--	--	--	--