SUPPLEMENTARY MATERIAL

Design, synthesis and cholinesterase inhibitory activity of *α*-mangostin derivatives

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α-mangostin, a polyphenol xanthone derivative, was mainly isolated from pericarps of the mangosteen fruit (*Garcinia mangostana* L.). In present investigation, a series of derivatives were designed, synthesised and evaluated *in vitro* for their inhibitory activity of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Among the synthesised xanthones, compounds **1**, **9**, **13** and **16** showed AChE selective inhibitory activity, **15** was a BuChE selective inhibitor while **2**，**3**，**5**，**6**，**7**，**12** and **14** were dual inhibitors. The most potent inhibitor of AChE was **16** while **5** was the most potent inhibitor of BuChE with IC_{50} values of 5.26 μM and 7.55 μM respectively.

Key Words: *Garcinia mangostana*; *α*-Mangostin; Synthesis; Cholinesterase inhibitors; AChE; BuChE

List of supplementary material

Experimental

1. General procedure

All reagents were purchased from Sigma-Aldrich or Aladdin or Innochem and were of commercial quality. They were used as received without further purification. Solvents were dried by standard methods prior to use. The other reagents were of analytical grade. Air and moisture sensitive reactions were performed under nitrogen atmosphere.

All synthesised target compounds were purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 1:1~20:1) and their structures were elucidated by ^{1}H NMR, ^{13}C NMR, electrospray ionization mass spectrometry (ESI-MS) and high-resolution mass spectrometry (HR-ESIMS). Mass spectra were performed on an API QSTAR time-of-flight spectrometer (MDS Sciqaszex, Concord, Ontario, Canada) and LCMS-IT-TOF (Shimadzu, Kyoto, Japan) spectrometer. NMR spectra were recorded on Bruker AM-400 and DRX-500 instruments with TMS as the internal standard (Bruker, Bremerhaven, Germany). The chemical shifts were given in δ (ppm) with reference to the solvent signal. ^{1}H NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiple resonances), number of protons, and coupling constant (J) in hertz (Hz).

Column chromatography was performed on silica gel (200-300 and 300-400 mesh, Qingdao Marine Chemical Inc., Qingdao, China) with the indicated solvents. The fractions were monitored by TLC and the spots were visualized by UV light and sprayed with 10% H_2SO_4 in EtOH, followed by heating.

2. Synthesis

2.1 General procedure for synthesis of compound 2-4

A 1% (w/v) osmium tetroxide solution (100 μl) in t-BuOH was added to a mixture of α-mangostin **(1)** (41 mg, 0.1 mmol), NMO (17.6 mg, 0.15 mmol), acetone (1 mL) and water (1 mL), and the whole was stirred at room temperature for 24h. Sodium sulfite was added to the resulting mixture and stirring was continued for a further 30min. The mixture was diluted with water, extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to give a yellow solid. The residue was purified on column chromatograph using petroleum ether/ethyl acetate (1: 1) to afford **2** (4.4 mg, 10%), **3** (5 mg, 12%) and **4** (37 mg, 78%).

1,3,6-trihydroxy-2-(2,3-dihydroxy-3-methylbutyl)-7-methoxy-8-(3-methyl-2-butenyl)xanthone (2) Yield 10%, ^{1}H NMR (CD_3OD, 500 MHz) δ 6.70 (s, 1H, H-5), 6.27 (s, 1H, H-4), 5.21 (br t, 1H, J = 6.5 Hz, H-2″), 4.07 (d, 2H, J = 6.5 Hz, H-1″), 3.75 (s, 3H, 7-OC$\underline{H}_3$), 3.61 (dd, 1H, J = 2.5, 10.0 Hz, H-2′), 3.04 (dd, 1H, J = 2.5, 14.0 Hz, H-1′), 2.68 (dd, 1H, J = 10.0, 14.0 Hz, H-1′), 1.82, 1.66 (each s, each 3H, H-4″, H-5″), 1.26 (s, 6H, H-4′, H-5′); ^{13}C NMR (CD_3OD, 125 MHz) δ 183.2 (C-9), 164.4 (C-3), 162.1 (C-1), 158.1 (C-6), 156.8 (C-4a), 156.6 (C-10a), 144.9 (C-7), 138.5 (C-8), 131.9 (C-3′), 125.1 (C-2″), 112.2 (C-8a), 109.8 (C-2), 103.8 (C-9a), 102.8 (C-5), 93.9 (C-2′), 80.0 (C-4), 74.0 (C-3′), 61.3 (OCH_3), 27.1 (C-1′), 26.0 (C-1″), 25.8, 25.6, 25.2, 18.3; negative ESIMS m/z 443 $[M - H]^-$.

1,3,6-trihydroxy-2-(3-methyl-2-butenyl)-7-methoxy-8-(2,3-dihydroxy-3-methylbutyl)xanthone (3) Yield 12%, ^{1}H NMR (CD_3OD, 500 MHz) δ 6.77 (s, 1H, H-5), 6.28 (s, 1H, H-4), 5.22 (m, 1H, H-2′), 3.84 (s, 3H, 7-OC$\underline{H}_3$), 3.66 (dd, 1H, J = 2.8, 10.2 Hz, H-2″), 3.54 (dd, 2H, J = 2.8, 12.3 Hz, H-1″), 3.33 (m, 2H, H-1′), 1.77, 1.65 (each s, each 3H, H-4″, H-5″), 1.34, 1.33 (each s, each 3H, H-4′, H-5′); ^{13}C NMR (CD_3OD, 125 MHz) δ 184.0 (C-9), 164.2 (C-3), 161.5 (C-1), 158.3 (C-4a), 156.7 (C-10a), 156.4 (C-6), 145.9 (C-7), 136.5 (C-8), 131.8 (C-3′), 123.7 (C-2′), 112.9 (C-8a), 111.8 (C-2), 103.7 (C-9a), 103.2 (C-5), 93.3 (C-4), 80.7 (C-2″), 74.3 (C-3″), 60.9 (OCH_3), 29.6 (C-1″), 26.0, 25.8, 25.4, 22.2 (C-1′), 17.9; negative ESIMS m/z 443 $[M - H]^-$.

1,3,6-trihydroxy-7-methoxy-2,8-bis(2,3-dihydroxy-3-methylbutyl)-9*H*-xanthen-9-one (4) Yield 78%, ^{1}H NMR (CD_3OD, 500 MHz) δ 6.74 (s, 1H, H-5), 6.29 (s, 1H, H-4), 3.85 (s, 3H, 7-OC$\underline{H}_3$), 3.65 (m, 1H, H-2″), 3.61 (m, 1H, H-2′), 3.56 (m, 2H, H-1″), 3.02 (dd, 1H, *J* = 2.4, 14.0 Hz, H-1′), 2.68 (dd, 1H, *J* = 10.2, 14.0 Hz, H-1′), 1.33, 1.32, 1.26, 1.25 (each s, each 3H, H-4′, H-5′, H-4″, H-5″); ^{13}C NMR (CD_3OD, 125 MHz) δ 183.9 (C-9), 164.9 (C-3), 161.9 (C-1), 158.3 (C-4a), 156.7 (C-10a), 156.7 (C-6), 145.9 (C-7), 136.5 (C-8), 112.8 (C-8a), 110.0 (C-2), 103.7 (C-9a), 103.3 (C-5), 94.0 (C-4), 80.6 (C-2″), 79.8 (C-2′), 74.3 (C-3″), 74.0 (C-3′), 61.0 (OCH_3), 29.6 (C-1″), 25.9, 25.8 (C-1′), 25.6, 25.4, 25.2; negative ESIMS *m/z* 477 $[M - H]^-$; HRESIMS *m/z* 477.1766 $[M - H]^-$ (calcd for $C_{24}H_{29}O_{10}$, 477.1766).

2.2 General procedure for synthesis of compound 5, 6 and 12

A solution of **1**, **2** or **3** (44 mg, 0.1 mmol) and 10% Pd/C (5 mg) in CH_3OH (2 mL) was placed under an atmosphere of hydrogen. After stirring for 24 h, the reaction mixture was filtered through filter paper and concentrated under reduced pressure. The crude product was purified on column chromatograph using petroleum ether/ethyl acetate (1: 1 ~ 2:1) to afford **12**, **5** or **6** respectively.

1,3,6-trihydroxy-2-(2,3-dihydroxy-3-methylbutyl)-7-methoxy-8-isopentyl-9*H*-xanthen-9-one (5) Yield 78%, ^{1}H NMR (CD_3OD, 500 MHz) δ 6.62 (s, 1H, H-5), 6.21 (s, 1H, H-4), 3.78 (s, 3H, 7-OC$\underline{H}_3$), 3.60 (dd, 1H, *J* = 2.4, 10.1 Hz, H-2′), 3.26 (m, 2H, H-1″), 3.01 (dd, 1H, *J* = 2.4, 14.1 Hz, H-1′), 2.65 (dd, 1H, *J* = 10.1, 14.1 Hz, H-1′), 1.71 (m, 1H, H-3″), 1.41 (m, 2H, H-2″), 1.26 (s, 6H, H-4″, H-5″), 1.00, 0.98 (each s, each 3H, H-4′, H-5′); ^{13}C NMR (CD_3OD, 125 MHz) δ 183.1 (C-9), 164.2 (C-1), 162.1 (C-3), 157.8 (C-4a), 156.7 (C-10a), 156.5 (C-6), 144.6 (C-7), 140.4 (C-8), 112.1 (C-8a), 109.6 (C-2), 103.8 (C-9a), 102.6 (C-5), 93.9 (C-4), 80.0 (C-2″), 74.0 (C-3″), 61.5 (OCH_3), 41.4 (C-2′), 30.1 (C-3′), 26.3 (C-1″), 25.8 (C-1′), 25.7, 25.1, 23.0; negative ESIMS *m/z* 445 $[M - H]^-$; HRESIMS m/z 445.1870 $[M - H]^-$ (calcd for $C_{24}H_{29}O_8$, 445.1868).

1,3,6-trihydroxy-2-isopentyl-7-methoxy-8-(2,3-dihydroxy-3-methylbutyl)-9*H*-xanthen-9-one (6) Yield 78%, ^{1}H NMR (CD_3OD, 500 MHz) δ 6.66 (d, 1H, *J* = 1.8 Hz, H-5), 6.18 (d, 1H, *J* = 1.6 Hz, H-4), 3.84 (s, 3H, 7-OC$\underline{H}_3$), 3.63 (dd, 1H, *J* = 2.7, 10.5

Hz, H-2″), 3.48 (m, 2H, H-1″), 2.56 (m, 2H, H-1′), 1.55 (m, 1H, H-3′), 1.37 (m, 2H, H-2′), 1.32 (s, 6H, H-4″, H-5″), 0.95, 0.93 (each s, each 3H, H-4′, H-5′); ^{13}C NMR (CD_3OD, 125 MHz) δ 183.8 (C-9), 164.2 (C-1), 161.5 (C-3), 158.0 (C-4a), 156.6 (C-10a), 156.1 (C-6), 145.7 (C-7), 136.3 (C-8), 112.8 (C-8a), 112.8 (C-2), 103.6 (C-9a), 103.2 (C-5), 93.3 (C-4), 80.8 (C-2′), 74.3 (C-3′), 60.9 (OCH_3), 39.1 (C-2″), 29.6 (C-1′), 29.5 (C-3″), 25.9, 25.3, 23.1, 21.2 (C-1″); negative ESIMS *m/z* 445 [M − H]$^-$; HRESIMS *m/z* 445.1867 [M − H]$^-$ (calcd for $C_{24}H_{29}O_8$, 445.1868).

Tetrahydro-*α*-mangostin (12) Yield 95%, ^{1}H NMR (CD_3OD, 500 MHz) δ 6.60 (s, 1H, H-5), 6.17 (s, 1H, H-4), 3.77 (s, 3H, 7-OC<u>H</u>$_3$), 3.24 (m, 2H, H-1″), 2.57 (m, 2H, H-1′), 1.70 (m, 1H, *J* = 6.6, 13.1 Hz, H-3′), 1.56 (m, 1H, *J* = 6.6, 13.1 Hz, H-3″), 1.39 (m, 4H, H-2′, H-2″), 0.99, 0.97, 0.95, 0.94 (each s, each 3H, H-4′, H-5′, H-4″, H-5″); ^{13}C NMR (CD_3OD, 125 MHz) δ 183.1 (C-9), 163.6 (C-1), 161.7 (C-3), 157.6 (C-4a), 156.7 (C-6), 156.0 (C-10a), 144.5 (C-7), 140.4 (C-8), 112.5 (C-8a), 112.2 (C-2), 103.7 (C-9a), 102.5 (C-5), 93.0 (C-4), 61.5 (7-OCH_3), 41.5 (C-2′), 39.1 (C-2″), 30.1 (C-3′), 29.5 (C-3″), 26.2 (C-1″), 23.1 (C-4′, C-5′), 23.0 (C-4″, C-5″), 21.2 (C-1′); negative ESIMS *m/z* 413 [M − H]$^-$.

2.3 General procedure for synthesis of compound 7-9

A solution of **2**, **4** or **5** (0.1 mmol) in mixed reagent (2 mL, THF: H_2O = 2: 1) was added $NaIO_4$ (26 mg, 0.12 mmol) at cool temperature. After the addition was completed, the reaction solution was allowed to warm to room temperature. After stirring for 4 h, the reaction mixture was diluted with water, extracted with ethyl acetate (3 × 10 mL). The organic phase solvent was washed with brine, dried over anhydrous sodium sulfate, and then concentrated *in vacuo* to give a yellow solid. The crude product was purified on column chromatograph using petroleum ether/ethyl acetate (2:1 ~ 4:1) to afford **7**, **8** or **9**.

1,3,6-trihydroxy-7-methoxy-8-(3-methylbut-2-en-1-yl)-2*H*-furo[3,2-*b*]xanthen-5(3*H*)-one (7) Yield 60%, ^{1}H NMR (CD_3OD, 500 MHz) δ 6.64 (s, 1H, H-5), 6.21 (s, 1H, H-4), 5.19 (m, 1H, H-2″), 4.83 (t, 1H, *J* = 5.7 Hz, H-2′), 4.02 (t, 2H, *J* = 6.2 Hz, H-1″), 3.74 (s, 3H, 7-OC<u>H</u>$_3$), 2.91 (m, 2H, H-1′), 1.81, 1.66 (each s, each 3H, H-4″, H-5″); ^{13}C NMR (CD_3OD, 125 MHz) δ 183.1 (C-9), 164.2 (C-3), 162.4 (C-1), 158.0 (C-6),

156.7 (C-4, C-10a), 144.8 (C-7), 138.5 (C-8), 131.8 (C-3″), 125.1 (C-2″), 112.1 (C-8a), 107.0 (C-2), 103.7 (C-9a), 102.8 (C-5), 99.0 (C-2′), 93.5 (C-4), 61.3 (OCH_3), 30.9 (C-1′), 27.1 (C-1″), 26.0, 18.3; negative ESIMS *m/z* 383 $[M - H]^-$; HRESIMS *m/z* 383.1134 $[M - H]^-$ (calcd for $C_{21}H_{19}O_7$, 383.1136).

1,3,6-trihydroxy-7-methoxy-8-(2,3-dihydroxy-3-methylbutyl)-2*H*-furo[3,2-*b*]xanthen-5(3*H*)-one (8) Yield 50%, ^{1}H NMR (CD_3OD, 500 MHz) δ 6.67 (s, 1H, H-5), 6.21 (s, 1H, H-4), 4.83 (t, 1H, *J* = 5.7 Hz, H-2′), 3.84 (s, 3H, 7-OC$\underline{H}_3$), 3.63 (m, 1H, H-2″), 3.48 (m, 2H, H-1″), 2.91 (dd, 2H, *J* = 5.7, 14.4 Hz, H-1′), 1.32, 1.31 (each s, each 3H, H-4″, H-5″); ^{13}C NMR (CD_3OD, 125 MHz) δ 183.8 (C-9), 164.7 (C-3), 162.3 (C-1), 158.2 (C-6), 156.7 (C-4a), 156.6 (C-10a), 145.9 (C-7), 136.4 (C-8), 112.7 (C-8a), 107.3 (C-2), 103.6 (C-9a), 103.3 (C-5), 98.9 (C-2′), 93.7 (C-4), 80.6 (C-2″), 74.3 (C-3″), 60.9 (OCH_3), 30.9 (C-1′), 29.6 (C-1″), 25.9, 25.4; negative ESIMS *m/z* 417 $[M - H]^-$; HRESIMS *m/z* 417.1187 $[M - H]^-$ (calcd for $C_{21}H_{21}O_9$, 417.1191).

1,3,6-trihydroxy-7-methoxy-8-isopentyl-2*H*-furo[3,2-*b*]xanthone-5(3*H*)-one (9) Yield 60%, ^{1}H NMR (CD_3OD, 500 MHz) δ 6.65 (s, 1H, H-5), 6.23 (s, 1H, H-4), 4.84 (t, 1H, *J* = 5.7 Hz, H-2′), 3.79 (s, 3H, 7-OC$\underline{H}_3$), 3.29 (m, 2H, H-1″), 2.94 (m, 2H, H-1′), 1.72 (m, 1H, H-3″), 1.42 (m, 2H, H-2″), 1.00, 0.99 (each s, each 3H, H-4″, H-5″); ^{13}C NMR (CD_3OD, 125 MHz) δ 183.1 (C-9), 164.2 (C-3), 162.5 (C-1), 157.9 (C-6), 156.7 (C-4a), 156.7 (C-10a), 144.7 (C-7), 140.4 (C-8), 112.1 (C-8a), 107.0 (C-2), 103.8 (C-9a), 102.6 (C-5), 99.0 (C-2′), 93.5 (C-4), 61.3 (OCH_3), 41.5 (C-2″), 30.9 (C-1′), 30.1 (C-3″), 26.2 (C-1″), 23.0; negative ESIMS *m/z* 385 $[M - H]^-$; HRESIMS *m/z* 385.1295 $[M - H]^-$ (calcd for $C_{21}H_{21}O_7$, 385.1293).

2.4 General procedure for synthesis of compound 10-11

A solution of **2** or **5** (0.1 mmol) and NaH (80 mg, 2 mM) in DMF (2 mL) was placed under an atmosphere of nitrogen, after stirring for 30 min, the reaction mixture was added CH_3I (0.2 mL, 3 mM). After stirring for 4 h, the reaction mixture was diluted with water, extracted with ethyl acetate (3 × 10 mL). The organic phase solvent was washed with brine, dried over anhydrous sodium sulfate, and then concentrated *in vacuo* to give a yellow solid. The crude product was purified on column chromatograph using petroleum ether/ethyl acetate (9: 1) to afford **10** or **11**.

2-(2,3-dimethoxy-3-methylbutyl)-1,3,6,7-tetramethoxy-8-(3-methylbut-2-en-1-yl)-9H-xanthen-9-one (10) Yield 60%, ^{1}H NMR (DMSO-d_6, 500 MHz) δ 6.98 (s, 1H, H-5), 6.82 (s, 1H, H-4), 5.15 (br t, 1H, J = 7.0 Hz, H-17), 3.99 (dd, 2H, J = 6.6, 15.6 Hz, H-16), 3.92, 3.77, 3.68 (each s, each 3H, 1-OC$\underline{H}_3$, 3-OC$\underline{H}_3$, 6-OC$\underline{H}_3$, 7-OC$\underline{H}_3$), 3.39 (dd, 1H, J = 3.0, 10.0 Hz, H-11), 3.15 (s, 3H, 12-OC$\underline{H}_3$), 2.93 (s, 3H, 13-OC$\underline{H}_3$), 2.85 (dd, 1H, J = 10.0, 13.4 Hz, H-12), 2.66 (dd, 1H, J = 3.0, 13.4 Hz, H-11), 1.76, 1.58, 1.15, 1.11 (each s, each 3H, C-14, C-15, C-19, C-20); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 175.2 (C-9), 162.5 (C-3), 158.5 (C-1), 157.0 (C-10a), 156.2 (C-4a), 153.7 (C-6), 143.6 (C-7), 135.6 (C-8), 130.3 (C-18), 123.9 (C-17), 118.4 (C-2), 113.7 (C-8a), 110.0 (C-9a), 98.5 (C-5), 94.5 (C-12), 84.6 (C-4), 77.2 (C-13), 61.3 (1-OCH$_3$), 60.4 (7-OCH$_3$), 60.1 (12-OCH$_3$), 56.3 (3-OCH$_3$, 6-OCH$_3$), 48.9 (13-OCH$_3$), 25.6, 25.3 (C-16), 23.8 (C-11), 22.1, 20.6, 18.0; positive ESIMS *m/z* 537 $[M + Na]^+$; HRESIMS *m/z* 537.2472 $[M + Na]^+$ (calcd for $C_{29}H_{38}NaO_8$, 537.2464).

2-(2,3-dimethoxy-3-methylbutyl)-8-isopentyl-1,3,6,7-tetramethoxy-9H-xanthen-9-one (11) Yield 60%, ^{1}H NMR (DMSO-d_6, 500 MHz) δ 6.93 (s, 1H, H-5), 6.78 (s, 1H, H-4), 3.92, 3.91, 3.76, 3.70 (each s, each 3H, 1-OC$\underline{H}_3$, 3-OC$\underline{H}_3$, 6-OC$\underline{H}_3$, 7-OC$\underline{H}_3$), 3.37 (dd, 1H, J = 3.0, 10.0 Hz, H-12), 3.24 (m, 2H, H-16), 3.14, 2.92 (each s, each 3H, 12-OC$\underline{H}_3$, 13-OC$\underline{H}_3$), 2.84 (m, 1H, H-11), 2.64 (dd, 1H, J = 3.0, 13.0 Hz, H-11), 1.14, 1.10, 0.95, 0.94 (each s, each 3H, C-14, C-15, C-19, C-20); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 175.1 (C-9), 162.4 (C-3), 158.6 (C-1), 156.8 (C-4a), 156.2 (C-10a), 153.7 (C-6), 143.4 (C-7), 137.5 (C-8), 118.3 (C-2), 113.7 (C-8a), 110.0 (C-9a), 98.3 (C-12), 94.4 (C-5), 84.6 (C-13), 77.2 (C-4), 61.2, 60.6, 60.1, 56.3, 56.2 (1-OCH$_3$, 3-OCH$_3$, 6-OCH$_3$, 12-OCH$_3$, 13-OCH$_3$), 48.9 (C-17), 28.3 (C-18), 24.2 (C-16), 23.7 (C-11), 22.5, 22.5, 22.1, 20.6; positive ESIMS m/z 539 $[M + Na]^+$; HRESIMS *m/z* 539.2625 $[M + Na]^+$ (calcd for $C_{29}H_{40}NaO_8$, 539.2621).

2.5 General procedure for synthesis of compound 13-17

A solution of **1** or **12** (0.1 mmol) and NBS or NCS (40 mg, 0.22 mM) in DCM or THF (2 mL) was placed under an atmosphere of nitrogen. After stirring for 24 h, the reaction mixture was diluted with saturated sodium thiosulfate solution, extracted with dichloromethane (3 × 10 mL). The organic phase solvent was washed with brine,

dried over anhydrous sodium sulfate, and then concentrated *in vacuo* to give a yellow solid. The crude product was purified on column chromatograph using petroleum ether/ethyl acetate (9: 1) to afford **13-17**.

4-chloro-*α*-mangostin (13) Yield 30%, ^{1}H NMR (CD_3OD, 500 MHz) δ 6.77 (s, 1H, H-5), 5.21 (br t, 2H, H-2′, H-2″), 4.05 (d, 2H, J = 6.5 Hz, H-1″), 3.76 (s, 3H, 7-OC$\underline{H}_3$), 3.34 (m, 2H, H-1′), 1.82, 1.78, 1.66, 1.65 (each s, each 3H, H-4′, H-5′, H-4″, H-5″); ^{13}C NMR (CD_3OD, 125 MHz) δ 182.7 (C-9), 160.5 (C-1), 159.6 (C-3), 158.8 (C-10a), 156.5 (C-6), 151.2 (C-4a), 145.4 (C-7), 138.5 (C-8), 132.1, 131.9 (C-3′, C-3″), 125.0, 123.5 (C-2′, C-2″), 112.8 (C-8a), 111.6 (C-2), 103.8 (C-9a), 103.0 (C-5), 98.5 (C-4), 61.3 (7-OCH_3), 27.1 (C-1″), 26.0, 26.0 (C-4′, C-4″), 22.9 (C-1′), 18.3, 18.0 (C-1′, C-1″); negative ESIMS *m/z* 443 $[M - H]^-$.

4-bromo-*α*-mangostin (14) Yield 12%, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 13.69 (s, 1H, 1-OH), 6.97 (s, 1H, H-5), 5.25 (br t, 2H, H-2′, H-2″), 4.08 (d, 2H, J = 6.5 Hz, H-1″), 3.82 (s, 3H, 7-OC$\underline{H}_3$), 3.46 (m, 2H, H-1′), 1.83, 1.82, 1.71, 1.69 (each s, each 3H, H-4′, H-5′, H-4″, H-5″); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 181.8 (C-9), 160.0 (C-1), 156.8 (C-3), 155.5 (C-10a), 155.0 (C-6), 150.7 (C-4a), 143.0 (C-7), 137.2 (C-8), 133.4, 132.4 (C-3′, C-3″), 122.9, 121.4 (C-2′, C-2″), 111.9 (C-8a), 110.6 (C-2), 104.3 (C-9a), 101.9 (C-5), 86.4 (C-4), 62.1 (7-OCH_3), 26.6 (C-1″), 25.9, 25.8 (C-4′, C-4″), 22.3 (C-1′), 18.3, 17.9 (C-1′, C-1″); negative ESIMS *m/z* 488 $[M - H]^-$.

4,5-dibromo-*α*-mangostin (15) Yield 50%, ^{1}H NMR (CD_3OD, 500 MHz) δ 5.20 (br t, 2H, H-2′, H-2″), 4.03 (d, 2H, J = 6.5 Hz, H-1″), 3.75 (s, 3H, 7-OC$\underline{H}_3$), 3.36 (d, 2H, J = 7.0 Hz, H-1′), 1.82, 1.79, 1.66, 1.66 (each s, each 3H, H-4′, H-5′, H-4″, H-5″); ^{13}C NMR (CD_3OD, 125 MHz) δ 182.6 (C-9), 160.4 (C-1), 160.1 (C-3), 156.1 (C-10a), 153.4 (C-6), 152.1 (C-4a), 145.2 (C-7), 137.3 (C-8), 132.5, 132.4 (C-3′, C-3″), 124.5, 123.1 (C-2′, C-2″), 113.2 (C-8a), 112.4 (C-2), 104.5 (C-9a), 97.6 (C-5), 87.8 (C-4), 62.0 (7-OCH_3), 27.1 (C-1″), 26.0, 26.0 (C-4′, C-4″), 23.1 (C-1′), 18.4, 18.0 (C-1′, C-1″); negative ESIMS *m/z* 567 $[M - H]^-$; HRESIMS *m/z* 564.9863 $[M - H]^-$ (calcd for $C_{24}H_{23}Br_2O_6$, 564.9867).

4-bromo-tetrahydro-*α*-mangostin (16) Yield 12%, ^{1}H NMR (DMSO-d_6, 500 MHz) δ 13.86 (s, 1H, 1-OH), 6.79 (s, 1H, H-5), 3.74 (s, 3H, 7-OC$\underline{H}_3$), 3.20 (m, 2H, H-1″),

2.61 (m, 2H, H-1′), 1.65 (dt, H, *J* = 6.5, 13.0 Hz, H-3″), 1.53 (dt, H, *J* = 6.5, 13.0 Hz, H-3′), 1.33 (dt, 4H, *J* = 16.5, 7.0 Hz, H-2′, H-2″), 0.95, 0.93, 0.91, 0.89 (each s, each 3H, H-4′, H-5′, H-4″, H-5″); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 181.2 (C-9), 159.0 (C-1), 158.5 (C-3), 157.2 (C-10a), 154.5 (C-6), 150.2 (C-4a), 143.6 (C-7), 138.5 (C-8), 112.4 (C-8a), 109.6 (C-2), 102.9 (C-9a), 101.6 (C-5), 86.7 (C-4), 60.4 (7-OCH_3), 39.0, 37.5 (C-2′, C-2″), 28.3, 27.7 (C-3′, C-3″), 24.6 (C-1″), 22.5, 22.4 (C-4′, C-4″, C-5′, C-5″), 20.6 (C-1′); negative ESIMS *m/z* 491 $[M - H]^-$; HRESIMS *m/z* 491.1072 $[M - H]^-$ (calcd for $C_{24}H_{28}BrO_6$, 491.1069).

4,5-dibromo-tetrahydro-*α*-mangostin (17) Yield 60%, ^{1}H NMR (DMSO-d_6, 500 MHz) δ 13.54 (s, 1H, 1-OH), 3.70 (s, 3H, 7-OC<u>H</u>$_3$), 3.16 (m, 2H, H-1″), 2.59 (m, 2H, H-1′), 1.63 (dt, H, *J* = 6.5, 13.0 Hz, H-3″), 1.53 (dt, H, *J* = 6.5, 13.0 Hz, H-3′), 1.32 (m, 4H, H-2′, H-2″), 0.93, 0.92, 0.90, 0.89 (each s, each 3H, H-4′, H-5′, H-4″, H-5″); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 182.7 (C-9), 160.7 (C-1), 160.6 (C-3), 156.3 (C-10a), 153.4 (C-6), 152.0 (C-4a), 145.4 (C-7), 139.2 (C-8), 114.6 (C-8a), 112.3 (C-2), 104.6 (C-9a), 98.1 (C-5), 88.8 (C-4), 63.3 (7-OCH_3), 41.0, 39.3 (C-2′, C-2″), 30.1, 29.5 (C-3′, C-3″), 26.4 (C-1″), 24.3, 24.2 (C-4′, C-4″, C-5′, C-5″), 22.4 (C-1′); negative ESIMS *m/z* 571 $[M - H]^-$; HRESIMS *m/z* 569.0170 $[M - H]^-$ (calcd for $C_{24}H_{27}Br_2O_6$, 569.0174).

3. Biological assays

Cholinesterase inhibitory activity of the compounds synthesized was assayed by the spectrophotometric method developed by Ellman et al with slightly modification (Ellman et al. 1961). *S*-Acetylthiocholineiodide, *S*-butyrylthiocholineiodide, 5,5’-dithio-bis-(2-nitrobenzoic) acid (DTNB, Ellman's reagent), acetylcholinesterase and butyrylcholinesterase derived from human erythrocytes were purchased from Sigma Chemical. Compounds were dissolved in DMSO. The reaction mixture (totally 200 μL) containing phosphate buffer (pH 8.0), test compound (50 μM), and acetylcholinesterase (0.02 U/mL) or butyrylcholinesterase (0.016 U/mL), was incubated for 20 min (37 °C). Then the reaction was initiated by the addition of 40μL of solution containing DTNB (0.625 mM) and acetylthiocholine iodide (0.625 mM) or butyrylthiocholine iodide (0.625 mM) for AChE or BuChE inhibitory activity assay, respectively. The hydrolysis of acetylthiocholine or butyrylthiocholine was monitored at 405 nm every 30 seconds for one hour. Tacrine was used as positive control with final concentration of 0.333 μM. All these actions were performed in triplicate. The percentage inhibition was calculated as follows: % inhibition = (E - S)/E × 100 (E is the activity of the enzyme without test compound and S is the activity of enzyme with test compound).

Reference

Ellman GL, Courtney KD, Andres V, Featherstone RM. 1961. A NEW AND RAPID COLORIMETRIC DETERMINATION OF ACETYLCHOLINESTERASE ACTIVITY. Biochem Pharmacol. 7(2):88-95.

Abbreviation

OsO_4	Osmium tetroxide
NMO	4-Methylmorpholine N-oxide
$NaIO_4$	Sodium periodate
CH_3I	Iodomethane
NaH	Sodium hydride
NBS	N-Bromosuccinimide
NCS	N-Chlorosuccinimide

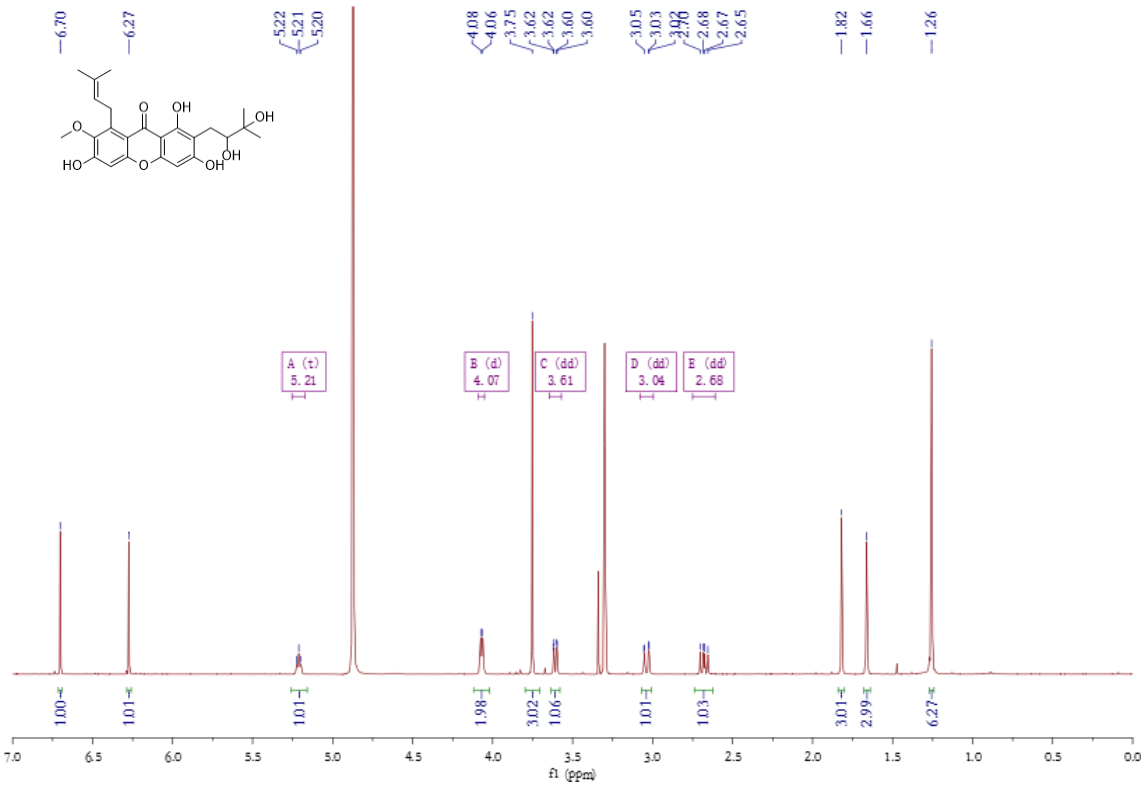


Figure 1S. ^{1}H NMR spectrum (CD_3OD, 500 MHz) of compound **2**

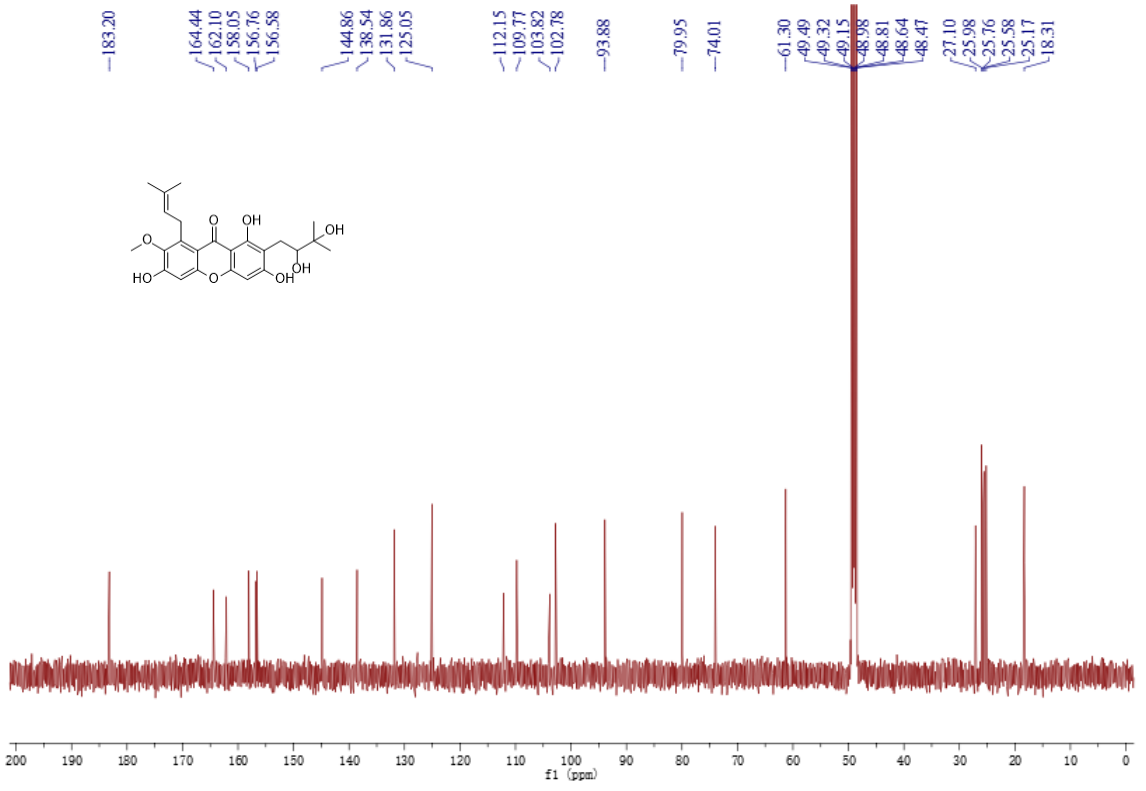


Figure 2S. ^{13}C NMR spectrum (CD_3OD, 125 MHz) of compound **2**

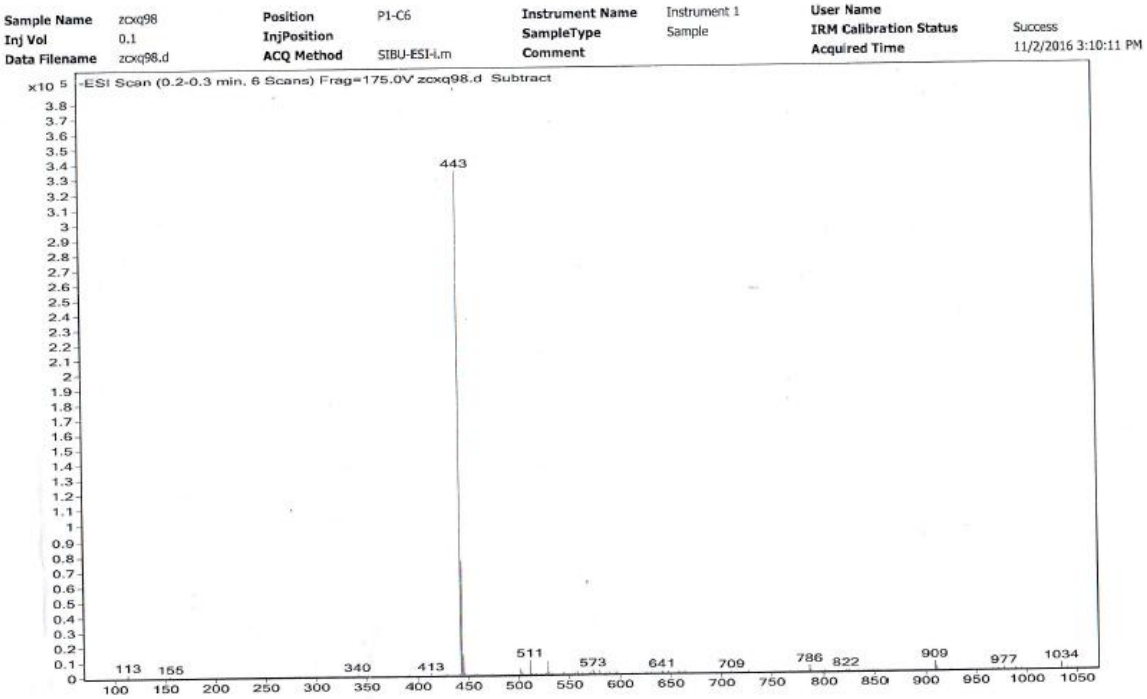


Figure 3S. Negative ESI-MS spectrum of compound **2**

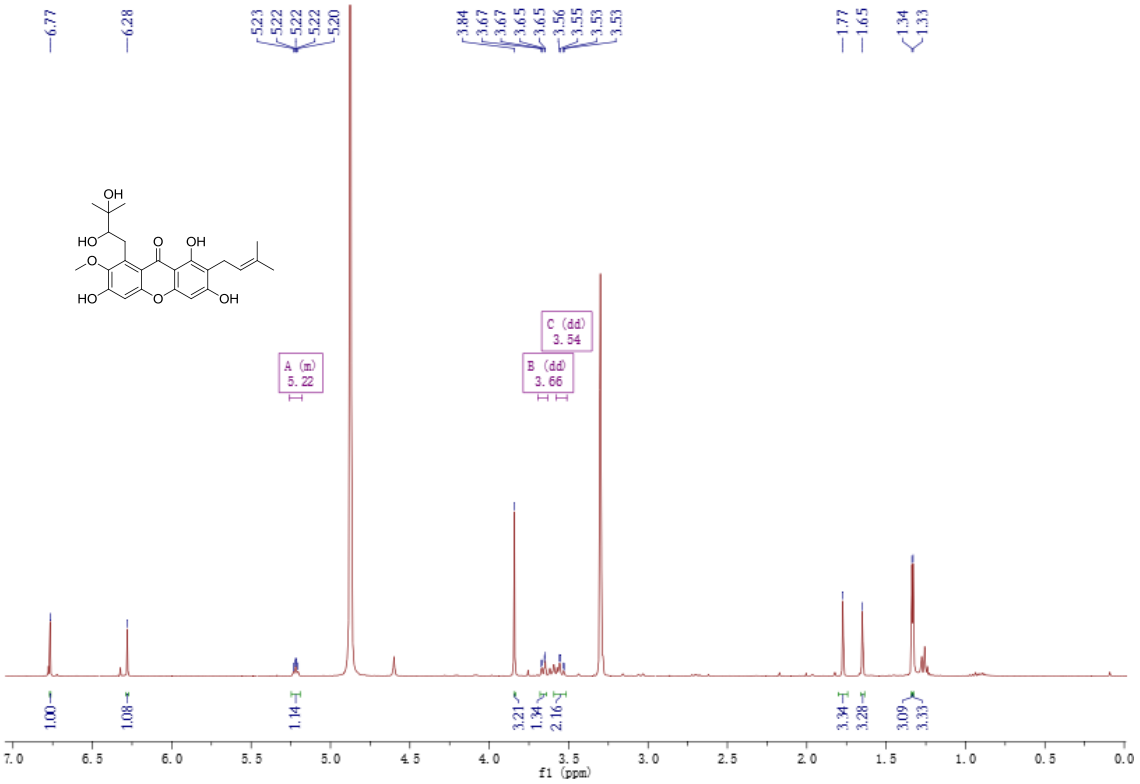


Figure 4S. ^{1}H NMR spectrum (CD_3OD, 500 MHz) of compound **3**

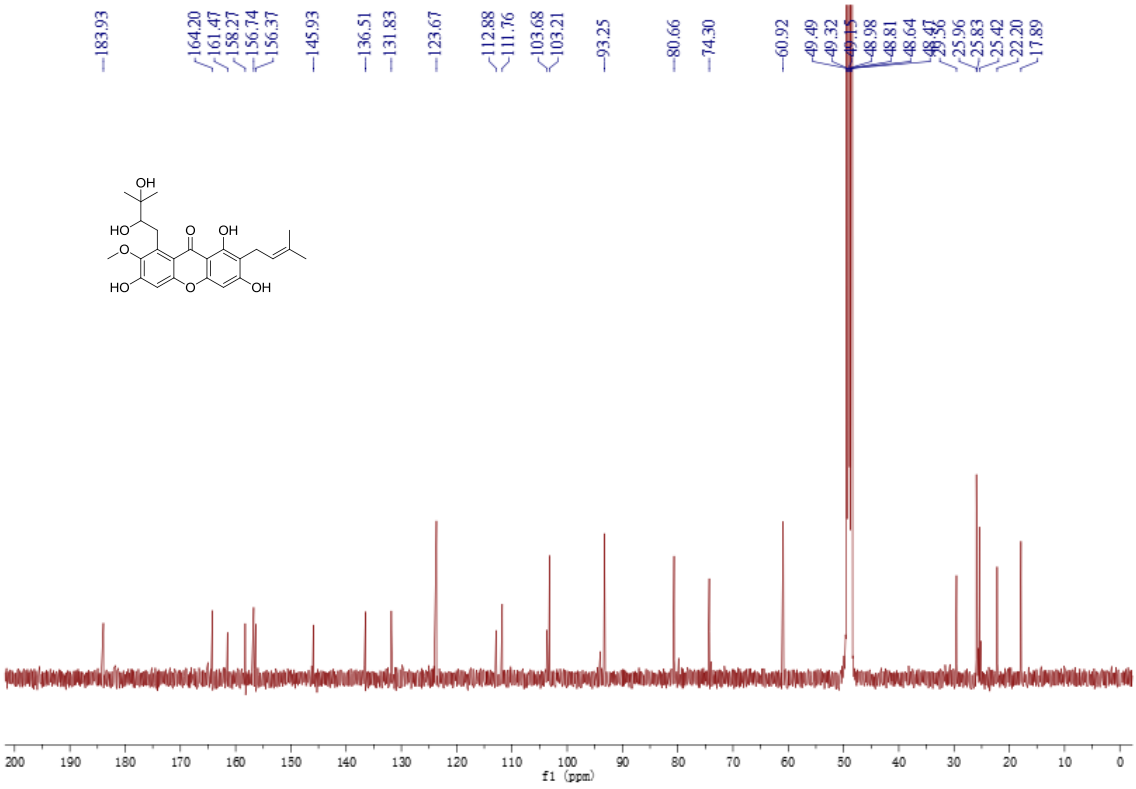


Figure 5S. ^{13}C NMR spectrum (CD_3OD, 125 MHz) of compound **3**

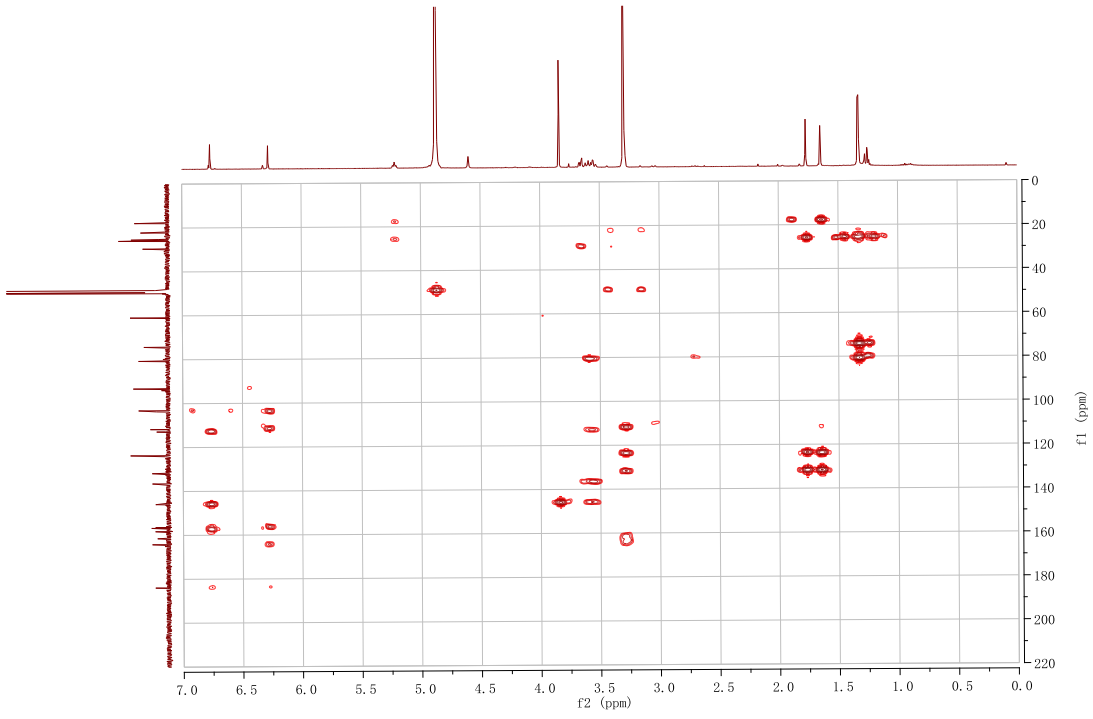


Figure 6S. HMBC spectrum (CD_3OD, 125 MHz) of compound **3**

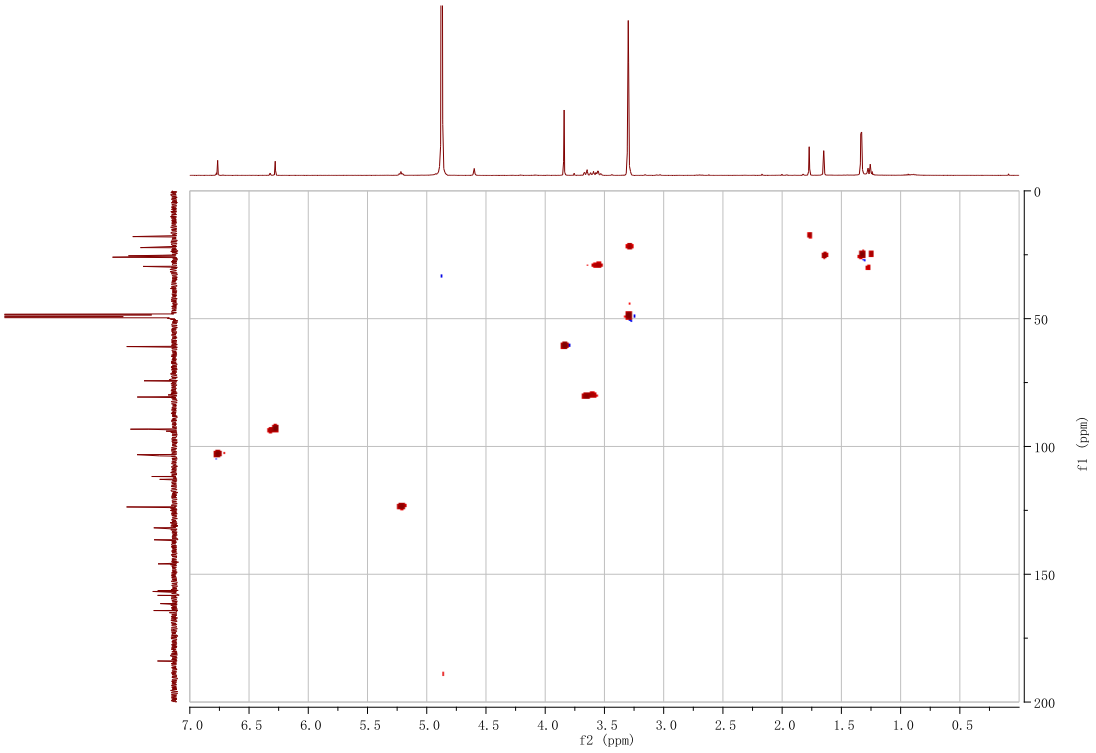


Figure 7S. HSQC spectrum (CD_3OD, 125 MHz) of compound **3**

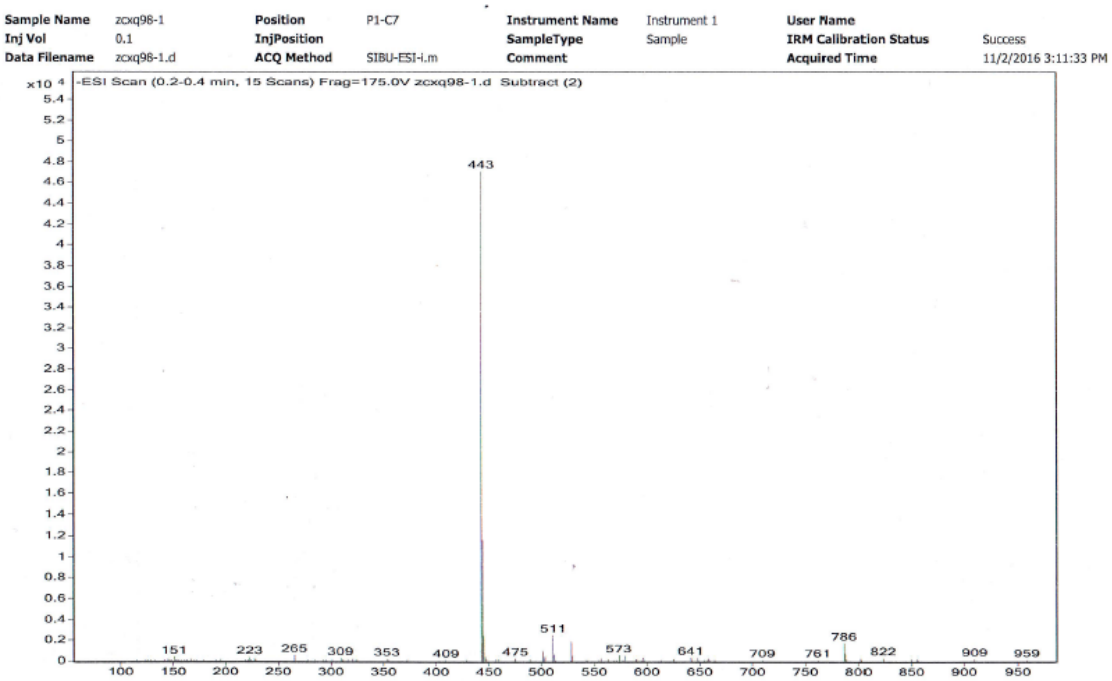


Figure 8S. Negative ESI-MS spectrum of compound **3**

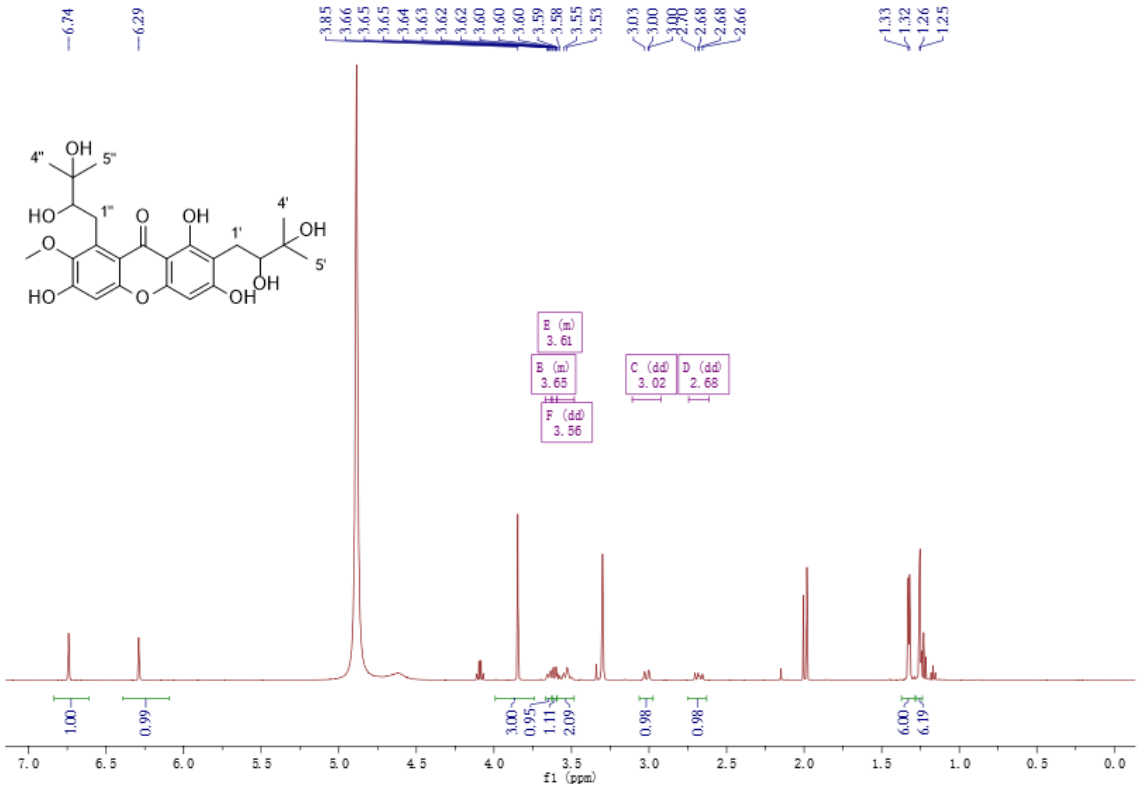


Figure 9S. ^{1}H NMR spectrum (CD_3OD, 500 MHz) of compound **4**

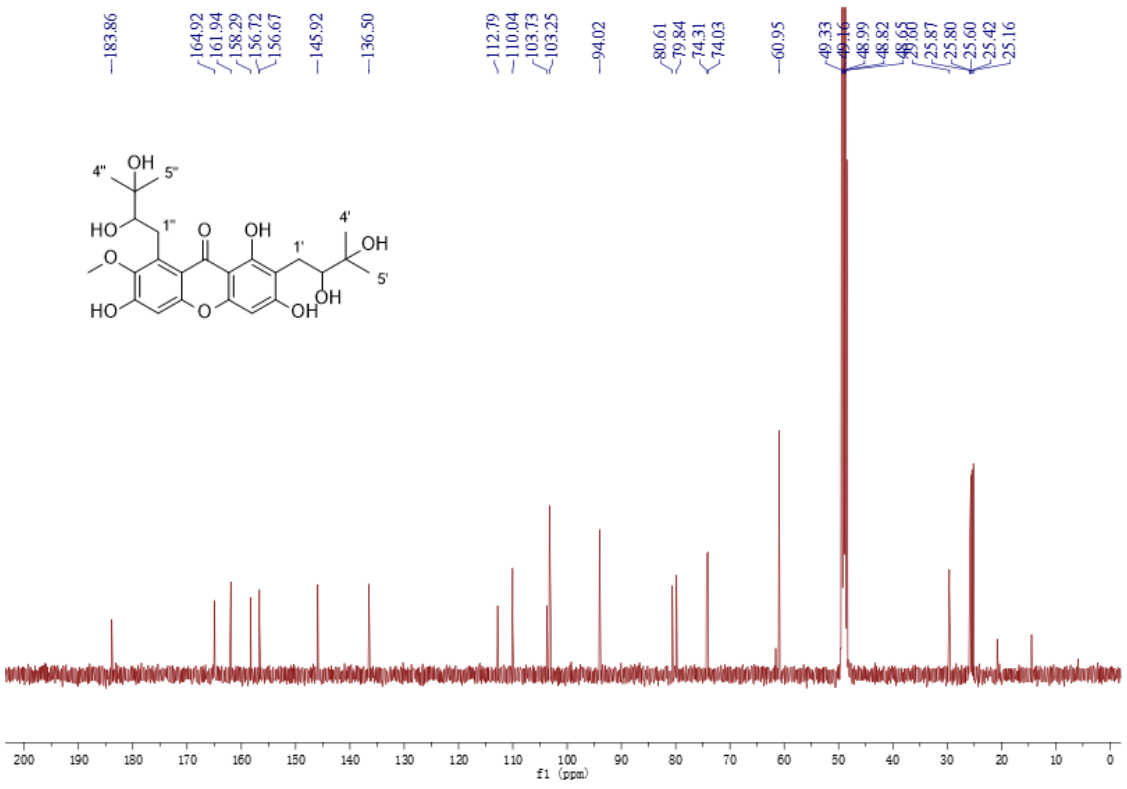


Figure 10S. ^{13}C NMR spectrum (CD_3OD, 125 MHz) of compound **4**

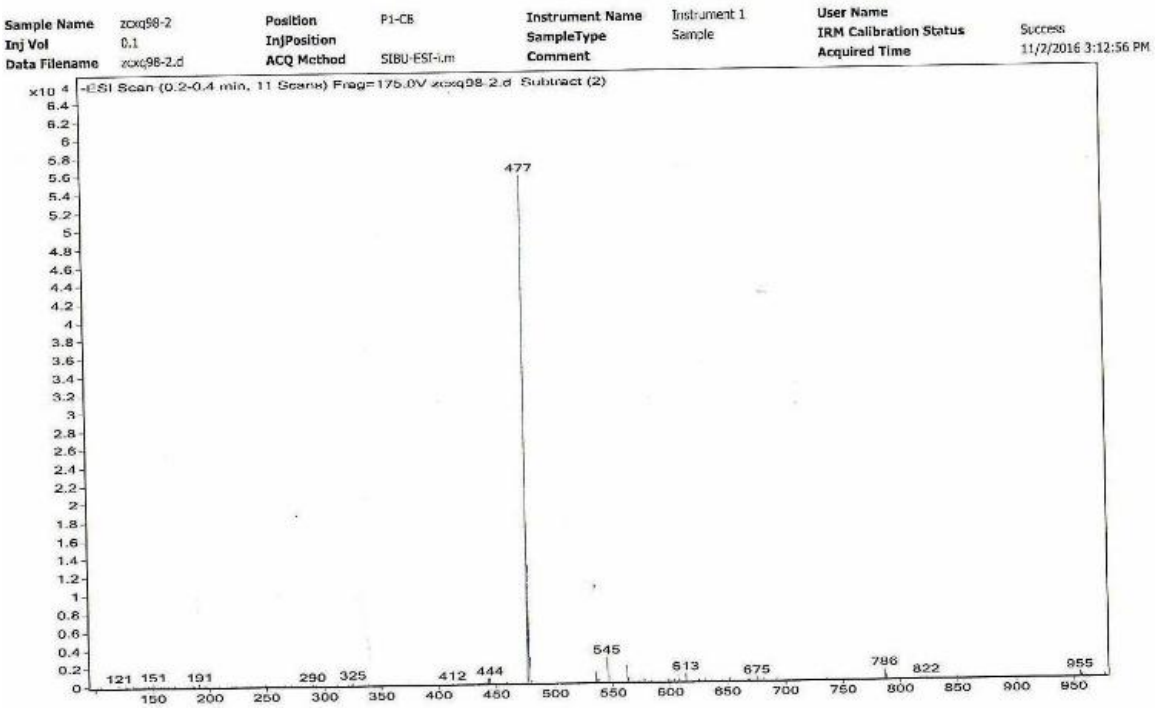


Figure 11S. Negative ESI-MS spectrum of compound **4**

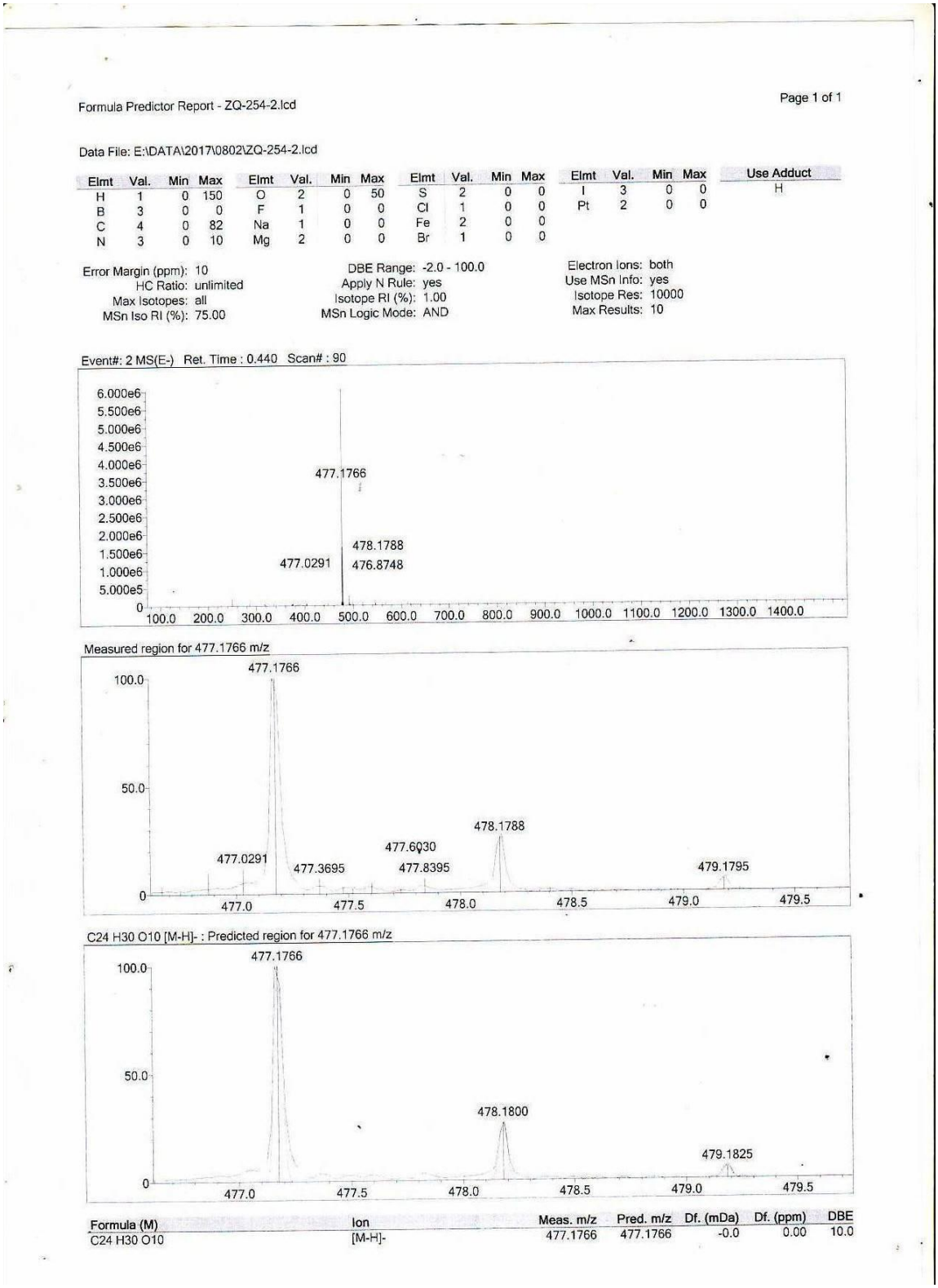


Figure 12S. Negative HR-ESIMS spectrum of compound **4**

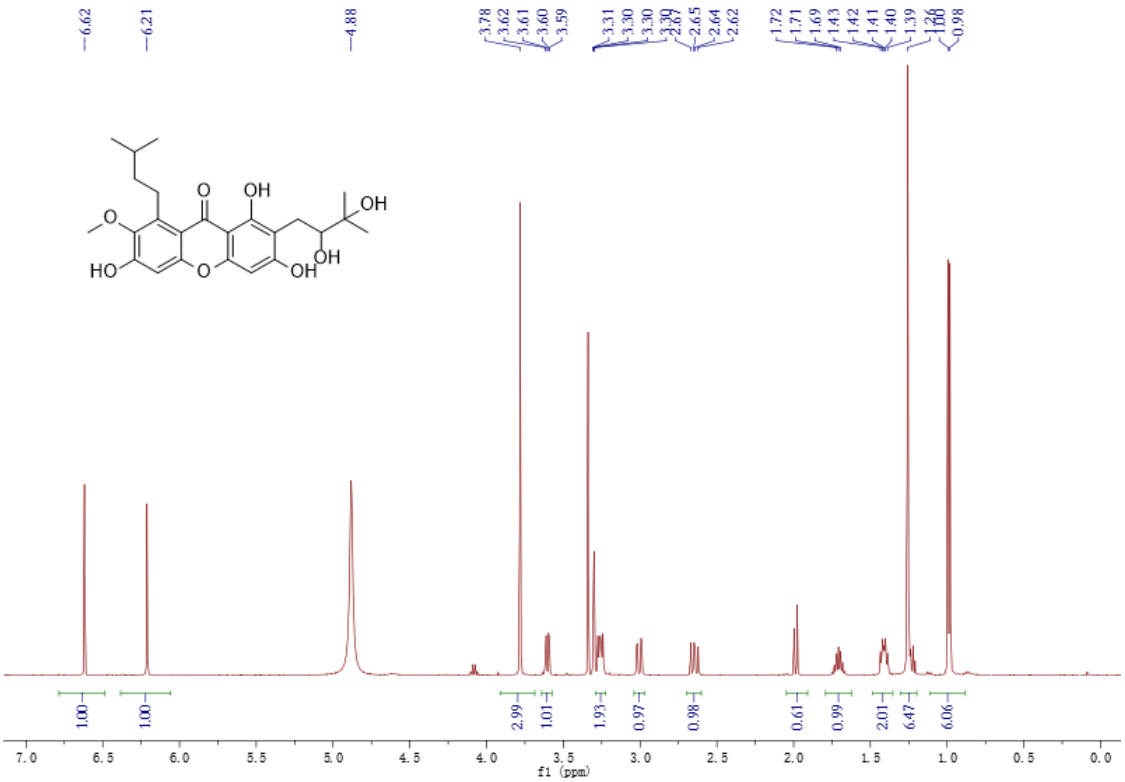


Figure 13S. ^{1}H NMR spectrum (CD_3OD, 500 MHz) of compound **5**

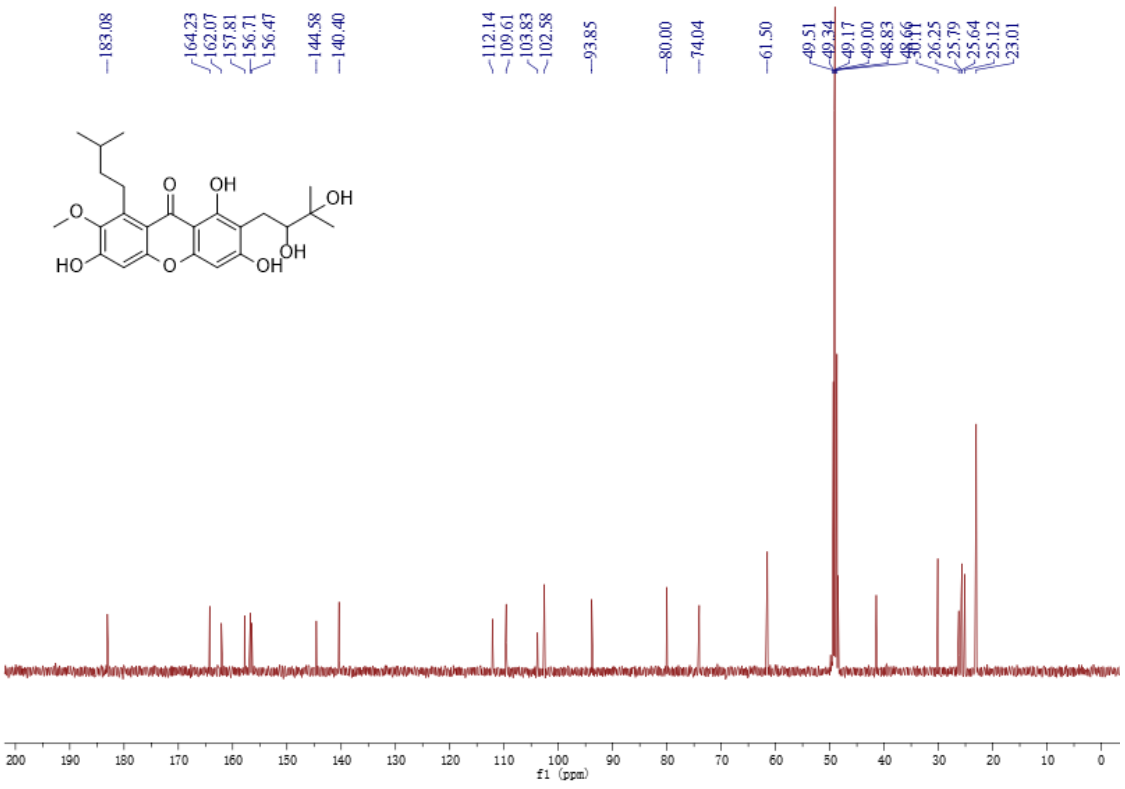


Figure 14S. ^{13}C NMR spectrum (CD_3OD, 125 MHz) of compound **5**

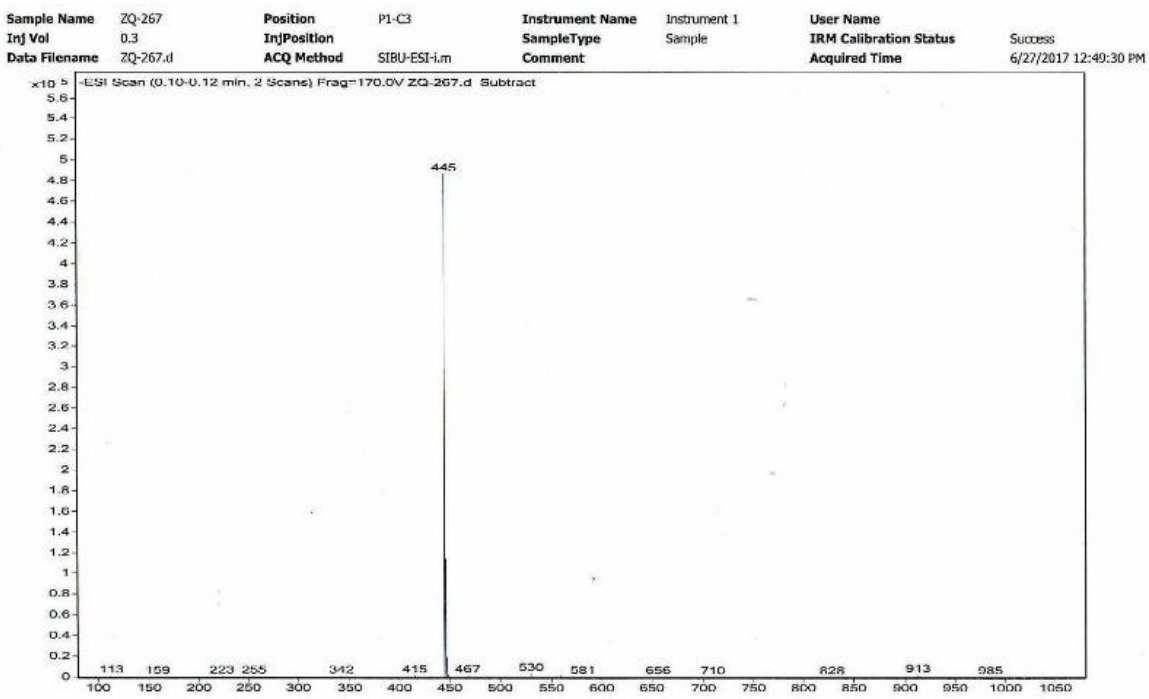


Figure 15S. Negative ESI-MS spectrum of compound **5**

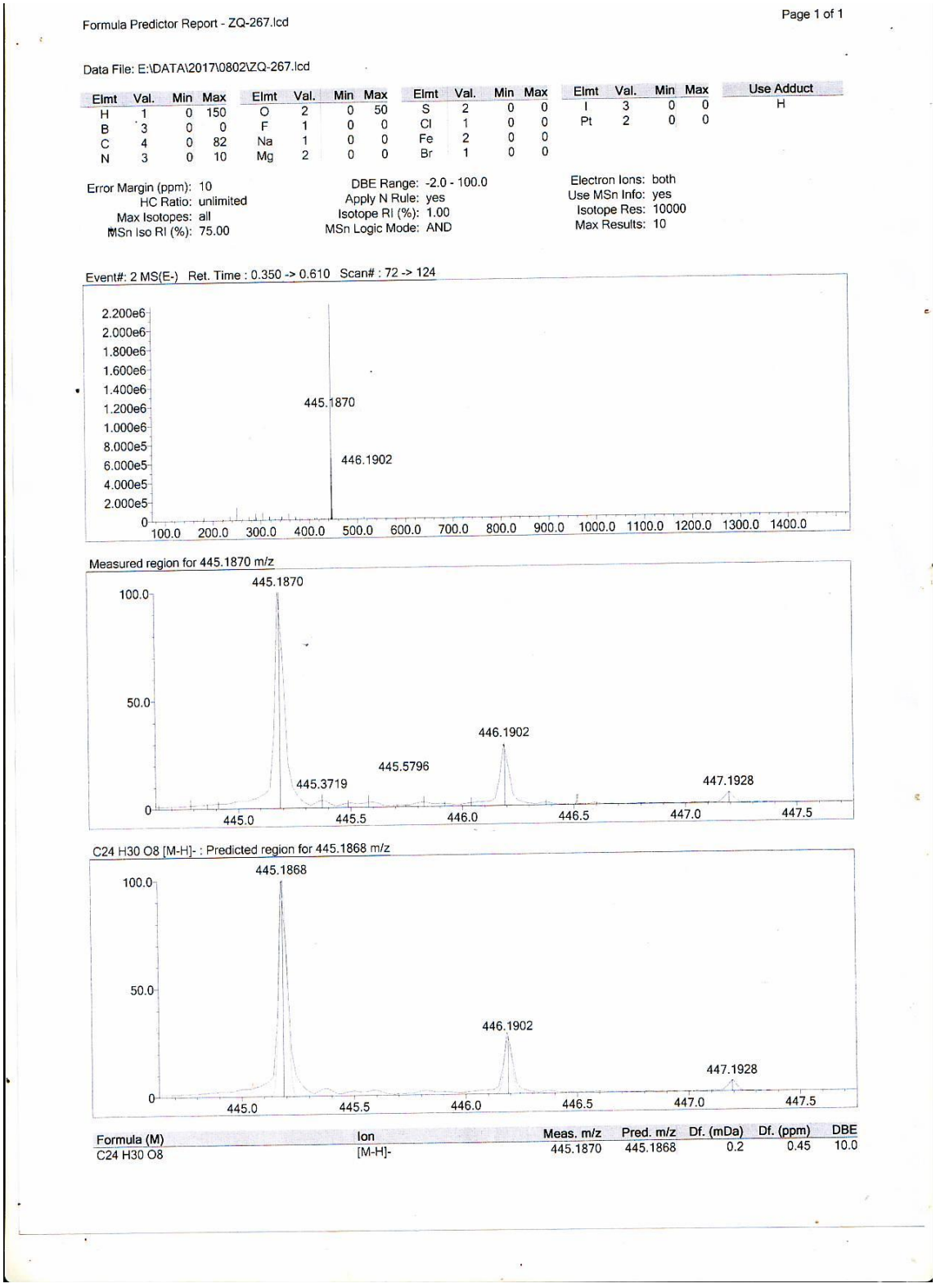


Figure 16S. Negative HR-ESIMS spectrum of compound **5**

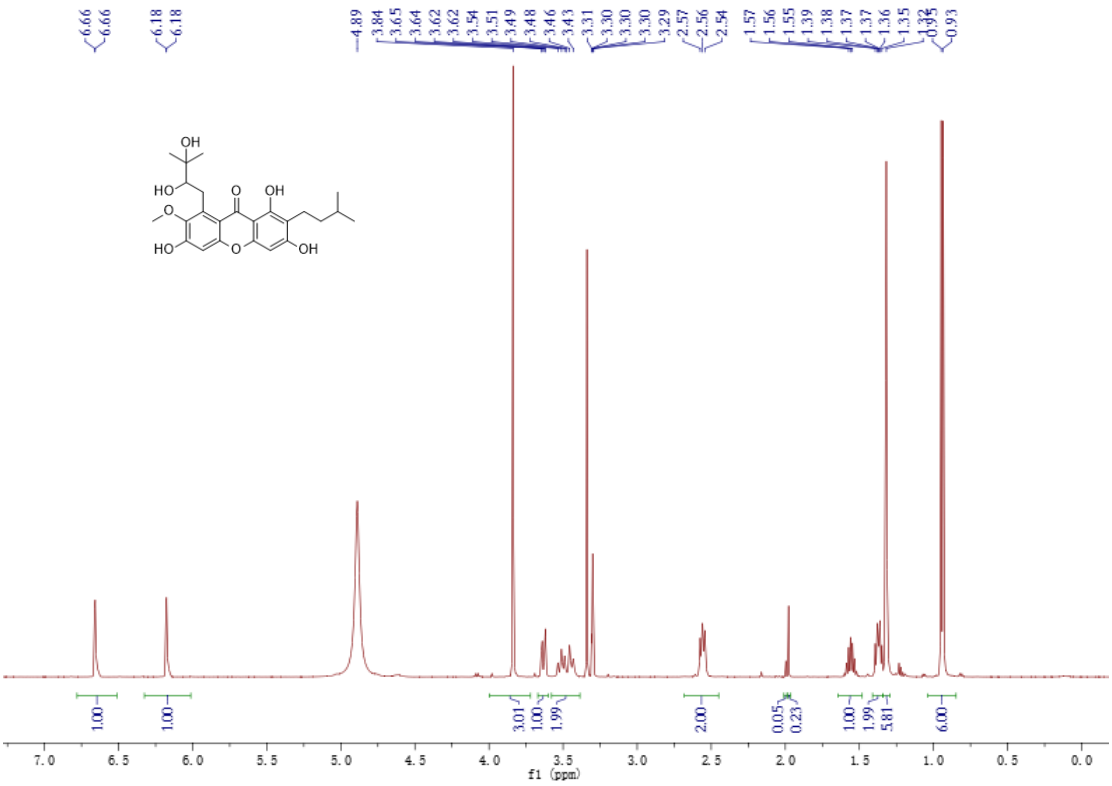


Figure 17S. ^{1}H NMR spectrum (CD_3OD, 500 MHz) of compound **6**

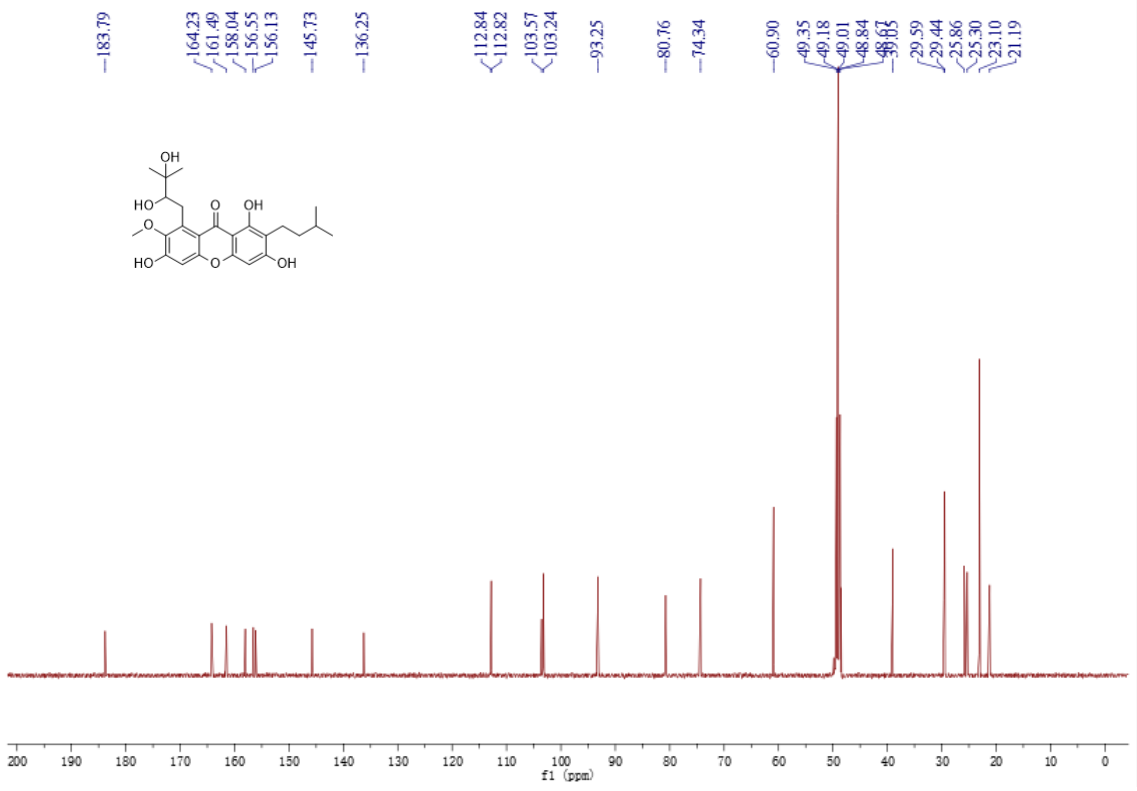


Figure 18S. ^{13}C NMR spectrum (CD_3OD, 125 MHz) of compound **6**

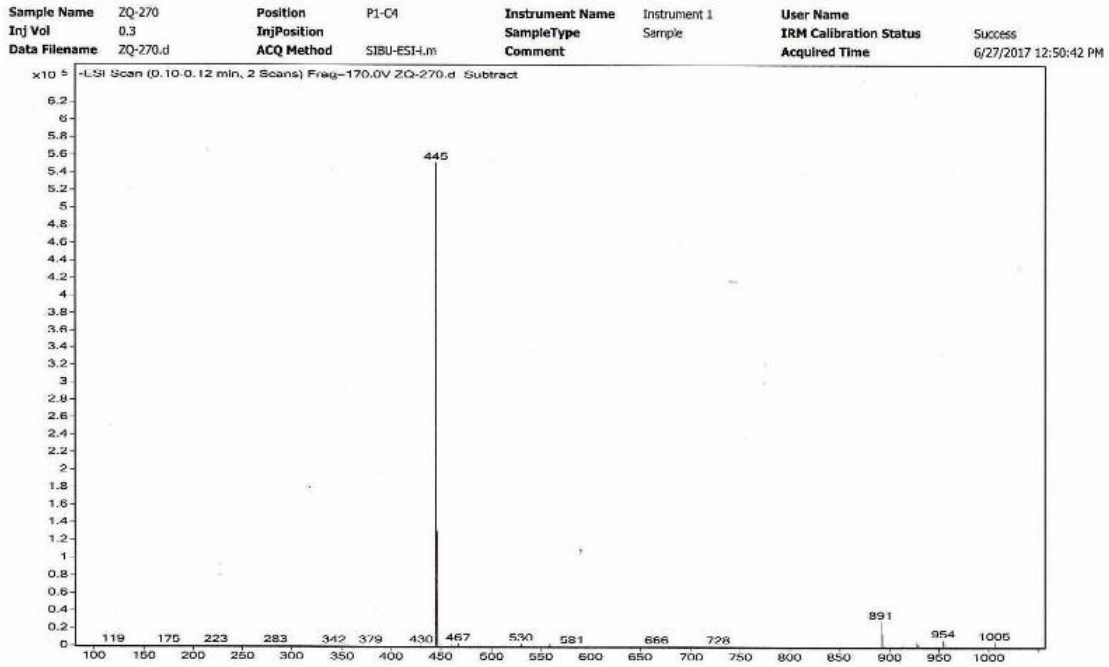


Figure 19S. Negative ESI-MS spectrum of compound **6**

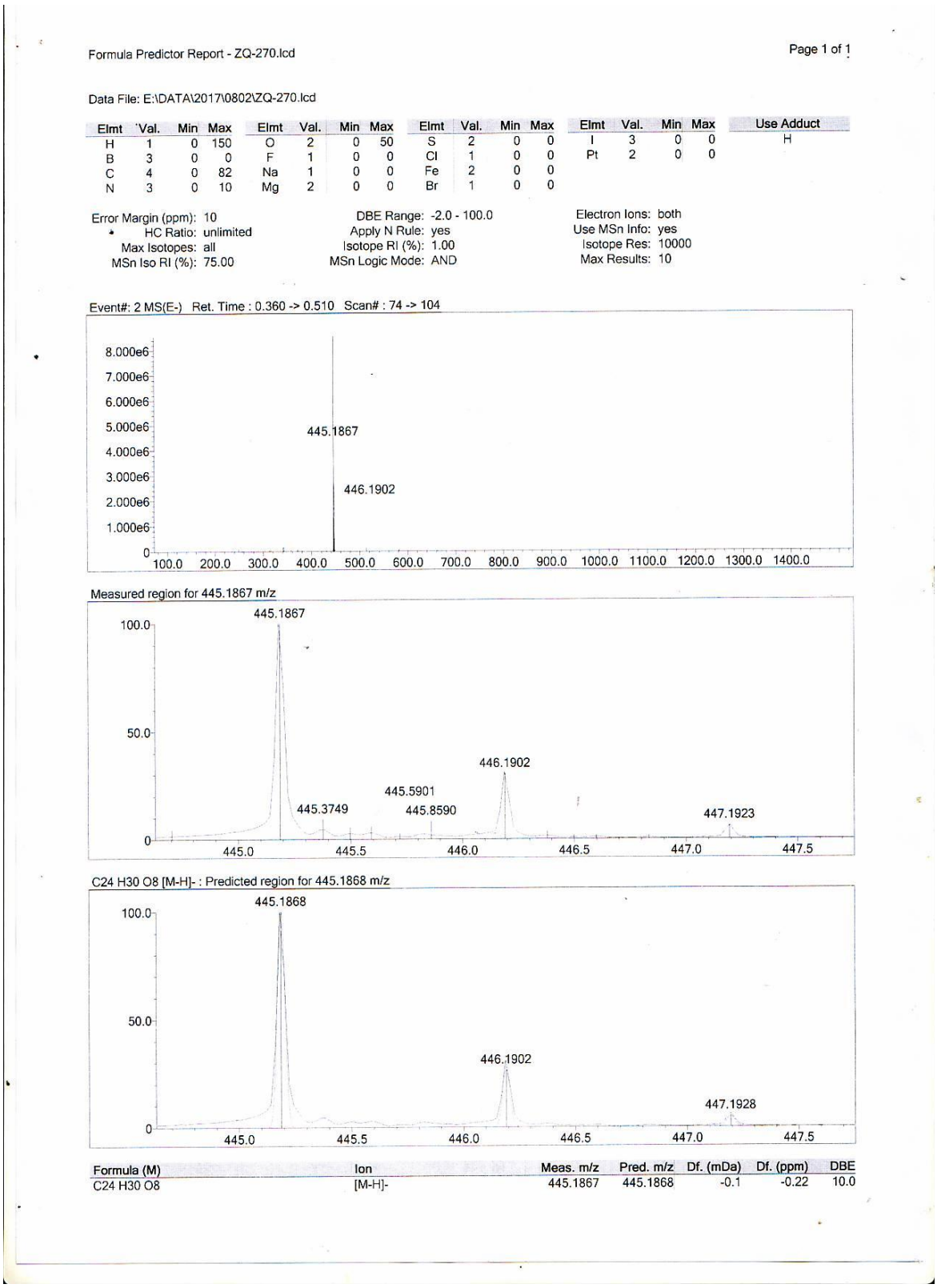


Figure 20S. Negative HR-ESIMS spectrum of compound **6**

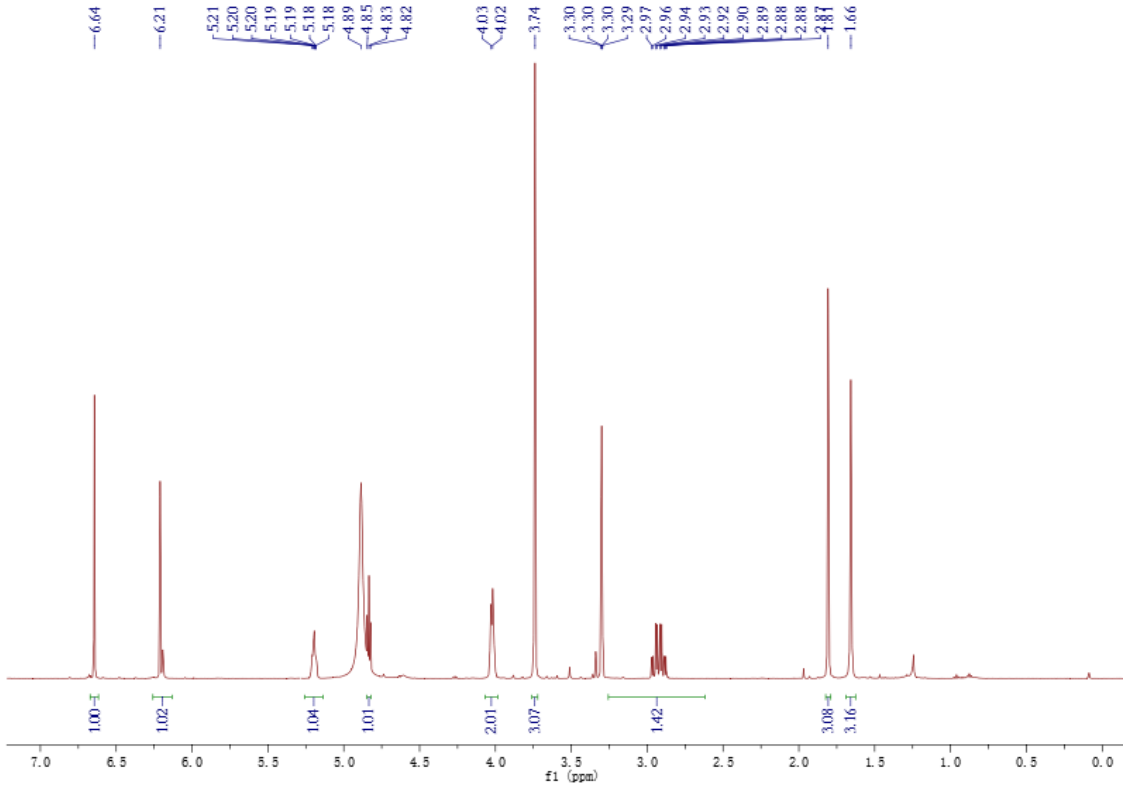


Figure 21S. ^{1}H NMR spectrum (CD_3OD, 500 MHz) of compound **7**

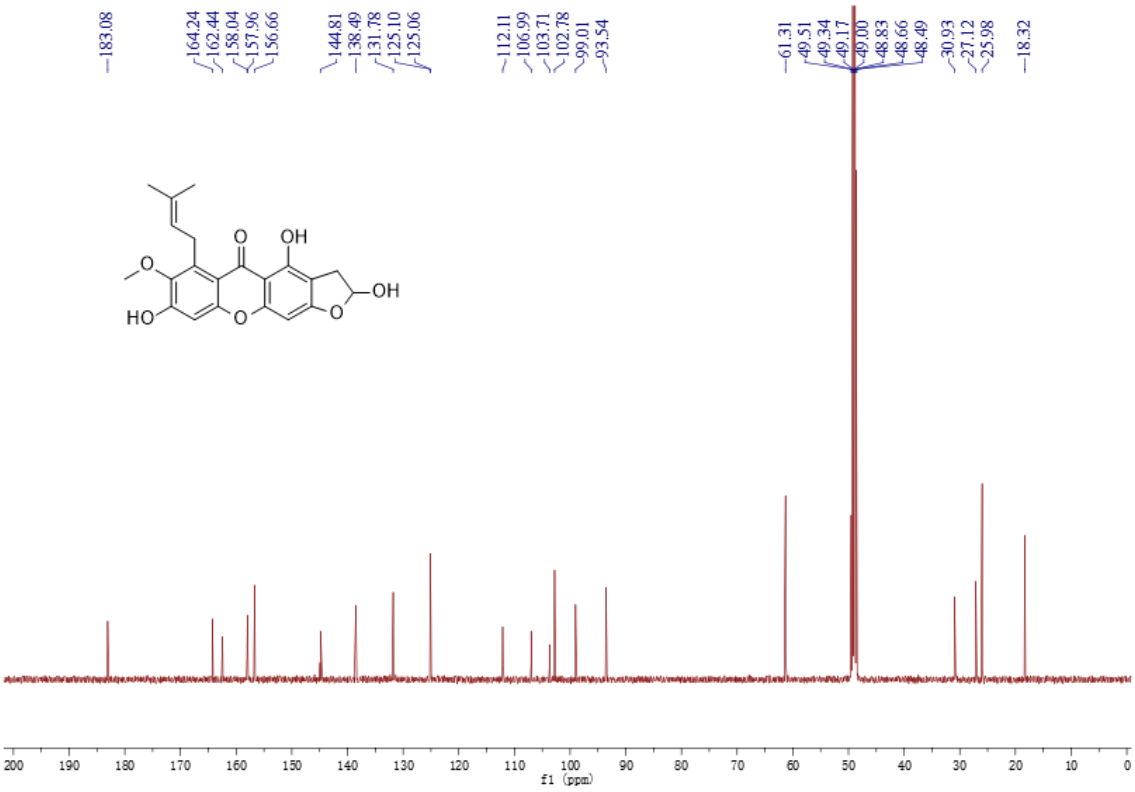


Figure 22S. ^{13}C NMR spectrum (CD_3OD, 125 MHz) of compound **7**

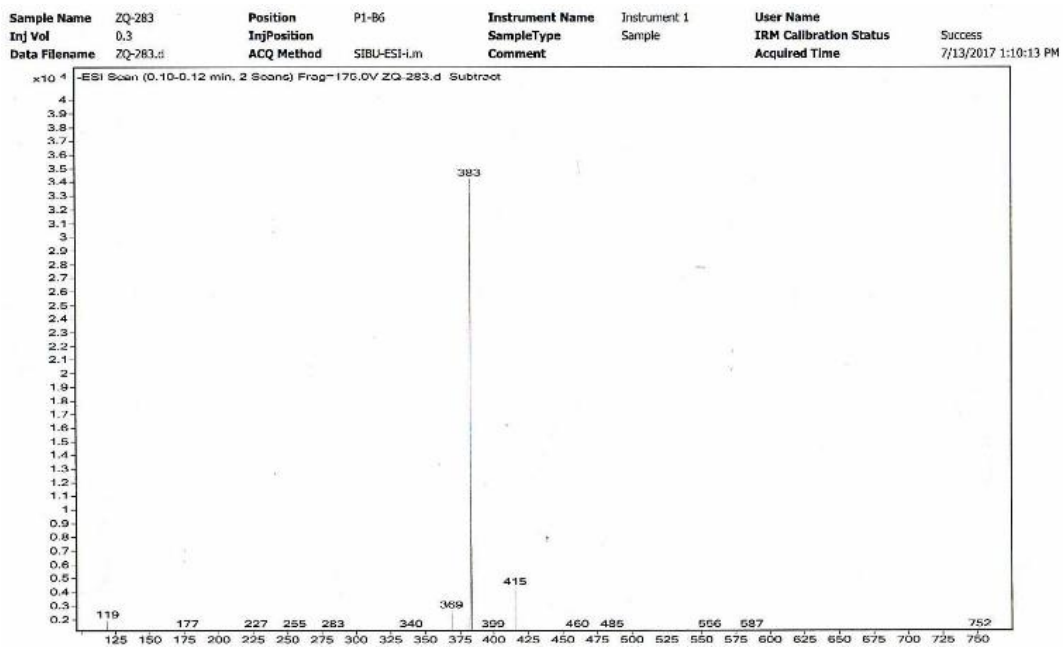


Figure 23S. Negative ESI-MS spectrum of compound **7**

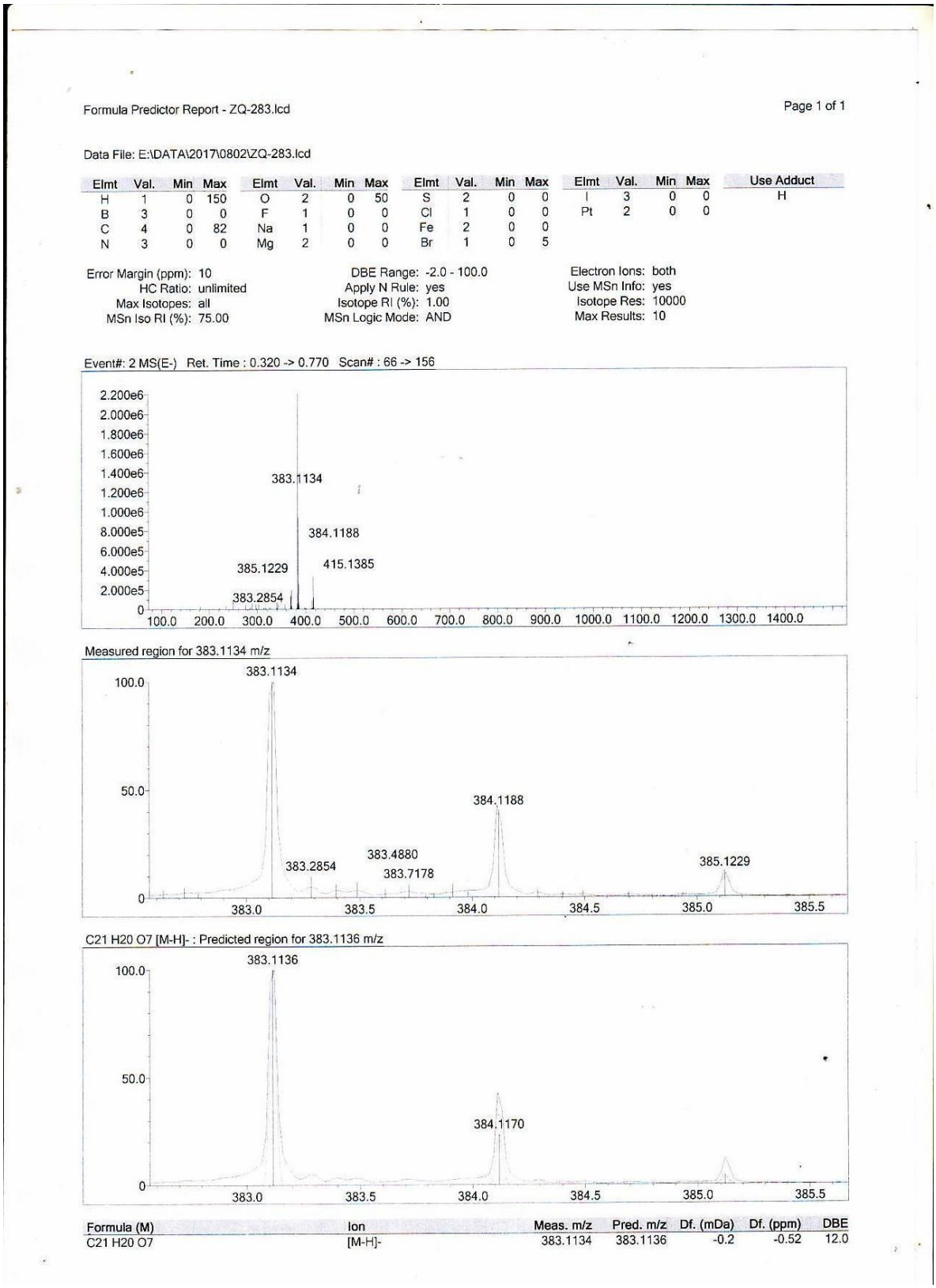


Figure 24S. Negative HR-ESIMS spectrum of compound **7**

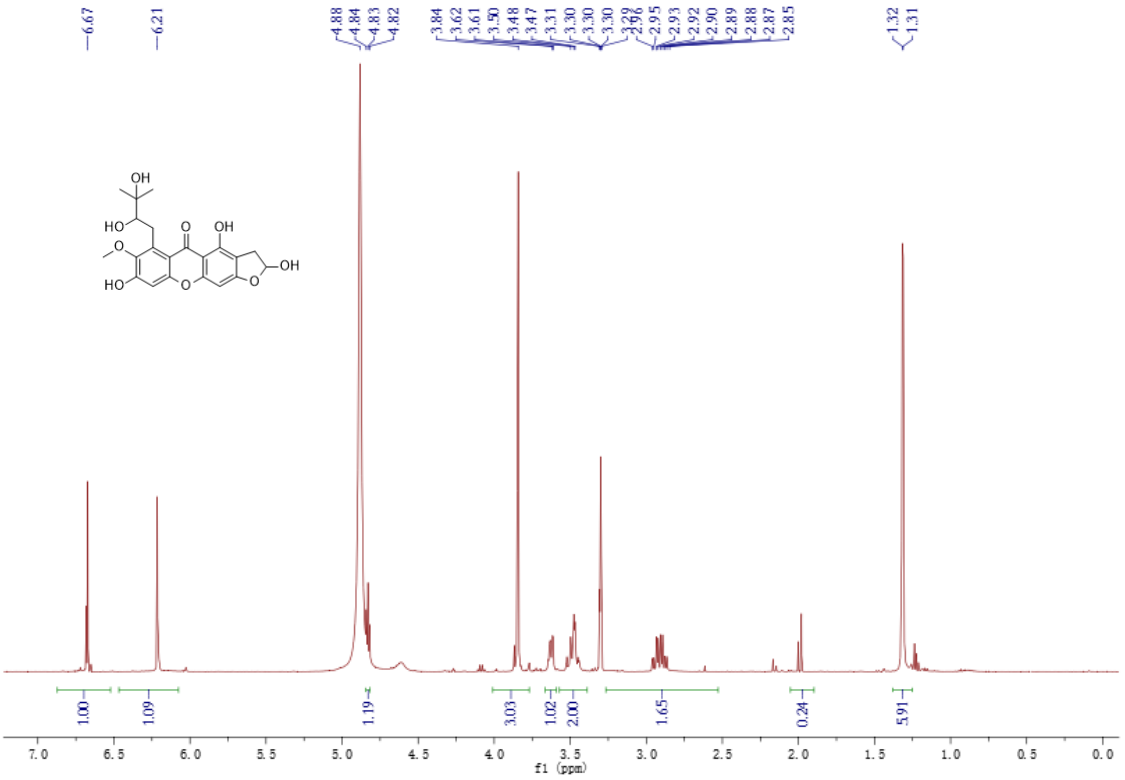


Figure 25S. ^{1}H NMR spectrum (CD_3OD, 500 MHz) of compound **8**

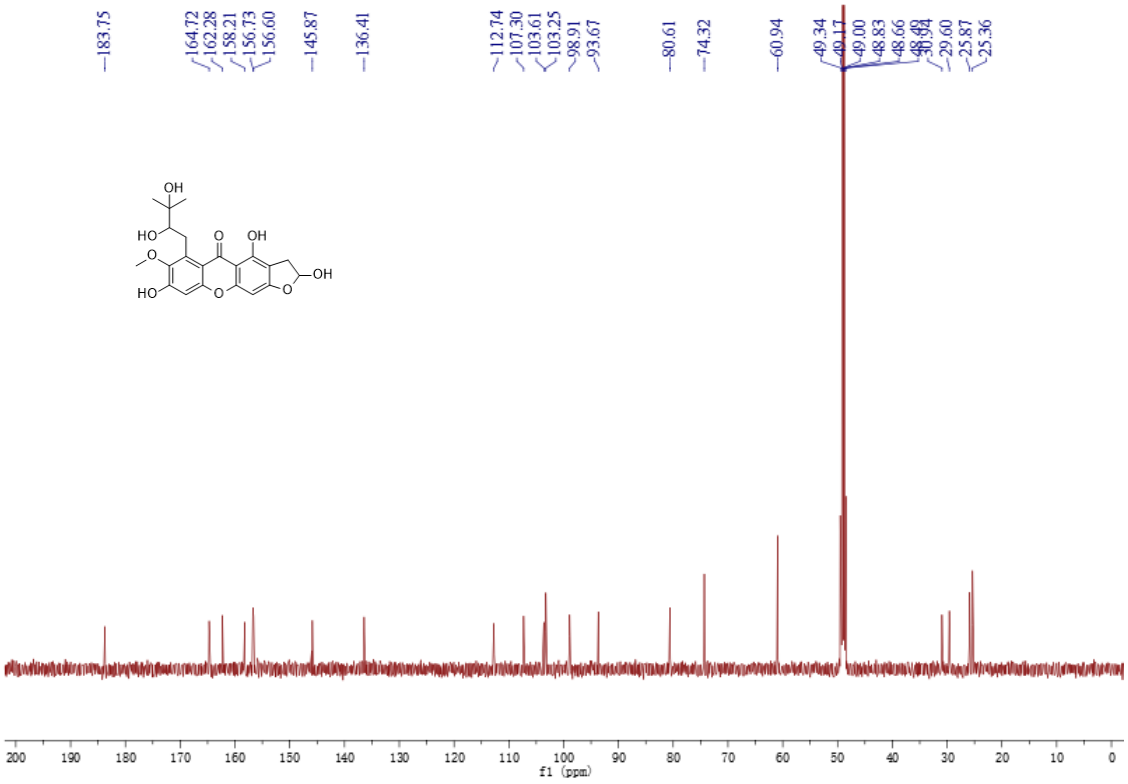


Figure 26S. ^{13}C NMR spectrum (CD_3OD, 125 MHz) of compound **8**

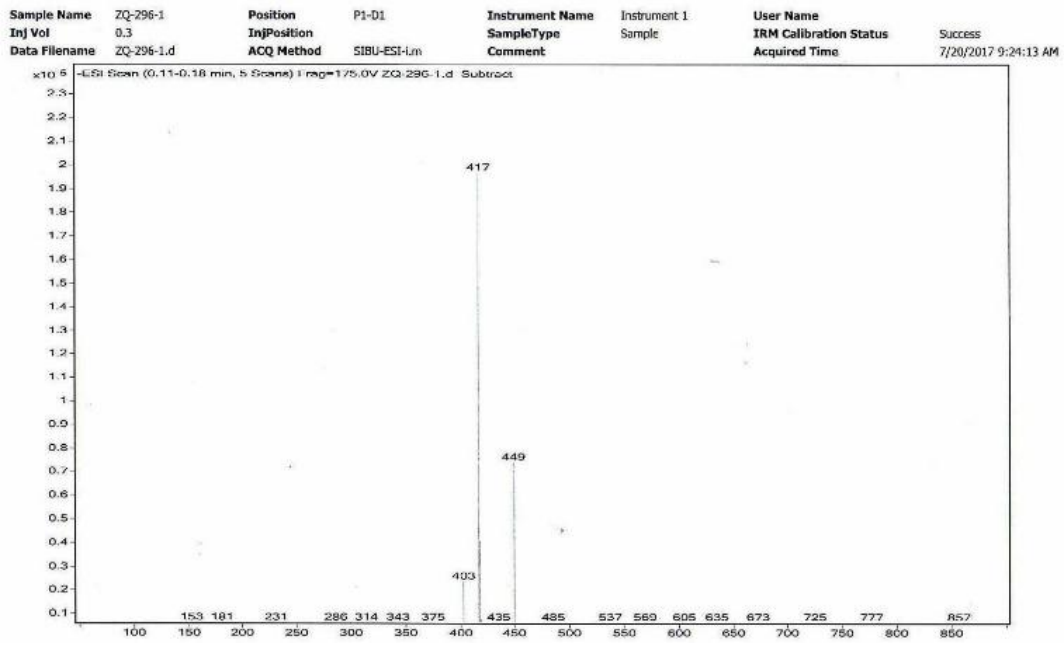


Figure 27S. Negative ESI-MS spectrum of compound **8**

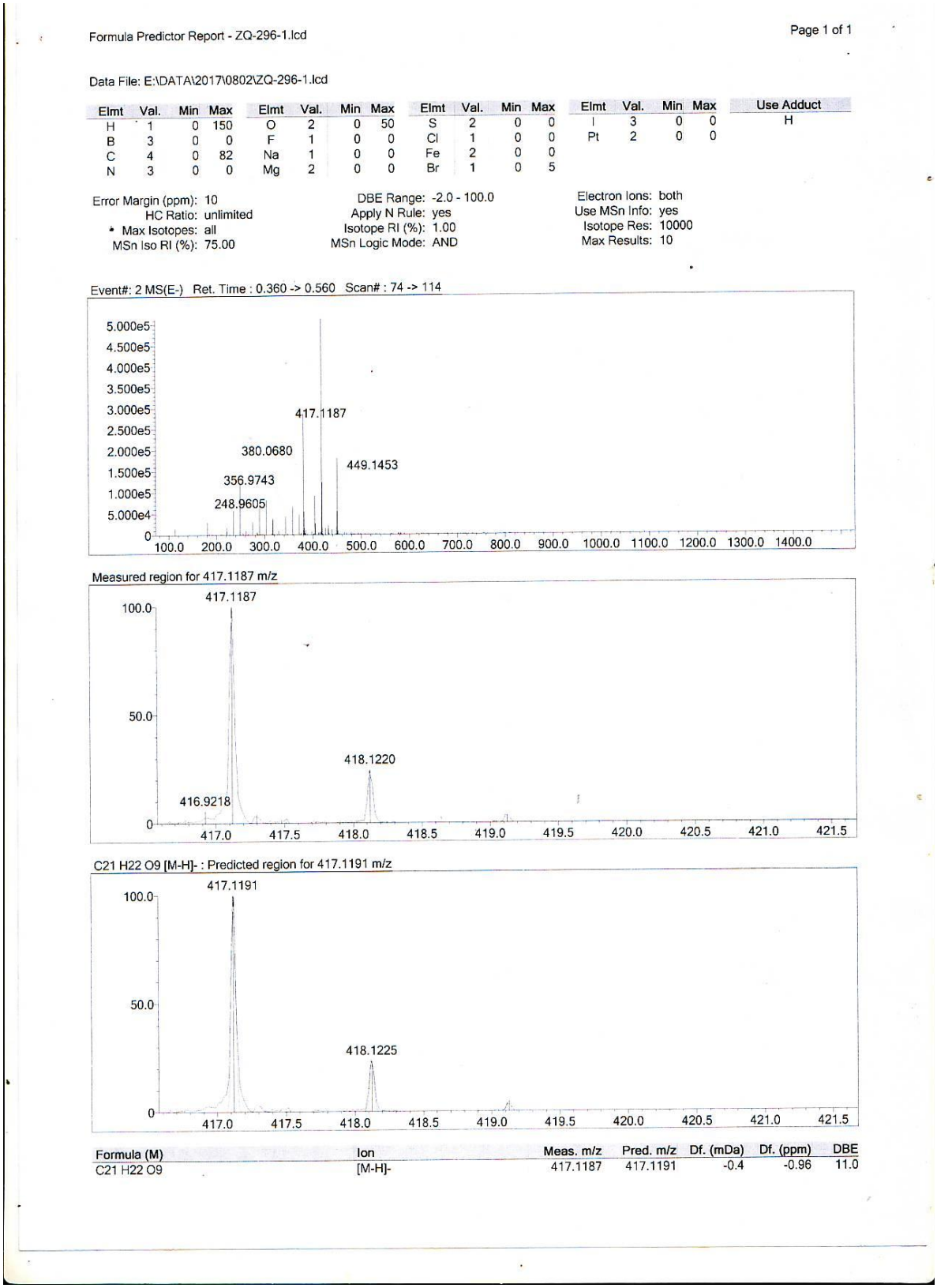


Figure 28S. Negative HR-ESIMS spectrum of compound **8**

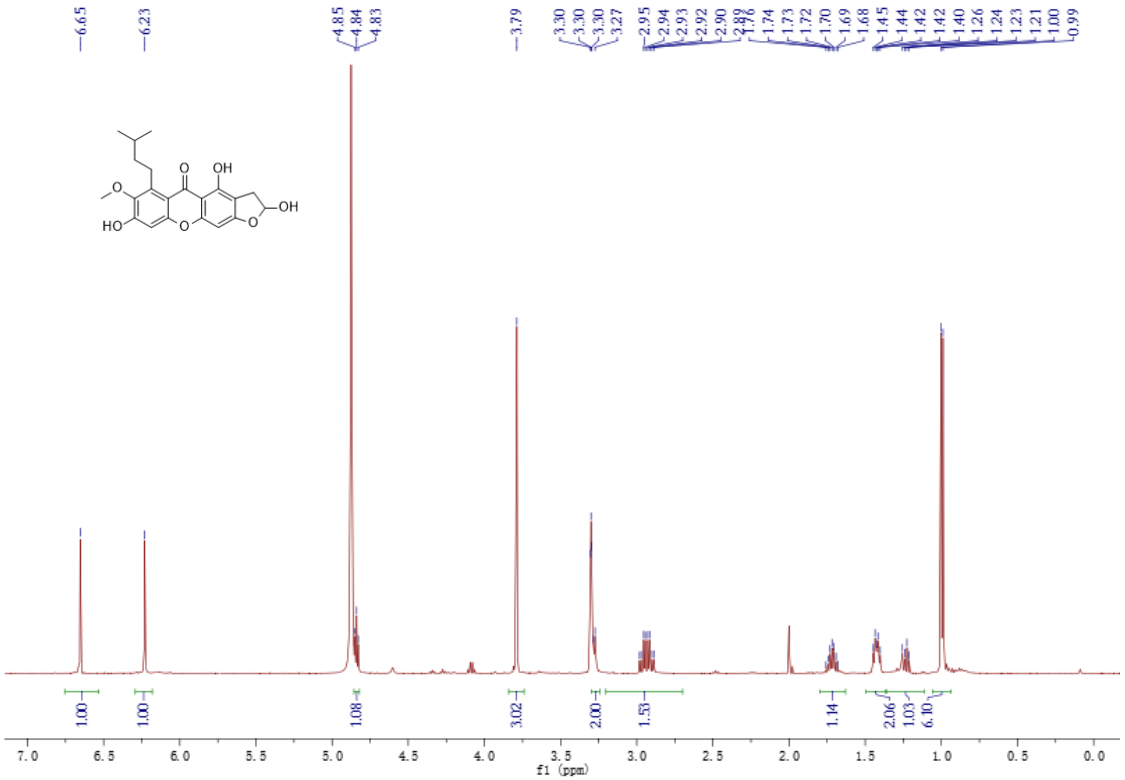


Figure 29S. ^{1}H NMR spectrum (CD_3OD, 500 MHz) of compound **9**

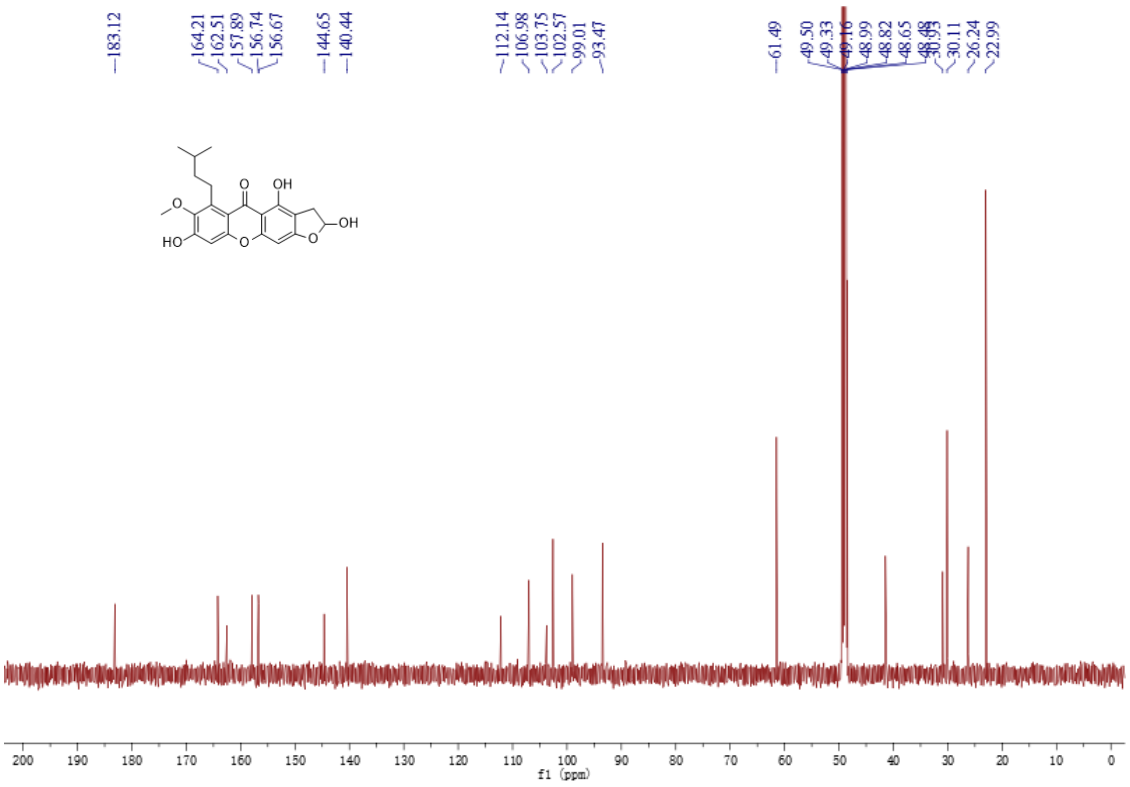


Figure 30S. ^{13}C NMR spectrum (CD_3OD, 125 MHz) of compound **9**

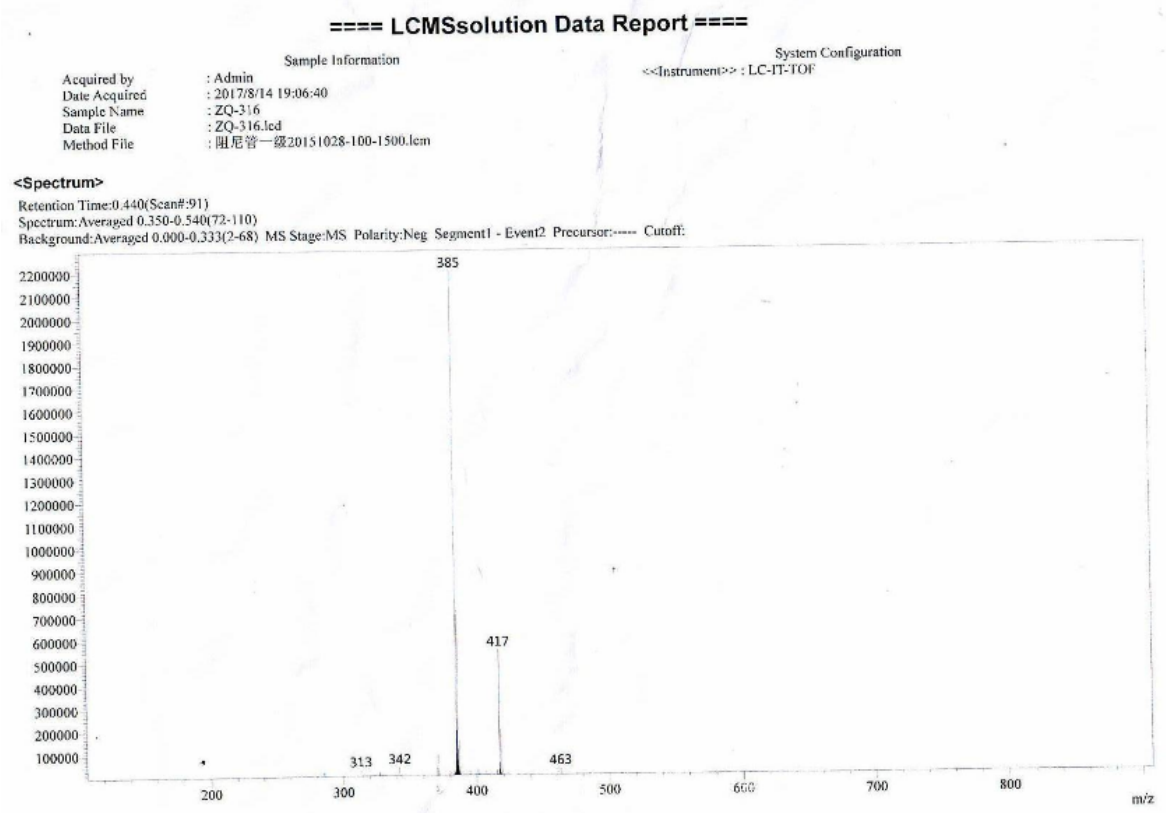


Figure 31S. Negative ESI-MS spectrum of compound **9**

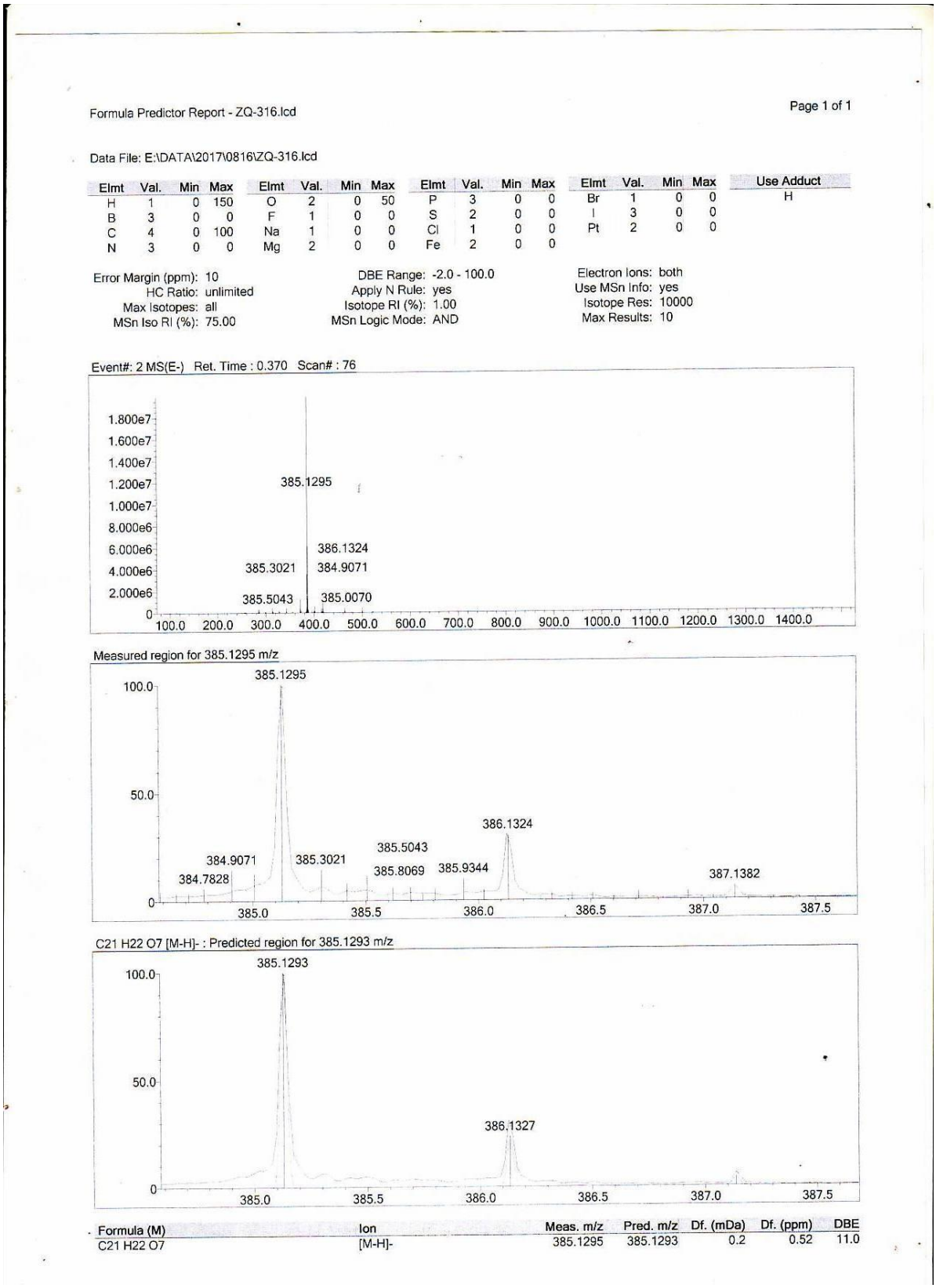


Figure 32S. Negative HR-ESIMS spectrum of compound **9**

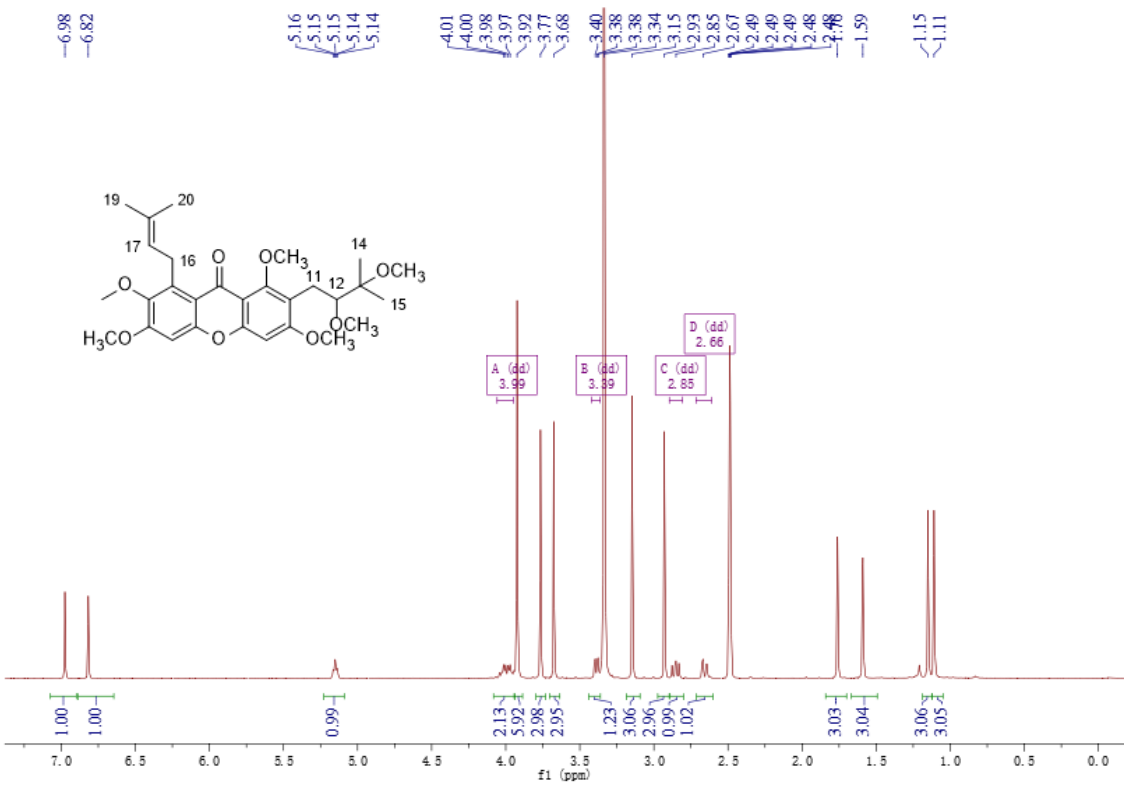


Figure 33S. ^{1}H NMR spectrum (DMSO-d_6, 500 MHz) of compound **10**

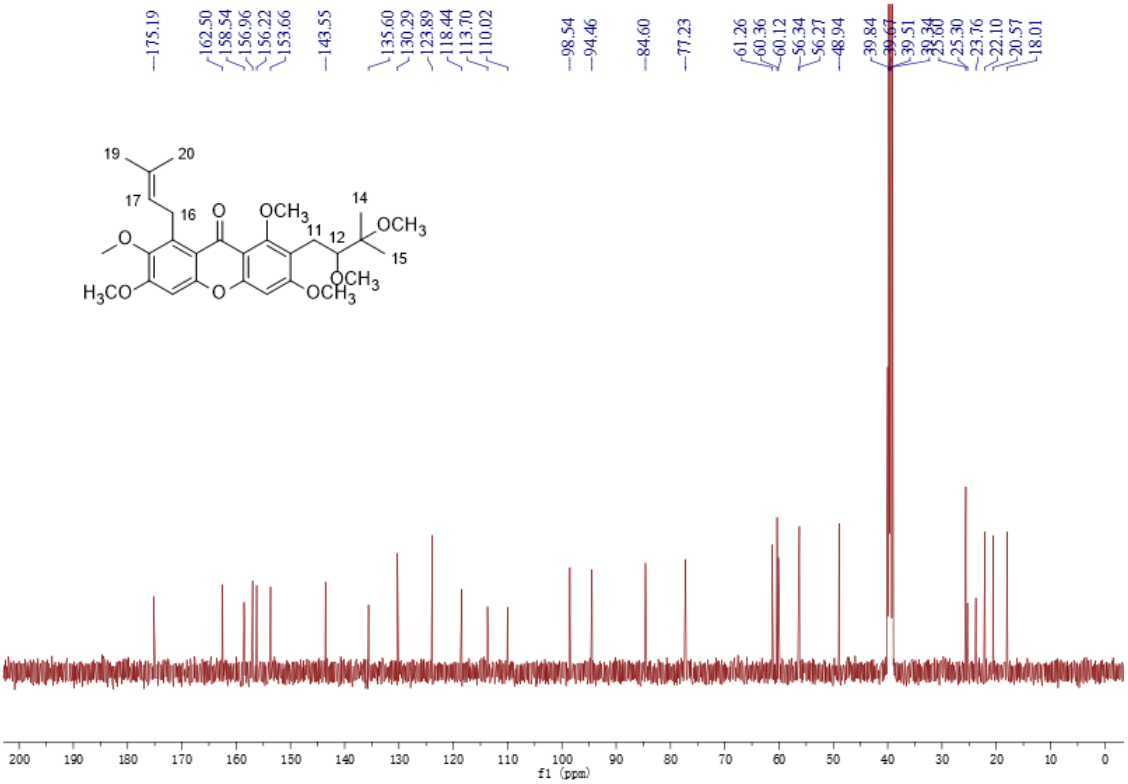


Figure 34S. ^{13}C NMR spectrum (DMSO-d_6, 125 MHz) of compound **10**

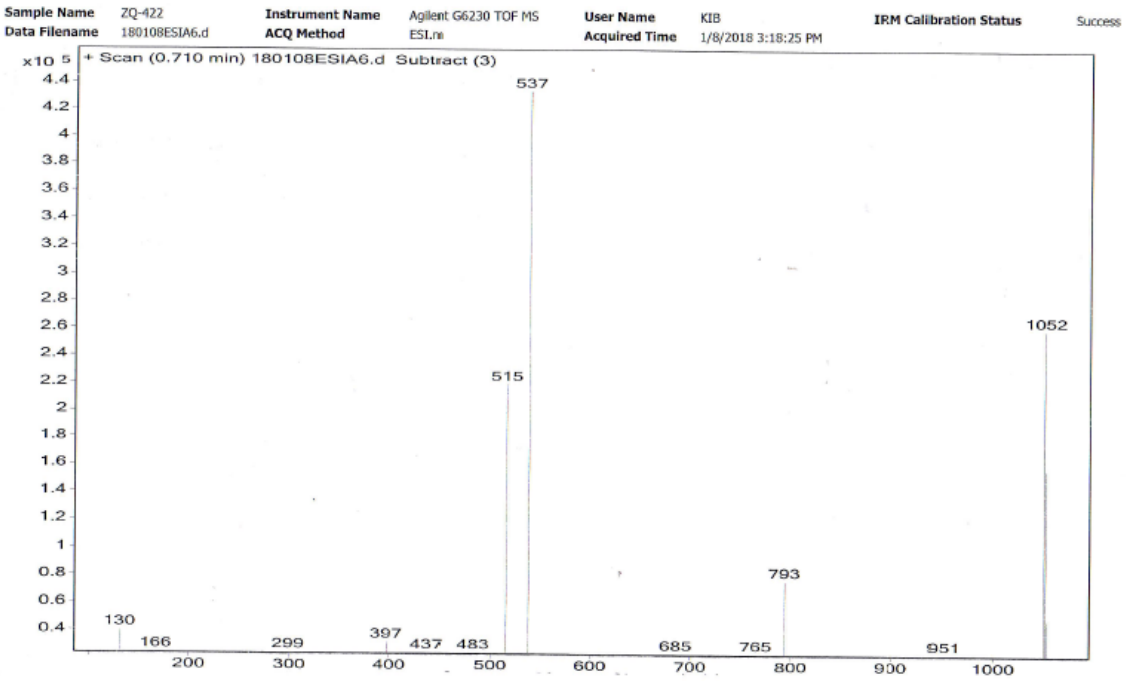
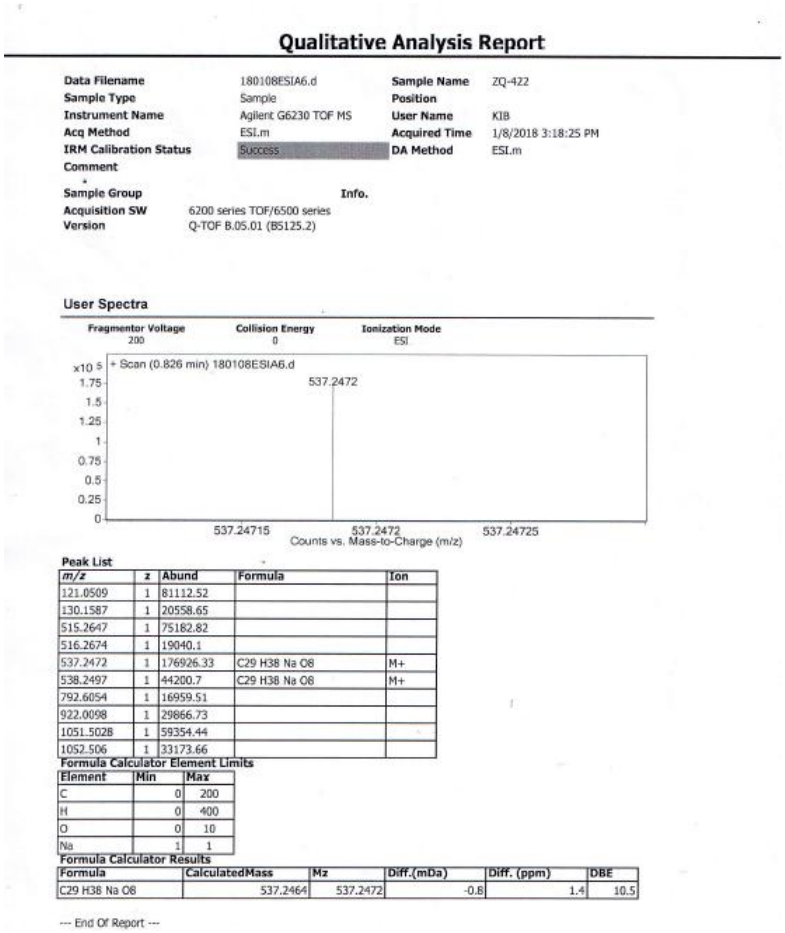


Figure 35S. Positive ESI-MS spectrum of compound **10**



Qualitative Analysis Report

Data Filename	180108ESIA6.d	Sample Name	ZQ-422
Sample Type	Sample	Position	
Instrument Name	Agilent G6230 TOF MS	User Name	KIB
Acq Method	ESI.m	Acquired Time	1/8/2018 3:18:25 PM
IRM Calibration Status	Success	DA Method	ESI.m
Comment			
Sample Group		Info.	
Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.05.01 (B5125.2)		

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
200	0	ESI

Peak List

m/z	z	Abund	Formula	Ion
121.0509	1	81112.52		
130.1587	1	20558.65		
515.2647	1	75182.82		
516.2674	1	19040.1		
537.2472	1	176926.33	C29 H38 Na O8	M+
538.2497	1	44200.7	C29 H38 Na O8	M+
792.6054	1	16959.51		
922.0098	1	29866.73		
1051.5028	1	59354.44		
1052.506	1	33173.66		

Formula Calculator Element Limits

Element	Min	Max
C	0	200
H	0	400
O	0	10
Na	1	1

Formula Calculator Results

Formula	CalculatedMass	Mz	Diff.(mDa)	Diff. (ppm)	DBE
C29 H38 Na O8	537.2464	537.2472	-0.8	1.4	10.5

--- End Of Report ---

Figure 36S. Positive HR-ESIMS spectrum of compound **10**

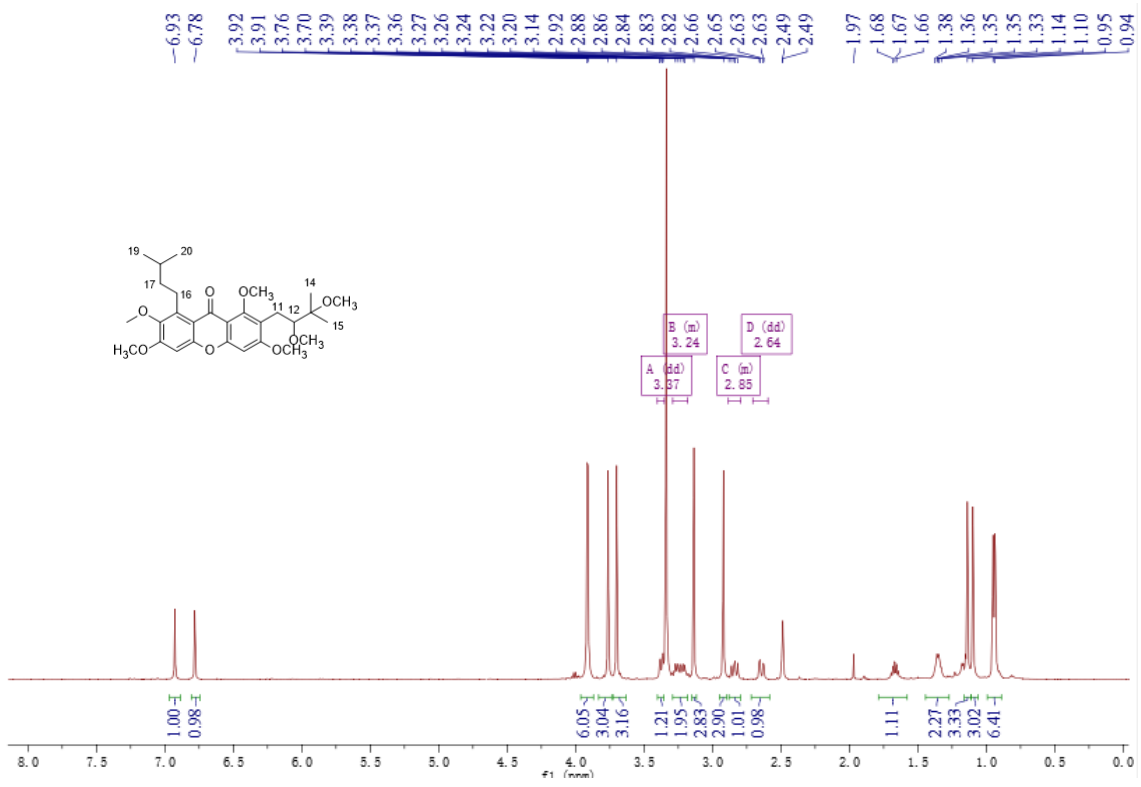


Figure 37S. ^{1}H NMR spectrum (DMSO-d_6, 500 MHz) of compound **11**

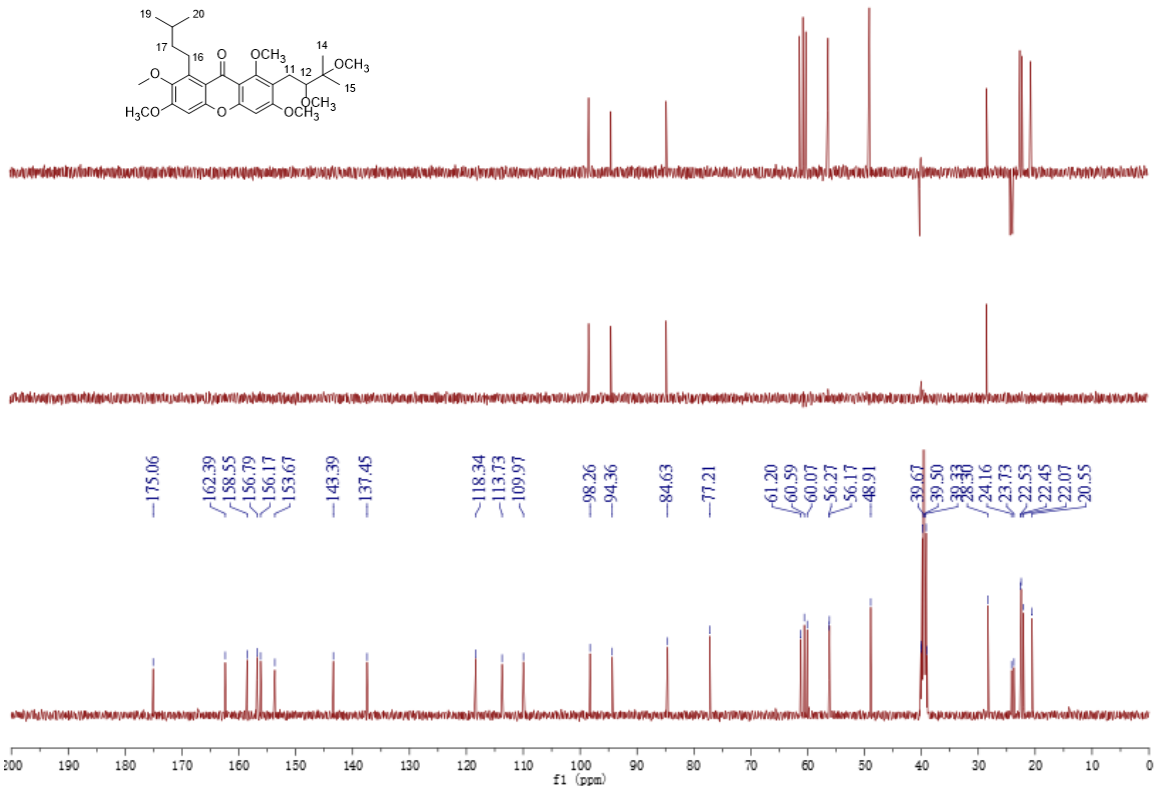


Figure 38S. ^{13}C NMR spectrum (DMSO-d_6, 125 MHz) of compound **11**

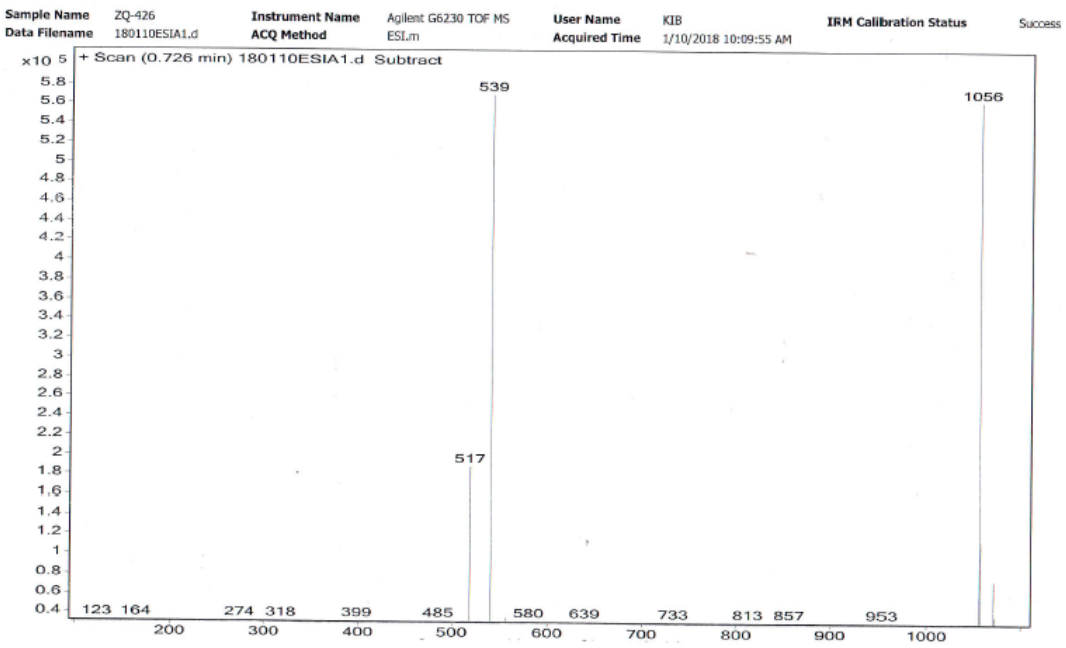
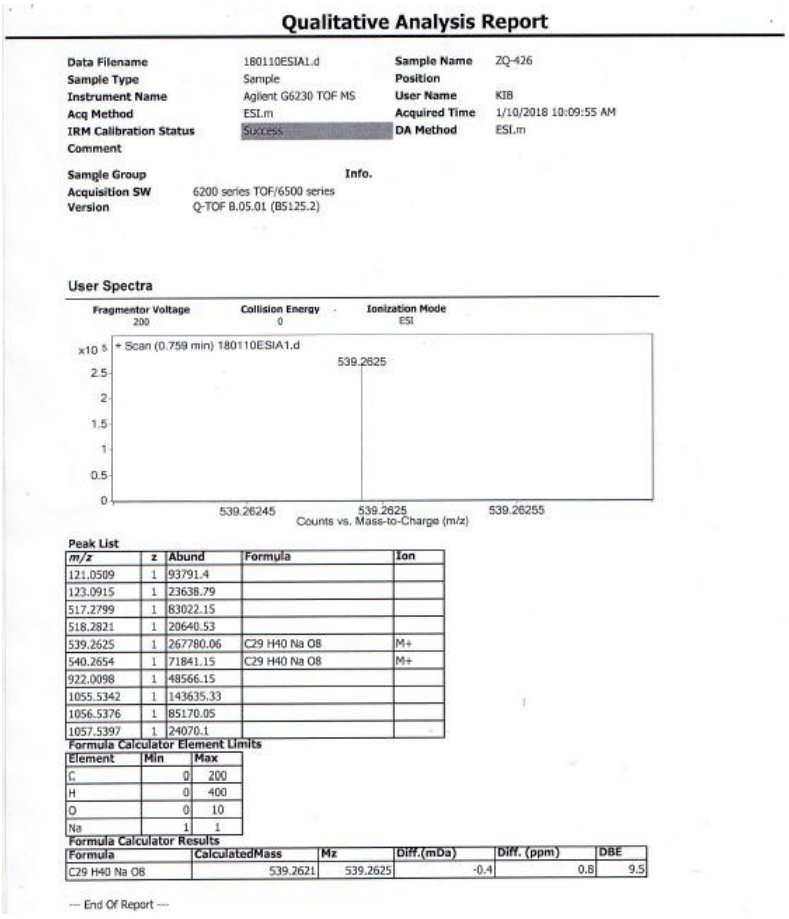


Figure 39S. Positive ESI-MS spectrum of compound **11**



Qualitative Analysis Report

Data Filename	180110ESIA1.d	Sample Name	ZQ-426
Sample Type	Sample	Position	
Instrument Name	Agilent G6230 TOF MS	User Name	KIB
Acq Method	ESI.m	Acquired Time	1/10/2018 10:09:55 AM
IRM Calibration Status	Success	DA Method	ESI.m
Comment			
Sample Group		Info.	
Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.05.01 (B5125.2)		

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
200	0	ESI

Peak List

m/z	z	Abund	Formula	Ion
121.0509	1	93791.4		
123.0915	1	23638.79		
517.2799	1	83022.15		
518.2821	1	20640.53		
539.2625	1	267780.06	C29 H40 Na O8	M+
540.2654	1	71841.15	C29 H40 Na O8	M+
922.0098	1	48566.15		
1055.5342	1	143635.33		
1056.5376	1	85170.05		
1057.5397	1	24070.1		

Formula Calculator Element Limits

Element	Min	Max
C	0	200
H	0	400
O	0	10
Na	1	1

Formula Calculator Results

Formula	CalculatedMass	Mz	Diff.(mDa)	Diff. (ppm)	DBE
C29 H40 Na O8	539.2621	539.2625	-0.4	0.8	9.5

--- End Of Report ---

Figure 40S. Positive HR-ESIMS spectrum of compound **11**

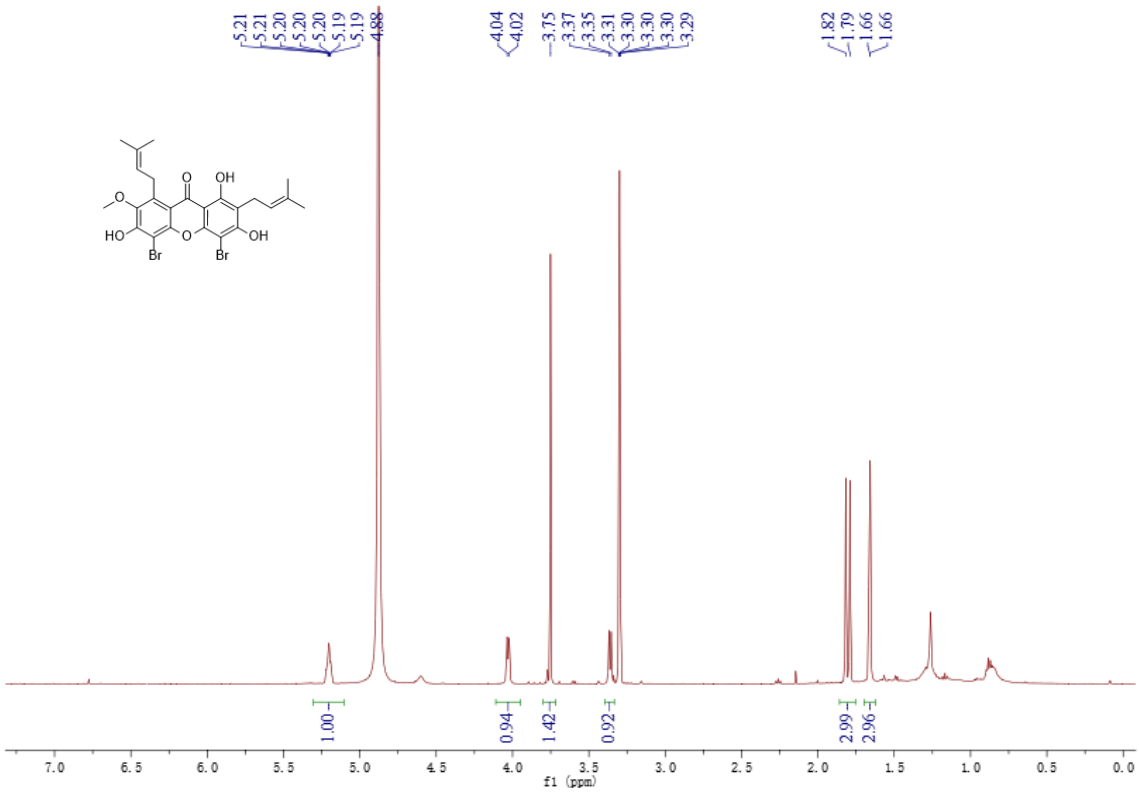


Figure 41S. ^{1}H NMR spectrum (CD_3OD, 500 MHz) of compound **15**

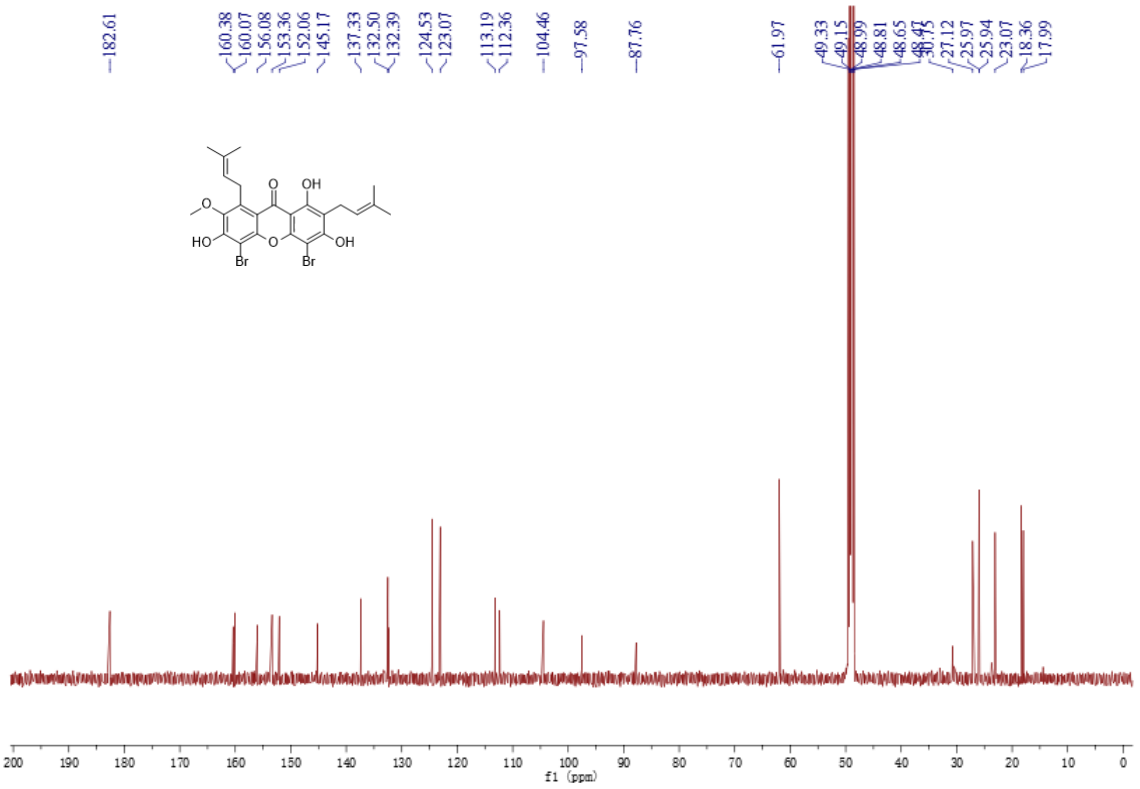


Figure 42S. ^{13}C NMR spectrum (CD_3OD, 125 MHz) of compound **15**

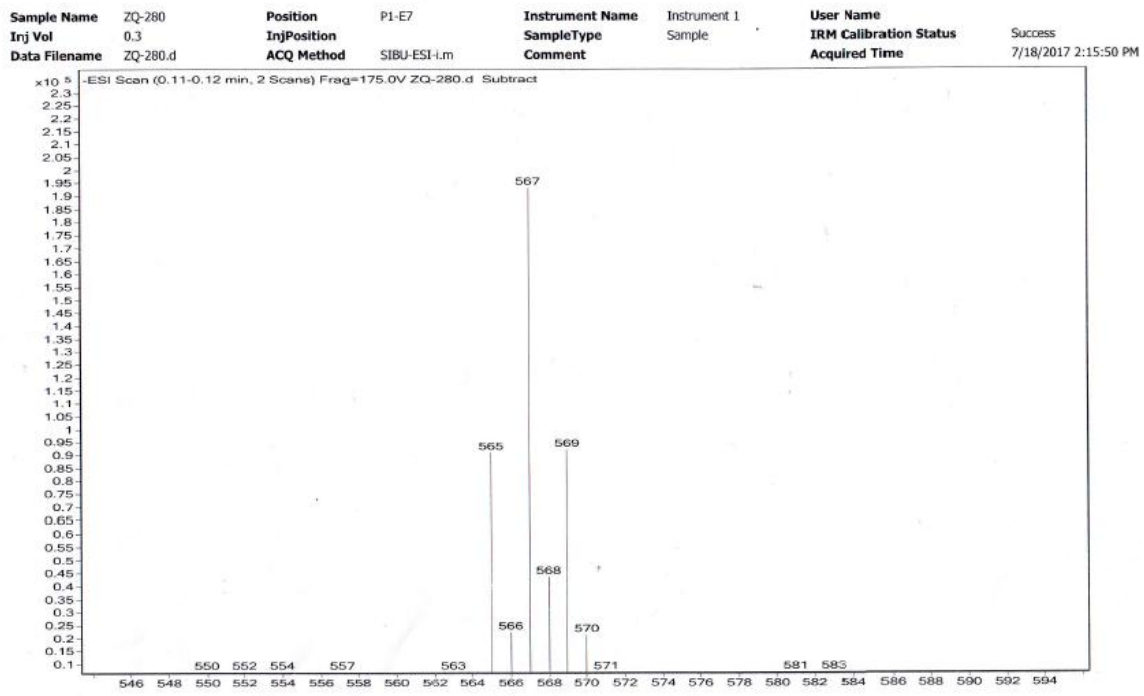


Figure 43S. Negative ESI-MS spectrum of compound **15**

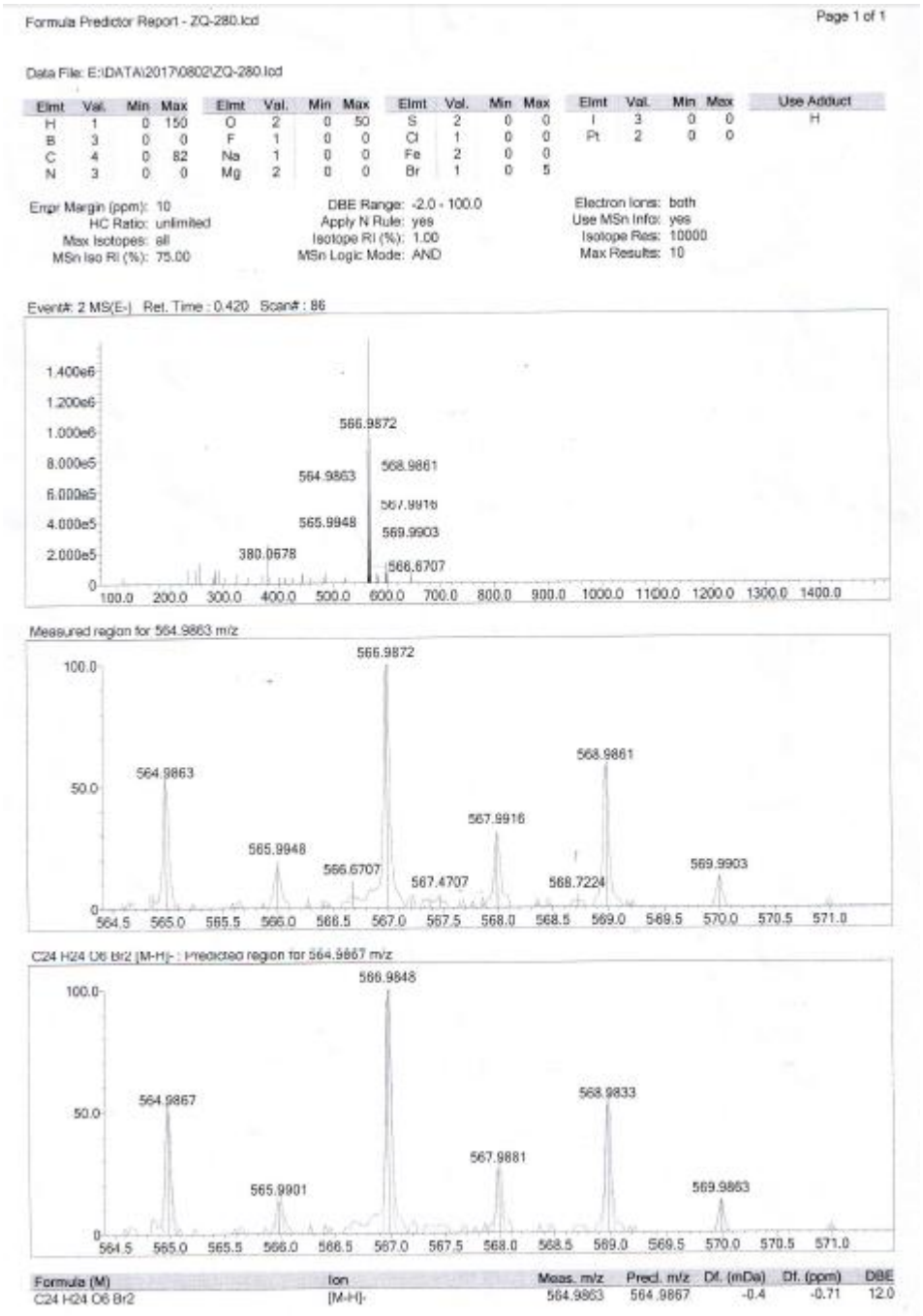


Figure 44S. Negative HR-ESIMS spectrum of compound **15**

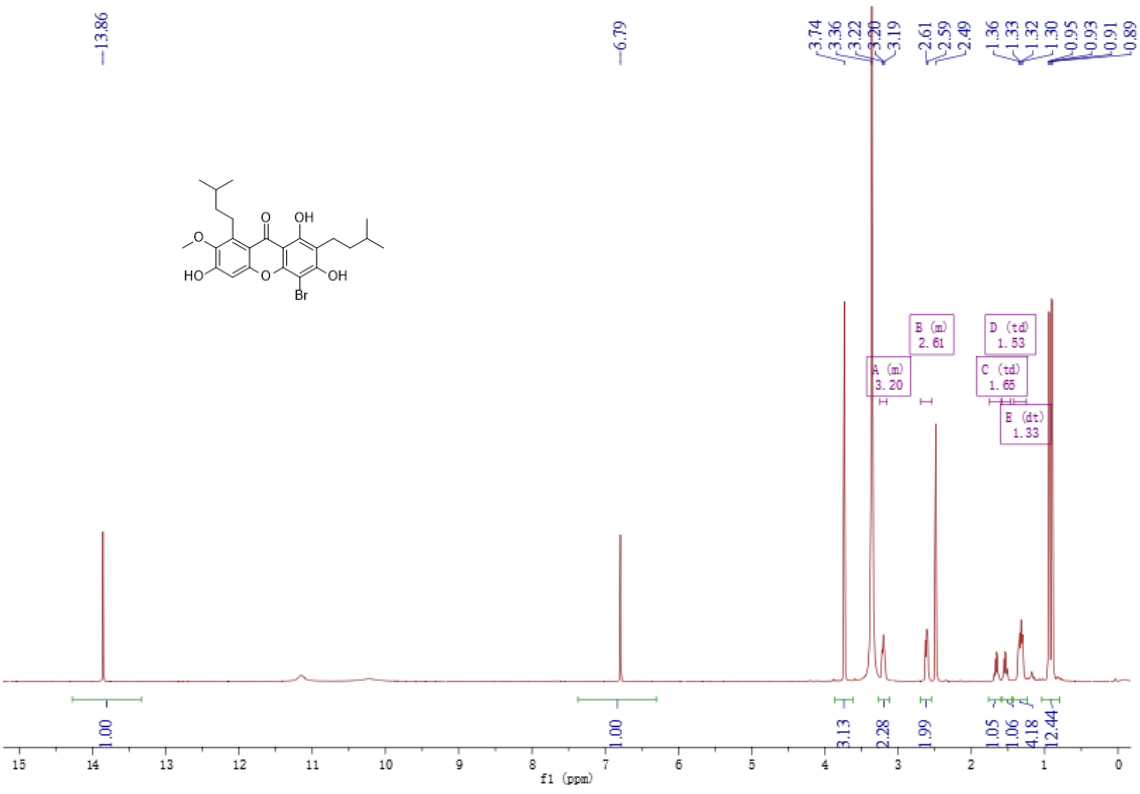


Figure 45S. ^{1}H NMR spectrum (DMSO-d_6, 500 MHz) of compound **16**

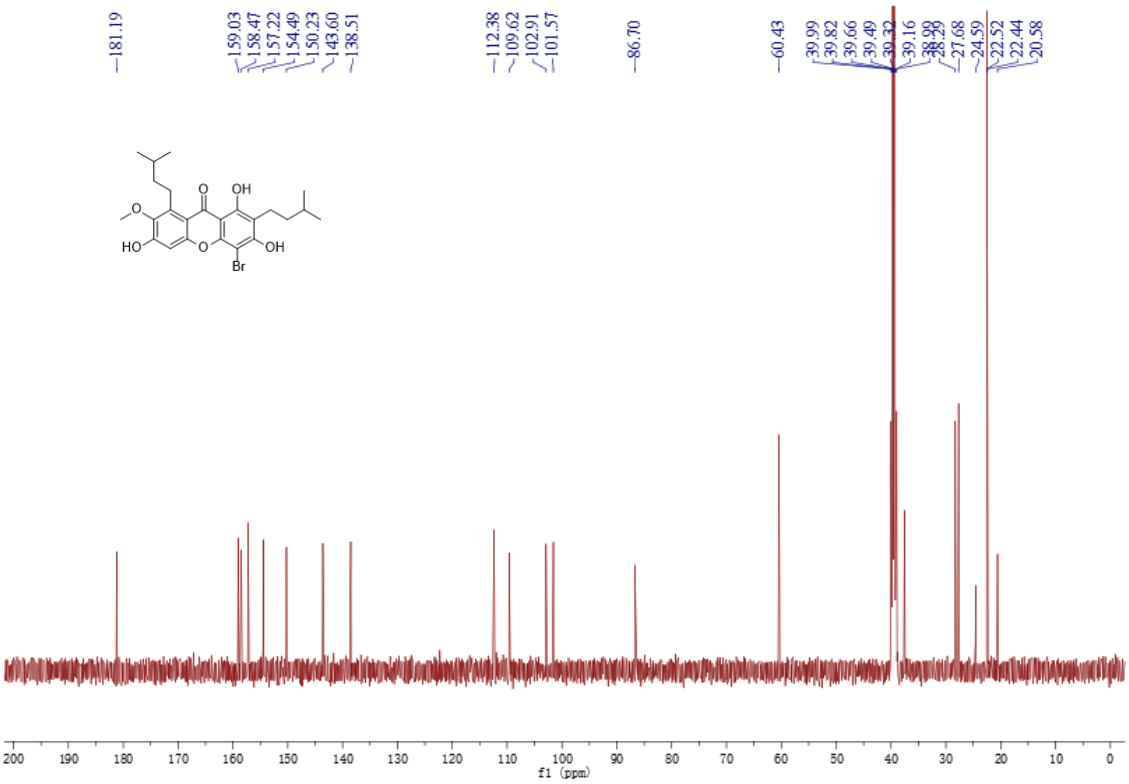


Figure 46S. ^{13}C NMR spectrum (DMSO-d_6, 125 MHz) of compound **16**

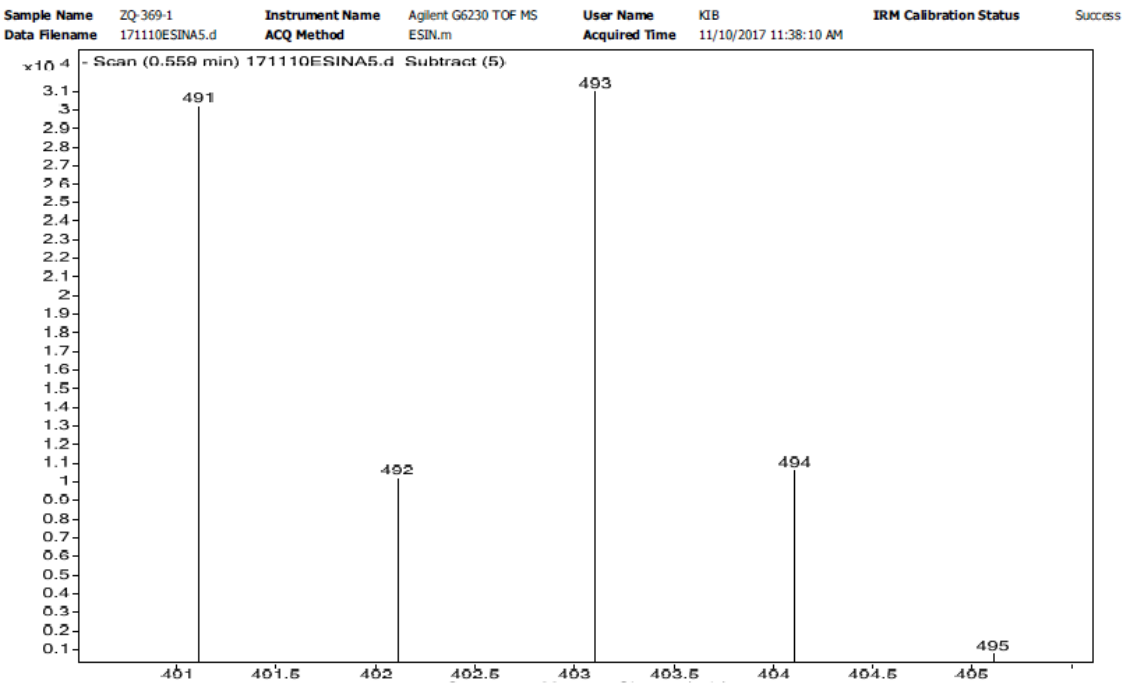
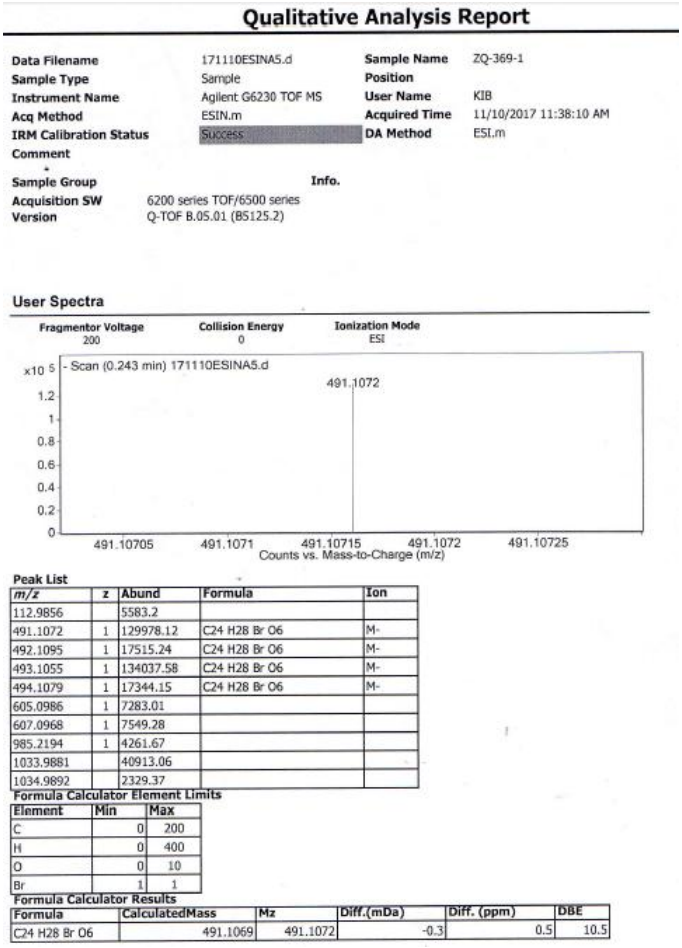


Figure 47S. Negative ESI-MS spectrum of compound **16**



Qualitative Analysis Report

Data Filename	171110ESINA5.d	Sample Name	ZQ-369-1
Sample Type	Sample	Position	
Instrument Name	Agilent G6230 TOF MS	User Name	KIB
Acq Method	ESIN.m	Acquired Time	11/10/2017 11:38:10 AM
IRM Calibration Status	Success	DA Method	ESI.m
Comment			
Sample Group		Info.	
Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.05.01 (B5125.2)		

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
200	0	ESI

- Scan (0.243 min) 171110ESINA5.d
491.1072
491.10705 491.1071 491.10715 491.1072 491.10725
Counts vs. Mass-to-Charge (m/z)

Peak List

m/z	z	Abund	Formula	Ion
112.9856		5583.2		
491.1072	1	129978.12	C24 H28 Br O6	M-
492.1095	1	17515.24	C24 H28 Br O6	M-
493.1055	1	134037.58	C24 H28 Br O6	M-
494.1079	1	17344.15	C24 H28 Br O6	M-
605.0986	1	7283.01		
607.0968	1	7549.28		
985.2194	1	4261.67		
1033.9881		40913.06		
1034.9892		2329.37		

Formula Calculator Element Limits

Element	Min	Max
C	0	200
H	0	400
O	0	10
Br	1	1

Formula Calculator Results

Formula	CalculatedMass	Mz	Diff.(mDa)	Diff. (ppm)	DBE
C24 H28 Br O6	491.1069	491.1072	-0.3	0.5	10.5

Figure 48S. Negative HR-ESIMS spectrum of compound **16**

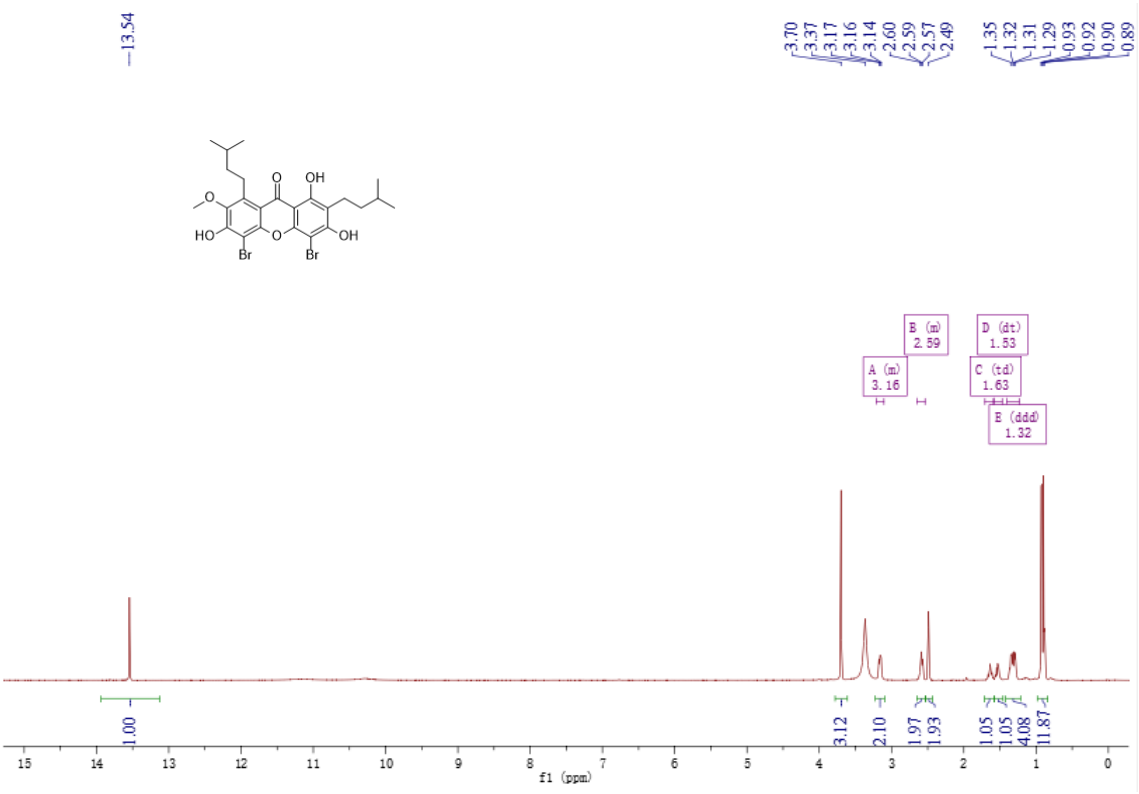


Figure 49S. ^{1}H NMR spectrum (DMSO-d_6, 500 MHz) of compound **17**

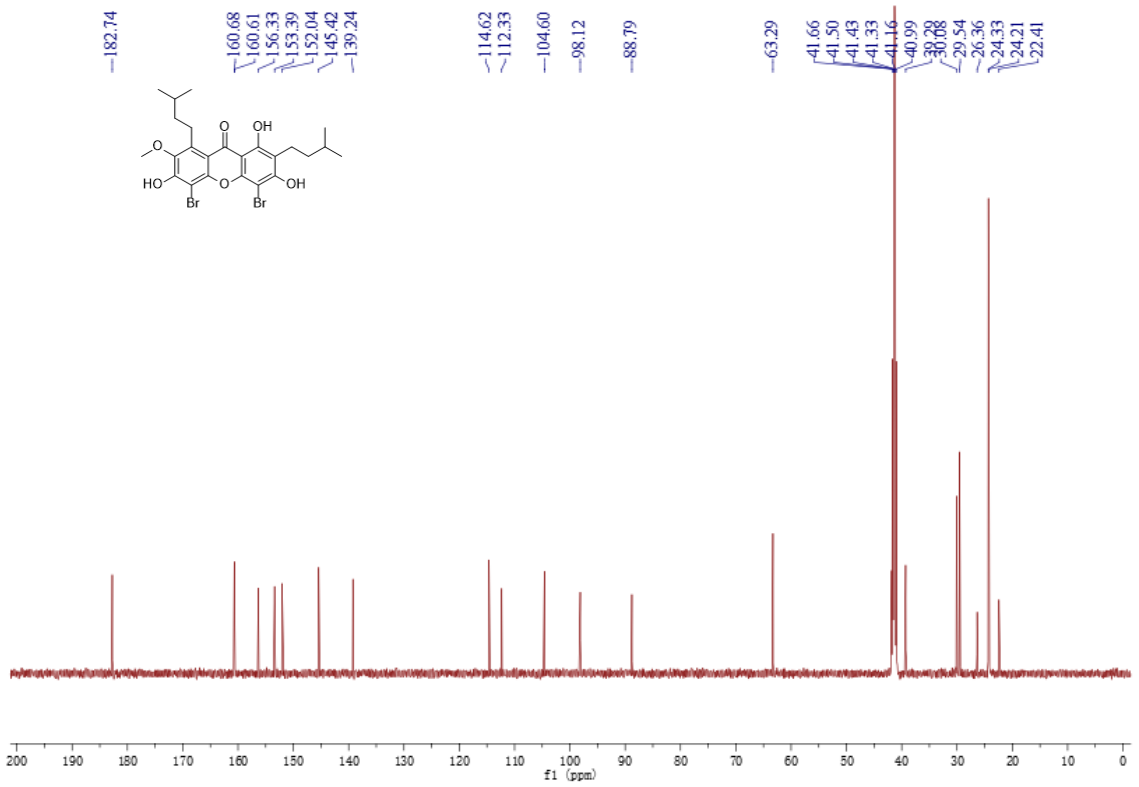


Figure 50S. ^{13}C NMR spectrum (DMSO-d_6, 125 MHz) of compound **17**

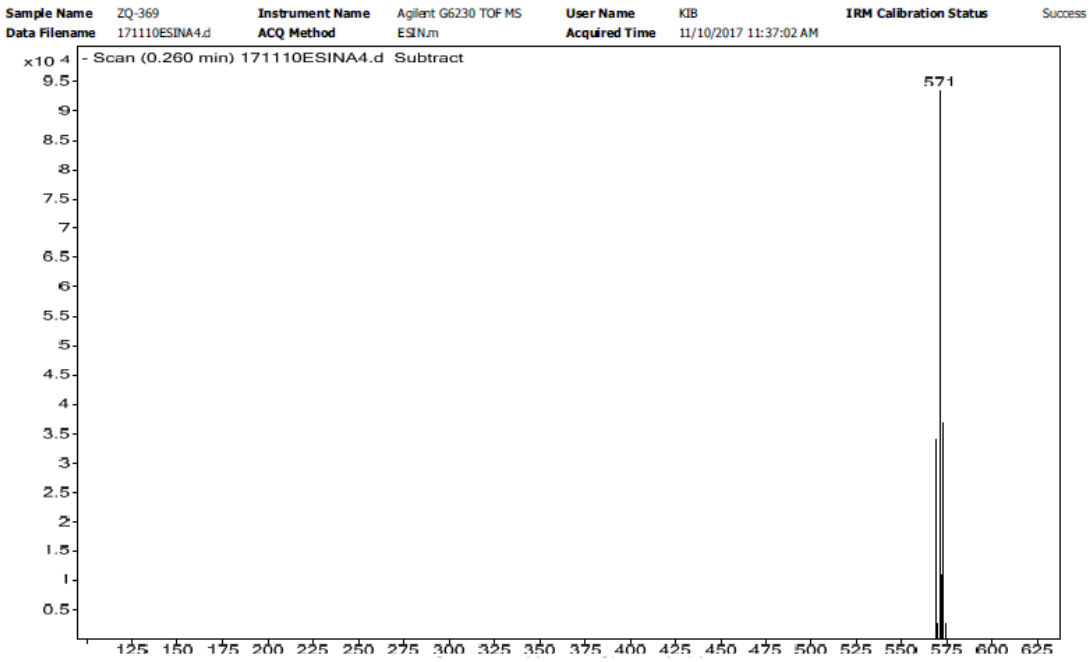


Figure 51S. Negative ESI-MS spectrum of compound **17**

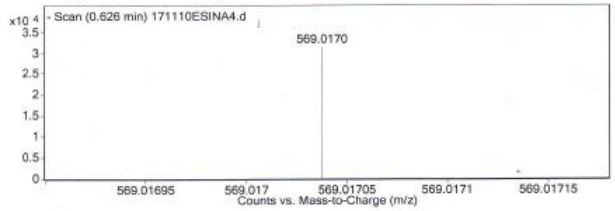
Qualitative Analysis Report

Data Filename	171110ESINA4.d	**Sample Name**	ZQ-369
Sample Type	Sample	**Position**	
Instrument Name	Agilent G6230 TOF MS	**User Name**	KIB
Acq Method	ESIN.m	**Acquired Time**	11/10/2017 11:37:02 AM
IRM Calibration Status	Success	**DA Method**	ESI.m
Comment			

Sample Group	**Info.**
Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.05.01 (B5125.2)

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
200	0	ESI



Peak List

m/z	z	Abund	Formula	Ion
112.9856		1100.16		
268.9542		2169.93		
569.017	1	31477.38	C24 H27 Br2 O6	M-
570.0199	1	2968.07	C24 H27 Br2 O6	M-
571.0155	1	82986.43		
572.0181	1	10970.78		
573.0136	1	33935.88		
574.0155	1	2833.97		
1033.9881	1	29246.97		
1034.989	1	1577.2		

Formula Calculator Element Limits

Element	Min	Max
C	0	200
H	0	400
O	2	10
Br	2	2

Formula Calculator Results

Formula	CalculatedMass	Mz	Diff.(mDa)	Diff. (ppm)	DBE
C24 H27 Br2 O6	569.0174	569.0170	0.4	0.8	10.5

Figure 52S. Negative HR-ESIMS spectrum of compound **17**