Heterogeneous nuclear ribonucleoprotein A2B1, a novel drug target for hepatitis B virus infection

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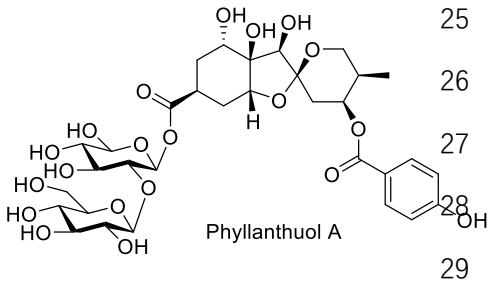
Part 1. Chemistry

1. General information

All solvents and reagents were purchased from Energy Chemical, Adamas, J&K Scientific and Sigma Aldrich, and used as received. ESI data was recorded on an Agilent 1290 UPLC/6540 Q-TOF mass spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AV 600 MHz spectrometer. Unless otherwise stated, the sample was dissolved in CD_3OD with TMS as an internal standard. The silica gel used for column chromatography was Fuji NH amino silicone filler (500 mesh). MeOH/DCM (0-10% gradient) was used as the mobile phase. HPLC analysis was performed using a Waters system (5 μM particle size, 4.6 mm × 250 mm) with a PDA detector and a GL InertSustain C18 column. A linear gradient of 5% to 100% water in acetonitrile was used in HPLC analysis at a flow rate of 1 mL/min. The purity of all test compounds was determined by HPLC analysis to be 95% or higher.

2. Isolation of phyllanthacidoid A (PA)



Phyllanthuol A

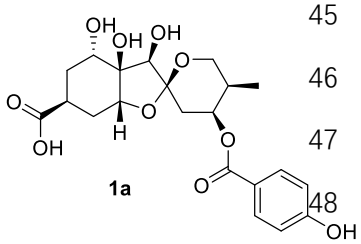
The air-dried stems of *P. acidus* (500 kg) were extracted with methanol solution at room temperature for three times to give the extract 4.21 kg. The methanol extract was resuspended in MeOH (5.0 L) and loaded onto a polyamide gel column (5200 g bed volume, pre-equilibrated with MeOH) to remove pigments and polyphenols. The column was eluted with MeOH (100.5 L), and the eluent evaporated to obtain a crude extract. The crude extract was subjected to passage over a silica gel column (200-300 mesh), eluting with ($CHCl_3$-MeOH-H_2O, 9:1:0-7:3:0.5), to afford five major fractions. Fraction 3 (700 g) was chromatographed on Sephadex LH20 (MeOH 0-100%) to afford five fractions. The first two fractions (400.3 g) were combined and chromatographed over MCI gel CHP-20P (MeOH/H_2O, 20-100%) to give seven sub-fractions (Fr. A-G). Fr. A was subjected to RP-8 (MeOH 30-80%), and preparative-HPLC with an isocratic flow of CH_3CN/H_2O (10 mL/min,

CH_3CN/H_2O 18:82, COSMOSIL Cholester, 21.1 × 250 mm) to afford phyllanthacidoid A (50.2 g, Rt = 21 min). The NMR data was reported in our previous publication.

3. Preparation and characterization of compounds

3.1.

(2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-Trihydroxy-4'-((4-hydroxybenzoyl)oxy)-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-6-carboxylic acid (1a)



1a

Phyllanthuol A (PA, 50 mg, 6.68×10^{-5} mol) was dissolved in K_2CO_3 aqueous solution (10%, 2.0 mL) and stirred at 60 °C for about two hours until a complete conversion was detected. The reaction solution was cooled to room temperature and acidified by adding 1 M hydrochloric acid to pH 2. The mixture was combined with brine (2.5 mL) and extracted with EtOAc (4.5 mL × 3). The organic layers were combined and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to obtain the titled compound as a white solid (27 mg, 92%).

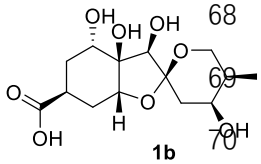
^{1}H NMR (600 MHz, CD_3OD) δ 7.99 (ddd, *J* = 8.8, 2.6, 1.8 Hz, 2H, H-17, H-21), 6.84 (ddd, *J* = 8.8, 2.6, 1.8 Hz, 2H, H-18, H-20), 5.25 (br d, *J* = 2.6 Hz, 1H, H-10), 4.09 (t, *J* = 3.3 Hz, 1H, H-5), 4.04 (t, *J* = 11.4 Hz, 1H, H-12), 3.85 (dd, *J* = 10.8, 4.9 Hz, 1H, H-1), 3.82 (s, 1H, H-7), 3.61 (dd, *J* = 11.1, 4.5 Hz, 1H, H-12), 2.56 (br s, 1H, H-3), 2.20 – 2.16 (m, 1H, H-9), 2.14 –2.06 (m, 2H, H-11, H-9), 2.03 – 1.87 (m, 3H, H-2, H-4), 1.62 (dt, *J* = 13.9, 10.1 Hz, 1H, H-2), 0.90 (d, J = 6.9 Hz, 3H, H-13).

^{13}C NMR (150 MHz, CD_3OD) δ 166.67 (C-22), 162.05 (C-19), 131.57 (C-17, C-21), 121.62 (C-16), 114.63 (C-18, C-20), 101.00 (C-8), 81.01 (C-5), 75.31 (C-6), 74.50 (C-7), 70.84 (C-1), 69.95 (C-10), 61.62 (C-12), 34.72 (C-3), 33.26 (C-9), 32.81 (C-11), 27.86 (C-2), 26.50 (C-4), 11.65 (C-13).

MS (ESI) *m/z*: 477 $[M + K]^+$ for $C_{21}H_{26}O_{10}$.

3.2.

(2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4,4'-tetrahydroxy-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-6-carboxylic acid (1b)



1b

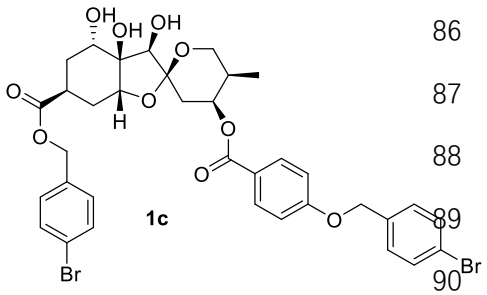
PA (30 mg, 4.01×10^{-5} mol) was dissolved in NaOH aqueous solution (2.0 M, 1.0 mL) and stirred at 70 °C for about one hour until a complete conversion was detected. The reaction solution was cooled to room temperature and acidified by adding 1 M hydrochloric acid to pH 1-2. The solution of crude product was purified by large pore adsorption resin column chromagraphy (Diaion HP20SS, water to methanol) to obtain the titled compound as a white solid (11 mg, 85%).

^{1}H NMR (600 MHz, CD_3OD) δ 4.07 (t, *J* = 3.6 Hz, 1H, H-5), 3.89 (br d, *J* = 2.7 Hz, 1H, H-10), 3.86 (dd, *J* = 10.5, 5.0 Hz, 1H, H-12), 3.83 (s, 1H, H-7), 3.81 (t, *J* = 11.6 Hz, 1H, H-1), 3.49 (dd, *J* = 11.2, 4.6 Hz, 1H, H-12), 2.86 (ddd, *J* = 15.1, 9.4, 3.8 Hz, 1H, H-3), 2.14 - 2.05 (m, 3H, H-9, H-2), 1.99 - 1.90 (m, 2H, H-4), 1.85 (dddd, *J* = 11.4, 8.9, 5.8, 3.4 Hz, 1H, H-11), 1.73 (ddd, *J* = 14.1, 10.2, 9.3 Hz, 1H, H-2), 0.91 (d, *J* = 7.0 Hz, 3H, H-13).

MS (ESI) *m/z*: 341 $[M + Na]^+$ for $C_{14}H_{22}O_8$.

3.3.

***4*-Bromobenzyl (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-4'-((4-((4b-bromobenzyl)oxy)benzoyl)oxy)-3,3a,4-trihydroxy-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-6-carboxylate (1c)**



1c

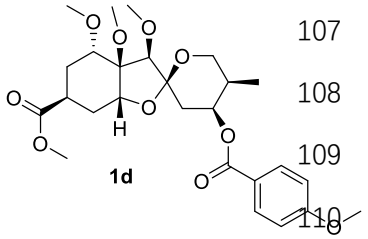
Compound **1a** (16 mg, 3.64×10^{-5} mol) was stirred with potassium carbonate (5.0 equiv, 25.4 mg) and 4-bromobenzyl bromide (2.0 eq, 18.2 mg) in dry DMF (1 mL) until a complete conversion was detected. The reacted mixture was diluted with water. The resulted precipitates were collected by centrifugation, washed with water, and dried to give the titled compound as a white solid (23.0 mg, 81%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, 2H *J* = 8.9, H-17, H-21), 7.51 (d, 2H, *J* = 8.3, H-4', H-6'), 7.43 (d, 2H, *J* = 8.4, H-4'', H-6''), 7.28 (d, 2H, *J* = 8.4, H-3'', H-7''), 7.12 (d, 2H, *J* = 8.3, H-3', H-7'), 6.96 (d, 2H, *J* = 8.9, H-18, H-20), 5.27 (d, 1H, *J* = 2.2, H-10), 5.05-4.97 (m, 4H, H-1', H-1''), 4.12 (br d, 1H, *J* = 3.7, H-5), 4.06 (br d, 1H, *J* = 11.5, H-12), 3.96 (s, 1H, H-7), 3.93 (dd, 1H, *J* = 9.9, 5.28, H-1), 3.64 (dd, 1H, *J* = 11.08, 4.40, H-12), 2.62 (ddd, 1H, *J* = 16.98, 13.44, 6.84, H-3), 2.18 - 2.06 (m, 4H, H-11, H-9, H-2), 1.95 (ddd, 1H, *J* = 14.58, 10.8, 3.78, H-4), 1.87 (ddd, 1H, *J* = 14.22, 9.30, 8.70, H-4), 1.73 – 1.65 (m, 1H, H-2), 0.88 (d, 3H, *J* = 6.90, H-13).

MS (ESI) *m/z*: 799 $[M + Na]^+$ for $C_{35}H_{36}Br_2O_{10}$.

3.4.

Methyl(2S,3R,3aR,4S,4'S,5'R,6S,7aR)-3,3a,4-trimethoxy-4'-((4-methoxybenzoyl)oxy)-5'- methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-6-carboxylate (1d)



Compound **1a** (16 mg, 3.64×10^{-5} mol) was stirred with sodium hydride (60% in mineral oil, 10.0 equiv, 14.6 mg) in dry DMF (1 mL) at room temperature for 2 hours. The mixture was cooled to -40 ºC, and methyl iodide (8.0 equiv) was added. The reaction was stirred at room temperature until a complete conversion was detected. The reaction was neutralized by adding 10% citric acid aqueous solution, and extracted with EtOAc (5.0 ml x 3). The combined organic layers were concentrated under reduced pressure. The crude product was purified by thin layer preparative chromatography to give the titled compound as a white solid (7.4 mg, 40%).

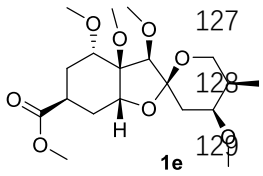
^{1}H NMR (600 MHz, CD_3OD) δ 8.03 (d, 2H, *J* = 8.9, H-17, H-21), 6.97 (d, 2H, *J* = 8.9, H-18, H-20), 5.15 (br d, 1H, *J* = 2.1, H-10), 4.18 (br d, 1H, *J* = 2.6, H-5), 4.04 (br d, 1H, *J* = 11.5, H-12), 3.85 (s, 3H, H-5'), 3.60 (s, 3H, H-1'), 3.58 (m, 1H, H-1, overlap), 3.56 (s, 1H, H-7), 3.52 (dd, 1H, *J* = 10.2, 5.1, H-12), 3.49 (s, 3H, H-2'), 3.38 (s, 3H, H-3'), 3.31 (s, 3H, H-4', overlap), 2.26 (m, 2H, H-11, H-3), 2.12 (m, 1H, H-9), 2.04 (m, 1H, H-9), 1.99 (br dd, 1H, *J* = 14.8, 2.9, H-2), 1.77 (ddd, 1H, *J* = 14.0, 6.6, 3.5, H-4),

1.68 (ddd, 1H, *J* = 14.8, 12.2, 2.8, H-4), 1.60 (m, 1H, H-2), 0.90 (d, 3H, *J* = 6.9, H-13).

MS (ESI) *m/z*: 531 $[M + Na]^+$ for $C_{26}H_{36}O_{10}$.

3.5.

Methyl (2S,3R,3aR,4S,4'S,5'R,6S,7aR)-3,3a,4,4'-tetramethoxy-5'-methyldecahydro-3H-spi- ro[benzofuran-2,2'-pyran]-6-carboxylate (1e)

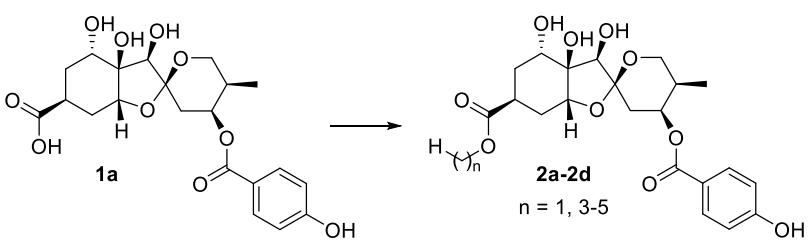


Compound **1b** (10 mg, 3.14 $\times 10^{-5}$ mol) was stirred with sodium hydride (60% in mineral oil, 10.0 equiv, 12.6 mg) in dry DMF (1 mL) at room temperature for 2 hours. The mixture was cooled to -40 ºC, and methyl iodide (8.0 equiv) was added. The reaction was stirred at room temperature until a complete conversion was detected. The reaction was stirred at room temperature until a complete conversion was detected. The reaction was neutralized by adding 10% citric acid aqueous solution, and extracted with EtOAc (5.0 ml x 3). The combined organic layers were concentrated under reduced pressure. The crude product was purified by thin layer preparative chromatography to give the titled compound as a white solid (**1e**, 6.0 mg, 49%).

^{1}H NMR (600 MHz, CD_3OD) δ 4.17 (br d, 1H, *J* = 2.8, H-5), 3.78 (br d, 1H, *J* = 11.3 Hz, H-12), 3.69 (s, 3H, H-1'), 3.59 (dd, 1H, *J* = 9.7, 3.6, H-12), 3.55 (s, 1H, H-7), 3.49 (s, 3H, H-2'), 3.46 (br d, 1H, *J* = 2.63, H-1), 3.40 (s, 3H, H-3'), 3.39 (s, 3H, H-4'), 3.32 (s, 3H, H-5'), 2.82 (td, 1H, *J* = 12.5, 12.4, 6.3, H-3), 2.26 (dd, 1H, *J* = 14.7, 2.5 Hz, H-11), 2.16 (m, 1H, H-9, overlap), 1.96 (ddd, 1H, *J* = 14.1, 5.4, 3.9, H-9), 1.91 (ddd, 1H, *J* = 14.4, 7.2, 4.5, H-2), 1.79-1.70 (m, 3H, H-4, H-4, H-2), 0.87 (d, 3H, *J* = 7.0, H-13).

MS (ESI) *m/z*: 388 $[M + Na]^+$ for $C_{19}H_{32}O_8$.

3.6. General procedure A: Preparation of ester derivatives of compound 1a

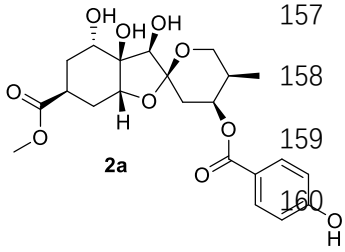


Compound **1a** (6 mg, 1.37×10^{-5} mol) was stirred with EDCI (10.0 equiv), DMAP (2.0 equiv) and the corresponding alcohol (10 equiv) in dry DMF (1.0 mL) at room temperature until a complete conversion was detected. The mixture was partitioned between EtOAc and brine, and the organic layer was washed with brine and concentrated. The crude product was purified by silica gel column chromatography to obtain the corresponding titled compound as a white solid.

Compounds prepared with this procedure: **2a**, 22%; **2b**, 43%; **2c**, 49%; **2d**, 40%.

3.6.1.

Methyl (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-trihydroxy-4'-((4-hydroxybenzoyl)oxy)-5'-me- thyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-6-carboxylate (2a)



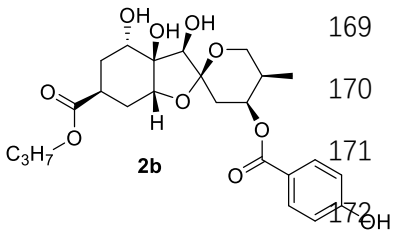
2a

^{1}H NMR (600 MHz, CD_3OD) δ 7.97 (br dd, *J* = 6.8, 1.9 Hz, 2H, H-17, H-21) ,6.83 (ddd, *J* = 6.8, 1.9 Hz, 2H, H-18, H-20), 5.22 (br d, *J* = 2.5 Hz, 1H, H-10), 4.06 – 3.99 (m, 2H, H-5, H-12), 3.82 – 3.75 (m, 2H, H-1, H-7), 3.61 (m, 4H, H-12, H-1'), 2.54 (br q, *J* = 5.6, 3.5 Hz, 1H, H-3), 2.17 – 2.07 (m, 3H, H-11, H-9), 1.98 – 1.90 (m, 2H, H-2, H-4), 1.85 – 1.78 (m, 1H, H-4), 1.61 – 1.52 (m, 1H, H-2), 0.87 (d, *J* = 6.91 Hz, 3H, H-13).

MS (ESI) *m/z*: 375 $[M + Na]^+$ for $C_{22}H_{28}O_{10}$.

3.6.2.

Propyl (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-trihydroxy-4'-((4-hydroxybenzoyl)oxy)-5'-me- thyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-6-carboxylate (2b)



2b

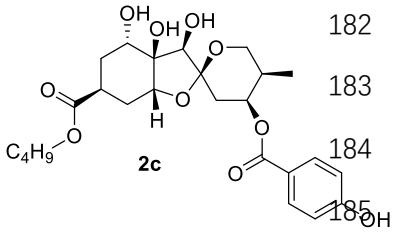
^{1}H NMR (600 MHz, CD_3OD) δ 7.97 (ddd, *J* = 8.82, 2.64, 1.98 Hz, 2H, H-17, H-21), 6.83 (ddd, *J* = 8.82, 2.67, 2.00 Hz, 2H, H-18, H-20), 5.22 (br d, *J* = 2.6 Hz, 1H, H-10), 4.08 – 4.03 (m, 2H, H-5, H-12), 4.03 – 3.96

(m, 2H, H-1'), 3.85 – 3.78 (m, 2H, H-1, H-7), 3.62 (dd, *J* = 11.0, 4.5 Hz, 1H, H-12), 2.54 (tt, *J* = 9.3, 5.7 Hz, 1H, H-3), 2.17 – 2.07 (m, 3H, H-11, H-9), 2.00 – 1.93 (m, 2H, H-2, H-4), 1.86 (ddd, *J* = 14.5, 11.5, 3.1 Hz, 1H, H-2), 1.67 – 1.52 (m, 2H, H-2'), 0.92 (t, *J* = 7.43 Hz, 3H, H-3'), 0.91 (d, *J* = 6.91 Hz, 3H, H-13).

MS (ESI) *m/z*: 503 $[M + Na]^+$ for $C_{24}H_{32}O_{10}$.

3.6.3.

Butyl (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-trihydroxy-4'-((4-hydroxybenzoyl)oxy)-5'-met- hyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-6-carboxylate (2c)



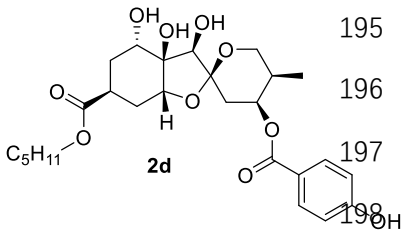
2c

^{1}H NMR (600 MHz, CD_3OD) δ 7.97 (br d, *J* = 8.7 Hz, 2H, H-17, H-21), 6.83 (br d, *J* = 8.7 Hz, 2H, H-18, H-20), 5.22 (br d, *J* = 2.5 Hz, 1H, H-10), 4.11 – 3.97 (m, 4H, H-5, H-12, H-1'), 3.81 (dd, *J* = 11.0, 4.5 Hz, 1H, H-1), 3.81 (s, 7-H), 3.62 (dd, *J* = 11.1, 4.6 Hz, 1H, H-12), 2.54 (qd, *J* = 11.3, 5.7 Hz, 1H, H-3), 2.17 – 2.07 (m, 3H, H-11, H-9), 2.01 – 1.91 (m, 2H, H-2, H-4), 1.86 (ddd, *J* = 14.5, 11.5, 3.1 Hz, 1H ,H-4), 1.60 – 1.55 (m, 3H, H-2, H-2'), 1.39 – 1.32 (m, 2H, H-3'), 0.95 (t, *J* = 7.41 Hz, 3H, H-4'), 0.91 (t, *J* = 6.93 Hz, 3H, H-13).

MS (ESI) *m/z*: 517 $[M + Na]^+$ for $C_{25}H_{34}O_{10}$.

3.6.4.

Pentyl (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-trihydroxy-4'-((4-hydroxybenzoyl)oxy)-5'-met- hyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-6-carboxylate (2d)



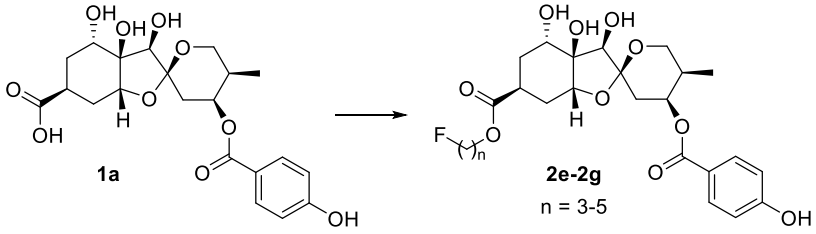
2d

^{1}H NMR (600 MHz, CD_3OD) δ 7.98 (ddd, *J* = 8.73, 2.63, 1.88 Hz, 2H, H-17, H-21), 6.83 (ddd, *J* = 8.72, 2.63, 1.85 Hz, 2H, H-18, H-20), 5.23 (br d, *J* = 2.6 Hz, 1H, H-10), 4.09 – 3.96 (m, 4H, H-5, H-12, H-1'), 3.82 (dd, *J* = 10.6 , 5.0 Hz, 1H, H-1), 3.82 (s, 1H, H-7), 3.62 (dd, *J* = 11.1, 4.5 Hz, 1H,

H-12), 2.54 (qd, J = 11.3, 5.7 Hz, 1H, H-3), 2.18 – 2.08 (m, 3H, H-11, H-9), 2.00 – 1.94 (m, 2H, H-2, H-4), 1.86 (ddd, J = 14.5, 11.5, 3.1 Hz, 1H, H-4), 1.64 – 1.55 (m, 3H, H-2, H-2'), 1.40 – 1.27 (m, 4H, H-3', H-4'), 0.93 (t, J = 7.2 Hz, 3H, H-5'), 0.91 (d, J = 6.9 Hz, 3H, H-13).

MS (ESI) *m/z*: 531 $[M + Na]^+$ for $C_{26}H_{36}O_{10}$.

3.7. General procedure B: Preparation of ester derivatives of compound 1a

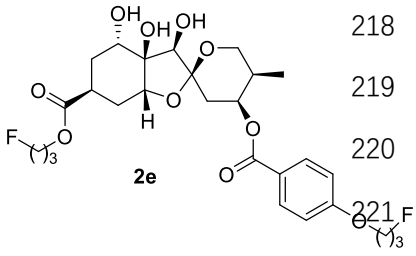


Compound **1a** (6 mg, 1.37×10^{-5} mol) was stirred with potassium carbonate (5.0 equiv) and the corresponding alkyl bromide (2-5 equiv) in dry DMF (1.0 mL) at room temperature until a complete conversion was detected. The mixture was partitioned between EtOAc and brine, and the organic layer was washed with brine and concentrated. The crude product was purified by silica gel column chromatography to obtain the corresponding titled compound as a white solid.

Compounds prepared with this procedure: **2e**, 49%; **2f**, 56%; **2g**, 83%.

3.7.1.

3-Fluoropropyl (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-4'-((4-(3-fluoropropoxy)benzoyl)oxy)-3,3a,4-trihydroxy-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-6-carboxylate (2e)



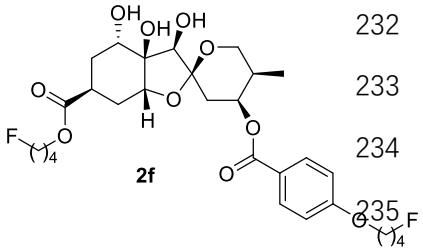
^{1}H NMR (600 MHz, CD_3OD) δ 8.08 (br d, J = 8.8 Hz, 2H, H-17, H-21), 7.03 (br d, J = 8.8 Hz, 2H, H-18, H-20), 5.24 (br d, J = 2.4 Hz, 1H, H-10), 4.40 (t, J = 5.8 Hz, 4H, H-3', H-3"), 4.19 (t, J = 6.2 Hz, 2H, H-1"), 4.17 – 4.10 (m, 2H, H-1'), 4.09 – 4.03 (m, 2H, H-5, H-12), 3.84 – 3.76 (m, 2H, H-1, H-7), 3.63 (dd, J = 11.1, 4.6 Hz, 1H, H-12), 2.53

(qd, *J* = 11.4, 5.7 Hz, 1H, H-3), 2.25 – 2.06 (m, 5H, H-11, H-9, H-2''), 2.01 – 1.90 (m, 4H, H-2, H-4, H-2'), 1.86 (ddd, *J* = 14.5, 11.6, 3.1 Hz, 1H, H-4), 1.58 (dt, *J* = 14.1, 9.7 Hz, 1H, H-2), 0.92 (d, *J* = 6.9 Hz, 3H, H-13).

MS (ESI) *m/z*: 581 $[M + Na]^+$ for $C_{27}H_{36}F_2O_{10}$.

3.7.2.

4-Fluorobutyl (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-4'-((4-(4-fluorobutoxy)benzoyl)oxy)-3,3a,4-tr- ihydroxy-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-6-carboxylate (2f)

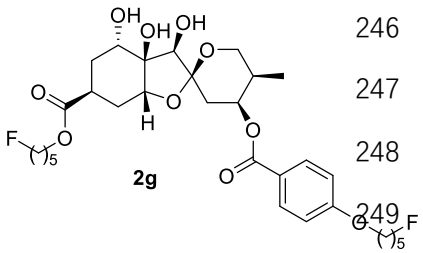


^{1}H NMR (600 MHz, CD_3OD) δ 8.08 (br d, *J* = 9.0 Hz, 2.7 Hz, 2.0 Hz, 2H, H-17, H-21), 7.01 (br d, *J* = 9.0 Hz, 2.7 Hz, 2.0 Hz, 2H, H-18, H-20), 5.24 (d, *J* = 2.6 Hz, 1H, H-10), 4.57 – 4.40 (4H, H-4', H-4''), 4.15 – 4.03 (m, 6H, H-5, H-12, H-1', H-1''), 3.84 – 3.76 (m, 2H, H-1, H-7), 3.66 – 3.59 (m, 1H, H-12), 2.58 – 2.50 (m, 1H, H-3), 2.22 – 2.09 (m, 3H, H-11, H-9, overlap with acetone), 2.01 – 1.83 (m, 7H, H-2, H-4, H-4, H-2', H-2''), 1.77 – 1.64 (m, 4H, H-3', H-3''), 1.59 (ddd, *J* = 14.1, 10.3, 9.2 Hz, 1H, H-2), 0.91 (d, *J* = 6.9 Hz, 2H, H-13).

MS (ESI) *m/z*: 609 $[M + Na]^+$ for $C_{29}H_{40}F_2O_{10}$.

3.7.3.

5-Fluoropentyl (2S,3R,3aS,4S,4'-S,5'R,6S,7aR)-4'-((4-((5-fluoropentyl)oxy)benzoyl)oxy)-3, 3a,4-trihydroxy-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-6-carboxylate (2g)

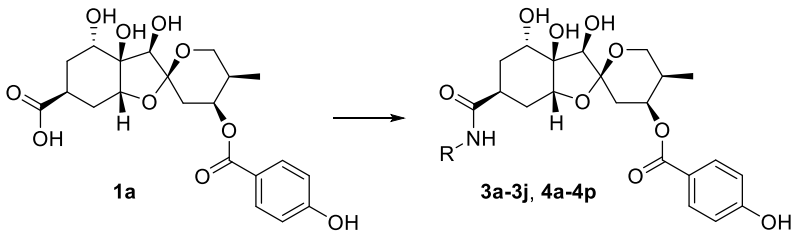


^{1}H NMR (600 MHz, CD_3OD) δ 8.07 (br d, *J* = 8.8 Hz, 2H, H-17, H-21), 7.00 (br d, *J* = 8.8 Hz, 2H, H-18, H-20), 5.24 (br d, *J* = 2.2 Hz, 1H, H-10), 4.39 (t, *J* = 6.0 Hz, 4H, H-5', H-5''), 4.14 – 3.98 (m, 6H, H-5, H-12, H-1', H-1'), 3.86 – 3.77 (m, 2H, H-1, H-7),

3.62 (dd, *J* = 11.1, 4.6 Hz, 1H, H-12), 2.54 (qd, *J* = 11.4, 5.7 Hz, 1H, H-3), 2.19 – 2.07 (m, 3H, H-11, H-9), 2.02 – 1.93 (m, 2H, H-2''), 1.91 – 1.39 (m, 14H, H-2, H-4, H-2', H-3', H-4', H-3'', H-4''), 0.91 (d, *J* = 6.9 Hz, 3H, H-13).

MS (ESI) *m/z*: 637 $[M + Na]^+$ for $C_{31}H_{44}F_2O_{10}$.

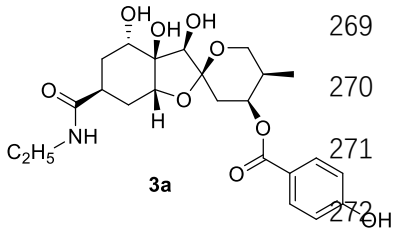
3.8. General procedure C: Preparation of amide derivatives of compound 1a



Compound **1a** (6 mg, 1.37×10^{-5} mol) was stirred with EDCI (10.0 equiv), DMAP (2.0 equiv), HOSu (5.0 equiv) and the corresponding amine (5.0 equiv) in dry DMF (1.0 mL) at room temperature until a complete conversion was detected. The mixture was partitioned between EtOAc and diluted hydrochloric acid, and the organic layer was washed with brine and concentrated. The crude product was purified by silica gel column chromatography to obtain the corresponding titled compound as a white solid.

Compounds prepared with this procedure: **3a**, 22%; **3b**, 43%; **3c**, 49%; **3d**, 7.5%; **3e**, 49%; **3f**, 69%; **3g**, 59%; **3h**, 66%; **3i**, 74%; **3j**, 47%; **4a**, 53%; **4b**, 54%; **4c**, 56%; **4d**, 54%; **4e**, 66%; **4f**, 72%; **4g**, 44%; **4h**, 27%; **4i**, 74%; **4j**, 76%; **4k**, 82%; **4l**, 59%; **4m**, 48%; **4n**, 30%; **4o**, 27%; **4p**, 22%.

3.8.1. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-6-(ethylcarbamoyl)-3,3a,4-trihydroxy-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (3a)

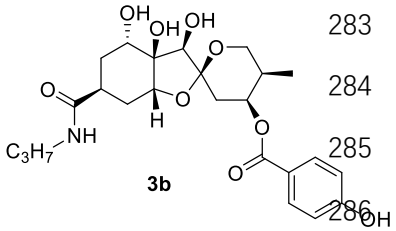


^{1}H NMR (600 MHz, CD_3OD) δ 7.98 (br d, *J* = 8.7 Hz, 2H, H-17, H-21), 6.84 (br d, *J* = 8.7 Hz, 2H, H-18, H-20), 5.24 (br d, *J* = 2.2 Hz, 1H, H-10), 4.12 (t, *J* = 3.1 Hz, 1H, H-5), 4.05 (t, *J* = 11.4 Hz, 1H, H-12), 3.90 (dd, *J* = 10.5, 5.5 Hz, 1H, H-1), 3.76 (s, 1H, H-7), 3.61 (dd, *J* = 11.1, 4.5 Hz, 1H, H-12), 3.16 – 3.08 (m, 2H, H-1'), 2.41 (qd, *J* = 11.2, 5.6 Hz, 1H, H-3), 2.17 (dd, *J* = 14.8, 3.1

Hz, 1H, H-11), 2.14 – 2.07 (m, 2H, H-9), 1.99 (ddd, *J* = 14.6, 11.8, 3.1 Hz, 1H, H-2), 1.80 (dt, *J* = 13.9, 5.6 Hz, 1H, H-4), 1.71 (ddd, *J* = 14.4, 5.2, 3.7 Hz, 1H, H-4), 1.57 (dt, *J* = 13.9, 9.9 Hz, 1H, H-2), 1.05 (t, *J* = 7.3 Hz, 3H, H-2'), 0.90 (d, *J* = 6.9 Hz, 3H, H-13).

MS (ESI) *m/z*: 488 $[M + Na]^+$ for $C_{23}H_{31}NO_9$.

3.8.2. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-trihydroxy-5'-methyl-6-(propylcarbamoyl)decahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (3b)

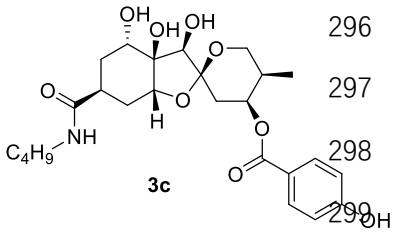


3b

^{1}H NMR (600 MHz, CD_3OD) δ 7.97 (br d, *J* = 8.7 Hz, 2H, H-17, H-21), 6.83 (br d, *J* = 8.7 Hz, 2H, H-18, H-20), 5.24 (br d, *J* = 2.3 Hz, 1H, H-10), 4.12 (t, *J* = 3.1 Hz, 1H, H-5), 4.05 (t, *J* = 11.4 Hz, 1H, H-12), 3.91 (dd, *J* = 10.5, 5.6 Hz, 1H, H-1), 3.76 (s, 1H, H-7), 3.62 (dd, *J* = 11.1, 4.5 Hz, 1H, H-12), 3.10 – 3.00 (m, 2H, H-1'), 2.48 – 2.40 (m, 1H, H-3), 2.17 (dd, *J* = 14.8, 3.1 Hz, 1H, H-11), 2.14 – 2.06 (m, 2H, H-9), 2.00 (ddd, *J* = 14.6, 11.8, 3.1 Hz, 1H, H-2), 1.81 (dt, *J* = 13.9, 5.7 Hz, 1H, H-4), 1.74 – 1.67 (m, 1H, H-4), 1.58 (dt, *J* = 14.0, 9.9 Hz, 1H, H-2), 1.48 – 1.40 (m, 2H, H-2'), 0.90 (d, *J* = 6.9 Hz, 1H, H-13), 0.87 (t, *J* = 7.4 Hz, 1H, H-3').

MS (ESI) *m/z*: 502 $[M + Na]^+$ for $C_{24}H_{33}NO_9$.

3.8.3. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-6-(butylcarbamoyl)-3,3a,4-trihydroxy-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (3c)



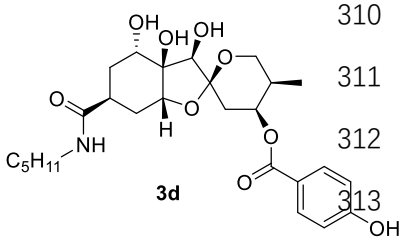
3c

^{1}H NMR (600 MHz, CD_3OD) δ 7.97 (ddd, *J* = 8.82, 2.64, 2.04 Hz, 2H, H-17, H-21), 6.84 (ddd, *J* = 8.82, 2.70, 1.98 Hz, 2H, H-18, H-20) ,5.24 (br d, *J* = 2.5 Hz, 1H, H-10), 4.12 (t, *J* = 3.2 Hz, 1H, H-5), 4.05 (t, *J* = 11.4 Hz, 1H, H-12), 3.91 (dd, *J* = 10.5, 5.6 Hz, 1H, H-1), 3.76 (s, 1H, H-7), 3.61 (dd, *J* = 11.0, 4.4 Hz, 1H, H-12), 3.09 (br ddd, *J* = 13.3, 7.1, Hz, 2H, H-1'), 2.44 (ddd, *J* = 15.0, 11.3, 5.6 Hz, 1H, H-3), 2.21 – 2.04 (m, 3H, H-11, H-9), 2.00 (ddd, *J* = 14.7, 9.4,

3.2 Hz, 1H, H-2), 1.81 (dt, *J* = 14.0, 5.7 Hz, 1H, H-4), 1.70 (ddd, *J* = 14.4, 5.3, 3.5 Hz, 1H, H-4), 1.58 (dt, *J* = 14.0, 9.8 Hz, 1H, H-2), 1.43 – 1.36 (m, 2H, H-2'), 1.33 – 1.25 (m, 2H, H-3'), 0.92 (t, *J* = 7.4 Hz, 3H, H-4'), 0.90 (d, *J* = 6.9 Hz, 3H, H-13).

MS (ESI) *m/z*: 516 $[M + Na]^+$ for $C_{25}H_{35}NO_9$.

3.8.4. (2S,3R,3aS,4S,4'-S,5'R,6S,7a-R)-3,3a,4-trihydroxy-5'-methyl-6-(pentylcarbamoyl)decahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (3d)



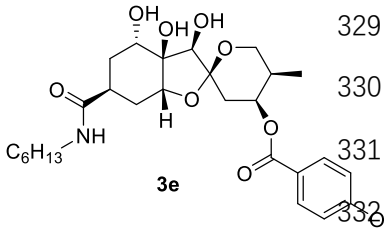
3d

^{1}H NMR (600 MHz, CD_3OD) δ 7.97 (ddd, *J* = 8.8, 2.6, 2.0 Hz, 2H, H-17, H-21), 6.84 (ddd, *J* = 8.8, 2.7, 2.0 Hz, 2H, H-18, H-20), 5.24 (br d, *J* = 2.5 Hz, 1H, H-10), 4.12 (t, *J* = 3.2 Hz, 1H, H-5), 4.05 (t, *J* = 11.4 Hz, 1H, H-12), 3.91 (dd, *J* = 10.5, 5.6 Hz, 1H, H-1), 3.76 (s, 1H, H-7), 3.61 (dd, *J* = 11.0, 4.4 Hz, 1H, H-12), 3.09 (br ddd, *J* = 13.3, 7.1, Hz, 2H, H-1'), 2.44 (ddd, *J* = 15.0, 11.3, 5.6 Hz, 1H, H-3), 2.21 – 2.04 (m, 3H, H-11, H-9), 2.00 (ddd, *J* = 14.7, 9.4, 3.2 Hz, 1H, H-2), 1.81 (dt, *J* = 14.0, 5.7 Hz, 1H, H-4), 1.70 (ddd, *J* = 14.4, 5.3, 3.5 Hz, 1H, H-4), 1.58 (dt, *J* = 14.0, 9.8 Hz, 1H, H-2), 1.43 – 1.36 (m, 2H, H-2'), 1.33 – 1.25 (m, 2H, H-3'), 0.92 (t, *J* = 7.4 Hz, 3H, H-4'), 0.90 (d, *J* = 6.9 Hz, 3H, H-13).

^{13}C NMR (150 MHz, CD_3OD) δ 177.01 (C-15), 166.71 (C-22), 162.14 (C-19), 131.67(C-17, C-21), 121.62 (C-16), 114.61 (C-18, C-20), 100.96 (C-8), 81.29 (C-5), 75.12 (C-6), 74.67 (C-7), 70.84 (C-1), 70.08 (C-10), 61.61 (C-12), 38.88 (C-1'), 34.51 (C-2'), 34.16 (C-3), 32.83 (C-9), 29.12 (C-11), 28.72 (C-3'), 28.61 (C-4'), 26.64 (C-2), 21.96(C-5'), 12.96 (C-5'), 11.67 (C-13).

MS (ESI) *m/z*: 530 $[M+Na]^+$ for $C_{26}H_{37}NO_9$.

3.8.5. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-6-(hexylcarbamoyl)-3,3a,4-trihydroxy-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (3e)



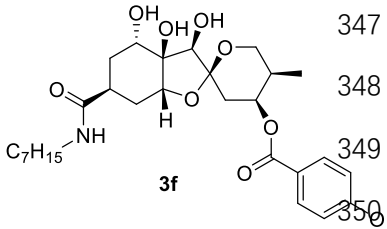
3e

^{1}H NMR (600 MHz, CD_3OD) δ 7.94 (br d, *J* = 8.7 Hz, 2H, H-17, H-21), 6.81 (br d, *J* = 8.7 Hz, 2H, H-18, H-20), 5.21 (br d, *J* = 1.9 Hz, 1H, H-10), 4.09 (t, *J* =2.9 Hz, 1H, H-5), 4.02 (t, *J* = 11.4 Hz, 1H, H-12), 3.88 (dd, *J* = 10.5, 5.6 Hz, 1H, H-1), 3.73 (s, 1H, H-7), 3.59 (dd, *J* = 11.2, 4.5 Hz, 1H, H-12), 3.05 (td, *J* = 7.1, 2.6 Hz, 2H, H-1'), 2.37 – 2.29 (m, 1H, H-3), 2.15 (dd, *J* = 14.8, 3.0 Hz, 1H, H-9), 2.11 – 2.02 (m, 2H, H-11, H-9), 2.00 – 1.93 (m, 1H, H-2), 1.78 (dt, *J* = 13.8, 5.7 Hz, 1H, H-4), 1.71 –1.64 (m, 1H, H-4), 1.55 (dt, *J* = 13.9, 10.0 Hz, 1H, H-2), 1.42 – 1.36 (m, 2H, H-2'), 1.35 – 1.21 (m, 6H, H-3', H-4', H-5'), 0.92 – 0.84 (m, 6H, H-6', H-13).

^{13}C NMR (150 MHz, CD_3OD) δ 178.41 (C-15), 168.14 (C-22), 163.53 (C-19), 133.07 (C-17, C-21), 123.03 (C-16), 116.02 (C-18, C-20), 102.37 (C-8), 82.70 (C-5), 76.54 (C-6), 76.07 (C-7), 72.23 (C-1), 71.50 (C-10), 63.01 (C-12), 40.31 (C-1'), 36.92 (C-2'), 35.91 (C-3), 35.58 (C-9), 34.23 (C-11), 32.59 (C-3'), 30.51 (C-4'), 30.28 (C-2), 27.58 (C-5'), 23.62 (C-4), 14.38 (C-6'), 13.05 (C-13).

MS (ESI) *m/z*: 544 $[M+Na]^+$ for $C_{27}H_{39}NO_9$.

3.8.6. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-6-(heptylcarbamoyl)-3,3a,4-trihydroxy-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (3f)



3f

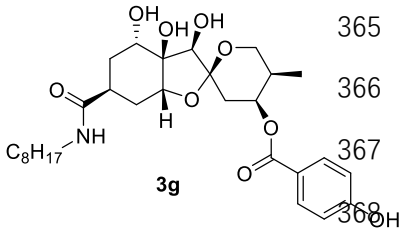
^{1}H NMR (600 MHz, CD_3OD) δ 7.93 (br d, *J* = 8.8 Hz, 2H, H-17, H-21), 6.79 (br d, *J* = 8.8 Hz, 2H, H-18, H-20), 5.21 (br d, *J* = 2.2 Hz, 1H, H-10), 4.09 (t, *J* =3.1 Hz, 1H, H-5), 4.02 (t, *J* = 11.4 Hz, 1H, H-12), 3.88 (dd, *J* = 10.5, 5.6 Hz, 1H, H-1),3.73 (s, 1H, H-7), 3.58 (dd, *J* = 11.0, 4.5 Hz, 1H, H-12), 3.05 (t, *J* = 7.1 Hz, 1H, H-1'), 2.48 – 2.37 (m, 1H, H-3), 2.19 – 2.02 (m, 3H, H-9, H-11), 2.00 – 1.93 (m, 1H, H-2), 1.78 (dt, *J* = 13.9, 5.6 Hz, 1H, H-4), 1.68 (ddd, *J* = 14.4, 5.2, 3.6 Hz, 1H, H-4), 1.61 – 1.50 (m, 1H, H-2), 1.44 – 1.19 (m, 10H, H-2', H-3', H-4', H-5', H-6'), 0.93 – 0.82 (m, 6H, H-13, H-7').

^{13}C NMR (150 MHz, CD_3OD) δ 177.01 (C-15), 166.71 (C-22), 162.13 (C-19), 131.67

(C-17, C-21), 121.63 (C-16), 114.60 (C-18, C-20), 100.96 (C-8), 81.29 (C-5), 75.11 (C-6), 74.68 (C-7), 70.84 (C-1), 70.07 (C-10), 61.61 (C-12), 38.90 (C-1'), 34.52 (C-3), 34.17 (C-2'), 32.84 (C-9), 31.53 (C-11), 29.13 (C-3'), 28.93 (C-4'), 28.64 (C-5'), 26.65 (C-6'), 26.48 (C-2), 22.28 (C-4), 13.03 (C-7'), 11.65 (C-13).

MS (ESI) *m/z*: 558 $[M+Na]^+$ for $C_{28}H_{41}NO_9$.

3.8.7. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-trihydroxy-5'-methyl-6-(octylcarbamoyl)decahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (3g)



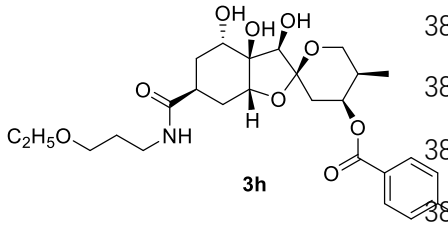
3g

^{1}H NMR (600 MHz, CD_3OD) δ 7.94 (br d, *J* = 8.7 Hz, 2H, H-17, H-21), 6.80 (br d, *J* = 8.7 Hz, 2H, H-18, H-20), 5.21 (br s, 1H, H-10), 4.09 (br s, 1H, H-5), 4.02 (t, *J* = 11.4 Hz, 1H, H-12), 3.88 (dd, *J* = 10.4, 5.6 Hz, 1H, H-1), 3.73 (s, 1H, H-7), 3.59 (dd, *J* = 11.1, 4.2 Hz, 1H, H-12), 3.05 (t, *J* = 7.0 Hz, 1H, H-1'), 2.41 (dq, *J* = 16.2, 5.5 Hz, 1H, H-3), 2.15 (dd, *J* = 14.7, 2.9 Hz, 1H, H-9), 2.07 (dd, *J* = 14.8, 2.4 Hz, 2H, H-11, H-9), 2.00 – 1.92 (m, 1H, H-2), 1.78 (dt, *J* = 13.7, 5.6 Hz, 1H, H-4), 1.72 – 1.64 (m, 1H, H-4), 1.55 (dt, *J* = 13.8, 10.0 Hz, 1H, H-2), 1.40 (dd, *J* = 14.0, 7.0 Hz, 2H, H-2'), 1.35 – 1.20 (m, 10H, H-3', H-4', H-5', H-6', H-7'), 0.95 – 0.83 (m, 6H, H-13, H-8').

^{13}C NMR (150 MHz, CD_3OD) δ 177.01 (C-15), 166.71 (C-22), 162.13 (C-19), 131.67 (C-17, C-21), 121.64 (C-16), 114.60 (C-18, C-20), 100.96 (C-8), 81.28 (C-5), 75.11 (C-6), 74.68 (C-7), 70.84 (C-1), 70.08 (C-10), 61.61 (C-12), 38.90 (C-1'), 34.52 (C-2'), 34.17 (C-3), 32.84 (C-9), 31.60 (C-3'), 29.13 (C-11), 28.96 (C-4'), 28.92 (C-5', C-6'), 26.66 (C-2), 26.51 (C-7'), 22.32 (C-4), 13.05 (C-8'), 11.65 (C-13).

MS (ESI) *m/z*: 572 $[M + Na]^+$ for $C_{29}H_{43}NO_9$.

3.8.8. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-6-((3-ethoxypropyl)carbamoyl)-3,3a,4-trihydroxy-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (3h)

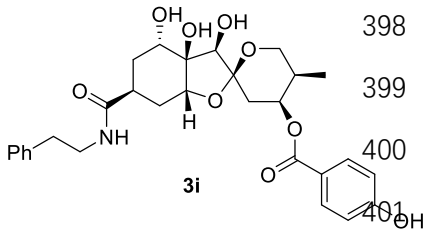


3h

^{1}H NMR (600 MHz, CD_3OD) δ 7.95 (br d, *J* = 8.7 Hz, 2H, H-17, H-21), 6.81 (br d, *J* = 8.7 Hz, 2H, H-18, H-20), 5.21 (br s, 1H, H-10), 4.10 (br s, 1H, H-5), 4.02 (t, *J* = 11.4 Hz, 1H, H-12), 3.88 (dd, *J* = 10.4, 5.6 Hz, 1H, H-1), 3.74 (s, 1H, H-7), 3.59 (dd, *J* = 10.9, 4.2 Hz, 1H, H-12), 3.43 (q, *J* = 7.0 Hz, 2H, H-4'), 3.38 (t, *J* = 6.2 Hz, 1H, H-3'), 3.15 (ddq, *J* = 20.3, 13.5, 6.9 Hz, 2H, H-1'), 2.41 (tt, *J* = 11.1, 5.5 Hz, 1H, H-3), 2.14 (dt, *J* = 10.5, 5.3 Hz, 1H, H-11), 2.11 – 2.03 (m, 2H, H-11, H-9), 2.00 – 1.93 (m, 1H, H-2), 1.79 (dt, *J* = 13.7, 5.6 Hz, 1H, H-4), 1.72 – 1.62 (m, 3H, H-4, H-2'), 1.56 (dt, *J* = 13.8, 10.0 Hz, 1H, H-2), 1.14 (t, *J* = 7.0 Hz, 3H, H-5'), 0.87 (d, *J* = 6.9 Hz, 3H, H-13).

MS (ESI) *m/z*: 546 $[M + Na]^+$ for $C_{26}H_{37}NO_{10}$.

3.8.9. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-trihydroxy-5'-methyl-6-(phenethylcarbamoyl)decahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (3i)



3i

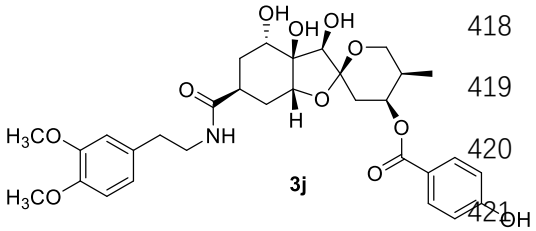
^{1}H NMR (600 MHz, CD_3OD) δ 7.94 (br d, *J* = 8.7 Hz, 2H, H-17, H-21),7.22 (t, *J* = 7.4 Hz, 2H, H-3', H-5'), 7.18 – 7.12 (m, 3H, H-2', H-4', H-6'), 6.82 (br d, *J*= 8.7 Hz, 2H, H-18, H-20), 5.20 (br s, 1H, H-10), 4.08 (br s, 1H, H-5), 4.01 (t, *J* =11.4 Hz, 1H, H-12), 3.86 (dd, *J* = 10.5, 5.5 Hz, 1H, H-1), 3.72 (s, 1H, H-7), 3.58 (dd, *J* = 11.0, 4.2 Hz, 1H, H-12), 3.36 – 3.24 (m, 4H, H-8', overlap), 2.69 (t, *J* = 7.3 Hz, 2H, H-7'), 2.37 (dq, *J* = 16.2, 5.4 Hz, 1H, H-3), 2.14 (dd, *J* = 14.7, 2.9 Hz, 1H, H-9), 2.11 – 2.01 (m, 2H, H-11, H-9), 1.96 – 1.87 (m, 1H, H-2), 1.75 (dt, *J* = 13.7, 5.5 Hz, 1H, H-4), 1.68 – 1.62 (m, 1H, H-4), 1.51 (dt, *J* = 13.8, 10.1 Hz, 1H, H-2), 0.87 (d, *J* =6.9 Hz, 3H, H-13).

^{13}C NMR (150 MHz, CD_3OD) δ 177.06 (C-15), 166.66 (C-22), 162.11 (C-19), 139.02 (C-3'), 131.68 (C-17, C-21), 128.41 (C-5', C-7'), 128.04 (C-4', C-8'), 125.92 (C-6'), 121.65 (C-16), 114.64 (C-18, C-20), 100.95 (C-8), 81.25 (C-5), 75.09 (C-6), 74.65 (C-7), 70.81 (C-1), 70.07 (C-10), 61.60 (C-12), 40.49 (C-2'), 35.11 (C-1'), 34.48 (C-3),

34.15 (C-9), 32.84 (C-11), 28.99 (C-2), 26.61 (C-4), 11.65 (C-13).

MS (ESI) *m/z*: 564 $[M + Na]^+$ for $C_{29}H_{35}NO_9$.

3.8.10. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-6-((3,4-dimethoxyphenethyl)carbamoyl)-3,3a,4-trihydroxy-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (3j)

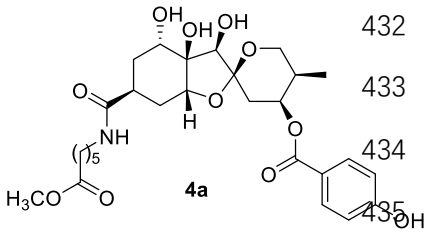


3j

^{1}H NMR (800 MHz, CD_3OD) δ 7.94 (d, *J* = 8.7 Hz, 2H, H-17, H-21), 6.83 – 6.81 (m, 3H, H-18, H-20, H-7'), 6.79 (d, *J* = 1.8 Hz, 1H, H-4'), 6.68 (dd, *J* = 8.1, 1.8 Hz, 1H, H-8'), 5.20 (d, *J* = 2.5 Hz, 1H, H-10), 4.08 (t, *J* = 3.2 Hz, 1H, H-5), 4.01 (t, *J* = 11.4 Hz, 1H, H-12), 3.86 (dd, *J* = 10.4, 5.5 Hz, 1H, H-1), 3.80 (s, 3H, H-10'), 3.78 (s, 3H, H-9'), 3.73 (s, 1H, H-7), 3.60 – 3.57 (m, 1H, H-12), 3.30 – 3.26 (m, 2H, H-2'), 2.67 – 2.60 (m, 2H, H-1'), 2.37 (ddd, *J* = 15.0, 11.3, 5.6 Hz, 1H, H-3), 2.10 (m, 3H, H-9, H-11), 1.93 (ddd, *J* = 14.6, 11.7, 3.1 Hz, 1H, H-2), 1.75 (dt, *J* = 14.0, 5.6 Hz, 1H, H-4), 1.69 – 1.62 (m, 1H, H-4), 1.51 (dt, *J* = 13.9, 9.9 Hz, 1H, H-2), 0.87 (d, *J* = 6.9 Hz, 3H, H-13).

MS (ESI) *m/z*: 624 $[M + Na]^+$ for $C_{31}H_{39}NO_{11}$.

3.8.11. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-trihydroxy-6-((6-methoxy-6-oxohexyl)carbamoyl)-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (4a)



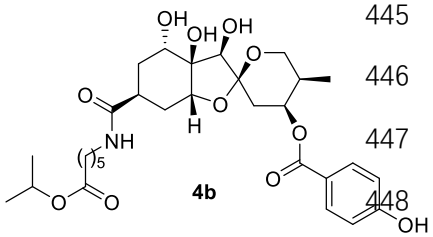
4a

^{1}H NMR (600 MHz, CD_3OD) δ 7.95 (d, *J* = 8.8 Hz, 2H, H-17, H-21), 6.84 (d, *J* = 8.8 Hz, 2H, H-18, H-20), 5.24 (br d, *J* = 2.4 Hz, 1H, H-10), 4.09 (t, *J* = 3.2 Hz, 1H, H-5), 4.02 (t, *J* = 11.2 Hz, 1H, H-12), 3.89 (dd, *J* = 10.4, 5.6 Hz, 1H, H-1), 3.74 (s, 1H, H-7), 3.64 (s, 1H, H-1''), 3.60 (dd, *J* = 11.1, 4.5 Hz, 1H, H-12), 3.10 – 3.02 (m, 2H, H-1'), 2.43 – 2.38 (m, 1H, H-3), 2.30 (t, *J* = 7.4 Hz, 2H, H-5'), 2.16 – 2.06 (m, 3H, H-9, H-11), 1.98 – 1.93 (m, 1H, H-2), 1.81

(dt, *J* = 13.7, 5.5 Hz, 1H, H-4), 1.70 – 1.66 (m, 1H, H-4), 1.64 – 1.52 (m, 3H, H-2, H-2'), 1.43 – 1.38 (m, 2H, H-4'), 1.31 – 1.25 (m, 2H, H-3'), 0.90 (d, *J* = 6.9 Hz, 2H, H-13).

MS (ESI) *m/z*: 588 $[M + Na]^+$ for $C_{28}H_{39}NO_{11}$.

3.8.12. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-trihydroxy-6-((6-isopropoxy-6-oxohexyl)carbamoyl)-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (4b)

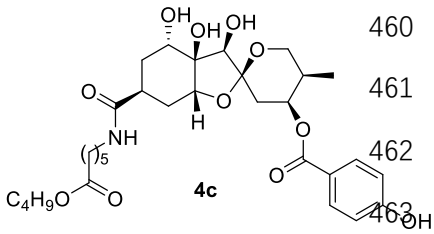


4b

^{1}H NMR (600 MHz, CD_3OD) δ 7.95 (br d, *J* = 8.8 Hz, 2H, H-17, H-21), 6.81 (br d, *J* = 8.8 Hz, 2H, H-18, H-20), 5.21 (br d, *J* = 2.2 Hz, 1H, H-10), 4.95 (tt, *J* = 12.6, 6.3 Hz, 1H, H-1"), 4.09 (t, *J* = 3.1 Hz, 1H, H-5), 4.02 (t, *J* = 11.4 Hz, 1H, H-12), 3.88 (dd, *J* = 10.5, 5.6 Hz, 1H, H-1), 3.73 (s, 1H, H-7), 3.59 (dd, *J* = 11.1, 4.7 Hz, 1H, H-12), 3.09 – 3.03 (m, 2H, H-1'), 2.44 – 2.37 (m, 1H, H-3), 2.25 (t, *J* = 7.4 Hz, 2H, H-5'), 2.18 – 2.04 (m, 3H, H-9, H-11), 2.00 – 1.92 (m, 1H, H-2), 1.78 (dt, *J* = 13.9, 5.7 Hz, 1H, H-4), 1.68 (ddd, *J* = 14.4, 5.1, 3.7 Hz, 1H, H-4), 1.61 – 1.50 (m, 3H, H-2, H-2'), 1.45 – 1.37 (m, 2H, H-3'), 1.31 – 1.24 (m, 2H, H-4'), 1.21 (d, *J* = 6.3 Hz, 6H, H-2", H-3"), 0.87 (d, *J* = 6.9 Hz, 2H, H-13).

MS (ESI) *m/z*: 616 $[M + Na]^+$ for $C_{30}H_{43}NO_{11}$.

3.8.13. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-6-((6-butoxy-6-oxohexyl)carbamoyl)-3,3a,4-trihydroxy-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (4c)



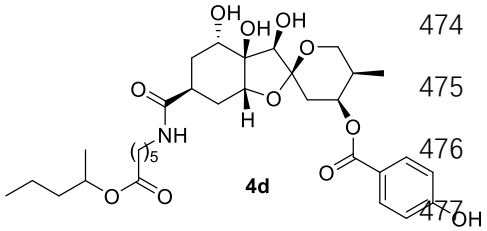
4c

^{1}H NMR (600 MHz, CD_3OD) δ 7.94 (d, *J* = 8.8 Hz, 2H, H-17, H-21), 6.81 (d, *J* = 8.8 Hz, 2H, H-18, H-20), 5.21 (br d, *J* = 2.2 Hz, 1H, H-10), 4.09 (t, *J* = 3.1 Hz, 1H, H-5), 4.06 (t, *J* = 6.6 Hz, 2H, H-1"), 4.02 (t, *J* = 11.4 Hz, 1H, H-12), 3.88 (dd, *J* = 10.5, 5.6 Hz, 1H, H-1), 3.73 (s, 1H, H-7), 3.60 – 3.56 (m, 1H, H-12), 3.09 – 3.03 (m, 1H, H-1'), 2.40 (ddd, *J* = 17.9, 8.9, 4.1 Hz, 1H, H-3), 2.29 (t, *J* = 7.4 Hz, 2H, H-5'), 2.17 – 2.04 (m, 3H, H-9, H-11), 1.99 – 1.93

(m, 1H, H-2), 1.78 (tt, *J* = 11.8, 5.9 Hz, 1H, H-4), 1.68 (ddd, *J* = 12.0, 7.9, 3.5 Hz, 1H, H-4), 1.63 – 1.50 (m, 5H, H-2, H-2', H-2''), 1.44 – 1.33 (m, 2H, H-3', H-3''), 1.30 – 1.24 (m, 1H, H-4'), 0.94 (t, *J* = 7.4 Hz, 3H, H-4''), 0.87 (d, *J* = 6.9 Hz, 3H, H-13).

MS (ESI) *m/z*: 630 $[M + Na]^+$ for $C_{31}H_{45}NO_{11}$.

3.8.14. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-trihydroxy-5'-methyl-6-((6-oxo-6-(pentan-2-yloxy)hexyl)carbamoyl)decahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (4d)

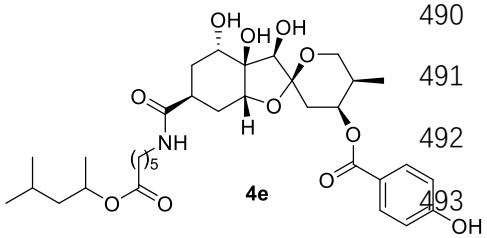


4d

^{1}H NMR (600 MHz, CD_3OD) δ 7.98 (ddd, *J* = 8.8, 2.6, 2.0 Hz, 2H, H-17, H-21), 6.84 (ddd, *J* = 8.8, 2.7, 1.9Hz, 2H, H-18, H-20), 5.24 (br d, *J* = 2.6 Hz, 1H, H-10), 4.94 – 4.91(m, 1H, H-2'' overlap), 4.12 (t, *J* = 3.2 Hz, 1H, H-5), 4.05 (t, *J* = 11.4 Hz, 1H, H-12), 3.90 (dd, *J* = 10.5, 5.6 Hz, 1H, H-1), 3.76 (s, 1H, H-7), 3.61 (dd, *J* = 11.1, 4.4 Hz, 1H, H-12), 3.13 – 3.05 (m, 2H, H-1'), 2.47 – 2.39 (m, 1H, H-3), 2.30 (t, *J* = 7.4 Hz, 2H, H-5'), 2.17 (dd, *J* = 14.8, 3.2 Hz, 1H, H-11), 2.14 – 2.06 (m, 2H, H-9), 1.99 (ddd, *J* = 14.6, 11.7, 3.1 Hz, 1H, H-2), 1.81 (dt, *J* = 13.9, 5.6 Hz, 1H, H-4), 1.72 (ddd, *J* = 14.4, 5.3, 3.6 Hz, 1H, H-4), 1.66 – 1.54 (m, 5H, H-2, H-2', H-3''), 1.52 – 1.26 (m, 8H, H-2', H-3', H-4', H-4''), 1.21 (d, *J* = 6.2 Hz, 3H, H-1''), 0.94 (t, *J* = 7.4 Hz, 3H, H-5''), 0.90 (d, *J* = 6.9 Hz, 3H, H-13).

MS (ESI) *m/z*: 644 $[M + Na]^+$ for $C_{32}H_{47}NO_{11}$.

3.8.15. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-trihydroxy-5'-methyl-6-((6-((4-methylpentan-2-yl)oxy)-6-oxohexyl)carbamoyl)decahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenz- oate (4e)



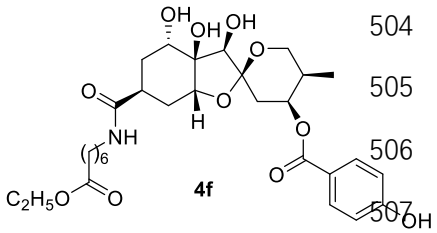
4e

^{1}H NMR (600 MHz, CD_3OD) δ 7.98 (br d, *J* = 8.8 Hz, 2H, H-17, H-21), 6.84 (br d, *J* = 8.8 Hz, 1H, H-18, H-20), 5.24 (br d, *J* = 2.6 Hz, 1H, H-10), 5.04 – 4.97 (m, 1H, H-2''), 4.12 (t, *J* = 3.2 Hz, 1H, H-5), 4.05 (t, *J* = 11.4 Hz, 1H, H-12),

3.90 (dd, *J* = 10.5, 5.6 Hz, 1H, H-1), 3.76 (s, 1H, H-7), 3.61 (dd, *J* = 11.1, 4.5 Hz, 1H, H-12), 3.13 – 3.05 (m, 1H, H-1'), 2.43 (ddd, *J* = 15.0, 11.3, 5.5 Hz, 1H, H-3), 2.30 (t, *J* = 7.4 Hz, 2H,), 2.20 – 2.06 (m, 2H), 2.04 – 1.95 (m, 1H), 1.81 (dt, *J* = 13.9, 5.6 Hz, 1H), 1.72 (ddd, *J* = 14.4, 5.3, 3.6 Hz, 1H), 1.68 – 1.53 (m, 3H), 1.47 – 1.41 (m, 1H), 1.33 – 1.26 (m, 2H), 1.21 (d, *J* = 6.2 Hz, 2H), 0.96 – 0.87 (m, 5H).

MS (ESI) *m/z*: 644 $[M + H]^+$ for $C_{33}H_{49}NO_{11}$.

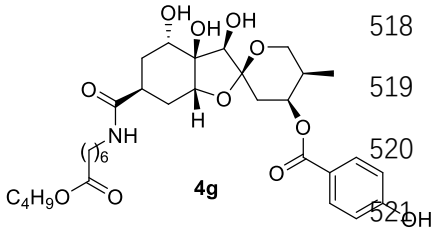
3.8.16. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-6-((7-ethoxy-7-oxoheptyl)carbamoyl)-3,3a,4-trihydroxy-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (4f)



^{1}H NMR (600 MHz, CD_3OD) δ 7.97 (br d, *J* = 8.7 Hz, 2H, H-17, H-21), 6.84 (br d, *J* = 8.7 Hz, 2H, H-18, H-20), 5.24 (br d, *J* = 2.1 Hz, 1H, H-10), 4.16 – 4.10 (m, 3H, H-5, H-1''), 4.05 (t, *J* = 11.4 Hz, 1H, H-12), 3.91 (dd, *J* = 10.5, 5.6 Hz, 1H, H-1), 3.76 (s, 1H, H-7), 3.61 (dd, *J* = 11.1, 4.5 Hz, 1H, H-12), 3.13 – 3.04 (m, 2H, H-1'), 2.50 – 2.38 (m, 1H, H-3), 2.32 (t, *J* = 7.4 Hz, 1H, H-6'), 2.17 (dd, *J* = 14.8, 3.1 Hz, 1H, H-11), 2.14 – 2.06 (m, 2H, H-9), 2.03 – 1.96 (m, 1H, H-2), 1.81 (dt, *J* = 13.8, 5.7 Hz, 1H, H-4), 1.74 – 1.68 (m, 1H, H-4), 1.64 – 1.53 (m, 3H, H-2, H-5'), 1.47 – 1.39 (m, 2H, H-2'), 1.37 – 1.22 (m, 7H, H-3', H-4', H-2''), 0.90 (d, *J* = 6.9 Hz, 2H, H-13).

MS (ESI) m/z: 616 $[M + Na]^+$ for $C_{30}H_{43}NO_{11}$.

3.8.17. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-6-((7-butoxy-7-oxoheptyl)carbamoyl)-3,3a,4-trihydroxy-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (4g)

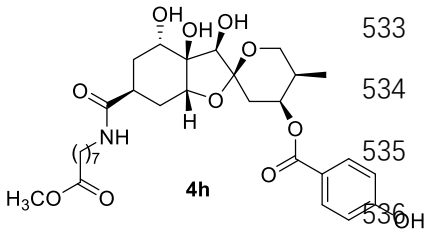


^{1}H NMR (600 MHz, CD_3OD) δ 7.98 (ddd, *J* = 8.8, 2.7, 2.0 Hz, 2H, H-17, H-21), 6.85 (ddd, *J* = 8.88, 2.7, 2.0 Hz, 2H, H-18, H-20), 5.24 (br d, *J* = 2.6 Hz, 1H, H-10), 4.12 (t, *J* = 3.2 Hz, 1H, H-5), 4.09 (t, *J* = 6.6 Hz, 2H, H-1''), 4.05 (t, *J* = 11.4 Hz, 1H, H-12), 3.91 (dd, *J* = 10.5, 5.6 Hz, 1H, H-

1), 3.76 (s, 1H, H-7), 3.61 (dd, *J* = 11.1, 4.4 Hz, 1H, H-12), 3.14 – 3.04 (m, 2H, H-1'), 2.44 (br ddd, *J* = 15.0, 11.3, 5.6 Hz, 1H, H-3), 2.32 (t, *J* = 7.4 Hz, 1H, H-6'), 2.17 (dd, *J* = 14.8, 3.2 Hz, 1H, H-11), 2.14 – 2.07 (m, 2H, H-9), 2.00 (ddd, *J* = 14.7, 11.7, 3.2 Hz, 1H, H-2), 1.81 (dt, *J* = 14.0, 5.7 Hz, 1H, H-4), 1.71 (ddd, *J* = 14.4, 5.3, 3.5 Hz, 1H, H-4), 1.66 – 1.56 (m, 5H, H-2, H-2', H-2''), 1.46 – 1.25 (m, 8H, H-3', H-3'', H-4', H-5'), 0.97 (t, *J* = 7.4 Hz, 3H, H-4''), 0.90 (d, *J* = 6.9 Hz, 3H, H-13).

MS (ESI) *m/z*: 644 $[M + Na]^+$ for $C_{32}H_{47}NO_{11}$.

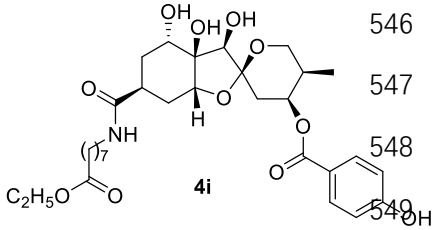
3.8.18. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-trihydroxy-6-((8-methoxy-8-oxooctyl)carbamoyl)-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (4h)



^{1}H NMR (600 MHz, CD_3OD) δ 7.97 (d, *J* = 8.7 Hz, 2H, H-17, H-21), 6.84 (d, *J* = 8.7 Hz, 2H, H-18, H-20), 5.24 (d, *J* = 2.2 Hz, 1H, H-10), 4.12 (t, *J* = 3.1 Hz, 1H, H-5), 4.05 (t, *J* = 11.4 Hz, 1H, H-12), 3.91 (dd, *J* = 10.5, 5.6 Hz, 1H, H-1), 3.76 (s, 1H, H-7), 3.67 (s, 3H, H-1''), 3.61 (dd, *J* = 11.1, 4.5 Hz, 1H, H-12), 3.15 – 3.02 (m, 1H, H-1'), 2.47 – 2.40 (m, 1H, H-3), 2.34 (t, *J* = 7.4 Hz, 2H, H-7'), 2.21 – 2.06 (m, 3H, H-9, H-11), 2.03 – 1.96 (m, 1H, H-2), 1.81 (dt, *J* = 13.9, 5.7 Hz, 1H, H-4), 1.74 – 1.68 (m, 1H, H-4), 1.60 – 1.50 (m, 3H, H-2, H-2'), 1.49 – 1.20 (m, 8H, H-3', H-4', H-5', H-6'), 0.90 (d, *J* = 6.9 Hz, 3H, H-13).

MS (ESI) *m/z*: 616 $[M + Na]^+$ for $C_{30}H_{43}NO_{11}$.

3.8.19. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-6-((8-ethoxy-8-oxooctyl)carbamoyl)-3,3a,4-trihydroxy-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (4i)

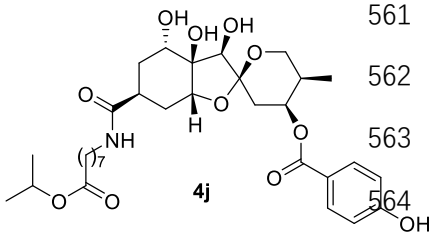


^{1}H NMR (600 MHz, CD_3OD) δ 7.97 (br d, *J* = 8.7 Hz, 2H, H-17, H-21), 6.84 (br d, *J* = 8.7 Hz, 2H, H-18, H-20), 5.24 (br d, *J* = 2.1 Hz, 1H, H-10), 4.18 – 4.09 (m, 3H, H-5, H-1''), 4.05 (t, *J* = 11.4 Hz, 1H, H-12), 3.91 (dd, *J* = 10.5, 5.6 Hz, 1H, H-1), 3.76 (s, 1H, H-7), 3.61 (dd, *J* = 11.1, 4.5

Hz, 1H, H-12), 3.13 – 3.04 (m, 2H, H-1'), 2.50 – 2.40 (m, 1H, H-3), 2.32 (t, *J* = 7.4 Hz, 2H, H-7'), 2.17 (dd, *J* = 14.8, 3.1 Hz, 1H, H-11), 2.14 – 2.05 (m, 2H, H-9), 2.03 – 1.96 (m, 1H, H-2), 1.81 (dt, *J* = 13.9, 5.7 Hz, 1H, H-4), 1.74 – 1.69 (m, 1H, H-4), 1.65 – 1.54 (m, 3H, H-2, H-2'), 1.46 – 1.38 (m, 2H, H-3'), 1.46 – 1.18 (m, 9H, H-4', H-5', H-6', H-2''), 0.90 (d, *J* = 6.9 Hz, 2H, H-13).

MS (ESI) m/z: 630 $[M + Na]^+$ for $C_{31}H_{45}NO_{11}$.

3.8.20. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-trihydroxy-6-((8-isopropoxy-8-oxooctyl)carbamoyl)-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (4j)

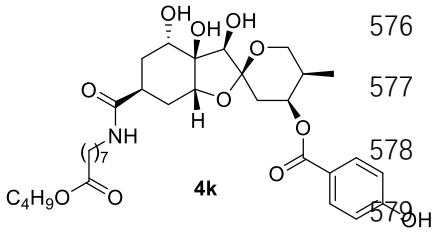


4j

^{1}H NMR (600 MHz, CD_3OD) δ 7.86 (ddd, *J* = 8.8, 2.7, 2.0 Hz, 2H, H-17, H-21), 6.73 (ddd, *J* = 8.88, 2.7, 2.0 Hz, 2H, H-18, H-20), 5.12 (br d, *J* = 2.6 Hz, 1H, H-10), 4.86 (dp, *J* = 12.5, 6.3 Hz, 1H, H-1''), 4.00 (t, *J* = 3.2 Hz, 1H, H-5), 3.93 (t, *J* = 11.4 Hz, 1H, H-12), 3.79 (dd, *J* = 10.5, 5.6 Hz, 1H, H-1), 3.64 (s, 1H, H-7), 3.49 (dd, *J* = 11.1, 4.4 Hz, 1H, H-12), 3.02 – 2.92 (m, 2H, H-1'), 2.32 (br ddd, *J* = 15.0, 11.3, 5.6 Hz, 1H, H-3), 2.17 (t, *J* = 7.4 Hz, 2H, H-7''), 2.09 – 1.94 (m, 3H, H-11, H-9, overlap),1.88 (ddd, *J* = 14.6, 9.8, 3.2 Hz, 1H, H-2), 1.69 (dt, *J* = 14.0, 5.7 Hz, 1H, H-4), 1.59 (ddd, *J* = 14.4, 5.3, 3.5 Hz, 1H, H-4), 1.52 – 1.41 (m, 3H, H-2, H-2'), 1.35 – 1.26 (m, 2H, H-3'), 1.24 – 1.05 (m, 12H, H-4', H-5', H-6', H-2'', H-3'', overlap), 0.78 (d, *J* = 6.9 Hz, 2H, H-13).

MS (ESI) *m/z*: 644 $[M + Na]^+$ for $C_{32}H_{47}NO_{11}$.

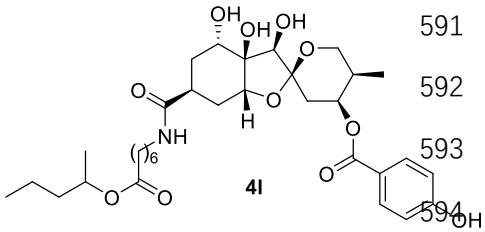
3.8.21. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-6-((8-butoxy-8-oxooctyl)carbamoyl)-3,3a,4-trihydroxy-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (4k)



^{1}H NMR (600 MHz, CD_3OD) δ 7.98 (ddd, *J* = 8.8, 2.7, 2.0 Hz, 2H, H-17, H-21), 6.85 (ddd, *J* = 8.8, 2.7, 2.0 Hz, 2H, H-18, H-20), 5.24 (d, *J* = 2.6 Hz, 1H, H-10), 4.12 (t, *J* = 3.2 Hz, 1H, H-5), 4.09 (t, *J* = 6.6 Hz, 2H, H-1''), 4.05 (t, *J* = 11.4 Hz, 1H, H-12), 3.91 (dd, *J* = 10.5, 5.6 Hz, 1H, H-1), 3.76 (s, 1H, H-7), 3.61 (dd, *J* = 11.1, 4.4 Hz, 1H, H-12), 3.14 – 3.03 (m, 2H, H-1'), 2.44 (ddd, *J* = 15.0, 11.3, 5.6 Hz, 1H, H-3), 2.33 (t, *J* = 7.4 Hz, 2H, H-7'), 2.20 – 2.06 (m, 3H, H-11, H-9, overlap), 2.00 (ddd, *J* = 14.6, 11.7, 3.2 Hz, 1H, H-2), 1.81 (dt, *J* = 14.0, 5.7 Hz, 1H, H-4), 1.71 (ddd, *J* = 14.4, 5.3, 3.5 Hz, 1H, H-4), 1.66 – 1.54 (m, 5H, H-2, H-6', H-2''), 1.48 – 1.21 (m, 10H, H-2', H-3', H-4', H-5', H-3''), 0.97 (t, *J* = 7.4 Hz, 3H, H-4''), 0.90 (d, *J* = 6.9 Hz, 3H, H-13).

MS (ESI) *m/z*: 658 $[M + Na]^+$ for $C_{33}H_{49}NO_{11}$.

3.8.22. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-trihydroxy-5'-methyl-6-((7-oxo-7-(pentan-2-yloxy)heptyl)carbamoyl)decahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (4l)

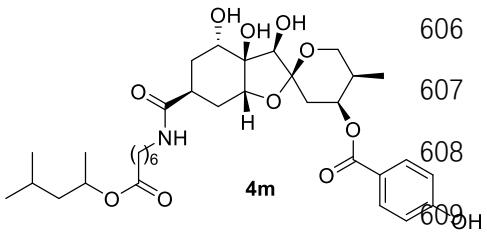


^{1}H NMR (600 MHz, CD_3OD) δ 7.97 (ddd, *J* = 8.8, 2.7, 2.0 Hz, 2H, H-17, H-21), 6.84 (ddd, *J* = 8.8, 2.7, 2.0 Hz, 2H, H-18, H-20), 5.24 (br d, *J* = 2.5 Hz, 1H, H-10), 4.92 (brq, *J* = 6.4 Hz, 1H, H-2''), 4.12 (t, *J* = 3.2 Hz, 1H, H-5), 4.05 (t, *J* = 11.4 Hz, 1H, H-12), 3.91 (dd, *J* = 10.5, 5.6 Hz, 1H, H-1), 3.76 (s, 1H, H-7), 3.61 (dd, *J* = 11.1, 4.4 Hz, 1H, H-12), 3.13 – 3.04 (m, 2H, H-1'), 2.44 (ddd, *J* = 15.0, 11.3, 5.6 Hz, 1H, H-3), 2.30 (t, *J* = 7.4 Hz, 2H, H-6'), 2.20 – 2.06 (m, 3H, H-11, H-9), 2.00 (ddd, *J* = 14.6, 9.4, 3.2 Hz, 1H, H-2), 1.81 (dt, *J* = 14.0, 5.7 Hz, 1H, H-4), 1.71 (ddd, *J* = 14.4, 5.3, 3.5 Hz, 1H, H-4), 1.64 – 1.25 (m, 13H, H-12, H-2', H-3', H-4', H-5', H-3'', H-4''), 1.22 (d, *J* = 6.3 Hz, 3H, H-1''), 0.94 (t, *J* = 7.4 Hz, 3H, H-5''), 0.90 (d, *J* = 6.9 Hz, 3H, H-13).

MS (ESI) *m/z*: 636 $[M + H]^+$ for $C_{33}H_{49}NO_{11}$.

3.8.23. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-trihydroxy-5'-methyl-6-((7-((4-

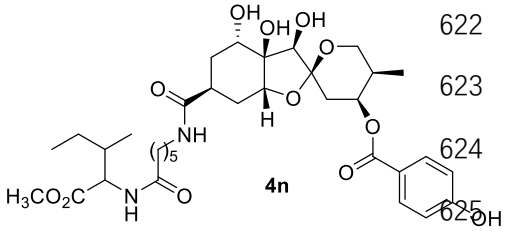
methylpentan-2-yl)oxy)-7-oxoheptyl)carbamoyl)decahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenz- ate (4m)



^{1}H NMR (600 MHz, CD_3OD) δ 7.97 (ddd, *J* = 8.8, 2.7, 2.0 Hz, 2H, H-17, H-21), 6.84 (ddd, *J* = 8.8, 2.7, 2.0Hz, 2H, H-18, H-20), 5.24 (br d, *J* = 2.6 Hz, 1H, H-10), 5.04 – 4.98 (m, 1H, H-2'), 4.12 (t, *J* = 3.2 Hz, 1H, H-5), 4.05 (t, *J* = 11.4 Hz, 1H, H-12), 3.91 (dd, *J* = 10.5, 5.6 Hz, 1H, H-1), 3.76 (s, 1H, H-7), 3.61 (dd, *J* = 11.1, 4.4 Hz, 1H, H-12), 3.13 – 3.04 (m, 1H, H-1'), 2.44 (ddd, *J* = 15.0, 11.3, 5.6 Hz, 1H, H-3), 2.30 (t, *J* = 7.4 Hz, 1H, H-7'), 2.17 (dd, *J* = 14.8, 3.2 Hz, 1H, H-11), 2.14 – 2.07 (m, 2H, H-9), 2.00 (ddd, *J* = 14.6, 9.3, 3.2 Hz, 1H, H-2), 1.81 (dt, *J* = 14.0, 5.7 Hz, 1H, H-4), 1.71 (ddd, *J* = 14.4, 5.3, 3.5 Hz, 1H, H-4), 1.68 – 1.54 (m, 5H, H-2, H-2', H-3''), 1.46 – 1.40 (m, 2H, H-3'), 1.37 – 1.26 (m, 5H, H-4', H-5', H-4''), 1.21 (d, *J* = 6.2 Hz, 3H, H-1''), 0.93 (d, *J* = 6.7 Hz, 3H, H-5''), 0.92 (d, *J* = 6.6 Hz, 3H, H-6''), 0.90 (d, *J* = 6.9 Hz, 3H, H-13).

MS (ESI) *m/z*: 650 $[M + H]^+$ for $C_{34}H_{51}NO_{11}$.

3.8.24. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-trihydroxy-6-((6-((1-methoxy-3-methyl-1-oxopentan-2-yl)amino)-6-oxohexyl)carbamoyl)-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (4n)



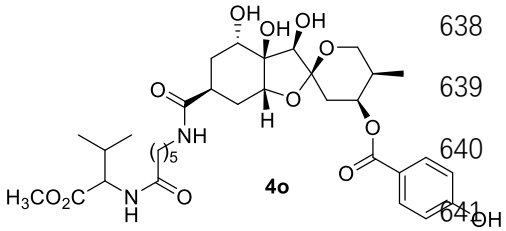
^{1}H NMR (600 MHz, CD_3OD) δ 7.94 (br d, *J* = 8.7 Hz, 2H, H-17, H-21), 6.81 (br d, *J* = 8.7 Hz, 2H, H-18, H-20), 5.21 (br d, *J* = 2.1 Hz, 1H, H-10), 4.36 (d, *J* = 6.2 Hz, 1H, H-2''), 4.09 (t, *J* = 3.1 Hz, 1H, H-5), 4.02 (t, *J* = 11.4 Hz, 1H, H-12), 3.88 (dd, *J* = 10.5, 5.5 Hz, 1H, H-1), 3.73 (s, 1H, H-7), 3.69 (s, 1H, H-1'''), 3.59 (dd, *J* = 11.1, 4.5 Hz, 1H, H-12), 3.11 – 3.00 (m, 2H, H-1'), 2.40 (tt, *J* = 11.2, 5.6 Hz, 1H, H-3), 2.27 – 2.20 (t, 2H, H-5'), 2.18 – 2.12 (m, 1H, H-9), 2.11 – 2.04 (m, 2H, H-11, H-9), 1.99 – 1.93 (m, 1H, H-2), 1.85 (br qt, *J* = 13.4, 6.8 Hz, 1H, H-3''), 1.78 (dt, *J* = 13.9, 5.6 Hz, 1H, H-4),1.72 – 1.66 (m, 1H, H-4), 1.62 – 1.20 (m, 9H, H-2), 0.93 – 0.89 (m, 6H, H-5', H-6'), 0.87 (d,

J = 6.9 Hz, 1H, H-3).

MS (ESI) *m/z*: 701 $[M + Na]^+$ for $C_{34}H_{50}N_2O_{12}$.

3.8.25. (2S,3-R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-trihydroxy-6-((6-((1-methoxy-3-methyl-1-oxobutan-2-yl)amino)-6-oxohexyl)carbamoyl)-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-

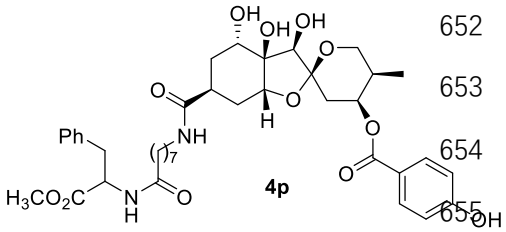
4'-yl 4-hydroxybenzoate (4o)



^{1}H NMR (600 MHz, CD_3OD) δ 7.95 (br d, J = 8.7 Hz, 2H, H-17, H-21),6.82 (br d, J = 8.7 Hz, 2H, H-18, H-20), 5.21 (br d, J = 2.1 Hz, 1H),4.30 (d, J = 6.2 Hz, 1H), 4.09 (t, J = 3.0 Hz, 1H, H-5), 4.02 (t, J = 11.4 Hz, 1H, H-12), 3.88 (dd, J = 10.5, 5.5 Hz, 1H, H-1), 3.74 (s, 1H, H-7), 3.70 (s, 3H), 3.59 (dd, J = 11.0, 4.9 Hz, 1H, H-12), 3.12 –3.02 (m, 2H), 2.40 (tt, J = 11.3, 5.6 Hz, 1H, H-3), 2.25 (t, J =7.5 Hz, 2H), 2.18 – 2.04 (m, 4H, H-9, H-11), 1.99 – 1.92 (m, 2H, H-2), 1.78 (dt, J = 13.9, 5.6 Hz, 1H, H-4), 1.72– 1.66 (m, 2H, H-4), 1.63 – 1.50 (m, 3H, H-2), 1.47 – 1.38 (m, 2H), 1.32 – 1.24 (m, 2H), 0.94 (dd, J = 6.8, 2.8 Hz, 6H), 0.87 (d, J = 6.9 Hz, 3H).

MS (ESI) *m/z*: 687 $[M + Na]^+$ for $C_{33}H_{48}N_2O_{12}$.

3.8.26. (2S,3R,3aS,4S,4'S,5'R,6S,7aR)-3,3a,4-trihydroxy-6-((8-((1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-8-oxooctyl)carbamoyl)-5'-methyldecahydro-3H-spiro[benzofuran-2,2'-pyran]-4'-yl 4-hydroxybenzoate (4p)



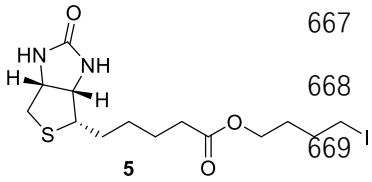
^{1}H NMR (600 MHz, CD_3OD) δ 7.85 (d, J = 8.7 Hz, 2H, H-17, H-21), 7.19 – 7.15 (m, 2H, H-6', H-8'), 7.11 (t, J = 6.6 Hz, 3H, H-5', H-7', H-9'), 6.72 (d, J = 8.7 Hz, 2H, H-18, H-20), 5.12 (d, J = 2.4 Hz, 1H, H-10), 4.58 (dd, J = 9.4, 5.5 Hz, 1H, H-2''), 4.01 (t, J = 3.2 Hz, 1H, H-5), 3.93 (t, J = 11.4 Hz, 1H, H-12), 3.79 (dd, J =10.5, 5.6 Hz, 1H, H-1), 3.65 (s, 1H, H-7), 3.59 (s, 3H, H-1'''), 3.50 (dd, J = 11.1, 4.6Hz, 1H, H-12), 3.06 (dd, J = 13.9,

5.5 Hz, 1H, H-3''), 3.00 – 2.91 (m, 2H, H-1'), 2.83 (dd, *J* = 13.9, 9.5 Hz, 1H, H-3''), 2.32 (qd, *J* = 11.3, 5.6 Hz, 1H, H-3), 2.09 – 1.95 (m, 5H, H-9, H-11, H-7'), 1.88 (ddd, *J* = 14.6, 11.8, 3.1 Hz, 1H, H-2), 1.70 (dt, *J* = 13.9, 5.7 Hz, 1H, H-4), 1.62 – 1.56 (m, 1H, H-4), 1.46 (dt, *J* = 13.9, 9.9 Hz, 1H, H-2), 1.42– 1.35 (m, 2H, H-2'), 1.33 – 1.03 (m, 8H, H-3', H-4', H-5', H-6'), 0.78 (d, *J* = 6.9 Hz, 3H, H-13).

MS (ESI) *m/z*: 763 $[M + Na]^+$ for $C_{39}H_{52}N_2O_{12}$.

3.9. Preparation of biotin probes

3.9.1. Biotin linker (5, blank control)

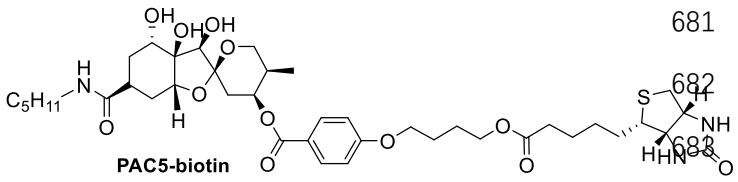


Biotin (10 mg, 4.1×10^{-5} mol) was stirred with 1,4-diiodobutane (27 μL, 2.1×10^{-4} mol) and potassium carbonate (28.3 mg, 2.1×10^{-4} mol) in DMF (1.0 mL) at room temperature until a complete conversion was detected. The mixture was concentrated. The crude product was purified by silica gel column chromatography to obtain the corresponding titled compound as a white solid (14.0 mg, 80.5%).

^{1}H NMR (600 MHz, CD_3OD) δ 4.48 (dd, *J* = 7.7, 4.9 Hz, 1H), 4.30 (dd, *J* = 7.8, 4.5 Hz, 1H), 4.10 (t, *J* = 6.3 Hz, 2H), 3.31 – 3.29 (m, 2H), 3.26 (t, *J* = 6.8 Hz, 2H), 3.23 – 3.18 (m, 1H), 2.93 (dd, *J* = 12.8, 5.0 Hz, 1H), 2.70 (d, *J* = 12.7 Hz, 1H), 2.35 (t, *J* = 7.3 Hz, 2H), 1.91 – 1.85 (m, 2H), 1.78 – 1.71 (m, 3H), 1.66 (dd, *J* = 16.2, 7.8 Hz, 2H), 1.60 (d, *J* = 8.4 Hz, 1H), 1.45 (dd, *J* = 15.5, 7.7 Hz, 2H).

MS (ESI) *m/z*: 427 $[M+H]^+$ for $C_{14}H_{23}INO_3S$.

3.9.2. PAC5-biotin probe (positive probe)



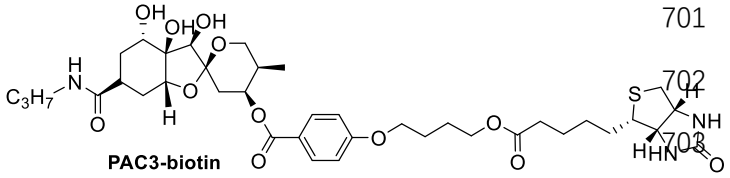
Compound **3d** (10 mg, 1.97×10^{-5} mol) was stirred with biotin linker **5** (3.28×10^{-5} mol) and potassium carbonate (11.3 mg, 8.2×10^{-5} mol) in dry DMF (1.0 mL) at room temperature

until a complete conversion was detected. The mixture was concentrated. The crude product was purified by silica gel column chromatography to obtain the corresponding titled compound as a white solid (13.5 mg, 84.8%).

^{1}H NMR (600 MHz, CD_3OD) δ 7.94 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 5.14 (d, *J* = 2.5 Hz, 1H), 4.38 (dd, *J* = 7.8, 4.6 Hz, 1H), 4.19 (dd, *J* = 7.9, 4.5 Hz, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 4.01 (t, *J* = 3.3 Hz, 1H), 3.98 (t, *J* = 6.0 Hz, 2H), 3.93 (t, *J* = 11.4 Hz, 1H), 3.79 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.65 (s, 1H), 3.50 (dd, *J* = 11.1, 4.5 Hz, 1H), 3.11 – 3.06 (m, 1H), 3.00 – 2.92 (m, 2H), 2.81 (dd, *J* = 12.8, 5.0 Hz, 1H), 2.60 (d, *J* = 12.7 Hz, 1H), 2.38 – 2.30 (m, 1H), 2.24 (t, *J* = 7.3 Hz, 2H), 2.06 (dd, *J* = 14.8, 3.2 Hz, 1H), 1.99 (dd, *J* = 14.8, 2.8 Hz, 2H), 1.88 (ddd, *J* = 14.6, 11.7, 3.2 Hz, 1H), 1.81 – 1.72 (m, 4H), 1.70 – 1.66 (m, 1H), 1.58 (dddd, *J* = 22.9, 19.9, 9.9, 5.1 Hz, 4H), 1.48 (ddd, *J* = 14.1, 10.3, 6.5 Hz, 2H), 1.32 (ddt, *J* = 22.2, 14.7, 7.4 Hz, 4H), 1.25 – 1.18 (m, 2H), 1.14 (ddd, *J* = 11.8, 7.1, 2.1 Hz, 2H), 0.82 – 0.74 (m, 6H).

MS (ESI) m/z: 828 $[M+Na]^+$ for $C_{40}H_{59}N_3O_{12}S$.

3.9.3. PAC3-biotin probe (negative probe)



Compound **3b** (5.3 mg, 1.10×10^{-5} mol) was stirred with biotin linker **5** (9.4 mg, 2.2×10^{-5} mol) and potassium carbonate (7.7 mg, 5.5×10^{-5} mol) in dry DMF (1.0 mL) at room temperature until a complete conversion was detected. The mixture was concentrated. The crude product was purified by silica gel column chromatography to obtain the corresponding titled compound as a white solid (1.3 mg, 15.1%).

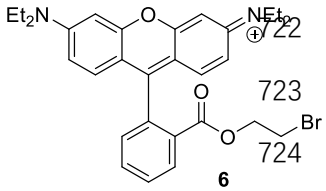
^{1}H NMR (800 MHz, CH_3OD) δ 8.03 (d, *J* = 8.9 Hz, 2H), 6.97 (d, *J* = 6.1 Hz, 2H), 5.23 (d, *J* = 2.7 Hz, 1H), 4.61 – 4.57 (m, 3H), 4.48 (dd, *J* = 7.9, 4.5 Hz,1H), 4.29 (dd, *J* = 7.9, 4.5 Hz, 1H), 4.16 (td, *J* = 6.3, 3.2 Hz, 2H), 4.12 (t, *J* = 3.2 Hz, 1H), 4.08 (t, *J* = 5.9 Hz, 2H), 4.04 (t, *J* = 11.5 Hz, 1H), 3.89 (dd, *J* = 10.3, 5.6 Hz, 1H), 3.76 (s, 1H), 3.60 (dd, *J* = 11.5, 4.6 Hz, 1H), 3.34 (s, 1H), 3.21 – 3.16 (m, 1H), 3.08 –2.97 (m, 1H), 2.90

(dd, *J* = 12.7, 4.9 Hz, 1H), 2.69 (d, *J* = 12.7 Hz, 1H), 2.46 – 2.39 (m, 1H), 2.32 (td, *J* = 7.4, 1.9 Hz, 1H), 2.16 (dd, *J* = 14.8, 3.2 Hz, 1H), 2.09 (dd, *J* = 14.8, 3.2 Hz, 2H), 1.97 (td, *J* = 14.8, 3.4 Hz, 1H), 1.89 – 1.85 (m, 2H), 1.85 – 1.78 (m, 3H), 1.74 – 1.63 (m, 4H), 1.61 – 1.55 (m, 2H), 1.46 – 1.39 (m, 4H), 1.30 (d, 1H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H).

MS (ESI) m/z: 800 $[M+Na]^+$ for $C_{38}H_{55}N_3O_{12}S$.

3.10. Preparation of rhodamine B probes

3.10.1. Rhodamine B linker (6, blank control)



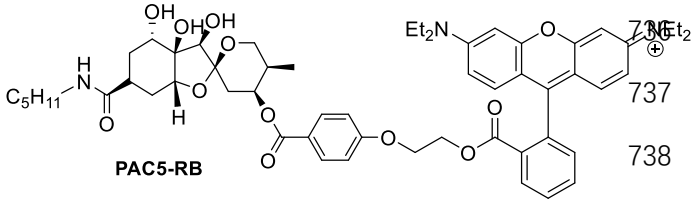
6

Rhodamine B (100 mg, 2.25×10^{-4} mol) was stirred with EDCI (80 mg, 4.18×10^{-4} mol), DMAP (25.5 mg, 2.09×10^{-4} mol) and 2-bromoethanol (45 μL, 4.18×10^{-4}mol) in dichloromethane (2.0 mL) under reflux until a complete conversion was detected. The mixture was concentrated. The crude product was purified by silica gel column chromatography to obtain the linker as a red solid (115 mg, 92.6%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.85 (td, *J* = 7.6, 1.2 Hz, 1H), 7.77 (td, *J* = 7.8, 1.2 Hz, 1H), 7.34 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.09 (dd, *J* = 9.5, 4.8 Hz, 2H), 6.94 (dd, *J* = 9.5, 2.4 Hz, 2H), 6.83 (d, *J* = 2.4 Hz, 2H), 5.31 (s, 1H), 4.31 (d, *J* = 5.3 Hz, 2H), 3.66 (dt, *J* = 14.5, 7.3 Hz, 8H), 3.53 (t, *J* = 5.3 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 12H).

MS (ESI) m/z 573: $[M+H]^+$ for $C_{30}H_{34}BrN_2O_3$.

3.10.2. PAC5-RB probe (positive probe)



PAC5-RB

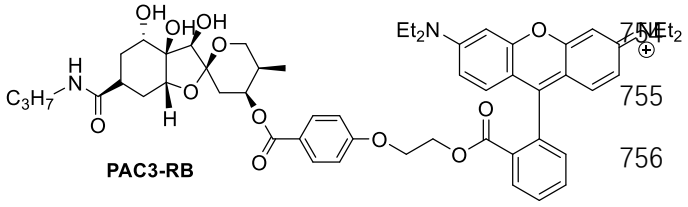
Compound **3d** (20 mg, 3.94×10^{-5} mol) was stirred with rhodamine B linker **6** (65.1 mg, 1.18×10^{-4} mol) and potassium carbonate (27.3 mg, 1.97×10^{-4} mol) in dry DMF (1.0 mL) at room

temperature until a complete conversion was detected. The mixture was concentrated. The crude product was purified by silica gel column chromatography to obtain the corresponding titled compound as a red solid (12.4 mg, 32.2%).

^{1}H NMR (600 MHz, CD_3OD) δ 8.49 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.87 (ddd, *J* = 10.5, 7.2, 1.7 Hz, 3H), 7.82 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.42 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.17 (d, *J* = 9.5 Hz, 1H), 7.14 (d, *J* = 9.5 Hz, 1H), 7.06 (dd, *J* = 9.5, 2.4 Hz, 2H), 7.00 (dd, *J* = 10.4, 2.4 Hz, 2H), 6.76 (dd, *J* = 6.9, 1.9 Hz, 2H), 3.75 – 3.72 (m, 2H), 3.69 (dt, *J* = 14.8, 7.3 Hz, 9H), 3.62 (d, *J* = 4.8 Hz, 1H), 3.03 (dd, *J* = 7.3, 3.1 Hz, 2H), 2.40 – 2.29 (m, 1H), 2.23 (dd, *J* = 14.7, 2.9 Hz, 1H), 1.77 (d, *J* = 14.9 Hz, 3H), 1.70 – 1.65 (m, 2H), 1.59 – 1.48 (m, 3H), 1.40 – 1.35 (m, 3H), 1.31 (dt, *J* = 7.1, 6.1 Hz, 18H), 1.24 – 1.19 (m, 3H), 0.91 – 0.87 (m, 5H), 0.74 (d, *J* = 6.9 Hz, 3H).

MS (ESI) m/z: 999 $[M+H]^+$ for $C_{56}H_{70}N_3O_{12}^+$.

3.10.3. PAC3-RB probe (negative probe)



PAC3-RB

Compound **3b** (6.0 mg, 1.25×10^{-5} mol) was stirred with rhodamine B linker **6** (20.7 mg, 3.75×10^{-5} mol) and potassium carbonate (8.7 mg, 6.26×10^{-4} mol) in dry DMF (0.7 mL) at room temperature until a complete conversion was detected. The mixture was concentrated. The crude product was purified by silica gel column chromatography to obtain the corresponding titled compound as a red solid (2.5 mg, 21.2%).

^{1}H NMR (600 MHz, MeOD) δ 8.49 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.87 (dd, *J* = 6.6, 5.0 Hz, 2H), 7.81 (td,, *J* = 7.9, 1.1 Hz, 1H), 7.42 (d,, *J* = 7.4 Hz, 1H),7.17 (d, *J* = 9.5 Hz, 1H), 7.14 (dd,, *J* = 9.5 Hz, 1H), 7.06 (dd, *J* = 9.5, 2.4 Hz, 2H), 7.00 (dd, *J* = 10.4, 2.4 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 3.83 (t,, *J* = 11.4 Hz, 1H), 3.73 (d, *J* = 4.9 Hz, 1H), 3.69 (dd, *J* = 14.5, 7.3 Hz, 6H), 3.62 (t,, *J* = 4.9 Hz, 1H), 3.03 – 2.98 (m, 2H), 2.38 – 2.31 (m, 1H), 2.24 (dd, *J* = 14.7, 1.5 Hz, 1H), 1.83 – 1.72 (m, 3H), 1.67 (d, *J* = 14.7 Hz, 1H),

1.59 – 1.49 (m, 2H), 1.42 – 1.36 (m, 2H), 1.31 (dt, *J* = 17.3, 8.6 Hz, 12H), 0.92 – 0.86 (m, 1H), 0.83 (t, *J* = 7.4 Hz, 3H), 0.74 (d, *J* = 6.9 Hz, 3H).

MS (ESI) *m/z*: 957 $[M+H]^+$ for $C_{54}H_{66}N_3O_{12}$.

Part 2. Pocket identification and molecular docking

The protein structure (ID: 5HO4) of HNRNPA2B1 is obtained from the PDB database (https://www.rcsb.org/). The potential binding pockets of HNRNPA2B1 were identified by Fpocket (v3) with default setting. Then the interaction of PAC5 and those pockets of HNRNPA2B1 was predicted by AutoDock Vina (v1.1.2). The structures (ID: 5HO4) of HNRNPA2B1 and PAC5 were prepared with AutoDock tools v1.5.6 as suggested in the user guide. The pocket center was set as the docking center. To allow free rotation of the compounds, the search space was set to 30 × 30 × 30 Å in each axis. The input molecular should be a pdbqt format. All other docking parameters were set to the default values. Each docking is performed by a command that contains space size and three-dimensional coordinates of the docking center. A lower energy score indicated a stronger binding affinity between the ligand and receptor. The binding pose with the lowest energy was selected as the best model for each docking test. The interaction between PAC5 and HNRNPA2B1 was displayed using the PyMOL (v1.7) program (https://pymol.org).

Table legends

Table S1. Anti-HBV activity of PAC5 Derivatives

Table S2. In *vivo* toxicity study of PAC5 in KM mouse.

Figure legends

Figure S1. Synthesis of PA derivatives

A, Synthesis of compounds **1a**-**1e**; B, Synthesis of esters **2** and amides **3**; C, Synthesis of amides **4**; D. Synthesis of biotin probes; E. Synthesis of rhodamine B probes. Reagents and conditions: (a) aq. K_2CO_3, 60 °C, 2 h; (b) aq. NaOH, 70 °C, 2 h; (c) (4-BrPh)CH_2Br, K_2CO_3, DMF, rt, overnight; (d) CH_3I, NaH, DMF, rt, overnight; (e) alcohol, EDCI, DMAP, DMF, 12h; (f) $Br(CH_2)_nF$, K_2CO_3, DMF, rt, overnight; (g) amine, EDCI, HOSu, DMAP, DMF, rt, overnight; (h) $I(CH_2)_4I$, K_2CO_3, DMF, rt, 12 h; (i) **3b** or **3d**, K_2CO_3, DMF, rt, 12 h; (j) $BrCH_2CH_2OH$, EDCI, DMAP, DMF, 45 °C, 5 h.

Figure S2. PAC5 inhibits HBV replication in *vitro* and *vivo*.

a-b, The expression level of HBcAg in the liver tissues of PAC5-treated mice infected by common HBV was examined by immunohistochemical staining (a) and western blotting (b). Scale bar = 50 μm. c, Serum ALT and AST activities in the infected mice treated with PAC5 were assessed at 10 weeks after rAAV8-1.3HBV challenge. d-e, The expression level of HBcAg in the liver tissues of PAC5-treated mice infected by drug-resistant HBV was examined by immunohistochemical staining (d) and western blotting (e). Scale bar = 50 μm.

Figure S3. Anti-HBV activity of PAC5 Probes

a, The levels of HBsAg and HBeAg in supernatant of HepG2. 2.15 cells cultured with PAC5 Probes were measured by CMIA. b, The expression level of HBcAg in the HepG2. 2.15 cells culture with PAC5 probe was examined by western blotting. c The levels of HBsAg and HBeAg in supernatant of HepG2.2.2.15 cells with blank control and negative control were measured by CMIA at indicated time points. d. The levels of HBsAg and HBeAg in supernatant of HepG2 cells transfected PBSk-rtM2041 cells cultured with PAC5 probe, NC and BC were measured by CMIA.

Figure S4. Proteome characteristics of HepG2.2.15 cells treated with the compound PAC5.

a, The bar graph showed the number of identified proteins only in negative control (NC) or PAC5 group, or both groups, respectively. b, The enriched GO biological processes for the proteins only in PAC5 or negative control (NC) group, respectively. c, The enriched KEGG pathways for the proteins only in PAC5 or negative control (NC) group, respectively.

Figure S5. Anti-HBV activity of Fluorescent PAC5 Probes

a, The levels of HBsAg and HBeAg in supernatant of HepG2 cells transfected PBSk-rtM2041 cells cultured with fluorescent PAC5 Probe and NC were measured by CMIA.

Figure S6. hnRNPA2B1 did not be activated by Fluorescent PAC3 Probe.

a, HepaG2.2.15 cells were treated with PAC3 (10 μM) for indicated time points. PAC3, an inactive analogue of PAC5, was taken as negative control. The intracellular localization of hnRNPA2B1 (green) was determined by confocal microscopy. The nuclei are stained with DAPI (blue). Scale bar = 5 μm.

Figure S7. Pocket identification, molecular docking and the binding of PAC to pocket 0 and 4

a, The potential pockets identified by Fpocket were distributed at the structure of HNRNPA2B. Pockets were shown as mesh with different color. Structure of HNRNPA2B was shown as cartoon. b, the boxplot showed the docking score of PAC5 to different pockets. The pocket 0 and pocket 4 are highlighted as relative favorable pocket for PAC5. c, (Top panel) the overview of Compound PAC5 binding to the pocket 3 and 4, respectively. (Bottom panel) Close-up view of the binding of compound PAC5 to the pocket 3 and 4 of HNRNPA2B, respectively. The side chains of the residues involved in binding are labeled and shown as sticks. The compound PAC5 was shown as magenta sticks. Secondary structural elements were colored from blue (N-terminus) to red (C-terminus). The residues involved point mutation experiment were marked with arrows. The pocket 0 and 4 were highlighted with red circles.

Figure S8 Transcriptional characteristics of HepG2.2.15 cells treated with the compound PAC5

a, Principal component analysis (PCA) showing the distribution of control, negative control (NC) and PAC5-treated samples based overall of the gene expression. b,

Heatmap showing the gene expression of negative control (NC) and PAC5-treated samples. The expression values (TPM) were log2 transformed. A gradient of blue, white, and red indicates low to high expression levels. c, The volcano plot displaying the differential expressed genes in HepG2.2.15 cell treated with the compound PAC5. The dotted line indicates the P value of 0.05, a threshold to identify differential expressed genes (DEG). d-e Bubble chart showing the enrichment result of biological process obtained by Gene set enrichment analysis (GSEA). In d, the top 20 most affected biological processes were shown with activated and suppressed states. In e, all "interferon" related biological processes were shown. Normalized enrichment score (NES) was shown with a gradient of blue and red. The size of bubble corresponds to the significance of biological process. The dotted line indicates the P value of 0.05 used to determine the significance of enrichment.

Figure S9 PAC5 did not enhance the secretion of the proinflammatory cytokines

a-d, After 2 weeks of intravenous injection of rAAV8-1.3HBV ayw (1×10^{11} Vg of each/mouse), C57BL/6 mice were assigned to 5 groups (n = 6 per group) and gavaged daily with indicated compound. The mice were stopped intragastric administration at 8 weeks and sacrificed at 10 weeks. The serum TNF-α (a), IL-6 (b), IL-1β (c), and IL-10 (d) levels were monitored by ELISA. *$p < 0.05$,**$p < 0.01$, compared to the vehicle group. e-h, C57BL/6 mice were hydrodynamically injected with 10 μg of PBSK-rtM204I plasmid through the tail vein. Two weeks later, the mice were assigned to 3 groups (n = 3 per group) and gavaged daily with the different compounds as indicated. The gavage was stopped at 8 weeks, and the mice were sacrificed at 10 weeks. The serum TNF-α (e), IL-6 (f), IL-1β (g), and IL-10 (h) levels were monitored by ELISA. *$p < 0.05$,**$p < 0.01$.

Figure S10 NMR and MS spectra of PA, PAC5, PAC5 derivatives and Probes

10-1, ^{1}H NMR spectrum of PA; 10-2. ^{13}C NMR and DEPT spectra of PA; 10-3. ESI spectrum of PA; 10-4. Figure 4. ^{1}H NMR spectrum of compound **1a;** 10-5. ^{13}C NMR spectrum of compound **1a**; 10-6. HSQC spectrum of compound **1a**; 10-7. HMBC spectrum of compound **1a**; 10-8. ROESY spectrum of compound **1a**; 10-9. ESI

spectrum of compound **1a**; 10-10. ^{1}H NMR spectrum of compound **1b**; 10-10. ESI spectrum of compound **1b**; 10-12. ^{1}H NMR spectrum of compound **1c**; 10-13. ESI spectrum of compound **1c**; 10-14. ^{1}H NMR spectrum of compound **1d**; 10-15. ESI spectrum of compound **1d;** 10-16. ^{1}H NMR spectrum of compound **1e;** 10-17. ESI spectrum of compound **1e;** 10-8. ^{1}H NMR spectrum of compound **2a;** 10-19. ESI spectrum of compound **2a;** 10-20. ^{1}H NMR spectrum of compound **2b;** 10- 21. ESI spectrum of compound **2b;** 10-22. ^{1}H NMR spectrum of compound **2c;** 10-23. ESI spectrum of compound **2c;** 10-24. ^{1}H NMR spectrum of compound **2d;** 10-25. ESI spectrum of compound **2d;** 10-26. ^{1}H NMR spectrum of compound **2e;** 10-27. ESI spectrum of compound **2e;** 10-28. ^{1}H NMR spectrum of compound **2f;** 10-29. ESI spectrum of compound **2f;** 10-30. ^{1}H NMR spectrum of compound **2g;** 10-31. ESI spectrum of compound **2g;** 10-32. ^{1}H NMR spectrum of compound **3a;** 10-33. ESI spectrum of compound **3a;** 10-34. ^{1}H NMR spectrum of compound **3b;** 10-35. ESI spectrum of compound **3b;** 10-36. ^{1}H NMR spectrum of compound **3c;** 10-37. ESI spectrum of compound **3c;** 10-38. ^{1}H NMR spectrum of compound **3d;** 10-39. ^{13}C NMR spectrum of compound **3d;** 10-40. HSQC spectrum of compound **3d;** 10-41. HMBC spectrum of compound **3d;** 10-42. ROESY spectrum of compound **3d;** 10-3. HRESI spectrum of compound **3d;** 10-44. ESI spectrum of compound **3d;** 10-45.CD spectrum of compound **3d;** 10-46. UV spectrum of compound **3d;** 10-47. ^{1}H NMR spectrum of compound **3e;** 10-48. ESI spectrum of compound **3e;** 10-49. ^{1}H NMR spectrum of compound **3f;** 10-50. ESI spectrum of compound **3f;** 10-51. ^{1}H NMR spectrum of compound **3g;** 10-52. ESI spectrum of compound **3g;** 10-53. ^{1}H NMR spectrum of compound **3h;** 10-54. ESI spectrum of compound **3h;** 10-55. ^{1}H NMR spectrum of compound **3i;** 10-56. ESI spectrum of compound **3i;** 10-57. ^{1}H NMR spectrum of compound **3j;** 10-58. ESI spectrum of compound **3j;** 10-59. ^{1}H NMR spectrum of compound **4a;** 10-60. ESI spectrum of compound **4a;** 10-61. ^{1}H NMR spectrum of compound **4b;** 10-62. ESI spectrum of compound **4b;** 10-63. ^{1}H NMR spectrum of compound **4c;** 10-64. ESI spectrum of compound **4;** 10-65. ^{1}H NMR spectrum of compound **4d;** 10-66. ESI spectrum of compound **4d;** 10-67. ^{1}H NMR spectrum of compound **4e;** 10-68. ESI spectrum of compound **4e;** 10-69. ^{1}H NMR

spectrum of compound **4f;** 10-70. ESI spectrum of compound **4f;** 10-71. ^{1}H NMR spectrum of compound **4g;** 10-72. ESI spectrum of compound **4g;** 10-73. ^{1}H NMR spectrum of compound **4h;** 10-74. ESI spectrum of compound **4h;** 10-75. ^{1}H NMR spectrum of compound **4i;** 10-76. ESI spectrum of compound **4i;** 10-77. ^{1}H NMR spectrum of compound **4j;** 10-78. ESI spectrum of compound **4j;** 10-79. ^{1}H NMR spectrum of compound **4k;** 10-80. ESI spectrum of **compound 4**; 10-81. ^{1}H NMR spectrum of compound **4l**; 10-82. ESI spectrum of compound **4l**; 10-83. ^{1}H NMR spectrum of compound **4m;** 10-84. ESI spectrum of compound **4m**; 10-85. ^{1}H NMR spectrum of compound **4n**; 10-86. ESI spectrum of compound **4n**; 10-87. ^{1}H NMR spectrum of compound **4o**; 10-88. ESI spectrum of compound **4o**; 10-89. ^{1}H NMR spectrum of compound **4p**; 10-90. ESI spectrum of compound **4p**; 10-91. ^{1}H NMR spectrum of blank control of ABPP Probes; 10-92. ESI spectrum of blank control of ABPP Probes; 10-93. ^{1}H NMR spectrum of positive probe of ABPP Probes; 10-94.ESI spectrum of positive probe of ABPP Probes (PAC5); 10-95. ^{1}H NMR spectrum of negative probe of ABPP Probes (PAC3); 10-96.ESI spectrum of negative probe of ABPP Probes; 10-97. ^{1}H NMR spectrum of blank control of fluorescence Probes; 10-98. ^{1}H NMR spectrum of positive probe of fluorescence Probes (PAC5); 10-99. ^{1}H NMR spectrum of negative probe of fluorescence Probes (PAC3).

Figure S1

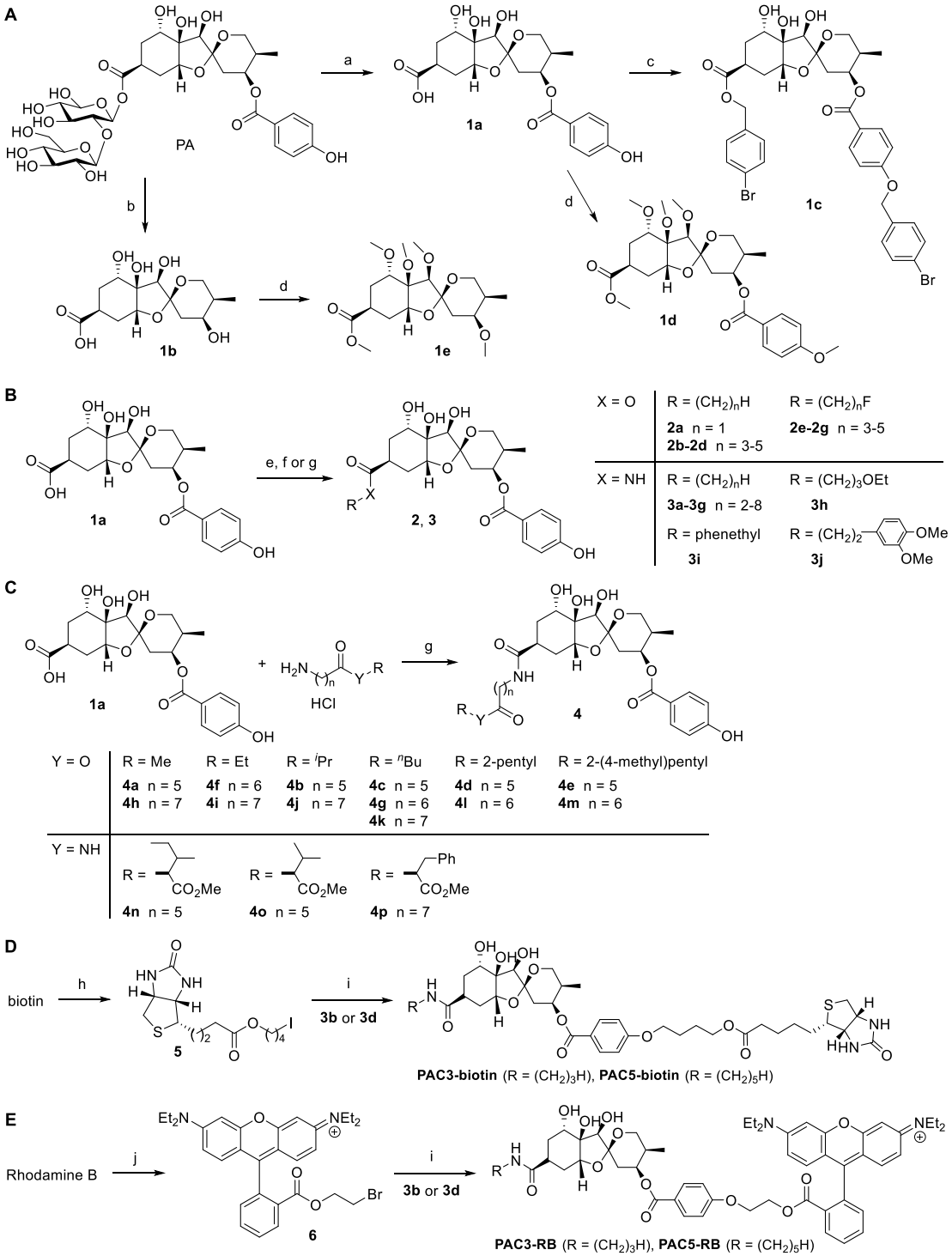

A
PA
1a
1b
1c
1d
1e
B
X = O
R = (CH2)nH
2a n = 1
2b-2d n = 3-5
R = (CH2)nF
2e-2g n = 3-5
X = NH
R = (CH2)nH
3a-3g n = 2-8
R = (CH2)3OEt
3h
R = phenethyl
3i
R = (CH2)2
OMe
OMe
3j
2, 3
C
HCl
4
Y = O
R = Me
4a n = 5
4h n = 7
R = Et
4f n = 6
4i n = 7
R = iPr
4b n = 5
4j n = 7
R = nBu
4c n = 5
4g n = 6
4k n = 7
R = 2-pentyl
4d n = 5
4l n = 6
R = 2-(4-methyl)pentyl
4e n = 5
4m n = 6
Y = NH
4n n = 5
4o n = 5
4p n = 7
D
biotin
5
3b or 3d
PAC3-biotin (R = (CH2)3H), PAC5-biotin (R = (CH2)5H)
E
Rhodamine B
6
3b or 3d
PAC3-RB (R = (CH2)3H), PAC5-RB (R = (CH2)5H)

Figure S2

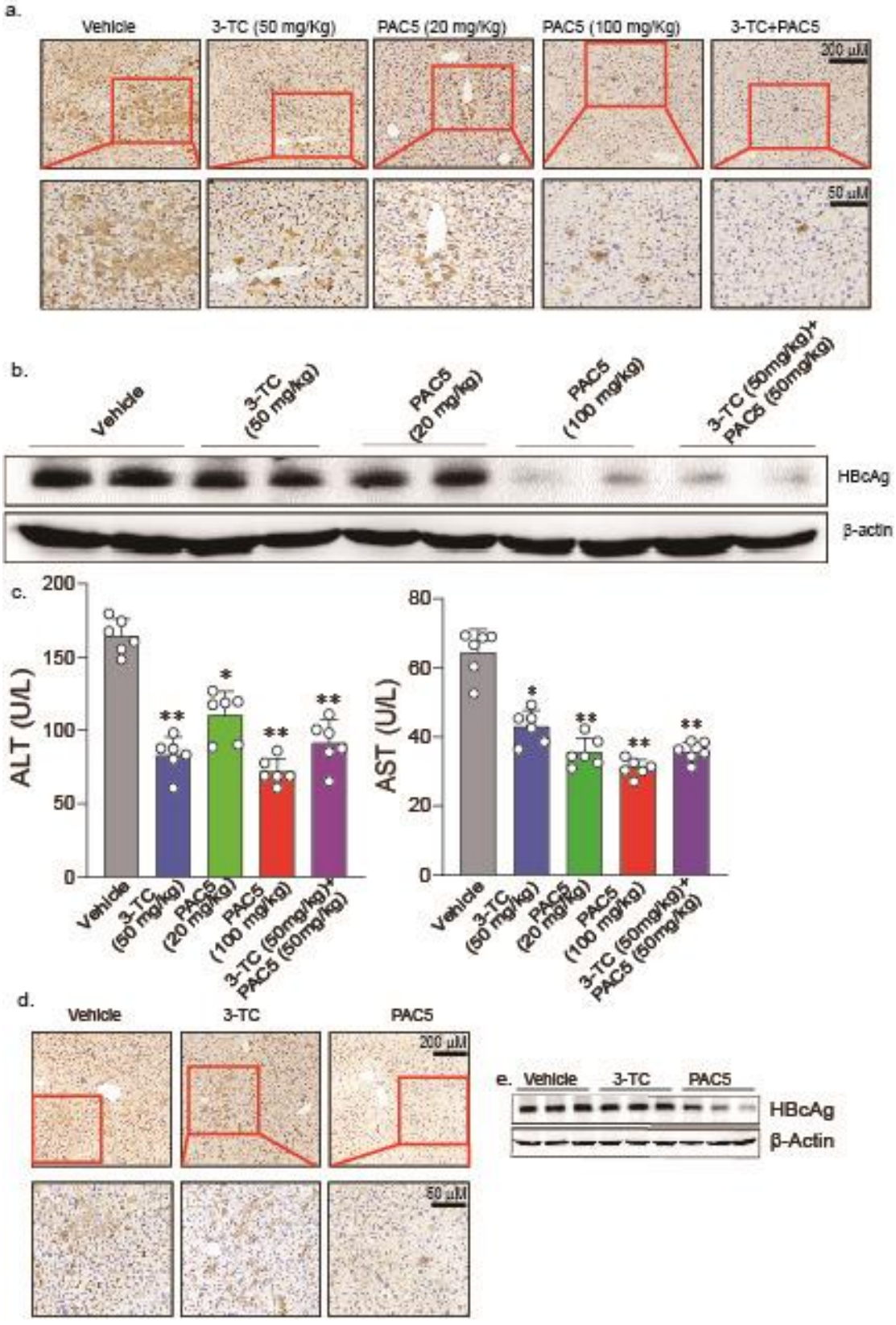

a.
Vehicle
3-TC (50 mg/Kg)
PAC5 (20 mg/Kg)
PAC5 (100 mg/Kg)
3-TC+PAC5
200 μM
50 μM
b.
Vehicle
3-TC (50 mg/kg)
PAC5 (20 mg/kg)
PAC5 (100 mg/kg)
3-TC (50mg/kg)+ PAC5 (50mg/kg)
HBcAg
β-actin
c.
ALT (U/L)
AST (U/L)
Vehicle
3-TC (50 mg/kg)
PAC5 (20 mg/kg)
PAC5 (100 mg/kg)
3-TC (50mg/kg)+ PAC5 (50mg/kg)
d.
Vehicle
3-TC
PAC5
200 μM
50 μM
e.
Vehicle
3-TC
PAC5
HBcAg
β-Actin

Figure S3

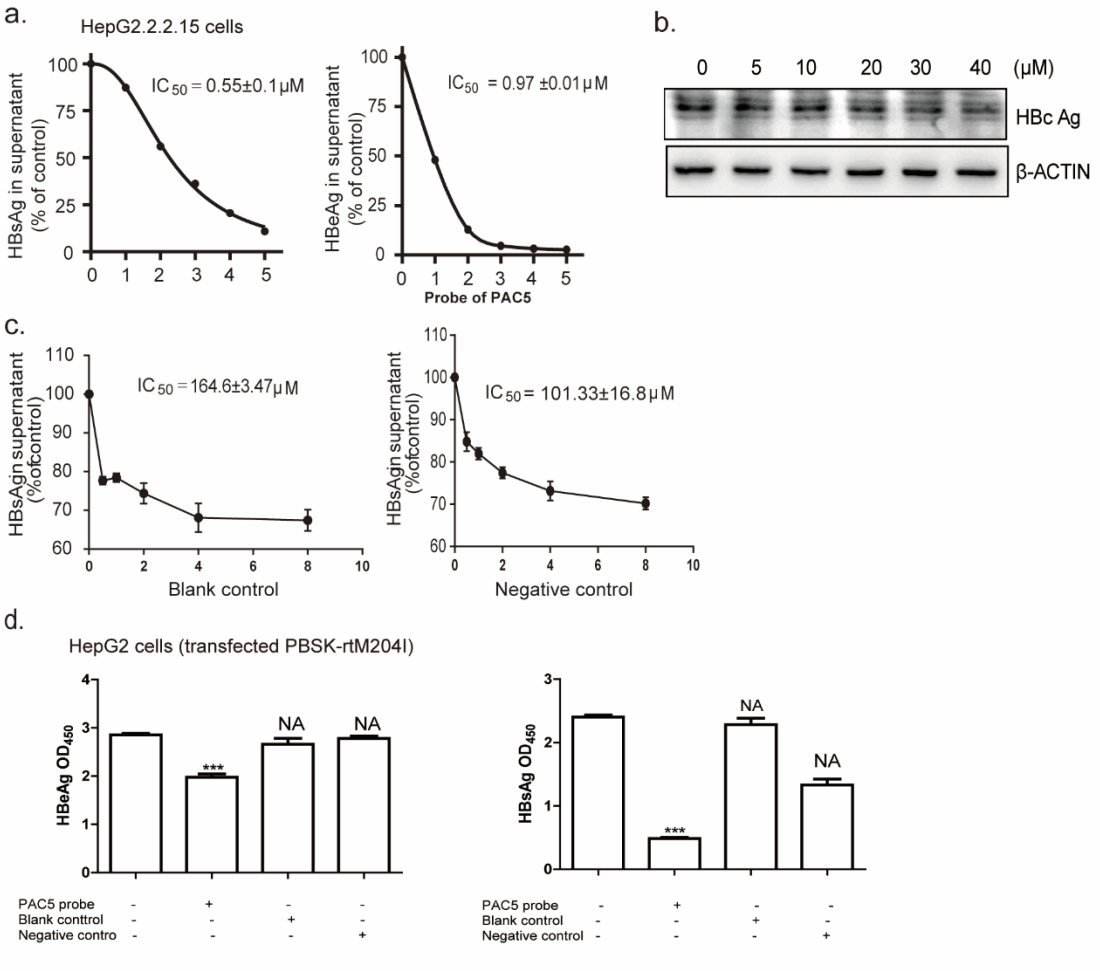
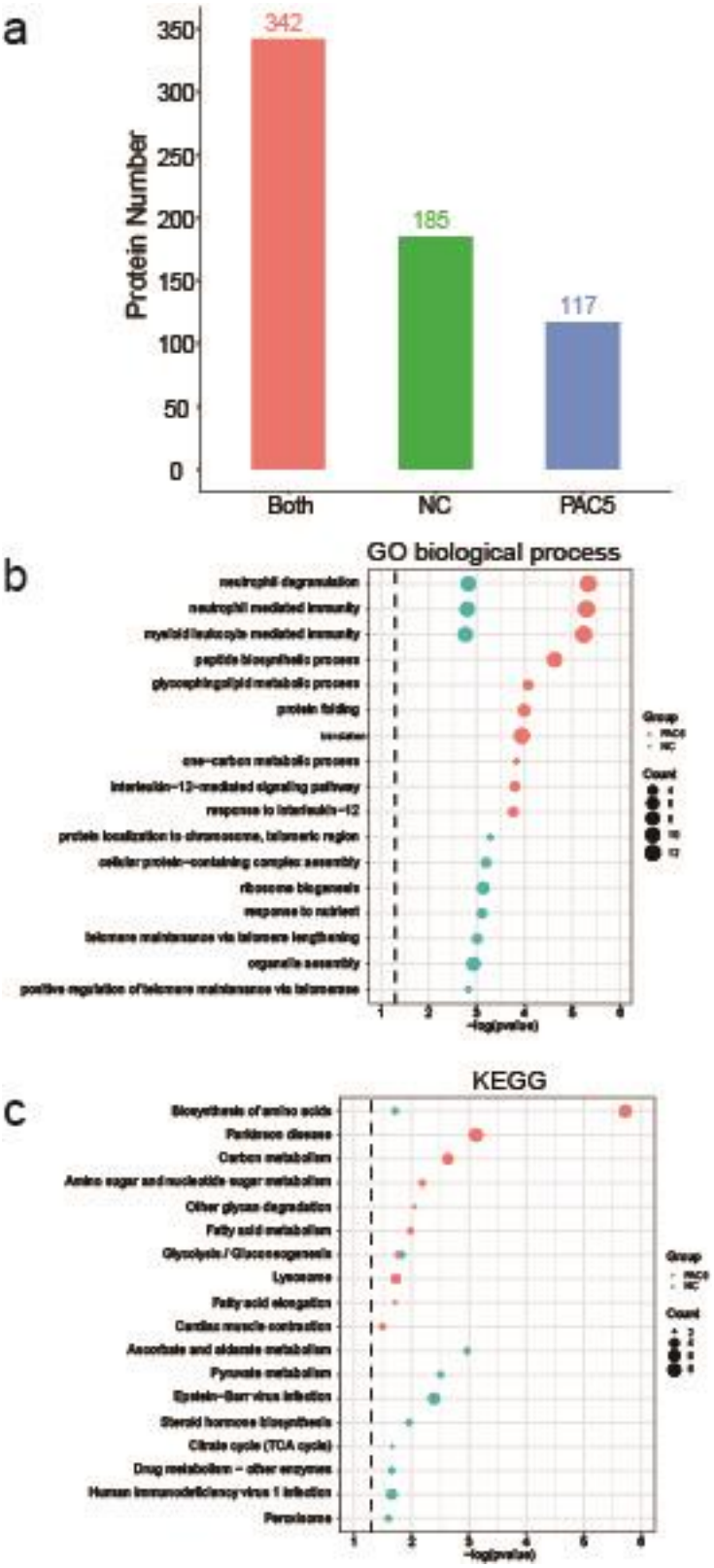
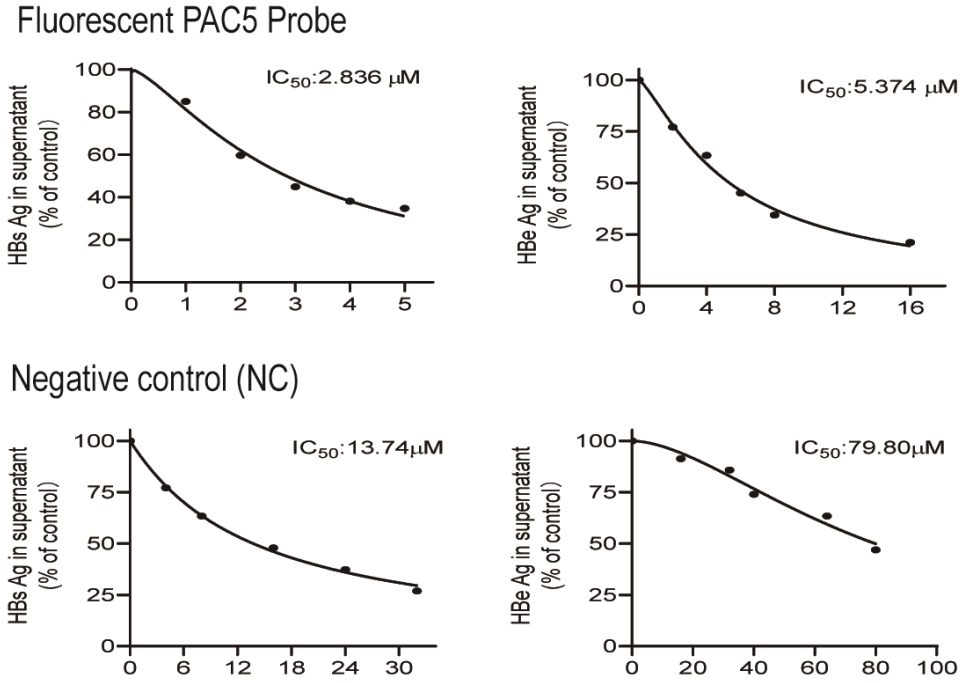

a.
HepG2.2.2.15 cells
HBsAg in supernatant (% of control)
IC50 = 0.55±0.1 μM
HBeAg in supernatant (% of control)
IC50 = 0.97 ±0.01 μM
Probe of PAC5
b.
0 5 10 20 30 40 (μM)
HBc Ag
β-ACTIN
c.
HBsAgin supernatant (%ofcontrol)
IC50 = 164.6±3.47 μM
Blank control
IC50 = 101.33±16.8 μM
Negative control
d.
HepG2 cells (transfected PBSK-rtM204I)
HBeAg OD450
HBsAg OD450
NA
***
PAC5 probe
Blank conttrol
Negative contro
Blank control
Negative control

Figure S4


a
Protein Number
342
185
117
Both
NC
PAC5
b
GO biological process
neutrophil degranulation
neutrophil mediated immunity
myeloid leukocyte mediated immunity
peptide biosynthetic process
glycosphingolipid metabolic process
protein folding
one-carbon metabolic process
interleukin-12-mediated signaling pathway
response to interleukin-12
ribosome biogenesis
response to nutrient
organelle assembly
Group
Count
-log(pvalue)
c
KEGG
Biosynthesis of amino acids
Parkinson disease
Carbon metabolism
Amino sugar and nucleotide sugar metabolism
Other glycan degradation
Fatty acid metabolism
Glycolysis / Gluconeogenesis
Lysosome
Fatty acid elongation
Cardiac muscle contraction
Ascorbate and aldarate metabolism
Pyruvate metabolism
Epstein-Barr virus infection
Steroid hormone biosynthesis
Citrate cycle (TCA cycle)
Drug metabolism - other enzymes
Peroxisome
Group
Count
-log(pvalue)

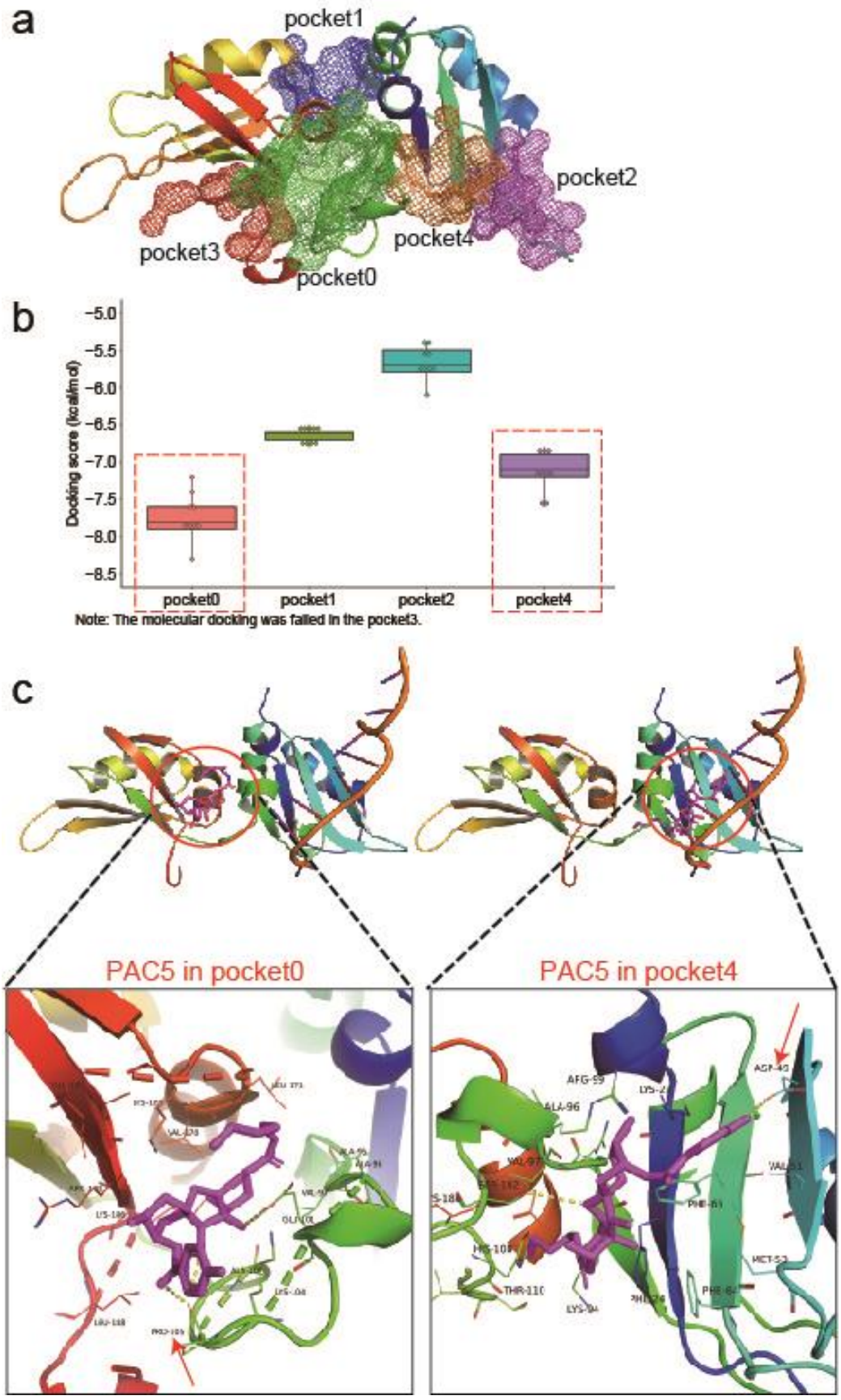
939 **Figure S5**



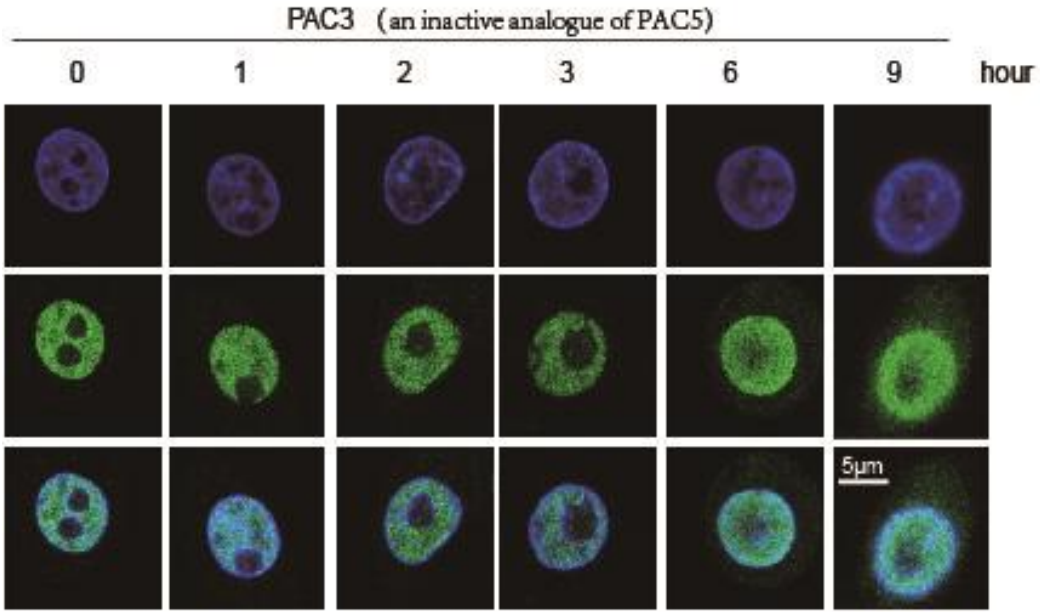
940

941

Figure S6


a
pocket1
pocket2
pocket3
pocket4
pocket0
b
Docking score (kcal/mol)
−5.0
−5.5
−6.0
−6.5
−7.0
−7.5
−8.0
−8.5
pocket0
pocket1
pocket2
pocket4
Note: The molecular docking was failed in the pocket3.
c
PAC5 in pocket0
PAC5 in pocket4

945 **Figure S7**



946

947

Figure S8

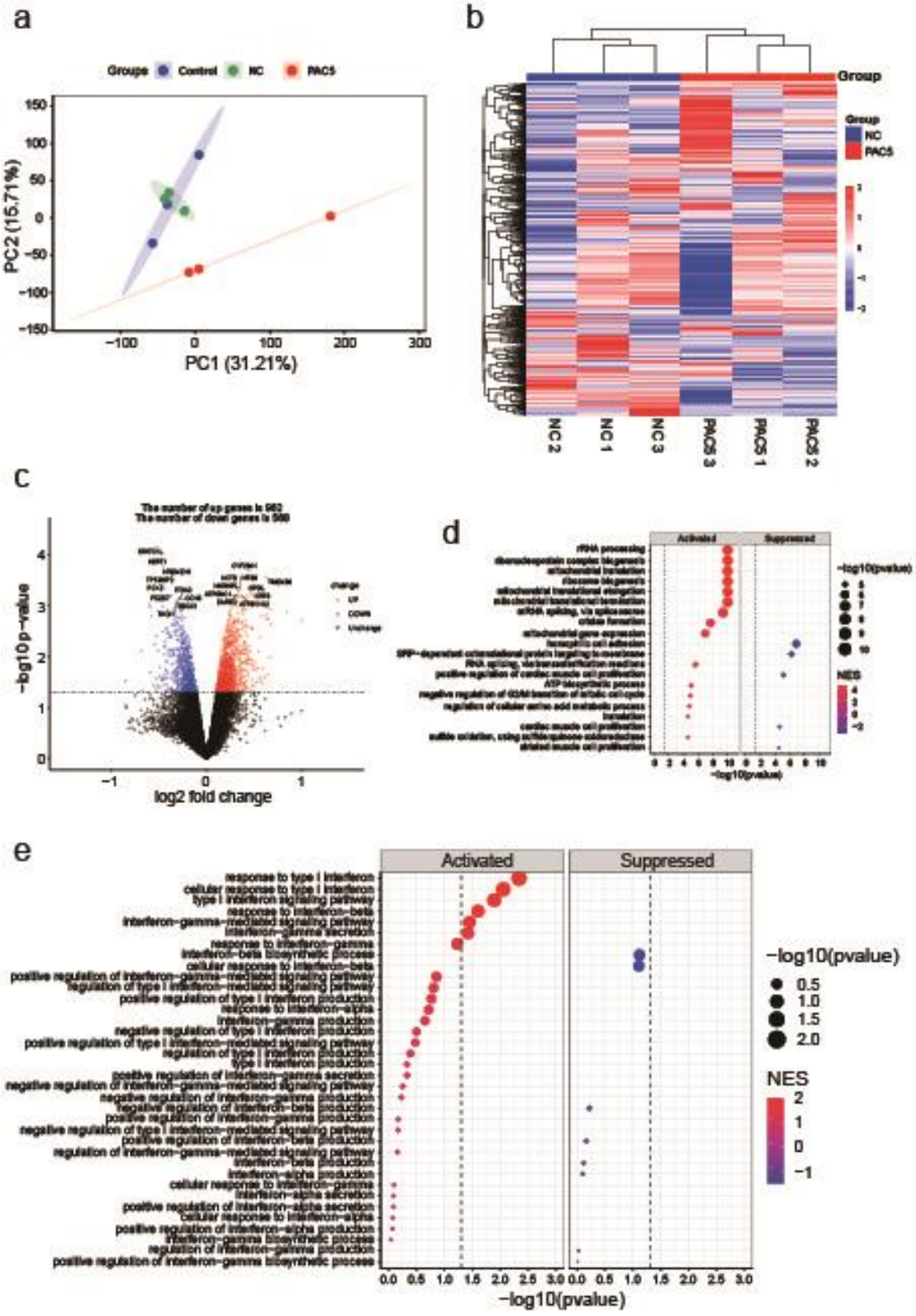

a
Groups Control NC PAC5
PC2 (15.71%)
PC1 (31.21%)
b
Group
NC2
NC1
NC3
PAC3
PAC1
PAC2
c
−log10 p−value
log2 fold change
d
Activated
Suppressed
−log10(pvalue)
NES
e
Activated
Suppressed
response to type I interferon
cellular response to type I interferon
type I interferon signaling pathway
response to interferon−beta
interferon−gamma−mediated signaling pathway
interferon−gamma secretion
response to interferon−gamma
interferon−beta biosynthetic process
cellular response to interferon−beta
positive regulation of interferon−gamma−mediated signaling pathway
regulation of type I interferon−mediated signaling pathway
positive regulation of type I interferon production
response to interferon−alpha
interferon−gamma production
negative regulation of type I interferon production
positive regulation of type I interferon−mediated signaling pathway
regulation of type I interferon production
type I interferon production
positive regulation of interferon−gamma secretion
negative regulation of interferon−gamma−mediated signaling pathway
negative regulation of interferon−gamma production
negative regulation of interferon−beta production
positive regulation of interferon−gamma production
negative regulation of type I interferon−mediated signaling pathway
positive regulation of interferon−beta production
regulation of interferon−gamma−mediated signaling pathway
interferon−beta production
interferon−alpha production
cellular response to interferon−gamma
interferon−alpha secretion
positive regulation of interferon−alpha secretion
cellular response to interferon−alpha
positive regulation of interferon−alpha production
interferon−gamma biosynthetic process
regulation of interferon−gamma production
positive regulation of interferon−gamma biosynthetic process
−log10(pvalue)
NES

Figure S9

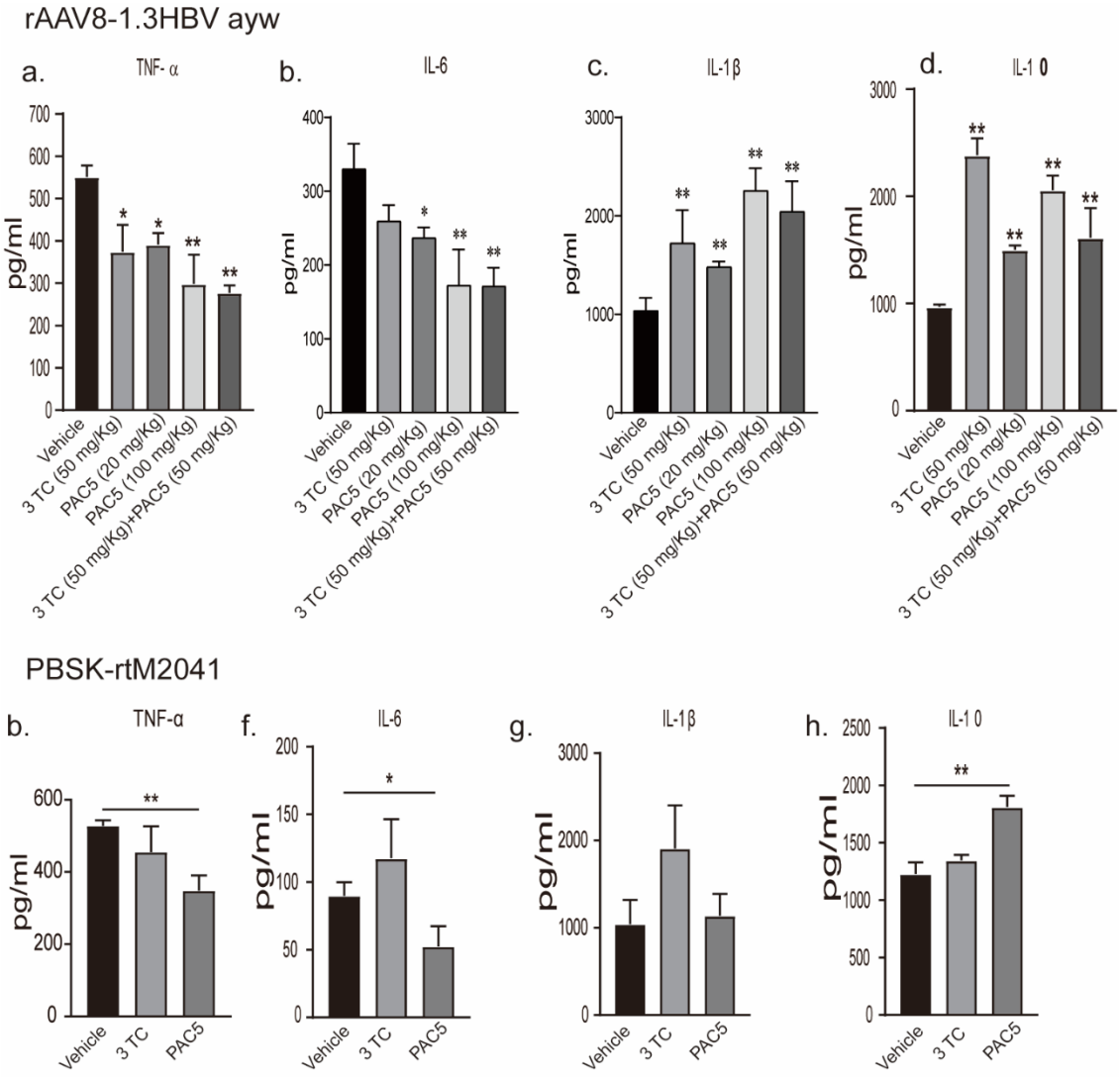
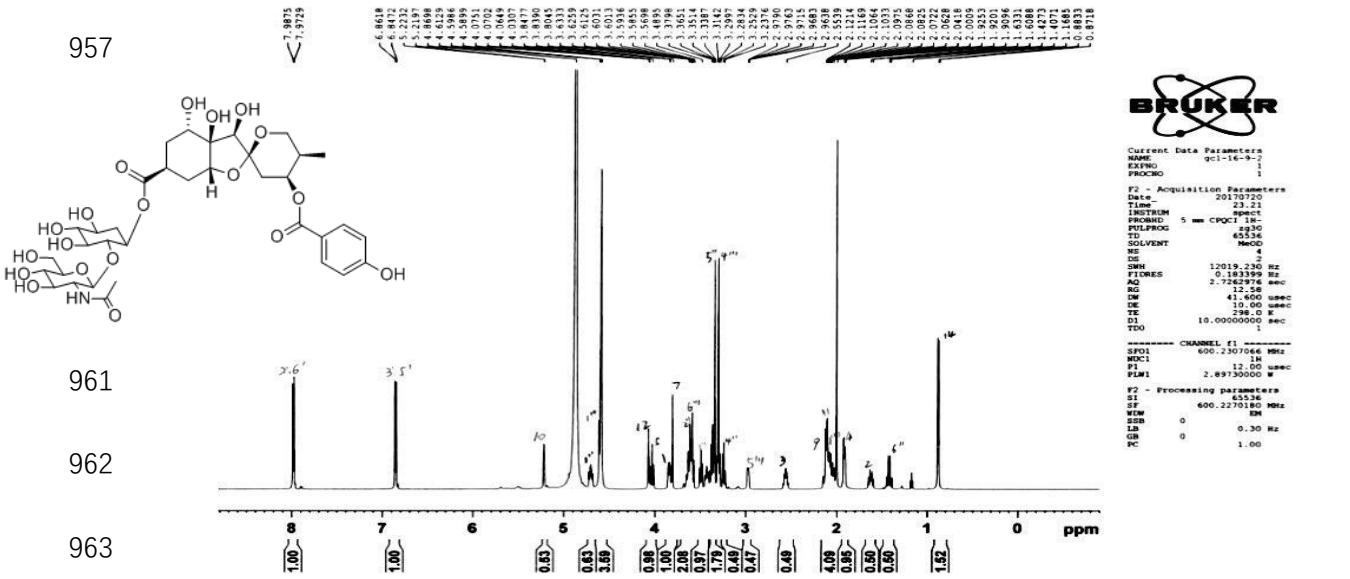
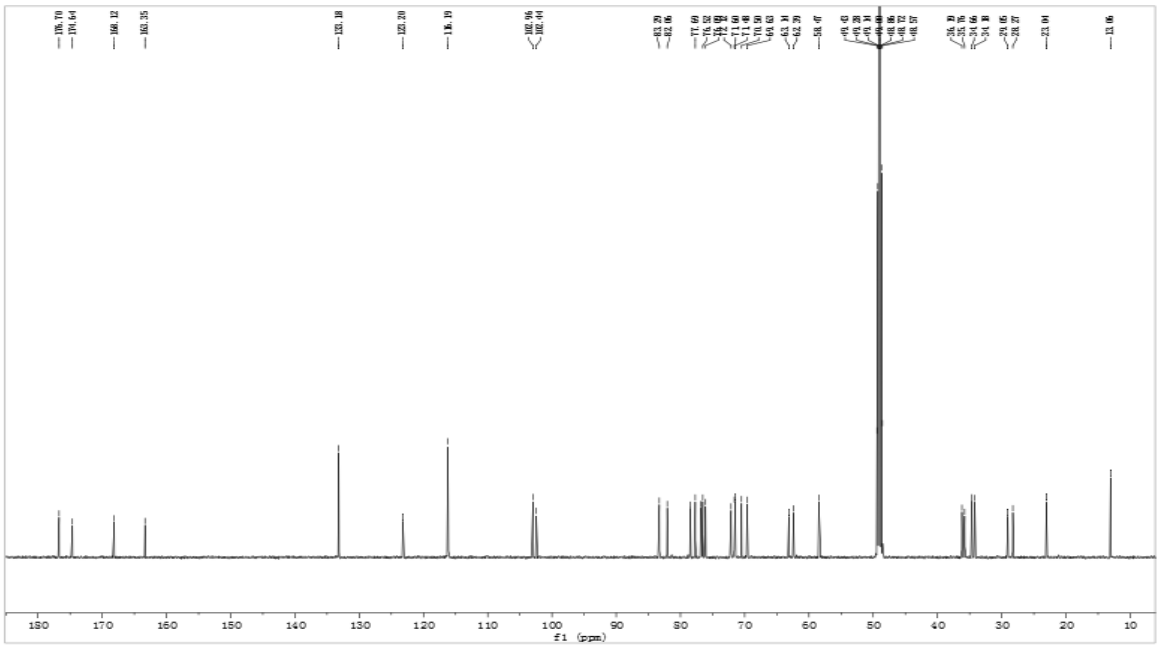

rAAV8-1.3HBV ayw
a.
TNF- α
b.
IL-6
c.
IL-1β
d.
IL-1 0
pg/ml
Vehicle
3 TC (50 mg/Kg)
PAC5 (20 mg/Kg)
PAC5 (100 mg/Kg)
3 TC (50 mg/Kg)+PAC5 (50 mg/Kg)
PBSK-rtM2041
b.
TNF-α
f.
IL-6
g.
IL-1β
h.
IL-1 0
Vehicle
3 TC
PAC5

Figure S10

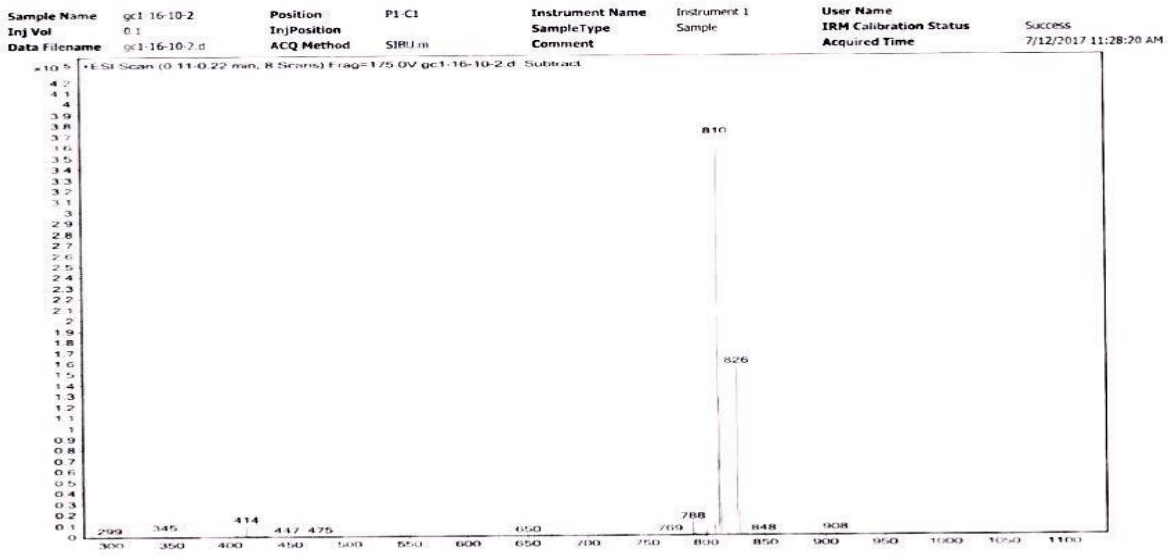
10-1. ^{1}H NMR spectrum of PA



10-2. ^{13}C NMR and DEPT spectra of PA



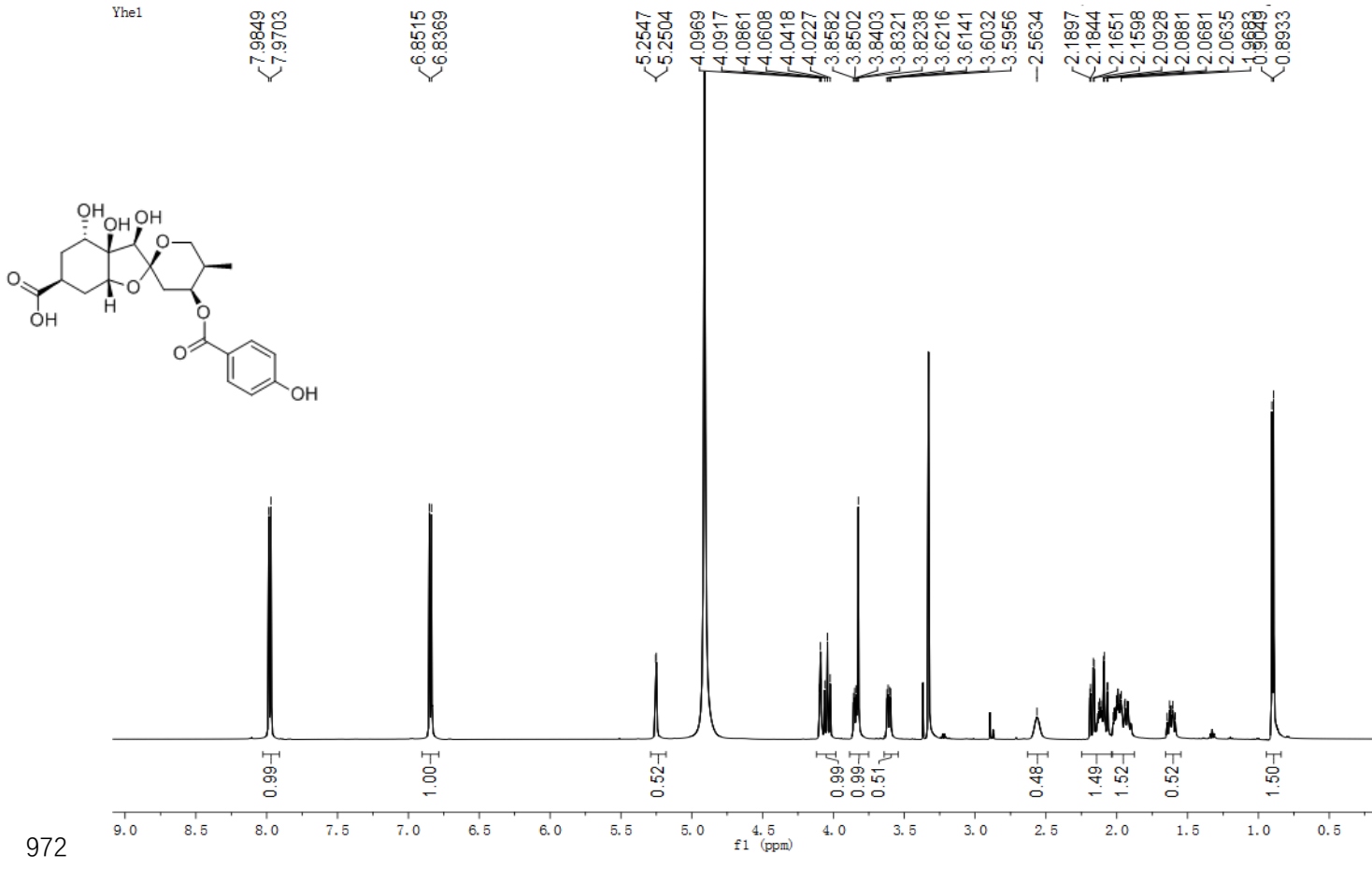
968 10-3. ESI spectrum of PA



969

970

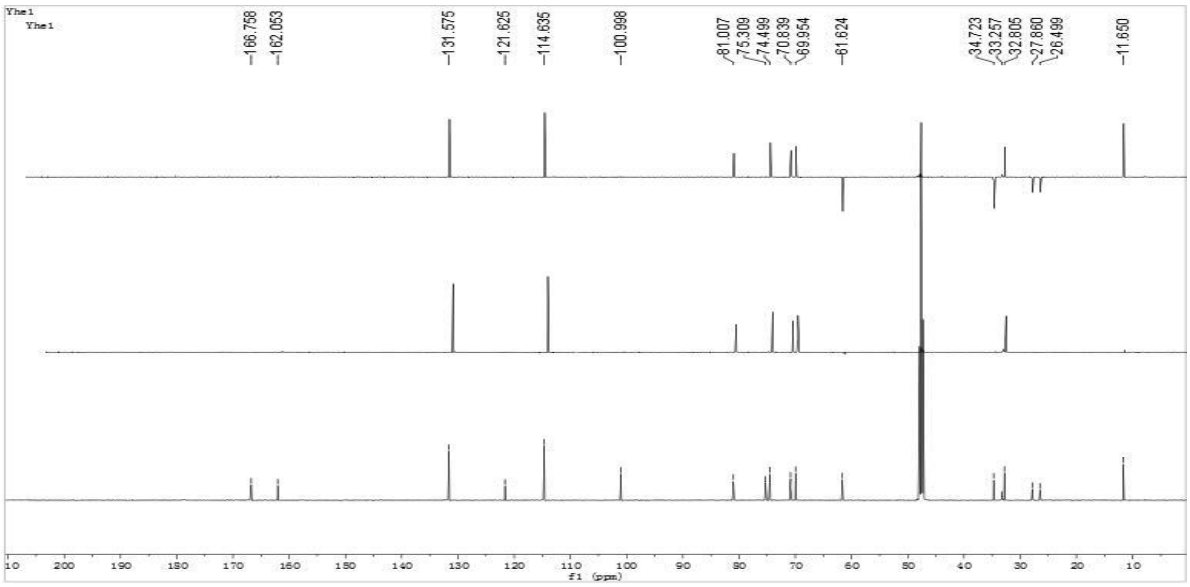
971 10- 4. ^{1}H NMR spectrum of compound **1a**



972

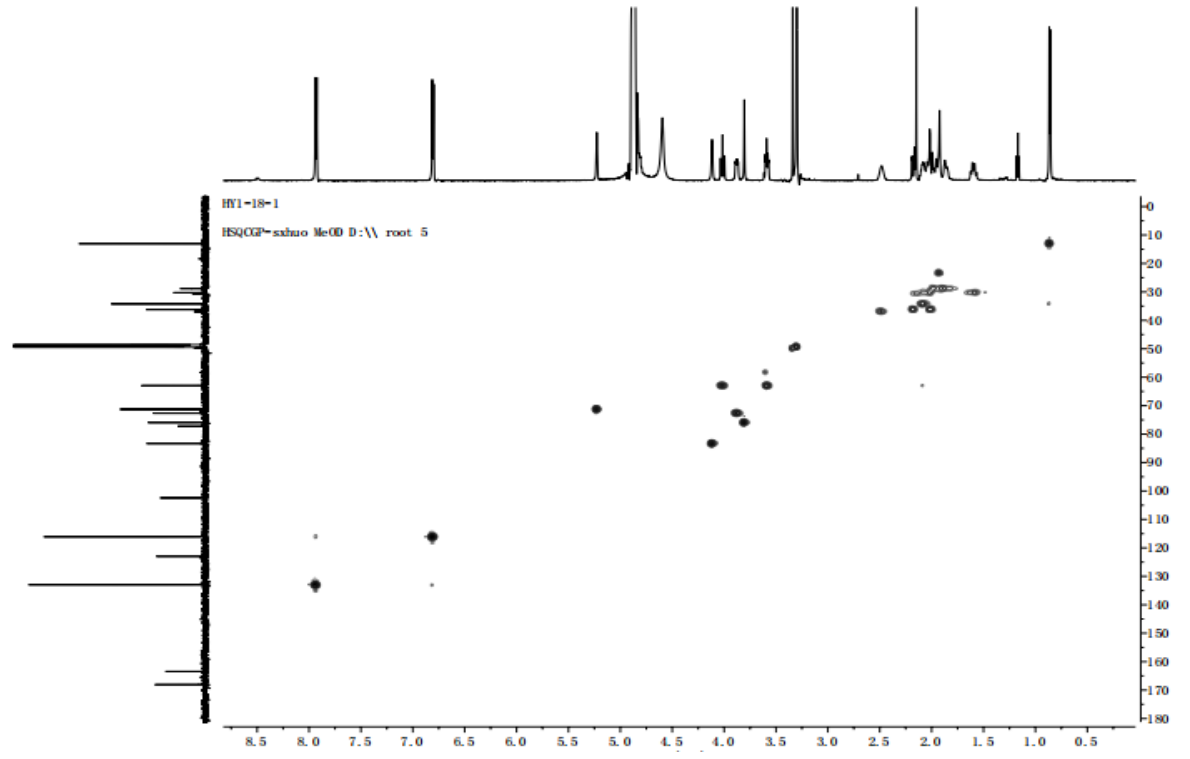
973

974 10- 5. ^{13}C NMR and DEPT spectra of **1a**



975

976 10- 6. HSQC spectrum of compound **1a**

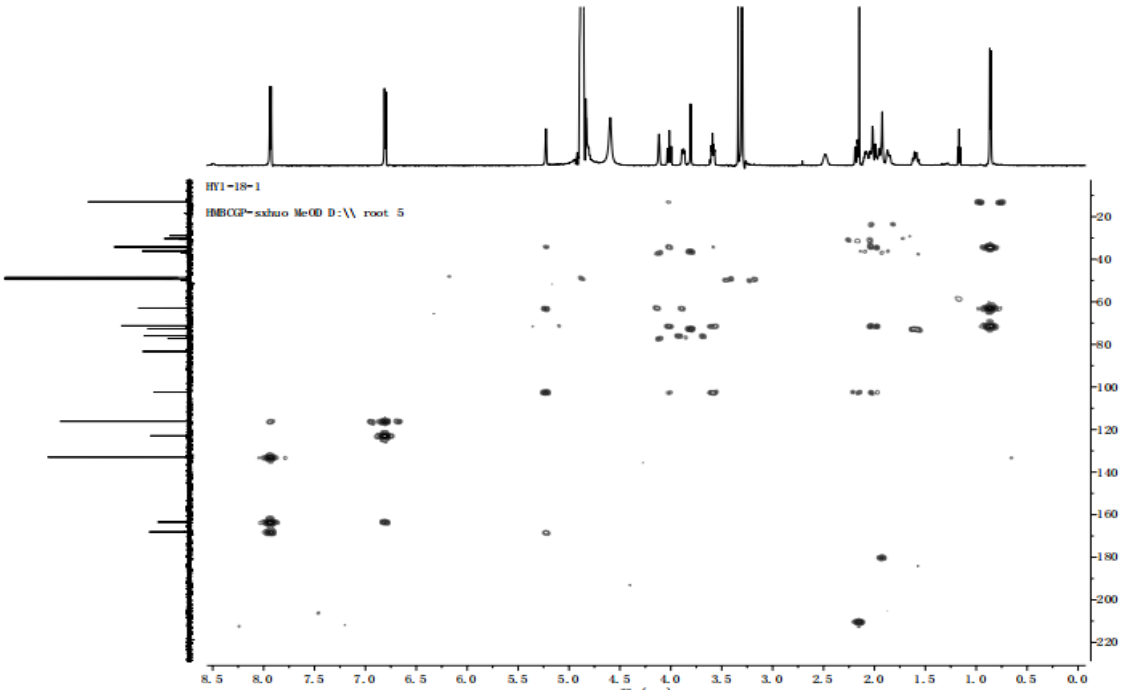


977

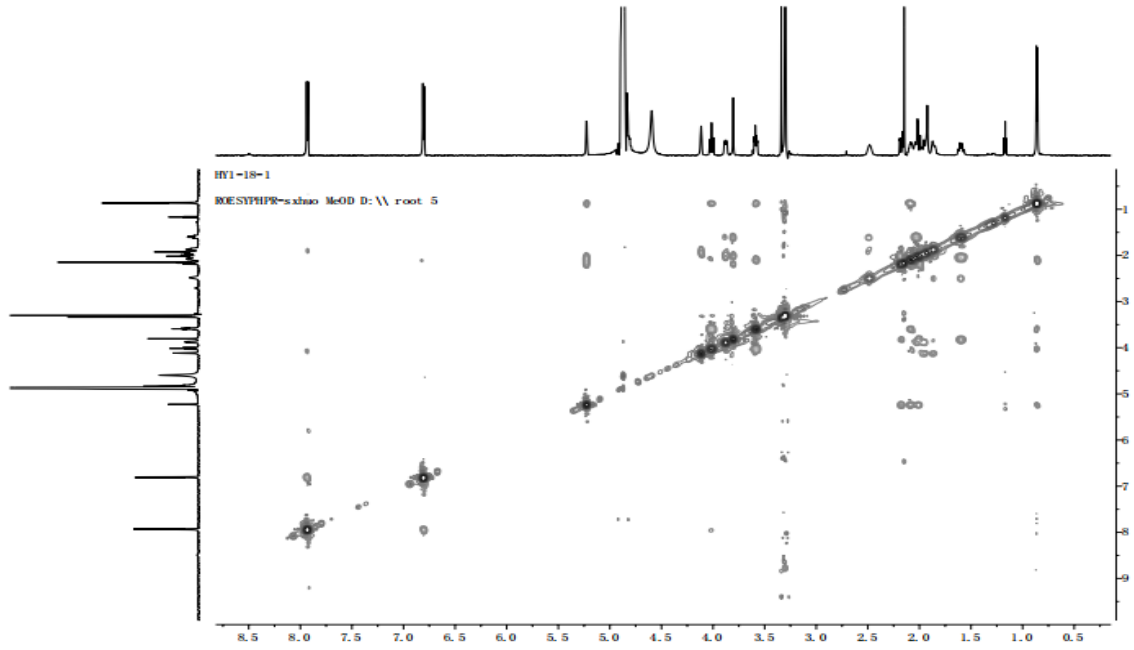
978

979

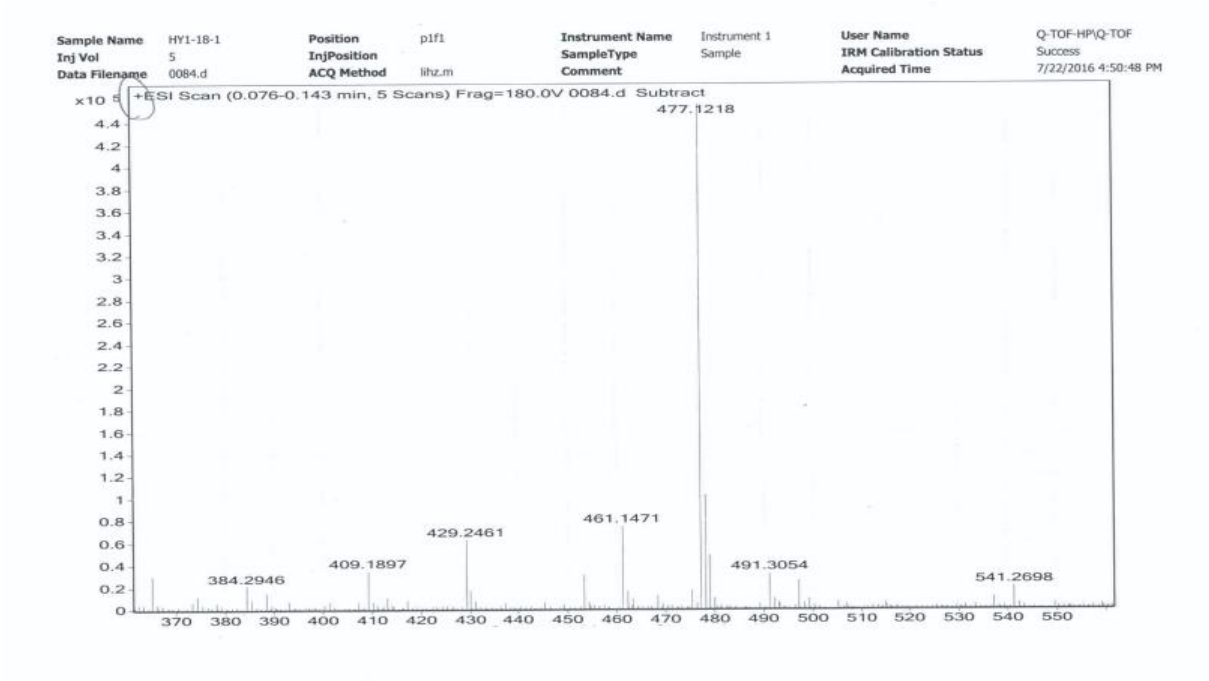
10- 7. HMBC spectrum of compound **1a**



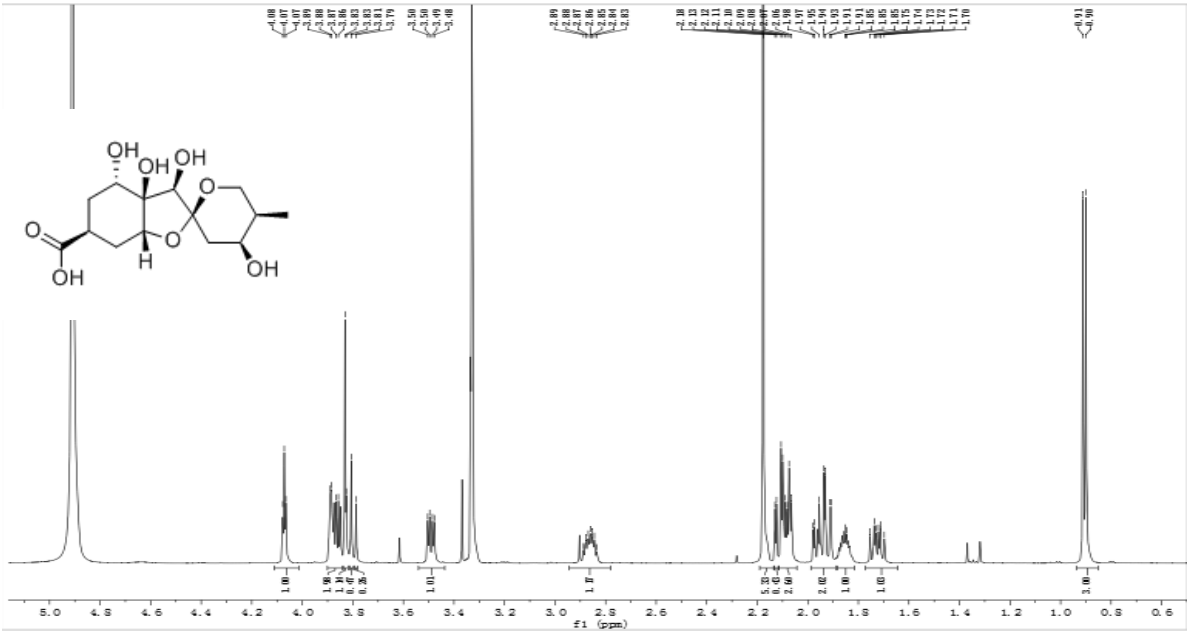
10- 8. ROESY spectrum of compound **1a**



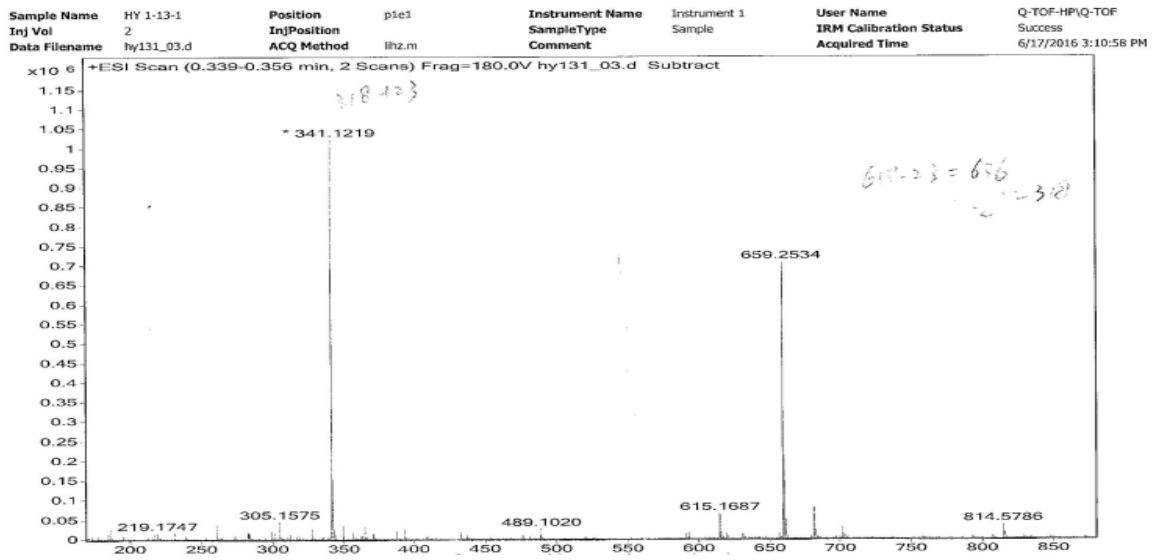
10- 9. ESI spectrum of compound **1a**



10- 10. ^{1}H NMR spectrum of compound 1b



993 10- 10. ESI spectrum of compound 1b

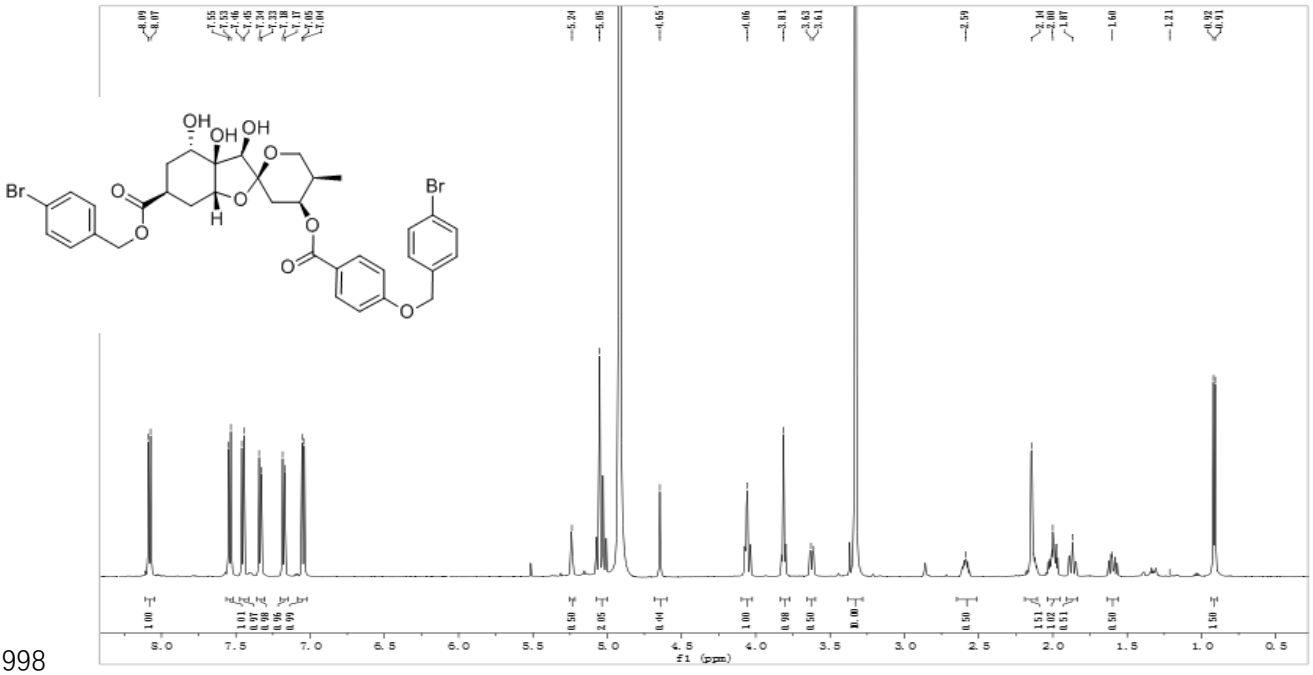


994

995

996

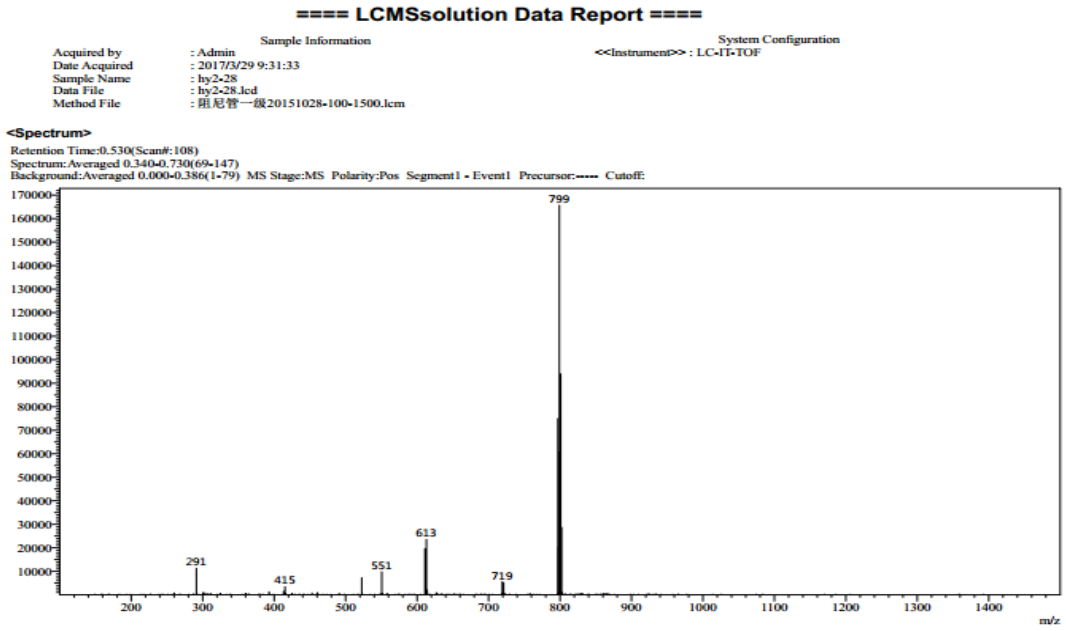
997 10- 12. ^{1}H NMR spectrum of compound **1c**



998

999

1000 10- 13. ESI spectrum of compound **1c**

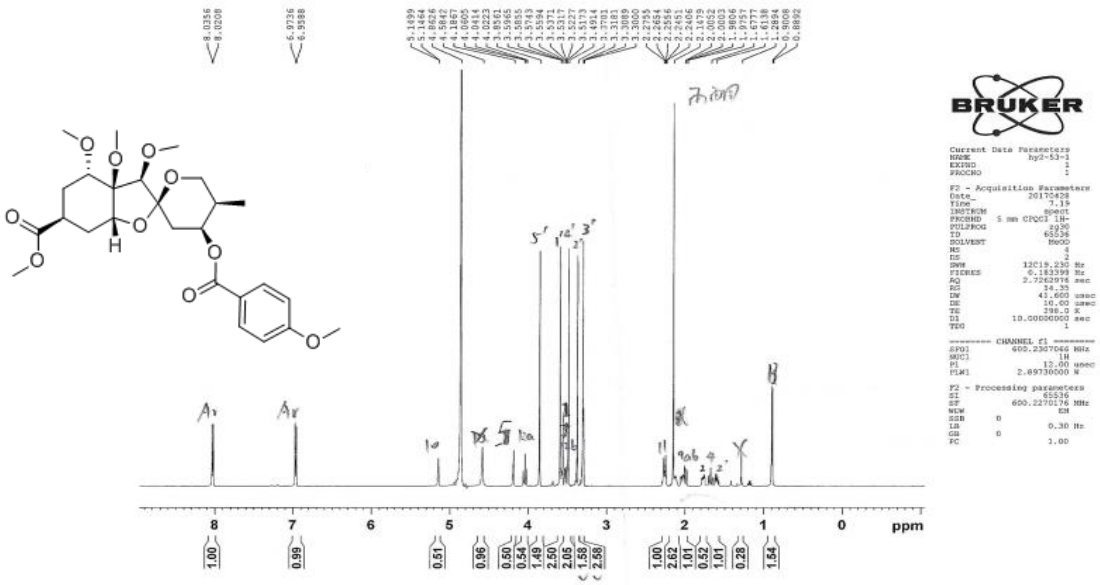


1001

1002

1003

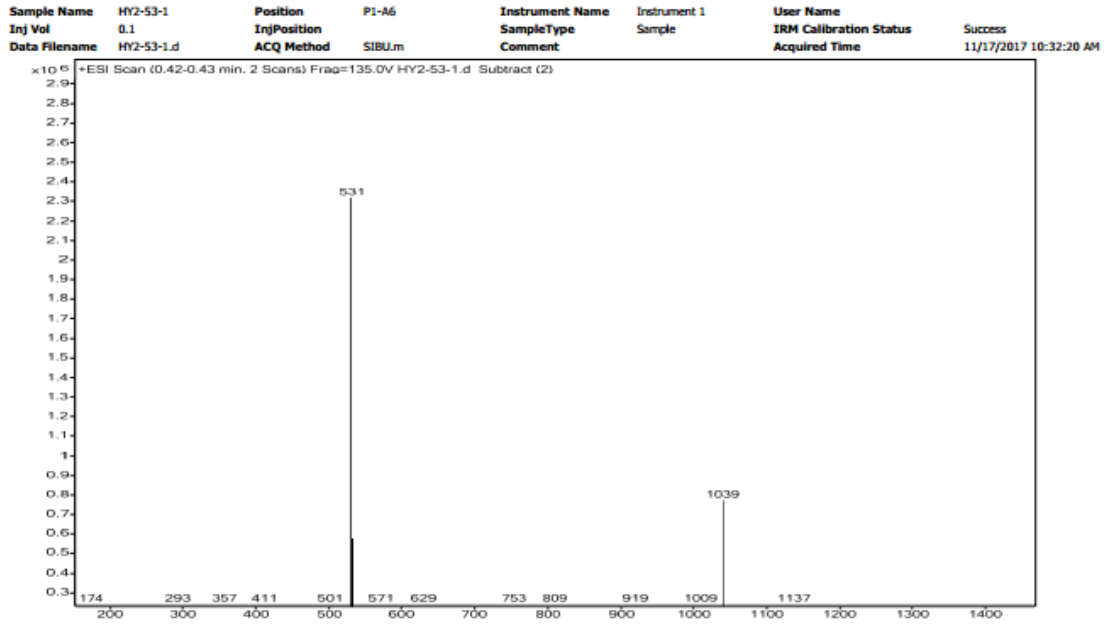
1004 10- 14. ^{1}H NMR spectrum of compound **1d**



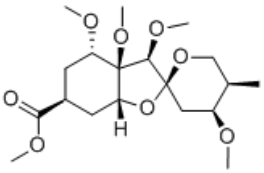
1005

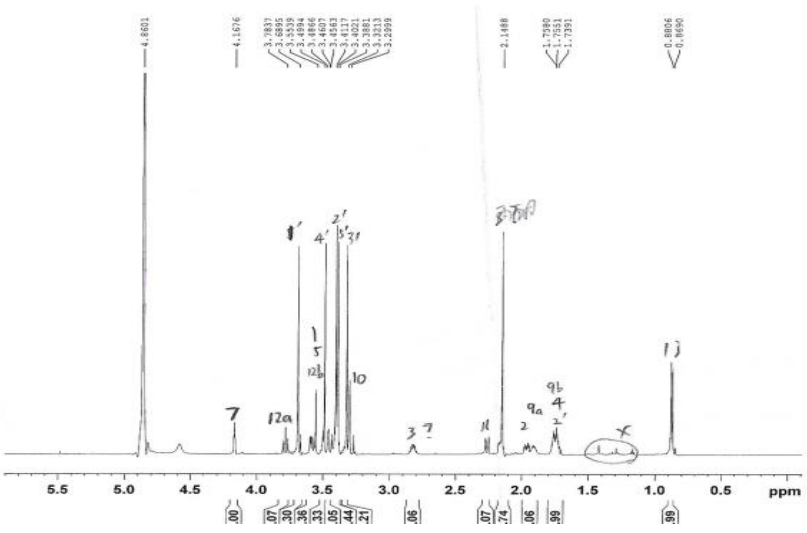
1006

10- 15. ESI spectrum of compound **1d**

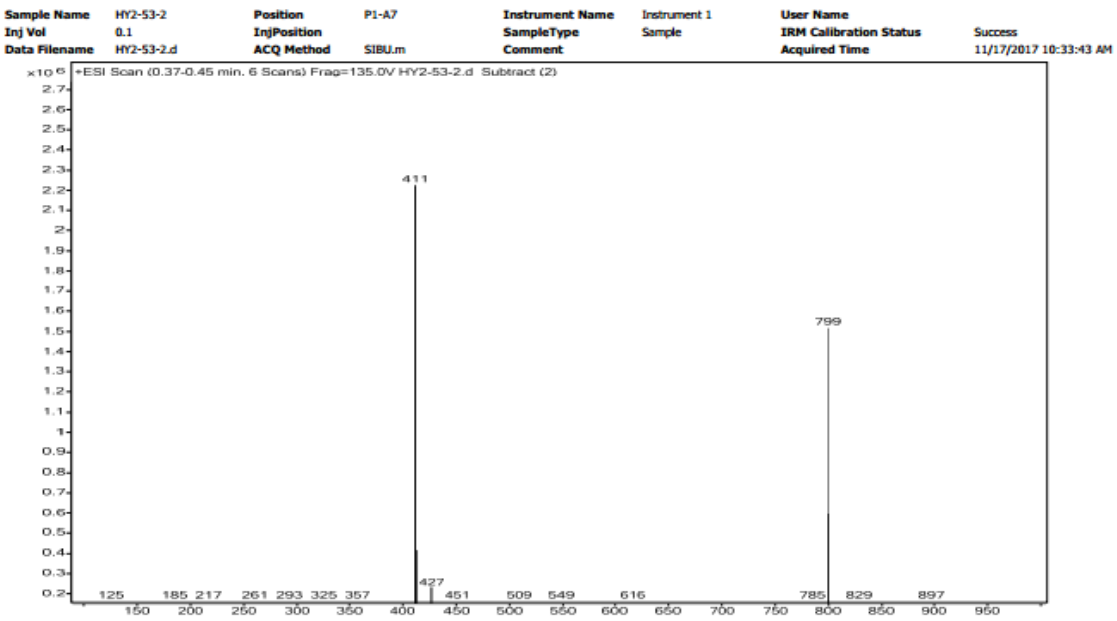


10- 16. ^{1}H NMR spectrum of compound **1e**

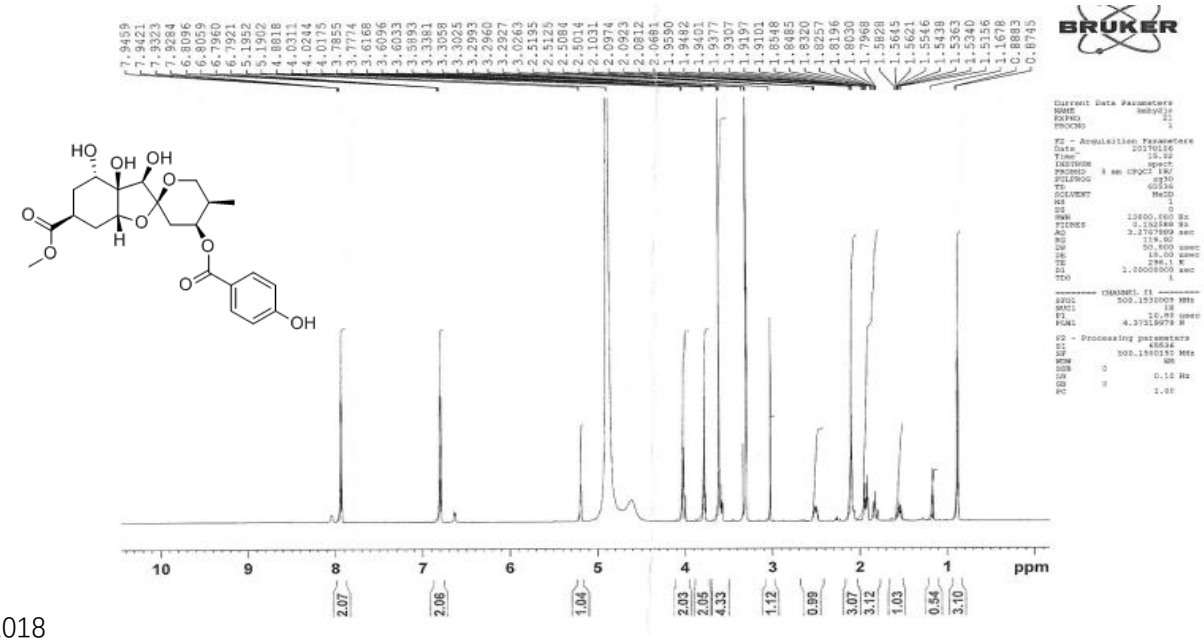




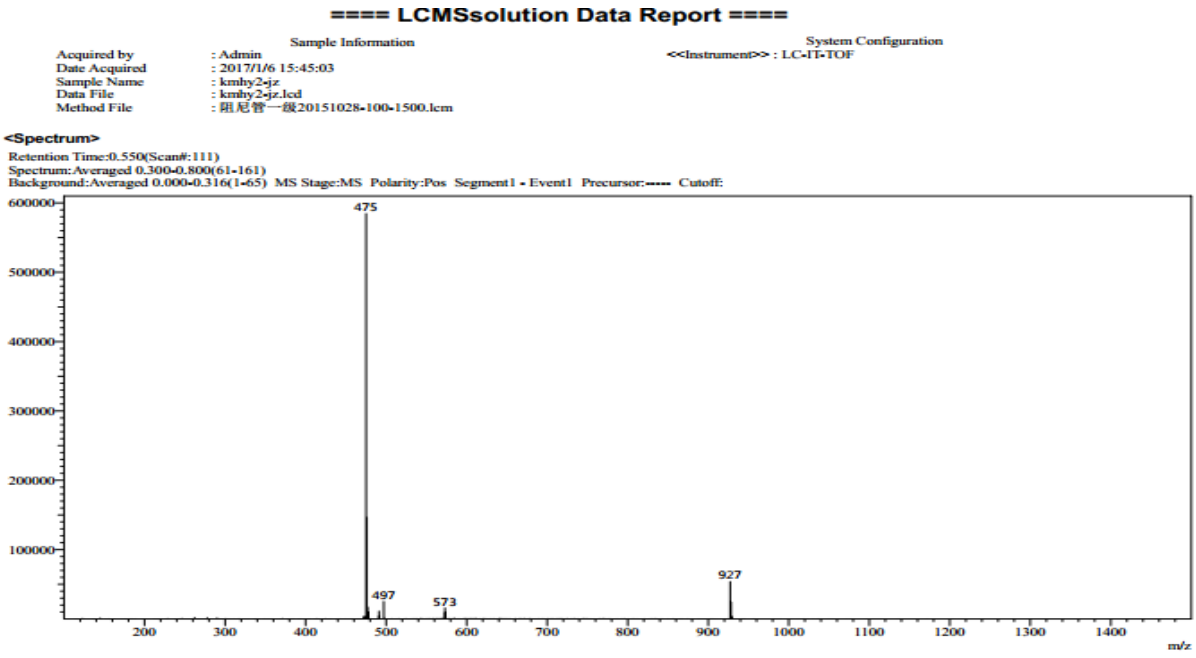
10- 17. ESI spectrum of compound **1e**



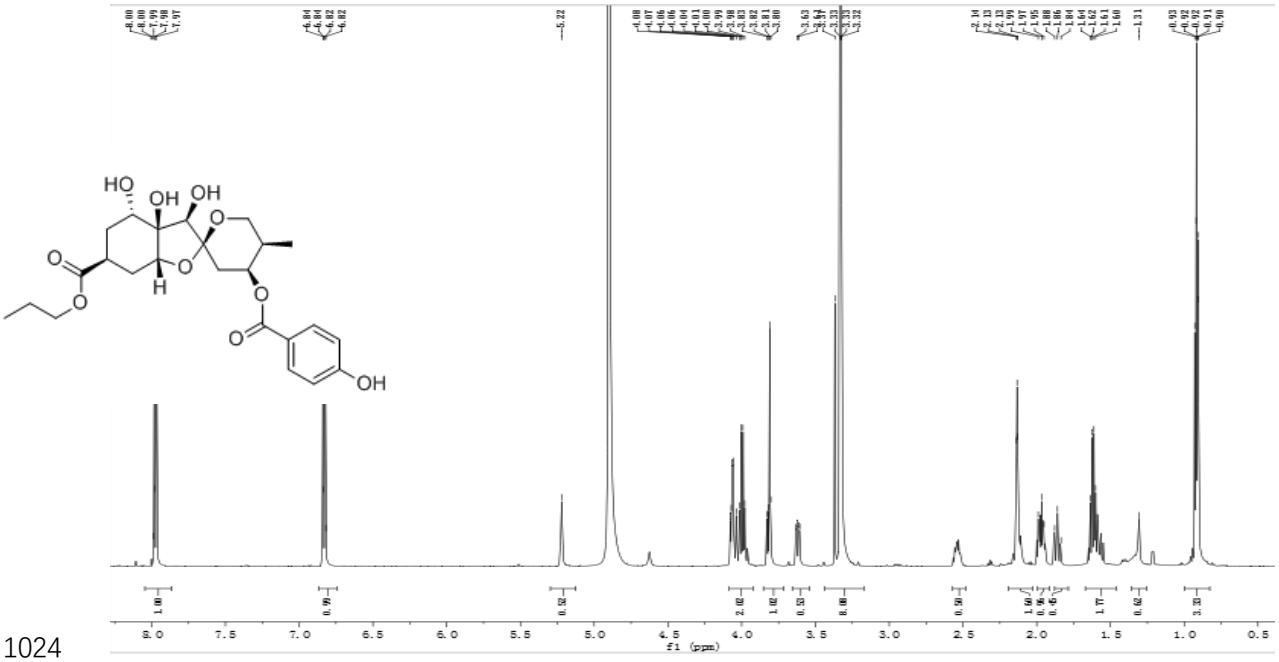
10- 18. ^{1}H NMR spectrum of compound **2a**



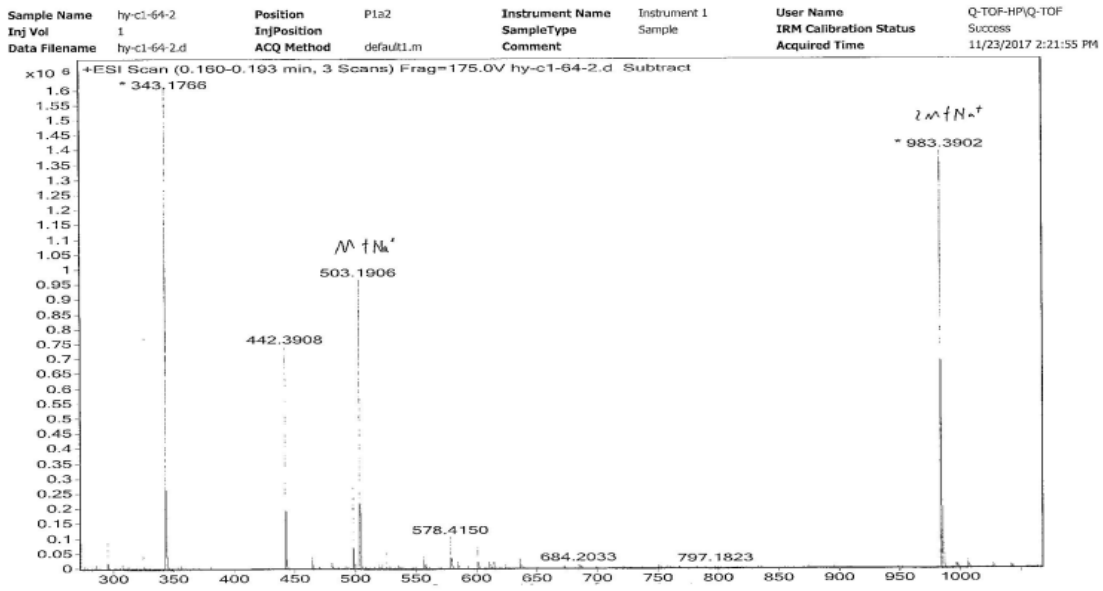
10- 19. ESI spectrum of compound **2a**



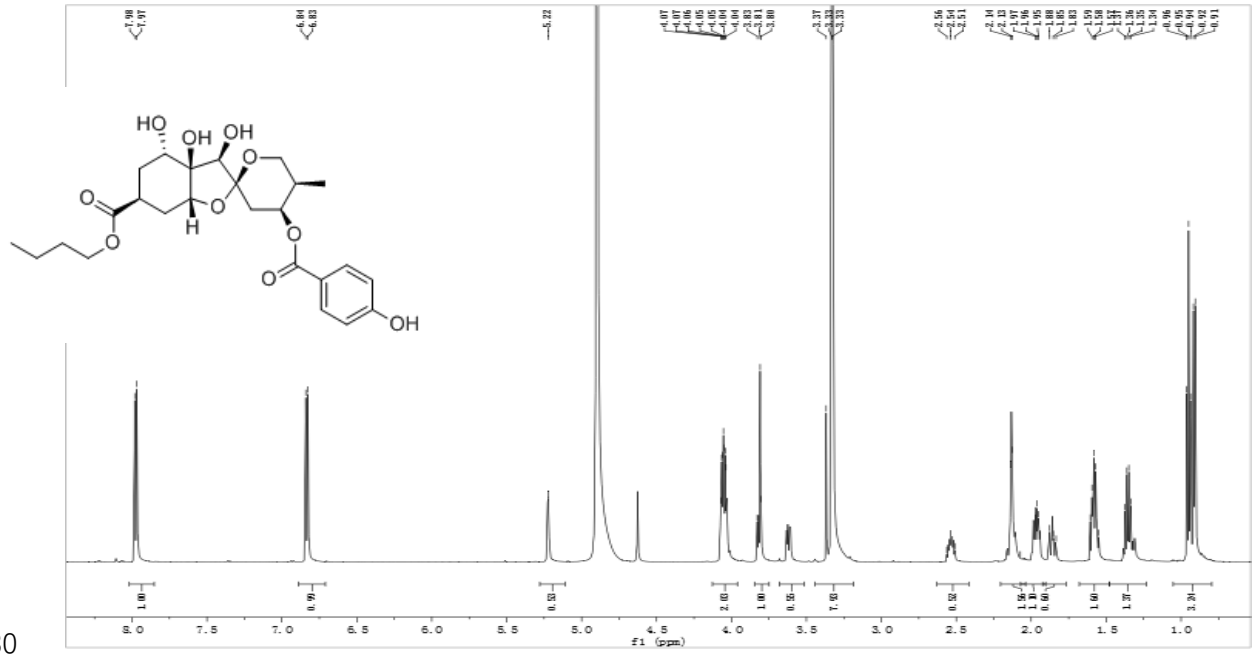
10- 20. ^{1}H NMR spectrum of compound **2b**



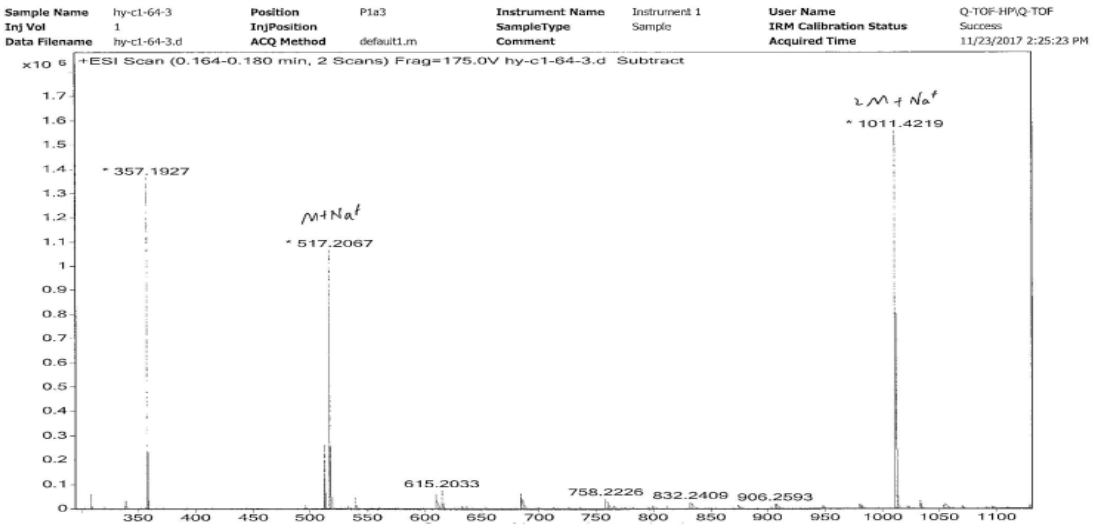
10- 21. ESI spectrum of compound **2b**



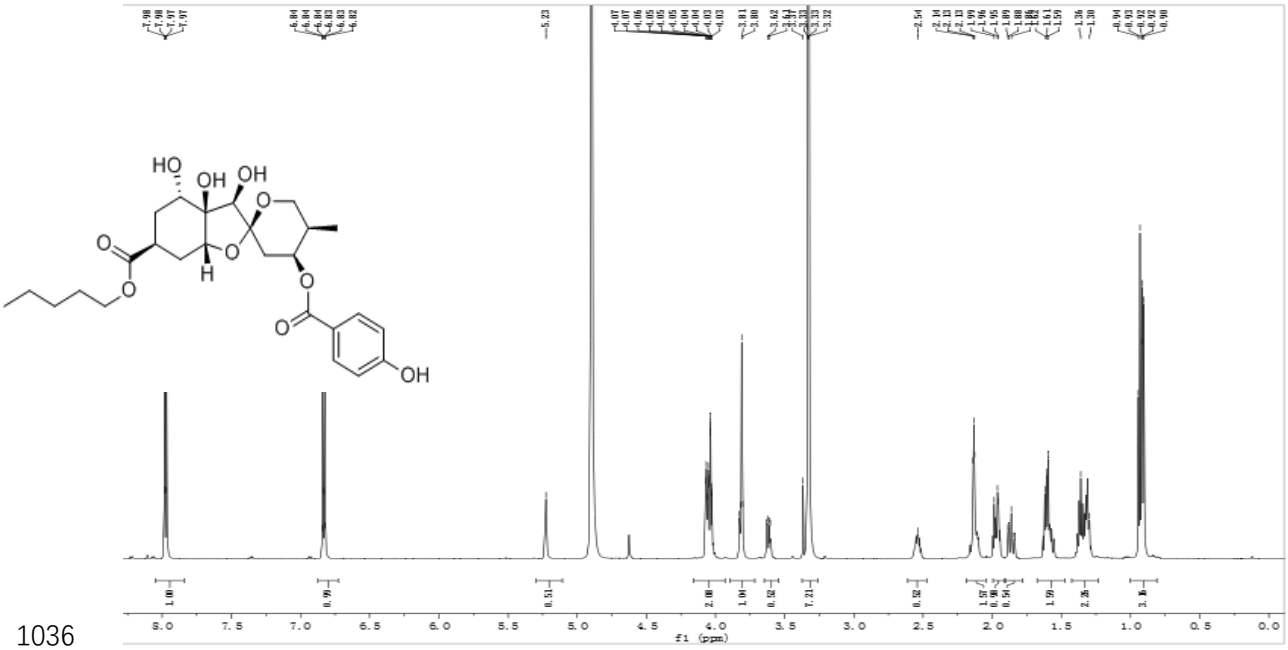
10- 22. ^{1}H NMR spectrum of compound **2c**



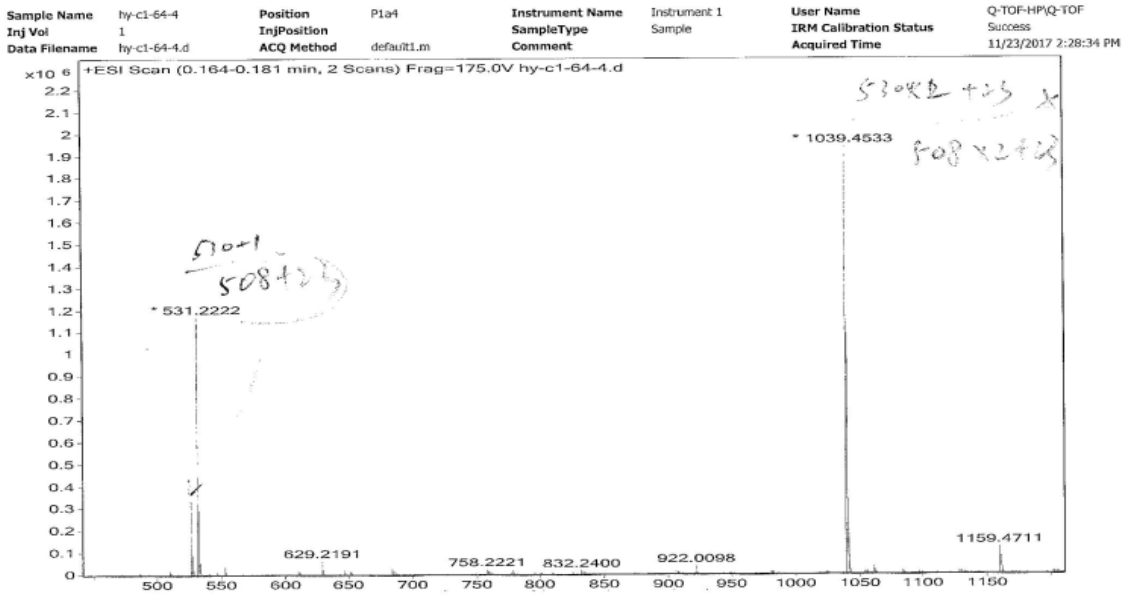
10- 23. ESI spectrum of compound **2c**



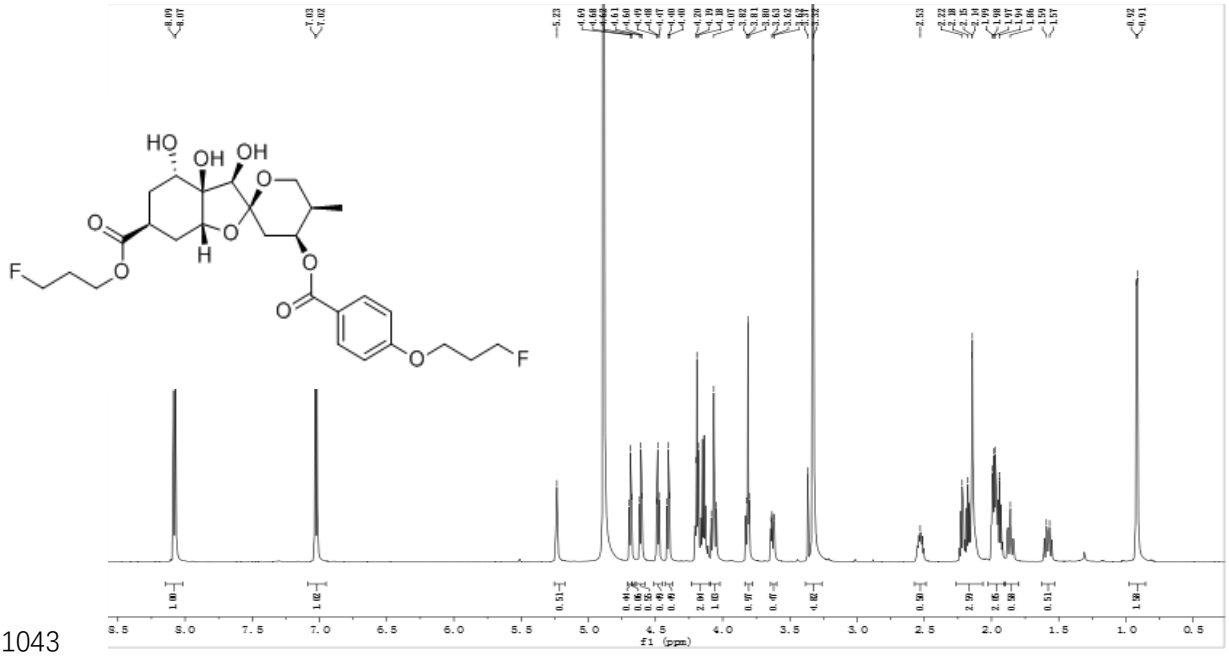
10- 24. ^{1}H NMR spectrum of compound **2d**



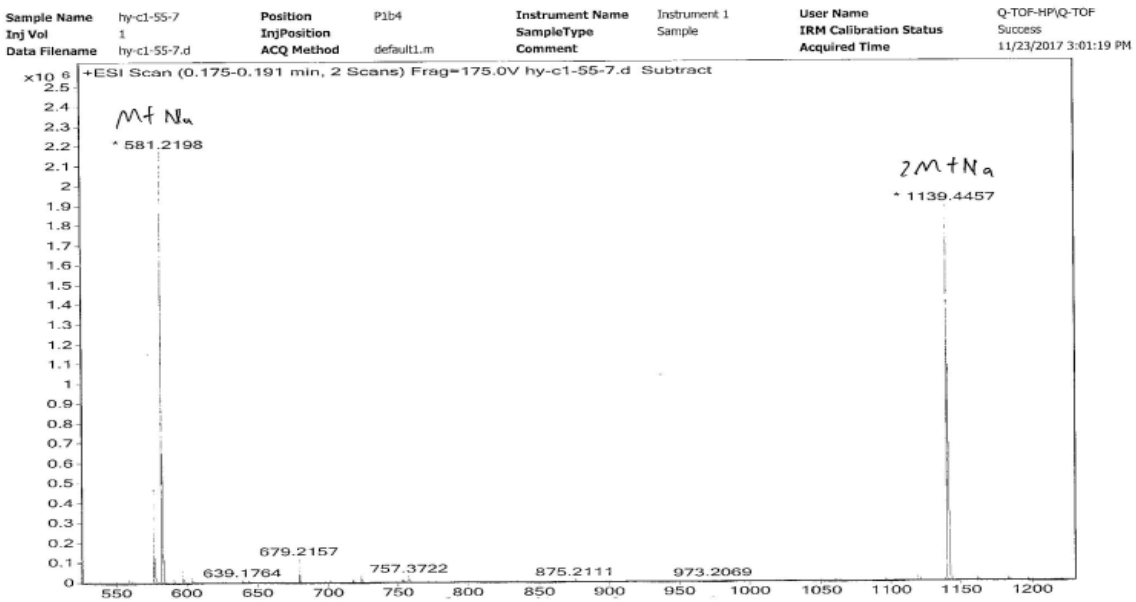
10- 25. ESI spectrum of compound **2d**



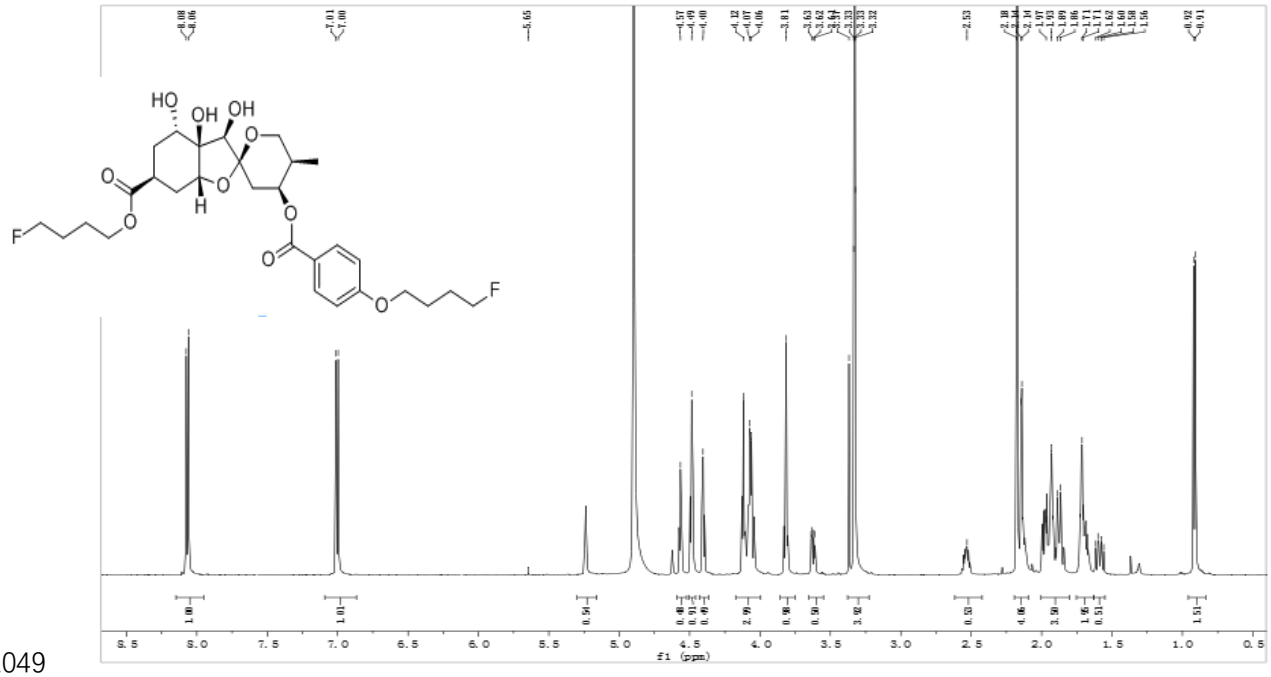
10- 26. ^{1}H NMR spectrum of compound **2e**



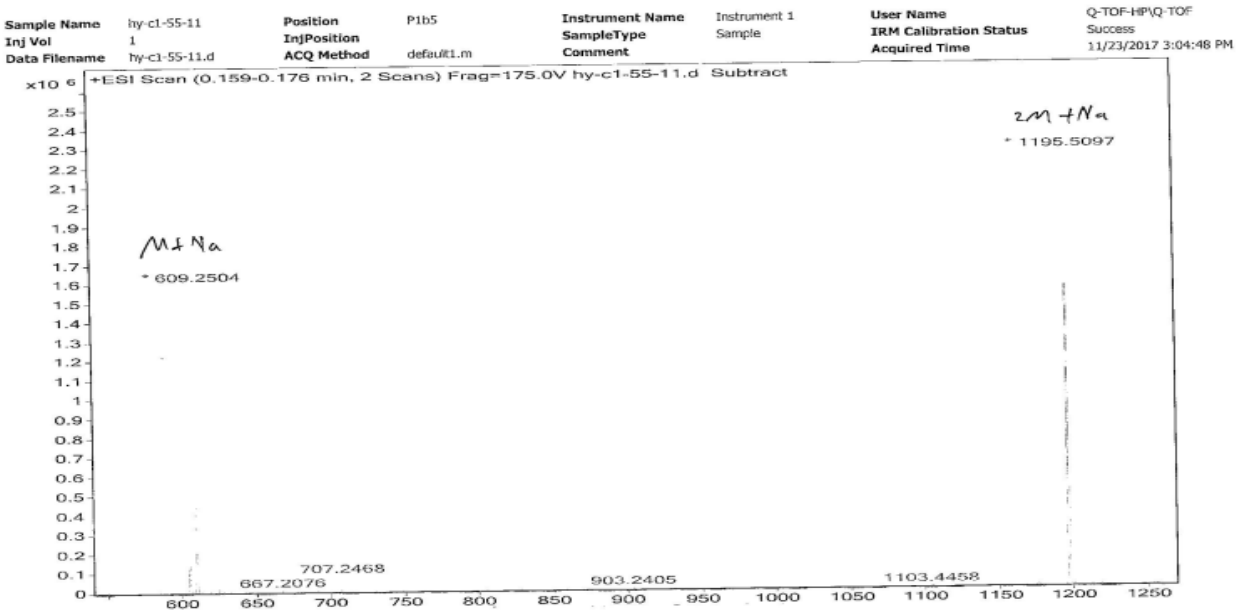
10- 27. ESI spectrum of compound **2e**



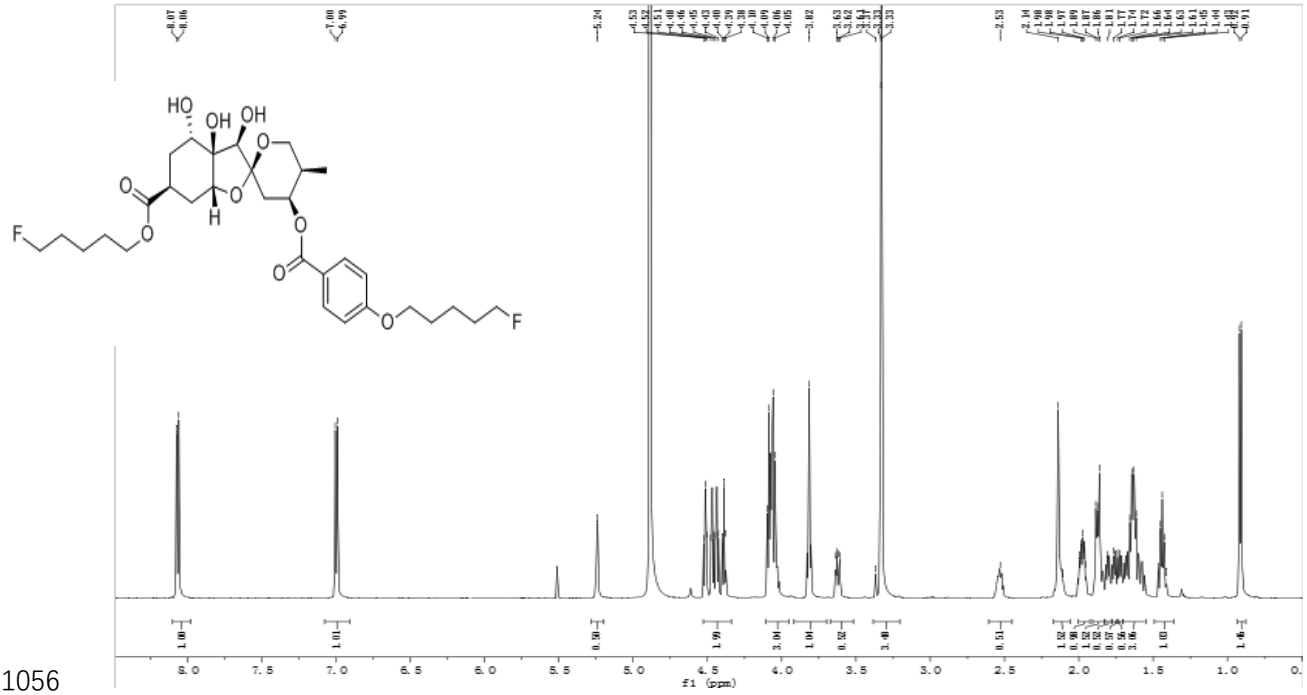
10- 28. ^{1}H NMR spectrum of compound **2f**



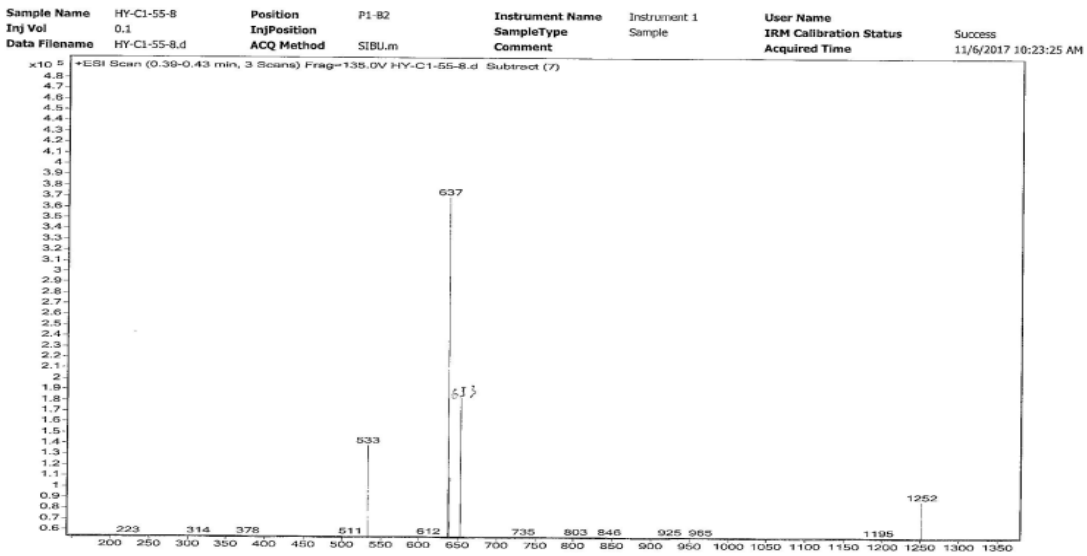
10- 29. ESI spectrum of compound **2f**



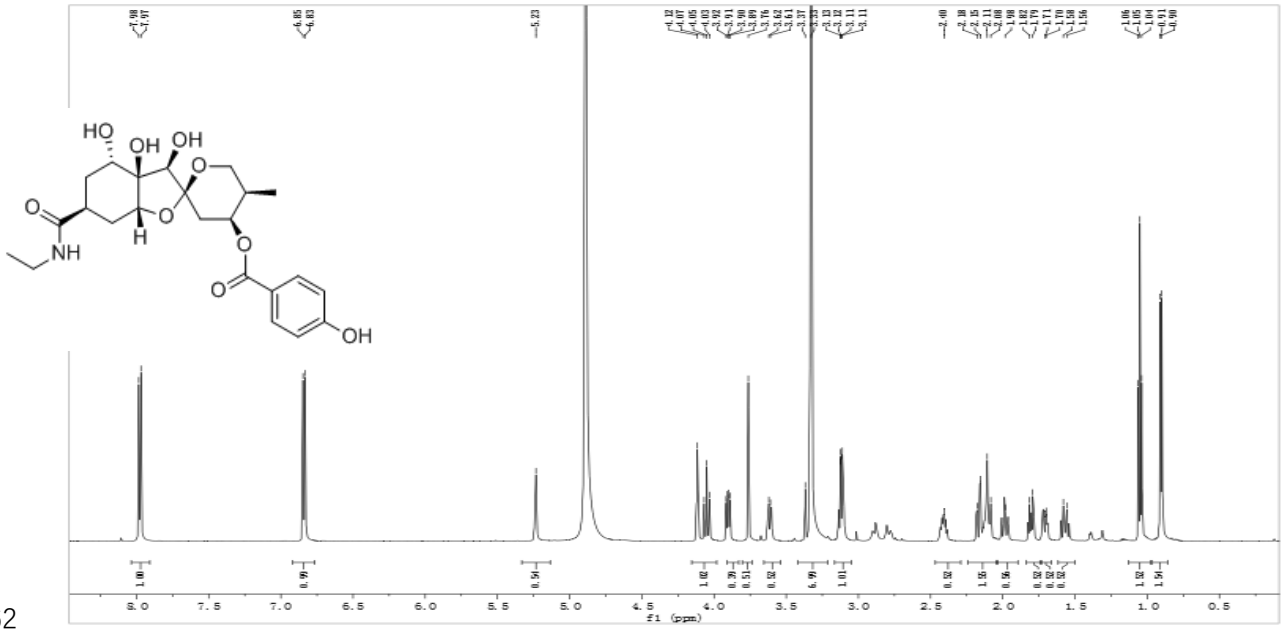
10- 30. ^{1}H NMR spectrum of compound **2g**



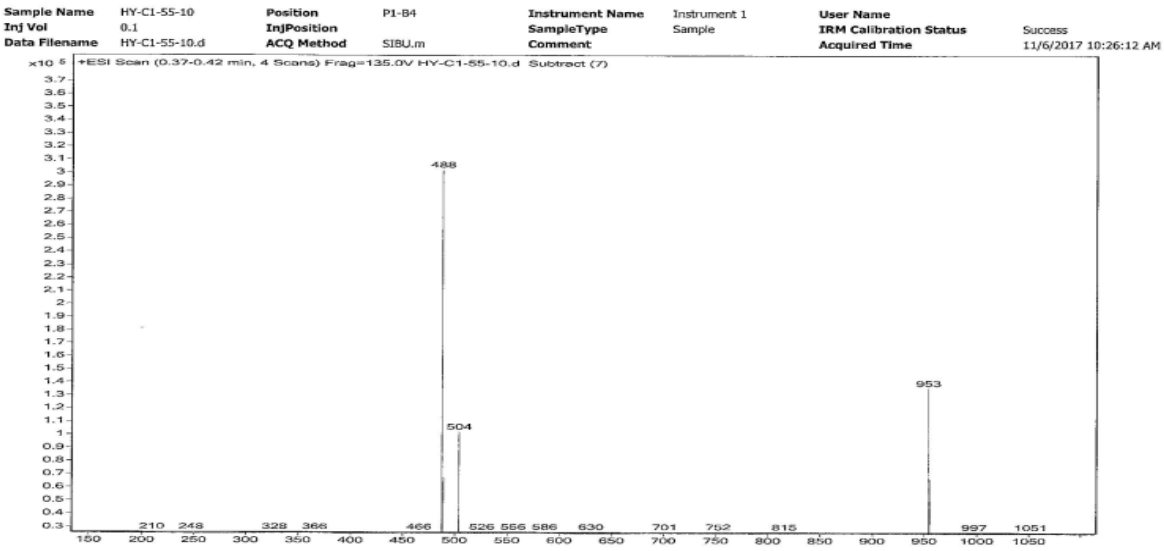
10- 31. ESI spectrum of compound **2g**



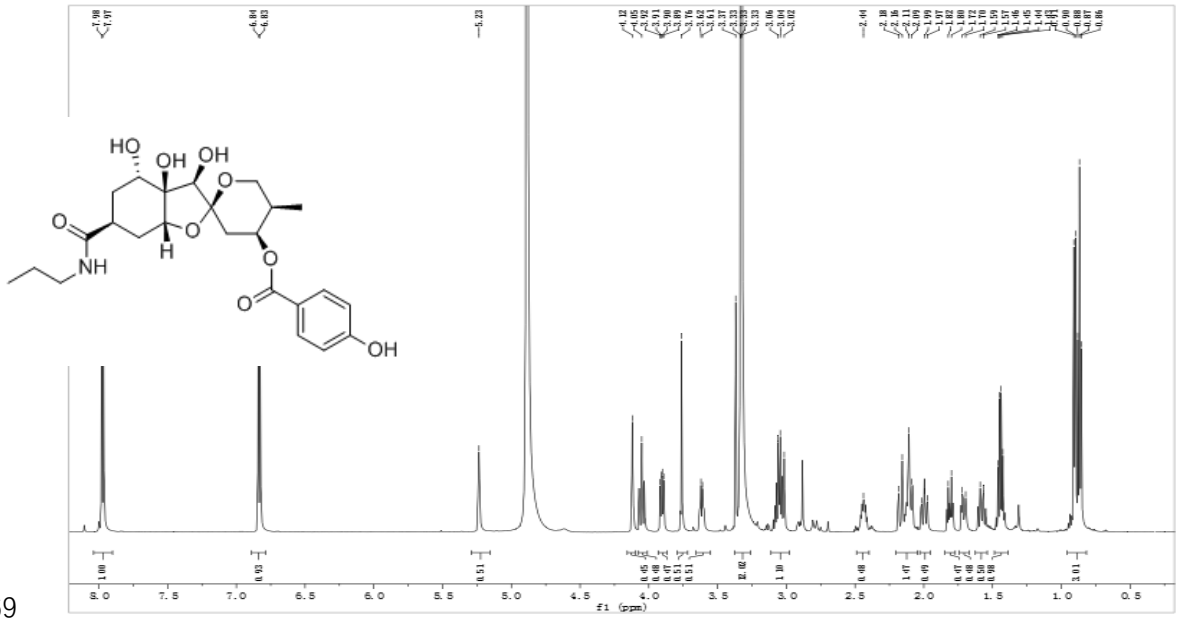
10- 32. ^{1}H NMR spectrum of compound **3a**



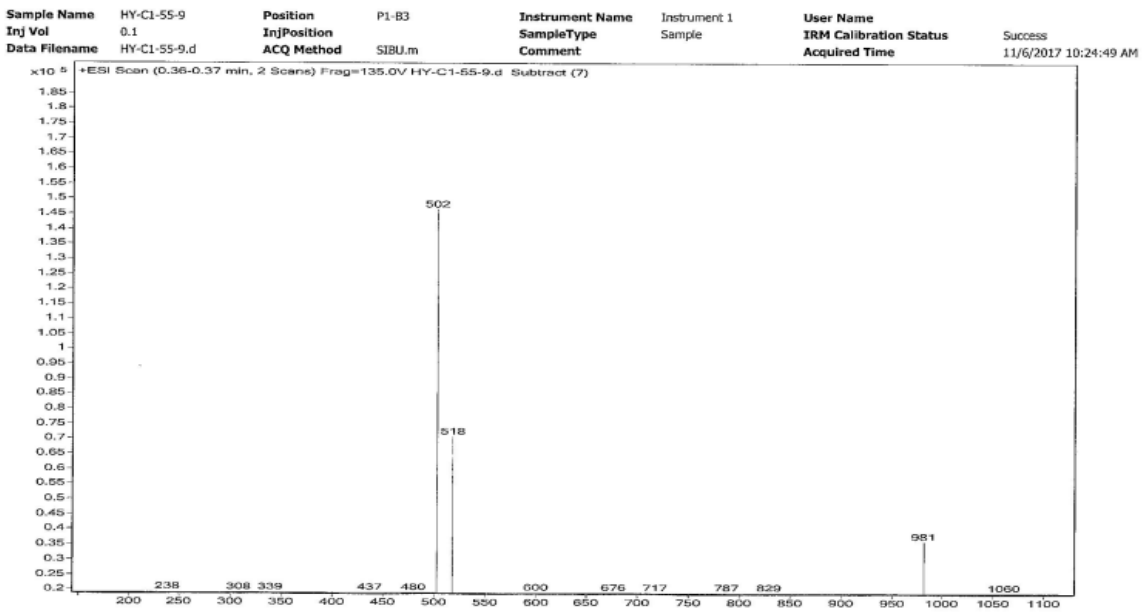
10- 33. ESI spectrum of compound **3a**



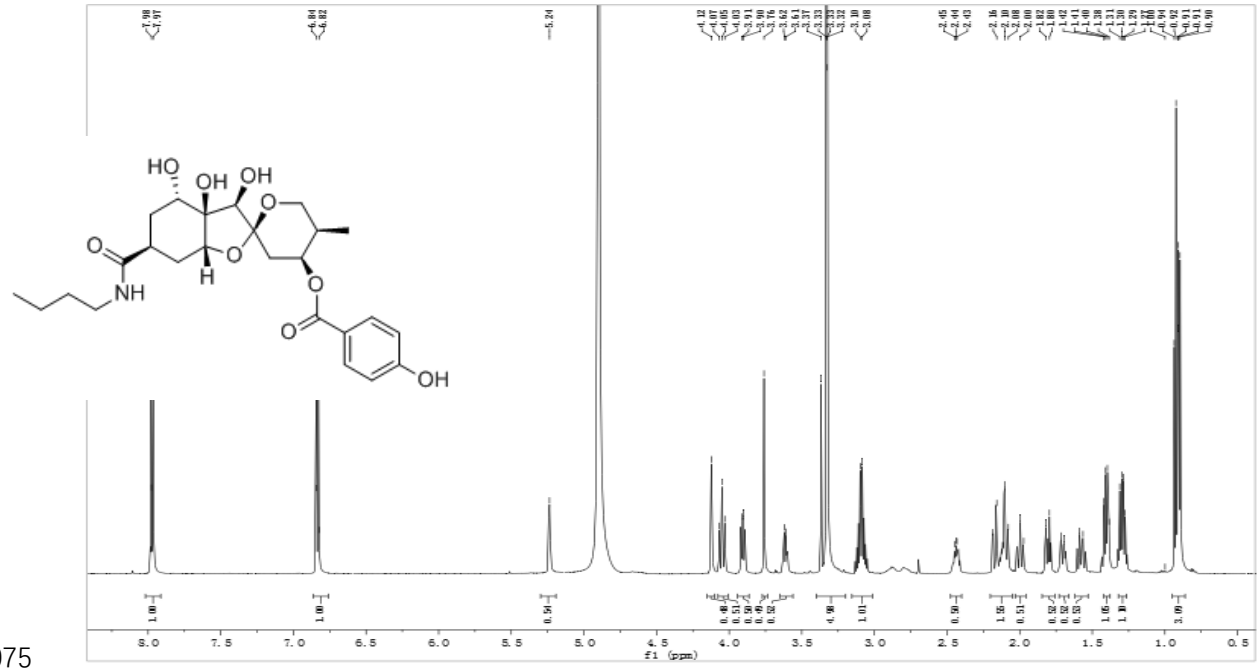
10- 34. ^{1}H NMR spectrum of compound **3b**



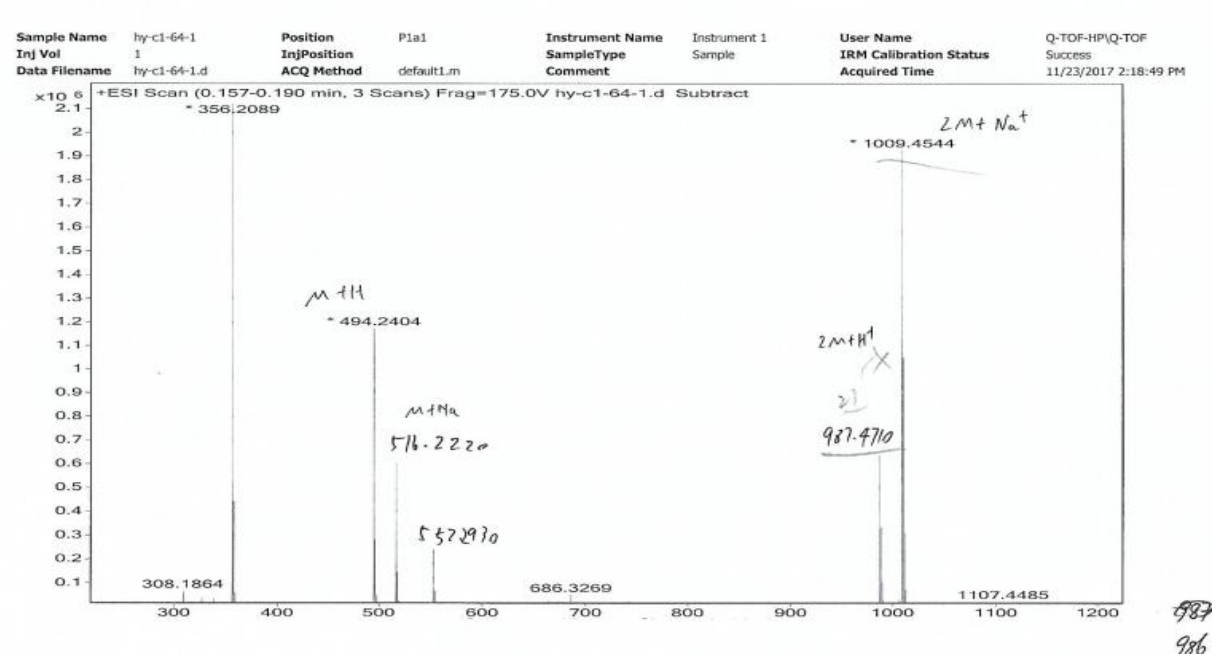
10- 35. ESI spectrum of compound **3b**



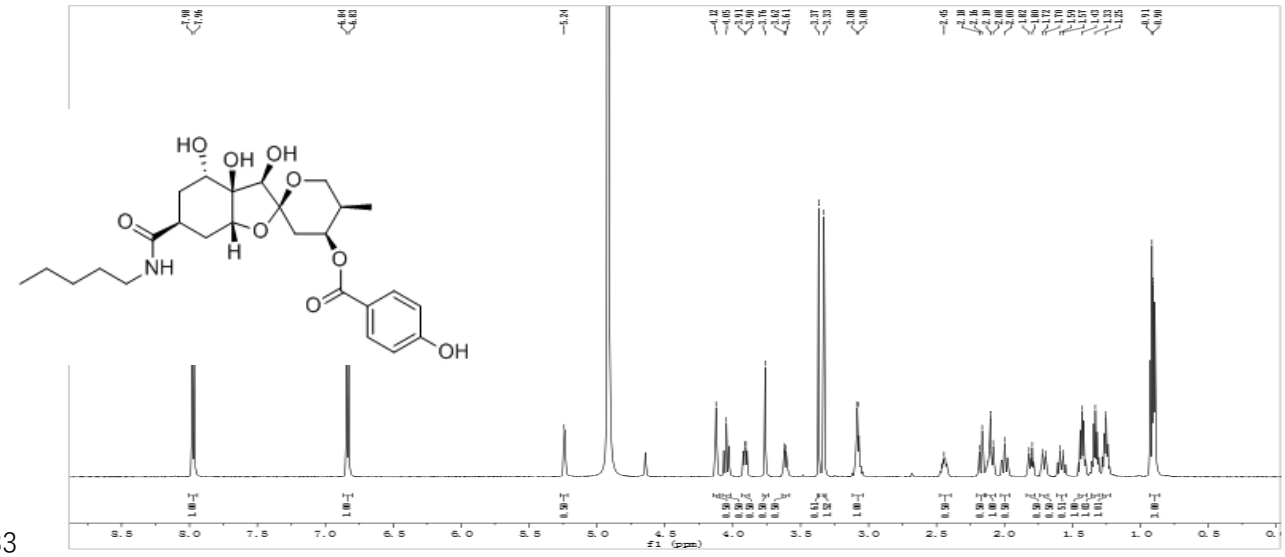
10- 36. ^{1}H NMR spectrum of compound **3c**



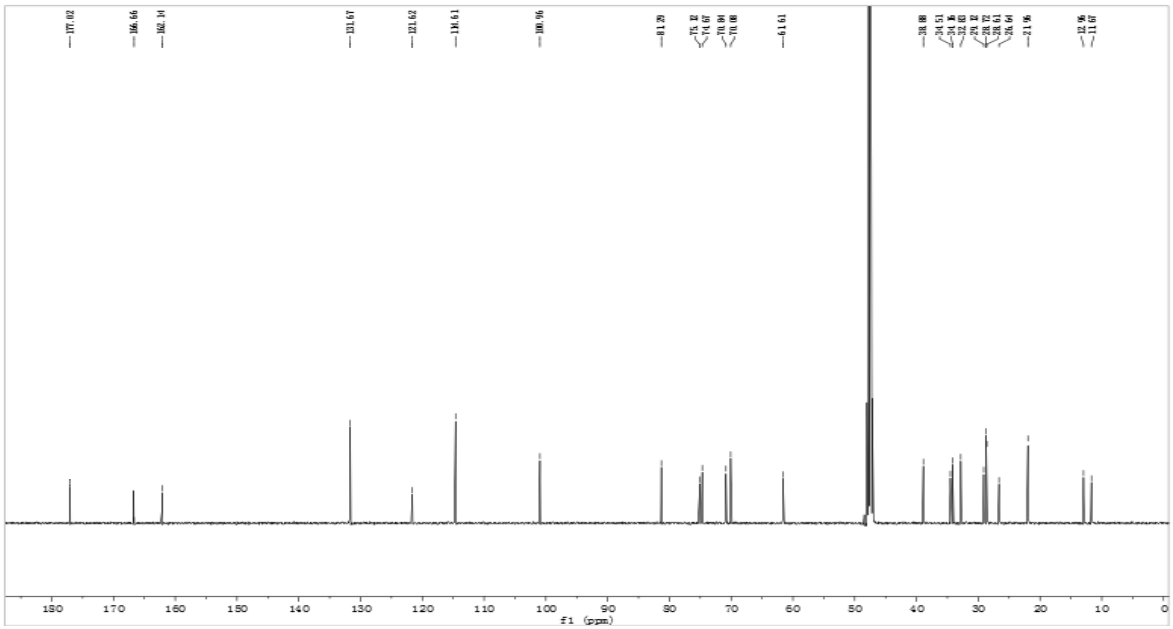
10- 37. ESI spectrum of compound **3c**



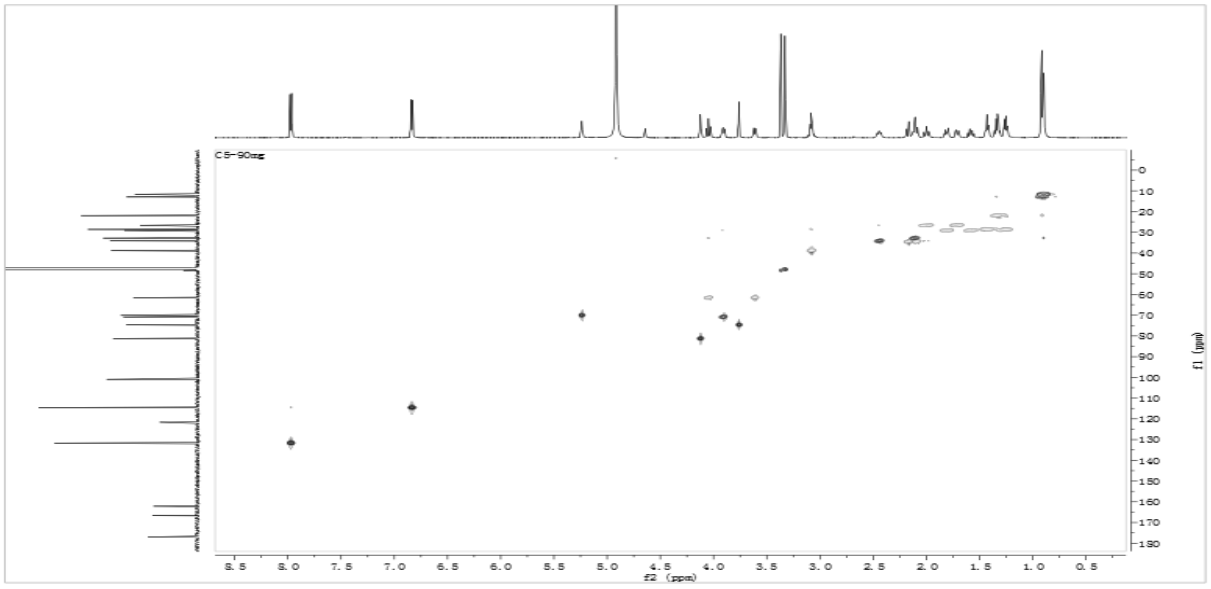
10- 38. ^{1}H NMR spectrum of compound **3d（PAC5）**



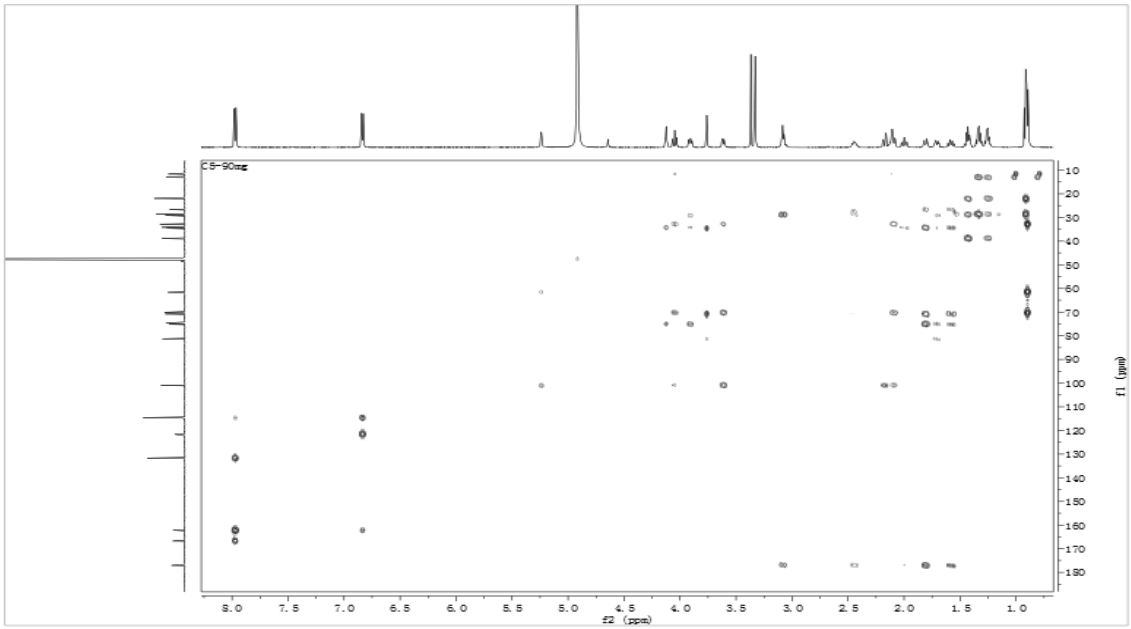
10- 39. ^{13}CNMR spectrum of compound **3d**



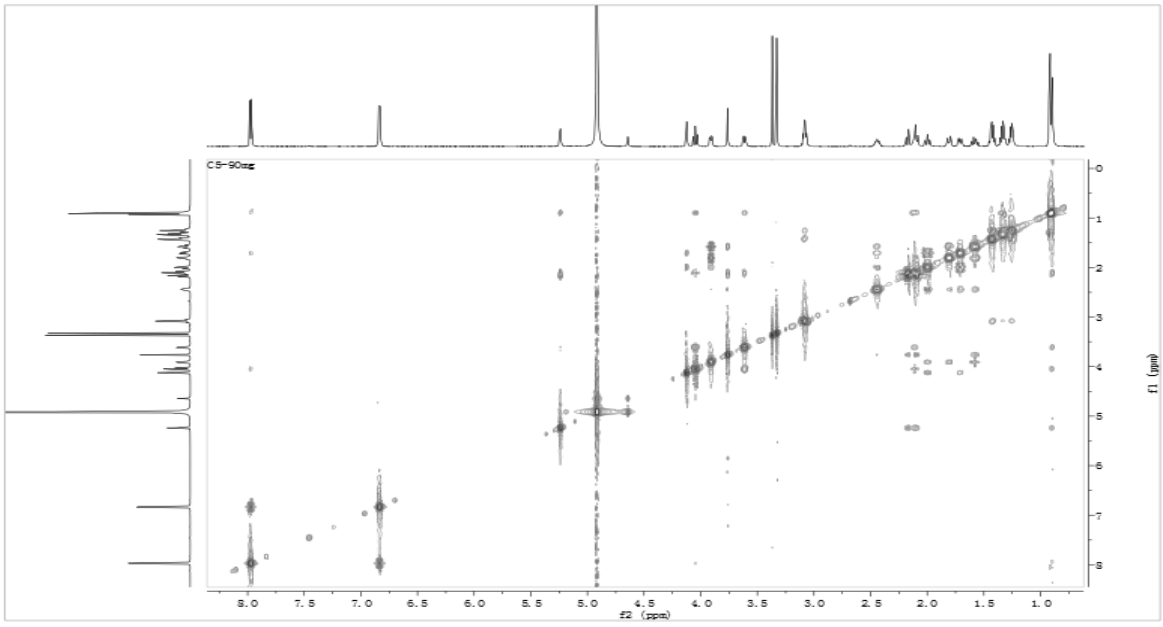
10- 40. HSQC spectrum of compound **3d**



10- 41. HMBC spectrum of compound **3d**



10- 42. ROESY spectrum of compound **3d**



1101 10- 43. HRESI spectrum of compound **3d**

Data File: E:\DATA\2018\0803\C5-90mg.lcd

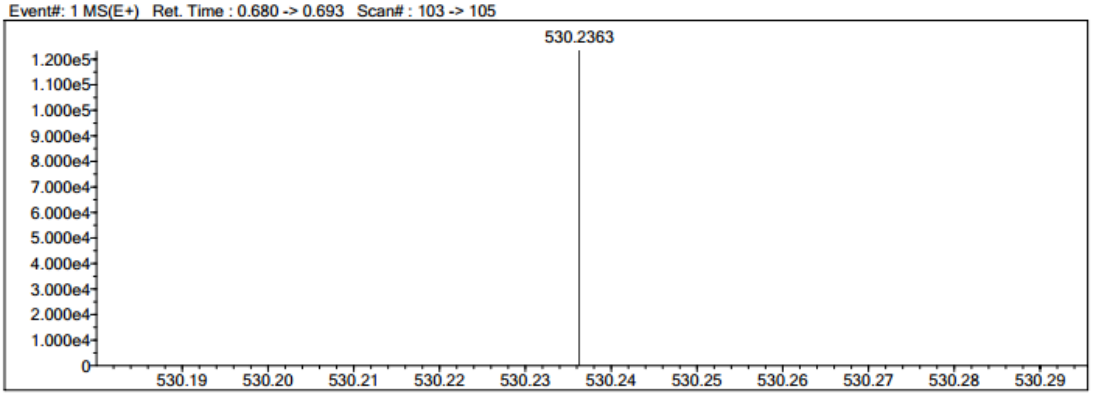
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	1	100	O	2	0	20	Si	4	0	0	Br	1	0	0	Na
C	4	10	50	F	1	0	0	S	2	0	0	I	3	0	0	
N	3	0	10	Na	1	0	0	Cl	1	0	0					

Error Margin (ppm): 5
HC Ratio: unlimited
Max Isotopes: all
MSn Iso RI (%): 75.00

DBE Range: -2.0 - 100.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: yes
Isotope Res: 10000
Max Results: 10

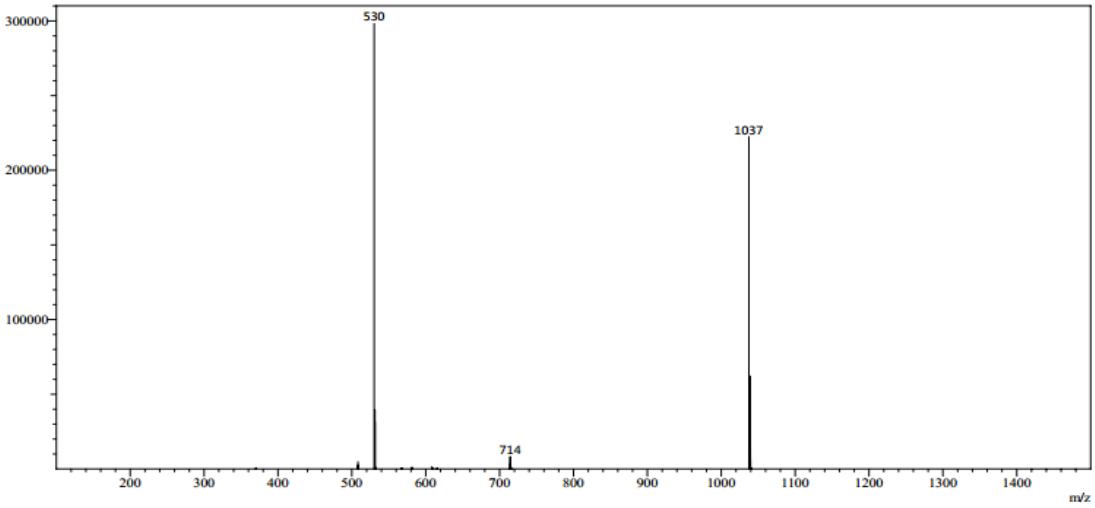
Event#: 1 MS(E+) Ret. Time : 0.680 -> 0.693 Scan# : 103 -> 105



1102

1103 10- 44. ESI spectrum of compound **3d**

<Spectrum>
Retention Time:0.573(Scan#:88)
Spectrum:Averaged 0.293-0.867(45-131)
Background:Averaged 0.000-0.333(1-51) MS Stage:MS Polarity:Pos Segment1 - Event1 Precursor:----- Cutoff:

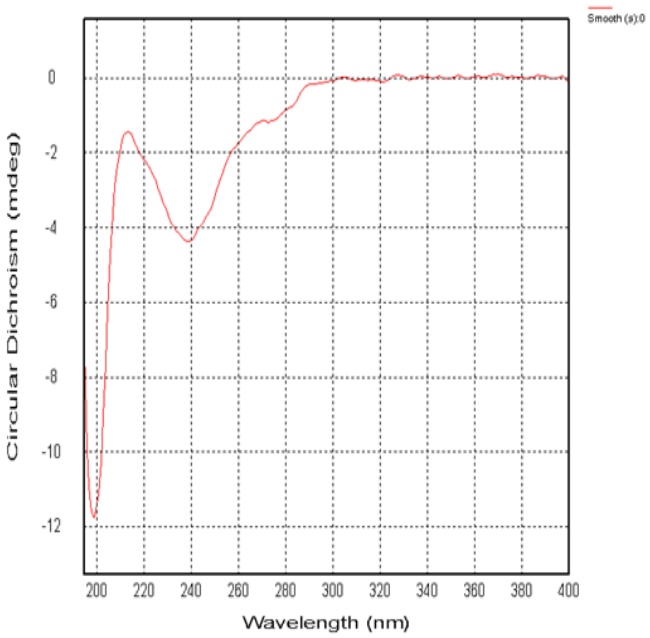


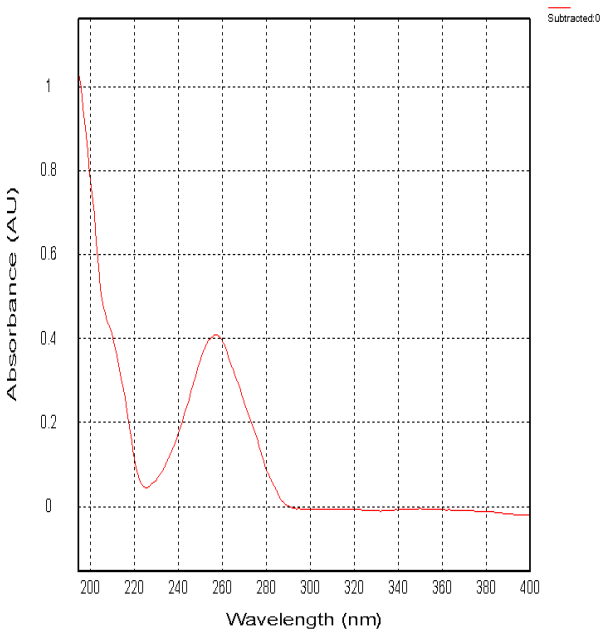
1104

1105

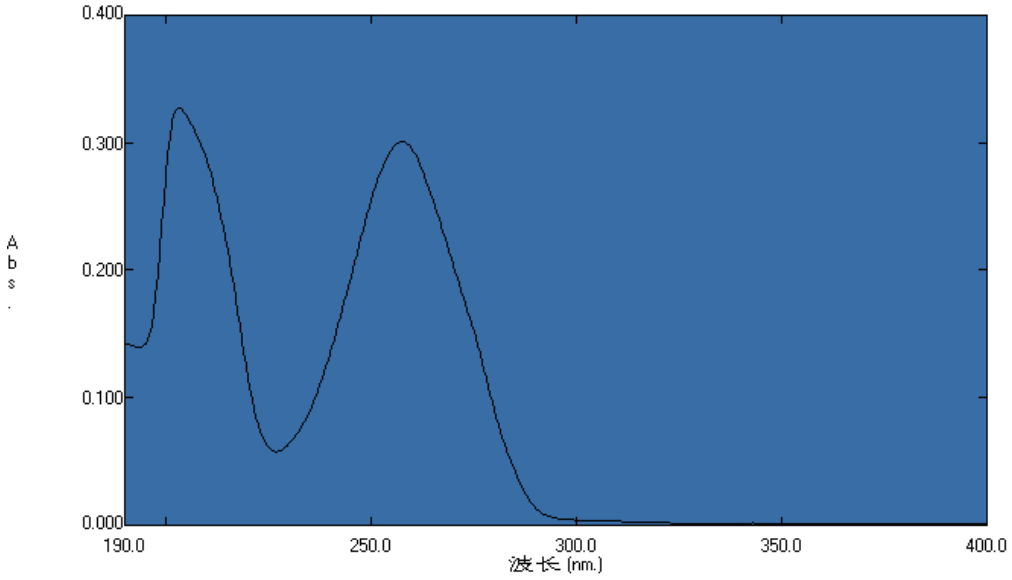
1106

10- 45. CD spectrum of compound **3d**

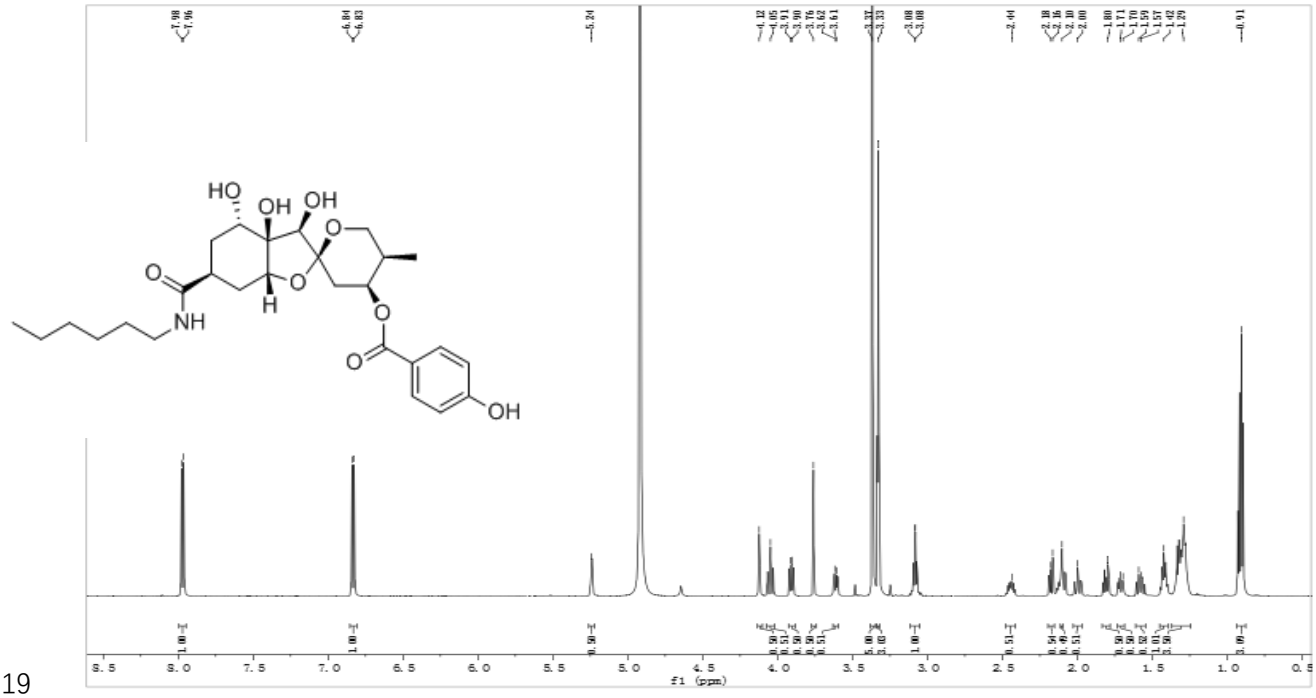




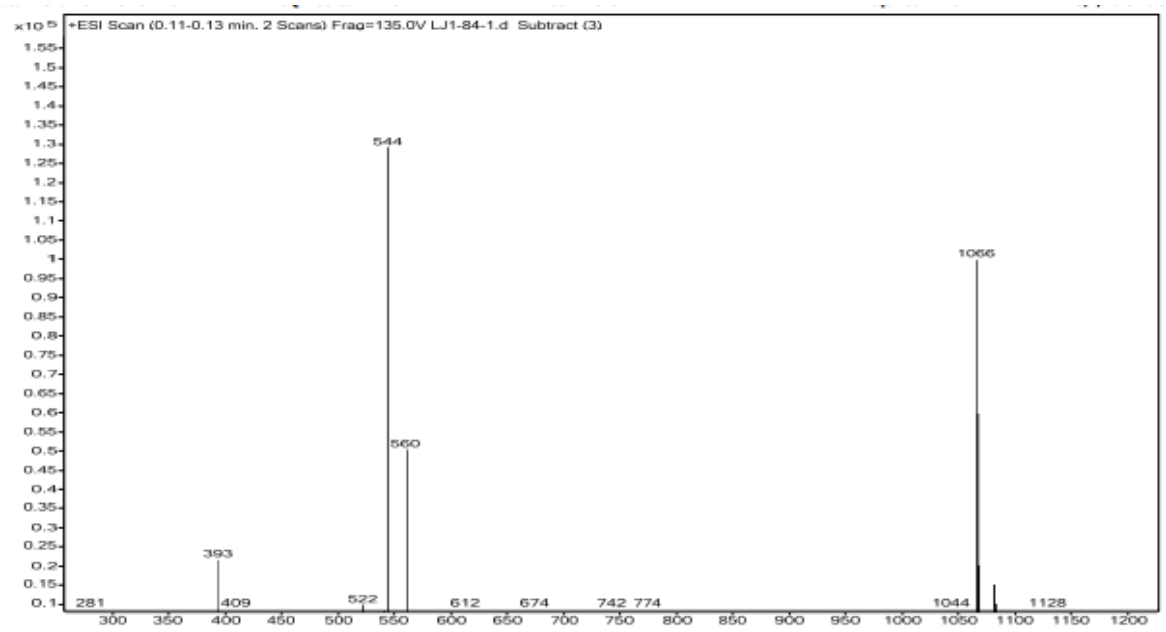
10- 46. UV spectrum of compound **3d**



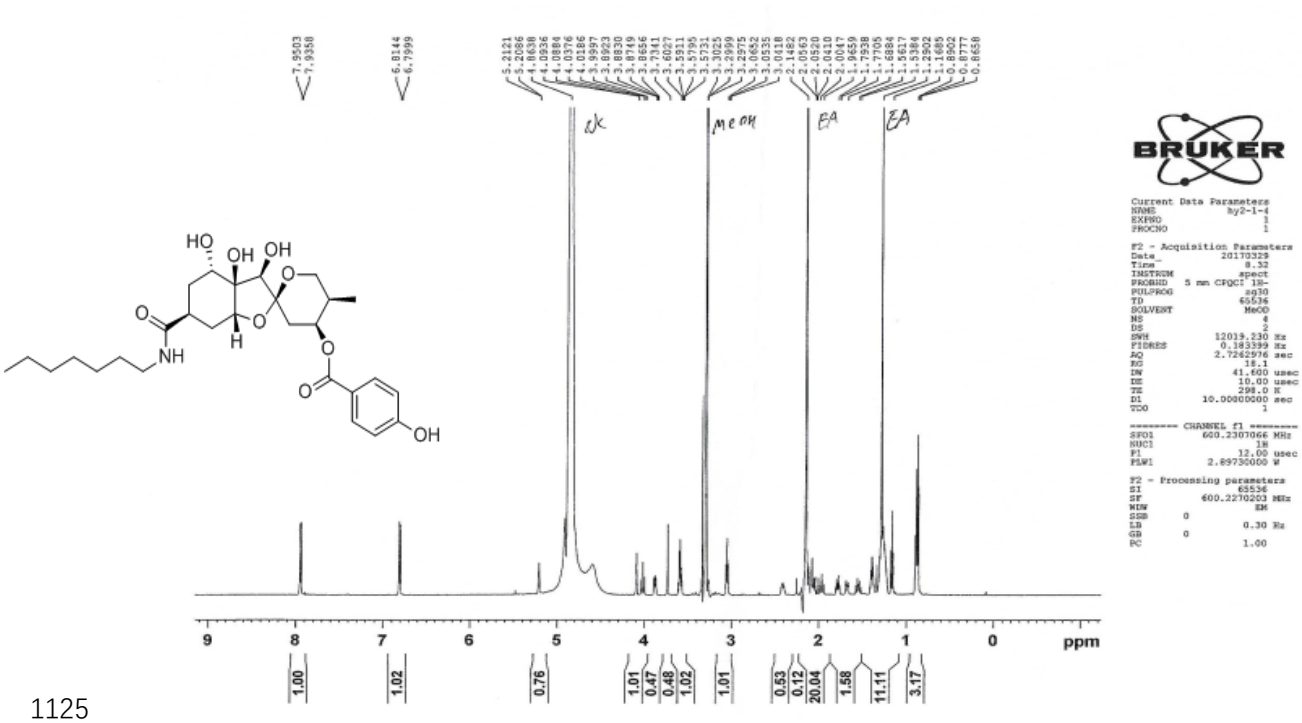
10- 47. ^{1}H NMR spectrum of compound **3e**



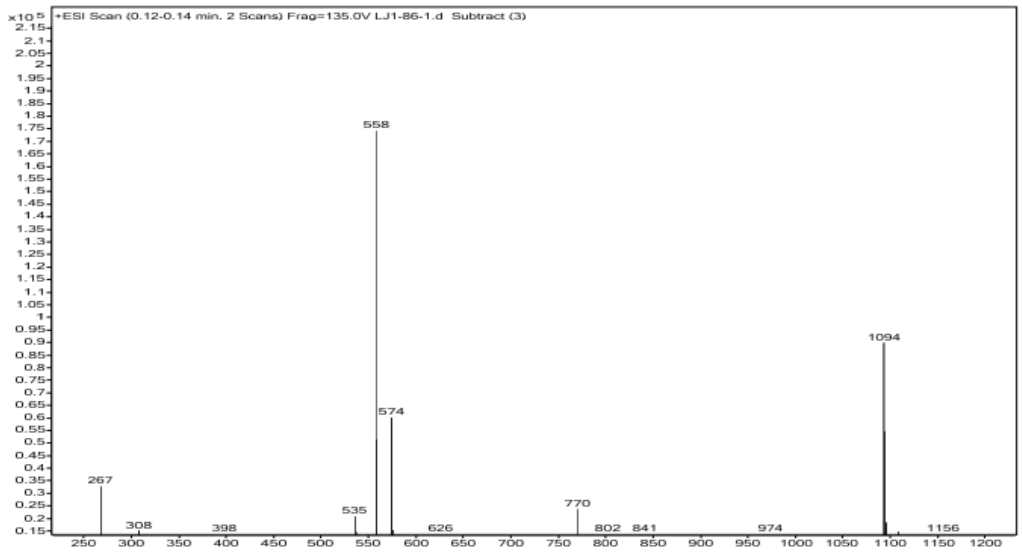
10- 48. ESI spectrum of compound **3e**



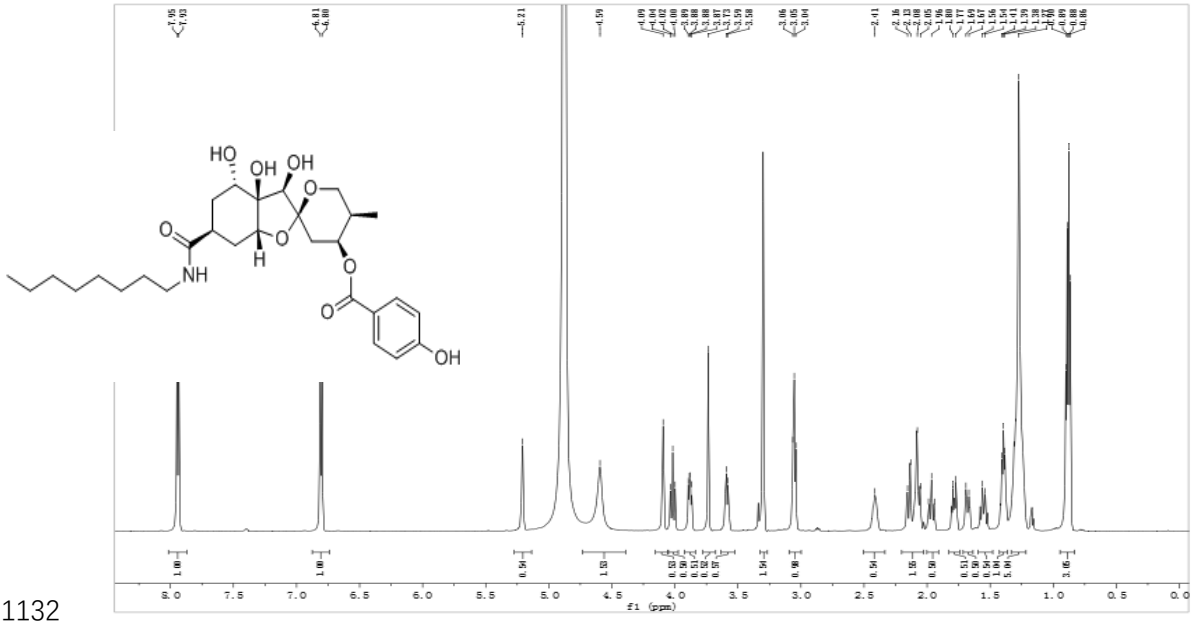
10- 49. ^{1}H NMR spectrum of compound **3f**



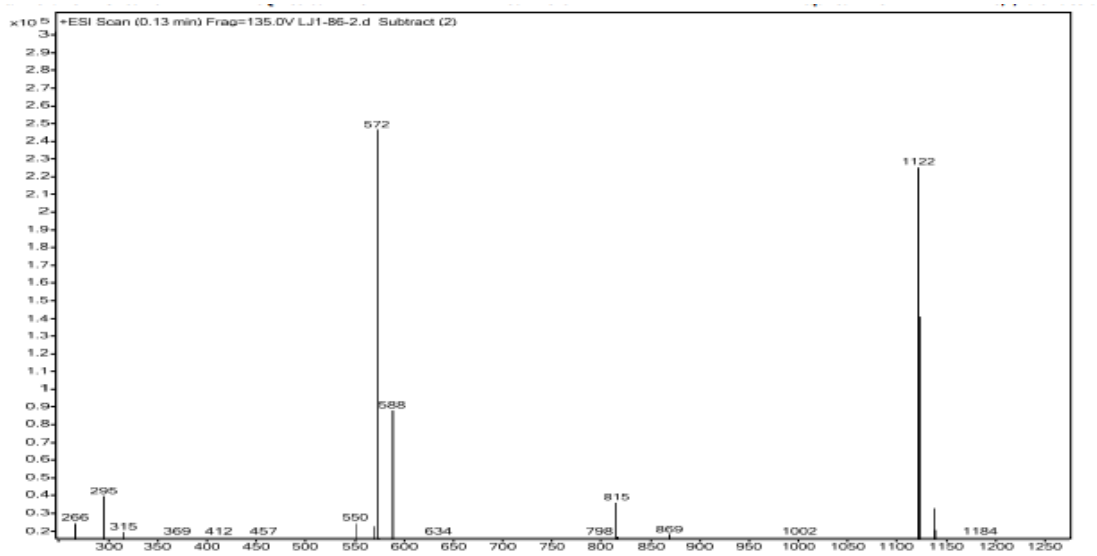
10- 50. ESI spectrum of compound **3f**



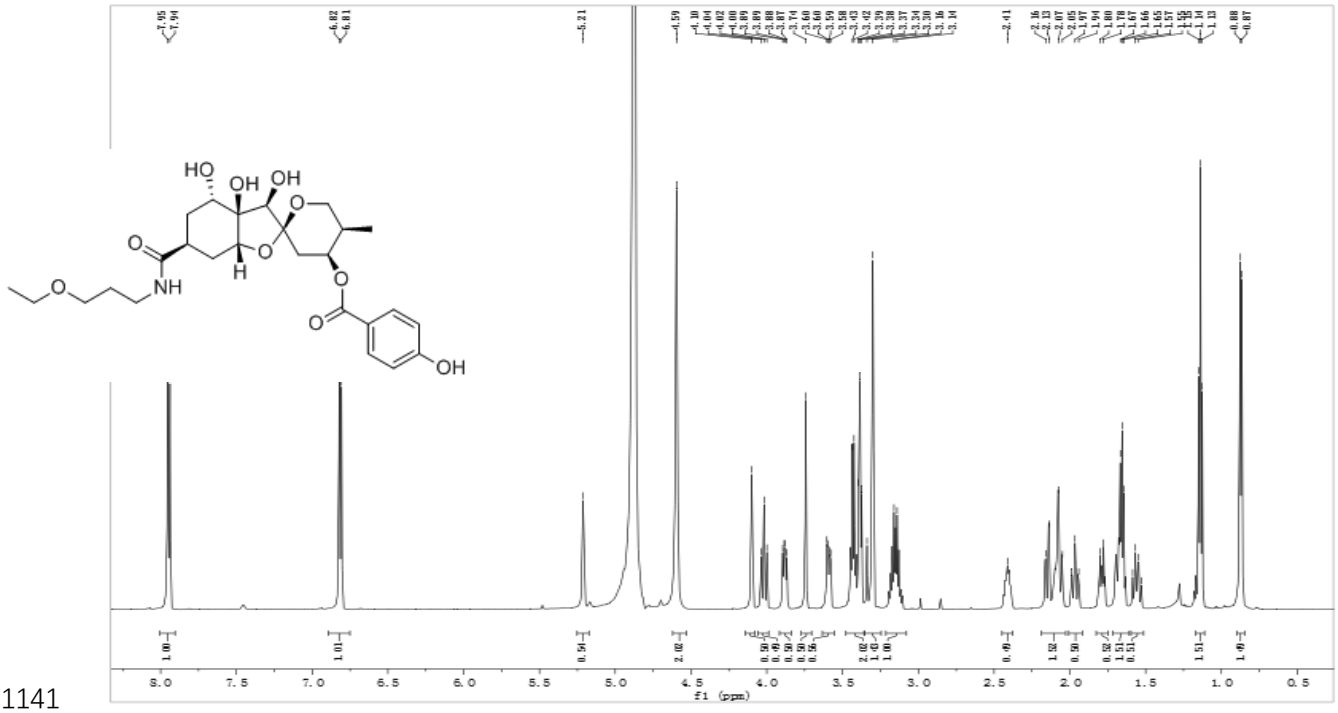
10- 51. ^{1}H NMR spectrum of compound **3g**



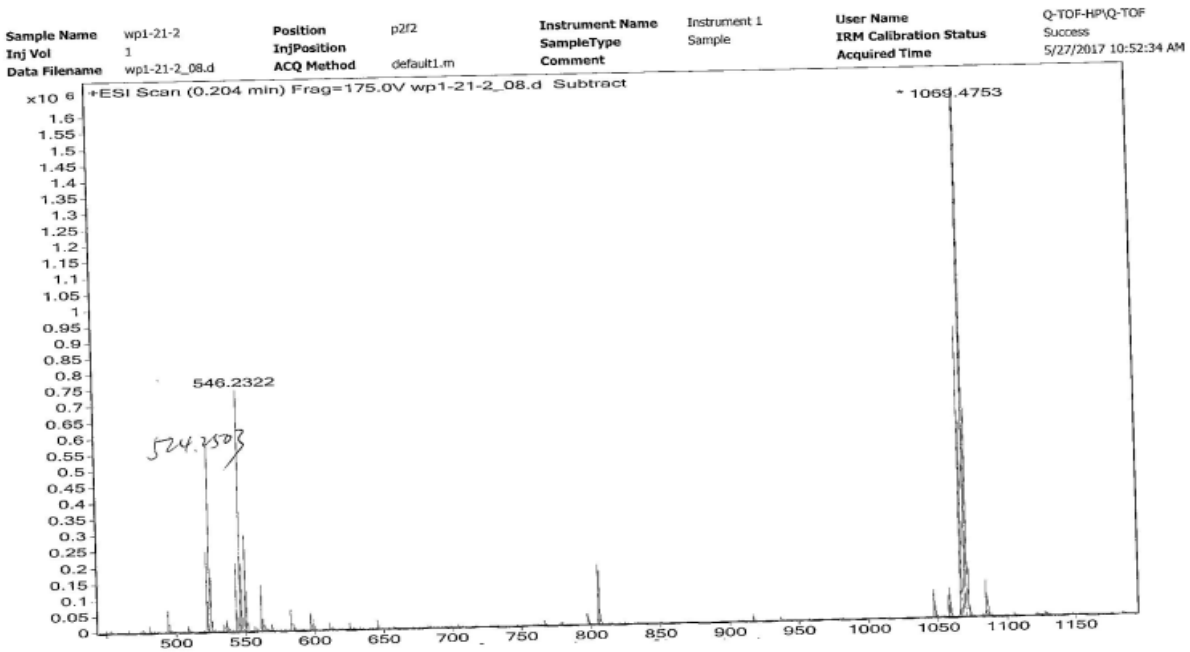
10- 52. ESI spectrum of compound **3g**



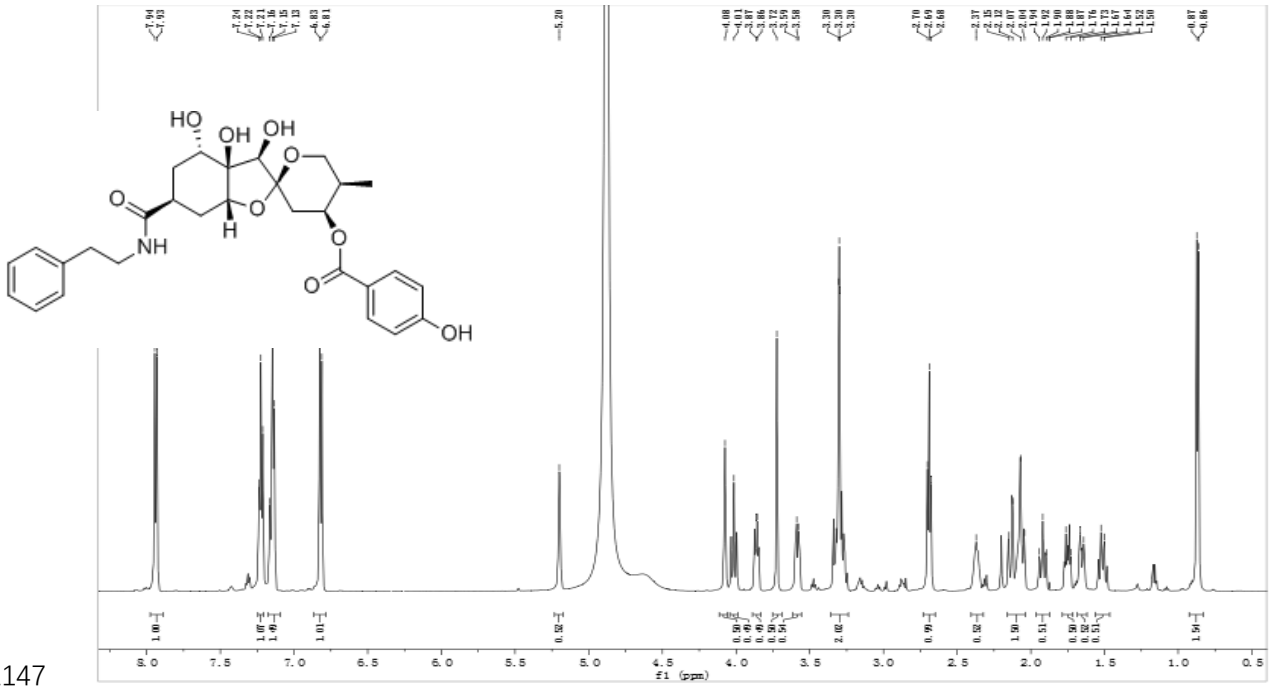
10- 53. ^{1}H NMR spectrum of compound **3h**



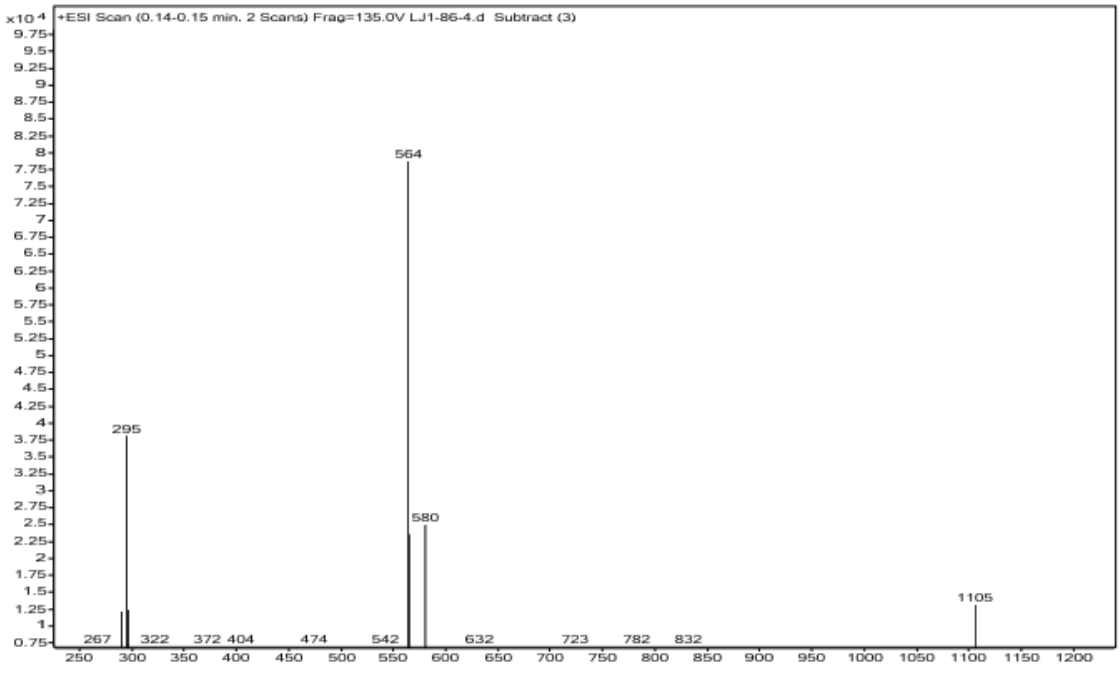
10- 54. ESI spectrum of compound **3h**



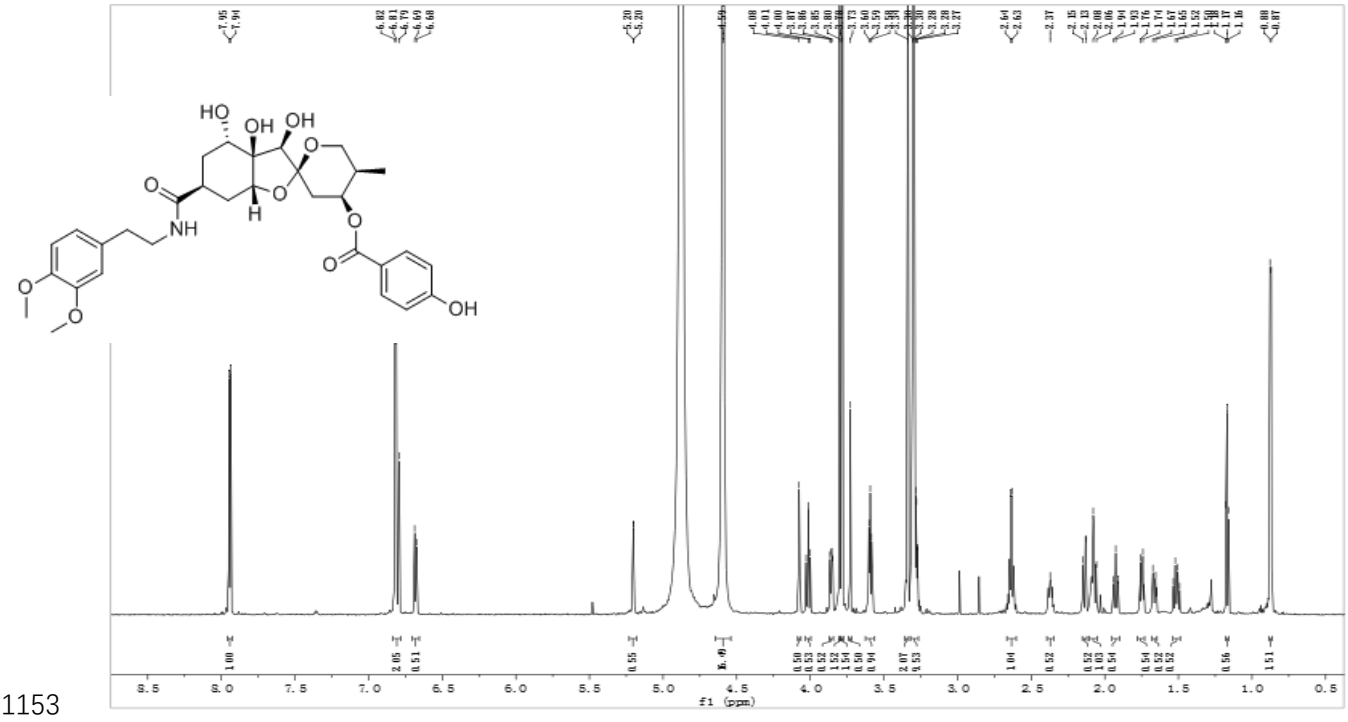
10- 55. ^{1}H NMR spectrum of compound **3i**



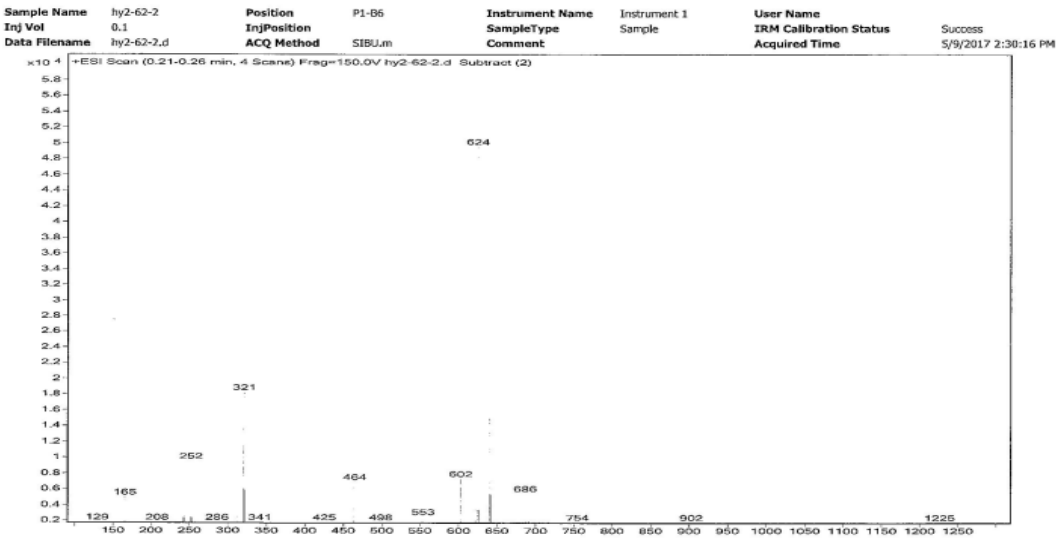
10- 56. ESI spectrum of compound **3i**



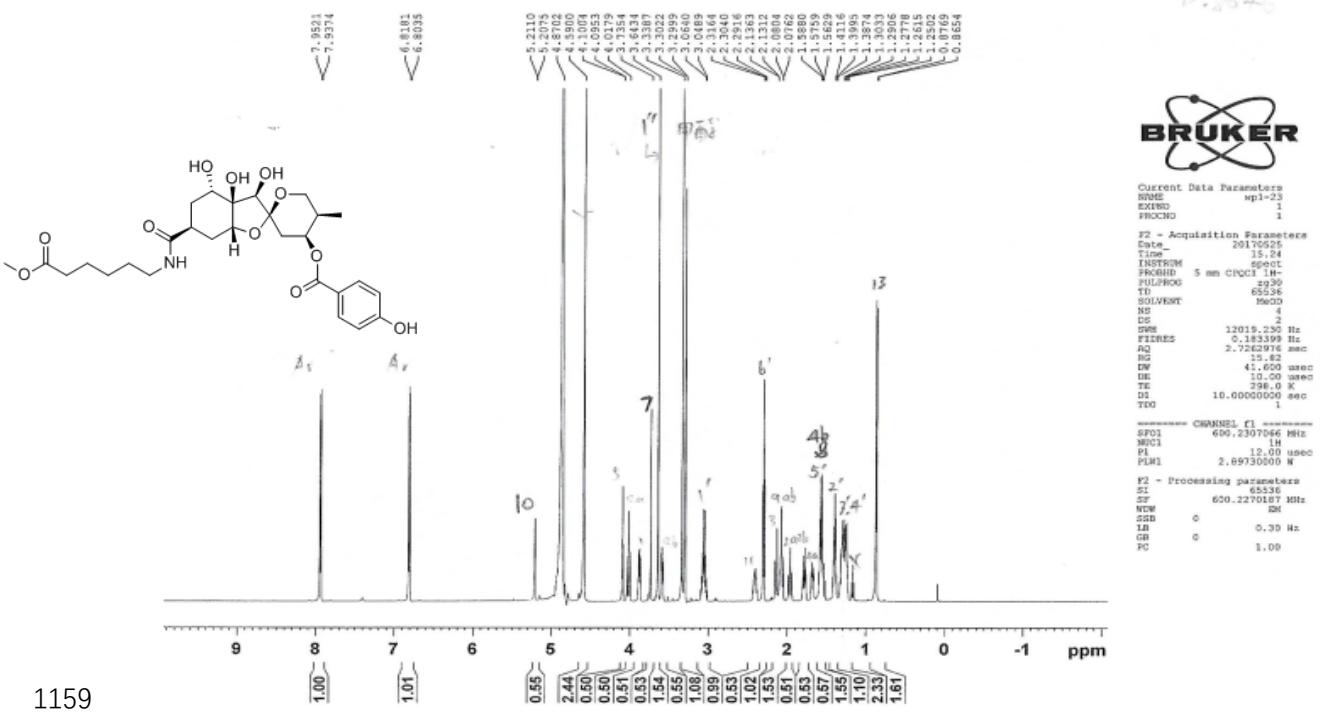
10- 57. ^{1}H NMR spectrum of compound **3j**



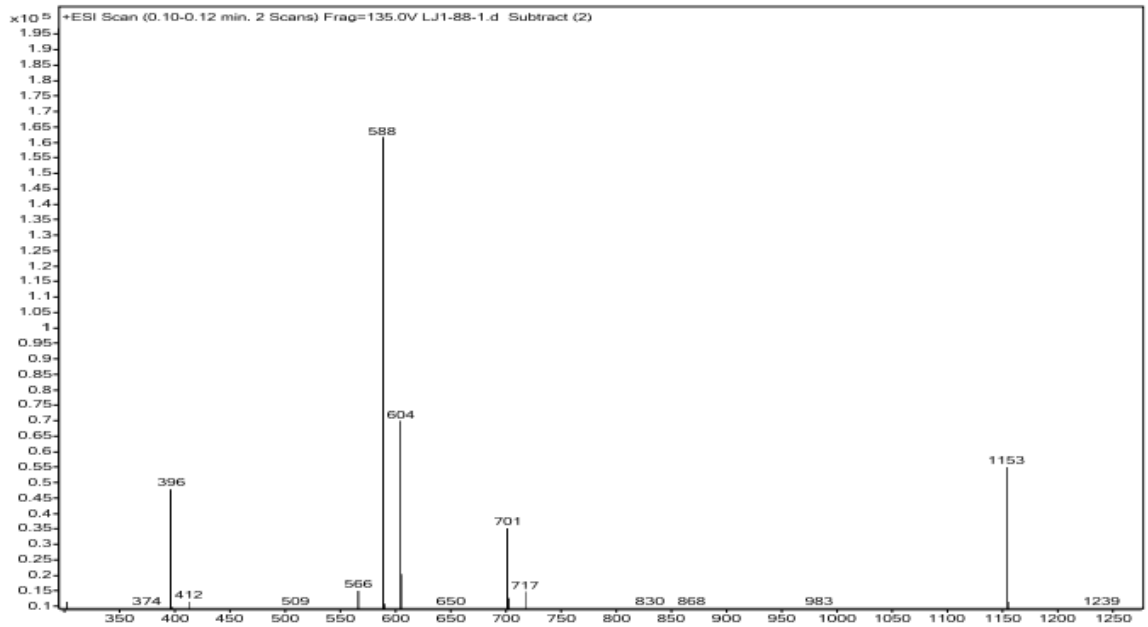
10- 58. ESI spectrum of compound **3j**



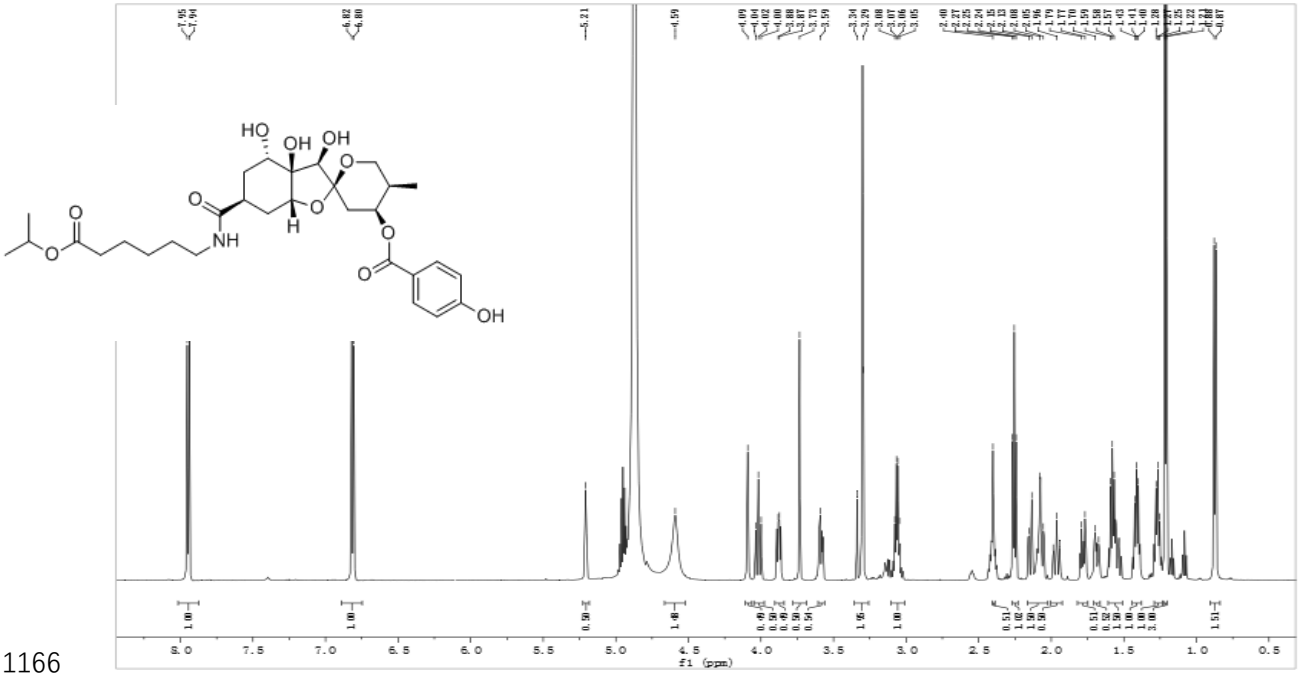
10- 59. ^{1}H NMR spectrum of compound **4a**



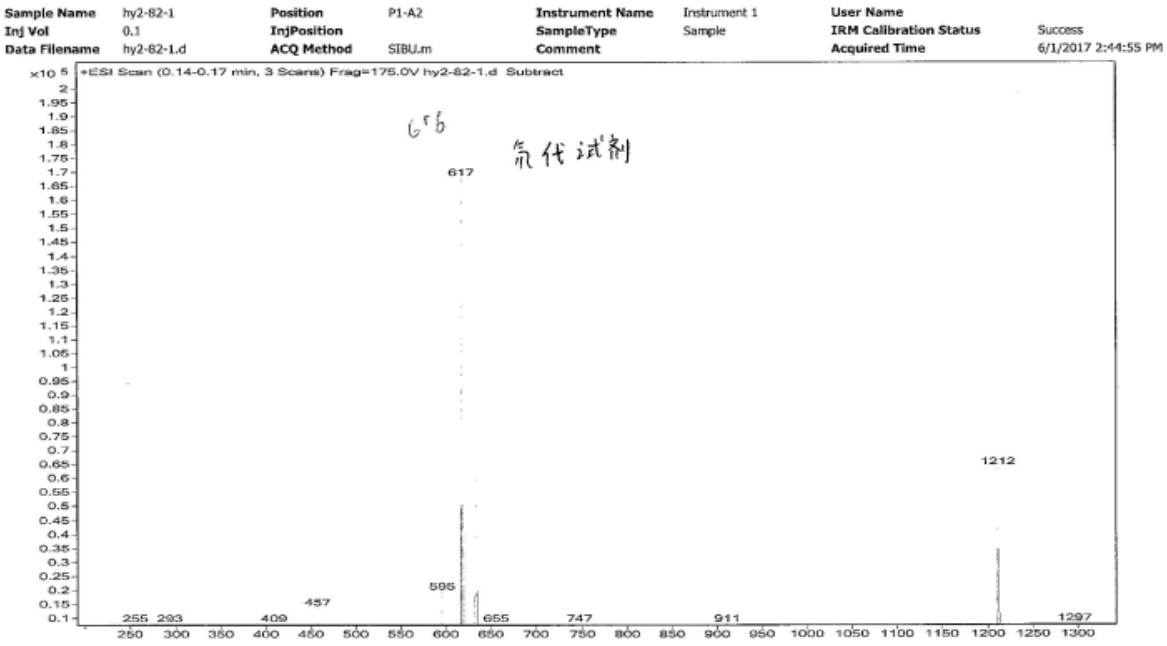
10- 60. ESI spectrum of compound **4a**



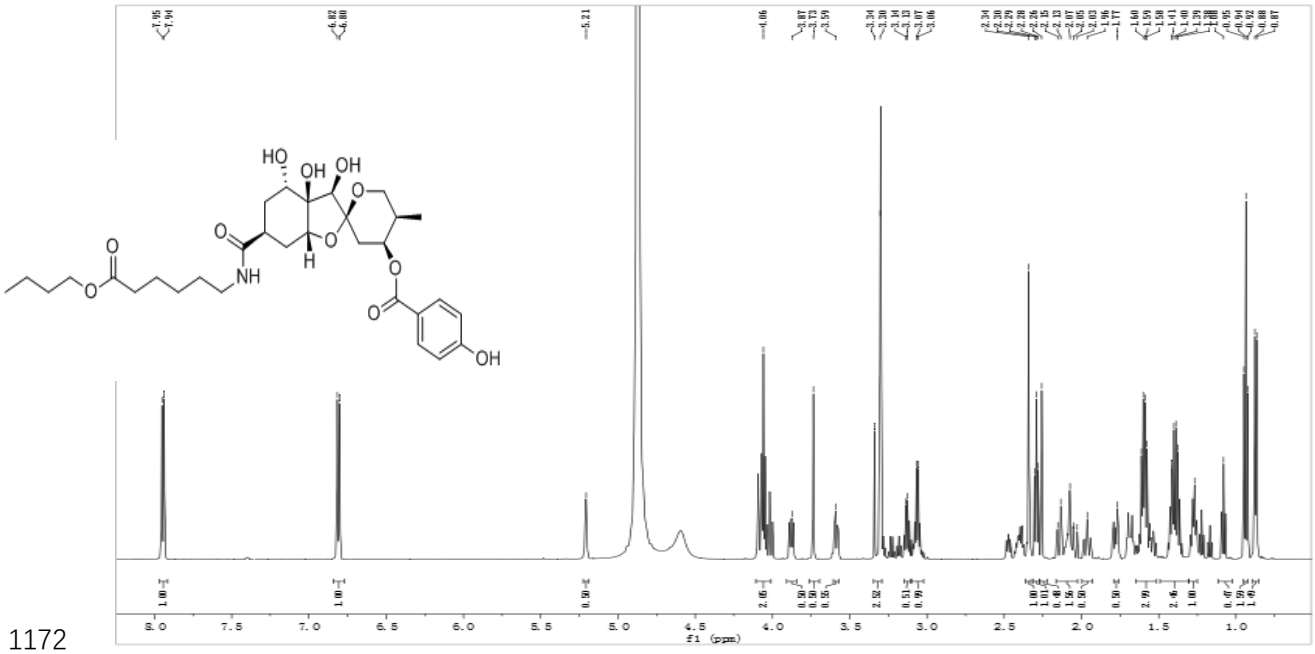
10- 61. ^{1}H NMR spectrum of compound **4b**



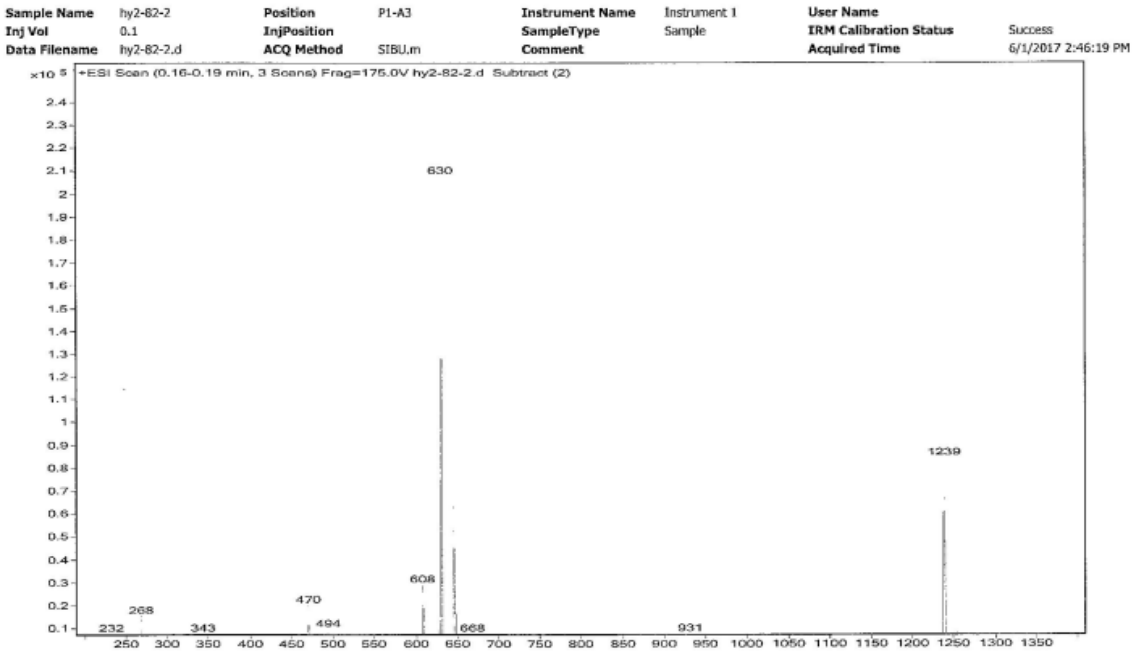
10- 62. ESI spectrum of compound **4b**



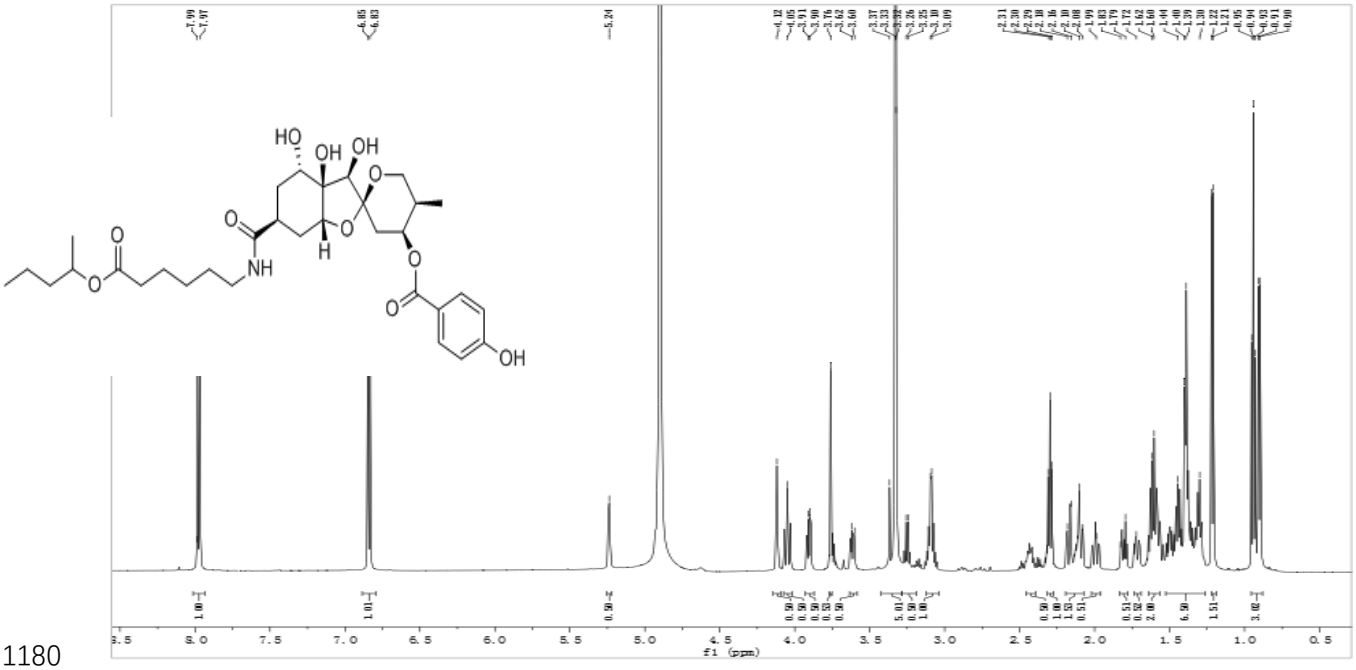
10- 63. ^{1}H NMR spectrum of compound **4c**



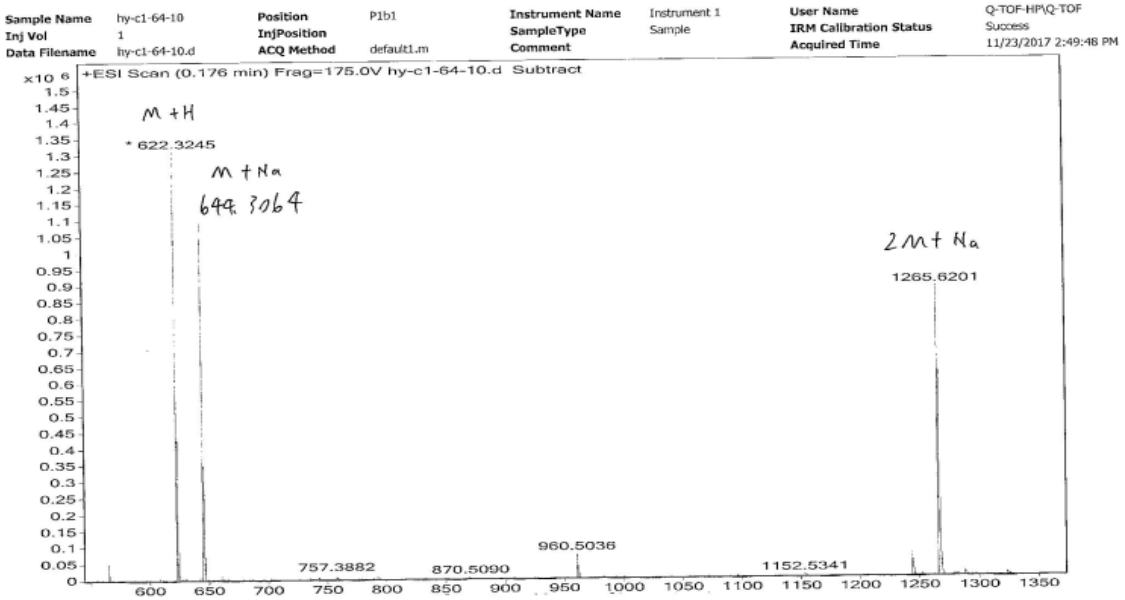
10- 64. ESI spectrum of compound **4c**



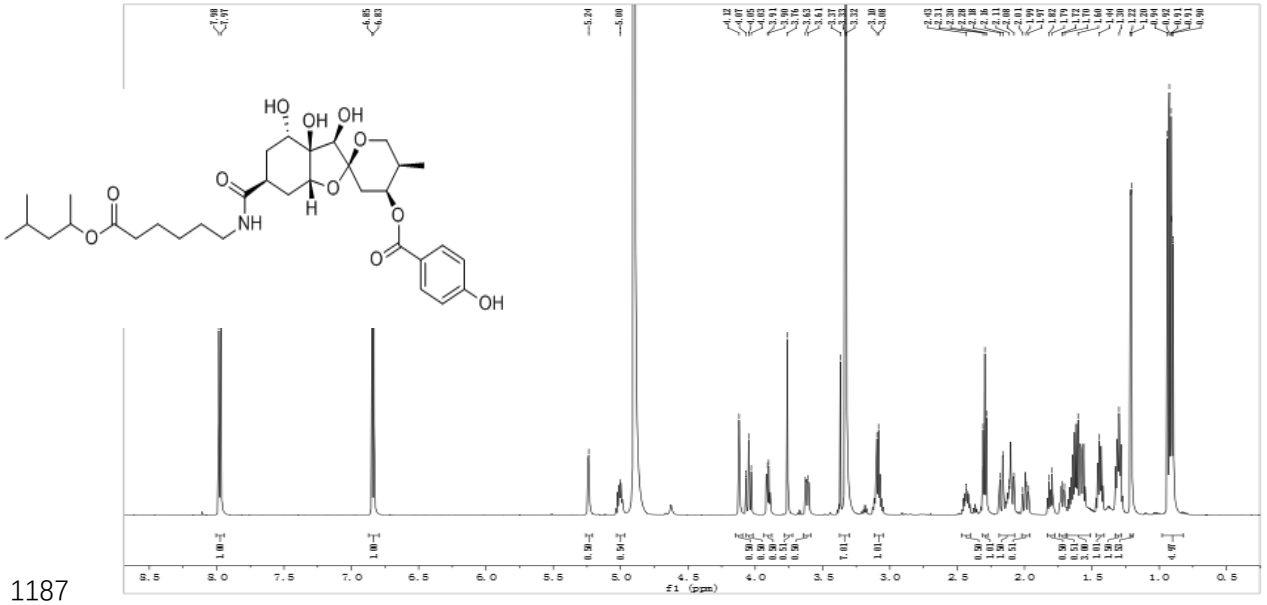
10- 65. ^{1}H NMR spectrum of compound **4d**



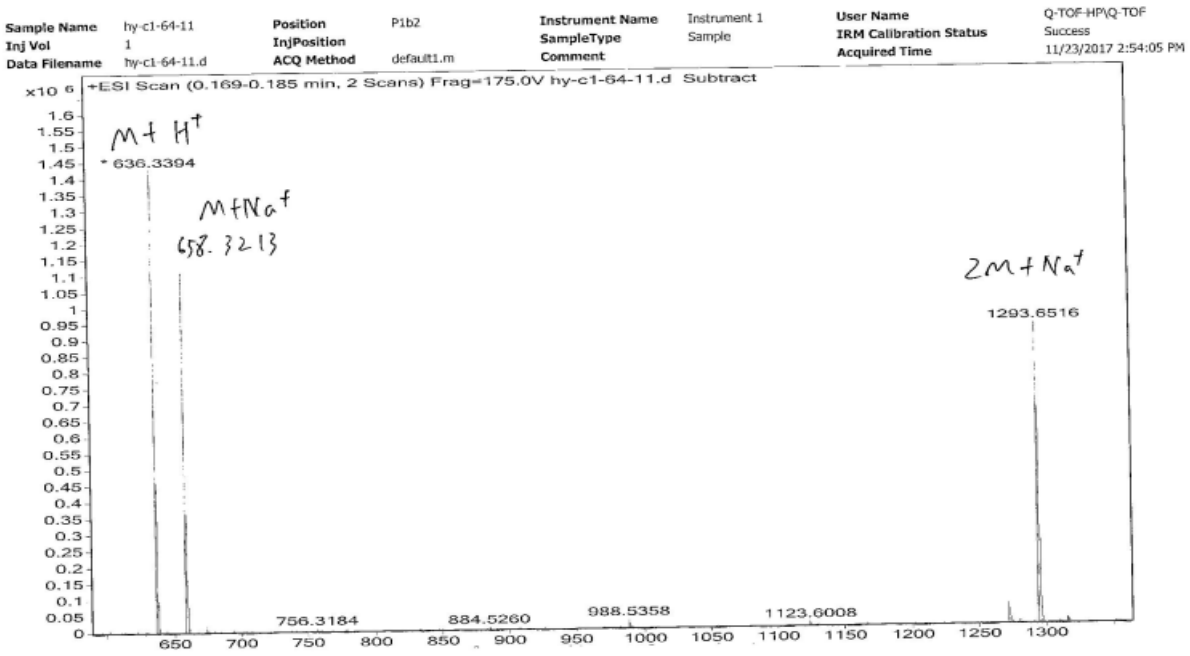
10- 66. ESI spectrum of compound **4d**



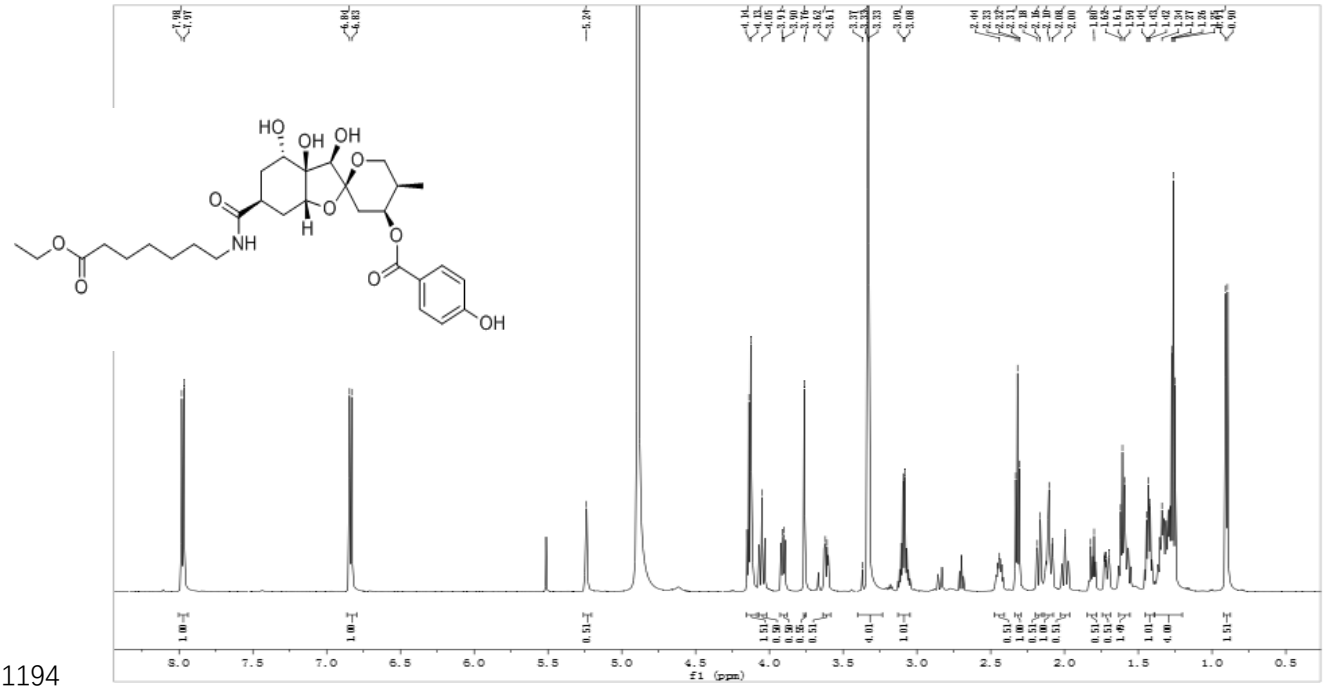
10- 67. ^{1}H NMR spectrum of compound **4e**



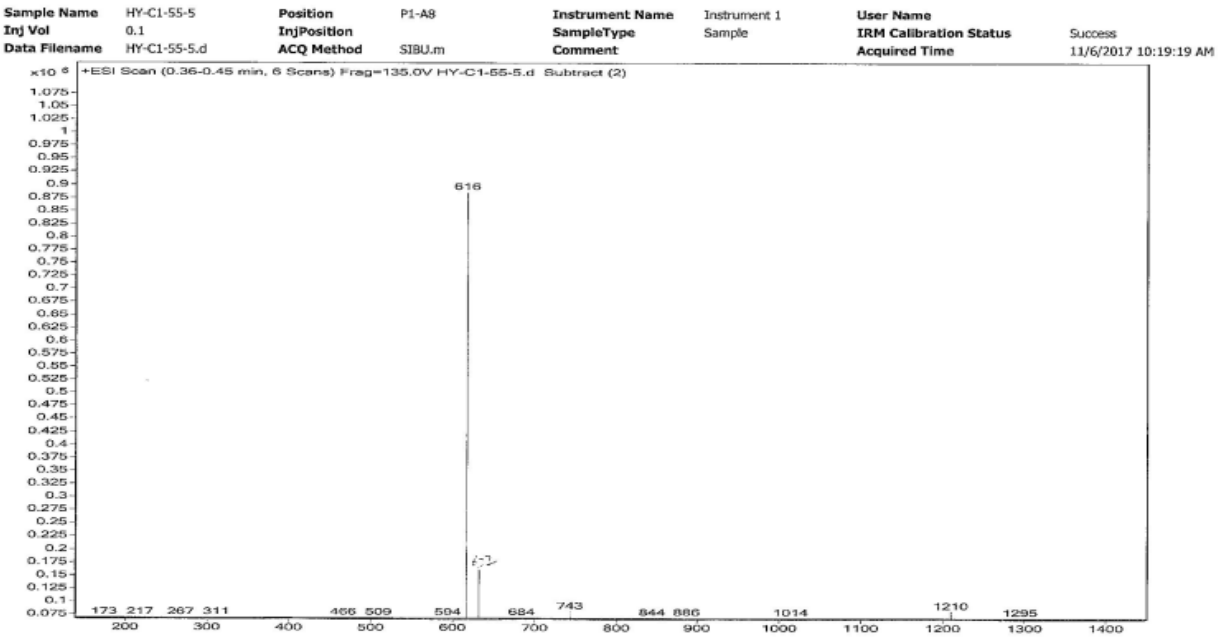
10- 68. ESI spectrum of compound **4e**



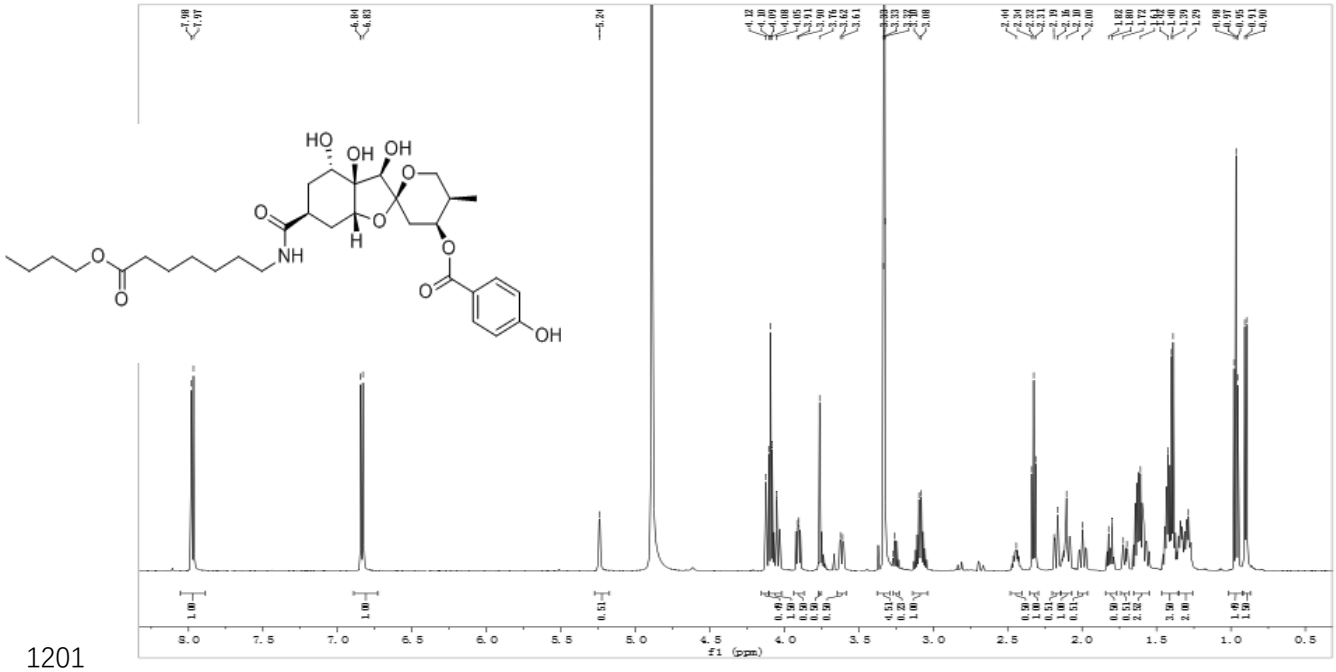
10- 69. ^{1}H NMR spectrum of compound **4f**



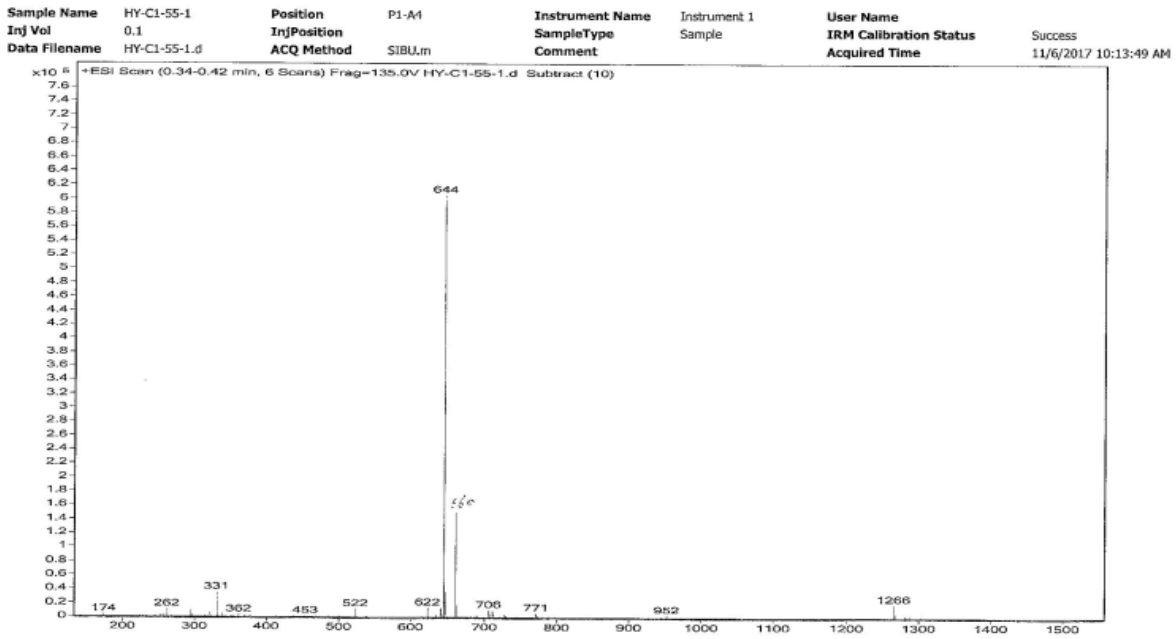
10- 70. ESI spectrum of compound **4f**



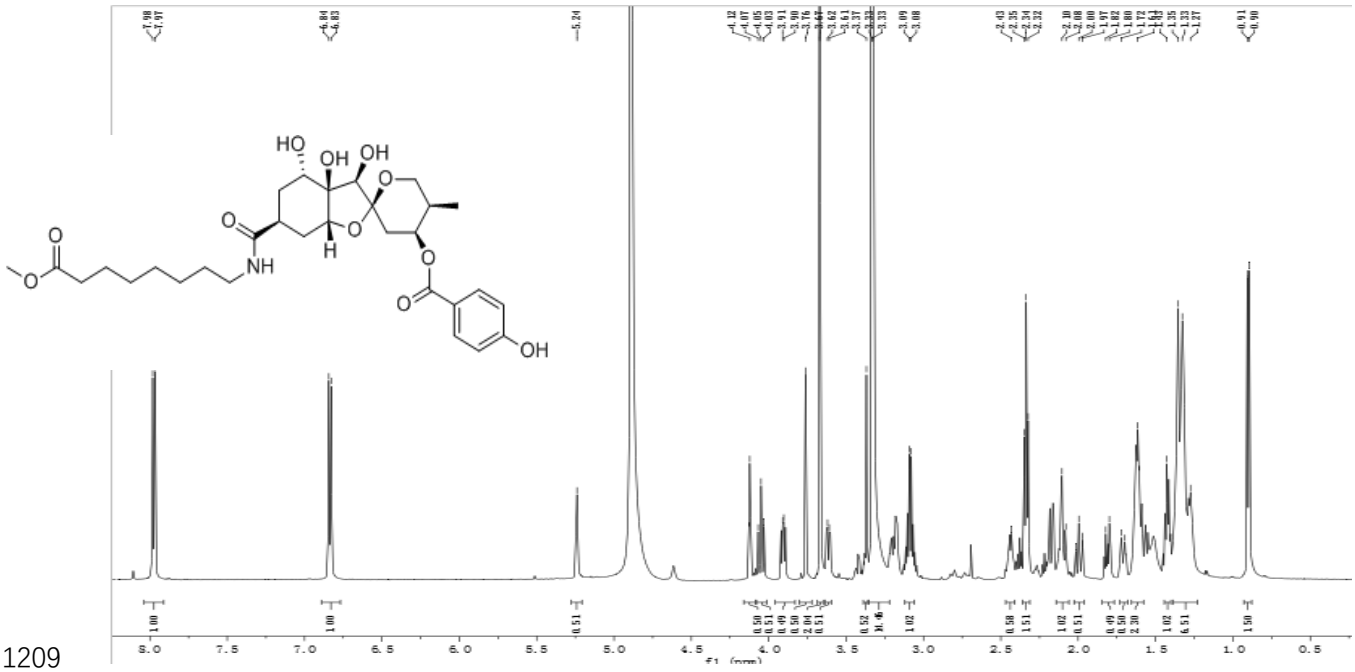
10- 71. ^{1}H NMR spectrum of compound **4g**



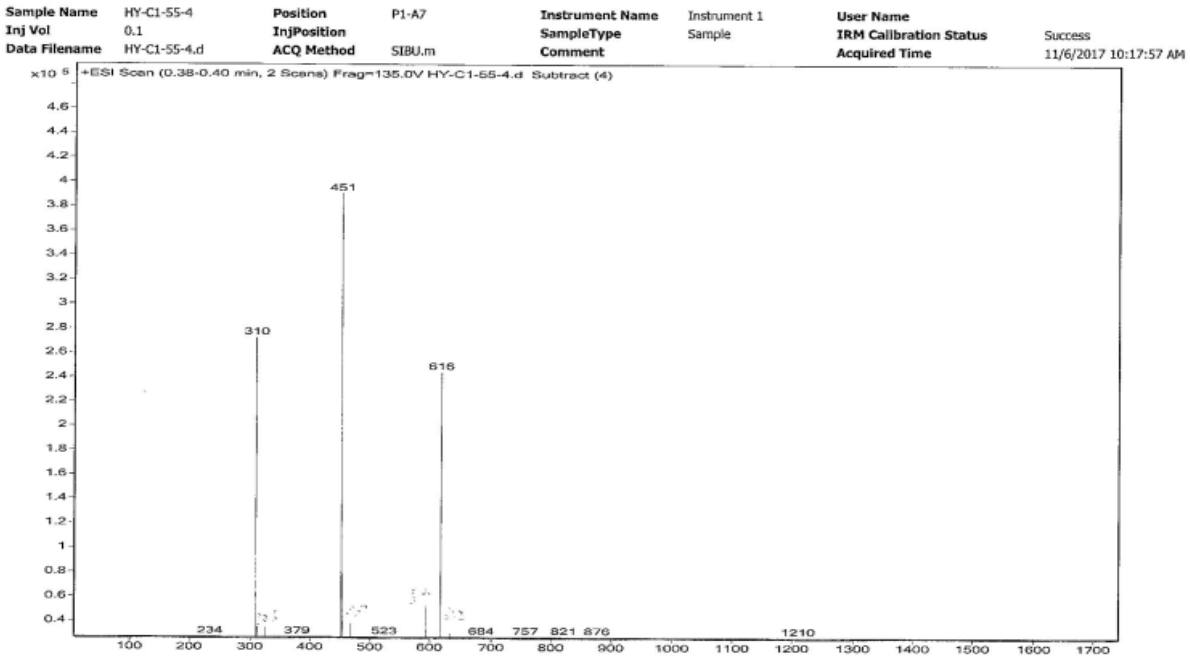
10- 72. ESI spectrum of compound **4g**



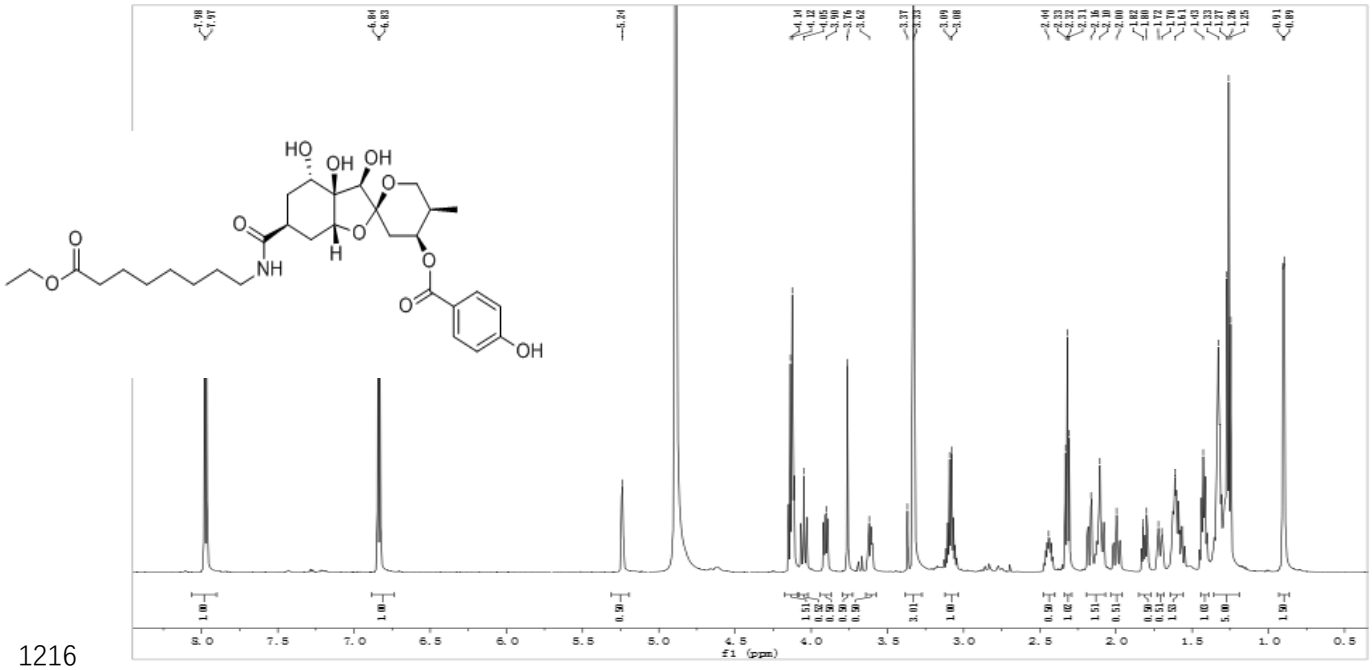
10- 73. ^{1}H NMR spectrum of compound **4h**



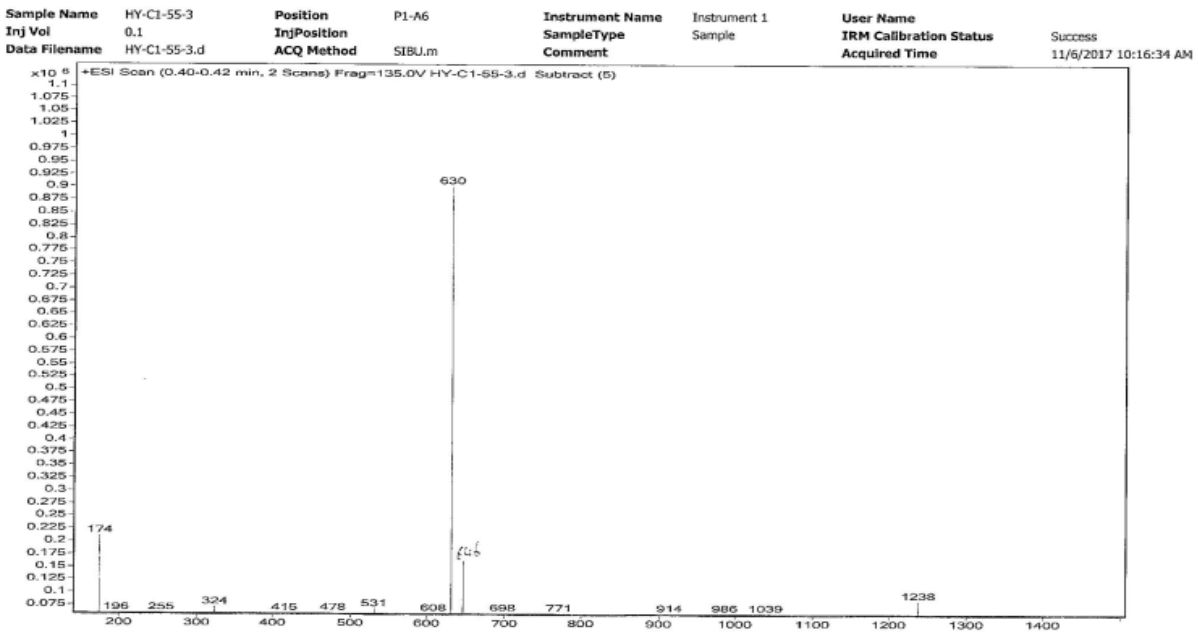
10- 74. ESI spectrum of compound **4h**



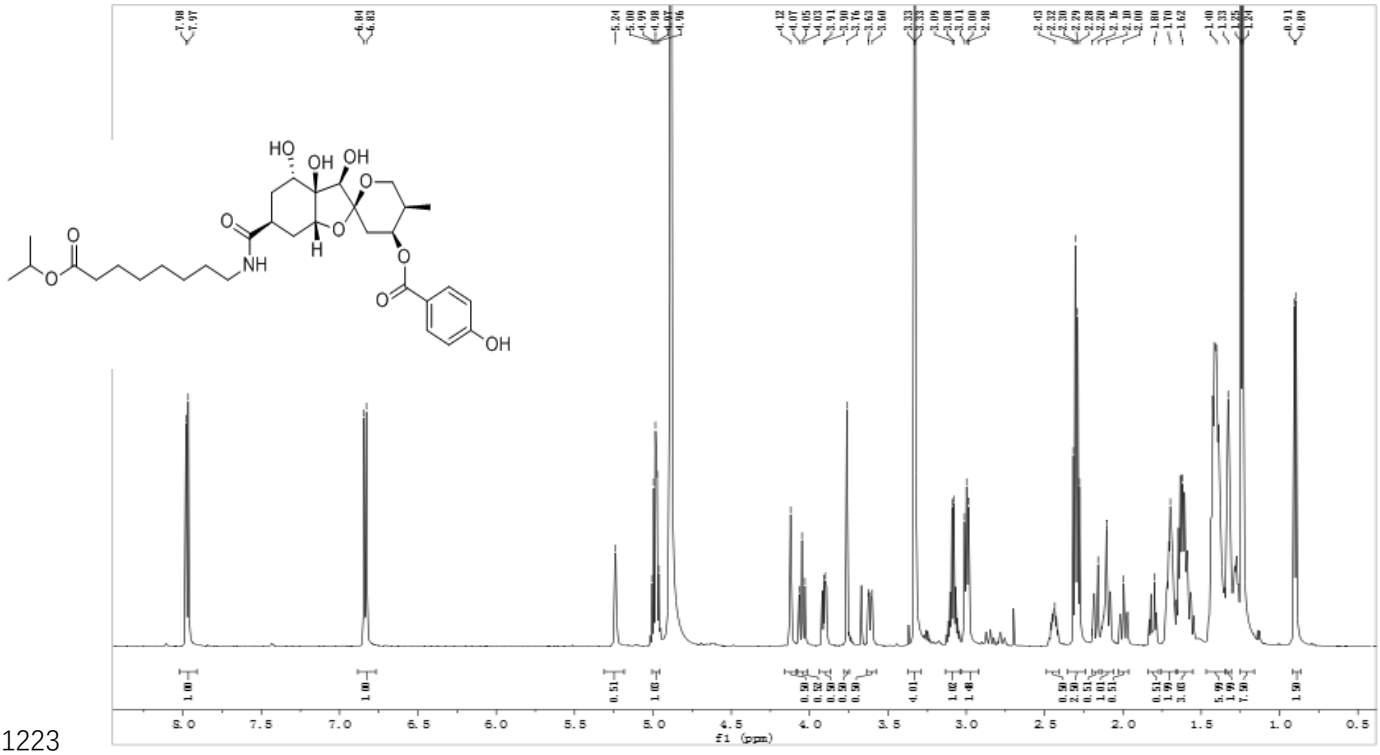
10- 75. ^{1}H NMR spectrum of compound **4i**



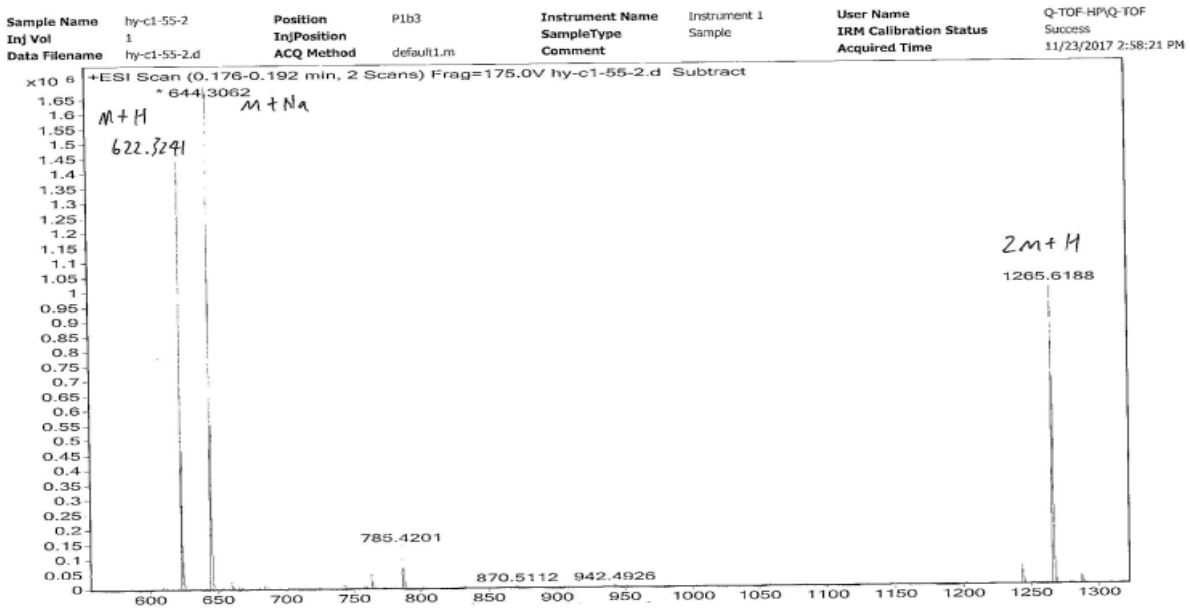
10- 76. ESI spectrum of compound **4i**



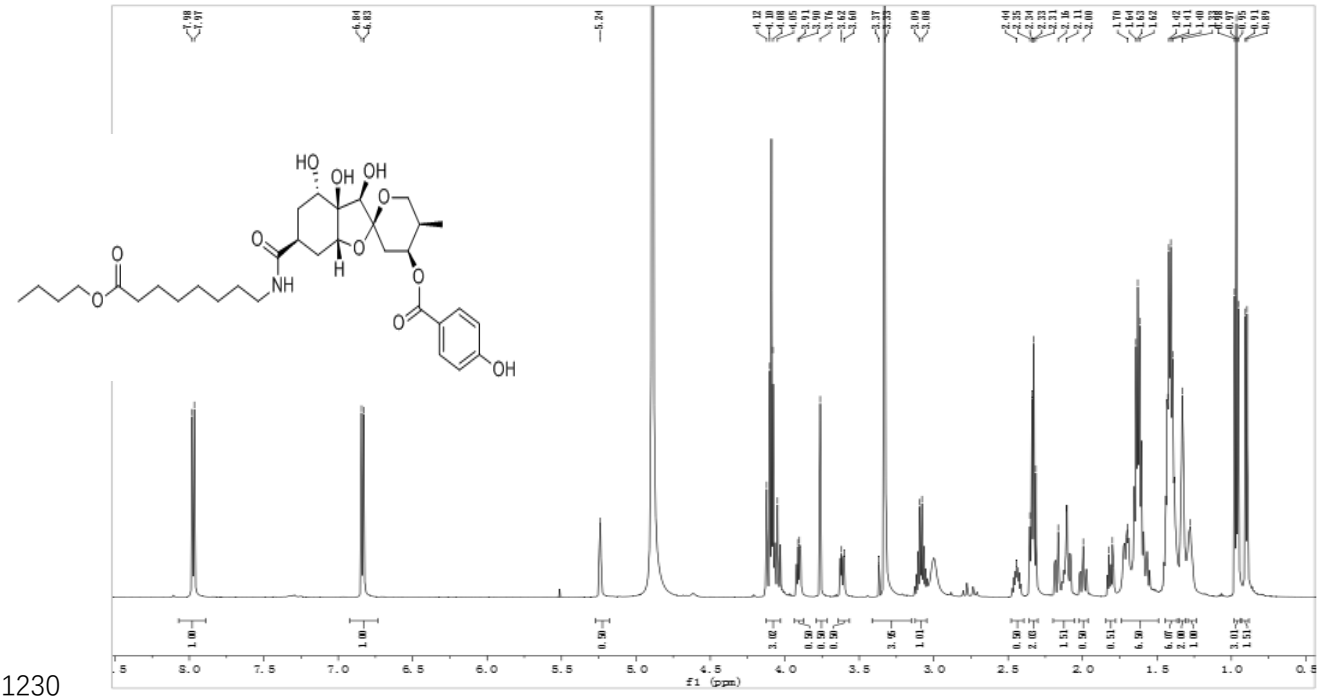
10- 77. ^{1}H NMR spectrum of compound **4j**



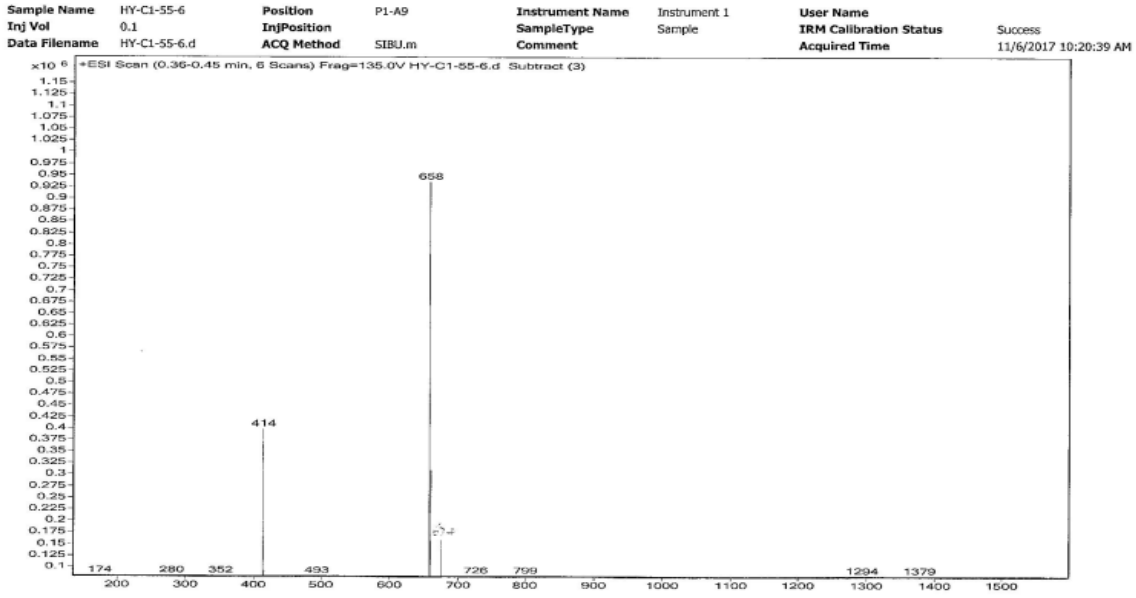
10- 78. ESI spectrum of compound **4j**



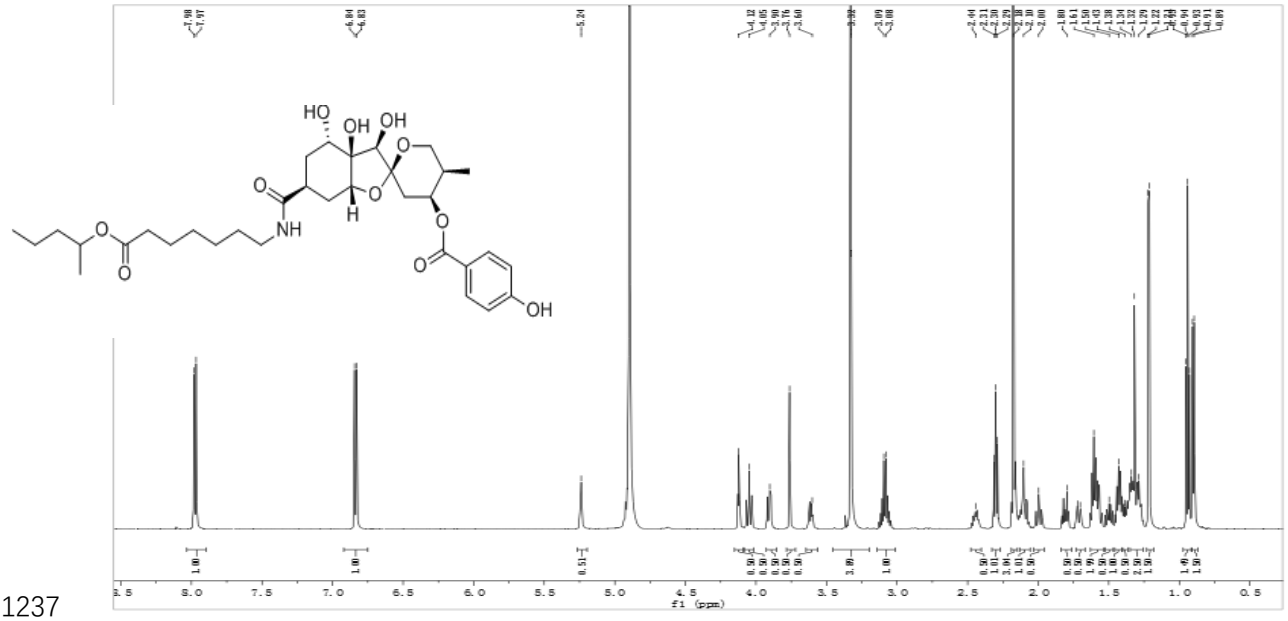
10- 79. ^{1}H NMR spectrum of compound **4k**



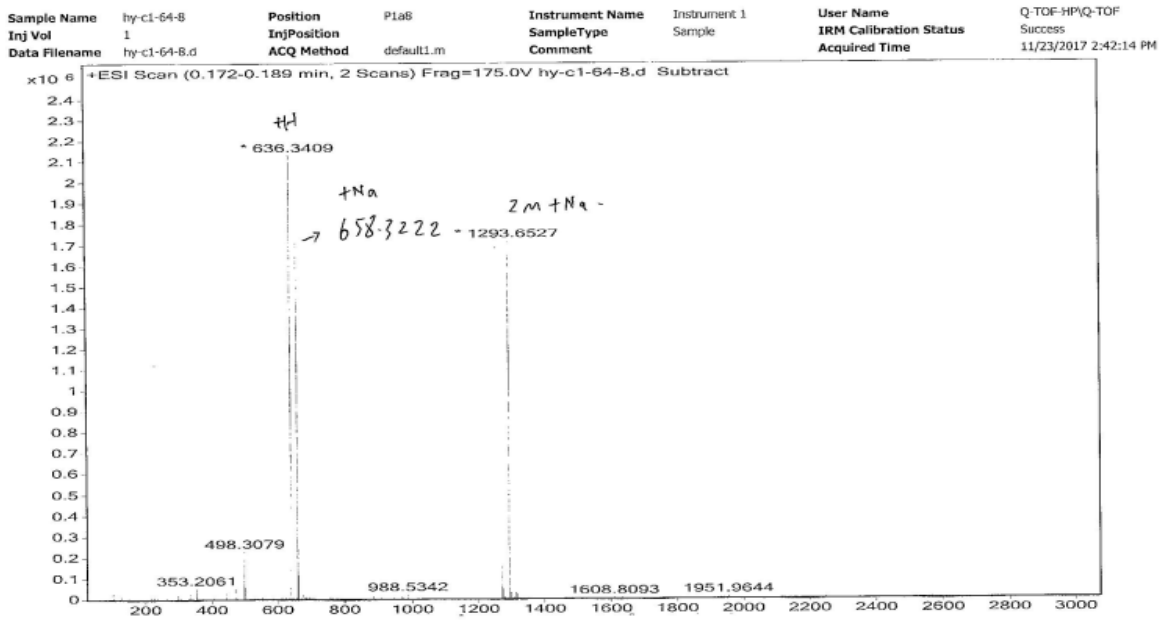
10- 80. ESI spectrum of compound **4k**



10- 81. ^{1}H NMR spectrum of compound 4l



1241 10- 82. ESI spectrum of compound **4l**



1242

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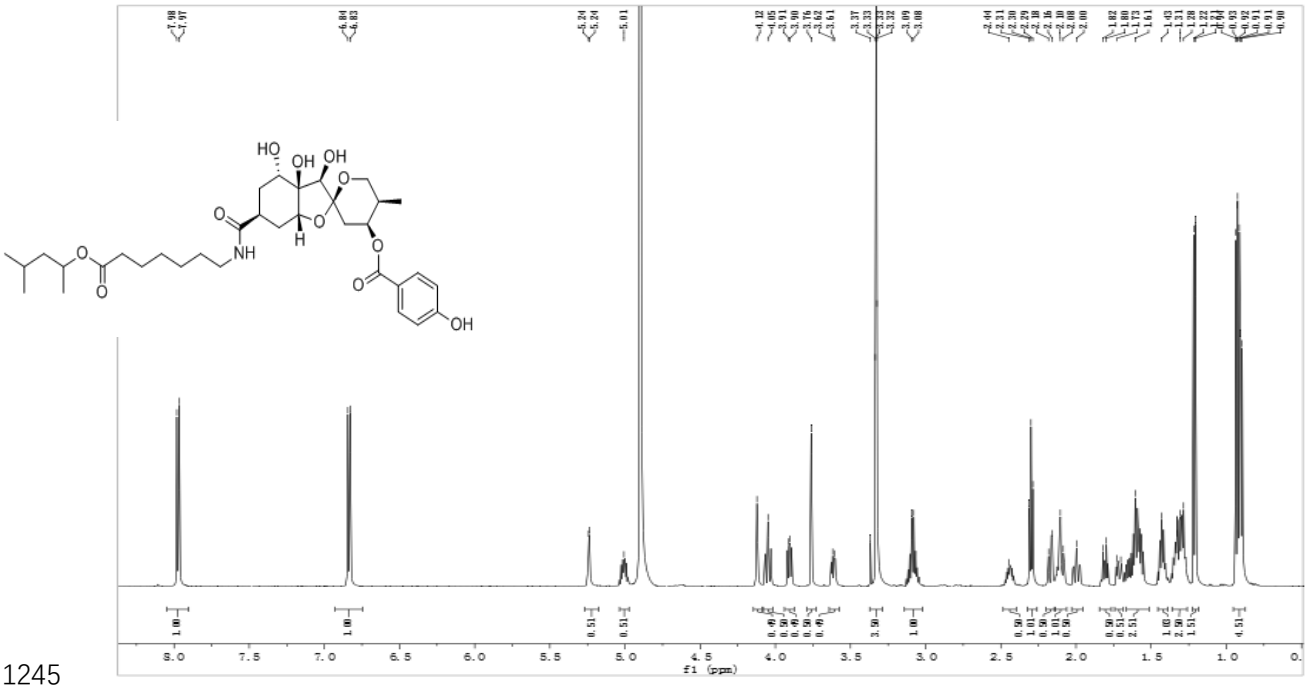
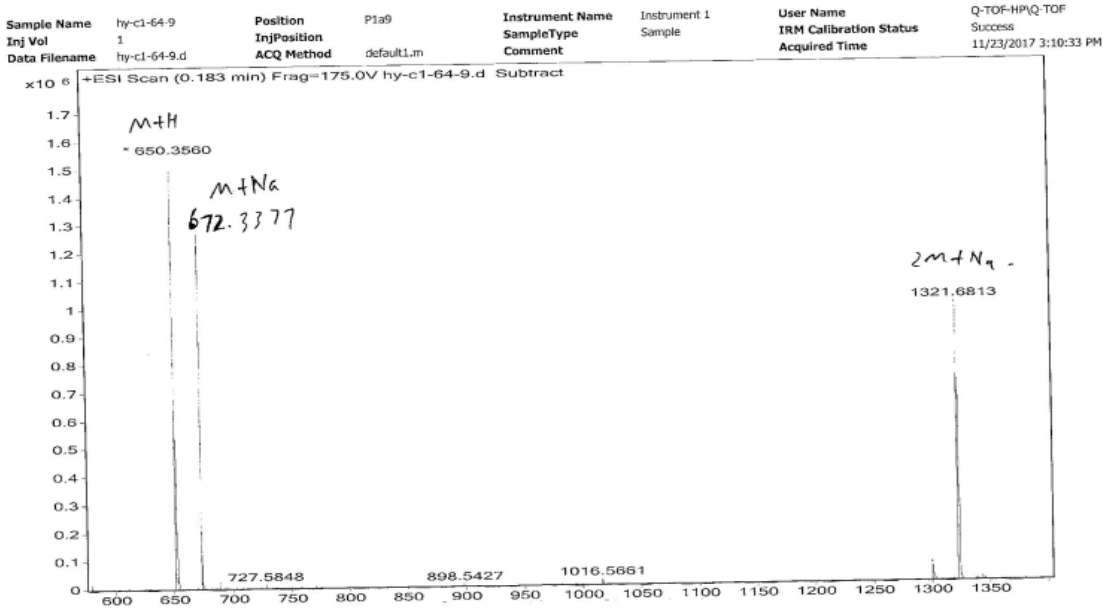
1244 10- 83. ^{1}H NMR spectrum of compound **4m**



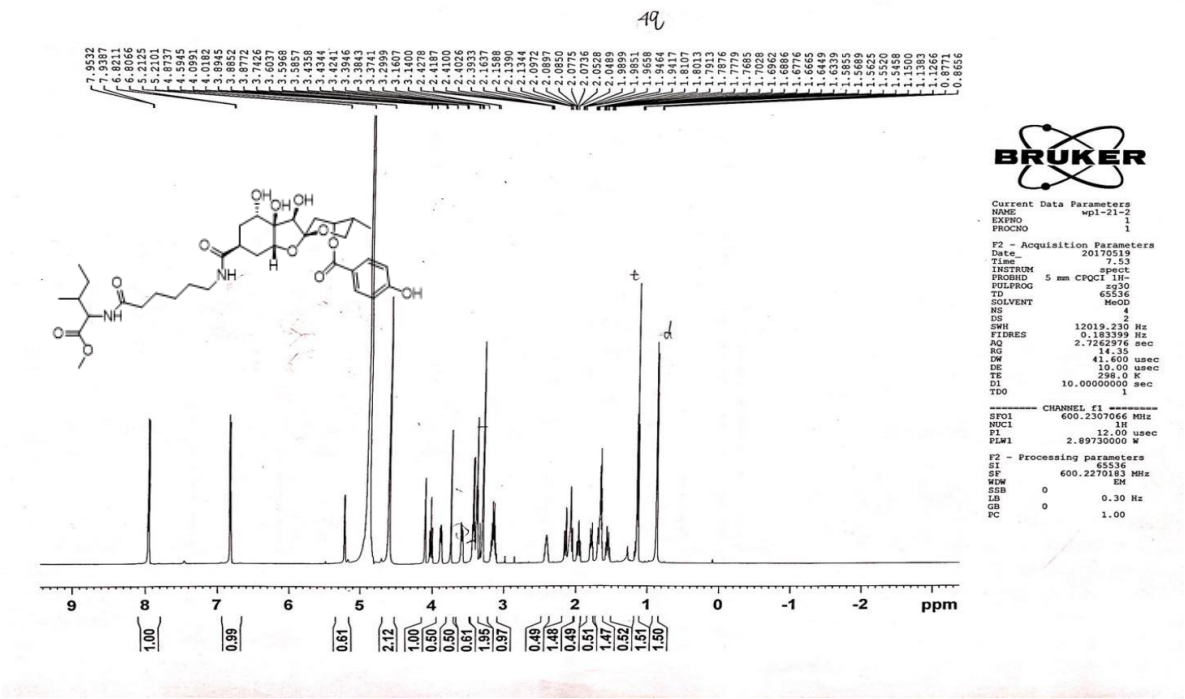
1245

1246

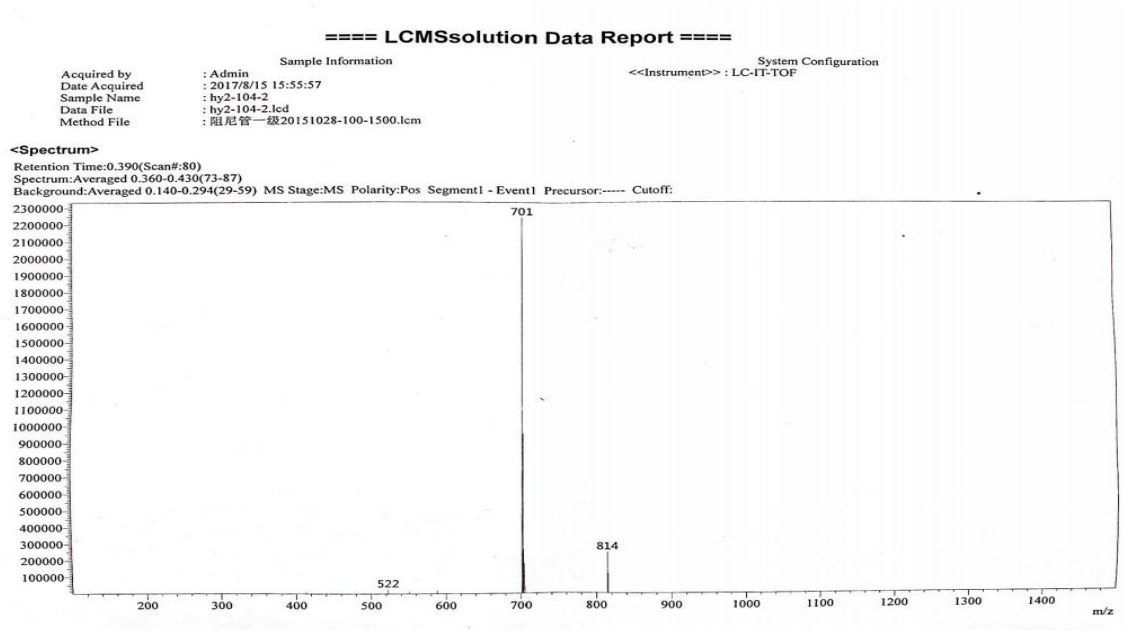
10- 84. ESI spectrum of compound **4m**



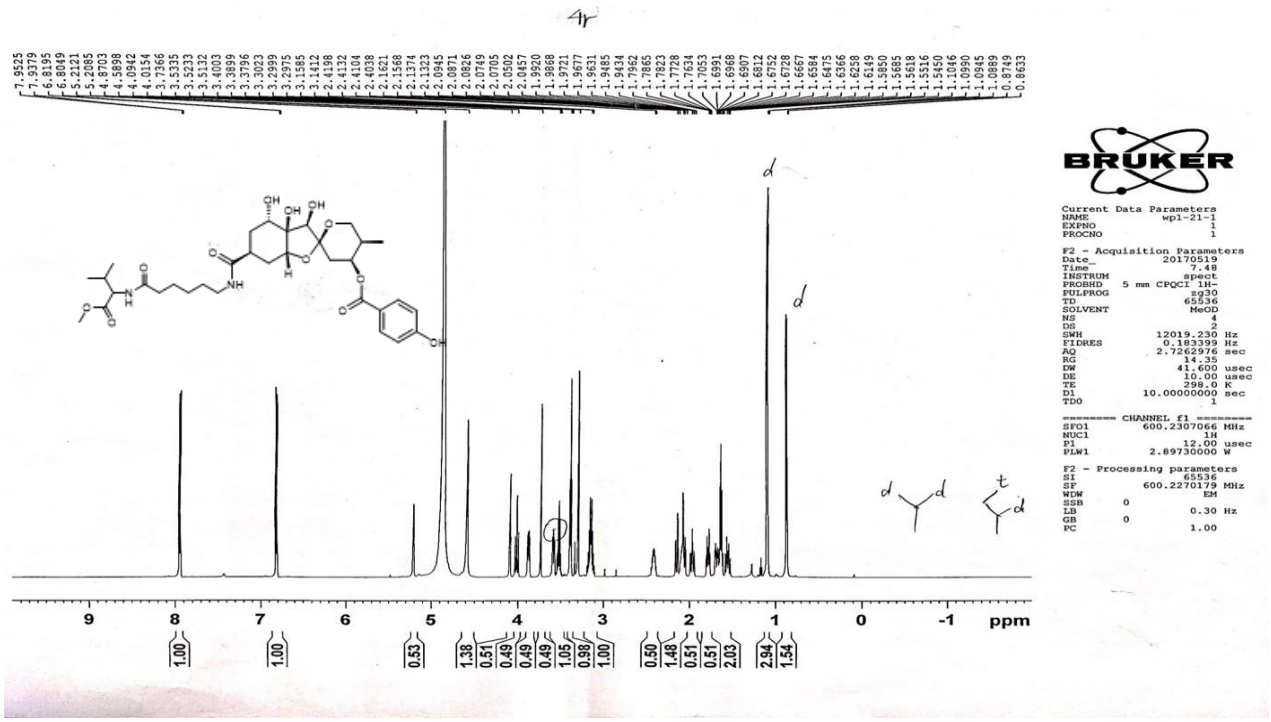
10- 85. ^{1}H NMR spectrum of compound **4n**



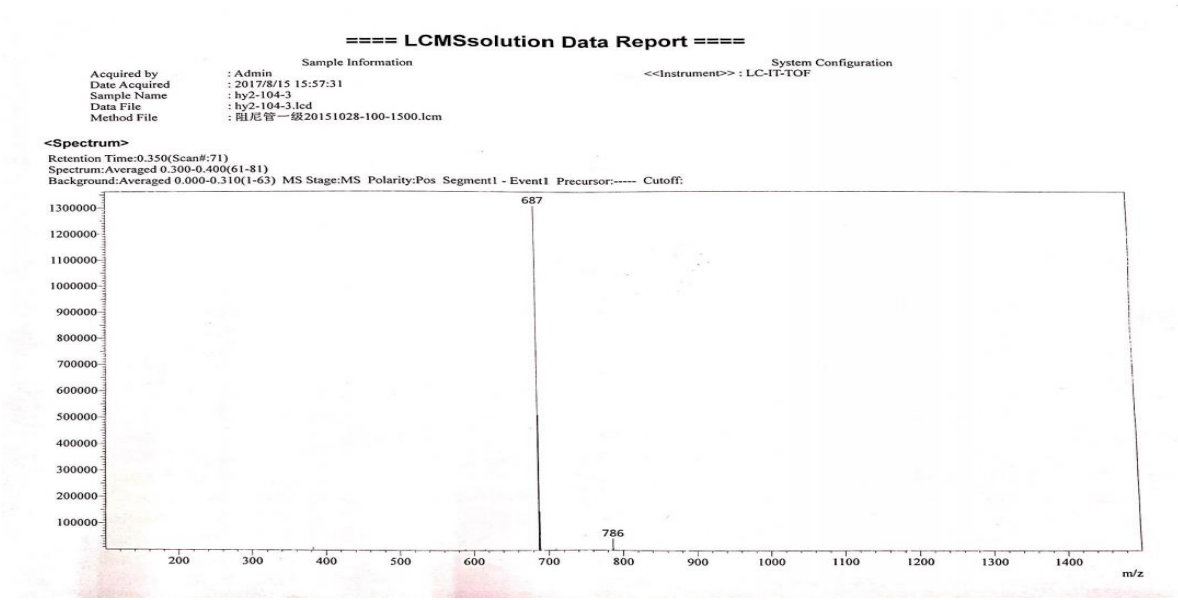
10- 86. ESI spectrum of compound **4n**



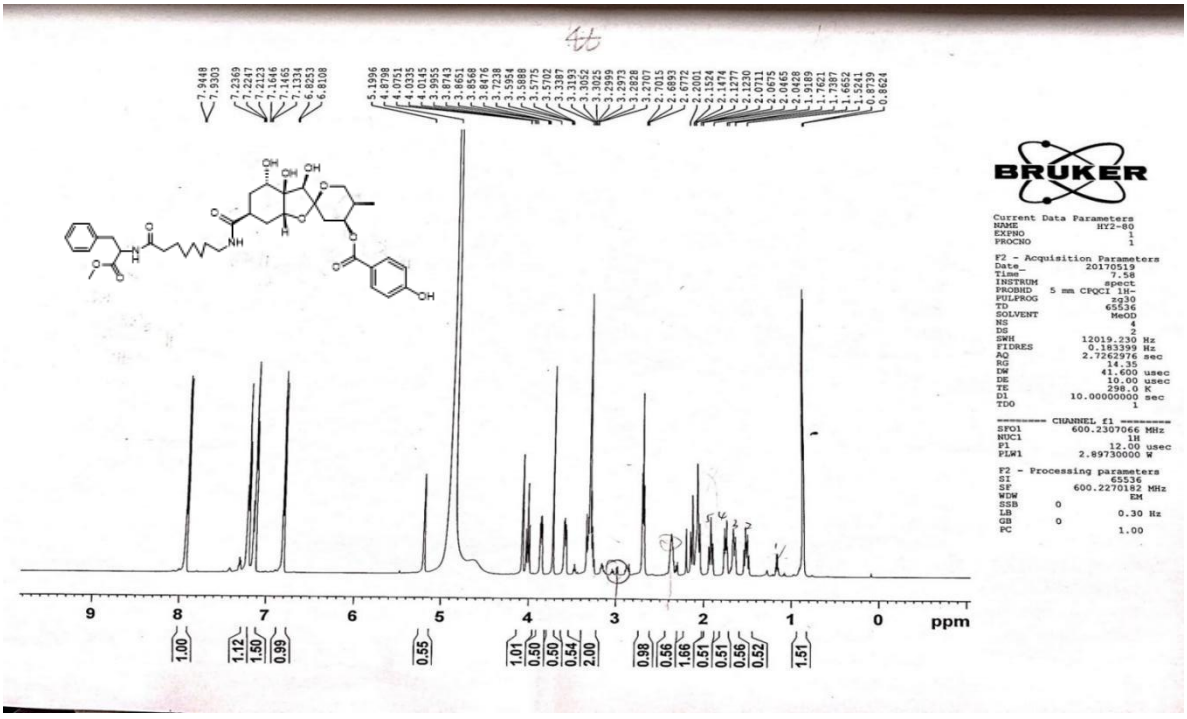
10- 87. ^{1}H NMR spectrum of compound **4o**



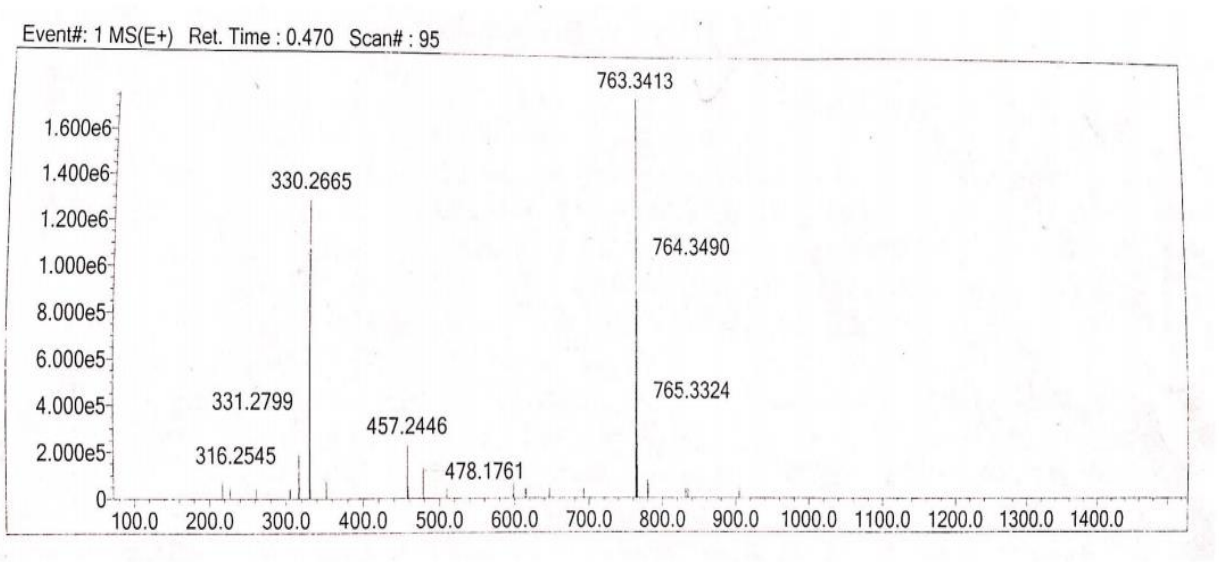
10- 88. ESI spectrum of compound **4o**



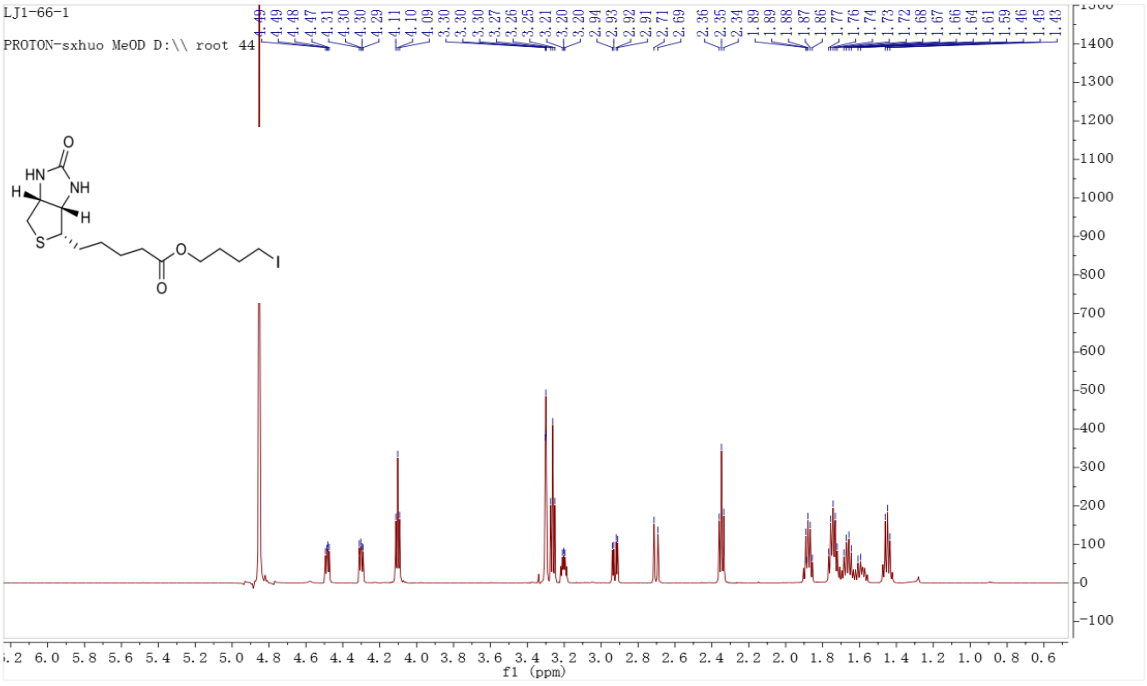
10- 89. ^{1}H NMR spectrum of compound **4p**



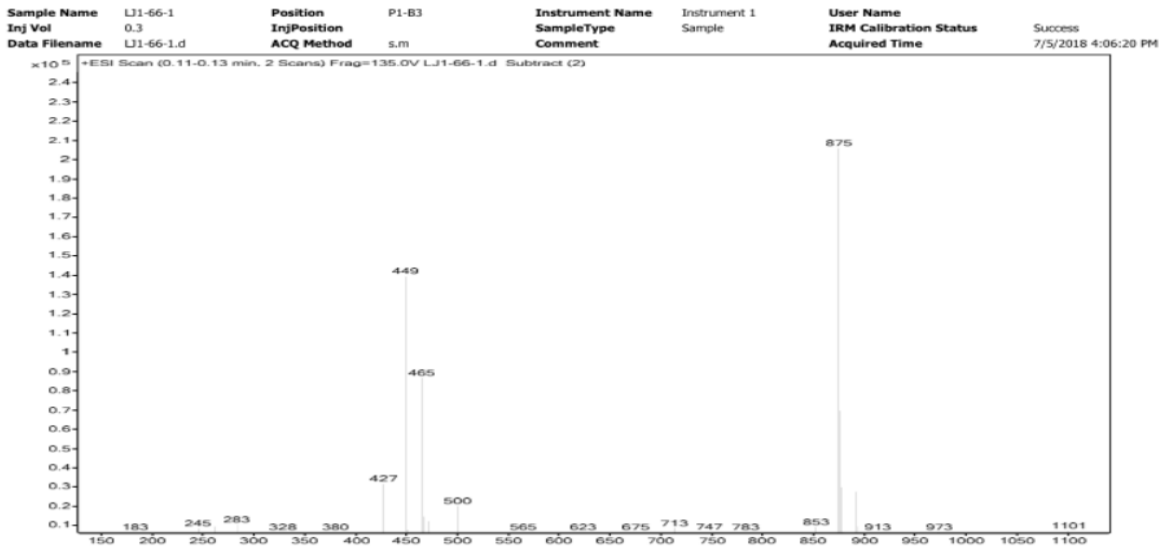
10- 90. ESI spectrum of compound **4p**



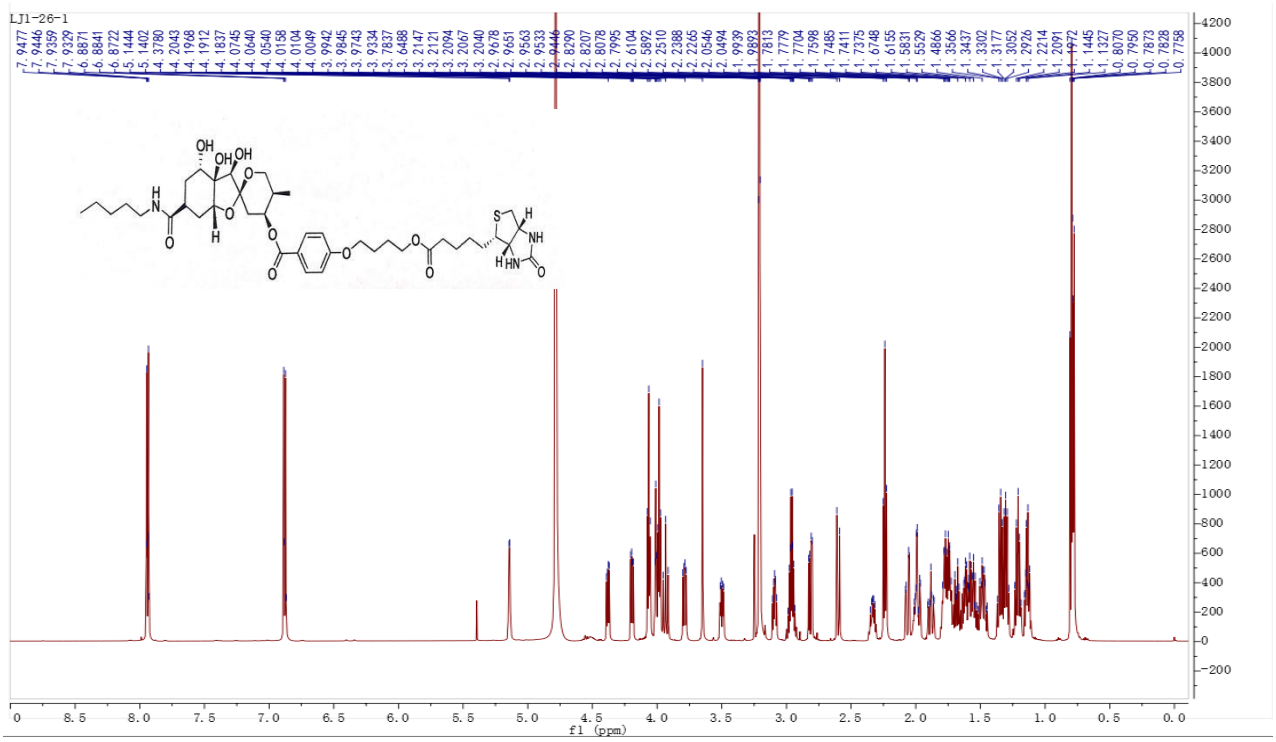
10- 91. ^{1}H NMR spectrum of the blank control of ABPP Probes



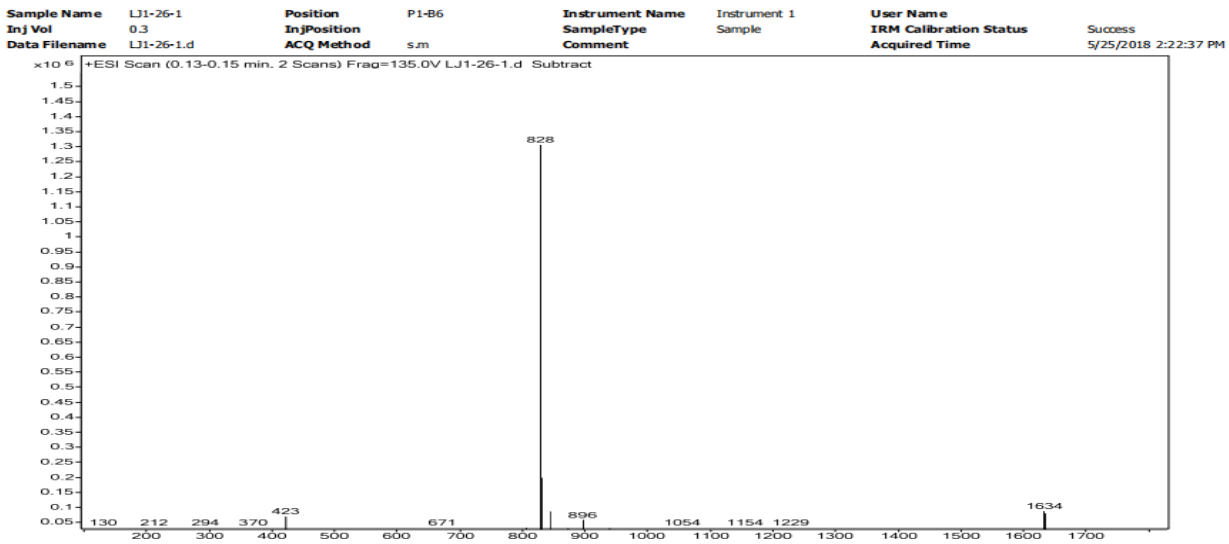
10- 92. ESI spectrum of the blank control of ABPP Probes



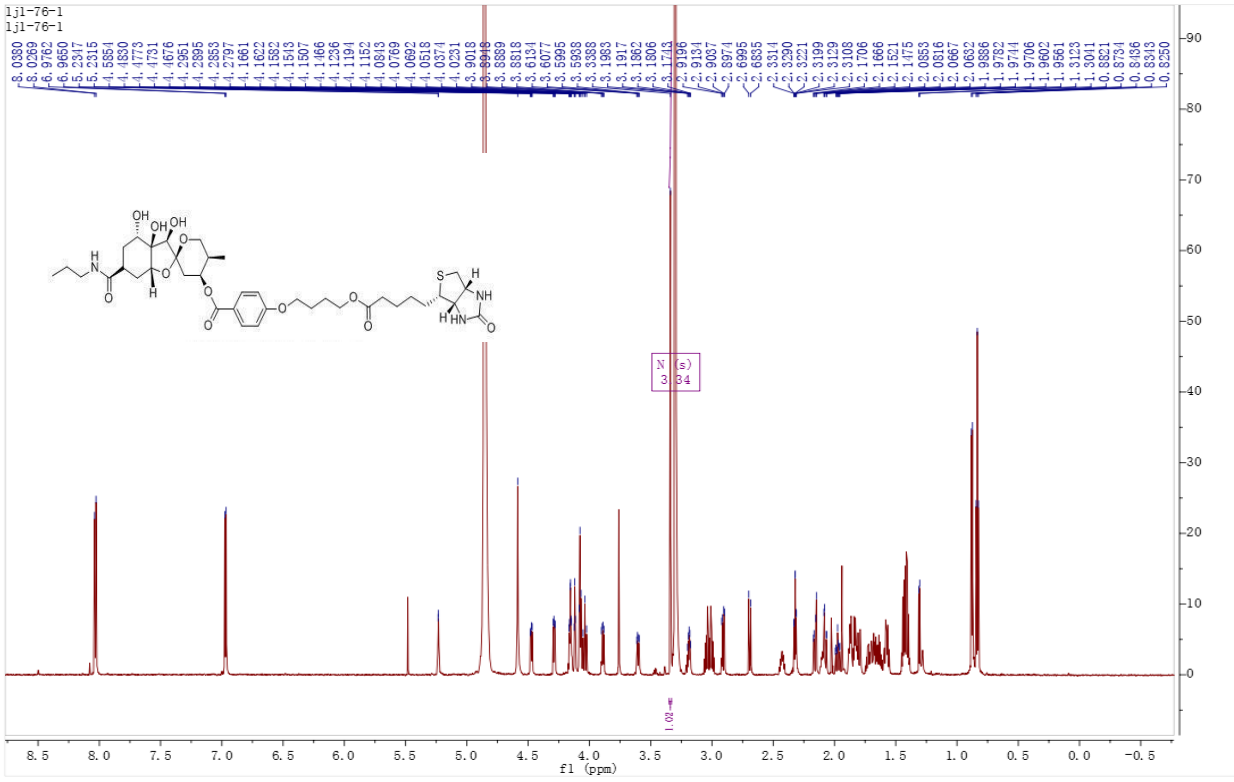
10- 93.[1]H NMR spectrum of positive probe of ABPP Probes



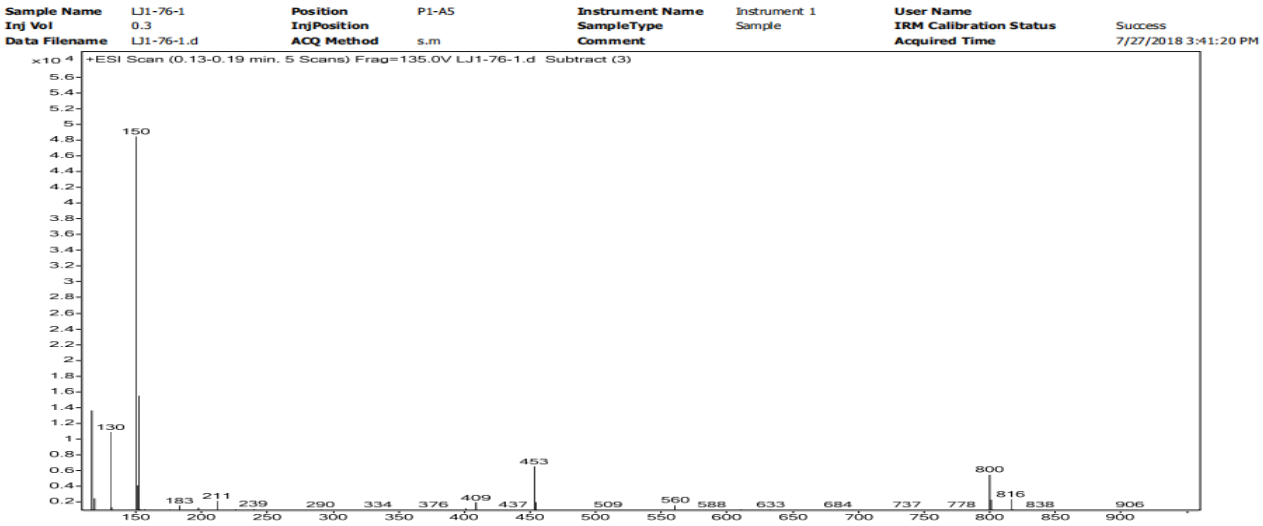
10- 94. ESI spectrum of positive probe of ABPP Probes



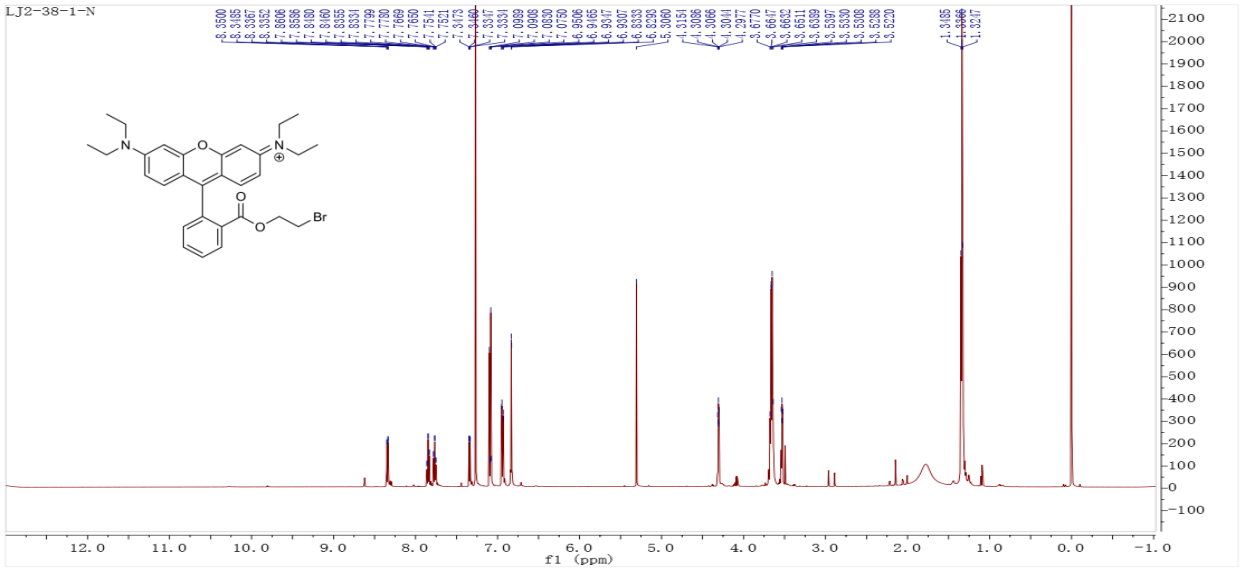
10- 95 ^{1}H NMR spectrum of negative probe of ABPP Probes



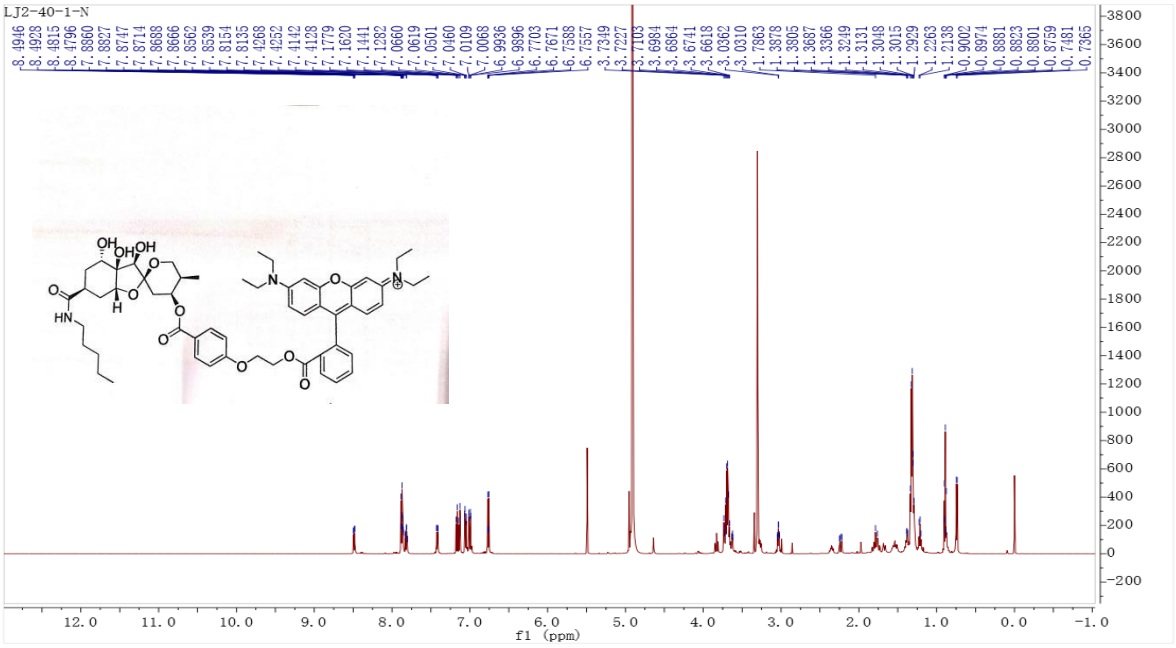
10- 96. ESI spectrum of negative probe of ABPP Probes



10- 97.[1]H NMR spectrum of blank control of fluorescence Probes



10- 98.[1]H NMR spectrum of positive probes of fluorescence Probes



10- 99.[1]H NMR spectrum of negative probe of fluorescence Probes