Supporting information

The enhanced antitumor activity of the polymeric conjugate covalently coupled with docetaxel and docosahexaenoic acid

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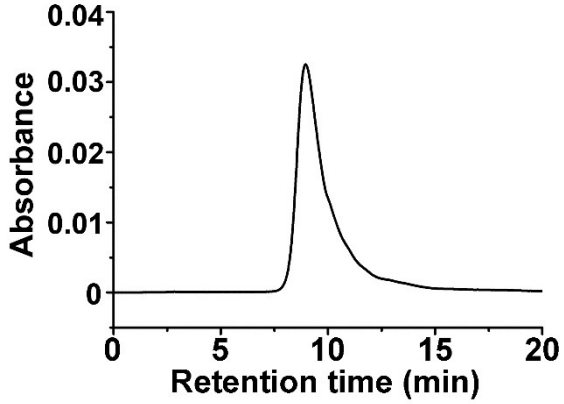


Figure S1. The purity of the conjugates quantified by HPLC analysis.

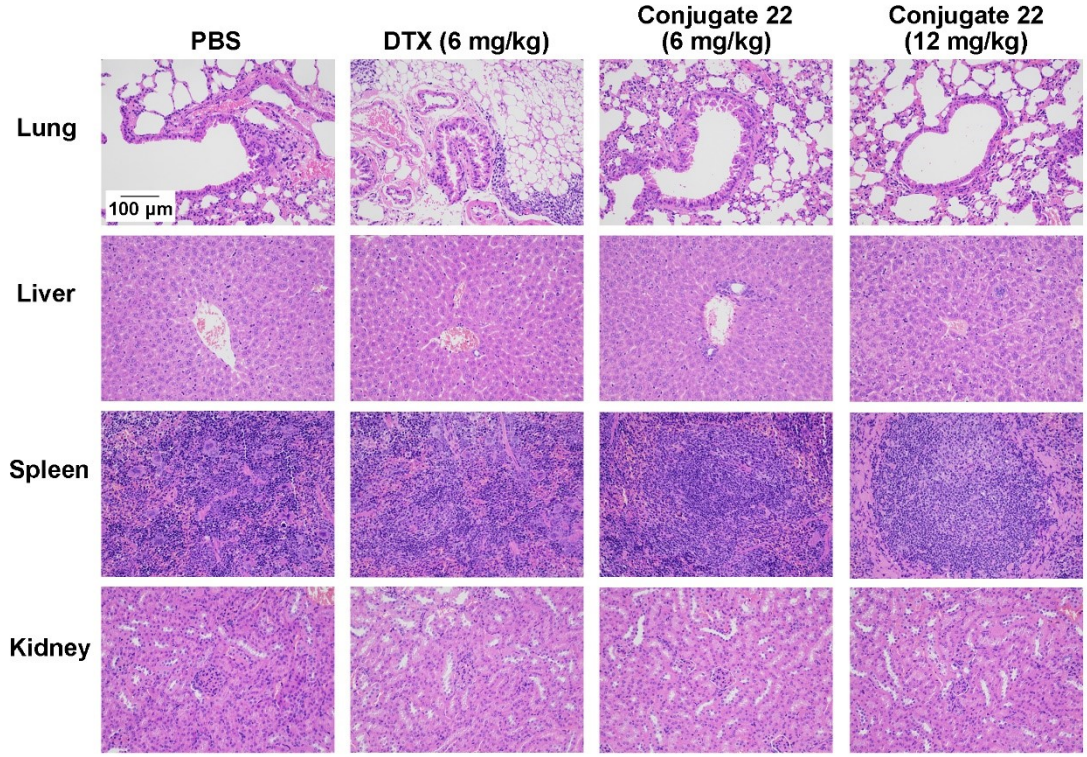


Figure S2. H&E staining of tumor and major organs of mice bearing H460 cells.

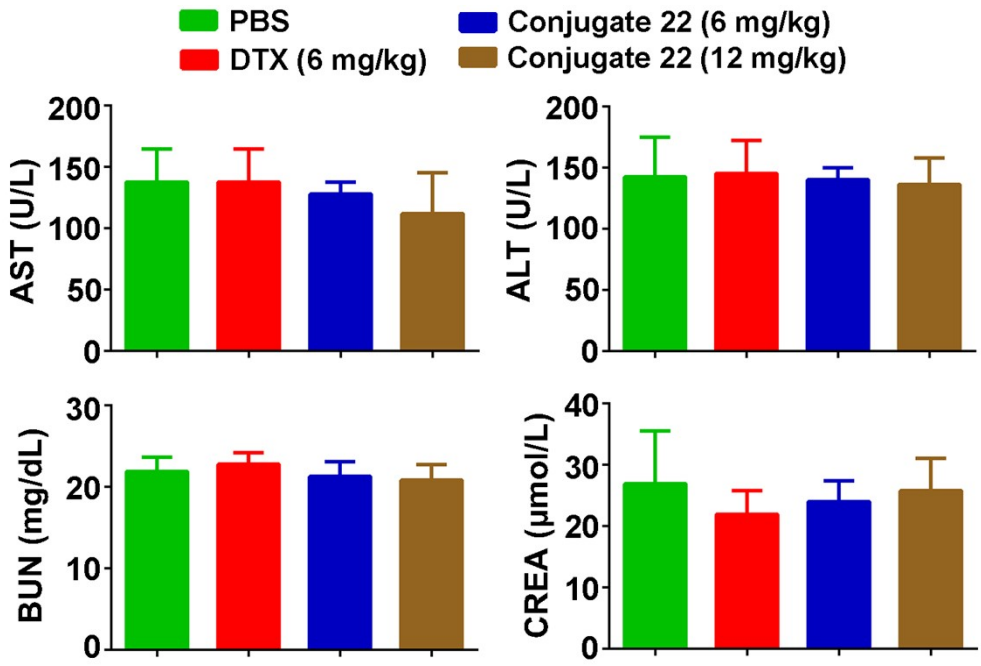


Figure S3. Biodistribution of the conjugate A in mice bearing H460 cells.

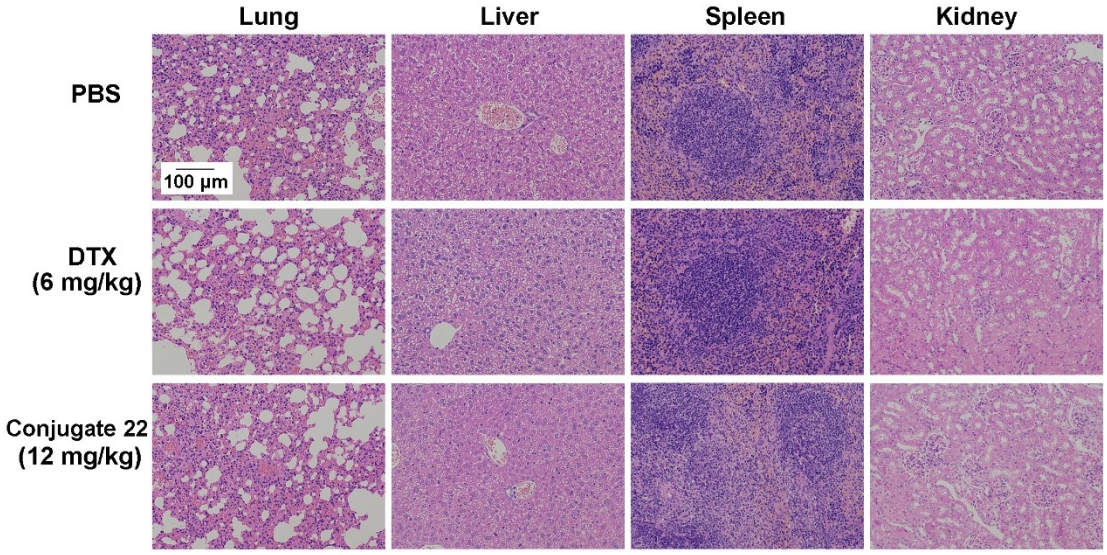


Figure S4. H&E staining of tumor and major organs of mice bearing MCF-7 cells.

2. Synthetic routes and procedures for dextran-DHA-DTX conjugate

2.1. Preparation of di-functionalized dextran 4

2.1.1. Preparation of compound 1

A 250 mL round-bottom flask charged with Boc-Lys(N_3)-OH (2.0 g, 7.3 mmol), HOBt (1.69 g, 11.01 mmol) and HBTU (4.17 g, 11.01 mmol), 10 mL of anhydrous DMF was added and stirred at room temperature for 30 min; and then 2.05 mL of triethylamine (1.49 g, 14.7 mmol) was dropwise added. After stirred for 5 minutes, 20.0 mL of anhydrous ethanol was added. The reaction was continuously stirred at room temperature overnight. Upon completion of the reaction, the reaction mixture was partitioned between ethyl acetate (100 mL) and brine (100 mL), and the organic phase washed with brine (100 mL×2), dried over anhydrous Na_2SO_4, filtered, concentrated and purified on a silica gel column eluted with ethyl acetate in petroleum (5 - 60%) to provide 1.11 g of compound **1**. Yield: 50.5%.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.04 (d, J = 6.0 Hz, 1H), 4.30 (m,1H), 4.21 (m,2H), 3.28 (t, J = 6.8 Hz, 2H), 1.84 (m,1H), 1.73 - 1.57 (m, 4H), 1.46 (s, 10H), 1.29 (t, J = 6.6 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 173.62, 156.34, 80.88, 78.20, 78.15, 62.35, 54.23, 52.15, 33.39, 29.43, 29.30, 23.48, 15.17.

ESI-MS (*m/z*): calcd for $C_{13}H_{25}N_4O_4$ $[M+H]^+$: 301.19; found: 301.84.

2.1.2. Preparation of compound 2

In a 250 mL round-bottom flask, 1.11g of compound **1** (3.70 mmol) was dissolved in 10.0 mL of hydrochloride ethanol solution (4.0N), and stirred at room temperature for 1 h. The reaction mixture was concentrated and purified on on a silica gel column eluted with methanol in chloroform (0 - 8%) to provide 1.08 g of compound **2**. Yield: 100%.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.19 (m, 2H), 3.51(t, J = 6.0 Hz, 1H), 3.28 (t, J = 7.2 Hz, 2H), 1.79 (m, 1H), 1.68 - 1.59 (m, 3H), 1.52 - 1.46 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H).

^{13}CNMR (150 MHz, $CDCl_3$): δ 175.12, 61.30, 53.08, 54.22, 51.30, 33.89, 28.72, 22.95, 14.36 ;

ESI-MS (*m/z*): calcd for $C_8H_{16}N_4O_2$ $[M+H]^+$: 201.14; found: 201.98.

2.1.3. Preparation of compound 3

In a 250 mL round bottom flask, compound **2** (1.07 g, 5.37 mmol) was dissolved in 50 mL of anhydrous DCM and 2.16 mL of pyridine (2.13 g, 26.9 mmol) under nitrogen protection and cooled down to 0°C, followed by slow addition of diphosgene (1.28 g, 6.44 mmol) in anhydrous DCM (30 mL) and stirred for 3h. The reaction mixture was diluted with DCM (100 mL) and washed with 1.0 N HCl solution three times (50 mL×3), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness to offer compound **3** (0.80 g)**.** Yield:65%. This compound was directly used in next step without purification.

^{1}H NMR (400 MHz, $CDCl_3$) 4.27 (q, *J* = 7.2 Hz, 2H), 4.02 (dd, *J* = 4.4 Hz, 1H), 3.30 (t, *J* = 6.8 Hz, 2H), 1.93 - 1.70 (m, 2H), 1.65 - 1.58 (m, 2H), 1.54 - 1.45 (m, 2H), 1.32 (t, *J* = 6.8 Hz, 3H), 1.25 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.11, 127.89, 63.54, 58.23, 52.04, 34.26, 30.66, 29.20, 23.72, 15.11.

MS (ESI, *m/z*): calcd for $C_9H_{18}N_5O_3$ $[M+NH_4]^+$:244.14; found: 244.69.

2.1.4. Preparation of di-functionalized dextran 4

1.5 g of dextran with average molecular weight of 100 k daltons was totally dried in oil bath at 60°C under high vacuum for 10 h, and then dissolved in 10 mL of anhydrous DMSO at 60°C. After cooled down to room temperature, the oil bath was removed. To the above solution, d*imethyl (S)-2-isocyanatopentanedioate* (2.91 g, 14.4 mmol), compound **3** (0.78 g, 3.46 mmol) and DMAP (6.55 g, 53.6 mmol) were slowly added and stirred at room temperature overnight. After the completion of the reaction, the reaction mixture was directly dialyzed against distilled water for 24 h, then concentrated and hydrolyzed with NaOH (2.86 g, 71.4 mmol) for 5 h. The resulting solution was adjusted to pH 3.0 - 5.0 with 4 N HCl solution, and continued to dialyzed against distilled water three times, concentrated, and lyophilized to provide di-functionalized dextran **4** (1.7 g). Yield:37%.

^{1}H NMR (selected characteristic signals, 400 MHz, DMSO-d_6, ppm): major signals: 4.50 - 5.25 (m, CHOH), 3.27 - 4.25 (m, CHOH, CH_2OH); minior signals: 1.50 -2.01 (m, CH_2).

2.2. Preparation of protected docetaxel

2.2.1. Preparation of compound 5

To a 250 mL round-bottom flask charged with 5.0 g (6.1 mmol) of docetaxel and 2.5 g (37.1 mmol) of imidazole, 15.0 mL of anhydrous DMF was added, followed by addition of 2.76 g (18.3 mmol) of TBDMSCl. The reaction mixture was stirred at room temperature for 12h. Upon completion of the reaction, the reaction mixture was partitioned between ethyl acetate (200 mL) and brine (200 mL), and the organic phase was further washed with brine (100 mL×2), dried over anhydrous Na_2SO_4, filtered, concentrated and purified on a silica gel column eluted with ethyl acetate in petroleum (10 - 40%) to provide 4.38 g of compound **5**. Yield: 78%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.32 - 7.24 (m, 3H), 6.34 (t, *J* = 9.6 Hz, 1H), 5.70 (d, *J* = 7.2 Hz, 1H), 5.43 (d, *J* = 9.6 Hz, 1H), 5.31 (d, *J* = 8.0 Hz, 1H), 4.98 (d, *J* = 8.4 Hz, 1H), 4.52 (s, 1H), 4.35 - 4.2 (m, 3H), 4.12 (q, *J* = 7.2 Hz, 1H), 3.96 (d, *J* = 7.2 Hz, 1H), 2.70 - 2.49 (m, 4H), 2.37 (dd, *J* = 16.8, 9.6 Hz, 1H), 2.15 (dd, *J* = 13.6, 4.8 Hz, 1H), 1.96 - 1.81 (m, 4H), 1.79 - 1.59 (m, 5H), 1.34 - 1.20 (m, 13H), 1.12(s, 1H),0.74 (s, 9H), -0.10 (s, 3H), -0.30 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 211.59, 171.33, 170.15, 167.10, 155.17, 139.12, 135.51, 133.61, 130.21, 129.24, 128.73, 128.57, 127.68, 126.45, 84.19, 81.05, 79.92, 79.10, 75.71, 75.08, 74.46, 71.95, 71.25, 60.39, 57.56, 46.37, 43.16, 36.97, 35.88, 28.16, 26.38, 25.47, 22.94, 21.16, 21.02, 18.18, 14.28, 14.19, 9.98, -5.37, -5.93;

ESI-MS (*m/z*): calcd for $C_{49}H_{68}NO_{14}Si$ $[M+H]^+$: 922.44; found: 922.03.

2.2.2. Preparation of compound 6

To a 250 mL round-bottom flask charged with 4.38 g (4.75 mmol) of compound **5** and 3.48 g (28.5 mmol) of DMAP, 15 mL of absolute THF was added under nitrogen protection and cooled down to 0^{o}C, followed by addition of 3.0 mL of AllocCl. After stirred for another 10 minutes, the cooled batch was removed and the reaction mixture allowed to warm up to room temperature and stirred for another 12h. Upon completion of the reaction, the reaction mixture was partitioned between dichloromethane (200 mL) and saturated sodium citrate solution (200 mL), and the

organic phase was further washed with saturated sodium citrate solution (100 mL×2), dried over anhydrous Na_2SO_4, filtered, concentrated and purified on a silica gel column eluted with ethyl acetate in petroleum (10 - 50%) to provide 3.75 g of compound **6**. Yield: 72%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.32 - 7.24 (m, 3H), 6.35 - 6.20 (m, 2H), 6.05 - 5.90 (m,2H), 5.71 (d, *J* = 8.4 Hz, 1H), 5.52 (dd, *J* = 10.8, 7.2 Hz, 1H), 5.45 - 5.20 (m, 6H), 4.98 (d, *J* = 7.6 Hz, 1H), 4.65 (m, 4H), 4.47 (d, *J* = 2.5 Hz, 1H), 4.20 (d, *J* = 8.0 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 1H), 3.97 (d, *J* = 7.6 Hz, 1H), 2.68 - 2.53 (m,4H), 2.39 (dd, *J* = 15.2, 9.6 Hz, 1H), 2.21 (dd, *J* = 16.0, 8.8 Hz, 1H), 2.08 - 1.95 (m, 5H), 1.84 (s, 2H), 1.64(s, 2H), 1.37 - 1.23(m, 13H) 1.19 (s, 3H), 0.74 (s, 9H), 0.07 (s, 3H), -0.31 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.63, 171.45, 171.10, 169.96, 166.97, 155.23, 154.00, 153.89, 142.36, 133.67, 132.18, 131.89, 131.51, 130.19, 129.12, 128.72, 128.58, 127.70, 126.43, 119.13, 118.64, 83.93, 80.86, 79.98, 78.92, 78.22, 76.38, 75.58, 75.25, 74.55, 71.22, 69.07, 68.88, 60.37, 56.09, 46.87, 43.24, 35.32, 33.39, 28.18, 26.25, 25.47, 22.91, 21.44, 21.03, 18.16, 14.65, 14.20, 10.73, -5.34, -5.92.

ESI-MS (*m/z*): calcd for $C_{57}H_{79}N_2O_{18}Si$ $[M+NH_4]^+$: 1107.51; found: 1107.91.

2.2.3. Preparation of compound 7

In a 250 mL round-bottom flask, 1.26 g (1.25 mmol) of compound **6** was dissolved in 15.0 mL of THF, and 2.5 mL of tetrabutylammonium fluoride solution (TBAF, 1.0 M) was added and stirred for 30 minutes at room temperature. Upon completion of the reaction, the reaction mixture was concentrated and purified on a silica gel column eluted with ethyl acetate in petroleum (10 - 40%) to provide 1.02 g of compound **7**. Yield: 84%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.1 (d, *J* = 8.0 Hz, 2H), 7.61 (t, *J* = 6.8 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.43 - 7.28 (m,5H), 6.25 - 6.14 (m, 2H), 6.04 - 5.91 (m,2H), 5.53 - 5.35(m,3H), 5.34 - 5.22 (m, 3H), 4.72 - 4.60 (m, 4H), 4.32 (d, *J* = 8.4 Hz, 1H), 4.22 - 4.07 (m, 3H), 3.92 (d, *J* = 6.8 Hz, 1H), 2.62 (m,1H), 2.45 - 2.25 (m, 4H), 2.10 -

2.02(m,3H) 1.99 - 1.92 (m, 3H), 1.83 (s, 3H), 1.36 (s, 9H), 1.30 - 1.23 (m, 6H), 1.20(s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.56, 171.12, 170.21, 166.93, 153.98, 153.85, 141.69, 138.46, 133.75, 132.62, 131.86, 131.49, 130.17, 129.09, 128.85, 128.71, 128.08, 126.80, 119.20, 118.67, 83.84, 80.92, 80.23, 78.70, 78.25, 76.42, 75.28, 74.34, 73.59, 72.32, 69.09, 68.92, 60.38, 56.23, 46.92, 43.17, 35.34, 33.42, 28.21, 26.37, 22.52, 21.02, 14.67, 14.19, 10.65;

ESI-MS (*m/z*): calcd for $C_{51}H_{65}N_2O_{18}$ $[M+NH_4]^+$: 993.42; found: 993.11.

2.3. Preparation of DTX-DHA-linker

2.3.1. Preparation of compound 8

To a 250 mL round-bottom flask charged with 5.0 g (50.1 mmol) of 4-pentynoic acid, 6.5 g of N-hydroxysuccinimide (NHS, 56.5 mmol) and 10.6 g of EDCI (88.6 mmol) were dissolved in 100 mL of anhydrous DCM and stirred for 3 h at room temperature. Upon completion of the reaction, the reaction mixture was washed with brine (100 mL×2), dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. Next, 12.6 g (51.2 mmol) of ε-BOC-L-lysine and 9.5 g of $NaHCO_3$ were combined in 100 mL of distilled water, followed by addition of 10.0g (51.3 mmol) of the above freshly prepared 4-pentynoic acid NHS ester in dry THF and stirred at room temperature overnight. Upon completion of the reaction, the reaction mixture was partitioned between dichloromethane (200 mL) and brine (200 mL), and the organic phase was further washed with brine twice (100 mL×2), dried over anhydrous Na_2SO_4, filtered, concentrated and purified on a silica gel column eluted with methanol in chloroform (0 - 10%) to provide 14.0 g of compound **8**. Yield:88%.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (d, J = 8.0 Hz, 1H), 6.73 (t, J = 4.8 Hz, 1H), 4.15 (m,1H), 2.87 (q, J = 5.6 Hz, 2H), 2.72 (m,1H), 2.41 - 2.23 (m, 4H), 1.66 (m, 1H), 1.54 (m,1H), 1.37 (s, 9H), 1.34 - 1.20 (m, 3H);

^{13}C NMR (100 MHz, DMSO-d_6): δ 174.17, 170.83, 156.04, 84.08, 77.82, 71.58, 52.28, 34.39, 31.35, 31.16, 29.54, 28.71, 23.17, 14.66;

ESI-MS (*m/z*): calcd for $C_{16}H_{25}N_2O_5$ $[M-H]^-$:325.18; found: 325.21.

2.3.2. Preparation of compound 9

In a 500 mL round-bottom flask, 14.0g (42.9 mmol) of compound **8** and 12.0 g (87.0 mmol) of K_2CO_3 were combined in 200 mL of acetonitrile, and 15.0 g of (105.7 mmol) MeI was dropwise added and stirred at 40℃ for overnight. After removal of volatiles, the residue was partitioned between dichloromethane (200 mL) and brine (200 mL), and the organic phase was further washed with brine twice (100 mL×2), dried over anhydrous Na_2SO_4, filtered, concentrated and purified on a silica gel column eluted with methanol in chloroform (0 - 10%) to provide 10.6g of compound **9**. Yield:73%.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (d, *J* = 8.0 Hz, 1H), 6.76 (t,*J* = 5.6 Hz, 1H), 4.21 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.61 (s, 3H), 2.88 (q, *J* = 6.8 Hz, 2H), 2.75 (m, 1H), 2.37 - 2.30 (m, 4H), 1.71 - 1.50 (m, 2H), 1.37 (s, 9H), 1.30 - 1.20 (m, 2H);

^{13}C NMR (100 MHz, DMSO-d_6): δ 173.10, 170.98, 156.03, 84.00, 77.81, 71.67, 52.30, 52.18, 34.30, 31.13, 29.50, 28.71, 23.10, 14.62;

ESI-MS (*m/z*): calcd for $C_{17}H_{27}N_2O_5[M-H]^-$:339.20; found: 339.34.

2.3.3. Preparation of compound 10

To a 250 mL round-bottom flask charged with 10.6 g (31.2 mmol) of compound **9**, 100 mL of hydrochloride ethanol solution (3.0 N) was added and stirred at room temperature for 2 h. After removal of volatiles, the residue was concentrated to provide 8.6 g of compound **10**. Yield: 89%. This compound was directly used in next step without purification.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.44 (d, *J* = 7.2 Hz, 1H), 4.16 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.58 (s,3H), 2.79 - 2.64 (m, 3H), 2.40 - 2.22 (m, 5H), 1.70 - 1.47 (m, 5H),1.41 - 1.26(m, 2H);

^{13}C NMR (100 MHz, DMSO-d_6) δ 172.97, 171.14, 84.02, 71.77, 52.29, 52.26, 48.98, 38.69, 34.23, 30.60, 26.79, 22.70, 14.59.

ESI-MS(*m/z*): calcd for $C_{12}H_{21}N_2O_3[M+H]^+$: 241.16; found: 241.03.

2.3.4. Preparation of compound 11

To a 250 mL round-bottom flask charged with 4.0 g (12.2 mmol) of docosahexaenoic acid (DHA), 3.0 g (15.6 mmol) of EDCI, 2.2 g (16.3 mmol) of HOBT

in 20 mL of dry DMF, 3.4g（14.2 mmol）of compound **10** and 4.3 mL（30.6 mmol）of triethylamine were added and stirred at room temperature for 2 h. Upon completion of the reaction, the reaction mixture was partitioned between ethyl acetate (150 mL) and brine (150 mL), and the organic phase was further washed with brine twice (100 mL×2), dried over anhydrous Na_2SO_4, filtered, concentrated and purified on a silica gel column eluted with methanol in DCM (1.0 - 6.0 %) to provide 4.8 g of compound **11**. Yield: 72%.

^{1}H NMR (400 MHz, CD_3OD): δ 5.36 (m, 12H), 4.39 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.71 (s, 3H), 3.15 (t, *J* = 7.2 Hz, 2H), 2.84 (m, 10H), 2.45 (d, *J* = 2.2 Hz, 3H), 2.49 - 2.42(m, 3H),2.38 (q, *J* = 7.6 Hz, 2H), 2.27 (m, 1H), 2.21 (t, *J* = 7.6 Hz, 2H), 2.13 - 2.02 (m, 2H), 1.82 (m, 1H), 1.69 (m,1H), 1.57 - 1.45 (m, 2H),1.45 - 1.33 (m, 2H), 0.97 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, DMSO-d_6): δ 173.10, 171.71, 170.97, 131.98, 129.34, 128.56, 128.53, 128.50, 128.34, 128.32, 128.29, 128.18, 128.13, 127.38, 83.98, 71.68, 52.27, 52.18, 38.60, 35.72, 34.29, 31.11, 29.18, 25.67, 25.63, 25.58, 23.64, 23.20, 20.51, 14.62, 14.56;

ESI-MS(*m/z*): calcd for $C_{34}H_{51}N_2O_4$ $[M+H]^+$:551.38; found: 551.05.

2.3.5. Preparation of compound 12

In a 250 mL round-bottom flask, 4.8g (8.72 mmol) of compound **11** was dissolved in 100 mL of anhydrous methanol, and then 700 mg (17.5 mmol) of NaOH was added and stirred at 40℃ for 1 h. Upon completion of the reaction, the reaction mixutre was acidified with 4.0N hydrochloride solution to pH =2.0 and partitioned between ethyl acetate (150 mL) and brine (150 mL), and the organic phase was further washed with brine twice (100 mL×2), dried over anhydrous Na_2SO_4, filtered, concentration and purified on a silica gel column eluted with methanol in DCM (1.0 - 15 %) to offer compound **12** (4.51g). Yield: 97%.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.52 (s, 1H), 8.12 (d, *J* = 7.6 Hz, 1H), 7.75 (t, *J* = 5.2 Hz, 1H), 5.34 (m,12H), 4.15 (m,1H), 2.99 (q, *J* = 6.8 Hz, 2H), 2.81 (m, 10H), 2.36 - 2.31 (m, 3H), 2.28 - 2.19(m, 2H),2.10 - 1.99 (m, 4H), 1.66 (m,1H), 1.54 (m, 1H), 1.33 (m, 4H), 0.92 (t, *J* = 7.6Hz, 3H);

^{13}C NMR (100 MHz, DMSO-d_6): δ 174.13, 171.72, 170.82, 131.97, 129.33, 128.55, 128.53, 128.49, 128.33, 128.31, 128.28, 128.17, 128.12, 127.37, 84.06, 71.58, 52.16, 38.71, 35.71, 34.38, 31.29, 29.23, 25.67, 25.63, 25.58, 23.63, 23.30, 20.52, 14.66, 14.56;

ESI-MS(*m/z*): calcd for $C_{33}H_{47}N_2O_4$ $[M-H]^-$: 535.35; found: 535.42.

2.3.6. Preparation of compound 13

62.0 g (140 mmol) of Fmoc-L-Lysine ethyl ester hydrochloride and 121.0 g (940 mmol) of DIEA were combined in 500 mL anhydrous ethyl alcohol and cooled down to 0℃, 87.0 g (312m mol) of triphenylmethyl chloride in THF was dropwise added and stirred at room temperautre overnight. Upon completion of the reaction, the reaction mixture was concentrated and purified on a silica gel column eluted with ethyl acetate in petroleum (10% - 80%) to provide 57.0 g of compound **13**. Yield:57%.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 - 7.85 (m, 2H), 7.74 - 7.67 (m, 3H), 7.42 - 7.36 (m, 8H), 7.33 - 7.23 (m, 9H), 7.20 - 7.13 (m, 3H), 4.31 - 4.28 (m, 2H), 4.2(m，1H), 4.11 - 4.01 (m, 2H),3.96 (m, 1H), 2.54(t, *J* = 8.0 Hz, 1H),2.01 - 1.89 (m, 2H), 1.59 (m, 1H), 1.49 - 1.37 (m, 2H), 1.36 - 1.25 (m, 2H), 1.14 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, DMSO-d_6): δ 172.42, 156.07, 146.23, 143.81, 143.71, 140.71, 128.36, 127.60, 126.99, 125.95, 125.20, 120.07, 70.39, 65.55, 60.35, 53.87, 46.65, 43.16, 30.73, 29.56, 23.39, 14.06;

ESI-MS(*m/z*): calcd for $C_{42}H_{43}N_2O_4$ $[M+H]^+$:639.32; found: 639.56.

2.3.7. Preparation of compound 14

To a 1.0 L round-bottom flask charged with 57.0 g (89 mmol) of compound **13** in 500 mL of anhydrous DCM, 37.9 g (450 mmol) of piperidine was slowly added and stirred at room temperature for 2 h. Upon completion of the reaction, the reaction mixture was concentrated and purified on a silica gel column eluted with ethyl acetate in petroleum (10 - 50%) to provide 33.0 g of compound **14**. Yield:89%.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.42 - 7.36 (m, 6H), 7.31 - 7.25 (m,6H), 7.20 - 7.14 (m, 3H), 4.09 - 4.00 (m,2H), 3.22 (d, *J* = 5.6Hz, 1H), 1.94 (q, *J* = 6.8 Hz, 2H), 1.69 (m,1H),1.53 - 1.24 (m, 6H), 1.16 (t, *J* = 7.6 Hz, 3H);

^{13}C NMR (100 MHz, DMSO-d_6): δ 175.83, 146.25, 128.37, 127.59, 125.94, 70.40, 59.83, 53.95, 43.21, 34.73, 29.90, 23.10, 14.11;

ESI-MS(*m/z*): calcd for $C_{27}H_{33}N_2O_2$ $[M+H]^+$: 417.25; found: 417.64 .

2.3.8. Preparation of compound 15

To a 1.0 L round-bottom flask charged with 25.2 g (94.6 mmol) of Cbz-Gly-Gly and 19.6g (102.2 mmol) of EDCI and 13.5g (99.9 mmol) in 300 mL of anhydrous DCM, 33.0 g (79.3 mmol) of compound **14** and 45.0 mL (198.3 mmol) of triethylamine were added. The reaction mixture was stirred at room temperature overnight. Upon completion of the reaction, the reaction mixture was washed with brine twice (300 mL×3), dried over anhydrous Na_2SO_4, filtered, concentrated and purified on a silica gel column eluted with methanol in chloroform (0 - 10%) to provide 34.0 g of compound **15**. Yield: 65%.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.14 (d, *J* = 7.2 Hz, 1H), 8.06 (t, *J* = 5.6 Hz, 1H), 7.50 (t, *J* = 6.4 Hz, 1H), 7.42 - 7.32 (m, 10H), 7.30 - 7.24 (m,6H),7.17 (t, *J* = 6.8 Hz, 3H), 5.02 (s, 2H), 4.18 (m, 1H), 4.10 - 4.02 (m, 2H), 3.77 - 3.71 (m, 2H), 3.62 (d, *J* = 6.0 Hz, 2H),2.53(t, *J* = 8.8 Hz, 1H) 1.96 - 1.89 (m, 2H), 1.66 - 1.51 (m, 2H), 1.49 - 1.4 (m, 2H), 1.0 (t, *J* = 7.6 Hz,2H),1.15 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, DMSO-d_6): δ 172.09, 169.37, 168.90, 156.60, 146.31, 137.05, 128.45, 128.42, 127.87, 127.78, 127.72, 126.06, 70.45, 65.59, 60.47, 52.07, 43.64, 43.21, 41.60, 31.07, 29.69, 23.27, 14.14;

ESI-MS (*m/z*): calcd for $C_{39}H_{45}N_4O_6$ $[M+H]^+$: 665.33; found: 665.67.

2.3.9. Preparation of compound 16

To a 1.0 L round-bottom flask charged with 34.0 g (51.2 mmol) of compound **15** in 500 mL anhydrous ethanol, 3.4 g of Pd/C was added. The reaction mixture was stirred under hydrogen bubbling for 4 h. Upon completion of the reaction, the reaction mixture was filtered, concentrated and purified on a silica gel column eluted with methanol in chloroform (3- 20%) to provide 6.2 g of compound 1**6**. Yield: 23%.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (d, *J* = 7.6 Hz, 1H), 8.03 (s, 1H), 7.43 - 7.35 (m, 6H), 7.28 (t, *J* = 7.6 Hz, 6H), 7.17 (t, *J* = 6.8 Hz, 3H), 5.76 (s, 1H), 4.19 (m,

1H), 4.11 - 4.02 (m, 2H), 3.76 (s, 2H), 3.09 (s, 2H), 2.54 (t, *J* = 8.0 Hz, 1H), 2.00 - 1.88 (m, 3H), 1.68 - 1.40 (m, 4H), 1.30 (q, *J* = 7.6 Hz, 2H), 1.16 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, DMSO-d_6):δ 173.12, 172.15, 169.04, 146.33, 128.47, 127.74, 126.08, 70.48, 60.51, 55.00, 52.09, 44.69, 43.24, 41.45, 31.09, 29.70, 23.30, 14.16;

ESI-MS(*m/z*): calcd for $C_{31}H_{39}N_4O_4$ $[M+H]^+$:531.30; found: 531.69.

2.3.10. Preparation of compound 17

To a 500 mL round-bottom flask charged with 4.5 g (8.4 mmol) of compound **12** and 2.0 g (10.4 mmol) of EDCI,1.5 g (11.1 mmol) were combined in 200 mL anhydrous DCM, 5.0 g (9.4 mmol) of compound **16** and 3.0 mL (21.7 mmol) of triethylamine were added. The reaction mixture was stirred at room temperature overnight. Upon completion of the reaction, the reaction mixture was washed with brine twice (200 mL×2), dried over anhydrous Na_2SO_4, filtered, concentrated and purified on a silica gel column eluted with methanol in chloroform (3- 15%) to provide 5.5 g of compound 1**7**. Yield: 64%.

^{1}H NMR (400 MHz, CD_3OD): δ 7.43 (t, *J* = 7.6 Hz, 6H), 7.25 (t, *J* = 7.2 Hz, 6H), 7.16 (t, *J* = 7.2 Hz,3H), 5.46 - 5.21 (m, 12H), 4.35 (q, *J* = 4.8 Hz, 1H), 4.22 - 4.09 (m, 3H), 3.94 - 3.77 (m, 4H), 3.15 (t, *J* = 7.2 Hz, 2H), 2.91 - 2.78 (m,10H), 2.52 - 2.42 (m, 4H), 2.41 - 2.32 (m, 2H), 2.27(t, *J* =2.0Hz, 1H), 2.20(t, *J* =7.2Hz, 2H), 2.15 - 2.02 (m, 4H), 1.86 - 1.63 (m, 4H), 1.58 - 1.33 (m, 9H),1.23 (t, *J* = 8.0 Hz, 3H), 0.96 (t, *J* = 8.8Hz, 3H);

^{13}C NMR (100 MHz, CD_3OD): δ 175.07, 175.05, 174.41, 174.38, 173.28, 171.70, 171.25, 147.34, 132.57, 129.92, 129.63, 129.23, 129.03, 128.97, 128.95, 128.92, 128.87, 128.69, 128.48, 127.94, 127.03, 83.56, 71.92, 70.31, 70.25, 62.04, 55.26, 53.59, 44.40, 43.69, 42.95, 39.80, 36.80, 36.75, 35.42, 35.38, 32.21, 31.81, 30.84, 29.84, 26.37, 26.35, 26.31, 26.24, 24.52, 24.46, 23.97, 21.29, 15.27, 14.52, 14.38;

ESI-MS(*m/z*): calcd for $C_{64}H_{85}N_6O_7$ $[M+H]^+$:1049.65; found: 1049.73.

2.3.11. Preparation of compound 18

To a 250 mL round-bottom flask charged with 5.5 g (5.2 mmol) of compound **17** in 50.0 mL anhydrous DCM, 5.0 mL(65.2 mmol) of TFA was slowly added at 0℃. After stirred for 0.5h, the ice bath was removed and the reaction was warmed up to

room temperature and stirred for another 1 h. Upon completion of the reaction, the reaction mixture was concentrated and purified on a silica gel column eluted with methanol in chloroform (6 - 20%) to provide 4.8 g of compound **18**. Yield:100%.

^{1}H NMR (400 MHz, CD_3OD): δ 5.45 - 5.25 (m, 12H), 4.45 (dd, *J* = 9.6, 4.8 Hz, 1H), 4.22 - 4.13 (m, 3H), 3.97 - 3.79 (m, 4H), 3.16 (t, *J* = 8.0 Hz, 2H), 2.93 (t, *J* =6.4 Hz) ,2.90 - 2.73 (m, 10H), 2.55 - 2.32 (m, 7H), 2.30(t, *J* = 2.4 Hz, 1H), 2.22 (t, *J* = 6.8 Hz, 2H), 2.13 - 2.03 (m, 2H), 1.96 - 1.60 (m, 7H), 1.56 - 1.36 (m, 7H), 1.26 (t, *J* = 6.8 Hz,3H), 0.97 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, CD_3OD): δ 175.48, 175.22, 174.62, 172.97, 172.17, 171.49, 132.59, 129.97, 129.24, 128.99, 128.92, 128.88, 128.70, 127.96, 83.56, 70.21, 62.27, 55.43, 53.01, 43.81, 43.35, 40.35, 39.80, 36.77, 35.37, 31.76, 31.55, 29.86, 27.56, 26.36, 26.34, 26.31, 26.23, 24.54, 24.03, 23.46, 21.29, 15.25, 14.47, 14.30;

ESI-MS(*m/z*): calcd for $C_{45}H_{71}N_6O_7$ $[M+H]^+$:807.54; found: 807.26.

2.3.12. Preparation of compound 19

To a 250 mL round-bottom flask charged with 4.8 g (6.0 mmol) of compound **18** in 50 mL of acetonitrile, 2.5 mL(18.0 mmol) of triethylamine and 1.4 g (12.1 mmol) of diglycolic acid anhydride were added and stirred at room temperature for 1h. Upon completion of the reaction, the reaction mixture was concentrated and purified on a silica gel column eluted with methanol in chloroform (7.0 - 20%) to provide 3.26 g of compound **19**. Yield:58%.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.59 (s, 1H), 9.02 (s, 1H), 8.54 (d, *J* = 6.4 Hz, 1H), 8.31 - 8.16 (m, 2H), 7.77 (t, *J* = 4.8 Hz, 1H), 5.41 - 5.22 (m, 12H), 4.21 (m, 1H),4.14 (m, 1H), 4.09 - 4.02 (m, 2H), 3.92 - 3.84(m, 2H),3.84 - 3.62 (m, 7H), 3.10 - 2.92 (m, 3H), 2.86 - 2.72 (m, 10H), 2.32 (s, 4H), 2.21 (d, *J* = 7.6 Hz, 2H), 2.08 - 1.96 (m, 6H), 1.73 - 1.55 (m,3H), 1.45 - 1.25 (m, 7H), 1.13 (t,*J* = 7.2 Hz, 3H),0.89 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, DMSO-d6): δ 172.30, 171.99, 171.47, 170.77, 169.06, 168.87, 168.70, 131.60, 128.97, 128.17, 128.14, 128.09, 127.96, 127.94, 127.90, 127.80, 127.75, 126.99, 83.77, 71.23, 70.23, 67.96, 60.49, 52.85, 52.03, 42.14, 41.65,

38.39, 37.90, 35.31, 34.08, 31.41, 30.65, 28.93, 28.70, 25.28, 25.23, 25.18, 23.22, 22.83, 22.69, 20.10, 14.22, 14.15, 14.10;

ESI-MS (*m/z*): calcd for $C_{49}H_{73}N_6O_{11}$ $[M-H]^-$:921.53; found: 921.52.

2.3.13. Preparation of compound 20

Compound **19** (100 mg，0.11 mmol), DMAP (27 mg，0.22 mmol) and EDCI (42 mg，0.22 mmol) were combined in 10.0 mL of anhydrous THF, followed by addition of compound **7** (215 mg, 0.22 mmol) and stirred at room temperature for 3 h. The reaction mixture was concentrated and purified on a silica gel column eluted with methanol in methylene chloride (1.0 - 5.0 %) to provide 70 mg of compound **20**. Yield:34%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.32 - 7.24 (m, 3H), 6.19 (d, *J* = 9.6 Hz, 2H), 6.07 - 5.91 (m, 3H), 5.52 - 5.27 (m, 12H), 5.00 (d, *J* = 6.8 Hz, 1H), 4.69 - 4.56 (m, 4H), 4.41 - 4.26 (m, 3H), 4.20 - 4.10(m,3H), 4.05 - 3.87 (m, 6H), 3.38 - 3.18 (m, 4H), 2.90 - 2.78 (m, 10H), 2.62 (m, 2H), 2.54 - 2.36 (m,8H), 2.24 (t, *J* = 8.0 Hz, 3H), 2.13 - 1.94 (m, 11H), 1.92 - 1.75 (m, 8H), 1.59 - 1.46 (m, 5H), 1.43 - 1.30 (m, 11H), 1.30 - 1.12(m, 19H), 0.97 (t, *J* = 7.6Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.64, 173.17, 172.37, 166.93, 132.41, 132.12, 131.84, 131.50, 130.23, 129.39, 129.21, 128.74, 128.67, 128.38, 128.12, 127.92, 127.07, 119.28, 118.79, 83.26, 80.87, 78.77, 76.36, 75.40, 74.44, 69.53, 69.21, 68.99, 64.49, 61.46, 56.08, 50.87, 43.16, 36.50, 34.79, 29.77, 28.25, 26.31, 25.72, 25.70, 25.62, 25.43, 23.49, 22.49, 21.31, 20.64, 14.99, 14.62, 14.35, 14.23, 10.78;

ESI-MS(*m/z*): calcd for $C_{100}H_{133}N_7NaO_{28}$ $[M+Na]^+$: 1902.91; found: 1902.04.

2.3.14. Preparation of compound 21

Compound 20 (385 mg，0.20 mmol), N, N-dimethylbarbituric acid (37 mg，0.24 mmol) and tetra(triphenylphosphine) palladium (16 mg，0.014 mmol) were dissolved in 10.0 mL of THF and stirred at room temperature for 1 h. Upon completion of the reaction, the reaction mixture was concentrated and purified on a silica gel column eluted with methanol in methylene chloride (1.0 - 6.0%) to provide 323 mg of compound **21**. Yield:94%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.32 - 7.24 (m, 3H), 6.24 (s, 1H), 5.73 (d, *J* = 5.6 Hz, 1H), 5.57 - 5.41 (m, 12H),5.41 - 5.33(m, 3H),5.04 (d, *J* = 9.2Hz,1H),4.59 (s, 1H), 4.47 - 4.33 (m, 4H), 4.31 - 4.20 (m, 4H),4.17 - 4.08 (m, 3H), 4.04 - 3.92 (m, 4H), 3.36 (s, 4H), 3.00 - 2.82 (m, 10H), 2.76 - 2.60 (m, 8H), 2.52 - 2.38 (m, 6H), 2.23 - 2.07(m, 5H),2.02 - 1.92(m, 5H),1.81 (s, 4H), 1.63 (s, 4H),1.53 - 1.39 (m, 14H), 1.38 - 1.28(m, 12H),1.20 (s, 3H), 1.05 (t, *J* = 6.8 Hz, 3H), 0.95 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.54, 173.13, 169.90, 167.11, 155.32, 133.74, 132.14, 130.25, 129.39, 129.06, 128.74, 128.69, 128.43, 128.41, 128.39, 128.35, 128.21, 128.18, 127.98, 127.13, 126.59, 100.09, 81.37, 78.97, 76.62, 75.16, 74.57, 71.55, 69.66, 61.65, 61.65, 46.73, 43.29, 43.00, 36.78, 36.51, 32.01, 29.78, 29.74, 29.60, 29.43, 29.23, 28.28, 26.56, 25.75, 25.74, 25.65, 23.53, 22.76, 20.97, 20.65, 14.97, 14.34, 14.24, 14.17, 10.17;

ESI-MS(*m/z*): calcd for $C_{92}H_{125}N_7NaO_{24}$ $[M+H]^+$:1734.87; found: 1734.34.

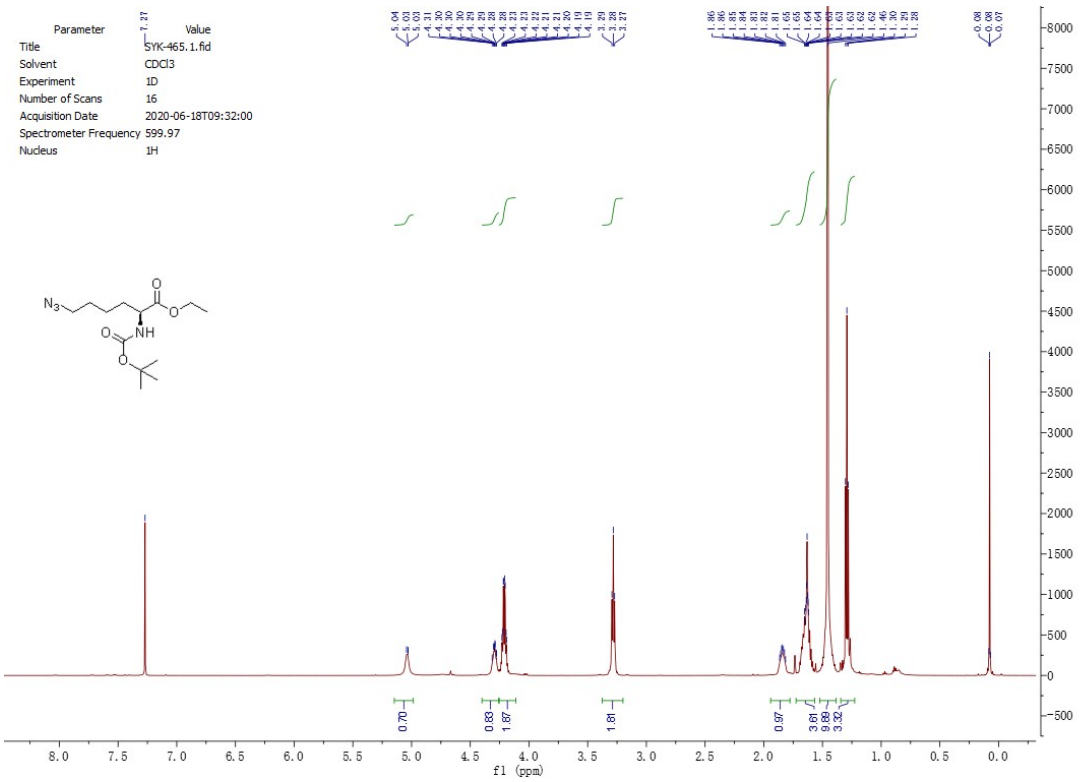
2.4. The synthesis of dual conjugate 22

The di-functionalized dextran **4** (200 mg) and compound **21** (72 mg, 0.042 mmol) were combined in 5.0 mL of DMSO, followed by addition of the mixture of $CuSO_4$ (42 μL, 0.042 mmol) and sodium ascorbate (85 μL, 0.085 mmol) under nitrogen protectionand and stirred at room temperature overnight. Upon completion of the reaction, the reaction mixture was diluted with distilled water (50 mL) and washed with methylene chloride (50 mL). The aqueous phase was dialyzed against distilled water three times, concentrated, lyophilized to provide dual conjugate **22** (326 mg). Yield: 88%.

^{1}H NMR (selected characteristic signals, 400 MHz, DMSO-d_6+D_2O, ppm): major signals: 4.50 - 5.00 (m, CHOH), 3.30 - 4.20 (m, CHOH, CH_2OH); minior signals: 7.10 – 8.50 (m, CONH, ArH), 5.30 (m, =CH), 1.23 (m, CH_3), 0.95 - 1.10 (m, CH_3).

3. ^{1}H NMR, ^{13}C NMR and MS spectra of compounds 1 to 22.

^{1}H NMR,^{13}C NMR and MS spectra of compound **1**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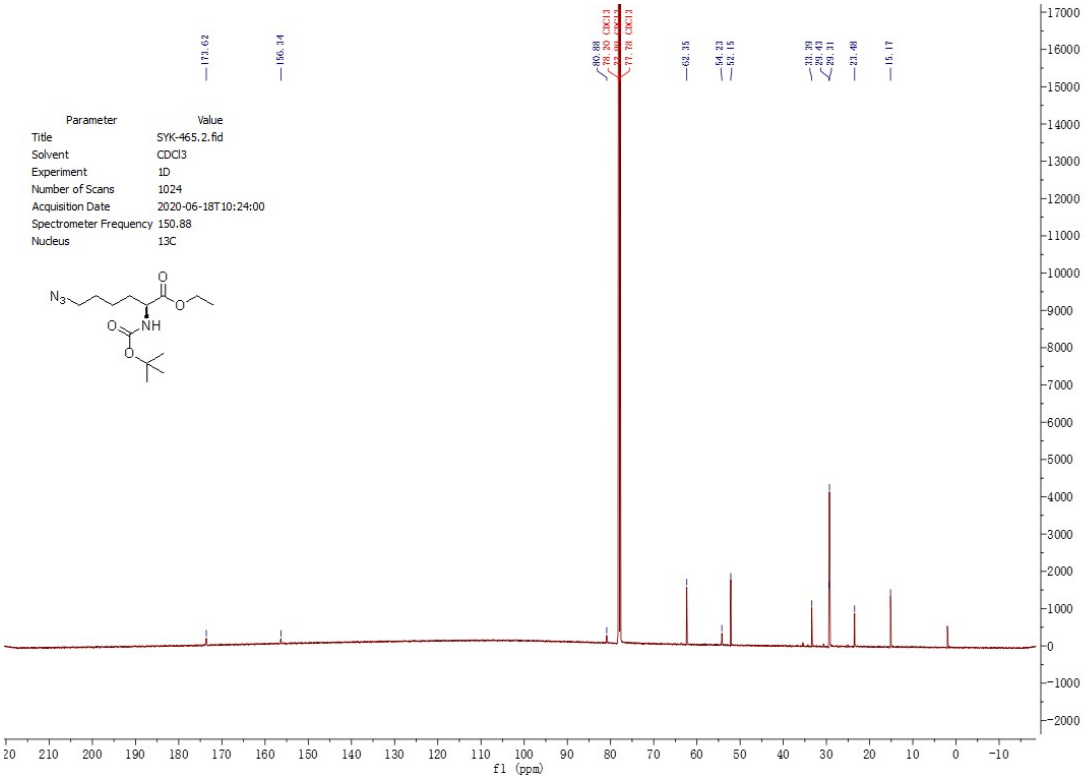
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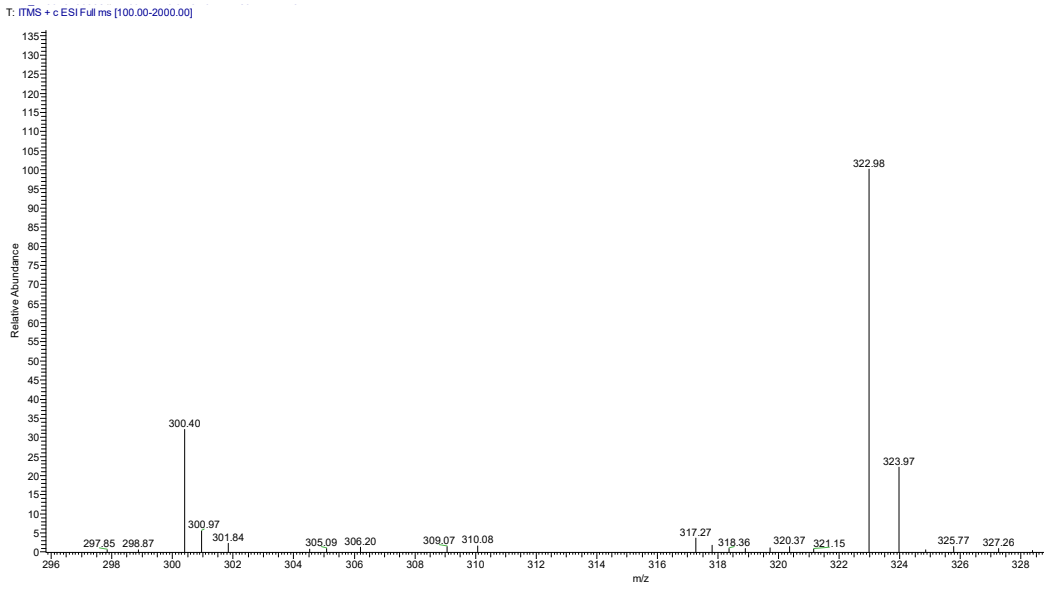
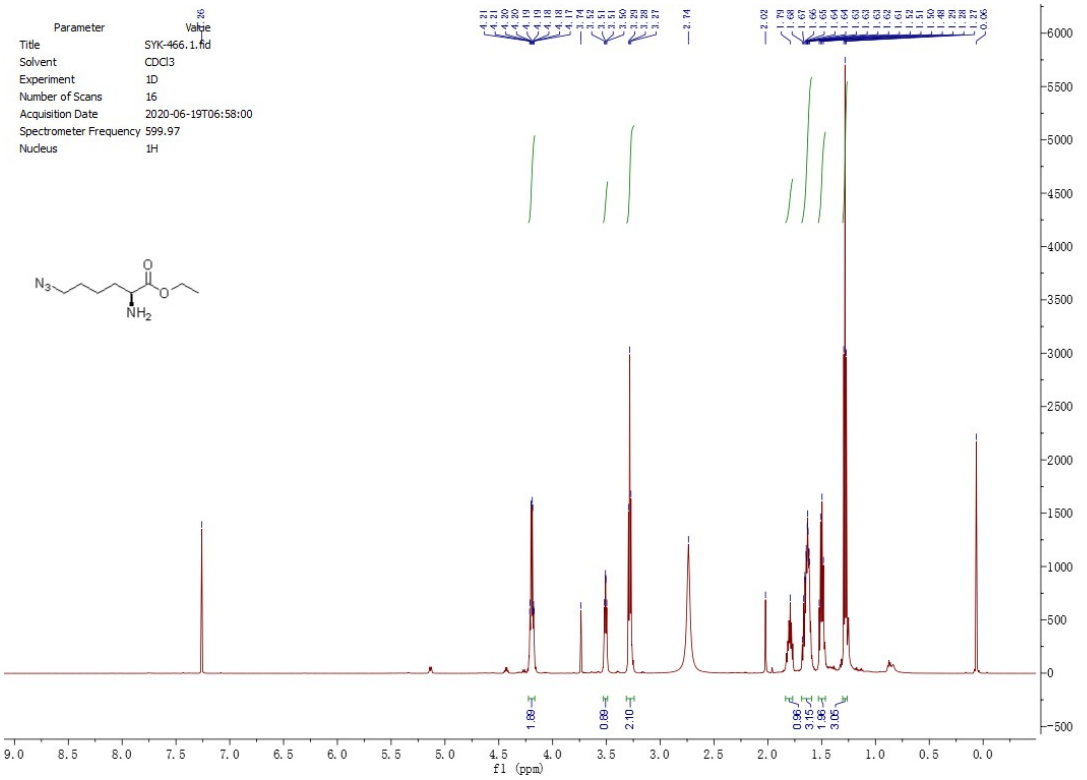


^{1}H NMR,^{13}C NMR and MS spectra of compound **2**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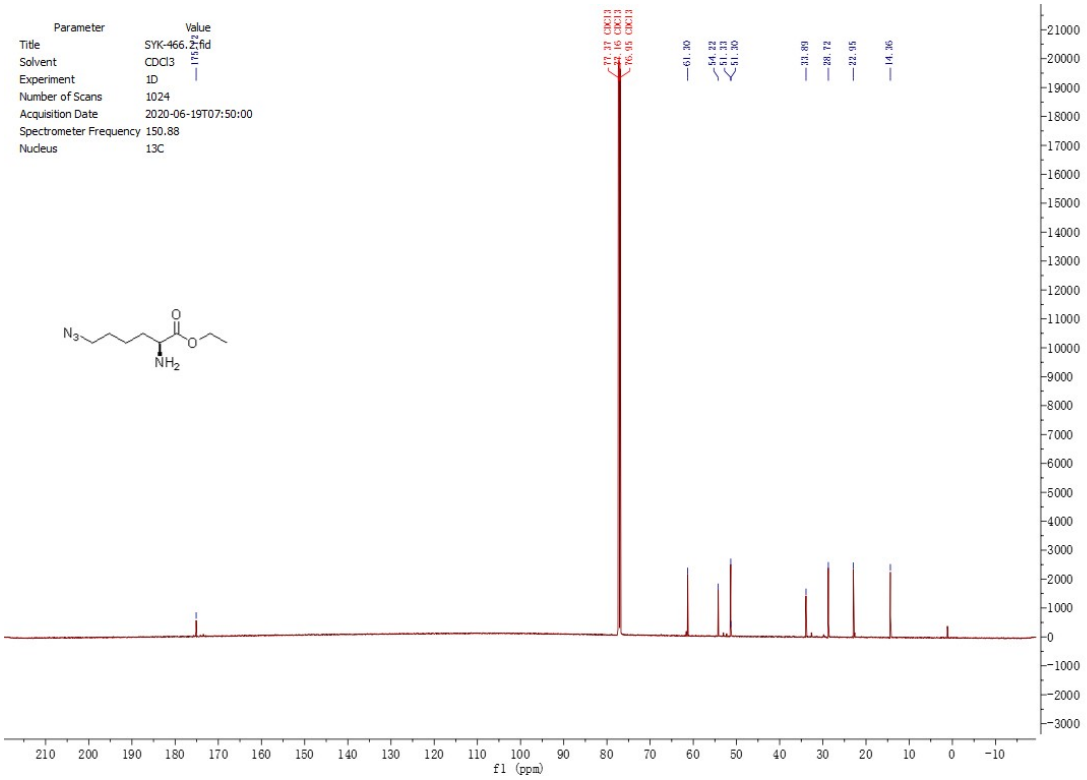
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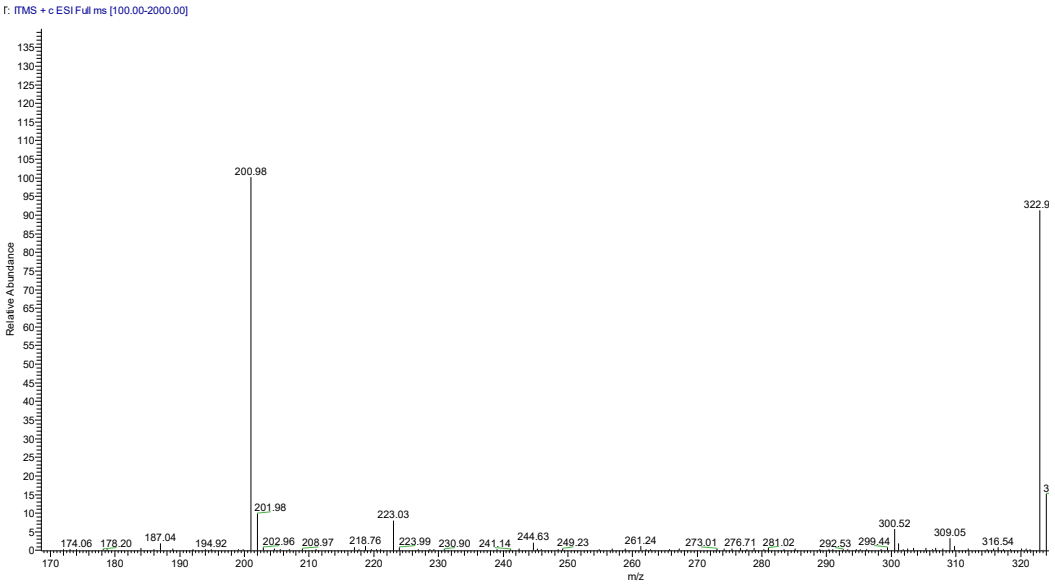
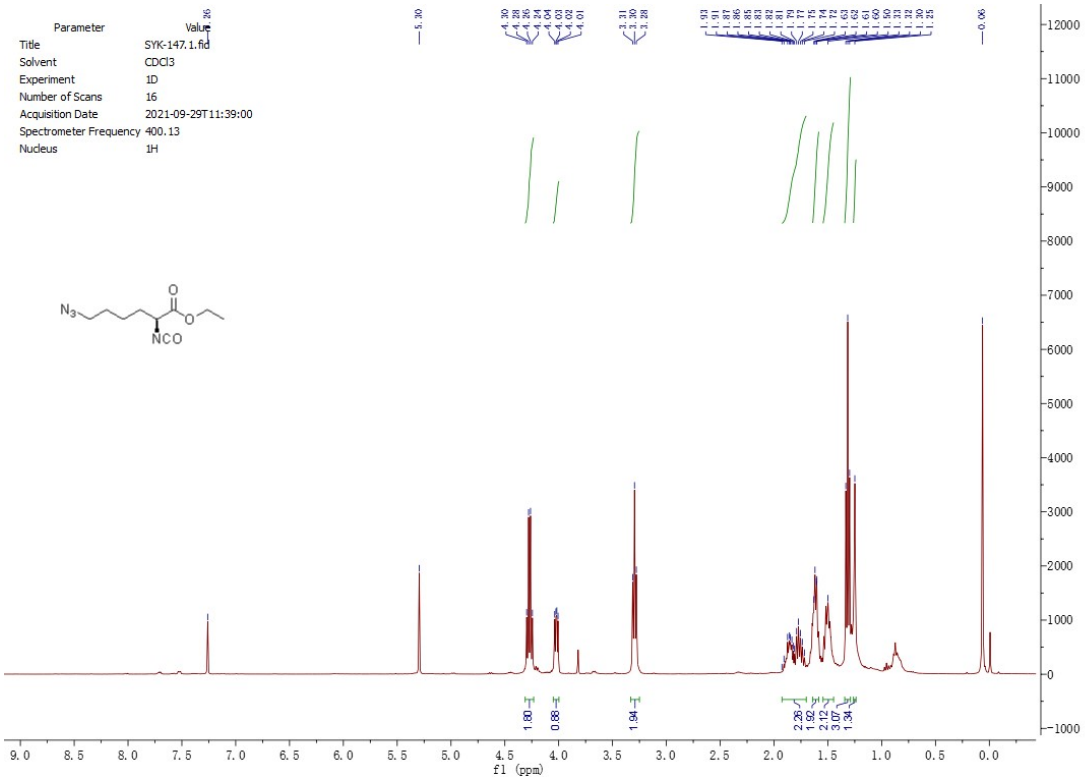
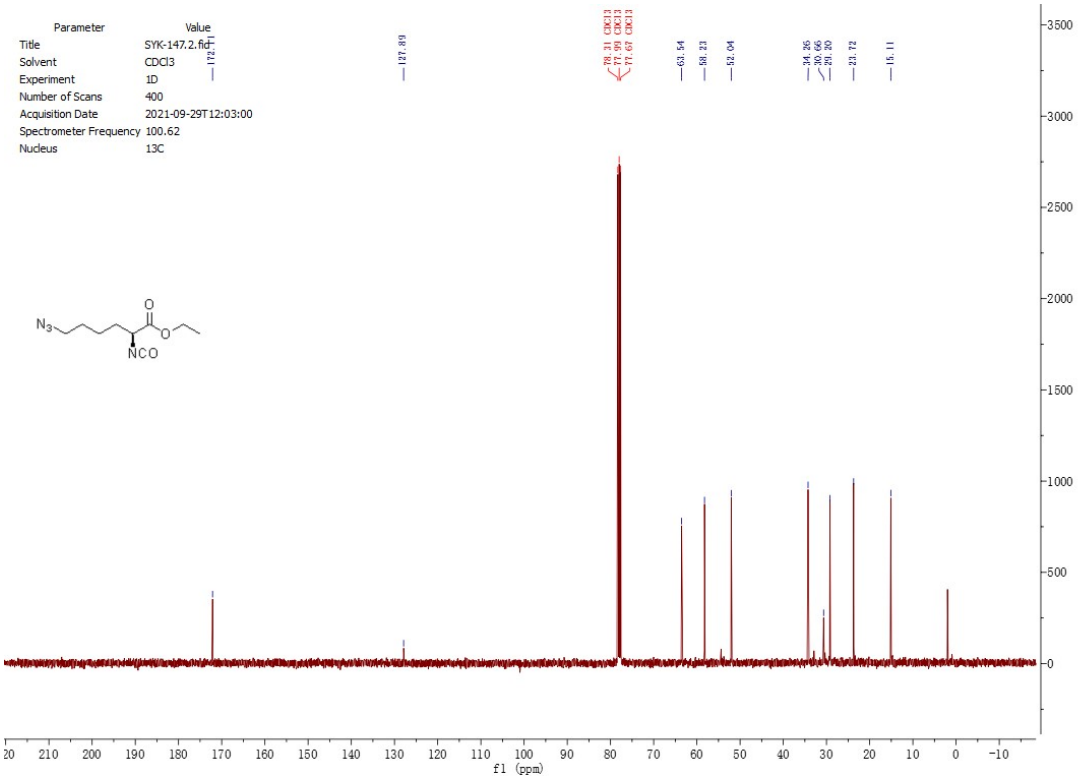


^{1}H NMR,^{13}C NMR and MS spectra of compound **3**

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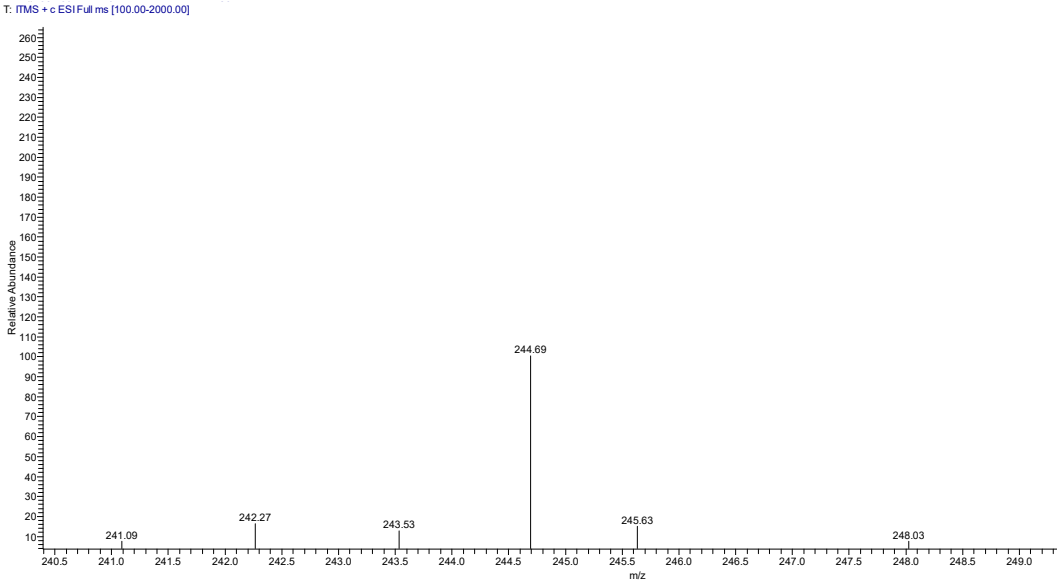
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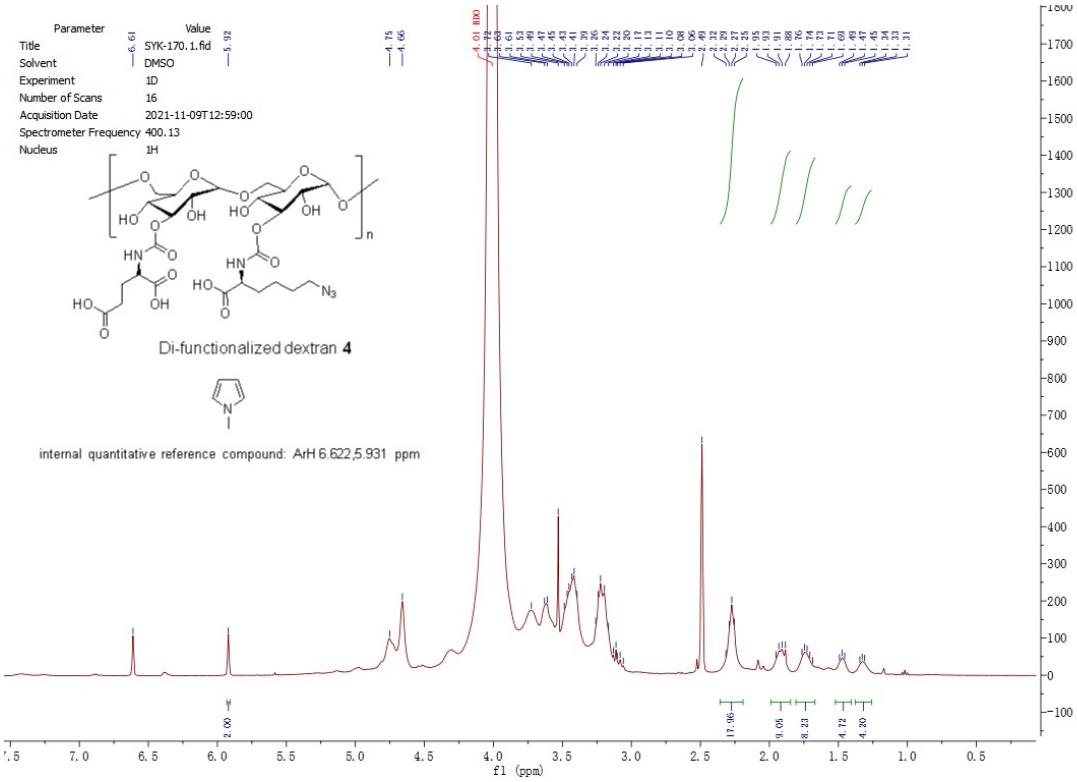
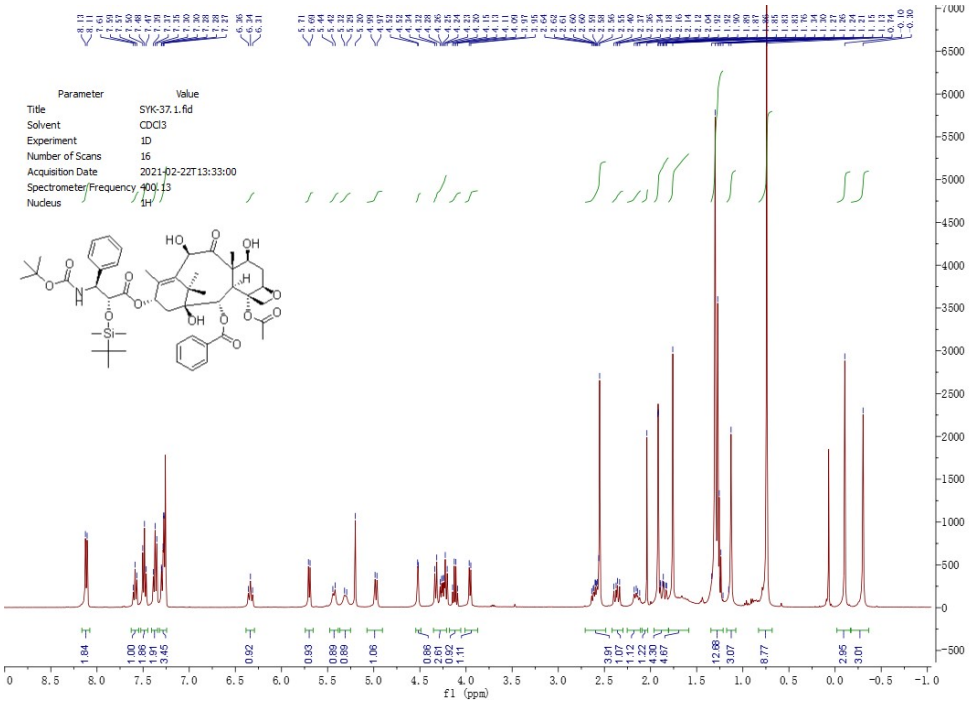
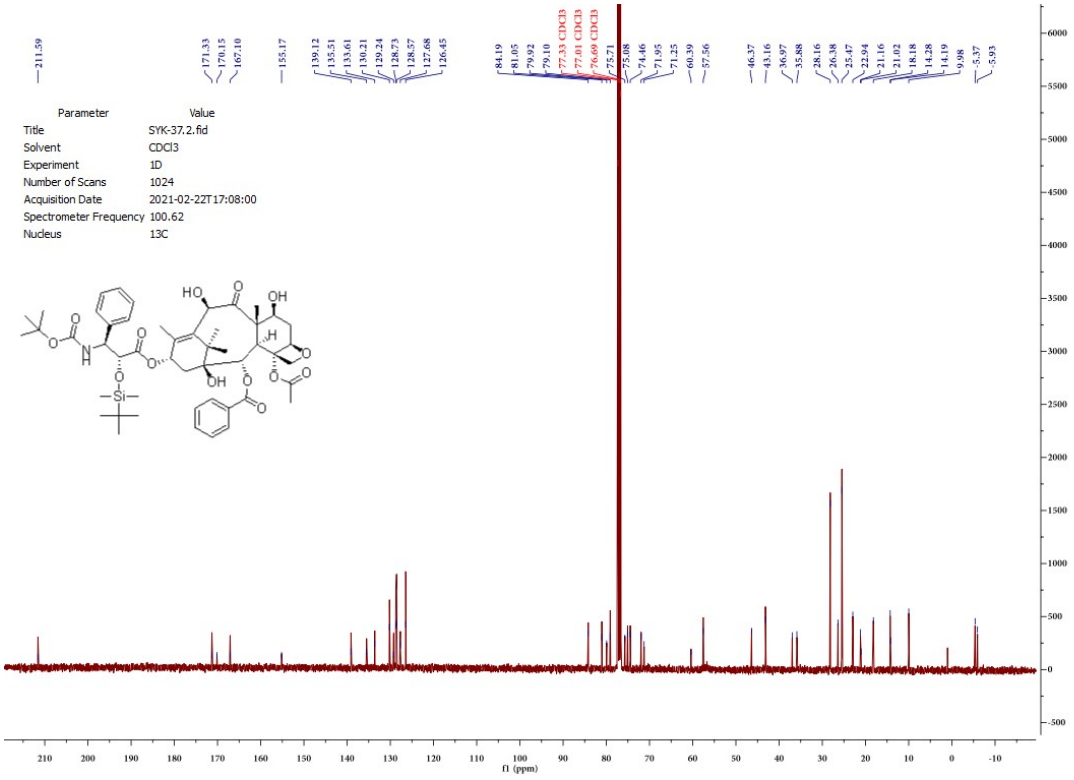
m/z

^{1}H NMR spectrum of compound **4**



^{1}H NMR,^{13}C NMR and MS spectra of compound **5**

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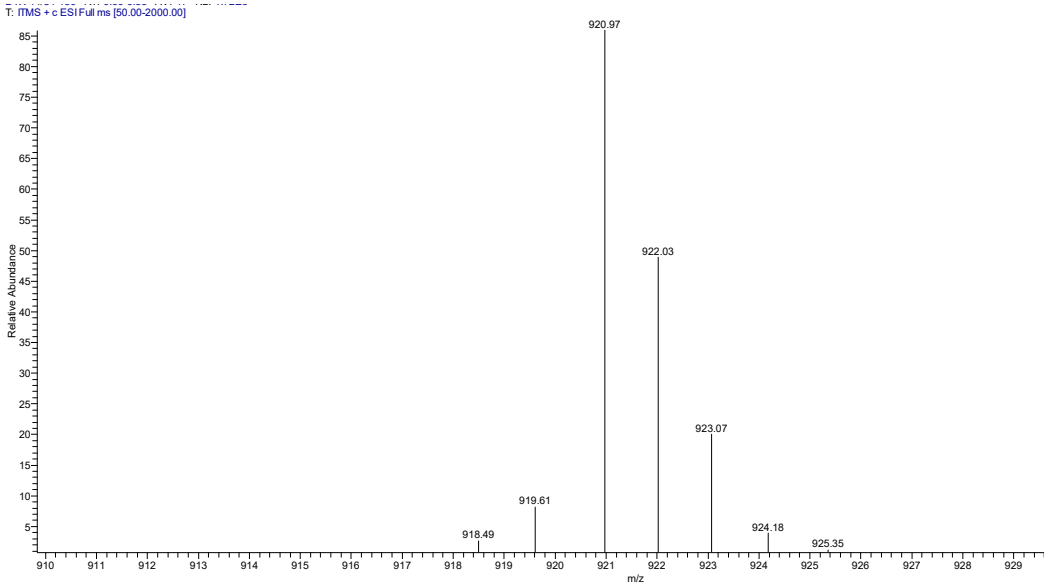
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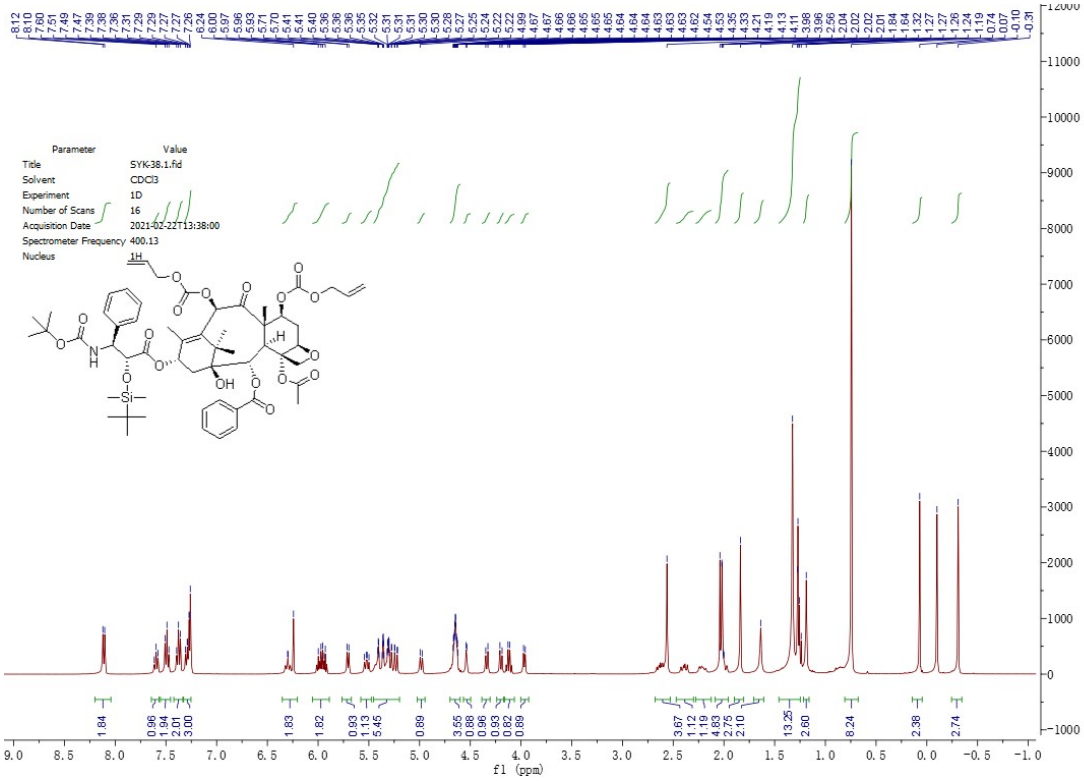
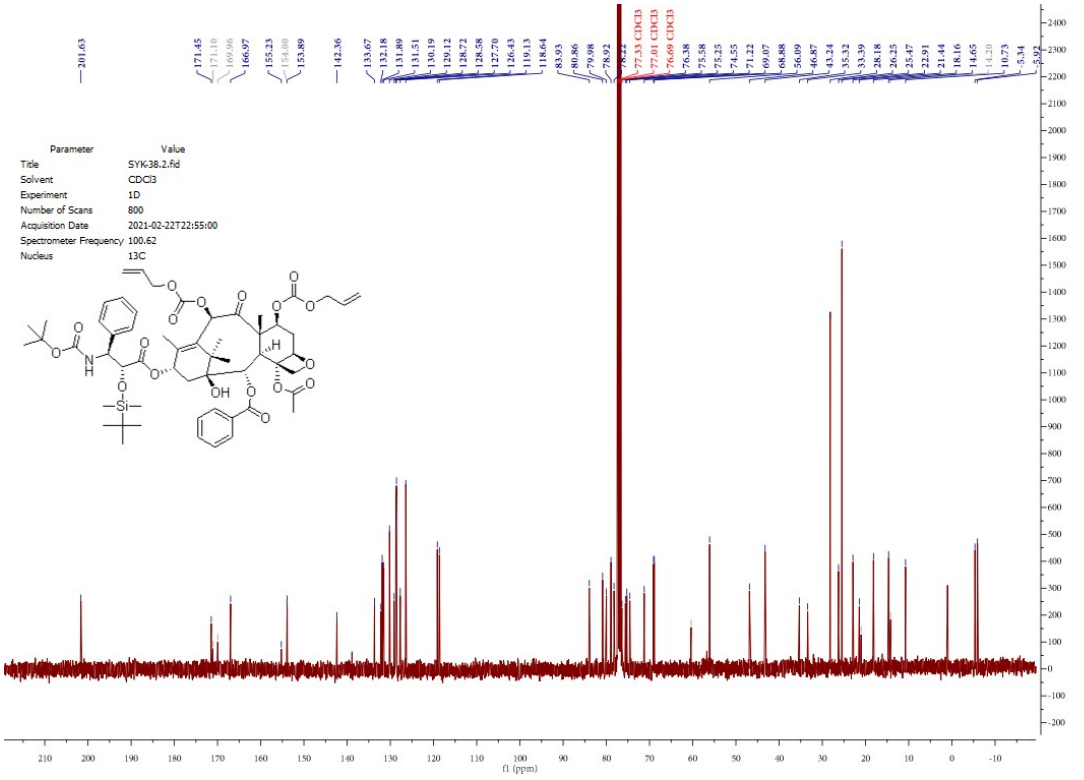
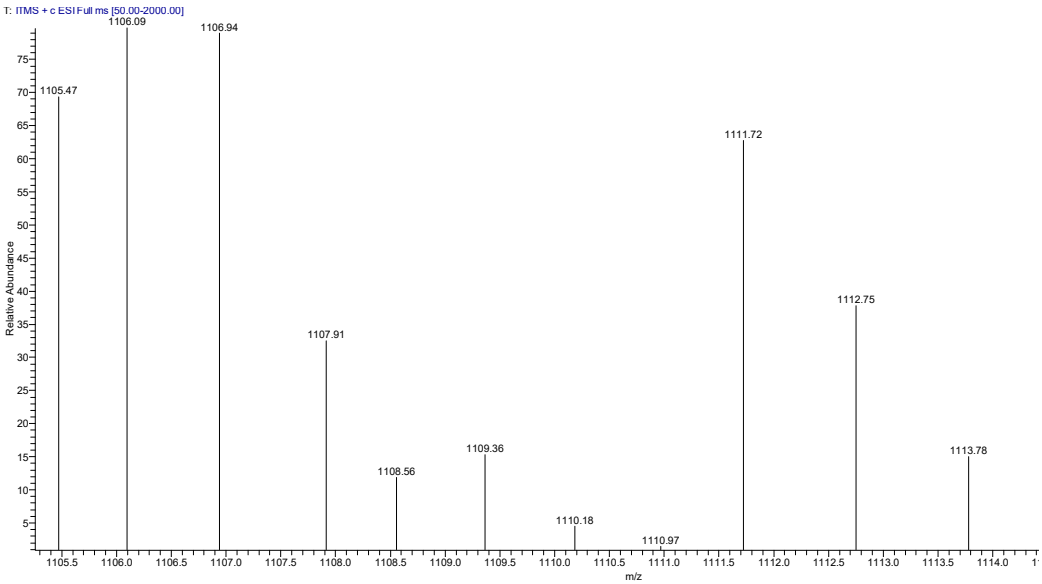
m/z

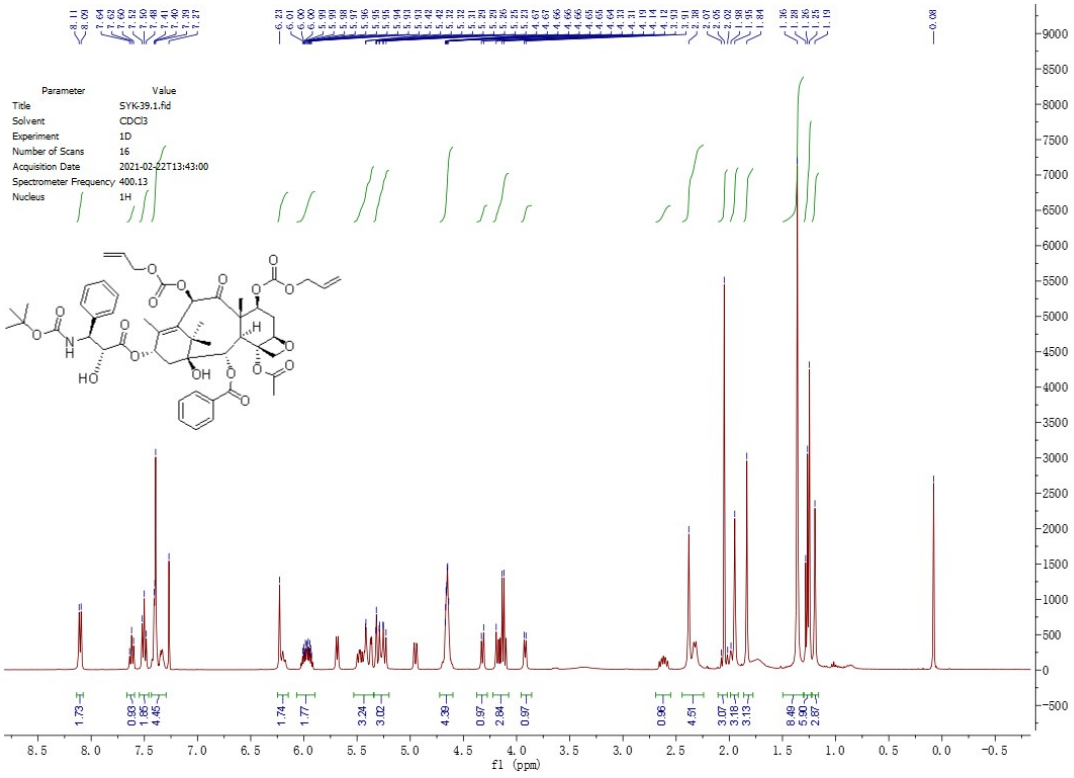
^{1}H NMR,^{13}C NMR and MS spectra of compound **6**

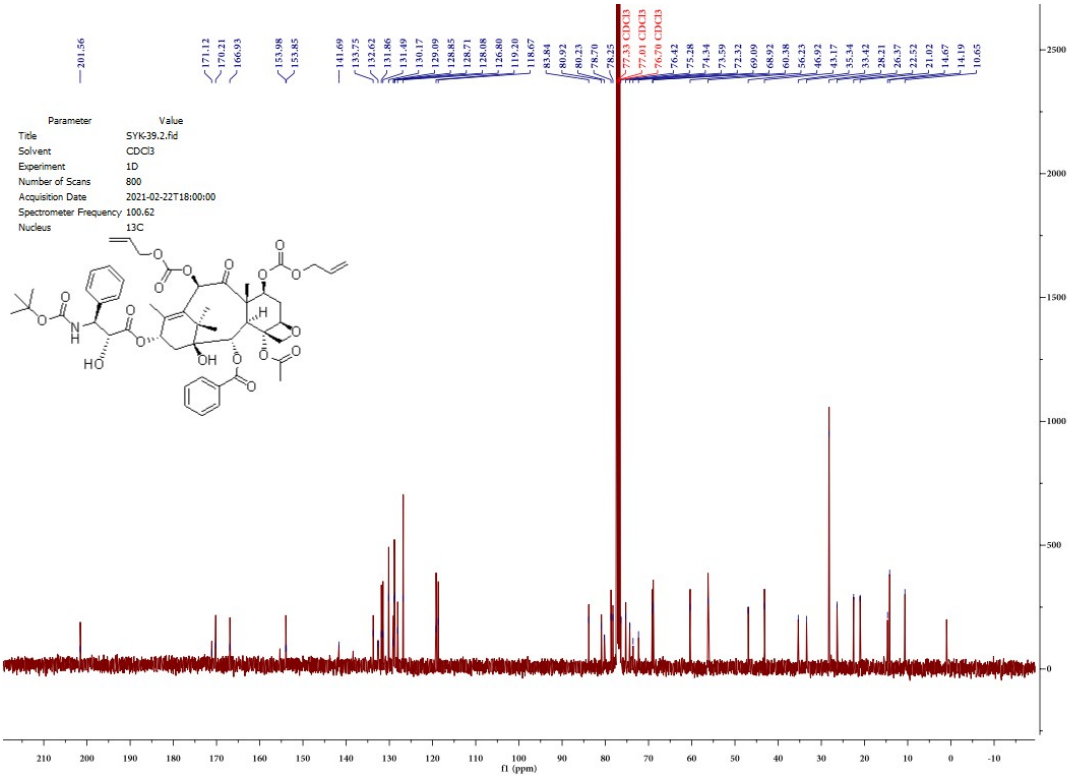


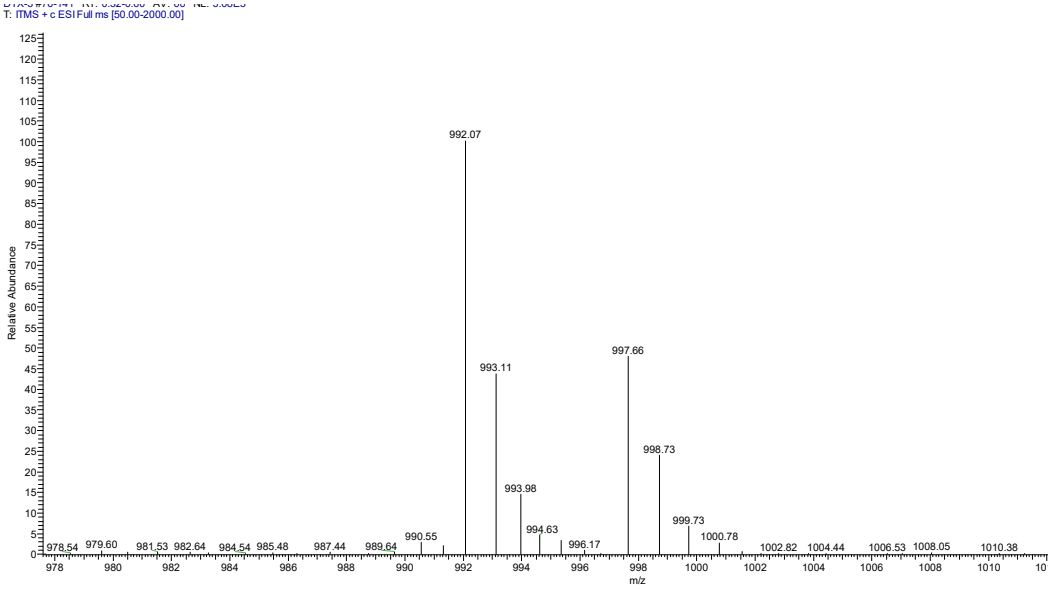




^{1}H NMR,^{13}C NMR and MS spectra of compound **7**




Parameter Value
Title SYK-39.2.fid
Solvent CDCl3
Experiment 1D
Number of Scans 800
Acquisition Date 2021-02-22T18:00:00
Spectrometer Frequency 100.62
Nucleus 13C
f1 (ppm)


T: ITMS + c ESI Full ms [50.00-2000.00]
Relative Abundance
m/z
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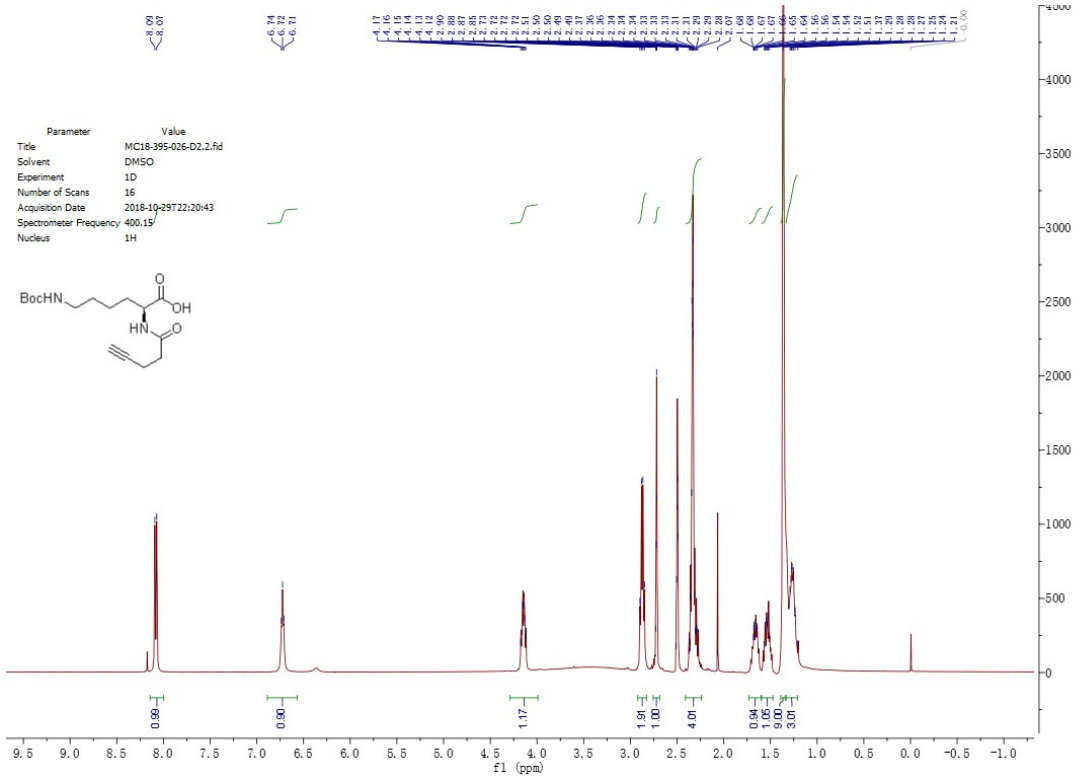
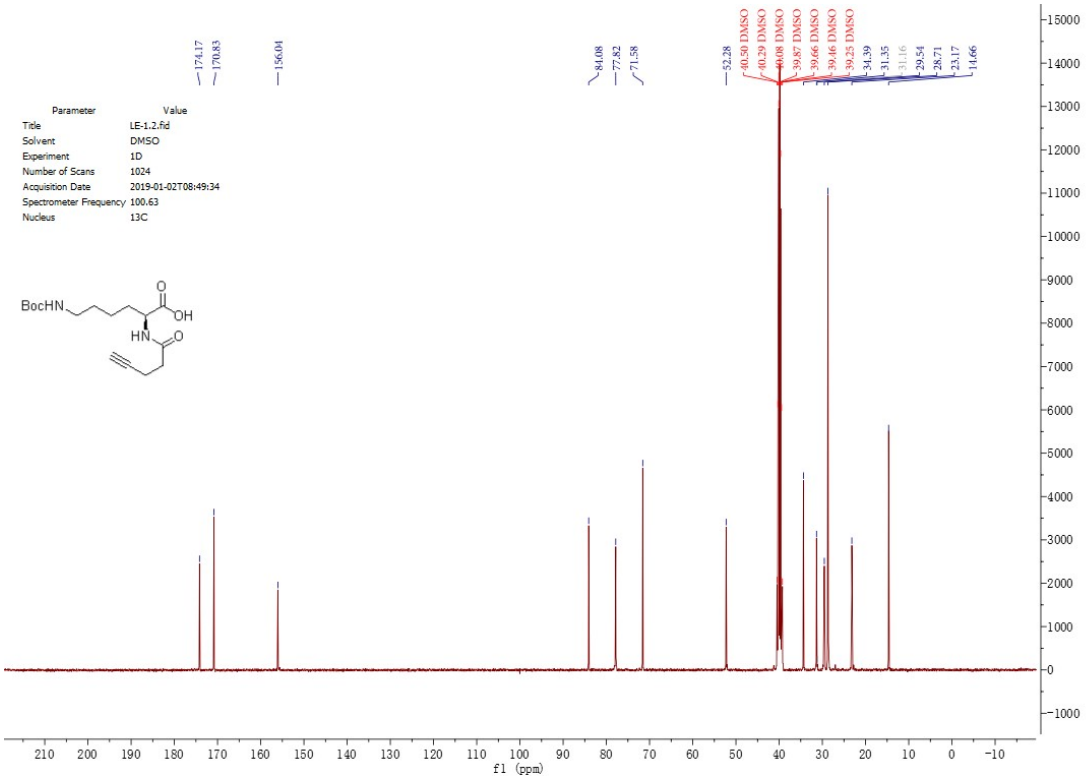
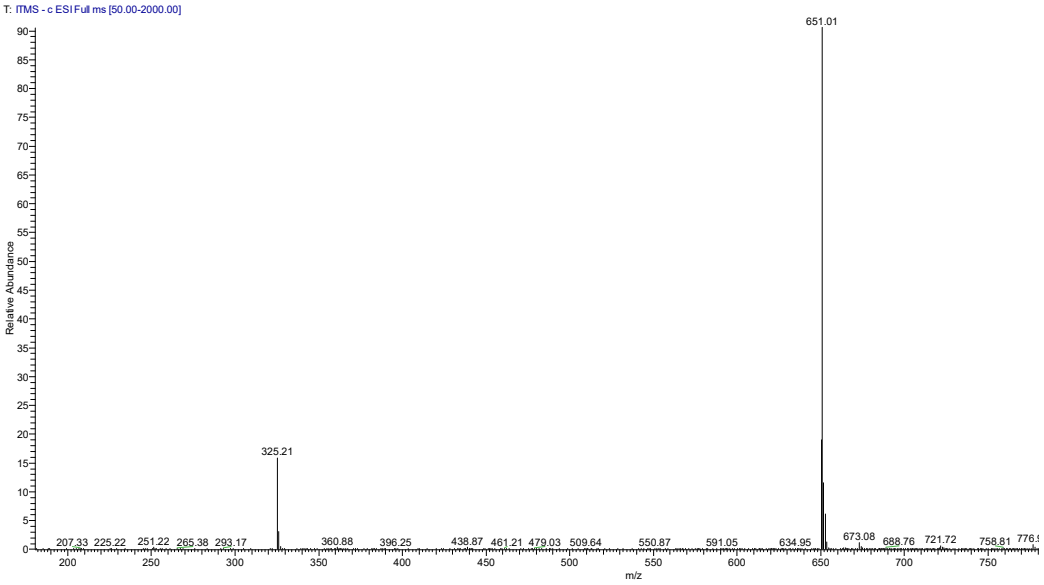
997.66
993.11
998.73
993.98
999.73
994.63
1000.78
990.55
996.17

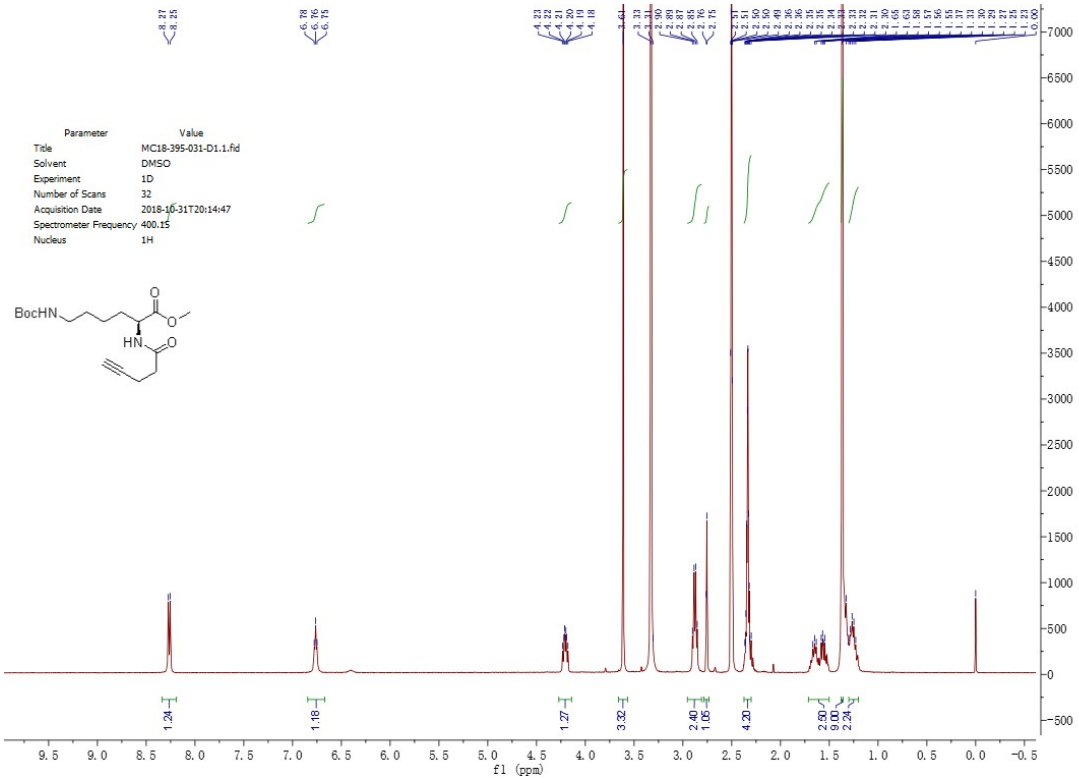
^{1}H NMR,^{13}C NMR and MS spectra of compound **8**

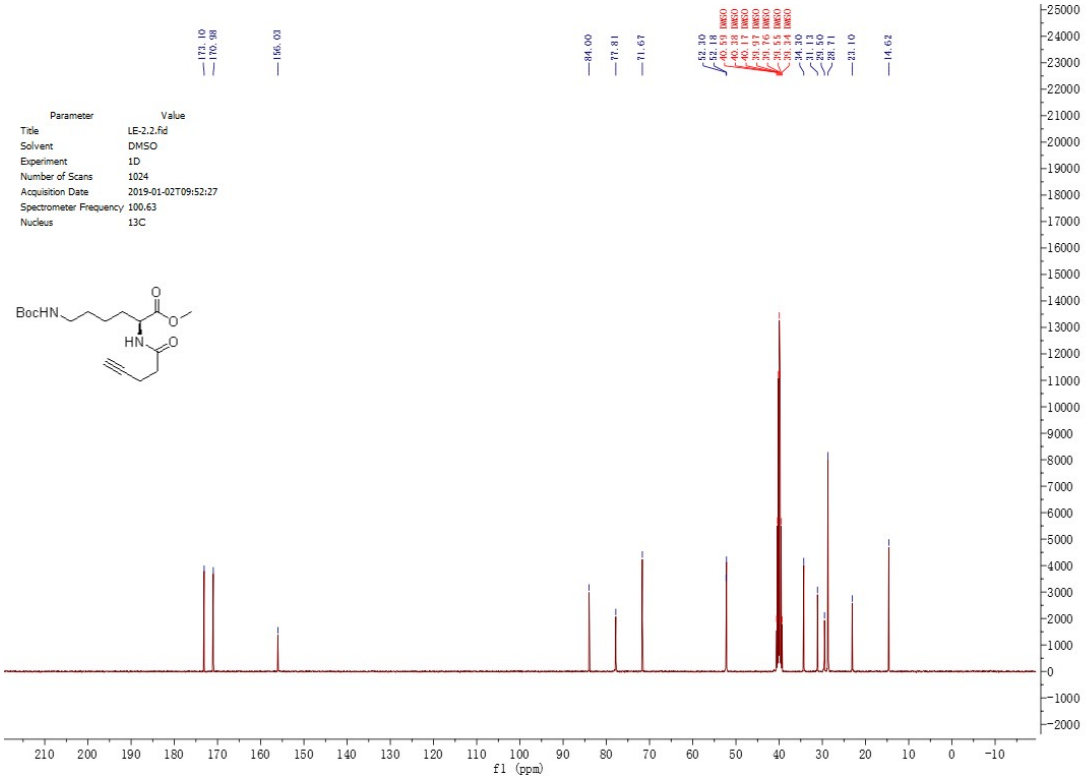


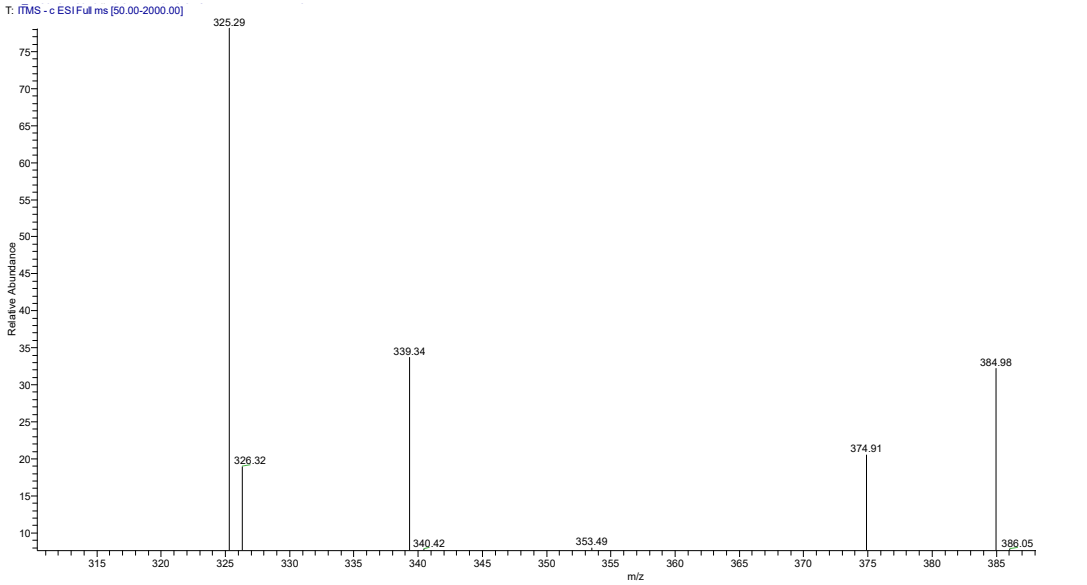




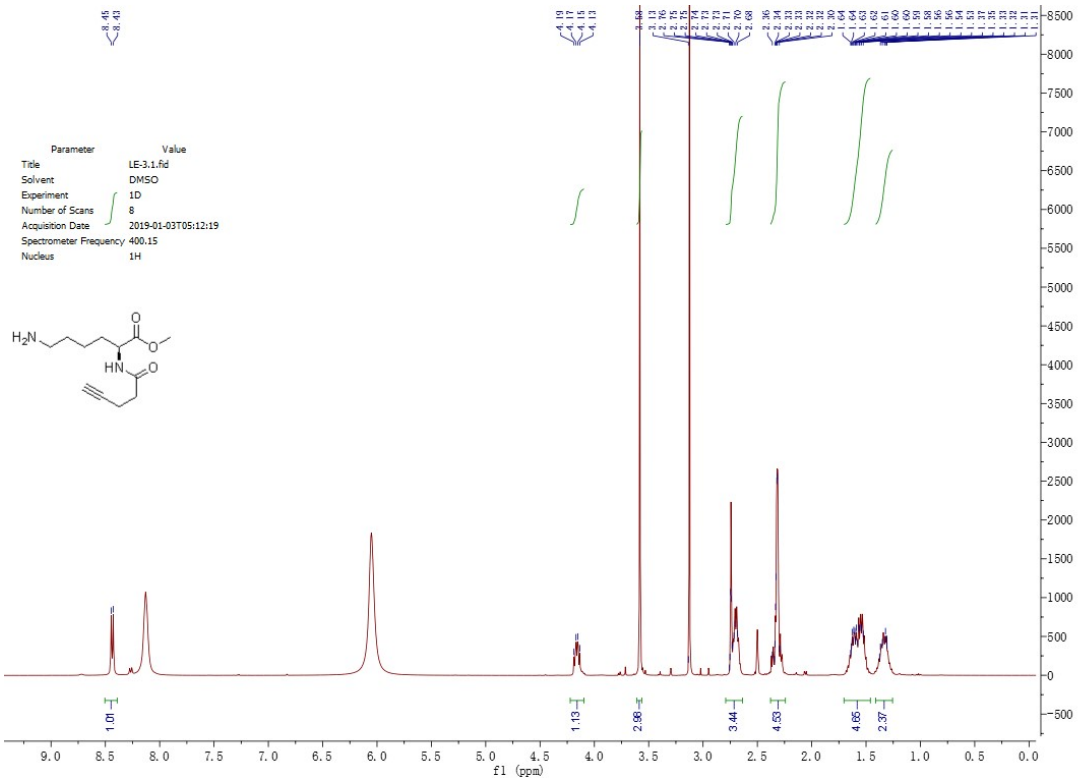
^{1}H NMR,^{13}C NMR and MS spectra of compound **9**

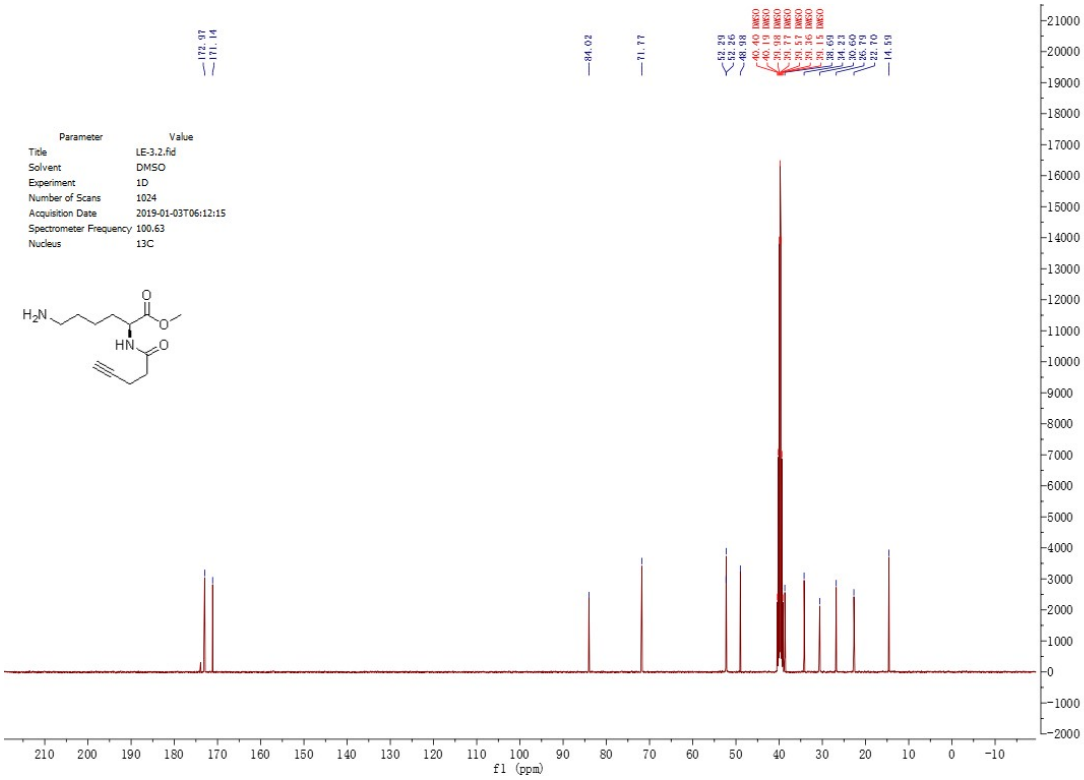


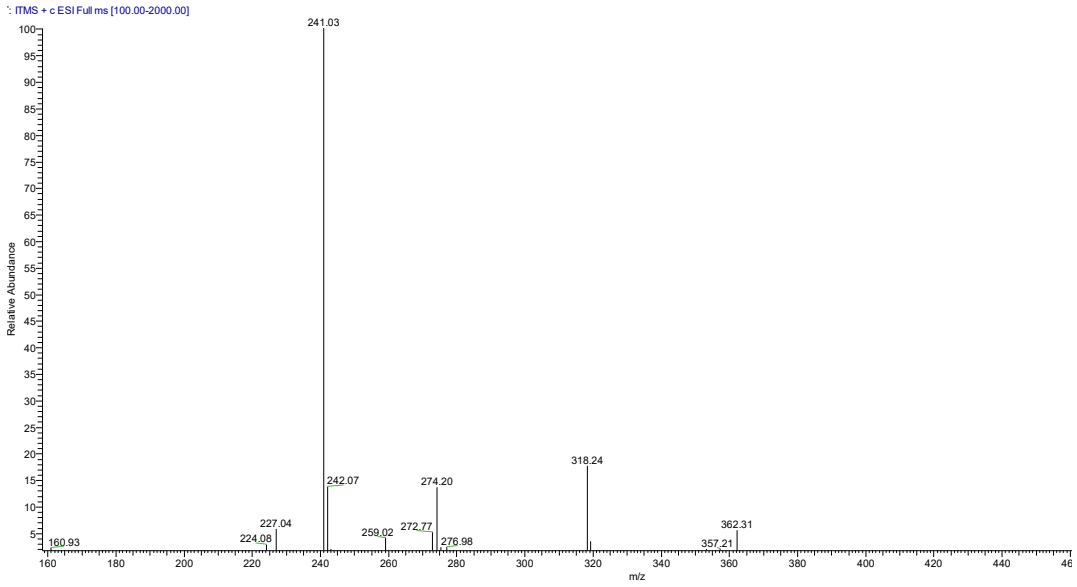

173.10
170.98
166.03
84.00
77.81
71.67
52.30
52.18
40.59
40.38
40.17
39.97
39.76
39.55
39.34
39.13
31.13
29.50
28.71
23.10
14.62
Parameter Value
Title LE-2.2.fid
Solvent DMSO
Experiment 1D
Number of Scans 1024
Acquisition Date 2019-01-02T09:52:27
Spectrometer Frequency 100.63
Nucleus 13C
BocHN
HN
O
f1 (ppm)


T: ITMS - c ESI Full ms [50.00-2000.00]
325.29
339.34
384.98
374.91
326.32
340.42
353.49
386.05
Relative Abundance
m/z

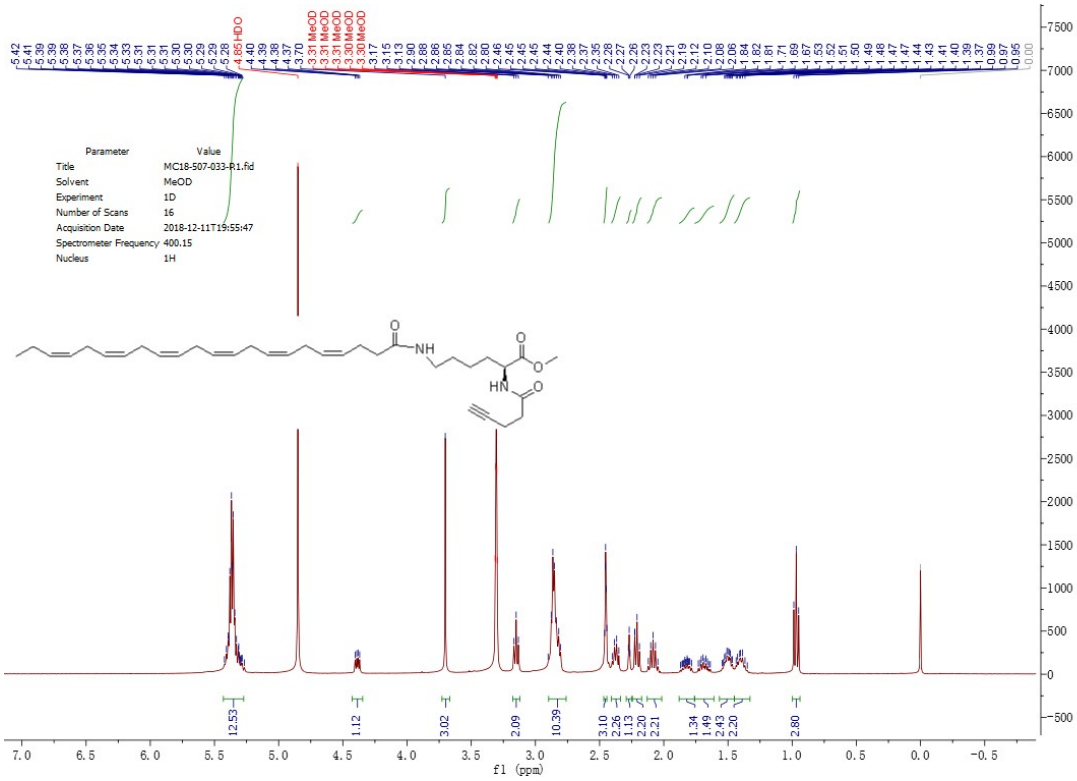
^{1}H NMR,^{13}C NMR and MS spectra of compound **10**

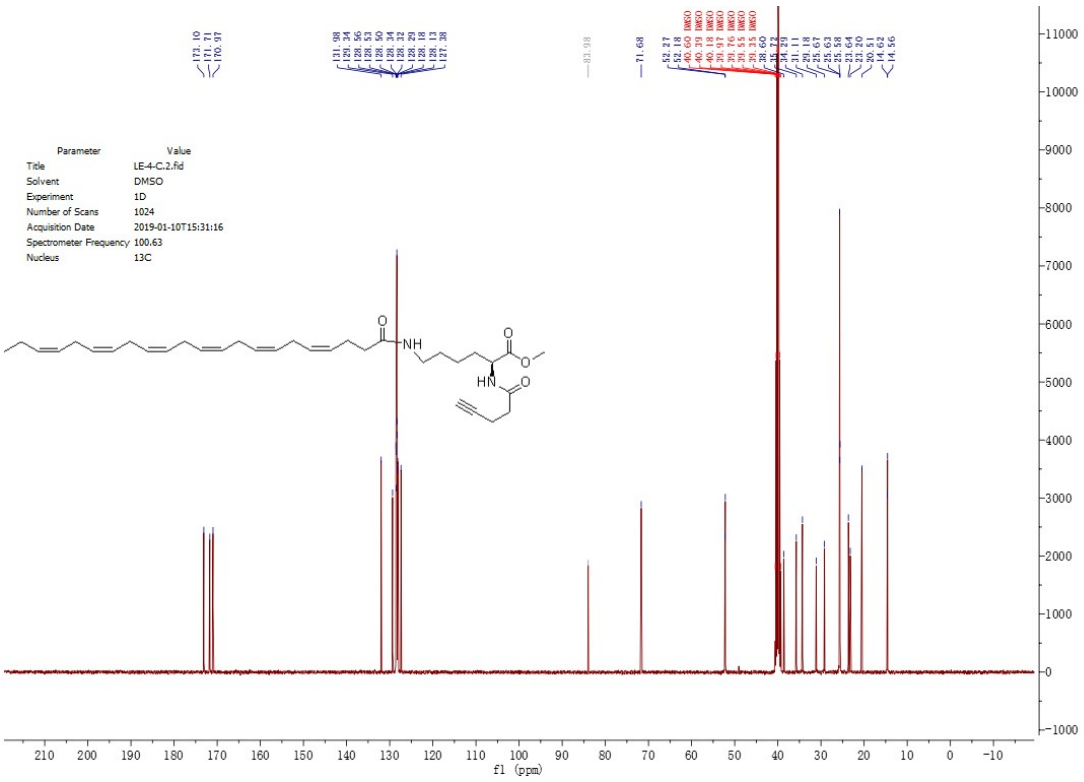


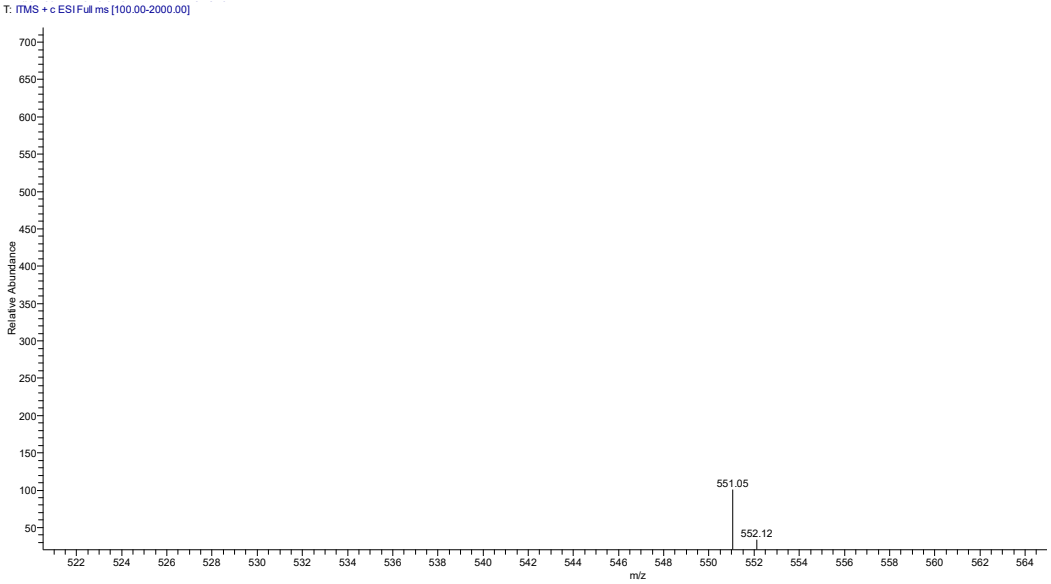




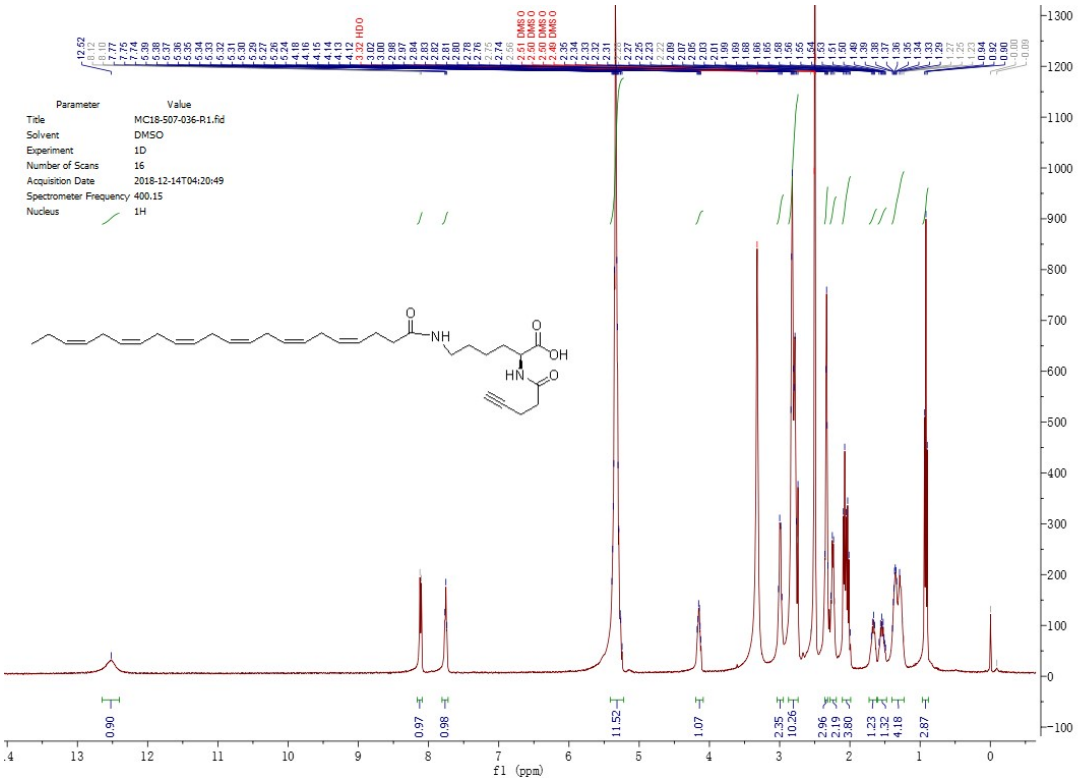
^{1}H NMR,^{13}C NMR and MS spectra of compound **11**

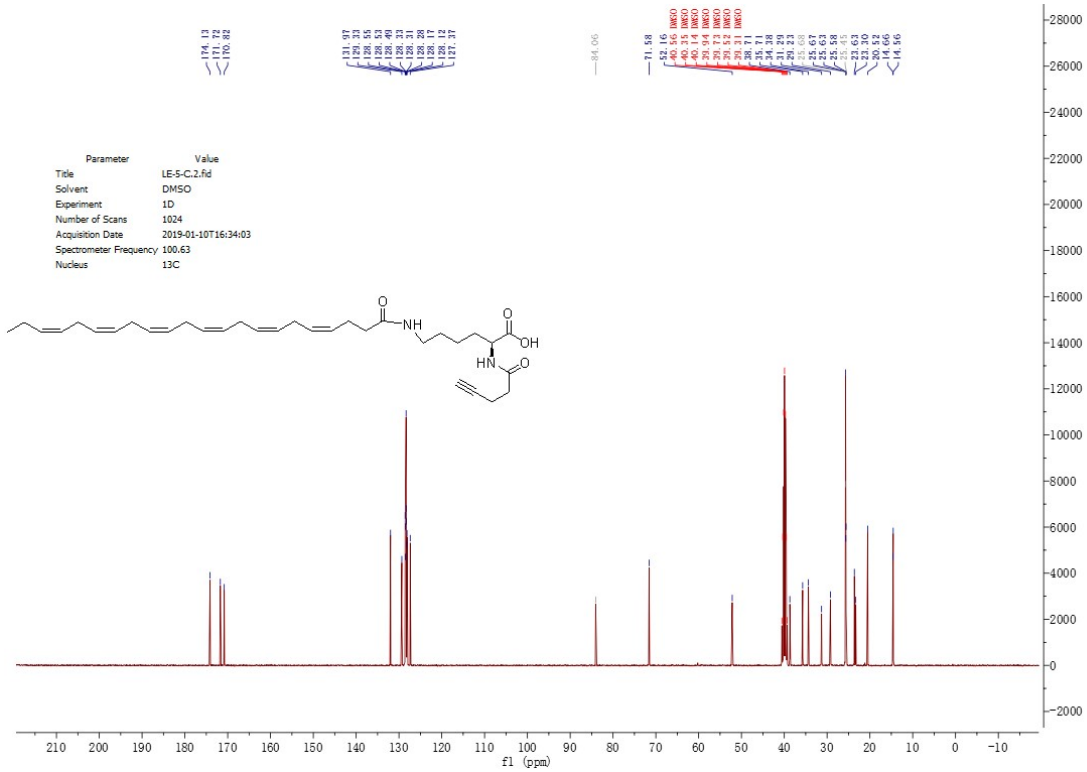


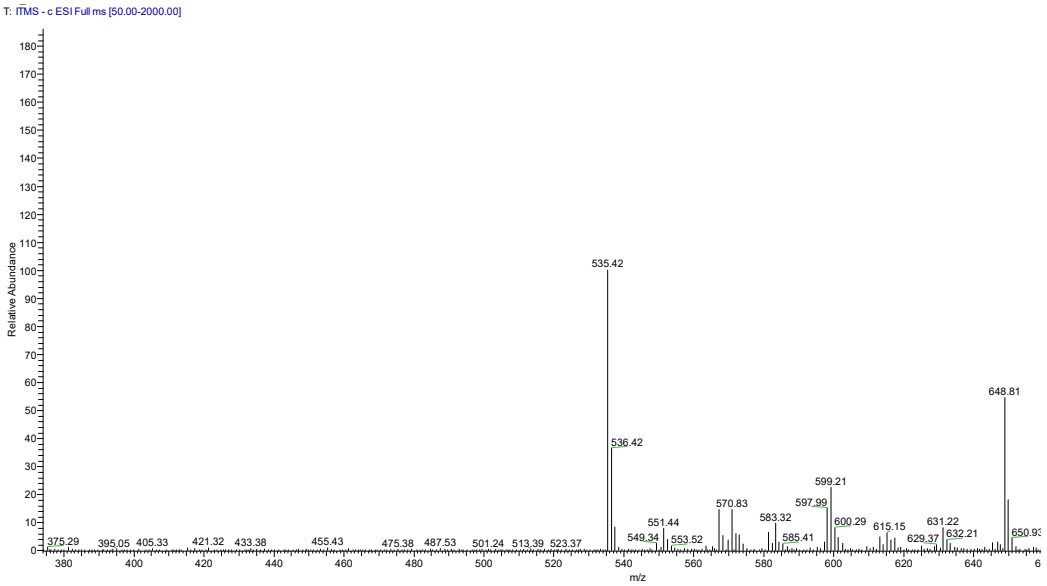

Parameter Value
Title LE-4-C.2.fid
Solvent DMSO
Experiment 1D
Number of Scans 1024
Acquisition Date 2019-01-10T15:31:16
Spectrometer Frequency 100.63
Nucleus 13C
f1 (ppm)


T: ITMS + c ESI Full ms [100.00-2000.00]
Relative Abundance
551.05
552.12
m/z

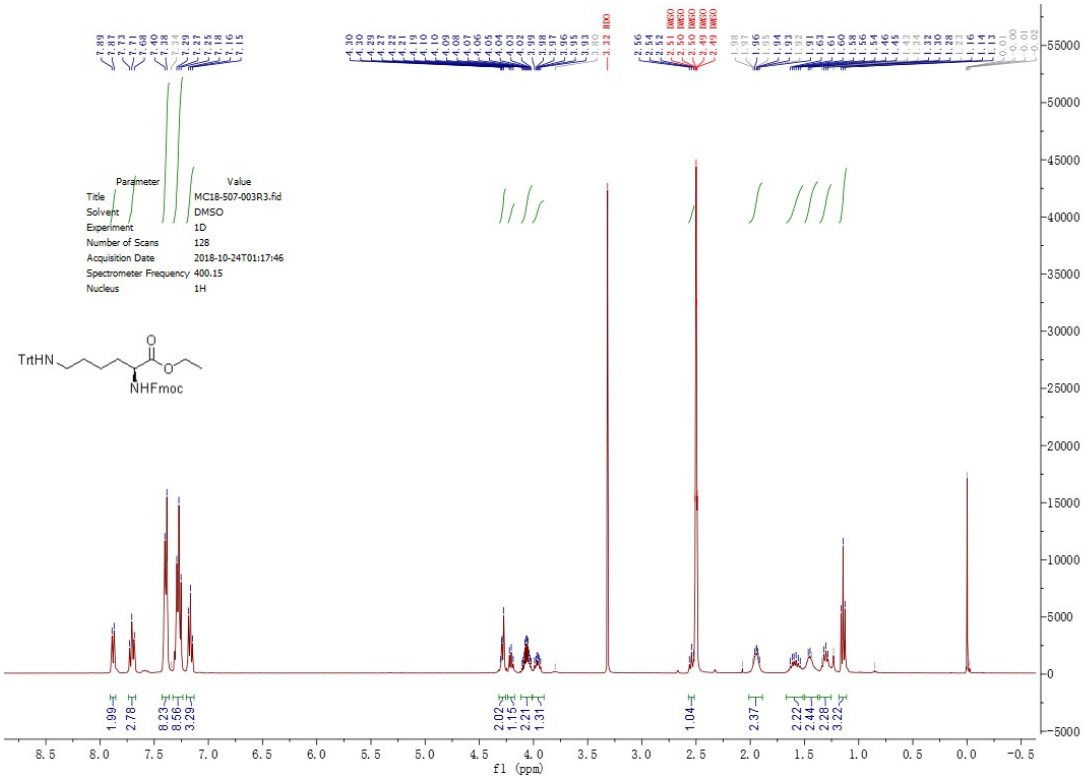
^{1}H NMR,^{13}C NMR and MS spectra of compound **12**

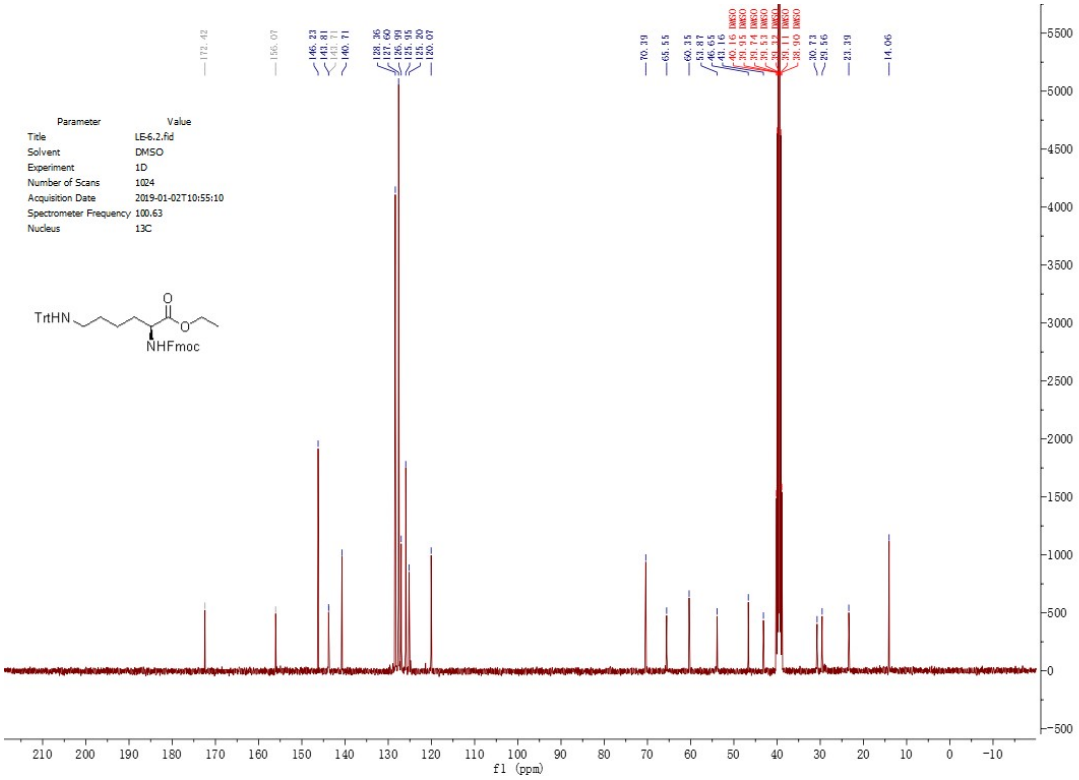


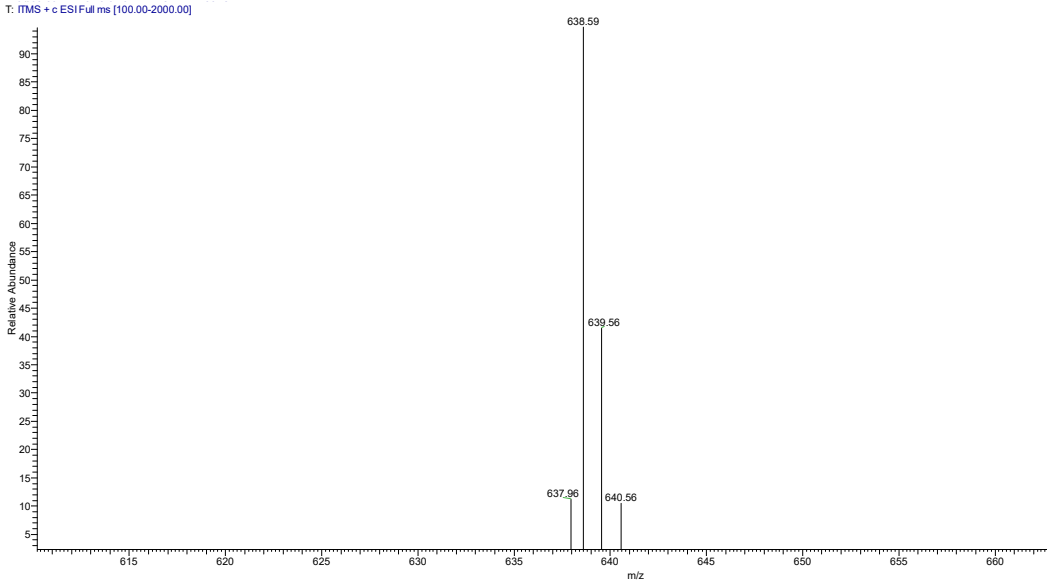




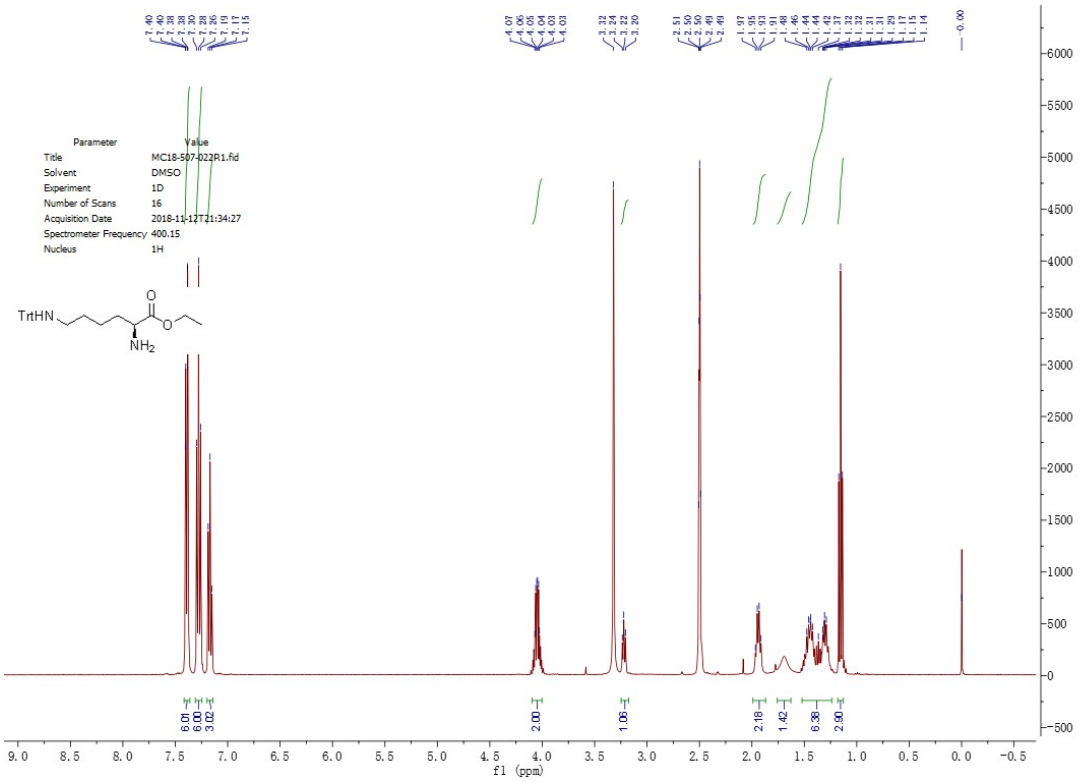
^{1}H NMR,^{13}C NMR and MS spectra of compound **13**

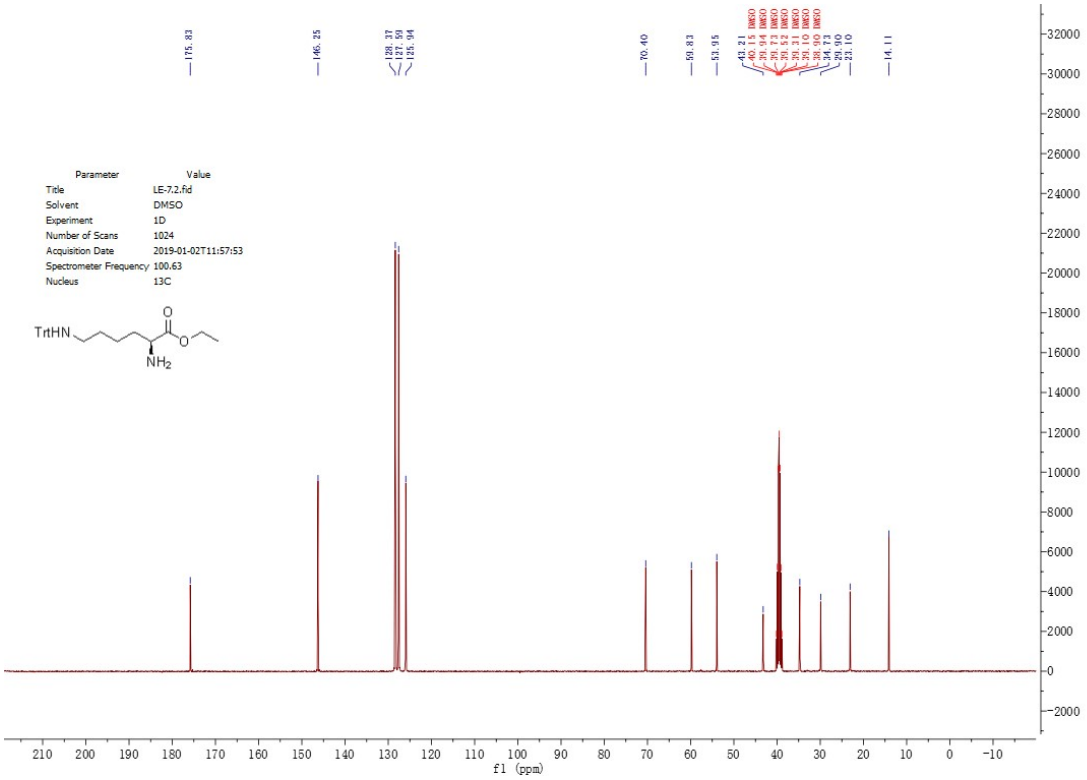


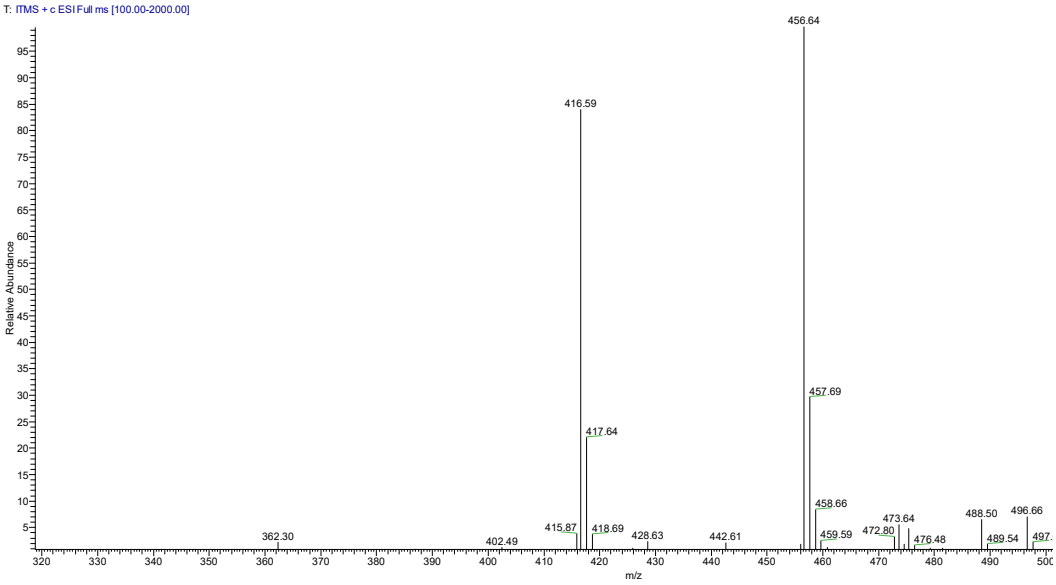

Parameter Value
Title LE-6.2.fid
Solvent DMSO
Experiment 1D
Number of Scans 1024
Acquisition Date 2019-01-02T10:55:10
Spectrometer Frequency 100.63
Nucleus 13C
TrtHN
NHFmoc
f1 (ppm)


T: ITMS + c ESI Full ms [100.00-2000.00]
638.59
639.56
637.96
640.56
Relative Abundance
m/z

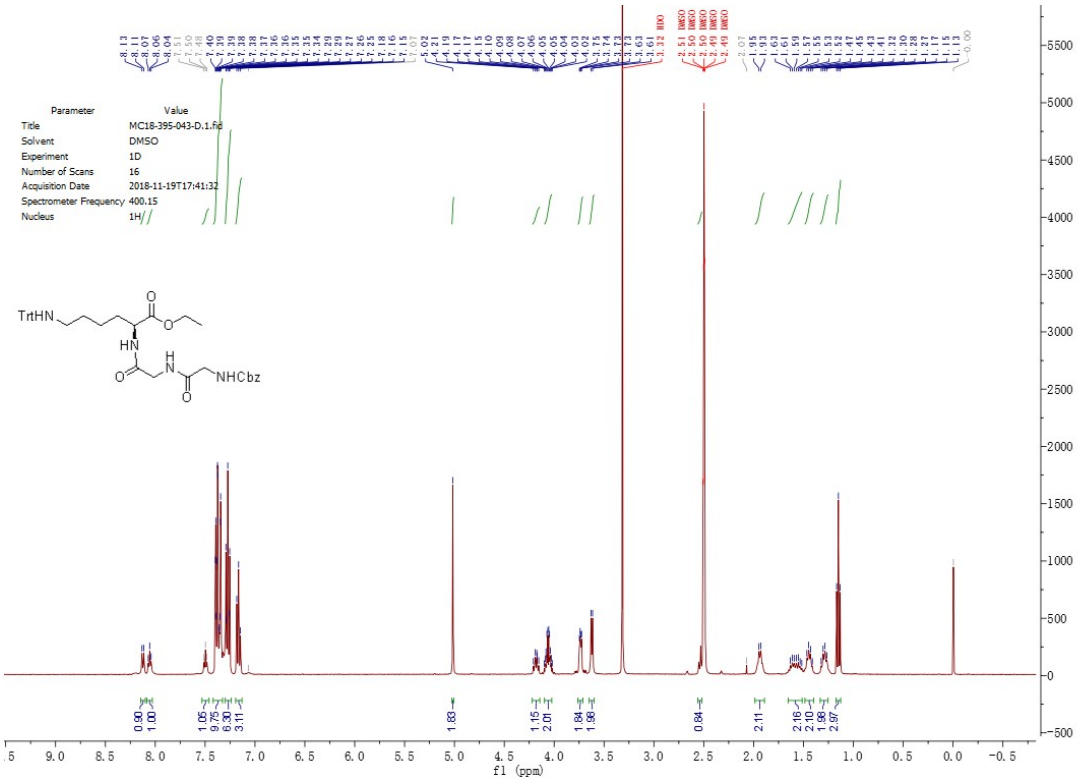
^{1}H NMR,^{13}C NMR and MS spectra of compound **14**

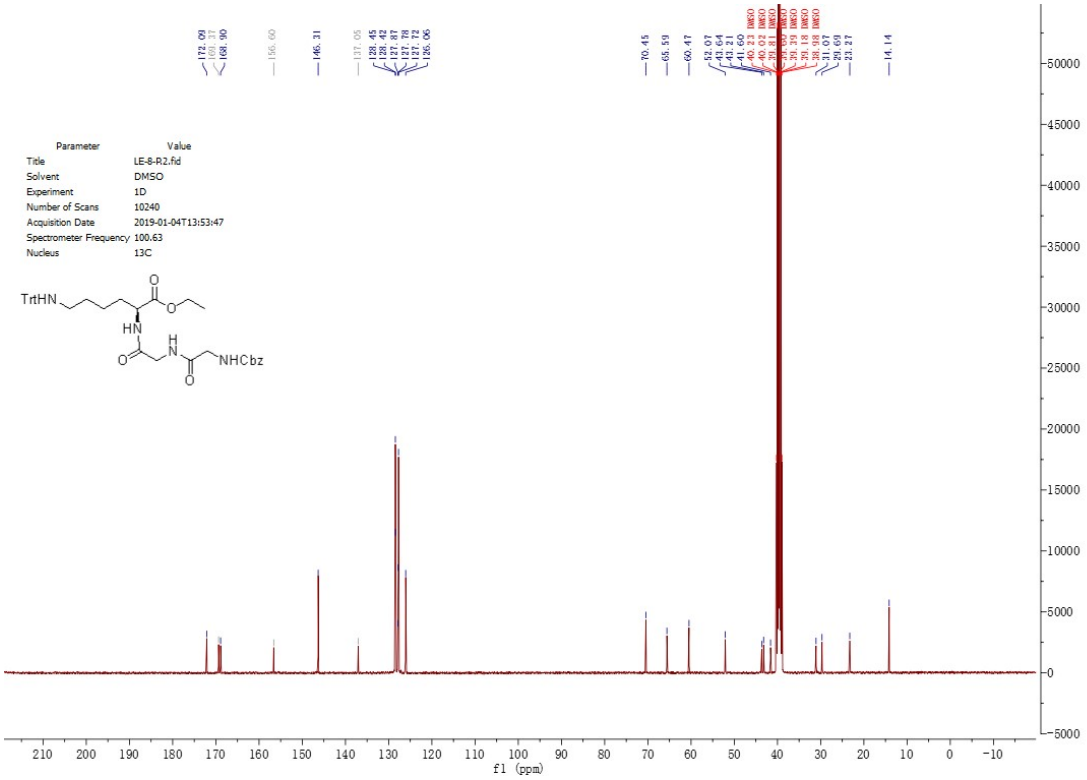


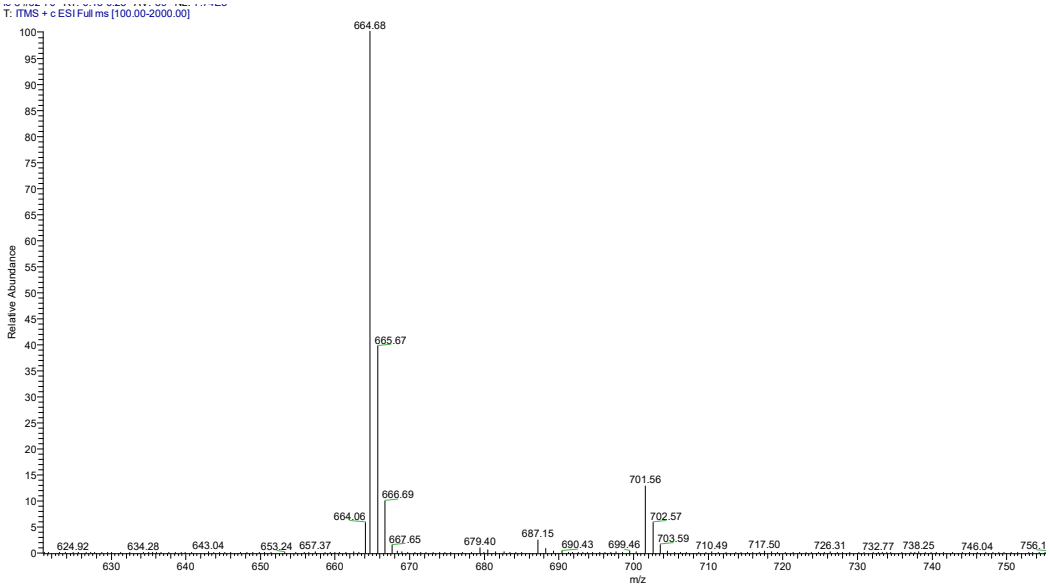




^{1}H NMR,^{13}C NMR and MS spectra of compound **15**




172.09
168.90
166.69
146.31
137.05
128.45
128.42
127.87
127.78
127.72
126.06
70.45
65.59
60.47
52.07
43.64
42.21
41.60
40.23 DMSO
40.02 DMSO
39.81 DMSO
39.60 DMSO
39.39 DMSO
39.18 DMSO
38.98 DMSO
31.07
29.69
23.27
14.14
Parameter Value
Title LE-8-R2.fid
Solvent DMSO
Experiment 1D
Number of Scans 10240
Acquisition Date 2019-01-04T13:53:47
Spectrometer Frequency 100.63
Nucleus 13C
TrtHN
HN
H
N
O
NHCbz
f1 (ppm)


T: ITMS + c ESI Full ms [100.00-2000.00]
Relative Abundance
m/z
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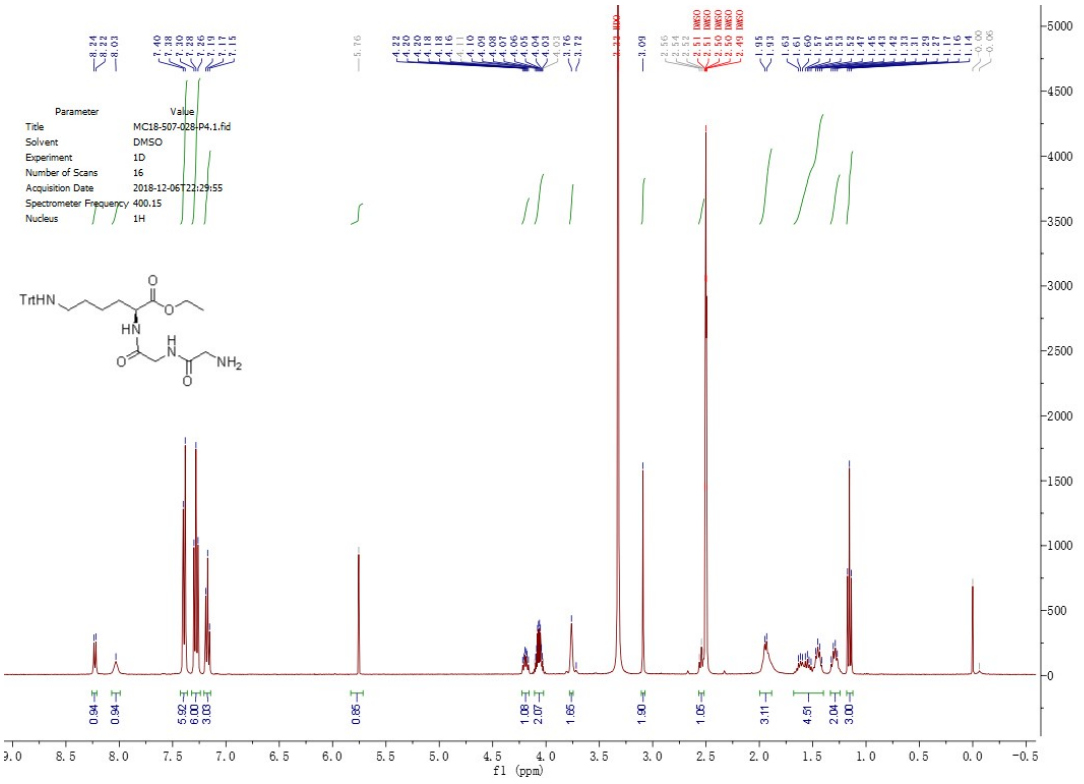
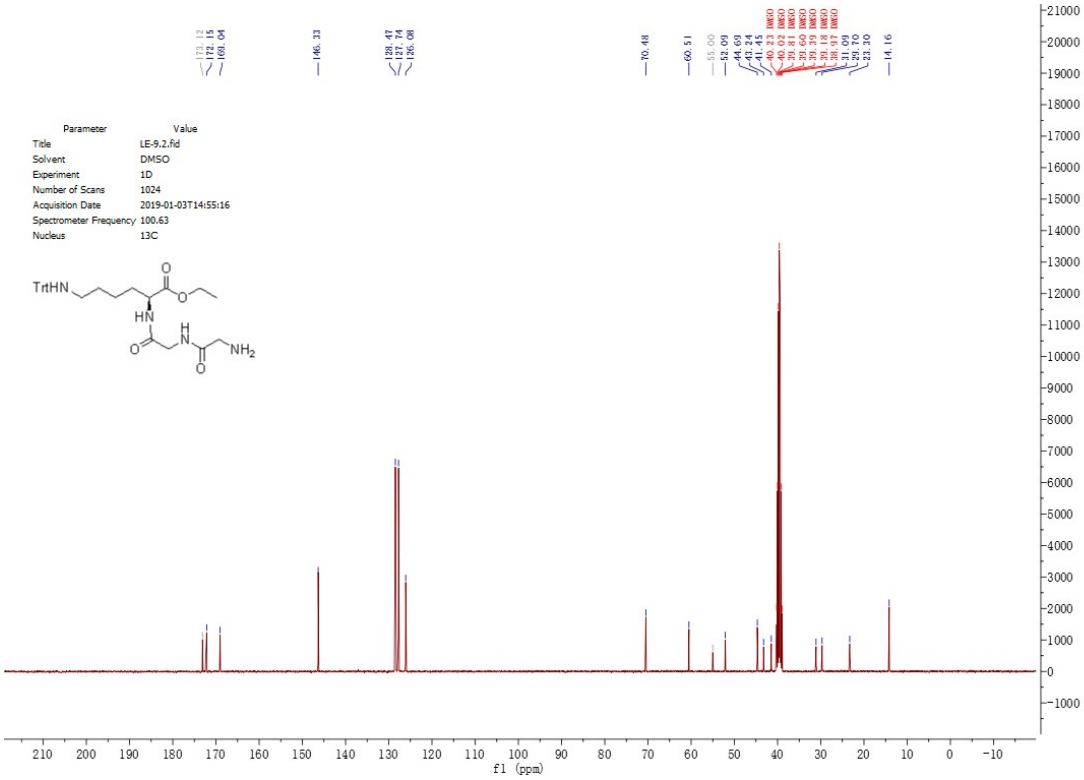
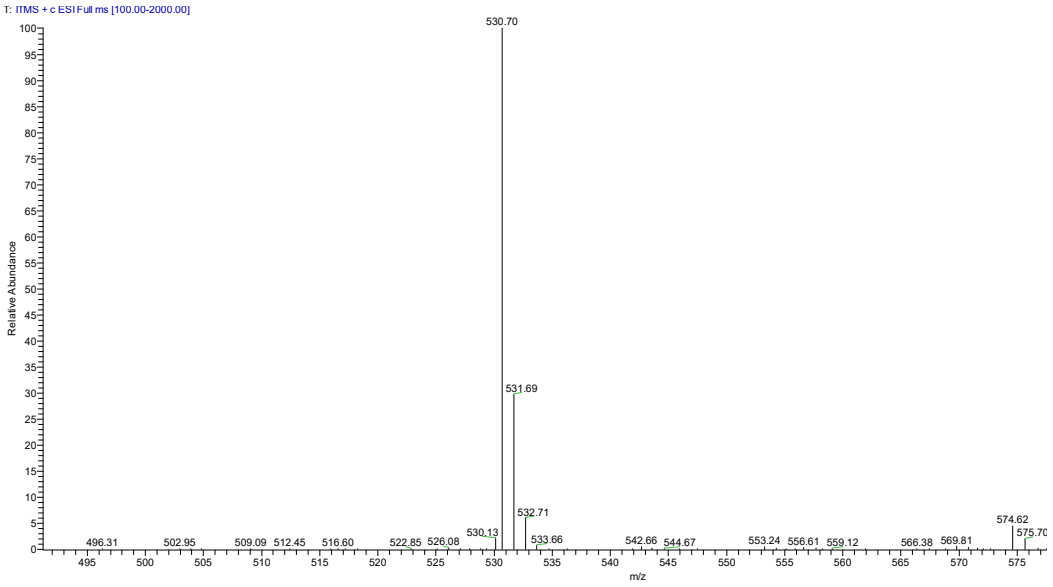
665.67
666.69
664.06
667.65
701.56
702.57
703.59
624.92
634.28
643.04
653.24
657.37
679.40
687.15
690.43
699.46
710.49
717.50
726.31
732.77
738.25
746.04
756.1

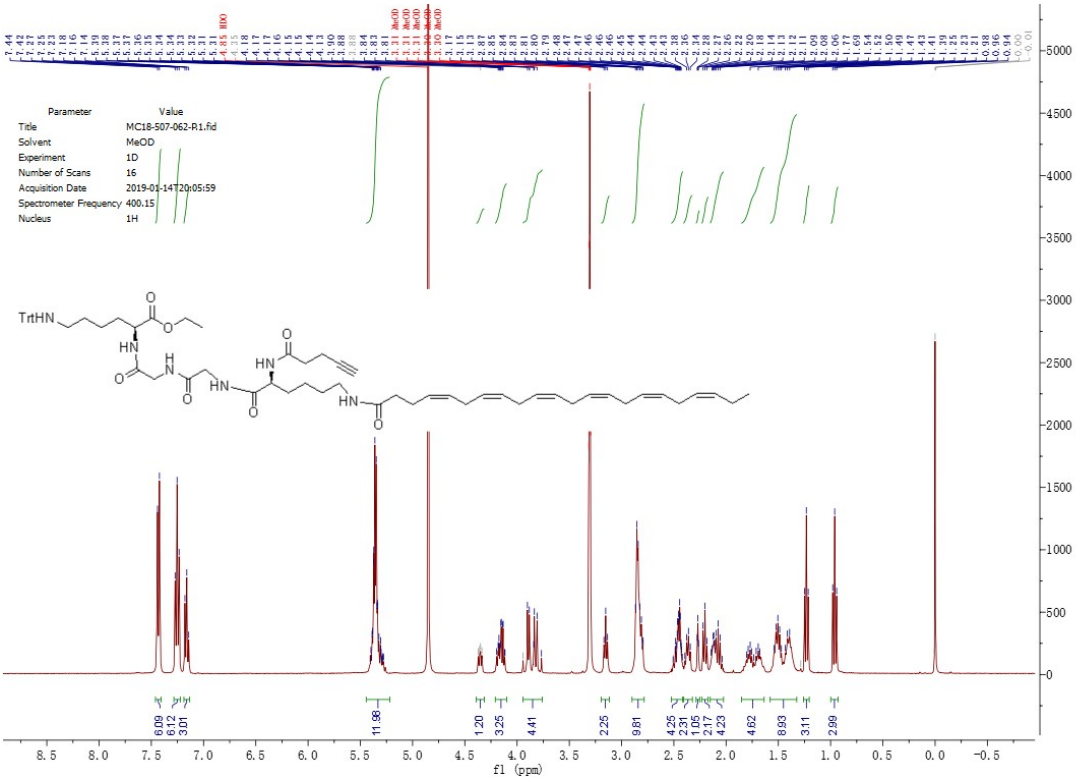
^{1}H NMR,^{13}C NMR and MS spectra of compound **16**

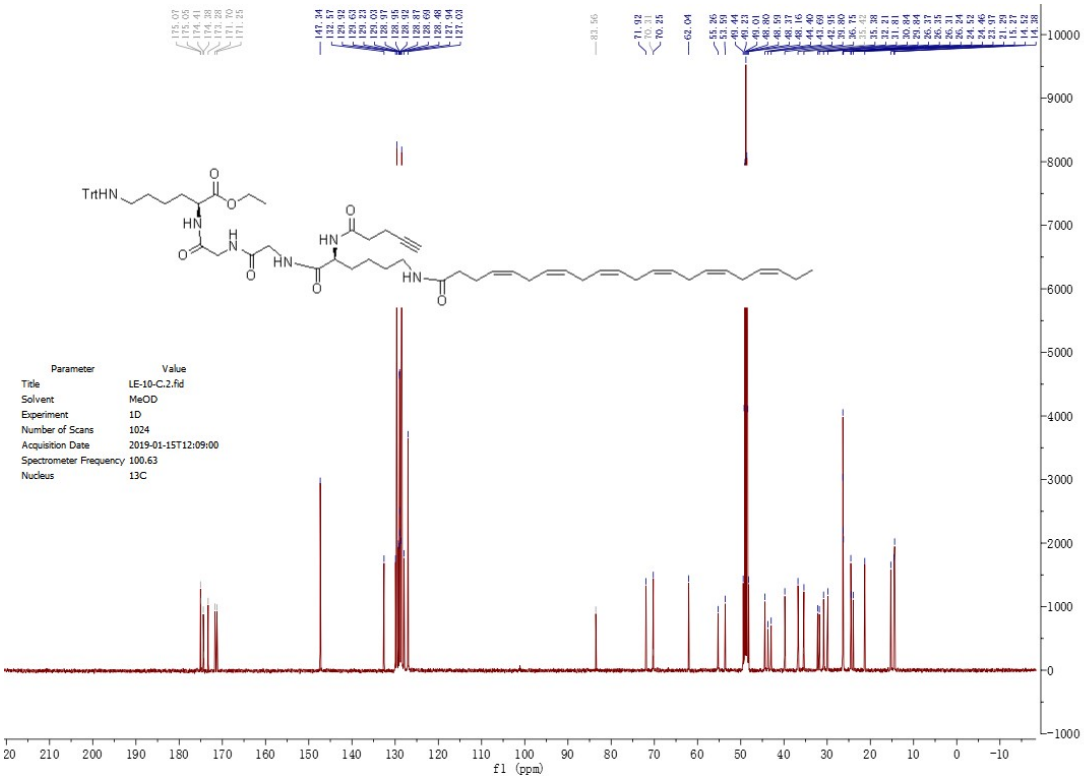


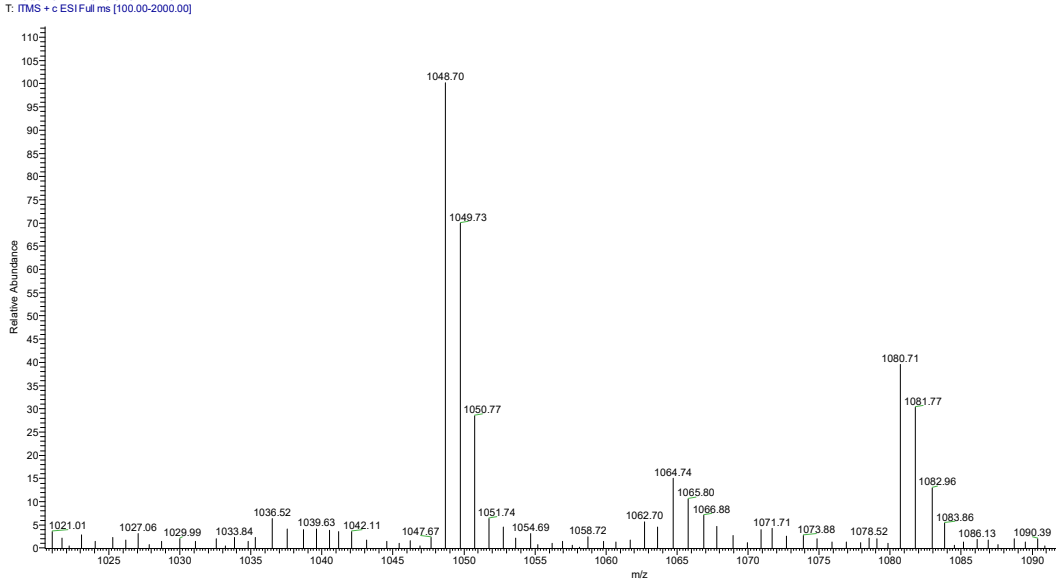




^{1}H NMR,^{13}C NMR and MS spectra of compound **17**




TrtHN
HN
O
HN
H
N
HN
HN
Parameter Value
Title LE-10-C.2.fid
Solvent MeOD
Experiment 1D
Number of Scans 1024
Acquisition Date 2019-01-15T12:09:00
Spectrometer Frequency 100.63
Nucleus 13C
f1 (ppm)


T: ITMS + c ESI Full ms [100.00-2000.00]
Relative Abundance
m/z
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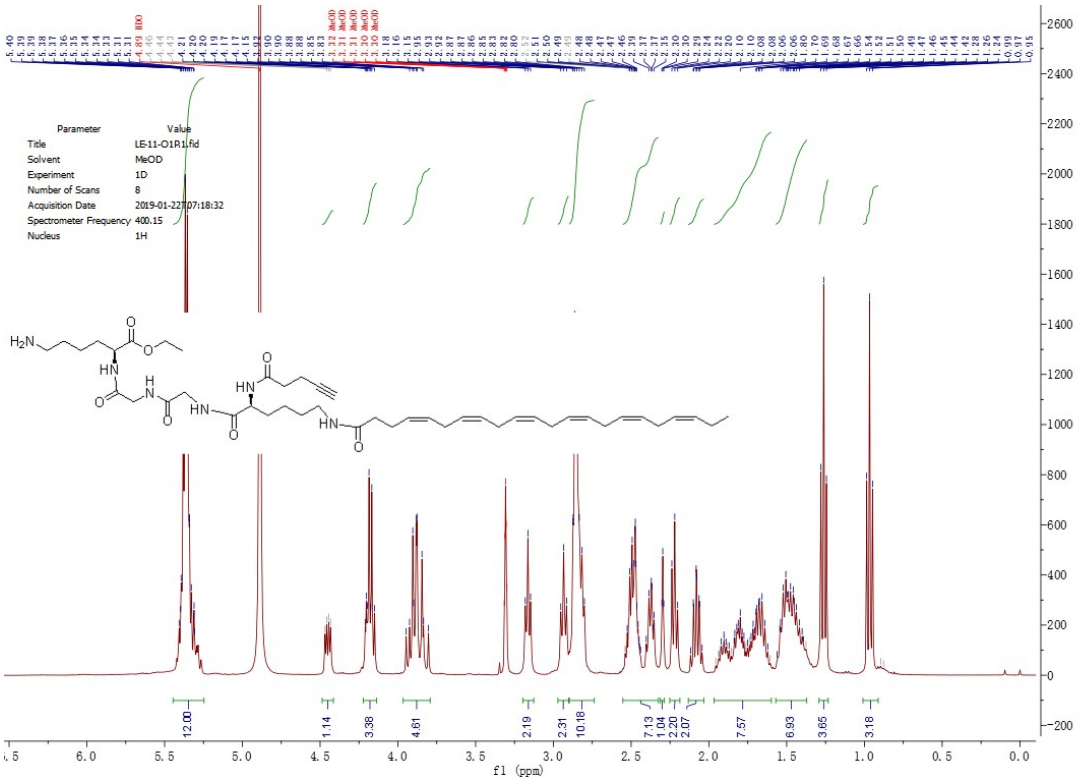
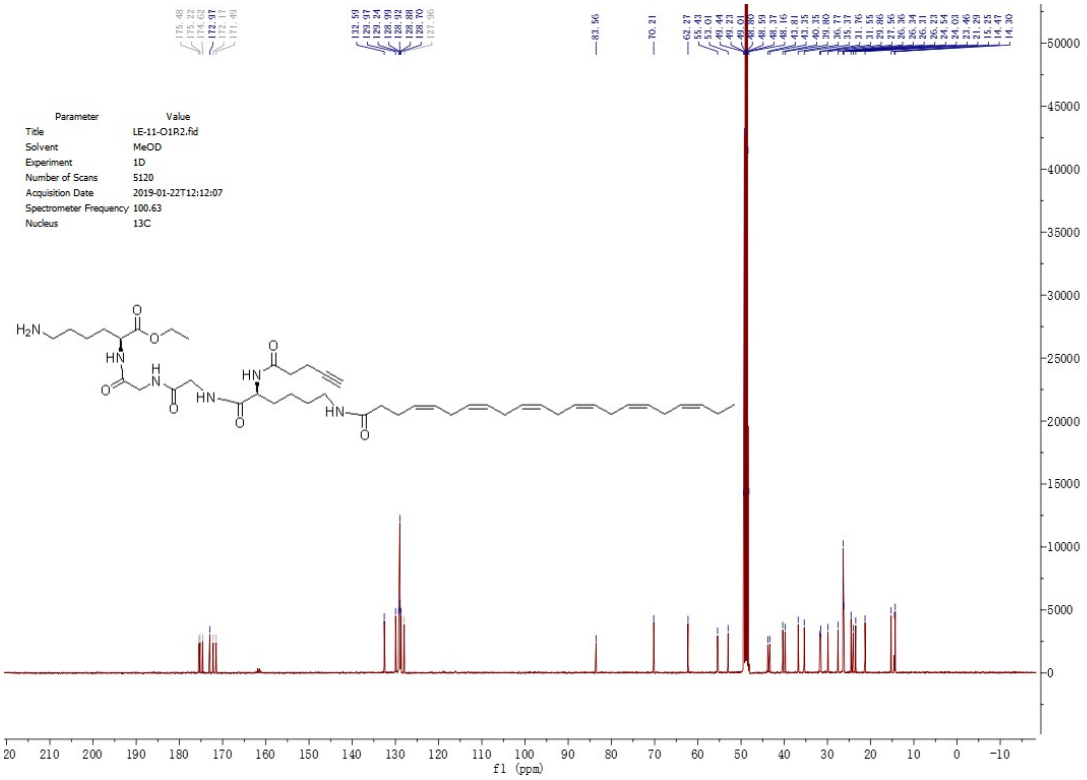
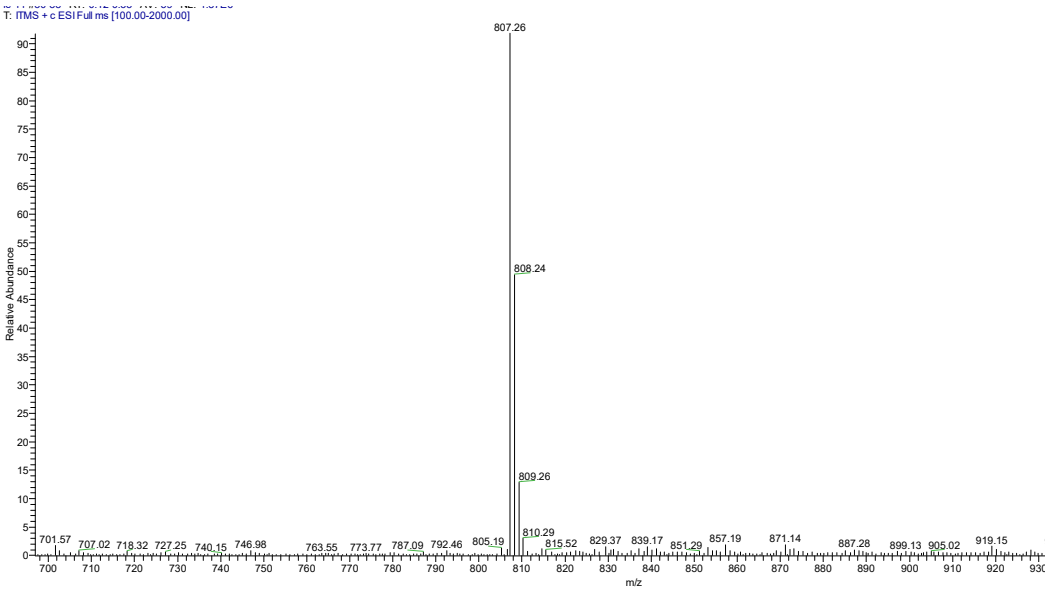
1049.73
1050.77
1051.74
1080.71
1081.77
1082.96
1083.86
1064.74
1065.80
1066.88
1036.52
1039.63
1042.11
1021.01
1027.06
1029.99
1033.84
1047.67
1054.69
1058.72
1062.70
1071.71
1073.88
1078.52
1086.13
1090.39

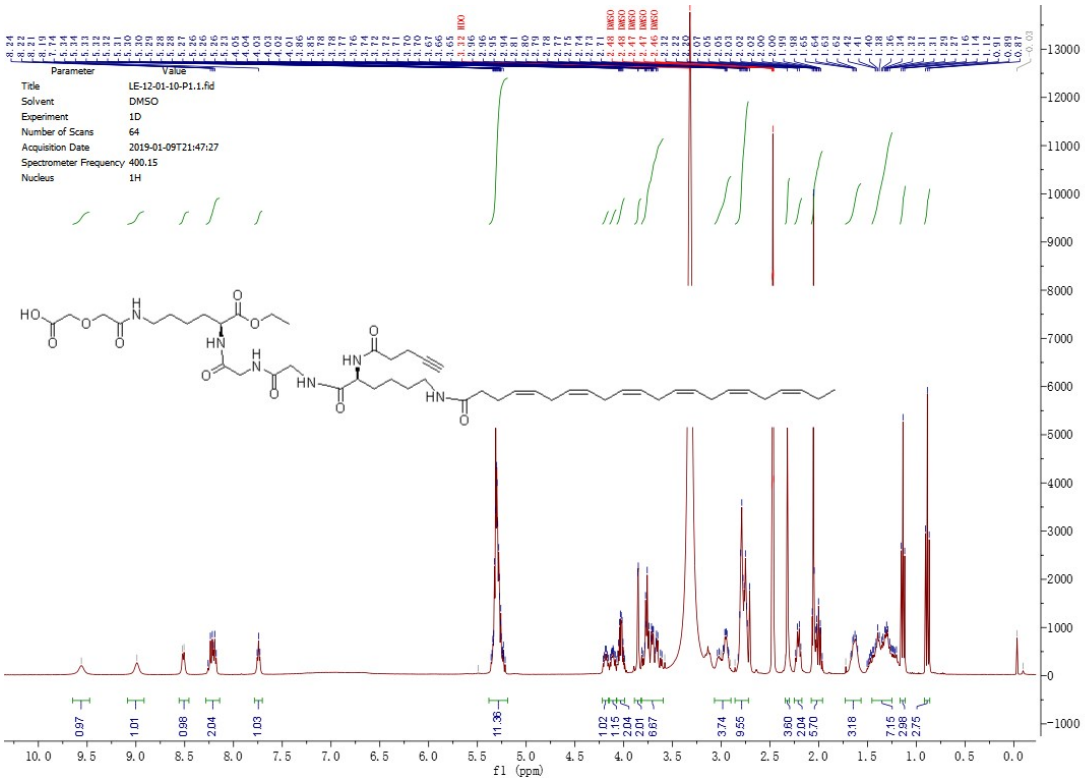
^{1}H NMR,^{13}C NMR and MS spectra of compound **18**

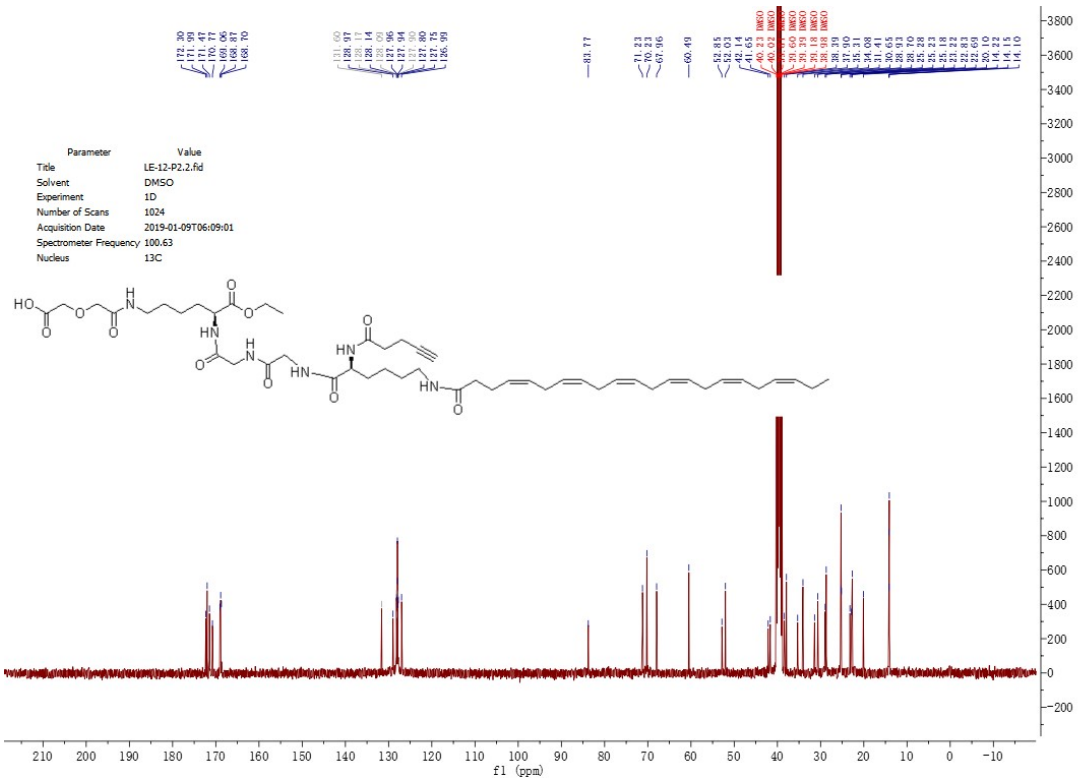


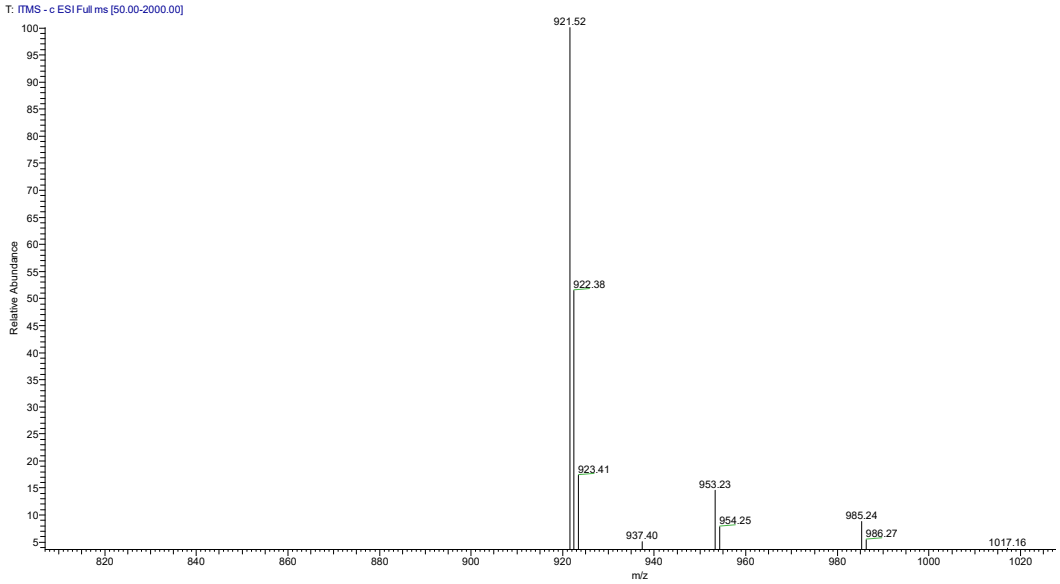




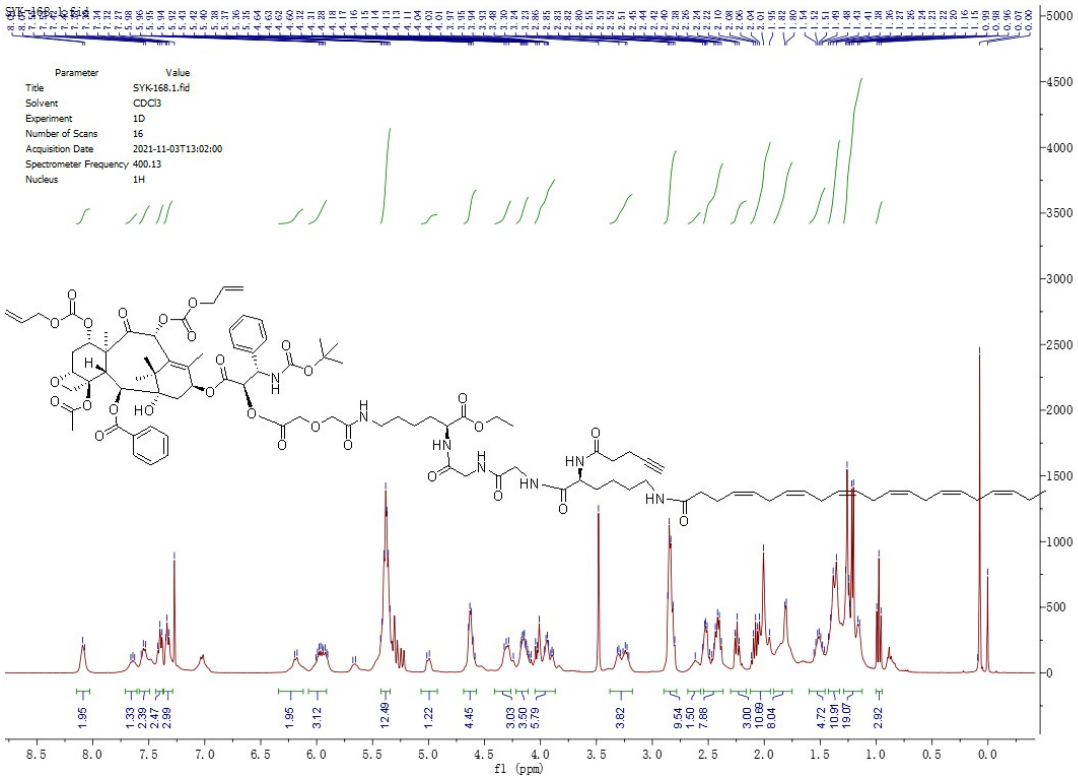
^{1}H NMR,^{13}C NMR and MS spectra of compound **19**

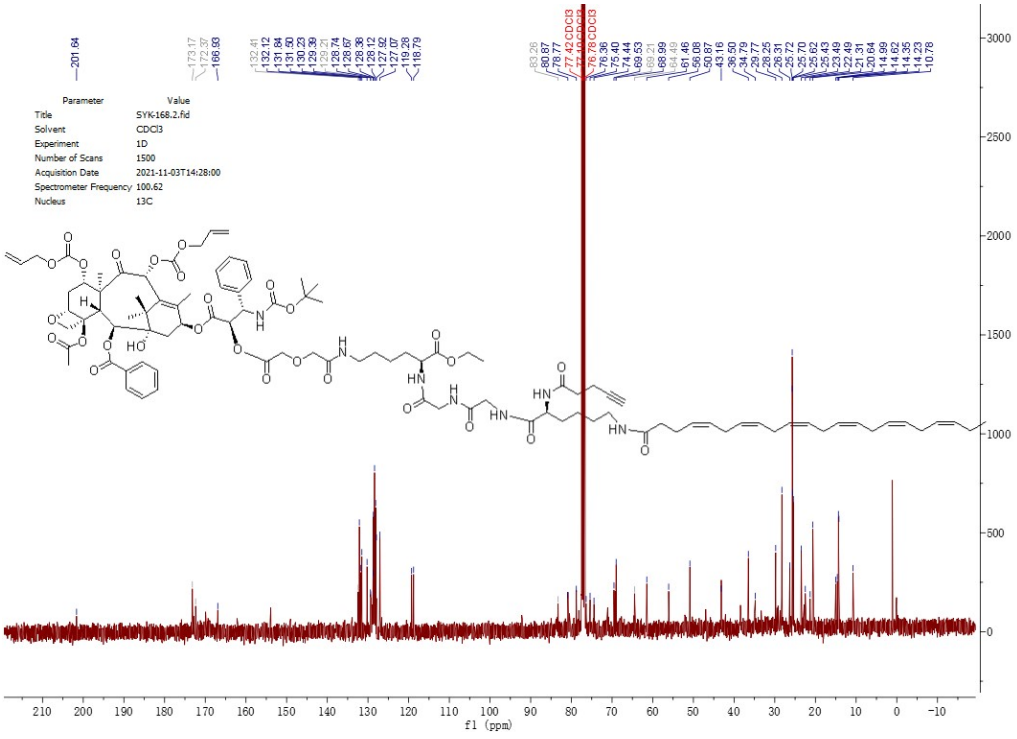


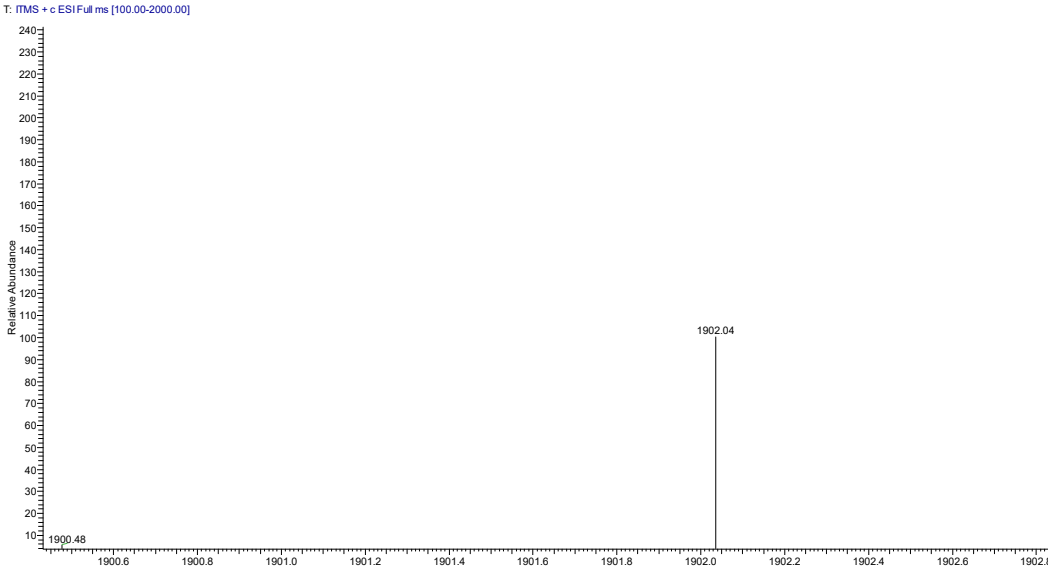

Parameter Value
Title LE-12-P2.2.fid
Solvent DMSO
Experiment 1D
Number of Scans 1024
Acquisition Date 2019-01-09T06:09:01
Spectrometer Frequency 100.63
Nucleus 13C
f1 (ppm)


T: ITMS - c ESI Full ms [50.00-2000.00]
Relative Abundance
m/z
921.52
922.38
923.41
953.23
954.25
985.24
986.27
937.40
1017.16

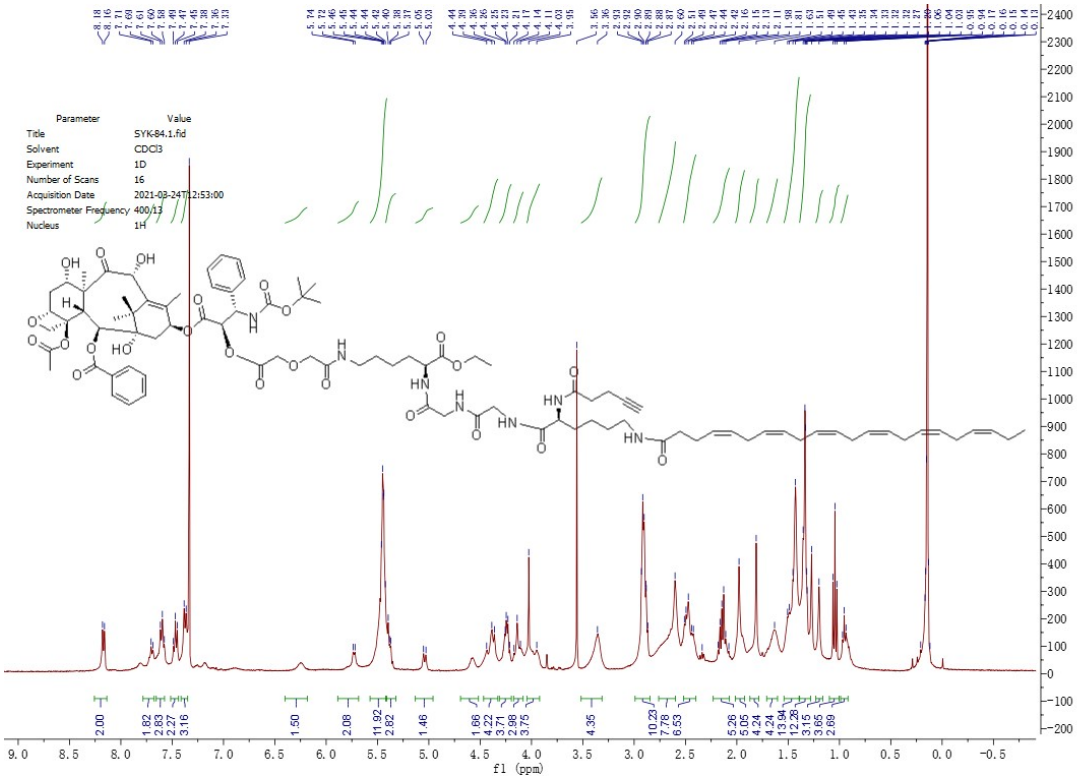
^{1}H NMR,^{13}C NMR and MS spectra of compound **20**

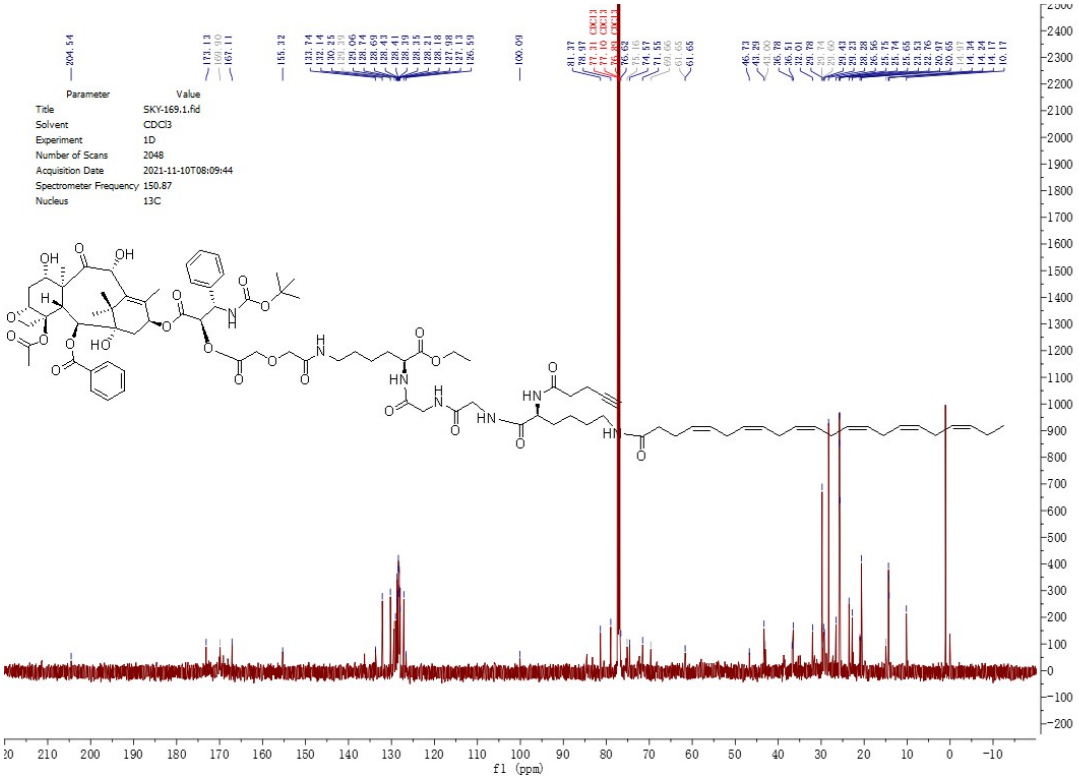






^{1}H NMR,^{13}C NMR and MS spectra of compound **21**

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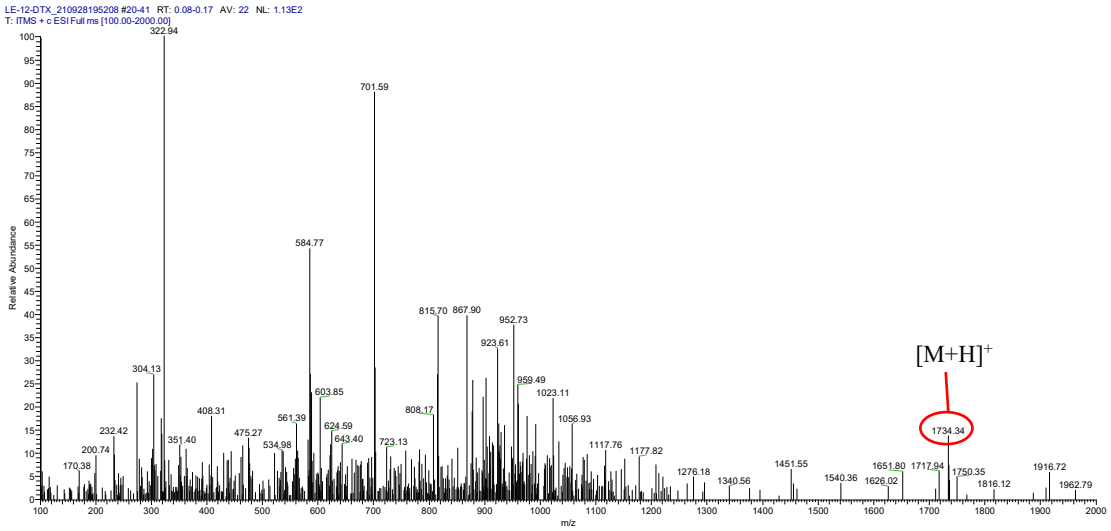
Title SKY-169.1.fid
Solvent CDCl3
Experiment 1D
Number of Scans 2048
Acquisition Date 2021-11-10T08:09:44
Spectrometer Frequency 150.87
Nucleus 13C
f1 (ppm)


LE-12-DTX_210928195208 #20-41 RT: 0.08-0.17 AV: 22 NL: 1.13E2
T: ITMS + c ESI Full ms [100.00-2000.00]
Relative Abundance
m/z
[M+H]+
1734.34

^{1}H NMR spectrum of compound **22**