Supporting information

Redox-Sensitive Dimeric Paclitaxel Choline Phosphate Nanoliposomes for Improved Anticancer Efficacy

Jinzhong Hu[1], Zhiguo Gao[3], Kai Sun[4], Min Liu[1], Zining Wang[1], Jiaying Yu[1], Wanying Wei[1], Xiaofan He[1], Senlin Wang[5], Yaojia Li[2]* and Baiwang Sun[1]*

[1]School of Chemistry and Chemical Engineering, Southeast University, Nanjing 211189, P. R. China

[2]School of Life Sciences and Technology, Xinxiang Medical University, 601 Jinsui Avenue, Xinxiang, 453003, P. R. China

[3]State Key Laboratory of Natural Medicines, Jiangsu Key Laboratory of Drug Metabolism and Pharmacokinetics and Jiangsu Key Laboratory of Drug Discovery for Metabolic Diseases, Center of Advanced Pharmaceuticals and Biomaterials, School of Life Science and Technology, China Pharmaceutical University, Nanjing 210009, P. R. China

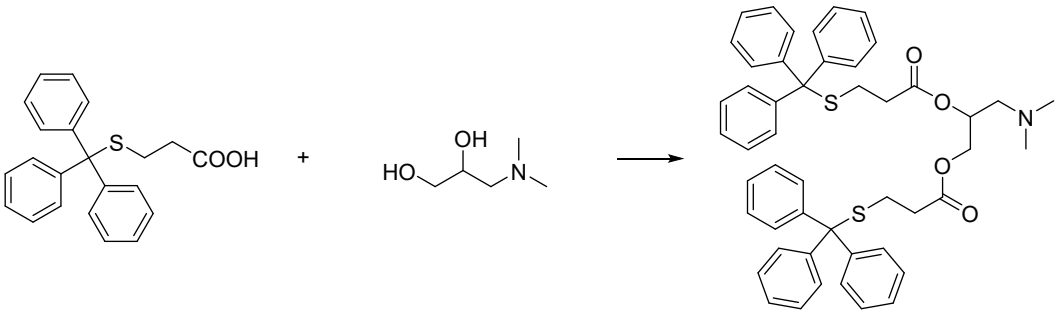
[4]Jiangsu Key Laboratory for Biomass-based Energy and Enzyme Technology, School of Chemistry and Chemical Engineering, Huaiyin Normal University, Huaian 223300, P.R. China China.

[5]School of Textiles and Fashion, Jiangsu College of Engineering and Technology, Nantong 226006, P.R. China

*E-mail address of Corresponding author: chmsunbw@seu.edu.cn[1], 211026@xxmu.edu.cn[2]

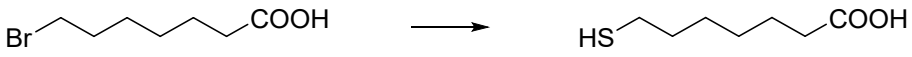
Contents

Detail synthesis methods of PTX-SS-CP



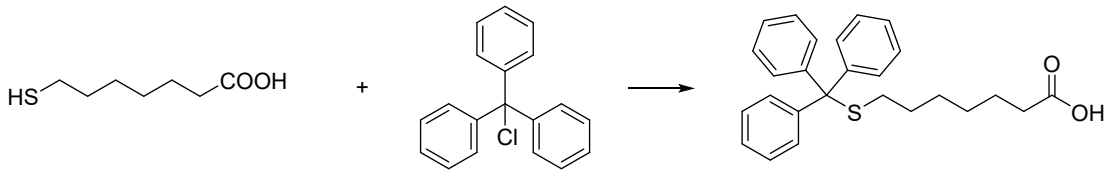
3-(tritylthio)propanoic acid **3-(dimethylamino)propane-1,2-diol** **1**

3-(tritylthio)propanoic acid (7.3 g, 20.98 mmol, 2.5 eq) and 3-(dimethylamino)propane-1,2-diol (1 g, 8.39 mmol) were added to a 250 mL three-necked round flask and it was added anhydrous DCM (80 mL) , followed by EDCI (4.025 g, 21 mmol, 2.5eq), DIPEA (4.329 g, 33.56 mmol, 4 eq) and DMAP (255.89 mg, 2.1 mmol, 0.25 eq). The reaction was stirred overnight under nitrogen. The mixture was diluted with DCM (100 mL) and washed with saturated $NaHCO_3$ (100 mL), water (200 mL) and saturated NaCl (100 mL). The organic phase was dried (Na_2SO_4) and concentrated to yield a yellow oil. It was purified by a flash column to obtain compound **1** as a pale oil (4.8 g, 73.34% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, J = 8.0 Hz, 12H), 7.29 – 7.26 (m, 12H), 7.20 (d, J = 7.2 Hz, 6H), 5.12 – 5.02 (m, 1H), 4.27 (dd, J = 11.9, 3.0 Hz, 1H), 4.02 (dd, J = 11.9, 6.3 Hz, 1H), 2.44 – 2.38 (m, 4H), 2.38 – 2.30 (m, 2H), 2.24 – 2.13 (m, 10H). ESI-MS calcd. for $C_{49}H_{49}NO_4S_2$: 779.31 found 780.40 $[M+H]^+$.



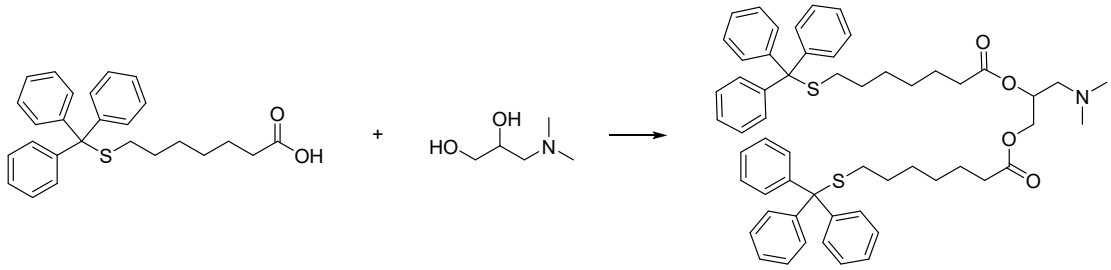
7-bromoheptanoic acid **2**

A solution of 7-bromoheptanoic acid (2 g, 9.53 mmol) and thiourea (3.64 g, 47.76 mmol, 5 eq) in 50 mL acetone was refluxed overnight under N_2 at 70℃. Then it was cooled to room temperature and dried residue was added to a solution of KOH (3.47 g, 66.71 mmol) in 80 mL of ethanol, refluxed for another 4h at 90°C under N_2, and cooled to room temperature. Acid-base extraction was performed to give compound **2** (910 mg, 58.86% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.52 (q, J = 7.4 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 1.63 (dt, J = 14.9, 7.5 Hz, 4H), 1.50 – 1.28 (m, 5H). ESI-MS calcd. for $C_7H_{14}O_2S$: 162.07 found 161.00 $[M-H]^-$.



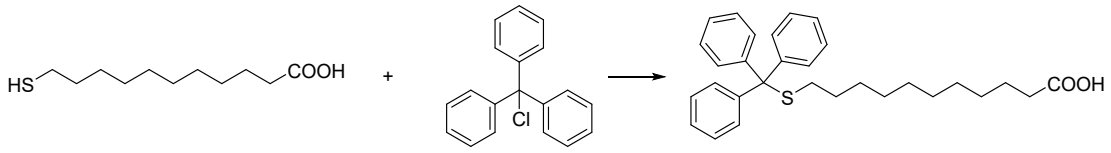
2 **(chloromethanetriyl)tribenzene** **3**

2 (910 mg, 5.6 mmol) was added into a single-mouth bottle containing 20 mL DCM, and then triphenylmethyl chloromethane (1.73 g, 6.2 mmol) was slowly added. The mixture was stirred at room temperature for 5 h, washed three times with deionized water, organic phase was collected and dried, and it was purified by silica gel column chromatography to give compound **3** a white solid (1.9 g, 83.88% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.14 (s, 1H), 7.41 (d, *J* = 7.8 Hz, 6H), 7.28 (t, *J* = 7.7 Hz, 5H), 7.21 (t, *J* = 7.3 Hz, 3H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.14 (t, *J* = 7.3 Hz, 2H), 1.60 – 1.49 (m, 2H), 1.39 (dt, *J* = 14.8, 7.2 Hz, 2H), 1.29 – 1.17 (m, 4H). ESI-MS calcd. for $C_{26}H_{28}O_2S$: 404.18 found 403.1 $[M-H]^-$.



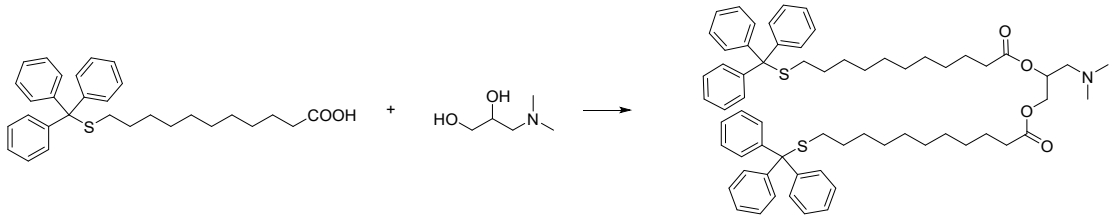
3 **3-(dimethylamino)propane-1,2-diol** **4**

3 (1.8 g, 4.45 mmol, 2eq) and 3-(dimethylamino)propane-1,2-diol (262 mg, 2.2 mmol) were added to a 100 mL three-necked round flask and it was added anhydrous DCM (20 mL) , followed by EDCI (1.054 g, 5.5 mmol, 2.5eq), DIPEA (1.135 g, 8.8 mmol，4eq) and DMAP (67.1 mg, 0.55 mmol, 0.25eq). The reaction was stirred overnight under nitrogen. The mixture was diluted with DCM (30 mL) and washed with saturated $NaHCO_3$ (30 mL), water (50 mL) and saturated NaCl (30 mL). The organic phase was dried (Na_2SO_4) and concentrated to yield a yellow oil. It was purified by a flash column to obtain compound **4** as a pale oil (730 mg, 37.22% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.8 Hz, 12H), 7.30 – 7.25 (m, 12H), 7.20 (t, *J* = 7.2 Hz, 6H), 5.16 (dd, *J* = 6.2, 3.0 Hz, 1H), 4.33 (dd, *J* = 11.9, 2.9 Hz, 1H), 4.06 (dd, *J* = 11.9, 6.4 Hz, 1H), 2.41 (ddd, *J* = 19.1, 12.8, 6.3 Hz, 2H), 2.31 – 2.18 (m, 10H), 2.12 (t, *J* = 7.2 Hz, 4H), 1.57 – 1.47 (m, 4H), 1.41 – 1.33 (m, 4H), 1.27 – 1.16 (m, 8H). ESI-MS calcd. for $C_{57}H_{65}NO_4S_2$: 891.43 found 892.50 $[M+H]^+$.



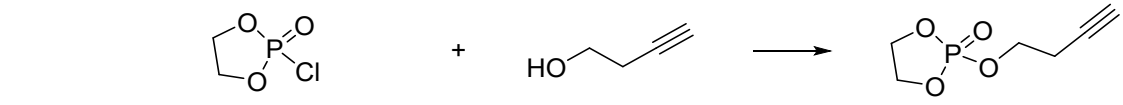
11-mercaptoundecanoic acid **(chloromethanetriyl)tribenzene** **5**

11-mercaptoundecanoic acid (2 g, 9.16 mmol) was added into a single-mouth bottle containing 20 mL DCM, and then triphenylmethyl chloromethane (3.064 g, 10.99 mmol) was slowly added. The mixture was stirred at room temperature for 5 h, washed three times with deionized water, organic phase was collected and dried, and it was purified by silica gel column chromatography to give compound **5** as a white solid (3.67 g, 86.95% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.20 (s, 1H), 7.40 (d, J = 7.7 Hz, 6H), 7.28 – 7.24 (m, 6H), 7.19 (t, J = 7.3 Hz, 3H), 2.32 (t, J = 7.5 Hz, 2H), 2.11 (t, J = 7.4 Hz, 2H), 1.68 – 1.53 (m, 2H), 1.37 (dt, J = 15.0, 7.4 Hz, 2H), 1.31 – 1.12 (m, 12H). ESI-MS calcd. for $C_{30}H_{36}O_2S$: 460.24 found 483.20 $[M+Na]^+$.



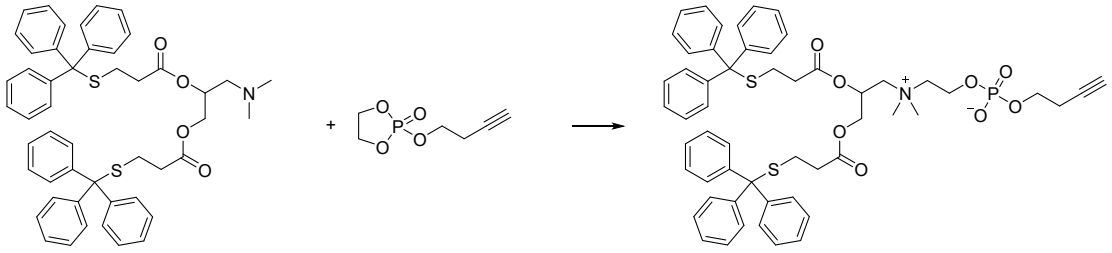
5 **3-(dimethylamino)propane-1,2-diol** **6**

5 (3.8 g, 8.25 mmol, 2.1eq) and 3-(dimethylamino)propane-1,2-diol (467.85 mg, 3.92 mmol) were added to a 100 mL three-necked round flask and it was added anhydrous DCM (40 mL) , followed by EDCI (1.878 g, 9.8 mmol, 2.5 eq), DIPEA (2.022 g, 15.68 mmol, 4 eq) and DMAP (119.56 mg, 0.98 mmol, 0.25eq). The reaction was stirred overnight under nitrogen. The mixture was diluted with DCM (50 mL) and washed with saturated $NaHCO_3$ (50 mL), water (50 mL) and saturated NaCl (50 mL). The organic phase was dried (Na_2SO_4) and concentrated to yield a yellow oil. It was purified by a flash column to obtain compound **6** as a pale oil (1.49 g, 37.84% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, J = 7.6 Hz, 12H), 7.29 – 7.25 (m, 12H), 7.20 (t, J = 7.3 Hz, 6H), 5.19 (dd, J = 6.3, 3.1 Hz, 1H), 4.35 (dd, J = 11.9, 3.1 Hz, 1H), 4.08 (dd, J = 11.9, 6.4 Hz, 1H), 2.43 (d, J = 6.3 Hz, 2H), 2.34 – 2.27 (m, 4H), 2.25 (s, 6H), 2.12 (t, J = 7.4 Hz, 4H), 1.62 – 1.55 (m, 4H), 1.41 – 1.35 (m, 4H), 1.29 – 1.14 (m, 24H). ESI-MS calcd. for $C_{65}H_{81}NO_4S_2$: 1003.56 found 1004.60 $[M+H]^+$.



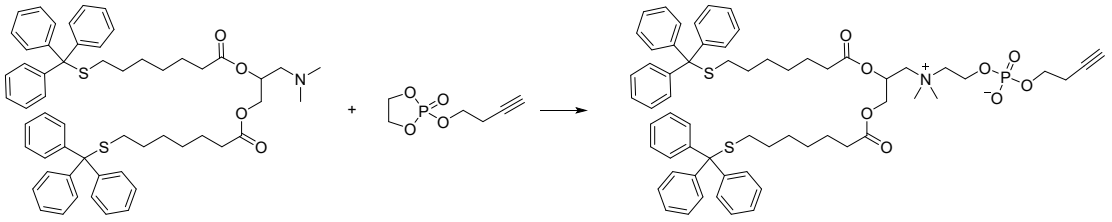
2-chloro-2-oxo-1,3,2-dioxaphospholane **3-butyn-1-ol** **7**

To a solution of 3-butyn-1-ol (1.4 g, 20 mmol, 1 equiv.) in anhydrous THF (15 mL) was added triethylamine (2.92 mL, 21 mmol, 1.05 equiv.) at -20°C under an argon atmosphere. After then, it was added dropwise slowly the solution of 2-chloro-2-oxo-1,3,2-dioxaphospholane (2.85 g, 20 mmol, 1 equiv.) in 10 mL anhydrous THF at -20°C, the mixture was allowed to warm to room temperature and stirred for 2 h. The white suspension was filtered over a sintered funnel, and the filtrate was concentrated by rotary evaporation and dried in vacuo to give compound **7** (crude) as a yellow oil. This was used without further purification due to decomposition of **7** on silica.



1 **7** **8**

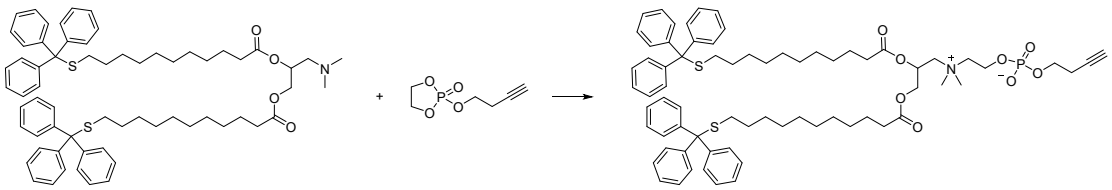
Compound **1** (780 mg, 1 mmol) was dissolved in dry MeCN (10 mL) in a 25 mL flame-dried flask under argon. Then compound **7** (176.11 mg, 1 mmol, 1 equiv.) was added, the flask was heated to 70 °C for 48 h. The crude mixture was concentrated in vacuo and purified by a flash column chromatography to obtain compound **8** (240 mg, 25.1% yield) as a transparent oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 7.7, 2.4 Hz, 12H), 7.25 (q, *J* = 7.4 Hz, 12H), 7.18 (dd, *J* = 14.8, 7.3 Hz, 6H), 5.54 (s, 1H), 4.44 (d, *J* = 9.8 Hz, 1H), 4.28 (d, *J* = 32.2 Hz, 2H), 4.17 (d, *J* = 13.8 Hz, 1H), 4.05 (dd, *J* = 11.9, 5.6 Hz, 1H), 3.88 (d, *J* = 6.2 Hz, 2H), 3.83 – 3.68 (m, 2H), 3.70 – 3.55 (m, 1H), 3.22 (t, *J* = 18.4 Hz, 6H), 2.51 – 2.25 (m, 6H), 2.23 – 2.06 (m, 4H), 2.02 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.41, 171.14, 144.67, 144.56, 129.69, 129.65, 128.18, 128.13, 127.00, 126.94, 81.89, 70.19, 67.19, 67.05, 66.41, 65.79, 64.90, 63.56, 59.08, 52.96, 52.61, 33.70, 33.37, 29.84, 26.94, 26.71. ^{31}P NMR (243 MHz, $CDCl_3$) δ -1.44. ESI-HRMS calcd. for $C_{55}H_{58}NO_8PS_2$: 955.3341 found 956.33739 $[M+H]^+$.



4 **7** **9**

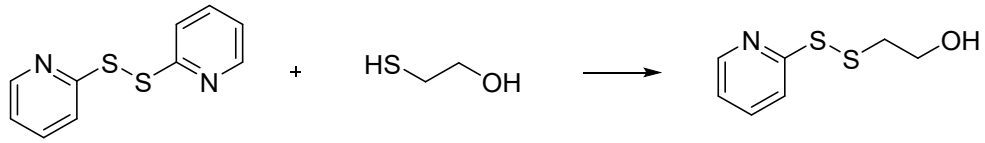
Compound **4** (400 mg, 0.448 mmol) was dissolved in dry MeCN (10 mL) in a 25 mL flame-dried flask under argon. Then compound **7** (88 mg, 0.5 mmol, 1 equiv.) was added, the flask was heated to 70 °C for 48 h. The crude mixture was concentrated in vacuo and purified by a flash column chromatography to obtain compound **9** (130 mg, 27.17% yield) as a transparent oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, J = 7.7 Hz, 12H), 7.26 (dd, J = 9.0, 6.0 Hz, 12H), 7.19 (t, J = 7.2 Hz, 6H), 5.62 (s, 1H), 4.49 (d, J

= 9.6 Hz, 1H), 4.31 (s, 2H), 4.19 (s, 2H), 4.08 (s, 1H), 3.93 (s, 3H), 3.72 (dd, J = 13.6, 6.1 Hz, 1H), 3.33 (s, 6H), 3.08 (dd, J = 14.6, 7.3 Hz, 1H), 2.50 (s, 2H), 2.24 (dt, J = 21.1, 7.3 Hz, 4H), 2.12 (td, J = 7.1, 3.9 Hz, 4H), 1.49 (dt, J = 14.9, 7.4 Hz, 4H), 1.35 (d, J = 7.4 Hz, 4H), 1.24 – 1.14 (m, 8H).^{13}C NMR (151 MHz, $CDCl_3$) δ 173.13, 172.77, 145.13, 129.71, 127.95, 126.42, 81.91, 70.17, 66.53, 66.41, 65.98, 63.58, 52.88, 52.67, 45.82, 34.16, 33.84, 32.04, 32.00, 28.81, 28.78, 28.71, 28.56, 28.53, 24.60, 24.51, 8.75. ^{31}P NMR (243 MHz, $CDCl_3$) δ -1.46. ESI-HRMS calcd. for $C_{63}H_{74}NO_8PS_2$: 1067.4593 found 1068.46498 $[M+H]^+$.



6 7 10

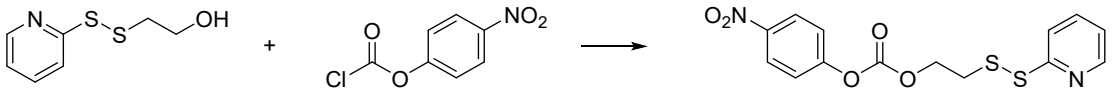
Compound **6** (1 g, 1 mmol) was dissolved in dry MeCN (10 mL) in a 25 mL flame-dried flask under argon. Then compound **7** (176.11 mg, 1 mmol, 1 equiv.) was added, the flask was heated to 70 °C for 48 h. The crude mixture was concentrated in vacuo and purified by a flash column chromatography to obtain compound **8** (110 mg, 9.3% yield) as a transparent oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, J = 7.4 Hz, 12H), 7.26 (t, J = 7.7 Hz, 12H), 7.19 (t, J = 7.3 Hz, 6H), 5.65 (s, 1H), 4.51 (d, J = 10.1 Hz, 1H), 4.37 (d, J = 36.7 Hz, 2H), 4.22 (d, J = 13.6 Hz, 1H), 4.10 (dd, J = 11.4, 5.6 Hz, 1H), 3.94 (s, 3H), 3.87 (s, 1H), 3.76 (d, J = 12.0 Hz, 1H), 3.35 (d, J = 10.0 Hz, 7H), 2.51 (s, 2H), 2.30 (dt, J = 22.5, 7.5 Hz, 4H), 2.13 – 2.10 (m, 4H), 1.55 (dt, J = 22.7, 7.5 Hz, 4H), 1.37 (dt, J = 14.4, 7.1 Hz, 4H), 1.26 – 1.12 (m, 24H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.27, 172.92, 145.20, 129.73, 127.92, 126.62, 81.95, 70.17, 66.48, 65.96, 65.79, 64.99, 63.71, 63.58, 59.19, 52.86, 52.68, 34.33, 34.01, 32.15, 29.83, 29.55, 29.53, 29.44, 29.40, 29.34, 29.28, 29.24, 29.16, 28.74, 24.87, 24.78. ^{31}P NMR (243 MHz, $CDCl_3$) δ -1.18. ESI-HRMS calcd. for $C_{71}H_{90}NO_8PS_2$: 1179.5845 found 1180.59026 $[M+H]^+$.



1,2-di(pyridin-2-yl)disulfane **2-mercaptoethan-1-ol** **11**

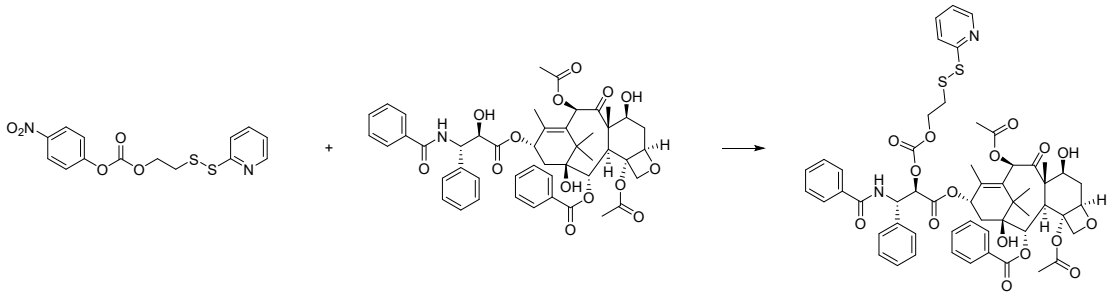
1,2-di(pyridin-2-yl)disulfane (4.71 g, 21.4 mmol) was dissolved in 20 mL of methanol in a 100 mL round-bottom flask and purge with N_2 gas. Then 2-mercaptoethanol (0.5 mL, 7.1 mmol) was added dropwise in the stirred mixture with N_2 gas and then it was stirred for 4 hours. Then the solvent was removed with a rotary evaporator and the residue was purified by column chromatography on silica gel to obtain compound **11**(1.1 g, 82.73% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (d, *J* = 4.9 Hz, 1H), 7.57 (td, *J* = 7.7, 1.7 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.21 – 7.06 (m, 1H), 5.76 (t, *J* = 6.9 Hz, 1H), 3.79 (dd, *J* = 10.7, 6.0 Hz, 2H), 3.04 – 2.71 (m, 2H). ESI-MS calcd. for

$C_7H_9NOS_2$: 187.01 found 209.9 $[M+Na]^+$.



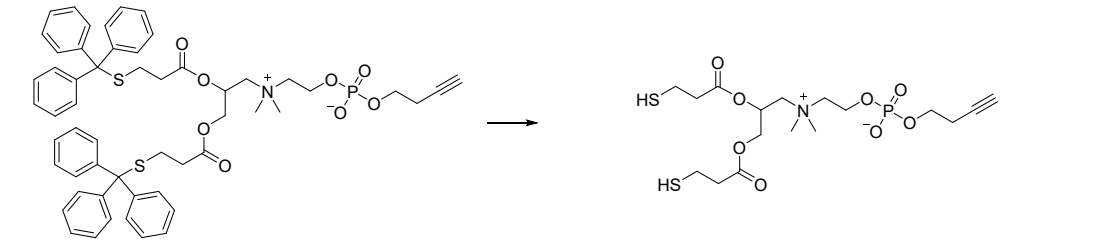
11 **4-nitrophenyl carbonochloridate** **12**

4-nitrophenyl chloroformate (1.014 g, 5.03 mmol) in 10 mL DCM was dropwise added into 10 mL DCM solutions containing compound **11** (942 mg, 5.03mmol) and DMAP (671 mg, 5.5 mmol) at 0℃. The reaction mixture was warmed to room temperature and stirred for 4 h. The organic phase was concentrated in vacuo, followed by purification by flash column chromatography to obtain compound **12** as a yellow oil (832 mg, 46.94% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (d, J = 4.7 Hz, 1H), 8.28 (d, J = 9.0 Hz, 2H), 7.74 – 7.62 (m, 2H), 7.38 (d, J = 9.0 Hz, 2H), 7.14 (t, J = 5.9 Hz, 1H), 4.56 (t, J = 6.4 Hz, 2H), 3.15 (t, J = 6.4 Hz, 2H).



12 **Paclitaxel** **13**

Compound **12** (352 mg, 1 mmol) and PTX (853.9 mg, 1 mmol) were dissolved into 20 mL DCM, followed by addition of DMAP (134.2 mg, 1.1 mmol). It was stirred overnight, concentrated in vacuo, followed by purification by a flash column to give white solid (840 mg, 78.71% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.44 (d, J = 4.5 Hz, 1H), 8.20 (s, 1H), 8.12 (t, J = 7.3 Hz, 2H), 8.05 (d, J = 9.1 Hz, 1H), 7.74 (d, J = 7.4 Hz, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.59 (t, J = 7.7 Hz, 2H), 7.49 (d, J = 5.0 Hz, 2H), 7.43 – 7.36 (m, 6H), 7.10 (dd, J = 6.7, 5.4 Hz, 1H), 7.00 (d, J = 9.3 Hz, 1H), 6.79 (d, J = 9.1 Hz, 1H), 6.32 – 6.25 (m, 2H), 5.98 (dd, J = 9.3, 2.5 Hz, 1H), 5.69 (d, J = 7.1 Hz, 1H), 5.41 (d, J = 2.7 Hz, 1H), 4.97 (d, J = 8.3 Hz, 1H), 4.43 (td, J = 11.6, 5.9 Hz, 2H), 4.39 (dd, J = 12.2, 5.7 Hz, 1H), 4.32 (d, J = 8.5 Hz, 1H), 4.20 (d, J = 8.5 Hz, 1H), 3.81 (d, J = 7.0 Hz, 1H), 3.05 (t, J = 6.5 Hz, 2H), 2.60 – 2.53 (m, 2H), 2.45 (s, 3H), 2.41 – 2.36 (m, 1H), 2.27 – 2.19 (m, 4H), 1.91 (s, 3H), 1.89 – 1.84 (m, 2H), 1.78 (d, J = 10.5 Hz, 2H), 1.23 (d, J = 14.6 Hz, 3H), 1.14 (s, 3H). ESI-MS calcd. for $C_{55}H_{58}N_2O_{16}S_2$: 1066.32 found 1089.50 $[M+Na]^+$.



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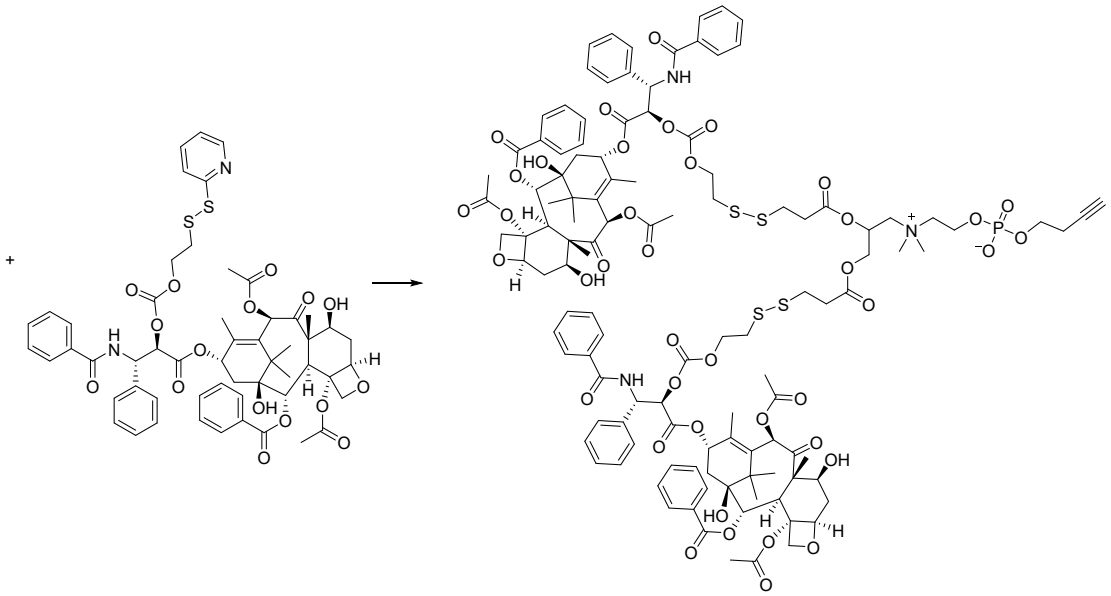
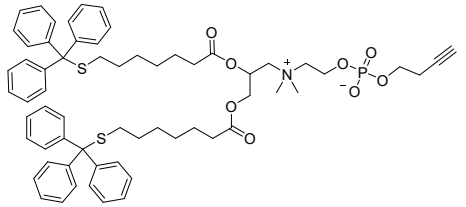


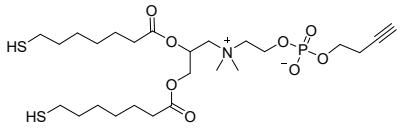
13 15

To solutions of compounds **8** (100 mg, 0.105 mmol) in 5 mL DCM was dropwise added trifluoroacetic acid (0.2 mL), followed by dropwise adding triethylsilane dropwise until the solution discolors from yellow to colorless. The reaction mixtures were stirred for 0.5 h and the solvent was removed. Then, the obtained intermediate products (compound **14**, without purification) were dissolved into 5 mL DCM, and compounds **13** (246.51 mg, 0.231 mmol, 2.2 equiv.) was added. The reactions were stirred overnight at room temperature. The solvent was removed and the crude products were purified by silica gel column chromatography to give compound **15** as a white solid (65 mg, 25.97% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (t, *J* = 16.2 Hz, 4H), 7.76 (d, *J* = 7.1 Hz, 4H), 7.61 (t, *J* = 7.4 Hz, 3H), 7.51 (t, *J* = 7.6 Hz, 4H), 7.47 – 7.42 (m, 6H), 7.37 (dt, *J* = 22.5, 7.5 Hz, 9H), 7.28 (d, *J* = 7.2 Hz, 2H), 6.31 (s, 2H), 6.15 (s, 2H), 5.90 (dd, *J* = 8.6, 4.0 Hz, 2H), 5.64 (d, *J* = 6.6 Hz, 3H), 5.47 (d, *J* = 3.8 Hz, 2H), 4.94 (d, *J* = 8.9 Hz, 2H), 4.50 (s, 1H), 4.41 – 4.31 (m, 6H), 4.26 (d, *J* = 8.1 Hz, 3H), 4.14 (d, *J* = 7.8 Hz, 3H), 3.97 (d, *J* = 12.0 Hz, 1H), 3.93 – 3.84 (m, 2H), 3.75 (t, *J* = 14.1 Hz, 4H), 3.65 (d, *J* = 11.8 Hz, 2H), 3.20 (s, 5H), 3.08 (q, *J* = 7.3 Hz, 1H), 2.89 (s, 7H), 2.74 (d, *J* = 30.7 Hz, 4H), 2.54 – 2.39 (m, 14H), 2.24 (d, *J* = 10.0 Hz, 2H), 2.17 (t, *J* = 11.2 Hz, 6H), 2.08 (d, *J* = 18.1 Hz, 4H), 1.87 (d, *J* = 28.1 Hz, 8H), 1.27 (d, *J* = 18.3 Hz, 6H), 1.19 (s, 6H), 1.12 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.89, 203.87, 171.42, 171.07, 171.03, 170.18, 168.48, 167.50, 167.03, 154.14, 142.24, 141.91, 136.90, 133.87, 133.76, 133.12, 132.07, 130.33, 129.38, 129.22, 128.86, 128.76,

128.72, 127.47, 127.17, 84.54, 82.02, 81.21, 78.93, 76.51, 75.77, 75.07, 72.20, 71.93, 70.34, 66.87, 63.79, 58.47, 53.43, 52.85, 46.16, 45.76, 43.33, 36.39, 36.07, 35.40, 29.91, 29.84, 29.66, 29.46, 27.35, 26.81, 22.94, 22.83, 21.97, 21.07, 14.91, 14.26, 9.93, 8.69. ^{31}P NMR (243 MHz, $CDCl_3$) δ -1.53. ESI-HRMS calcd. for $C_{117}H_{136}NO_{40}PS_4$: 2382.7354 found 2383.73464 $[M+H]^+$.



9



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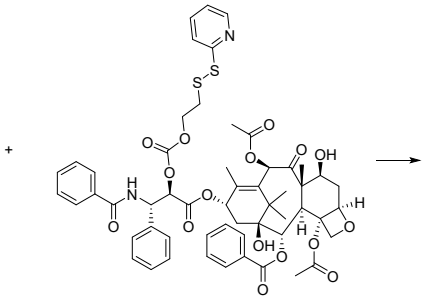
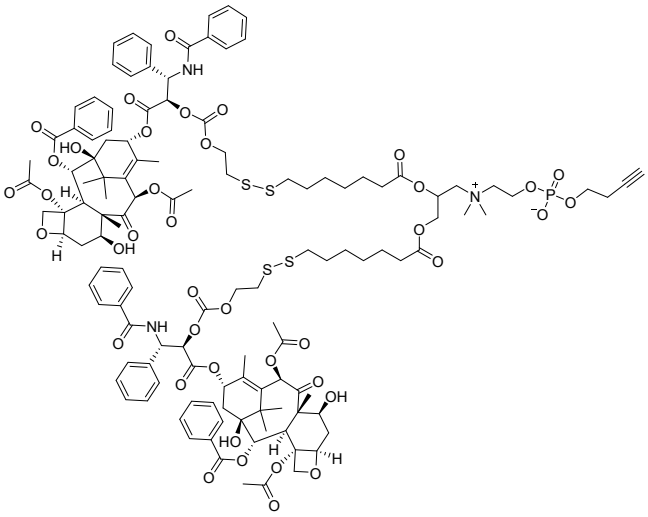


13



17

To solutions of compounds **9** (100 mg, 0.094 mmol) in 5 mL DCM was dropwise added trifluoroacetic acid (0.2 mL), followed by dropwise adding triethylsilane dropwise until the solution discolors from yellow to colorless. The reaction mixtures were stirred for 0.5 h and the solvent was removed. Then, the obtained intermediate products (compound **16**, without purification) were dissolved into 5 mL DCM, and compounds **13** (220 mg, 0.207 mmol, 2.2 equiv.) was added. The reactions were stirred overnight at room temperature. The solvent was removed and the crude products were purified by silica gel column chromatography to give compound **15** as a white solid (58 mg, 24.71% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.6 Hz, 4H), 7.76 (d, *J* = 7.1 Hz, 4H), 7.60 (t, *J* = 7.3 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 4H), 7.47 (t, *J* = 7.3 Hz, 2H), 7.39 (dt, *J* = 15.5, 7.5 Hz, 12H), 7.31 (s, 4H), 6.31 (s, 2H), 6.21 (s, 2H), 5.93 (d, *J* = 8.5 Hz, 2H), 5.66 (d, *J* = 6.7 Hz, 2H), 5.60 (s, 1H), 5.45 (s, 2H), 4.95 (d, *J* = 9.2 Hz, 2H), 4.49 (d, *J* = 9.2 Hz, 1H), 4.42 – 4.35 (m, 6H), 4.28 (d, *J* = 8.3 Hz, 3H), 4.16 (d, *J* = 8.1 Hz, 3H), 4.05 (d, *J* = 27.4 Hz, 2H), 3.92 (s, 2H), 3.79 (d, *J* = 6.4 Hz, 3H), 3.68 (d, *J* = 48.5 Hz, 2H), 3.24 (d, *J* = 10.9 Hz, 6H), 3.09 (dd, *J* = 14.6, 7.3 Hz, 2H), 2.87 (t, *J* = 6.4 Hz, 4H), 2.65 (s, 5H), 2.54 (s, 2H), 2.49 (s, 2H), 2.43 (s, 6H), 2.31 (dd, *J* = 15.2, 6.8 Hz, 6H), 2.19 (s, 6H), 2.11 (s, 3H), 1.99 (t, *J* = 19.5 Hz, 3H), 1.94 – 1.84 (m, 8H), 1.63 – 1.53 (m, 8H), 1.35 (s, 4H), 1.31 (t, *J* = 7.3 Hz, 8H), 1.25 (s, 4H), 1.20 (s, 6H), 1.13 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.92, 173.19, 172.75, 171.03, 170.99, 170.95,

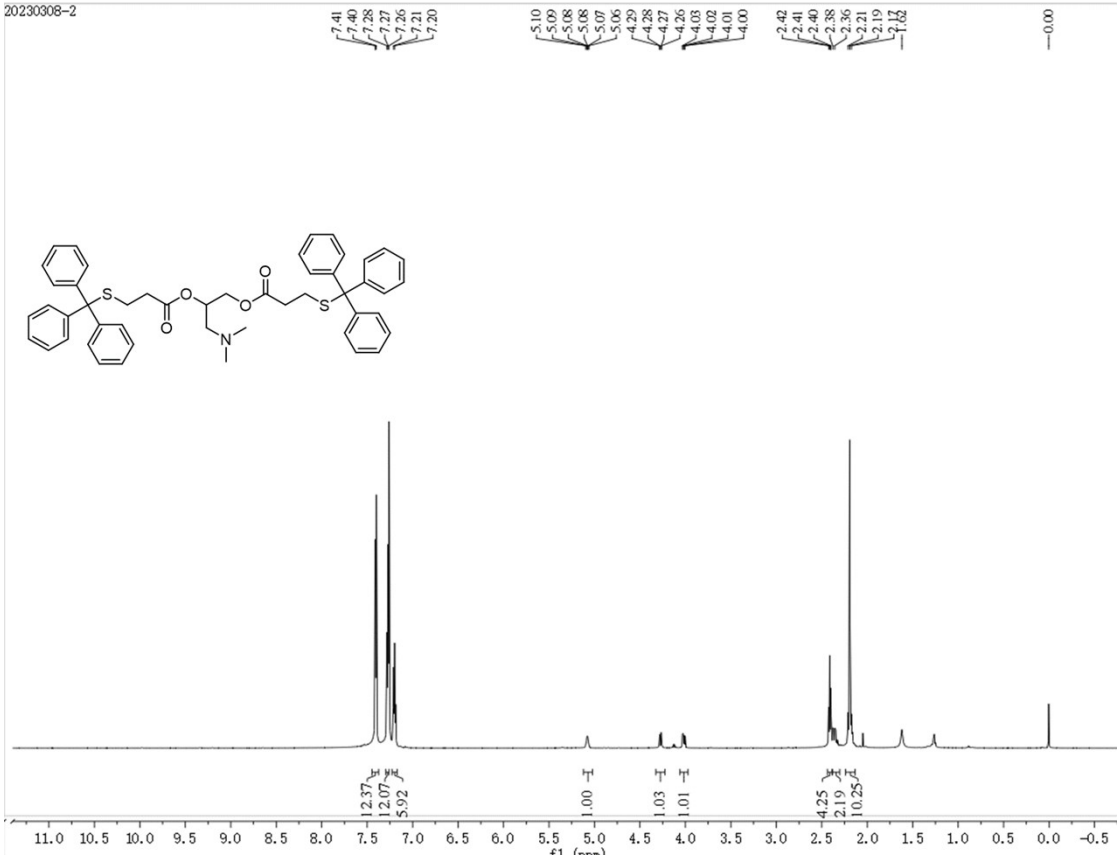
170.04, 168.24, 167.33, 167.09, 154.09, 142.22, 142.19, 136.90, 133.84, 133.71, 133.06, 132.10, 130.33, 129.35, 129.23, 128.87, 128.78, 128.70, 127.39, 126.97, 84.56, 81.19, 79.06, 76.53, 75.73, 75.16, 72.17, 72.06, 70.23, 67.05, 65.99, 58.56, 53.19, 52.85, 45.97, 45.76, 43.33, 39.06, 36.35, 35.95, 35.52, 34.07, 33.76, 29.83, 29.45, 28.88, 28.85, 28.79, 28.63, 28.62, 28.61, 28.05, 28.03, 27.98, 26.86, 24.59, 24.44, 22.91, 22.10, 22.08, 21.03, 14.90, 9.88, 8.67. ^{31}P NMR (243 MHz, $CDCl_3$) δ -2.30. ESI-HRMS calcd. for $C_{125}H_{152}NO_{40}PS_4$: 2494.8606 found 2495.85691 $[M+H]^+$.

10 18 13 19

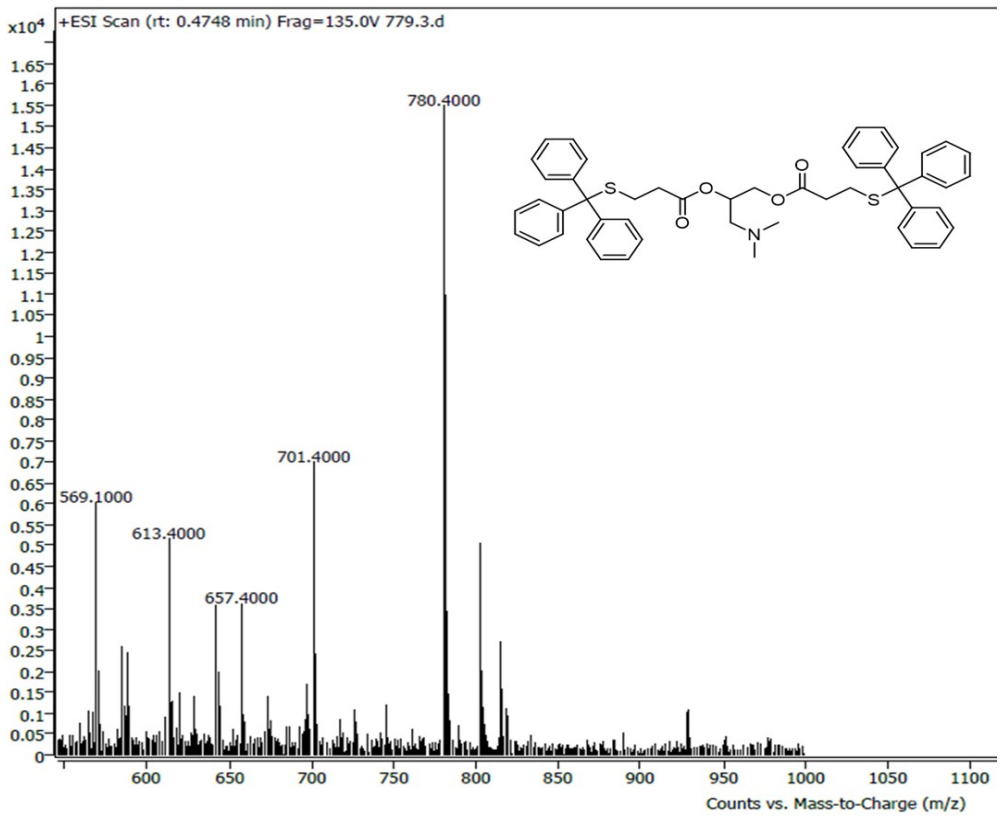
To solutions of compounds **10** (100 mg, 0.085 mmol) in 5 mL DCM was dropwise added trifluoroacetic acid (0.2 mL), followed by dropwise adding triethylsilane dropwise until the solution discolors from yellow to colorless. The reaction mixtures were stirred for 0.5 h and the solvent was removed. Then, the obtained intermediate products (compound **18**, without purification) were dissolved into 5 mL DCM, and compounds **13** (199.6 mg, 0.187 mmol, 2.2 equiv.) was added. The reactions were stirred overnight at room temperature. The solvent was removed and the crude products were purified by silica gel column chromatography to give compound **19** as a white solid (50 mg, 22.56% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.6 Hz, 4H), 7.73 (d, *J* = 7.5 Hz, 4H), 7.62 – 7.58 (m, 3H), 7.53 – 7.46 (m, 10H), 7.39 – 7.33 (m, 11H), 6.27 (dd, *J* = 19.4, 10.8 Hz, 4H), 5.97 (d, *J* = 9.1 Hz, 2H), 5.67 (d, *J* = 6.6 Hz, 2H), 5.61 (s, 1H), 5.43 (s, 2H), 4.95 (d, *J* = 9.2 Hz, 2H), 4.47 (s, 2H), 4.38 (d, *J* = 5.4 Hz, 7H), 4.29 (d, *J* = 8.2 Hz, 2H), 4.18 (d, *J* = 8.1 Hz, 2H), 4.05 (s, 3H), 3.93 (s, 3H), 3.80 (d, *J* = 6.5 Hz, 3H), 3.22 (s, 6H), 2.87 (t, *J* = 6.5 Hz, 5H), 2.65 (t, *J* = 7.0 Hz, 6H), 2.55 – 2.40 (m, 14H), 2.38 – 2.25 (m, 10H), 2.18 (d, *J* = 24.1 Hz, 14H), 1.89 (d, *J* = 25.6 Hz, 12H), 1.60 (dd, *J* = 28.2, 20.8 Hz, 16H), 1.33 (d, *J* = 4.9 Hz, 18H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.91, 171.23, 170.00, 168.04, 167.31, 167.09, 154.06, 142.97,

142.67, 142.50, 136.80, 133.83, 133.62, 132.99, 132.19, 130.35, 129.31, 129.28, 128.89, 128.85, 128.71, 127.33, 127.27, 126.83, 84.58, 81.17, 79.15, 76.56, 75.70, 75.17, 72.21, 67.12, 58.59, 52.93, 45.80, 43.31, 39.26, 36.40, 36.11, 35.64, 29.81, 29.61, 29.59, 29.55, 29.50, 29.36, 29.19, 29.19, 29.04, 28.57, 28.57, 26.92, 22.95, 22.22, 14.94, 9.81. ^{31}P NMR (243 MHz, $CDCl_3$) δ -2.76. ESI-HRMS calcd. for $C_{133}H_{168}NO_{40}PS_4$: 2606.9858 found 2607.92248 $[M+H]^+$.

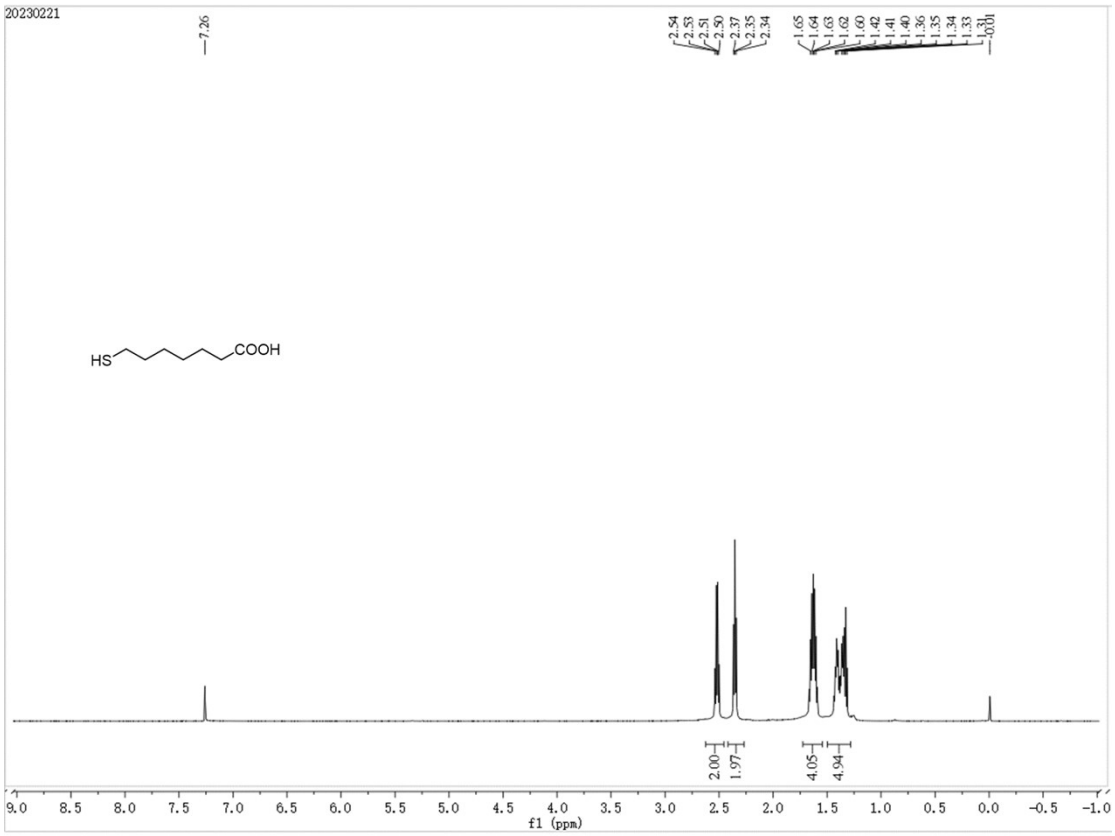
NMR and MS Spectras



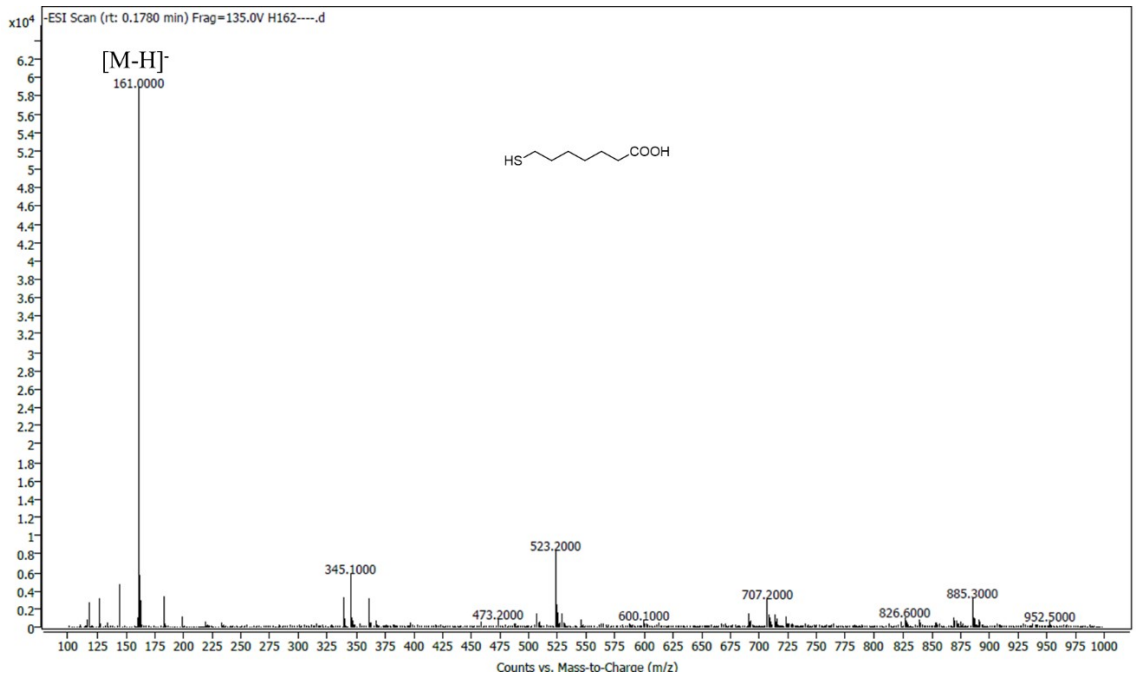
^{1}H NMR spectrum of compound **1**



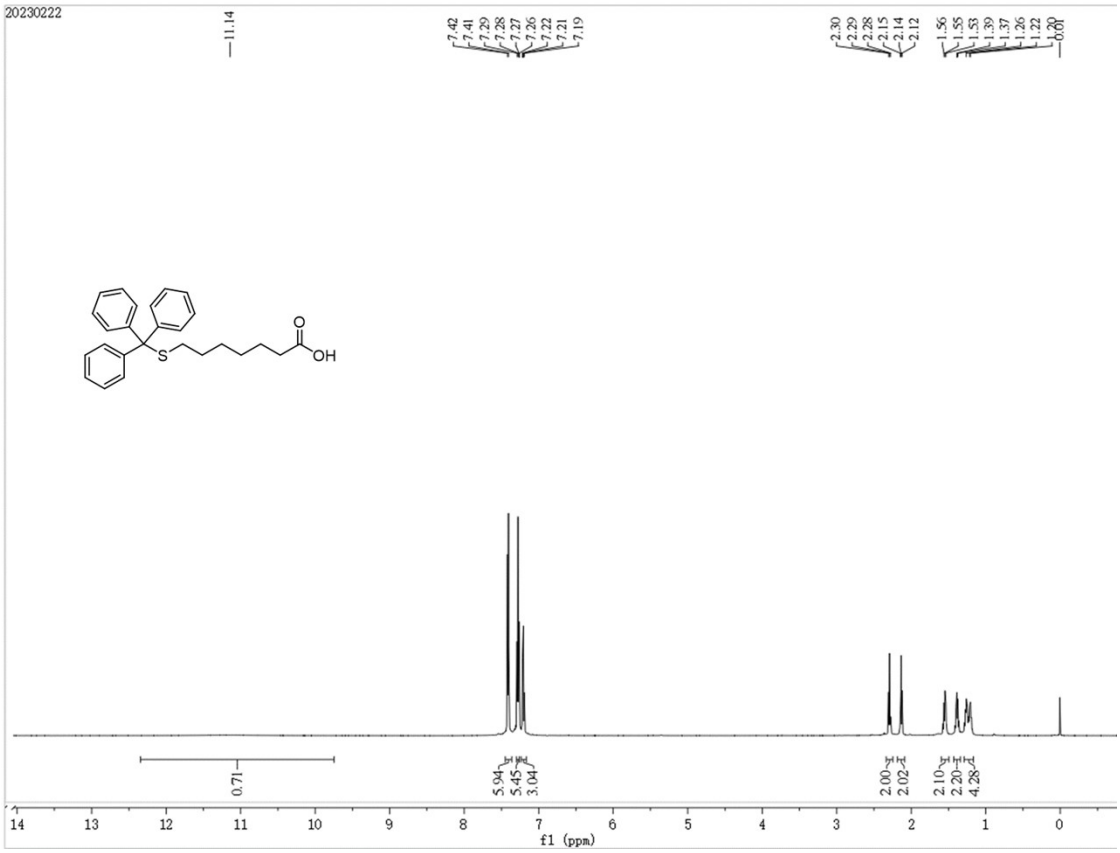
ESI-MS spectrum of compound **1**



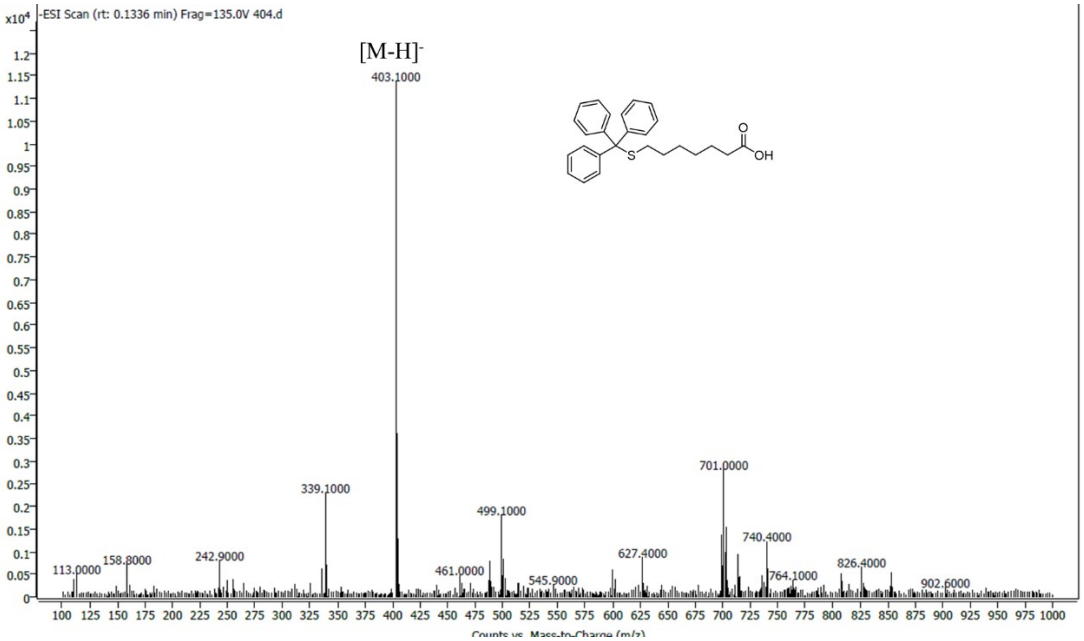
^{1}H NMR spectrum of compound **2**



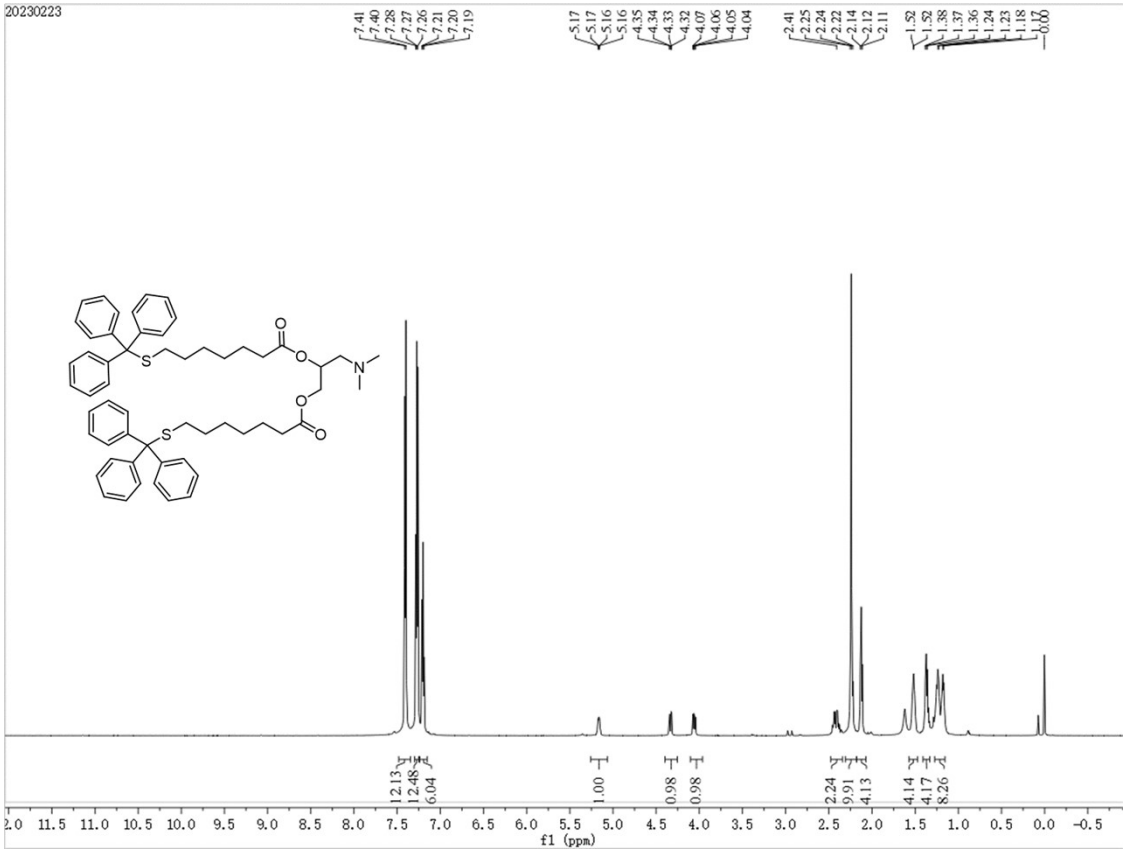
ESI-MS spectrum of compound **2**



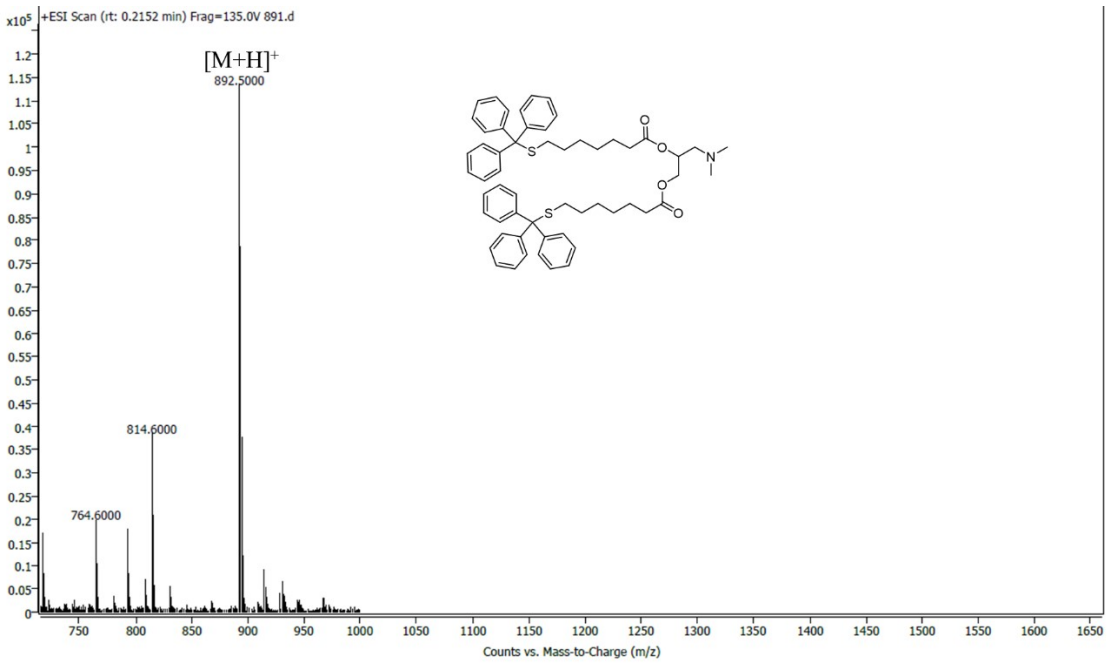
^{1}H NMR spectrum of compound **3**



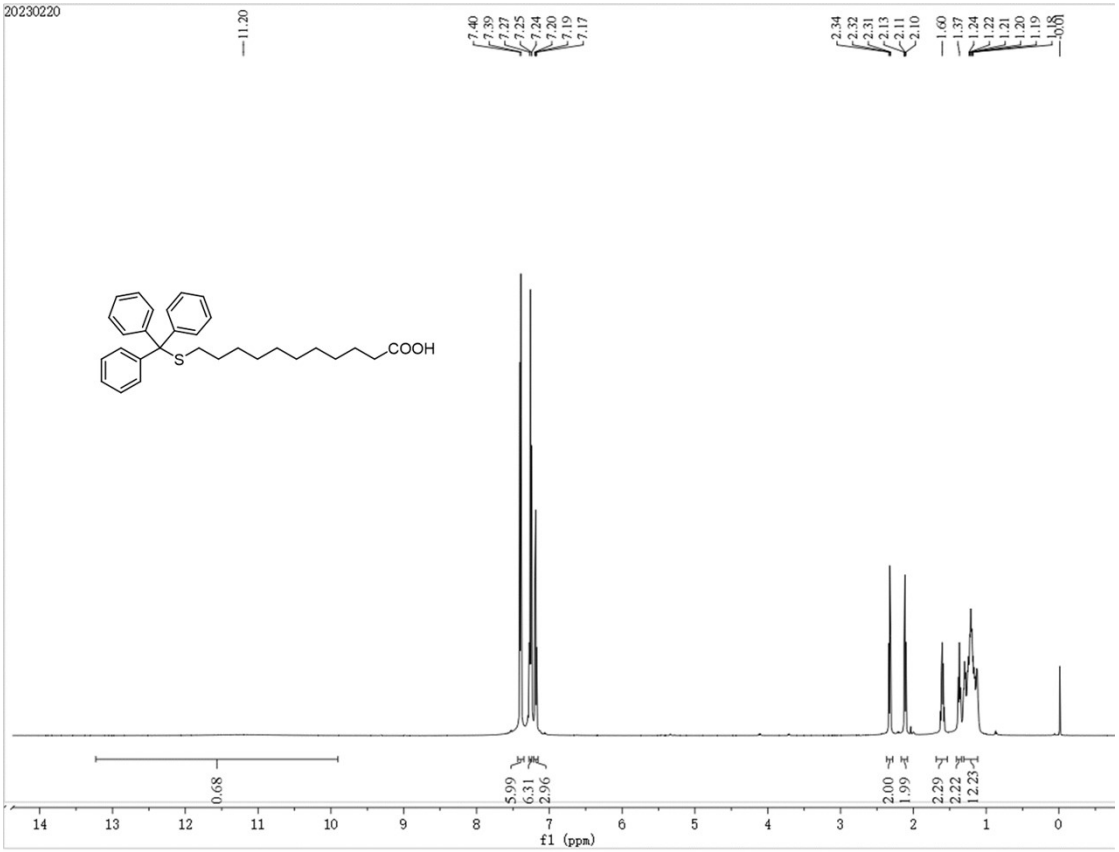
ESI-MS spectrum of compound **3**



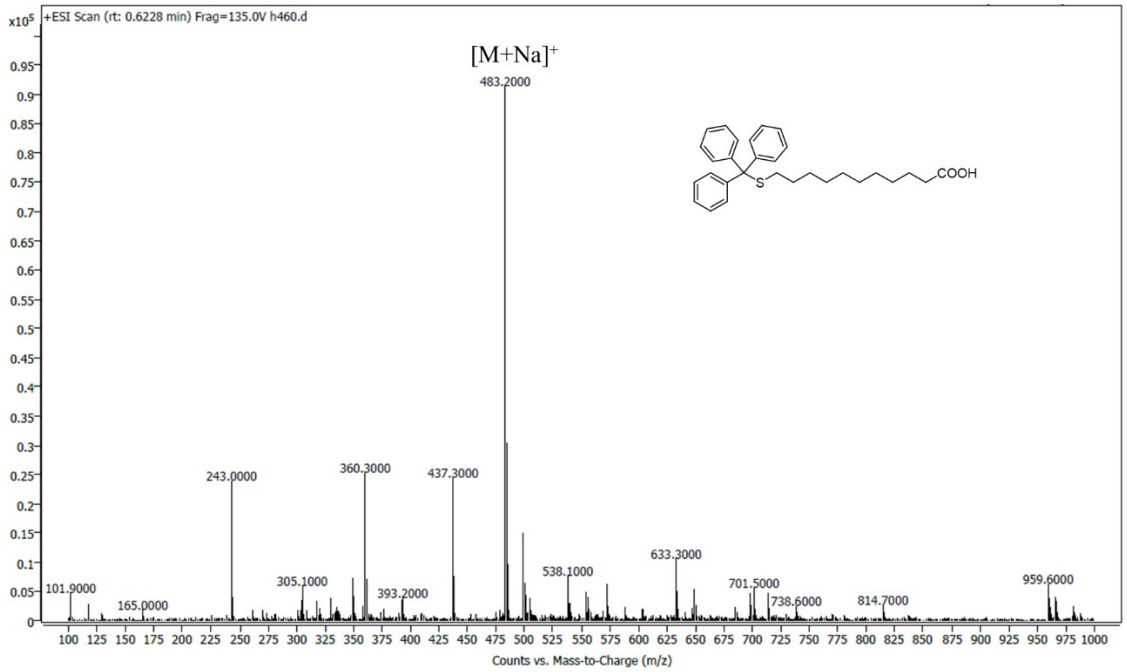
^{1}H NMR spectrum of compound **4**



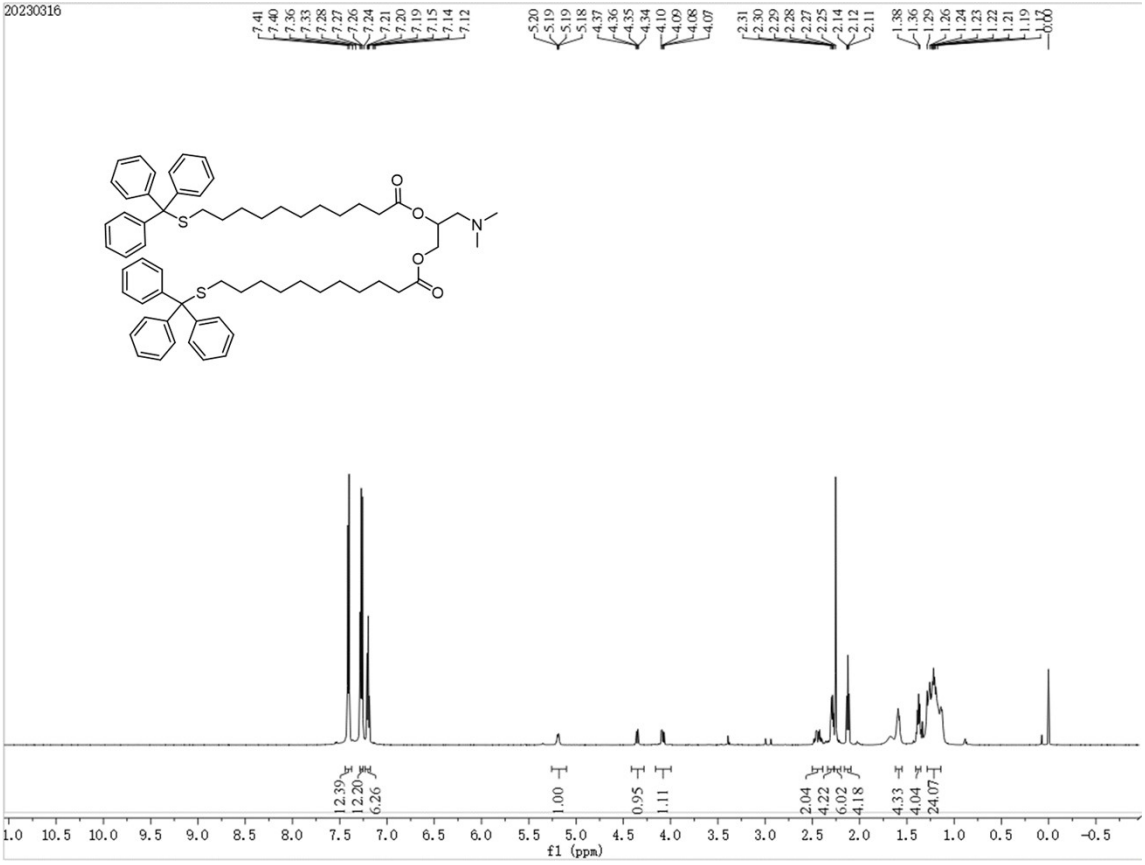
ESI-MS spectrum of compound **4**



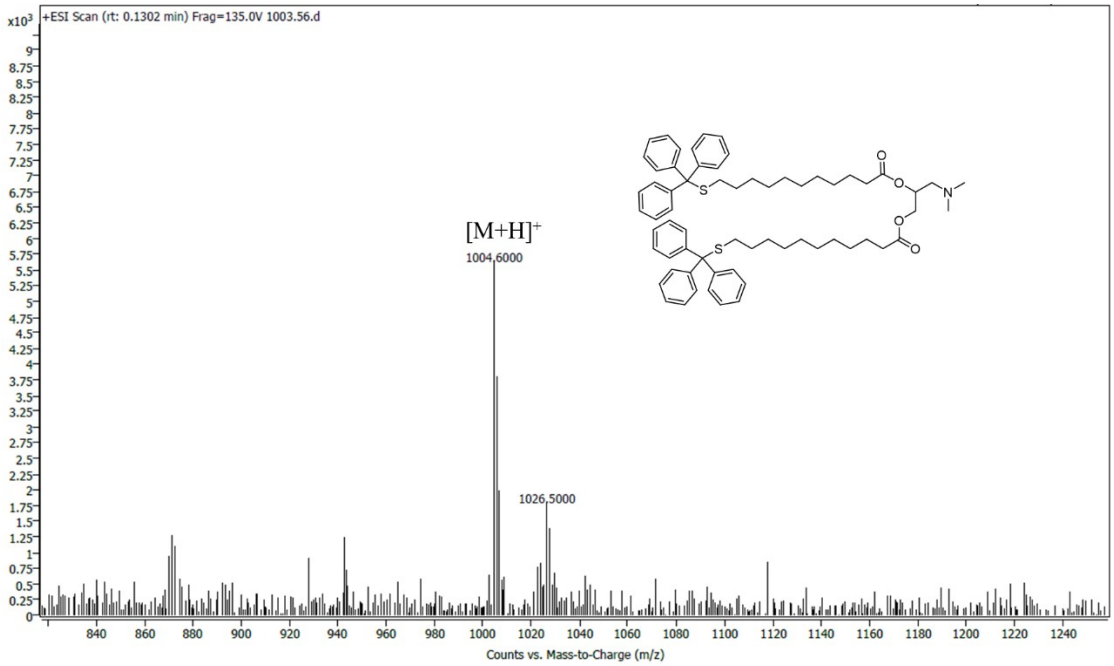
^{1}H NMR spectrum of compound **5**



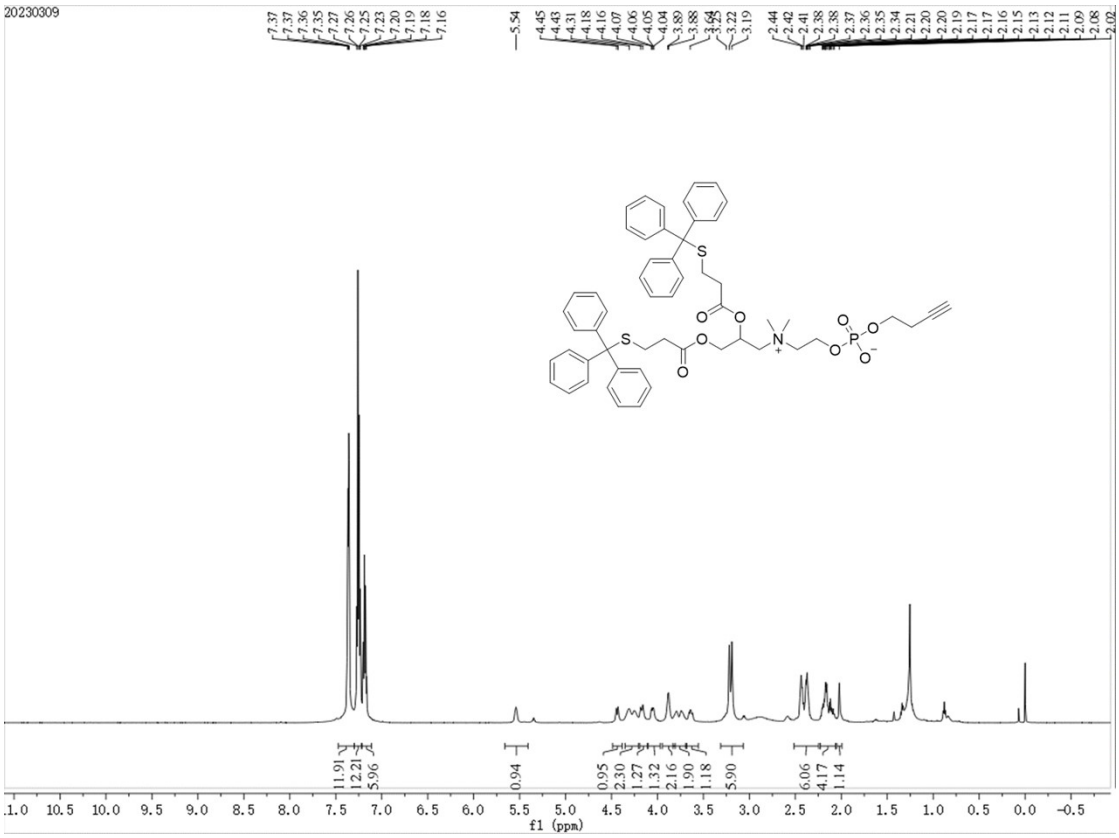
ESI-MS spectrum of compound **5**



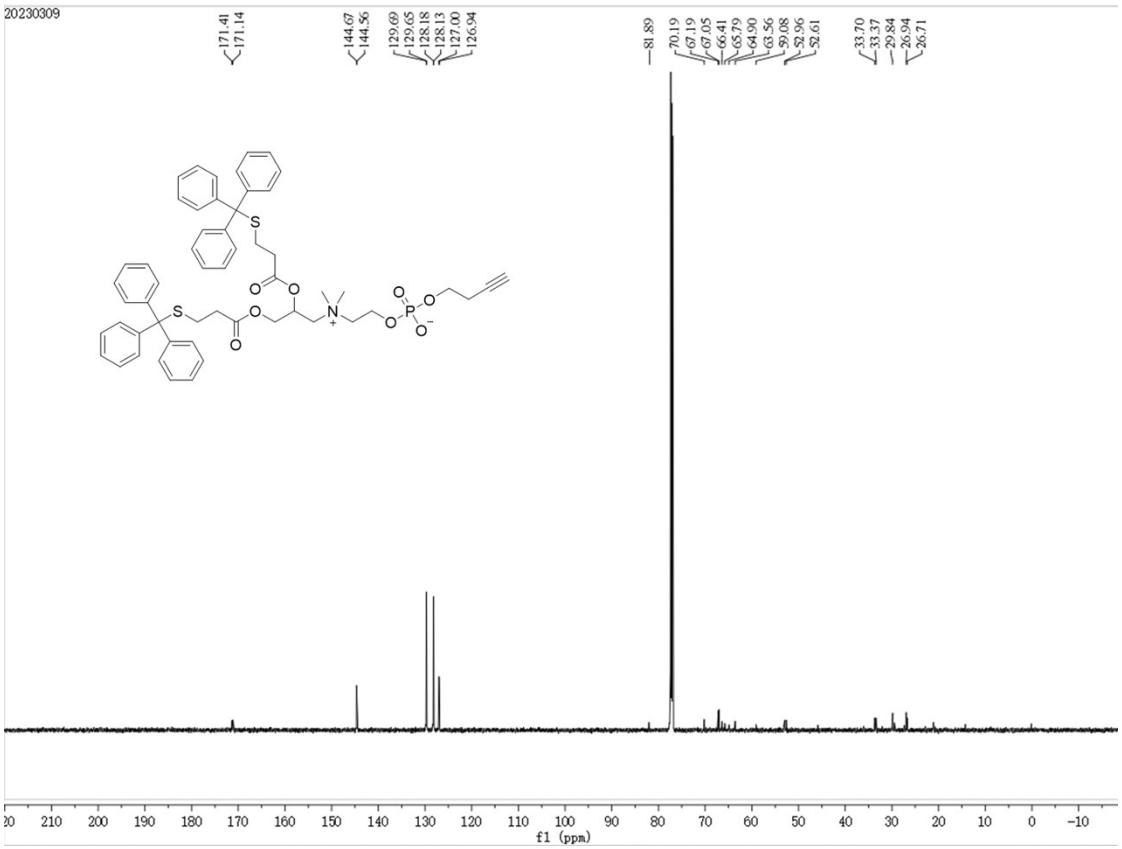
^{1}H NMR spectrum of compound **6**



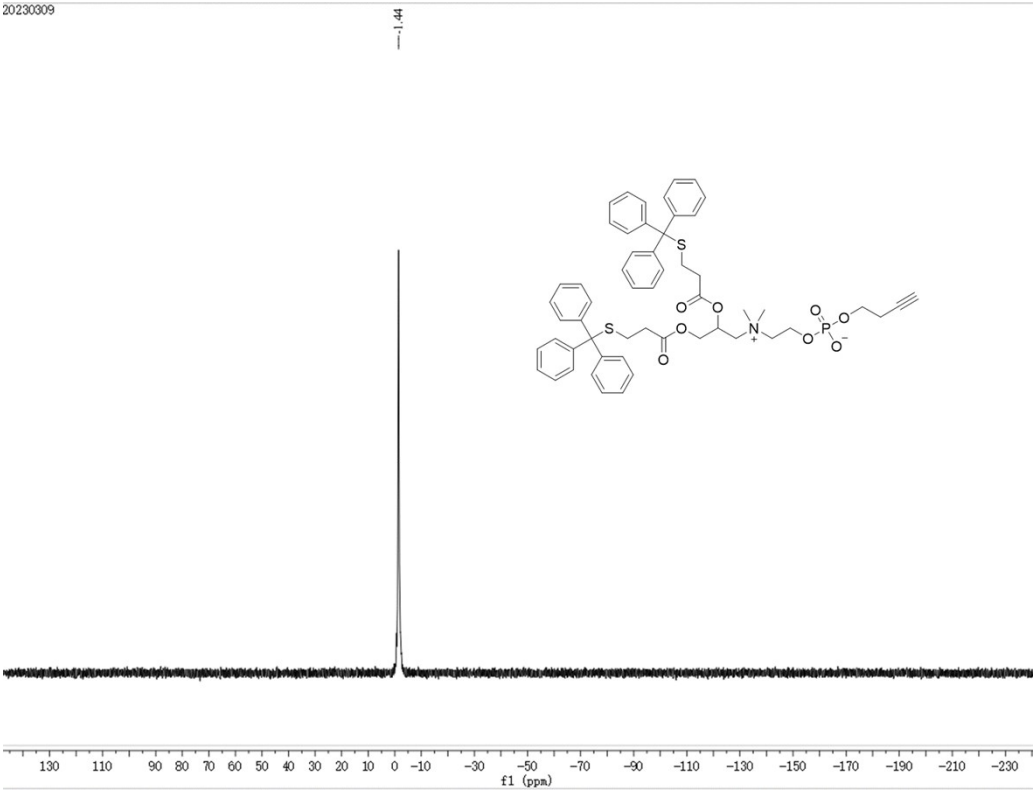
ESI-MS spectrum of compound **6**



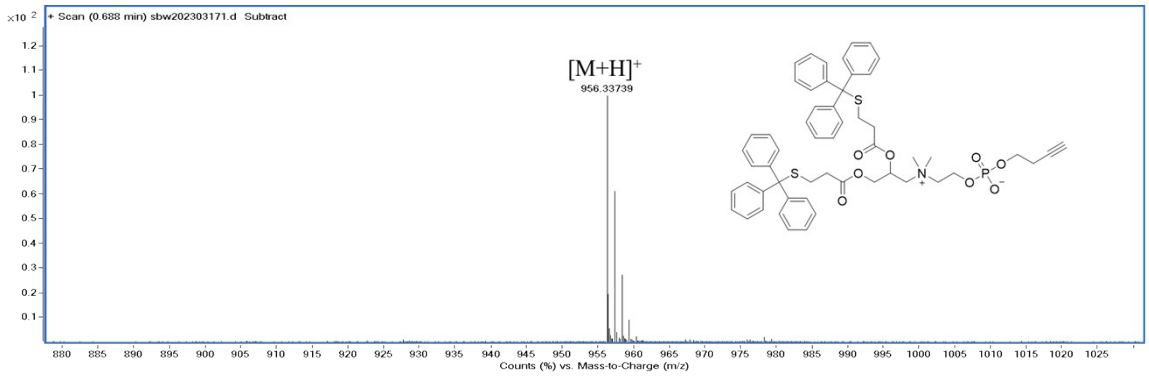
^{1}H NMR spectrum of compound **8**



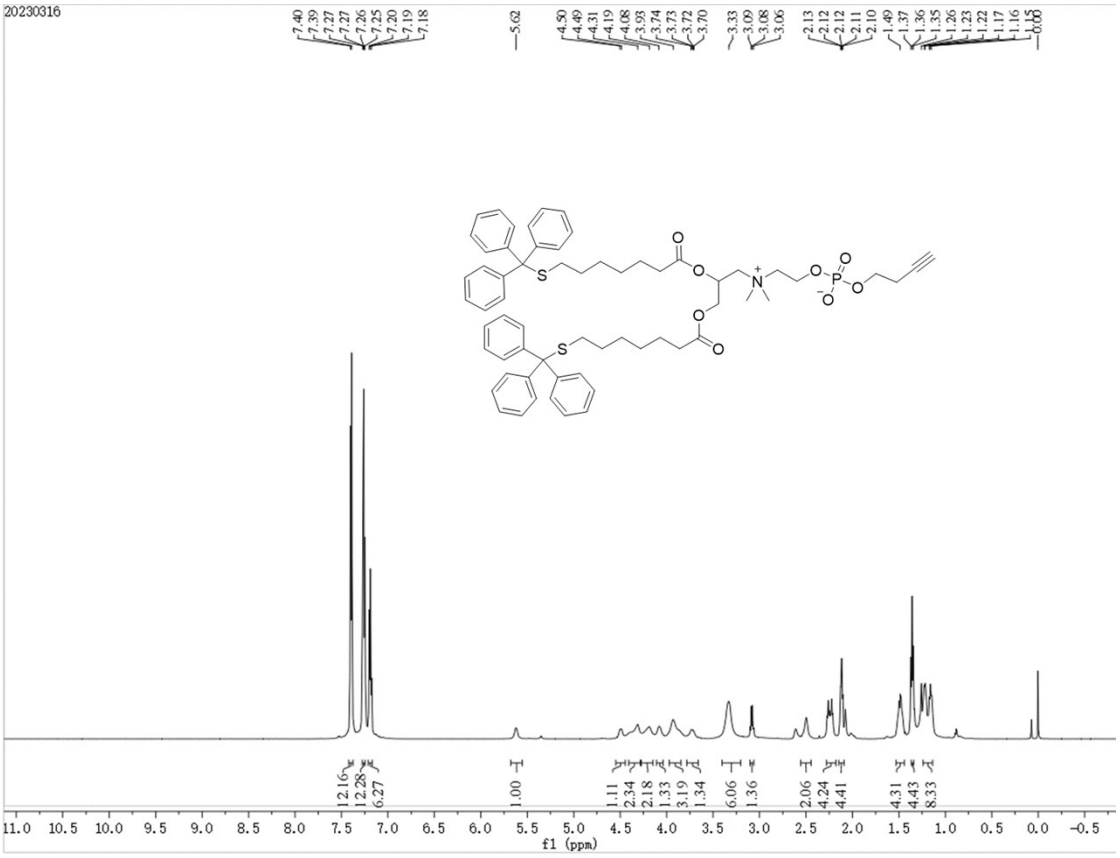
^{13}C NMR spectrum of compound **8**



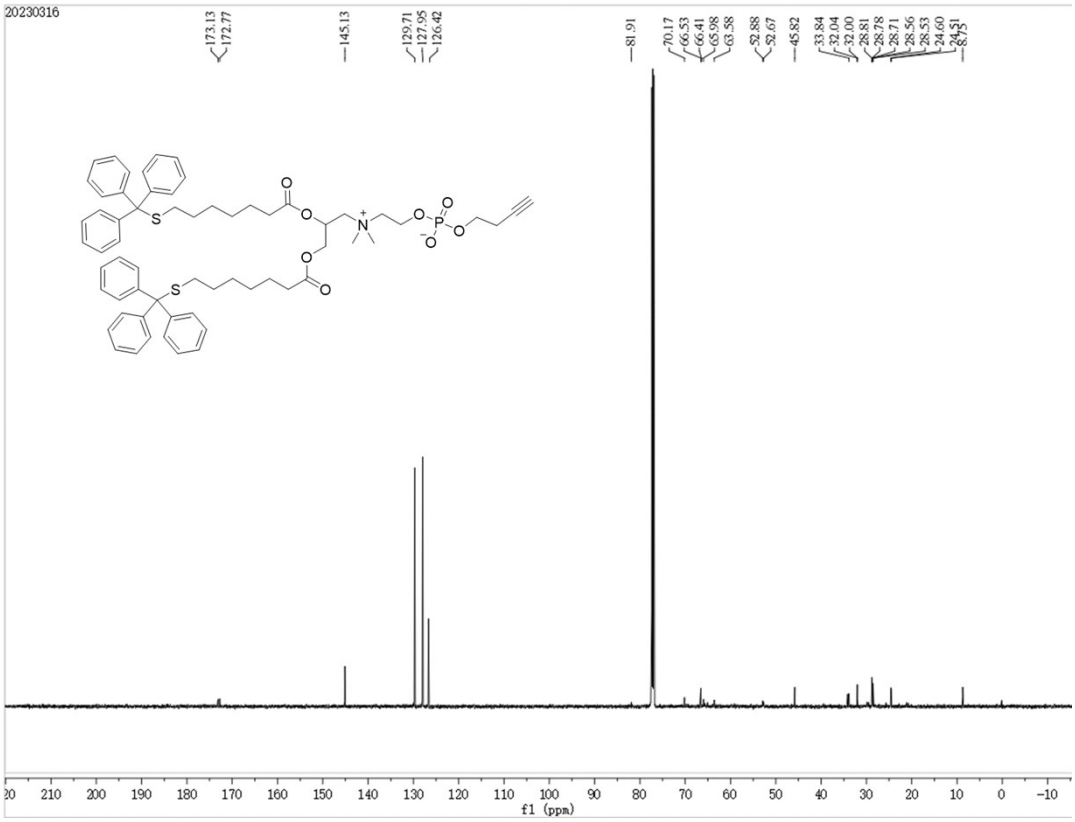
^{31}P NMR spectrum of compound **8**



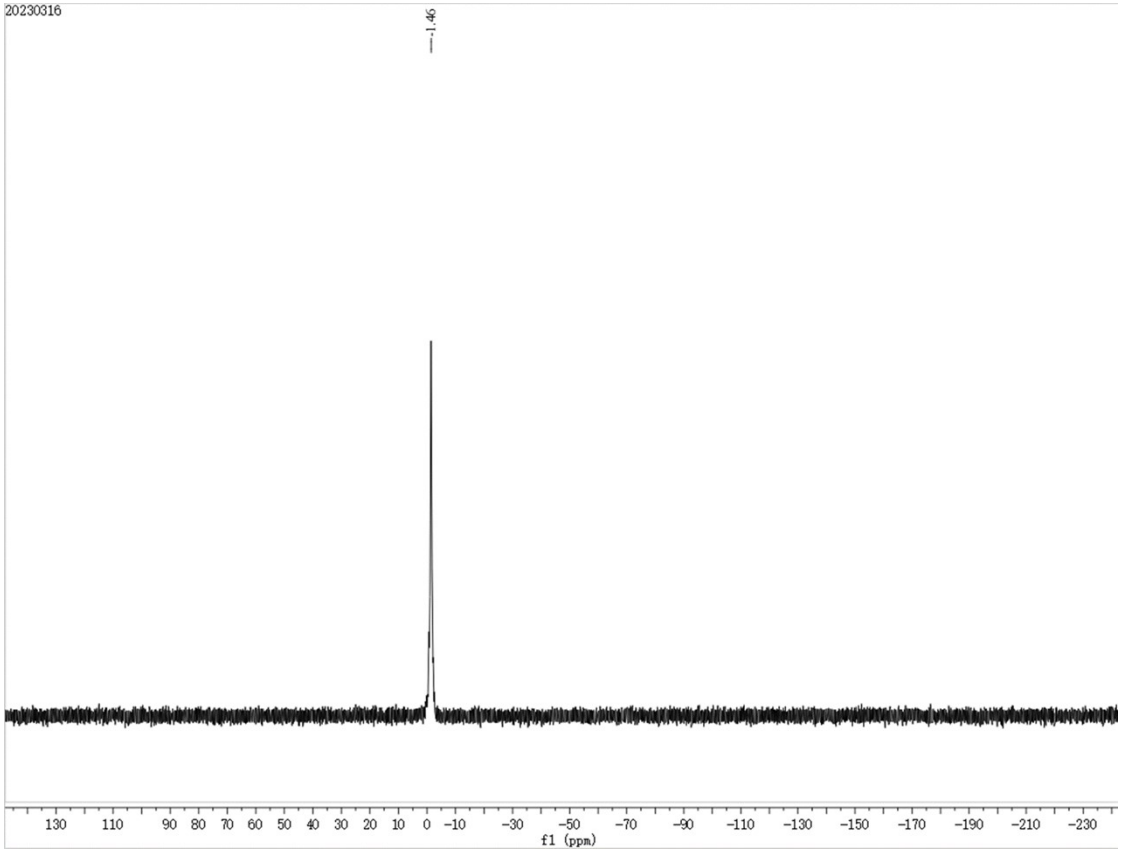
ESI-HRMS spectrum of compound **8**



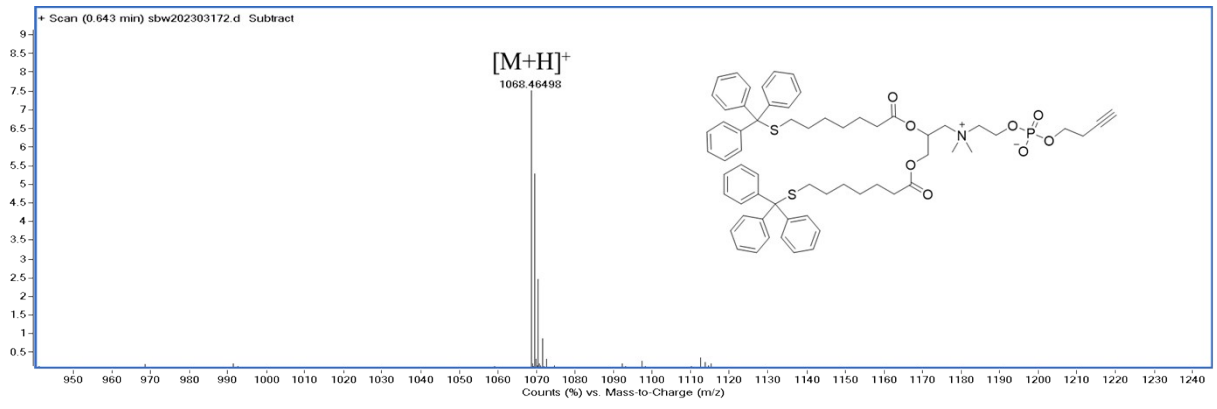
^{1}H NMR spectrum of compound **9**



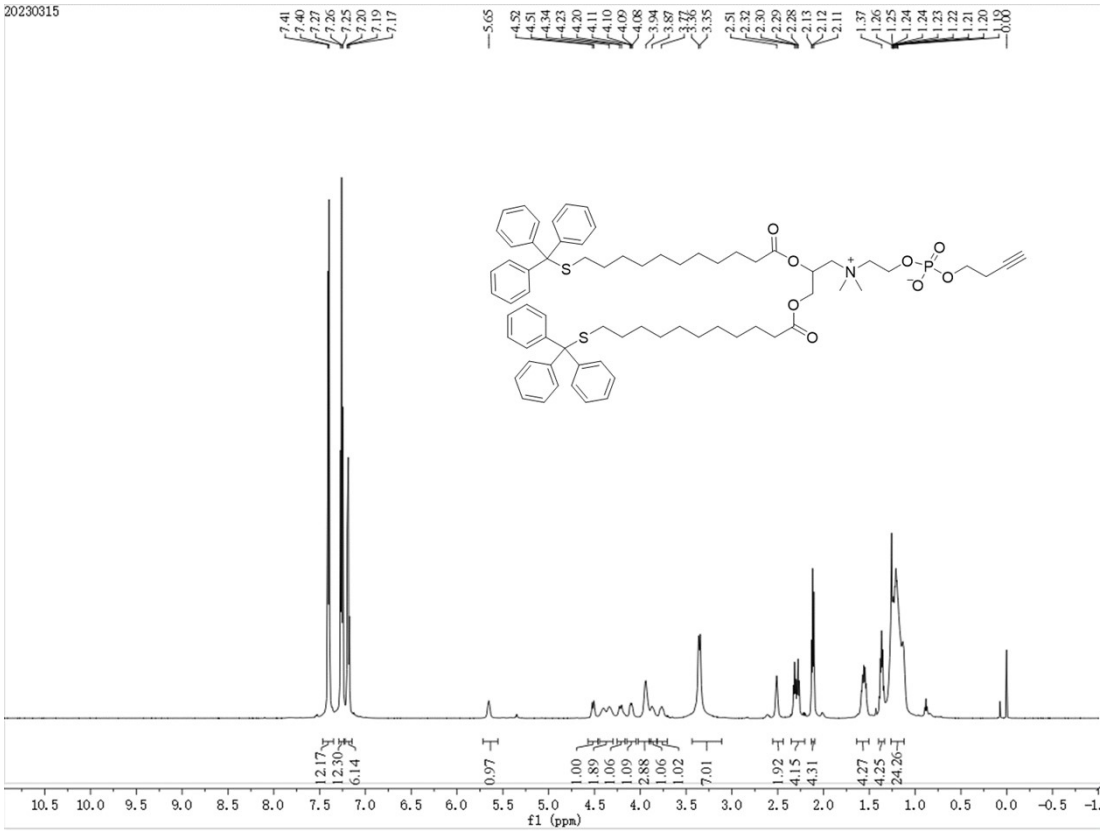
^{13}C NMR spectrum of compound **9**



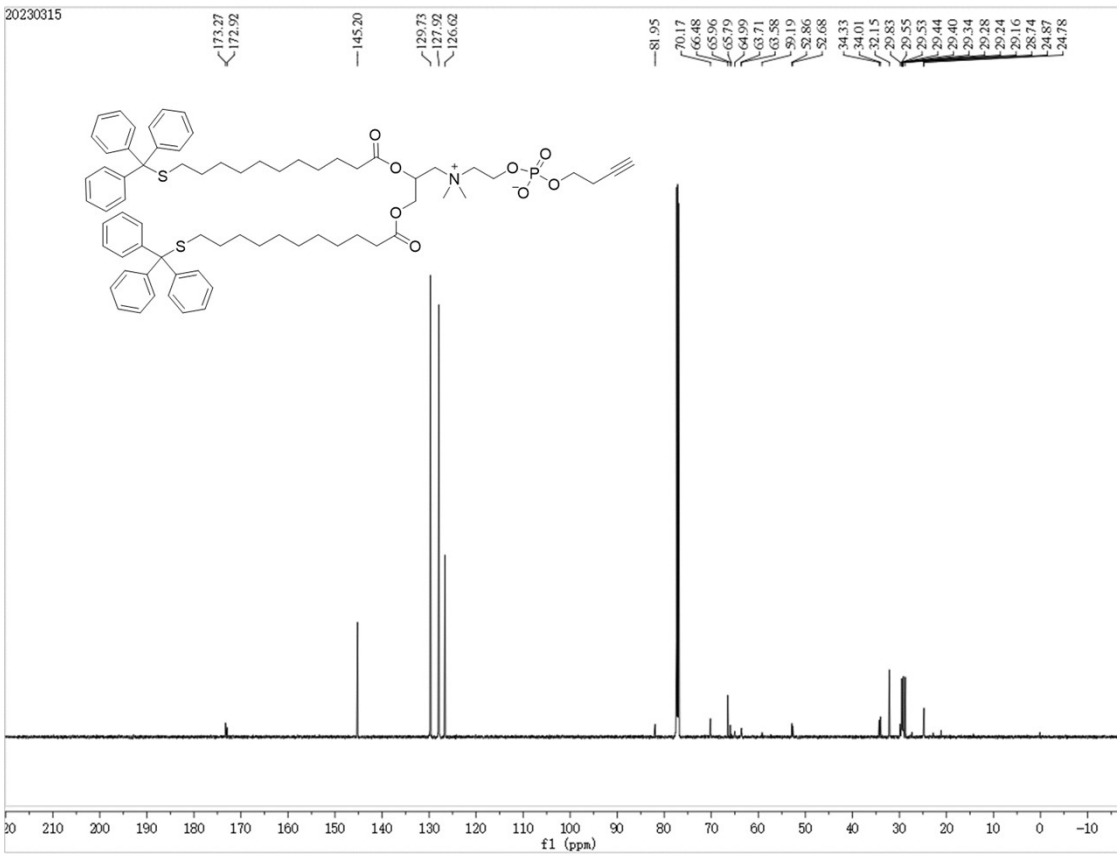
^{31}P NMR spectrum of compound **9**



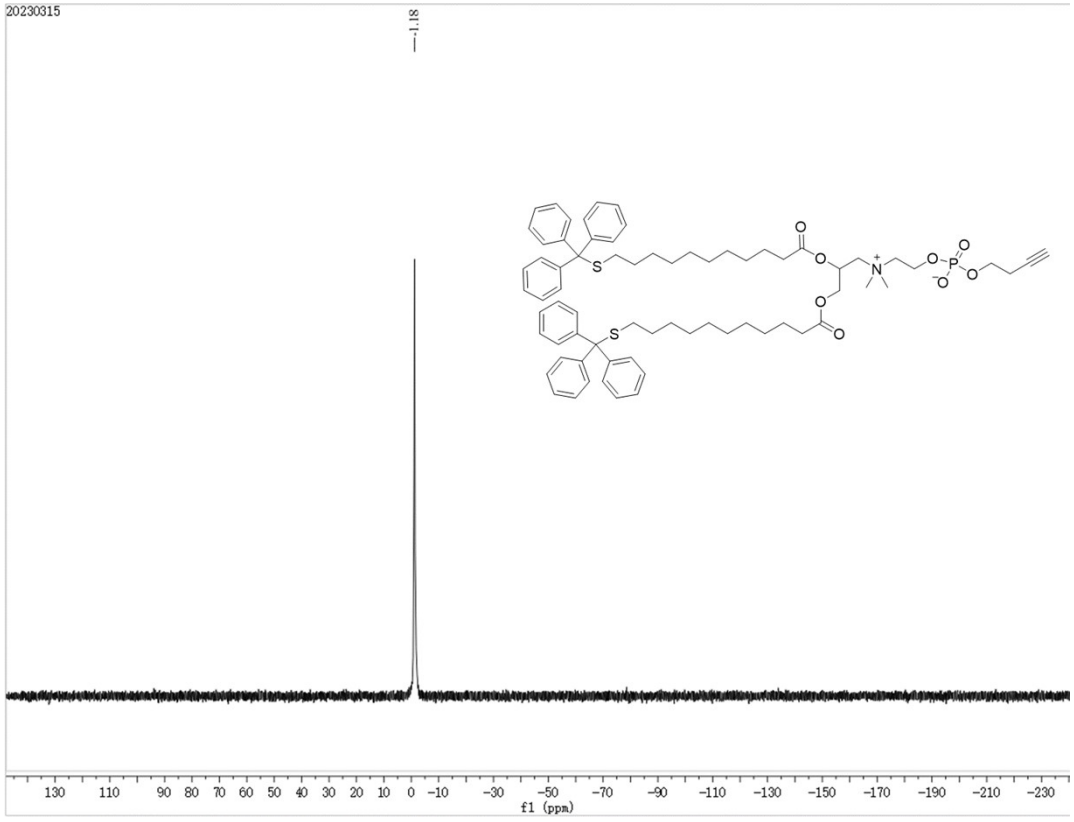
ESI-HRMS spectrum of compound **9**



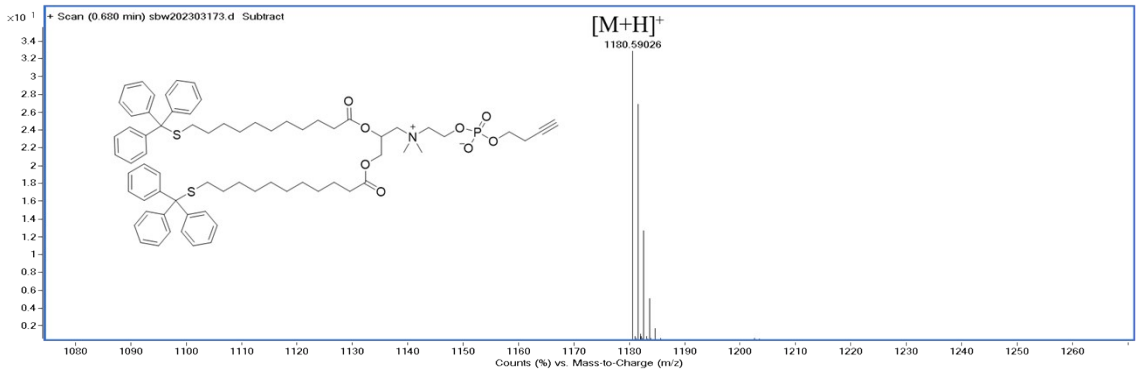
^{1}H NMR spectrum of compound **10**



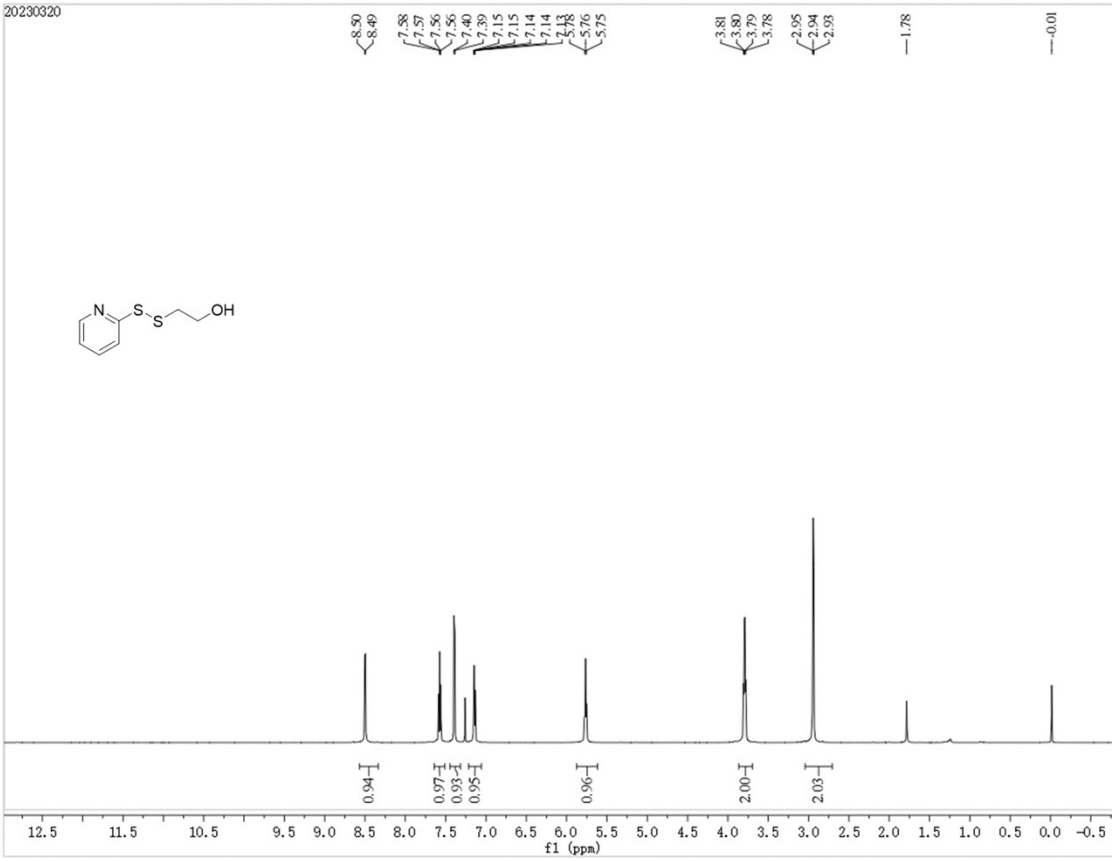
^{13}C NMR spectrum of compound **10**



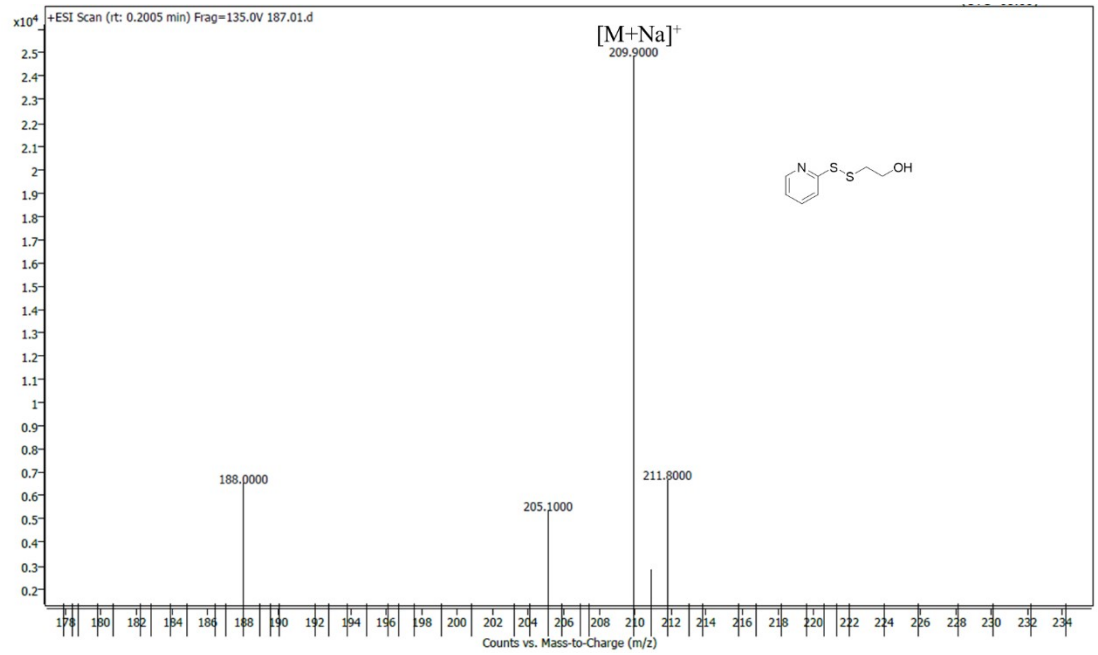
^{31}P NMR spectrum of compound **10**



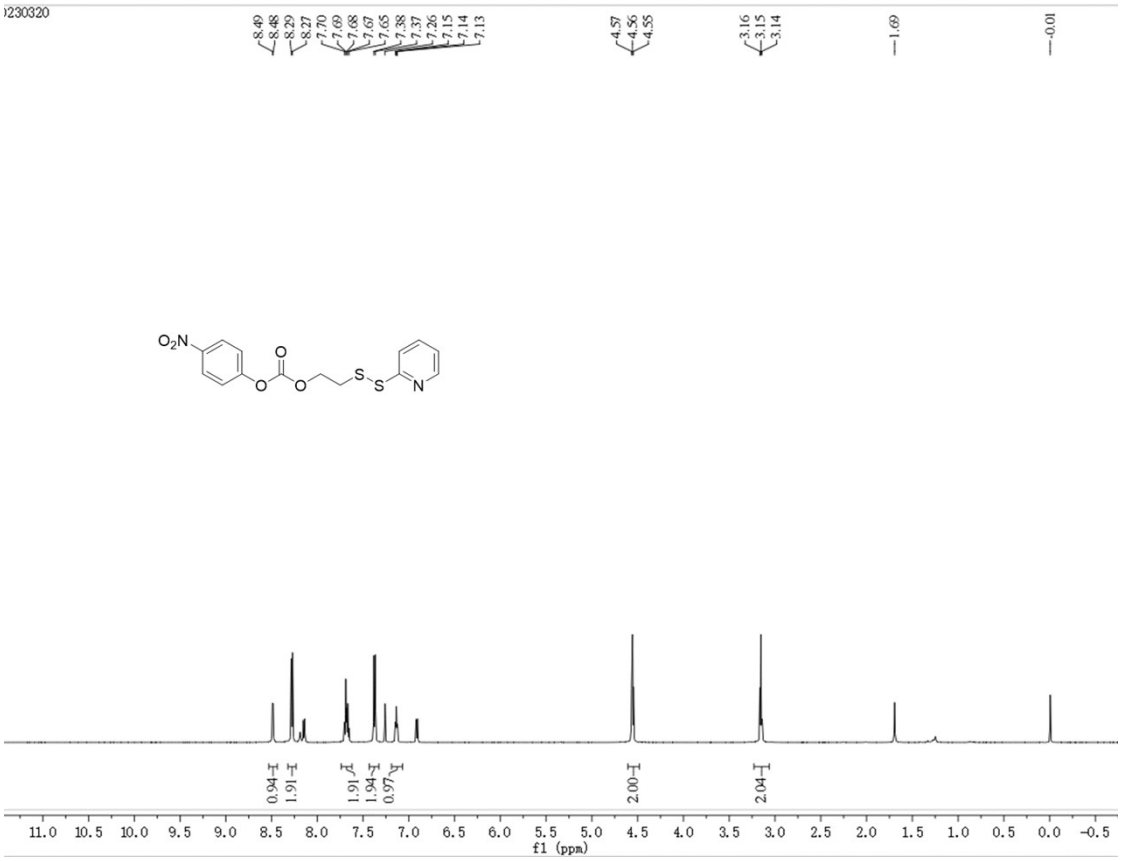
ESI-HRMS spectrum of compound **10**



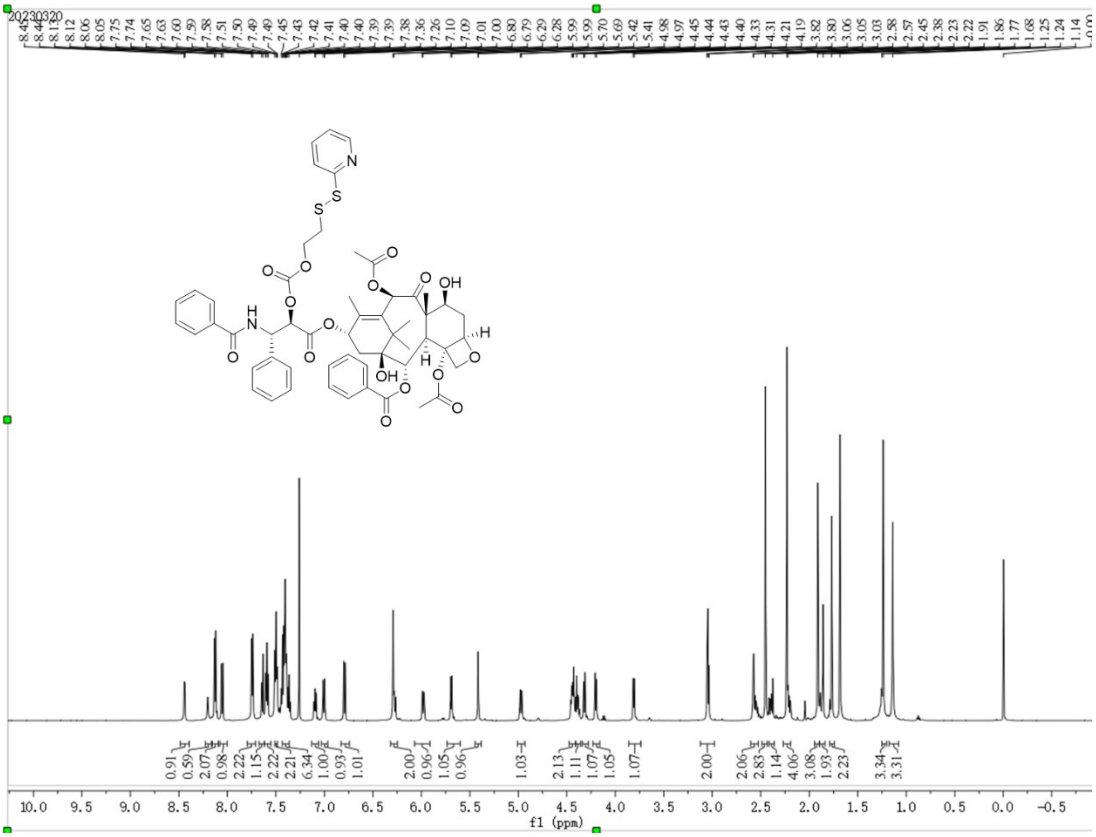
^{1}H NMR spectrum of compound **11**



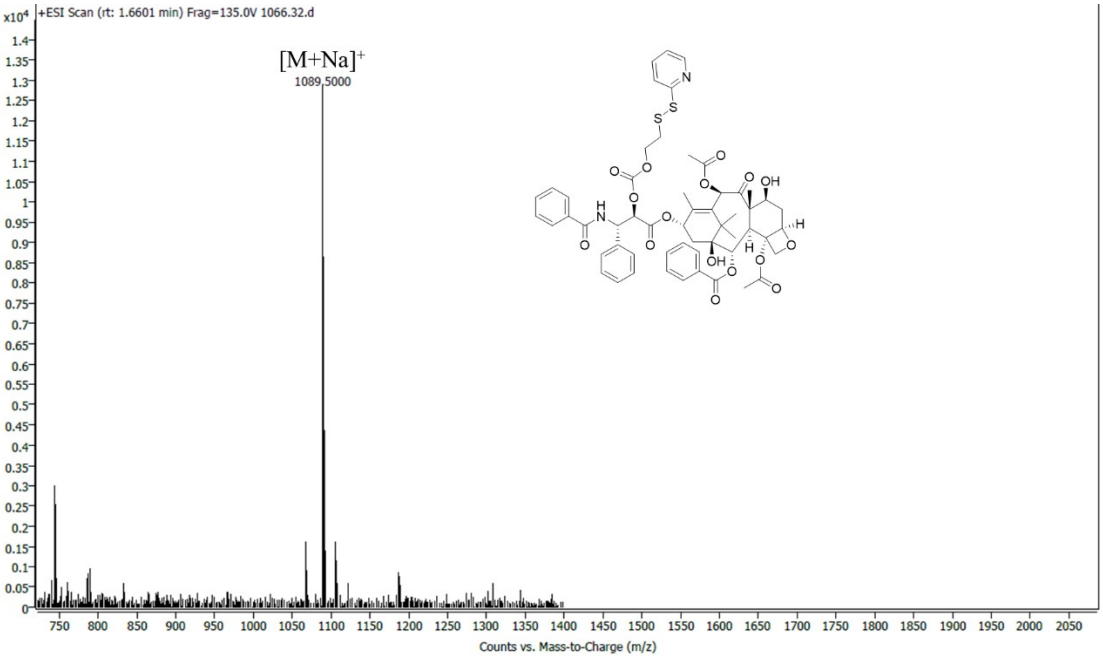
ESI-MS spectrum of compound **11**



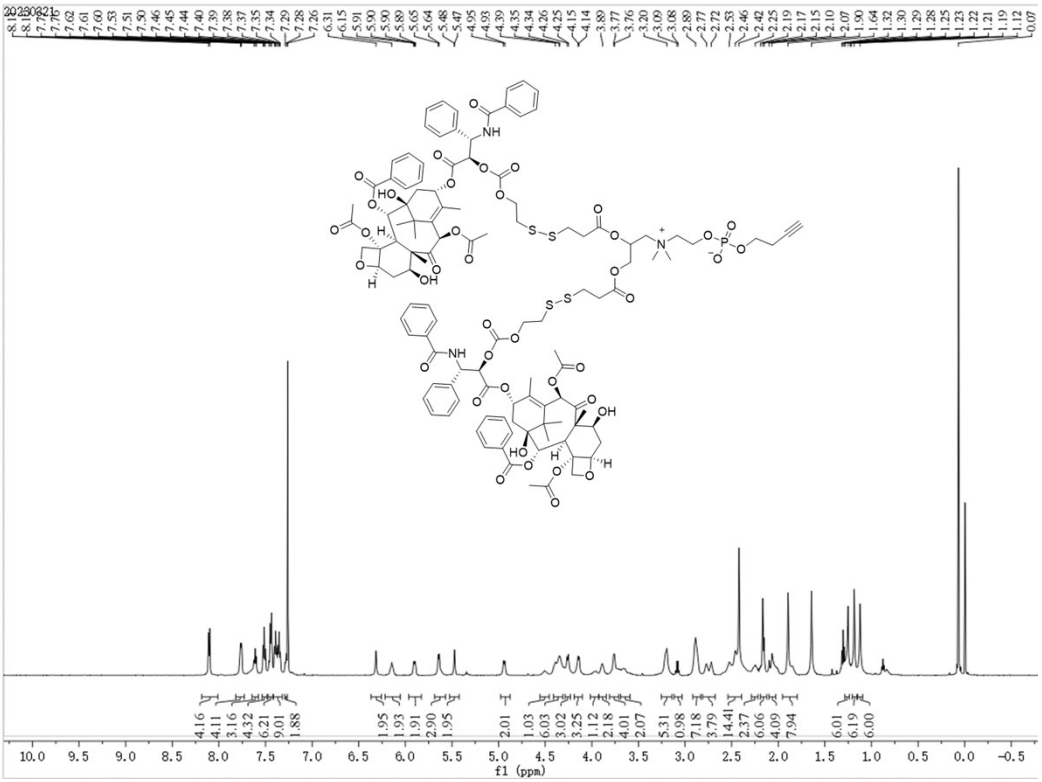
^{1}H NMR spectrum of compound **12**



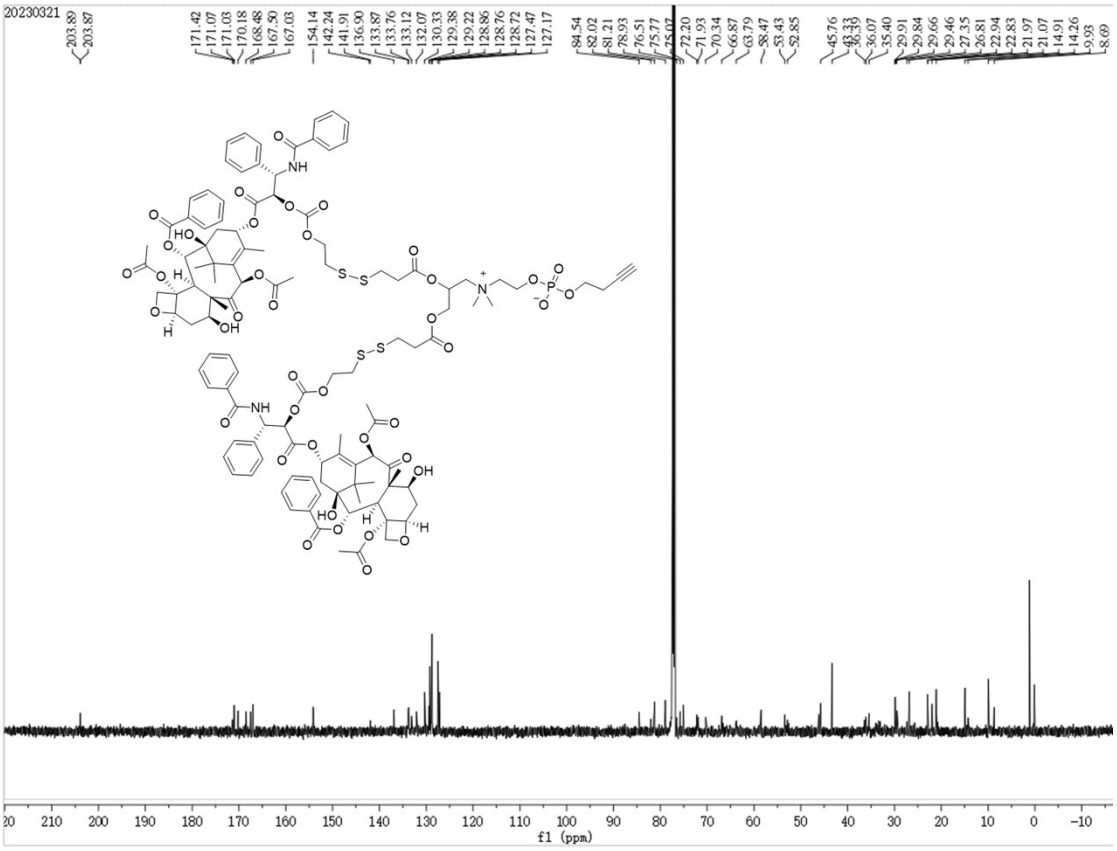
^{1}H NMR spectrum of compound **13**



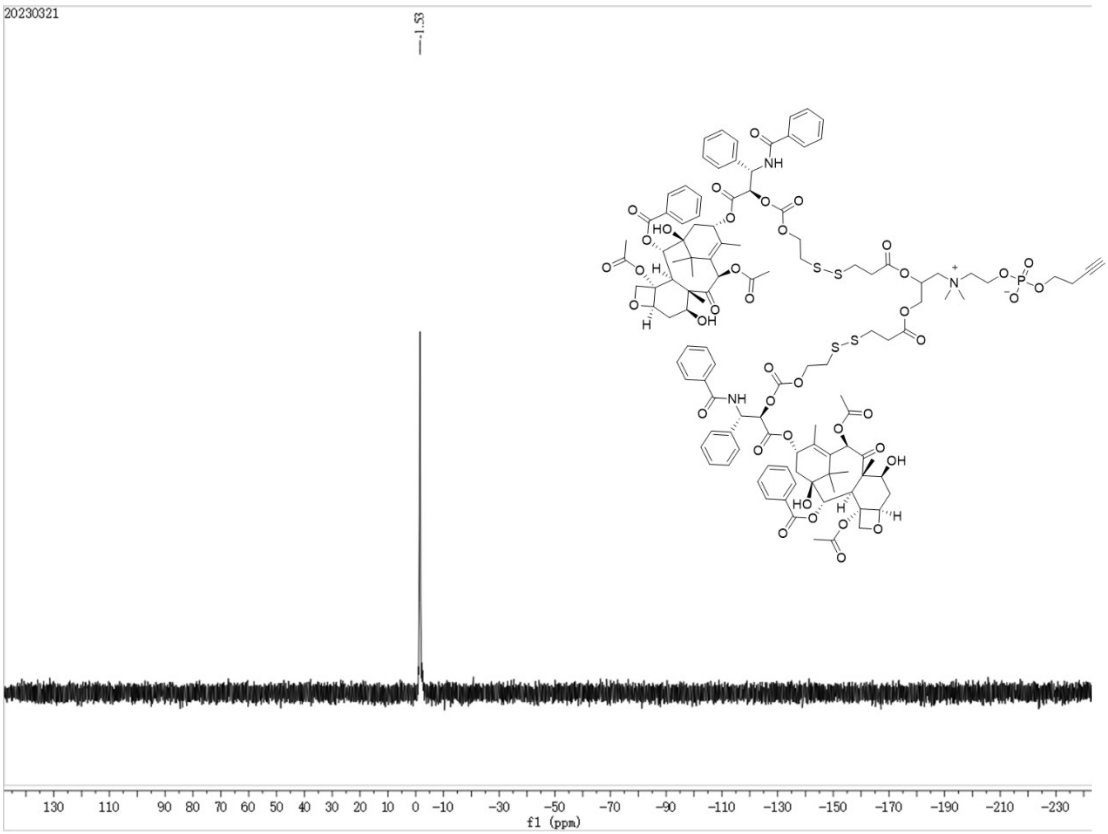
ESI-MS spectrum of compound **13**



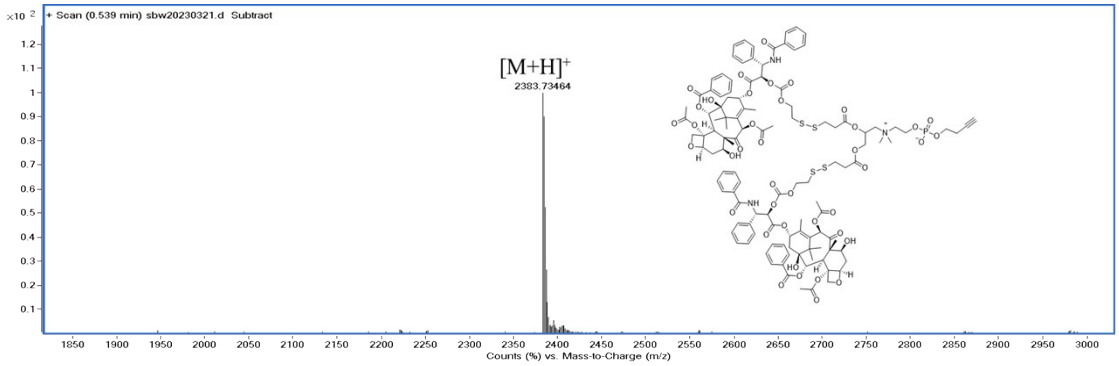
^{1}H NMR spectrum of compound **15**



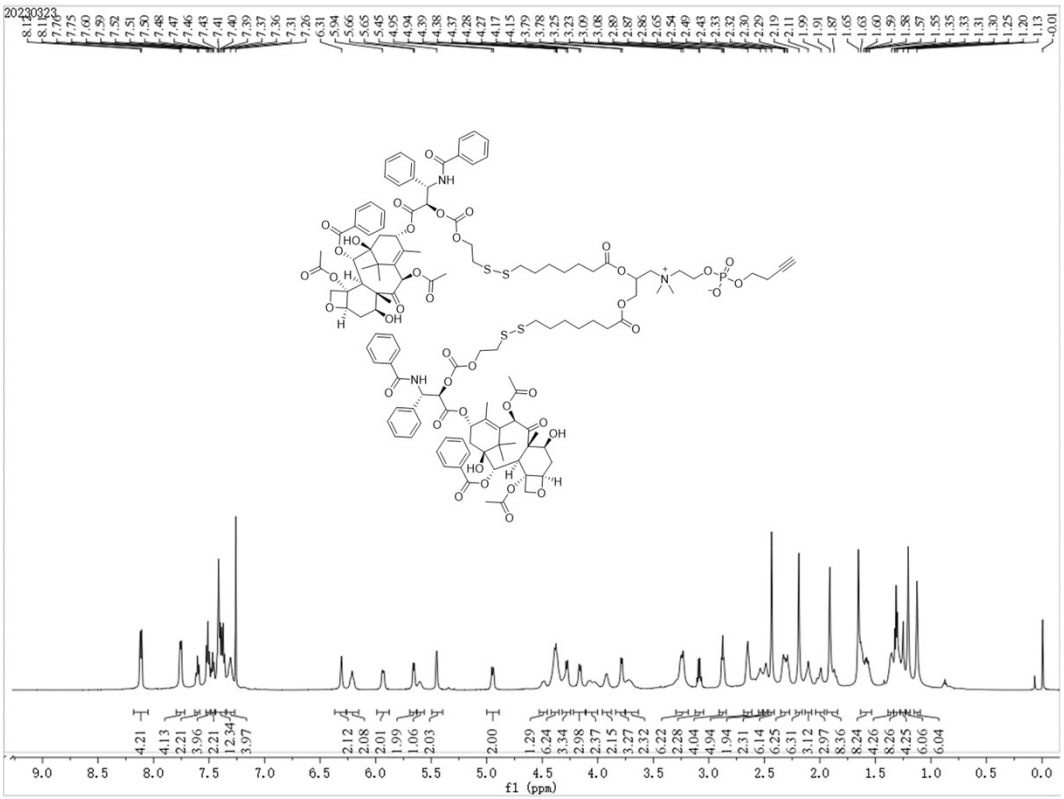
^{13}C NMR spectrum of compound **15**



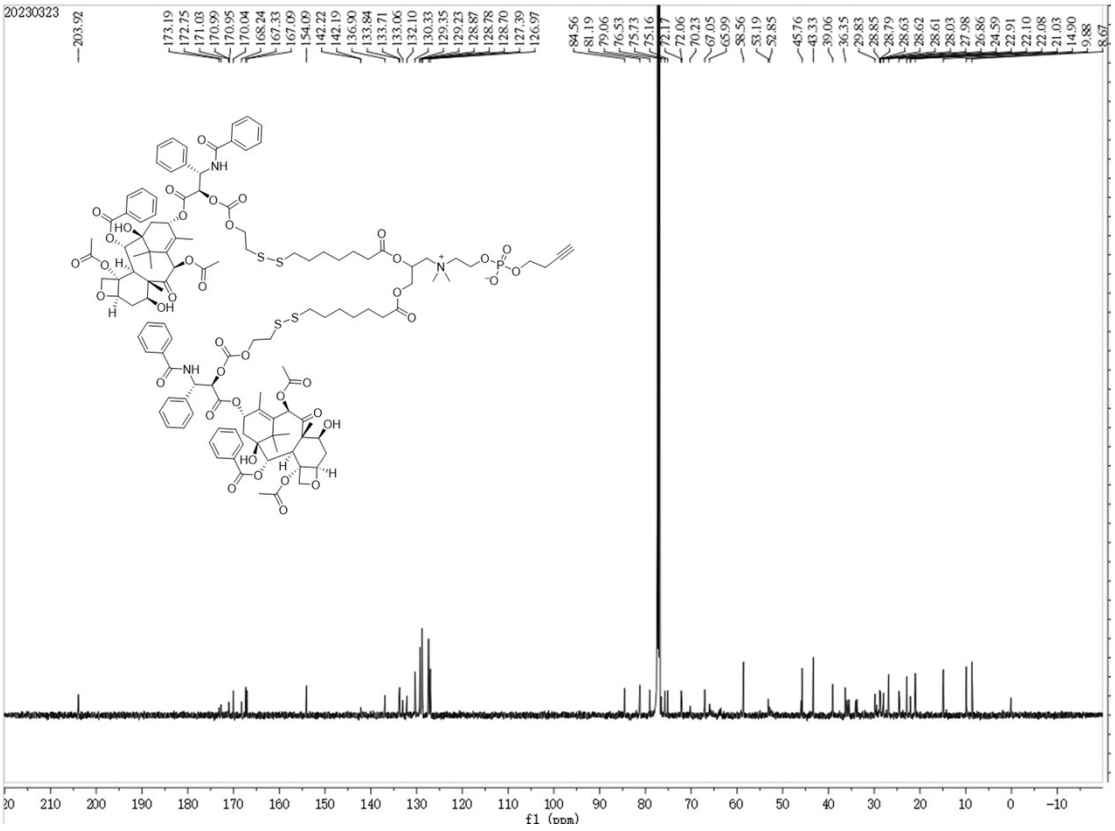
^{31}P NMR spectrum of compound **15**



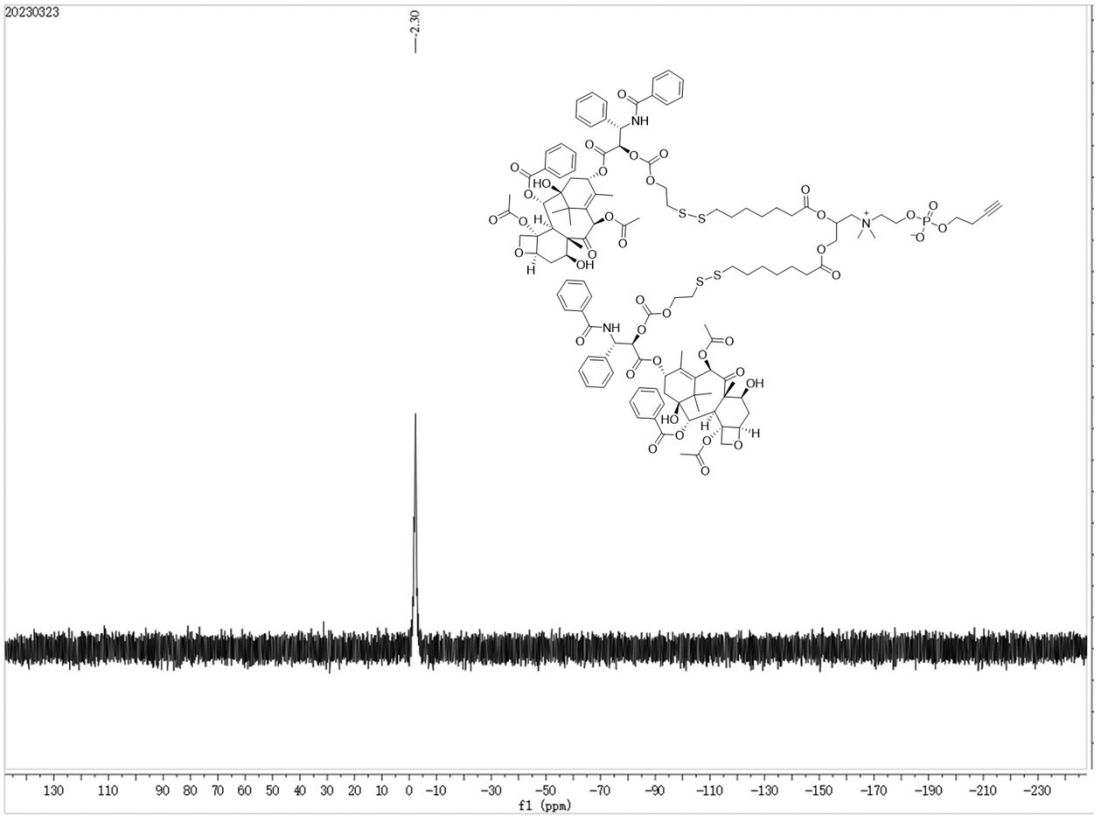
ESI-HRMS spectrum of compound **15**



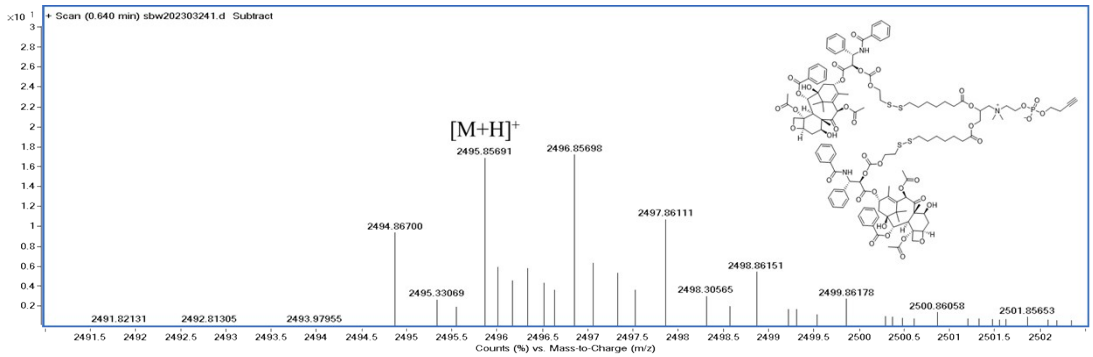
^{1}H NMR spectrum of compound **17**



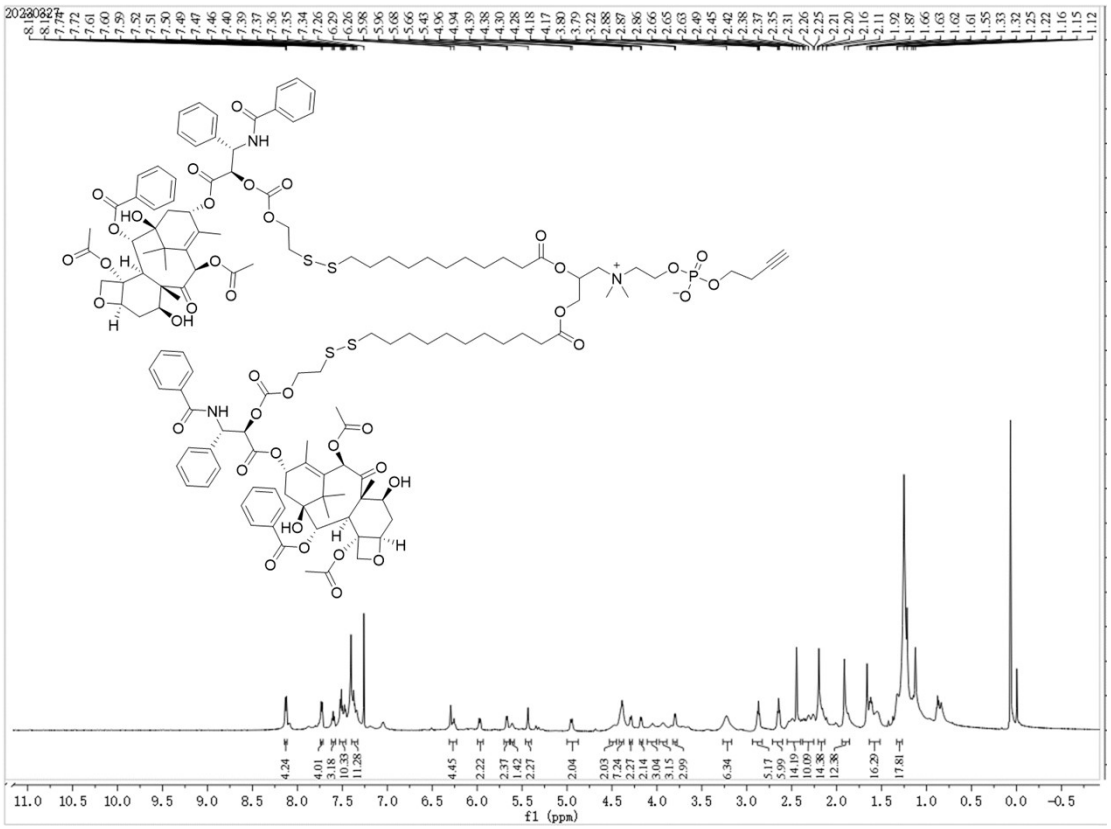
^{13}C NMR spectrum of compound **17**



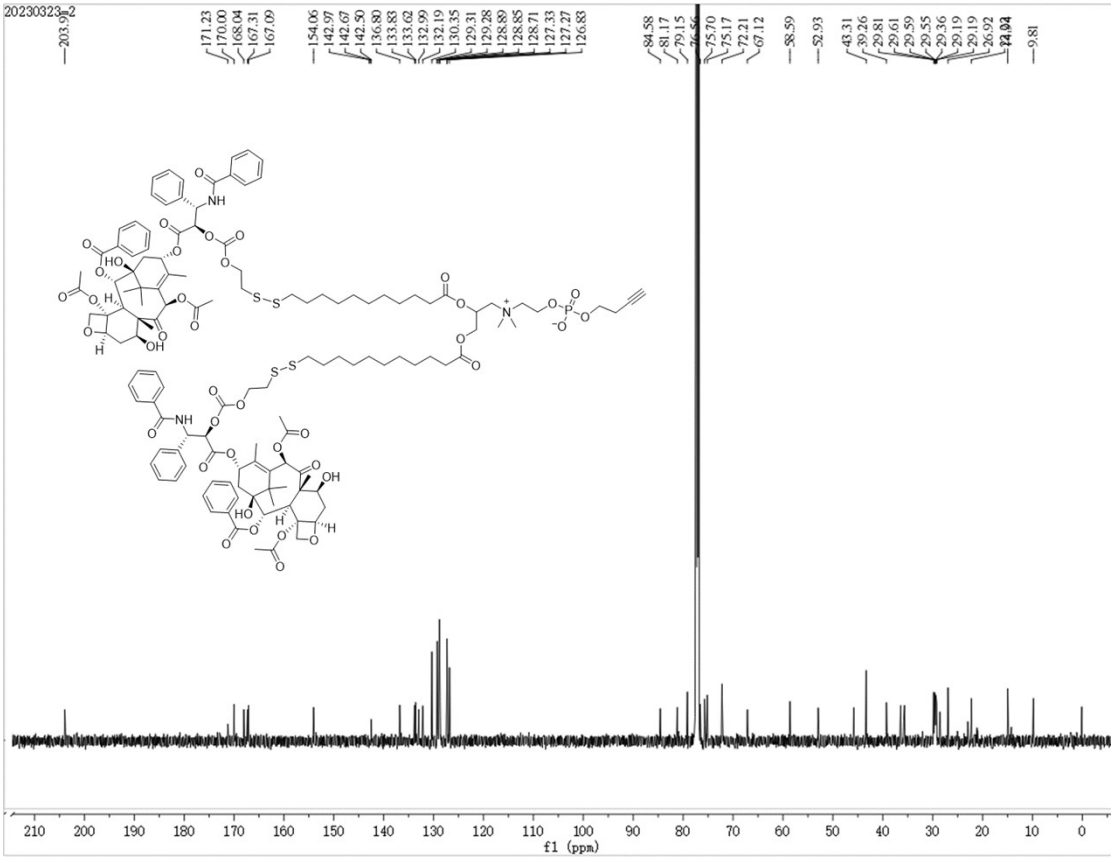
^{31}P NMR spectrum of compound **17**



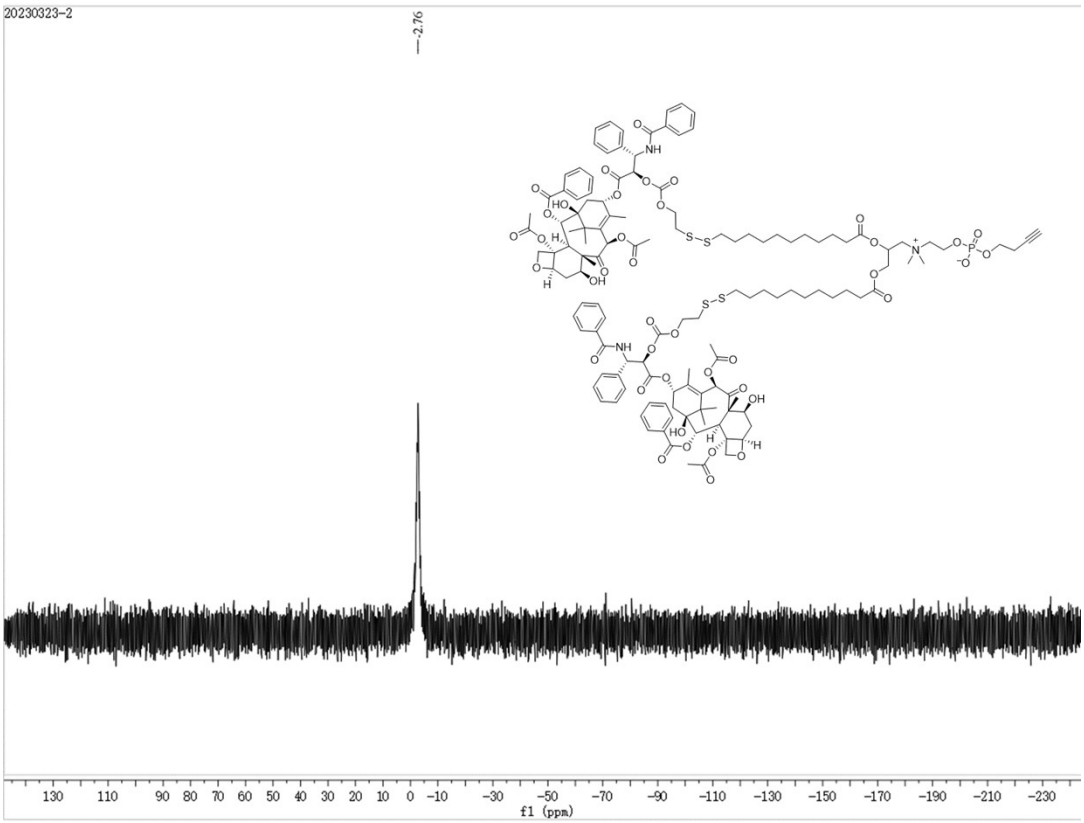
ESI-HRMS spectrum of compound **17**



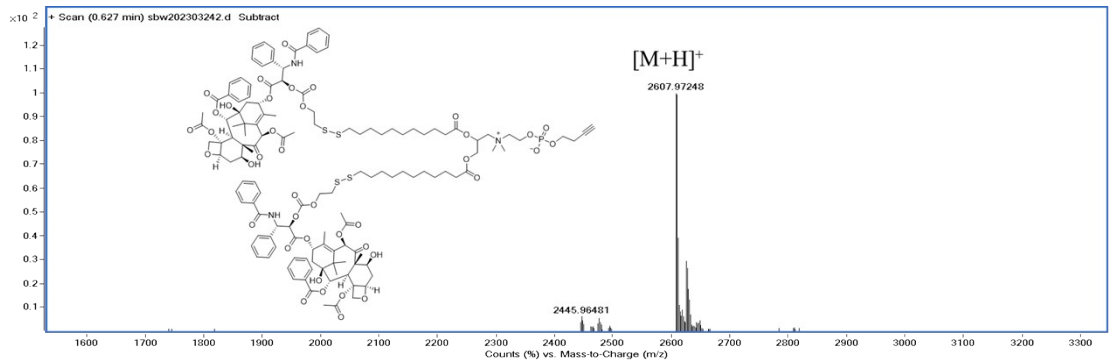
^{1}H NMR spectrum of compound **19**



^{13}C NMR spectrum of compound **19**



^{31}P NMR spectrum of compound **19**



ESI-HRMS spectrum of compound **19**

Tables

Table S1. The size distribution of liposomes via DLS.

Entry	Chemicals	Size[a]	PDI
1	SPCs	157.25 ± 4.5 nm	0.214 ± 0.031
2	PTX/SPCs	161.27± 1.1 nm	0.199± 0.040
3	PTX-SS-3-CPs	138.9 ± 2.5 nm	0.225± 0.021
4	PTX-SS-7-CPs	160.6 ± 3.2 nm	0.208± 0.033
5	PTX-SS-11-CPs	172.05± 3.5 nm	0.217± 0.017

Table S2. The DLC of three PTX-SS-CPs and PTX/SPCs

Entry	Liposomes	DLC (%)
1	PTX/SPCs	3.9±0.5
2	PTX-SS-3-CPs	39.4±0.2
3	PTX-SS-7-CPs	37.7±0.3
4	PTX-SS-11-CPs	36.1±0.2

Table S3. Calculated IC_{50} toward 4T1 Cells after 24 h incubation by Prism software.

Entry	Group	IC_{50}[a] (μg/mL)
1	PTX	0.229 ± 0.017
2	PTX/SPCs	5.911 ± 0.093
3	PTX-SS-3-CPs	1.177 ± 0.069
4	PTX-SS-7-CPs	2.089 ± 0.117
5	PTX-SS-11-CPs	1.450 ± 0.077

[a] IC_{50} value was calculated based on the concentration of PTX.

Table S4. Pharmacokinetic parameters of PTX, PTX/SPCs, and three PTX-SS-CPs

Parameter (unit)	PTX	PTX/SPCs	PTX-SS-3-CPs	PTX-SS-7-CPs	PTX-SS-11-CPs
C_{max}[a](μg/mL)	4.53 ± 0.78	12.8 ± 2.56	13.9 ± 2.11	15.1 ± 1.92	17.3 ± 2.88
AUC_{0-t}[b] (mg/L•h)	4.49 ± 0.81	35.45 ± 5.30	33.67 ± 3.39	39.24 ± 7.80	48.81 ± 9.21
$t_{1/2}$[c] (h)	2.05 ± 0.55	3.62 ± 0.41	3.61 ± 0.38	3.77 ± 0.21	6.6 ± 0.69
CL[d] (L/h/kg)	2.22 ± 0.18	0.28 ± 0.48	0.29 ± 0.31	0.26 ± 0.43	0.21 ± 0.19
Vd[e] (L/kg)	2.20 ± 0.22	0.77 ± 0.14	0.7 ± 0.11	0.65 ± 0.08	0.57 ± 0.07
MRT[f](0-t)	2.84 ± 0.33	5.21 ± 0.36	3.75 ± 0.51	5.62 ± 0.73	6.59 ± 0.92

[a]Maximum PTX concentration in plasma

[b]Area under the plasma PTX concentration versus time curves

[c]Elimination half-life

[d]Clearance

[e]Apparent volume of distribution

[f]Mean residence time

Table S5. The tumor inhibition rate (TIR) of PTX/SPCs, and three PTX-SS-CPs

Entry	Group	TIR (%)
1	Control	0 ± 0.000
2	PTX/SPCs	45.4 ± 4.6
3	PTX-SS-3-CPs	59.8 ± 3.7
4	PTX-SS-7-CPs	62.9 ± 4.0
5	PTX-SS-11-CPs	71.3 ± 3.6

Figures

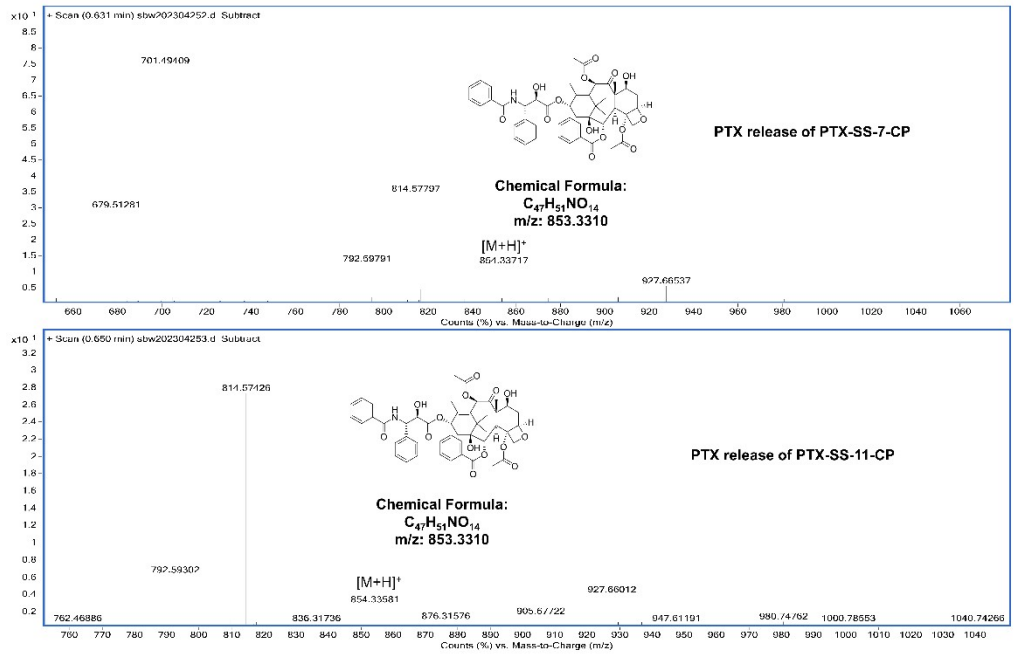
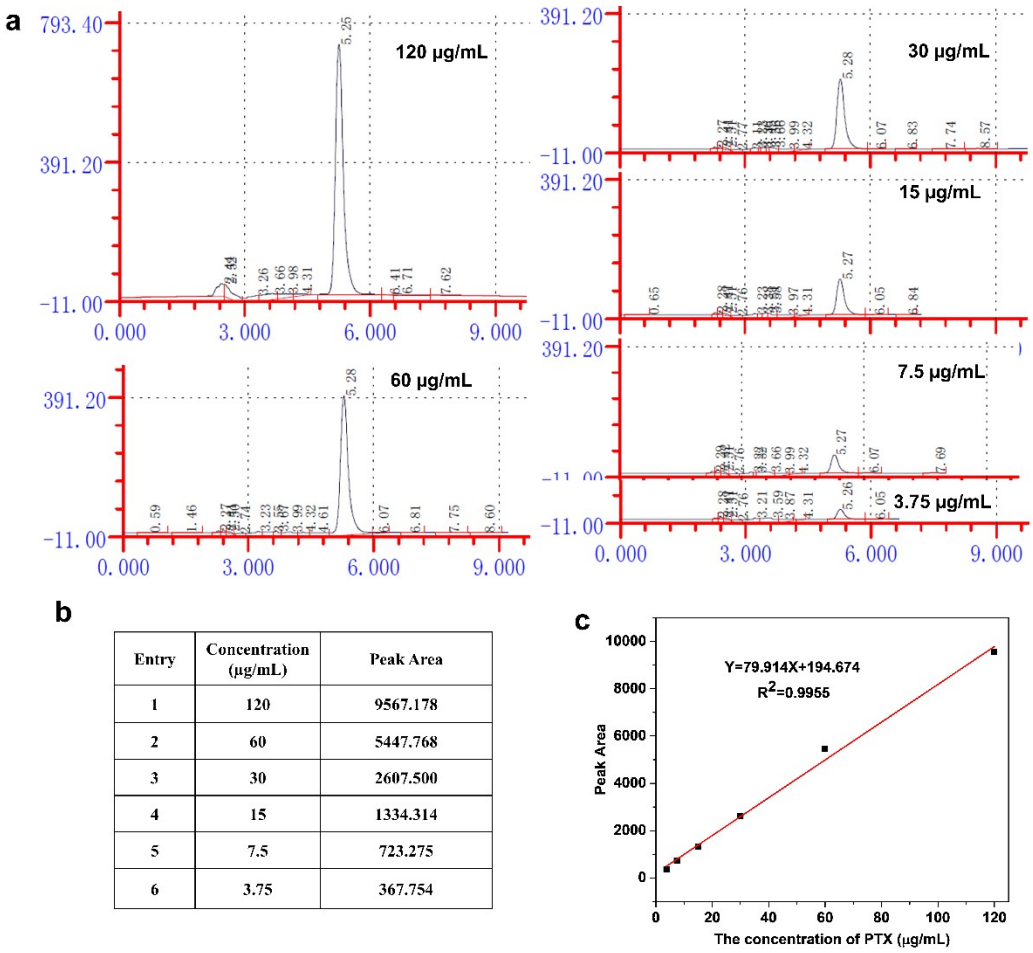


Figure S1. The PTX molecular ion peaks of 854.33 by HRMS after PTX-SS-7-CP and PTX-SS-11-CP treated with 10 mM GSH.



b

Entry	Concentration (μg/mL)	Peak Area
1	120	9567.178
2	60	5447.768
3	30	2607.500
4	15	1334.314
5	7.5	723.275
6	3.75	367.754

Figure S2. HPLC analysis of PTX. (a) The HPLC test diagrams with the concentration of 3.75 - 120 μg/mL. (b) The peak areas with the concentration of 3.75 - 120 μg/mL. (c) The standard curve of PTX with the concentration of 3.75 - 120 μg/mL by HPLC. HPLC Method: elution solvents of acetonitrile and H_2O (70:30), 1.0 mL/min, and 230 nm detection wavelength.

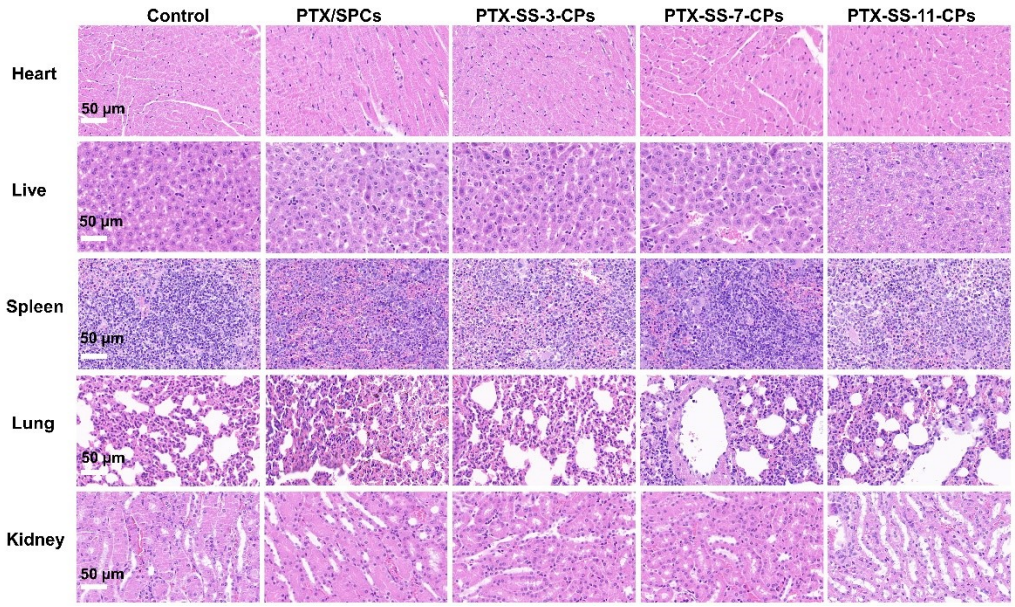


Figure S3. Hematoxylin and eosin (H&E) analysis of normal tissues (including heart, liver, spleen, lung, kidney) after treated via three PTX-SS-CPs and PTX/SPCs, scale bar: 50 μm.