Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information for

Lipoic Acid Based Core Cross-linked Micelles for Multivalent Platform: Design, Synthesis and Application in Bio-imaging and Drug Delivery

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General Method

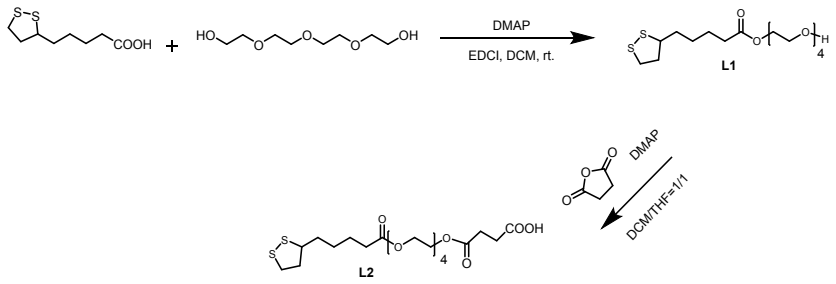
Routine NMR spectra were obtained on a Bruker AV II-400. The ^{1}H NMR chemical shifts were measured relative to D_2O or $CDCl_3$ as the internal reference (D_2O: δ 4.79 ppm; $CDCl_3$: δ 7.26 ppm). The ^{13}C NMR chemical shifts were given using $CDCl_3$ as the internal standard ($CDCl_3$: δ 77.16 ppm). Mass spectrometry was performed on a Waters Q-Tof premier instrument. The fluorescence emission intensity of Nile red at the wavelength of 525 nm (excited at 485 nm) was measured using a Hitachi F-7000 fluorescence spectrometer. The solvent was remmoved by pressure blowing concentrator (YGC-12, YaYuan) when determination of the CMC. The particle size and zeta potential were measured with a Dynamic Light Scattering (DLS) Analyzer (Malvern ZetasizerNano ZS90). TEM studies were carried out using a TecnaiG2F20S-TWIN instrument, operating at 120 kV. The TEM specimens were prepared by gently placing a carbon-coated copper grid on the surface of the sample. The TEM grid was then removed, stained with an aqueous solution of 2% phosphotungstic acid, dried for 0.5 h at room temperature, and then subjected to TEM observation. The drug loading was measured with UV-5301PC (Shimadzu, Japan) Human cervical cancer (HeLa) was obtained from Chinese Academy of Science Cell Bank for Type Culture Collection (Shanghai, China) and used for all of cell experiments and animal experiments. The cell line was grown in Dulbecco's modification of Eagle's medium Dulbecco supplemented with 10% (v/v) fetal bovine serum (FBS) and 1% (v/v) penicillin/streptomycin in an incubator under 5% CO_2 at 37 ^{o}C. Cell toxicity was evaluated by measuring the percentage of cell viability via the Cell Counting Kit-8 assay (CCK-8). The absorbance at 450 nm was then measured using a microplate reader Varioscan Flash (ThermoFisher SCIENTIFIC). The cell viability (%) was obtained according to the manufacturer's instructions. The cellular uptake of HeLa cells incubated with Hoachest 33342 for cell nuclei staining and DOX@LA-CCM/**L2** was observed under confocal laser

scanning microscopy (CLSM, LSM780). Cell-associated Hoachest 33342 was excited with an argon laser (406 nm) and the emitted fluorescence was detected at 460 nm.

Chemicals: Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Lipoic acid and 3-Bromopropyne were purchased from Adamas-beta Ltd. Tetraethylene glycol and SAA was purchased from Alfa Aesar. All solvents for reactions were freshly distilled prior to use. Deionized water was used in all aqueous experiments.

Synthesis of compounds L1-L5.

Scheme 1S. Synthesis of compound **L1** and **L2**

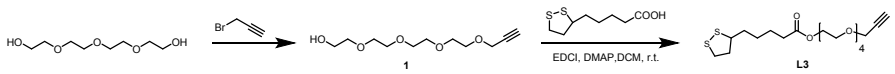


Compound L1. Under N_2 atmosphere, to a stirred solution of compound lipoic acid (800 mg, 3.88 mmol) in dry dichloromethane (CH_2Cl_2, 3.0 mL) was syringed a solution of 1-Ethyl-3-(3-dimethyllaminopropyl) carbodiimide hydrochloride (EDCI) (892.6 mg, 4.66 mmol), 4-dimethylaminopyridine (DMAP) (94.8 mg, 0.78 mmol) and tetraethylene glycol (904 mg, 4.66 mmol) in dichloromethane (3.0 mL) at 0 ^oC. The reaction was allowed to warm to room temperature and proceed until completion as monitored by TLC. The reaction mixture was concentrated by removing the solvent under vacuum and 10% HCl in water were added to the mixture. The biphasic mixture was extracted three times with CH_2Cl_2. The organic phase was further washed with $NaHCO_3$ and brine. The combine

organic layer was dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by chromatography on silica gel with CH_2Cl_2/MeOH (v/v = 30/1) to afford a yellow oil (682 mg, 46% yield). ^1H NMR ($CDCl_3$, 400 MHz): δ 1.37-1.54 (m, 2 H), 1.58-1.75 (m, 4 H), 1.86-1.94 (m, 1 H), 2.30-2.37 (m, 4H), 2.42-2.50 (m, 1H), 3.08-3.12 (m, 2 H), 3.53-3.58 (m, 1 H), 3.59-3.62 (m, 2 H), 3.64-3.73 (m, 12 H), 4.22-4.24 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.7, 28.9, 34.0, 38.6, 40.4, 56.5, 61.9; 63.6, 69.3, 70.6, 70.7, 173.6. High resolution ESI-MS: $[M+Na]^+$ calcd for $C_{16}H_{30}NaO_6S_2^+$ 405.1381, found 405.1336.

Compound L2. Under N_2 atomosphere, compound **L1** (191.1 mg, 0.5 mmol) was disolved in dry dichloromethane (CH_2Cl_2)/tetrahydrofuran (THF) (1.5mL/1.5mL). Then dihydrofuran-2,5-dione (100 mg, 1.0 mmol) and DMAP (6.1 mg, 0.05 mmol) was added. The reaction mixture was allowed to stir for 24 h under room temperature and proceed until completion as monitored by TLC. The reaction mixture was concentrated by removing the solvent under vacuum. The residue was added brine (50 mL) and extracted with CH_2Cl_2 (50 mL × 3). The combine organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was purified by chromatography on silica gel with DCM/MeOH (v/v = 20/1) to afford a yellow oil (217.2 mg, 90%). ^1H NMR ($CDCl_3$, 400 MHz): δ 1.43-1.53 (m, 2 H), 1.65-1.70 (m, 4 H), 1.87-1.93 (m, 1 H), 2.33-2.37 (t, J = 7.4 Hz, 2 H), 2.42-2.50 (m, 1 H), 2.61-2.71 (m, 5 H), 3.08-3.21 (m, 2 H), 3.53-3.60 (m, 1 H), 3.63-3.71 (m, 12 H), 4.22-4.28 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.7, 28.8, 28.9, 29.2, 29.6, 34.1, 34.7, 38.6, 40.4, 52.1, 56.5, 63.5, 69.3, 70.5, 70.6, 70.9, 172.1, 173.7, 175.4. High resolution ESI-MS: $[M+Na]^+$ calcd for $C_{20}H_{34}NaO_9S_2^+$ 505.1542, found 505.1544.

Scheme 2S. Synthesis of compound **L3**

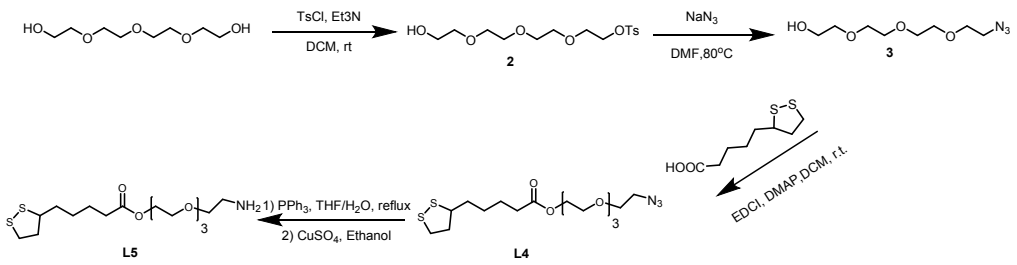


Compound 1. To a stirred suspension of sodium hydride (4.81 g, 100.8 mmol) in THF (80 mL) was added the solution of tetraethylene glycol (39.12 g, 201.6 mmol) in portions. The solution of propargyl bromide (3.54 g, 29.7 mmol) in THF (15 mL) was then added dropwise to the mixture in one hour. The reaction mixture was stirred at room temperature for two hours. After addition of H_2O (100 mL) and stirring vigorously for 10 minutes, the solvent was evaporated in vacuo. The residue was extractd by CH_2Cl_2 (200 mL × 3). The organic layer was dried over $MgSO_4$, filtrated and concentrated *in vacuo*. The residual oil was purified by column chromatography on silica gel with ethyl acetate/petroleum (v/v = 1/1) to afford a yellow oil (5.82 g, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (t, *J* = 2.4 Hz, 1 H), 2.73 (s, 1 H), 3.58 (t, *J* = 6.0 Hz, 2 H), 3.57−3.71 (m, 14 H), 4.18 (d, *J* = 2.4 Hz, 2 H).

Compound L3. Under N_2 atmosphere, a solution of EDCI (892.6 mg, 4.66 mmol), DMAP (94.8 mg, 0.78 mmol) and the compound **2** (1080 mg, 4.66 mmol) in dichloromethane (3.0 mL). was added to the solution of compound lipoic acid (800 mg, 3.88 mmol) in dry dichloromethane (3.0 mL) at 0 ^{o}C. The reaction was allowed to warm to room temperature and proceed until completion as monitored by TLC. The reaction mixture was concentrated by removing the solvent under vacuum and 10% HCl in water were added to the mixture. The biphasic mixture was extracted three times with CH_2Cl_2. The organic phase was further washed with $NaHCO_3$ and brine. The combine organic layer was dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by chromatography on silica gel with CH_2Cl_2/MeOH (v/v = 30/1) to afford a yellow oil (883 mg, 54% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.37-1.54 (m, 2 H), 1.58-1.74 (m, 4 H), 1.86-1.95 (m, 1 H), 2.33-2.37 (t, *J* = 7.2 Hz, 2 H),

2.43-2.50 (m, 2 H), 3.08-3.21 (m, 2 H), 3.53-3.58 (m, 1 H), 3.53-3.69 (m, 12 H), 4.20-4.22 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.7, 28.9, 34.1, 34.7, 38.6, 40.4, 56.5, 58.5, 63.6, 69.2, 69.3, 70.5, 70.7, 76.8, 77.2, 77.5, 79.8, 173.6. High resolution ESI-MS: $[M+Na]^+$ calcd for $C_{19}H_{32}O_6S_2Na^+$ 443.1538, found 443.1334.

Scheme 3S. Synthesis of compound **L4** and **L5**



Compound 2. To a stirring solution of tetraethylene glycol (10.4 mL, 60 mmol), triethylamine (13.9 mL, 100 mmol) in CH_2Cl_2 (30 mL) at 25 °C was slowly added a solution of tosyl chloride (3.81 mL, 20 mmol, in 20 mL CH_2Cl_2) over an hour. After addition, the reaction was allowed to stir overnight and quenched with brine (100 mL). Organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (80 mL × 4). The combined organic layer was dried over anhydrous $MgSO_4$, filtrated, concentrated under vacuum. The residue was purified by flash chromatography on silica gel with ethyl acetate as eluents to give compound **2** (4.21 g, 61% yield) as yellow oil liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.25 (s, 1 H), 2.44 (s, 3 H), 3.58-3.72 (m, 14 H), 4.15-4.17 (m, 2 H), 7.34 (d, J = 8.0 Hz, 2 H), 7.79 (d, J = 8.4 Hz, 2 H).

Compound 3. Under N_2 atmosphere, compound **2** (2.04 g, 6.0 mmol) and NaN_3 (1.2 g, 18.0 mmol) were disolved in anhydrous DMF (30 mL) and stirring for 16 h. The reaction mixture was filtered and concentrated under vacuum (note: the temperature was kept within 45 °C). Then the brine was added.

The aqueous layer was extracted with CH_2Cl_2 (50 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$, filtrated, concentrated under vacuum. The residue was purified by flash chromatography on silica gel with PE/EA (v/v = 1/1) as eluents to give compound **3** as clear colorless liquid (720 mg, yield 55%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.19 (s, 1 H), 3.40 (t, *J* = 4.6 Hz, 2 H), 3.60-3.74 (m, 14 H).

Compound L4. Under N_2 atmosphere, a solution of EDCI (460.0 mg, 2.4 mmol), DMAP (48.8 mg, 2.2 mmol) and the compound **3** (482.0 mg, 2.2 mmol) in dichloromethane (3.0 mL) was added a solution of lipoic acid (412.6 mg, 2.0 mmol) in dry dichloromethane (3.0 mL) at 0 °C. The reaction was allowed to warm to room temperature and proceed until completion as monitored by TLC. The reaction mixture was concentrated by removing the solvent under vacuum and 10% HCl in water were added to the mixture. The biphasic mixture was extracted three times with CH_2Cl_2. The organic phase was further washed with $NaHCO_3$ and brine. The combine organic layer was dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by chromatography on silica gel with CH_2Cl_2/MeOH (v/v = 60/1) to afford a yellow oil (498.8 mg, 61% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ1.37-1.54 (m, 2 H), 1.58-1.76 (m, 4 H), 1.86-1.95 (m, 1 H), 2.35 (t, *J* = 7.4Hz, 2 H), 2.42-2.50 (m, 1 H), 3.08-3.21 (m, 2 H), 3.38 (t, *J* = 5.2Hz, 2 H), 3.53-3.60 (m, 1 H), 3.64-3.71 (m, 12 H), 4.22-4.24(m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.4, 28.9, 34.1, 34.7, 38.6, 40.4, 50.8, 56.5, 63.6, 70.7, 70.8, 70.8, 100.1, 173.6. High resolution ESI-MS: $[M+Na]^+$ calcd for $C_{16}H_{29}N_3O_5S_2Na^+$ 403.1446, found 403.1450.

Compound L5.[1] Under N_2 atmosphere, the mixture of compound **L4** (85.6 mg, 0.21 mmol) and PPh_3 (165.4 mg, 0.63 mmol) was refluxing for 8 h in THF/H_2O (5.0 mL/1.0 mL, v/v). The resulting reaction mixture was cooled to room temperature and extracted with EA (25 mL×3). The combine

organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was dissolved in alcohol (5.0 mL) and $CuCl_2 \cdot 2H_2O$ (71 mg, 0.42 mmol) was added dropwise at room temperature. After 6 h, then compound **L5** was evaporated in vacuo and purified by chromatography on silica gel with CH_2Cl_2/MeOH (v/v = 15/1) to afford a yellow oil (68 mg, 85% yield). ^1H NMR ($CDCl_3$, 400 MHz): δ 1.37-1.54 (m, 2 H), 1.58-1.76 (m, 4 H), 1.86-1.95 (m, 1 H), 2.35 (t, *J* = 7.4 Hz, 2 H), 2.42-2.50 (m, 1 H), 3.08-3.21 (m, 2 H), 3.38 (t, *J* = 5.2 Hz, 2 H), 3.53-3.60 (m, 1 H), 3.64-3.71 (m, 12 H), 4.22-4.24 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.4, 28.9, 34.1, 34.7, 38.6, 40.4, 50.8, 56.5, 63.6, 70.7, 70.8, 70.8, 100.1, 173.6. High resolution ESI-MS: $[M+Na]^+$ calcd for $C_{16}H_{29}N_3O_5S_2Na^+$ 403.1446, found 403.1450.

Compound CF-N_3. a) Under N_2 atmosphere, the compound 5 (6)-carboxyfluorescein (10 mg, 0.026 mmol) and 1-bromo-3-chloropropane (6.2 mg, 0.040 mmol) was dissolved in DMF (1.5 mL) and stirred for 24 h at 50 ^oC. After finishing the reaction, the crude product was evaporated in vacuo and give flash chromatography by eluent with CH_2Cl_2/MeOH (v/v = 10/1) to give CF-Br (yellow liquid, 12 mg). b) Under N_2 atmosphere, compound NaN_3 (1.5 mg, 5.0 equiv.) was added the CF-Br in DMF (1.0 mL) and stirred for 24 h at 80 ^oC. Until completing reaction, the crude product was evaporated in vacuo and give flash chromatography by eluent with CH_2Cl_2/MeOH (v/v = 8/1) to give CF-N_3 (yellow liquid, 7 mg).

Typical preparation of lipoic Acid based uncross-linked micelles (LA-CCM/L3). Compound **L3** (25 μL, 0.1 mmol/mL in DMF) was added dropwise into 5.0 mL of deionized water with ultrasound at room temperature. The resulting solution was then left to stand and the micelles formed spontaneously within minutes as a pale blue emulsion. The dynamic light scatter-ing (DLS) of uncross-linked **L1-L5** (see figure 2s).

Typical preparation of lipoic Acid based core cross-linked micelles (LA-CCMs/L3). The uncross-linked micelle LA-UCM/**L3** was made at first. The DTT (10 mol%) was added dropwise and stirred overnight. Then the LA-UCM/**L3** was cross-linked by air pump for half an hour and dialyzed against deionized water using a 1 KDa molecular weight cut-off tubing to give LA-CCM/**L3**. The dynamic light scatter-ing (DLS) of cross-linked **L1-L5** (see figure 2s).

Typical prepartion of mixture lipoic Acid based core cross-linked micelles (LA-CCMs/L23). The mononer micelle **L3** (10 mg, 0.023 mmol in 50 μL DMF) and **L2** (11 mg, 0.023 mmol in 50 μL DMF) was added dropwise into 10.0 mL of deionized water with ultrasound at room temperature. And DTT (10 mol%) was added dropwise and stirred overnight. Then the LA-UCM/**L23** was cross-linked by air pump for half an hour and dialyzed against deionized water using a 1 KDa molecular weight cut-off tubing to give LA-CCM/**L23**.

Determination of the critical micelle concentration(CMC) of amphiphile L1-L5.[2] A known amount of nile red in CH_2Cl_2 was added to a series of vials and the CH_2Cl_2 was evaporated. The amount was chosen to give a nile red concentration of 1×10^{-6} M in the final solution. A measured amount of **L1**-**L5** solution was added to each vial and the deionized water was added to the vials to make the concentrations of amphiphile **L1**-**L5** ranging from 2 to 1024 μM. The vials were vibrated at room temperature overnight, and then the fluorescence emission intensity at the wavelengths of 525 nm (excited at 485 nm) was measured. The critical micelle concentration was obtained as the intersection of the tangents to the two linear portions of the graph of the fluorescence intensity. The CMC of each amphiphile was ~55 μg/mL for **L1**, 82 μg/mL for **L2**, 13 μg/mL for **L3**, 41 μg/mL for **L4**, 31 μg/mL for **L5**.

^{1}H NMR comparison of small-molecule micelles before and after core cross-linking. At first, the compound **L3** was dissolved in D_2O for ^{1}H NMR. The LA-CCM/**L3** was cross-linked by air pump for half an hour and dialyzed against deionized water using a 1 KDa molecular weight cut-off tubing. Then the LA-CCM/**L3** was lyophilized and redissolved in D_2O for ^{1}H NMR.

Stability test of lipoic Acid based core cross-linked micelles (LA-CCMs/L3). The LA-CCM/**L3** was lyophilized and redissolved in MeOH (see figure 4s). The LA-UCM/**L3** and LA-CCM/**L3** ([**L3**] = 8 μg/mL) were incubation with 10% (v/v) FBS, respectively. Finally stability of core cross-linked micelles was tested by DLS.

Typical prepartion of hydrophobic drug (DOX) with LA-CCMs/L2 (DOX@ LA-CCMs/L2). The mixture LA-CCM/**L2** (22 mg, about 0.046 mmol), triethylamine (1.0 equvi.), EDCI (1.8 mg, 20 mol%) and *N*-Hydroxysuccinimide (NHS) (1.6 mg, 30 mol%) was stirred for 6 h at 35 ^{o}C. And then DOX·HCl (40 mol%) was added slowly in 5 mins and stirred overnight at 35 ^{o}C. At last, the mixture was dialyzed against deionized water using a 1 KDa molecular weight cut-off tubing for 24 h. The solution was lyophilized to give total weight. Then the compound was degraded by 50 mM DTT in DMSO, and the amount of DOX in the solution was determined by using a UV spectrometer using an established calibration curve. (The calibration curve was obtained with DOX/DMSO solutions with different DOX concentrations). And the procedure of Gemcitabine linked with **LA-CCMs/L2** is same as DOX@LA-CCM/**L2.**

$$DLC\% = \frac{weight\ of\ DOX\ in\ the\ micelle}{weight\ of\ the\ loaded\ drug\ and\ micelle} \times 100\%$$

$$EE\% = \frac{weight\ of\ DOX\ in\ the\ micelle}{weight\ of\ DOX\ added} \times 100\%$$

By following formula calculation, the DOX loading is upto 13.2% and Gem's is upto 28.3%.

Cellular uptake evaluation by confocal laser scanning microscopy (CLSM). HeLa cells (5×10^4 cells/mL) were seeded in a Φ = 35 mm glass Petri dish and incubated at 37 °C/5% CO_2 for 24 h. Subsequently, the cells were cultured with equal concentration of DOX loaded LA-CCM/**L2** ([DOX] = 2.5 μg/mL, λ_{Ex} = 480 nm, λ_{Em} = 578 nm) at 37 °C for 1 h, 3 h, respectively. The culture medium was removed and the cells were washed three times with 10 mM PBS. Then the nuclei were stained by blue molecular probe (Hoechst 33342, λ_{Ex} = 350 nm, λ_{Em} = 460 nm) for 15 min. The medium was removed and washed three times with 10 mM PBS and another 1 mL PBS was added. The cellular uptake was observed under CLSM. The RhB@LA-CCM/**L5** ([RhB]= 2.5 μg/mL, λ_{Ex} = 480 nm, λ_{Em} = 573 nm) is the same as the above.

Cytotoxicity assay. In vitro cytotoxicity was assessed by the Cell Counting Kit-8 assay (CCK-8). Briefly, HeLa cells (5000/well) were seeded in 96-well culture plates and incubated at 37 °C/5% CO_2. After 24 h, culture media was removed and fresh media (200 μL) containing free DOX, DOX@LA-CCM/**L2**, at various DOX concentration which ranging from 0.05 μg/mL to 20 μg/mL were added to each well, separately. Cells without any treatment were set as control. After 24 h, culture media was removed and fresh media (100 μL) containing CCK-8 (10 μL) was added to each well and the plates were incubated at 37 °C for another 2 h. Then, the absorbance at 450 nm of each sample was measured using a microplate reader Varioscan Flash. Similarly, A549 cells (5000/well) were seeded in 96-well culture plates and incubated at 37 °C/5% CO_2. After 24 h, culture media was removed and fresh media (200 μL) containing free gemcitabine, gem@LA-CCM/**L2**, at various gemcitabine concentration which ranging from 0.05 μg/mL to 20 μg/mL were added to each well, separately. Cells without any treatment were set as control. After 24 h, culture media was removed and fresh media (100 μL) containing CCK-8 (10 μL) was added to each well and the plates were incubated at 37 °C for another 2 h. Then, the

absorbance at 450 nm of each sample was measured using a microplate reader Varioscan Flash. To assess the toxicity of the blank material, the cytotoxicity of LA-CCM/**L2** was also assessed using the same protocol in the concentration range from 2 μg/mL to 400 μg/mL against A539 and HeLa cells.

Typical prepartion of double-fluorophore functionalized mixed core cross-linked micelles.[3] The mixture LA-CCM/**L23** (**L2** = 11mg, **L3** = 10 mg, about 0.023 mmol), triethylamine (1.0 equvi.), EDCI (0.9 mg, 20 mol%) and NHS (0.8 mg, 30 mol%) was stirred for 6 h at 35 ^{o}C. The donor dyes (1.5 mol%) was added slowly in 5 mins and stirred for 24 h at 35 ^{o}C. And acceptor CF-N_3 (1.5 mol%) was added. Then $CuCl_2$ aqueous ([Cu] = 0.15 mol‰) and Sodium ascorbate (1.5 mol‰) were added dropwise and stirred overnight. At last, the mixture was dialyzed against deionized water using a 1 KDa molecular weight cut-off tubing for 24 h. The FRET phenomenon was determined by fluorescence spectrometer. (1,5-EDANS Ex:335 nm, Em: 480 nm; CF λ_{Ex} = 490 nm, λ_{Em} = 520 nm)

References

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3. Zhang S, Zhao Y. Controlled release from cleavable polymerized liposomes upon redox and pH stimulation. *Bioconjugate Chem.*, **2011**, *22*, 523-528.

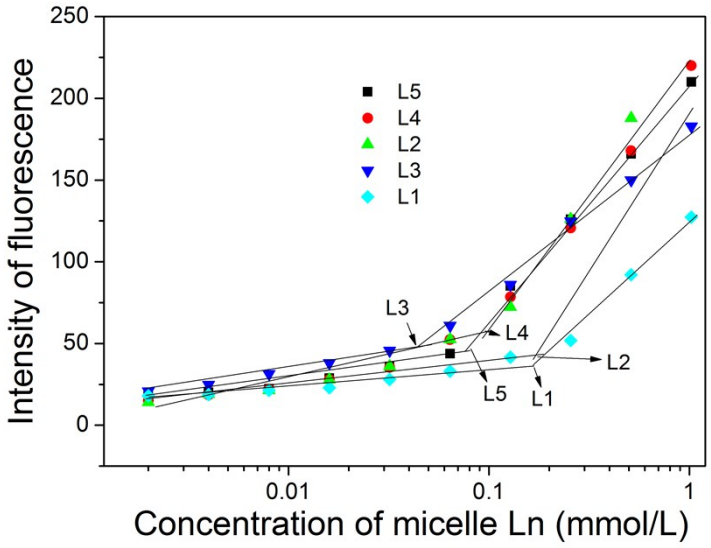


Figure 1S. Emission intensity at 525 nm of nile red as a function of concentrations of **L1-L5** in water. [nile red] = 1.0×10^{-6} mol/L, λex = 485 nm.

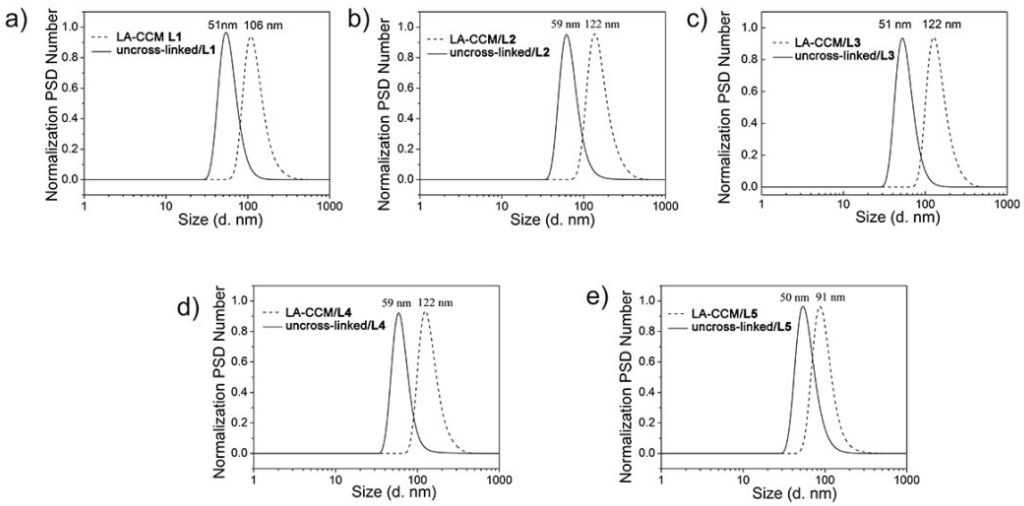


Figure 2S. DLS of small-molecule micelles formed by **L1-L5** before (solid lines) and after core cross-linking (dash lines).

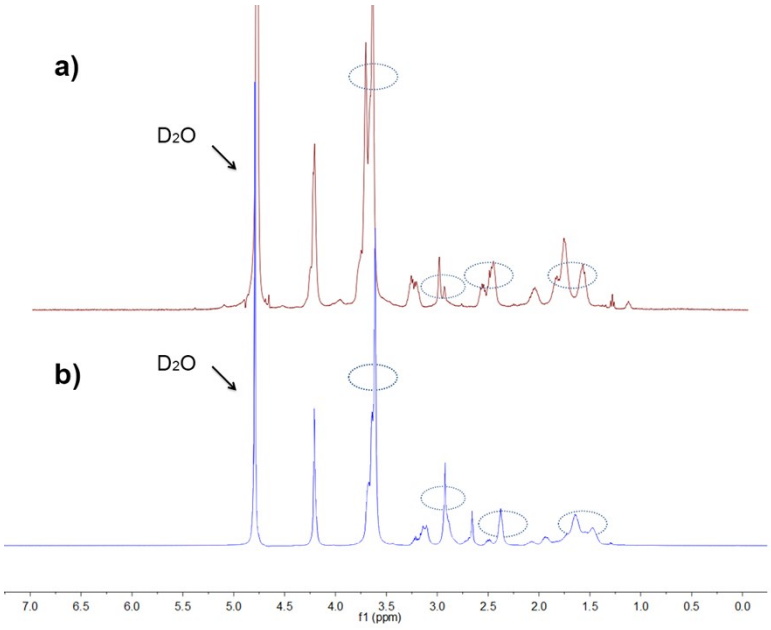


Figure 3S. ^{1}H NMR comparison of small-molecule micelles formed by **L3** in D_2O before (red line) and after core cross-linking (blue line).

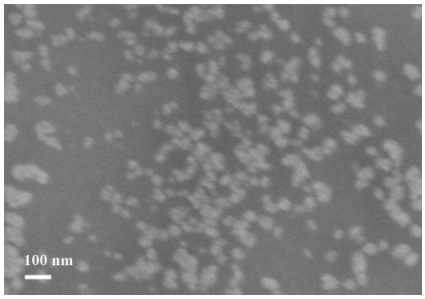


Figure 4S: SEM of the multivalent platform LA-UCM/**L3**.

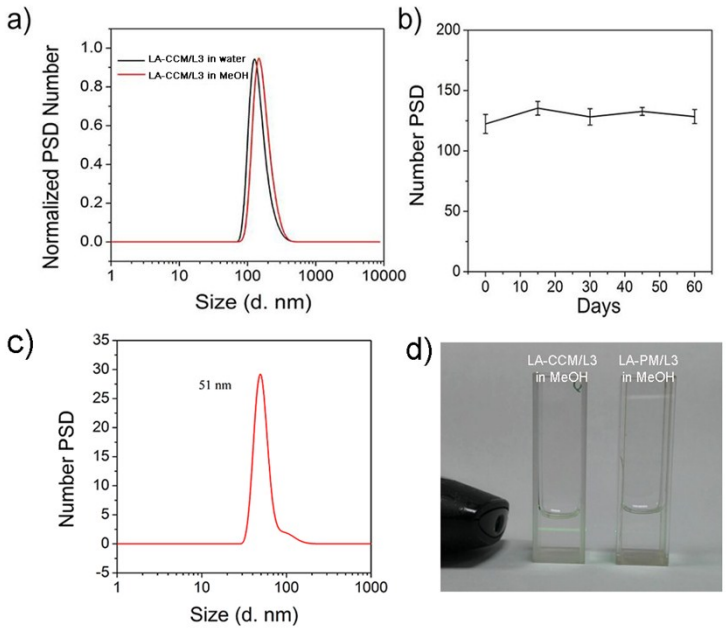


Figure 5S. a) DLS of the LA-CCM/**L3** in water and methanol; b) the PSD number of LA-CCM/**L3** in water over 60 days; c) DLS of the LA-PM/**L3** (PM = polymer micelle) in water; d) the picture shows the water solution of LA-CCM/**L3** and LA-PM/**L3** in MeOH irradiated with a 532 ± 10 nm continuous laser.

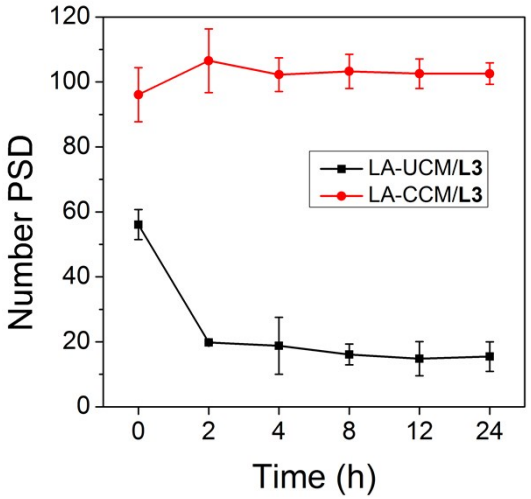


Figure 6S. Stability tests of LA-UCM/L3 and LA-CCM/**L3**. (a) Size of LA-UCM/**L3** and LA-CCM/**L3** as a function of the concentration of **L3** in 10% FBS at 37 °C over time. ([**L3**] = 8 μg/mL).

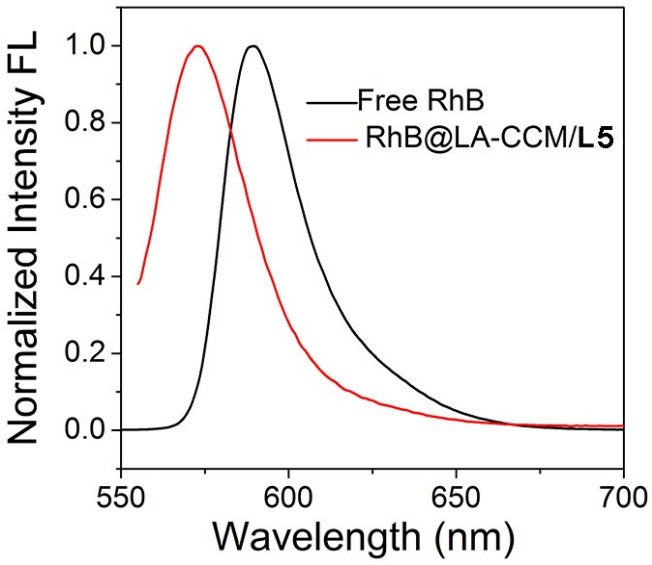


Figure 7S. The fluorescence spectrum of RhB@LA-CCM/**L5** (black line) and free RhB (red line).

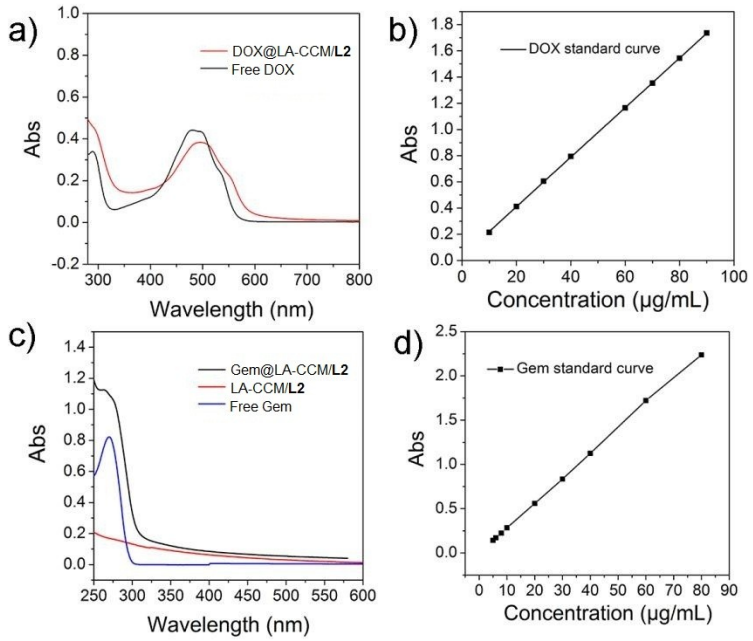


Figure 8S. a) Fluorescence spectra of DOX@LA-CCM/**L2** and free DOX under Ex 480nm; the standard curve line of free DOX b) and free Gem d); c) UV-vis Spectra of aqueous solutions of free Gem (balck line), Gem@LA-CCM/**L2** (red line), and LA-CCM/**L2** (blue line).

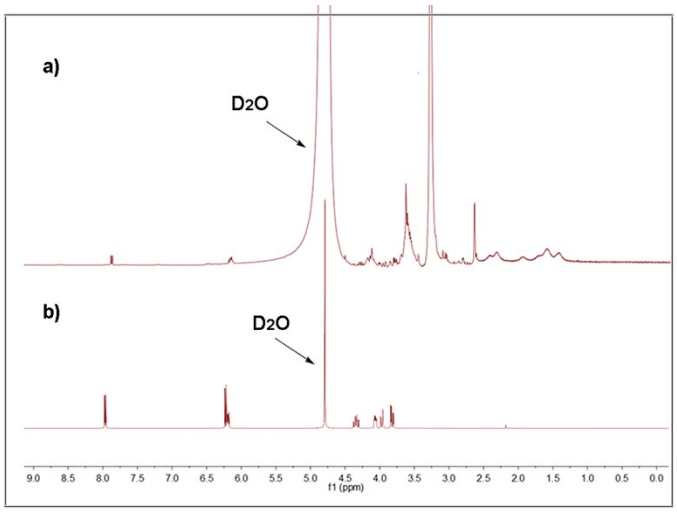


Figure 9S. ^{1}H NMR of Gem@LA-CCM/L2 (a) in D_2O and free Gem in D_2O (b).

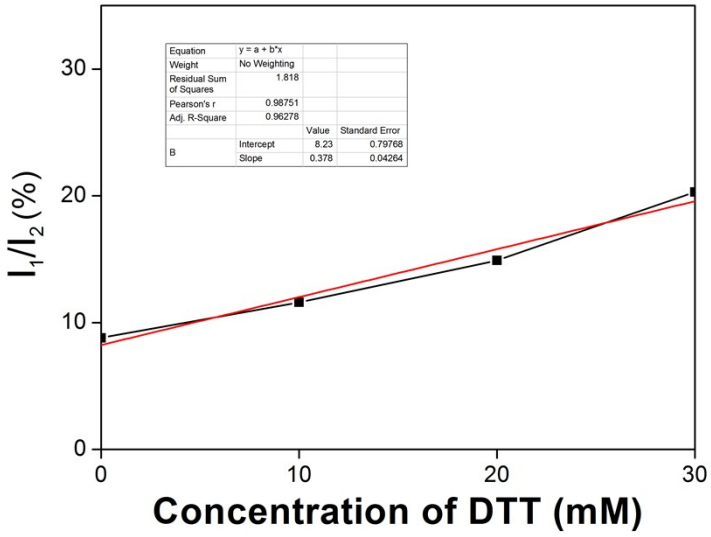


Figure 10S. The fluorescence intensity ratio of acceptor to donor I_1/I_2 (%).

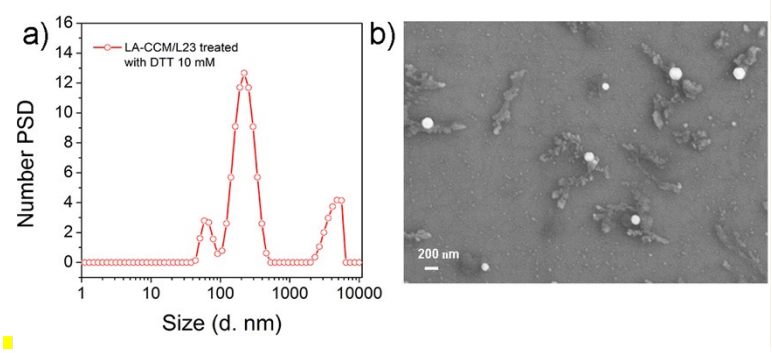
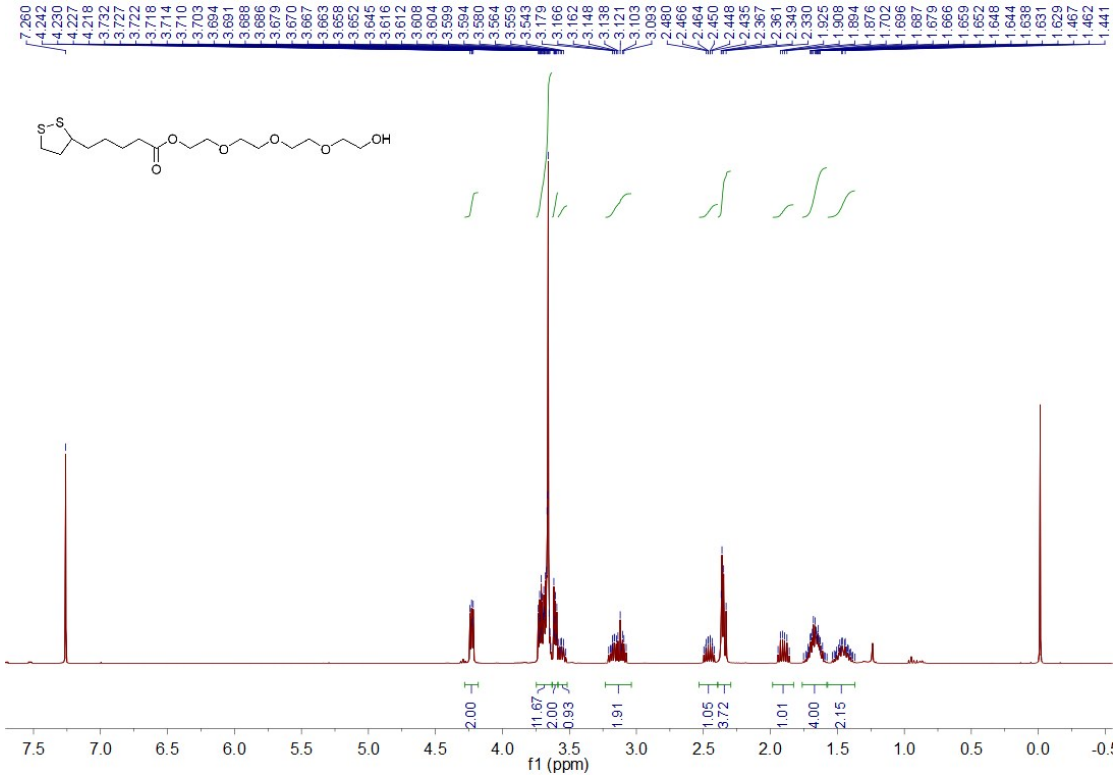
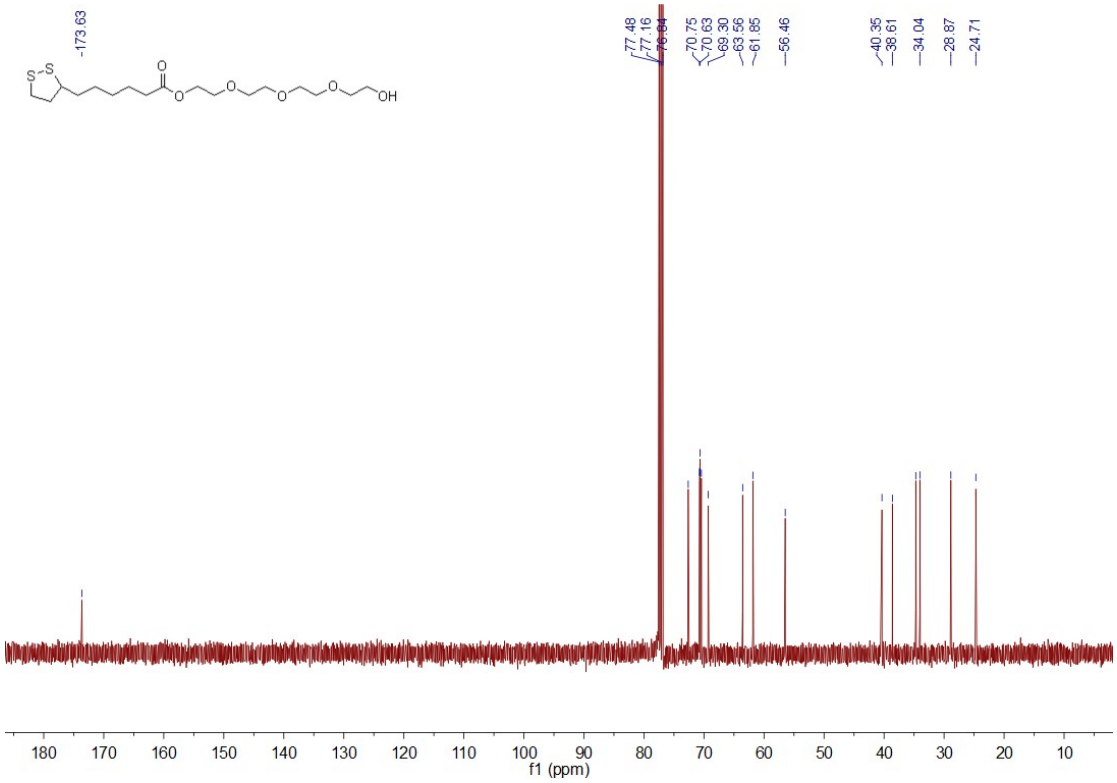
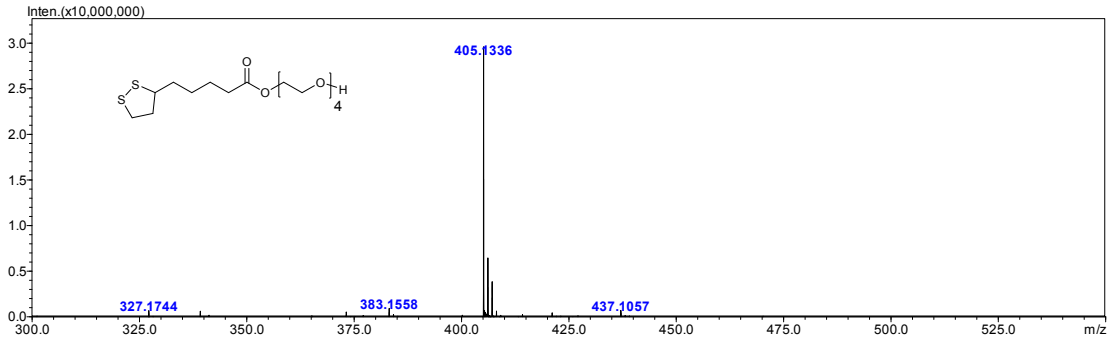


Figure 11S: DLS (a) and SEM (b) of the multivalent platform LA-CCM/L23 by adding DTT (10 mM) at 37 °C in 5 mins.

[1]H, [13]C NMR, and MS Spectra of Key Compounds L1-L5.



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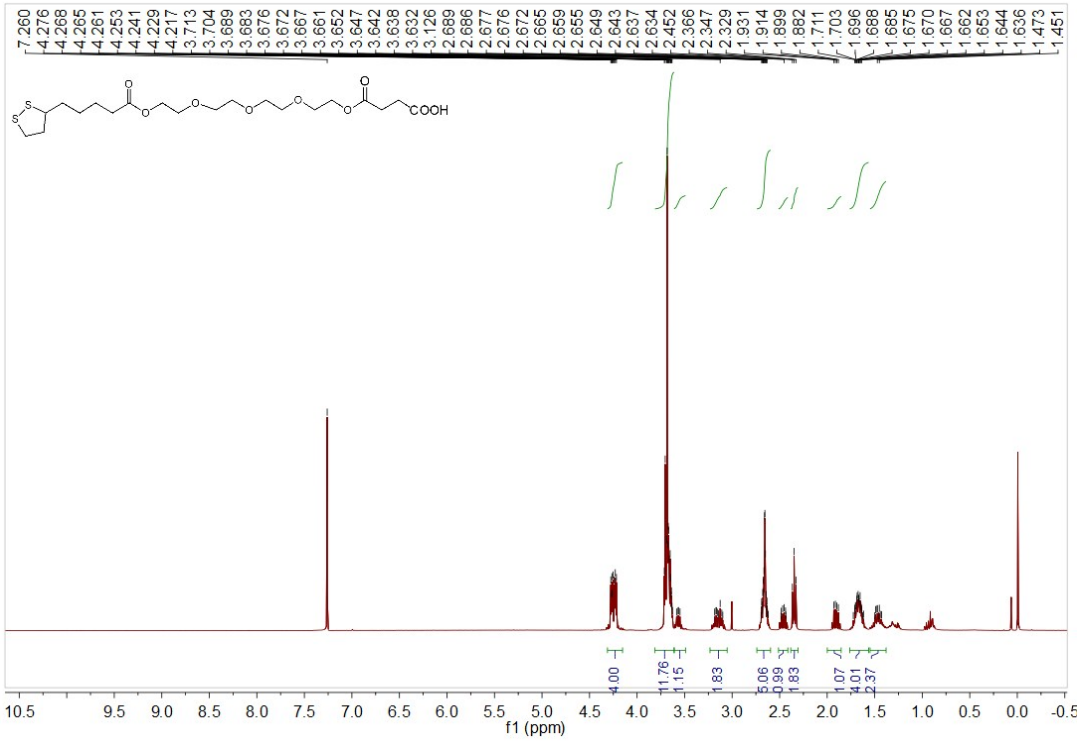
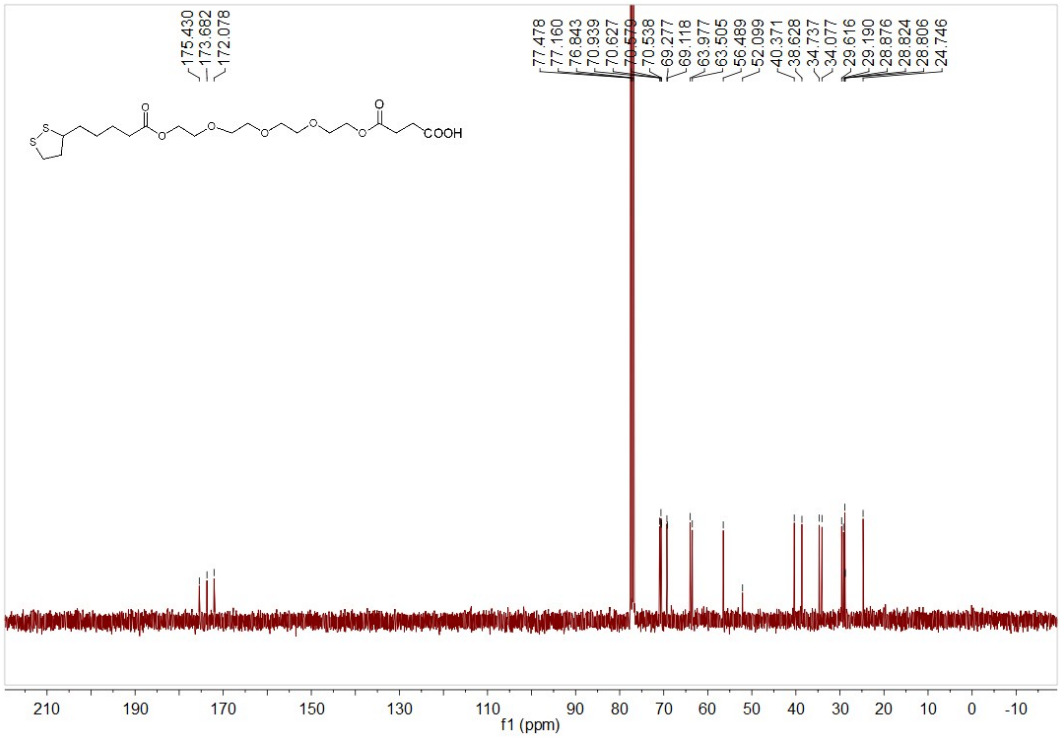
383.1558
437.1057
m/z


COOH
f1 (ppm)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172.078
77.478
77.160
76.843
70.939
70.627
70.538
69.277
69.118
63.977
63.505
56.489
52.099
40.371
38.628
34.737
34.077
29.616
29.190
28.876
28.824
28.806
24.746
COOH
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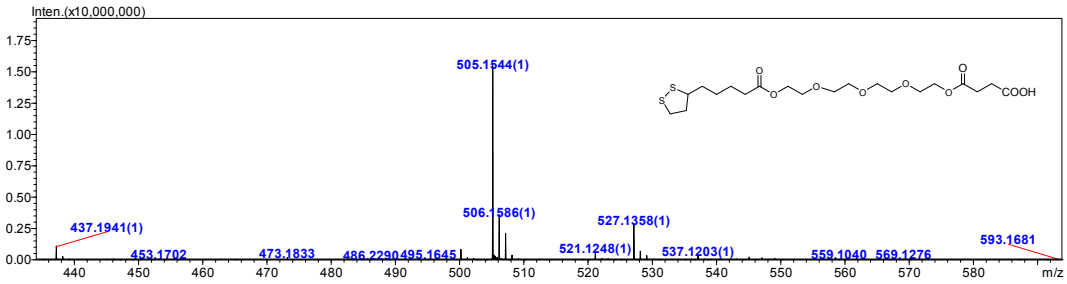
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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1.25
1.00
0.75
0.50
0.25
0.00
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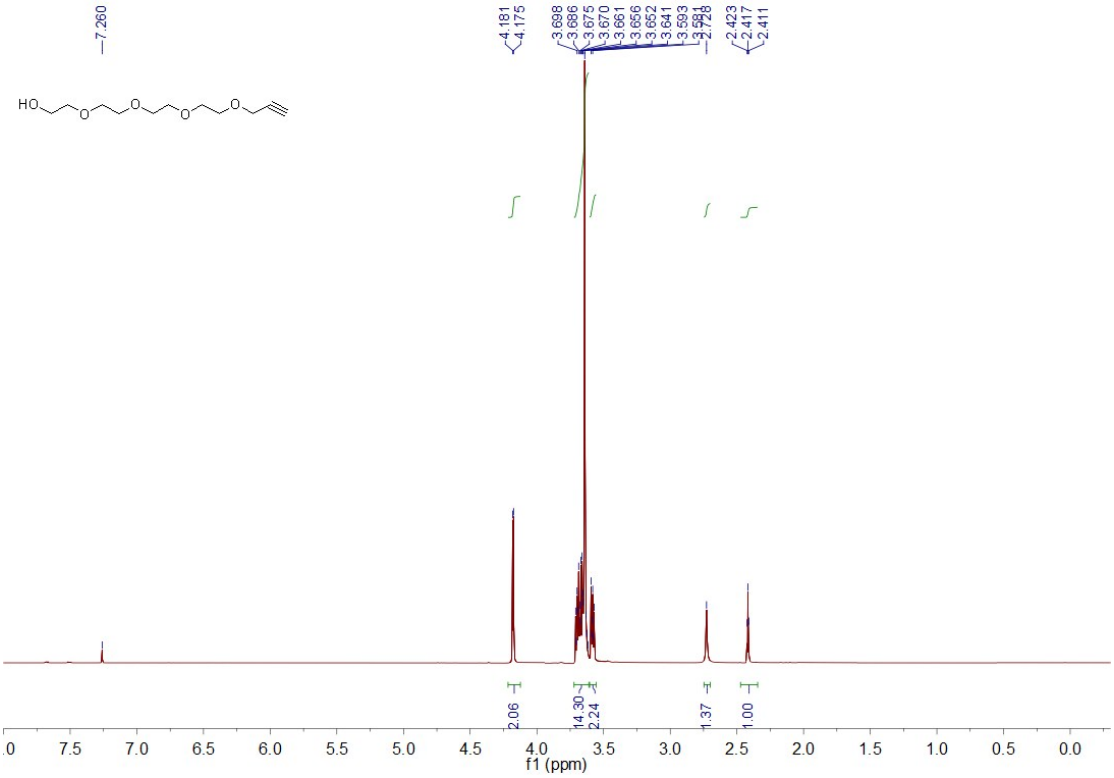
506.1586(1)
527.1358(1)
437.1941(1)
453.1702
473.1833
486.2290
495.1645
521.1248(1)
537.1203(1)
559.1040
569.1276
593.1681
COOH
440
450
460
470
480
490
500
510
520
530
540
550
560
570
580
m/z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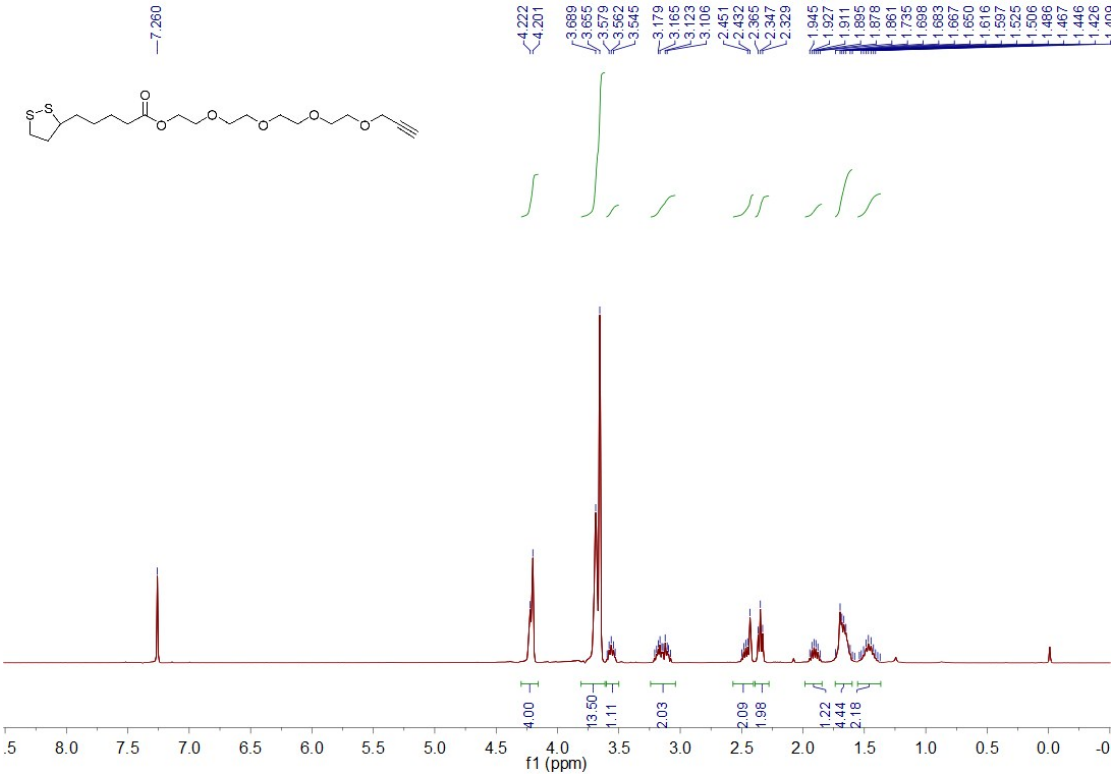
4.181
4.175
3.698
3.686
3.675
3.670
3.661
3.656
3.652
3.641
3.593
2.728
2.423
2.417
2.411
2.06
14.30
2.24
1.37
1.00
f1 (ppm)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3.655
3.579
3.562
3.545
3.179
3.165
3.123
3.106
2.451
2.432
2.365
2.347
2.329
1.945
1.927
1.911
1.895
1.878
1.861
1.735
1.698
1.683
1.667
1.650
1.616
1.597
1.525
1.506
1.486
1.467
1.446
1.426
4.00
13.50
1.11
2.03
2.09
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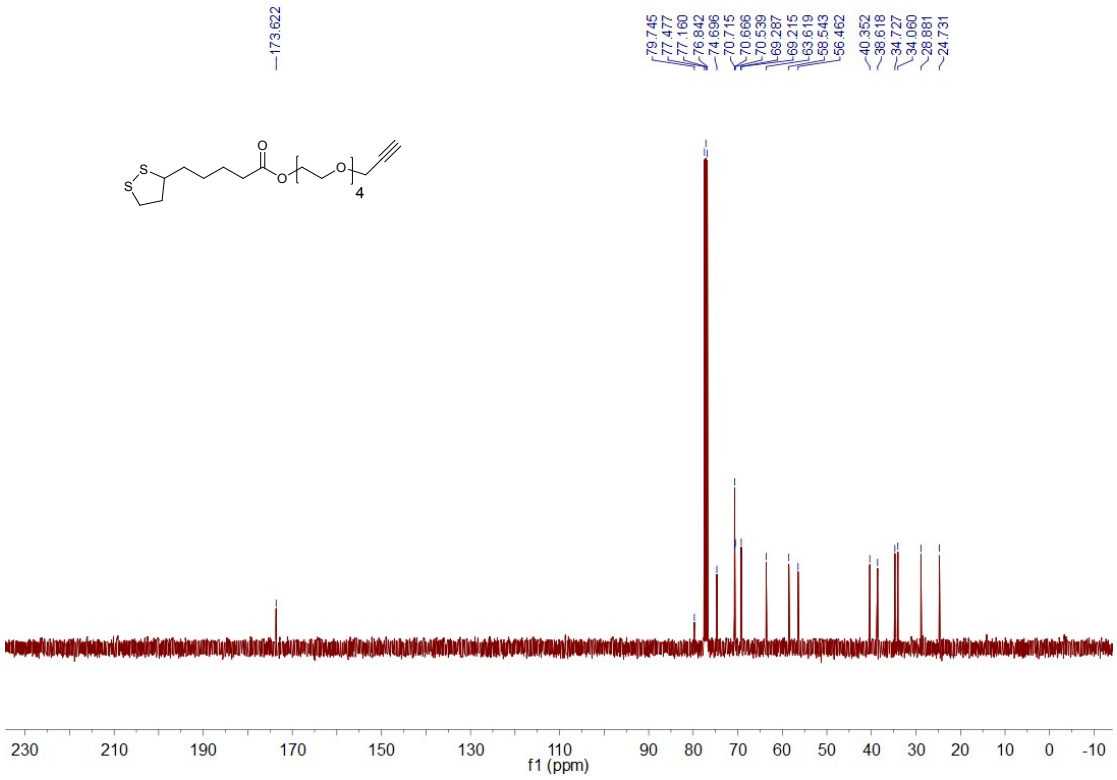
1.22
4.44
2.18
f1 (ppm)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69.215
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58.543
56.462
40.352
38.618
34.727
34.060
28.881
24.731
O
S
S
O
O
4
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190
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150
130
110
90
80
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40
30
20
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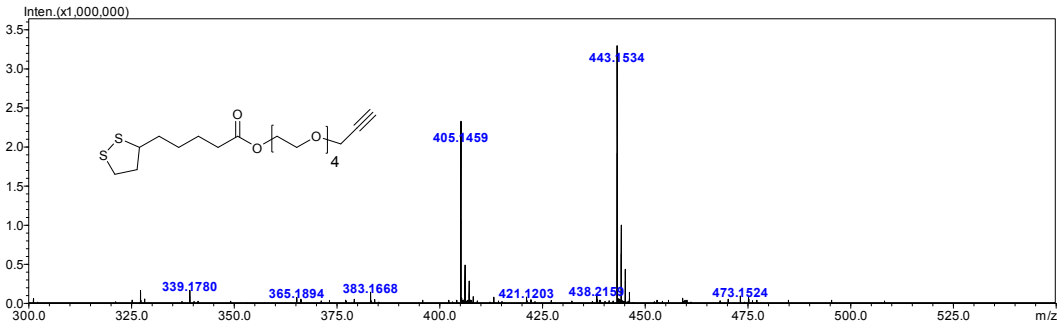
0
-10
f1 (ppm)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339.1780
365.1894
383.1668
421.1203
438.2159
473.1524
O
S
S
O
O
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325.0
350.0
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450.0
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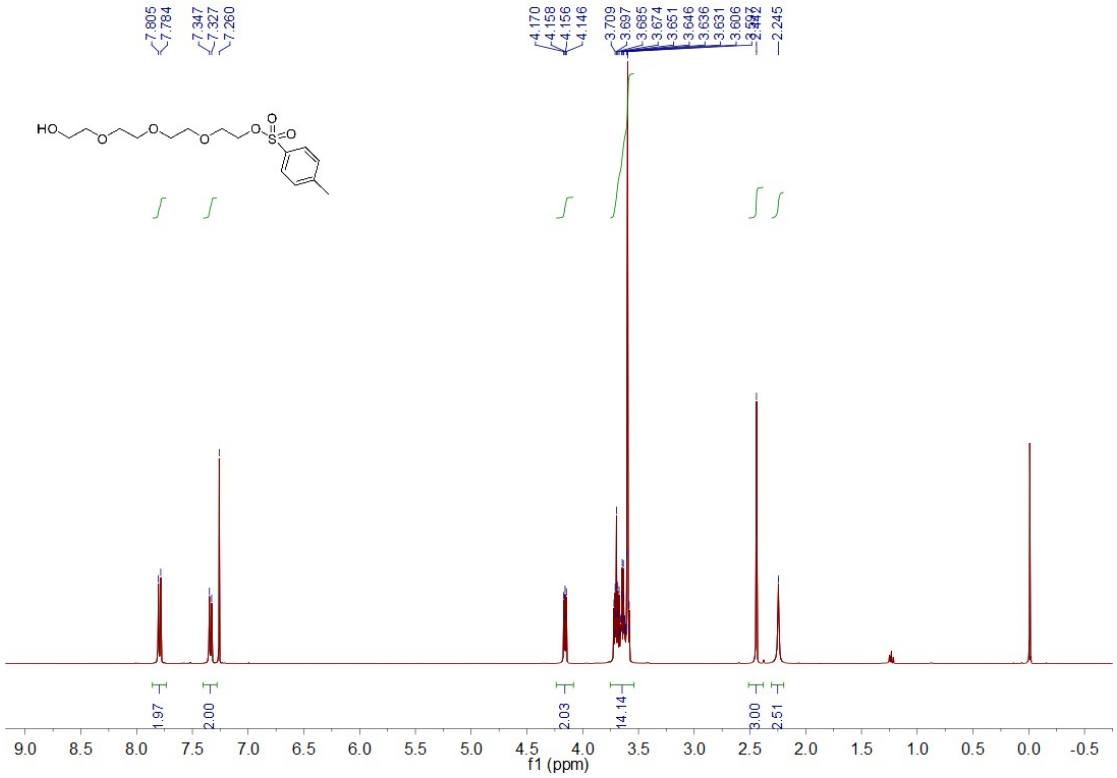
500.0
525.0
m/z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7.347
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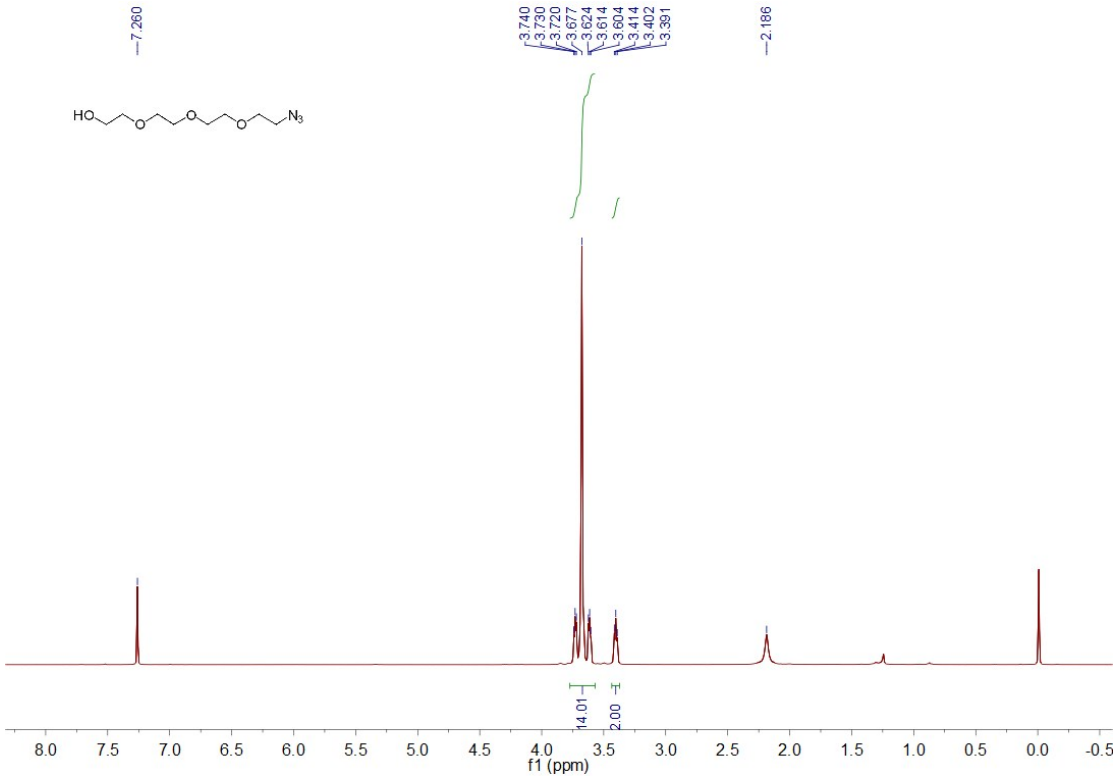
4.158
4.156
4.146
3.709
3.697
3.685
3.674
3.651
3.646
3.636
3.631
3.606
2.245
HO
O
O
O
O
S
O
O
1.97
2.00
2.03
14.14
3.00
2.51
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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3.624
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3.604
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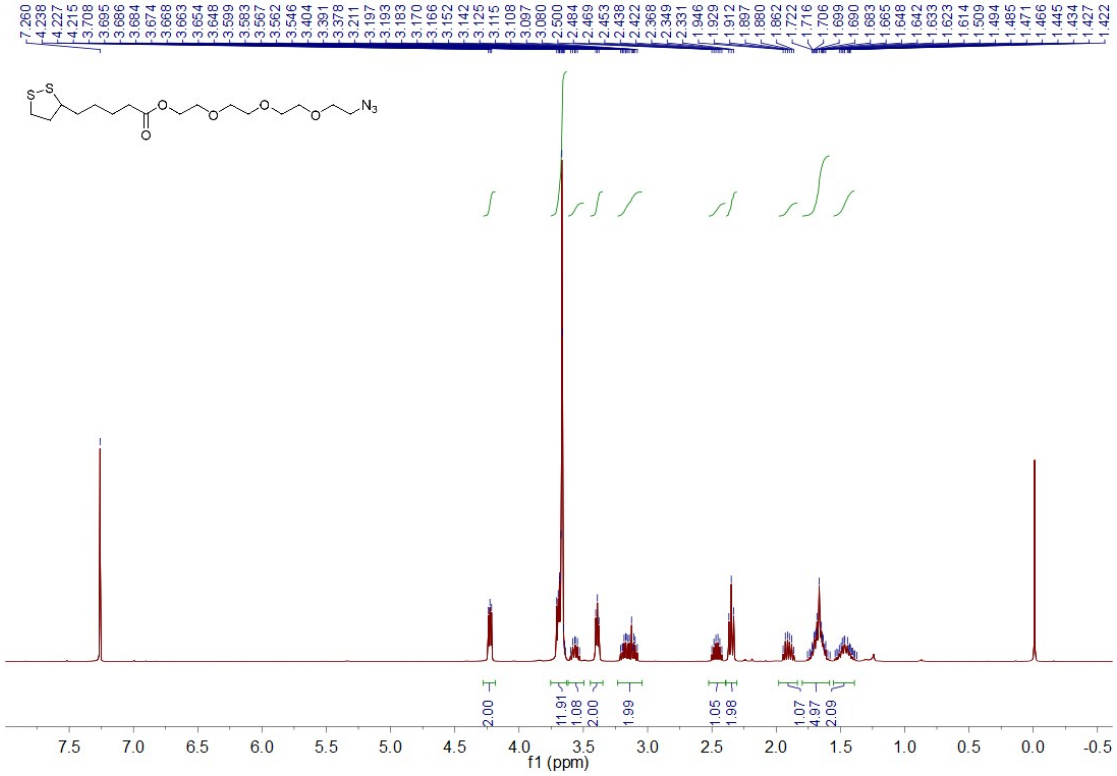
3.402
3.391
2.186
HO
O
O
O
N3
14.01
2.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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3.668
3.663
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3.648
3.599
3.583
3.567
3.562
3.546
3.404
3.391
3.378
3.211
3.197
3.193
3.183
3.170
3.166
3.152
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3.125
3.115
3.108
3.097
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2.349
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1.912
1.897
1.880
1.862
1.722
1.716
1.706
1.699
1.690
1.683
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1.648
1.642
1.633
1.623
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1.509
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1.485
1.471
1.466
1.445
1.434
1.427
1.422
S
S
O
O
O
O
O
O
N3
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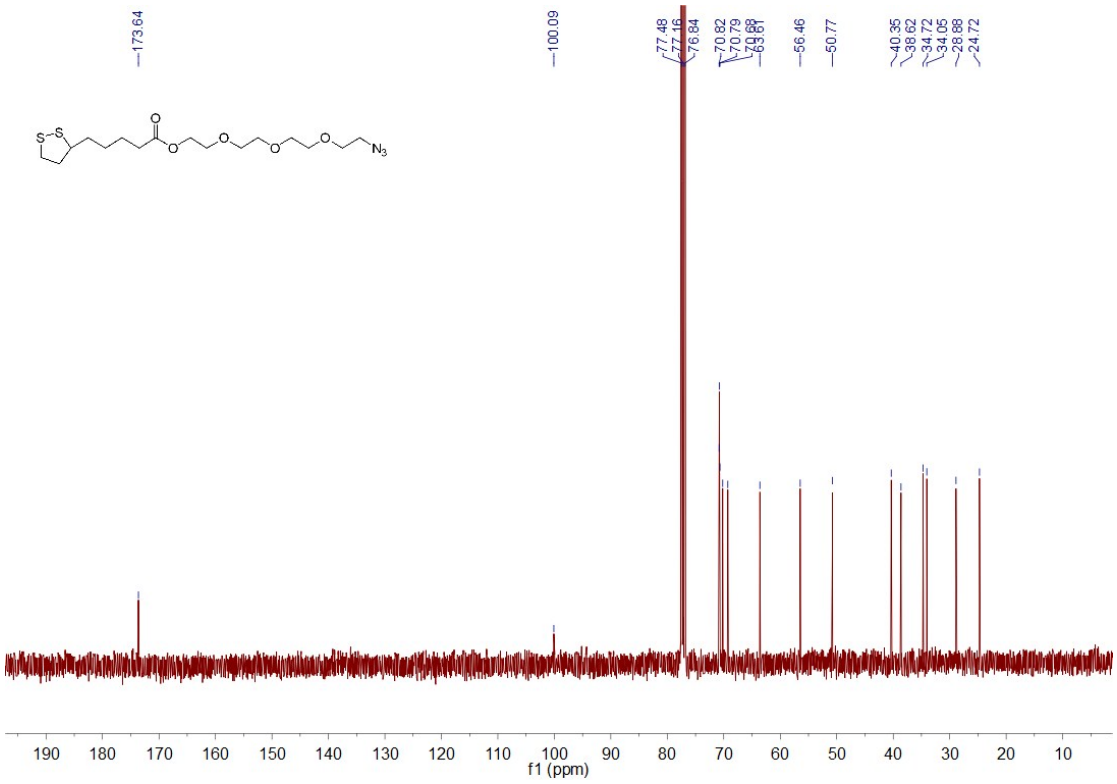
11.91
1.08
2.00
1.99
1.05
1.98
1.07
4.97
2.09
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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70.68
70.61
63.87
56.46
50.77
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38.62
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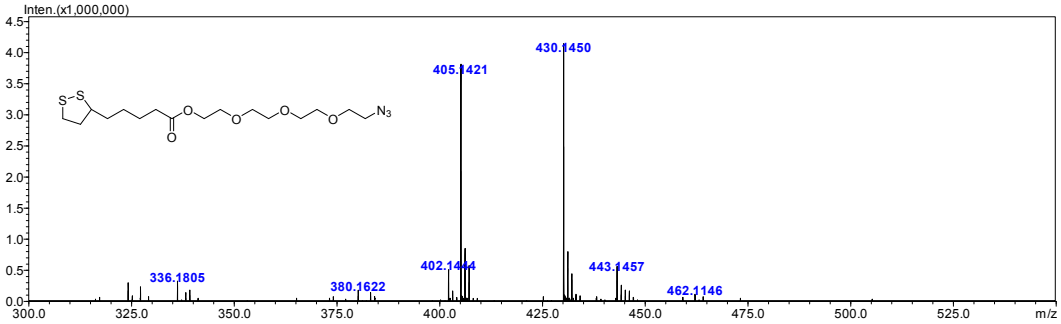
34.05
28.88
24.72
S
S
O
O
O
O
O
O
N3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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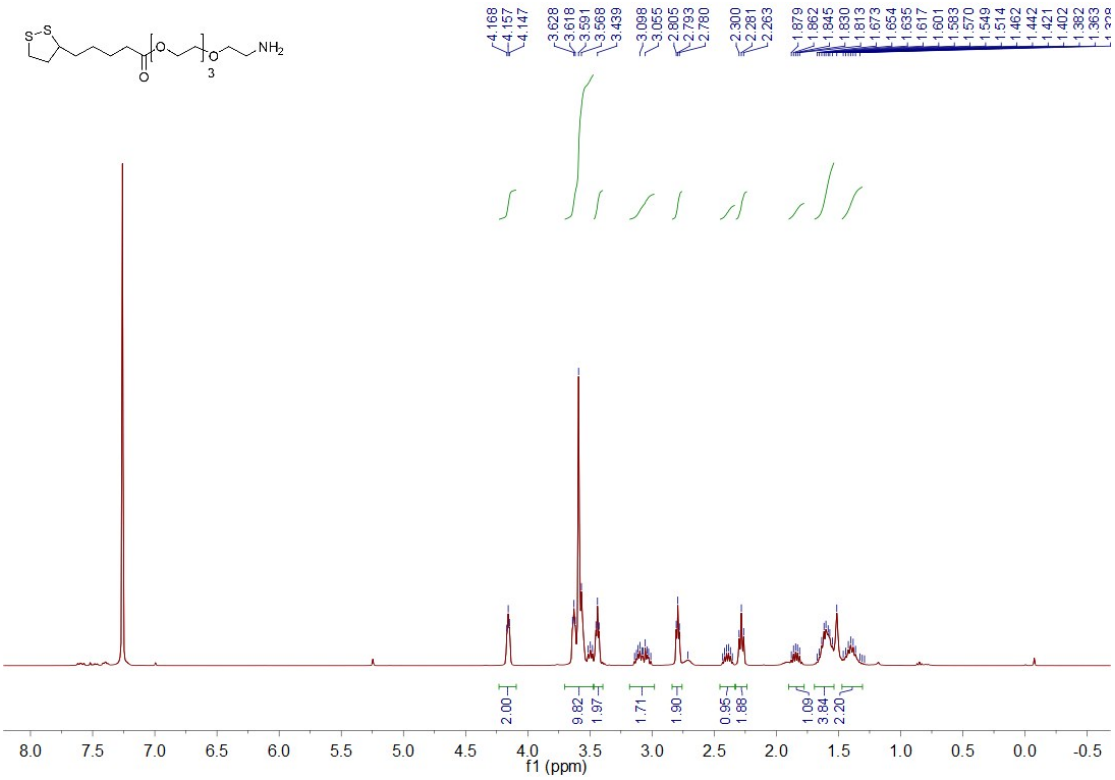
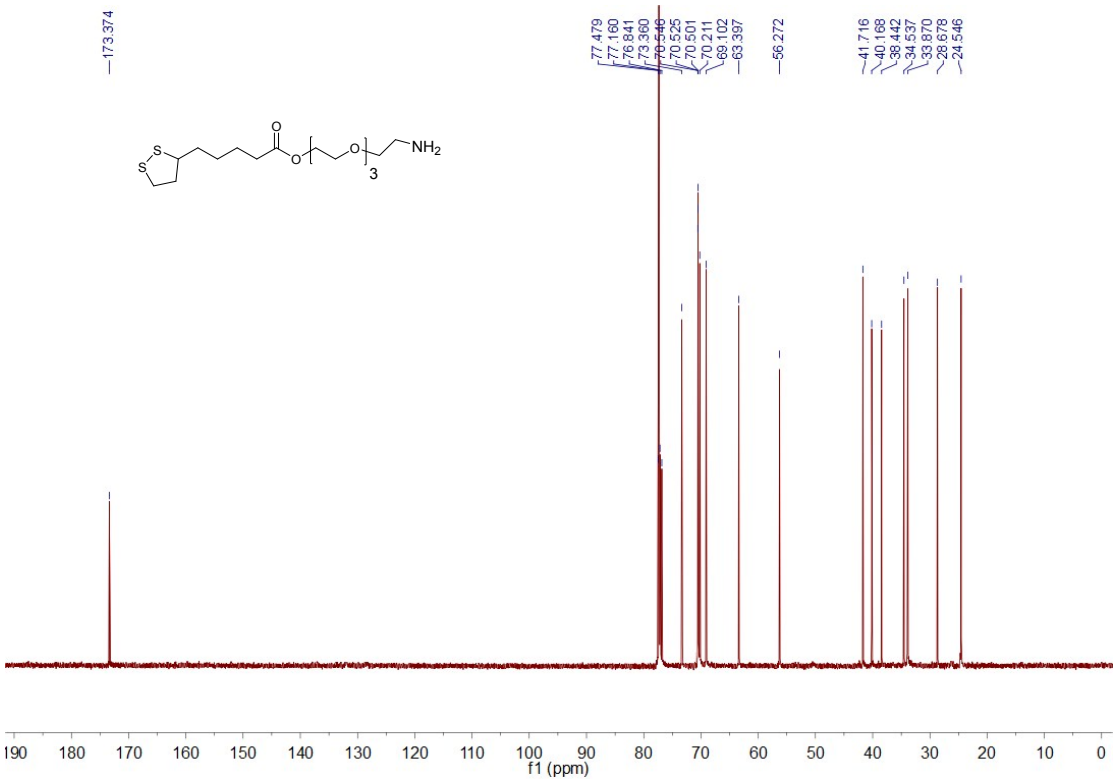
402.1444
443.1457
336.1805
380.1622
462.1146
m/z


f1 (ppm)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69.102
63.397
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41.716
40.168
38.442
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28.678
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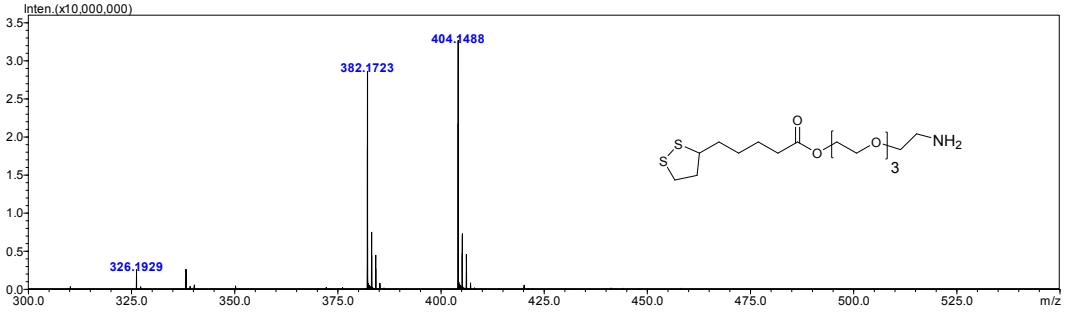
NH2
3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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382.1723
326.1929
NH2
3
300.0 325.0 350.0 375.0 400.0 425.0 450.0 475.0 500.0 525.0 m/z