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Supplementary Information

Dandelion Flower-like Micelles

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General Methods

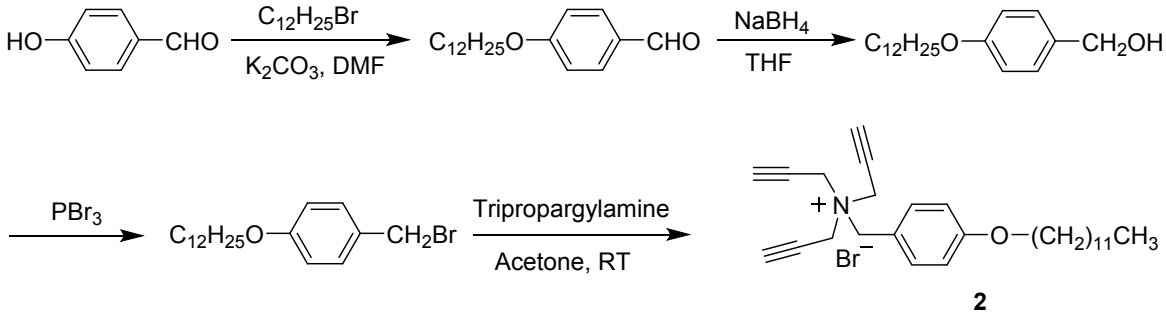
Routine NMR was carried out using a Bruker AV II-400. The ^{1}H NMR chemical shifts were measured relative to DMSO-d_6, $CDCl_3$, or D_2O as internal references (DMSO-d_6: 2.50 ppm, $CDCl_3$: δ 7.26 ppm, D_2O: δ 4.71 ppm). Gel permeation chromatography (GPC) was measured with a Waters-1515 instrument and tetrahydrofuran (THF) was used as the mobile phase at a flow rate of 1.0 mL min^{-1} at 40°C. The molecular weights were reported relative to polystyrene (PS) standards. The particle size was obtained on a Malvern ZetasizerNano ZS90 dynamic light scattering (DLS) analyzer. TEM studies were performed on a Tecnai G2F20S-TWIN instrument operating at 120 kV. Elemental analysis was measured an elemental analyser (Vario MICRO cube, Elementar, Germany) to study the chemical composition of the samples. The Nile Red standard curve and the *in vitro* release of Nile Red (λ_{ex} = 539 nm, λ_{em} = 581 nm) was carried out using a Hitachi F-7000 fluorescence spectrometer with bandwidths of 5.0 nm for excitation and 5.0 nm for emission. Nanoparticle Tracking Analysis (NTA) indirectly measures the size of each nanoparticle from direct observations of diffusion and visualizes populations of nanoparticles in liquids down to 10 nm, providing high-resolution nanoparticle size distributions, which differs from traditional light scattering and other ensemble techniques. We used NTA techniques to measure the changes in the size and trajectories of the DFMs after addition of 20 μM GSH using the following equations: (1) $\mathrm{MSD} = \langle r^2(t) \rangle = \langle \frac{1}{N} \sum_{i=0}^{N} (r_i(t) - r_i(0))^2 \rangle$; (2) $\mathrm{MSD}(t) = 2dD_t$; (3) $\frac{\overline{(x, y)^2}}{4} = D_t$ (where MSD is mean squared displacement, d is dimensionality and D_t is the diffusion coefficient). The directness is studied by comparing the Euclidian distance to the Accumulated distance. The directionality calculations were performed on a Chemotaxis and Migration Tool 2.0 software (Ibidi Company). ($D = \frac{1}{n} \sum_{i=1}^{n} D_i = \frac{1}{n} \sum_{i=1}^{n} \frac{d_{i,euclid}}{d_{i,accum}}$, where D is directness of the particle, $d_{i,euclid}$ is Euclidean

distance (length of straight line between the particle start and end point) and $d_{i,accum}$ is Accumulated distance). Human lung adenocarcinoma cancer (A549) cells were used for all cell experiments and purchased from the Chinese Academy of Science Cell Bank for Type Culture Collection (Shanghai, China). The cells were cultivated in Roswell Park Memorial Institute (RPMI-1640) medium supplemented with 1% (v/v) penicillin/streptomycin and 10% (v/v) fetal bovine serum (FBS) at 37^{o}C under 5% CO_2. Cell toxicity was obtained by measuring the percentage of cell viability using the Cell Counting Kit-8 (CCK-8) solution (Shanghai Qcbio Science & Technologies Co., Ltd.). Fluorescence images of the A549 spheroids were obtained by light sheet fluorescence microscopy (LSFM, Carl Zeiss Lightsheet Z.1) or confocal laser scanning microscopy (CLSM, Leica TCP SP5). Nile Red fluorescence in tumor cells was analyzed by flow cytometry (Becton Dickinson, USA).

Chemicals: 2-hydroxyethyl disulfide, triethylamine (TEA), carbon tetrabromide, ε-caprolactone, stannous octoate, acryloyl chloride, 2-bromoethanol, bromoacetyl bromide, dansyl sulfonyl chloride, n-butylamine, naphthalene, Nile Red, glutathione (GSH), calcein AM and ethidium homodimer-1 were purchased from Tansoole (Shanghai, China). Carmofur (HCFU) was purchased from Aladin (Shanghai, China). All solvents were distilled before use. Deionized water (18.2 MΩ) was used for all aqueous experiments. Spectra/Por® Dialysis Membrane was used for dialysis of materials.

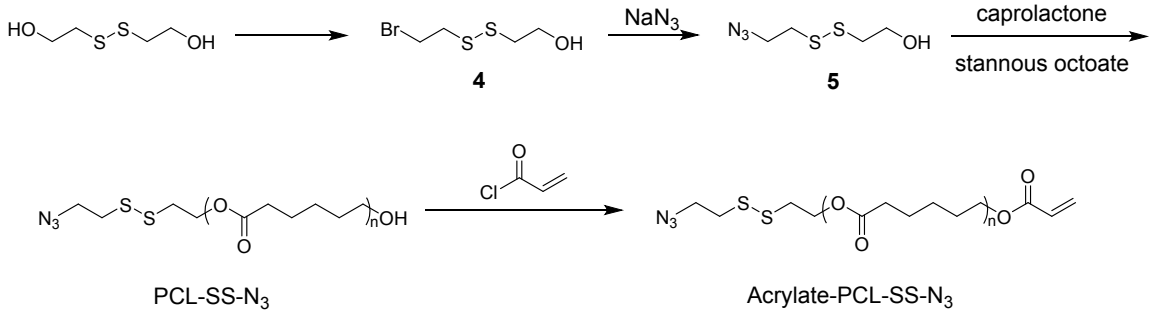
Synthesis

Scheme S1. Synthesis of surfactant **2**.



The above-mentioned compounds were prepared according to our previously reported reference.[1]

Scheme S2. Synthesis of acrylate–PCL–SS–N_3.



2-((2-bromoethyl)disulfanyl)ethanol (4).[2] Triphenylphosphine (1.3 g, 5.0 mmol) was added to an ice-cold solution of 2-hydroxyethyl disulfide (0.77 g, 5.0 mmol) in dichloromethane (300 mL). After the mixture was stirred at 0°C for 15 min, carbon tetrabromide (1.66 g, 5.0 mmol) was added slowly. The mixture was stirred for a further 10 h and then washed with water (2 × 150 mL) and brine (150 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography (20% ethyl acetate in petroleum ether) to afford compound **4** (0.675 g, 62%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.90 (dd, J = 5.9 Hz, 2H, -CH_2CH_2Br), 3.59–3.64 (m, 2H, -CH_2CH_2OH), 3.07–3.12 (m, 2H, -$CH_2SSCH_2CH_2$Br), 2.88–2.90 (m, 2H, -$CH_2SSCH_2CH_2$OH), 2.06 (s, 1H, -$CH_2SSCH_2CH_2OH$).

2-((2-azidoethyl)disulfanyl)ethanol (5).[1] Sodium azide (0.65 g, 10 mmol) was added to a solution of compound **4** (1.08 g, 5 mmol) in dry N,N-dimethylformamide (40 mL), and the mixture was stirred at

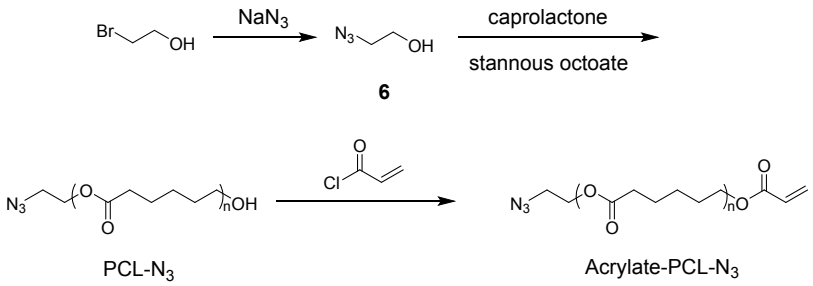
80°C for 10 h. The product was extracted three times with ethyl ether. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Following filtration and evaporation, the product was dried under a vacuum to give compound **5** (0.643 g, 78%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.89 (t, J = 5.8 Hz, 2H, -CH_2CH_2OH), 3.60 (t, J = 6.8 Hz, 2H, -$CH_2CH_2N_3$), 2.85–2.89 (m, 4H, -CH_2SSCH_2-), 1.99 (s, 1H, -CH_2CH_2OH).

PCL–SS–N_3.[3] PCL–SS–N_3 was synthesized by ring-opening polymerization (ROP) of ε-caprolactone (CL), with compound **5** as the initiator and $Sn(Oct)_2$ as the catalyst. The feed ratio of CL to compound 5 was 100/1 (M_{CL}/M_5). Briefly, CL (11.4 g, 100 mmol), compound **5** (179 mg, 1 mmol), and $Sn(Oct)_2$ (0.003 mg) were added to a 50-mL reactor. The reactor was degassed with three freeze-evacuate-thaw cycles. The reaction was stirred at 100°C under N_2 for 12 h. The resulting PCL–SS–N_3 was dissolved in dichloromethane and precipitated four times in methanol. The purified PCL–SS–N_3 was dried under a vacuum at 25°C (yield: 80%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.33 (t, J = 6.5 Hz, 2H, -$SSCH_2CH_2$OCO-), 4.05 (t, J = 6.7 Hz, 158H, -$CH_2CH_2CH_2CH_2CH_2$OCO-), 3.58 (t, J = 6.8 Hz, 2H, $N_3CH_2CH_2$SS-), 2.93 (t, J = 6.5 Hz, 2H, $N_3CH_2CH_2SSCH_2CH_2$-), 2.86 (t, J = 6.8 Hz, 2H, $N_3CH_2CH_2SSCH_2CH_2$-), 2.29 (t, J = 7.5 Hz, 161H, -$CH_2CH_2CH_2CH_2CH_2$OCO-), 1.60–1.68 (m, 326H, -$CH_2CH_2CH_2CH_2CH_2$OCO-), 1.35–1.41 (m, 167H, -$CH_2CH_2CH_2CH_2CH_2$OCO-).

Acrylate–PCL–SS–N_3.[4] The terminal esterification of PCL–SS–N_3 to synthesize acrylate–PCL–SS-N_3 was performed as follows: PCL–SS–N_3 6 (930 mg, 0.1 mmol) and TEA (101 mg, 1 mmol) were dissolved in 5 mL 1,2-dichloroethane. After the mixture was stirred at 0°C for 15 min, acryloyl chloride (80%, 113 mg, 1 mmol) in 5 mL 1,2-dichloroethane was added dropwise. Subsequently, the reaction mixture was stirred at 25°C for a further 3 h and then refluxed for 1 day. The resulting Acrylate–PCL–SS–N_3 was dissolved in dichloromethane and precipitated four times in methanol. The purified acrylate–

PCL–SS–N_3 was dried under a vacuum at 25°C (701 mg, yield: 75%).[1]H NMR (400 MHz, $CDCl_3$, δ): 6.37–6.42 (m, 1H, -CH_2CH_2OCOCH=C*H*H), 6.08–6.15 (m, 1H, -CH_2CH_2OCOC*H*=CH_2), 5.80–5.83 (m, 1H, -CH_2CH_2OCOCH=CH*H*), 4.33 (t, J = 6.4 Hz, 2H, -$SSCH_2C$*H*$_2OCO$-), 4.05 (t, J = 6.7 Hz, 170H, -$CH_2CH_2CH_2CH_2C$*H*$_2OCO$-), 3.64–3.67 (m, 2H, N_3C*H*$_2CH_2SS$-), 2.88–2.93 (m, 4H, N_3CH_2C*H*$_2SSC$*H*$_2CH_2$-), 2.30 (t, J = 7.5 Hz, 167H, -C*H*$_2CH_2CH_2CH_2CH_2OCO$-), 1.60–1.68 (m, 338H, -CH_2C*H*$_2CH_2C$*H*$_2CH_2OCO$-), 1.34–1.41 (m, 172H, -CH_2CH_2C*H*$_2CH_2CH_2OCO$-).

Scheme S3. Synthesis of acrylate–PCL–N_3.



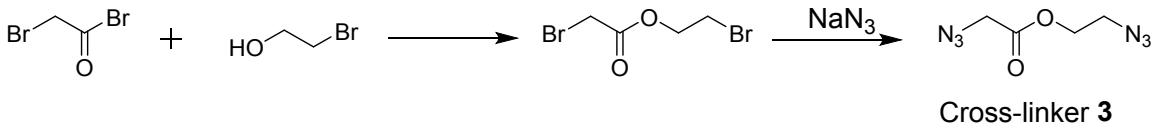
2-azidoethanol (6).[1, 5] Sodium azide (3.90 g, 50.0 mmol) was added to a solution of 2-bromoethanol (6.24 g, 60.0 mmol) in water (15 mL). The reaction mixture was heated at 100°C for 12 h, quenched with water (200 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was washed with saturated NaCl solution (3 × 30 mL) and concentrated under a vacuum to give compound **6** as a colorless oil (3.51 g, 86%). [1]H NMR (400 MHz, $CDCl_3$, δ): 3.78 (t, J = 5.08 Hz, 2H, -C*H*$_2$OH), 3.44 (t, J = 4.84 Hz, 2H, -C*H*$_2N_3$), 1.99 (s, 1H, -CH_2O*H*).

PCL–N_3.[3] PCL-N_3 was synthesized by the ROP of CL, with 2-azidoethanol as the initiator. $Sn(Oct)_2$ was used as the catalyst. The feed ratio of CL to 2-azidoethanol was 100/1 (M_{CL}/M_6). Briefly, CL (11.4 g, 100 mmol), 2-azidoethanol (87 mg, 1 mmol), and $Sn(Oct)_2$ (0.003 mg) were added to a 50-mL reactor. The reactor was degassed with three freeze-evacuate-thaw cycles. The reaction was stirred to reflux under N_2 for 12 h. The resulting PCL-N_3 was dissolved in dichloromethane and precipitated four

times in methanol. The purified PCL–N_3 was dried under a vacuum at 25°C (9.7 g, yield: 85.0%).^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.25 (t, J = 5.0 Hz, 2H, $N_3CH_2CH_2OCO$-), 4.05 (t, J = 6.7 Hz, 169H, -$CH_2CH_2CH_2CH_2CH_2OCO$-), 3.64 (t, J = 6.5 Hz, 2H, $HOCH_2CH_2CH_2CH_2CH_2OCO$-), 3.47 (t, J = 5.1 Hz, 2H, $N_3CH_2CH_2OCO$-), 2.30 (t, J = 7.5 Hz, 173H, -$CH_2CH_2CH_2CH_2CH_2OCO$-), 1.62–1.66 (m, 351H, -$CH_2CH_2CH_2CH_2CH_2OCO$-), 1.35–1.40 (m, 181H, -$CH_2CH_2CH_2CH_2CH_2OCO$-).

Acrylate–PCL–N_3.[4] The terminal esterification of PCL–N_3 to synthesize acrylate–PCL–N_3 was performed as follows: PCL–N_3 (890 mg, 0.1 mmol) and TEA (101 mg, 1 mmol) were dissolved in 5 mL 1,2-dichloroethane at 0°C. Acryloyl chloride (80%, 113 mg, 1 mmol) in 10 mL 1,2-dichloroethane was added dropwise. Subsequently, the reaction mixture was stirred at 25°C for 3 h and then refluxed for 1 day. The resulting acrylate–PCL–N_3 was dissolved in dichloromethane and precipitated four times in methanol. The purified acrylate–PCL–SS–N_3 was dried under a vacuum at 25°C (676 mg, yield: 71.7%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.37–6.42 (m, 1H, -CH_2CH_2OCOCH=CHH), 6.08–6.15 (m, 1H, -CH_2CH_2OCOCH=CH_2), 5.80–5.83 (m, 1H, -CH_2CH_2OCOCH=CHH), 4.23 (t, J = 6.3 Hz, 2H, $N_3CH_2CH_2OCO$-), 4.05 (t, J = 6.7 Hz, 152H, -$CH_2CH_2CH_2CH_2CH_2OCO$-), 3.47–3.68 (m, 2H, $N_3CH_2CH_2OCO$-), 2.30 (t, J = 7.5 Hz, 152H, -$CH_2CH_2CH_2CH_2CH_2OCO$-), 1.60–1.68 (m, 303H, -$CH_2CH_2CH_2CH_2CH_2OCO$-), 1.34–1.41 (m, 163H, -$CH_2CH_2CH_2CH_2CH_2OCO$-).

Scheme S4. Synthesis of crosslinker **3**.



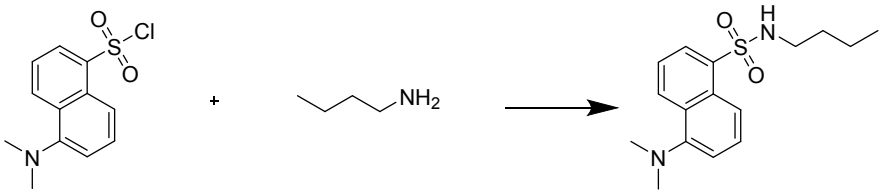
Cross-linker **3**

2-Bromoethyl bromoacetate.[6] Potassium carbonate (13 mmol, 1.79 g) in water (30 mL) was added to an ice-cold solution of 2-bromoethanol (10 mmol, 1.24 g) in dichloromethane (300 mL). After the

mixture was stirred at 0°C for 15 min, bromoacetyl bromide (13 mmol, 2.61 g) in dichloromethane (30 mL) was added drop-wise. The mixture was stirred for 3 h, and the organic phase was separated, dried over Na_2SO_4, filtered, and evaporated to give the product at 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.63 (dd, J = 6.1 Hz, 2H, -OCOCH_2CH$_2$Br), 3.88 (s, 2H, BrCH_2OCO-), 3.53 (t, J = 6.1 Hz, 2H, -OCOCH$_2$CH_2Br).

Crosslinker 3.[7] Sodium azide (1.95 g, 30 mmol) was added to a solution of 2-bromoethyl bromoacetate (1.22 g, 5 mmol) in DMF (30 mL), and the mixture was heated at 80°C for 10 h. The product was extracted three times with ethyl acetate. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Following filtration and evaporation, the product was dried under a vacuum to give crosslinker **3** as a yellow oil (714 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.36 (t, J = 5.2 Hz, 2H, -OCOCH_2CH$_2$N$_3$), 3.94 (s, 2H, N$_3$CH_2OCO-), 3.53 (t, J = 5.0 Hz, 2H, -OCOCH$_2$CH_2N$_3$).

Scheme S5. Synthesis of dansyl-n-butyl sulfonamide.



Dansyl-n-butyl sulfonamide.[8] N-butylamine (1.46 g, 20 mmol) in acetonitrile (10 mL) was added to a solution of dansyl sulfonyl chloride (1.35 g, 5 mmol) in acetonitrile (30 mL), and the mixture was heated at 40°C for 3 h. The solvent was removed and the residue solid was dissolved in CH_2Cl_2 (40 mL). The organic phase were washed with brine and dried over anhydrous Na_2SO_4. Following filtration and evaporation, the product was dried under a vacuum to give dansyl-n-butyl sulfonamide as light-green solid (1.25 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.58 (d, J = 8.2 Hz, 1H, aryl H), 8.32 (d, J = 8.6 Hz, 1H, aryl H), 8.25 (d, J = 7.3 Hz, 1H, aryl H), 7.52–7.59 (m, 2H, aryl H), 7.21 (d, J = 7.4 Hz, 1H,

aryl H), 4.65 (t, J = 5.8 Hz, 1H, -N*H*$CH_2CH_2CH_2CH_3$), 2.85–2.91 (m, 6H, –N(CH_3)$_2$), 1.32–1.39 (m, 2H, -NHC*H*$_2CH_2CH_2CH_3$), 1.09–1.13 (m, 4H, -$NHCH_2CH_2CH_2CH_3$), 0.71–0.75 (m, 3H, -$NHCH_2CH_2CH_2CH_3$).

Preparation of the SCMs.[1] SCMs were synthesized in our laboratory according to our previously reported procedures. Briefly, $CuCl_2$ (10 μL 6.7 mg/mL aqueous solution, 0.5 μmol) and crosslinker **3** (4.3 mg, 0.025 mmol) were added to a solution of **2** (9.7 mg, 0.02 mmol) in deionized water (2.0 mL). Sodium ascorbate (10 μL 99 mg/mL aqueous solution, 5 μmol) was added drop-wise to the above solution. The solution was stirred slowly at 25°C for 36 h and further purified by dialysis against deionized water (Spectra/Pore, MWCO 1000).

Typical preparation of the DMFs and nDMFs.[9] The SCMs were prepared as described above. After cross-linking, acrylate–PCL–SS–N_3 or acrylate–PCL–N_3 (3.7 mg) in THF (4 mL), and $CuCl_2$ (10 μL 6.7 mg/mL aqueous solution, 0.5 μmol) were added to the solution of SCMs (10 mM, 2.0 mL). Sodium ascorbate (10 μL 99 mg/mL aqueous solution, 5 μmol) was added drop-wise to the above solution. Following another 12-h incubation at 25°C, the PCL-functionalized SCMs were further purified by dialysis against deionized water (MWCO: 350 kDa) to obtain a translucent solution with good Tyndall phenomenon. The cross-linked procedure of DFMs is described as follows. Divinylbenzene (DVB, 5.6 μL, 0.01 mmol in DMSO) was added to the above solution. The mixture was subjected to ultrasonication for 10 min and purified by dialysis against deionized water (MWCO: 1000 Da) to remove excess DVB. Then the 2,2-dimethoxy-2-phenylacetophenone (DMPA,10 μL 13.0 mg/mL solution in DMSO, 0.0005 mmol) were added to the solution. The reaction mixture was purged with N_2 for 30 min, transferred to a glass vial, and irradiated in a Rayonet reactor for 6 h to obtain a solution of DMFs or nDMFs. Routine ^{1}H NMR was used to monitor the progress of reaction. Since the value of

reactivity ratios in copolymerization of DVB and racrylate group is both less than 1 ($r_{DVB} < 1$, $r_{racrylate\ group} < 1$), the chain radicals prefer to react with another monomer.[10, 11] At the end of the copolymerization between DVB and acrylate group, the chain architecture of copolymers alternately arrange DVB and acrylate groups (**Figure** S3). Therefore, almost all DVB molecules involving in photoreaction tended to participate in the cross-linking process to obtain the core cross-linked DFMs.

Moreover, for calculation of DVB entrapment efficiency (EE), the DVB in DFMs was extracted with ethyl acetate for three times. The content of the hydrophobic DVB measured by UV spectroscopy (**Figure** S4), and the EE was calculated as follows: EE (%) = (weight of loaded DVB / initial weight of DVB) × 100%. The encapsulation efficiency for DVB loaded DFMs are in the range of 23.5 ~ 26.9%.

Typical preparation of the SCMs@D, SCMs@NR, and SCMs@HCFU.[7, 12] The materials were synthesized following our previous method. Briefly, naphthalene (D), Nile Red (NR), or HCFU in acetone (3 mg/mL, 100 μL) was added to a glass vial. Acetone was evaporated overnight, and a micellar solution of **2** (10 mM, 2.0 mL) was added. The combined solution was sonicated for 4 h in the dark until the D, NR, or HCFU dissolved. Crosslinker **3** (4.3 mg, 0.025 mmol), $CuCl_2$ (10 μL 6.7 mg/mL aqueous solution, 0.5 μmol), and sodium ascorbate (10 μL 99 mg/mL aqueous solution, 5 μmol) were added to the above mixture, which was stirred slowly at room temperature for 24 h and further purified by dialysis against deionized water (Spectra/Pore, MWCO 1000) to obtain SCMs@D (8.5 ± 1.6 nm), SCMs@NR (8.9 ± 1.9 nm), or SCMs@HCFU (12.5 ± 2.3 nm). The excess cargo was removed using a 0.45 μm filter. The loading content of SCMs@D and SCMs@NR were evaluated by fluorescence spectra (**Figure** S11 and **Figure** S18). The loading content (LC) for SCMs@D and SCMs@NR are in the range of 1.54–4.22% and 2.12–5.61%, respectively. The loading content of SCMs@HCFU was

analyzed using a high-performance liquid chromatography (HPLC) system (Waters Isocratic HPLC Pump, US). The loading content (LC) for SCMs@HCFU is in the range of 2.54–5.43%.

Typical preparation of the DMFs@NR, nDMFs@NR, DMFs@HCFU, nDMFs@HCFU, DMFs@D, DMFs@A and DMFs@D&A.[7, 12] DMFs@D, DMFs@NR, nDMFs@NR, DMFs@HCFU, and nDMFs@HCFU used in our work were synthesized similar to empty DFMs and nDMFs. DMFs@A and DMFs@D&A were synthesized using a micelle extraction technique (**Figure** S9). Prior to loading, the given solution of dansyl-n-butyl sulfonamide (A, 3 mg/mL, 100 μL) was added in a vial. Acetone was evaporated overnight, and a micellar solution of DMFs (2.0 mL) or DMFs@D (2.0 mL) was added and ultrasonicated for 3 h to achieve maximum loading, respectively. The excess A was filtered using a 0.45μm filter. The A loading content (LC) for DMFs@A and DMFs@D&A are in the range of 3.21–4.18% and 3.19–4.09%, respectively (**Figure** S12).

Characterization of acrylate–PCL–SS–SCMs and acrylate–PCL–SCMs.[12] The critical micelle concentration (CMC) of the obtained acrylate–PCL–SS–SCMs and acrylate–PCL–SCMs was studied by fluorescence spectroscopy using pyrene as a probe. The material concentration was varied from 1.0×10^{-2} to 200 μg/mL. The pyrene concentration was finally fixed at 5.4×10^{-6} M. The mixed solution was sonicated for 2 h. Fluorescence excitation spectra were obtained using a Hitachi F-7000 fluorescence spectrometer at a wavelength range of 285 to 355 nm, with bandwidths of 5.0 nm for excitation and 5.0 nm for emission.

DFMs@HCFU and nDFMs@HCFU release assay.[13] Evaluation of the release of the DFMs@HCFU and nDFMs@HCFU was carried out using the dialysis method (**Figure** S21). In brief, 10 mL DFMs@HCFU or nDFMs@HCFU solution (3 mg/mL) was added to a dialysis bag (MWCO: 350 kDa). The dialysis bag was immersed in 100 mL PBS buffer containing 20 μM GSH. The dialysis

system was maintained at 37°C in a thermostatic incubator with a shaking speed of 120 rpm. 1.0 mL solution was collected from the corresponding different reservoirs, and 1.0 mL buffer solution (pH = 7.4) was simultaneously added to the reservoir at predetermined periods. Candida antarctica lipase B (5 U/mL) was added to the aqueous sample solutions. Following a further 24 h at 37°C in a thermostatic incubator, HCFU was extracted three times with ethyl acetate. The samples were detected by a high-performance liquid chromatography (HPLC) system (Waters Isocratic HPLC Pump, US). The release data were averaged from triplicate.

Cell viability assay.[13] To evaluate the cytocompatibility of drug-free DFMs and nDFMs, A549 cells were seeded in 96-well culture plates and incubated at 37 °C under 5% CO_2. The culture media were removed and replaced with of fresh media (200 μL) containing various concentrations of micelle solutions. After 48 h, the culture media were removed and fresh media (100 μL) containing 10 μL Cell Counting Kit-8 (CCK-8) solution was added to each well. The culture plates were incubated at 37 °C for another 2 h. The absorbance of each sample at 450 nm was recorded using a Varioscan Flash microplate instrument.

Penetrating ability of the DFMs@NR, DFMs@NR, and SCMs@NR into multicellular tumor spheroids (MTSs).[14] Human lung adenocarcinoma A549 cell-based multicellular tumor spheroids were cultivated using the liquid overlay method. Briefly, 6-well plates were coated with 1 mL sterile 1% agar, followed by seeding of a single-cell suspension. Cells were cultured at 37°C with 5% CO_2 until the MTSs reached approximately 300 μm in diameter. According to our previously research, flow cytometry data showed the cell influx amount of the nanoparticles with similar surface properties in 3 h was less than 5% of that in 12 h.[15, 16] So the MTSs were firstly co-incubated with DFMs@NR, nDFMs@NR, or SCMs@NR (20 μg/mL, NR) for 3 h, confirming that overwhelming majority of the

nanopaticles would permeate into the extracellular matrix of the MTSs. Followed by a 24-h incubation in the presence of 20 μM GSH, the spheroids were subjected to LSFM scanning after washing with PBS buffer. For quantitative cellular uptake analysis, the single-cell suspension was obtained from the MTSs using Accutase™ reagent (Invitrogen, USA), and washed with PBS (pH = 7.4) and subjected to flow cytometry analysis in triplicate.

***In vitro* antitumor effect on MTSs.**[17] Three-day-old A549 cell-based multicellular tumor spheroids were incubated with 2 mL fresh medium containing DMFs@HCFU or nDMFs@HCFU (11.36 μg/mL, HCFU) for 3 h, followed by a 48-h incubation in the presence of 20 μM GSH. For the LIVE/DEAD® assay, the MTS culture medium was replaced with 1 mL PBS solution containing 4 μM ethidium homodimer-1 (dead cells) and 2 μM calcein AM (live cells). Following a 20-min incubation at 37°C, single spheroids were transferred to a glass dish, washed twice with PBS, and analyzed using confocal laser scanning microscopy (CLSM, Leica TCP SP5). Bright-field microscopy was used to monitor the morphological changes in MTSs induced by the treatments. In addition, A549 MTSs seeded on 6-well plates were treated in the same manner and assessed for cell viability. Briefly, MTSs were gently transferred to a new 96-well plate, to which fresh media (100 μL) containing 10 μL CCK-8 solution was added. Following a 4-h incubation, the medium containing the CCK8 reagent was transferred to empty wells prior to measuring the absorbance at 450 nm.

To evaluate the antitumor efficacy of DMFs@HCFU or nDMFs@HCFU, A549 MTSs were treated with DMFs@HCFU or nDMFs@HCFU (11.36 μg/mL, HCFU) for 3 h, followed by a 48-h incubation in the presence of 20 μM GSH. The culture medium was replaced with 2 mL medium and cultured for another 48 h. The A549 MTSs were imaged every 24 h. The diameter of A549 MTSs was measured by ImageJ software. The volume of A549 MTSs was calculated according to the equation $V = 4\pi R^3/3$ (15

MTSs in each group). The A549 MTSs inhibition ratio was calculated according to the equation inhibition ratio (%) = $(V_{control} - V_t)/ V_{control} \times 100\%$ ($V_{control}$ is average A549 MTS volume of control group, V_t is that of treated group).

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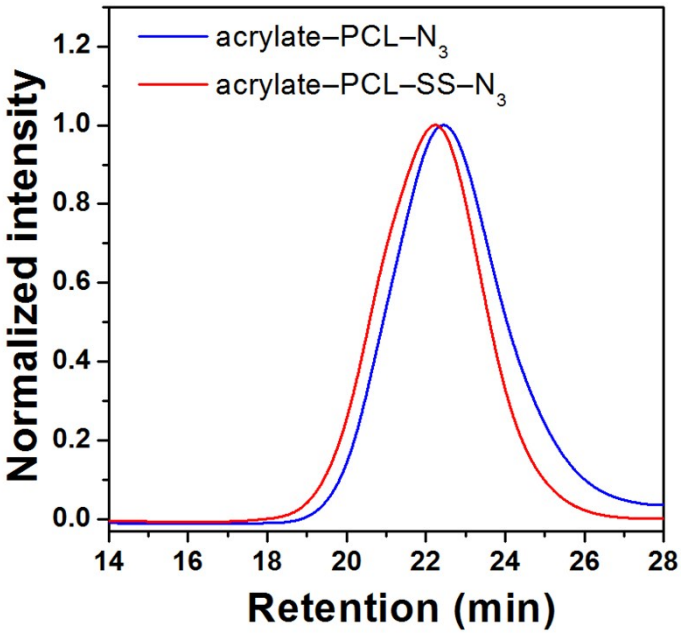


Figure S1. The gel permeation chromatography (GPC) profile of acrylate–PCL–SS–N_3 (red, *M*n = 9.3 kDa, *M*w/*M*n = 1.59) and acrylate–PCL–N_3 (blue, *M*n = 8.9 kDa, *M*w/*M*n = 1.73).

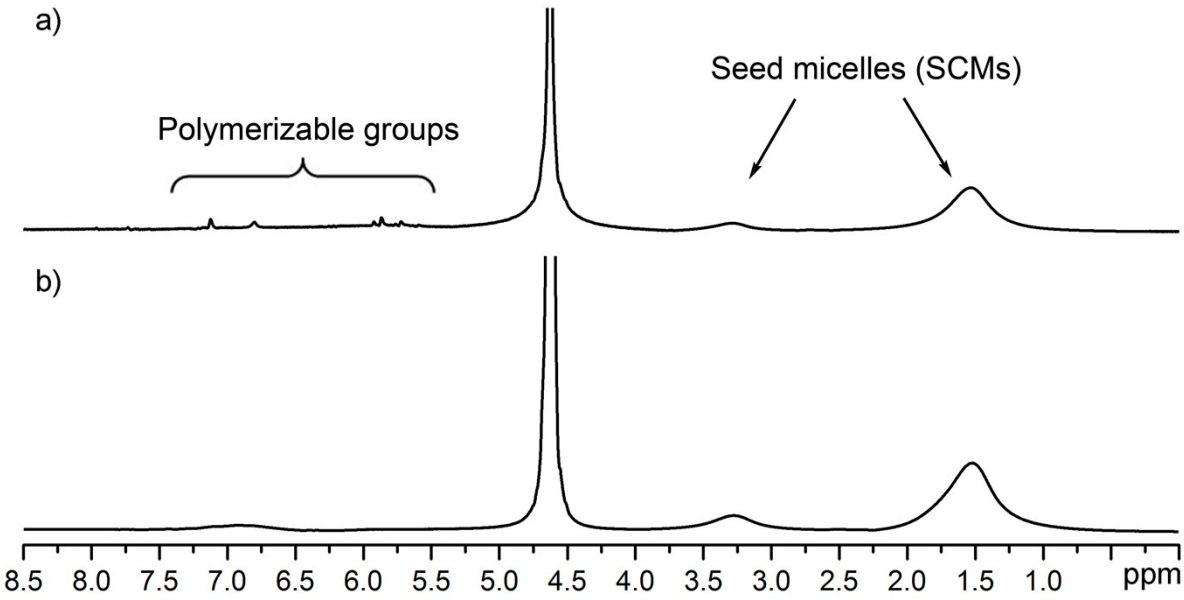


Figure S2. ^{1}H NMR spectrum of the D_2O solution of the DFMs (a) before and (b) after cross-linking (3 mg/mL).

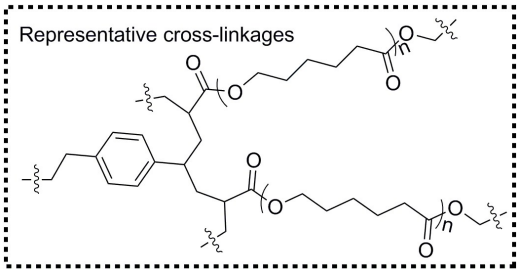


Figure S3. The cross-linking of the DFMs in the presence of DVB.

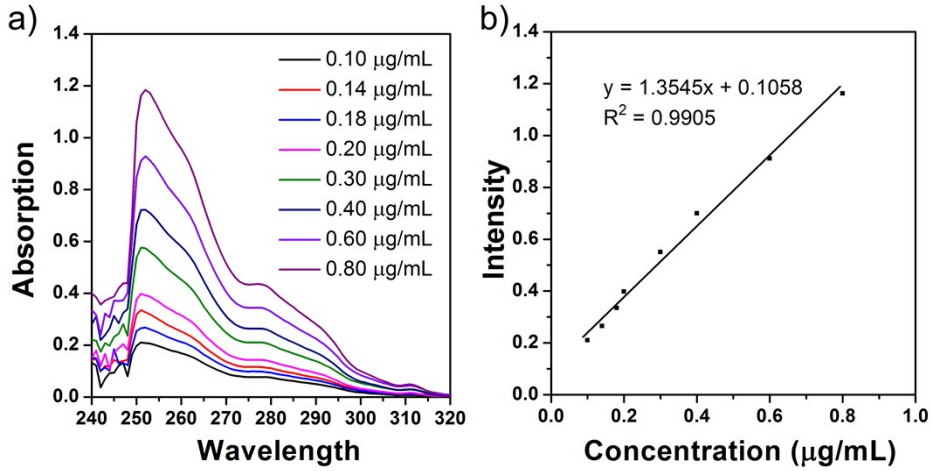


Figure S4. (a) The UV spectra of different concentrations of DVB in ethyl acetate solution and (b) the corresponding standard curve.

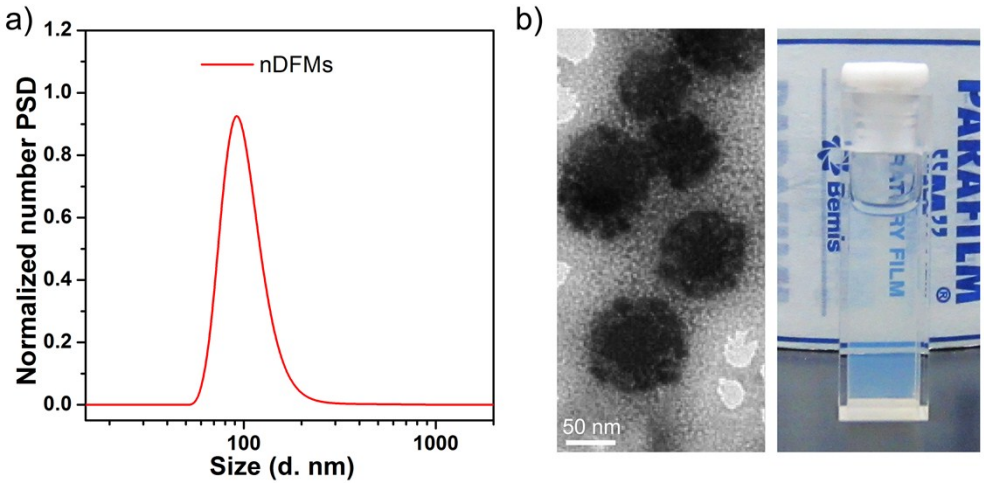


Figure S5. (a) Distribution of the dynamic diameters of the nDFMs following cross-linking under UV irradiation. (b) TEM image (left) and the corresponding photograph (right) of the nDFMs in water (1mg/mL).

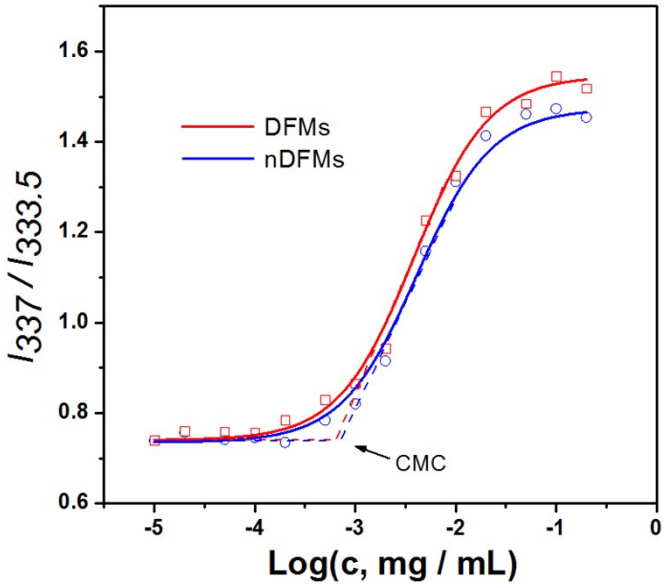


Figure S6. $I_{337.0}/I_{333.5}$ ratios of the excitation spectra as a function of micellar concentration (Log C). Shown by the arrows, the critical micelle concentrations (CMCs) are calculated from the intersection of the two tangent lines. CMC_{DFMs} = 5.7 × 10^{-4} mg/mL (acrylate–PCL–SS–SCMs), CMC_{nDFMs} = 6.6 × 10^{-4} mg/mL (acrylate–PCL–SCMs).

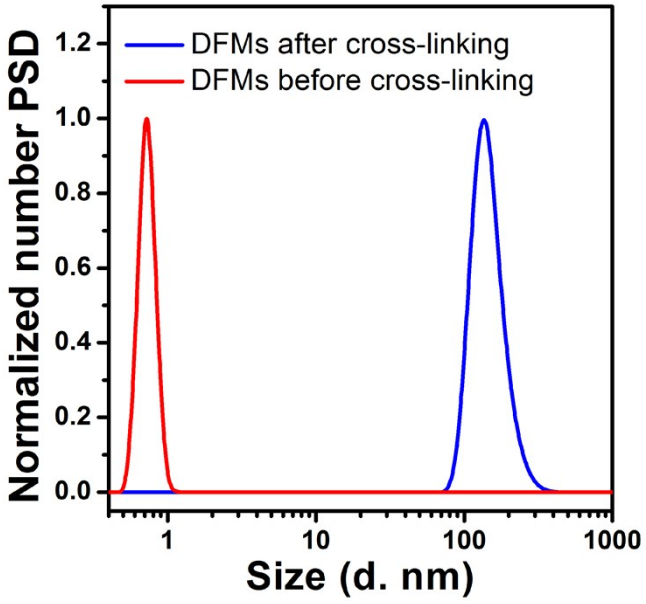


Figure S7. Distribution of the dynamic diameters of the DFMs dissolved in tetrahydrofuran before or after cross-linking (1 mg/mL).

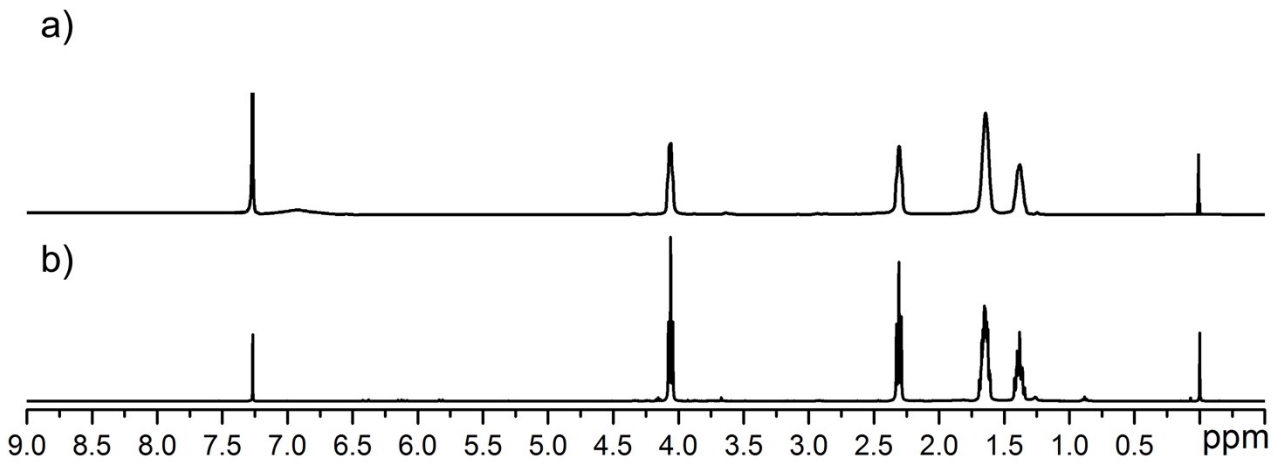


Figure S8. ^{1}H NMR of (a) a small amount of the precipite from the DMFs incubated in the presence of 20 μM glutathione (GSH), and (b) acrylate–PCL–SS–N_3 in $CDCl_3$.

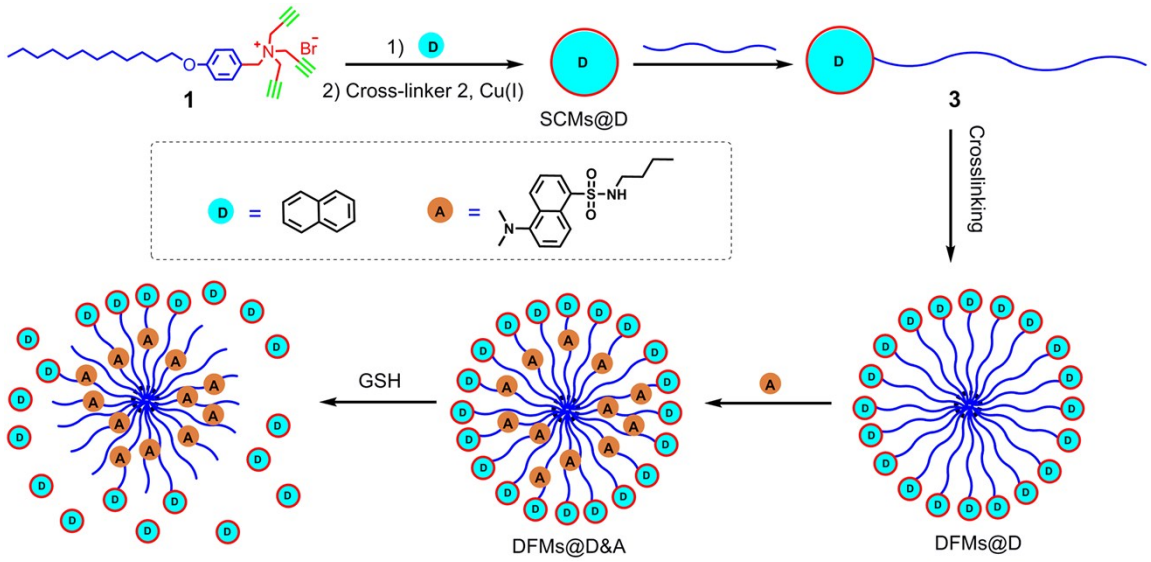


Figure S9. Chemical structure, self-assembly, and structural change of DFMs@D&A in response to reductive environments.

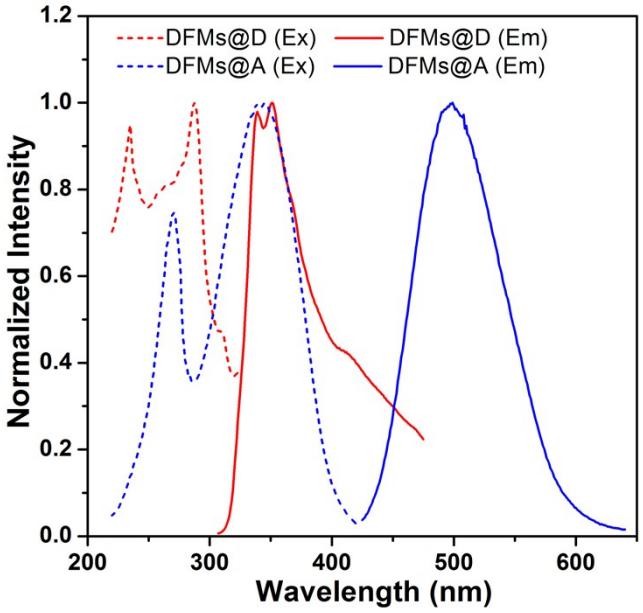


Figure S10. The excitation (dotted lines) and emission spectra (solid lines) of the DFMs@D (Ex = 287 nm) and DFMs@A (Ex = 345 nm). The emission spectra of the DFMs@D overlaps the excitation spectra of the DFMs@A.

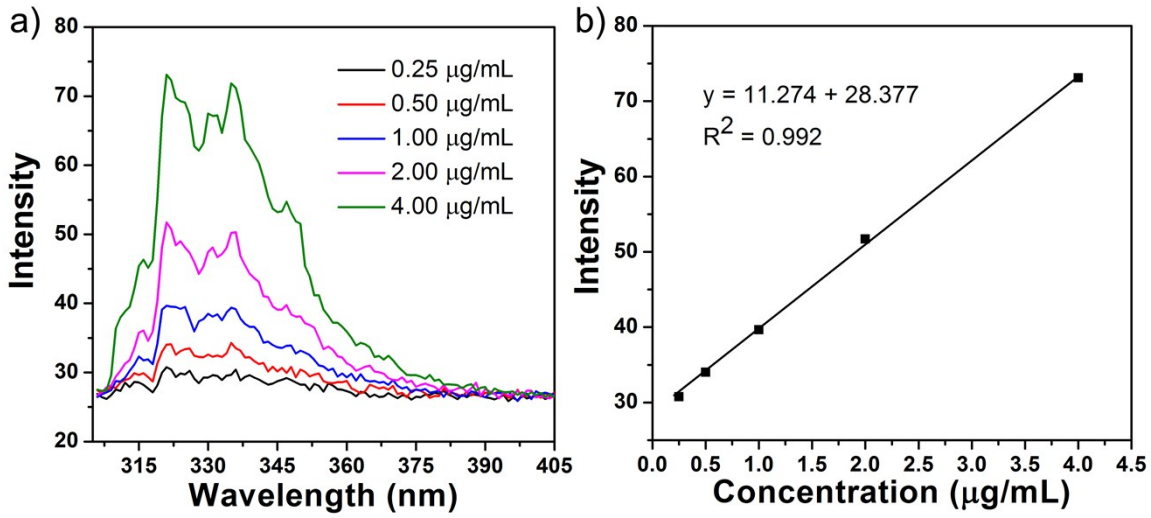


Figure S11. (a) The fluorescence spectra of different concentrations of naphthalene in ethyl acetate solution and (b) the corresponding standard curve.

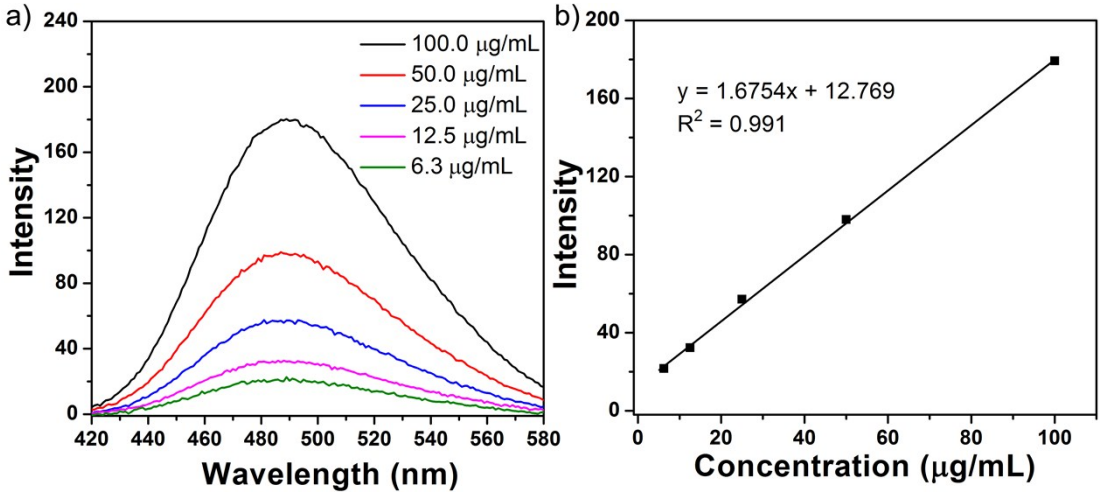


Figure S12. (a) The fluorescence spectra of different concentrations of dansyl-n-butyl sulfonamide in ethyl acetate solution and (b) the corresponding standard curve.

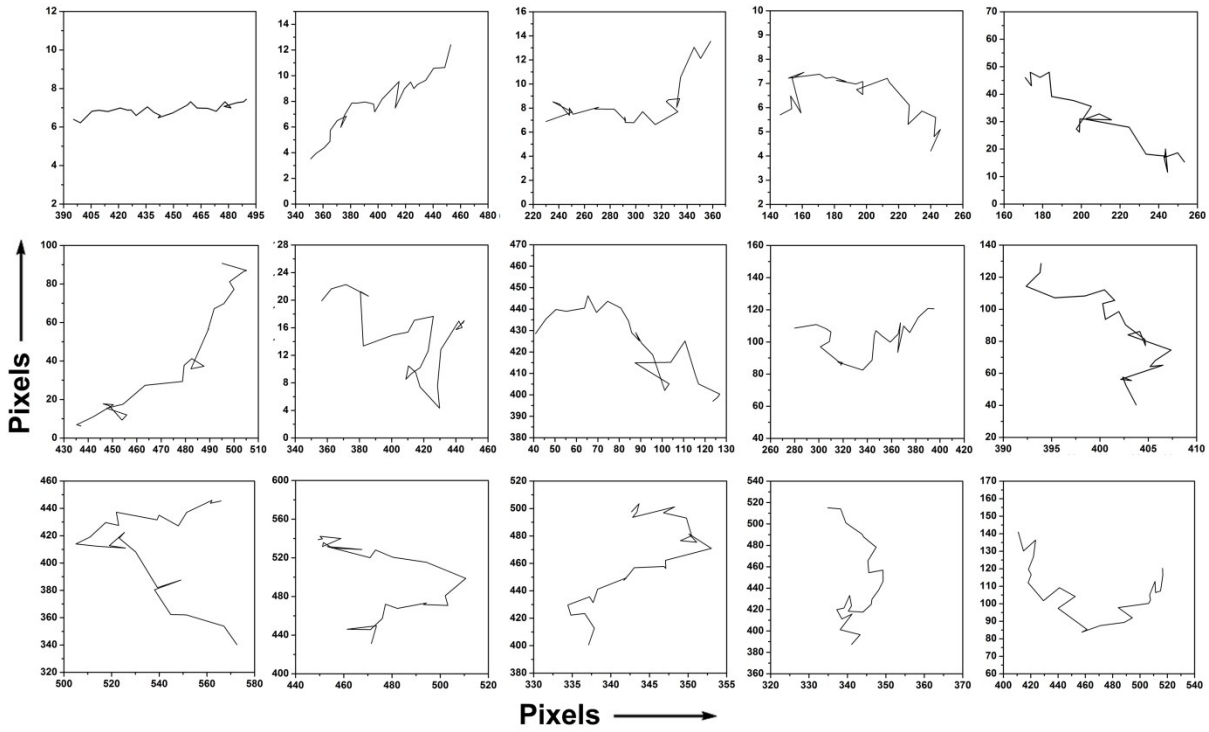


Figure S13. Samples of trajectories of SCMs released from DFMs in the presence of GSH.

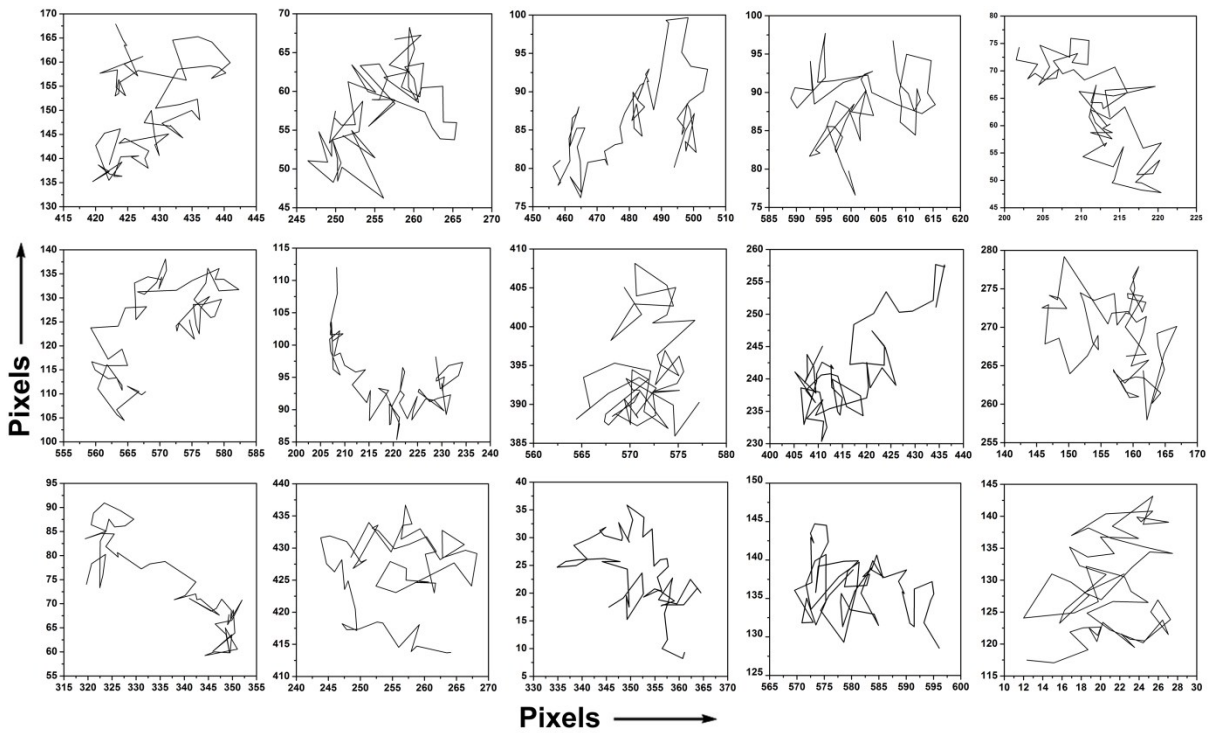


Figure S14. Samples of trajectories of SCMs in the presence of GSH.

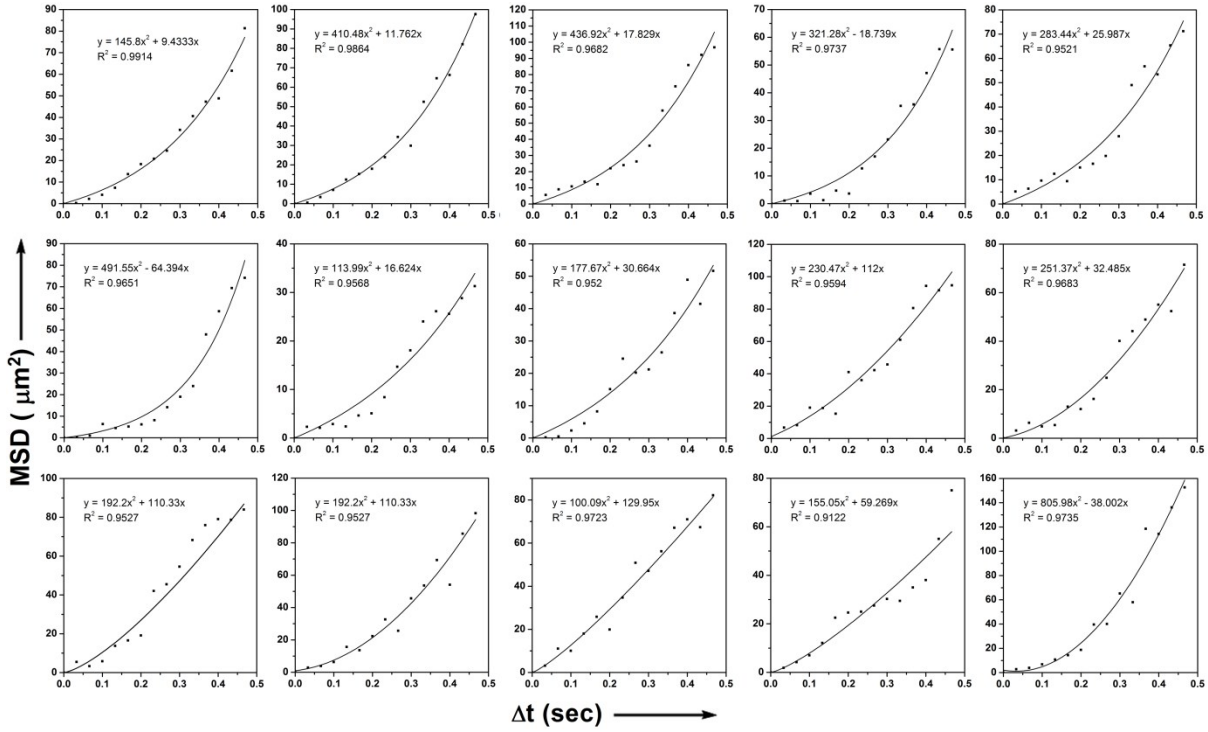


Figure S15. Samples of MSD of SCMs released from DFMs in the presence of GSH.

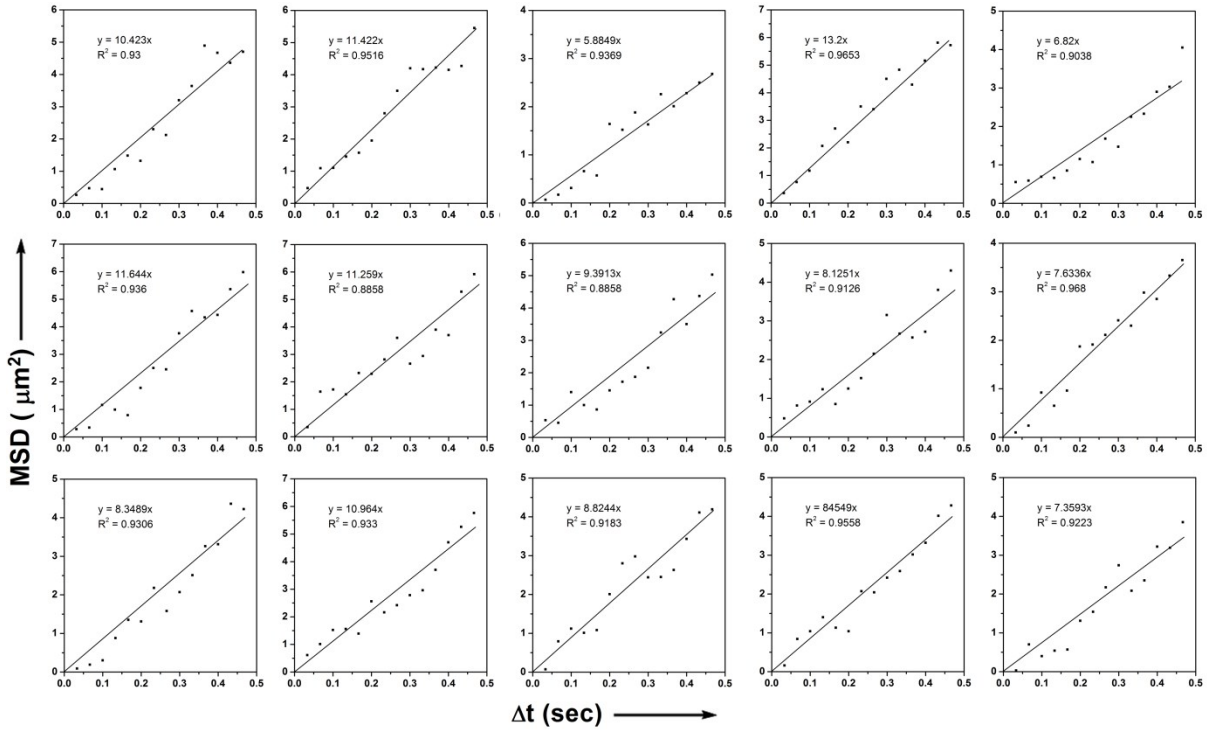


Figure S16. Samples of MSD of SCMs in the presence of GSH.

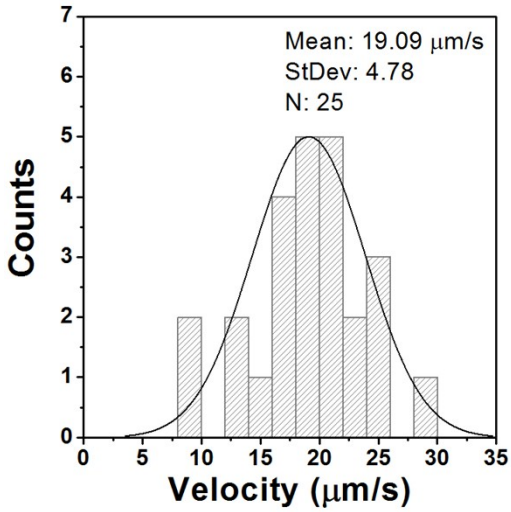


Figure S17. Histogram representing the velocity distributions of 25 SCMs released from DFMs after the addition of the GSH.

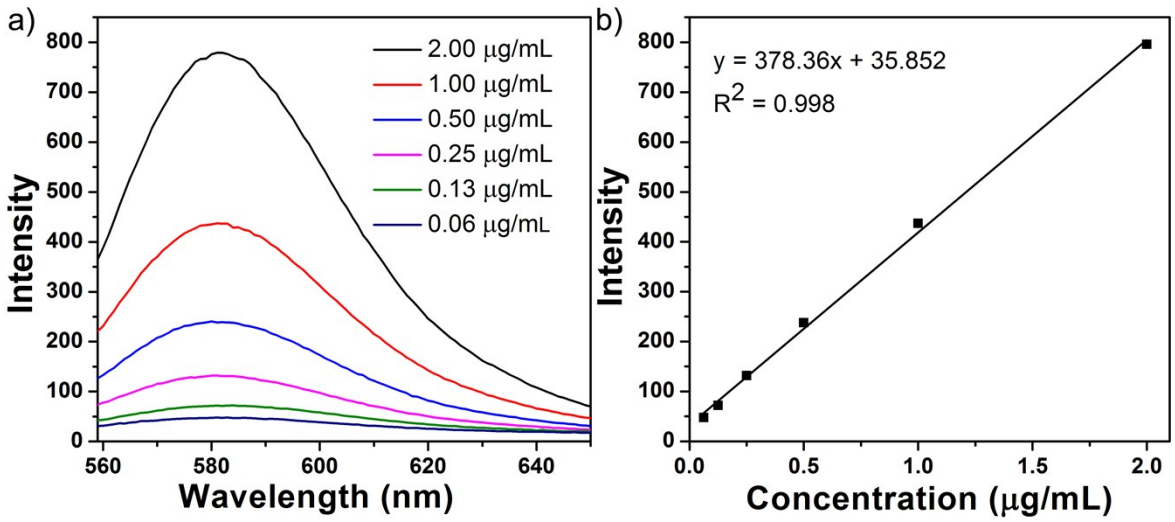


Figure S18. (a) The fluorescence spectra of different concentrations of Nile Red (NR) in ethyl acetate solution and (b) the corresponding standard curve.

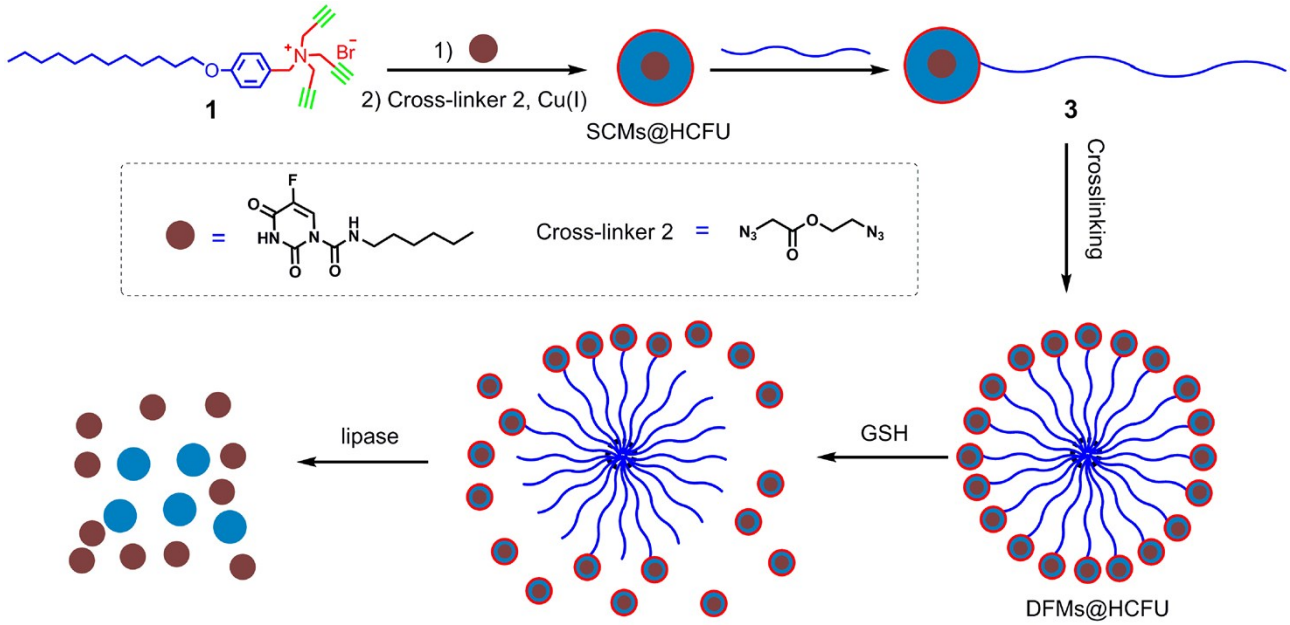


Figure S19. Chemical structure, self-assembly, and structural change of DFMs@HCFU in response to reductive and lipase environments.

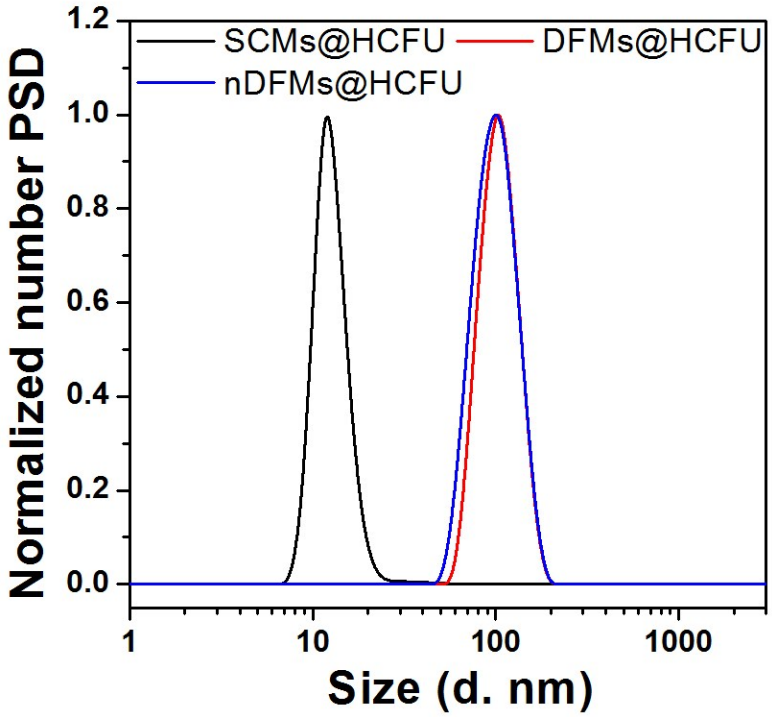


Figure S20. Size distribution of SCMs@HCFU, DFMs@HCFU, and nDFMs@HCFU as determined by dynamic light scattering (DLS).

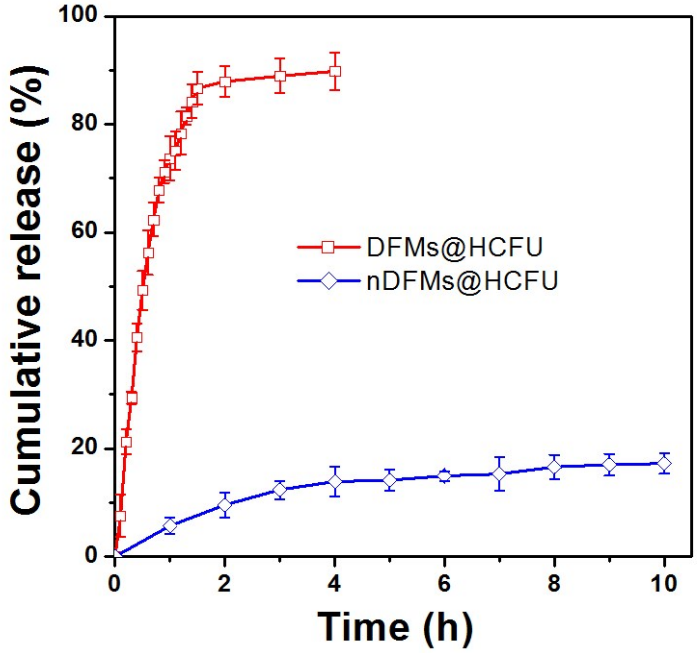


Figure S21. Release of HCFU from DFMs@HCFU or nDFMs@HCFU was evaluated by equilibrium dialysis at 37°C in phosphate buffer solution (PBS, pH 7.4) with 20 μm GSH. The content of HCFU presented in SCMs@HCFU was detected by an high-performance liquid chromatography (HPLC) system after lipase degradation.

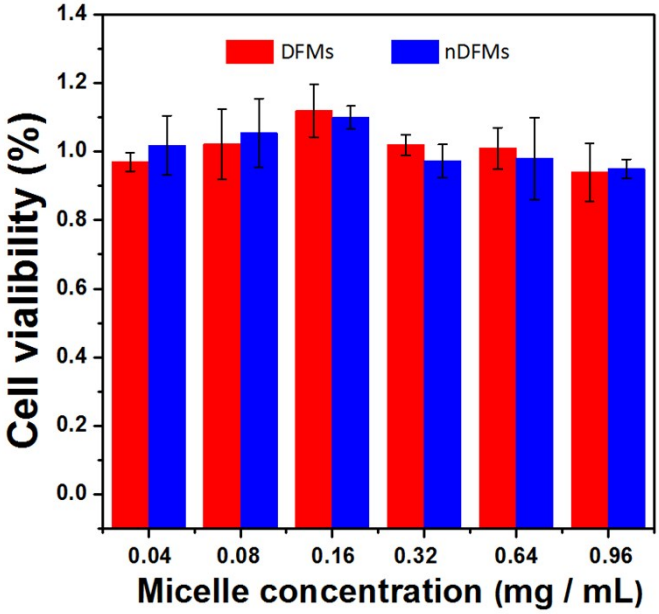


Figure S22. Viability of A549 cells following 48-h incubation with various concentrations of empty micelles.

Table S1. Elemental analysis results of the nanoparticles after dialysis.

Sample	N (%)	C (%)	H (%)	S (%)
acrylate–PCL–SS–SCM[a]	12.55	58.42	7.35	0.19
the nanoparticles[b]	16.68	56.05	6.84	0.09
SCMs	16.65	57.09	6.82	_

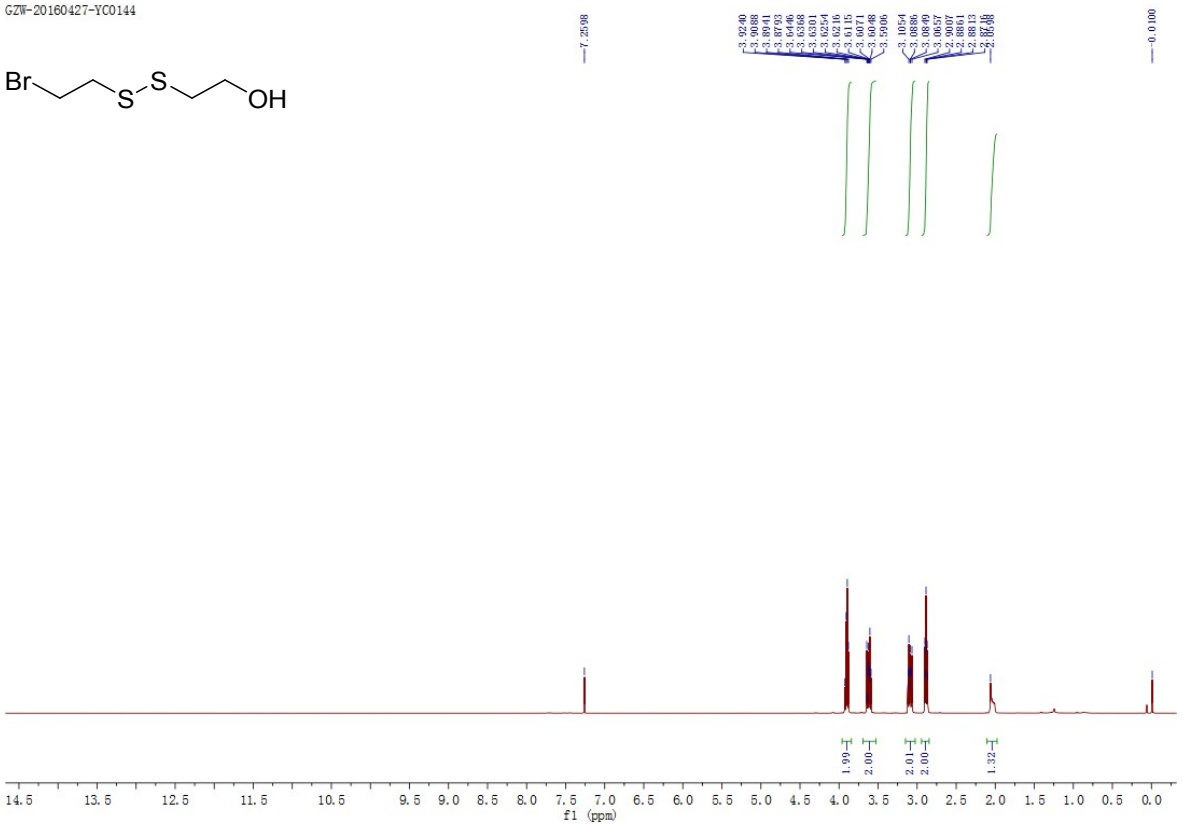
[a]According to the elemental analysis, the number of acrylate–PCL–SS–N_3 grafted onto the surface of the SCMs is calculated as follow. The copper-catalyzed reaction of an azide with an alkyne is the cycloaddition reaction to form a 5-membered heteroatom ring compound as an only addition product. Firstly, therefore, suppose that one SCM contains x molecules of compound **2** (MW = 486.5 g/mol, Nitrogen content = 2.88%) and y molecules of compound **3** (MW = 170.1 g/mol, Nitrogen content = 49.40%). According to the element analysis of SCMs, the equation (**1**) about nitrogen contnet is obtained, (486.5 × x ×2.88% + 170.1 × y × 49.40%) / (486.5 × x + 170.1 × y) = 16.65% (**1**). Secondly, suppose that acrylate–PCL–SS–SCM contain one SCM and z molecules of compound acrylate–PCL–SS–N_3 (MW based on ^{1}H NMR = 9750 g/mol, Nitrogen content = 0.0043%). According to the element analysis of acrylate–PCL–SS–SCM, the equation (**2**) is obtained about nitrogen contnet, (486.5 × x

×2.88% + 170.1 × *y* × 49.40% + 9750 × *z* × 0.0043%) / (486.5 × *x* + 170.1 × *y* + 9750.1 × *z*) = 12.55% (**2**). From equations (**1**) and (**2**), the value of *x*/*z* is about 42/1. Since an SCM contained approximately 40–50 small molecule **2** surfactants according to our previous study,[1] the SCM on average grafted one acrylate–PCL–SS–N_3 group. [b]The nanoparticles are materials released from the DFMs upon a specific stimulus.

Table S2. Summary of the size and zeta potential of SCM, SCMs@NR, DFMs@NR, and nDFMs@NR

Sample	SCMs	SCMs@NR	nDFMs@NR	DFMs@NR
Size (nm)	9.2 ± 1.2	8.9 ± 1.9	91.4 ± 3.2	92.7 ± 2.8
Zeta potential (mV)	39.1 ± 2.4	40.5 ± 3.4	20.9 ± 2.5	21.8 ± 2.2

[1]H NMR of key compounds



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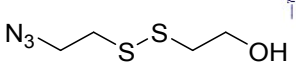

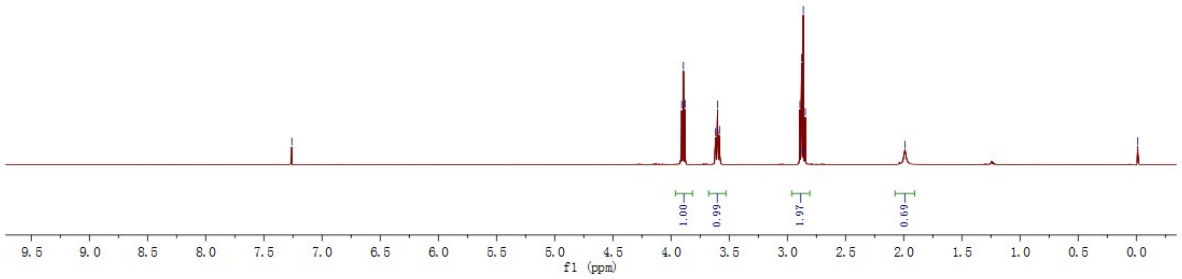

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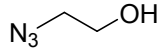

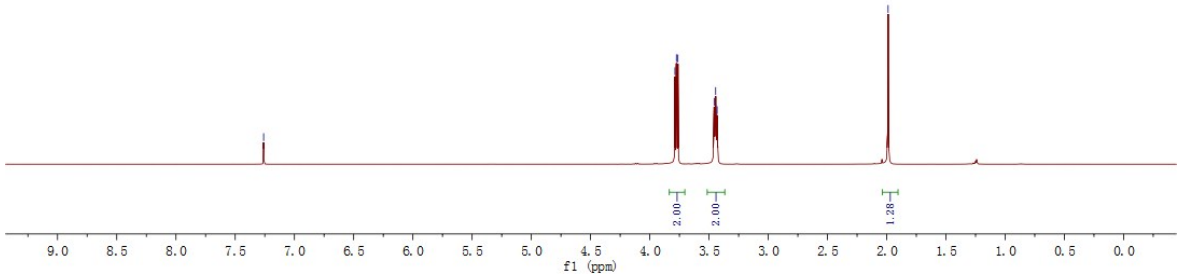

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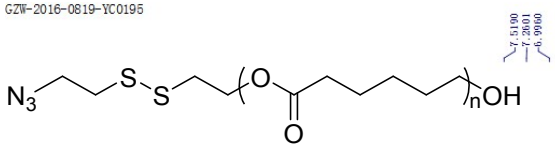

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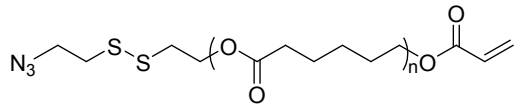

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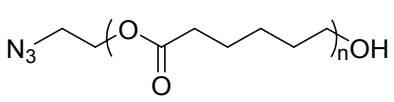

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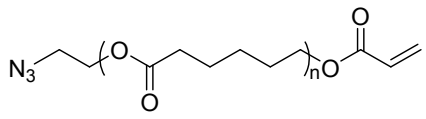

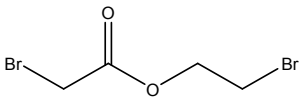

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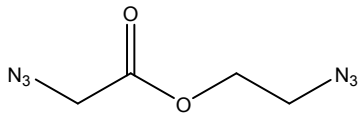

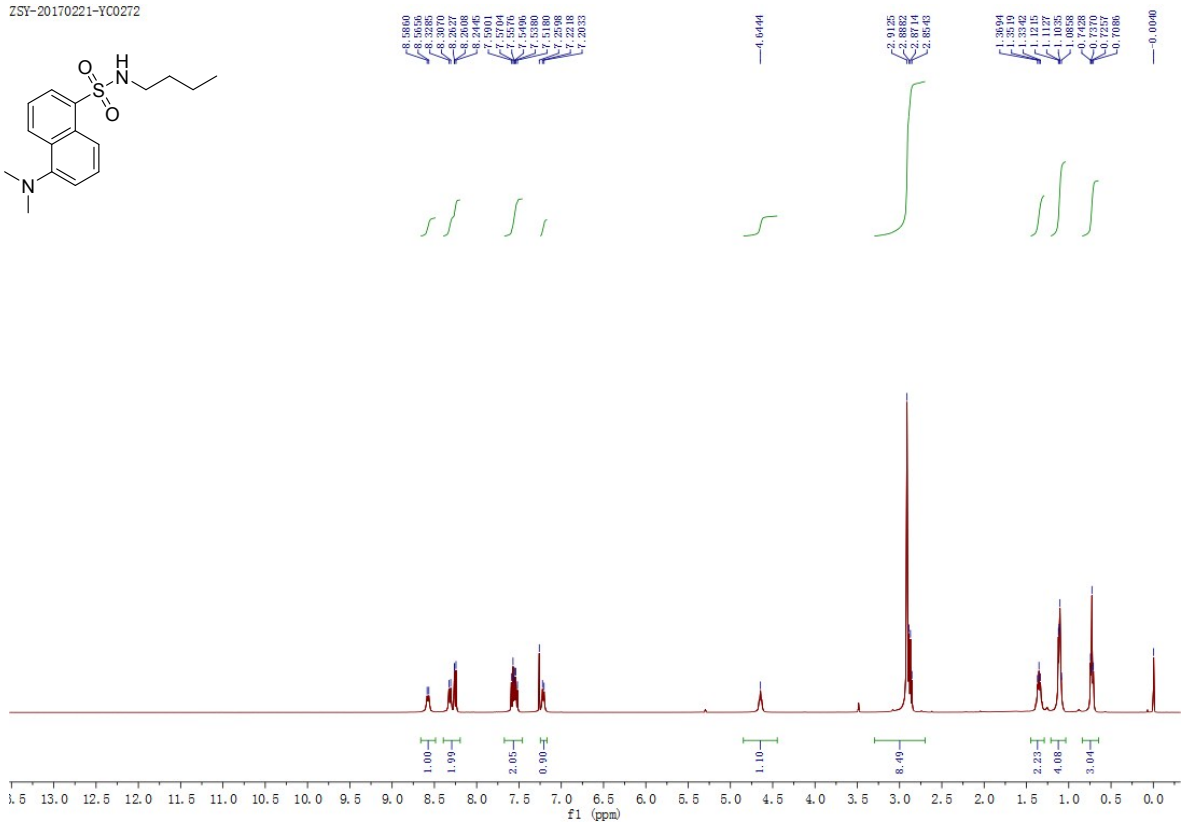
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f1 (ppm)