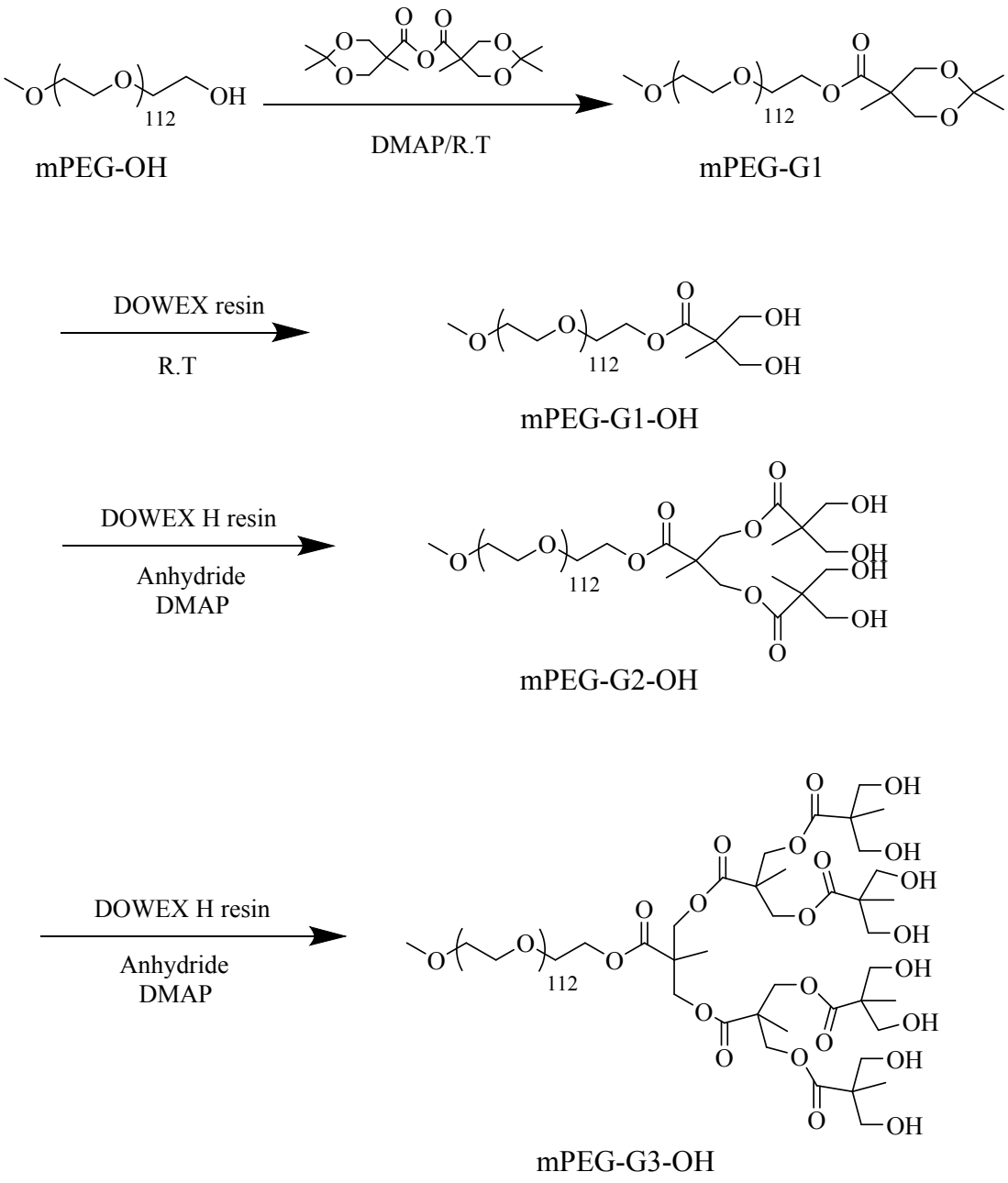
Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information

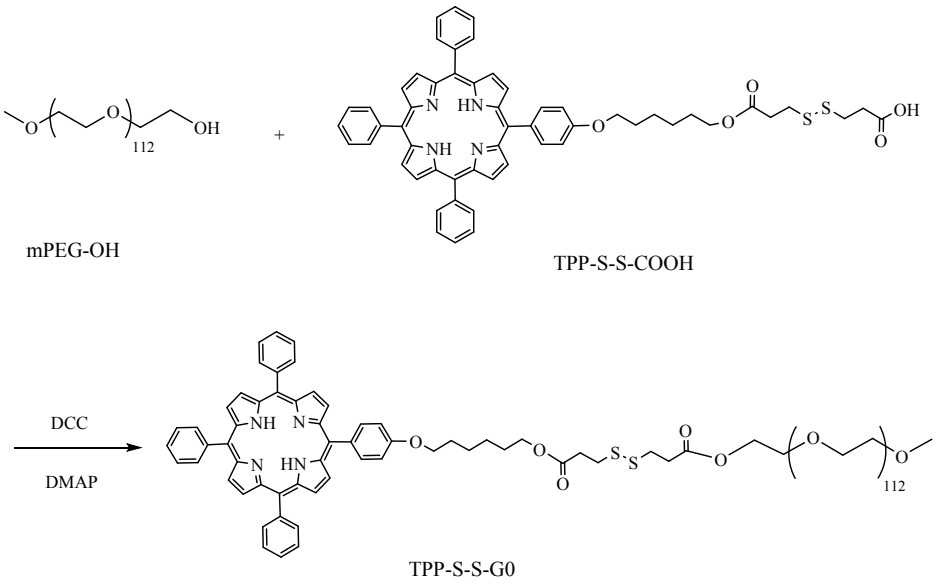
Doxorubicin-loaded Redox-Responsive Amphiphilic Dendritic Porphyrin Conjugates for Chemotherapy and Photodynamic Therapy

Feng Liu, Yang Zhang, Xiuwei Pan, Lei Xu, Yudong Xue, Weian Zhang*

Shanghai Key Laboratory of Functional Materials Chemistry, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, P. R. China



Scheme S1 Synthesis of the mPEG-G3-OH.



Scheme S2 Synthesis of the TPP-S-S-G0.

Synthesis of First-Generation Dendronized PEG (PEG-G1 dendron)

PEG (5 g, 1 mmol), 1 g anhydride (3 mmol) and 0.34 g DMAP (3 mmol) were dissolved in 30 mL of CH_2Cl_2 and stirred at room temperature for 24 h. 3 mL methanol was added for 24 h. The flask was opened and the product filtered off and precipitated in diethyl ether. The precipitate was dried under vacuum at room temperature for 24 h to obtain PEG-G1 dendron. ^{1}H-NMR (500 MHz, $CDCl_3$), δ ppm: 3.38 (s, 3H), 3.65 (t, 452H), 4.28-4.32 (m, 2H), 1.21 （s, 3H), 4.17-4.22 (m, 2H), 1.38 (s, 3H), 1.43 (s, 3H).

Synthesis of PEG-G1-OH

PEG-G1 dendron (5 g) was dissolved in 125 mL of methanol. After one teaspoon of Dowex H^+ resin was added, the reaction mixture was stirred for 24 h at room temperature. Once the reaction was complete, the Dowex H^+ resin was filtered off and washed with methanol. The methanol solution was condensed to about 10 mL and precipitated in 50 mL of diethyl ether to give the product as a reddish solid. ^{1}H-NMR (500 MHz, $CDCl_3$), δ ppm: 3.38 (s, 3H), 3.45-3.85 (m, 452H), 4.32-4.36 (m, 2H), 1.13 (d, 3H).

Synthesis of PEG-G2-OH and PEG-G3-OH

With the same method as described in the two preceding subsections, PEG-G2-OH, PEG-G3-OH were separately prepared as shown in **Scheme S1**. The product of each generation was also a white solid, and the yields were all above 85%. ^{1}H-NMR (500 MHz, $CDCl_3$), δ ppm: PEG-G2: 3.38 （s, 3H），3.55-3.75 (m, 452H), 4.27 (t, 2H）, 1.27 (s, 3H), 4.14 (t, 2H), 4.31 (t, 4H), 1.14 (s, 6H), 1.35 (s, 6H), 1.41 (s, 6H); PEG-G2-OH: 3.38 (s, 3H), 3.45-3.75 (m, 452H), 4.41 (t, 2H), 1.32 (s, 3H), 4.32 (t, 2H), 1.08 (s, 6H); PEG-G3: 3.38 (s, 3H), 3.45~3.85 (m, 452H), 4.25-4.33 (m, 8H), 1.28 (s, 9H), 4.15 (s, 8H), 1.15 (s, 12H), 1.35 (s, 12H), 1.42 (s, 12H); PEG-G3-OH: 3.38 (s, 3H), 3.45-3.85 (m, 452H), 4.27-4.37 (m, 8H), 1.28-1.38 (m, 9H), 1.04-1.11 (s, 12H).

Synthesis of Disulfide-Modified Carboxyl Terminal Porphyrin (TPP-S-S-COOH)

A representative example for the synthesis of TPP-S-S-COOH is as follows: TPPC6-OH (0.67 g, 1 mmol), 3, 3'-dithiodipropionic acid (0.42 g, 2 mmol) and DMAP (0.12 g, 1 mmol) were dissolved in 30 mL of anhydrous DMF under Argon, and DCC (0.41 g, 2 mmol) in DMF (5 mL) was added drop-wise into the mixture in an ice-water bath. Then the mixture was washed with saturated sodium chloride solution, dried with $MgSO_4$ and filtered. After removing DCM by evaporation, the crude product was purified on a silica gel column with petroleum ether/ethyl acetate (3 : 2, v/v) as the eluent. ^{1}H-NMR (400 MHz, $CDCl_3$), δ ppm: PEG-G2: 8.87 (m, 8H), 8.21 (m, 6H), 8.11 (m, 2H), 7.75 (m, 9H), 7.26 (m, 2H), 4.26 (t, 2H), 4.20 (t, 2H), 2.96 (m, 4H), 2.76 (m, 4H), 1.99 (m, 2H), 1.80-1.69 (m, 6H), -2.77 (s, 2H).

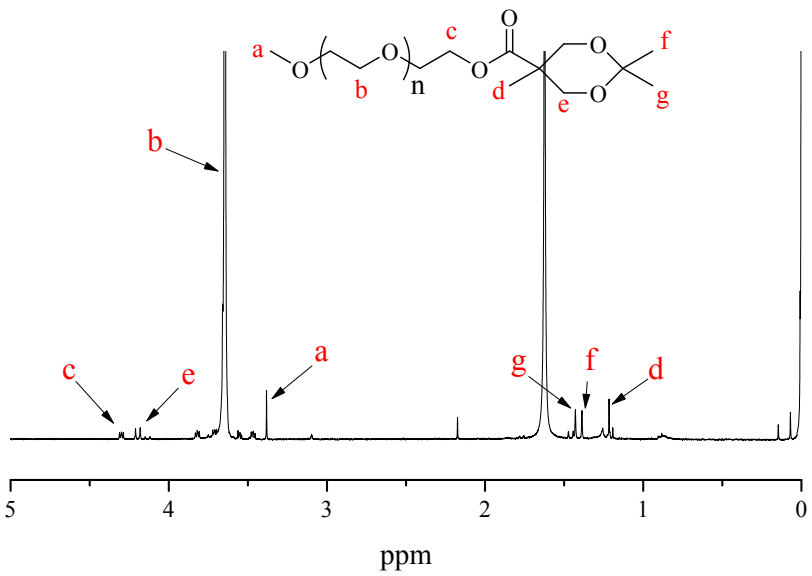


Fig. S1 ^{1}H-NMR spectrum of PEG-G1 in $CDCl_3$.

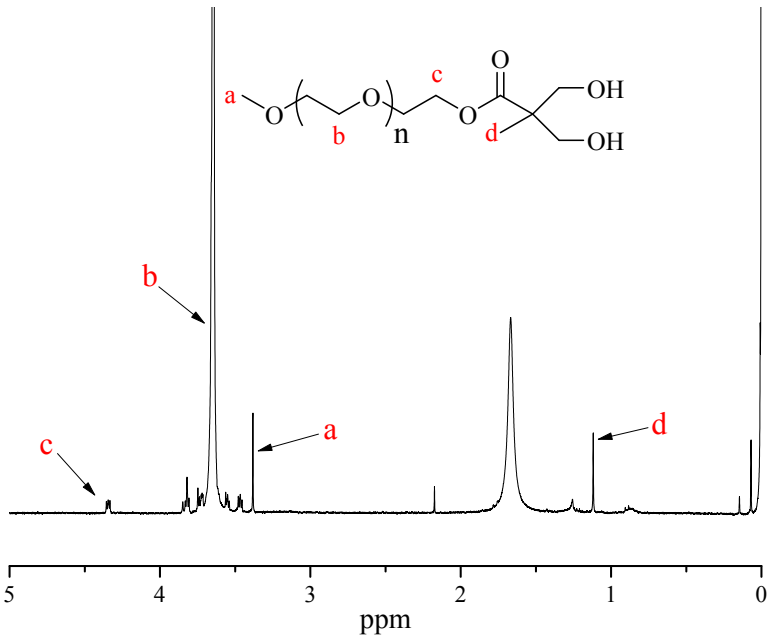


Fig. S2 ^{1}H-NMR spectrum of PEG-G1-OH in $CDCl_3$.

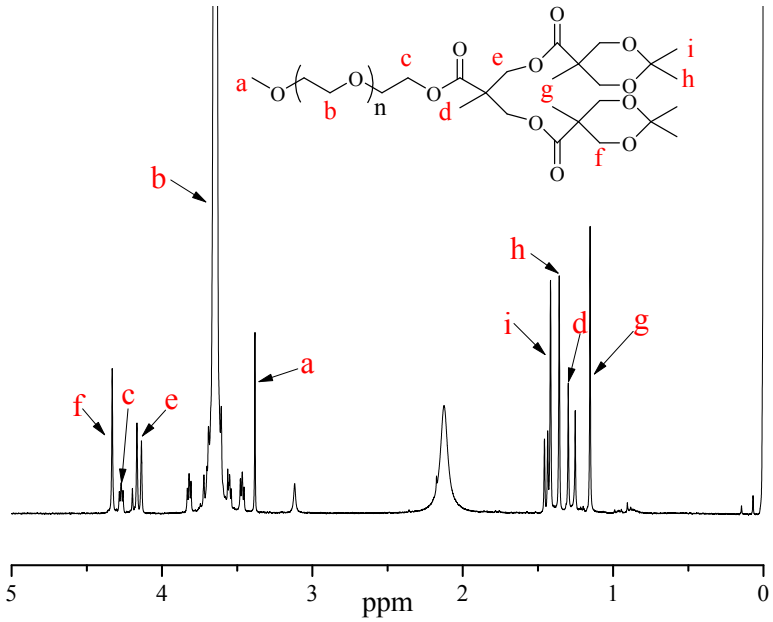


Fig. S3 ^{1}H-NMR spectrum of PEG-G2 in $CDCl_3$.

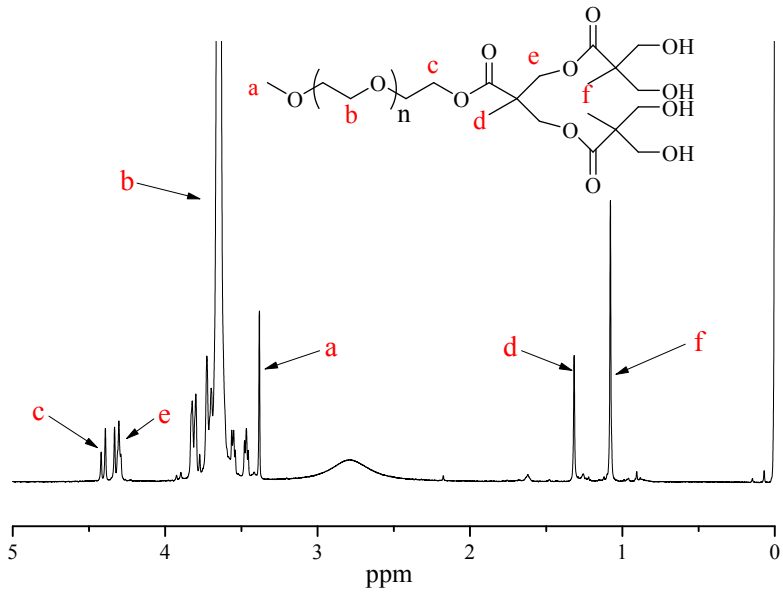


Fig. S4 ^{1}H-NMR spectrum of PEG-G2-OH in $CDCl_3$.

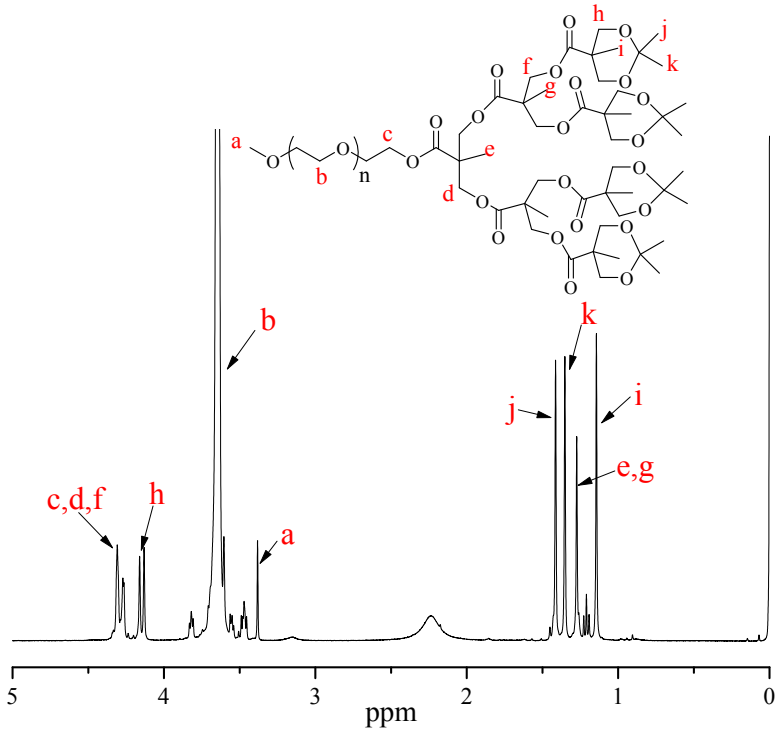


Fig. S5 ^{1}H-NMR spectrum of PEG-G3 in $CDCl_3$.

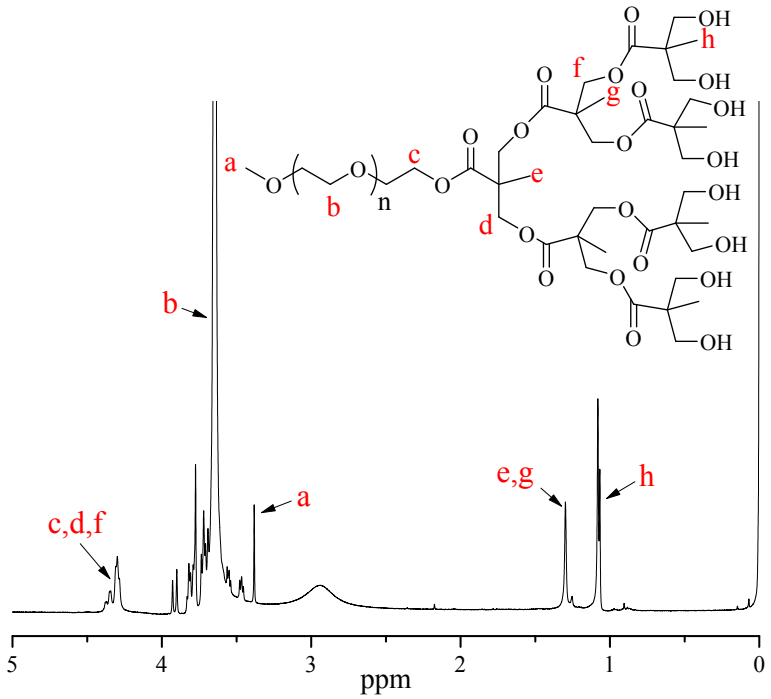


Fig. S6 ^{1}H-NMR spectrum of PEG-G3-OH in $CDCl_3$.

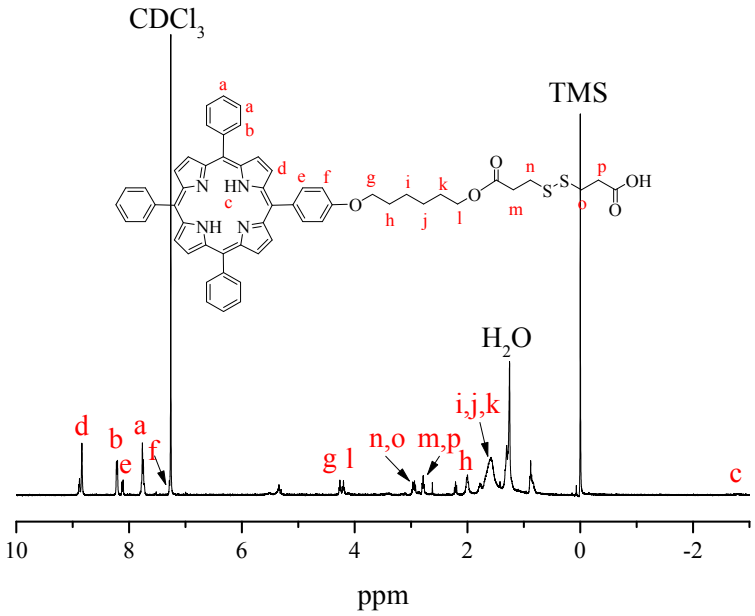


Fig. S7 ^{1}H-NMR spectrum of TPP-S-S-COOH in $CDCl_3$.

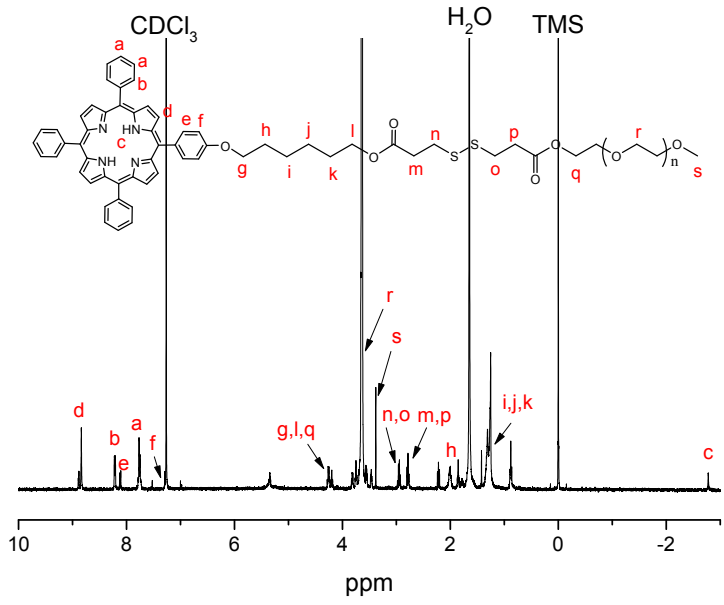


Fig. S8 ^{1}H-NMR spectrum of TPP-S-S-G0 in $CDCl_3$.

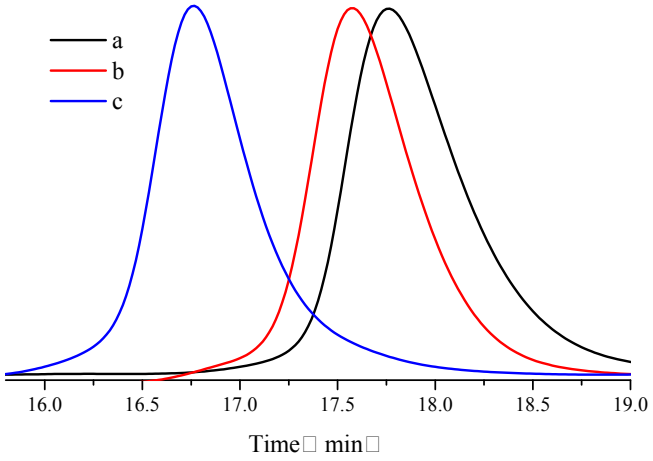


Fig. S9 GPC curves of (a) PEG, (b) TPP-S-S-G0 and (c) TPP-S-S-G3.

Table S1 Characterization of PEG and TPP-S-S-Gn (n = 0, 3) Copolymers

Samples	M_n[a] (g mol^{-1})	M_n[b] (g mol^{-1})	PDI[b]
PEG	5 000	4 871	1.05
TPP-S-S-G0	5 905	5 637	1.03
TPP-S-S-G3	13 053	8 870	1.03

[a]Determined by the ^{1}H-NMR results,
[b]Number-average weight and molecular weight distribution (PDI) were evaluated by GPC.

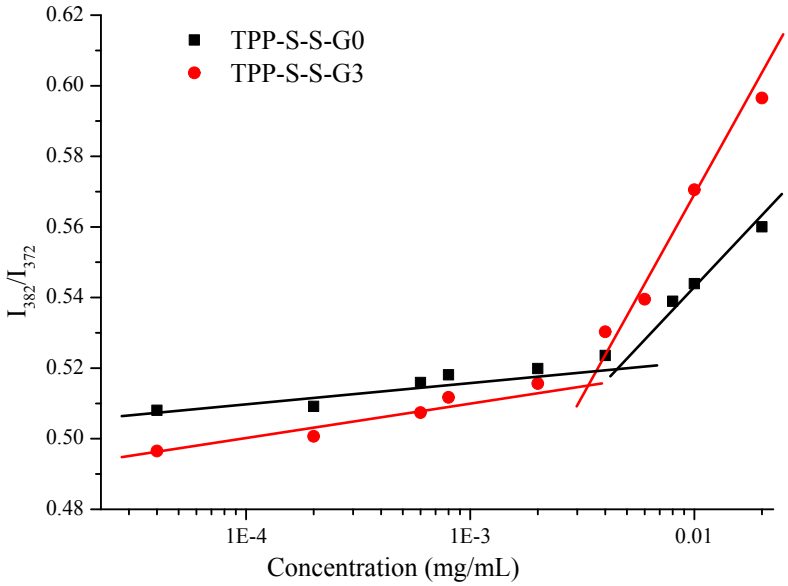


Fig. S10 The CMC values of TPP-S-S-Gn (n = 0, 3) determined from the plot of fluorescence intensity ratio I_{382}/I_{372} of pyrene as a function of their concentrations.

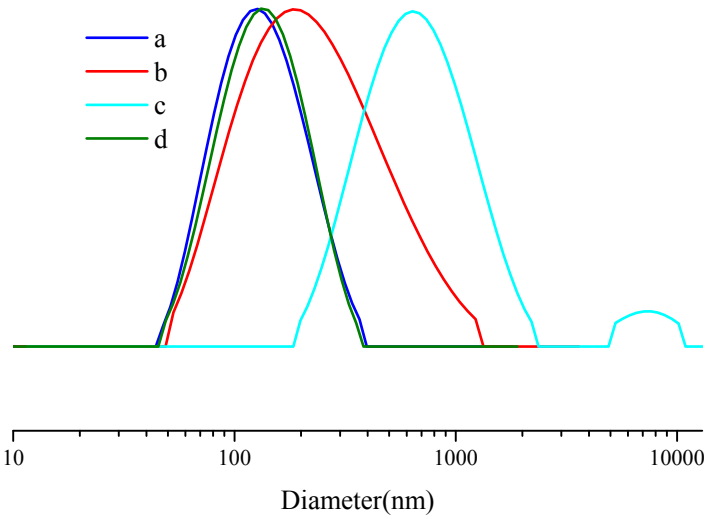


Fig. S11 Size distribution of TPP-S-S-G3 micelles (a), TPP-S-S-G3 micelles treated with 10 mM of GSH for 4 h (b) and 24 h (c), and without GSH for 24 h (d).

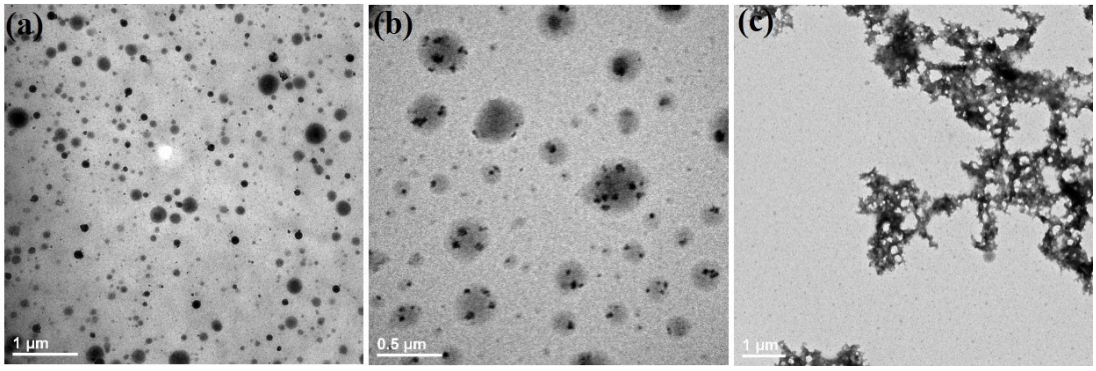


Fig. S12 TEM images of TPP-S-S-G0 micelles with treatment using GSH at different times; GSH for 0 h (a), GSH for 4 h (b), and GSH for 24 h (c).

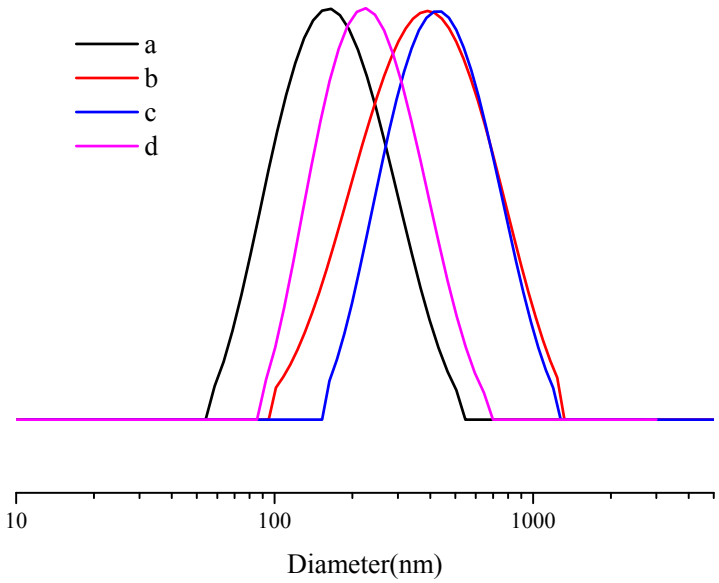


Fig. S13 Size distribution of TPP-S-S-G0 micelles (a), TPP-S-S-G0 micelles treated with 10 mM of GSH for 4 h (b) and 24 h (c), and without GSH for 24 h (d).

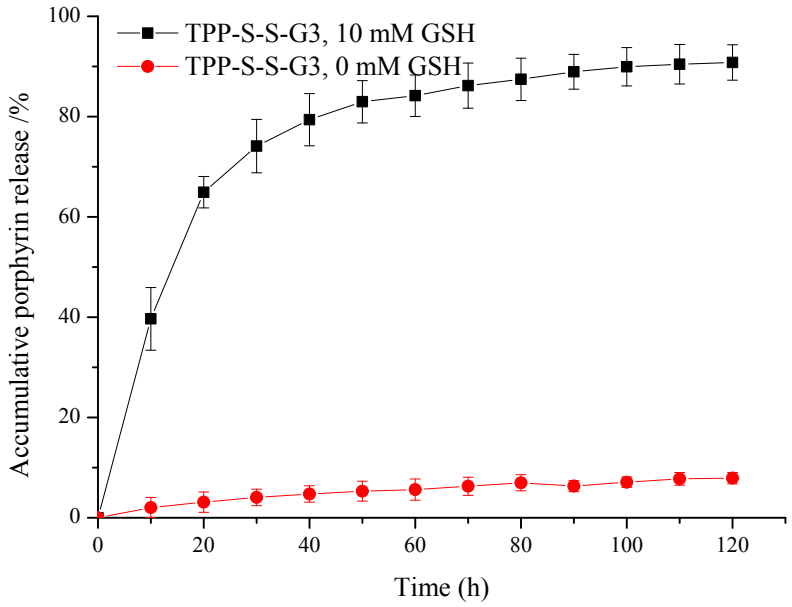


Fig. S14 Reduction-release of porphyrin from TPP-S-S-G0 micelles treated with 10 mM GSH and without GSH.

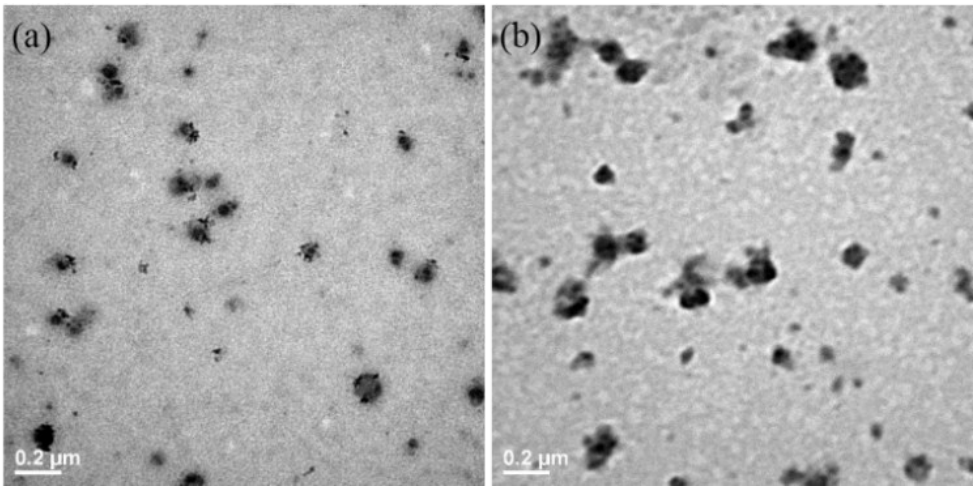


Fig. S15 TEM images of DOX-loaded TPP-S-S-G3 micelles (a) and DOX-loaded TPP-S-S-G0 micelles (b).

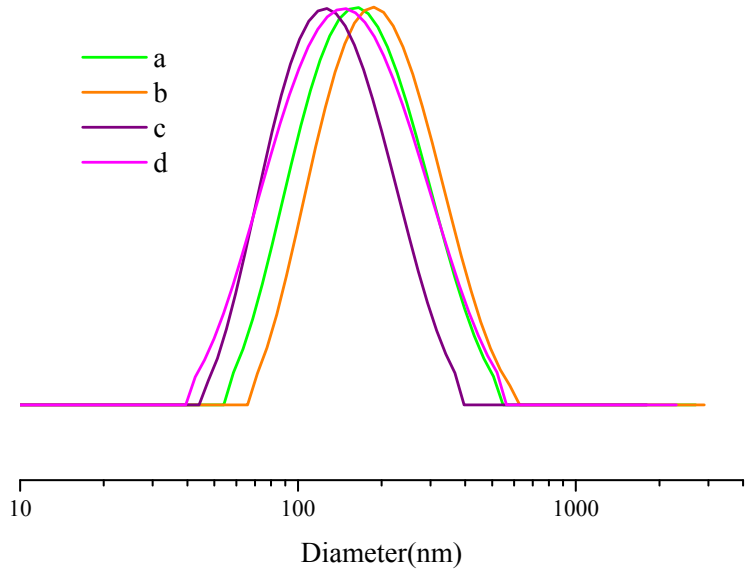


Fig. S16 Size distribution of TPP-S-S-G0 micelles (a), DOX-loaded TPP-S-S-G0 micelles (b), TPP-S-S-G3 micelles (c), and DOX-loaded TPP-S-S-G3 micelles (d).

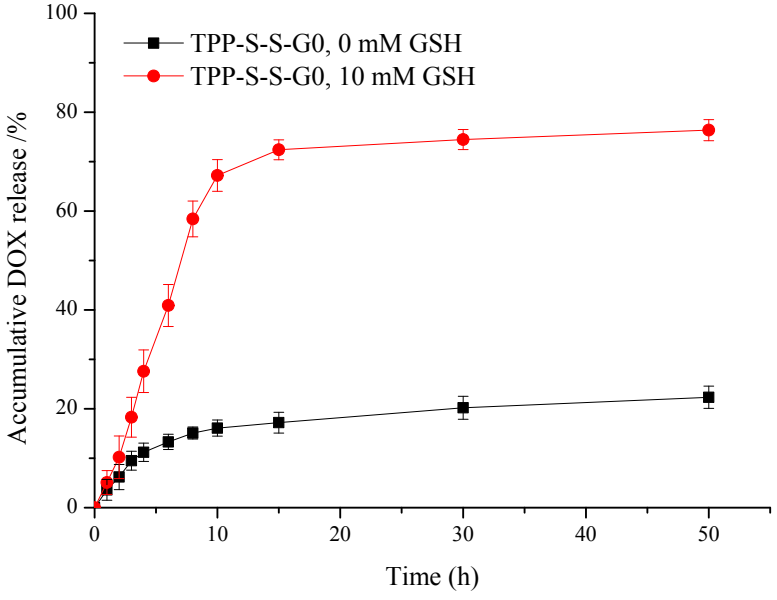


Fig. S17 Reduction-release of DOX from DOX-loaded TPP-S-S-G0 micelles treated with GSH (10 mM) and without GSH.

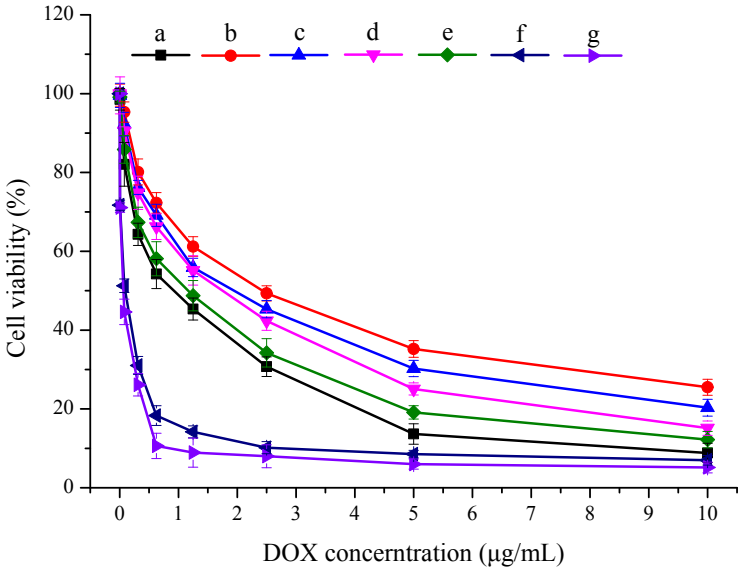


Fig. S18 Viability of MCF-7 cells cultured with free DOX and DOX-loaded TPP-S-S-Gn (n = 0, 3) micelles at different concentrations. The cells were pretreated with or without 10 mM GSH-OEt. a: DOX-loaded TPP-S-S-G0, b: DOX-loaded TPP-S-S-G3, c: DOX-loaded TPP-S-S-G0 with 10 mM GSH, d: DOX-loaded TPP-S-S-G3 with 10 mM GSH, e: DOX, f: DOX-loaded TPP-S-S-G3 micelles with irradiation, g: DOX-loaded TPP-S-S-G3 micelles with irradiation and 10 mM GSH-OEt.