# Therapeutic polymeric nanomedicine: GSH-responsive release promotes drugs release for cancer synergistic chemotherapy

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## Electronic Supplementary Information (7 pages)

*1. Synthesis of reduction-responsive CPT monomer (**CPTM**)*

Typical procedures for the synthesis of CPTM are as follows. Camptothecin (CPT, 2.0 g, 5.74 mmol) and DMAP (2.11 g, 17.3 mmol) were suspended in dry DCM (50 mL) under argon atmosphere. Triphosgene (0.567 g, 1.92 mmol) was added and the mixture was stirred for 30 min at room temperature. **HSEMA**[S1](1.40 g, 6.31 mmol, in 15 mL dry THF) was added dropwise via a constant pressure funnel. The reaction mixture was stirred overnight during which a white precipitate was formed. After filtration and evaporating all the solvents, the residues were diluted with diethyl acetate and washed once with water, twice with 1.0 M HCl, and twice with brine, respectively. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator. The crude product was purified by column chromatography using ethyl acetate as eluent to give **CPTM** as a pale solid powder with a yield of 72.6%. $^1$H NMR (300 MHz, DMSO-$d_6$, room temperature) $\delta$(ppm): 8.70 (s, 1H), 8.15-8.10 (t, 2H), 7.87-7.82 (t, 1H), 7.73-7.68 (t, 1H), 7.09 (s, 1H), 5.97 (s, 1H), 5.63 (s, 1H), 5.53 (s, 2H), 5.31 (s, 2H), 4.35-4.24 (m, 4H), 3.04-2.97 (m, 4H), 2.23-2.15 (m, 2H), 1.82 (s, 3H), 0.95-0.90 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-$d_6$, room temperature) $\delta$ (ppm): 167.49, 166.70, 156.94, 153.27, 152.64, 148.34, 146.70, 145.22, 136.03, 132.04, 130.87, 130.19, 129.41, 128.97, 128.46, 128.20, 126.46, 119.64, 94.83, 78.36, 66.91, 66.72, 62.51, 50.77, 49.06, 36.81, 36.68, 30.77, 18.33, 8.02.

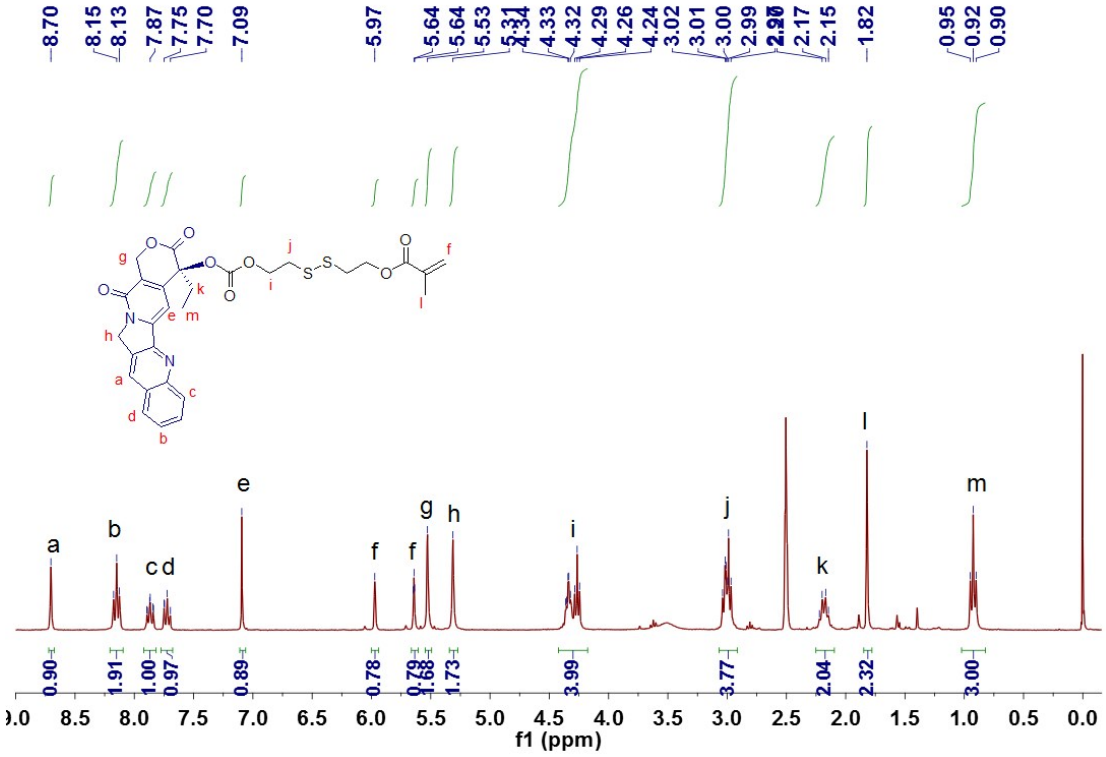


***Fig. S1*** $^{1}$H NMR spectrum (300 MHz, DMSO-$d_6$, room temperature) of **CPTM**.

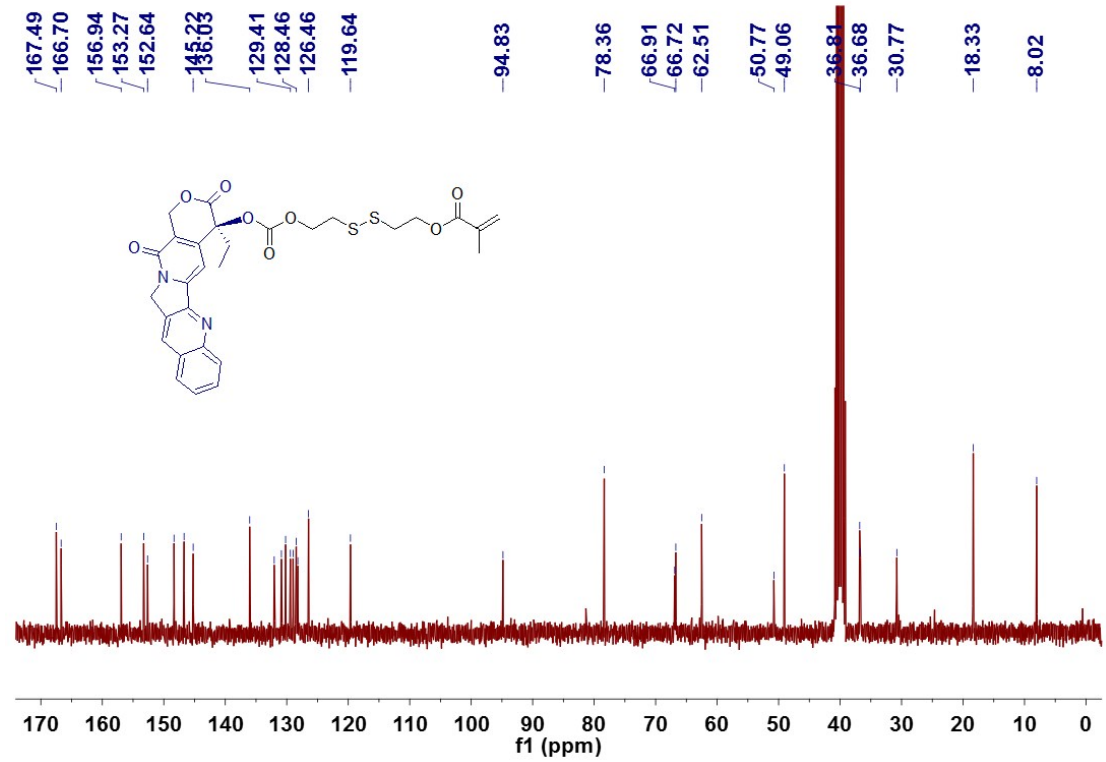


***Fig. S2*** $^{13}$C NMR spectrum (75 MHz, DMSO-$d_6$, room temperature) of **CPTM**.

*2. Synthesis of **mPEG-b-PCPT***

Reversible addition-fragmentation chain transfer (RAFT) polymerization technique was employed for the synthesis of **mPEG-*b*-PCPT**. Typically, **mPEG-CTA** (92 mg, 0.04mmol), **CPTM** (1.26 g, 2.10mmol), and AIBN (0.33 mg, 0.002 mmol) were charged into a glass ampoule containing 4 mL 1,4-dioxane and DMSO mixed solvents (1:1, *v*/*v*). The ampoule was then degassed via three freeze-pump-thaw cycles and flame-sealed under vacuum. It was then immersed into an oil bath thermostated at 80 $^{o}$C to start the polymerization. After 24 h, the ampoule was quenched into liquid nitrogen to terminate the polymerization. The mixture was precipitated into an excess of diethyl ether to generate pale residues, the residues were dissolved in DCM and precipitated into diethyl ether, and the above dissolution-precipitation cycle was repeated for three times. The final product was dried in a vacuum oven overnight at room temperature, yielding a pale solid powder (1.14 g, yield: 86.3 %). The molecular weight and molecular weight distribution of **PEG-*b*-PCPT** were determined by GPC using DMF as the eluent, revealing an $M_n$ of 34.7 kDa and $M_w/M_n$ of 1.27 (Figure S4). The actual degree of polymerization (DP) of the **PEG-*b*-PCPT** was determined to be 50 by $^{1}$H NMR analysis recorded in $CDCl_3$.

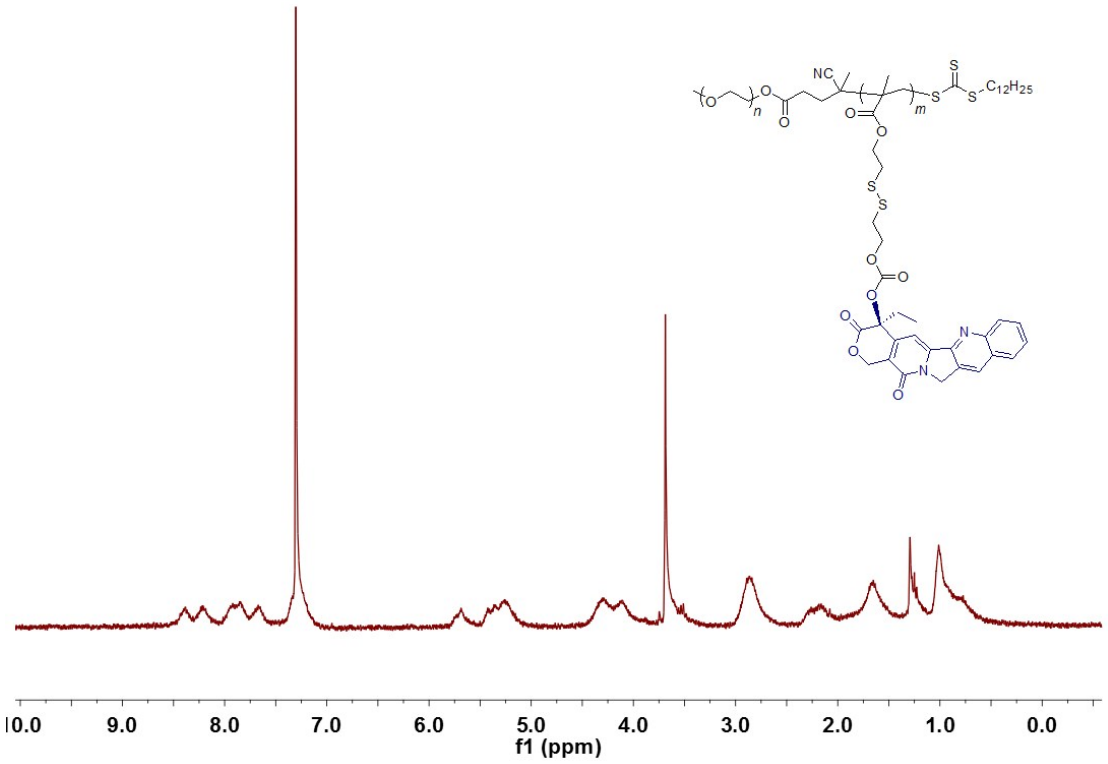


***Fig. S3*** $^{1}$H NMR spectrum (300 MHz, $CDCl_3$, room temperature) of **mPEG-*b*-PCPT**.

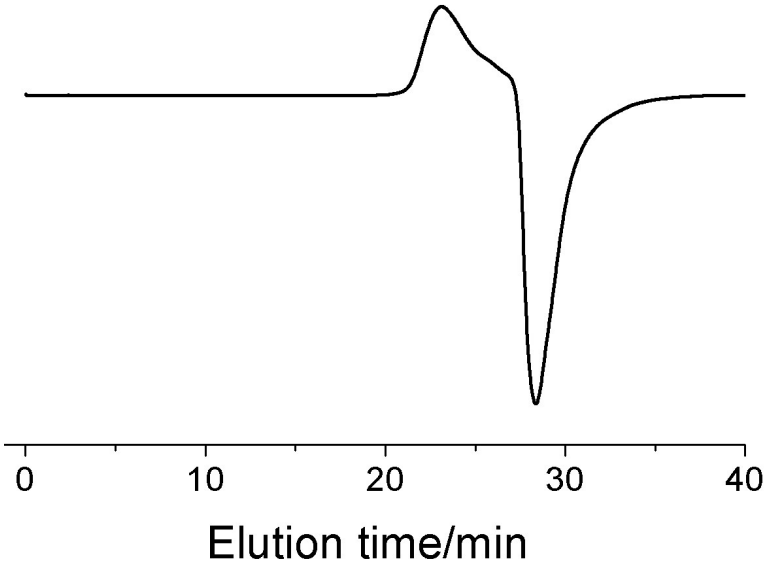


***Fig. S4*** The GPC curve of **mPEG-*b*-PCPT.**

*3. Cytotoxicity and $IC_{50}$ of DOX and CPT in HepG-2 cells*

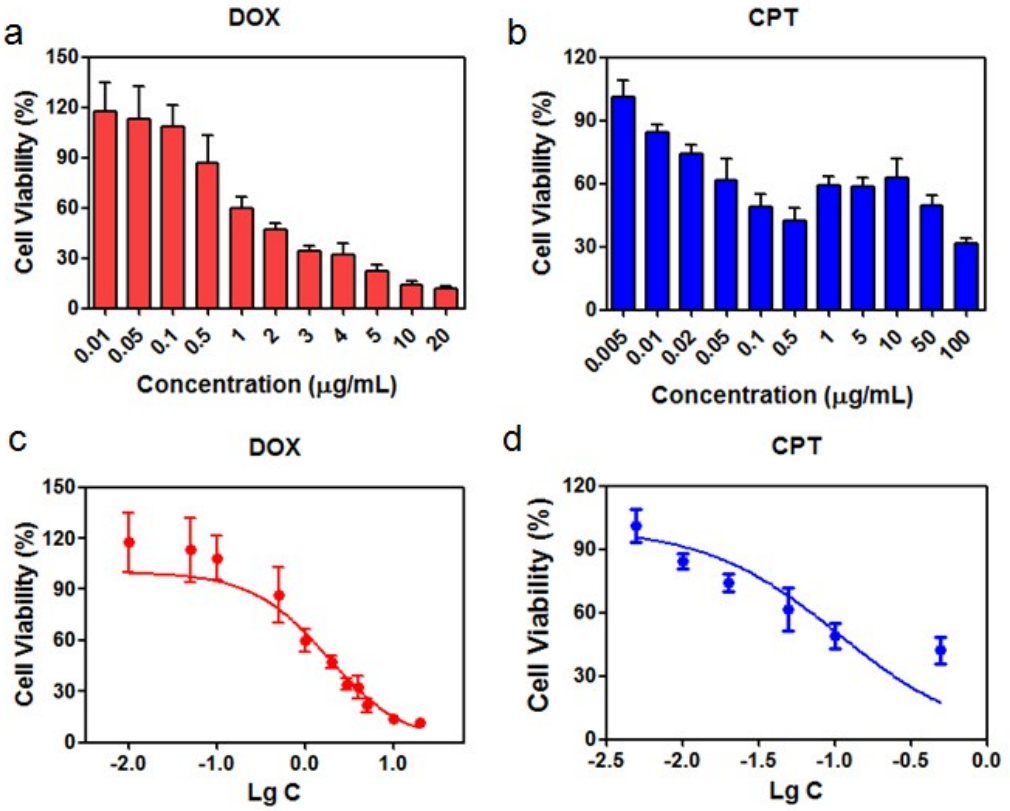


***Fig. S5*** Viability of HepG-2 cells treated with DOX (a) and CPT (b) respectively at various concentrations for 24 h. $IC_{50}$ of DOX (c) and CPT (d) were calculated via the nonlinear regression analysis using graphpad prism 5 software. Data represent mean ± SD ($n$ = 4).

*4. Cytotoxicity of DOX and CPT in HUVEC cells*

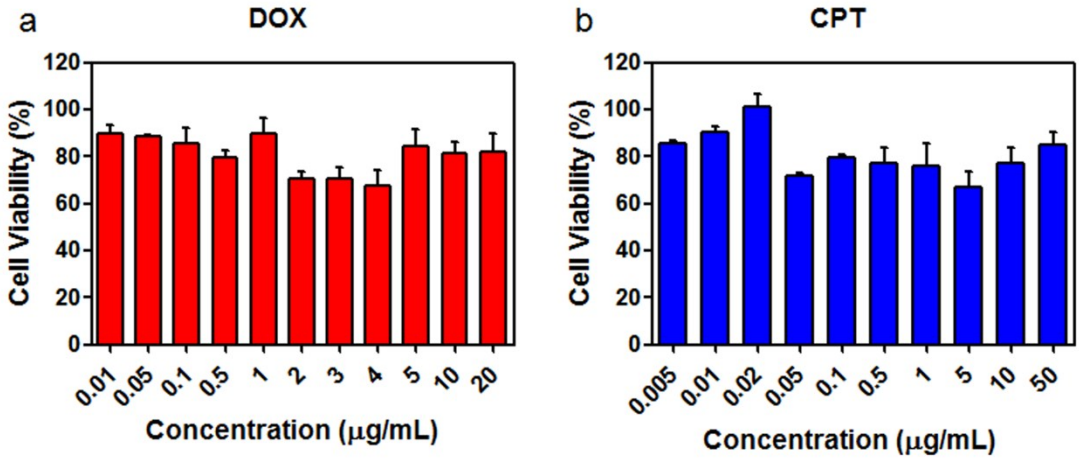


***Fig. S6*** Viability of HUVEC cells treated with DOX (a) and CPT (b) respectively at various concentrations for 24 h.

*5. CI values of different drug combinations*

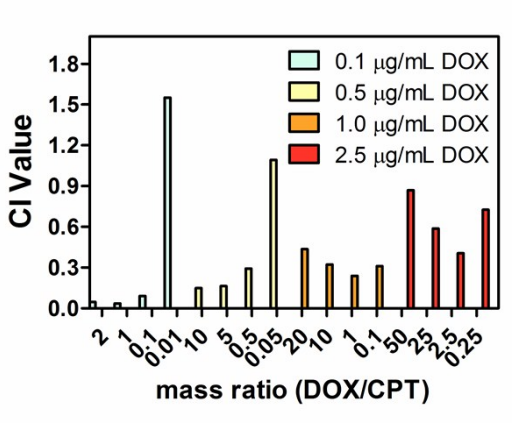


***Fig. S7*** CI values against different mass ratio of DOX and CPT at different level of DOX concentrations**.**

***References****:*

S1 X. Hu, J. Hu, J. Tian, Z. Ge, G. Zhang, K. Luo and S.J. Liu, *J. Am. Chem. Soc*. 2013, **135**, 17617−17629.