

Supporting information

**Dual-responsive click-crosslinked micelles designed for enhanced
chemotherapy in solid tumor**

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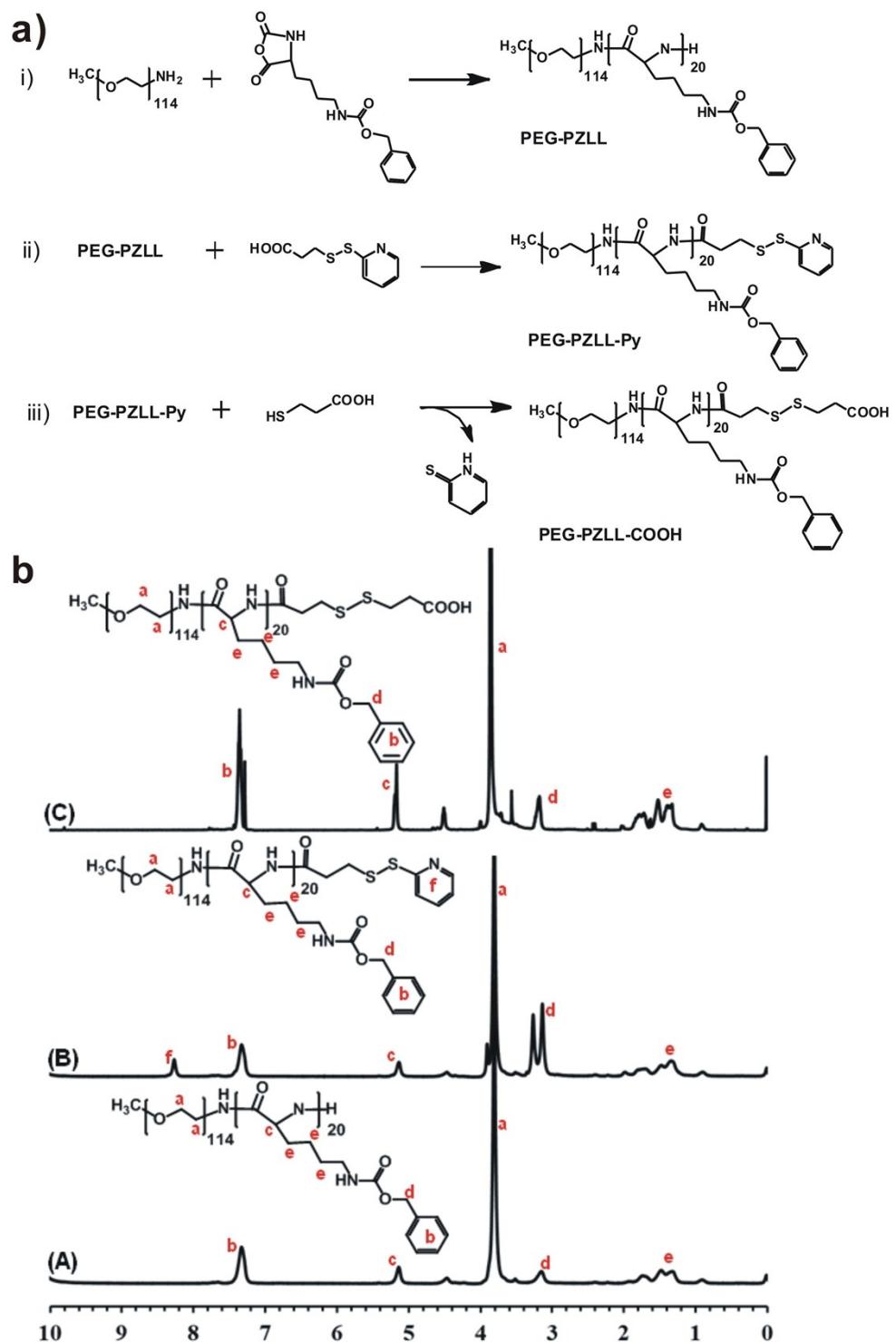


Fig. S1. a) Synthesis route of PEG-PZLL-COOH copolymer; b) ^1H NMR spectrum of (A) PEG-PZLL, (B) PEG-PZLL-Py and (C) PEG-PZLL-COOH in $\text{CDCl}_3/\text{CF}_3\text{COOD}$ (2/1, v/v).

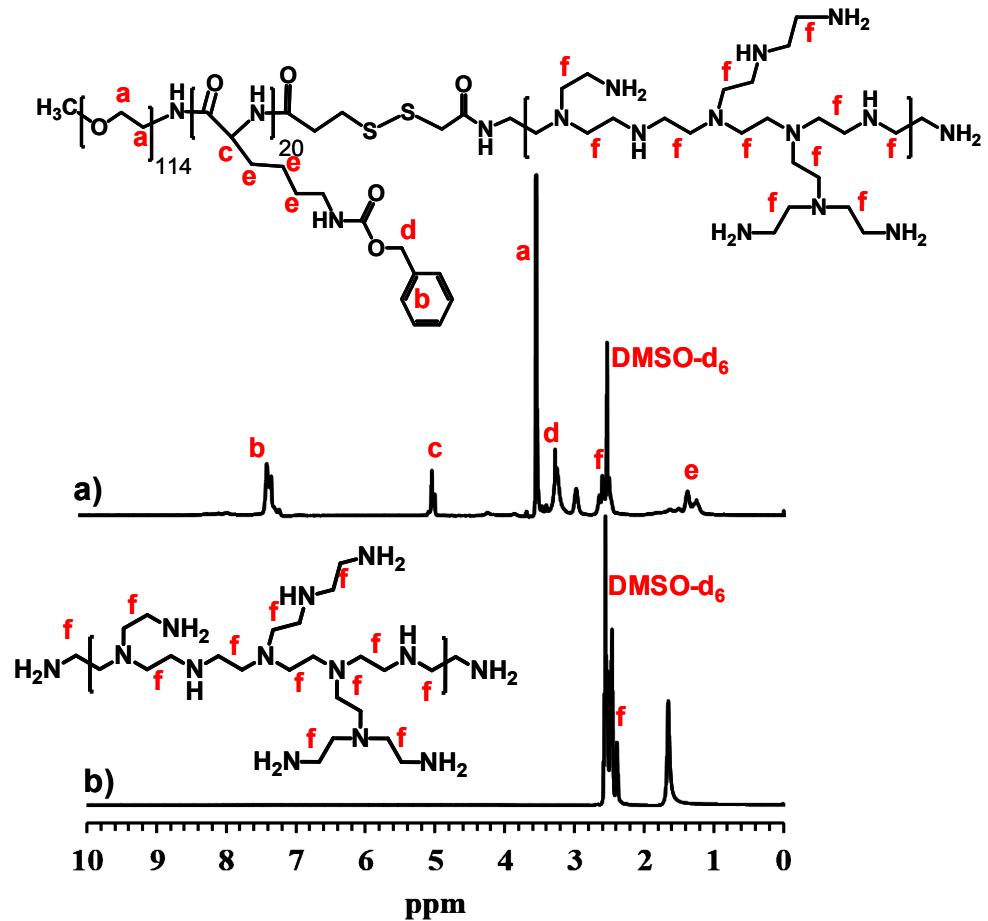


Fig. S2. ¹H NMR spectrum of a) PEG-PZLL-BPEI copolymer and b) BPEI

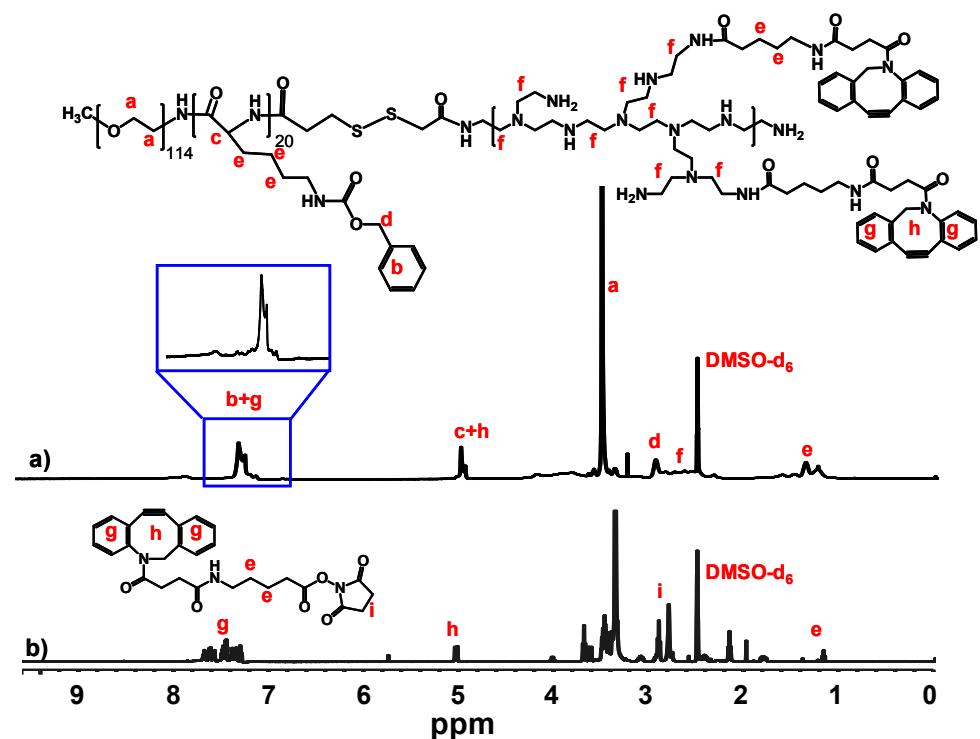


Fig. S3. ¹H NMR spectrum of a) PDBCO4 and b) DBCO-NHS.

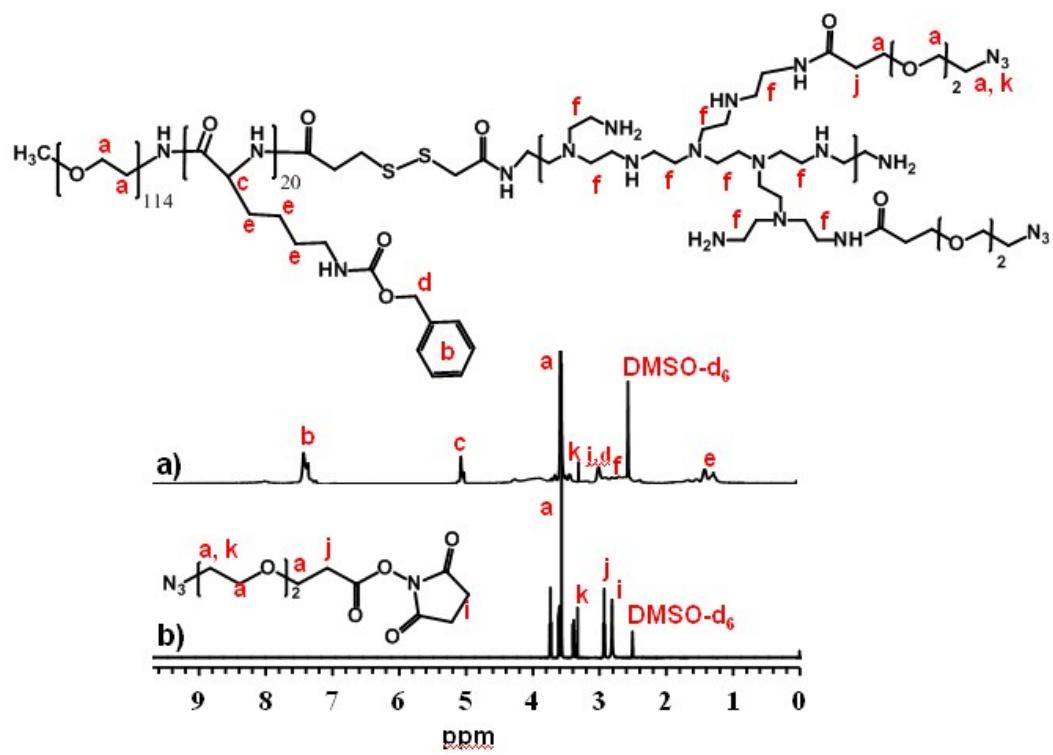


Fig. S4. ¹H NMR spectrum of a) PAZ4 and b) N₃-PEG₂-NHS.

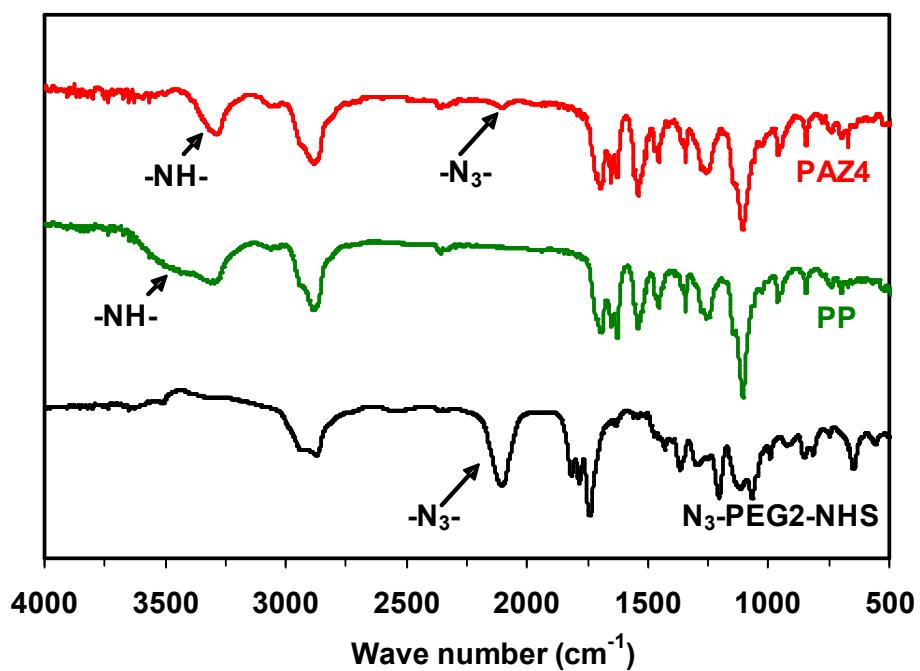


Fig. S5. FT-IR spectrum of PAZ4, PEG-PZLL-PEI(PP) and N₃-PEG2-NHS.

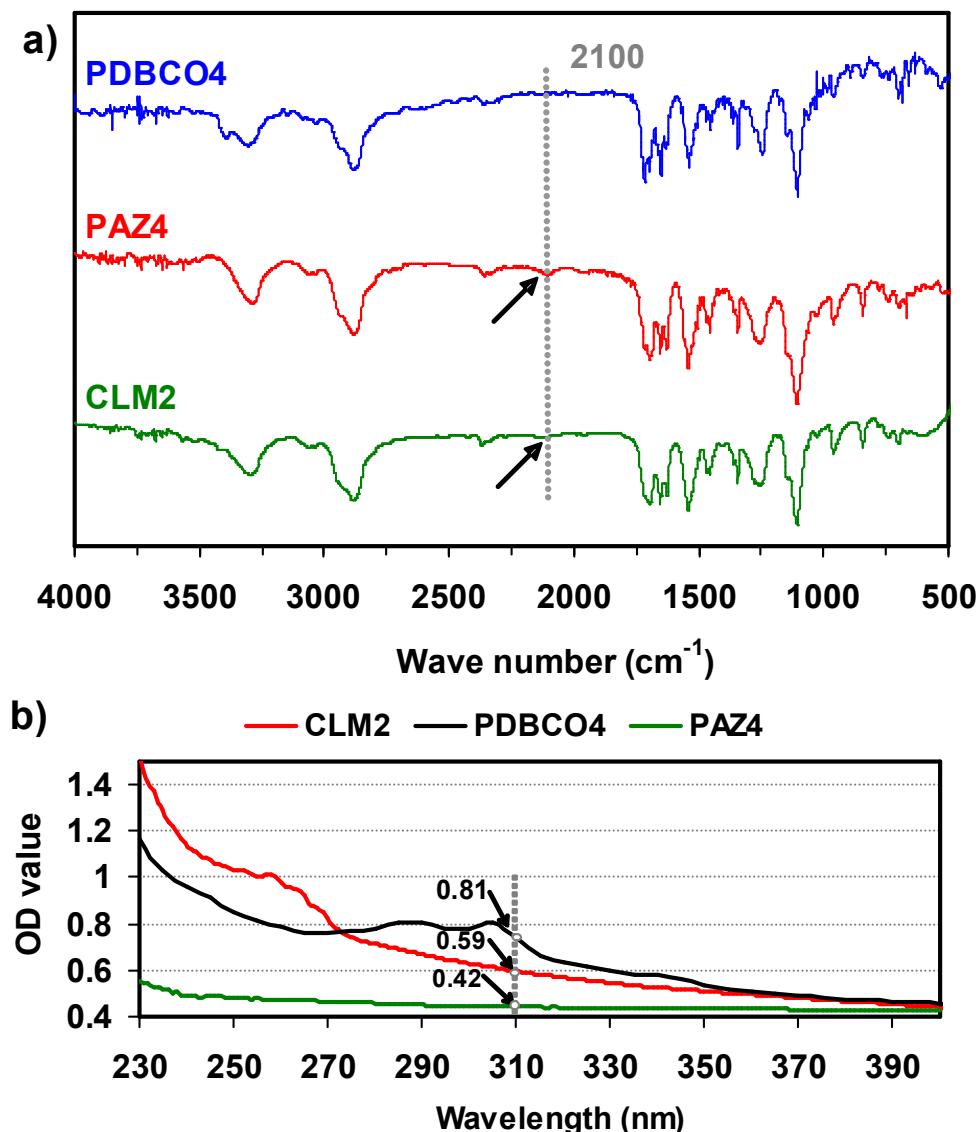


Fig.S6. a) FT-IR and b) UV-vis spectrum of PDBCO4, PAZ4 and crosslinked PDBCO4/PAZ4 micelles (CLM2). The PDBCO4, PAZ4 and CLM2 at a concentration of 1 mg/mL were tested by UV-vis measurement.

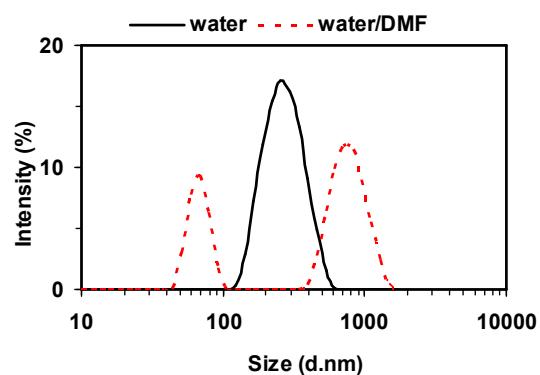


Fig. S7. DLS analysis of crosslinked micelles from PDBCO2/PAZ2 in water and water/DMF mixed solvent (1/1, v/v).

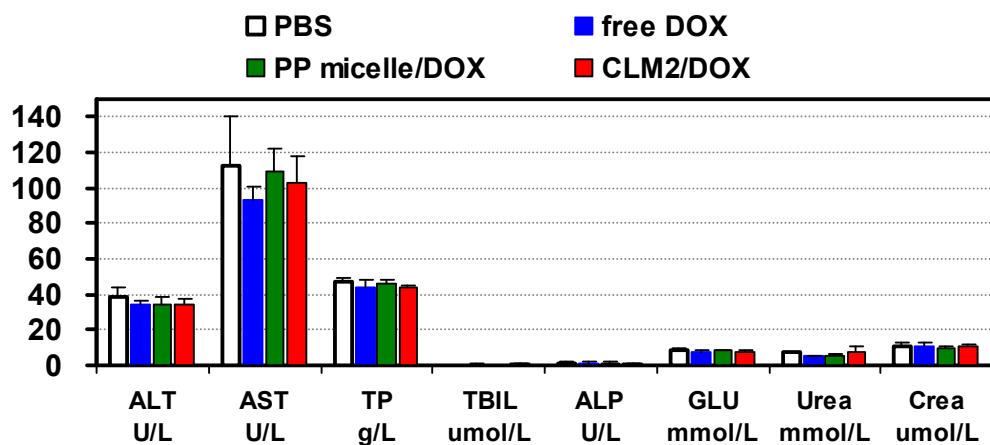


Fig. S8. Routine blood analysis showing the level of different serum bio-markers.

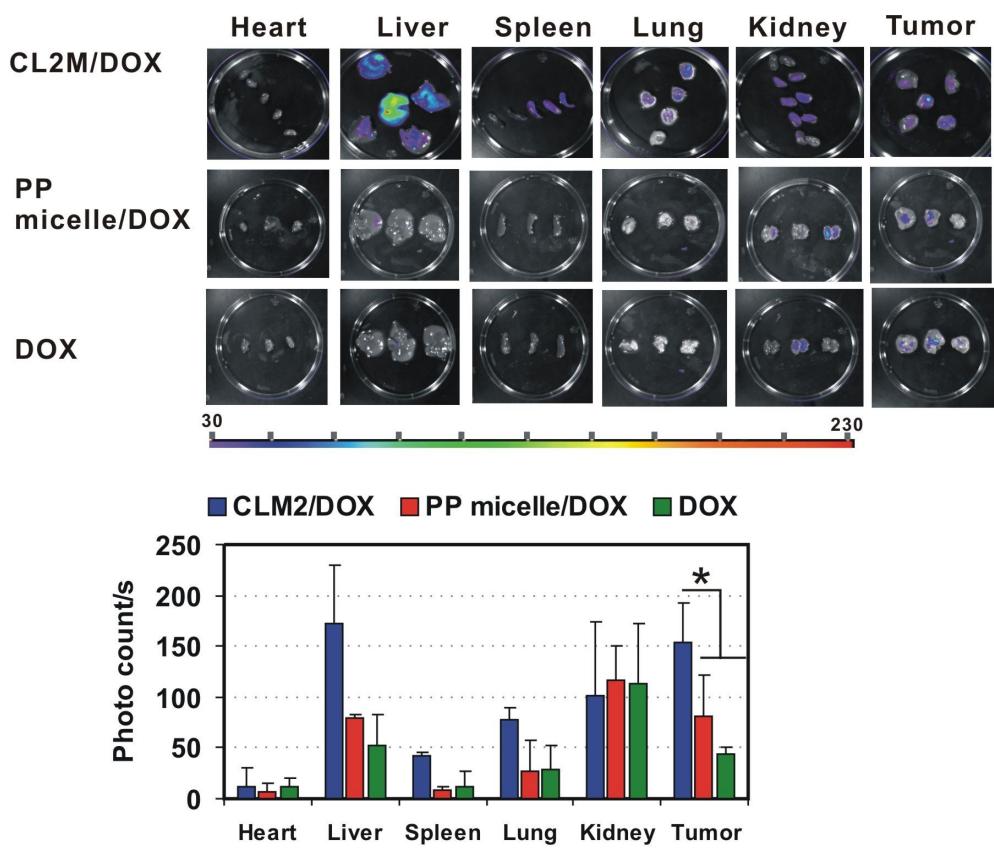


Fig.S9. *Ex vivo* fluorescence imaging of organs and tumors 24 h after tail-vein injection of DOX-loaded CLM2 micelles, PP micelles or DOX alone into SKOV-3 bearing nude mice (n=3-5). The DOX fluorescence intensities of the tissues (heart, liver, spleen, lung, kidneys and tumor) were imaged and quantified under a fluorescence imaging system (NightOWL LB983, Germany).

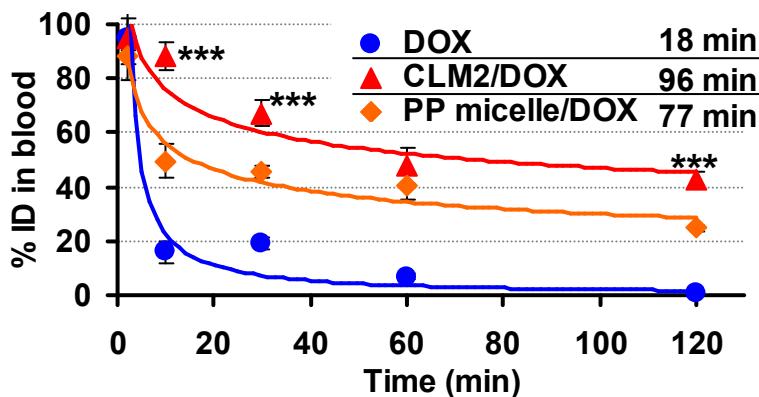


Fig. S10. Pharmacokinetics curves of DOX in the blood of mice after IV injection with the free DOX, DOX-loaded CLM2 micelles and DOX-loaded PP micelles. The DOX dose (DOX/mouse weight), 4 mg kg^{-1} , was used in a BALB/c mouse model ($n=4$). * $P<0.05$: CLM2 vs. PP micelles. The inserted gives half-life time of DOX released by the micelles, as calculated by PK solver 2.0 software.

Table S1. The effect of mixing time of PDBCO and PAZ on the size of crosslinked micelles

Code	Compositions	Mixing time (min.)	DLS (d.nm)	PDI	Surface charge of micelles (mV)
CLM1	PDBCO2/PAZ2	0.5	277.3	0.18	+0.1
CLM2	PDBCO4/PAZ4	0.5	200.6	0.16	+0.5
CLM3	PDBCO6/PAZ6	0.5	Gel	N/A	N/A
CLM4	PDBCO4/PAZ4	15	278.1	0.25	+0.2
CLM5	PDBCO4/PAZ4	30	295.3	0.29	+0.2
PP	N/A	N/A	99.3	0.12	+1.2
PDBCO4	N/A	N/A	167.3	0.15	+1.2

Table S2. Characterization of micelles and DOX-loaded micelles

Sample code	Surface charge of micelles (mV)	Size (d.nm)	PDI	DLC (%)	DLE (%)
PP/DOX	+0.8	103.2	0.16	5.2	26.5
PDBCO4/DOX	+0.6	140.4	0.16	5.2	22.5
CLM2/DOX	+1.1	150.4	0.21	8.1	36.8