

Support information

ROS-Responsive Mitochondria-targeting Blended Nanoparticles: Chemo-and Photodynamic Synergistic Therapy for Lung Cancer with On-Demand Drug Release upon Irradiation with a Single Light Source

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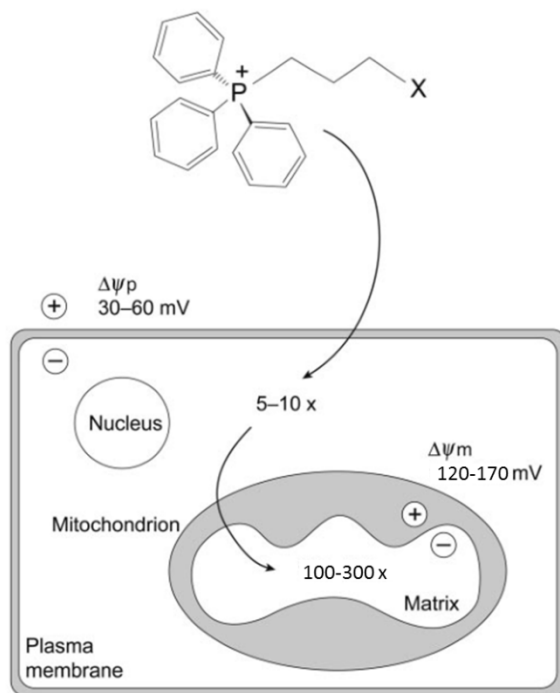


Fig.S1. Uptake of alkyl triphenylphosphonium cations by mitochondria within cells. The lipophilic triphenylphosphonium cation is covalently attached to a biologically active molecule (X). The lipophilic cation is accumulated 5- to 10-fold into the cytoplasm from the extracellular space by the plasma membrane potential ($\Delta\Psi_p$) and then further accumulated 100- to 300-fold into the mitochondrial matrix by the mitochondrial membrane potential ($\Delta\Psi_m$).

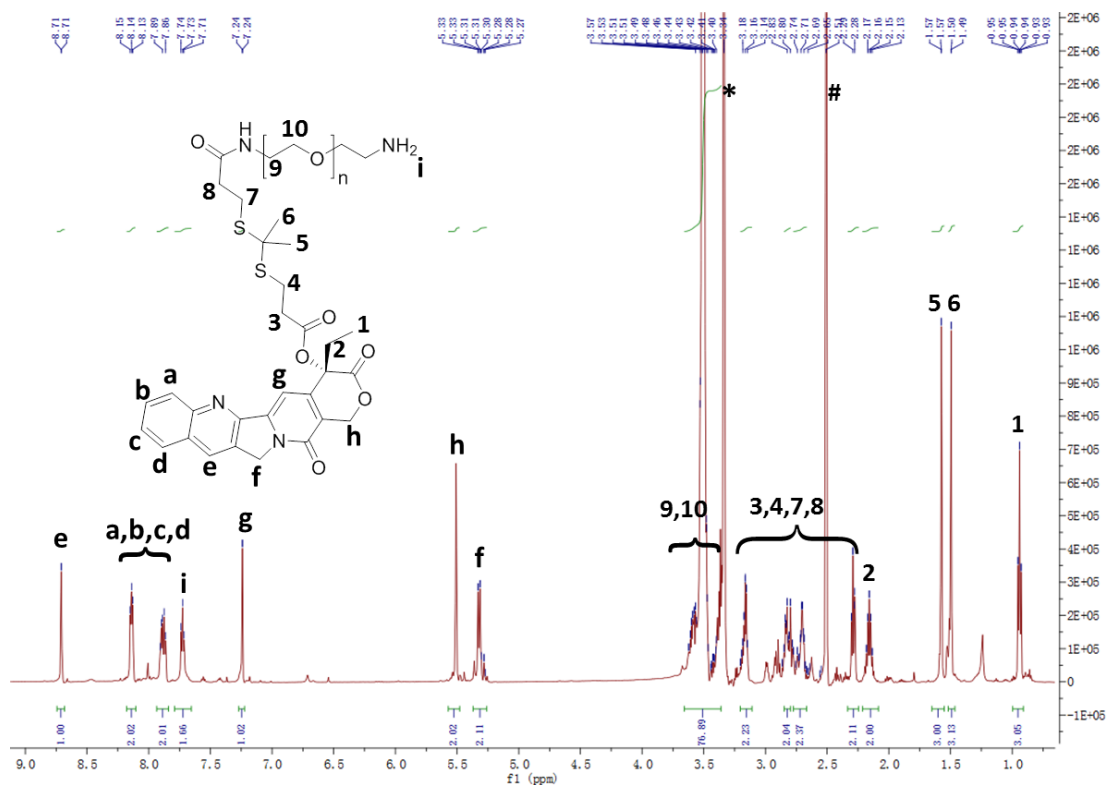


Fig.S2. $^1\text{H-NMR}$ spectrum of TL-CPT-PEG_{1K}-NH₂ in DMSO-*d*₆.

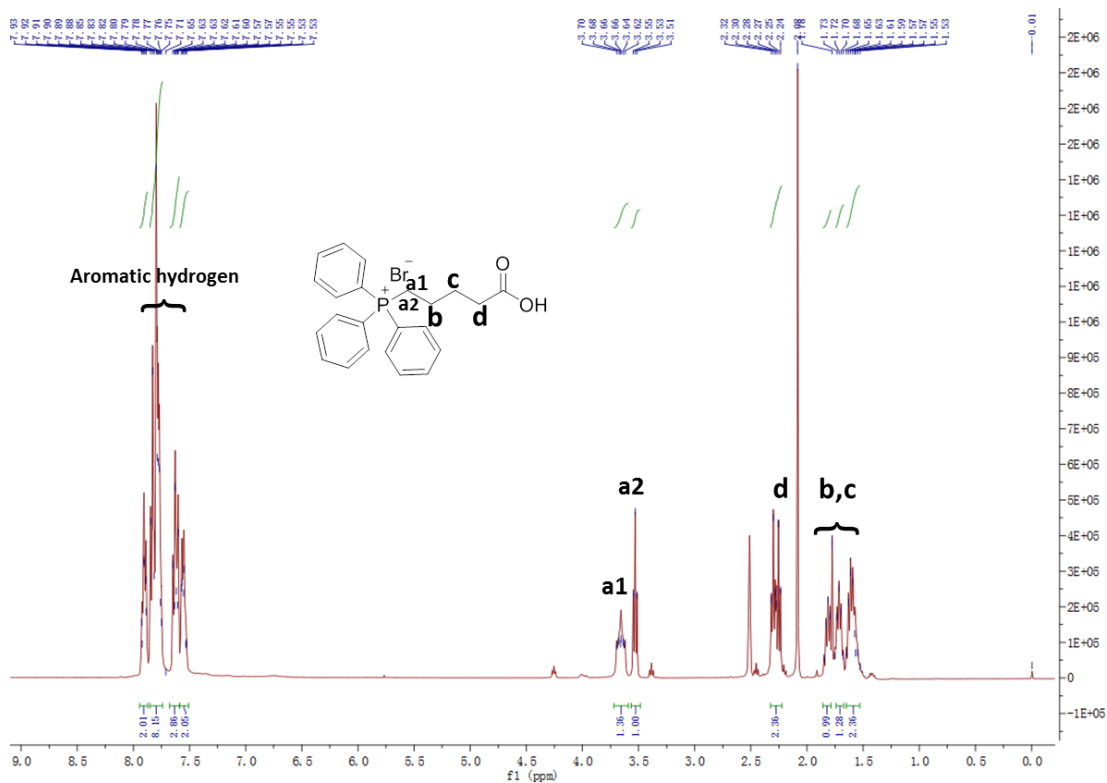


Fig.S3. $^1\text{H-NMR}$ spectrum $\text{PPh}_3\text{Br}-(\text{CH}_2)_4\text{-COOH}$ (TPP) in $\text{DMSO-}d_6$.

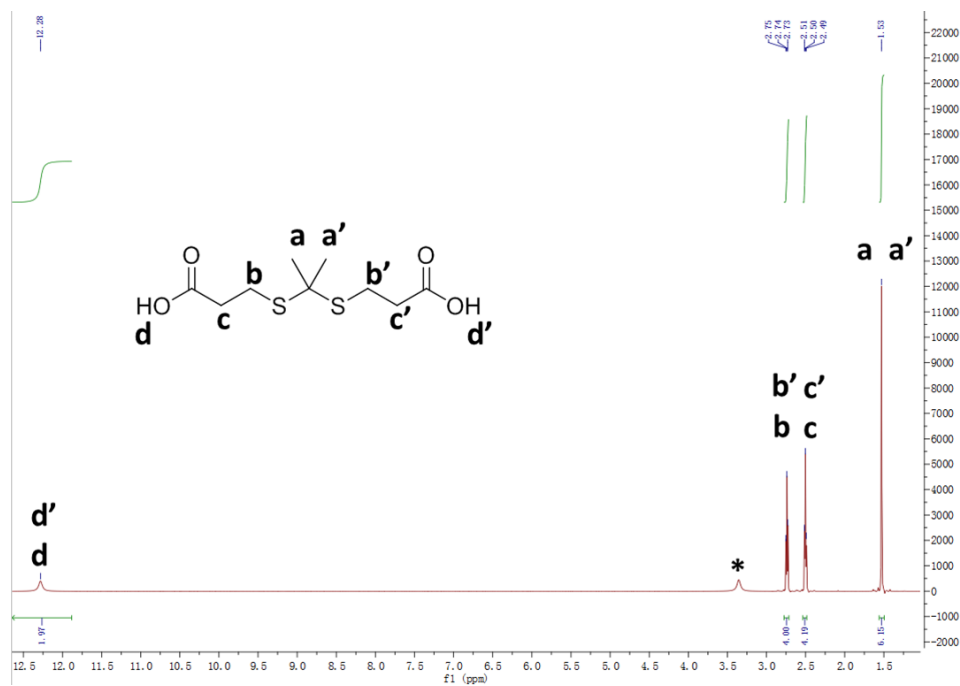


Fig.S4. $^1\text{H NMR}$ spectrum of ROS responsive linker TL in $\text{DMSO-}d_6$.

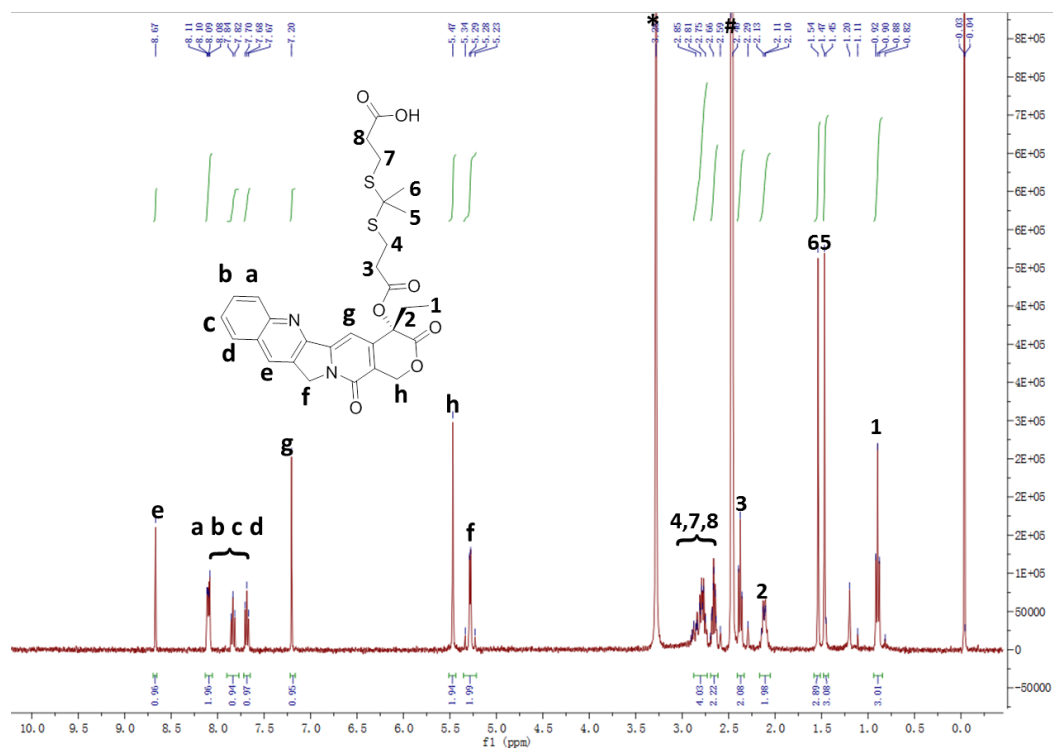


Fig.S5. ¹H NMR spectrum of ROS responsive CPT (TL-CPT) in DMSO-d₆.

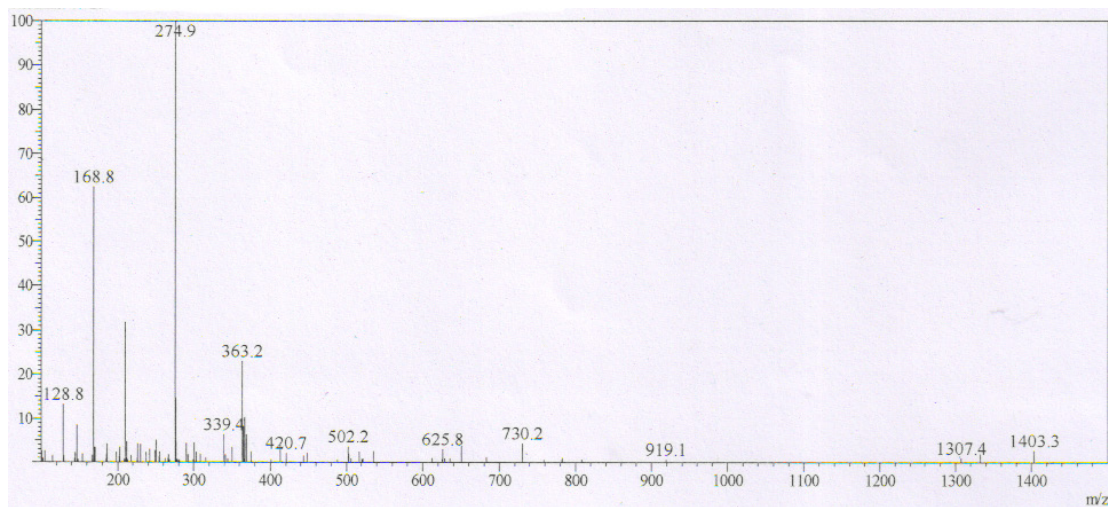


Fig.S6. Mass spectrum of ROS-cleavable thioketal linker (TL). The mass-to-charge ratio (m/z) of 274.9 $[M+Na]^+$ corresponded to TL.

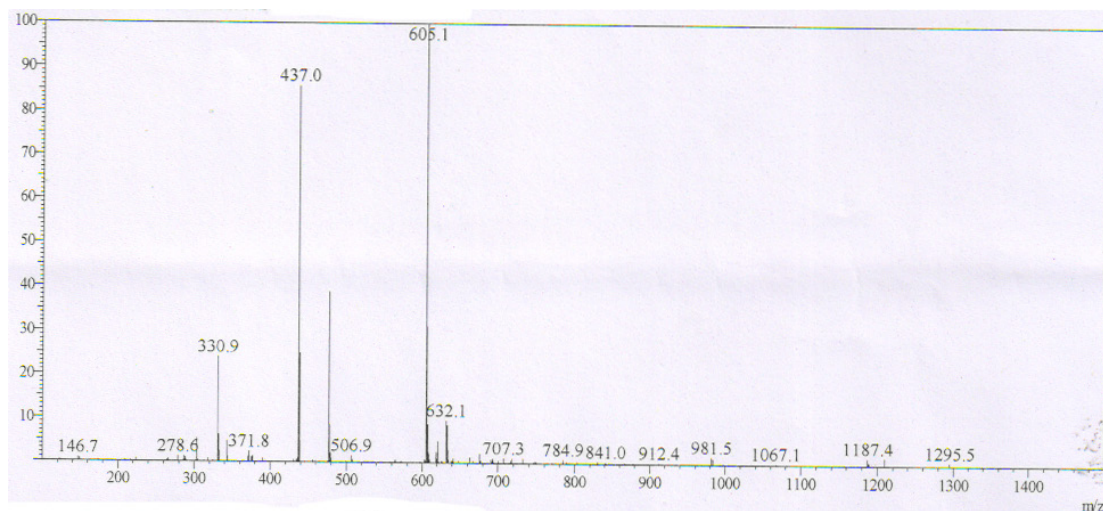


Fig.S7. Mass spectrum of ROS responsive camptothecin (TL-CPT). The mass-to-charge ratio (m/z) of 605.1 $[M+Na]^+$ corresponded to TL-CPT.

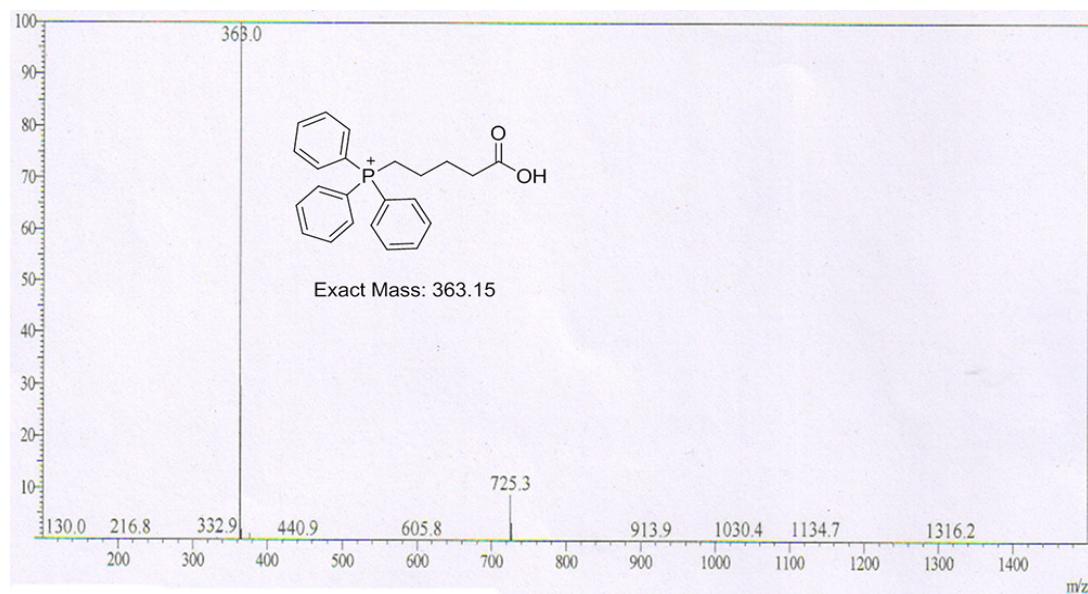


Fig.S8. Mass spectrum of mitochondria targeted small molecule PPh₃Br-(CH₂)₄-COOH (TPP).

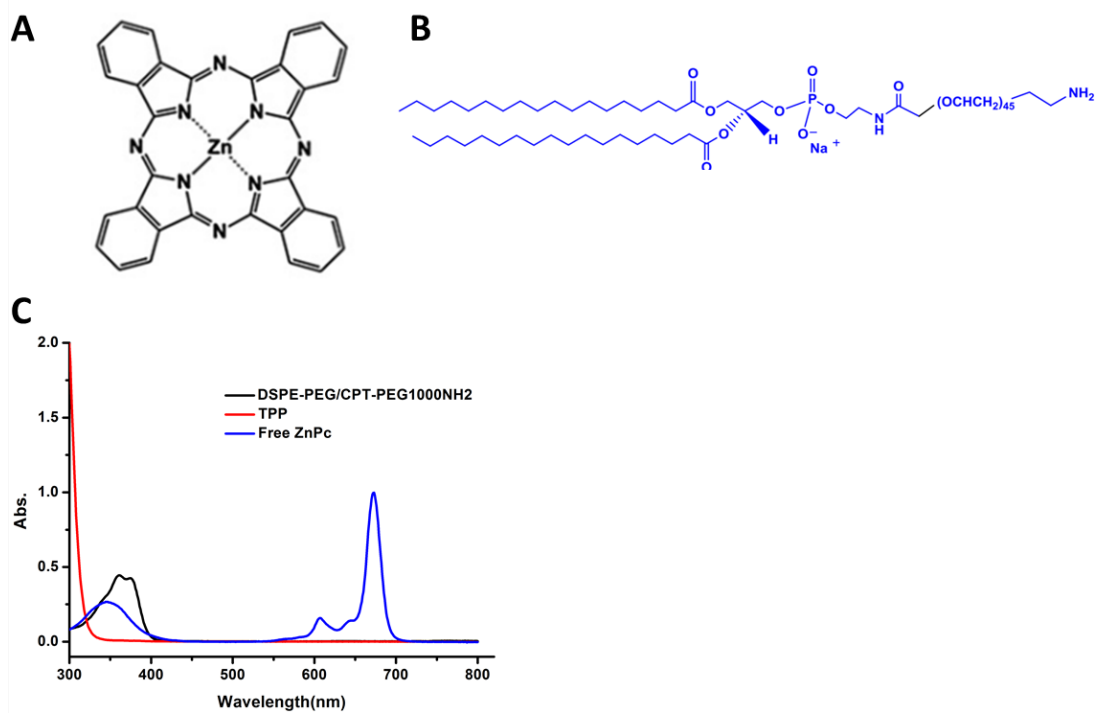


Fig.S9.(A)(B)Structural formula of ZnPc and DSPE-PEG_{2K}NH₂ (C)Normalized UV/Vis absorption spectra of DSPE-PEG_{2K}NH₂/CPT-PEG_{1K}NH₂ mixture, TPP and free ZnPc in DMSO solution.

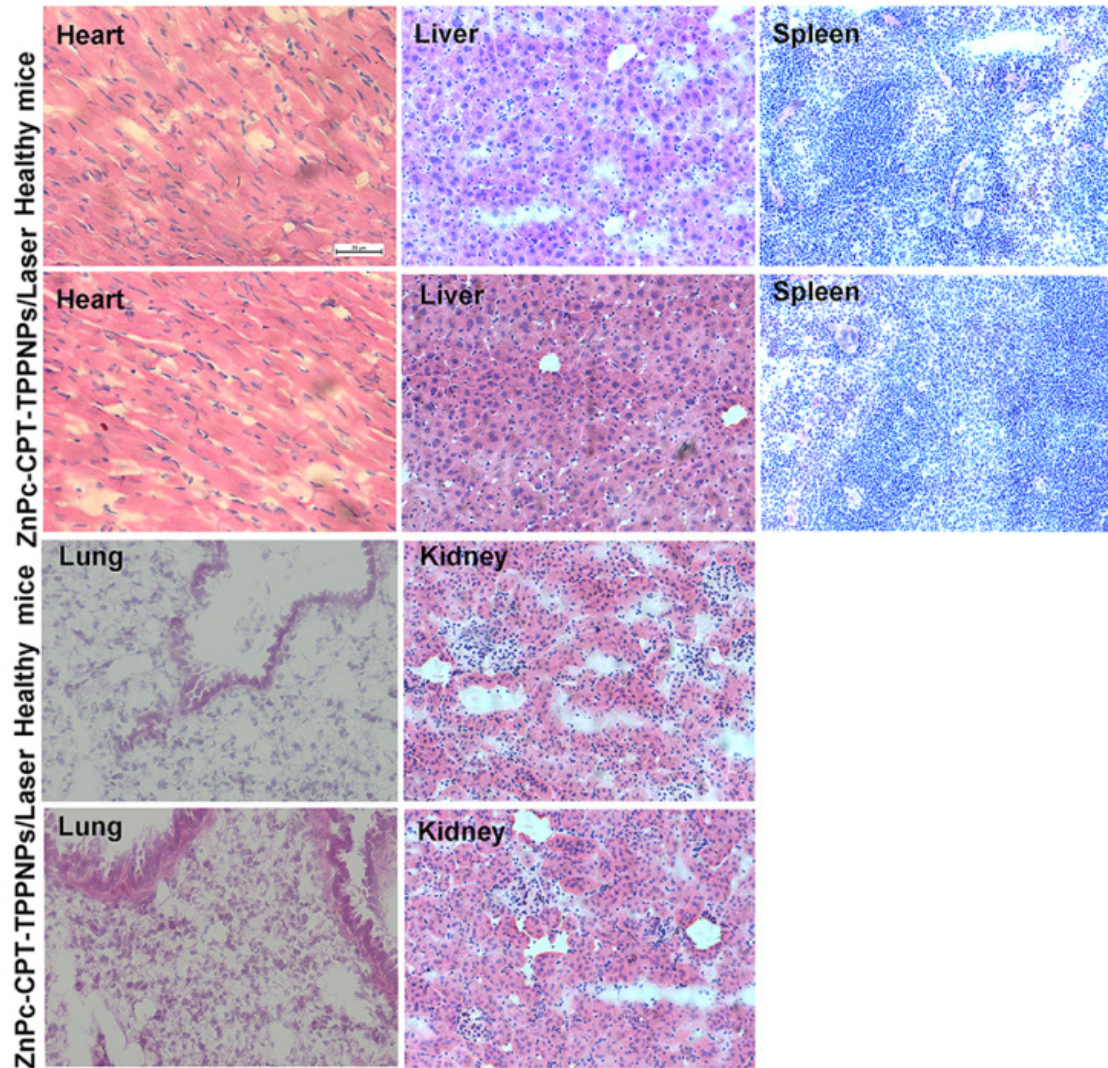


Fig.S10.H&E stained images of major organs. Scale bar = 25 μ m, 50 days after ZnPc-CPT-TPPNPs plus laser treatment, the mice were sacrificed and no noticeable abnormality was observed in heart,liver, spleen, kidney and lung.

***In vitro* the released CPT structure detected by LC-HRMS**

The ZnPc/CPT-TPPNPs were irradiated with or without 50mW/cm² 633 nm laser for different time, then the nanoparticles were detected by LC-HRMS.

LC-HRMS condition and method

LC-HRMS was performed on a Waters ACQUITY UPLC system equipped with binary solvent delivery manager and a sample manager, coupled with a Waters Micromass Q-TOF Premier Mass Spectrometer equipped with an electrospray interface (Waters Corporation, Milford, MA) at the Instrumental Analysis Center of Shanghai Jiao Tong University.

LC Conditions:

Column: Acquity BEH C18 column (100 mm×2.1 mm i.d., 1.7 μm; Waters, Milford, USA).
Solvent: The column was maintained at 50 °C and eluted with gradient solvent from A: B (95: 5) to A: B (0: 100) at a flow rate of 0.40mL/min, where B is acetonitrile (0.1% (v/v) formic acid) and A is aqueous formic acid (0.1% (v/v) formic acid) . Wavelength: 360nm. Injection Volume (μ l): 5.00. Column Temperature: 50.0 °C.

MS Conditions:

polarity: positive; capillary voltage: 3.0kV; Sampling cone: 35V; collision energy: 4eV; Source temperature: 115°C; Desolvation temperature: 350°C; Desolvation gas: 600l/hr; Scan range: *m/z* 50~1000; Scan time: 0.3s; Interscan time: 0.02s. MS collision energy: 4eV. MS/MS collision energy: ramp10~20eV.

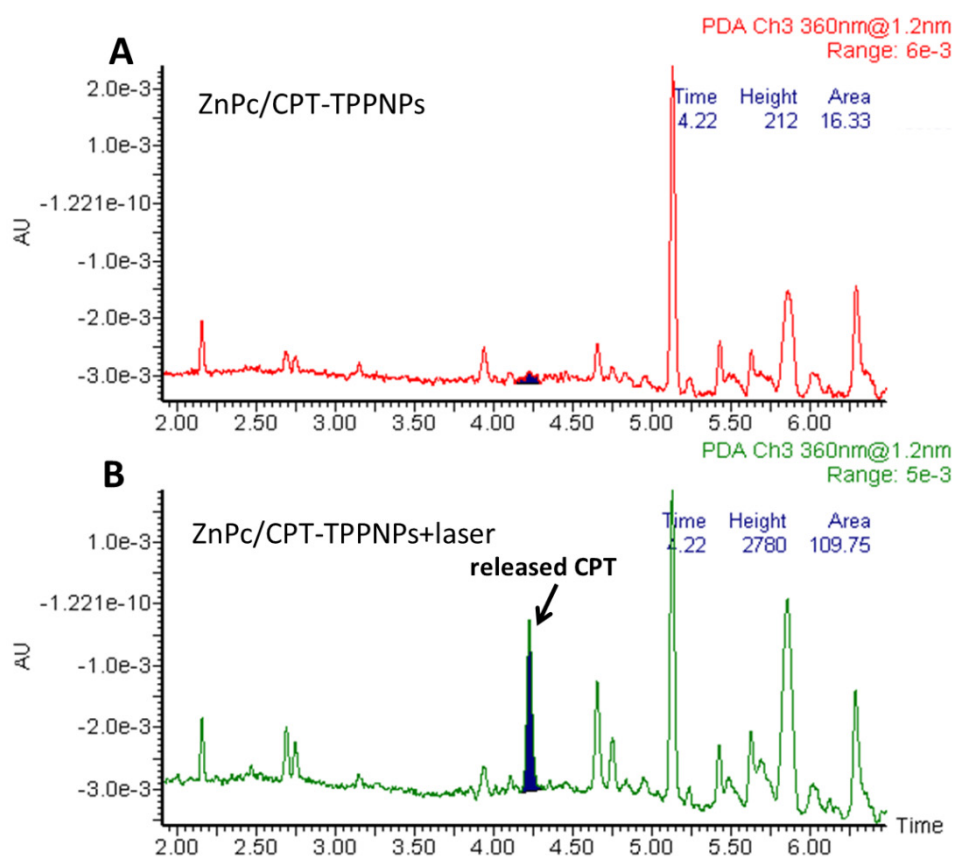


Fig.S11. Analysis of the release of CPT by LC-HRMS: (A) Chromatogram at UV 360 nm of ZnPc/CPT-TPPNPs without 633 nm laser. (B) Chromatogram at UV 360 nm of ZnPc/CPT-TPPNPs with 633 nm laser. The area of peak at 4.22 min can indicate the release of CPT.

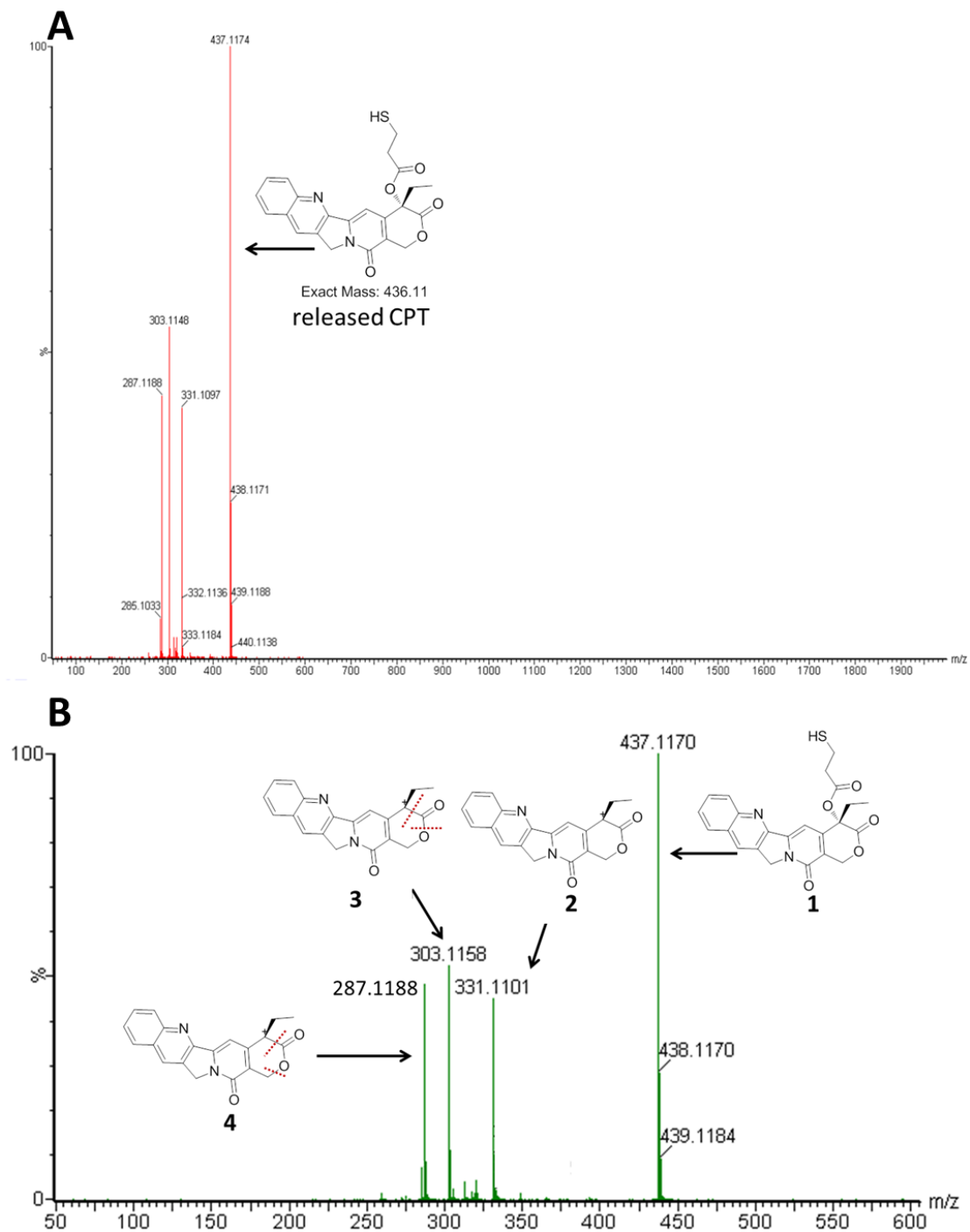


Fig.S12. (A) Mass spectrum of the peak at 4.22 min in chromatogram at UV 360 nm of ZnPc/CPT-TPPNPs with 633 nm laser. The mass-to-charge ratio (m/z) of 437.117 $[M+H]^+$ corresponded to the compound of released CPT.(B)The secondary mass spectrum of the m/z 437.11 peak of (A). The position marked with the red line in (B) may be cut off easily.