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Supporting Information

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Chain-Shattering Polymeric Therapeutics with On-Demand Drug-Release Capability**

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Experimental section

Materials. 10-Hydroxylcamptothecin (HCPT) and 9-aminocamptothecin (ACPT) were purchased from Wilshire Technologies, Inc. (Princeton, NJ, USA) and used as received. Pd/C (10%), hydrazine hydrate, anhydrous pyridine, ammonium chloride, camptothecin (CPT), 4-(hydroxymethyl)phenylboronic acid pinacol ester, phosgene (20 % w/w in toluene), triphosgene, trifluoroacetic acid (TFA), *tert*-butyldimethylsilyl chloride (TBDMS-Cl), dibutyltin dilaurate (DBTL), azelaic acid dichloride (**3**), and other reagents and solvents were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used as received unless otherwise specified. Anhydrous dimethylformamide (DMF) was dried with a column packed with 4Å molecular sieves. Tetrahydrofuran (THF) and hexane were dried with a column packed with alumina. Poly(ethylene glycol)-*block*-poly(L-lactide) (PEG_{113}-*b*-$PLLA_{18}$, PEL, M_n = 6,300 g/mol, PDI = 1.06) was synthesized via ring-opening polymerization of L-lactide using stannous(II) octanoate ($Sn(Oct)_2$) as catalyst and poly(ethylene glycol) methyl ether with M_n of 5,000 g/mol as initiator.[1] 2-Nitro-1,3-phenylenedimethanol was prepared according to a previously reported procedure.[2] Balb/c mice (female) were purchased from Charles River Laboratories (Wilmington, MA, USA). Feed and water were available ad libitum. The study protocol was reviewed and approved by the Illinois Institutional Animal Care and Use Committee (IACUC) of the University of Illinois at Urbana−Champaign.

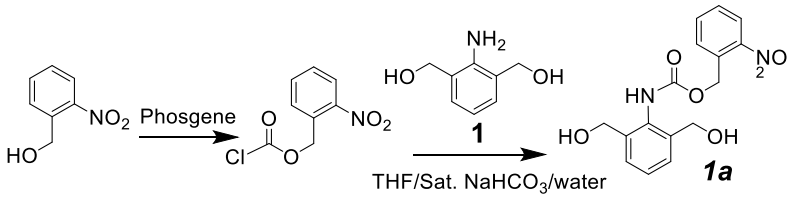
Instrumentation. NMR spectra were recorded on a Varian UI400 (400 MHz), UI500NB (500 MHz), or VXR-500 (500 MHz) spectrometer. Tandem gel permeation chromatography (GPC) was performed on a system equipped with an isocratic pump (Model 1100, Agilent Technologies, Santa Clara, CA, USA), a DAWN HELEOS 18-angle laser light scattering detector (also known

as multi-angle laser light scattering (MALLS) detector; Wyatt Technology, Santa Barbara, CA, USA), and an Optilab rEX refractive index detector (Wyatt Technology). The detection wavelength of the HELEOS was set at 658 nm. Separations were performed on serially connected size exclusion columns (100 Å, 500 Å, 10^3 Å and 10^4 Å Phenogel columns, 5 μm, 300 × 7.8 mm, Phenomenex, Torrance, CA, USA) at 60 °C with DMF containing 0.1 M LiBr as the mobile phase. The HELEOS detector was calibrated with pure toluene without using external polymer standards and was used for the determination of the absolute molecular weights. The molecular weight of each polymer was determined from the *d*n/*d*c value calculated offline by means of the internal calibration system processed by the ASTRA V software (Version 5.1.7.3, Wyatt Technology). Particle sizes and polydispersities were measured with a ZetaPlus dynamic light scattering (DLS) detector (15 mW laser, incident beam = 676 nm, Brookhaven Instruments, Holtsville, NY, USA). HPLC was performed on a System Gold system (Beckman Coulter, Fullerton, CA, USA) equipped with a 126P solvent module, a System Gold 128 UV detector, and an analytical C18 column (Luna C18, 250 mm × 4.6 mm, 5 μm, Phenomenex). The UV wavelength for the analysis of CPT, HCPT, and ACPT were set at 370 nm.

Synthesis of 2,6-bis(hydroxymethyl)aniline (1). A mixture of 2-nitro-1,3-benzenedimethanol (1.464 g, 8 mmol) and Pd/C (0.12 g, 10 wt%) in MeOH (30 mL) was refluxed under N_2 for 30 min. Hydrazine hydrate (1.25 mL, 25.8 mmol) was then added slowly. The resulting mixture was refluxed for 8 h. The catalyst was removed by suction filtration, and the solvent was removed under reduced pressure. The crude residue was dissolved in EtOAc (150 mL); the organic layer was washed with brine (3 × 10 mL) and dried over anhydrous $MgSO_4$. The organic solvent was removed under reduced pressure to afford 2,6-bis(hydroxymethyl)aniline (**1**) as a white solid (0.9 g, yield 63%). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.98 (d, J = 7.4 Hz, 2H, Ar*H*), 6.50 (s, 1H,

Ar*H*), 5.02 (s, 2H, Ar–NH_2), 4.79 (s, 2H, O*H*), 4.40 (d, *J* = 5.4 Hz, 4H, ArCH_2–OH). ^{13}C NMR (DMSO-d_6, 500 MHz): δ 143.1, 125.3, 118.6, 60.2. ESI-MS (low resolution, positive mode): calculated for $C_8H_{12}NO_2$, *m*/*z*, 154.1 $[M + H]^+$; found 154.1 $[M + H]^+$.

Scheme S1. Chemical route for the synthesis of UV-responsive trigger **1a**.

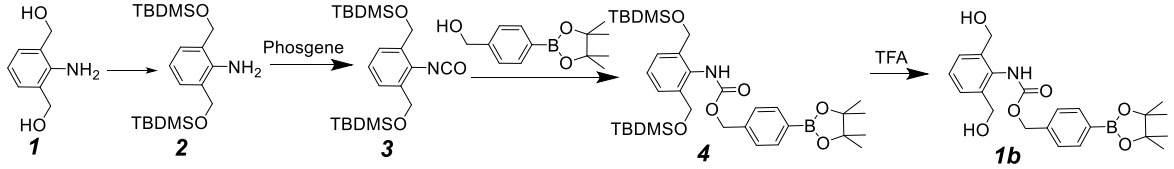


Synthesis of 2-nitrobenzyl (2,6-bis(hydroxymethyl)phenyl)carbamate (1a). 1-(Chlorocarbonyl-oxy-methyl)-2-nitrobenzene was first prepared. A phosgene solution in toluene (15 mL, 20% w/w, 28.8 mmol) was added to a stirred solution of 2-nitrobenzyl alcohol (1.84 g, 12 mmol) in dry THF (20 mL). The mixture was stirred for 16 h at room temperature. The excess phosgene and solvents were removed under reduced pressure, and the phosgene in the vacuum traps was deactivated by aqueous NaOH. The resulting yellowish, oily residue (1-(chlorocarbonyl-oxy-methyl)-2-nitrobenzene) was used in the subsequent reaction without further purification.

Compound **1** (1.50 g, 10 mmol) was dissolved in a mixed solvent (30 mL, THF: saturated $NaHCO_3$: water = 2:2:1, v/v/v). 1-(Chlorocarbonyl-oxy-methyl)-2-nitrobenzene (2.60 g, 12 mmol) in dry THF (6 mL) was added dropwise and stirred for 1 h. The mixture was extracted with EtOAc (3 × 50 mL). The organic phase was washed with brine (3 × 50 mL) and dried with Na_2SO_4. The solvent was evaporated under vacuum. Recrystallization from EtOAc gave **1a** as a white crystalline solid (1.50 g, yield 45%). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.88 (s, 1H, –CO–N*H*–Ar–), 8.13 (d, *J* = 8.1 Hz, 1H, NO_2–Ar–*H*), 7.83 (t, *J* = 7.5 Hz, 1H, NO_2–Ar–*H*), 7.76 (d, *J* =

7.7 Hz, 1H, NO_2–Ar–*H*), 7.63 (t, *J* = 7.9 Hz, 1H, NO_2–Ar–*H*), 7.36 (d, *J* = 7.6 Hz, 2H, –CH_2–Ar*H*), 7.28 (t, *J* = 7.6 Hz, 1H, –CH_2–Ar*H*), 5.44 (s, 2H, NO_2–Ar–CH_2–), 5.10 (t, *J* = 5.7 Hz, 2H, –CH_2O*H*), 4.45 (d, *J* = 5.7 Hz, 4H, –CH_2OH). ^{13}C NMR (DMSO-d_6, 500 MHz): δ 155.6, 149.3, 134.6, 130.7, 129.6 128.5, 125.3, 124.3, 61.8, 60.0. ESI-MS (low resolution, positive mode): calculated for $C_{16}H_{17}N_2O_6$, *m*/*z*, 333.1 $[M + H]^+$; found 333.4 $[M + H]^+$.

Scheme S2. Synthesis of **1b** from **1**.



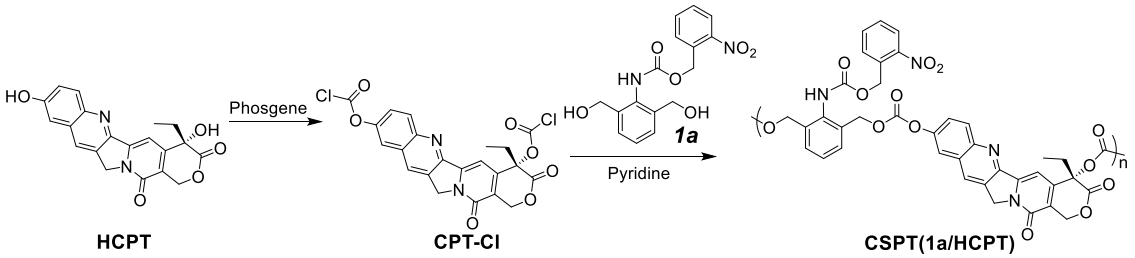
Synthesis of 1b. Compound **1** (0.61 g, 4 mmol) in THF (15 mL) was added to an ice bath cooled suspension of sodium hydride (0.23 g, 8.8 mmol, 1.1 equiv.) in THF (10 mL). The reaction mixture was stirred for 15 min followed by dropwise addition of TBDMS-Cl (1.45 g, 9.6 mmol, 1.2 equiv.) in THF (5 mL). The reaction solution was allowed to gradually warm to room temperature and stirred overnight. The reaction mixture was poured into a brine solution (100 mL) and extracted with EtOAc (3 × 50 mL). The organic phase was dried with anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The compound **2** as colorless oil was obtained and used directly without purification (1.43g, yield 94 %).

To a dried flask, phosgene (20% in toluene, 20 mL, 38 mmol) was added under nitrogen followed by dropwise addition of **2** (1.43 g, 3.75 mmol) in 10 mL of toluene. The reaction mixture was stirred for 30 min at reflux and monitored by TLC. After 1 h, the solvent was removed under reduced pressure. 4-(Hydroxymethyl)phenylboronic acid pinacol ester (1.0 g, 4.4 mmol) in toluene (10 mL) was added, followed by DBTL (100 µL, 0.163 mmol). The reaction

mixture was heated to reflux (110 ºC) for 1 h. The solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/Hex, 1:6) to give **4** (1.5 g, yield 60%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.83 (d, *J* = 7.8 Hz, 2H, B-Ar-H), 7.38 (dd, *J* = 7.8 Hz, 2H, OCH_2-Ar-*H*), 7.30 – 7.19 (m, 3H, CONH-Ar-*H*), 5.22 (s, 2H, NHCOO-C*H*$_2$-Ph), 4.70 (s, 4H, SiO-C*H*$_2$-Ph), 1.37 (s, 12H, (C*H*$_3$)$_2$-CC-(C*H*$_3$)$_2$), 1.02 – 0.84 (m, 18H, (C*H*$_3$)$_3$-CSi), 0.09 (s, 12H, (C*H*$_3$)$_2$-Si). ESI-MS (low resolution, positive mode): calculated for $C_{34}H_{57}BNO_6Si_2$, *m*/*z*, 642.3 $[M + H]^+$; found 642.3 $[M + H]^+$.

Compound **4** (500 mg, 0.8 mmol) was dissolved in a mixture of TFA and DCM (1:1, v/v, 6 mL), and stirred for 25 min. The solvents were then removed under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/Hex, 1:1) to give compound **1b** (250 mg, yield 77%) as a white solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.71 (d, *J* = 7.6 Hz, 2H, B-Ar-*H*), 7.45 – 7.25 (m, 5H, OCH_2-Ar-*H* and CONH-Ar-*H*), 5.18 – 5.06 (m, 3H, NHCOO-C*H*$_2$-Ph and CON*H*), 4.46 (s, 4H, Ph-C*H*$_2$-OH), 1.30 (s, 12H, (C*H*$_3$)$_2$-CC-(C*H*$_3$)$_2$). ^{13}C NMR (DMSO-d_6, 500 MHz): δ 156.6, 148.2, 135.6, 133.5, 130.7, 128.6 126.5, 124.3, 88.9, 67.2, 60.0, 25.3. ESI-MS (low resolution, positive mode): calculated for $C_{22}H_{29}BNO_6$, *m*/*z*, 414.3 $[M + H]^+$; found 414.4 $[M + H]^+$.

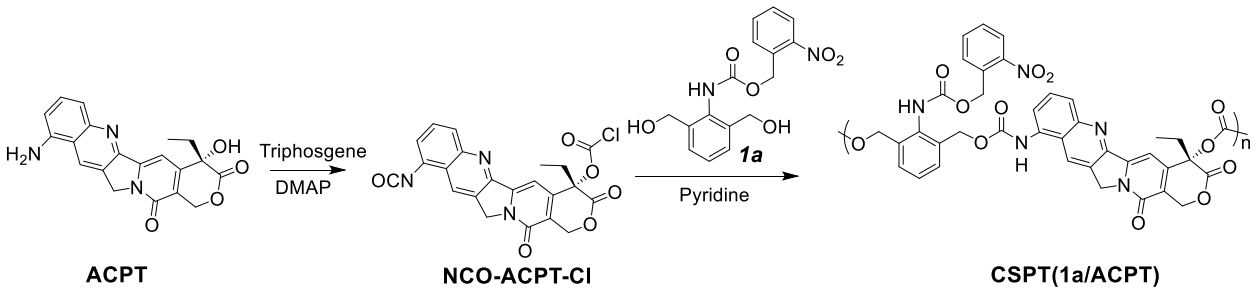
Scheme S3. Synthesis of the CSPT(**1a**/HCPT).



General procedure for the synthesis of CSPT(1a/HCPT). HCPT (50 mg, 0.132 mmol) was

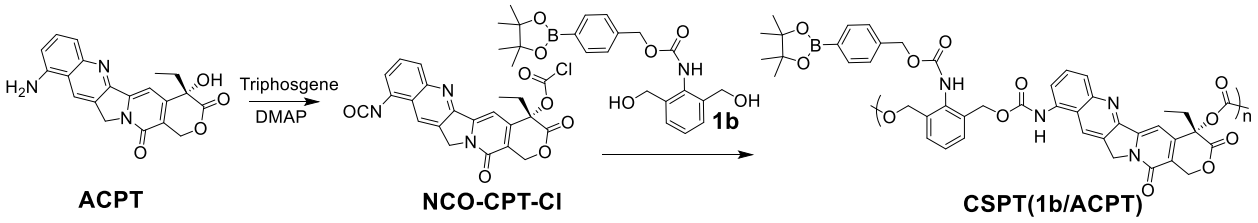
first mixed with phosgene (20% in toluene, 2 mL, 3.8 mmol) and DCM (2 mL). The mixture was stirred overnight at room temperature. The solvent was then removed under reduced pressure and dried under vacuum for an additional 2 h. Dry DCM (6 mL) was then added to dissolve the residue, to which **1a** (44 mg, 0.132 mmol) and pyridine (100 μL) were added. The solution was stirred for 24 h at room temperature. The mixture was subsequently poured into ethyl ether (30 mL). The precipitation was collected by centrifugation, washed with methanol (3 × 20 mL) to remove pyridine and other low molecular weight (MW) materials, and dried under vacuum. CSPT(**1a**/HCPT) was obtained as a slight yellow solid (yield 49%). M_n = 4,200 g/mol; PDI = 1.48.

Scheme S4. Synthesis of CSPT(**1a**/ACPT).



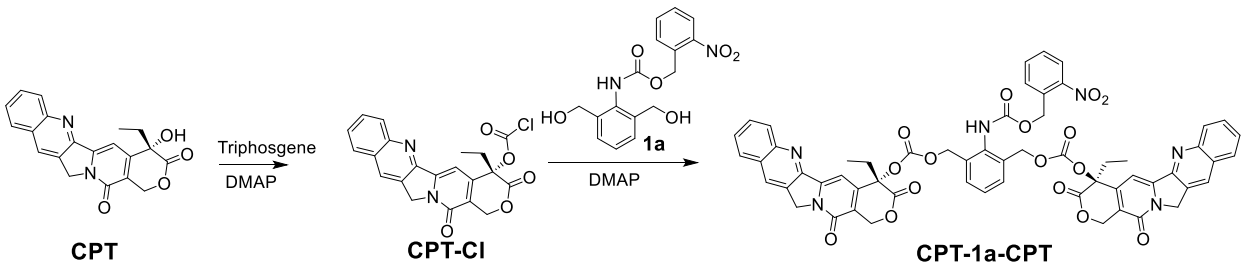
General procedure for the synthesis of CSPT(1a/ACPT). ACPT (36 mg, 0.1mmol) and triphosgene (22 mg, 0.067 mmol) were dispersed in dry DCM (15 mL) under nitrogen. DMAP (78 mg, 0.64 mmol) was added to the mixture. The mixture was stirred for 15 min, followed by addition of **1a** (33 mg, 0.1 mmol). The solution was stirred for 24 h at room temperature. The mixture was subsequently poured into ethyl ether (30 mL). The precipitation was collected by centrifugation, washed with methanol (3 × 20 mL) to remove DMAP and other low MW materials, and dried under vacuum. CSPT(**1a**/ACPT) was obtained as a slight yellow solid (yield 33%). M_n = 4,800 g/mol; PDI = 1.50.

Scheme S5. Synthesis of CSPT(**1b**/ACPT).



General procedure for the CSPT(1b/ACPT) polymerization. ACPT (36 mg, 0.1mmol) and triphosgene (22 mg, 0.067 mmol) were dispersed in dry DCM (15 mL) under nitrogen. DMAP (78 mg, 0.64 mmol) was added to the mixture. The mixture was stirred for 15 min, followed by addition of **1b** (41 mg, 0.1 mmol). The solution was stirred for 24 h at room temperature. The mixture was subsequently poured into ethyl ether (30 mL). The precipitation was collected by centrifugation, washed with methanol (3 × 20 mL) to remove DMAP and other low MW materials, and dried under vacuum. CSPT(**1b**/ACPT) was obtained as a slight yellow solid (yield 39%). M_n = 5,200 g/mol; PDI = 1.52.

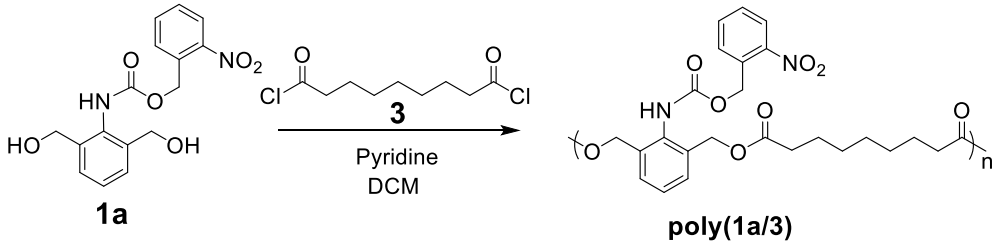
Scheme S6. Synthesis of CPT-**1a**-CPT.



Synthesis of CPT-1a-CPT. CPT (70 mg, 0.2 mmol) and triphosgene (22 mg, 0.067 mmol) were dispersed in DCM (10 mL), to which DMAP (78 mg, 0.64 mmol) was added. The mixture was stirred at room temperature for 15 min. trigger **1a** (20 mg, 0.06 mmol) was added. The solution was stirred at room temperature overnight, diluted with DCM (50 mL) and washed with HCl (pH 1, 3 × 20 mL) and then with water (3 × 20 mL). The organic phase was dried with Na_2SO_4. After

the solvent was removed under vacuum, CPT-**1a**-CPT was purified by preparative HPLC equipped with silica gel column (EtOAc/IPA) to give a slight yellow solid (35 mg, yield 53%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.37 (s, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 7.98 – 7.91 (m, 1H), 7.85 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.69 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.48–7.28 (m, 4H), 5.72 (d, *J* = 17.1 Hz, 1H), 5.40 (d, *J* = 17.1 Hz, 1H), 5.38 – 5.22 (m, 2H), 5.21 – 5.09 (m, 3H), 2.30 (dq, *J* = 15.5, 8.1, 7.7 Hz, 1H), 2.18 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.04 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 500 MHz): δ 168.2, 160.3, 156.2, 154.1, 149.0, 147.8, 145.9, 145.6, 134.8, 134.6, 131.9, 130.7,130.0, 129.0, 128.4, 127.2, 126.5, 125.1, 124.3, 119.8, 98.3, 81.2, 68.2, 65.0, 62.5, 52.6, 32.6, 9.5. ESI-MS (low resolution, positive mode): calculated for $C_{58}H_{45}N_6O_{16}$, *m*/*z*, 1081.3 $[M + H]^+$; found 1081.6 $[M + H]^+$.

Scheme S7. Synthesis of poly(**1a**/3).



General procedure for the synthesis of poly(1a/3). Azelaic acid dichloride (**3**, 99 μL, 0.5 mmol) and **1a** (166 mg, 0.5 mmol) were dissolved in dry DCM (2 mL) under nitrogen, to which pyridine (200 μL, 2.5 mmol) was added dropwise over the course of 3 min. The polymerization was allowed to proceed for 16 h at room temperature. The reaction mixture was concentrated to 0.5 mL. Subsequent addition of cold EtOH (20 mL) yielded a yellow polymer. Precipitation of the polymerization solution with cold ethanol followed by centrifugation for 3 times afforded poly(**1a/3**) as a white solid (yield 68%). M_n = 13,800 g/mol; PDI = 1.46. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.30 (s, 1H, –CON*H*–Ar), 8.11 (d, 1H, Ar*H*), 7.81–7.59 (m, 3H, Ar*H*) 7.35–7.20

(m, 3H, Ar*H*), 5.45 (s, 2H, –PhC*H*$_2$O–CO–), 5.05 (s, 4H, –PhC*H*$_2$O–CO–), 2.26 (m, 4H, –OCO–C*H*$_2$–CH$_2$–), 1.45 (m, 4H, –OCO–CH$_2$–C*H*$_2$–), 1.17 (br m, 8H, –OCO–CH$_2$–C*H*$_2$–C*H*$_2$–).

General procedure for the photolysis of CPT-1a-CPT and analysis of drug release by HPLC. CPT-**1a**-CPT (0.1 mg/mL) in ACN/H$_2$O (9:1, v/v) in a quartz cuvette was placed inside a photoreactor (365 nm) and irradiated for a specified period of time. The solution was centrifuged at 15,000 rpm for 15 min and the upper layer of the solution was used for HPLC analysis.

General procedure for the photolysis of CSPTs and analysis of the MWs by GPC. A DMF solution (1 mL) of CSPT(**1a**/HCPT) or CSPT(**1a**/ACPT) (5 mg/mL) in a quartz cuvette was placed inside a photoreactor (365 nm, 40 mW/cm^2) and irradiated for 20 min. The DMF solution was directly used for the MW analysis by GPC.

General procedure for the photolysis of polymers and analysis of the MWs by GPC. A poly(**1a**/**3**) solution (10 mg/mL) in DMF/water (95:5 v/v) in a quartz cuvette was placed inside a photoreactor (365 nm, 40 mW/cm^2) and irradiated for 30 min. The resulting solution was directly used for the MW analysis by GPC.

General procedure for the photolysis of CSPTs and analysis of drug release by HPLC. CSPT(**1a**/HCPT) (or CSPT(**1a**/ACPT)) (0.2 mg/mL) in DMF/H$_2$O (9:1, v/v) in a quartz cuvette was placed inside a photoreactor and irradiated for a specified period of time. The solution was centrifuged at 15,000 rpm for 15 min and the upper layer of the solution was incubated for additional 2 h at room temperature and then tuned to pH 2 by phosphoric acid addition, which resulted in a yellow solution used for HPLC analysis.

General procedure for the preparation of nanoparticles and UV-triggered drug release from the nanoparticles. CSPT(**1a**/HCPT) (or CSPT(**1a**/ACPT)) (3 mg) and PEG_{113}-*b*-$PLLA_{18}$ (PEL, 3 mg) were first dissolved in DMF (1 mL) and then added to a vigorously stirred phosphate buffered saline (PBS, 1 ×) solution (20 mL, pH 7.4) to form the CSPT(**1a**/HCPT)/PEL (or CSPT(**1a**/ACPT)/PEL) nanoparticles (NPs). The NP suspension was stirred at 1000 rpm for 10 min, transferred to a quartz cuvette, and then treated with UV for a specified period of time. The solution was centrifuged at 15,000 rpm for 15 min and the upper layer of the solution was incubated for additional 2 h at room temperature and then tuned to pH 2 by phosphoric acid addition, which resulted in a yellow solution used for HPLC analysis.

General procedure for the drug release from CSPT(1b/ACPT) in the presence of H_2O_2. CSPT(**1b**/ACPT) in DMF/H_2O (9:1, v/v) (0.2 mg/mL) was stirred with H_2O_2 (calc. 80 mM) for a specified period of time. A $FeCl_3$ aqueous solution (10 mM, 10 μL) was added to quench the excess H_2O_2. After 5 min, the solution was centrifuged at 15,000 rpm for 15 min and the upper layer of the solution was used for HPLC analysis.

General procedure for the formulation of PEL nanoparticles containing CPT derivatives, CPT-1a-CPT, or CSPTs. Drugs or CSPTs-loaded PEG_{113}-*b*-$PLLA_{18}$ NPs were prepared by the nanoprecipitation method. Typically, CPT, HCPT, ACPT, CPT-**1a**-CPT, CSPT(**1a**/HCPT), CSPT(**1a**/ACPT), or CSPT(**1a**/ACPT) (3 mg) and PEG_{113}-*b*-$PLLA_{18}$ (PEL, 3 mg) were first dissolved in DMF (1 mL) and then added to a vigorously stirred phosphate buffered saline (PBS, 1 ×) solution (20 mL, pH 7.4) to form the drug/PEL NPs. Particle sizes and polydispersities were measured with a ZetaPlus dynamic light scattering (DLS) detector.

For determining of drug loading content and drug loading efficiency, the drug-loaded NPs solution were centrifuged at 1000 rpm for 15 min to remove the unloaded free drugs or CSPTs and the upper layer of the solution was used for HPLC analysis. The drug loading content and drug loading efficiency of drug/PEL NPs were determined accordingly.

Cytotoxicity of poly(1a/3) before and after UV treatment. A poly(**1a**/**3**) solution (10 mg/mL) in DMF/water (95:5 v/v) in a quartz cuvette was placed inside a photoreactor (365 nm, 40 mW/cm^2) and irradiated for 30 min. The resulting solution was diluted by PBS (1×, pH 7.4) to different concentration and directly used as UV treated samples for the MTT assay in the HeLa cells.

The HeLa cells (ATCC, Manassas, VA, USA) used for MTT assays were cultured in MEM medium containing 10% Fetal Bovine Serum (FBS), 100 units/mL aqueous Penicillin G and 100 μg/mL streptomycin (Invitrogen, Carlsbad, CA, USA). They were placed in a 96-well plate for 24 h (3,000 cells per well). Cells were then washed once with PBS (1×, 100 μL). Freshly prepared solutions of poly(**1a**/**3**) (before or after UV treatment) at different concentrations in cell medium (100 μL/well) were added to the cells. After incubation at 37 °C for 72 h, the medium was removed. Standard MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay protocols were followed.[3] The absorbance wavelength on a microplate reader (Perkin Elmer, Victor$^3{}_{TM}$ V, Waltham, MA, USA) was set at 590 nm for the MTT assay.

Cytotoxicity evaluation of CSPT/PEL NPs in the presence and absence of trigger condition using MTT assay. CSPT(**1a**/HCPT) (or CSPT(**1a**/ACPT), CSPT(**1b**/ACPT)) (3 mg) and PEG_{113}-*b*-$PLLA_{18}$ (PEL, 3 mg) were first dissolved in DMF (1 mL) and then added to a

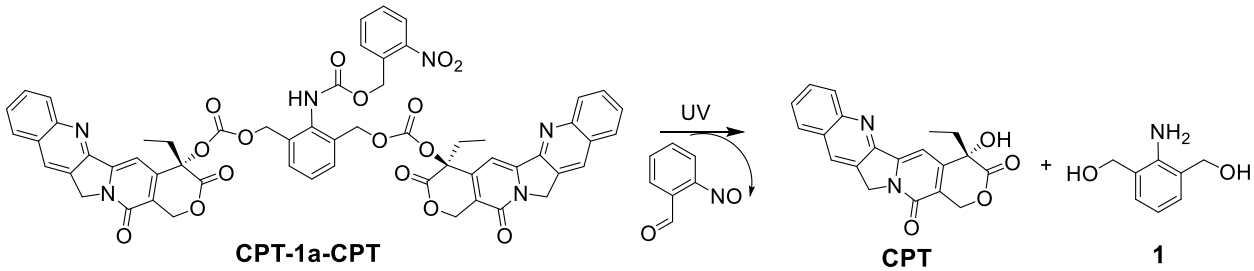
vigorously stirred PBS solution (9 mL, pH 7.4) to form the CSPT(**1a**/HCPT)/PEL (or CSPT(**1a**/ACPT)/PEL, CSPT(**1b**/ACPT)/PEL) NPs for MTT test.

The HeLa cells (ATCC, Manassas, VA, USA) used for MTT assays were cultured in MEM medium containing 10% Fetal Bovine Serum (FBS), 100 units/mL aqueous Penicillin G and 100 μg/mL streptomycin (Invitrogen, Carlsbad, CA, USA). HeLa cells were placed in a 96-well plate for 24 h (3,000 cells per well). Cells were then washed once with PBS (1×, 100 μL). Freshly prepared solutions of HCPT, ACPT, CSPT(**1a**/HCPT)/PEL NPs, CSPT(**1a**/ACPT)/PEL NPs or CSPT(**1b**/ACPT)/PEL NPs of different concentrations in cell medium (100 μL/well) were added to the cells. For UV treated CSPT(**1a**/HCPT)/PEL NP and CSPT(**1a**/ACPT)/PEL NP groups, the plates were treated with UV irradiation (365 nm, 20 mW/cm^2 for 10 min) after 1 h incubation; the percentage of cell viability was calculated by normalization against cells with the same UV treatment (90 ± 3% cell viability as compared to untreated cells). For the H_2O_2 treated CSPT(**1b**/ACPT)/PEL NP group, the H_2O_2 solution (10 mM, 10 μL/well) was added after 1 h incubation; the percentage of cell viability was calculated by normalization against cells with the same H_2O_2 treatment. After incubation at 37 °C for 72 h, the medium was removed. Standard MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay protocols were followed.[3] The absorbance wavelength on a microplate reader (Perkin Elmer, Victor$^3{}_{TM}$ V, Waltham, MA, USA) was set at 590 nm for the MTT assay. The half maximal inhibitory concentration (IC_{50}) was determined by half-cell viability concentration from the MTT assay test.

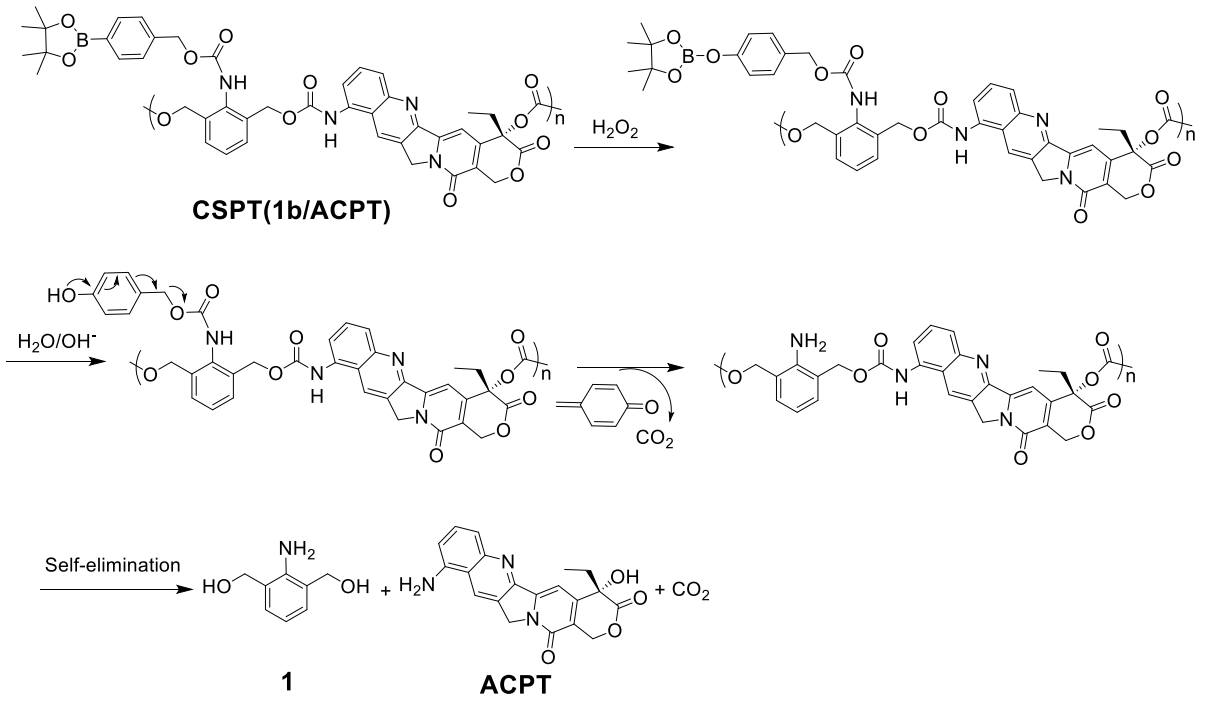
Apoptosis analysis of 4T1 tumors with terminal deoxynucleotidyl transferase–mediated deoxyuridine triphosphate nick end (TUNEL) assay. Balb/c mice (female, 6-8 weeks old) bearing subcutaneous 4T1 tumors (average tumor size was 500 mm^3) were grouped to minimize the difference of tumor size and body weight in all the groups (n = 4). The mice received

intratumoral injection of PBS (1 ×, 100 μL), H_2O_2 (10 mM, 100 μL), ACPT/PEL (5 mg/mL of ACPT, in 100 μL PBS), CSPT(**1b**/ACPT)/PEL NPs (without H_2O_2; 0.5 mg of ACPT/tumor, in 100 μL PBS) or CSPT(**1b**/ACPT)/PEL NPs (0.5 mg of ACPT/tumor, in 100 μL PBS) followed by intratumoral injection of H_2O_2 (10 mM, 100 μL; 1h post the injection of NPs). The mice were euthanized 48 h post injection. All the tumors were collected and freshly frozen with optimum cutting temperature (O.C.T.) compound (Sakura Finetek USA, Torrance, CA, USA). Tumor sections of 8 μm thickness were collected by cryostat (Leica CM3050S). Cell apoptosis in tumors was analyzed using in situ cell death detection kit (Roche Diagnostics GmbH, Mennheim, Germany) and TUNEL staining was performed following the manufacture's procedure. Positive cells were green fluorescent and background cells were blue fluorescent (stained with 4',6-diamidino-2-phenylindole (DAPI)). The entire tumor tissues were imaged with Nanozoomer Virtual Microscopy (Hamamatsu). The sections were further imaged with the confocal laser scanning microscopy (LSM 700, Zeiss) at 20 × magnification. The total number of cells (blue) and apoptotic cells (green) was counted in multiple sections per tumor (≥20 sections were counted for each tumor) by ImageJ to quantify the apoptosis index (ratio of apoptotic cell number to the total cell number). Data are represented as average ± SEM (standard error of the mean) and are analyzed by One-way ANOVA (Fisher) (*$p \leq 0.05$).

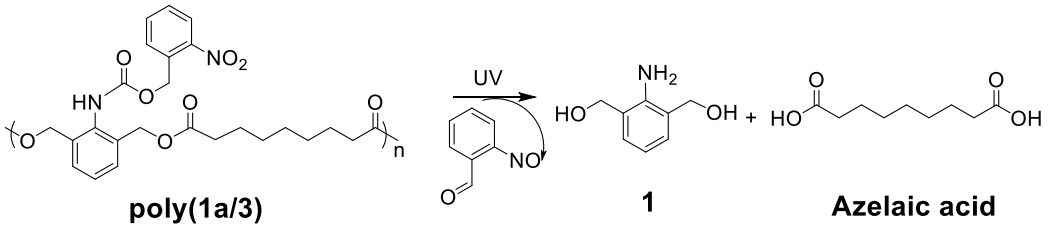
Scheme S8. Proposed degradation for UV-triggered disassembly of CPT-**1a**-CPT.



Scheme S9. Proposed degradation mechanism for H_2O_2-triggered disassembly of CSPT(**1b**/ACPT).



Scheme S10. Proposed degradation for UV-triggered disassembly of poly(**1a**/**3**).



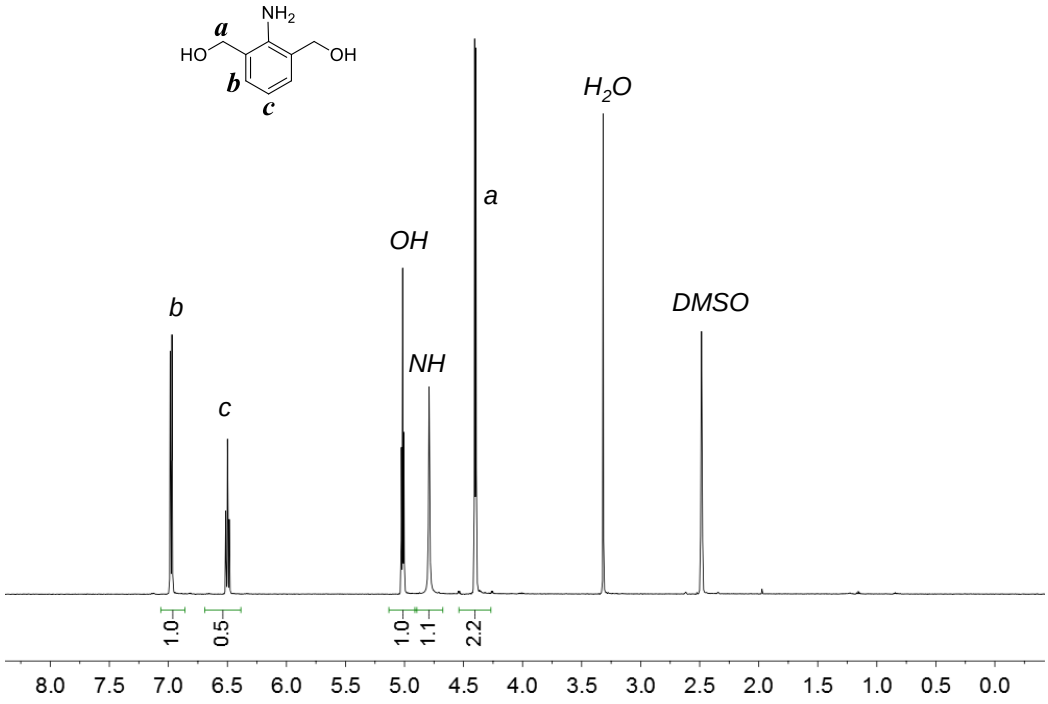


Figure S1. ^{1}H NMR spectrum of 2,6-bis(hydroxymethyl)aniline (**1**) in DMSO-d_6.

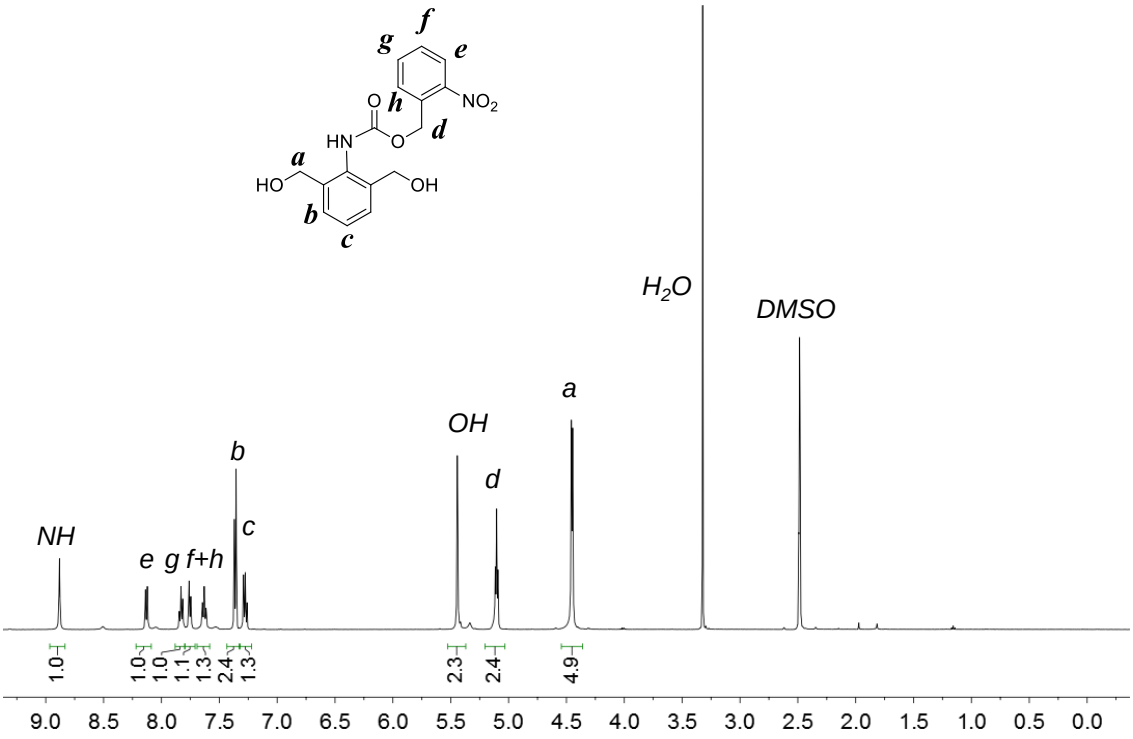


Figure S2. ^{1}H NMR spectrum of **1a** in DMSO-d_6.

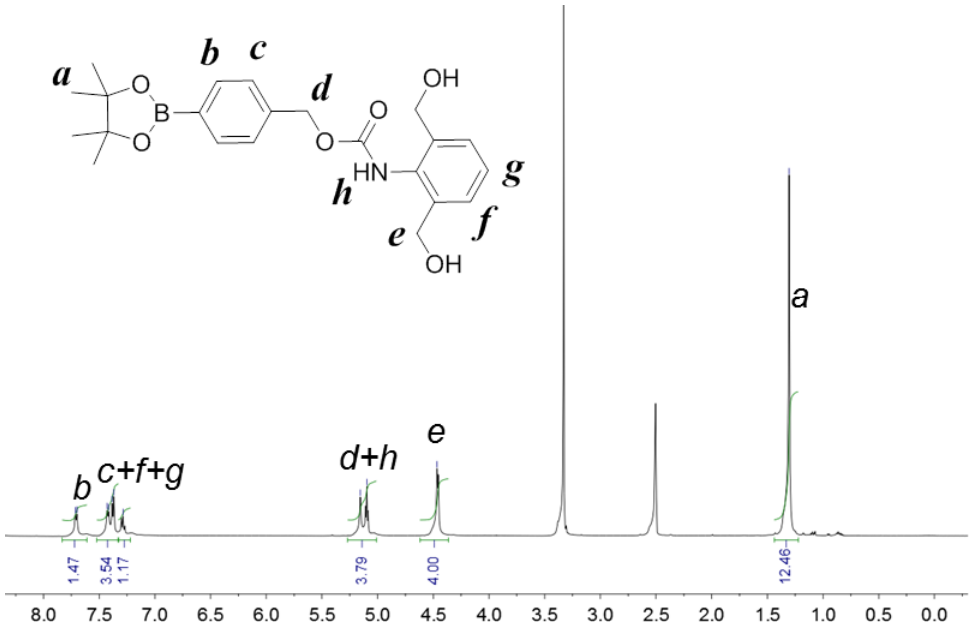


Figure S3. ^{1}H NMR spectrum of **1b** in DMSO-d_6.

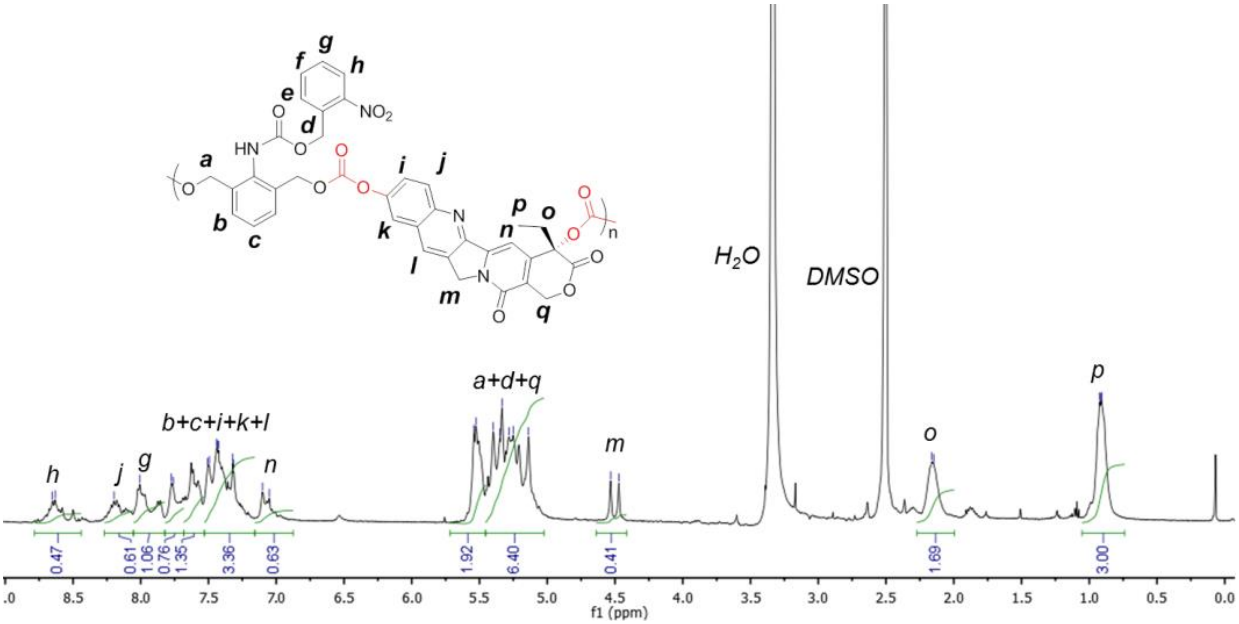


Figure S4. ^{1}H NMR spectrum of CSPT(**1a**/HCPT) in DMSO-d_6.

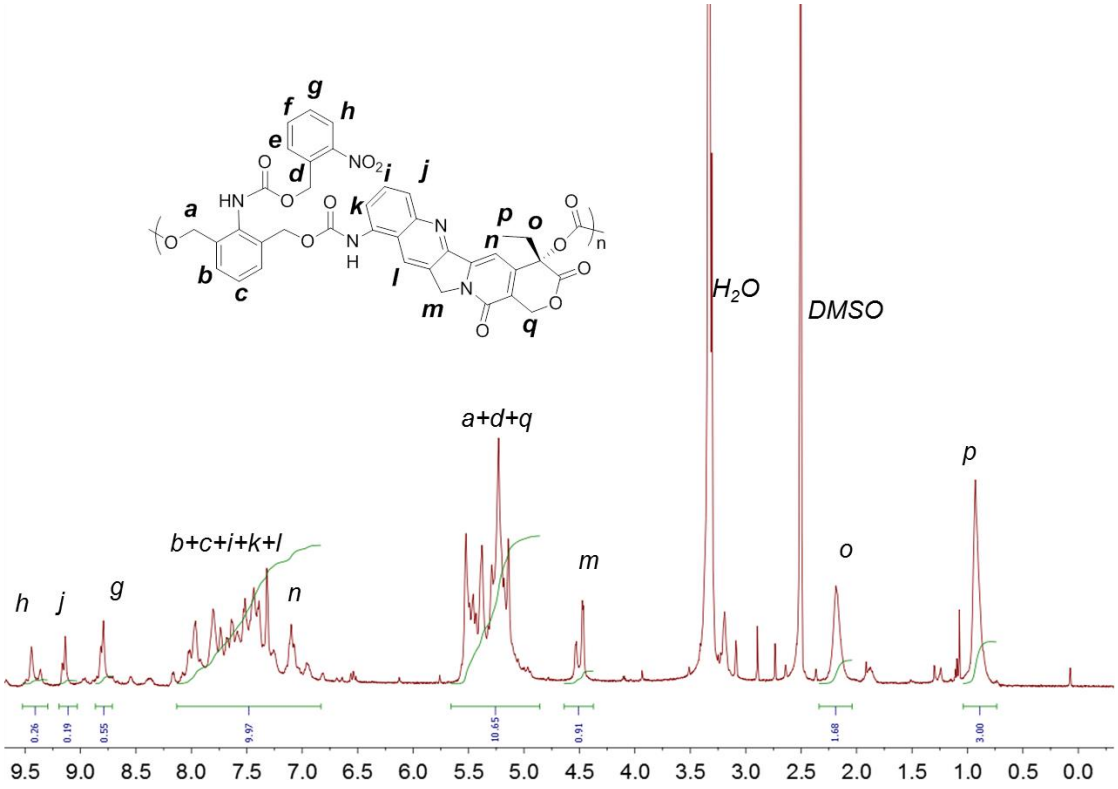


Figure S5. ^{1}H NMR spectrum of CSPT(**1a**/ACPT) in DMSO-d_6.

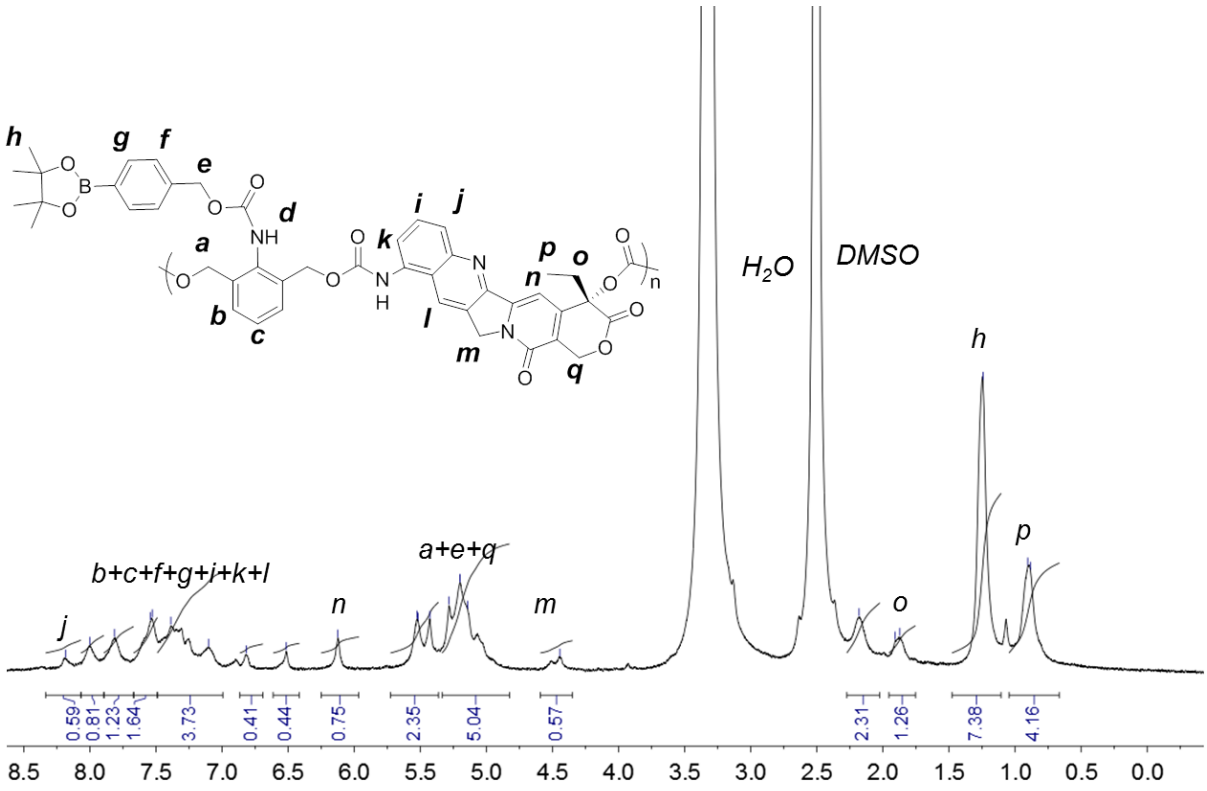


Figure S6. ^{1}H NMR spectrum of CSPT(**1b**/ACPT) in DMSO-d_6.

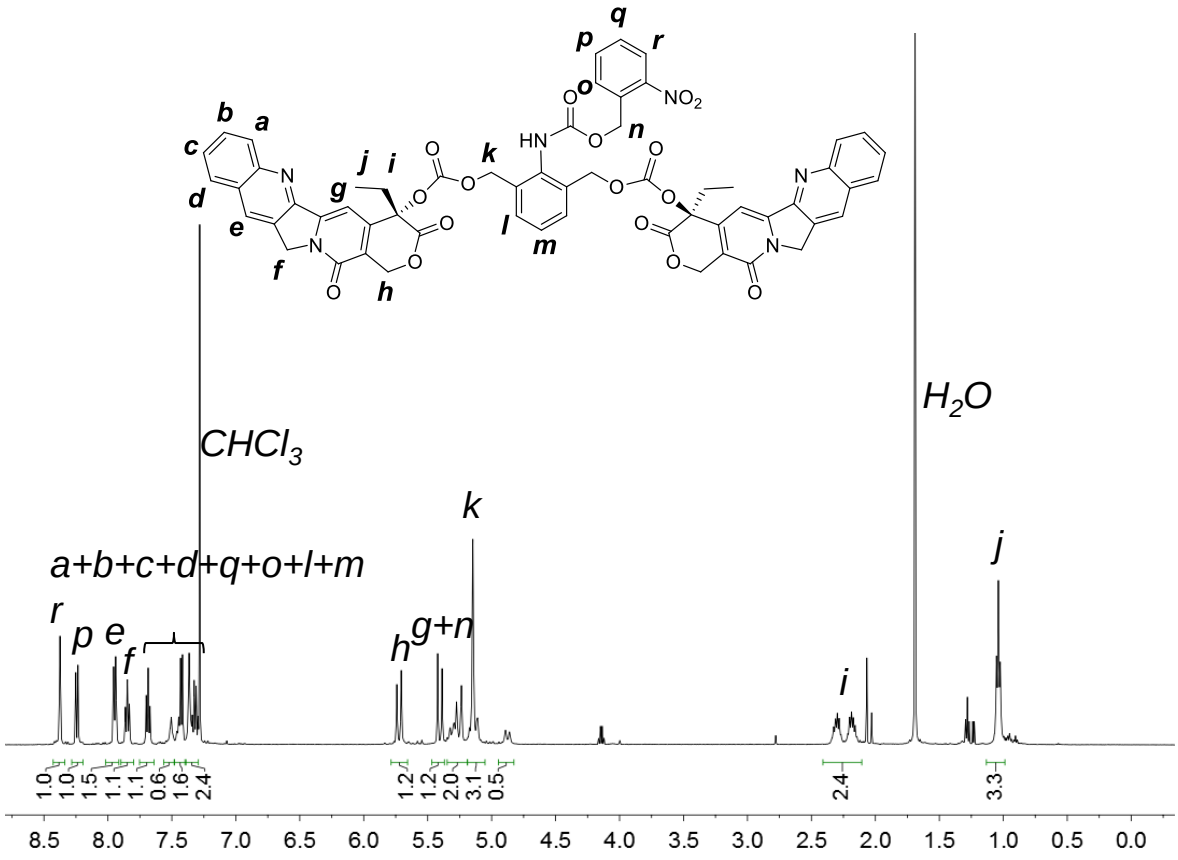


Figure S7. ^{1}H NMR spectrum of CPT-**1a**-CPT in $CDCl_3$.

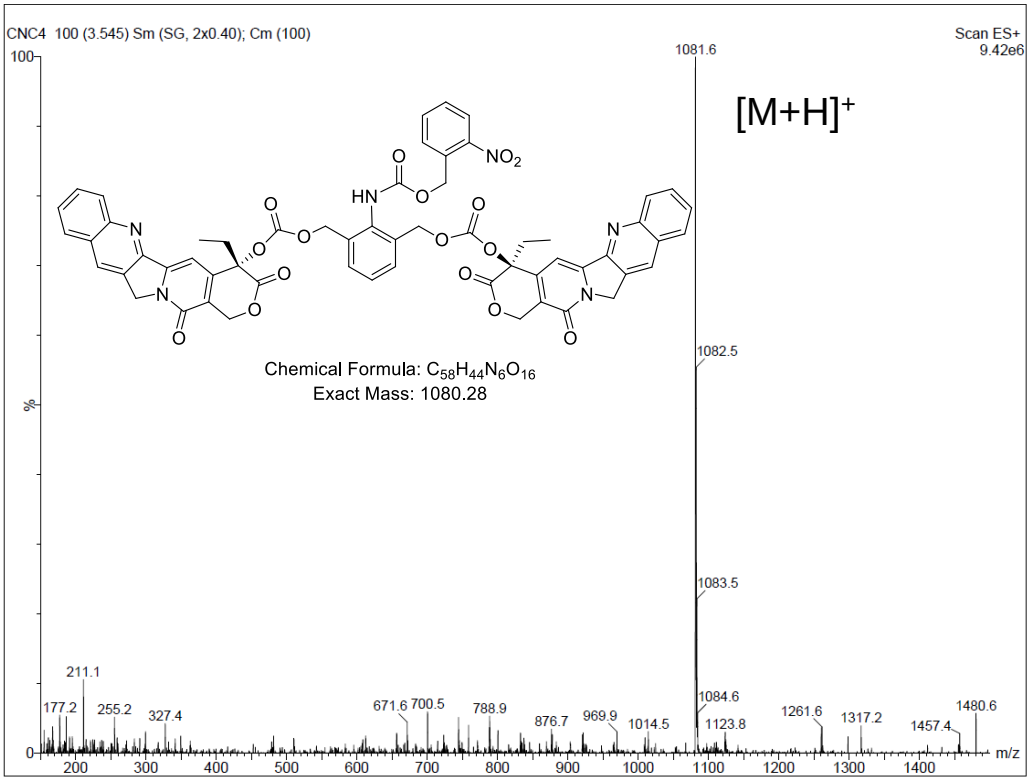


Figure S8. ESI-MS spectrum of CPT-**1a**-CPT.

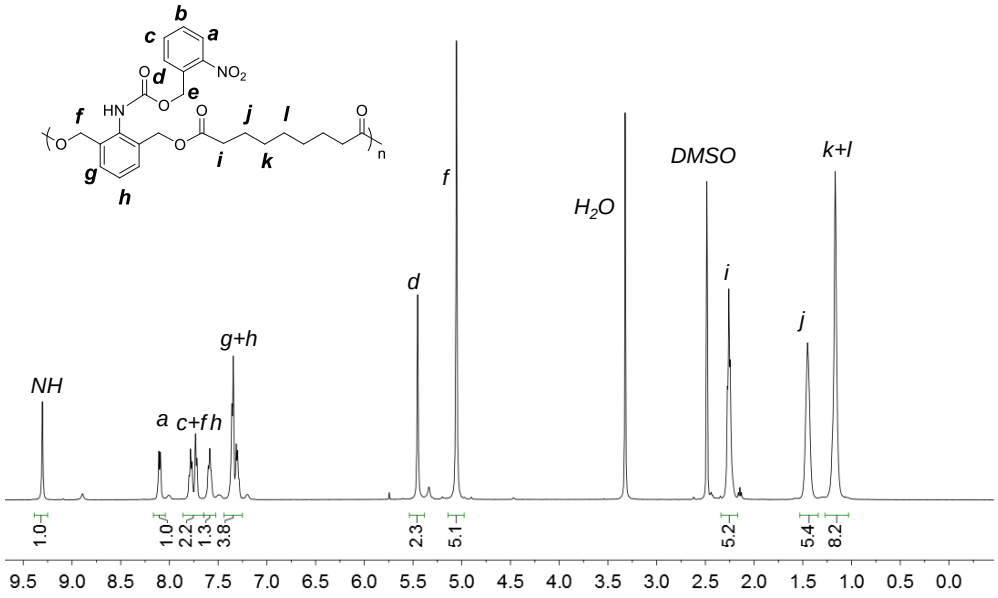


Figure S9. ^{1}H NMR spectrum of poly(**1a**/**3**) in DMSO-d_6.

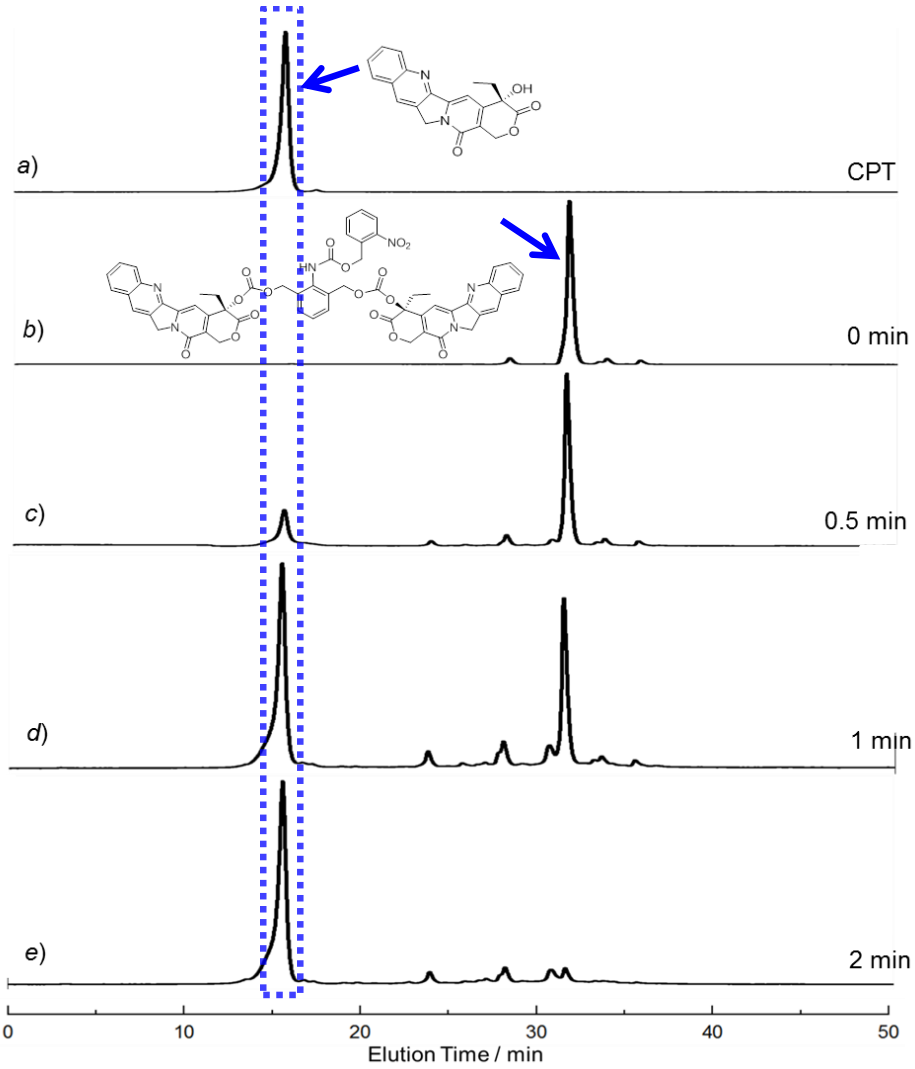


Figure S10. HPLC curves of CPT (a) and CPT-**1a**-CPT before (b) and after (c-e) UV treatment for different periods of time (0.1 mg/mL in ACN/water (9:1, v/v), 40 mW/cm^2).

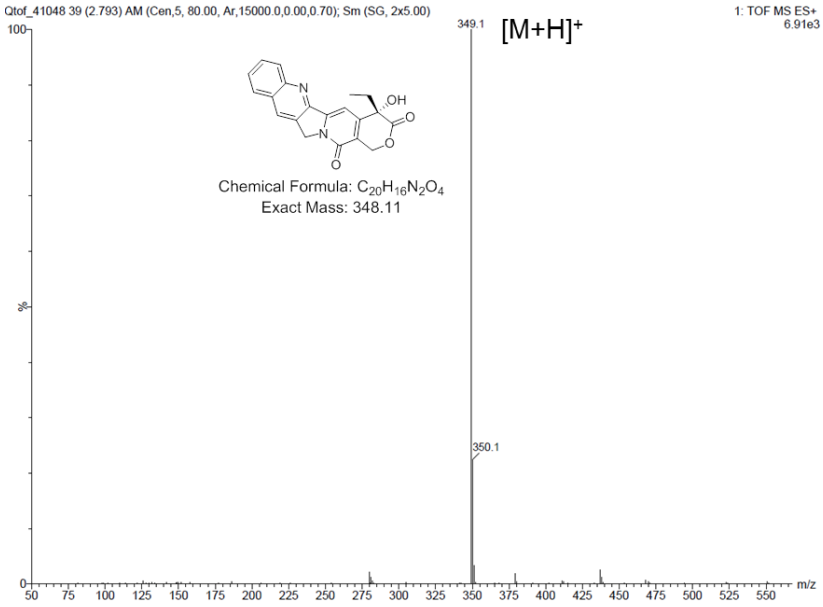


Figure S11. ESI-MS analysis of the recovered CPT from CPT-**1a**-CPT after UV treatment (1 mg/mL in ACN/water (9:1, v/v), 40 mW/cm^2 for 3 min) followed by purification with preparative HPLC.

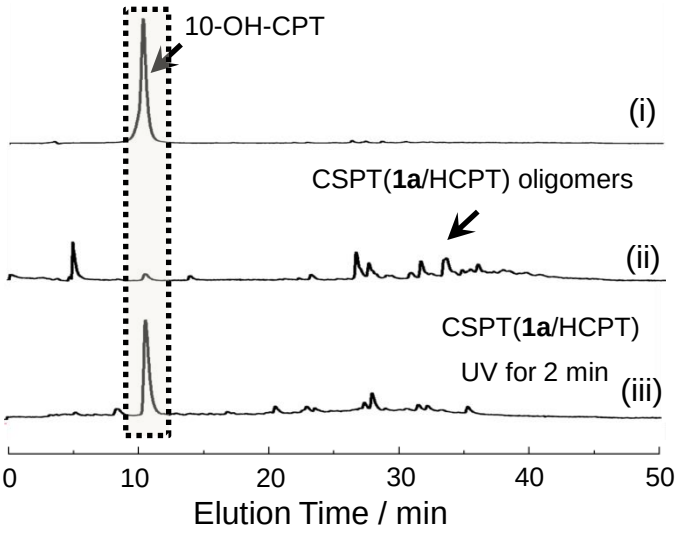


Figure S12. HPLC curves of HCPT(i), CSPT(**1a**/HCPT) before (ii) and after (iii) UV treatment for 2 min (0.1 mg/mL in DMF, 40 mW/cm^2).

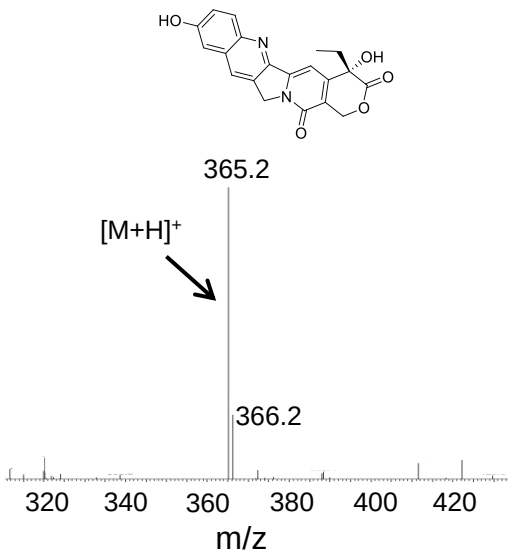


Figure S13. ESI-MS analysis of the recovered HCPT from CSPT(**1a**/HCPT) after UV treatment (1 mg/mL in DMF, 40 mW/cm^2 for 10 min) followed by purification with preparative HPLC.

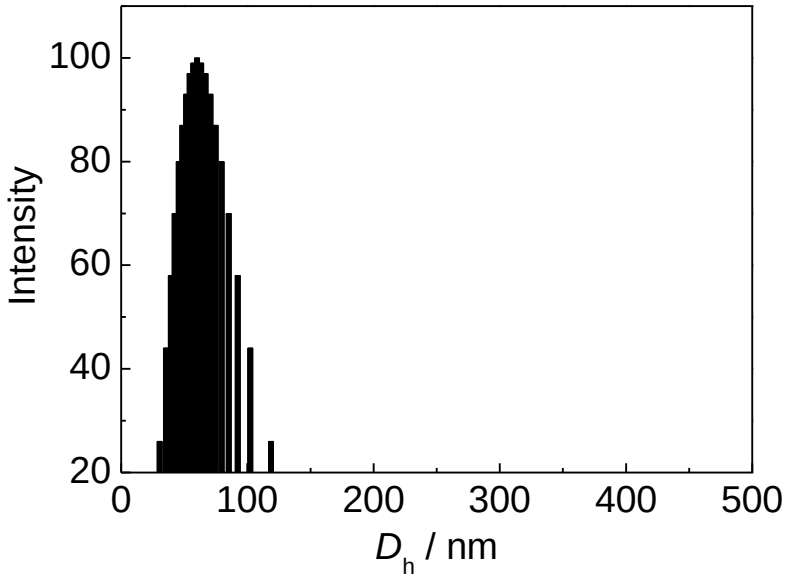


Figure S14. The hydrodynamic diameter distribution of nanoparticles of CSPT(**1a**/HCPT)/PEL in PBS (pH 7.4).

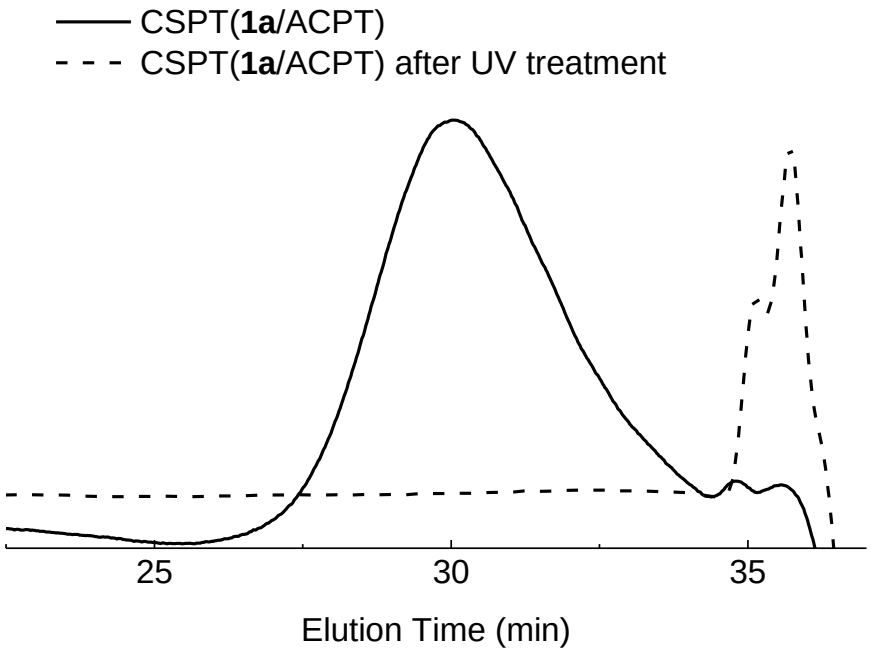


Figure S15. GPC curves the CSPT(**1a**/ACPT) before and after UV-treatment (365 nm, 40 mW/cm^2, 20 min).

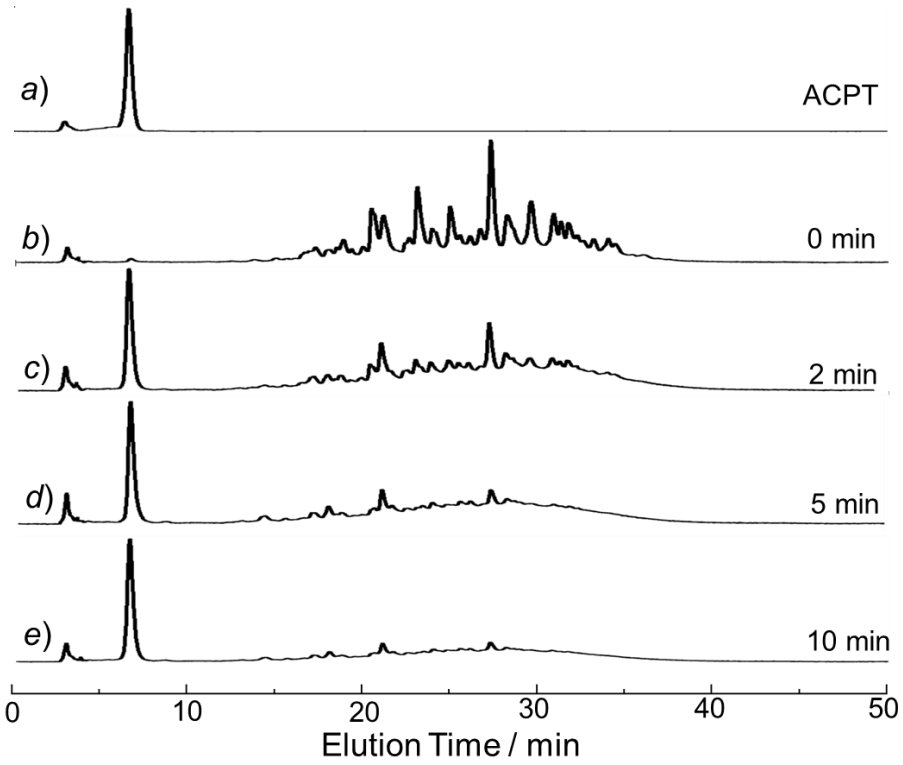


Figure S16. HPLC curves of ACPT (a), CSPT(**1a**/ACPT) before (b) and after (c-e) UV treatment for a specified period of time (0.2 mg/mL in DMF/water (9:1, v/v), 40 mW/cm^2).

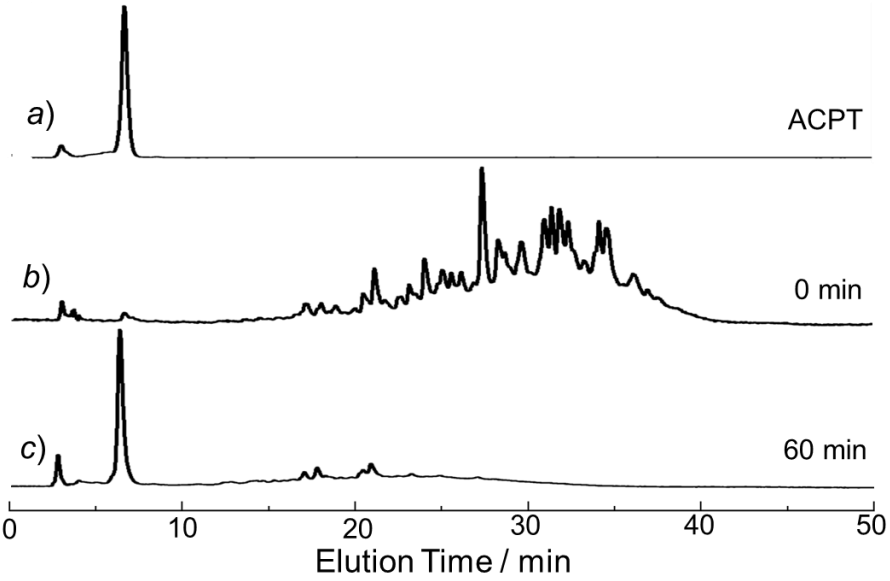


Figure S17. HPLC curves of ACPT (a), CSPT(**1b**/ACPT) before (b) and after (c) H_2O_2 treatment for 60 min (0.2 mg/mL in DMF/water (9:1, v/v), 80 mM of H_2O_2).

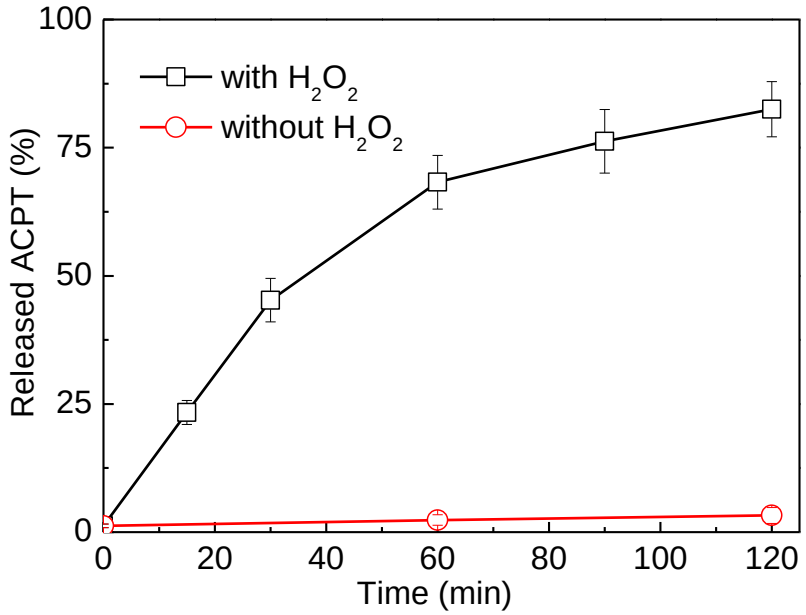


Figure S18. Release of ACPT from CSPT(**1a**/ACPT) in response to UV treatment for a specified period of time (0.2 mg/mL in DMF/water (9:1, v/v), 80 mM of H_2O_2).

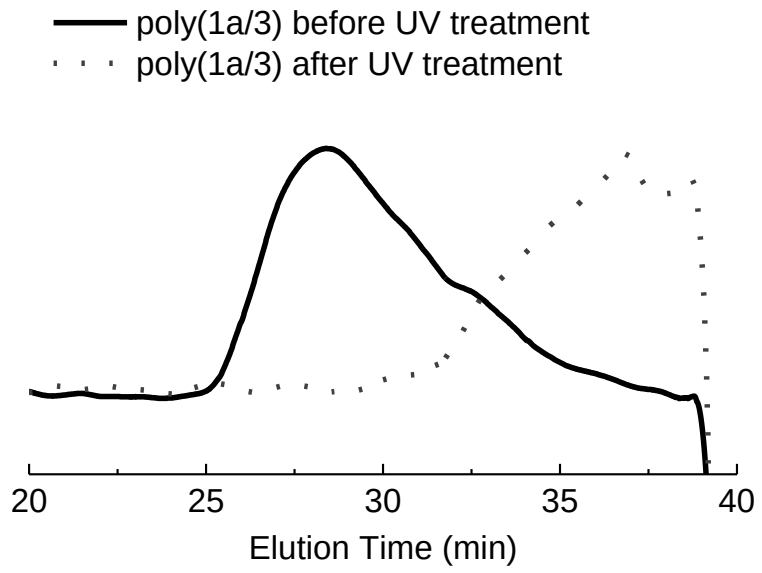


Figure S19. GPC curves the poly(**1a**/**3**) before and after UV-treatment (365 nm, 40 mW/cm^2, 30 min).

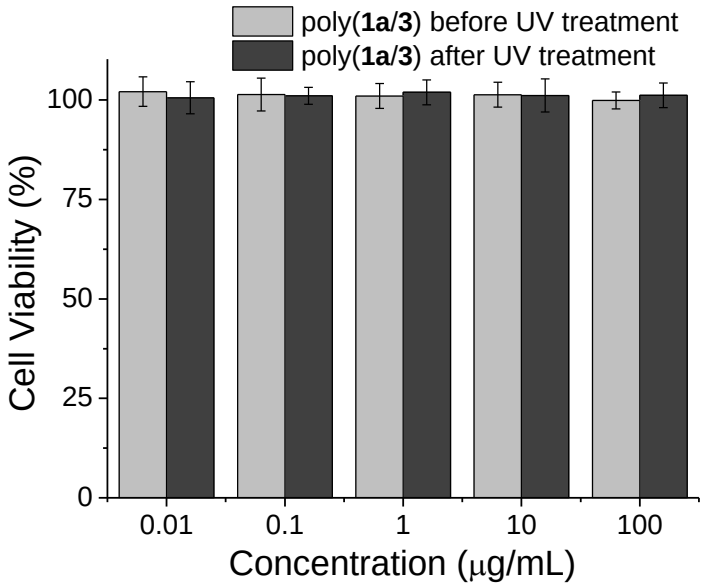


Figure S20. The cell viability at different concentration of poly(**1a**/**3**) before and after UV treatment (365 nm, 40 mW/cm^2 for 30 min) determined by microculture tetrazolium (MTT) assay in HeLa cells.

To demonstrate the cytotoxicity of degradation byproducts from this kind of polymeric system, we designed and synthesized a control polymer without drugs, the poly(**1a**/**3**), from **1a** and azelaic acid dichloride (Scheme S7, Figure S9 and S19). Poly(**1a**/**3**) exhibited the expected UV-induced degradation, and its M_n decreased from 6.9 kDa to 1.8 kDa after UV treatment for 30 min (Figure S19). Poly(**1a**/**3**), before and after UV treatment, showed no cytotoxicity in HeLa cells using the MTT assay at a concentration up to 100 μg/mL (Figure S20). PEL is a very safe, non-toxic material, based on many other prior studies. This experiment demonstrates that the degradation byproducts of CSPTs have negligible contribution for the tumor killing and the observed cytotoxicity of various trigger-responsive CSPTs/PEL NPs were indeed from the anticancer drugs released from CSPTs.

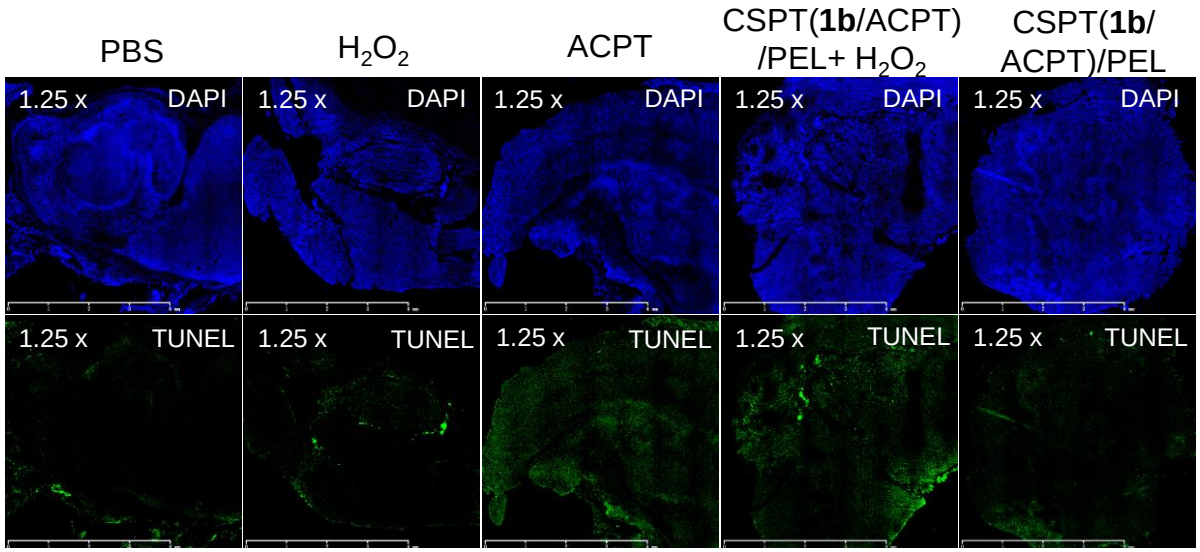


Figure S21. BALB/c mice bearing subcutaneous 4T1 tumors received a single intratumoral injection of phosphate buffered saline (PBS), H_2O_2, ACPT or CSPT(**1b**/ACPT)/PEL NPs (0.5 mg ACPT equiv/tumor) with or without H_2O_2. H_2O_2 was administered intratumorally 1h after the injection of CSPT(**1b**/ACPT)/PEL NPs. The mice were sacrificed 48 h post injection. The 4T1 tumors were collected, sectioned and stained with TUNEL for apoptosis analyses. Representative images of TUNEL stains are shown. Scale bar: 4 mm. The apoptosis index was determined as the ratio of apoptotic cells (TUNEL, green) to the total cell number (DAPI, blue).

Table S1: Formulation of NPs from CPT derivatives, CPT-**1a**-CPT, and CSPTs with PEL.

entry	Drug/PEL	Diameter (nm)[a]	PDI[a]	Loading (wt. %)[b]	Loading Efficiency (wt. %)[b]
1	CPT/PEL	1563	0.31	4.5 ± 2.4	4.7 ± 2.5
2	HCPT/PEL	1128	0.40	5.8 ± 3.4	6.2 ± 3.5
3	ACPT/PEL	1210	0.22	3.6 ± 2.3	3.7 ± 2.3
4	CPT-**1a**-CPT/PEL	1231	0.23	8.7 ± 3.3	9.5 ± 3.4
5	CSPT(**1a**/HCPT)/PEL	75	0.11	48.4 ± 2.7	93.7 ± 2.8
6	CSPT(**1a**/ACPT)/PEL	124	0.13	48.1 ± 3.4	92.6 ± 3.5
7	CSPT(**1b**/ACPT)/PEL	131	0.15	48.6 ± 2.5	94.5 ± 2.6

[a]Determined by dynamic light scattering; [b]Determined by HPLC analysis.

Reference

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(2) Han, D. H.; Tong, X.; Zhao, Y. *Macromolecules* **2011**, *44*, 437-439.

(3) Romijn, J. C.; Verkoelen, C. F.; Schroeder, F. H. *Prostate* **1988**, *12*, 99-110.