Electronic Supplementary Information

for

Mechanochemical activation of disulfide-based multifunctional polymers for theranostic drug release

Zhiyuan Shi,[a,b] Qingchuan Song,[a,b] Robert Göstl[a,*] and Andreas Herrmann[a,b,c,*]

[a] DWI – Leibniz Institute for Interactive Materials, Forckenbeckstr. 50, 52056 Aachen, Germany

[b] Institute of Technical and Macromolecular Chemistry, RWTH Aachen University, Worringerweg 1, 52074 Aachen, Germany

[c] Zernike Institute for Advanced Materials, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

*E-mail: goestl@dwi.rwth-aachen.de, herrmann@dwi.rwth-aachen.de

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Experimental procedures

Materials

All commercial starting reagents and solvents were used without further purification unless otherwise stated. Camptothecin (≥90%, Sigma-Aldrich), gemcitabine hydrochloride (≥98%, Sigma-Aldrich), umbelliferon (99%, Sigma-Aldrich), 4-bromo-1,8-naphthalic anhydride (95%, Sigma-Aldrich), butylamine (99.5%, Sigma-Aldrich), hydroiodic acid (57 wt% in H_2O, distilled, stabilized, 99.95%, Sigma-Aldrich), triphosgene (98%, TCI), 2-bromoisobutyric anhydride (98%, Sigma-Aldrich), 1-thioglycerol (≥97%, Sigma-Aldrich), hydrogen peroxide solution (30 wt% in H_2O, Sigma-Aldrich), tris(2-(dimethylamino)ethyl)amine (Me_6TREN, >98.0%, TCI), copper(II) bromide ($CuBr_2$, 99%, Sigma-Aldrich), *N*,*N*-diisopropylethylamine (99.5%, Sigma-Aldrich), and *N,N′*-disuccinimidyl carbonate (≥95%, Sigma-Aldrich) were used as received. Oligo(ethylene glycol) methyl ether acrylate (OEGMEA, M_n ~ 300, Sigma-Aldrich) was purified prior to polymerization by passing over a short column of inhibitor remover. Copper wire (d = 0.25 mm) was pre-treated by washing in hydrochloric acid for 15 min, rinsed thoroughly with MiliQ water and acetone, dried under N_2, and used immediately. HeLa cell line was obtained from ATCC: The Global Bioresource Center.

Methods

Analytical instrumentation

^{1}H- and ^{13}C-NMR spectra were recorded at room temperature in DMSO-d_6 or $CHCl_3$-d on a 300 MHz Bruker DPX 300 spectrometer (^{13}C: 75 MHz) or a 600 MHz Bruker DPX-600 FT-NMR (^{13}C: 131 MHz). The chemical shifts are reported in δ units using residual protonated solvent signals as internal standard[1] (^{1}H: DMSO-d_6 (δ_H = 2.50 ppm) or $CHCl_3$-d (δ_H = 7.26 ppm), ^{13}C: DMSO-d_6 (δ_C = 39.52 ppm) or $CHCl_3$-d (δ_C = 77.16 ppm). The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, sept. = septet, dd = doublet of doublets etc., m = multiplet. Coupling constants (J) are given in Hz and refer to the respective H,H-couplings. Note that quaternary carbon signals are present in ^{13}C DEPT-135 spectra due to large two-bond ^{13}C-^{1}H coupling constants in combination with non-optimized standard DEPT-135 sequences.
TLC was performed on Merck TLC Silica gel 60 F_{254} TLC plates with a fluorescence indicator employing a 254 nm or 365 nm UV hand lamp for visualization. Silica gel for chromatography (40-63 µm) was used for flash column chromatography.
Gel permeation chromatography (GPC/SEC) with THF (HPLC grade, VWR) was performed using a HPLC pump (PU-2080plus, Jasco) equipped with a refractive index detector (RI-2031plus, Jasco). The sample solvent contained 250 mg·mL^{-1} 3,5-di-*t*-4-butylhydroxytoluene (BHT, ≥99%, Fluka) as internal standard. One pre-column (8×50 mm) and four SDplus gel columns (8×300 mm, SDplus, MZ Analysentechnik) were applied at a flow rate of 1.0 mL·min^{-1} at 20 °C. The diameter of the gel particles was 5 µm, the nominal pore widths were 50, 102, 103, and 104 Å. Calibration was achieved using narrowly distributed poly(methyl methacrylate) (PMA) standards (Polymer Standards Service). Molar masses ($M_{n,SEC}$ and $M_{w,SEC}$) and molar mass distributions (M_w/M_n) were calculated by using the PSS WinGPC UniChrom software (Version 8.1.1).

UV-vis and fluorescence spectroscopy

UV-vis absorption spectroscopy was performed on a Thermo Evolution 300 spectrometer and fluorescence spectroscopy on a Horiba Fluoromax-4P spectrometer at room temperature. The absorption spectra were acquired with a background correction function. For fluorescence

spectra measurements of **1** or $\mathbf{P_1}$, samples were excited at 450 nm. For the kinetic measurements, the fluorescence emission increasing with time was measured with excitation wavelength at 450 nm and emission wavelength at 550 nm. For the fluorescence spectra measurements of **2** or $\mathbf{P_2}$, samples were excited at the wavelength of 325 nm. For the kinetic measurements, the fluorescence emission increasing with time was measured with excitation wavelength at 325 nm and emission wavelength at 450 nm. The spectral bandwidths were set to 3 nm for both excitation and emission. The data interval was set to 1 nm and the integration time was 0.1 s. All spectroscopic measurements were carried out with quartz cuvettes purchased from Hellma Analytics.

Ultrasonication experiments

Sonication experiments were carried out using a Sonics VCX 500 W ultrasonic processor with a 13 mm probe, f = 20 kHz and 30% of the maximum amplitude of 125 μm. Pulsed sonication (2 s on, 1 s off) was used. The disulfide polymers were dissolved in MeCN:H_2O (v:v = 2:3) and injected into a cooled Suslick cell (immersed in an ice-water bath) with a constant flow of N_2. Then, the mixture was exposed to constant sonication for a given time and samples for UV-vis and for fluorescence spectroscopy were taken during the process. The samples were then kept for 48 h to complete the downstream thermal release reactions at rt before the UV-vis and fluorescence measurements.

Cell imaging

HeLa cells used for imaging were cultured in Dulbecco's Modified Eagle's Medium (DMEM) containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 U/mL of penicillin and 100 μg/mL streptomycin at 37 °C under a humidified atmosphere containing 5% CO_2. The HeLa cells were seeded in a 24-well plate at a density of 10^5 cells per well in culture medium. After 24 h, they were incubated with different concentrated sonicated or non-sonicated samples in PBS for 30 min at 37 °C, and washed with phosphate-buffered saline (PBS) three times. Then the fluorescence imaging of cells was performed on a confocal laser scanning microscope (STP8, Leica) (confocal excitation: a diode laser at 458 nm) and analyzed by ImageJ.

Flow cytometry measurements

HeLa cells were seeded in T 25 Flask at 1×10^6 cells per flask in 4 mL of growth medium and incubated for 48 h at 37 °C, and then, the cells were incubated with different concentrated sonicated or non-sonicated samples in PBS for 30 min. After incubation and rinsing with PBS buffer for 3 times, cells were measured with the flow cytometer (BD Accuri C6, DB Biosciences) with 500 000 events collected.

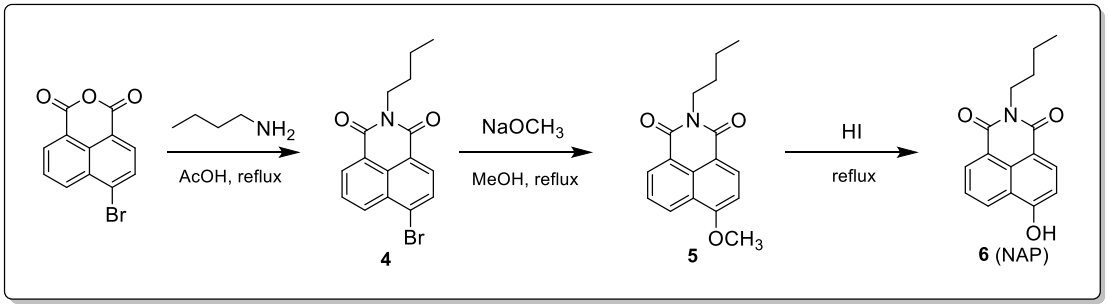
MTS proliferation assays

HeLa cells were used to evaluate the cytotoxicity of CPT, **1**, $\mathbf{P_1}$, and POEGMEA with sonicated $\mathbf{P_1}$. Therefore, HeLa cells were cultured in a basal medium consisting of DMEM, supplemented with 10% fetal bovine serum and 1% antibiotics/antimycotics, at 37 °C, 5% CO_2 and 95% humidity. Actual cell viability was monitored by using a tetrazolium compound 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (inner salt, MTS reagent) and a chemical electron acceptor dye (phenazine ethosulfate; PES) (Promega, Germany) in an assay according to the manufacturer's instructions. Briefly, approximately 5,000 cells in 100 μL of medium were seeded into 96-well microtitre plates. After overnight incubation, the culture medium was removed and exchanged with fresh medium (100 μL) containing different concentrated testing compounds. Control cultures were

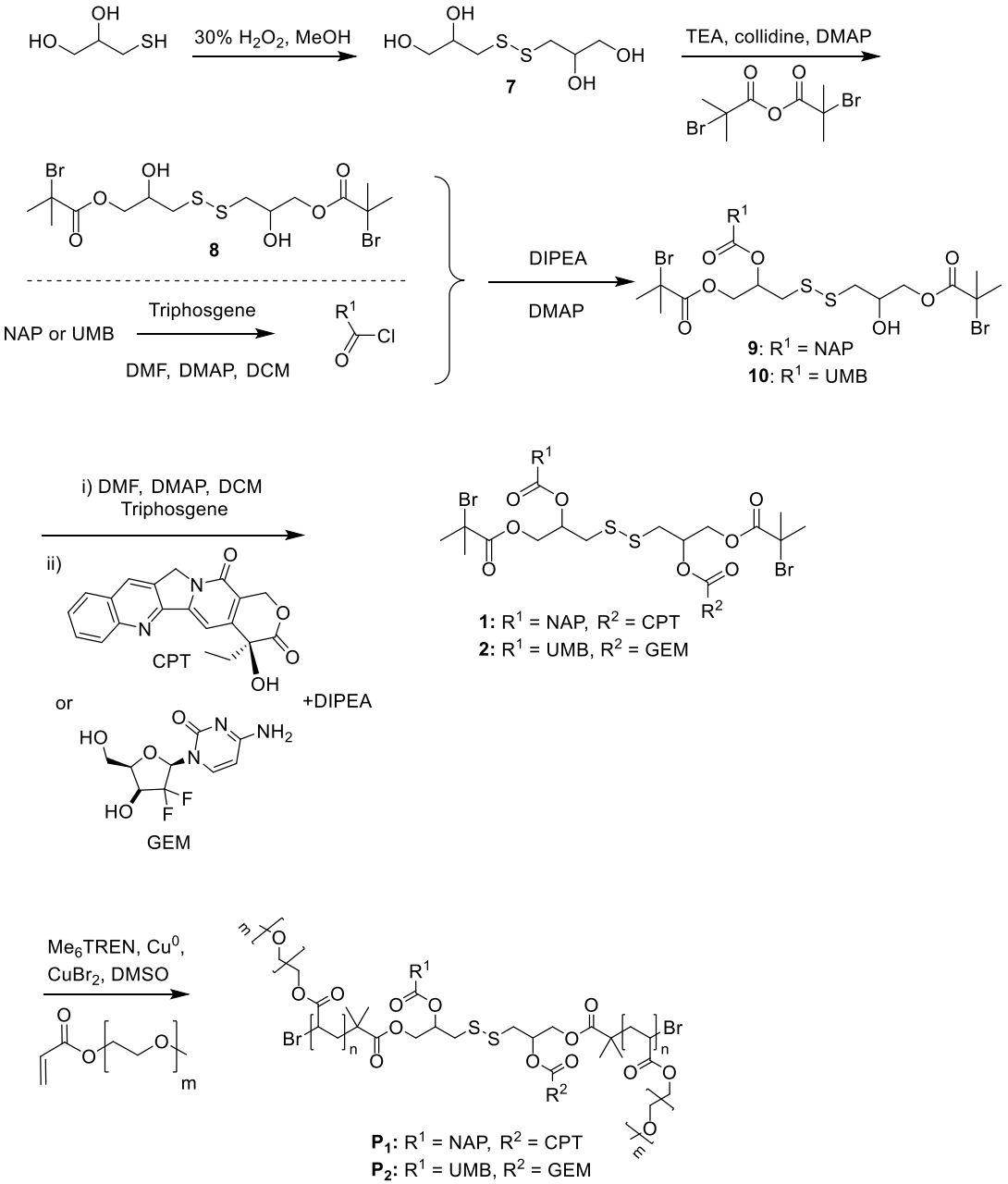
treated with DMSO alone. The final concentration of DMSO in the medium did not exceed 0.5%. After 48 h incubation, the cell culture media were removed, and the cells were washed with 100 µL PBS buffer, then 20 µL MTS reagent with 100 µL fresh medium was added to the cells. The mixture of MTS reagent with cell culture medium served as negative control. The resulting suspension was mixed thoroughly, and the absorbance was monitored using a microplate spectrophotometer at 490 nm (SpectraMax M3 microplate reader, Molecular Devices). MTS signals after 2 h were used for survival and proliferation determination. All the cultures were performed at least in triplicates.

Synthetic procedures and characterization data

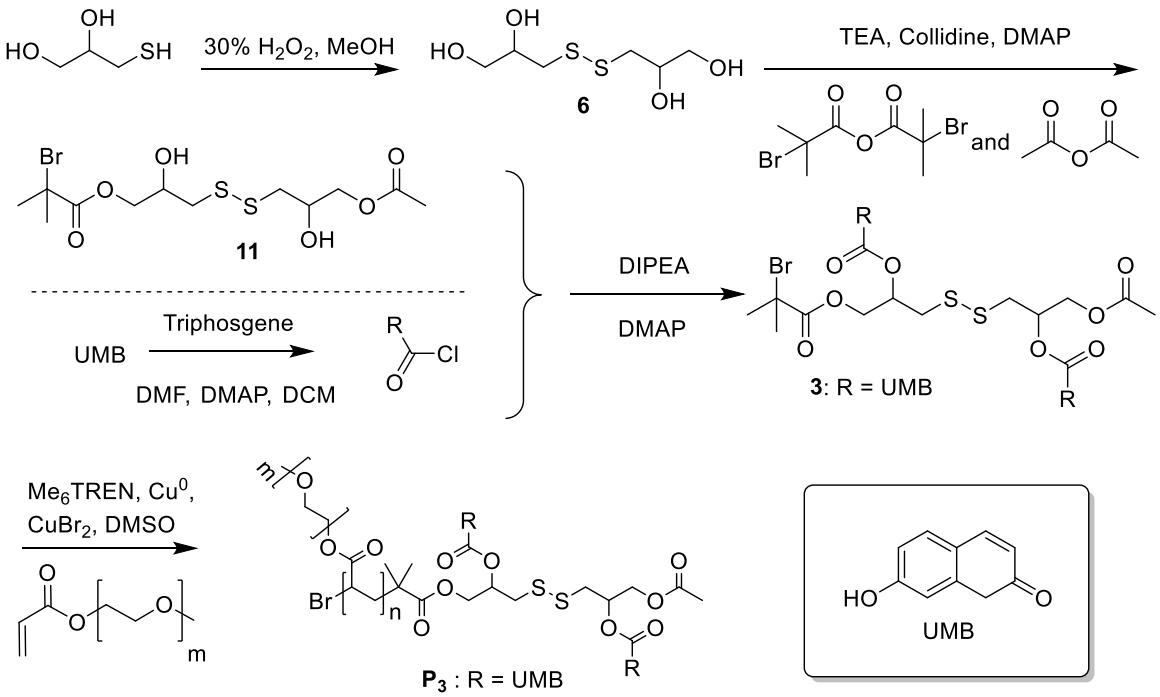
Synthesis of **6** (NAP)



Synthesis of polymeric prodrugs:

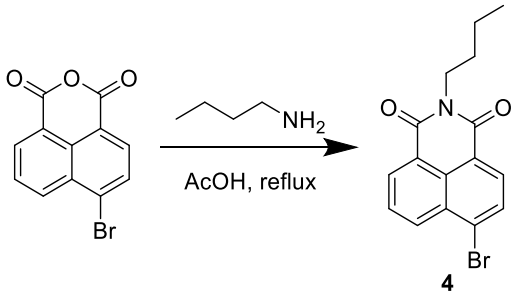


Scheme S1. Synthesis pathway towards $\mathbf{P_1}$ and $\mathbf{P_2}$.



Scheme S2. Synthetic pathway of the control initiator **3** and corresponding polymer $\mathbf{P_3}$.

*6-Bromo-2-butyl-1H-benzo[de]isoquinoline-1,3(2H)-dione **4***



The preparation followed an adapted literature protocol.[2,3] A mixture of 4-bromo-1,8-naphthalic anhydride (20 g, 72 mmol, 1 eq.) and butylamine (5.8 g, 93.3 mmol, 1.3 eq.) in 200 mL AcOH was stirred under reflux in a nitrogen atmosphere overnight. After the completion of the reaction, the reaction mixture was poured into a mixture of ice and water, and then filtered to get a pale yellow solid. The crude product was recrystallized from chlorobenzene to give a light gray solid (20.4 g, 61.2 mmol, 85%). **^{1}H-NMR** (300 MHz, Chloroform-d) δ [ppm] = 8.44 (dd, J = 7.3, 1.2 Hz, 1H), 8.31 (dd, J = 8.5, 1.2 Hz, 1H), 8.18 (d, J = 7.9 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.65 (dd, J = 8.5, 7.3 Hz, 1H), 4.03 (t, J = 7.2 Hz, 2H), 1.60 (dd, J = 15.1, 7.4 Hz, 2H), 1.35 (td, J = 14.7, 7.3 Hz, 2H), 0.88 (t, J = 7.3 Hz, 3H). See Figure S1. **^{13}C-NMR** (75 MHz, CDCl3) δ [ppm] = 163.37, 132.95, 131.82, 130.99, 130.33, 130.00, 128.69, 127.95, 122.96, 122.10, 40.34, 30.13, 20.38, 13.85. See
Figure **S2**.

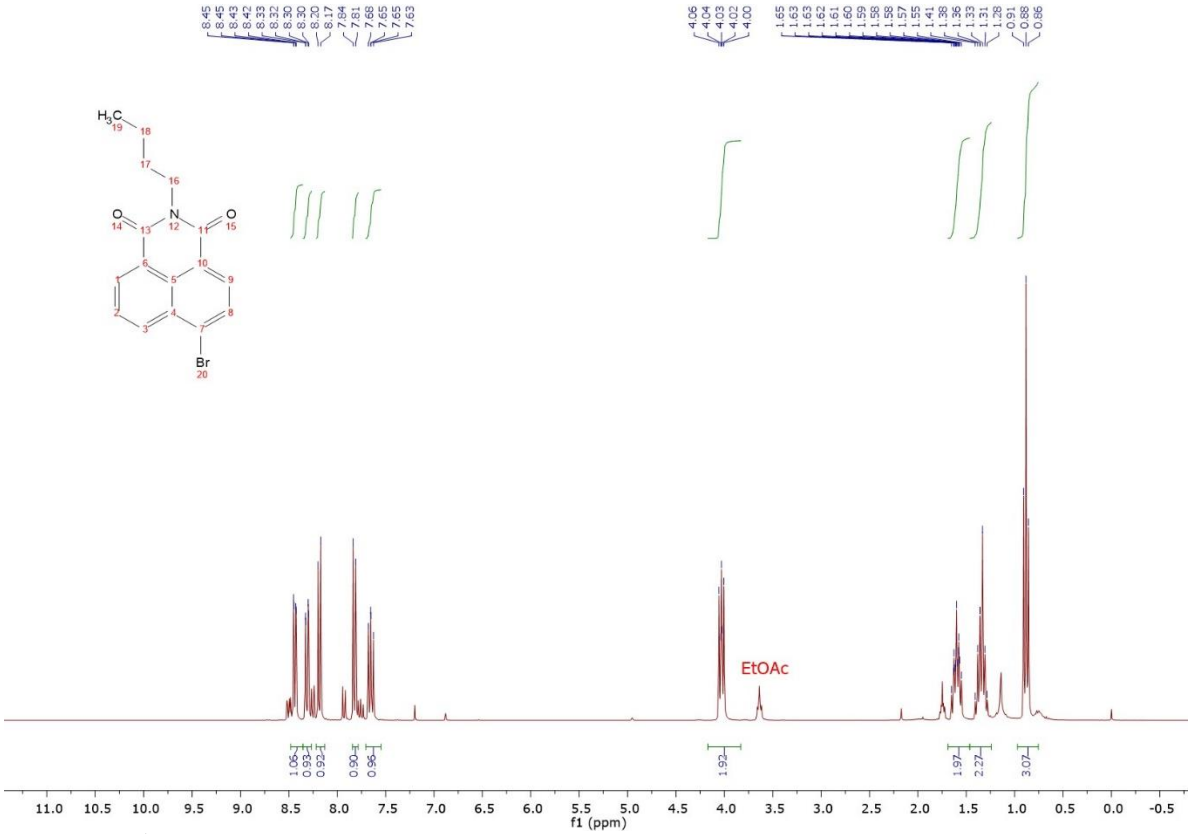


Figure S1. [1]H-NMR spectrum of 6-bromo-2-butyl-1H-benzo[de]isoquinoline-1,3(2H)-dione **4**.

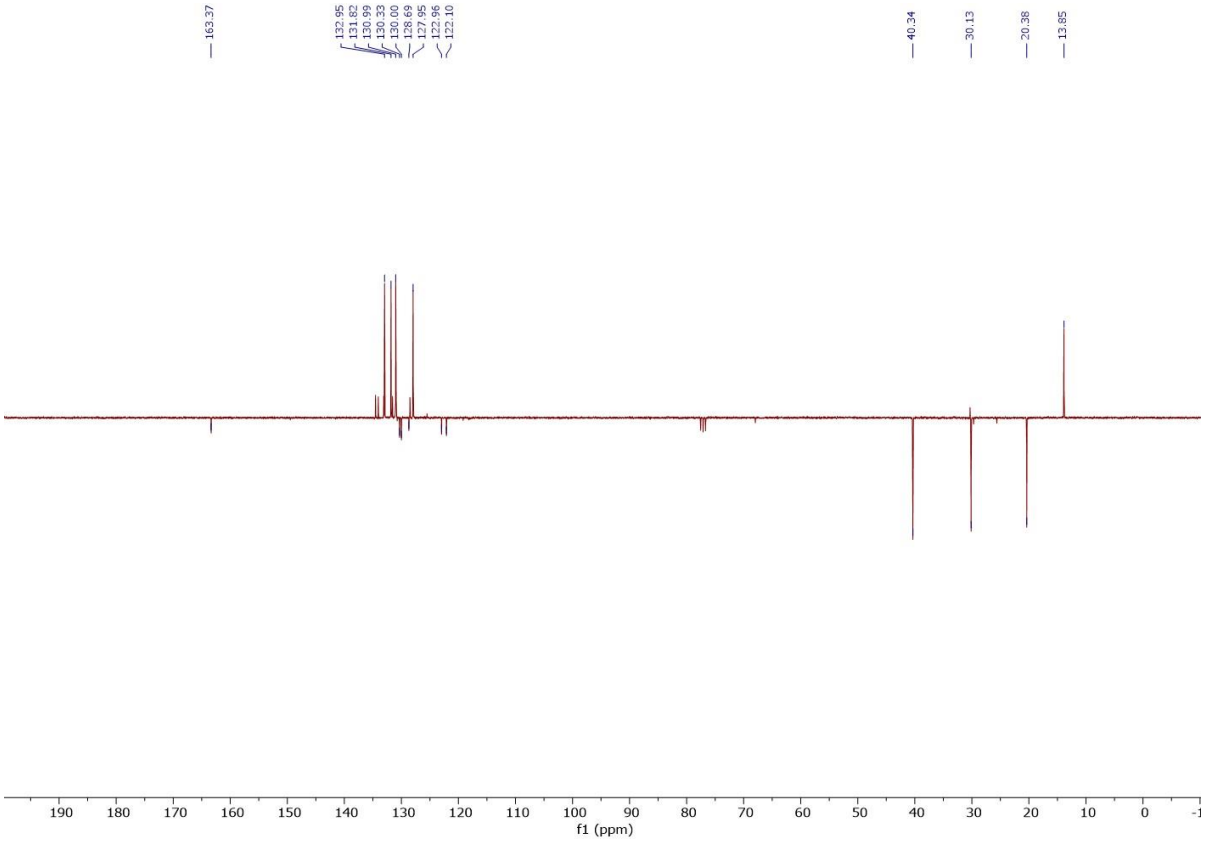
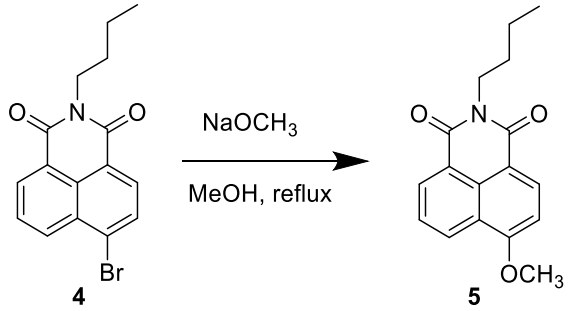


Figure S2. [13]C-NMR DEPT-135 spectrum of 6-bromo-2-butyl-1H-benzo[de]isoquinoline-1,3(2H)-dione **4**.

2-Butyl-6-hydroxy-1H-benzo[de]isoquinoline-1,3(2H)-dione 5



4 **5**

The preparation followed an adapted literature protocol.[2,3] A mixture of 6-bromo-2-butyl-1H-benzo[de]isoquinoline-1,3(2H)-dione (compound **4**) (20 g, 60.4 mmol), $CuSO_4 \cdot 5H_2O$ (2 g, 4.0 mmol), and CH_3ONa (28 g, 520 mmol) in 200 mL MeOH was heated under reflux for 12 h. After the removal of the solvent, the reaction mixture was dissolved in 200 mL CH_2Cl_2 and washed with H_2O (3×200 mL). The product was obtained as yellow solid (14.7 g, 51.9 mmol, 86 %). **^{1}H-NMR** (300 MHz, Chloroform-d) δ [ppm] = 8.53 – 7.86 (m, 3H), 7.39 (dd, J = 8.4, 7.3 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 4.58 – 3.51 (m, 5H), 1.57 (dd, J = 15.5, 7.8 Hz, 2H), 1.33 (dd, J = 17.2, 7.3, 5.7 Hz, 2H), 0.87 (t, J = 7.3 Hz, 3H). See Figure S3. **^{13}C-NMR** (75 MHz, Chloroform-d) δ [ppm] = 164.14, 163.54, 160.38, 132.97, 131.06, 128.86, 128.15, 125.59, 122.99, 122.06, 114.75, 104.90, 56.05, 39.95, 30.18, 20.37, 13.86. See Figure S4.

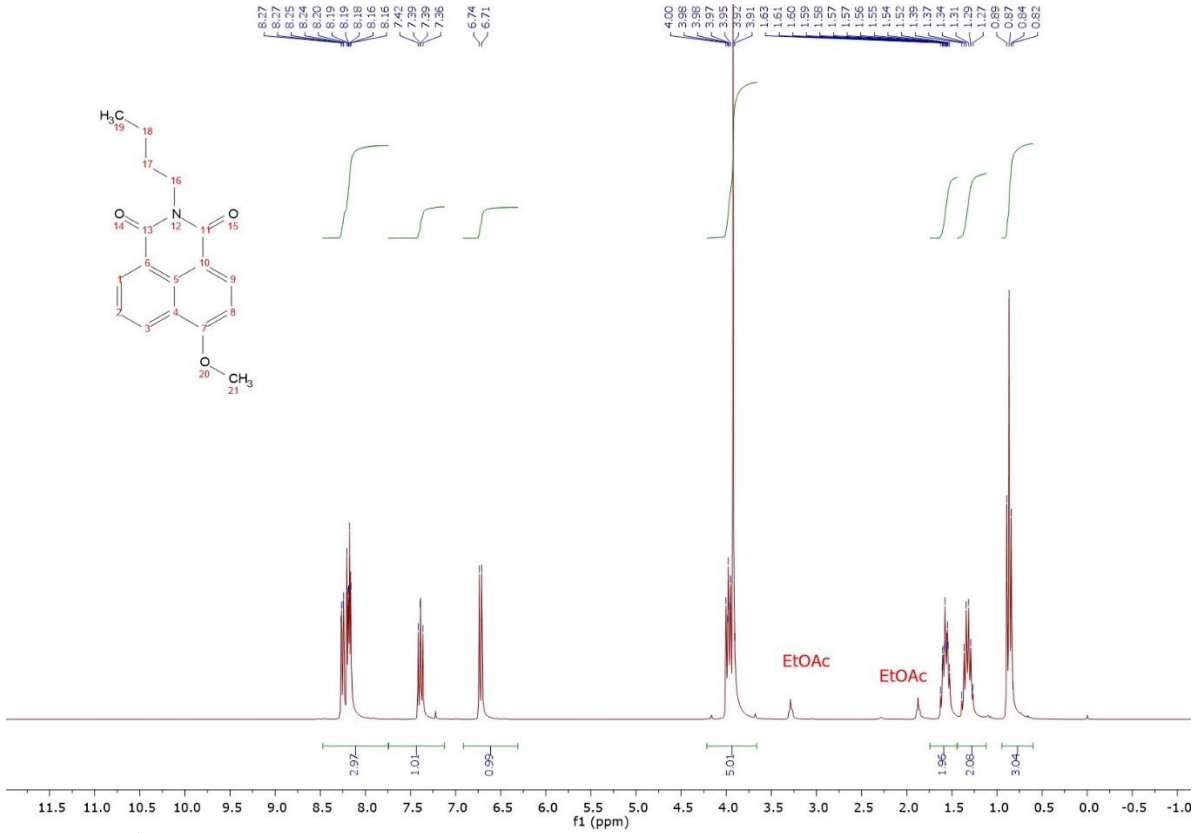


Figure S3. [1]H-NMR spectrum of 2-butyl-6-hydroxy-1H-benzo[de]isoquinoline-1,3(2H)-dione **5**.

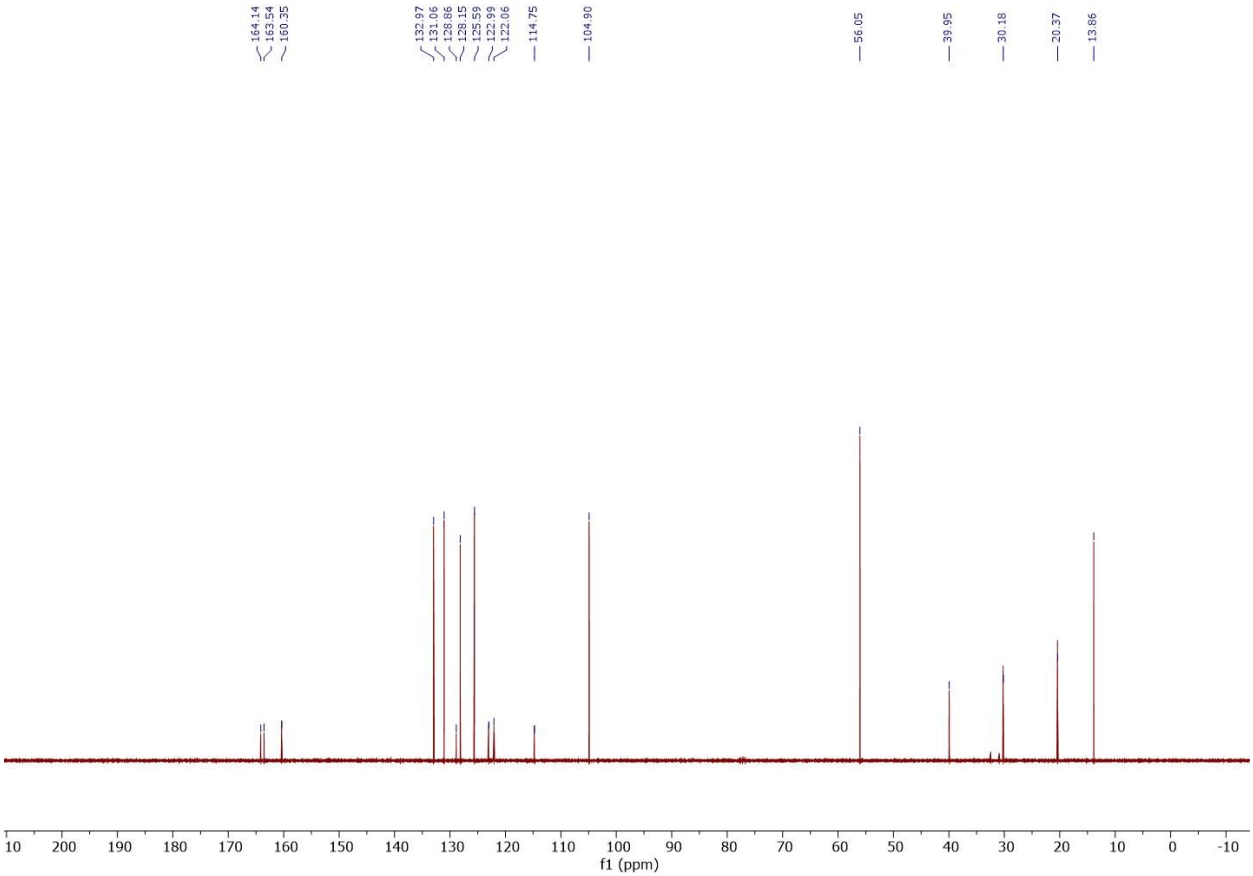
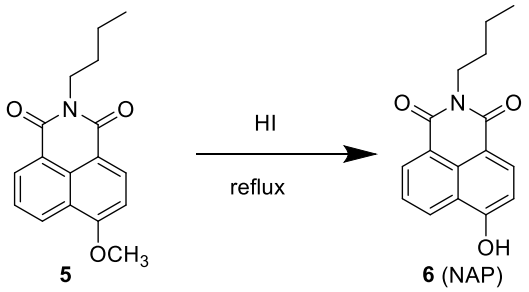


Figure S4. [13]C-NMR spectrum of 2-butyl-6-hydroxy-1H-benzo[de]isoquinoline-1,3(2H)-dione **5**.

N-Butyl-4-hydroxy-1,8-naphthalimide ***6*** *(NAP)*



5 **6** (NAP)

The preparation followed an adapted literature protocol.[2,3] A mixture of 2-butyl-6-hydroxy-1H-benzo[de]isoquinoline-1,3(2H)-dione (compound **5**) (10 g, 35 mmol) in 150 mL concentrated HI (57%) was reflux for 12 h. After cooling down the reaction mixture to room temperature, the solution was neutralized with 200 mL 2 M Na_2CO_3 solution. After filtration and wash with water, the pure product was obtained as a yellow solid (8.3 g, 30.8 mmol, 88%). **^{1}H-NMR** (300 MHz, DMSO-d6) δ [ppm] = 11.82 (ws, 1H), 8.95 – 8.14 (m, 3H), 7.71 (t, J = 7.8 Hz, 1H), 7.12 (d, J = 8.2 Hz, 1H), 3.99 (t, J = 7.4 Hz, 2H), 1.58 (ddd, J = 12.2, 8.6, 6.3 Hz, 2H), 1.33 (h, J = 7.3 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H). See Figure S5. **^{13}C-NMR** (75 MHz, DMSO) δ [ppm] = 163.57, 162.90, 160.15, 133.42, 130.98, 129.06, 128.76, 125.46, 122.27, 121.70, 112.54, 109.86, 38.95, 29.71, 19.81, 13.69. See Figure S6. **MS(ESI$^+$):** *m/z* Calcd for $C_{16}H_{15}NO_3$ $[M+H]^+$ 270.11, Found for $[M+H]^+$ 270.12. See Figure S7.

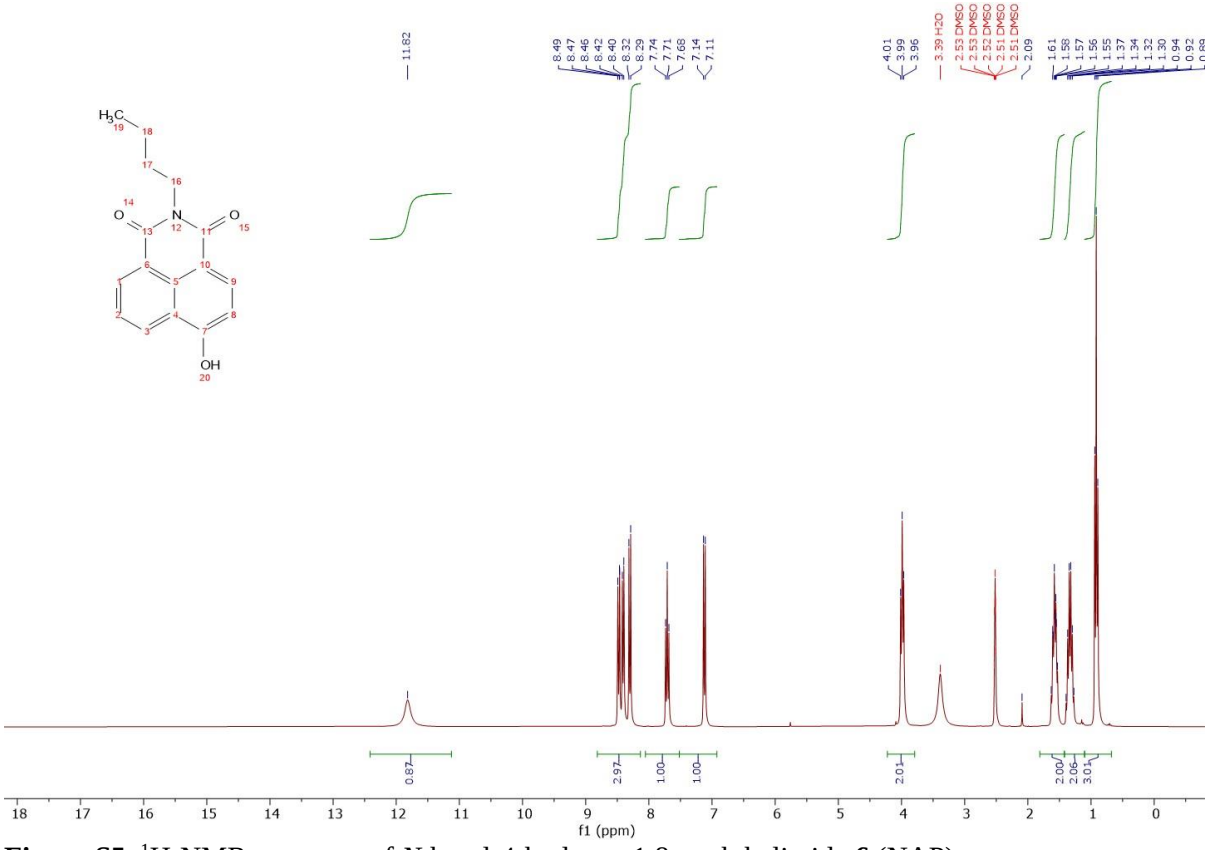


Figure S5. ^{1}H-NMR spectrum of *N*-butyl-4-hydroxy-1,8-naphthalimide **6** (NAP).

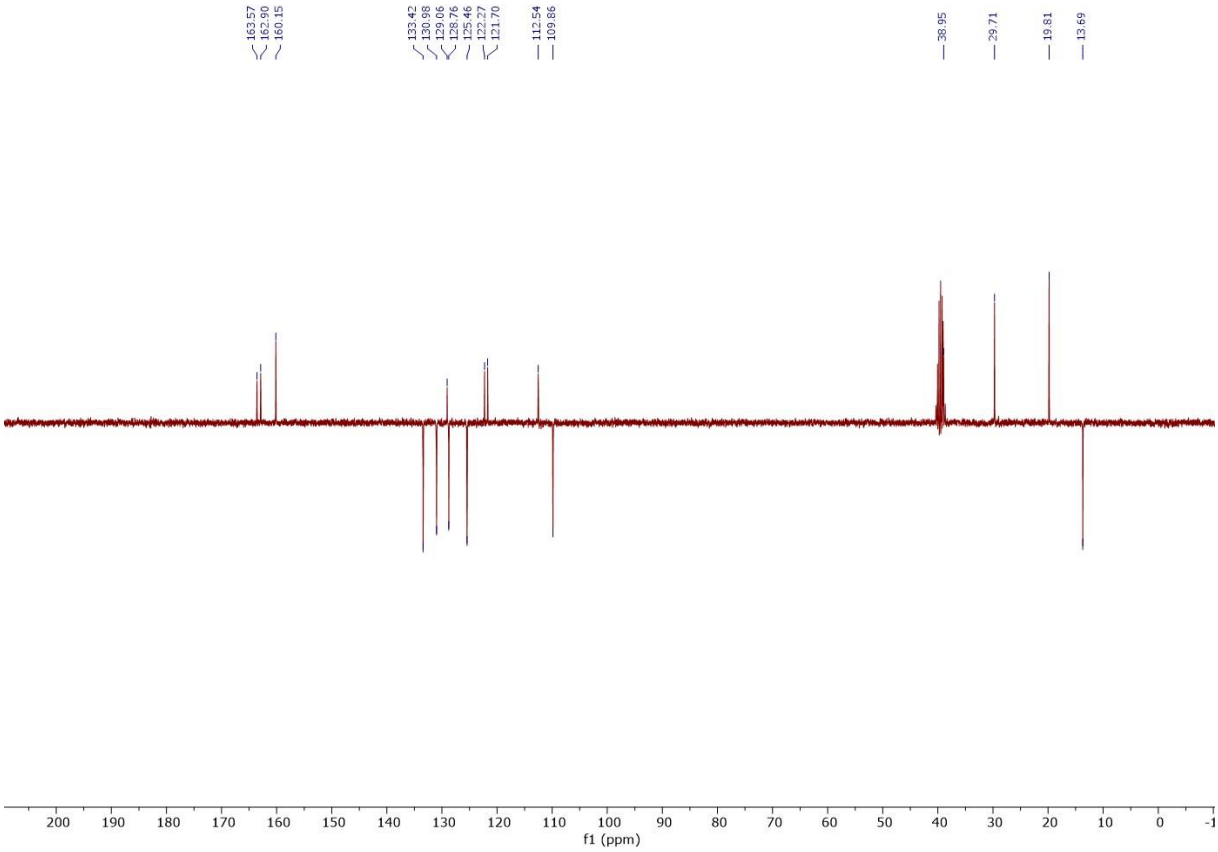


Figure S6. ^{13}C-NMR APT spectrum of *N*-butyl-4-hydroxy-1,8-naphthalimide **6** (NAP).

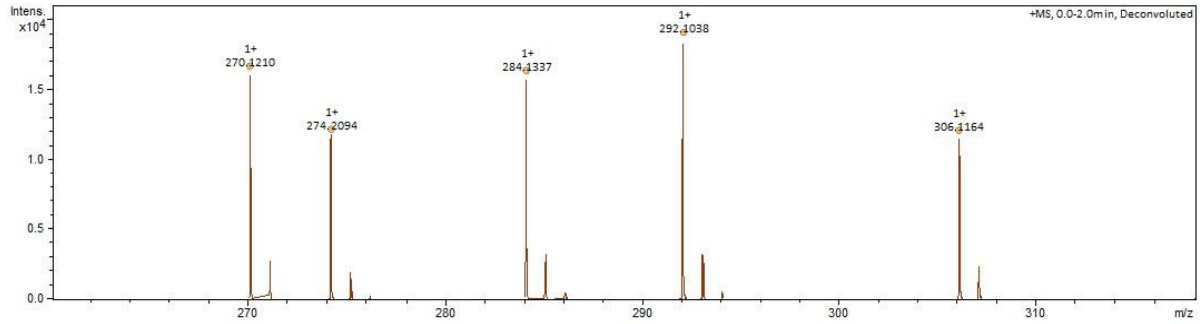
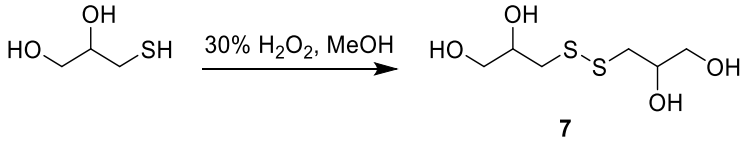


Figure S7. ESI$^+$ mass spectrum of *N*-butyl-4-hydroxy-1,8-naphthalimide **6** (NAP).

3,3-Disulfanediylbis(propane-1,2-diol) ***7***



7

3-Mercaptopropane-1,2-diol (92.45 mmol, 10 g) was dissolved in MeOH (25 mL) and then H_2O_2 solution (35%, 8 mL) was added dropwise. The reaction mixture was stirred for 12 h at room temperature until completion. Afterwards, the solvent was removed and the residue was recrystallized in CH_2Cl_2 to obtain a white solid **7** (42.46 mmol, 9.10 g, 84%). **^{1}H-NMR** (300 MHz, DMSO-d_6) δ [ppm] = 4.74 (ws, 4H,), 3.69-3.61 (dq, J = 7.4, 5.3 Hz, 2H, 2, 7), 3.41-3.30 (ddd, J = 15.3, 11.1, 5.3 Hz, 4H,), 2.94-2.66 (dddd, J = 60.4, 13.1, 4.7, 0.9 Hz, 4H). See Figure S8. **^{13}C-NMR** (75 MHz, DMSO-d6) δ [ppm] = 70.19, 64.52, 43.19. See Figure S9. **MS(ESI$^+$):** *m/z* Calcd for $C_6H_{14}O_4S_2$ $[M+H]^+$ 215.04, Found for $[M+H]^+$ 215.04. See Figure S10.

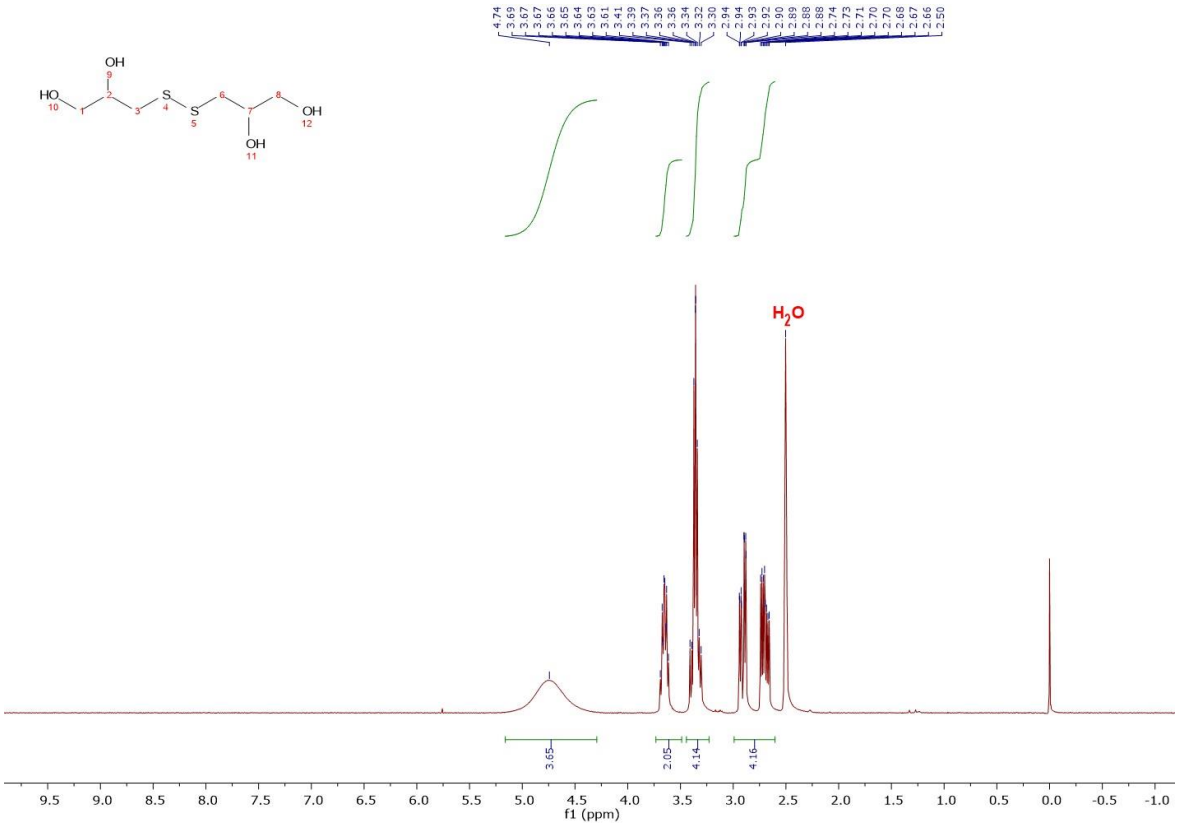


Figure S8. ^{1}H-NMR Spectrum of 3,3-disulfanediylbis(propane-1,2-diol) **7**.

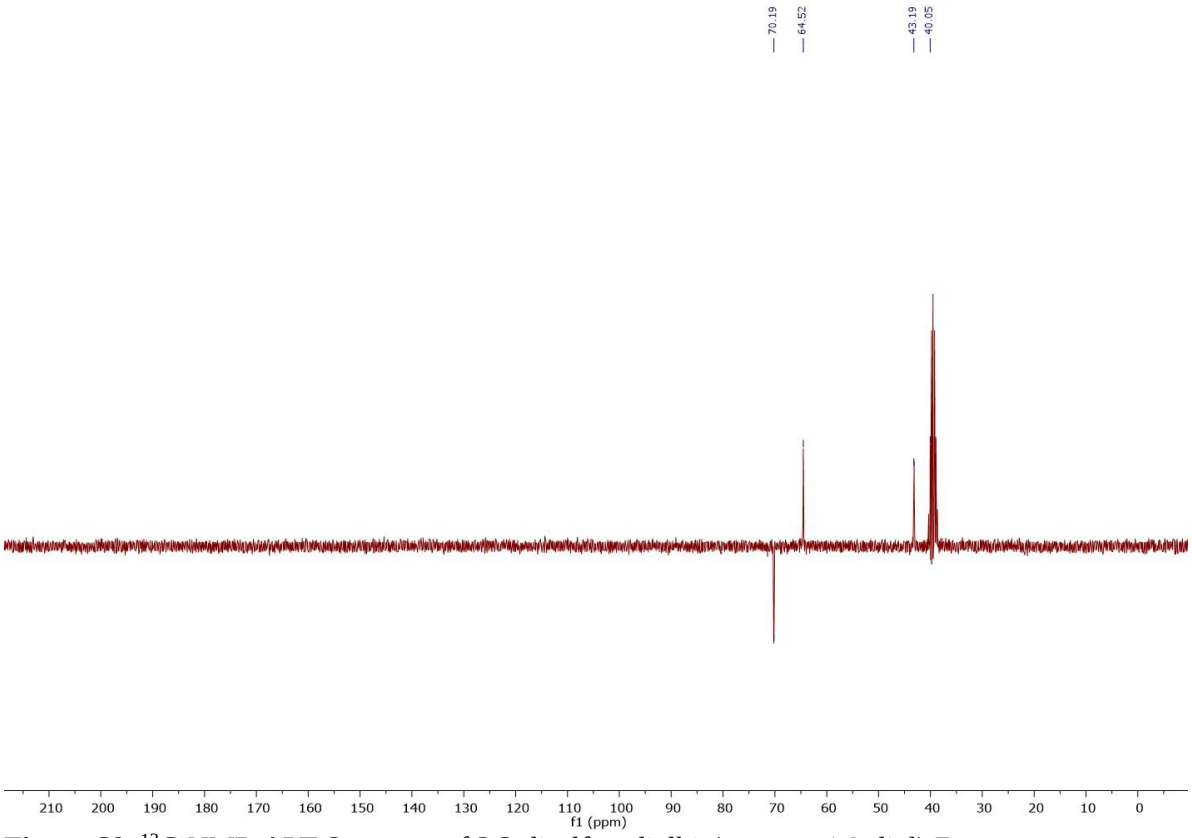


Figure S9. ^{13}C-NMR APT Spectrum of 3,3-disulfanediylbis(propane-1,2-diol) **7**.

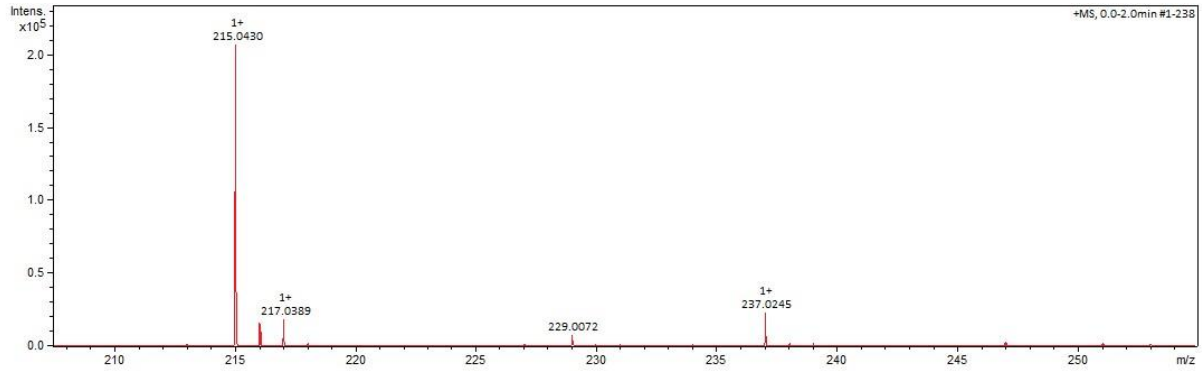
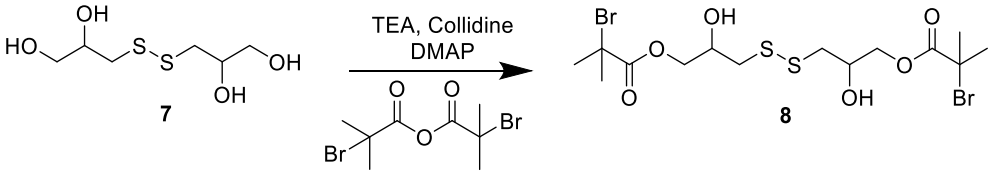


Figure S10. ESI$^+$ mass spectrum of 3,3-disulfanediylbis(propane-1,2-diol) **7**.

*Modifiable initiator **8***



In a reaction flask, compound **7** (1 mmol, 214 mg, 1 eq.) and Et_3N (10 mmol, 0.95 mL, 10 eq.) were dissolved in collidine (15 mL) and were then cooled down to -20 °C in an ice-salt bath. Afterwards, a solution consisting of 2-bromoisobutryic anhydride (2 mmol, 632 mg, 2 eq.), DMAP (0.1 mmol, 12 mg, 0.1 eq.) and 5 mL CH_2Cl_2 were added dropwise. The reaction mixture was stirred until complete consumption of the starting material as indicated by TLC, then washed three times with 1 N aq. HCl and H_2O. Afterwards, the crude product was purified by column chromatography on silica gel (hexane:EtOAc = 2:1) to give compound 7 as a colourless liquid (0.36 mmol, 184 mg, 36%). **^{1}H-NMR** (300 MHz, chloroform-d) δ [ppm] = 4.38 – 4.03 (m, 6H), 3.17 (s, 2H), 2.89 (dddd, J = 39.3, 14.2, 4.7, 1.8 Hz, 4H), 1.93 (s, 12H). See Figure S11. **^{13}C-NMR** (75 MHz, chloroform-d) δ [ppm] = 171.61, 68.25, 68.19, 55.72, 42.10, 30.95. See Figure S12. **MS(ESI$^+$):** *m/z* Calcd for $C_{14}H_{24}Br_2O_6S_2$ $[M+H]^+$ 510.95, Found for $[M+H]^+$ 510.95. See Figure S13.

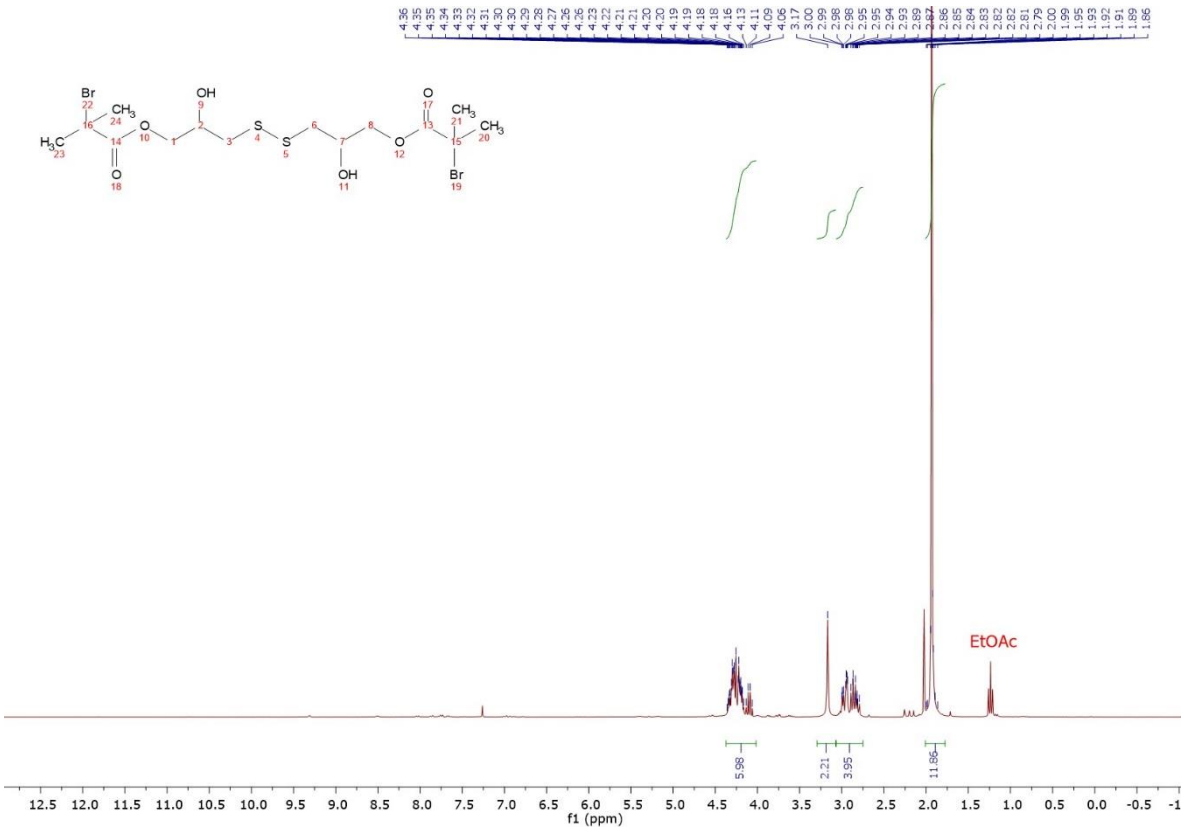


Figure S11. ^{1}H-NMR Spectrum of modifiable initiator **8**.

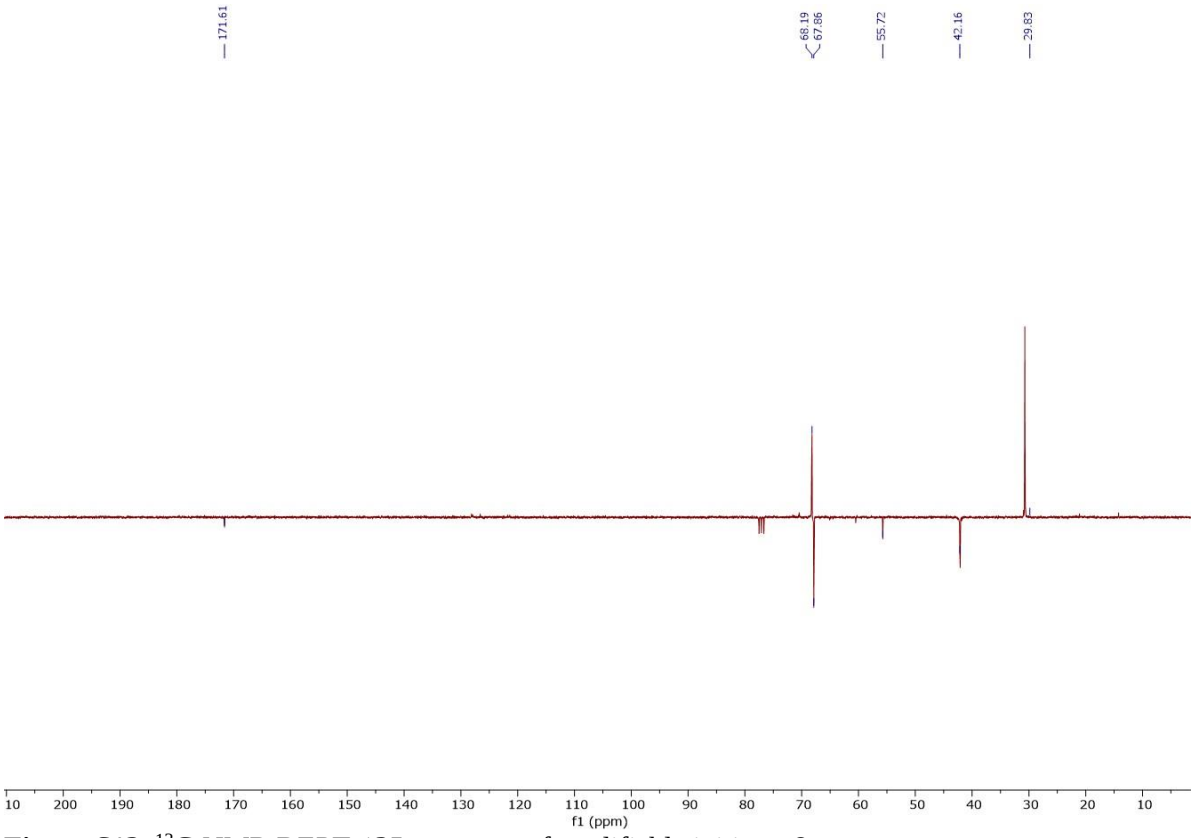


Figure S12. ^{13}C-NMR DEPT-135 spectrum of modifiable initiator **8**.

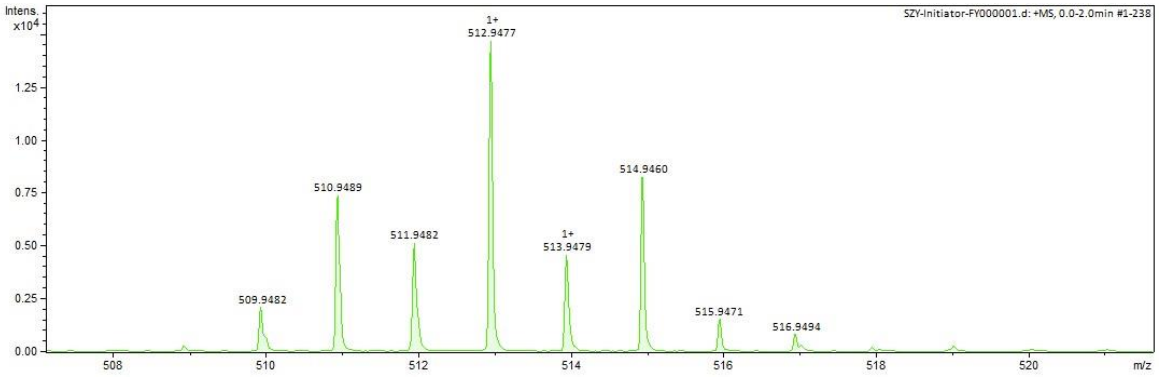
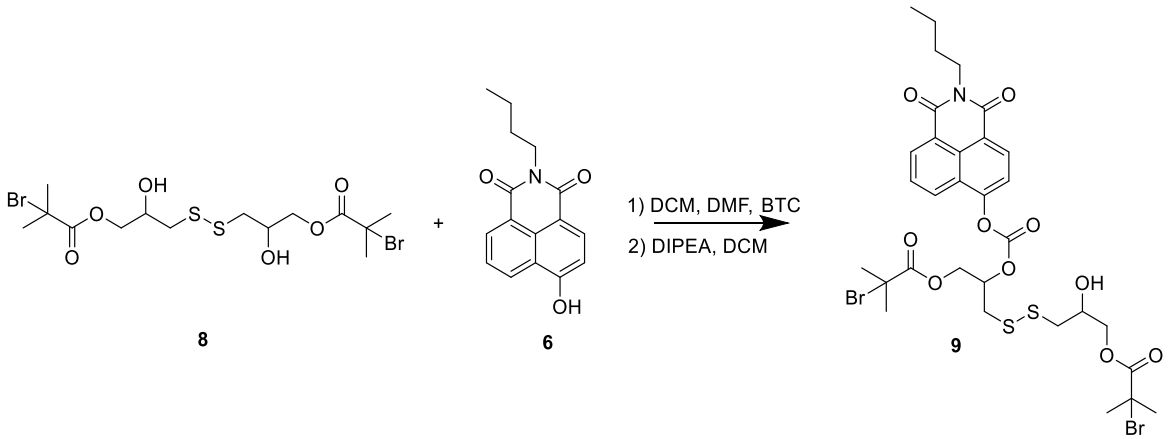


Figure S13. ESI$^+$ mass spectrum of modifiable initiator **8**.

*Compound **9***



8 **6** **9**

Compound **6** (NAP, 225 mg, 0.84 mmol, 0.7 eq) was dissolved in 4 mL DMF, then added dropwise to an ice cold CH_2Cl_2 solution (5 mL) of triphosgene (356 mg, 1.20 mmol, 1 eq) and stirred for 4 h submerged in an ice bath. Subsequently, the excess phosgene was removed by Ar purging and neutralized by bubbling the exhaust gas through 2 M NaOH solution. To this reaction mixture, compound **8** (614 mg, 1.2 mmol, 1 eq.), DIPEA (836 µL, 4.80 mmol, 4 eq) in 5 mL dichloromethane were added and stirred overnight at rt. After completion of the reaction, the reaction mixture was dissolved in EtOAc, washed with HCl and H_2O, dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (Hexane: EtOAc = 3:1), to give the product as a yellow oil (157 mg, 0.336 mmol, 28%). **^{1}H-NMR** (300 MHz, Chloroform-d) δ [ppm] = 8.52 (m, 2H), 8.30 (d, J = 8.3 Hz, 1H), 7.72 (t, J = 7.9 Hz, 1H), 7.59 (dd, J = 8.3, 4.5 Hz, 1H), 5.54 – 5.13 (m, 1H), 4.64 (m, 1H), 4.52 – 3.93 (m, 6H), 3.20 – 2.69 (m, 5H), 1.95 – 1.72 (m, 12H), 1.63 (p, J = 7.6 Hz, 2H), 1.36 (h, J = 7.3 Hz, 2H), 0.89 (t, J = 7.3 Hz, 3H). See Figure S14. **^{13}C-NMR** (75 MHz, $CDCl_3$) δ [ppm] = 171.53, 170.53, 163.96, 162.08, 152.18, 150.62, 131.70, 129.24, 127.54, 124.78, 122.85, 120.77, 118.75, 75.61, 68.23, 67.78, 64.47, 56.61, 55.26, 42.56, 42.46, 40.33, 38.51, 30.17, 19.81, 15.08. See Figure S15.

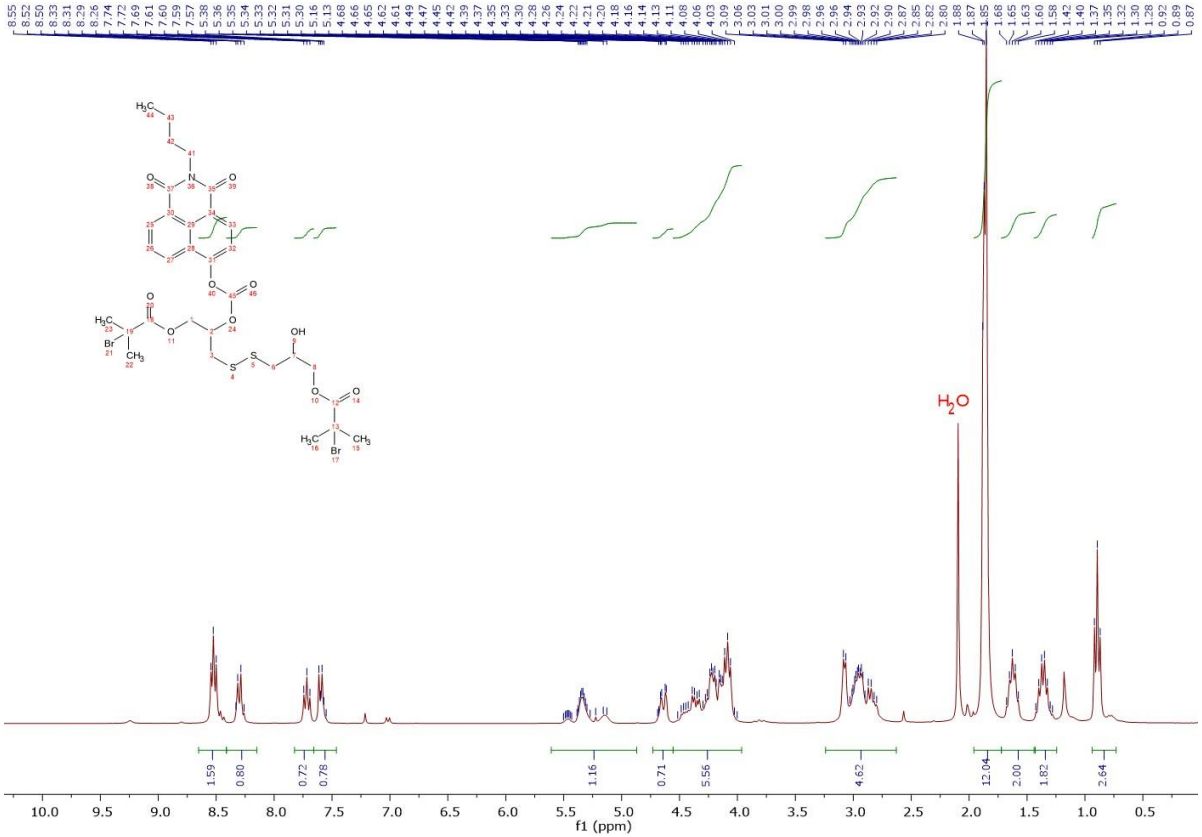


Figure S14. ^{1}H-NMR spectrum of **9**.

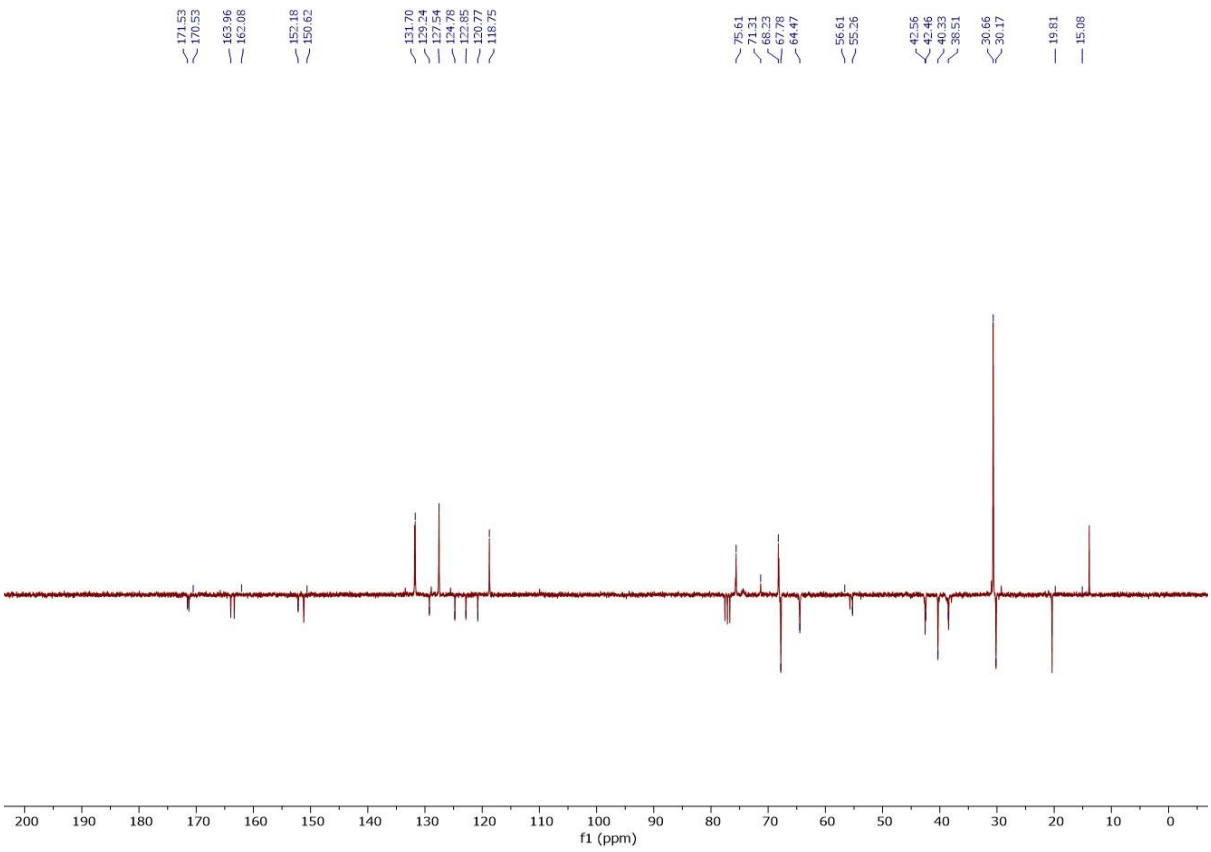
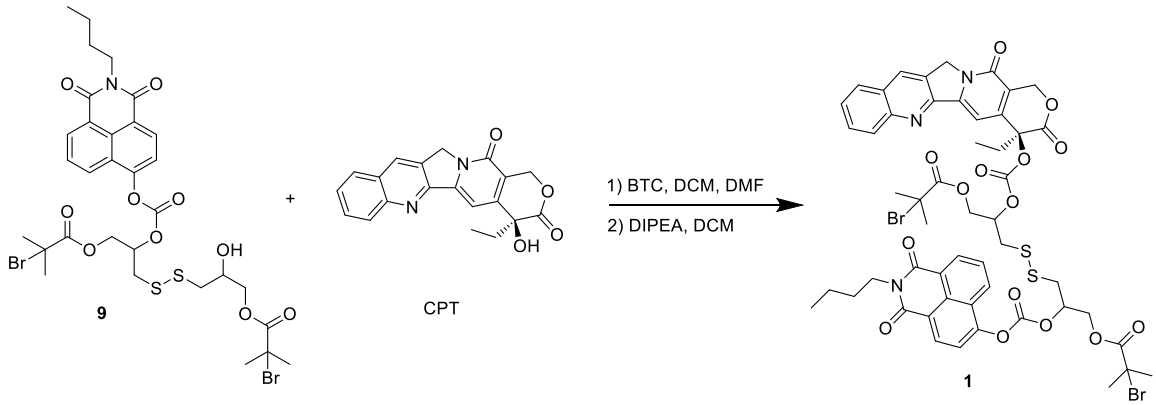


Figure S15. ^{13}C-NMR DEPT-135 spectrum of **9**.

*Compound **1***



Camptothecin (69 mg, 0.2 mmol, 2 eq) was dissolved in 5 mL DMF and then added dropwise to a CH_2Cl_2 solution of triphosgene (BTC) (237 mg, 0.8 mmol, 8 eq.) and stirred for 4 h at rt. Subsequently, the excess phosgene was removed by Ar purging and neutralized by bubbling the exhaust gas through 2 M NaOH solution. To this reaction mixture, compound **9** (80 mg, 0.1 mmol, 1 eq.) and DIPEA (156 µL, 0.9 mmol, 9 eq.) in 5 mL CH_2Cl_2 was added, and the reaction mixture was allowed to stir overnight at rt. After completion of the reaction, the reaction mixture was dissolved in 100 mL EtOAc and washed with HCl and H_2O. Subsequently, the mixture was dried *in vacuo* and the crude product was purified by column chromatography on silica gel (33 mg, 0.026 mmol, 25.7%). **^{1}H-NMR** (600 MHz, Chloroform-d) δ [ppm] = 8.70 – 8.06 (m, 5H), 7.94 – 7.55 (m, 5H), 7.44 – 7.17 (m, 1H), 5.73 – 5.31 (m, 2H), 5.31 – 5.13 (m, 4H), 4.50 – 4.21 (m, 4H), 4.20 – 4.00 (m, 2H), 3.08 – 2.89 (m, 4H), 2.42 – 2.19 (m, 2H), 1.93 – 1.86 (m, 12H), 1.71 – 1.56 (m, 2H), 1.46 – 1.31 (m, 2H), 1.03 – 0.87 (m, 6H). See Figure S17. **^{13}C-NMR** (151 MHz, $CDCl_3$) δ [ppm] = 171.21, 171.10, 166.45, 163.82, 163.20, 157.17, 152.12, 151.54, 150.94 , 148.85, 146.90, 146.57, 144.97, 131.78, 131.45, 131.22, 130.94, 130.71, 129.62, 129.49, 129.18 , 128.49, 128.26, 128.16, 127.74, 127.56, 124.60, 122.77, 120.22, 118.69, 95.41, 79.44, 75.53, 74.39, 67.16, 66.94, 64.11, 55.74, 55.33, 50.11, 40.26, 40.00, 38.58, 31.85, 30.94, 30.64, 30.16, 30.11, 29.27, 20.35, 13.85, 7.64. See Figure S18. **MS(ESI$^+$):** *m/z* = 1180.13 (calcd. 1180.12 for $C_{52}H_{52}Br_2N_3O_{15}S_2^+$). See Figure S16.

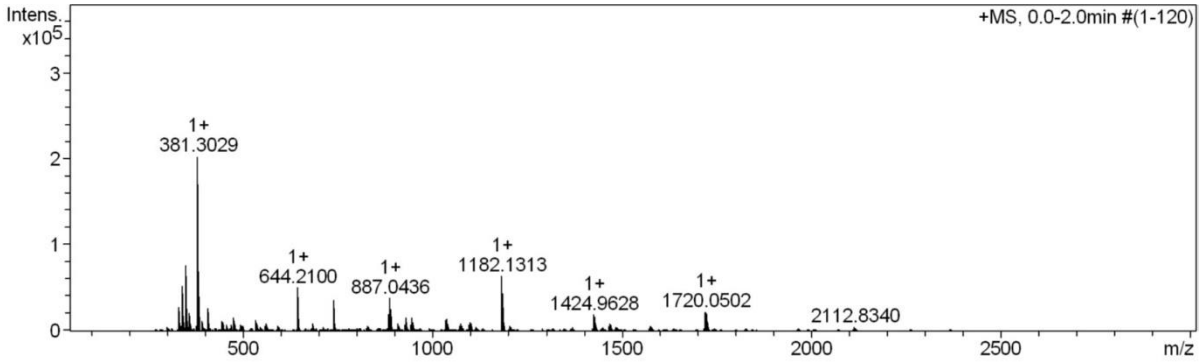


Figure S16. ESI$^+$ mass spectrum of **1**.

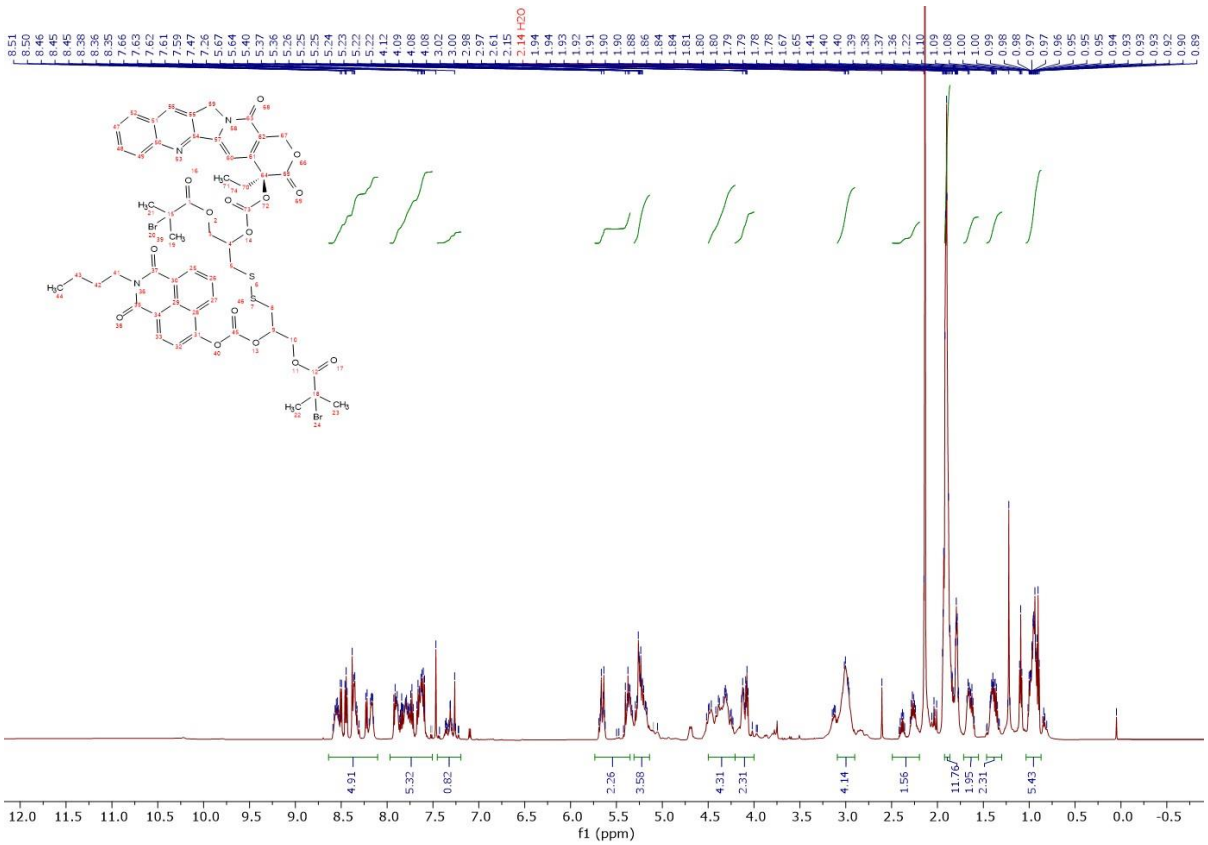


Figure S17. ^{1}H-NMR spectrum of **1**.

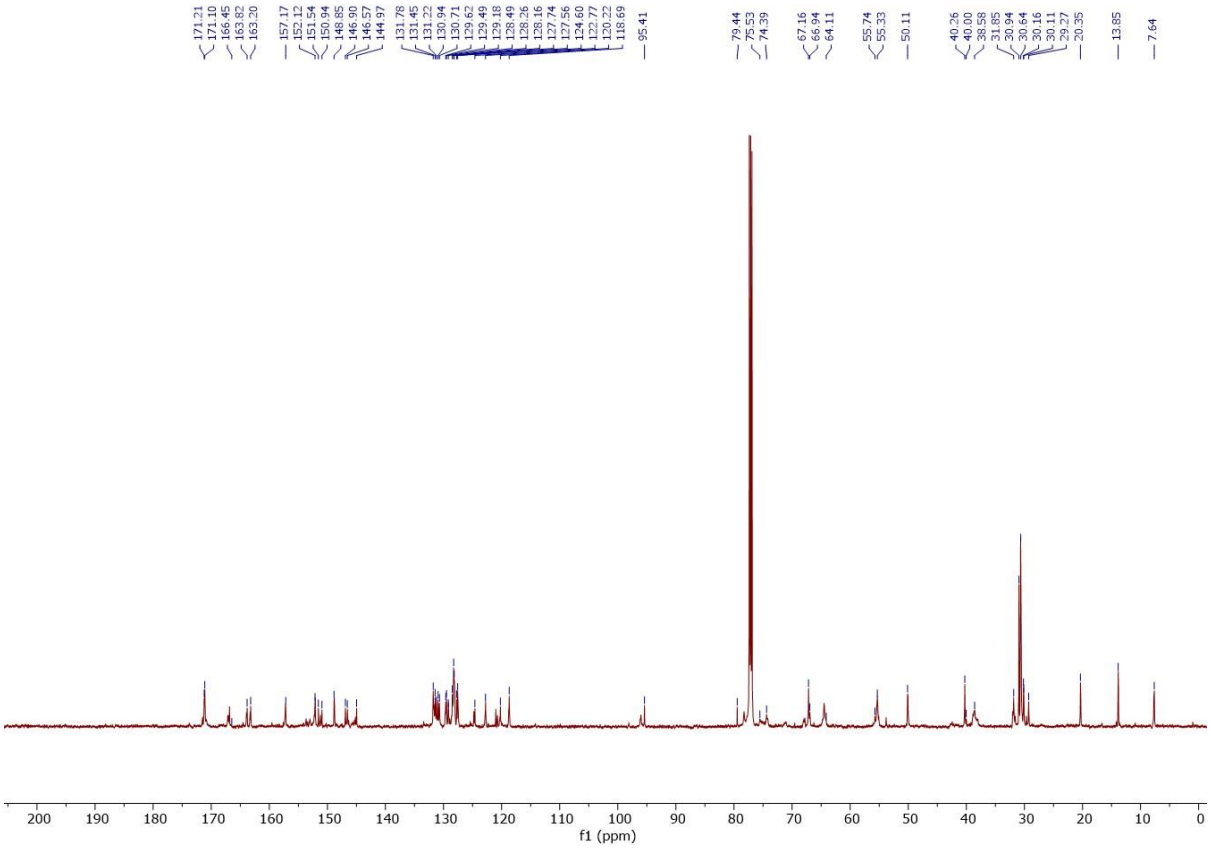
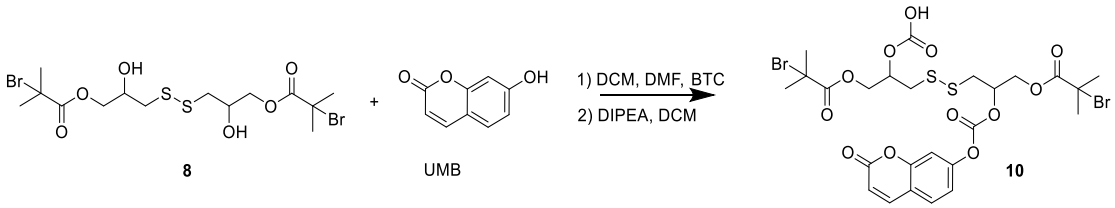


Figure S18. ^{13}C-NMR spectrum of **1**.

*Compound **10***



8 UMB 10

Umbelliferon (97 mg, 0.6mmol, 1eq.) was dissolved in 3.5 mL DMF, then added dropwise to a 5 mL CH_2Cl_2 solution of triphosgene (356 mg 1.2 mmol, 1 eq.) immersed in an ice bath. The whole mixture was allowed to stir for 4 h. Subsequently, the excess phosgene was removed by Ar purging and neutralized by bubbling the exhaust gas through 2 M NaOH solution. To this reaction mixture, compound **8** (614 mg, 1.2 mmol, 1 eq), DIPEA (836 µL, 4.80 mmol, 4 eq.) in 5 mL CH_2Cl_2 were added and stirred overnight at rt. After completion of the reaction, the reaction mixture was washed with HCl and H_2O, dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (CH_2Cl_2:MeOH = 30:1) to give a white gel-like solid (243.6 mg, 0.35 mmol, 58%). **^{1}H-NMR** (300 MHz, Chloroform-d) δ [ppm] = 7.64 (dt, J = 9.6, 2.0 Hz, 1H), 7.44 (ddd, J = 8.6, 3.7, 1.8 Hz, 1H), 7.29 – 6.98 (m, 2H), 6.34 (dd, J = 9.6, 1.8 Hz, 1H), 5.21 (ddt, J = 30.9, 10.8, 4.2 Hz, 2H), 4.74 – 4.09 (m, 5H), 3.26 – 2.80 (m, 4H), 1.89 – 1.83 (m, 12H). See Figure S19. **^{13}C-NMR** (75 MHz, Chloroform-d) δ [ppm] = 171.13, 160.68, 154.64, 153.67, 153.16, 152.15, 142.76, 128.82, 117.73, 117.01, 116.38, 109.95, 75.15, 74.28, 64.47, 55.26, 38.65, 30.68. See Figure S20.

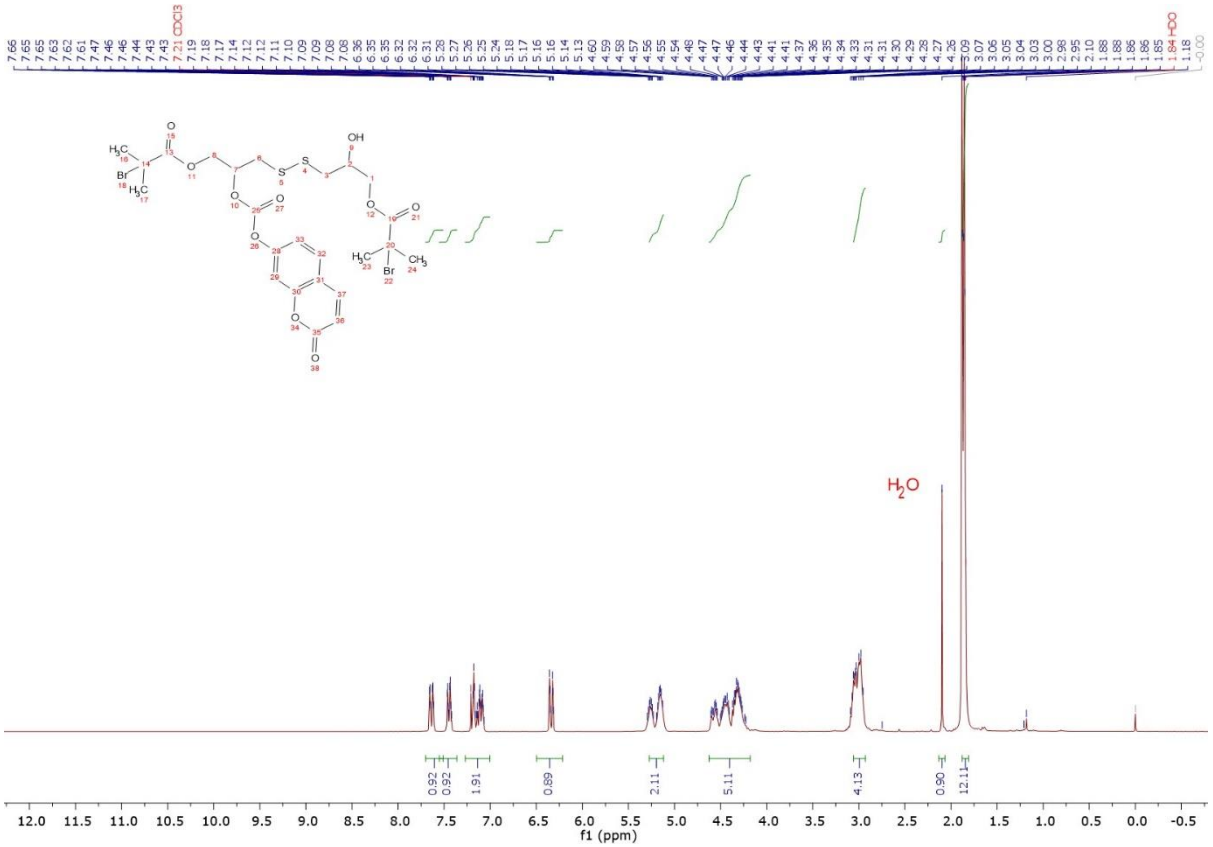


Figure S19. ^{1}H-NMR spectrum of **10**.

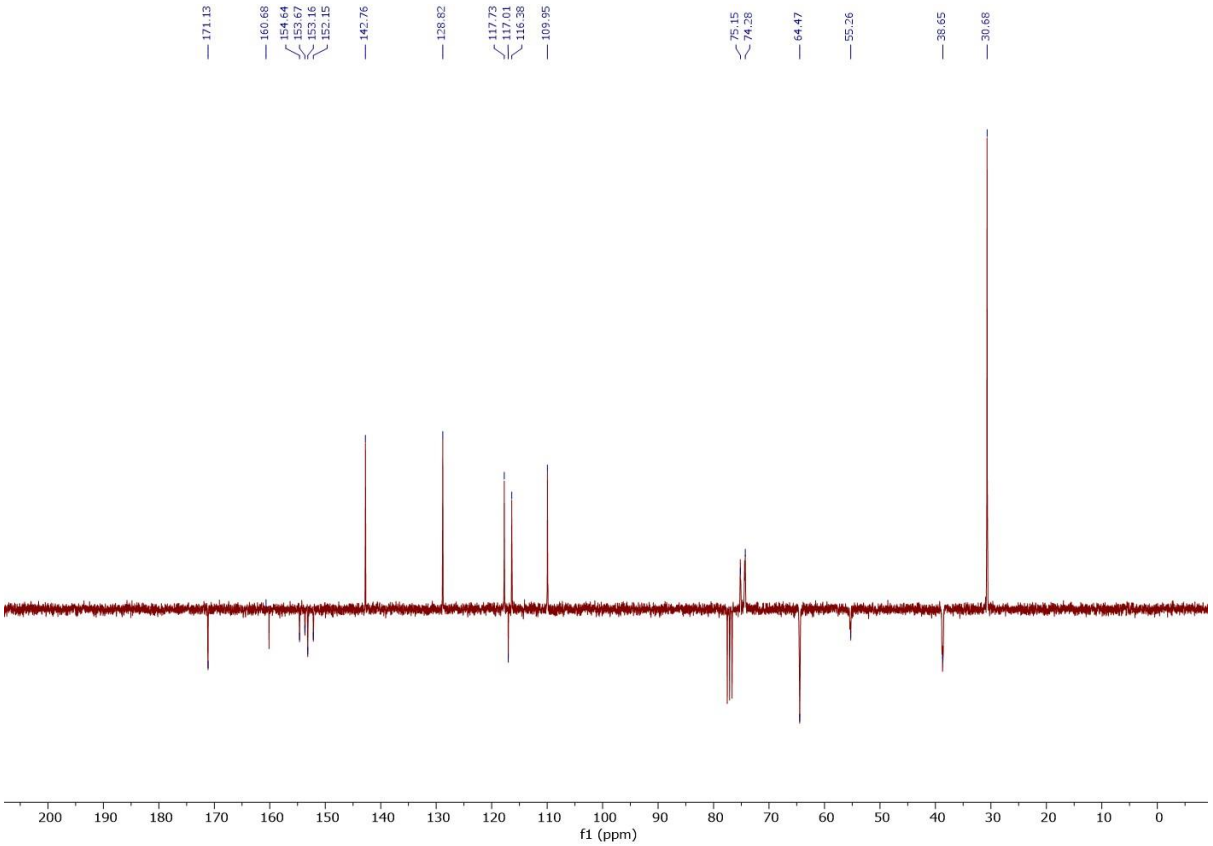
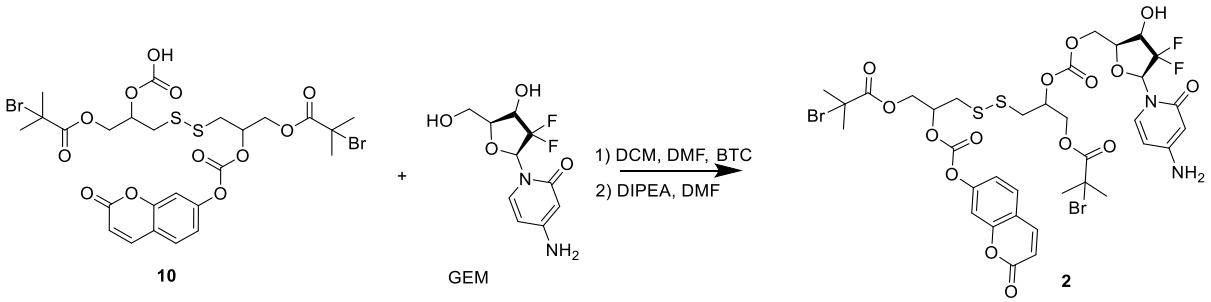


Figure S20. ^{13}C-NMR DEPT-135 spectrum of **10**.

*Compound **2***



To an ice cold solution of triphosgene (BTC) (593 mg 2 mmol, 2 eq.) in 5 mL CH_2Cl_2, a mixture of **10** (700 mg, 1 mmol, 1 eq.) pre-dissolved in 2 mL DMF was added dropwise, and the whole mixture was allowed to stir for 4 h immersed in an ice bath. Subsequently, the excess phosgene was removed by Ar purging and neutralized by bubbling the exhaust gas through 2 M NaOH solution. Afterwards, the mixture of Gemcitabine (262 mg,1 mmol, 1 eq.) with DIPEA (696 µL, 4 mmol, 4 eq.) in 5 mL DMF was added and stirred overnight at room temperature. After completion of the reaction, the reaction mixture was precipitated by adding Et_2O and subsequently purified by column chromatography on silica gel (CH_2Cl_2:MeOH = 20:1) to give 2 as a light yellow solid (366.3 mg, 0.37 mmol, 37%). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ [ppm] = 11.00 (s, 1H, 54), 8.37 – 6.91 (m, 5H), 6.50 – 6.10 (m, 3H), 5.33 (m, 3H), 4.53 – 4.22 (m, 6H), 3.88 – 3.57 (m, 3H), 3.29 – 3.01 (m, 4H), 1.88 (s, 12H). See Figure S21. **^{13}C-NMR** (151 MHz, DMSO) δ [ppm] = 170.92, 163.7, 160.0 , 154.5 , 154.2, 153.2 , 153.0, 152.3, 145.6 , 144.1, 130.0, 123.3 , 118.0, 117.4, 116.3, 109.8, 102.6, 95.4, 81.5, 75.6, 71.3, 65.5, 59.2, 57.2, 38.0, 30.7 See Figure S22. **MS(ESI$^+$):** *m/z* = 988.01 (calcd. 988.01 for $C_{34}H_{38}Br_2F_2N_3O_{15}S_2^+$). See Figure S23

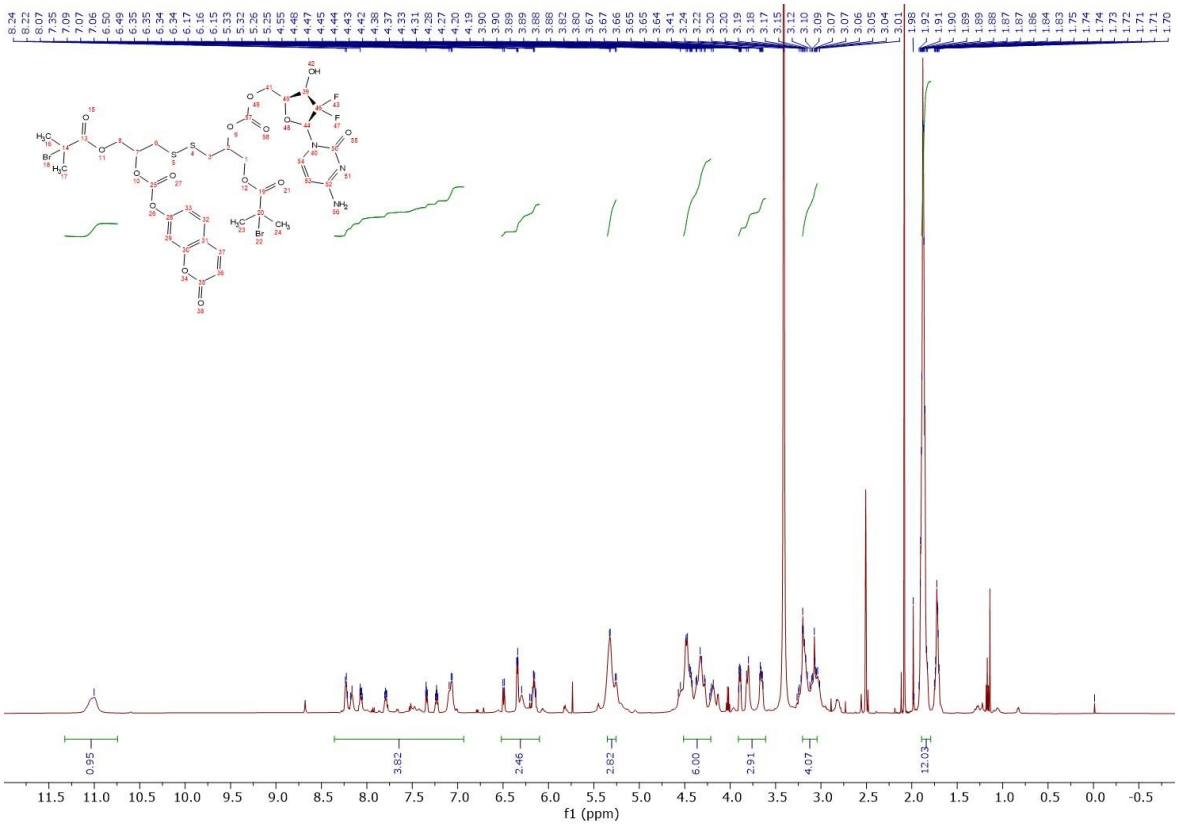


Figure S21. ^{1}H-NMR spectrum of **2**.

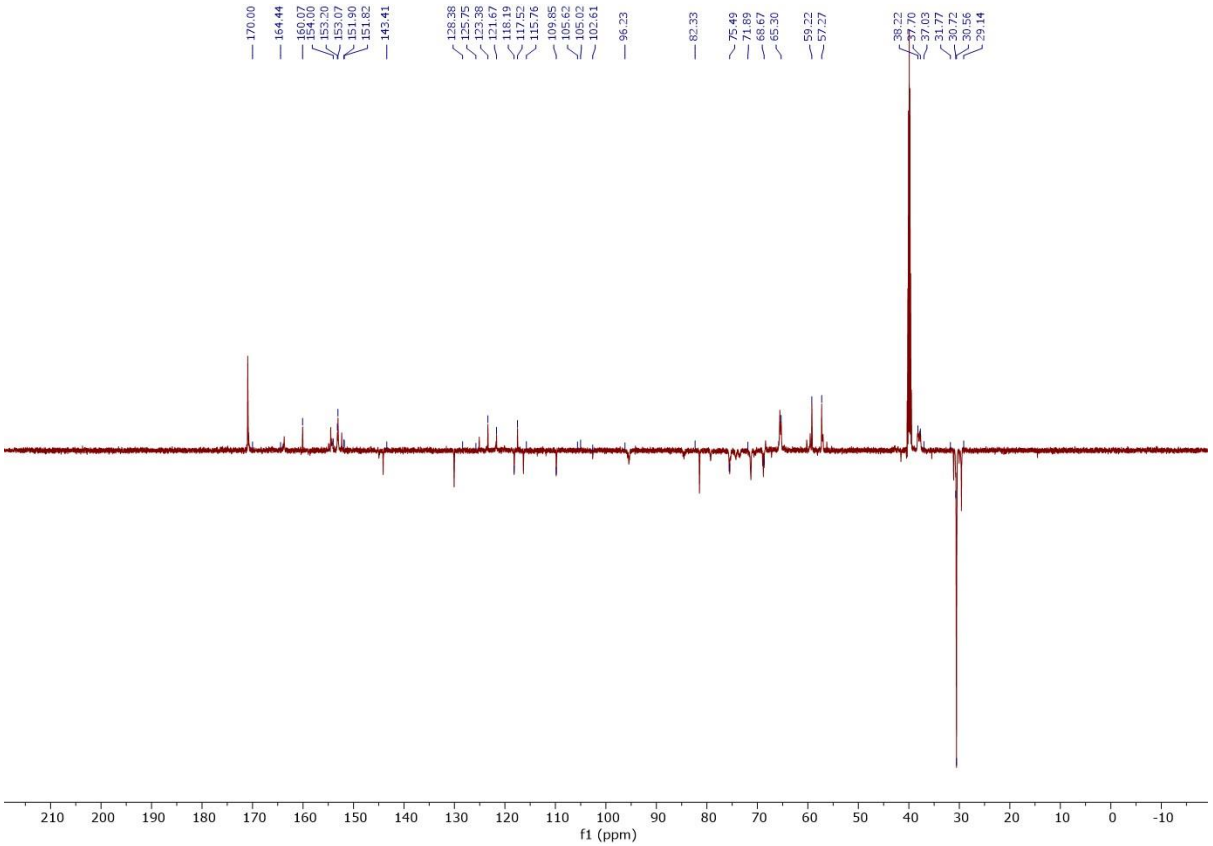


Figure S22. ^{13}C-NMR APT spectrum of **2**.

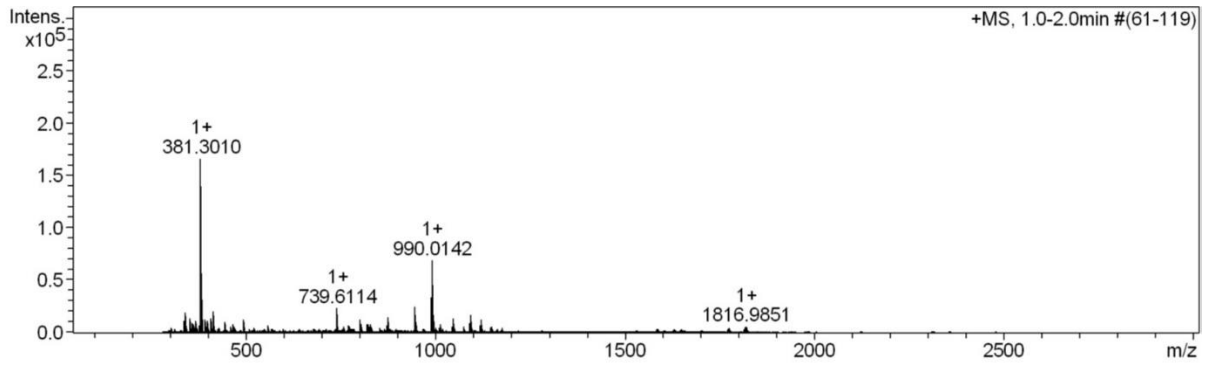
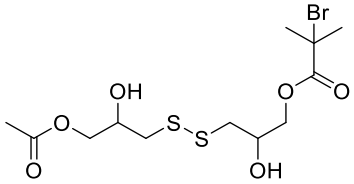


Figure S23. ESI$^+$ mass spectrum of **2**.

*Synthesis of control initiator building block **11***



11

In a reaction flask, compound **7** (10 mmol, 2.14 g, 1 eq.), DMAP (0.5 mmol, 6.1 mg, 0.05 eq.), and Et_3N (40 mmol, 3.8 mL, 4 eq.) were dissolved in collidine (35 mL) and were then cooled down to -20 °C in an ice-salt bath. Afterward, a solution of 2-bromo-2-methylpropanoic anhydride (3.20 g, 10 mmol, 1 eq.) in 5 mL CH_2Cl_2 was added dropwise. The reaction mixture was stirred while immersed in an ice bath for 2 h, then a solution of Ac_2O (1.02 g, 10 mmol, 1 eq.) in 5 mL CH_2Cl_2 was added and left to react for another two hours on ice batch. Subsequently, the reaction mixture was washed three times with 1 N aq. HCl and three times with H_2O. Afterwards, the crude product was purified by column chromatography on silica gel (hexane:EtOAc = 2:1) to give compound 11 as light yellow oil (1.49 mmol, 0.76g, 15%). **^{1}H-NMR** (300 MHz, DMSO-d_6) δ [ppm] = 5.35 (d, J = 24.7 Hz, 2H), 4.21 – 3.79 (m, 6H), 3.03 – 2.71 (m, 4H), 2.04 (s, 3H), 1.92 (s, 6H). See Figure S24. **^{13}C-NMR** (75 MHz, DMSO-d_6) δ [ppm] = 170.67, 169.66, 69.05, 66.78, 65.88, 57.28, 42.30, 30.25, 19.11. See Figure S25.

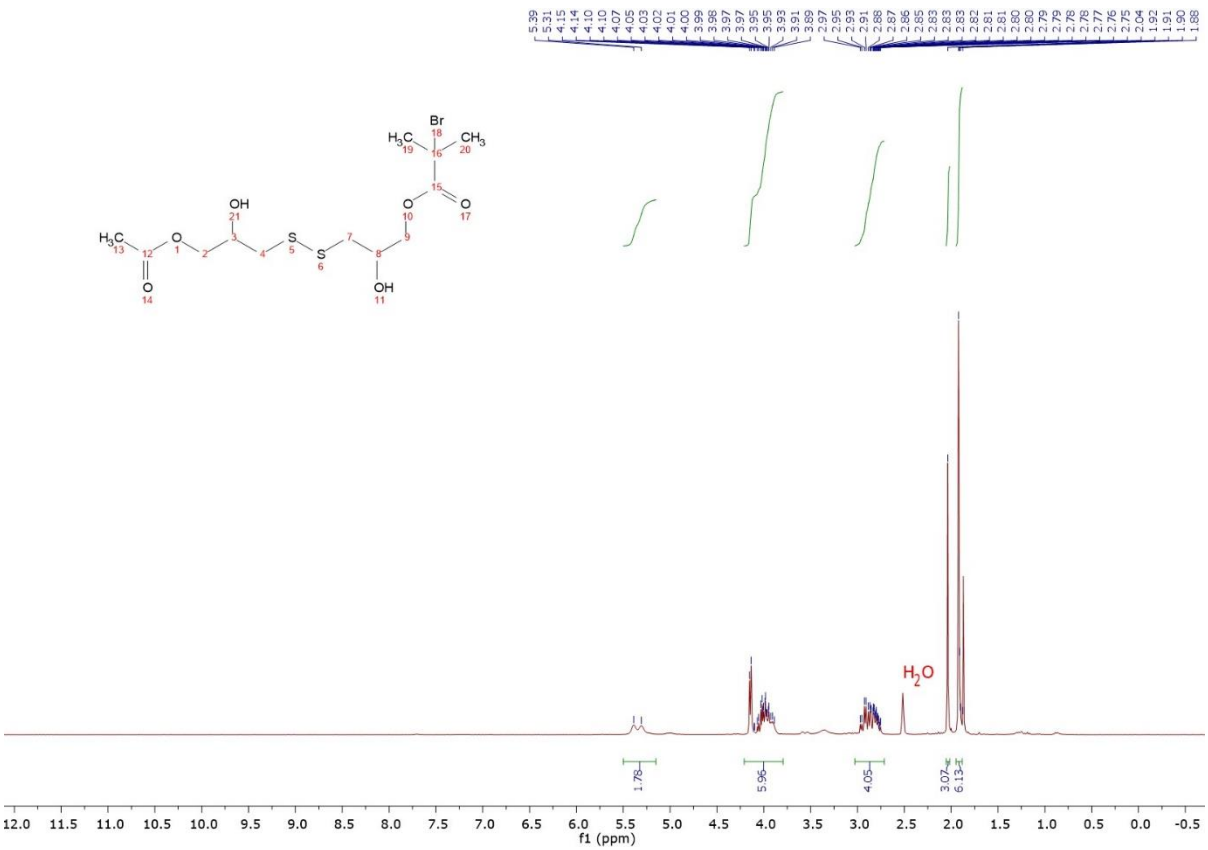


Figure S24. ^{1}H-NMR spectrum of **11**.

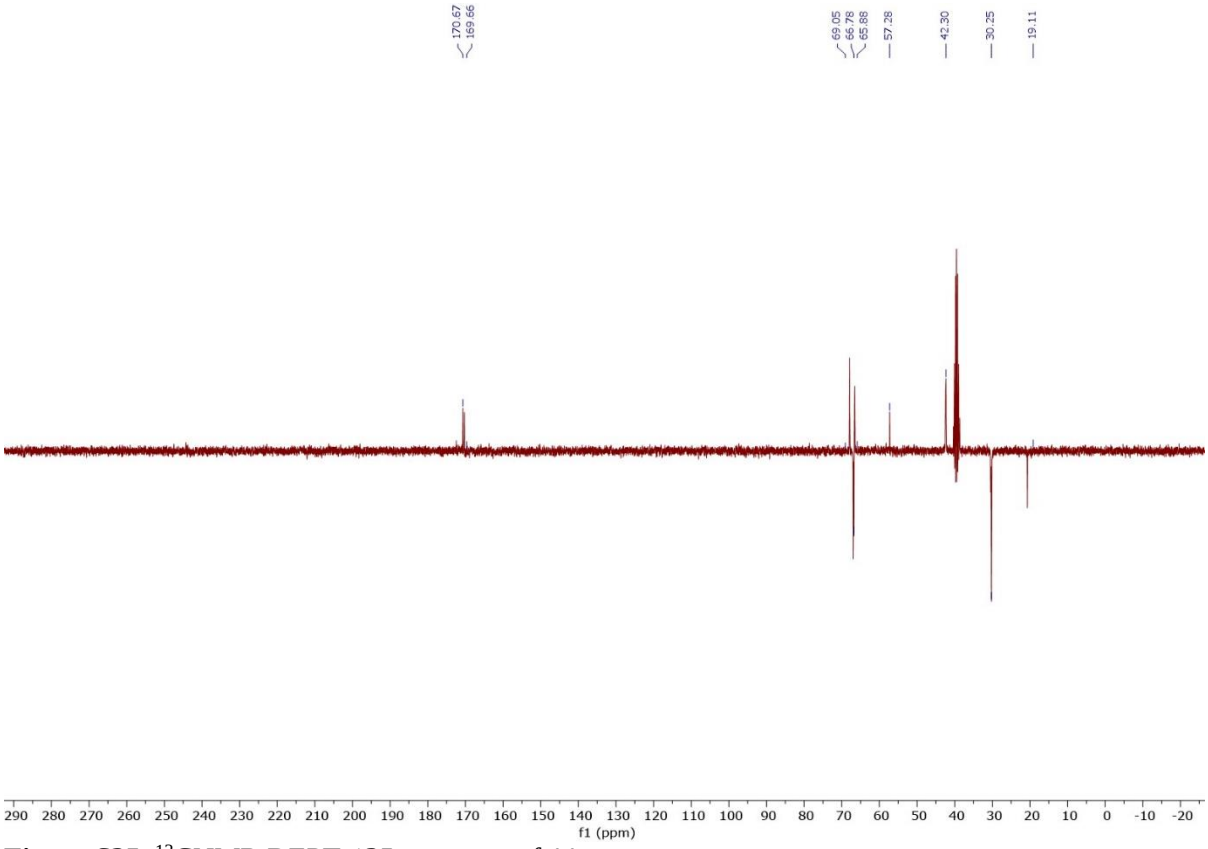
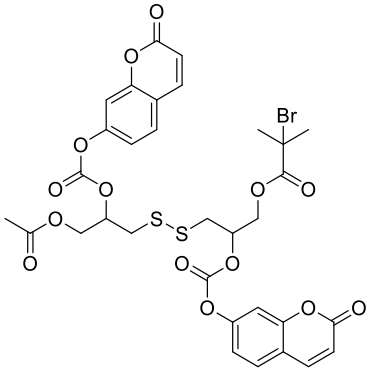


Figure S25. ^{13}CNMR DEPT-135 spectrum of **11**.

*Control initiator **3***



Umbelliferon (1 mmol, 162 mg, 2 eq.) and DMAP (0.05 mmol, 6 mg, 0.1 eq.) were dissolved in DMF (2 mL) and then added dropwise to a CH_2Cl_2 solution (15 mL) of triphosgene (2.5 mmol, 741 mg, 5 eq.) under Ar atmosphere. The reaction was stirred for 1 h at 0 °C and 1 h at room temperature. Afterwards, the excess phosgene was removed by argon purging and neutralized by bubbling the exhaust gas through ammonia solution. Then, a solution of CH_2Cl_2 (15 mL) with compound **11** (0.2 g, 0.5 mmol, 1 eq.) and DIPEA (2 mmol, 348 µL, 4 eq.) was added to the reaction mixture and stirred overnight at room temperature. After completion of the reaction, the mixture was washed 3× with 1 N aq. HCl and H_2O, dried over Na_2SO_4, then filtered, and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane:EtOAc = 1:1) to yield the product as yellow solid (128 mg, 0.165 mmol, 33%). **^{1}H-NMR** (300 MHz, Chloroform-*d*) δ [ppm] = 7.64 (d, *J* = 9.5 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.28 – 7.00 (m, 4H), 6.32 (d, *J* = 9.5Hz, 2H), 5.23 (d, *J* = 16.6 Hz, 2H), 4.70 – 3.78 (m, 4H), 3.04 (dddd, *J* = 18.7, 16.0, 9.8, 4.9 Hz, 4H), 2.09 (s, 3H), 1.87 (s, 6H). See Figure S27. **^{13}C-NMR** (75 MHz, $CDCl_3$) δ [ppm] = 171.72, 169.91, 160.12, 154.54, 153.09, 151.45, 143.50, 130.32, 117.62, 116.93, 114.90, 109.24, 75.41, 75.15, 64.35, 63.12, 55.31, 38.71, 31.66, 30.62, 18.96. See Figure S28. **MS(ESI$^+$):** *m/z* = 781.03 (calcd. 781.03 for $C_{32}H_{30}Br_1O_{14}S_2^+$). See Figure S26.

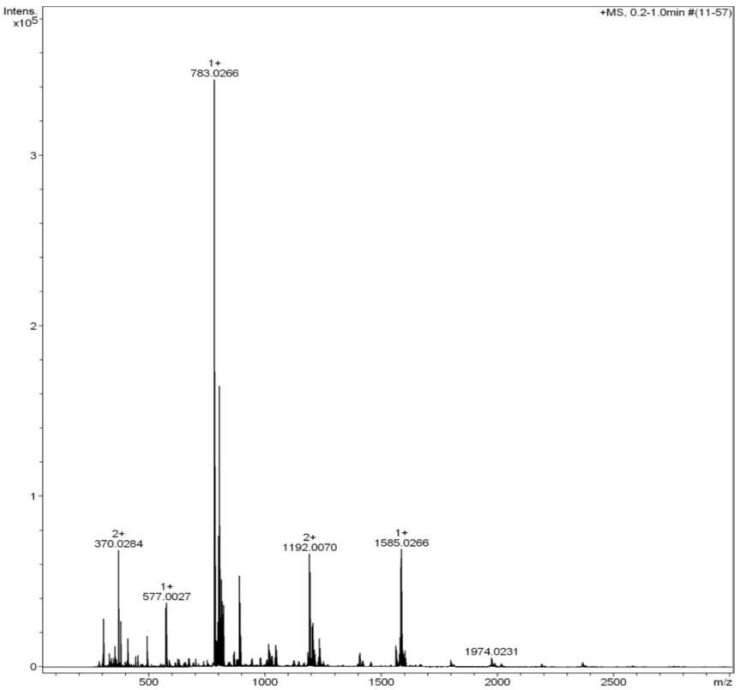


Figure S26. ESI$^+$ mass spectrum of **2**.

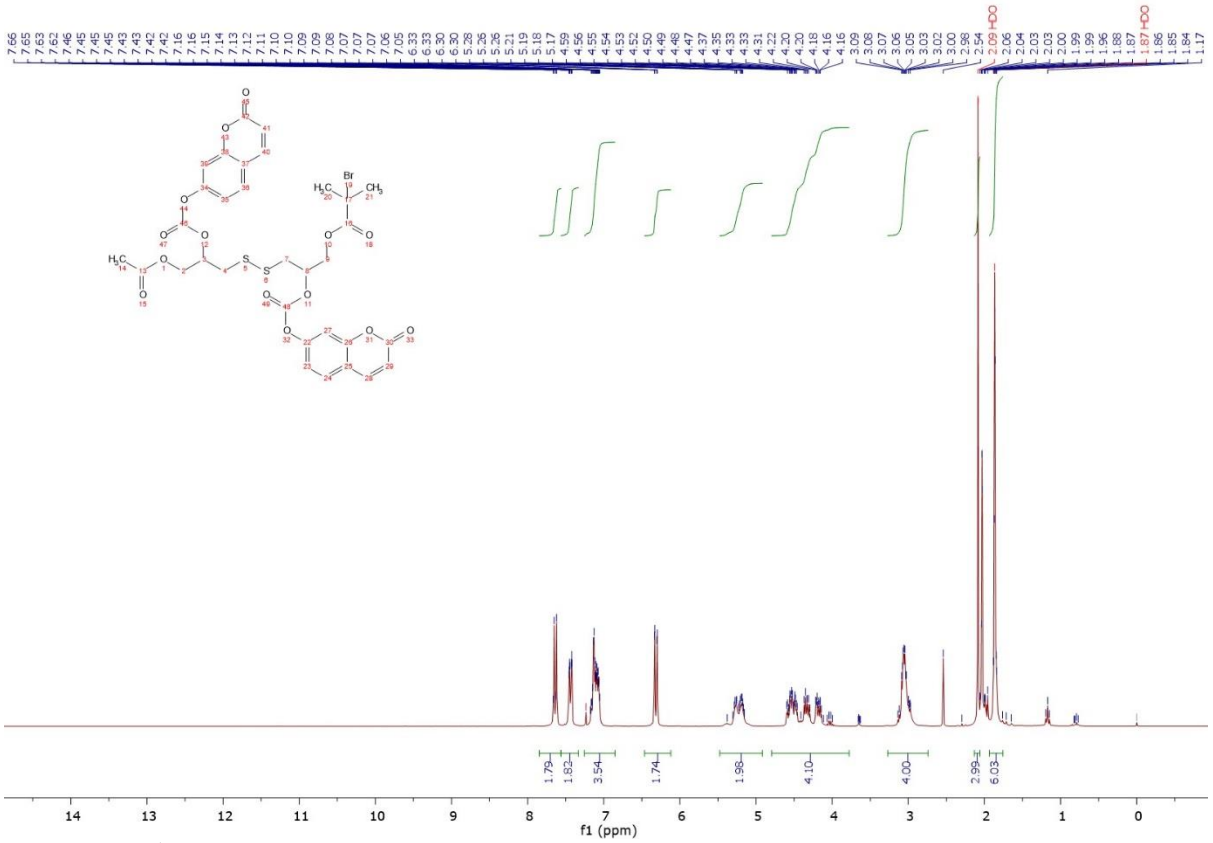


Figure S27. ^{1}H-NMR spectrum of control initiator **3**.

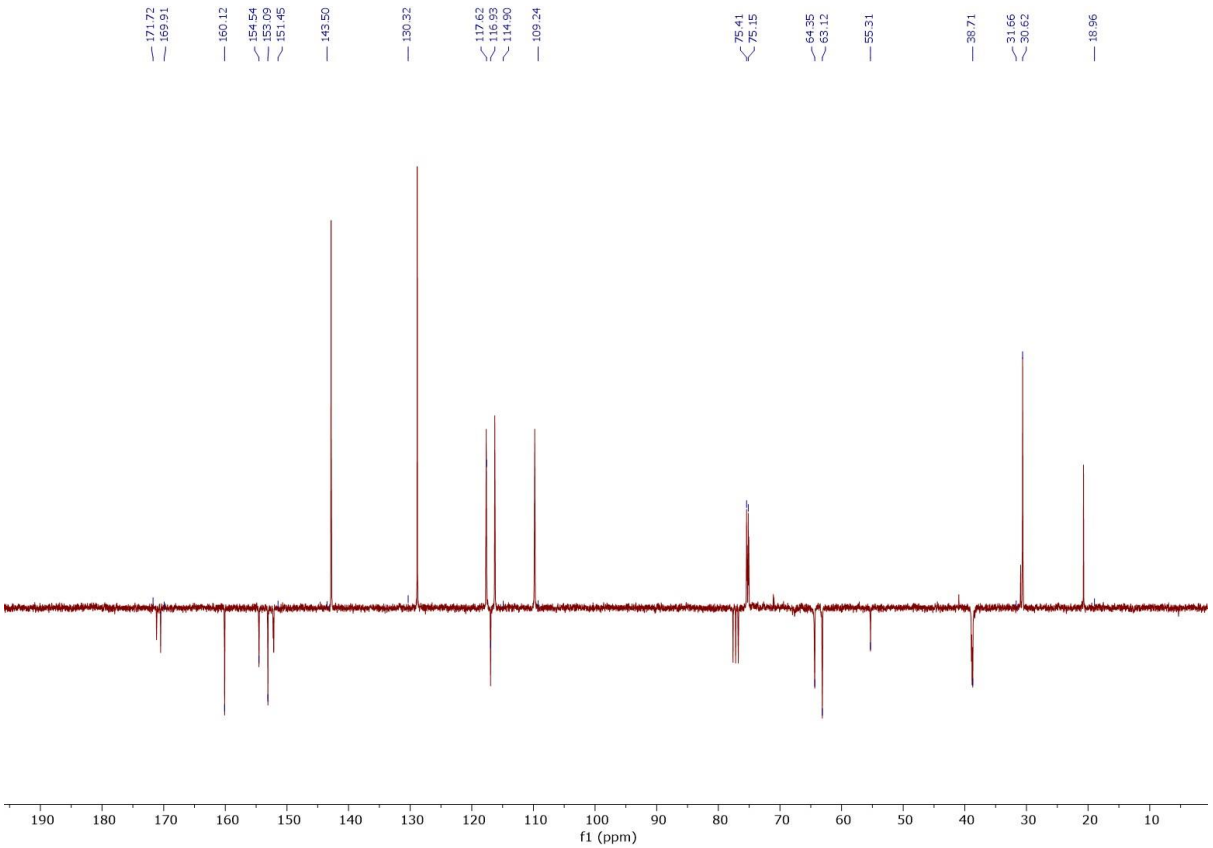


Figure S28. ^{13}C-NMR DEPT-135 spectrum of control initiator **3**.

Cu^0-catalyzed CRP for the synthesis of polymers ***P*****$_1$**, ***P*****$_2$**, *and* ***P*****$_3$**

Compound **1** (15.4 mg, 0.13 mmol), **2** (12.9 mg, 0.13 mmol), or **3** (10.1 mg, 0.13 mmol), Me_6TREN (0.48 mg, 8.00 µmol), OEGMEA (3.9 g, 13 mmol), and $CuBr_2$ (0.15 mg, 2.50 µmol) were dissolved in DMSO (3.2 mL) in a Schlenk flask and degassed by three consecutive freeze-pump-thaw cycles. During that time, copper wire (0.5 cm) was activated in conc. aq. HCl, subsequently washed with water and acetone, and dried. The wire was then added to the solution and the polymerization was allowed to run for 6 h at rt. Then, the viscous solution was diluted with THF, passed through a plug of basic Al_2O_3, and after concentration *in vacuo*, added dropwise to stirred, ice-cold Et_2O. Et_2O was decanted and the viscous polymer was redissolved in THF whereupon after concentration *in vacuo* it was again precipitated dropwise in fresh Et_2O. After repeating the precipitation process 3 times, the polymer was dried *in vacuo* and the polymer **P$_1$** was received as a colorless solid (0.98 g, 0.007 mmol, 54%), **P$_2$** as a colorless solid (1.46 g, 0.010 mmol, 77%), and **P$_3$** as a colorless solid (1.1 g, 0.010 mmol, 76%). GPC see Figure S29 and Figure S30.

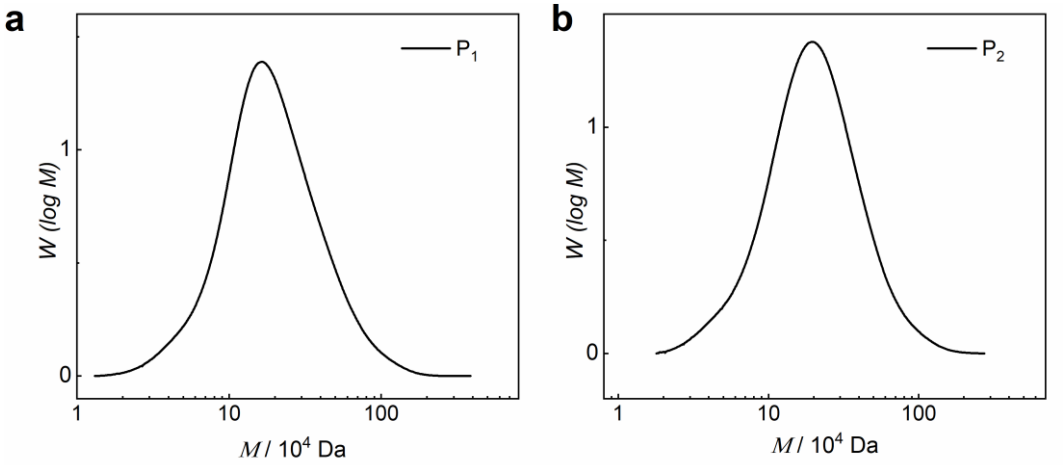


Figure S29. Differential molar mass distributions of GPC RI elugrams of **P$_1$** (M_n = 140.9 kDa, $Đ_M$ = 1.65) and **P$_2$** (M_n = 146.3 kDa, $Đ_M$ = 1.69).

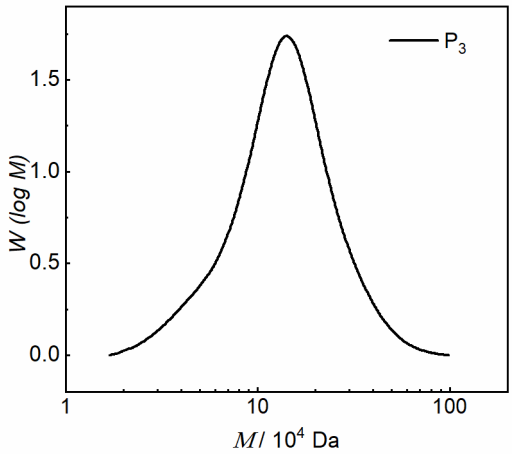


Figure S30. Differential molar mass distributions of GPC RI elugrams of **P$_3$** (M_n = 109.7 kDa, $Đ_M$ = 1.45).

Results and discussion

Fluorescence calibration curve for small molecule NAP

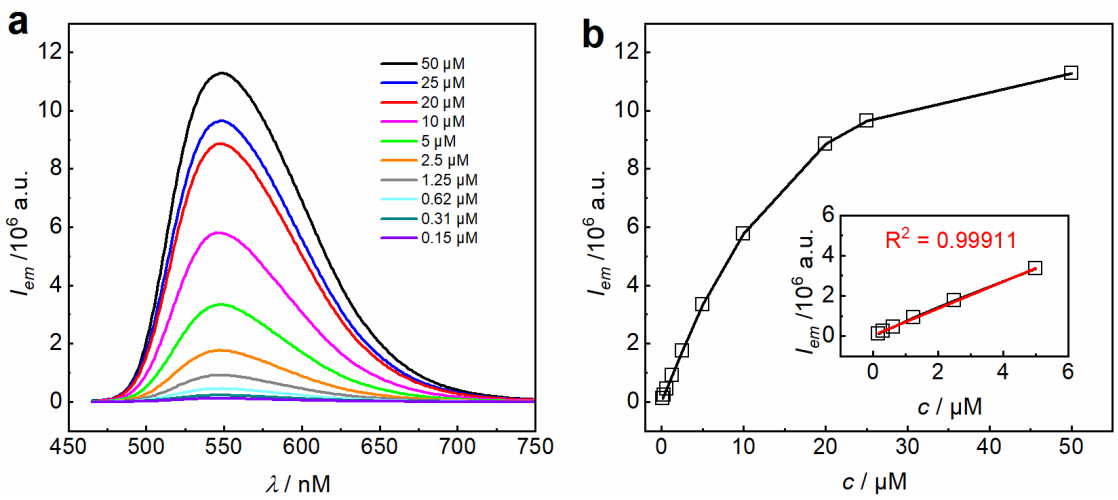


Figure S31. Calibration of NAP fluorescence in dependence of NAP concentration. Excitation was performed at λ_{exc} = 450 nm, with spectral bandwidths of 3 nm for excitation and emission, respectively. a) Fluorescence spectra of different concentrations of NAP in MeCN:H_2O = 2:3 (v/v) at rt. b) Fluorescence intensity at different concentrations of NAP at the 550 nm peak maximum in MeCN:H_2O = 2:3 (v/v) at room temperature. The inset shows the linear region of the calibration curve including linear regression used for calculating concentrations of released NAP in Figure 1 and 2 of the manuscript.

UPLC-MS monitoring of NAP and CPT release

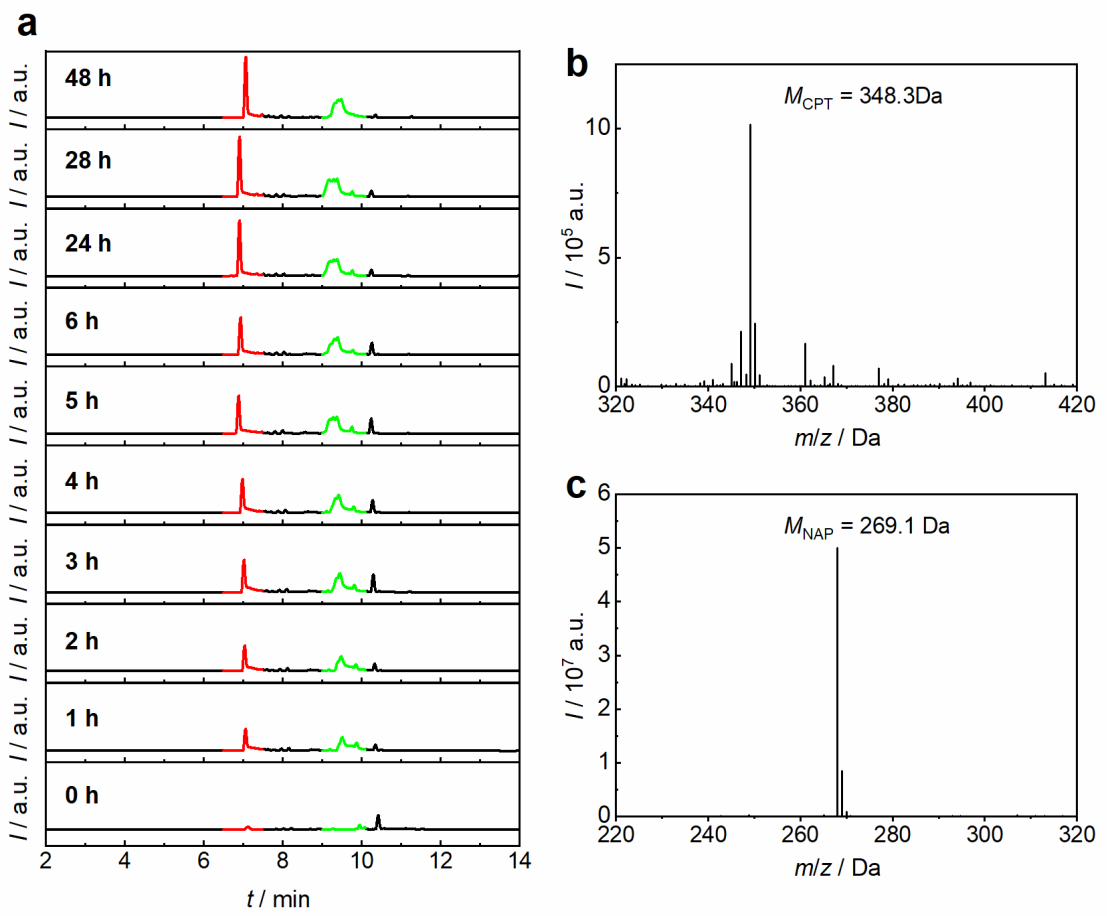


Figure S32. TCEP-induced release of NAP and CPT from **1**. a) UPLC photodiode array detector elugrams monitored at 335 nm of compound 1 (200 µM) treated with TCEP (20 eq.) over different reaction times. The peaks marked in red indicate the release of CPT, while the peaks marked in green correspond to the release of NAP. b) ESI^+ Mass spectrum at retention time t = 7.1 min. $M_{CPT,cal.}$ = 348.3 Da, $M_{CPT,meas}$ = 349.1 Da. c) ESI^- mass spectrum at retention time t = 9.3 min. $M_{NAP,calc}$ = 269.1 Da , $M_{NAP,meas}$ = 268.1 Da. Data corresponds to Figure 1c of the manuscript.

Reduction of P_1 by TCEP as monitored by UV-vis, fluorescence, and UPLC-MS

To investigate whether the disulfide bond in the center of the polymer chain is cleavable by reducing agents, P_1 was reacted with excess TCEP and the absorbance and fluorescence changes were recorded (Figure S33). In the UV-vis spectra (Figure S33b), the appearance of a strong band at λ_{max} = 450 nm indicated the successful release of NAP from **P_1**. Moreover, the emergence of fluorescence emission at λ_{max} = 550 nm (Figure S33c and Figure S33d) is consistent with the emission spectrum of NAP. Further evidence of CPT release occurring alongside the observed fluorescence changes upon disulfide bond scission was obtained from the UPLC-MS data (Figure S33e and f). The peak at retention time 5.8 min corresponds to CPT (348.3 Da). These results led us to conclude that both compounds, NAP and CPT, were released from **P_1** after the disulfide bond cleavage upon TCEP reduction.

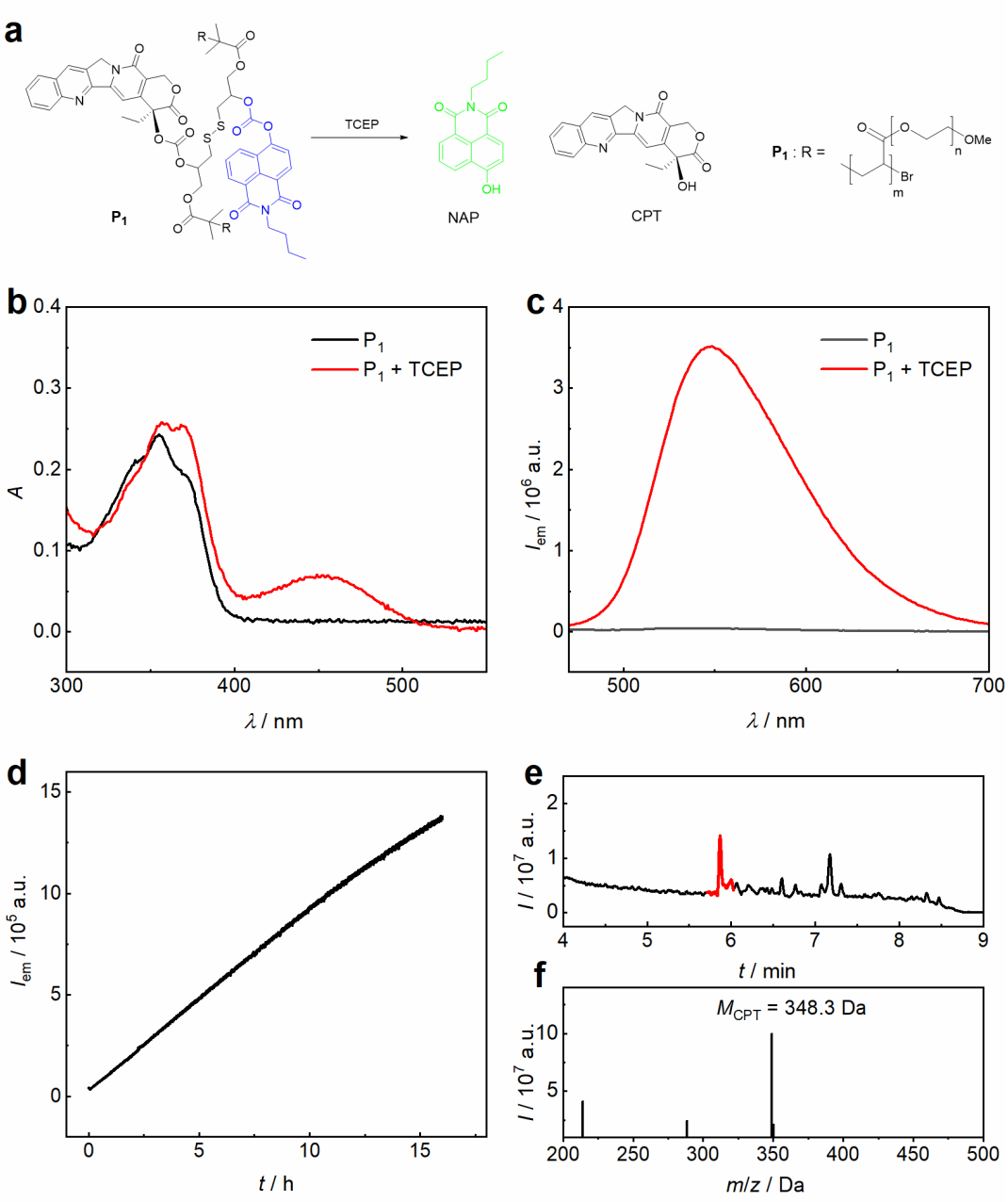


Figure S33. TCEP induced release of NAP and CPT from **P₁**. a) Reaction Scheme. b) UV-vis spectra of **P₁** (3.3 mg·mL^{-1}) and **P₁** reacted with TCEP (150 µM) overnight at rt. c) Fluorescence spectra of **P₁** (2.5 mg·mL^{-1}) before and after TCEP overnight treatment. Fluorescence spectra were recorded at λ_{exc} = 450 nm with spectral bandwidths of 3 nm for excitation and emission. d) Fluorescence evolution of **P₁** (3 mg·mL^{-1}) after addition of TCEP (100 µM). Excitation was performed at λ_{exc} = 450 nm, and emission was recorded at λ_{em} = 550 nm with spectral bandwidths of 3 nm for excitation and emission, respectively. All spectra were recorded in MeCN:H_2O = 2:3 (v/v) at rt. e) UPLC total ion current elugram. f) ESI$^+$ mass spectrum at retention time t = 5.8 min. $M_{CPT,calc}$ = 348.3 Da, $M_{CPT,meas}$ = 349.2 Da.

Ultrasonication of small molecule control 1 monitored by UV-vis and fluorescence spectroscopy

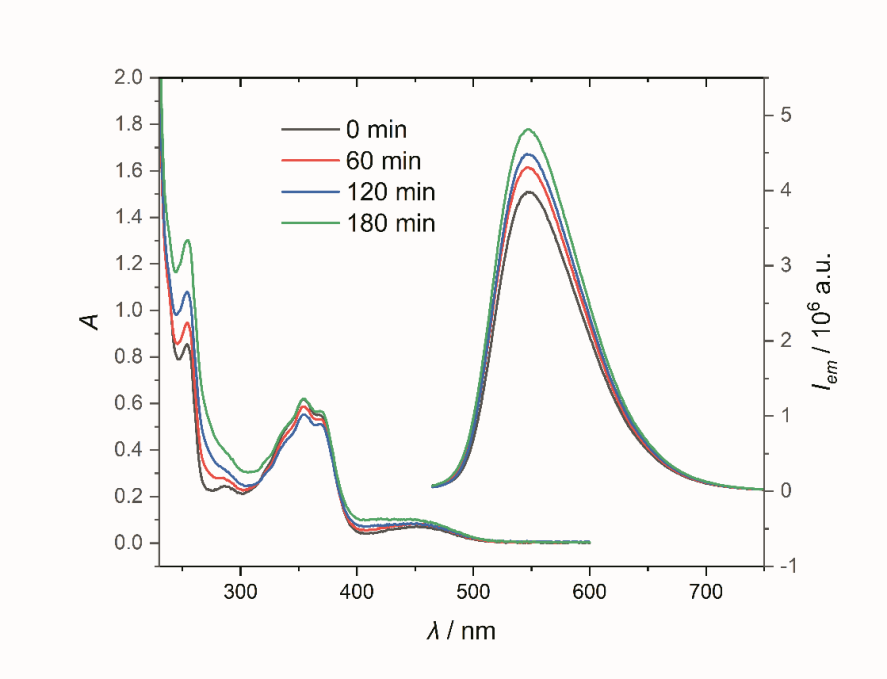


Figure S34. Absorption and fluorescence (λ_{exc} = 450 nm) spectra of sonicated **1** corresponding to Figure 2a and b, yellow lines. 25 µM **1** were used for the control sonication experiment. The samples were collected before sonication and every 1 h for 3 h and filtrated with a 0.45 µm syringe filter. All spectra were recorded in MeCN:H_2O = 2:3 (v/v) at rt.

UPLC-MS of ultrasonicated P_1 before CLSM using stained HeLa cells

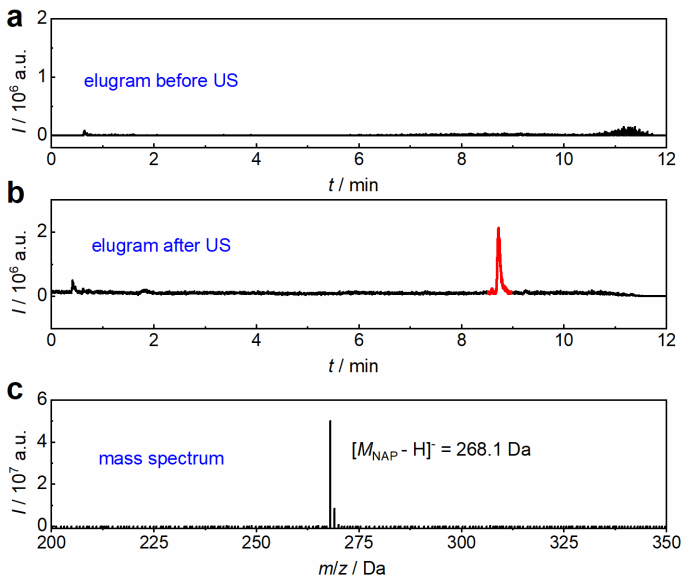


Figure S35. UPLC total ion current elugrams and mass spectra of $\mathbf{P_1}$ (3 mg·mL^{-1} in MeCN:H_2O = 2:3 (v/v) a) before and b) after sonication. c) ESI$^-$ mass spectrum of $\mathbf{P_1}$ after sonication at retention time t = 8.9 min. $M_{NAP,calc}$ = 269.1 Da , $M_{NAP,meas}$ = 268.1 Da.

MTS proliferation assays for CLSM and FACS analysis

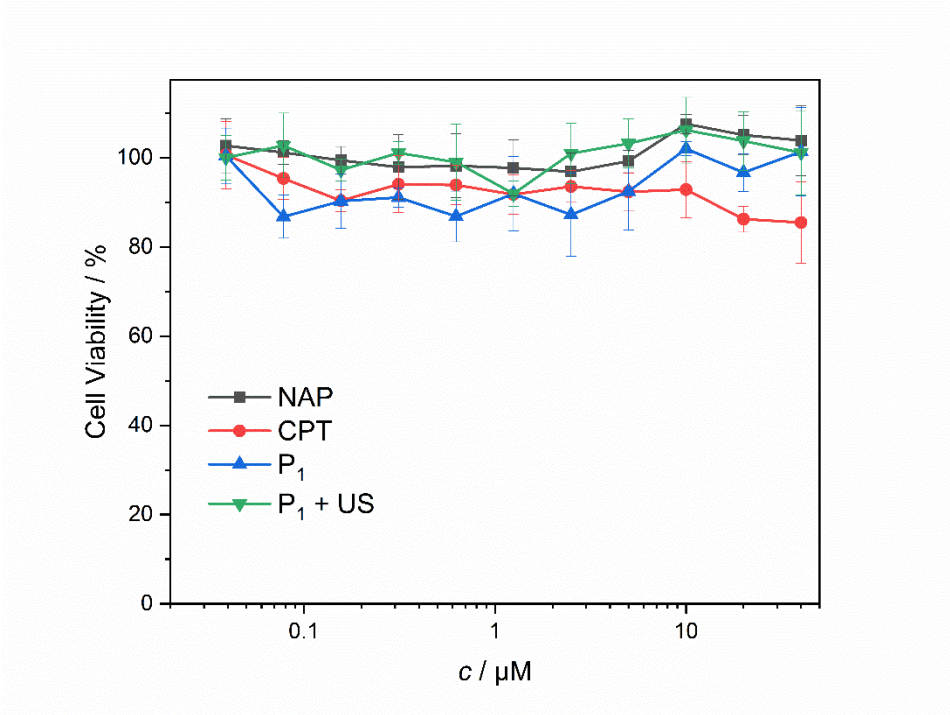


Figure S36. MTS proliferation assays of HeLa cells under the same conditions as the cells stained for CLSM and FACS analysis. HeLa cells were incubated for only 30 min to warrant their viability as opposed to 48 h incubation time used for MTS assays assessing CPT toxicity.

Enlarged CLSM section of Figure 3a of HeLa cells stained for 30 min with sonicated P_1

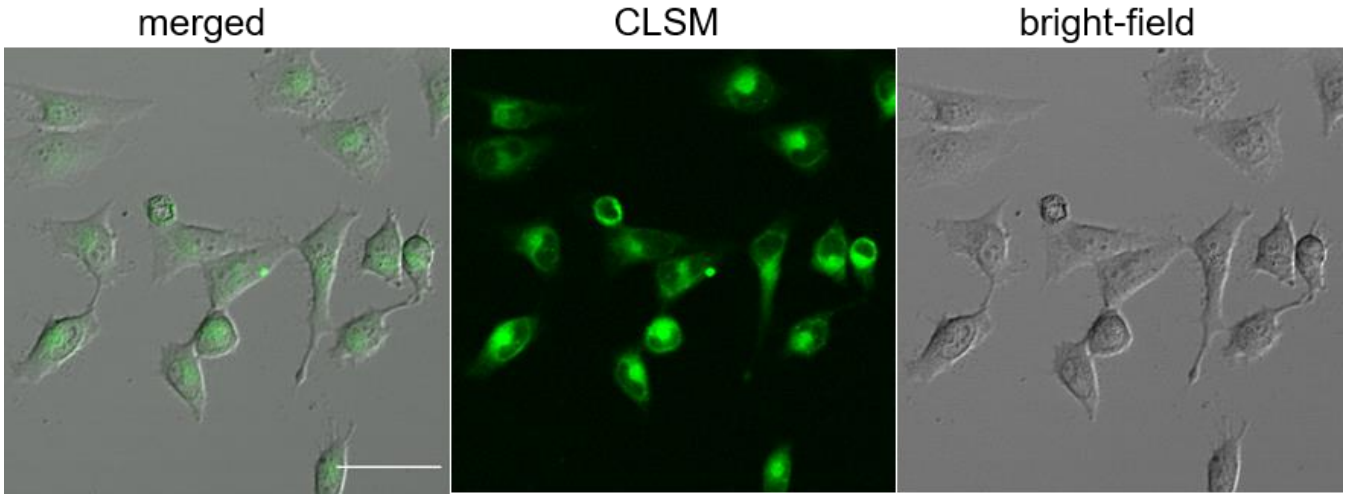


Figure S37. Enlarged CLSM micrographs merged with bright-field micrographs of HeLa cells stained with sonicated **P_1** for 30 min corresponding to Figure 3a of the manuscript (scale bar = 50 µm).

UPLC-MS of ultrasonicated P_1 before MTS proliferation assays using HeLa cells

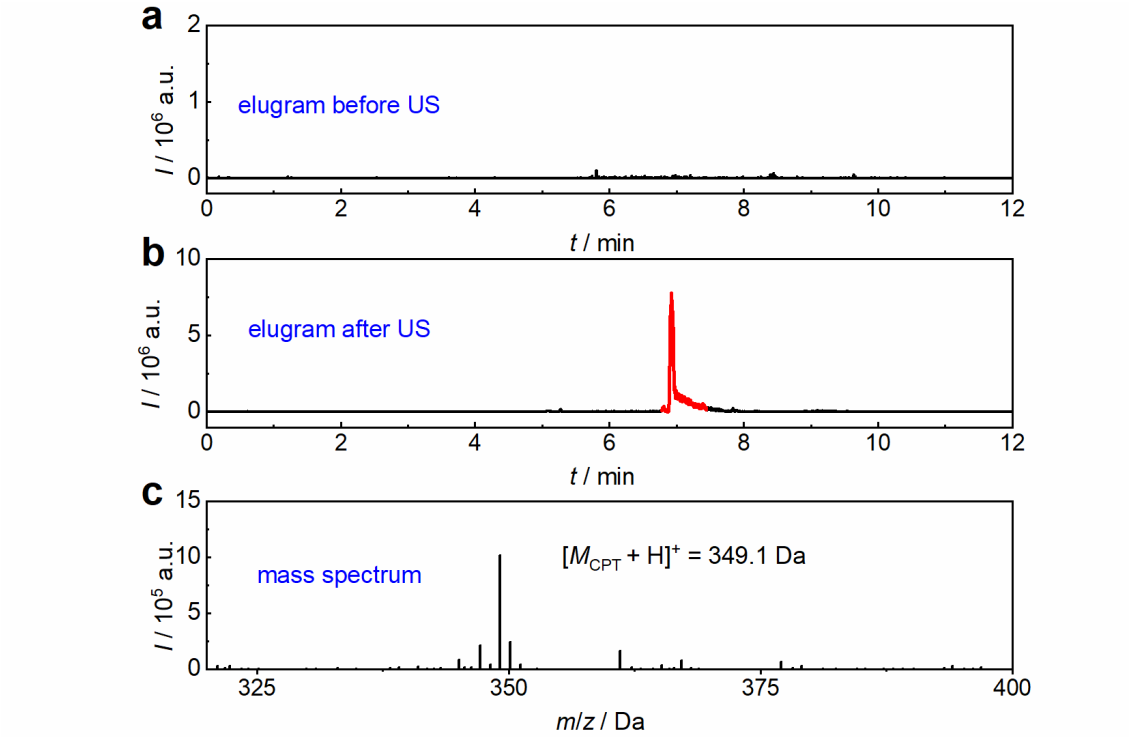


Figure S38. US-induced release of CPT from $\mathbf{P_1}$ (3 mg·mL^{-1} in MeCN:H_2O = 2:3 (v/v)). a) UPLC total ion current elugram of $\mathbf{P_1}$ before sonication. b) UPLC total ion current elugram of $\mathbf{P_1}$ after sonication. c) ESI$^+$ of $\mathbf{P_1}$ after sonication at retention time t = 7.1 min. $M_{CPT,calc}$ = 348.4 Da, $M_{CPT,meas}$ = 349.1 Da.

Reduction of 2 by GSH as monitored by UV-vis, fluorescence, and UPLC-MS

To demonstrate whether the disulfide bond between UMB and GEM is cleavable with reducing agents, **2** was reacted with excess GSH overnight at room temperature, and the alterations in its absorption and fluorescence spectra were monitored (Figure S39). Although the solution of **2** exhibits weak fluorescence centered at 450 nm on excitation at 325 nm (Figure S39c), upon addition of GSH the enhancement of the fluorescence intensity of the reaction mixture was considerable implying the continuous release of active UMB as monitored at λ_{max} = 450 nm (Figure S39d). In the UV-vis absorption spectrum, **2** exhibited a strong absorption band at λ_{max} = 370 nm increasing by ca. 2 fold upon the addition of GSH (Figure S39e). These results indicate that the disulfide bond of **2** can be readily cleaved by GSH.

UPLC-MS was used to confirm the anticipated GEM release along with UMB liberation following exposure to TCEP. Therefore, **2** (200 µM) was treated with 4 mM TCEP at room temperature for 24 h, and the aliquot was subjected to UPLC-MS. ESI$^+$ mass spectra revealed the presence of fragments consistent with GEM ([M+H]$^+$ = 264.1 Da) and UMB ([M+H]$^+$ = 163.0 Da) (Figure S40).

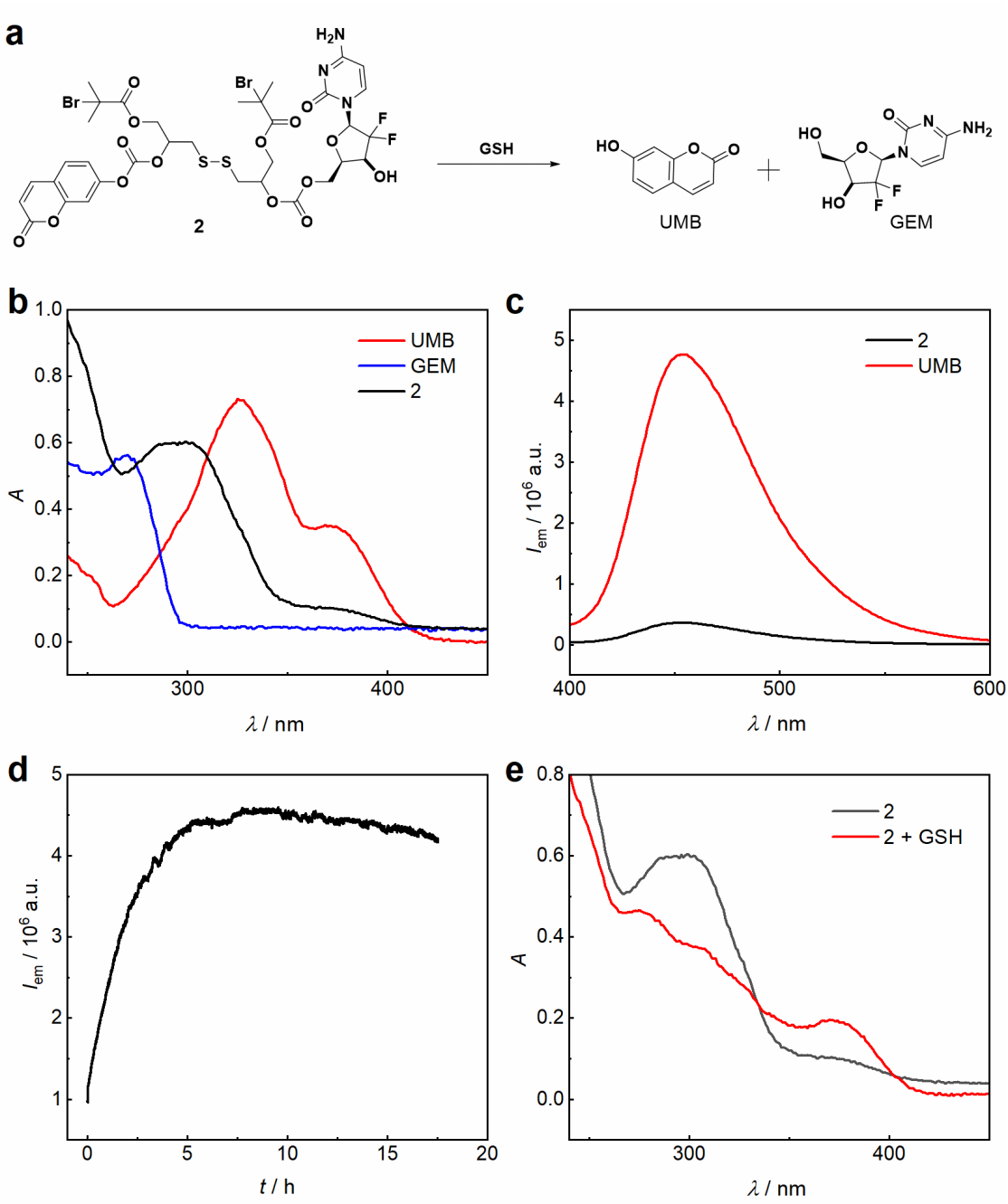


Figure S39. GSH-induced release of UMB and GEM from small molecule control **2**. a) Reaction scheme. b) UV-vis absorption spectra of **2** (50 µM), GEM (50 µM), and UMB (50 µM). c) Fluorescence spectra of **2** (0.78 µM) and UMB (0.78 µM). Fluorescence spectra were recorded at λ_{exc} = 325 nm with spectral bandwidths of 3 nm for excitation and emission. d) Fluorescence changes of **2** (5 µM) against GSH (20 eq.) in MeCN:H_2O = 2:3 (v/v) at rt. Excitation was performed at λ_{exc} = 325 nm, and emission was recorded at λ_{em} = 450 nm with spectral bandwidths of 3 nm for excitation and emission, respectively. e) Absorption spectra of **2** (50 µM) in the presence and absence of GSH (20 eq.) after overnight reaction at rt. All spectra were recorded in MeCN:H_2O = 2:3 (v/v) at rt.

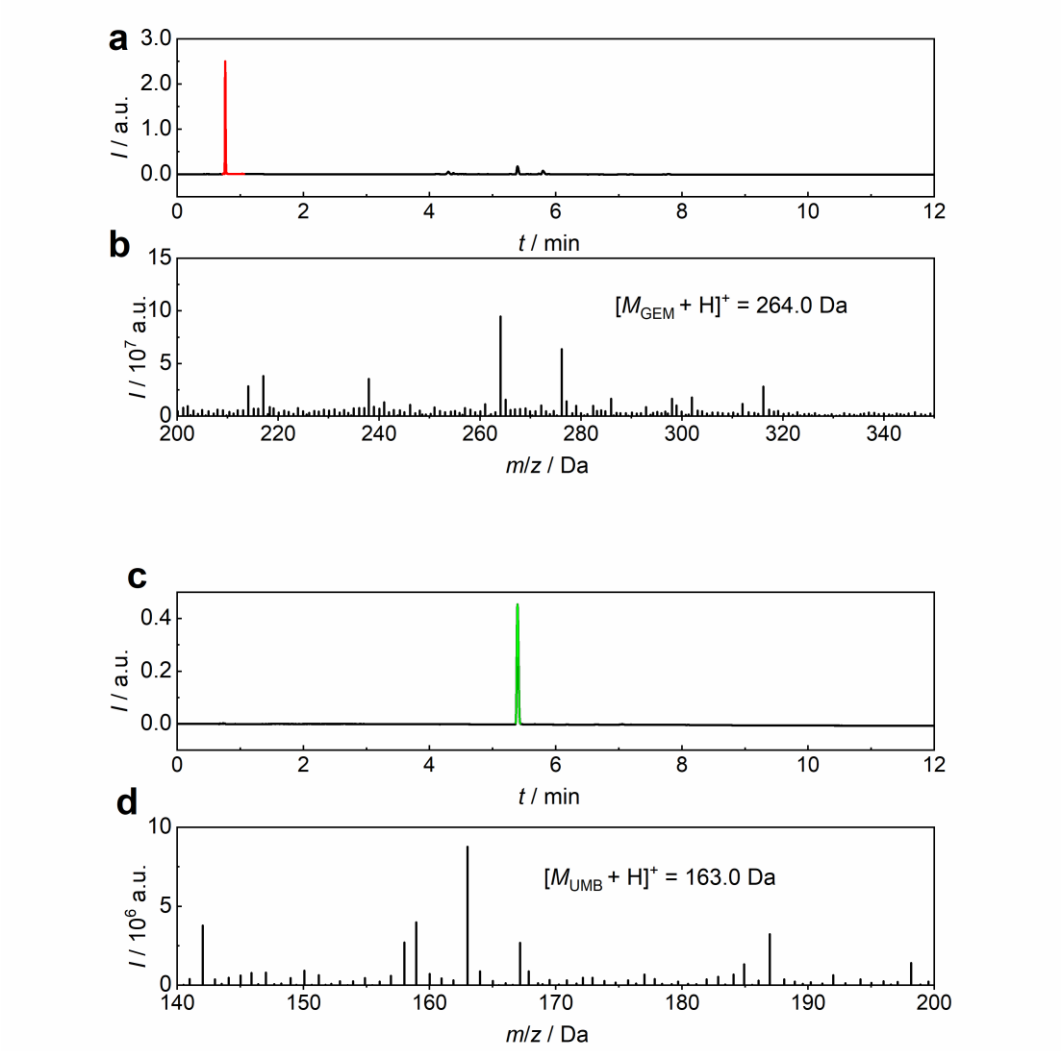


Figure S40. TCEP-induced release of GEM and UMB from **2** observed by UPLC-MS. a) Photodiode array detector elugram of **2** treated with TCEP at the absorption wavelength of 280 nm. b) The corresponding ESI^+ mass spectrum of GEM at the retention time t = 0.7 min (black line). $M_{GEM,calc}$ = 263.1 Da, $M_{GEM,meas}$ = 264.0 Da. c) Photodiode array detector elugram of **2** treated with TCEP at the absorption wavelength of 335 nm, respectively. d) The corresponding ESI^+ mass spectrum of UMB at the retention time t = 5.3 min. $M_{UMB,calc}$ = 162.1 Da, $M_{UMB,meas}$ = 163.0 Da.

Reduction of P_2 by GSH as monitored by UV-vis, fluorescence, and UPLC-MS

After successfully releasing both the GEM and UMB from **2** by GSH, we released the small molecules from their corresponding polymer $\mathbf{P_2}$. First, $\mathbf{P_2}$ was reacted with excess TCEP, and the absorption and emission changes were recorded (Figure S41). For the UV-vis measurements, $\mathbf{P_2}$ was allowed to react with excess TCEP overnight at room temperature. The clearly observed band centered at λ_{max} = 370 nm indicated the release of UMB (Figure S41b). Moreover, $\mathbf{P_2}$ was allowed to react with excess TCEP, and the kinetics of the fluorescence alteration over time at room temperature was recorded. The considerable fluorescence enhancement at λ_{em} = 450 nm shows a continuous increase (Figure S41d). Although the solution of $\mathbf{P_2}$ exhibited weak fluorescence centered at 450 nm by excitation at λ_{exc} = 325 nm, upon addition of TCEP (150 µM) a 17-fold increase was observed (Figure S41c) indicating the release of UMB. Similar to the release from **2**, we could observe both the UV-vis alterations and the fluorescence intensity increase.

Additionally, UPLC-MS was used to confirm the anticipated GEM release following the TCEP-induced disulfide cleavage. **P₂** (3 mg·mL^{-1}) was treated with 150 µM TCEP overnight at room temperature and an aliquot was subjected to mass analysis. It was found that a major peak appeared at a retention time of t = 0.7 min (Figure S41e) corresponding to the molar mass of GEM $[M+H]^+$ = 264.1 (Figure S41f).

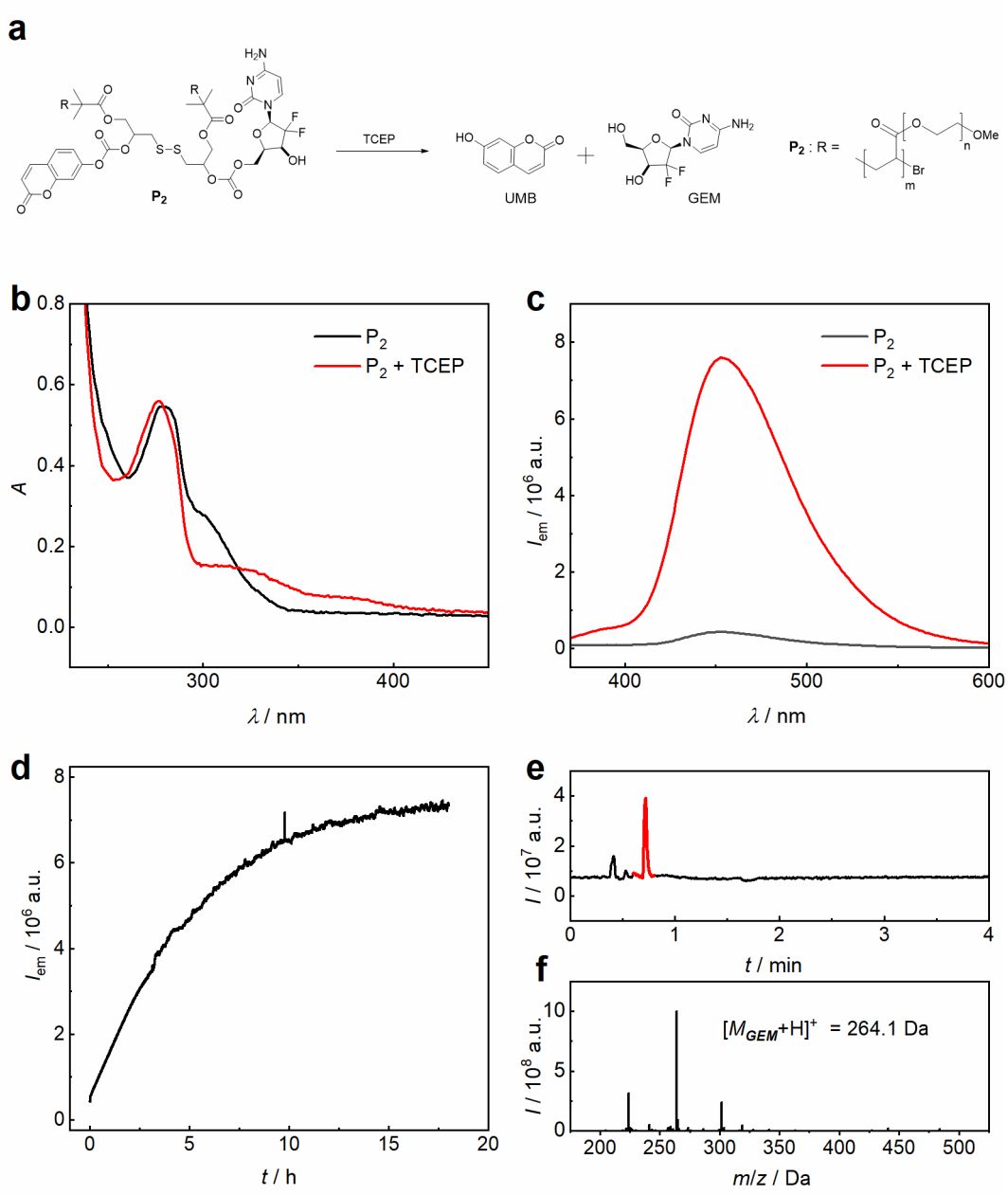


Figure S41. TCEP-induced release of UMB and GEM from **P₂**. a) Reaction scheme. b) UV-vis absorption spectra of **P₂** (2.5 mg·mL^{-1}) in the presence and absence of TCEP (150 µM) after overnight reaction at rt. c) Fluorescence spectra of **P₂** (2.5 mg·mL^{-1}) before and after overnight TCEP (150 µM) treatment. Fluorescence spectra were recorded at λ_{exc} = 325 nm with spectral bandwidths of 3 nm for excitation and emission. d) Fluorescence change of **P₂** (2.5 mg·mL^{-1}) in the presence of TCEP (150 µM) in MeCN:H_2O = 2:3 (v/v) at rt over reaction time monitored at the UMB emission maximum. Excitation was performed at λ_{exc} = 325 nm, and emission was recorded at λ_{em} = 450 nm with spectral bandwidths of 3 nm for excitation and emission, respectively. All spectra were recorded in MeCN:H_2O = 2:3 (v/v) at rt. e) UPLC total ion current elugram. f) ESI^+ mass spectrum at the retention time t = 0.7 min. $M_{GEM,calc}$ = 263.1 Da, $M_{GEM,meas}$ = 264.1 Da.

Fluorescence calibration curve for small molecule UMB

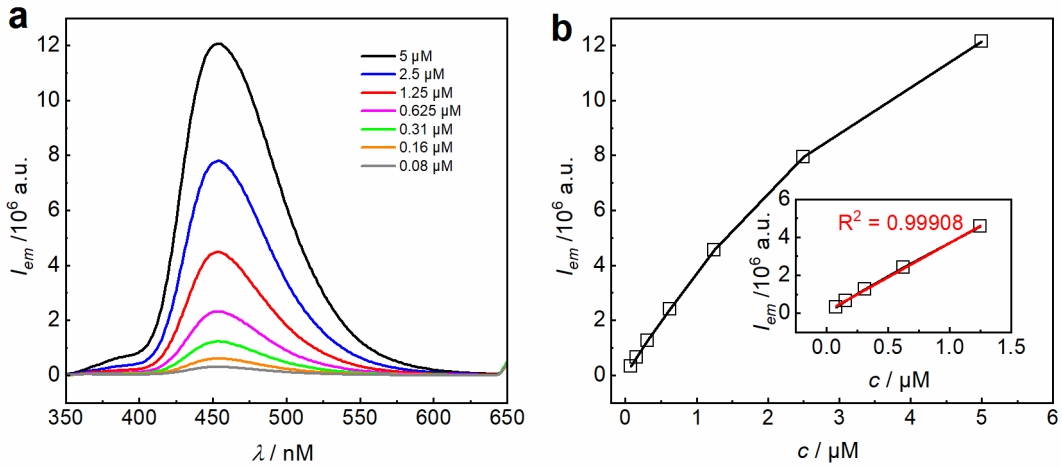


Figure S42. Calibration of UMB fluorescence in dependence of UMB concentration. Excitation was performed at λ_{exc} = 325 nm, with spectral bandwidths of 3 nm for excitation and emission, respectively. a) Fluorescence spectra of different concentrations of UMB in MeCN:H_2O = 2:3 (v/v) at rt. b) Fluorescence intensity of UMB at the 450 nm peak maximum in MeCN:H_2O = 2:3 (v/v) at rt. The inset shows the linear region of the calibration curve including linear regression used for calculating concentrations of released UMB in subsequent experiments.

Ultrasonication of small molecule control 2 and terminal control polymer P_3 monitored by UV-vis and fluorescence spectroscopy as well as UPLC-MS

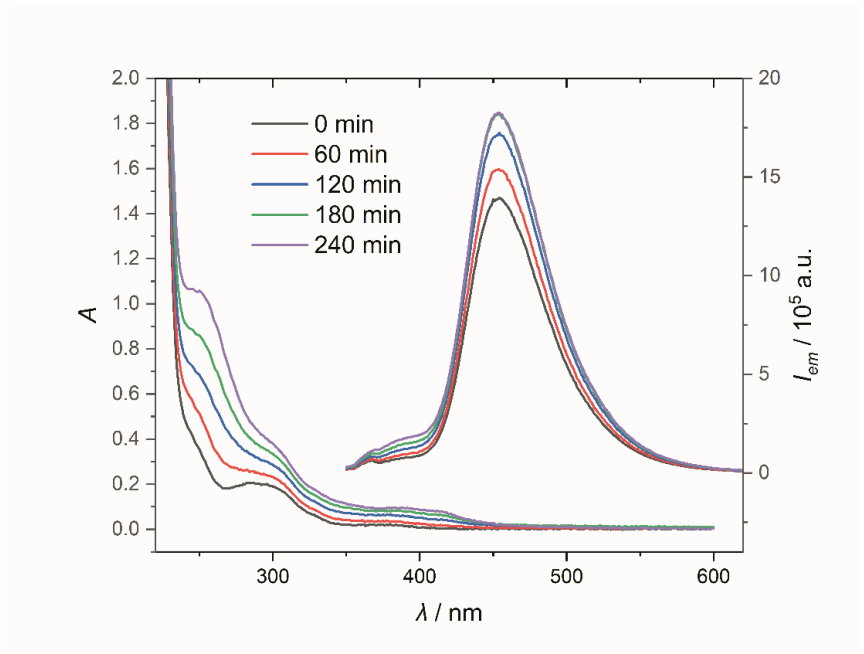


Figure S43. Absorption and fluorescence (λ_{exc} = 325 nm) spectra of **2** over the course of sonication corresponding to Figure 5b of the manuscript. 25 µM **2** were used for the reference sonication experiment. The samples were collected before sonication and every 1 h for 4 h and filtrated with a 0.45 µm syringe filter. For the absorption measurements the solution was directly used, while the solutions were diluted by a factor of 5 for the fluorescence measurements. All spectra were recorded in MeCN:H_2O = 2:3 (v/v) at rt.

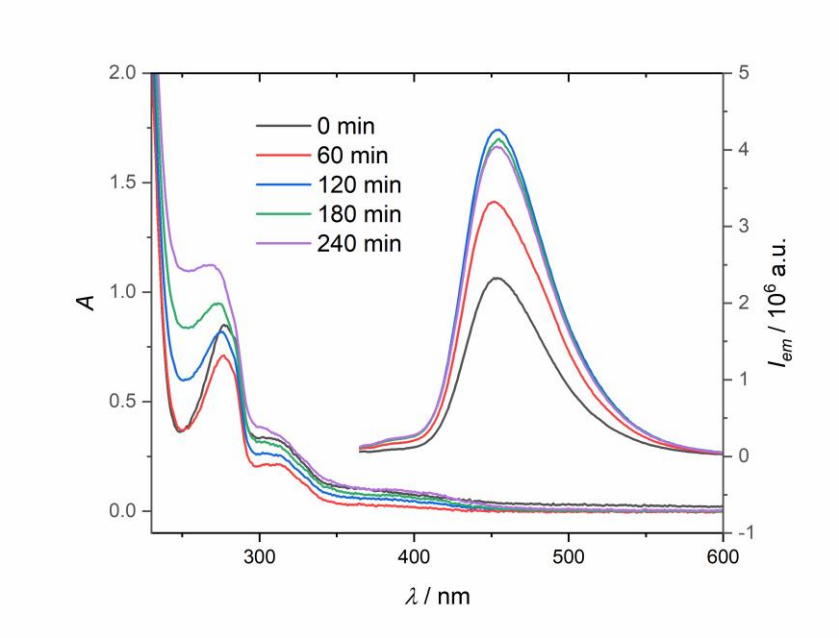


Figure S44. Absorption and fluorescence (λ_{exc} = 325 nm) spectra of $\mathbf{P_3}$ over the course of sonication (3 mg·mL^{-1} in MeCN:H_2O = 2:3 (v/v)) corresponding to Figure 5b of the manuscript. For absorption, samples from the solution were directly used, while diluted by a factor of 10 for fluorescence measurements. All spectra were recorded in MeCN:H_2O = 2:3 (v/v) at rt.

UPLC-MS of ultrasonicated P_2

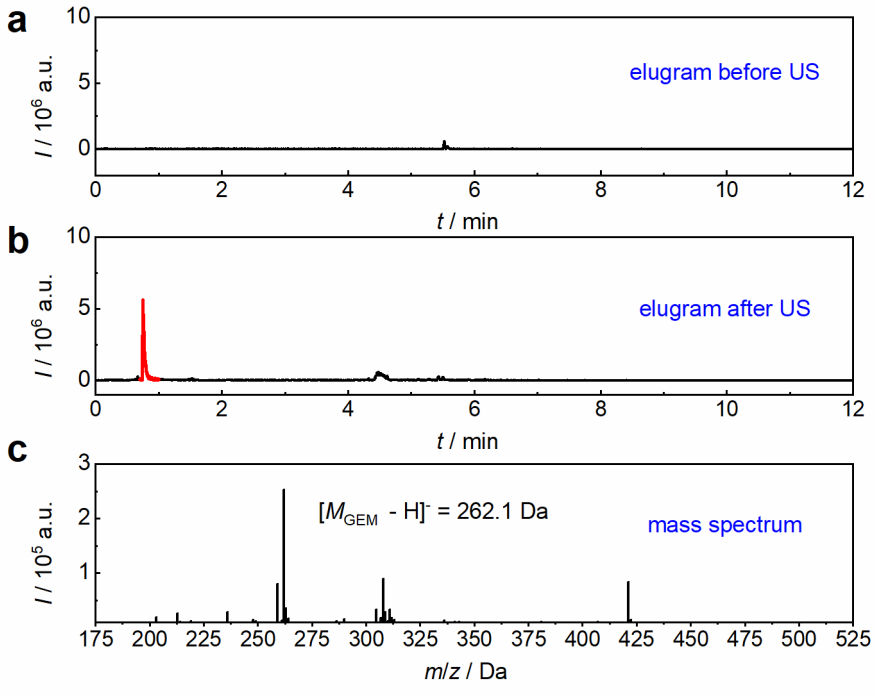


Figure S45. US-induced release of GEM from $\mathbf{P_2}$ (3 mg·mL^{-1} in MeCN:H_2O = 2:3 (v/v) after 4 h sonication observed by UPLC elugrams and mass spectra. a) Diode-array detector elugram of $\mathbf{P_2}$ before US treatment. b) Diode-array detector elugram of $\mathbf{P_2}$ after US treatment. c) ESI$^-$ mass spectrum at the retention time t = 0.7 min. $M_{GEM,calc}$ = 263.1 Da, $M_{GEM,meas}$ = 262.1 Da.

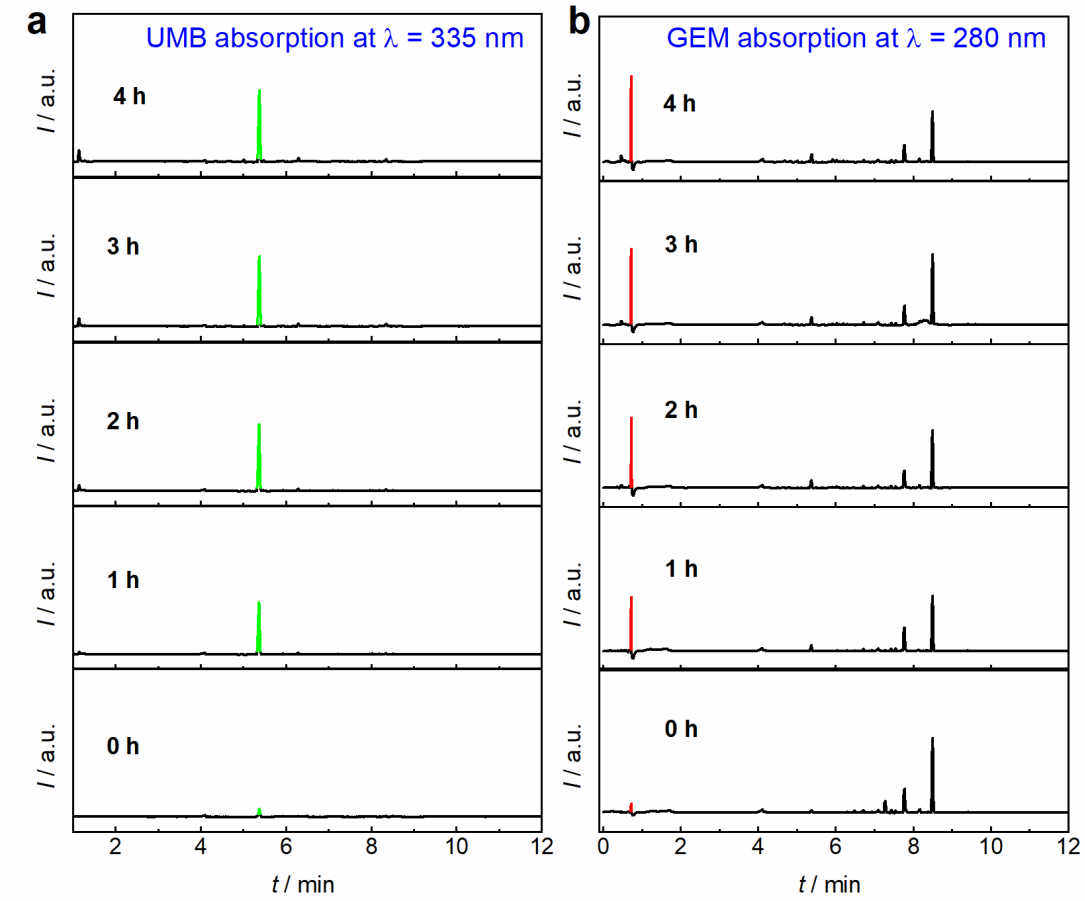


Figure S46. UPLC photodiode array detector elugrams of sonicated $\mathbf{P_2}$ (3 mg·mL^{-1} in MeCN:H_2O = 2:3 (v/v) with progressing sonication time. a) Photodiode array detector elugrams of UMB (marked in green) at absorption wavelength at λ = 335 nm. b) Photodiode array detector elugrams of GEM (marked in red) at absorption wavelength at λ = 280 nm.

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