Electronic Supplementary Information (ESI)

Sequence-activated AND logic dual-channel fluorescent probe for tracking programmable drug release

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Contents

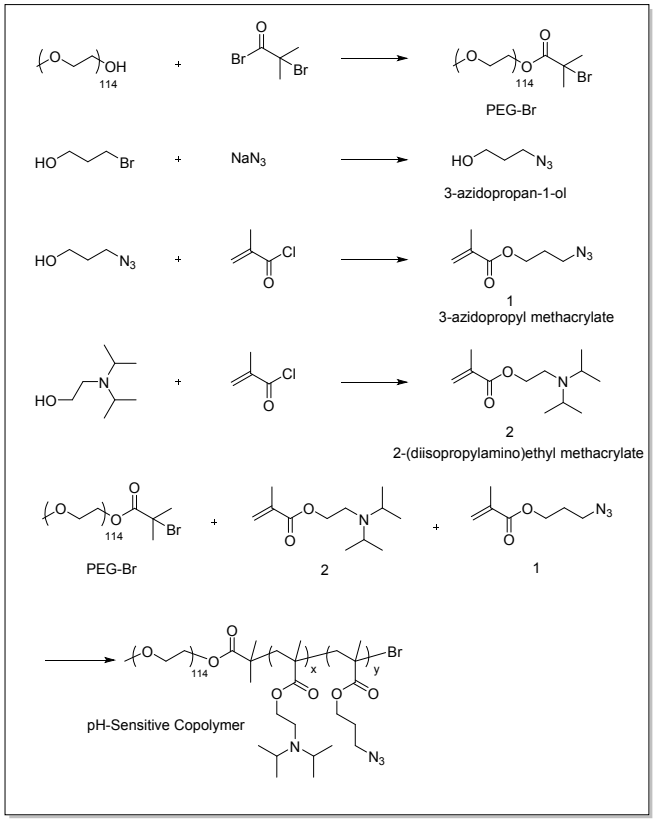
1. Experimental Section

Materials and General Methods

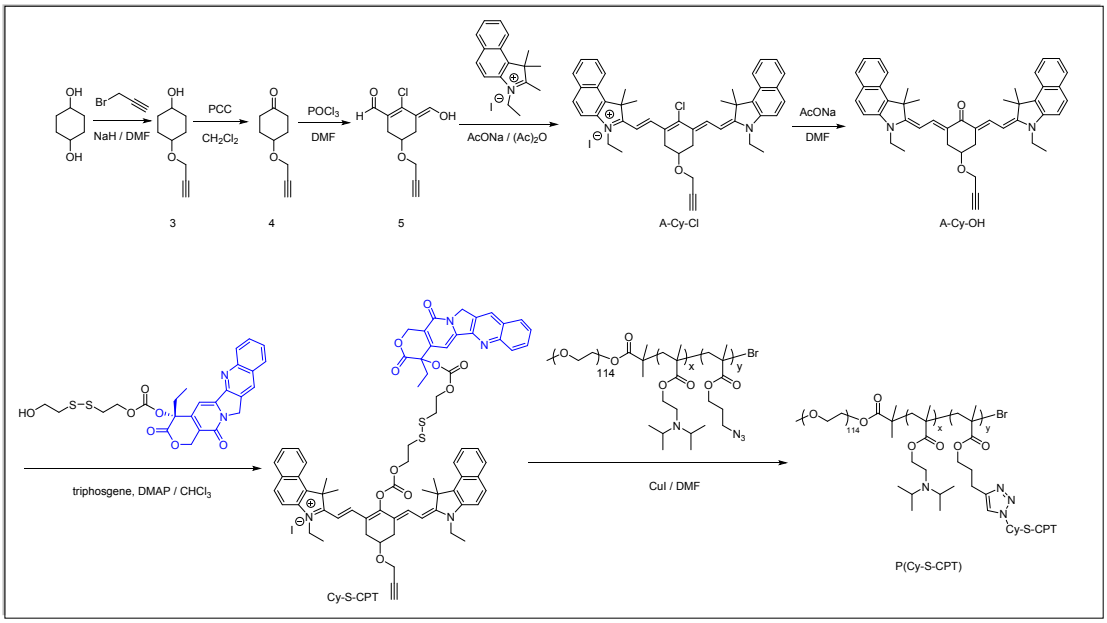
Unless special stated, all solvents and chemicals were purchased from commercial suppliers in analytical grade and used without further purification. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 400 spectrometer, using TMS as an internal standard. High resolution mass spectrometry data were obtained with a Waters LCT Premier XE spectrometer. GPC analysis was performed on a Waters 1515-2414. Absorption spectra were collected on a Varian Cary 500 spectrophotometer, and fluorescence spectra measurements were performed on a Varian Cary Eclipse fluorescence spectrophotometer. Transmission electron microscopy (TEM) images were obtained on a JEOL 100CX transmission electron microscope operating at an accelerating bias voltage of 100 kV. Particle size was measured by dynamic light scattering (DLS) with a NICOMP 380 ZLS. HPLC analysis was performed on an Agilent 1100 series. Confocal fluorescence images were taken on a Leica TCS SP8 (63 × oil lens). In vivo fluorescence images and three-dimensional (3D) *in vivo* fluorescence images were measured with a PerkinElmer IVIS Lumina Kinetic Series III imaging system and IVIS Spectrum CT imaging system, respectively.

Synthesis of pH-Sensitive Copolymer and P(Cy-S-CPT)

The intermediate compound PEG-Br[1], 3-azidopropan-1-ol[2], compound 5[3] and CPT-S-OH[4] was synthesized by the established procedures.



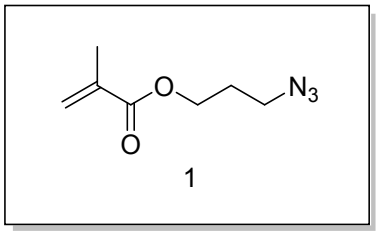
Scheme S1. Synthetic route of pH-sensitive copolymer



Scheme S2. Synthetic route of Cy-S-CPT and P(Cy-S-CPT)

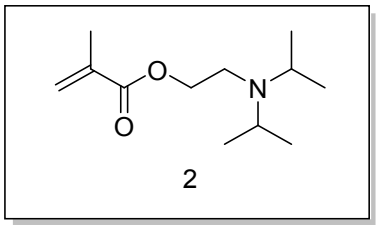
Synthesis of Some Methacrylate Monomers

The methacrylate monomers (compound 1 and compound 2) were synthesized following a similar method. Synthesis of 3-azidopropyl methacrylate (compound 1) is described as a representative procedure. First, 3-azidopropan-1-ol (10.1 g, 0.1 mol), triethylamine (10.1 g, 0.1 mol), and inhibitor hydroquinone (0.11 g, 0.001 mol) were dissolved in 100 mL THF and then methacryloyl chloride (10.4 g, 0.1 mol) was added dropwise into a threeneck flask. The solution was refluxed in THF for 2 hours. After reaction, the solution was filtered to remove the precipitated triethylamine-HCl salts, and THF solvent was removed by rotovap. The resulting residue was distilled in vacuo (83~87 °C at 0.05 mm Hg) as a colorless liquid. The characterization and yield for the monomers are as following:



3-azidopropyl methacrylate (compound 1)

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 1.94 (s, 3H), 1.95-2.01 (m, 2H), 3.42 (t, J = 6.8 Hz, 2H), 4.24 (t, J = 6.4 Hz, 2H), 5.58 (s, 1H), 6.12 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 167.17, 136.12, 125.67, 61.50, 48.23, 28.13, 18.25. Yield: 77 %.



2-(diisopropylamino)ethyl methacrylate (compound 2)

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 1.00 (s, 6H), 1.02 (s, 6H), 1.94 (s, 3H), 2.68 (t, J = 7.2 Hz, 2H), 3.06-2.95 (m, 2H), 4.08 (t, J = 7.2 Hz, 2H), 5.54 (s, 1H), 6.10 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 167.43, 136.49, 125.16, 65.50, 49.27, 43.61, 20.79, 18.34. Yield: 59 %.

Synthesis of pH-Sensitive Copolymer

pH-sensitive copolymer were synthesized by atom transfer radical polymerization (ATRP) method. First, compound 1 (101 mg, 0.6 mmol), compound 2 (1.71 g, 8 mmol), PMDETA (17.3 mg, 0.1 mmol), and PEG-Br (0.5 g, 0.1 mmol) were charged into a polymerization tube. Then a mixture of anhydrous DMF (2 mL) was added to dissolve the monomer and initiator. After three cycles of freeze-pump-thaw to remove oxygen, CuBr (14 mg, 0.1 mmol) was added into the reaction tube under nitrogen atmosphere, and the tube was sealed in vacuo. The polymerization was carried out at 40 ^{o}C for 8 hours. After polymerization, the reaction mixture was diluted with 10 mL THF, and passed through an Al_2O_3 column to remove the catalyst. The THF solvent was removed by rotovap. The residue was dialyzed in distilled water and lyophilized to obtain a white powder.

Synthesis of A-Cy-Cl

Compound 5 (0.43 g, 2 mmol), 3-ethyl-1,1,2-trimethyl-1*H*-benzo[*e*]indol-3-ium (1.67 g, 5 mmol), and NaOAc (0.41 g, 5 mmol) were dissolved in 20 mL Ac_2O. Then the mixture was stirred for 2 h under an argon atmosphere at 100 ^{o}C. The solvent was removed under reduced pressure, and then the crude product was purified by silica gel chromatography using dichloromethane as the eluent to afford A-Cy-Cl as green powder (1.0 g), yield 63 %. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 1.53 (t, J = 7.2 Hz, 6H, -$CH_2C\boldsymbol{H}_3$), 2.02 (s, 12H, -$C\boldsymbol{H}_3$), 2.51 (s, 1H, alkyne-H), 2.92-2.85 (m, 2H, -$C\boldsymbol{H}_2$-), 3.16-3.10 (m, 2H, -$C\boldsymbol{H}_2$-), 4.31-4.25 (m, 1H, -$C\boldsymbol{H}$-), 4.49-4.32 (m, 4H, -$C\boldsymbol{H}_2$-CH_3), 4.49 (s, 2H, -O-$C\boldsymbol{H}_2$), 6.27 (d, J = 14.0 Hz, 2H, alkene-H), 7.55-7.45 (m, 4H, Ph-H), 7.67-7.60 (t, J = 7.6 Hz, 2H, Ph-H), 8.01-7.93 (m, 4H, Ph-H), 8.14 (d, J = 8.8 Hz, 2H, Ph-H), 8.51 (d, J = 14.4 Hz, 2H, Ph-H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ 12.91, 27.62, 32.04, 40.46, 51.23, 56.93, 70.84, 74.55, 80.40, 100.76, 110.68, 122.08, 123.58, 125.22, 127.83, 128.14, 130.21, 130.92, 132.02, 134.11, 139.16, 144.15, 148.86, 173.52. Mass spectrometry (ESI positive ion mode for [IR-794 - I]): m/z: calcd for $C_{45}H_{46}ClN_2O^+$: 665.3299; found: 665.3293.

Synthesis of A-Cy-OH

A-Cy-Cl (196 mg, 0.247 mmol), NaOAc (61.5 mg, 0.75 mmol) were dissolved in 15 mL anhydrous DMF, then the mixture was stirred for 24 h at 90 ^{o}C. The solution was added with dichloromethane (50 mL) and washed with water (20 mL × 5), dried over Na_2SO_4, filtered and evaporated to dryness. Then the crude product was purified by silica gel chromatography using dichloromethane/ methanol (v/v, 100:1) as the eluent to afford A-Cy-OH as a red solid (77 mg): Yield 40%. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 1.34 (t, J = 7.2 Hz, 6H, -$CH_2C\boldsymbol{H}_3$), 2.01 (s, 12H, -$C\boldsymbol{H}_3$), 2.45 (s, 1H, alkyne-H), 2.60-2.51 (m, 2H, -$C\boldsymbol{H}_2$-), 3.21-3.12 (m, 2H, -$C\boldsymbol{H}_2$-), 3.86 (t, J = 7.2 Hz, 4H, -$C\boldsymbol{H}_2CH_3$), 4.03-4.01 (m, 1H), 4.37 (s, 2H), 5.50 (d, J = 13.6 Hz, 2H, alkene-H), 7.10 (d, J = 8.8 Hz, 2H), 7.29 (t, J = 8.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H), 8.04 (d, J = 8.4 Hz, 2H), 8.38 (d, J = 13.6 Hz, 2H, alkene-H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ 11.58, 28.01, 31.60, 37.26, 48.78, 55.83, 73.98, 74.27, 80.39, 91.61, 109.09, 121.86, 122.28, 122.70, 126.89, 129.79, 130.08, 134.74, 140.90, 164.77, 184.68. Mass spectrometry (ESI-MS, m/z): calcd for $[C_{45}H_{47}N_2O_2]^+$: 647.3632; found: 647.3638.

Synthesis of Cy-S-CPT

CPT-S-OH (120 mg, 0.23 mmol), DMAP (122 mg, 1 mmol) and triphosgene (80 mg, 0.27 mmol) were dissolved in 10 mL anhydrous chloroform, then the mixture was stirred for 30 min in ice bath, the solution changed from white to yellow. A-Cy-OH (278 mg, 0.36 mmol) and DIPEA (0.5 mL) in chloroform (10 mL) were added into mixture. The mixture was stirred for 24 h. Then the solution was poured into 200 mL diether ether, collected the solid and the product was purified by column chromatography (silica gel column, dichloromethane : methanol = 100 : 1) to get a green powder (61 mg), yield 20 %. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 0.97 (t, J = 7.2 Hz, 3H), 1.51 (t, J = 7.2 Hz, 6H), 1.92 (s, 12H), 2.15-2.10 (m, 1H), 2.28-2.20 (m, 1H), 2.52 (s, 1H), 2.81-2.71 (m, 2H), 3.07 (t, J = 6.0 Hz, 2H), 3.22-3.11 (m, 4H), 4.44-4.31 (m, 5H), 4.51 (s, 3H), 4.70-4.60 (m, 2H), 5.32-5.21 (m, 2H), 5.36 (d, J = 17.2 Hz, 1H), 5.66 (d, J = 17.2 Hz, 1H), 6.22 (d, J = 14.0 Hz, 2H), 7.50-7.43 (m, 4H), 7.68-7.58 (m, 3H), 7.79 (t, J = 7.6 Hz, 1H), 8.02-7.85 (m, 8H), 8.17-8.08 (m, 3H), 8.45 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ 7.63, 12.84, 14.13, 22.64, 27.65, 30.09, 31.57, 31.84, 36.68, 37.07, 40.07, 51.06, 56.57, 66.45, 66.78, 67.09, 71.20, 74.66, 78.17, 80.37, 95.78, 100.22, 110.65, 118.45, 120.01, 122.11, 125.22, 127.85, 128.03, 128.16, 128.24, 128.44, 129.39, 130.12, 130.77, 130.91, 131.52, 131.97, 134.03, 139.07, 139.47, 145.40, 146.60, 148.72, 152.06, 153.51, 157.38, 167.38, 173.10. Mass spectrometry (ESI-MS, m/z): calcd for $[C_{71}H_{69}N_4O_{10}S_2]^+$, 1201.4455; found, 1201.4452.

Synthesis of P(Cy-S-CPT)

To a mixture of Cy-S-CPT (34 mg, 0.022 mmol), pH-sensitive copolymer (30 mg) and anhydrous DMF (2 mL) was added dropwise under an nitrogen atmosphere at room temperature. After three cycles of freeze-pump-thaw to remove oxygen, CuI (8 mg, 0.042 mmol) was added into the reaction tube under nitrogen atmosphere, and the tube was sealed in vacuo. Then the reaction mixture was stirred overnight at room temperature. The copolymers were purified by dialysis (molecular weight cutoff = 2,000 g mol^{-1}) to remove the free dye molecules. The produced P(Cy-S-CPT) copolymers were lyophilized and kept at -20 °C for storage.

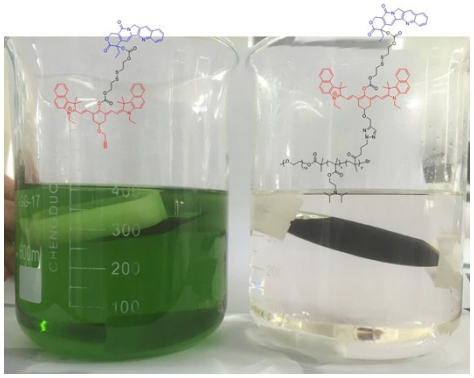


Table S1. Characterization of pH-sensitive copolymer and P(Cy-S-CPT) copolymers

Copolymer	M_n (kDa)[a]	Polydispersity
pH-sensitive Copolymer	13.4	1.29
P(Cy-S-CPT)	17.2	1.63

[a] Number-averaged molecular weights (M_n) were determined by GPC using THF as the eluent.

Transmission Electron Microscopy (TEM) Protocol

All 10 μM sample solutions were prepared from a stock solution of 1 mM in water. Samples were aged overnight prior to sample preparation. Samples were prepared by depositing 10 μL of the appropriate solution onto a carbon-coated copper grid (Electron Microscopy Services, Hatfield, PA), wicking away the excess solution with a small piece of filter paper. The sample grid was then allowed to dry at room temperature (25 °C) prior to imaging. TEM imaging was performed on a JEOL 100CX transmission electron microscope operating at an accelerating bias voltage of 100 kV.

CMC Measurements

Critical micelle concentration (CMC) value is the concentration at which micelles would form in solution. CMC of P(Cy-S-CPT) in the 0.2 M sodium phosphate buffer at pH 7.4. First, the stock solution (5 mg/ml) was diluted to different concentrations with the same buffer. In each solution, 5 μL pyrene in THF solution (2×10^{-4} M) was added to 2 mLP(Cy-S-CPT) solution to produce the final pyrene concentration at 5 $\times 10^{-7}$ M. The fluorescence spectra were recorded with the excitation wavelength of 339 nm and the excitation. The I_1 and I_3 values were measured as the maximum emission intensity at ca. 372 and 382 nm, respectively. I_3/I_1 ratio was plotted as a function of polymer concentration. I_3/I_1 ratio reflects the polarity of the pyrene environment where partition of pyrene in the hydrophobic micelle core leads to increased I_3/I_1 values.

Cell experiment

Cell lines

The cell lines was purchased from the Institute of Cell Biology (Shanghai, China). Cells were all propagated in T-75 flasks cultured at 37 ºC under a humidified 5% CO_2 atmosphere in RPMI-1640 medium or DMEM medium (GIBCO/Invitrogen, Camarillo, CA, USA), which were supplemented with 10% fetal bovine serum (FBS, Biological Industry, Kibbutz Beit Haemek, Israel) and 1% penicillin-streptomycin (10,000 U mL^{-1} penicillin and 10 mg/ml streptomycin, Solarbio life science, Beijing, China).

In vitro cytotoxicity assay

The cell cytotoxicity of Cy-S-CPT and P(Cy-S-CPT) to A549 cells and QSG-7701 cells (normal cells) were measured by 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay. The cytotoxicity was evaluated by Cell Counting Kit-8 (Dojindo, Tokyo, Japan) according to the factory's instruction. Cells were plated in 96-well plates in 0.1 mL volume of DMEM or RPMI-1640 medium with 10% FBS, at a density of 1×10^4 cells/well and added with desired concentrations of Cy-S-CPT and P(Cy-S-CPT). After incubation for 24 h, absorbance was measured at 450 nm with a Tecan GENios Pro multifunction reader (Tecan Group Ltd., Maennedorf, Switzerland). Each concentration was measured in triplicate and used in three independent experiments. The relative cell viability was calculated by the equation: cell viability (%) = $(OD_{treated}/OD_{control}) \times 100\%$.

In vitro Cellular Imaging

The A549 cells at 1×10^5 cells/well were seeded onto glass-bottom petri dishes with complete medium (1.5 mL) for 12 h. Then the cells pre-incubated with and without NEM or $NaHCO_3$ were exposed to desired concentrations of Cy-S-CPT and P(Cy-S-CPT) for 3 h. PBS (pH 7.4) was used to washed cells for three times to clean the background. 4 % paraformaldehyde was added at room temperature for 20 min. The fixed cells were rinsed with PBS (pH 7.4) twice. The images were then photographed by using a Confocal laser scanning microscope Leica TCS SP8 (63 × oil lens).

Animals

The 3-4-week-old female BALB/cA nude mice were producted from Shanghai Genechem Co.,Ltd., and maintained under standard conditions. The animals were housed in sterile cages within laminar airflow hoods in a specific pathogen-free room with a 12-h light/12-h dark schedule and fed autoclaved chow and water ad libitum.

Real-time *in vivo* imaging in tumor-bearing mice

The nude mice were inoculated with A549 cell on their right flanks by injecting 10^6 cells subcutaneously. When the tumors grew up to 10 mm in diameter, Cy-S-CPT and P(Cy-S-CPT) (administered at a CPT-equivalent dose of 0.1 mg/kg) in PBS were intravenously injected via tail vein into the A549 cell tumor-bearing nude mice. The real-time in vivo imaging was recorded at different time internals after Cy-S-CPT and P(Cy-S-CPT) injection. In vivo fluorescence images and three-dimensional (3D) in vivo fluorescence images were measured with a PerkinElmer IVIS Lumina Kinetic Series III imaging system and IVIS Spectrum CT imaging system, respectively. After injection, the mice were sacrificed at 24 h. The grafted tumor tissues and major organs, including kidney, lung, spleen, liver, heart, were excised and washed with 0.9% saline. The optical images of the organs and tissues were taken using a PE in vivo Professional Imaging System as described above.

In Vivo Antitumor Studies

A549 tumor-bearing mice were randomly assigned to five treatment groups (n =5/group): (a) PBS, (b) camptothecin (CPT) at 10 mg/kg, (c) Cy-S-CPT, (d) P(Cy-S-CPT) at a CPT-equivalent dose of 10 mg/kg. The mice were intravenously injected with PBS, CPT, Cy-S-CPT and P(Cy-S-CPT) via the tail vein every 3 days. Each animal was earmarked and followed individually throughout the experiment. Tumor volume (mm^3) was calculated by V (mm^3) = 1/2 × A (mm) × B $(mm)^2$, where A and B were respectively the longest and widest diameters of tumor. The curve of tumor growth was drawn based on tumor volume and corresponding time (days). Animals were sacrificed after the 15 days treatment according to institutional guidelines. Tumors were resected, weighed. To evaluate the therapeutic efficacy of the treatment, inhibition rates (IRT) of tumor growth were calculated using the following equation: IRT = 100% × (mean tumor weight of control group - mean tumor weight of experimental group)/mean tumor weight of control group.

2. Reversibility Study of P(Cy-S-CPT)

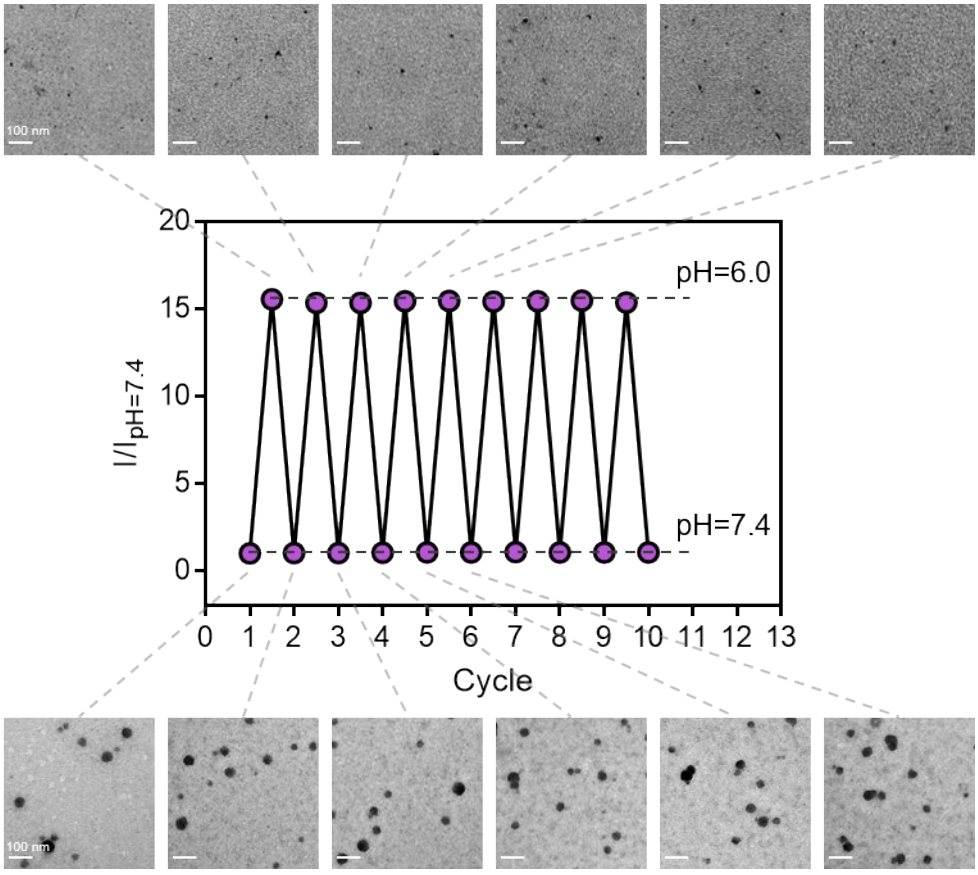


Fig. S1. Reversibility study of P(Cy-S-CPT) toward pH at 37 °C (λ_{ex} = 730 nm, λ_{em} = 830 nm), clearly indicative of reversible structure and fluorescence properties of P(Cy-S-CPT) micelles.

3. ACQ of Cy-S-CPT

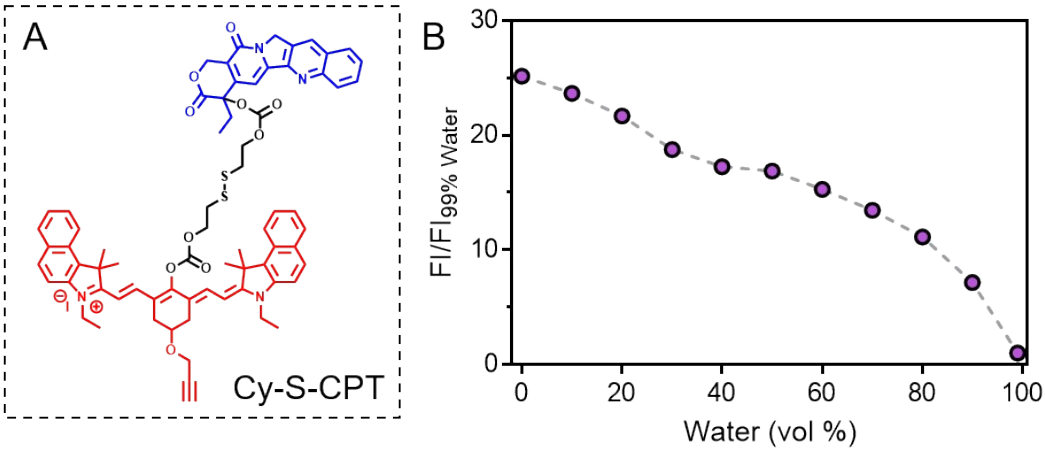


Fig. S2. (A) Structure of Cy-S-CPT. (B) Fluorescence intensity at 830 nm of Cy-S-CPT in THF/water mixtures with different fractions of water, showing typical ACQ (Aggregation-Caused Quenching) effects at 37 °C.

4. TEM Image of P(Cy-S-CPT)

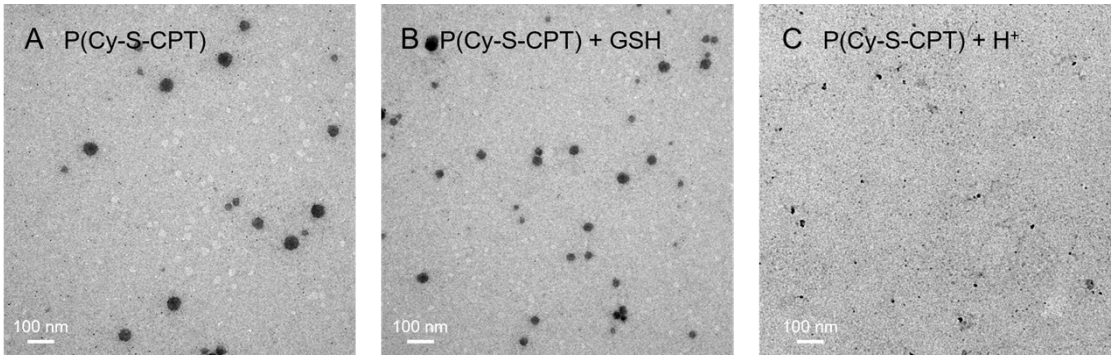


Fig. S3. TEM image of P(Cy-S-CPT) (A), P(Cy-S-CPT) & GSH (B) and P(Cy-S-CPT) & H^+ (C).

5. CPT Release of P(Cy-S-CPT)

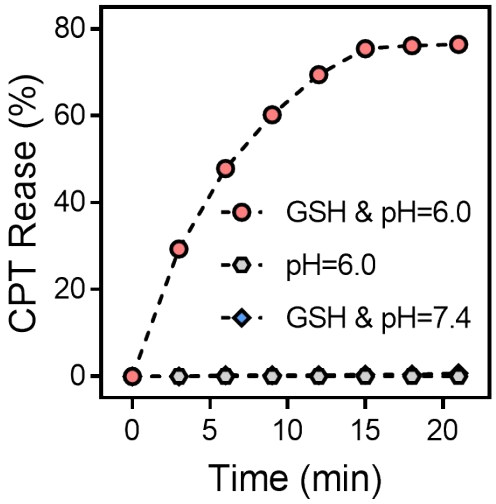


Fig. S4. HPLC analysis of GSH and H^+-driven active CPT release from P(Cy-S-CPT) by monitoring the UV/Vis absorption at 254 nm.

6. CMC of P(Cy-S-CPT)

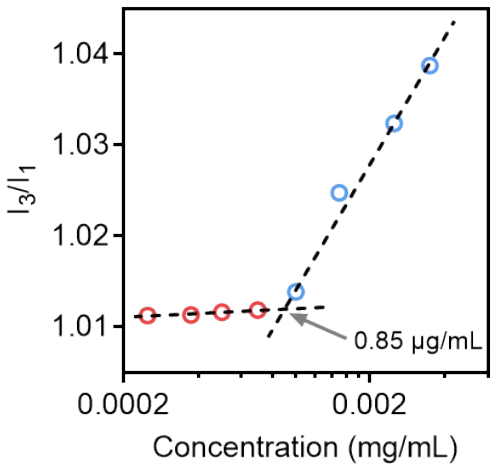


Fig. S5. Critical micelle concentration (CMC) of P(Cy-S-CPT) (0.85 μg mL^{-1}) at 37 °C.

7. Selectivity of P(Cy-S-CPT)

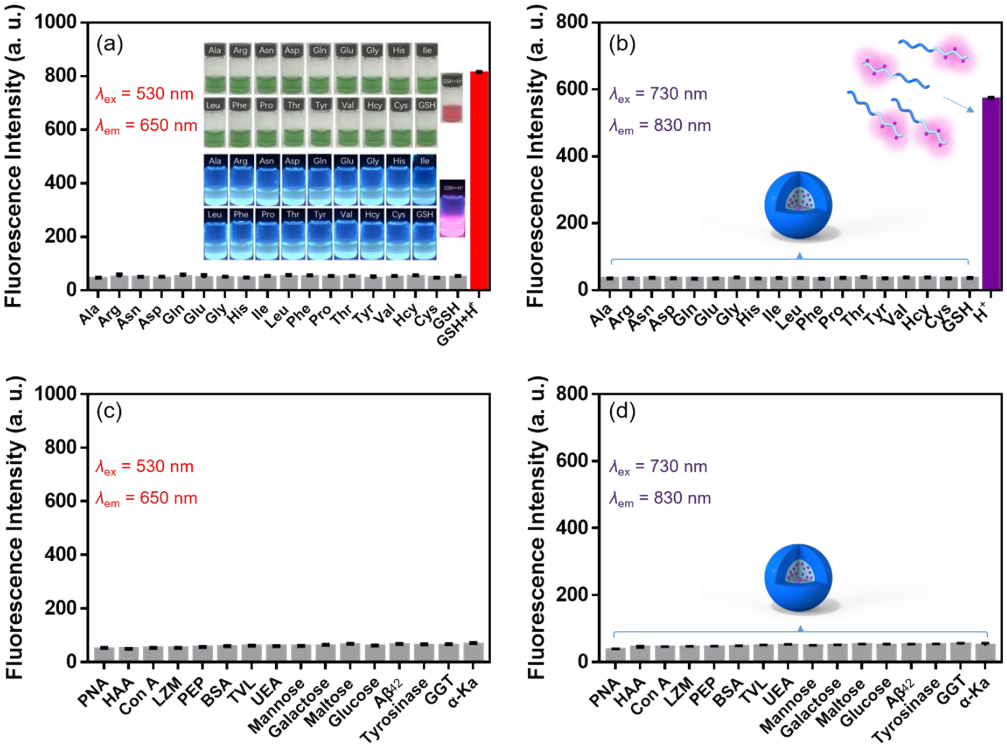


Fig. S6. Fluorescence responses (a, λ_{em} = I_{650} nm; b, λ_{em} = I_{830} nm) of P(Cy-S-CPT) toward various amino acids including GSH (pH = 7.4 and 6.0), Arg, Asn, Ala, Asp, Gln, Glu, Gly, His, Ile, Leu, Phe, Pro, Thr, Tro, Tyr, Val at 37 °C. Fluorescence responses (c, λ_{em} = I_{650} nm; d, λ_{em} = I_{830} nm) of P(Cy-S-CPT) toward enzymes and serum markers including PNA (peanut agglutinin), HAA (snailagglutinin), Con A (concanavalin A), LZM (lysozyme), PEP (pepsin), BSA (bovine albumin), TVL (triticum vulgaris lectin), UEA (ulex europaeus lectin), tyrosinase, GGT (gamma-glutamyl transpeptidase), $A\beta_{42}$ (amyloid β-protein); metabolic substance including D-(+)-mannose, D-galactose, D-(+)-Maltose monohydrate, D-glucose, α-Ka (α-ketoglutaric acid) in PBS (pH = 7.4) at 37 °C.

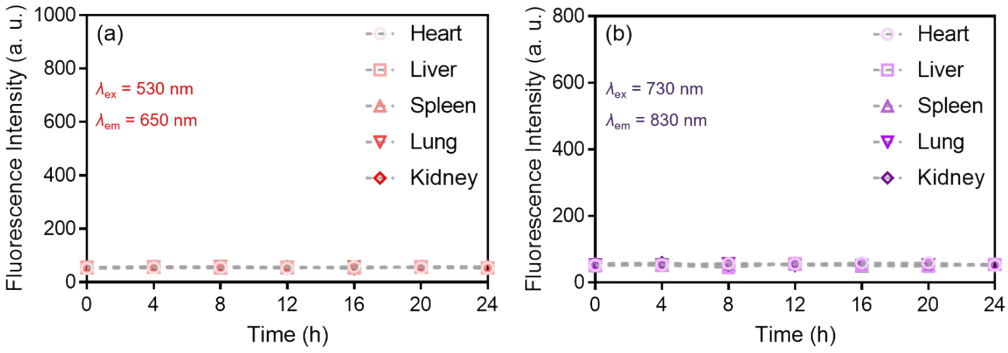


Fig. S7. Fluorescence responses (a, λ_{em} = I_{650} nm; b, λ_{em} = I_{830} nm) of P(Cy-S-CPT) toward various tissue homogenate including heart, liver, spleen, lung and kidney of nude mice at 37 °C.

8. Cytotoxicity of Cy-S-CPT and P(Cy-S-CPT)

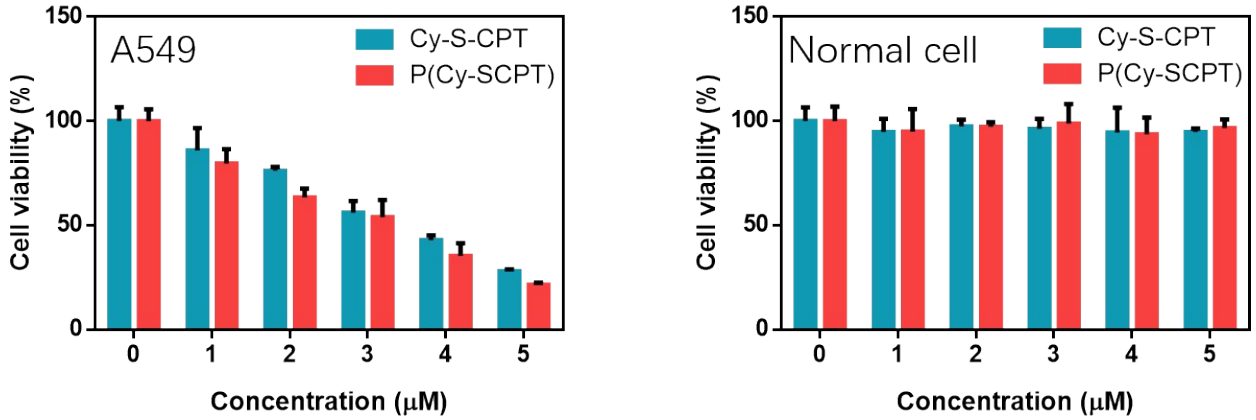


Fig. S8. A549 cells and QSG-7701 cells were incubated with various concentrations (0-5 μM) of Cy-S-CPT and P(Cy-S-CPT) for 24 h. Data are shown as mean ± s.d., with n = 3.

9. Characterization of Intermediate Compounds and Cy-S-CPT

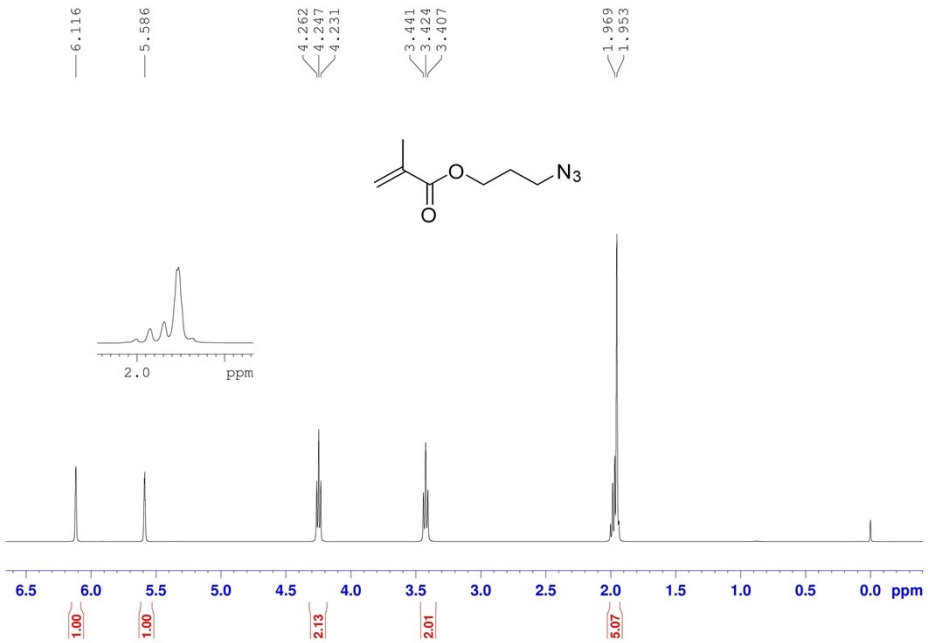


Fig. S9. ^{1}H NMR spectrum of compound 1 in $CDCl_3$

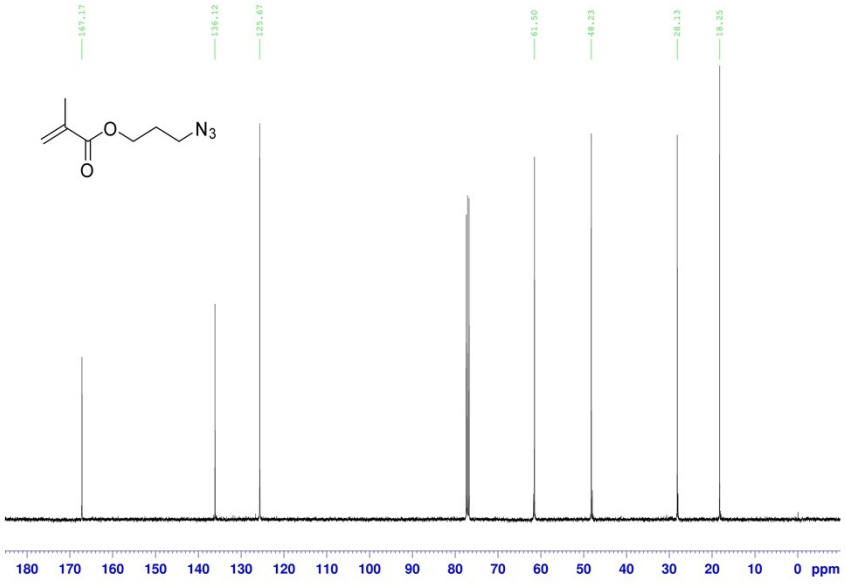


Fig. S10. ^{13}C NMR spectrum of compound 1 in $CDCl_3$

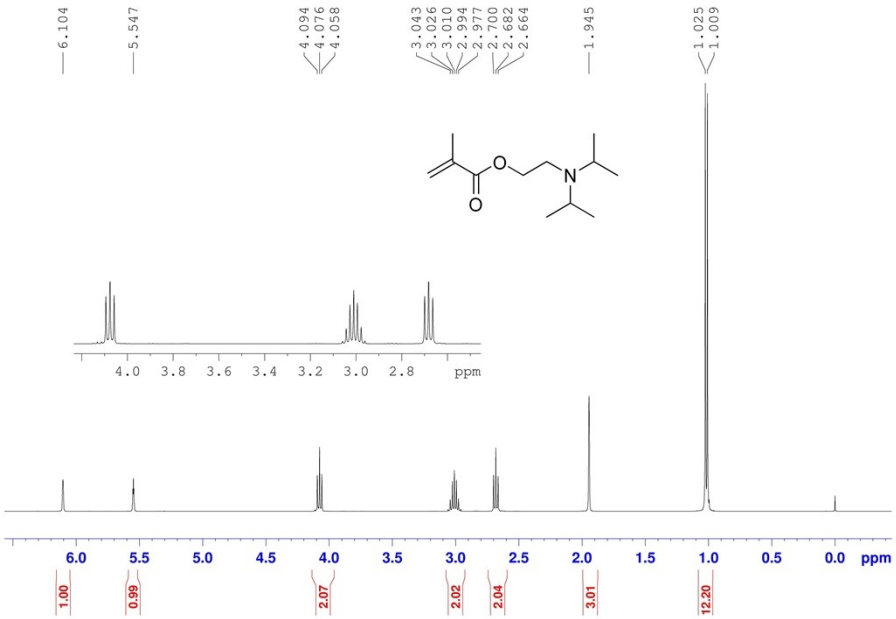


Fig. S11. ^{1}H NMR spectrum of compound 2 in $CDCl_3$

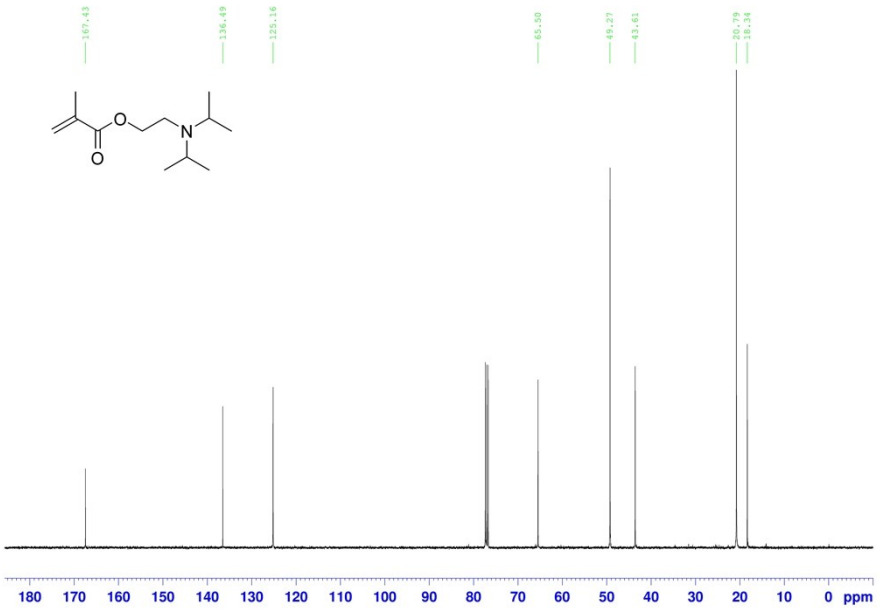


Fig. S12. ^{13}C NMR spectrum of compound 2 in $CDCl_3$

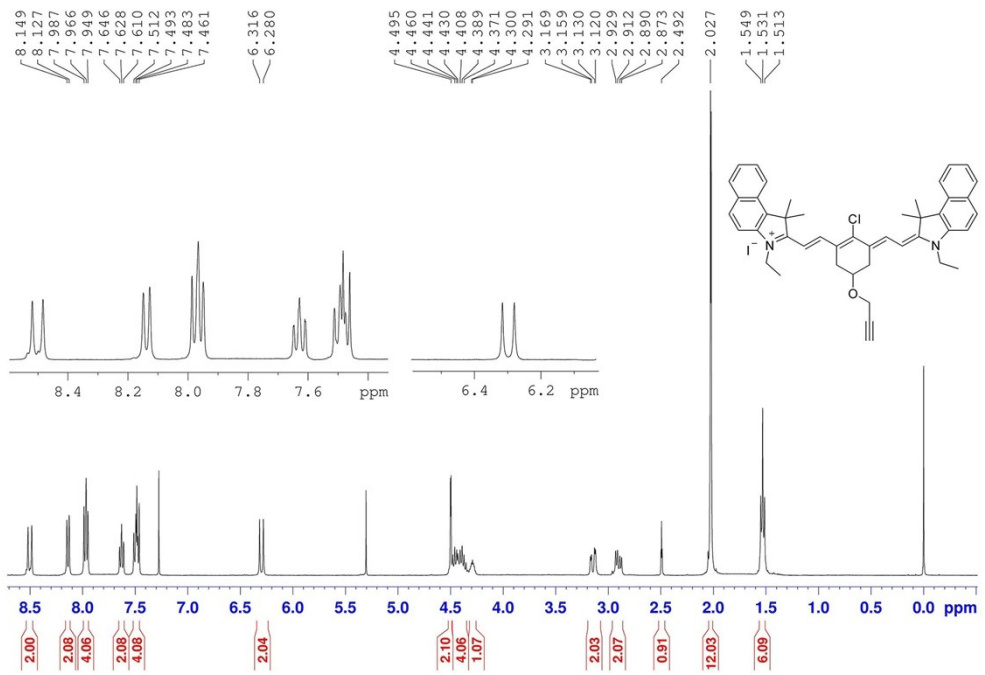


Fig. S13. ^{1}H NMR spectrum of A-Cy-Cl in $CDCl_3$

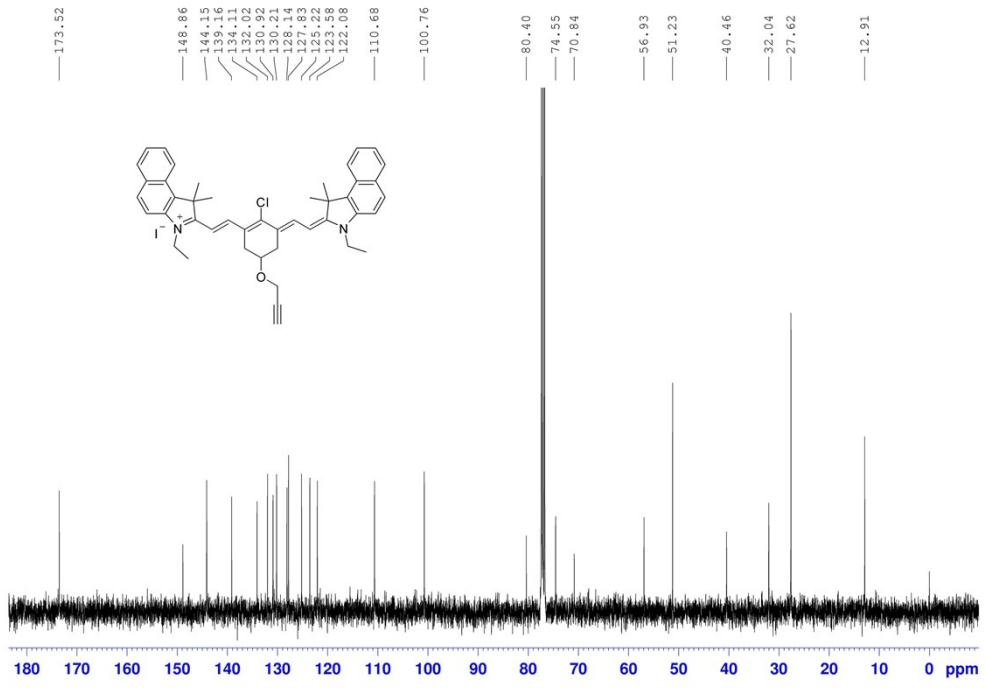


Fig. S14. ^{13}C NMR spectrum of A-Cy-Cl in $CDCl_3$

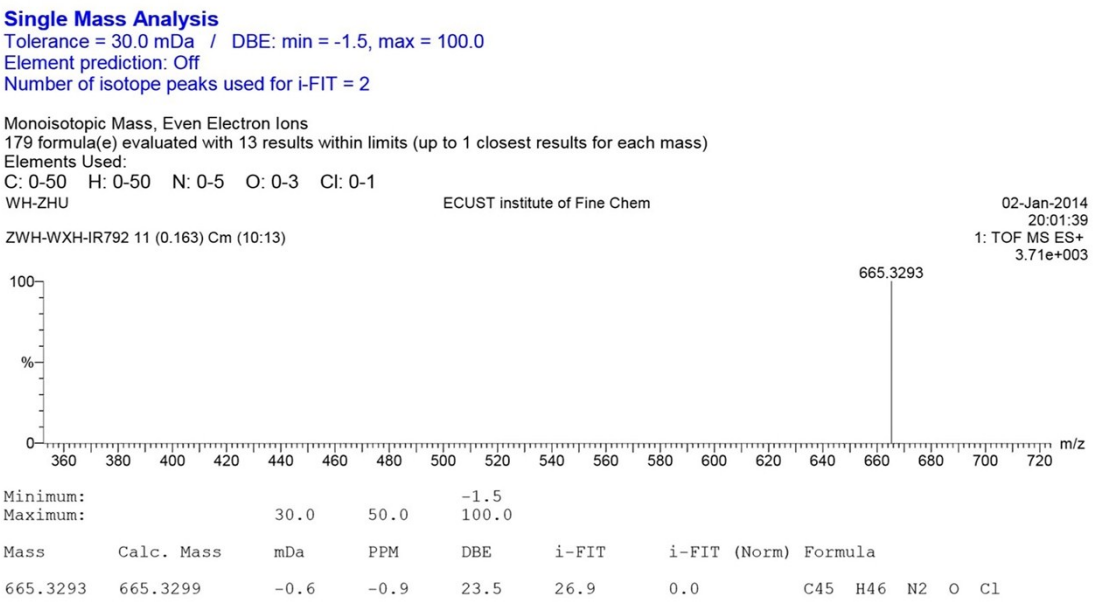


Fig. S15. HRMS spectrum of A-Cy-Cl.

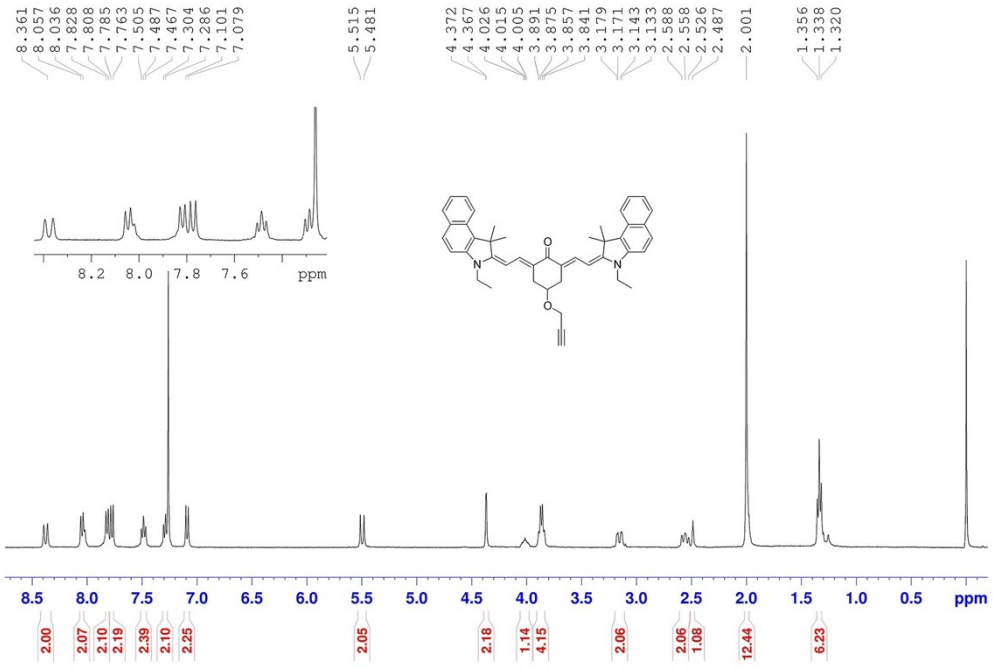


Fig. S16. ^{1}H NMR spectrum of A-Cy-OH in $CDCl_3$

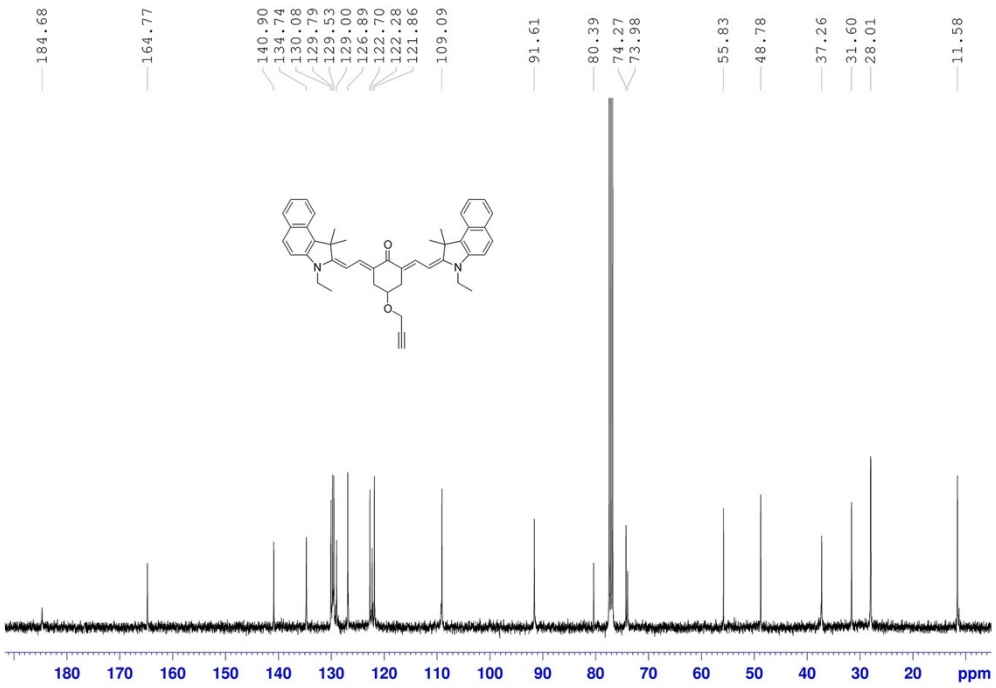


Fig. S17. ^{13}C NMR spectrum of A-Cy-OH in $CDCl_3$

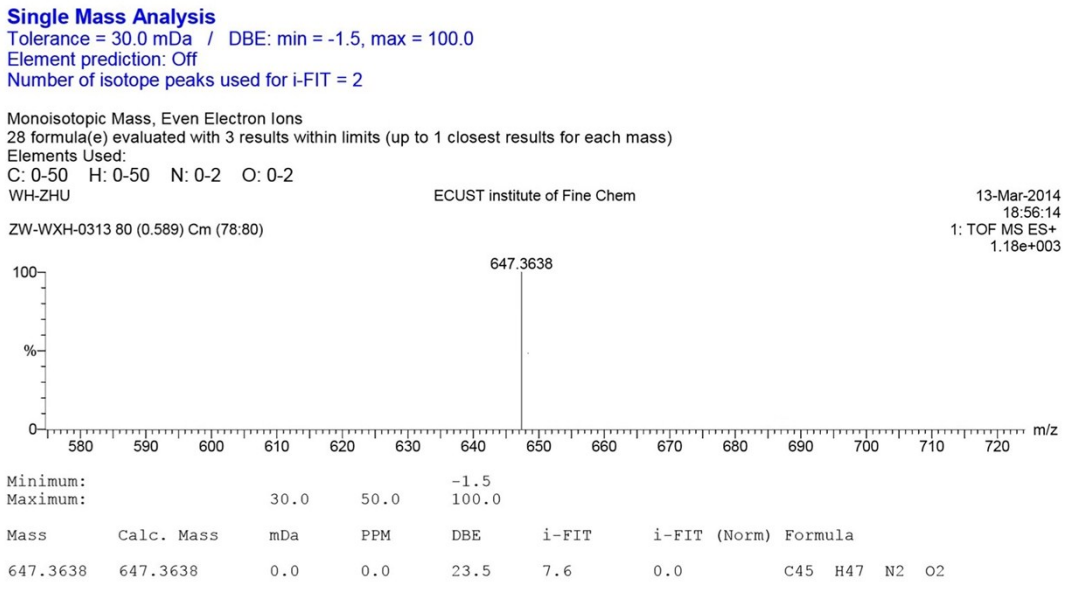


Fig. S18. HRMS spectrum of A-Cy-OH.

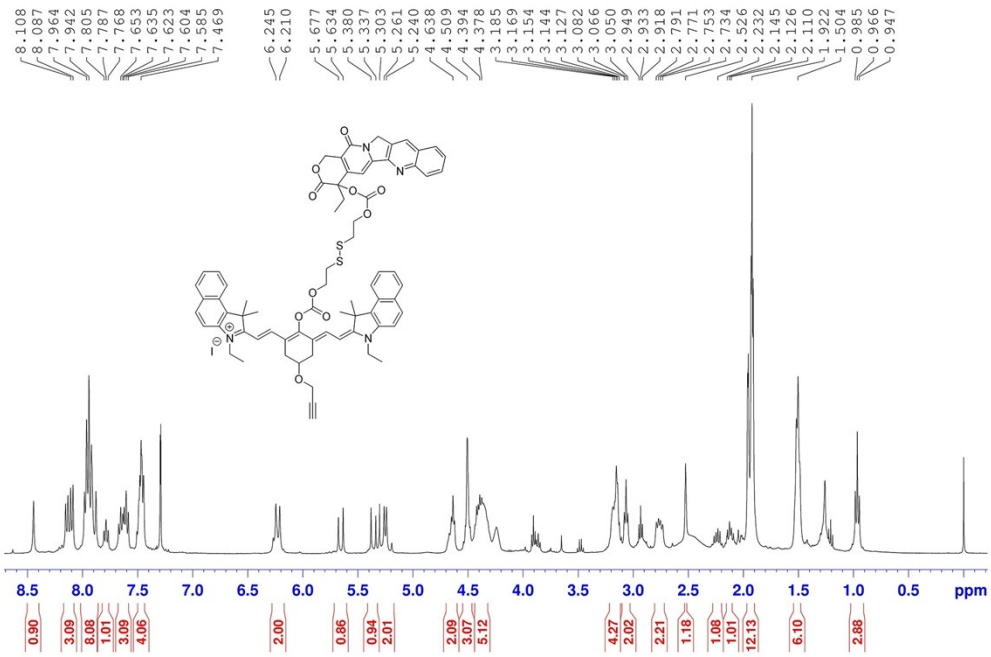


Fig. S19. ^{1}H NMR spectrum of Cy-S-CPT in $CDCl_3$

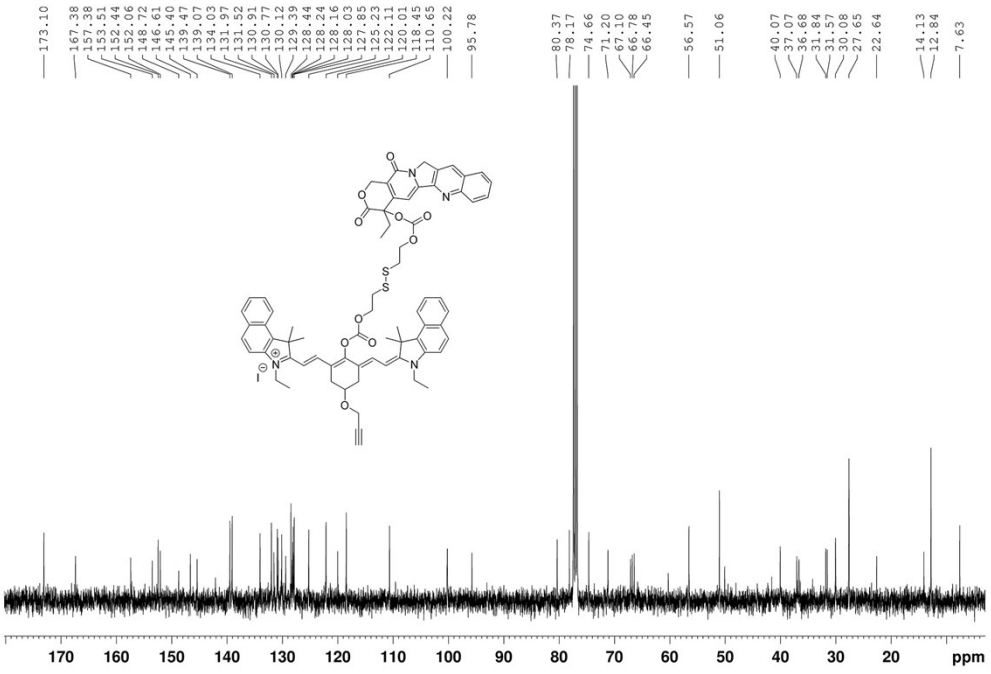


Fig. S20. ^{13}C NMR spectrum of Cy-S-CPT in $CDCl_3$

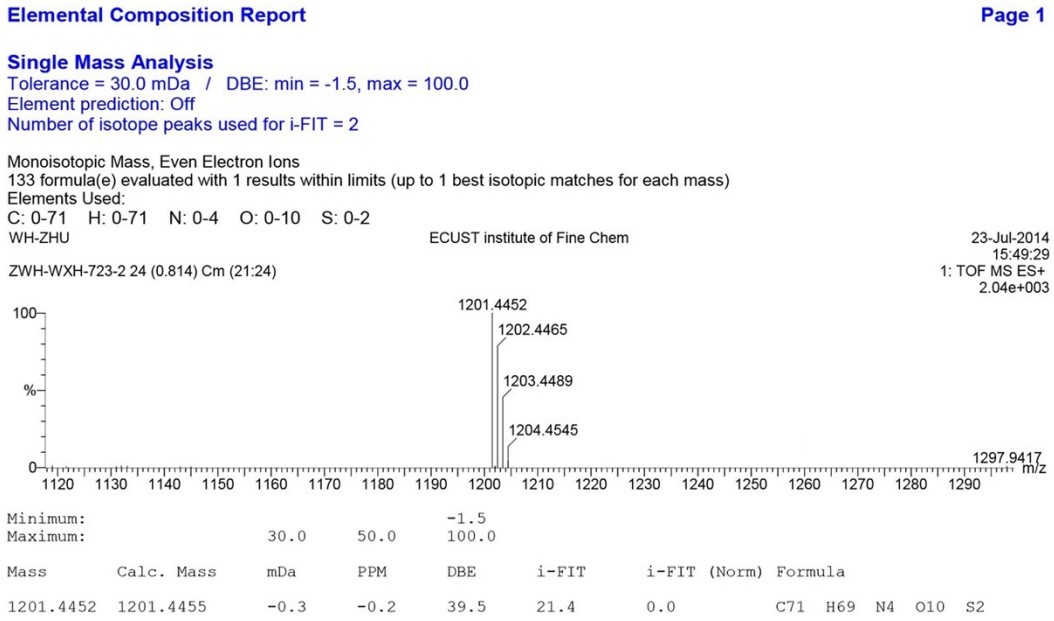


Fig. S21. HRMS spectrum of Cy-S-CPT.

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