Supporting Information

Enhanced Photodynamic Therapy through Supramolecular Photosensitizers with Adamantyl-functionalized Porphyrin and Cyclodextrin-dimer

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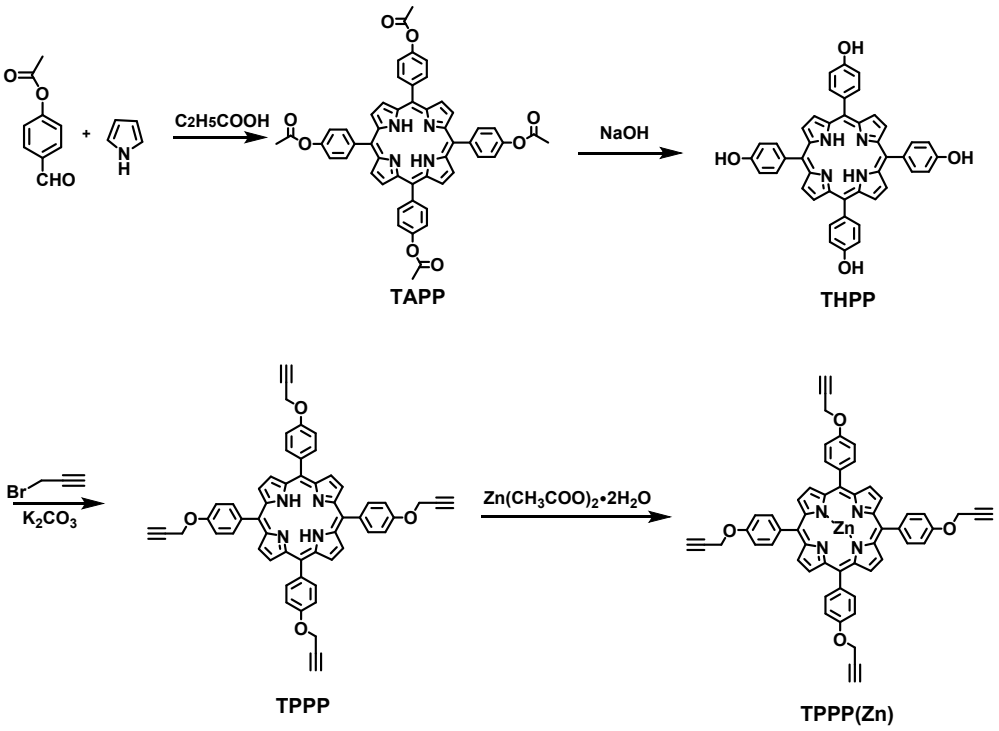
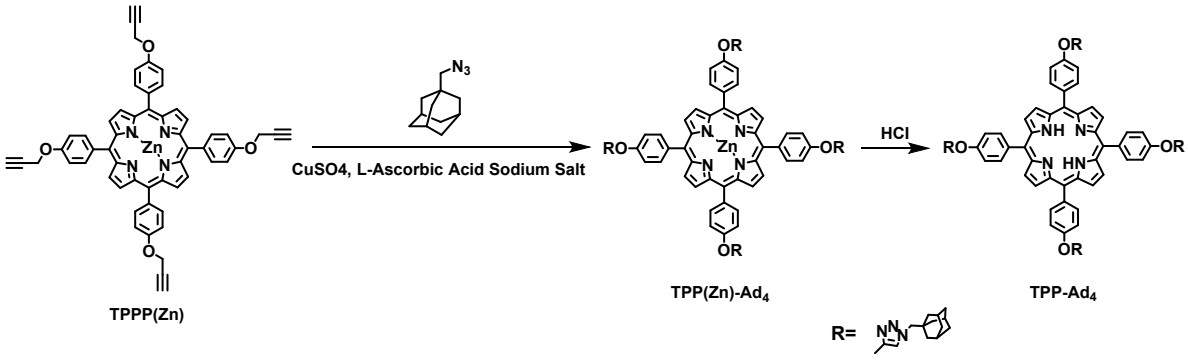
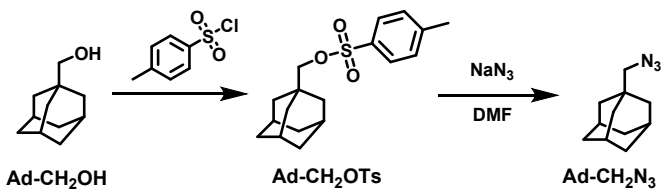


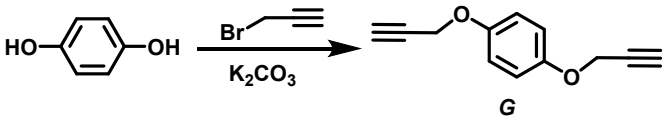
Scheme S1. Synthesis of **THPP** and **TPPP(Zn)**



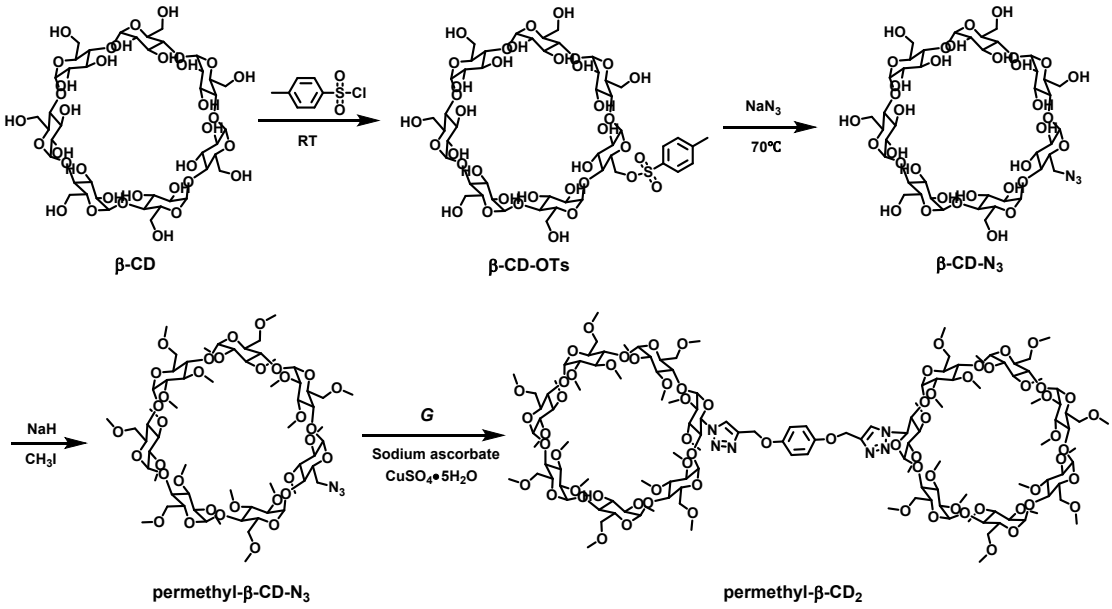
Scheme S2. Synthesis of **TPP-Ad$_4$**



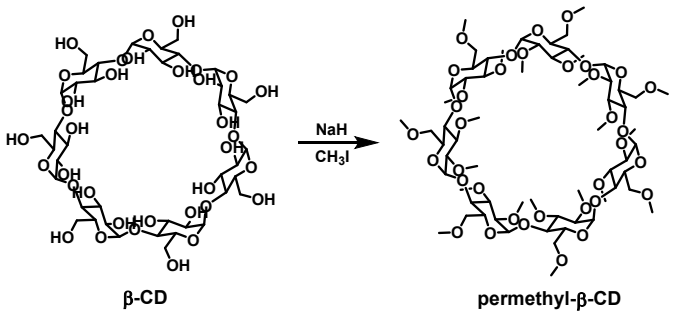
Scheme S3. Synthesis of **Ad-CH$_2$N$_3$**



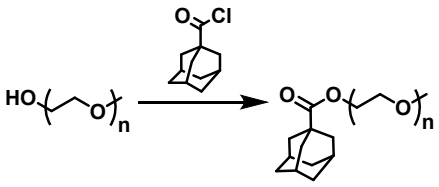
Scheme S4. Synthesis of ***G***



Scheme S5. Synthesis of permethyl-β-Cyclodextrin-dimer（**β-CD$_2$**）



Scheme S6. Synthesis of permethyl-β-Cyclodextrin（**PM-CD**）



Scheme S7. Synthesis of **PEG-Ad**

Experimental Section

1 Materials and methods

1.1 Materials

Permethyl-β-cyclodextrin-dimer (β-CD_2), permethyl-β-Cyclodextrin (PM-CD), ***G*** and PEG-Ad (M_n=5000) were synthesized according our previous literature.[1] Dichloromethane (DCM) and N,N-dimethylformamide (DMF) were dried over calcium hydride and distilled before use. Pyrrole, 4-acetoxybenzaldehyde, sodium hydride (60% dispersion in mineral oil), iodomethane, hydroquinone, propargyl bromide, sodium ascorbate, 1-adamantane methanol, sulfate pentahydrate, zinc acetate dihydrate, trifluoroacetic acid (TFA), methoxypolyethylene glycols (average Mn 5000), potassium carbonate, and hydrochloric acid were all purchased from Aladdin Reagents of China and used without further purification. 3-(4,5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) and Hoechst 33342 were purchased from Beyotime and used as received. Other reagents and solvents were purchased from Sinopharm Chemical Reagent Co. Ltd (SRC) and purified by standard procedure.

1.2 Methods

^{1}H nuclear magnetic resonance spectroscopy (^{1}H NMR, 400 MHz) spectrum was recorded using a BRUKER AV400 Spectrophotometer, in deuterium water (D_2O) or deuterium chloroform ($CDCl_3$) with tetramethylsilane (TMS) as an internal reference. Fluorescence spectra measurements were performed on a Varian's Cary Eclipse fluorescence spectrophotometer at room temperature with excitation and emission slit

width of 10 nm and 10 nm, respectively. The ultraviolet-visible (UV-vis) absorption spectra were determined on a SHIMADZU UV-2550 UV spectrophotometer using in quartz Cuvette with 1 cm beam path length. Mass spectra were obtained by using a XEVO G2 TOF and MALDI-TOF-mass spectra. Dynamic light scattering (DLS) measurements were performed using a Beckman Coulter Delasa Nano C particle analyser and samples were characterized in an aqueous solution. All the measurements were carried out at room temperature.

2 Synthesis of compounds

2.1 Synthesis of zinc porphyrins containing propargyl group (**TPPP(Zn)**)

2.1.1 Synthesis of 5,10,15,20-Tetra(4-acetoxyphenyl)-Porphyrin (**TAPP**)

4-Acetoxybenzaldehyde (2.3 g, 14 mmol) was dissolved in a three-necked flask containing 50 mL of propionic acid, and the reaction system was heated to 135 °C under a nitrogen atmosphere. Pyrrole (1.0 g, 15.4 mmol) was diluted with 15 mL of propionic acid and added dropwise to the reaction solution under a nitrogen atmosphere. The reaction solution was further reacted at 135 °C for 4 h. After the reaction, the reaction solution was concentrated and poured into a beaker, and 200 mL of ice methanol was added and sealed in a refrigerator at -20 °C overnight. After filtration the next day, the residue was washed three times with methanol. The residue was then dissolved in dichloromethane and purified by column chromatography. The resulting product solution was evaporated under reduced pressure and dried in vacuum oven to obtain the purple solid (0.6 g, 18.1%).

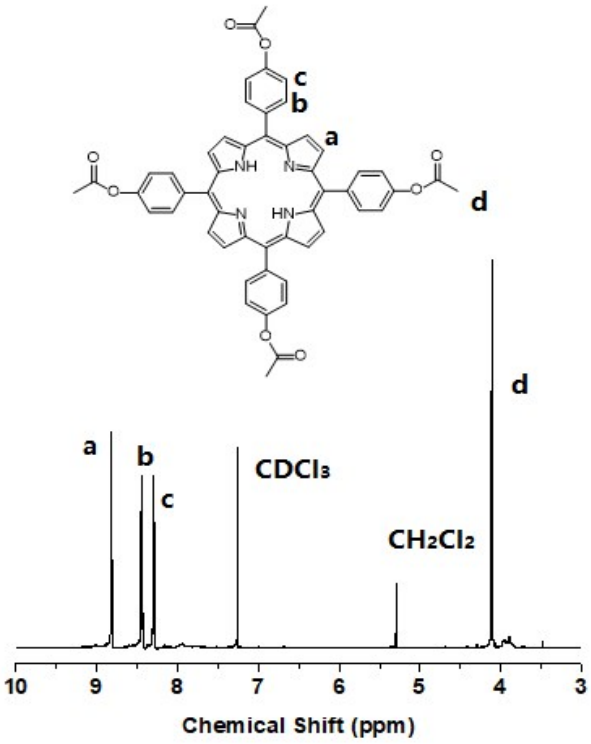


Fig. S1 ^{1}H NMR spectrum of **TAPP**.

2.1.2 Synthesis of 5,10,15,20-Tetra(4-hydroxyphenyl)-Porphyrin (**THPP**)

TAPP (1 g, 1.2 mmol) was dissolved in 40 mL of the mixture solution of methanol, tetrahydrofuran and water (v:v:v = 1:1:1), and then added sodium hydroxide (1.8 g, 48 mmol). The reaction solution was stirred at 60 °C for 24 h. After completion of the reaction, methanol and tetrahydrofuran were removed by rotary evaporation, and the pH of the solution was adjusted to 6 with a 10% diluted hydrochloric acid solution. A green solid was obtained by filtration, and the solid was washed with triethylamine until the solid color changed from green to purple. The crude product was dissolved in ethyl acetate and purified by column chromatography. The final product was dried under vacuum to give a purple solid (0.93 g, 93%).

^{1}H NMR (400 MHz, *d*-DMSO) δ = 8.88 (s, 8H), 8.32 (s, 4H), 8.00 (d, *J* = 8.4 Hz, 8H), 7.22 (d, *J* = 8.4 Hz, 8H).

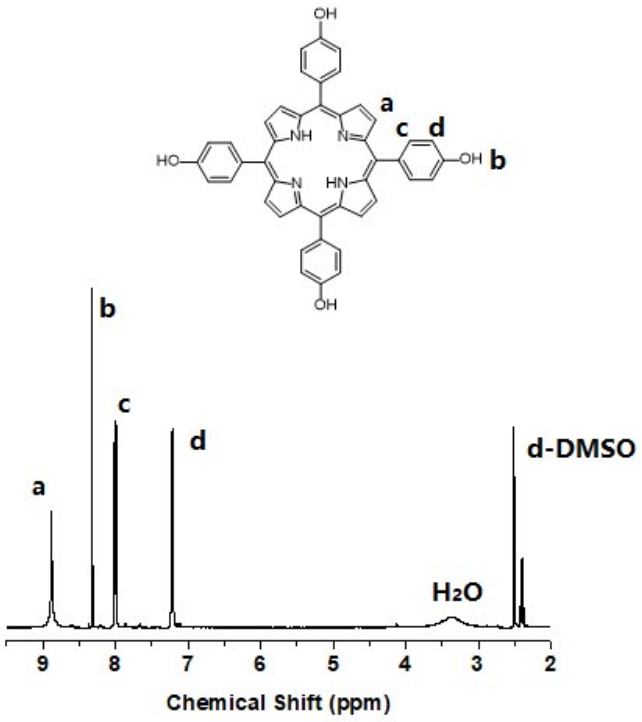


Fig. S2 ^{1}H NMR spectrum of **THPP**.

2.1.3 Synthesis of 5,10,15,20-Tetra(4-propargyloxyphenyl)-Porphyrin (**TPPP**)

THPP (0.5 g, 0.74 mmol) was dissolved in 20 mL of DMF, then added propargyl bromide (0.7 g, 5.9 mmol) and potassium carbonate (2 g, 14.8 mmol). The mixed solution was reacted at 100 °C for 24 h. After the reaction, potassium carbonate was removed by filtration, and DMF was distilled off under reduced pressure. The residual liquid was dissolved in dichloromethane and purified by column chromatography. The final product was dried under vacuum to give a purple solid (0.5 g, 81.3%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.86 (s, 8H), 8.18 – 8.10 (m, 8H), 7.37 (d, J = 8.6 Hz, 8H), 4.99 (d, J = 2.4 Hz, 8H), 2.72 – 2.66 (m, 4H).

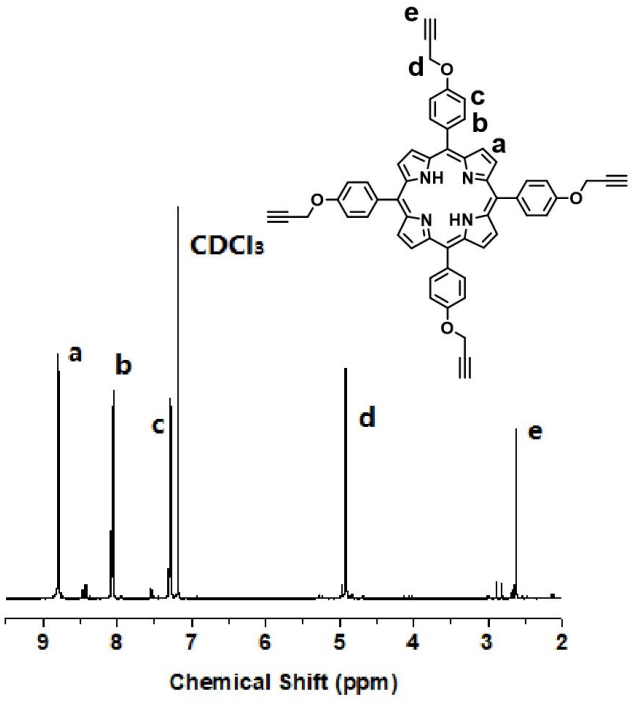


Fig. S3 ^{1}H NMR spectrum of **TPPP**.

2.1.4 Synthesis of 5,10,15,20-Tetra(4-propargyloxyphenyl)-zinc Porphyrin (**TPPP(Zn)**)

TPPP (0.5 g, 0.6 mmol) was dissolved in a mixed solution of dichloromethane and methanol (v:v = 1:1), and then added zinc acetate dihydrate (1.1 g, 6 mmol). The reaction solution was stirred at room temperature. After 24 hours, the solution was washed by saturated aqueous solution of NaCl for three times and dried to give purple greenish solid (0.52 g, 98.3%).

2.2 Synthesis of azide adamantane (**Ad-CH_2N_3**)

2.2.1 Synthesis of **Ad-CH_2OTs**

1-adamantane methanol (0.5 g, 3 mmol) was dissolved in pyridine (15 mL) in a 50 mL flask. p-Toluenesulfonyl chloride (1.72 g, 9 mmol) was dissolved in pyridine (5 mL) and slowly added dropwise into flask under ice bath. After stirring for 24 h at room temperature, dichloromethane (50 mL) was added into reaction system. Then, the organic phase was washed 3 times with a 10% dilute hydrochloric acid solution. After concentration of the organic phase, the product was purified by column chromatography. The final product was dried under vacuum to get a white solid (0.63

g, 65.5%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 3.48 (s, 2H), 2.38 (s, 3H), 1.88 (s, 3H), 1.66 – 1.48 (m, 6H), 1.40 (d, *J* = 2.4 Hz, 6H).

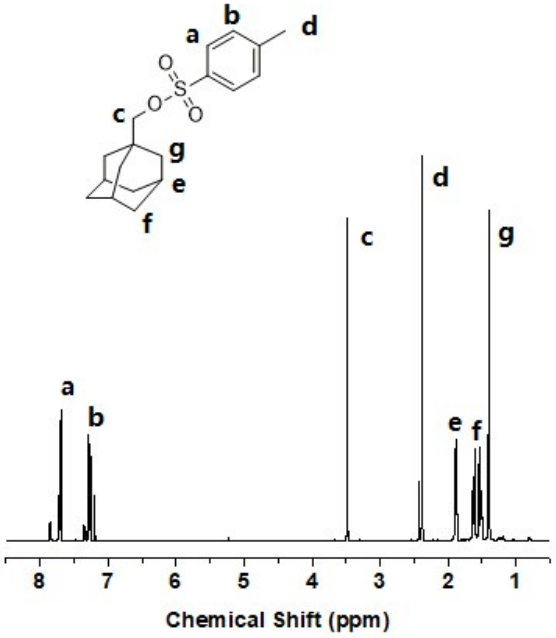


Fig. S4 ^{1}H NMR spectrum of **Ad-CH_2OTs**.

2.2.2 Synthesis of **Ad-CH_2N_3**

Ad-CH_2OTs (0.5 g, 1.5 mmol) was dissolved in DMF (15 mL), and added sodium azide (0.5 g, 7.5 mmol). After reacting at 100 ℃ for 24 hours, dichloromethane (50 mL) was added into reaction system, and the solution was washed by saturated aqueous solution of NaCl for three times. Then the solvent was evaporated under reduced pressure and the residue was dissolved in dichloromethane to purified by column chromatography. Final product was obtained under vacuum for 24 h to give Ad-CH_2N_3 as a white solid (0.11 g, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.95 (s, 2H), 1.99 (s, 3H), 1.76 – 1.59 (m, 6H), 1.52 (d, *J* = 2.5 Hz, 6H).

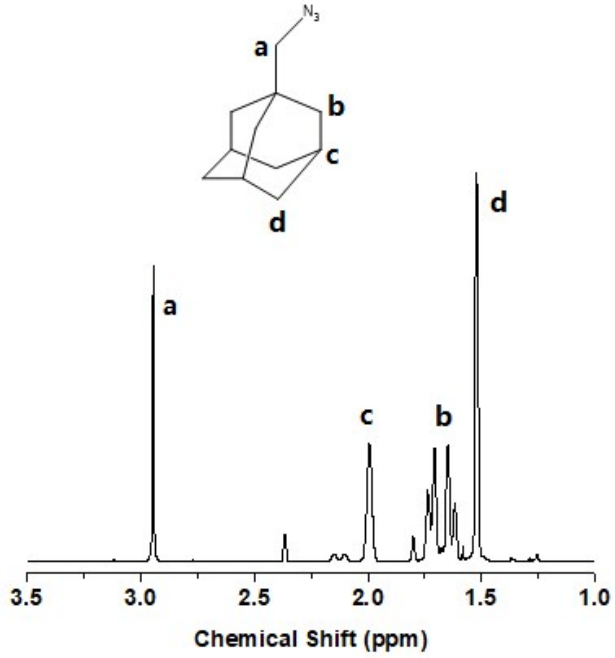


Fig. S5 ^{1}H NMR spectrum of **Ad-CH_2N_3**.

2.3 Synthesis of **TPP-Ad_4**

2.3.1 Synthesis of **TPP(Zn)-Ad_4**

TPPP(Zn) (30 mg, 0.036 mmol), Ad-CH_2N_3 (51 mg, 0.29 mmol), and sodium ascorbate (57 mg, 0.29 mmol) were dissolved in 20 mL THF. Copper sulfate pentahydrate (72 mg, 0.29 mmol) dissolved in 1 mL of water was added to the reaction system under nitrogen atmosphere. After continuing the reaction at 45 °C for 24 h, 50 mL of dichloromethane was added into system. Subsequently, the solution was washed with a saturated sodium chloride solution for three times. The dichloromethane layer was then concentrated and the product was purified by column chromatography. The final product solution was decanted under reduced pressure and dried in vacuo to give a purple solid (12 mg, 20%).

2.3.2 Synthesis of **TPP-Ad_4**

TPP(Zn)-Ad_4 (20 mg, 0.012 mmol) was dissolved in DCM (10 mL), and 100 μL of hydrochloric acid solution was added to the solution. After stirring at room temperature for 2 h, hydrochloric acid was neutralized by adding triethylamine. Then the solution was washed for three times with a saturated sodium chloride solution. Finally, the organic phase was dried to get a purple solid (19 mg, 99.2%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.86 (s, 8H), 8.13 (d, *J* = 8.0 Hz, 8H), 7.75 (s, 4H), 7.41 (s, 8H), 5.50 (d, *J* = 11.1 Hz, 8H), 4.10 (d, *J* = 14.9 Hz, 8H), 2.04 (s, 12H), 1.78 – 1.63 (m, 24H), 1.59 (m, 24H). LRESIMS: m/z 1593.85 $[M - H]^-$ (100%).

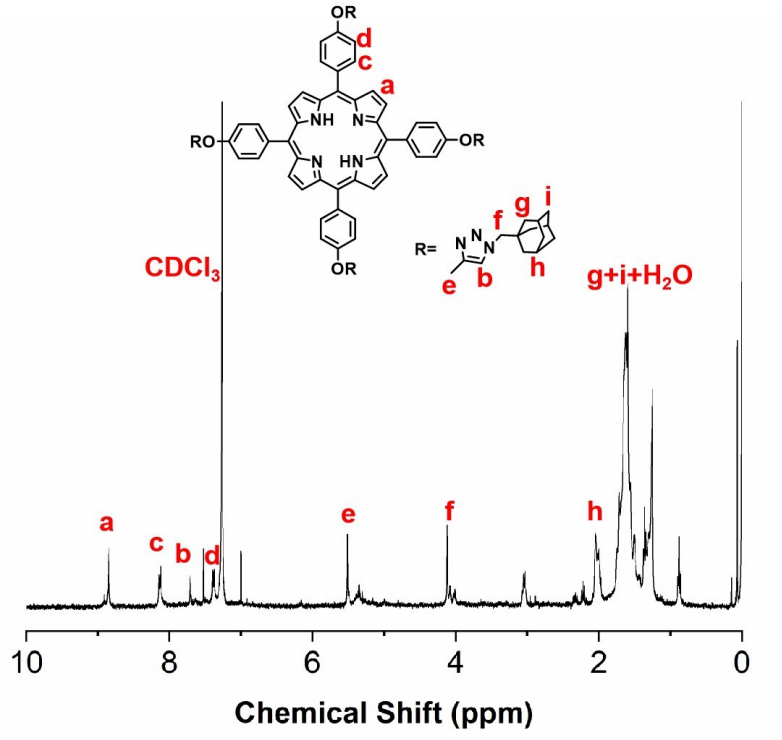


Fig. S6 ^{1}H NMR spectrum of **TPP-Ad$_4$**.

2.4 Synthesis of permethyl-β-cyclodextrin-dimer（**β-CD$_2$**）

2.4.1 Synthesis of permethyl-β-cyclodextrin-N_3 (**PM-CD-N$_3$**)

β-cyclodextrin-N_3 (0.2 g, 0.17mmol) was dissolved in anhydrous DMF (15 mL) in a 50 mL flask. The flask was cooled to 0 ℃ in an ice water bath. Sodium hydride (0.18 g, 4.5 mmol) was slowly added to solution under nitrogen atmosphere. After stirring for 1 h at room temperature, iodomethane (0.91 g, 6.4 mmol) in 10 mL anhydrous DMF was added dropwise. The reaction solution was stirred for 24 h at room temperature. Then water (50 mL) was added dropwise to quench unreacted sodium hydride and ethyl acetate (50 mL×3) was used to extract the product. The organic phase was concentrated under vaccum to give permethyl-β-cyclodextrin-N_3 as a pale-yellow solid (166 mg, 70%). LRESIMS: m/z 1462.63 $[M + Na]^+$ (100%).

The **PM-CD** was synthesized in the similar way.

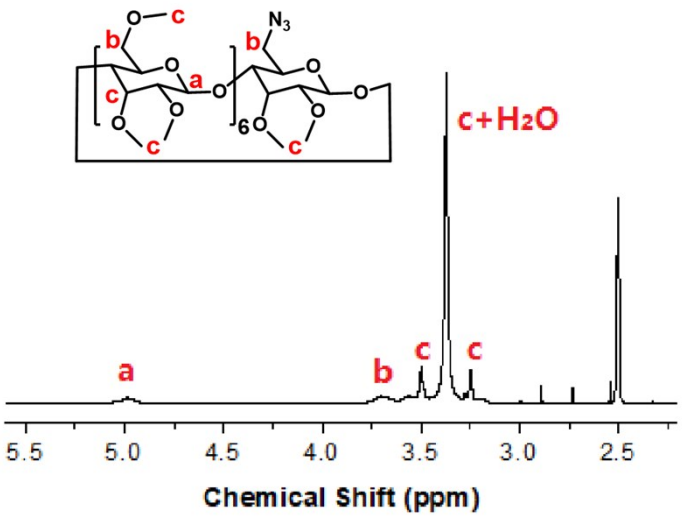


Fig. S7 ^{1}H NMR spectrum of **PM-CD-N_3**.

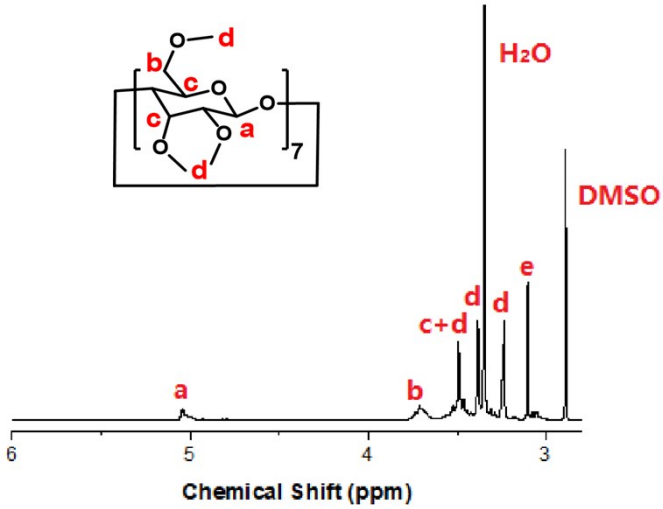


Fig. S8 ^{1}H NMR spectrum of **PM-CD**.

2.4.2 Synthesis of **β-CD_2**

PM-CD-N_3 (1.0 g, 0.70 mmol), ***G*** (0.04 g, 0.23 mmol) and sodium ascorbate (0.20 g, 1.0 mmol) was dissolved in 30 mL DMF. $CuSO_4 \cdot 5H_2O$ (0.18 g, 0.7 mmol) in 5 mL deionized water was added to the solution under nitrogen atmosphere. The reaction solution was stirred in a 60 ℃ oil bath for 24 h. Then the solution was concentrated in vacuo and the residue was dissolved in $CHCl_3$. The $CHCl_3$ was washed by saturated NaCl solution and concentrated. The crude product was purified by column chromatography on silica gel by using dichloromethane/methanol (50:1, v/v) as the eluent. Final product was obtained under vacuum for 24 h to give β-CD_2 as a yellow

solid (180 mg, 25%). MALDI-MS: m/z 3022.4 $[M-H]^-$.

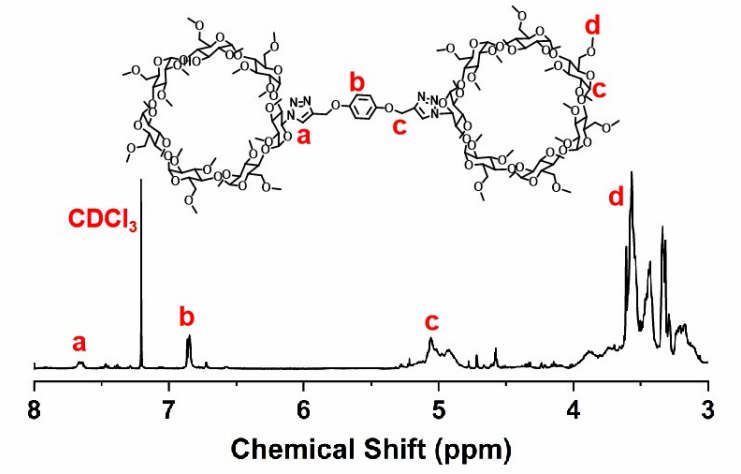


Fig. S9 ^{1}H NMR spectrum of **β-CD$_2$**.

3 Investigation of the interactions between TPP-Ad$_4$ and β-CD$_2$

3.1 ^{1}H NMR titration experiments

NMR titration experiment was utilized to study the complexation between β-CD_2 and TPP-Ad_4. A *d*-DMSO/D_2O (1/100, v/v) mixed solvent was used due to the poor solubility of TPP-Ad_4 in D_2O. In this mixed solvent, we kept the concentration of TPP-Ad_4 fixed at 5 mM, and β-CD_2 had a varying concentration of 5, 10, 20 and 40 mM. The NMR titration experiment was performed on the BRUKER AV400 Spectrophotometer (400 MHz).

3.2 Fluorescence titration experiments

We used fluorescence spectrum to investigate the host-guest complexation constant between host molecule and guest molecule. TPP-Ad_4 had a constant concentration of 1×10^{-5} M, ([Ad] = 4×10^{-5} M) in a DMF/H_2O (1/100, v/v) mixed solution, while β-CD_2 had a varying concentration (0, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0×10^{-5} M, [CD] = 0, 2.0, 3.0, 4.0, 8.0, 12.0, 16.0×10^{-5} M). The complexation constant K_a was calculated by a non-linear curve-fitting method.

The non-linear curve-fittings were based on the following equation:

$$\Delta F = (\Delta F_\infty/[H]_0)(0.5[G]_0 + 0.5([H]_0+1/K_a) - (0.5([G]_0^2 + (2[G]_0(1/K_a - [H]_0)) +(1/K_a$$

$+ [H]_0)^2)^{0.5}))$

In this formula, ΔF is the change in fluorescence intensity at 660 nm when the host concentration is $[H]_0$. ΔF_∞ is the fluorescence intensity at 660 nm when the guest molecule is fully complexed with the host molecule. $[H]_0$ is the initial concentration of the host molecule, and $[G]_0$ is the initial concentration of the guest molecule.

3.3 UV-*vis* titration experiments

The changes of UV-*vis* spectrum of TPP-Ad_4/CD_2 complexes were used to study the host-guest complexation behavior. In a mixed solvent of DMF/H_2O (1/100, v/v), the concentration of TPP-Ad_4 was fixed at 1×10^{-5} M, ([Ad] = 4×10^{-5} M), and β-CD_2 had a varying concentration (0, 0.5, 1.5, 2.0, 4.0, 6.0, 8.0×10^{-5} M, [CD] = 0, 1.0, 3.0, 4.0, 8.0, 12.0, 16.0×10^{-5} M). The absorption was recorded on a UV-*vis* spectrometer.

4 Self-assembly of the TPP-Ad_4/CD, TPP-Ad_4/CD_2 and TPP-Ad_4/CD_2/PEG complexes in aqueous solution

TPP-Ad_4 (1.6 mg, 0.001 mmol) and PM-CD (5.7 mg, 0.004 mmol) were dissolved in 0.3 mL DMSO and stirred at room temperature for 2 h.With stirring, 0.7 mL of deionized water was added dropwise to the solution in 20 minutes. The mixed solution was further stirred for 12 h under a water bath at 25 °C. The DMSO was then removed by dialysis (MWCO 12 kDa) against deionized water (changing water for 3 times) to obtain **TPP-Ad_4/CD** assembly. The final concentration of the assembly was 1.33 mg/mL (calculated by the concentration of TPP-Ad_4).

The assembly of **TPP-Ad_4/CD_2** in aqueous solution was prepared in the same manner as above. TPP-Ad_4 (1.6 mg, 0.001 mmol) and β-CD_2 (6.2 mg, 0.002 mmol) were used. The final concentration of this assembly was determined to be 1.33 mg/mL (calculated by the concentration of TPP-Ad_4).

TPP-Ad_4/CD_2/PEG assembly was prepared by adding a small amount of PEG-Ad (1 mg, 0.0002 mmol) to the TPP-Ad_4/CD_2 assembly solution. DMSO and free PEG-Ad were removed by dialysis (MWCO 12 kDa) against deionized water (changing water for 3 times). The final concentration of this assembly was 1.33 mg/mL (calculated by

the concentration of TPP-Ad_4).

5 Singlet oxygen generation test

1,3-Diphenylisobenzofuran (DPBF) was used as a singlet oxygen ($^1O_2$) detecting reagent in a mixed solution of DMF/H_2O (1:100, v/v) (1% DMF was used to improve the solubility of DPBF and TPP-Ad_4).Singlet oxygen production was compared by monitoring the UV-*vis* spectral change of DPBF at 425 nm with a 660 nm laser.

The concentration of four sample solution are as follow:

TPP-Ad_4 in mixed solution

TPP-Ad_4 = 1.0 ×10^{-5} M

TPP-Ad_4/CD assembly in mixed solution

TPP-Ad_4 = 1.0 ×10^{-5} M, PM-CD = 4.0×10^{-5} M

TPP-Ad_4/CD_2 assembly in mixed solution

TPP-Ad_4 = 1.0 ×10^{-5} M, β-CD_2 = 2.0×10^{-5} M

TPP-Ad_4/CD_2/PEG assembly in mixed solution

TPP-Ad_4 = 1.0 ×10^{-5} M, β-CD_2 = 2.0×10^{-5} M, PEG-Ad = 0.1 ×10^{-5} M

6 Cell Culture

4T1 mouse breast cancer cells were used for this work. The cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) containing 10% FBS and 1% penicillin and streptomycin at 37 °C in a humidified environment containing 5% CO_2.

6.1 Cellular uptake studies

Confocal laser scanning microscope (CLSM) was used for analysis of cell uptake. 4T1 cells were cultured in 2 mL culture medium on polylysine-coated glass slides in 30 mm glass culture dishes and allowed to grow to 50−70% at 37 °C. Then, cells (on glass slides) were washed with PBS, and further incubated in DMEM medium containing 10% sample solutions (the concentration of TPP in samples used in CLSM was 5.0 μmol/mL) at 37 °C under 5% CO_2 for 4h and 24 h. After predetermined time,

the medium was removed and washed with PBS for three times. Subsequently, Hoechst 33342 was added to stain the nuclei. The cells were imaged directly via CLSM after washing three times with PBS .

6.2 *In vitro* dark cytotoxicity

We studied the cytotoxicity of each sample to 4T1 cells by MTT assay. The cells were seeded in 96-well plates at a density of 5000 per well in 200 μL DMEM. After 24 h of incubation in 96-well plates at 37 °C, the medium was removed and washed with PBS. Then, samples with various concentrations were added to each well. All the samples were subjected to incubation for 24 h. After that, the medium containing samples was washed away with PBS, and the cells were incubated for another 4 h with RPMI 1640 medium containing 5 mg mL^{-1} MTT. After discarding the culture medium, 150 μL DMSO was added to each well to extract the formazan products. The absorbance at 492 nm was measured using a spectrophotometric microplate reader (Thermo Multiskan MK3 spectrometer).

The cell viability was calculated as follows: cell viability (%) = $(OD_{test})/(OD_{control}) \times 100$, where OD_{test} is the absorbance in the presence of sample solutions and $OD_{control}$ is the absorbance without treatment.

6.3 *In vitro* phototoxicity

The phototoxicity of samples was evaluated by similar procedure as above. After 12 h of incubation with medium containing samples, the plate with cells was irradiated with a 660 nm laser light for 15 min. The cells continued to incubate at 37 °C for 24 h, and the cell viability was also estimated using the MTT assay as described above.

4T1 Tumor and Animals Models

All animal experiments were approved by the Animal Experimental Ethics Committee and in accordance with the international ethical norms of animal experiments. Female BALB/c nude mice (4-6 weeks old) were raised in a pathogen free environment under controlled temperature (24 °C). The nude mice were then injected subcutaneously in the forelimb armpit area mice and allow the tumor grow to 100 mm^3 before experiments.

Tumor volume = (tumor length) × (tumor width)^2/2.

In Vivo Fluorescence Imaging

The solution of **TPP-Ad$_4$/CD$_2$/PEG** (200 μL, 1 mg/mL) were injected into five nude mice *via* the tail vein when the tumors grew to 100 mm^3. *In vivo* fluorescence imaging was performed at 1 h, 3 h, 6 h, 12 h and 24 h after injection, respectively.

In Vivo Photodynamic Therapy

Tumor-bearing mice were divided into six groups (5 mice in each group) randomly for different treatments: (1) saline alone; (2) TPP-Ad$_4$/CD$_2$; (3) TPP-Ad$_4$ with light; (4) TPP-Ad$_4$/CD with light; (5) TPP-Ad$_4$/CD$_2$ with light; (6) TPP-Ad$_4$/CD$_2$/PEG with light. The sample solution of different groups (200 μL, 1 mg/mL) was injected into the mice *via* the tail vein and irradiated with a 660 nm laser (0.5 W cm^{-2}) for 10 min after 24 h. Tumor volume and mouse body weight were recorded every two days after injection. The mice were dissected after two weeks; tumor and major organs were excised.

Ex Vivo Histological Staining

For histological analysis, the excised tumor and organs were fixed with 4% paraformaldehyde solution for 24 h. Tissue samples were made into 5 mm thick paraffin sections according to standard protocols and stained with hematoxylin and eosin (H&E) for microscopic observation.

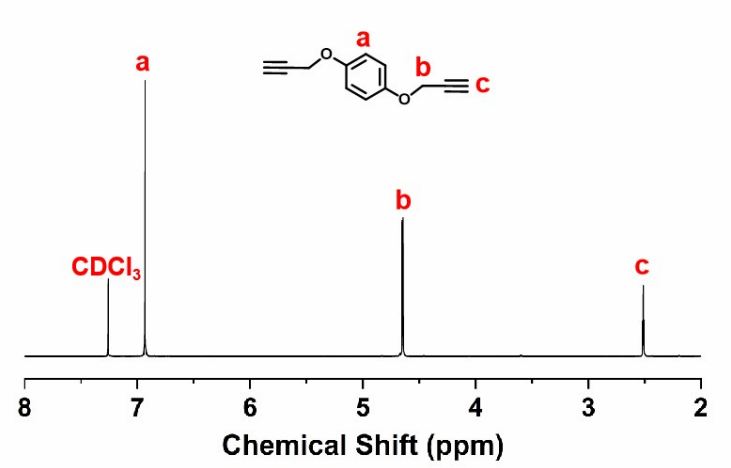


Fig. S10 ^{1}H NMR spectrum of ***G***.

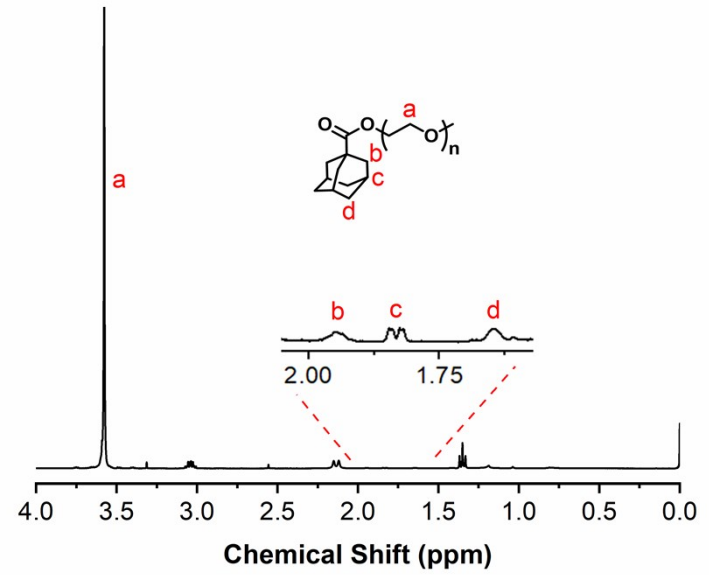


Fig. S11 ^{1}H NMR spectrum of **PEG-Ad**.

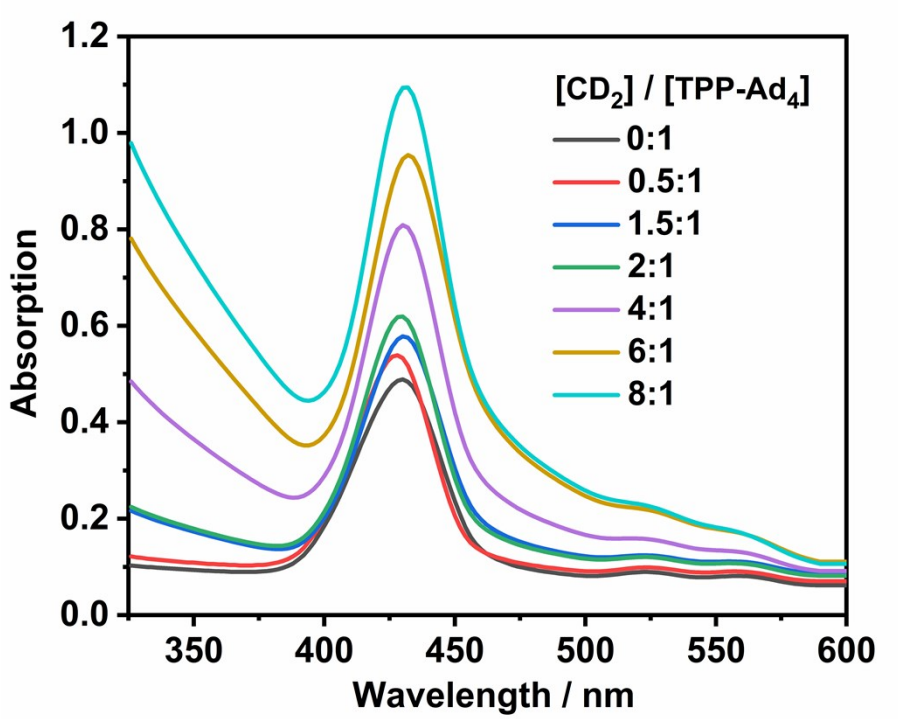


Fig. S12 UV-*vis* absorption spectra of TPP-Ad_4 (1.0×10^{-5} M, [Ad] = 4×10^{-5} M) in aqueous solution with various concentrations of β-CD_2 (0, 0.5, 1.5, 2.0, 4.0, 6.0, 8.0 $\times10^{-5}$M,[CD] = 0, 1.0, 3.0, 4.0, 8.0, 12.0, 16.0×10^{-5} M).

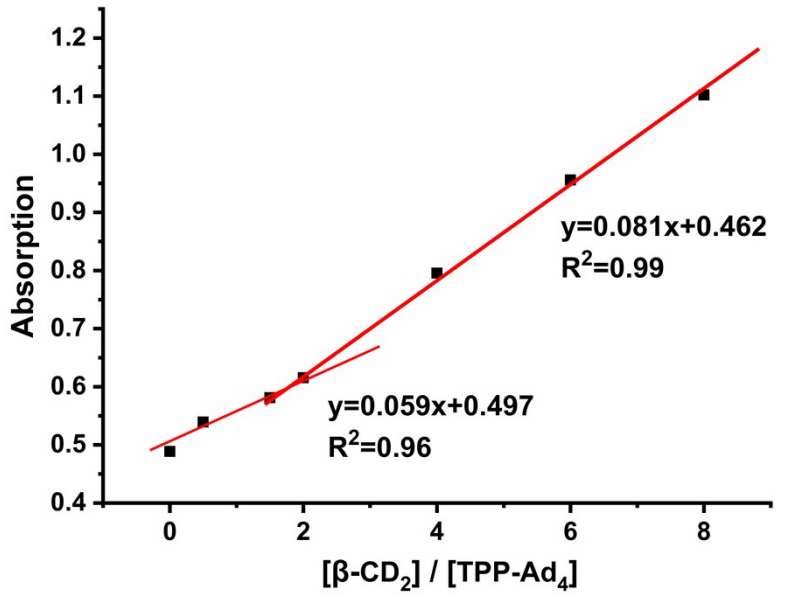


Fig. S13 Molar ratio plot for β-CD_2 and TPP-Ad_4 (according to UV-*vis* titration), indicating a 2:1 stoichiometry.

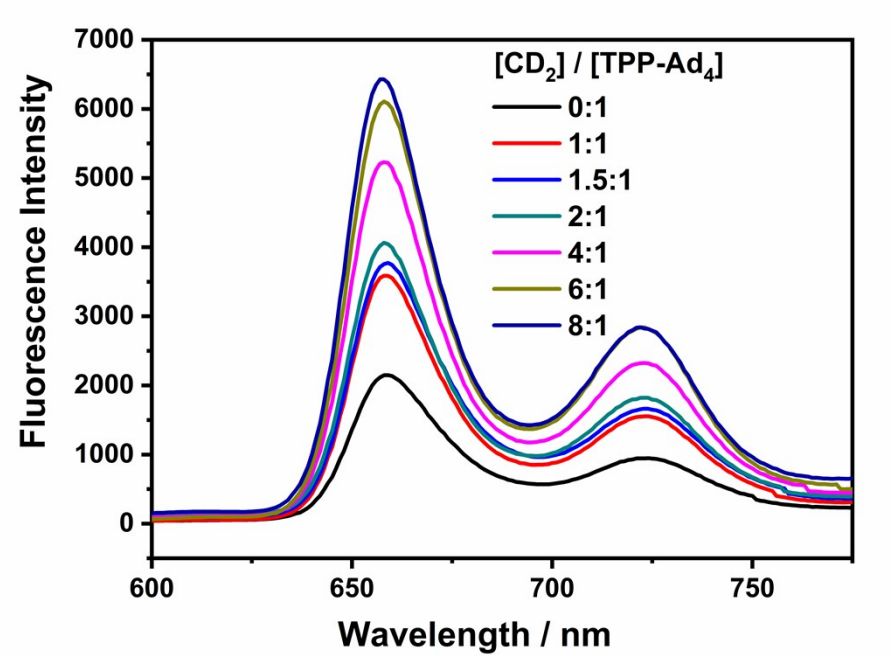


Fig. S14 The fluorescence intensity changes of the mixture of TPP-Ad_4 (1×10^{-5} M, [Ad] = 4×10^{-5} M) and β-CD_2 in aqueous solution with different concentrations of β-CD_2 (0, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0×10^{-5} M, [CD] = 0, 2.0, 3.0, 4.0, 8.0, 12.0, 16.0×10^{-5} M).

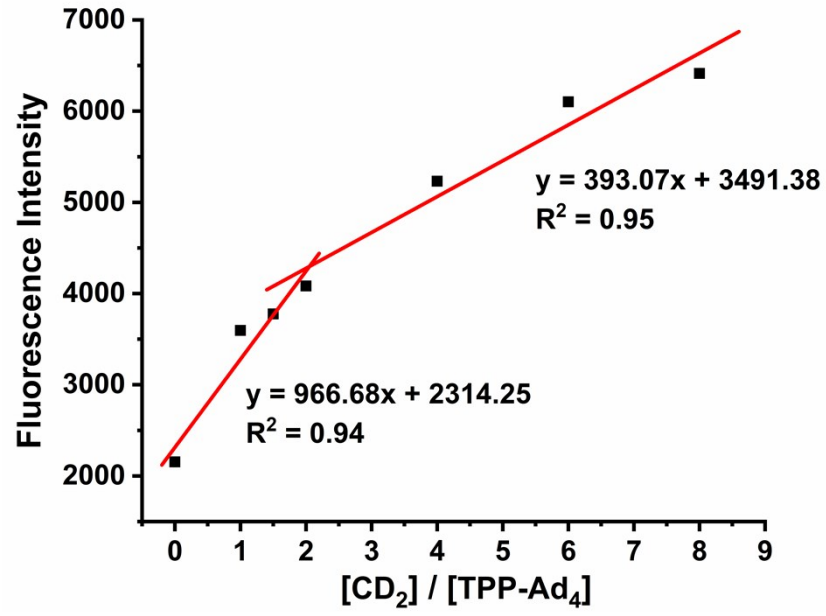


Fig. S15 Molar ratio plot for β-CD_2 and TPP-Ad_4, indicating a 2:1 stoichiometry.

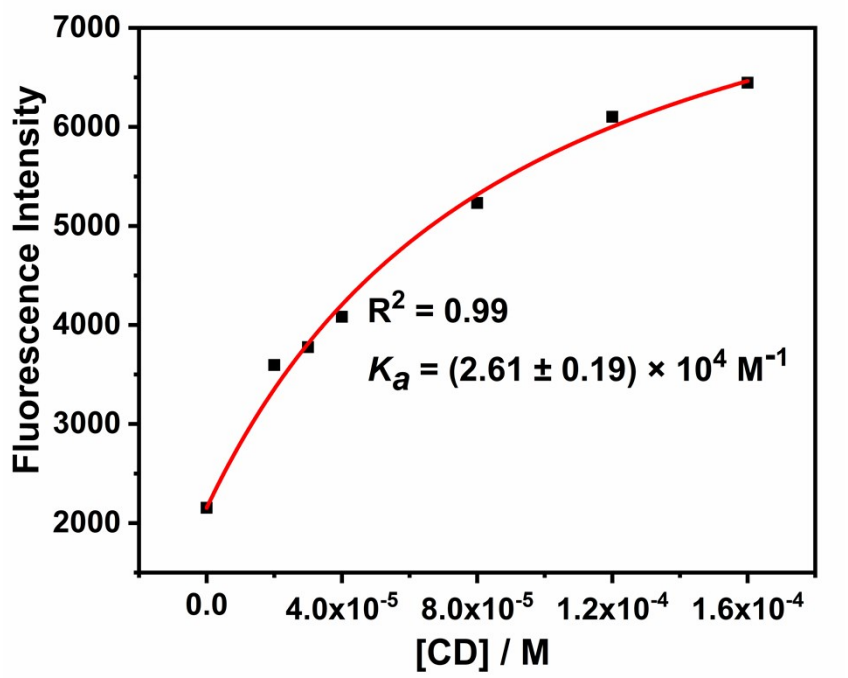


Fig. S16 The fluorescence intensity changes upon addition of β-CD_2 ([CD] = 0, 2.0, 3.0, 4.0, 8.0, 12.0, 16.0×10^{-5} M). The red solid line was obtained from the non-linear curve-fitting.

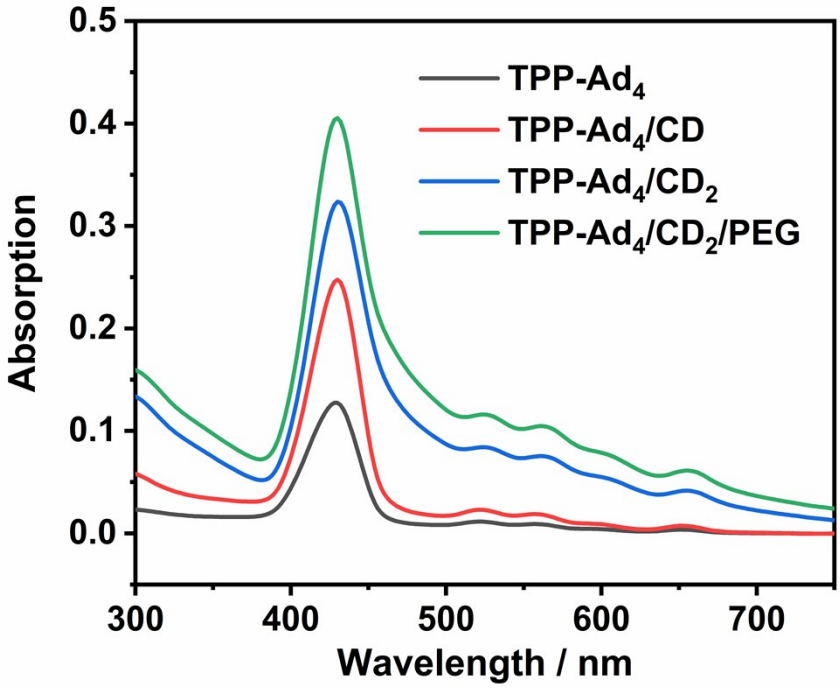


Fig. S17 UV-*vis* absorption spectra of **TPP-Ad_4**, **TPP-Ad_4/CD**, **TPP-Ad_4/CD_2** and **TPP-Ad_4/CD_2/PEG** in aqueous solution.

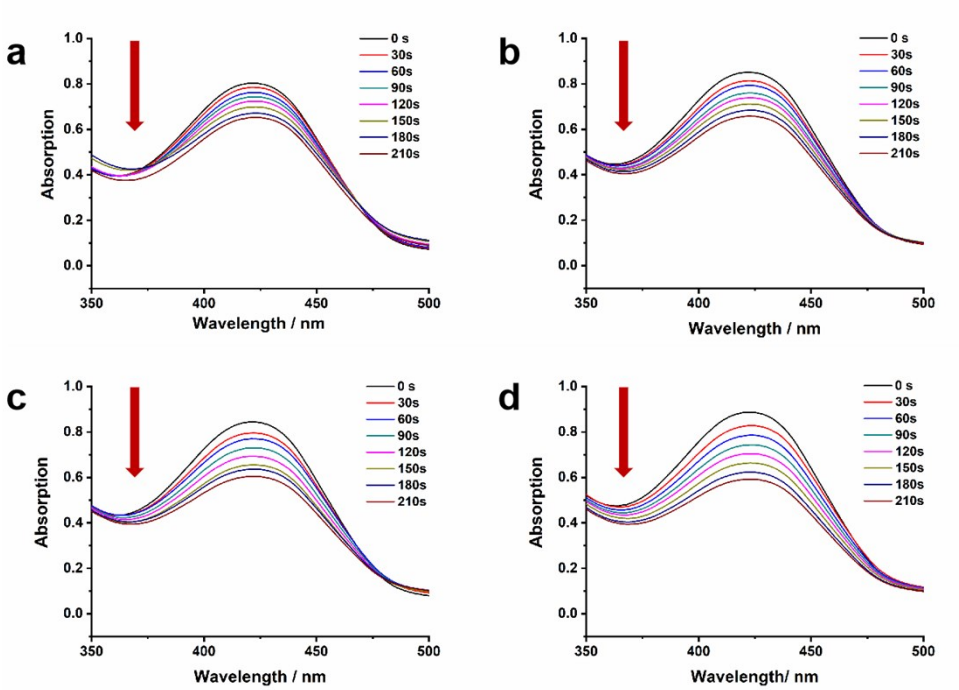


Fig. S18 UV-*vis* spectra changes of DPBF in aqueous solution of **(a) TPP-Ad$_4$**, **(b) TPP-Ad$_4$/CD**, **(c) TPP-Ad$_4$/CD$_2$** and **(d) TPP-Ad$_4$/CD$_2$/PEG** under a 660 nm laser light, respectively.

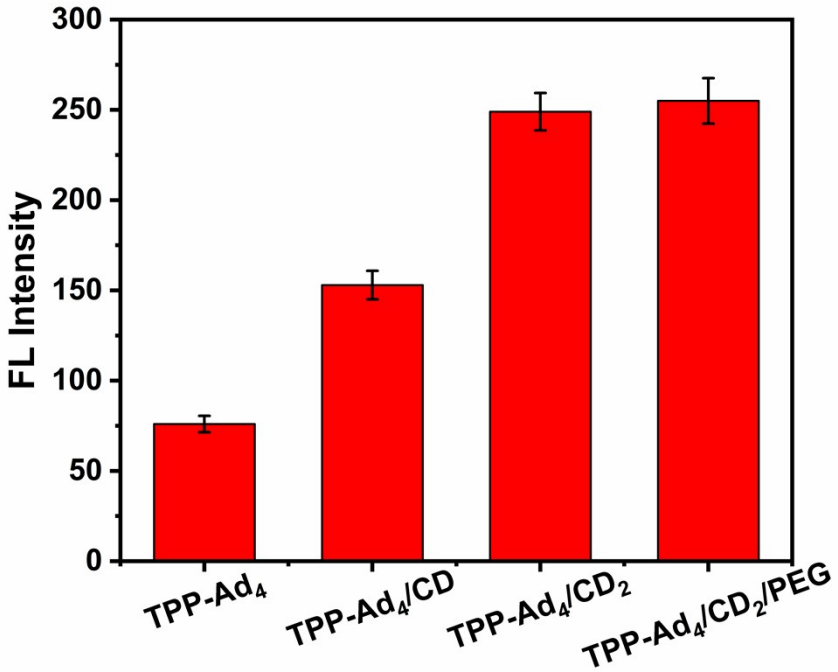


Fig. S19 The average fluorescence intensity of TPP-Ad$_4$, TPP-Ad$_4$/CD, TPP-Ad$_4$/CD$_2$ and TPP-Ad$_4$/CD$_2$/PEG from the CLSM images of cells cultured for 24 h.

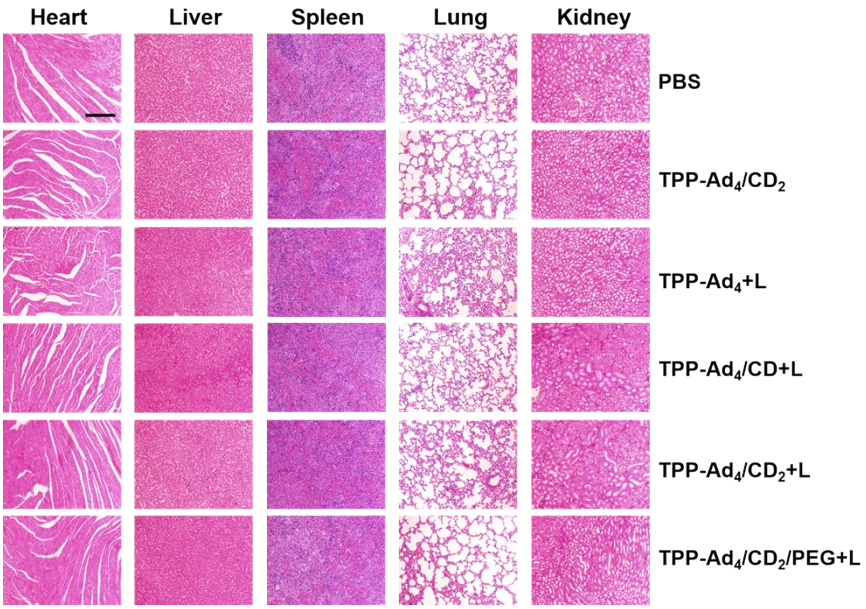


Fig. S20 H&E stained major organs slices in different treatment groups. Scale bar: 300 μm.

Reference：

1. J. Tian, L. Xia, J. Wu, B. Huang, H. Cao and W. Zhang, *ACS Appl. Mater. Interfaces*, 2020. DOI: 10.1021/acsami.0c07333.