Supporting Information

Experiments

1. Materials

All of the chemicals used were of analytical grade and were used as received without further purification. 1,1,1-Tris(hydroxymethyl)ethane (TME), propiolic acid, p-toluenesulfonic acid were purchased from Adamas Co., Ltd., 10-Hydroxycamptothecin (HCPT), camptothecin (CPT), tetrahydrocurcumin (THC)，daidzein (DAI) and honokiol (HNK) were purchased from Shanghai Bidepharm Co., Ltd.. Toluene, and other solvents were obtained from Sinopharm Chemical Reagent Co., Ltd. HeLa, 4T1, LO2 and H9C2 cells were obtained from the American Type Culture Collection (ATCC). High-glucose Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum (FBS), and trypsin were purchased from Gibco BRL, and 4,6-diamidino-2-phenylindole dihydrochloride (DAPI, 98%) was obtained from Bioworld Technology Co. The CCK-8 cell viability assay kit was purchased from Beyotime Biotechnology Co., Ltd. Ultrapure water (18.2 $M \cdot cm^{-1}$) used throughout the experiments was obtained using a Millipore Milli-Q purification system.

2. Characterizations

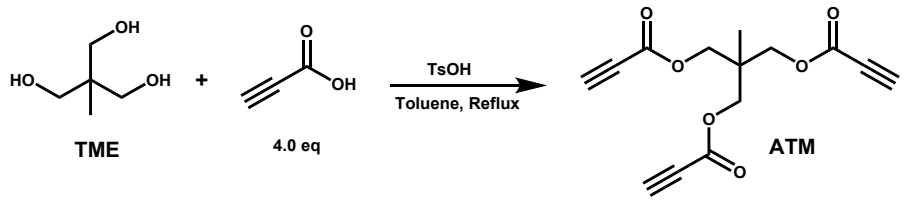
^1H nuclear magnetic resonance (^1H-NMR) spectra were performed on AVANCE-III 400 spectrometer (Bruker, Switzerland). High-resolution TEM images were recorded on a JEOL-2100 electron microscope at 200 kV. Prior to analysis, the TEM samples were prepared by depositing 5 μL of the clarifying suspensions on a carbon film with a 230-mesh copper micro-grid in air at ambient temperature. Gel Permeation Chromatography (GPC) were recorded on a Advanced Polymer Chromatography (Waters Acquity APC，Malvern Omnisec Reveal). Ultraviolet–visible (UV–vis) absorption spectra were recorded on a Lambda 20 spectrometer (Perkin Elmer, Inc.). Fourier-transform infrared (FTIR) spectra were recorded on a Paragon 1000 (Perkin Elmer) spectrometer by KBr tableting method. Zeta (ζ) potential and particle sizes were measured using a Malvern Nano ZS90 (Malvern, UK) instrument. The cell culture viability was measured using a microplate reader (Thermo Fisher). The fluorescent

images of cells were determined on a STED SP8 confocal laser scanning microscopy (Leica, Germany). The apoptosis of cells was evaluated on a CytoFLEX flow cytometry (Beckman, USA). The fragmentation structure of degradation products of PHH in different conditions was determined by liquid chromatograph mass spectrometer (LC-MS) on WATERS I-Class VION IMS QTof.

3. Monomer and polymer preparation

3.1 Synthesis of ATM

The trimethylolethane tripropiolate (ATM) was synthesized according to a previously reported method. Briefly, trimethylolethane (1.20 g, 10 mmol), propiolic acid (2.80 g, 40 mmol) and TsOH (0.38 g, 2 mmol) were dissolved in 50 ml dry toluene in a 100 mL round-bottom flask equipped with a Dean–Stark device and then refluxed for 48 h at 125 °C. Afterward, the reaction mixture was concentrated, washed with 5% of $NaHCO_3$ solution (50 mL × 3) and water (50 mL × 1), and then dried with anhydrous $MgSO_4$ overnight. Crude products were filtered, and the solvent was re- moved by rotating evaporated. The crude product was recrystallized in n-hexane, a brown solid was obtained with a yield of 52.2% (1.44 g). IR (thin film), ν (cm^{-1}): 3249 (≡C-H stretching), 2111 (C≡C stretching), 1716 (C=O stretching), 1625, 1452, 1353, 1222, 1107, 946, 754. ^{1}H-NMR (400 MHz, DMSO-d_6), δ (TMS, ppm): 4.62 (s, 3H, ≡C-H), 4.12 (s, 6H, CH_2), 0.97 (s, 3H, CH_3).

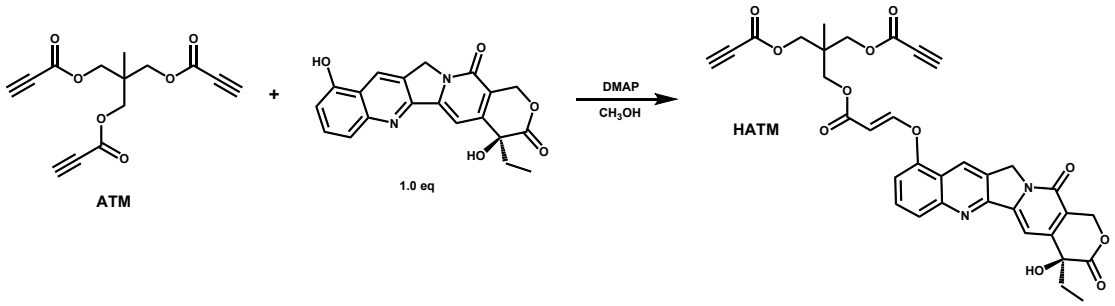


Scheme S1. Synthesis route of ATM

3.2 synthesis of HATM

As shown in the Scheme S2, HATM was synthesized according the following route: First, 0.165 g (0.6 mmol) of ATM and 0.109 g (0.3 mmol) of 10-HCPT were dissolved in 50 mL of DMF and stirred at 40 °C for 4 hours, DMAP was utilized as catalyst to accelerate the phenol-acylalkynyl click reaction. After removed the solvent by rotary evaporation, the residue was purified by silica gel column chromatography using a

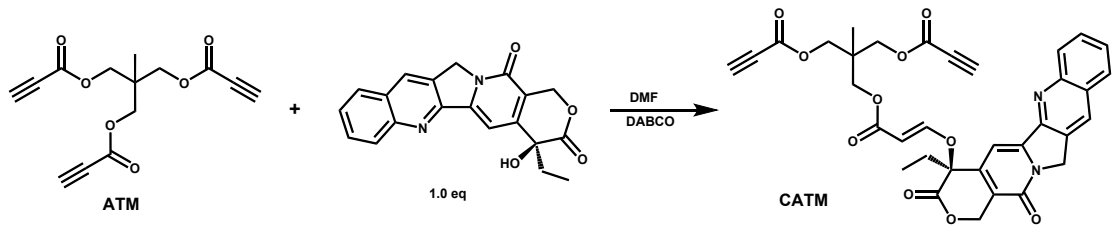
petroleum ether acetate (1:3) eluent, yielding a dark yellow powder.



Scheme S2. Synthesis route of HATM

3.3 synthesis of CATM

The synthesis of CATM was carried out using DABCO as a catalyst in order to improve the reaction efficiency (Scheme S3). 0.174 g (0.5 mmol) of CPT and 0.156 g (0.6 mmol) ATM was dissolved in 50 ml of DMF under stirring. Subsequently, 5.6 mg (0.05 mmol) DABCO in 0.5 mL DMF was added slowly dropwise and the reaction was carried out at 40 °C for 4 hours. Then, the excess ATM and catalyst DABCO can be removed by precipitation in water, followed by centrifugation and lyophilization, yielding a yellowish CATM powder.

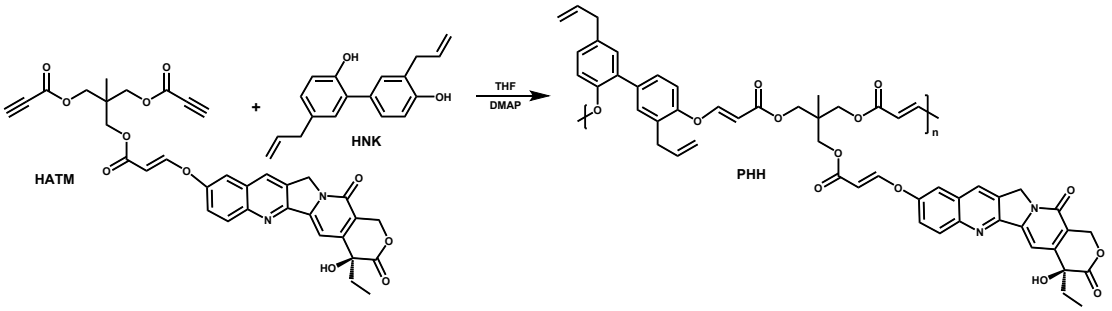


Scheme S3. Synthesis route of CATM

3.4 Preparation of PHH

As shown in Scheme S4, 0.321 g (0.6 mmol) of HATM was dispersed in 4.8 mL of THF, and 0.133 (0.5 mmol) of HNK was dissolved in 2 mL of THF, then mixed the two solutions at room temperature. 0.02 mmol of DABCO in 0.2 mL THF was added dropwise as catalyst under stirring and keep stirring at 30 °C overnight. Then, the mixture was transferred to a dialysis bag (MWCO=10 kDa) and dialyzed in ultrapure water/THF (10:1, V/V) for 72h, and the yellow powder product was obtained after freeze-drying. PHH with different molecular weights were also obtained by adjusting

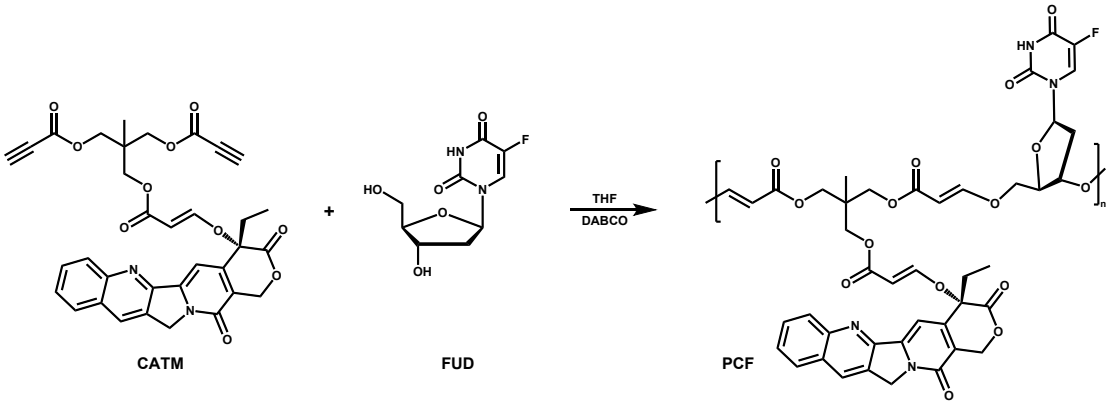
the ratios of HATM and HNK from 1.2:1, 1.5:1 to 1.7:1.



Scheme S4. Synthesis route of PHH

3.5 Preparation of PCF

In order to verify that this click-polymerization can be used for the preparation of a variety of polyprodrugs, FUD and other drugs were subjected to preparation different dual-drug combination polyprodrugs, the experimental procedure was as follows: 0.125 g (0.2 mmol) of CATM was dispersed in 12 mL of THF and 0.074 (0.3 mmol) of FUD was dissolved in 10 mL of THF then mixed the two solutions at room temperature. 0.01 mmol of DABCO in 0.2 mL THF was added dropwise under stirring and keep stirring at 30 °C overnight. Then, the mixture was transferred to a dialysis bag (MWCO=10 kDa) and dialyzed in ultrapure water/THF (10:1, V/V) for 72h, and the white powder product was obtained after freeze-drying.

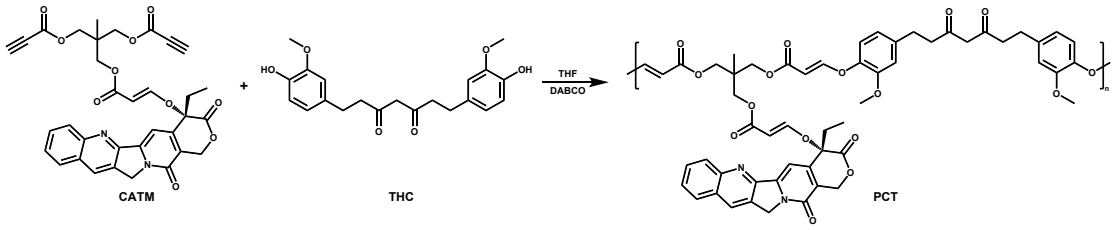


Scheme S5. Synthesis route of PCF

3.6 Preparation of PCT

As shown in Scheme S6, 0.125 g (0.2 mmol) of CATM was dispersed in 12 mL of THF and 0.112 g (0.3 mmol) of THC was dissolved in 10 mL of THF, then mixed the two solutions at room temperature. 0.01 mmol of DABCO in 0.2 mL THF was added dropwise under stirring and keep stirring at 30 °C overnight. Then, the mixture was

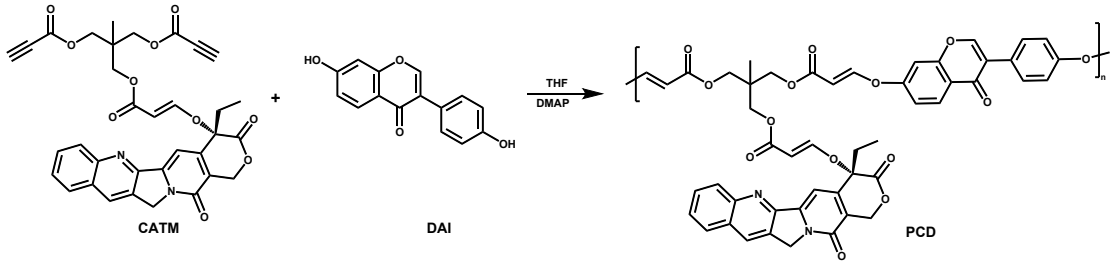
transferred to a dialysis bag (MWCO=10 kDa) and dialysed in ultrapure water/THF (10:1, V/V) for 72h, and the light-yellow powder product was obtained after freeze-drying.



Scheme S6. Synthesis route of PCT

3.7 Preparation of PCD

As shown in Scheme S7,0.125 g (0.2 mmol) of CATM was dispersed in 12 mL of THF and 0.109 g (0.3 mmol) of DAI was dissolved in 10 mL of THF, then mixed the two solutions at room temperature. 0.01 mmol of DMAP in 0.2 mL THF was added dropwise under stirring and keep stirring at 30 °C overnight. Then, the mixture was transferred to a dialysis bag (MWCO=10 kDa) and dialysed in THF/DMF (10:1, V/V) for 72h, and the yellow powder product was obtained after freeze-drying.



Scheme S7. Synthesis route of PCD

3.8 Preparation of PHH nanoparticles

10 mg of PHH was dissolved in 0.1 mL of DMSO, and then added 10 mg of DSPE-PEG-5000. The resulting mixed solution was added drop by drop to 0.9 ml of water under vigorous stirring in 1 min to obtain 10 mg/mL of PHH nanoparticles dispersion.

4. pH-responsive drug release of PHH

The PHH solution was dispersed in DI water and transferred to dialysis tube (MWCO = 5000 Da) and then placed in PBS with different pH (5.0, 6.5, 7.4) and shaken at 200 rpm and 37 ℃. At every time point, 2 mL dialysate was replaced by 2 mL fresh PBS. The cumulative releases of HCPT were calculated at 384 nm according to

calibrate curves.

5. Cell experiments

5.1 Cell culture and cytotoxicity studies

In a typical procedure, tumor cell of 4T1, HeLa and normal cell of L929, LO2 (from ATCC) were cultured in DMEM containing 10% FBS and 1% antibiotics (penicillin 50 units·mL^{-1}, streptomycin 50 units·mL^{-1}) at 37 °C, 5% CO_2. In the cytotoxicity test, cells were seeded in 96-well plates with a density of 1×10^4 cells per well and cultured for 24 h. Then the cells were incubated with HCPT, HNK and PHH at different concentration for 24 h. After washing with PBS, each well was incubated in fresh medium with 10 μL of CCK-8 reagent for 4 h. The cell viability was determined by absorption at 450 nm using a microplate spectrophotometer. We used untreated cells as controls and screened five replicates for each condition.

5.2 Cell live/dead imaging

Cell uptake behaviors were studied by confocal laser scanning microscopy (CLSM). 4T1, Hela, LO2 and L929 cells were inoculated in confocal culture dishes and cultured in DMEM medium with 5×10^4 cells per well. After incubation for 24 h, discarded the DMEM medium and the sample HCPT、HNK、HCPT+HNK diluted with medium was added, the concentration of drugs were calculated as 50 μg·mL^{-1}, and then incubated 24h. Followed with the culture medium removed and the cells were stained using FDA/PI for 30 min.

5.3 Flow Cytometry

To further evaluate the apoptosis induced by HCPT or PHH, 4T1, HeLa and L929 cells were seeded in 6-wells plates at a density of 1.0×10^6 cells per well with complete DMEM culture medium and incubated for 24 h. The HCPT and PHH (HCPT concentration: 10 μg·mL^{-1}) were then added and incubated for another 12 h, and the cells were washed with PBS twice and collected by centrifugation (800 rpm, 2 min). Finally, the cells were dispersed in staining buffer, 5 μL of Annexin FITC and 10 μL of PE dyestuff was then added and incubated for 20 min under light-proof conditions for flow cytometry test.

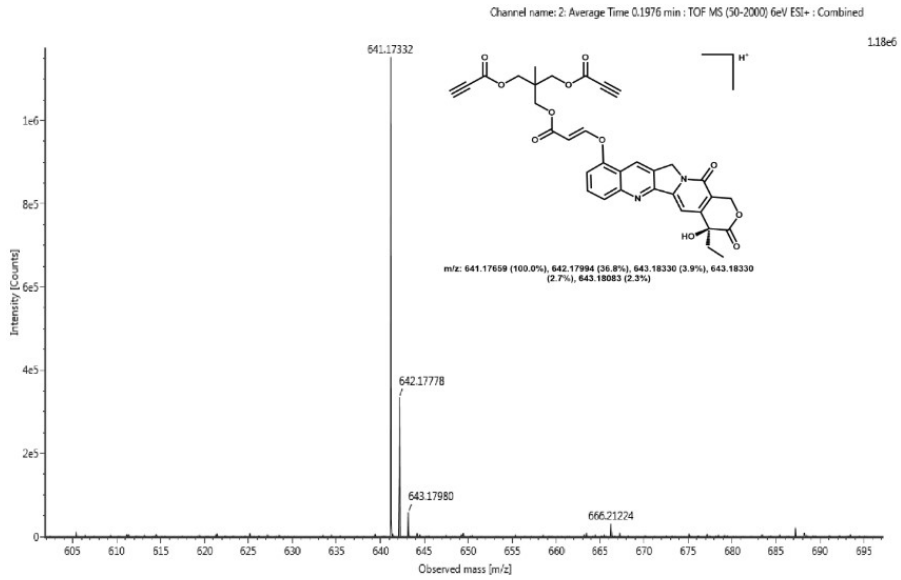


Figure S1. High Resolution Mass Spectrometry of HATM.

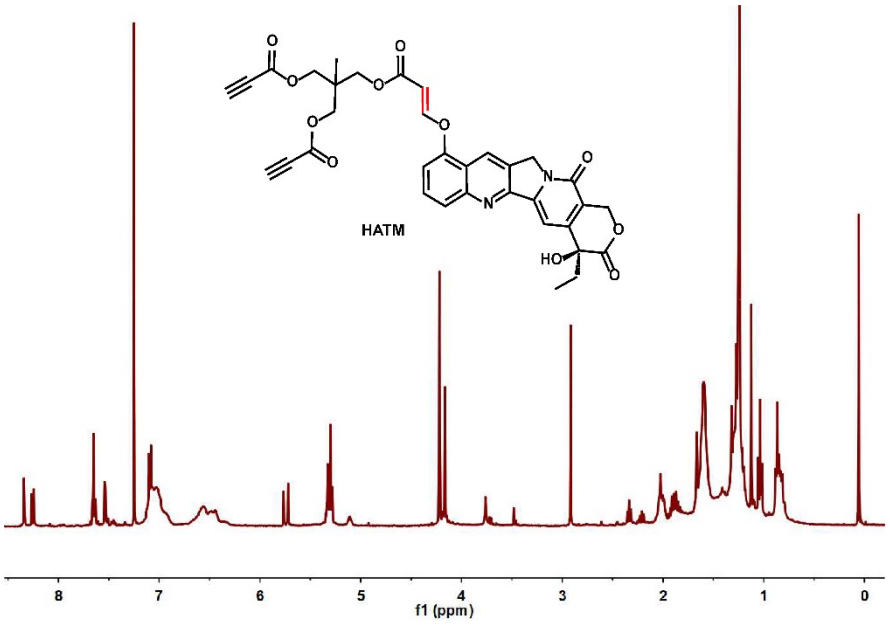


Figure S2. ^{1}H-NMR spectrum of HATM

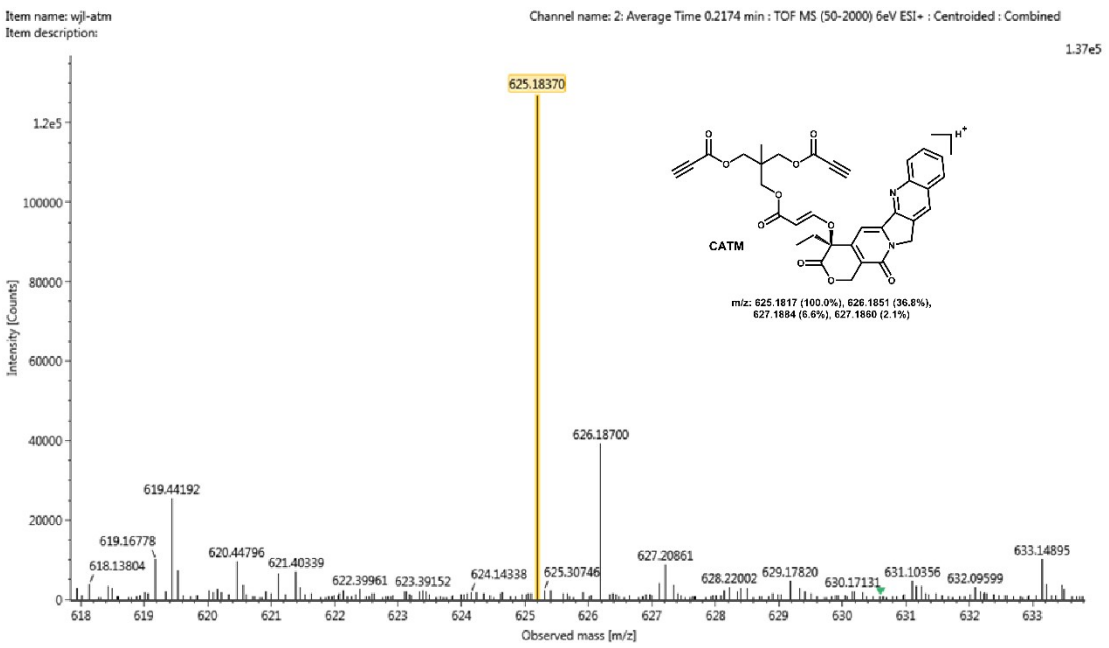


Figure S3. High Resolution Mass Spectrometry of CATM.

Figure S4. ^{1}H-NMR spectrum of CATM.

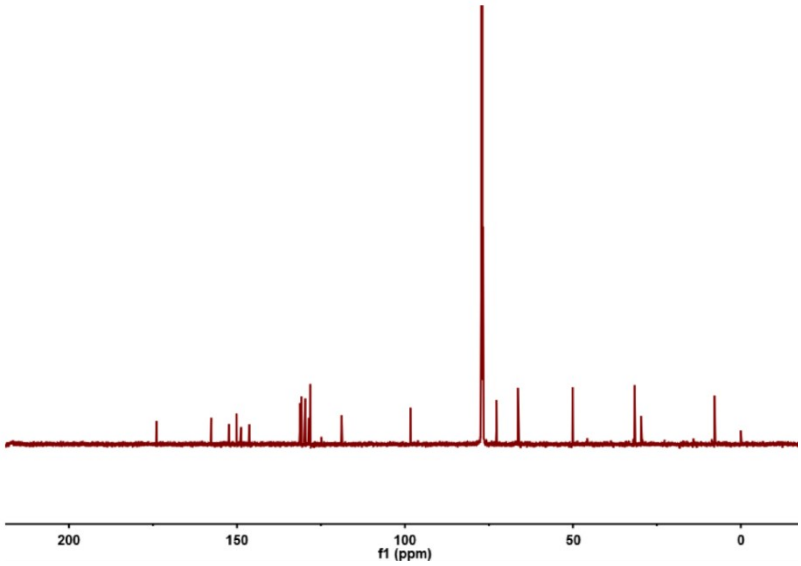


Figure S5. ^{13}C-NMR spectrum of CATM.

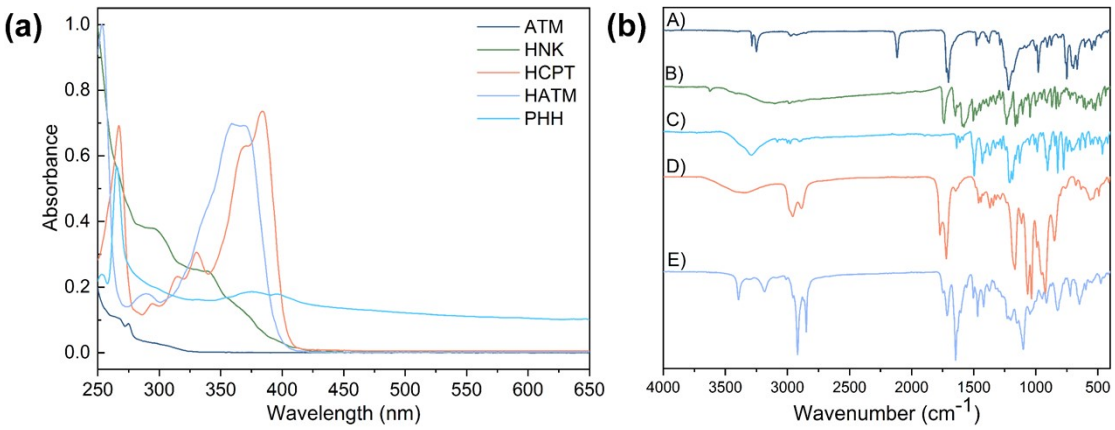


Figure S6. (a) UV-vis absorption and (b) FT-IR spectrums of A) ATM, B) HCPT, C) HNK, D) HATM, E) PHH.

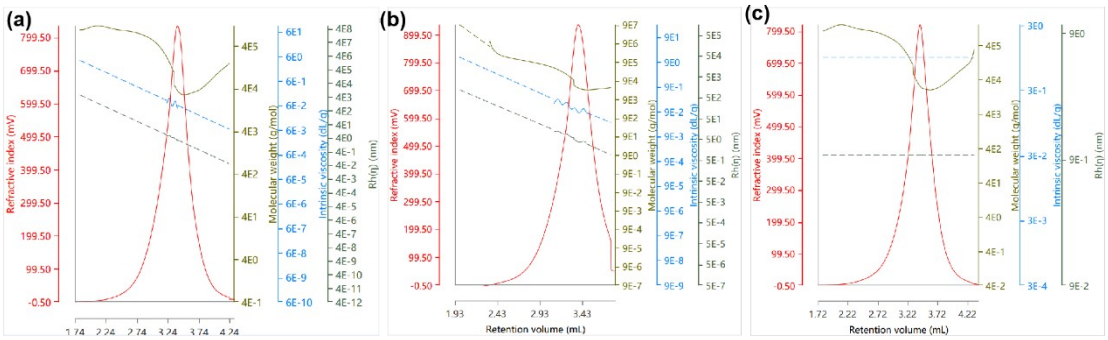


Figure S7. GPC spectra of PHH with different molecule weight (M_n) and PDI. (a) $PHH_{1.2}$, (b) $PHH_{1.5}$ and (c) $PHH_{1.7}$.

Table. S1 Properties of the prepared polyprodrugs.

Entry	Drug monomer	Polymer	DLR	M_w	M_w/M_n (PDI)
1	HCPT+HNK (1:1.2)	$PHH_{1.2}$		$1.91*10^5$	3.42
2	HCPT+HNK (1:1.5)	$PHH_{1.5}$	69.54%	$1.85*10^5$	3.62
3	HCPT+HNK (1:1.7)	$PHH_{1.7}$		$1.38*10^5$	4.28

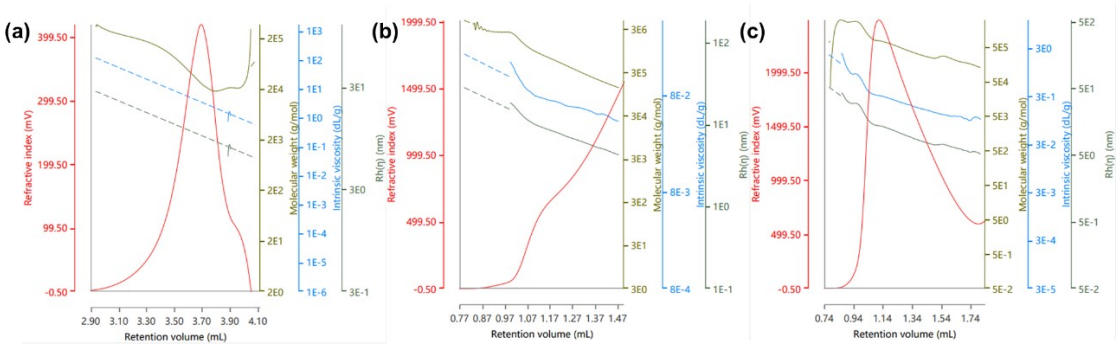


Figure S8. GPC spectra of polyprodrugs. (a) PCF that containing drugs of CPT and FUD, (b) PCD that containing drugs of CPT and DAI; (c) PCT that containing drugs of CPT and THC.

Table. S2 Properties of the prepared polyprodrugs.

Entry	Drug	Polymer	DLR	M_w	M_w/M_n (PDI)
4	CPT + FUD	PCF	68.27%	58759	1.663
5	CPT + DAI	PCD	68.56%	497121	1.456
6	CPT + THC	PCT	72.29%	375168	1.580

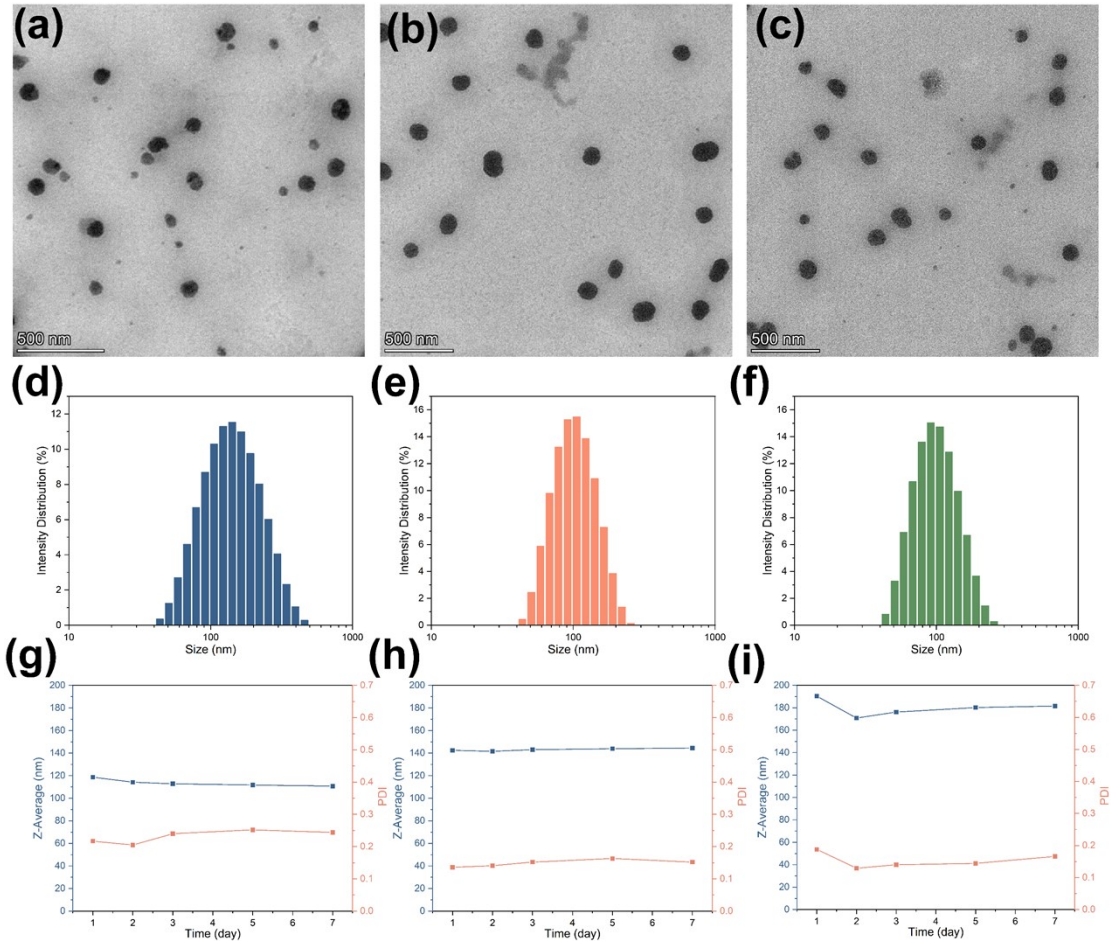


Figure S9. TEM images, particles size distribution and colloids stability of the prepared PHH nanoparticles based on different monomer ratio. (a, d, g) $PHH_{1.2}$, (b, e, h) $PHH_{1.5}$ and (c, f, i) $PHH_{1.7}$, (a-c) TEM images, (d-f) size distribution, (g-i) average hydrodynamic diameter and PDI at different time point of corresponding polyprodrug nanoparticles.

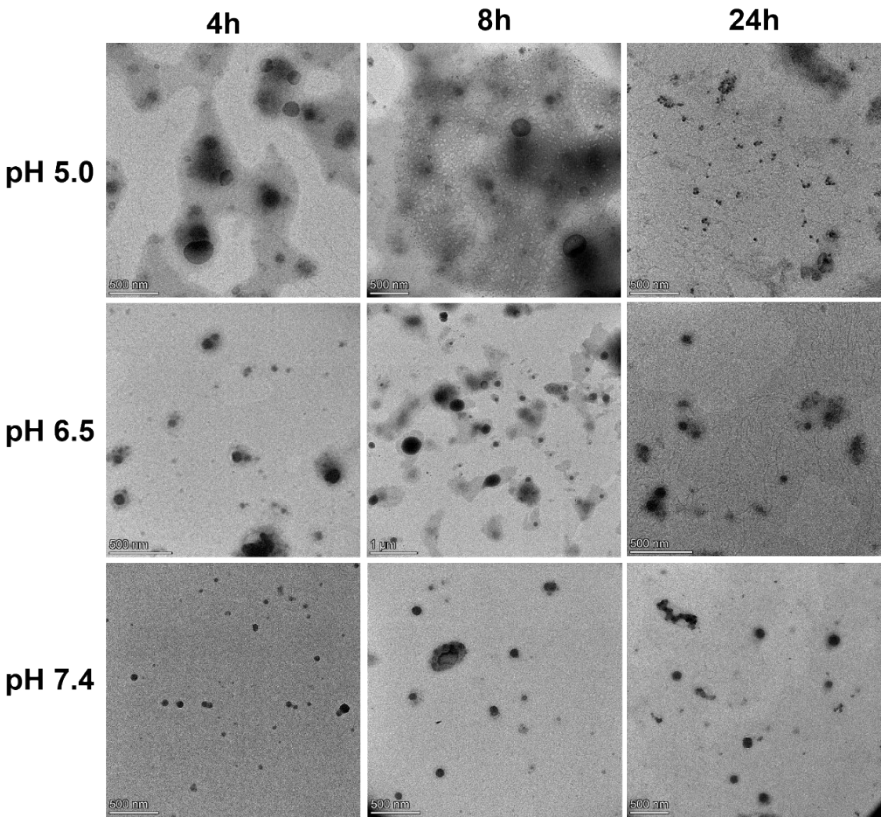


Figure S10. TEM images of pH-responsive degradable of $PHH_{1.5}$ nanoparticles in different PBS solutions after different time.

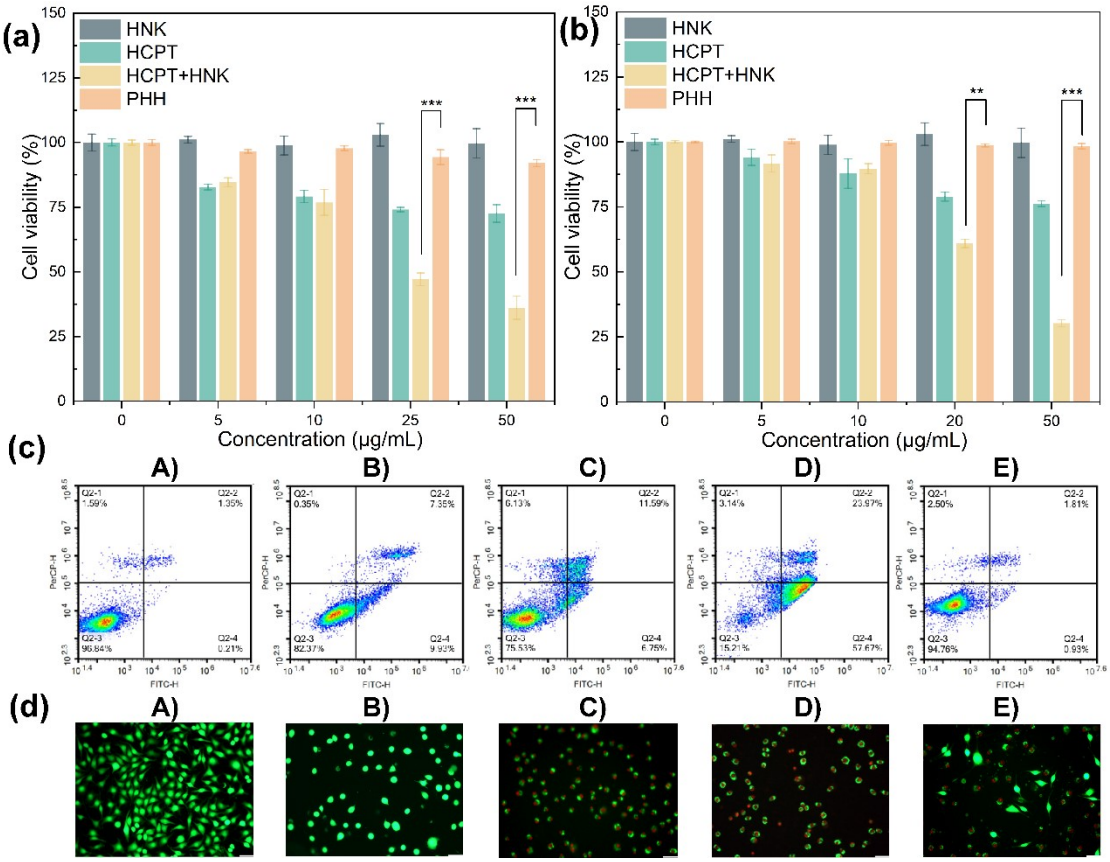


Figure S11. Physiological safety of the prepared polyprodrug PHH. Cell viability of (a) LO2 and (b) L929 cells after incubated with HNK, HCPT, HCPT+HNK and PHH as a function of concentration for 24 h. (*P < 0.05, **P < 0.01, ***P < 0.001) (c) Flow cytometry and (d) confocal laser scanning microscopy (CLSM) images of L929 cells after incubation with A) PBS, B) HNK, C) HCPT, D) HCPT+HNK, E) PHH for 24 h. Q2-4, necrotic cells; Q2-2, late apoptotic cells; Q2-1, early apoptotic cells; and Q2-3, living cells. Red fluorescence means death cells, green fluorescence means living cells. Scale bar = 50 μm.