Supporting Information for

A Supramolecular Nanovehicle toward Systematic, Targeted Cancer and Tumor Therapy

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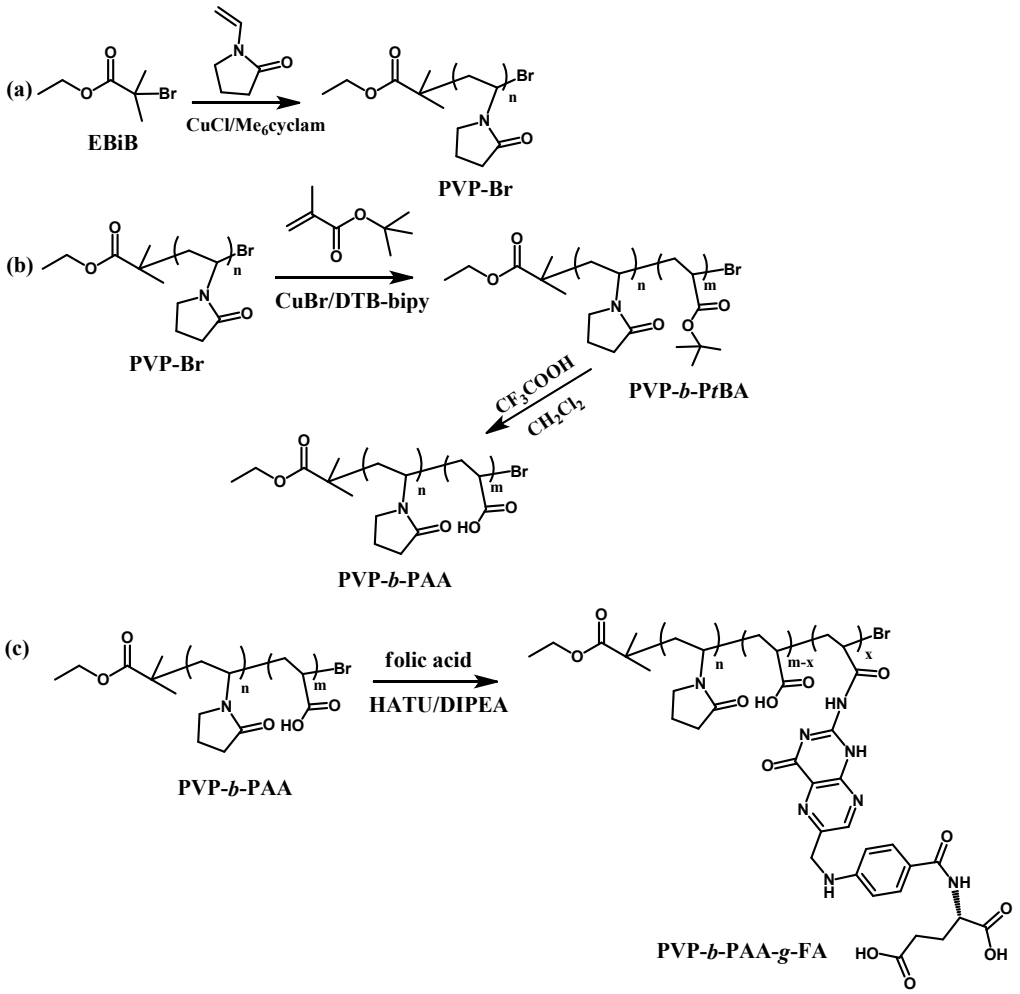
Figure S14. Drug Effect on apoptosis of HepG2 cells by flow cytometry: (A) blank, (B) ZnPc, (C) DOX, (D) ZnPc-DOX/SNV. The results are representative of three independent experiments.

Figure S15. *In vivo* fluorescence imaging of mice before intravenous injection with ZnPc-DOX/SNV and ZnPc-DOX/PVP-Br.

Table S1. Summary of polymer parameters

Experimental section

General polymerization procedure. Atom transfer radical polymerization (ATRP) of *N*-vinylpyrrolidone (NVP) was carried out using 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetra-azacyclo-tetradecane (Me_6Cyclam) as ligand in butanone-water mixture. The sequential polymerization gave a kind of block copolymer: PVP-b-PAA. The grafting of folic acid (FA) onto PVP-*b*-PAA yielded the final copolymer PVP-*b*-PAA-*g*-FA as a light yellow powder (Scheme S1).



Scheme S1. Synthesis route of PVP-*b*-PAA-*g*-FA: (a) EBiB, NVP, 65 °C, 24 h; (b) PVP-Br, *t*BA, 90 °C, 10 h; PVP-*b*-P*t*BA, CH_2Cl_2/CF_3COOH, 25 °C, 24 h; (c) PVP-*b*-PAA, folic acid, HATU/DIPEA, 25 °C, 12 h.

Polymerization of PVP-Br. Polymerization of PVP-Br was conducted with Me_6Cyclam as ligand. Typically EBiB (21.8 μL, 0.15 mmol), NVP (3.3 g, 30 mmol) and solvents (butanone/water, 1:3, 10 mL) were added to a reaction tube. After degassed by three freeze-pump-thaw cycles, Me_6Cyclam (42.6 mg, 0.15 mmol) and CuCl (8.46 mg, 0.085 mmol) were added into the tube under nitrogen. The solution was further deoxygenated by three freeze-pump-thaw cycles. The polymerization was carried out at 65 °C for 24 h. The reaction mixture was diluted with CH_2Cl_2 and passed through a basic alumina column to remove ATRP catalyst. The resulting solution was then concentrated and the precipitation into excess diethyl ether was dried under vacuum to yield polymer PVP-Br (Scheme S1a). The polymerization conversion was measured by gravimetric determination (conversion: 30%). ^{1}H NMR (400 MHz, D_2O) δ ppm: 1.52-1.68 (2H, $-CH_2-CH_2-C=O$); 1.97 (2H, $-CH_2-CH-N-$); 2.26-2.39 (2H, $-CH_2-CH_2-C=O$); 3.26 (2H, $-N-CH_2-CH_2$); 3.59 (1H, $-CH_2-CH-N-$).

Polymerization of PVP-*b*-PAA. The macroinitiator PVP-Br (500 mg, 0.075 mmol), *t*BA (960 mg, 7.5 mmol) and dry 2-butanone (3.0 mL) were added into a reaction tube. After degassed by three freeze-pump-thaw cycles, CuBr (10.7 mg, 0.075 mmol) and DTB-bipy (40.2 mg, 0.15 mmol) were added, followed by stirring for 10 min to ensure the formation of catalyst complex. The polymerization was carried out under N_2 atmosphere at 90 °C for 10 h. Subsequently, the solution was poured into excess methanol/water solvent (1:1, v/v) to induce the polymer precipitate. The precipitate was then dissolved in CH_2Cl_2 and purified using an alumina column to eliminate the used copper salt, followed by a recrystallization in methanol. After dried under vacuum, the block copolymer PVP-*b*-P*t*BA was obtained as a

white powder (Scheme S1b). The polymerization conversion was calculated from ^{1}H NMR spectrum of the reaction mixture (conversion: 60%). ^{1}H NMR (400 MHz, D_2O) δ ppm: 1.52–1.66 (2H, –*CH_2*–CH_2–C=O; 9H, –O–CH–*$(CH_3)_3$*); 1.97 (2H, –*CH_2*–CH–N–; 2H, –*CH_2*–CH–C=O); 2.27–2.41 (2H, –CH_2–*CH_2*–C=O; 1H, –CH_2–*CH*–C=O); 3.26 (2H, –N–*CH_2*–CH_2); 3.60 (1H, –CH_2–*CH*–N–).

PVP-*b*-P*t*BA (1.0 g) was placed in a Schlenk flask, which was evacuated and purged with nitrogen three times. Dichloromethane (20 mL) was added to dissolve the sample, followed by the addition of trifluoroacetic acid (TFA, 10 mL). The mixture was stirred at room temperature for 24 h. The solvent was removed from the resulting heterogeneous mixture, and the residual solid was washed with diethyl ether three times followed by drying under vacuum at room temperature for 10 h to give PVP-*b*-PAA (Scheme S1b). ^{1}H NMR (400 MHz, D_2O) δ ppm: 1.52–1.67 (2H, –*CH_2*–CH_2–C=O); 1.97 (2H, –*CH_2*–CH–N–; 2H, –*CH_2*–CH–C=O); 2.26–2.38 (2H, –CH_2–*CH_2*–C=O; 1H, –CH_2–*CH*–C=O); 3.28 (2H, –N–*CH_2*–CH_2); 3.60 (1H, –CH_2–*CH*–N–).

Synthesis of PVP-*b*-PAA-*g*-FA. PVP-*b*-PAA (300 mg, 1.8 mmol -COOH) was dissolved by dry DMF (5 mL) in a round-bottom flask. HATU (684 mg, 1.8 mmol) and DIPEA (0.35 mL, 3.6 mmol) were added under nitrogen. After agitation at room temperature for 30 min, FA (1.2 g, 2.7 mmol) in DMF was added dropwise. The solution was stirred for another 12 h to ensure a thorough reaction of PVP-b-PAA with FA. Finally, the solution was dialyzed against pure water followed by lyophilization to give the final copolymer PVP-*b*-PAA-*g*-FA (Scheme S1c). ^{1}H NMR (400 MHz, D_2O) δ ppm: 1.52–1.66 (2H, –*CH_2*–CH_2–C=O); 1.97 (2H, –*CH_2*–CH–N–; 2H, –*CH_2*–CH–C=O; 2H, –*CH_2*–CH_2–COOH); 2.24 (2H,

–CH_2–*CH_2*–C=O; 1H, –CH_2–*CH*–C=O; 2H, –CH_2–*CH_2*–COOH); 3.25 (2H, –N–*CH_2*–CH_2); 3.56 (1H, –CH_2–*CH*–N–); 4.24 (2H, –*CH_2*–NH–); 6.78–7.65 (aromatic H).

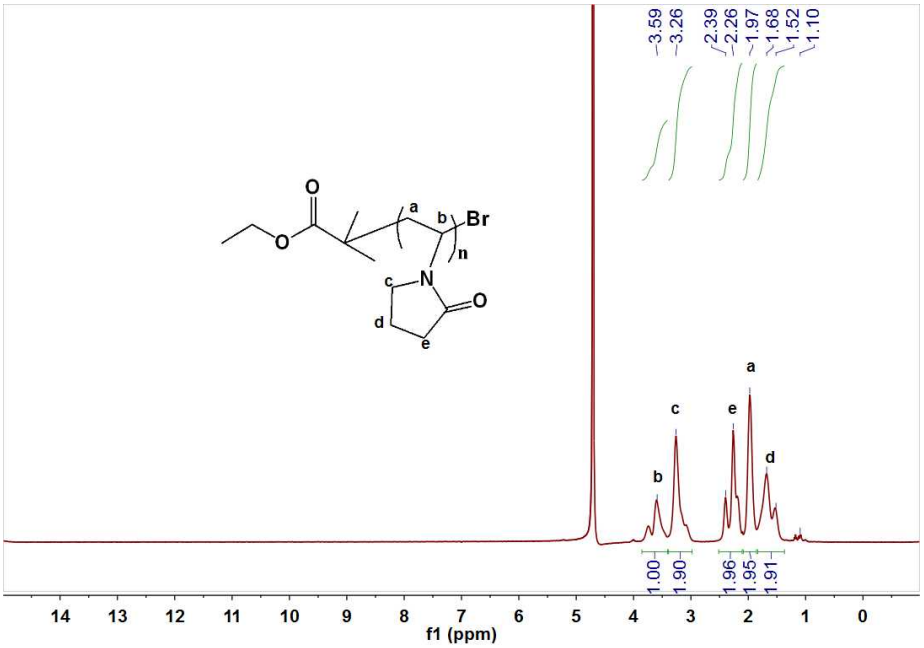


Figure S1. ^{1}H NMR spectrum of PVP-Br in D_2O.

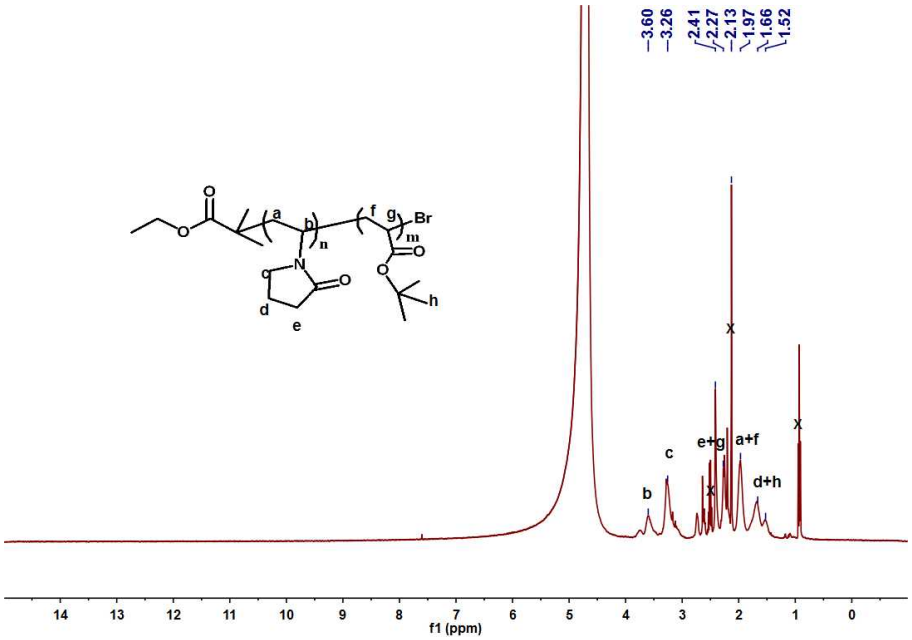


Figure S2. ^{1}H NMR spectrum of PVP-*b*-P*t*BA in D_2O.

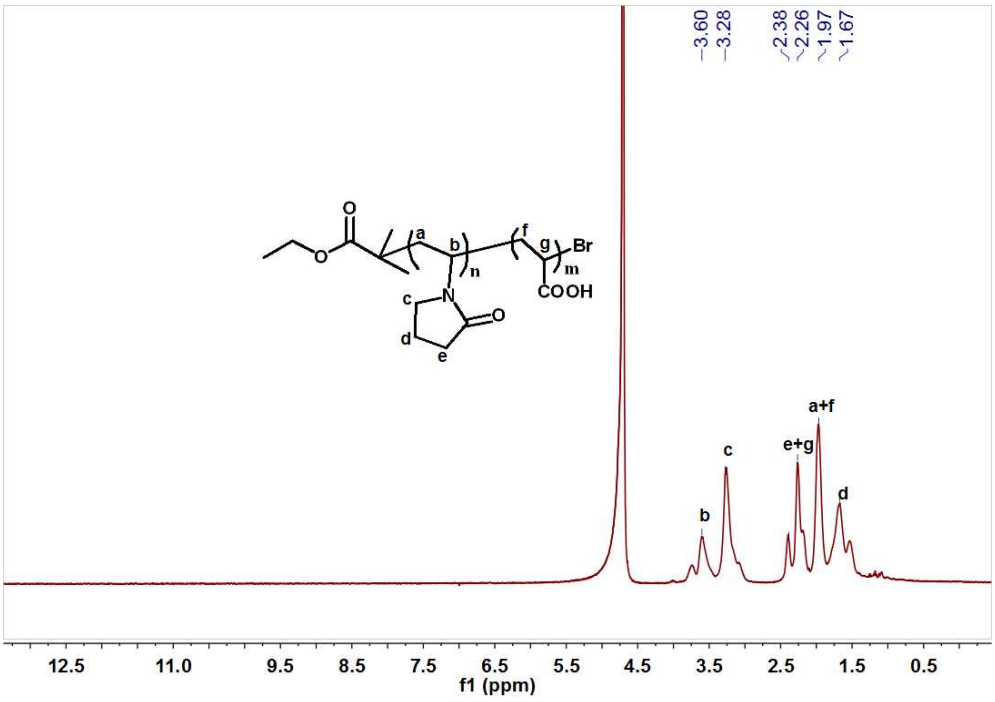


Figure S3. ^{1}H NMR spectrum of PVP-*b*-PAA in D_2O.

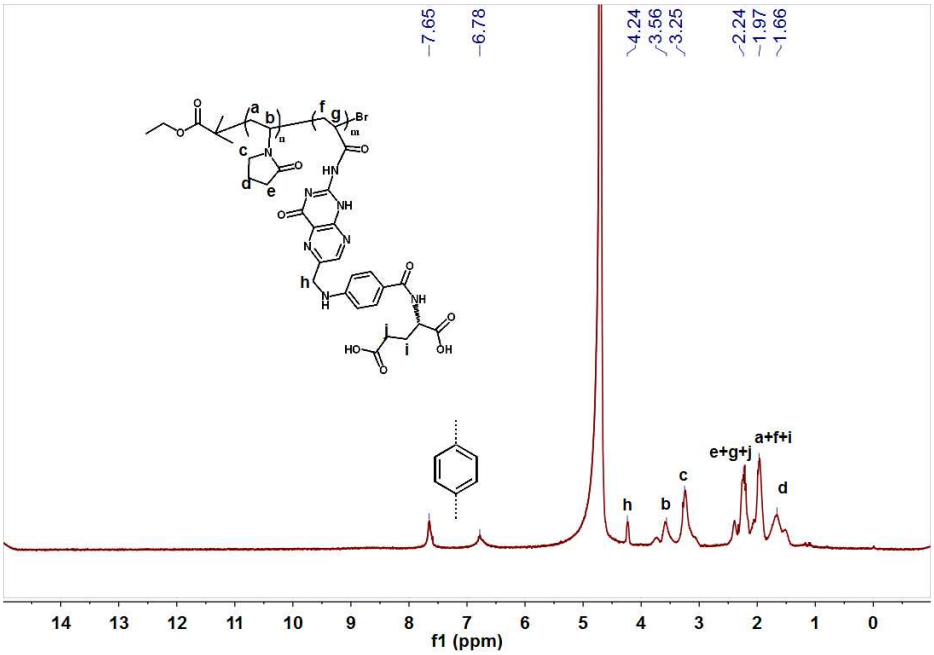


Figure S4. ^{1}H NMR spectrum of PVP-*b*-PAA-*g*-FA in D_2O.

Table S1 Summary of polymer parameters

Polymer	r.u.[a]	$M_{n,NMR}$[b] (g/mol)	$M_{n,GPC}$[c] (g/mol)	M_w/M_n
PVP-Br	60	6855	4200	1.07
PVP-b-P*t*BA	60/60	14535	13000	1.01
PVP-b-PAA	60/60	11175	11700	1.01
PVP-*b*-PAA-*g*-FA	60/60	37635	36100	1.08

[a] repeat units; [b] calculated from ^{1}H NMR spectra; [c] determined from GPC.

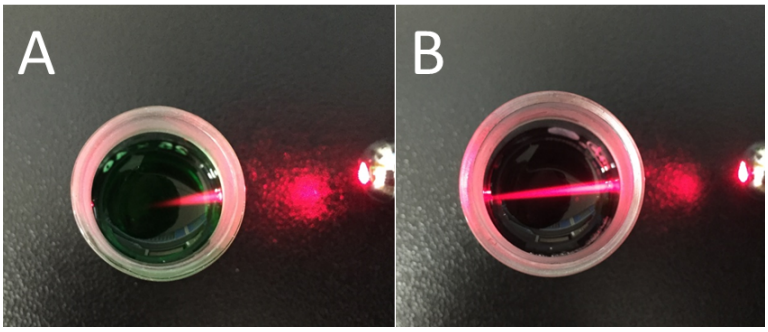


Figure S5. The Tyndall effect of (A) ZnPc/SNV and (B) ZnPc-DOX/SNV, indicating the formation of micelle by the introduction of DOX into a clear solution of ZnPc/SNV.

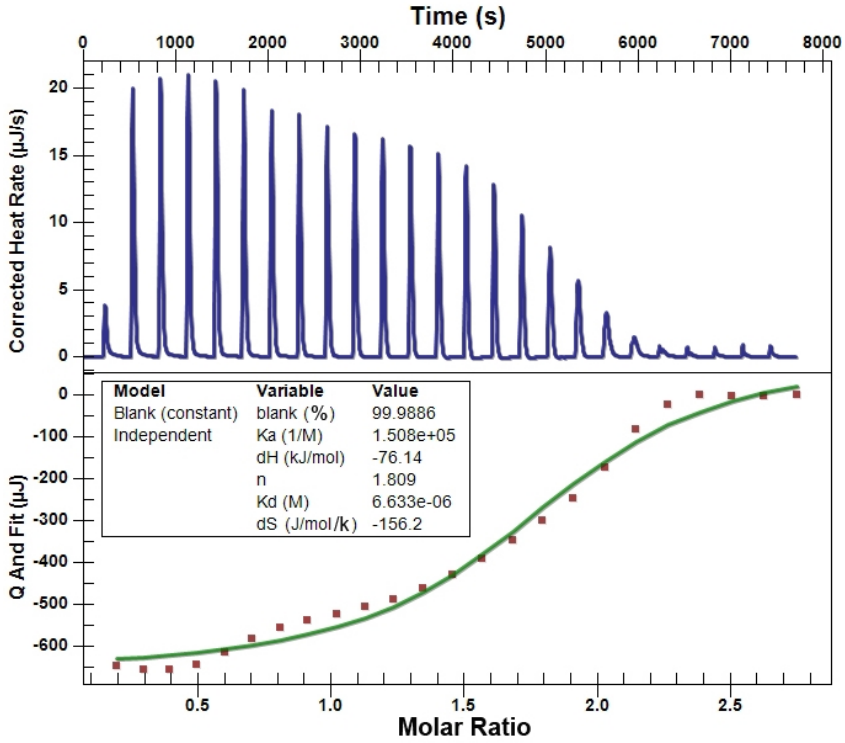


Figure S6. ITC titration measurements of PVP-Br (1.0×10^{-4} mol/L) and ZnPc (1.0×10^{-3} mol/L): the integrated heat for each injection as well as the fitting parameters are depicted (the green line represents the best fit obtained for an independent model).

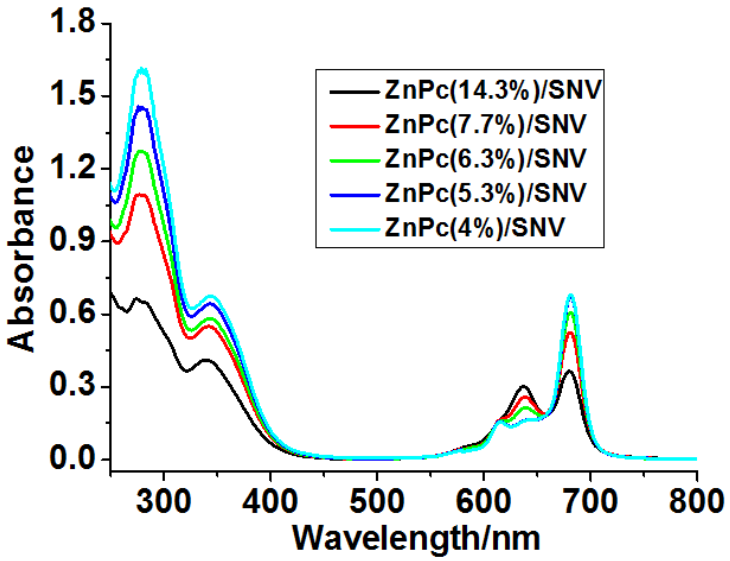


Figure S7. UV-vis absorption spectra of ZnPc(*x*%)/SNV (ZnPc equivalent to 20 μg/mL) aqueous suspension with *x* ranging in 4–14.3% (mass ratio).

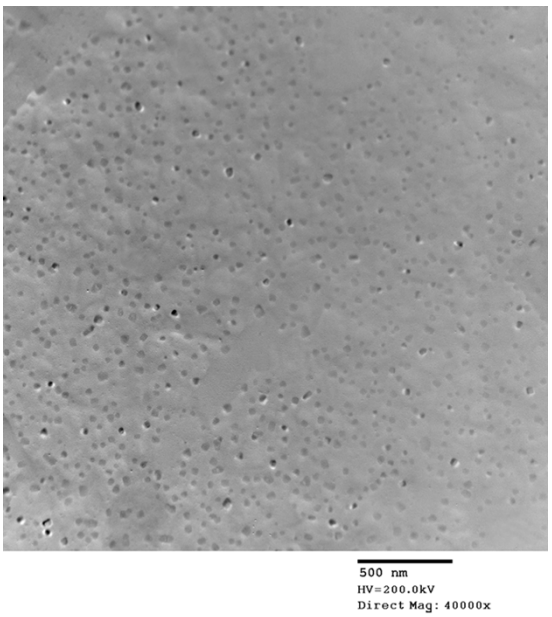


Figure S8. TEM image of ZnPc-DOX/SNV.

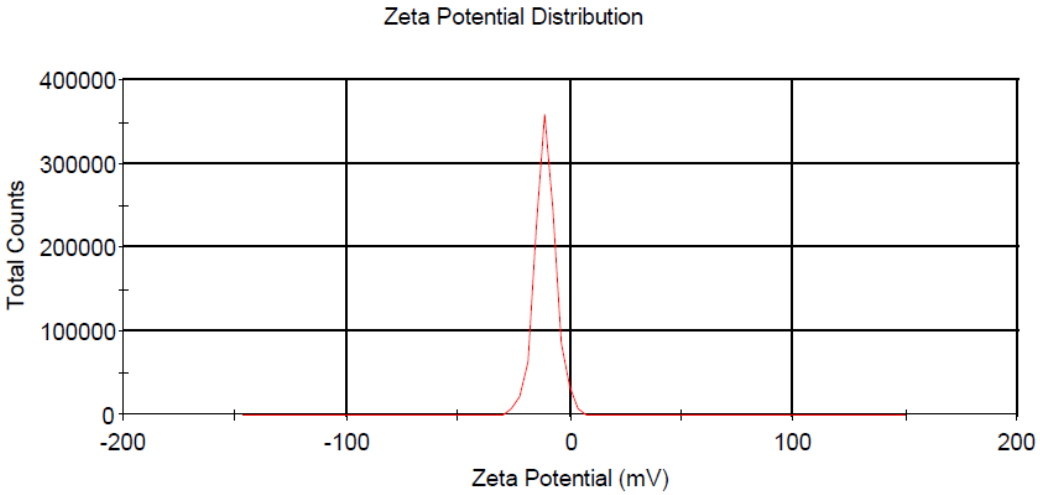


Figure S9. Zeta potential of ZnPc-DOX/SNV (−11.1 mV).

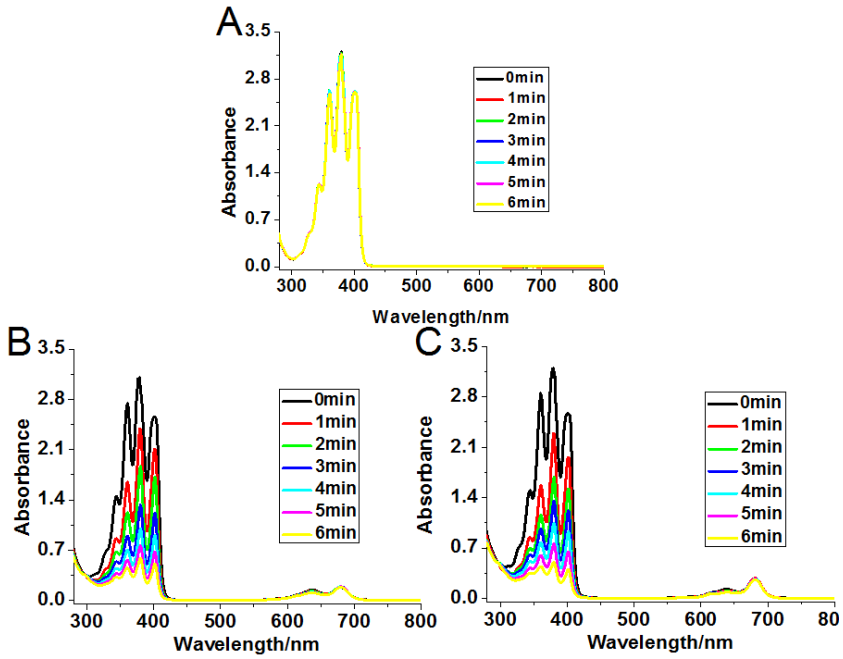


Figure S10. Decay curves of the absorbance of disodium salt of 9,10-anthracenedipropionic acid (APDA) at 378 nm in the presence of (A) blank, (B) ZnPc(14.3%)/SNV, (C) ZnPc(7.7%)/SNV as a function of irradiation time (excitation light: 650 nm).

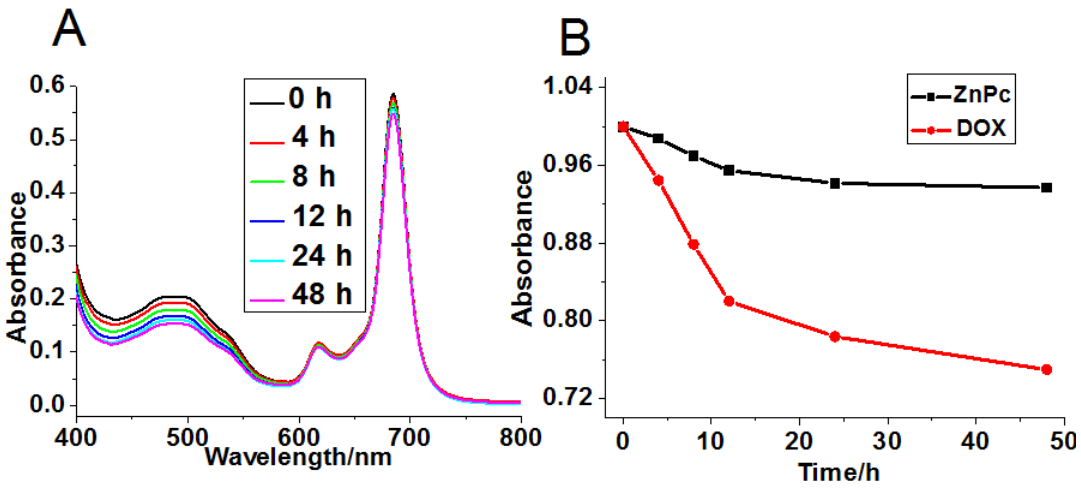


Figure S11. (A) Dialysis curves of ZnPc-DOX/SNV; (B) normalized release curves of ZnPc and DOX within 48 h.

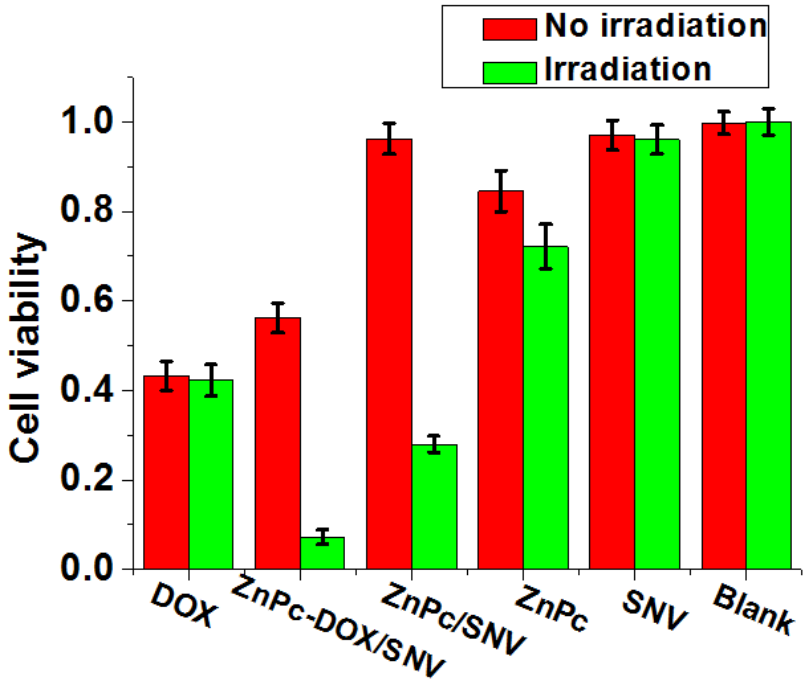


Figure S12. Phototoxicities of DOX (5 μg/mL), ZnPc-DOX/SNV (equivalent DOX: 2.5 μg/mL; ZnPc: 2.5 μg/mL), ZnPc/SNV (equivalent ZnPc: 5 μg/mL), ZnPc (5 μg/mL), SNV (0.5 mg/mL) and blank after 24 h incubation.

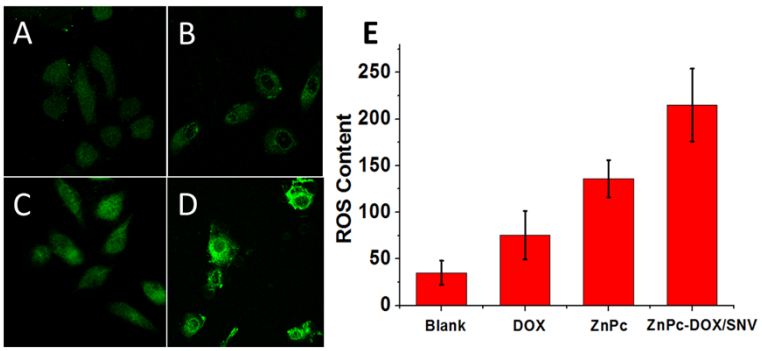


Figure S13. Drug Effect on ROS levels of HepG2 cells by using a laser scanning confocal microscopy (×600): (A) blank sample, (B) DOX, (C) ZnPc, (D) ZnPc-DOX/SNV. (E) The fluorescence intensity of ROS contents for these samples.

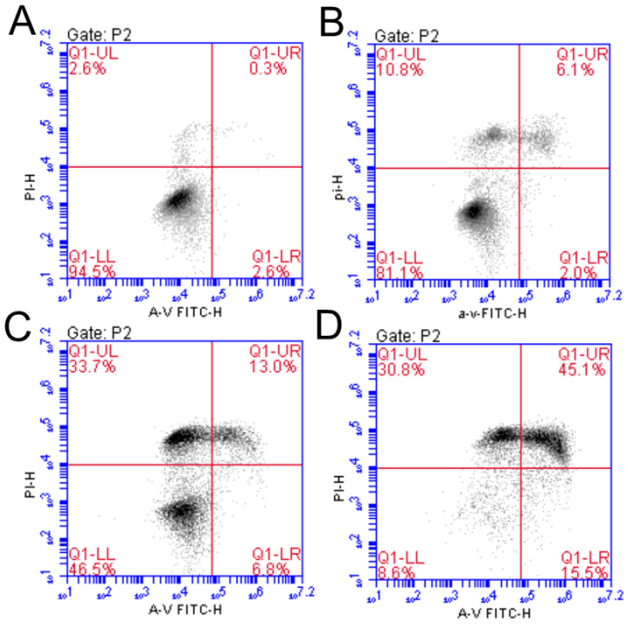


Figure S14. Drug Effect on apoptosis of HepG2 cells by flow cytometry: (A) blank, (B) ZnPc, (C) DOX, (D) ZnPc-DOX/SNV. The results are representative of three independent experiments.

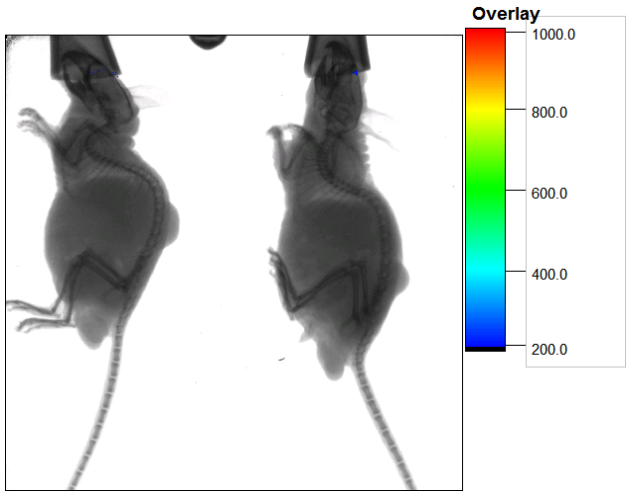


Figure S15. *In vivo* fluorescence imaging of mice before intravenous injection with ZnPc-DOX/SNV and ZnPc-DOX/PVP-Br.