Supporting Information

Diselenium-bridged covalent organic framework with pH/GSH/photo-triple-responsiveness for highly controlled drug release toward joint chemo/photothermal/chemodynamic cancer therapy

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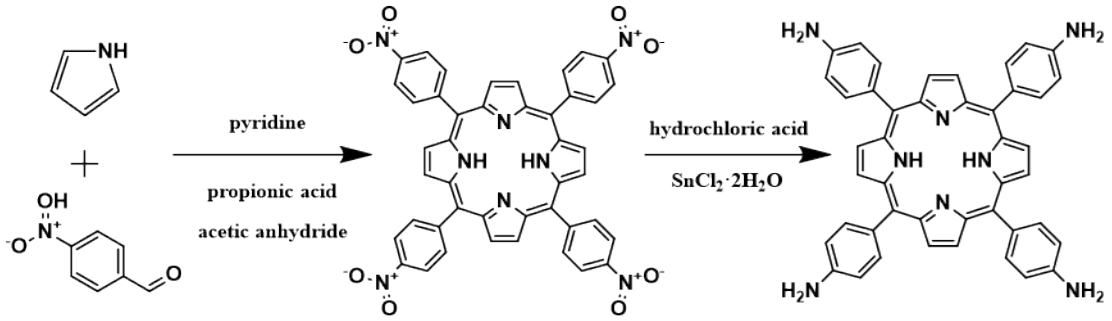
Section 1. Materials and Methods

1.1 Reagents and materials

4-Bromobenzaldehyde was purchased from Energy Chemical Co., Ltd (99%, Shanghai, China). Dibai Biological Technology Co., Ltd. (Shanghai, China) afforded the catalogue of acetic anhydride, propionic acid, anhydrous dimethyl sulfoxide (DMSO), and doxorubicin hydrochloride (DOX·HCl, >99%). GSH assay kit and ROS Assay Kit (DCFH-DA) were obtained from Beyotime Biotechnology (Shanghai, China). 4′, 6-diamidino-2-phenylindole dihydrochloride (DAPI) were bought from Sigma-Aldrich (St. Louis, MO, USA). 3-(4, 5-dimethyl-2-thiazyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) was bought from Aladdin Industrial Co., Ltd. (China). CalceinAM/PI Double Stain Kit was got from Shanghai Yisheng Biotechnology Co., LTD. PC-3 cell lines (human prostate cancer cell line) were obtained from American type culture collection (ATCC), which was cultured in RPMI 1640 medium (Gibco, NY, USA) supplemented with 10% fetal bovine serum (Beijing, China), 100 U mL^{-1} penicillin and 100 mg mL^{-1} streptomycin. Cells were maintained at 37^{o}C with 5% CO_2 in a humidified incubator. Male BALB/C mice and nude mice (4~6 weeks, 18~22 g) were gained from Vital River Company (Beijing, China). All experimental procedures were performed according to the guidelines for laboratory animals established by the Animal Care and Use Committee of Wei Fang Medical University.

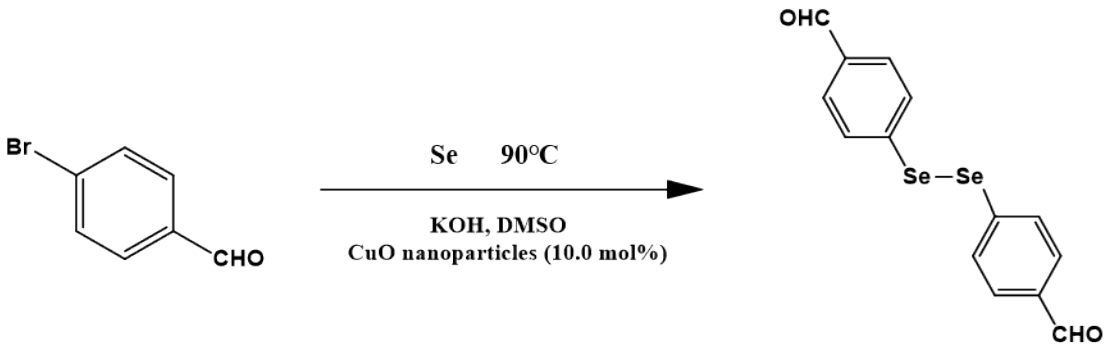
^{1}H NMR spectra of prepared monomers was recorded on an Avance Bruker DPX 400 (400 MHz) in the solvent of DMSO. Fourier Transform Infrared Spectroscopy (FTIR) was performed on KBr pellets in the range from 4000 to 400 cm^{-1} using Spectrum Spotlingt 400. The morphologies of powder samples were evaluated by field-emission scanning electron Microscopy (FESEM, Ultra 55) and transmission electron microscopy (TEM, Tecnai G2 20 TWIN) via dipping the prepared samples on a Cu-net. The adsorption and desorption measurements for N_2 were performed on a Belsorp max analyzer (Japan) at low temperature of 77K. Before test, all these samples were degassed overnight under high vacuum at the temperature of 150^{o}C to remove the solvent or the water absorbed in the porous skeleton. The absorption wavelength of DOX was obtained through the automatic enzyme immunoassay instrument (Multiskan Go, America). Thermo-gravimetric analysis (TGA) and Differential scanning calorimetry (DSC) were recorded using Microcomputer differential thermal balance (HCT-1, Hengjiu, Beijing, China) analyzer under the protection of N_2.

1.2 Preparation of 5,10,15,20-tetrakis(4-aminophenyl)-21-H,23-H-porphine (Por)



Briefly, pyrrole (3.30 mL, 47.5 mmol) was dropwise added to a solution of 4-nitrobenzaldehyde (7.25 g, 48 mmol) and acetic anhydride (7.91 mL, 48 mmol) in propionic acid (100 mL). The solution was refluxed at 120°C for 0.5 h. After cooling, the solid was filtrated, followed by cleaning with water and methanol, respectively. Subsequently, the crude product was stirred in pyridine (55 mL) at 120°C for 1 h, followed by cooling and filtrating. The precipitate was cleaned with acetone and dried under a vacuum to give a purple powder of 5,10,15,20-tetrakis(4-nitrophenyl) porphyrin in 13% yield. Afterward, the resulting powder was suspended in hot concentrated hydrochloric acid (200 mL), and $SnCl_2.2H_2O$ (7.83 g, 34.7 mmol) was added and refluxed at 70°C for 1 h. The solution was cooled in an ice–water bath and neutralized with $N_2H_4 \cdot H_2O$, followed by filtrating and washing with water. The solid was extracted by the Soxhlet extraction method with acetone. A purple crystal was finally collected in 90% yield, after being dried by rotary evaporation under a vacuum. ^{1}H-NMR (400 MHz, DMSO-d6): δ -2.73 (s, 2H), 5.58 (s, 8H), 6.98 (s, 8H), 7.83 (s, 8H), 8.86 (s, 8H).[1]

1.3 Synthesis of 4,4'-diselenidediyldibenzaldehyde (DiSe)



To a stirred solution of Se metal (2.0mmol) and 4-Bromobenzaldehyde (1.0 mmol) in dry DMSO (2.0 mL) was added CuO nanoparticles (10.0 mol%) followed by KOH (2.0 equiv) under nitrogen atmosphere at 90 °C. The progress of the reaction was monitored by TLC. After

the reaction was complete, the reaction mixture was allowed to cool, which was subjected to column chromatographic separation to give pure 4, 4-diselenidediyldibenzaldehyde in 68% yield. The identity and purity of the product was confirmed by ^{1}H-NMR spectroscopic analysis. ^{1}H NMR (400 MHz, DMSO-d6): δ 9.95 (s, 2H), 7.81 (d, J = 7.9 Hz, 4H), 7.73 (d, J = 7.9 Hz, 4H).[2]

1.4. Preparation of DiSe-Por

Por (0.338 g, 0.50 mmol) and DiSe (0.368 g, 1.0 mmol) were put in a Pyrex tube containing 30 mL 1, 4-dioxane which was sonicated for 30 min. The tube was carefully degassed by three freeze–pump–thaw cycles and then sealed under vacuum. After being thermostated at 120°C for 24 h, purple crude product was isolated by filtration. For further purification, the purple product was washed with successively tetrahydrofuran (THF) and N, N - Dimethylformamide (DMF), until the filtrate is colorless, followed by continuous stirring with THF for 24 h. And the final DiSe-Por COF was dried in an oven vacuum.

1.5. Preparation of DiSe-Por-DOX

Briefly, 3 mg of DiSe-Por was added into 3 mL of PBS solution, which was sonicated with a sonic tip (ultrasonic frequency: 19-25 kHz) in ice bath for 1 h (period of 3 s with the interval of 3 s) with a power of 500 W, obtaining the resulting DiSe-Por dispersion solution. Then, DiSe-Por dispersion solution and DOX were mingled and kept for vigorous stirring for 12 h in the dark. The DOX loaded COF was collected as pellets after centrifugation (11000 rpm, 10 min). Then, the redundant DOX was removed by dialysis against water for 24 h in the dark. Finally, the prepared nanoparticles were obtained by freeze-drying.[3]

1.6. Photothermal properties of DiSe-Por and DiSe-Por-DOX

500 μL of DiSe-Por and DiSe-Por-DOX aqueous solution with different concentrations were added into Eppendorf tubes and irradiated by 808 nm laser for 6 min with different power intensities. The temperature change was recorded by using a thermal imager (FLIR E5, FLIR System AB, Täby, Sweden). The temperature change of materials under irradiation and laser shutdown was recorded. Then the photothermal conversion efficiency was calculated based on the previous report.[4] Calculation of photothermal conversion efficiency:

The DiSe-Por-DOX aqueous solution was irradiated by an 808 nm laser for 5min (1.5W/cm^{2}). Then the heated aqueous dispersion cooled down naturally and the temperatures

during the cooling process were also carefully monitored every 10 s by a thermometer with a thermocouple probe. The photothermal conversion efficiency (η) was calculated by the following equation (Equ 1):

$$\eta = [hS(T_{max} - T_{surr}) - Q_{Dis}]/I\ (1 - 10^{-A\lambda}) \quad \text{(E1)}$$

Where 'h' is the heat transfer coefficient, 'S' refers to the surface area of the container, 'Tmax' represents the equilibrium temperature after 5min irradiation, 'QDis' expresses the heat dissipation by the test cell, 'I' is 808 nm CW laser power (1.5W/cm^2), and A808 is the absorbance of the DiSe-Por-DOX aqueous solution at 808 nm. The value of hS is determined according to the following equation (Equ 2 and S3):

$$hS = \frac{m_d C_d}{ts} \quad \text{(E2)}$$

$$t = -ts(ln\theta) \quad \text{(E3)}$$

Where 'md' is the mass (0.5 g) and 'Cd' is the heat capacity (4.2 J/g) of the aqueous solvent, 'τ_s' is the sample system time constant, and 'θ' is defined as the ratio of ΔT and ΔTmax.

In this study, Tmax-Tsur = 56℃ - 25.0℃ = 31℃, A808 = 0.456; I =1.5 W/cm^2

$$\eta = [hS(T_{max} - T_{surr}) - Q_{Dis}]/I\ (1 - 10^{-A808}) = 24.59\%$$

1.7. Drug loading capacity (LC) and entrapment efficiency (EE)

1.7.1 DOX calibration by UV-Vis spectroscopy: Standard solution series in a fixed DOX concentration of 10, 15, 20, 30, 40, 50 μg mL^{-1} are accurately prepared by diluting a certain number of products weighed accurately into the accurate number of standard solutions. The detection wavelength was 483 nm.

1.7.2 The drug encapsulation efficiency (EE) was measured indirectly by calculating the free drug in the filtrate. Briefly, DiSe-Por evenly dispersed in different concentrations of DOX, respectively, was centrifuged at 11000 rpm in 25^{o}C for 10 min after 12 hours of mixing. The supernatant was filtered by 0.22 microfilter membrane, using UA-vis to detect the absorption wavelength. The free drug concentration was calculated through the standard curve.[5] The EE% and LC% of DiSe-Por-DOX were calculated using equation as follows:

$$LC\% = \frac{W_1 - W_2}{W_3} \times 100 \quad (E4)$$

$$EE\% = \frac{W_1 - W_2}{W_1} \times 100 \quad (E5)$$

W_1 refers to the total amount of DOX added, W_2 is the free DOX in suspension, and W_3 is the weight of the final nanovectors complex.

1.8 Drug release studies *in vitro*

1.8.1. Release profiles of DOX from DiSe-Por-DOX were measured at various releasing media using a dialysis method. Typically, DiSe-Por-DOX were dispersed in PBS (equivalent to 2 mg of DOX), and the suspensions were transferred into dialysis bags (MWCO: 3500). Every sample was gently shaken with an appropriate speed at 37°C in the dark. At predetermined time points, 1 mL of the solution outside the dialysis bag was removed and replaced with an equal volume of fresh PBS with different pH respectively. The amount of DOX released from the DiSe-Por-DOX was filtered by a 0.22-micron filter membrane and determined using the UV-Vis spectrum. The DOX content of each point was calculated according to the standard curve of DOX.

1.8.2. The thermo-responsive release behavior of DiSe-Por-DOX was evaluated by intermittent exposure to 808 nm laser. The DiSe-Por-DOX is irradiated at a specific time that lasts for 5 mins per exposure. The separated solution is obtained by centrifugation (9000 rpm, 15 min). The releasing amounts of DOX at different time points were detected by Automatic enzyme immunoassay instrument. And the DOX content of each point was calculated according to the standard curve of DOX.[6]

1.9. Cellular uptake

1.9.1. The qualitative cellular uptake of the DiSe-Por-DOX was observed by inverted fluorescence microscope (Leica DMI4000B, Germany). PC-3 cells were seeded into 6-well tissue culture plate with a density of 2×10^6 cells in each well and incubated for 24 h. Then, the culture medium was replaced by 1640 medium with different concentrations of DiSe-Por-DOX in different media. After 6 h incubation, the medium in each well was discarded and washed three times by 1640 medium. Then DAPI was added and stained for 5 min. Afterward, the fluorescence was observed under an inverted fluorescence microscope.

1.9.2. The cellular uptake of DiSe-Por-DOX was observed by flow cytometry toward PC-3 cells. The cells were incubated in a 6-well plate (2×10^5 cells/well) containing 2 mL of RPMI

1640 culture medium per well. After incubation for 24 h, the growth medium was replaced with fresh RPMI 1640, and cells were incubated with freshly prepared DiSe-Por-DOX (the concentration of DOX is 5μg/mL). After being incubated for 6 h, the cells were collected and detected by flow cytometer according to the fluorescence intensity of FITC.

1.9.3. L02 cells and L929 cells were seeded into a 6-well tissue culture plate with a confluence of 2×10^6 cells in each well and incubated for 24 h. Then, the culture medium was replaced by DMEM medium with different concentrations of DiSe-Por-DOX at different process modes. After 4 h or 6 h incubation, the medium in each well was discarded and washed three times by DMEM medium. The fluorescence was observed under an inverted fluorescence microscope.

1.10. Intracellular ROS generation

Intracellular ROS in PC-3 cells was detected by ROS Assay Kit DCFH-DA. PC-3 cells were plated in 6-well plates and treated with DOX, DiSe-Por and DiSe-Por-DOX for 12 h. After that, the cells were incubated with 10 μM fluorescent probe of 2′,7′-dichlorodihydroflfluorescein diacetate (DCFH-DA) for 30 min in the dark at 37°C. After washing off the excess probes with PBS, inverted fluorescence microscope was used to detect the green fluorescence intensity which represents the intracellular ROS levels. After washing off the excess fluorescent dye with PBS, check the green fluorescence intensity under an inverted fluorescence microscope which represents the level of intracellular ROS.[7]

1.11. GSH Detection

The intracellular GSH levels were measured with a GSH assay kit (Beyotime, Nanjing, China). A total of 2×10^5 PC-3 cells was seeded in six-well plates after treatment in different ways. Cells were harvested and washed with PBS thrice. The GSH levels were measured using GSH assay kit as recommended in the manufacturer's recommendations. The GSH percentage was obtained by comparing the GSH content of untreated cells.[8]

1.12. Hemolysis assay

Mouse blood was suspended in PBS, and the mixture was centrifuged for 15 min at 2000 rpm. The separated red blood cells were washed three times with PBS and then diluted to 4% by volume with PBS. Then, particles with different concentrations (dispersed in PBS) were mixed with RBCS suspension to a volume concentration of 200 μL. The same volumes of water, PBS, RBCS suspension were mixed to a volume concentration of 2% which were used as positive

and negative controls, respectively. All treated groups were incubated at 37°C for 3 hours and then centrifuged at 2000 rpm for 15 minutes. The supernatant of each group was added to a 96-well microtiter plate, and the absorbance was measured at 545 nm[9]. The hemolysis ratio was calculated by the equation below:

$$Hemolysis\ ratio\ (\%) = \frac{A(sample) - A(negative)}{A(water) - A(negative)} \times 100\% \qquad (E6)$$

1.13. *In vitro* cell cytotoxicity

1.13.1. The cell viability was assayed using MTT assay. Cells were seeded in 96-well plates with a density of 8×10^3 cells per well, preincubated for 24 h, and subsequently treated with different composites with specified concentrations. After incubation for 24 h, the supernatant was discarded. The cells requiring laser intervention incubated for 12 h. Afterward, the cells were treated with experiment condition (808 nm, 1.5 W/cm^2, 5 min). Then, at 37°C, 10 μL of MTT solution (5 mg mL^{-1}) in PBS was added to each well for 4 h coincubation in the dark. DMSO (100 μL) was replenished to dissolve the MTT-formazan crystals after removing the medium carefully. Finally, the absorbance (abs.) was recorded at the wavelength of 490 nm in an Automatic enzyme marker (BioTek Instruments Inc., USA). Each experiment repeats for three times and the relative cell viability were measured by the following equation:

$$Cell\ viability\ (\%) = \frac{mean\ of\ abs.\ value\ of\ treatment\ group}{mean\ abs.\ value\ of\ control} \times 100\% \quad (E7)$$

1.13.2. Live/dead cell staining assay was also performed to evaluate the cytotoxicity. Briefly, PC-3 cells seeded in 12-well plates at a density of 5×10^4 cells per well were incubated with DOX, DiSe-Por and DiSe-Por-DOX + Laser (the concentration of DOX is 5 μg mL^{-1}). After incubation for 12 h, the cells were treated with laser (808 nm, 1.5 W/cm^2, 5 min). Then, following incubation of another 12 h, cells were stained with Calcein AM for visualization of live cells and propidium iodide for visualization of dead/late apoptotic cells for 10 min, washed with PBS three times, and subsequently observed and photographed by Inverted Fluorescent Microscope.

1.14. Tumor models

Human prostate cancer (PC-3) cells were cultured and expanded before the treatment. About 100 μL PBS containing 3×10^6 cells were subcutaneously injected into the hind leg of the male nude BALB/c mice (age: 6 weeks, weight: 14~17 g; Vital River, Beijing, China) to generate

subcutaneous xenograft tumor.

1.15. Biodistribution of DiSe-Por-DOX

The mice were intraperitoneal injected with DiSe-Por-DOX at the dose of 2.5 mg/kg of DOX. To observe the thermally responsive drug release behavior of the material, the mice were subjected to a laser intervention after the injection of 12 hours (808 nm, 1.5 W/cm^2, 5 min). After 6, 12, and 24 h post-injection, the mice were euthanized, and the major organs such as heart, liver, spleen, lung, kidney, and tumor of mice were carefully collected for imaging by a Maestro *In Vivo* Imaging System (Cambridge Research & Instrumentation, Inc., USA).

1.16. Pharmacokinetics[10]

1.16.1 DOX calibration by fluorescence spectrophotometer: DOX molecules dispersed in PBS with various concentrations were applied for calibration. DOX was excited at 480 nm and the emission was collected from 570 to 590 nm.

1.16.2 Pharmacokinetics study was performed on SD rats intravenously injected with free DOX, Fc-Ma at a dose of 3 mg/kg of DOX. Blood samples of each group were collected at various time points in heparin-treated tubes. The intensity of DOX in blood at different time periods was detected by fluorimeter and calculated by fluorescent standard curve of DOX examined.

1.17. *In Vivo* Thermal Imaging.

To evaluate the *in vivo* photothermal capacity of different groups (PBS, DOX, DiSe-Por and DiSe-Por-DOX (5 mg kg^{-1} of DiSe-Por), they were intraperitoneal injected into the tumor-bearing mice with 5 mg kg^{-1} (calculated according to DiSe-Por). After 12 hours, thermal imaging was recorded by an infrared thermal imaging camera when the tumors were exposed to 808 nm laser with a power density of 1.5 W/cm^2 for 5 min.[11]

1.18. *In Vivo* Antitumor Efficiency.

Mice bearing PC-3 tumors reached approximately 100 mm^3, a total of 40 nude BALB/c mice were randomly divided into eight groups. The treatment schemes were given as follows: (1) PBS; (2) PBS irradiation; (3) DiSe-Por (5 mg kg^{-1}); (4) DiSe-Por (5 mg kg^{-1}) + irradiation; (5) DOX (2.5 mg kg^{-1}); (6) DOX (2.5 mg kg^{-1}) + irradiation; (7) DiSe-Por-DOX (5 mg kg^{-1}, calculation according to DiSe-Por); (8) DiSe-Por-DOX + irradiation (5 mg kg^{-1}, calculation according to DiSe-Por). The mice were irradiated (808 nm, 1.5 W/cm^2 for 5 min) at 12 h after

the intraperitoneal injection. The tumor size was measured using a caliper every 2 days during 14 days. The body weights were inspected every 2 days. The tumor volume was estimated using the formula, tumor volume = length × $(width)^2/2$. All the mice were sacrificed on Day 14. The tumors and major organs were dissected, collected, and utilized for H&E staining.

1.19. Statistical analysis

All treatments were performed more than or equal to three replicates. The data were expressed as mean ± standard deviation. For analysis between two groups, student's t test was used to evaluate the statistical discrepancy. Comparisons among multiple groups were performed by one-way analysis of variance (ANOVA). *$p < 0.05$ was considered statistically significant. **$p < 0.01$ and ***$p < 0.001$ were considered extremely significant.

Section 2. ^{1}H NMR spectrum

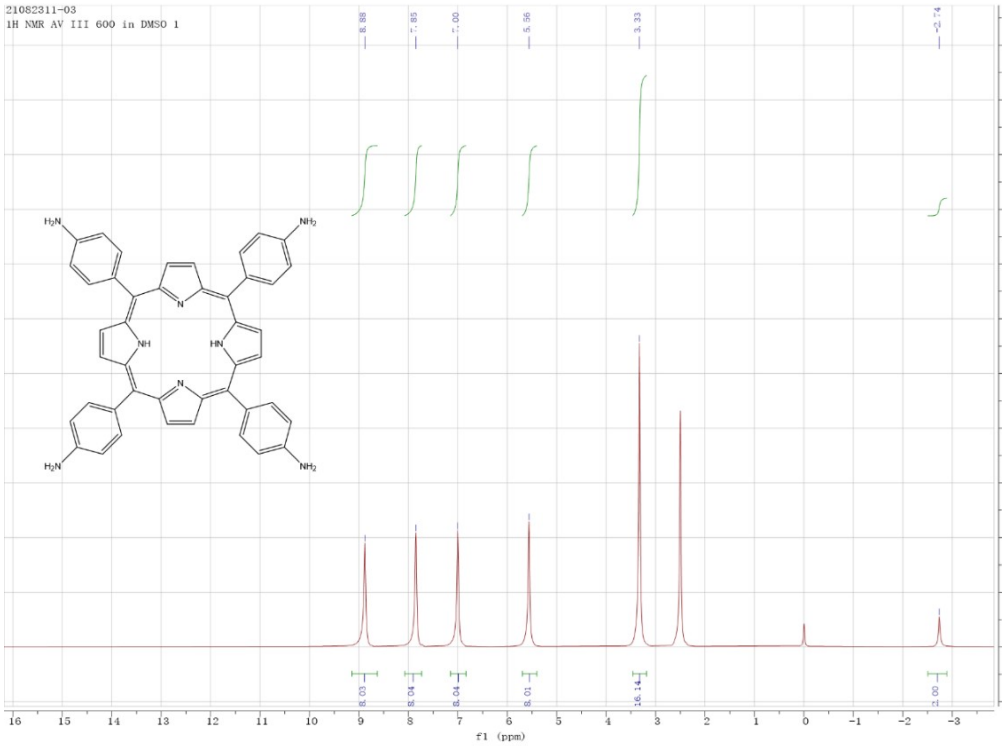


Figure S1. ^{1}H-NMR spectrum of Por (solvent: d6-DMSO).

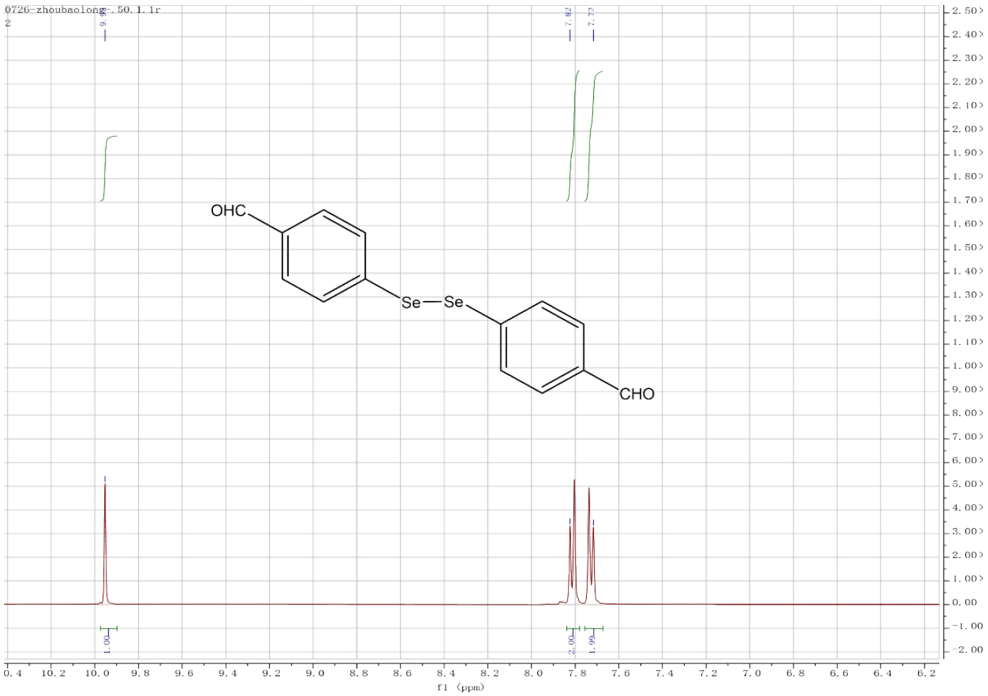


Figure S2. ^{1}H-NMR spectrum of DiSe (solvent: d6-DMSO).

Section 3. Mapping and EDS

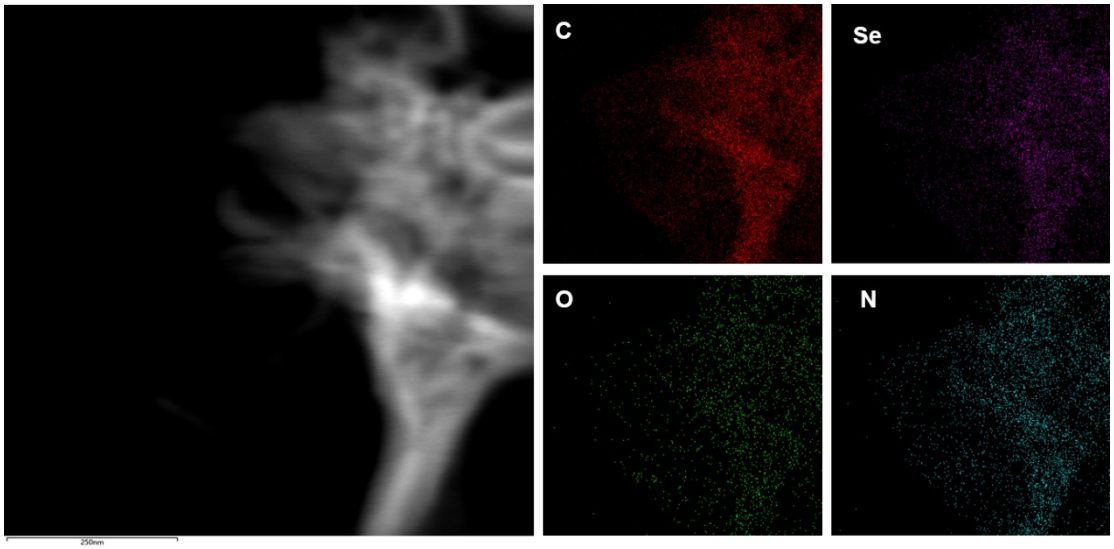


Figure S3. Element mappings of DiSe-Por.

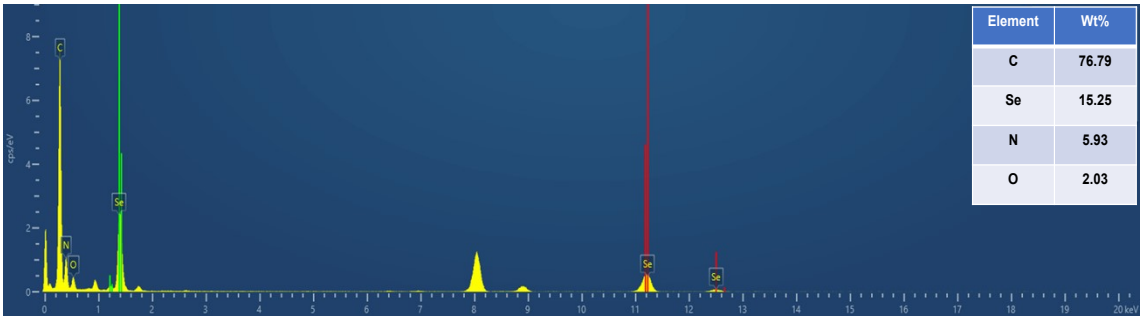


Figure S4. Energy dispersive spectrum of DiSe-Por.

Section 4. Standard curve of DOX

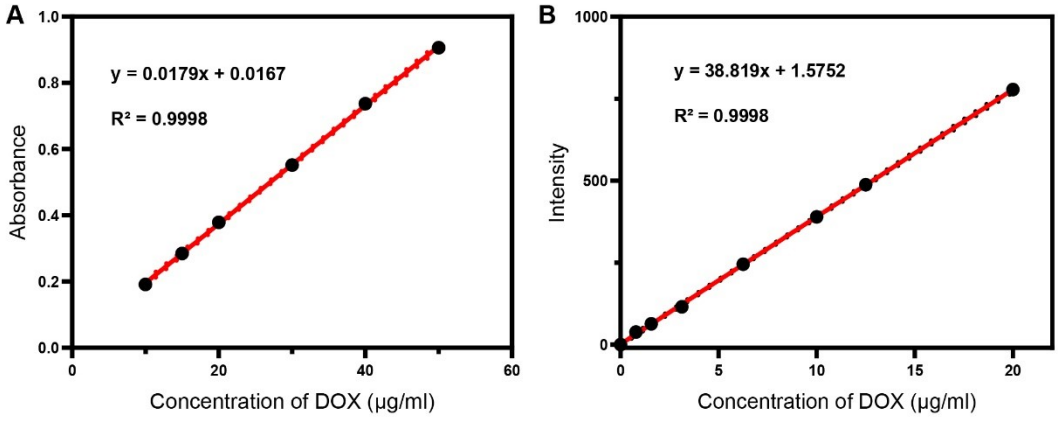


Figure S5. (A) UV-vis standard curve of DOX measured. (B) Fluorescent standard curve of DOX examined.

Section 5. Cell uptake and Localization

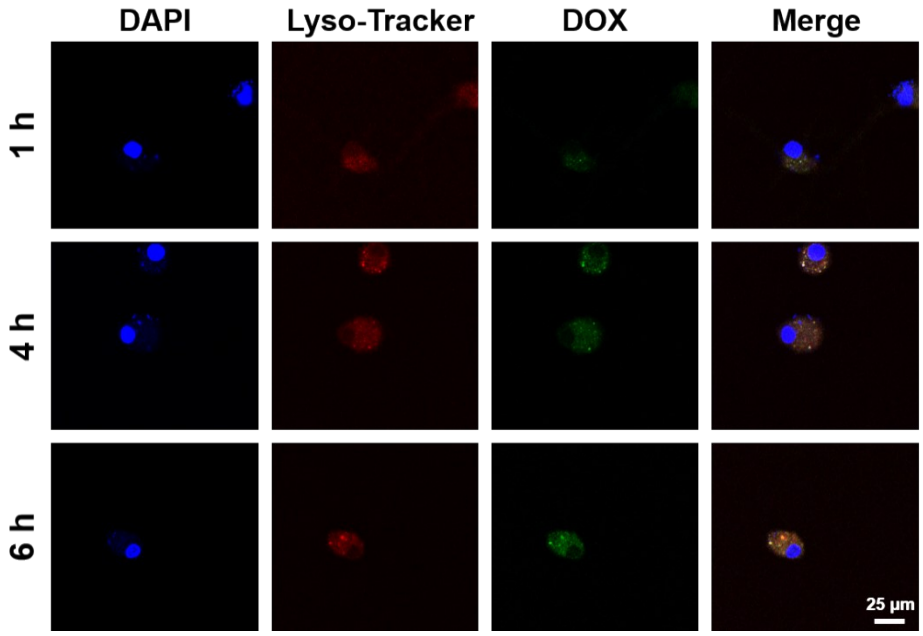


Figure S6. Localization of DiSe-Por-DOX in tumor cells by confocal laser scanning microscopy (CLSM). For each panel, the images from top to underside show cell nuclei stained by DAPI (blue), LysoTracker (red) and DOX (green) fluorescence in cells and overlays of the three images. (The scale bar is 25 μm.)

Section 6. Biosafety detection

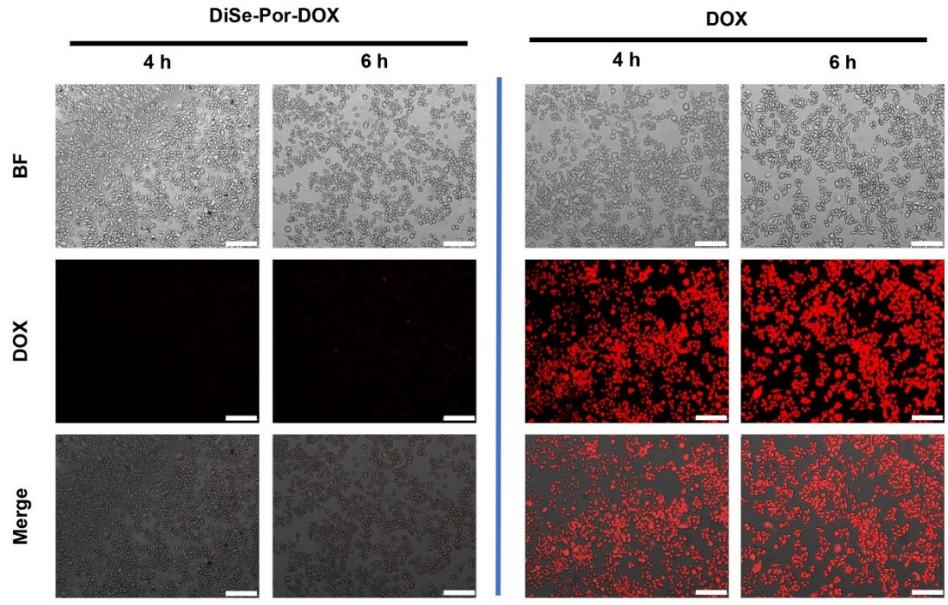


Figure S7. Fluorescence images of L929 cells incubated with DiSe-Por-DOX with different treatments (The bar is 200 μm).

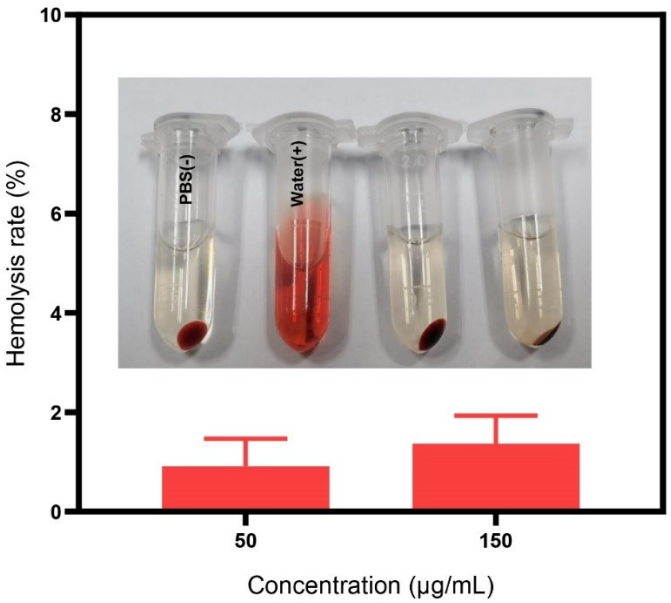


Figure S8. Hemolysis ratio and images of RBCs treated with DiSe-Por of different concentrations.

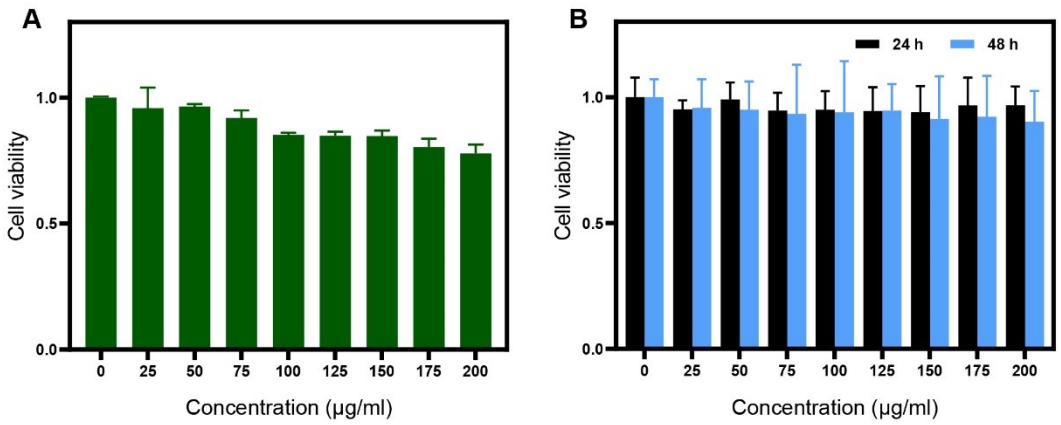


Figure S9. (A) Cell viabilities of L929 cells treated with DiSe-Por in various concentrations after 24 h and 48 h. (B) Cell viability of L02 treated with DiSe-Por with various concentrations.

Section 7. Tumor cell viability

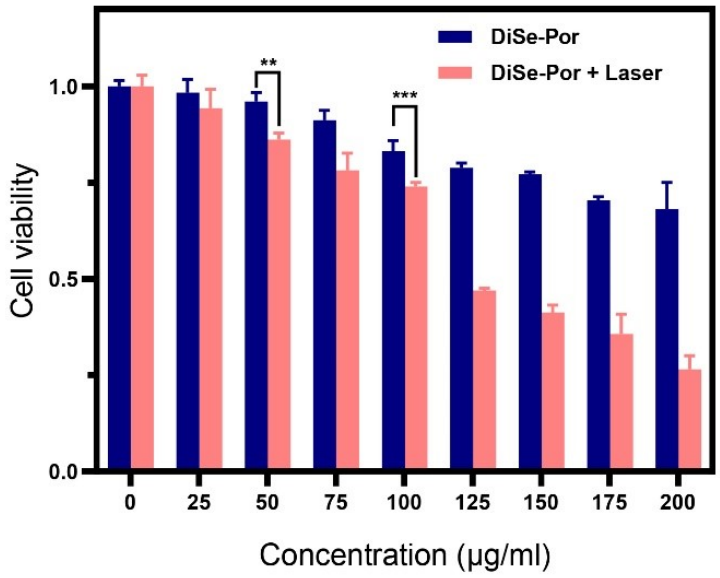


Figure S10. Cell viability of PC-3 treated with DiSe-Por, DiSe-Por +laser (808 nm, 1.5 W/cm^2, and 5 min) with various concentrations (*P < 0.05, **P < 0.01, ***P < 0.001).

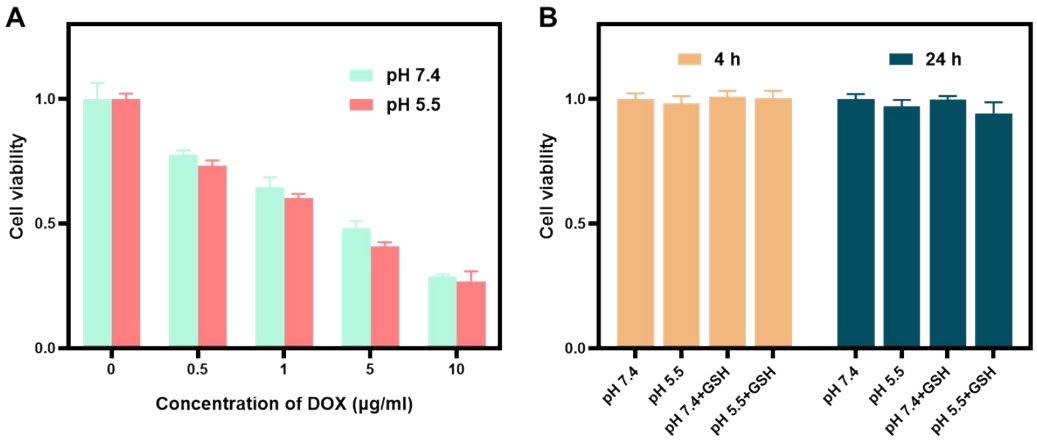


Figure S11. (A) *In vitro* cell viabilities of PC-3 cells treated with DiSe-Por-DOX in various pH media. (B) Cell viability of PC-3 in various pH media after 4 h or 24 h.

Section 8. Mean tumor weights

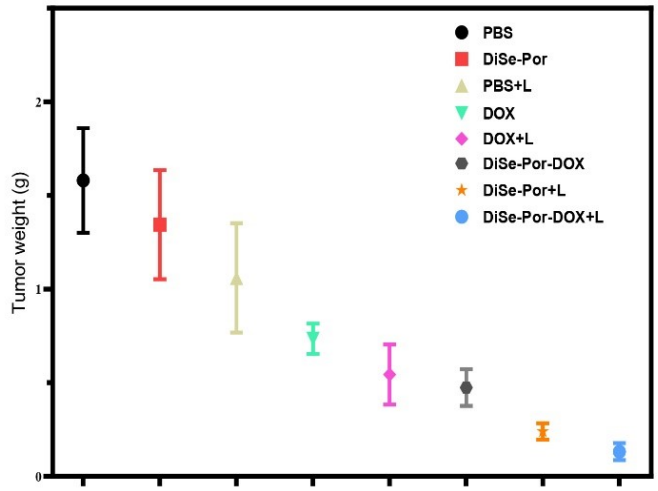


Figure S12. Mean tumor weights in different groups after 14 days of treatment.

Section 9. Body weight of the mice

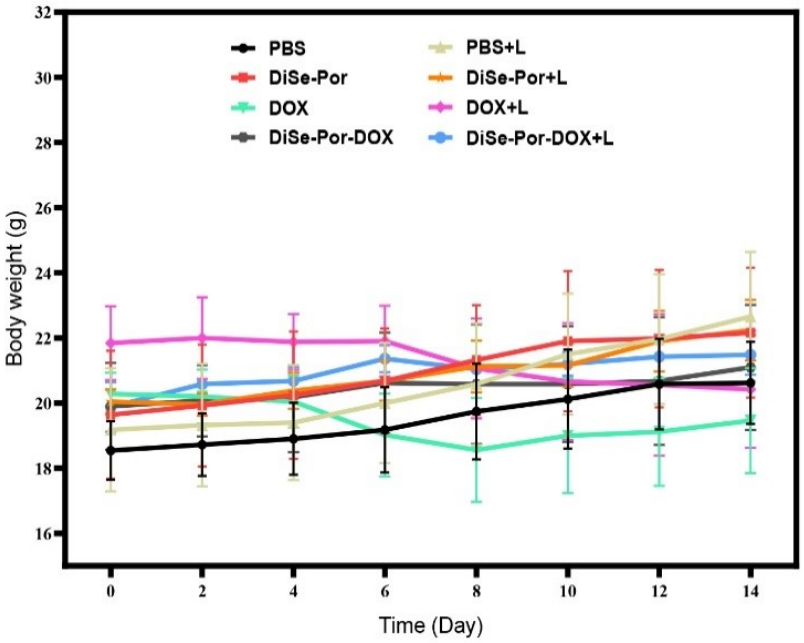


Figure S13. Body weight of the mice for various treatment groups.

Section 10. H&E staining of major organs

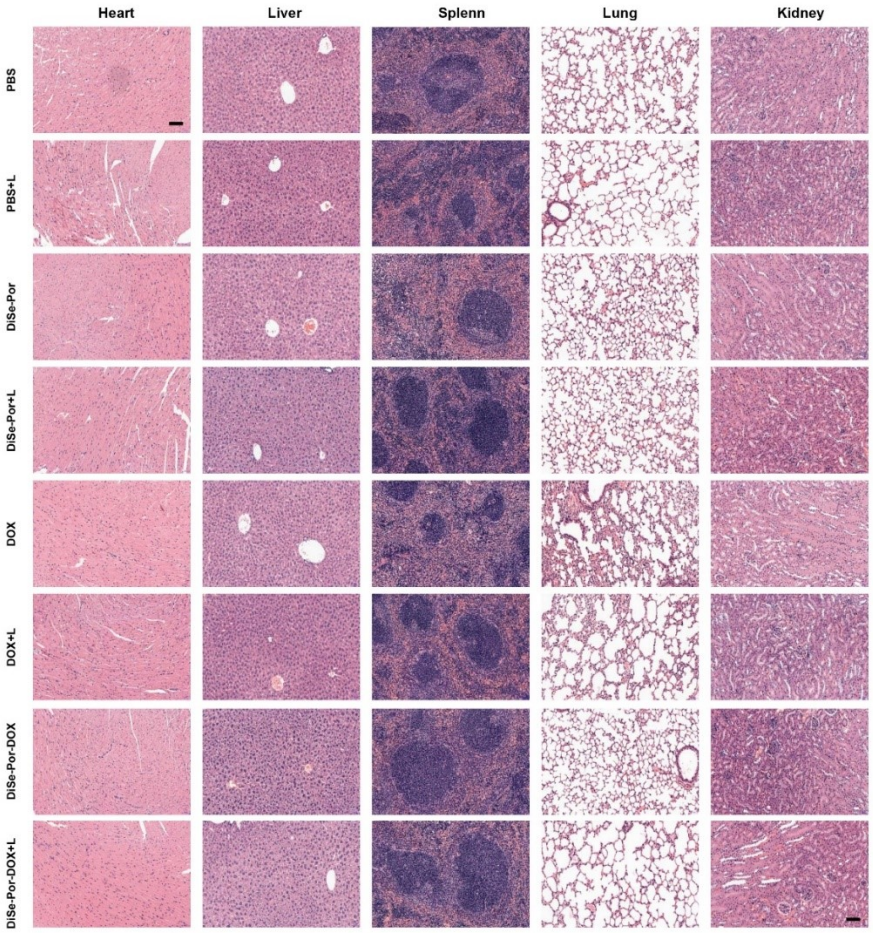


Figure S14. H&E staining of major organs (heart, liver, spleen, lung, kidney) at the 14th day (The scale bar is 100 μm).

Section 11. Pharmacokinetics

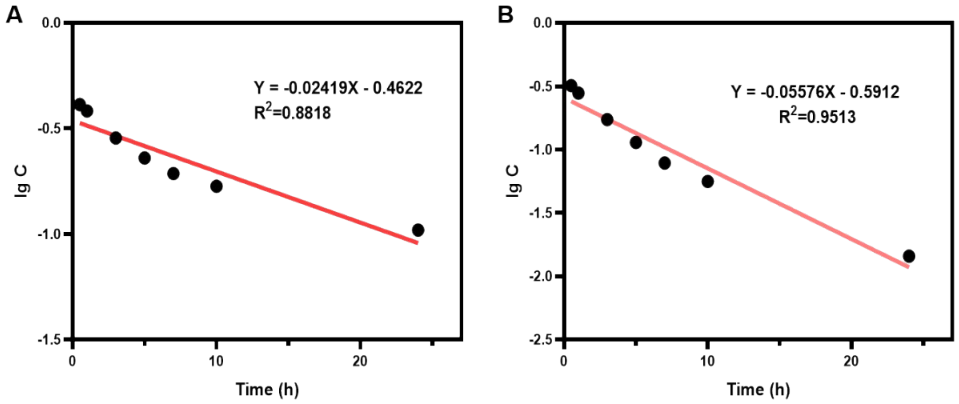


Figure S15. Single-compartment model blood concentration-time curve for (A) DiSe-Por-DOX and (B) free-DOX**.**

Section 12. Supporting Table

Table S1. Porosity Parameters of prepared polymers and corresponding catalysts.

Sample	S_{BET}(m^2/g)	V_{Total} (cm^3/g)	Main pore diameter (nm)
DiSe-Por	73.46	0.108	0.5625/0.7625
DiSe-Por-DOX	7.86	0.071	0.7875/1.1625

Table S2. Encapsulation efficiency (EE%) and % loading of DOX with different ratio (Mean ± SD, n = 3)

Mass ratio (Carrier: drug)	LC (%)	EE (%)
1 ：3	38.07±0.70	20.5±0.61
1 ：2	35.12±2.25	27.15±2.65
1 ：1	8.54±1.57	8.92±1.81
2 ：1	6.29±1.08	12.82±2.37
3 ：1	5.90±0.33	17.93±1.06
4 ：1	4.41±0.22	17.54±0.92

Section 13. Supporting References

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