Supporting Information

1. Experimental details

1.1. Reagents

Doxorubicin hydrochloride (DOX·HCl, 99.4%) was bought from Beijing Huafang United Technology Co., Ltd. Triethylamine (TEA, >99.0%) was bought from Xilong Science Co., Ltd. 2,2-Dimethoxypropane (DMP, 98%) was bought from Adamas Co., Ltd. *p*-Toluenesulfonic acid (TsOH, 99%) was purchased from Tianjin Guangxia Fine Chemical Research Institute. Thioglycolic acid (98%) was bought from Shanghai Aladdin Biochemical Technology Co., Ltd. Hydrogen peroxide (H_2O_2, 30%) was bought from Tianjin Damao Chemical Reagent Factory. 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC·HCl, 99%) was bought from Beijing J&K Scientific Co., Ltd. Other reagents and solvents were analytical grade and used as received. Double distilled water was used throughout the experiments.

1.2. Analysis and Characterization

The UV-vis spectra and drug content were detected using a TU-1901 UV/vis spectrometer (Beijing Purkinje General Instrument Co. Ltd, Beijing, China) at 480 nm at room temperature. The fluorescent emission spectra were recorded by a Hitachi F-7500 fluorescence spectrometer. BI-200SM dynamic light scattering (DLS) was used to measure the hydrodynamic diameter (D_h) and distribution of the nanomedicines in aqueous solution at 25℃. The morphology of the nanomedicines was observed with a transmission electron microscope (TEM, JEM-2100, Tokyo, Japan), sampling with aqueous dispersion.

1.3. In vitro drug release

1.0 mg of dimeric prodrug-based nanomedicine was dispersed in 10 mL of different buffer solution. The dispersion was then dialyzed in 140 mL of the corresponding buffer solution (MWCO of 1.0 kDa). After shaking for a certain time, 5.0 mL of the dialysate was taken out to measure the concentration of DOX on a TU-1109 UV/vis spectrophotometer. Meanwhile, 5.0 mL of fresh corresponding buffer solution was replenished to keep the solution volume constant. All drug release data are the average of three experiments.

1.4. In vitro cytotoxicity

The HepG2 cells were incubated in a 96-well plate with a concentration of 1×10^5 per well at 37°C for 48 h. The MTT assay was used to evaluate the cytotoxicity of the dimeric prodrug-based nanomedicines on the HepG2 cells. After co-incubation with the nanomedicines for 48 h, MTT (5.0 mg/L) was added into each well, followed by incubation for another 4 h. Finally, the cell viability was measured using the Enzyme-linked Immunosorbent Assay Appliance at 490 nm, after removing the crystals by dissolving in 150 μL of DMSO for 20 min.

1.5. Calculations

The calculations were performed using Dmol3 software. Geometry optimization had been performed via LDA-PWC. The dispersion function was Tkatchenko-Scheffer (TS) in all calculations because of considering the van der Waals force. The localized double numerical basis sets with polarization functions (DNP) basis sets were used to expand

the Kohn–Sham orbitals. During geometry optimization, the convergence criteria, including energy, force, and displacement, were set as 2×10^{-5} Ha, 0.004 Ha/Å, and 0.005Å, respectively.

2. Supporting figures

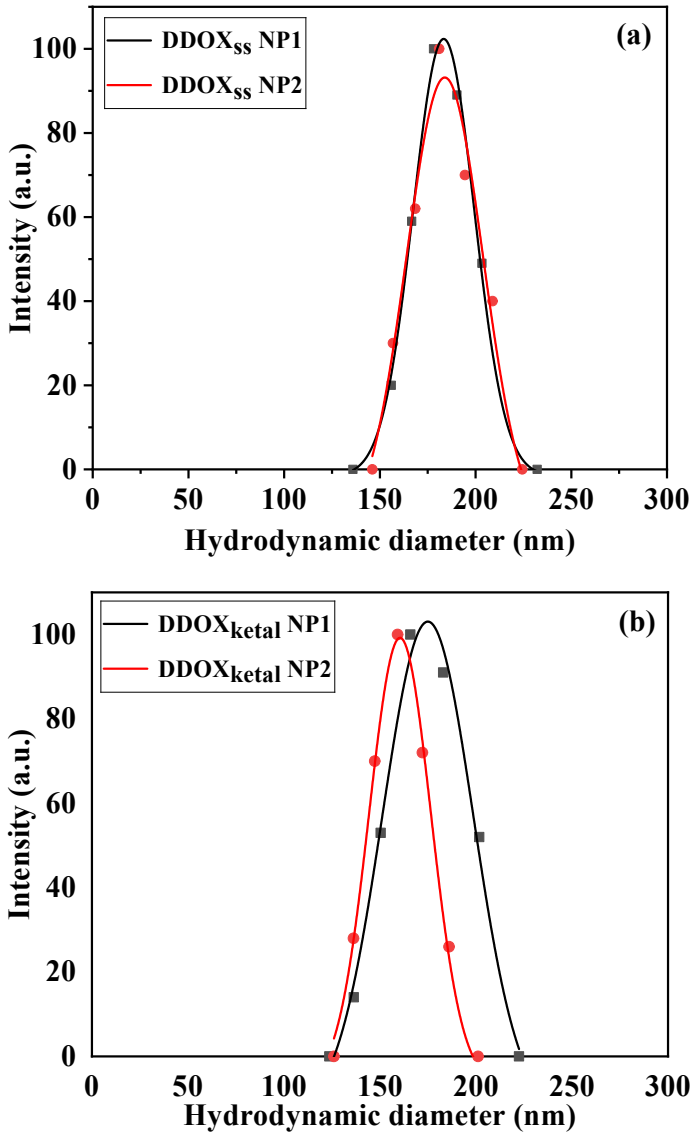

Fig. S1. Typical hydrodynamic diameter and distribution of the $DDOX_{SS}$ (a) and $DDOX_{ketal}$ (b) nanomedicines.