Supporting Information

A Versatile Stimulus-Responsive Metal-Organic Framework for Size/Morphology Tunable Hollow Mesoporous Silica and pH-Triggered Drug Delivery

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Experimental section

Materials: 2-methylimidazole was purchased from Sigma-Aldrich. Doxorubicin hydrochloride (DOX) was obtained from Hualan Chemistry Technology Co., Ltd (Shanghai, China). Tetraethyl orthosilicate (TEOS, ≥99%), zinc nitrate hexahydrate ($Zn(NO_3)_2 \cdot 6H_2O$, ≥98%), HCl solution (37%), and sodium hydroxide (NaOH) were obtained from Sinopharm Chemical Reagent Co., Ltd. Heochst-33342 was obtained from Invitrogen Life Technologies Corporation (Tianjing, China). Hexadecyltrimethylammonium chloride (CTAC, ≥98%) was purchased from Alfa Aesar (Tianjing, China). Other reagents and solvents were provided by Dingguo reagent company (Beijing, China). All chemical reagents used in this study were analytical grade and without further purification. Ultrapure water (18.2 MΩ cm) from the Millipore Milli-Q system was used for preparation of solution.

Synthesis of size-tuned ZIF-8 dodecahedral crystals: Typically, 0.082 g 2-methylimidazole and 0.298 g $Zn(NO_3)_2 \cdot 6H_2O$ were dissolved in 40 ml methanol, respectively. The two solutions were mixed and reacted at room temperature for 24 hours with stirring rates of 600, 400, 200 and 0 rpm. The products were purified by centrifugation and washing with methanol.

Synthesis of ZIF-8 cubic nanocrystals: 0.196 g 2-methylimidazole and 0.116 g $Zn(NO_3)_2 \cdot 6H_2O$ were dissolved in 16ml water, respectively. The two solutions were mixed and 0.02 g CTAC was added. Then, the mixture was placed in a reaction kettle

and heated at 50 °C for 6 h. The crude product was purified by centrifugation and washing three times with water.

Synthesis of HMSNs: The obtained ZIF-8 crystals were dispersed in 40 ml water. Then 1.6 g CTAC and 400 μL of 0.1 M NaOH solution were added upon stirring. Following this step, three 150 μL injections of 20% TEOS in methanol was added under gentle stirring at 30 minute intervals. The reaction mixture was reacted for 4 h. The crude products were centrifuged (10000 rpm, 10 min), washed thoroughly with water and ethanol for several times. To remove the surfactant template (CTAC) and core template (ZIF-8), the as-prepared samples were redispersed in 30 mL dilute HCl solution (0.1M) for 5 min. The cloudy solution becomes clear. Subsequently, the product was collected and washed using deionized water and ethanol for several times to obtain HMSNs.

Synthesis of HMSN@ZIF-8 and DOX loaded HMSN@ZIF-8 (DOX/HMSN@ZIF-8): 0.1 g of as-synthesized HMSNs was added to 1.89 g of 2-methylimidazole dissolved in 10 ml H_2O, and sonicated for 5 min. Subsequently, a solution of 0.0975 g $Zn(NO_3)_2 \cdot 6H_2O$ in 1 ml H_2O was added. The mixture was stirred at room temperature for 5 min, followed by centrifugation and washing with deionized water. The ZIF-8 capped HMSN was then obtained donating as HMSNs@ZIF-8.

For the preparation of DOX/HMSN@ZIF-8, 0.1 g HMSNs were diffusion-filled with DOX by immersing the particles in 500 μL solution of DOX (0.01 M, pH 7.2)

overnight, followed by centrifuging to remove excess DOX solution. Then, the DOX loaded HMSN was coated with ZIF-8 using aforementioned method.

Release of DOX from DOX/HMSN@ZIF-8 at different pHs: DOX release experiments were performed at pH values of 3.0, 4.0, 5.0, 6.0, and 7.4 respectively. 10 mg sample of DOX/HMSN@ZIF-8 was immersed in 200 μL of different buffer solutions with various pH values. Subsequently, the release medium was sampled at each time point and measured by fluorescence spectrophotometer with the excitation wavelength at 488 nm and the emission wavelength at 560 nm. The release percentages of DOX were calculated according to the formula *release percentage (%)* = m_r/m_l, in which m_r is the amount of released DOX while m_l is the total amount of loaded DOX.

Hemolysis assay: Red blood cells (RBCs) were isolated from human blood samples by centrifugation (10000 rpm, 10 min) and washed with 10 mL of PBS solution until the supernatants became clear. Subsequently, 0.1 mL HMSNs with varied concentrations (in PBS buffer) was added in 0.1 mL of isolated RBC suspension and kept mixing at room temperature for 6 h. D.I. water and PBS were also incubated with RBCs as the positive and negative controls, respectively. Then, the mixtures were centrifuged and photographed. The absorbance values of the supernatants at 570 nm were determined by using a microplate reader with absorbance at 655 nm as a reference.

***In vitro* cytotoxicity:** SMMC-7721 human hepatoma cells were seeded at 1×10^4 cells per well into 96-well plates and cultured in RPMI 1640 media containing 10%

fetal calf serum. Then DOX/HMSN@ZIF-8 at systematically varied concentrations were added in each well and cultivated at 37 °C for 24 h. For comparison, the cell viability of unloaded HMSN@ZIF-8 and DOX were also investigated. After the incubation with particular nanoparticles, MTT solution (20 μL, 5 mg mL^{-1}) was added to each well and the cells were further incubated for another 4 h. Subsequently, the MTT medium was removed and DMSO (150 μL) was added to each well. The optical density (OD) was measured at 570 nm with amicroplate reader (BIO-RAD Benchmark Plus).

Cellular uptaking and localization: To testify efficient cellular uptake, 7721 cells were seeded in coverglass bottom dishes (35 mm×10 mm) and incubated in 1640 medium (2 mL) with 10% FBS. After the cultured for 24 h, DOX/HMSN@ZIF-8 (60 μg mL^{-1}) was added and further cultured for another 4 h. After the cells were washed with PBS buffer to remove residual nanoparticles, Heochst-33342 was added for staining nuclear. 15 min later, the cells were softly washed with PBS buffer and visualized under a confocal laser scanning microscope.

Materials characterization: Microstructure of the prepared samples was characterized by transmission electron microscopy (TEM, F20 microscope with an accelerating voltage of 100 kV) and scanning electron microscope (SEM, Hitachi S-4800 microscope). The crystallographic information was obtained in a Scintag XDS-2000 powder diffractometer using CuKα irradiation. N_2 adsorption–desorption isotherm was obtained at 77 K on a Micromeritics ASAP 2010 sorptometer by static adsorption procedures. Samples were degassed at 373 K and 10^{-3} Torr for a minimum

of 12 h prior to analysis. Brunauer–Emmett–Teller (BET) surface area was calculated from the linear part of the BET plot according to IUPAC recommendations. Zeta potential experiments were performed at 25 °C using a Malvern Zeta-Sizer Nano instrument. UV-vis spectra were recorded on a Shimadzu UV-2600 spectrophotometer. The fluorescence spectra was obtained on a Hitachi F-7000 FL Spectrophotometer. The Confocal laser scanning microscopy (CLSM) images were obtained on a Fluoview FV500, Olympus. The MTT assay was recorded on a Benchmark Plus, Biorad Instruments Inc, Japan.

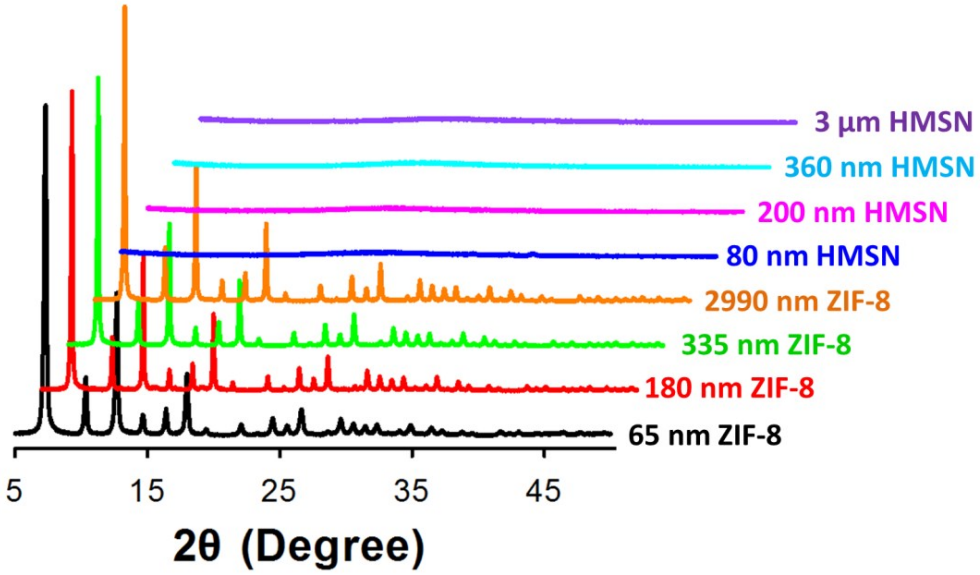

Figure S1. XRD patterns of ZIF-8 and HMSNs with different sizes.

Figure S2. Photographs of aqueous solutions of (a) mesoporous silica shells coated ZIF-8 (ZIF-8@MSN); (b) ZIF-8@MSN after dilute HCl etching to produce HMSN.

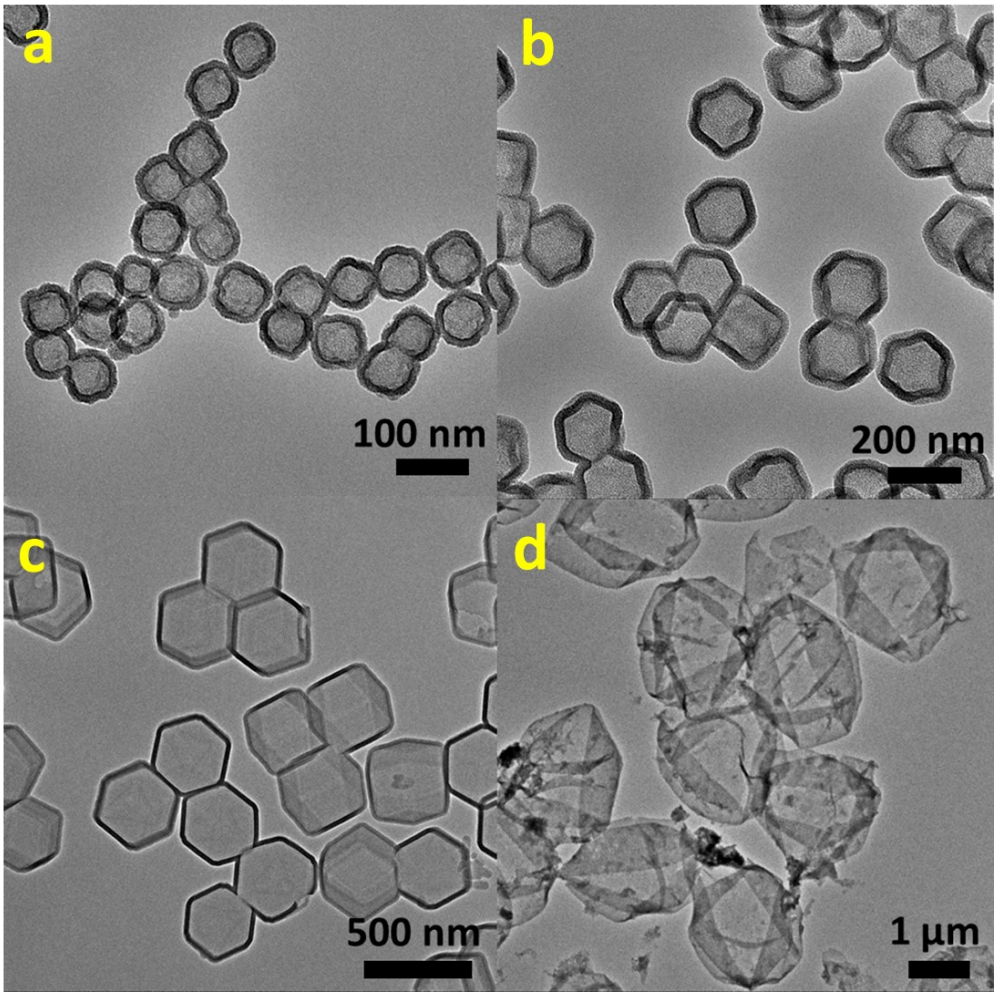

Figure S3.TEM images of (a) 65 HMSN, (b) 200 nm HMSN, (c) 335 HMSN, and 3000 nm HMSN.

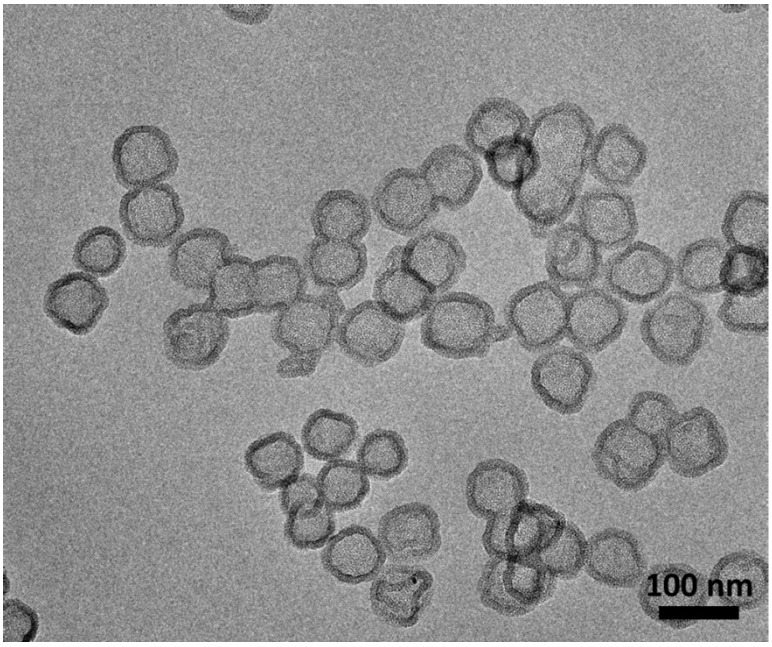

Figure S4.TEM image of 80 nm HMSN synthesized at 80 °C.

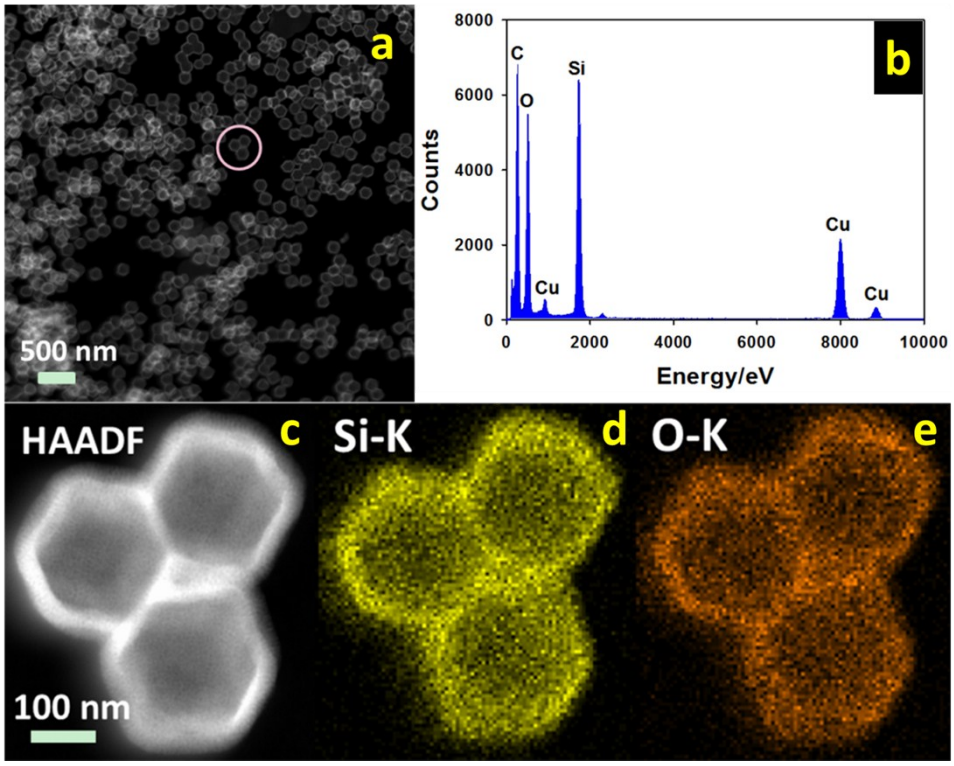

Figure S5. Structure and composition characterizations of 200 nm dodecahedral HMSN. (a) and (c) dark-field TEM images; (b) EDS elemental analysis; (d) and (e) EDS elemental mapping of Si and O.

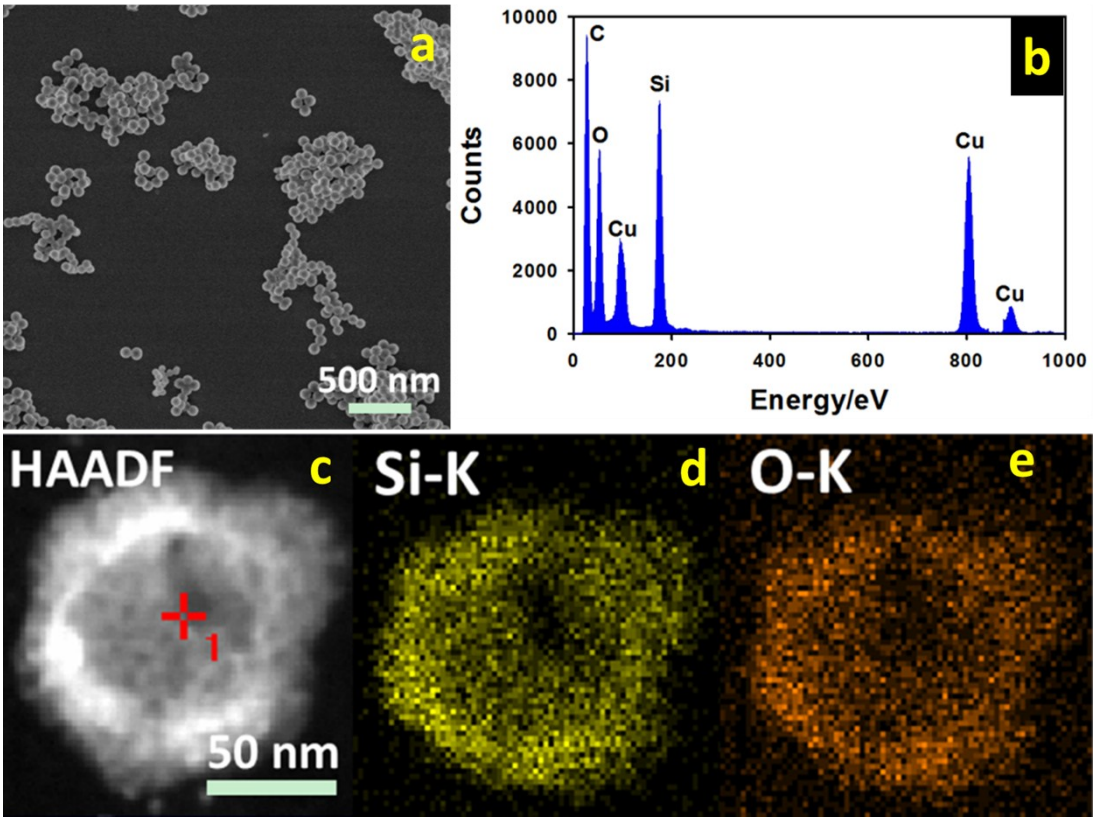

Figure S6. Structure and composition characterizations of 80 nm dodecahedral HMSN. (a) SEM image; (b) EDS elemental analysis; (c) dark-field TEM image; (d) and (e) EDS elemental mapping of Si and O.

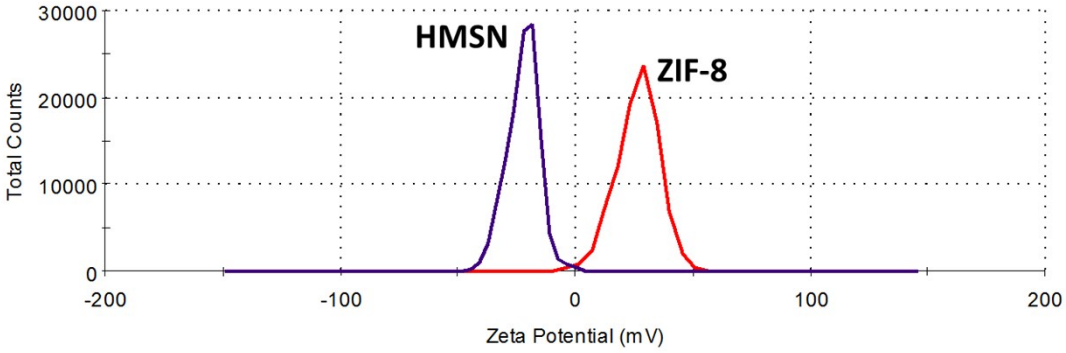

Figure S7. The value of zeta potential of HMSN and ZIF-8.

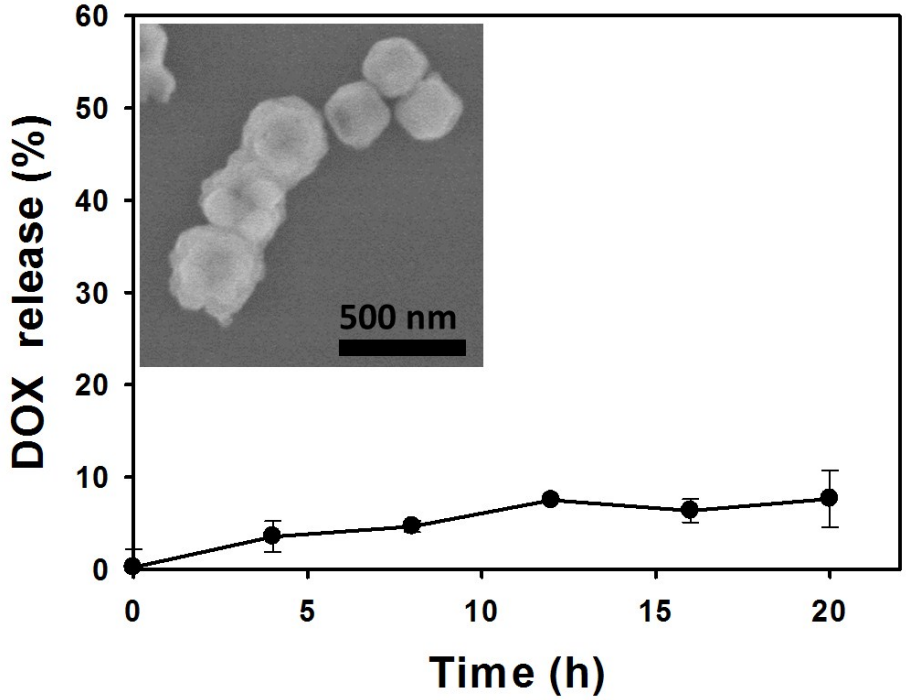

Figure S8. Time course of DOX release profile in human serum at 37 °C. Inset: SEM of HMSN@ZIF-8 after treating with human serum for 20 h.

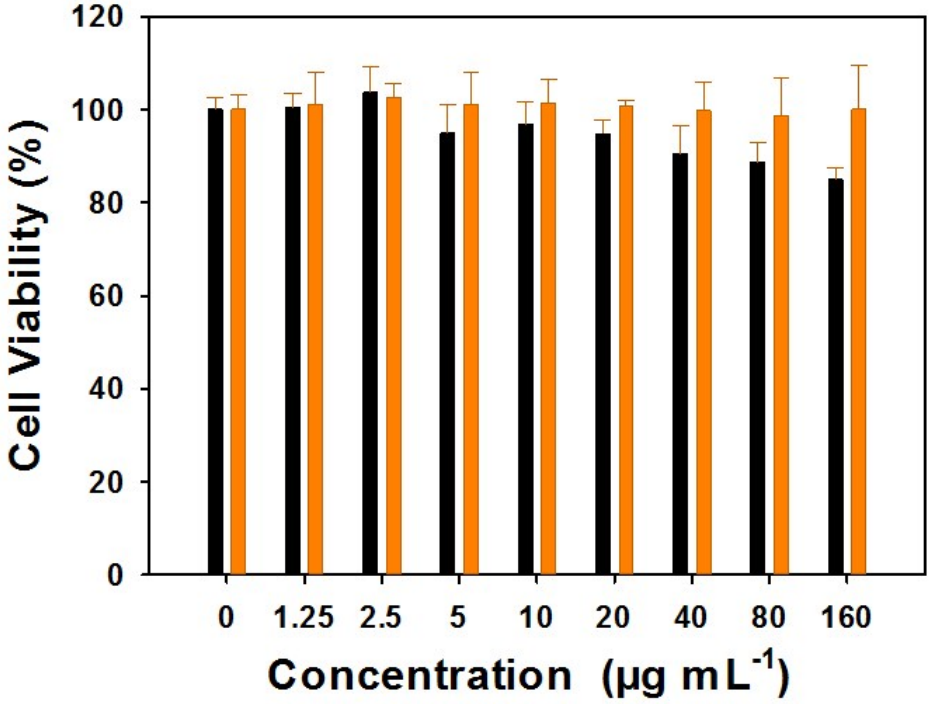

Figure S9. Viability of SMMC-7721 cells incubated for 24 h with different concentrations of HMSN@ZIF-8 (black) and HMSN (orange).