Electronic Supplementary Information (ESI) for Chemical Communications

Transformable upconversion metal-organic frameworks for near-infrared light-programmed chemotherapy

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Experimental Procedures

Materials and Reagents. Azobenzene-4,4'-dicarboxylic acid (H_2AZB), $ZrCl_4$ (anhydrous, 99.99%), glacial acetic acid, (4-carboxybutyl) triphenylphosphonium bromide (CTPP), anhydrous ytterbium chloride ($YbCl_3$) (99.9%), anhydrous yttrium chloride (YCl_3) (99.9%), anhydrous thulium chloride ($TmCl_3$) (99.9%), sodium hydroxide, cyclohexene, ammonium fluoride, 1-octadecene (ODE), oleic acid (OA), ethanol, tetrahydrofuran, dimethyl sulfoxide (DMSO), diethylene glycol (DEG), N, N-dimethylformamide (DMF), and tris-hydroxymethyl-aminomethane as gel loading buffer were purchased from Sigma-Aldrich (Merck, USA) and used directly without further purification. Cell Counting Kit-8 (CCK-8) and annexin V-FITC apoptosis detection kit were obtained from Keygen Biotech (Nanjing, China). The supercoiled pBR322 plasmid DNA was obtained from Takara Biotechnology Company. Mito-Tracker and TMRE were purchased from Thermo Fisher Scientific. The cell culture media (Dulbecco's Modified Eagle's medium (DMEM)) were from WISENT (China). All aqueous solutions were prepared using ultrapure water ($\geq$ 18 MΩ·cm, Milli-Q, Millipore).

Characterizations. The energy dispersive X-ray spectroscopy mapping images and transmission electron microscopic (TEM) images were recorded on a JEM-2100 high resolution transmission electron microscope (JEOL Ltd., Japan). The scanning electron microscopic (SEM) images were obtained from a S-4800 scanning electron microscope (Hitachi, Japan). Powder X-ray diffraction (PXRD) data was obtained by a X'TRA diffractometer (ARL, Switzerland). The ultraviolet absorption spectra were obtained with a UV-3600 UV-Vis-NIR spectrophotometer (Shimadzu Co., Japan). Fourier transform infrared (FTIR) spectra were taken with a spectrum on a FTIR spectrophotometer (Nicolet 6700, USA) at room temperature. Upconversion luminescence (UCL) spectra were recorded with ZolixScan ZLX-UPL spectrometer with an external continuous-wave laser (980 nm) as the excitation source. CCK-8 assays were carried out on a Synergy hybrid 1 multimode microplate reader (BioTek). The cell images were

gained on a TCS SP8 laser scanning confocal microscope (Leica, Germany). Flow cytometric analysis was performed on a Coulter FC-500 flow cytometer (Beckman-Coulter). The liquid chromatographic data were obtained with Agilent 1200 liquid chromatograph (Aglient Technologies Inc, America).

Synthesis of $NaYF_4$: 30 % Yb, 0.5 % Tm@$NaYF_4$ Core-Shell-UCNPs. The $NaYF_4$:Tm,Yb core UCNPs were synthesized according to a previously reported method.[S1] Briefly, YCl_3 (0.695 mmol), $TmCl_3$ (0.005 mmol) and $YbCl_3$ (0.300 mmol) were mixed with 6 mL oleic acid and 15 mL 1-octadecene, heated to 150 °C under vacuum condition and stirred for 40 min. After cooling down to 50 °C, 10 mL methanol solution containing 148 mg NH_4F and 100 mg NaOH was added and stirred for 30 min. The mixture was heated to 110 °C and kept for 15 min to remove methanol. The temperature was then increased to 300 °C and kept for 80 min under nitrogen. After the solution was cooled down to room temperature, the as-obtained core UCNPs were precipitated with 20 mL acetone, washed with ethanol for several times, and re-dispersed in 5 mL cyclohexane. In the meantime, YCl_3 (0.80 mmol) was mixed with 6 mL oleic acid and 15 mL 1-octadecene with subsequent heating to 150 °C under nitrogen atmosphere for 40 min. Once the reaction solution was cooled down to 40 °C, 5 mL of the synthesized $NaYF_4$:Tm,Yb core UCNPs was added into the mixture and heated to 80 °C to evaporate cyclohexane, and then cooled down to 50 °C. Afterward, 10 mL methanol solution containing 118 mg NH_4F and 80 mg NaOH was added and stirred for 30 min, and the mixed reaction solution was subsequently heated at 110 °C for 15 min and 300 °C for 80 min under nitrogen to get $NaYF_4$:Tm,Yb@$NaYF_4$. The product was precipitated with acetone, washed with ethanol several times, and re-dispersed in 10 mL THF for further experiments.

Carboxylic Acid Group Anchoring to UCNP. The carboxylic acid modification of UCNPs was referred to the previous report.[S2] 30 mg of UCNP in 2 mL of THF was introduced to 8 mL of THF containing 50 mg of 3,4-dihydroxyhydrocinnamic acid (Dopacid). The resulting solution was heated to 50 °C, and kept for 3 h. After cooling to room temperature, 200 μL of aqueous NaOH (0.2 M) was dropped to the solution

to precipitate UCNP. UCNP was collected by centrifugation and washed with ethanol and further resuspended in DMF for future use.

Synthesis of $Ru^{(II)}$ Complex $[\{RuCl(bpy)_2\}_2(bipy)](PF_6)_2 \cdot 2H_2O$. The $Ru^{(II)}$ complex was synthesized by binding the $Ru^{(II)}$ complexes with bridged-ligand. 4,4'-bipyridine (bpy) (3 mg, 20 μM) and $[Ru_2(bpy)_2(Cl)_2] \cdot 2H_2O$ (50 mg, 40 μmol) were added to 2 mL of degassed ethylene glycol in a sealable tube, Then the mixture was heated to 80 °C in the dark for 8 h. All the steps were operated in argon (Ar)-filled glovebox to guarantee the argon and water-free environment. After full extraction with the mixture of CH_2Cl_2 and KPF_6 saturated aqueous solution, the combined CH_2Cl_2 layers were washed with KPF_6-saturated water to remove ethylene glycol. After evaporation *in vacuo*, the crude was purified by flash chromatography (silica gel, 0.1% saturated KNO_3, 2% H_2O in MeCN ramped to 9% H_2O). Yield: 21.3 mg (78%). ^1H NMR (600 MHz, DMSO) δ 9.83 (d, J = 5.5 Hz, 2H), 8.84 (d, J = 8.2 Hz, 2H), 8.74 – 8.64 (m, 8H), 8.48 (d, J = 5.5 Hz, 2H), 8.21 – 8.16 (m, 4H), 7.93 (ddt, J = 15.9, 12.6, 6.2 Hz, 8H), 7.85 (d, J = 5.5 Hz, 2H), 7.77 (d, J = 5.2 Hz, 4H), 7.72 – 7.69 (m, 2H), 7.57 (d, J = 5.4 Hz, 2H), 7.37 (t, J = 6.3 Hz, 2H), 7.31 (t, J = 6.5 Hz, 2H). ^{13}C NMR (151 MHz, DMSO) δ 162.82, 159.30, 158.36, 158.08, 157.75, 153.07, 152.76, 152.21, 151.93, 143.39, 137.25, 136.89, 136.75, 136.24, 127.82, 127.69, 127.20, 126.70, 124.54, 124.23, 124.11, 123.72, 122.72.

Synthesis of UiO-AZB, UMOF, H-tMOF, R-tMOF and HR-tMOF.

UiO-AZB: H_2AZB (0.0270 g, 0.1 mmol) and $ZrCl_4$ (0.0234 g, 0.1 mmol) were mixed with 5 mL DMF in a round-bottomed flask, and sonicated for 5 min to give the orange solution. Then the resulting solution was heated to 100 °C and added glacial acetic acid (172 μL, 3 mmol) dropwise. After 12 h, the orange precipitates were separated via centrifugation at 8000 rpm for 15 min and further purified with DMF for several times.

UMOF: H_2AZB (0.0270 g, 0.1 mmol) and $ZrCl_4$ (0.0234 g, 0.1 mmol) were mixed with 5 mL DMF in a round-bottomed flask, and sonicated for 5 min to give the orange solution. Then the solution was heated to 100 °C, and added glacial acetic acid (172 μL, 3 mmol) and carboxylicacid-anchored UCNPs dropwise. The orange solid product was collected via centrifugation (12,000 rpm for 15 min) and washed with fresh DMF for several times. Lastly, the product was dried in vacuum drying oven to get solid UMOF.

H-tMOF, R-tMOF and HR-tMOF: To load 10-hydroxycamptothecine (HCPT) into MOF structures, 1 mg UMOF was introduced into CH_3CH_2OH solution of HCPT (1 mL, 5 mg mL^{-1}). The mixture was stirred for 24 h at room temperature in the dark, then collected via centrifugation (12,000 rpm for 20 min) to obtain the HCPT-loaded UMOF (H-UMOF). For loading another drug **Ru-Ru** prodrug $[\{RuCl(bpy)_2\}_2(bipy)](PF_6)_2 \cdot 2H_2O$, the CH_3CH_2OH solution with **Ru-Ru** prodrug (0.5 mL, 10 mg mL^{-1}) was mixed with 1 mg UMOF for 24 h at room temperature in the dark to get R-UMOF. To obtain the HR-UMOF, the HCPT and **Ru-Ru** prodrug were loaded following the similar loading procedure. The drug-loaded nanoparticles were centrifuged and washed three times to remove the remaining unloaded drug. The loading capacities were determined using UV-vis spectroscopy of the characteristic absorption bands of HCPT at 376 nm and **Ru-Ru** prodrug at 442 nm, respectively. For targeting mitochondria, the MOFs were further functionalized with the CTPP at molar ratio of CTPP: MOFs (400:1), and stirred overnight at room temperature in the dark. The obtained mitochondria-targeted MOFs such as H-tMOF, R-tMOF and HR-tMOF were concentrated by centrifugation, washed with CH_3CH_2OH to remove excessive free drugs. These MOFs were stored in argon-filled glovebox under darkness to guarantee the air and water-free environment. The energy transfer efficiency can be calculated as $1-\tau_{DA}/\tau_D$, where τ_{DA} and τ_D is the UCL lifetime of the donor with and without energy acceptor pairs.[S3]

Photo-Transformation of UMOF. To verify the photo-driven transformation, 1.0 mg UMOF was dispersed in 2.5 mL water by a mild ultrasonication for 30 min. The suspension was irradiated under 980

nm light (2.2 W cm^{-2}) for different time. The control experiment was carried out without NIR irradiation. The morphology and photo-isomerism of UMOF were studied by TEM, UV-vis spectroscopy, and IR spectroscopy.

HPLC Analysis. To verify the photo-cleavage reaction, 1.0 mg R-UMOF was dispersed in 1.0 mL water by a mild ultrasonication for 30 min. And then, the suspension was irradiated under 980 nm light (2.2 W cm^{-2}) at 37 °C for 30 min. Then, the solution was centrifuged at 14000 rpm for 20 min and the supernatant was injected on an Agilent 1100 Series HPLC equipped with a model G1311A quaternary pump, G1315B UV diode array detector. Chromatographic conditions were optimized on a Column Technologies Inc. C18, 120 Å (250 mm x 4.6 mm inner diameter, 5 μm) fitted with a Phenomenex C18 (4 mm x 3 mm) guard column. 15 μL injection volume of 30 μM the complex solution was used while the detection wavelength was 280 nm. Mobile phases were 0.1 % formic acid in H_2O and 0.1 % formic acid in HPLC grade acetonitrile (Fisher Brand). The gradient is shown in the Table S1.

DNA Gel Electrophoresis. The photoinduced DNA cleavage by $Ru^{(II)}$ complexes was carried out by agarose gel electrophoresis. pBR322 DNA (200 ng mL^{-1}) was treated with different $Ru^{(II)}$ complexes in 5 mM Tris-HC buffer (pH = 7.5), and the mixture was irradiated with 450 nm or dark at 37 °C for 1 h. The samples were subjected to electrophoresis on a 1.0% agarose gel in TAE buffer (40 mM Tris, 20 mM acetic acid, 1 mM EDTA, pH 8.0) at 120 V and 80 mA for 50 min. The gel was stained with 2 μL Gel-Red and photographed for analysis with a gel imager (ProteinSimple, Santa Clara, CA).

NIR Light Triggered Drug Release. The NIR light triggered drug release was determined by a dialysis method.[S4] 1.0 mg H-tMOF was dispersed in 1.0 mL H_2O by a mild ultrasonication for 20 min. And then, the suspension was injected into a dialysis cartridge (3.5 K MWC, Fisher Scientific). The solution was irradiated with a 980 nm NIR laser (2.2 W cm^{-2}) for different time. The control experiment was done without NIR irradiation. At predetermined time intervals, the released medium was collected for analysis

and the dialysis medium was replenished with a fresh one. After the release solution was centrifuged at 12000 rpm for 20 min, the supernatant was measured by UV−vis spectroscopy to obtain the amount of released drug with the standard calibration curve.

Cell Culture. 4T1 cells were provided by the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences. The cells cultured in regular growth medium consisting DMEM medium (high glucose) supplemented with 10% (v/v) fetal bovine serum (FBS), penicillin (100 U mL^{-1}) and streptomycin (100 μg mL^{-1}) at 37°C in a humidified incubator under 5% CO_2. The cells were routinely harvested by the use of a trypsin-EDTA (ethylenediaminetetraacetic acid) solution (0.25 %) until the confluence was reached.

Cell Cytotoxicity Assay by CCK**-8 Protocol.** *In vitro* cytotoxicity was assessed by the standard CCK-8 assay. Firstly, 4T1 cells were seeded in a 96 well-plate at a density of 5×10^3 cells per well for 24 h. Then the cells were incubated with different concentration of samples dispersed in fresh DMEM. The cells were irradiated with a 980 nm NIR laser (2.2 W cm^{-2}) for different times, and the control experiment was done without NIR irradiation. After the cells were further incubated for 24 h, the medium was removed, 100 μL of fresh medium with 10 μL of CCK-8 solution were added and incubated for another 3 h. The absorbance at 450 nm was measured to calculate the cell viability by a microplate reader. The statistical evaluation of data was performed using a two-tailed unpaired Student's t-test. Each data point is represented as mean ± standard deviation (SD) of independent experiments (n = 5, n indicates the number of wells in a plate for each experimental condition).

Observation of Cellular Uptake of tMOF and Co-Localization in 4T1 cells. To prove the mitochondria-located specificity, 4T1 cells (10^4 cells per dish) were seeded in 35-mm confocal dishes and incubated for 12 h at 37 °C. Then cells were treated with fresh medium containing 100 μg ml^{-1} FITC-labeled tMOF for different durations to observe the intracellular delivery. Afterwards, 0.5 mL of Mito-tracker Deep Red agent in PBS was added and incubated for 15 min to stain the mitochondria. Then, 0.5

ml PBS containing Hoechst 33342 was added to stain the nuclei for another 10 min. After the incubation, the cells were softly washed twice to remove excessive Hoechst 33342 and visualized with a confocal laser scanning microscope under 60×oil-immersion objective. The CLSM images were collected from 500 to 560 nm at 488-nm excition for FITC channel, from 650 to 690 nm at 640-nm excition for Mito-tracker Deep Red channel and 420 to 480 nm at 405 nm excition for Hoechst 33342 channel. For examining the DNA staining effect of the photo-cleavage Ru drug on cells, the 4T1 cells were incubated with R-tMOF (100 μg mL^{-1}) for 2 h and then irradiated with 980 nm light (2.2 W cm^{-2}) for different times. The cells were further incubated for 4 h stained with Mito-tracker Red for 15 min and then Hoechst 33342 for 10 min to collect the CLSM images. The fluorescence signal of DNA stained with Ru drug was collected from 600 to 660 nm excited at 488 nm.

Cell Apoptosis Analysis by Flow Cytometry. Cell apoptosis was detected using the Annexin V-FITC/PI apoptosis detection kit. The 4T1 cells were seeded in the 6-well plates at the density of 1×10^5 cells per well. After adherent, the cells were cultured with tMOF, R-tMOF, H-tMOF and HR-tMOF (with concentration of 100 μg mL^{-1}) for 2 h and irradiated under 980 nm light (2.2 W cm^{-2}) for 20 min. After further incubated for 24 h, cells (1×10^6) were harvested, washed twice with precooled PBS (pH = 7.4), and resuspended in binding buffer according to the manufacturer's protocols. The annexin-V-FITC and PI were added to cells and incubated for 15 min at room temperature in the dark. The induction of apoptosis was determined by Coulter FC-500 flow cytometer (Beckman-Coulter), and the data were processed using Flow Jo software.

Mitochondrial Membrane Potentials Assay. Mitochondrial membrane potential ($\Delta\Psi_m$) was assessed by tetramethylrhodamine ethyl ester (TMRE; Molecular probes). First, 4T1 cells (10^4 cells per dish) were seeded in 35-mm confocal dishes and incubated overnight at 37 °C. Then, these dishes were incubated with tMOF, R-tMOF, H-tMOF and HR-tMOF (with concentration of 100 μg mL^{-1}) for 2 h and irradiated

under 980 nm light (2.2 W cm^{-2}) for 20 min. After further incubated for 4 h, the cells were washed with PBS and treated with 200 nM TMRE for 20 minutes, Mito-Tracker green (10 nM) for 15 min. After incubation, the cells were washed with PBS for three times and added with 200 μL PBS. Then, the fluorescence signal of TMRE was collected the emission 575 nm under the excitation at 549 nm, and the emission 520 nm under the excitation at 490 nm for Mito-tracker Green channel.

Western Blot Analysis. Total Protein Extraction: The 4T1 cells were seeded in the 6-well plates at the density of 1×10^5 cells per well. After adherent, the cells were incubated with tMOF, R-tMOF, H-tMOF and HR-tMOF (with concentration of 100 μg mL^{-1}) for 2 h and irradiated under 980 nm light (2.2 W cm^{-2}) for 20 min. The control experiment was done without NIR irradiation. After further incubated for 24 h, cells were washed twice with cold PBS and extracted by RIPA buffer with protease inhibitors (Roche). After scraped and centrifugation at 10,000 g at 4 °C for 20 min, the supernatants were collected and stored frozen in single-dose vials. Protein concentration is measured by the BCA method. Western Blotting Analysis: Protein samples (30-50 μg) were denatured in 4 × SDS-PAGE sample buffer and were subjected to SDS-PAGE on 4-12% Tris-glycine gels, separated and then transferred to polyvinylidene difluoride membrane. The protein was incubated with rabbit anti-mouse polyclonal antibody (anti-Cleaved Caspase-3, CST; anti-Bax, CST; anti-β-Actin, CST, dilution ratio: 1:1000), horseradish peroxidase-conjugated secondary antibody (anti-rabbit secondary antibody, CST, dilution ratio: 1:2000). Protein bands were visualized using Supersignal West Pico chemiluminescent substrate (PIERCE) according to manufacturer's directions.

Mitochondria Morphology Analysis by TEM. Bio-TEM was used to investigate the effect of HR-tMOF on the ultrastructure of cell organelles. 4T1 cells were incubated with HR-tMOF (100 μg mL^{-1}) for 2 h, and irradiated under 980 nm light (2.2 W cm^{-2}) for 20 min. The control experiment was performed without NIR irradiation. After further incubated for 24 h, cells fixed with 1 mL of general fixative (containing

2.5% glutaraldehyde in 0.1 M phosphate buffer) at 4 °C for 2 h. After dehydration, cells were embedded in epoxy resin, and the resin was stored at 55 °C for 48 h to allow resin polymerization. The embedded samples were then sliced with a thickness of 50−70 nm. Finally, the cell sections were observed under TEM (HITACHI, HT7700). Mitochondria in about 20 cells were analyzed for each group.

Antitumor Effect in a Subcutaneous Model. All animal assays obeyed the institutional animal use and care regulations approved by the Model Animal Research Center of Nanjing University (MARC). To establish a 4T1 tumor xenograft mouse model, female BALB/c mice (6-8 weeks-old) were chosen to be inoculated with 4T1 cells (1.0×10^6) subcutaneously into the right flank position. The tumor volumes were calculated using formula $V = 0.5 \times A \times B^2$ (A refers to the tumor length and B refers to the tumor width). After the tumor volume of mice approached about 100 mm^3, mice were randomly divided into different groups: (1) PBS, (2) tMOF, (3) H-tMOF, (4) R-tMOF, (5) HR-tMOF, (6) PBS+laser, (7) tMOF+laser, (8) H-tMOF+laser, (9) R-tMOF+laser, (10) HR-tMOF+laser. Then, the tumor-bearing mice were intravenously (n = 10 mice per group) injected with different formulations (100 μg per mouse) via tail vein. All injections were administered in total, at 2-day intervals. After 4 h-injection, the tumors of the mice in groups (6), (7), (8), (9) and (10) were exposure under 980-nm laser (1.0 W cm^{-2}) for 20 min (5-min break for each 10-min exposure), while groups (1), (2), (3), (4) and (5) were not irradiated as controls. Tumor volumes were measured every day for 14 days. Five mice of every groups were selected to be euthanized and the tumors were harvested, the major organs and tumors were sectioned for hematoxylin-eosin staining (H&E) and immunofluorescence analyses. The rest of mice was asphyxiated at 22 days, and the lungs were harvested and measured to determine metastasis.

Statistical Analysis. Data were presented as mean ± standard deviation (SD) through at least three experiments. Statistical analyses were performed using the two-tailed Student's t-test. *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ were considered statistically significant.

Supporting Figures

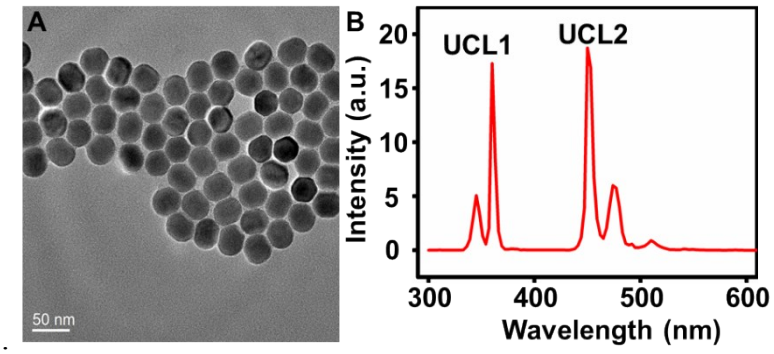


Figure S1. (A) TEM image and (B) UCL spectra of UCNPs.

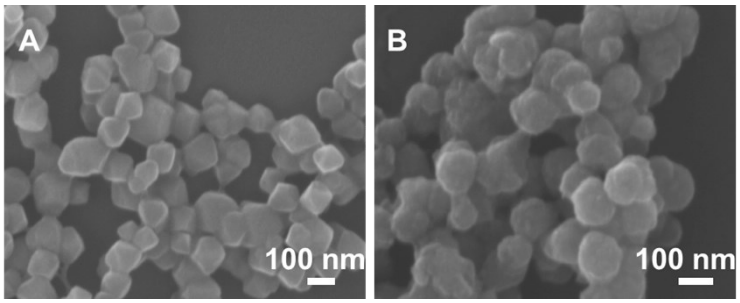


Figure S2. SEM images of (A) UiO-AZB and (B) UMOF.

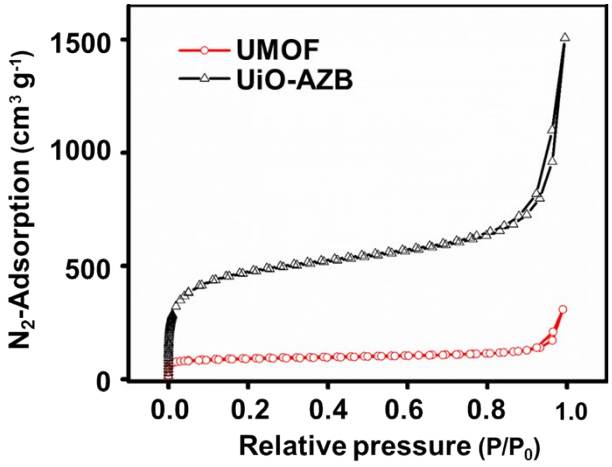


Figure S3. N_2 adsorption isotherms of UiO-AZB and UMOF. UiO-AZB has a larger surface area with BET surface area of 1637.39 $m^2\ g^{-1}$ than 312.12 $m^2\ g^{-1}$ of UMOF.

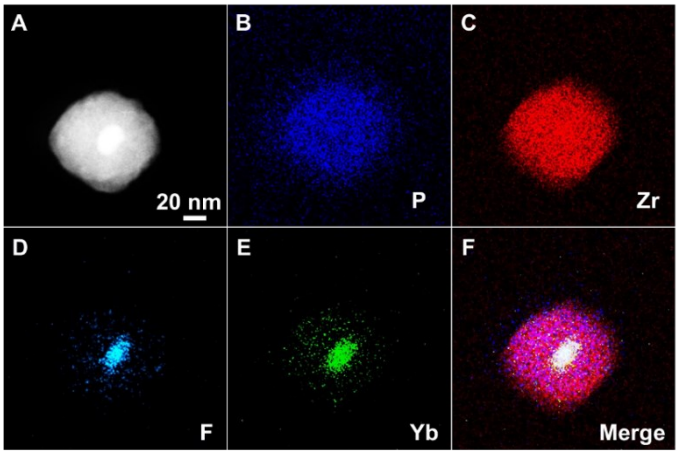


Fig. S4. (A) TEM and (B-F) the corresponding elemental mapping images of a single tMOF.

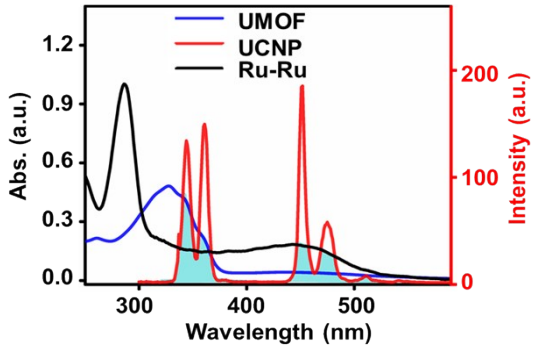


Figure S5. Absorption spectra of the UMOF, **Ru-Ru** prodrug and UCL spectrum of UCNPs. The overlap is indicated in blue.

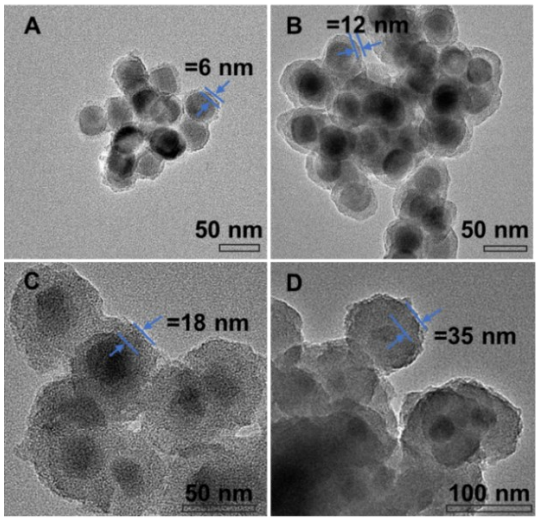


Figure S6. TEM images of UMOF synthesized with different reaction time of (A) 5 min, (B) 20 min, (C) 2 h and (D) 5 h. The blue arrows indicate the thickness of MOF shell.

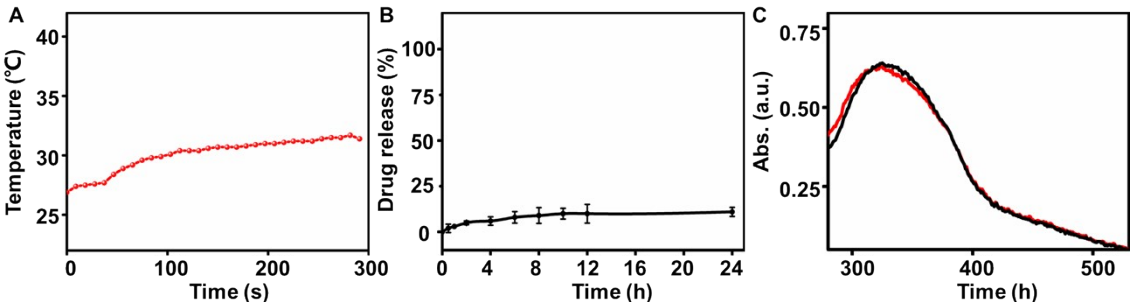


Figure S7. (A) Photothermal heating curve of water under 980 nm light irradiation (2.2 W cm^{-2}). (B) The cumulative drug release of H-UMOF under 37 ℃. (C) Absorption spectra of UMOF at 37 ℃ (red) and 25 ℃ (black).

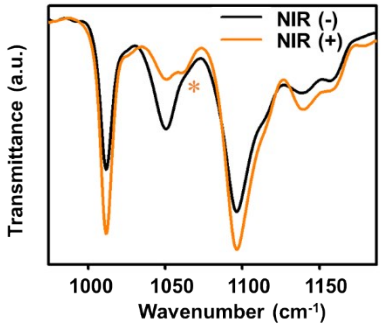


Figure S8. FT-IR of UMOF with (orange) and without (black) NIR light irradiation for 30 min. The new peak at 1062 cm^{-1} appeared after light irradiation.

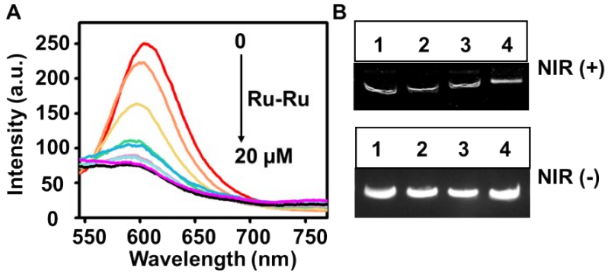


Figure S9. (A) Emission spectral traces of EB (ethidium bromide, 5 μM) bound ct-DNA (100 μM) with varying concentration of **Ru-Ru** prodrug (0, 2, 4, 6, 8, 10, 15, 18, 20 μM) in 5 mM tris buffer (5 mM Tris-HCl pH 7.5) upon light irradiation (450 nm) for 1 h. The arrow indicates the decrease in intensity on increasing complex concentration. (B) Agarose gel electrophoresis showing pattern of pBR322 DNA (200 ng mL^{-1}) in Tris-HCl (5 mM, pH = 7.5) in the presence of complexes in 50 mM Tris-HCl/NaCl buffer (pH = 7.5) at different concentration of **Ru-Ru** prodrug upon light irradiation (450 nm) or dark for 1 h. Lane 1: DNA control, lanes 2-4: DNA + **Ru-Ru** prodrug with concentration of 4, 10, and 20 μM.

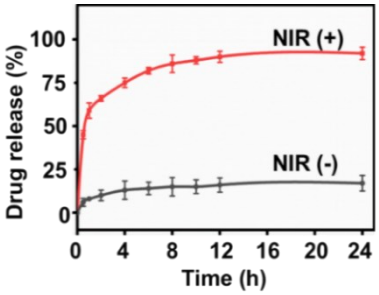


Figure S10. The cumulative drug release of H-UMOF in aqueous solution under NIR light or dark. Quantitatively, less than 20% drug leakage of HCPT was observed in the dark, whereas the accumulative drug release reached more than 80% under NIR light irradiation.

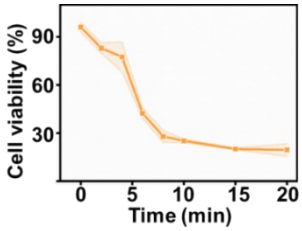


Figure S11. Cytotoxicity assays of 4T1 cells treated with HR-tMOF (100 μg mL^{-1}) irradiated under NIR light with different time.

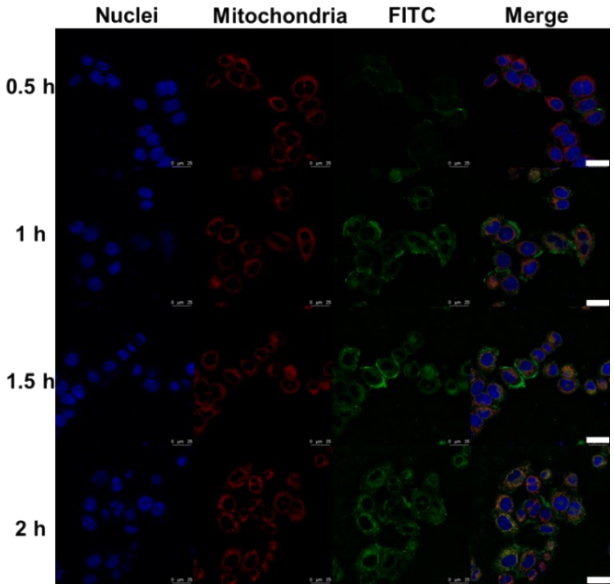


Figure S12. Confocal fluorescence imaging of 4T1 cells incubated with FITC-labeled tMOF (100 μg mL^{-1}) at different time. The nuclei were stained with Hoechst 33342, the mitochondria were labeled with Mito-tracker Red. The FITC-labeled tMOFs were used to track the tMOF in cells. Scale bars = 25 μm.

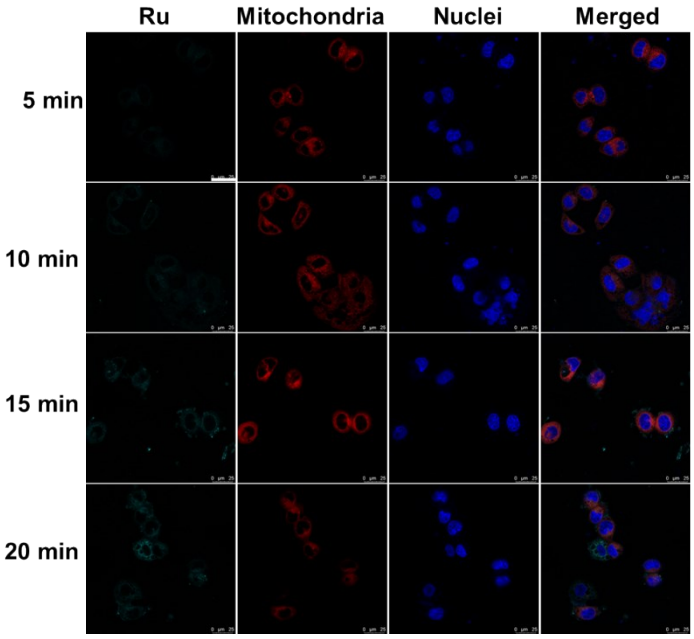


Figure S13. Colocation of the active **Ru** drug cleaved from R-tMOF (100 μg mL^{-1}) in 4T1 cells with Mito-Red under 980 nm NIR irradiation. The nuclei were stained with Hoechst 33342, Scale bars: 25 μm.

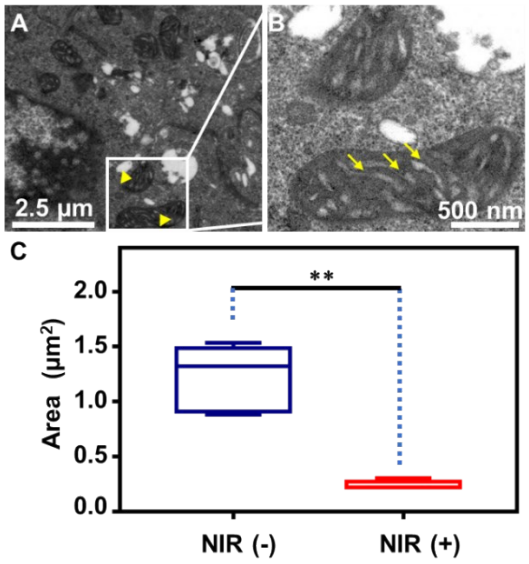


Figure S14. (A) Ultrastructural analysis and (B) the corresponding magnified views of 4T1 cancer cells treated with HR-tMOF (100 μg mL^{-1}) without NIR light by TEM and (C) quantitative analysis of the average mitochondrion area in two groups. Box plots are collected from in 20 cells' mitochondria. **$p < 0.01$ (two-tailed Student's t-test).

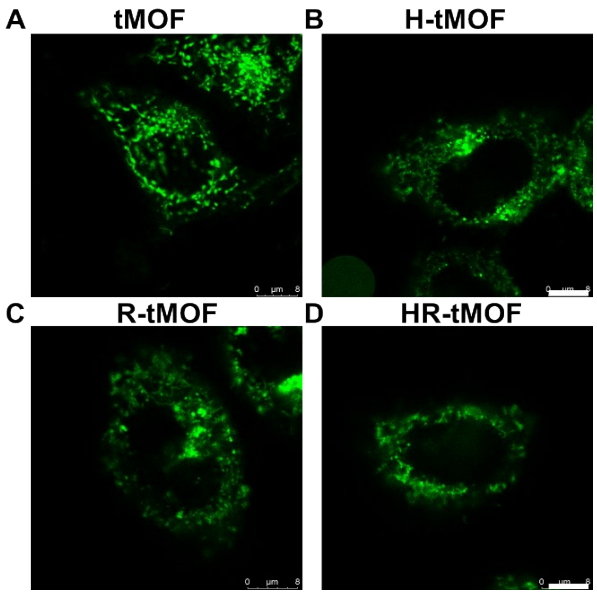


Figure S15. Morphological changes of 4T1 cells mitochondria after treated with tMOF, H-tMOF, R-tMOF and HR-tMOF (100 μg mL^{-1}) and irradiated under NIR light for 20 min. The mitochondria were stained by Mito-tracker Green. Scale bar = 8 μm.

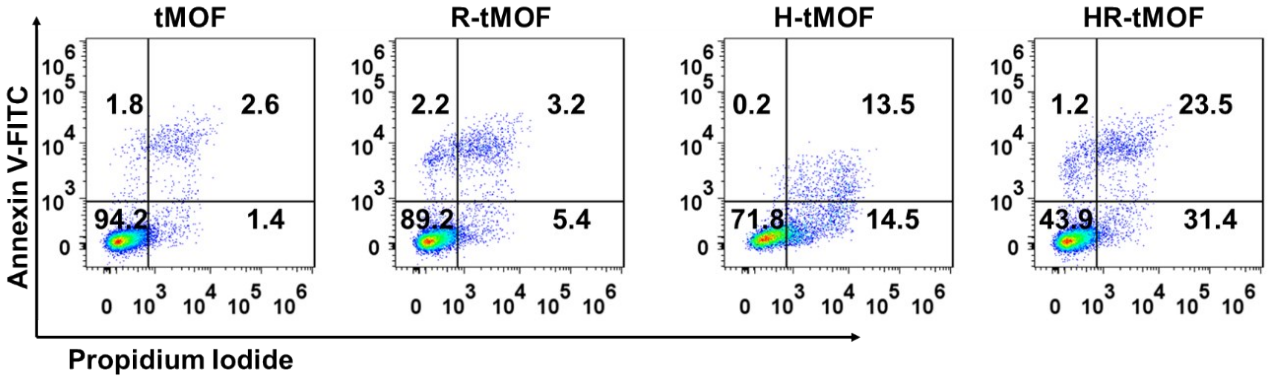


Figure S16. The apoptosis analysis of 4T1 cells after incubated with tMOF, R-tMOF, H-tMOF and HR-tMOF (100 μg mL^{-1}) and irradiated under NIR light for 20 min and then culture for 24 h. Cells were stained with Propidium Iodide and Annexin V-FITC.

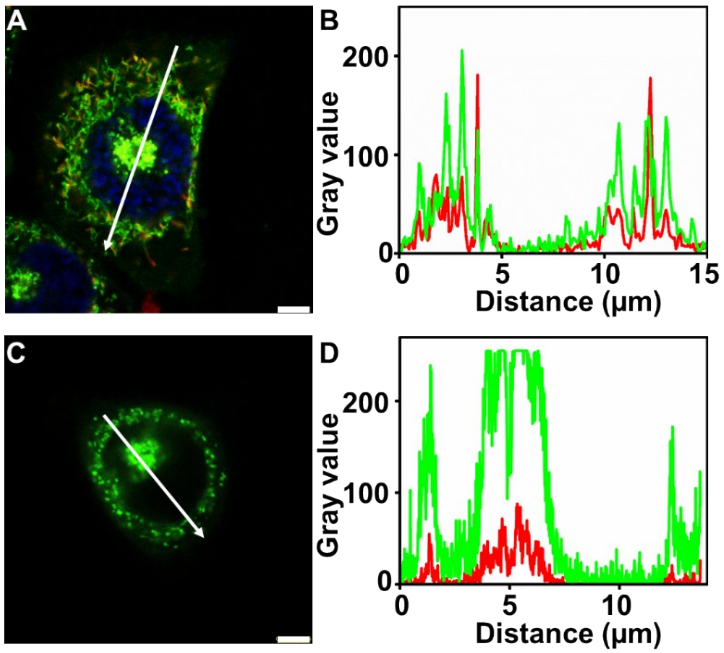


Figure S17. Confocal fluorescence images of 4T1 cells treated with HR-tMOF (100 μg mL^{-1}) irradiated without (A) and (C) with NIR light. The relative fluorescence intensity distributed along with the white lines was shown in (B) and (D), respectively, the red line indicated the TMRE and the green line indicated the Mito-Green. Scale bars = 5 μm.

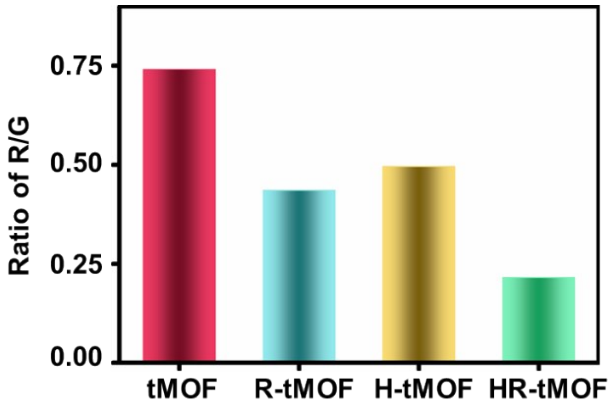


Fig. S18. R/G ratio of fluorescence mean intensities from confocal images of treated 4T1 cells under NIR light. R and G represent the mean intensity of TMRE and Mito-tarcker channels, respectively.

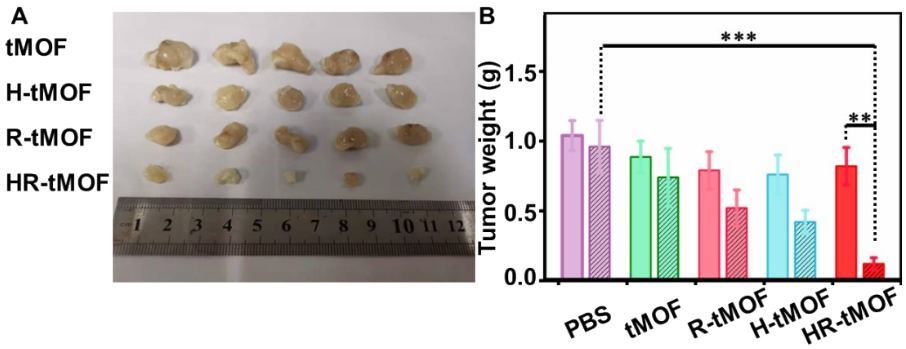


Figure S19. (A) Representative images of xenograft tumors after 14-day treatment with different samples under NIR light irradiation. (B) Tumor weight analysis of mice after 14-day treatment. The solid column and the striped column represent cells were treated without and with NIR light, respectively. The concentration of samples was 100 μg mL^{-1}. **p < 0.01, ***p < 0.001 (two-tailed Student's t-test).

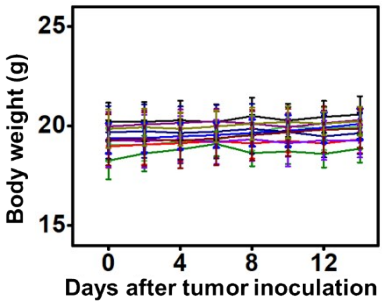


Figure S20. The change of average body weight of tumor-bearing mice with different treatment. The error bars indicate means ±S. D. (n = 5). There is no significant change in mice body weight during the treatment.

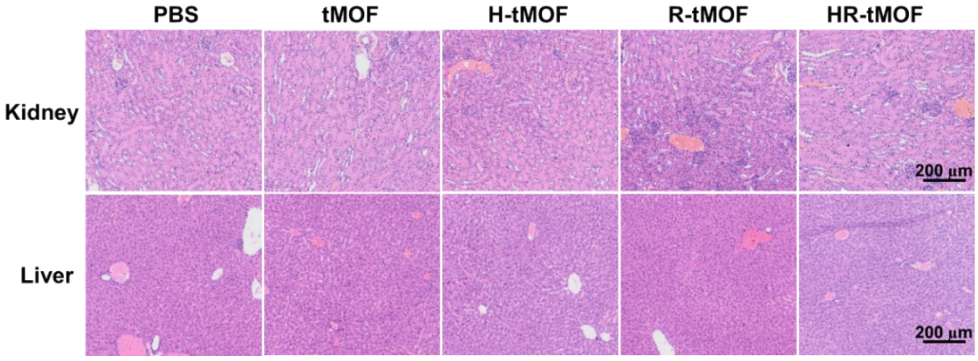


Figure S21. Histological observation of the kidney and liver after 14-day treatment with various samples under NIR light irradiation. The sections were stained with haematoxylin and eosin (H&E).

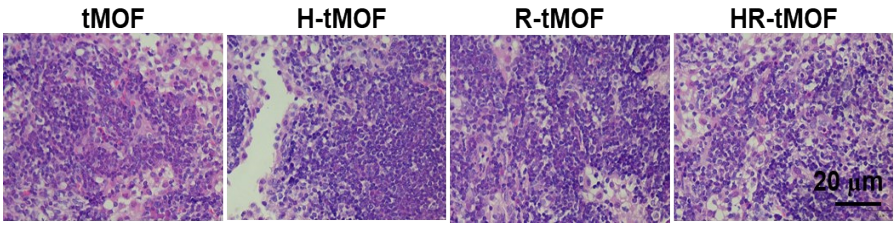


Figure S22. Histological observation of the tumor tissues after 14-day treatment with various samples without NIR light irradiation.

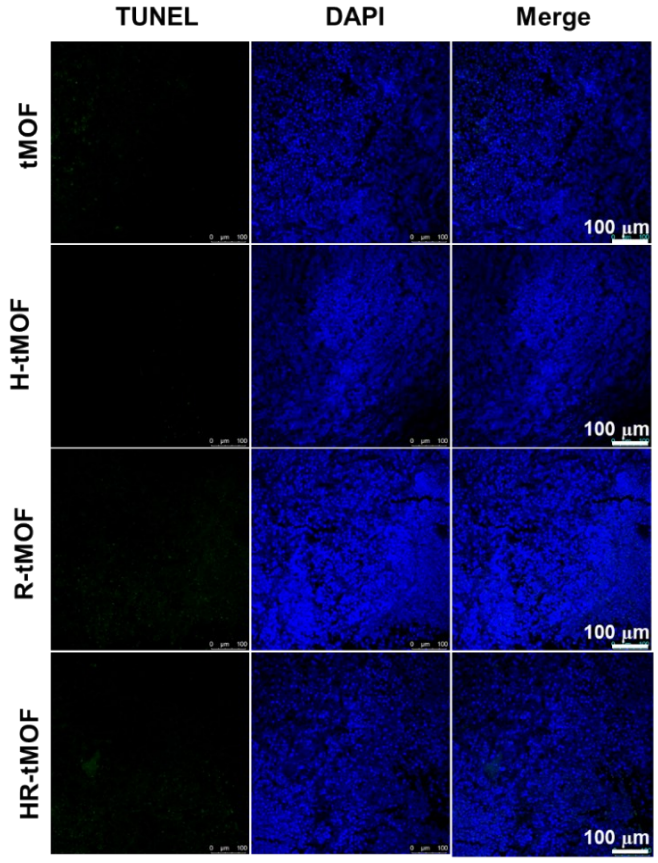
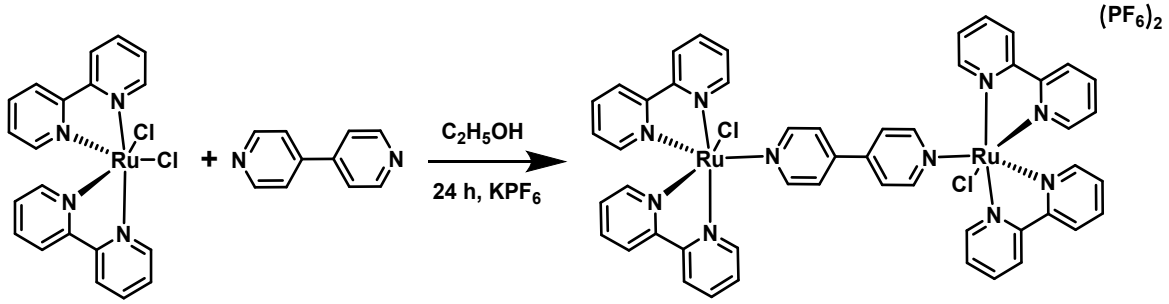


Figure S23. TUNEL staining images of the tumor slices after 14-day treatment with various samples without NIR light irradiation. The TUNEL staining was indicated by the green channel and the nuclei were collected with the blue channel.



Scheme S1. Synthesis route of Ru-Ru prodrug.

Table S1. Gradient elution program of HPLC analysis.

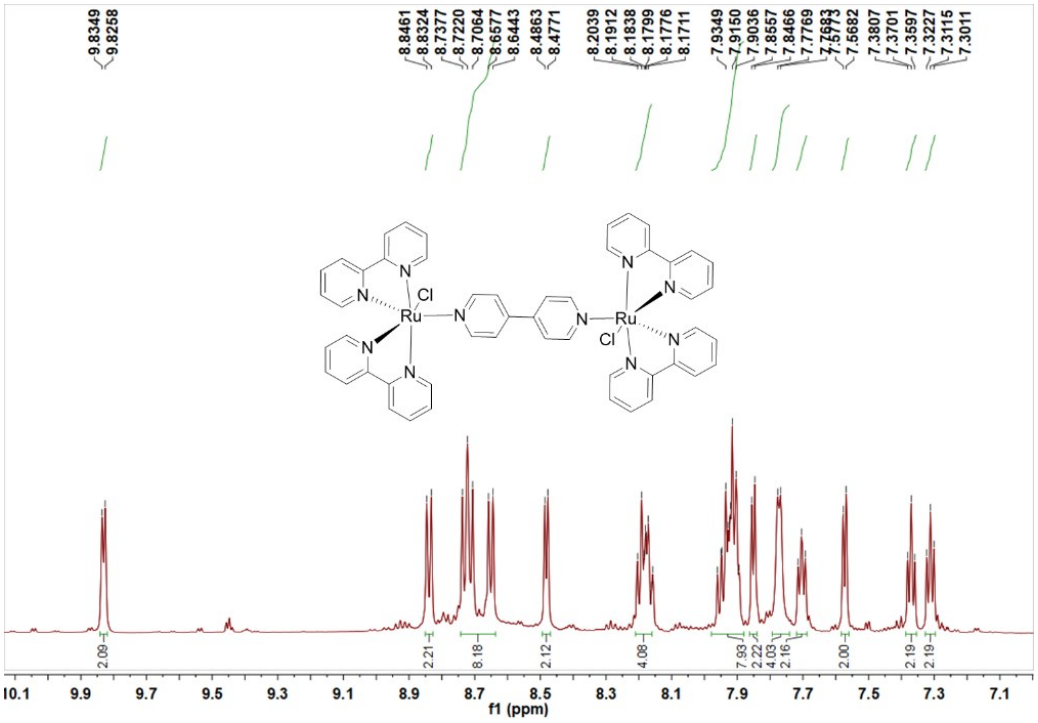
Time (min)	0.1% formic acid in H_2O	0.1% formic acid in MeCN
0	80	20
10	60	40
15	0	100
20	0	100

Table S2. Quantitative analysis of the photoluminescence spectra of UMOF with different thickness of MOF shell.

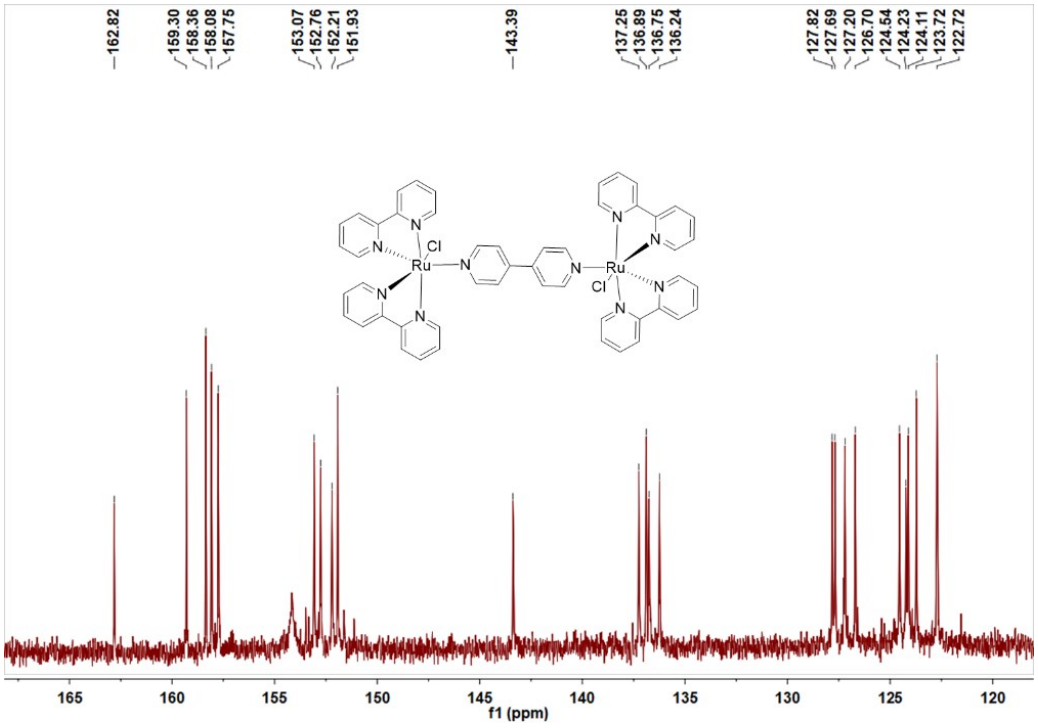
Thickness of UMOF shell (nm)	Lifetime of Tm^{3+} emissio at 345 nm (μs)	Energy transfer efficiency (%)	Thickness of UMOF shell (nm)
0	211	—	0
18	76	64.0	18

Appendix 1H NMR and 13C NMR spectra

^{1}H NMR spectrum of **Ru-Ru** prodrug (DMSO)



^{13}C NMR spectrum of **Ru-Ru** prodrug (DMSO).



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