Supporting Information

Core-shell metal-organic frameworks with fluorescence switch to trigger an enhanced photodynamic therapy

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Experimental Section

Materials: All reagents used were purchased from Sigma-Aldrich, unless otherwise stated. Live/dead cell staining kit, $KMnO_4$, and GSH were purchased from Fisher Scientific. Zinc nitrate hexahydrate, 2-methylimidazole were purchased from Fisher Scientific. Singlet oxygen sensor green (SOSG) and fetal bovine serum were purchased from Invitrogen. Meso-tetra(4-carboxyphenyl) porphine (TCPP) was purchased from Frontier Scientific. The water used was purified with a Milli-Q Biocell System. All aforementioned chemicals were used as received without further processing. The U87MG human glioblastoma cell line was obtained from the American Type Culture Collection and cultured with DMEM in a cell culture flask. Athymic nude mice were purchased from Envigo laboratories. The tumor model was established by subcutaneously injection of around 5×10^6 U87MG cells into the right hind limb of the mice. All the experimental procedures had been conducted following a protocol approved by the Animal Care and Use Committee (ACUC) of the National Institutes of Health Clinical Center (NIHCC).

Characterization: Transmission electron microscopy (TEM) images were acquired on a Tecnai TF30 transmission electron microscope (TEM) (FEI, Hillsboro, OR). The X-ray diffraction measurements were performed on a Bruker D8 ADVANCE diffractometer, employing the standard setup in reflection geometry. UV-Vis absorption was measured by a Genesys 10S UV-vis spectrophotometer. The concentrations of platinum were collected by inductively coupled plasma optical emission spectroscopy (ICP-OES, Agilent 720-ES).

Synthesis of ZIF-8: In a typical synthesis of 50 nm ZIF-8 nanoparticles [1], $Zn(NO_3)_2$ (150 mg) was dissolved in 7 mL of methanol. Then, 2-methylimidazole (330 mg) was seperately dissolved in 7 mL of methanol, and the resulting solution was injected into the Zn solution with vigorous

stirring. After 5 minutes, the mixture turned cloudy. The reaction was stopped and the ZIF-8 nanoparticles were washed with methanol and resuspended in DMF for further use.

Synthesis of zirconium-based porphyrinic MOF (ZrMOF) nanoparticles: In a typical synthesis [2], $ZrOCl_2$ (30 mg), meso-tetra(4-carboxyphenyl)porphyrin (TCPP) (10 mg) and benzoic acid (270 mg) were dissolved in 10 mL of DMF in a 20 mL vial. The solution was sonicated and incubated in an oil bath at 90°C for 5 h. The resulting product was collected by centrifugation, washed with DMF, and resuspended in DMF for further use.

***In situ* growth of MnO_2 nanodots on ZIF-8 nanoparticles:** Typically, ZIF-8 nanoparticles were washed with methanol and finally redispersed in deionized water. Aqueous $KMnO_4$ solution (2mL, 1mg/mL) was introduced to the aqueous ZIF-8 nanoparticle solution with vigorous stirring at room temperature. After 30 min, the resulting ZIF-MnO_2 core-satellites hybrid nanoparticles were washed with water and resuspended in water.

***In situ* growth of MnO_2 nanosheet on the surface of porphyrinic ZrMOF nanoparticles:** In a typical synthesis, ZrMOF nanoparticles were first washed with water and resuspended in water. Aqueous $KMnO_4$ solution (2mL, 1mg/ mL) was introduced to the aqueous ZrMOF nanoparticle solution with strong stirring at room temperature. The resulting mixture was incubated for 30 min. Finally the product was washed with water and resuspended in water.

LC-MS: To prepare the sample for LC-MS, GSH was dissolved in water with a concentration of 5 mM. To confirm the GSSH conversion from GSH, GSH solution (5 mM) was treated with ZrMOF@MnO_2 fro 30 min. The resulting mixture was centrifuged for 5 min at 14000 RPM and the supernatant was collected. Finally, GSH and GSSH solution were characterized by LC-MS.

GSH-activated in vitro and in vivo MRI: Different concentrations of aqueous ZrMOF@MnO_2 nanoparticles were treated with GSH for 5 min. The resulting solutions were scanned by a MRI

system. For the in vivo MRI study, PEGylated ZrMOF@MnO_2 nanoparticles were intraveniously injected into U87MG tumor-bearing mice. Magnetic resonance imges were aquired at different time.

In vitro cytotoxicity study: MTT assay was conducted to investigate photodynamic therapy and cytotoxicity. Typically, U87MG cells were seeded in a 96-well plate at a concentration of 5,000 cells per well and cultured at 37 °C, 5% CO_2 for 24 h. The cells were washed with fresh medium and then corresponding MOF nanoparticles were added. The cells with MOF nanoparticles were incubated at 37 °C, 5% CO_2 for 48 h. Then, 10 μL of MTT (5 mg/mL in PBS) was added to the cells and incubated for 4 h. Finally, the medium was replaced with 100 μL of DMSO. The absorbance of each well was measured at 490 nm with a plate reader.

Confocal microscopy: The U87MG cells were first seeded in an 8-well Lab-Tek cover-glass slide with a concentration of 25,000 cells per well. MOF nanoparticles were added and incubated with cells for 2 hours at 37 °C, 5% CO_2. After washing with PBS for three times, Z-Fix solution was added to fix the cells at 37 °C, 5% CO_2 for 20 min. Mounting medium with DAPI was then added to stain for 30 min. Confocal images were obtained from a fluorescence microscope (Zeiss LSM 780).

Live and dead assay: Cell live/dead assay was conducted with a staining kit. U87MG cells (25,000) were seeded in an 8-well Lab-Tek cover-glass slide for an overnight incubation. ZrMOF and ZrMOF@MnO_2 nanoparticles were added and incubated with U87MG cells for 5 hours. Subsequently, laser irradiation (650 nm, 0.2 W/cm^2) was applied for 5 min. The Calcium AM/PI working solutions were added to cells and incubated for 30 min. The cells were then washed with PBS after removing the cell culture media. The slides were finally observed under a fluorescence microscope.

References

1. Zhuang J, Kuo C-H, Chou L-Y, Liu D-Y, Weerapana E, Tsung C-K. Optimized metal–organic-framework nanospheres for drug delivery: evaluation of small-molecule encapsulation. ACS Nano. 2014; 8: 2812-9.

2. Park J, Jiang Q, Feng D, Mao L, Zhou H-C. Size-controlled synthesis of porphyrinic metal–organic framework and functionalization for targeted photodynamic therapy. J Am Chem Soc. 2016; 138: 3518-25.

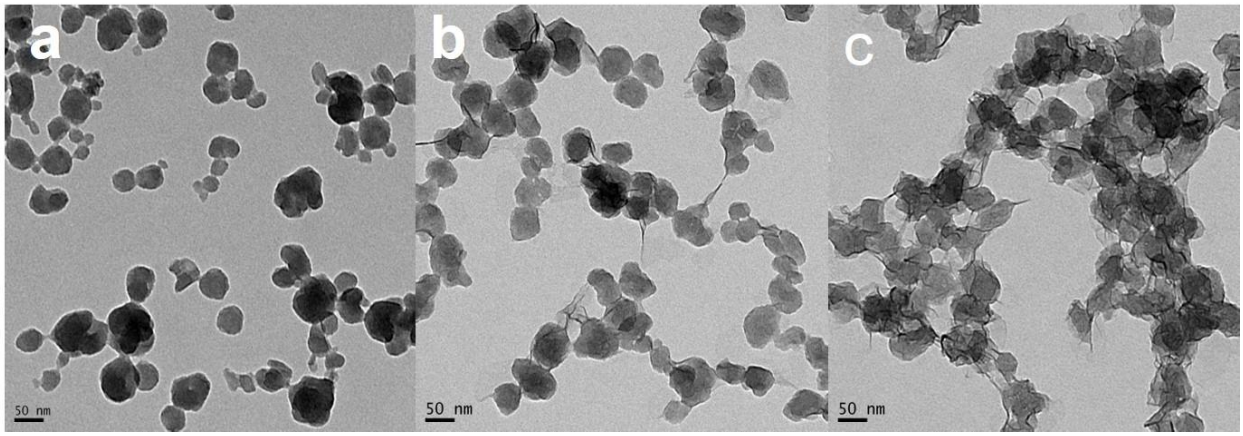

Figure S1. a TEM of ZrMOF nanoparticles. **b** TEM of ZrMOF@MnO_2-1. **c** TEM of ZrMOF-2. ZrMOF@MnO_2-1 was prepared with 2 mL of 1mg/mL of $KMnO_4$. ZrMOF@MnO_2-2 was prepared with 4 mL of 1mg/mL of $KMnO_4$.

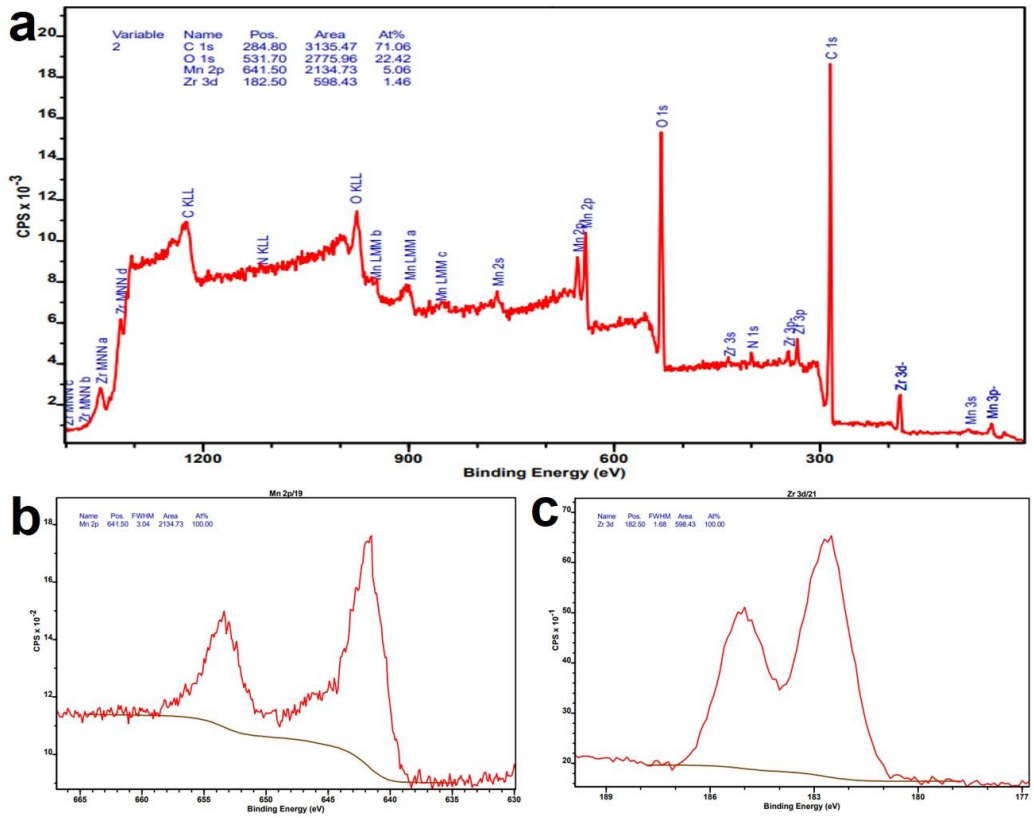

Figure S2. a XPS of ZrMOF@MnO_2 nanoparticles. **b** Mn binding energy. **c** Zr binding energy.

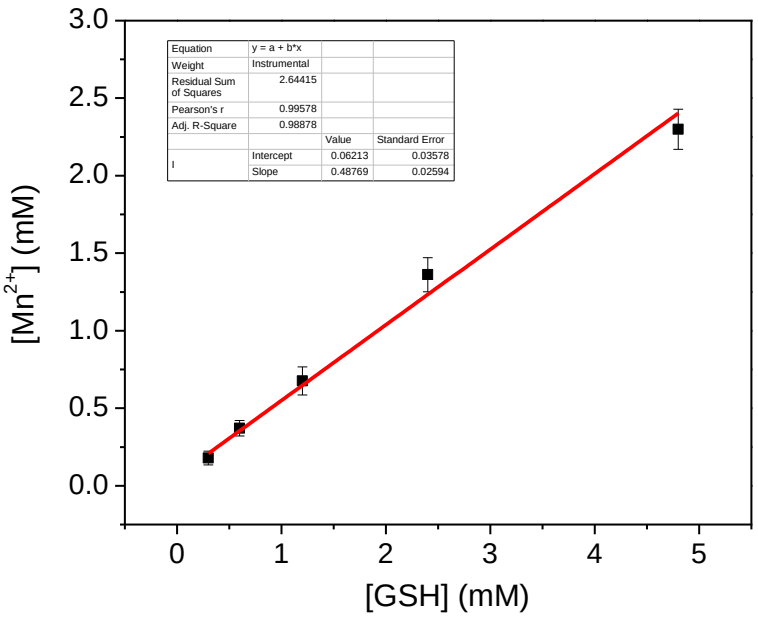

Figure S3. Standard curve of Mn^{2+} released from ZrMOF@MnO_2 with treatment of different concentration of GSH.

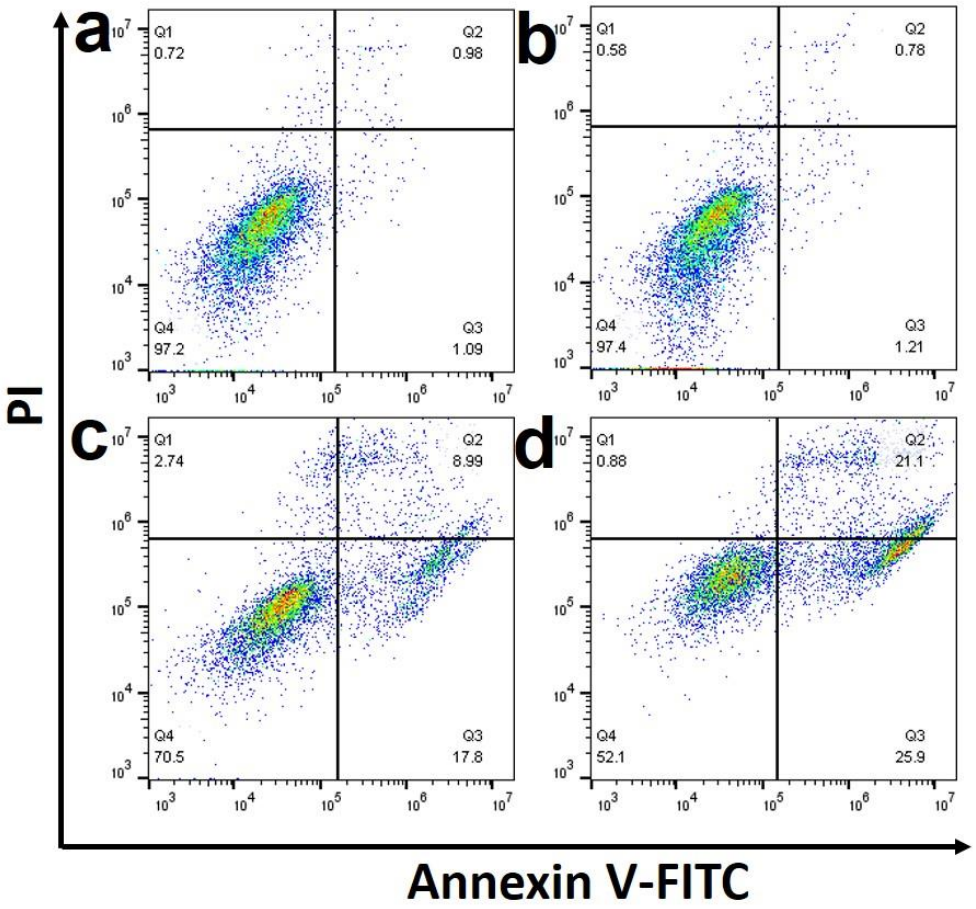

Figure S4. The cell apoptosis-based flow cytometry. **a** Cell only. **c** Cell + laser. **c** ZrMOF + laser. **d** ZrMOF@MnO_2 + laser.

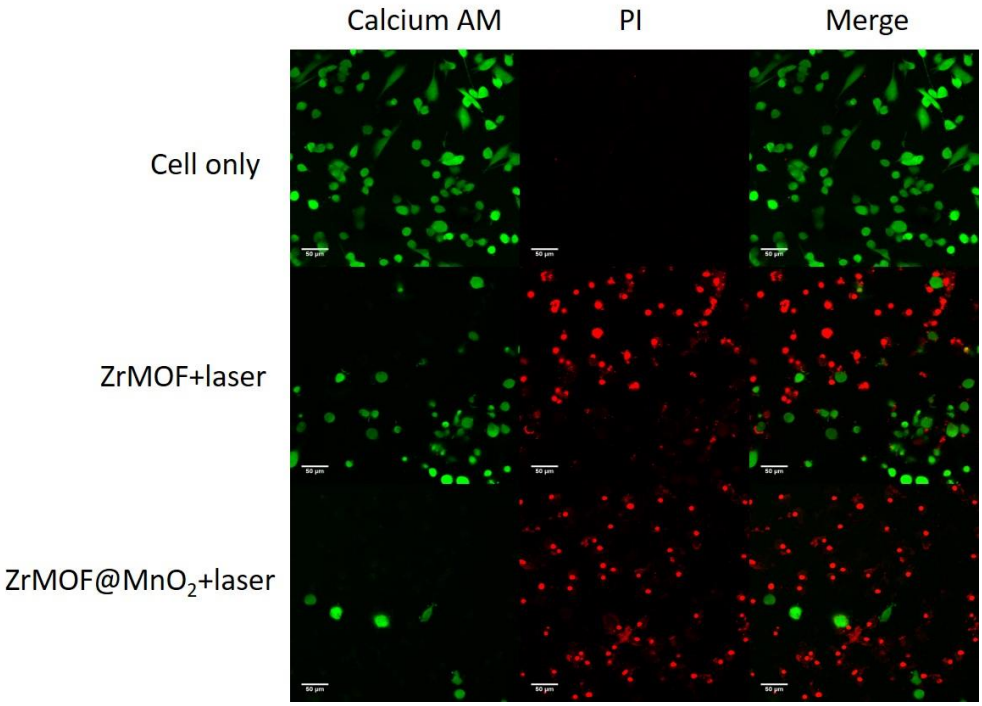

Figure S5. Live/dead cell staining of ZrMOF + laser and ZrMOF@MnO_2 + laser nanoparticles.

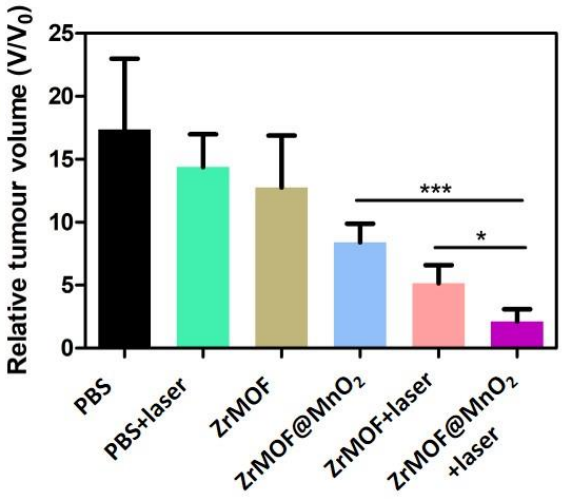

Figure S6. Relative tumor volume of various groups after 11 days. (*P* values, **P* < 0.05, ****P* < 0.001, are calculated by t-test).

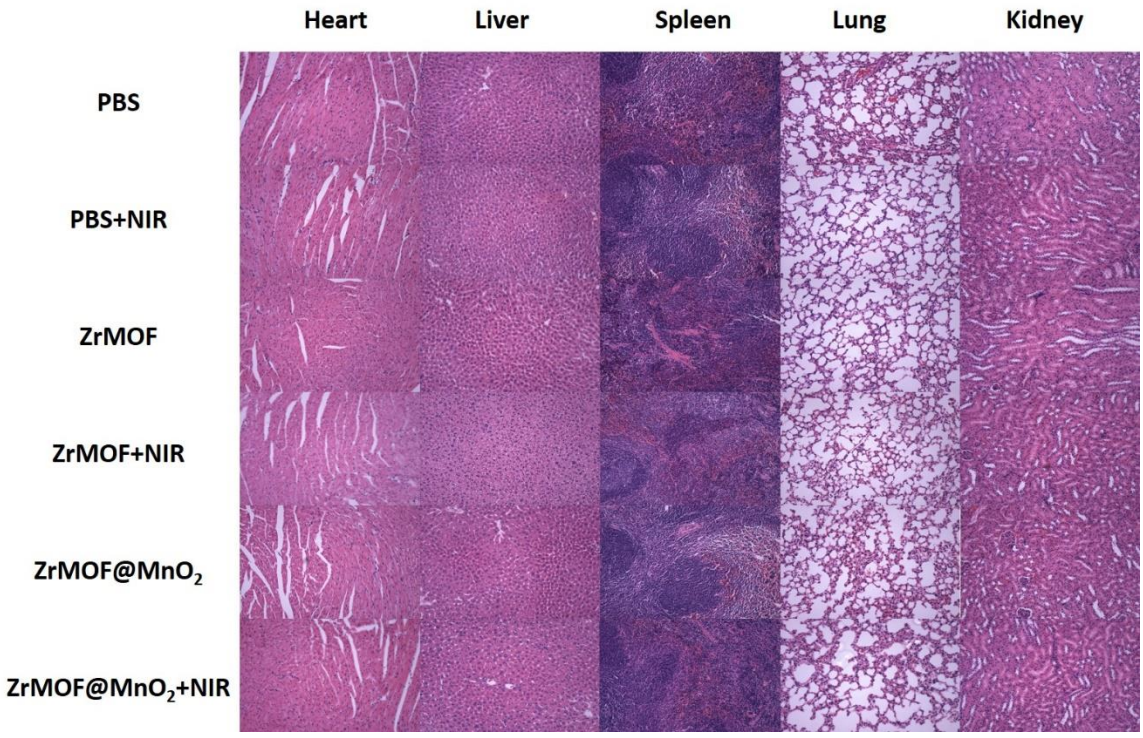

Figure S7. H&E staining images of organs acquired from different groups of mice after 11 days post-treatment.

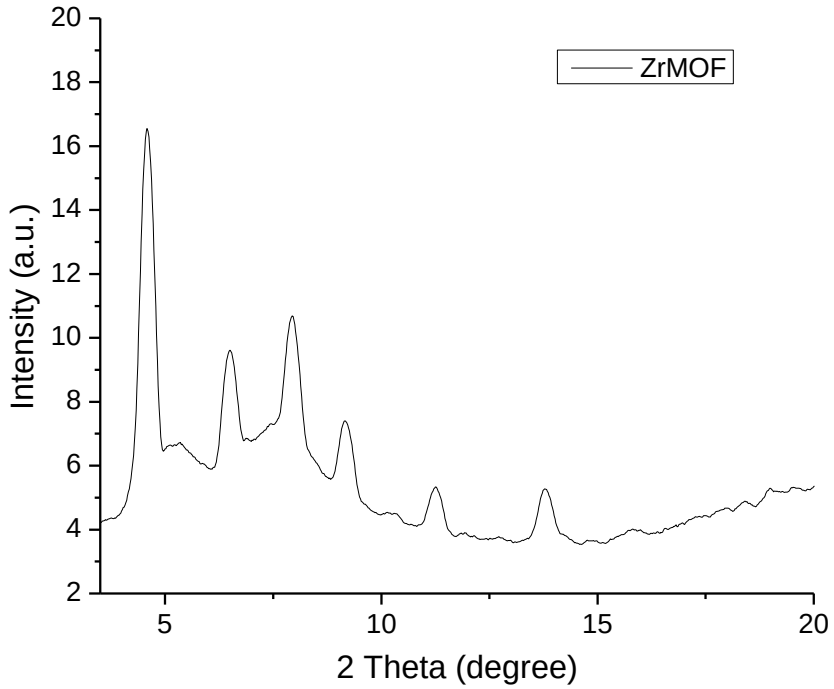

Figure S8. Powder X-Ray of ZrMOF nanoparticles.

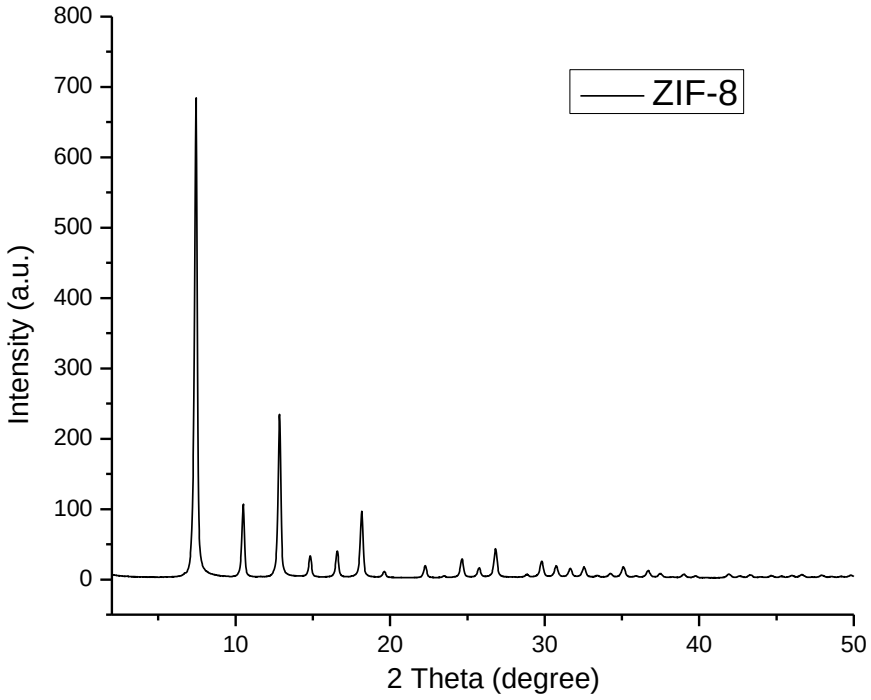

Figure S9. Powder X-Ray of ZIF-8 nanoparticles.