Supporting Information

Self-reported and Self-facilitated Theranostic Oxygen Nano-economizer for Precise and Hypoxia Alleviation-potentiated Photodynamic Therapy

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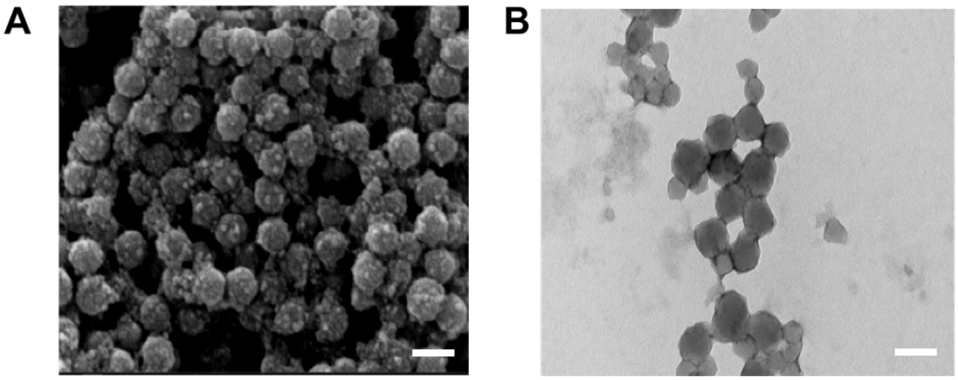

Figure S1. (A) SEM image and (B)TEM image of DPA-MOF, scale bar = 200 nm.

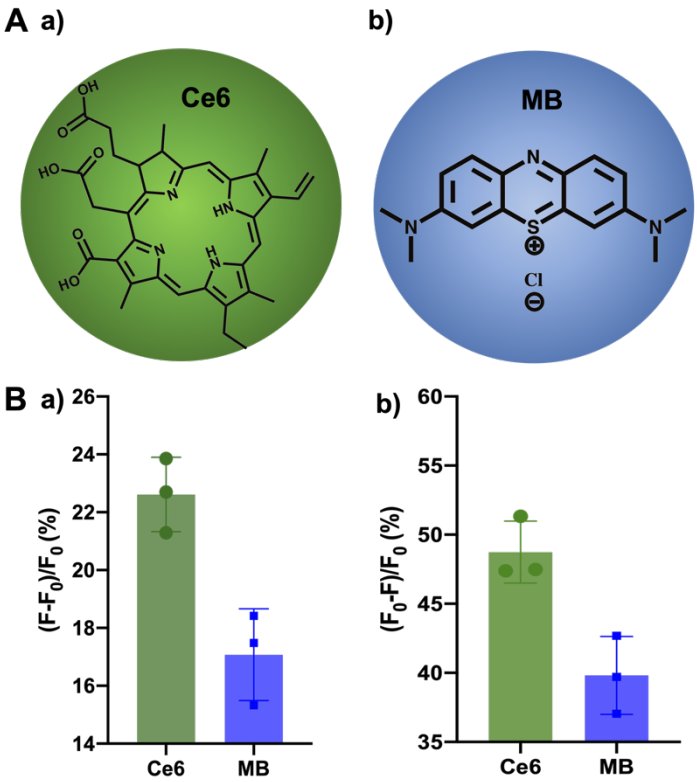

Figure S2. (A) Chemical structures of (a) Ce6 and (b) MB; and (B) Singlet oxygen generated by Ce6 and MB were reported via (a) SOSG probe and (b) DPA-MOF under laser (660 nm, 50 mW/cm^2).

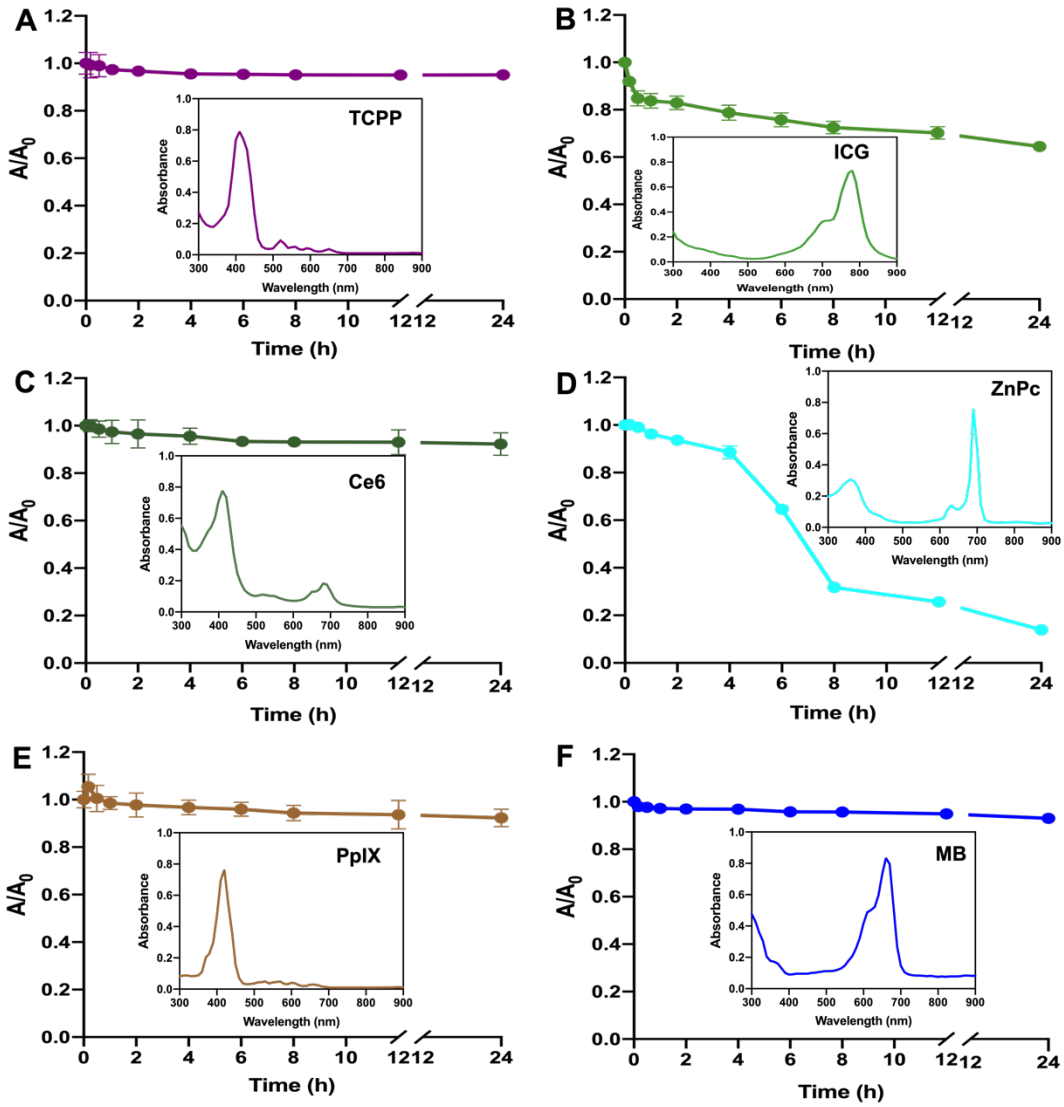

Figure S3. Photostability of (A) TCPP, (B) ICG, (C) Ce6, (D) ZnPc, (E) PpIX and (F) MB upon laser irradiation (660 nm, 50 mW/cm^2), A_0 is the initial absorbance maximum and A is the absorbance maximum of the samples.

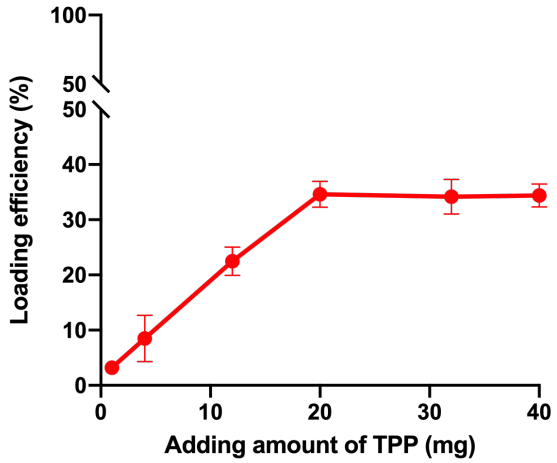

Figure S4. Loading efficiency of TPP with different adding amount.

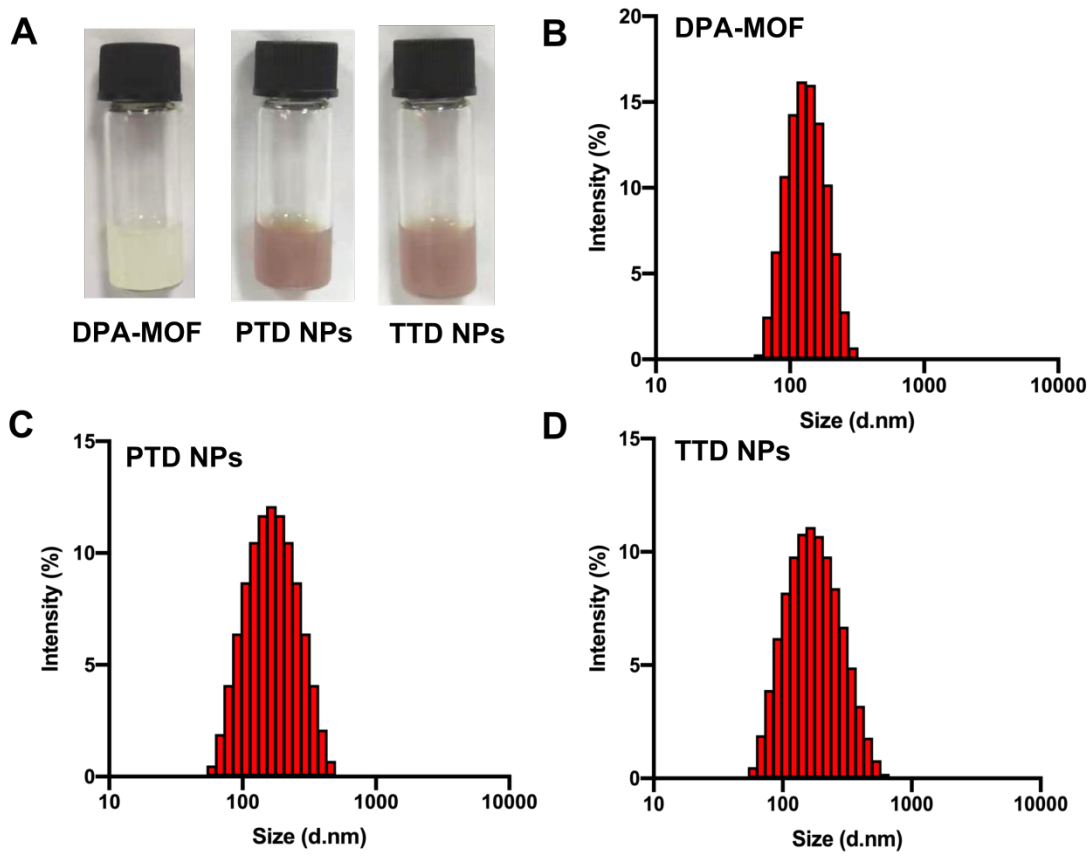

Figure S5. Appearance photos and particle size distribution profiles of DPA-MOF, PTD NPs and TTD NPs.

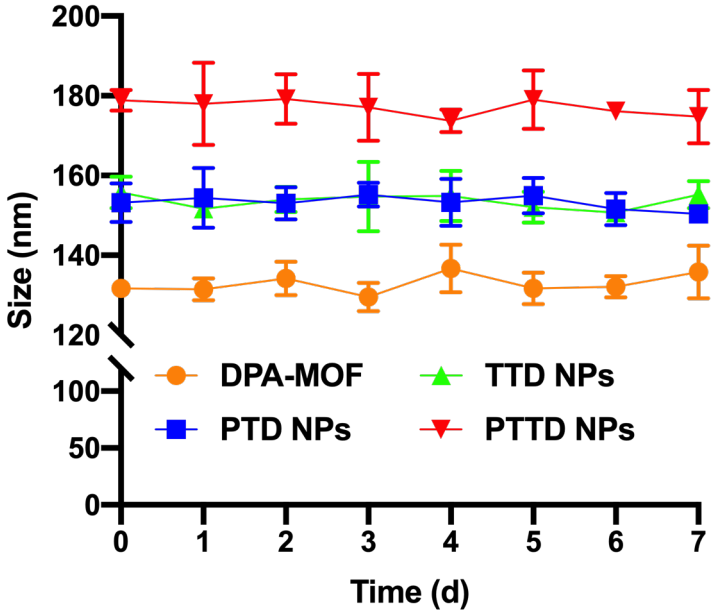

Figure S6. Long-term stability of DPA-MOF, PTD NPs, TTD NPs and PTTD NPs stored at 4 ℃ refrigerator for one week.

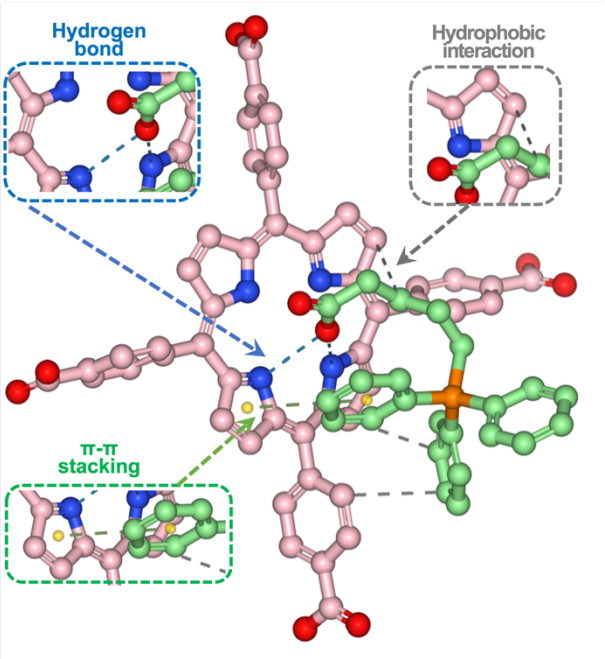

Figure S7. Molecular docking simulation of TCPP and TPP.

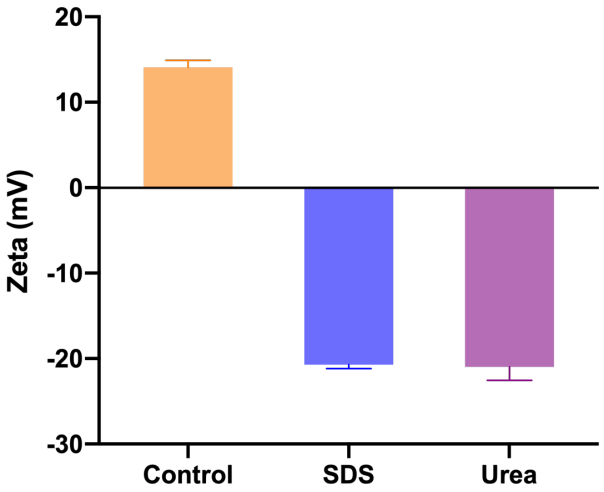

Figure S8. Zeta potential changes of TTD NPs treated with SDS (200 mM) and urea (200 mM).

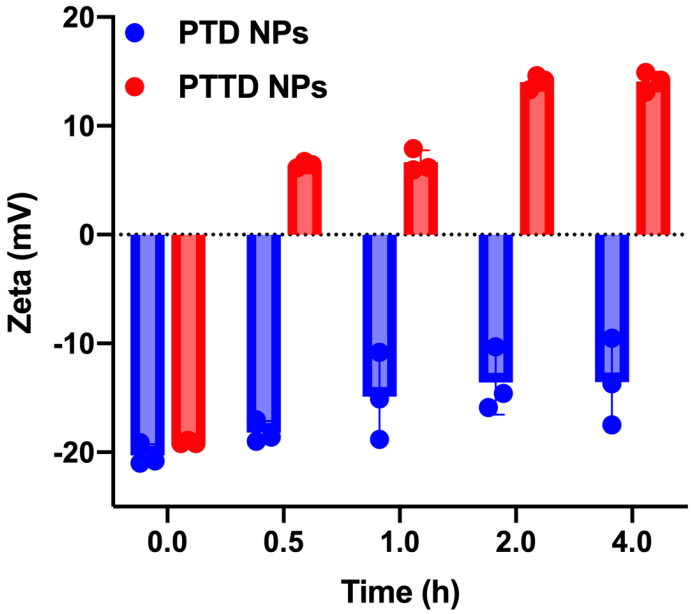

Figure S9. Zeta potential changes of PTD NPs and PTTD NPs in the presence of DTT (1 mM).

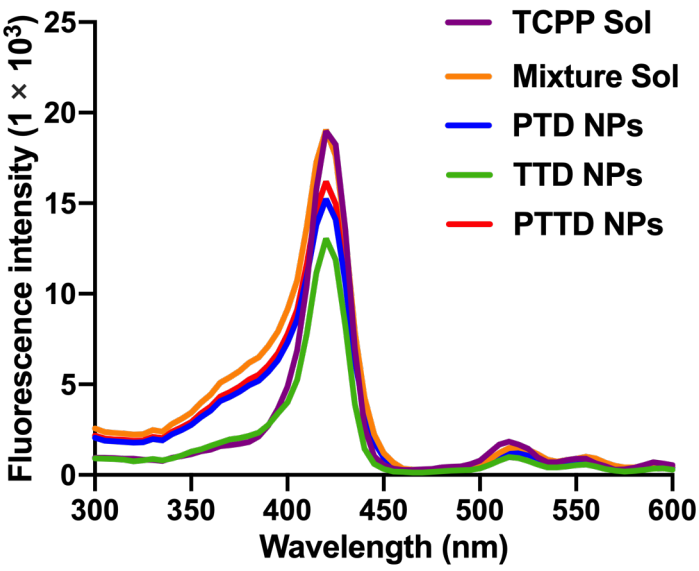

Figure S10. Fluorescence excitation peak of TCPP solution, mixture solution of DPA-MOF and TCPP, PTD NPs, TTD NPs and PTTD NPs.

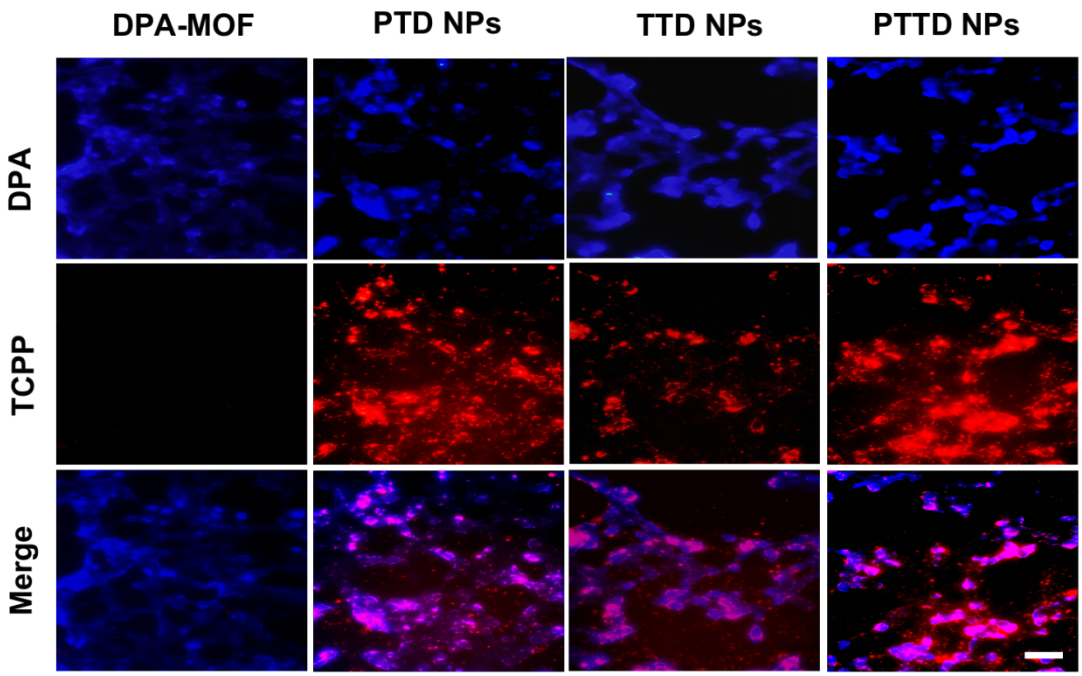

Figure S11. Fluorescence colocalization of TCPP and DPA-MOF in 4T1 cells, scale bar = 20 μm.

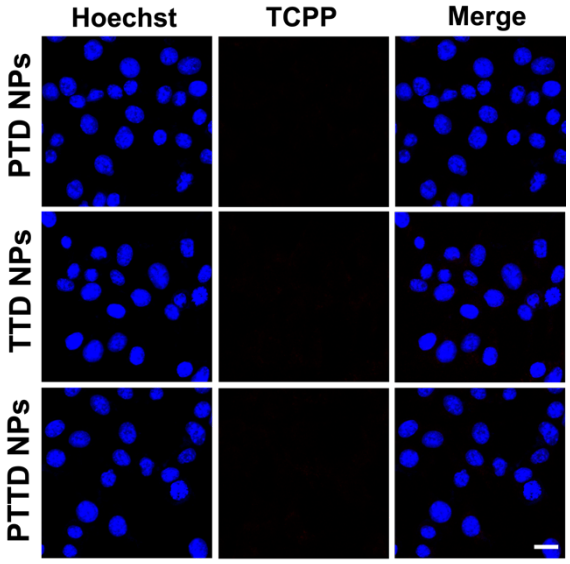

Figure S12. Cellular uptake: confocal imaging of 4T1 cells treated with PTD NPs, TTD NPs and PTTD NPs for 0 h, scale bar = 10 μm.

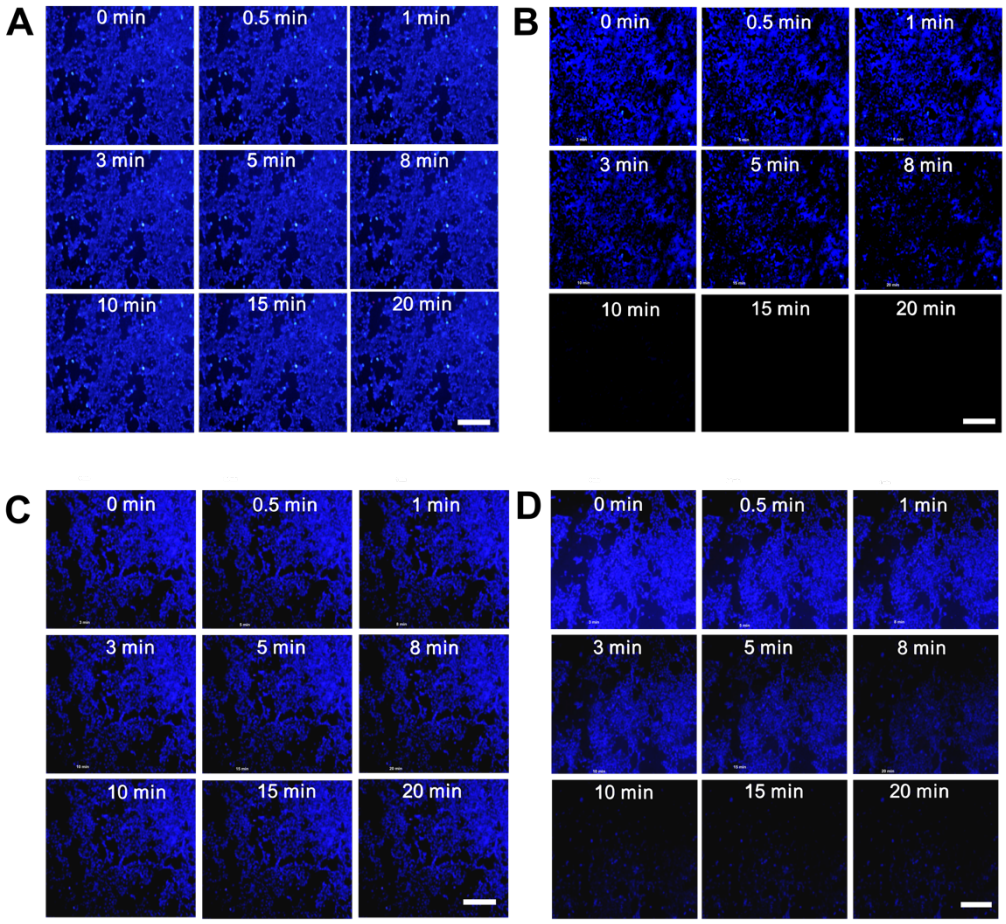

Figure S13. Dynamic fluorescence changes of 4T1 cells treated with (A) DPA-MOF, (B) PTD NPs, (C) TTD NPs and (D) PTTD NPs with laser (660 nm, 50 mW/cm^2).

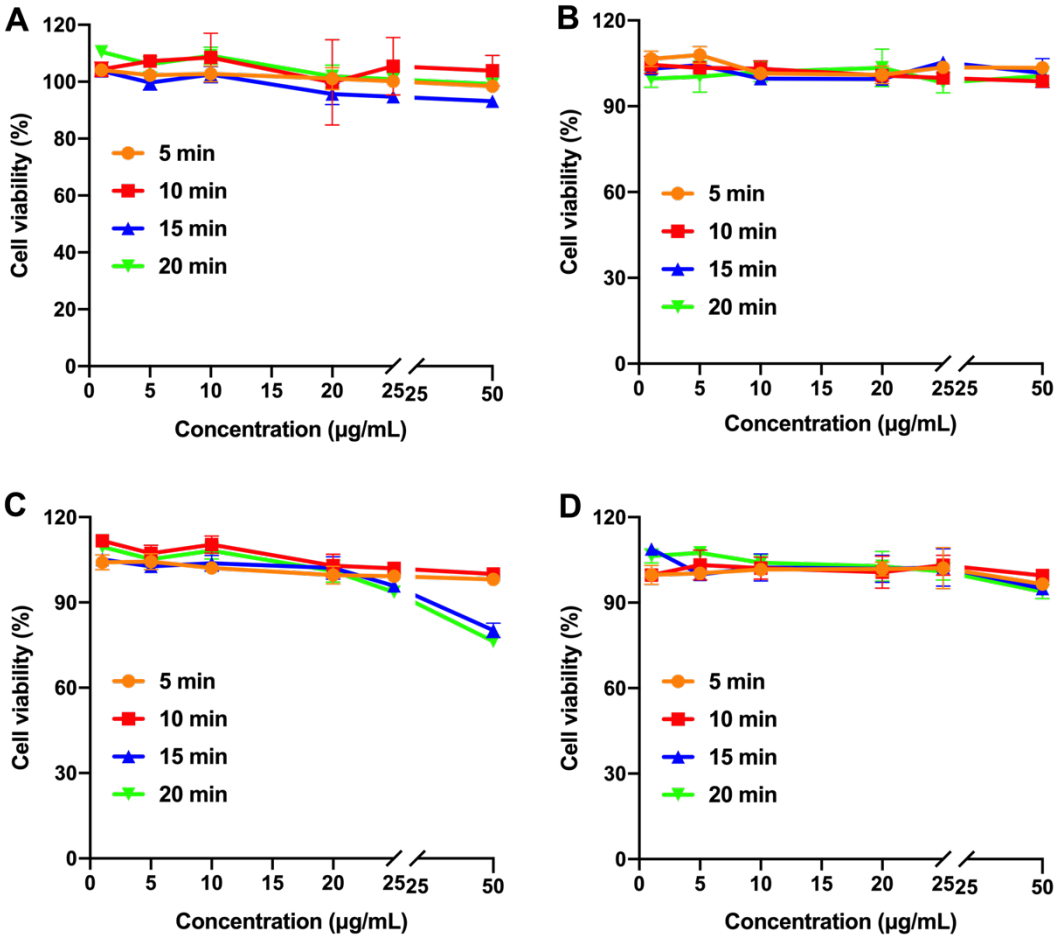

Figure S14. Cytotoxicity against (A) 4T1 cells treated with DPA-MOF and cytotoxicity against 3T3 cells treated with (B) DPA-MOF, (C) PTD NPs, and (D) TTD NPs with laser irradiation in 5, 10, 15, 20 min (660 nm, 50 mW/cm^2).

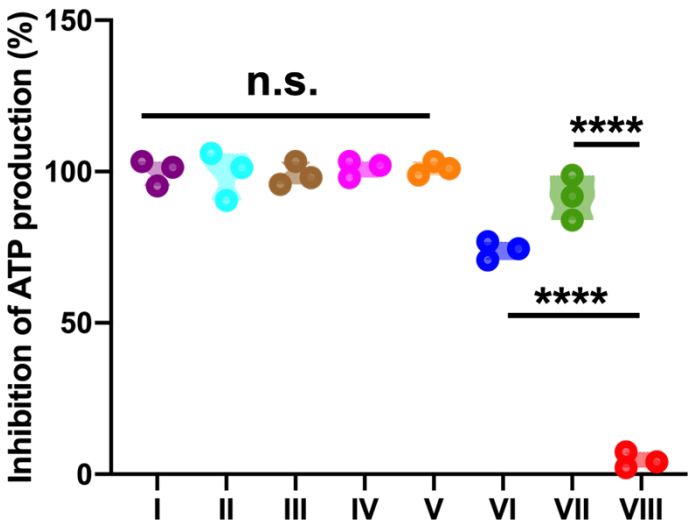

Figure S15. The ATP content after treatment by different formulations, (I, PBS; II, PTD NPs; III, TTD NPs; IV, PTTD NPs; V, PBS + L; VI, PTD NPs + L; VII, TTD NPs + L; VIII, PTTD NPs + L). Error bars represent ± SD. Statistics: ****P < 0.0001.

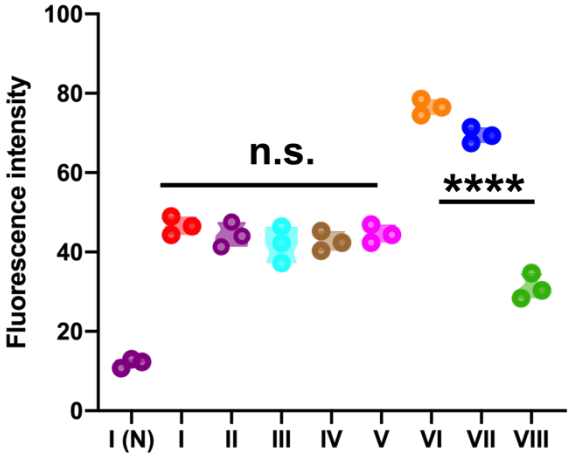

Figure S16. Quantitative analysis of HIF-1α expression in 4T1 cells under normoxia and hypoxia conditions (I (N), PBS (Normoxia); I, PBS; II, PTD NPs; III, TTD NPs; IV, PTTD NPs; V, PBS + L; VI, PTD NPs + L; VII, TTD NPs + L; VIII, PTTD NPs + L). Error bars represent ± SD. Statistics: ****P < 0.0001.

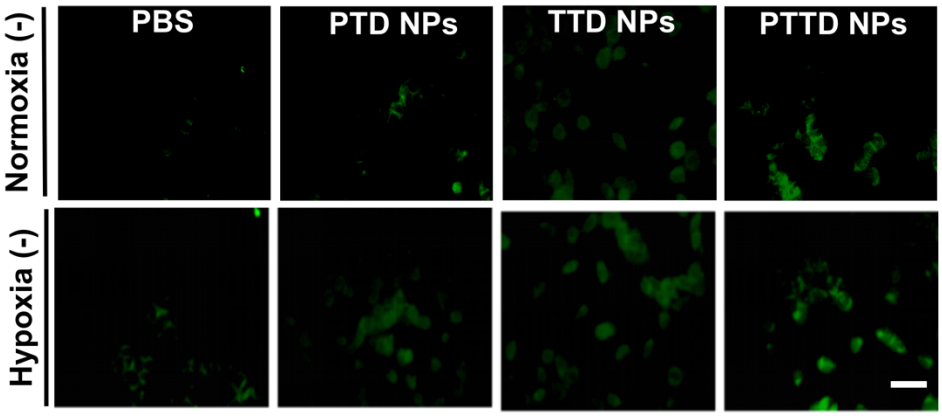

Figure S17. Cellular ROS generation in 4T1 cells treated with PBS, PTD NPs, TTD NPs and PTTD NPs without laser under normoxia and hypoxia conditions, scale bar = 20 μm.

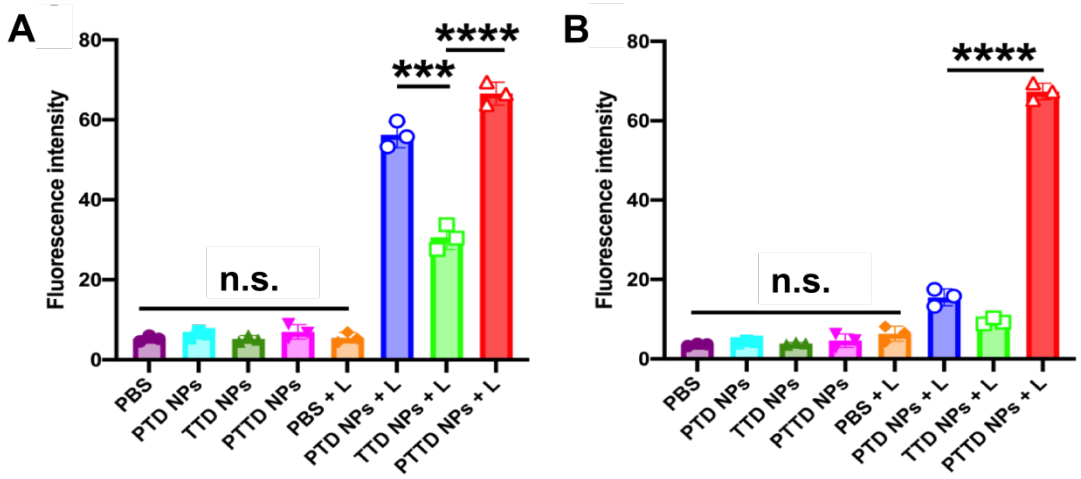

Figure S18. Quantitative analysis of cellular singlet oxygen generation in 4T1 cells under (A) normoxia and (B) hypoxia conditions. Error bars represent ± SD. Statistics: ***P < 0.001 and ****P < 0.0001.

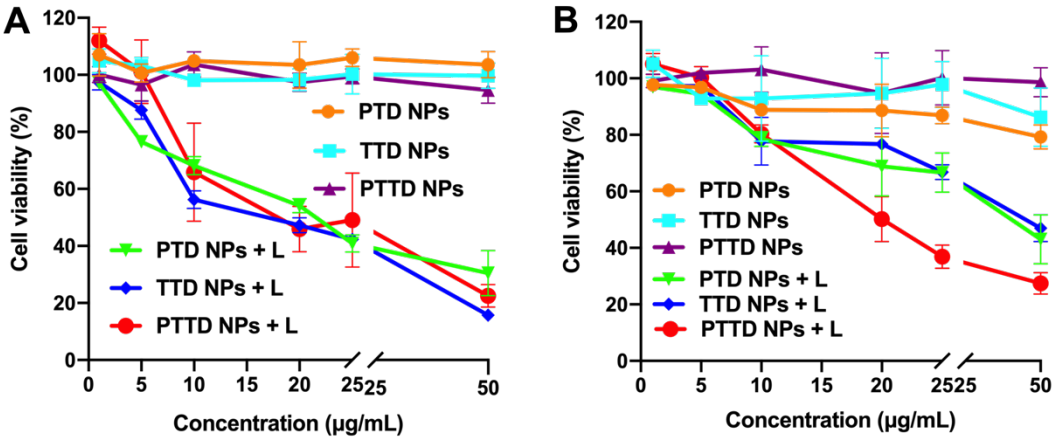

Figure S19. Cytotoxicity against CT26 cells with or without laser irradiation under (A) normoxic and (B) hypoxic conditions (660 nm, 50 mW/cm^2).

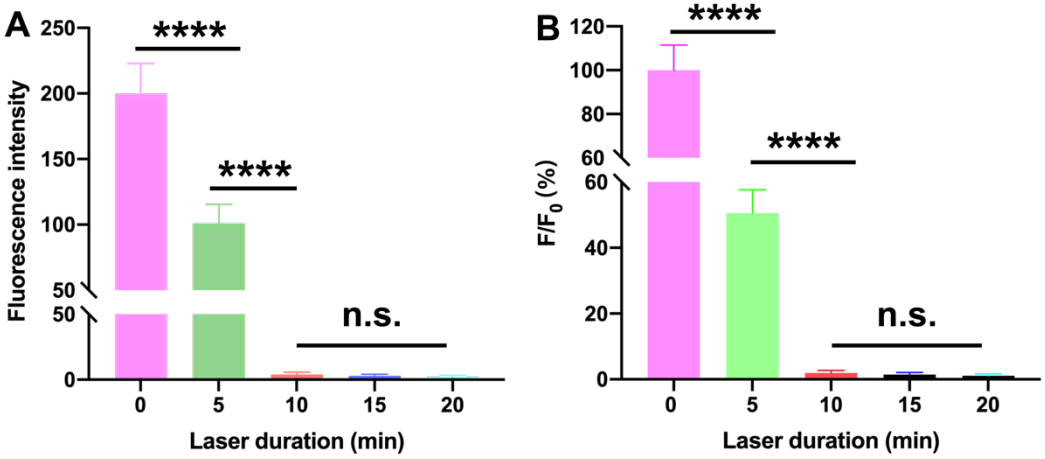

Figure S20. Fluorescence quantification of PTTD NPs at different laser duration (660 nm, 50 mW/cm^2). (A) Quantitative fluorescence values of PTTD NPs + L (0, 5, 10, 15, 20 min); and (B) Fluorescence percentage of PTTD NPs at different laser duration, (F, fluorescence value of PTTD NPs at 0, 5, 10, 15 and 20 min under laser; F_0, the initial fluorescence value of PTTD NPs). Statistics: ****P < 0.0001.

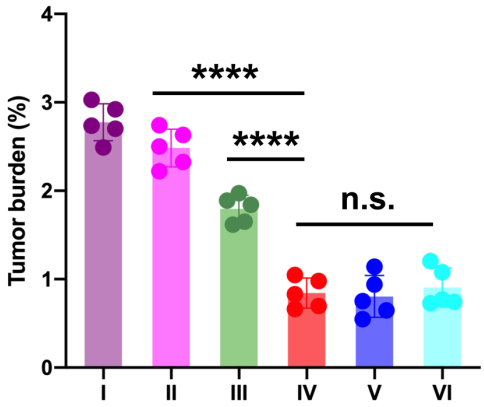

Figure S21. Tumor burden at 11 days post-administration. I, saline; II, PTTD NPs + L (0 min); III, PTTD NPs + L (5 min); IV, PTTD NPs + L (10 min); V, PTTD NPs + L (15 min); VI, PTTD NPs + L (20 min). Statistics: ****P < 0.0001.

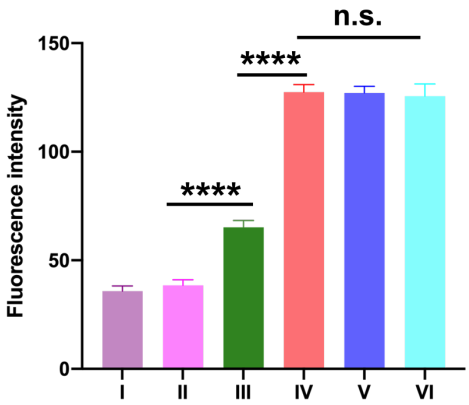

Figure S22. Quantitative results of TUNEL assay. I, saline; II, PTTD NPs + L (0 min); III, PTTD NPs + L (5 min); IV, PTTD NPs + L (10 min); V, PTTD NPs + L (15 min); VI, PTTD NPs + L (20 min). Statistics: ****P < 0.0001.

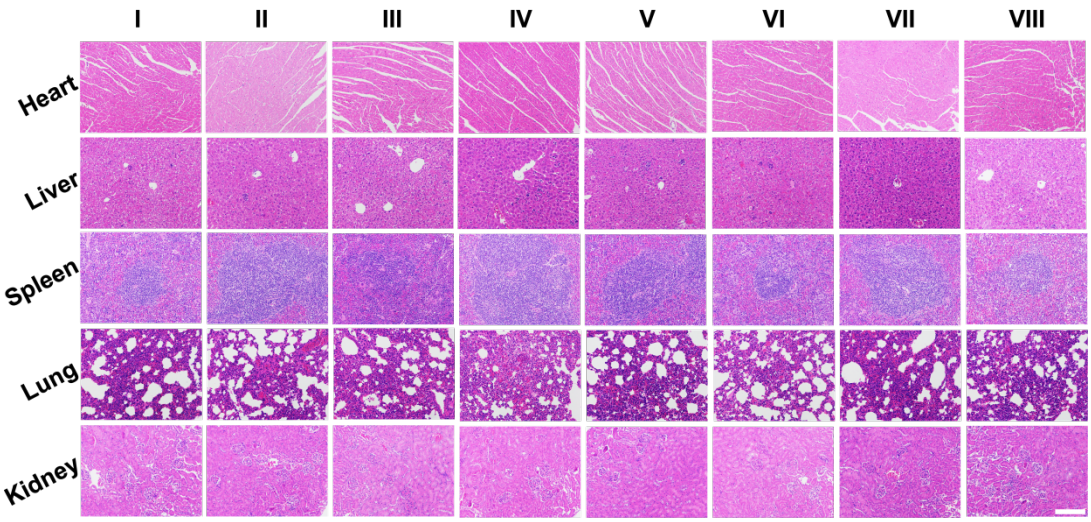

Figure S23. H&E staining images of heart, lung, spleen, lung and kidney after treatments. H&E staining: 200×magnification. Scale bar = 100 μm.

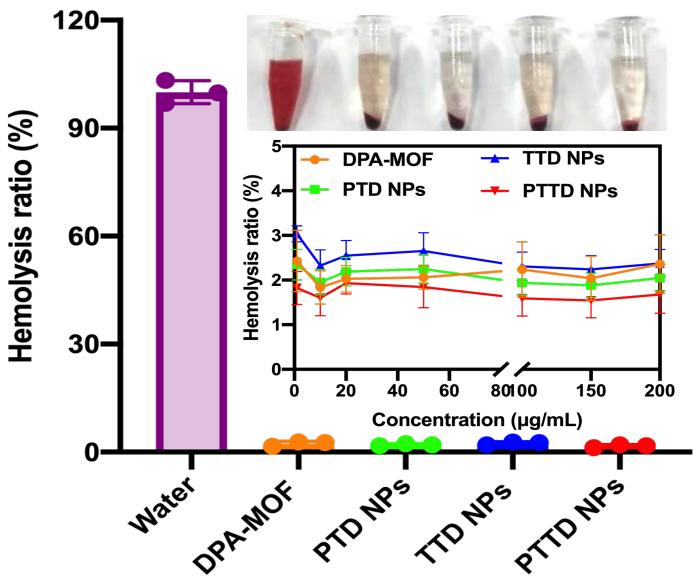

Figure S24. Hemolysis assay after incubation with DPA-MOF, PTD NPs, TTD NPs and PTTD NPs with concentration of 200 μg/mL.

Table S1. Singlet oxygen detection of DPA and DPA-MOF.

Probe	Linear range	Linear equation	Correlation	LOD
DPA	0-3 mM	y = 0.2781*x + 1.003	0.9906	244.74 μM
DPA-MOF	0-4 mM	y = 1.490*x + 1.591	0.9908	49.46 μM

Table S2. Screening the optimal dose of TPP at various mass ratios.

Applied TD NPs	Added TPP	TD NPs: TPP	[a)]LE (%) of TPP	[b)]EE (%) of TPP
4 mg	1.33 mg	3:1	3.20%	9.97%
4 mg	4 mg	1: 1	8.48%	9.42%
4 mg	12 mg	1: 3	22.48%	9.70%
4 mg	20 mg	1: 5	34.61%	10.61%
4 mg	32 mg	1: 8	34.18%	6.52%
4 mg	40 mg	1: 10	34.38%	5.25%

[a)]Loading efficiency (LE): WL/WNP*100; [b)]Encapsulated efficiency (EE):WL/WT*100; (WL, weight of loading drugs; WT, weight of total drugs; and WNP, weight of nanoparticles).

Table S3. Characterization of DPA-MOF, PTD NPs, TTD NPs and PTTD NPs.

Nanoassemblies	[a)]Size (nm)	[b)]PDI	[c)]DL_{DPA}	[c)]DL_{TCPP}	[c)]DL_{TPP}	[d)]Zeta (mV)
DPA-MOF	135.0 ± 4.10	0.18 ± 0.05	73.98%	_	_	-6.53 ± 0.33
PTD NPs	156.4 ± 2.47	0.18 ± 0.05	49.90%	22.50%	_	-10.2 ± 0.65
TTD NPs	155.8 ± 3.96	0.12 ± 0.06	40.77%	18.38%	34.64%	14.0 ± 0.77
PTTD NPs	178.9 ± 2.59	0.16 ± 0.04	32.62%	14.70%	27.71%	-19.0 ± 0.21

[a)] Mean diameters of nanoassemblies were determined by DLS. [b)] Polydispersity index of micelles size. [c)] Drug-loading of DPA, TCPP or TPP was calculated by the weight of drugs, nanoparticles and the amount of DSPE-SS-$PEG_{2k.}$ [d)] Zeta potential of nanoassemblies were determined by DLS.

Table S4. Cytotoxicity IC_{50} (μg/mL) values of PTD NPs, TTD NPs and PTTD NPs under different laser duration in 4T1 cells (MTT assay).

Laser duration	5 min	10 min	15 min	20 min
PTD NPs	28.52	17.46	17.29	17.42
TTD NPs	30.24	23.84	23.38	23.77
PTTD NPs	14.83	7.52	7.68	7.60

Table S5. Cytotoxicity IC_{50} values of PTD NPs, TTD NPs and PTTD NPs under laser (MTT assay).

Formulations	4T1 (μg/mL)		CT26 (μg/mL)	
	Normoxia Laser (+)	Hypoxia Laser (+)	Normoxia Laser (+)	Hypoxia Laser (+)
PTD NPs	17.23	101.90	27.69	104.20
TTD NPs	23.62	100.90	28.74	181.60
PTTD NPs	7.47	8.53	12.51	14.14