Supporting Information

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Near-Infrared Light Triggered Photothermal and Photodynamic Therapy with an Oxygen-Shuttle Endoperoxide of Anthracene against Tumor Hypoxia

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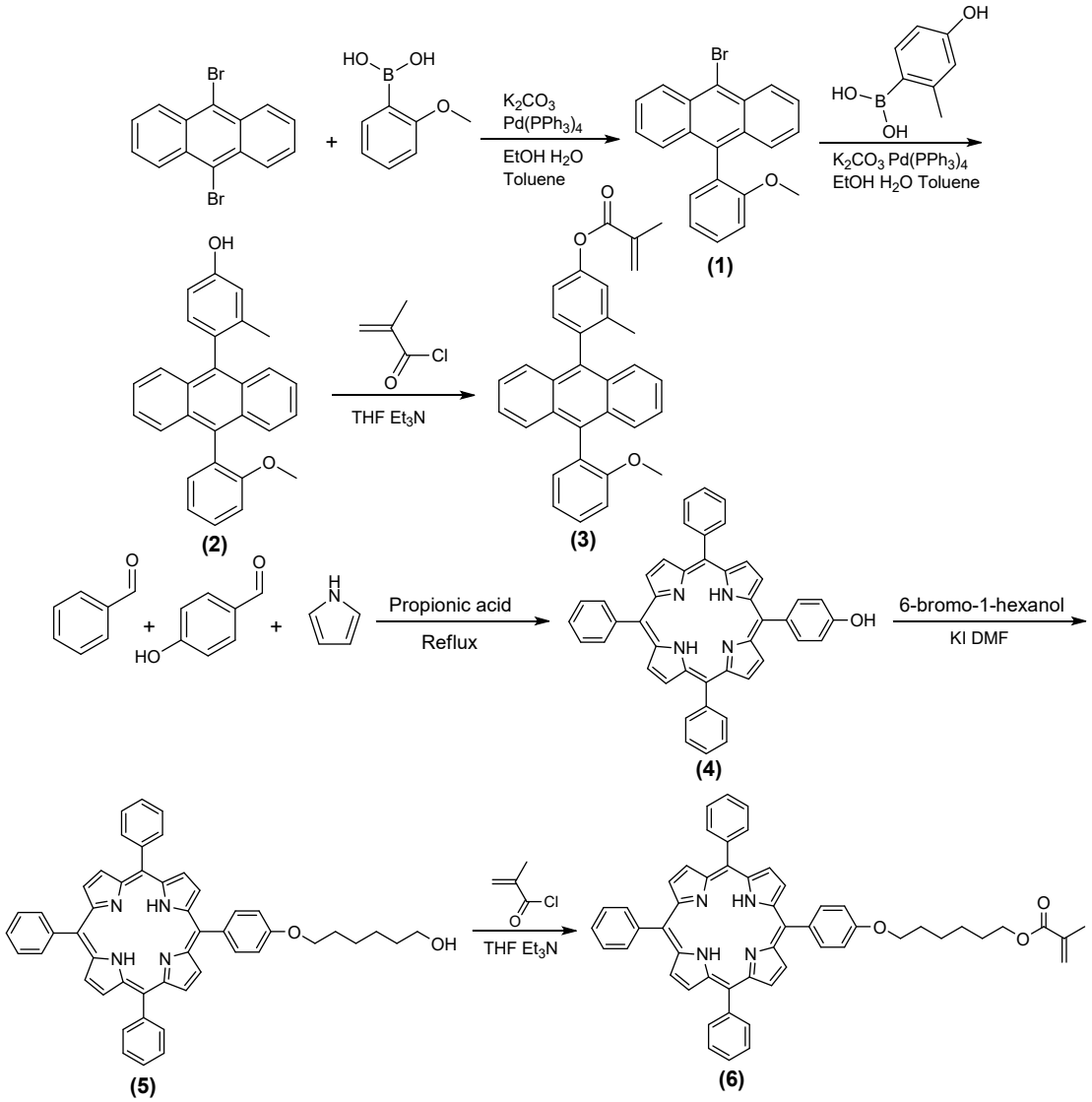
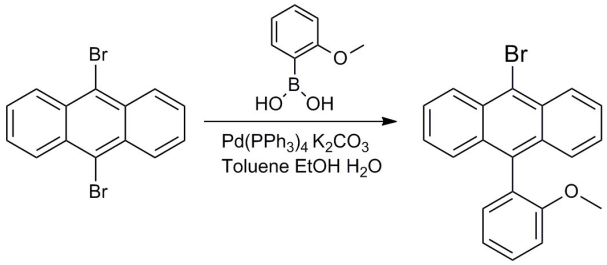
Experimental

Synthetic Procedures and Characterization



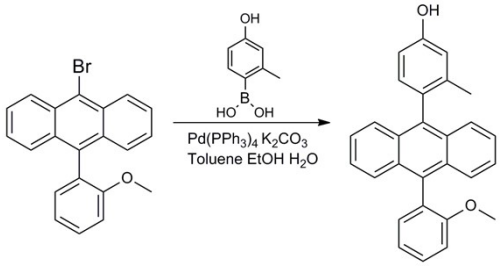
Scheme S1. Synthesis of 4-(10-(2-methoxy phenyl)anthracen-9-yl)-3-methylphenylmethacrylate (MDMA) **(3)** and 21H,23H-5-(2-(4-phenoxy) hexylmethacrylate)-10,15,20-trisphenylporphyrin (TPPMA) **(6)** monomers.

9-bromo-10-(2-methoxyphenyl) anthracene (1):



9,10-Dibromoanthracene (5.00 g, 14.88 mmol), (2-methoxyphenyl) boronic acid (2.26 g, 14.88 mmol), K_2CO_3 (10.28 g, 74.40mmol) and $Pd(PPh_3)_4$ (257.9 mg, 0.22 mmol) were added to a mixture of toluene: ethanol: water (3:1:1, 200 mL). The resulting suspension was purged for 30 min with a stream of argon and stirred for 48 h at 85 °C under argon atmosphere. The mixture was extracted with ethyl acetate and the organic phase was washed with brine, and dried with Mg_2SO_4.Then the solvent was evaporated under reduced pressure. Purification by silica gel column chromatography (hexane) afforded as a light green solid (**1**) (2.88g, yield = 53.3%).^{1}H NMR (400 MHz, CD_2Cl_2) : δH 8.52-8.45 (m, 2H ArH) 7.53-7.43 (m, 5H ArH) 7.31-7.24 (m, 2H ArH) 7.15-7.03 (m, 3H ArH) 3.50 (s, 3H -OCH_3) ppm.

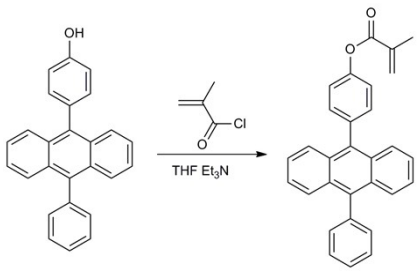
4-(10-(2-methoxyphenyl)anthracen-9-yl)-2-methylphenol(2):



9-Bromo-10-(2-methoxyphenyl)anthracene (2.50 g, 6.88 mmol), (4-hydroxy-3-methylphenyl) boronic acid (1.05 g, 6.88 mmol), K_2CO_3 (4.76 g, 34.4 mmol) and $Pd(Ph_3)_4$ (127.1 mg, 0.11 mmol) were added to a mixture of toluene : ethanol : water (3 : 1 : 1, 100 mL). The resulting suspension was purged for 30 min with a stream of argon and stirred for 48 h at 90 °C under argon atmosphere. The mixture was extracted with ethyl acetate and the organic phase was washed with brine, and dried with Mg_2SO_4.Then the solvent was evaporated under reduced pressure. Purification by silica gel column chromatography (hexane: EtOAc = 40 : 1) afforded as a white solid. (537.0 mg, yield = 19.98%). ^{1}H NMR (400 MHz, DMSO-d_6) : δH 9.64 (s, 1H -OH) 7.69-7.60

(m, 1H ArH) 7.59-7.50 (m, 4H ArH) 7.47-7.20 (m, 7H ArH) 7.17-7.03 (m, 1H ArH) 7.01-6.94 (m, 1H ArH) 6.94-6.85 (m, 1H ArH) 3.65 (s, 3H -OCH_3) 1.83-1.77 (d, 3H -CH_3) ppm.

4-(10-(2-methoxyphenyl)anthracen-9-yl)-3-methylphenyl methacrylate(3):



3 (500.0 mg,1.28mmol) was dissolved in dry THF (20 mL) followed by adding TEA (0.32 mL, 2.3 mmol). Methacryloylchloride (0.22 mL, 2.3 mmol) was added dropwise at 0 °C, and the reaction was carried out overnight at room temperature. Saturated $NaHCO_3$ aqueous solution was added and the mixture was extracted with ethyl acetate. The organic phase was combined and washed with brine. After drying over Mg_2SO_4, the organic phase was concentrated. The residue was purified by column chromatography (hexanes: EtOAc = 20:1) and subsequent recrystallization to obtain MDMA (534.0 mg, yield = 91%) as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δH 7.61-7.55 (m, 2H ArH) 7.52-7.44 (m, 3H ArH) 7.33-7.20 (m, 6H ArH) 7.19-7.16 (m, 1H ArH) 7.14-7.07 (m, 2H ArH) 6.39 (t, *J* =1.2 Hz, 1H CH_2=C), 5.80 (t, *J* =1.2Hz, 1H CH_2=C) 3.58 (s, 3H -OCH_3) 2.08 (s, 3H CH_2=CC*H*$_3$) 1.85 (s, 3H -CH_3).

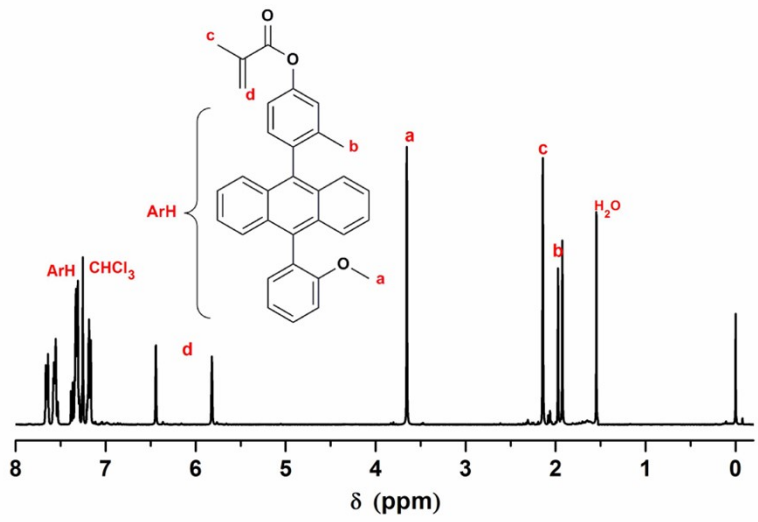


Figure S1. ^{1}H NMR spectrum of MDMA monomer in $CDCl_3$.

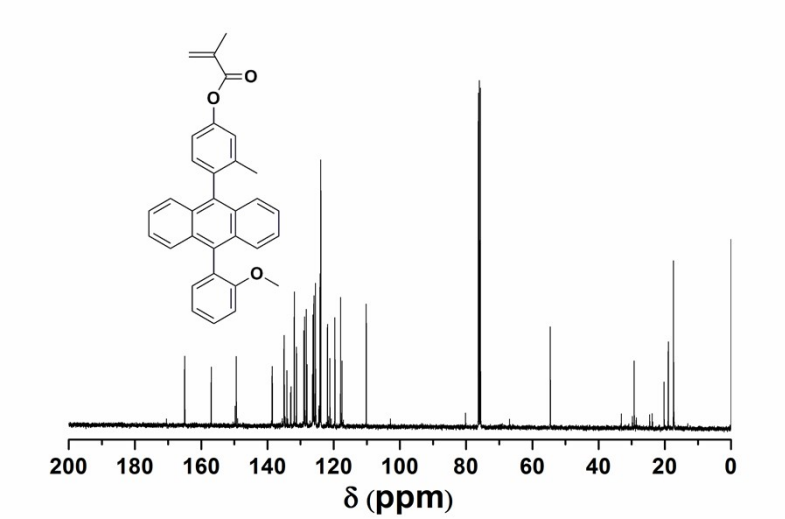
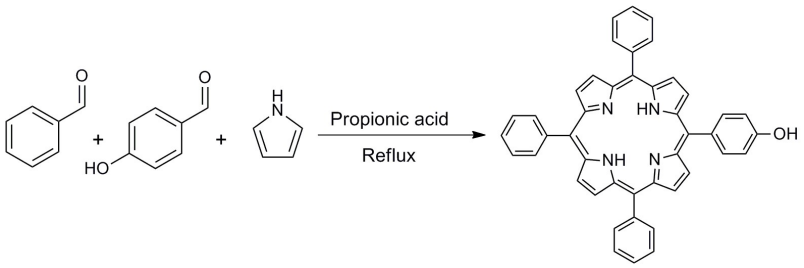


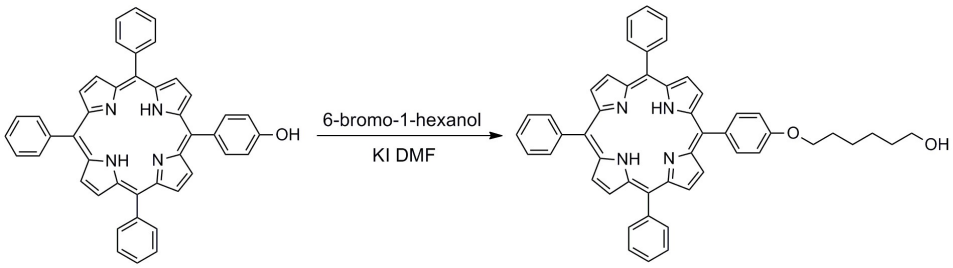
Figure S2. ^{13}C NMR spectrum of MDMA monomer in $CDCl_3$.

21H,23H-5-(2-(4-Phenolic hydroxyl))-10,15,20-Tris(phenyl)Porphyrin (4):



4-Hydroxybenzaldehyde (4.88 g, 0.04 mol), pyrrole (11.10 mL, 0.16 mol), and benzaldehyde (12.74 g, 0.12 mol) were dissolved in dichloromethane. Trifluoroacetic acid (TFA) was added slowly at room temperature. The reaction was carried out for 4 hours. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone was added to quench the reaction. The mixture was stirred for 12 hours. Et_3N (5 mL) was finally added to consume the residual TFA. The solution was filtered through alkaline Al_2O_3 and concentrated under reduced pressure. The residue was purified by column chromatography (hexane: EtOAc= 5:2) to obtain as dark brown solid (2.62 g, yield = 10.4%). ^{1}H NMR (400 MHz, $CDCl_3$) : δH 8.84-8.71 (m, 4H pyrrole) 8.19-8.08 (m, 3H ArH) 8.01-7.94 (d, 1H ArH) 7.74-7.60 (m, 4H ArH) 7.12-7.03 (d, 1H ArH) -2.86 (s, 2H NH) ppm.

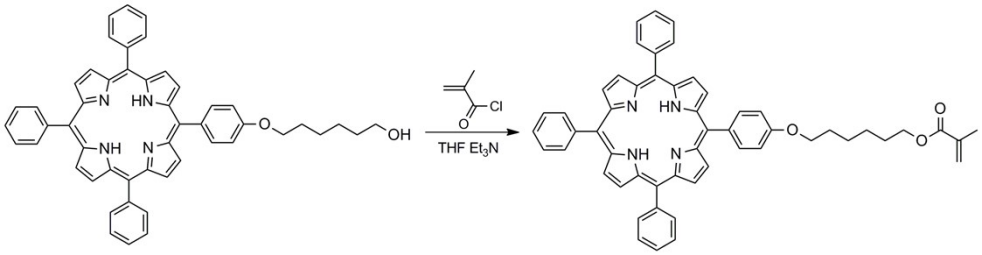
21H,23H-5-(2-(4-Hydroxyphenyl)-hexanol)-10,15,20-Tris(phenyl)Porphyrin (5):



4 (2.50 g, 3.96 mmol), 6-bromo-1-hexanol (1.03 mL, 7.92 mmol), KI (50.0 mg, 0.3 mmol), and K_2CO_3 (1.38 g, 10.00 mmol) were dissolved in DMF. The mixture was stirred at 80 °C for 36 h. After cooling to room temperature, the mixture was poured into water and filtered. The residue was purified by column chromatography (hexane : EtOAc = 10 : 3) to obtain as dark brown solid (2.14 g, yield = 74.0%). ^{1}H NMR (400 MHz, $CDCl_3$) : δH 8.92-8.79 (m, 4H pyrrole) 8.26-8.17 (m, 3H ArH) 8.14-8.06 (m, 1H ArH) 7.81-7.69 (m, 4H ArH) 7.27-7.24 (m, 1H ArH) 4.25-4.16 (t, 2H -OC$\underline{H_2}$CH$_2$-) 3.75-3.65 (t, 2H HOC$\underline{H_2}$CH$_2$) 2.03-1.90 (m, 2H -OCH$_2$C$\underline{H_2}$-) 1.72-1.59 (t, 2H

$HOCH_2C\underline{H_2}$) 1.58-1.46 (t, 2H -OCH_2CH_2 $C\underline{H_2}$) 1.25 (s, 1H $\underline{H}OCH_2$-) -2.86 (s, 2H NH) ppm.

21H,23H-5-(2-(4-Hydroxyphenyl)-hexylmethacrylate)-10,15,20-Tris(phenyl)-Porphyrin (5):



4 (2.0 g, 2.74 mmol) was dissolved in dry THF (20 mL) followed by adding TEA (0.57 mL, 4.11 mmol). Methacryloylchloride (0.40 mL, 4.11 mmol) was added dropwise at 0 °C, and the reaction was carried out overnight at room temperature. Saturated $NaHCO_3$ aqueous solution was added and the mixture was extracted with ethyl acetate. The organic phase was combined and washed with brine. After drying over Mg_2SO_4, the organic phase was concentrated. The residue was purified by column chromatography (hexane: EtOAc= 25:1) to obtain as dark brown solid (1.88 g, yield = 86.1%). ^{1}H NMR (400 MHz, $CDCl_3$) : δH 8.92-8.76 (m, 4H pyrrole) 8.26-8.15 (m, 3H ArH) 8.11-8.02 (m, 1H ArH) 7.77-7.65 (m, 4H ArH) 7.20-7.18 (m, 1H ArH) 6.13 (t, *J* =1.2 Hz, 1H CH_2=C), 5.56 (t, *J* =1.2Hz, 1H CH_2=C) 4.23-4.18 (t, 2H $HOC\underline{H_2}CH_2$-) 4.14-4.08 (t, 2H -$OC\underline{H_2}CH_2$) 2.03-1.90 (m, 2H -$OCH_2C\underline{H_2}$-) 1.97 (t, 3H CH_3) 1.72-1.59 (t, 2H $HOCH_2C\underline{H_2}$) 1.58-1.46 (t, 2H -OCH_2CH_2 $C\underline{H_2}$) 1.25 (s, 1H $\underline{H}OCH_2$-) -2.86 (s, 2H NH) ppm.

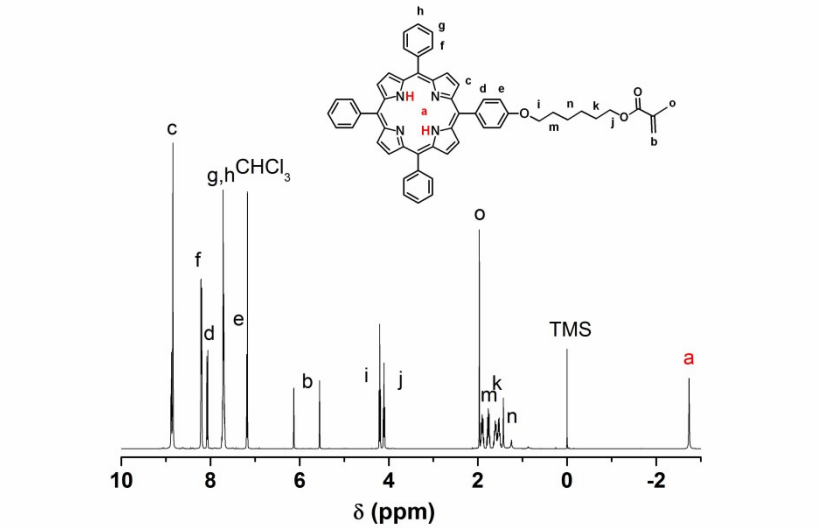


Figure S3. ^{1}H NMR spectrum of TPPMA monomer in $CDCl_3$.

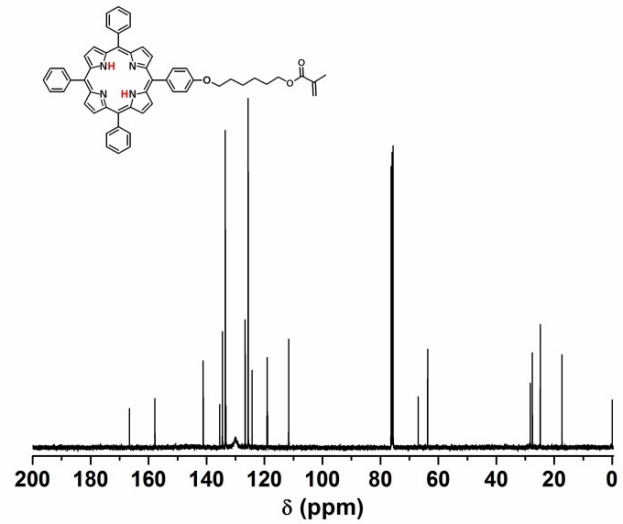


Figure S4. ^{13}C NMR spectrum of TPPMA monomer $CDCl_3$.

Synthesis of poly[oligo (ethylene glycol) methyl ether methacrylate] (POEGMA) with tunable chain length.

RAFT strategy with CDB as the chain transfer agent and AIBN as the initiator was used to perform the polymerization. In a typical polymerization, OEGMA (3.0g, 6 mmol), CDB (6.8 mg, 0.025 mmol), and AIBN (1.025 mg, 0.006 mmol) were dissolved in 5.5 mL anisole to form a transparent solution. After degassing under argon by three freeze-pump-thaw cycles, the tube was placed in a preheated oil bath at 70 °C for 13 h. Then the reaction mixture was cooled to room temperature by liquid nitrogen and precipitated into the diethyl ether. The polymer was collected after centrifugation at 3000 rpm for 10 min and dried in a vacuum at 25 °C for 24 h (1.86 g, yield = 62%). ^{1}H

NMR (400 MHz, $CDCl_3$) δH = 4.08 (s, O=CO$\underline{CH_2}\underline{CH_2}$), 3.65 (s, O-C$\underline{H_2}C\underline{H_2}$-O), 3.31 (s, -OCH_3), 1.75 (s, -CH_2), 0.83 (s, C-CH_3) ppm.

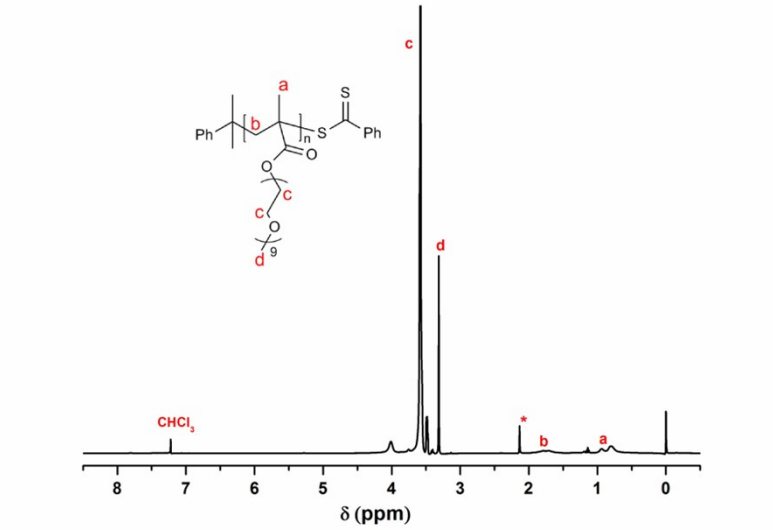


Figure S5. ^{1}H NMR spectrum of POEGMA in $CDCl_3$.*:acetone.

Scheme S2. Synthesis of diphenyl anthracene and porphyrin-containing block copolymers.

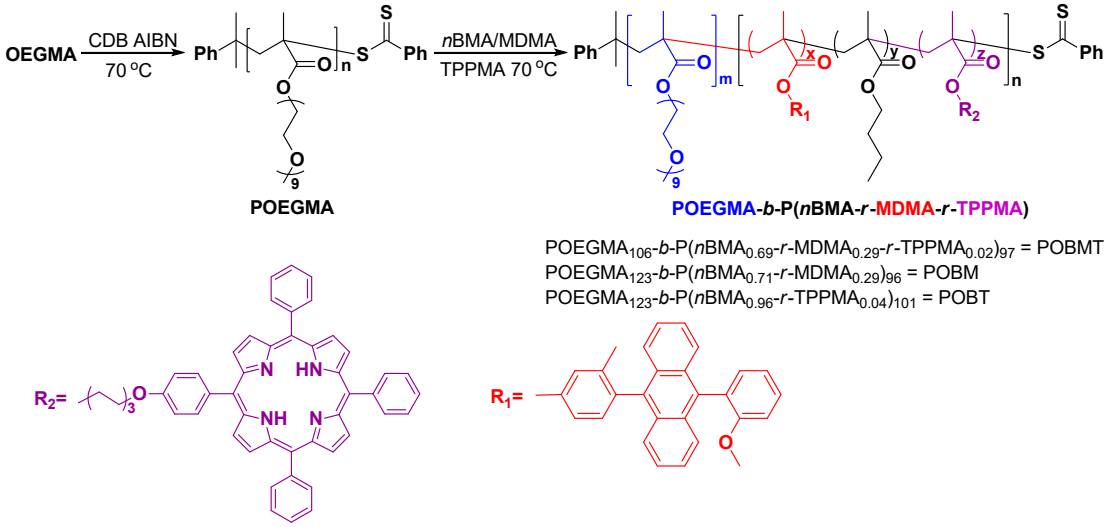


Table S1 Homo-polymerization of OEGMA and random copolymerization of *n*-butyl methacrylate (*n*BMA), MDMA and TPPMA to synthesize block copolymers at 70 °C in anisole.

Sample	Polymers	[M]/[CTA]/[I][a)]	Time (h)	Temp. (°C)	Conv.[b)] (%)	$M_{n,\,calc}$ (kDa)[c)]	$M_{n,SEC}$ (kDa)[d)]	$Đ$[d)]
PO1	$POEGMA_{106}$[b)]	640/4/1	13.2	70	66.55	31.1	31.1	1.15
PO2	$POEGMA_{123}$[b)]	640/4/1	10.0	70	76.60	37.2	37.2	1.19
POBMT	$POEGMA_{106}$-*b*-P(*n*$BMA_{0.69}$[b)]-*r*-$MDMA_{0.29}$[b)]-*r*-$TPPMA_{0.02}$[b)])$_{97}$	420/3/1	21.0	70	69.10	43.0	43.0	1.25
POBM	$POEGMA_{123}$-*b*-P(*n*$BMA_{0.71}$[b)]-*r*-$MDMA_{0.29}$[b)])$_{96}$	411/3/1	21.0	70	69.50	54.9	54.9	1.29
POBT	$POEGMA_{123}$-b-P(*n*$BMA_{0.96}$[b)]-*r*-$TPPMA_{0.04}$[b)])$_{101}$	396/3/1	21.0	70	76.40	52.6	52.6	1.36

a) Molar ratio of monomer (M), CTA (CDB or POEGMAs) and AIBN (I) in feed; b) Trioxymethylene was used as an initial sample to monitor the monomer conversion by ^{1}H-NMR spectroscopy, and DPs were measured by comparing the experimental conversion with desired conversion, because there is an integral signal overlap among three different monomers; c) $M_{n,calc} = M_{monomer} \times ([M]/[CTA]) \times Conversion + M_{CTA}$; d) Determined by SEC in THF calibrated by PS standards;

Synthesis of [POEGMA-*b*-P(*n*BMA-*r*- MDMA-*r*-TPPMA)] diblock copolymer.

POEGMA was used as a macro-CTA. In a typical block copolymerization, $POEGMA_{106}$ ($M_{n,nmr}$ = 53.2 kDa, 405.9 mg), TPPMA (17.4 mg, 0.02 mmol), *n*BMA (110.8 mg, 0.78 mmol), MDMA (120 mg, 0.26 mmol), and AIBN (0.42 mg, 0.003 mmol) were dissolved in 2 mL anisole in a Schlenk vial. After degassing under argon by three freeze-pump-thaw cycles, the tube was placed in a preheated oil bath at 70 °C for 21 h. Then the reaction mixture was cooled to room temperature and precipitated three times into the cold diethyl ether. After being dried in vacuum at 30 °C for 24 h to obtain purple solid (384.0 mg, yield = 69.12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.73 (s, pyrrole), 8.10 (s, ArH) 7.70-6.80 (m, ArH) 4.00 (s, O=CO$\underline{CH_2}\underline{CH_2}$), 3.58 (s, O-C$\underline{H_2}C\underline{H_2}$-O), 3.31 (s, -OCH_3), 1.75 (s, C-CH_2), 1.63-1.03 (m, alkyl), 0.83 (s, C-CH_3), -2.87 (s, NH) ppm.

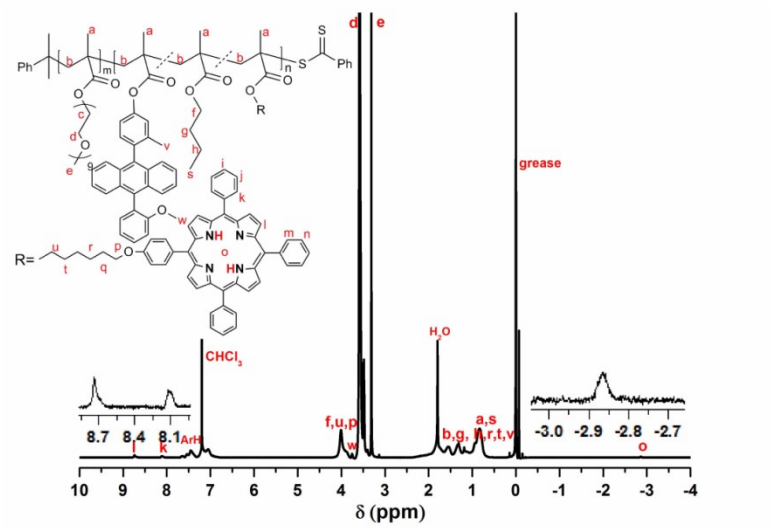


Figure S6. ^{1}H NMR spectrum of POEGMA-*b*-P(*n*BMA-*r*-MDMA-*r*-TPPMA) in $CDCl_3$.

Photooxidation of the [$POEGMA_{106}$-*b*-P(*n*$BMA_{0.69}$-*r*-$MDMA_{0.29}$-*r*-$TPPMA_{0.02}$)$_{97}$]

[$POEGMA_{106}$-*b*-P(*n*$BMA_{0.69}$-*r*-$MDMA_{0.29}$-*r*-$TPPMA_{0.02}$)$_{97}$] (100 mg) was dissolved in THF (25 mL) and cooled to -78°C. The mixture was stirred with continuous oxygen bubbling for 24 h. LED light (200 W) irradiation was performed throughout the reaction. Finally the reaction mixture was precipitated into the cold diethyl ether and dried to give purple solid (87 mg, yield = 87%).

NMR characterization of [POEGMA-*b*-P(*n*BMA-*r*-MDMA)] diblock copolymer.

^{1}H NMR (400 MHz, $CDCl_3$) 7.62-6.90 (m, ArH) 4.01 (s, O=CO$\underline{CH_2}\underline{CH_2}$), 3.58 (s, O-C$\underline{H_2}$-C$\underline{H_2}$-O), 3.31 (s, -OCH_3), 1.85 (s, C-CH_2), 1.63-1.03 (m, alkyl), 0.83 (s, C-CH_3) ppm.

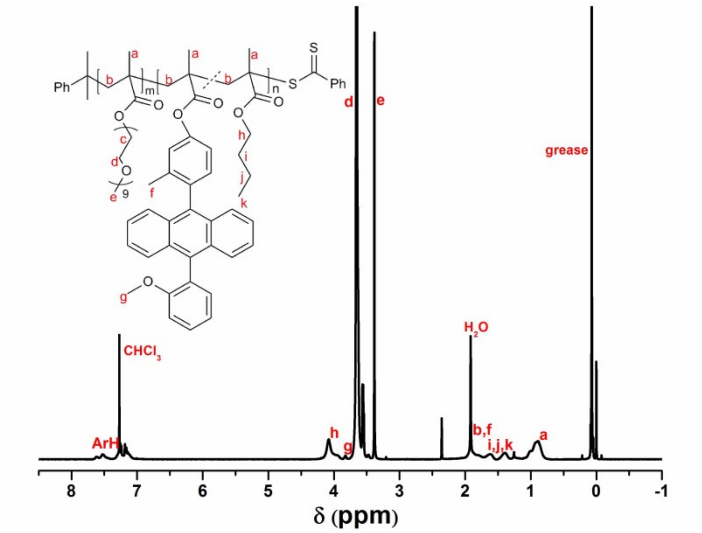


Figure S7. ^{1}H NMR spectrum of POEGMA-*b*-P(MDMA-*r*-*n*BMA) in $CDCl_3$.

NMR characterization of [POEGMA-*b*-P(*n*BMA-*r*-TPPMA)] diblock copolymer.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.77 (s, pyrrole), 8.13 (s, ArH) 7.68 (s, ArH) 4.01 (s, O=CO$\underline{CH_2}\underline{CH_2}$), 3.58 (s, O-C$\underline{H_2}C\underline{H_2}$-O), 3.31 (s, -OCH_3), 1.75 (s, C-CH_2), 1.60-1.10 (m, alkyl), 0.88 (s, C-CH_3), -2.85 (s, NH) ppm.

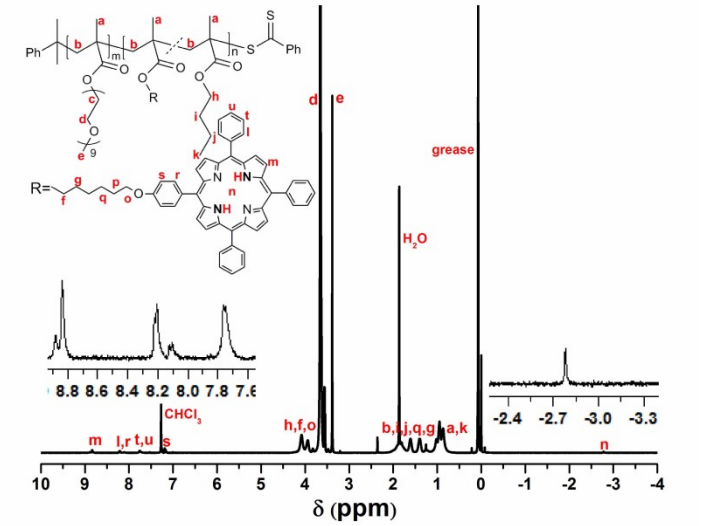


Figure S8. ^{1}H NMR spectrum of POEGMA-*b*-P(*n*BMA-*r*-TPPMA) in $CDCl_3$.

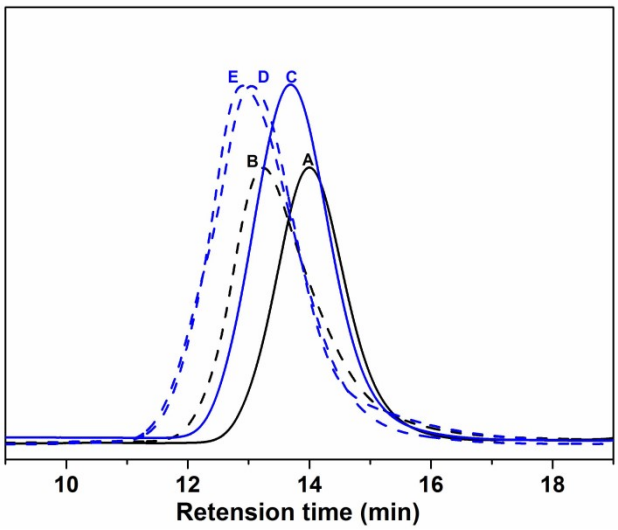


Figure S9. SEC traces of homo-polymers of PO1 (A), and PO2 (C) in solid lines, and block co-polymers of POBMT (B), POBM (D) and POBT (E) in dash lines.

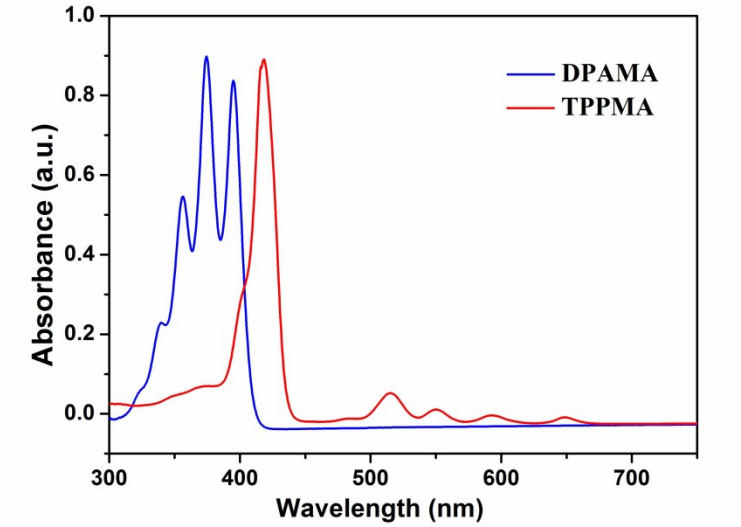


Figure S10. The UV-Vis absorption spectra of DPAMA and TPPMA in toluene.

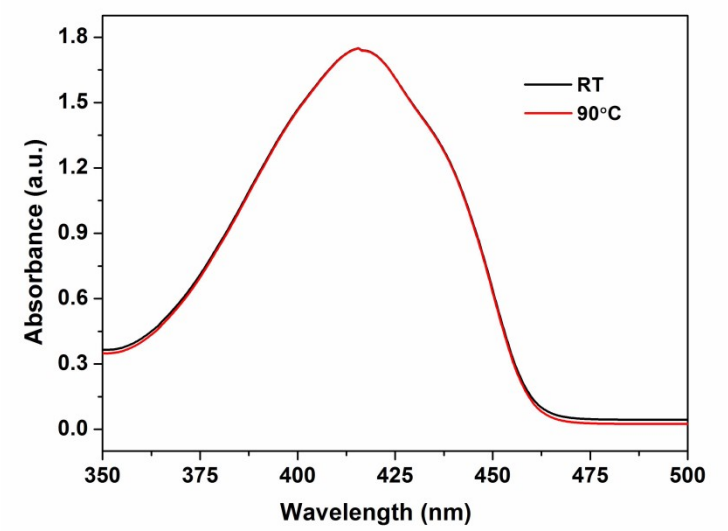


Figure S11. The UV-Vis absorption spectra of DPBF in DMSO, which were obtained at room temperature and after heating at 90 °C for 3 hours, respectively.

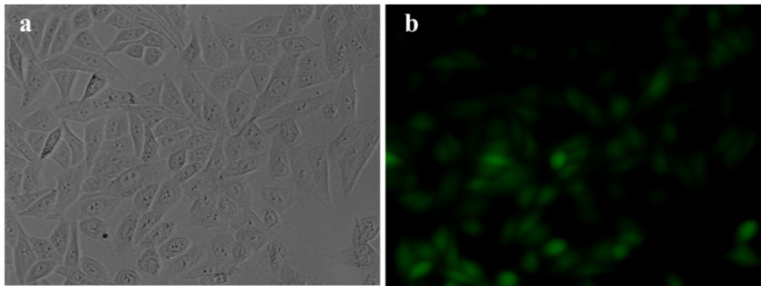


Figure S12. Phase contrast image (a) and fluorescent image (b) of untreated HepG2 cells, stained with 10 μM DCFH-DA for 30 min.

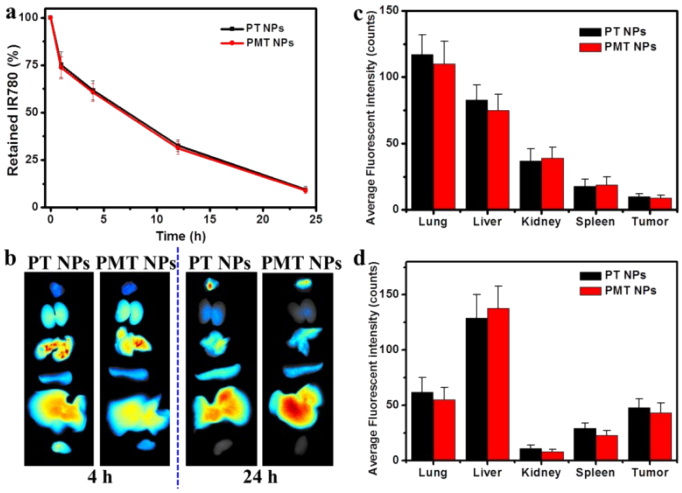


Figure S13. (a) Plasma concentration of IR780 in mice vs time after administration of PT and PMT NPs, respectively. (b) Fluorescent images and normalized fluorescent intensity of different organs from mice with xenograft tumor, after (c) 4 h and (d) 24 h post-injection of IR780 loaded PT and PMT NPs, respectively. The organs in (b) are tumor, kidneys, lung, spleen, liver and heart, from top to bottom.

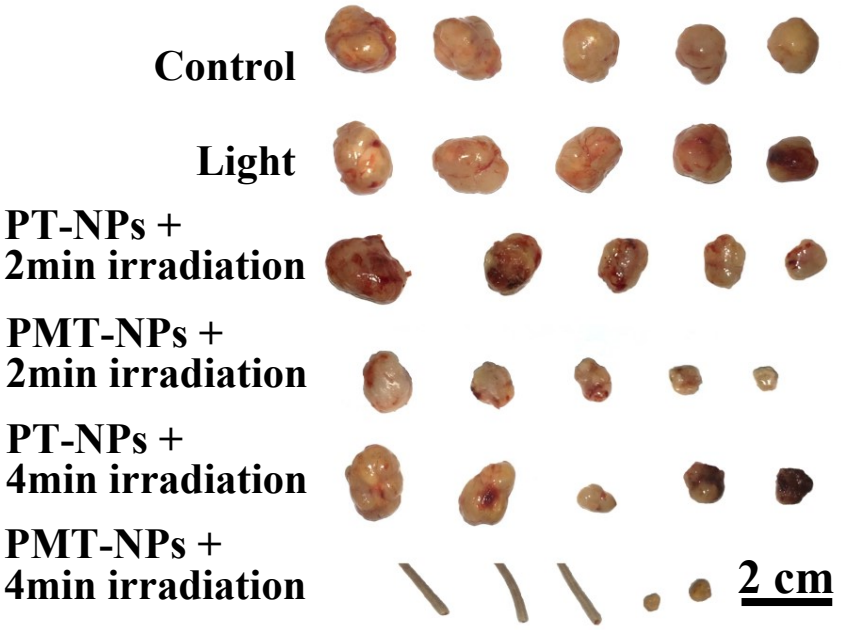


Figure S14. Digital photos of tumors collected from mice intravenously injected with 1) 200 μL physiological saline, 2) 200 μL physiological saline + 4 min NIR laser irradiation, 3) 200 μL 10 mg/mL PT-NPs + 2 min NIR laser irradiation, 4) 200 μL 10 mg/mL PMT-NPs + 2 min NIR laser irradiation, 5) 200 μL 10 mg/mL PT-NPs + 4 min NIR laser irradiation, 6) 200 μL 10 mg/mL PMT-NPs + 4 min NIR laser irradiation. The tails represent mice without tumor.

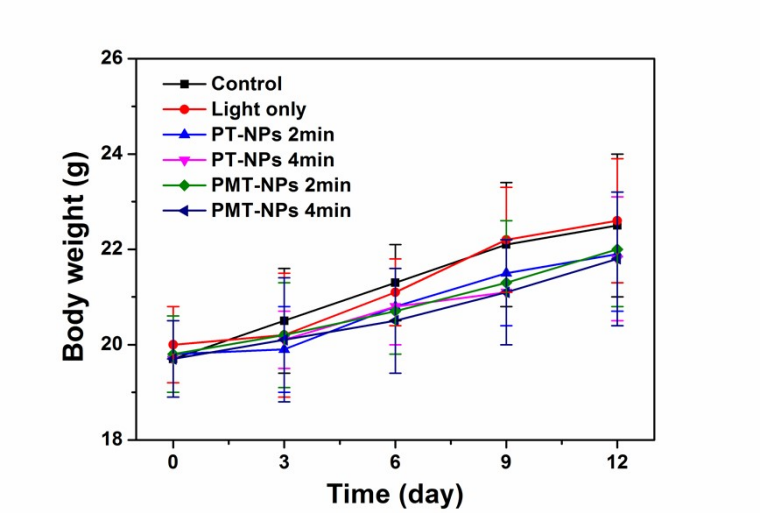


Figure S15. Body weight of mice in different groups.

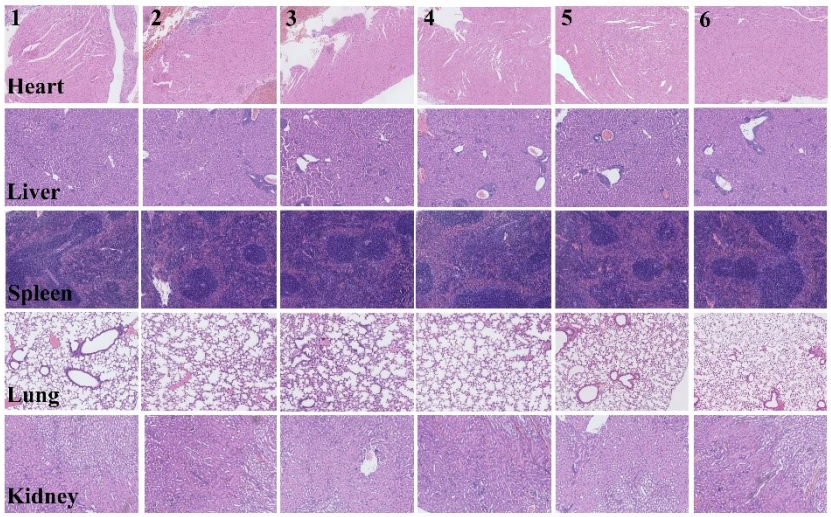


Figure S16. H&E staining of major organs from different groups: 1) 200 μL physiological saline, 2) 200 μL physiological saline + 4 min NIR laser irradiation, 3) 200 μL 10 mg/mL PT-NPs + 2 min NIR laser irradiation, 4) 200 μL 10 mg/mL PMT-NPs + 2 min NIR laser irradiation, 5) 200 μL 10 mg/mL PT-NPs + 4 min NIR laser irradiation, 6) 200 μL 10 mg/mL PMT-NPs + 4 min NIR laser irradiation.