Supporting information

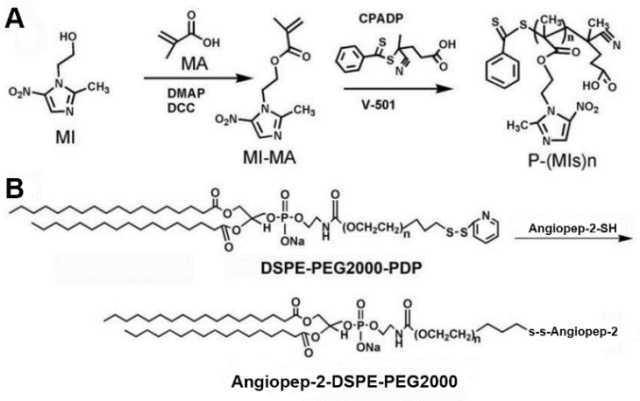

Figure S1. Synthetic routes of (A) P-(MIs)n; (B) Angiopep-2-DSPE-PEG2000.

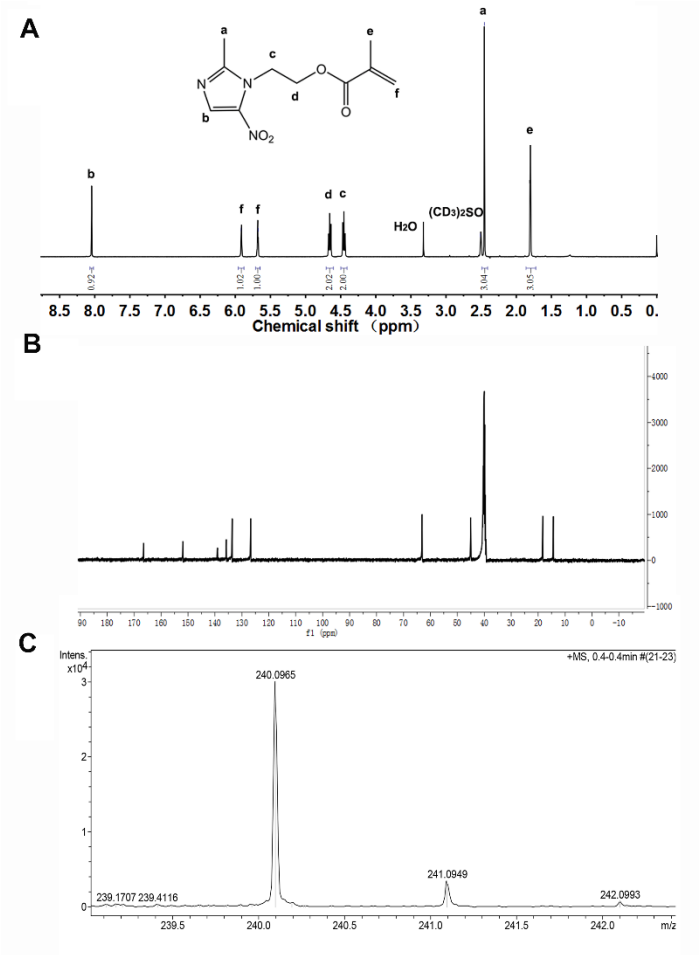

Figure S2. (A) ^{1}H-NMR spectra of MI-MA. It were solubilized in DMSO-*d*6 for ^{1}H-NMR analysis (300 MHz). (B)^{13}C NMR spectra of MI-MA. (C) The synthesis of MI-MA was further examined by high-resolution mass spectroscopy.

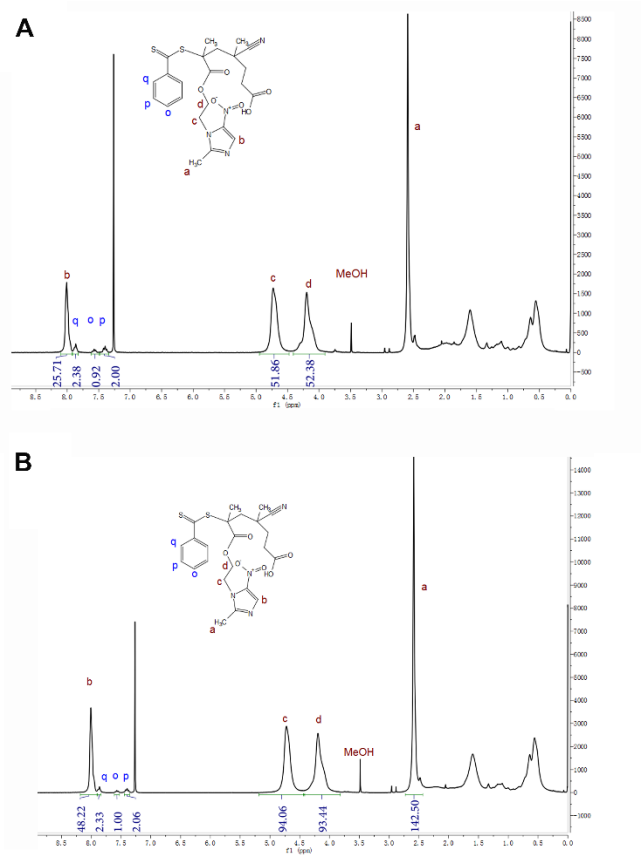

Figure S3. ^{1}H-NMR spectra of a) P-(MIs)25 and b) P-(MIs)48. It were solubilized in $CDCl_3$ for ^{1}H-NMR analysis (300 MHz).

Table S1. Molecular characteristics of P-(MIs)25 and P-(MIs)48

Polymer	M_n (design)	M_n[a] (^{1}H NMR)	PDI[b] (GPC)
P-(MIs)25	6000	6200	1.12
P-(MIs)48	12000	11800	1.15

[a]determined by ^{1}H NMR. [b]determined byGPC. *Mn and Mw/Mn* was determined by GPC measurements in DMF (0.35 mL min^{-1}, 40 °C, and polystyrene standards).

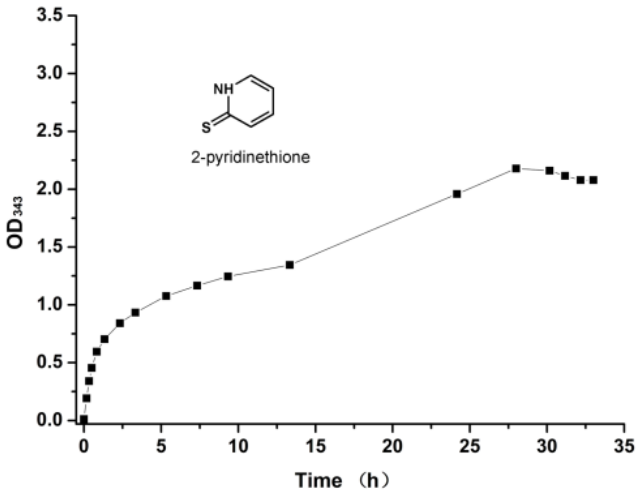

Figure S4. The extent of thiol exchange reaction of angiopep-2-DSPE-PEG2000 conjugates with time measured by UV-vis spectroscopy at 343 nm.

Table S2. The hydrodynamic sizes, and poly dispersion indexes of nanoparticulate systems

molar ratio: Lecithin：DSPE-PEG2000：angiopep-2-DSPE-PEG2000 = 9: 0.8: 0.2

(DSPE-PEG2000: Lecithin: angiopep-2-DSPE-PEG2000)/Polymer mass ratio (%) = 10%

Nanoparticulate systems	Hydrodynamic size (nm)	Poly dispersion index
ALP-(MIs)25	152.75 ± 2.39	0.31 ± 0.03
ALP-(MIs)48	146.13 ± 3.02	0.27 ± 0.11
AL-PLGA	147.71 ± 1.84	0.32 ± 0.06

Table S3. The hydrodynamic sizes, and poly dispersion indexes of nanoparticulate systems

molar ratio: Lecithin：DSPE-PEG2000：angiopep-2-DSPE-PEG2000 = 9: 0.8: 0.2

(DSPE-PEG2000: Lecithin: angiopep-2-DSPE-PEG2000)/Polymer mass ratio (%) = 15%

Nanoparticulate systems	Hydrodynamic size (nm)	Poly dispersion index
ALP-(MIs)25	149.63 ± 2.07	0.52 ± 0.21
ALP-(MIs)48	140.14 ± 2.83	0.33 ± 0.20
AL-PLGA	143.69 ± 1.52	0.38 ± 0.12

Table S4. The hydrodynamic sizes, and poly dispersion indexes of nanoparticulate systems

molar ratio: Lecithin：DSPE-PEG2000：angiopep-2-DSPE-PEG2000 = 9: 0.8: 0.2

(DSPE-PEG2000: Lecithin: angiopep-2-DSPE-PEG2000)/Polymer mass ratio (%) = 20%

Nanoparticulate systems	Hydrodynamic size (nm)	Poly dispersion index
ALP-(MIs)25	144.07 ± 1.83	0.35 ± 0.16
ALP-(MIs)48	138.52 ± 2.44	0.40 ± 0.11
AL-PLGA	129.77 ± 1.12	0.33 ± 0.04

Table S5. The hydrodynamic sizes, and poly dispersion indexes of nanoparticulate systems

molar ratio: Lecithin：DSPE-PEG2000：angiopep-2-DSPE-PEG2000 = 8: 1.8: 0.2

(DSPE-PEG2000: Lecithin: angiopep-2-DSPE-PEG2000)/Polymer mass ratio (%) = 10%

Nanoparticulate systems	Hydrodynamic size (nm)	Poly dispersion index
ALP-(MIs)25	128.41 ± 1.05	0.42 ± 0.01
ALP-(MIs)48	124.25 ± 2.63	0.30 ± 0.06
AL-PLGA	127.09 ± 2.07	0.25 ± 0.08

Table S6. The hydrodynamic sizes, and poly dispersion indexes of nanoparticulate systems

molar ratio: Lecithin：DSPE-PEG2000：angiopep-2-DSPE-PEG2000 = 8: 1.8: 0.2

(DSPE-PEG2000: Lecithin: angiopep-2-DSPE-PEG2000)/Polymer mass ratio (%) = 15%

Nanoparticulate systems	Hydrodynamic size (nm)	Poly dispersion index
ALP-(MIs)25	113.15 ± 1.73	0.21 ± 0.13
ALP-(MIs)48	106.40 ± 2.09	0.18 ± 0.07
AL-PLGA	107.82 ± 3.01	0.29 ± 0.07

Table S7. The hydrodynamic sizes, and poly dispersion indexes of nanoparticulate systems

molar ratio: Lecithin：DSPE-PEG2000：angiopep-2-DSPE-PEG2000 = 8: 1.8: 0.2

(DSPE-PEG2000: Lecithin: angiopep-2-DSPE-PEG2000)/Polymer mass ratio (%) = 20%

Nanoparticulate systems	Hydrodynamic size (nm)	Poly dispersion index
ALP-(MIs)25	99.23 ± 2.14	0.14 ± 0.12
ALP-(MIs)48	95.64 ± 3.12	0.12 ± 0.05
AL-PLGA	96.07 ± 2.15	0.20 ± 0.04

Table S8. The hydrodynamic sizes, and poly dispersion indexes of nanoparticulate systems

molar ratio: Lecithin：DSPE-PEG2000：angiopep-2-DSPE-PEG2000 = 7: 2.8: 0.2

(DSPE-PEG2000: Lecithin: angiopep-2-DSPE-PEG2000)/Polymer mass ratio (%) = 10%

Nanoparticulate systems	Hydrodynamic size (nm)	Poly dispersion index
ALP-(MIs)25	125.08 ± 2.74	0.20 ± 0.11
ALP-(MIs)48	118.23 ± 3.05	0.35 ± 0.09
AL-PLGA	113.74 ± 2.19	0.13 ± 0.06

Table S9. The hydrodynamic sizes, and poly dispersion indexes of nanoparticulate systems

molar ratio: Lecithin：DSPE-PEG2000：angiopep-2-DSPE-PEG2000 = 7: 2.8: 0.2

(DSPE-PEG2000: Lecithin: angiopep-2-DSPE-PEG2000)/Polymer mass ratio (%) = 15%

Nanoparticulate systems	Hydrodynamic size (nm)	Poly dispersion index
ALP-(MIs)25	88.81 ± 0.98	0.15 ± 0.02
ALP-(MIs)48	76.76 ± 2.31	0.22 ± 0.05
AL-PLGA	80.38 ± 1.07	0.19 ± 0.04

Table S10. The hydrodynamic sizes, and poly dispersion indexes of nanoparticulate systems

molar ratio: Lecithin：DSPE-PEG2000：angiopep-2-DSPE-PEG2000 = 7: 2.8: 0.2

(DSPE-PEG2000: Lecithin: angiopep-2-DSPE-PEG2000)/Polymer mass ratio (%) = 20%

Nanoparticulate systems	Hydrodynamic size (nm)	Poly dispersion index
ALP-(MIs)25	93.41 ± 1.07	0.19 ± 0.02
ALP-(MIs)48	84.23 ± 2.76	0.25 ± 0.03
AL-PLGA	86.71 ± 2.08	0.13 ± 0.07

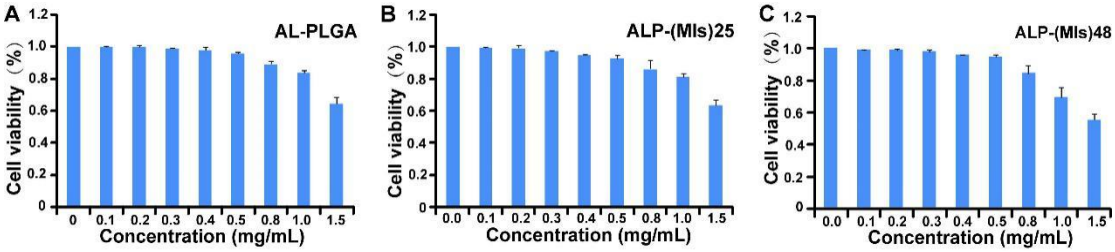

Figure S5. The viability of C6 cells cultured with different concentration of (A) AL-PLGA, **(B)** ALP-(MIs)25, **(C)** ALP-(MIs)48 for 48 h by MTT assay. Data are presented as the Mean ± SD, n = 3.

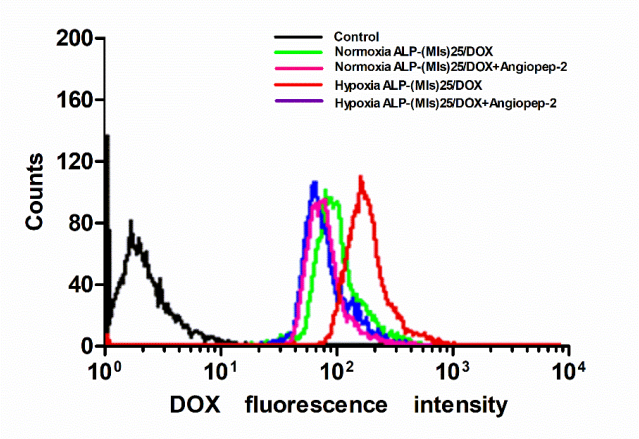

Figure S6. Cellular uptake of ALP-(MIs)25/DOX was analyzed with flow cytometry after 4 h incubation under normoxic, hypoxic, normoxic + angiopep-2 and hypoxic + angiopep-2 conditions.

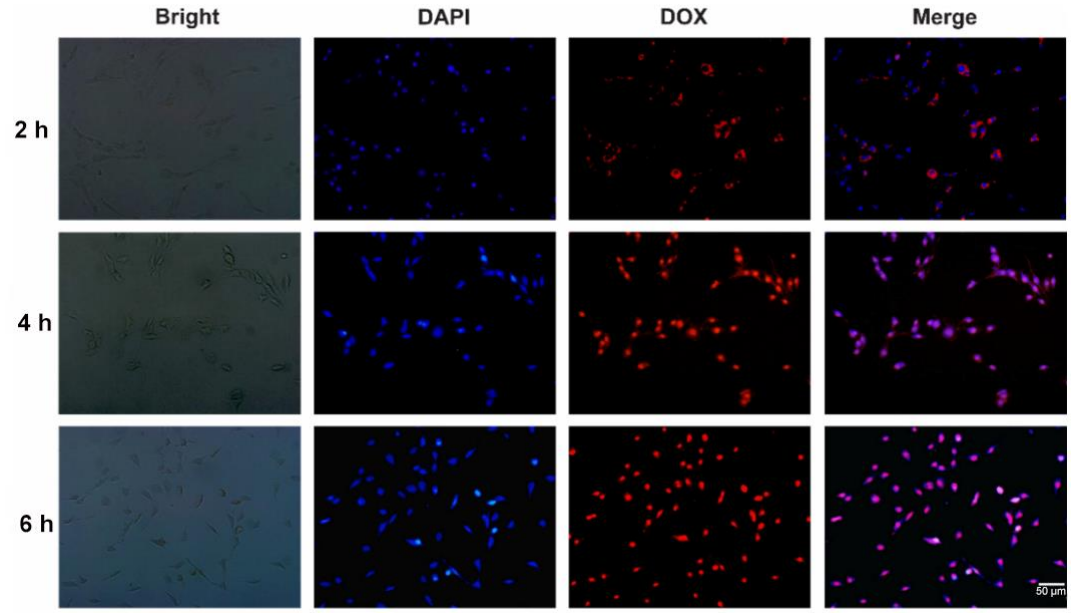

Figure S7. Intracellular release of DOX from ALP-(MIs)25/DOX. Samples were incubated with C6 cells under hypoxic conditions for 2 h, 4 h and 6 h. Scale bar, 50 μm.

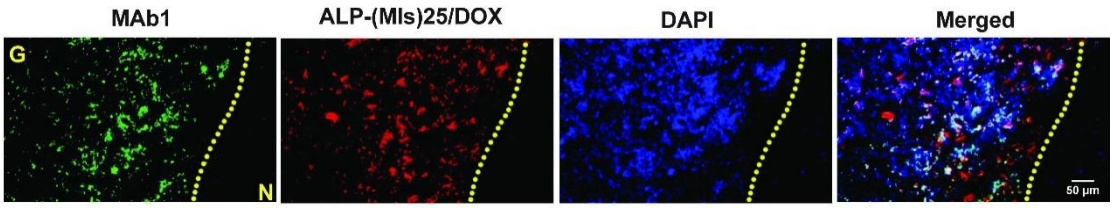

Figure S8. Immunofluorescence assay after MAb1 (HypoxyprobeTM-1 Kit), which could bind to proteins, peptides and amino acid adducts of 2-nitroimidazole in hypoxic cells, in addition to tumor tissue sections: green regions are hypoxic tissues, and red regions are DOX fluorescence of LP-(MIs)25/DOX or ALP-(MIs)25/DOX. Compared with normal brain tissues, glioma cells showed abnormal proliferation, and thus C6-bearing brain tumor tissue was identified based on areas of hypercellularity, as evidenced by the DAPI-stained cell nuclei (blue). Scale bar, 50 μm.

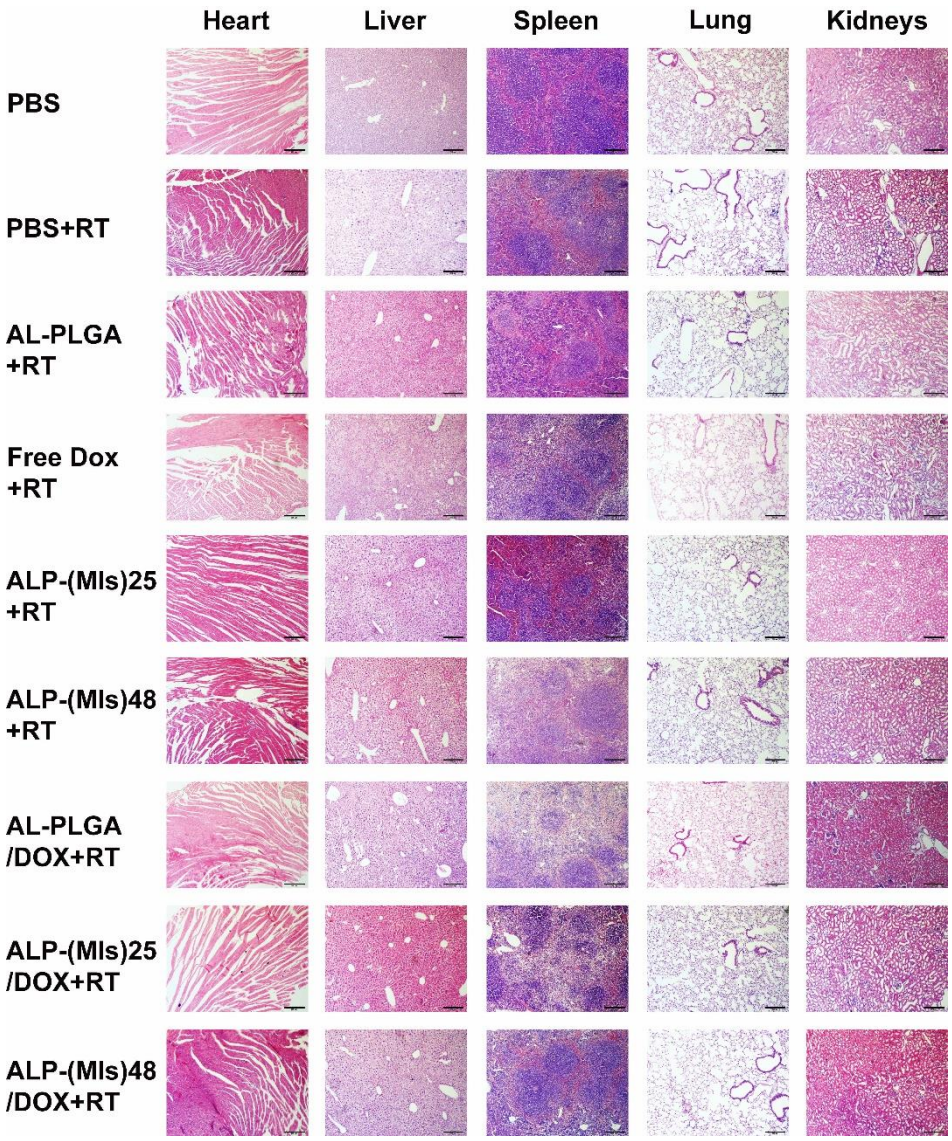

Figure S9. Histopathological examination of major organs collected after treatment on the animals.H&E staining of major organs. No noticeable abnormality was found in the heart, liver, spleen, lung, or kidneys. Scale bar, 200 μm.

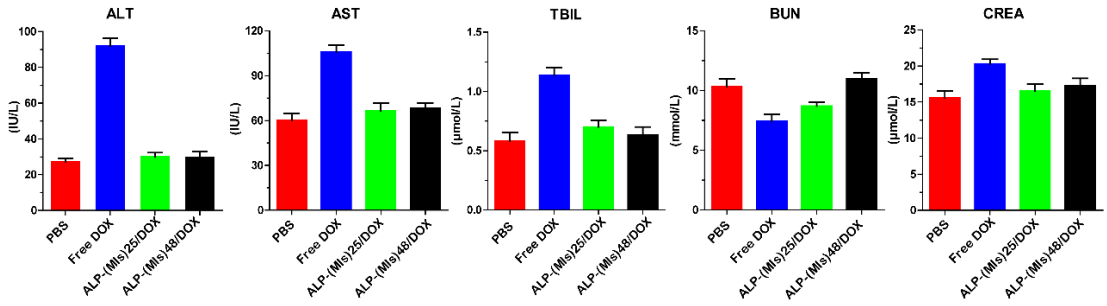

Figure S10. The hemanalysis and biochemical analyses. The hemanalysis and biochemical analyses were performed on blood withdrawn from the mice on 24 h post drug treatment. Data are presented as the Mean ± SD, n = 3.