Supplementary Materials

ROS-sensitive tegafur-PpIX heterodimer loaded in-situ injectable thermosensitive hydrogel for photodynamic therapy combined with chemotherapy to enhance tegafur treatment of breast cancer

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^{1}H-NMR data of TTP/TSP its intermediate:

Tegafur. ^{1}H-NMR (600MHz, DMSO-d_6): δ 7.85 (d, 1H, C=CH), 5.89 (ddd, 1H, OCH), 4.22 (dt, 1H, OCH_2), 3.80 (q, 1H, OCH_2'), 2.21 (m, 1H, CH_2), 2.01 (m, 1H, CH_2'), 1.93 (m, 2H, CH_2).

TF-TA. ^{1}H-NMR (600MHz, DMSO-d_6): δ 12.65 (s, 1H, COOH), 8.03 (d, 1H, C=CH), 5.94 (ddd, 1H, OCH), 5.83 (q, 2H, NCH_2O), 4.26 (q, 1H, OCH_2), 3.83 (q, 1H, OCH_2'), 3.46 (s, 2H, SCH_2COOH), 3.37 (s, 2H, $COOCH_2S$), 2.24 (m, 1H, CH_2), 2.06 (m, 1H, CH_2'), 1.92 (m, 2H, CH_2).

TF-TA-EG. ^{1}H-NMR (600MHz, DMSO-d_6): 8.03 (d, 1H, C=CH), 5.94 (ddd, 1H, OCH), 5.83 (q, 2H, NCH_2O), 4.80 (t, 1H, OH), 4.26 (q, 1H, OCH_2), 4.05 (q, 2H, CH_2OH), 3.83 (q, 1H, OCH_2'), 3.56 (q, 2H, OCH_2), 3.50 (s, 2H, SCH_2COO), 3.47 (s, 2H, $COOCH_2S$), 2.25 (m, 1H, CH_2), 2.04 (m, 1H, CH_2'), 1.93 (m, 2H, CH_2).

TTP. ^{1}H-NMR (600MHz, DMSO-d_6): 10.32 (s, 1H, PpIX), 10.25 (d, 2H, PpIX), 10.21 (s, 1H, PpIX), 8.51 (m, 2H, PpIX), 7.90 (d, 2H, TF), 6.48 (dt, 2H, PpIX), 6.24 (dt, 2H, PpIX), 5.79 (ddd, 2H, TF), 5.66 (q, 2H, TF), 4.38 (t, 4H, PpIX), 4.21-4.11 (m, 8H, TF), 3.84-3.62 (m, 12H, PpIX), 3.36 (s, 4H, TF), 3.30-3.28 (t, 4H, TF), 3.25 (d, 4H, TF), 2.09 (m, 2H, TF), 1.94 (m, 2H, TF), 1.77 (m, 4H, TF).

TF-SA. ^{1}H-NMR (600MHz, DMSO-d_6): 12.23 (s, 1H, COOH), 8.02 (d, 1H, C=CH), 5.96 (ddd, 1H, OCH), 5.78 (q, 2H, NCH_2O), 4.27 (q, 1H, OCH_2), 3.82 (q, 1H, OCH_2'), 2.52 (t, 2H, CH_2COOH), 2.46 (t, 2H, $COOCH_2$), 2.25 (m, 1H, CH_2), 2.04 (m, 1H, CH_2'), 1.93 (m, 2H, CH_2).

TF-SA-EG. ^{1}H-NMR (600MHz, DMSO-d_6): 8.02 (d, 1H, C=CH), 5.95 (ddd, 1H, OCH), 5.78 (q, 2H, NCH_2O), 4.78 (t, 1H, OH), 4.26 (q, 1H, OCH_2), 4.01 (t, 2H, CH_2OH), 3.82 (q, 1H, OCH_2'), 3.55 (q, 2H, $COOCH_2$), 2.57 (dt, 4H, $COOCH_2$ and CH_2COO), 2.26 (m, 1H, CH_2), 2.05 (m, 1H, CH_2'), 1.93 (m, 2H, CH_2).

TSP. ^{1}H-NMR (600MHz, DMSO-d_6): 10.23 (s, 1H, PpIX), 10.17 (s, 1H, PpIX), 10.15 (d, 2H, PpIX), 8.46 (m, 2H, PpIX), 7.88 (d, 2H, TF), 6.45 (d, 2H, PpIX), 6.22 (d, 2H, PpIX), 5.77 (ddd, 2H, TF), 5.50 (m, 4H, TF), 4.36 (t, 4H, PpIX), 4.20-4.11 (m, 8H, TF), 3.70 (d, 6H, PpIX), 3.61 (d, 6H, PpIX), 2.22 (t, 4H, TF), 2.14 (t, 4H, TF), 2.09 (m, 2H, TF), 1.87 (m, 2H, TF), 1.80 (m, 4H, TF).

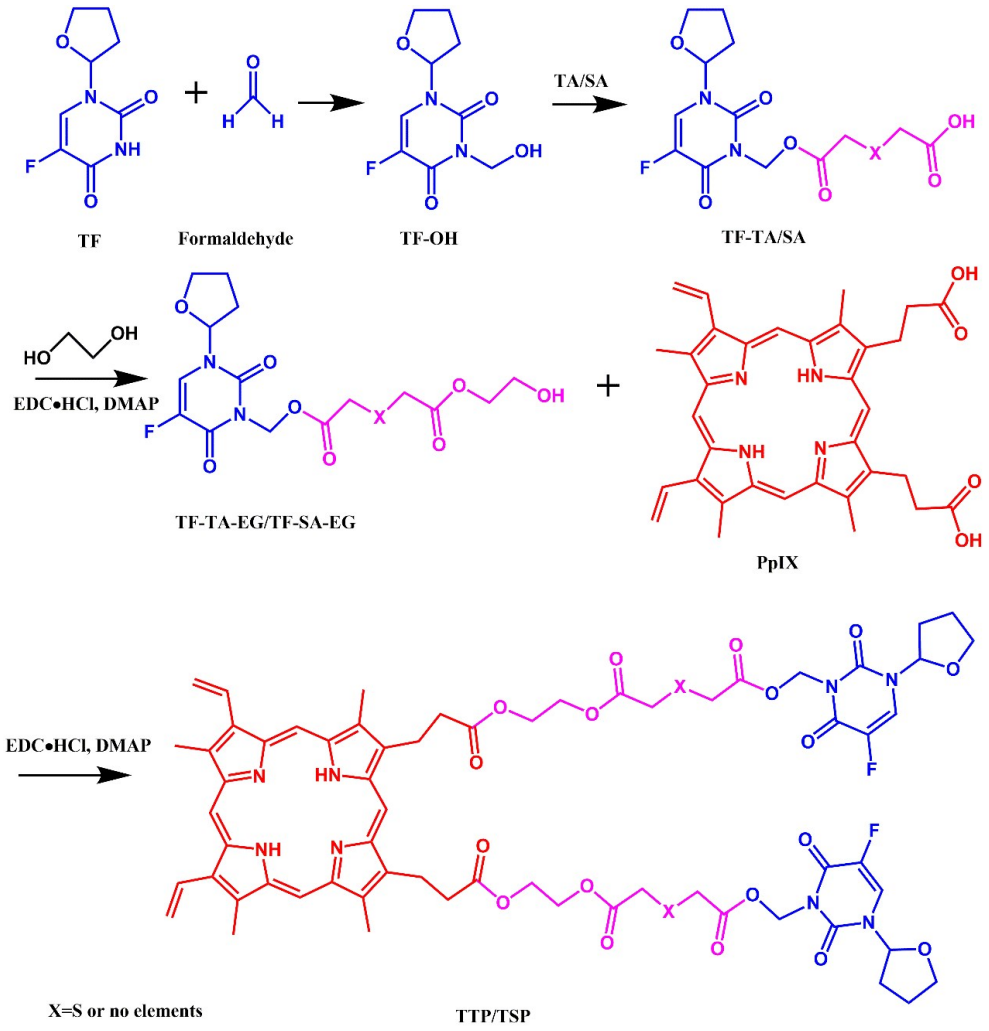

Figure S1. Synthesis process of TTP/TSP.

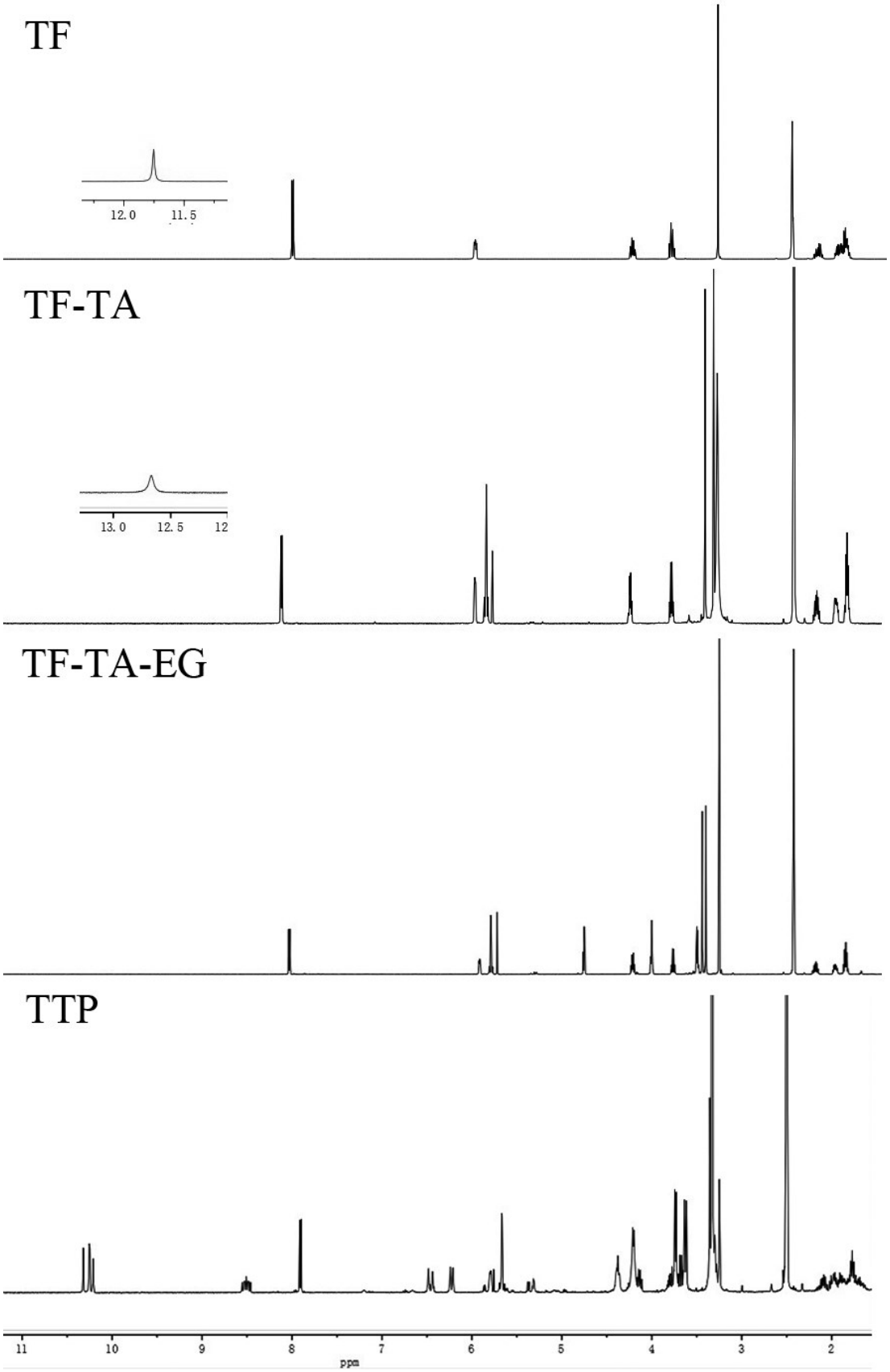

Figure S2. [1]H-NMR spectrum of TF, TF-TA, TF-TA-EG and TTP.

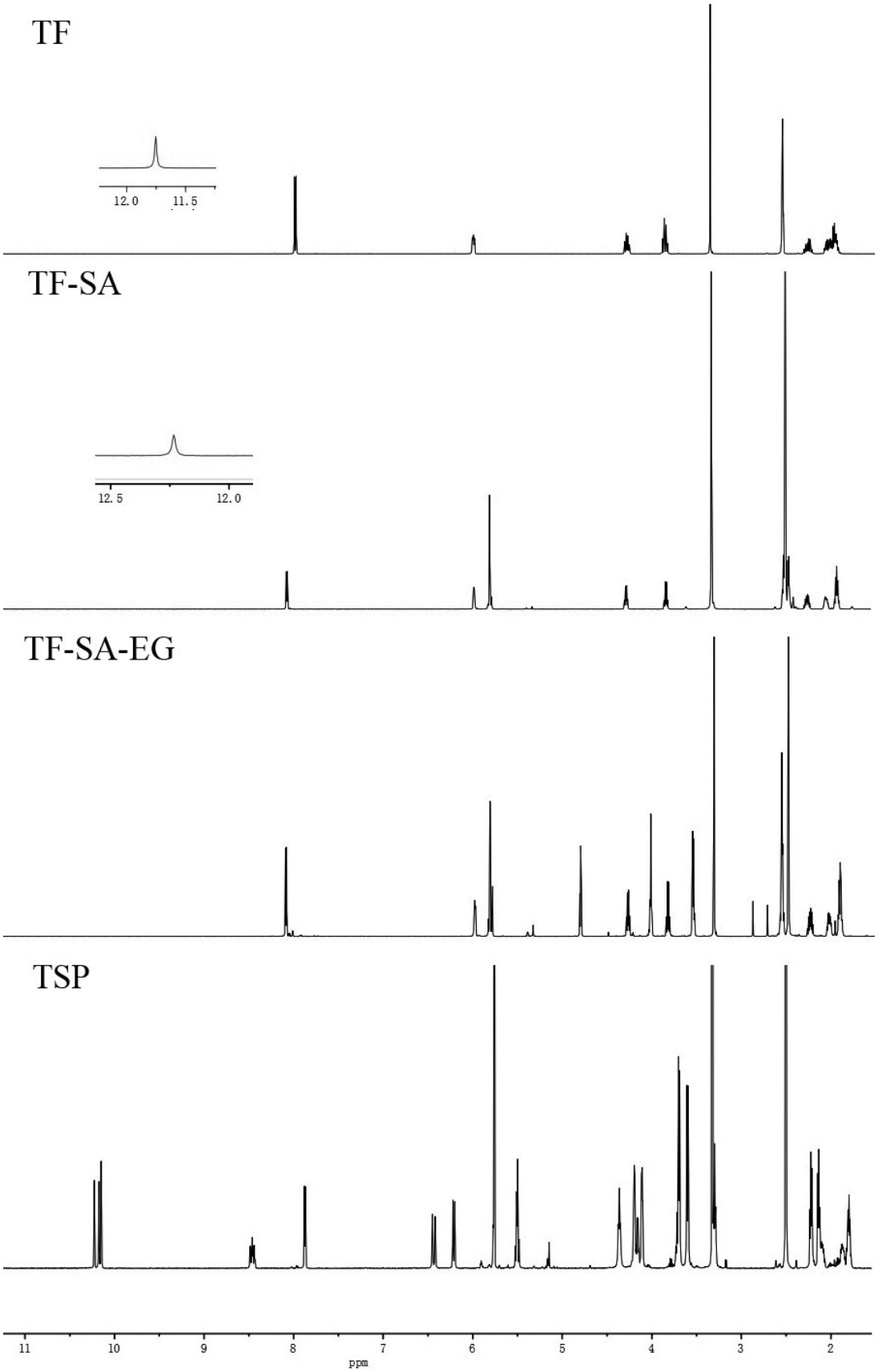

Figure S3. [1]H-NMR spectrum of TF, TF-SA, TF-SA-EG and TSP.

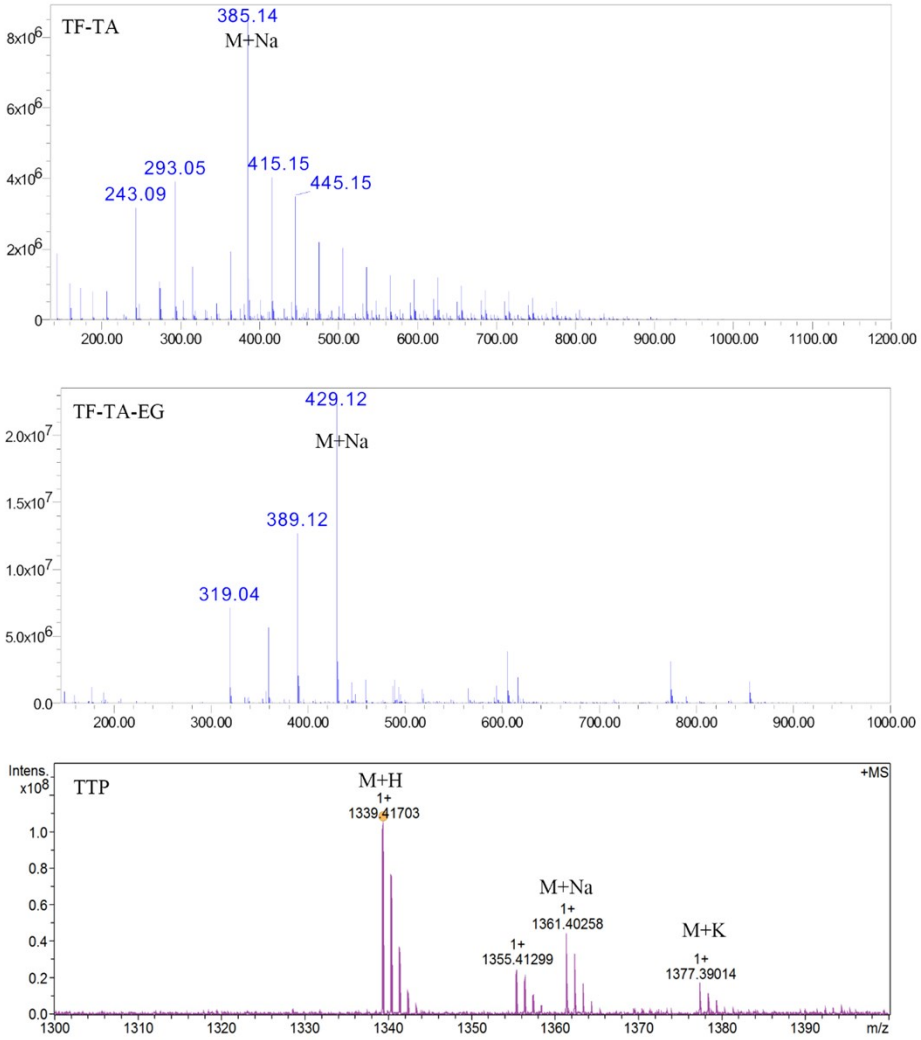

Figure S4. MS spectrum of TF-TA, TF-TA-EG and TTP.

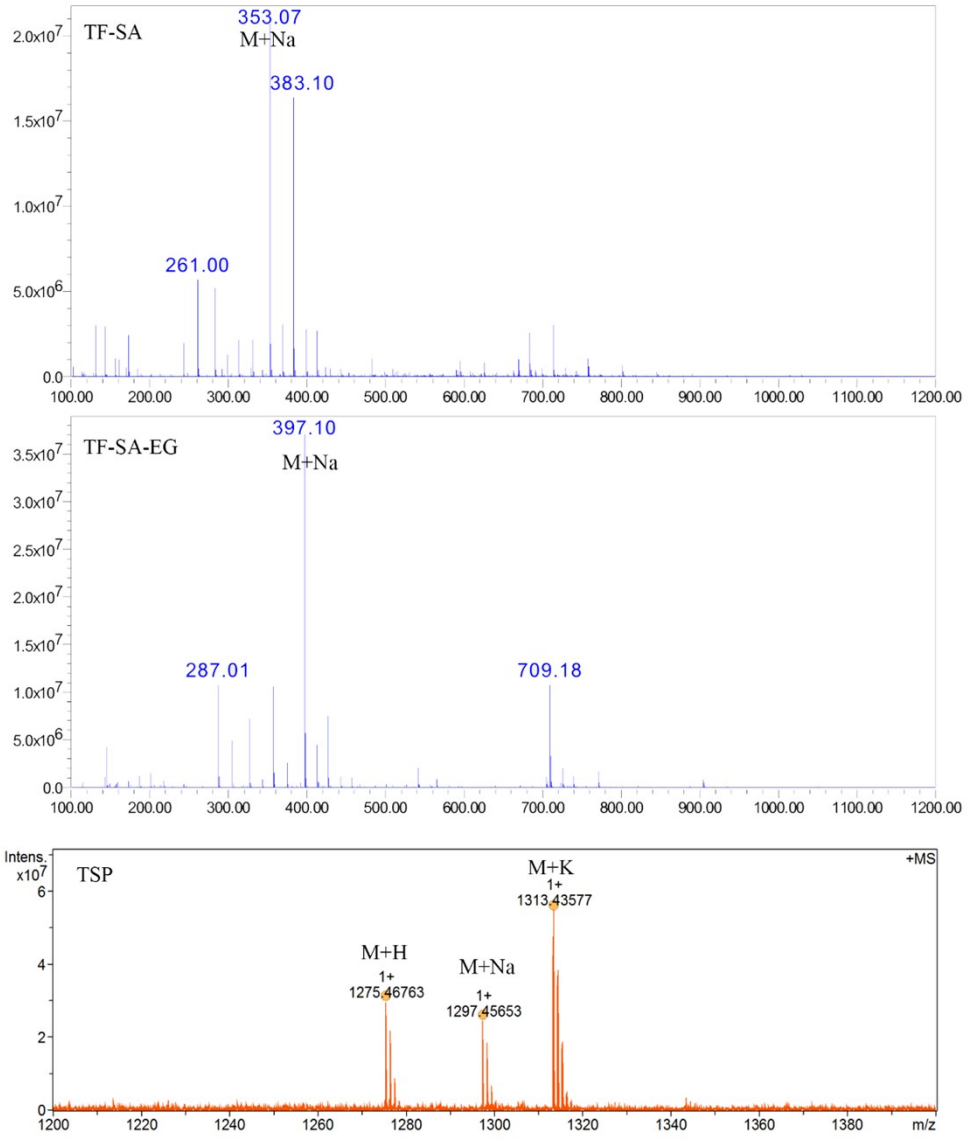

Figure S5. MS spectrum of TF-SA, TF-SA-EG and TSP.

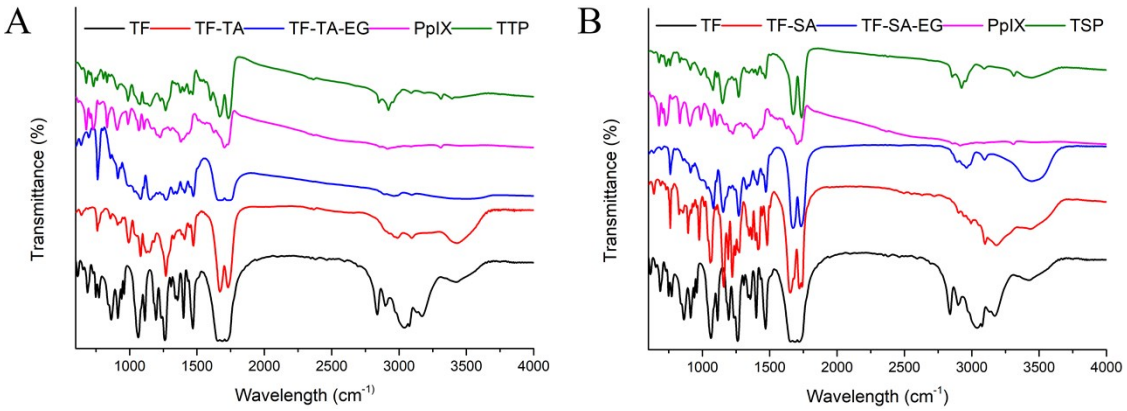

Figure S6. FT-IR spectra of TTP/TSP and their intermedium.

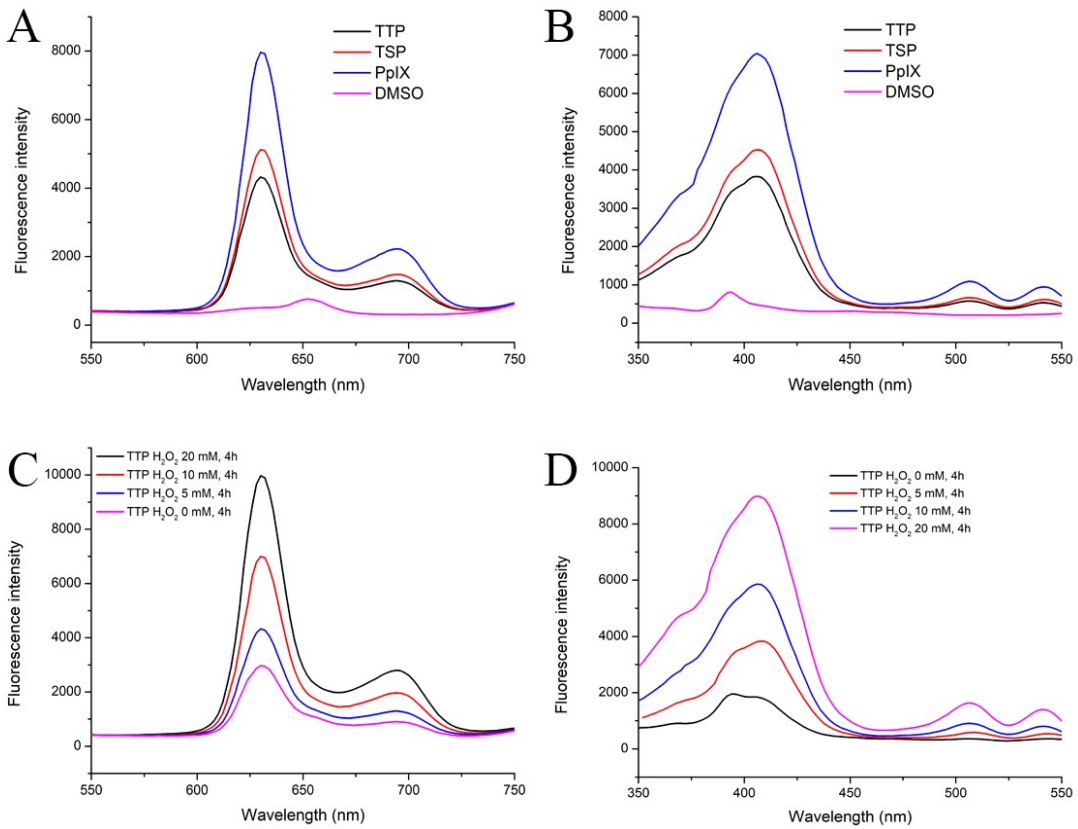

Figure S7. Fluorescence emission and excitation spectra at a PpIX concentration of 10 μg/mL. (A) Fluorescence emission spectra at a fixed excitation of 409 nm; (B) Fluorescence excitation spectra at a fixed emission of 630 nm; (C) Fluorescence emission spectra of TTP when incubated with different concentration of H_2O_2. (D) Fluorescence excitation spectra of TTP when incubated with different concentration of H_2O_2.

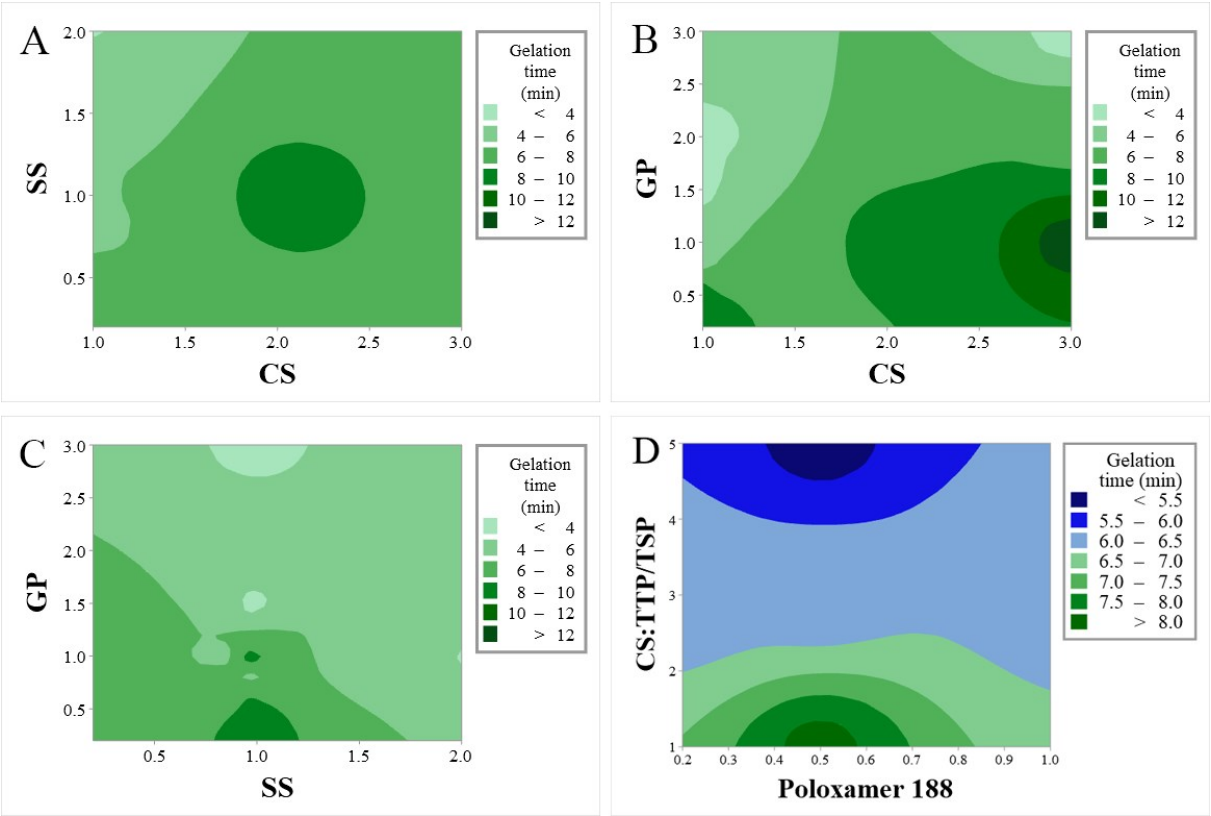

Figure S8. Influencing factors on gel time of (A) the ratio of CS to SS; (B) the ratio of CS to β-GP; (C) the ratio of SS to β-GP and(D) the ratio of CS: TTP or TSP and Poloxamer 188.

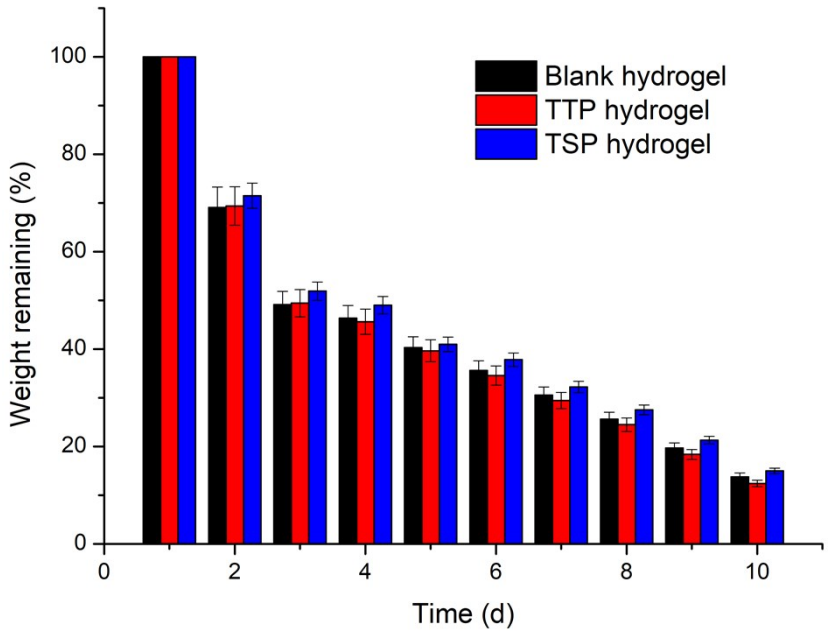

Figure S9. *In vitro* degradation study of blank hydrogel, TTP hydrogel and TSP hydrogel within 10 days.

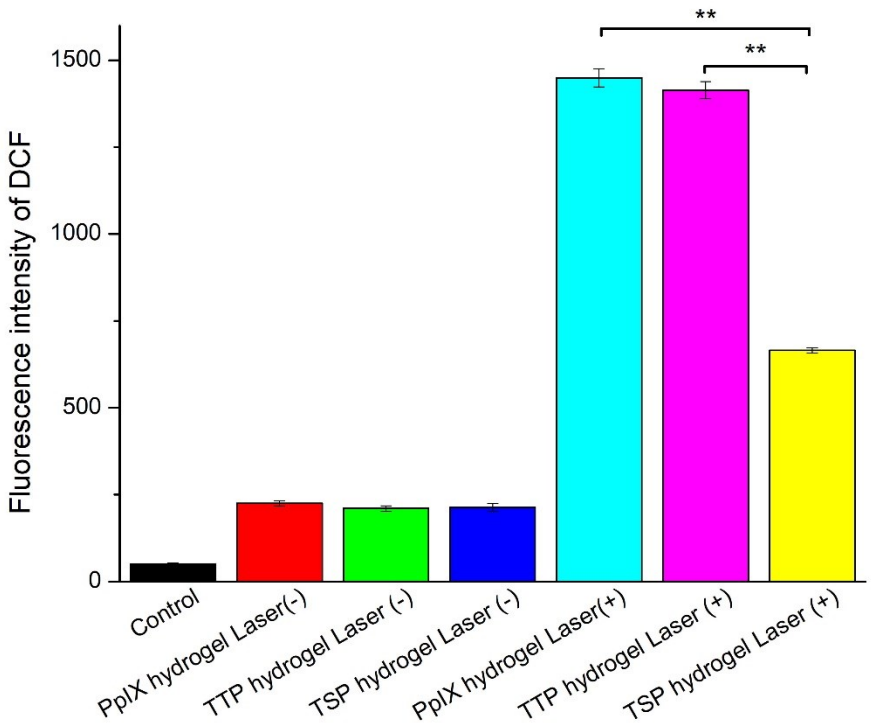

Figure 10. The flurescence intensity of DCF after cells incubated with PpIX hydrogel, TTP hydrogel and TSP hydrogel. **, $p < 0.01$, extremely significant difference.

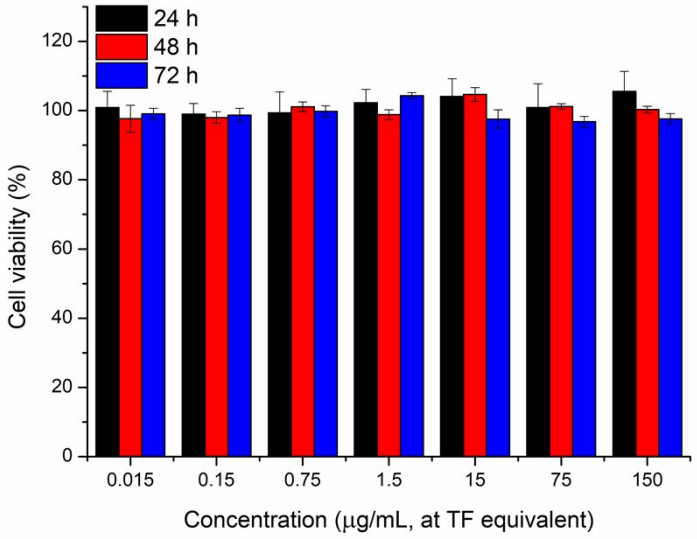

Figure S11. Cell viability to after 4T1 cells co-incubated with blank hydrogel for 24, 48 and 72 h.

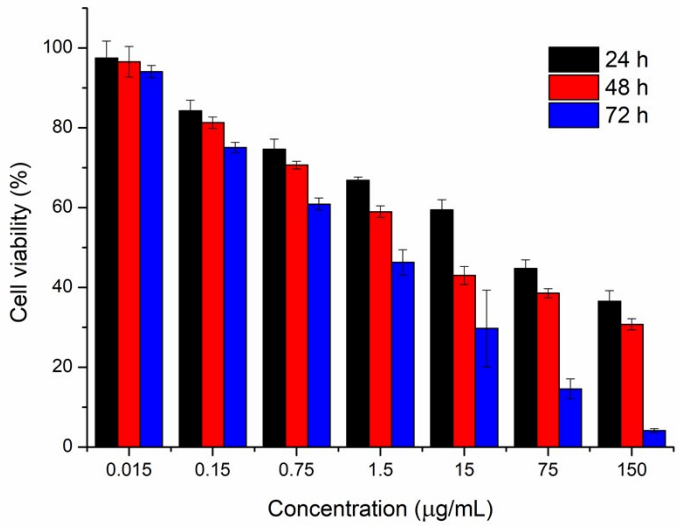

Figure S12. Cell viability to after 4T1 cells co-incubated with Fangke® for 24, 48 and 72 h.

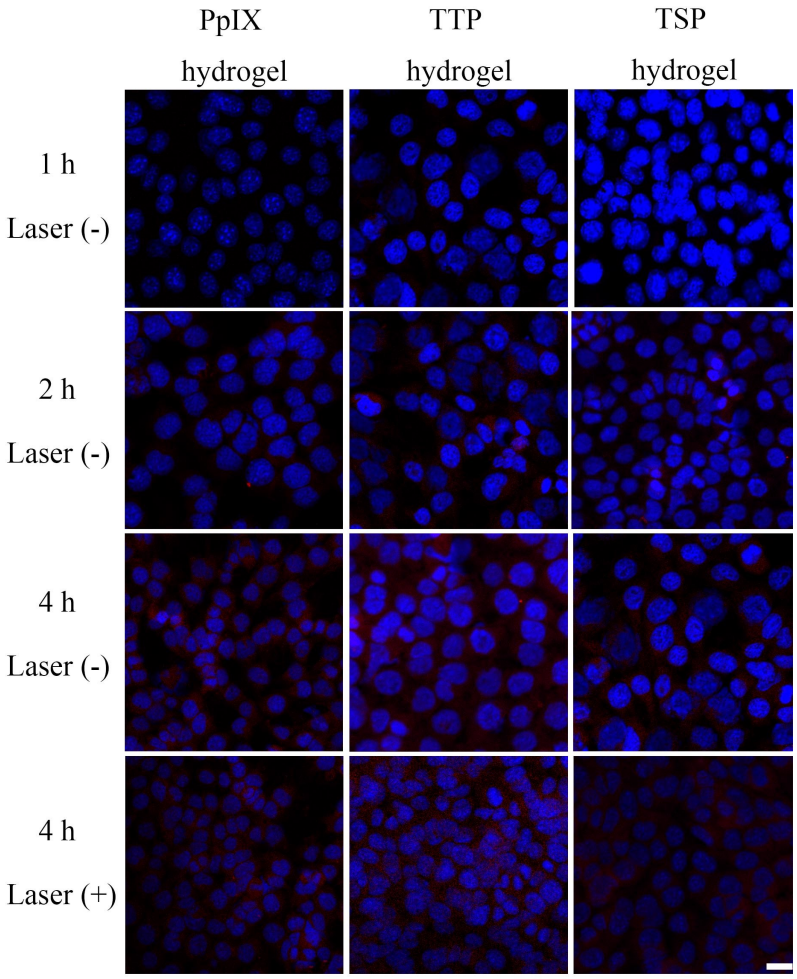

Figure S13. Cellular uptake of hydrogels with/without laser irradiation imaged by CSLM. Scale bar = 20 μm.

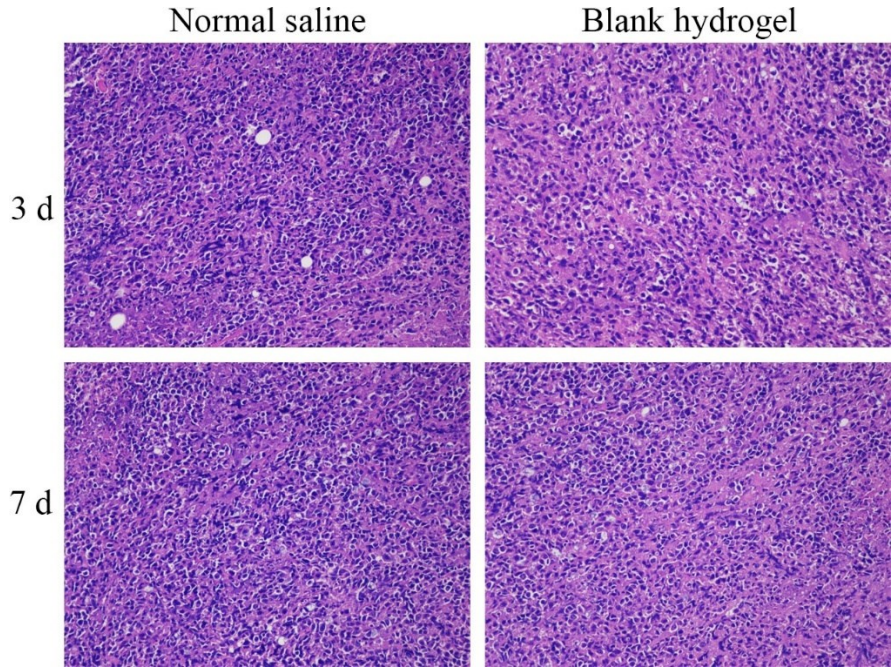

Figure S14. H&E staining images of tumors treated with normal saline or blank hydrogel after 3 and 7 days.

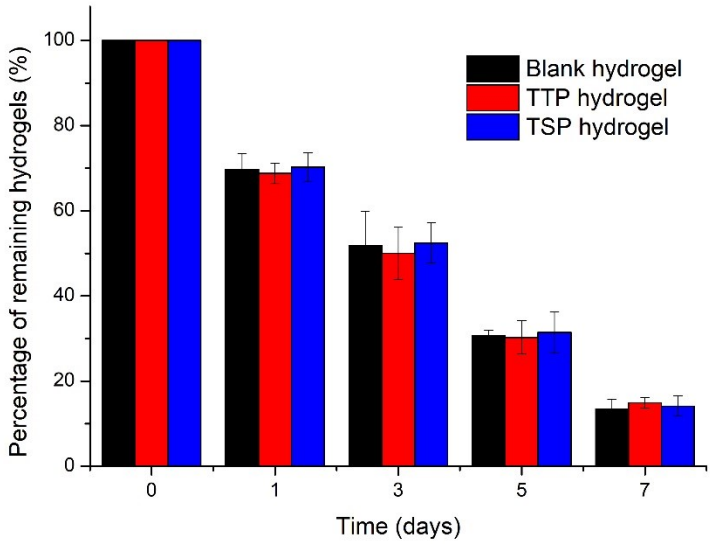

Figure S15. The intratumoral degradation of blank hydrogel, TTP hydrogel and TSP hydrogel in tumor-bearing Balb/c mice.

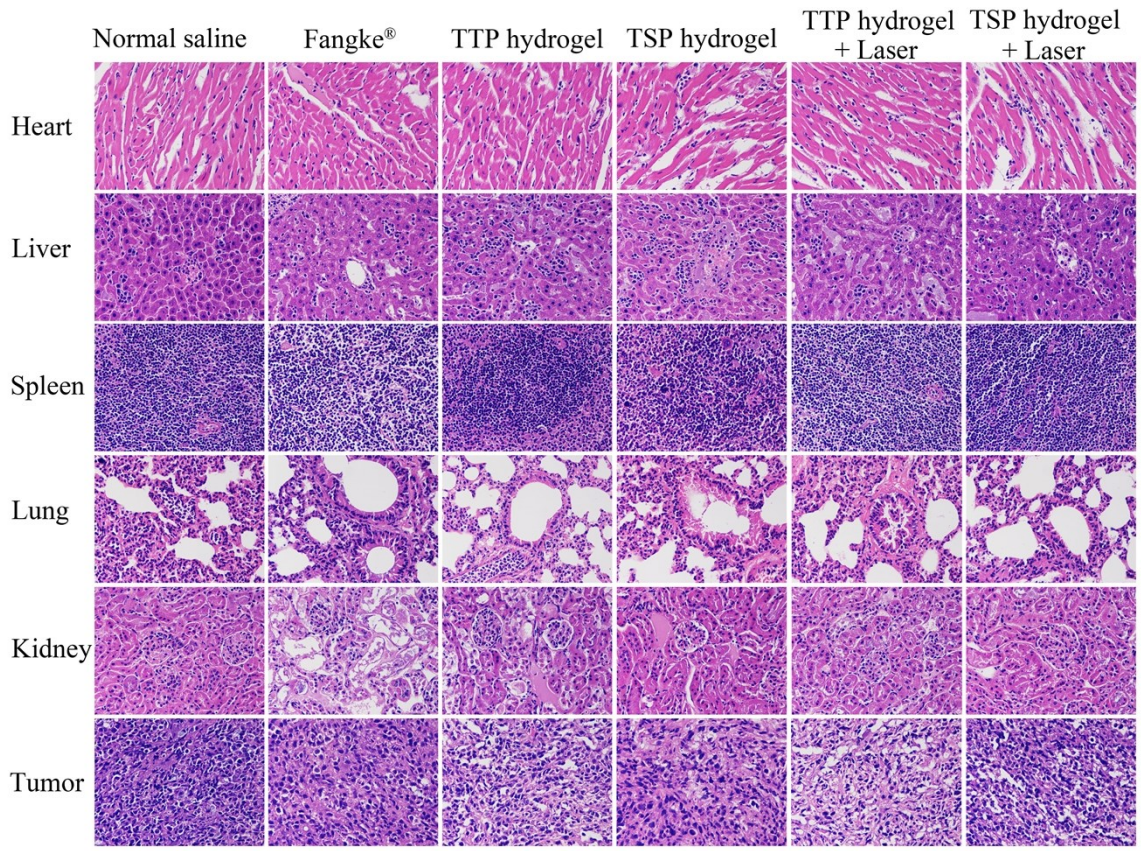

Figure S16. H&E staining images of hearts, livers, spleens, lungs, kidneys and tumors after 14 days of treatment of normal saline, Fangke®, TTP hydrogel, TSP hydrogel, TTP hydrogel with laser irradiation and TSP hydrogel with laser irradiation.

Table S1. TF and its prodrugs content in tumors, plasma and major organs after 3 days of intratumorally injection.

Determined substances	Content (μg/g)						
	Tumor	Plasma	Heart	Liver	Spleen	Lung	Kidney
TF of TTP hydrogel	941.30 ± 175.36	-	-	-	-	-	-
TF of TSP hydrogel	929.86 ± 137.03	-	-	-	-	-	-
TTP	7071.33 ± 926.67	-	-	-	-	-	-
TSP	10314.09 ± 935.27	-	-	-	-	-	-

"-" represents no drugs or prodrugs were determined.