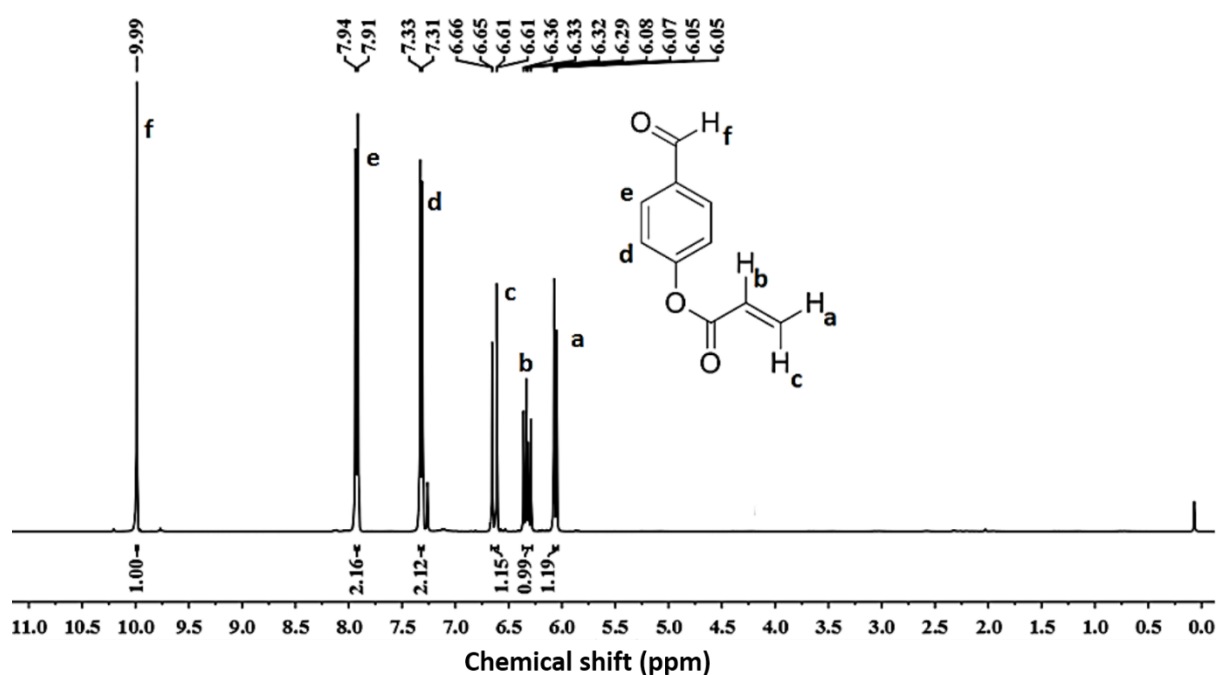


## ELECTRONIC SUPPLEMENTARY MATERIAL

### Copper-Free Click Reaction for Synthesis of Redox-Responsive Water-soluble Core Cross-Linked Nanoparticles for Drug Delivery in Cancer Therapy

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**Figure S1.** <sup>1</sup>H NMR (in CDCl<sub>3</sub>) of 4-formylphenyl acrylate (FPA).

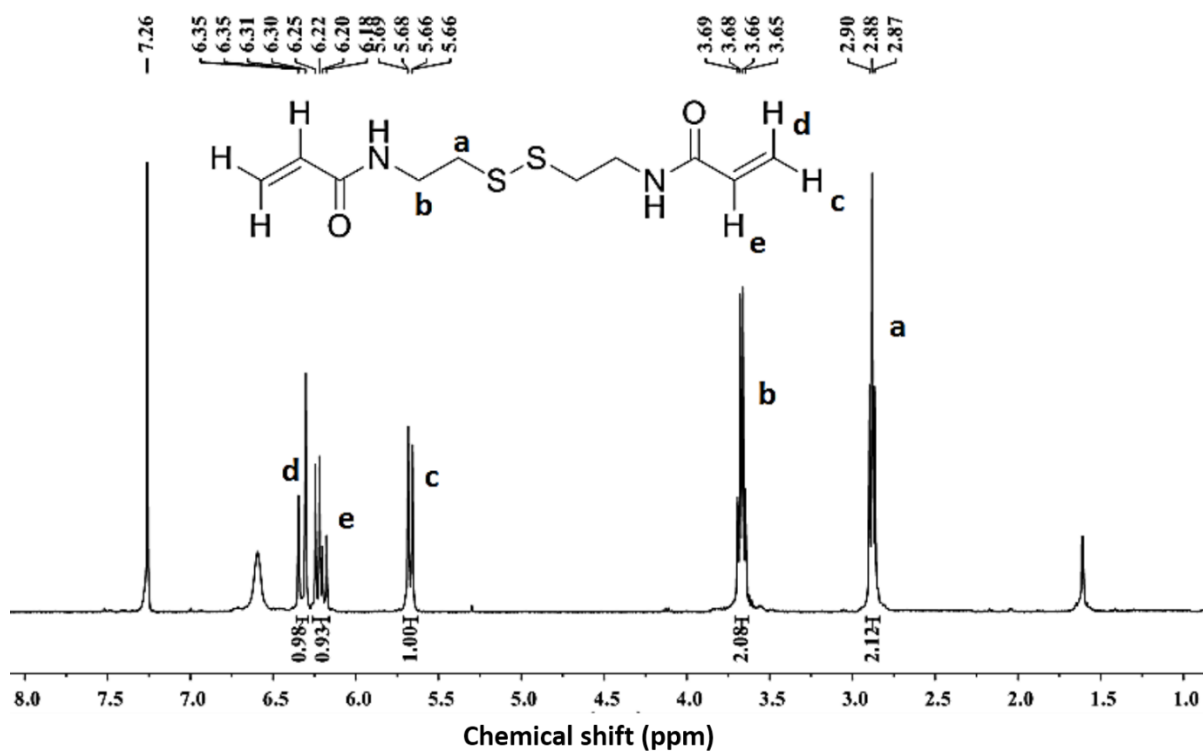


Figure S2. <sup>1</sup>H NMR (in CDCl<sub>3</sub>) of *N,N'*-Bis(acryloyl)cystamine (BAC).

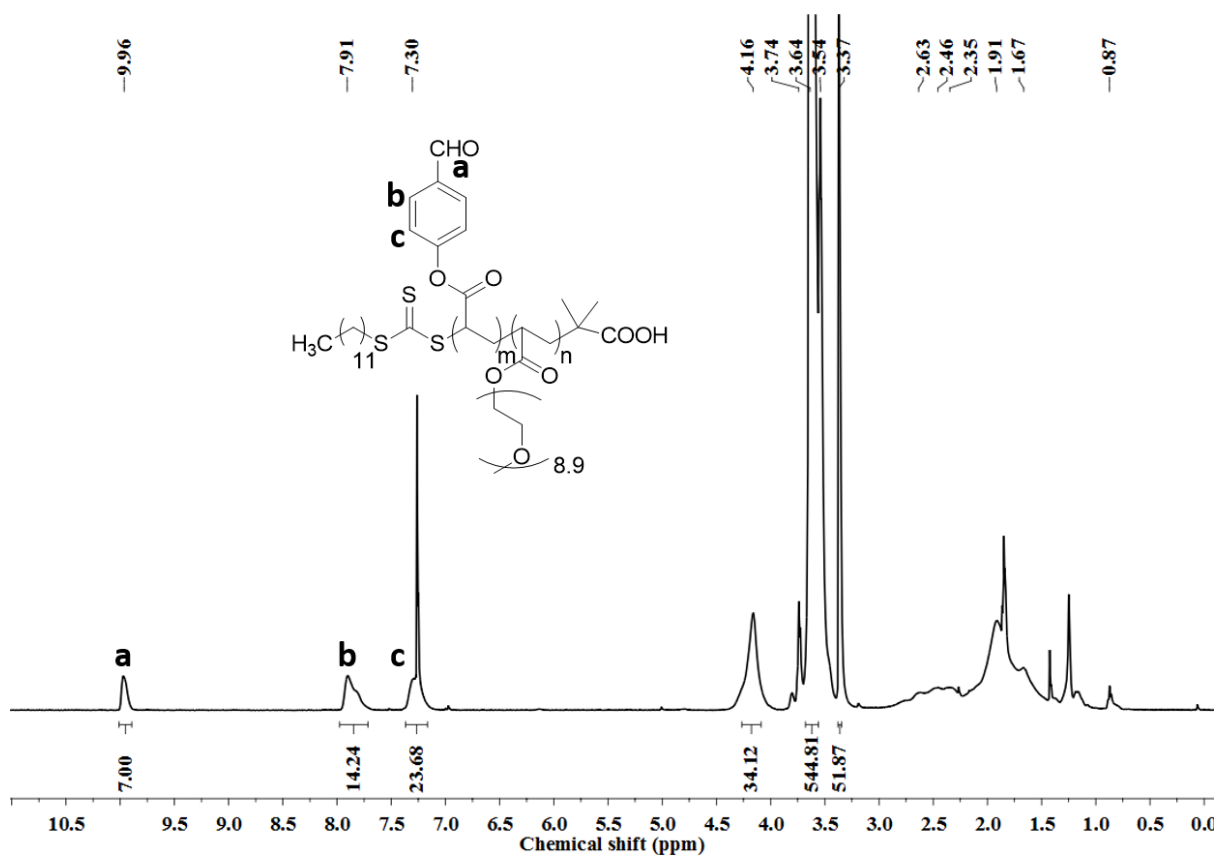
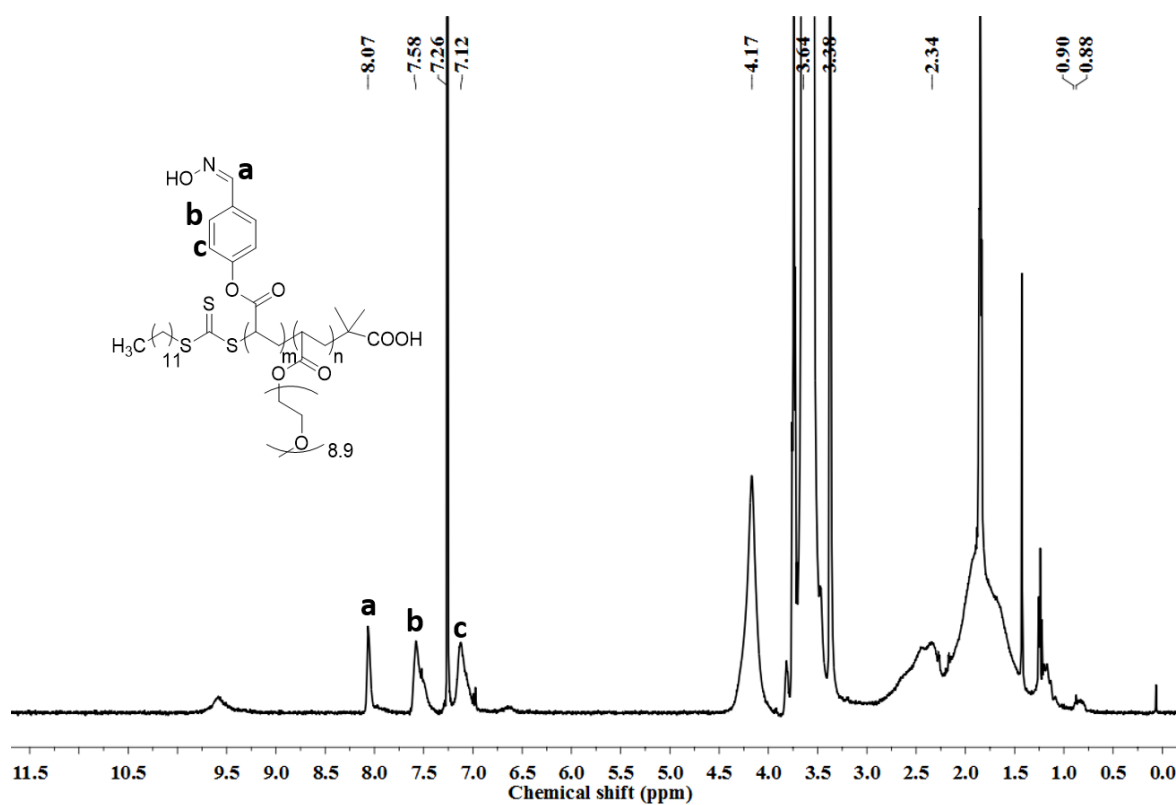
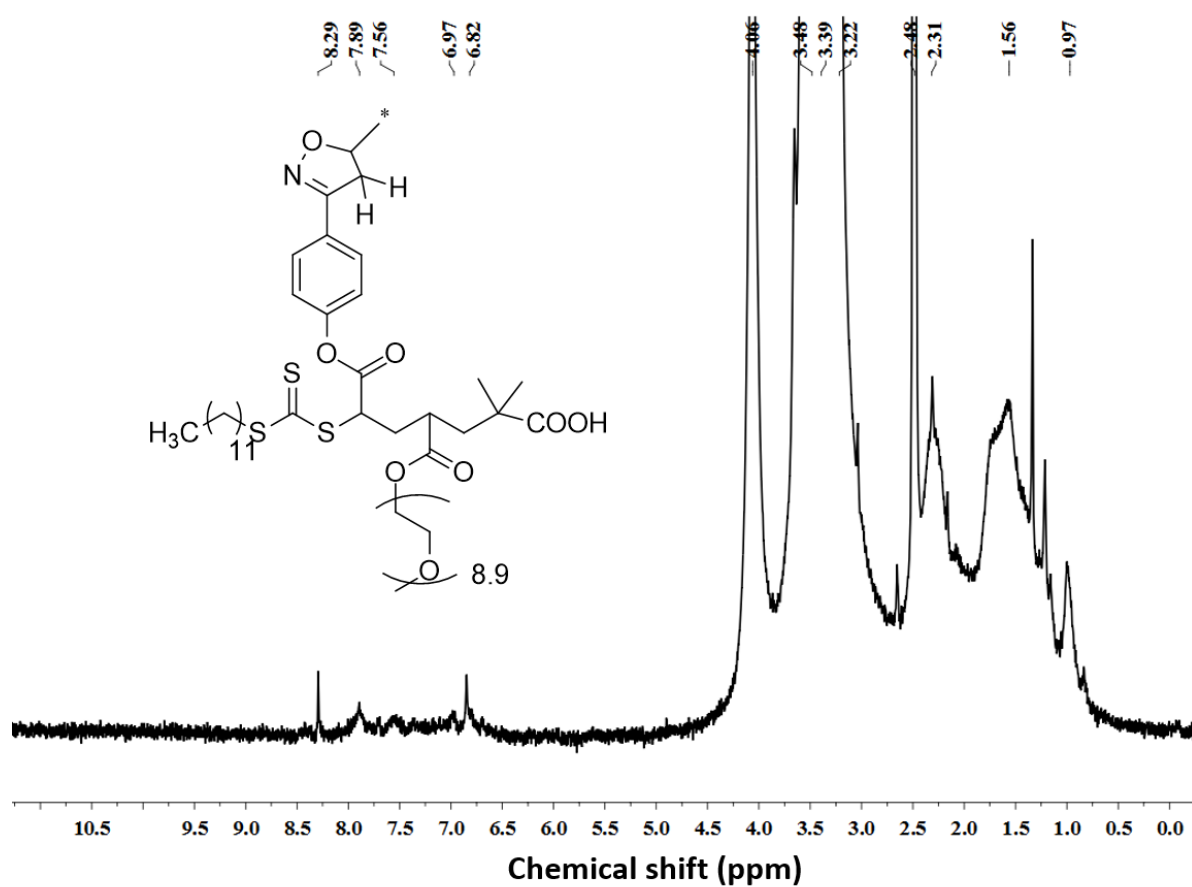


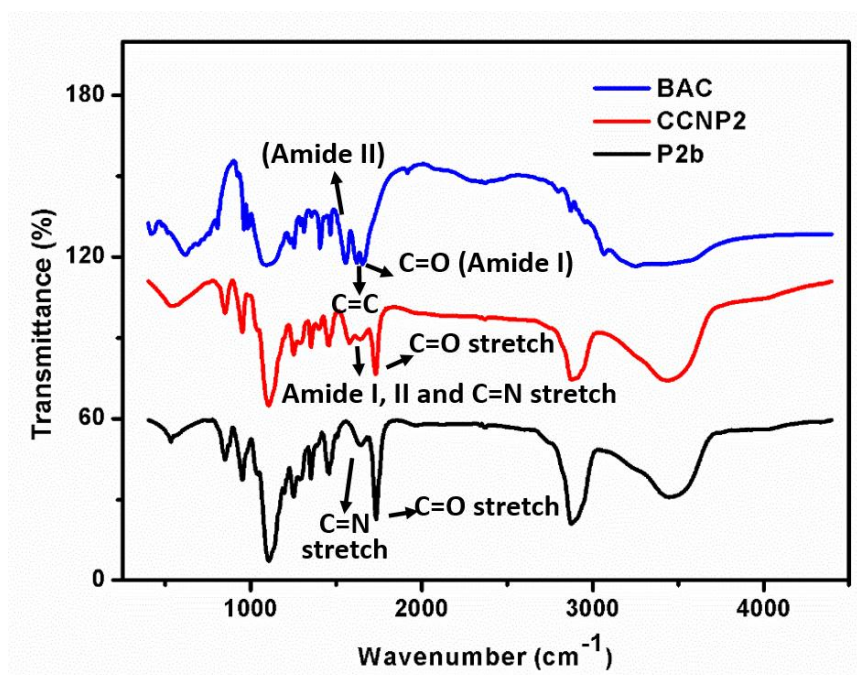
Figure S3. <sup>1</sup>H NMR (in CDCl<sub>3</sub>) of poly(FPA-co-PEGMEA) (P2a).



**Figure S4.**  $^1\text{H}$  NMR (in  $\text{CDCl}_3$ ) of poly(FOPA-co-PEGMEA) (P2b).

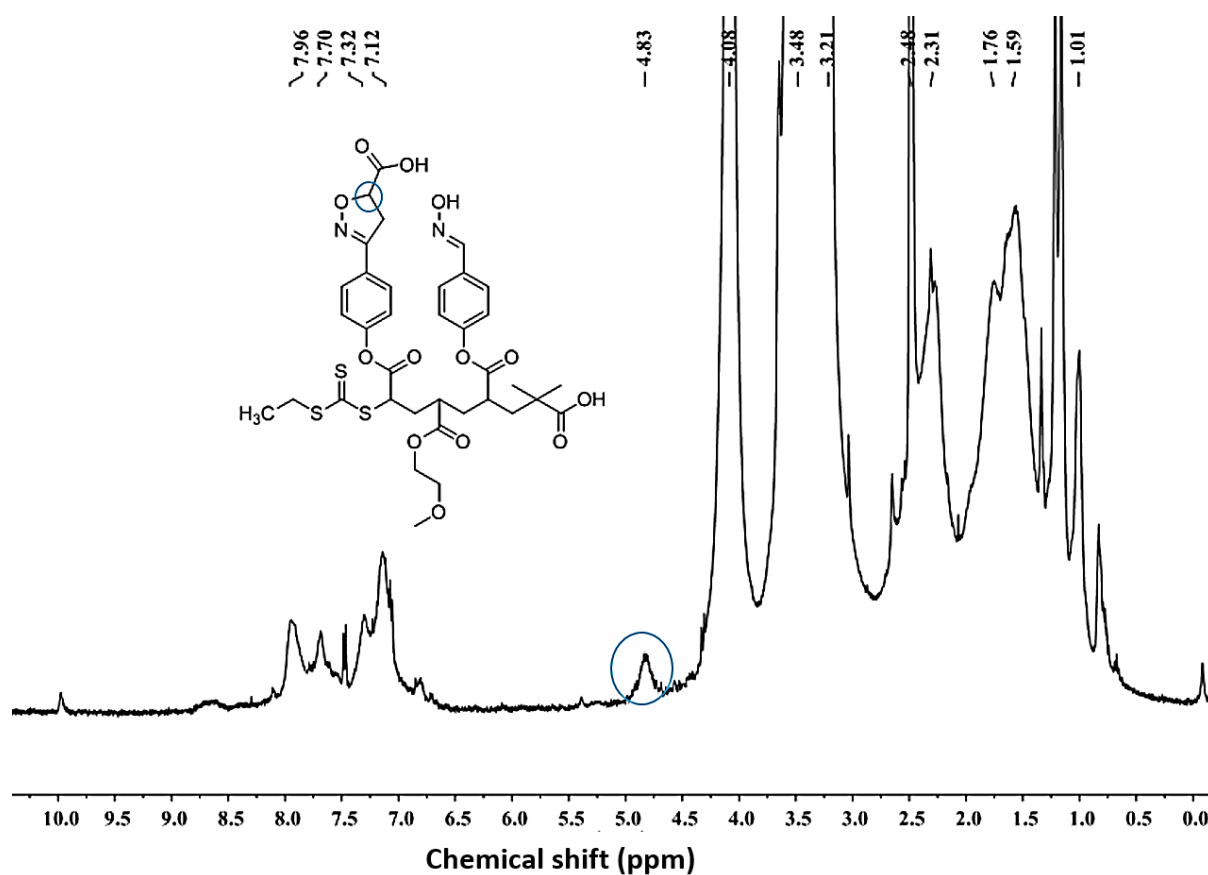


**Figure S5.**  $^1\text{H}$  NMR (in  $\text{DMSO-d}_6$ ) of core cross-linked nanoparticle CCNP2.

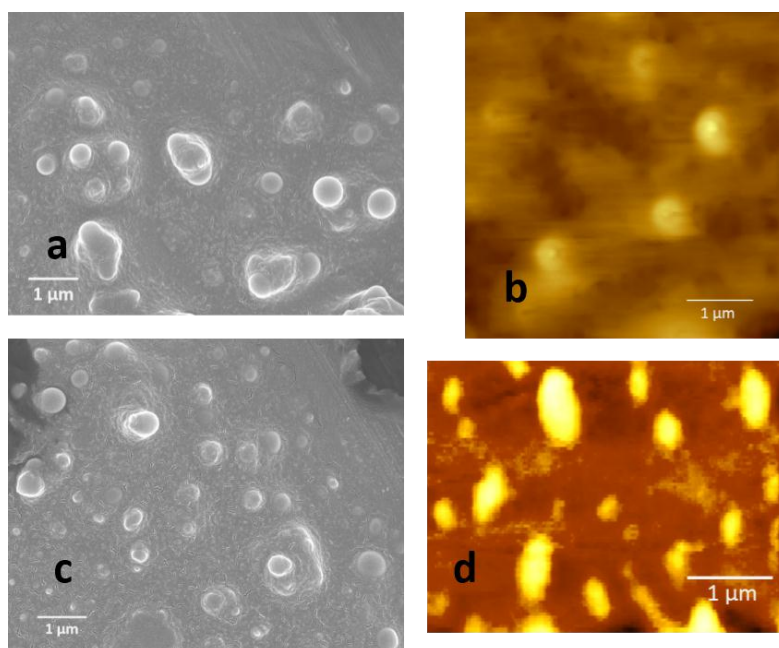


**Figure S6.** FT-IR spectra of cross-linker BAC, oxime functionalized copolymer P2b and CCNP2.

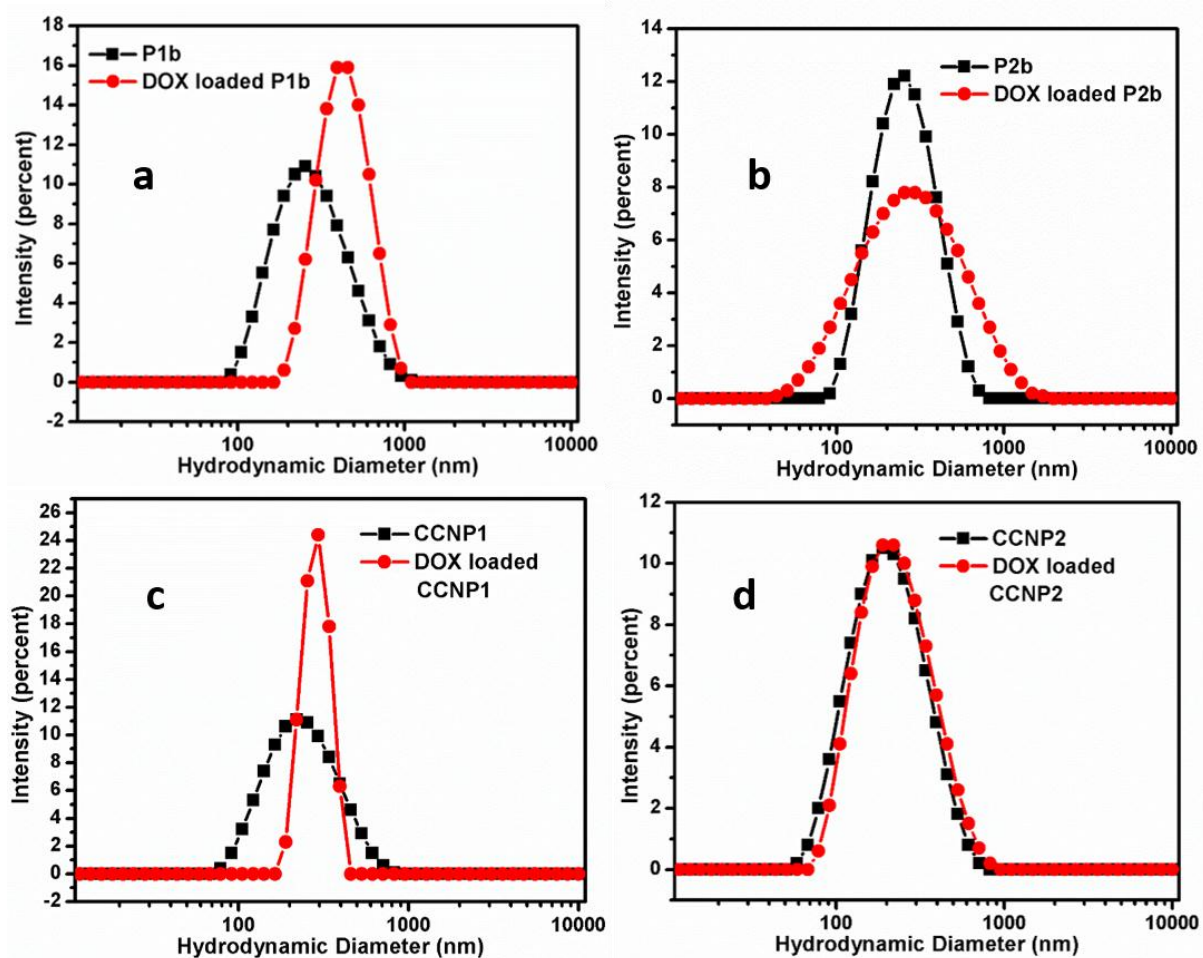
*Synthesis of click product P3 by P2b and acrylic acid:* P3 was synthesized in a similar way of CCNPs. Shortly, aqueous NaOCl (0.084 ml, 0.135 mmol) was added to dissolved P2b (0.05 mg, 0.054 mmol) in 1.5 ml H<sub>2</sub>O-THF (1:1.5) at 5 °C. After 20 min stirring, acrylic acid (3.9 mg, 0.054 mmol) was added slowly to the mixture and kept it in a stirring condition for 24 h at room temperature. Excess NaOCl and acrylic acid were removed by dialysis with water and product was dried by lyophilisation. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz) (Figure S7, Supplementary Information): δ (ppm) 1.59 (polymer backbone), 1.76 (polymer backbone), 2.31 (polymer backbone), 4.08 (CH<sub>2</sub>-CH<sub>2</sub>-O- of PEGMEA), 4.83 (CH of isoxazoline ring), 7.12 (Ar protons), 7.32 (Ar protons), 7.70 (Ar protons), 7.96 (unreacted oxime CH).



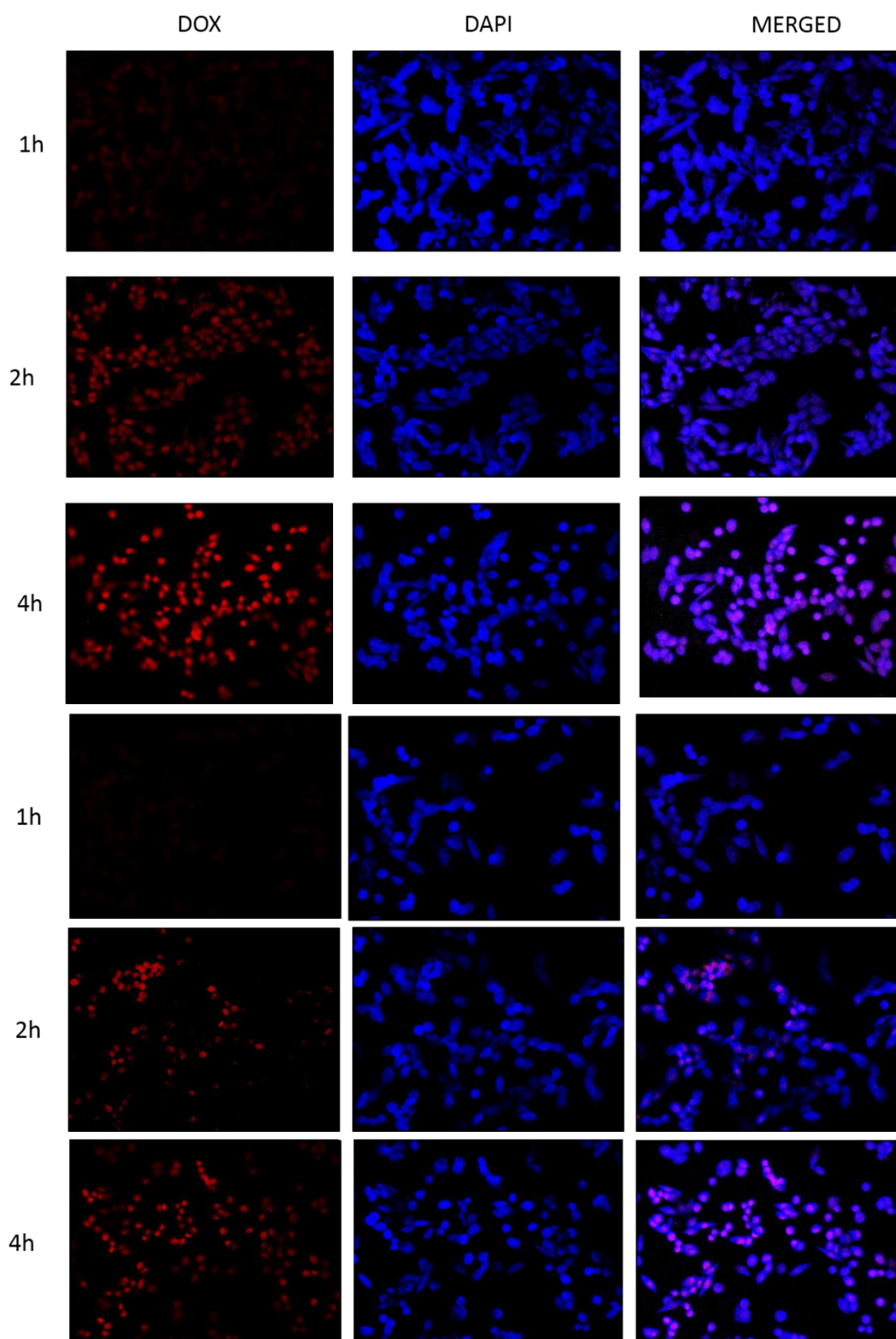
**Figure S7.** <sup>1</sup>H NMR (in DMSO-d<sub>6</sub>) of model isoxazoline formation from P2b and acrylic acid.



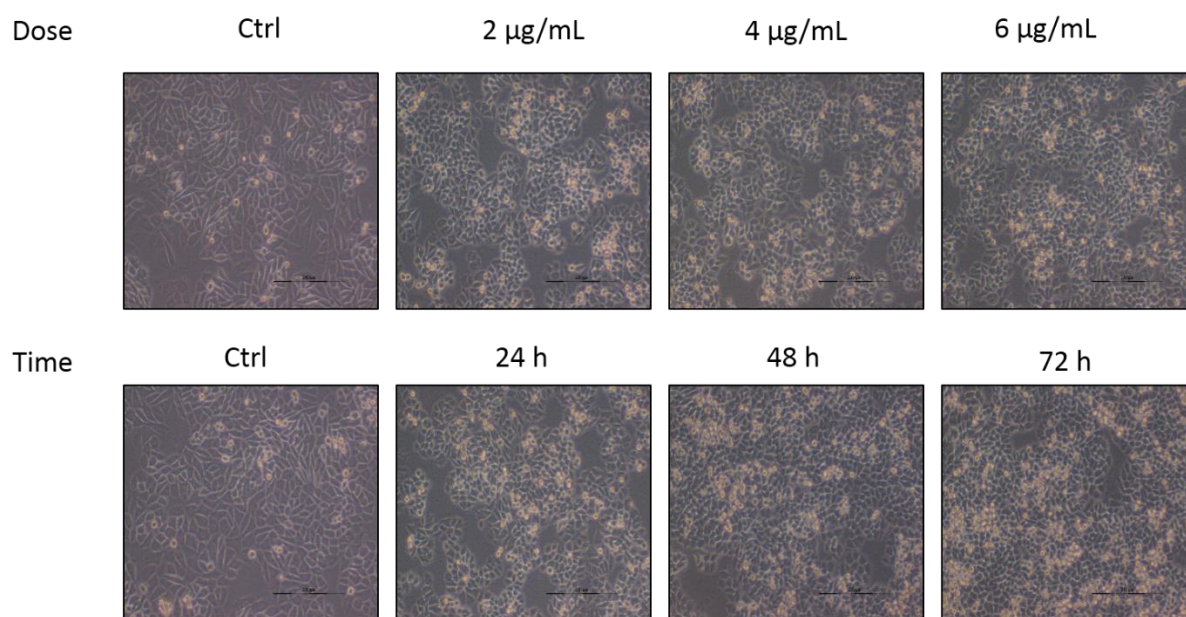
**Figure S8.** FESEM images after 4 days of 10 mM GSH treatment - (a) CCNP1 and (c) CCNP2; corresponding AFM image of (b) CCNP1 and (d) CCNP2.



**Figure S9.** DLS data of oxime functionalized copolymers and CCNPs before and after DOX loading: a) P1b, b) P2b, c) CCNP1 and d) CCNP2.



**Figure S10.** Fluorescent images of breast cancer cell line MDA MB 468 over a time span of 1-4 h. DOX emits red fluorescence whereas nuclei stained with DAPI produces blue fluorescence. The top 9 panels are for DOX loaded CCNP1 and bottom 9 panels are for free DOX samples done at same time.



**Figure S11.** Phase contrast microscopy images of MDA MB 468 treated with DOX loaded CCNP1 in dose (top, after 48 h) and time (bottom, for 4  $\mu\text{g}/\text{mL}$ ) dependent manner.

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