Electronic Supplementary Information (ESI) for

Functional 2-methylene-1,3-dioxepane copolymer: a versatile platform to construct biodegradable polymeric prodrug for intracellular drug delivery

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1. Synthesis of MDO.

2-Methylene-1,3-dioxepane (MDO) was synthesized according to the published procedure[1].

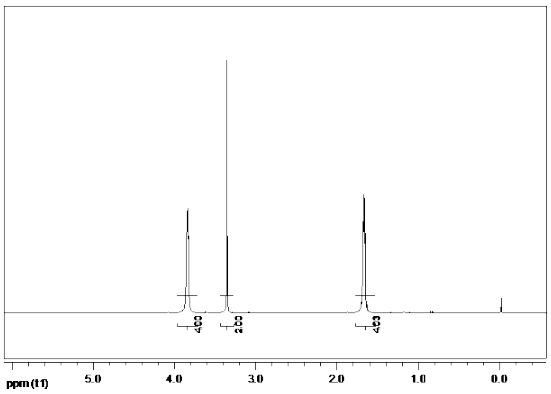

Fig. S1. ^{1}H NMR spectrum of MDO in $CDCl_3$.

2. Synthesis of pyridyldisulfide ethylmethacrylate (PDSMA)

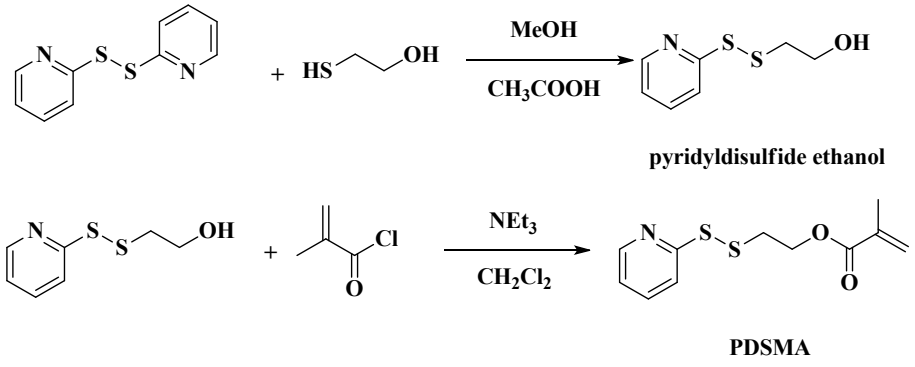

Fig. S2. Schematic illustration of the synthesis of PDSMA.

Synthesis of pyridyldisulfide ethanol

1,2-Di(pyridin-2-yl)disulfane (15g, 0.068 mol) was dissolved in 75 mL of methanol and 1 mL of glacial acetic acid was added to it. To this mixture, a solution of mercaptoethanol (2.65 g, 33.97 mmol) in 15 mL methanol was added drop-wise at room temperature with continuous stirring. Once the addition was over, the reaction mixture was stirred at room temperature for additional 3 h. The stirring was stopped and the solvent was evaporated to get the crude product as yellow oil which was purified by flash column chromatography using silica gel as stationary phase and mixture of ethyl acetate/hexane as eluent to get the desired product as colorless oil.

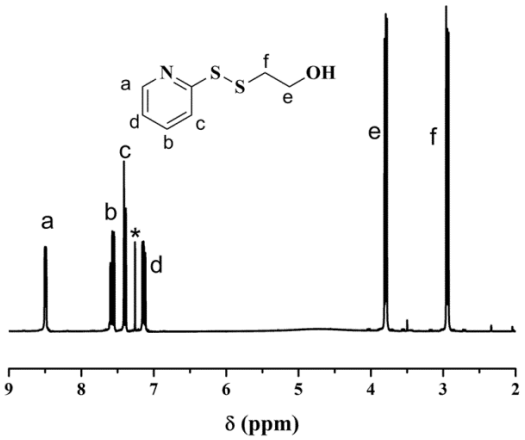

Fig. S3. ^{1}H NMR spectrum of pyridyldisulfide ethanol in $CDCl_3$.

Synthesis of PDSMA

To a solution of pyridyldisulfide ethanol (4.62 g, 24.7 mmol) in 20 mL of dry dichloromethane was added 3 g (29.7 mmol) of triethylamine and the mixture was cooled in an ice-bath. To this cold mixture, a solution of purified methacryloyl chloride (2.58g, 24.7 mmol) in 10 mL dichloromethane was added drop-wise with continuous stirring. After the addition was over the reaction mixture was stirred at room temperature for 6 h. The stirring was stopped and the reaction mixture was washed with 30 mL distilled water for 3 times and then with 30 mL of brine. The organic layer was collected, dried over anhydrous Na_2SO_4 and concentrated to get the crude product as yellow oil. It was purified by column chromatography using silica gel as stationary phase and mixture of ethyl acetate/hexane as eluent.

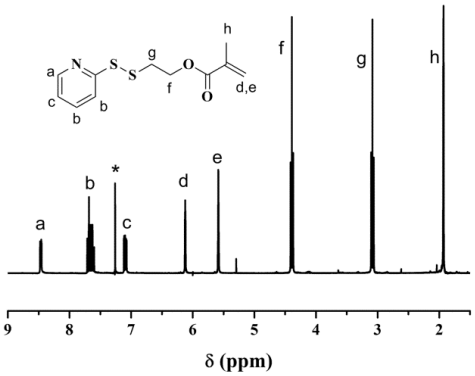

Fig. S4. ^{1}H NMR spectrum of PDSMA in $CDCl_3$.

3. Synthesis of (6-Maleimidocaproy1)hydrazone of DOX (Mal-DOX)

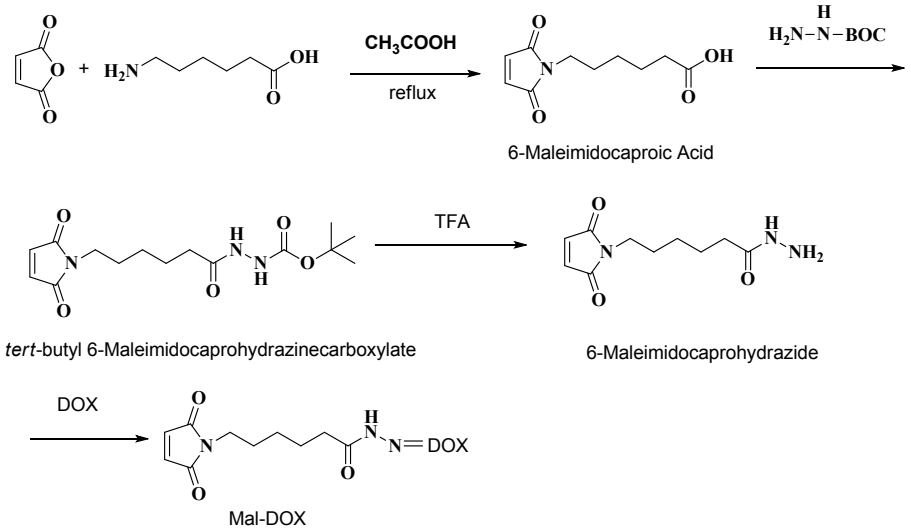

Fig. S5 Schematic illustration of the synthesis of Mal-DOX.

Synthesis of 6-Maleimidocaproic Acid

Maleic anhydride (29.4 g, 0.3 mol) and 6-aminocaproic acid (39.35 g, 0.3 mol) were refluxed in glacial acetic acid (900 mL) for 16 h. Acetic anhydride (30.6 g, 0.3 mol) was added dropwise over a period of 2 hand reflux was continued for 1 h. The acetic acid was removed under vacuum at 70 °C to yield yellow syrup which solidified. The material was chromatographed over silica using dichloromethane-methanol-acetic acid (100:5:1) affording a crystalline solid.

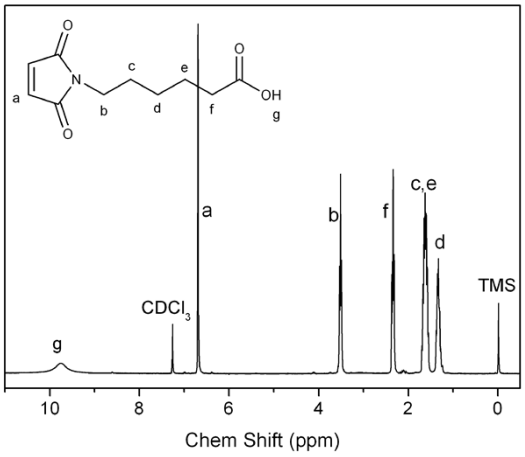

Fig. S6. ^{1}H NMR spectrum of 6-Maleimidocaproic Acid in $CDCl_3$.

Synthesis of tert-butyl 6-Maleimidocaprohydrazinecarboxylate

6-Maleimidocaproic acid (2.11 g, 10 mmol) in dry THF (200 mL) was stirred under nitrogen at 4 °C with N-methylmorpholine (1.01 g, 10 mmol) followed by dropwise addition of isobutyl chloroformate (1.36 g, 10 mmol) in THF (10 mL). After 5 min, a solution of tert-butyl carbazate (1.32 g, 10 mmol) in THF (10 mL) was added dropwise. The reaction mixture was kept at 4 °C for 30 min and at room temperature for 1 h. The solvent was evaporated and the residue was

partitioned between ethyl acetate and water. The organic layer was washed with dilute HCl solution, water, and dilute sodium bicarbonate and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residual foam was chromatographed over silica using a gradient solvent system of methylene chloride-methanol (100:l:2).

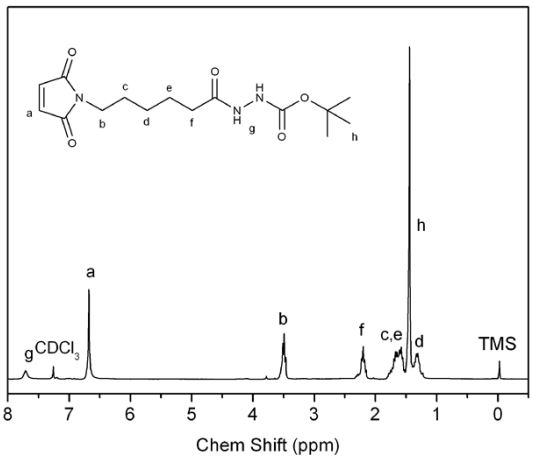

Fig. S7 ^{1}H NMR spectrum of tert-butyl 6-Maleimidocaprohydrazinecarboxylate in $CDCl_3$.

Synthesis of 6-Maleimidocaprohydrazide

2 g of tert-butyl 6-Maleimidocaprohydrazinecarboxylate was dissolved in ice-cold trifluoroacetic acid (10 mL) and stirred in an ice bath for 8 min. The acid was removed under high vacuum at room temperature. The residue was triturated with ether to yield the crystalline trifluoroacetic acid salt of 6-maleimidocaprohydrazide.

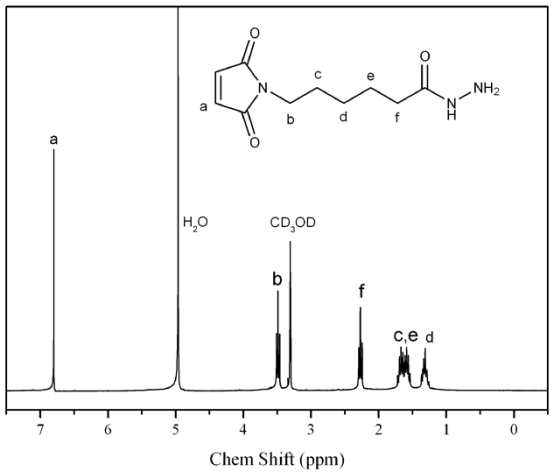

Fig. S8. ^{1}H NMR spectrum of 6-Maleimidocaprohydrazide in CD_3OD.

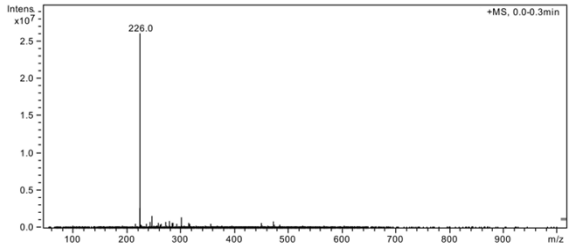

Fig. S9. Mass spectrum of 6-Maleimidocaprohydrazide

Synthesis of Mal-DOX.

DOX hydrochloride (50 mg) and 6-maleimidocaprohydrazide (80 mg) were dissolved in 50 mL of methanol. Trifluoroacetic acid (10 μL) was added and the solution was stirred at room temperature for 24 h while being protected from light. The methanolic solution was concentrated under reduced pressure. Acetonitrile was added and the resulting suspension was allowed to stand at 4 °C for 48 h for crystallization of the product. The red solid hydrazone was isolated by centrifugation, washed with fresh ethanol-acetonitrile (1:l0), and dried under vacuum to yield Mal-DOX.

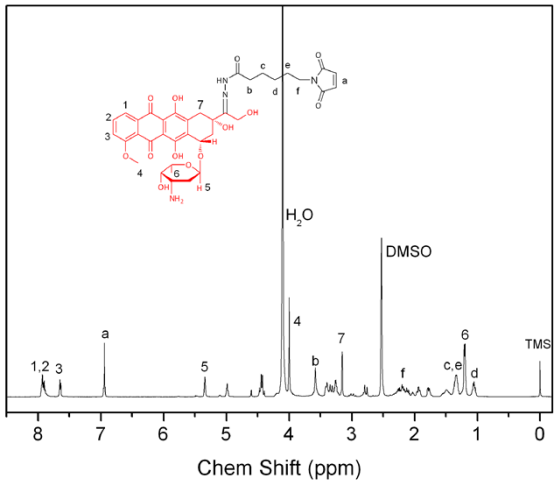

Fig. S10. ^{1}H NMR spectrum of Mal-DOX in DMSO-d6.

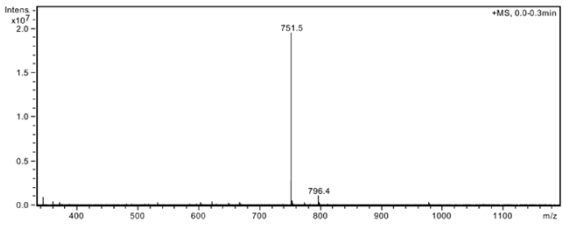

Fig. S11. Mass spectrum of Mal-DOX.

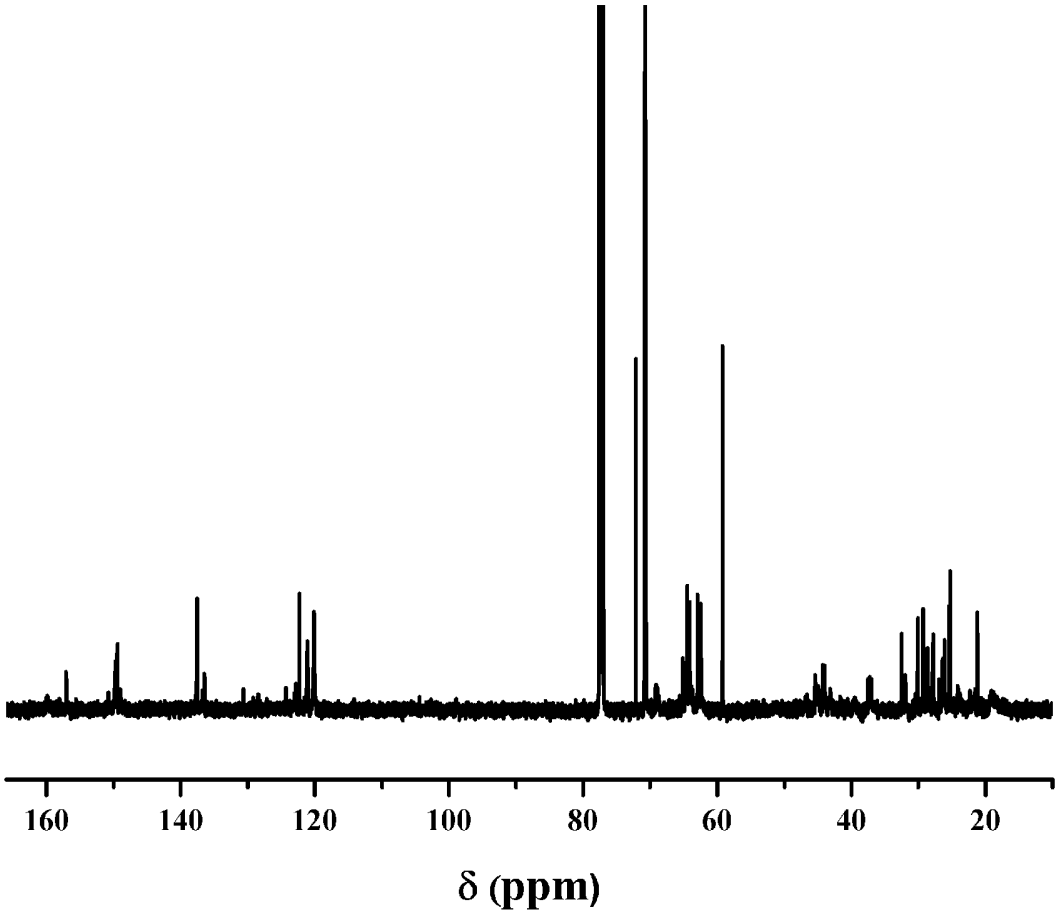

Fig. S12. ^{13}C NMR spectrum of P3.

References:

[1] W. J. Bailey, S. R. Wu, Z. D. Ni, *Makromol. Chem.*, 1982, **183**, 1913.