Electronic Supplementary Material (ESI) for Soft Matter.
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Hydrogen Bonding Enhanced Drug-Polymer Interaction for Efficient Drug Loading and Delivery

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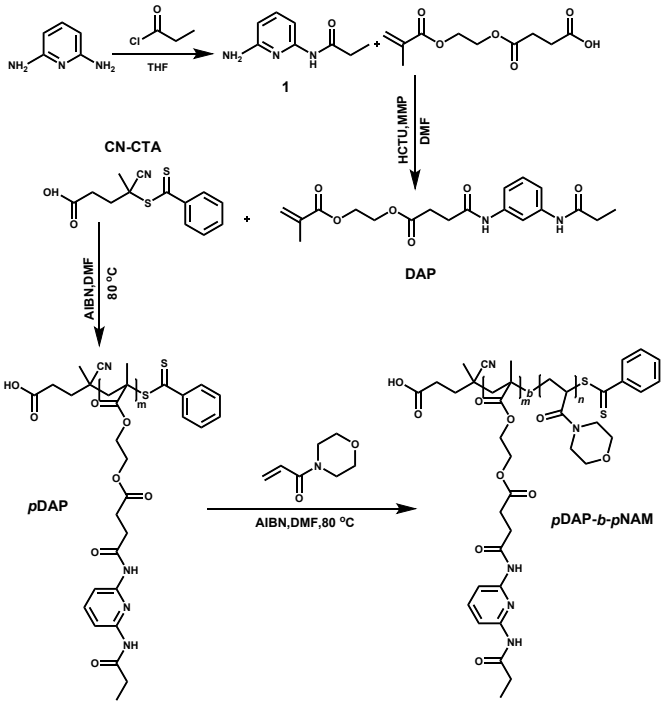
Electronic Supplementary Information (11 pages)

1. Materials and methods

All reagents were commercially available and used as supplied without further purification. Solvents were either employed as purchased or dried according to procedures described in the literature. ^{1}H NMR spectra were measured using either a Bruker Avance III HD 300 or Bruker Avance III HD 400 MHz NMR. The residual solvent peaks were used as internal references. GPC was carried out on a Polymer Laboratories PL-GPC 50 Plus system using a Polar Gel-M guard column (7.5 × 50 mm) followed by two Polar Gel-M columns (7.5 × 300 mm). DMF (0.1% LiBr) was used as eluent at 1.0 mL/min at 50 °C. Commercial narrow linear poly(methyl methacrylate) standards in the range of 2.0×10^{2}–1.0×10^{6} g/mol were used to calibrate the DMF GPC system. UV-*vis* spectra were taken on a SHIMADZU UV-2700 UV-*vis* spectrophotometer by using 1 cm quartz cells at room temperature. The version of the laser particle size analyzer is Bruker Tensor-27. Bright field TEM micrographs were obtained with a JEOL 2100Plus microscope operating at 200 kV, equipped with a Gatan OneView IS camera.

2. *Synthesis*



Scheme S1. The synthetic route of pDAP-*b*-pNAM.

Synthesis of Monomer DAP

2-Amino-6-propionylamidopyridine (**1**)

2,6-Diaminopyridine (11.79 g,108 mmol) was dissolved in dry tetrahydrofuran (200 mL). At the same time, triethylamine (15 mL) was added to it. A solution of propionylchloride (9.38 mL, 108 mmol) was added dropwise over more than 1 h to the solution of 2,6-Diaminopyridine. The mixture was stirred for 3 h at RT. The solution is filtered to remove the precipitate. The crude product was recrystallized twice in ethanol/tolune (v/v, 1:6). Yield: 22%. ^{1}H-NMR (DMSO, 400 MHz, 298 K) (δ, ppm): 9.78 (s, 1H), 7.32 (t, J = 8 Hz, 1H), 7.22 (d, J = 4 Hz, 1H), 6.14 (s, 1H), 5.71 (s, 1H), 2.35-2.29 (q, J = 8 Hz, 2H), 1.03 (t, J = 4 Hz, 3H). The ^{13}C NMR (100 MHz, DMSO, 298 K) δ (ppm):172.87, 158.89, 151.01, 139.26, 103.58, 101.20, 29.75, 10.05.

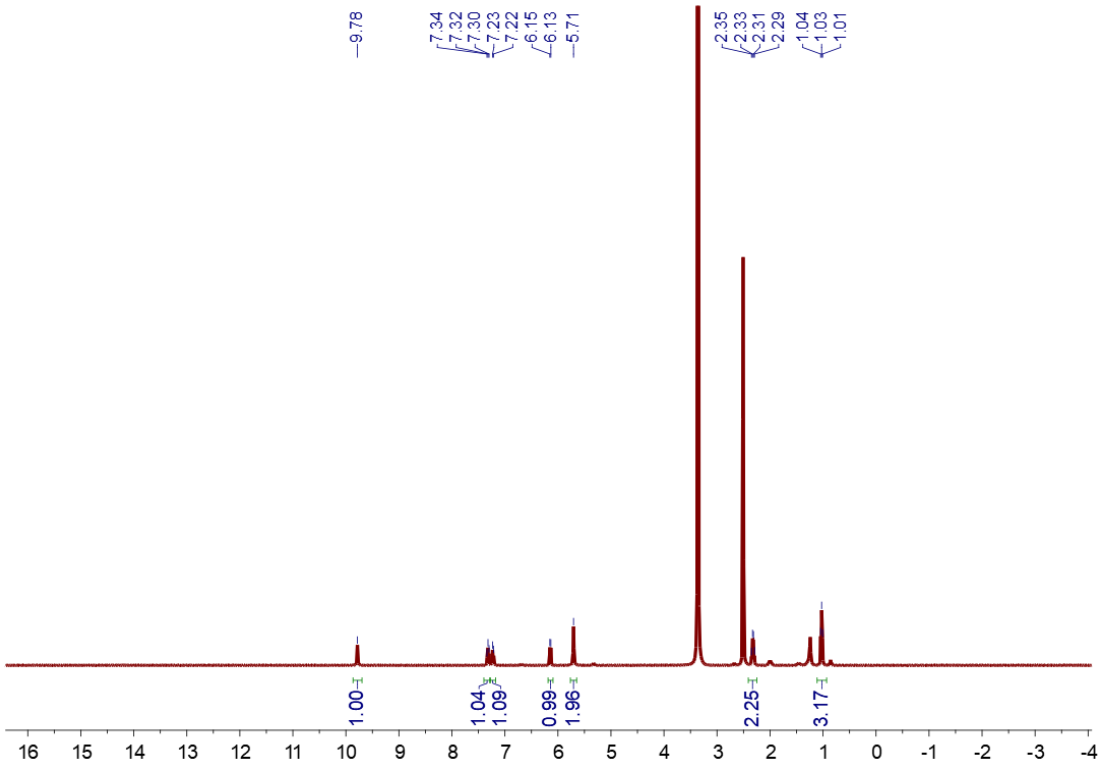


Figure S1. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, 298 K) of **1**

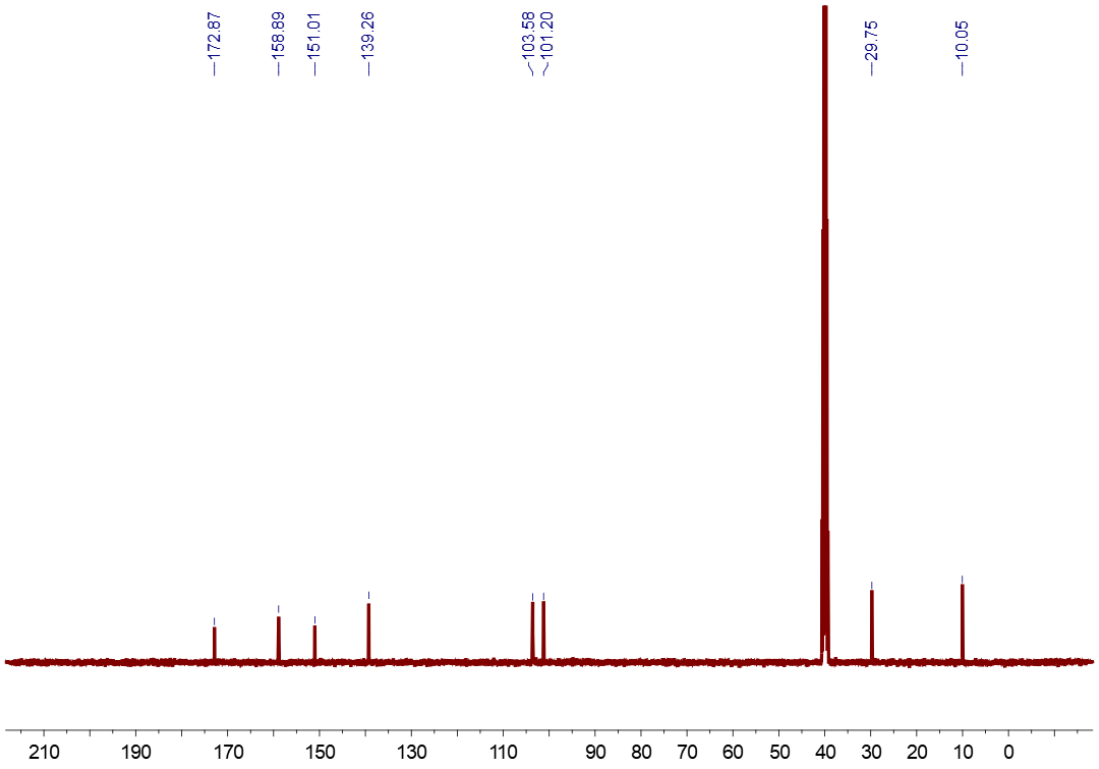


Figure S2. ^{13}C NMR spectrum (100 MHz, DMSO-d_6, 298 K) of **1**.

DAP

4-Methylmorpholine (6.76 g, 66.84 mmol), 2-amino-6-propionylamidopyridine (1) (4.6 g, 27.85 mmol), mono-2-(Methacryloyloxy) ethyl succinate (7.70 g, 33.42 mmol) were dissolved in dry

N,N-Dimethylformamide, then 5-Chloro-1-[bis(dimethylamino)methylene]-1H-benzotriazoli-um 3-oxide hexafluorophosphate (13.83 g,33.42 mmol) was added. The mixture was stirred for 24 h at RT. Then the product is precipitated in a large amount of water, finally the product is obtained by suction filtration, and the product is washed with water for several times. Yield: 85%. ^{1}H-NMR (DMSO, 400 MHz, 298K) (δ, ppm):10.13 (s, 1H),10.00 (s, 1H),7.72-7.68 (t, *J* = 8Hz, 3H), 6.03 (d, *J* = 8Hz, 2H), 5.65 (s, 1H), 4.28 (s, 1H),2.70 (t, *J* = 4 Hz, 3H), 2.61(t, *J* = 8 Hz, 2H), 2.44-2.38 (m, 2H),1.87 (d, *J* = 8 Hz, 3H),1.06 (t, *J* = 8 Hz, 3H). The ^{13}C NMR (100MHz, DMSO, 298K) δ (ppm):173.37, 172.75, 171.18, 150.83, 150.69, 136.01, 126.60, 109.31, 109.23, 62.93, 62.30, 31.17, 29.79, 28.85, 18.39, 9.92.

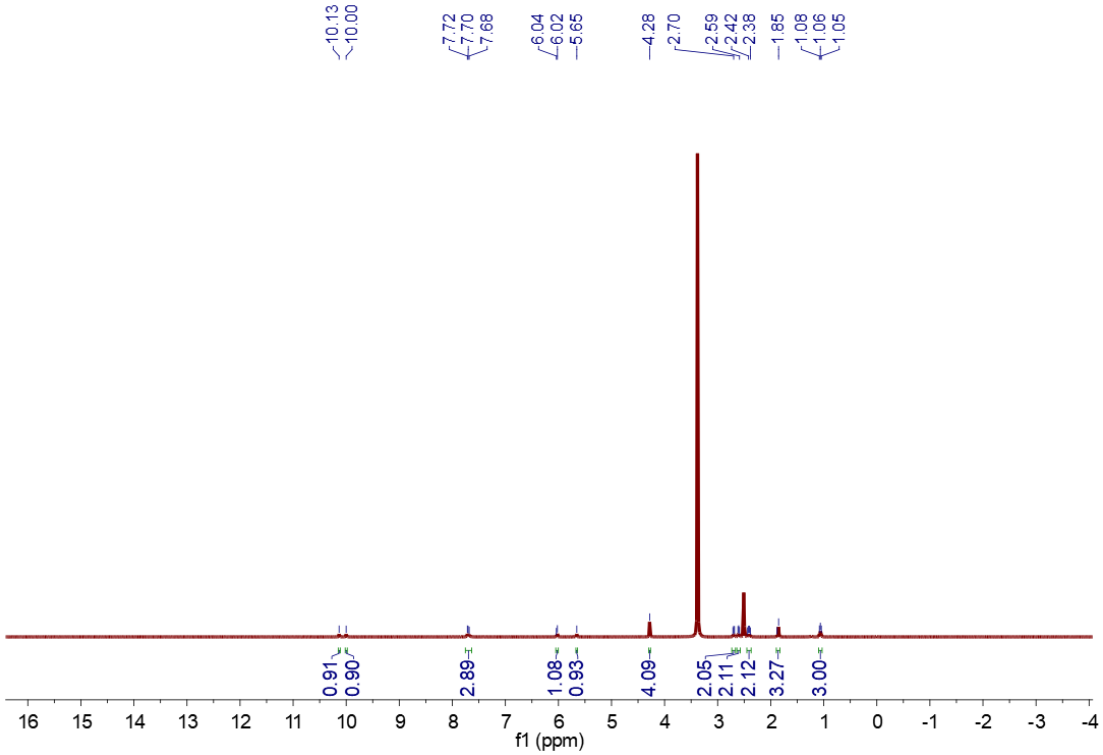


Figure S3. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, 298 K) of **DAP**.

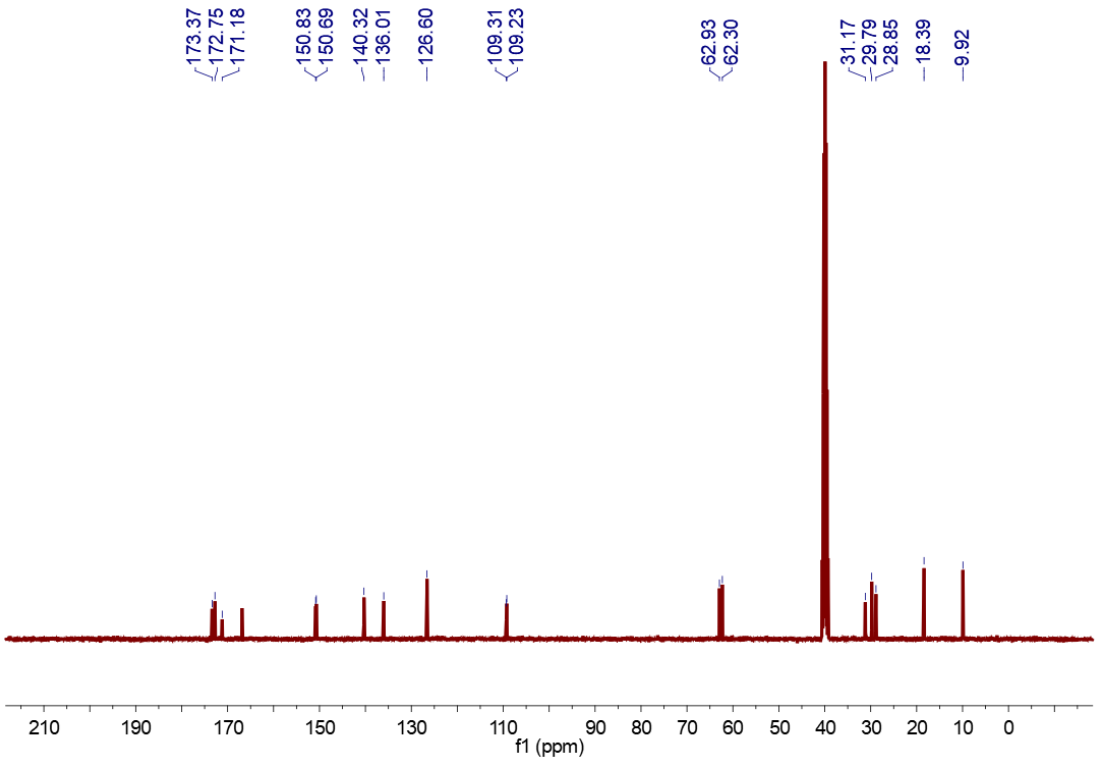


Figure S4. ^{13}C NMR spectrum (100 MHz, DMSO-d_6, 298 K) of **DAP**.

Synthesis of Polymers

Homopolymer pDAP

The monomer DAP (638 mg, 1.7 mmol), chain initiator CN-CTA (7.9 mg, 0.028 mmol), AIBN (1.24 mg, 0.0075 mmol), and DMF as solvent (1.88 mL) were added to a schlenk flask closed with a rubber stopper. The flask was deoxygenated by flushed with nitrogen. The reaction mixture was stirred at 65 ℃. After 5 h, the mixture was precipitated in cold ether. Then the mixture was centrifuged for 5 min under a centrifuge of 10000 r/min. The polymer was dried in a vacuum oven for 24 h. Yield: 62%.

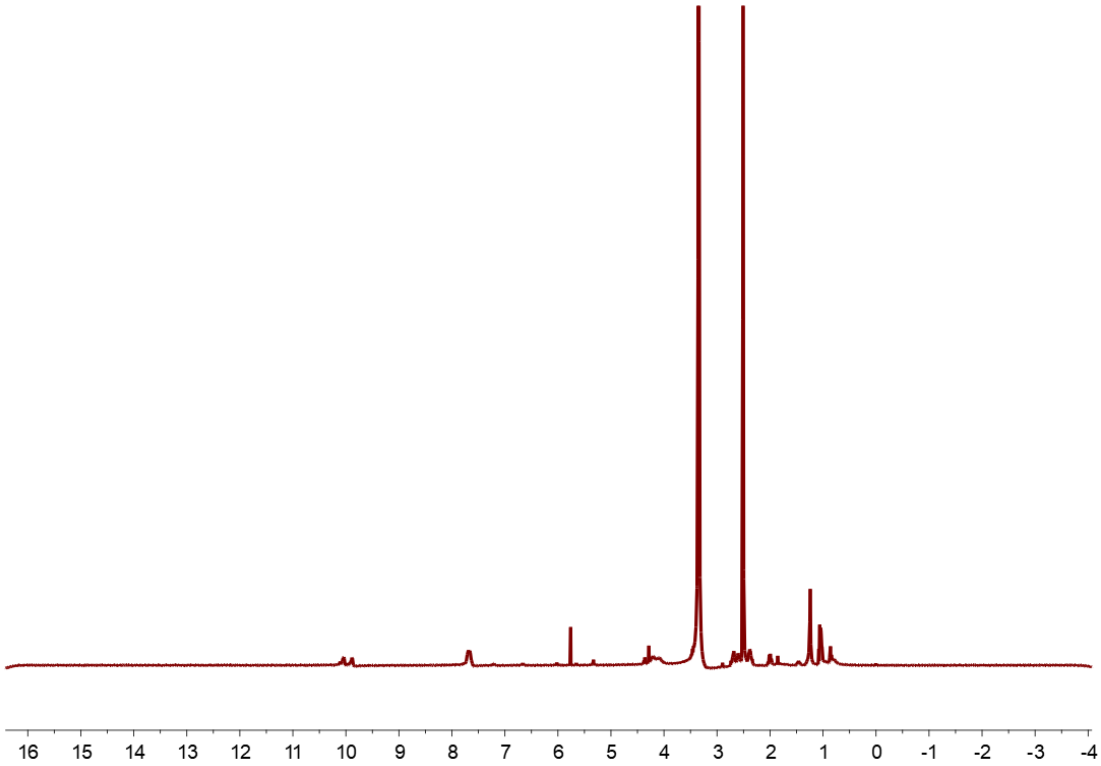


Figure S5. ^{1}H NMR spectrum spectrum (400 MHz, DMSO-d_6, 298 K) of **pDAP**.

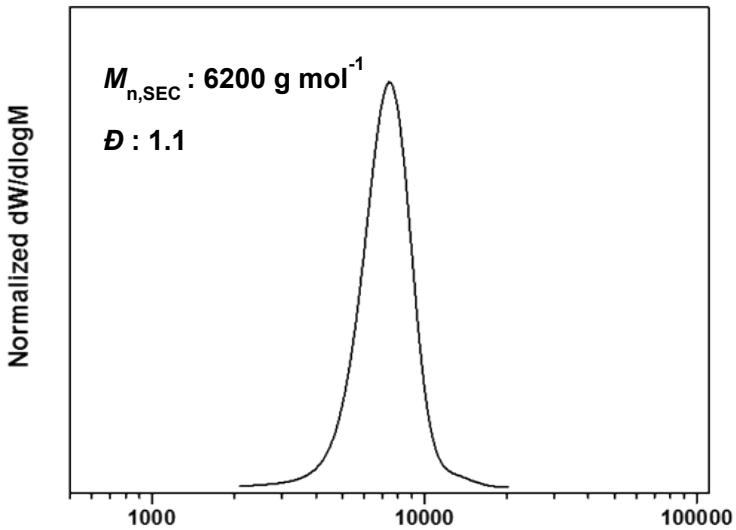


Figure S6. GPC trace (DMF + 0.1% LiBr) of homopolymer **pDAP**. The GPC was calibrated with PMAA standards.

Block Copolymers pDAP-*b*-pNAM

pDAP (252 mg, 0.018 mmol), NAM (175 mg,1.2 mmol), AIBN (0.68 mg, 0.0041 mmol), and DMF as solvent (1.22 ml) were added to a Schlenk flask closed with a rubber stopper. The flask was deoxygenated by flushed with nitrogen. The reaction mixture was stirred at 65 ℃. After 24 h, the mixture was precipitated in cold ether. Then the mixture was centrifuged for 5 min under a centrifuge of 10000 r/min. The polymer was dried in a vacuum over for 24 h. Yield: 50%.

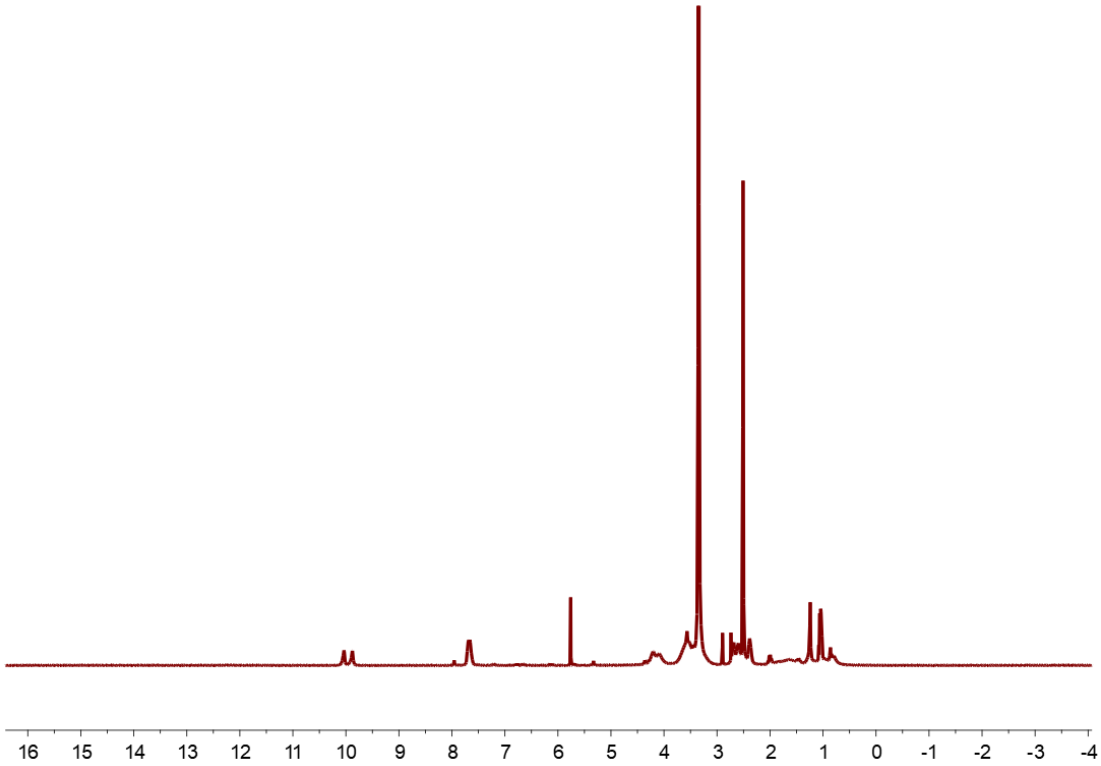


Figure S7. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, 298 K) of pDAP-*b*-pNAM.

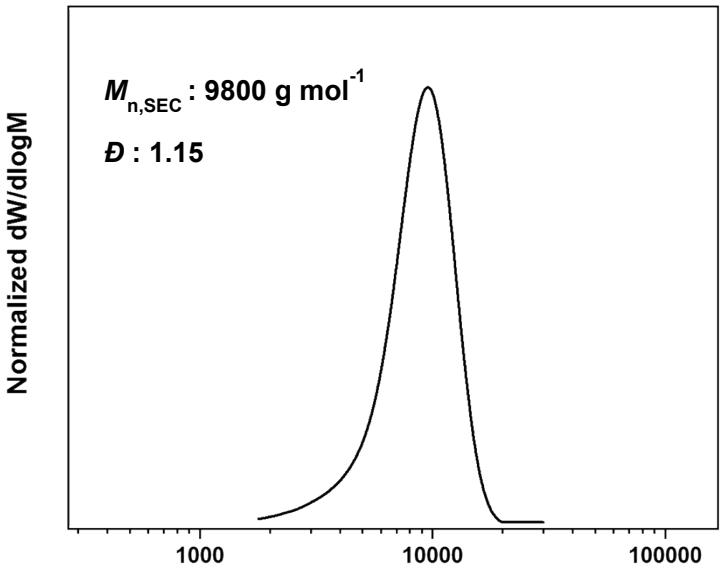
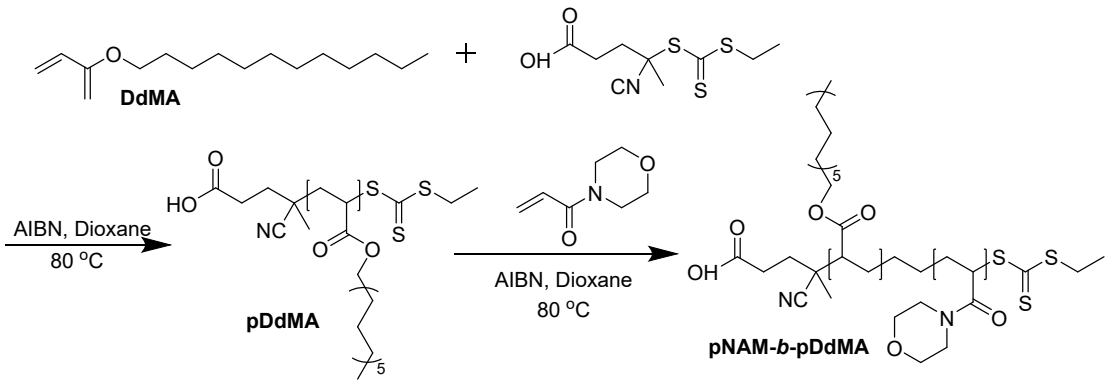


Figure S8. GPC trace (DMF + 0.1% LiBr) of block copolymer pDAP-*b*-pNAM. The GPC was calibrated with PMAA standards.



Scheme S2. The synthetic route of pDAP-*b*-pDdMA.

The synthetic method is similar to pDAP-*b*-pNAM.

3. Characterization of H-bonding association between DAP and 5-FU

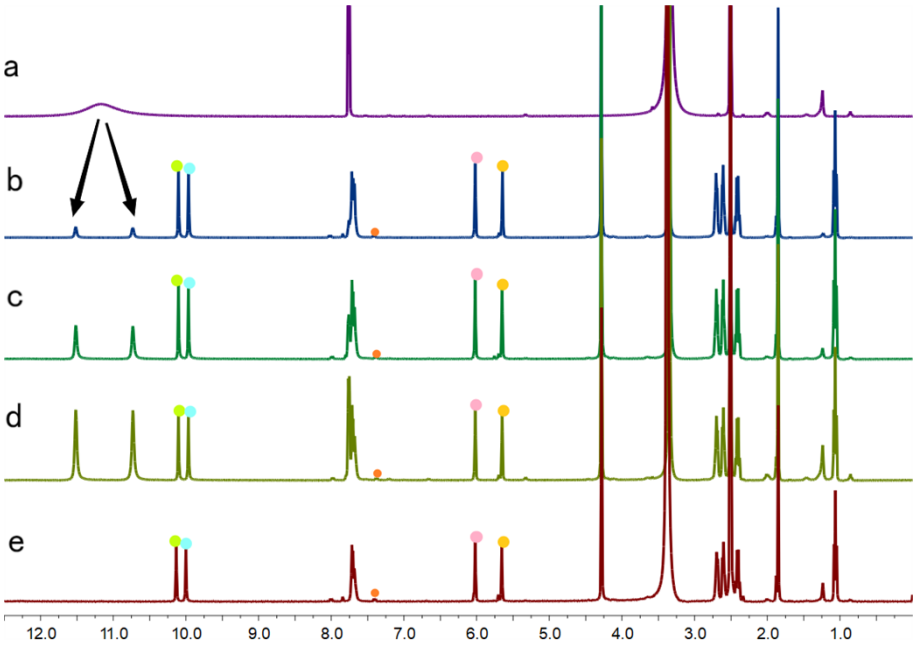


Figure S9. ^{1}H NMR spectra of: (a) 5-FU (top), (b) 5-FU/DAP (1:3), (c) 5-FU/DAP (1:1), (d) 5-FU/DAP (3:1) and (e) DAP recorded in DMSO-d_6.

4. Lyophilisation stability and serum stability of the drug-loaded micelles

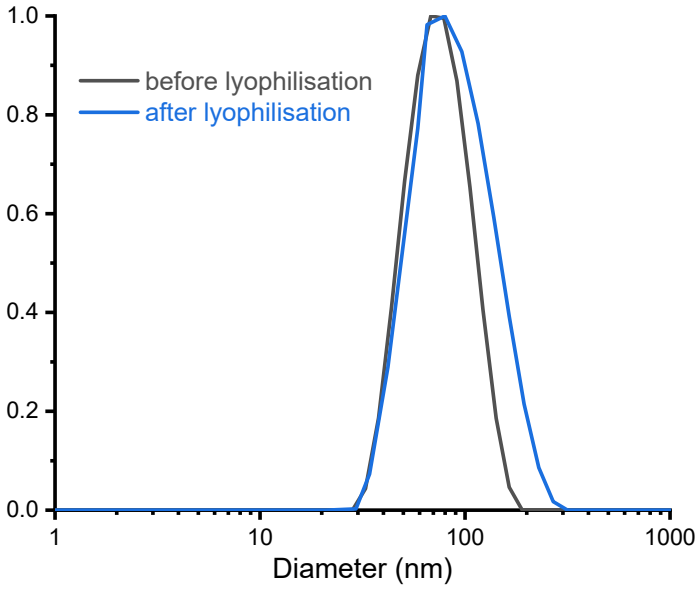


Figure S10. Size distributions pNAM-*b*-pDAP loaded with 5-FU (DLC, 12%) before and after lyophilisation.

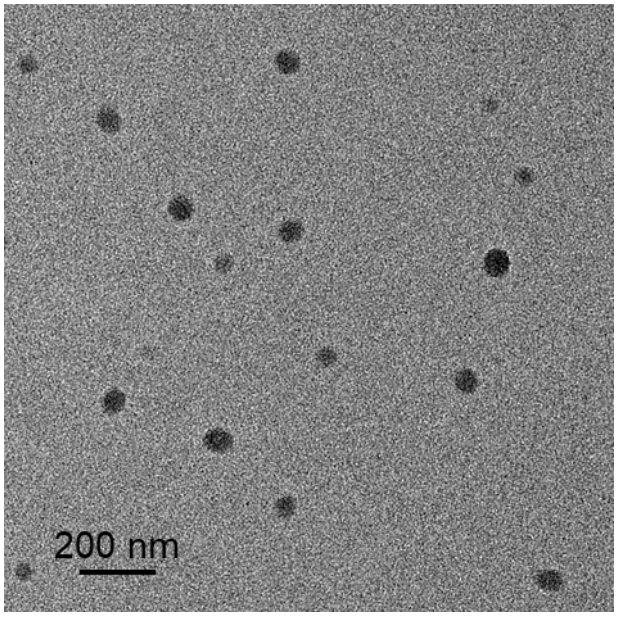


Figure S11. TEM image of pNAM-*b*-pDAP loaded with 5-FU (DLC, 12%) after lyophilisation.

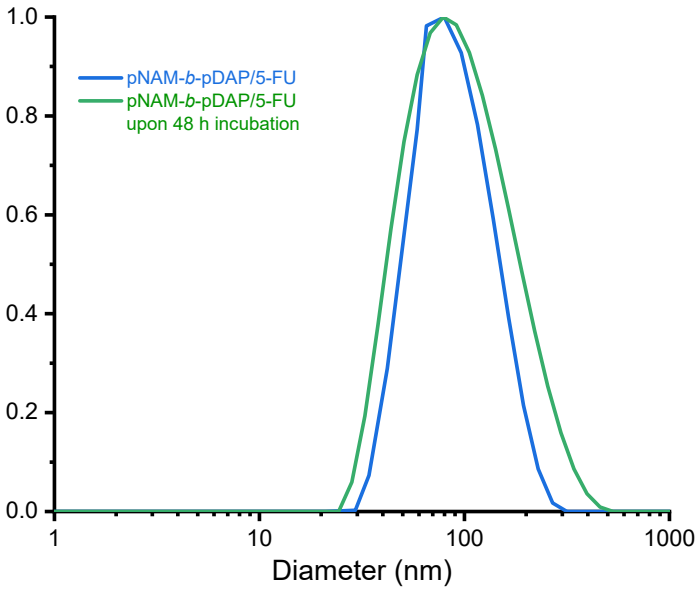


Figure S12. Size distributions pNAM-*b*-pDAP loaded with 5-FU (DLC, 12%) before and after 48 h incubation in PBS with 10% serum.

5. Evaluation of Cytotoxicity

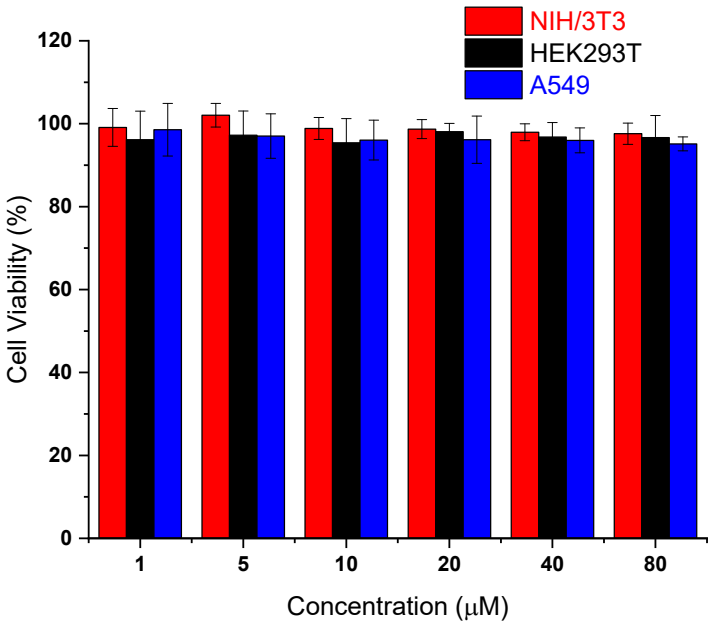


Figure S13. Cytotoxicity of pNAM-*b*-pDAP to different cells by XTT assay. Data represent mean ± SD (n = 3).