Supporting Information

Experimental and Computational Simulation Reveal the Dipeptide-Based Supramolecular Assembly as an Efficient Camptothecin-Encapsulated Carrier for Anticancer Therapy

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1. Synthesis of 4,5 - dihydroxy - 9,10 - dioxo - 9,10 - dihydroanthracene - 2 - carbonyl chloride (2)

Abbreviations used in the description of the examples that follow are the following: deuterated dimethylsulfoxide (DMSO-d_6); dichloromethane (CH_2Cl_2); dimethylsulfoxide (DMSO); ethanol (EtOH); ethyl acetate (EtOAc); N, N-dimethylformamide (DMF); magnesium sulfate ($MgSO_4$); nuclear magnetic resonance (NMR); room temperature (rt); potassium carbonate (K_2CO_3); tetrahydrofuran (THF); thin layer chromatography (TLC); thionylchloride ($SOCl_2$).

Rhein (1) (2g, 7.04mmol), $SOCl_2$ (30ml, 413.5mmol) and DMF (0.1mL) were dissolved in 300 mL of CH_2Cl_2 under the ice-water bath. The resulting suspension was heated at reflux for 8h. After cooling to ambient temperature, solvent was removed under reduced pressure, and the yellow powder (2) was used without further disposal. Yield 2.1 g, 95%.

2. **Synthesis of 2 - bromoethyl 4,5 - dihydroxy - 9,10 - dioxo - 9,10 - dihydroanthracene - 2 - carboxylate (3)**

The crude product 2 (2.2g, 7.27mmol) were dissolved in THF (100 mL) and 2-Bromoethanol (20ml, 282.2 mmol) were dropwise added. The mixture was heated at 50 °C for 4 h. After cooling, the solvent was evaporated to under reduced pressure. The residue was taken up with CH_2Cl_2 (2×30 mL) and the organic layer was washed with water, dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 50:1) to yield the yellow powder 3 (2.2 g, 68%). MS (+ESI) m/z: 392.1 [M+H] +.

3. Synthesis of (2 - ((4,5 - dihydroxy - 9,10 - dioxo - 9,10 - dihydroanthracene - 2 - carbonyl) oxy) ethyl) phenylalanyl phenylalanine (4)

The L-Phe-Phe (1.17g, 3.75 mmol) and K_2CO_3 (0.6g, 4.34 mmol) were dissolved in DMSO (10 mL) at 30 °C for 0.5 h. Then the product 3 (2.2 g, 5.62 mmol) in DMSO (10 mL) was dropwise added and the reaction was heated at 50 °C for 20 h. The mixture was then cooled to room temperature and quenched with water (50 mL). Then solvent was extracted with EtOAc (2×30 mL) and the organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The crude product was purified by column

chromatography (silica gel, CH_2Cl_2/MeOH = 50:1) to yield the yellow powder 4 (0.7 g, 30%). MS (+ESI) m/z: 623.6 [M+H] +. ^{1}H-NMR (600 MHz, DMSO-d6)：δ（ppm）11.91 (d, J = 24.2 Hz, 5H), 8.15 (d, J = 1.7 Hz, 2H), 7.85-7.82 (m, 2H), 7.81 (d, J = 1.7 Hz, 2H), 7.78 (dd, J = 6.6, 1.6 Hz, 1H), 7.75-7.73 (m, 2H), 7.43-7.41 (m, 2H), 4.74-4.61 (m, 4H), 4.38 (t, J = 6.3 Hz, 1H), 4.05-3.73 (m, 5H), 3.64 (t, J = 6.6 Hz, 2H), 2.03-1.81 (m, 2H).

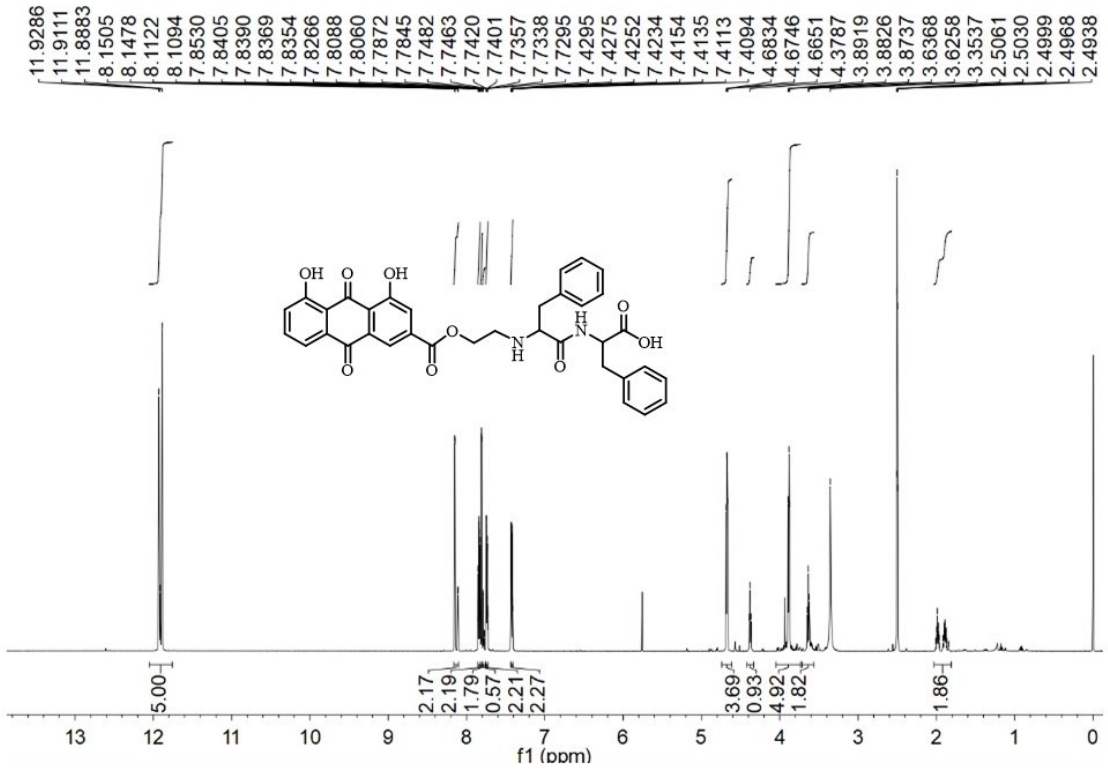

Figure S1. ^{1}H NMR spectra of Rhein-diphenylalanine dipeptide (400 MHz, DMSO).

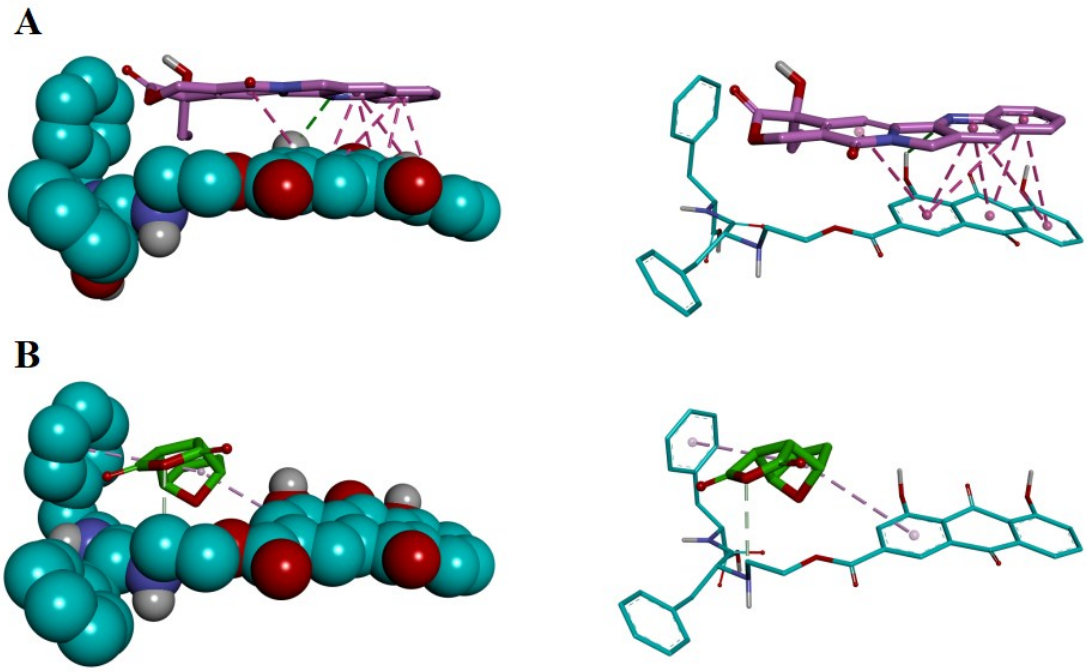

Figure S2. The chemical structures snapshots from a horizontal direction with interactions between A) CPT and nanocarrier; B) NCTD and nanocarrier. The carbon atoms of CPT are light pink and that of NCTD are green. The oxygen atoms of both drugs are red. The nitrogen atoms of CPT are dark blue. The pink maginary lines represent π–π stacking interactions. The green maginary lines represent hydrogen bonds.

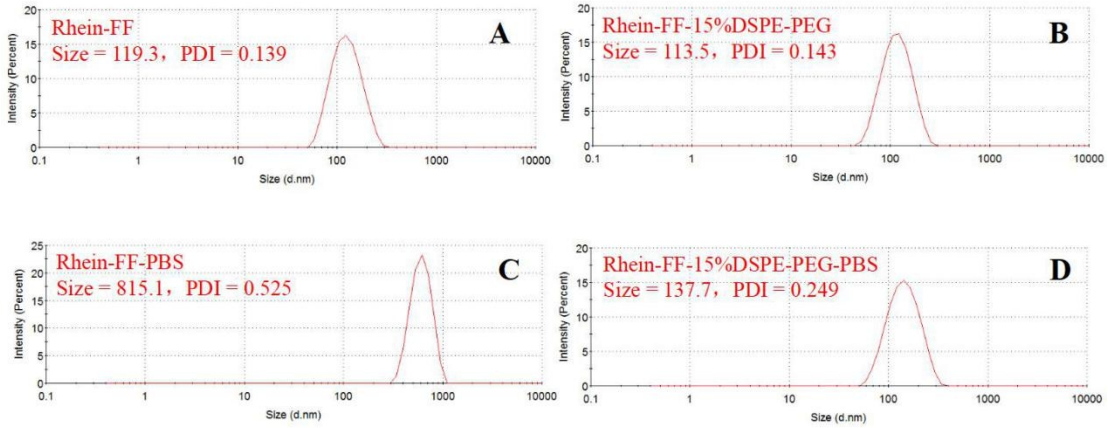

Figure S3. Particle size and distribution of A) Rhein-FF; B) Pegylated rhein-FF; C) Rhein-FF assembly in PBS; D) Pegylated rhein-FF assembly in PBS.

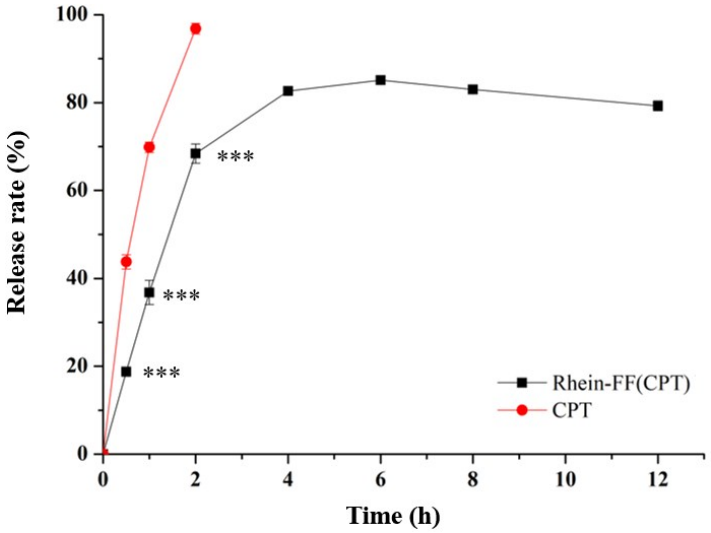

Figure S4. Cumulative CPT release from Rhein-FF (CPT) NPs and CPT solution in PBS (pH 7.4) containing 20% (v/v) DMSO and incubated with gentle shaking (100 r/min) from 0 to 12 h at 37 ± 0.5 °C. Each value indicates the mean ± standard deviation and is representative of results obtained from three independent experiments (n = 3), ***$p < 0.001$.

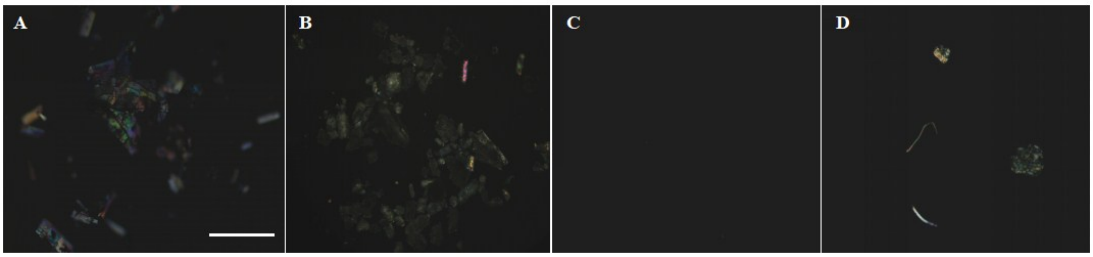

Figure S5. Polarized light microscopy (PLM) images of A) bulk CPT; B) bulk NCTD; C) CPT assembly under 60^{o}C temperature in 5 days; D) NCTD assembly under 60^{o}C temperature in 5 days. The scale bars of PLM represent 100 mm.

Table S1 Solubility Parameter

	Beads	Solubility Parameter
Rhein-dipeptide	a1	25.83
	a2	22.21
	a3	28.21
CPT	c	23.87
NCTD	d	24.76
Water	w	46

Table S2 The interaction parameters (a_{ij}) in DPD simulation (DPD-reduced unit: k_BT/r_c)

	a1	a2	a3	c	d	w
a1	78					
a2	78.93	78				
a3	78.40	80.57	78			
c	78.27	78.20	79.34	78		
d	78.08	78.46	78.85	78.06	78	
w	107.00	118.35	100.56	112.91	110.16	78