Electronic Supplementary Information for

Sugar based nanotube assembly for the construct of sonication triggered hydrogel: an application of the entrapment of tetracycline hydrochloride

Zichuan Ma[a], Ping Zhang[a], Xudong Yu[c,] *, Haichuang Lan[b] Yajuan Li[c], Dongyan Xie[c], Jingyin Li[c], Tao Yi[b,] *

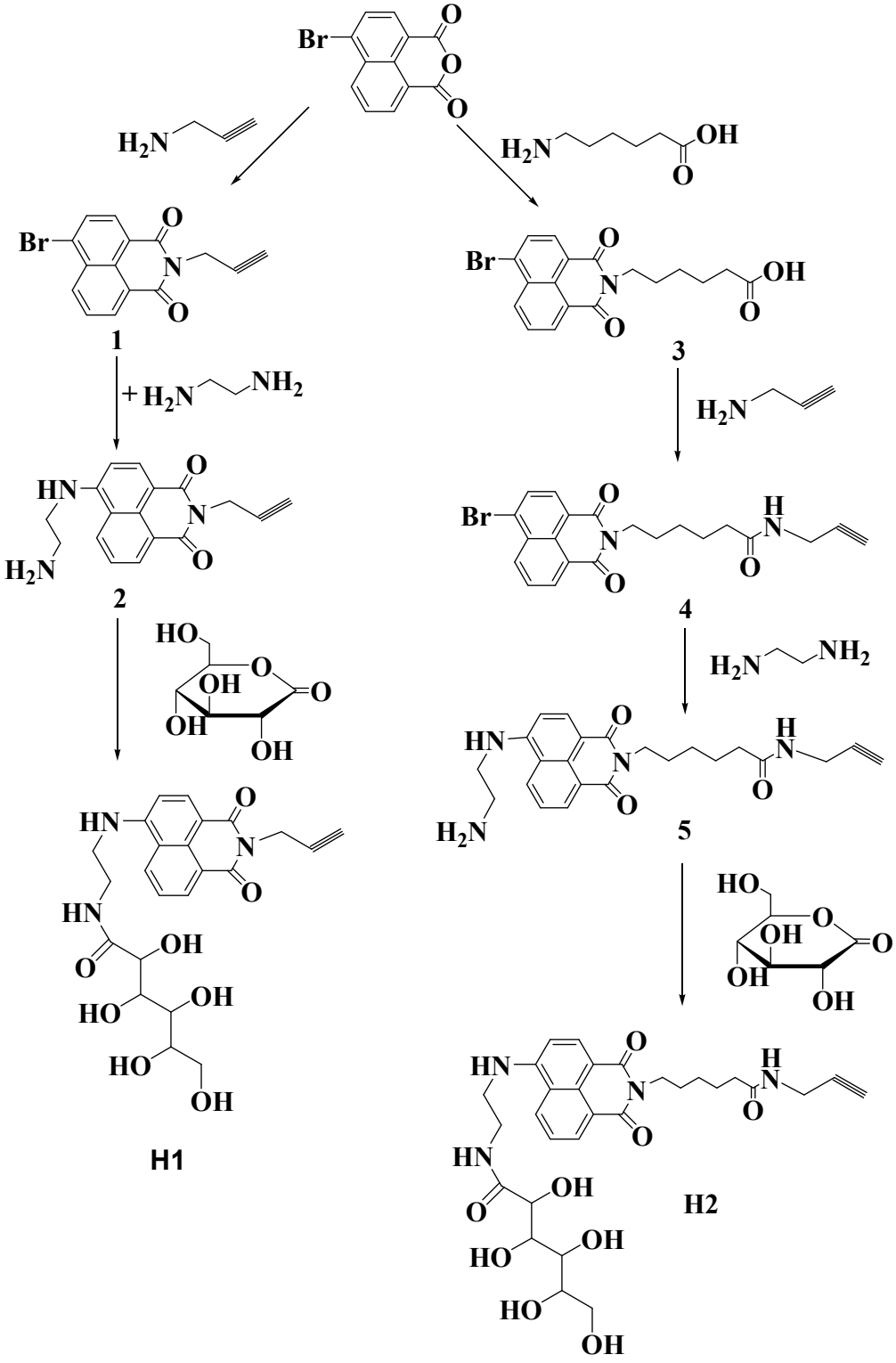
[a]College of Chemistry and Material Sciences, Hebei Normal University, Shijiazhuang 050024, PR China

[b]Department of Chemistry, and Collaborative Innovation Center of Chemistry for Energy Materials, Fudan University, 220 Handan Road, Shanghai 200433, China

[c]College of Science, and Hebei Research Center of Pharmaceutical and Chemical Engineering, Hebei University of Science and Technology, Yuhua Road 70, Shijiazhuang 050080, PR China

E-mail for corresponding author: 081022009@fudan.edu.cn (X. Yu), yitao@fudan.edu.cn (T. Yi)

1. Experimental details



Scheme S1. The synthesis procedure of **H1** and **H2**

Synthesis of 1: 4-Br-1, 8-naphthalic anhydride (277 mg, 1 mmol) and propargylamine (54 mg, 1 mmol) were refluxed in ethanol for 8 hours. The mixture was then concentrated and purified by column chromatography (SiO_2: CH_2Cl_2/CH_3OH = 100: 1) to yield **1** as a white solid (191 mg, 60%). Mp: 239-241 °C; ^{1}HNMR (500M, $CDCl_3$, δ): 2.22-2.23 (t, 1H, J = 2.5 Hz), 4.98 (d, 2H, J = 2.5 Hz), 7.88-7.91 (t, 1H, J = 8Hz), 8.08-8.10 (d, 1H, J = 8 Hz), 8.48-8.50 (d, 1H, J = 7.5 Hz), 8.64-8.63 (d, J = 8.5 Hz), 8.72-8.74 (d, 1H, J = 7.5 Hz); ^{13}CNMR (125M, $CDCl_3$, δ): 29.56, 70.72, 78.33, 121.89, 122.77, 128.17, 130.73, 130.79, 131.21, 131.60, 132.46, 133.72, 162.81; HRMS calc. for $[C_{15}H_8BrNO_2+H]^+$: 313.9817, 315.9790; Found: 313.9807, 315.9790.

Synthesis of 2: Compound **1** (313 mg, 1 mmol)**,** ethylenediamine (600 mg, 10 eq) were refluxed in ethanol for 8 hours, then ethanol was removed under vacuum, and the reaction mixture was purified by column chromatography to yield **2** as a yellow solid (118 mg, 40%). Mp: 217-219 °C; ^{1}HNMR (400M, $CDCl_3$, δ): 2.16-2.17 (t, 1H, J = 2.4 Hz), 3.18-3.20 (t, J = 6 Hz, 2H), 3.40-3.45 (t, J = 6 Hz, 2H), 4.95-4.96 (d, J = 2. 4 Hz, 2H), 6.71-6.73 (d, J = 8.8 Hz, 1H), 7.62-7.66 (t, J = 7.6 Hz, 1H), 8.19-8.21 (d, J = 8.4 Hz, 1H), 8.49-8.51 (d, J = 8.4 Hz, 1H), 8.62-8.64 (d, J = 7.2 Hz, 1H); ^{13}CNMR (125M, $CDCl_3$, δ): 29.11, 47.02, 72.93, 84.44, 104.46, 107.45, 120.59, 121.86, 124.70, 129.52, 129.93, 131.38, 135.00, 151.69, 162.47, 163.52; HRMS calc. for $[C_{17}H_{15}N_3O_2+H]^+$: 294.1243; Found: 294.1242.

Synthesis of **H1**: compound **2** (733 mg, 2.5 mmol) and D-(+)-Gluconic acid δ-lactone (445 mg, 2.5 mmol) were dissolved in ethanol (60 mL). The mixed solution was stirred and heated to reflux for 8 h, yellow precipitate was obtained by hot filtration (377 mg, 32%). Mp > 200 °C; ^{1}HNMR (500M, $CDCl_3$, δ): 3.04-3.05 (t, 1H, J = 2.5 H), 3.35-3.58 (m, 6H), 4.45-4.47 (d, J = 1.2 Hz, 1H), 4.52-4.53 (m, 2H), 4.71-4.72 (d, J = 2.5 Hz, 2H), 5,46-5.48 (d, J = 4.5 Hz, 1H), 6.88-6.89 (d, J = 8.5 Hz, 1H),7.67-7.70 (t, J = 7.5 Hz, 1H), 8.25-8.26 (d, J = 8.5 Hz, 1H), 8.43-8.44 (d, J = 7.5 Hz, 1H), 8.60-8.62 (d, J = 8.5 Hz, 1H); ^{13}CNMR (125M, $CDCl_3$, δ): 29.10, 37.51, 43.29, 63.83,

70.63, 71.98, 72.73, 72.93, 73.95, 80.44, 104.30, 107.72, 120.42, 121.79, 124.75, 129.12, 129.69, 131.27, 134.83, 151.25, 162.41, 163.43, 174.08; HRMS calc. for $[C_{23}H_{25}N_3O_8]^+$: 471.1642; Found: 471.1624.

Synthesis of 3: A mixture of aminocaproic acid (1 mmol, 131 mg), and sodium hydroxide (40 mg, 1 mmol) was stirred at 40 °C for 20 minutes, then 4-Br-1,8-naphthalic anhydride (277 mg, 1 mmol) was added, and refluxed for 24 hours under nitrogen atmosphere. The reaction mixture was concentrated in vacuum, the residue was neutralized by dilute hydrochloric acid, the filtrate was purified by column chromatography (SiO_2: CH_2Cl_2/CH_3OH = 20: 1) to yield **3** as a white solid (179 mg, 46%). Mp: 166-168 °C. ^{1}HNMR (400M, $CDCl_3$, δ): 1.45-1.52 (m, 2H, CH_2), 1.69-1.80 (m, 4H, CH_2), 2.36-2.40 (t, 2H, J = 7.6 Hz, CH_2), 4.16-4.19 (t, 2H, J=7.6 Hz, CH_2), 4.43-4.60 (m, 1H), 7.83-7.87 (t, 2H, J=7.2 Hz, ArH), 8.03-8.05(d, 1H, J = 8 Hz, ArH), 8.40-8.42 (d, 1H, J = 8 Hz, ArH), 8.56-8.58 (d, 1H, J = 7.2 Hz), 8.64-8.67 (d, 1H, J = 7.2 Hz, ArH). ^{13}CNMR (125M, $CDCl_3$, δ): 24.68, 26.51, 27.60, 33.96, 122.11, 122.89, 128.39, 129.01, 129.48, 129.97, 131.19, 131.61, 131.83, 132.81.HRMS calc. for $[C_{18}H_{16}BrNO_4+H]^+$: 390.0296, 392.0276; Found: 390.0328, 392.0310.

Synthesis of 4: Compound **3** (390 mg, 1 mmol), propargylamine (54 mg, 1 mmol), DCC (618 mg, 3 mmol), and HOBt (405 mg, 3mmol) were stirred in $CHCl_3$ for 24 hours, then the reaction mixture was concentrated and purified by column chromatography (SiO_2: CH_2Cl_2/CH_3OH = 100: 1) to yield **4** as white solid (281 mg, 66%). Mp: 181-183 °C; ^{1}HNMR (500M, $CDCl_3$, δ): 1.44-1.50 (m, 2H), 1.71-1.79 (m, 4H), 2.20-2.21 (t, 1H, J = 2.5 Hz), 2.22-2.25 (t, 2H, J = 7.5 Hz), 4.04-4.06 (m, 2H), 4.16-4.19 (t, 2H, J = 2.5 Hz), 7.84-7.86 (t, 1H, J = 8.5 Hz), 8.04-8.06 (d, 1H, J = 8.5 Hz), 8.41-8.43 (d, 1H, J = 8.5 Hz), 8.58-8.59 (d, 1H, J = 8.5 Hz), 8.66-8.67 (d, 1H, J = 8.5 Hz); ^{13}CNMR (125 M, $CDCl_3$, δ): 25.06, 26.51, 27.58, 20.19, 36.17, 40.21, 71.55, 79.70, 122.27, 123.14, 128.13, 129.07, 130.34, 130.71, 131.15, 131.30, 132.11, 133.35; HRMS calc. for $[C_{21}H_{19}BrN_2O_3+H]^+$: 429.0637; Found: 429.0622.

Synthesis of 5: Compound **4** (426 mg, 1 mmol)**,** ethylenediamine (600 mg, 10 eq) were refluxed in ethanol for 48 hours, the reaction mixture was then concentrated and washed with water, the filtrate was purified by column chromatography (SiO_2: CH_2Cl_2/CH_3OH = 10: 1) to yield **5** as a yellow solid (401 mg, 23%). Mp: 98-100 °C; ^{1}HNMR (400M, $CDCl_3$, δ): 1.75-1.81 (m, 2H), 2.22-2.23 (t, 1H, J = 6.4 Hz), 2.25-2.28(t, 2H, J = 7.2 Hz), 3.20-3.23 (t, 2H, J = 7.2 Hz), 3.20-3.23(t, 2H, J = 5.6 Hz), 3.43-3.47 (m, 2H), 3.52 (s, 2H), 4.06-4.08 (m, 2H), 4.17-4.21 (t, 2H, J = 5.6 Hz), 6.73-6.75 (d, 1H, J = 8.4 Hz), 7.64-7.68 (t, 1H, J = 8.4 Hz), 8.20-8.22 (d, 1H, J = 8.8 Hz), 8.48-8.50 (d, 1H, J = 8.4 Hz), 8.61-8.63 (d, 1H, J = 8.4 Hz); ^{13}CNMR (125 M, DMSO, δ): 25.41, 26.73, 27.97, 28.19, 35.43, 46.76, 73.18, 81.84, 104.19, 108.03, 120.50, 122.18, 124.50, 128.95, 129.75, 130.95, 134.54, 151.20, 163.27, 164.12, 172.30; HRMS calc. for $[C_{23}H_{26}N_4O_3+H]^+$: 407.2083; Found: 407.2071.

Synthesis of **H2:** compound **5** (1 g, 2.5 mmol) and D-(+)-Gluconic acid δ-lactone (445 mg, 2.5 mmol) were refluxed in ethanol (60 mL) for 14 hours. The mixture was concentrated and washed with water, then the yellow solid was recrystallized in water for twice (439 mg, 30%). Mp: 202-203 °C; ^{1}HNMR (400M, $CDCl_3$, δ): 1.27-1.33 (m, 2H), 1.51-1.63 (m, 4H), 2.07-2.10 (t, J = 7.5 Hz, 2H), 3.04-3.05 (t, J = 2.5 Hz, 1H), 3.38-3.61 (m, 5H), 3.82-3.83 (m, 2H), 3.98-4.01 (t, J = 7.5 Hz, 1H), 4.04-4.06 (t, J = 4 Hz, 1H), 4.33-4.36 (t, J = 5.5 Hz, 1H), 4.47-4.49 (d, J = 7.5 Hz, 1H), 4.54-4.56 (t, J = 5.5 Hz, 2H), 5.48-5.49 (d, J = 4. 5 Hz, 1H), 6.90-6.92 (d, J = 8.5 Hz, 1H), 7.69-7.72 (t, J = 8 Hz, 1H), 8.27-8.29 (d, J = 8.5 Hz, 1H), 8.44-8.46 (d, J = 7 Hz, 1H), 8.62-8.63 (d, J = 8.5 Hz, 1H); ^{13}CNMR (125 M, DMSO, δ): 25.39, 26.70, 27.98, 28.18, 35.41, 37.47, 43.23, 63.83, 70.62, 71.97, 72.71, 73.22, 73.93, 81.83, 104.28, 108.36, 120.55, 122.34, 124.86, 128.82, 129.80, 131.12, 134.65, 151.02, 163.36, 164.18, 172.29, 174.03; HRMS calc. for $[C_{29}H_{36}N_4O_9+H]^+$: 585.2561; Found: 585.2577.

2. Additional images and spectra

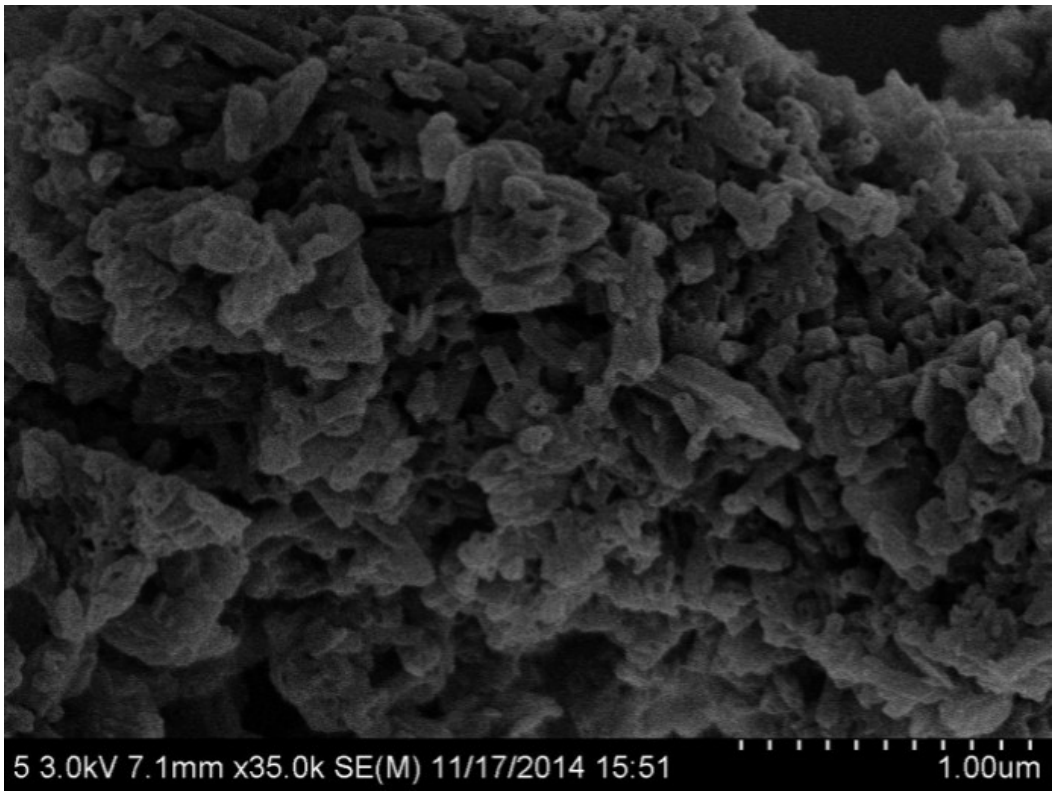


Fig. S1 SEM image of the large area tubes of **N1** assembly from ethanol via reaction method (78 ºC).

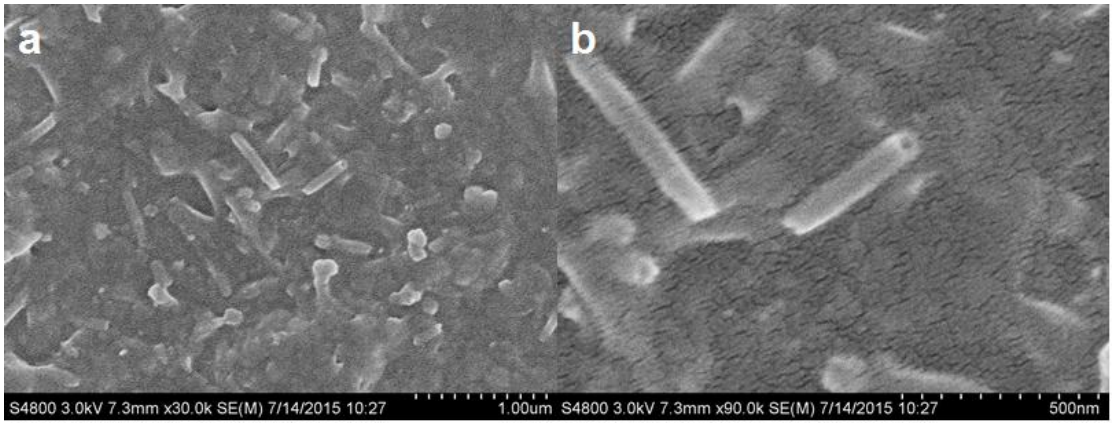


Fig. S2 a) SEM images of **H1** assembly obtained at 60 ºC; b) the magnified image of a).

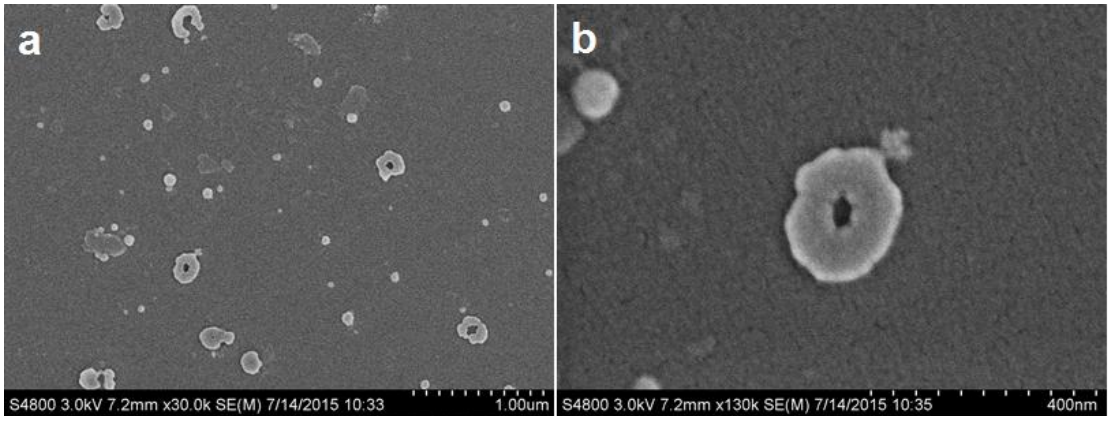


Fig. S3 a) SEM images of **H1** assembly obtained at 50 ºC; b) magnified image of a).

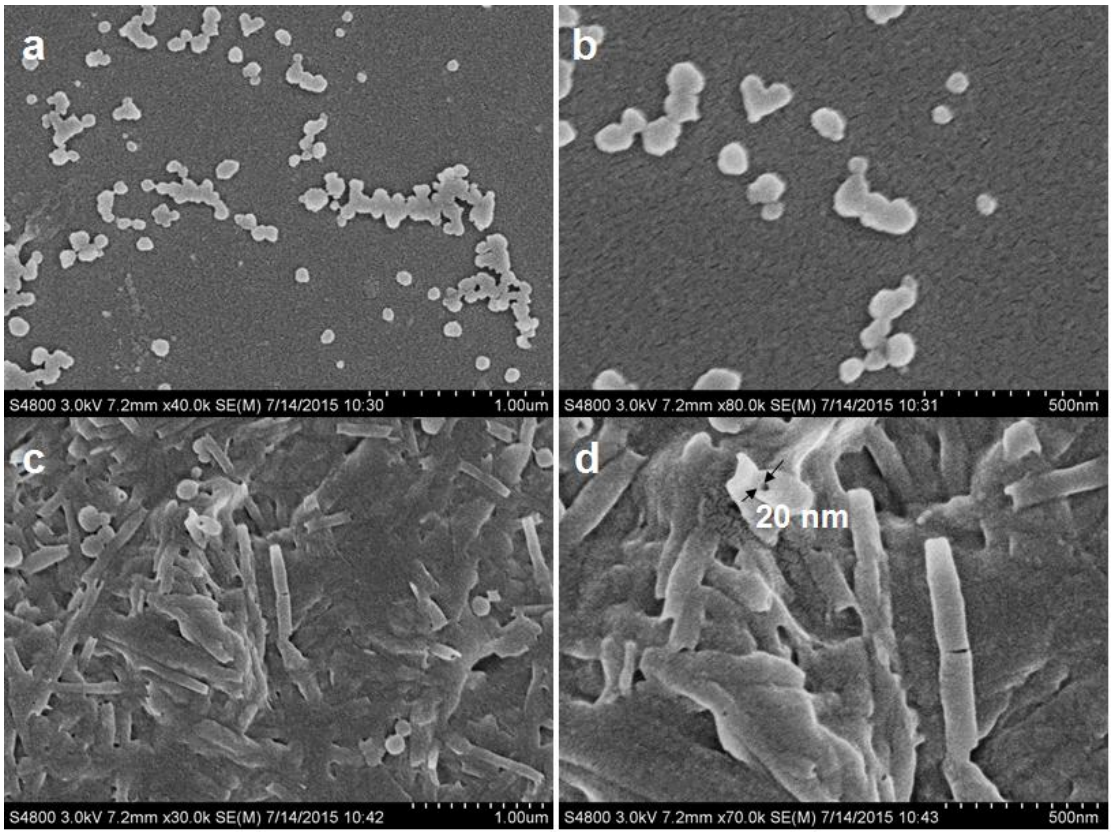


Fig. S4 SEM images of **H1** assembly at different concentrations from the reactions at 78 ºC. a) 0.03 M, ethanol; b) magnified image of a); c) 7.5×10^{-3} M ethanol; d) magnified image of c).

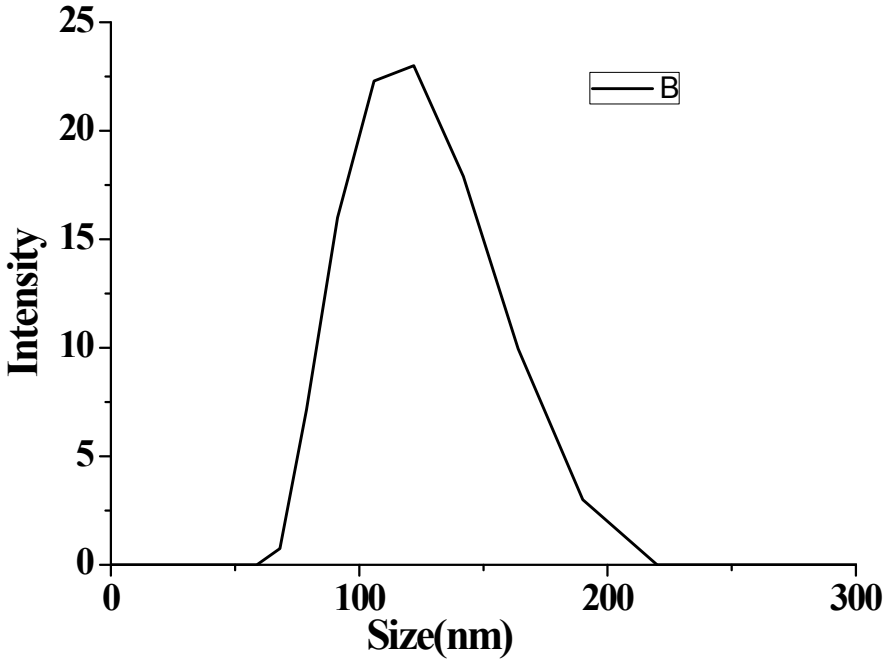


Fig. S5 The dynamic light scattering spectra of **H1** tube assembly dispersed in water.

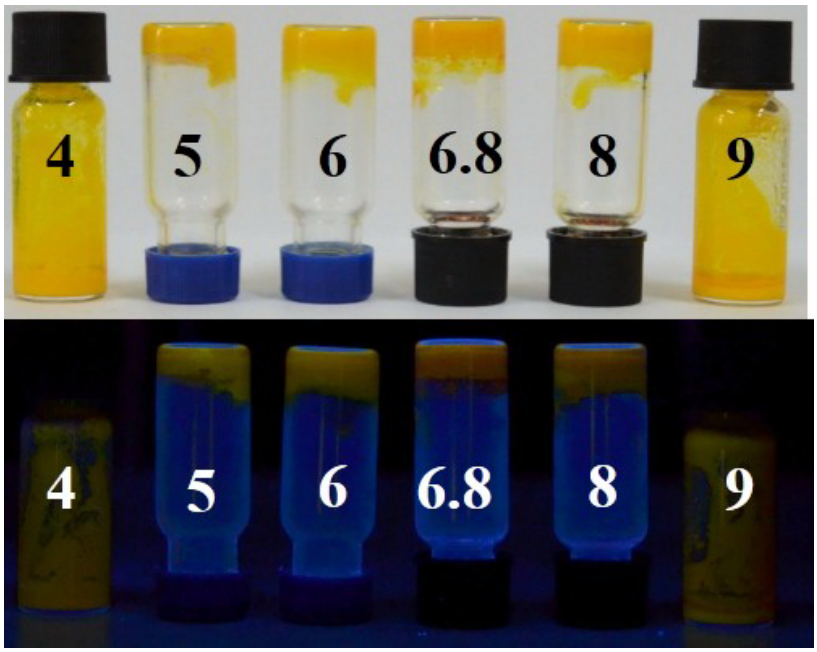


Fig. S6 Photos of **H1** hydrogel at different pH values in light and in dark (irradiated by 365 nm).

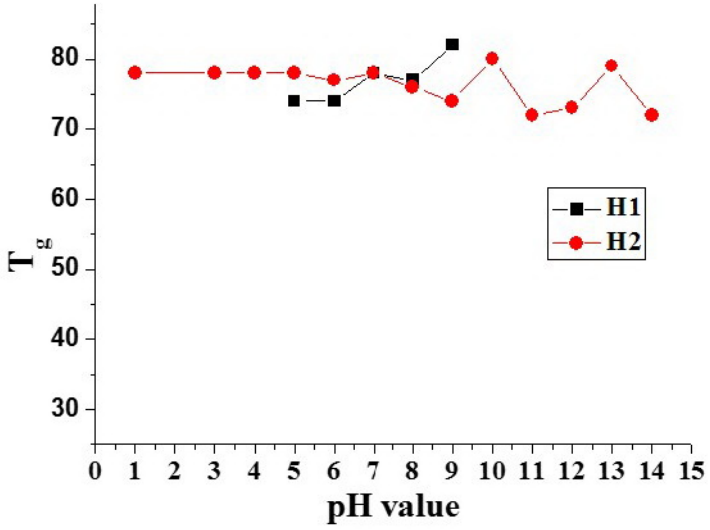


Fig. S7 T_g (gel collapsing temperature) of **H1** and **H2** hydrogels (25 mg/mL) at different pH values.

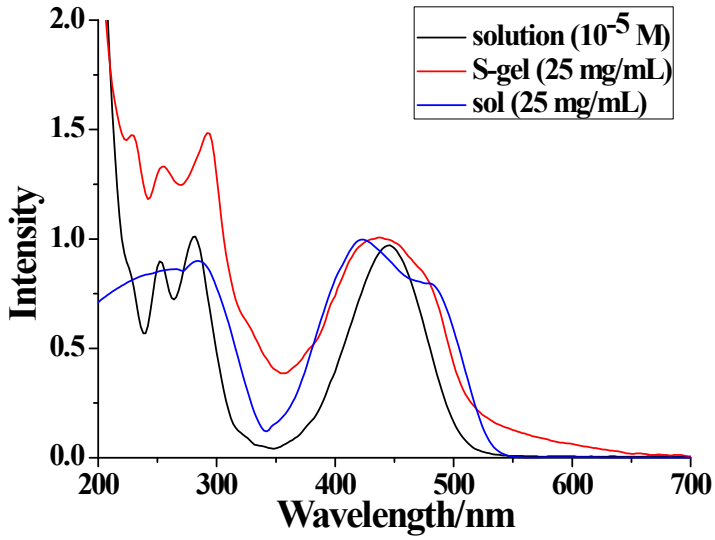


Fig. S8 The UV-vis spectra of **H1** solution (10^{-5} M), concentrated sol (25 mg/mL) and S-gel (25 mg/mL).

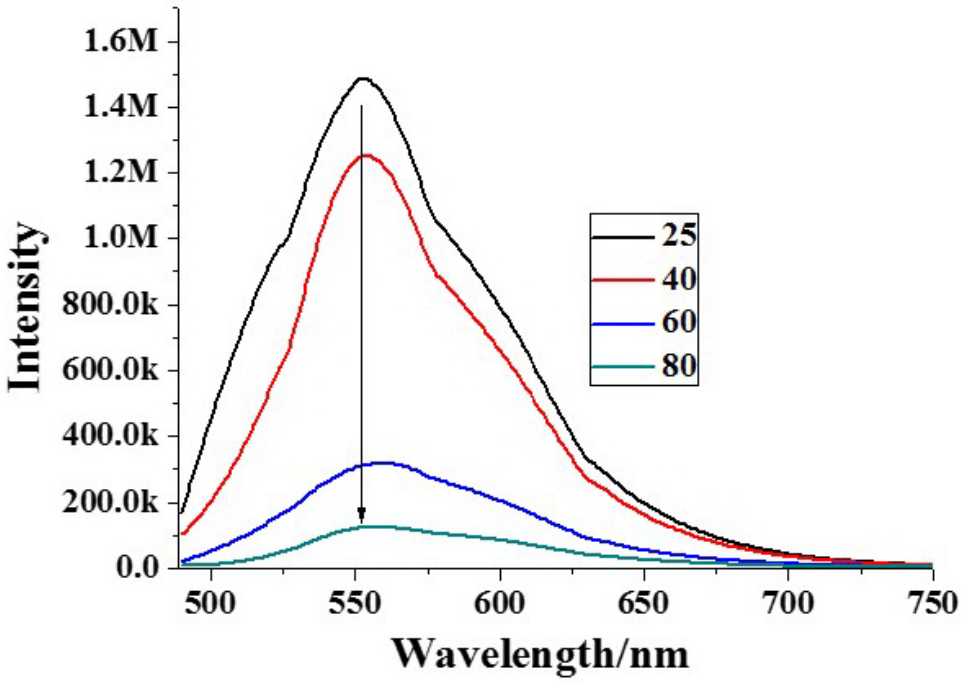


Fig. S9 Temperature dependent fluorescence changes of **H1** hydrogel (25 mg/mL) with gel-to-suspension transformation. Unit: °C.

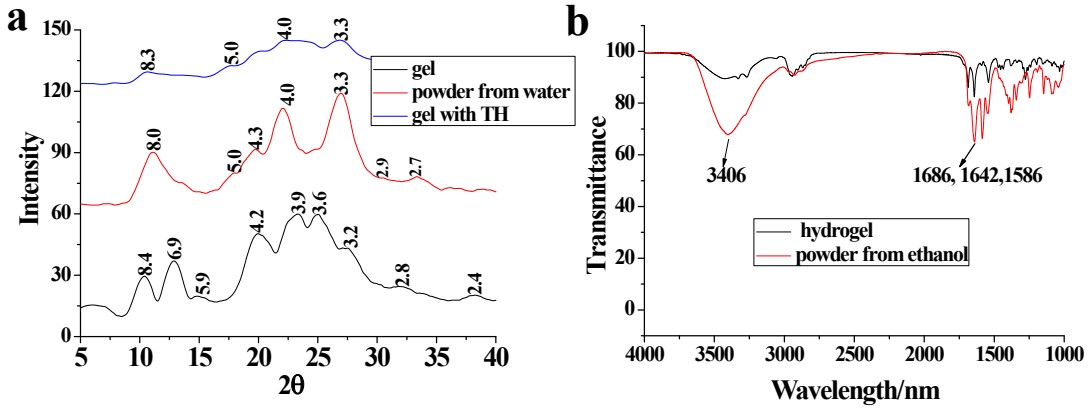


Fig. S10 a) XRD data of hydrogel **H1**, powder **H1** from water via evaporation method and gel with TH; b) IR spectra of the tube assembly and hydrogel of **H1**.

Table S1 The assembly properties of **H1** (25 mg/mL) in different organic solvents

solvent	H1	
	Heating-cooling	Sonication
acetone	I	I
chloroform	I	I
n-propyl alcohol	I	I
methylbenzene	I	I
tetrahydrofuran	I	I
ethanol	I	I
methyl alcohol	I	I
N,N-dimethylformamide	S	S
dimethyl sulfoxide	S	S

Note: I, insoluble; S, soluble

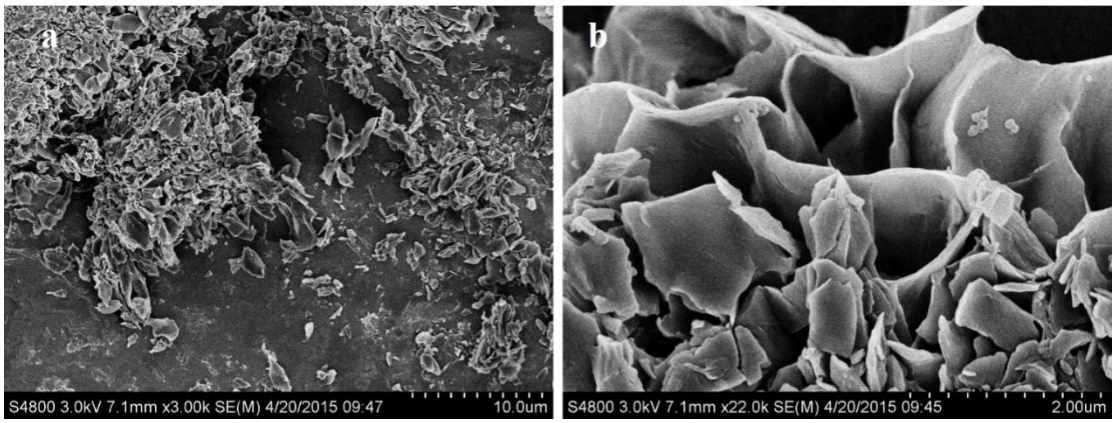


Fig. S11 SEM images of **H2** precipitate from ethanol (25 mg/mL).

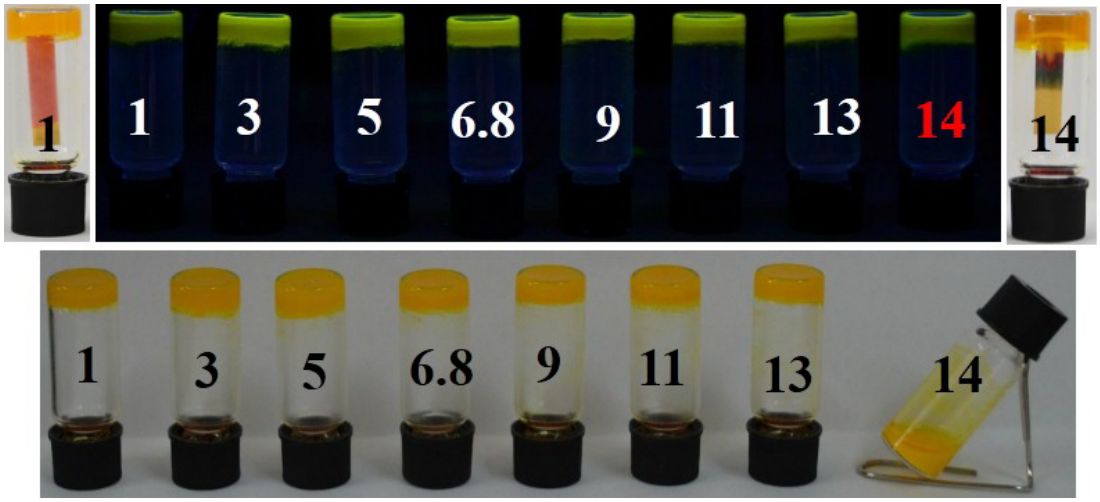


Fig. S12 Photos of hydrogels of **H2** at different pH values in light and in dark (irradiated by 365 nm).

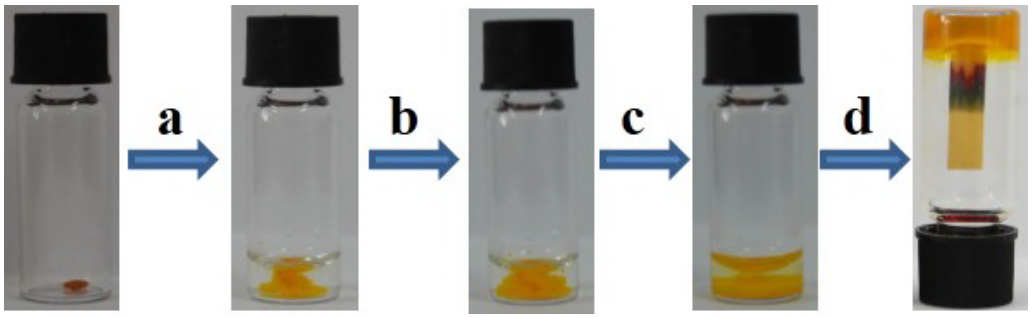


Fig. S13 The gel formation process of hydrogel **H2** (25 mg/mL) in water (pH = 14) triggered by sonication at room temperature. a) Solid of **H2** crystalized from water; b) added with water (pH = 14) for 1 min; c) staying for 3 min; d) after sonication for 20 s.

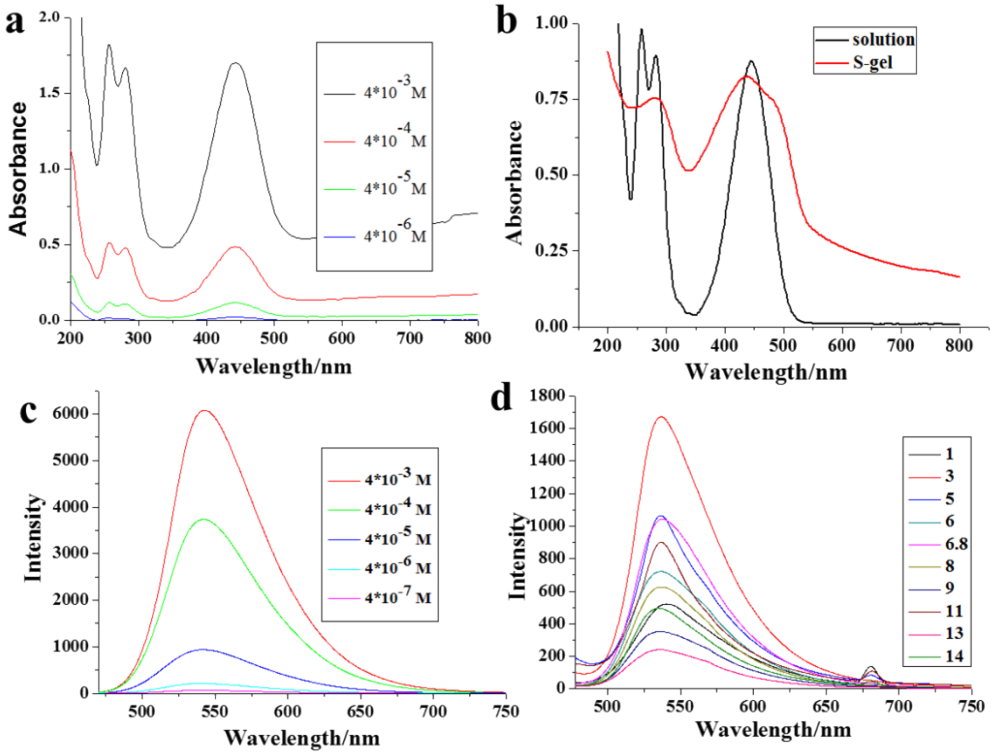


Fig. S14 The UV-vis and fluorescent spectra of **H2**. a) The UV-vis spectra of **H2** solution in different concentrations, b) the UV-vis spectra of sol and S-gel of **H2** (25 mg/mL) in distilled water, c) the fluorescent spectra of **H2** solution in different concentrations and d) the fluorescence spectra of hydrogels **H2** at different pH values.

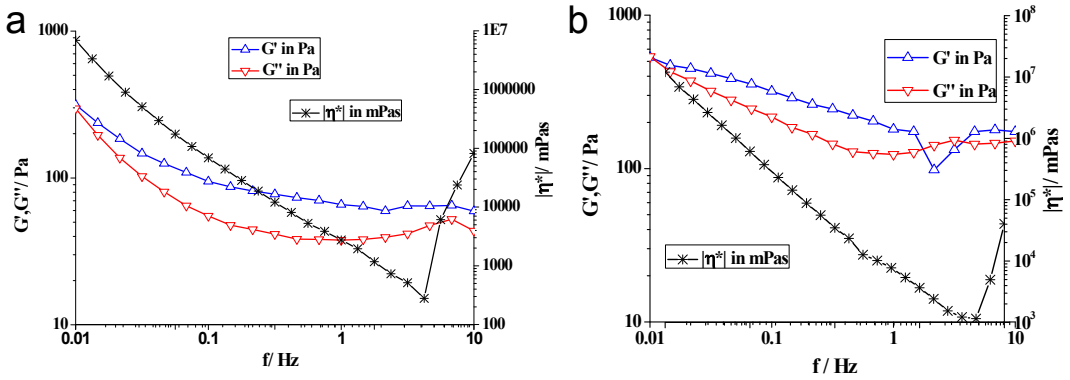


Fig. S15 a) Dynamic frequency sweep data of original hydrogel **H1**, and plots of viscosity (η^*) *vs* frequency (f); b) Dynamic frequency sweep data of original hydrogel **H2**, and plots of viscosity (η^*) *vs* frequency (f). Strain kept at 1% without deformation.

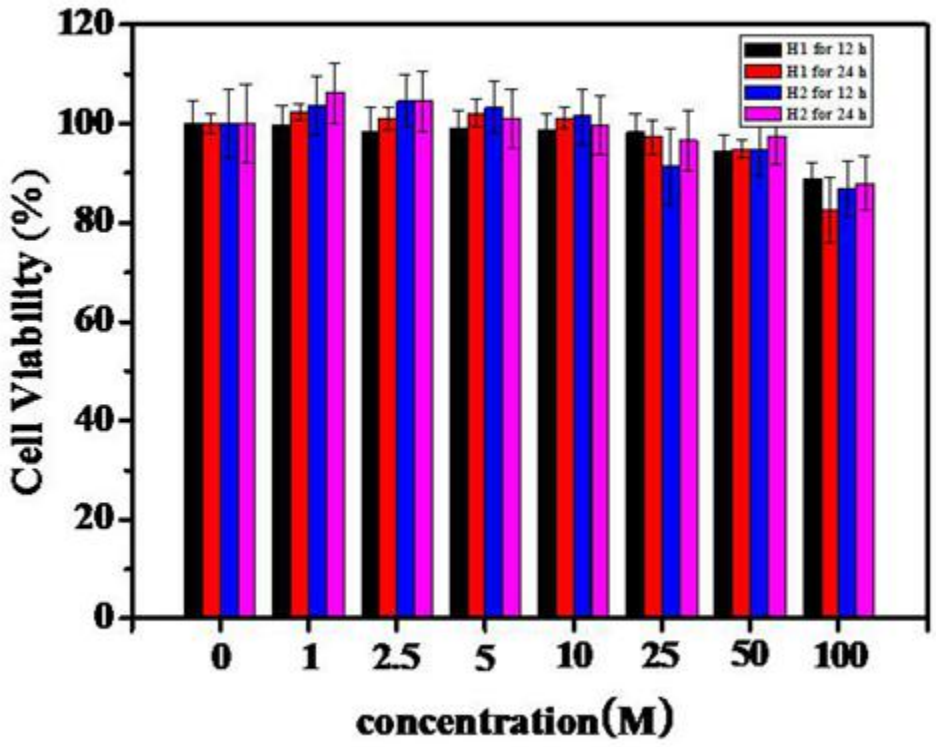


Fig. S16 MTT assays of **H1** and **H2** cultured for 12 hours or 24 hours at 37 ºC.

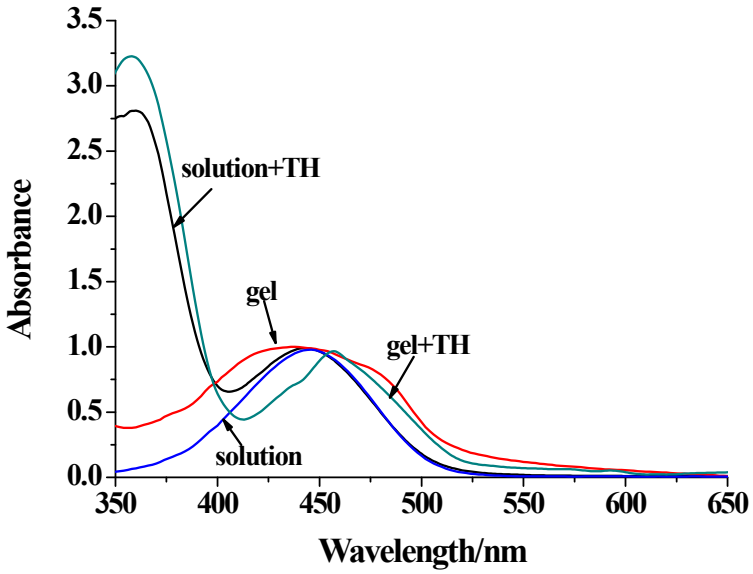


Fig. S17 The Uv-vis spectra of solution (10^{-5} M), hydrogel of **H1** and solution (10^{-5} M) and hydrogel of **H1** with TH (1 eq.).

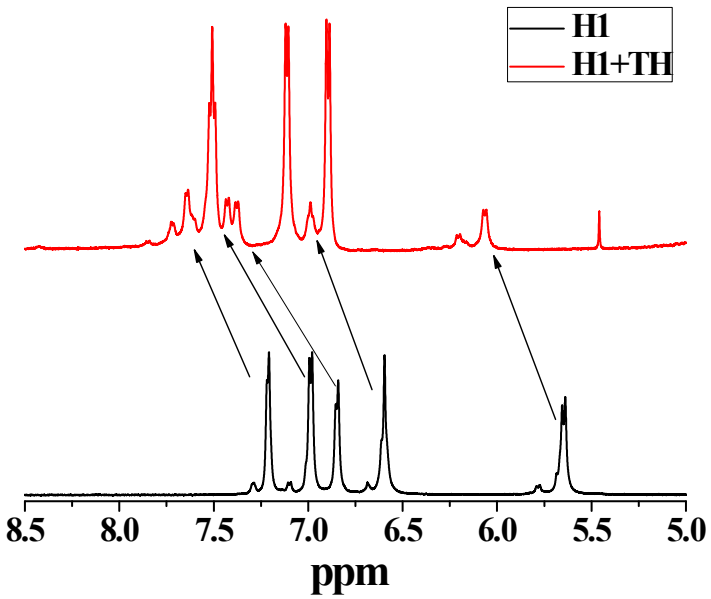


Fig. S18 The ^{1}H NMR titrations of **H1** with TH (1.2 eq).

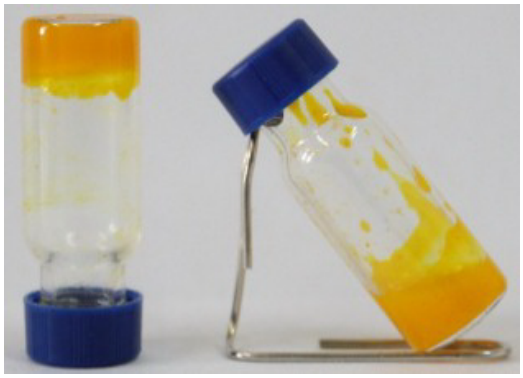


Fig. S19 Photos of the hydrogels of **H2** (25 mg/mL) with TH of 10 mg/mL (left) and 12 mg/mL (right), formed at room temperature via sonication.

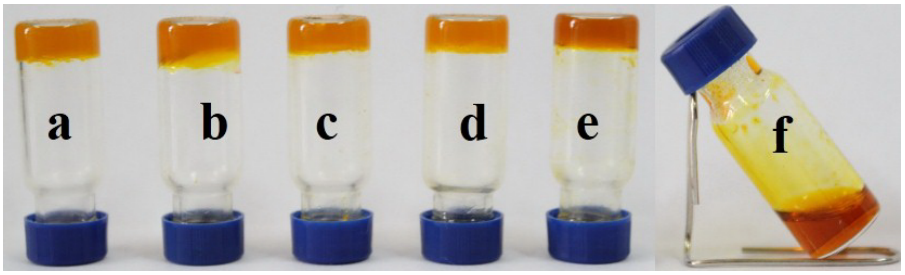


Fig. S20 Photos of hydrogels of **H2** with different concentration of TH with the aid of heat followed by sonication. a) 25 mg/mL, b) 50 mg/mL, c) 75 mg/mL, d) 100 mg/mL, e) 150 mg/mL and f) 160 mg/mL.

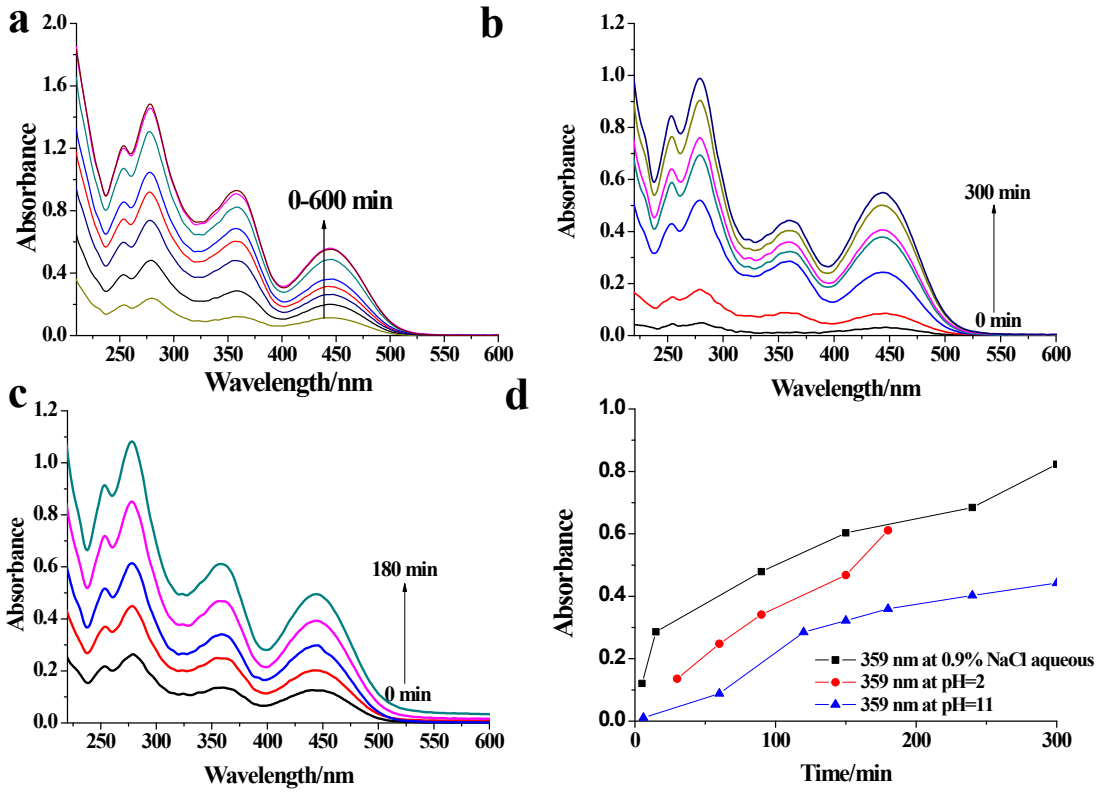


Fig. S21 a) The absorption spectral change in the release experiment of **H1** hydrogel (a) in the condition of Stroke-physiological saline solution, b) in pH = 11 and c) in pH = 2. d) The release rate of **H1** hydrogel at 359 nm (absorbance value *vs* time) in different conditions.

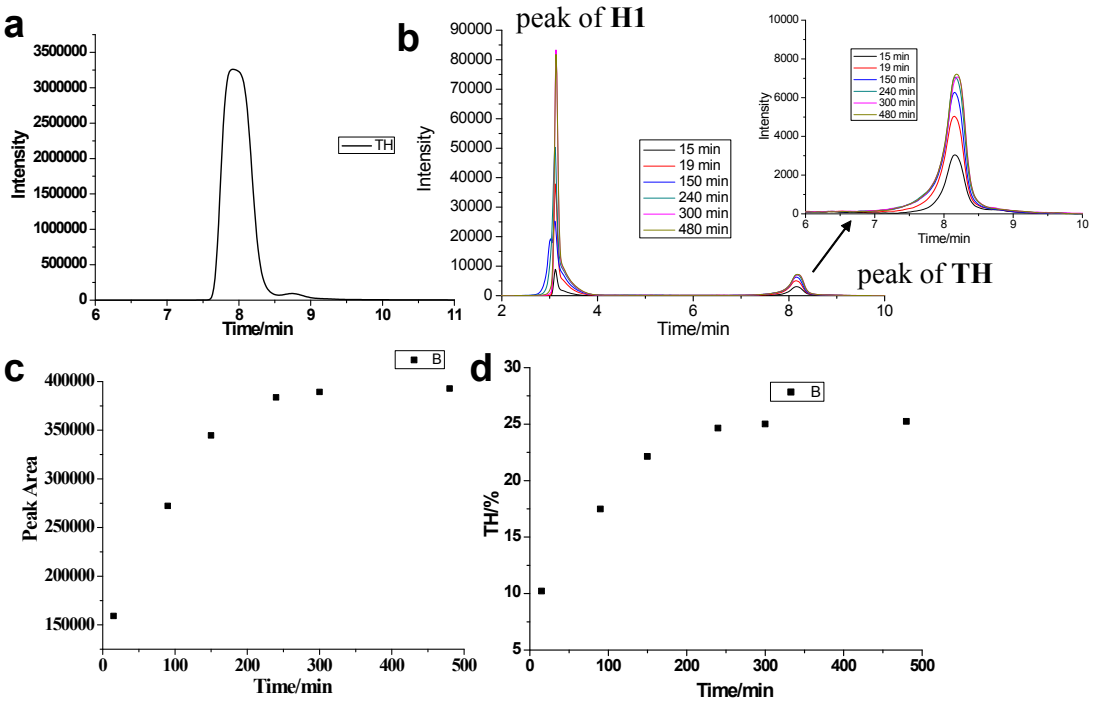


Fig. S22 HPLC experiments of the drug release of **H1** with TH. a) The HPLC spectrum of TH; b) the HPLC spectral changes in the release experiment of **H1** hydrogel with TH; c) plots of the peak area of TH *vs.* time in the release experiment; d) the release rate of TH, plots of TH% *vs.* time.