Supplementary data for

(-)-Menthol based thixotropic hydrogel as a eurytopic antibacterial carrier

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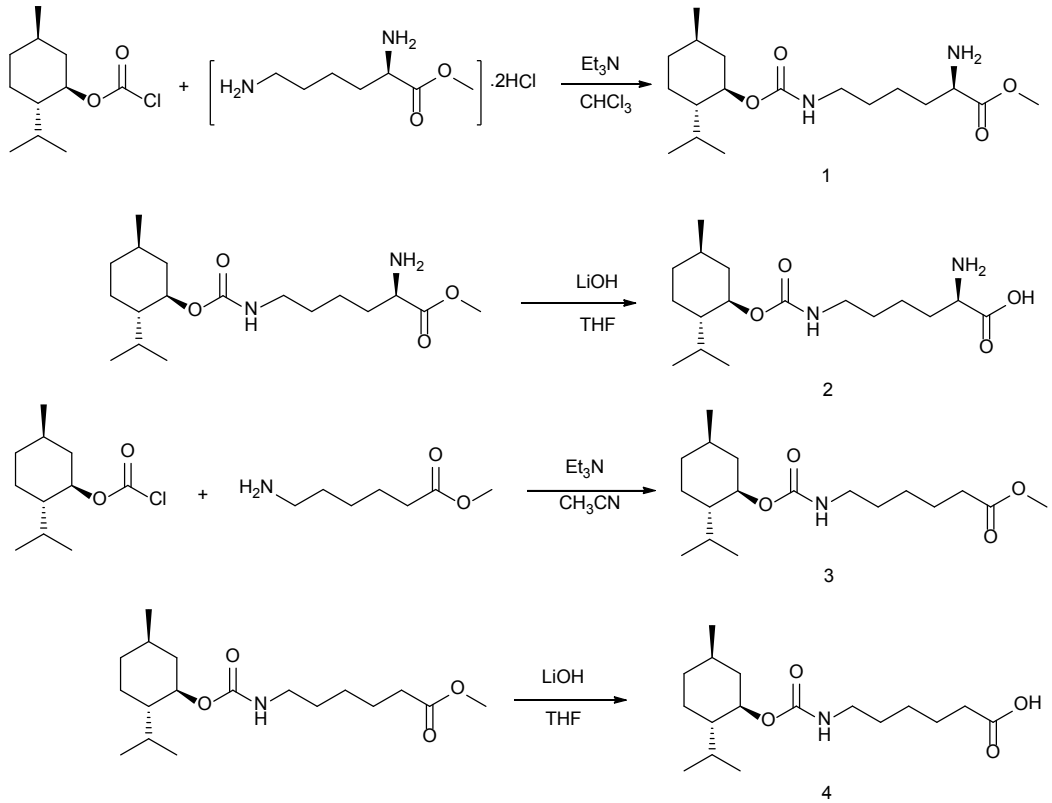
1. Synthesis details of compounds 1-4



Scheme S1 Synthetic procedures of compounds **1-4**.

The synthetic routes for compounds **1-4** are shown in Scheme S1.

Synthesis of 1: 10 mL triethylamine was added to the chloroform solution of L-lysine methyl ester·2HCl (1.273 g, 5.5 mmol) until the pH value reached 8-9. The reactant was stirred for 30 minutes at room temperature, followed by dropwise addition of a chloroform solution of (1R)-(-)-menthyl chloroformate (1 g, 4.6 mmol), and the reaction continued overnight until complete consumption of the reactants based on TLC monitoring. The crude product was subjected to column chromatography (dichloromethane/ methanol = 40: 1, v/v) to give **1** as a transparent colloid solid with mint smell and a slightly cooling effect. Yield 83.3%; mp 73-75ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (s, 1H), 4.54 (s, 1H), 3.73 (s, 3H), 3.51 – 3.35 (m, 1H), 3.17 (d, J = 5.3 Hz, 2H), 2.03-1.91 (m, 2H), 1.75 – 1.25 (m, 10H), 1.10 – 0.79 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.39, 156.56, 74.35, 54.23, 51.91, 47.42, 41.06, 40.50, 34.34, 31.35, 29.73, 26.31, 23.56, 22.77, 22.05, 20.80, 16.50; HR-MS (ESI^+) calcd for $C_{18}H_{35}N_2O_4$ [$M+H^+$]: 344.2630; found: 344.2654.

Synthesis of 2: An aqueous solution of lithium hydroxide (20 mL, 3.6 M) was added to a THF solution of **1** and the slurry was stirred for two days at room temperature. The pH value was modulated to 2-3 by addition of hydrochloric acid. After solvent was evaporated in vacuum, the solid was filtered out and freeze-dried to give **2** as a white powder. Yield 73%; mp 174-177 ºC; ^{1}H NMR (400 MHz, DMSO-D6) δ 13.7 (s, 1H), 8.27 (s, 3H), 7.02 (s, 1H), 4.39 (m, 1H), 3.84 (t, 1H), 2.94 (m, 2H), 1.87 (d, J = 7.9 Hz, 2H), 1.75 (s, 2H), 1.60-0.61 (m, 19H); ^{13}C NMR (100 MHz, DMSO-D6) δ 171.37, 156.59, 73.22, 52.36, 47.43, 41.91, 34.39, 31.44, 30.08, 29.41, 26.26, 23.65, 22.47, 22.09, 21.07, 16.80; HR-MS (ESI^+) calcd for $C_{17}H_{33}N_2O_4$ [$M+H^+$]: 329.2440; found: 329.2469.

Synthesis of 3: A methanol solution (10 mL) of dichlorosulfoxide (2 mL) was stirred at 10ºC for ten minutes, then 6-aminohexanoic acid (0.718 g, 5.5 mmol) was added. 20 minutes later, the solvent was evaporated in vacuum to dryness and the solid was dissolved in acetonitrile (10 mL) and triethylamine (5 mL), followed by dropwise addition of (1R)-(-)-menthyl chloroformate (1 g, 4.6 mmol) in ice-bath. The reaction proceeded overnight at room temperature, the crude product was subjected to column chromatography (petroleum/ethyl acetate = 20: 1, v/v) to give **3** as a white crystalline solid. Yield 84%; mp 30-31ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (s, 1H), 4.54 (s, 1H), 3.67 (s, 3H), 3.16 (s, 2H), 2.32 (t, J = 7.3 Hz, 2H), 2.03 (m, 1H), 1.90 (m, 1H), 1.73 – 1.56 (m, 4H), 1.48 (m, 2H), 1.33 (m, 4H), 1.14 – 0.56 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.80, 156.53, 74.13, 51.25, 47.37, 41.47, 40.54, 34.26, 33.67, 31.27, 29.63, 26.14, 24.46, 23.47, 21.98, 20.69, 16.37; HR-MS (ESI^+) calcd for $C_{18}H_{33}NO_4Na$ [$M+Na^+$]: 350.2307; found: 350.2320.

Synthesis of 4: An aqueous solution of lithium hydroxide (20 mL, 3.6 M) was added to the tetrahydrofuran (THF, 50 mL) solution of **3** (0.3 g, 0.9 mmol) and stirred for three days at room temperature. After that, hydrochloric acid was added in ice-bath until the pH value of the solution reached 2-3 and THF was

removed by evaporation. The product was extracted with dichloromethane (3 × 25 mL) and the organic layer was evaporated to give **4** as a white granular solid. Yield 62.7%; mp 205-208ºC; ^{1}H NMR (400 MHz, D_2O) δ 4.49 (s, 1H), 3.14 (t, J = 12 Hz, 2H), 2.20 (t, J = 7.5 Hz, 2H), 1.90 (m, 2H), 1.70 (d, J = 10.5 Hz, 2H), 1.63 – 1.42 (m, 5H), 1.41 – 1.23 (m, 3H), 1.18 – 0.70 (m, 12H); ^{13}C NMR (100 MHz, D_2O) δ 183.40, 157.72, 74.54, 47.39, 41.33, 40.65, 37.67, 34.43, 31.17, 29.39, 26.36, 26.07, 25.75, 23.52, 21.99, 20.67, 16.30; HR-MS (ESI^+) calcd for $C_{17}H_{31}NO_4Na$ [M+Na^+]: 336.2151; found: 336.2168.

2. Addition characteristic of gel 2 and 2+ lincomycin

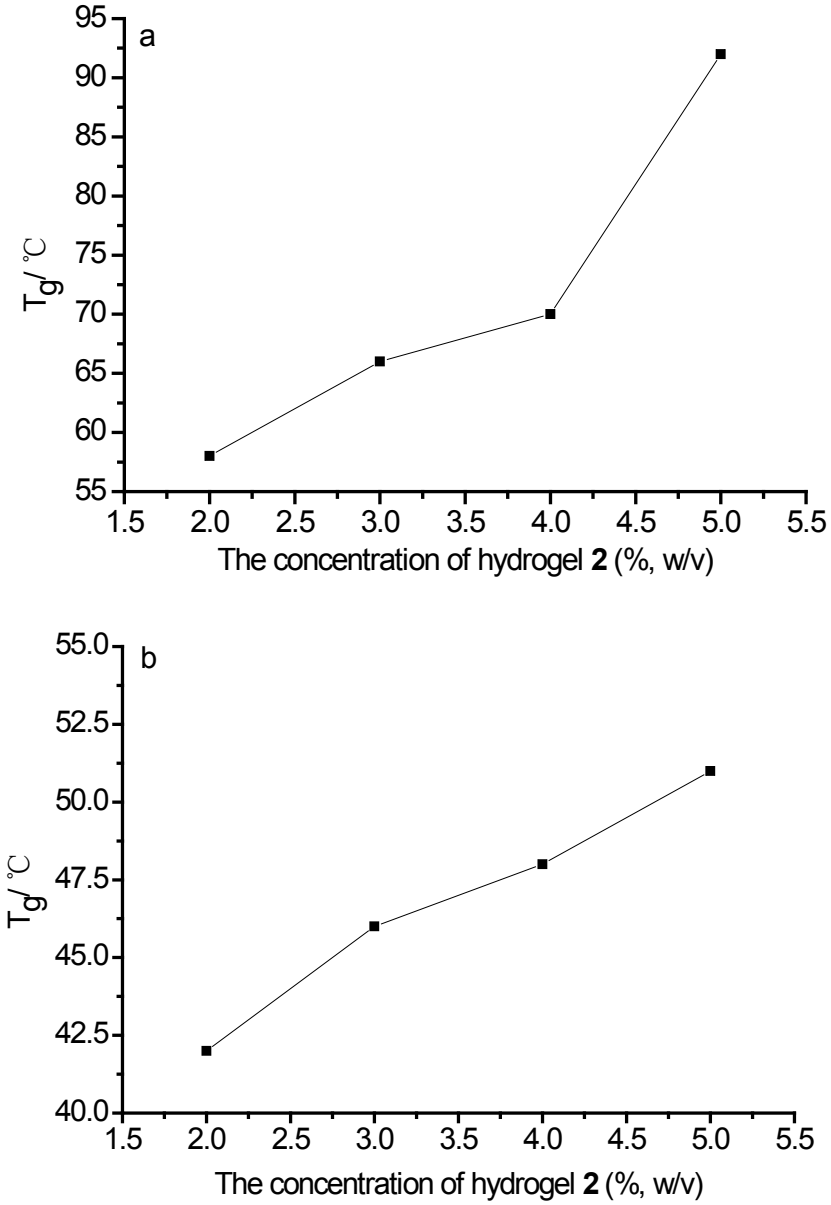


Fig. S1 The T_g value of (a) hydrogel **2** and (b) **2**+ lincomycin (0.001 M) with the increase of the gelator's concentration.

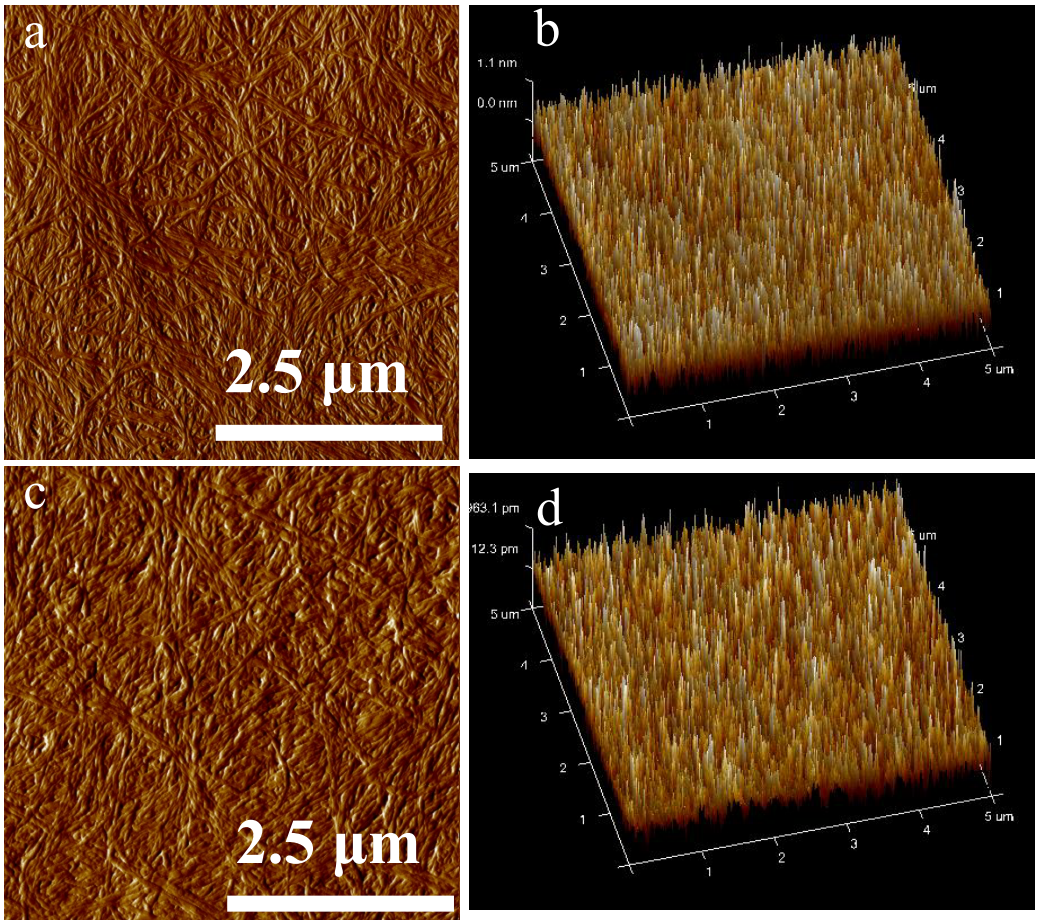


Fig. S2 Tapping-mode AFM images of (a, b) hydrogel **2** (c=0.83%, w/v) and (c, d) sol state of **2** after vigorously mechanical damage; (b) and (d) were surface topography of (a) and (c), respectively.

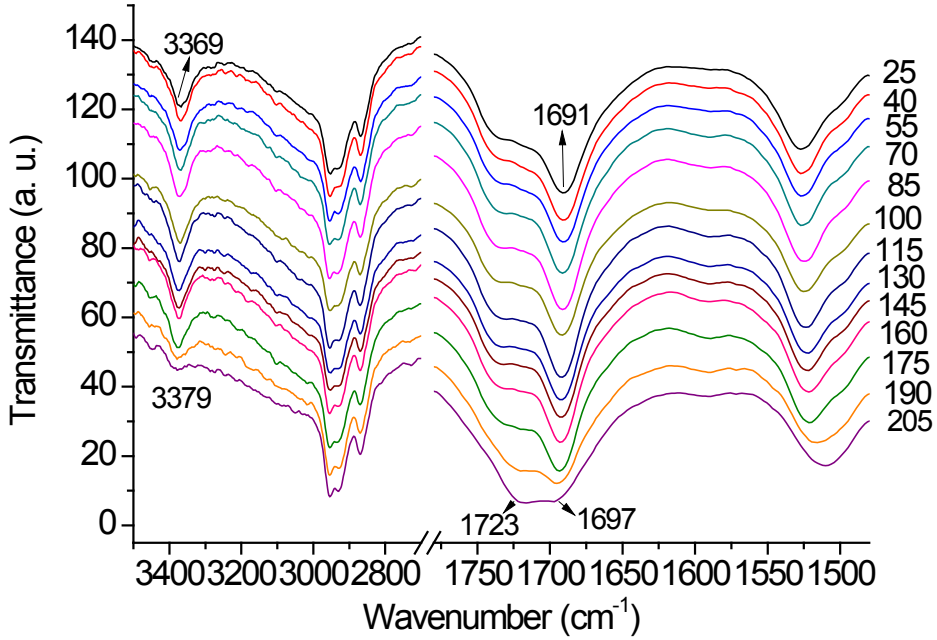


Fig. S3 Temperature-dependent IR spectra of the xerogel **2** from water in the temperature range of 25-205ºC.

Fig. S4 The self-repairing phenomenon of hydrogel **2** with lincomycin added.

3. Antimicrobial susceptibility tests

Antimicrobial susceptibility tests were made by using oxford cup method: Ampicillin (10% w/v, 40 μL), a kind of efficient antibiotic, as a control, was added in the first test hole of each tested petri dish. And the last one of the test holes was the blank control (hydrogel without Zn^{2+}). When the C_{Zn}^{2+} was in a smaller concentration of 5.0×10^{-3} M, the bacteriostatic circle diameter was 1.13 cm, similar with that of the blank control, which could be as the initial bacteriostatic concentration. By comparison, we could clearly find that all the tested hydrogel and solution showed visual bacteriostatic circles.

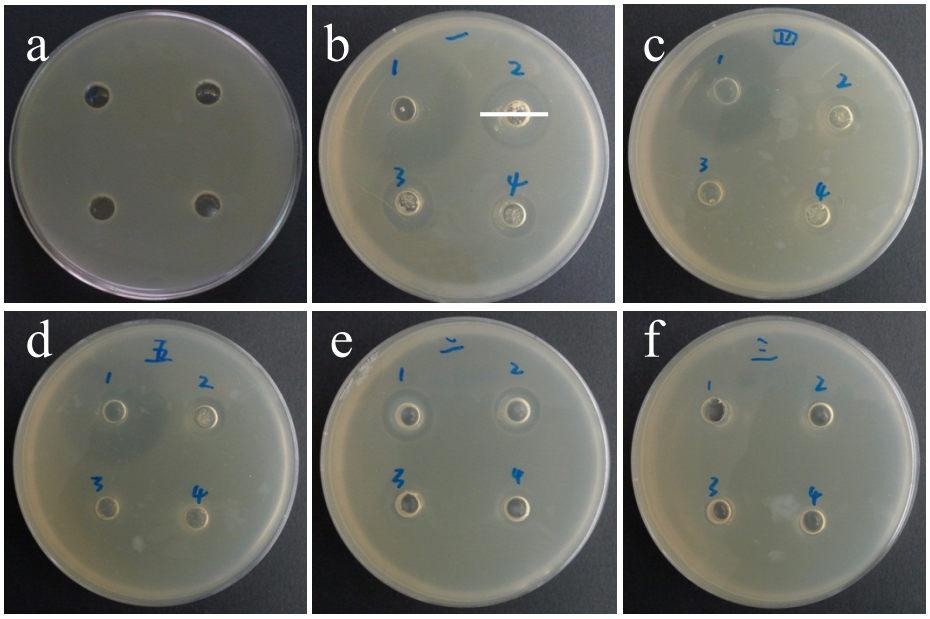


Fig. S5 The photographs of the bacteriostatic circles on *Escherichia coli*: a) blank control; (b-d) hydrogel **2** loaded with Zn^{2+} (every first hole is ampicillin; C_{Zn}^{2+} is decreasing gradually as b2, b3 and b4 being 0.03, 0.02 and 0.01 M, respectively; c2, c3 and c4 being 0.009, 0.008 and 0.007 M, respectively; d2 and d3 is 0.006 and 0.005 M, respectively and d4 is blank); (e, f) Zn^{2+} aqueous solution (C_{Zn}^{2+} is decreasing from e1-f4 as e1, e2, e3 and e4 being 0.03, 0.02, 0.01 and 0.009 M, respectively; f1, f2, f3 and f4 are 0.008, 0.007, 0.006 and 0.005 M, respectively).

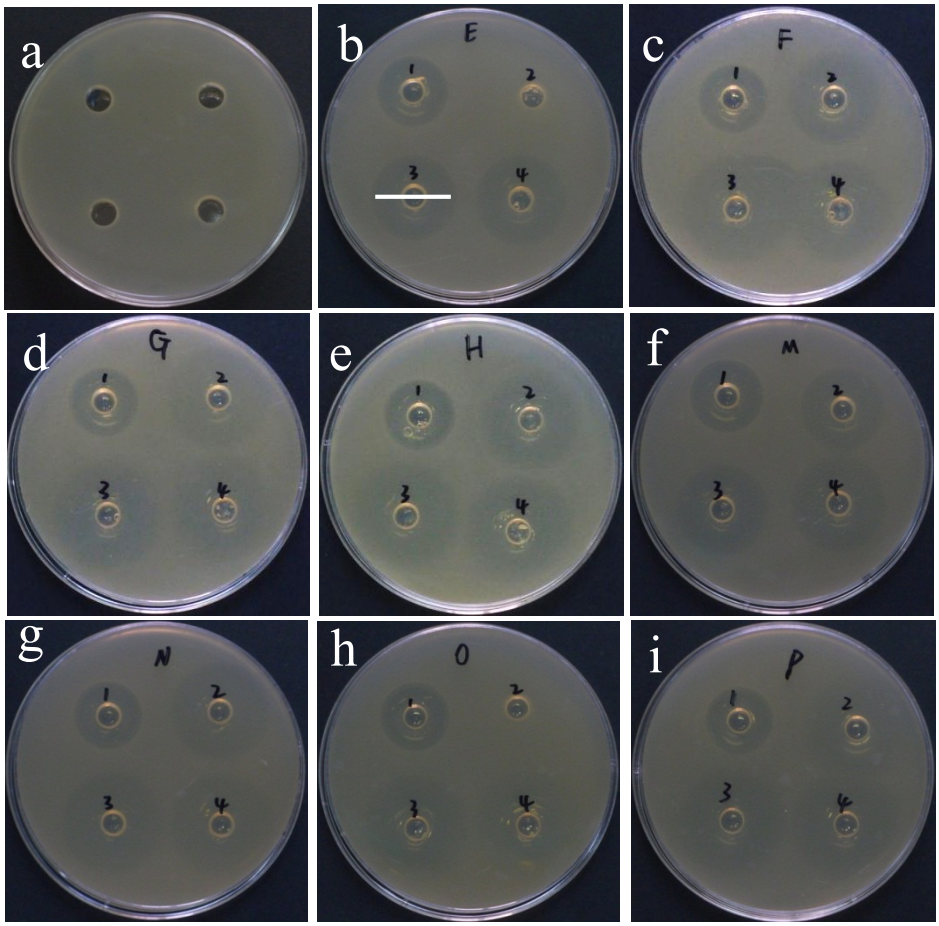


Fig. S6 The photographs of the bacteriostatic circles on *Staphylococcus epidermidis*: (a) blank control; (b-e) hydrogel **2** loaded with lincomycin (every first hole is ampicillin; b2 is blank); the concentration of lincomycin hydrochloride increasing gradually from b3 to e4 as b3 and b4 being 0.0001 and 0.0002 M, respectively; c2, c3 and c4 being 0.0004, 0.0006, 0.0008 M, respectively; d2, d3 and d4 being 0.001, 0.002 and 0.004 M, respectively; e2, e3 and e4 being 0.006, 0.008 and 0.01 M, respectively); (f-i) lincomycin hydrochloride aqueous solution (every first hole is ampicillin; the concentration of lincomycin hydrochloride increased gradually as f2, f3 and f4 being 0.0001, 0.0002 and 0.0004 M, respectively; g2, g3 and g4 being 0.0006, 0.0008 and 0.001 M, h2 is blank, h3, h4, i2, i3 and i4 are 0.002, 0.004, 0.006, 0.008 and 0.01 M, respectively).