Electronic Supplementary Material for Chemical Communications

Supplementary Information

An insulin-sensing sugar-based fluorescent hydrogel

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Contents

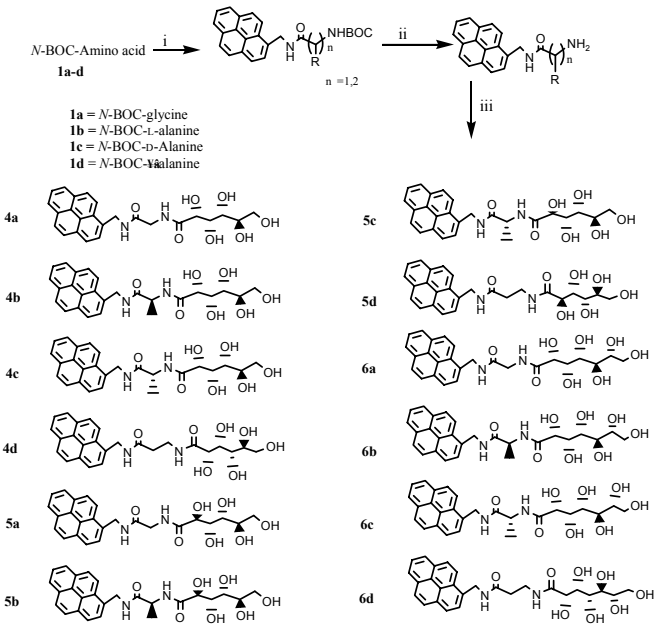
Experimental

General Information

All chemicals were obtained from Aldrich Chemical Company and were used without further purification. Each reaction was executed under an inert atmosphere of dry argon using glassware that was flame-dried under vacuum. Flash chromatography was performed using silica gel 60 (230–400 mesh; ASTM). Melting points are uncorrected and were obtained using an Electrothermal 1A 9000 series apparatus. FTIR spectra were recorded on a Bruker PS55+ FT-IR spectrometer. Low-resolution FAB^+ mass spectra were obtained using a JEOL JMS-AX505WA (FAB-HRMS) spectrometer. ^1H and ^{13}C NMR spectra were recorded using a Bruker Aspect 300 NMR spectrometer. Chemical shifts are reported in parts per million (ppm) downfield relative to the internal standard, tetramethylsilane (TMS). Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as s, singlet; d, doublet; dd, double doublet; dt, distorted triplet; t, triplet; m, multiplet; and br, broad. SEM images were obtained using a Philips XL30S FEG SEM analyzer. Fluorescence spectra was recorded using an MD-5020-PTI analyser.

Sample Preparation and Tests for Gelation. To avoid evaporation of the liquid components, for most studies the gels were prepared in sealed 5-mm (i.d.) glass tubes. Weighed quantities of a gelator and a liquid were heated until dissolution occurred. The tubes were then maintained at room temperature for 2–5 min. We deemed the samples to be gels if (a) they were not visually phase-separated and (b) did not flow perceptibly when the vessels were inverted.

Synthesis of hydrogelators:



i: EDC, DMAP, DMF, r.t. 12h; ii: 15%TFA in CH_2Cl_2, 0 °C-r.t. 2h; iii: MeOH, reflux, 6h, ¥á(D)- gluconolactone/¥á(D)-mannonolactone/(D)-glucoheptanoic-γ–lactone

Synthesis of Gelators 4a–d

General procedures:

An *N*-BOC amino acid (1 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide·HCl (EDC; 191 mg, 1 mmol), and *N,N*-dimethyl-4-aminopyridine (DMAP; 122 mg, 1 mmol) were dissolved in dry DMF (25 mL) and placed in a two-neck round-bottom flask equipped with an argon gas inlet. 1-Pyrenemethylamine hydrochloride (268 mg, 1 mmol) was added and then the mixture was stirred for 12 h. When the reaction was complete, the mixture was poured into water and extracted with CH_2Cl_2. The product was isolated and purified by column chromatography (SiO_2; hexane/EtOAc, 80:20). Product yields: **1a**, 320mg (72%); **1b**, 350 mg (81%); **1c**, 362 mg (82%); **1d**, 344 mg (71%).

Compound **2** was placed in a two-neck round-bottom flask, a 15% solution of trifluoroacetic acid in dichloromethane (10 ml) was added, and then the reaction was continued for 2 h at room temperature. The product was isolated and purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 85/15). Yields: **3a**, 265 mg (92%); **3b**, 280 mg (91%); **3c**, 285 mg (97%); **3d**, 285 mg (97%).

Compound **3** (1 mmol) was placed in a round-bottom flask, a solution of δ-D-gluconolactone in methanol (1 mmol, 30 mL) was added, and then the mixture was heated under reflux for 6 h. After cooling the reaction mixture, a white product separated out; it was washed with methanol repeatedly and then dried under vacuum. **4a**: 265 mg (60%); m.p. 219 °C; **4b**: 275 mg (65%); m.p. 208 °C; **4c**: 260 mg (56%); m.p. 199 °C; **4d**: 280 mg (67%); m.p. 202 °C.

***N*-D-Gluconyl-*N′*-1-pyrenemethylglycinamide (4a)**: ^{1}H NMR (300 MHz, DMSO-d_6): 8.57 (s, 1H; NH), 8.44 (d, J = 7.20 Hz, 2H; ArH), 8.32 (m, 1H; ArH), 8.27 (d, J = 3.20 Hz, 4H; ArH), 8.17 (s, 1H; NH), 8.07 (d, J = 4.00 Hz, 2H; ArH), 5.62 (d, J = 3.01 Hz, 1H; CH), 5.01 (d, J = 3.67 Hz, 2H; CH_2), 4.64 (dt, J = 3.61 Hz, 1H; CH), 4.42 (d, J = 3.34 Hz, 1H; CH), 3.89 (m, 1H; CH), 3.84 (dd, J = 6.01 Hz, J_{gem} = 11.2 Hz, 2H; CH_2), 3.34 (d, J = 5.56 Hz, 2H; CH_2). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 174.09, 169.72, 133.51, 131.63, 131.14, 130.89, 128.79, 128.43, 128.23, 127.84, 127.27, 127.08, 126.07, 125.99, 125.56, 124.82, 124.76, 123.97, 74.02, 72.32, 71.43, 64.17, 42.88. HRMS-FAB (*m*/*z*): $[M + Na]^+$ Calcd. for $C_{25}H_{26}N_2O_7Na$: 489.4804; Found: 489.4816. Anal. Calcd. for $C_{25}H_{26}N_2O_{7:}$

***N*-D-Gluconyl-*N′*-1-pyrenemethyl-L-alaninamide (4b)**: ^{1}H NMR (300 MHz, DMSO-d_6): 8.50 (s, 1H; NH), 8.40 (d, J = 7.20 Hz, 2H; ArH), 8.22 (m, 1H; ArH), 8.07 (d, J = 3.20 Hz, 4H; ArH), 7.98 (s, 1H; NH), 7.88 (d, J = 4.00 Hz, 2H; ArH), 5.56 (d, J = 3.62 Hz, 1H; CH), 5.05 (s, 2H; CH_2), 4.59 (d, J = 3.62 Hz, 1H; CH), 4.39 (d, J = 3.34 Hz, 1H; CH), 4.05 (m, 1H; CH), 3.52 (q, 1H; CH), 3.37 (dd, J = 6.11 Hz, J_{gem} = 11.2 Hz, 2H; CH_2), 1.30 (d, J = 5.6 Hz, 3H; CH_3). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 174.09, 169.72, 133.51, 131.63, 131.14, 130.89, 128.79, 128.43, 128.23, 127.84, 127.27, 127.08, 126.07, 125.99, 125.56, 124.82, 124.76, 123.97, 74.02, 72.32,

71.43,64.17, 48.46, 19.52. HRMS-FAB (*m*/*z*): $[M + Na]^+$ Calcd. for $C_{26}H_{28}N_2O_7Na$: 503.5073; Found: 503.5086. Anal. Calcd. for $C_{26}H_{28}N_2O_{7:}$

***N*-D-Gluconyl-*N*′-(1-pyrene)methyl-D-alaninamide (4c):** ^{1}H NMR (300 MHz, DMSO-d_6): 8.60 (s, 1H; NH), 8.55 (d, *J* = 7.27 Hz, 2H; ArH), 8.29 (m,1H; ArH), 8.17 (d, *J* = 3.60 Hz, 4H; ArH), 8.09 (s, 1H; NH), 7.98 (d, *J* = 4.10 Hz, 2H; ArH), 5.56 (d, *J* = 3.69 Hz, 1H; CH), 5.15 (s, 2H; CH_2), 4.69 (d, *J* = 3.72 Hz, 1H; CH), 4.49 (d, *J* = 3.30 Hz, 1H; CH), 4.15 (m,1H; CH), 3.72 (q, 1H; CH), 3.57 (dd, *J* = 6.11 Hz, J_{gem} = 11.2 Hz, 2H; CH_2), 1.37 (d, *J* = 5.6 Hz, 3H; CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.09, 169.72, 133.51, 131.63, 131.14, 130.89, 128.79, 128.43, 128.23, 127.84, 127.27, 127.08, 126.07, 125.99, 125.56, 124.82, 124.76, 123.97, 74.02, 72.32, 71.43, 64.17, 48.46, 18.74. HRMS-FAB (*m*/*z*): $[M + Na]^+$ Calcd. for $C_{26}H_{28}N_2O_7Na$: 503.5073; Found: 503.5086.

***N*-D-Gluconyl-*N*′-1-pyrenemethyl-β-alaninamide (4d):** ^{1}H NMR (300 MHz, DMSO-d_6): 8.57 (s, 1H; NH), 8.44 (d, *J* = 7.20 Hz, 2H; ArH), 8.32 (m,1H; ArH), 8.27 (d, *J* = 3.20 Hz, 4H; ArH), 8.17 (s, 1H; NH), 8.07 (d, *J* = 4.00 Hz, 2H; ArH), 5.6 (d, *J* = 5.01 Hz, 2H; CH), 5.15 (s, 2H; CH_2), 4.70 (d, *J* = 3.67 Hz, 1H; CH), 4.42 (d, *J* = 3.34 Hz, 1H; CH), 3.80 (m, 1H; CH), 3.74 (dd, *J* = 6.01 Hz, J_{gem} = 11.2 Hz, 2H, CH_2), 3.50 (t, *J* = 7.26 Hz, 2H; CH_2), 2.39 (t, *J* = 6.21 Hz, 2H; CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): 172.76, 170.92, 133.13, 131.10, 130.63, 130.41, 128.38, 127.71, 172.34, 126.97, 126.58, 125.50, 125.09, 124.24, 123.50, 73.79, 72.60, 71.82, 70.43, 63.68, 35.42, 35.37. HRMS-FAB (*m*/*z*): $[M + Na]^+$ Calcd. for $C_{26}H_{28}N_2O_7Na$: 503.5073; Found: 503.5086.

Synthesis of Gelators 5a–d: The procedures for the synthesis of gelators **5a**–**d** are same as those described for the synthesis of **4a**–**d**. **5a**: 255 mg, 58%; m.p. 216 °C; **5b**: 278 mg (65%); m.p. 189 °C; **5c**: 269 mg (56%); m.p. 206 °C; **5d**: 282 mg (67.2%); m.p. 186 °C.

***N*-(D)-Mannonyl-*N*′-1-pyrenemethylglycinamide (5a)**: ^{1}H NMR (300 MHz, DMSO-d_6): 8.590 (d, *J* = 7.20 Hz, 2H; ArH), 8.57 (m, 1H; ArH), 8.41 (d, *J* = 3.20 Hz, 4H; ArH), 8.31 (s, 1H; NH), 8.08 (d, *J* = 4.00 Hz, 2H; ArH), 5.56 (d, *J* = 5.57 Hz, 1H; CH), 5.06 (d, *J* = 6.01 Hz, 2H, CH_2), 4.69 (d, *J* = 3.2 Hz, 1H; CH), 4.54 (d, *J* = 5.23 Hz, 1H; CH), 4.40 (dt, *J* = 6.01 Hz, 1H; CH), 3.97 (m, 2H; CH_2); 3.58 (d, *J* = 3.10 Hz, 2H; CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.09, 169.72, 133.51, 131.63, 131.14, 130.89, 128.79, 128.43, 128.23, 127.84, 127.27, 127.08, 126.07, 125.99, 125.56, 124.82, 124.76, 123.97, 74.02, 72.32, 71.43, 64.17, 42.88. HRMS-FAB (*m*/*z*): $[M + Na]^+$ Calcd. for $C_{25}H_{26}N_2O_7Na$: 489.4804; Found: 489.4816.

***N*-D-Mannonyl-N′-1-pyrenemethyl-D-alaninamide (5b)**: ^{1}H NMR (300 MHz, DMSO-d_6): 8.70 (s, 1H; NH), 8.48 (d, *J* = 7.27 Hz, 2H; ArH), 8.39 (m,1H; ArH), 8.27 (d, *J* = 3.60 Hz, 4H; ArH), 8.19 (s, 1H; NH), 7.90 (d, *J* = 4.10 Hz, 2H; ArH), 5.47 (d, *J* = 5.2 Hz, 1H; CH), 5.08 (d, *J* = 5.41 Hz, 2H; CH_2), 4.67 (d, *J* = 3.67 Hz, 1H; CH), 4.54 (m, H; CH), 4.42 (dt, *J* = 4.52 Hz, 1H; CH), 3.89 (m, 1H; CH), 3.52 (d, *J* = 6.37 Hz, 2H; CH_2), 1.30 (d, *J* = 6.2 Hz, 3H; CH_3). ^{13}C

NMR (75 MHz, DMSO-d_6): 174.09, 169.72, 133.51, 131.63, 131.14, 130.89, 128.79, 128.43, 128.23, 127.84, 127.27, 127.08, 126.07, 125.99, 125.56, 124.82, 124.76, 123.97, 74.02, 72.32, 71.43, 64.17, 48.46, 19.52. HRMS-FAB (*m*/*z*): $[M + Na]^+$ Calcd. for $C_{26}H_{28}N_2O_7Na$: 503.5073; Found: 503.5086.

***N*-D-Mannonyl-N′-1-pyrenemethyl-L-alaninamide (5c):** ^{1}H NMR (300 MHz, DMSO-d_6): 8.70 (s, 1H; NH), 8.34 (d, *J* = 7.27 Hz, 2H; ArH), 8.30 (m,1H; ArH), 8.25 (d, *J* = 3.60 Hz, 4H; ArH), 8.16 (s, 1H; NH), 8.04 (d, *J* = 4.10 Hz, 2H; ArH), 5.47 (d, *J* = 5.2 Hz, 1H; CH), 5.08 (d, *J* = 5.41 Hz, 2H; CH_2), 4.67 (d, *J* = 3.67 Hz, 1H; CH), 4.54 (m, 1H; CH), 4.40 (dt, *J* = 4.52 Hz, 1H; CH), 3.63 (m, 1H; CH), 3.52 (d, *J* = 6.37 Hz, 2H; CH_2), 1.33 (d, *J* = 6.2 Hz, 3H; CH_3). ^{13}C NMR (75.5 MHz, DMSO-d_6): 174.09, 169.72, 133.51, 131.63, 131.14, 130.89, 128.79, 128.43, 128.23, 127.84, 127.27, 127.08, 126.07, 125.99, 125.56, 124.82, 124.76, 123.97, 74.02, 72.32, 71.43,64.17, 48.46, 18.74. HRMS-FAB (*m*/*z*): $[M + Na]^+$ Calcd. for $C_{26}H_{28}N_2O_7Na$: 503.5073; Found: 503.5086.

***N*-D-Mannonyl-*N*′-1-pyrenemethyl-β-alaninamide (5d):** ^{1}H NMR (300 MHz, DMSO-d_6): 8.47 (s, 1H; NH), 8.34 (d, *J* = 7.20 Hz, 2H; ArH), 8.22 (m,1H; ArH), 8.17 (d, *J* = 3.20 Hz, 4H; ArH), 7.8 (s, 1H; NH), 5.49 (d, *J* = 2.3 Hz, 1H; CH), 5.03 (d, *J* = 5.4 Hz, 2H; CH_2), 4.56 (d, *J* = 2 Hz, 1H; CH), 4.48 (d, 1H, *J* = 5.87 Hz, 1H; CH), 4.38 (t, *J* = 4.5 Hz, 2H; CH_2), 4.03 (m, 1H; CH), 3.96 (m, 1H; CH), 3.62 (m, 1H; CH), 3.35 (dt, *J* = 3.2 Hz, 2H; CH_2), 2.42 (t, *J* = 6.7 Hz, 2H; CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.76, 170.92, 133.13, 131.10, 130.63, 130.41, 128.38, 127.71, 172.34, 126.97, 126.58, 125.50, 125.09, 124.24, 123.50, 73.79, 72.60, 71.82, 70.43, 63.68, 35.482, 35.39. HRMS-FAB (*m*/*z*): $[M + Na]^+$ Calcd. for $C_{26}H_{28}N_2O_7Na$: 503.5073; Found: 503.5086.

Synthesis of Gelators 6a–d: The procedures for the synthesis of gelators **6a–d** are the same as those described for **4a–d**. **5a**: 275 mg (58%), m.p. 209 °C; **6b**: 298 mg (65%), m.p. 181 °C; **6c**: 289 mg (56%), m.p. 192 °C; **6d**: 300 mg (67.2%), m.p. 180 °C.

***N*-D-Heptagluconyl-*N*′-1-pyrenemethylglycinamide (6a)**: ^{1}H NMR (300 MHz, DMSO-d_6): 8.17 (s, 1H; NH), 8.04 (d, *J* = 7.20 Hz, 2H; ArH), 8.02 (m, 1H; ArH), 7.97 (d, *J* = 3.20 Hz, 4H; ArH), 7.88 (s, 1H; NH), 7.77 (d, *J* = 4.00 Hz, 2H; ArH), 5.08 (s, 2H; CH_2), 4.73 (d, *J* = 3.6 Hz, 1H; CH), 4.44 (m, 1H; CH), 4.21 (m, 1H; CH), 3.89 (dt, *J* = 1.2 Hz, 1H; CH), 3.58 (d, *J* = 2.5 Hz, 2H; CH_2), 3.42 (d, *J* = 2.5 Hz, 1H; CH), 3.36 (d, *J* = 6.37 Hz, 2H; CH_2). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 173.09, 169.92, 133.51, 131.63, 131.14, 130.89, 128.79, 128.43, 128.23, 127.84, 127.27, 127.08, 126.07, 125.99, 125.56, 124.82, 124.76, 123.97, 74.02, 72.32, 71.43, 64.17, 42.88. HRMS-FAB (*m*/*z*): $[M + Na]^+$ Calcd. for $C_{26}H_{28}N_2O_8Na$: 519.5067; Found: 519.5079.

***N*-D-Heptagluconyl-*N*′-1-pyrenemethyl-D-alaninamide (6b)**: ^{1}H NMR (300 MHz, DMSO-d_6): 8.21 (s, 1H; NH), 8.14 (d, *J* = 7.20 Hz, 2H; ArH), 8.09 (m, 1H; ArH), 8.00 (d, *J* = 3.20 Hz,

4H; ArH), 7.92 (s, 1H; NH), 7.87 (d, *J* = 4.00 Hz, 2H; ArH), 5.68 (d, *J* = 3.5 Hz, 1H; CH), 5.08 (d, *J* = 4.5 Hz, 2H; CH_2), 4.73 (d, *J* = 3.71 Hz, 1H; CH), 4.54 (m, 1H; CH), 4.42 (m, 1H; CH), 4.11 (dt, 1H; CH), 3.89 (m, 1H; CH), 3.52 (d, *J* = 6.37 Hz, 1H; CH_2), 1.30 (d, *J* = 6.2 Hz, 3H; CH_3). ^{13}C NMR (75.5 MHz, DMSO-d_6): 174.09, 169.72, 133.51, 131.63, 131.14, 130.89, 128.79, 128.43, 128.23, 127.84, 127.27, 127.08, 126.07, 125.99, 125.56, 124.82, 124.76, 123.97, 74.02, 72.32, 71.43, 64.17, 48.46, 19.52. HRMS-FAB (*m*/*z*): $[M + Na]^+$ Calcd. for $C_{27}H_{30}N_2O_8Na$: 533.5336; Found: 533.5349.

***N*-D-Heptagluconyl-*N′*-1-pyrenemethyl-L-alaninamide (6c):** ^{1}H NMR (300 MHz, DMSO-d_6): 8.31 (s, 1H; NH), 8.24 (d, *J* = 7.20 Hz, 2H; ArH), 8.19 (m, 1H; ArH), 8.09 (d, *J* = 3.20 Hz, 4H; ArH), 8.02 (s, 1H; NH), 7.92 (d, *J* = 4.00 Hz, 2H; ArH), 5.58 (d, *J* = 3.5 Hz, 1H; CH), 5.03 (d, *J* = 4.5 Hz, 2H; CH_2), 4.70 (d, *J* = 3.71 Hz, 1H; CH), 4.65 (m, 1H; CH), 4.51 (m, 1H; CH), 4.32 (m, 1H; CH), 4.01 (dt, 1H, CH), 3.81 (m, 1H; CH), 3.50 (d, *J* = 6.37 Hz, 1H; CH_2), 1.33 (d, *J* = 6.2 Hz, 3H; CH_3). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 174.09, 169.72, 133.51, 131.63, 131.14, 130.89, 128.79, 128.43, 128.23, 127.84, 127.27, 127.08, 126.07, 125.99, 125.56, 124.82, 124.76, 123.97, 74.02, 72.32, 71.43, 64.17, 48.46, 18.74. HRMS-FAB (*m*/*z*): $[M + Na]^+$ Calcd. for $C_{27}H_{30}N_2O_8Na$: 533.5336;Found: 533.5349.

***N*-D-Heptagluconyl-*N′*-1-pyrenemethyl-β-alaninamide(6d):** ^{1}H NMR (300 MHz, DMSO-d_6): 8.65 (s, 1H; NH), 8.38 (d, *J* = 7.20 Hz, 2H; ArH), 8.28 (m, 1H; ArH), 8.11 (d, *J* = 3.20 Hz, 4H; ArH), 7.8 (s, 1H; NH), 5.69 (d, 1H, *J* = 2.3 Hz; CH), 5.06 (d, *J* = 5.4 Hz, 2H; CH_2), 4.58 (d, *J* = 3.7 Hz; CH), 4.48 (d, *J* = 5.87 Hz; CH), 4.38 (t, *J* = 2.87 Hz, 1H; CH), 4.03 (m, 1H; CH), 3.96 (m, 1H; CH), 3.62 (m, 1H; CH), 3.35 (d, *J* = 3.2 Hz, 2H; CH_2), 2.43 (t, *J* = 7.2 Hz, 2H; CH_2), 2.41 (t, *J* = 7.2 Hz, 2H; CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.56, 170.82, 133.13, 131.10, 130.63, 130.41, 128.38, 127.71, 172.34, 126.97, 126.58, 125.50, 125.09, 124.24, 123.50, 73.79, 72.60, 71.82, 70.43, 63.68, 35.48, 35.39. HRMS-FAB (*m*/*z*): $[M + Na]^+$ Calcd. for $C_{27}H_{30}N_2O_8Na$: 533.5336; Found: 533.5349.

FTIR Spectra of hydrogelators in their solid amorphous and xerogel states.

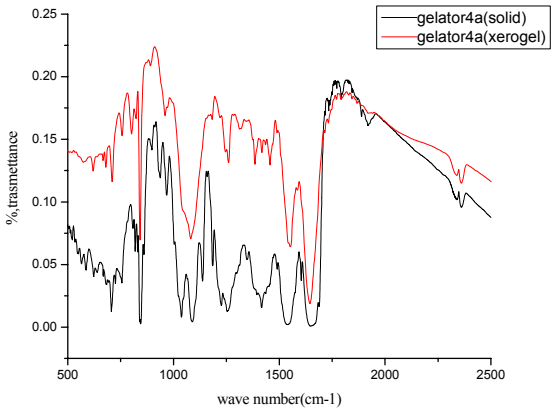


Figure **S1**

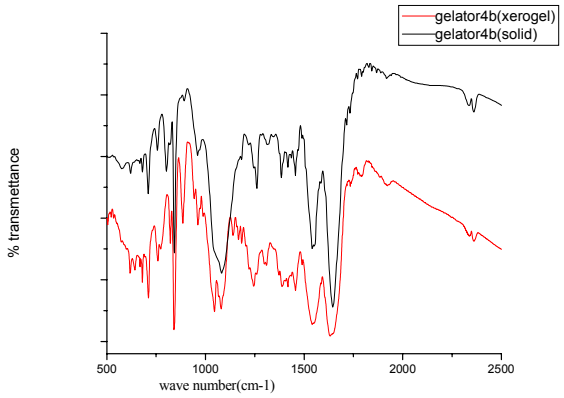


Figure **S2**

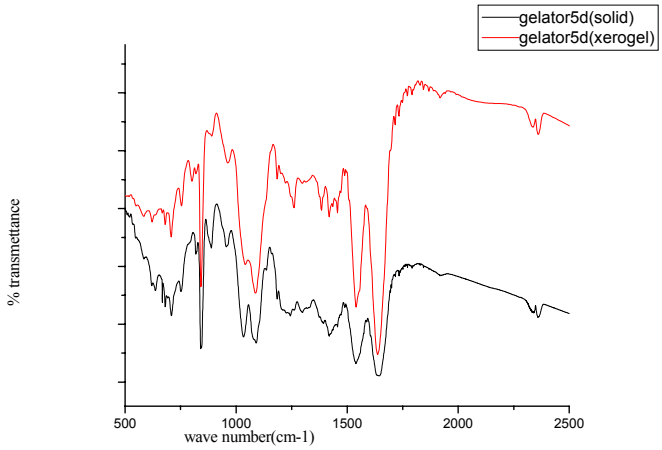


Figure **S3**

Fluorescence spectra of hydrogelators

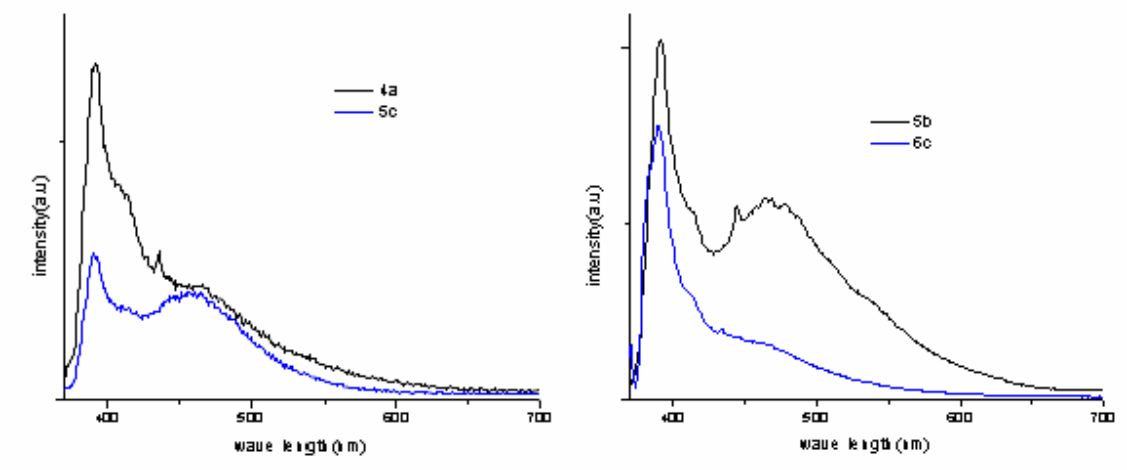


Figure **S4**: Fluorescence spectra (λ_{ex} = 380 nm) of hydrogelators at their gel states.

(A) (B)

Figure **S5**: Hydrogel of gelator **4b** in (A) the absence and (B) in the presence of insulin (5 μg).

Measurement of fluorescence spectra of insulin-containing gelators:

Gelator **4b** (3mg) or **5d** (1.4 mg) was dissolved in distilled water (2 ml) upon heating at 100 °C. The solution was transferred immediately to the fluorescence cell containing different doses of insulin (1–5 μg) and then maintained at room temperature for 10 min to complete the gelation process. Finally, the emission spectra were recorded after exciting the sample at λ_{max} 370 nm.

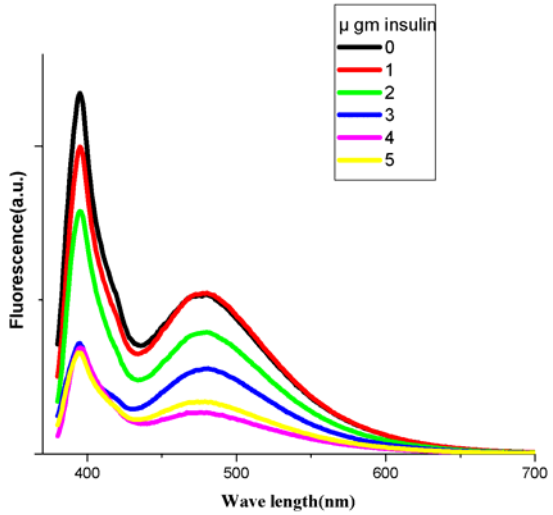


Figure **S6:** Emission spectra of gelator **5d**(0.05 % w/w) in the presence of insulin at various concentrations (excitation λ_{max} = 370 nm).