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# Peptide based hydrogels for cancer drug release: Modulation of stiffness, drug release and proteolytic stability of hydrogels by incorporating D-amino acid residue(s)

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## Experimental Section

**Materials and methods:** (L)- and (D)-Phenylalanine were purchased from Sisco Research Laboratory, India. HOBt, sodium dihydrogen phosphate, and disodium hydrogen phosphate were purchased from Merck. DCC, NaOH, MeOH, silica gel (100–200 mesh), $Et_2O$, petroleum ether, ethyl acetate, and DMF were purchased from SRL (India). Dulbecco Modified Eagle Medium (DMEM), Kanamycin sulfate, trypsin –EDTA, potassium chloride, sodium chloride, fetal bovine serum and 3-(4, 5-dimethyl thiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were purchased from Sigma-Aldrich. 2-[4-(2-Hydroxyethyl)piperazin-1-yl] ethanesulfonic acid (HEPES) was purchased from Himedia. Sodium bicarbonate and penicillin-streptomycin were purchased from Merck and Invitrogen respectively. Breast cancer cell line (MCF-7 cell line) was brought from NCCS, Pune (India) and cultured in dulbecco modified eagle medium (DMEM) containing 10% fetal bovine serum at 37 °C and 5% carbon dioxide atmosphere in our lab. The water used in all experiments was of Millipore MilliQ grade.

## Synthesis of gelator peptides

All tripeptides were synthesized by conventional solution phase method by using racemization free fragment condensation strategy. Boc group was used for the N-terminal protection and the C-terminus was protected as a methyl ester. Coupling was mediated by N, N-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole monohydrate ($HOBt.H_2O$). C-terminal methyl group was de-protected by using aqueous sodium hydroxide in methanol. The final compounds were fully characterized by $^1$H-NMR spectroscopy, $^{13}$C NMR spectroscopy and high resolution mass spectrometry (Fig. S1-S24).

Synthesis of the tripeptide **P1**:

**Synthesis of Boc-(L)Phe-OH:** 1.65 g (10 mmol) of L-Phenylalanine (L-Phe) was taken in a round bottomed flask. Then 10 mL 1(N) NaOH, 10 mL water and 20 mL1,4-dioxane were added to it and cooled to $0^{o}$ C. 2.20 g (10.1 mmol) di-tert-butyl dicarbonate (Boc anhydride) was added to the reaction mixture and stirred for 10 hours at room temperature. Then volume of the solution was reduced to one third in vacuum. The resulting mixture was acidified with saturated $KHSO_4$ solution and the aqueous layer was extracted with ethyl acetate (3 × 40 mL). The ethyl acetate extract was dried over anhydrous sodium sulfate and evaporated in vacuum to obtain the white powdered product.

Yield: 2.387 g (9.04 mmol, 90.36 %).

**Synthesis of Boc-(L)Phe-(L)Phe-OMe:** 2.387 g (9.04 mmol) of Boc-(L)Phe-OH was dissolved in 12 mL dry N, N-dimethyl formamide (DMF) and it was cooled in an ice bath. H-(L)Phe-OMe was obtained by neutralization with saturated $Na_2CO_3$ from its hydrochloride salt and subsequent extraction with ethyl acetate. The ethyl acetate solution was then concentrated to 10 mL and added to the DMF solution followed by 1.38 g (9.04 mmol) of $HOBt.H_2O$ and 1.95 g (9.5 mmol) of N, N-dicylohexylcarbodiimide (DCC). The reaction mixture was allowed to come at room temperature and stirred for 24 hours. After 24 hrs reaction mixture was diluted with ethyl acetate and filtered to separate N, N-dicyclohexyl urea (DCU). The ethyl acetate layer was washed with 1(N) HCl (3 × 30 mL), brine (2 × 30 mL), saturated sodium carbonate solution (2 × 30 mL) and brine (2 × 30 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to obtain the yellowish product. The product was purified through silica gel column chromatography using pet ether/ethyl acetate (8:1) as eluent to obtain the pure white product.

Yield: 2.71 g (6.38 mmol, 70.63 %,).

$^{1}$H NMR (500 MHz, $CDCl_3$) δ: 1.42 (9H, s, $CH_3$ of Boc), 2.95-3.13 (4H, m, $\beta$-$CH_2$ of Phe), 3.71 (3H, s, ester -$OCH_3$), 4.40 (1H, brs, $\alpha$-CH of Phe), 4.84-4.89 ( 1H, m, $\alpha$-CH of Phe), 4.98 (1H, brs, NH), 6.44-6.45 ( 1H, d, J= 8 Hz, NH), 6.97 (2H, d, J= 6.5 Hz, aromatic CH of Phe), 7.19-7.35 (8H, m, aromatic CH of Phe) $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 28.37, 38.06, 38.53, 52.36, 53.22, 127.09, 127.28, 128.74, 128.80, 129.30, 129.48, 135.72, 136.77, 171.00. HRMS (m/z): Calculated for $C_{24}H_{30}N_2O_5$: 426.215, Found: 449.3081. $(M+Na)^+$.

**Synthesis of Boc-(L)Phe-(L)Phe-OH :** 2.7 g (6.28 mmol) of Boc-(L)Phe-(L)Phe-OMe was taken in a round bottomed flask and dissolved in 50 mL of methanol. 16 mL of 1(N) NaOH was added to it and kept under stirring condition for 6 hours. The progress of hydrolysis was monitored by thin layer chromatography (TLC). After the completion of the reaction, as indicated by TLC, the methanol was removed in vacuum. The aqueous part was then taken in 50 mL water and washed with diethyl ether (2 × 30 mL). The remaining solution was acidified with 1(N) HCl and extracted with ethyl acetate (3 × 40 mL). The ethyl acetate extract was dried over anhydrous sodium sulfate and evaporated in vacuum to obtain a white powdered product.

Yield: 2.5 g (6.07 mmol, 96.66 %).

$^{1}$H NMR (500 MHz, $(CD_3)_2SO$) δ: 1.28 (9H, s, $CH_3$ of Boc), 2.64-3.10 (4H, m, $\beta$-$CH_2$ of Phe), 4.15 (1H, m, $\alpha$-CH of Phe), 4.46-4.49 (1H, m, $\alpha$-CH of Phe), 6.86-6.87 (1H, d, J= 9Hz, NH), 7.06-7.07 (1H, d, J= 8Hz, NH), 7.17-7.29 (15H, m, aromatic CH of Phe), 12.76 (1H, brs, -COOH). $^{13}$C NMR (125 MHz, $(CD_3)_2SO$) δ: 24.40, 25.28, 27.72, 28.06, 28.10,33.29, 36.43, 36.78, 37.40, 53.29, 55.07, 55.62, 78.00, 126.08, 126.23, 126.38, 127.91, 128.06128.11, 128.31, 129.03, 129.10, 129.16, 129.78, 137.31,138.03, 155.02, 155.36, 171.53, 172.67, 173.50. HRMS (m/z): Calculated for $C_{23}H_{28}N_2O_5$: 412.479, Found: 413.387 $(M+H)^+$, 435.377 $(M+Na)^+$, 451.3665 $(M+K)^+$.

**Synthesis of Boc-(L)Phe-(L)Phe-(L)Phe-OMe:** 2.06 g (5.0 mmol) of Boc-(L)Phe-(L)Phe-OH was dissolved in 8 mL dry N, N-dimethylformamide (DMF) and it was cooled in an ice bath. H-(L)Phe-OMe was obtained by neutralization with saturated $Na_2CO_3$ from its hydrochloride salt and subsequent extraction with ethyl acetate. The ethyl acetate solution was then concentrated to 8 ml and added to the DMF solution followed by 0.77 g (5.03 mmol) of HOBt.$H_2O$ and 1.09 g (5.3 mmol) of N, N-dicylohexylcarbodiimide (DCC). The reaction mixture was allowed to come at room temperature and stirred for 24 hours. The reaction mixture was diluted with ethyl acetate and filtered to separate N, N-dicyclohexyl urea (DCU). The ethyl acetate layer was washed with 1(N) HCl (3 × 30 mL), brine (2 × 30 mL), saturated sodium carbonate solution (2 × 30 mL) and brine (2 × 30 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to obtain the yellowish product. The product was purified through silica gel column chromatography using pet ether/ethyl acetate (5:1) as eluent to obtain the pure white product.

Yield: 2.05 g (3.37 mmol, 67.40 %,).

$^1$H NMR (400 MHz, $CDCl_3$) δ: 1.38 (9H, s, $CH_3$ of Boc), 2.92-3.08 (6H, m, $\beta$-$CH_2$ of Phe), 3.65 (3H, ester -$OCH_3$), 4.25-4.33 (1H, m, $\alpha$-CH of Phe), 4.62-4.65(1H, m, $\alpha$-CH of Phe), 4.69-4.75 (1H, m, $\alpha$-CH of Phe), 4.98 (1H, d, J= 8 Hz, NH), 6.45 (1H,d,J= 6.4 Hz, NH), 6.52 (1H, d, J= 7.6 Hz, NH), 6.99-7.29 (15H, m, aromatic CH of Phe) .$^{13}$C NMR (125 MHz, $CDCl_3$) δ: 28.39, 29.85, 38.00, 52.42, 53.69, 54.48, 127.22, 127.29, 128.76, 128.82, 128.92, 129.32, 129.44, 135.90, 136.37,136.57, 170.07, 171.20, 171.37. HRMS (m/z): Calculated for $C_{33}H_{39}N_3O_6$: 573.284, Found: 574.4792 $(M+H)^+$ , 596.4573 $(M+Na)^+$.

**Synthesis of Boc-(L)Phe-(L)Phe-(L)Phe-OH (P1):** 2.05 g (3.37 mmol) of Boc-(L)Phe-(L)Phe-(L)Phe-OMe was taken in a round bottomed flask and dissolved in 50 mL methanol. 12 mL of 1(N) NaOH was added to it and then kept under stirring for 6 hours. The progress

of hydrolysis was monitored by thin layer chromatography (TLC). After the completion of the reaction, as indicated by TLC, the methanol was removed in vacuum. The aqueous part was then taken in 50 mL water and washed with diethyl ether (2 × 30 mL). The remaining solution was acidified with 1(N) HCl and extracted with ethyl acetate (3 × 40 mL). The ethyl acetate extract was dried over anhydrous sodium sulfate and evaporated in vacuum to obtain a white powdered product.

Yield: 1.71 g (3.07 mmol, 91.09 %).

$^{1}$H NMR (400 MHz, $(CD_3)_2SO$) δ: 1.26 (9H, s, $CH_3$ of Boc), 2.49-3.10 (6H, m, $\beta$-$CH_2$ of Phe), 4.07-4.11 (1H, m, $\alpha$-CH of Phe), 4.43-4.48 (1H, m, $\alpha$-CH of Phe), 4.57-4.6 (1H, m, $\alpha$-CH of Phe), 6.85 (1H, d, J= 7 Hz, NH), 7.05-7.28 (15H, m, aromatic CH of Phe), 7.89-8.21 (1H, m, NH), 8.36(1H, m, NH), 12.52 (1H, brs, --COOH).$^{13}$C NMR (100 MHz, $(CD_3)_2SO$) δ: 24.39, 25.27, 27.65, 28.04, 33.28, 36.68, 53.26, 53.41, 53.54, 55.33, 55.71, 77.90, 78.01, 125.96, 126.01, 126.15, 126.36, 127.77, 127.89, 128.13, 129.02, 129.18, 129.23, 129.29, 137.30, 137.34, 137.41, 137.61, 138.04, 154.93, 170.80, 171.00, 171.15, 172.56, 172.72. HRMS (m/z): Calculated for $C_{32}H_{37}N_3O_6$: 559.268, Found: 582.1097 $(M+Na)^+$, 598.1666 $(M+K)^+$, Specific optical rotation: (-) 6.94±0.139.

**Synthesis of tripeptide P2:**

**Synthesis of Boc-(D)Phe-OH:**1.65 g (10 mmol) of (D)-Phenylalanine (D-Phe) was taken in a round bottomed flask. Then 10 mL 1(N) NaOH, 10 mL water and 20 mL 1, 4-dioxane were added to it and cooled to $0^o$ C. 2.20 g (10.1 mmol) di-tert-butyl dicarbonate (Boc anhydride) was added to the reaction mixture and it was stirred for 10 hours at room temperature. Then volume of the solution was reduced to one third in vacuum. The resulting mixture was acidified with saturated $KHSO_4$ solution and the aqueous layer was extracted with ethyl

acetate (3 × 40 mL). The ethyl acetate extract was dried over anhydrous sodium sulfate and evaporated in vacuum to obtain the white powdered product.

Yield: 2.38 g (9.05 mmol, 90.36 %).

**Synthesis of Boc-(D)Phe-(L)Phe-OMe:** 2.38 g (9.05 mmol) of Boc-(D)Phe-OH was dissolved in 12mL dry N, N-dimethylformamide (DMF) and it was cooled in an ice bath. H-(L)Phe-OMe was obtained by neutralization with saturated $Na_2CO_3$ from its hydrochloride salt and subsequent extraction with ethyl acetate. The ethyl acetate solution was then concentrated to 10 mL and added to the DMF solution followed by 1.38 g (9.04 mmol) of HOBt.$H_2O$ and 1.95 g (9.5 mmol) of N, N-dicylohexylcarbodiimide (DCC). The reaction mixture was allowed to come at room temperature and stirred for 24 hours. The reaction mixture was diluted with ethyl acetate and filtered to separate N, N- dicyclohexyl urea (DCU). Then the ethyl acetate layer was washed with 1(N) HCl (3 × 30 mL), brine (2 × 30 mL), saturated sodium carbonate solution (2 × 30 mL) and brine (2 × 30 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to obtain the yellowish product. The product was purified through silica gel column chromatography using pet ether/ethyl acetate (8:1) as eluent to obtain the pure white product.

Yield: 2.72 g (6.4 mmol, 70.7 %).

$^1$H NMR (400 MHz, $CDCl_3$) δ: 1.38 (9H, s, $CH_3$ of Boc), 2.94-3.06 (4H, m, $\beta$-$CH_2$ of Phe), 3.67 (3H, s, ester -$OCH_3$), 4.82-4.84 (2H, m, $\alpha$-CH of Phe), 6.39 (1H, brs, NH), 6.91-6.93 (1H, m, NH) 7.15-7.31 (10H, m, aromatic CH of Phe) $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 28.37, 38.01, 38.53, 52.36, 53.26, 127.10, 127.28, 128.74, 128.80, 129.30, 129.48, 135.72, 136.80, 171.00, 171.65. HRMS (m/z): Calculated for $C_{24}H_{30}N_2O_5$: 426.215, Found: 449.3349 $(M+Na)^+$.

**Synthesis of Boc-(D)Phe-(L)Phe-OH:** 2.72 g (6.4 mmol) of Boc-(D)Phe-(L)Phe-OMe was taken in a round bottomed flask and dissolved in 50 mL methanol. 16 mL of 1(N) NaOH was added to it and kept under stirring for 6 hours. The progress of hydrolysis was monitored by thin layer chromatography (TLC). After the completion of the reaction, as indicated by TLC, the methanol was removed in vacuum. The aqueous part was then taken in 50 mL water and washed with diethyl ether (2 × 30 mL). The remaining solution was acidified with 1(N) HCl and extracted with with ethyl acetate (3 × 40 mL). The ethyl acetate extract was dried over anhydrous sodium sulfate and evaporated in vacuum to obtain a white powdered product.

Yield: 2.5 g (6.07 mmol, 96.66 %).

$^{1}$H NMR (400 MHz, $(CD_3)_2SO$) δ: 1.32 (9H, s, $CH_3$ of Boc) 2.50-3.10 (4H, m, $\beta$-$CH_2$ of Phe), 4.14-4.19 (1H, m, $\alpha$-CH of Phe), 4.45-4.49 (1H, m, $\alpha$-CH of Phe), 4.45-4.49 (1H, m, $\alpha$-CH of Phe), 6.85-6.87 (1H, d, J= 7.6 Hz, NH), 7.16-7.29 (11H, m, aromatic CH of Phe, NH), 15.76 (1H, brs, -COOH). $^{13}$C NMR (100 MHz, $(CD_3)_2SO$) δ: 20.99, 24.41, 25.29, 27.71, 28.07, 33.30, 36.78, 37.03, 37.43, 53.29, 55.62, 77.90, 78.01, 126.09, 126.40, 127.84, 127.92, 128.13, 129.12, 129.16, 137.29, 138.02, 155.23, 171.53, 172.68. HRMS (m/z): Calculated for $C_{23}H_{28}N_2O_5$: 412.200,Found: 413.3875 $(M+H)^+$, 435.3773 $(M+Na)^+$, 451.3665 $(M+K)^+$.

**Synthesis of Boc-(D)Phe-(L)Phe-(L)Phe-OMe:** 2.5 g (6.0 mmol) of Boc-(D)Phe-(L)Phe-OH was dissolved in 8 mL dry N, N-dimethylformamide (DMF) and cooled in an ice bath. H-(L)Phe-OMe was obtained by neutralization with saturated $Na_2CO_3$ from its hydrochloride salt and subsequent extraction with ethyl acetate. The ethyl acetate solution was then concentrated to 8 mL and added to the DMF solution followed by 0.77 g (5.03 mmol) of HOBt.$H_2O$ and 1.33 g (6.5 mmol) of N, N-dicylohexylcarbodiimide (DCC). The reaction mixture was allowed to come at room temperature and it was stirred for 24 hours. The reaction mixture was diluted with ethyl acetate and filtered to separate N, N- dicyclohexyl

urea (DCU).The ethyl acetate layer was washed with 1(N) HCl (3 × 30 mL), brine (2 × 30 mL), saturated sodium carbonate solution (2 × 30 mL) and brine (2 × 30 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to obtain the yellowish product. The product was purified through silica gel column chromatography using pet ether/ethyl acetate (5:1) as eluent to obtain the pure white product.

Yield: 2.05 g (3.5 mmol, 59 %,).

$^{1}$H NMR (400 MHz, $CDCl_3$) δ: 1.38 (9H, s, $CH_3$ of Boc), 2.78-3.09(6H, m, $\beta$-$CH_2$ of Phe), 3.64 (3H, ester -$OCH_3$), 4.21-4.23 (1H, m, $\alpha$-CH of Phe), 4.60-4.73 (2H, m, $\alpha$-CH of Phe), 5.05-5.07 (1H, d, J= 6.4 Hz, NH), 6.43 (1H, brs, NH), 6.56 (1H, brs, NH), 6.98-7.30 (15H, m, aromatic CH of Phe) . $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 28.39, 29.82, 38.58, 52.42, 53.69, 54.69, 127.22, 127.29, 128.79, 128.84, 128.92, 129.32, 129.44, 135.90, 136.37, 136.57, 170.43, 171.23, 171.37. HRMS (m/z): Calculated for $C_{33}H_{39}N_3O_6$: 573.284, Found: 574.4792 $(M+H)^+$, 596.4573$(M+Na)^+$.

**Synthesis of Boc-(D)Phe-(L)Phe-(L)Phe-OH (P2):** 2.05 g (3.37 mmol) of Boc-(D)Phe-(L)Phe-(L)Phe-OMe was taken in a round bottomed flask and dissolved in 50 mL methanol. 12 mL of 1(N) NaOH was added to it and kept under stirring for 6 hours. The progress of hydrolysis was monitored by thin layer chromatography (TLC). After the completion of the reaction, as indicated by TLC, the methanol was removed in vacuum. The aqueous part was then taken in 50 mL water and washed with diethyl ether (2 × 30 mL). The remaining solution was acidified with 1(N) HCl and extracted with ethyl acetate (3 × 40 mL). The ethyl acetate extract was dried over anhydrous sodium sulfate and evaporated in vacuum to obtain a white powdered product.

Yield: 1.69 g (3.07 mmol, 91.08 %).

$^1$H NMR (400 MHz, $(CD_3)_2SO$) δ: 1.26 (9H, s, $CH_3$ of Boc), 2.37-3.10 (6H, m, $\beta$-$CH_2$ of Phe), 4.11-4.62 (3H, m, $\alpha$-CH of Phe), 6.63-6.65 (1H, d, J= 6.8Hz, NH), 7.05-7.96 (15H, m, aromatic CH of Phe), 8.20-8.22 (1H, d, J=7.2 Hz, NH), 8.32-8.33 (1H, d, J=6.5 Hz, NH), 12.86 (1H, br, -COOH).13C NMR (100 MHz, $(CD_3)_2SO$) δ: 24.38, 25.26, 27063, 28.05, 33.28, 36.65, 37.45, 37.60, 55.33, 53.51, 55.32, 77.89, 109.67, 124.24, 125.95, 126.19, 126.36, 127.76, 127.86, 128.09, 128.16, 129.01, 129.09, 129.23, 129.30, 137.31, 137.60, 137.95, 137.98, 171.01, 171.16, 172.56. HRMS (m/z): Calculated for $C_{32}H_{37}N_3O_6$: 559.268, Found: 581.8284 $(M+Na)^+$, Specific optical rotation: (-) 8.20±0.112.

**Synthesis of tripeptide P3:**

**Synthesis of Boc-(L)Phe-OH:** It has been prepared maintaining previous procedure as mentioned during the synthesis of **P1**. Yield: 2.387 g (9.04 mmol, 90.36 %).

**Synthesis of Boc-(L)Phe-(D)Phe-OMe:** 2.387 g (9.04 mmol) of Boc-(L)Phe-OH was dissolved in 12mL dry N, N-dimethyl formamide (DMF) and cooled in an ice bath. H-(D)Phe-OMe was obtained by neutralization with saturated $Na_2CO_3$from its hydrochloride salt and subsequent extraction with ethyl acetate. The ethyl acetate solution was then concentrated to 10 mL and added to the DMF solution followed by 1.38 g (9.04 mmol) of HOBt.$H_2O$ and 1.95 g (9.5 mmol) of N, N-dicylohexylcarbodiimide (DCC). The reaction mixture was allowed to come at room temperature and stirred for 24 hours. The reaction mixture was diluted with ethyl acetate and filtered to separate N, N- dicyclohexyl urea (DCU). The ethyl acetate layer was washed with 1(N) HCl (3 × 30 mL), brine (2 × 30 mL), saturated sodium carbonate solution (2 × 30 mL) and brine (2 × 30 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to obtain the yellowish product. The product was purified through silica gel column chromatography using pet ether/ethyl acetate (8:1) as eluent to obtain the pure white product.

Yield: 2.71 g (6.38 mmol, 70.63 %,).

$^{1}$H NMR (400 MHz, $CDCl_3$) δ: 1.42 (9H, s, $CH_3$ of Boc), 2.95-3.13 (4H, $\beta$-$CH_2$ of Phe), 3.70 (3H, ester -$OCH_3$), 4.40 (1H, m, $\alpha$-CH Phe), 4.84-4.89 (1H, m, $\alpha$-CH Phe), 4.98 (1H, m, NH), 6.41-6.43 (1H, d, J= 7.6 Hz, NH), 6.96-6.98 (2H, d, J= 5 Hz, aromatic CH of Phe), 7.19-7.34 (8H, m, aromatic). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 28.37, 38.06, 38.53, 52.36, 53.21, 127.10, 127.28, 128.74, 128.80, 129.30, 129.48, 135.72, 136.78, 171.00, 171.65. HRMS (m/z): Calculated for $C_{24}H_{30}N_2O_5$: 426.215,Found: 449.3349 $(M+Na)^+$.

**Synthesis of Boc-(L)Phe-(D)Phe-OH:** 2.72 g (6.4 mmol) of Boc-(L)Phe-(D)Phe-OMe was taken in a round bottomed flask and dissolved in 50 mL methanol. 16 mL of 1(N) NaOH was added to it and kept under stirring for 6 hours. The progress of hydrolysis was monitored by thin layer chromatography (TLC). After the completion of the reaction, as indicated by TLC, the methanol was removed in vacuum. The aqueous part was then taken in 50 mL water and washed with diethyl ether (2 × 30 mL). The remaining solution was acidified with 1(N) HCl and extracted with with ethyl acetate (3 × 40 mL). The ethyl acetate extract was dried over anhydrous sodium sulfate and evaporated in vacuum to obtain a white powdered product.

Yield: 2.55 g (6.07 mmol, 96.66 %).

$^{1}$H NMR (300 MHz, $(CD_3)_2SO$) δ: 1.27 (9H, s, $CH_3$ of Boc), 2.67-3.10 (4H, $\beta$-$CH_2$ of Phe), 4.16-4.18 (1H, m, $\alpha$-CH of Phe), 4.46-4.49 (1H, m, $\alpha$-CH of Phe), 6.69-6.71 (1H, d, J= 8.8 Hz, NH), 7.16-7.29 (11H, m, aromatic CH of Phe, NH), 12.76 (1H, brs, -COOH). $^{13}$C NMR (75 MHz, $(CD_3)_2SO$) δ: 24.41, 25.29, 27.73, 28.08, 33.31, 36.79, 37.03, 37.42, 37.54, 47.49, 53.26, 55.29, 55.62, 77.89, 78.01, 126.02, 126.09, 126.42, 127.84, 127.92, 128.09, 128.13, 129.13, 129.20, 137.29, 137.36, 138.03, 155.01, 171.38, 171.56, 172.68, 172.76. HRMS (m/z): Calculated for $C_{23}H_{28}N_2O_5$: 412.200, Found: 435.3773 $(M+Na)^+$, 451.3665 $(M+K)^+$.

**Synthesis of Boc-(L)Phe-(D)Phe-(L)Phe-OMe:** 2.5 g (6.0 mmol) of Boc-(L)Phe-(D)Phe-OH was dissolved in 8 mL dry N, N-dimethylformamide (DMF) and cooled in an ice bath. H-(L)Phe-OMe was obtained by neutralization with saturated $Na_2CO_3$ from its hydrochloride salt and subsequent extraction with ethyl acetate. The ethyl acetate solution was then concentrated to 8 mL and added to the DMF solution followed by 0.77 g (5.03 mmol) of HOBt.$H_2O$ and 1.33 g (6.5 mmol) of N, N-dicylohexylcarbodiimide (DCC). The reaction mixture was allowed to come at room temperature and stirred for 24 hours. The reaction mixture was diluted with ethyl acetate and filtered to separate N, N-dicyclohexyl urea (DCU).The ethyl acetate layer was washed with 1(N) HCl (3 × 30 mL), brine (2 × 30 mL), saturated sodium carbonate solution (2 × 30 mL) and brine (2 × 30 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to obtain the yellowish product. The product was purified through silica gel column chromatography using pet ether/ethyl acetate (5:1) as eluent to obtain the pure white product.

Yield: 2.05 g (3.5 mmol, 59 %,).

$^1$H NMR (400 MHz, $CDCl_3$) δ: 1.37 (9H, s, $CH_3$ of Boc), 2.90-3.07(6H, m, $\beta$-$CH_2$ of Phe), 3.66 (3H, ester -$OCH_3$), 4.30 (1H, brs, $\alpha$-CH of Phe), 4.51-4.56 (1H, m, $\alpha$-CH of Phe), 4.68-4.72 (1H, m, $\alpha$-CH of Phe) 4.81 (1H, brs, NH), 6.18 (1H, brs, NH), 6.41-6.43 (1H, d, J= 7 Hz, NH), 7.00-7.29 (15H, m, aromatic) . $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 28.39, 29.85, 38.85, 52.42, 53.69, 54.69, 127.22, 127.26, 128.79, 128.82, 128.92, 129.32, 129.44, 135.90, 136.37, 136.57, 170.44, 171.20, 171.37. HRMS (m/z): Calculated for $C_{33}H_{39}N_2O_6$: 462.3094, Found: 596.4573 $(M+Na)^+$, 612.4429 $(M+K)^+$.

**Synthesis of Boc-(L)Phe-(D)Phe-(L)Phe-OH (P3):** 2.05g (3.37 mmol) of Boc-(L)Phe-(D)Phe-(L)Phe-OMe was taken in a round bottomed flask and dissolved in 50 mL methanol. 12 mL of 1(N) NaOH was added to it and it was kept under stirring for 6 hours. The progress

of hydrolysis was monitored by thin layer chromatography (TLC). After the completion of the reaction, as indicated by TLC, the methanol was removed in vacuum. The aqueous part was then taken in 50 mL water and washed with diethyl ether (2 × 30 mL). The remaining solution was acidified with 1(N) HCl and extracted with ethyl acetate (3 × 40 mL). The ethyl acetate extract was dried over anhydrous sodium sulfate and evaporated in vacuum to obtain a white powdered product.

Yield: 1.69 g (3.07 mmol, 91.08 %).

$^{1}$H NMR (400 MHz, $(CD_3)_2SO$) δ: 1.25 (9H, s, $CH_3$ of Boc), 2.39-3.12 (6H, m, $\beta$-$CH_2$ of Phe), 4.45-4.48 (1H, m, $\alpha$-CH of Phe), 4.58-4.59 (2H, m, $\alpha$-CH of Phe), 6.99-7.39 (18H, m, aromatic CH of Phe, NH), 12.75 (1H, br, -COOH).$^{13}$C NMR (100 MHz, $(CD_3)_2SO$) δ: 22.31, 27.69, 28.08, 36.70, 36.78, 37.55, 37.80, 53.28, 53.43, 53.47, 53.56, 55.37, 55.78, 77.93, 78.04, 126.00, 126.06, 126.22, 126.36, 126.42, 127.81, 127.92, 128.14, 128.19, 129.01, 129.06, 129.15, 129.23, 129.28, 129.35, 137.30, 137.35, 137.46, 137.64, 137.70, 138.08, 154.98, 155.04, 169.19, 170.89, 171.09, 171.21, 172.60, 173.14. HRMS (m/z): Calculated for $C_{32}H_{37}N_3O_6$: 559.28, Found: 582.1486 $(M+Na)^+$, Specific optical rotation: (+) 7.50±0.530

**Synthesis of tripeptide P4:**

**Synthesis of Boc-(L)Phe-OH:** It has been prepared by maintaining procedure as mentioned in the synthesis of **P1**.

Yield: 2.387 g (9.04 mmol, 90.36 %).

**Synthesis of Boc-(L)Phe-(L)Phe-OMe:** It has been prepared and characterized by following procedure as mentioned in the synthesis of **P1**.

Yield: 2.78 g (6.3 mmol, 96.66 %).

**Synthesis of Boc-(L)Phe-(L)Phe-OH:** It has been prepared and characterized by following procedure as mentioned in the synthesis of **P1**.

Yield: 2.56 g (6.2 mmol, 95%)

**Synthesis of Boc-(L)Phe-(L)Phe-(D)Phe-OMe:** 2.06 g (5.0 mmol) of Boc-(L)Phe-(L)Phe-OH was dissolved in 8 mL dry N, N-dimethylformamide (DMF) and cooled in an ice bath. H-(D)Phe-OMe was obtained by neutralization with saturated $Na_2CO_3$ from its hydrochloride salt and subsequent extraction with ethyl acetate. The ethyl acetate solution was then concentrated to 8 mL and added to the DMF solution followed by 0.77 g (5.03 mmol) of HOBt.$H_2O$ and 1.09 g (5.3 mmol) of N, N-dicylohexylcarbodiimide (DCC). The reaction mixture was allowed to come at room temperature and stirred for 24 hours. The reaction mixture was diluted with ethyl acetate and filtered to separate N, N- dicyclohexyl urea (DCU).The ethyl acetate layer was washed with 1(N) HCl (3 × 30 mL), brine (2 × 30 mL), saturated sodium carbonate solution (2 × 30 mL) and brine (2 × 30 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to obtain the yellowish product. The product was purified through silica gel column chromatography using pet ether/ethyl acetate (5:1) as eluent to obtain the pure white product.

Yield: 2.05 g (3.37 mmol, 67.40 %,).

$^1$H NMR (400 MHz, $CDCl_3$) δ: 1.35 (9H, s, $CH_3$ of Boc), 2.89-3.09(6H, m, $\beta$-$CH_2$ of Phe), 4.24-4.26 (1H, m, $\alpha$-CH of Phe), 4.56-4.62(1H, m, $\alpha$-CH of Phe), 4.69-4.74 (1H, m, $\alpha$-CH of Phe), 4.80(1H, br, NH), 6.35(1H, br, NH), 6.45(1H, br, NH), 6.95-7.31 (15H, m, aromatic CH of Phe).$^{13}$C NMR (100 MHz, $CDCl_3$) δ: 28.39, 29.85, 38.85, 52.42, 53.69, 54.69, 127.22, 127.29, 128.76, 128.82, 128.92, 129.32, 129.44, 135.90, 136.37, 136.57, 170.4, 171.20, 171.37. HRMS (m/z): Calculated for $C_{33}H_{39}N_3O_6$:573.284, Found: 596.3392 $(M+Na)^+$, 612.3098 $(M+K)^+$.

**Synthesis of Boc-(L)Phe-(L)Phe-(D)Phe-OH (P4):** 2.05g (3.37 mmol) of Boc-(L)Phe-(D)Phe-(L)Phe-OMe was taken in a round bottomed flask and dissolved in 50 mL methanol. 12 mL of 1(N) NaOH was added to it and it was kept under stirring for 6 hours at. The progress of hydrolysis was monitored by thin layer chromatography (TLC). After the completion of the reaction, as indicated by TLC, the methanol was removed in vacuum. The aqueous part was then taken in 50 mL water and washed with diethyl ether (2 × 30 mL). The remaining solution was acidified with 1(N) HCl and extracted with ethyl acetate (3 × 40 mL). The ethyl acetate extract was dried over anhydrous sodium sulfate and evaporated in vacuum to obtain a white powdered product.

Yield: 1.69 g (3.07 mmol, 91.08 %).

$^{1}$H NMR (500 MHz, $(CD_3)_2SO$) δ: 1.25 (9H, s, $CH_3$ of Boc), 2.84-3.09(6H, m, $\beta$-$CH_2$of Phe), 4.14-4.58 (3H, m, $\alpha$-CH of Phe), 6.99-7.45 (16H, aromatic CH of Phe, NH), 13.09 (1H, br, -COOH).$^{13}$C NMR (125 MHz, $(CD_3)_2SO$) δ: 28.04, 36.68, 36.99, 37.12, 37.47, 38.03, 48.54, 53.20, 53.41, 55.34, 55.74, 77.88, 78.05, 109.69, 118.93, 124.18, 125.95, 126.01, 126.08, 126.14, 126.36, 126.41, 126.76, 127.77, 127.81, 127.88, 128.10, 129.03, 129.09, 129.17, 129.23, 137.44, 138.00, 142.77, 154.94, 170.56, 171.04, 172.72. HRMS (m/z): Calculated for $C_{32}H_{37}N_3O_6$: 559.268 Found: 581.8242 $(M+Na)^+$, Specific optical rotation: (-) 11.14±0.497

**Synthesis of tripeptide P5:**

**Synthesis of Boc-(D)Phe-OH:** Has been synthesized following the procedure mentioned in the synthesis of P2.

Yield: 2.387 g (9.04 mmol, 90.36 %).

**Synthesis of Boc-(D)Phe-(D)Phe-OMe:** 2.387 g (9.04 mmol) of Boc-(D)Phe-OH was dissolved in 12mL dry N, N-dimethylformamide (DMF) and cooled in an ice bath. H-(D)Phe-

OMe was obtained by neutralization with saturated $Na_2CO_3$from its hydrochloride salt and subsequent extraction with ethyl acetate. The ethyl acetate solution was then concentrated to 10 mL and added to the DMF solution followed by 1.38 g (9.04 mmol) of HOBt.$H_2O$ and 1.95 g (9.5 mmol) of N, N-dicylohexylcarbodiimide (DCC). The reaction mixture was allowed to come at room temperature and stirred for 24 hours. The reaction mixture was diluted with ethyl acetate and filtered to separate N, N- dicyclohexyl urea (DCU). The ethyl acetate layer was washed with 1(N) HCl (3 × 30 mL), brine (2 × 30 mL), saturated sodium carbonate solution (2 × 30 mL) and brine (2 × 30 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to obtain the yellowish product. The product was purified through silica gel column chromatography using pet ether/ethyl acetate (8:1) as eluent to obtain the pure white product.

Yield: 2.71 g (6.38 mmol, 70.63 %,).

$^1$H NMR (400 MHz, $CDCl_3$) δ: 1.42 (9H, s, $CH_3$ of Boc), 2.95-3.13 (4H, m, $\beta$-$CH_2$ of Phe), 3.67 (3H, s, ester –$OCH_3$), 4.40 (1H, m, $\alpha$-CH of Phe), 4.84-4.89 (1H, m, $\alpha$-CH of Phe), 4.98 (1H, m, NH), 6.42-6.44 (1H, d, J= 7.2 Hz, NH),6.96-7.35 (10H, m, aromatic CH of Phe). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 28.37, 38.06, 38.53, 52.31, 53.21, 127.18, 127.28, 128.74, 128.80, 129.30, 129.48, 135.72, 136.78, 171.00, 171.65. HRMS (m/z): Calculated for $C_{24}H_{30}N_2O_5$: 426.215,Found: 449.1143 $(M+Na)^+$, 465.0876 $(M+K)^+$.

**Synthesis of Boc-(D)Phe-(D)Phe-OH:** 2.71 g (6.38 mmol) of Boc-(D)Phe-(D)Phe-OMe was taken in a round bottomed flask and dissolved in 50 mL methanol. 16 mL of 1(N) NaOH was added to it and kept under stirring for 6 hours. The progress of hydrolysis was monitored by thin layer chromatography (TLC). After the completion of the reaction, as indicated by TLC, the methanol was removed in vacuum. The aqueous part was then taken in 50 mL water and washed with diethyl ether (2 × 30 mL). The remaining solution was acidified with 1(N) HCl

and extracted with with ethyl acetate (3 × 40 mL). The ethyl acetate extract was dried over anhydrous sodium sulfate and evaporated in vacuum to obtain a white powdered product.

Yield: 2.5 g (6.07 mmol, 96.66 %).

$^{1}$H NMR (400 MHz, $(CD_3)_2SO$) δ: 1.32 (9H, s, $CH_3$ of Boc), 2.50-3.34 (4H, m, $\beta$-$CH_2$ of Phe), 4.14-4.19 (1H, m, $\alpha$-CH of Phe), 4.47-4.49 (1H, m, $\alpha$-CH of Phe), 6.85-6.87 (1H, d, J=7.2 Hz, NH), 7.15-7.29 (11H, m, aromatic CH of Phe, 1 NH), 12.76 (1H, brs, -COOH). $^{13}$C NMR (100 MHz, $(CD_3)_2SO$) δ: 20.99, 24.41, 25.29, 27.71, 28.07, 33.30, 36.78, 37.03, 37.40, 53.26, 55.62, 77.88, 78.01, 126.06, 126.40, 127.84, 127.92, 128.13, 129.12, 129.16, 137.29, 138.03, 155.03, 171.57, 172.68. HRMS (m/z): Calculated for $C_{23}H_{28}N_2O_5$: 412.20, Found: 413.3875 $(M+H)^+$,435.3773 $(M+Na)^+$, 451.3665 $(M+K)^+$.

**Synthesis of Boc-(D)Phe-(D)Phe-(D)Phe-OMe:** 2.06 g (5.0 mmol) of Boc-(D)Phe-(D)Phe-OH was dissolved in 8 mL dry N, N-dimethylformamide (DMF) and cooled in an ice bath. H-(D)Phe-OMe was obtained by neutralization with saturated $Na_2CO_3$ from its hydrochloride salt and subsequent extraction with ethyl acetate. The ethyl acetate solution was then concentrated to 8 mL and added to the DMF solution followed by 0.77 g (5.03 mmol) of HOBt.$H_2O$ and 1.09 g (5.3 mmol) of N, N-dicylohexylcarbodiimide (DCC). The reaction mixture was allowed to come at room temperature and stirred for 24 hours. The reaction mixture was diluted with ethyl acetate and filtered to separate N, N- dicyclohexyl urea (DCU).The ethyl acetate layer was washed with 1(N) HCl (3 × 30 mL), brine (2 × 30 mL), saturated sodium carbonate solution (2 × 30 mL) and brine (2 × 30 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to obtain the yellowish product. The product was purified through silica gel column chromatography using pet ether/ethyl acetate (5:1) as eluent to obtain the pure white product.

Yield: 2.06 g (3.38 mmol, 67.44 %,).

$^{1}$H NMR (500 MHz, $CDCl_3$) δ: 1.37 (9H, s, $CH_3$ of Boc), 2.90-3.07 (6H, m, $\beta$-$CH_2$ of Phe), 3.66 (3H, s, ester –$OCH_3$), 4.30 (1H, m, $\alpha$-CH of Phe), 4.52-4.56 (1H, m, $\alpha$-CH of Phe), 4.67-4.71 (1H, m, $\alpha$-CH of Phe), 4.81 (1H, m, NH), 6.12 (1H, m, NH), 6.42-6.43 (1H, d, J= 7.0 Hz, NH), 7.00-7.29 (15H, m, aromatic CH of Phe).$^{13}$C NMR (125 MHz, $CDCl_3$) δ: 28.39, 29.85, 38.00, 52.42, 53.69, 54.48, 127.22, 127.29, 128.76, 128.82, 128.92, 129.32, 129.44, 135.90, 136.37, 136.57, 170.07, 171.20, 171.37. HRMS (m/z): Calculated for $C_{33}H_{37}N_3O_6$: 573.284, Found: 574.5050 $(M+H)^+$, 596.4967 $(M+Na)^+$, 612.4695 $(M+K)^+$.

**Synthesis of Boc-(D)Phe-(D)Phe-(D)Phe-OH (P5):** 2.06g (3.38 mmol) of Boc-(D)Phe -(D)Phe -(D)Phe-OMe was taken in a round bottomed flask and dissolved in 50 mL methanol. 12 mL of 1(N) NaOH was added to it and it was kept under stirring condition for 6 hours. The progress of hydrolysis was monitored by thin layer chromatography (TLC). After the completion of the reaction, as indicated by TLC, the methanol was removed in vacuum. The aqueous part was then taken in 50 mL water and washed with diethyl ether (2 × 30 mL). The remaining solution was acidified with 1(N) HCl and extracted with ethyl acetate (3 × 40 mL). The ethyl acetate extract was dried over anhydrous sodium sulfate and evaporated in vacuum to obtain a white powdered product.

Yield: 1.71 g (3.07 mmol, 91 %).

$^{1}$H NMR (400 MHz, $(CD_3)_2SO$) δ: 1.22 (9H, s, $CH_3$ of Boc), 2.4-3.1 (6H, m, $\beta$-$CH_2$ of Phe), 4.07-4.59 (3H, m, $\alpha$-CH of Phe), 6.63-7.26 (18H, m, aromatic CH of Phe, NH), 12.76 (1H, br, -COOH).$^{13}$C NMR (100 MHz, $(CD_3)_2SO$) δ: 22.31, 27.69, 28.08, 36.70, 36.78, 37.55, 37.80, 53.28, 53.43, 53.46, 53.57, 55.38, 55.77, 77.93, 78.04, 126.00, 126.06, 126.20, 126.36, 126.42,127.81, 127.92, 128.14, 128.19, 129.01, 129.06, 129.15, 129.23, 129.28, 129.35, 137.30, 137.35, 137.44, 137.66, 137.70, 138.08, 154.98, 155.04, 169.19, 170.89, 171.09,

171.21, 172.63, 173.14. HRMS (m/z): Calculated for $C32H_{37}N_3O_6$: 559.268, Found: 582.1097 $(M+Na)^+$, 598.1660 $(M+K)^+$, Specific optical rotetion: (+) 7.01±0.103.

**Synthesis of tripeptide P6**

**Synthesis of Boc-(L)Phe-OH:** It has been synthesized by following procedure as mentioned during the synthesis of **P1**, **P3** and **P4.**

Yield: 2.387 g (9.04 mmol, 90.36 %).

**Synthesis of Boc-(L)Phe-(D)Phe-OMe:** It has been synthesized and characterised following procedure as mentioned in the synthesis of **P3**.

Yield: 2.71 g (6.38 mmol, 70.63 %,).

**Synthesis of Boc-(L)Phe-(D)Phe-OH:** It has been synthesized and characterized following procedure as mentioned in the synthesis of **P3**.

Yield: 2.55 g (6.07 mmol, 96.66 %).

**Synthesis of Boc-(L)Phe-(D)Phe-(D)Phe-OMe:** 2.06 g (5.0 mmol) of Boc-(L)Phe-(D)Phe-OH was dissolved in 8 mL dry N, N-dimethylformamide (DMF) and cooled in an ice bath. H-(D)Phe-OMe was obtained by neutralization with saturated $Na_2CO_3$ from its hydrochloride salt and subsequent extraction with ethyl acetate. The ethyl acetate solution was then concentrated to 8 mL and added to the DMF solution followed by 0.77 g (5.03 mmol) of HOBt.$H_2O$ and 1.09 g (5.3 mmol) of N, N-dicylohexylcarbodiimide (DCC). The reaction mixture was allowed to come at room temperature and stirred for 24 hours. The reaction mixture was diluted with ethyl acetate and filtered to separate N, N-dicyclohexyl urea (DCU).The ethyl acetate layer was washed with 1(N) HCl (3 × 30 mL), brine (2 × 30 mL), saturated sodium carbonate solution (2 × 30 mL) and brine (2 × 30 mL). The organic layer

was dried over anhydrous sodium sulfate and evaporated to obtain the yellowish product. The product was purified through silica gel column chromatography using pet ether/ethyl acetate (6:1) as eluent to obtain the pure white product.

Yield: 3.43 gm (6.00 mmol, 98%)

$^{1}$H NMR (400 MHz, $CDCl_3$) δ: 1.36 (9H, s, $CH_3$ of Boc), 2.79-3.08 (6H, m, $\beta$ $CH_2$ of Phe), 3.65 (3H, s, eater –$OCH_3$), 4.20-4.25 (1H, m, $\alpha$-CH of Phe), 4.61-4.65 (1H, m, $\alpha$-CH of Phe), 4.69-4.73 (1H, m, $\alpha$-CH of Phe), 5.06-5.07 (1H, m, NH), 6.44 (1H, brs, NH), 6.57 (1H, brs, NH), 6.98-7.29 (15H, m, aromatic CH of Phe). $^{13}$C (100 MHz, $CDCl_3$) δ: 28.39, 29.85, 38.85, 52.42, 53.69, 54.69, 127.22, 127.26, 128.76, 128.82, 128.92, 129.32, 129.44, 135.90, 136.37, 136.57, 170.44, 171.20, 171.37. HRMS (m/z): Calculated for $C_{33}H_{39}N_3O_6$: 573.284, Found: 574.4792 $(M+H)^+$, 596.4573 $(M+Na)^+$, 612.4429 $(M+K)^+$.

**Synthesis of Boc-(L)Phe-(D)Phe-(D)Phe-OH (P6):** (Peptide 6 or P6): 2.06g (3.38 mmol) of Boc-(L)Phe-(D)Phe-(D)Phe-OMe was taken in a round bottomed flask and dissolved in 50 mL methanol. 12 mL of 1(N) NaOH was added to it and kept under stirring for 6 hours. The progress of hydrolysis was monitored by thin layer chromatography (TLC). After the completion of the reaction, as indicated by TLC, the methanol was removed in vacuum. The aqueous part was then taken in 50 mL water and washed with diethyl ether (2 × 30 mL). The remaining solution was acidified with 1(N) HCl and extracted with ethyl acetate (3 × 40 mL). The ethyl acetate extract was dried over anhydrous sodium sulfate and evaporated in vacuum to obtain a white powdered product.

Yield: 3 g (5.3 mmol, 87 %).

$^{1}$H NMR (500 MHz, $(CD_3)_2SO$) δ: 1.25 (9H, s, $CH_3$ of Boc), 2.55-3.07 (6H, m, $\beta$-$CH_2$ of Phe), 4.11-4.58 (3H, m, $\alpha$-CH of Phe), 6.59-6.62 (1H, m, NH), 7.03-7.39 (15H, aromatic CH

of Phe), 8.170-8.19 (1H, m, NH), 8.29 (1H, m, NH), 12.71 (1H, br, -COOH).$^{13}$C NMR (125 MHz, $(CD_3)_2SO$) δ: 27.67, 28.07, 36.66, 37.47, 37.63, 53.35, 53.53, 55.35, 77.91, 78.03, 109.55, 125.97, 126.03, 126.22, 126.40, 127.28, 127.79, 127.89, 128.16, 128.19, 129.03, 129.12, 129.20, 129.25, 129.33, 137.32, 137.45, 137.63, 137.98, 155.01, 171.06, 171.19, 172.59, 172.75 . HRMS (m/z): Calculated for $C_{32}H_{37}N_3O_6$: 559.268, Found: 582.1486 $(M+Na)^+$, Specific optical rotation: (+) 8.53±0.305.

**Synthesis of peptide P7:**

**Synthesis of Boc-(D)Phe-OH:** It has been synthesized by following procedure as mentioned during the synthesis of **P2** and **P5.**

**Synthesis of Boc-(D)Phe-(L)Phe-OMe:** It has been synthesized and characterised following procedure as mentioned in the synthesis of **P2**.

**Synthesis of Boc-(D)Phe-(L)Phe-OH:** It has been synthesized and characterized following procedure as mentioned in the synthesis of **P2**.

**Synthesis of Boc-(D)Phe-(L)Phe-(D)Phe-OMe:** 2.07 g (5.0 mmol) of Boc-(D)Phe-(L)Phe-OH was dissolved in 8 mL dry N, N-dimethylformamide (DMF) and cooled in an ice bath. H-(D)Phe-OMe was obtained by neutralization with saturated $Na_2CO_3$ from its hydrochloride salt and subsequent extraction with ethyl acetate. The ethyl acetate solution was then concentrated to 8 mL and added to the DMF solution followed by 0.77 g (5.03 mmol) of HOBt.$H_2O$ and 1.09 g (5.3 mmol) of N, N-dicylohexylcarbodiimide (DCC). The reaction mixture was allowed to come at room temperature and stirred for 24 hours. The reaction mixture was diluted with ethyl acetate and filtered to separate N, N-dicyclohexyl urea (DCU).The ethyl acetate layer was washed with 1(N) HCl (3 × 30 mL), brine (2 × 30 mL), saturated sodium carbonate solution (2 × 30 mL) and brine (2 × 30 mL). The organic layer

was dried over anhydrous sodium sulfate and evaporated to obtain the yellowish product. The product was purified through silica gel column chromatography using pet ether/ethyl acetate (7:1) as eluent to obtain the pure white product.

Yield: 3.44 gm (6.00 mmol, 98%)

$^{1}$H NMR (400 MHz, $CDCl_3$) δ: 1.37 (9H, s, $CH_3$ of Boc), 2.90-3.03 (6H, m, $\beta$-$CH_2$ of Phe), 3.62 (3H, s, ester –$OCH_3$), 4.23-4.25 (1H, m, $\alpha$-CH of Phe), 4.66-4.68 (1H, m, $\alpha$-CH of Phe), 4.75-4.77 (1H, m, $\alpha$-CH of Phe), 5.10-5.12 (1H, m, NH), 6.53 (2H, brs, NH), 6.93-7.29 (15H, m, aromatic CH of Phe). $^{13}$C (100 MHz, $CDCl_3$) δ: 28.31, 28.34, 37.88, 37.96, 38.45, 52.26, 52.29, 52.39, 53.26, 53.51, 53.65, 54.09, 56.28, 80.28, 127.06, 127.12, 127.15, 127.20, 128.63, 128.65, 128.71, 128.80, 129.28, 129.33, 129.36, 129.40, 129.49, 129.52, 135.93, 135.99, 136.35, 136.46, 136.69, 155.48, 169.78, 170.29, 171.30, 171.60, 171.65, 172.31. HRMS (m/z): Calculated for $C_{33}H_{39}N_3O_6$: 573.284, Found: 574.5050 $(M+H)^+$, 596.4977 $(M+Na)^+$, 612.4659 $(M+K)^+$.

**Synthesis of Boc-(D)Phe-(L)Phe-(D)Phe-OH (Peptide 7 or P7):** 3.4g (4.38 mmol) of Boc-(L)Phe-(D)Phe-(D)Phe-OMe was taken in a round bottomed flask and dissolved in 50 mL methanol. 12 mL of 1(N) NaOH was added to it and kept under stirring for 6 hours. The progress of hydrolysis was monitored by thin layer chromatography (TLC). After the completion of the reaction, as indicated by TLC, the methanol was removed in vacuum. The aqueous part was then taken in 50 mL water and washed with diethyl ether (2 × 30 mL). The remaining solution was acidified with 1(N) HCl and extracted with ethyl acetate (3 × 40 mL). The ethyl acetate extract was dried over anhydrous sodium sulfate and evaporated in vacuum to obtain a white powdered product.

Yield: 3 g (4 mmol, 92 %).

$^{1}$H NMR (500 MHz, $(CD_3)_2SO$) δ: 1.26 (9H, s, $CH_3$ Boc), 2.41-3.13 (6H, m, $\beta$-$CH_2$ of Phe), 4.14-4.60 (3H, m, $\alpha$-CH of Phe), 6.64-6.65 (1H, m, NH), 7.00-7.27 (15H, aromatic CH of Phe), 8.12-8.15 (H, m, NH), 8.17-8.45 (1H, m, NH), 12.76 (1H, br, -COOH).$^{13}$C NMR (125 MHz, $(CD_3)_2SO$) δ: 28.06, 36.67, 36.76, 37.00, 37.13, 37.48, 53.21, 53.45, 53.55, 55.35, 55.77, 77.88, 78.06, 125.96, 126.03, 126.10, 126.15, 126.32, 126.37, 126.43, 127.79, 127.83, 127.90, 127.98, 128.11, 128.98, 129.03, 129.11, 129.21, 129.25, 137.35, 137.43, 137.47, 137.69, 138.03, 154.95, 169.13, 170.57, 170.66, 171.06, 172.59, 172.75, 173.09. HRMS (m/z): Calculated for $C_{32}H_{37}N_3O_6$: 559.268, Found: 581.9066 $(M+Na)^+$, Specific optical rotation: (-) 7.50±0.420

**Synthesis of Boc-(D)Phe-OH:** It has been synthesized and characterized following procedure mentioned during the synthesis of **P5**.

**Synthesis of Boc-(D)Phe-(D)Phe-OMe:** It has been synthesized and characterised following procedure as mentioned in the synthesis of **P5**.

**Synthesis of Boc-(D)Phe-(D)Phe-OH:** It has been synthesized and characterized following procedure as mentioned in the synthesis of **P5**.

**Synthesis of Boc-(D)Phe-(D)Phe-(L)Phe-OMe:** 2.07 g (5.0 mmol) of Boc-(D)Phe-(D)Phe-OH was dissolved in 8 mL dry N, N-dimethylformamide (DMF) and cooled in an ice bath. H-(L)Phe-OMe was obtained by neutralization with saturated $Na_2CO_3$ from its hydrochloride salt and subsequent extraction with ethyl acetate. The ethyl acetate solution was then concentrated to 8 mL and added to the DMF solution followed by 0.77 g (5.03 mmol) of HOBt.$H_2O$ and 1.09 g (5.3 mmol) of N, N-dicylohexylcarbodiimide (DCC). The reaction mixture was allowed to come at room temperature and stirred for 24 hours. The reaction mixture was diluted with ethyl acetate and filtered to separate N, N-dicyclohexyl urea (DCU).The ethyl acetate layer was washed with 1(N) HCl (3 × 30 mL), brine (2 × 30 mL),

saturated sodium carbonate solution (2 × 30 mL) and brine (2 × 30 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to obtain the yellowish product. The product was purified through silica gel column chromatography using pet ether/ethyl acetate (7:1) as eluent to obtain the pure white product.

Yield: 3.44 gm (6.00 mmol, 98%)

$^{1}$H NMR (400 MHz, $CDCl_3$) δ: 1.36 (9H, s, $CH_3$ of Boc), 2.79-3.03 (6H, m, $\beta$-$CH_2$ of Phe), 3.62 (3H, s, ester –$OCH_3$), 4.22-4.24 (1H, m, $\alpha$-CH of Phe), 4.63-4.68 (1H, m, $\alpha$-CH of Phe), 4.73-4.78 (1H, m, $\alpha$-CH of Phe), 5.09-5.12 (1H, d, J= 7.2 Hz, NH), 6.55-6.57 (1H, brs, NH), 6.93-7.44 (16H, m, aromatic CH of Phe, NH). $^{13}$C (100 MHz, $CDCl_3$) δ: 28.35, 37.74, 37.86, 37.95, 38.41, 52.31, 52.44, 53.32, 53.57, 54.17, 56.36, 111.09, 117.72, 126.08, 126.79, 127.11, 127.18, 127.25, 128.55, 128.66, 128.76, 128.85, 129.29, 129.34, 129.36, 129.40, 129.49, 129.52, 135.90, 136.30, 136.40, 136.63, 155.54, 170.38, 171.43, 171.59, 171.65. HRMS (m/z): Calculated for $C_{33}H_{39}N_3O_6$: 573.284, Found: 574.4792 $(M+H)^+$, 596.4573 $(M+Na)^+$, 612.4429 $(M+K)^+$.

**Synthesis of Boc-(D)Phe-(D)Phe-(L)Phe-OH (Peptide 7 or P7):** 3.4g (4.38 mmol) of Boc-(L)Phe-(D)Phe-(D)Phe-OMe was taken in a round bottomed flask and dissolved in 50 mL methanol. 12 mL of 1(N) NaOH was added to it and kept under stirring for 6 hours. The progress of hydrolysis was monitored by thin layer chromatography (TLC). After the completion of the reaction, as indicated by TLC, the methanol was removed in vacuum. The aqueous part was then taken in 50 mL water and washed with diethyl ether (2 × 30 mL). The remaining solution was acidified with 1(N) HCl and extracted with ethyl acetate (3 × 40 mL). The ethyl acetate extract was dried over anhydrous sodium sulfate and evaporated in vacuum to obtain a white powdered product.

Yield: 3 g (4 mmol, 92 %).

$^{1}$H NMR (500 MHz, $(CD_3)_2SO$) δ: 1.26 (9H, s, $CH_3$ of Boc), 2.40-3.13 (6H, m, $\beta$-$CH_2$ of Phe), 4.10-4.60 (3H, m, $\alpha$-CH of Phe), 6.64 (1H, m, NH), 6.82-6.84 (1H, m, NH), 7.00-7.94 (17H, aromatic CH of Phe, 2 NH), 13.06 (1H, br, -COOH).$^{13}$C NMR (125 MHz, $(CD_3)_2SO$) δ: 27.68, 28.05, 36.68, 37.01, 37.14, 37.48, 38.05, 53.22, 53.43, 55.35, 55.77, 77.88, 78.06, 109.74, 118.94, 124.17, 125.97, 126.03, 126.11, 126.15, 126.38, 126.44, 126.71, 127.75, 127.79, 127.83, 127.90, 128.01, 128.12, 128.46, 129.05, 129.11, 129.20, 129.25, 129.53, 137.24, 137.34, 137.42, 137.47, 137.63, 138.03, 142.79, 154.95, 170.58, 170.67, 171.07, 172.60, 172.76. HRMS (m/z): Calculated for $C_{32}H_{37}N_3O_6$: 559.268, Found: 581.9195 $(M+Na)^+$,597.8782 $(M+K)^+$. Specific optical rotation: (-) 11.10±0.507.

**Gelation Study with P1, P2, P3, P4, P5 and P6:** All peptides were taken in same amount in equal volume of freshly prepared phosphate buffer solution at pH 7.46 and they were strongly heated to dissolve followed by cooling. Then they were kept at room temperature. It was seen surprisingly that, **P1** and **P2** and their respective enantiomers **P5** and **P6** formed gel instantaneously, **P3** and its enantiomer **P7** took 12 hours and **P4** and its enentiomer **P8** did not form gel at all rather they formed a viscous aggregate after 24 hours. Minimum gelation concentration (MGC) was measured and found to be 850, 926, 1020 $\mu$M for **P1**, **P2**, **P3**, 853, 910 and 1000 $\mu$M for **P5**, **P6** and **P7** respectively. Gel melting temperature ($T_{gel}$) was measured for each hydrogel at different concentrations (Fig. S25) using a digital water bath. It is clear from the Fig. S25 that $T_{gel}$ curve for different gelator is different and at higher concentration where a plateau has been found for all hydrogel, the $T_{gel}$ value is maximum for hydrogel obtained from **P1** and minimum for **P3** in the series **P1**, **P2** and **P3**. The enantiomeric pair that is **P1/ P5**; **P2/ P6** and **P3/ P7** show almost same trends.

**Drug release experiment:** In 1ml of hydrogels of **P1**, **P2**, **P5** and **P6** of same concentration, same amount of Doxorubicin hydrochloride was loaded (concentration measured by UV-Visible spectrophotometer). 1 ml of phosphate buffer solution was placed over each gel. At

regular time interval the concentration of the released drug was measured using UV-Visible spectrophotometer. The experiment was repeated three times to get an average release profile for each gel.

**Proteolytic stability of peptides:** 1 mg of each samples were incubated in a solution of a proteolytic enzyme proneinase K in 30 mM HEPES buffer solution at 37 °C for 52 hours and time to time assay of the peptides were done by high resolution mass spectroscopy (Fig. S37-S40). In this case **P1** is proteolytically cleavable, so it has been used as a control peptide. The proteolysis curve has been shown in Fig. S36.

**Cytotoxicity Study:** Cancer cells (Breast cancer cell line, MCF-7) proliferation study were performed by using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction into purple formazon. MCF-7 cells were seeded at a density of 10,000 cells per well in 96-well plate for twenty four hours before treatment of hydrogelator. After that, DMEM medium containing different concentrations (600 $\mu$M, 300 $\mu$M, 150 $\mu$M, 75 $\mu$M, 37.5 $\mu$M, 18.75 $\mu$M, 9.375 $\mu$M and 4.68 $\mu$M) of hydrogelator were added into the cells and kept for twenty four hours. Next, MTT solution was added and kept it for four hours in incubation 37 °C. Finally, cell viability was checked by absorbance study at 550 nm.

Percent of cell viability = [A550 (treated cells)-background]/[A550(untreated cells)-background] × 100.

**Cellular morphology study**: Cellular morphologies of MCF-7 cells after the hydrogelator treatment were checked by following method. Cells were seeded on confocal disk at a density of 5000 per disk for twenty four hours before the hydrogelator treatment. Then DMEM medium, containing the different concentrations (600 $\mu$M, 37.5 $\mu$M and 4.68 $\mu$M) of the compound was added and kept for twenty four hour. One disk was kept for control study.

Next, cellular morphologies were observed by inverted microscope (Olympus IX83 fluorescence microscope, at 40 X objective) in DIC mode.

**Anticancer activity of Doxorubicin loaded P6 gel:** So far we have found **P6** as the most useful gelator for release of the drug Doxorubicin. Comparative cell viability study between gel loaded Doxorubicin and free Doxorubicin starting from 15 μM to 1.875 μM concentration of Doxorubicin has been performed over breast cancer cell line MCF-7. It has been found that gel loaded Doxorubicin shows higher cell killing ability than the free Doxorubicin at different concentrations (About 11% more cell killing ability at 15 μM) after 24 hours. Hence, it shows that gel loaded Doxorubicin has advantageous effect over free Doxorubicine (Fig. S42).

**Instrumentation:**

**Field emission scanning electron microscopic (FE-SEM) study:** Experiments with all samples were performed by placing a small portion of gel samples of each compound on a microscope cover glass. Then, these samples were dried first in air and then in vacuum and coated with platinum for 90 s at 10 kV voltages and 10 mA current. The average thickness of the coating layer of platinum was 3 to 4 nm. After that micrographs were taken by using a Jeol Scanning Microscope JSM-6700F.

**Wide Angle Powder X-ray diffraction study:** X-ray diffraction study of the xerogel was carried out by placing all the samples on a glass plate. Experiments were carried out by using an X-ray diffractometer (Bruker AXS, Model No. D8 Advance). The instrument was operated at a 40 kV voltages and 40 mA current using Ni-filtered $CuK_{\alpha}$ radiation and the instrument was calibrated with a standard $Al_2O_3$ (corundum) sample before use. For scan 5°–30°, the Lynx Eye super speed detector was used with scan speed 0.5 s and step size 0.02°.

**Small Angle X-Ray Scattering (SAXS):** SAXS Measurements were performed using a Bruker Nanostar instrument using $CuK_{\alpha}$ radiation and a Vantec 2000 detector. The sample-

to-detector distance was 1.07 m. The $q = 4\pi\sin\theta/\lambda$ (scattering angle $2\theta$) scale was calibrated using silver behenate. Samples were mounted in quartz capillaries.

**Circular dichroism (CD) study:** Circular dichroism spectrum was recorded by using a quartz cuvette of 1 mm path length in a Jasco J-815 spectropolarimeter.

**Rheology:** The rheology experiment was performed by using an AR 2000 advanced rheometer (TA Instruments) using cone-plate geometry in a Peltier plate.

**UV/Vis spectroscopy:** UV/Vis absorption spectra were recorded on a hewlett-packard (model 8453) UV/Vis spectrophotometer (varian carry 50.bio).

**FTIR spectroscopy:** The FTIR spectrum of the xerogel were recorded on a Shimadzu (Japan) FTIR spectrophotometer. In the solid-state FTIR studies, the powdered samples were mixed with KBr to prepare the thin films.

**Mass spectrometry:** Mass spectra were recorded on a Q-Tof microTM (Waters Corporation) mass spectrometer by positive mode electro spray ionization process.

## Figures

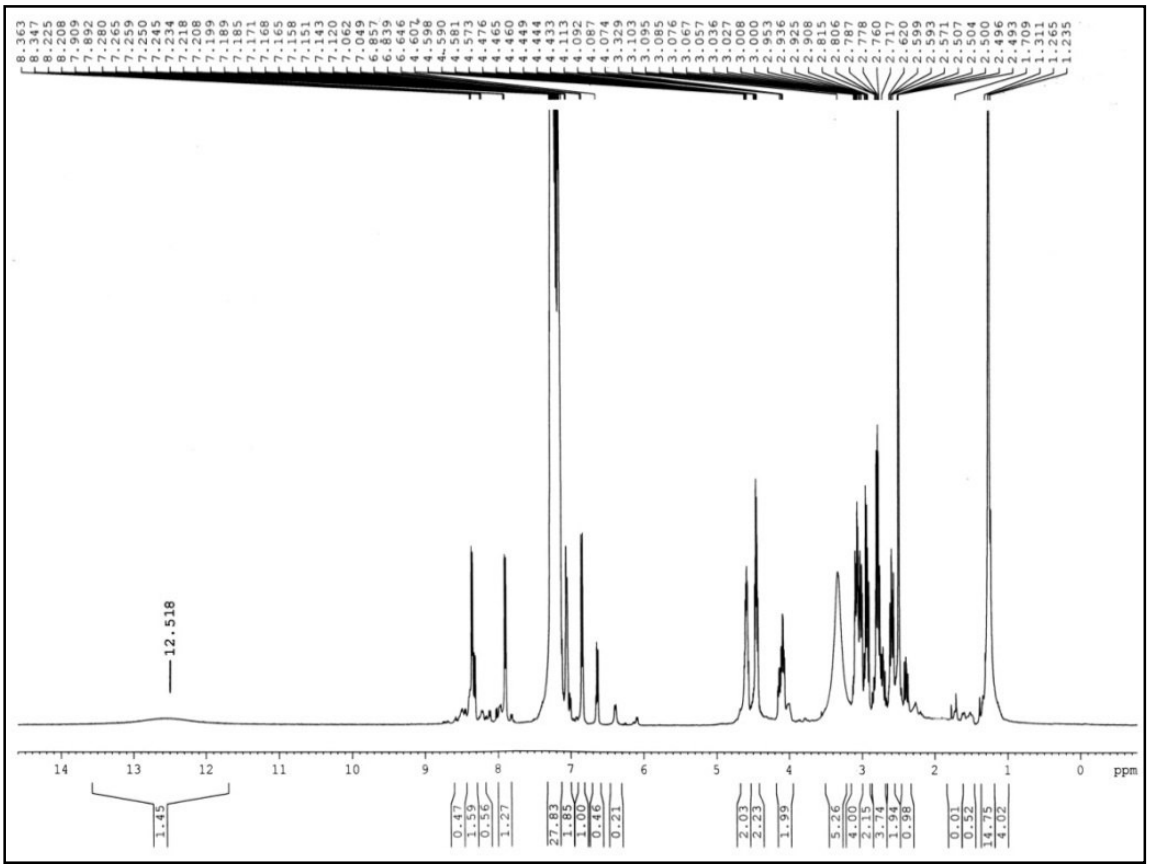


**Fig. S1** $^{1}$H NMR of the gelator peptide **P1**.

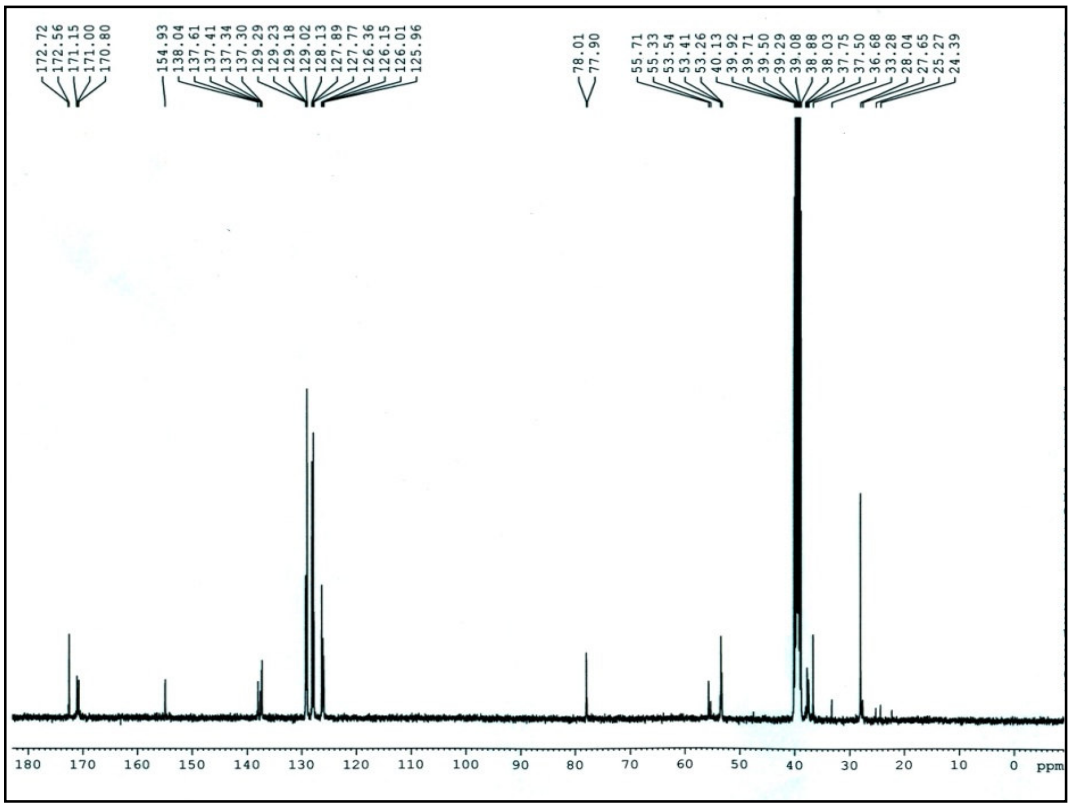


**Fig. S2** $^{13}$C NMR of the gelator peptide **P1**.

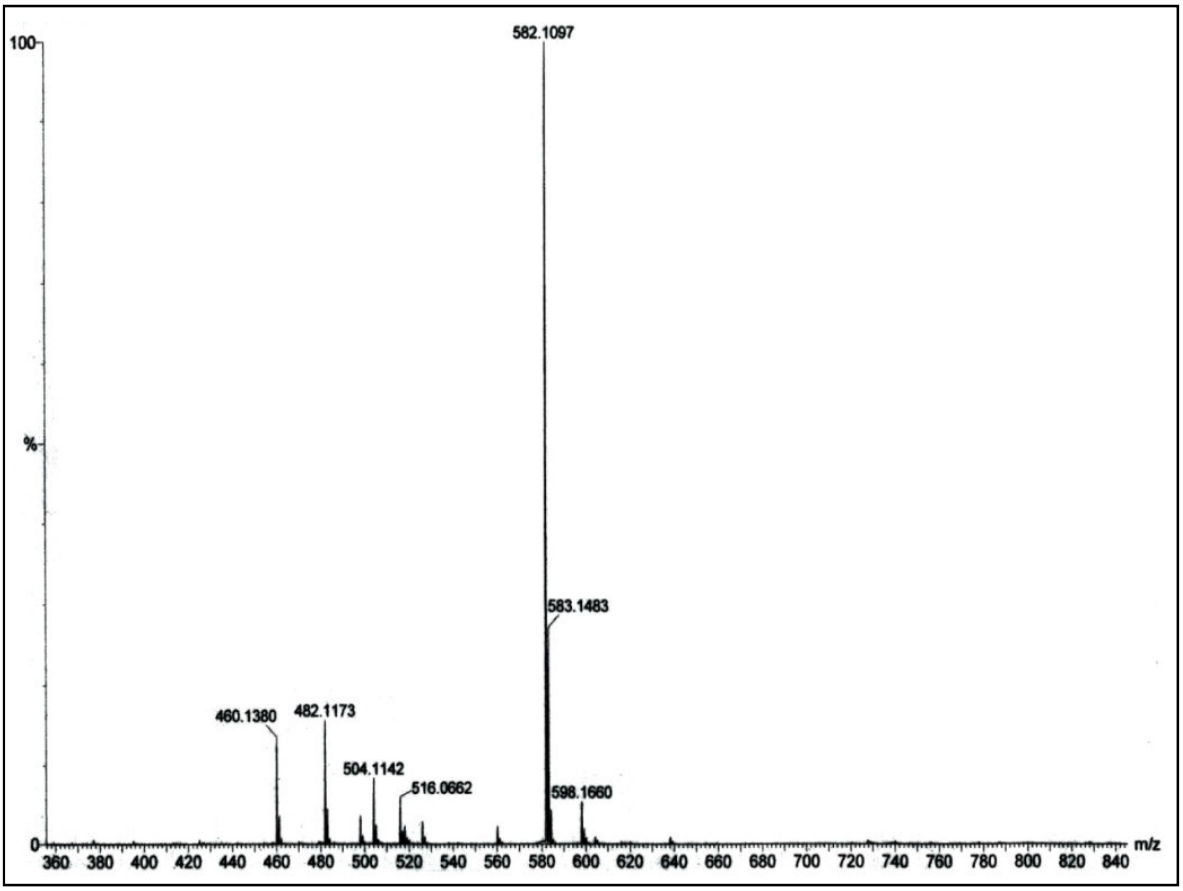


**Fig. S3** High resolution mass spectrum of the gelator peptide **P1**.

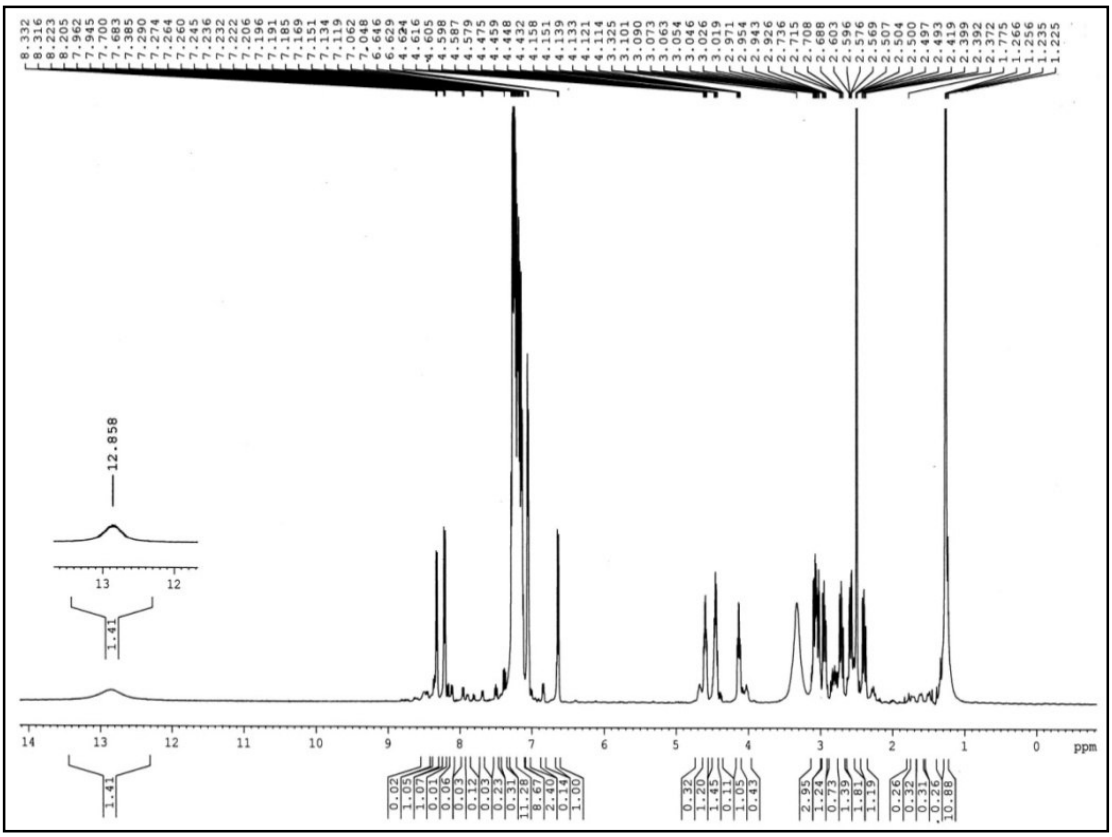


**Fig. S4** $^{1}$H NMR of the gelator peptide **P2**.

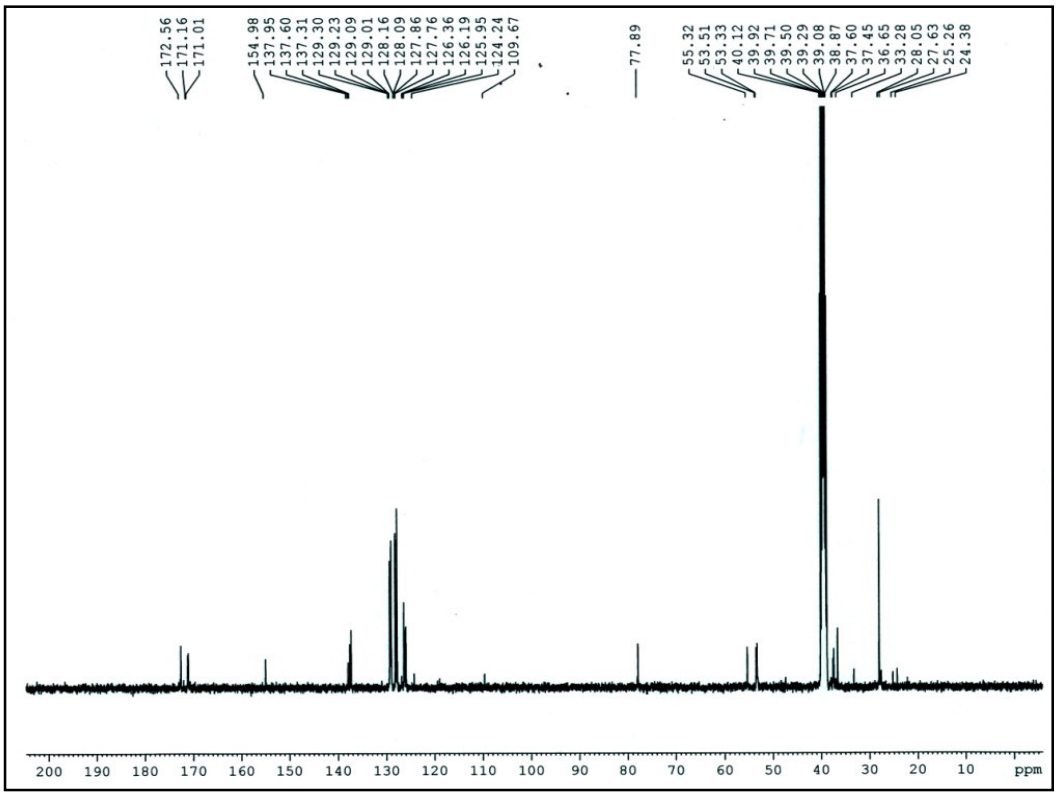


**Fig. S5** $^{13}$C NMR of gelator peptide **P2**.

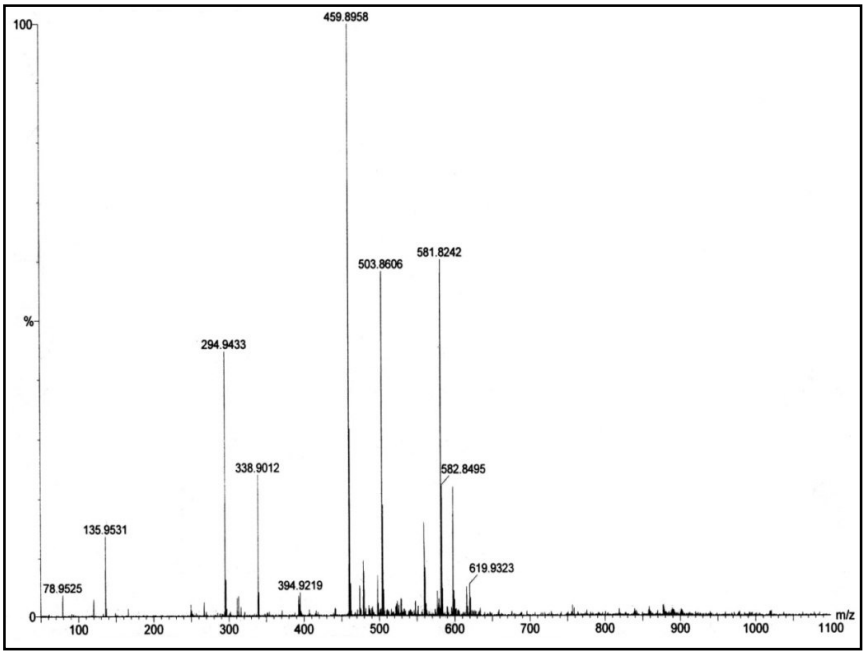


**Fig. S6** High resolution Mass spectrum of the gelator peptide **P2**.

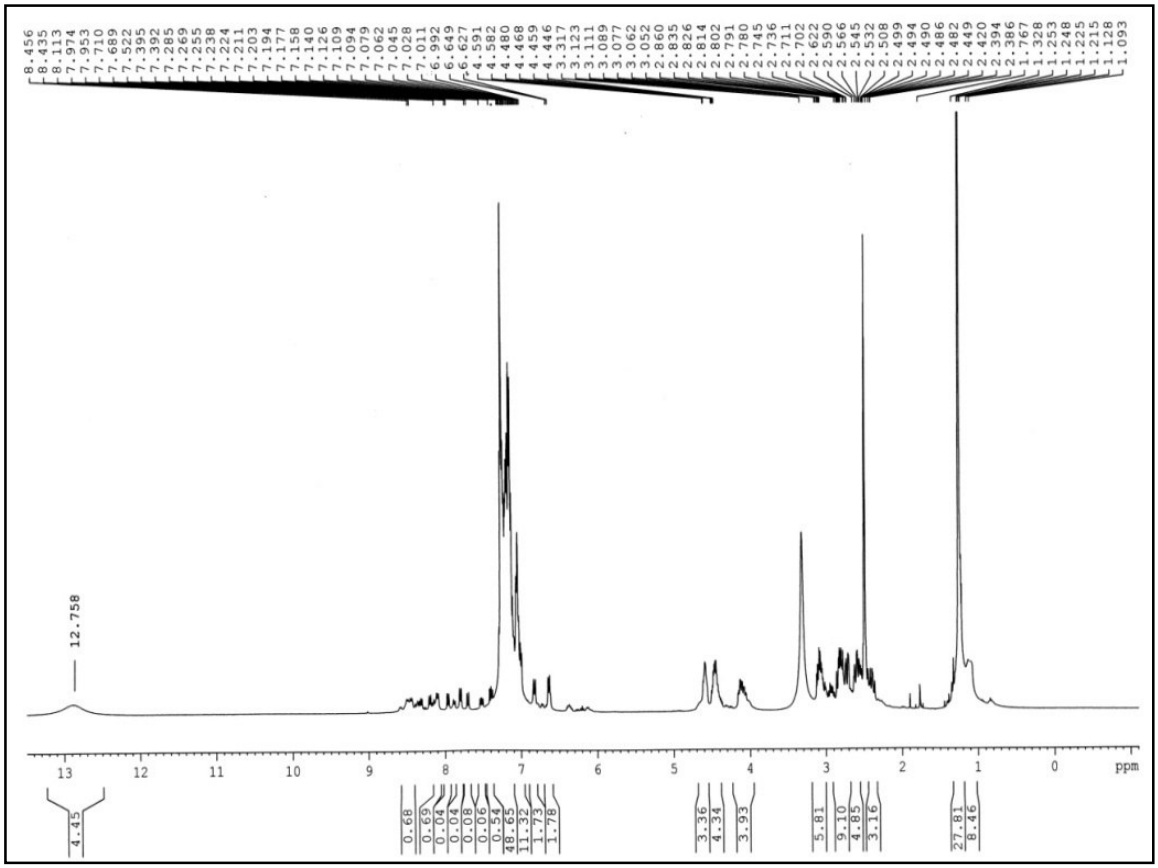


**Fig. S7** $^{1}$H NMR of the gelator peptide **P3**.

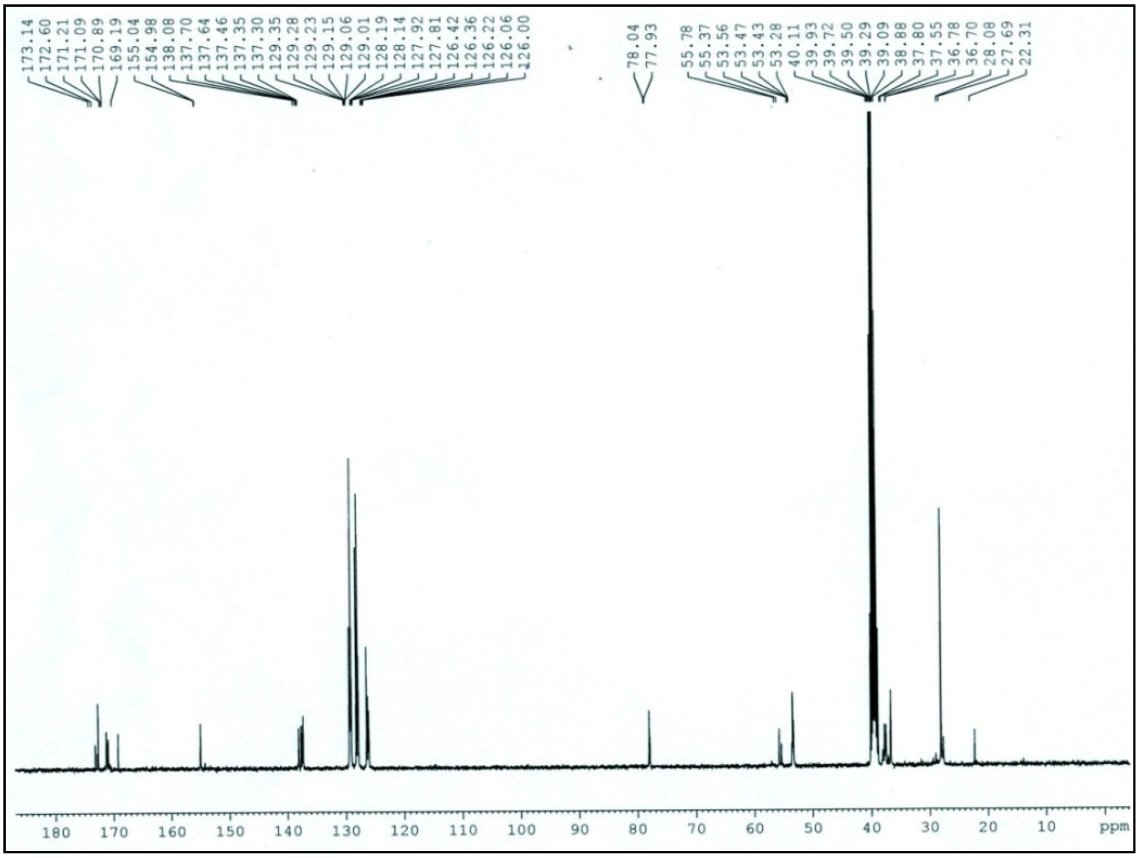


**Fig. S8** $^{13}$C NMR of the gelator peptide **P3**.

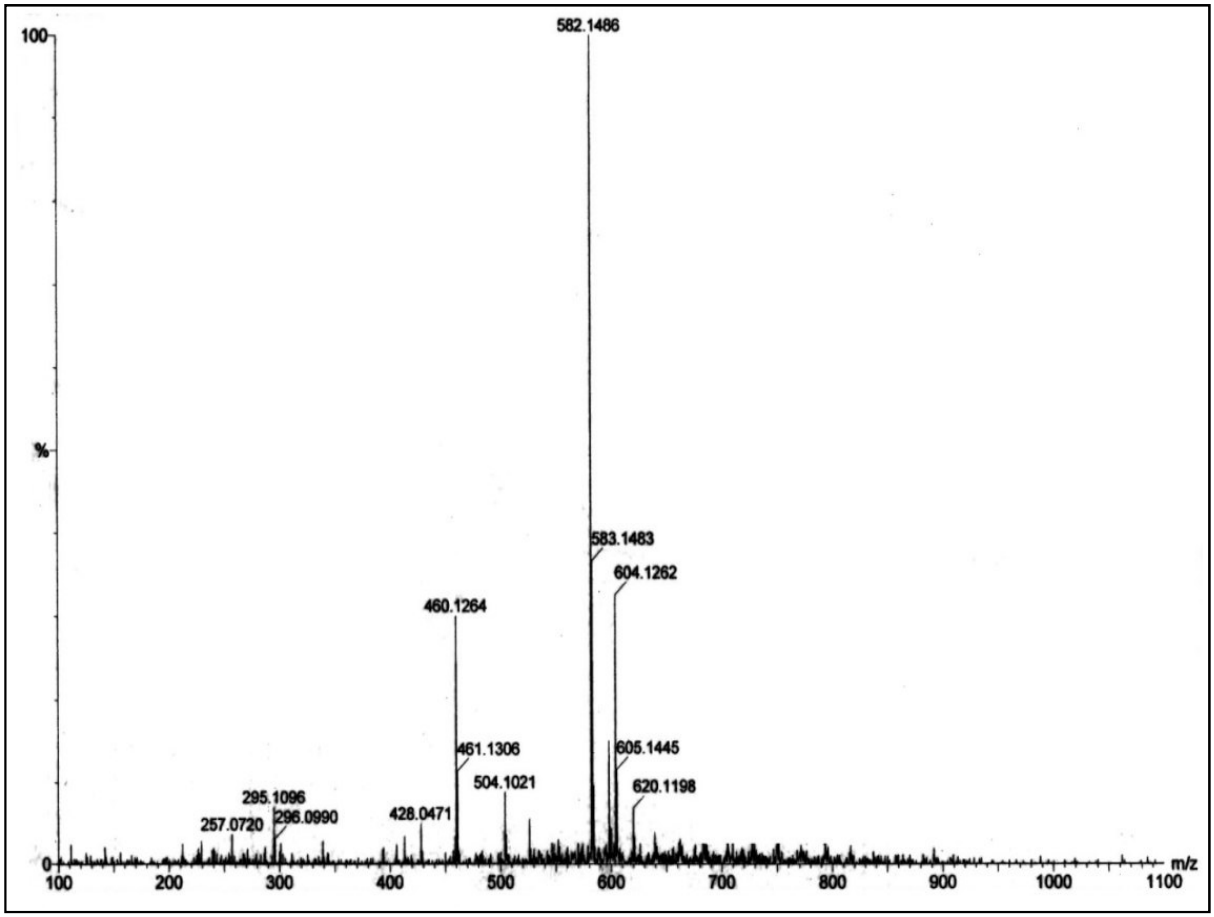


**Fig. S9** High resolution mass spectrum of the gelator peptide **P3**.

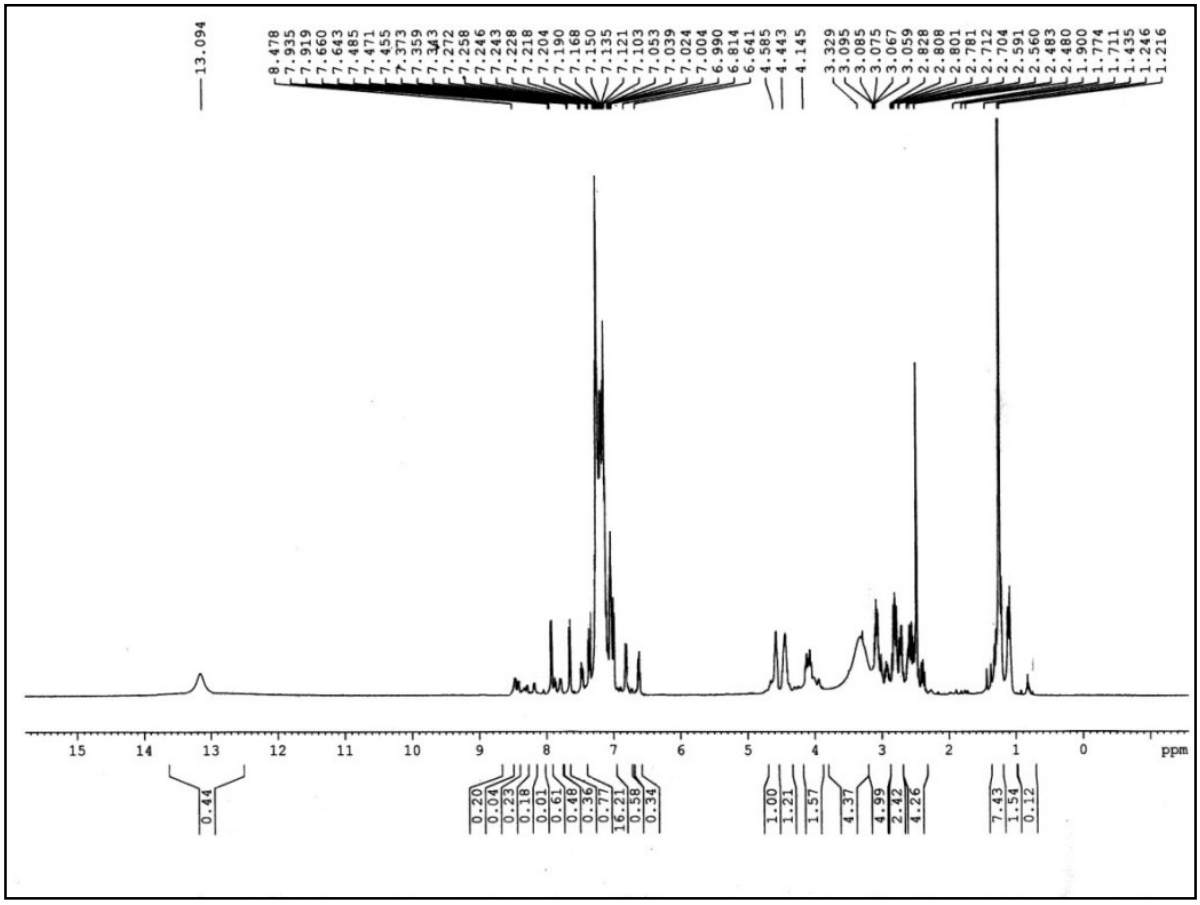


**Fig. S10** $^{1}$H NMR of nongelator peptide **P4**.

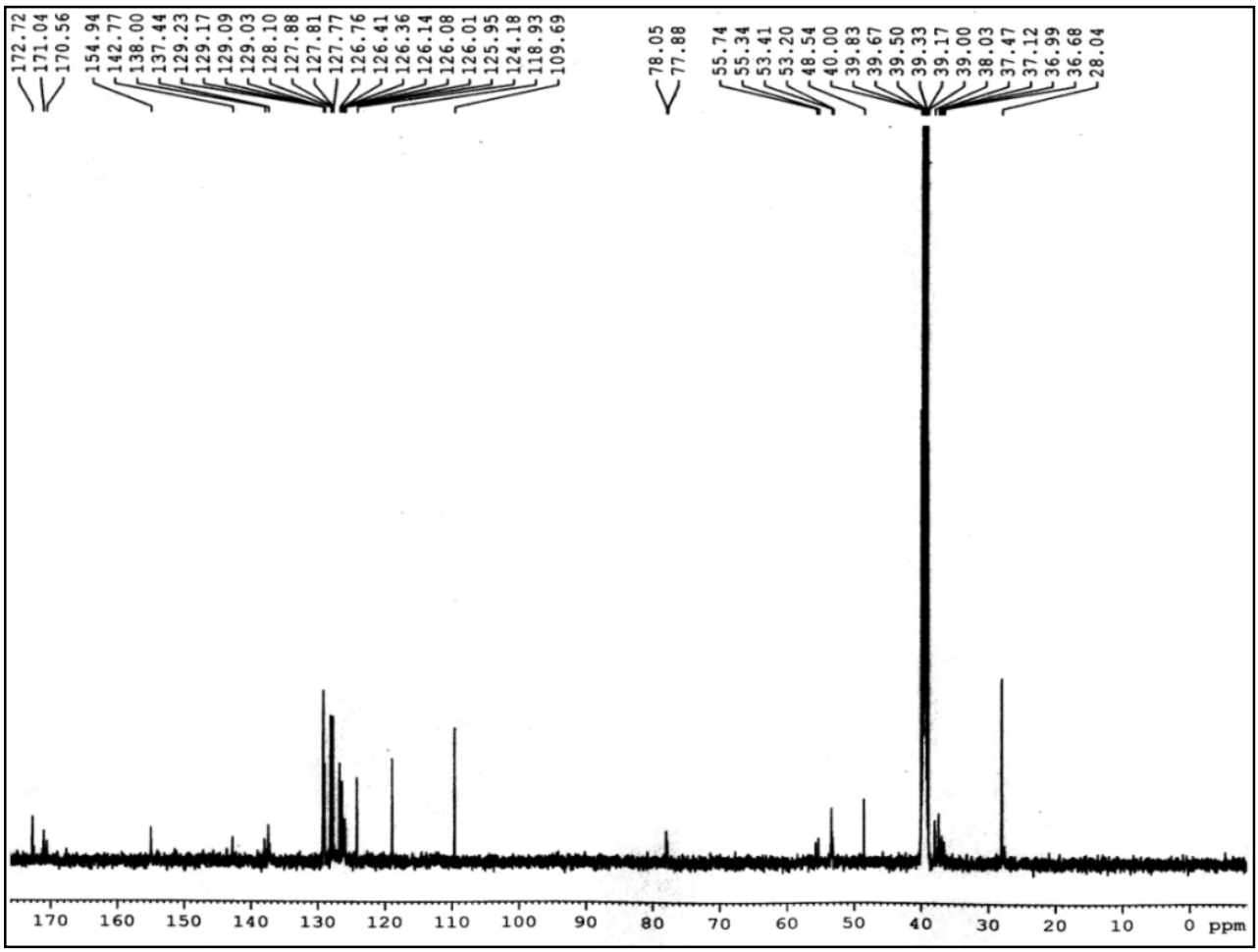


**Fig. S11** $^{13}$C-NMR spectrum of the nongelator peptide **P4**.

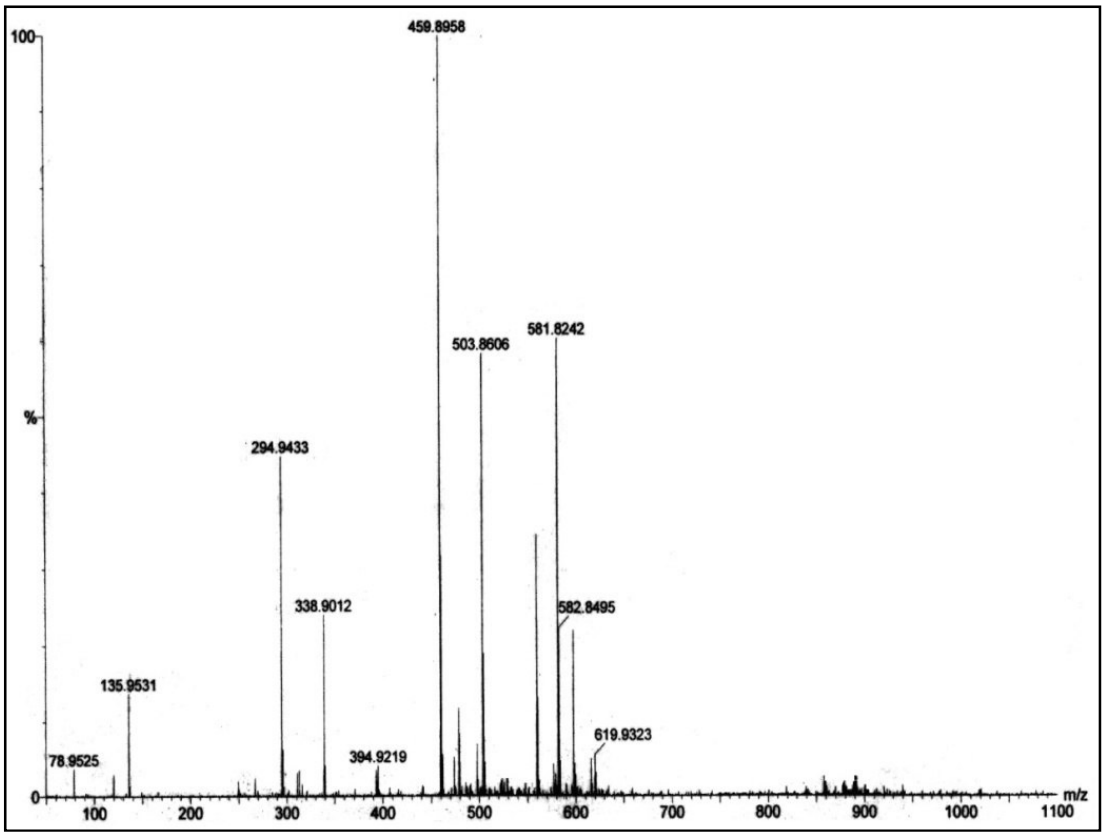


**Fig. S12** High resolution mass spectrum of the nongelator peptide **P4**.

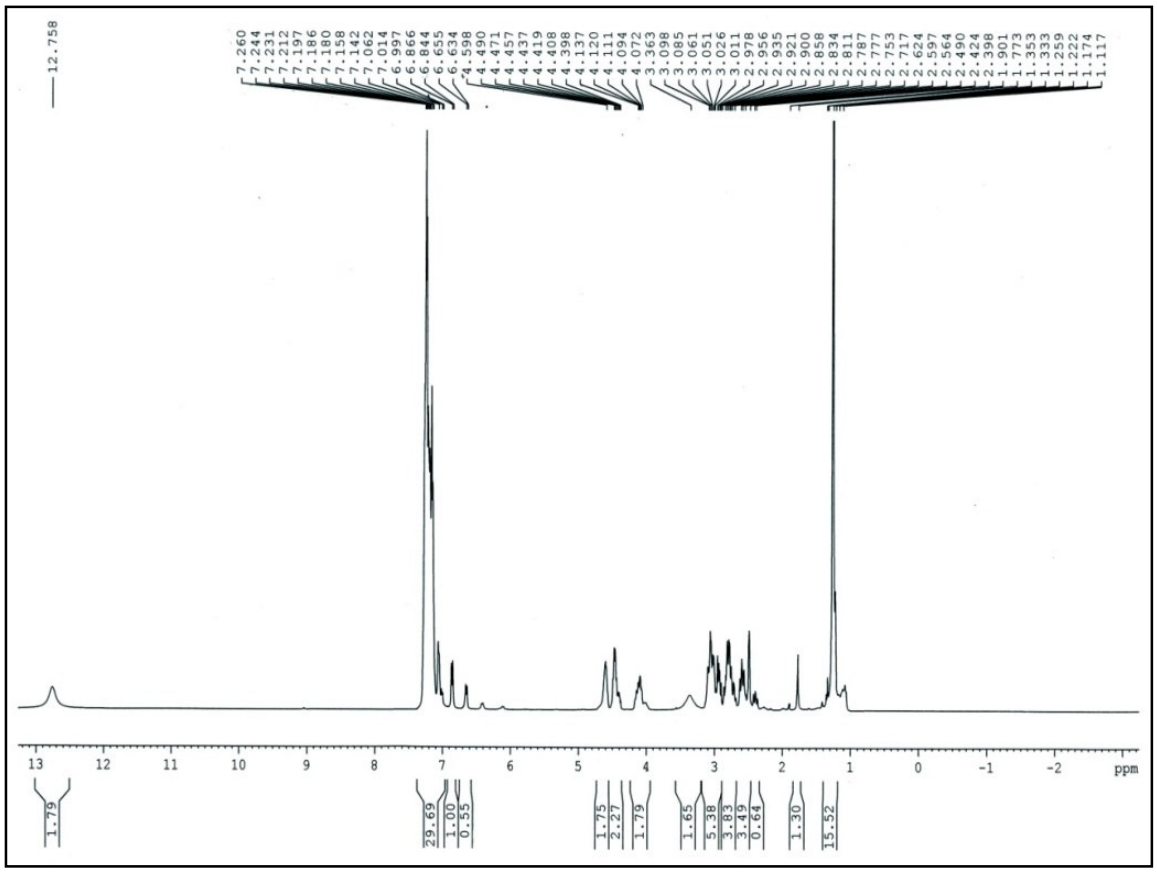


**Fig. S13** $^{1}$H NMR of the gelator peptide **P5**.

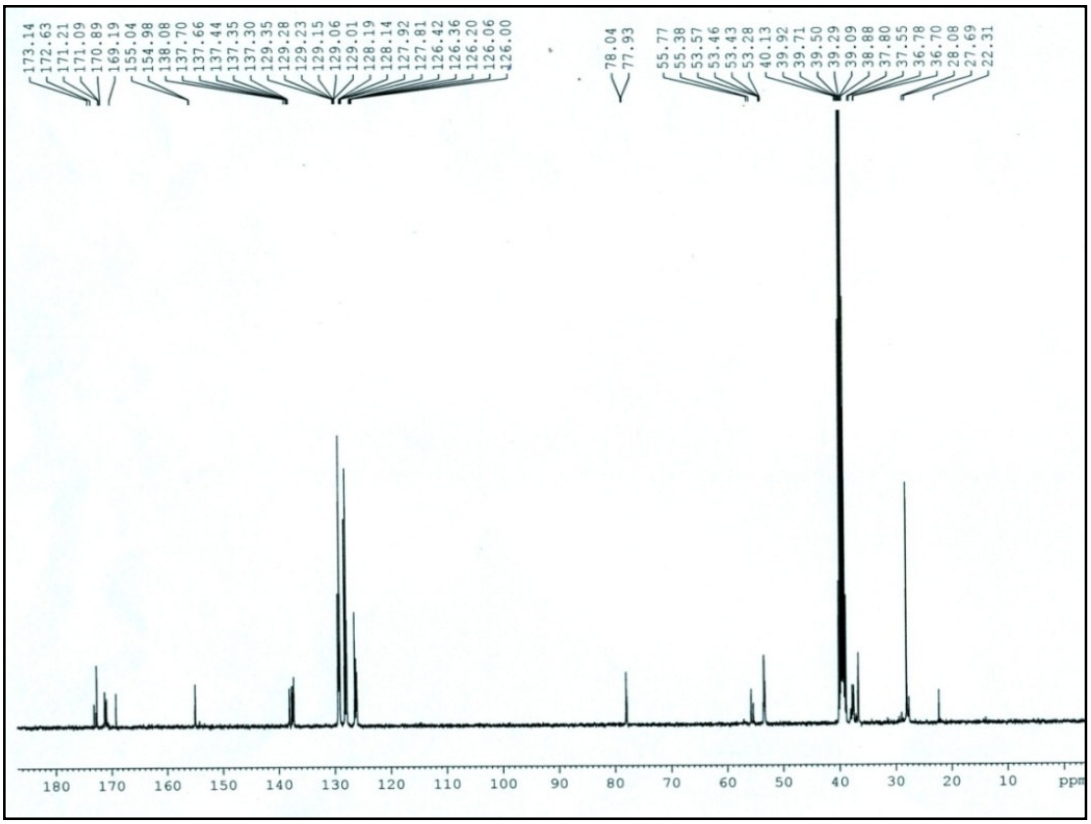


**Fig. S14** $^{13}$C NMR of the gelator peptide **P5**.

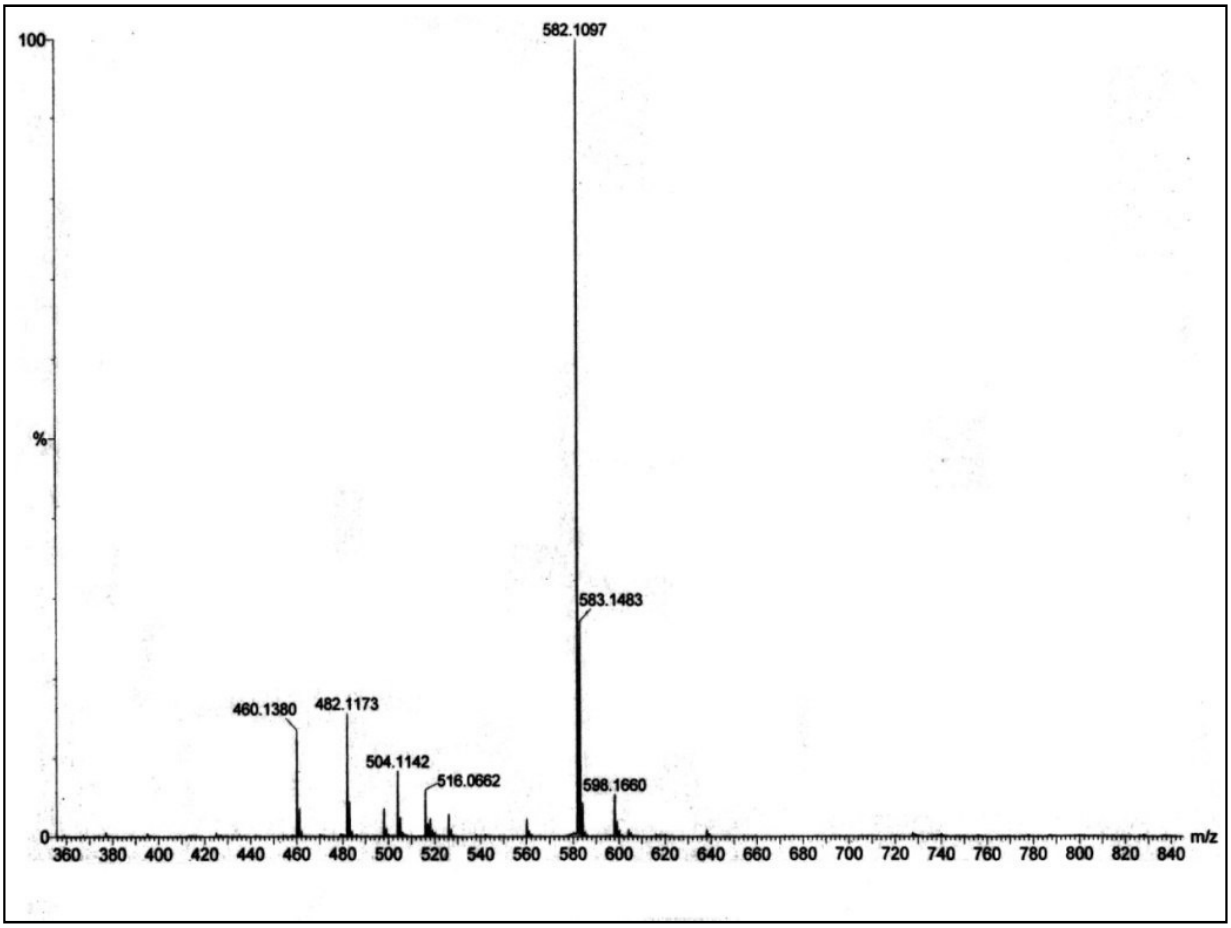


**Fig. S15** High resolution mass spectrum of the gelator peptide **P5**.

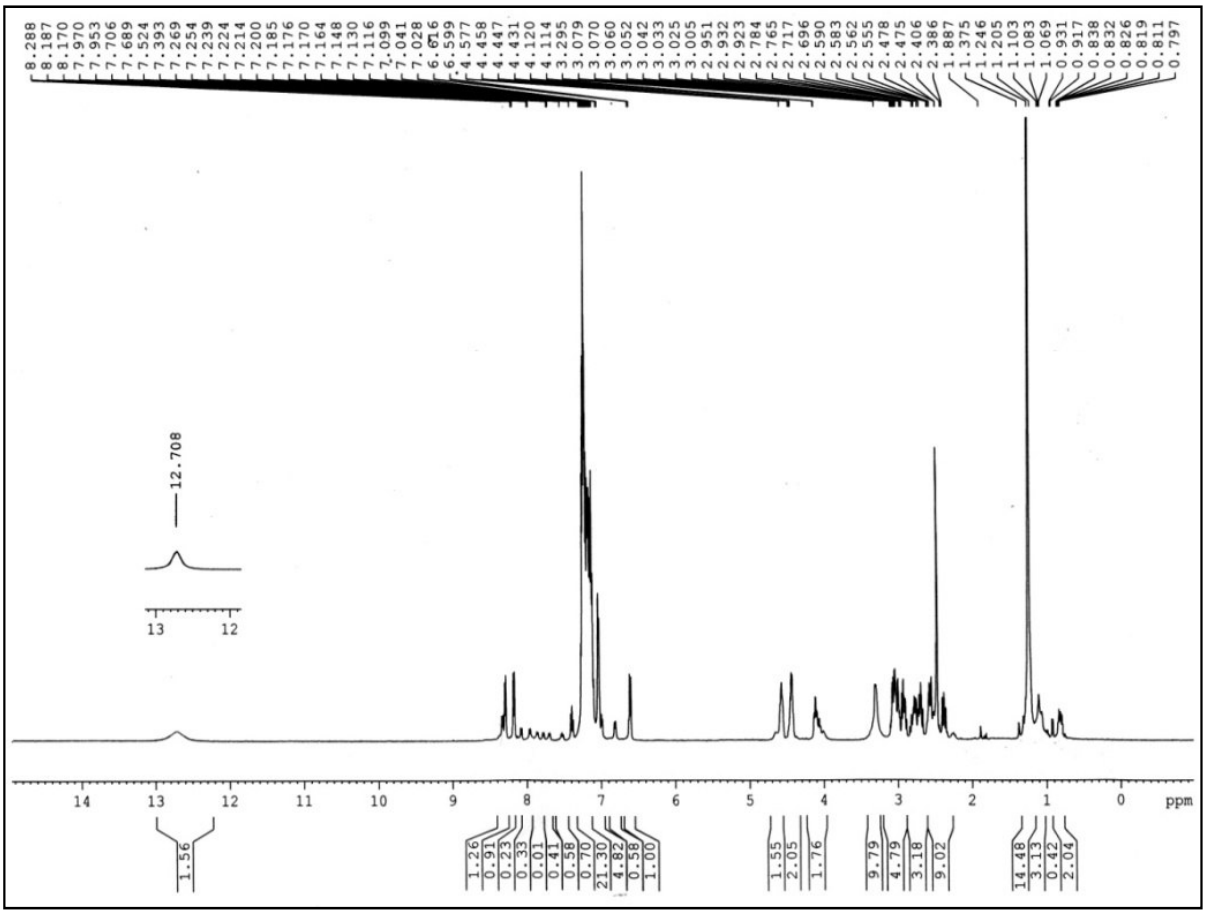


**Fig. S16** $^{1}$H NMR of the gelator peptide **P6**.

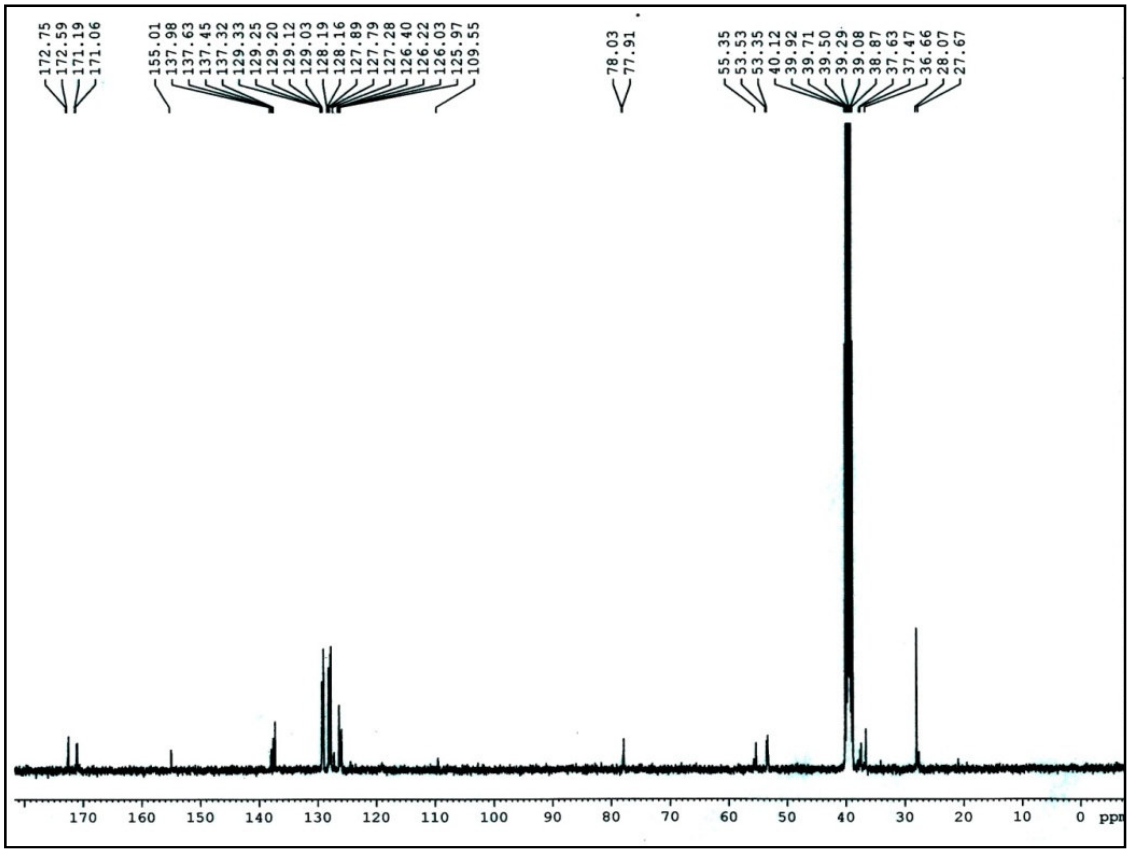


**Fig. S17** $^{13}$C NMR of the gelator peptide **P6**.

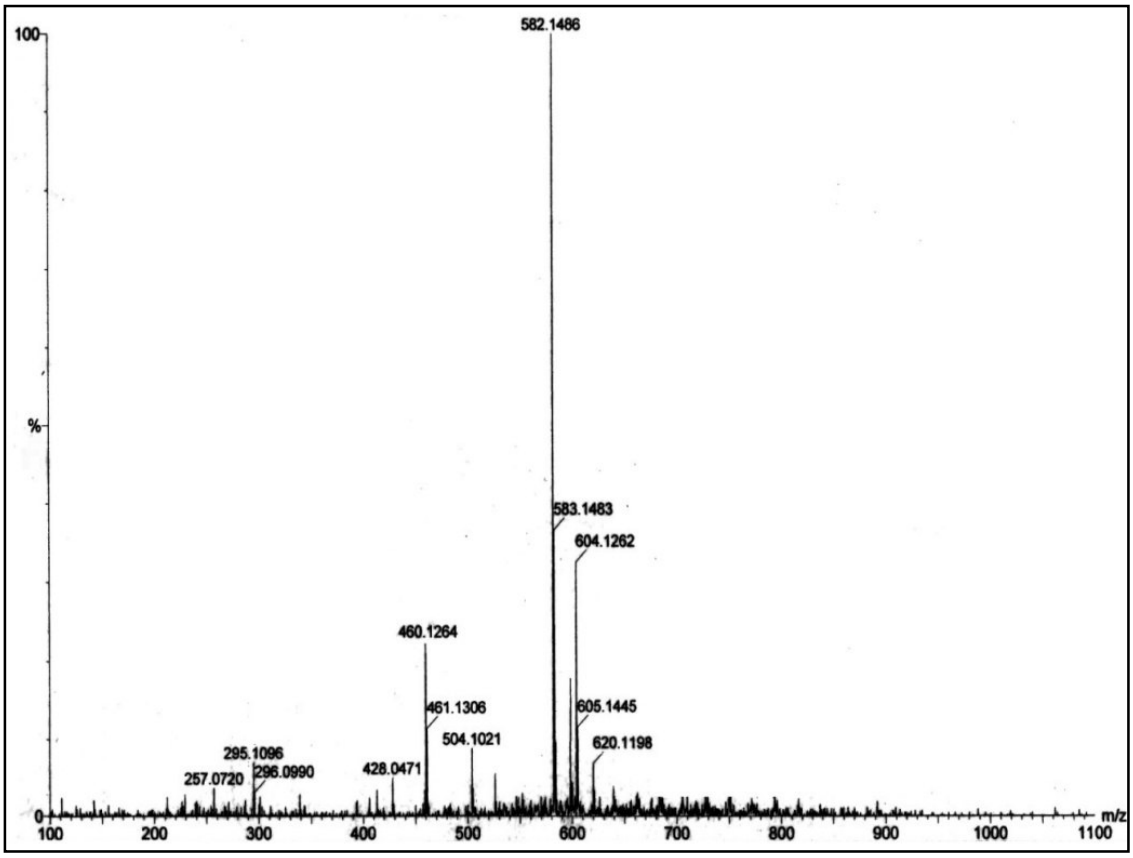


**Fig. S18** High resolution mass spectrum of the gelator peptide **P6**.

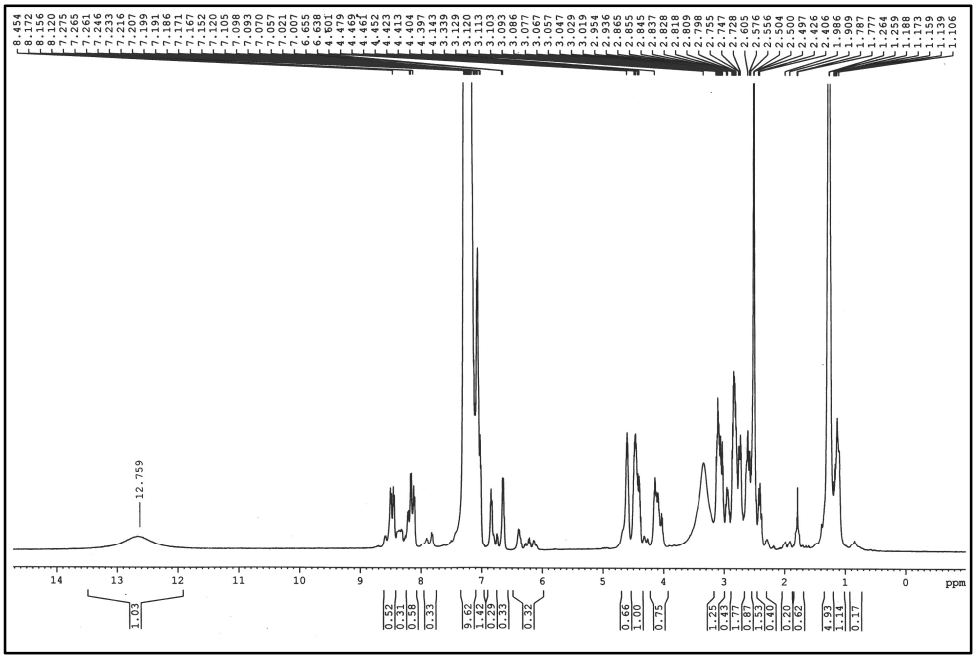


**Fig. S19** $^{1}$H NMR of the gelator peptide **P7.**

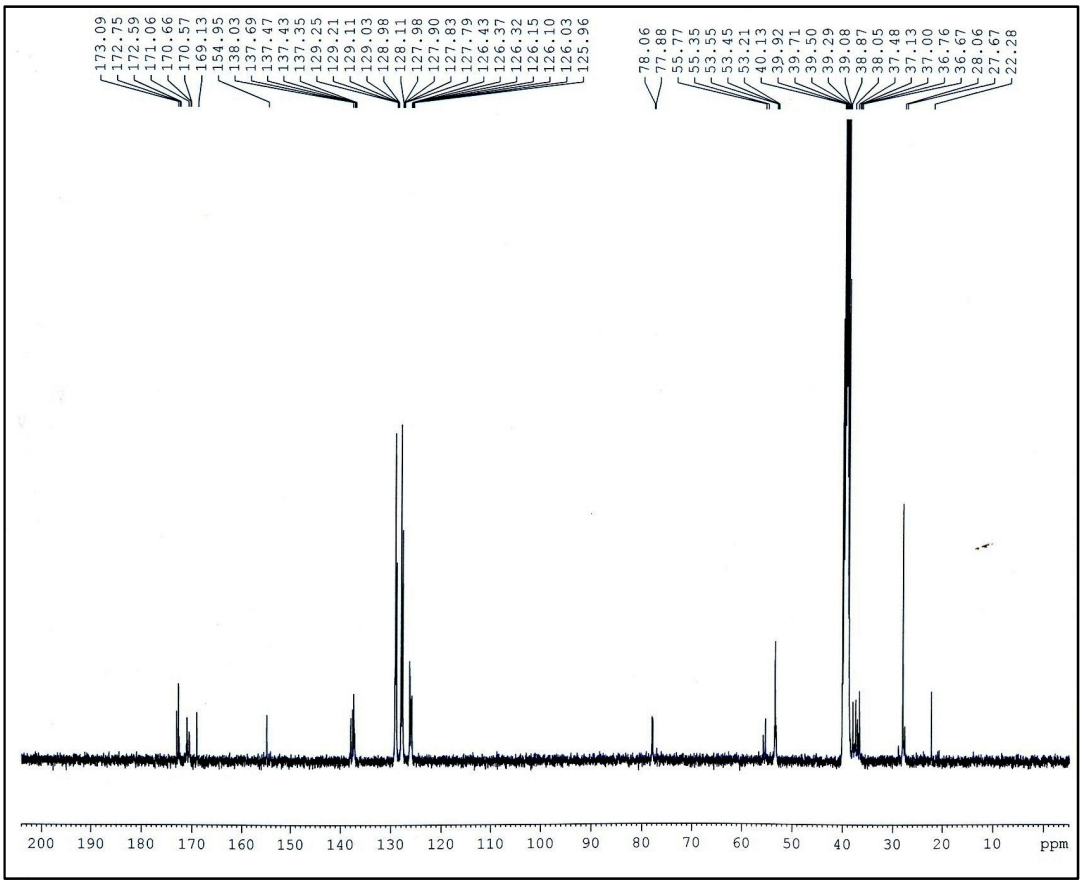


**Fig. S20** $^{13}$C NMR of the gelator peptide **P7.**

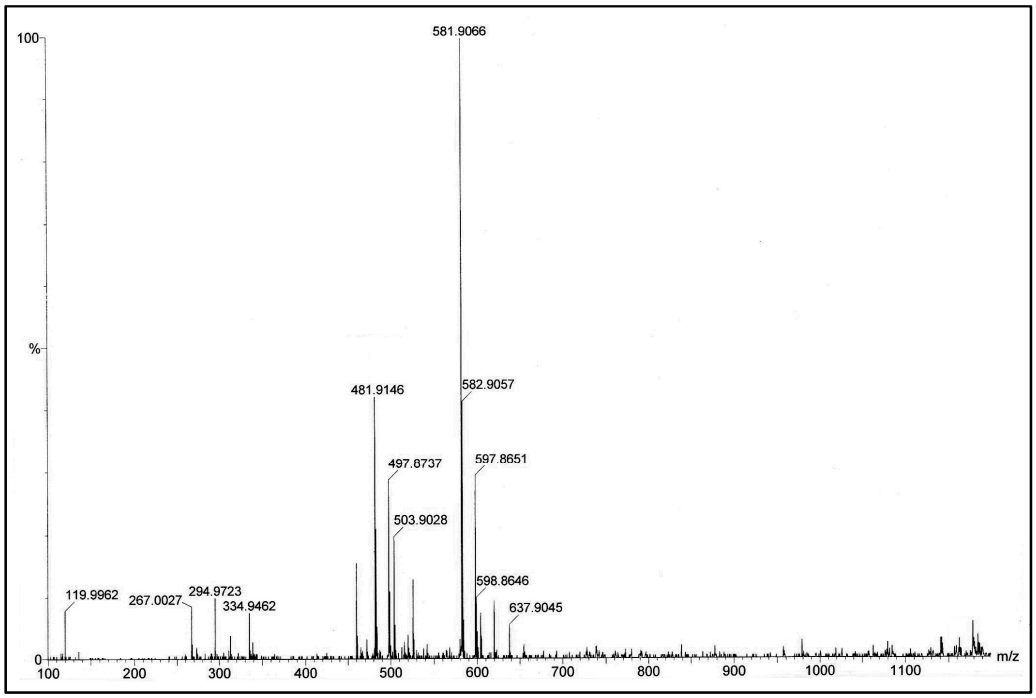


**Fig. S21** High resolution mass spectrum of the gelator peptide **P7.**

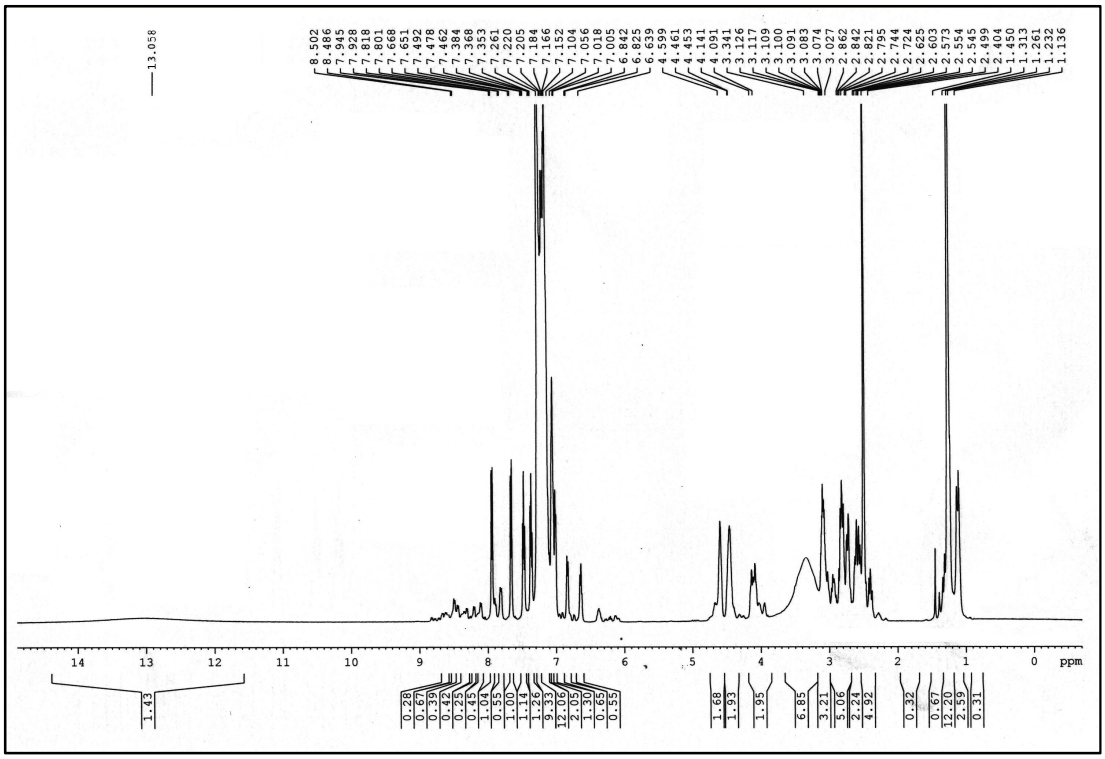

**Fig. S22** $^{1}$H NMR of the gelator peptide **P8.**

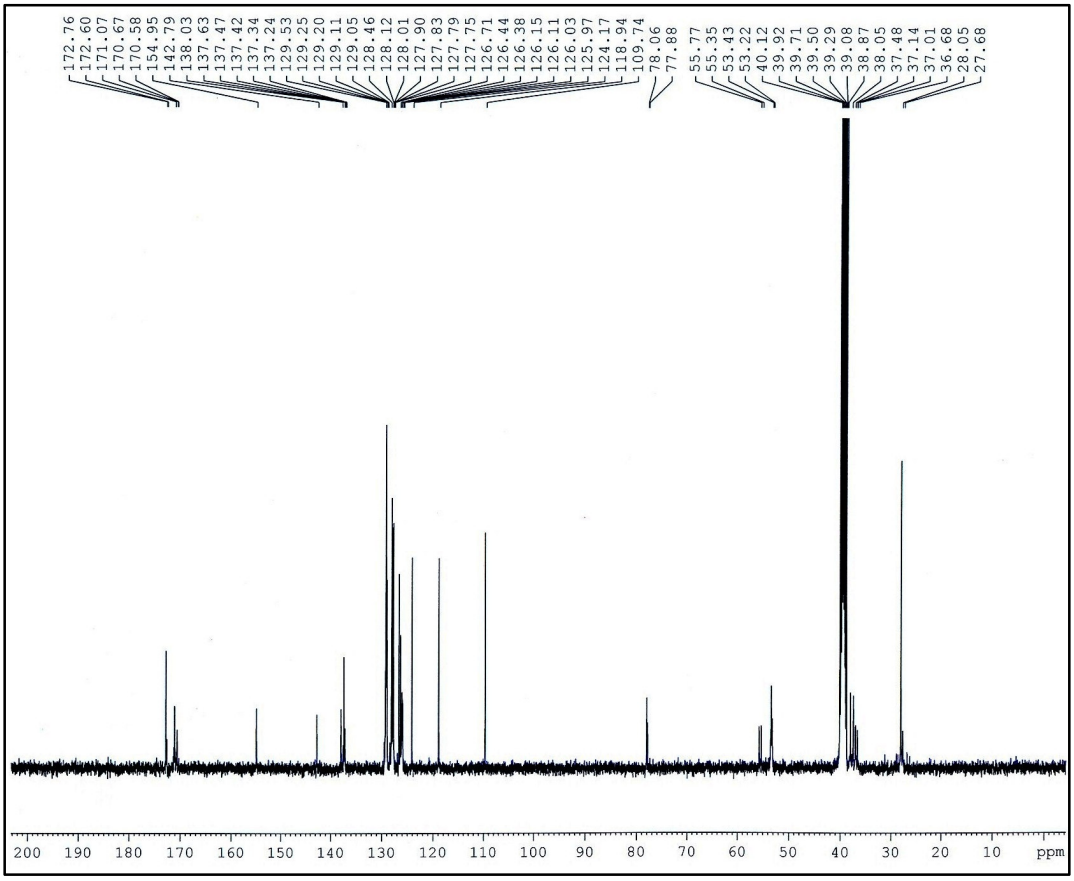


**Fig. S23** $^{13}C$ NMR of the gelator peptide **P8.**

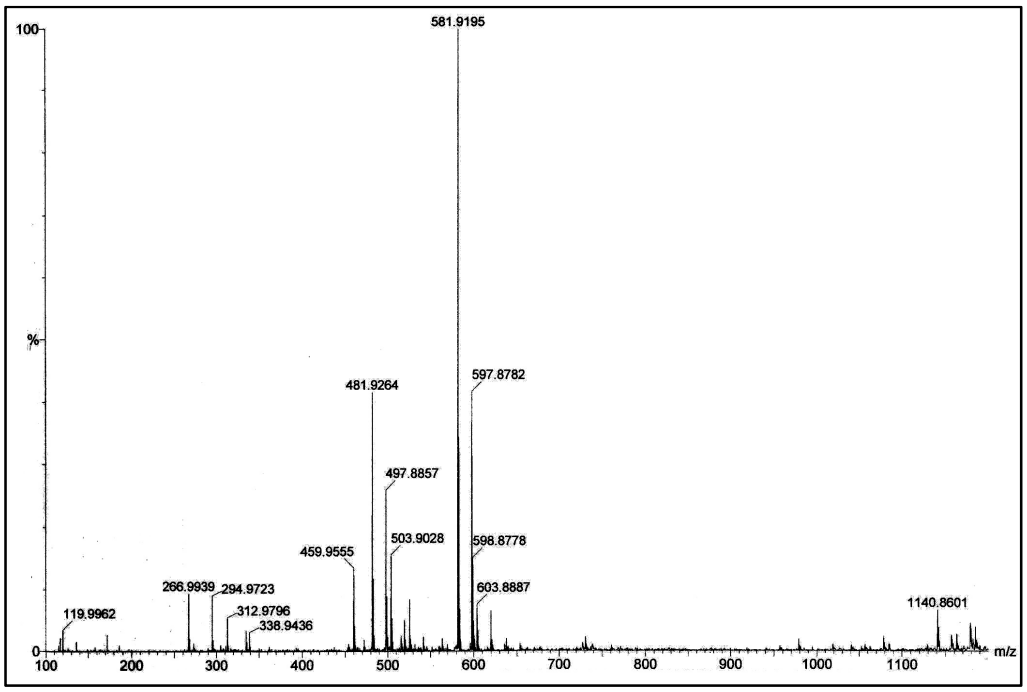


**Fig. S24** High resolution mass spectrum of the gelator peptide **P8.**

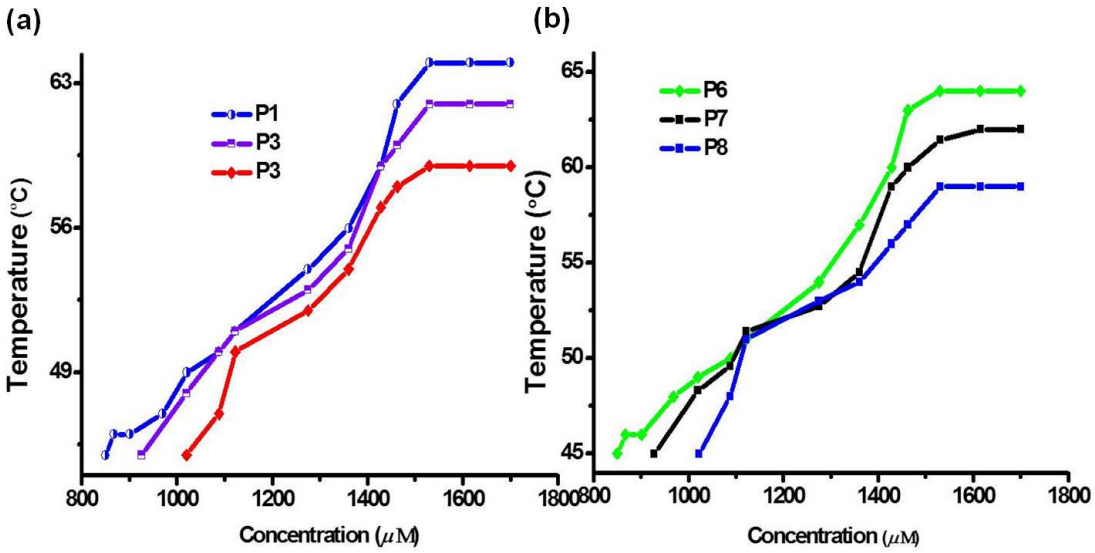


**Fig. S25** $T_{gel}$ vs. concentration plots of (a) **P1**, **P2** and **P3;** (b) **P5**, **P6** and **P7**.

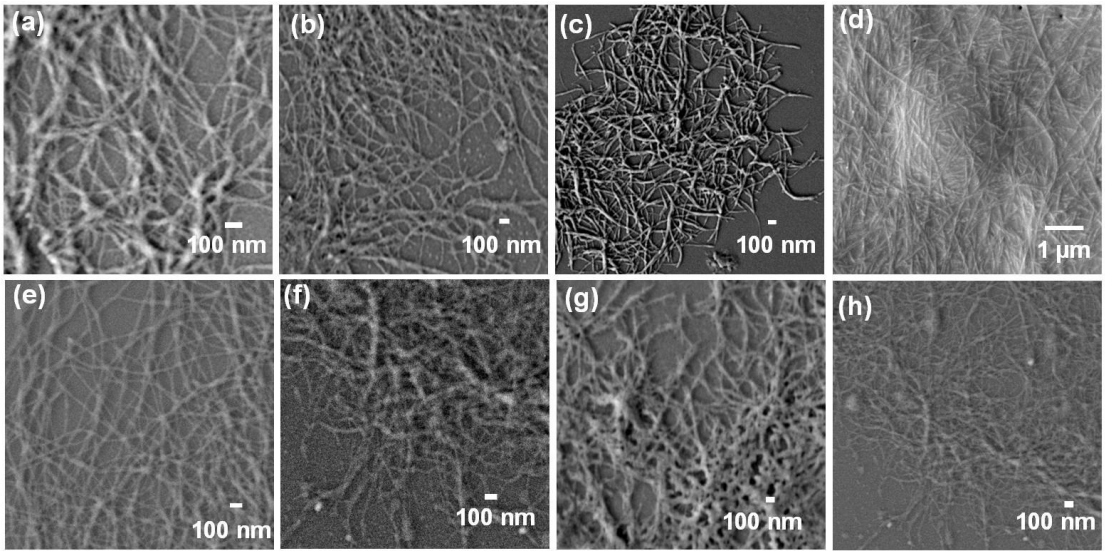


**Fig. S26** Field emission scanning electron microscopic (FE-SEM) images of xerogels of (a) **P1**, (b) **P2**, (c) **P3**, (d) **P4**, (e) **P5**, (f) **P6**, (g) **P7** and (h) **P8**.

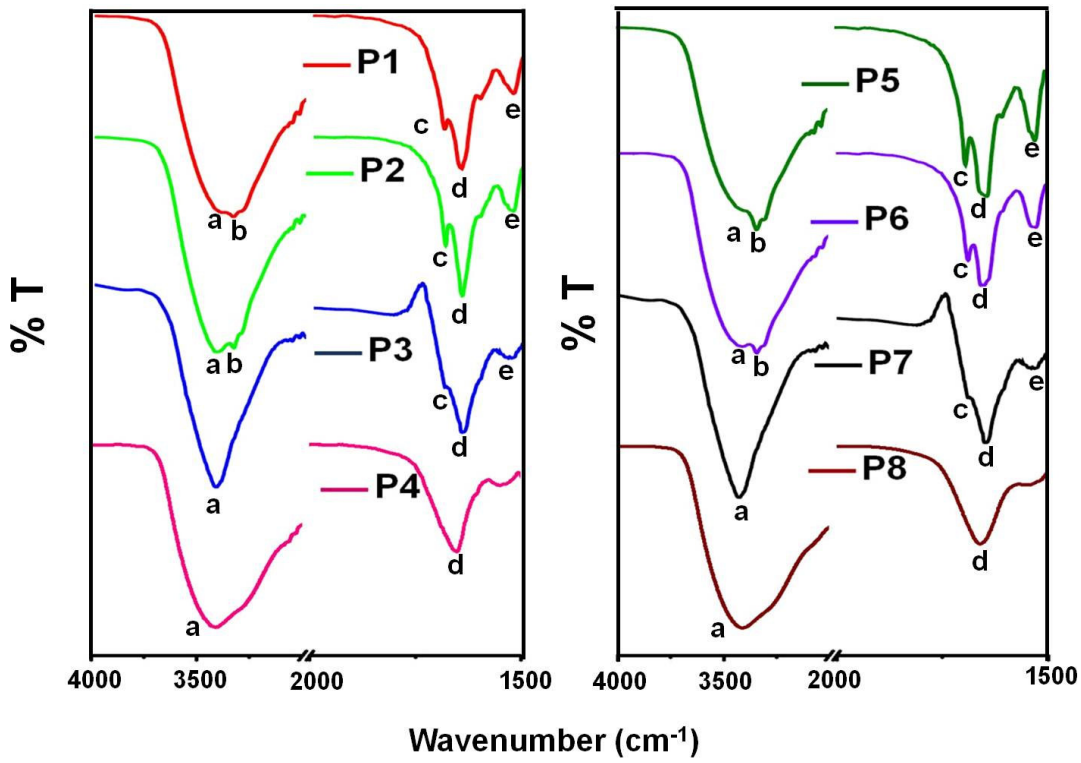


**Fig. S27** FT-IR of all hydrogels (**P1**-**P3** and **P5**-**P7**) in dried form and dried solution of **P4** and **P8**. a, b, c, d, e denotes the positions of the peaks around 3420, 3340, 1690, 1650 and 1528 $cm^{-1}$ range.

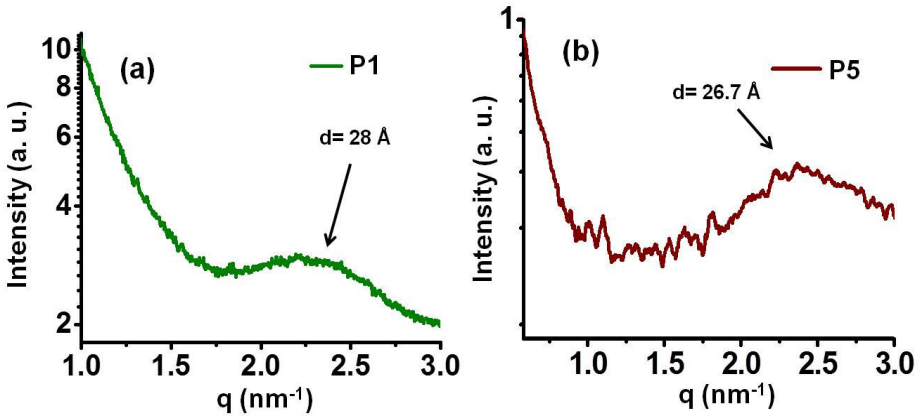


**Fig. S28** Small angle X-ray scattering (SAXS) plot of the hydrogels of (a) **P1**, (b) **P5**.

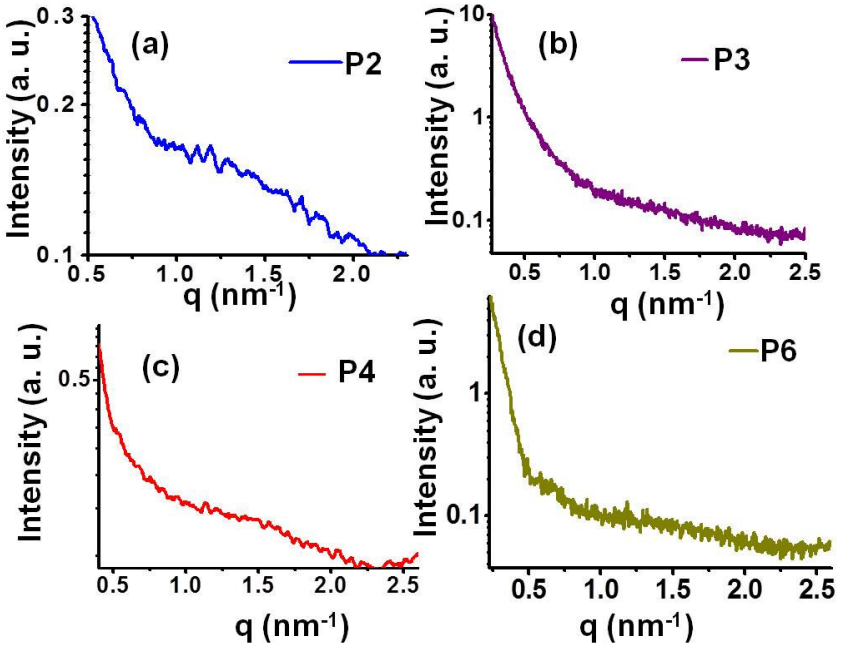


**Fig. S29** Small angle X-ray scattering (SAXS) plots of the hydrogels (a) **P2**, (b) **P3**, (d) **P6** and aggregated solution of (c) **P4**.

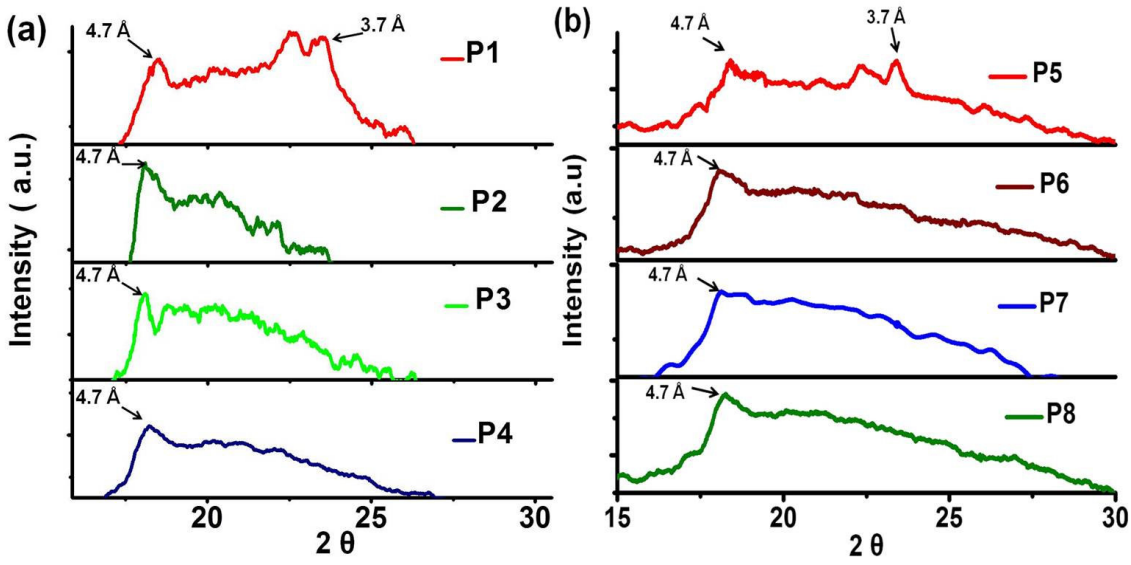


**Fig. S30** Comparison with X-Ray powder diffraction (XRPD) pattern between (a) **P1, P2**, **P3** and **P4**, and (b) **P5**, **P6, P7** and **P8**.

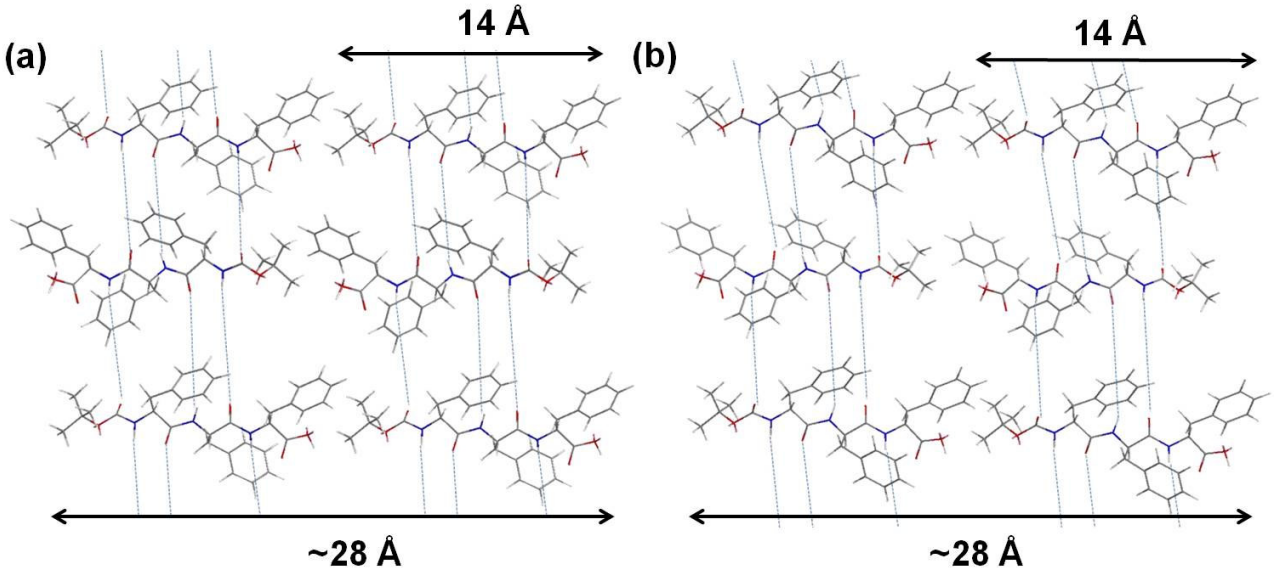


**Fig. S31** Proposed schematic model for molecular arrangements (a) **P1**and (b) **P2**.

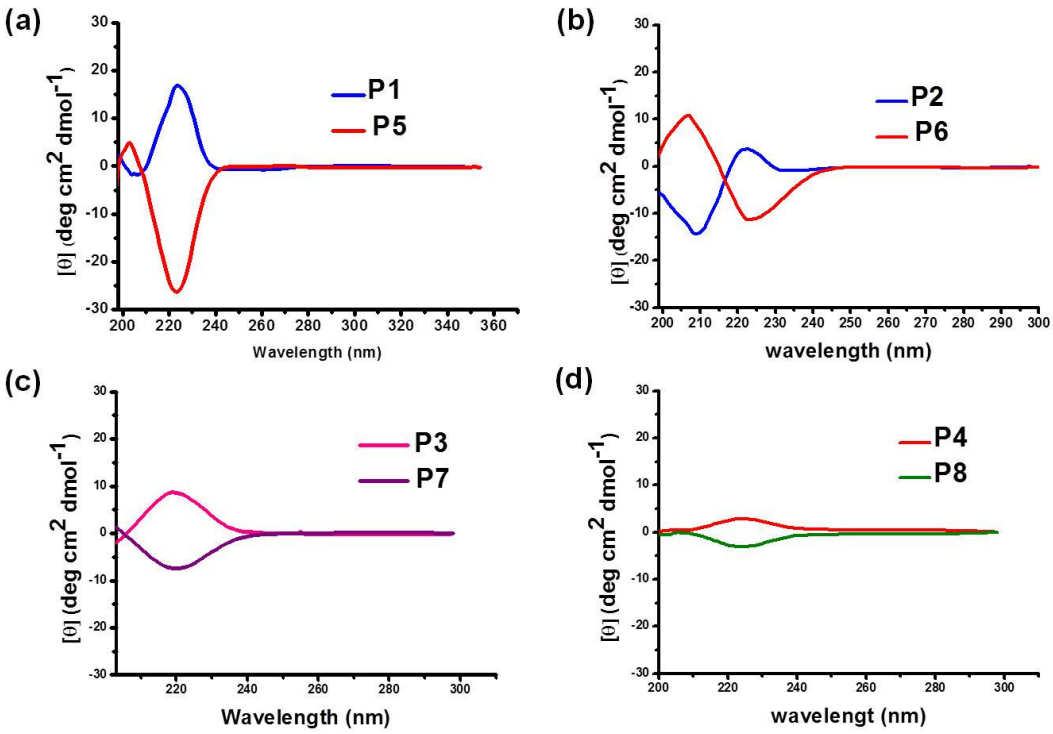


**Fig. S32** Circular Dichroism (CD) spectra of (a) **P1** and its enantiomer **P5**, (b) **P2** and its enantiomer **P6**, (c) **P3** and its enantiomer **P7** and (d) **P4** and its enantiomer **P8**.

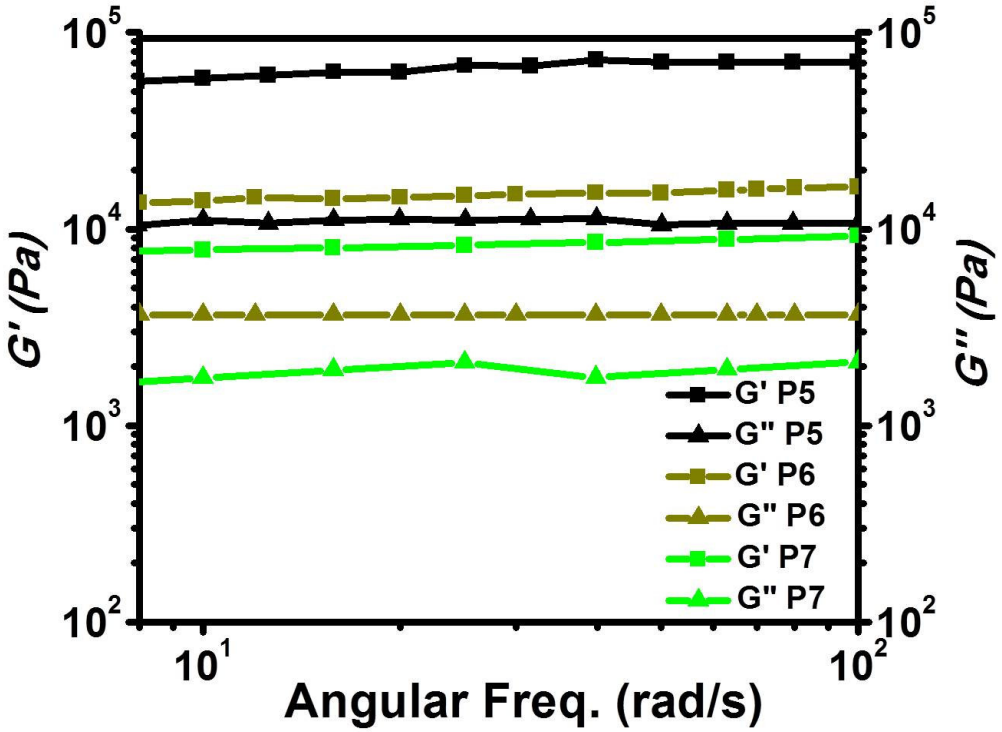


**Fig. S33** Frequency sweeps of dynamic shear modulus for hydrogels **P5**, **P6** and **P7**.

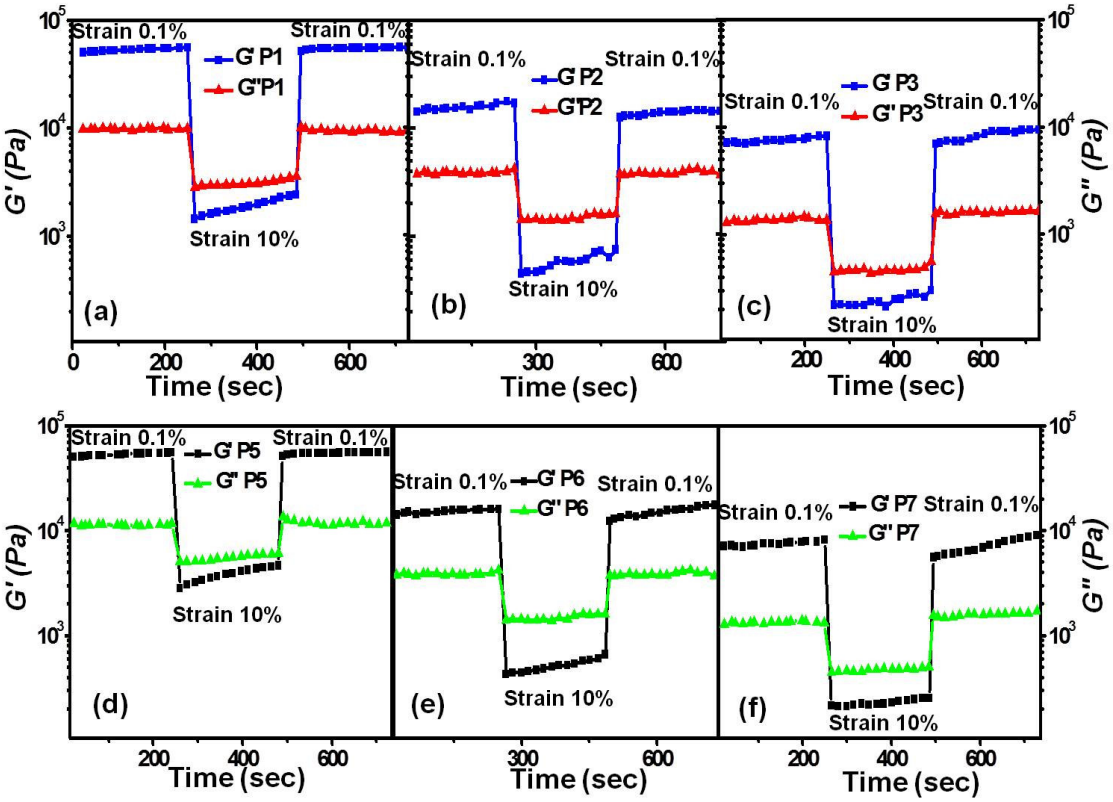


**Fig. S34** Step-strain rheological experiments with hydrogels of (a) **P1**, (b) **P2**, (c) **P3**, (d) **P5**, (e) **P6** and (f) **P7**.

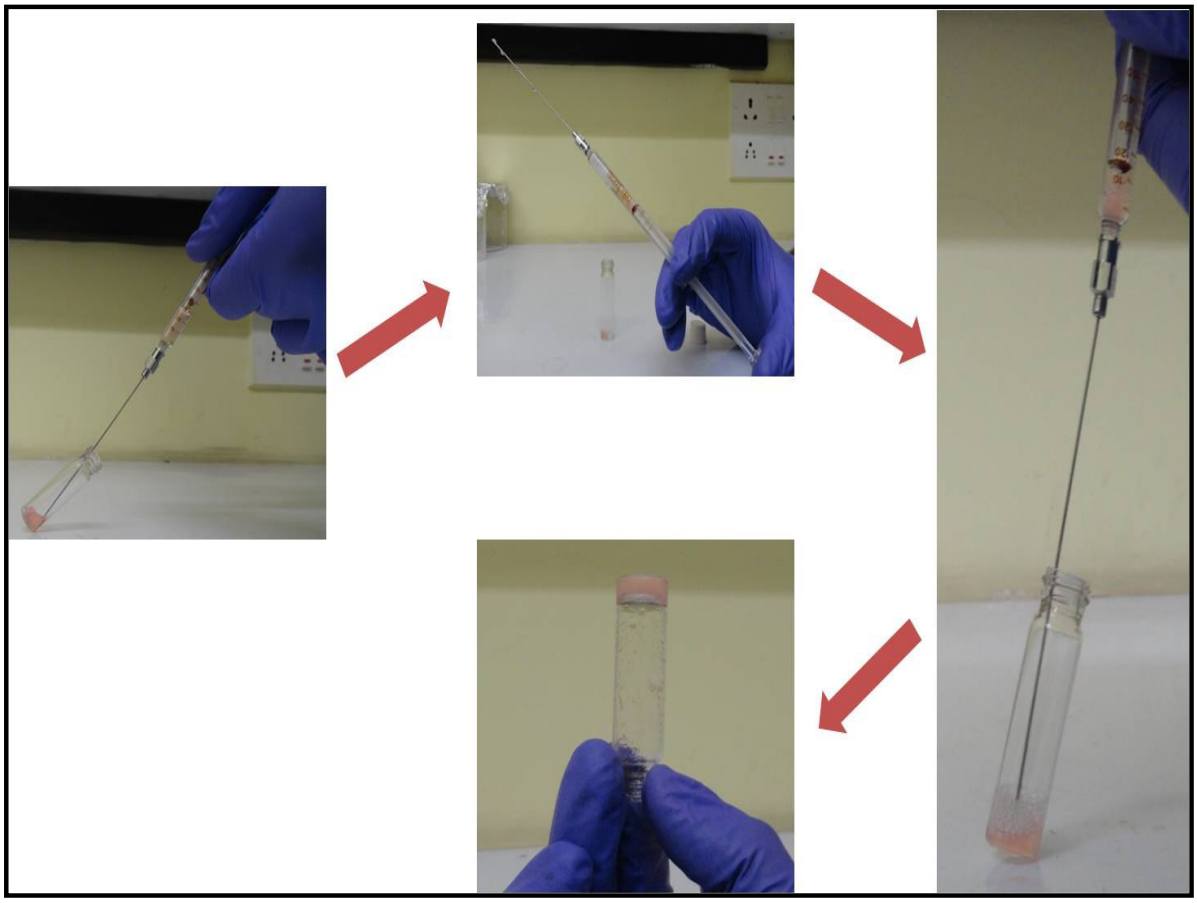

**Fig. S35** Injectability experiment with doxorubicin loaded hydrogel of **P4**.

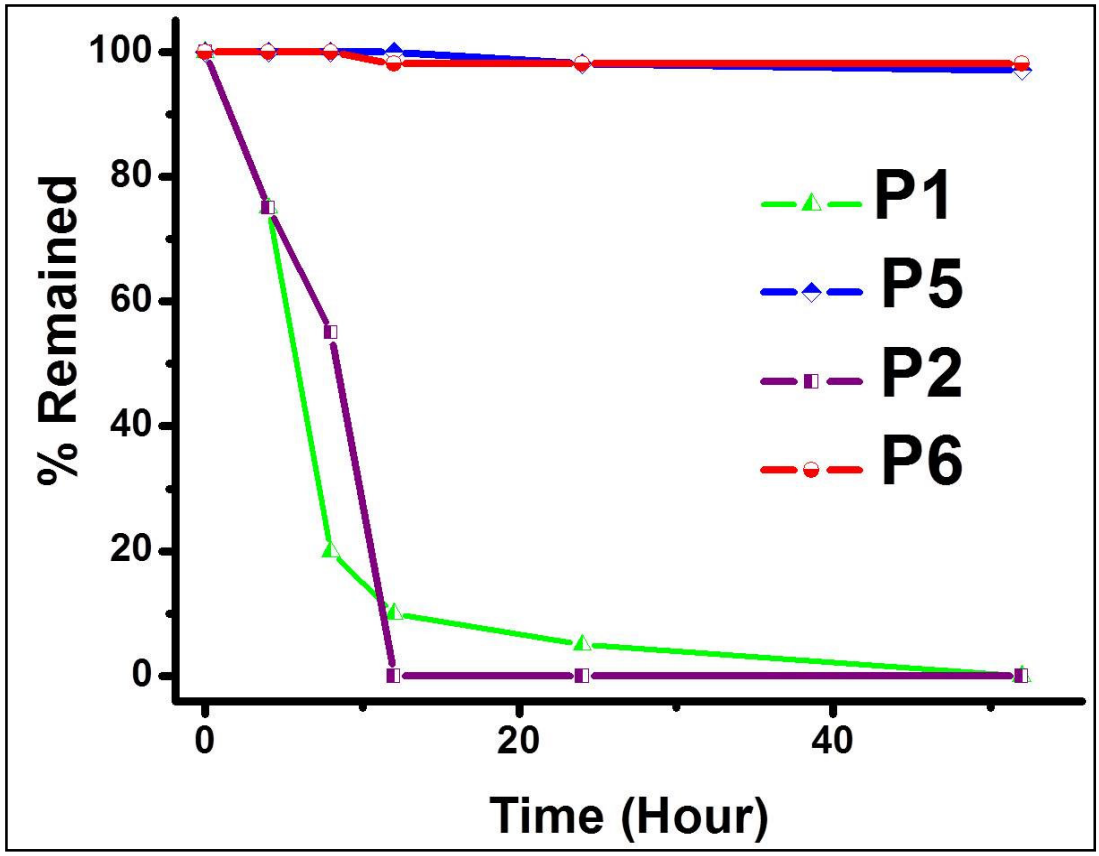


**Fig. S36** Proteolytic stability curve of **P1** and its enantiomer **P5** and **P2** and its enantiomer **P6** with respect to proteinase K.

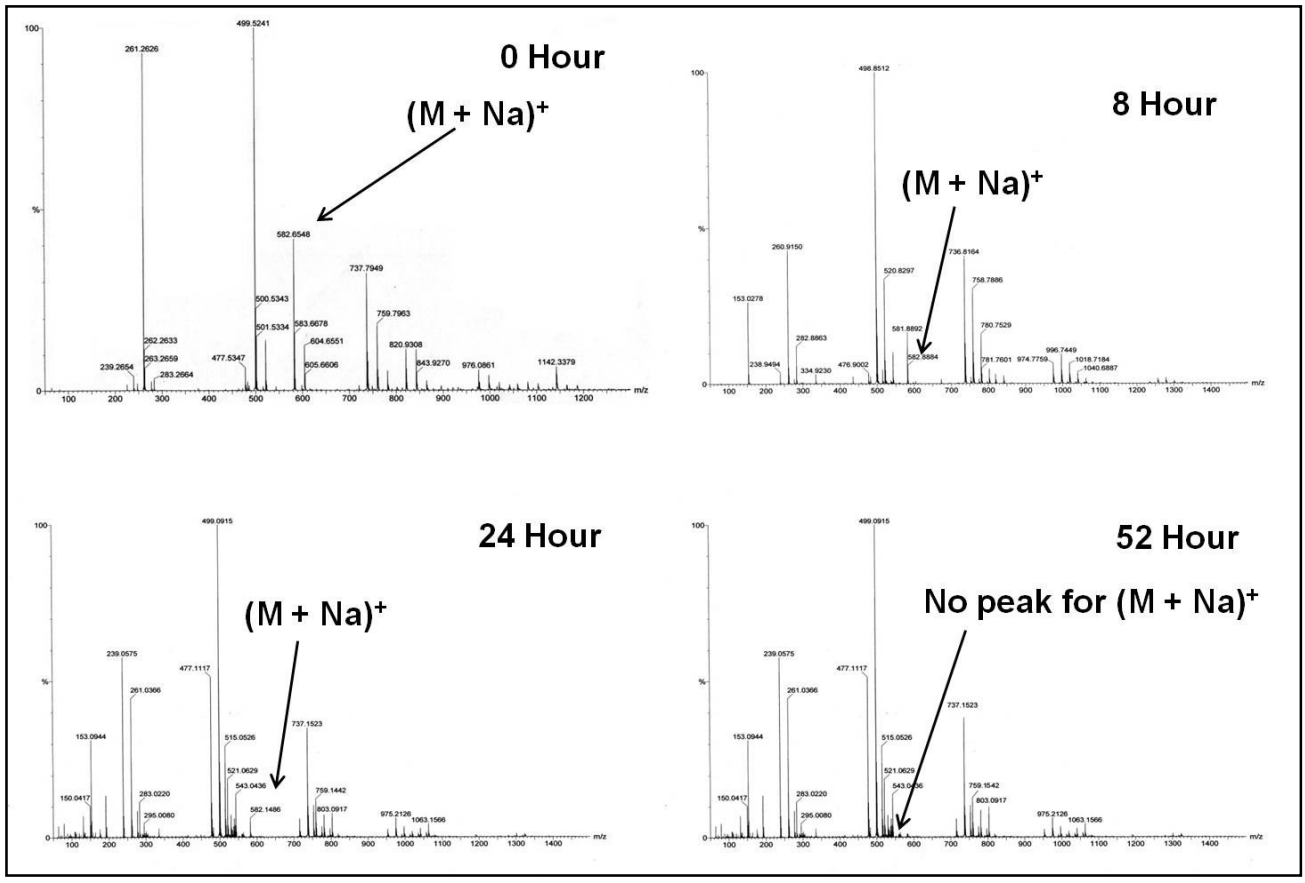


**Fig. S37** High resolution mass spectral data for the proteolytic stability experiment of **P1** (molecular weight shown as M) with respect to proteinase K in HEPES buffer. m/z = 239, 261, 499 corresponds to $(M+H)^+$, $(M+Na)^+$, $(2M+Na)^+$, where M (HEPES) = 238 m/z.

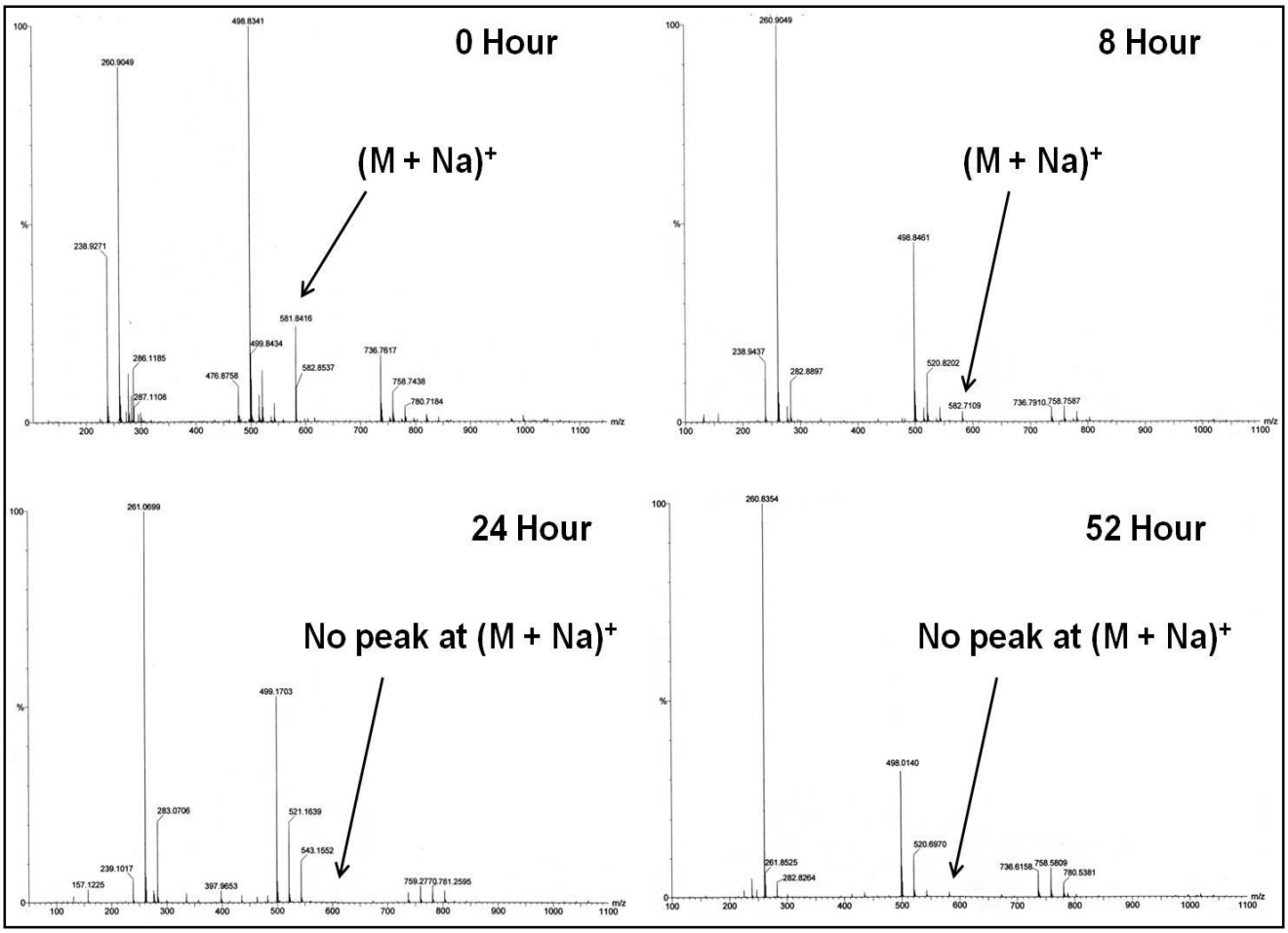


**Fig. S38** High resolution mass spectral data for the proteolytic stability experiment of **P2** (molecular weight shown as M) with respect to proteinase K in HEPES buffer. m/z = 239, 261, 499 corresponds to $(M+H)^+$, $(M+Na)^+$, $(2M+Na)^+$, where M (HEPES) = 238 m/z.

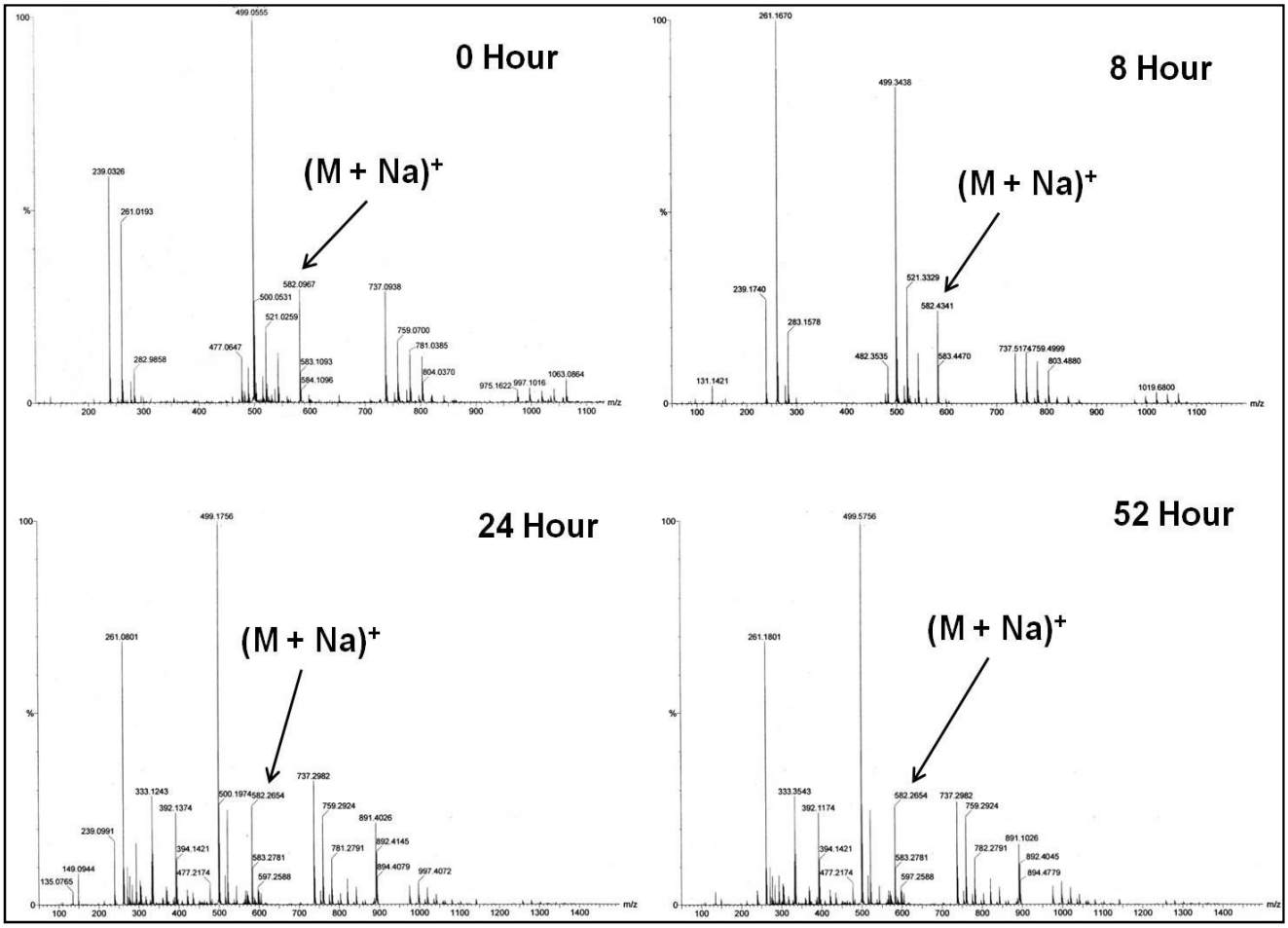


**Fig. S39** High resolution mass spectral data for the proteolytic stability experiment of **P5** (molecular weight shown as M in Fig.) with respect to proteinase K in HEPES buffer. m/z = 239, 261, 499 corresponds to $(M+H)^+$, $(M+Na)^+$, $(2M+Na)^+$, where M (HEPES) = 238 m/z.

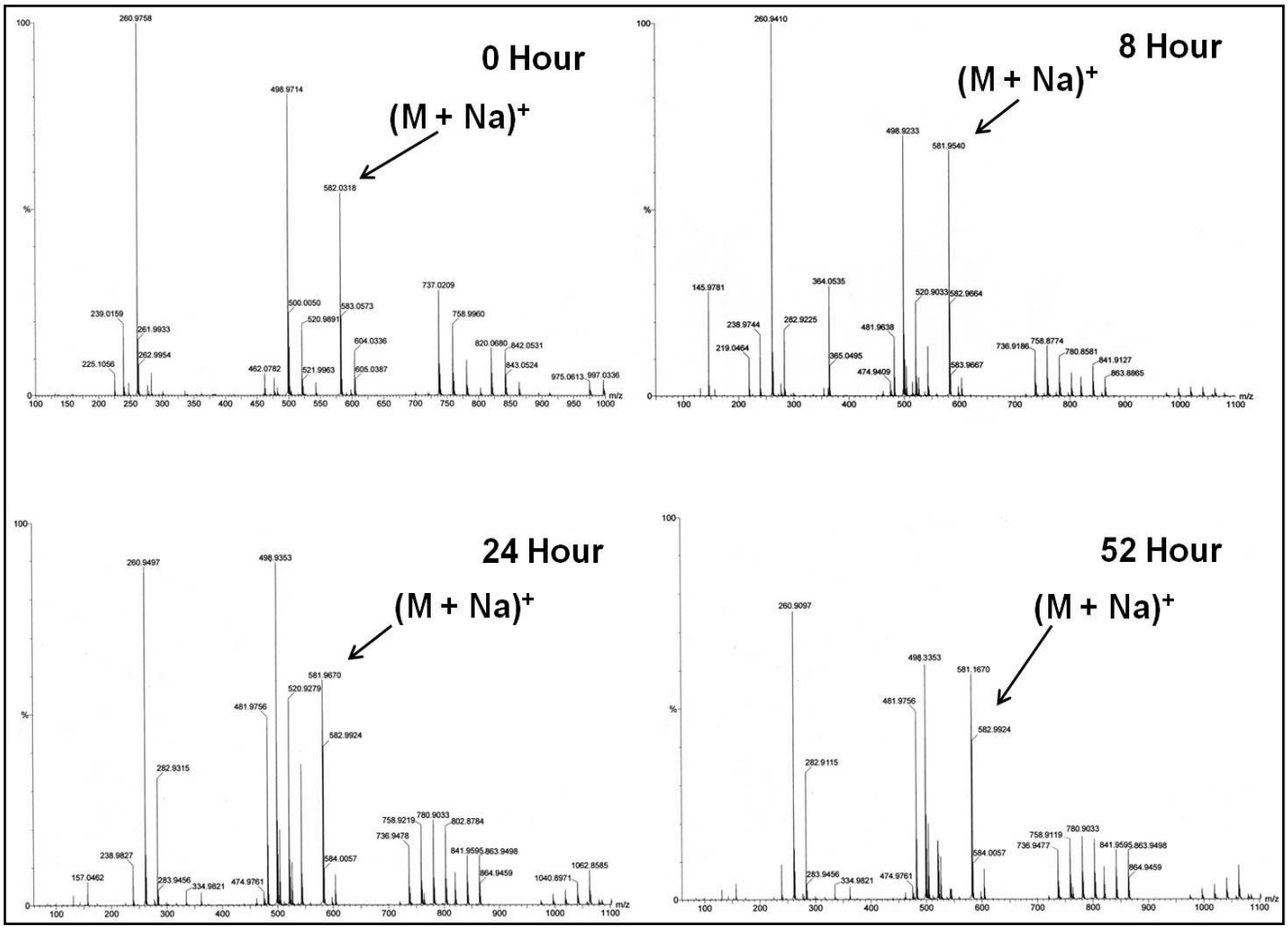


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**Fig. S40** High resolution mass spectral data for the proteolytic stability of **P6** (molecular weight shown as M) with respect to proteinase K in HEPES buffer. m/z = 239, 261, 498.9 corresponds to $(M+H)^+$, $(M+Na)^+$, $(2M+Na)^+$, where M (HEPES) = 238 m/z.

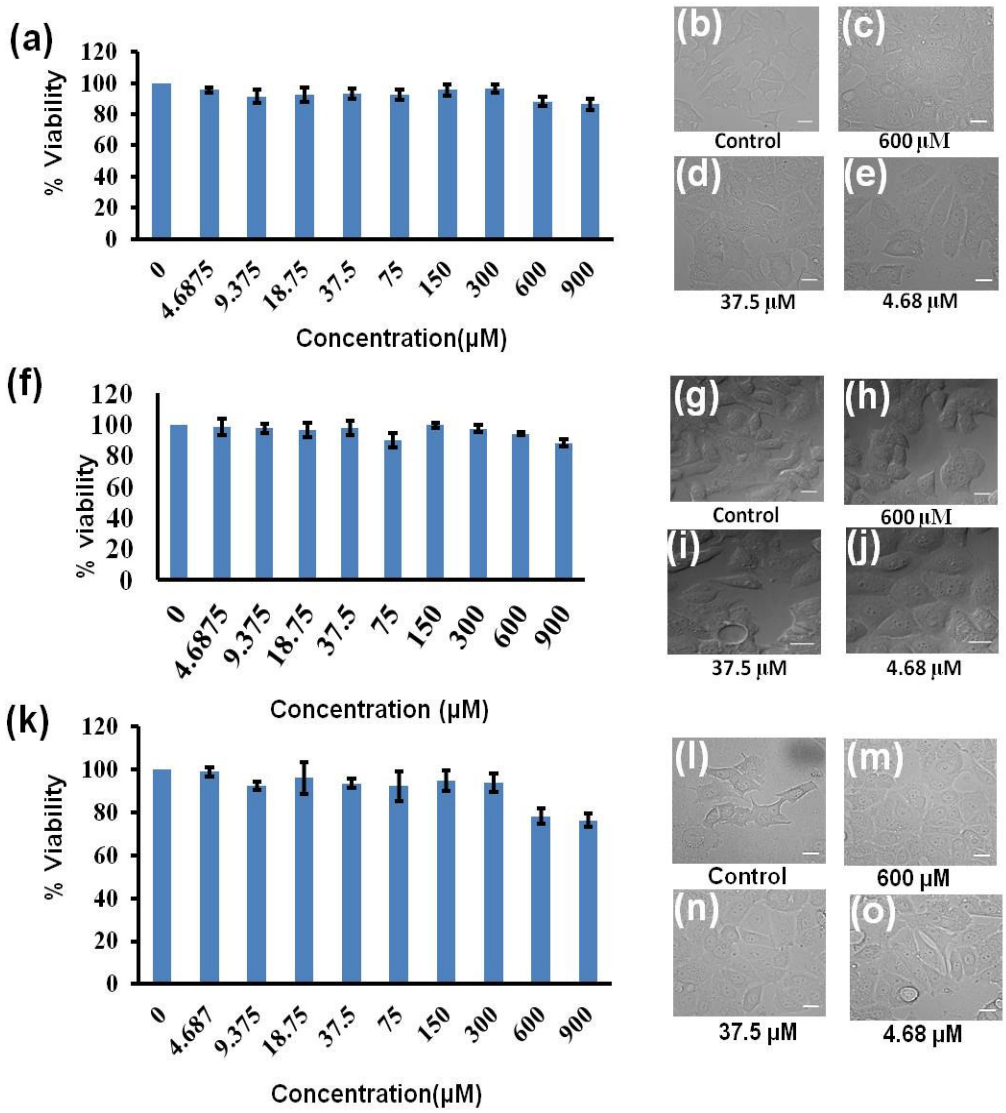


**Fig. S41** MTT assay study of MCF-7 cells after treatment with gelators (a) **P1** (f) **P2** and (k) **P5.** (b-e) Cell morphology of the MCF-7 cells (at 40X objective) after 24 h with **P1**, (b) control (without treatment with **P1**), (c) 600 $\mu$M, (d) 37.5 $\mu$M and (e) 4.68 $\mu$M of **P1**. (g-j) Cell morphology of the MCF-7 cells (at 40 X objective) after 24 h with **P2**, (g) control (without treatment with **P2**), (h) 600 $\mu$M, (i) 37.5 $\mu$M and (j) 4.68 $\mu$M of P2. (l-o) Cell morphology of the MCF-7 cells (at 40 Xobjective) after 24 h with **P5**, (l) control (without treatment with **P5**), (m) 600 $\mu$M, (n) 37.5 $\mu$M and (o) 4.68 $\mu$M of P5.Scale bar corresponds to 20 μm.

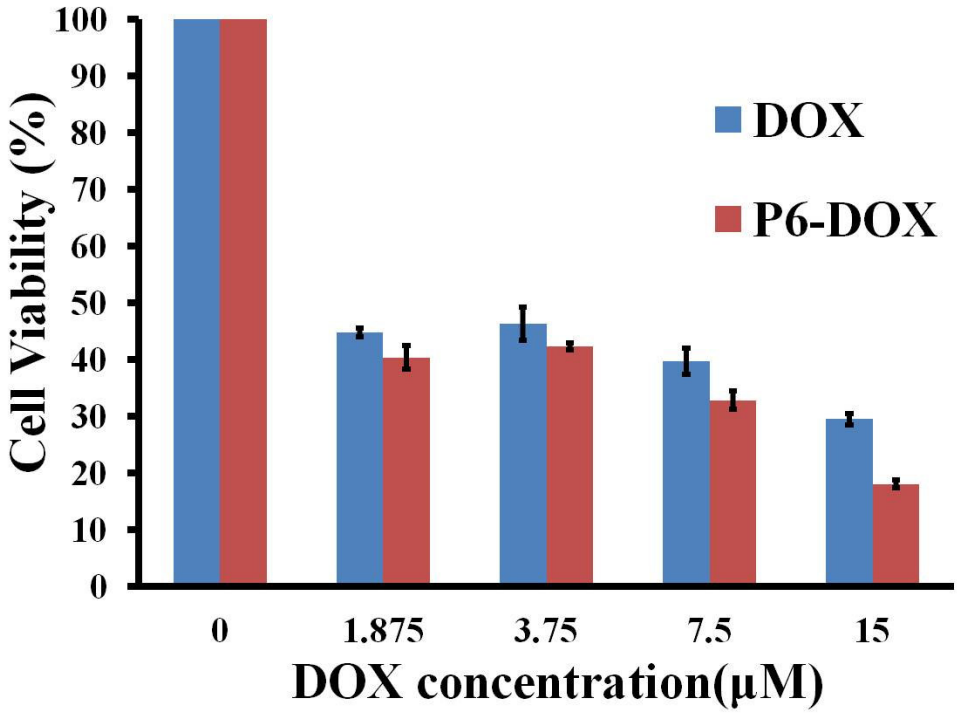


**Fig. S42** MTT assay of MCF-7 cells after treatment with free Doxorubicin (blue column) and Doxorubicin-loaded **P6** hydrogel (red column) at different concentrations of Doxorubicin.