Electronic Supplementary Information (ESI)

Dynamic self-shrinking peptide hydrogels with shape memory and self-healing properties

Biplab Mondal, [†a] Sandip Mandal,[†b] Tanushree Mondal,[a] Prabal K. Maiti,[b] Arindam Banerjee*[a]*

[a]School of Biological Sciences, Indian Association for the Cultivation of Science, 2A & 2B Raja S. C. Mullick Road, Jadavpur, Kolkata-700032.

[b]Center for Condensed Matter Theory, Department of Physics, Indian Institute of Science, Bangalore 560012, India.

E-mail: maiti@iisc.ac.in, bcab@iacs.res.in

*** Corresponding author**

† Contributed equally

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Instrumentations.

NMR experiments: All NMR studies were carried out on Bruker DPX 400 MHz and Brüker DPX 500MHz spectrometers at 300 K. Compounds concentrations were in the range 1–10 mM in $CDCl_3$ or DMSO-d_6.

Mass spectrometry: Mass spectra were recorded on a Q-Tof micro^{TM} (Waters Corporation) mass spectrometer by positive mode electro spray ionisation process.

MALDI-TOF MS study: The MALDI-TOF MS analyses were done using Bruker Daltonics flex Analysis mass spectrometer.

FT-IR Spectroscopy: FTIR spectroscopy was performed using Nicolate 380 FT-IR spectrophotometer (Thermo Scientific). FTIR spectra were recorded using a cell with CaF_2 windows.

Field Emission Scanning Electron Microscopic Study (FE-SEM)

FE-SEM experiments were performed by placing a small portion of gel sample on a microscope cover glass. Then, these samples were dried first in air and then in vacuum and coated with platinum for 90 sec at 10 kV voltages and 10 μA 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.

High Resolution-Transmission Electron Microscopy (HR-TEM): TEM images were recorded on a JEM 2010 electron microscope at an accelerating voltage of 200 KV. During HR-TEM experiment, 20 μL of gel (concentration of gelator is 31.68 mM) was taken in a screw cap vial and diluted with 2 mL milli-Q water. Then, a drop of dilute solution was

placed on a carbon coated copper grid (300 mesh) and dried by slow evaporation. The grid was then allowed to dry in a vacuum for two days and then images were taken.

Cryogenic Transmission Electron Microscopy (Cryo-TEM): Cryo-TEM images were recorded on a JEOL JEM-210 PLUS Cryogenic transmission electron microscope at an accelerating voltage of 200 KV.

Powder X-ray diffraction: X-ray diffraction measurements on the xerogel were carried out by placing the sample on a glass plate. Experiments were carried out using an X-ray diffractometer (Bruker D8 Advance) with a parallel beam optics attachment. The instrument was operated at 35 kV voltages and 30 mA current using Ni-filtered CuKα radiation and the instrument was calibrated with a standard silicon sample before use. Samples were scanned from 2º to 30º (2θ) in the step scan mode (step size 0.03°, present time 2s) and diffraction patterns were recorded using a scintillation scan detector.

Rheometer: Rheology experiments were performed with a SDT Q Series AR 2000 advanced rheometer (TA Instruments) using cone-plate geometry in a Peltier plate.

Dynamic Light-Scattering (DLS) and Zeta Potential Study

Zen 3690 Zetasizer (Malvern Instrument Ltd.) was used for measurement of mean hydrodynamic diameter and zeta potential. The scattering intensity was at 173° angle and Malvern Zetasizer software was used for data analysing to determine the Zeta potential.

Detailed Synthetic Procedure of Gelator G1, G2 and G3

1. Synthesis of C_{14}-Trp-OMe (C_{14} = Myristoyl group; "$CH_3(CH_2)_{12}$-CO-"): Myristic acid (2.28 g, 10 mM) was taken in a 250 mL round bottom flask and 10 mL (dimethyl formamide) DMF was added to dissolve it. After that the mixture was cooled in an ice-water bath having temperature 0 °C–10 °C. H-Trp-OMe was isolated from the corresponding methyl ester hydrochloride (3.054 g, 12 mM) by neutralization, subsequent extraction with ethyl acetate

and concentration to 50 mL. Then it was added to the reaction mixture, followed immediately by DCC (2.472 g, 12 mM) and HOBt (1.62 g, 12 mM). The reaction mixture was stirred for 36 h in nitrogen atmosphere. The reaction mixture was filtered through a sintered glass crucible and the DCU (dicyclohexylurea) was filtered off. The organic layer was washed with brine (2 × 50 mL) and then dried over anhydrous sodium sulphate and evaporated in vacuum to yield peptide as a white solid. Purification was done using a silica gel column (100–200 mesh) using chloroform and ethyl acetate as eluents. Yield: 3.89 g, (9.09 mM, 90.89 %).

^{1}H NMR (500 MHz, $CDCl_3$, TMS, 25 °C): δ 8.57 (1H, s, NH), 7.53 (1H, d, J= 8.0 Hz, aromatic), 7.34 (1H, d, J= 8.0 Hz, aromatic), 7.19 (1H, t, J= 7.5 Hz, aromatic), 7.11 (1H, t, J= 7.5 Hz, aromatic), 6.95 (1H, d, J= 7.6 Hz, aromatic), 6.06 (1H, d, J= 8.0 Hz, NH of amide), 4.99–4.96 (1H, m, α –CH of Trp), 3.68 (3H, s, $–OCH_3$), 3.33–3.31 (2H, m, β $–CH_2$ of Trp), 2.14 (2H, t, J= 7.5 Hz, α $–CH_2$ of myristyl), 1.58–1.55 (2H, m, β $–CH_2$ of myristyl), 1.33–1.24 (20H, m, 10 $–CH_2$ of myristyl chain), 0.9 (3H, t, J= 6.5 Hz, $–CH_3$ of myristyl) (Fig. S1).

^{13}C NMR (125 MHz, $CDCl_3$, TMS, 25 °C): δ 173.09, 172.66, 136.31, 127.82, 122.89, 122.23, 119.66, 118.57, 111.45, 110.00, 53.06, 52.35, 36.66, 32.00, 29.77, 29.73, 29.70, 29.55, 29.43, 29.41, 29.31, 27.77, 25.57, 22.76, 14.18 (Fig. S2).

HRMS (m/z): Calculated for $C_{26}H_{40}N_2O_3$: 428.30 (M) Found: 429.3571 $(M + H)^+$, 452.3448 $(M + Na)^+$ (Fig. S3).

2. Synthesis of C_{14}-Phe-OMe: Myristic acid (1.14 g, 5 mM) was taken in a 250 mL round bottom flask and 8 mL (N, N'-Dimethylformamide) DMF was added to dissolve it. After that the mixture was cooled in an ice-water bath having temperature 0 °C–10 °C. H-Phe-OMe was isolated from the corresponding methyl ester hydrochloride (1.186 g, 5.5 mM) by neutralization, subsequent extraction with ethyl acetate and concentration to 50 mL. Then it was added to the reaction mixture, followed immediately by DCC (1.133 g, 5.5 mM) and

HOBt (0.697 g, 5.5 mM). The reaction mixture was stirred for 48 h. The reaction mixture was filtered through a sintered glass crucible and the DCU (dicyclohexyl urea) was filtered off. The organic layer was washed with brine (2 × 50 mL) and then dried over anhydrous sodium sulphate and evaporated in vacuum to yield peptide as a white solid. Purification was done using a silica gel column (100–200 mesh) using chloroform and ethyl acetate as eluents.

Yield: 1.46 g (3.75 mM, 74.90%).

^{1}H NMR (500 MHz, $CDCl_3$, TMS, 25 °C): δ 7.27 (m, 3H, aromatic), 7.09 (d, 2H, J=6.5 Hz, aromatic) 5.89 (d, J= 7.5 Hz, 1H, NH of amide), 4.90 (m, 1H, α–CH of Phe), 3.73 (s, 3H,–OCH_3), 3.12 (m, 2H, β–CH_2 of Phe), 2.17 (t, 2H, J= 7.5 Hz, α–CH_2 of myristyl C=O), 1.58 (m, 2H, β–CH_2 of myristyl C=O), 1.25 (m, 20H, 10–CH_2 of myristyl chain), 0.88 (t, 3H, J= 6.75 Hz, –CH_3 of myristyl) (Fig. S4).

^{13}C NMR (125 MHz, $CDCl_3$, TMS, 25 °C): δ 172.8, 172.3, 136.0, 129.4, 128.7, 127.2, 53.0, 36.7, 32.1, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 29.3, 25.7, 22.8, 14.2 (Fig. S5).

MALDI-TOF MS (m/z): Calculated for $C_{24}H_{39}NO_3$ (M): 412.283 $(M + Na)^+$, 428.256 $(M + K)^+$ Found: 412.920 $(M + Na)^+$, 428.919 $(M + K)^+$ (Fig. S6).

3. Synthesis of C_{14}-Trp-OH: C_{14}–Trp–OMe (3.78 g, 8.83 mM) was taken in a 250 mL round bottom flask. The solid was dissolved in MeOH (40 mL) and 1N NaOH (15 mL) was added to the mixture. The reaction mixture was stirred for 12 h in nitrogen atmosphere and the progress of saponification was monitored by thin layer chromatography (TLC). After 12 h methanol was removed under vacuum, the residue was taken in 50 mL of water, washed with diethyl ether (2 × 50 mL). Then the pH of the aqueous layer was adjusted to 2 using 1(N) HCl and it was extracted with ethyl acetate (3 × 50 mL). The extracts were dried over anhydrous sodium sulphate, and evaporated in vacuum to yield as a white solid product.

Purification was done using a silica gel column (100–200 mesh) using chloroform and methanol as eluents. Yield: 3.43 g, (8.36 mM, 94.68 %).

^{1}H NMR (500 MHz, DMSO–d_6, TMS, 25 °C): δ 12.53 (1H, br, –COOH), 10.80 (1H, s, NH), 8.01 (1H, d, J= 8.0 Hz, NH), 7.52 (1H, d, J= 8.0 Hz, aromatic), 7.32 (1H, d, J= 8.5 Hz, aromatic), 7.11 (1H, s, aromatic), 7.05 (1H, t, J= 7.5 Hz, aromatic), 6.97 (1H, t, J= 7.5 Hz, aromatic), 4.49–4.45 (1H, m, α –CH), 3.17–2.96 (2H, m, β –CH_2 of Trp), 2.05 (2H, t, J= 7.5 Hz, α –CH_2 of myristyl), 1.42–1.38 (2H, m, β –CH_2 of myristyl), 1.28–1.14 (20H, m, 10 –CH_2 of myristyl chain), 0.85 (3H, t, J= 6.5 Hz, –CH_3 of myristyl) (Fig. S7).

^{13}C NMR (125 MHz, DMSO–d_6, TMS, 25 °C): δ 173.52, 172.12, 136.04, 127.19, 123.40, 120.79, 118.22, 118.11, 111.27, 110.00, 52.78, 35.06, 31.25, 29.00, 28.98, 28.87, 28.76, 28.67, 28.51, 27.11, 25.11, 22.04, 13.88 (Fig. S8).

HRMS (m/z): Calculated for $C_{25}H_{38}N_2O_3$: 414.29 (M) Found: 415.315 $(M + H)^+$, 437.2995 $(M + Na)^+$ (Fig. S9).

4. Synthesis of C_{14}-Phe-OH: C_{14}-Phe-OMe (1.4 g, 3.6 mM) was taken in a 250 mL round bottom flask. The solid was dissolved in MeOH (40 mL) and 1N NaOH (15 mL) was added to the mixture. The reaction mixture was stirred for 12 h and the progress of saponification was monitored by thin layer chromatography (TLC). After 12 h methanol was removed under vacuum, the residue was taken in 50 mL of water, washed with diethyl ether (2 × 50 mL). Then the pH of the aqueous layer was adjusted to 2 using 1N HCl and it was extracted with ethyl acetate (3 × 50 mL). The extracts were dried over anhydrous sodium sulphate, and evaporated in vacuum to yield as a white solid product. Purification was done using a silica gel column (100–200 mesh) using chloroform and methanol as eluents.

Yield: 1.28 g (3.41 mM, 95%).

^{1}H NMR (400 MHz, DMSO-d_6, TMS, 25 °C): δ 12.63 (1H, br, –COOH), 8.08 (d, J=7.6 Hz, 1H, NH), 7.23 (m, 5H, aromatic), 4.43 (m, 1H, α–CH of Phe), 2.95 (m, 2H, β–CH_2 of Phe), 2.03 (t, J= 7.2 Hz, 2H, α –CH_2 of myristyl C=O), 1.38 (m, 2H, β –CH_2 of myristyl C=O), 1.18 (m, 20H, 10–CH_2 of myristyl chain), 0.86 (t, J= 6.8 Hz, 3H, –CH_3 of myristyl) (Fig. S10).

^{13}C NMR (100 MHz, DMSO-d_6, TMS, 25 °C): δ 173.1, 172.0, 137.7, 129.0, 128.0, 126.2, 53.1, 36.7, 35.0, 31.2, 29.0, 28.9, 28.8, 28.7, 28.6, 28.4, 25.1, 22.0, 13.8 (Fig. S11).

MALDI-TOF MS (m/z): Calculated for $C_{23}H_{37}NO_3$ (M): 376.285 $(M + H)^+$, 398.267 $(M + Na)^+$, 414.241 $(M + K)^+$ Found: 376.864 $(M + H)^+$, 398.857 $(M + Na)^+$, 414.890 $(M + K)^+$ (Fig. S12).

5. **Synthesis of C_{14}-Trp-Trp-OMe:** C_{14}–Trp–OH (8 mM, 3.32 g) was taken in a 250 mL round bottom flask and 10 mL DMF was added to dissolve it. After that the mixture was cooled in an ice-water bath having temperature 0 °C–10 °C. H–Trp–OMe was isolated from the corresponding methyl ester hydrochloride (2.42 g, 10 mM) by neutralization, subsequent extraction with ethyl acetate and concentration to 50 mL. Then it was added to the reaction mixture, followed immediately by DCC (2.06 g, 10 mM) and HOBt (1.36 g, 10 mM). The reaction mixture was stirred for 48 h in nitrogen atmosphere. The reaction mixture was filtered through sintered glass crucible and the DCU (dicyclohexylurea) was filtered off. The organic layer was washed with brine (2 × 50 mL) and then dried over anhydrous sodium sulphate and evaporated in vacuum to yield peptide as a white solid. Purification was done using a silica gel column (100–200 mesh) using chloroform and methanol as eluents.

Yield: 3.92 g (6.42 mM, 85%).

^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 °C): δ 8.25 (1H, NH), 8.20 (1H, NH), 7.70–7.68 (1H, d, J = 7.6 Hz), 7.33–7.08 (6H, m), 6.93–6.92 (1H, m), 6.83–6.80 (1H, t, J = 7.4 Hz), 6.62

(1H, m), 6.24–6.22, 6.18–6.16, 4.80–4.72, 3.59, 3.34–3.04 (4H, m), 1.99–1.92 (2H, m), 1.46–1.43 (2H, m), 1.32–1.19 (20H, m), 0.90–0.86 (3H, t, J = 6.6 Hz) (Fig. S13).

^{13}C NMR (125 MHz, $CDCl_3$, TMS, 25 °C): δ 173.31, 171.84, 171.16, 162.72, 136.35, 136.20, 127.70, 127.45, 123.75, 123.27, 122.29, 122.22, 119.88, 119.59, 119.06, 118.42, 111.43, 111.37, 110.54, 109.39, 53.68, 52.95, 52.41, 36.65, 36.60, 32.04, 31.58, 29.81, 29.78, 29.59, 29.47, 29.43, 29.43, 29.30, 28.31, 27.50, 25.61, 22.80, 14.23 (Fig. S14).

HRMS (m/z): Calculated for $C_{37}H_{50}N_4O_4$: 614.3832 (M) Found: 615.0584 $(M + H)^+$, 637.0395 $(M + Na)^+$, 653.0159 $(M + K)^+$ (Fig. S15).

6. Synthesis of C_{14}-Trp-Phe-OMe: C_{14}–Trp–OH (8 mM, 3.32 g) was taken in a 250 mL round bottom flask and 10 mL DMF was added to dissolve it. After that the mixture was cooled in an ice-water bath having temperature 0 °C–10 °C. H–Phe–OMe was isolated from the corresponding methyl ester hydrochloride (2.16 g, 10 mM) by neutralization, subsequent extraction with ethyl acetate and concentration to 50 mL. Then it was added to the reaction mixture, followed immediately by DCC (2.06 g, 10 mM) and HOBt (1.35 g, 10 mM). The reaction mixture was stirred for 48 h in nitrogen atmosphere. The reaction mixture was filtered through sintered glass crucible and the DCU (dicyclohexylurea) was filtered off. The organic layer was washed with brine (2 × 50 mL) and then dried over anhydrous sodium sulphate and evaporated in vacuum to yield peptide as a white solid. Purification was done using a silica gel column (100–200 mesh) using chloroform and methanol as eluents.

Yield: 3.78 g, (8.57 mM, 82.17 %).

^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 °C): δ 8.28 (1H, s, NH), 7.73 (1H, d, J= 8 Hz, aromatic), 7.38–7.06 (8H, m, aromatic), 6.86 (1H, d, J= 6.8 Hz, aromatic), 6.25 (1H, d, J= 7.6 Hz, NH), 6.18 (1H, d, J= 7.6 Hz, NH), 4.78–4.68 (2H, m, 2α –CH), 3.65 (3H, s, $–OCH_3$), 3.36–3.08 (2H, m, 2β $–CH_2$), 3.03–2.9 (2H, m, 2β $–CH_2$), 2.17 (2H, t, J= 7.5 Hz, α $–CH_2$ of

myristyl), 1.562 (2H, m, β –CH_2 of myristyl), 1.36–1.26 (20H, m, 10 –CH_2 of myristyl chain), 0.91 (3H, t, J= 6.8 Hz, –CH_3 of myristyl) (Fig. S16).

^{13}C NMR (100 MHz, $CDCl_3$, TMS, 25 °C): δ 173.21, 171.4, 171.12, 136.38, 135.7, 129.38, 129.22, 128.77, 128.71, 127.14, 123.55, 122.38, 119.94, 119.01, 111.37, 110.72, 53.72, 53.52, 53.52, 51.96, 38.00, 37.94, 36.78, 32.03, 29.80, 29.77, 29.75, 29.58, 29.46, 29.45, 29.34, 28.37, 26.07, 25.64, 25.64, 22.80, 14.22 (Fig. S17).

HRMS (m/z): Calculated for $C_{34}H_{47}N_3O_4$: 575.3723 (M) Found: 576.5914 $(M + H)^+$, 598.5812 $(M + Na)^+$, 1174.2277 $(2M + Na)^+$ (Fig. S18).

7. Synthesis of C_{14}-Phe-Trp-OMe: C_{14}–Phe–OH (8 mM, 3.00 g) was taken in a 250 mL round bottom flask and 10 mL DMF was added to dissolve it. After that the mixture was cooled in an ice-water bath having temperature 0 °C–10 °C. H–Trp–OMe was isolated from the corresponding methyl ester hydrochloride (2.41 g, 10 mM) by neutralization, subsequent extraction with ethyl acetate and concentration to 50 mL. Then it was added to the reaction mixture, followed immediately by DCC (2.06 g, 10 mM) and HOBt (1.35 g, 10 mM). The reaction mixture was stirred for 48 h in nitrogen atmosphere. The reaction mixture was filtered through sintered glass crucible and the DCU (dicyclohexylurea) was filtered off. The organic layer was washed with brine (2 × 50 mL) and then dried over anhydrous sodium sulphate and evaporated in vacuum to yield peptide as a white solid. Purification was done using a silica gel column (100–200 mesh) using chloroform and methanol as eluents.

Yield: 3.61 g, (6.28 mM, 78.50 %).

^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 °C): δ 8.23 (1H, NH, Trp), 7.35–6.88 (10H, aromatic), 6.41–6.39 (1H, NH), 5.95–5.93 (1H, NH), 4.84–4.83 (1H, m, α–CH), 4.70–4.68 (1H, m, α–CH), 3.65 (3H, s, –OMe), 3.24–3.22 (2H, m, β–CH_2), 3.04–3.02 (2H, m, β–CH_2), 1.97–1.93

(2H, t, J= 7.6 Hz), 1.46–1.40 (2H, m, –CH_2 myristyl), 1.32–1.15 (20H, myristyl), 0.90–0.86 (3H, t, J= 6.4 Hz) (Fig. S19).

^{13}C NMR (125 MHz, $CDCl_3$, TMS, 25 °C): δ 173.21, 171.80, 170.75, 136.64, 136.24, 129.55, 128.71, 127.61, 127.11, 123.24, 122.33, 119.76, 118.54, 111.49, 109.70, 54.06, 53.12, 52.47, 38.26, 36.59, 32.05, 29.82, 29.80, 29.77, 29.60, 29.49, 29.45, 29.26, 27.63, 25.66, 22.82, 14.24 (Fig. S20).

MALDI-TOF MS (m/z): $C_{34}H_{47}N_3O_4$: 575.3723 (M) Found: 597.100 $(M + Na)^+$, 613.099 $(M + K)^+$ (Fig. S21).

8. Synthesis of C_{14}-Trp-Trp-OH: C_{14}–Trp–Trp–OMe (3.07 g, 5.0 mM) was taken in a 250 mL round bottom flask. The solid was dissolved in MeOH (60 mL) and 1(N) NaOH (25 mL) was added to the mixture. The reaction mixture was stirred for 12 h in nitrogen atmosphere and the progress of reaction was monitored by thin layer chromatography (TLC). After 12 h methanol was removed under vacuum, the residue was taken in 50 mL of water. Then the pH of the aqueous layer was adjusted to 2 using 1(N) HCl and it was extracted with ethyl acetate (3 × 50 mL). The extracts were dried over anhydrous sodium sulphate, and evaporated in vacuum to yield as a white solid sample. Purification was done by silica gel column (100–200 mesh) using chloroform and methanol as eluents.

Yield: 2.68 g, (95.54 %)

^{1}H NMR (500 MHz, DMSO-d_6, TMS, 25 °C): δ 10.84, 10.74, 8.11–8.09 (1H, d, J = 7.5 Hz), 7.84–7.82 (1H, d, J = 8.5 Hz), 7.57–7.56 (1H, d, J = 7.5 Hz), 7.51–7.49 (1H, d, J = 7.5 Hz), 7.32–7.27 (2H, m), 7.13–6.92 (6H, m), 4.57–4.55 (1H, m), 4.50–4.47 (1H, m), 3.19–2.83 (4H, m), 1.97–1.94 (2H, m), 1.31–1.04 (22H, m), 0.85–0.82 (3H, t, J = 6.5 Hz) (Fig. S22).

^{13}C NMR (125 MHz, DMSO-d_6, TMS, 25 °C): δ 173.07, 172.06, 171.71, 136.01, 127.35, 127.24, 123.70, 123.57, 123.44, 120.84, 120.70, 118.38, 118.31, 118.13, 118.05, 111.29,

111.16, 110.22, 109.53, 53.00, 52.87, 35.24, 31.25, 29.00, 28.84, 28.75, 28.65, 28.49, 27.51, 26.99, 25.08, 22.04, 13.90 (Fig. S23).

MALDI-TOF MS (m/z): $C_{34}H_{47}N_3O_4$: 600.3676 (M) Found: 623.067 $(M + Na)^+$, 639.012 $(M + K)^+$ (Fig. S24).

9. Synthesis of C_{14}-Trp-Phe-OH: C_{14}–Trp–Phe–OMe (2.88 g, 5.0 mM) was taken in a 250 mL round bottom flask. The solid was dissolved in MeOH (60 mL) and 1(N) NaOH (25 mL) was added to the mixture. The reaction mixture was stirred for 12 h in nitrogen atmosphere and the progress of reaction was monitored by thin layer chromatography (TLC). After 12 h methanol was removed under vacuum, the residue was taken in 50 mL of water. Then the pH of the aqueous layer was adjusted to 2 using 1(N) HCl and it was extracted with ethyl acetate (3 × 50 mL). The extracts were dried over anhydrous sodium sulphate, and evaporated in vacuum to yield as a white solid sample. Purification was done by silica gel column (100–200 mesh) using chloroform and methanol as eluents.

Yield: 2.56 g, (91.23 %)

^{1}H NMR (400 MHz, DMSO–d_6, TMS, 25 °C): δ 12.79 (1H, br, –COOH), 10.77 (1H, s, –NH of indole), 8.15 (1H, d, J= 7.6Hz, NH), 7.85 (1H, d, J= 8.4Hz, NH), 7.58(1H, d, J= 7.6Hz, aromatic, ortho –CH of indole –NH), 7.32–6.94 (9H, m, aromatic), 4.6–4.54(1H, m, α –CH), 4.49–4.43 (1H, m, α –CH), 3.10–3.05 (2H, m, β–CH_2), 2.97–2.82 (2H, m, β–CH_2), 2.01–1.97 (2H, m, α –CH_2 of myristyl), 1.37–1.28 (22H, m, 11–CH_2 of myristyl chain), 0.86 (3H, t, J= 6.6 Hz, –CH_3 of myristyl) (Fig. S25).

^{13}C NMR (100 MHz, DMSO–d_6, TMS, 25 °C): δ 172.63, 171.93, 171.68, 137.36, 135.98, 129.2, 129.09, 128.08, 127.32, 126.34, 123.39, 120.68, 118.33, 118.03, 111.14, 110.18, 53.32, 52.91, 36.64, 35.21, 31.23, 28.97, 28.81, 28.74, 28.64, 28.47, 27.53, 25.05, 22.03, 13.88 (Fig. S26).

HRMS (m/z): Calculated for $C_{34}H_{47}N_3O_4$: 561.36 (M) Found: 584.7161 $(M + Na)^+$, 585.7310 $(M + H + Na)^+$, 586.7324 $(M + 2H + Na)^+$ (Fig. S27).

10. Synthesis of C_{14}-Phe-Trp-OH: C_{14}-Phe-Trp-OMe (2.88 g, 5.0 mM) was taken in a 250 mL round bottom flask. The solid was dissolved in MeOH (40 mL) and 1N NaOH (15 mL) was added to the mixture. The reaction mixture was stirred for 12 h and the progress of saponification was monitored by thin layer chromatography (TLC). After 12 h methanol was removed under vacuum, the residue was taken in 50 mL of water, washed with diethyl ether (2 × 50 mL). Then the pH of the aqueous layer was adjusted to 2 using 1N HCl and it was extracted with ethyl acetate (3 × 50 mL). The extracts were dried over anhydrous sodium sulphate, and evaporated in vacuum to yield as a white solid product. Purification was done using a silica gel column (100–200 mesh) using chloroform and methanol as eluents.

Yield: 3.78 g, (8.83 mM, 88.32 %).

^{1}H NMR (400 MHz, DMSO–d_6, TMS, 25 °C): δ ^{1}H NMR (400 MHz, DMSO, TMS, 25 °C): δ 12.67 (s, 1H), 10.90 – 10.85 (m, 1H), 8.16 (d, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.28 – 7.16 (m, 4H), 7.20 – 7.11 (m, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 4.54 (dtd, *J* = 27.1, 8.8, 7.6, 4.6 Hz, 2H), 3.20 (dd, *J* = 14.8, 5.4 Hz, 1H), 3.14 – 2.98 (m, 2H), 2.71 (dd, *J* = 13.9, 10.5 Hz, 1H), 1.98 (dt, *J* = 8.4, 4.3 Hz, 2H), 1.31 (d, *J* = 7.0 Hz, 1H), 1.25 (s, 14H), 1.23 – 1.11 (m, 6H), 1.04 (t, *J* = 7.4 Hz, 2H), 0.87 (t, *J* = 6.7 Hz, 3H) (Fig. S28).

^{13}C NMR (400 MHz, DMSO–d_6, TMS, 25 °C): δ 173.09, 172.01, 171.46, 138.04, 136.03, 129.15, 127.83, 127.21, 126.03, 123.59, 120.85, 118.33, 118.14, 111.30, 109.51, 53.43, 52.85, 37.37, 35.18, 31.27, 29.03, 28.99, 28.87, 28.77, 28.69, 28.40, 26.98, 25.15, 22.07, 13.92 (Fig. S29).

HRMS (m/z): Calculated for $C_{34}H_{47}N_3O_4$: 561.36 (M) Found: 562.2708 $(M + H)^+$, 584.2351 $(M + Na)^+$, 585.2495 $(M + H + Na)^+$, 586.2516 $(M + 2H + Na)^+$ (Fig. S30).

11. Synthesis of C_{14}-Trp-Phe-Trp-OMe: C_{14}-Trp-Phe-OH (1.13 g, 2.0 mM) was taken in a 250 mL round bottom flask and 10 mL DMF was added to dissolve it. After that the mixture was cooled in an ice-water bath having temperature 0 °C–10 °C. H–Trp–OMe was isolated from the corresponding methyl ester hydrochloride (0.61 g, 2.5 mM) by neutralization, subsequent extraction with ethyl acetate and concentration to 50 mL. Then it was added to the reaction mixture, followed immediately by DCC (0.52 g, 2.5 mM) and HOBt (0.34 g, 2.5 mM). The reaction mixture was stirred for 48 h in nitrogen atmosphere. The reaction mixture was filtered through sintered glass crucible and the DCU (dicyclohexylurea) was filtered off. The organic layer was washed with brine (2 × 50 mL) and then dried over anhydrous sodium sulphate and evaporated in vacuum to yield peptide as a white solid. Purification was done using a silica gel column (100–200 mesh) using chloroform and methanol as eluents.
Yield: 1.19 g, (1.56 mM, 78.12 %).

^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 ºC): δ 8.19 (1H, NH of Trp), 7.71 (1H, NH of Trp), 7.69–6.63 (15H, aromatic), 6.35–6.33 (1H, d, J= 7.6 Hz, NH), 6.08–6.06 (1H, d, J= 7.6 Hz, NH), 5.75–5.73 (1H, d, J= 7.6 Hz, NH), 4.85–4.83 (1H, m, α–CH), 4.59–4.58 (1H, m, α–CH), 4.48–4.46 (1H, m, α–CH), 3.72 (3H, –OMe), 3.28–2.75 (6H, β–CH_2), 2.09–2.05 (2H, t, J= 7.6 Hz, α–CH_2 of myristyl C=O), 1.52 (2H, m), 1.30–1.24 (20H, –CH_2 of myristyl), 0.90–0.86 (3H, t, J = 6.8 Hz, –Me of myristyl) (Fig. S31).

^{13}C NMR (100 MHz, $CDCl_3$, TMS, 25 °C): δ 173.29, 172.16, 171.34, 170.09, 136.33, 136.16, 129.53, 129.46, 129.29, 128.75, 128.67, 127.78, 127.28, 126.99, 123.34, 123.30, 122.60, 122.42, 120.06, 119.84, 119.15, 118.78, 111.62, 111.47, 110.61, 109.96, 54.64,

53.58, 53.15, 52.58, 37.74, 36.70, 32.06, 29.83, 29.80, 28.62, 29.49, 29.40, 28.27, 27.59, 25.59, 22.82, 14.24 (Fig. S32).

HRMS (m/z): Calculated for $C_{46}H_{59}N_5O_5$: 761.4516 (M) Found: 761.6418 $(M)^+$, 783.5808 $(M + Na)^+$, 800.5589 $(M + K)^+$, 801.5329 $(M + H + K)^+$, 802.5073 $(M + 2H + K)^+$ (Fig. S33).

12. Synthesis of C_{14}-Trp-Trp-Phe-OMe: C_{14}-Trp-Trp-OH (1.20 g, 2.0 mM) was taken in a 250 mL round bottom flask and 10 mL DMF was added to dissolve it. After that the mixture was cooled in an ice-water bath having temperature 0 °C–10 °C. H–Phe–OMe was isolated from the corresponding methyl ester hydrochloride (0.54 g, 2.5 mM) by neutralization, subsequent extraction with ethyl acetate and concentration to 50 mL. Then it was added to the reaction mixture, followed immediately by DCC (0.52 g, 2.5 mM) and HOBt (0.34 g, 2.5 mM). The reaction mixture was stirred for 48 h in nitrogen atmosphere. The reaction mixture was filtered through sintered glass crucible and the DCU (dicyclohexylurea) was filtered off. The organic layer was washed with brine (2 × 50 mL) and then dried over anhydrous sodium sulphate and evaporated in vacuum to yield peptide as a white solid. Purification was done using a silica gel column (100–200 mesh) using chloroform and methanol as eluents.
Yield: 1.12 g, (1.47 mM, 73.50 %).

^{1}H NMR (500 MHz, $CDCl_3$, TMS, 25 ºC): δ 8.16 (1H, NH of Trp), 7.84–7.83 (1H, NH of Trp), 7.71–7.70 (1H, d, J= 8.0 Hz), 7.41–7.40 (1H, d, J= 8.0 Hz), 7.27–6.46 (13H, aromatic), 6.45–6.31 (1H, d, J= 8.0 Hz, NH), 6.08–6.07 (1H, d, J= 7.5 Hz, NH), 5.94–5.93 (1H, d, J= 7.0 Hz, NH), 4.74–4.73 (1H, m, α–CH), 4.65–4.63 (2H, m, α–CH), 3.67 (3H, –OMe), 3.18–2.78 (6H, β–CH_2), 1.62–1.61 (2H, m, α–CH_2 of myristyl C=O), 1.30–1.14 (22H, –CH_2 of myristyl), 0.89–0.87 (3H, –Me of myristyl) (Fig. S34).

^{13}C NMR (100 MHz, $CDCl_3$, TMS, 25 ºC): δ 173.61, 171.75, 171.18, 170.86, 136.62, 136.53, 136.02, 129.42, 128.55, 127.59, 127.39, 126.82, 123.79, 123.51, 122.71, 122.28, 120.20,

119.66, 119.06, 118.42, 111.64, 111.36, 110.44, 109.36, 54.06, 53.89, 53.57, 52.45, 37.67, 36.16, 32.05, 29.83, 29.80, 29.64, 29.49, 29.47, 29.37, 29.32, 27.71, 26.85, 25.42, 22.82, 14.25 (Fig. S35).

MALDI-TOF MS (m/z): Calculated for $C_{46}H_{59}N_5O_5$: 761.4516 (M) Found: 784.607 $(M + Na)^+$, 800.798 $(M + K)^+$ (Fig. S36).

13. Synthesis of C_{14}-Phe-Trp-Trp-OMe: C_{14}-Phe-Trp-OH (1.13 g, 2.0 mM) was taken in a 250 mL round bottom flask and 10 mL DMF was added to dissolve it. After that the mixture was cooled in an ice-water bath having temperature 0 °C–10 °C. H–Trp–OMe was isolated from the corresponding methyl ester hydrochloride (0.61 g, 2.5 mM) by neutralization, subsequent extraction with ethyl acetate and concentration to 50 mL. Then it was added to the reaction mixture, followed immediately by DCC (0.52 g, 2.5 mM) and HOBt (0.34 g, 2.5 mM). The reaction mixture was stirred for 48 h in nitrogen atmosphere. The reaction mixture was filtered through sintered glass crucible and the DCU (dicyclohexylurea) was filtered off. The organic layer was washed with brine (2 × 50 mL) and then dried over anhydrous sodium sulphate and evaporated in vacuum to yield peptide as a white solid. Purification was done using a silica gel column (100–200 mesh) using chloroform and methanol as eluents.
Yield: 1.18 g, (1.55 mM, 77.50 %).

^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 ºC): δ 8.51 (s, 1H), 8.01 (s, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.38 – 7.24 (m, 7H), 7.24 – 7.16 (m, 2H), 7.13 (d, *J* = 7.3 Hz, 2H), 7.08 (dd, *J* = 13.2, 7.5 Hz, 2H), 6.78 (d, *J* = 2.3 Hz, 1H), 6.76 (s, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 6.62 (d, *J* = 7.9 Hz, 1H), 5.79 (d, *J* = 7.8 Hz, 1H), 4.94 – 4.77 (m, 2H), 4.68 (q, *J* = 6.6 Hz, 1H), 3.71 (s, 3H), 3.35 (dd, *J* = 14.7, 4.8 Hz, 1H), 3.22 (d, *J* = 6.2 Hz, 2H), 3.08 – 2.99 (m, 1H), 2.96 (d, *J* = 9.2 Hz, 2H), 2.24 (s, 2H), 1.77 (d, *J* = 7.6 Hz, 2H), 1.33 (s, 9H), 1.31 (s, 8H), 1.17 (q, *J* = 7.0 Hz, 4H), 0.96 (t, *J* = 6.7 Hz, 3H) (Fig. S37).

^{13}C NMR (100 MHz, $CDCl_3$, TMS, 25 ºC): δ 173.70, 171.88, 170.88, 170.72, 136.16, 136.11, 136.01, 129.29, 128.78, 127.54, 127.48, 127.26, 124.09, 123.31, 122.05, 121.99, 119.60, 119.39, 118.51, 118.39, 111.43, 111.33, 109.64, 109.33, 53.94, 53.72, 52.69, 52.41, 37.49, 36.07, 31.95, 30.95, 29.69, 29.53, 29.39, 29.12, 27.38, 27.01, 25.41, 22.72, 14.15 (Fig. S38).

HRMS (m/z): Calculated for $C_{46}H_{59}N_5O_5$: 761.4516 (M) Found: 761.6418 $(M)^+$, 783.5808 $(M + Na)^+$, 801.5329 $(M + K + H)^+$ (Fig. S39).

15. Synthesis of C_{14}-Trp-Phe-Trp-OH (G1): C_{14}-Trp-Phe-Trp-OMe (1.00 g, 1.31 mM) was taken in a 250 mL round bottom flask. The solid was dissolved in MeOH (40 mL) and 1N NaOH (15 mL) was added to the mixture. The reaction mixture was stirred for 12 h and the progress of saponification was monitored by thin layer chromatography (TLC). After 12 h methanol was removed under vacuum, the residue was taken in 50 mL of water, washed with diethyl ether (2 × 50 mL). Then the pH of the aqueous layer was adjusted to 2 using 1N HCl and it was extracted with ethyl acetate (3 × 50 mL). The extracts were dried over anhydrous sodium sulphate, and evaporated in vacuum to yield as a white solid product. Purification was done using a silica gel column (100–200 mesh) using chloroform and methanol as eluents.

Yield: 0.84 g, (1.12 mM, 85.83 %).

^{1}H NMR (400 MHz, DMSO-d_6, TMS, 25 ºC): δ 12.44 (s, 1H, br, -OH of –COOH group), 10.83 (d, J = 11.9 Hz, 2H), 8.22 (d, J = 7.5 Hz, 1H), 7.99 (d, J = 7.9 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.53 (d, J = 4.1 Hz, 1H), 7.33 (t, J = 8.2 Hz, 2H), 7.15 (d, J = 21.8 Hz, 6H), 7.06 (d, J = 8.2 Hz, 2H), 6.98 (t, J = 8.0 Hz, 2H), 4.61 (q, J = 8.9 Hz, 1H), 4.49 (d, J = 14.6 Hz, 2H), 3.23 – 3.05 (m, 3H), 2.96 (dd, J = 15.5, 8.0 Hz, 2H), 2.72 – 2.62 (m, 1H), 2.09 (s, 1H), 1.92 (s, 4H), 1.19 (d, J = 45.2 Hz, 23H), 0.88 – 0.83 (m, 3H) (Fig. S40).

^{13}C NMR (100 MHz, DMSO-d_6, TMS, 25 ºC): δ 173.65, 173.59, 172.59, 172.50, 171.78, 171.73, 171.45, 138.57, 136.54, 136.50, 129.63, 129.61, 128.56, 128.32, 127.78, 126.50, 124.37, 124.09, 121.36, 121.27, 119.10, 118.91, 118.84, 118.67, 111.82, 111.70, 110.28, 110.06, 54.12, 53.66, 53.51, 37.73, 35.69, 31.79, 31.18, 29.55, 29.52, 29.38, 29.29, 29.21, 28.97, 28.93, 28.16, 27.64, 25.64, 22.59, 21.55, 14.45 (Fig. S42).

HRMS (m/z): Calculated for $C_{45}H_{57}N_5O_5$: 747.4360 (M) Found: 747.9550 $(M)^+$, 770.3571 $(M + Na)^+$, 771.3569 $(M + Na + H)^+$ (Fig. S42).

14. Synthesis of C_{14}-Trp-Trp-Phe-OH (G2): C_{14}-Trp-Trp-Phe-OMe (1.00 g, 1.31 mM) was taken in a 250 mL round bottom flask. The solid was dissolved in MeOH (40 mL) and 1N NaOH (15 mL) was added to the mixture. The reaction mixture was stirred for 12 h and the progress of saponification was monitored by thin layer chromatography (TLC). After 12 h methanol was removed under vacuum, the residue was taken in 50 mL of water, washed with diethyl ether (2 × 50 mL). Then the pH of the aqueous layer was adjusted to 2 using 1N HCl and it was extracted with ethyl acetate (3 × 50 mL). The extracts were dried over anhydrous sodium sulphate, and evaporated in vacuum to yield as a white solid product. Purification was done using a silica gel column (100–200 mesh) using chloroform and methanol as eluents.

Yield: 0.89 g, (1.19 mM, 90.94 %).

^{1}H NMR (500 MHz, DMSO-d_6, TMS, 25 ºC): δ 12.62 (s, 1H, br, –OH of –COOH group), 10.81–10.68 (2H, NH of tryptophan), 8.23–6.90 (15H aromatic and 3H of amide –NH), 4.58–4.43 (3H, α–CH of amino acids), 3.10–2.64 (6H, β–CH_2 of amino acids), 1.99–1.93 (2H, m, α–CH_2 of myristyl C= O), 1.35–1.05 (22H, myristyl CH_2), 0.86–0.84 (3H, –Me of myristyl) (Fig. S43).

^{13}C NMR (100 MHz, DMSO-d_6, TMS, 25 ºC): δ 172.72, 172.55, 172.16, 172.12, 171.57, 171.45, 171.11, 137.54, 137.47, 137.30, 135.99, 135.95, 129.16, 129.05, 128.11, 128.08,

127.36, 127.29, 127.25, 126.32, 123.67, 123.47, 123.34, 120.70, 118.37, 118.26, 118.10, 118.01, 111.14, 110.28, 110.09, 110.00, 109.70, 53.64, 53.50, 53.42, 53.20, 53.09, 36.75, 36.65, 35.18, 35.08, 31.23, 28.98, 28.81, 28.73, 28.63, 28.48, 27.52, 25.01, 24.95, 22.02, 13.88 (Fig. S44).

HRMS (m/z): Calculated for $C_{45}H_{57}N_5O_5$: 747.4360 (M) Found: 748.5205 $(M + H)^+$, 770.4542 $(M + Na)^+$, 771.4695 $(M + H + Na)^+$, 772.4706 $(M + 2H + Na)^+$ (Fig. S45).

16. Synthesis of C_{14}-Phe-Trp-Trp-OH (G3): C_{14}-Phe-Trp-Trp-OMe (1.00 g, 1.31 mM) was taken in a 250 mL round bottom flask. The solid was dissolved in MeOH (40 mL) and 1N NaOH (15 mL) was added to the mixture. The reaction mixture was stirred for 12 h and the progress of saponification was monitored by thin layer chromatography (TLC). After 12 h methanol was removed under vacuum, the residue was taken in 50 mL of water, washed with diethyl ether (2 × 50 mL). Then the pH of the aqueous layer was adjusted to 2 using 1N HCl and it was extracted with ethyl acetate (3 × 50 mL). The extracts were dried over anhydrous sodium sulphate, and evaporated in vacuum to yield as a white solid product. Purification was done using a silica gel column (100–200 mesh) using chloroform and methanol as eluents.

Yield: 0.94 g, (1.25 mM, 95.42 %).

^{1}H NMR (400 MHz, DMSO-d6, TMS, 25 ºC): δ 10.72 (s, 1H, -OH of –COOH group) 10.70 (2H, NH aromatic), 8.04 (br, 1H, NH of amide), 7.87 (2H, NH of amide), 7.56–6.91 (15H, aromatic), 4.50 (2H, α–CH of amino acids), 4.33 (1H, α–CH of amino acids), 3.05–2.74 (6H, β–CH_2 of amino acids), 1.97–1.96 (2H, t, J = 6.6 Hz), 1.31–1.05 (22H, myristyl –CH_2), 0.86–0.84 (3H, t, J = 6.4 Hz, –Me of myristyl) (Fig. S46).

^{13}C NMR (100 MHz, DMSO-d_6, TMS, 25 ºC): δ 172.00, 171.46, 170.07, 137.86, 135.97, 135.88, 129.20, 127.88, 127.31, 126.03, 123.42, 123.37, 120.64, 120.49, 118.54, 118.41,

118.01, 117.95, 111.14, 111.01, 110.36, 54.08, 53.20, 37.50, 35.22, 31.25, 28.99, 28.82, 28.66, 28.51, 27.49, 25.05, 22.04, 13.90 (Fig. S47).

HRMS (m/z): Calculated for $C_{45}H_{57}N_5O_5$: 747.4360 (M) Found: 747.9550 $(M)^+$, 770.8783 $(M + Na)^+$, 771.9089 $(M + Na + H)^+$ (Fig. S48).

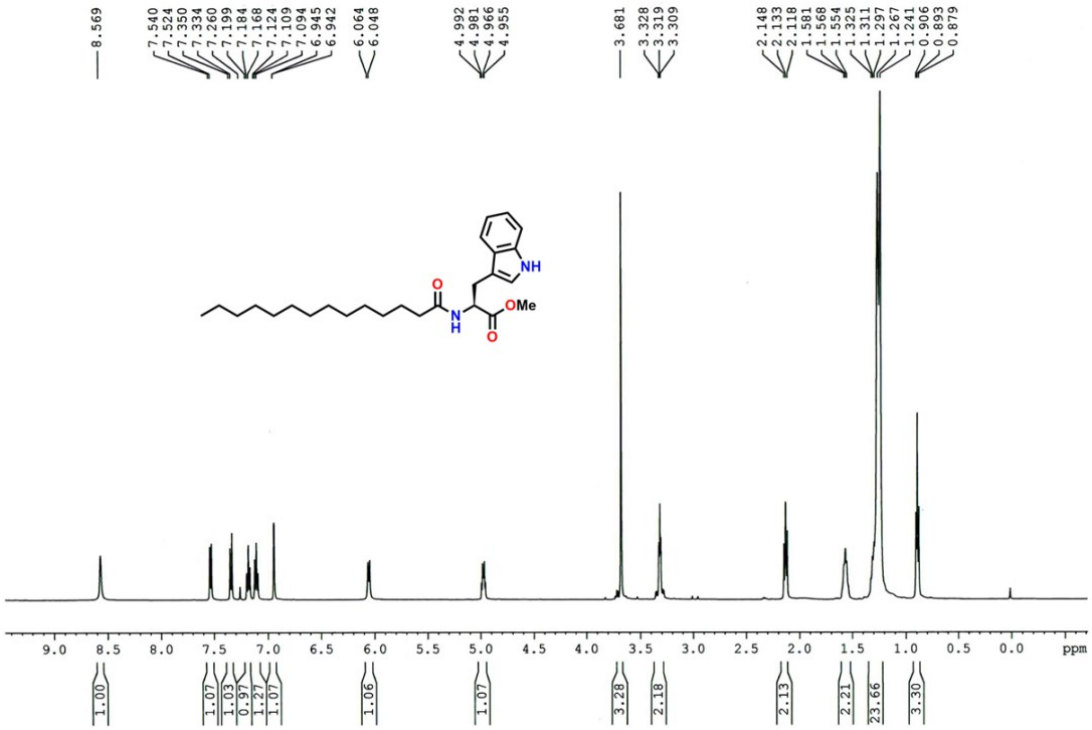

Fig. S1 ^{1}H-NMR spectrum of **C_{14}-Trp-OMe** in $CHCl_3$.

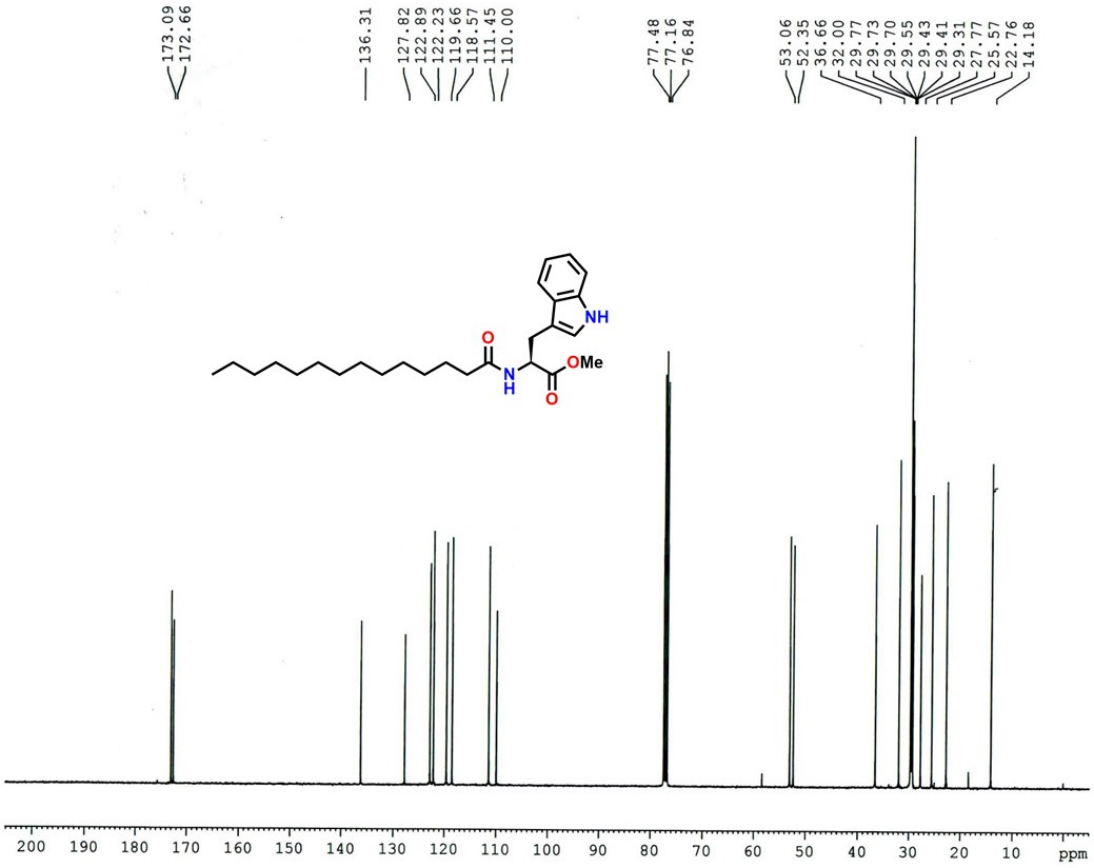

Fig. S2[13]C-NMR spectrum of **C_{14}-Trp-OMe** in $CHCl_3$.

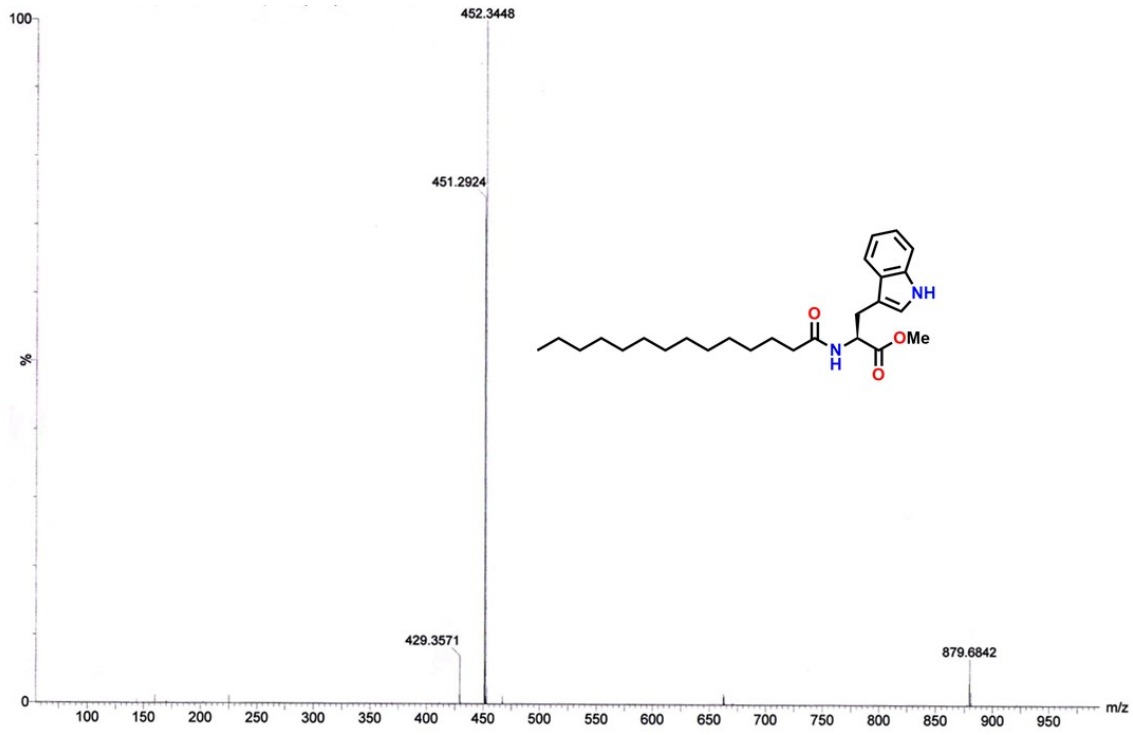

Fig. S3 HR-MS spectrum of **C_{14}-Trp-OMe**.

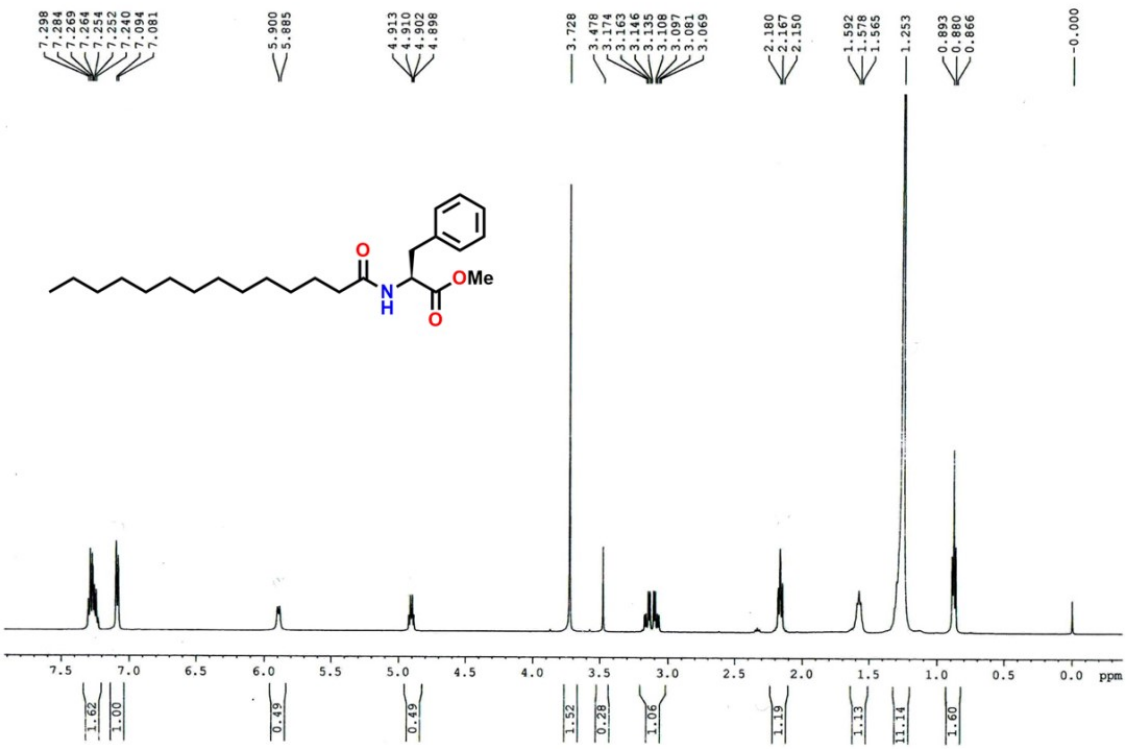

Fig. S4 ^{1}H NMR spectrum of **C_{14}-Phe-COOMe** in $CDCl_3$.

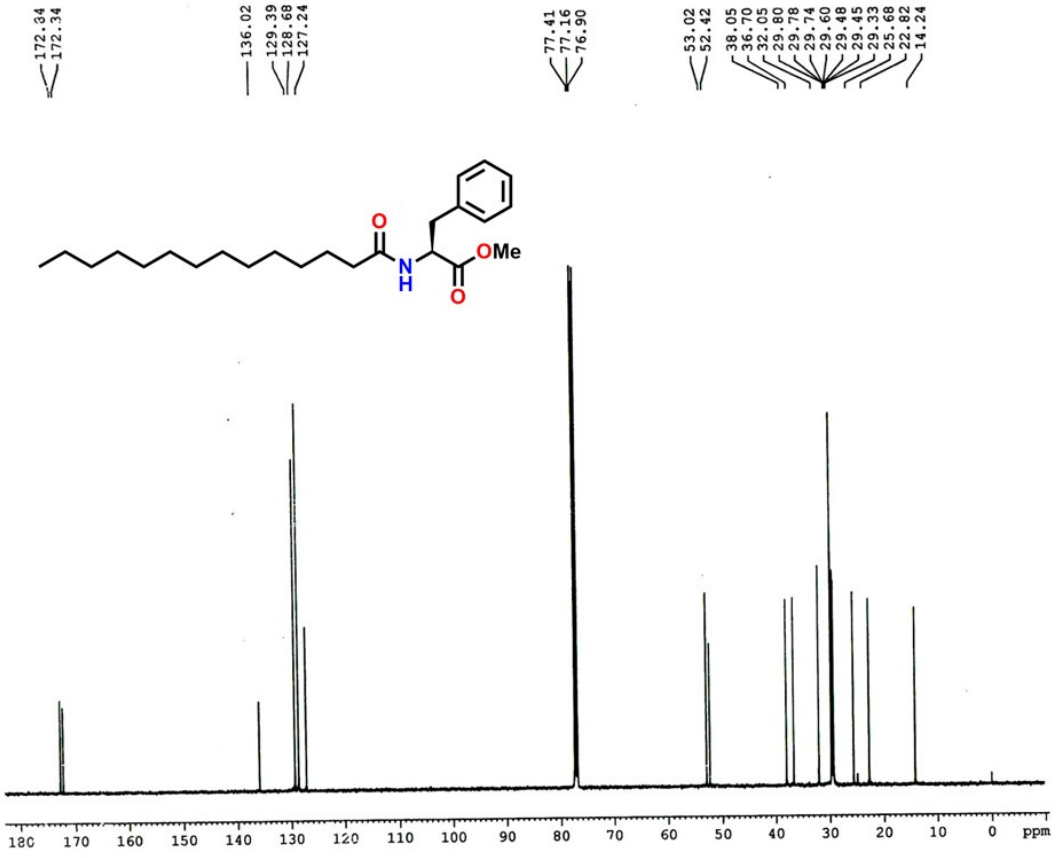

Fig. S5 ^{13}C NMR spectrum of **C_{14}-Phe-COOMe** in $CDCl_3$.

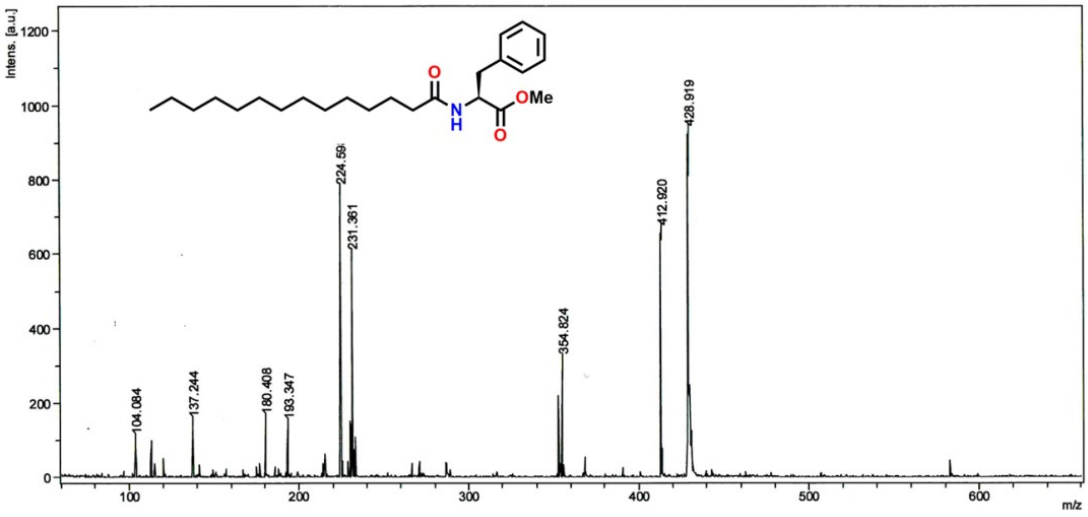

Fig. S6 MALDI-TOF MS spectrum of **C_{14}-Phe-COOMe**.

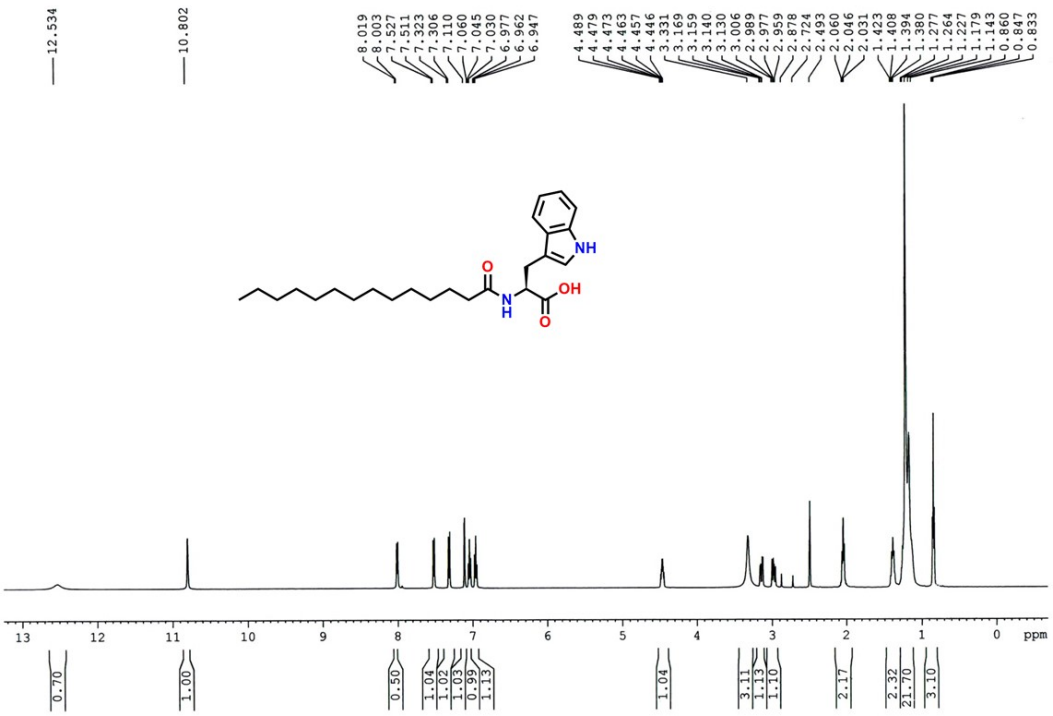

Fig. S7 ^{1}H-NMR spectrum of **C_{14}-Trp-OH** in DMSO-d_6.

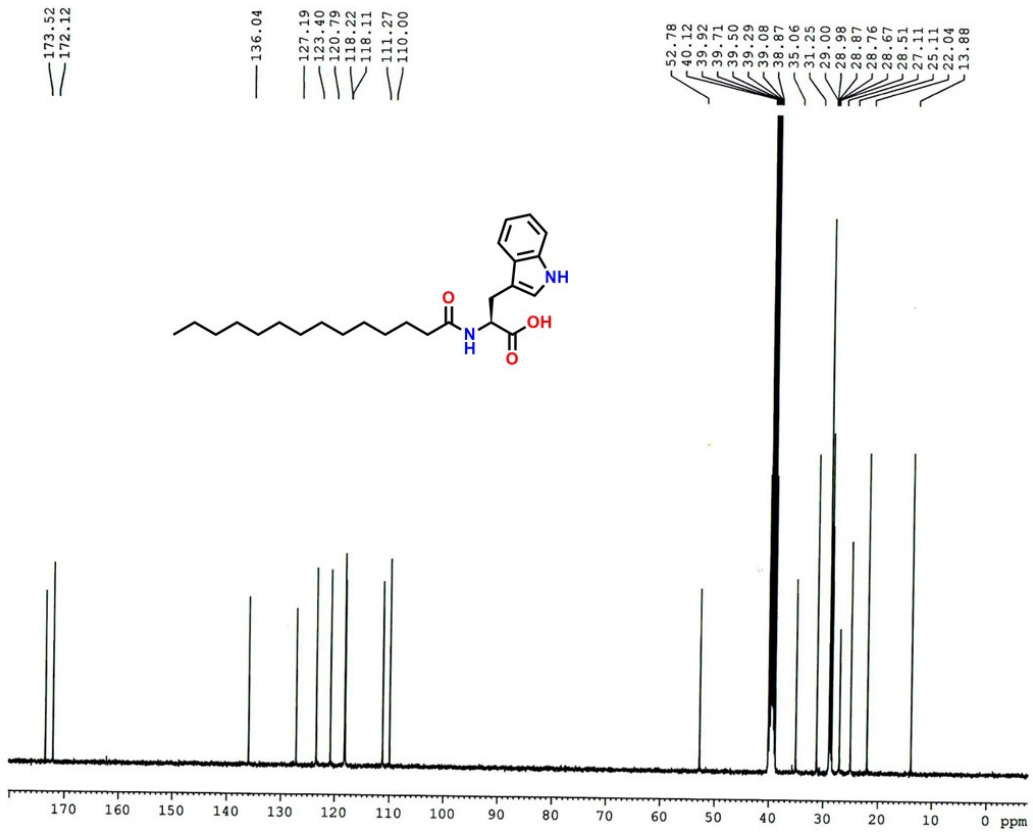

Fig. S8 ^{13}C-NMR spectrum of **C_{14}-Trp-OH** in DMSO-d_6.

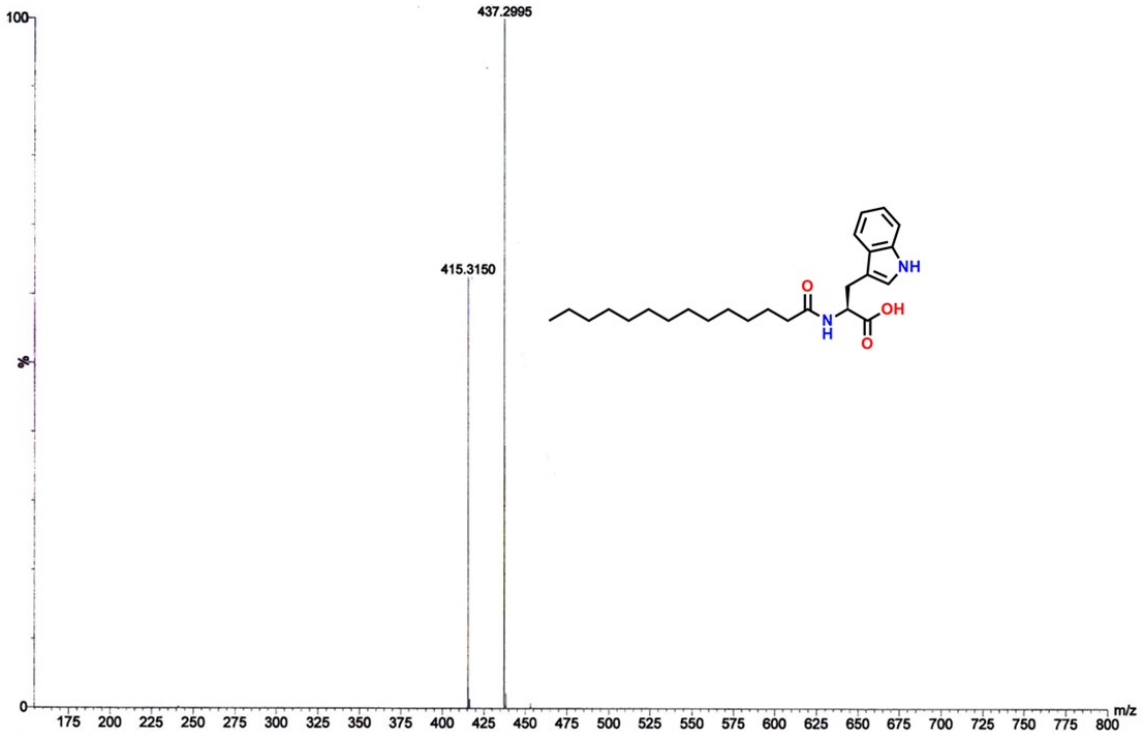

Fig. S9 HR-MS spectrum of **C_{14}-Trp-OH**.

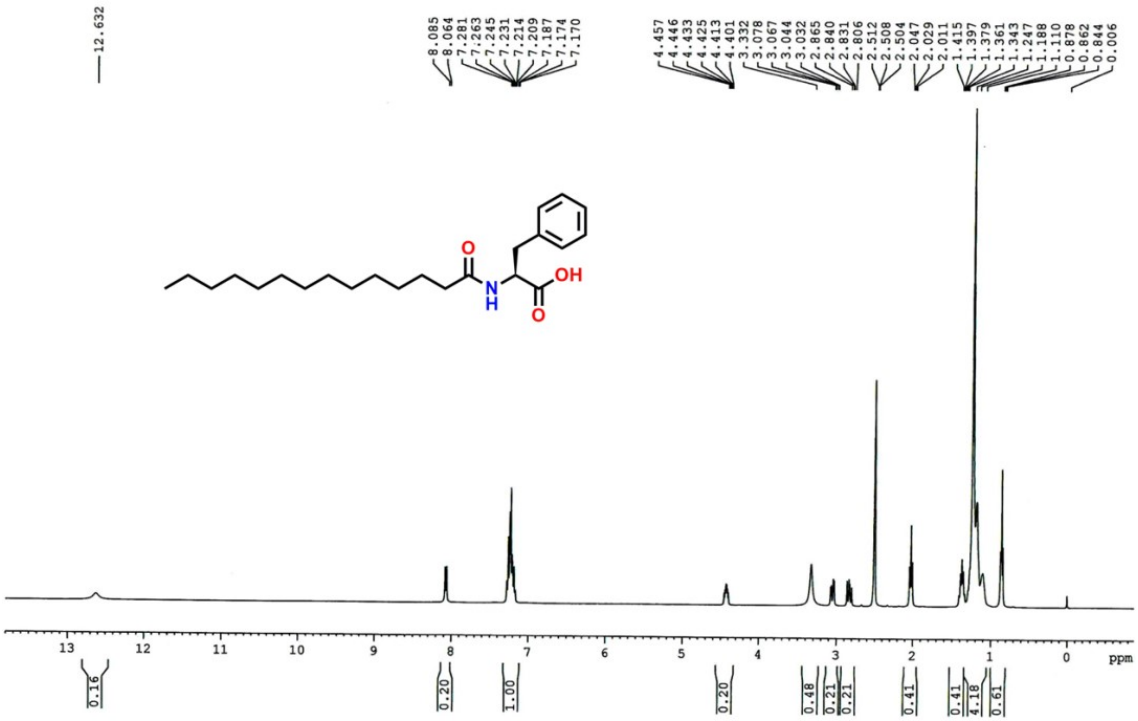

Fig. S10 ^{1}H NMR spectrum of **C_{14}-Phe-COOH** in DMSO-d_6.

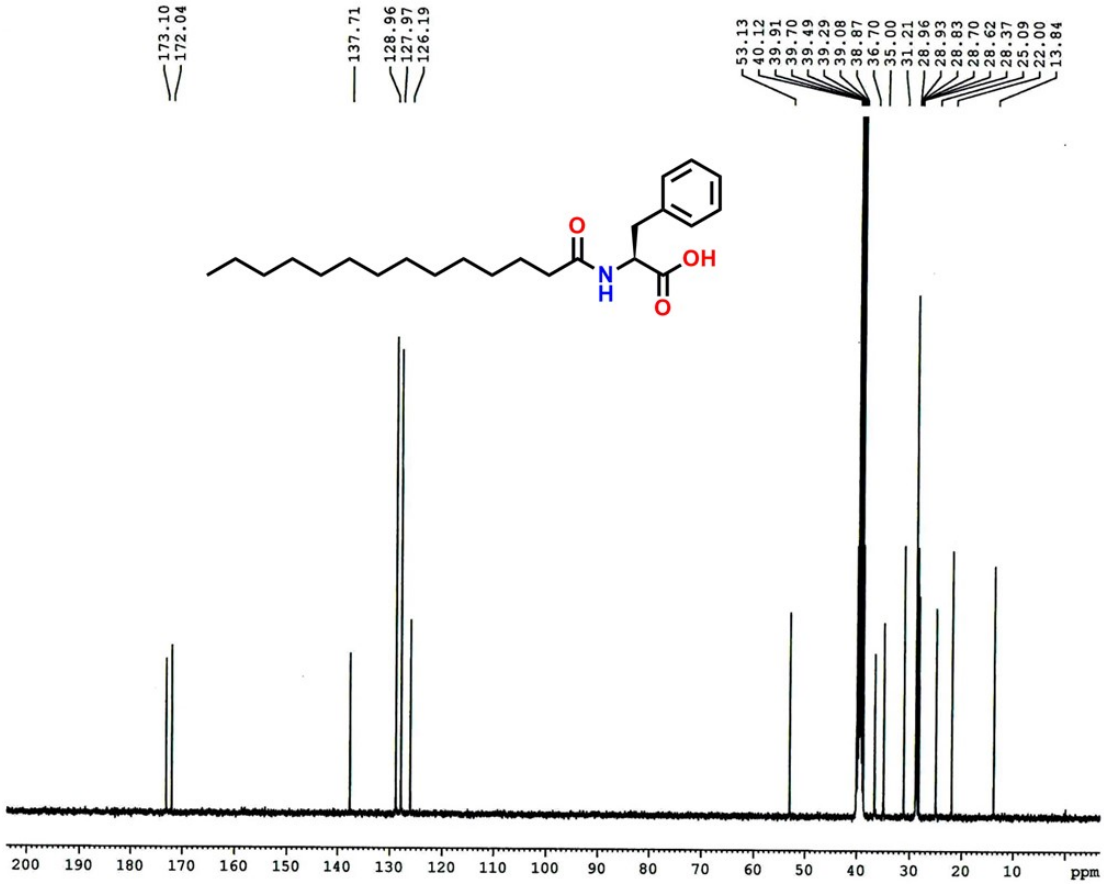

Fig. S11 ^{13}C NMR spectrum of **C_{14}-Phe-COOH** in DMSO-d_6.

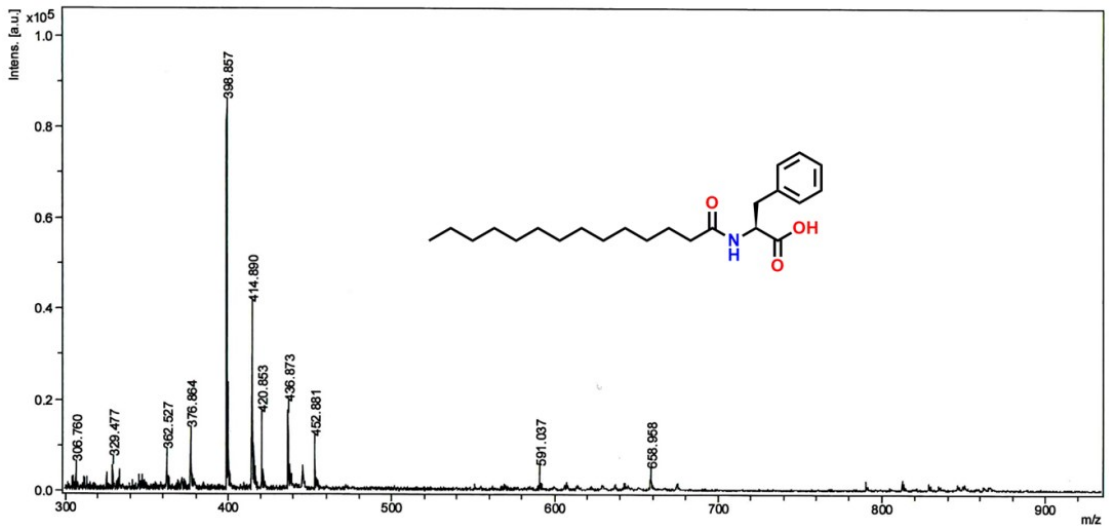

Fig. S12 MALDI-TOF MS spectrum of **C_{14}-Phe-COOH**.

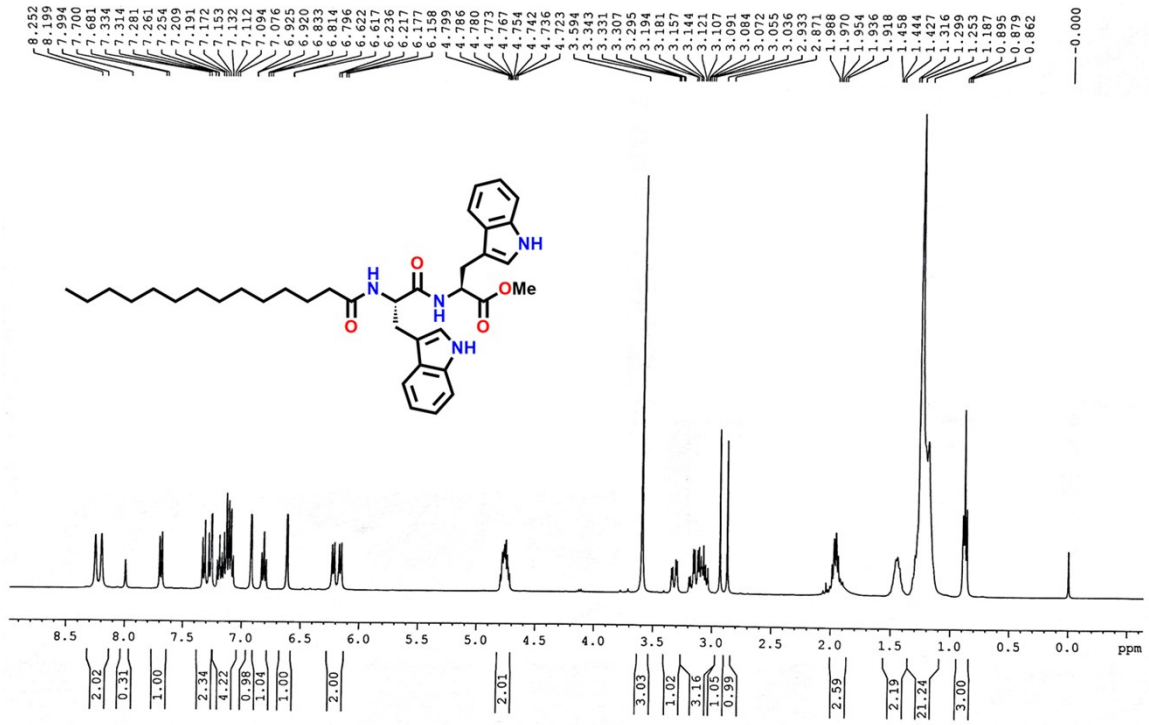

Fig. S13 ^{1}H NMR spectrum of **C_{14}-Trp-Trp-COOMe** in $CDCl_3$.

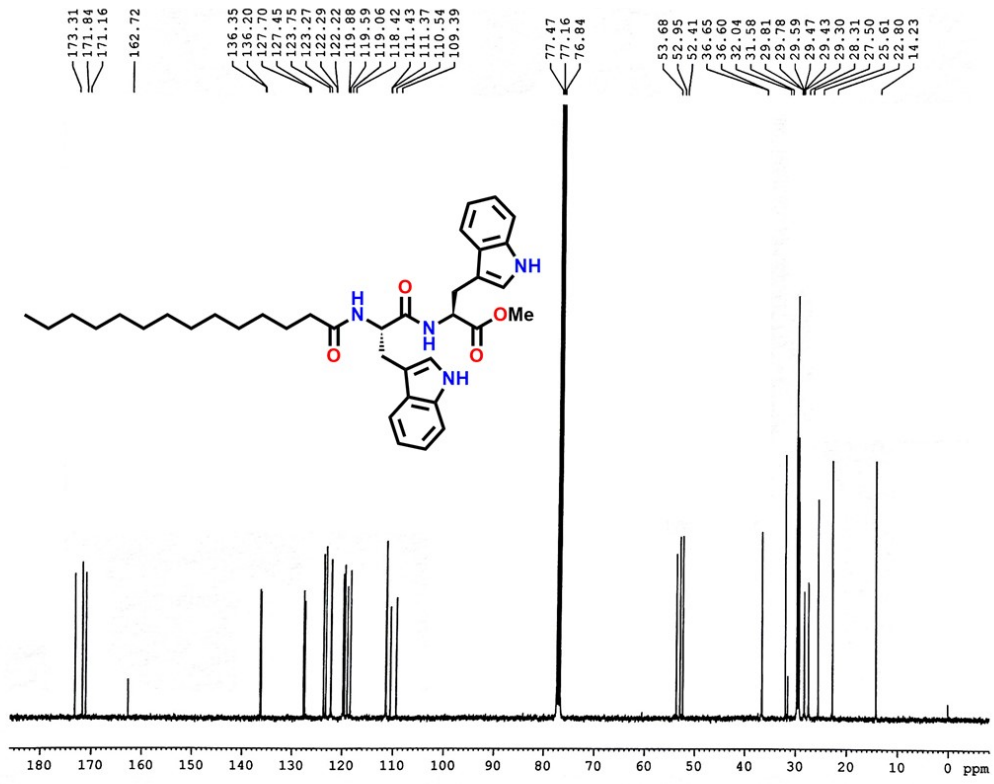

Fig. S14 ^{13}C NMR spectrum of **C_{14}-Trp-Trp-COOMe** in $CDCl_3$.

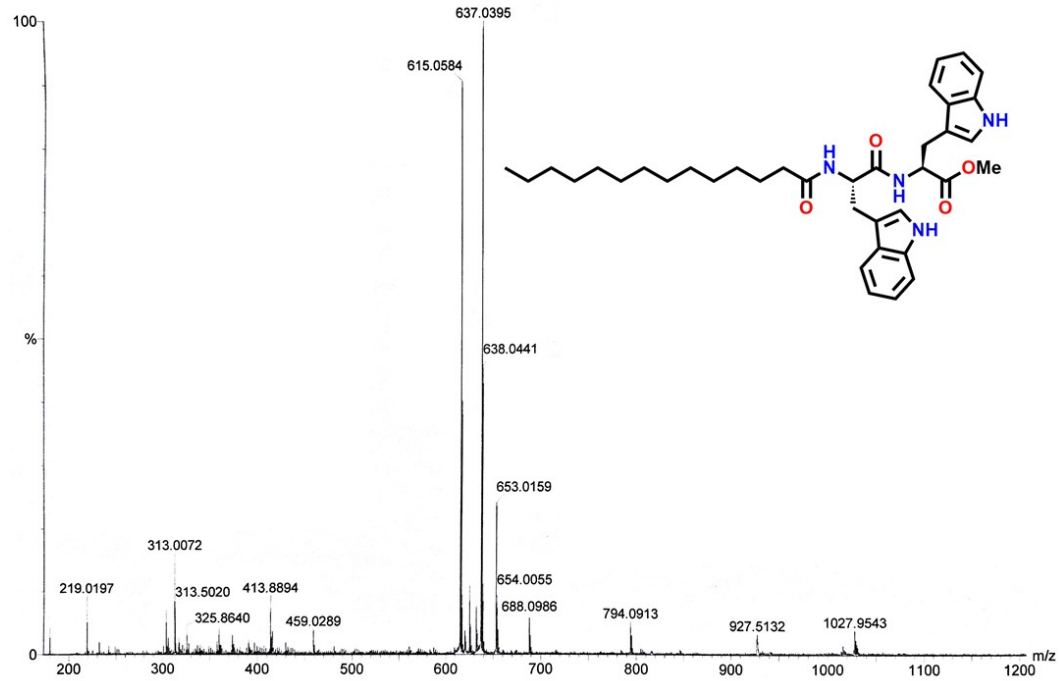

Fig. S15 HRMS spectrum of **C_{14}-Trp-Trp-COOMe**.

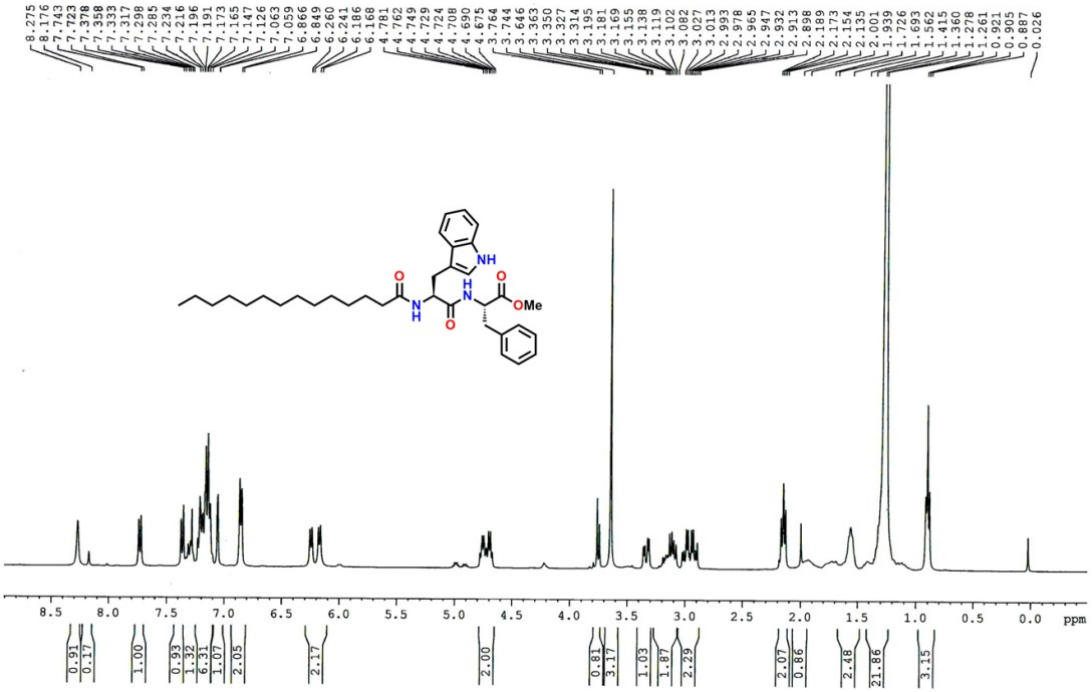

Fig. S16 ^{1}H-NMR spectrum of **C_{14}-Trp-Phe-OMe** in $CHCl_3$.

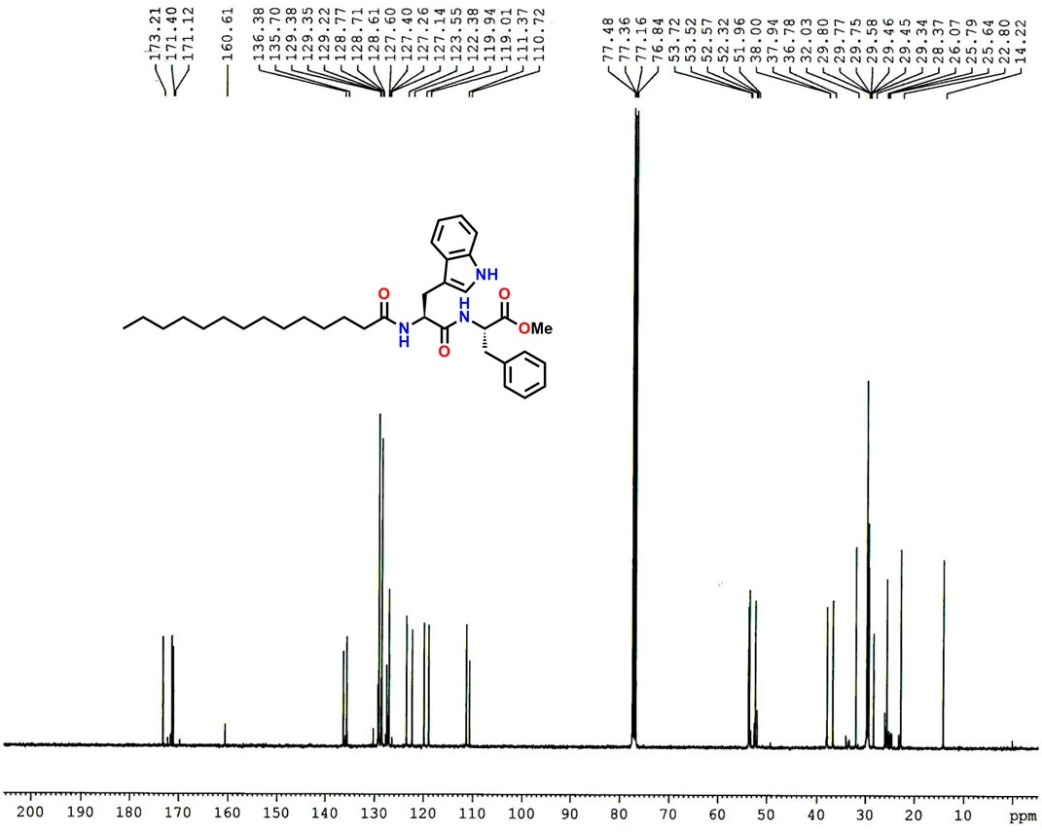

Fig. S17 ^{13}C-NMR spectrum of **C_{14}-Trp-Phe-OMe** in $CHCl_3$.

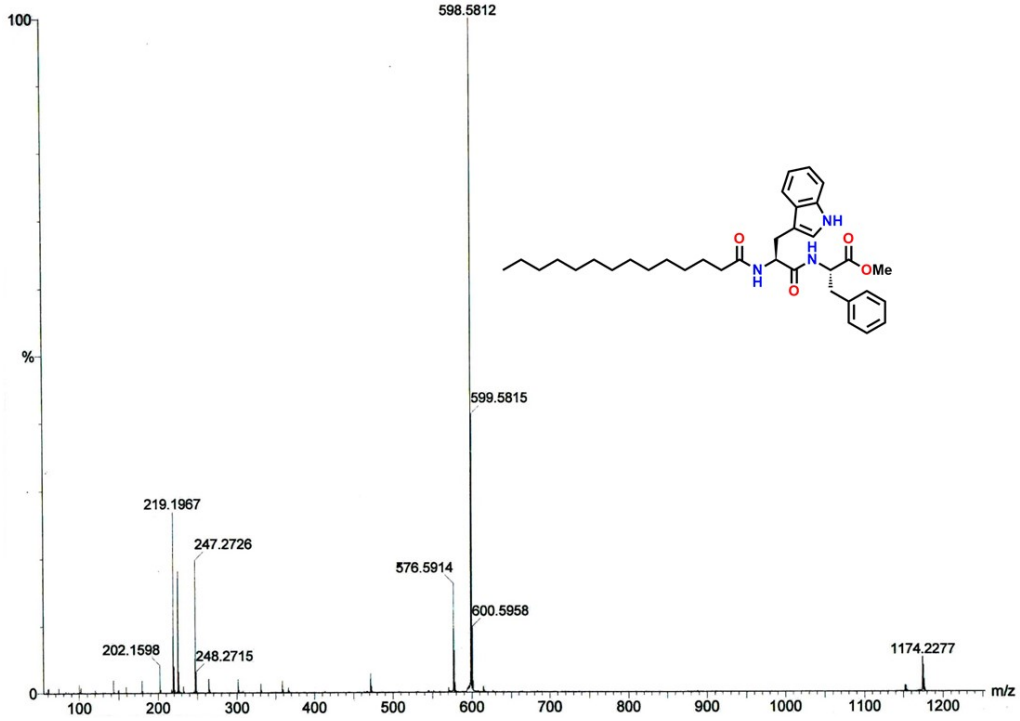

Fig. S18 HR-MS spectrum of **C_{14}-Trp-Phe-OMe**.

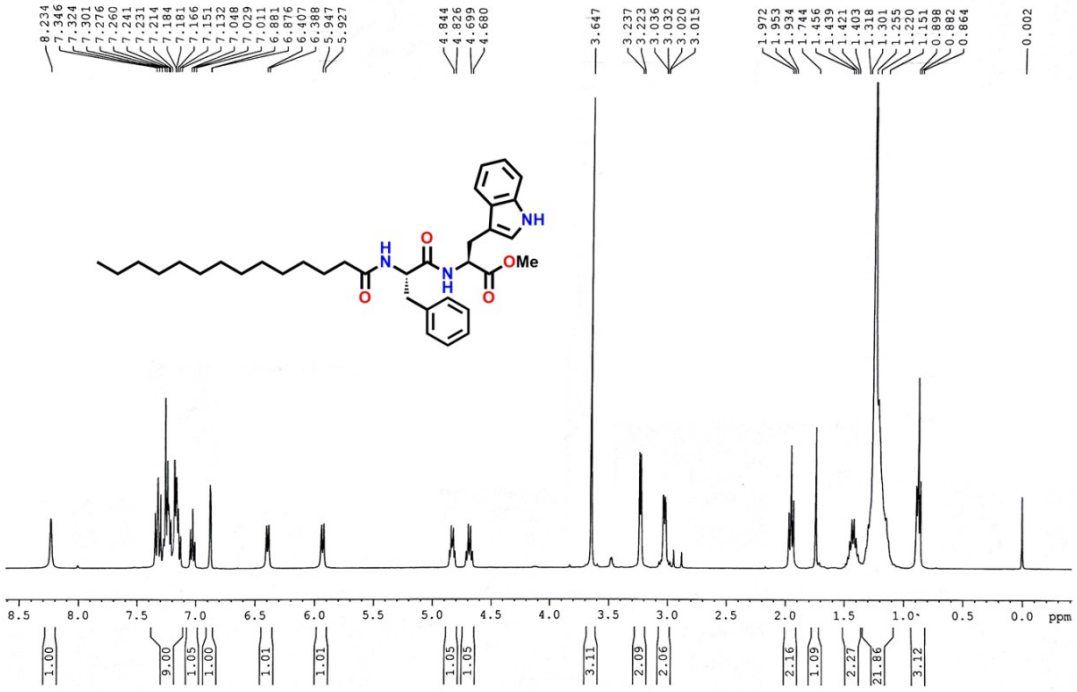

Fig. S19 ^{1}H-NMR spectrum of **C_{14}-Phe-Trp-OMe** in $CHCl_3$.

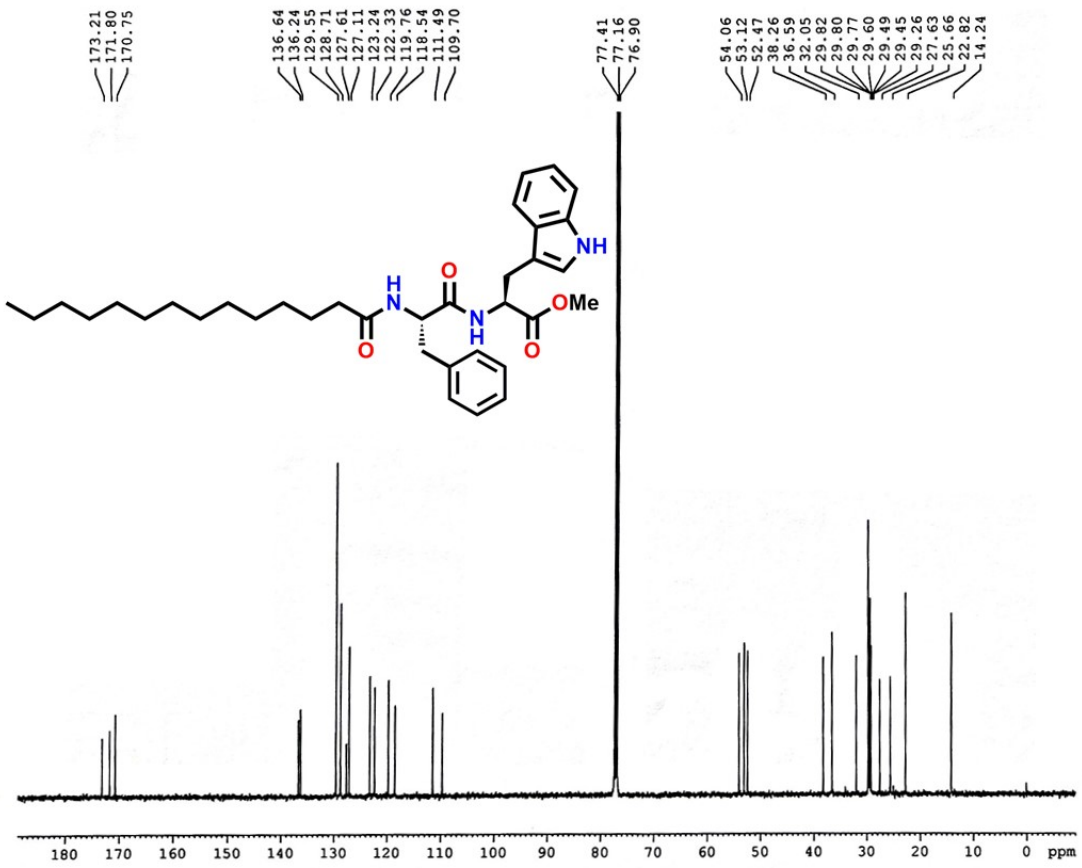

Fig. S20 ^{13}C-NMR spectrum of **C_{14}-Phe-Trp-OMe** in $CHCl_3$.

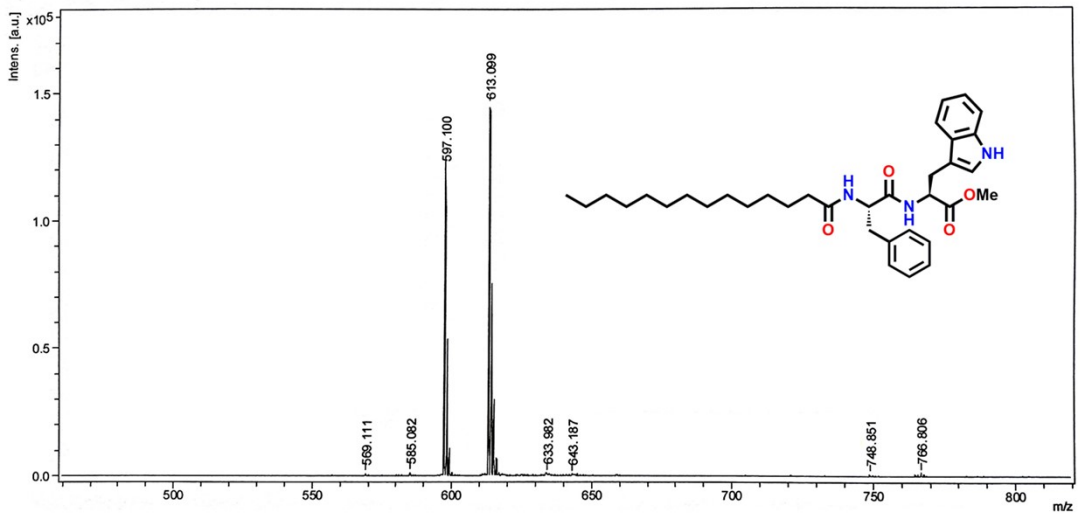

Fig. S21 HRMS spectrum of **C_{14}-Phe-Trp-OMe**.

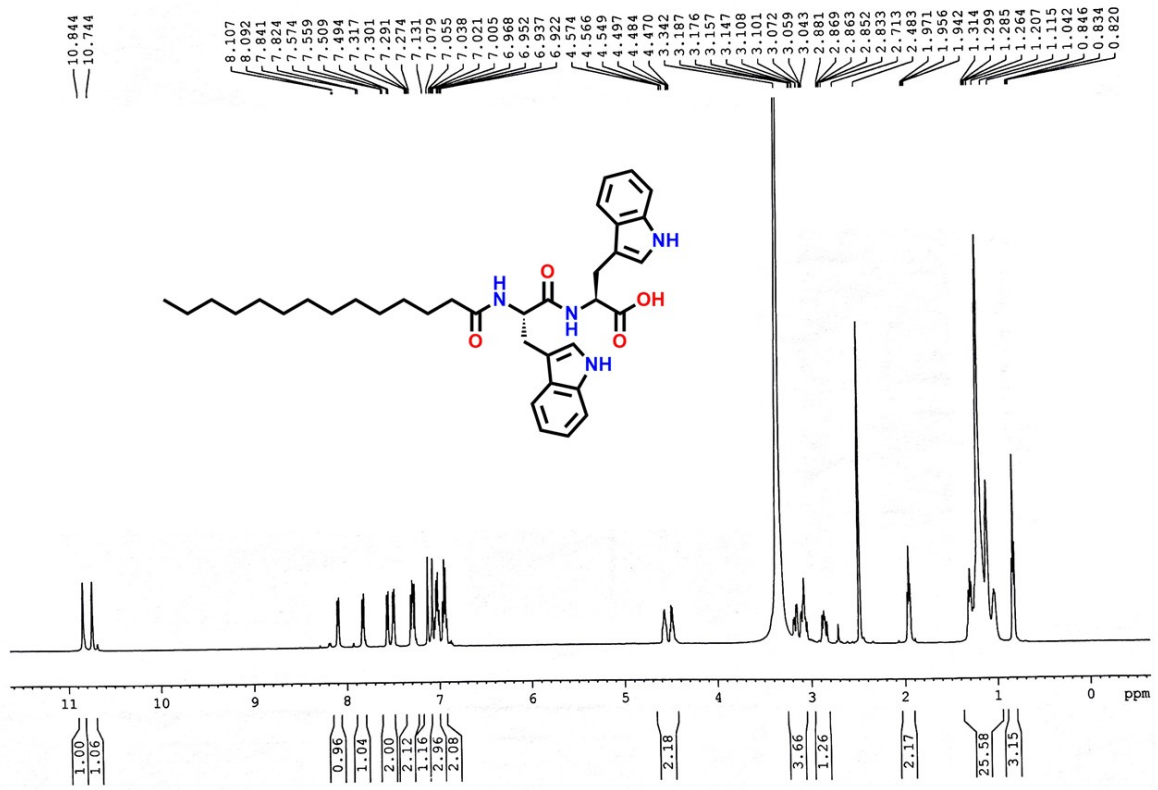

Fig. S22 ^{1}H-NMR spectrum of **C_{14}-Trp-Trp-OH** in DMSO-d_6.

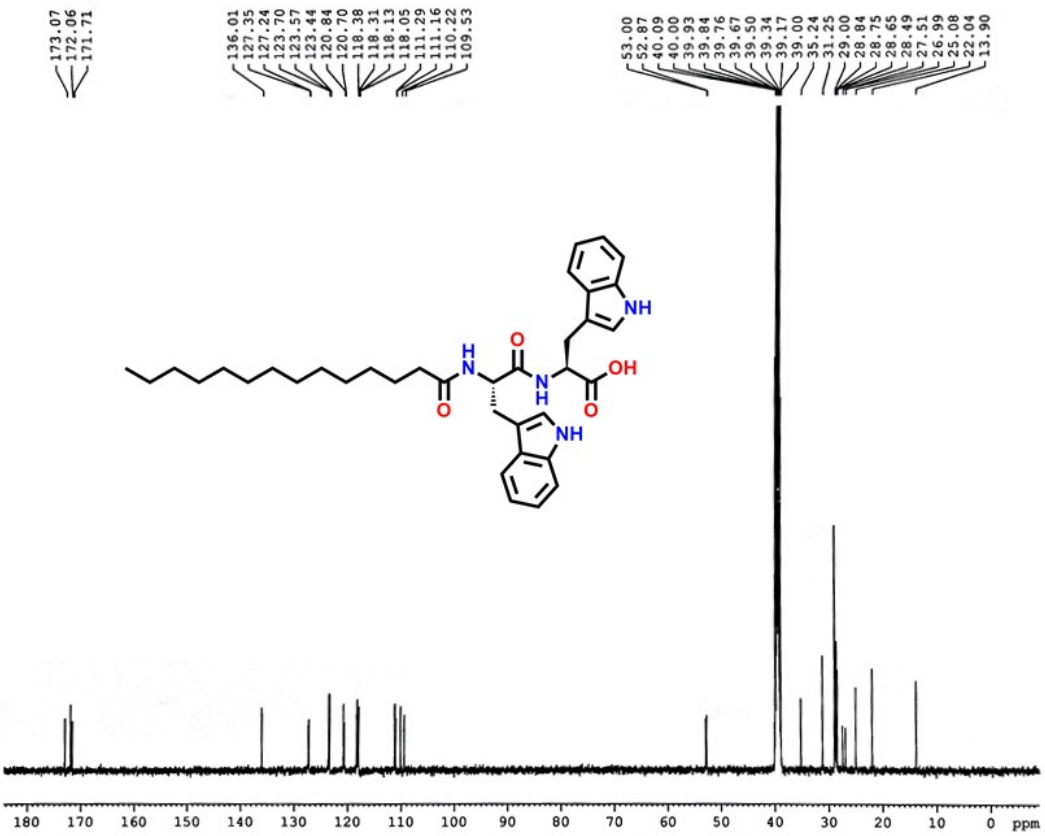

Fig. S23 ^{13}C-NMR spectrum of **C_{14}-Trp-Trp-OH** in DMSO-d_6.

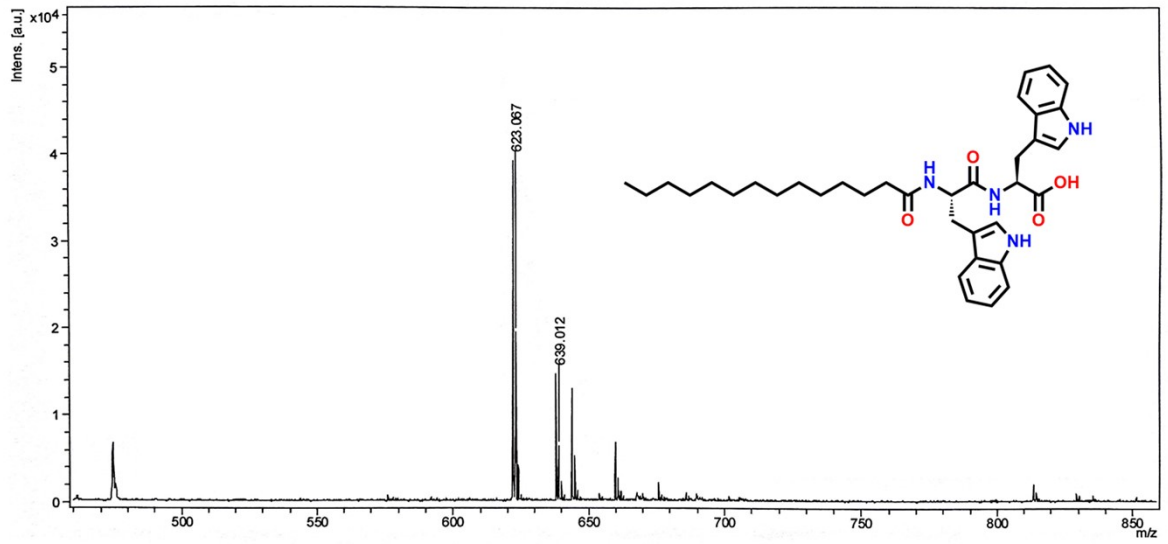

Fig. S24 MALDI-TOF MS spectrum of **C_{14}-Trp-Trp-OH**.

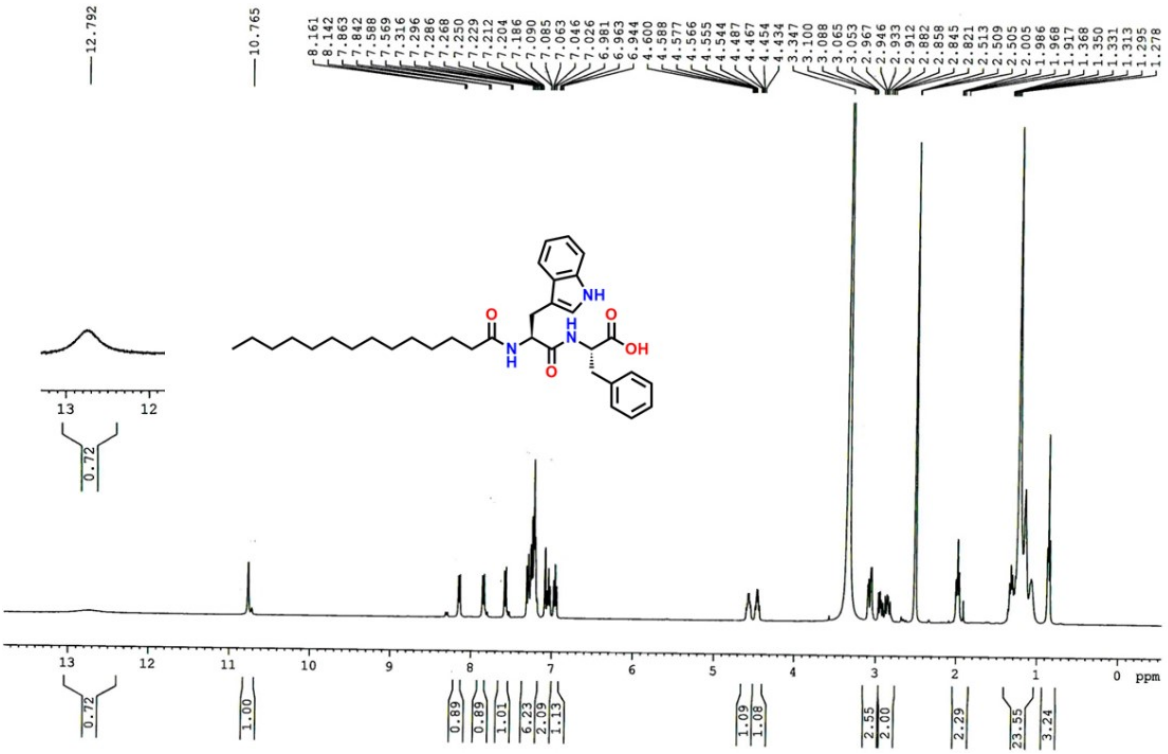

Fig. S25 ^{1}H-NMR spectrum of **C_{14}-Trp-Phe-OH** in DMSO-d_6.

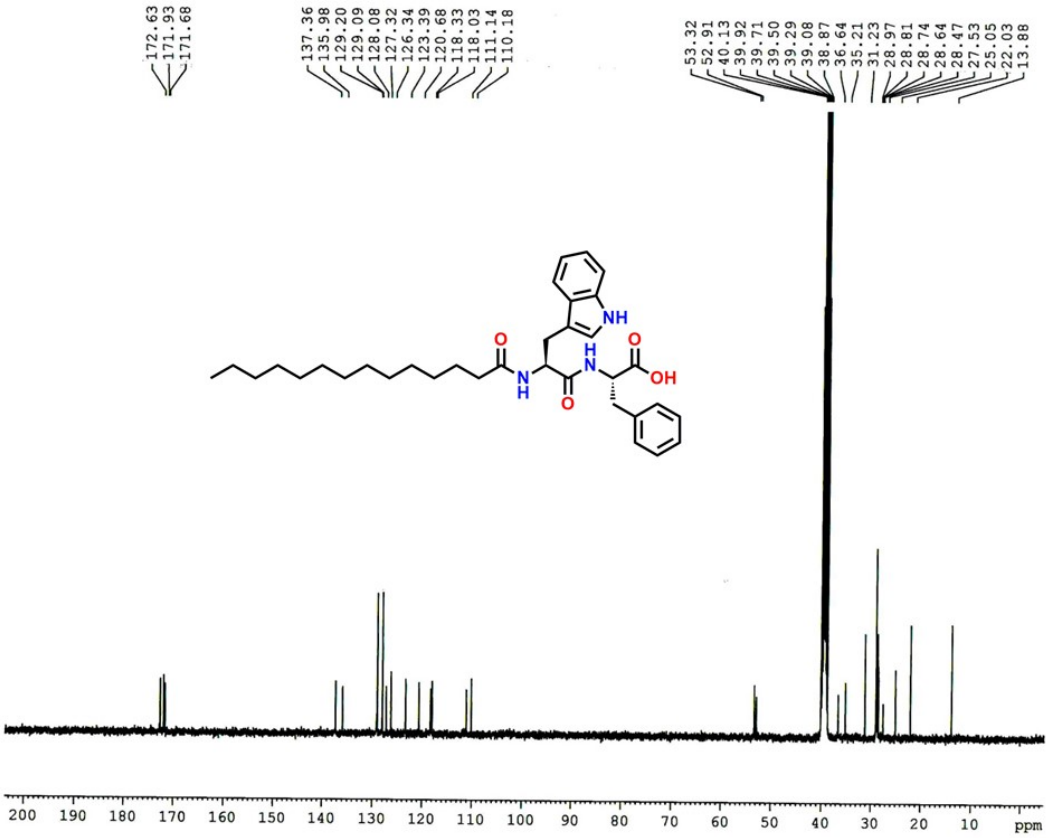

Fig. S26 ^{13}C-NMR spectrum of **C_{14}-Trp-Phe-OH** in DMSO-d_6.

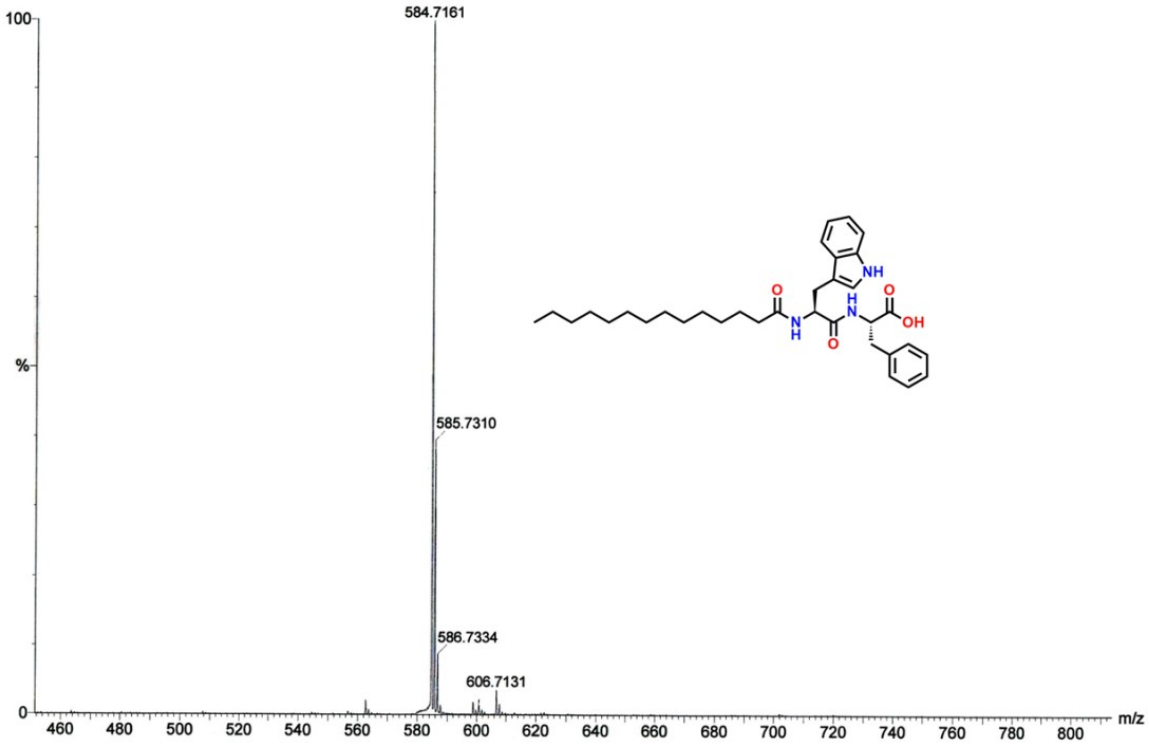

Fig. S27 HR-MS spectrum of **C_{14}-Trp-Phe-OH**.

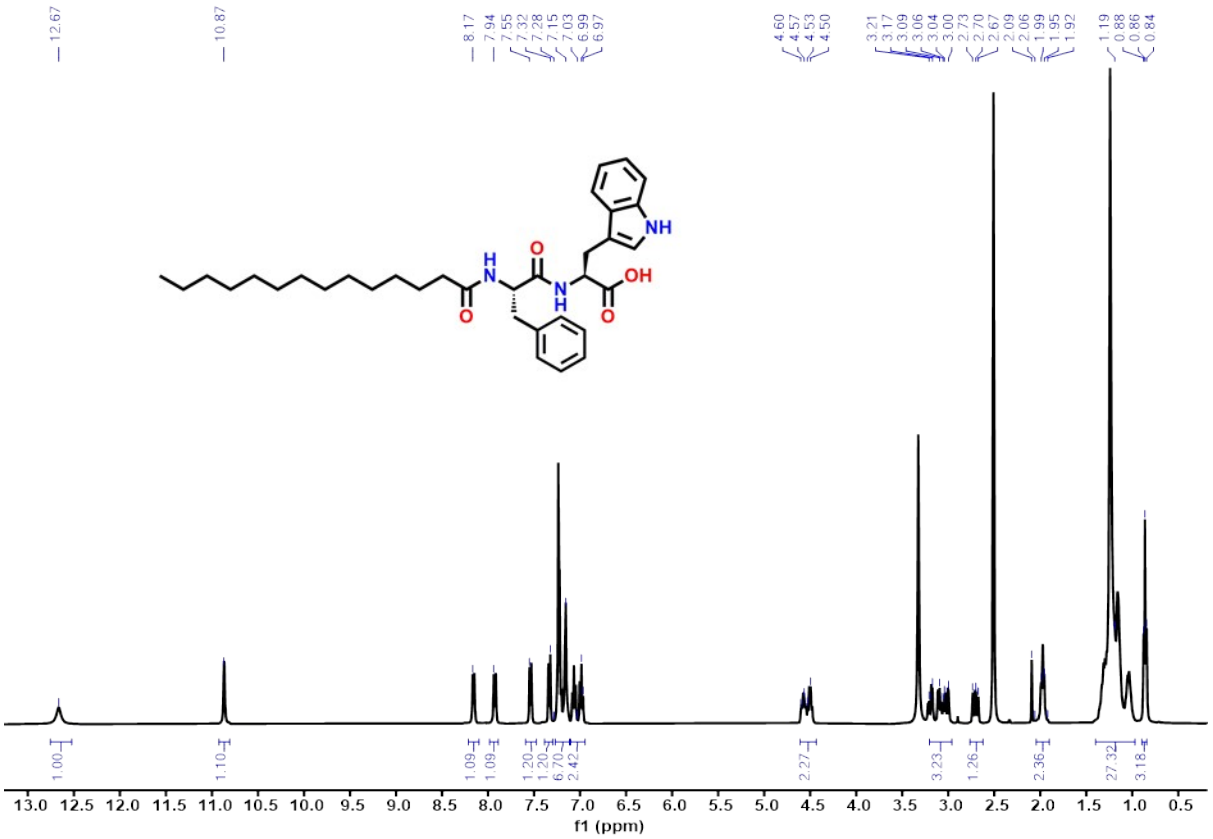

Fig. S28 ^{1}H-NMR spectrum of **C_{14}-Phe-Trp-OH** in DMSO-d_6.

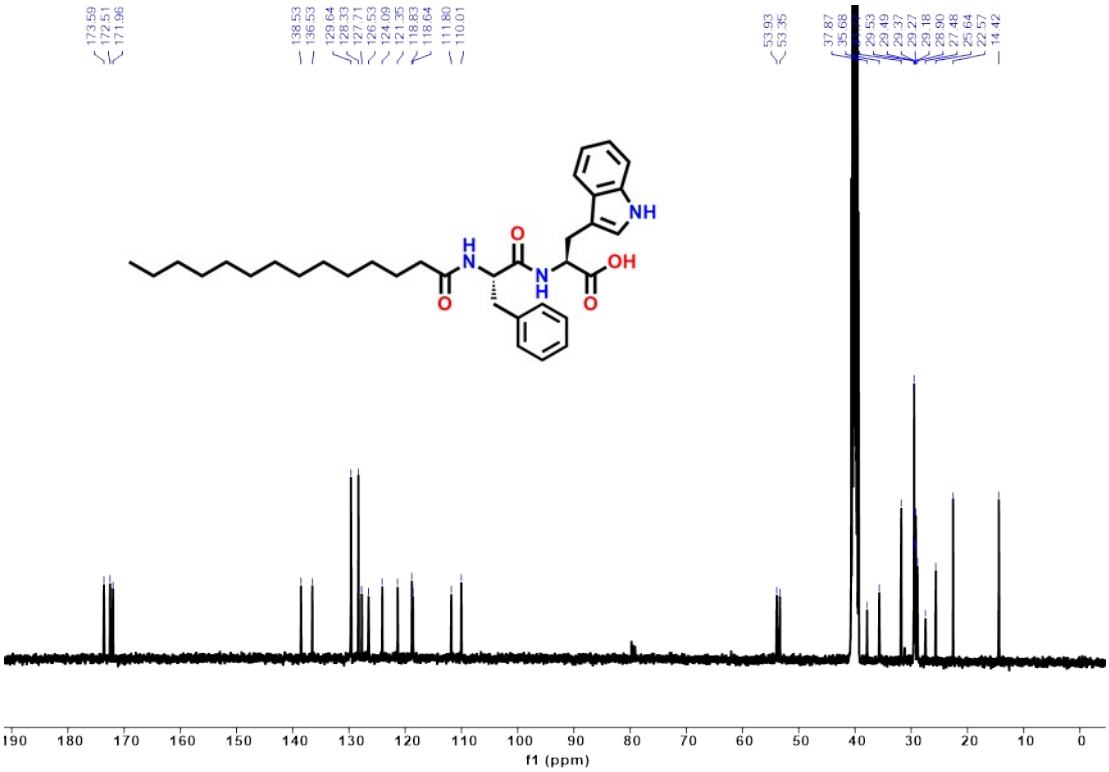

Fig. S29 ^{13}C-NMR spectrum of **C_{14}-Phe-Trp-OH** in DMSO-d_6.

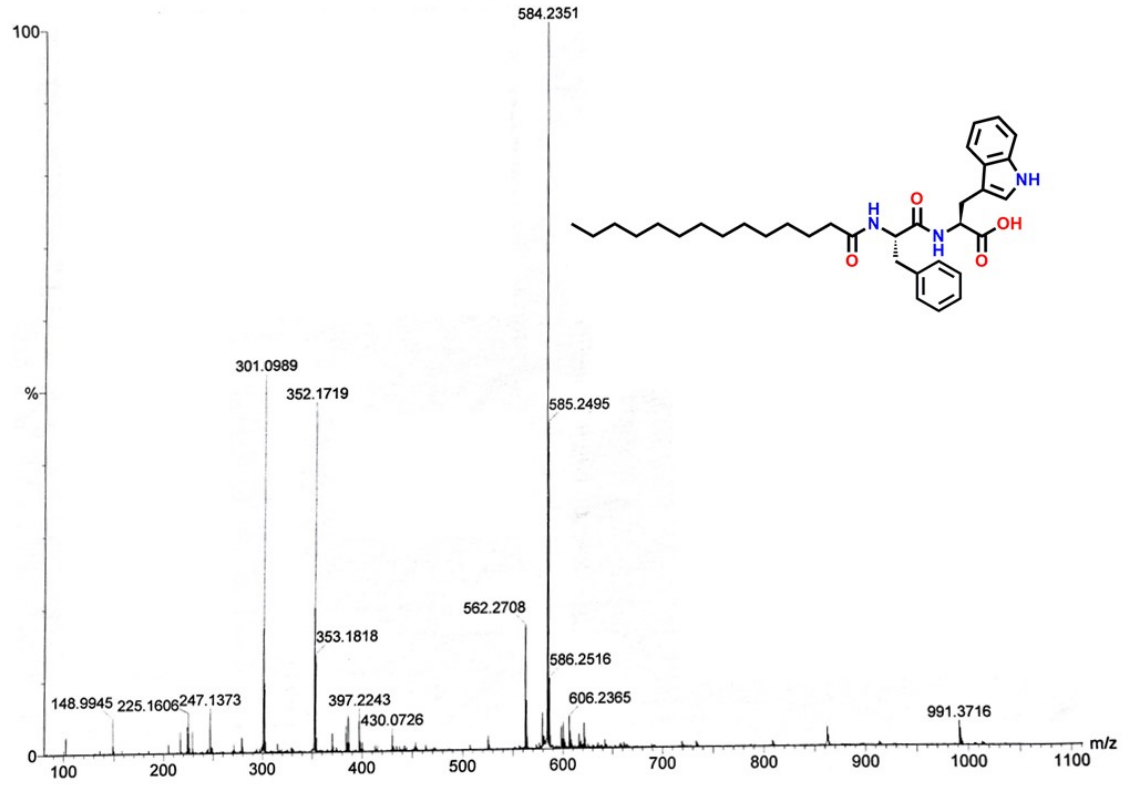

Fig. S30 HR-MS spectrum of **C_{14}-Phe-Trp-OH**.

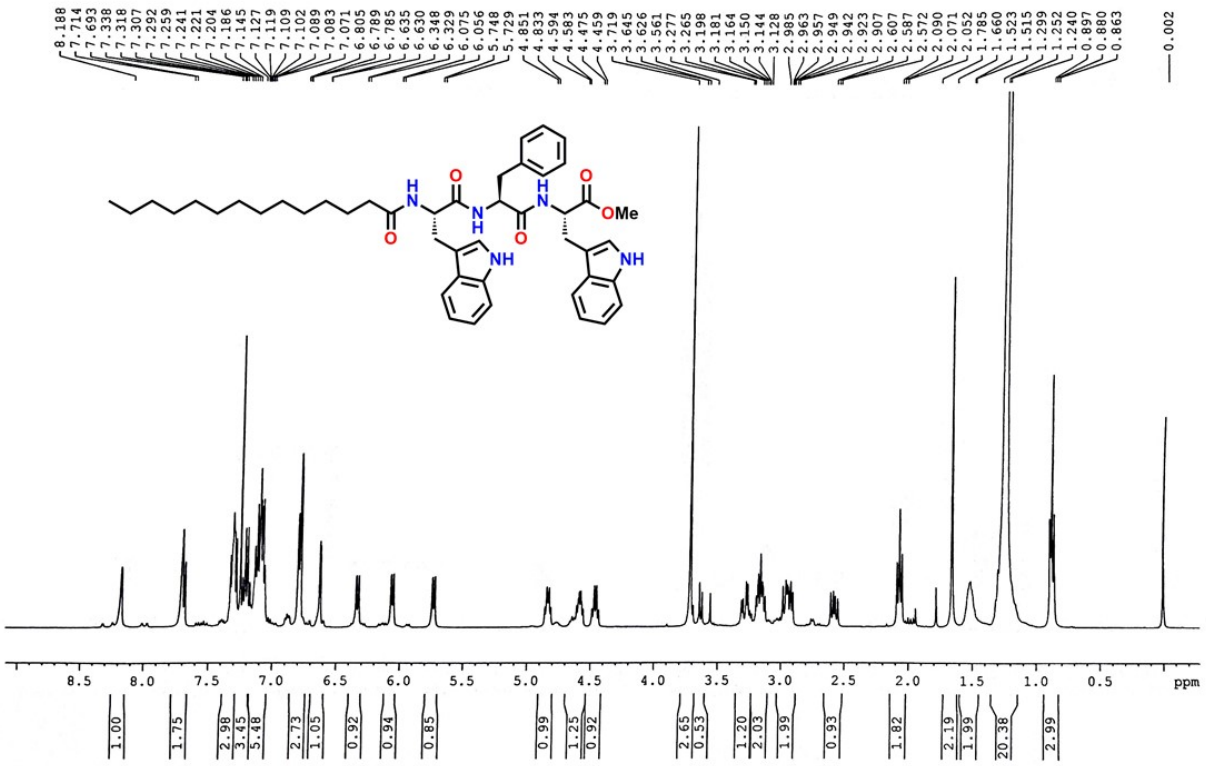

Fig. S31 ^{1}H-NMR spectrum of peptide gelator **C_{14}-Trp-Phe-Trp-OMe** in $CDCl_3$.

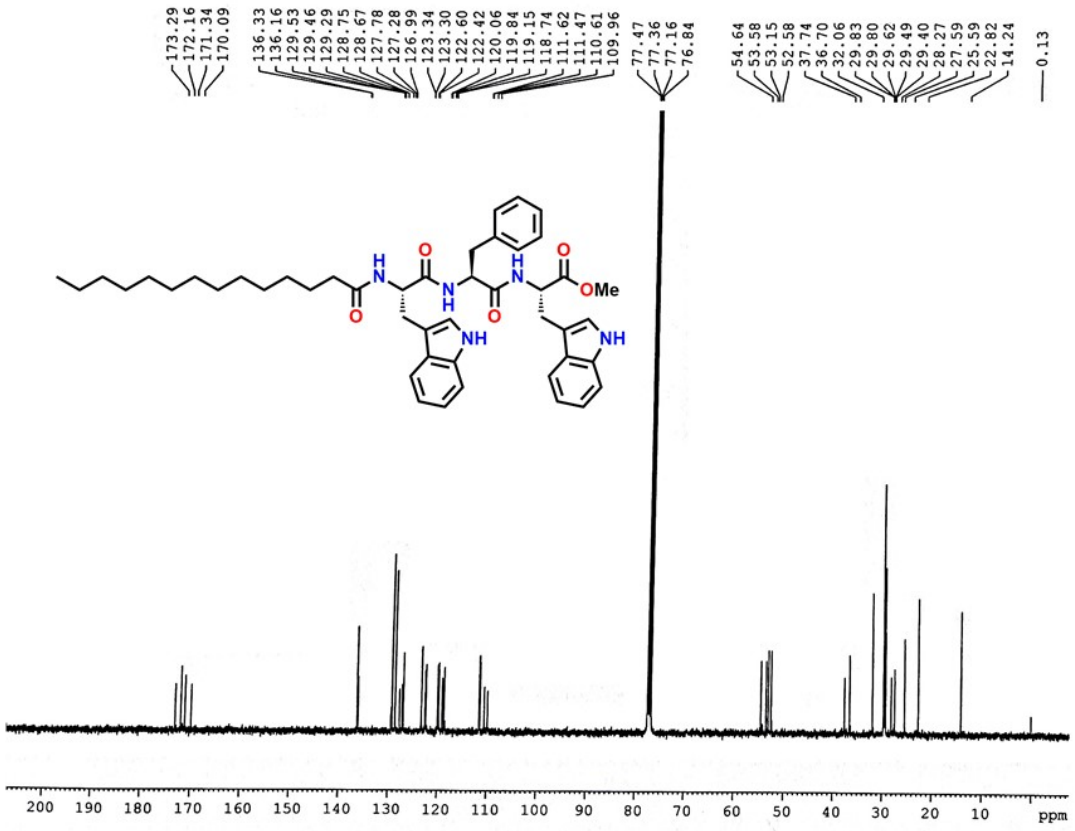

Fig. S32 ^{13}C-NMR spectrum of peptide gelator **C_{14}-Trp-Phe-Trp-OMe** in $CDCl_3$.

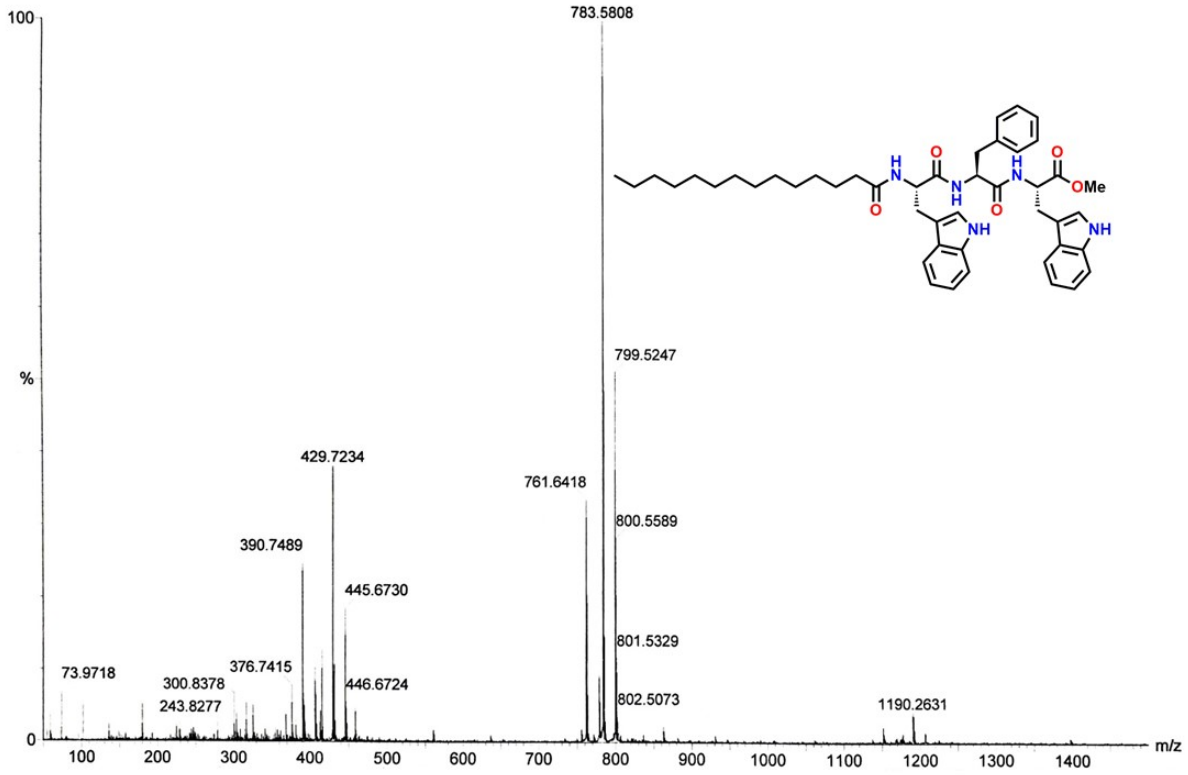

Fig. S33 HR-MS spectrum of **C_{14}-Trp-Phe-Trp-OMe**.

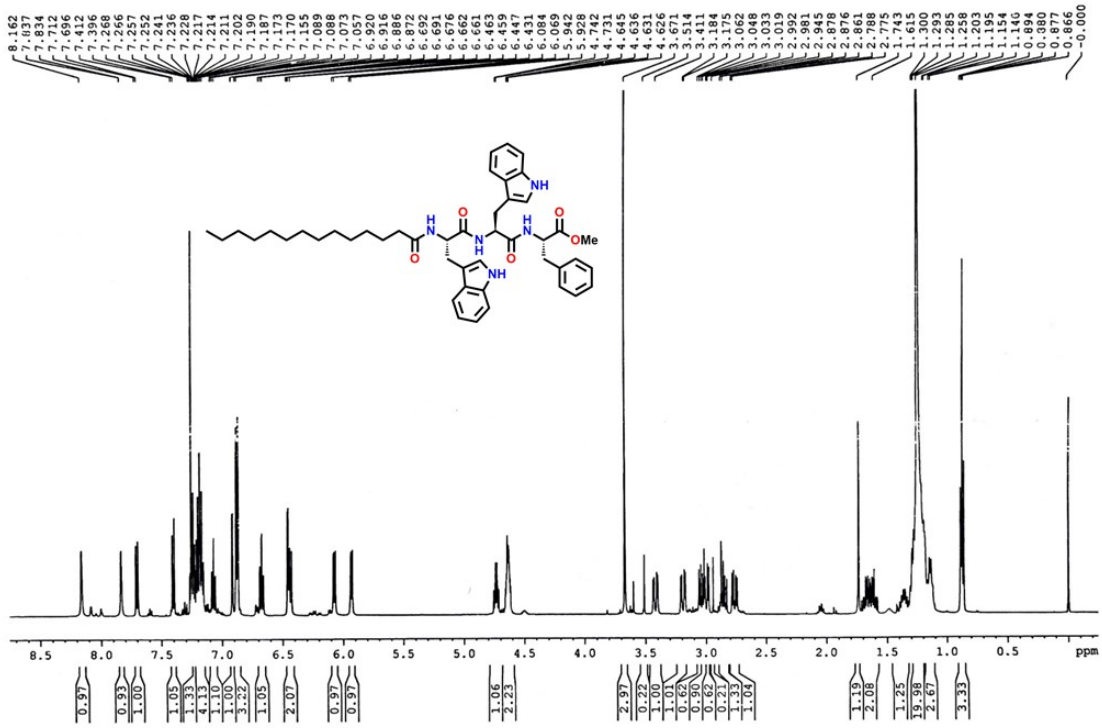

Fig. S34 ^{1}H-NMR spectrum of peptide gelator **C_{14}-Trp-Phe-Trp-OMe** in $CDCl_3$.

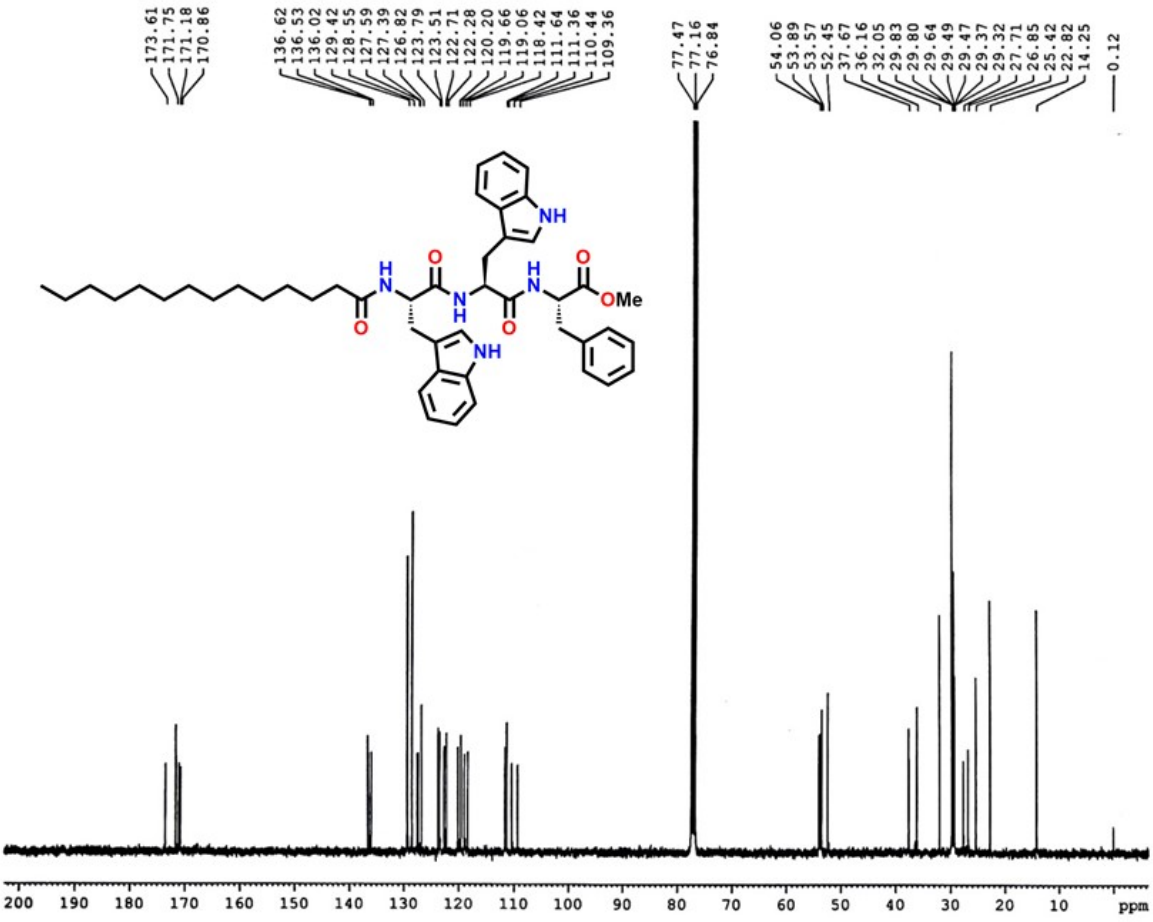

Fig. S35 ^{13}C-NMR spectrum of peptide gelator **C_{14}-Trp-Trp-Phe-OMe** in $CDCl_3$.

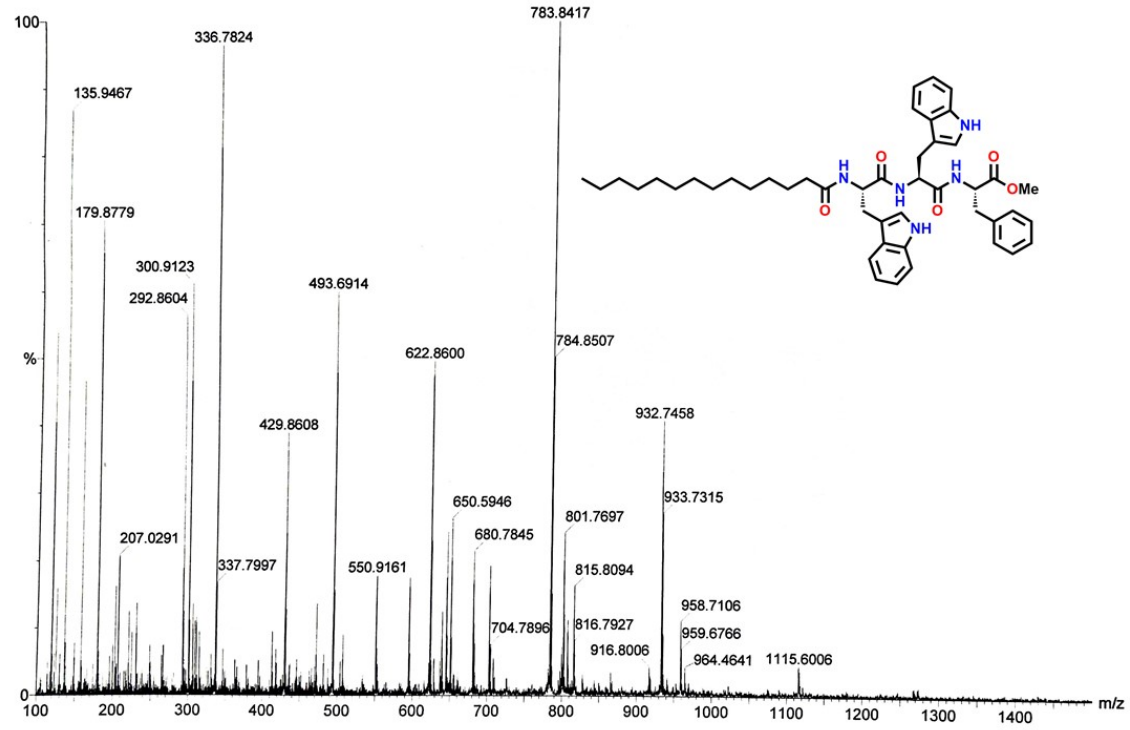

Fig. S36 HR-MS spectrum of **C_{14}-Trp-Trp-Phe-OMe**.

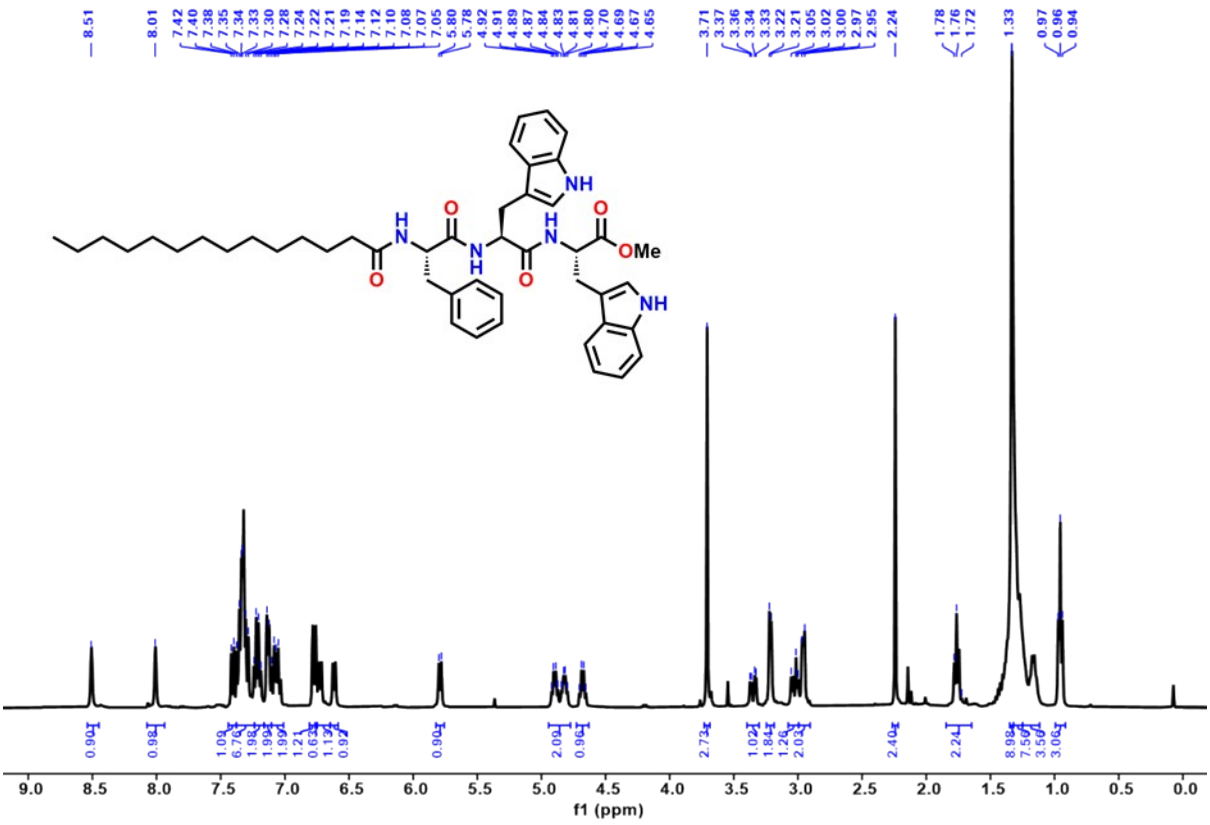

Fig. S37 ^{1}H-NMR spectrum of peptide gelator **C_{14}-Trp-Phe-Trp-OMe** in $CDCl_3$.

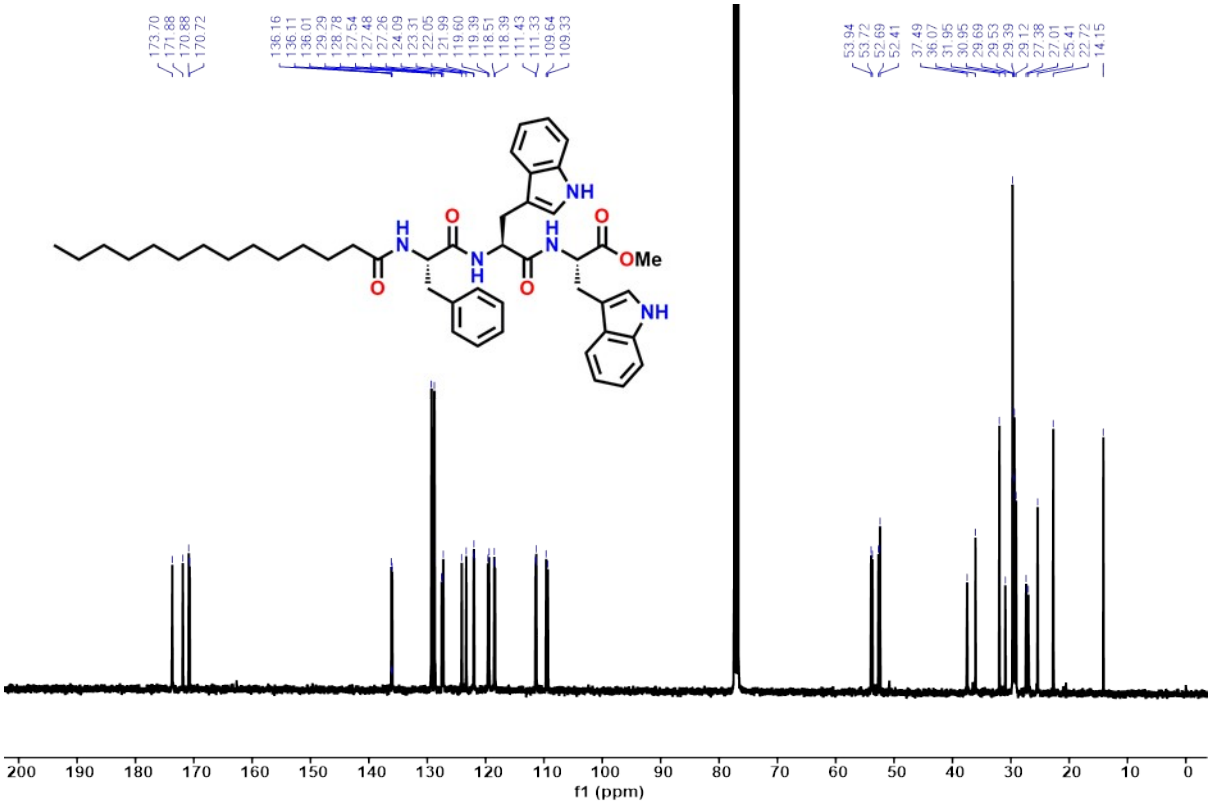

Fig. S38 ^{13}C-NMR spectrum of peptide gelator **C_{14}-Trp-Trp-Phe-OMe** in $CDCl_3$.

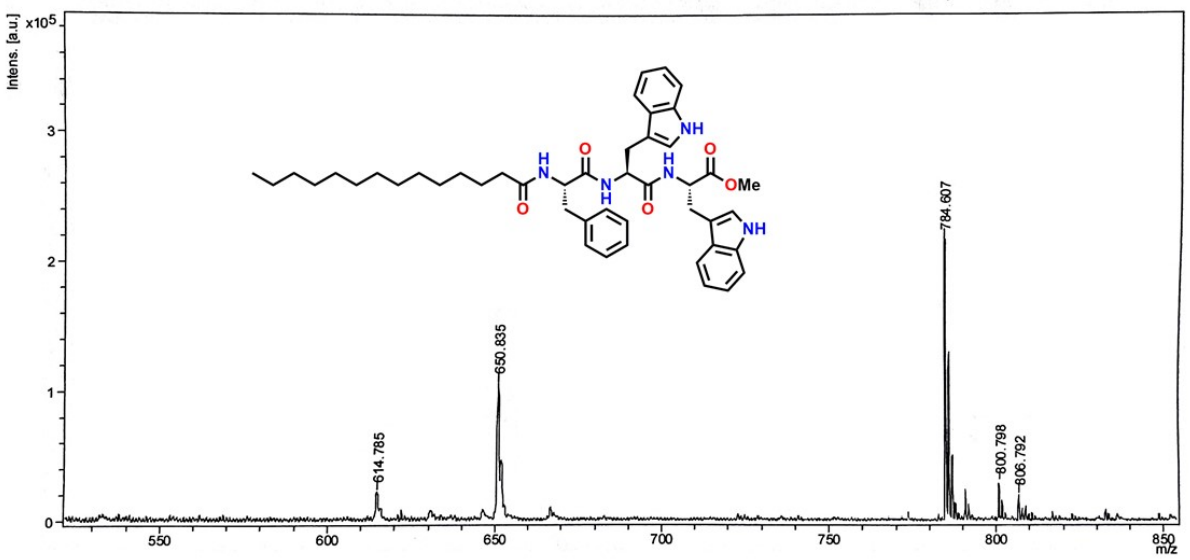

Fig. S39 HR-MS spectrum of **C_{14}-Trp-Trp-Phe-OMe**.

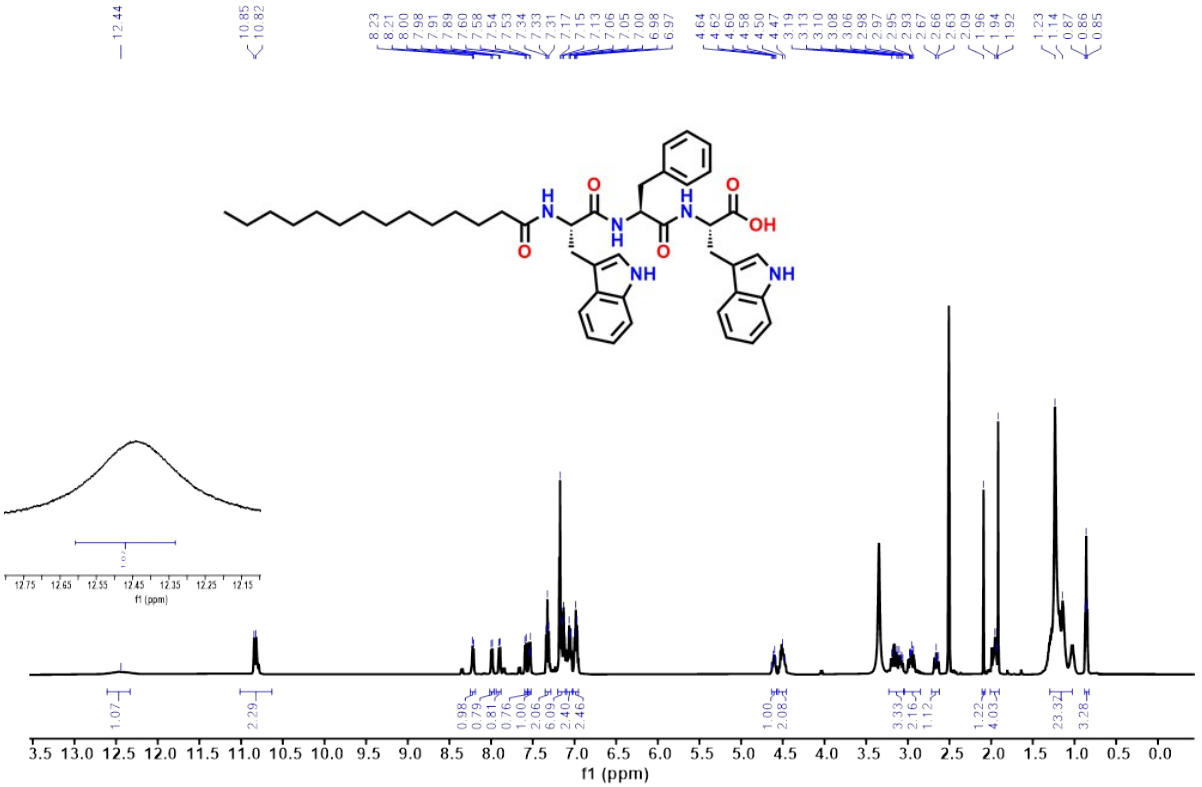

Fig. S40 ^{1}H-NMR spectrum of peptide gelator **G1** in DMSO-d_6.

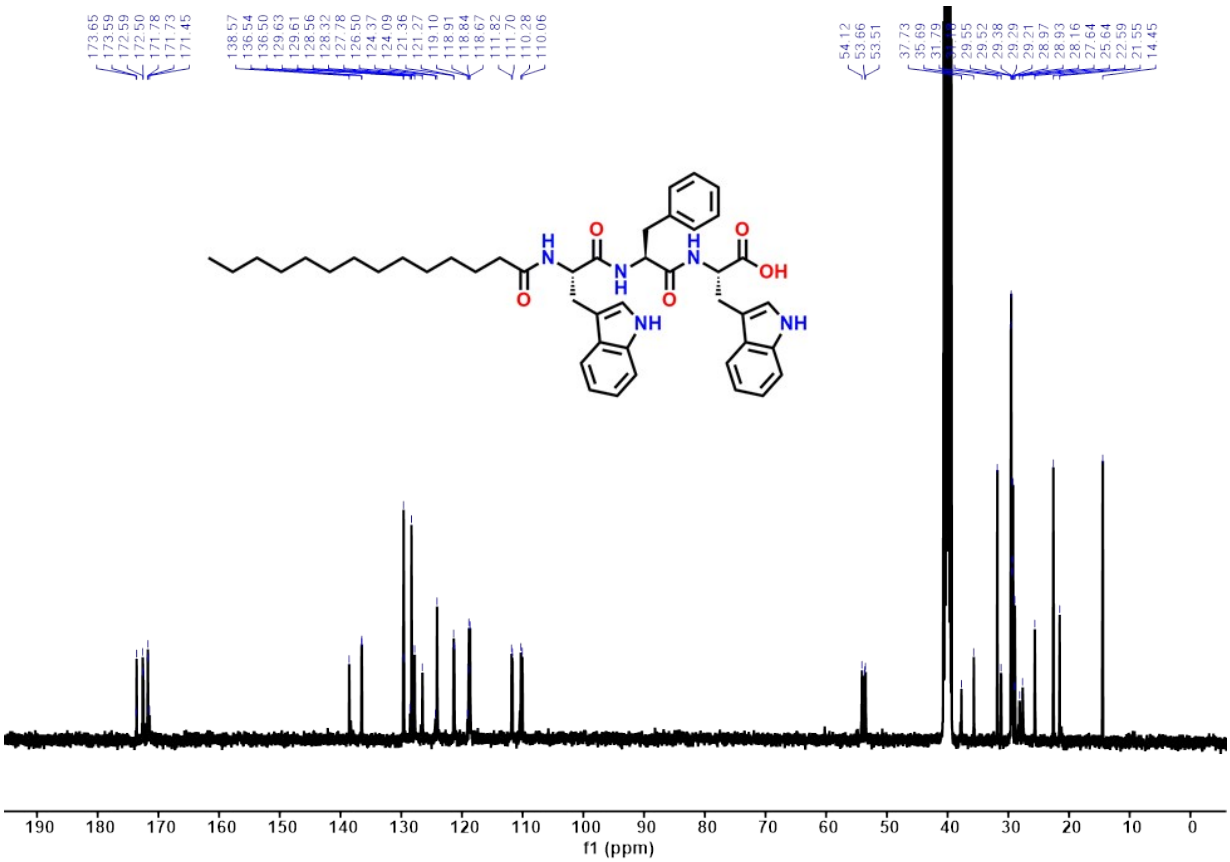

Fig. S41 ^{13}C-NMR spectrum of peptide gelator **G2** in DMSO-d_6.

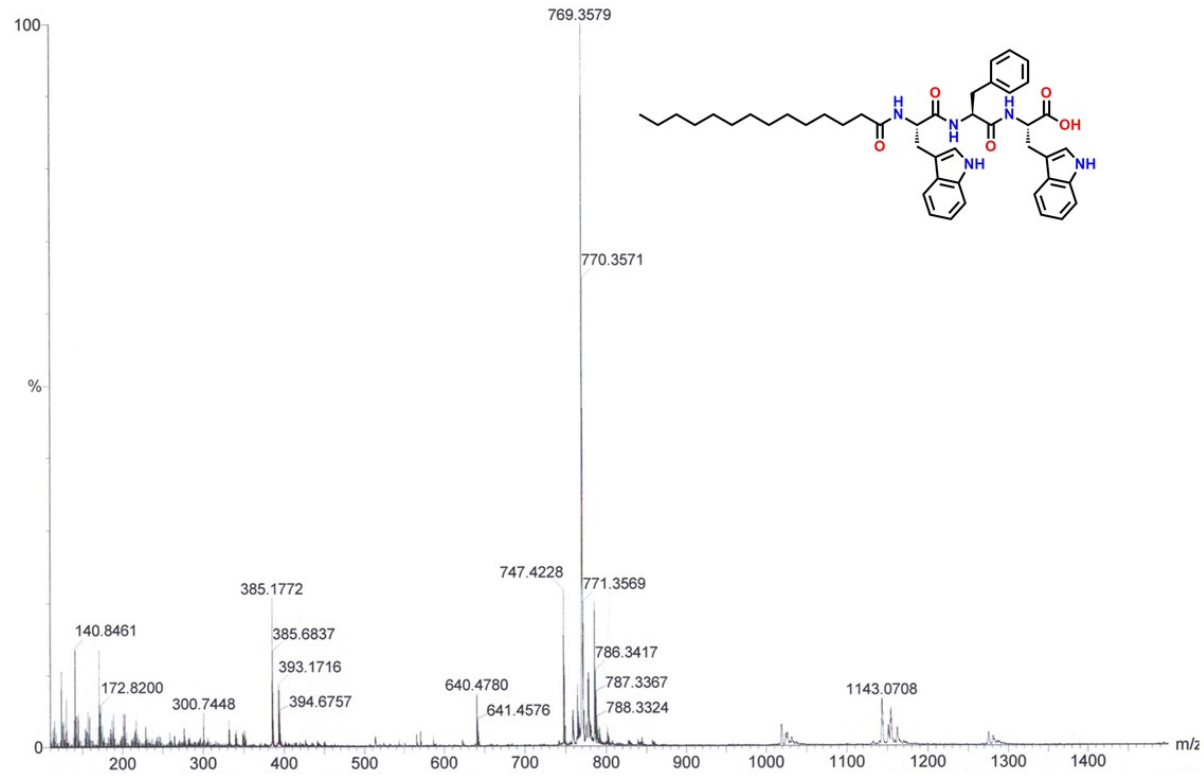

Fig. S42 HR-MS spectrum for peptide gelator **G1**.

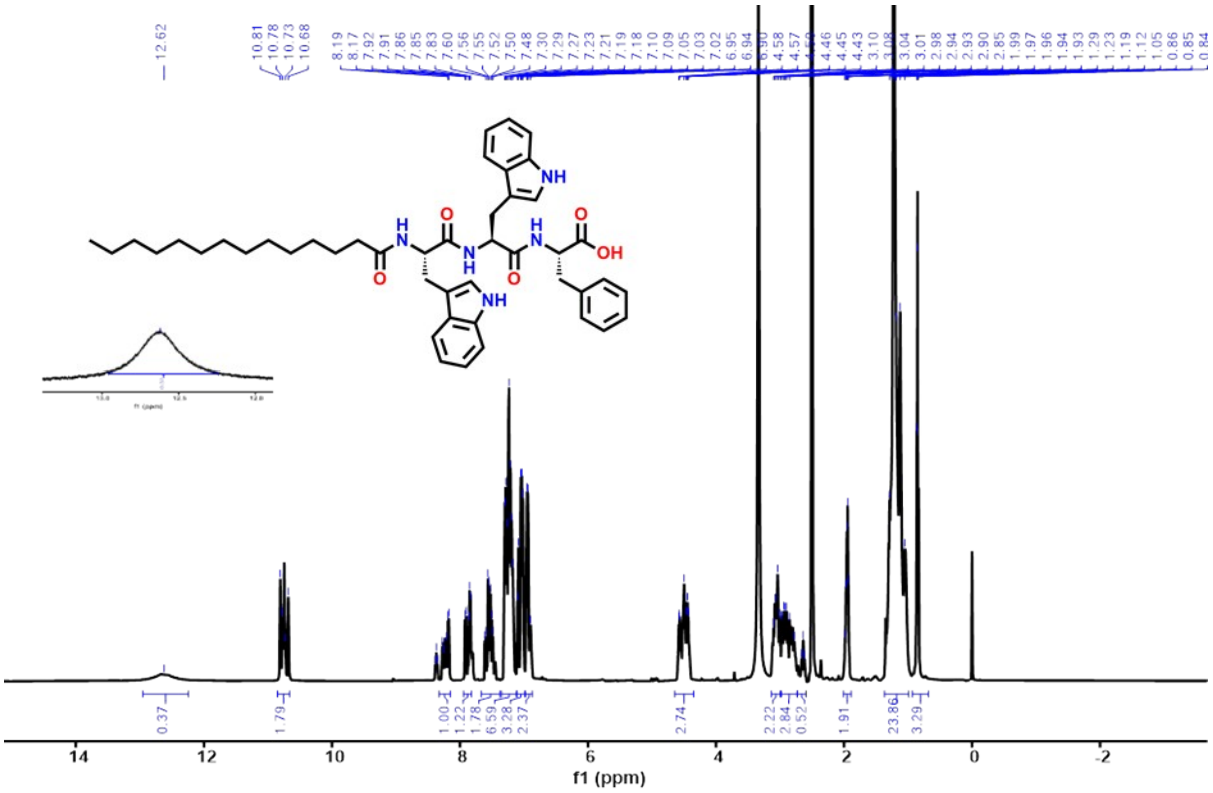

Fig. S43 ^{1}H-NMR spectrum of peptide gelator **G2** in DMSO-d_6.

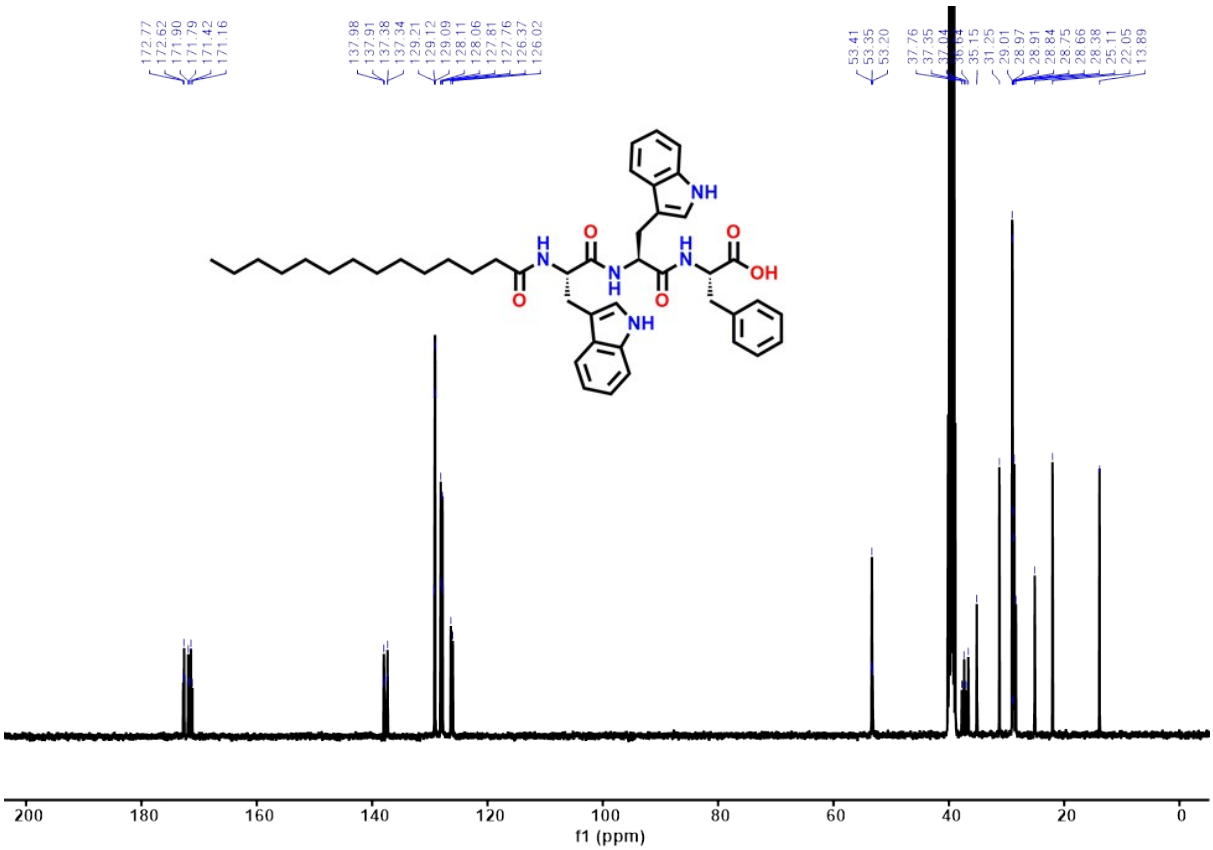

Fig. S44 ^{13}C-NMR spectrum of peptide gelator **G2** in DMSO-d_6.

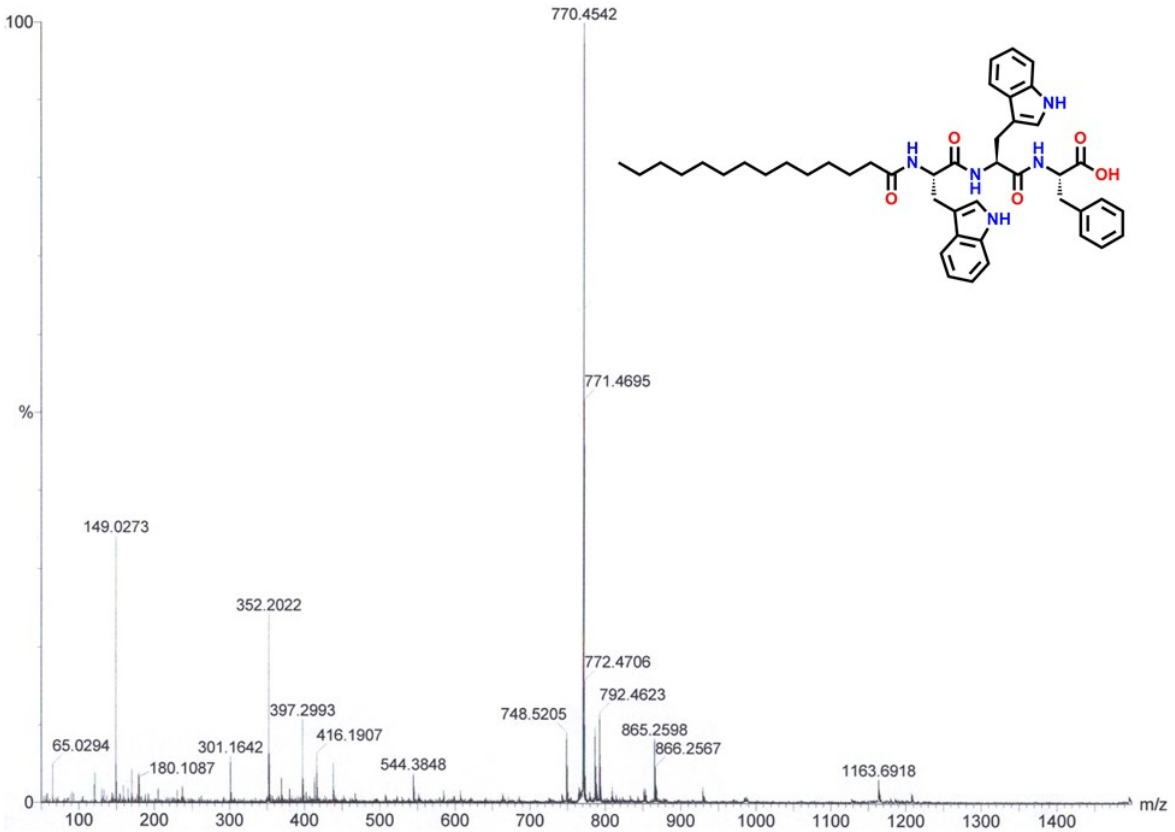

Fig. S45 HR-MS spectrum for peptide gelator **G2**.

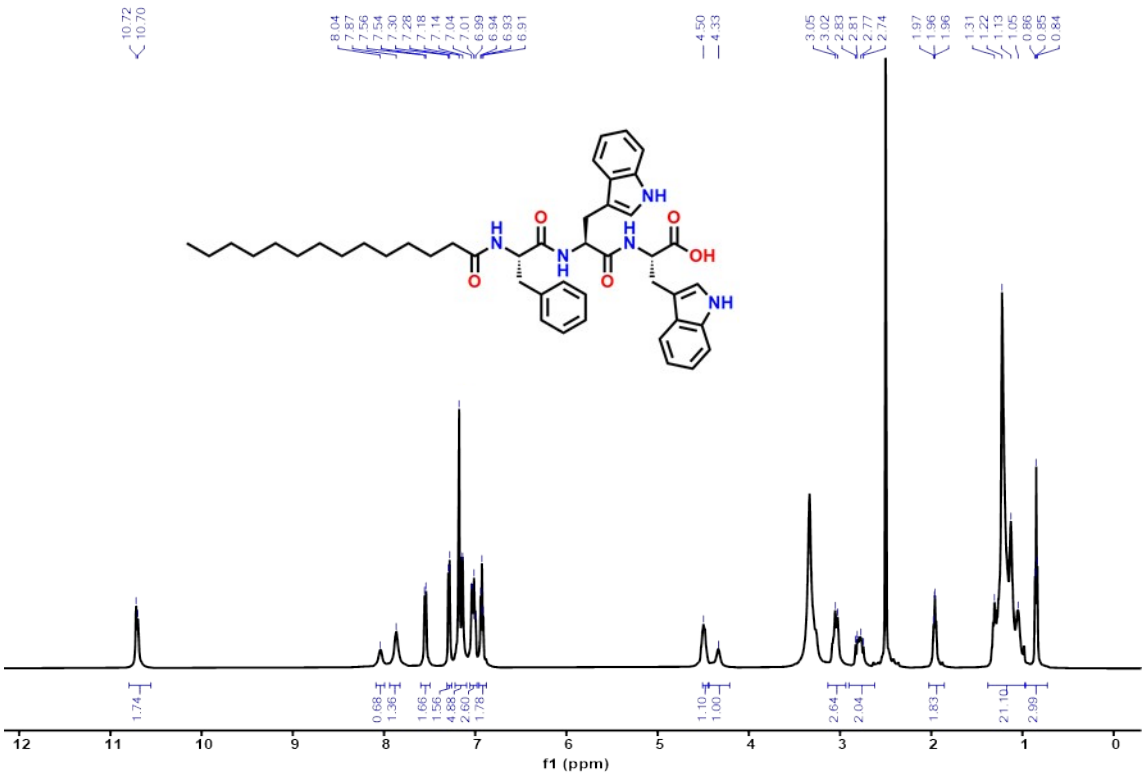

Fig. S46 ^{1}H-NMR spectrum of peptide gelator **G3** in DMSO-d_6.

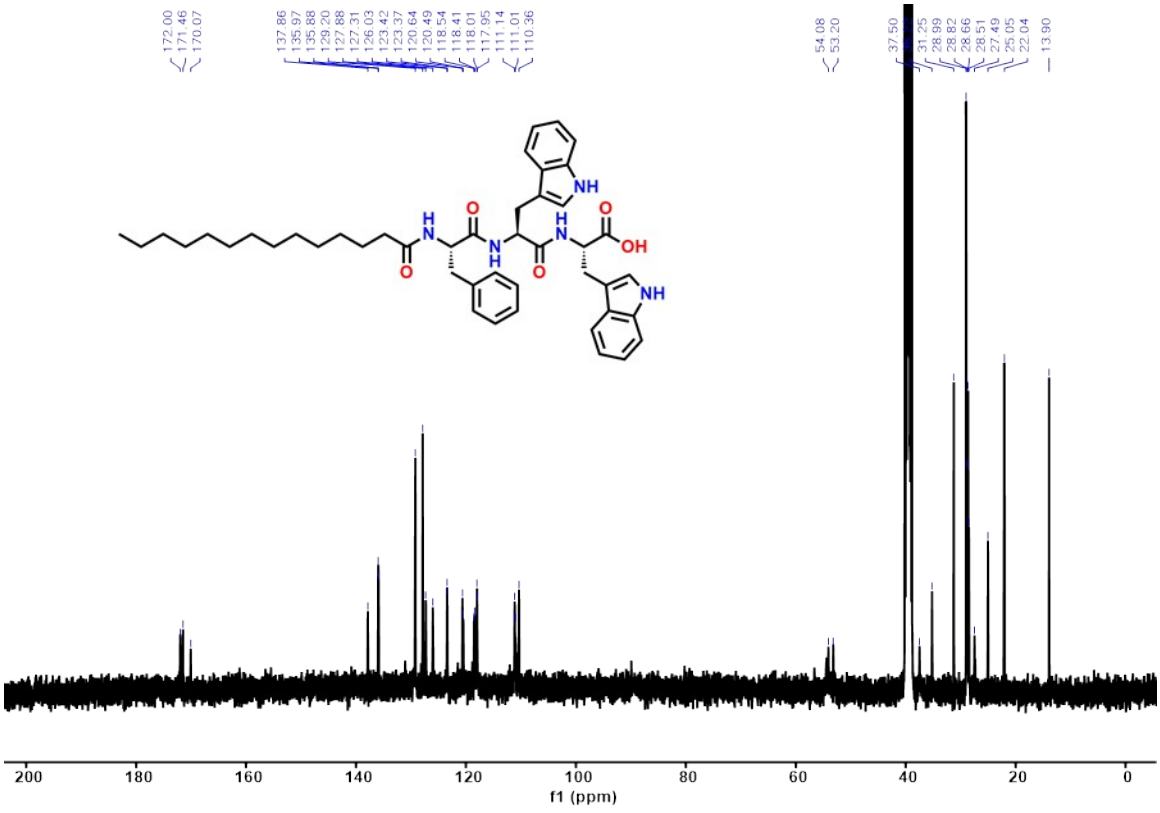

Fig. S47 ^{13}C-NMR spectrum of peptide gelator **G3** in DMSO-d_6.

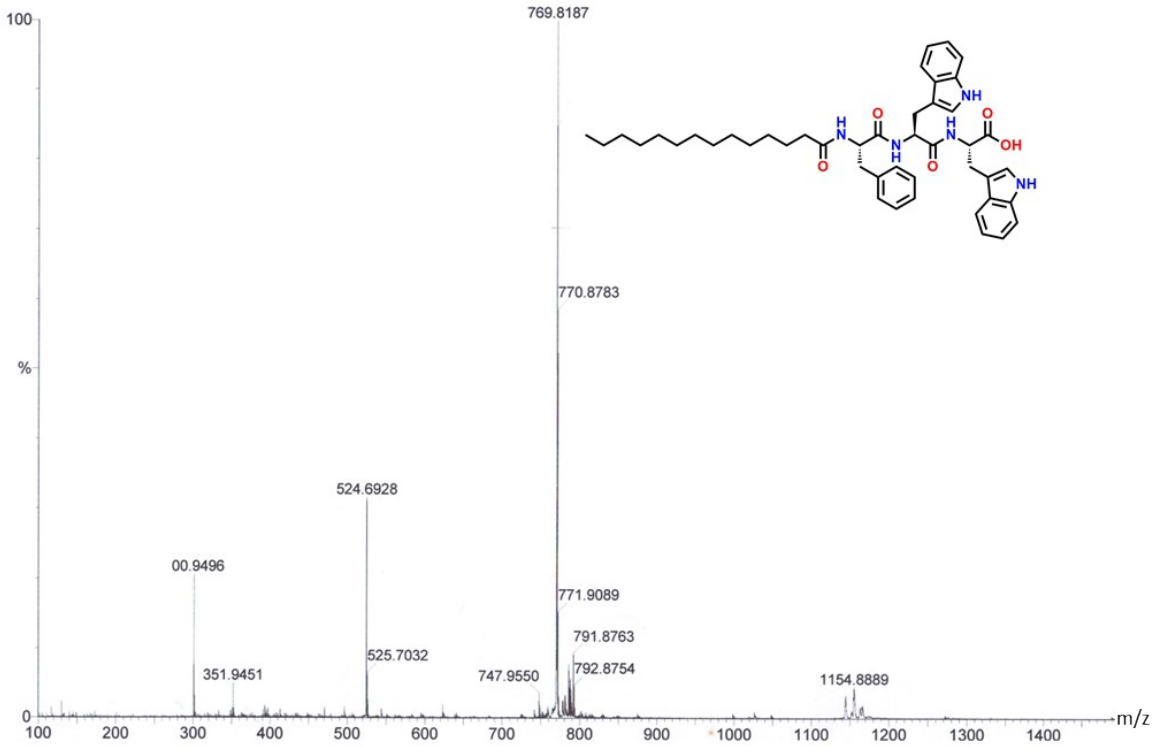

Fig. S48 HR-MS spectrum for peptide gelator **G3**.

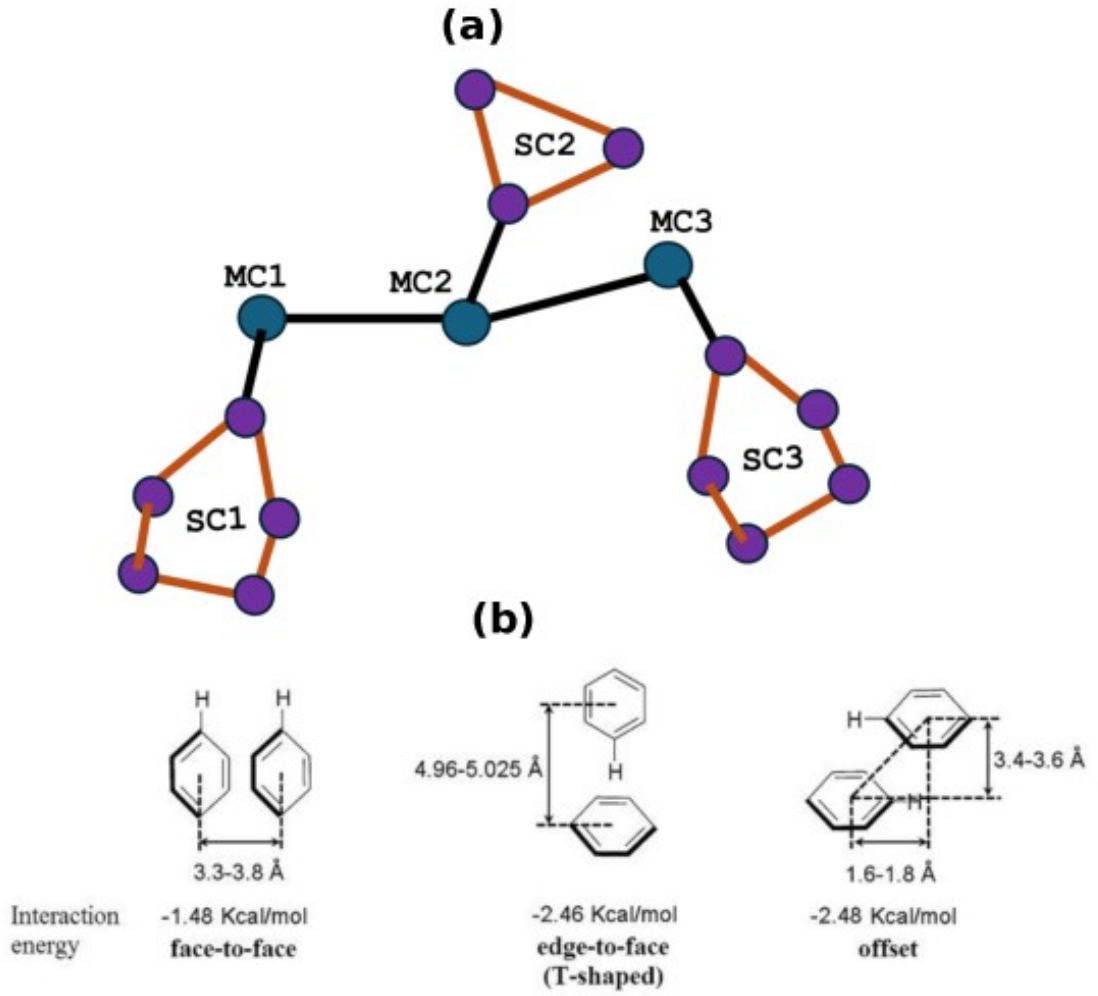

Fig. S49 Schematics of tripeptide side chains (SC) and main chains (MC) for G1 (C14WFWOH): (a) The three side chains designated as: SC1, SC2, and SC3, are key to understanding the orientation and stacking interactions that contribute to the final morphology of hydrogels. In the three hydrogel systems studied, the strength of stacking interactions varies due to the different spatial positions of amino acid side chains within the tripeptide sequence. In this sequence, the first residue is designated as SC1, while the second and third residues are referred to as SC2 and SC3, respectively. (b) Stacking interactions between aromatic side chains can vary in both strength and orientation. As illustrated in the figure, among the three stacking modes, the offset/T-shaped orientation exhibits the strongest interaction. In the case of the G1 gelator, the first residue is Trp (W), is assigned as SC1, the central Phe (F) as SC2, and the final Phe (W) as SC3.

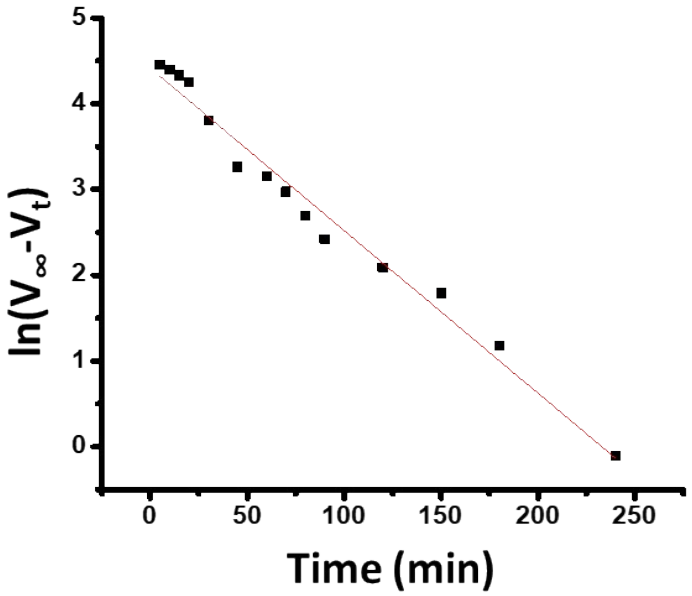

Fig. S50 First order like water release kinetics during self-shrinking of **G1** hydrogel (where V_t is the cumulative volume (or mass) of water released at time t and V_∞ is the plateau value from the experiment).

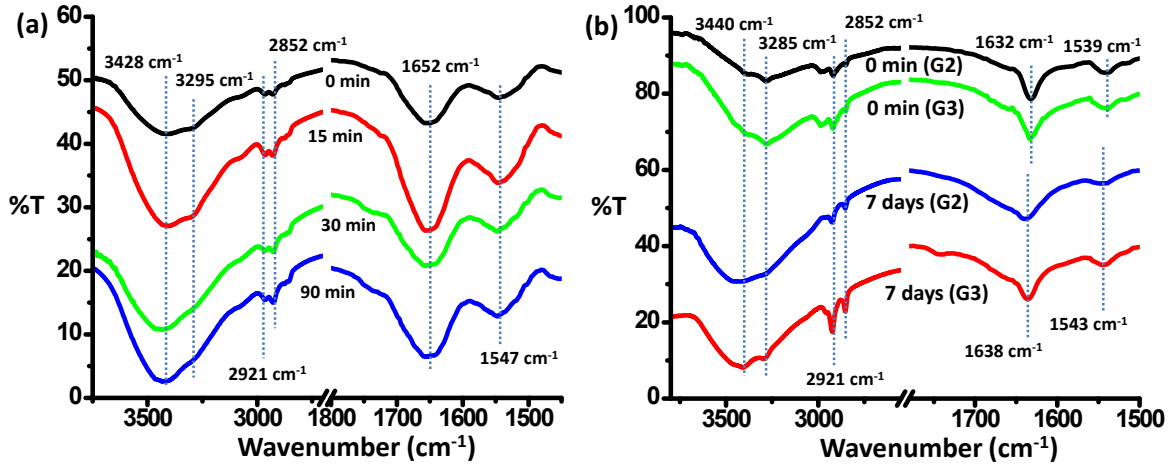

Fig. S51 Time dependent FTIR data of self-shrinking hydrogel for (a) G1 and (b) G2 and G3 tripeptide based gelator.

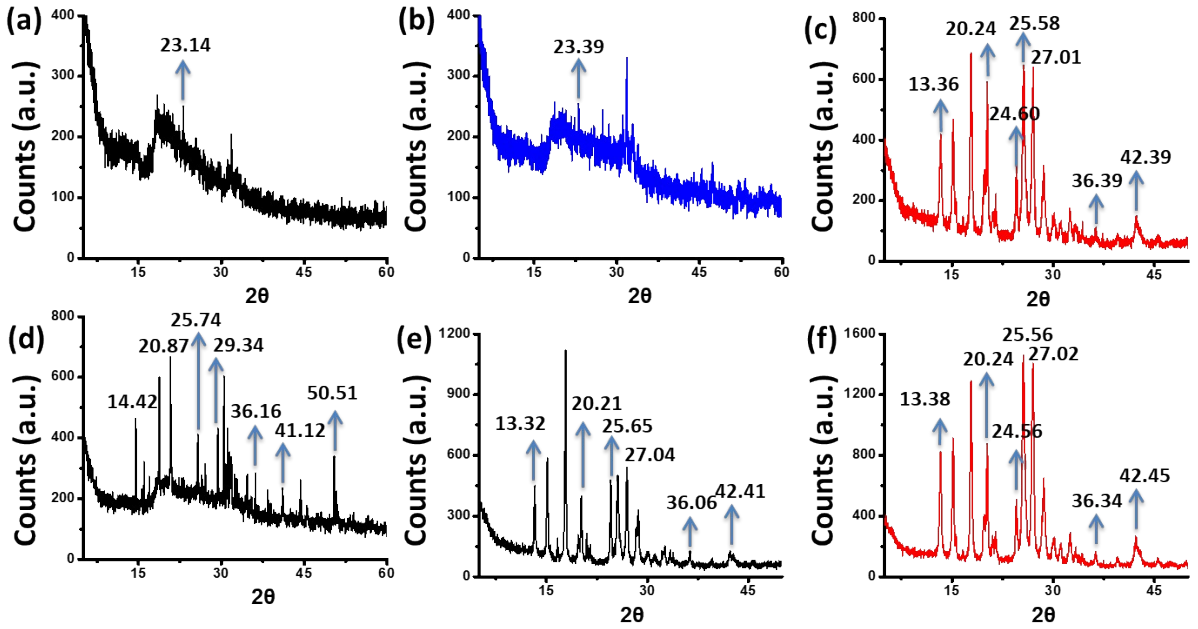

Fig. S52 XRD data of tripeptide-based hydrogelators G1, G2, and G3 before shrinking (a–c) and after shrinking (d–f), respectively.

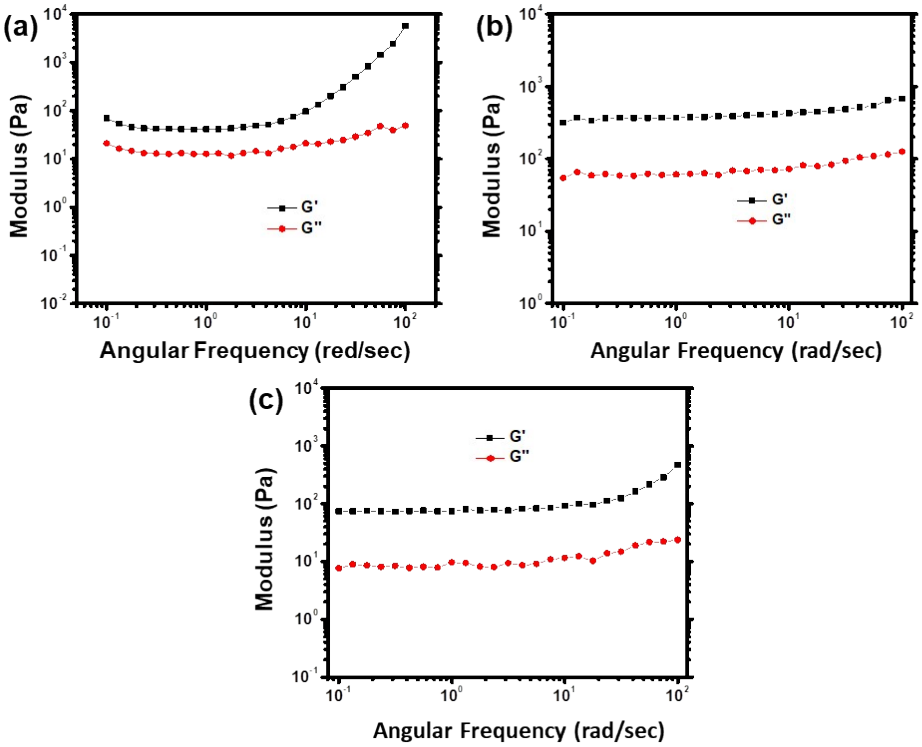

Fig. S53 (a)-(c) Frequency sweep analysis of hydrogel formed by the gelators G1, G2 and G3, respectively at a constant strain of 0.05%.

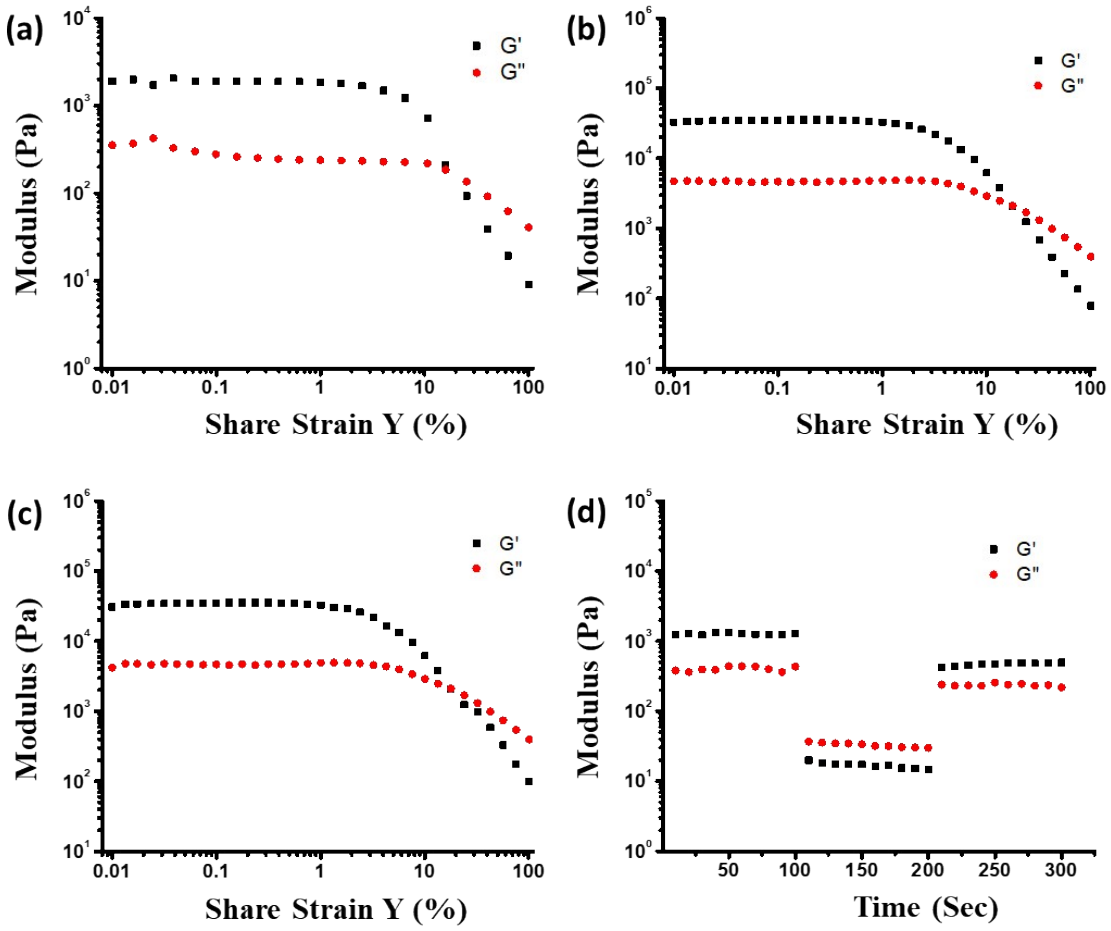

Fig. S54 Amplitude sweep analysis of hydrogels obtained from (a) **G1**, (b) **G2** and (c) **G3** amphiphilic gelators. (d) Step strain experiment for **G1** hydrogel, showing thixotropic behaviour of both the gels.

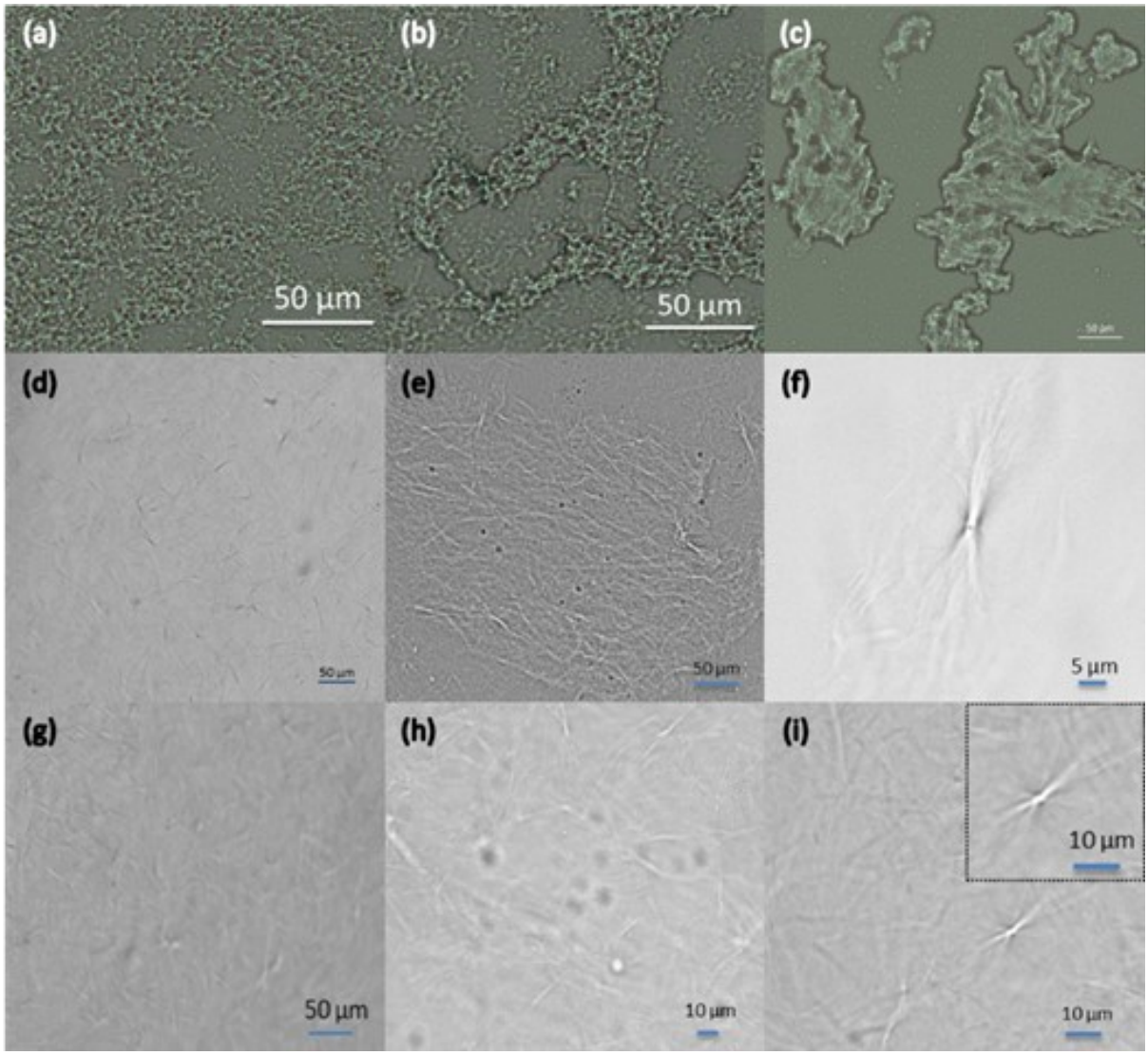

Fig. S55 Optical microscopic images illustrating the morphological changes occurring during the self-shrinking process of hydrogels formed by **G1** hydrogelators at (a) 0 minutes, (b) 30 minutes, and (c) 90 minutes. Images (d) and (g) display the initial morphologies of hydrogels formed by **G2** and **G3** gelators, respectively. Optical images (e-f) and (h-i) depict the morphological changes observed after 7 days of self-shrinking for **G2** and **G3**-based hydrogels, respectively.

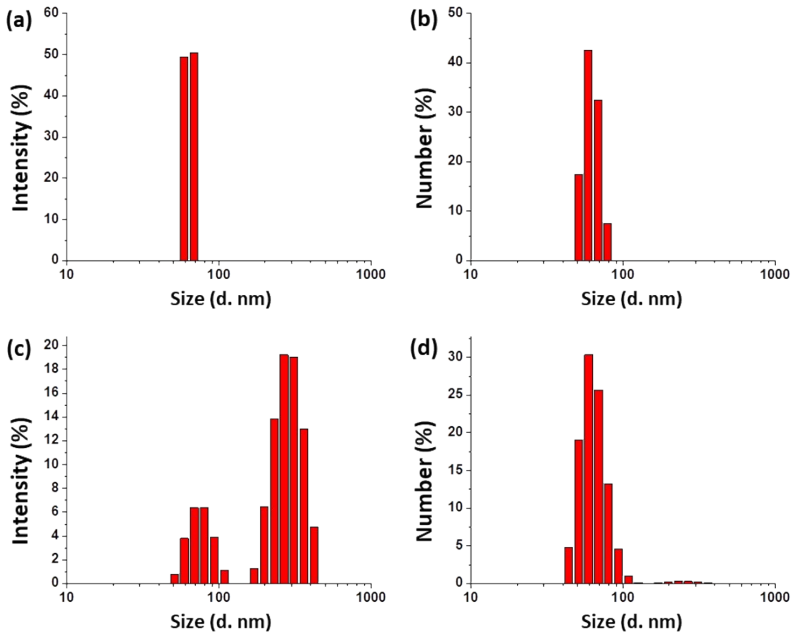

Fig. S56 Intensity percentage and number percentage vs size (d. nm) of the **G1** based hydrogel in its before shrinking (a, b) and after shrinking (c, d) state.

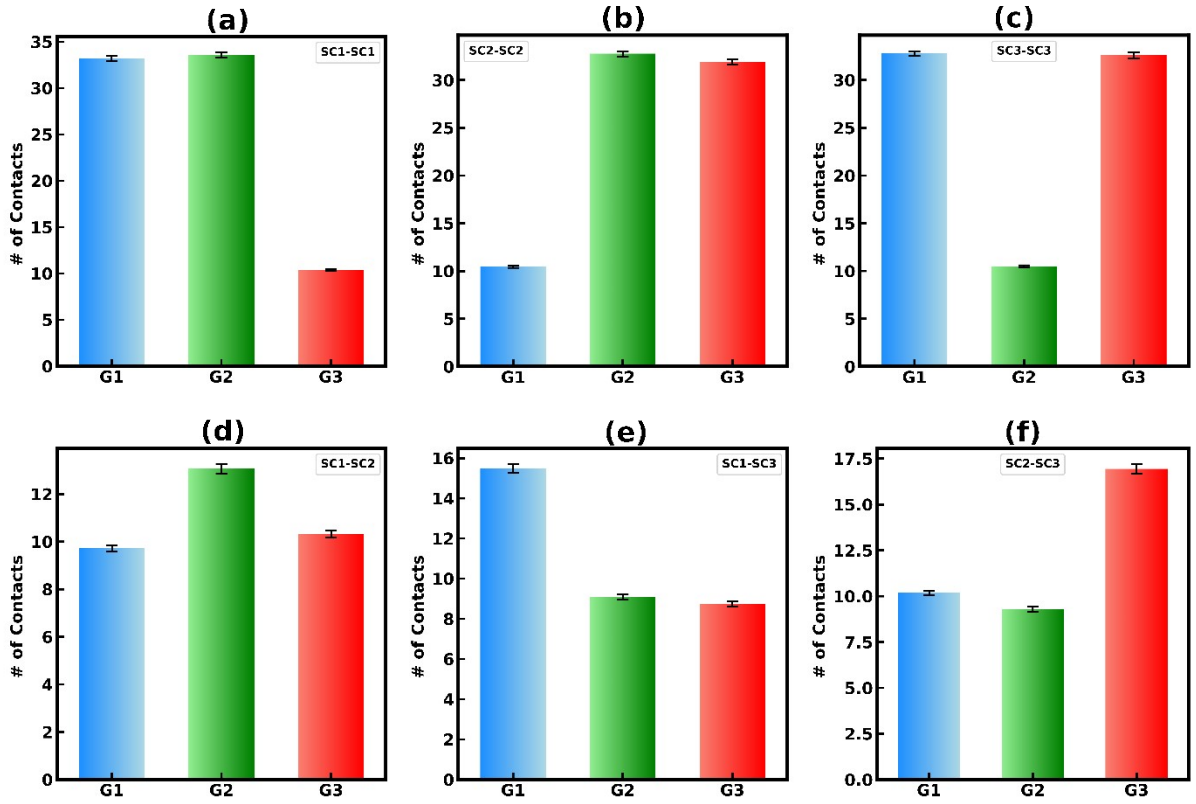

Fig. S57 Number of contacts between similar side chains (e.g., SC1-SC1, SC2-SC2, Sc3-SC3) of the G1, G2, and G3 tripeptides are shown in panels a-c. Based on the sequence of amino acids, the first residue is denoted as SC1, the second as SC2, and the third as SC3. Trp (W) is represented by five coarse-grained (CG) beads, while Phe (F) is represented by three CG beads. (d-f) illustrates contacts between different types of side chains for G1, G2, and G3 tripeptides. In the case of G1, strong π-π stacking interactions lead to both parallel and anti-parallel alignments, resulting in a higher number of SC1-SC3 (anti-parallel) contacts (as shown in panel e) compared to G2 and G3. For G2 and G3, the F residue is located at the terminal position, and so the peptide assemblies undergo more reorganization. As a result, parallel or anti-parallel stacking is less probable, and a zigzag arrangement becomes more prominent. This leads to a higher frequency of SC1-SC2 contacts in G2 and SC2-SC3 contacts in G3, corresponding to their stacking modes.

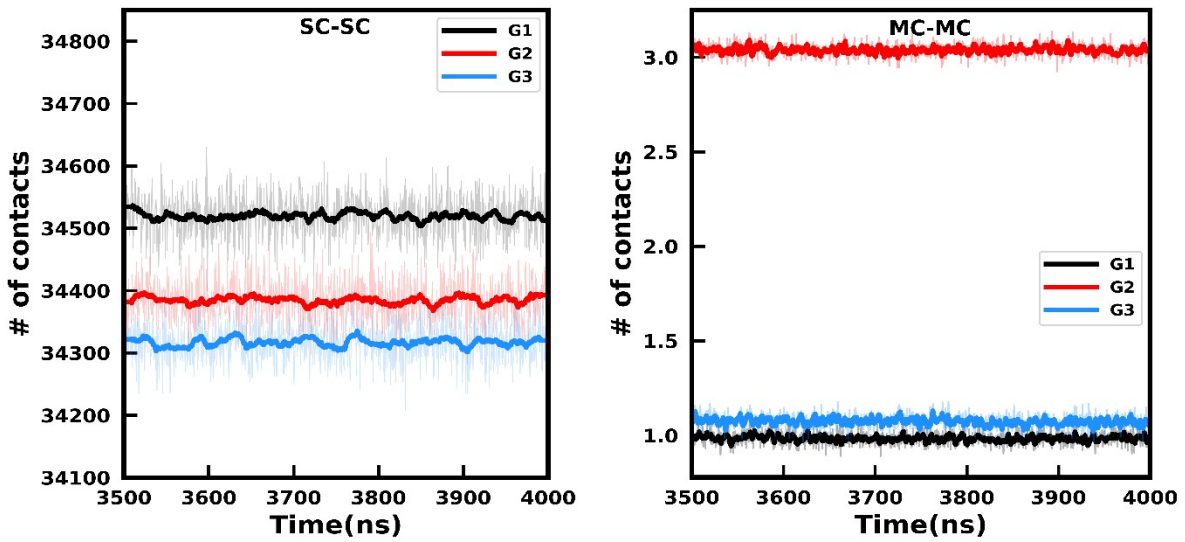

Fig. S58 Time evolution of the total number of contacts observed over the 4 μs CG-MD simulation for all possible side chain-side chain (SC-SC) interactions is shown in the left panel. The right panel presents the contact profiles between the backbone main chains (MC-MC) for the G1, G2, and G3 tripeptide hydrogels. A distance cutoff of 0.65 nm was used to define a contact.

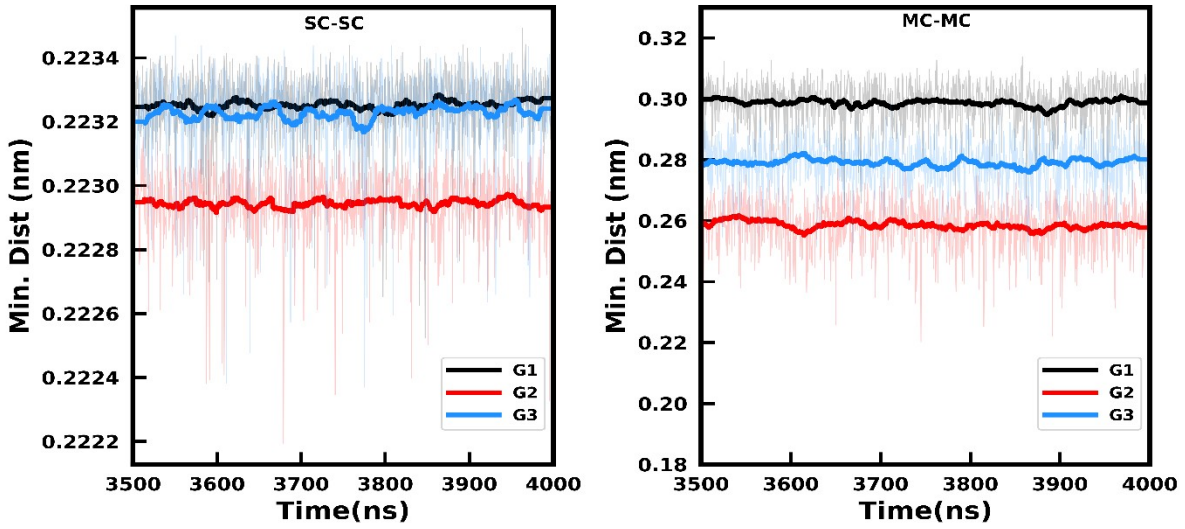

Fig. S59 Left Panel: Minimum distances between all possible side chain-side chain (SC-SC) pairs. Right Panel: Minimum distances between main chain-main chain (MC-MC) interactions for G1, G2, and G3 tripeptides. In the case of G1 tripeptides, strong stacking interactions result in a relatively constant inter-chain distance. In contrast, G2 and G3 exhibit weaker stacking and increased zigzag reorganization, allowing both side chains and main chains to come into closer proximity. As a result, the minimum distances for G2 and G3 are lower compared to those in G1 hydrogels.

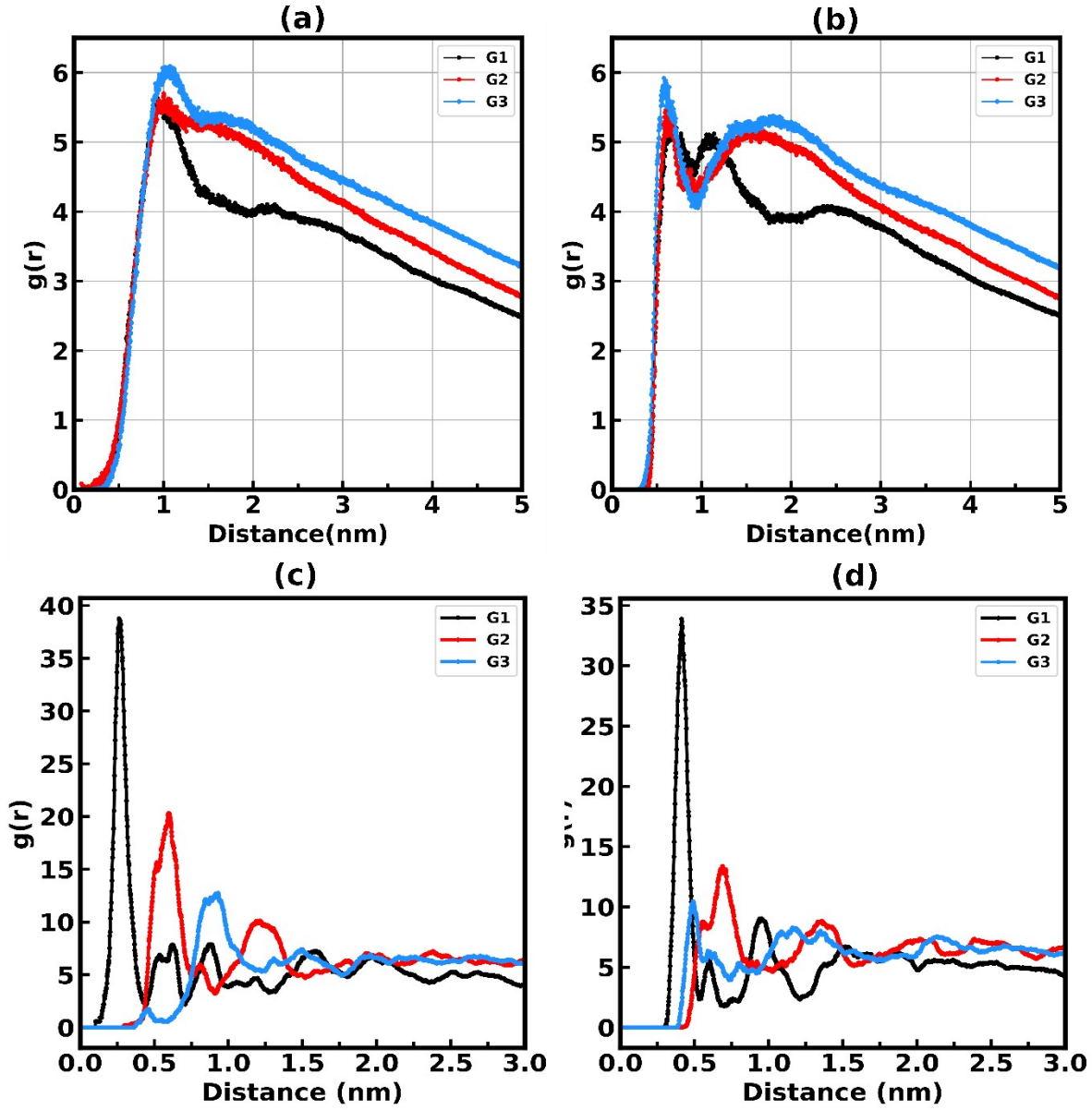

Fig. S60 (a) Pair distribution function g(r) between all combinations of side chains (SC-SC), and (b) between all combinations of main chains (MC-MC). In G1, the presence of strong π-π stacking interactions and its network-like morphology result in a sharp drop in g(r) around 1.3 nm. In contrast, G2 and G3 display a more gradual decline, highlighting the distinct structural differences among the three morphologies. (c) Radial distribution function of side chains from the centre-of-mass (COM) of the self-assembled aggregates. (d) Radial distribution function of main chain beads from the COM of the self-assembly. Due to stronger π-π stacking in G1, both side chains and main chains are more densely packed around the COM, as indicated by the sharper and more pronounced black curves.