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Supporting Information

Smart oligopeptide gels: *In situ* formation and stabilization of gold and silver nanoparticles within supramolecular organogel networks

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Experimental section:

Peptide Synthesis

Peptides **1, 2** and **3** were synthesized by conventional solution phase methods by using racemization free fragment condensation strategy. The Boc group was used for N-terminal protection and the C-terminus was protected as a methyl ester. Deprotections were performed using saponification method. Couplings were mediated by dicyclohexylcarbodiimide-1-hydroxybenzotriazole (DCC/HOBt). All the intermediates were characterized by ^{1}H-NMR (300 MH_Z) and thin layer chromatography (TLC) on silica gel and used without further purification. The final products were purified by column chromatography using silica (100-200-mesh size) gel as stationary phase and ethyl acetate-toluene mixture as eluent. The purified final compounds were fully characterized by 300 MH_Z ^{1}H -NMR spectroscopy, FT-IR spectroscopy and Mass spectrometry.

Syntheses of peptides **1, 2** and **3**:

(a) **Synthesis of Boc-Phe(1)-OH** : A solution of phenylalanine 3.30 g (20 mmol) in a mixture of dioxan (40 mL), water (20 mL) and 1 M NaOH (20 mL) was stirred and cooled in an ice-water bath. Di-*tert*-butylpyrocarbonate 5.28 g (22 mmol) was added and stirring was continued at room temperature for 6 h. Then the solution was concentrated in *vacuo* to about 25 to 30 mL, cooled in an ice-water bath, covered with a layer of ethyl-acetate (about 50 mL) and acidified with a dilute solution of $KHSO_4$ to pH 2-3 (Congo red). The aqueous phase was extracted with ethyl acetate and this operation was done repeatedly. The ethyl acetate extracts were pooled, washed with water and dried over anhydrous Na_2SO_4 and evaporated in *vacuo*. The pure material was obtained.

Yield = 4.77 g (18 mmol, 90%); (Found: C, 62.3; H, 6.92; N, 5.01%. $C_{14}H_{19}NO_4$ (265) requires: C, 63.39; H, 7.16; N, 5.28%).

(b) **Boc-Phe(1)-Tyr(2)-OMe** : 4.50 g (17 mmol) of Boc-Phe-OH was dissolved in 10 mL of dimethylformamide (DMF) in an ice-water bath. H-Tyr-OMe was isolated from 7.87 g (34 mmol) of the corresponding methyl ester hydrochloride by neutralization, subsequent extraction with ethyl acetate and concentration to 10 mL and this was added to the reaction mixture, followed immediately by 3.50 g (17 mmol) of di-cyclohexaylcarbodiimide (DCC) and 2.29 g (17 mmol) of HOBT. The reaction mixture was allowed to come to room temperature and stirred for 24 h. DCM was evaporated, residue was taken in ethyl acetate (60 mL), and dicyclohexylurea (DCU) was filtered off. The organic layer was washed with 2M HCl (3 × 50 mL), brine (2 × 50 mL), 1M sodium carbonate (3 × 50 mL) and brine (2 × 50 mL) respectively. Then dried over anhydrous sodium sulfate, and evaporated in *vacuo* to yield the solid compound.

Yield = 7.07 g (16 mmol, 98%); (Found: C, 65.2; H, 6.67; N, 6.03%. $C_{24}H_{30}N_2O_6$ (442) requires: C, 65.15; H, 6.78; N, 6.33%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.26, 7.19-7.16 (4H, m); 6.95-6.84, 6.70-6.67 (5H, m); 6.37 (1H, d, J = 7.5 Hz); 5.01 (1H, d, J = 7.4 Hz); 4.77-4.71 (1H, m); 4.33 (1H, m); 3.67 (3H, s); 3.02 (2H, m); 2.97 (2H, m); 1.40 (9H, s).

(c) **Boc-Phe(1)-Tyr(2)-OH**: To 7 g (15.8 mmol) of Boc-Phe(1)-Tyr(2)-OMe, 20 mL MeOH and 10 mL of 2 M NaOH were added. The reaction mixture was stirred and the progress of saponification was monitored by thin layer chromatography (TLC). After 10 h methanol was removed under *vacuo*, 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 M HCl and it was extracted with ethyl acetate (3 × 50 mL). The extracts were pooled, dried over anhydrous sodium sulfate and evaporated in *vacuo* to obtain white solid compound.

Yield = 6.5 g (15.2 mmol, 96%); (Found: C, 64.45; H, 6.62; N, 6.02%. $C_{23}H_{28}N_2O_6$ (428) requires: C, 64.48; H, 6.54, N, 6.54%);

^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 9.13 (1H, s); 7.89 (1H, d, *J* = 7.47 Hz); 7.16-7.11 (4H, m); 6.96-6.91, 6.58-6.55 (5H, m); 6.77 (1H, d, *J* = 8.64 Hz); 4.28 (1H, m); 4.05 (1H, m); 2.89-2.69 (2H, m); 2.62-2.54 (2H, m); 1.19 (9H, s).

(d) **Boc-Phe(1)-Tyr(2)-Phe(3)-OMe 1:** 2.14 g (5 mmol) of Boc-Phe(1)-Tyr(2)-OH was taken in 10 mL of DMF then cooled in an ice-water bath. The H-Phe-OMe was isolated from 2.15 g (10 mmol) of the corresponding methyl ester hydrochloride by neutralization, subsequent extraction with ethyl acetate and concentration of 10 mL and it was added to the reaction mixture, followed immediately by 1.03 g (5 mmol) of DCC and 0.67 g (5 mmol) of HOBt. The reaction mixture was stirred for three days. The residue was taken in ethyl acetate (60 mL) and the DCU was filtered off. The organic layer was washed with 2 M HCl (3 × 50 mL), brine (2 × 50 mL), 1 M sodium carbonate (3 × 50 mL) and brine (2 × 50 mL) respectively. Then dried over anhydrous sodium sulfate and evaporated in *vacuo* to yield a white solid. Purification was done by silica gel column (100-200 mesh) using 1:1 ethyl acetate - toluene as eluent.

Yield = 2.7 g (4.6 mmol, 91.6 %); (Found: C, 67.03; H, 6.45; N, 7.02%. $C_{33}H_{39}N_3O_7$ (589) requires: C, 67.23; H, 6.62; N, 7.13%);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.20 (5H, m); 7.18-7.16, 7.03-7.00 (4H, m); 6.93-6.90, 6.70-6.67 (5H, m); 6.46 (1H, d, *J* = 6 Hz); 6.20 (1H, d, *J* = 9Hz); 4.85 (1H, d, *J* =

9Hz); 4.69 (1H, m); 4.51-4.44 (1H, m); 4.30 (1H, m); 3.67 (3H, s); 3.12-2.79 (6H, m); 1.37 (9H, s); HR-MS $(M+Na)^+$ = 612.8578, M_{calcd} = 589; FT-IR (KBr): 3325, 1747, 1718, 1691, 1649, 1527 cm^{-1}; $[\alpha]_D^{20}$ –20.4 (*c* 0.64, CH_3OH).

(e) **Synthesis of Boc-Tyr(1)-OH** : A solution of tyrosine 2.71 g (15 mmol) in a mixture of dioxan (30 mL), water (15 mL) and 1M NaOH (15 mL) was stirred and cooled in an ice-water bath. Di-*tert*-butylpyrocarbonate 3.6 g (16.5 mmol) was added and stirring was continued at room temperature for 6 h. Then the solution was concentrated in *vacuo* to about 15 to 20 mL, cooled in an ice-water bath, covered with a layer of ethyl acetate (about 30 mL) and acidified with a dilute solution of $KHSO_4$ to pH 2-3 (Congo red). The aqueous phase was extracted with ethyl acetate and this operation was done repeatedly. The ethyl acetate extracts were pooled, washed with water and dried over anhydrous Na_2SO_4 and evaporated in *vacuo*. The pure material was obtained.

Yield: 3.37 g (12 mmol, 80%); (Found: C, 58.9; H, 6.4; N, 4.7%. $C_{14}H_{19}NO_5$ (281): C, 59.78; H, 6.76; N, 4.98%).

(f) **Boc-Tyr(1)-Phe(2)-OMe** : 1.46 g (5.2 mmol) of Boc-Tyr-OH was dissolved in 10 mL dimethylformamide (DMF) in an ice-water bath. H-Phe-OMe was isolated from 2.23 g (10.4 mmol) of the corresponding methyl ester hydrochloride by neutralization, subsequent extraction with ethyl acetate and concentration to 10 mL and this was added to the reaction mixture, followed immediately by 1.07 g (5.2 mmol) of di-cyclohexaylcarbodiimide (DCC) and 0.70 g (5.2 mmol) of HOBT. The reaction mixture was allowed to come to room temperature and stirred for 24 h. DCM was evaporated, residue was taken in ethyl acetate (60 mL), and dicyclohexylurea (DCU) was filtered off. The organic layer was washed with 2 M HCl (3 × 50 mL), brine (2 × 50 mL), 1M sodium

carbonate (3 × 50 mL) and brine (2 × 50 mL) respectively. Then dried over anhydrous sodium sulfate, and evaporated in *vacuo* to yield solid compound.

Yield = 2 g (4.5 mmol, 87%). (Found: C, 65.21; H, 6.57; N, 6.23%. $C_{24}H_{30}N_2O_6$ (442) requires: C, 65.15; H, 6.78; N, 6.33%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.21 (5H, m); 7.00-6.97, 6.74-6.70 (4H, m); 6.27 (1H, d, *J* = 8.58 Hz); 4.98 (1H, d, *J* = 7.71 Hz); 4.76 (1H, m); 4.25 (1H, m); 3.66 (3H, s); 3.10-3.03 (2H, m); 2.98-2.92 (2H, m); 1.41 (9H, s).

(g) **Boc-Tyr(1)-Phe(2)-OH**: To 1.85 g (4.2 mmol) of Boc-Tyr(1)-Phe(2)-OMe, 20 mL MeOH and 10 mL of 2 M NaOH were added. The reaction mixture was stirred and the progress of saponification was monitored by thin layer chromatography (TLC). After 10 h methanol was removed under *vacuo*, 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 M HCl and it was extracted with ethyl acetate (3 × 50 mL). The extracts were pooled, dried over anhydrous sodium sulfate, and evaporated in *vacuo* to yield a solid compound.

Yield = 1.6 g (3.75 mmol, 89%). (Found: C, 64.52; H, 6.57; N, 6.42%. $C_{23}H_{28}N_2O_6$ (428) requires: C, 64.48; H, 6.54, N, 6.54%);

^{1}H NMR (300MHz, $(CD_3)_2SO$) δ 9.13 (1H, b); 7.97 (1H, d, *J* = 6 Hz); 6.98-6.90 (5H, m); 6.71 (1H, d, *J* = 9 Hz); 6.61-6.56 (4H, m); 4.39 (1H, m); 4.02-3.91 (1H, m); 2.91-2.80 (2H, m); 2.76-2.61 (2H, m); 1.28 (9H, s).

(h) **Boc-Tyr(1)-Phe(2)-Tyr(3)-OMe 2**: 1.5 g (3.5 mmol) of Boc-Tyr(1)-Phe(2)-OH dissolved in 10 mL of DMF was cooled in an ice-water bath and H-Tyr-OMe was isolated from 1.61 g (7 mmol) of the corresponding methyl ester hydrochloride by neutralization, subsequent extraction with ethyl acetate and concentration to 10 mL and it

was added to the reaction mixture, followed immediately by 0.72 g (3.5 mmol) DCC and 0.47 g (3.5 mmol) of HOBt. The reaction mixture was stirred for three days. The residue was taken in ethyl acetate (60 mL) and the DCU was filtered off .The organic layer was washed with 2 M HCl (3 × 50 mL), brine (2 × 50 mL), 1 M sodium carbonate (3 × 50 mL), and brine (2 × 50 mL) respectively. Then dried over anhydrous sodium sulfate and evaporated in *vacuo* to yield a white solid. Purification was done by silica gel column (100-200 mesh) using 3:1 ethyl acetate-toluene as eluent.

Yield = 2 g (3.3 mmol, 94.4%). (Found: C, 65.25; H, 6.6; N, 7.23%. $C_{33}H_{39}N_3O_8$ (605) requires: C, 65.45; H, 6.44; N, 6.94%);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.21, 7.12-7.10 (4H, m); 7.17 (1H, d, *J* = 9 Hz); 6.96-6.93, 6.88-6.85 (4H, m); 6.79 (1H, d, *J* = 9 Hz); 6.75-6.67 (5H, m); 5.23 (1H, d, *J* = 6 Hz); 4.67-4.55 (2H, m); 4.20-4.08 (1H, m); 3.65 (3H, s); 3.04-3.00 (2H, m); 2.98-2.93 (2H, m); 2.92-2.85 (2H, m); 1.37 (9H, s).

ES-MS $(M+H)^+$ = 606.3, M_{calcd} = 605. FT-IR (KBr): 3325, 1750, 1686, 1646, 1516 cm^{-1}; $[\alpha]_D^{20}$ –13.7 (*c* 0.60, CH_3OH).

(i) **Boc-Tyr(1)-Tyr(2)-OMe** : 1.68 g (6 mmol) of Boc-Tyr-OH was dissolved in 10 mL dimethylformamide (DMF) in an ice-water bath. H-Tyr-OMe was isolated from 2.77 g (12 mmol) of the corresponding methyl ester hydrochloride by neutralization, subsequent extraction with ethyl acetate and concentration to 10 mL and this was added to the reaction mixture, followed immediately by 1.23 g (6 mmol) of di-cyclohexylcarbodiimide (DCC) and 0.81 g (6 mmol) of HOBT. The reaction mixture was allowed to come to room temperature and stirred for 24 h. DCM was evaporated, residue was taken in ethyl acetate (60 mL), and dicyclohexylurea (DCU) was filtered off. The organic layer was

washed with 2 M HCl (3 × 50 mL), brine (2 × 50 mL), 1M sodium carbonate (3 × 50 mL) and brine (2 × 50 mL) respectively. Then dried over anhydrous sodium sulfate, and evaporated in *vacuo* to yield solid compound.

Yield = 2.2 g (5 mmol, 80%). (Found: C, 62.41; H, 6.57; N, 6.23%. $C_{24}H_{30}N_2O_7$ (458) requires: C, 62.88; H, 6.55; N, 6.11%);

^{1}H NMR (300 MH_Z, $CDCl_3$) δ 6.98 (1H, d, *J* = 6 Hz); 6.82-6.79 (4H, m); 6.69-6.66 (4H, m); 5.11 (1H, m); 4.73 (1H, d, *J* = 6 Hz); 4.26 (1H, m); 3.69 (3H, s); 2.95 (2H, m); 2.86 (2H, m); 1.43 (9H, s).

(j) **Boc-Tyr(1)-Tyr(2)-OH**: To 2 g (4.3 mmol) of Boc-Tyr(1)-Tyr(2)-OMe, 20 mL MeOH and 10 mL of 2M NaOH were added. The reaction mixture was stirred and the progress of saponification was monitored by thin layer chromatography (TLC). After 10 h methanol was removed under *vacuo*, 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 M HCl and it was extracted with ethyl acetate (3 × 50 mL). The extracts were pooled, dried over anhydrous sodium sulfate, and evaporated in *vacuo* to yield a solid compound.

Yield = 1.5 g (3.37 mmol, 79%). (Found: C, 62.12; H, 6.31; N, 6.42%. $C_{23}H_{28}N_2O_7$ (444) requires: C, 62.16; H, 6.3; N, 6.3%);

^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 11.53 (1H, b); 7.54 (1H, d, *J* = 6 Hz); 6.67-6.51 (4H, m); 6.42 (1H, d, *J* = 9 Hz); 6.25 (4H, m); 3.98 (1H, m); 3.65 (1H, m); 2.59-2.53 (2H, m); 2.47-2.39 (2H, m); 0.92 (9H, s).

(k) **Boc-Tyr(1)-Tyr(2)-Phe(3)-OMe 3**: 1.42 g (3.2 mmol) of Boc-Tyr(1)-Tyr(2)-OH dissolved in 10 mL of DMF was cooled in an ice-water bath and H-Phe-OMe was isolated from 1.37 g (6.4 mmol) of the corresponding methyl ester hydrochloride by

neutralization, subsequent extraction with ethyl acetate and concentration to 10 mL and it was added to the reaction mixture, followed immediately by 0.66 g (3.2 mmol) DCC and 0.43 g (3.2 mmol) of HOBt. The reaction mixture was stirred for three days. The residue was taken in ethyl acetate (60 mL) and the DCU was filtered off .The organic layer was washed with 2 M HCl (3 × 50 mL), brine (2 × 50 mL), 1 M sodium carbonate (3 × 50 mL), and brine (2 × 50 mL) respectively. Then dried over anhydrous sodium sulfate and evaporated in *vacuo* to yield a white solid. Purification was done by silica gel column (100-200mesh) using 3:1 ethyl acetate - toluene as eluent.

Yield = 1.6 g (2.64 mmol, 84.2%). (Found: C, 65.72; H, 6.21; N, 6.83%. $C_{33}H_{39}N_3O_8$ (605) requires: C, 65.45; H, 6.44; N, 6.94%);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.21 (5H, m); 7.07 (1H, d, J = 6 Hz); 6.90 (4H, m); 6.85 (1H, d, J = 9 Hz); 6.83-6.69 (4H, m); 5.15 (1H, d, J = 6 Hz); 4.68 (1H, m); 4.51 (1H, m); 4.23 (1H, m); 3.65 (3H, s); 3.12-3.08 (2H, m); 3.07-2.94 (2H, m); 2.88-2.87 (2H, m); 1.37 (9H, s).

HR-MS $(M+Na)^+$ = 628.7220, M_{calcd} = 605. FT-IR (KBr): 3415, 3321, 1723, 1690, 1648, 1516 cm^{-1}. $[\alpha]_D^{20}$ –13.3 (*c* 0.85, CH_3OH).

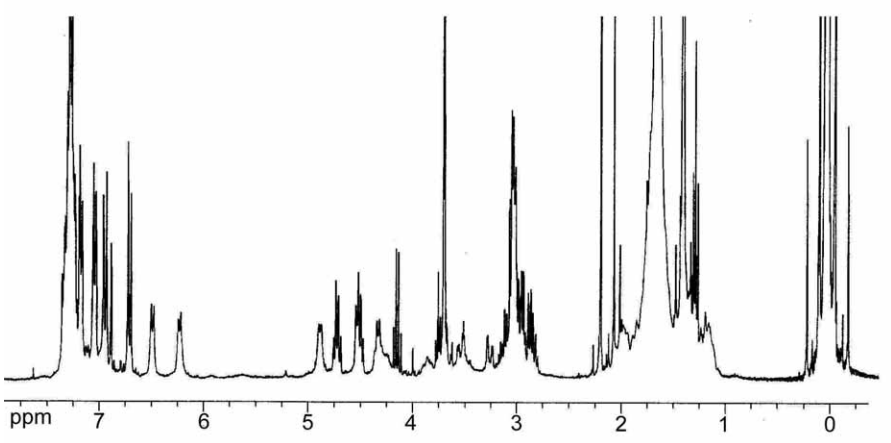


Figure S1. 300 MHz ^{1}H NMR spectrum of peptide **1.**

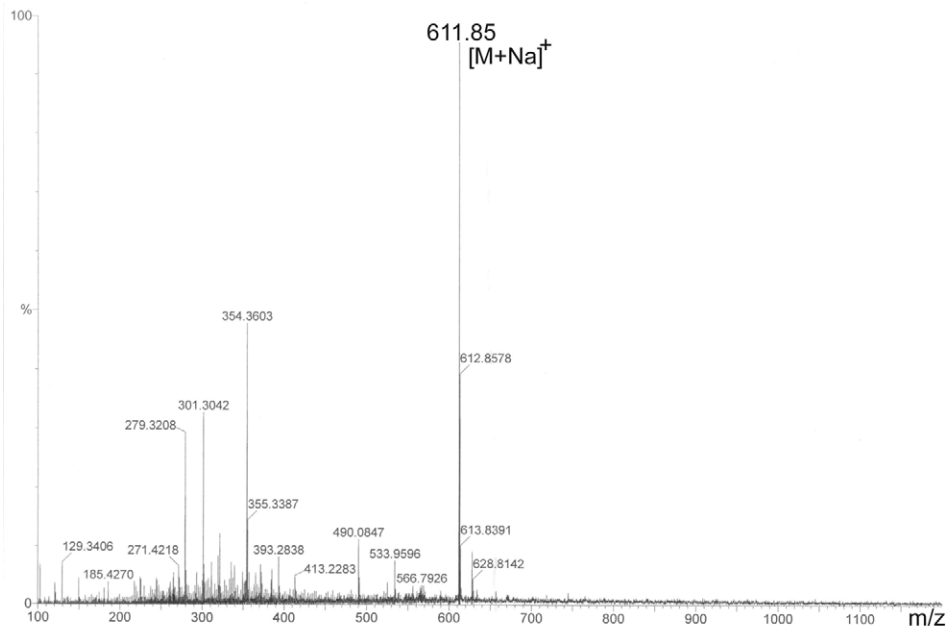


Figure S2. HR-MS spectrum of peptide **1**.

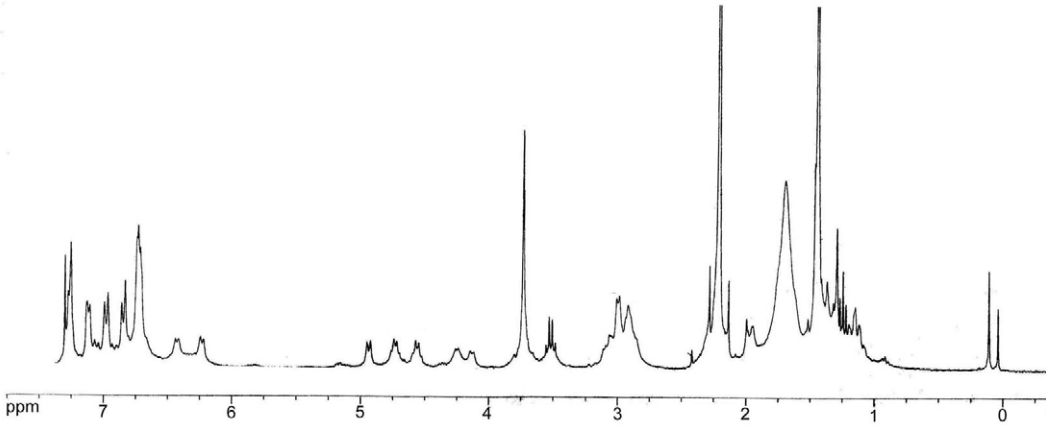


Figure S3. 300 MHz ^{1}H NMR spectrum of peptide **2.**

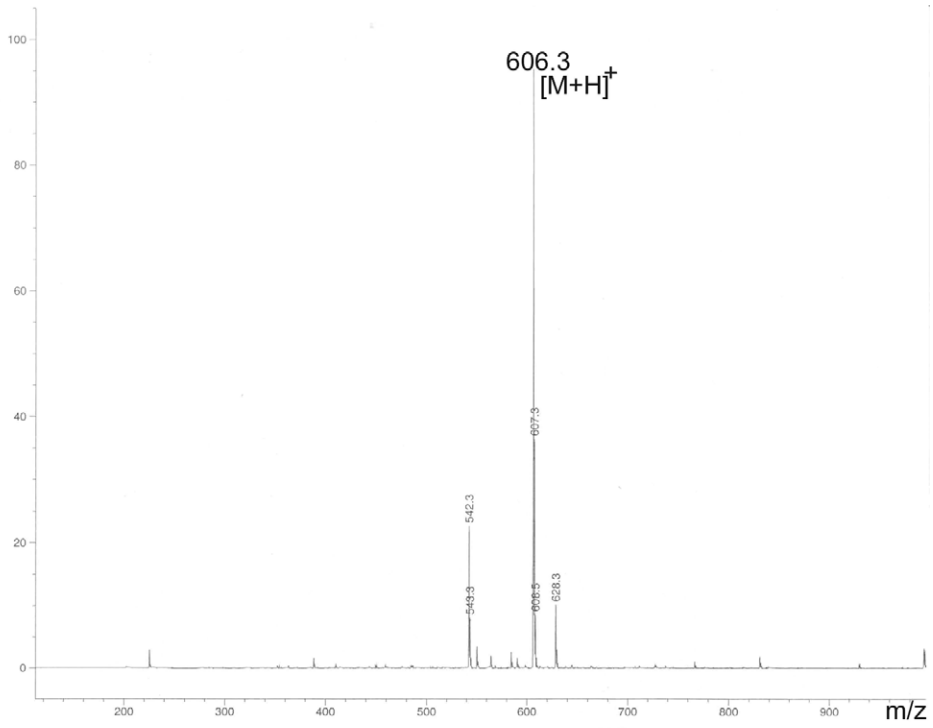


Figure S4. ESI-MS spectrum of peptide **2.**

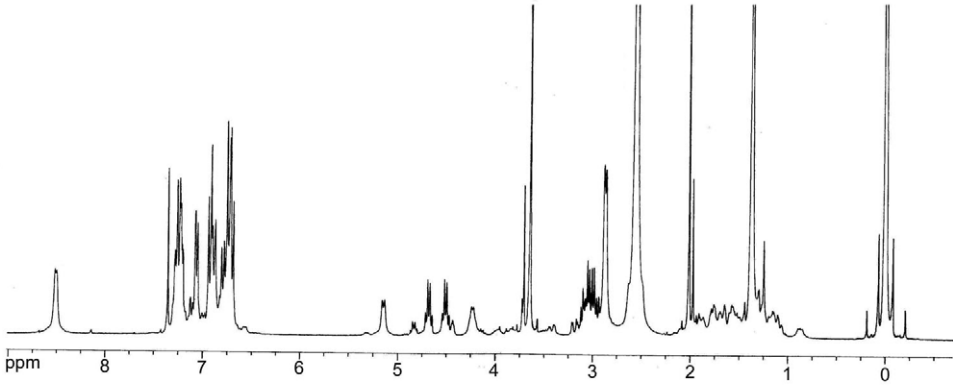


Figure S5. 300 MHz ^{1}H NMR spectrum of peptide **3.**

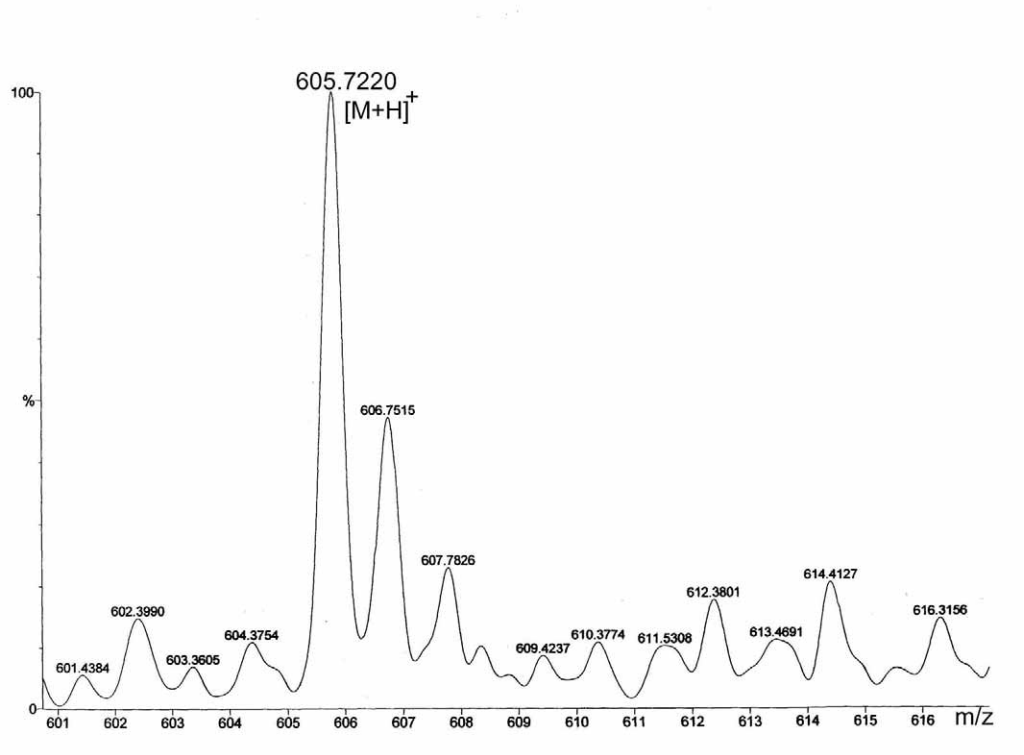
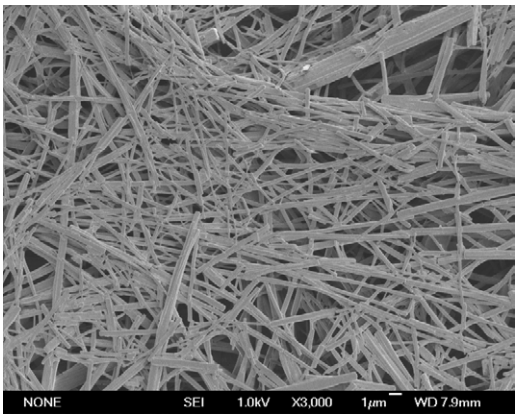


Figure S6. HR-MS spectrum of peptide **3**.

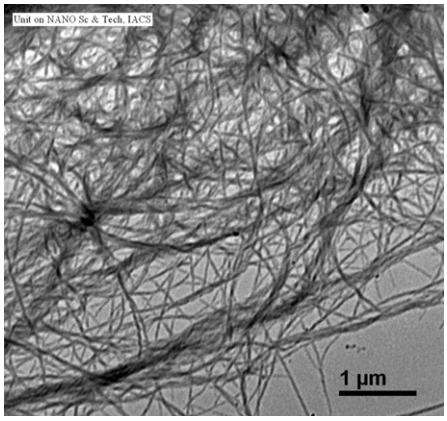
Table S1. Gelation properties of peptides **1**-**3** in organic solvents[a]

Solvent	Peptide **1**	Peptide **2**	Peptide **3**
Benzene	G(3.3)	G(1.25)	P
o-Dichlorobenzene	G(1)	G(1)	G(2.5)
Toluene	G(1.25)	G(1.25)	P
p-Xylene	G(1.25)	G(1.25)	P
m-Xylene	G(1.25)	G(1.25)	P
DMSO	G(5)	S	S
Nitrobenzene	G(5)	G(10)	G(2.5)
Tetraline	G(10)	G(10)	P
Methanol	S	S	S
Ethanol	S	S	S
Chloroform	S	G(1.25)	S
Ethyl acetate	S	S	S
DMF	S	S	S
Methanol-Water (1:1)	S	P	G(5)

[a]G: stable gels formed at room temperature; in parentheses: minimum gel concentration (% w/v); S: soluble; P: precipitate.



(a)



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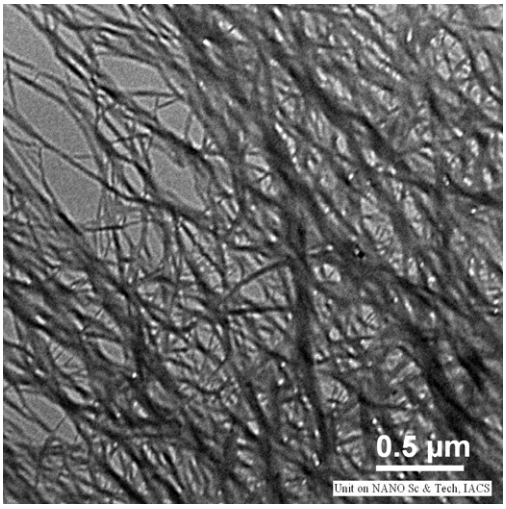


(c)

Figure S7. (a) FE-SEM image of xerogels of peptide **1** prepared from toluene, (b) TEM image of xerogels of peptide **2** prepared from toluene and (c) TEM image of xerogels of peptide **3** prepared from methanol:water (1:1) system.

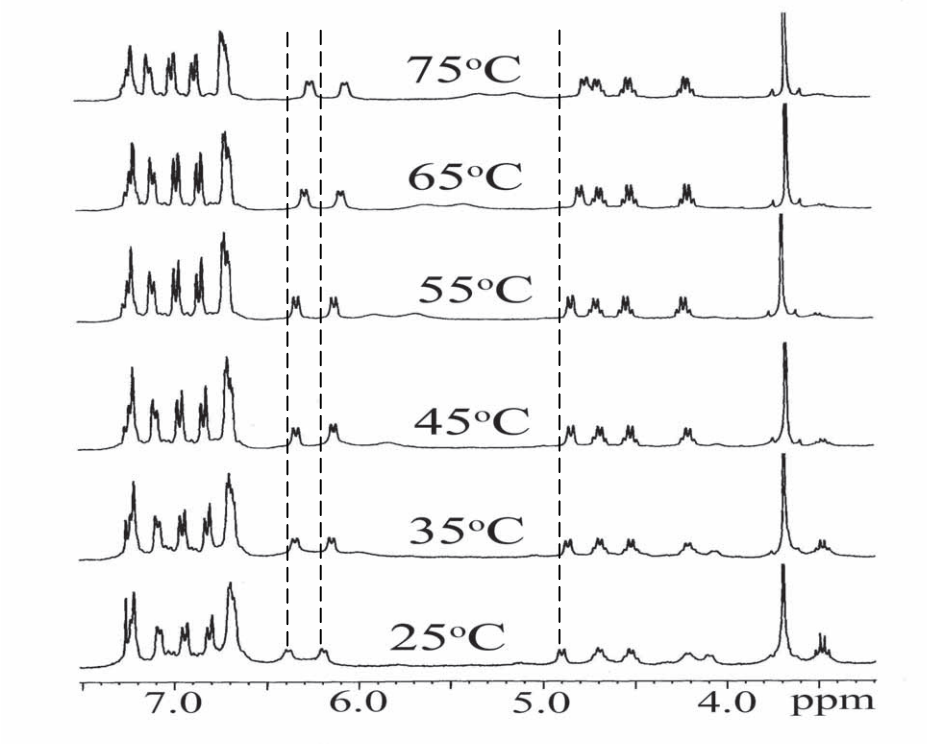


Figure S8. Temperature variable ^{1}H-NMR chemical shifts of peptide **2** gel in $CDCl_3$.

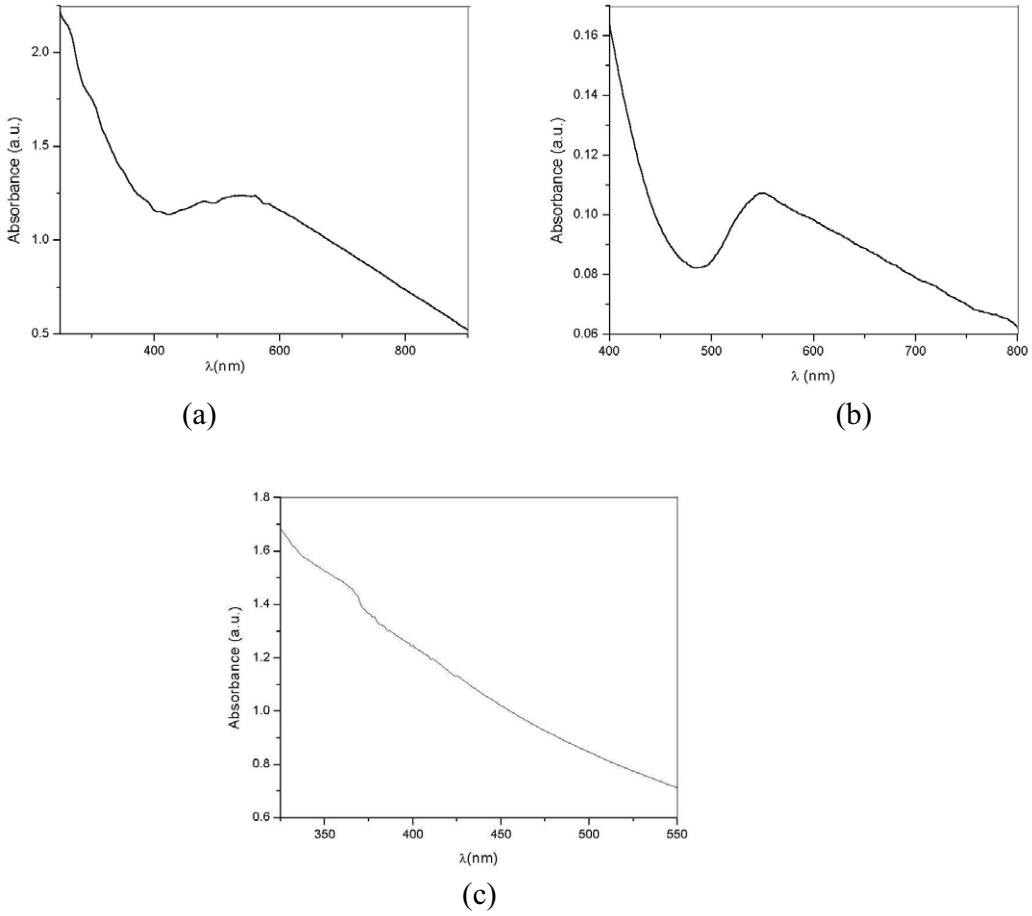
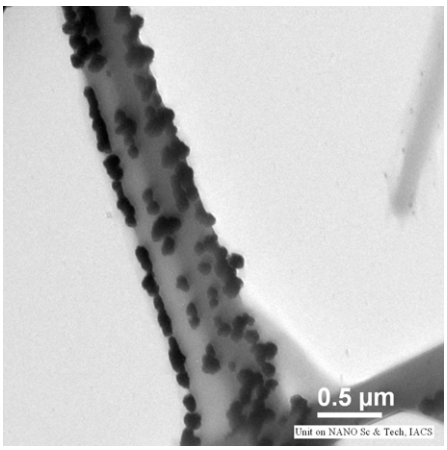
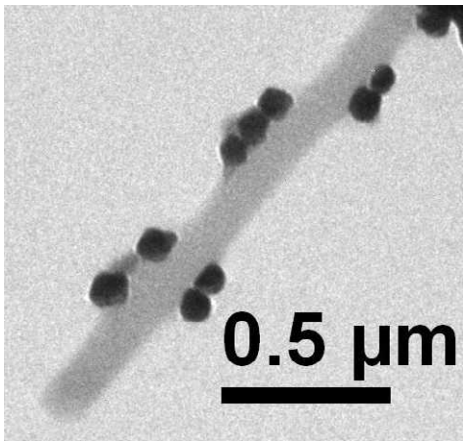


Figure S9. UV-vis spectra of nanoparticles embedded organogels (a) of peptide **1** in toluene showing the characteristic plasmon band of gold nanoparticle at 548 nm; (b) of peptide **3** in methanol-water showing the characteristic plasmon band of gold nanoparticle at 551 nm and (c) of peptide **3** in methanol-water showing the characteristic plasmon band of silver nanoparticle at 363 nm.



(a)



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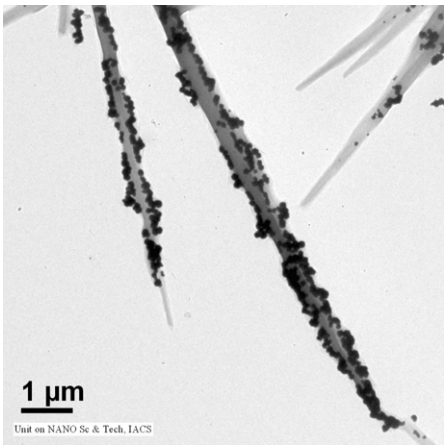
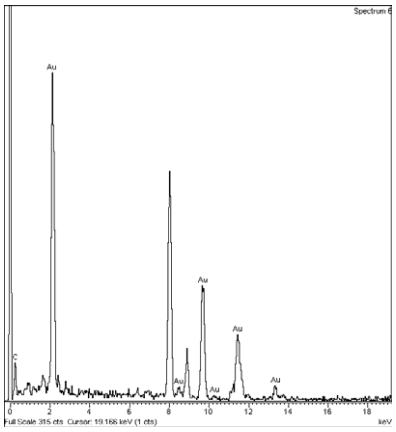
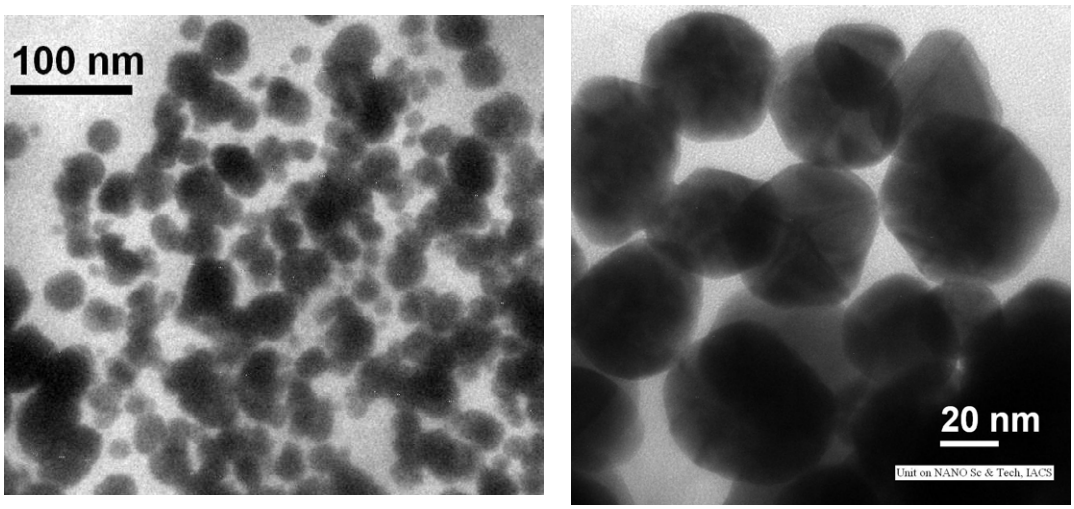


(c)



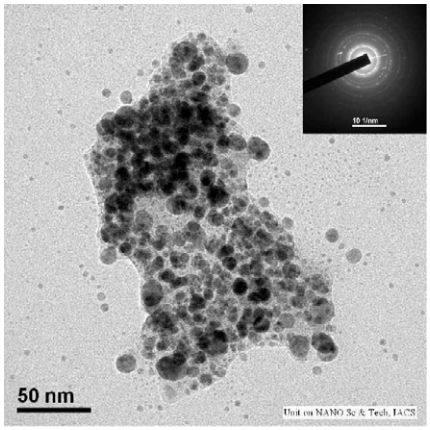
(d)

Figure S10. (a), (b) & (c) TEM images of aligned array of gold nanoparticles along the gel fibers obtained from peptide **1-**toluene gel and (d) EDX profile of gold nanoparticles.

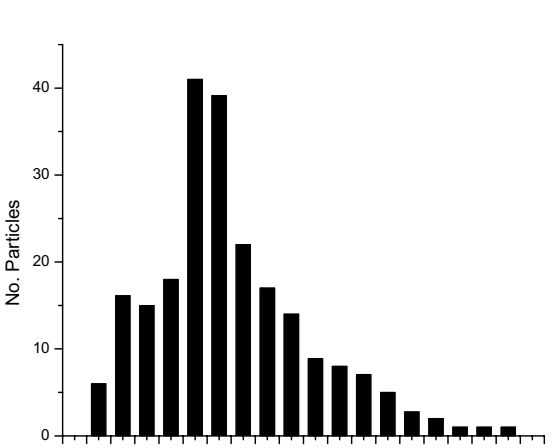


(a) (b)

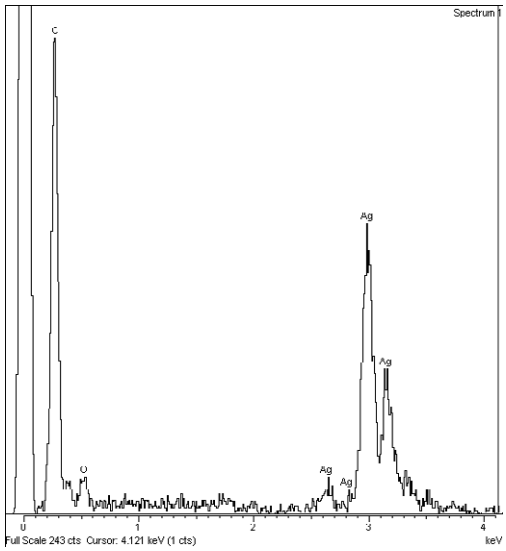
Figure S11. (a) & (b) Typical TEM images of gold nanoparticles within the gel phase network of peptide **3** in methanol-water (1:1) .



(a)



(b)



(c)

Figure S12. (a) Representative TEM image of silver nanoparticles within the gel phase network of peptide **3-** methanol:water (1:1) gel. The electron diffraction pattern of the silver nanoparticles in image (a) is shown as the inset. (b) Particle size distribution histogram of the silver nanoparticles measured from TEM image (a). (c) EDX profile of silver nanoparticles.

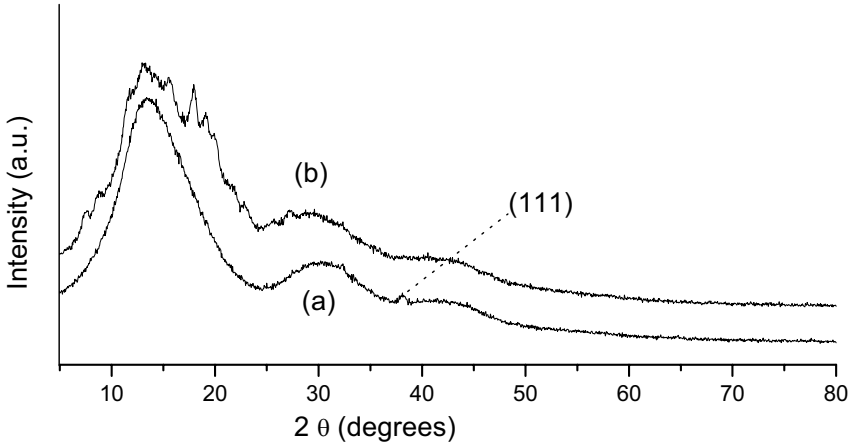


Figure S13. Powder X-ray diffraction patterns of (a) the peptide **3** gel embedded gold nanoparticles and (b) peptide **3** gel without gold nanoparticles. (arrow shows peak corresponding to typical gold (111) plane).

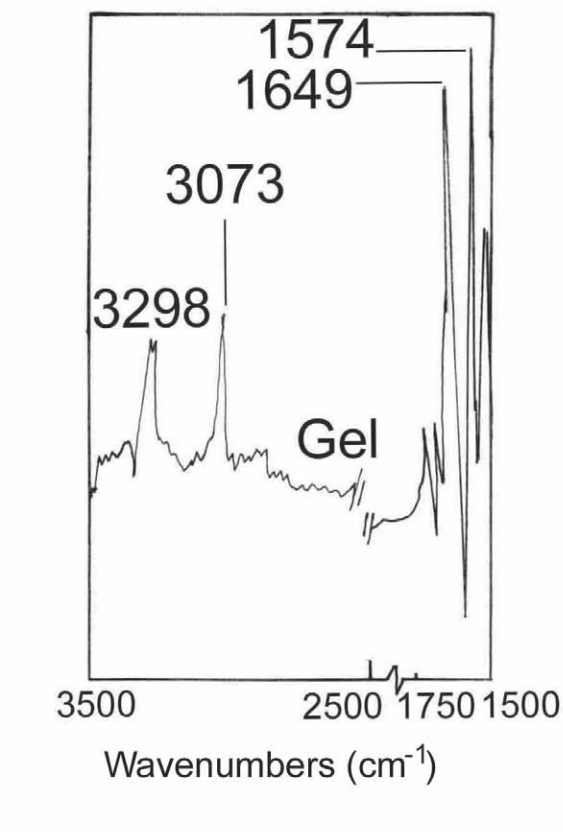


Figure S14. Solvent subtracted FT-IR spectrum at the region 2500-3500 cm^{-1} and 1500-1750 cm^{-1} of peptide **2** gel in toluene.

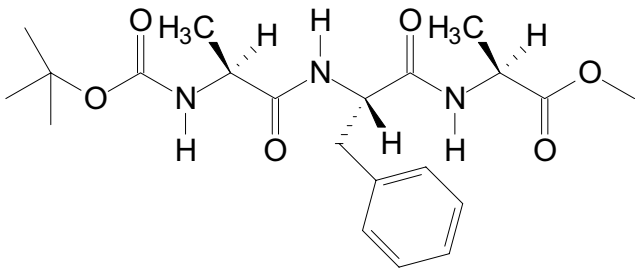


Figure S15. Chemical structure of the tripeptide Boc-Ala-Phe-Ala-OMe (AFA).

Synthesis of Peptide AFA:

(a) Synthesis of Boc-Ala(1)-OH: A solution of Alanine (1.35 g, 15 mmol) in a mixture of dioxan (30 mL), water (15 mL) and 1 M NaOH (15 mL) was stirred and cooled in an ice-water bath. Di-*tert*-butylpyrocarbonate (3.5 g, 16 mmol) was added and stirring was continued at room temperature for 6 hrs. Then the solution was concentrated in *vacuum* to about 40-60 mL, cooled in an ice water bath, covered with a layer of ethyl acetate (about 50 mL) and acidified with a dilute solution of $KHSO_4$ to pH 2-3 (Congo red). The aqueous phase was extracted with ethyl acetate and this operation was done repeatedly. The ethyl acetate extracts were pooled, washed with water and dried over anhydrous Na_2SO_4 and evaporated in *vacuum*. Pure material was obtained as white solid.

Yield = 2.55 g (13.5 mmol, 90%). Anal. Calcd. for $C_8H_{15}NO_4$ (189): C, 50.79; N, 7.40; H, 7.93. Found: C, 50.81; N, 7.43; H, 7.90.

(b) Boc-Ala(1)-Phe(2)-OMe: 1.89 g (10 mmol) of Boc-Ala-OH was dissolved in a mixture of 30 mL dichloromethane (DCM) in an ice-water bath. H-Phe-OMe was isolated from 4.31 g (20 mmol) of the corresponding methyl ester hydrochloride by neutralization and subsequent extraction with ethyl acetate and the ethyl acetate extract was concentrated to 10 mL. This was added to the reaction mixture, followed immediately by 2.06 g (10 mmol) of di-cyclohexylcarbodiimide (DCC). The reaction mixture was allowed to come to room temperature and stirred for 24 h. DCM was evaporated, and the residue was taken up in ethyl acetate (60 mL), and dicyclohexylurea (DCU) was filtered off. The organic layer was washed with 2 M HCl (3×50 mL), brine (2×50 mL), then 1 M sodium carbonate (3×50 mL) and brine (2×50 mL) and dried over anhydrous sodium sulfate, and evaporated in *vacuum* to yield as a white solid.

Yield = 2.9 g (8.3 mmol, 83%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.27 & 7.02-7.06 (5H, m); 6.44 (1H, d, *J* = 6.4 Hz); 4.84 (1H, d, *J* = 8.4 Hz); 4.76 (1H, m); 4.05 (1H, m); 3.65 (3H, s); 2.96-3.13 (2H, m); 1.37 (9H, s); 1.24 (3H, d, *J* = 7.05 Hz). Anal. Calcd. for $C_{18}H_{26}N_2O_5$ (350): C, 61.71; N, 8.0; H, 7.43. Found: C, 61.69; N, 7.78; H, 7.46.

(c) Boc-Ala(1)-Phe(2)-OH: To 2.8 g (8 mmol) of Boc-Ala-Phe-OMe, 50 mL MeOH and 20 mL of 2 M NaOH were added and the progress of saponification was monitored by thin layer chromatography (TLC). The reaction mixture was stirred. After 10 h methanol was removed under *vacuum*, the residue was taken up 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 M HCl and it was extracted with ethyl acetate (3 × 50 mL). The extracts were pooled, dried over anhydrous sodium sulfate, and evaporated in *vacuum* to yield as a white solid.

Yield = 2.05 g (6.1 mmol, 76%). ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 12.61 (1H, b); 7.68 (1H, d, *J* = 6 Hz); 6.39 (1H, d, *J* = 8.5 Hz); 6.93-7.04 (5H, m); 4.14-4.21 (1H, m); 3.81-3.87 (1H, m); 3.69-3.73 (2H, m); 1.12 (9H, s); 0.87 (3H, d, *J* = 7 Hz). Anal.Calcd. for $C_{17}H_{24}N_2O_5$ (336): C, 60.71; N, 8.33; H, 7.14. Found: C, 60.73; N, 8.30; H, 7.16.

(d) Boc-Ala(1)-Phe(2)-Ala(3)-OMe (AFA): 2.02 g (6 mmol) of Boc-Ala(1)-Phe(2)-OH in 15 mL of DMF was cooled in an ice-water bath and H-Ala-OMe was isolated from 1.67 g (12 mmol) of the corresponding methyl ester hydrochloride by neutralization and subsequent extraction with ethyl acetate and the ethyl acetate extract was concentrated to 8 mL. It was then added to the reaction mixture, followed immediately by 1.24 g (6 mmol) DCC and 0.81 g (6 mmol) of HOBt. The reaction mixture was stirred for three days. The residue was taken up in ethyl acetate (40 mL) and the DCU was filtered off.

The organic layer was washed with 2 M HCl (3 × 40 mL), brine (2 × 50 mL), 1 M sodium carbonate (3 × 40 mL), brine (2 × 40 mL), dried over anhydrous sodium sulfate and evaporated in *vacuum* to yield AFA as a white solid. Purification was done by silica gel column (100-200mesh) using chloroform-methanol (9:1) as eluent.

Yield = 2.15 g (5.1 mmol, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.33 (5H, m); 6.60 (1H, d, *J* = 7.83 Hz); 6.47 (1H, d, *J* = 11.19 Hz); 4.81 (1H, d, *J* = 8.95 Hz); 4.62-4.69 (1H, m); 4.33-4.53 (1H, m); 4.01-4.11 (1H, m); 3.71 (3H, s); 3.02-3.20 (2H, m); 1.40 (9H, s); 1.32-1.35 (3H, d, *J* = 7.17 Hz); 1.27-1.31 (3H, d, *J* = 7.17 Hz). Anal.Calcd. for $C_{21}H_{31}N_3O_6$ (421): C, 59.86; N, 9.98; H, 7.36%. Found: C, 59.89; N, 9.94; H, 7.38%. ES-MS *m/z* 444.2 $(M+Na)^+$, *m/z* 865.5 $(2M+Na)^+$, $[\alpha]_D^{20}$ –40.9 (*c* 1.2, $CHCl_3$).

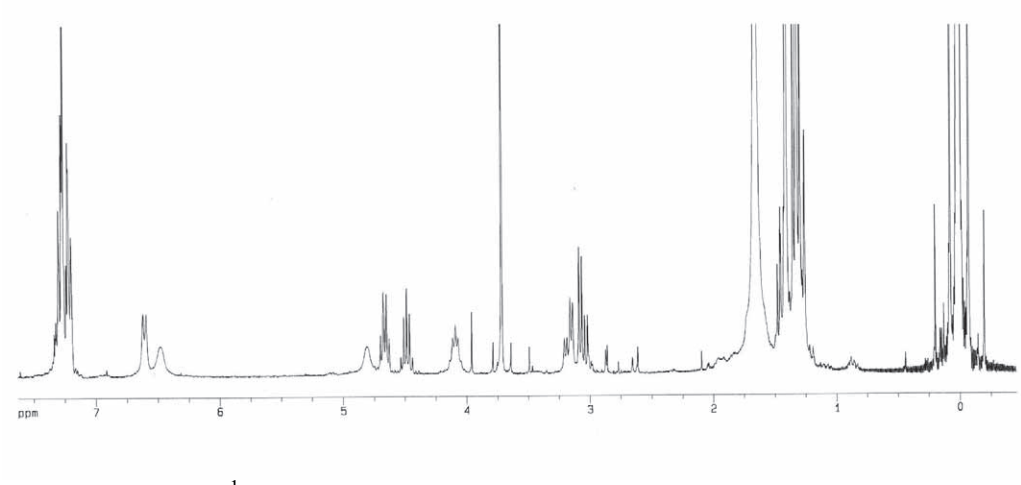


Figure S16. 300 MHz ^{1}H NMR spectrum of peptide **AFA**.

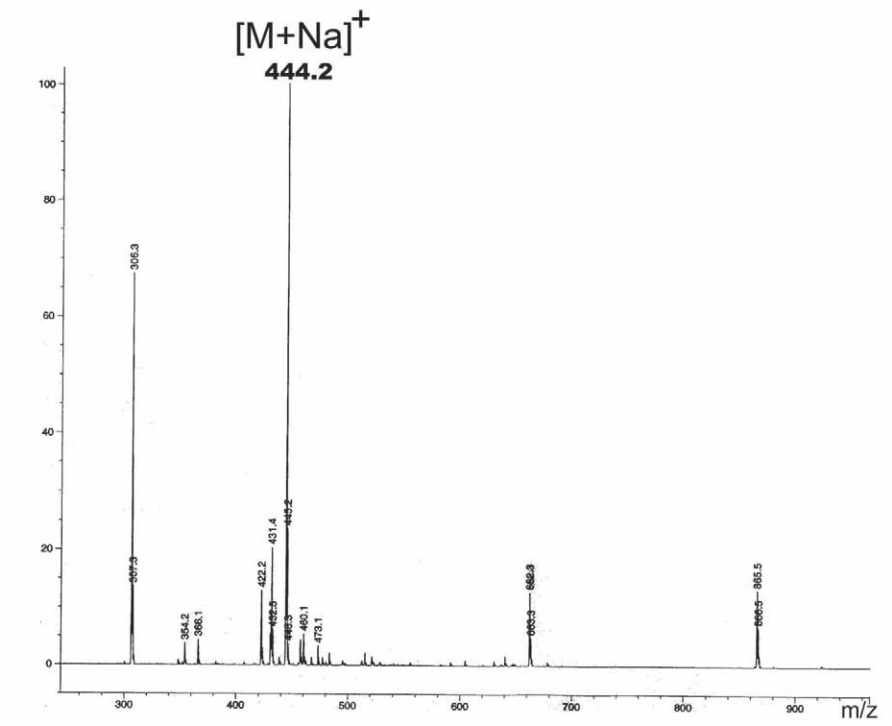


Figure S17. ESI-MS spectrum of peptide **AFA**.