Electronic Supplementary Material (ESI) for RSC Advances.

SUPPLEMENTARY INFORMATION

Effect of C-terminus amidation of $A\beta_{39-42}$ fragment derived peptides as potential inhibitors of Aβ aggregation

Akshay Kapadia,[1†] Aesan Patel,[1†] Krishna K. Sharma,[1] Indresh Kumar Maurya,[2] Varinder Singh,[3] Madhu Khullar[3] and Rahul Jain[1*]

[1]Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Sector 67, S.A.S Nagar, Punjab 160 062, India

[2]Department of Microbial Biotechnology, Punjab University, Sector 25, Chandigarh, Punjab 160 014, India

[3]Post Graduate Institute of Medical Education and Research, Sector 11, Chandigarh, Punjab, 160 014, India

[†] Equal contribution

**rahuljain@niper.ac.in*

Table of Contents

1. Peptide Synthesis

1.1. Materials and Methods

All the chemicals were purchased from Sigma-Aldrich, Missouri, U.S.A. and Chem-Impex International, Illinois, U.S.A., and used without further purification, unless specified. All solvents used for synthesis were of analytical grade and used without further purification, unless otherwise stated. Microwave assisted solid phase peptide synthesis was performed on a CEM Liberty1® microwave reactor employing Fmoc-protection-deprotection protocol on Rink amide resin.

1.2. General method for the synthesis of tetrapeptides (Series 1-5)

All tetrapeptides were synthesized using microwave-assisted solid phase peptide synthesis protocol using Rink amide resin as the solid support employing Fmoc-protection-deprotection cycles.[1,2] Tetrapeptide synthesis was initiated from the 4th Amino acid (amidated C-terminus) to the 1st Amino acid (uncapped N-terminus). The 4th amino acid was loaded on the Rink amide resin solid support, thus being the first amino acid to be attached to the resin. Commercially available, Fmoc-protected Rink amide resin was utilized for the synthesis of all five series of peptides. Pre-weighed-amino acids, coupling reagent-TBTU, activator-Base, piperidine (20%) in DMF and main wash DMF were stored in the respective reagent bottles in the Liberty-1® module. Fmoc-Rink amide resin beads (1 equiv.) were allowed to swell in DMF for 15-20 mins in the MW reaction vessel. Once swelling was complete, evaluated by visualization, the RV body was connected to the RV assembly and subsequently attached to the MW unit. A suitable program was designed for the synthesis of the tetrapeptides starting from the C-terminus to the N-terminus, as per the following:

Fmoc deprotection: All Fmoc-deprotection was carried out in two cycles of 1.5 min and 3 min each, employing 7 mL of 20% piperidine in DMF solution, MW: 40 W, 60^{o}C. On completion of the reaction, RV was drained, ensuring only solid resin beads to remain in the RV. After each deprotection step, washing of beads was carried out using 7 mL DMF in four wash cycles [Wash: Top-Top-Bottom-Top] thus ensuring removal of any residual piperidine remaining in the RV.

Coupling: Pre-activation of the C-terminus is done by reacting with O-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluroniumtetrafluoroborate (TBTU) and *N,N*-di-isopropyl-ethylamine (DIEA), to substitute a better leaving group on the C-terminus, thus ensuring the coupling to occur at a faster rate. Coupling of the pre-activated Fmoc-AA_n-OH with the AA_{n+1} attached

to the solid support was done using MW-assisted coupling reaction protocol; Fmoc-AA_n-OH (4 equiv.), TBTU (4 equiv.), HoBt (4 equiv.), DIEA (5 equiv.), DMF 3.5 mL, MW 40 W, 60^{o}C, 13.5 min, thus furnishing Fmoc-AA_n-AA_{n+1}-Rink amide Resin. On completion of the reaction, program was modified to sufficiently cool the RV and drain the RV contents, followed by subsequent washing cycles [Wash: DMF 7 mL, Top-Bottom-Top].

Reaction Monitoring: Completion of the reaction was monitored by -

A) Fmoc deprotection-dibenzofulvene adduct monitoring: In-build parameter for determining the same after the deprotection is complete, UV measurements are made and data computed is compared for relative coupling of the deprotected amino acid, B) Kaiser test (for primary amines)[3], C) Acetaldehyde Test (For secondary amine)[4]:

Chain elongation: Coupling reactions was carried out similarly as above until the final synthesis of desired tetrapeptide. Once the synthesis was complete, final washing steps were performed. Resin beads were washed with DMF, MeOH and DCM (3 x 5mL) and then transferred from the RV to round bottom flask for cleavage of peptide from the beads.

Cleavage of peptide from resin: Resin beads were treated with cleavage cocktail (TFA: TIPS: H_2O: 9.5: 0.25: 0.25) for 2.5 h at ambient temperature with optimum stirring. On completion of the reaction, reaction mixture was filtered through a G3 sintered glass funnel, filtrate evaporated until 0.5-1 mL and precipitated with diethyl ether. Subsequent washes with DEE yielded sufficiently pure products (>90%). Few drops of DCM, MeCN and AcOH were also added to DEE mixture to speed-up the process of precipitation.

Peptide analysis and purification: Peptide purity was analysed using Shimadzu Analytical C-18 RP-HPLC system. Samples were prepared using HPLC grade MeOH (Concentration: 1mg/mL). Solvent system: **A**. 0.008% TFA in MeCN; **B**. 0.008% TFA in H_2O. Program: Phase **B** concentration: 95-5-95%, 45 min, gradient flow system. Purification of crude peptide was done using Preparative C-18 RP-HPLC (Shimadzu). Program was modified based on retention time of the peptides and impurities to be excluded. Solvent system: **A**. 0.008% TFA in MeCN; **B**. 0.008% TFA in H_2O. Test-tubes containing the isolated compound were pooled, evaporated and again analysed for purity. Pure isolated compound was analysed by ^{1}H and ^{13}C NMR, APCI/ESI and HRMS.

Lyophilization of peptides: On complete analysis of the peptide, lyophilization was done using Virtis bench top freeze dryer to increase the stability of the peptides. Peptides were dissolved in minimal amount of 80% Ac-OH in H_2O, pre-freezed at -70^{o}C and lyophilized at -100^{o}C at 0-10 mTorr until fluffy appearance was seen (approx. 6-8 hours). Peptides were stored at -80^{o}C.

2. Characterisation of compounds

2.1. Characterization data

Val-Val-Ile-Ala (11) ^{1}H NMR [400 MHz, CD_3OD + DMSO-$_{d6}$] δ 4.38-4.29 (M, 3H), 3.80 (d, *J* = 5.32, 1H), 2.23-2.19 (m, 1H), 2.10-2.04 (m, 1H), 1.91-1.85 (m, 1H), 1.62-1.56 (m, 1H), 1.41 (d, *J* = 7.28, 3H), 1.25-1.20 (m, 1H), 1.18-0.98 (m, 9H), 0.9167 (t, *J* = 7.36, 3H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-$_{d6}$] d 174.1, 171.4, 168.0, 59.0, 57.8, 57.2, 47.8, 36.8, 30.6, 30.3, 24.4, 18.6, 18.2, 17.8, 17.3, 17.2, 16.9, 16.6, 14.7, 12.3; HRMS(ESI-TOF): calculated for $C_{19}H_{36}N_4O_5$ m/z [M+H$^+$]: 401.2764, found: 401.2761; HPLC: t_R = 12.784 min, 100%

Val-Val-Ile-Ala-NH$_2$ (11a) ^{1}H NMR [400 MHz, CD_3OD + DMSO-$_{d6}$] δ 4.39–4.34 (m, 1H), 4.28-4.25 (m, 2H), 3.7812 (d, *J* = 5.56, 1H), 2.22-2.17 (m, 1H), 2.08-2.03 (m, 1H), 1.90-1.85 (m, 1H), 1.59-1.53 (m, 1H); 1.3694 (d, *J* = 7.12, 3H), 1.22-1.18 (m, 1H), 1.06-1.00 (m, 15H), 0.98-0.89 (m, 3H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-$_{d6}$] δ 175.6, 171.7, 171.5, 168.1, 65.5, 59.1, 57.9, 57.5, 48.5, 36.4, 30.3, 24.4, 18.4, 17.9, 17.6, 17.2, 16.5, 14.5, 9.91; HRMS(ESI-TOF): calculated for $C_{19}H_{37}N_5O_4$ m/z [M+Na$^+$]: 422.5258, found: 422.2741; HPLC: t_R = 11.664 min, 90.06%

D-Val-Val-Ile-Ala-NH$_2$-(12a) ^{1}H NMR [400 MHz, CD_3OD + DMSO-$_{d6}$] δ 4.39–4.37 (m, 1H), 4.21 (t, *J* = 7.14, 2H), 3.77 (d, *J* = 6.0, 1H), 2.24-2.13 (m, *J* = 5.56, 2H), 1.87-1.84 (m, 1 H), 1.64-1.58 (m, 1H), 1.37 (d, *J* = 7.12, 3H), 1.22-1.16 (m, 1H), 1.10-1.07 (t, *J* = 7.32, 6H), 1.06-0.97 (m, 12H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-$_{d6}$] δ 175.7, 172.2, 171.6, 168.4, 61.4, 59.1, 58.3, 57.8, 48.6, 36.5, 30.0, 24.5, 18.4, 17.6, 17.0, 16.7, 16.1, 14.4, 9.8; HRMS (ESI-TOF): calculated for $C_{19}H_{37}N_5O_4$ m/z [M+Na$^+$]: 422.5258, found: 422.2727; HPLC: t_R = 17.088 min, 94.7%

Phe-Val-Ile-Ala-NH$_2$ (12b) ^{1}H NMR [400 MHz, CD_3OD + DMSO-$_{d6}$] δ 7.35-7.32 (m, 5H), 4.39–4.37 (m, 1H), 4.34-4.28 (m, 1H), 3.26-3.22 (m, 1H), 3.27 (s, 1H), 2.12-2.05 (m, 1H), 1.89-1.84 (m, 1H), 1.65-1.59 (m, 1H), 1.37 (d, J= 7.12, 3H),1.25-1.18 (m, 1H), 1.00-0.96 (m, 14H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-$_{d6}$] δ 175.6, 171.6, 171.5, 168.1, 134.1, 129.3, 128.7, 127.5, 58.8, 57.7, 53.9, 48.5, 37.1, 36.6, 30.8, 24.6, 18.4, 17.65, 17.2, 14.65, 10.1; HRMS (ESI-TOF): calculated for $C_{23}H_{37}N_5O_4$ m/z [M+Na$^+$]: 470.5698, found: 470.4278; HPLC: t_R = 14.998 min, 100%

D-Phe-Val-Ile-Ala-NH$_2$ (12c) ^{1}H NMR [400 MHz, CD_3OD + DMSO-$_{d6}$] δ 7.42–7.34 (m, 5H), 4.38–4.33 (m, 1H), 4.25-4.20 (m, 1H), 3.24-3.19 (m, 1H), 3.12-3.07 (m, 1H), 1.88 (d, *J* = 6.96, 1H), 1.63-1.58 (m, 1H), 1.37 (d, *J* = 7.08, 3H), 1.21-1.15 (m, 1H), 1.17-1.15 (d, 1H), 1.10-1.04 (m, 1H), 0.98-0.91 (m, 6H), 0.84-0.77 (m, 6H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-$_{d6}$] δ 175.4, 171.8, 171.4, 168.3, 134.6, 134.6, 129.3, 128.8, 127.5, 58.9, 57.8, 54.2, 37.4, 36.5, 30.7, 24.6, 18.5, 17.4, 14.7, 10.2; HRMS(ESI-TOF): calculated for $C_{23}H_{37}N_5O_4$ m/z [M+Na$^+$]: 470.5698, found: 470.2743; HPLC: t_R = 16.817 min, 94.9%

Pro-Val-Ile-Ala-NH$_2$ (12d) ^{1}H NMR [400 MHz, CD_3OD + DMSO-$_{d6}$] δ 4.33 (m, 1H), 4.25-4.19 (m, 2H), 3.29-3.23 (m, 1H), 2.40–2.34 (m, *J* = 5.56, 1H), 2.03-1.98 (m, 1H), 1.91-1.88 (m, 2H), 1.83-1.80 (m, 2H), 1.46-1.42 (m, 1H), 1.21-1.19 (d, *J* = 7.32, 3H), 1.09-1.04 (m, 1H), 0.99-.95(m, 1H), 0.85-0.81 (m, 12H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-$_{d6}$] δ 174.5, 170.9, 170.8, 168.3, 59.5, 58.1, 57.4, 54.7, 45.9, 36.5, 31.2, 30.4, 24.6, 23.8, 19.1, 18.2, 17.8, 15.3, 10.9; HRMS (ESI-TOF): calculated for $C_{19}H_{35}N_5O_4$ m/z [M+Na$^+$]: 420.5098, found: 420.2572; HPLC: t_R = 15.698 min, 95.6%

Nva-Val-Ile-Ala-NH$_2$- (12e) ^{1}H NMR [400 MHz, CD_3OD + DMSO-$_{d6}$]δ 4.43-4.35 (t,2H), 4.01(br. s, 1H), 2.05 (*J* = 6.56, 1H), 1.81 (br. s, 3H), 1.56-1.50 (m, 1H), 1.41-1.35 (m, 5H), 1.21-1.14 (m, 1H),

1.00-0.89 (m, 15H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-$_{d6}$]δ 173.1, 173.0, 170.3, 60.4, 58.8, 54.1, 49.9, 38.1, 35.0, 32.1, 25.8, 19.7, 19.2, 19.1, 18.7, 15.9, 14.1, 11.3; HRMS(ESI-TOF): calculated for $C_{19}H_{37}N_5O_4$ m/z [M+Na$^+$]: 422.5258, found: 422.2731; HPLC: t_R = 15.594 min, 95.9%

Aib-Val-Ile-Ala-NH$_2$ (12f) ^{1}H NMR [400 MHz, CD_3OD + DMSO-$_{d6}$] δ 4.40–4.35 (m, 1H), 4.28-4.23 (m,2H), 2.13-2.08 (m, 1H), 1.86 (d, *J* = 6.68, 1H), 1.62 (d, *J* = 16.8, 6H), 1.36 (d, *J* = 6.96, 3H), 1.21-1.15 (m, 2H), 0.97-0.90 (m,12H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-$_{d6}$] δ 177.1, 173.4, 173.0, 172.9, 60.9,59.0, 58.3, 49.9, 38.0, 31.7, 25.8, 24.1, 24.0, 19.8, 19.2, 18.5, 15.8, 11.3; HRMS (ESI-TOF): calculated for $C_{18}H_{35}N_5O_4$ m/z [M+Na$^+$]: 408.4988, found: 408.2569; HPLC: t_R = 14.753 min, 90.2%

Gly-Val-Ile-Ala-NH$_2$ (12g) ^{1}H NMR [400 MHz, CD_3OD + DMSO-$_{d6}$] δ 4.39–4.33 (m, 1H), 4.33 (d, *J* = 7.0, 1H), 4.24 (d, *J* = 8.20, 1H), 3.76 (m, 1H), 3.24-3.19 (m, 1H), 2.12-2.07 (m, 1H), 1.89-1.87 (m, 1H), 1.61-1.55 (m, 1H), 1.37 (d, *J* = 7.12, 3H), (d, *J* = 7.32, 3H), 1.20-1.16 (m, 1H), 0.98-0.95 (m, 12H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-$_{d6}$] δ 177.1, 173.5, 173.1, 167.6, 60.4, 59.7, 59.1, 50.1, 37.9,32.1, 11.2; HRMS (ESI-TOF): calculated for $C_{16}H_{31}N_5O_4$ m/z [M+Na$^+$]: 380.4448, found: 380.2261; HPLC: t_R = 16.043 min, 98.6%

Val-D-Val-Ile-Ala-NH$_2$ (13a) ^{1}H NMR [400 MHz, CD_3OD + DMSO-$_{d6}$] δ 4.39–4.34 (m, 1H), 4.28-4.25 (m, 2H), 3.7812 (d, *J* = 5.56, 1H), 2.22-2.17 (m, 1H), 2.08-2.03 (m, 1H), 1.90-1.85 (m, 1H), 1.59- 1.53 (m, 1H); 1.3694 (d, *J* = 7.12, 3H), 1.22-1.18 (t, 1H), 1.06-1.00 (m, 15H), 0.98-0.89 (m, 3H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-$_{d6}$]δ 175..6, 171.7, 171.5, 168.1, 65.5, 59.1, 57.9, 57.5, 48.5, 36.4, 30.5, 30.3, 24.4, 18.4, 17.9, 17.6, 17.2, 16.5, 14.5, 9.91; HRMS (ESI-TOF): calculated for $C_{19}H_{37}N_5O_4$ m/z [[M+Na$^+$]: 422.5258, found: 422.2728; HPLC: t_R = 17.045 min, 86.76%.

Val-D-Ile-Ile-Ala-NH$_2$ (13b) ^{1}H NMR [400 MHz, CD_3OD + DMSO-$_{d6}$] δ 4.48–4.43 (m, 1H), 4.30-4.25 (m, 2H), 3.75 (d, *J* = 5.92, 1H), 2.23-2.18(m, 2H), 2.08-2.06 (d, *J* = 6.56, 1H), 1.90-1.88 (m, 1H), 1.65-1.62 (m, 1H), 1.50-1.46 (m, 1H), 1.41 (d, *J* = 7.12, 3H), 1.30-1.24 (m, 2H), 1.10-1.06 (m, 6H), 0.99-0.94 (m, 12H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-$_{d6}$] δ 174.9, 172.3, 170.7, 168.2, 68.4, 57.5, 51.5, 48.9, 35.1, 34.4, 29.3, 23.9, 23.3, 16.8, 16.3, 15.6, 14.2, 13.6, 9.7, 8.5; HRMS (ESI-TOF): calculated for $C_{20}H_{39}N_5O_4$ m/z [M+Na$^+$]: 436.5528, found: 436.2893; HPLC: t_R = 18.838 min, 100%.

Val-Pro-Ile-Ala-NH$_2$ (13c) ^{1}H NMR [400 MHz, CD_3OD + DMSO-$_{d6}$] δ 4.58–4.56 (m, 1H), 4.39-4.34 (m, 1H), 4.20 (d, *J* = 4.20, 1H), 3.77–3.72 (m, 1H), 2.29- 2.23 (m, 2H), 2.12-2.09 (m, 1H), 2.0-1.97 (m, 1H), 1.89-1.86 (m, 1H), 1.60 (t, *J* = 6.76, 1H), 1.37 (d, *J* = 7.12, 3H), 1.13-0.91 (m, 15H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-$_{d6}$] δ 175.8, 172.6, 171.8, 167.1, 60.2, 58.5, 58.0, 56.5, 36.8, 36.6, 29.7, 29.2, 24.8, 17.9, 17.7, 16.8, 15.8, 14.5, 9.9; HRMS (ESI-TOF): calculated for $C_{19}H_{35}N_5O_4$ m/z [M+Na$^+$]: 420.5098, found: 420.2578; HPLC: t_R = 11.395 min, 95.9%

Val-Aib-Ile-Ala-NH$_2$ (13d) ^{1}H NMR [400 MHz, CD_3OD + DMSO-$_{d6}$] δ 4.48–4.43 (m, 1H), 4.30-4.25 (m,2H), 3.75 (d, *J* = 5.56, 1H), 3.67 (d, *J* = 5.60, 1H), 2.20-2.15 (m,1 H), 2.08-2.03 (m, 1H), 1.87-1.80 (m, 1H), 1.69-1.62 (m, 2H), 1.39 (d, *J* = 7.32, 3H), 1.04-0.94 (m, 15H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-$_{d6}$] δ 174.2, 172.2, 171.7, 169.5, 58.3, 58.2, 57.1, 48.6, 36.6, 30.0, 24.6, 24.2, 23.5, 17.6, 16.7, 16.3, 14.5, 10.0; HRMS (ESI-TOF): calculated for $C_{18}H_{35}N_5O_4$ m/z [M+Na$^+$]: 408.4988, found: 408.2580; HPLC: t_R = 26.24 min, 93.2%.

Val-Phe-Ile-Ala-NH$_2$ (13e) ^{1}H NMR [400 MHz, CD_3OD + DMSO-$_{d6}$] δ 7.28–7.21 (m, 5H), 4.82–4.78 (m, 1H), 4.35-4.30 (m, 1H), 4.24-4.20 (m, 1H), 3.69 (d, *J* = 5.19,

1H), 3.16-3.11 (m, 1H), 2.97-2.92 (m, 1H), 2.23-2.19 (m,1 H), 1.84-1.79 (m, 1H), 1.58-1.53 (m, 1H), 1.37-1.34 (t, *J* = 7.16, 3H), 1.19-1.17 (m, 1H), 1.06-1.04 (m, 3H), 1.01-1.00 (m, 3H), 0.94-0.86 (m, 6H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-*d6*] δ 127.5, 171.5, 171.4, 168.0, 136.6, 128.8, 128.1, 126.4, 122.1, 114.8, 57.9, 57.6, 57.5, 54.6, 37.3, 36.8, 30.2, 24.4, 17.5, 17.0, 16.1, 14.3, 9.8; HRMS (ESI-TOF): calculated for $C_{23}H_{37}N_5O_4$ m/z [M+H$^+$]: 448.2924, found: 448.2915; HPLC: t_R = 14.665 min, 92.3%.

Val-D-Phe-Ile-Ala-NH$_2$ (13f) ^{1}H NMR [400 MHz, CD_3OD + DMSO-*d6*] δ 7.29–7.22 (m, 5H), 4.80–4.74 (m, 1H), 4.43–4.38 (m, 1H), 4.17–4.14 (m, 1H), 3.67–3.65 (d, *J*= 5.8, 1H), 3.14–3.29 (m, 1H), 2.99–2.94 (m, 1H), 2.05–2.00 (m, 1H), 1.90–1.84 (m, 1H), 1.41–1.39 (d,*J*= 6.8, 2H), 1.34–1.29(m, 2H), 1.07–1.04 (m, 1H), 1.04–0.82 (m, 9H), 0.76–0.74 (d, *J*= 8.16, 3H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-*d6*] δ 175.9, 172.4, 171.8, 168.5, 136.3, 128.9, 126.6, 58.3, 58.2, 55.0, 48.3, 37.0, 36.1, 29.9, 24.1, 17.3, 17.0, 16.2, 14.5, 10.3; HRMS(ESI-TOF): calculated for $C_{23}H_{37}N_5O_4$ m/z [M+H$^+$]: 470.5698, found: 470.2741; HPLC: t_R = 19.59 min, 100%.

Val-Val-D-Ile-Ala-NH$_2$ (14a) ^{1}H NMR [400 MHz, CD_3OD + DMSO-*d6*] δ 4.51–4.48 (m, 1H), 4.39–4.33 (m, 1H), 4.25–4.21 (d, *J*= 8.34, 1H), 3.68–3.56 (d, *J*= 6.89, 1H), 2.22–2.18 (m, 1H), 2.12–2.06 (m, 1H), 1.55–1.48 (m, 3H), 1.32–1.24 (m, 4H), 1.01–0.88 (m, 17H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-*d6*] d 175.7, 172.4, 171.9, 168.2, 59.1, 57.8, 51.5, 48.8, 40.3, 31.7, 31.3, 24.8, 22.7, 20.4, 18.4, 17.2, 17.0, 16.5, 9.3; HRMS (ESI-TOF): calculated for $C_{19}H_{37}N_5O_4$ m/z [M+Na$^+$]: 422.5258, found: 422.2837; HPLC: t_R = 11.54 min, 94.80%.

Val-Val-Leu-Ala-NH$_2$ (14b) ^{1}H NMR [400 MHz, CD_3OD + DMSO-*d6*] δ 4.48–4.45 (m, 1H), 4.37–4.32 (m, 1H), 4.24–4.22 (d, *J*= 8.32, 1H), 3.78–3.76 (d, *J*=5.56, 1H), 2.21–2.16 (m, 1H), 2.11–2.05 (m, 1H), 1.65–1.60 (m, 3H), 1.37–1.28 (m, 4H), 1.03–0.96(m, 17H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-*d6*] δ 175.8,172.6, 171.8, 168.0, 59.0, 57.9, 51.4, 48.5, 40.2, 30.4, 30.3, 24.2, 22.1, 20.4, 18.3, 17.4, 16.4, 9.2; HRMS (ESI-TOF): calculated for $C_{19}H_{37}N_5O_4$ m/z [M+Na$^+$]: 422.5258, found: 422.2830; HPLC: t_R = 11.86 min, 93.10%.

Val-Val-Ile-D-Ala-NH$_2$ (15a) ^{1}H NMR [400 MHz, CD_3OD + DMSO-*d6*] δ 4.33–4.27 (m, 2H), 4.11–4.09 (d,*J* =5.58, 2H), 2.23–2.18 (m, 1H), 2.11–2.04 (m, 1H), 1.86–1.81 (m, 1H), 1.63–1.59 (m, 1H), 1.39–1.37 (d, *J* =7.24, 3H), 1.27–1.20 (m, 1H), 0.99–0.93 (m, 18H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-*d6*] d 176.0, 172.1, 171.9, 168.1, 58.8, 58.3, 57.9, 48.5, 36.5, 30.4, 24.8, 18.4, 17.9, 17.6, 16.9, 14.4, 9.8; HRMS (ESI-TOF): calculated for $C_{19}H_{37}N_5O_4$ m/z [M+Na$^+$]: 422.5258, found: 422.2724; HPLC: t_R = 15.25 min, 90.05%.

Val-Val-Ile-Aib-NH$_2$ (15b) ^{1}H NMR [400 MHz, CD_3OD + DMSO-*d6*] δ 4.30–4.28 (d, *J* = 8.2,1H), 4.07–4.03 (t, *J*=8.81, 1H), 3.82–3.77 (m, 1H), 2.23–2.19 (m, 1H), 2.10–2.03 (m, 1H), 1.86–1.83 (m, 1H), 1.65–1.60 (m, 1H), 1.51–1.47 (d, *J*=19.6, 6H),1.25–1.19 (m, 1H), 1.02–0.94(m, 18H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-*d6*] δ 178.2, 172.1, 171.6, 167.9, 58.7, 58.3, 57.8, 56.5, 35.8, 30.5, 30.3, 25.5, 24.9, 23.1, 18.5, 17.6, 17.0, 14.4, 12.3, 9.8; HRMS (ESI-TOF): calculated for $C_{20}H_{39}N_5O_4$ m/z [M+H$^+$]: 414.3080, found: 414.3066; HPLC: t_R = 15.77 min, 90.95%.

Val-Val-Ile-Gly-NH$_2$ (15c) ^{1}H NMR [400 MHz, CD_3OD + DMSO-*d6*] δ 4.29–4.27 (d, *J* = 8.36, 1H), 4.14–4.12 (d,*J* =8.52, 1H), 3.78–3.74 (m, 1H), 2.21–2.16 (m, 1H), 2.07–2.01 (m, 1H), 1.87–1.83 (m,1H), 1.62–1.60 (m, 1H), 1.24–1.19 (m, 1H), 1.04–0.96 9(m, 19H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-*d6*] δ 172.7, 172.6, 172.1, 168.0, 58.9, 57.9, 53.4, 41.6, 36.0, 30.3, 24.7, 18.2, 17.6,

17.4, 16.4, 14.3, 9.7; HRMS (ESI-TOF): calculated for $C_{18}H_{35}N_5O_4$ m/z [M+H$^+$]: 386.2767, found: 386.2757; HPLC: t_R = 11.58 min, 90.72%.

Val-Val-Ile-Val-NH$_2$ (15d) ^{1}H NMR [400 MHz, CD_3OD + DMSO-*d6*] δ 4.30–4.25 (m, 3H), 3.71–3.70 (d, *J*=5.2,1H), 2.22–2.16 (m, 1H), 2.06–2.01 (m, 3H), 1.86–1.83 (m, 1H), 1.57–1.53 (m, 1H), 1.22–1.17 (m, 1H), 1.02–0.90 (m, 23H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-*d6*] δ 174.5, 174.5, 174.3, 172.1, 171.5, 59.0, 58.1, 57.5, 53.4, 36.4, 32.5, 31.6, 30.5, 24.5, 18.3, 18.2, 17.7, 17.5, 17.0, 16.4, 14.3, 9.6; HRMS (ESI-TOF): calculated for $C_{21}H_{41}N_5O_4$ m/z [M+H$^+$]: 428.3237, found: 428.3230; HPLC: t_R = 17.6 min, 90.61%.

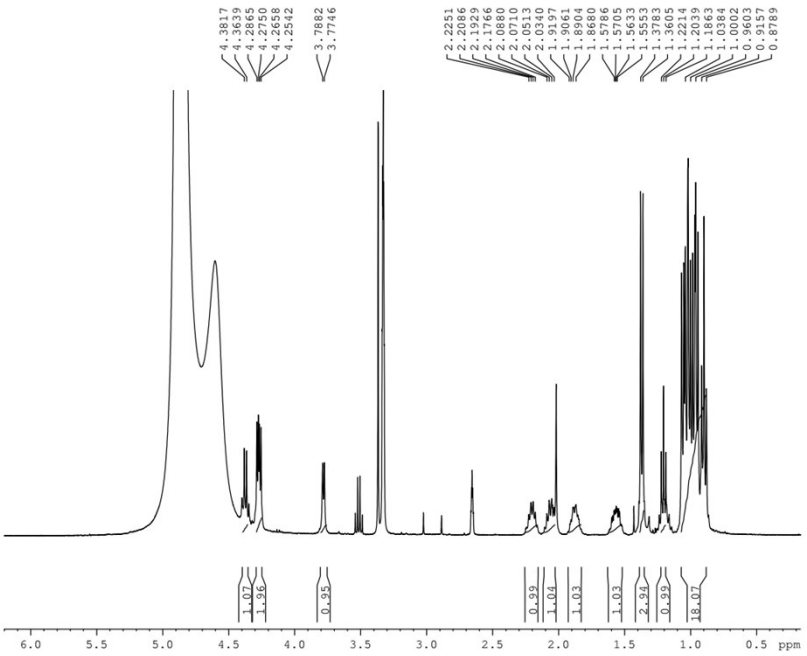
Val-Val-Ile-Leu-NH$_2$ (15e) ^{1}H NMR [400 MHz, CD_3OD + DMSO-*d6*] δ 4.51–4.48 (m, 1H), 4.36–4.32 (m, 2H), 3.85–3.84 (d, *J*= 4.88, 1H), 2.23–2.17 (m, 1H), 2.07–2.01 (m, 1H), 1.86–1.79 (m, 1H), 1.68–1.53 (m, 4H), 1.22–1.16 (m, 1H), 1.01–0.90 (m, 24H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-*d6*] δ 175.5, 171.4, 171.3, 167.9, 695.4, 58.8, 57.3, 51.2, 40.9, 36.5, 30.8, 30.3, 24.6, 24.4, 22.3, 30.7, 18.4, 18.0, 17.6, 16.7, 14.6, 9.9; HRMS (ESI-TOF): calculated for $C_{22}H_{43}N_5O_4$ m/z [M+H$^+$]: 442.3393, found: 442.3390; HPLC: t_R = 21.6 min, 90.61%.

Val-Val-Ile-Ile-NH$_2$ (15f) ^{1}H NMR [400 MHz, CD_3OD + DMSO-*d6*] δ 4.32–4.27 (m, 3H), 3.81–3.76 (m,1H), 2.20–2.11 (m,2H), 1.84 (s, 1H), 1.56 (s,1H), 1.45–1.41 (m, 2H), 1.26–1.20 (m,2H), 1.00–0.90 (m, 24H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-*d6*] δ 173.1, 171.9, 171.5, 168.0, 58.2, 57.9, 57.4, 48.5, 36.5, 36.0, 30.6, 30.3, 24.5, 24.4, 18.3, 17.8, 17.5, 16.5, 14.5, 14.4, 9.9, 9.6; HRMS (ESI-TOF): calculated for $C_{22}H_{43}N_5O_4$ m/z [M+H$^+$]: 442.3393, found: 442.3390; HPLC: t_R = 20.23 min, 100.0%.

Pro-Pro-Ile-Ala-NH$_2$- (16a) δ ^{1}H NMR [400 MHz, CD_3OD + DMSO-*d6*] δ 4.30–4.25 (m, 3H), 3.71–3.70 (d,*J*=5.2,1H), 2.22–2.16 (m, 1H), 2.06–2.01 (m, 3H), 1.86–1.83 (m, 1H), 1.57–1.53 (m, 1H), 1.22–1.17 (m, 1H), 1.02–0.90 (m, 23H); ^{13}C NMR [100 MHz, CD_3OD + DMSO-*d6*] d 174.5, 174.3, 172.1, 171.5, 59.0, 58.1, 57.5, 53.4, 36.4, 32.5, 31.6, 30.5, 24.5, 18.3, 18.2, 17.7, 17.5, 17.0, 16.4, 14.3, 9.6; HRMS (ESI-TOF): calculated for $C_{19}H_{33}N_5O_4$ m/z [M+Na$^+$]: 418.4938, found: 418.1395; HPLC: t_R = 14.26 min, 91.04%.

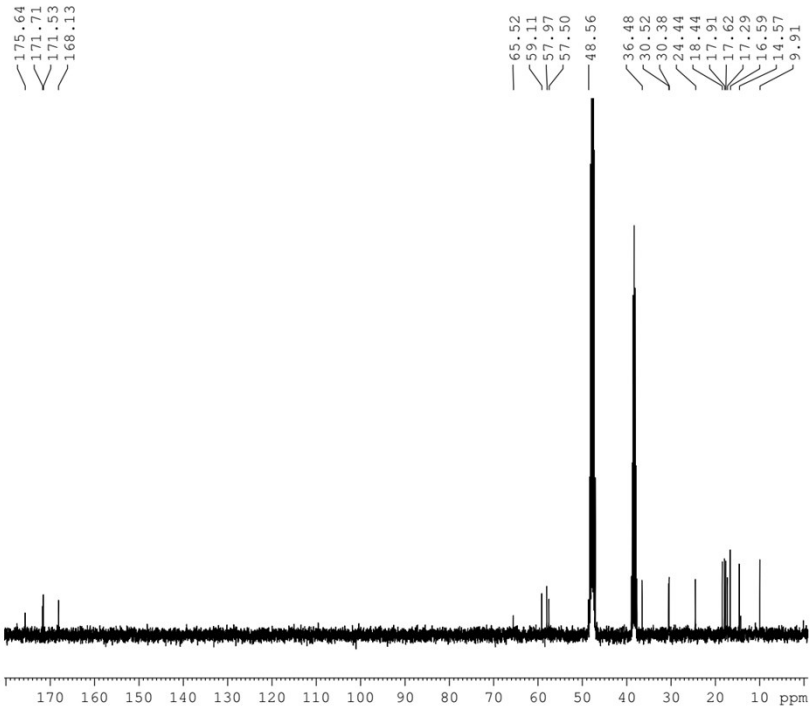
2.2. Characterisation spectra and chromatograms for representative compounds

^{1}H NMR spectra for Val-Val-Ile-Ala-NH_2 (11a)



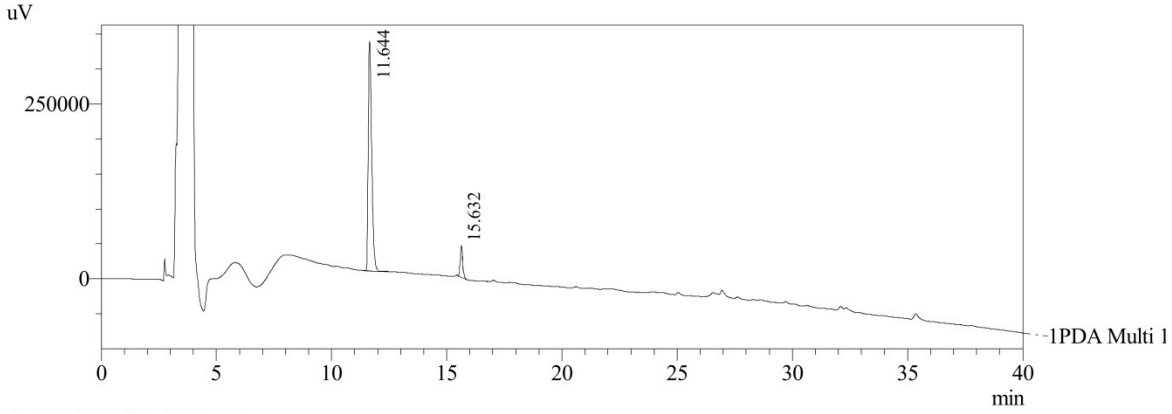

```
Current Data Parameters
NAME                  app-2
EXPNO                    10
PROCNO                    1

F2 - Acquisition Parameters
Date_              20160730
Time                   8.52
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                MeOD
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES            0.125483 Hz
AQ                3.9845889 sec
RG                      114
DW                   60.800 use
DE                    6.50 use
TE                   292.8 K
D1                1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     1H
P1                   12.20 use
PL1                  -2.00 dB
PL1W           14.80958652 W
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                    32768
SF              400.1300000 MHz
WDW                      EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.40
```

^{13}C NMR spectra for Val-Val-Ile-Ala-NH_2 (11a)




```
Current Data Parameters
NAME                  app-2
EXPNO                    10
PROCNO                    1

F2 - Acquisition Parameters
Date_              20160801
Time                   9.16
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG               zgpg30
TD                    65536
SOLVENT                MeOD
NS                     1024
DS                        4
SWH               24038.461 Hz
FIDRES            0.366798 Hz
AQ                1.3631488 sec
RG                      203
DW                   20.800 use
DE                    6.50 use
TE                   293.5 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                    9.50 use
PL1                  -1.00 dB
PL1W          44.90434265 W
SFO1          100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG[2          waltz16
NUC2                     1H
PCPD2                80.00 use
PL2                  -2.00 dB
PL12                 14.33 dB
PL13                 18.33 dB
PL2W          14.80958652 W
PL12W          0.34478071 W
PL13W          0.13725966 W
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                    32768
SF              100.6127690 MHz
WDW                      EM
SSB          0
```

HPLC Chromatogram for Val-Val-Ile-Ala-NH_2 (11a)



1 PDA Multi 1 / 215nm 4nm

PeakTable

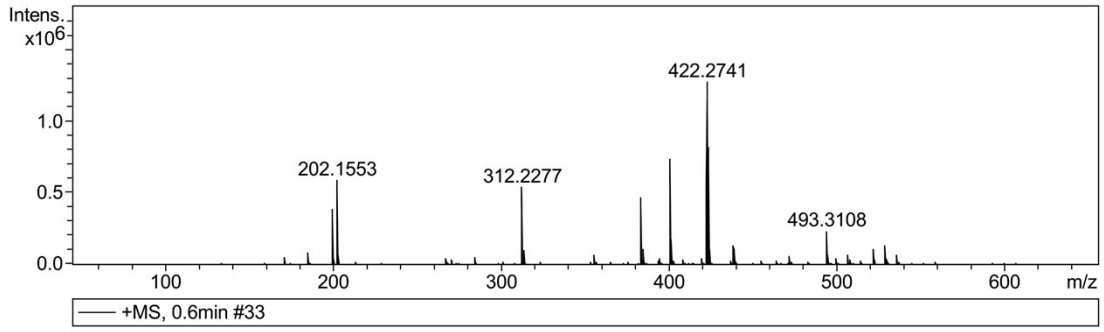
PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	11.644	3708881	328479	90.063
2	15.632	409194	55946	9.937
Total		4118075	384425	100.000

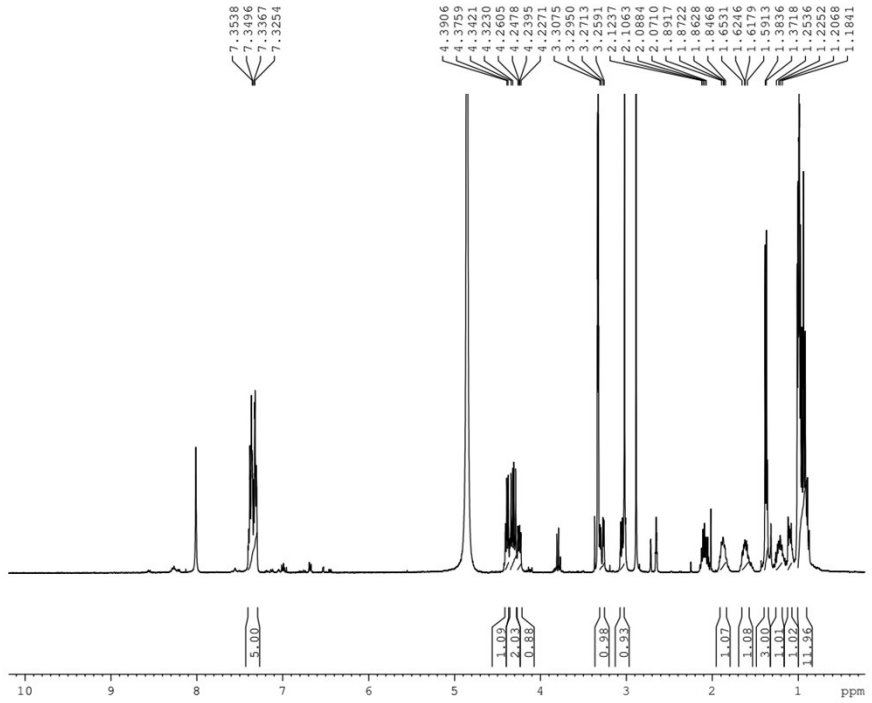
HRMS chromatogram for Val-Val-Ile-Ala-NH_2 (11a)

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	1.2 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	250 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	5.0 l/min
Scan End	650 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Waste

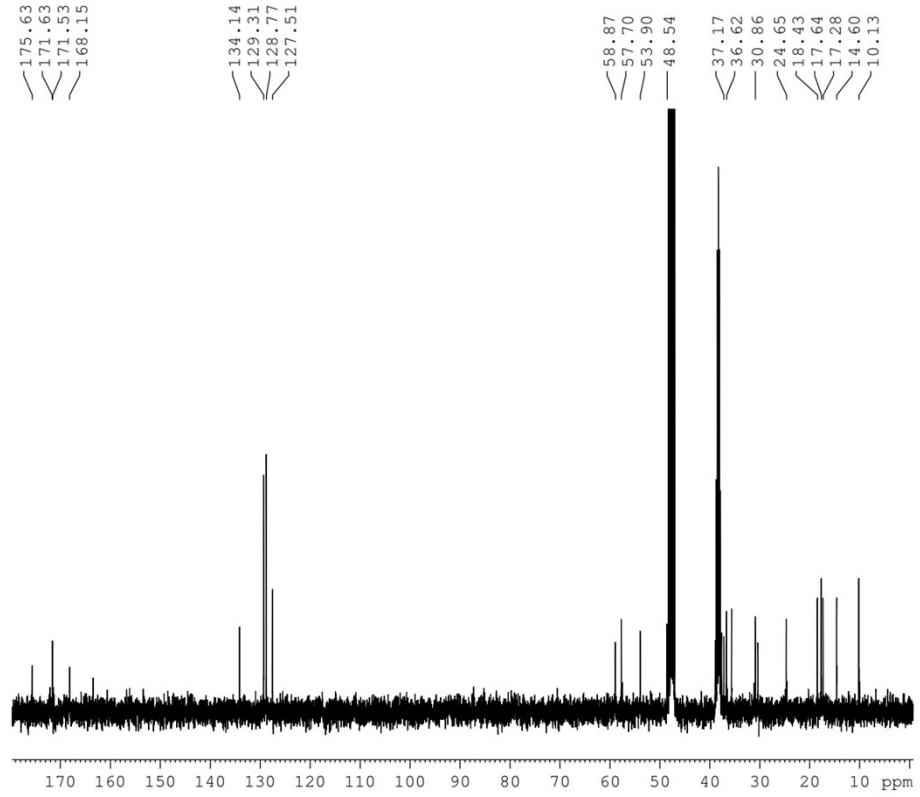


^{1}H NMR spectra for D-Phe-Val-Ile-Ala-NH_2 (12c)



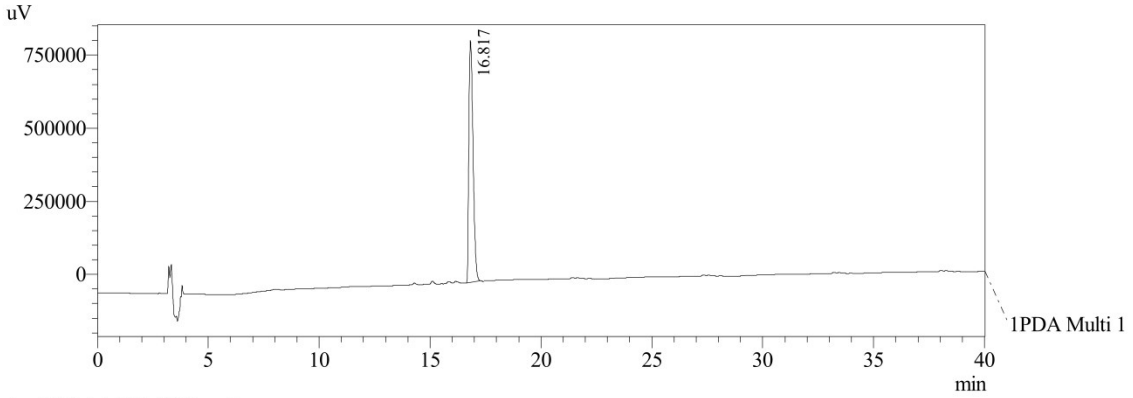

```
Current Data Parameters
NAME                  app-3
EXPNO                    10
PROCNO                    1

F2 - Acquisition Parameters
Date_              20160808
Time                  0.24
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG               zg30
TD                   65536
SOLVENT               MeOD
NS                      16
DS                       2
SWH                8223.685 Hz
FIDRES            0.125483 Hz
AQ                3.9845889 sec
RG                     203
DW                  60.800 use
DE                   6.50 use
TE                  673.2 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   12.20 use
PL1                  -2.00 dB
PL1W           14.80958652 W
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                   32768
SF             400.1300000 MHz
WDW                     EM
SSB       0
LB                    0.30 Hz
GB        0
PC                    1.40
```

^{13}C NMR spectra for D-Phe-Val-Ile-Ala-NH_2 (12c)




```
Current Data Parameters
NAME                  app-3
EXPNO                    11
PROCNO                    1

F2 - Acquisition Parameters
Date_              20160808
Time                 16.05
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT               MeOD
NS                    1024
DS                       4
SWH               24038.461 Hz
FIDRES            0.366798 Hz
AQ                1.3631488 sec
RG                     203
DW                  20.800 use
DE                   6.50 use
TE                  673.2 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.50 use
PL1                  -1.00 dB
PL1W           44.90434265 W
SFO1           100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG[2          waltz16
NUC2                    1H
PCPD2                80.00 use
PL2                  -2.00 dB
PL12                 14.33 dB
PL13                 18.33 dB
PL2W           14.80958652 W
PL12W           0.34478071 W
PL13W           0.13725966 W
SFO2           400.1316005 MHz

F2 - Processing parameters
SI                   32768
SF             100.6127690 MHz
WDW                     EM
SSB       0
```

HPLC Chromatogram for D-Phe-Val-Ile-Ala-NH_2 (12c)



1 PDA Multi 1 / 215nm 4nm

PeakTable

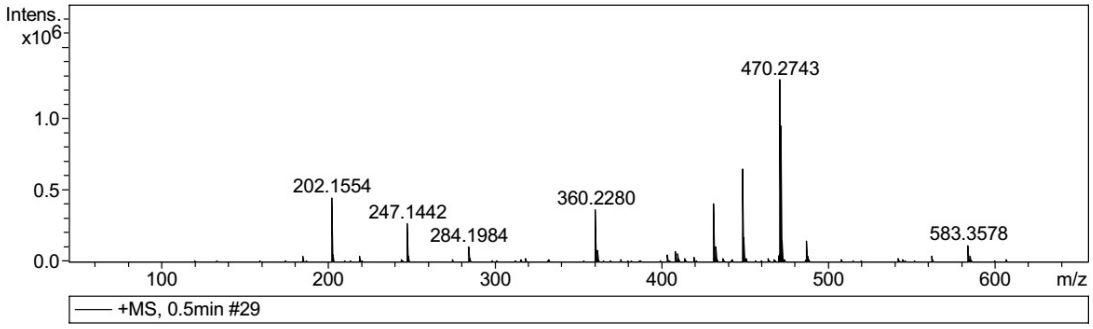
PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	16.817	10767984	826462	99.999
2	39.936	152	54	0.001
Total		10768136	826516	100.000

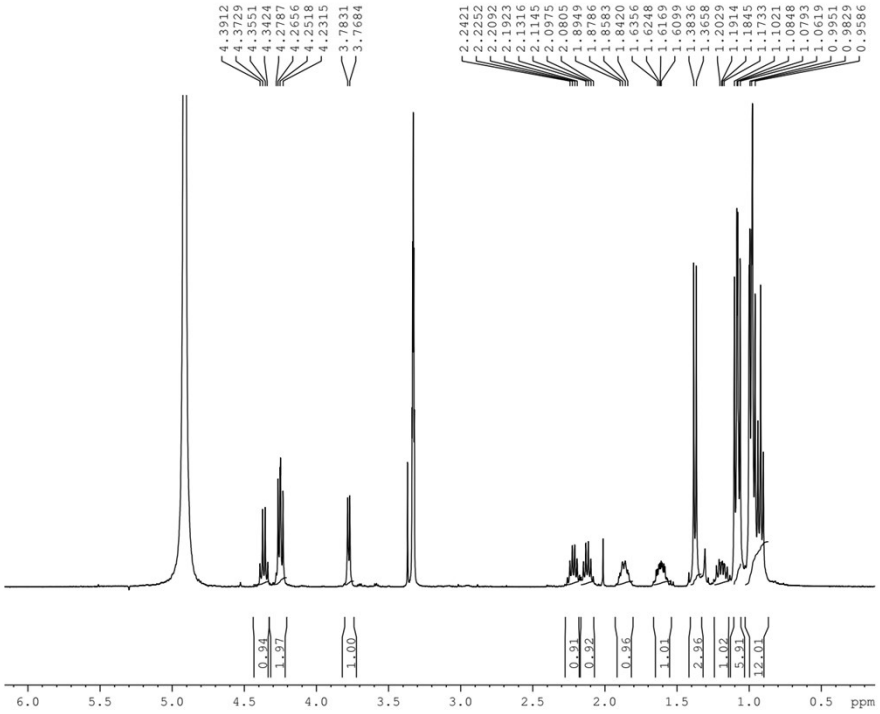
HRMS chromatogram for D-Phe-Val-Ile-Ala-NH_2 (12c)

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	1.2 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	250 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	5.0 l/min
Scan End	650 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Waste

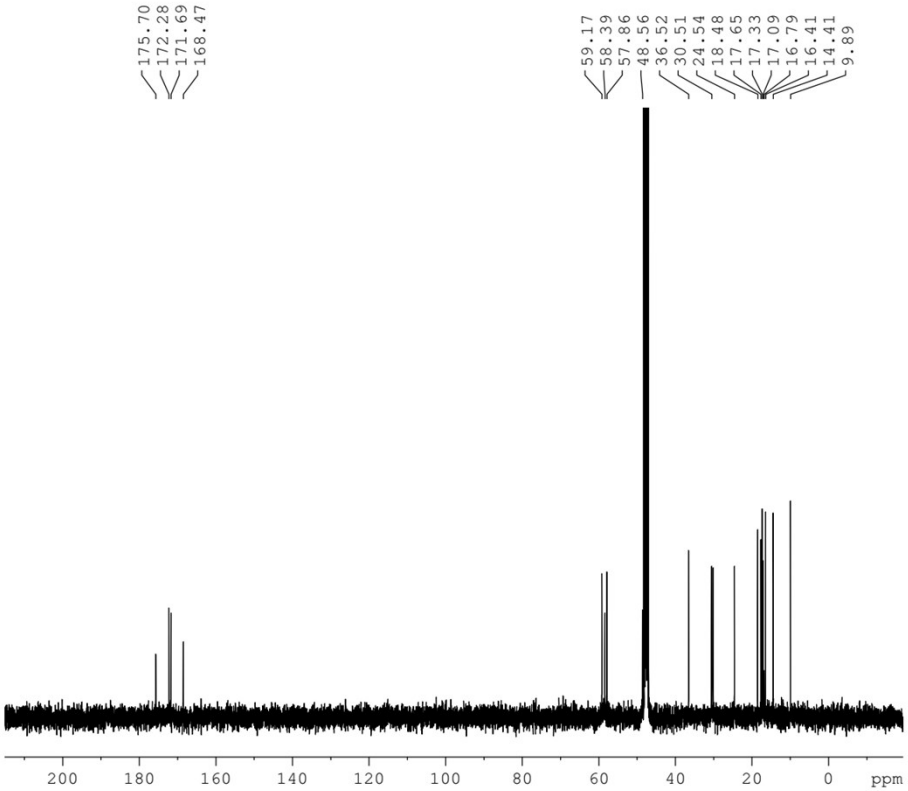


^{1}H NMR spectra for Val-Val-Leu-Ala-NH_2 (14b)



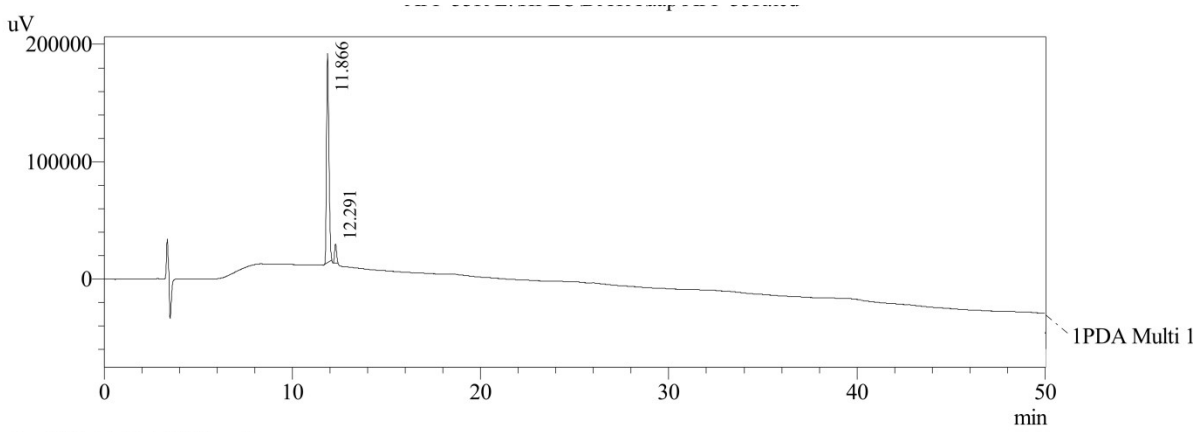

```
Current Data Parameters
NAME                  app-14
EXPNO                     10
PROCNO                     1

F2 - Acquisition Parameters
Date_              20161004
Time                   2.56
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                MeOD
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES            0.125483 Hz
AQ                3.9845889 sec
RG                      203
DW                   60.800 use
DE                    6.50 use
TE                   294.1 K
D1                1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                      1H
P1                     12.20 use
PL1                    -2.00 dB
PL1W           14.80958652 W
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                    32768
SF             400.1300000 MHz
WDW                      EM
SSB       0
LB                    0.30 Hz
GB        0
PC                    1.40
```

^{13}C NMR spectra for Val-Val-Leu-Ala-NH_2 (14b)




```
Current Data Parameters
NAME                  app-14
EXPNO                     11
PROCNO                     1

F2 - Acquisition Parameters
Date_              20161004
Time                  10.25
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT                MeOD
NS                     2048
DS                        4
SWH               24038.461 Hz
FIDRES            0.366798 Hz
AQ                1.3631488 sec
RG                      203
DW                   20.800 use
DE                    6.50 use
TE                   295.0 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     13C
P1                     9.50 use
PL1                   -1.00 dB
PL1W           44.90434265 W
SFO1           100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG[2          waltz16
NUC2                      1H
PCPD2                80.00 use
PL2                   -2.00 dB
PL12                  14.33 dB
PL13                  18.33 dB
PL2W           14.80958652 W
PL12W           0.34478071 W
PL13W           0.13725966 W
SFO2           400.1316005 MHz

F2 - Processing parameters
SI                    32768
SF             100.6127690 MHz
WDW                      EM
SSB       0
```

HPLC Chromatogram for Val-Val-Leu-Ala-NH_2 (14b)



1 PDA Multi 1 / 215nm 4nm

PeakTable

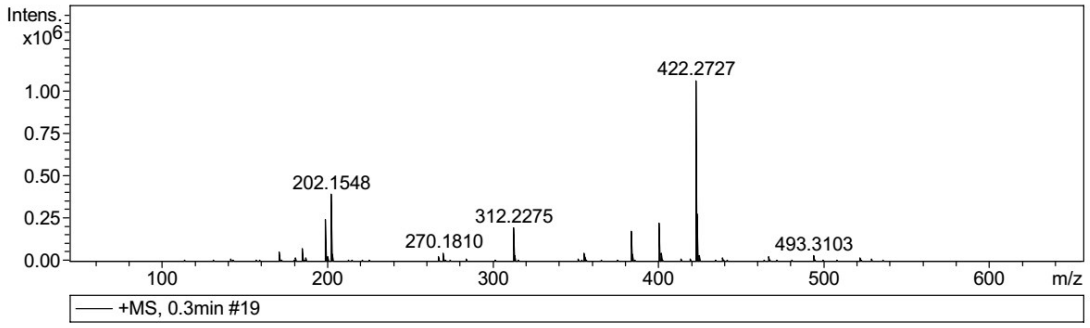
PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	11.866	1555967	178271	93.102
2	12.291	115291	16362	6.898
Total		1671258	194634	100.000

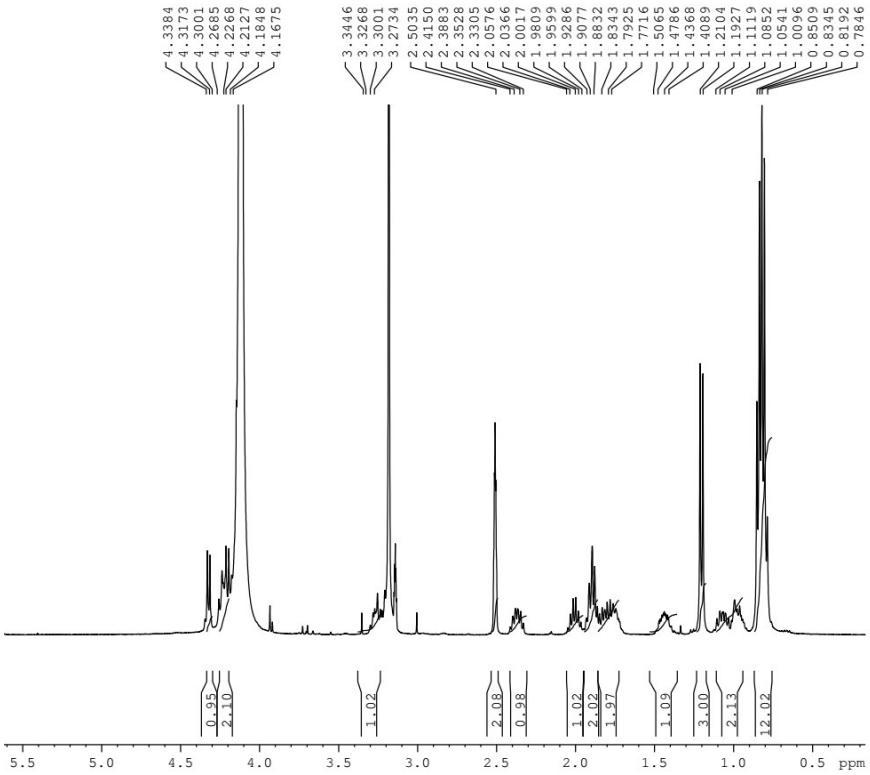
HRMS chromatogram for Val-Val-Leu-Ala-NH_2 (14b)

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	1.2 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	250 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	5.0 l/min
Scan End	650 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Waste

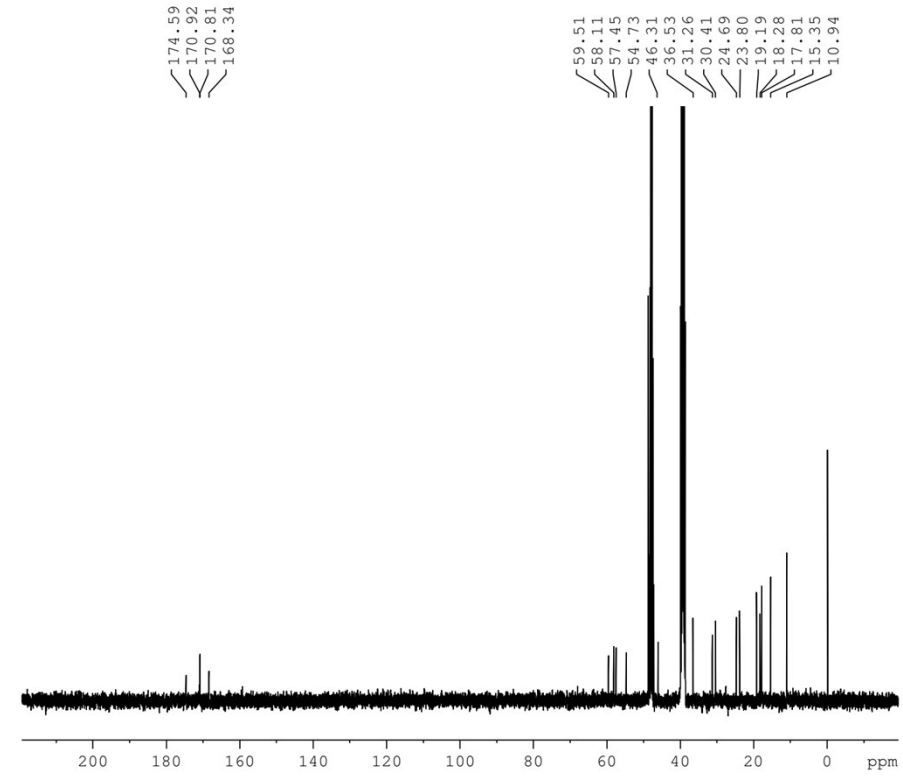


^{1}H NMR spectra for D-Pro-Val-Ile-Ala-NH_2 (12d)



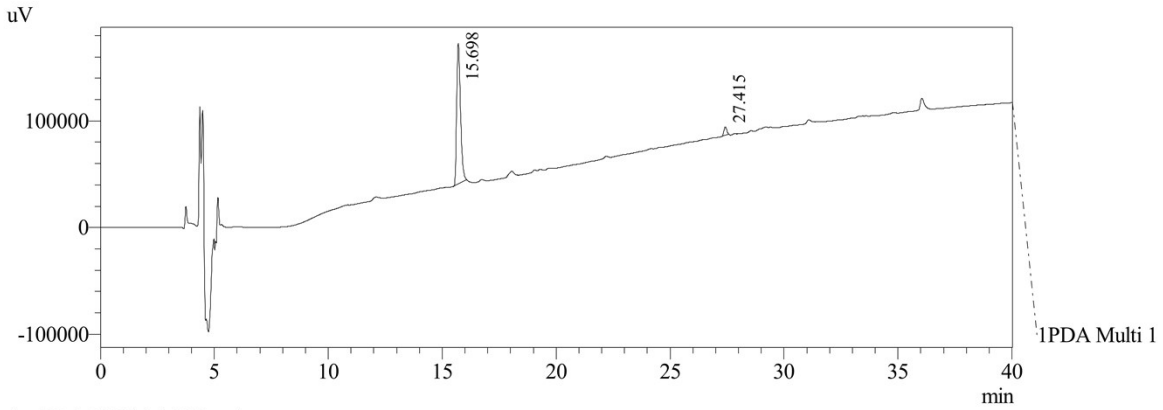

```
Current Data Parameters
NAME                  app-15
EXPNO                     10
PROCNO                     1

F2 - Acquisition Parameters
Date_              20161025
Time                  21.01
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                        16
DS                         2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9845889 sec
RG                       128
DW                    60.800 use
DE                     6.50 use
TE                    294.1 K
D1              1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     12.20 use
PL1                    -2.00 dB
PL1W           14.80958652 W
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF              400.1300000 MHz
WDW                        EM
SSB       0
LB                     0.30 Hz
GB        0
PC                     1.40
```

^{13}C NMR spectra for D-Pro-Val-Ile-Ala-NH_2 (12d)




```
Current Data Parameters
NAME                  app-15
EXPNO                     20
PROCNO                     1

F2 - Acquisition Parameters
Date_              20161026
Time                  11.57
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG               zgpg30
TD                    65536
SOLVENT                DMSO
NS                      1024
DS                         4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631488 sec
RG                       203
DW                    20.800 usec
DE                     6.50 usec
TE                    295.2 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                     9.50 usec
PL1                   -1.00 dB
PL1W           44.90434265 W
SFO1          100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG[2          waltz16
NUC2                      1H
PCPD2                 80.00 usec
PL2                   -2.00 dB
PL12                  14.33 dB
PL13                  18.33 dB
PL2W           14.80958652 W
PL12W           0.34478071 W
PL13W           0.13725966 W
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                        32768
SF              100.6127690 MHz
WDW                        EM
SSB       0
```

HPLC Chromatogram for D-Pro-Val-Ile-Ala-NH_2 (12d)



1 PDA Multi 1 / 215nm 4nm

PeakTable

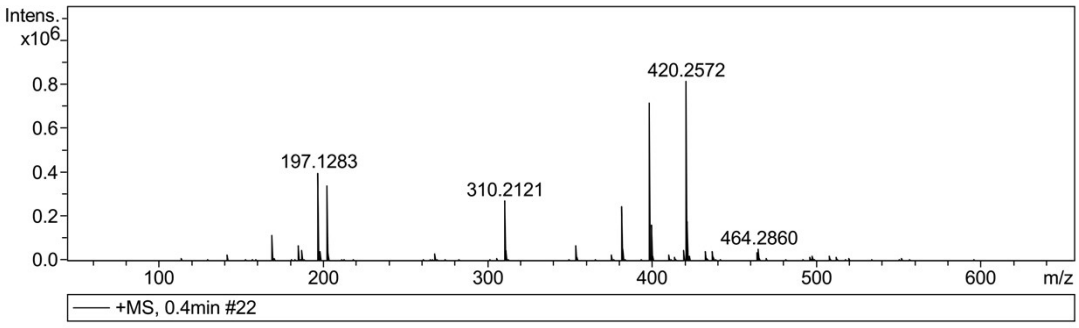
PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	15.698	1528114	131567	95.649
2	27.415	69513	7832	4.351
Total		1597626	139399	100.000

HRMS chromatogram for D-Pro-Val-Ile-Ala-NH_2 (12d)

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	1.2 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	250 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	5.0 l/min
Scan End	650 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Waste



3. MTT cell viability assay

The cell viability assay was performed at the Department of Experimental Medicine and Biotechnology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. $A\beta_{42}$ was purchased from AnaSpec Inc., USA. Rat pheochromocytoma (PC-12) cells were procured from National Centre for Cell Science (NCCS), Pune, India. Horse serum was purchased from HiMedia Laboratories, India. 96-Well; flat-bottomed microtiter plates (Costar), Corning® tissue-culture treated dishes, MTT, sodium bicarbonate, foetal bovine serum (heat inactivated), penicillin/streptomycin, nerve growth factor (NGF), F-12K growth media and molecular biology grade dimethyl sulphoxide (DMSO) were purchased from Sigma-Aldrich Chemicals, Saint Louis, MO, USA. Phosphate buffered saline (PBS, pH 7.4) was purchased from Gibco (Life Technologies). All the solutions were pre-sterilized using 0.2 μm syringe filters. The optical density (OD_{570}) measurements were made using a microtiter plate reader (VERSA max tunable; Molecular Devices, Sunnyvale, CA).

3.1. Aβ Pre-treatment

To ensure uniformity of Aβ in the monomeric state in the experiments, the $A\beta_{42}$ peptides was brought in complete monomeric state by employing Zagorski's protocol.[5] Briefly, the peptides were first dissolved in trifluoroacetic acid (TFA) at an approximate 1:1 ratio (mg/mL) and ultrasonicated for 10 minutes. The solution was kept at room temperature for 1-2 h before drying under dry N_2 gas. The peptides formed a thin coat on walls of the glass vial. The cycle was repeated three times. To remove the traces of TFA, hexafluoroisopropanol (HFIP) was added and the cycle of sonication and removal of the HFIP with dry N_2 gas was repeated three times. Finally, 1 mL of HFIP was added and aliquot containing 125 μg of $A\beta_{42}$ were prepared as stocks, trace amounts of HFIP were removed under vacuum (0.5 mm Hg, 2 h) and N_2 flushing. To ensure no residual metal impurities that could promote aggregation of the Aβ peptide, high purity molecular grade TFA and HFIP (Sigma Aldrich) were used.

3.2. Cell Culture

Cells were primarily cultured in F-12K growth media supplemented with of 10% horse serum, 5% FBS and 1% penicillin/streptomycin in a humidified atmosphere with 5% CO_2 at 37°C. Cells were sub-cultured and grown in tissue-culture treated dishes and were used for the experiments when 70% confluent. Disaggregation of masses of cells was done by trypsin treatment. On the day of study, the media was replaced with fresh F-12K media containing

10% FBS and 1% penicillin/streptomycin. The cells were differentiated by treatment with 100 μM nerve growth factor (horse serum) for 48 h. To ensure uniformity of Aβ in the monomeric state in the experiments, the $A\beta_{42}$ peptides was brought in complete monomeric state by employing Zagorski's protocol (detailed procedure in supplementary information).

3.3. Assay

An aliquot of Aβ was taken and immediately before the experiment; 20 mM NaOH was added to make up a concentration of 200 μM. The peptide was diluted in 10 mM sodium phosphate buffer (pH 7.4) to 20 μM. Test peptides were dissolved in dimethyl sulphoxide (DMSO) as 5 mM stock solutions and were diluted in phosphate buffered saline (PBS) to the concentrations of 100 μM, 40 μM and 20 μM. Care was taken to maintain the total concentration of DMSO not more than 0.2% after the final dilution for the experiments. Cells in their exponential growth phase were seeded in 96 well-plates, at a rate of 17000 cells per well per 80 μL, and were incubated overnight. Next morning, $A\beta_{42}$ (10 μL) was added in each well followed by the addition of test peptides (10 μL). The final concentration of $A\beta_{42}$ was kept 2 μM and that of inhibitors as 10, 4, and 2 μM so that their ratios were as 1:5, 1:2, and 1:1 ($A\beta_{42}$: test peptides). The plates were incubated at 37 ^{o}C for 6 h. The cell samples containing $A\beta_{42}$ without the test peptides, but other components in the same concentration as in the test wells were taken as control. After 6 h incubation, 20 μL of MTT (5 mg/mL in PBS) was added and plates were incubated for 4 h. The plate was centrifuged at 4°C for 10 minutes. Supernatant was carefully removed from the wells and DMSO (200 μL, per well) was added. The resulting suspension was mixed well, and OD_{570} were measured. Each experiment was done in triplicates (n=3). The percentage inhibition of Aβ-induced cytotoxicity to PC-12 cells, by each test peptide was calculated by using the formula: as 100 * [Test OD_{570} - $A\beta_{42}$ OD_{570} / Control OD_{570} - $A\beta_{42}$ OD_{570}]. Blank ODs were subtracted from each sample OD and the triplicate ODs were averaged. ODs of samples with untreated cells were set to 100%, and percentage cell viabilities were calculated for the test and $A\beta_{42}$ treated cells samples.

4. Thioflavin-T assay

Black, clear bottom, 96 well-plates and Thioflavin-T were purchased from Sigma-Aldrich Chemicals, Saint Louis, MO, USA. All the solutions were pre-sterilized using 0.2 μm syringe filters. Phosphate buffered saline (PBS, pH 7.4) was purchased from Gibco (Life

Technologies). All fluorescence recordings were performed on Cary Eclipse-Variance Spectrofluorometer: Advance Reads – 96 well plate reader.

Protocol pre-established in the laboratory was followed.[6,7] Monomeric $A\beta_{42}$ was dissolved in 20 mM NaOH to obtain a concentration of 400 μM, and then diluted in sodium phosphate buffer (pH 7.4) to 20 μM. 120 μL of ThT (20 μM), dissolved in glycine-NaOH buffer (pH 8.5) was added in each well of a black, 96 well-plate with clear bottom. Inhibitor peptides were dissolved in DMSO at 5 mM stock solution and diluted in Phosphate buffer saline (pH 7.4) to obtain concentrations of 100 μM, 40 μM and 20 μM. 15 μL of the test peptides were added to each well, followed by the addition of 15 μL of Lower concentrations tested were 1, 0.5 and 0.1 μM, maintaining ratios with $A\beta_{42}$ as 1:0.5, 1:0.25 and 1:0.05 respectively. Care was taken to maintain the total concentration of DMSO not more than 0.2% after the final dilution for the experiments. Plates were kept wrapped in aluminium foil to prevent any degradation from light and were stored at 37^{o}C, in a rotary shaker incubator. Shaking speed was intermittently provided and controlled from 100-200 rpm. The plates were read on Cary Eclipse-Variance Spectrofluorometer: Advance Reads – 96 well plate reader with excitation and emission wavelengths at 445 nm and 485 nm respectively. Excitation and emission slits widths were kept constant at 5 nm. Excitation filter was kept on the auto mode and emission filter was kept open. Centre of the well was kept as the read position. An average of three readings was taken as the final reading.

Active peptides were also studied in a time dependent manner for a period of 7 days and readings were recorded at regular intervals of 24 h. Most active test peptide **12c** was studied on $A\beta_{40}$ (5 μM) at concentrations 5 μM, 2.5 μM and 1.25 μM concentrations to keep the ratios of Aβ : test peptides as 1:1, 1:0.5, 1:0.25. Samples were incubated at 37 °C and readings were taken at regular intervals of 24h for a time period of 3 days. Further, these peptides were evaluated against the mixture of $A\beta_{40}$:$A\beta_{42}$ (5μM:0.5μM such that the ratio of $A\beta_{40}$:$A\beta_{42}$ was 10:1). The inhibitor peptides taken in 5 μM, 2.5 μM and 1.25 μM concentrations, maintaining the ratios of Aβ : test peptides as 1:1, 1:0.5, and 1:0.25.

To evaluate the effect of the most active peptide **12c** on preformed amyloid fibrils, $A\beta_{42}$ (2 μM) was pre-aggregated for 24 h and was treated in a time dependent manner for 5 days at 24 h intervals. Dose concentrations taken for this experiment was 2, 1 and 0.5 μM, keeping the ratios of Aβ : test peptides as 1:1, 1:0.5, 1:0.25 respectively. Minimal volumes of the test

peptide stock concentrations were added to the wells (≤10 μL) to maintain the desired concentration of test peptides and $A\beta_{42}$.

Table S1. Observed %RFU and % Inhibition of $A\beta_{42}$ aggregation exhibited by most active test peptides.

No.	% RFU values			% Inhibition[c]		
	Test peptide concentration range					
	10 μM	4 μM	2 μM	10 μM	4 μM	2 μM
12c	52.4	53.1	53.4	100	100	100
12f	57.2	69.9	70.5	93.8	66.0	64.5
12g	55.2	70.5	61.5	98.1	64.5	84.4
13e	73.9	71.8	54.0	57.2	61.7	100
$A\beta_{42}$[a]		100				
ThT[b]		53.3				

[a]The % relative enhancement in fluorescence (%RFU) exhibited by binding to Aβ fibrils was taken as 100%. [b]ThT dye alone was taken as control and [c]percentage inhibition of fluorescence was calculated by using the formula: 100 * [100 - ($A\beta_{42}$ + Test RFU_{485} - Control RFU_{485}/$A\beta_{42}$ RFU_{485} - Control RFU_{485})]. [d]Data was recorded for triplicate samples from individual experiments and the readings were averaged (<5% variation). In a subset of triplicate wells, SD values ranged 1.22-4.83.

Table S2. Activities against $A\beta_{42}$ induced neurotoxicity exhibited by test peptide 12c at lower dose concentrations.

Peptide: 12c	Test peptide concentration range		
	1.0 μM	0.5 μM	0.1 μM
% Viable cells[a]	100.0	89.1	86.0
% Inhibition[b]	91.8	88.4	78.0
% RFU	46.1	48.9	57.3

[a]Cell viability studies were performed using MTT cell viability assay against PC-12 cells. The percentage of untreated cells was considered 100% (positive control); percentage cell viability was calculated for the cells incubated along with $A\beta_{42}$ in absence (negative control: 73.4% cell viability) and presence of the test peptide 12c in respective dose concentrations. % Viable cells were calculated by the formula as 100 * [$A\beta_{42}$ + Test peptide OD_{570} - Aβ OD_{570}/Control OD_{570} - Aβ OD_{570}]. In a subset of triplicate wells, standard deviation values ranged 1.41-4.88. [b]Inhibition of $A\beta_{42}$ aggregation was calculated by Thioflavin-T fluorescence assay. % relative fluorescence units (% RFU) exhibited by Aβ fibrils were considered as 100%. ThT dye incubated alone was considered as control (43.5%) and % RFU units were computed when $A\beta_{42}$ was co-incubated with the test peptides. % Inhibition of ThT fluorescence was calculated by using the formula: 100 * [100 - ($A\beta_{42}$ + Test peptide RFU_{485} - Control RFU_{485}/$A\beta_{42}$ RFU_{485} - Control RFU_{485})]. In a subset of triplicate wells, SD values ranged 3.47- 4.97. Data for both the experiments, readings were recorded for triplicate samples from three individual experiments and were averaged (<5% variation).

Table S3. Observed %RFU exhibited by test peptides against $A\beta_{40}$ aggregation.

Peptide	% RFU values [c]		
	Test peptide concentration range ($A\beta_{42}$:Test peptide)		
	5μM (1:1)	2.5μM (1:0.5)	1.25μM (1:0.25)
Time: 24h			
12c	**99.6**	**103.7**	**100.2**
Control[b]	**80.2**		
Time: 48h			
12c	**98.5**	**101.7**	**103.3**
Control[b]	**84.5**		
Time: 72h			
12c	**138.53**	**122.67**	**127.07**
Control[b]	**96.67**		
$A\beta_{40}$ [a]	**100.0**		

[a]The % relative enhancement in fluorescence (%RFU) exhibited by binding to Aβ fibrils was taken as 100%. [b]ThT dye alone was taken as control. [c]Data was recorded for triplicate samples from three individual experiments and the readings were averaged (<5% variation). In a subset of triplicate wells SD values ranged 1.18-4.97.

Table S4. Observed %RFU and % Inhibition of $A\beta_{40}$: $A\beta_{42}$ aggregation exhibited by test peptides.

No.	% RFU values [d]			% Inhibition [c]		
	Test peptide concentration range					
	5μM (1:1)	2.5μM (1:0.5)	1.25μM (1:0.25)	5μM (1:1)	2.5μM (1:0.5)	1.25μM (1:0.25)
	Time: 24h					
12c	71.8	77.2	85.4	67.2	54.4	34.9
Control[b]		58.1				
	Time: 48h					
12c	79.1	82.8	87.9	67.7	55.8	39.3
Control[b]		69.2				
$A\beta_{40}$:$A\beta_{42}$ [a]		100.0				

[a]The % relative enhancement in fluorescence (%RFU) exhibited by binding to Aβ fibrils was taken as 100%. [b]ThT dye alone was taken as control and [c]percentage decrease of fluorescence was calculated by using the formula: 100 * [100-{Test RFU_{485} - Control RFU_{485} / Aβ RFU_{485} - Control RFU_{485}}]. [d]Data was recorded for triplicate samples from three individual experiments and the readings were averaged (<5% variation). In a subset of triplicate wells, SD values ranged 0.28-4.87.

Table S5. Observed %RFU and % deformation exhibited by test peptides on preformed $A\beta_{42}$ fibrils.

No.	% RFU values [d]			% Deformation [c]		
	Test peptide concentration range[a] (Aβ:Test peptide)					
	2μM (1:1)	1μM (1:0.5)	0.5μM (1:0.1)	2μM (1:1)	1μM (1:0.5)	0.5μM (1:0.1)
Time: 24h						
12c	85.4	91.1	91.4	57.5	34.9	33.7
Control[b]		74.5				
Time: 48h						
12c	94.0	99.7	100.7	33.0	2.2	0.0
Control[b]		81.7				
Aβ[a]		100.0				

[a]The % relative enhancement in fluorescence (%RFU) exhibited by binding to Aβ fibrils was taken as 100%. In order to normalise the readings, equivalent amount of buffer was added to the wells containing pre-aggregated $A\beta_{42}$. [b]ThT dye alone was taken as control and [c]percentage decrease of fluorescence was calculated by using the formula: 100 * [100-{Test RFU_{485} - Control RFU_{485} / $A\beta_{42}$ RFU_{485} - Control RFU_{485}}]. [d]Data was recorded for triplicate samples from three individual experiments and the readings were averaged (<5% variation). In a subset of triplicate wells, SD values ranged 1.82-4.18.

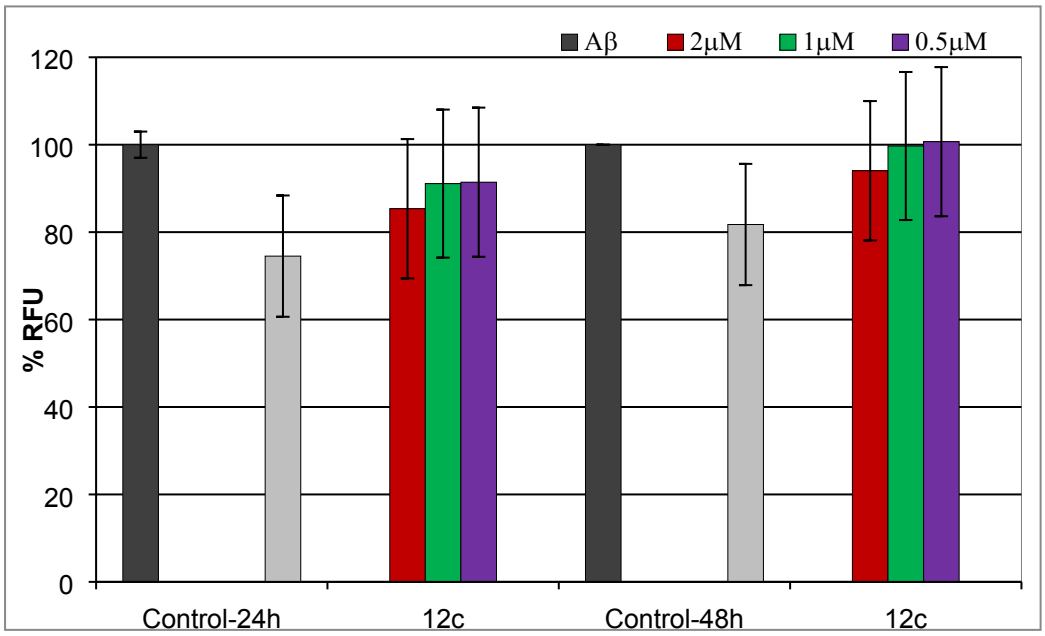


Figure S1. Time dependent RFU exhibiting the effect of tetrapeptides 12c on pre-aggregated fibrils of $A\beta_{42}$. Black bar represents RFU of $A\beta_{42}$ fibrils pre-aggregated alone and red, green and purple bars represent the RFU on co-incubation with test peptides **12c** and **13e** respectively. Error bars represent mean ± SD (n=3). Data were analysed by one way anova test.

Table S6. Time dependent % inhibition of $A\beta_{42}$ polymerisation exhibited by test peptide 12c.

Peptide	Conc. (μM)	% Inhibition of $A\beta_{42}$ aggregation [a]						
		24 h	48 h	72 h	96 h	120 h	144 h	168 h
12c	2.0	100.0	100.0	96.0	94.0	82.2	73.4	65.4
	1.0	88.4	89.0	72.6	76.0	74.6	64.9	53.5
	0.5	87.4	78.8	70.3	69.2	60.1	63.1	46.8

The enhancement in fluorescence (% RFU) exhibited by binding to $A\beta_{42}$ fibrils was taken as 100% and [a]percentage inhibition of fluorescence was calculated by using the formula: 100 * [100-{Test RFU_{485} - Control RFU_{485} / $A\beta_{42}$ RFU_{485} - Control RFU_{485}}]. Data was recorded for triplicate samples and the readings were averaged (<5% variation). In a subset of triplicate wells, SD values ranged 1.87-4.57.

5. ANS Fluorescence assay

8-anilino-1-naphthalenesulfonic acid (ANS) was obtained from Sigma Aldrich. All the solutions were pre-sterilized using 0.2 μm syringe filters. All the measurements were performed on Cary Eclipse-Variance Spectrofluorometer: Scan – Cuvette method and Advance Reads – 96 well plate reader.

2μM solution of $A\beta_{42}$ was prepared and analysed for calibrating the reading for ANS fluorescence. Dye concentration was kept constant at 50-fold excess to that of $A\beta_{42}$, such that the relative fluorescence intensity obtained was measureable and reproducible. Equimolar mixtures of $A\beta_{42}$ (2μM) and test peptides were incubated in the ratio of 1:1, 1:0.5 and 1:0.25 at 37 ^{o}C for 24 hours. ANS dye solution (50 fold excess) was added and incubated in a rotary shaker and incubator, 30 mins prior before recording the readings. 2 μM Solution of $A\beta_{42}$ was prepared and analysed for calibrating the reading for ANS fluorescence. A 400 μL quartz cuvette having 0.4 cm path length, magnetically stirred, thermostatic cuvette compartment was utilized for the recording the fluorescence emission readings of the samples. Excitation wavelength was set at 380 nm and emission intensities were collected at a range of 400 to 600 nm. Slit width for both, excitation and emission was kept constant at 5 nm. All readings were recorded at 25 ^{o}C. Reading were computed for the maximum value of wavelength, $\lambda_{em.\ max}$ = 535 nm. % RFU of the respective concentrations of the inhibitor peptide **12c** co-incubated with the differential states of $A\beta_{42}$ peptide (2mM) for 24 h. ANS dye incubated alone was considered as control and individual values were was calculated by normalizing the values to the dye control.

For studying the interaction of $A\beta_{42}$ with the neuronal membranes, GUV's were prepared with composition mimicking the rat neuronal myelin. Phospholipid solutions (25 mg/ml) obtained from Avanti Polar lipids, Sphingomyelin and cholesterol was obtained from Sigma. The composition of the lipids was used in the following proportion.[8]

Cell	PC	PE	PS	SM	Ste
Rat myelin (brain)	11	14	7	6	22

PC: phosphatidylcholine, PE: phosphatidylethanolamine, PS: phosphatidylserine, SM: sphingomyelin, Ste: sterols (mostly cholesterol)

Method of preparation was the protocol mentioned in the literature by Avanti Polar Lipids. All lipids were obtained at a concentration of 25 mg/mL in chloroform; sphingomyelin and cholesterol too were prepared of the same ratio in chloroform: methanol mixture of 1:1. Maintaining the desired ratios, all lipid solutions were taken in a 15 mL vial, vortexed to ensure proper mixing of all the components. This was dried over a stream of N_2 gas. Additional 2 mL of chloroform was added to the lipid mixture and revortexed to ensure complete solubilization. The mixture was completely freezed and the organic phase was evaporated under low vacuum, leaving a thin film on the walls of the vial. A day prior to the experiment, PBS pH 7.4 was added to the lipid cake in the vial and was kept standing for 30 mins. GUV's visible to the naked eye was seen forming and were collected using a pasteur pipette. Vesicles were stored at cool temperatures and care was taken not to freeze the samples. On the day of the experiment, 100 μL of the GUV solution was added to each microtube. Microtubes contained $A\beta_{42}$ alone and equimolar ratio of test peptides was added to the other respective microtubes. For control, only PBS was added to one of the microtubes as buffer blank as well as only vesicles were added as a vesicle blank, also equimolar concentrations of test peptides without $A\beta_{42}$ were also prepared to eliminate the readings obtained due to the presence of the hydrophobic peptides themselves. Samples prepared were incubated at 37 ^{o}C for 24 h. Before recording the reading, concentrated ANS stock solution was added to each of the wells, maintaining 50-fold molar excess of the ANS: $A\beta_{42}$ concentration. Readings obtained for PBS, vesicles and test peptides alone was subtracted from each of the respective readings and corrected $A\beta_{42}$ and $A\beta_{42}$ co-incubated along with the test peptides was utilized for comparative analysis.

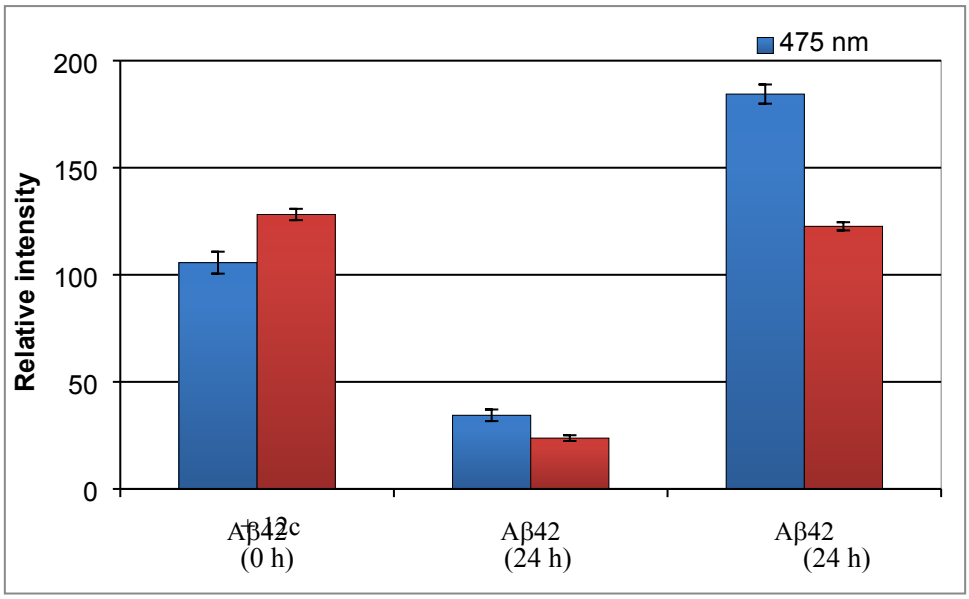


Figure S2. Bar graph representation showing the relative shifts of λmax from 525nm to 475 nm in the presence of test peptide 12c.

6. Tyrosine fluorescence studies

Phosphate buffered saline (PBS, pH 7.4) was purchased from Gibco (Life Technologies). All solutions were pre-sterilized using 0.2 µm syringe filters. Samples prepared were incubated in a rotary shaker incubator at 37 ^{o}C for 24 h. Measurements were performed on Cary Eclipse-Variance Spectrofluorometer: Scan - Cuvette reader. 5 µM Solution of $A\beta_{42}$ was prepared and analyzed for calibrated reading in the fluorescence of Tyr within the sequence of $A\beta_{42.}$ Since the relative fluorescence intensity obtained was greater than 10, 5 µM $A\beta_{42}$ was used as a standard concentration in the whole experiment. A 400 µL black bottom, magnetically stirred quartz cuvette was utilized for the recording the fluorescence spectra of the samples. Excitation wavelength was set at 260 nm and emission intensities were collected at a range of 270 to 440 nm. Slit width for both, excitation and emission was kept constant at 5 nm.

200 µM solution of Aβ in 10mM NaOH was further diluted in PBS to obtain a 10 µM solution of $A\beta_{42.}$ Similarly, 10 µM working solutions of test peptides were also prepared. 200 mL of each were mixed together to obtain a ratio of 1:1 and final concentration of 5 µM for both, the test peptide as well as $A\beta_{42.}$ For the control, $A\beta_{42}$ was incubated alone. Test samples were incubated at 37 ^{o}C for a period of 24 h. Readings were recorded by the optimized protocol. An average of three readings was taken as the final reading. Readings obtained for the test peptides incubated alone were subtracted from the readings obtained for $A\beta_{42}$

incubated with the test peptides. Corrected readings for $A\beta_{42}$ incubated with test peptides were used for comparison.

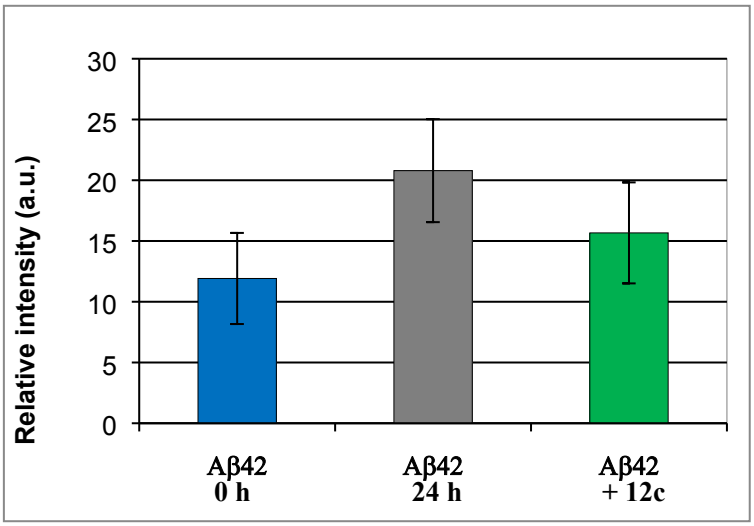


Figure S3. Intrinsic fluorescence of $A\beta_{42}$ during fibrillation. Comparative bar graph depicting relative fluorescence intensity ratio. Fluorescence of $A\beta_{42}$ monomer (*blue*), $A\beta_{42}$ incubated alone (*black*), $A\beta_{42}$ incubated along with the test peptides, **12c** (*green*). An average of three readings was taken as the final reading. Readings obtained for the test peptides incubated alone were subtracted from the readings obtained for $A\beta_{42}$ incubated with the test peptides. Corrected readings for $A\beta_{42}$ incubated with test peptides were used for comparison. All readings were recorded at pH 7.4.

7. Circular Dichroism

All readings were taken in PBS pH 7.4 and were all solutions were pre-sterilized using 0.2 μM filter. Samples were incubated at 37°C for 24 h. All measurements were performed on JASCO, J-815 spectrometer. The CD spectrometer was primarily calibrated with the freshly prepared (0.6% w/v) ammonium salt of (+)-camphor-10-sulfonic acid as a reference. A complimentary experiment was carried out to determine the aggregation pattern of both the type of amyloid-β, present in human brain i.e. $A\beta_{40}$ and $A\beta_{42}$ as well as the mixture of $A\beta_{40}$ and $A\beta_{42}$ in a specific ratio of 10:1.[12-15]

All samples were prepared by dissolving in phosphate buffer saline (pH 7.4). 20μM stock solutions of $A\beta_{42}$ and test peptides were prepared and were mixed in a ratio of 1:1 to get the desired concentration of 10 μM. Sample solutions were filtered through 0.2 μm filters, sonicated and incubated at 37 °C and subsequent readings were taken at time point intervals of 0 h and 24 h respectively. Phosphate buffer saline was considered as a blank reference. Studies were performed using a 300 μL, 1 mm quartz cell in the far-UV wavelength range of 180-350 nm at 37 °C. Data points were collected in 0.2 nm intervals at a speed of 50 nm per

minute, with a response time of 1 second and a band width of 2 nm. Triplicate scans were acquired to improve the signal-to-noise ratio. The final CD spectrum for a given sample was determined by subtracting the blank spectrum from that acquired for the sample. The CD spectra were smoothened by using the noise reducing option in the software (Smoothening factor: Binomial^99). The direct CD measurements (θ, in mdeg) were also converted to molar ellipticity, using [θ] = θ/(10•C•l), where C represents the molar concentration of the sample (mol/l) and l represents the path length. The molar ellipticity [θ] is in units, deg cm^2 $dmol^{-1}$. At least three scans were recorded for each run sample and data were averaged. Spectra were de-convoluted and the relative percentages of various forms of secondary structures were calculated using standard values based on standard Yang protocol[16] provided by the software.

Table S7. Predicted relative percentages of secondary structures.

Sample	Estimated Secondary structure (%)*				
	α-helix	β-sheet	Turn	Random	Total
$A\beta_{42}$_0 h	6.3	49.4	30.3	13.9	100.0
$A\beta_{42}$_24 h	17.0	66.4	11.6	5.0	100.0
$A\beta_{42}$ + 12c	12.4	0.0	46.6	41.0	100.0
$A\beta_{42}$ + 13a	1.2	74.6	18.9	5.3	100.0
12c	4.0	14.4	12.4	69.2	100.0
13a	3.7	46.4	33.1	16.8	100.0

*Values were predicted by the software by de-convoluting individual spectra, based on comparison with the Yang protocol[16] standard values.

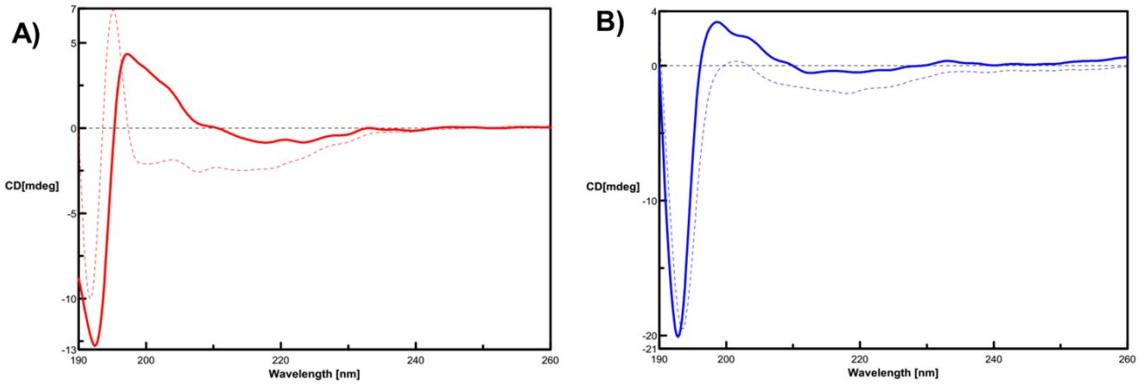


Figure S4. CD spectra depicting conformational changes of active peptides 12c (A) and inactive peptide 13a (B) incubated alone (bold lines) and in presence of $A\beta_{42}$ (dashed lines).

8. HRMS Analysis

ESI-MS experiments were carried out to identify the site(s) where the test peptide **12c** interact with $A\beta_{42}$.[17-19] All readings were taken in PBS pH 7.4 and were all solutions were pre-sterilized using 0.2μM filter. Samples were incubated at 37 ^{o}C for 24 h. The readings were recorded on a Bruker Maxis HRMS instrument. Pre-treated $A\beta_{42}$ in its monomeric state was utilized for the experiments. $A\beta_{42}$ was dissolved in 20 mM NaOH solution to get a desired concentration of 200μM. This was diluted in PBS to obtain a 20 μM solution of $A\beta_{42.}$ Similarly, 20 μM working solution of test peptide **12c** was prepared. 100mL of each were mixed together to obtain a ratio of 1:1 and final concentration of 10 μM for both, the test peptide as well as $A\beta_{42.}$ The experiments were carried out by co-incubating monomeric $A\beta_{42}$ with the test peptide **12c** at 37 °C in for 24 h. After incubation, just before recording the readings, the samples diluted with 100 μL MeOH and injected in the ESI source immediately, to observe the fragmentation and interaction patterns. The ESI-MS experiments were performed by using a Bruker Maxis HRMS operating in the positive ion mode and the focus mode was set to inactive. Sample solutions were injected into the ion source at a flow-rate of 5μl/min, using nitrogen as drying gas. The mass spectrometer operated with a capillary voltage of 4200 V and capillary temperature of 250 °C.

9. Electron Microscopy Studies

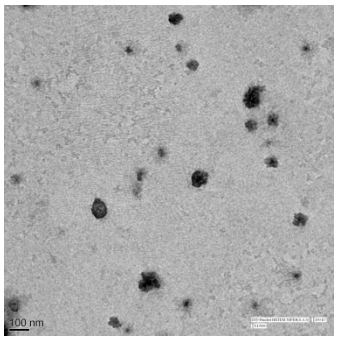
Uranyl acetate and glutaraldehyde (EM grade) were purchased from Sigma Aldrich chemicals, Saint Louis, MO, USA. Electron microscopy grids of copper (carbon coated, 200# mesh) were purchased from Electron Microscopy Sciences. High resolution transmission electron microscopy (TEM) images and scanning transmission electron microscopy (STEM) analysis, FEI Tecnai (G2 F20) operating at 120 keV was used. An aliquot of Aβ peptide was dissolved in 20 mM NaOH to make it 500 μM and then diluted in 10 mM sodium phosphate buffer (pH 7.4) to reach a concentration of 50 μM. The test peptides that were pre-dissolved in DMSO at 5 mM concentration stock were diluted in sodium phosphate buffer to a final concentration of 50 μM. 25 μL of Aβ was mixed with 25 μL of test peptides so as to arrive at a concentration ratio of 1:1 ($A\beta_{42}$: test peptides). The solution was mixed well and incubated at 37 °C for 72 h. One drop of sample was placed on a copper coated glow discharged grid, blotted by a filter paper and was allowed to air dry. The sample was fixed on the grid by applying equal volume of 0.5% of glutaraldehyde solution by droplet procedure 3-5 times.

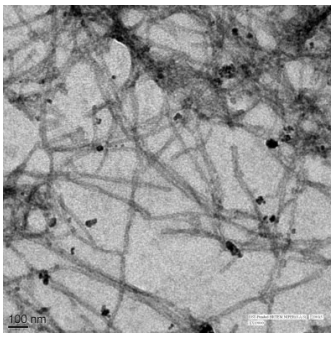
The grid was washed with ultrapure water (3-5 μL) three times by single droplet method. Grids were negatively stained by 2% uranyl acetate. The sample was air dried for 20-30 mins. Excess liquid was wicked away at every step using filter paper carefully through the grid edges, without letting the grid dry. At last, the grid was examined under the electron microscope. $A\beta_{42}$ alone plus the buffers in similar ratios and concentrations was used as a control. A representative examination of Aβ fibril formation/inhibition and image capturing for all the samples was made at several positions (>10) across each EM grid, for the classification of fibril/aggregate/particle density and morphology, and to avoid inadvertent production of a biased/subjective data selection. Best images have been provided in the article, remaining captured images have been provided in the supplementary information.

9.1. Additional Images

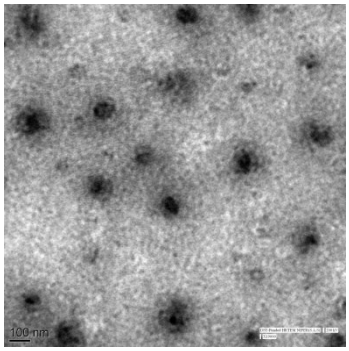
Figure S5. Images on the left (L) show a scale bar of 100 nm and on the right (R) show a scale bar of 0.2 nm respectively.

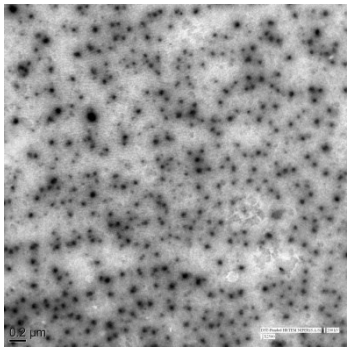
a. $A\beta_{42}$ at 0 h **b. $A\beta_{42}$ incubated alone for 24 h**



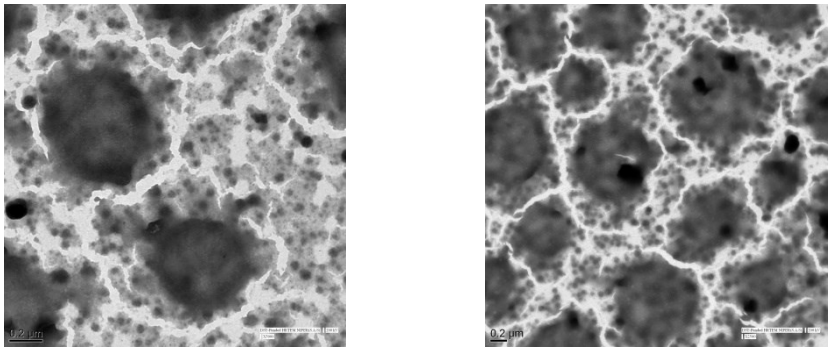


c. $A\beta_{42}$ incubated with test peptide 12c for 24 h

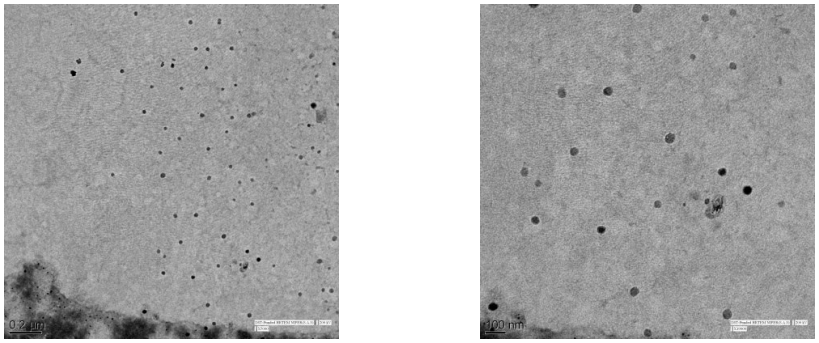




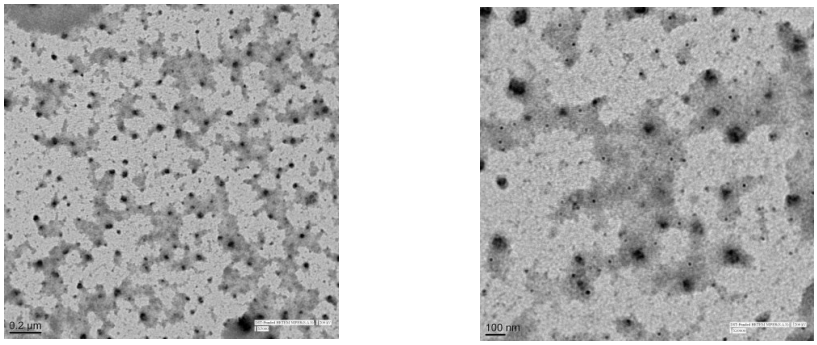
d. $A\beta_{42}$ incubated with test peptide 13a for 24 h



e. Test peptide 12c incubated alone for 24 h



f. Test peptide 13a incubated alone for 24 h



10. Cytotoxicity studies

Test peptides were tested upto a highest tested concentration of 20 μM upon rat pheochromocytoma (PC-12) cells. Similar protocol as mentioned in the MTT Cell Viability Assay was used. (Section 4.1) Peptides were tested for cytotoxicity in PC-12 cells using MTT assay at a concentration of 20 μM. The cells in their exponential growth phase were seeded in 96 well plates, at the rate of 17000 cells per well per 90 μL and incubated overnight. Next morning, the inhibitor peptides (10 μL of 200 μM stock solution in PBS) was added to make their final nominal concentration of 20 μM. The plates were incubated for 6 h. Cell samples without the test peptides with DMSO in the same concentration as in the test wells were taken as control. After 6 h, 20 μL of MTT (5 mg/mL in PBS) was added and incubated further for 4

h. The plate was centrifuged at 4 °C for 10 min. Supernatant was carefully removed from the wells, and DMSO (200 µL, per well) was added. The resulting suspension was mixed well and OD_{570} was measured using a microtiter plate reader. Each experiment was done in triplicates (n= 3). The percentage of MTT cellular reduction in the presence of inhibitors was determined by comparing the OD_{570} of each test sample to the OD_{570} of the cells alone in control sample. Blank ODs were subtracted from each sample OD and the triplicate sample ODs were averaged. ODs of samples with untreated cells were set to 100%.

11. BBB Permeation Assay

All samples were prepared in PBS pH 7.4 and all solutions were pre-sterilized using 0.2 µm filter. Samples were incubated in a thermostat incubator at 37 ^{o}C for 24 h. PAMPA-BBB assay in vitro was carried out according to reported literature protocols.[40-42] Briefly, the test peptides were dissolved in DMSO (5 mM stock solutions) which was diluted in PBS (pH 8.0) to make secondary stock solutions (100 µM). After the required pre-treatment, the filter membrane (hydrophobic PVDF) on the 96-well filtration plate was coated with 6 µL of PBL solution in cyclohexane (20 mg/mL) in each well. The donor well was filled with 250 µL of the secondary stock solution and the acceptor plate which was prefilled with equal volumes of blank receiving solution. After 6 h at 25 °C, the absorbance of solutions in the acceptor wells was determined by a multiwavelength UV plate reader. P_e was calculated according to the formula: $P_e = -V_dV_a/[(V_d + V_a)S_t] \ln(1 - A_a/A_e)$, where V_d and V_a are the mean volumes of the donor and acceptor solutions, S is the surface area of the artificial membrane, t is the incubation time, and A_a and A_e are the UV absorbance of the acceptor well and the theoretical equilibrium absorbance, respectively. Data was recorded for triplicate samples in three individual experiments and the readings were averaged (<5% variation).

12. Trypsin Digestion Assay

All samples were prepared in PBS pH 7.4 and all solutions were pre-sterilized using 0.2 µm filter. 2 mM stock concentration of trypsin was used. 20 µM working solution of test peptide was prepared. 200 mL of each were mixed together to obtain a concentration ratio of 1:100 of the test peptide : trypsin. Samples were incubated in a rotary shaker incubator at 37 ^{o}C for 24 h, shaking speed was kept constant at 200 rpm. Peptide stability was measured by analysing its AUC at the respective retention time, using Shimadzu Analytical C-18 RP-HPLC system. Samples were prepared using HPLC grade MeOH (Concentration: 1mg/mL). Solvent system:

A. 0.008% TFA in MeCN; **B**. 0.008% TFA in H_2O. Program: Phase **B** concentration: 95-5-95%, 30 min, gradient flow system.

13. Serum stability studies

All readings were taken in PBS pH 7.4 and all solutions were pre-sterilized using 0.2 µm filter. Fetal bovine serum (FBS) was obtained from Hi-media Laboratories and was used without any purification. Since, the composition of various components in FBS is proportional to that of the human serum, thus FBS was used in this experiment. Samples were incubated in a rotary shaker incubator at 37 ^{o}C for 24 h, shaking speed was kept constant at 200 rpm. Peptide stability was measured by analysing using Analytical C-18 RP-HPLC as in Trypsin stability studies. Samples were also further analysed by LCQ analysis. Mass spectrums were further analysed by ACD Mass Fragmenter tool.

The extrapolated data helped us to determine the degradation rate of the peptide in serum.[20,21]

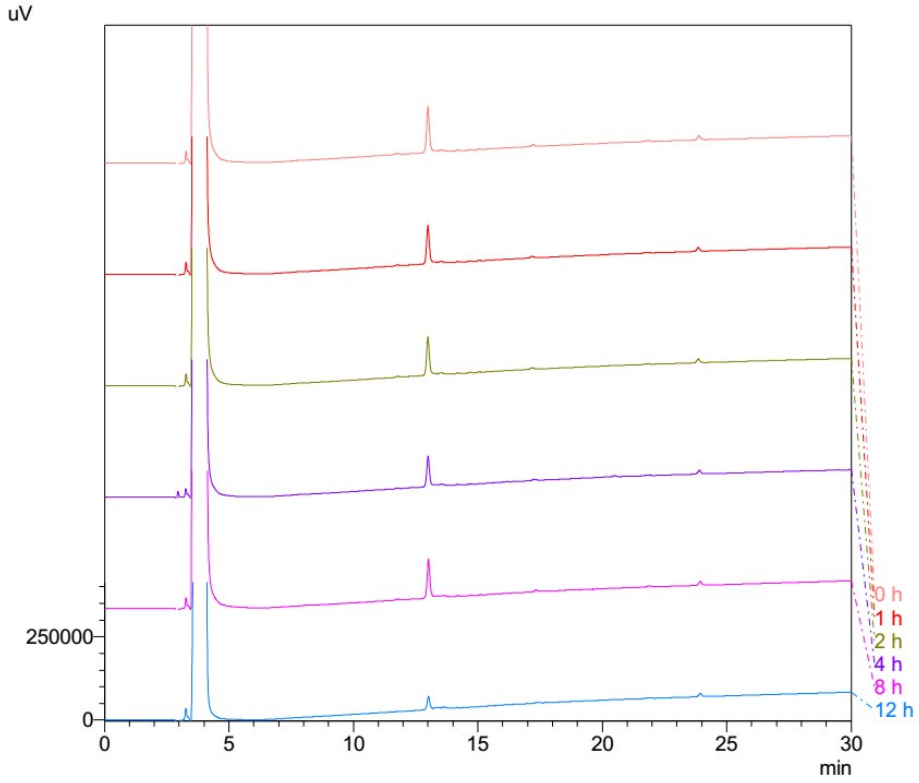


Figure S6. Superimposed HPLC chromatograms of most active peptide 12c at time intervals of 0, 2, 4, 8, 12 h after serum treatment.

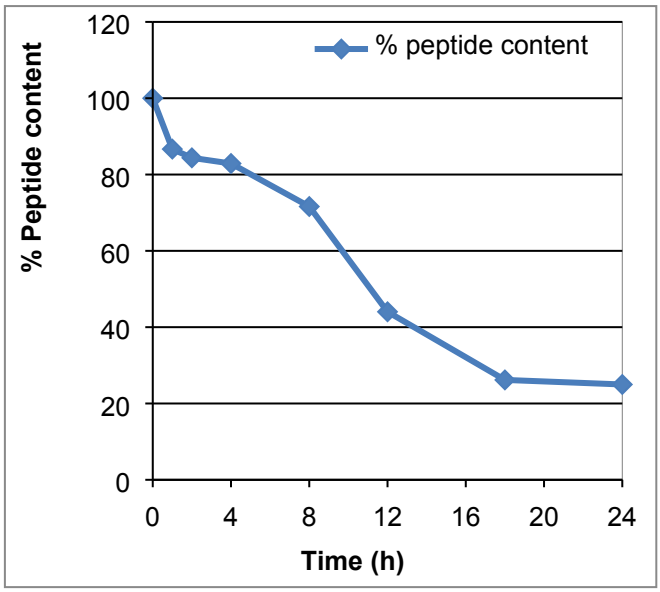


Figure S7. Graphical representation showing time dependent decrement in % content of peptide 12c.

Based on the above calculations we were able to determine the half-life ($t_{1/2}$) of the peptide in serum. The calculated % degradation for both the peptides have been summarized in table **S7**.

Table S8. Calculated % degradation time for peptide 12c.

Peptide **12c**	**Time (h)**
t_{25}	5.4
t_{50}	13.2
t_{75}	21.0
t_{90}	25.7

*t_x ,where x = % degradation. % Peptide degradation time is calculated by back extrapolating the values in the equation generated by the above trendline series for the individual peptides **12c** (y = -3.2003x + 92.247), where x = time in hours and y = % of degraded peptide.

14. Computational Studies

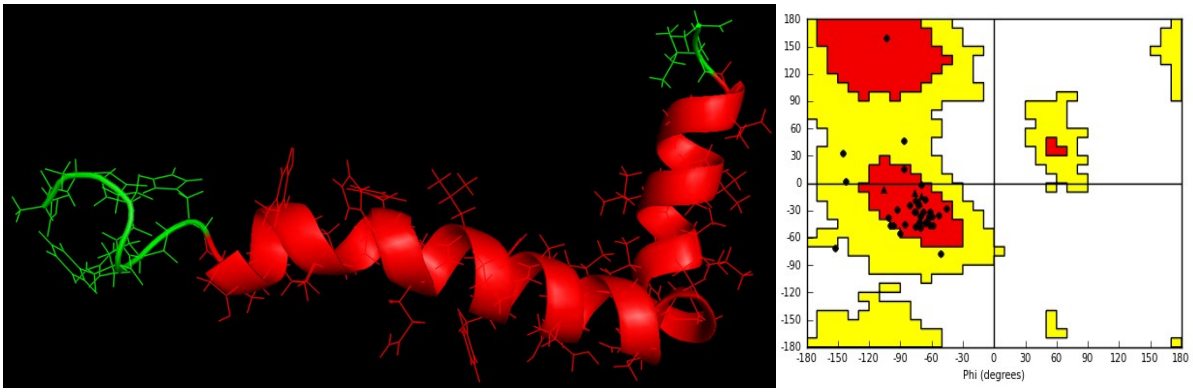


Figure S8. Solution state NMR structure of monomeric of amyloid-β_{42} PDB Id: **1IYT-10.** Indicated by secondary structure (*left*), α-helix regions represented by red spirals and random coiling shown in green; along with its Ramchandran plot (*right*). Structure reported by Crescenzi, O. *et. al.* (2002). Image saved from Pymol interface.

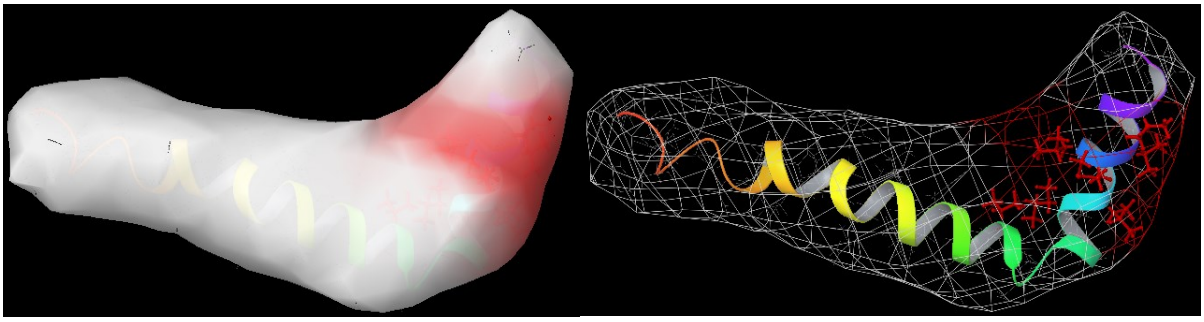


Figure S9. Predicted aggregation prone sites (A) and reactive residues (B) for 1IYT-10. Red to white representing most to least aggregating surfaces. Residues highlighted in red sticks, amino acid backbones not shown for ease of visualisation. Image saved from Maestro interface.

Table S9. Docking and glide scores along with literature ligand protein interaction energies.

igand	Docking score	Glide gscore	Glide emodel	Glide energy	Glu_{11}	Gln_{15}	Phe_{19}	Phe_{20}	Glu_{22}	Asp_{23}	Val_{24}	Ala_{31}
Thioflavin*												
MSB	-4.513	-4.513	-44.670	-31.062	15.907	-1.317	-0.592	-6.086	21.299	21.925	-4.219	-0.911
MPY*												
imetamol	-4.478	-4.495	-28.149	-22.946	-0.211	-0.042	-0.274	-3.508	-0.574	-10.628	-2.215	-4.486
Florbetapir*												
Florbetaben*												
KLVFF	-6.771	-6.943	-75.902	-48.878	-11.728	-1.885	-5.379	-4.582	-36.530	-102.01	-3.862	-6.123
EN-606	-7.124	-7.208	-71.064	-52.644	-8.250	-3.955	-6.371	-7.917	-22.583	-86.796	-2.446	-6.078
EN-304	-6.211	-6.353	-63.741	-45.598	-7.508	-1.784	-10.580	-4.891	-72.152	-52.299	-0.457	0.506
I-1019	-6.291	-6.380	-66.953	-47.156	-10.465	-2.214	-10.713	-6.831	-32.854	-95.118	-1.414	-1.413
rp-Aib	-4.894	-5.165	-38.497	-28.482	3.381	-4.956	-11.881	-3.617	-6.923	-49.569	-0.620	0.190
PFFD	-5.200	-5.325	-58.176	-43.858	11.579	-3.240	-3.249	-6.258	-32.747	9.279	-1.451	0.060
PFFD*a*	-6.264	-6.389	-62.513	-49.046	-2.875	-3.830	-12.864	-6.087	-23.148	-52.698	-0.641	-0.624
LPFFD*a*	-4.924	-4.924	-48.343	-41.458	13.985	-7.309	-10.838	-8.120	10.734	-8.967	-2.255	-3.461
LMVG*a*	-6.950	-7.083	-83.377	-53.866	-8.161	-2.678	-10.983	-9.498	-52.568	-85.197	-1.327	-0.101
-Aib-IA	-5.378	-5.555	-56.682	-39.321	5.471	-6.455	-15.682	-4.875	-54.200	-23.310	-0.560	0.281
GVIA	-5.721	-5.903	-53.161	-37.092	4.025	-8.421	-6.715	-6.031	-6.659	-50.367	-1.117	-1.308
FVIA	-5.253	-5.443	-59.919	-41.181	5.990	-7.125	-15.894	-5.904	-46.334	-26.991	-0.680	0.280
VVIA	-5.769	-5.828	-57.482	-43.075	5.607	-7.423	-17.146	-5.739	-51.857	-28.561	-0.539	0.264

Amino acid residues of the protein mentioned using three letter abbreviations respectively. Subscript numbering refers to sequential position on the amyloid 1-42. *No docking was observed.

Table S10. Docking and Glide scores for synthesized tetrapeptides (1IYT-10).

Code	Molecule	DS	GS	EMod
11a	Val-Val-Ile-Ala-NH_2	-5.875	-6.004	-52.839
12a	**D-Val**-Val-Ile-Ala-NH_2	-5.746	-5.875	-57.516
12b	**Phe**-Val-Ile-Ala-NH_2	-5.733	-6.003	-58.079
12c	**D-Phe**-Val-Ile-Ala-NH_2	-5.636	-5.906	-62.112
12d	**D-Pro**-Val-Ile-Ala-NH_2	-5.501	-5.56	-57.27
12e	**Nva**-Val-Ile-Ala-NH_2	-5.969	-5.932	-58.199
12f	**Aib**-Val-Ile-Ala-NH_2	-6.012	-6.189	-56.26
12g	**Gly**-Val-Ile-Ala-NH_2	-5.969	-6.145	-55.742
13a	Val-**D-Val**-Ile-Ala-NH_2	-5.001	-6.053	-61.171
13b	Val-**D-Ile**-Ile-Ala-NH_2	-5.524	-5.653	-52.35
13c	Val-**Pro**-Ile-Ala-NH_2	-5.799	-5.126	-45.56
13d	Val-**Aib**-Ile-Ala-NH_2	-5.187	-5.824	-50.597
13e	Val-**Phe**-Ile-Ala-NH_2	-5.691	-5.938	-62.277
13f	Val-**D-Phe**-Ile-Ala-NH_2	-5.516	-5.645	-50.264
14a	Val-Val-**D-Ile**-Ala-NH_2	-5.754	-5.882	-62.413
14b	Val-Val-**Leu**-Ala-NH_2	-5.493	-5.621	-59.234
15a	Val-Val-Ile-**D-Ala**-NH_2	-6.002	-6.13	-55.704
15b	Val-Val-Ile-**Aib**-NH_2	-5.957	-6.086	-58.582
15c	Val-Val-Ile-**Gly**-NH_2	-6.122	-6.25	-56.294
15d	Val-Val-Ile-**Val**-NH_2	-5.733	-5.862	-58.454
15e	Val-Val-Ile-**Leu**- NH_2	-5.978	-6.107	-62.475
15f	Val-Val-Ile-**Ile**-NH_2	-5.754	-5.882	-62.413
16a	**Pro-Pro**-Ile-Ala-NH_2	-5.787	-5.245	-51.98

Table S11. Interaction energies exhibited by test peptides with specified residues of the monomeric $A\beta_{42}$.

Molecule	Glu_{11}	Gln_{15}	Phe_{19}	Phe_{20}	Ala_{21}	Glu_{22}	Asp_{23}	Val_{24}
11a	-10.064	-1.774	-4.865	-6.916	-0.249	-19.061	-95.739	-1.41
12a	-7.827	-1.306	-10.874	-7.597	-0.672	-16.602	-87.464	-1.031
12b	-8.931	-1.697	-12.427	-4.123	-0.171	-30.788	-91.139	-0.394
12c	-9.334	-2.228	-11.777	-6.069	-0.187	-29.06	-90.815	-0.67
12d	-7.588	-1.398	-12.271	-5.951	-0.74	-32.973	-87.158	-1.149
12e	-10.004	-2.724	-13.338	-6.407	0.209	-26.048	-88.29	-0.359
12f	-9.598	-1.42	-6.56	-5.731	-0.364	-19.811	-96.581	0.204
12g	-9.64	-1.444	-5.91	-6.03	-0.355	-19.4	-96.276	-1.146
13a	-8.543	-1.797	-12.628	-6.006	-0.446	-35.565	-90.838	-0.666
13b	-10.193	-2.588	-5.647	-8.068	-0.266	-18.66	-93.473	-1.363
13c	-10.141	-2.849	-11.068	-6.23	0.123	-25.247	-80.465	-0.549
13d	-9.658	-1.312	-6.062	-4.91	-0.269	-21.707	-95.235	-0.888
13e	-9.522	-2.025	-6.565	-6.691	-0.353	-22.043	-97.889	-1.179
13f	-9.137	-1.428	-4.985	-7.703	-0.314	-19.53	-83.462	-1.551
14a	-8.453	-1.787	-11.548	-6.006	-0.446	-35.565	-90.809	-0.562
14b	-7.56	-1.545	-11.509	-5.437	-0.652	-53.348	-72.235	-0.596
15a	-9.529	-1.39	-5.996	-5.893	-0.403	-19.325	-97.075	-1.15
15b	-9.632	-1.489	-7.303	-4.644	-0.36	-20.104	-96.458	-0.336
15c	-9.708	-1.977	-7.926	-5.538	-0.321	-20.248	-94.566	-0.655
15d	-10.065	-2.518	-12.083	-6.498	0.159	-25.058	-89.677	-0.801
15e	-9.961	-2.576	-10.759	-7.272	0.106	-26.151	-90.059	-1.333
15f	-9.863	-2.645	-13.07	-6.705	0.182	-27.512	-90.809	-0.562
16a	-7.63	-1.573	-11.348	-5.759	-0.662	-37.657	-79.664	-0.891

Amino acid residues of the protein mentioned using numbers referring to sequential position on the amyloid 1-42.

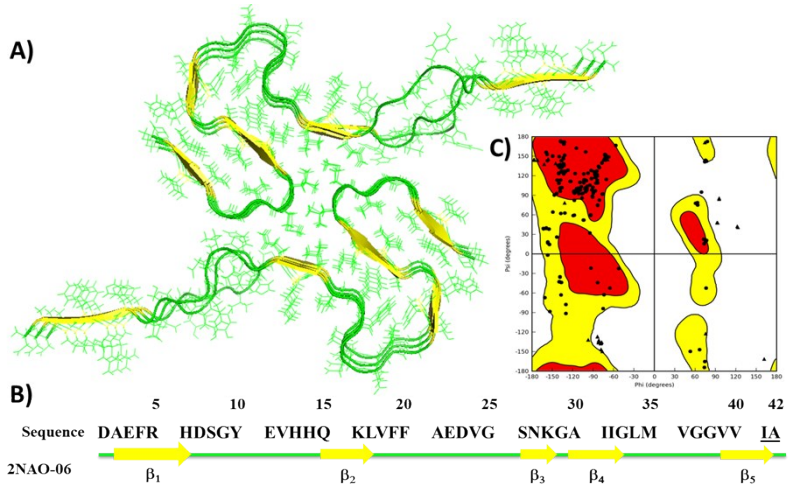


Figure S10. (A) 3D structure of 2NAO-06 and (B) Conformation of the Aβ sequence highlighting the five indicated β-sheet regions (*yellow arrows*) and remaining random coiled residues (*green*). Image saved from Pymol interface. (C) Ramchandran plot for 2NAO-06. predicted using Protein Preparation wizard suite. Image saved from Maestro interface.

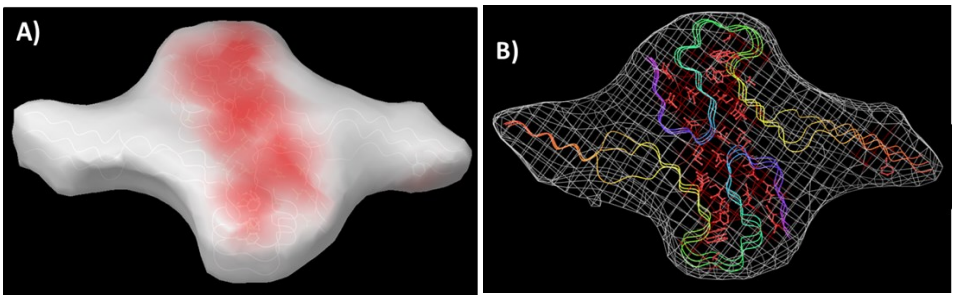


Figure S11. (A) Aggregation prone region and (B) reactive residues for 2NAO-06. Red to white representing most to least aggregating surface. Residues highlighted in red sticks, amino acid backbones not shown for ease of visualisation. Image saved from Maestro interface.

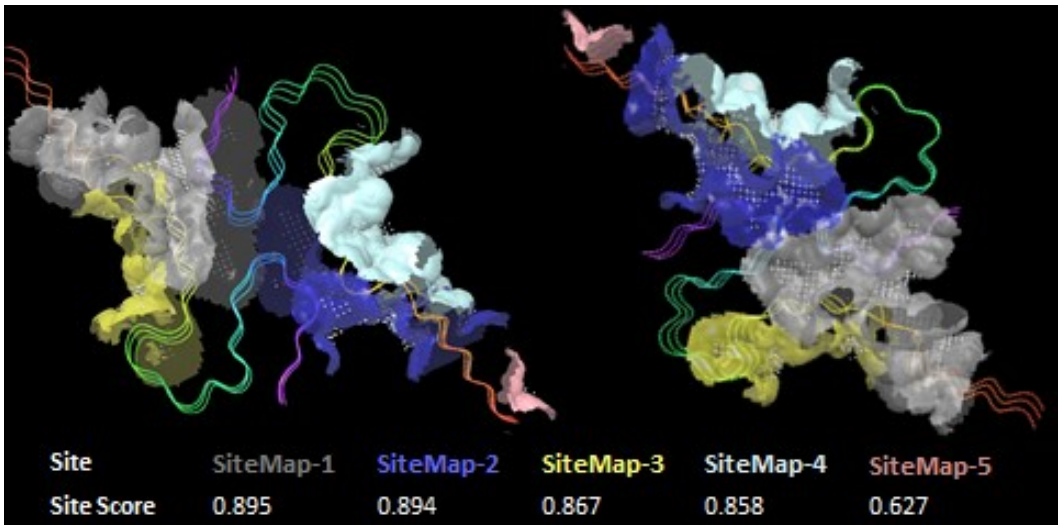


Figure S12. Ligand binding sites for 2NAO predicted by SiteMap feature. Predicted sites indicated with different colours, Site scores also indicated. Image processed and saved from Maestro interface.

Table S12. Docking and Glide scores for all standard molecules from the literature for Site Map-2.

Type	Compound	*DS*	*GS*	Glide emodel	Glide energy
Diagnostic agents	ThioflavinT	-4.21	-4.21	-35.148	-26.232
	IMSB	-4.318	-4.318	-46.867	-38.523
	IMPY	-4.445	-4.461	-35.219	-28.244
	Flutimetamol	-5.022	-5.04	-40.700	-30.744
	Florbetapir	-4.402	-4.402	-40.697	-36.064
	Florbetaben	-4.555	-4.555	-43.216	-35.878
Amyloid aggregation Inhibitors					
Type	**Compound**	***DS***	***GS***	**Glide emodel**	**Glide energy**
Peptidomimetic	KLVFF	-8.332	-8.504	-112.13	-66.398
	SEN-606	-7.85	-7.934	-88.451	-58.576
	SEN-304	-7.923	-8.065	-94.088	-64.362
	PPI-1019	-6.946	-7.035	-84.079	-59.208
	Trp-Aib	-5.376	-5.97	-48.522	-34.622
	LPFFD	-6.481	-6.606	-83.182	-49.749
	LPFFD*a*	-8.003	-8.128	-89.552	-56.327
	Ac-LPFFD*a*	-7.193	-7.193	-71.945	-54.128
	IGLMVG*a*	-7.439	-7.572	-92.786	-61.581
	GV-Aib-IA	-6.36	-6.537	-71.108	-50.018
	GGVIA	-6.693	-6.875	-81.716	-53.997
	GFVIA	-6.351	-6.541	-79.957	-55.855
	PVVIA	-5.592	-5.651	-69.046	-50.893

DS, Docking scores; GS, Glide Scores. Lowercase '*a*' represents amidated C-terminus.

Table S13. Ligand-protein residues interaction energies for Site Map-2.

Ligand	A_Ser$_8$	A_Glu$_{11}$	A_His$_{13}$	A_His$_{14}$	A_Gln$_{15}$	A_Lys$_{16}$	D_Met'$_{35}$	D_Val'$_{36}$
ThioflavinT	-0.835	-30.227	-4.603	-5.035	-3.829	11.401	-1.792	-1.909
IMSB	0.636	26.079	-3.505	-1.757	-6.723	-22.014	-5.358	-1.011
IMPY	-0.004	-0.459	-2.398	-3.008	-5.014	-0.780	-4.647	-1.393
Flutimetamol	-1.922	-0.178	-0.048	0.116	-0.076	0.459	-0.019	-0.020
Florbetapir	0.043	1.438	-2.830	-2.455	-4.243	-2.316	-1.853	-2.019
Florbetaben	-0.116	-4.430	-5.317	-4.085	-4.560	-2.643	-2.094	-0.995
KLVFF	-6.692	-57.262	-7.088	-1.827	-6.243	9.765	-12.465	-6.705
SEN-606	-4.323	-53.797	-4.882	-2.826	-0.468	9.510	0.009	-0.574
SEN-304	-5.370	-25.888	-3.725	-2.473	-0.582	9.788	-0.223	-0.241
PPI-1019	-2.759	-26.442	-4.342	-2.164	-2.662	9.432	-5.148	-8.511
Trp-Aib	0.136	11.492	-3.386	-2.690	-6.512	-9.765	-13.629	-5.720
LPFFD	-1.049	3.208	-0.071	-2.769	1.214	-81.758	0.516	0.076
LPFFD*a*	0.009	-44.090	-9.112	-4.232	-4.681	2.299	-6.377	-8.447
Ac-LPFFD*a*	-2.340	-1.117	-2.188	-2.486	-0.380	-6.666	0.134	-0.176
IGLMVG*a*	-4.844	-34.953	-1.594	-1.227	-0.535	9.375	-0.365	0.021
GV-Aib-IA	-5.816	-10.782	-9.674	-2.567	-3.596	-0.788	-3.084	2.721
GGVIA	-1.945	9.081	-6.711	-0.662	1.231	-4.993	0.073	0.542
GFVIA	-2.117	10.227	-4.148	-2.702	1.160	-3.568	-0.067	0.917
PVVIA	-1.568	5.837	-2.365	-0.524	1.946	-3.303	0.266	1.101

Amino acid residues of the protein mentioned using three letter abbreviations respectively, indicated by their respective chain. D_Met'35 and D_Val'36 refer to amino acid residues on the neighbouring unit i.e. chain D. Subscript numbering refers to sequential position on the amyloid 1-42.

Table S14. Docking, Glide and interaction energy scores for synthesized tetrapeptides.[a]

Molecule	DS	GS	glide emodel	glide energy	A_Lys$_{16}$	A-_Glu$_{11}$	A_Gly$_9$	A_Ser$_8$	D_Val'$_{39}$	D_Gly'$_{38}$
11a	-6.658	-6.787	-68.285	-49.558	10.173	-10.476	-1.636	-3.750	-0.182	-4.410
12a	-6.175	-6.304	-66.746	-48.816	10.273	-10.451	-1.718	-3.934	-0.188	-2.831
12b	-6.745	-7.015	-77.651	-53.742	10.114	-10.496	-1.505	-3.639	-0.184	-2.539
12c	-6.855	-7.125	-77.171	-54.526	10.503	-29.883	-0.726	-7.031	-0.221	-1.805
12d	-6.289	-6.349	-63.722	-47.498	9.968	-10.361	-2.014	-3.445	-0.181	-2.653
12e	-6.463	-6.608	-67.071	-49.412	10.171	-10.527	-1.517	-3.515	-0.189	-2.683
12f	-6.399	-6.576	-63.663	-47.766	10.495	-10.933	-1.604	-3.981	-0.206	-2.359
12g	-6.236	-6.412	-64.008	-46.185	10.124	-10.442	-1.796	-3.821	-0.181	-2.762
13a	-6.015	-6.144	-66.011	-47.207	9.729	-9.237	-2.307	-7.812	-0.088	0.276
13b	-5.870	-5.999	-54.698	-41.452	9.836	-63.388	0.577	-3.476	-0.306	0.859
13c	-5.574	-5.699	-59.081	-46.133	8.140	-18.368	0.335	-0.482	-0.618	-3.857
13d	-6.072	-6.205	-61.229	-44.340	10.337	-30.138	1.462	-2.486	-0.401	1.606
13e	-6.379	-6.518	-69.979	-49.960	9.184	-19.015	-0.226	-8.580	-0.332	-0.369
13f	-6.650	-6.779	-75.076	-51.205	9.614	-8.418	-0.561	-1.592	-0.321	-2.431
14a	-6.289	-6.205	-69.222	-46.185	9.729	-10.527	-0.079	-3.920	0.577	-3.476
14b	-6.417	-6.545	-67.239	-48.089	10.083	-10.278	-1.726	-4.021	-0.198	-2.668
15a	-6.685	-6.813	-71.031	-50.708	10.346	-10.688	-1.378	-3.985	-0.201	-2.402
15b	-6.463	-6.591	-67.629	-48.744	10.079	-10.487	-1.780	-3.638	-0.182	-2.792
15c	-6.698	-6.827	-71.519	-50.364	10.304	-10.537	-1.227	-3.920	-0.191	-2.471
15d	-6.606	-6.734	-69.222	-49.692	10.216	-11.190	-1.700	-3.912	-0.156	-2.331
15e	-6.564	-6.693	-69.347	-49.459	10.257	-10.919	-0.687	-2.602	-0.143	-1.554
15f	-6.473	-6.602	-71.331	-51.148	10.116	-11.390	-1.539	-3.794	-0.157	-2.385
16a	-5.720	-5.778	-57.418	-43.495	9.938	-17.842	-0.079	-8.539	-0.332	2.887

[a]Scores are mentioned for SiteMap-2.

15.References

1) Sabatino, G. and Papini, A.M., 2008. Advances in automatic, manual and microwave-assisted solid-phase peptide synthesis. *Curr. Opin. Drug Discov. Devel*. **2008**, *11*, 762-770.
2) Fields, G. B.; Noble, R. L. Solid phase peptide synthesis utilizing 9-fluorenylmethoxycarbonyl amino acids. *Int. J. Pep. Protein Res.* **1990**, *35*, 161-214.
3) Kaiser, E., Colescott, R.L., Bossinger, C.D. and Cook, P.I. Color test for detection of free terminal amino groups in the solid-phase synthesis of peptides. *Anal. Biochem.***1970**, *34*, 595-598.
4) Boas, U. and Mirsharghi, S. Color test for selective detection of secondary amines on resin and in solution. *Org. Lett.* **2014**, *16*, 5918-5921.
5) Zagorski, M. G., Yang, J., Shao, H., Ma, K., Zeng, H., and Hong, A. Methodological and chemical factors affecting amyloid-β peptide amyloidogenicity. *Methods Enzymol.* **1999**, *309*, 189−204.
6) Bansal, S.; Maurya, I.K.; Yadav, N.; Thota, C.K.; Kumar, V.; Tikoo, K.; Chauhan, V.S.; Jain R. C-Terminal Fragment, Aβ32–37, Analogues Protect Against Aβ Aggregation-Induced Toxicity *ACS Chem. Neurosci.* **2016**, *7*, 615-623.
7) Bansal, S., Maurya, I.K., Shenmar, K., Yadav, N., Thota, C.K., Kumar, V., Tikoo, K., Chauhan, V.S. and Jain, R. Aβ 1–42 C-terminus fragment derived peptides prevent the self-assembly of the parent peptide. *RSC Adv.***2017***, 7*, 4167-4173.
8) Warschawski, D.E., Arnold, A.A., Beaugrand, M., Gravel, A., Chartrand, É. and Marcotte, I. Choosing membrane mimetics for NMR structural studies of transmembrane proteins. *Biochim. Biophys. Acta-Biomembranes.* **2011**, *1808*, 1957-1974.
9) Lindgren, M., Sörgjerd, K. and Hammarström, P. Detection and characterization of aggregates, prefibrillar amyloidogenic oligomers, and protofibrils using fluorescence spectroscopy. *Biophys. J.* **2005**, *88*, 4200-4212.
10) Eftink, M.R. Fluorescence techniques for studying protein structure. *Methods of Biochemical Analysis: Protein Structure Determination.* **2006***, 35*, 127-205.
11) Munishkina, L.A. and Fink, A.L. Fluorescence as a method to reveal structures and membrane-interactions of amyloidogenic proteins. *Biochim. Biophys. Acta-Biomembranes.* **2007**, *1768*, 1862-1885.
12) Simmons, L.K., May, P.C., Tomaselli, K.J., Rydel, R.E., Fuson, K.S., Brigham, E.F., Wright, S., Lieberburg, I., Becker, G.W. and Brems, D.N. Secondary structure of amyloid beta peptide correlates with neurotoxic activity in vitro. *Mol. Pharmacol.*, **1994**, *45*, 373-379.
13) Bitan, G., Fradinger, E.A., Spring, S.M. and Teplow, D.B. Neurotoxic protein oligomers—what you see is not always what you get. *Amyloid* **2005**, *12*, 88-95.

14) Rahimi, F., Maiti, P. and Bitan, G. Photo-induced cross-linking of unmodified proteins (PICUP) applied to amyloidogenic peptides. *JoVE (Journal of Visualized Experiments)* **2009**, *23*, e1071-e1071.

15) Bitan, G., Kirkitadze, M.D., Lomakin, A., Vollers, S.S., Benedek, G.B. and Teplow, D.B. Amyloid β-protein (Aβ) assembly: Aβ40 and Aβ42 oligomerize through distinct pathways. *Proc. Nat. Acad. Sci.* **2003**, *100*, 330-335.

16) Yang, Jen Tsi, Chuen-Shang C. Wu, and Hugo M. Martinez. Calculation of protein conformation from circular dichroism. *Method Enzymol*. **1986**, *130*, 208-269.

17) Parhi, A.K., Kung, M.P., Ploessl, K. and Kung, H.F. Synthesis of fluorescent probes based on stilbenes and diphenylacetylenes targeting β-amyloid plaques. *Tetrahedron Lett.* **2008**, *49*, 3395-3399.

18) Bernstein, S.L., Dupuis, N.F., Lazo, N.D., Wyttenbach, T., Condron, M.M., Bitan, G., Teplow, D.B., Shea, J.E., Ruotolo, B.T., Robinson, C.V. and Bowers, M.T. Amyloid-β protein oligomerization and the importance of tetramers and dodecamers in the aetiology of Alzheimer's disease. *Nat. Chem.* **2009**, *1*, 326-331.

19) Sakono, M. and Zako, T. Amyloid oligomers: formation and toxicity of Aβ oligomers. *FEBS J.* **2010**, *277*, 1348-1358.

20) Adessi, C., Frossard, M.J., Boissard, C., Fraga, S., Bieler, S., Ruckle, T., Vilbois, F., Robinson, S.M., Mutter, M., Banks, W.A. and Soto, C. Pharmacological profiles of peptide drug candidates for the treatment of Alzheimer's disease. *J. Biol. Chem.* **2003**, *278*, 13905-13911.

21) Chiang, H.L. and Dice, J.F. Peptide sequences that target proteins for enhanced degradation during serum withdrawal. *J. Biol. Chem.* **1988**, *263*, 6797-6805.