Alzheimer’s disease (AD), first reported by Alois Alzheimer in 1906, is manifested by the abnormal misfolding of proteins, amyloid-β (Aβ) and tau. An alarming number of patients, 44 million currently and set to triple by 2050, would create challenges for society on medical and economical fronts. 

Despite the current focus on the etiology of AD, deposition of neuritic plaques due to the misfolding of proteins, deposition of amyloid β (Aβ) fibrils and tau aggregation regulators currently being investigated.

Acetylcholinesterase inhibitors such as tacrine, donepezil, rivastigmine and galantamine, and N-methyl-D-aspartate (NMDA)-receptor antagonist memantine were among the first drugs approved by FDA, however none could prevent or reverse the disease progression. 

However, out from more than two hundred molecules tested in the clinical trials from 2002–12, only one (memantine) is approved as a drug in 2003. Also, the therapeutics that are currently being tested in clinical trials, don’t offer much hope. Due to low efficacy or side effects, a large number of promising candidates couldn’t proceed beyond phase II, and very few progressed to the phase III clinical trials.

Aβ is known to play positive modulatory role in memory and neurotransmission, hence, the inhibition of Aβ aggregation, is currently being investigated. 

A number of studies have shown that modified fragments of Aβ inhibit the aggregation of parent peptide specifically. 

PPI-1019, a modified pentapeptide derivative of fragment Aβ17–21, has been tested up to phase II clinical trials. Similarly, N-methylated pentapeptide, SEN-606 has reached in pre-clinical developmental phases. 

Since hydrophobic interactions are known to play a significant role in protein misfolding, and considering the importance of the peptide fragments in their specific binding with the main peptide chain, a number of Aβ aggregation inhibitors derived from the hydrophobic C-terminus of Aβ were reported. Fragments Aβ31–42 and Aβ39–42 were found to inhibit Aβ aggregation significantly. 

In a study, poly-N-methylated hexapeptides based on Aβ32–37 were reported as efficient inhibitors of Aβ self-assembly. We reported a hexapeptide based on the Aβ32–37 fragment that mitigate Aβ toxicity completely at submicromolar concentrations. 

Despite the current focus on the C-terminus of Aβ, the region still remains relatively less explored. In order to scrutinize the C-terminus region, we performed a full peptide scan on a C-terminus pentapeptide fragment, Aβ38–42. About 32 new peptides were synthesized by Fmoc solid phase peptide synthesis protocol. All amino acids of the pentapeptide fragment were substituted by physico-chemically

Aβ1–42 C-terminus fragment derived peptides prevent the self-assembly of the parent peptide†

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In an attempt to design Aβ aggregation inhibitors to combat Alzheimer’s disease, herein we report a full peptide scan performed on a pentapeptide fragment (Aβ38–42) derived from the C-terminus of Aβ1–42 peptide. More than thirty new peptides were synthesized and tested for their inhibition activity towards Aβ self-assembly. In the cell viability assay, when co-incubated with Aβ, three peptides were found to completely prevent the toxicity induced by Aβ aggregation. Most active pentapeptides were also studied by ThT fluorescence assay and the results were well correlated to the MTT study. The inhibition potential of a pentapeptide (15) was further confirmed by CD spectroscopy and transmission electron microscopy.
analogous amino acid residues. Moreover, amino acids such as proline (Pro) and α-aminobutyric acid (Aib) were chosen because of their β-sheet breaking properties. Scheme 1 shows the general route for the synthesis of peptides on Wang resin.

Since it is well known that protein misfolding is preceded by intramolecular as well as intermolecular interactions between the monomer units, the synthesized pentapeptide derivatives of fragment Aβ_{18–42} are supposed to exhibit high affinity to specifically interact with full-length Aβ peptide. MTT assay was performed to evaluate the newly synthesized pentapeptides for the inhibitory effects against Aβ_{1–42} aggregation and toxicity using PC-12 cells. Cell viability data for all the synthesized pentapeptides and the conversion in percentage inhibition of Aβ aggregation have been shown in Table 1. The lead peptide (1, Gly–Val–Val–Ile–Ala) previously reported to prevent Aβ_{1–42} toxicity by 70% when taken in ten-fold excess, was observed to exhibit significant activity in this study as well. In the cell viability assay, peptide 1 reduced the Aβ_{1–42} toxicity by 43% at 10 μM and 65% at 20 μM. Among the newly synthesized pentapeptide analogues, four peptides (6, Pro–Val–Val–Ile–Ala), (9, Gly–Gly–Val–Val–Ile–Ala), (15, Gly–Phe–Val–Ile–Ala), and (21, Gly–Val–Aib–Ile–Ala) were found to prevent Aβ_{1–42} toxicity in the range of 90–100%. Cell samples treated with premonomerized Aβ_{1–42} (2 μM), showed a viability of about 70% relative to untreated cells (control, taken as 100%). However, in the presence of peptides 6 (10 μM), 9 (20 μM), and 15 (20 μM), incubated along with Aβ_{1–42}, no loss of cell viability was observed. While, in the presence of the peptide 1, only 89.5% cells were observed to be viable. In the co-presence of peptide 21 (10 μM), about 97% cells were viable. Also, in the presence of peptides 13 (Gly–Pro–Val–Ile–Ala, 20 μM), 14 (Gly–Aib–Val–Ile–Ala, 20 μM), and 29 (Gly–Val–Val–Ile–Gly, 2 μM), about 88%, 93.4%, and 89.5% cells were observed to be viable, respectively.

Table 1 shows the cell viability values of the control (untreated cells) and, PC-12 cells treated with Aβ, with and without the presence of pentapeptides. Cell viability values were correspondingly converted into the percentage inhibition values of Aβ toxicity.

Seven other pentapeptides 18 (Gly–Val–Leu–Ile–Ala), 19 (Gly–Val–Ile–Ile–Ala), 23 (Gly–Val–Val–Val–Ala), 24 (Gly–Val–Val–Ala–Ala), 27 (Gly–Val–Val–Aib–Ala), 28 (Gly–Val–Val–Phe–Ala), and 33 (Gly–Val–Val–Ile–Phe) showed moderate inhibition (21–50%) of Aβ_{1–42} toxicity while rest of the peptides did not show any inhibition activity. Pentapeptides 6, 9, and 15 showing complete protection for PC-12 cells against Aβ_{1–42} aggregation related toxicity were also tested against shorter and relatively lesser aggregating peptide Aβ_{1–40}. However, none of the peptides showed inhibition potential towards Aβ_{1–40} toxicity in PC-12 cells (data not shown). The cell viabilities did not improve when the peptides 6, 9 or 15 were incubated with Aβ_{1–40} indicating their inefficiency towards attenuation of Aβ_{1–40} assembly. Fig. 1 represents effects of the most active pentapeptides on the restoration of cell viabilities against the toxicity of Aβ_{1–42} peptide.

In ThT assay, significant reduction in the ThT fluorescence was observed when the pentapeptides 6, 9, 14, 15 or 21, were co-incubated with the monomeric Aβ_{1–42} peptide. Fig. 2A shows the bar graph representation of the relative fluorescence exhibited by ThT when incubated with Aβ_{1–42} alone, and plus the inhibitor pentapeptides. In the ThT assay, reporting % inhibition of Aβ_{1–42} along with RFU values provide better correlation of results. To convert the RFU values into % inhibition values, we also determined and reported RFU values of ThT alone. Relative to blank wells, the enhanced fluorescence shown by Aβ_{1–42} sample alone was taken as 100% and RFU values were calculated for the dye alone and samples containing inhibitor peptides co-incubated with Aβ_{1–42}. ThT incubated alone (control) exhibited a RFU of nearly 27%. It was observed that the RFU values in the presence of the inhibitor peptides were similar to that of the control. For example, in the presence of the peptides, 6, 9, and 15, RFU values of 28.5%, 27%, and 27% were observed at 10, 20, and 20 μM, respectively. Similarly, samples containing 14 and 21 showed RFU of 34.3% and 49.7% at 20 and 10 μM, respectively (Table T1, ESI†). Reduction in ThT fluorescence in the co-presence of pentapeptides 6, 9, 14, 15 or 21 with Aβ_{1–42} clearly indicates the inhibition of self-assembly of Aβ_{1–42} and provides support to the results obtained in the MTT viability assay. Similar to the MTT assay, none of the tested pentapeptides showed inhibitory activity against the shorter form of amyloid peptide (Aβ_{1–40}) in the ThT assay (data not shown). The RFU values remained close to that of Aβ_{1–40} alone, indicating the presence of aggregates and the inefficiency of the peptides to inhibit the aggregation of Aβ_{1–40} peptide. However, the inhibitor peptide 6 was found to reduce the aggregation of 11-residue Aβ peptide fragment (Aβ_{25–35}) by 98%, while the other four pentapeptides (9, 14, 15 and 21) didn’t show any significant activity (Fig. 2B, Table T2, ESI†). The control exhibited RFU as 57%, and in the co-presence of peptide 6 along with Aβ_{25–35}, RFU value of 57.7% was observed. Using the ThT fluorescence measurement assay, we also studied the pentapeptide 15 in a time-dependent manner against the Aβ_{1–42} aggregation-mediated fluorescence. The peptide 15 was incubated with the Aβ_{1–42} peptide and fluorescence was measured at regular intervals for a total duration of 168 h. As shown in Fig. 3, in the absence of 15, when Aβ_{1–42} was aged alone with ThT dye, there was a dramatic enhancement in the fluorescence indicating the aggregation of Aβ_{1–42} peptide. The fluorescence reached a plateau at about 120 h. The enhancement in
Table 1  Cell viabilities and inhibition (%) of Aβ$_{1-42}$ toxicity by the synthesized peptides

| No. | Peptides         | Tested concentration range of pentapeptides | Cell viability | Inhibition$^a$ (%) of Aβ$_{1-42}$ (2 μM) |
|-----|------------------|--------------------------------------------|----------------|----------------------------------------|
|     |                  | 20 μM | 10 μM | 2 μM | 20 μM | 10 μM | 2 μM |
| 1   | Gly–Val–Val–Ile–Ala | 89.5   | 82.9  | 73.6  | 65.0  | 43.0  | 12.0 |
| 2   | Val–Val–Val–Ile–Ala | 71.5   | 70.0  | 70.0  | 5.0   | 0     | 0    |
| 3   | Ala–Val–Val–Ile–Ala | 70.0   | 70.0  | 70.0  | 0     | 0     | 0    |
| 4   | Leu–Val–Val–Ile–Ala | 70.6   | 72.1  | 70.0  | 2.0   | 0     | 0    |
| 5   | Ile–Val–Val–Ile–Ala | 70.0   | 70.0  | 70.0  | 0     | 0     | 0    |
| 6   | Pro–Val–Val–Ile–Ala | 72.1   | 100   | 88.0  | 7.0   | 100   | 60.0 |
| 7   | Aib$^b$–Val–Val–Ile–Ala | 70.0   | 70.0  | 70.3  | 0     | 0     | 1.0  |
| 8   | Phe–Val–Val–Ile–Ala | 70.0   | 70.0  | 70.0  | 0     | 0     | 0    |
| 9   | Gly–Gly–Val–Ile–Ala | 100    | 85.0  | 84.7  | 100   | 50.0  | 49.0 |
| 10  | Gly–Ala–Val–Ile–Ala | 70.0   | 70.0  | 70.0  | 0     | 0     | 0    |
| 11  | Gly–Leu–Val–Ile–Ala | 70.0   | 70.0  | 70.3  | 0     | 0     | 0    |
| 12  | Gly–Ile–Val–Ile–Ala | 70.0   | 70.0  | 72.1  | 0     | 0     | 7.0  |
| 13  | Gly–Pro–Val–Ile–Ala | 88.0   | 82.0  | 70.3  | 60.0  | 40.0  | 1.0  |
| 14  | Gly–Aib–Val–Ile–Ala | 93.4   | 75.1  | 73.6  | 78.0  | 17.0  | 12.0 |
| 15  | Gly–Phe–Val–Ile–Ala | 100    | 84.7  | 73.3  | 100   | 49.0  | 11.0 |
| 16  | Gly–Val–Gly–Ile–Ala | 70.0   | 70.0  | 70.3  | 0     | 0     | 0    |
| 17  | Gly–Val–Ala–Ile–Ala | 70.0   | 70.0  | 70.0  | 0     | 0     | 0    |
| 18  | Gly–Val–Leu–Ile–Ala | 78.1   | 77.2  | 74.8  | 27.0  | 24.0  | 16.0 |
| 19  | Gly–Val–Ile–Ile–Ala | 78.4   | 84.4  | 84.4  | 28.0  | 48.0  | 48.0 |
| 20  | Gly–Val–Pro–Ile–Ala | 72.7   | 71.2  | 71.8  | 6.0   | 4.0   | 6.0  |
| 21  | Gly–Val–Aib–Ile–Ala | 88.3   | 97.0  | 85.6  | 61.0  | 90.0  | 52.0 |
| 22  | Gly–Val–Phe–Ile–Ala | 71.8   | 70.0  | 70.0  | 32.0  | 41.0  | 40.0 |
| 23  | Gly–Val–Val–Val–Ala | 79.6   | 82.3  | 82.0  | 38.0  | 36.0  | 29.0 |
| 24  | Gly–Val–Val–Ala–Ala | 81.4   | 80.8  | 78.7  | 5.0   | 0     | 0    |
| 25  | Gly–Val–Val–Leu–Ala | 71.5   | 70.0  | 70.0  | 0     | 0     | 4.0  |
| 26  | Gly–Val–Val–Pro–Ala | 70.0   | 70.0  | 71.2  | 0     | 0     | 4.0  |
| 27  | Gly–Val–Val–Aib–Ala | 79.0   | 74.5  | 73.9  | 30.0  | 15.0  | 13.0 |
| 28  | Gly–Val–Val–Phe–Ala | 76.9   | 75.7  | 74.5  | 23.0  | 19.0  | 15.0 |
| 29  | Gly–Val–Val–Ile–Gly | 74.5   | 82.3  | 89.5  | 15.0  | 41.0  | 65.0 |
| 30  | Gly–Val–Val–Ile–Val | 74.8   | 73.3  | 72.7  | 16.0  | 11.0  | 9.0  |
| 31  | Gly–Val–Val–Ile–Leu | 70.4   | 72.0  | 70.0  | 4.0   | 1.0   | 0    |
| 32  | Gly–Val–Val–Ile–Ile | 70.6   | 70.0  | 72.1  | 2.0   | 0     | 7.0  |
| 33  | Gly–Val–Val–Ile–Phe | 84.7   | 82.6  | 82.3  | 49.0  | 42.0  | 41.0 |

$^a$ Each experiment was performed in triplicates (n = 3). ODs (absorbance) of samples with untreated cells were set to 1. Taking the cell viability of untreated cells as 100, percentage cell viabilities were calculated for the cell samples treated with Aβ alone or plus the test peptides. Subsequently, the percentage inhibition of Aβ toxicity by each test peptide was calculated by using the formula: 100 × [OD$_{570}$ (test peptide with Aβ$_{1-42}$) – OD$_{570}$ (Aβ$_{1-42}$)]/[OD$_{570}$ (control) – OD$_{570}$ (Aβ$_{1-42}$)].

$^b$ ODs were subtracted from each sample OD and the triplicate ODs were averaged. In a subset of triplicate wells, ODs did not deviate much from the mean and SD ranged between 1.68 and 4.40. Aib denotes aminoisobutyric acid.

fluorescence observed in the Aβ$_{1-42}$ sample relative to control (ThT alone) at saturation point was considered as 100%, and the relative fluorescence (RFU) values were calculated for the inhibit peptide 15 co-incubated with the aggregating Aβ$_{1-42}$ peptide. The fluorescence shown by the blank wells were subtracted from the test samples. In the presence of peptide 15, fluorescence measurements showed RFU of 62% at 12 h (Fig. 3).

At 24 h, peptide 15 co-incubated samples showed only a relative fluorescence of only 15%, while RFU values of 8%, 13% and 6%, were observed at the end of 72, 120, and 168 h, respectively. Summarily, in the presence of peptide 15, very low RFU values (6–15%) were observed especially once the fluorescence reached its saturation point (24–168 h). Since, the fluorescence values correspond to the aggregation state of the Aβ peptide, retardation in the fluorescence indicates the ability of peptide 15 to interfere with the Aβ$_{1-42}$ peptide self-assembly.

CD spectroscopy was performed to study the inhibitory effects of pentapeptide 15 on the conformational transition of Aβ$_{1-42}$ peptide. Monomeric Aβ$_{1-42}$ incubated alone, showed a conformational change from random coil towards an increase in the β-sheet content indicated by the shift from a sharp minima at 198 nm to broad negative peak at 217–218 nm (Fig. 4). At the start, Aβ$_{1-42}$ occupied a conformation as a mixture of 61.8% of random coil, 28.7% β-turn and only 9.5% of β-sheet, while at the end of 12 h of incubation, Aβ$_{1-42}$ exhibited about 47.1% of β-sheet component, with the random coil being only 42.3%. However, after 12 h (t$_{1/2}$) of co-incubation with peptide 15, Aβ$_{1-42}$ exhibited only 16.2% of β-sheet conformation and 59% random
represents the untreated cell samples while A
6 h, after which their ability to reduce the MTT was measured. Control
| represent mean
| expressed as percentage of untreated cells (control). Error bars
| represent the cell samples where the pentapeptides
| aggregating A
aggregate, and thus may not be available to interact with the
| that when taken at 10-fold excess, the peptides themselves
| higher activity at low concentration and vice versa. We envision
| when taken at 10-fold excess, the peptides themselves aggregate, and thus may not be available to interact with the aggregating Aβ peptides in the solution. Hence, enhancement in the β-sheet content of the peptides 6 and 29 as shown by CD spectroscopy provides support to the pattern of results observed in the MTT and ThT.

Finally, visual investigation of the inhibitory effects of peptide 15 on the morphology and abundance of Aβ1-42 fibrils was performed by high resolution transmission electron microscopy (HR-TEM). Shapes and appearance of the fibrils were also examined using scanning transmission electron microscopy (STEM). Peptide 17 observed as inactive in the MTT cell viability assay was selected as a negative control. In the control sample when monomeric Aβ1-42 was incubated alone, we observed long, rod like cylindrical fibrils with no ends in successive images (Fig. 5A, HRTEM and Fig. 6A, STEM). However, no such fibrils were observed when the peptide 15 was co-incubated with the Aβ1-42 peptide (Fig. 5B, HRTEM and Fig. 6B, STEM).

Upon incubating peptide 15 alone under similar conditions, no aggregates of fibrillar morphology were observed. Instead very small globular structures were seen (Fig. 5C, HRTEM and Fig. 6C, STEM). An extensive network of very fine thread-like fibrils was observed when the peptide 17 was co-incubated with Aβ1-42 peptide (Fig. 5D, HRTEM and Fig. 6D, STEM). Though the thickness of the fibrils was much lesser than that

$$\text{Fig. 1: Effects of pentapeptides 1, 6, 9, 13, 14, 15, 21, and 29 on the Aβ1-42-induced cytotoxicity in PC-12 cells. Cells were treated with Aβ1-42 (2 μM) alone or Aβ1-42 plus 1, 6, 9, 13, 14, 15, 21, and 29 (2–20 μM) for 6 h, after which their ability to reduce the MTT was measured. Control represents the untreated cell samples while Aβ1-42 bar represents the cell viability upon treatment with Aβ1-42 peptide. Subsequent bars represent the cell samples where the pentapeptides 1, 6, 9, 13, 14, 15, 21, or 29 were co-incubated along with Aβ1-42 peptide. Viabilities are expressed as percentage of untreated cells (control). Error bars represent mean ± standard deviation (SD, n = 3). Data were analyzed by one way ANOVA test followed by Dunnett’s multiple comparison test \(p < 0.05, *p < 0.01, *p < 0.001, \text{vs. Aβ1-42} \) using software (Graph pad Prism, ISI, San Diego, CA).}$

$$\text{Fig. 2: Effects of the pentapeptides 6, 9, 14, 15 and 21 on (A) Aβ1-42 and (B) Aβ25-35 aggregation-mediated ThT fluorescence. Control represents the dye alone while Aβ1-42 and Aβ25-35 represents the Aβ peptides incubated along with the dye. Subsequent bars represent the inhibitor peptides (indicated by numbers), co-incubated with the corresponding Aβ peptides and ThT dye. Error bars represent mean ± SD (n = 3). Data were analyzed by one way ANOVA test followed by Dunnett’s multiple comparison test \(p < 0.05, *p < 0.01, *p < 0.001, \text{vs. control} \) using software (Graph pad Prism, ISI, San Diego, CA).}$

$$\text{Fig. 3: Effects of pentapeptide 15 on Aβ1-42 peptide aggregation, studied in a time-dependent manner for 7 days. Red line shows the Aβ1-42 peptide aged alone. Green line represents Aβ1-42 peptide co-incubated with peptide 15. Error bars represent mean ± SD (n = 3). Data were analyzed by t-test \(p < 0.001, \text{vs. Aβ1-42} \) using software Graph pad Prism, ISI, San Diego, CA).}$$
observed in control (Aβ alone), the complex of fibrils was much more extensive. This probably might have resulted by the endwise association of Aβ monomers in the presence of peptide 17. The peptide 17 was also seen to form large clusters of amorphous aggregates when incubated alone under similar conditions (Fig. 5E, HRTEM and Fig. 6E, STEM). Constituted by highly hydrophobic amino acid residues, the plausible self-aggregation might be the reason for the inactivity of pentapeptide 17. Therefore, the absence of Aβ_{1–42} fibrils as observed in the electron microscopy study provides further support for the inhibitory activities of pentapeptide 15.

Being a part of the hydrophobic C-terminus of Aβ_{1–42}, the most active pentapeptides 6, 9 and 15 were tested for the self-aggregation related toxicity by MTT cell assay. As described earlier for MTT viability procedure, sampling and assay was adopted for the activity study. The peptides did not show any toxic effect on the cells under study at the highest tested concentration of 20 μM (Fig. S1, ESI†). All sample wells containing peptides 6, 9 and 15 showed MTT reduction quite similar to that of untreated cells (control).

Considering the activity of the lead peptide (1, 65% inhibition at 20 μM) as the reference, inhibition potential of the newly synthesized pentapeptides was correlated with the replacement amino acid residues and structure–activity relationship was established (Fig. 7). The replacement of the first amino acid residue (Gly_{18}), by proline resulted in a very efficient Aβ_{1–42} polymerization inhibitor. The resulting peptide (Pro–Val–Val–Ile–Ala, 6) prevented the Aβ_{1–42} aggregation completely. The substitutions at the Val_{19} residue yielded the best inhibitor peptides. The peptide wherein Val_{19} was replaced with proline (Gly–Pro–Val–Ile–Ala, 13) showed 60% inhibition of Aβ_{1–42} fibrillation; the replacement by Aib afforded a peptide (Gly–Aib–Val–Ile–Ala, 14) with significant (78%) inhibition potential. Two more highly promising peptides were discovered by modification at this position with Gly (Gly–Gly–Val–Ile–Ala, 9) and Phe (Gly–Phe–Val–Ile–Ala, 15) residues, exhibiting 100% inhibition.
of A\textsubscript{\(\beta\)}\textsubscript{1–42} aggregation. The peptide synthesized by replacing Val\textsubscript{40} with Alb (Gly–Val–Alb–Ile–Ala, 21) showed 90% inhibitory activity. Lastly, most of the replacements at the next two amino acids (Ile\textsubscript{41} and Ala\textsubscript{42}) resulted in the peptides that were only moderately active, showing a maximum of 40% and 65% inhibition, respectively. Conclusively, the substitutions, specifically at the residues, A\textsubscript{\(\beta\)}\textsubscript{39}→Pro/Alb and A\textsubscript{\(\beta\)}\textsubscript{40}→Pro/Alb, have resulted in peptides with significant inhibition potential towards the A\textsubscript{\(\beta\)}\textsubscript{1–42} peptide self-assembly.

### Conclusions

More than thirty new peptides were synthesized by performing a full peptide scan on fragment A\textsubscript{\(\beta\)}\textsubscript{38–42} of A\textsubscript{\(\beta\)}\textsubscript{1–42}. The synthesized pentapeptides were bio-evaluated for their inhibitory activity against the aggregation of A\(\beta\) peptides. Three of the best peptides identified in the initial screening by MTT assay, showing significant to complete reduction in amyloid toxicity were taken forward for further studies. ThT fluorescence assay results were found to be in good agreement with the cell-based MTT assay. CD spectral analysis and electron microscopy further provided confirmative supports to the observations. As observed in several studies earlier, the selective activity of pentapeptides (6, 9, 15) against the longer form (A\textsubscript{\(\beta\)}\textsubscript{1–42}) than shorter amyloid peptide (A\textsubscript{\(\beta\)}\textsubscript{1–40}) suggests their probable interactions with the last two residues (Ile\textsubscript{41} and Ala\textsubscript{42}) of hydrophobic C-terminus of A\textsubscript{\(\beta\)}\textsubscript{1–42}. Further, it is well known that hydrophobic interactions play an important role in peptide aggregation. Two best peptides [GGVIA (9) and GFVIA (15)] consist of only hydrophobic amino acid residues, therefore it is very probable that the interaction of pentapeptide fragments with hydrophobic C-terminus of A\(\beta\) may outrace that between A\(\beta\) monomers and intercalate between them, leading to the formation of non-fibrillar structures. Another active peptide (PVVIA, 6) with an anti-\(\beta\)-sheet residue (proline) probably interact with A\(\beta\) and prevent the formation of cross-\(\beta\)-sheet structures, which is a pre-requisite for A\(\beta\) aggregation. We envision that the peptides discovered herein by peptide scan approach, may, with further modifications, yield promising therapeutics to reach to advanced studies for treatment against Alzheimer’s disease.

### Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| CD           | Circular dichroism |
| DIEA         | N,N-Diisopropylethylamine |
| FDA          | Food and drug administration |
| Fmoc         | 9-Fluorenylmethoxycarbonyl |
| HPLC         | High-performance liquid chromatography |
| HR-TEM       | High resolution transmission electron microscopy |
| MTT          | 3-(4,5-Dimethylthiazol-2-yl)-2′-5-diphenyltetrazolium bromide |
| OD           | Optical density |
| PC-12        | Pheochromocytoma-12 cells |
| RFU          | Relative fluorescence unit |
| SD           | Standard deviation |
| STEM         | Scanning transmission electron microscopy |
| TBTU         | O-(Benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate |
| TIPS         | Triisopropylsilylether |
| ThT          | Thioflavin T |

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