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# Exploring Foldamers for the Inhibition of Amyloid-β (Aβ) Aggregation: Current Trends and Future Perspective

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Alzheimer's disease is becoming more prevalent, affecting individuals of various age groups; with individuals above the age of 85 being the most susceptible. Despite significant treatment efforts, the disease remains incurable. Over the years, variety of small molecules and peptide derivatives have been designed and developed to inhibit Aß-oligomerization, but the development of highly efficient inhibitors has still eluded researchers. Recently, bioinspired peptidomimetics, particularly foldamers, have emerged as a new alternative for inhibiting Aß-aggregation due to their structural tunability, high proteolytic stability, and versatile functionality. Foldamers have shown to effectively modulate Aß-aggregation with minimal cytotoxicity, making them intriguing candidates for the next generation of anti-amyloid therapeutic agents. In this mini-review, we will discuss a few of the most important studies regarding the potential use of foldamers to inhibit Aß-aggregation.

## Introduction

Alzheimer's Disease (AD) is one of the most prevalent neurodegenerative diseases accounting for majority of Dementia cases.[1] As a result of chromosomal mutation, the sequential cleavage of transmembrane Amyloid Precursor Protein (APP) by ß-secretase and γ-secretase generates 37-43 amino acids containing isoforms of Aß-peptide amongst which 42-isoform is the most toxic one.[2] Further, these sticky monomers aggregate to form plaques of cross-amyloid-ß fibrils. These not only hinder the synaptic signaling, but also trigger immune responses and cause inflammation, ultimately damaging the surrounding neurons. A secondary pathogenic event often thought to be triggered by this plaque deposition is the hyperphosphorylation of τ-proteins resulting in its decreased tendency to support the microtubules and further disintegration of the entire axonal membrane.[3]

Although the pathway for Aß aggregation is not of complete clarity yet, it follows a typical sigmoidal pattern. The transient native form of Aß monomer is a $3_{10}$-helix before it transforms to a ß-folded structure. They further associate to form dimers and multimers, all of which fall into the Initial lag phase. Rapid polymerization leads to protofibril and cross-ß fibril formation ultimately reaching the Plateau phase.[4,5,6,7] Such a mechanistic process provides ample opportunities for intervention, like either inhibiting the formation of the misfolded protein, or if formed, interfere with its polymerization by stabilizing the monomers.[8,9]

Decades of research went into designing small molecules for inhibition of Aß aggregation as well as the respective proteases involved- ß-secretase and γ-secretase.[10] However, the small molecule amyloid precursors do not form uniquely defined three-dimensional structures which makes structure-based drug design very complex and molecules so developed lack selectivity and have poor affinity. In contrast, peptides exhibit a notable binding affinity to proteins due to formation of multiple hydrogen bonds and the presence of various hot-spot binding residues.[11] Furthermore, they exhibit minimal cellular toxicity as the metabolites generated are simple amino acids. Several peptides have been developed to inhibit amyloid protein aggregation by assessing

**Keywords:** Alzheimer's Disease, amyloid ß, self-aggregation, ß-peptides, γ-peptides, oligoarylamide foldamers

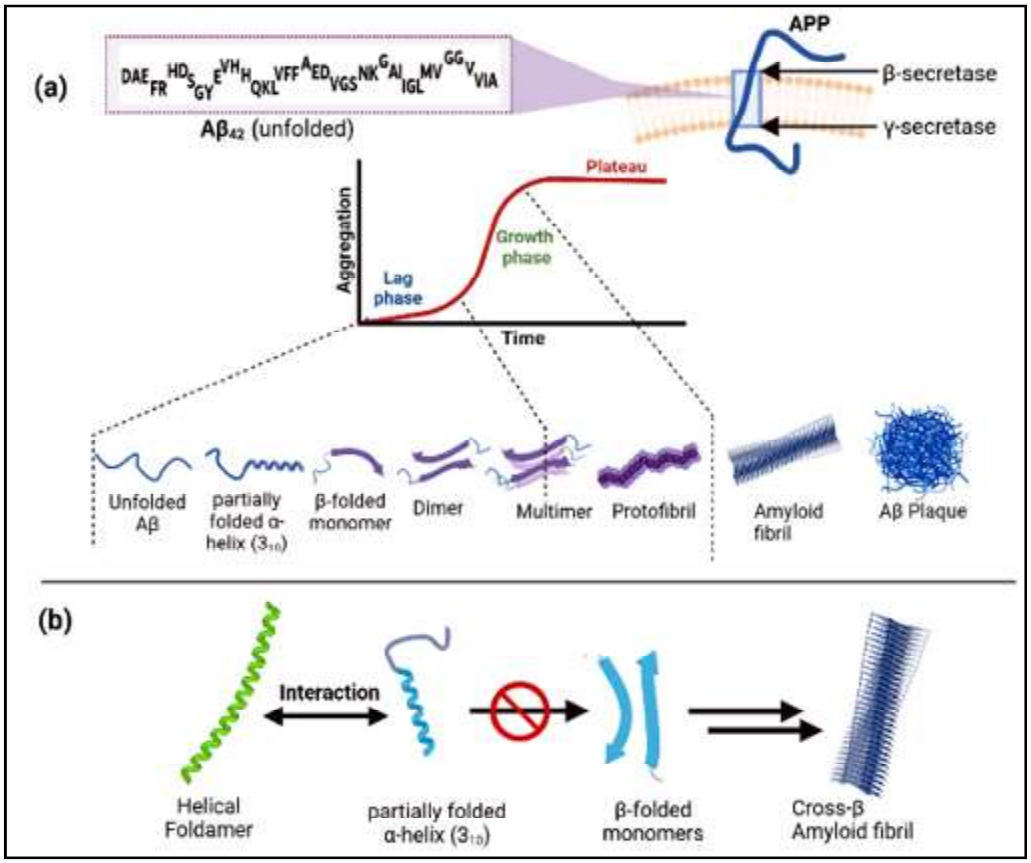


Fig. 1. (a) The mechanism of action of ß-secretase and γ-secretase on Amyloid Precursor Protein (APP) generates an unfolded Aß monomer which further undergoes misfolding and aggregation to ultimately generate the Aß-plaque. The sigmoidal curve shows kinetics of Aß aggregation with distinct Lag, Growth/Elongation and Plateau phases. (b) Inhibition of ß-structure mediated Aß oligomerization through foldamers.

native amyloid sequences, along with proline substitution, and other approaches.[12] However, such peptides made of natural amino acids are an easy target of proteases thus, have a low serum half-life. Hence, there has been a growing interest for unnatural amino acid-based peptides and foldamers which are not easily recognizable by native proteases and have a much longer half- life as compared to the native ones. Foldamers are synthetic oligomers which inherently fold into definite conformation through a variety of non-covalent interactions such as hydrogen bonding, van der Waals interactions, π-π stacking, electrostatic forces and hydrophobic interactions.[13] They possess a variety of functional groups which enhances their affinity towards biomacromolecules.[14] They lack a canonical backbone while having a tendency to adopt a conformationally ordered state in solution even with fewer monomeric units. In addition, they show structural tunability and have better pharmacokinetic properties than small molecule or protein-like drug candidates.[15] Their semi-rigid nature, proteolytic stability, along with their ability to mimic the natural peptide conformation makes them attractive therapeutic candidates for amyloid inhibition.

In this article, we present an overview of some recent advances in the use of foldamers derived from ß -amino acids, γ-amino acids and oligoarylamides for the inhibition of Aß fibrilization.

## ß-amino acid based foldamers

ß-Amino acids result from mono homologation of α-amino acids. This elongated backbone enhances their flexibility as well as helical propensity. ß-peptide can form wide range of helical conformation including 14-, 10-, 8-, 10/12-helices depending on the stoichiometry and substitution patterns of amino acids in the backbone.[15] Among these various helical conformations, the 14-helix has been the most extensively studied. This helical conformation is stabilized by fourteen atoms containing H-bonded pseudo-rings between the N-H (i) and C=O (i+2) atoms having approximately three residues per turn. The morphological similarity of ß-peptide foldamers with the biomolecules could be used as an advantage and be utilized for targeting protein-protein interactions. Another significant advantage is that the incorporation ß-amino acid into a native peptide sequence increases its serum half-life by several fold due to protease resistance.[16] ß-Peptide foldamers earlier have proved useful as antibacterial,[17] for cell penetration,[18] and therapy for HIV-AIDS.[19] In addition, ß-peptides can also prove to be a novel and potent therapeutic against Alzheimer's Disease. Such unnatural amino acid oligomers that take up specific helical conformations can mimic the transmembrane domain of Amyloid Precursor Protein (APP), and thus interfere with γ-secretase functioning.

In one interesting example, Imamura and his colleagues designed a series of ß-peptides comprised of sterically-constrained, enantiomeric ß-amino acids: *(S,S)-trans*-2-aminocyclopentane carboxylic acid (ACPC) and *(R,R)*-ACPC (Fig. 2a).[20] The

designed peptides (P1-P6) are intended to form 12-helical conformation that mimics the APP transmembrane domain. Furthermore, due to hydrophobic nature of the foldamers they could be good candidates for binding to γ-secretase, which generally prefers to target hydrophobic substrates. The secondary structures of the oligomers were confirmed through CD spectroscopy; oligomers composed of *(R, R)-trans*-2-aminocyclopentane carboxylic acid (ACPC) (P1-P3) showed a low minimum at ~222 nm and a maximum at 204-205 nm, which are in good agreement with previously studied left-handed 12-helical ß-peptides (Fig. 2b). In contrast, the oligomers of *(S, S)*-ACPC (P4-P6) showed exactly opposite CD spectra suggesting right-handed 12-helical conformation (Fig. 2b). Interestingly, the intensity of signal increased proportionally with increase the length of oligomers (6→9→12). This enhanced intensity pointed towards the occurrence of a higher proportion of 12-helices upon increasing the chain length. Subsequent *in vitro* and cell-based studies demonstrated that the shortest oligomers exhibited either no or moderate inhibitory activity, whereas the dodecamers exhibited the highest inhibitory activity (in the nanomolar range) (Fig. 2c). This shows that, along with hydrophobicity, helicity is also a key factor for their inhibitory potential. Strikingly, it was observed that ß-peptides comprised of *(S,S)*-ACPC residues were far more effective inhibitors than their *(R,R)*-ACPC counterparts. The dodecapeptide of *(S,S)*-ACPC (P6) exhibited strong APP specificity while exhibiting no activity towards other hydrophobic-substrate cleaving proteases (such as α-secretase) and no action on intra-membrane cleaving proteases. Further, *in vivo* inhibitory potency of the dodecapeptide of *(S, S)*-ACPC was assessed using N2a cells confirming it to be a strong and direct inhibitor of γ-secretase (Fig. 2d, 2e). Moreover, reported inhibitory activity of helical ß-peptide is comparable to other established γ-secretase Inhibitors (GSIs) and could serve as a good lead for developing newer highly specific GSIs.

## γ-Amino acid based foldamers

γ-peptides are bio-inspired synthetic oligomers whose backbone is double homologated as compared to α-peptides. The additional methylene units in their backbone limit the potential H-bonding interactions instead, make them more flexible and enhance the helical propensity. γ-peptides have exhibited their ability to mimic diverse secondary structures observed in natural proteins, such as helices, sheets and turns. In their seminal work, Seebach[21] and Hanessian[22] reported the formation of stable 14- and 9-helical conformations of γ-peptides in solution, which was further supported by Hoffman's computational methods.[23] In addition to their ability to form stable helical structures, proteolytically stable γ-peptides have been explored for the development of effective and less cytotoxic antimicrobial agents,[24] prospective cellular-uptake agents,[25] binders of somatostatin receptor,[26] and transmembrane ion and water channels.[27] Very recently, helical γ-peptides have been shown to function as inhibitors of Aß aggregation. Foldamers

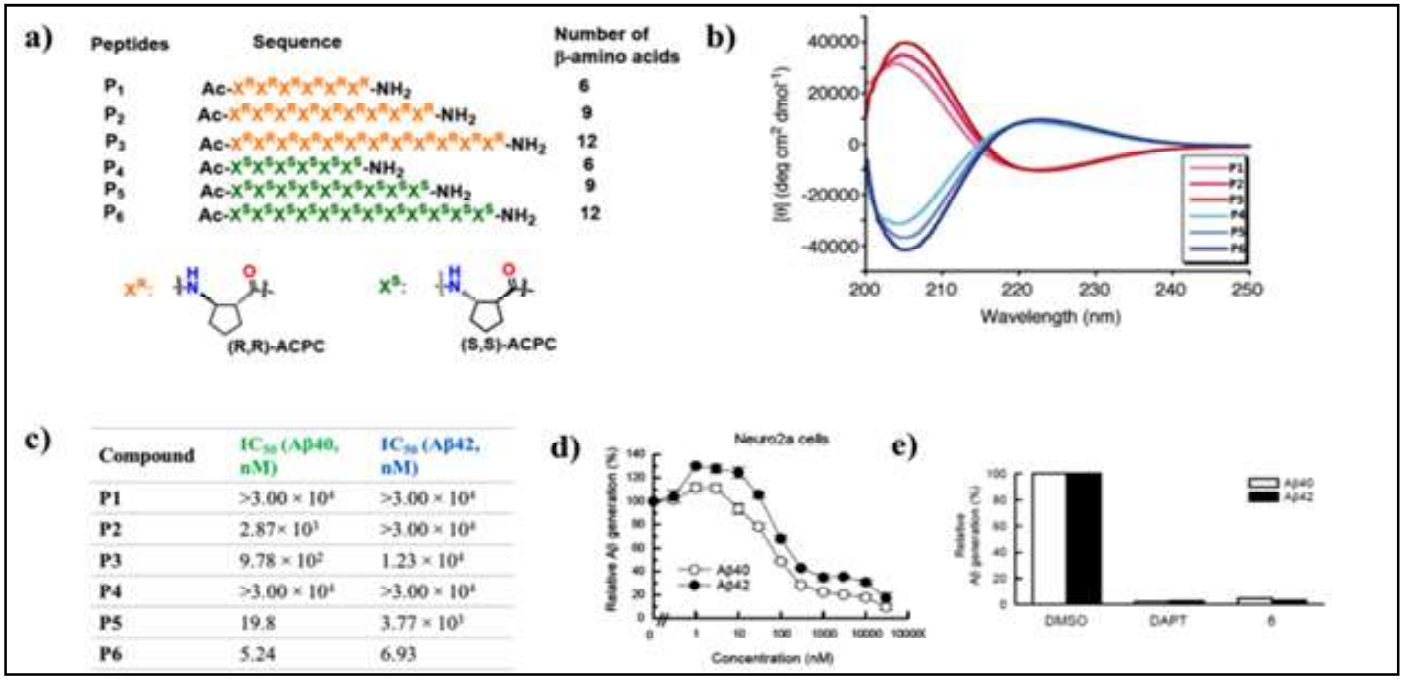


Fig. 2. (a) Sequence of the synthesized ß-peptide foldamers. (b) CD spectra of the foldamers P1-P6. (c) Inhibitory effect of ß-Peptides P1-P6 against γ-Secretase. (d), (e) Inhibitory effect of foldamer P6 on cell based γ-secretase activity. Reproduced from ref. 20. Copyright 2009 American Chemical Society.

which are reminiscent of native $3_{10}$-helix can be designed such that they can interact with the transient $3_{10}$-helical conformation of the Aß-peptide so that its transformation to a ß-sheet structure followed by oligomerization can be prevented.

Ongeri and colleagues have demonstrated the efficacy of γ-peptide foldamers in taking control of the Aß fibrillization process. Their aim was to target the Aß-peptides in their monomeric form using sterically constrained γ-amino acid based foldamers.[28] They designed and synthesized a series of helical γ-peptide foldamers comprised of 4-amino(methyl)-1,3-thiazole-5-carboxylic acid (ATC) (Fig. 3a). Six different γ-peptides (Fig. 3b, 3c) were synthesized with various side chains to enhance their interaction with the $3_{10}$-helix (P7-P12). Keeping in mind that the KLVFF segment of Aß is mainly involved in ß-sheet formation, they designed the first series of $\gamma^4$-dipeptide, tetrapeptide and hexapeptide containing benzylic substitution that could recognize the phenylalanine residues in the amyloidogenic sequences (P7-P9) (Fig. 3b). Additionally, amino group at the 2nd carbon atom of thiazole enhanced the solubility and promoted H-bond formation with amyloid. In the second series, the aim was to utilize cationic groups to antagonize the amyloidogenesis. Here, instead of hydrophobic side chains, the γ-position was substituted with cationic aminobutyl group with the attempt of establishing electrostatic interaction with the negatively charged Asp and Glu residues of Aß (P10-P12) (Fig. 3c). 2D NMR spectroscopy and circular dichroism studies revealed that the designed γ-peptides adopted a 9-helical conformation reminiscent of native $3_{10}$-helical structure. Further, *in vitro* Thioflavin-T assay was conducted to investigate the dose-dependence of ATC foldamers on plaque inhibition. Intriguingly, the inhibitory activity increased in the second series of γ-peptide foldamers with increasing length from di to hexamers. Most significant activity was shown by the cationic hexapeptide (P12). Complete absence of fluorescence was observed with ratio of 10:1 for P12/$Aß_{1-42}$. An inhibitory action was observed even with a minimal ratio of 0.1:1 (Fig. 3c). On the contrary, benzylic side chain containing 6-ATC due to its high hydrophobicity underwent self-aggregation and thus, failed to interact with the monomers. In subsequent TEM images, use of cationic P12/$Aß_{1-42}$= 10:1 showed a significant decrease in the fibrillar material as compared to the $Aß_{1-42}$ control (Fig. 3e, 3f and 3g). Furthermore, mass spectroscopy (MS) and capillary electrophoresis (CE) studies revealed that most active foldamer P12 predominantly interacts with the monomer species and monomeric form $Aß_{1-42}$ endures for prolonged period in the presence of foldamer P12. The result demonstrated the utility of thiazole γ-peptide

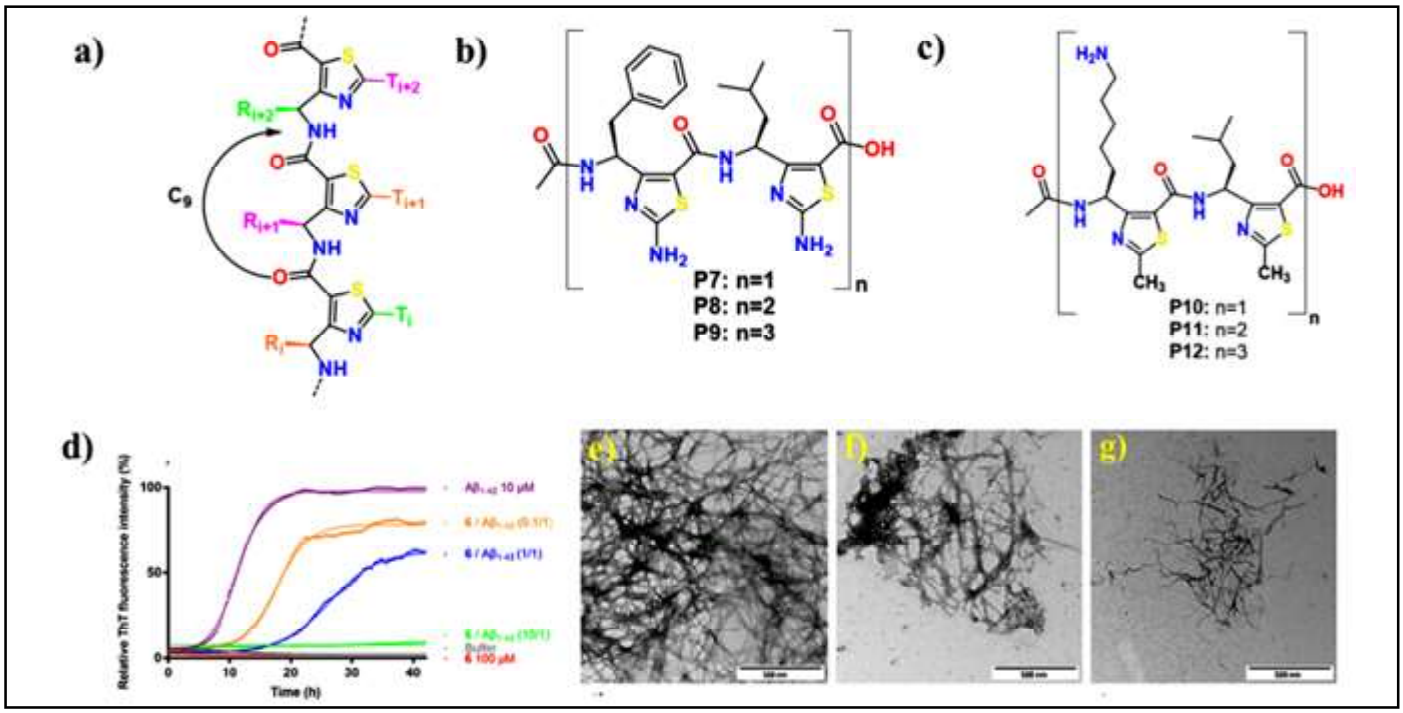


Fig. 3. (a) $C_9$ helical conformation of 4-amino(methyl)-1,3-thiazole-5-carboxylic acid(ATC) oligomers, T and R represents the thiazole and γ substituent. (b), (c) Chemical structure of divergent ATC foldamers. (d) ThT fluorescence curve in presence different ratio of conc. $Aß_{1-42}$ and foldamer P12. (e), (f), (g) Effect of fibril formation of $Aß_{1-42}$ peptide in the presence of foldamer P12 at various time intervals, as depicted in Fig. g, indicates that fibrils are significantly less dense after 42 hours. Reproduced with permission from ref. 28 . Copyright 2021 Wiley-VCH.

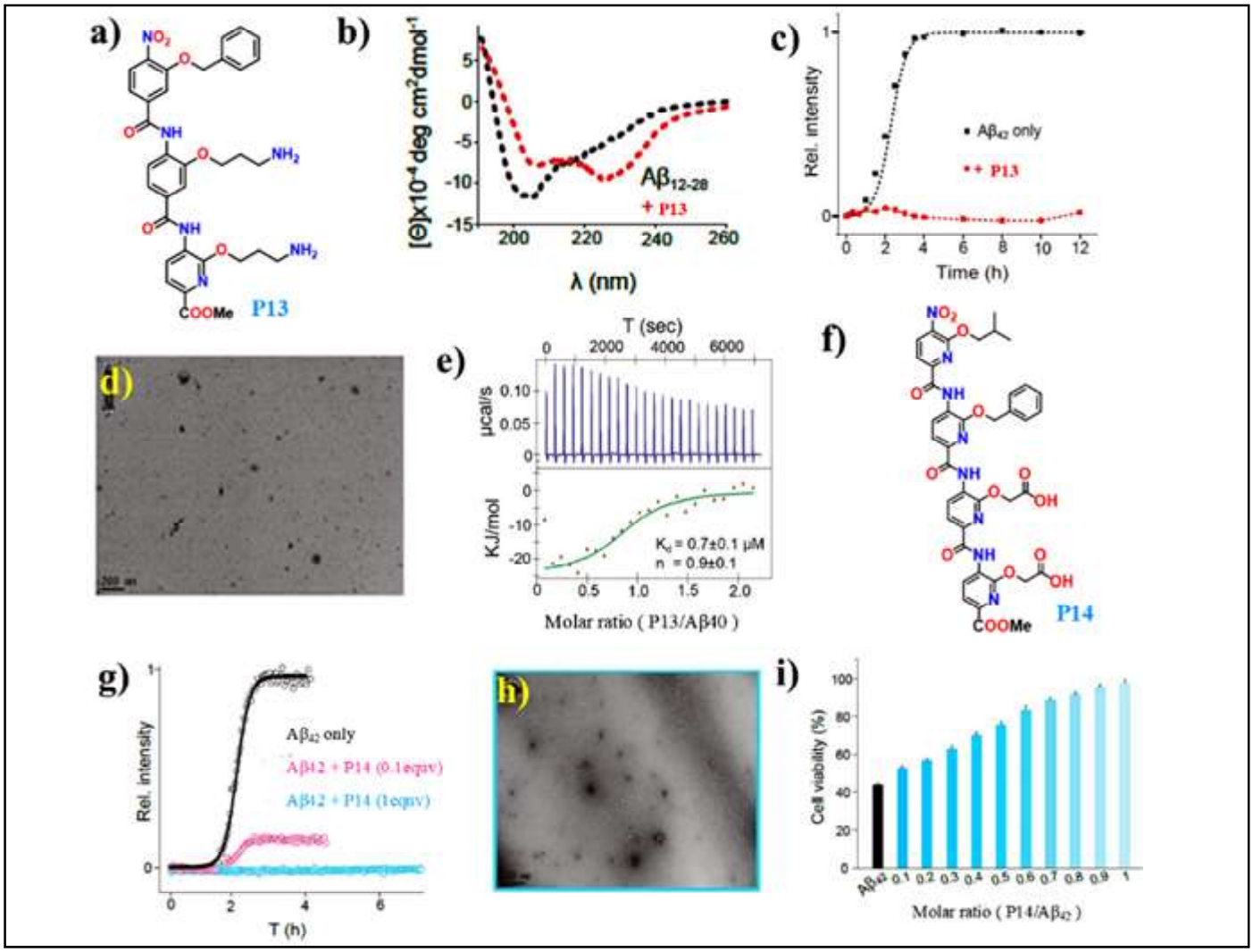


Fig. 4. (a) Chemical structure of helical peptidomimetic P13. (b) CD spectra of 1: 1 $A\beta_{12-28}$ and P13. (c) Kinetic study of Aß fibrilization via ThT fluorescence assay in the presence and absence of P13. (d) TEM image of Aß in the presence of 0.1 equivalent of P13 after hours. (e) Binding affinity of P13 and Aß1-40 measured through ITC. (f) Chemical structure of helical peptidomimetic P14. (g) Kinetic study of Aß fibrilization in the presence and absence of P14 in different ratio. (h) TEM image of Aß in the presence of equimolar ratio of P14 after 6 hours. (i) Cytotoxicity of N2a cells treated with 5 µM $A\beta_{42}$ in the absence or presence of P14 after 72 hours. Reproduced from ref. 34 and 35. Copyright 2018 American Chemical Society.

foldamers in intervening the amyloidogenesis during its initial stages and how the side chain substitutions on the γ-amino acids can be modified synthetically to modulate their interactions with the amyloid proteins.

## Aromatic oligoamide based foldamers

Aromatic oligoamides are amide sequences with aryl/heteroaryl moieties that can form intramolecular H-bonds between ring components and adjacent amide-NH, thereby adopting rigid conformations.[29] Aromatic oligoamides can mimic diverse secondary structures of protein, including helices, ß-sheets, and linear strands, depending on the monomer employed and the formation of inter-amide hydrogen bonds. In their pioneering work, Huc and Gong have shown the applicability of oligoarylamides as biomodulators.[30,31] Numerous quinoline-, pyridine-, and pyrrole-based monomers have been employed to construct oligoarylamide foldamers. They exhibit an impressive mix of structural predictability, tunability, stability, and synthetic ease. More importantly, their length can be easily altered and the backbones and side chains can be readily functionalized. As a result, this foldamer family has been extensively used for protein-protein interaction[32] and molecular recognition.[33] In addition, these foldamers are recently employed as modulators of Aß aggregation.

In this context, Hamilton and his colleagues have developed a series of α-helical mimetic oligopyridylamide sequences that can target the helical domain of Aß-peptide.[34] Among the various oligopyridylamide sequences, the most potent is P13; a tripyridylamide with one benzyloxy group and two primary ammonium residues (Fig. 4a). The detailed

HSQC NMR studies revealed that, the aromatic benzyl moiety interacts with the hydrophobic ($Leu^{17}$-$Phe^{20}$) region and positively charged ammonium with anionic residues of Aß ($Glu^{22}$-$Asp^{23}$). Circular dichroism studies demonstrated that the helical peptidomimetic induces a-helical conformations in the $Aß_{42}$ peptide and prohibits its transformation into the amyloid ß-sheet structure (Fig. 4b). The inhibition was further supported by TEM and Thioflavin T assay (Fig. 4c, 4d) Further ITC studies reflected that P13 formed stable 1:1 complex with $Aß_{40}$ and inhibit the aggregation (Fig. 4e). In continuation of their previous work, the same group screened another series of anionic tetrapyridylamide scaffolds and identified that compound P14 was the most effective.[35] The side chains of foldamers; isobutyl and phenyl groups, collectively interacted with the hydrophobic residues of Aß, while two carboxylate groups interacted with ($His^{13}$-$Lys^{16}$) to stabilize Aß in a helical state. The efficacy of inhibiting this aberrant self-assembly has been supported with an array of biophysical techniques for instance, TEM (Fig. 4h), AFM, Thioflavin T assay (Fig. 4g), ELISA, CD spectroscopy, fluorescence titration and so on. More intriguingly, it also inhibited the Aß42 mediated toxicity in N2a cells at a sub-stoichiometric concentration (Fig. 4i). As evident from this study, the surface functionalities on the oligopyridylamides mainly influence their binding to Aß, making them the primary deciding factor for generation of a stable Aß helix. Any alteration in the substitutions resulted in compounds with reduced antagonistic activity.

## Conclusion and Future perspectives

In conclusion, we have summarized recent progress regarding the potential use of foldamers in the treatment of Alzheimer's disease. The reported foldamers could inhibit the pathogenesis either at the initial stage of Aß monomer synthesis or the formation of the Aß oligomers. Notably, despite their ability to mimic the APP recognition surface, these foldamers exhibit no amyloidogenic potential. They also have a longer serum half-life due to their proteolytic resistance. However, certain important criteria such as the ability of foldamers to cross the Blood Brain Barrier under therapeutically relevant condition need to be addressed for their future use as drug candidates for the treatment of Alzheimer's disease. Nevertheless, the non-natural oligomers have been and will continue to be important platforms for advancing our understanding of protein folding and how these folded structures may be used to modulate the Aß aggregation and other rare diseases. The quest to find a highly specific and efficient treatment for neurodegenerative diseases continues and such inhibitors would be important tools for identifying newer drug prototypes.

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