



Peptidomimetics: A Synthetic Tool to Treat Alzheimer's Disease

Shubham Patil & Pratham Lotia

Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Mumbai

Abstract:

Peptidomimetics is nothing but the modification of the peptide structure by bioisosterism so that there is a significant improvement in the pharmacokinetic properties erstwhile the peptide structure is mimicked in such a way that each building block of a peptidomimetic resembles an amino acid which was the building block for the peptide that was mimicked. Different approaches are used to get a potent and efficient inhibitor by peptide stapling, modifying sequences, and in many other designing ways. Here we are using these approaches to target the amyloid- β receptors by using inhibitors by preventing or breaking the amyloid aggregation.

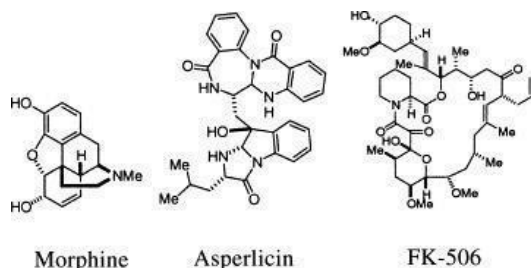


Figure 1: Examples of peptidomimetics

Keywords:

Peptidomimetics, Alzheimer's, Amyloid- β , μ receptors, Peptide Stapling

A Brief Introduction to Alzheimer's Disease (AD)

Alzheimer's is one of the incurable disease's which has no antidote to treat it as it is neuro degenerative and there is no drug that is clinically accepted to halt its progression. Lots of efforts are put in to develop inhibitors that are peptide-based to inhibit amyloid- β aggregation. A better understanding is achieved of the AD pathology from what has been done in the discovery of effective therapeutic

agents. Peptide-based aggregation inhibitors have higher effectiveness, selectivity, good tolerance, low accumulation in tissues, low toxicity, and highly developed methods for analyzing their mode of action, proteolytic stability, and permeability for blood brain barrier makes these inhibitors have significant promise for future of alzheimer's therapy.

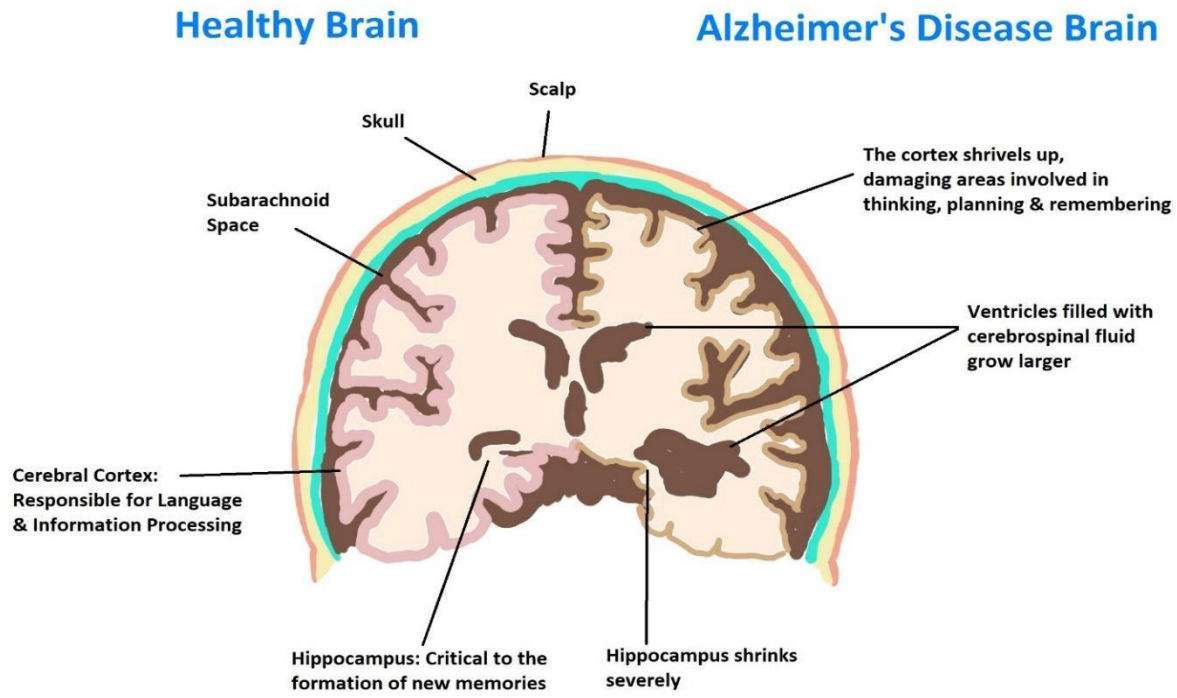


Figure 2: Diagrammatic representation of a Healthy Brain vs. Alzheimer's Disease Brain

Alzheimer's is a disease of aggregation. Amyloid- β is a protein made by the neurons in the brain and the important tasks are performed by its monomers. But due to Alzheimer's, oligomers are formed these monomers which are small clumps of a dozen proteins that stack on

each other to make longer strands resulting in large deposits called plaques. Earlier, scientists believed that these plaques used to trigger the MCI of Alzheimer's. But in recent times, it is found out that the elements causing toxicity are the diminutive aggregates of amyloid- β .

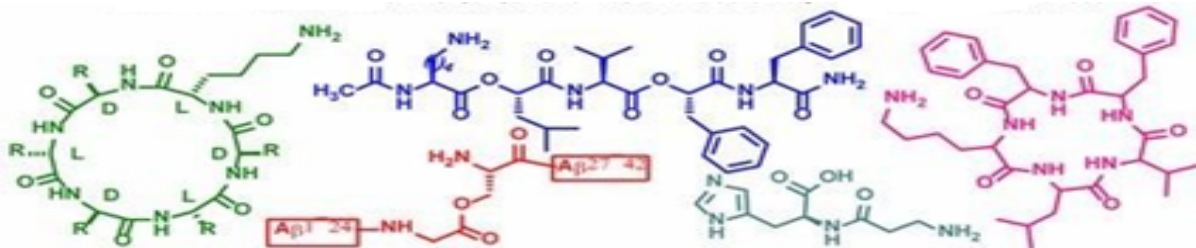


Figure 3: Peptide and peptidomimetic inhibitors of Amyloid- β aggregation

MEDICATION

Although, there's no permanent cure for Alzheimer's, current medications might improve the condition of the patients by reducing confusion and memory loss.

The cerebroactive drugs which are used to treat Alzheimer's disease are classified as Cholinergic activators and Miscellaneous cerebroactive drugs

Cholinergic activators

As acetyl choline in the brain are significantly

reduced, cholinergic neurotransmission suffers

the most in Alzheimer's disease. Hence, various approaches to increase acetyl choline are being tried. Substrates like choline or lecithin are not in shortages in the brain which have been tried by precursor loading resulting in failure. So conventional anticholinesterases like physostigmine and cholinergic agonists like

bethanechol help in symptom improvement. But all of these do the job at the cost of the side effects. Four cerebroselective anti-cholinesterase have been introduced in the past two decades and out of which three are widely used in Alzheimer's disease.

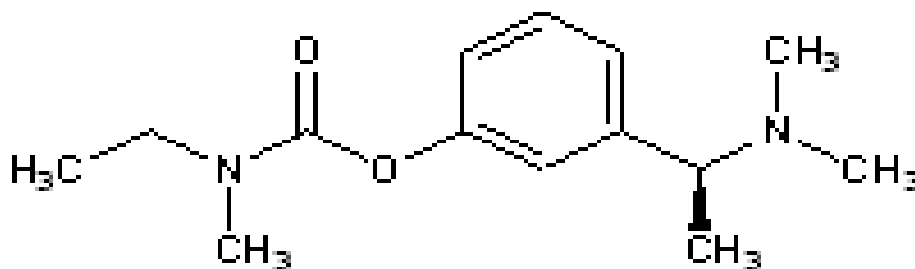


Figure 4: Rivastigmine

1. Rivastigmine

This is a drug that comes under the class of carbamate derivatives of physostigmine. It is an inhibitor of Acetylcholinesterase and Butyryl cholinesterase, Acetylcholinesterase's G1 isoform is dominantly found in many areas of the brain. This is selectively more inhibited by rivastigmine. Rivastigmine is extremely lipophilic in nature which means that it crosses the blood-brain barrier. Rivastigmine introduces a residue into the acetylcholinesterase molecule

so that ACH can dissociate slowly which results in inhibition of the cerebral acetylcholinesterase for up to ten hours despite the 2hr plasma t_{1/2} of the drug. Other symptoms like indifference, misconception, illusion, and anxiety have also been ameliorated but to a meagre extent. The drug has no hepatotoxicity. Rivastigmine is prescribed not in the severe cases, but in moderate cases

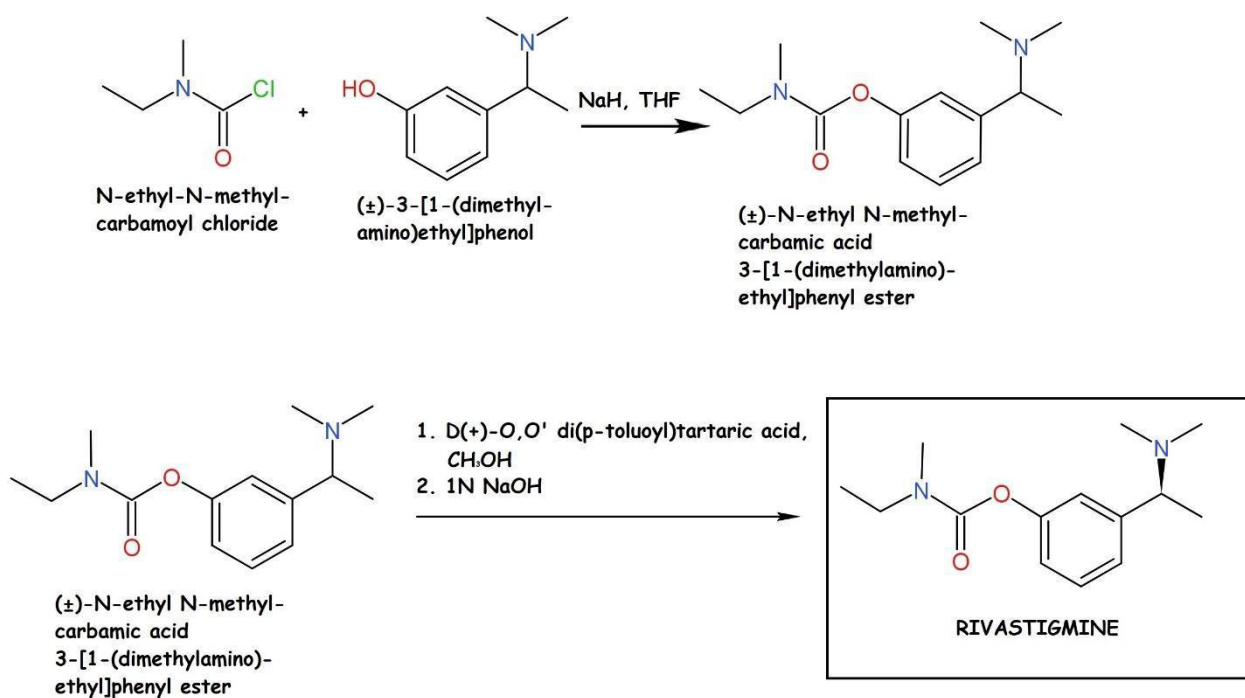


Figure 5: Synthesis of Rivastigmine

Miscellaneous cerebroactive drugs

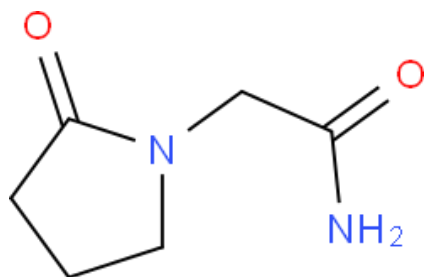


Figure 6: Piracetam

Piracetam:

This is a cyclic GABA (Gamma amino Butyric acid) derivative but has no Gamma-aminobutyric acid like activity and has been used to improve intelligence (nootropic). Piracetam may reduce blood viscosity but it does not dilate the blood

vessels. In countries like India, it has been promoted for mental retardation, dementia, and MCI. Although a recent review had reported that this drug does not have a nootropic use. Also, some studies have demonstrated a CNS protective effect of this

drug during a bypass surgery of the heart. Its

side-effects are mild

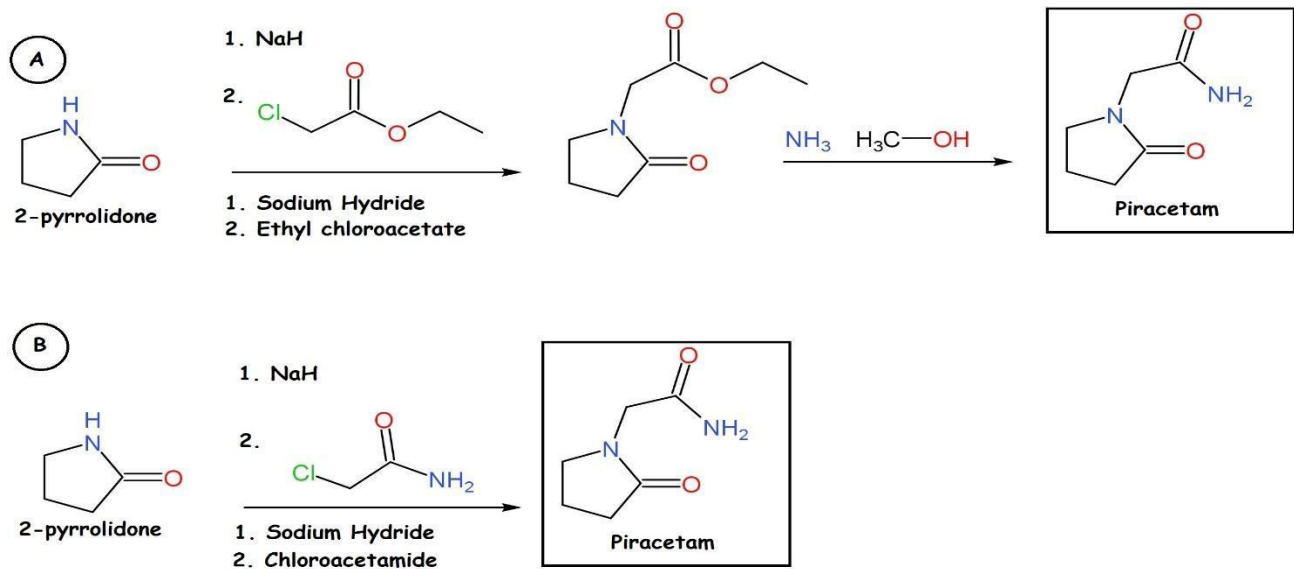


Figure 7: Synthesis of Piracetam

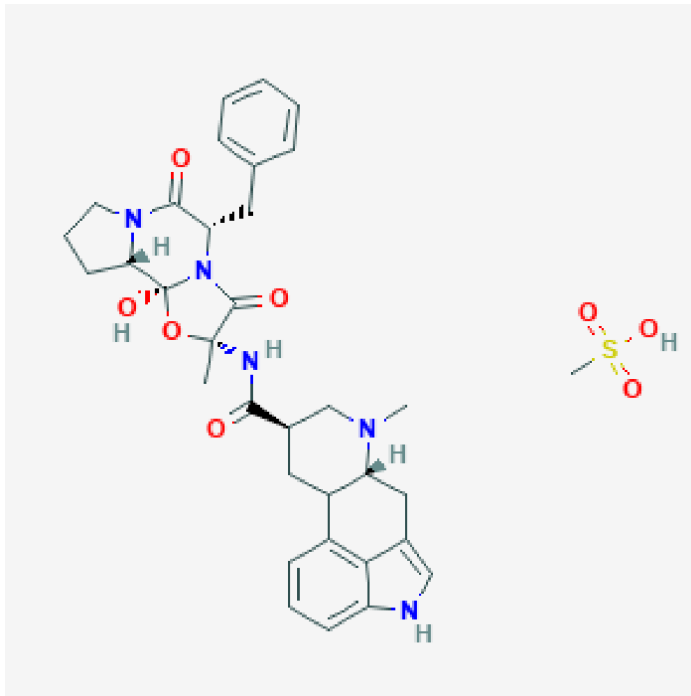


Figure 8: Dihydroergotamine

Dihydroergotamine (Co-dergocrine):

This drug, an alkaloid, which selectively increases blood flow in the brain. It protects the

brain via an alternating mechanism. It is suggested for MCI, and dementia. It has an

undetermined beneficial value.

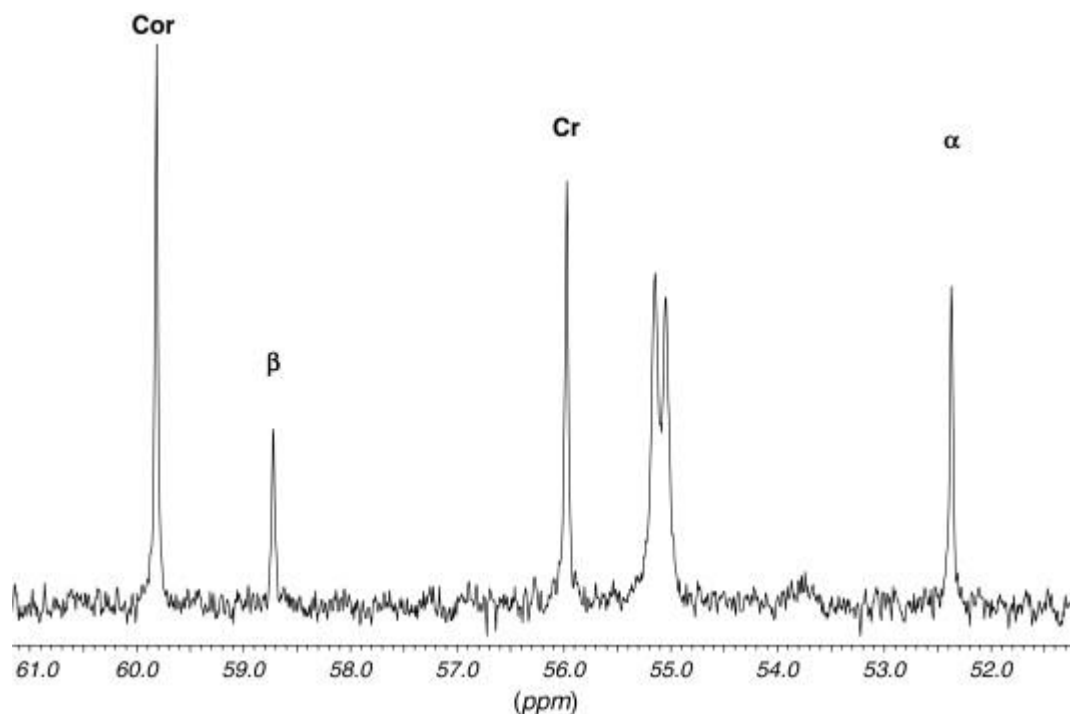


Figure 9: NMR of Dihydroergotaxine

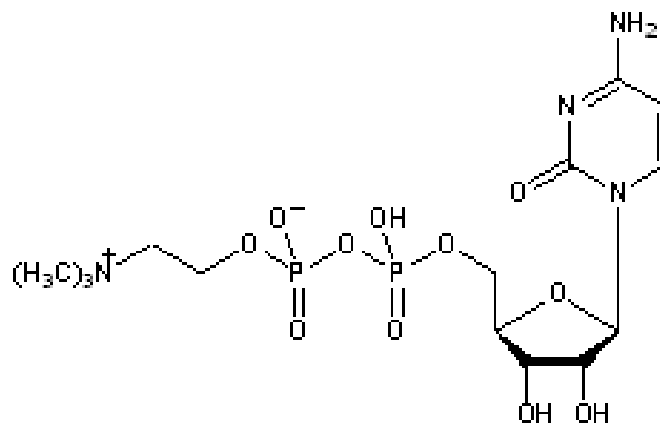


Figure 10: Citicoline

Citicoline

It's a compound involved in the biosynthesis of lecithin and derived from choline and cytidine. Citicoline is a drug which enhances the cerebral metabolism and improves the cerebral activities of the brain as it increases the blood flow. There is no clear usage or benefit of citicoline but

citicoline acts as a memory enhancer for a short-period of time. Citicoline is prescribed for impeded brain activities.

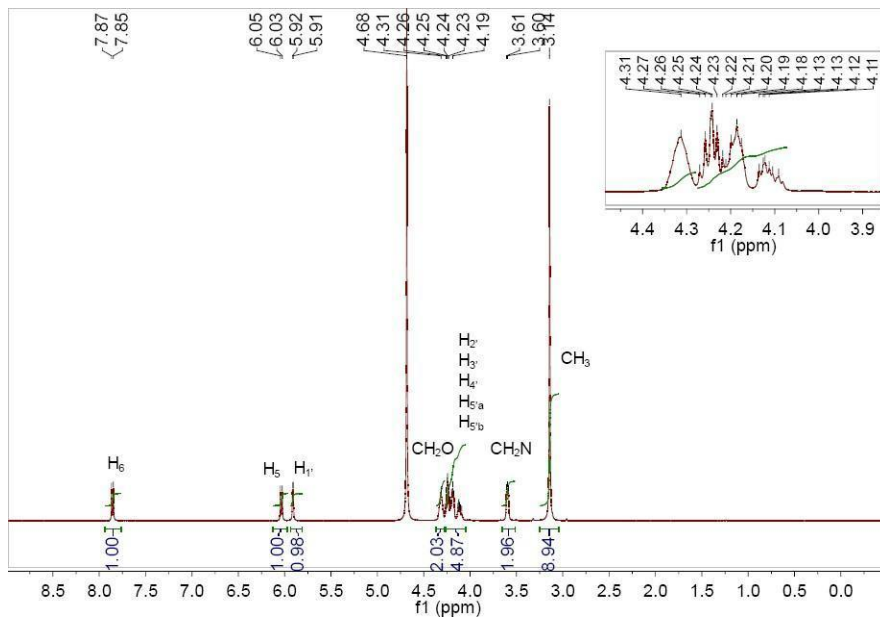


Figure 11: NMR of Citicoline

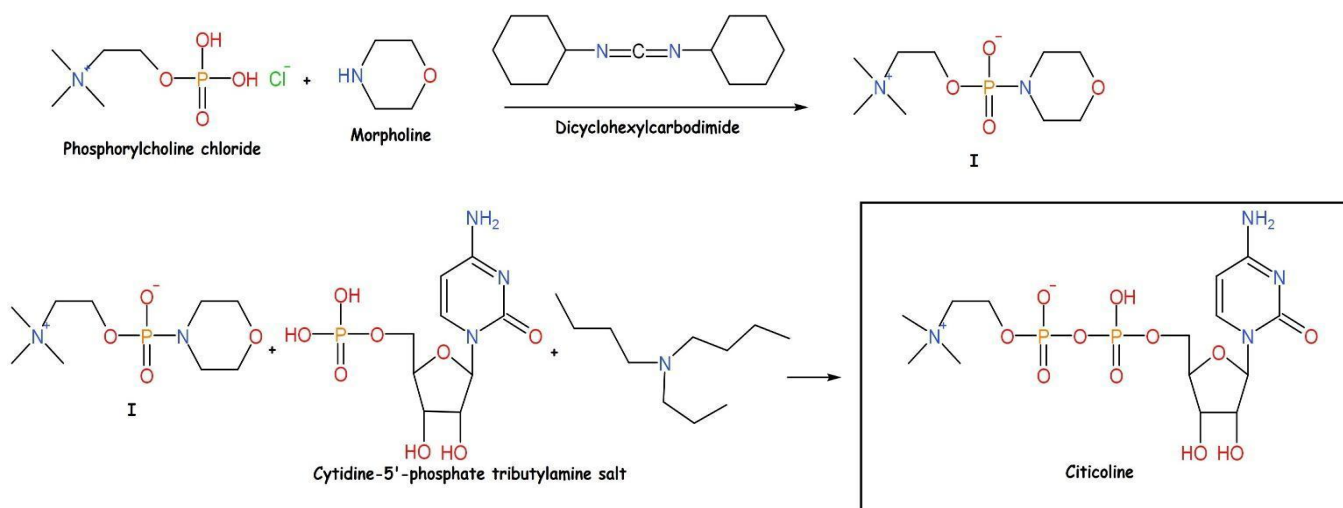
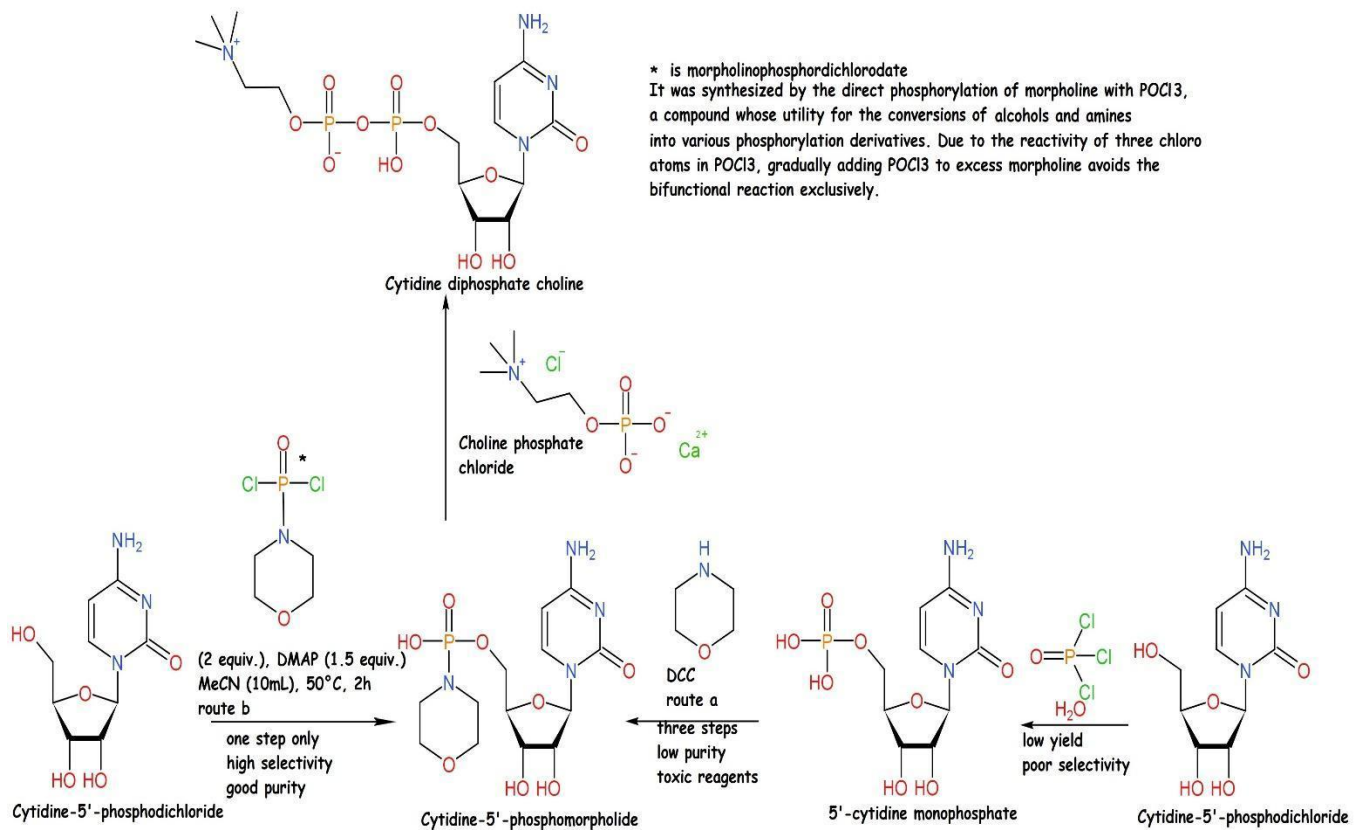


Figure 12.1: Synthesis of Citicoline



* is morpholinophosphordichloridate
 It was synthesized by the direct phosphorylation of morpholine with POCl₃, a compound whose utility for the conversions of alcohols and amines into various phosphorylation derivatives. Due to the reactivity of three chloro atoms in POCl₃, gradually adding POCl₃ to excess morpholine avoids the bifunctional reaction exclusively.

Figure 12.2: Synthesis of Citicoline

PEPTIDES AND PEPTIDOMIMETICS IN ALZHEIMER'S DISEASE

(Inhibition of Amyloid-Beta Peptide Aggregation and Amyloid Formation)

Amyloid- β peptide Sequence Derived Peptides

These structure-based peptides have a central hydrophobic core (CHC) sequence of Amyloid- β along with peptides which maybe essential or non-essential amino-acids. The A β aggregation is inhibited by natural amino-acids peptides, but have cons like monomers stack into fibrils and are less susceptible to proteolysis. Many modifications like methylation of the nitrogen, incorporation of retro-inverse peptides, D-amino acid, substitute of amide by ester bonds, and cyclization are done to improve these limitations.

Natural Amyloid- β peptide series derivative peptides

A good example of a biological Amyloid- β sequence would be an oligopeptides iAb5p, an oligopeptide. In this series, an aspartic acid amide and a proline substitute the alanine and the valine respectively. The mechanism of action is that this peptide crosses the blood-brain barrier in-vivo and promotes the breaking down of the formed amyloid plaques and also it inhibits the formation of amyloid fibrils. The efficacy of the peptide is contributed by the residues of proline that taper off the beta - sheet conformation of the biological Amyloid- β peptides.

•_Modified Amyloid- β peptide series derivative peptides

Amyloid- β series derivative peptides that are fluorinated are an example of the modified peptides which are fabricated by fluorination of the lipophilic amino acids like valine and phenylalanine. These peptides inhibit the aggregation as the fluorinated amino acids bind to the hydrophobic deposits of Amyloid- β peptides and preventing the contact between Amyloid- β peptide molecules.

D-peptides are the more unaffected ones to protein-breaking biological-catalysts than the L-isomers and they also inhibit the Amyloid- β aggregation in an animal model.

Peptides like SEN304 and SEN1576 are examples of N-methylated peptides that are another type of modified peptides that inhibit Amyloid- β peptide mediated toxicity. They do not inhibit directly Amyloid- β peptide aggregation but dramatically change the Amyloid beta peptide accumulation into detoxified forms and also excrete the biologically-toxic oligomers. The α -sheet peptides have sporadic L-amino acids and D-amino acids and they lessen the Amyloid- β accumulation and noxiousness but do not cross the blood-brain barrier.

Peptides not developed from Amyloid beta peptide series

Peptides that are not a derivative from Amyloid- β peptide series share hydrophobicity properties with the peptides derived from A β sequence and have the capacity to integrate into beta-pleated sheets and hence impeding Amyloid- β peptide accumulation.

•_Peptides which are not derivative from Amyloid- β peptide series including essential amino acids

Examples are NAP, carnosine, and hexapeptides. All of them impede Amyloid- β peptide accumulation. NAP also reduces MCI in phase II clinical trials.

• Peptides which are not derivative from Amyloid- β peptide series including enhanced amino acids

Upon oral administration of D-4F to mice, it was observed that the deposition of amyloid- β peptide was impeded and enhanced the cognitive utility. PP-Leu is a cyclic tridecapeptide equivalent of θ -defensins. This peptide coalesces the capacity to impede Amyloid- β oligomer and amyloid fibril

proliferations, by isolation of Amyloid- β peptides into fabrications that are colloidal-like, with a increased impediment to

endo-proteinase K.

Table 1. AD modifying peptides with brief description. Abbreviations: act. (activity); agg. (aggregation); att. (attenuates); hyperph. (hyperphosphorylation); infl. (inflammation); NFF (neurofilament formation); pII. c.t. (phase II clinical trials); pl. form. (plaque formation); ref. (reference); stim. (stimulates); α -S (α -secretase); ● (observed effect).

Peptide Name and Ref.	Att. Brain Infl.	Att. A β p Agg./Pl. Form.	Att. Tau Hyperph./NFF	Stim. Neurog.	Improves Cognition	Stim. α -S Act.
Ac-Leu-Pro-Phe-Phe-Asp-NH ₂ (iAb5p), [249]		●				
LPFFFD-PEG, [253,254]		●				
D-(PGKLVYA), [255]		●				
RI-OR2-TAT, [260]	●	●		●		
cyclo(17, 21)-(Lys17, Asp21)A β (1-28), [366]		●				
SEN304, SEN1576, [265,266]		●				
α sheet peptides, [267]		●				
NAP, [268,273,361]		●	●		● (pII. c.t.)	
D4-F, [274]		●			●	
D3, [356]		●			●	
PP-Leu, [275]		●				
TFP5, [355]	●	●	●			
wtNBD, [358]	●	●			●	
PACAP38, [360]					●	●
insulin, [181,183,189,191,362-365]					● (pII. c.t.)	

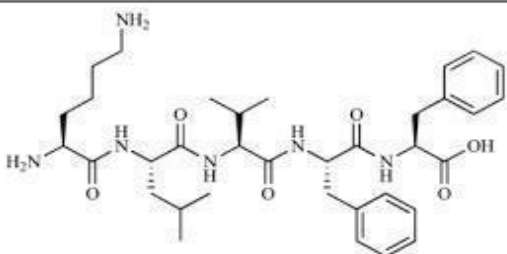
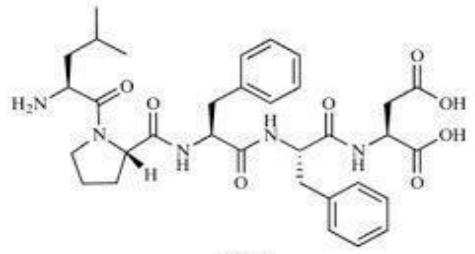
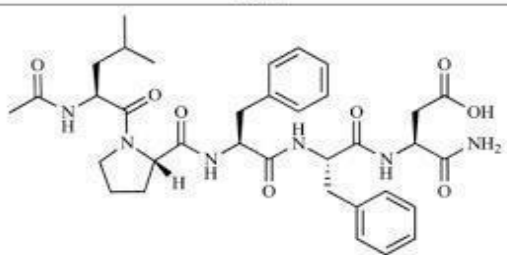
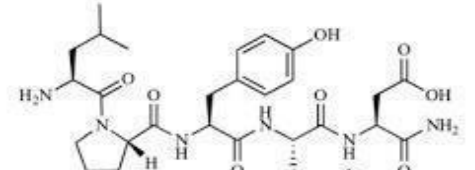
Name	Structure	D/L
KLVFF		L
iAβ5: LPFFD	 L-form	L/D
Ac-4Aβ5-amid		L
LPYFDa		L

Table 2: Examples of Amyloid-β inhibitors

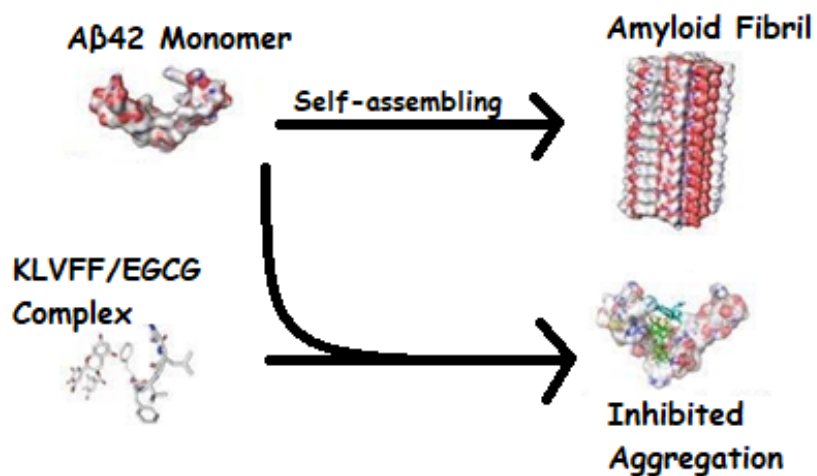


Figure 13: KLVFF inhibitor peptide of Amyloid-beta

BACE-1 INHIBITOR

BACE stands for beta-site Amyloid- β polypeptide precursor cleaving enzyme 1. It is responsible for the cleavage of proteins and as it is a predecessor, it is the essential biological-catalyst in the formation of Amyloid- β peptide.

This polypeptide has been an essential object of ridicule, that can modify the disease, for the drug advancement to treat alzheimer's.

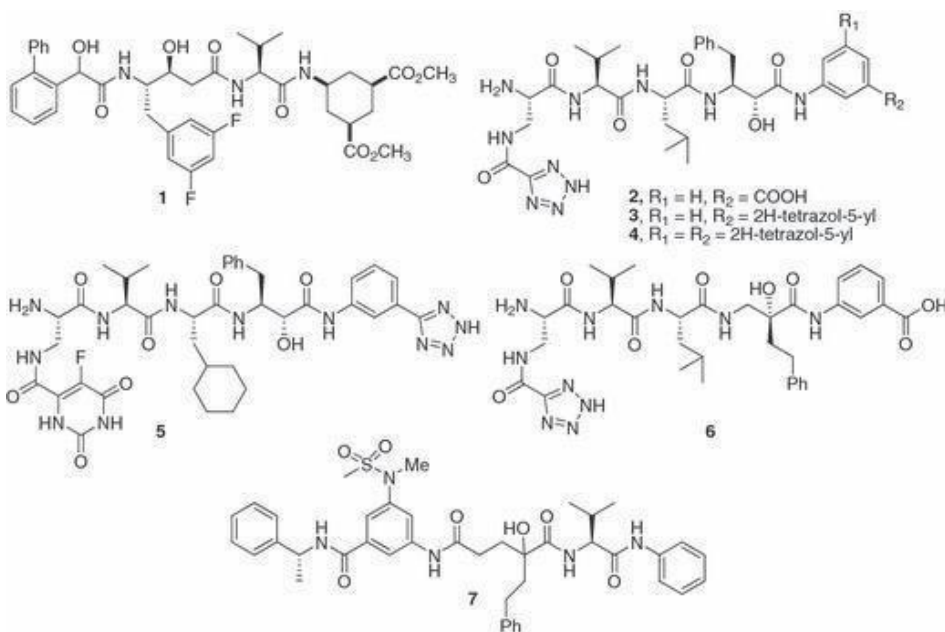
The different categories of beta-secretase inhibitors are:-

Pseudopeptide β -secretase inhibitors

The first is OM99 - 2 that is a highly potent inhibitor that was developed upon the scaffold of the substrate of

β -secretase where the amide bond that is undergoing scission is being replaced by a transition-state isostere, Leu-Ala hydroxyethylene.

Figure 14: Examples of Pseudopeptide β -secretase inhibitors



Hydroxyethylene-based inhibitors

This is a transition state isostere which was found to be a scaffold that provided

small molecule, and potent inhibitors of β -secretase

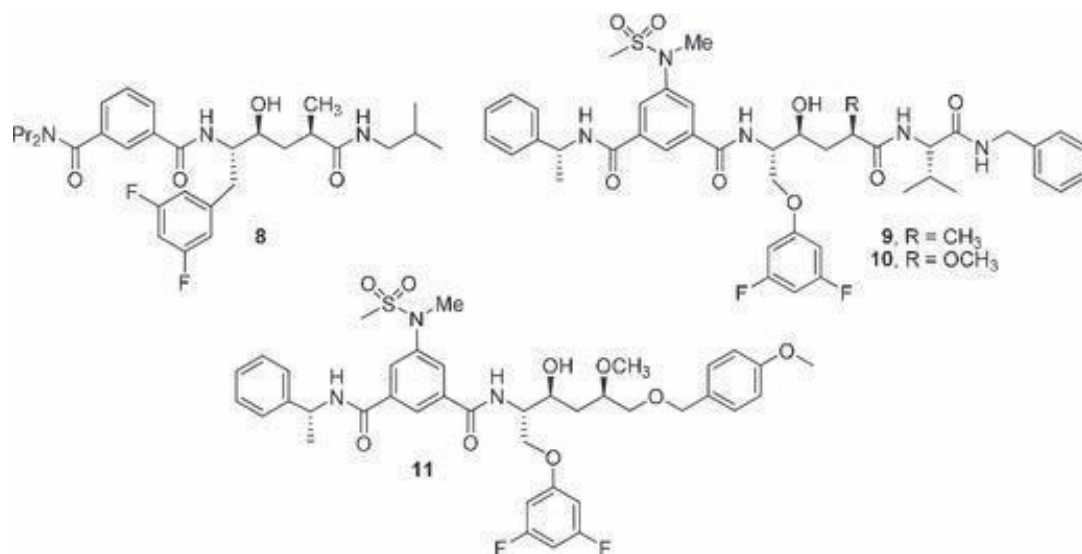
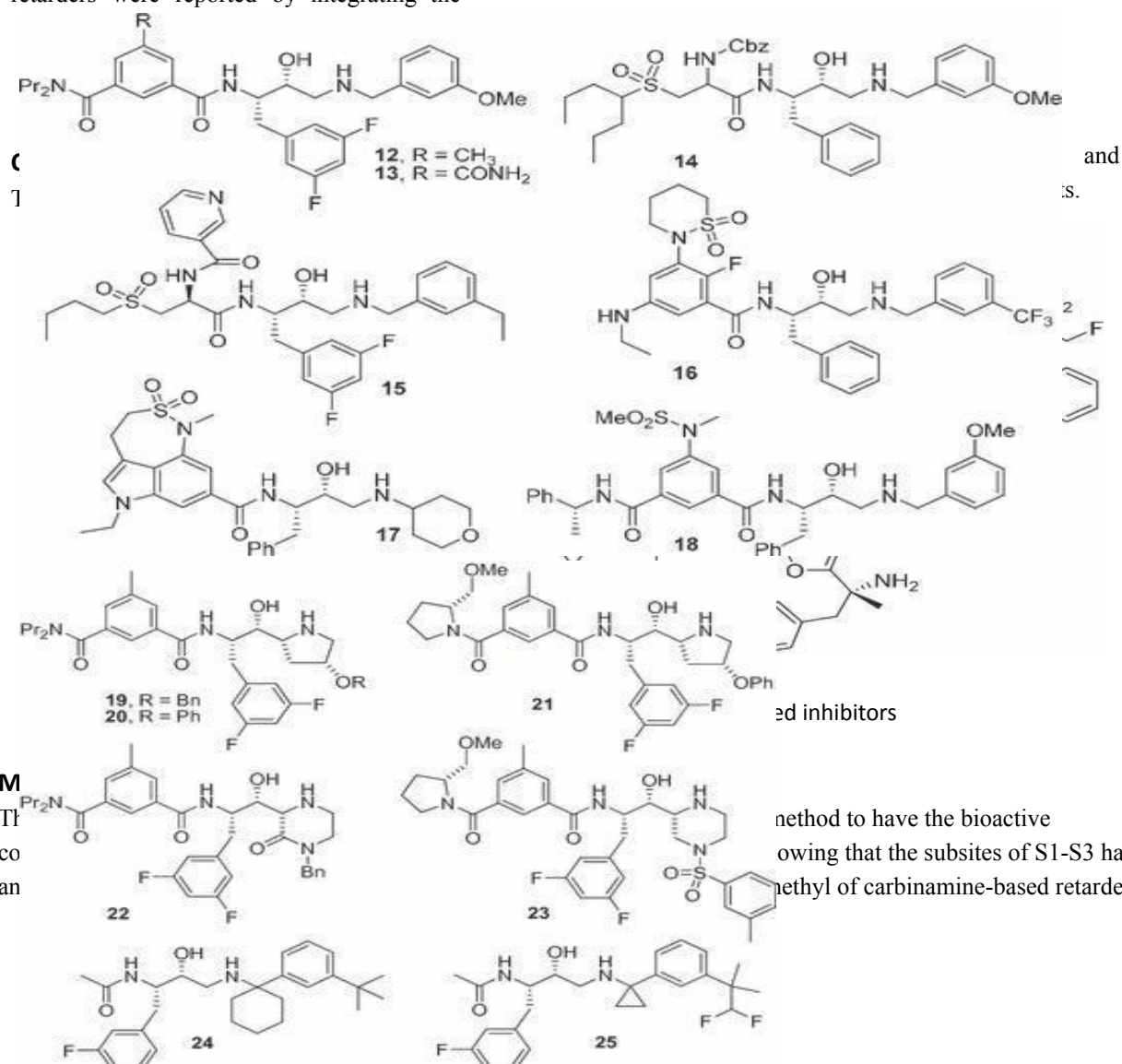


Figure 15: Examples of Hydroxyethylene-based inhibitors

Hydroxyethylamine (HEA)-based inhibitors

A sequence of Hydroxyethylamine-based retarders were reported by integrating the

isostere of HEA along iso-phthalamide moiety. A P1 aryl group being the 3,5-difluorophenyl fragment.



M
T
co
an

ed inhibitors

method to have the bioactive owing that the subsites of S1-S3 have methyl of carbinamine-based retarder at

P3 and the P1 aryl group which may increase the potency as it stabilizes the bioactive conformation and also enhancing the physicochemical accountability of the non-cyclic series with the formation of macrocyclic ethers and macro-lactones.

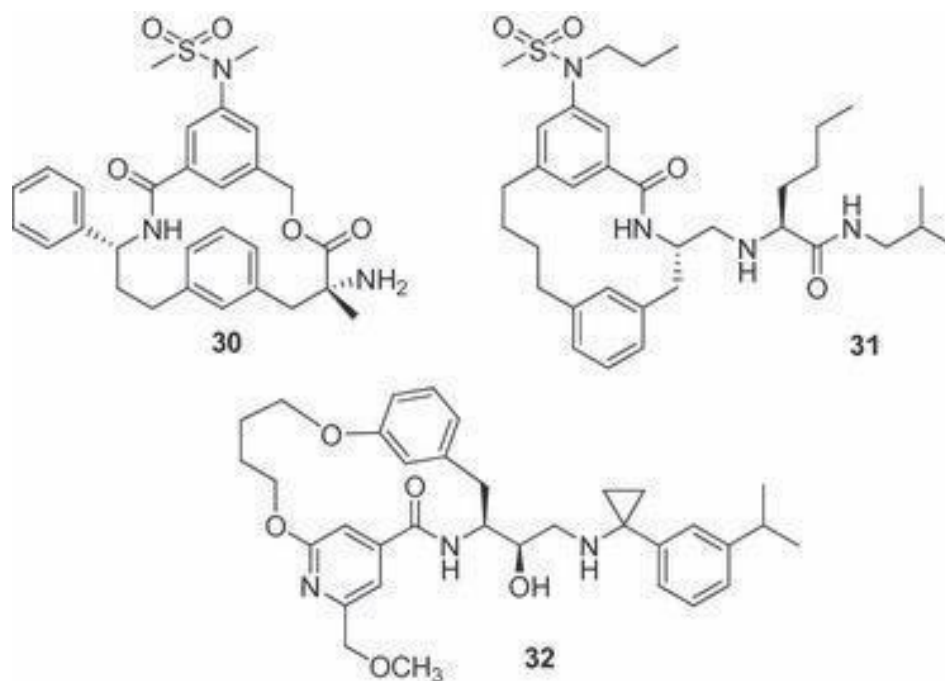


Figure 18: Examples of Macrocyclic inhibitors

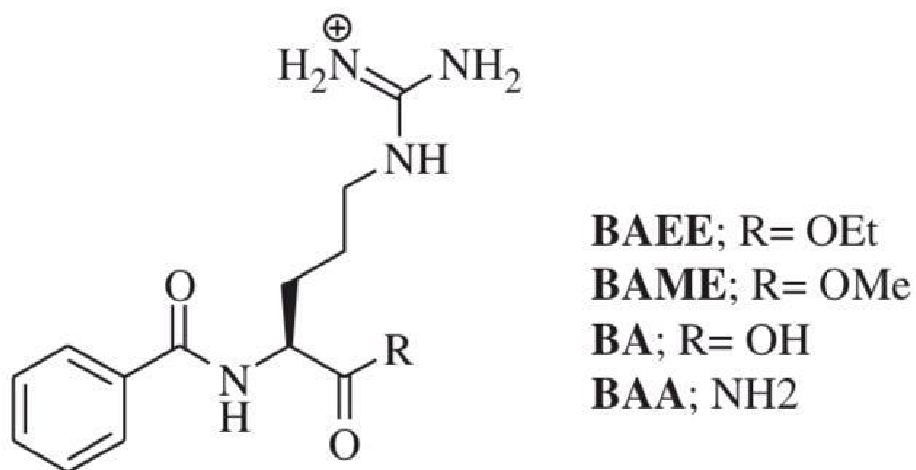


Figure 19: Structures of the known PAD4 (Protein Arginine Deiminase 4) – reversible inhibitors

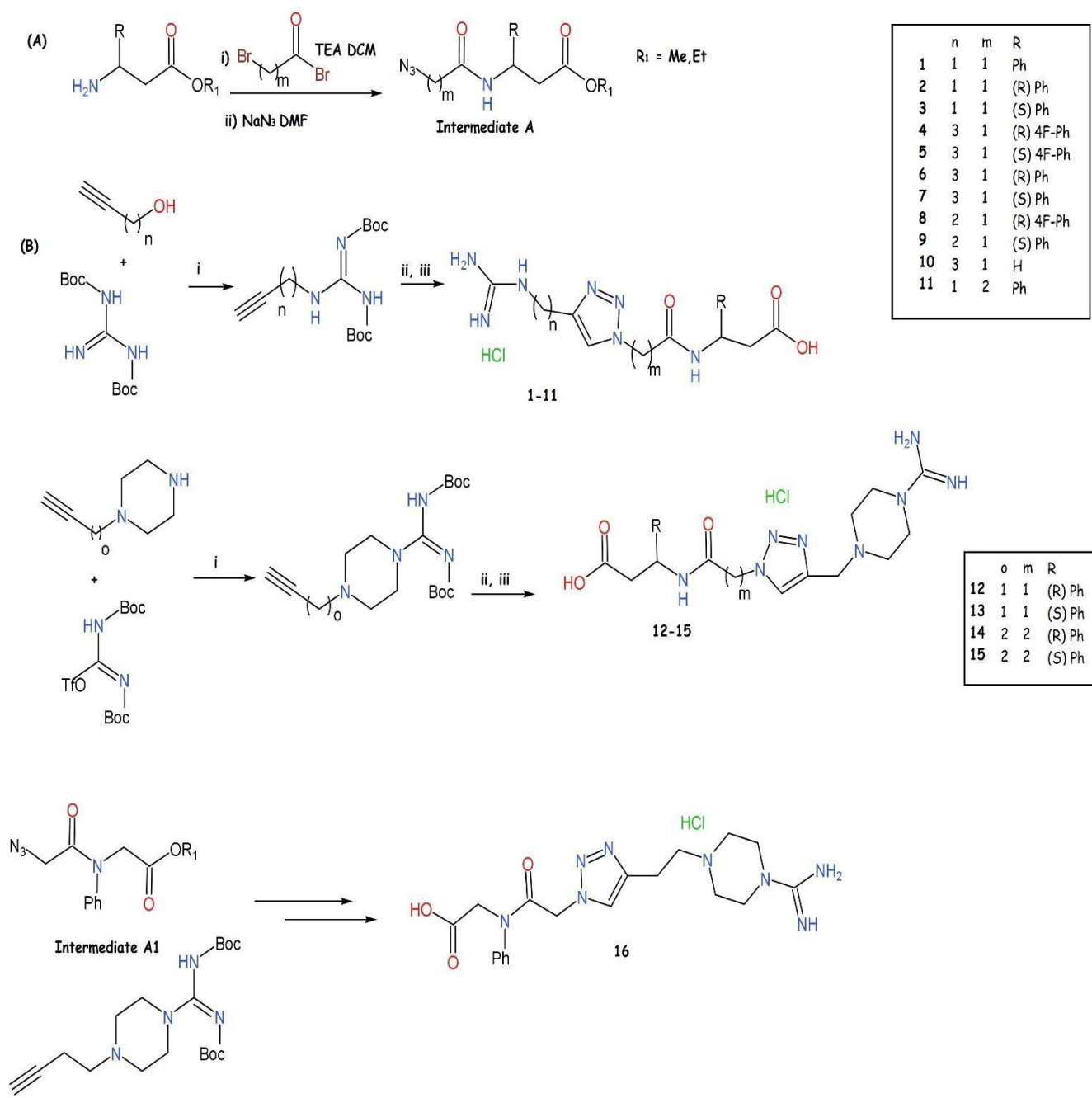


Figure 20: Synthesis of PAD4-reversible inhibitors

Peptidomimetic Approach to Targeting Pre-amyloidogenic States in Type II Diabetes

Diseases like Alzheimer's and type II diabetes are associated with the formation of protein fibers. Systems like the one from type II diabetes which is IAPP (islet amyloid polypeptide); lipid bilayers can catalyze the formation of fibers. Contradictory but true, amyloid fibers are beta-sheets' opulent though the α -helical are the membrane-stabilized states. IS5, a helix mimetic, is a small molecule that shows to impede the double-layer facilitator of fiber formation and to reduce the islet amyloid polypeptide-stimulated noxiousness. The interactions between islet amyloid polypeptide and IS5 confine to the alpha-helical zone of islet amyloid polypeptide. This reveals, the alpha-helical zones are on route in the proliferation of fibers. islet amyloid polypeptide doesn't stack up like amyloid because insulin prevents that self-assembly. Hence, insulin produces synergistic effect with IS5 inhibition. Therefore, IS5 is a new method to inhibit amyloid.

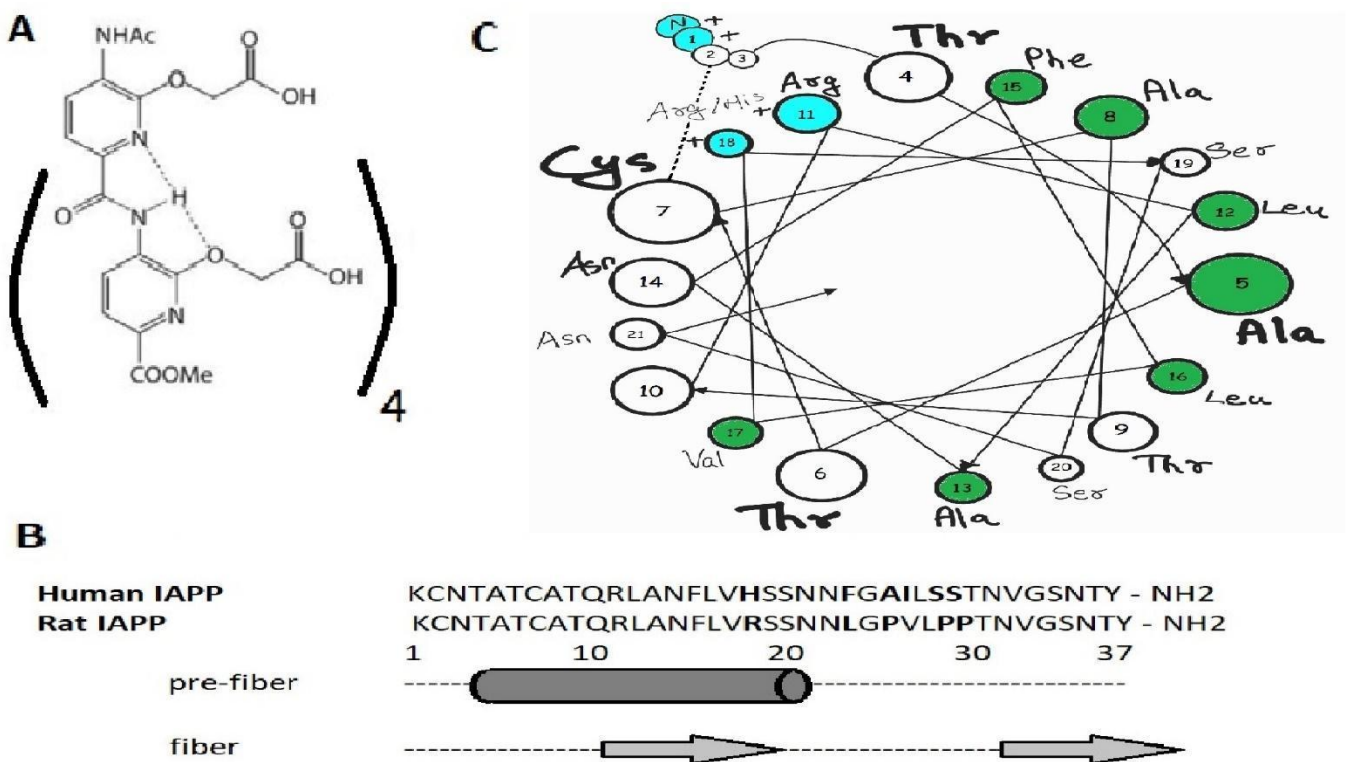


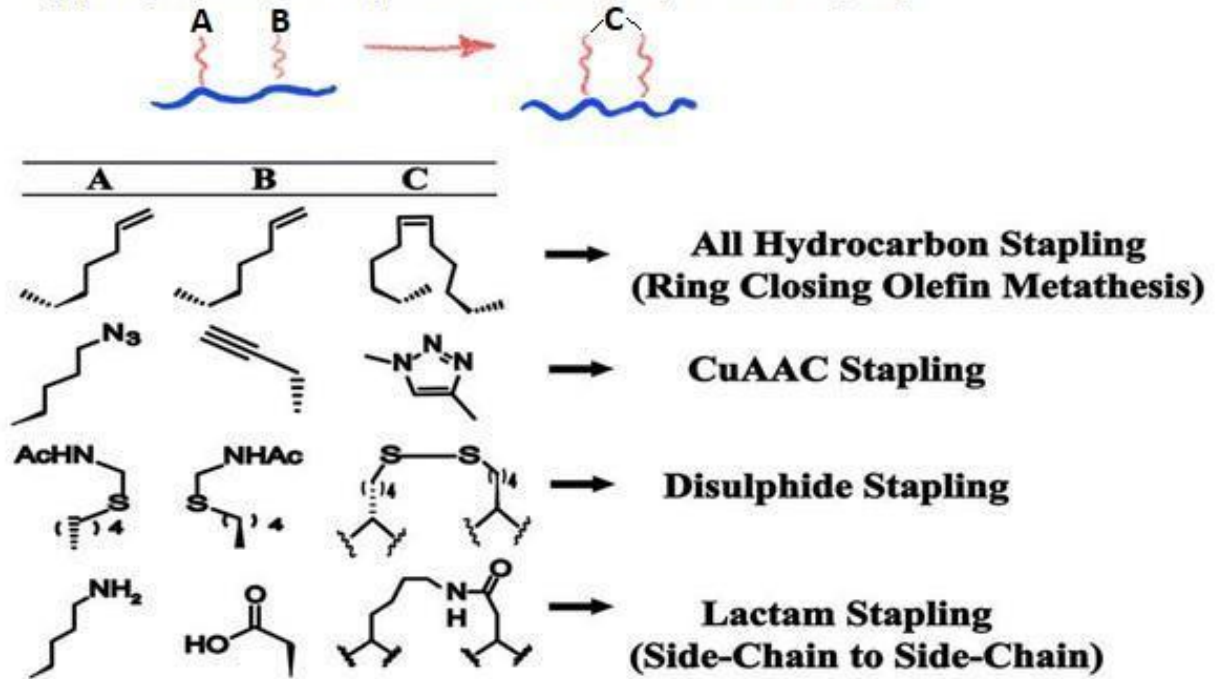
Figure 21: Structural Representation of IS5 and IAPP

PEPTIDE STAPLING

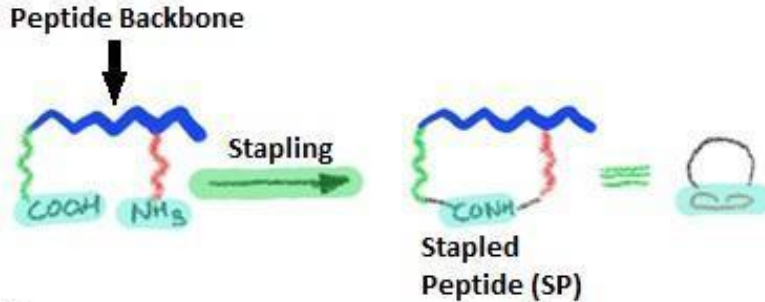
Stapling of a peptide is a new strategy for oligomers into structurally organized macrocycles by “stapling” or covalent linking, by use of a linker, the side chains of the two amino acids of the peptide. This approach morphed and ameliorate the binding properties of peptides as it increased their target binding affinity, proteolytic resistance, and cell penetration affinity. Stapled peptides are known for their potency and represent a class of α -helical peptidomimetics of stable macrocyclic. This

results in an efficient binding to the targets.

(a) Reported Techniques on One - Component Stapling



(b) Present Work (Tail to Side-Chain Stapling)



(c) Proposed Mechanism for Inhibition of A β Aggregation

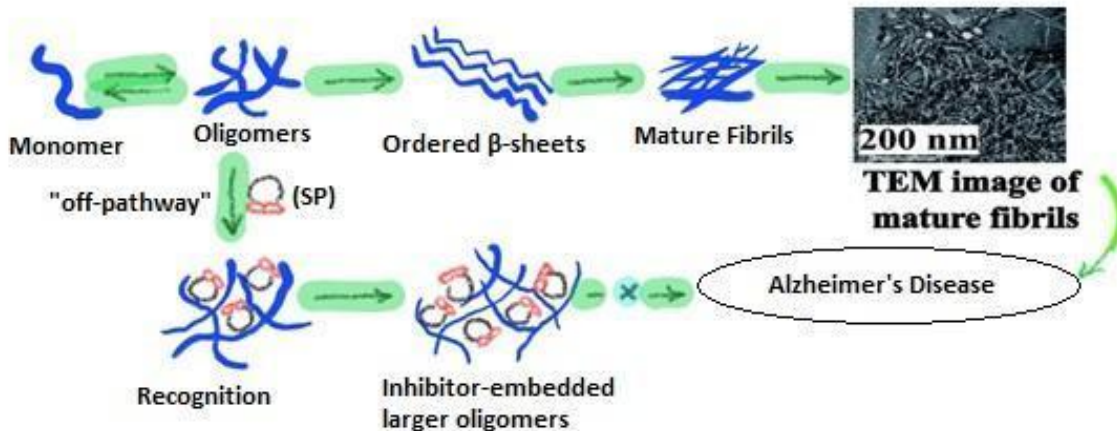


Figure 22: Peptide Stapling

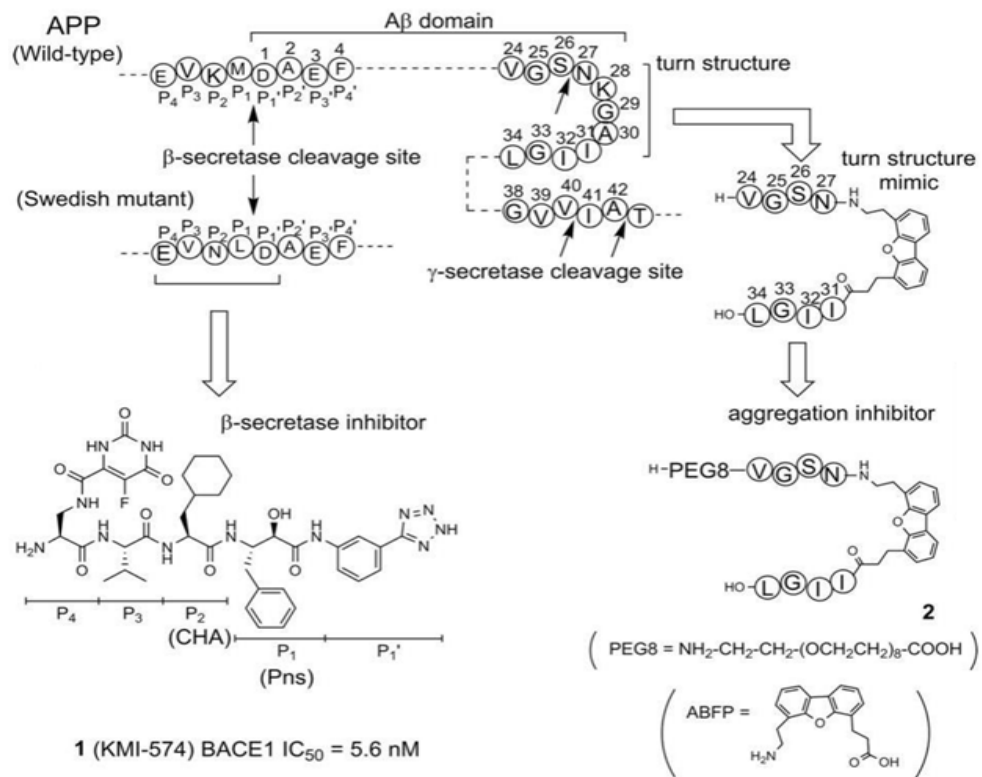


Figure 23: Few more structures of inhibitors

REFERENCES

1. Yoshio Hamada, and Zyta M. Ziora, *Methods Mol Biol.* **2020**, 2103, 215-223
2. Cheng X, Zhou Y, Gu W, Wu J, Nie A, Cheng J, Zhou J, Zhou W, Zhang Y, *Journal of Alzheimer's Disease* **2013**, 37(4)
3. Deepti Goyal, Suniba Shuaib, Sukhmani Mann, and Bhupesh Goyal, *ACS Comb Sci.* **2017**, 19(2), 55-80
4. K. Rajasekhar, S. N. Suresh, Ravi Manjithaya, and T. Govindaraju, *Sci Rep.* **2015**, 5, 8139
5. Synthetic peptide can inhibit toxicity, aggregation of protein in Alzheimer's disease, *University of Washington*, **2019**
6. Medications for Memory, Cognition, and Dementia-related Behaviors
7. A. Spagnoli, and G. Tognoni, *Springer Clin. Pharmacol. Ther.* **1983**, 26, 44-69
8. Arun K. Ghosh, Margherita Brindisi, and Jordan Tang, *J Neurochem.* **2012**, 120, 71-83
9. β fibrillogenesis – Sujan Kalita, Sourav Kalita, Ashim Paul, Amar Sarkar, and Bhubhaneshwar Mandal, *RSC Chem. Sci.* **2020**, 11, 4171-4179
10. James A. Hebda, Ishu Saraogi, Mazin Magzoub, Andrew D. Hamilton, Andrew D. Miranker, *Chem. Biol.* **2009**, 9, 943-950
11. Andrea Trabocchi, Nicolino Pala, Ilga Krimmelbein, Gloria Menchi, Antonio Guarna, Mario Sechi, *J Enzyme Inhib Med Chem.* **2015**, 30(3), 466-471
12. Roy K. Hom, Andrea F. Gailunas, Shumeye Mamo, Larry Y. Fang, Jay S. Tung, Donald E. Walker, David Davis, Eugene D. Thorsett, Nancy E. Jewett, Joseph B. Moon, and Varghese John, *J Med Chem.* **2004**, 47(1), 158-164
13. Andrew Stamford, and Corey Strickland, *Curr Opin Chem Biol.* **2013**, 17(3), 320-328
14. Zhili Zuo, Xiamin Luo, Weiliang Zhu, Jianhua Shen, Xu Shen, Hualing Jiang, and Kaixian Chen, *Bioorg. Med. Chem.* **2005**, 13(6), 2121-2131
15. Schwarze B, Korn A, Höfling C, Zeitschel U, Krueger M, Roßner S, Huster D., *Sci Rep.* **2021**, 11(1), 23767
16. Ndemazie NB, Inkoom A, Morfaw EF, Smith T, Aghimien M, Ebesoh D, Agyare E., *AAPS PharmSciTech.* **2021**, 23(1), 11
17. Kanchi PK, Dasmahapatra AK, *J Mol Model.* **2021**, 27(12), 356
18. Mamsa SSA, Meloni BP, *Front Mol Neurosci.* **2021**, 14, 759729
19. Santoro A, Grimaldi M, Buonocore M, Stillitano I, D'Ursi AM, *Pharmaceuticals (Basel).* **2021**, 14(8), 732
20. Zhang Z, Wang Z, Ling Z, Li Y, Pan J, Gao Q, Zhang J, Yan L, Zhang Z, Li J, Xiao F, *Appl Microbiol Biotechnol.* **2021**, 105(11), 4649-4662
21. Windsor PK, Plassmeyer SP, Mattock DS, Bradfield JC, Choi EY, Miller BR 3rd, Han BH, *Int J Mol Sci.* **2021**, 22(6), 2888
22. Caporale A, Adorinni S, Lamba D, Saviano M., *Molecules.* **2021**, 26(5), 1219
23. Park KW, Wood CA, Li J, Taylor BC, Oh S, Young NL, Jankowsky JL, *Mol Ther.* **2021**, 29(7), 2294-2307
24. Ahmad M, Esposto J, Golec C, Wu C, Martic-Milne S, *Mol Cell Biochem.* **2021**, 476(6), 2393-2408
25. Maiti BK, Govil N, Kundu T, Moura JIG, *iScience.* **2020**, 23(12), 101792
26. Ziaunys M, Sakalauskas A, Smirnovas V, *Biomacromolecules.* **2020**, 21(12), 4989-4997
27. Saini RK, Shuaib S, Goyal D, Goyal B, *ACS Omega.* **2020**, 5(36), 23219-23228
28. Pandey G, Ramakrishnan V, *Biophys Rev.* **2020**, 12(5), 1175-1186
29. Sakalauskas A, Ziaunys M, Smirnovas V, *Sci Rep.* **2020**, 10(1), 14466
30. Kaur A, Kaur A, Goyal D, Goyal B, *ACS Omega.* **2020**, 5(25), 15606-15619
31. Stanciu GD, Bild V, Ababei DC, Rusu RN, Cobzaru A, Paduraru L, Bulea D, *J Clin Med.* **2020**, 9(6), 1713
32. Khan S, Barve KH, Kumar MS, *Curr Neuropharmacol.* **2020**, 18(11), 1106-1125
33. Horsley JR, Jovcevski B, Wegener KL, Yu J, Pukala TL, Abell AD, *Biochem J.* **2020**, 477(11), 2039-2054
34. Goyal B, Goyal D, *ACS Comb Sci.* **2020**, 22(6), 297-305
35. Ali N, Shamoona A, Yadav N, Sharma T, *ACS Omega.* **2020**, 5(11), 5781-5783
36. Jiang X, Halmes AJ, Licari G, Smith JW, Song Y, Moore EG, Chen Q, Tajkhorshid E, Rienstra CM, Moore JS, *ACS Macro Lett.* **2019**, 8(10), 1365-1371
37. Veraldi N, Zouggari N, de Agostini A, *Molecules.* **2020**, 25(2), 390
38. Sneideris T, Sakalauskas A, Sternke-Hoffmann R, Peduzzo A, Ziaunys M, Buell AK, Smirnovas V, *Biomolecules.* **2019**, 9(12), 855
39. Yang H, Li X, Zhu L, Wu X, Zhang S, Huang F, Feng X, Shi L, *Adv Sci (Weinh).* **2019**, 6(22), 1901844
- Armiento V, Spanopoulou A, Kapurniotu A, *Angew Chem Int Ed Engl.* **2020**, 59(9), 3372-3384
40. Gandbhir O, Sundaram P, *J Alzheimers Dis Rep.* **2019**, 3(1), 77-94
41. Jiang Y, Jiang X, Shi X, Yang F, Cao Y, Qin X, Hou Z, Xie M, Liu N, Fang Q, Yin F, Han W, Li

