Synthesis and simulation of new cyclodextrin derivatives breaker for Aβ42

Abstract
The amyloid Aβ-42, a peptide involved, following a conformational change in β sheets in the pathology of the main neurodegenerative disorder of Alzheimer’s disease, is targeted in our study, the latter of which reports the synthesis of two inhibitors linked to a specific recognition sequence synthesized during this work (Tryp-Val-Val-COOH), one linked to an aziridine and the other to a methylated β-CD in order to be able to stop the aggregation of the peptide involved.

Keywords: Alzheimer, peptidomimetic, cyclodextrin, fibrillogenesis

Nomenclature: CD, cyclodextrin; Tryp, Tryptophan; Val, Valin

Introduction
Alzheimer disease (AD) is a neurodegenerative disorder and is associated with accumulation of amyloid and tau depositions in the brain.1-3 If we succeed in blocking fibrillogenesis, we must first block the aggregation of amyloid Aβ42, targeting as far as chemists residues responsible for folding. Several studies have been carried out to identify the minimum sequence necessary for the fibrillation of the Aβ peptide. The Aβ19-28 sequence is sufficient to form amyloid fibers.4 As for the first 17 residues of the N-terminal part of the Aβ peptide are not necessary for the formation of amyloid fibers.5 Their elimination makes it possible to amplify the fibrillation. The Aβ16-20 sequence, KLVFF (Figure 1), is designated as necessary for the interaction between Aβ peptides.6,7 Many inhibitors have been developed in recent years, most of which are of peptide nature or are peptide mimics. A large part of the inhibitors is based on the hydrophobic core of the β sheet of the N-terminal domain: the LVFF sequence (Aβ17-20).8–20

Figure 1 Structure of Aβ40 and Aβ42 that is involved in fibril formation.21

Materials and methods
All the reactions with dry solvents were carried out under dry nitrogen. THF was dried over sodium /benzophenone and freshly distilled before use; CH2Cl2 was distilled and dried over phosphorus pentoxide (P2O5). I.R spectra were collected from a Mattson Genesis II FTIR. NMR spectra were recorded in CDC13 on a Bruker 300MHz instrument, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in β (ppm) and coupling constant (J) values in Hertz (Hz). ESI-MS data were recorded in the positive ion mode on a quadrupole instrument (Waters-Micromass ZQ). Melting points were determined on an Electrothermal T1A F3.15A instrument. Column chromatography was performed on silica gel 230-270 mesh (Merck) using CH2Cl2, MeOH and ether. Elemental analysis was performed only for solids on a LECO CHN 900 instrument.

Results and discussion
Synthesis of β-Sheet breakers A and B

Our approach consists to develop β-sheet breaker peptides. Several derivatives peptides have been synthesized. The amyloid deposition could be stopped by synthetic peptides partially homologous to the Aβ hydrophobic region and containing residues disrupting β-sheet formation (Figure 2). Our synthetic pathways to our target aziridines 6a-c are presented in Schemes 1 and 2. The synthesis of tosylate aziridine 4, was achieved by the O-protection of glycidol 1 with p-toluenesulfonyl chloride (TsCl). And was treated with ammonium chloride and sodium azide to give the azido alcohol 3, which was reacted in the next step with a solution of triphenylphosphine (PPh3). The biological activity of aziridines is highly related to the establishment of covalent bond with DNA.22 In a previous investigation of our group we noted the synthesis of aziridinyl that had antitumor activities against breast cancer cells (Figure 3).23,34

Figure 2 Structure of β-sheet breakers A with aziridine moiety as disrupting group.
We have already reported the synthesis of several aziridines, 25–27 that moiety of amino acids phthaloyl group with a phosphonate, surprisingly, the biological activity of ser of phosphonates aziridines shifted from antiviral to an antibacterial one. 28–31 For the second inhibitor, we choose β-cyclodextrine (β-CD) as disrupting group coupled with the same specific recognition sequence of tripeptid (Try-Val-Val) (Figure 4).

Cyclodextrins (CDs) are compounds that are produced by the enzymatic degradation of starch. The three most common CDs have 6, 7, and 8 glucopyranose units in the cyclic and are named α-CD, β-CD, and γ-CD, respectively. 32 Whereas the depth of the cavity for these CDs is 8 Å, the sizes of the cavity are different for α-CD, β-CD, and γ-CD, being 6, 8, and 10 Å, respectively (Figure 5). 33–44

So our idea to incorporate a cyclodextrine for improvement of vectorization of tripeptid in vivo and to insert a large disturbing group between the β-sheet of Aβ aggragation which will imply the rupture of the hydrogen bonds. In addition, the intra-inclusion study of chain Try-Val-Val or inclusion of (Aβ-42) inside the cavity of CD can improve the interaction and blocked the Amyloid Fibrillogenesis.

Tripeptid Try-Val-Val 5 was reacted either with thionyl chloride in the presence of TEA to yield, an acyl chloride that was reacted with aziridine 4 to give breakers A, or coupled in the presence of dicyclohexylcarbodiimide (DCC) as coupling agent with CD at room temperature, giving the breakers B in medium yield (50-65%) (Figure 6).

The study by MOE docking showed that structure of brekears A with only aziridine moiety group was the best interaction than B with Aβ42 (Figure 7). Only biological evaluation in vivo can give wish are the best inhibitors (Figure 8).
Conclusions

To conclude we can say that eradicating Alzheimer’s disease in a radical way, we are not yet there but the fact to look into this problem by studying the issue of beta amyloid (Aβ–42) remains a fairly studious approach. We developed two inhibitors A and B with aziridine or CD as disrupting group to be able to stop the fibrillar aggregation, a way still remains to be done to really develop them. In order to ensure their effectiveness, it is necessary to confirm their aggregation, a way still remains to be done to really develop them.

References

1. Aileen Funkel S, Willbold D. Peptides for Therapy and Diagnosis of Alzheimer’s Disease. Current Pharmaceutical Design. 2012;18:755–767.
2. Alzheimer A. About a strange disease of the cerebral cortex. All Z Psychiat. 1907;64:146–148.
3. Lin LX, Bo XY, Tan YZ, et al. Feasibility of β-Sheet Breaker Peptide –H102 Treatment for Alzheimer’s Disease Based on β –Amyloid Hypothesis. Plosone. 2004.
4. Gorevic P, Castano E, Sara R, et al. Ten to fourteen residue peptides of Alzheimer’s disease protein are sufficient for amyloid fibril formation and its characteristic Xray diffraction pattern. Biochem Biophys Res Commun. 1987;147:846–862.
5. Pike CI, Overman MJ, Cotman CW. Amino – terminal deletions enhance aggregation of β –amyloid peptides in vitro. J Biol Chem. 1995;270:23895–23898.
6. Tjernberg LO, Náslund J, Lindqvist F, et al. Arrest of β –Amyloid Fibril Formation by a Pentapeptide Ligand. J Biol Chem. 1996;271:8545–8548.
7. Tjernberg LO, Lillienhök C, Callaway DJE, et al. Controlling Amyloid β –Peptide Fibril Formation with Protease –stable Ligands. J Biol Chem. 1999;272:12601–12605.
8. Tjernberg LO, Callaway DJE, Tjernberg A, et al. A molecular model of Alzheimer amyloid β –peptide fibril formation. J Biol Chem. 1999;274:12619–12625.
9. Soto C, Sigurdsson EM, Morelli L, et al. β –sheet breaker peptides inhibit fibrillogenesis in a rat brain model of amyloidosis: Implications for Alzheimer’s therapy. Nat Med. 1998;4:822–826.
10. Dufour E. Inhibitors and molecular models of beta and tau amyloid fibers involved in Alzheimer’s disease: design. Synthesis and characterization. 2006.
11. Bett CK, Ngunjiri JN, Serem WK, et al. Effects of Peptides Derived from Terminal Modifications of the Ap ꞏCentral Hydrophobic Core on Aβ Fibrilization. ACS Chem Neurosci. 2010;1:608–626.
12. Hamada Y, Miyamoto N, Kiso Y, et al. Novel β –amyloid aggregation inhibitors possessing a turn mimic. Bioorganic & Medicinal Chemistry Letters. 2015;25:1572–1576.
13. Bartolini M, Andrisano V. Strategies for the Inhibition of Protein Aggregation in Human Diseases. Chem Bio Chem. 2010;11:1018–1035.
14. DeToma AS, Salamekh S, Ramamoorthy A, et al. Misfolded Proteins in Alzheimer’s Disease and Type II Diabetes. Chem Soc Rev. 2012;41:620–621.
15. Convertino M, Pellarin R, Catto M, et al. 9,10 –Anthraquinone hinders beta – aggregation: how does a small molecule interfere with Abeta – peptide amyloid fibrillation?” Protein Sci. 2009;18:792–800.
16. Guizar N, Bajda M, Rakoczy J, et al. Isoindoline –1,3 –dione derivatives targeting cholinesterases: design, synthesis and biological evaluation of potential anti –Alzheimer’s agents. Bioorg Med Chem. 2015;23:1629–1637.
17. Więckowska A, Więckowski K, Bajda M, et al. Synthesis of new N –benzy/1piperidine derivatives as cholinesterase inhibitors with β – amyloid anti –aggregation properties and beneficial effects on memory in vivo. Bioorg Med Chem. 2015;23:2445–2457.
18. Guizar N, Bajda M, Skrok M, et al. Development of multifunctional, heterodimeric isoidoline –1,3 –dione derivatives as cholinesterase and β –amyloid aggregation inhibitors with neuroprotective properties. Eur J Med Chem. 2015;92:738–749.
19. Panek D, Więckowska A, Wichur T, et al. Design, synthesis and biological evaluation of new phthalimide and saccharin derivatives with alicyclic amines targeting cholinesterases, beta –secrectase and amyloid beta aggregation. European Journal of Medicinal Chemistry. 2017;125:676–695.
20. Lu C, Gao Y, Li J, et al. Design, synthesis, and evaluation of resveratrol derivatives as Aβ(42) aggregation inhibitors, antioxidants, and neuroprotective agents. Bioorg & Medicinal Chemistry Letter. 2012;22:7683–7687.
21. Singh SK. Overview of Alzheimer’s Disease and Some Therapeutic Approaches Targeting Aβ by Using Several Synthetic and Herbal Compounds. Oxidative Medicine and Cellular Longevity. 2016;22:7361613.
22. Trost BM, Fandrick DR. DYKAT of Vinyl Aziridines: Total Synthesis of (+)-Pseudodistomin D. Org Lett. 2005;7:823–825.
23. Yadav VK, V Srimurthy V. Silylmethyl - Substituted Aziridine and Azetidines Through Staudinger Reaction of 3-Azido-1,2-diols. J Biol Chem. 2005;127:16366–16367.
24. Ihata O, Kayaki Y, Ikariya T. Aliphatic Poly(urethane–amine)s Synthesized by Copolymerization of Aziridines and Supercritical Carbon Dioxide. Macromolecules. 2005;38:6429–6434.
25. Kajima Mulengi J, Keniche A, Mezrai A. Unexpected Formation of Azidines Through Staudinger Reaction of 3-Azido-1,2-diols. Asian Journal of Materials Chemistry. 2016;1:38–44.
26. Kajima Mulengi J, Keniche A, Slama H, et al. Synthesis of novel 2-hydroxymethyl- phosphonoaziridines as antibacterial agents. Eur J Med Chem. 2012;22:7361613.
27. Kajima Mulengi J, Keniche A, Mezrai A. Unexpected Formation of Azidines Through Staudinger Reaction of 3-Azido-1,2-diols. Asian Journal of Materials Chemistry. 2016;1:38–44.
28. Kajima Mulengi J, Keniche A, Slama H, et al. Synthesis of novel 2-hydroxymethyl- phosphonoaziridines as antibacterial agents. Eur J Med Chem. 2012;22:7361613.
32. Kicuntod J, Sangpheak K, Mueller M, et al. Theoretical and Experimental Studies on Inclusion Complexes of Pinostrobin and β-Cyclodextrins. Sci Pharm. 2018; 30:86–90.

33. Davis ME, Brewster ME. Cyclodextrin-based pharmaceuticals: past, present and future. Nature Rev Drug Discov. 2004;3:1023–1035.

34. Szejtli J. Introduction and General Overview of Cyclodextrin Chemistry. Chem Rev. 1988;98:1743–1754.

35. M. Del Valle EM. Cyclodextrins and their Uses: A Review. Process Biochem. 2004;39:1033–1046.

36. Hedges A. Industrial Applications of Cyclodextrins. Chem Rev. 1998;98:2035–2044.

37. Singh M, Sharma R, Banerjee U. Biotechnological applications of cyclodextrins. Biotechnol Adv. 2003;20:341–359.

38. Szejtli J. Cyclodextrins in the textile industry. Starch/Staerke. 2003;55:191–196.

39. Szente L, Szejtli J. Cyclodextrins as food ingredients. Trends Food Sci Technol. 2004;15:137–142.

40. Buschmann HJ, Knittel D, Schollmeyer E. New textile applications of cyclodextrins. J Incl Phenom Macrocycl Chem. 2001;40:169–172.

41. Marcelino VA, Zanin GM, Durrant LR, et al. Interaction of curcumin and bixin with β-cyclodextrin: complexation methods, stability, and applications in food. Journal of Agricultural and Food Chemistry. 2011;59:3348–3357.

42. Kant A, Linforth RST, Hort J, et al. Effect of beta cyclodextrin on aroma release and flavor perception. J Agric Food Chem. 2004;52:2028–2035.

43. Rekharsky MV, Inoue Y. Complexation Thermodynamics of Cyclodextrins. Chem Rev. 1998;98:1875–1918.

44. Connors KA. The Stability of Cyclodextrin Complexes in Solution. Chem Rev. 1997;97:1325–1358.