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# In Silico Design of Preventive Drugs for Alzheimer's Disease

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1. Introduction

Alzheimer's disease is a debilitating dementia occurring in the elderly. Its pathological symptoms include forgetfulness and memory loss (Mattson, 2004). Disease imposes financial burden on family and society. Current line of treatment only provides symptomatic relief (Davis & Powchik 1995; Sugimoto et al., 1995). Drugs of purely curative or preventive type are still not marketed. Commonly used drugs are Acetylcholine esterase inhibitors (Sugimoto et al., 1995) which temporarily alleviate symptoms by raising levels of neurotransmitter Acetylcholine and thus improving cognitive behavior. These drugs are associated with a number of adverse side effects as well (Davis & Powchik, 1995). The aim of this chapter is to discuss strategies and hurdles in the design of preventive drugs. In the following section we briefly discuss causes behind onset and progression of disease as it is imperative to understand these issues.

1.1 Generation of amyloid beta peptides and pathological condition of AD

This disease is characterized by production of amyloid beta (Aβ) plaques and intracellular neurofibrillary tangles in the brain (cf. fig.1). Amyloid plaques are formed by aggregation of Aβ peptide (Glenner & Wong, 1984) and neurofibrillary tangles are composed of hyper phosphorylated Tau protein (Alonso et al., 2001). 42 amino acid form of Aβ has been identified as the predominant constituent of plaques (Yin et al., 2007). Therefore preventive and curative strategies deal with reduction in Aβ 42 production. Aβ peptides are generated by successive cleavages of amyloid precursor protein (APP) by β and γ secretase (Potter & Dressal, 2000) enzyme. Aβ can also be cleaved by α secretase enzyme. Cleavage by α followed by γ secretase leads to formation of another truncated form of Aβ called P3. Aβ 42 is produced by cleavages taking place in Golgi (Hartman et al., 1997) apparatus. Cleavage of APP giving rise to different forms of Aβ is shown in fig.2. Discovery and isolation of these enzymes has provided us the benefit of a target for preventive drug designing. β secretase being the key enzyme involved has been assigned several popular names out of which β amyloid precursor protein cleaving enzyme (BACE 2) is the most frequently used. BACE is a transmembrane protein with aspartyl protease family catalytic motif as in pepsin (Yan et al., 2001). It is a homologous protein and interestingly not expressed in brain (Bennett et al., 2000). It is still an important enzyme target as transgenic mice lacking BACE gene produce little or no Aβ (Luo et al., 2003).
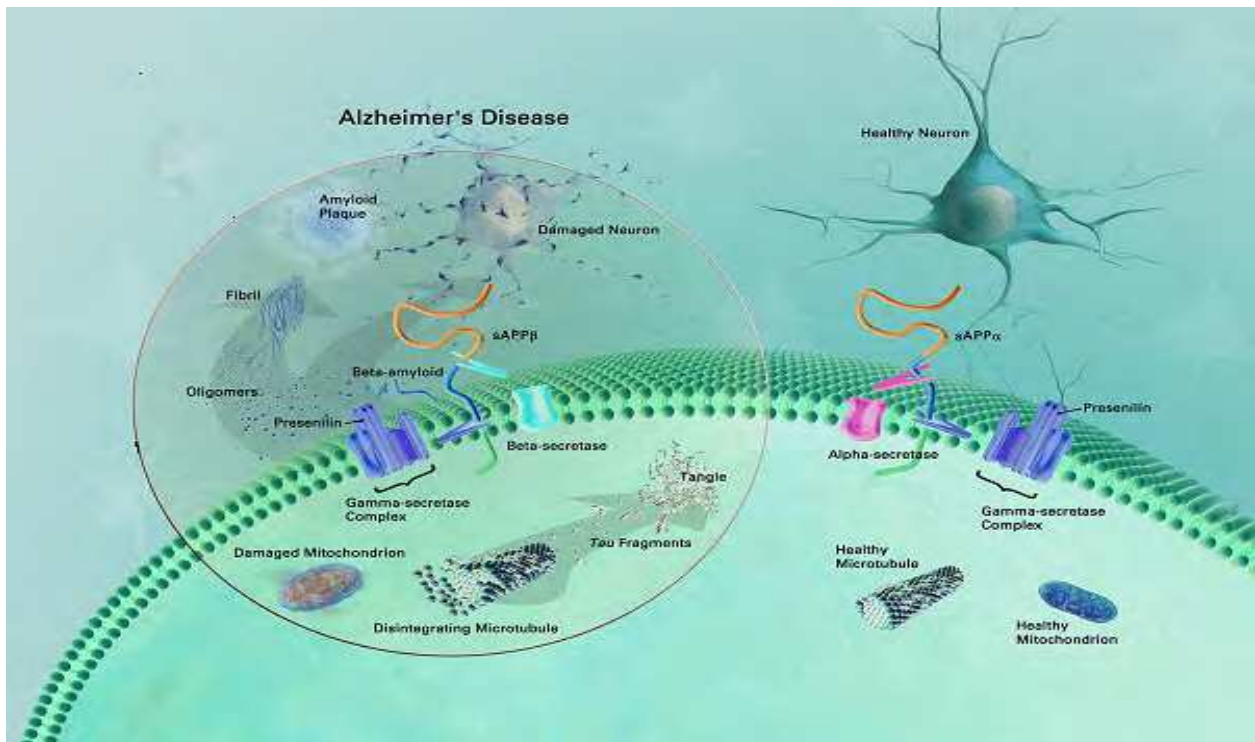
Damaged neuron in Alzheimer's Disease

Fig. 1. Shows a healthy neuron and presence of various enzymes. Encircled region shows formation of amyloid plaques and how they damage a healthy neuron
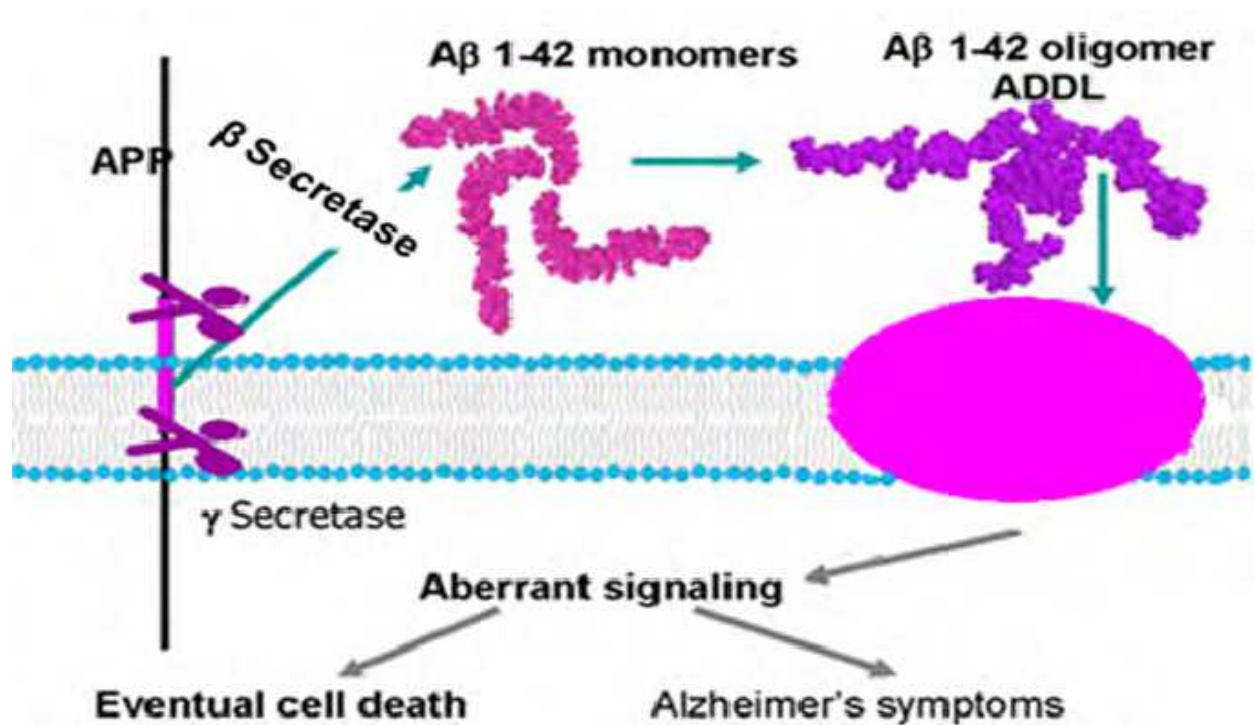
Production of amyloid derived diffusible ligands

Fig. 2. Shows formation of Aβ 42 monomers, their subsequent oligomerization to form diffusible ligands and generation of Alzheimer's symptoms

1.2 Past strategies for design of preventive drugs

Researchers involved in developing drugs for AD have employed numerous strategies to combat this disease. Most of the techniques involved interfere in formation of Aβ at some stage.

1.2.1 Secretase inhibition

Secretase enzyme is the most promising target. Inhibitors of β secretase as well as γ secretase have been synthesized. Both type of inhibitors stop formation of toxic Aβ. Chemical structures for some of these potency values (Kazikowsky et al., 1996; Harel et al., 1996; Camps et al., 1999; Weihofen et al., 2003) are shown in fig.3. Despite numerous efforts these preventive drugs have not been able to reach our markets due to their poor pharmacodynamics and bioavailability problems. These problems have been largely associated with peptidic nature of BACE inhibitors and failure to design low molecular weight inhibitors. These compounds also show inhibitory effect on other signal transduction pathways and are hence undesirable from this point of view as well.

1.2.2 Metal chelation

Aβ aggregation has been observed to be induced by several metal species including aluminum, iron, zinc and copper (Barnham et al., 2004). Therefore, apart from secretase inhibition anti aggregatory agents like metal chelators have been used which will remove metal ion thus reducing aggregation of Aβ peptide. Clioquinol, Deferriprone, Curcumin etc are such drugs (Hanson et al., 2007) (c. f. fig. 4). Although metal chelators lead to behavioral improvements but they have not emerged as preventive alternatives. Energetic aspects related to inefficiency of these drugs have been studied in this chapter.

1.2.3 NMDA receptor antagonism

Persistent activation of CNS NMDA receptor has been hypothesized in AD patients. Therefore, NMDA receptor antagonists have also been tried out as possible AD drugs (Kemp & Mc Kernan 2002). Memantine (c.f. fig. 4) is such a recent FDA approved drug for AD. It protects neuro cells against excess glutamate by partially blocking NMDA receptor.
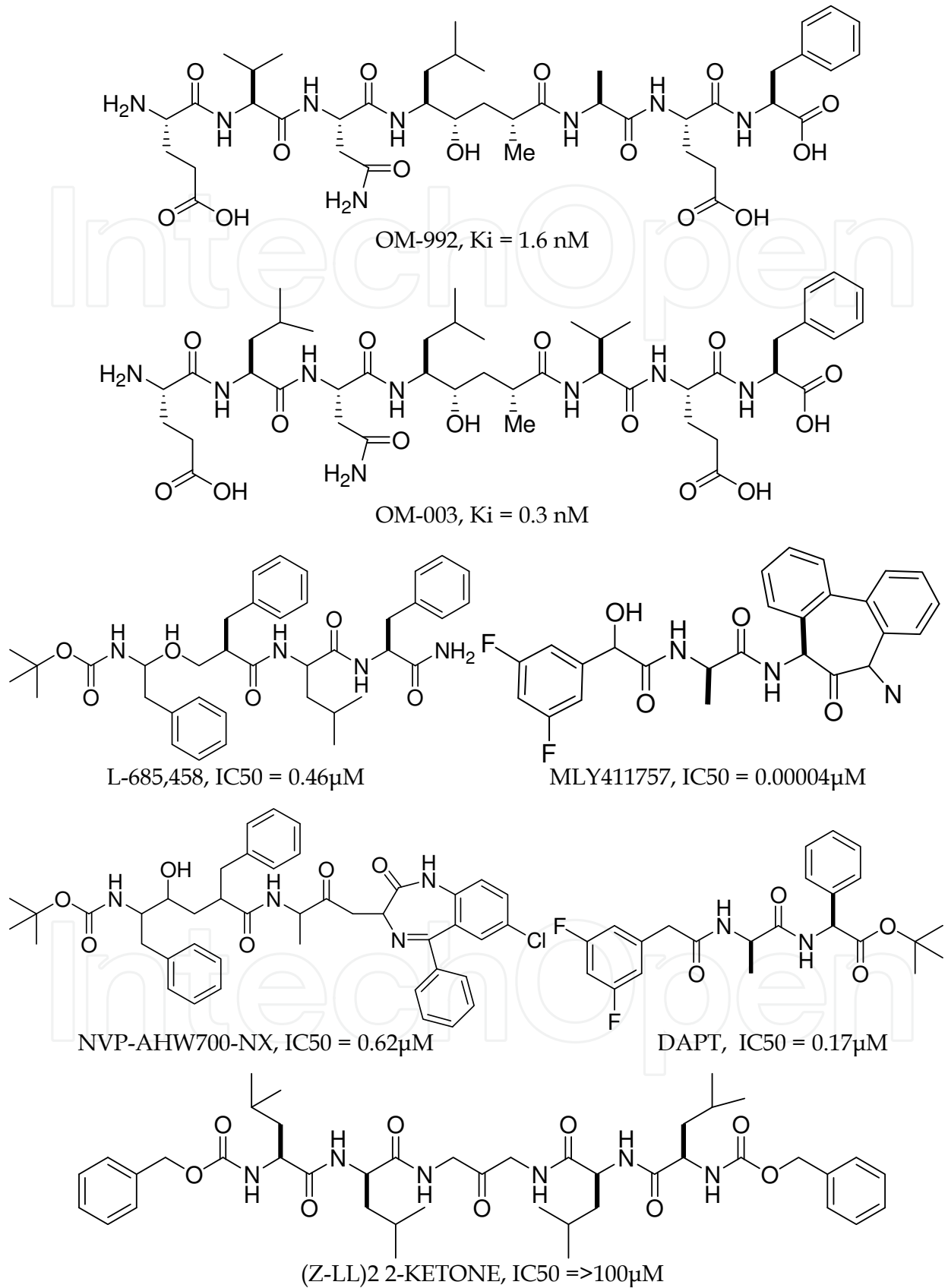
1.2.4 MAO inhibitor

Monoamine oxidase (MAO) inhibitors have shown neuroprotective activities; For example, selegiline, TVP1022, rasagiline (Sano et al., 1997; Ridderer et al., 2004; Yaudin & Buccafusco 2005; Huang et al., 1999) (cf. fig 5) have shown delayed progression of AD. MAO inhibition has also been considered as a strategy for controlling AD.

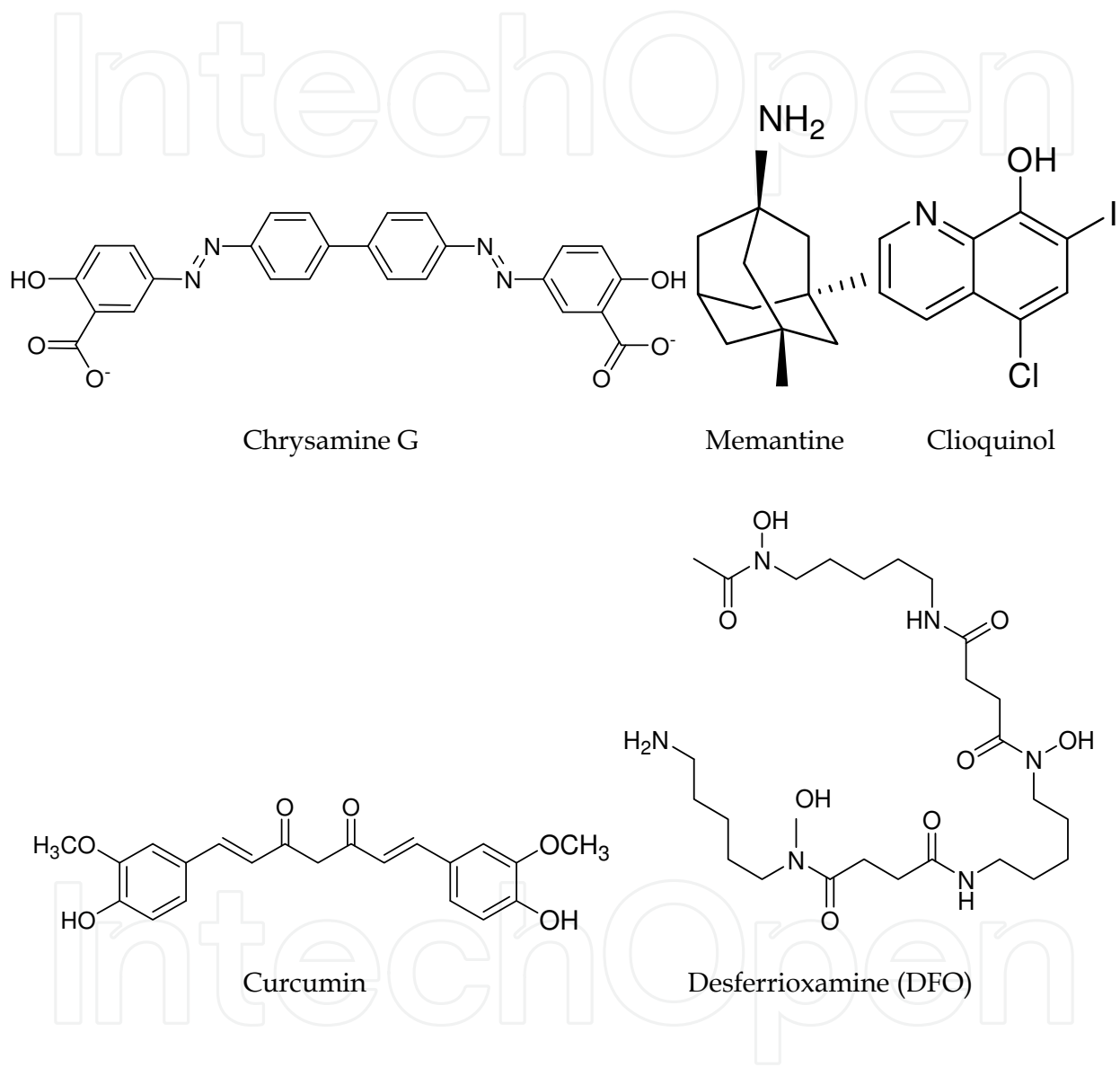### 1.2.5 Dual inhibition for synergistic effects

In this strategy either two compounds are joined together to achieve better inhibition at a receptor (c. f. dual tacrine in fig. 5) or two compounds showing inhibitory activity at different receptors are joined to produce synergistic effects. Such examples include AChE/SERT dual inhibitors (Bolognesi et al., 2005; Camps et al., 2005; Rosini et al., 2005; Kogen et al., 2002; Toda et al., 2002; Abe et al., 2003; Toda et al., 2003) (c. f. fig. 5).

The aim of this chapter is to explain energetics involved in self aggregation of Aβ. In silico design of a preventive drug based on understanding of underlying energetic aspects has been explored. A possible explanation for failures encountered in design of low molecular weight BACE 2 inhibitors has been provided. Design of low molecular weight preventive drugs is attempted.
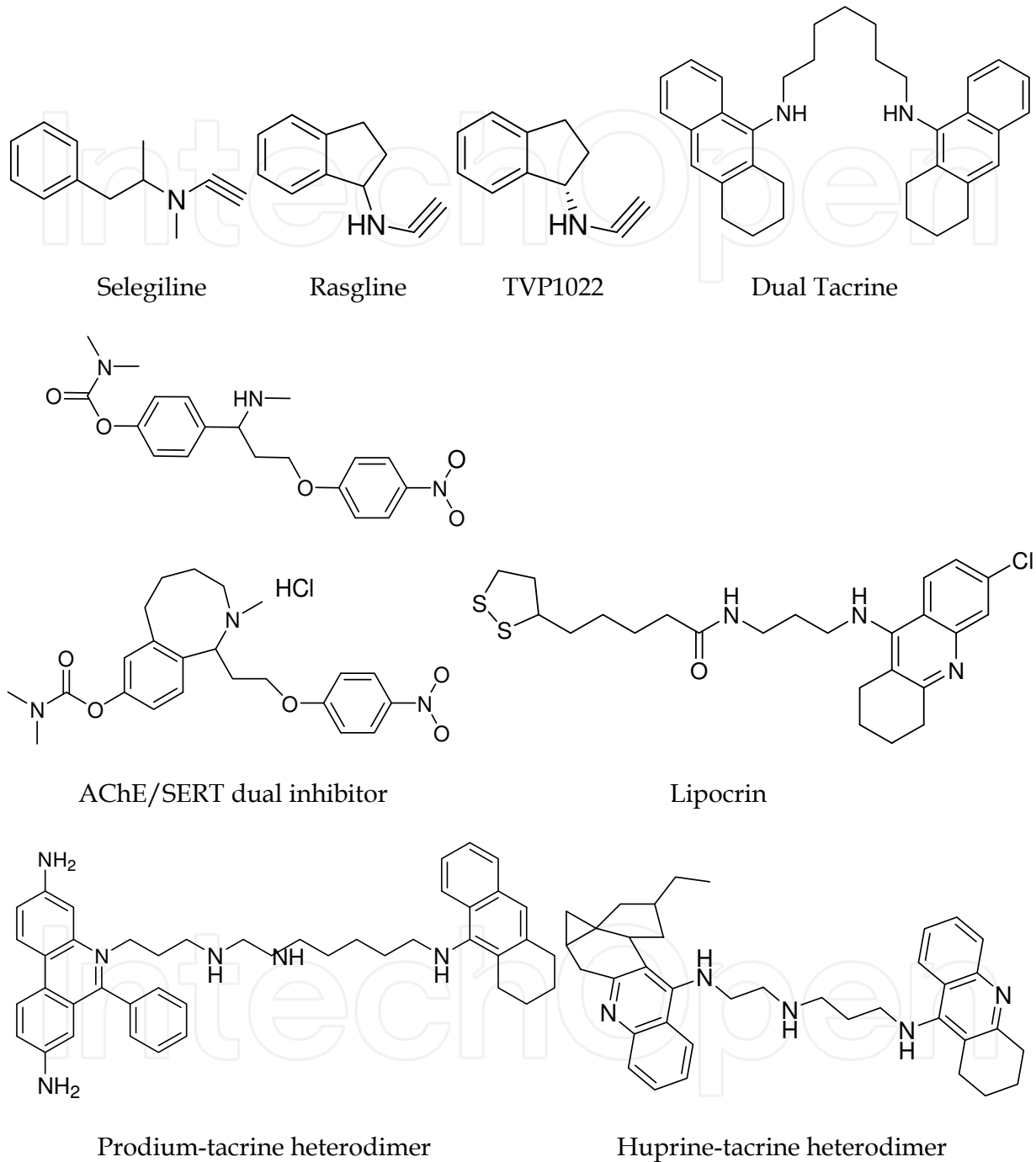
OM-992, Ki = 1.6 nM

OM-003, Ki = 0.3 nM

L-685,458, IC50 = 0.46μM

MLY411757, IC50 = 0.00004μM

NVP-AHW700-NX, IC50 = 0.62μM

DAPT, IC50 = 0.17μM

(Z-LL)2 2-KETONE, IC50 =>100μM

Secretase inhibitors

Fig. 3. Shows chemical structures of some β and γ-secretase inhibitors

Chrysamine G   Memantine   Clioquinol

Curcumin   Desferrioxamine (DFO)

Metal chelators

Fig. 4. Shows chemical structures for some selected metal chelators

Selegiline   Rasgline   TVP1022   Dual Tacrine

AChE/SERT dual inhibitor   Lipocrin

Prodium-tacrine heterodimer   Huprine-tacrine heterodimer

Dual inhibitors

Fig. 5. Shows dual inhibitors which inhibit two targets (AChE/ SERT dual inhibitor) or show enhanced activity at single target (Huprine-tacrine heterodimer-enhanced activity at acetylcholinesterase enzyme)

2. Methodology

Ab initio molecular orbital calculations in conjunction with intermolecular interaction calculations and docking studies have been performed to study energetics involved in self aggregation of Aβ and drug……Aβ interactions. Automated docking tools provided in Glide have been used for flexible ligand docking studies and generating poses for drug interacting with Aβ or BACE. The whole procedure in brief may be summarized as follows. Aβ solution structure was taken and minimized using Macromodel. Middle portion of Aβ was taken for accurate ab initio calculations. Drugs and ions were docked in different poses (500 poses were generated) using GLIDE. Interaction energies were calculated ab initio for relevant poses using supermolecule calculations. All calculations have been carried out utilizing MAESTRO module of SCHRODINGER software (Maestro, 2010).

3. Results and discussion

Foremost Aβ solution structure has been minimized keeping ionizable residues in ionized form. Middle piece of Aβ (c.f. fig.6) was extracted to study Aβ……ion interactions and possibility of self aggregation.
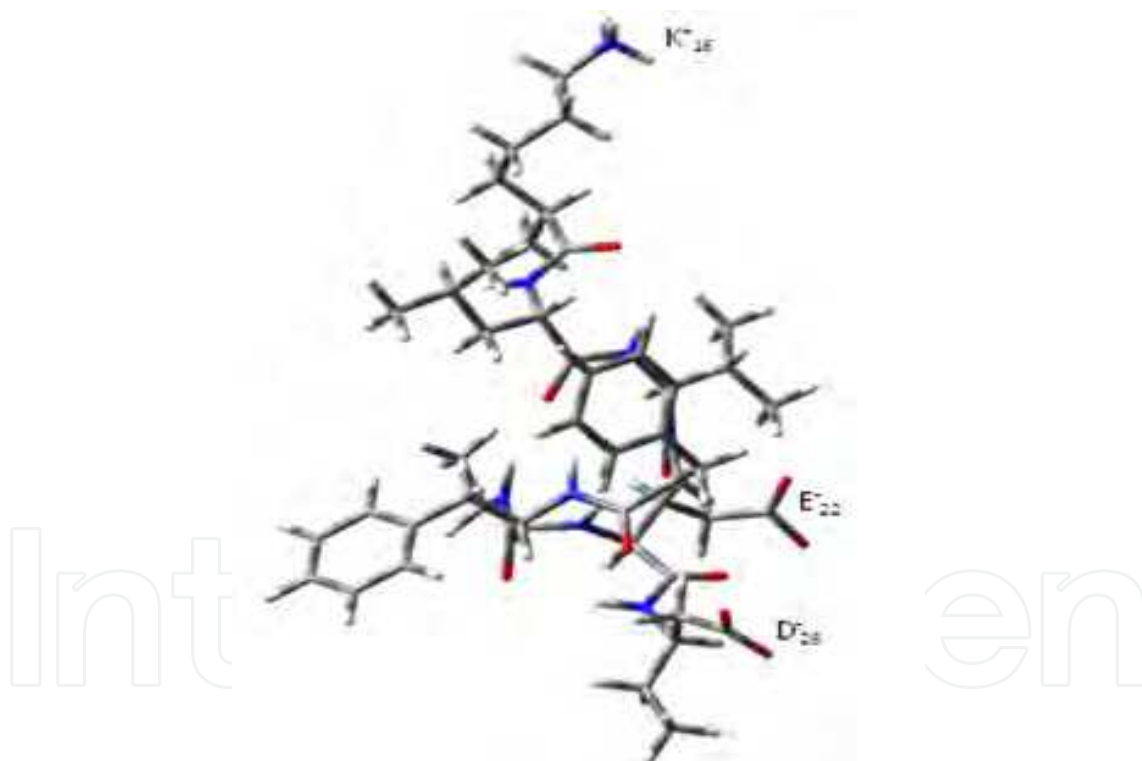

Middle piece of Aβ (16-23 residues)

Fig. 6. Depicts optimized conformation of middle portion of amyloid peptide at physiological pH

3.1 Energetics of self aggregation of Aβ

It is not clear from literature whether self aggregation of Aβ is metal induced or not. However, Zn^{2+} ions are known to play the dual role of neuroprotection as well as being neurotoxic. To understand neurotoxic role of Zn^{2+} ions we have studied affinity of Aβ for

Int.en. =--499.70kCal/mol
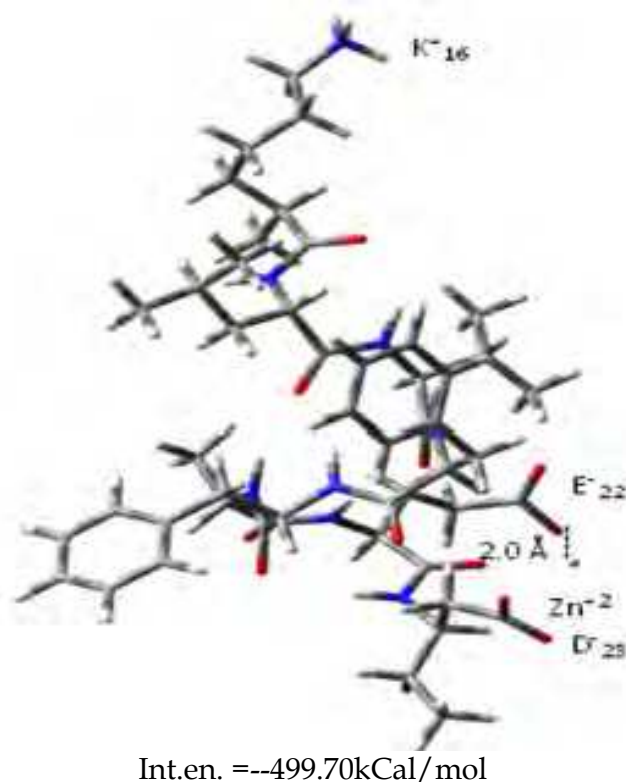
Affinity of Aβ for Zn²⁺ ion

Fig. 7. Depicts that amyloid beta peptide has great affinity for zinc ions.

these ions and tendency for aggregation in presence of these ions. Fig. 7 indicates highly favored metal induced aggregation tendency.
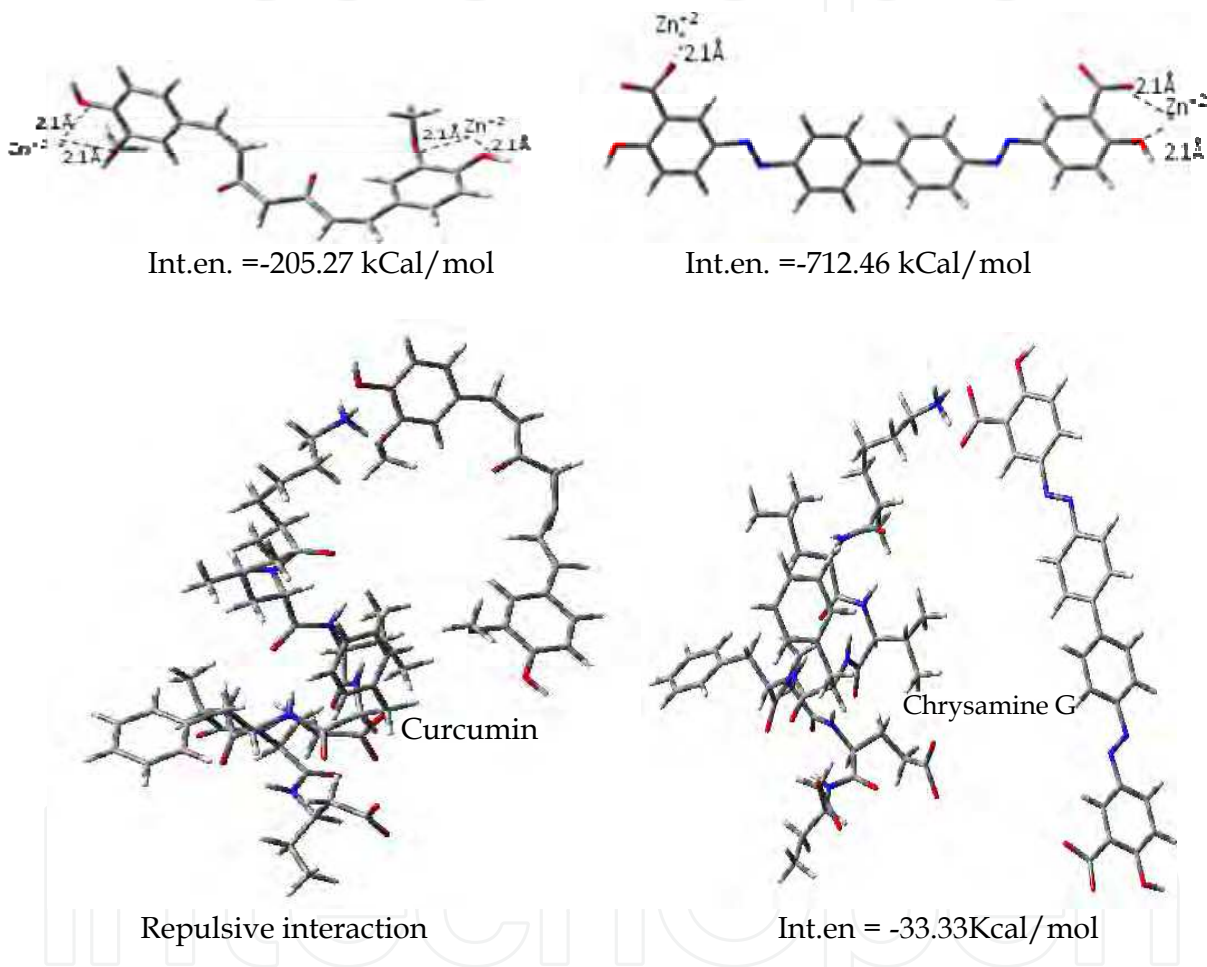
3.2 Role of an anti aggregatory compound

Any compound may act as anti aggregatory in two possible ways –
1. By removing toxic metal ions from brain
2. By intercalating on to Aβ and masking its portion actively involved in aggregation.

Any attempt at designing anti aggregatory compound is bound to succeed if we first try to understand why metal chelator drugs used for removal of metal toxicity in the past are not so effective in present case. For a compound to be an efficient anti aggregation agent, it must be sufficiently competitive with metal ion for interaction at Aβ. Curcumin and Chrysamine G are known to possess anti aggregation property as well as brain permeability. To understand their mode of action we have studied their metal chelation property and intercalative power. Fig. 8 depicts that both the drugs can remove metal toxicity. However, Curcumin will not be sufficiently competitive with Aβ for metal ions. Chrysamine G can competitively inhibit metal induced aggregation by removing metal ion toxicity. Exploration of intercalative property of these compounds indicates that Curcumin cannot intercalate and Chrysamine G intercalates poorly. Therefore, it is understood that efficiency of preventive drugs depends on their ability to compete with Aβ for metal ions which is extremely difficult as Aβ has very high affinity for metal ions especially the middle piece. On the basis of this understanding we have tried to design a preventive compound that can compete with metal ions for Aβ and can also intercalate to Aβ.

Int.en. =-205.27 kCal/mol   Int.en. =-712.46 kCal/mol

Curcumin

Chrysamine G

Repulsive interaction   Int.en = -33.33Kcal/mol

Metal chelation and intercalation of Aβ by Curcumin and Chrysamine G

Fig. 8. Shows possible modes of action for known anti aggregatory agents

3.3 Design of an intercalative preventive drug

A peptidomimetic lead compound has been designed keeping in mind charge complementarity and conformational aspects of middle piece of Aβ. A peptidomimetic compound has been designed to exploit peptide……peptide interactions for intercalation and to bring about specificity with the help of same. This compound contains peptide bonds in backbone here and there and substituents similar to amino acid residues toned according to needs to achieve good charge and conformational complementarity with Aβ. Design of compound is based on visual examination of length required for intercalation and anionic / cationic sites required for interaction to middle portion of Aβ.

Optimized conformation of lead compound and calculation of its metal removal efficiency are shown in fig. 9. Calculated metal interaction energies indicate that the compound will efficiently remove metal ions from brain. To study intercalative property of compound, flexible ligand docking studies have been performed. Drug……Aβ interaction energies have been calculated in various poses and results of best poses are shown in fig. 10. Some of the important energetically filtered poses are shown in fig. 11. Calculated Aβ……lead compound interaction energies clearly indicate that designed lead compound can compete with metal ions for Aβ. At the same time it will also reduce concentration of metal ions from brain due to its metal ion removal efficiency.

Intercalation is not through covalent linkage so that it does not bring about physical or chemical changes in the state of Aβ peptide. The availability and concentration of metal ions in brain will decide on exact role of compound. This strategy of designing a curative drug is superior as compared to previous efforts where researchers have tried to break down aggregated Aβ into smaller soluble Aβ fragments as they only increase concentration of amyloid derived diffusible ligands (ADDLs). ADDLs have also been reported to cause certain problems due to their diffusible nature and high permeability. Our designed compound not only avoids aggregation of Aβ 42 it also avoids ADDLs from diffusing inside brain as they would increase molecular weight of ADDLs by intercalation. Pharmacokinetic aspects of lead compound can also be judged by considering compliance with rule of five.

Designed compound has molecular weight slightly above 500, less than 5 hydrogen bond donor groups and less than 10 hydrogen bond acceptor groups. Thus it is expected to show sufficiently good pharmacokinetics. Being peptidomimetic it may show moderate bioavailability. Synthetic considerations and associated efficacy remain to be experimentally verified. This work emphasizes need for energetics based designing to attain desired efficacy.

3.4 Design of a low molecular weight BACE inhibitor

As mentioned in introduction BACE catalyzes cleavage of APP leading to formation of neurotoxic Aβ peptide. Therefore, it is an obvious target for development of preventive drugs. Compounds inhibiting this enzyme are expected to block extracellular first cleavage of APP that subsequently leads to formation of Aβ. BACE being an aspartyl protease catalyzes cleavage of APP assisted by two active site aspartyl residues which operate cooperatively with a net charge of -1. Most of the BACE inhibitors are transition state analogs derived from natural product pepstatin. Statine isostere has been derived from pepstatin and used to design transition state analogs for BACE that engage catalytic aspartics with a hydroxyl group. Some peptidic BACE inhibitors employing statine isostere are shown in fig. 12. These compounds have shown activity in enzymatic preparations but do not show appreciable activity in cellular assays. This attribute has been associated with the fact that they are peptides. The aim of this study is to understand mechanistic aspects of BACE
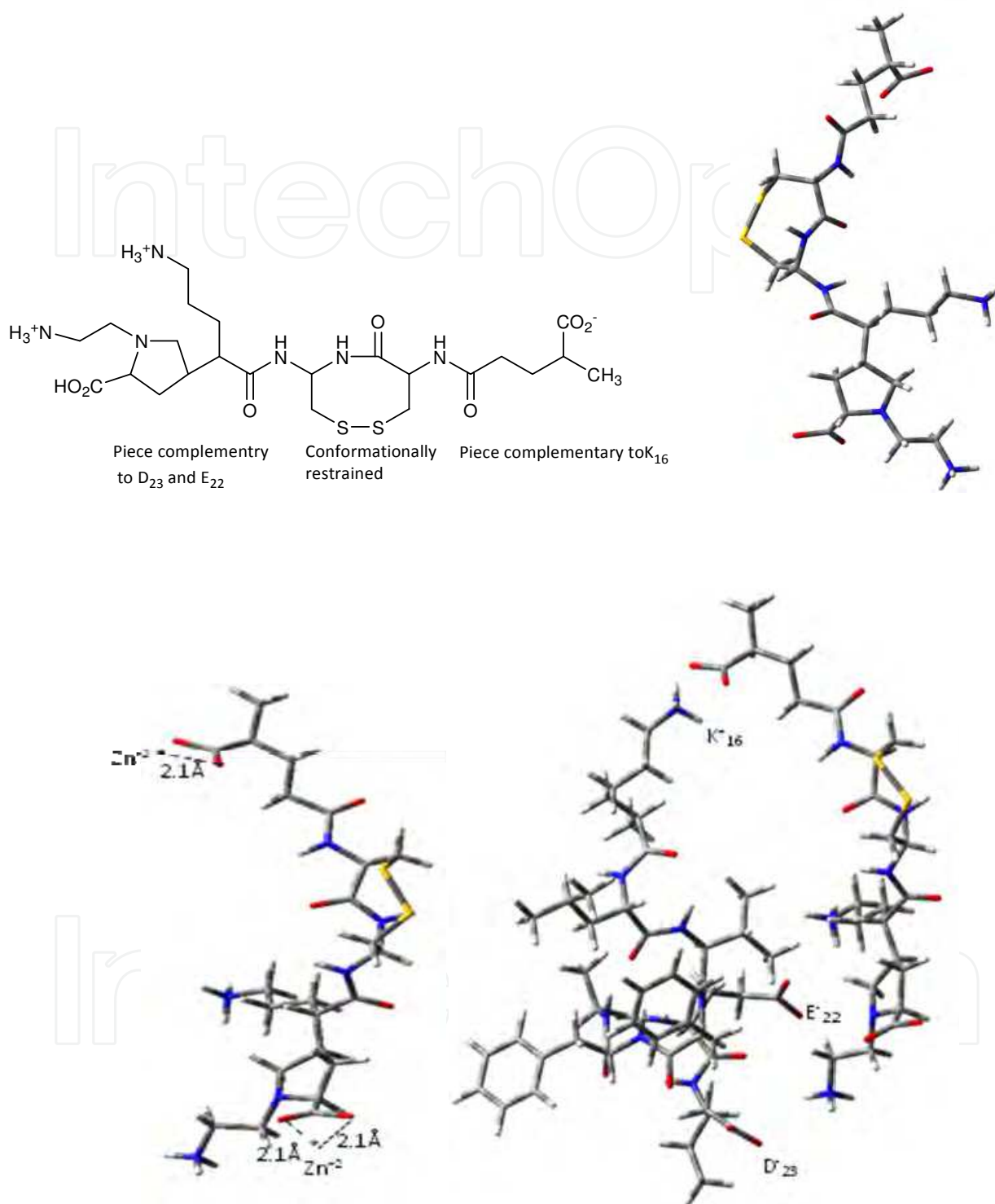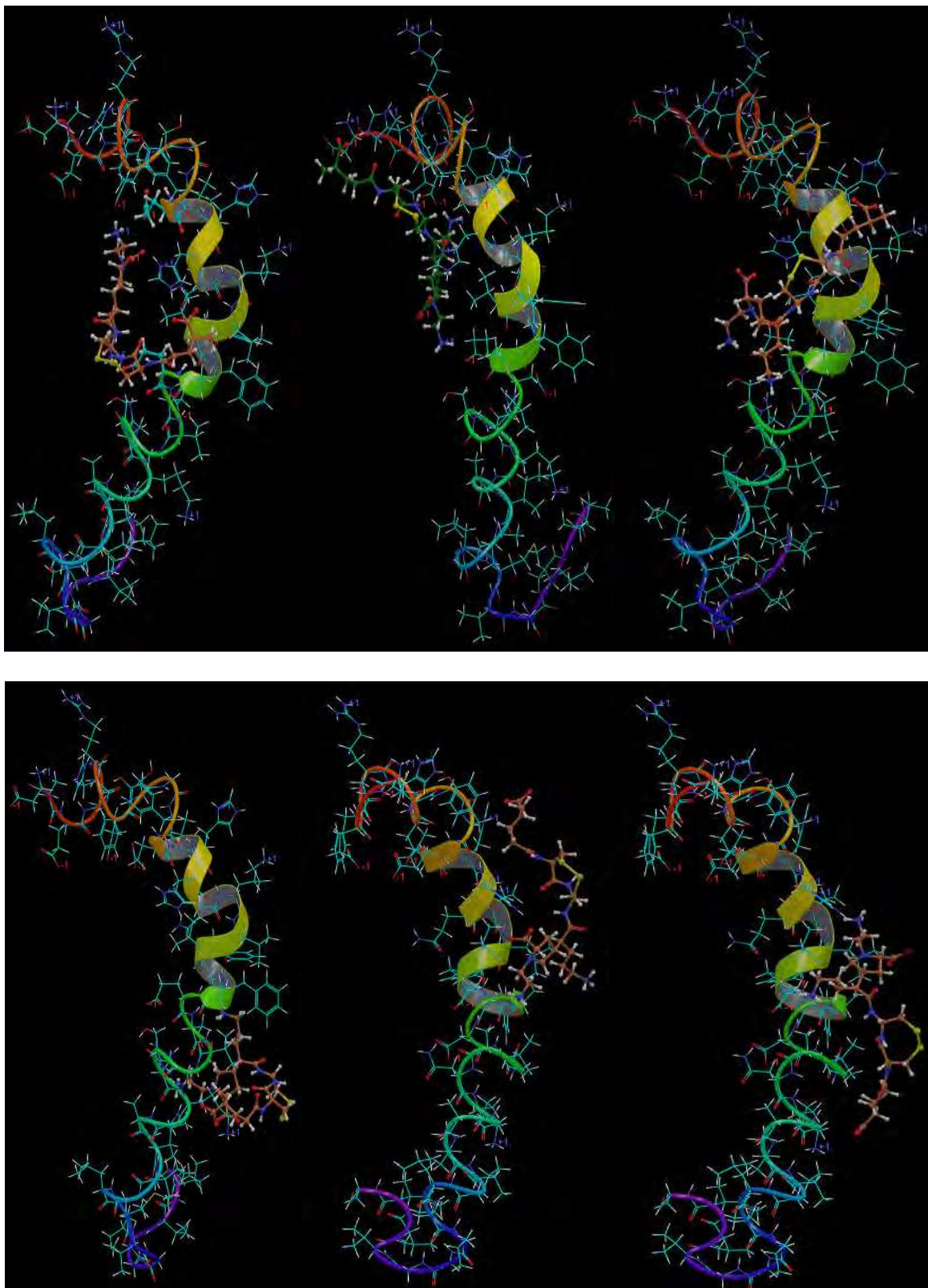
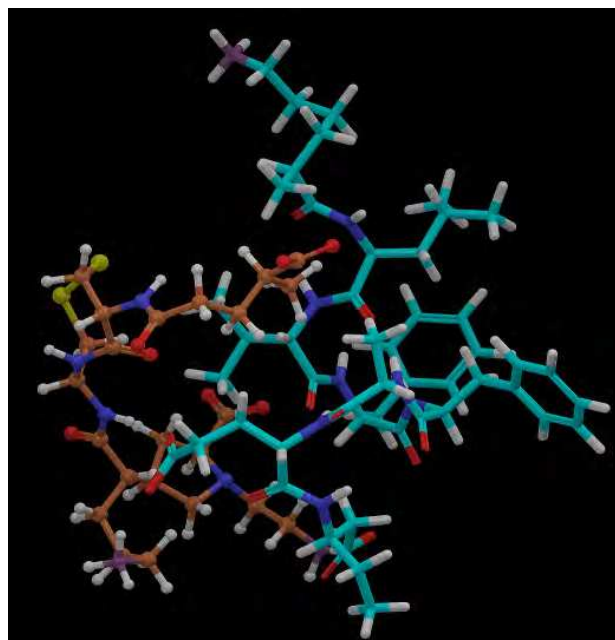Int. en. = -405.53 kCal/mol   Int. en. = -173.39 kCal/mol

Metal chelation and intercalation of Aβ by designed lead compound

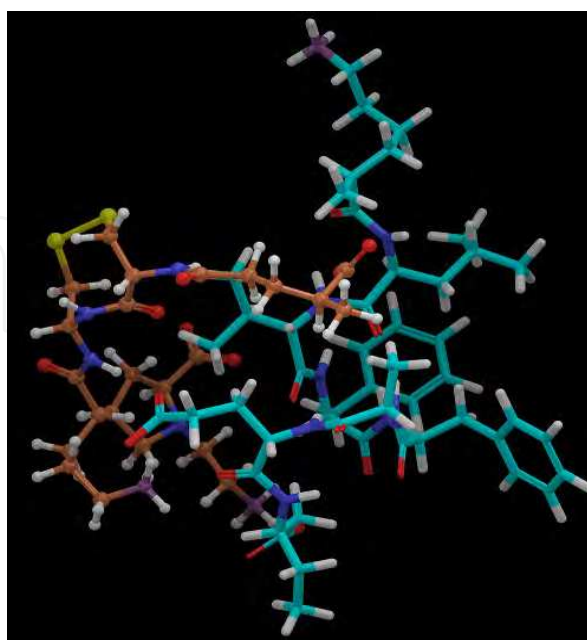Fig. 9. Shows predicted modes of action of designed lead compound

Various poses for designed lead compound intercalating Aβ 42
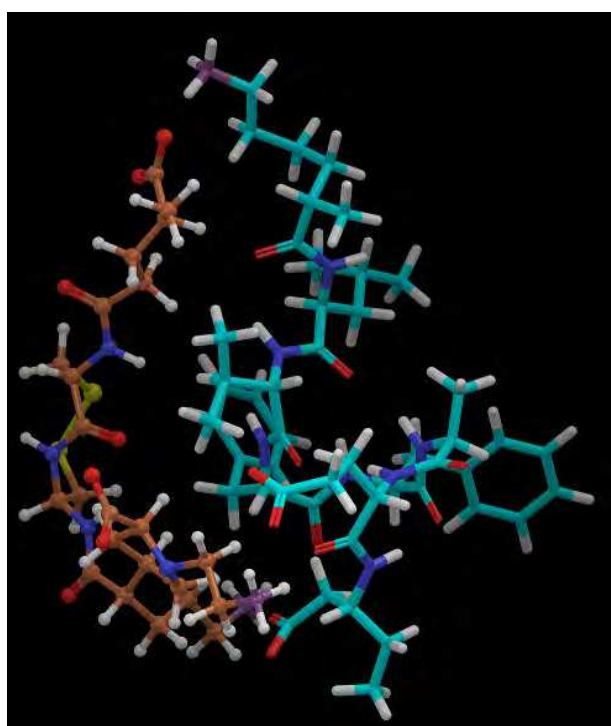
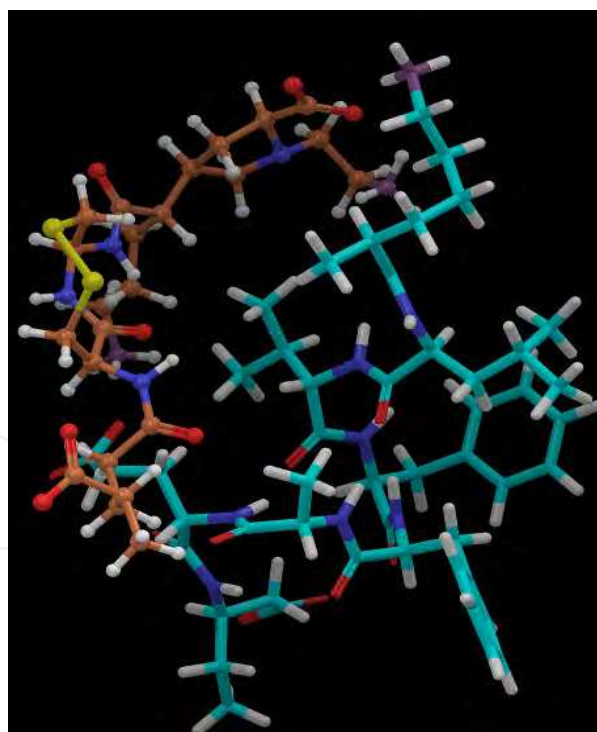Fig. 10. Shows automated flexible ligand docking results for designed lead compound

Int.en. = -259.76 kCal/mol   Int.en. = -249.83 kCal/mol

Int.en. = -223.39 kCal/mol   Int.en. = -136.32 kCal/mol

Interaction energies for designed lead compound masking middle portion of Aβ 42

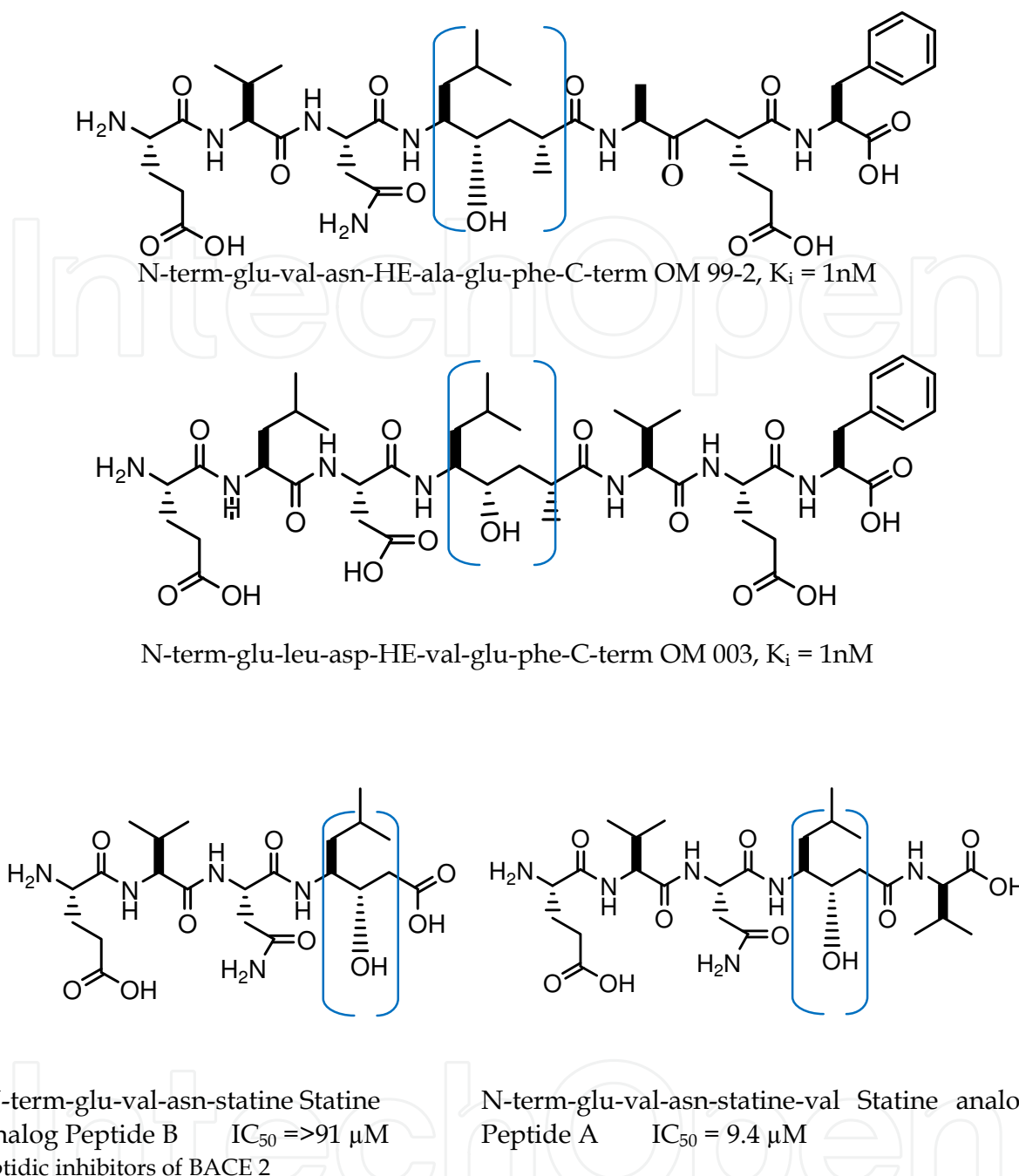Fig. 11. Shows preferred mode of action of designed lead compound

N-term-glu-val-asn-HE-ala-glu-phe-C-term OM 99-2, K_i = 1nM

N-term-glu-leu-asp-HE-val-glu-phe-C-term OM 003, K_i = 1nM

N-term-glu-val-asn-statine Statine
analog Peptide B IC_{50} =>91 µM

N-term-glu-val-asn-statine-val Statine analog
Peptide A IC_{50} = 9.4 µM

Peptidic inhibitors of BACE 2

Fig. 12. Shows chemical structures of some peptidic inhibitors and their potencies

inhibitors through molecular docking studies and intermolecular interaction calculations. Aim being to design reduced molecular weight compound with more 'drug like features'. We first try to understand why low molecular weight peptide inhibitors have not been successful so far and why truncation of amino acid residues on either side of isostere leads to drastic loss in potency.

3.4.1 Mechanistic aspects of small statine analog inhibitor of BACE

Peptide inhibitors containing hydroxyethylene isostere or statine isostere show significant variation in potency from µM to nM range (c.f. fig. 12). Calculations and docking studies

have been performed on Peptide A to understand causes of loss in activity. Peptides possess conformational flexibility. A number of conformations (c.f. fig. 13) for Peptide A were generated using Ligprep module of SCHRODINGER. These conformations were energetically filtered for docking studies. Energetically filtered conformations were cyclic as small peptides (typically less than 10 amino acids) cannot attain stabilization through secondary structure that is β-turn etc. Therefore, they possess greater tendency to cyclize and attain stabilization. To understand bioactive conformation and perform docking studies a model of BACE 2 active site has been prepared utilizing X- ray crystallography data for OM003 complexed in human BACE 2 (1M4H. pdb). This model covers 8Å environment around active site. All amino acid residues are taken in their normal occurring ionization states. For example, asp, glu, are negatively charged and lys, arg are positively charged. All possible protonation states of catalytic motif have been tried out in search of best mechanistic option. Best interaction energies obtained for peptide A conformation 1 and 2 are shown in figs. 14 and 15. Flexible ligand, rigid protein dockings have been carried out. Asp 228 has been kept in ionized form in these calculations. Fig. 14 clearly indicates that the inhibitor cannot fit properly in the active site so as to interact efficiently with catalytic motif. In fact transition state isostere is oriented away from catalytic motif. The transition state isostere does not come in contact with catalytic motif. Interactions with asp 228 have been completely lost. There is no utilization of enhanced binding interactions that is, interacting residues in pockets of enzyme close to catalytic motif. Fig. 15 depicts docking results with conformation 2 of peptide A. Conformation 2 is still worse in terms of interactions with active site residues. Inhibitor can fit in active site only at distances 6 and 8Å from catalytic motif due to its conformation. At these distances very little interaction with catalytic motif can be achieved. Interaction with asp 228 becomes impossible due to highly spatially constrained active site of BACE 2 and the conformational aspects of inhibitor.

These docking results when compared with X-ray crystallography data for OM003 complexed in BACE 2 reveal that low molecular weight peptide inhibitors show conformationally controlled mechanistic aspects leading to decrease in their potency. Cyclic type conformations impart stability to small peptides but render them unsuitable for spatial requirements of BACE 2 active site leading to drastic reduction in activity. This understanding led us to design conformationally stable low molecular weight lead compound.

## 3.5 Design of low molecular weight BACE inhibitor

Designing has been strategically and systematically pursued. Peptide backbone has been replaced with peptidomimetic backbone to control conformational problems. Residues similar to natural substrate have been retained for specificity. Drug has been designed to be a competitive inhibitor as opposed to transition state analog. Transition state isostere containing hydroxyl group to engage catalytic aspartic dyad has been replaced with a positive site to electrostatically interact with ionized asp 228 of active site for binding interactions (c.f. fig. 16). Conformational aspect is not an issue in this case. Designed compound was subjected to in silico testing that is, docking studies were performed to judge its activity. Best results of docking studies are shown in fig. 16. Designed lead compound can fit in active site and interact with catalytic motif. Fig. 16 shows that interaction energy predicted is not particularly attractive but indicates that lead compound may bind with retention of conformation leading to perhaps enhanced bioavailability and good potency.

Conformation 1   Conformation 2
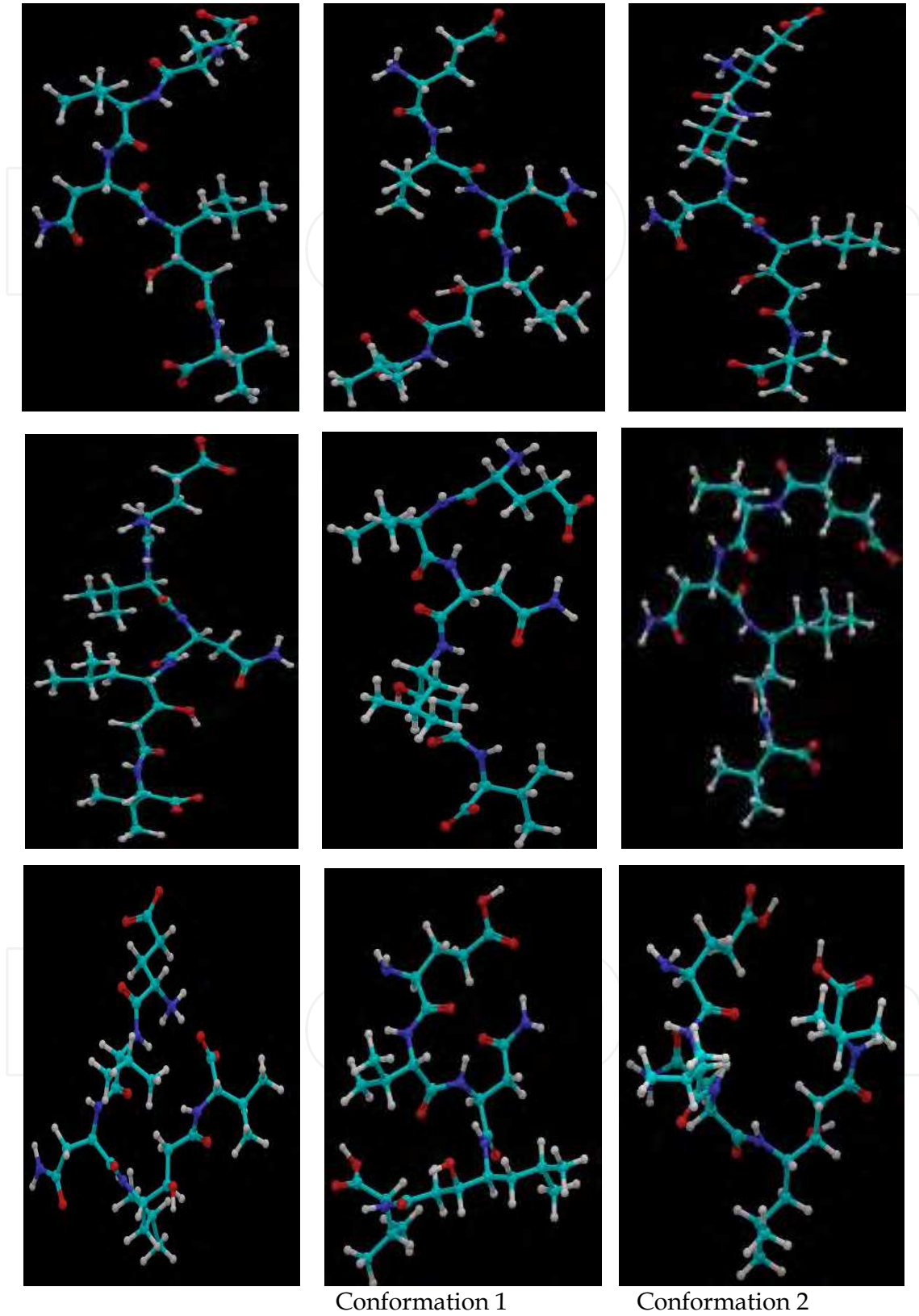
Energetically filtered conformations of Statine isostere containing Peptide A

Fig. 13. Shows bioactive conformations of peptide A

Int.en. = -17.93 kCal/mol   Int.en. = -17.71 kCal/mol
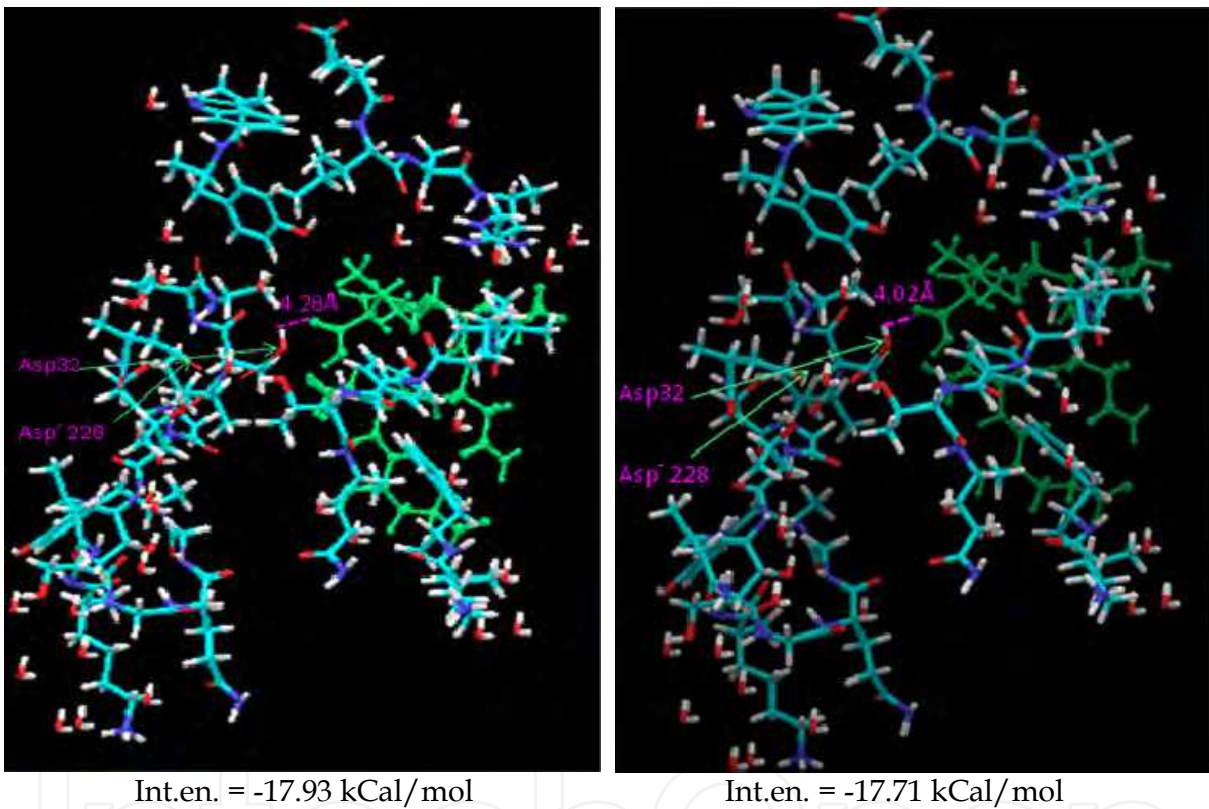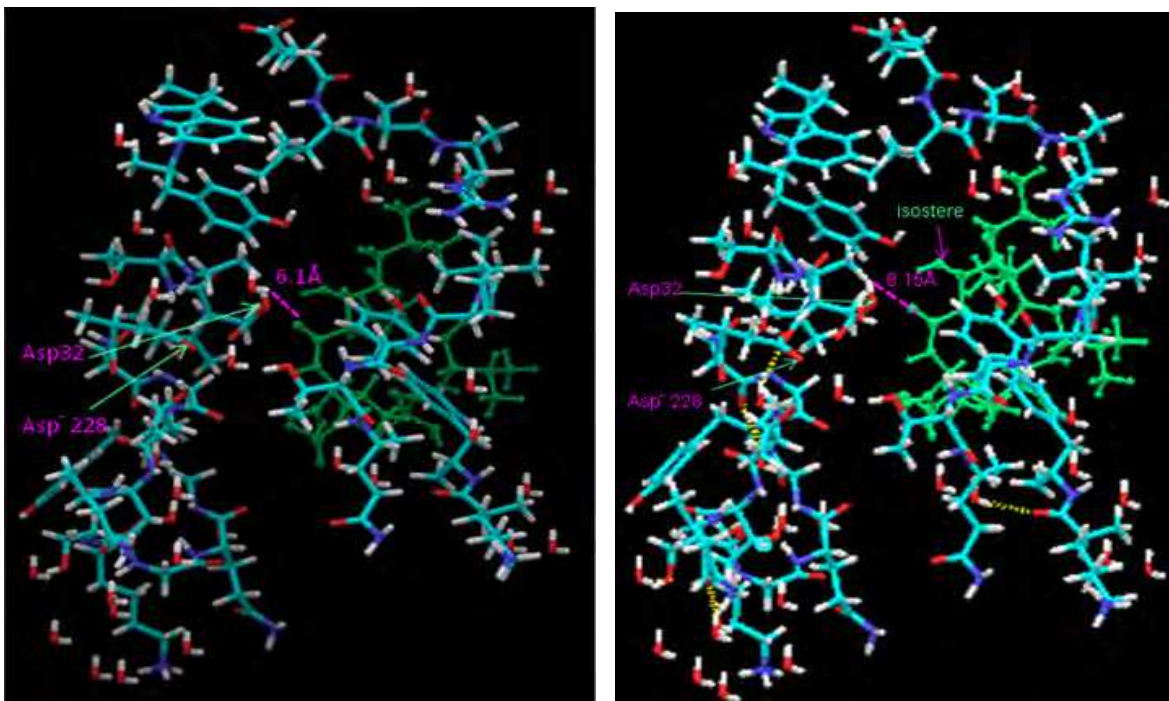
Peptide A (conformation 1) interacting with BACE 2 catalytic motif

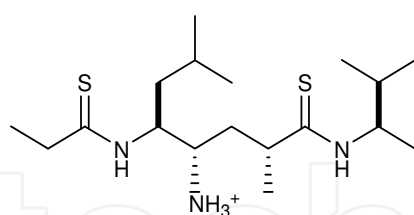Fig. 14. Shows mode of action of a small peptidic inhibitor of BACE 2

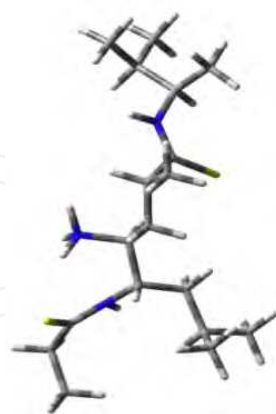Int.en. = -10.58 kCal/mol   Int.en. = -12.18 kCal/mol

Peptide A (conformation 2) interacting with BACE 2 catalytic motif
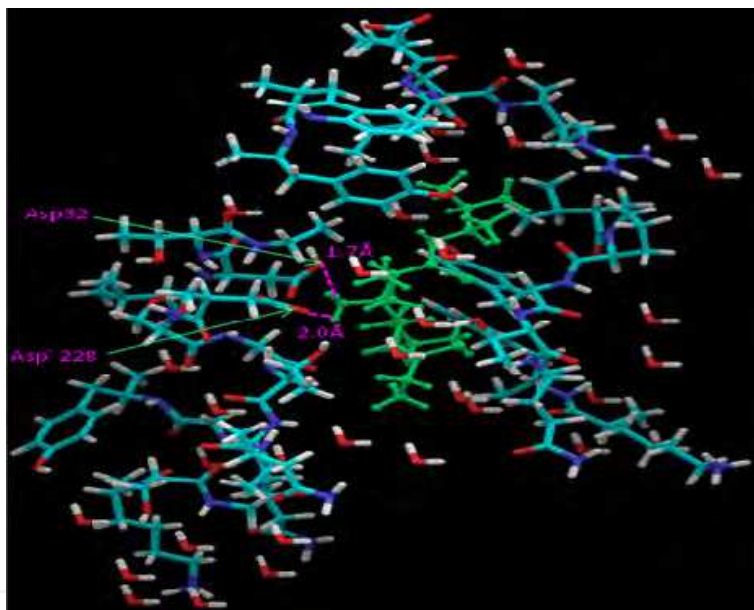
Fig. 15. Shows mode of action of a small peptidic inhibitor of BACE 2

Int. en. = -9.95 kCal/mol

Designed competitive inhibitor interacting with BACE 2 catalytic motif

Fig. 16. Shows predicted mode of action of a designed compound as competitive inhibitor of BACE 2

4. Conclusions

This chapter describes ab initio Hartree Fock molecular orbital calculations combined with docking tools and intermolecular interaction calculations on amyloid beta peptide. Energetics involved in metal ion induced self aggregation of amyloid beta peptide has been studied. Study indicates that metal induced self assemblage of Aβ is highly favored. Any compound can act as an anti aggregatory agent if it can compete with Aβ for metal ions. To be competitive it must have an interaction energy of ~500 kCal/mol with metal ions like Zn^{2+} ion. Intercalative and metal detoxification properties are desired in prospective preventive drug for AD. A peptidomimetic lead compound with these properties has been designed and tested in silico.

Mechanistic aspects of peptide inhibitors of BACE 2 have been studied in detail. Mode of action of peptide transition state analog drugs has been highlighted. Conformationally controlled mechanistic aspects of low molecular weight peptide inhibitors have been discussed. Low molecular weight peptide inhibitors tend to possess cyclic type conformation which is not suitable for interactions with catalytic motif. Large peptide inhibitors on the other hand show bioavailability problems due to their poor pharmacokinetics and membrane permeability problems. An attempt has been made at designing conformationally stable, reduced molecular weight lead compound that follows Lipinski's rule and is expected to cross cell membranes. Designed compound is competitive inhibitor as opposed to transition state analog. Designed lead compound is reduced molecular weight and is expected to retain specificity as it utilizes same sequence of amino acid residues as in natural substrate APP. Designed compound is expected to overcome conformational complications, bioavailability however remains to be asserted by experimental studies.

5. Acknowledgment

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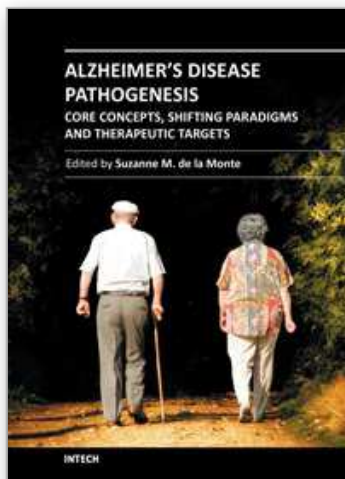
Alzheimer's Disease Pathogenesis-Core Concepts, Shifting Paradigms and Therapeutic Targets

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Alzheimer's Disease Pathogenesis: Core Concepts, Shifting Paradigms, and Therapeutic Targets, delivers the concepts embodied within its title. This exciting book presents the full array of theories about the causes of Alzheimer's, including fresh concepts that have gained ground among both professionals and the lay public. Acknowledged experts provide highly informative yet critical reviews of the factors that most likely contribute to Alzheimer's, including genetics, metabolic deficiencies, oxidative stress, and possibly environmental exposures. Evidence that Alzheimer's resembles a brain form of diabetes is discussed from different perspectives, ranging from disease mechanisms to therapeutics. This book is further energized by discussions of how neurotransmitter deficits, neuro-inflammation, and oxidative stress impair neuronal plasticity and contribute to Alzheimer's neurodegeneration. The diversity of topics presented in just the right depth will interest clinicians and researchers alike. This book inspires confidence that effective treatments could be developed based upon the expanding list of potential therapeutic targets.

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