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Hydroxyethylamine Based Small Molecules as Inhibitors of BACE-1

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ABSTRACT

β-Secretase or BACE-1 is a popular target for the treatment of Alzheimer disease (AD) and responsible for the formation of amyloid-β peptide. In recent years BACE-1 has emerged as one of the best characterized targets for Alzheimer therapy. The inhibition of BACE-1 activity is a crucial step for the treatment of AD. This mini-review summarizes some popular BACE-1 inhibitors possessing hydroxyethylamine and peptide scaffolds.

Keywords: Alzheimer's Disease, BACE-1, β-Amyloid, Hydroxyethylamine, Peptide

INTRODUCTION

Alzheimer's disease (AD) is a most prevalent age related neurodegenerative disease characterized by loss of memory, reasoning, language, abstraction and emotional control (cognitive loss).[1] Globally more than 30 million people are affected from AD and also number of people affected with this kind of ailment is increasing with aging human population which is a result of age demographics.[2-5]The pathological hallmarks for AD have been known for some time.[6-7] AD histopathology of person affected with this neurodegenerative disorder shows two different types of aberrant protein: Aβ-42 and neurofibrillary tangles (NFT_S).[8] A protein, tau also known as microtubules associated protein tau (MAPT) facilitates microtubules stabilization in cells and particularly abundant in neurons. Microtubules serve as 'tracks' in cellular cargo system along with the lengths of axon in neurons. It is believed that tau function is compromised in Alzheimer's disease and in other tauopathies. This probably occurs from tau hyperphosphorylation that results in reduced tau binding to microtubules and the sequestration of hyperphosphorylated tau into neurofibrillary tangles (NFT_S) amounts to reduction of tau available to bind microtubules.[9-10]

A small peptide with 40-42 amino acids, called as amyloid-β (Aβ) plays an important role in the pathogenesis of AD. Aβ is produced by amyloid precursor protein (APP) by various proteolytic steps.[11,12] Aβ-42 amino acid variant normally a minor product enhanced under pathological condition while Aβ-40, a normal peptide produced during the normal metabolism of APP. β-Secretase (BACE-1) better known as beta site APP cleaving enzyme-1 or aspartyl protease 2 is an enzyme that in human is encoded by BACE-1 gene.[13] BACE-1, an enzyme involved in the processing of the amyloid precursor protein[5,6] to form Aβ, that is validated target for AD. BACE-1 is an aspartyl protease with an active site containing two conserved aspartic acid residue at Asp32 and Asp 228. The inhibition of β-site amyloid precursor protein cleaving enzyme (BACE-1) is considered as a crucial target for the treatment and prevention of AD.[14-15]

Hydroxyethylamine (HEA) has been demonstrated as an important and robust scaffold for the construction of BACE-1 inhibitors.[14-15] The generic structure of HEA is shown in Figure 1.

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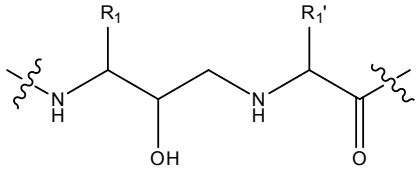


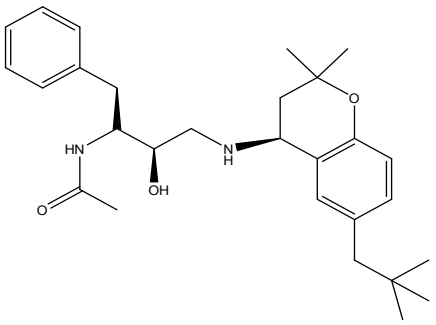
Figure 1. Generic Structure of HEA isostere

The progress towards the drug development for the treatment of AD has been reviewed by Shawn Stachel in 2009.[16] Here we review some of popular small BACE-1 inhibitors possessing HEA scaffold.

2. Hydroxyethylamine (HEA) Based Small Molecules

2.1 Acyclic HEA Scaffolds

Small peptidomimetics possessing 4,5,7-tetrahydrobenzazole[22] and 4,5,6,7-tetrahydropyridinozole skeleton have been reported as strong inhibitors of BACE-1.[17] Compound **1**, analogue of 2,2-dimethylchroman was shown to inhibit the activity of BACE-1 (IC_{50}=12 nM) high cellular activity (11 nM, cell based assay). Unfortunately, the molecule **1** was observed as metabolically unstable in human liver microsomes (HLM). Subsequently, another molecule, **2** with low molecular weight was prepared anticipating high activity against BACE-1. Compound **2** showed better enzyme inhibition (IC_{50}=8.5 nM) and improved cellular activity (18 nM, cell based assay). It was observed that both enzyme activity and cellular activity were dependent on the heteroatom present in bicyclic ring.



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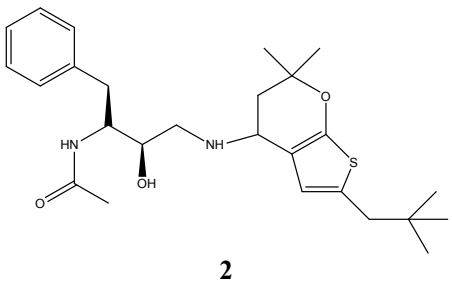

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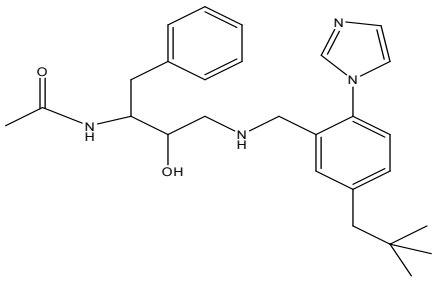
A novel hydoxyethylamine (HEA) based inhibitor (**3**) showed the inhibition of BACE-1 by lowering down Aβ levels in brain and plasma by 15% and 47%, respectively at 100 mg/kg.[16] Moreover, compound **3** was claimed to have an oral bioavailability of 15% in the rats.



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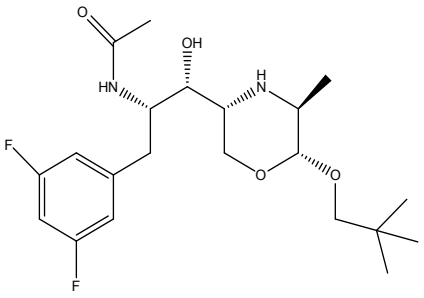
Another molecule, **4** possessing HEA based BACE-1 inhibitor lacking most of non prime binding elements was reported to inhibit the activity of BACE-1.[16] Compound **4** showed inhibitory activity by lowering down plasma and cerebrospinal fluid (CSF) Aβ concentration by 39% and 40%, respectively.



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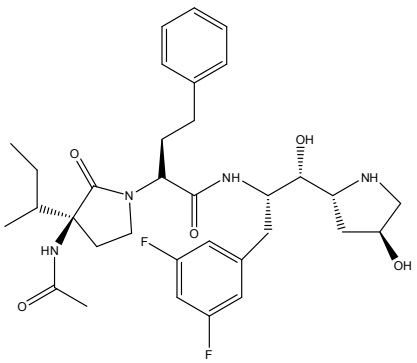
4-(s)-Hydroxypyrrolidine[18] based BACE-1 inhibitors have been reported to possess significant enzyme activity.[16] The most potent molecule, **5** showed excellent activity with IC_{50} value 0.8 nM and a cellular IC_{50} value of 11 nM. This compound exhibited potency by lowering down the plasma Aβ levels without altering brain Aβ levels.



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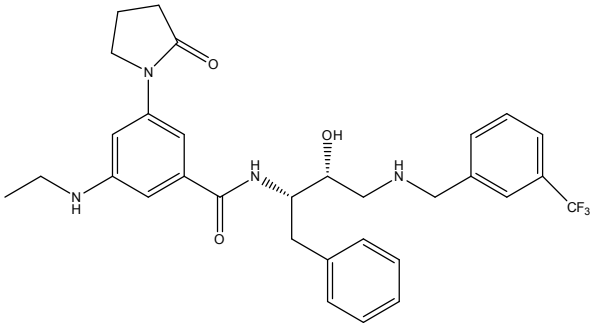
Molecule **6**, hydroxyethylamine (HEA) based BACE-1 inhibitor showed in potency against enzyme at IC_{50} value of 0.04 μM and in cell based assay at IC_{50} value of 0.18 μM.[19,20]



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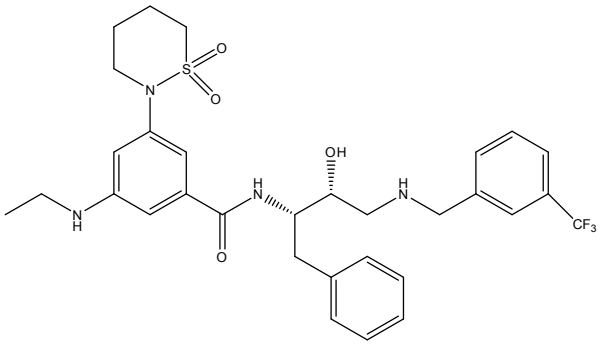
Another HEA based molecule **7** in which pyrrolidinone ring was replaced by six membered cyclic sulfonamide ring showed inhibition against enzyme at IC_{50} value of 0.003µM and in cell based assay at IC_{50} value of 0.02µM.[19,21]



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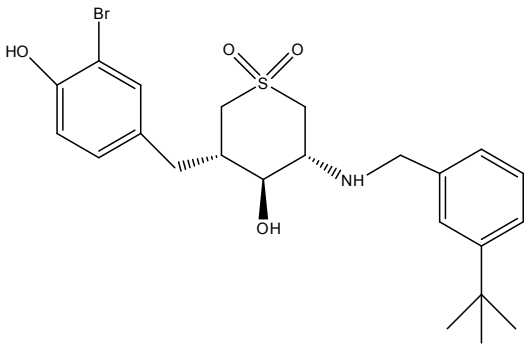
2.2. Cyclic HEA Scaffold

A number of cyclic HEA based inhibitors of BACE-1 have been reported with good inhibitory activity. A novel sulfone based BACE-1 inhibitor, **8** showed prominent inhibitory activities at IC_{50} 55 nM.[23] The high inhibition capacity of this compound was attributed to the presence of sulfone group that acts as hydrogen bond acceptor and subsequently enhancing the biological efficacy.



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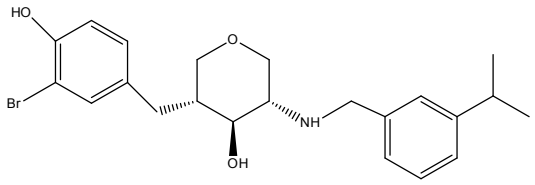
Another molecule **9**, an analogue of amino pyranol cyclic HEA scaffold was reported to possess potency of BACE-1 inhibition at IC_{50} 55µM.[24]



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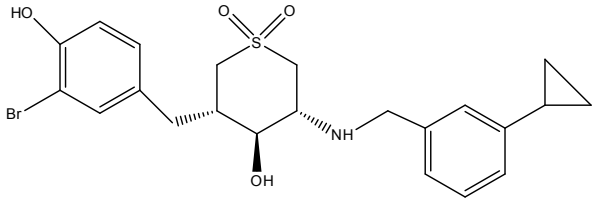
Molecule **10**, derivative of aminodioxo-hexahydro-thiopyranol was reported to possess significant activity against BACE-1 at IC_{50} 0.95 µM.[24] Sulfone fragment present in the molecule lowers down the basicity of amine group and forms optimal hydrogen bond.



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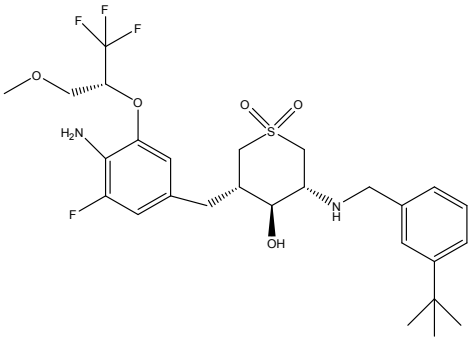
Molecule **11**, cyclic hyroxyethylamine based BACE-1 inhibitor showed robust potency in inhibition of enzyme activity with IC_{50} value of 2.0 nM and is expected to save millions of life from this devastating neurodegenerative disease, prevail in old age with so many consequences.[23]



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3. Conclusion

The number of AD patients are increasing enormously globally and losing their normal life span due to devastating neurodegenerative disorders. BACE 1 has emerged as crucial target for the treatment of AD. A number of small molecules (peptides or non-peptides) have been examined for their potency against BACE 1. However, more sincere efforts need to be explored in order to acquire the success towards diagnosis[25] and treatment.[26,27]

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