# Docking studies to explore novel inhibitors against human beta-site APP cleaving enzyme (BACE-1) involved in Alzheimer's disease

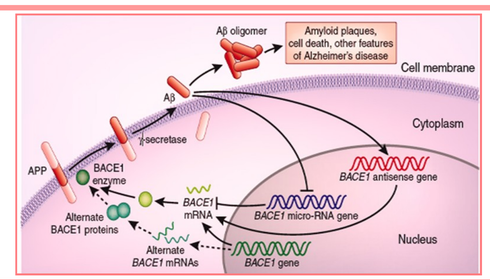
[1]S.Anjum Mobeen*, [2]Manne Munikumar, [2]Amineni Umamaheswari**

[1] Dept. of Biotechnology & Bioinformatics, Yogi Vemana University, Kadapa- 516001. [2]Bioinformatics Centre, Department of Bioinformatics, SVIMS University, Tirupati -517507.

*Presenting Author, ** Corresponding Author, Email: svims.btisnet@nic.in

KEYPOINTS

- ⇒ Alzheimer's disease is an intractable neurodegenerative disorder, characterized by the formation of senile plaques and neurofibrillary tangles (NFTs) which are the pathological hallmarks of the disease particularly in elder persons of age 65 and above.
- ⇒ Beta-site APP cleaving enzyme (BACE-1) is an aspartyl protease, which initiates the processing of amyloidogenic pathway and is responsible for the formation of Senile plaques, a causative agent of the disease.
- ⇒ Elevated level of BACE-1 causes the accumulation of insoluble form of Aβ peptides.
- ⇒ Five published inhibitors of BACE-1 such as thiazolidinediones, rosiglitazone, pioglitazone, Sc7 and tartaric acid are available with poor pharmacological properties. Therefore, a computational approach was undertaken to design novel inhibitors against human BACE-1 with good pharmacological properties.



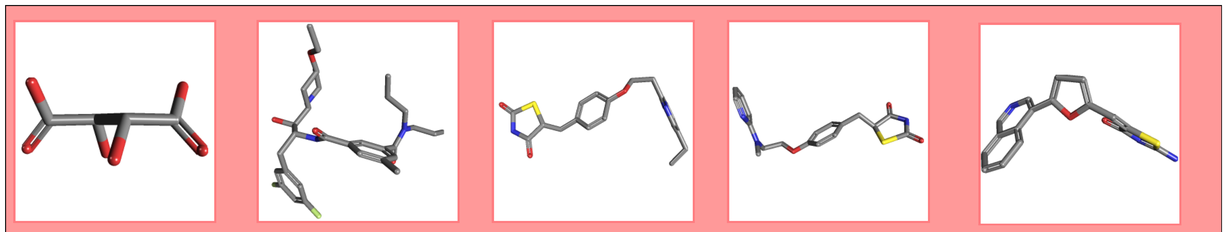




**Figure: 1** Five existing inhibitors of human BACE-1.

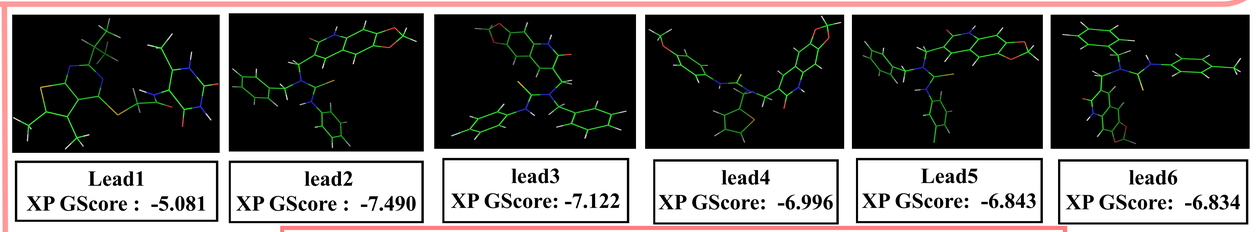
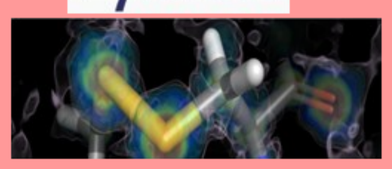



**Figure: 2** Six proposed leads for human BACE-1

## MATERIAL AND METHODS


LIGAND DATABASE

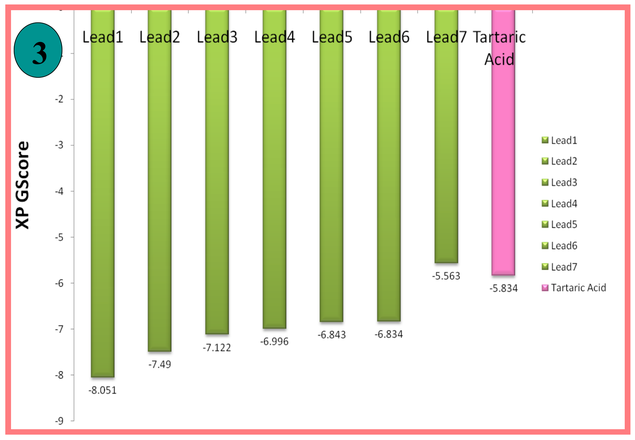

PyMOL

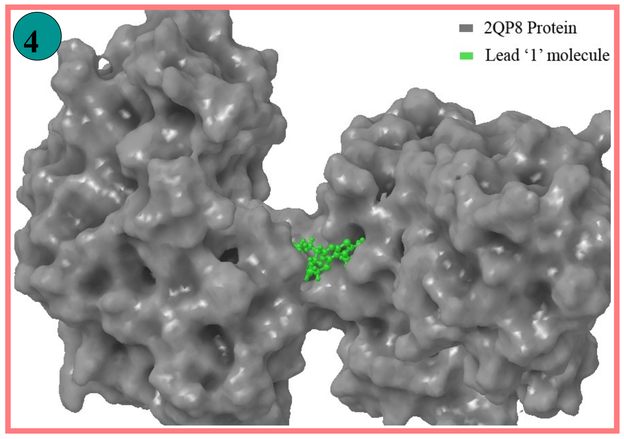


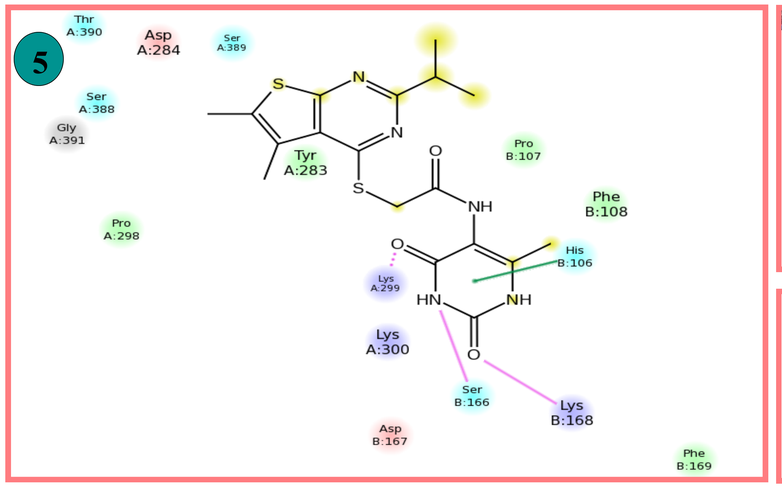
VIRTUAL SCREENING

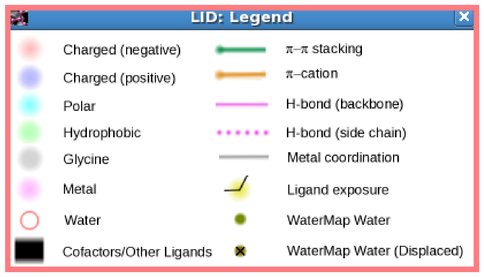

DOCKING STUDIES

Lead compounds




| H-Bond Interactions | ¶-¶ Interactions |
|---|---|
| Lys 299 | His 106 |
| Lys 168 | |
| Ser 166 | |

**Figure:3** Comparison of XP GScore between leads and published inhibitor.
**Figure:4** Docking complex of lead '1' with human BACE-1.
**Figure:5** Interactions of lead '1' with human BACE-1 protein.

## CONCLUSION

Seven leads were obtained and among them, six were proposed as potential leads based on XP GScore with better binding affinity and good pharmacological properties compared with existing inhibitors.

Lead 1 with XP GScore -8.051Kcal/mol, would be intriguing for rational drug design against Alzheimer's disease and would be highly encouraging for future Alzheimer's therapy if tested in animal models.

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