ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 12, Issue, 09, pp.13774-13778, September, 2020

DOI: https://doi.org/10.24941/ijcr.39834.09.2020

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

FARNESOL AS A POTENTIAL INHIBITOR IN NEUROPATHOLOGY OF ALZHEIMER'S DISEASE: AN *IN SILICO* STUDY

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ARTICLE INFO

Article History:
Received 19th June, 2020
Received in revised form
17th July, 2020
Accepted 24th August, 2020
Published online 30th September, 2020

Key Words:

Alzheimer's disease, In silico study, Acetylcholinesterse, Butyrylcholinesterase, Angiotensin converting enzyme, Accelrys discovery studio 4.1 client.

ABSTRACT

Objective: To estimate*insilico* studies on farnesol as a potential inhibitor of Acetylcholinesterase (AchE), Butyrylcholinesterase (BchE), Angiotensin converting enzyme (ACE) in the treatment of Alzheimer's disease. **Methods:** In the present *in silico* study, bioactive terpene farnesol were analysed for their inhibitory role on Acetylcholinesterase, Butyrylcholinesterase, Angiotensin converting enzyme activity by molecular docking studies. The *in silico* docking studies were carried out by using Accelrys Discovery Studio 4.1 client. **Results:** The CDOCKER energy of farnesol with Acetylcholinesterase showed binding energy -32.06 kcal/mol whereas Galantamine(S) showed binding energy 0.364 kcal/mol. Farnesol with Butyrylcholinesterase showed binding energy -34.21kcal/mol whereas Tacrine(S) showed binding energy 12.60 kcal/mol. Farnesol with Angiotensin converting enzyme showed binding energy -33.12 kcal/mol whereas Lisinopril(S) showed binding energy 38.65 kcal/mol. **Conclusion:** The present study reported that the bioactive terpene farnesol have good binding interactions with Acetylcholinesterase, Butyrylcholinesterase, Angiotensin converting enzyme when compared to the standard drugs Galantamine, Tacrine and Lisinopril respectively.

Citation: ***Mohamed Fiaz, A., Haja Sherief S. and Sengottuvelu S.*** **2020.** "Farnesol as a potential inhibitor in neuropathology of alzheimer's disease: an in silico study", *International Journal of Current Research*, 12, (09), 13774-13778.

INTRODUCTION

Alzheimer's disease is a neurodegenerative disorder. Alzheimer's disease is characterised by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This loss results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus. It is the cause of 60-70% of cases of dementia. About 70% of the risk is believed to be inherited from a person's parents with many genes usually involved. Acetylcholinesterase (AchE) is the primary cholinesterase in the body. It is an enzyme that catalyses the breakdown of acetylcholine and some of other choline esters that functions as neurotransmitters. AchE is found mainly at neuromuscular junctions and in chemical synapses of cholinergic type, where its activity serves to terminate synaptic transmission. This termination of actions in the synaptic cleft leads to etiology of Alzheimer's disease. Butyrylcholinesterase (BchE) is a nonspecific cholinesterase enzyme that hydrolyses many different choline-based esters.

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This make termination of nerve impulse transmissions at cholinergic synapses by rapid hydrolysis of acetylcholine. Moreover, function and location of BchE is similar to Acetylcholinesterase. The brain renin-angiotensin system (RAS) has available the necessary functional components to produce the active ligands angiotensin II, angiotensin III, angiotensin IV. Angiotensin II and IV have been shown to play opposing roles in memory acquisition and consolidation.

Angiotensin converting enzyme has positive effects of Aβ degradation and angiotensin II has inhibitory effects on acetylcholine release. Thereby, ACE inhibitors, by reducing the level of both ACE and angiotensin II, generate both beneficial and negative effects for AD. Farnesol is a 3,7,11-Trimethyl-2,6,10-dodecatrein-1-ol, a sesquiterpene alcohol found in essential oils. Terpenes are naturally occurring compound found in higher quantities. It presents an uncoloured liquid or slightly yellow coloured liquid oil with a sweet smell. Thus, Terpenesshow different pharmacological properties such as anti-fungal, anti-bacterial, anti-tumor, anti-parasitic, anti-allergic, anti-inflammatory, anti-viral and analgesic effects.

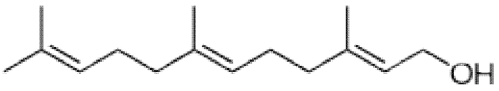

Figure 1. Structure of Farnesol

Computer methods of drug design are based on a postulate that pharmacologically active compounds act by interaction with their macro molecule targets, mainly proteins and nucleic acids. Major factors of such interactions include steric complementary of interacting surfaces of molecules, electrostatic forces, hydrophobic interactions, and hydrogen bond formation. These factors are mainly considered during analysis and prediction of interaction of two molecules.

MATERIALS AND METHODS

Ligand: The chemical structure of Farnesol were downloaded from Pubchem (Pubchem ID: 445070) database with possible structure definition file format for docking studies.

Preparation of protein target: The crystal structure of Acetylcholinesterase (1QTI), Butyrylcholinesterase (4BDS), Angiotensin converting enzyme (1O8A) were downloaded from RCSB PDB and the protein was prepared for molecular dockingby eliminating the unessential water molecules, heteroatoms present, small ions, and alternate confirmations; completing the structure by modelling the missing loop, inserting the missing atoms. Checking the potential energy, Vander Waals energy, electrostatic energy and RMS gradient of the complex before and after protein minimization and then fully merging the hydrogen to the target molecule using Accelrys discovery studio 4.1 client.

Active site prediction: Proteins have specific binding sites, the residues form an active cavity where the ligands are capable to bind and are called active site. The binding sites of preferred target proteins Acetylcholinesterase (1QTI), Butyrylcholinesterase (4BDS), Angiotensin converting enzyme (1O8A) were identified by using Accelrys discovery studio 4.1 to predict the ligand-binding site.

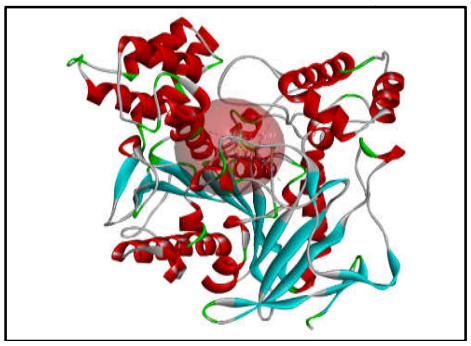

Figure 2. Binding site of AchE

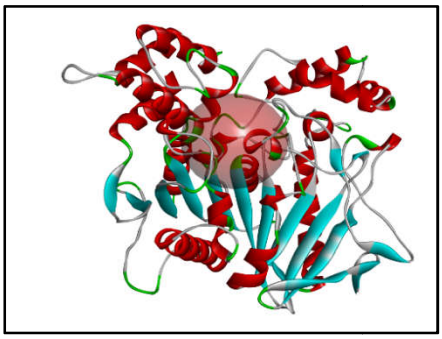

Figure 3. Binding site of BchE

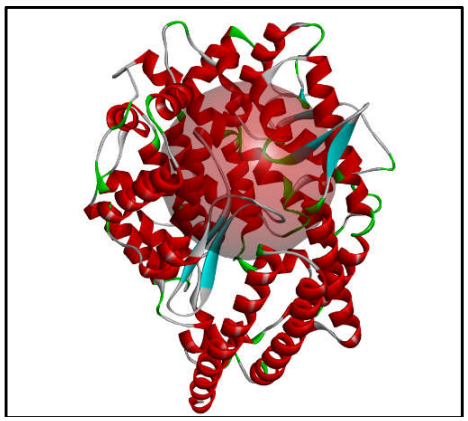

Figure 4. Binding site of ACE

CDOCKER studies: Interaction of ligand with many proteins were treated to be fully flexible and protein rigid was evaluated. The compound were minimized used as input ligand in the protocol explorer of CDOCKER. Molecular dynamic protocol was used to generate various conformations for ligand and the initially generated structures were refined using simulated annealing protocol. The type of interaction to be existed between the ligand and proteins were predicted.

Docking studies: Drug compound that qualify the tests are docked with the receptors 1QTI, 4BDS, 1O8A using CDOCKER available on Accelrys discovery studio 4.1 client. 30 poses were obtained (10 for each receptor). One with the minimum CDOCKER energy is considered to the best binding fit. Interaction of drug with that particular receptor is visualized and determined.

RESULTS

The selected terpene farnesol and the synthetic drug Galanthamine, Tacrine, Lisinopril (standards) were docked in the active site of optimized and energy minimized Acetylcholinesterase, Butyrylcholinesterase, Angiotensin converting enzyme respectively. The results were analysed to identify natural compound with good inhibitory activity considering the interactions binding energy. The compound had very good interactions with active site residues. The interactions of farnesol and Acetylcholinesterase, Butyrylcholinesterase, Angiotensin converting enzyme with their specific targets are shown in the figures.

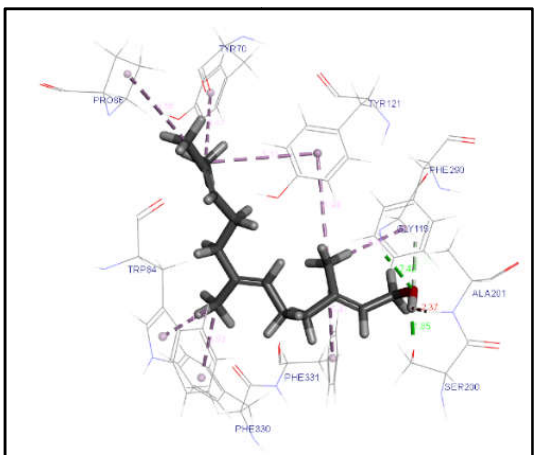

Figure 5. Interactions between AchE and Farnesol

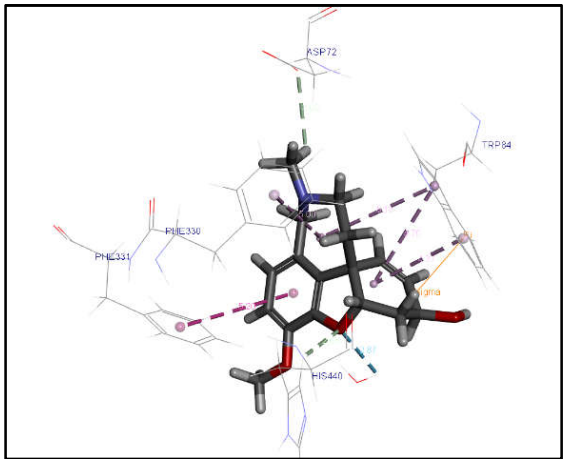

Figure No.6 Interactions between AchE and Galantamine(s)

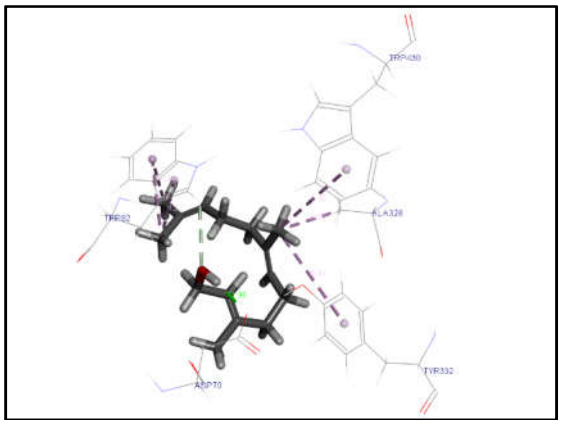

Figure 7. Interactions between BchE and Farnesol

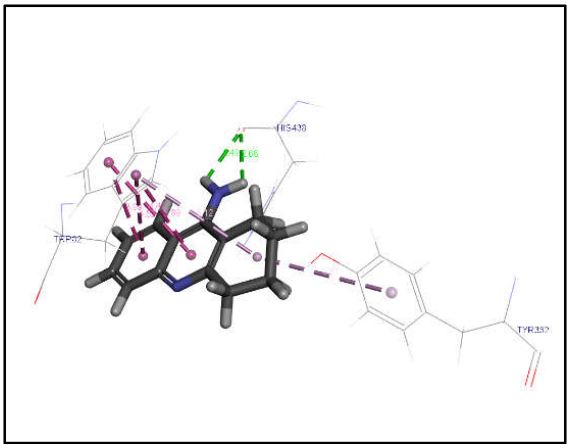

Figure 8. Interactions between BchE and Tacrine(S)

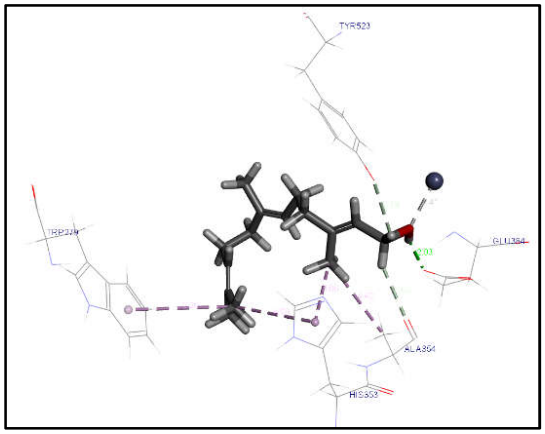

Figure 9. Interactions between ACE and Farnesol

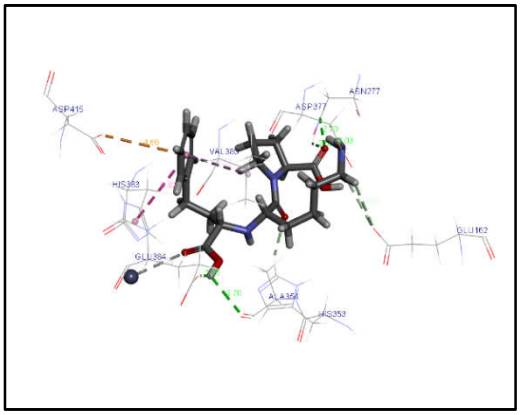

Figure 10. Interactions between ACE and Lisinopril(S)

Similarly, interactions of amino acid, H bond distance and CDOCKER energies of AchE, BchE, ACE with Farnesol and standards Galanthamine, Tacrine, Lisinopril respectively are shown in the Table No.1-3.

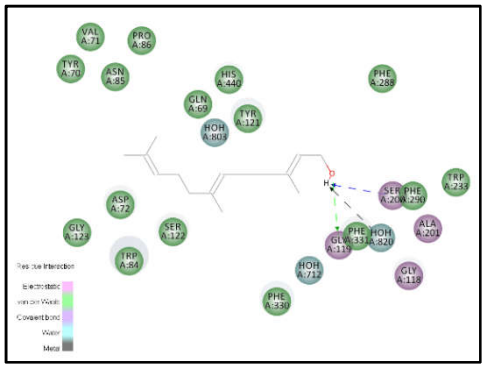

Figure 11. 2D diagram for the binding site of farnesol with AchE

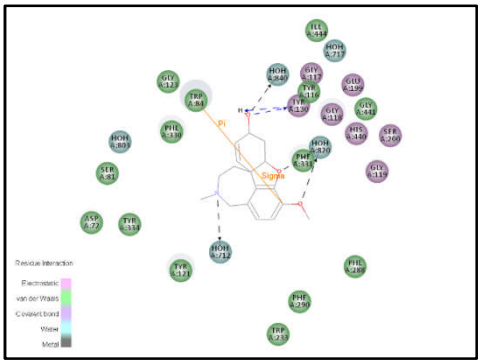

Figure 12. 2D diagram for the binding site of galantamine with AchE

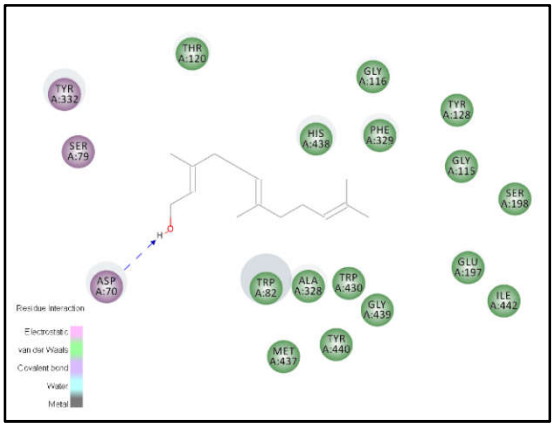

Figure13. 2D diagram for the binding site of Farnesol with BchE

Table 1. Interaction of amino acids, H-bonds distance and CDOCKER energies of AchE with Farnesol and Galantamine

S.No	Ligand	Interaction residues	Bond length(Å)	CDOCKER energies Kcal/mol
1	Farnesol	TYR70, TRP84, TRP84, PHE290, PHE330, PHE331, TYR334, HIS440, HIS440	5.11, 3.57, 4.37, 4.95, 3.94, 5.35, 4.91, 4.92, 5.36	-32.06
2	Galantamine(S)	HIS440, PHE331, TRP84, TRP84, TRP84, PHE330	2.60, 5.31, 4.84, 5.20, 4.38, 5.16	0.364

Table 2. Interaction of amino acids, H-bond distance and CDOCKER energies of BchE with Farnesol and Tacrine

S.No	Ligand	Interaction residues	Bond length(Å)	CDOCKER energies Kcal/mol
1	Farnesol	ASP70, TRP82, ALA328, TRP82, TRP82, TRP82, TYR332, TRP430	1.99, 2.98, 3.94, 4.27, 4.05, 4.00, 5.43, 5.30	-34.21
2	Tacrine (S)	HIS438, HIS438, TRP82, TRP82, TRP82, TRP82, TRP82, TYR332	2.49, 2.66, 4.52, 3.88, 3.98, 4.49, 5.11, 5.31	12.60

Table 3. Interaction of amino acids, H-bond distance and CDOCKER energies of ACE with Farnesol and Lisinopril

S.No	Ligand	Interaction residues	Bond length(Å)	CDOCKER energies Kcal/mol
1	Farnesol	GLU384, ALA354, TYR 523, ZN701, ALA354, TRP279, HIS353, HIS353	2.02, 2.62, 2.78, 2.41, 4.42, 5.26, 4.06, 4.88	-33.12
2	Lisinopril(S)	ASN277, ASN277, ASP377, ALA354, GLU384, HIS353, GLU162, GLU162, ZN701, ASP415, HIS383, VAL380	2.70, 2.51, 2.03, 2.69, 2.14, 2.45, 2.92, 3.00, 3.25, 4.66, 5.01, 5.32	38.65

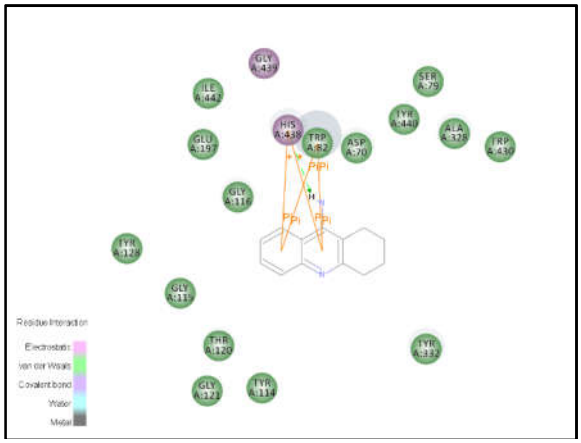

Figure 14. 2D diagram for the binding of tacrine with BchE

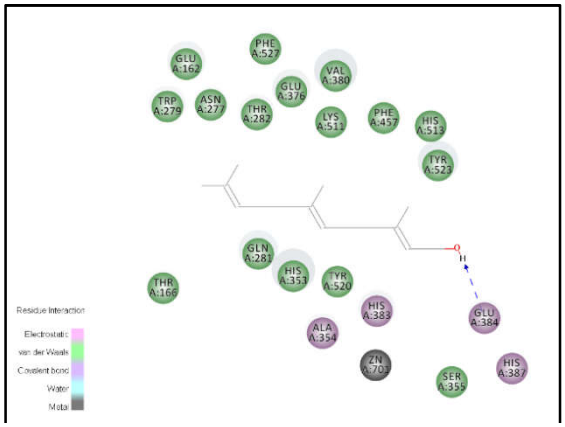

Figure 15. 2D diagram for the binding site of Farnesol With ACE

DISCUSSION

The docking interactions of Acetylcholinesterase, Butyrylcholinesterase, Angiotensin converting enzyme with Farnesol and Galanthamine, Tacrine, Lisinopril were shown in Figures 5-10.

Interactions of hydrophobic and hydrogen bonds with the target proteins plays an prominent role for their pharmacological properties.

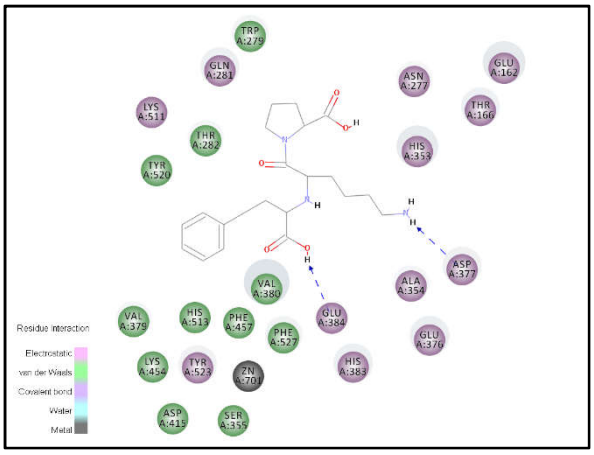

Figure 16. 2D diagram for the binding site of Lisinopril with ACE

In Table No.1the Compound showed CDOCKER ENERGY -32.06 Kcal/mol when compared to the standatrd Galantamine (0.36 Kcal/mol). Further, Farnesol exhibited hydrogen bond and hydrophobic bond interactions with AchE. H bond interactions were seen between Farnesol and GLY119, SER2OO, GLY119. Hydrophobic bond interactions were seen between PRO86, TYR70, TRP84, TYR121, PHE29.The CDOCKER energies and the amino acid interactions clearly reveal that the compound has greatest binding affinity towards the enzyme AchE than the standard. Whereas, Galantamine (S) exhibited hydrogen and hydrophobic bond interactions with AchE. Hydrogen bond interactions were seen between Galanthamine and HOH820, HIS440, ASP72. Hydrophobic bond interactions were seen between PHE331, TRP84, PHE330. In Table No.2the Compound showed CDOCKER ENERGY -34.21 Kcal/mol when compared to the standard Tacrine (12.60 Kcal/mol).Further, Farnesol exhibited hydrogen and hydrophobic bond interactions with BchE. H bond interactions were seen between Farnesol and ASP70,

TRP82. Hydrophobic bond interactions were seen between ALA328, TRP82, TRP82, TYR332, TRP340.The CDOCKER energies and the amino acid interactions clearly indicated that the compound has greatest binding affinity towards the enzyme BchE than the standard. Whereas, Tacrine(S) exhibited hydrogen and hydrophobic bond interactions with BchE. Hydrogen bond interactions were seen between Tacrine and HIS438, HIS438. Hydrophobic interactions were seen between TRP82, TRP82, TRP82, TRP82, TYR332.In Table No.3the Compound showed CDOCKER ENERGY -33.12 Kcal/mol when compared to the standard Lisinopril (38.65 Kcal/mol).Further, Farnesol exhibited hydrogen bond, hydrophobic bond and other interactions with ACE. H bond interactions were seen between Farnesol and GLU384, ALA354, TYR523. Hydrophobic interactions were seen between Farnesol and ALA354, TRP279, HIS353. Other interactions were seen between farnesol and ZN701. The CDOCKER energies and the amino acid interactions clearly reveal that the compound has greatest binding affinity towards the enzyme ACE than the standard. Whereas, Lisinopril (S) exhibited hydrogen, hydrophobic, electrostatic bond and other interactions with ACE. Hydrogen bond interactions were seen between lisinopril and ASN277, ASP377, ALA354, GLU384, HIS353, GLU162. Hydrophobic interactions were seen between HIS383, VAL380 and other interactions were seen between ZN701. Interaction of compound with metal atom ZN01 increases the binding affinity.

Conclusion

Based on *in silico* docking studies the present study clearly showed that farnesol had better binding affinity with all the three therapeutic targetsAchE, BchE, ACE than the standards Galanthamine, Tacrine, Lisinopril respectively. Hence, all the targets play a key therapeutic role in Alzhimer's disease by their enzyme inhibition. Further *in vitro and in vivo* studies are necessary to develop a potent therapeutic targets for the treatment of Alzheimer's disease.

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