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Research Article

IN-SILICO VIRTUAL SCREENING OF PROBABLE HUMAN Γ-SECRETASE INHIBITORS AS ATTRACTIVE THERAPEUTICS IN ALZHEIMER'S DISEASE (AD)

[1*]Subhasree Panigrahy, [2]Koushik Sarker, [3]Purna Nagasree Kurre
[1]Baratam Sandhya Rani and [1]Konna Balakrishna

[1*]Raghu College of Pharmacy, Visakhapatnam, Andhra Pradesh, Pin-531162
[2]College of Pharmaceutical Sciences, Berhampur, Odisha, Pin-760002
[3]Avanthi Institute of Pharmaceutical Sciences, Vizianagaram, Andhra Pradesh, Pin-531162

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative condition with two distinct neuropathological features. i.e, Extracellular amyloid plaque depositions & intracellular neurofibrillary tangles. AD is a neurological disorder that mainly affects memory but may also impair other cognitive functions. The inability to remember recent events is an early symptom of Alzheimer's disease. Reductions of Aβ-level with the help of γ-secretase inhibitor (GSI) could slow down the progression of alzheimer's disease. Molecular docking study of gamma secretase inhibitors (PDB accession code: 6LQG) was performed using CDOCKER protocol in reference with Avagacestat. In total 61, 95, 989 compounds were collected from different databases [Asinex BioDesign library (1,70,269), Asinex Elite library (91,001), Enamine HTS collection (21,02,303), Maybridge HitCreator_V2 (39,197), Zinc15 (40,013), BIONET key organics complete collection (2,05,137) Chemspace Lead-like compounds (12,08,582), FCH group screening libraries (22,44,487), and OTAVA (95,000)] & screened against the target protein human γ-secretase. Out of them four best HITs were identified as Hit-1/Code 14355, Hit-2/Code 15656, Hit-3/Code 46593, Hit-4/Code 52641. The present study revealed that all the Hit compounds have a higher dock score (-53.222, -96.086, -107.279, -134.855 Kcal/mol respectively) than the reference compound (- 26.295 Kcal/mol) and better binding affinities (93.44, 78.78, 101.65, 106.74) than the reference compound (76.71). Hit-4 has the highest dock score and high binding affinity. Based upon our observations using in silico analysis, hit compounds can be utilize in the management of Alzheimer's disease as potent gamma secretase inhibitors.

Keywords: Alzheimer's disease, BIOVIA, Gamma secretase inhibitors, Molecular docking.

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia among the elderly population. Around the world, approx 55 million individuals are suffering from this disease, with no successful treatment currently available AD is a worsening disease that causes neurons to die and severe shrinkage in hippocampus & cerebral cortex, resulting in brain atrophy (Taylor-C-Harris *et al*.,2018) AD is a brain disorder that mainly affects memory but may also impair other cognitive functions. The inability to remember recent events is an early symptom of Alzheimer's disease. Memory loss, language difficulties, cognitive dysfunction, confusion, mood swings, disorientation, behavioural changes, & incapability to think, recall and make decisions are all signs that appear as the disease progresses. This disease commonly strikes people in their late forties and fifties when they are over the age of 65. Risk factors for AD include Depression, asthma, head trauma, CVS disorders, diabetes, and genetics (Dr. Yildiz Dincer *et al*., 2016). For the treatment of AD, currently, four drugs are approved by FDA. 3 among them are acetylcholinesterase enzyme inhibitors (Donepezil, Galantamine, Rivastigmine). Acetylcholinesterase Inhibitors Increase cholinergic neurotransmission by preventing hydrolysis of

*Corresponding Author: Subhasree Panigrahy, Raghu College of Pharmacy, Visakhapatnam, Andhra Pradesh, India, Email: subhasreepanigrahy463@gmail.com.

Acetylcholine. Result in increased acetylcholine synaptic level. 1 is nmda receptor antagonist (Memantine) (Miguel Vaz *et al*.,2020) NMDA receptor antagonist reduces the excitotoxicity effect of glutamate. These drugs are moderately affected in symptoms management but does not prevent progression of AD. Lecanemab & donanemab are immunotherapy drugs approved by FDA. These drugs target the protein β-amyloid to help reduce amyloid plaque in AD. These drugs have possible adverse effect i.e, amyloid-related imaging abnormalities (Rade B. Vukmir *et al*.,2024) Alzheimer's disease progression could be slow down by the reductions of Aβ-level & amyloid plaque with the help of BACE 1 Inhibitors (β-secretase inhibitors) & γ-secretase inhibitor (GSI) (Devendra Kumar *et al*.,2018). B-secretase (bace 1)**:** β-secretase commonly referred as Beta-site APP cleaving enzyme 1 (BACE 1). It catalyzes the initial step of Aβ productions from APP (Robert-Vassar *et al*.,2003). In the pathology of Alzheimer's disease amyloid-beta (Aβ) peptide as an invariable component. Amyloid-beta is design by endoproteolytic cleavage of the Amyloid precursor protein (APP) by the enzyme β and γ-secretase. Bace 1 inhibitors: It abolishes β-secretase activities results in decreased in Aβ productions (Sarah L Cole *et al*., 2007) Examples of BACE 1 inhibitors are- Verubecestat, Lanabecestat, Atabecestat, Umibecestat, Elenbecestat._Γ-secretase:_Gamma-secretase is a transmembrane aspartyl protease composed of four subunits, which include: APH-1 (Anterior Pharynx Defective Phenotype), PSEN (Presenilin), Nct (Nicastrin), PEN2 (Presenilin 2 Enhancer) **(**Arun Evr *et al*.,2013) Examples of γ-secretase inhibitors are- Avagacestat.

MATERIALS AND METHODS

γ- secretase has been the primary target for drug discovery. It is a multimeric protein complex that split single-pass transmembrane proteins at specific residues located within the transmembrane domain. The enzyme γ-secretase facilitates The concluding phase in the synthesis of Aβ40 and Aβ42 from the APP (Amyloid Precursor Protein). Due to its essential function in the progression of Alzheimer's disease it has been selected. **(**Sharie Haugabook *et al*.,2007) As evidence suggests that Aβ is critical to Alzheimer's pathogenesis, Gamma secretase is regarded as a crucial target for the development of therapeutics aimed at modifying disease progression. **(**Michael S Wolfe *et al*.,2012) For all in-silico work, Discovery Studio (D.S.) Version 4.1 software (Now known as BIOVIA) has been used (Dassault Systemes *et al*.,2017) The physicochemical properties of both the hit and reference compounds were determined utilizing Swiss ADME (Daina *et al*.,2017). The γ-secretase protein (PDB accession code: 6LQG) was sourced from the Protein Data Bank (www.rcsb.org). The small molecule databases were imported from their web links. The databases used are Asinex BioDesign library (1,70,269), Asinex Elite library (91,001), Enamine HTS collection (21,02,303)(https://enamine.net/compound-collections/screening-collection/hts-collection), Maybridge HitCreator_V2 (39,197) (https://www.alfa.com/en/maybridge-pre-plated-screening-compounds-and-fragment-libraries/), Zinc15 (40,013) (https://zinc15.docking.org/), BIONET key organics complete collection (2,05,137) (https://www.keyorganics.net/services/bionet-products/screening-compounds/), Chemspace Lead-like compounds (12,08,582) . (https://chem-space.com/compounds), FCH group screening libraries (22,44,487) **(**http://fchgroup.net/screening-compounds.php), and OTAVA (95,000) (https://otavachemicals.com/products/compound-libraries-for-hts/lead-like-library). In total 61, 95, 989 compounds were screened against the target protein human γ-secretase.

Retrieval of human γ-secretase in complex with small molecule Avagacestat and its preparation

The crystal structure of γ-secretase (transmembrane protein hydrolase) in complex with Avagacestat [B (EN9701)] was obtained from the PDB. The co-crystal structure was elucidated using the cryoelectron microscopy (cryo-EM) method at 3.10 Å (Guanghui Yang *et al*.,2020). The protein preparation wizard facilitates the preparation of proteins for docking by executing several essential tasks. These include the - deleting any connected ligand, putting missing atoms into incomplete residues, modeling the missing loop regions, removing alternate conformations (disorder), removal of waters, standardization of atom names, and protonation of titratable residues based on predicted pKs values.

Preparation of database ligands for virtual screening (High Throughput Screening)

The Prepare Ligands wizard assists in the preparation of ligands for integration into docking protocols. It carries out various functions, including setting standard formal charges to common functional groups, kekulizing molecules, attach bad valencies, eliminating duplicates and discarding compounds with unfavorable characteristics, listing isomers and canonical tautomers, producing three-dimensional conformations utilizing Catalyst, identifying valid ionization states within a specified pH range. The 3D structures of the ligands were imported in DS for preparation. For reliable docking results, pH-based ionization method was selected with a pH range of 6.5-8.5. To accurately forecast the appropriate binding mode of the ligands through docking, tautomers are generated by the default setting. Ligands with Rule of five violations were eliminated from consideration at the beginning. (Lipinski *et al*.,2004)

Define and edit the binding site

A Binding Site refers to a set of point on a grid located within a cavity. The Binding Site tools enable the identification, modification, and visualization of binding sites associated with a receptor. PDB files frequently include SITE records to defined active site. When importation of 6LQG groups is generated for each SITE.

The site sphere is characterized by the parameter x, y, z, r, where x, y and z represent the coordinates of the center, while r denotes radius of the sphere. The values are listed as follows-24.7343, 0.359175, -10.9519, and 10.6 in that order. The active site of gamma secretase was found to consist of 47 amino acid residues, namely LEU75, GLY78, HIS81, VAL82, LEU85, PHE86, PRO88, VAL89, TYR256, ASP257, ALA260, PRO267, LEU268, ARG269, VAL272, GLN276, ASN279, ILE287, TYR288, ARG377, VAL379, LYS380, LEU381, GLY382, ASP385, PHE386, PHE388, TYR389, SER390, CYS410, PHE411, ILE414, LEU415, GLY417, LEU418, CYS419, THR421, LEU422, LEU423, LEU424, LEU425, LEU426, LYS429, ALA434, LEU435, SER438, GLY442.

Molecular docking by CDOCKER protocol

The CDOCKER protocol utilizes a CHARMm-based molecular dynamics (MD) approach to facilitate the docking of ligands into a receptor binding site. Random ligand conformations are produced from the initial ligand structure through the application of high-temperature molecular dynamics. (Wu, *et al*., 2003). The conformations are then integrated into the binding site. Conformations were produced on the fly utilizing catConf, is a conformer generation tool from Catalyst. (Guner, *et al*.,2001). Candidate poses are generated through a combination of random rigid-body rotations and grid-based simulated annealing techniques. A concluding minimization step is employed to enhance the positioning of the ligands. Throughout the refinement process, the receptor remains rigid, while the ligand is permitted to flex its conformation. Few important parameters are described only. The pose cluster radius to obtain the top 10 diverse hits was set at 0.1.

The number of initial random conformations produced from the equilibration and minimization of the initial ligand structure was set to 10. The number of steps employed in high-temperature Molecular Dynamics (MD) to generate random starting conformations was set to 1000. The target temperature in the high-temperature Molecular dynamic (MD) utilize to induce random starting conformations (K) was set to 1000. In the simulated annealing refinement process, the number of steps for the heating phase was established at 2000, with a target temperature of 700 for the heating stage. The cooling phase was defined to consist of 5000 steps, aiming for a target temperature of 300. The Momany-Rone method was selected for assigning ligand's partial charge. CHARMm forcefield was selected for atom typing.

In Situ Ligand Minimization

This wizard reduces a series of ligands. If a specific receptor molecule is designated, minimization takes place while the receptor present (in situ). In contrast, ligands are subjected to minimization in a vacuum. For in situ minimizations, the receptor is kept rigid. However, residues that contain atoms situated within the defined sphere or those included in a list of flexible residues are permitted to move. The CHARMm, cff, or MMFF force field may be designated. The server categorizes both ligands and receptors.

Score Ligand Poses

Ligand scoring serves as a technique for the prompt evaluation of a ligand's binding affinity, achieved by analyzing the geometric arrangement of candidate ligand poses that have been docked within the structure of a target receptor. Scoring methods typically utilize empirical functions developed by fitting various functional forms that represent different aspects of receptor-ligand interactions in connection with binding affinity data. An alternative method utilizes statistical analysis of known ligand-receptor structures in conjunction with the occurrence of specific receptor-ligand interactions, eliminating the requirement for binding affinity data. This method is widely referred to as a knowledge-based approach. The application offers both categories of scoring function methods, which include Jain, LigScore1, LigScore2, Ludi, PLP (Piecewise Linear Potential), and PMF (Potential of Mean Force). The initial four methods mentioned above were created through the empirical fitting approach. The knowledge-based statistical system was employed to derive the PMF function. The PLP function was initially created as a docking function, but it has shown a significant relationship with binding affinities. PLP is an efficient and straightforward docking method that has shown a significant relationship with the binding affinities in protein-ligand interactions. Elevated PLP scores indicate a greater affinity for receptor-ligand binding.

Some protocols allow us to specify a set of ligands known to be active and can be used as controls. One can remove this control information if it is already present. In virtual screening protocols, including a set of potent inhibitors, if known as control ligands, can be helpful for the following reasons: The correct docking and scoring of potential control ligands are essential in ensuring that the methodologies and parameters applied for docking and scoring are appropriate for the target receptor. By ranking suitable control ligands, researchers can more effectively identify hit ligands within the pool of randomly selected input ligands. Including control ligands allow you to visualize enrichment rates using Hit Rate Plots and ROC plots.

Calculate Binding Energies

The Calculate Binding Energies protocol enable to calculate the binding energy between a receptor and it's ligand. It is possible to calculate the average binding energy for a group of related poses if desired. Additionally, one can determine the reduction in conformational entropy and the energy linked to a bound ligand, as noted by Tirado-Rives and Jorgensen in 2006. To calculate the binding energy and conformational entropy, it is necessary to define a specific receptor structure along with a collection of ligand poses. To calculate the average, it is necessary to categorize the ligands based on a specific property, ensuring that each category contains multiple members. The calculation of binding energy is performed using the

equation provided below: $Energy_{Binding} = Energy_{Complex} - Energy_{Ligand} - Energy_{Receptor}$

RESULTS AND DISCUSSION

At first, the interaction of Avagacestat in complex with γ-secretase was studied. One conventional hydrogen bond was found between the carbonyl oxygen atom of Avagacestat with -NH- of GLY382 amino acid residue and six alkyl hydrophobic interactions are present with ALA434, LEU268, VAL272, LEU381, LEU418, and LEU422 residues. A pictorial depiction of the interaction of Avagacestat in complex with γ-secretase is presented along with an H-bond surface projected around the receptor-ligand complex (Figure 1 and 2). Three π-alkyl hydrophobic interactions are observed with LYS380, LEU381, and ALA434 residues. To compare the docking results of the designed compounds and Avagacestat, all the compounds were docked together. High throughput screening of 61, 00, 989 diverse lead-like compounds from different databases ultimately returned four Hit compounds. The best dock pose of the compounds was analyzed using ROC plots. These plots are an objective, quantitative measure of whether a test (such as a Bayesian model or a docking algorithm) discriminates between two populations (typically active/inactive compounds). The plots are similar to Hit-rate plots, but the results are more quantifiable and can be compared between different data sets. The Hit Compounds were sorted from the Maybridge HitCreator_V2 database. The Maybridge Hit compound codes are 14355, 15656, 46593, and 52641. The dock score, binding energy, and binding affinity data are given in table 1.

Table 1. Comparative Score of Docking parameters of Avagacestat and the Hit compounds.

Code	Dock Score (Kcal/mol)	Binding Energy (Kcal/mol)	Binding Affinity (-PLP1)
Avagacestat	- 26.295	-16.8027	76.71
Hit-1/Code14355	-53.222	-17.7421	93.44
Hit-2/Code15656	-96.086	-60.8849	78.78
Hit-3/Code46593	-107.279	-48.1326	101.65
Hit-4/Code52641	-134.855	-56.0729	106.74

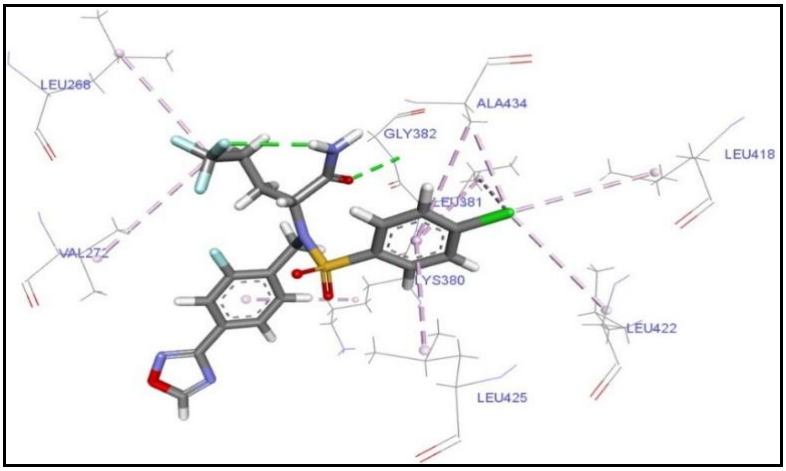

Figure 1. Docking interaction of Avagacestat with the amino acid residues of γ-secretase protein (PDB accession code: 6LQG).

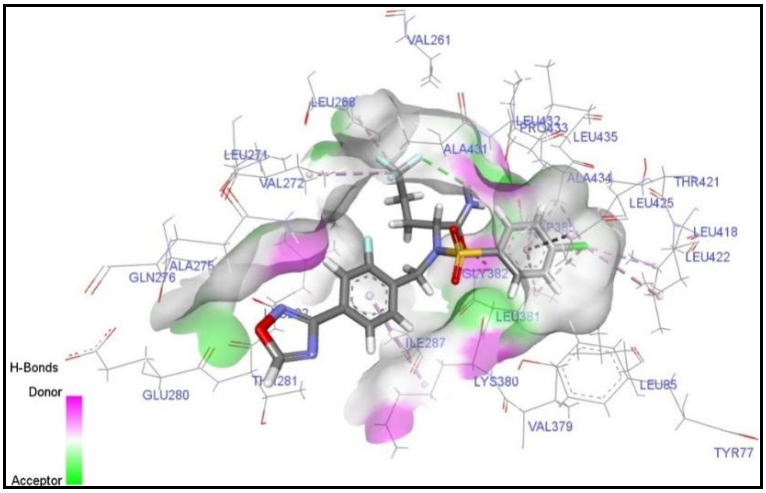

Figure 2. Receptor surface colored by hydrogen bond type, with receptor donors colored in green and receptor acceptors in cyan of the complex γ-secretase protein (PDB accession code: 6LQG).

Several data can be predicted upon analysis of the non-bond interactions between the γ-secretase protein structure and the Hits. Non-bond interactions describe the interactions that occur between pairs of molecules or the intimate contacts present within macromolecular structures. Identifying and improving the interactions between a ligand and a protein is often a primary goal in the field of structure-based drug design. The various form of interaction vary in strength, however, the overall impact of even the weaker forms can be substantial. The data are given in the following table. Some critical Physico-chemical properties of the Avagacestat and Hit compounds are computed (Table 3). The 3D docking interaction of the Hit compounds is depicted in Figure 3.

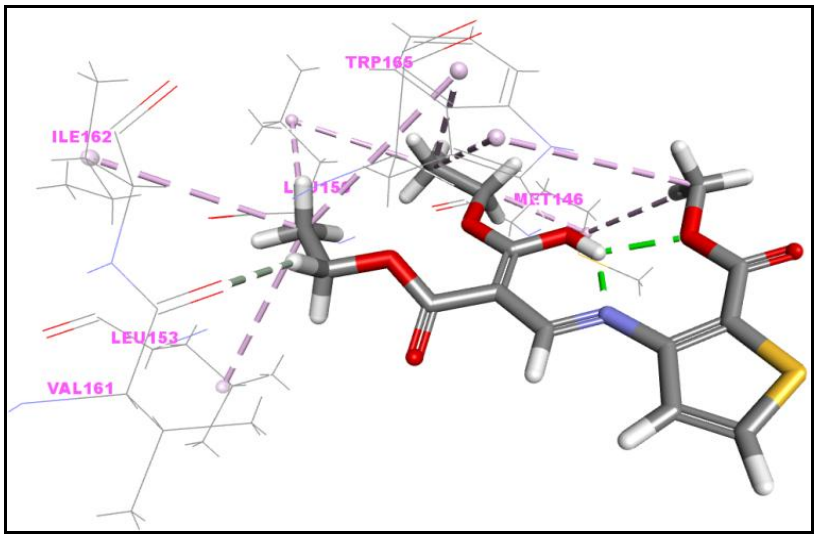

Figure 3. Docking interaction of Hit-1 with the amino acid residues of γ-secretase protein (PDB accession code: 6LQG).

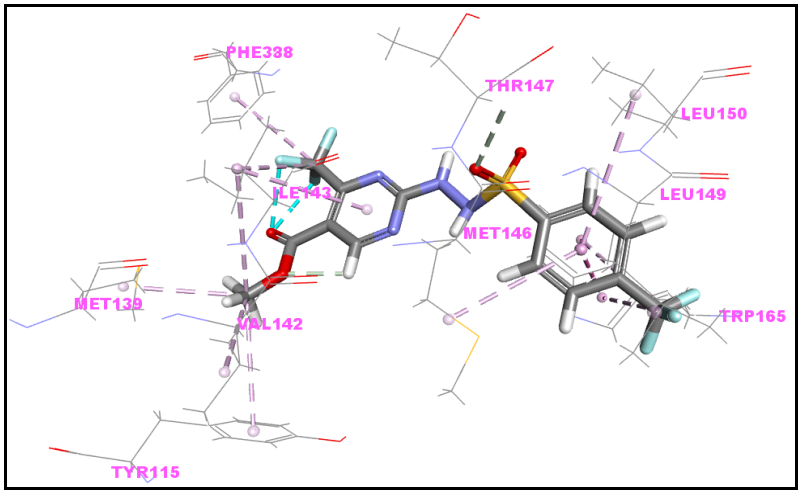

Figure 4. Docking interaction of Hit-2 with the amino acid residues of γ-secretase protein (PDB accession code: 6LQG).

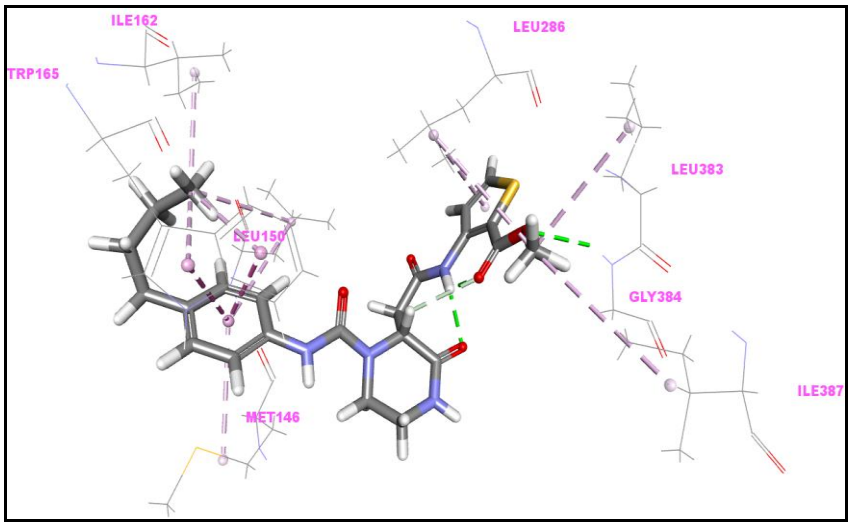

Figure 5. Docking interaction of Hit-3 with the amino acid residues of γ-secretase protein (PDB accession code: 6LQG).

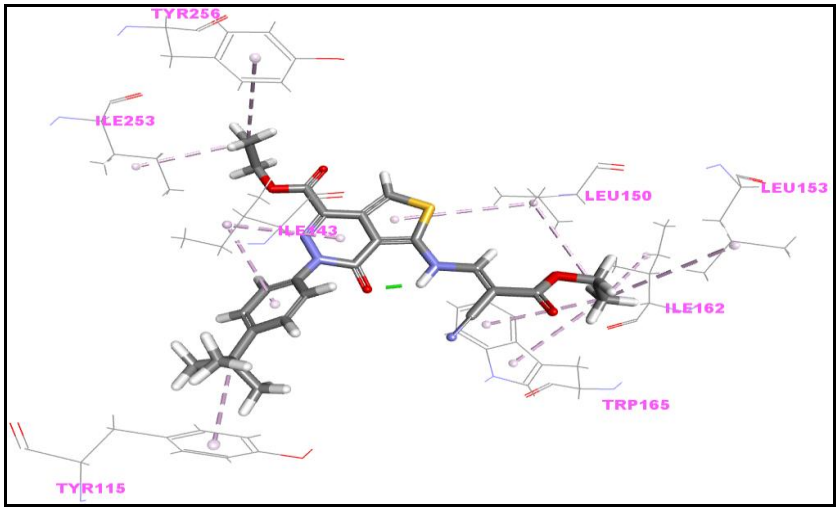

Figure 6. Docking interaction of Hit-4 with the amino acid residues of γ-secretase protein (PDB accession code: 6LQG)

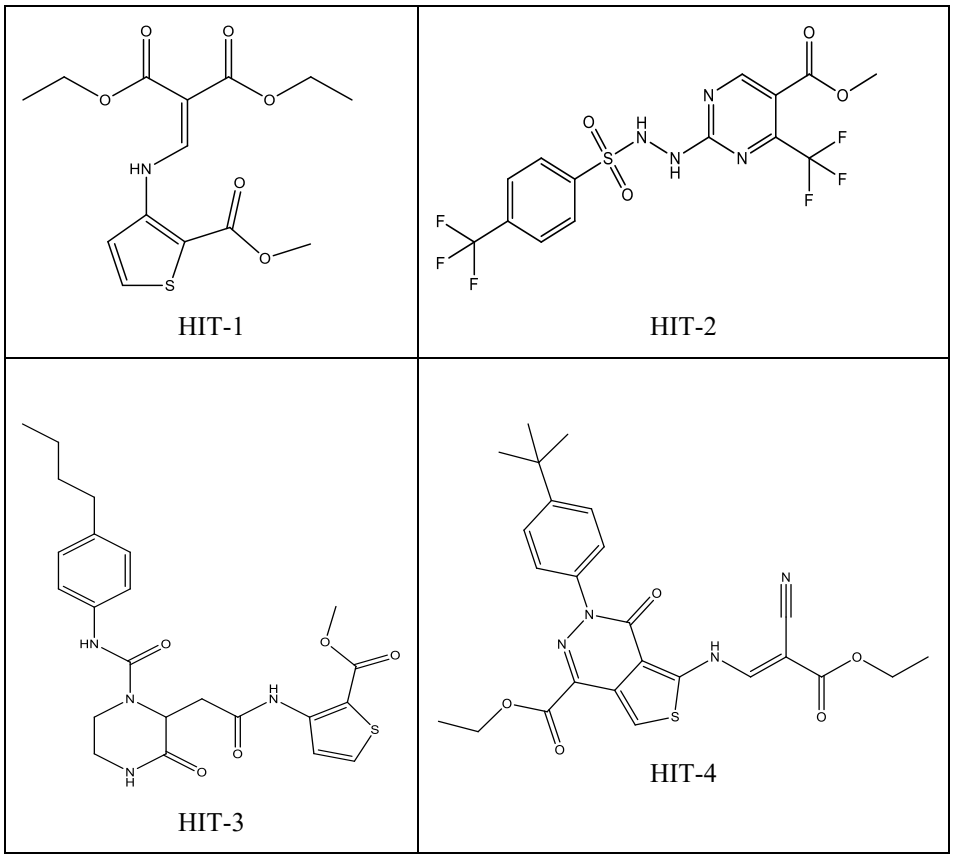

Figure 7. 2D-structure of the Hit compounds.

Hit-1 Diethyl 2-({[2-(methoxycarbonyl)-3-thienyl] amino} methylidene) malonate;
Hit-2 Methyl4-(trifluoromethyl)-2-(2-{[4-(trifluoromethyl) phenyl] sulfonyl} hydrazino) pyrimidine-5-carboxylate;
Hit-3 Methyl 3-[(2-{1-[(4-butylanilino) carbonyl]-3-oxo-2-piperazinyl} acetyl) amino]-2-thiophenecarboxylate;
Hit-4 Ethyl3-[4-(tert-butyl) phenyl]-5-[(2-cyano-3-ethoxy-3-oxoprop-1-enyl) amino]-4-oxo-3,4-dihydrothieno[3,4-d] pyridazine-1-carboxylate.

Table 3. Comparison of physicochemical properties of Avagacestat and the Hit compounds.

Sl.No	Code	M.W.	AlogP	HBA	HBD	Ring aromatic	Rotatable bonds	PSA
1	***Avagacestat***	***520.895***	***3.364***	***6***	***1***	***3***	***10***	***0.269***
2	Hit-1/Code 14355	327.353	2.26	6	1	1	10	0.323
3	Hit-2/Code 15656	444.309	3.25	6	2	2	8	0.302
4	Hit-3/Code 46593	472.557	2.486	5	3	3	9	0.293
5	Hit-4/Code 52641	494.577	4.055	6	1	3	10	0.289

Table 2. Non-bond Interactions of the Avagacestat (reference) and Hit compounds with the amino acid residues of the γ-secretase protein.

S. No	Compound	Category	Types of interaction	Residues	Bond Distance (Å)
1	Avagacestat (Reference)	Hydrogen Bond	Conventional	GLY382	2.82049
		Hydrophobic	Pi-Alkyl	LYS380	5.47759
				LEU381	5.36073
				LEU425	4.84647
				ALA434	4.83917
			Alkyl-Alkyl	ALA434 LEU268	3.59056
				VAL272 LEU381	4.8665
				LEU418 LEU422	5.38883
					4.89189
					5.07673
					4.67152
2	Hit-1/Code 14355	Hydrogen Bond	Conventional	VAL161	2.72355
		Hydrophobic	Pi-Alkyl	TRP165	5.1631
				TRP165	4.82626
				TRP165	5.04261
				TRP165	3.87993
			Alkyl-Alkyl	MET146	4.70671
				LEU150	4.42792
				LEU153	4.66927
				ILE162	4.39308
				MET146	4.77514
				LEU150	4.02088
3	Hit-2/Code 15656	Hydrogen Bond	Conventional	THR147	2.36787
		Hydrophobic	Pi-Alkyl	TYR115	4.53845
				TRP165	4.08438
				TRP165	4.86887
				PHE388	5.09531
				ILE143	4.71509
				MET146	4.63258
				LEU150	4.87246
			Alkyl-Alkyl	ILE143	4.63685
				LEU149	5.01291
				MET139	3.85672
				VAL142	5.0189
				ILE143	4.89939
			π –π stacked	TRP165	3.90753
				TRP165	3.42612
4	Hit-3/Code 46593	Hydrogen Bond	Conventional	GLY384	2.74334
		Hydrophobic	Pi-Alkyl	TRP165	4.37763
				TRP165 LEU286	4.13558
				MET146	4.58243
				LEU150	4.23776
					5.02688

			Alkyl-Alkyl	LEU286	4.69279
				LEU383	4.38802
				ILE387	5.47157
				LEU150	4.62127
				ILE162	4.10072
5	Hit-4/Code 52641	Hydrogen Bond	Conventional intramolecular	Ligand-ligand	1.99119
		Hydrophobic	Pi-Alkyl	TYR115	4.39402
				TRP165	4.48688
				TRP165	4.58338
				TYR256	5.03565
				ILE143	5.06632
				LEU150	5.33402
				ILE143	4.12153
			Alkyl-Alkyl	LEU150	5.12673
				LEU153	5.26805
				ILE162	4.34013
				ILE253	4.36178

CONCLUSION

The present study revealed that all the Hit compounds have a higher dock score than the reference compound (Avagacestat). Hit-4 has the highest dock score and binding affinity; Hit-2 has the highest binding energy. All the Hits were found to form H-bond with the protein leaving Hit-4, which forms an intramolecular hydrogen bond. The Hit compounds were found to interact with the crucial amino acid residues present at the active site also at the allosteric site. Following the initial positioning of the ligand within the binding site, a rigid body minimization is performed on the ligand utilizing the steepest descent (SD) algorithm. This may be succeeded by a Broyden-Fletcher-Goldfarb-Shanno (BFGS) Quasi-Newton minimization, if desired. The rigid body minimized ligand pose is then compared to the poses already in the saved list to determine if the candidate pose should be accepted. The saved list is updated accordingly. The goal is to retain the best ligand poses (based on Dock Score value) having either a different Dock Score or RMSD from each other. The docked pose of the hit compounds was studied to the reference.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

FUNDING

This study received no specific funding from public, commercial, or not-for-profit funding agencies.

AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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