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Research Article

# Exploration of Newly Synthesized Derivative from Carbamate as a Potential Memory Enhancer: Molecular Docking Analysis and Comprehensive ADME-Tox Profiling

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## Abstract

Alzheimer is a neurodegenerative disease of the brain interrelated with decrease of brain function, memory amnesia, and behavioral changes. More than 25 million people in the universe are affected by schizophrenia, most suffering from Alzheimer in both developed and developing nations. Alzheimer's disease has had tremendous impact on the affected individuals, caregivers, and society. The duration of the disease can vary between 2 years and 20 years. The general therapeutic approaches are reliant on the use of acetyl cholinesterase inhibitors (AChE) which can preserve brain cholinergic nerve function in some patients. With the advancement in studies of the pathogenic mechanisms in AD. The target of new AD drug development has been directed to modifying the pathology.

**Keywords:** Alzheimer; Molecular Docking; Newly Derived

## Introduction

Alzheimer's disease is associated with neurobiological, cognitive and behavioral problems and is one of the leading mental disorders among children and adolescents in the world today. billion people. In addition, 4.6% of women and 2.6% of men worldwide are affected by Alzheimer's disease2. Symptoms are responses to internal or externally perceived variables. Many neurotransmitter systems are involved in one or more of these regulatory mechanisms. Alzheimer's disease (AD) is a neurodegenerative brain disease that affects millions of people and often manifests as cognitive impairment and memory loss [1]. The main symptoms of AD include neurodegeneration, impaired brain function, apathy, anxiety, delusions, and depression [2-4]. The lack of a specific treatment for AD emphasizes the importance of accurate diagnosis. AD is usually diagnosed by magnetic resonance imaging (MRI) or positron emission tomography (PET). MRI provides similar images with similar tissues and provides better assessment without posing a risk to the patient [2], while PET uses radiation to visualize, measure and record metabolism, neurotransmitters, blood flow and more. Physical changes. Based on the fact that AD is characterized by the appearance of extracellular amyloid (Aβ) plaques and neurofibrillary tangles, gliosis, synaptic loss and inflammation in the intracellular environment, various theories have been proposed to explain AD. These include (a) the Aβ-amyloid hypothesis, (b) the Aβ-amyloid oligomer hypothesis, (c) the tau hypothesis, (d) the Ca2+ dysregulation hypothesis, (e) the presenilin hypothesis and (f) the lysozyme body hypothesis. According to the Aβ-amyloid related hypothesis, overproduction of the Aβ-amyloid peptide leads to synaptic amyloid plaques, neurotoxicity and neurodegeneration [10]. Abnormal phosphorylation of tau (tubulin-related unit) according to requirements leads to abnormal neurogenesis. Tau protein in normal cells binds to microtubules and promotes their stability and polymerization [11]. The Ca2+ dysregulation hypothesis is based on the calcium-sensing receptor (CaSR), a member of the G protein-coupled receptor (GPCR) C family that regulates calcium homeostasis and intracellular signaling [12]. CaSR dysregulation has been shown to be associated with inflammation and neurodegenerative diseases such as AD [13,14]. The presenilin (PS) hypoth-

esis is based on a genetic mutation in the gene encoding presenilin, the catalytic subunit of γ-secretase that degrades amyloid precursor protein (APP), contributing to brain damage and AD [15]. Finally, the lysosomal hypothesis is based on a genetic mutation that regulates lysosomal pH and leads to destruction of the autophagy-lysosomal pathway [16]. and butyrylcholinesterase (BChE). It has been shown that they can accelerate the aggregation of Aβ peptide into Alzheimer-type aggregates and increase its neurotoxicity [17]. AD patients exhibit low acetylcholine levels, abnormal beta-amyloid levels, T protein aggregation, inflammation and oxidative stress (18). Alzheimer's disease research focuses on the cholinergic system, primarily acetylcholinesterase (AChE) inhibitors. Type B carboxylesterases are a family of related proteins [19]. It is a serine hydrolase that catalyzes the destruction of acetylcholine and other choline esters that act as neurotransmitters [20]. Acetylcholinesterase, produced by muscles, nerves, and hematopoietic cells, is considered one of the most efficient enzymes due to its catalytic speed. The AChE active site is a 20x deep groove where three amino acids (Ser203, Glu334, and His447) form a catalytic triad. There is a binding site near Tyr337. AChE inhibitors can interact with two sources [21]. Kinetic studies have shown that AChE has two different regions, the ester group and the anion, corresponding to the catalytic mechanism and the choline binding pocket [22]. The esterification site for the hydrolysis of acetylcholine to acetate and choline includes the catalytic triad (Ser203, Glu334, and His447). Serine and histidine residues are also found in other serine proteases, but our amino acid is aspartate. Additionally, the catalytic triad in AChE has a different chirality compared to other proteases [23]. Mechanistically, after the carboxylate is hydrolyzed to free choline and acylase, the acylase will be nucleophilically attacked by water molecules and promoted by histamine. The result of this reaction is the release of acetate and free enzyme [24]. Studies have shown that the anionic surface is lipophilic, has no charge, and has a strong odor at the active surface [22], donepezil, rivastigmine, xaliproden, and lecozotan. These compounds are often used as reference materials for the discovery of new compounds. Recently, several classes of compounds have been studied as AChE inhibitors targeting the active site of the enzyme. In the past five years (2018 to 2022), many new derivatives related to acetylcholinesterase have been developed and studied. The new derivatives and materials used, together with their inhibition and coupling results, are briefly described in the supplementary material. This review collects the latest information based on molecular modeling, docking and simulation techniques. The results for the new compounds are classified according to their molecular structure and mechanism of action.

Alzheimer's disease is associated with neurobiological, cognitive and behavioral problems and is one of the leading mental disorders among children and adolescents in the world today. billion people. In addition, 4.6% of women and 2.6% of men worldwide are affected by Alzheimer's disease2. Symptoms are responses to internal or externally perceived variables. Many neurotransmitter systems are involved in one or more of these regulatory mechanisms. Alzheimer's disease (AD) is a neurodegenerative brain disease that affects millions of people and often manifests as cognitive impairment and memory loss [1]. The main symptoms of AD include neurodegeneration, impaired brain function, apathy, anxiety, delusions, and depression [2-4]. The lack of a specific treatment for AD emphasizes the importance of accurate diagnosis. AD is usually diagnosed by magnetic resonance imaging (MRI) or positron emission tomography (PET). MRI provides similar images with similar tissues and provides better assessment without posing a risk to the patient [2], while PET uses radiation to visualize, measure and record metabolism, neurotransmitters, blood flow and more. Physical changes. Based on the fact that AD is characterized by the appearance of extracellular amyloid (Aβ) plaques and neurofibrillary tangles, gliosis, synaptic loss and inflammation in the intracellular environment, various theories have been proposed to explain AD. These include (a) the Aβ-amyloid hypothesis, (b) the Aβ-amyloid oligomer hypothesis, (c) the tau hypothesis, (d) the Ca2+ dysregulation hypothesis, (e) the presenilin hypothesis and (f) the lysozyme body hypothesis. According to the Aβ-amyloid related hypothesis, overproduction of the Aβ-amyloid peptide leads to synaptic amyloid plaques, neurotoxicity and neurodegeneration [10]. Abnormal phosphorylation of tau (tubulin-related unit) according to requirements leads to abnormal neurogenesis. Tau protein in normal cells binds to microtubules and promotes their stability and polymerization [11]. The Ca2+ dysregulation hypothesis is based on the calcium-sensing receptor (CaSR), a member of the G protein-coupled receptor (GPCR) C family that regulates calcium homeostasis and intracellular signaling [12]. CaSR dysregulation has been shown to be associated with inflammation and neurodegenerative diseases such as AD [13,14]. The presenilin (PS) hypothesis is based on a genetic mutation in the gene encoding presenilin, the catalytic subunit of γ-secretase that degrades amyloid precursor protein (APP), contributing to brain damage and AD [15]. Finally, the lysosomal hypothesis is based on a genetic mutation that regulates lysosomal

pH and leads to destruction of the autophagy-lysosomal pathway [16] and butyrylcholinesterase (BChE). It has been shown that they can accelerate the aggregation of Aβ peptide into Alzheimer-type aggregates and increase its neurotoxicity [17]. AD patients exhibit low acetylcholine levels, abnormal beta-amyloid levels, T protein aggregation, inflammation and oxidative stress [18]. Alzheimer's disease research focuses on the cholinergic system, primarily acetylcholinesterase (AChE) inhibitors. Type B carboxylesterases are a family of related proteins [19]. It is a serine hydrolase that catalyzes the destruction of acetylcholine and other choline esters that act as neurotransmitters [20]. Acetylcholinesterase, produced by muscles, nerves, and hematopoietic cells, is considered one of the most efficient enzymes due to its catalytic speed. The AChE active site is a 20x deep groove where three amino acids (Ser203, Glu334, and His447) form a catalytic triad. There is a binding site near Tyr337. AChE inhibitors can interact with two sources [21]. Kinetic studies have shown that AChE has two different regions, the ester group and the anion, corresponding to the catalytic mechanism and the choline binding pocket [22]. The esterification site for the hydrolysis of acetylcholine to acetate and choline includes the catalytic triad (Ser203, Glu334, and His447). Serine and histidine residues are also found in other serine proteases, but our amino acid is aspartate. Additionally, the catalytic triad in AChE has a different chirality compared to other proteases [23]. Mechanistically, after the carboxylate is hydrolyzed to free choline and acylase, the acylase will be nucleophilically attacked by water molecules and promoted by histamine. The result of this reaction is the release of acetate and free enzyme [24]. Studies have shown that the anionic surface is lipophilic, has no charge, and has a strong odor at the active surface [22], donepezil, rivastigmine, xaliproden, and lecozotan. These compounds are often used as reference materials for the discovery of new compounds. Recently, several classes of compounds have been studied as AChE inhibitors targeting the active site of the enzyme. In the past five years (2018 to 2022), many new derivatives related to acetylcholinesterase have been developed and studied. The new derivatives and materials used, together with their inhibition and coupling results, are briefly described in the supplementary material. This review collects the latest information based on molecular modeling, docking and simulation techniques. The results for the new compounds are classified according to their molecular structure and mechanism of action.

Molecular docking study is a research method used to analyze the potency of each candidate produced at the initial immune level related to the target [20]. "Primary" candidate. In fact, natural compounds or phytochemicals have various biological effects [21]. In this case, molecular docking is a better way to determine the potency of the synthetic material needed before randomized trials [22]. In fact, molecular docking is now recognized as a convenient and effective technique that avoids complications or "tried and used" approaches to drug screening [23]. To save time in drug screening. Case studies show that in silico predictions compare with *in vitro* and *in vivo* results [25]. New Medicine. The docking studies of new lead molecules are based on the estimation of binding free energy. In addition, the physicochemical, chemical similarities and properties of ADMET were investigated to ensure its safety and efficacy in the treatment of Alzheimer's disease.

## Materials and Methods

### Physicochemical and drug-likeness properties

The drug-likeness properties as described in Lipinski's rule of five were calculated using DruLiTo, offline opensource software. DruLiTo is an open-source virtual screening tool in which drug likeliness descriptors such as Molecular weight (MW), log P, Alog P, H-bond acceptor (HBA), H-bond donor (HBD),Total Polar surface area (TPSA), Atom Molar Refractivity (AMR), number of rotatable bonds (nRB), number of atom, number of acidic groups, rotatable bond count (RC), Number of Rigid bond (nRigidB), nAtom Ring, and Number of Hydrogen Bonds (nHB) parameters can be predicted [27]. The 3D Structure of the ligands was retrieved from the PubChem online database. The generated Ligands were then saved in the Standard Database format (SDF) [28]. All the prepared ligands were then tested for drug likeliness properties using the software. The calculations were based on various drug likeliness rules like Lipinski's rule, Veber rule, BBB rule, CMC-50, etc. Overall, compounds that do not violate Lipinski's rule of five are predicted to have superior folding, polarity, and molecular size and to have more potential therapeutic effects [29]. ADME Properties The Swiss ADME web server was used to predict the ADME properties (http://www.swissadme.ch/). This website allows you to compute physicochemical descriptors as well This website allows you to compute physicochemical descriptors as well as to predict ADME Parameters, pharmacokinetic properties, drug like nature

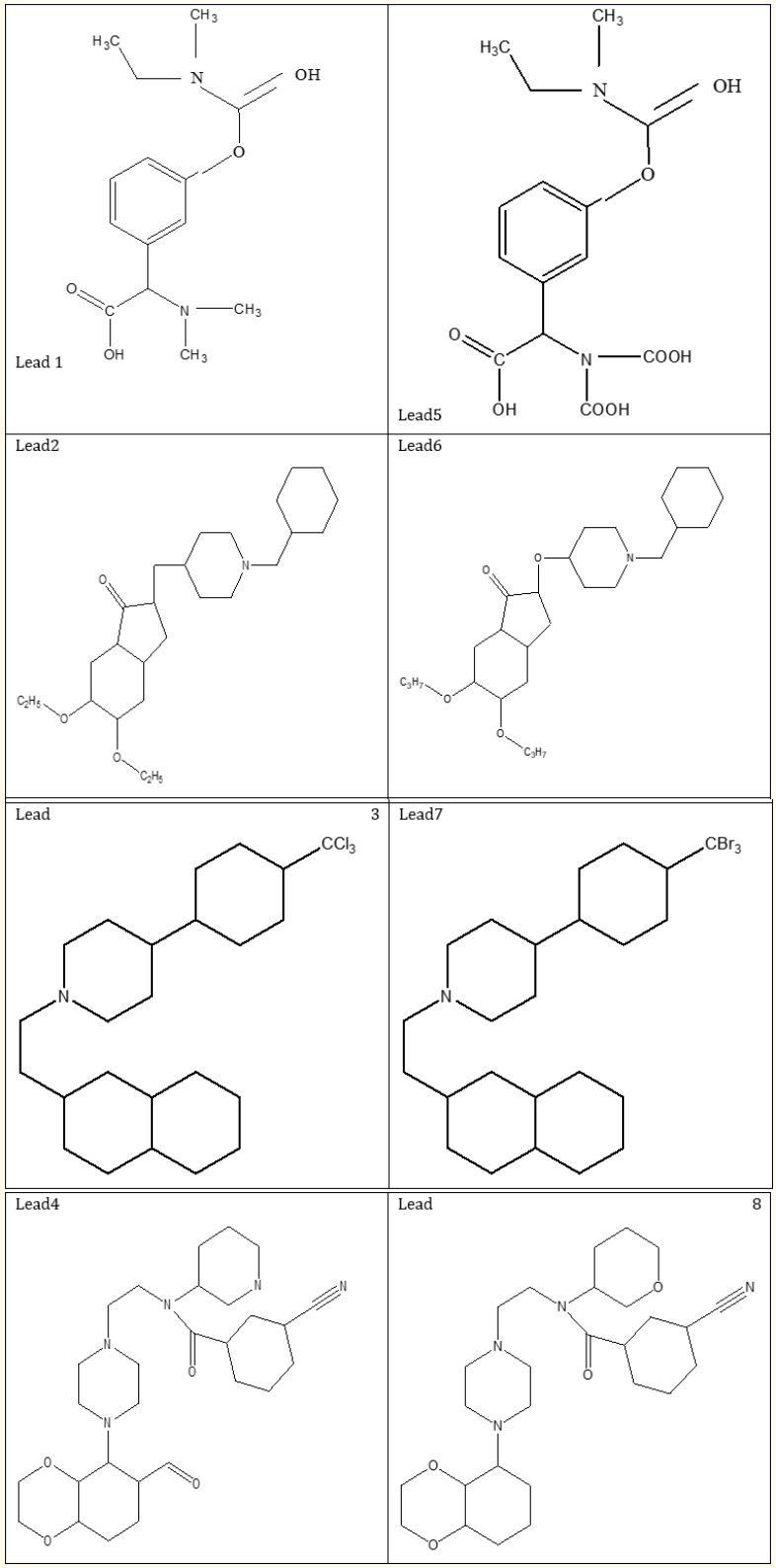



**Figure 1:** Lead molecules.

and medicinal chemistry friendliness of one or multiple small molecules to support drug discovery [30]. Toxicity Estimation The Toxicity Estimation Software Tool (TEST) was developed to allow users to easily estimate the toxicity of chemicals using Quantitative Structure Activity Relationships (QSARs) methodologies [31]. LC50 threshold was calculated using TEST (https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test) software based on predictions from each model and the consensus average of the component models [32]. The hierarchical technique, the single-model method, the group contribution method, the consensus method, and the nearest neighbour method are the QSARs methodologies used in this study effort. A compound can be imported into the software using the following methods a) Using the provided molecular structure drawing tool, b) Importing from an MDL mol file, c) Searching by CAS number, SMILES string, or name. T.E.S.T. allows the user to estimate the value for several toxicity endpoints: ● Oral rat LD50 (amount of chemical in mg/kg body weight that is lethal to 50% of rats after oral ingestion). ● Developmental toxicity (binary indication of whether or not a chemical can intervene with normal development of humans or animals). ● Ames mutagenicity (a compound is positive for mutagenicity if it induces revertant Colony growth in any strain of Salmonella typhimurium). In silico studies of anxiolytic compounds In the docking method, ligand structure and orientation inside a specified binding site were predicted. The two main goals of docking research are precise structural modelling and accurate activity prediction. The process of docking is typically represented as a series of steps, each of which adds a new degree (or layers) of complexity [33]. Docking methods are first used to place tiny molecules in the active site of a cell. In order to anticipate biological activity, these algorithms are enhanced by scoring functions that assess interactions between molecules and prospective targets [34]. Four human targets associated with Alzheimer were chosen to investigate the new lead molecule anxiolytic effects based on an in silico molecular docking approach.

| Target in Alzheimer | | | |
|---|---|---|---|
| **Disorder** | **Targets** | **Reason for Selected Targets** | **References** |
| Alzheimer | Ace(1GQR) | Inhibit the enzyme acetylcholinesterase from breaking down the neurotransmitter acetylcholine into choline and acetate, thereby increasing both the level and duration of action of acetylcholine in the central nervous system | [33] |
| | 5HT1(5V54) | Activation of the serotonergic system blocks the beta-amyloid (Aβ) oligomer-induced inflammatory response | [34] |

**Table 1:** Summarizes the targets and the criteria for selection used in the present investigation.

As per the requirements, the retrieved three-dimensional (3D) crystal structure of selected targets was from the protein data bank (PDB) with individual PDB IDs.

The receptors ACECTYL CHOLIN ESTERASE (PDB Id: 1GQR), 5HT1(5V54) which are responsible for Alzheimer and are selected as the targets for anxiolytic action, were chosen as the targets for docking investigations. The target for the disease was first chosen, and then the 3D structures of numerous targets were obtained from the protein data bank in.pdb format (https://www.rcsb.org). It is commonly known that the PDB file format cannot provide bond order information and that PDB files frequently feature incorrect or missing assignments of explicit hydrogen. As a result, the MVD was used to assign the appropriate bonds, bond orders, hybridization, and charges. MVD's integrated cavity detection technique was used to determine the possible binding locations of both targets. A subset zone of 25.0 Å around the active side cleft used as the study area for the search space of the simulation used in the docking investigations. The replacement water molecules received a score of 0.50 when the water molecules are also taken into account. The major 8 synthesize compound are identified from the selected molecular library of rivastigmine group namely Lead 1, Lead3, Lead4, Lead2, Lead7, Lead8, Lead5, and Lead6 the 3D structures of the active constituents are retrieved From PubChem Chemical databases and saved in.mol format. The ligands are imported to the Workspace and preparation is done for docking studies. The Docking scores of the active Constituents are compared against the Standard drugs such as rivastigmine, donepezil and galantamine obtained from the drug bank in mol format (https://pubchem.ncbi.nlm.nih.gov/). As per docking software, both target and ligand structures were saved in dot PDB (.pdb) file format for a docking study using the software (Molegro virtual Docker 6.0 offline open-source software). The mo-

lecular docking investigation was conducted using Molegro Virtual Docker 6.0, and the findings were compared (http://molexus.io/molegro-virtual-docker/, accessed on 26 September 2022), MVD 2013.6.0.1– 2013-12-13 academic license). Analysis Pose Organizer was used to see the returned postures from the docking engine. Pose organiser has the ability to dynamically load postures from a docking run, allowing users to explore thousands of ligands. More sophisticated re-raking calculations combined with binding affinity measurements were made while many energy terms and interactions were simultaneously examined. When changing positions, electrostatic interactions and hydrogen bonds were dynamically updated. Selected ligands' SPDVP scores were compared to those of the reference drug. The ligands with the highest binding affinity to the target protein are those with the lowest binding energy. The top ligands and potential lead molecules for a treatment for Alzheimer were those whose ligands displayed the highest SPDVP scores.

## Results

### Physicochemical, Drug-Likeness Properties and ADME properties

All the new lead molecule from pyridine and pyrimidine derivatives that are Lead1, Lead2, Lead3, Lead4, Lead5, Lead6, Lead7 and Lead8 appears to follow all the five rules of Lipinski's drug-likeness criteria (Table 2). According to the data acquired from DruLiTo and Swiss ADME software, Lead1, Lead2, Lead3, Lead4, Lead5, Lead6, Lead7 and Lead8 also passed Veber's rule, the blood-brain barrier (BBB) likeness rule was passed by all except Lead1and Lead4, the constituents also passed the Ghose filter except the new lead molecule Lead1, Lead4 and Lead6 as shown in table 2. The GI absorption was high in all the constituents except Lead4 which showed low GI absorption. Only Lead4 cannot cross the Blood Brain Barrier (BBB). Lead5, Lead6, Lead2 and Lead3 may produce the inhibition of CYP 1A2 as showed in table 2.

| Property | Lead1 | Lead2 | Lead 3 | Lead4 | Lead5 | Lead6 | Lead7 | Lead8 |
|---|---|---|---|---|---|---|---|---|
| Molecular weight (g/mol) | 422.69 | 495.78 | 495.78 | 525.12 | 482.65 | 449.67 | 582.29 | 515.69 |
| Hydrogen bond donors | | | | | | | | |
| Hydrogen bond acceptors | 2 | 1 | 1 | 1 | 6 | 4 | 0 | 2 |
| Hydrogen bond donar | 3 | 1 | 2 | 2 | 7 | 6 | 1 | 3 |
| Rotatable bonds | 4 | 1 | 3 | 2 | 1 | 1 | 0 | 2 |
| Log P (Partition coefficient, Predicted value) | 2.78 | 2.24 | 2.37 | 1.90 | -2.79 | 1.70 | 4.55 | 0.95 |
| Molar refractivity | 74.01 | 48.01 | 49.06 | 45.37 | 78.20 | 76.01 | 133.92 | 45.13 |
| Topological polar surface area in Å² | 41.13 | 20.23 | 29.46 | 29.10 | 134.52 | 111.13 | 17.07 | 57.53 |
| Lipinski's rule of five | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Ghose filter | Yes | No | Yes | Yes | Yes | Yes | No | Yes |
| Veber's rule | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| BBB likeness rule | Yes | Yes | Yes | Yes | Yes | Yes | No | No |
| GI absorption | High | High | High | High | High | High | Low | High |
| BBB Permeability | YES | YES | YES | YES | YES | YES | NO | YES |
| Bioavailability score | 0.55 | 0.55 | 0.55 | 0.55 | 0.55 | 0.55 | 0.55 | 0.85 |

**Table 2:** Physicochemical, drug-likeness and ADME properties of anxiolytic compounds.

All of the above findings indicate that all have a good potential drug-like molecule and a useful therapeutic agent against a variety of disorders including Alzheimer.

Toxicity Estimation The endpoint of the oral rodent LD50 is the measure of the compound (chemical mass per rodent body weight) that destroys half of the rodents when administered orally. The oral rodent LD50 directed in four methods for the selected compound and the discoveries were relatively assessed. All new lead molecule have been shown to have an acceptable toxicity limit as shown in Table no 3 for drug production and preclinical and clinical appraisal. Developmental toxicity was performed in four approaches with all of the chosen compounds and the findings were comparatively analysed. Toxicity is indicated by a predicted value greater than 0.5. Except Lead7 all the other new lead molecule shows developmental toxicity. Ames Mutagenicity was conducted in four methods for all of the chosen compounds and the findings were comparatively analysed in Table 3.

| Method | End point | Lead 1 | Lead 2 | Lead 3 | Lead 4 | Lead 5 | Lead 6 | Lead 7 | Lead8 |
|---|---|---|---|---|---|---|---|---|---|
| Consensus | Oral rat LD50 | 2.95 | 2.18 | - | 1.85 | 1.77 | 2.15 | 1.67 | 2.30 |
| | Developmental toxicity | 0.35 | 0.77 | - | 0.82 | 0.60 | 0.75 | 0.63 | 0.83 |
| | mutagenicity | -0.14 | 0.41 | - | 0.25 | 0.32 | 0.62 | 0.43 | 0.10 |
| Hierarchical clustering | Oral rat LD50 | 2.78 | 2.21 | _ | 1.94 | 1.78 | 2.24 | 1.86 | 2.73 |
| | Developmental toxicity | 0.28 | 0.9 | _ | 0.87 | 0.56 | 0.98 | 0.82 | 0.78 |
| | mutagenicity | -0.26 | 0.48 | _ | 0.16 | 0.3 | 0.58 | 0.53 | 0.21 |
| Single model | Oral rat LD50 | 2.95 | 2.18 | _ | - | 1.77 | 2.15 | 1.67 | 2.30 |
| | Developmental toxicity | 0.35 | 0.77 | _ | 0.60 | 0.60 | 0.76 | 0.63 | 0.83 |
| | mutagenicity | -0.14 | 0.41 | _ | - | 0.32 | 0.62 | 0.43 | 0.10 |
| Group contribution | Oral rat LD50 | 2.95 | 2.19 | _ | _ | 1.77 | 2.15 | 1.57 | 2.30 |
| | Developmental toxicity | 0.35 | 0.77 | _ | _ | 0.60 | 0.76 | 0.63 | 0.83 |
| | mutagenicity | -0.14 | 0.41 | _ | _ | 0.32 | 0.62 | 0.43 | 0.10 |
| Nearest neighbor | Oral rat LD50 | 3.13 | 2.15 | - | 1.76 | 1.76 | 2.07 | 1.49 | 1.87 |
| | Developmental toxicity | N/A | 1.00 | - | 1.00 | 0.67 | N/A | 0.67 | 1.00 |
| | mutagenicity | 0.00 | 0.33 | _ | 0.33 | 0.33 | 0.67 | 0.33 | 0.00 |

**Table 3:** Predicted value for Oral rat LD50 - Log10 (mol/kg), Developmental toxicity, Ames Mutagenicity.

Toxicity is indicated by a predicted value greater than 0.5. All the new lead molecule except Lead 3 are not mutagens based on the results on the Ames mutagenicity as predicted by TEST software as shown in Table 3.

*In-silico* studies of anxiolytic compounds The ability of the new lead molecule to bind with the targets is given in terms of SPDVP Score. The SPDVP Score is used as the parameter for analysing the docking results. The new lead molecule are ranked according to their SPDVP Score; rank score and hydrogen bond interaction. The pose of the ligand which has least SPDVP score shows a strong affinity towards its enzyme target. The ligand having the most elevated SPDVP and re rank score shows a strong affinity towards its target receptor. In-silico docking analysis was performed for all 8 new lead molecule such as Lead1, Lead2, Lead3, Lead4, Lead5, Lead6, Lead7 and Lead8 and Compared with Marketed drugs using Molegro virtual Docker on ACECTYL CHOLIN ESTERASE (PDB ID: 1GQR)receptors. The pose is represented in ball and stick model along with the molecular weight and the amino acids in protein are represented in stick frame model with the residue numbers. As per the MVD software, the docking score is always expressed in a negative value, where a higher negative value indicates a better potency. The SPDVP score of the ligands Lead5, Lead6, Lead4, Lead8, Lead2, Lead7, Lead3 and Lead 1against ACECTYL CHOLIN ESTERASE re-

ceptor was found to be -53.0226, -47.3339, -76.5405, -46.6556, -71.9564, -57.4265, -58.7002, -65.6419 and -37.7307 respectively shown in Table 4. For ACECTYL CHOLIN ESTERASE SPDVP score of Lead4, shows -76.5405 followed by Lead2 shows -71.9564 which is higher than the other ligands and marketed drug -37.7307, the docking pose seen in figure 1.

The SPDVP score of the ligands Lead5, Lead6, Lead4, Lead8, Lead2, Lead7, 4- hydroxy cinnamic acid, Lead3 and rivastigmine against ace receptor was found to be -29.0959, - 41.9634, -76.2877, -30.5221, -58.338, -59.0293, -58.3074, -46.7278 and -35.9252 respectively as shown in Table 5. For 5HT1 SPDVP score of Lead4, shows -76.2877 followed by Lead7 shows --59.0293 which is higher than the score of marketed drug Donepezil shows -35.9252, the docking pose seen in figure 2.

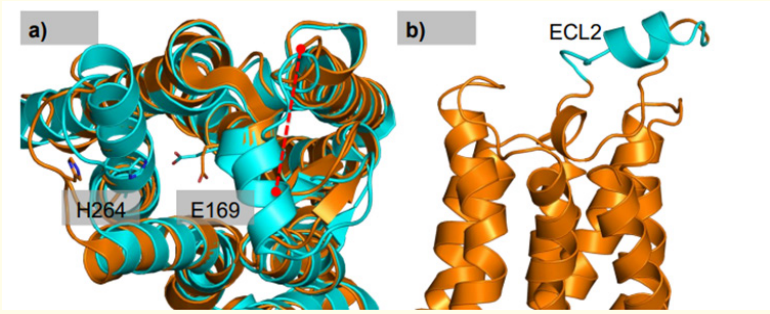



**Figure 2:** a. Superposition of 5HT1A(cyan) and drug mole 35 (orange) X-ray structures. Reported in the same color code and in stick the residues undergoing the greatest conformational changes.
b. The refined hybrid Ace receptor, in orange the mole -17 cartoon and in cyan the cartoon extracted from Ace -17 complex.

| Name | Ligand | MolDock Score | Rerank Score | HBond |
|---|---|---|---|---|
| Lead1 | 3314 | -53.0226 | -45.9211 | -6.58917 |
| Lead2 | 10364 | -47.3339 | -41.1804 | -4.479 |
| Lead3 | 92785 | -76.5405 | -56.3844 | 0 |
| Lead4 | 92987 | -46.6556 | -42.0722 | -4.02252 |
| Lead5 | 128853 | -71.9564 | -61.329 | -12.616 |
| Lead6 | 5280863 | -65.6419 | -59.9399 | -4.35857 |
| Lead7 | 443143 | -57.4265 | -47.1977 | 0 |
| Lead8 | 637542 | -58.7002 | -50.2235 | -6.84347 |

**Table 4**

Superposition of the Ace -17 complex Superposition of the Ace -17 complex.

The new lead molecule such as Lead5, Lead6, Lead4, Lead8, Lead2, Lead7, 4-hydroxy cinnamic acid, Lead3 and Galantamine as standard drug, in silico docking analysis was performed against Acetylcholine esterase receptor was found as -68.999, -57.675, -92.8193, -60.3203, -70.0025, -76.5438, -74.4535, -55.326 and -103.838 respectively as shown in Table 6. For Dopamine D3 SPDVP score of Lead4, shows -92.8193 followed by Lead7 shows -76.5438 when compared to the score of marketed drug Galantamine shows - 103.838, the docking pose seen in figure 3.

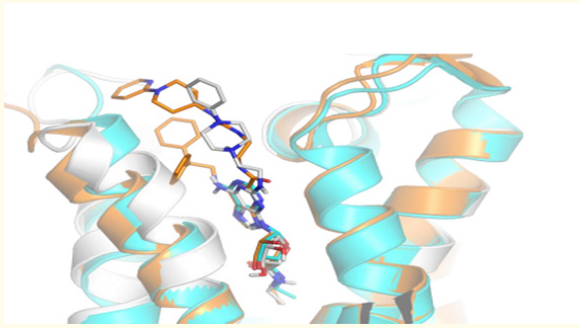
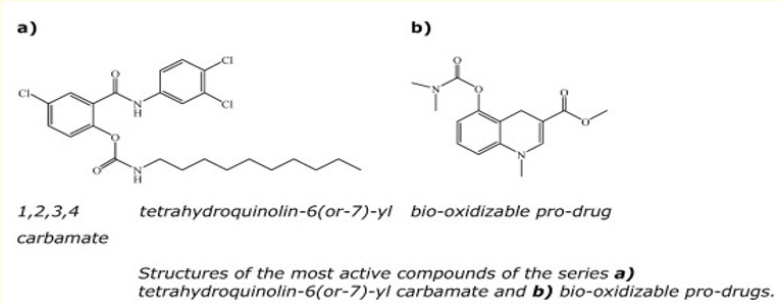


**Figure 3**



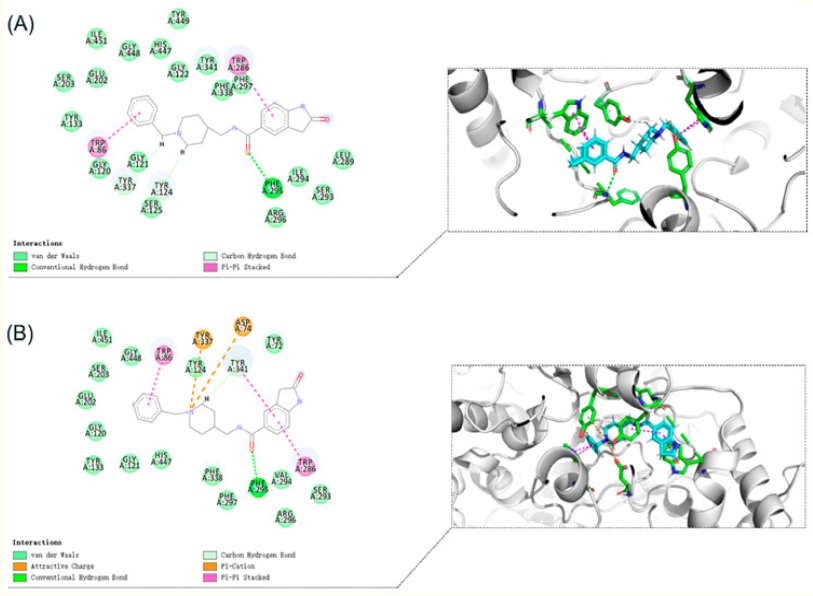




**Figure 4:** (A) Binding mode prediction of compound 8i with AChE (PDB ID: 1GQR) (B) Binding mode prediction of compound 8i with AChE (PDB ID: 1GQR).

## Discussion

In neonates, less than 1% of patients experience laryngospasm and/or bronchospasm, ventricular arrhythmias including ventricular bigeminy or premature ventricular contractions, vasovagal syncope, bradycardia, or tachycardia. Rivastigmine is a selective ace inhibitor with a minor antagonistic activity at ace receptors also used in treatment of Alzheimer. The adverse effects of rivastigmine are attributed to both peripheral and central dopaminergic stimulation. In this work, an e-pharmacophore hypothesis strategy was used to identify potent AChE inhibitors from the PubChem database. The e-pharmacophore model design is composed of a hydrogen bond donor (D2), a hydrogen bond acceptor (A1), an aromatic ring (R8), and an ionizable (positive ionic) group (P7). The model's quality was assessed using rigorous enrichment analysis. The bioactive compounds were sorted based on their scores during the phase selection; the information collected from their alignment was used to identify several novel HUP-substituted compounds that may act as AChE inhibitors. The developed molecules were also docked in SP and XP modes, and certain derivatives, The pharmacokinetic features of these four top hits were subsequently investigated using ADMET analysis. Notably, for all the selected compounds, the pharmacokinetic properties were within the required range. In addition, the biomolecular stability and dynamics of the generated complexes demonstrated the pharmacological potential of the developed inhibitors for blocking the enzymatic and biological activities of AChE. Overall, these results are incredibly significant and might lead researchers to develop novel AChE receptor inhibitors for the treatment of Alzheimer's disease. In silico research has the power to quicken the pace of discovery while lessening the demand for expensive lab work and clinical trials [49]. The benefit of using computational methods is that they can deliver new drug candidates more quickly and for less money which include Drug likeness, Toxicity estimation and Molecular docking to choose the best drug candidate and carried to perform *in vitro, in vivo* studies easily. The 'drug likeness properties' of the new lead molecule was evaluated according to the 'The Lipinski rule of five' and to develop them as potential lead compound for anti-Alzheimer activity. All the new lead molecule are Lead5, Lead6, Lead4, Lead8, Lead2, Lead7, 4-hydroxy cinnamic acid; Lead3 passes the drug likeness properties. All substances have been shown within limit toxicity of Oral LD50 which can be further taken for drug production and preclinical and clinical appraisal. The phytochemical constituents Lead4 which is present in medicinal plant Convolvulus prostratus Frossk (shankhpushpi) shows SPDVP score of -76.5405, -76.2877 and -92.8193 against ACECTYL CHOLIN ESTERASE, 5HT1 which is higher and nearer than to the standard drug Rivastigmine -37.7307, Galantamine -35.9252 and Metrifonate shows -103.838 respectively. Lead4 exhibits a good modulatory effect on the immune system and proves to be a potent drug for the treatment of many allergic disorders. Lead4 is used as anti-parasitic, antifungal, allopathic, antibacterial (which is comparable to the activity of ampicillin against Escherichia coli and other strains), antioxidant, antitumor, and antiviral against herpes simplex viruses. It can prevent catalase and superoxide dismutase, and reduce glutathione concentration. The inhibitory effect of Lead4 on nitric oxide generation was significantly more effective than that of caffeic acid and/or Gallic acid. Lead4 exhibited comparable antioxidant capacities with butylated hydroxyl toluene (BHT) by the DPPH ($p = 0.117$) and FRAP ($p = 0.179$) assays. Convolvulus prostratus Forssk, one such cognitive booster herb is mainly endowed with neuroprotective, nootropic and neuro modulatory activities. Besides, it also possesses several other therapeutic properties, antidiabetic and cardio protective activities. Therefore, maximum chances of Lead4 to show anti-Alzheimer active since it is active constituent of Convolvulus prostratus Forssk. For serotonin SPDVP score of Lead3, shows -81.0347 which is nearer to the score of marketed drug paroxetine shows -95.7425. Lead3 has therapeutic effects on inflammation associated diseases, including allergies, arthritis, diabetes, cardiovascular diseases, cancers and neurological regression by inhibiting protein kinases and transcription factors. If there are chances to work on *in vitro* and *in vivo* activity of Lead3 against Alzheimer disorder, more chances to get a good drug candidate without any side effects for the treatment of Alzheimer. The eight new lead molecule were docked against ACECTYL CHOLIN ESTERASE. Lead4 showed highest binding affinity when compared with standard drugs against ACECTYL CHOLIN ESTERASE inhibitors and 5HT1 agonist can be a good drug candidate and possess potential anxiolytic activity against Alzheimer disorder.

Additional research can be done to determine the Lead4's *in-vitro* and *in-vivo* Alzheimer activity as well as the pharmacokinetic characteristics of the new lead molecule to learn about their absorption, distribution, metabolism, and excretion.

## Conclusion

In our current research, we have chosen eight new lead molecules namely Lead1, Lead2, Lead3, Lead4, Lead5, Lead6, Lead7 and Lead8 to test its affinity towards ACECTYL CHOLIN ESTERASE and 5HT1 receptors. Synthetic drugs has led to a rise in demand for AD newly synthesis medicines are introduce to market, which have been approved or are in various stages of clinical trials for a variety of diseases in recent decades. Despite the fact that synthetic chemistry dominates the current drug development and manufacturing field, the importance of newly-derived compounds in the treatment and prevention of various diseases cannot be neglected. In this study, eight ligands were investigated in order to find out the significant ligand against Alzheimer disorder. The ligand was selected based on its binding affinity against receptors and comparing their activity with the standard drugs available in the market. Findings of this experiment suggested that Lead4 can be administered if the treatment of Alzheimer focuses on inhibiting the ACECTYL CHOLIN ESTERASE. Further studies can be performed in *invitro* and *in-vivo* experimental animal models of Alzheimer disorder to establish the efficacy of promising drug.

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