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Computational Design and Evaluation of Novel Rivastigmine Analogues Targeting *hAChE* in Alzheimer 's disease

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ABSTRACT

***Introduction*:**
Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by memory loss and cognitive decline. One therapeutic strategy involves inhibiting acetylcholinesterase (hAChE), the enzyme responsible for acetylcholine degradation in synaptic clefts. This study aimed to identify and evaluate novel hAChE inhibitors structurally related to Rivastigmine using computational techniques, including virtual screening and molecular docking, to discover potential lead compounds for AD therapy.

Materials and Methods:
The crystal structure of hAChE (PDB ID: 6M0E) was obtained from the Protein Data Bank. Ligands with over 95% structural similarity to Rivastigmine, were retrieved from PubChem. The ligands screened virtually using PyRx. Then, Molecular docking was performed with AutoDock 4.2 on lead ligands. Furthermore, in silico toxicity prediction was performed using the ProTox-II server to assess the preliminary safety of the top-performing compounds against Rivastigmine.

Results:
Molecular docking analysis revealed that Ligand 13 exhibited the most potent binding affinity and the lowest calculated inhibition constant, indicating superior interaction with key catalytic gorge residues compared to Rivastigmine. However, the toxicity assessment showed a critical disparity: Ligand 13 was predicted to have high acute toxicity (low LD50), whereas Ligand 16, the second-best binding affinity, demonstrated a favorable toxicity profile and retained BBB permeability, matching the reference drug.

Conclusion:
This study successfully confirmed Ligand 16 as the most promising candidate, offering a compelling balance between high affinity and a predicted safety profile superior to that of the strongest binder, Ligand 13. These findings provide a solid foundation for future in vitro and in vivo studies aimed at developing novel therapies for Alzheimer's disease.

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Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia and represents a progressive neurodegenerative disorder characterized by memory impairment, cognitive decline, and the gradual loss of independence. The global rise in its prevalence imposes a major medical and socioeconomic burden worldwide. Although several therapeutic agents are available, none can completely cure or halt the disease; existing treatments are primarily symptomatic and aim to preserve cognitive functions and slow disease progression (1, 2). One of the principal mechanisms underlying AD therapy is the inhibition of human acetylcholinesterase (hAChE)—the enzyme responsible for hydrolyzing acetylcholine (ACh) into choline and acetate within synaptic clefts. Dysfunction or overactivity of hAChE significantly reduces acetylcholine concentration, leading to impaired cholinergic neurotransmission. Enhancing hACh levels through hAChE inhibition can partially restore synaptic signaling, resulting in improved memory and cognition. Approved hAChE inhibitors, such as donepezil, galantamine, and Rivastigmine, have shown therapeutic benefits in early-to-moderate stages of AD; however, these agents are limited by gastrointestinal side effects, modest efficacy, and short half-life (3–5).

To elucidate the molecular basis of enzymatic inhibition, the structural organization of human acetylcholinesterase (hAChE) offers essential insight. The high-resolution structure determined by Gerlitsa et al. (2019) (6) through room-temperature X-ray crystallography (PDB ID: 6O4W) represents hAChE in complex with the inhibitor fasciculin-II. The enzyme forms a globular protein comprising approximately 550 amino acid residues. A narrow, deep catalytic gorge of about 20 Å extends from the protein surface to the active center, creating a path lined with aromatic residues such as Trp86, Tyr337, Phe338, Tyr341, and Trp286, which guide substrates and inhibitors toward the catalytic site through hydrophobic and π–π interactions. At the bottom of this gorge lies the catalytic triad—Ser203, His447, and Glu334—responsible for acetylcholine hydrolysis via a charge-relay mechanism typical of serine hydrolases. Adjacent to this triad, the oxyanion hole, composed of Gly121, Gly122, and Ala204, stabilizes the transient tetrahedral intermediate formed during catalysis. Near the gorge entrance, the peripheral anionic site (PAS)—comprising Tyr72, Tyr124, Trp286, and Tyr341—serves as a ligand-recognition region, mediating initial substrate anchoring and contributing to inhibitor selectivity.

In inhibitor design, these structural determinants—particularly the catalytic triad and PAS—are crucial in predicting molecular docking outcomes and understanding ligand–enzyme interactions (7,8). Hence, utilizing the high-resolution crystal structure (6O4W) enables accurate computational modeling of how candidate Rivastigmine analogues occupy and interact within the enzyme's active groove through different interactions. Despite the achievements of existing AhChE inhibitors, there remains an urgent need for safer and more potent alternatives with optimized pharmacokinetic profiles. Structural modification of Rivastigmine offers a rational path toward designing such analogues with improved potency, blood–brain barrier permeability, and metabolic stability (9, 10). Computational techniques including virtual screening and molecular docking—provide efficient, cost-effective means to predict binding affinity and inhibition potential prior to experimental validation (11,12).

Therefore, the objective of this study is to employ advanced computational analysis based on structure-guided screening and docking using the hAChE crystal structure to identify novel Rivastigmine-like compounds with enhanced inhibition potential. It is postulated that some Rivastigmine analogues, through favorable structural modifications and enhanced interactions within the catalytic gorge of acetylcholinesterase, may exhibit stronger binding affinities and lower inhibition constants than Rivastigmine. Such behavior, if confirmed by further computational and experimental evaluations, could suggest an improved inhibitory potential and better pharmacological properties for these analogues in the management of Alzheimer's disease.

Materials and Methods

Protein Preparation: The crystal structure of acetylcholinesterase (PDB ID: 6O4W) was obtained from the Protein Data Bank (http://www.rcsb.org). Initially, the enzyme structure was loaded into UCSF Chimera software (https:// www.cgl. ucsf. edu/chimera/) for molecular docking preparation. The PDB structure's Chain A, which has 543 amino acid residues, was chosen. Gasteiger charges and hydrogen atoms were introduced after the ligands were eliminated. The constructed enzyme was then saved for docking investigations in PDB format (13,14).

Virtual Screening and Molecular Docking: Several accessible chemical compound databases have been established, storing millions of chemical molecules. In this study, the PubChem chemical library (https://pubchem.ncbi.nlm.nih.gov/) was used to identify and screen chemical molecules similar to Rivastigmine as a reference structure for shape-based screening. The number of chemical compounds that were similar to Rivastigmine was lowered to 19 following screening with a Tanimoto coefficient of 95%. Following the use of the B3LYP/6-31G base set with HyperChem 7.5 software to minimize the structural energy of the molecules, Autodock Vina (PyRx) was used to carry out the second stage of virtual screening. PyRx is a computational drug design tool that uses a sophisticated docking approach for virtual screening (15). The ligands with the best binding energy from this phase were selected for the third screening phase, which was conducted through docking of each selected ligand from the previous step using AutoDock4.2 software. It has been shown that AutoDock4.2 performs better than AutoDock Vina in ligand docking analysis (14). Using docking methods, the ability to estimate performance, scoring, and evaluating the protein-ligand interactions can be used to predict binding affinity. The crystal structure 6O4W was used to define the acetylcholinesterase binding site. The binding site was defined after ligand removal from the enzyme's crystal structure and using the central points of the grid box with coordinates: X: -3.333, Y: 4.250, and Z: 13.528, and the grid spacing was set to 0.375 Å. The number of grid points in X, Y, and Z dimensions were chosen to be 36, 38, and 36, respectively, such that the grid box volume was appropriate for each ligand and covered the entire active site. During docking, the protein was considered rigid, while the ligands were flexible. The interactions between the ligand and protein were analyzed using the Genetic Algorithm (GA), a stochastic search algorithm inspired by natural selection and genetics for computational optimization. The number of GA runs for each independent run was fixed at 100. AutoDock's other settings were left at their default settings. For all reference and target ligands, the same grid box size and comparable characteristics were employed. The optimal conformations were found by molecular docking using the Lamarckian genetic method. The outcomes were stored for further docking interaction analysis. PyMOL 2.5 software was also used to examine the binding interactions between the ligands and the enzyme (15, 16).

In Silico Toxicity Prediction: To assess the potential safety profiles of the Rivastigmine analogues prior to experimental validation, in silico toxicity prediction was performed using computational toxicity models integrated within the ProTox-II web server (https://tox-new.charite.de/protox_II) and supported by additional QSAR-based screening modules in the ADMETlab 2.0 platform (https://admetmesh.scbdd.com/). Both systems apply machine-learning classifiers trained on large bioactivity datasets to estimate major toxicological endpoints, including acute oral toxicity (LD_{50}), hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity. Additionally, the ability of each compound to cross the blood–brain barrier (BBB) was evaluated, considering the necessity for central-nervous-system (CNS) accessibility in Alzheimer's therapeutics. Parameters of clinical and nutritional toxicity were also considered to identify compounds with low predicted systemic risk. The outcomes of these toxicity estimations formed the basis of Table 2,

enabling comparative evaluation between Rivastigmine and its analogues. The in-silico toxicity profiles provide an early screening step for safety and pharmacological feasibility, helping to prioritize lead compounds for further in vitro cytotoxicity testing and in vivo validation in subsequent stages of drug development.

Results

Structure-Based Virtual Screening

Based on similarity searches against Rivastigmine, the reference molecule for therapeutic development, a total of 19 compounds were retrieved from database. The PyRx program was utilized for the second stage of structure-based virtual screening.

Four ligands with the highest binding energies were chosen as response ligands in this stage, as shown in (Figure 1).

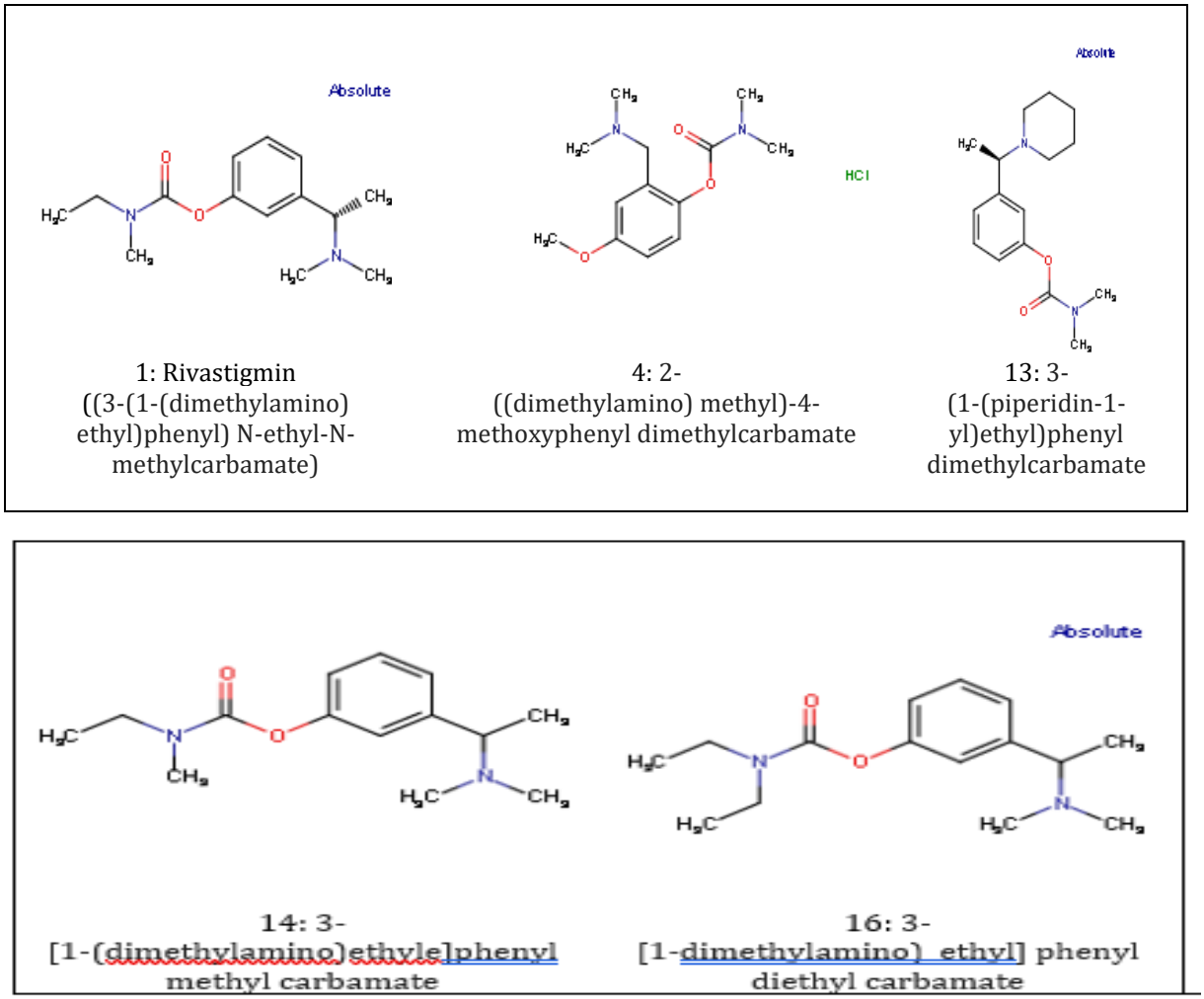

Fig 1. Two-dimensional structure of Rivastigmine (as the reference ligand), and the top 4 compounds identified through structure-based virtual screening.

Molecular Docking and Binding Affinity

The potential of the four selected ligands (Ligands 4, 13, 14, and 16) and the reference compound, Rivastigmine, was quantitatively assessed by their docking scores, specifically the binding free energy ($\Delta G_{binding}$ in kcal/mol) and the calculated inhibition constant (Ki in nM), as detailed in Table 1. Higher negative values for $\Delta G_{binding}$ and lower values for Ki indicate a stronger and more favorable inhibitory interaction with the hAChE active site.

The results clearly demonstrated that Ligand 13 achieved the most favorable binding profile, yielding the highest negative binding energy (−10.85 kcal/mol) and the lowest inhibition constant (11.14 nM) among all tested compounds. This indicates superior inhibitory potency compared to the standard treatment,

Rivastigmine, which exhibited a binding energy of −10.14 kcal/moland a Ki of 36.93 nM. Ligand 16 also showed promising results with a $\Delta G_{binding}$ of −10.45 kcal/mol and a Ki of 21.92 nM, positioning it second in overall affinity. Ligands 14 and 4 followed, with binding energies of −9.97 and −9.65 kcal/mol, respectively. The observed energetic superiority is critically linked to specific molecular interaction profiles within the hAChE active-site gorge, as visualized in Figure 2. In the case of Ligand 13, while its precise hydrogen bond count may vary across docking clusters, its dominant affinity is supported by a high total number and diversity of stabilizing interactions. Figure 2 suggests that Ligand 13 forms several van der Waals (vdW) interactions along with other stabilizing forces within the catalytic gorge. The most significant factor, however, is its reported interaction with key residues Tyr337, Trp286, Trp86, Phe338, Tyr341, Tyr341, Trp286, and Tyr124, which—regardless of the exact bond type (hydrogen bond vs. carbon–hydrogen bond)—locks the molecule more effectively into the narrow, deep catalytic gorge than the reference compound.

In contrast, Rivastigmine and Ligand 16, although interacting with catalytic gorge amino acids similar to those of Ligand 13, exhibit lower binding energies and higher *K*i values. Their interaction profiles in Figure 2 indicate that each forms one explicit hydrogen bond, supplemented by various van der Waals, π–alkyl, and carbon–hydrogen interactions. This comparative analysis suggests that the structural architecture of Ligand 13 facilitates a more optimal spatial fit and stronger net energy contribution—whether through a higher number of vdW contacts or superior geometric alignment—relative to Rivastigmine and other analogues. This enhanced binding affinity directly accounts for the markedly lower predicted inhibition constant (*K*i = 11.14 nM) of Ligand 13, highlighting it as a promising lead candidate for further investigation in Alzheimer's therapy.

Table 1. Binding energy and inhibition constant of compounds against hAChE

Compound	$\Delta G_{binding}$ (kcal/mol)	Ki (nM)
4	-9.65	84.07
13	-10.85	11.14
14	-9.97	49.22
16	-10.45	21.92
Rivastigmine	-10.14	36.93

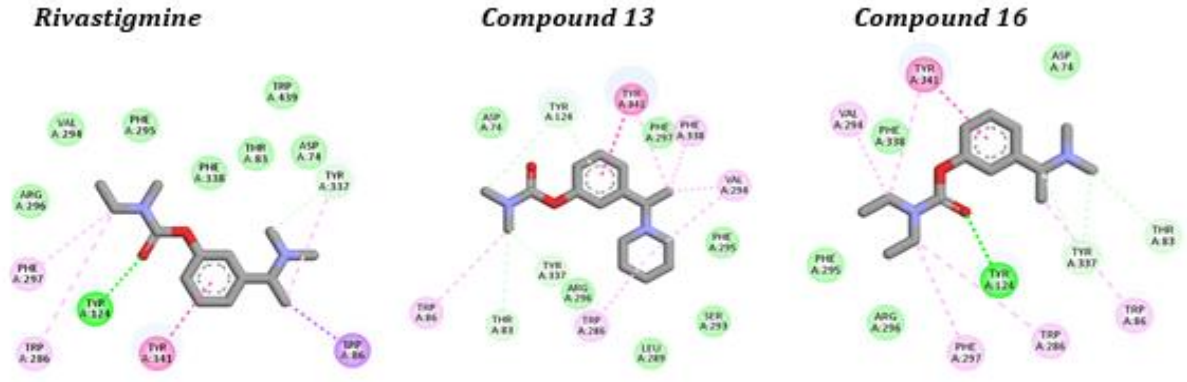

Fig 2. Two-dimensional interaction image of each ligand with the catalytic gorge of hAChE.

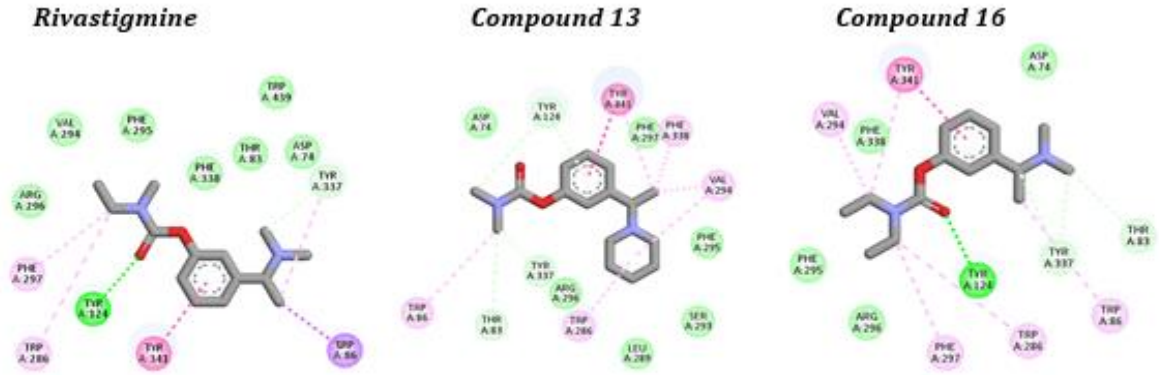

Fig 2. Two-dimensional interaction image of each ligand with the catalytic gorge of hAChE.

Table 2. Prediction of the toxicity of Rivastigmine and compounds with binding energy greater than 10 kcal/mol.

Toxicity parameters	Rivastigmine	Compound13	Compound16
Predicted LD50 (mg/kg)	1000	160	1000
Hepatotoxicity	Inactive	Inactive	Inactive
Carcinogenicity	Inactive	Inactive	Inactive
Immunotoxicity	Active	Inactive	Inactive
Mutagenicity	Inactive	Inactive	Inactive
Cytotoxicity	Inactive	Inactive	Inactive
BBB-barrier	Active	Active	Active
Clinical toxicity	Inactive	Inactive	Inactive
Nutritional toxicity	Active	Active	Active

In Silico Toxicity Prediction Analysis

Following the successful identification of superior binding affinity for Ligands 13 and 16, a critical secondary evaluation involved *in silico* prediction of potential toxicity profiles, as summarized in Table 2. This step is crucial to ensure that enhanced inhibitory potency is not coupled with unacceptable safety risks. The table compares predicted toxicity parameters for Ligand 13, Ligand 16, and Rivastigmine (when $\Delta G_{binding} > -10.00$ kcal/mol in the initial filtering, though the table includes Rivastigmine for reference).

The toxicity prediction analysis reveals a dualistic profile for the lead candidates:

1. Advantage in Specific Toxicities: Both Ligand 13 and Ligand 16 show a favorable profile concerning Immunotoxicity, where they are predicted Inactive, in contrast to Rivastigmine which is predicted Active. Furthermore, both candidates share the favorable prediction of being Inactive for Hepatotoxicity, Carcinogenicity, and Mutagenicity, similar to the reference drug. All three molecules are predicted to cross the BBB-barrier, which is essential for CNS drugs treating AD.

2. Concern Regarding Acute Toxicity: The most significant difference lies in the predicted LD50 value. Ligand 13 is predicted to have an acute toxicity (LD50=160 mg/kg) that is five times lower (i.e., five times more toxic) than both Rivastigmine and Ligand 16 (LD50=1000 mg/kg). This low predicted LD50for Ligand 13 represents a major safety concern that must be addressed in subsequent *in vitro* and *in vivo* validation studies, as highlighted in the Limitations section of the paper.

While Ligand 13 is the superior inhibitor based on binding affinity, its predicted acute toxicity warrants a highly cautious approach. Ligand 16 presents a potentially better balance, offering comparable binding strength to Rivastigmine while eliminating the predicted immunotoxicity and maintaining a safe LD50 profile, making it a more attractive candidate from a preliminary safety perspective.

Discussion

The current computational investigation aimed to design and evaluate novel analogues of Rivastigmine with enhanced inhibitory potential against human acetylcholinesterase (hAChE) as a therapeutic strategy for Alzheimer's disease (AD). Molecular docking and toxicity prediction analyses provided mechanistic insight into how subtle structural modifications can influence both potency and safety profiles (17,18). Among the screened analogues, Ligand 13 exhibited the most favorable docking score ($\Delta G_{binding}$ = −10.85 kcal/mol) and the lowest inhibition constant (Ki = 11.14 nM), suggesting a substantially stronger affinity for the hAChE catalytic gorge than the reference drug Rivastigmine ($\Delta G_{binding}$ = −10.14 kcal/mol, Ki = 36.93 nM). The enhanced stabilization of Ligand 13 appears to be mediated by multiple van der Waals and π–π interactions with key aromatic residues lining the catalytic gorge—particularly Trp86, Tyr337, Phe338, Tyr341, Tyr124, and Trp286. These residues are known to play crucial roles in substrate guidance and inhibitor recognition within the active site, implying that the analog achieves a more optimal conformational fit compared to rivastigmine. While Ligand 16 displayed slightly lower binding energy (−10.45 kcal/mol) and a correspondingly higher Ki value (21.92 nM), its interaction pattern and predicted safety profile indicate a more balanced pharmacological potential. In contrast, Ligand 13, despite its superior binding affinity, demonstrated an estimated LD_{50} of 160 mg/kg, suggesting significantly higher acute oral toxicity than both Ligand 16 and Rivastigmine (LD_{50} = 1000 mg/kg). This discrepancy highlights the importance of integrating in silico toxicity assessments into early-stage virtual screening workflows to avoid false-positive leads with unfavorable safety margins.

Notably, both leading analogues were predicted to be inactive for hepatotoxicity, carcinogenicity, mutagenicity, and immunotoxicity, and both maintained the ability to penetrate the blood–brain barrier (BBB)—a critical requirement for central nervous system therapeutics. The inactive immunotoxicity prediction for both Ligands 13 and 16 compared to Rivastigmine suggests a potentially improved immunological tolerance, which may translate to reduced systemic adverse effects in vivo. Taken together, these findings illustrate that Ligand 13 can be considered a high-affinity inhibitor with exceptional binding complementarity but requires further optimization to mitigate its predicted acute toxicity. Conversely, Ligand 16 represents a more pharmacologically balanced candidate, combining strong binding to the catalytic gorge with a safer predicted toxicity profile. Future investigations should employ molecular dynamics simulations to assess the stability of the ligand–enzyme complexes under physiological conditions, alongside ADMET and in vitro cytotoxicity tests to validate the computational predictions. If confirmed experimentally, Ligand 16 in particular could serve as a scaffold for the next generation of CNS-active acetylcholinesterase inhibitors, potentially offering improved efficacy and safety over current therapeutic options.

Conclusion

This study successfully employed structure-based virtual screening and molecular docking to evaluate novel Rivastigmine analogues targeting the human acetylcholinesterase (hAChE) enzyme, utilizing the crystal structure PDB ID: 6O4W. The computational assessment identified Ligand 13 and Ligand 16 as superior inhibitors compared to the reference compound, Rivastigmine. Quantitatively, Ligand 13 demonstrated the highest affinity, exhibiting the most favorable binding free energy ($\Delta G_{binding}$=−10.85 kcal/mol) and the lowest predicted inhibition constant (Ki=11.14 nM). However, subsequent in silico toxicity prediction revealed a significant safety concern for this compound, marked by a low predicted LD50 (160 mg/kg). In contrast, Ligand 16 presented a more pharmacologically viable profile, achieving a strong binding energy of −10.45 kcal/mol (Ki=21.92 nM) while sharing the favorable predicted toxicity profile of the reference

drug for most endpoints, notably maintaining an acceptable LD50 (1000 mg/kg) and showing Inactive predictions for hepatotoxicity, carcinogenicity, and immunotoxicity. Both lead candidates were predicted to successfully cross the Blood-Brain Barrier (BBB). In summary, while structural modification successfully yielded high-affinity candidates, Ligand 16 represents the most promising lead scaffold due to its optimal balance between potent hAChE inhibition and a predicted safety margin suitable for further preclinical development. Future work will involve refinement through molecular dynamics simulations, followed by empirical validation using comprehensive in vitro cytotoxicity assays (19,20).

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