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Open Access Research Article

In-silico and Physicochemical Predictions Studies of Piperidine Containing Compounds as Anti-Alzheimer's Agents

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ABSTRACT

Background: Alzheimer's disease is a neurodegenerative condition marked by memory decline and reduced acetylcholine levels. The objective of this study was to design and evaluate novel piperidine analogs as potential inhibitors of acetylcholinesterase (AChE) enzyme.

Materials and Methods: From molecular hybridization and pharmacophore optimization technique fifteen new piperidine-hydrazone derivatives were designed. Using AutoDock and AutoDock Vina, molecular docking studies were performed against the AChEenzyme (PDB ID: 4PQE).

Results & Discussion: Based on the comprehensive docking data, compound 12 exhibited the strongest binding affinity with a score of -11.2 kcal/mol. Compounds 1 and 2 also demonstrated highly favourable binding energies of -10.8 kcal/mol and -10.7 kcal/mol, respectively. All of these top candidates significantly outperformed the standard therapeutic drugdonepezil, which displayed score -8.6 kcal/mol. Pharmacokinetic assessments from Lipinski's rule of fiveand toxicity prediction study supportedtheir anti-alzheimerspotential.

Conclusion: Piperidine-hydrazone scaffold exhibited an optimal balance of flexibility and rigidityenabling simultaneous dual-site inhibition at the enzyme's CAS and PAS. In-silico ADMET prediction study validated thesepiperidine analogs are strong lead candidates for subsequent anti-alzhiemer's development.

Keywords: Piperidine, alzheimer's disease, acetylcholinesterase, AChE, molecular docking, In silico, ADME.

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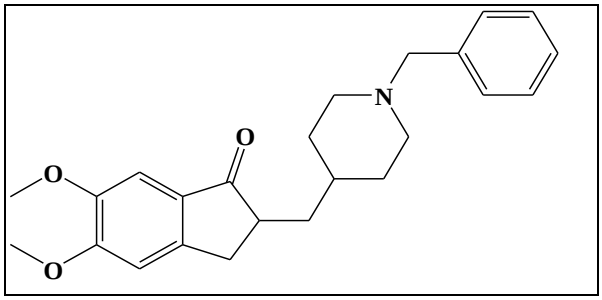
INTRODUCTION

Alzheimer's Disease (AD) is one such progressive neurodegenerative disease that affects memory and cognitive abilities owing to the deterioration of brain cells.[1]Decreased level of the neurotransmitter, acetylcholine, is one such pathological characteristic of AD.[2]A major pathological feature of AD is the reduced level of the neurotransmitter acetylcholine, which plays a crucial role in memory and learning processes. The enzyme acetylcholinesterase (AChE) hydrolyzes acetylcholine, and hence AChE is a therapeutic target in the treatment of AD.[3]The heterocyclic compound, piperidine is one such promising compound that finds wide applications in medicinal chemistry due to its various biological activities.[4] Being a privileged heterocyclic core, the piperidine scaffold has shown promising neuroactive potential.[5] Computer-Aided Drug Design (CADD) and molecular docking are some promising methods that play a key role in the evaluation of ligand-receptor interactions in the drug discovery process.[6] This paper focuses on the design of fifteen novel piperidine analogs as AChE inhibitors using molecular docking and pharmacokinetics studies.

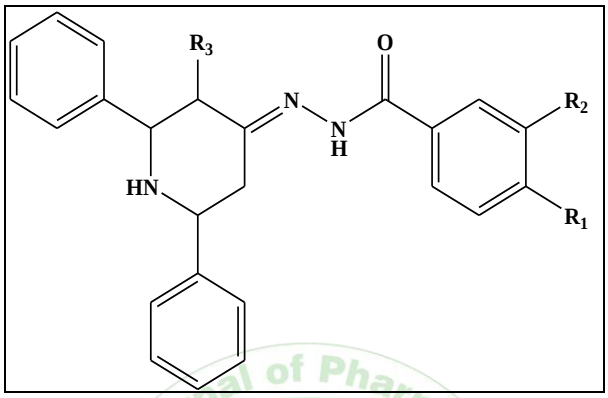
'The Cholinergic Hypothesis' appears to be the best possible way for the symptomatic treatment of AD. According to this

hypothesis, the reduction of cholinergic neurotransmission is the reason why patients develop their cognitive impairments.[7]

Acetylcholinesterase (AChE) is the enzyme that degrades ACh. By blocking the action of AChE, the quantity of ACh is increased, and some degree of cognitive functioning could be achieved.[8]



Donepezil



Designed compounds (1-15)

Table 1: R_1, R_2& R_3substitutions of designed Piperidinecompounds (1–15)

Compound	R_1	R_2	R_3
Compound 1	-H	$-CF_3$	-H
Compound 2	-H	-I	-H
Compound 3	-CN	-H	$-OCH_3$
Compound 4	$-N(CH_3)_2$	-H	$-OCH_3$
Compound 5	-H	-H	$-OCH_3$
Compound 6	$-OCF_3$	-H	$-OCH_3$
Compound 7	-Cl	-Cl	-H
Compound 8	-H	$-OCH_2CH_3$	-H
Compound 9	-F	-Cl	-H
Compound 10	-H	$-OCF_3$	-H
Compound 11	-CN	-H	-H
Compound 12	$-N(CH_3)_2$	-H	-H
Compound 13	-H	-OH	-H
Compound 14	- Br	-H	-H
Compound 15	$- CH_3$	$- CH_3$	-H

In designing of the current set of derivatives (1–15; Table 1) we have adopted structure-based drug design (SBDD) approach based on privileged scaffold piperidine ring.In our design approach, the structure contains three components: core scaffold, a flexible linker, and a capcomponent. The piperidine ring was chosen owing to its property of mimicking the quaternary ammonium group of acetylcholine, while the substituents at (state precise location, e.g., the N-terminal or C-4)position can reach PAS of AChE.[9]

Materials and Methods

Rational Design Strategy

The designing of these piperidine derivatives was performed using the pharmacophore hybridization method.The hydrazone scaffoldshave exhibited potent AChE inhibitory activity. These hydrazones also bind target enzymes and receptors that possess both nucleophilic and electrophilic properties with its specific -C=N=NH- pharmacophore.[10]The hydrophobic surface recognition (piperidine ring), linker, and variable cap groups were introduced to enhance the interaction with the catalytic active site (CAS) and peripheral anionic site (PAS) of the enzyme acetylcholinesterase (AChE).[11]

Software and Tools

Computational modelling and molecular docking studies were performed through the following computational software programs:

- ChemDraw 8.0: Structure generation and prediction of physicochemical properties[12]
- AutoDock Tools and AutoDock Vina: Molecular docking study[13]
- Open Babel: Chemical file format conversion[14]
- SwissADME& pkCSM: Prediction of ADMET properties[15,16]
- PyMol: Visualization of protein-ligand complexes[17]

Protein Preparation

The X-ray crystal structure of Human Acetylcholinesterase (PDB ID: 4PQE) was obtained from RCSB Protein Data Bank.[18]In preparation, water molecules were stripped off, the B chain was deleted, and hydrogen atoms and Kollman charges were added to the active site residues. The center point for docking was established with the coordinates X: -25.27, Y: 22.432, Z: 0.665 having a grid dimension of 40x40x40 Å.

Ligand Preparation

A standard Donepezil molecule and fifteen piperidine derivatives were designed and converted to PDBQT format.

Results and Discussion

Molecular Docking Analysis

The docking was performed on the target enzyme called acetylcholinesterase (AChE) (PDB ID: 4PQE) (**Figures 1-7**). It is a catalytic gorge located deep in 20 Å in which docking of small molecules was done. In order to establish a control value for comparison purposes, donepezil (the standarddrug) exhibited the binding score of -8.6 kcal/mol interacting through his residue (HIS447) and tryptophan residue (TRP86) with the Catalytic Active Site (CAS).

The docking analysis showed that most of the synthesized compounds have stronger binding affinity toward acetylcholinesterase than the reference drug Donepezil (−8.6 kcal/mol) (Table 2). Amongthem, compound 12 displayed the best result with a docking score of −11.2 kcal/mol, indicating very stable binding interactions with key active site residues. Compounds 1 (−10.8 kcal/mol) and 2 (−10.7 kcal/mol) also showed high affinity, followed by compounds 6, 9 and 15 (−10.3 kcal/mol), all of which formed interactions with important amino acids such as tyrosine, phenylalanine, and serine residues within the binding pocket. Other compounds demonstrated moderate binding (−9.0 to −10.0 kcal/mol), while compound 5 (−8.1 kcal/mol) showed the lowest affinity among the series. Overall, from series of compounds, especially compound 12, exhibited better docking performance than Donepezil, suggesting their potential as promising acetylcholinesterase inhibitors

Table 2: Binding Affinities and Key Residue Interactions of compounds (1-15) for AChE (4PQE)

Compound	Dock Score (kcal/mol)	Key Interactions
Donepezil	**-8.6**	HIS447, TYR337, TYR286, TRP86
Compound 1	**-10.8**	SER125, TYR341, PHE338, TYR124
Compound 2	**-10.7**	ASP74, PHE296, VAL254, GLY121
Compound 3	-9.3	SER293, TRP286, PHE297, TYR337
Compound 4	-9.4	GLY121, GLY120, TYR124, HIS441
Compound 5	-8.1	TRP286, TYR124, PHE297, SER293
Compound 6	**-10.3**	TYR341, TYR124, PHE295, SER293
Compound 7	**-10.0**	TYR341, SER293, TRP286, LEU289
Compound 8	-9.7	TYR341, TYR337, TRP286, PHE338
Compound 9	**-10.3**	TYR341, TYR124, TYR72, PHE295
Compound 10	-9.0	GLY121, TYR341, GLY120, ASP74
Compound 11	-9.3	TYR124, TYR341, PHE297
Compound 12	**-11.2**	TRP286, TYR194, TYR337,GLY121
Compound 13	-9.0	SER263, PHE295, TYR341, HIS441
Compound 14	-9.3	TRP84, TYR341, PHE297, TYR337
Compound 15	**-10.3**	TYR124, TYR341, SER126, TYR337

High-Affinity Ligands (compounds 1, 2, 6, 7, 9, 12, 15): This set of molecules exhibited high binding affinity (from -11.2 to -10.3 kcal/mol). Compounds 1 and 12 scored the highest of all ligands. This combination achieved dual-site inhibition optimally. The piperidine ring fit perfectly into the CAS while other groups bound well by forming hydrophilic bonds with PAS (residues SER125, TYR341, and ASP74).[19]

Moderately Binding Ligands (compound 3, 4, 8, 10, 11, 13, 14): Although they showed binding ability (with binding energy -9 to -10 kcal/mol), these molecules could not penetrate gorge effectively because they were bulkier. The least binding compound 5 with binding score of -8.1 kcal/mol was the only compound that failed to beat the control molecule (donepezil). To summarize, 3D analysis by PyMOL showed how best electronegative groups bind to the piperidine ring.

Molecular Docking ofStandard and Designed Organic Compounds

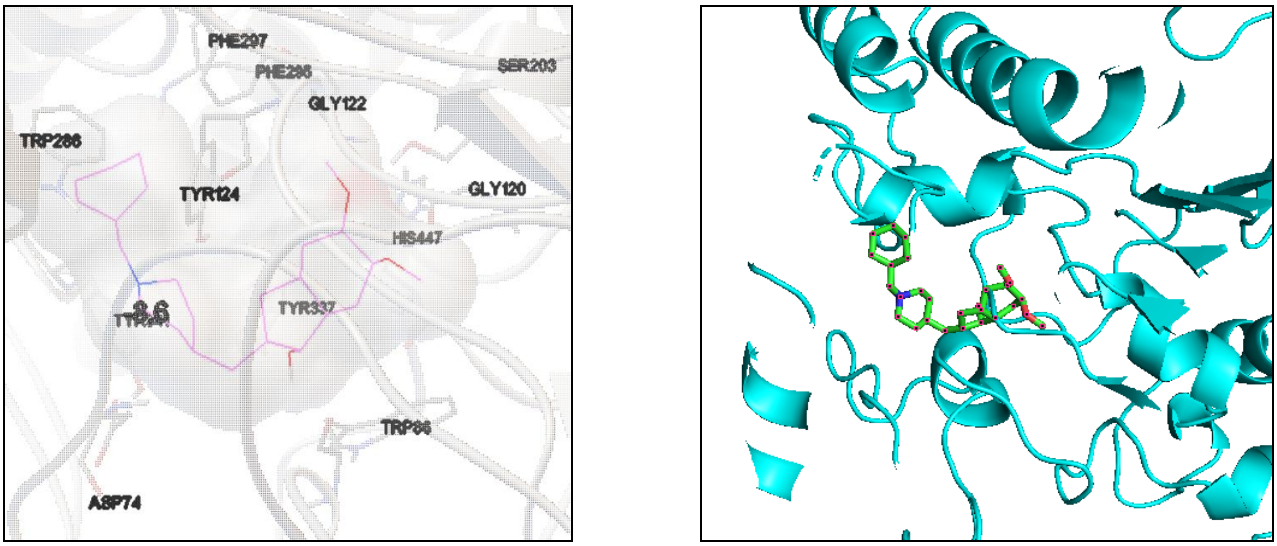


Figure1: Binding interactions of standard **Donepezil**(-8.6Kcal/mol)

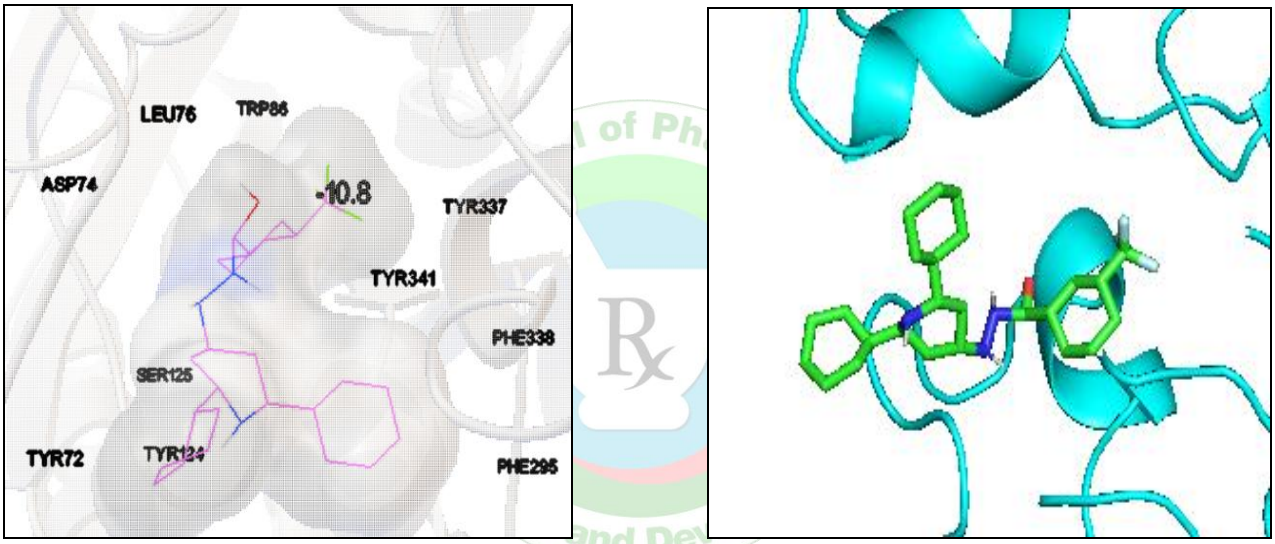


Figure2: Binding interactions of **compound 1**(-10.8Kcal/mol)

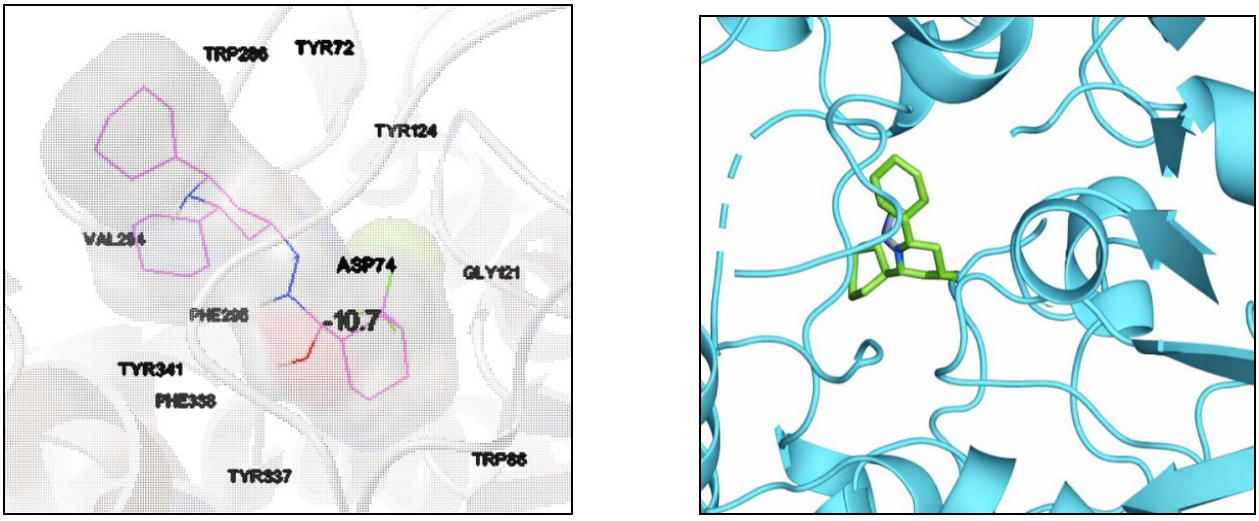


Figure3: Binding interactions of **compound 2**(-10.7Kcal/mol)

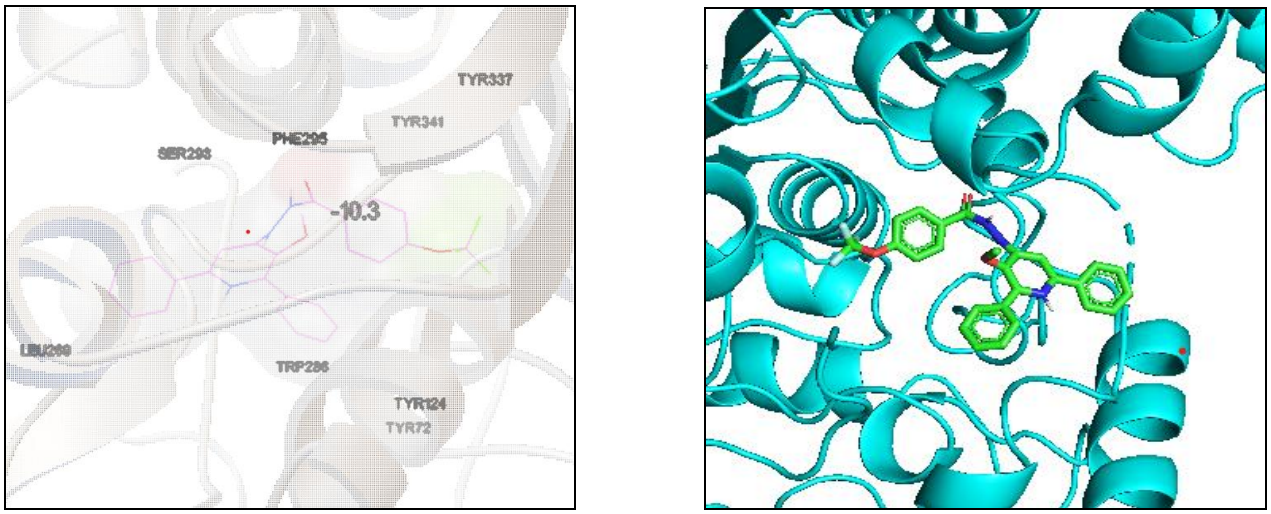


Figure 4: Binding interactions of **compound 6**(-10.3Kcal/mol)

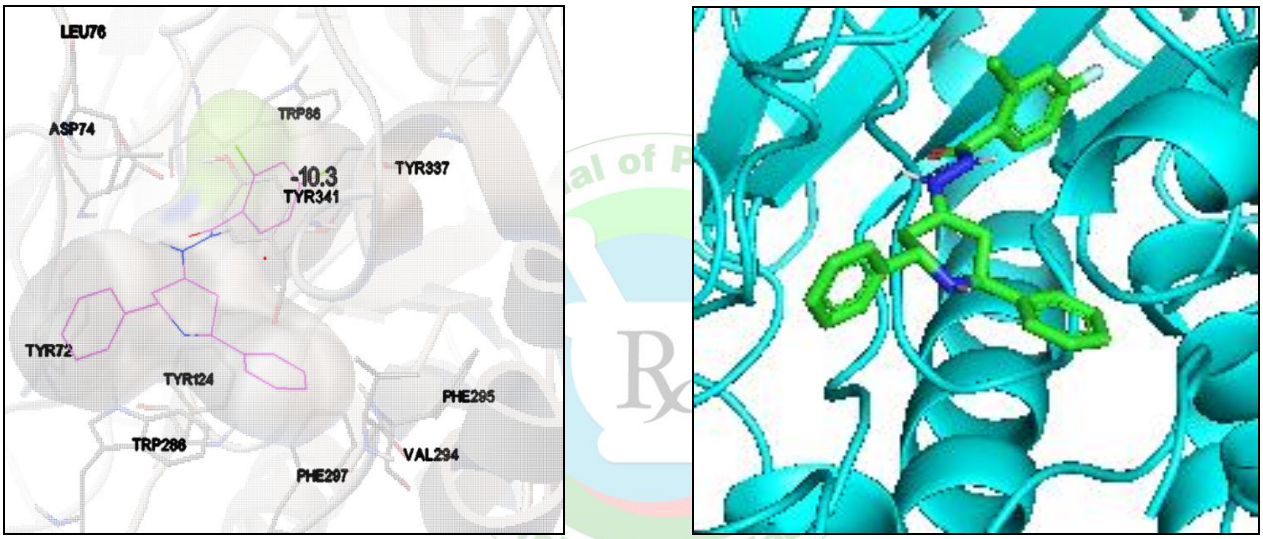


Figure 5: Binding interactions of **compound 9**(-10.3Kcal/mol)

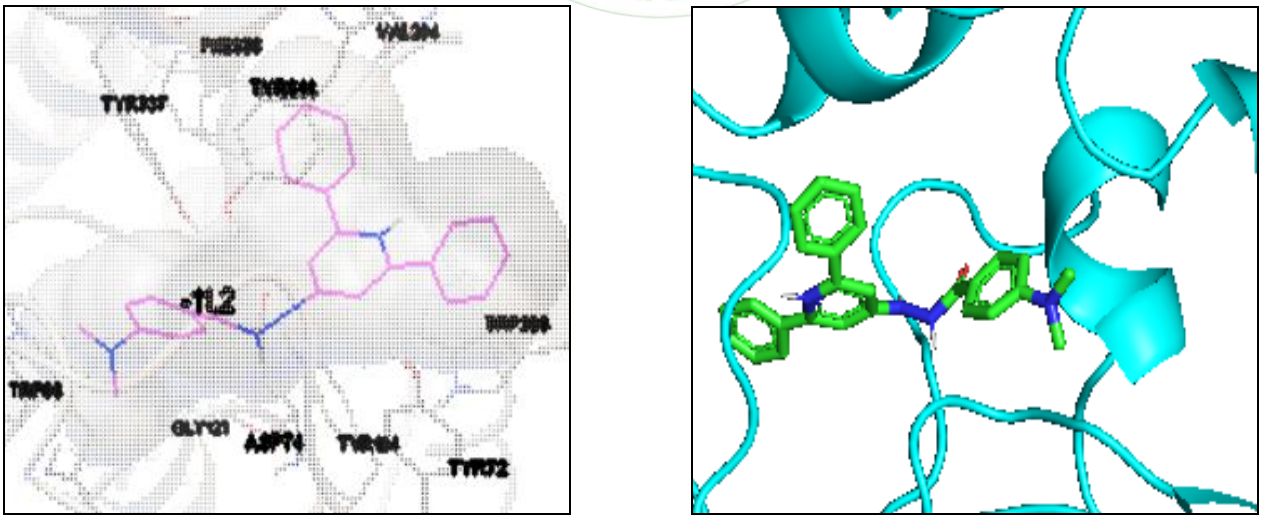


Figure 6: Binding interactions of **Compound 12**(-11.2Kcal/mol)

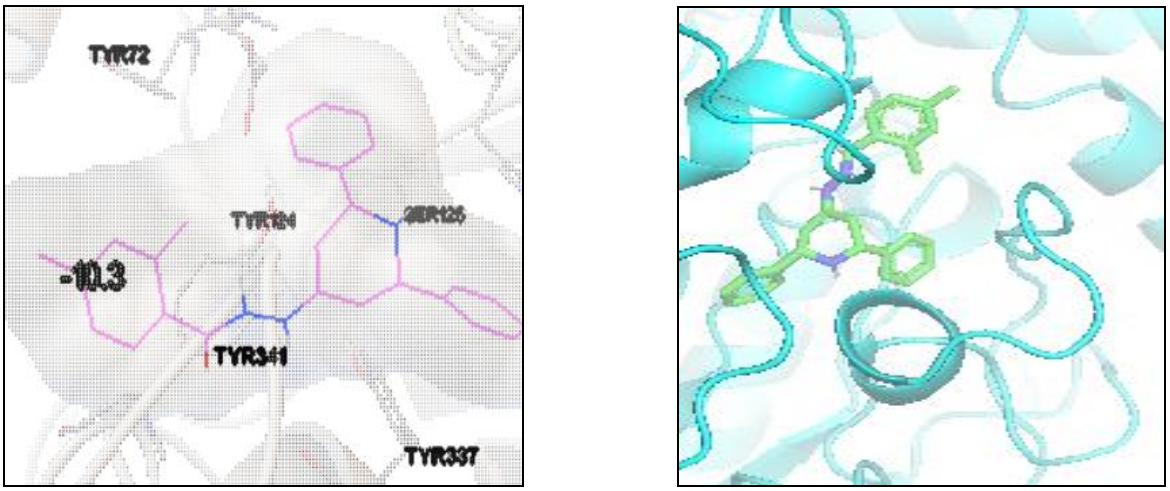


Figure 7: Binding interactions of **compound 15**(-10.3Kcal/mol)

Physicochemical and Drug-likeness Profiling

Evaluation of the pharmacokinetics of compounds 1-15 revealed their adherence to Lipinski's rule of five.[20] Compound 12exhibited strong affinity (-11.2 kcal/mol), a molecular weight of 437.46 g/mol and bioavailability value of 0.55. Compound 3, 4, & 8showed good safety characteristics as they are AMES negative yet possess good docking affinity. Donepezil exhibited zero Lipinski violation but showed AMES and hepatic toxicity.

The pharmacokinetic properties of designed piperidine derivatives were studied via the SwissADME web server platform to establish their desirable characteristics to become viable oral drugs (**Figure 8**). As shown in**Table 3**, the derivatives (1-15) were found to have ideal physicochemical properties.

Besides Lipinski criteria, the use of Topological Polar Surface Area (TPSA) became an important filter for predicting central nervous system activity of the compounds. All lead derivatives showed relatively low TPSA values, always remaining within 56.73 Å², which is considered the optimal criterion for BBB penetration ability. Therefore, the derivatives molecular structures, despite the level of complexity involved, remain compact enough and possess favourable electronic surface that would allow them to penetrate into the brain tissue via passive diffusion.

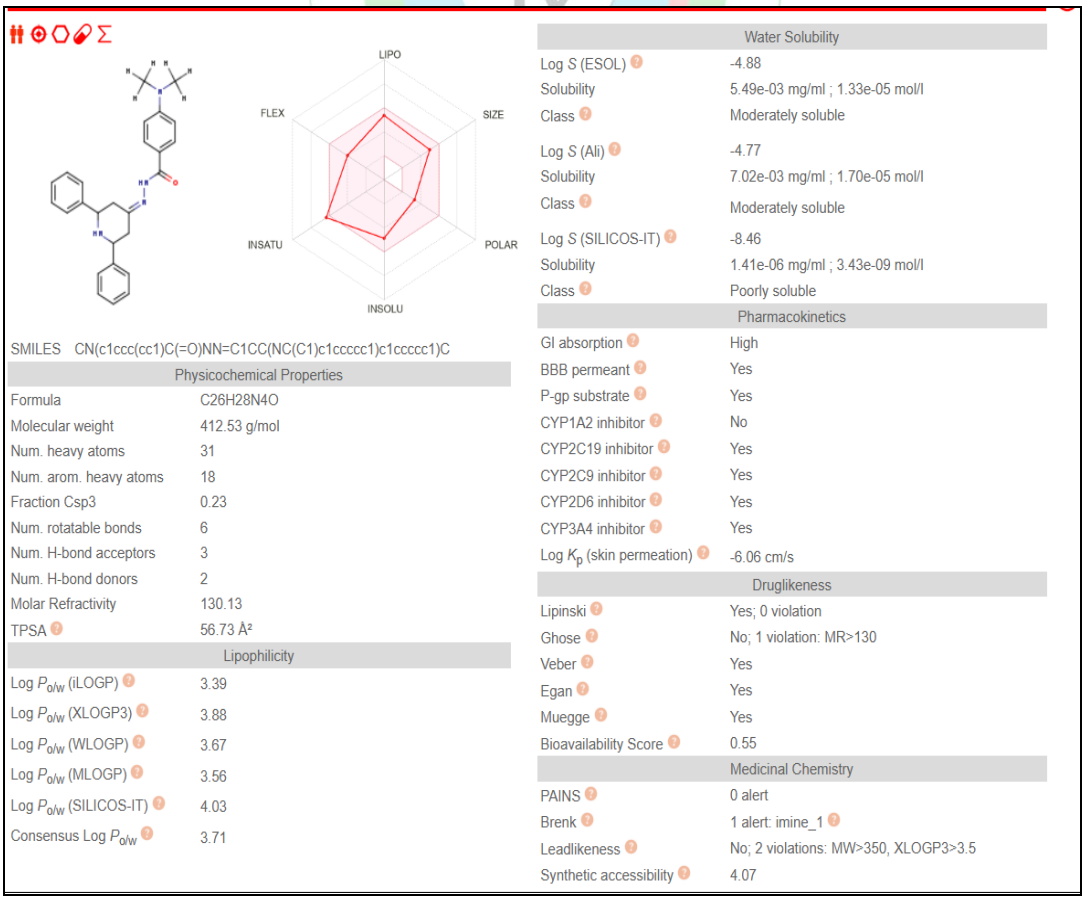


Figure 8: Pharmacokinetic and Drug-likeness Analysis of compound 12

The absence of any violations in the drug-likeness filter based on Lipinski, Veber, and Ghose rules is especially encouraging. With the bioavailability score equal to 0.55 and high predictions of GI absorption for almost all derivatives, one can conclude that designed piperidines possess desirable properties to become efficient drugs.

BOILED-Egg Predictive Model Analysis

BOILED-Egg (Brain or Intestinal Estimate D permeation) is an essential tool for predicting the absorption and brain penetration potential of a drug compound during SwissADME prediction.[21] It is pertinent to note that any drug candidate used in treating Alzheimer's needs.

Table 3: In Silico Physicochemical and ADME Properties

Compound	Rotatable Bonds	H-Bond Acceptors	H-Bond Donors	TPSA (Å²)	Lipinski Violations
Donepezil	7	6	1	51.47	0
Compound 1	6	6	2	53.49	1
Compound 2	7	6	1	51.47	0
Compound 3	6	5	2	86.51	0
Compound 4	7	4	2	66.96	0
Compound 5	6	5	2	75.61	0
Compound 6	8	8	2	71.95	0
Compound 7	5	3	2	125.49	1
Compound 8	7	7	2	122.46	0
Compound 9	6	3	2	105	0
Compound 10	6	5	1	108	1
Compound 11	5	4	2	77.28	0
Compound 12	6	3	2	56.73	0
Compound 13	4	5	3	90.79	0
Compound 14	4	4	2	70.56	0
Compound 15	6	4	2	75	0

to pass through the blood-brain barrier (BBB). The BOILED-Egg model from the SwissADME web server was employed to predict gastrointestinal absorption and brain penetration potential of the lead compounds. According to the BOILED-Egg model, the white area signifies high human intestinal absorption (HIA), whereas the yellow area (yolk) denotes high brain penetration (BBB). As seen in Figure 9, the standard drug Donepezil, alongside the most potent piperidine derivatives (Compounds 2, 9, and 12), fall entirely in the yellow yolk zone. This implies that these drug candidates have good physiochemical characteristics required for crossing the blood-brain barrier, which is vital for CNS active therapeutic drugs against Alzheimer's disease. Compounds 1 and 6 falls in the white area, implying high gastrointestinal absorption and relatively low brain penetrability.

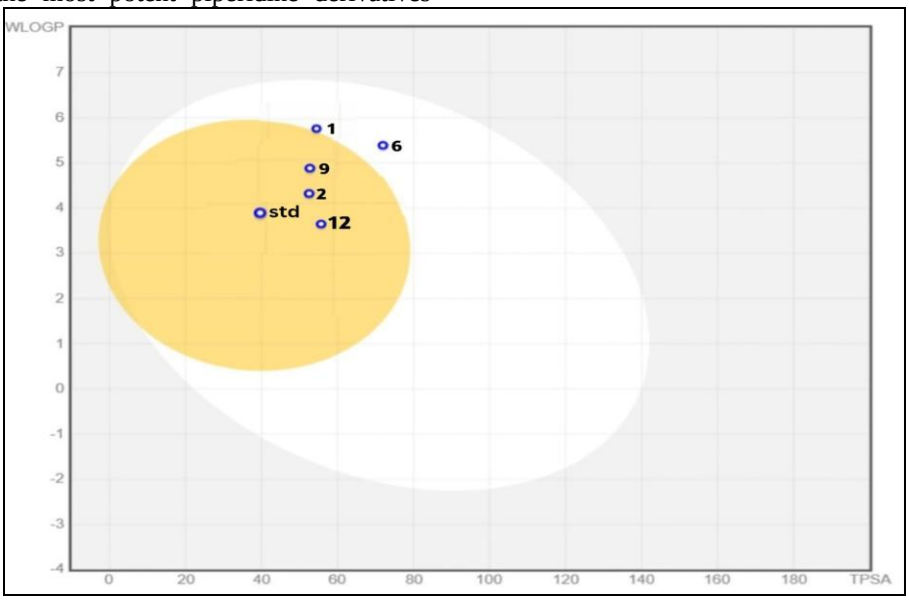


Figure 9: BOILED-Egg predictive model for the top-scoring piperidine derivatives (Compounds 1, 2, 6, 9, 12) and the standard drug Donepezil.

Toxicity Prediction

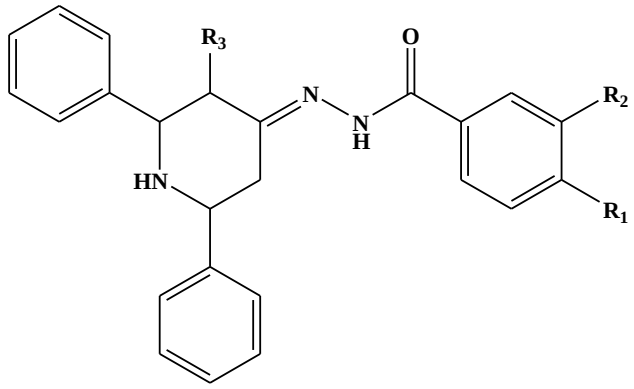
Safety assessments of the best-performing hits were evaluated using the pk CSM tool.[22]The conventional drug donepezil had safety concerns regarding hERG and hepatotoxicity.[23] Although some molecules may have the typical toxicity alerts found in most early lead molecules, compounds 3, 4, 5, 8 and 12 possessed an extremely good safety profile without any AMES toxicity (**Table 4**).

Table 4: Predicted Toxicity Parameters

Compound	Bioavailability Score	AMES Toxicity	Hepatotoxicity	Skin Sensitization
Donepezil	0.55	Yes	Yes	No
Compound 1	0.55	Yes	Yes	No
Compound 2	0.55	Yes	Yes	No
Compound 3	0.55	No	Yes	No
Compound 4	0.55	No	Yes	No
Compound 5	0.55	No	Yes	No
Compound 6	0.55	Yes	Yes	Yes
Compound 7	0.55	Yes	Yes	No
Compound 8	0.55	No	Yes	No
Compound 9	0.55	Yes	Yes	No
Compound 10	0.55	Yes	Yes	No
Compound 11	0.55	Yes	Yes	No
Compound 12	0.55	No	Yes	No
Compound 13	0.55	No	Yes	No
Compound 14	0.55	No	Yes	No
Compound 15	0.55	Yes	Yes	No

Discussion

The analysis of docking score indicated the impact of introducing some specific aromatic substituents to piperidine core on the energy of binding (Table 5). For example, molecules possessing electron-withdrawing substituents exhibited higher affinity in comparison with molecules with electron-donating substituents, similar to observations made in AChE research. The detailed SAR study of piperidines has shown that electronic properties and spatial features of peripheral substituents play a crucial role in the AChE inhibitory activity.[24]



A piperidine coreprovided high flexibility and enabled the molecules to penetrate into the enzyme gorge and make efficient pi-pi and hydrophobic contacts with peripheral anionic site (PAS).It should be noted that piperidine derivatives with electron-withdrawing substituents (halogen or nitro), compounds 1, 2, 6, scoring below -10.0 kcal/mol) exhibited better interactions than unsubstituted or electron-donating counterparts. This fact is in accordance with the need of creating strong electrostatic contacts near catalytic triad. Some interactions with TYR341 and SER125 were found.These designed molecules all featured a single pharmacophore model featuring three components, specifically optimized to interact with the 20 Å deep pocket at the gorge of AChE.[25]

Table 5: Structural Substitutions and Corresponding Target Affinities of compounds

Compound	R	Electronic Nature	Dock Score	Structural & Binding Impact
Compound 1	$-CF_3$	Strong EWG / H-Bonding	-10.8	Optimal electronegativity; maximizes hydrogen bonding (SER125) and pi-pi stacking at PAS.
Compound 2	-I	EWG / Hydrophobic	-10.7	High lipophilicity favors gorge penetration; establishes highly stable hydrophobic contacts.
Compound 3	-CN	Mixed / EDG	-9.3	Reduced pi-pi interactions strength due to shifts in ring electron density.
Compound 4	$-N(CH_3)_2$	Mixed / EDG	-9.4	Increased electron density slightly weakens the required localized dipole.
Compound 5	$.OCH_3$	Strong EDG / Steric	-8.1	High entropic penalty and severe steric hindrance cause a significant drop in affinity.
Compound 6	$-OCF_3$	Halogen / EWG	-10.3	Strong dipole moment enhances electrostatic affinity and halogen bonding.
Compound 7	-Cl	Moderate EWG / Bulky	-10.0	Good binding affinity, but slight steric bulk limits deeper gorge penetration.
Compound 8	$-OC_2H_5$	Moderate	-9.7	Balanced electronic distribution yields moderate PAS interaction.
Compound 9	-F	Halogen / EWG	-10.3	Similar to Compound 6, stabilizes the complex via localized electronegativity.
Compound 10	$-OCF_3$	Bulky EDG	-9.0	No Steric clashes within the narrow AChE gorge reduce overall thermodynamic stability.
Compound 11	-CN	Strong EWG	-9.3	The para-cyno group increases molecular rigidity and electron deficiency.
Compound 12	$-N(CH_3)_2$	Strong EDG	-11.2	Increases flexibility and electron density, improve receptor binding affinity.
Compound 13	-OH	EDG	-9.0	It inhances hydrogen binding ability, improving binding interaction.
Compound 14	- Br	EWG	-9.3	Increases lipophilicity and enables halogen binding.
Compound 15	$- CH_3$	EDG	-10.3	Increases lipophilicity and steric bulk, enhancing hydrophobic interaction.

1. **Core (Piperidine Ring):** The protonated nitrogen atom from the core piperidine ring at physiological pH can fit into the CAS of the enzyme and establish essential cation-pi interactions with critical amino acids, such as TRP86.
2. **Linker:** An alkyl or heterocyclic chain linking the CAS-bound molecule to its peripheries provide the needed geometric shape and flexibility. These chains must be of appropriate length and stiffness to allow simultaneous binding within the CAS and PAS (at the gorge entrance) without an excessively high entropy penalty.
3. **Peripheral Substituted Ring (R-groups):** Aromatic compound with EDG or EWG substituents. This region is specifically designed to interact with the peripheral anionic site (PAS) through pi-pi stacking and hydrophobic interactions. Bulky or electron-donating groups ($-OCH_3$, extra aliphatic) reduce binding (compounds 5 & 10; scoring from -8.1 to -9.0 kcal/mol). Such groups produce steric hindrance in the 20 Å wide AChE active site gorge, necessitating a strained conformation.Peripherally substituted rings with high electronegativity or halogen groups (-Cl, -F, $-NO_2$) greatly improve binding affinity (compounds 1, 2, 6 & 9; scoring from -10.3 to -10.8 kcal/mol).

CONCLUSION

The computational design and assessment successfully yielded novel, multi-target piperidine derivatives with high potential as AChE inhibitors for Alzheimer's disease. Integration of the full docking dataset revealed that compound 12 is the most potent molecule in the series, achieving a docking score of -11.2 kcal/mol. It is closely followed by compounds 1 and 2, which also proved to be highly efficacious compared to the conventional drug donepezil (-8.6 kcal/mol). The unique piperidine-hydrazone scaffold provided an optimal balance of flexibility and rigidity, enabling simultaneous dual-site inhibition at the enzyme's CAS and PAS. Supported by in silico ADMET predictions that verify their drug-likeness, excellent BBB permeability, and safe toxicity profile, these highscoring piperidine analogs are strong candidates for subsequent anti-alzhiemer's development.

Ethical Consideration: Not applicable as no animal study was performed.

Conflicts of Interest

There are no conflicts of interest.

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