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Theoretical Examination of Molecular Docking, Pharmacokinetics and In-Silico Design of Specific Tacrine Derivatives as Anti-Alzheimer Agents

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Abstract

A common neurological illness that affects many individuals globally is Alzheimer's disease *(AD). Its cause is currently unknown. One of the symptoms of AD is a reduction in cholinergic transmission, which has been linked to memory loss and cognitive impairment. Acetylcholinesterase (AChE) inhibitors such as donepezil, galantamine, and rivastigmine are used in medicine. However, their unfavourable side effects have caused them to be taken off the market. Because tacrine inhibits the enzyme AChE, molecular docking modelling has been used to simulate and create a variety of derivatives. The purpose of this work was to develop some strong Alzheimer's inhibitors and to calculate the binding scores of tacrine derivatives theoretically. Following docking, molecule A8 was selected as a template for creating new compounds since it had the greatest binding scores (-9.8 kcal/mol). The B3, B5, B6, B8, and B10 hypothetical molecules were constructed. The developed compounds' ADMET prediction and drug-likeness demonstrate strong pharmacokinetic properties. Furthermore, comparable strong inhibitor drugs against AD might be created using the in-silico methodologies used in this work.*

Keywords: Molecular docking, Alzheimer's disease, pharmacokinetics, design chemical compounds, binding score

INTRODUCTION

Alzheimer's disease (AD) is a disorder that collectively destroys cognitive and psychological functioning and is often diagnosed in adults. It is characterized by a loss of thinking capacity (Breijyeh and Karaman, 2020). There are attempts to elucidate the characteristics of AD, which include a marked degeneration of the cholinergic system and changes in other neurotransmitter systems (Chen *et al*., 2022). Acetylcholinesterase (AChE) has been a target for drug design in the treatment of AD, and this has garnered substantial attention. The only comforting medication available on the market right now for the treatment of AD is AChE(Nadri *et al*., 2013; R Saxena M., 2019). Unfortunately, the most prevalent therapeutic uses for AChE inhibitors include severe toxicities in tacrine(Bautista-Aguilera et al., 2014; Fagnani et al., 2004; Id *et al*., 2019), short half-lives, and purpuric rash as rivastigmine(Correa-Basurto et al., 2007). These factors have also resulted in restrictions on the availability of palliative medications on the market. Researchers concentrated not only on developing potent AChE inhibitors with an inverse connection between toxicity and potency but also on making these inhibitors affordable, biodisponible, and low in toxicity (Correa-Basurto et al., 2007). A CADD approach will be used to find a more effective and targeted therapy since all of the medications have been pulled off the market due to various adverse effects, including hepatotoxicity and problems with drug metabolism(Solomon *et al*., 2009).

Computer-Aided Drug Design (CADD) and chemo-informatics research are two of the key cutting-edge techniques used by the pharmaceutical industry in drug discovery, design, and development strategies in the recent past (Liu *et al*., 2022; Muegge *et al*., 2017). Molecular docking analysis, pharmacokinetics study, bioactivity predictions, and structure-based drug layout strategies have therefore been employed as quick and low-cost techniques to examine binding interactions, inspect pharmacokinetic houses and bioactivity parameters, and layout of recent compounds to look for novel inhibitors with higher biochemical interactions *(Batool et al*., 2018; Vilar *et al*., 2011) and top-notch pharmacological houses as capacity anti-Alzheimer marketers to consolidate findings from the previous study.

Considering the intricacy of Alzheimer's disease (AD), a multi-drug, multi-target strategy could prove to be more effective than conventional monotherapy. This led some scientists to use a computational method to find approved drug combinations that would lessen microglial

inflammation in AD more successfully than single therapies. Using the distinct advantages of two separate computer programming languages—one declarative and the other imperative—this novel approach (Anastasio, 2015; Batool *et al*., 2018; Hung and Chen, 2014; Meng *et al*., 2014).

Additionally, additional hurdles associated with multi-target AD drug development include the need for ligands to have strong binding affinities for numerous targets, optimum ADME/T characteristics, minimal off-target adverse effects, and blood-brain barrier bridging. As computational approaches have been successfully used to single target drug development projects, these obstacles may be overcome by in-silico methods for an effective solution in less time and money(Abduljelil *et al*., 2022; Babu *et al*., 2012).

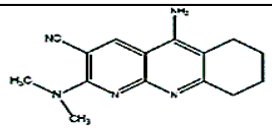
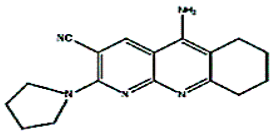
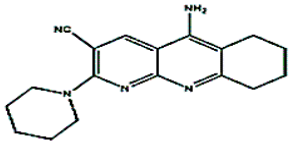
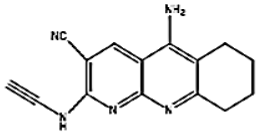
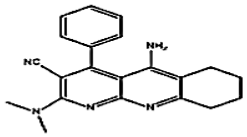
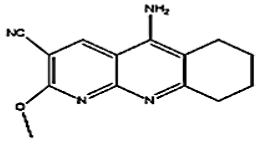
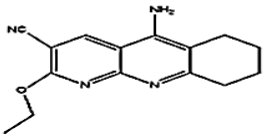
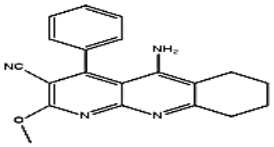
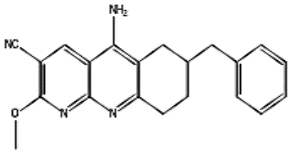
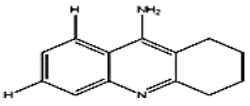
This research uses a molecular docking approach to virtually screen tacrine derivatives against the AChE crystal structure to enhance the binding scores and molecular interactions between molecules and the receptor. The aim is to identify a potential lead ligand with improved properties. Lastly, to evaluate the pharmacokinetic properties of the developed compounds.

MATERIAL AND METHODS.

Data sets from experiments and ligand preparation

In light of this study, the following criteria were used in the computing system used for the investigation: a pair of 2.30 GHz Intel® Core i5-3210M processors and 12.00 GB of RAM. (Samadi *et al*., 2011), Nine powerful dataset ligands (Table 1) were found and chosen from a trustworthy body of research. Spartan 14 software was used to convert the 2D structures of the tacrine products in the experimental dataset from version 16.0 of the ChemDraw program to 3D structures (Hassan *et al*., 2023). The resulting three-dimensional structures were then geometrically optimized using the DFT approach with Spartan 14. The calculation was set to equilibrium geometry at the ground state using density functional theory at the B3LYP (Ajala et al., 2018; Derakhshan et al., 2020; Flores-Holguín *et al*., 2021; Gao *et al*., 2018; Sun *et al*., 2018; Umar and Uzairu, 2023) (Becke88 three-parameter hybrid exchange potentials with Lee–Yang–Parr correlation potential) level of theory and 6-311G (d) basis set for the geometrical optimization of the cleansed structures, a software package from Wave function Inc (Derakhshan *et al*., 2020; Golipour *et al*., 2020). The optimized ligands were then saved in PDB file format as prepared for molecular docking simulations study (Hassan *et al*., 2023; Madhavi Sastry *et al*., 2013).

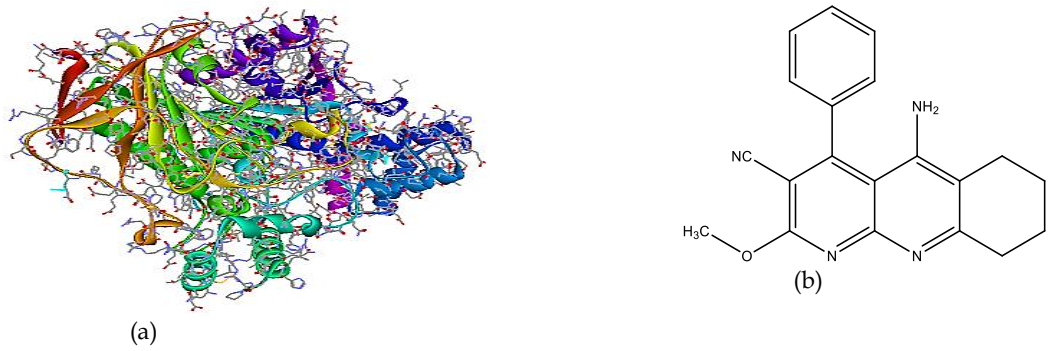
Table 1: Tacrine derivatives' Molecular Binding Affinities as Anti-Alzheimer Agents

S/NO	Ligand	IC_{50}(μM)	BE(kcal/mol)
M1		0.100	-9.2
M2		0.160	-9.5
M3		1.000	-9.4
M4		0.153	-9.5
M5		4.400	-9.4
M6		1.600	-9.0
M7		1.000	-9.2
M8		5.000	-9.8
M9		5.000	-8.3
Tacrine		0.109	-8.8

BE= Binding Energy

Retrieval of the receptor and setup

The protein complex's 3D structure (PDB: 4EY7) was acquired from Protein Databank to build the receptor display. From the downloaded 3D structure of the amino acid, the heteroatoms and water molecules of the receptors were manually deleted, and the refined/prepared receptor was then saved in PDB file format (Abdulganiyyu *et al*., 2020; Ajayi *et al*., 2011).



(a) (b)

Fig. 1: (A) The established receptor's three-dimensional structure; (B) the newly developed Template compound's two-dimensional structure.

Calculating binding energy

A molecular interaction study was conducted to calculate the scoring function and investigate protein-ligand interactions to forecast the ligand's binding affinity and biological activity(Vieira *et al*., 2019). The 2016 edition of the Discovery Studio Visualizer program was employed to investigate the visualization of protein-ligand interactions via non-bonding and hydrophobic interactions, whereas AutoDock Vina 4.2 of.PyRx software was used to estimate the binding affinity(Issack *et al*., 2012; S Olasupo S. B., 2020). The protein structure (PDB ID: 4EY7) was opened in pdbqt format using PyRx, a virtual screening tool. Following the selection of the molecules, the pdbqt layout was generated automatically. The lattice box was automatically constructed for 4EY7 "(X =2.9286, Y = 40.538, Z = 31.022217)". After both were chosen, the centre of the mark position and its dimensions were assigned. The auto dock vina completed the docking and tracked the situation's correctness.

Characteristics of the ligands utilized in ADMET

Drug analysis SwissADME and pkcsm online platforms were used to assess the nine substances listed in Table 1. According to (Matlock *et al*., 2018), the techniques used throughout these stages accurately predict false-positive results in biochemical assays utilized in chemotherapy. The pharmacokinetic radar plots show the oral bioavailability of our targeted bioactive compounds (Figure 4), which provide a graphic depiction of the molecule's drug-likeness measure.

Results and Discussions

Docking of Molecules and Virtual Screening

Molding a complex result in the best possible form (Abdullahi *et al*., 2022; Ibrahim *et al*., 2020) The top pose's selected target conformations are shown in Table 1. These target conformations are made up of nine compounds that were synthesized in experiments and ranked according to their score values. The M8 molecule was chosen as the template based on its highest binding score of -9.8 kcal/mol due to the complexes' varying binding affinities ranging from -8.3 to -9.8 kcal/mol. The subsequent structural alterations aimed to find new hypothetical compounds.

Figure 2 displays the five acetylcholinesterase (AChE) inhibitors that were particularly developed. Table 2 lists these inhibitors' structures and the International Union of Pure and Applied Chemistry (IUPAC) nomenclature corresponding to them. After calculating their docking scores, it was found that they demonstrated stable interactions (Figure 2) with the target receptor (AChE). The five suggested AChE inhibitors had better docking energies than all of the experimental compounds gathered from the literature, according to the data acquired (Samadi *et al*., 2011). Furthermore, the docking binding energy of the currently available AD drug was -8.8 kcal/mol, lower than that of all hypothesized AChE inhibitors (Figure 2). The three-dimensional interactions between the AChE receptor and a commercially available drug for Alzheimer's disease are shown in Figure 3. We performed pharmacological similarity and in silico ADMET studies on the nine compounds in Table 1. Table 3, which shows the pertinent parameters for the tacrine derivatives, presents the findings from these investigations.

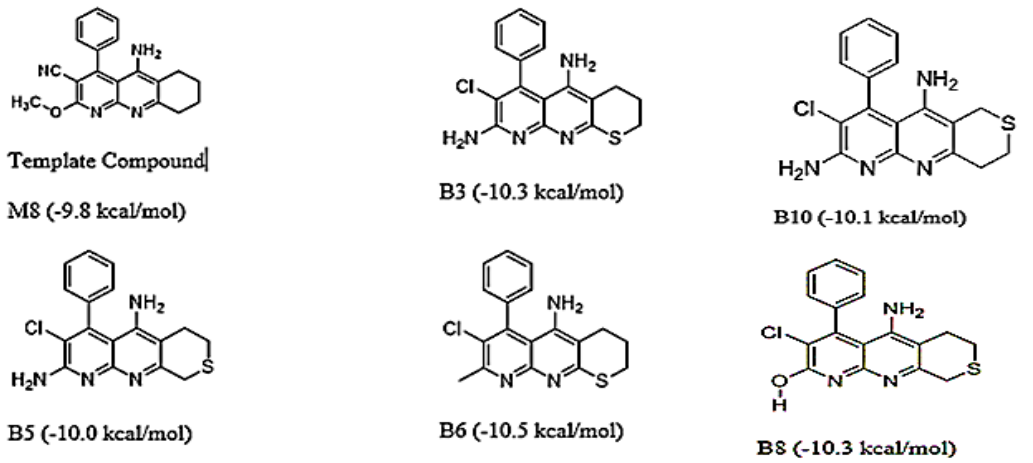
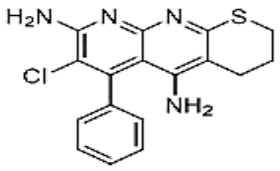
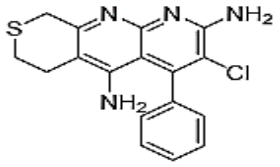
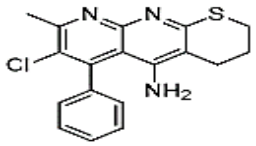
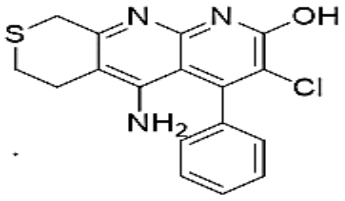
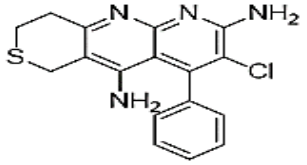


Fig. 2: 2D structures and binding affinities of generated tacrine derivatives derived from a template.

Table 2: The IUPAC names of designed molecules

S/NO	Designed molecules	Name of Molecule
B3		7-chloro-6-phenyl-3,4-dihydro-2H-thiopyrano[2,3-b][1,8]naphthyridine-5,8-diamine
B5		3-chloro-4-phenyl-7,9-dihydro-6H-thiopyrano[3,4-b][1,8]naphthyridine-2,5-diamine
B6		7-chloro-8-methyl-6-phenyl-3,4-dihydro-2H-thiopyrano[2,3-b][1,8]naphthyridin-5-amine
B8		5-amino-3-chloro-4-phenyl-7,9-dihydro-6H-thiopyrano[3,4-b][1,8]naphthyridin-2-ol
B10		3-chloro-4-phenyl-8,9-dihydro-6H-thiopyrano[4,3-b][1,8]naphthyridine-2,5-diamine

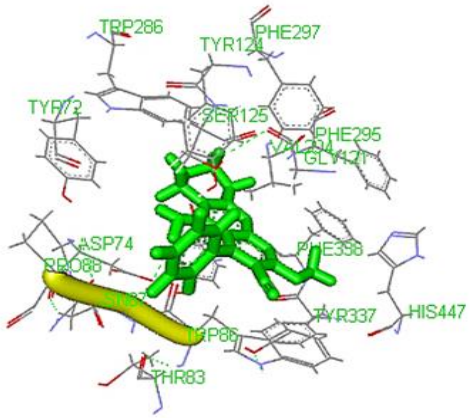
Bioavailability Forecasts for the AChE inhibitors that are being developed and tested docking experiments were performed on the developed compounds in demand using the SwissADME and pkcsm online platforms to assess their potential to reach the targets in a bioactive form. These phases' approaches are answerable for properly forecasting false-positive findings in chemotherapeutic biochemical studies (Matlock *et al.,* 2018). The pharmacokinetic radar plots (Figure 4) highlight the oral bioavailability of our targeted bioactive compounds by providing a visual depiction of the drug-likeness measure of the molecule. Oral bioavailability has been predicted for the following five chemicals: B3, B5, B6, B8, and B10.

Table 3 displays the discovered compounds' P-glycoprotein (B3, B5, B6, B8, and B10), ADMET, and drug similarity. They are also highly absorbable in the gastrointestinal system. All medications exhibited advantageous oral availability because of the ideal CaCO2 cell permeability and HIA (>0.5 and >90 percent, respectively, Table 3), which were repeated in the values shown in Table 3. The volume of distribution (VDss) and the unbound fraction,

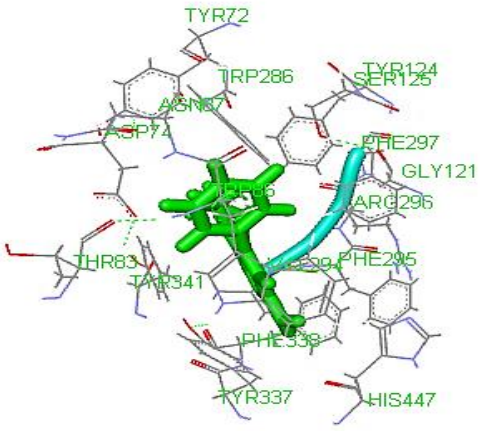
which show how the treatment will be distributed in tissue and plasma, are two important pharmacokinetic drug characteristics. The amount of medicine distributed is VDss, while the unbound fraction is the percentage of treated cells in plasma that may gradually increase. These findings imply that the chemicals are usually distributed throughout plasma and contain significant unbound material that interacts with the pharmacological target. Following the expected total clearance values (Table 3), which show how efficiently the body eliminates a medication, all drugs have a tolerable renal clearance and are not substrates of the kidney's organic cation transporter 2 (OCT2).

Table 3: Variable of drug metabolism and health effects of designed compounds

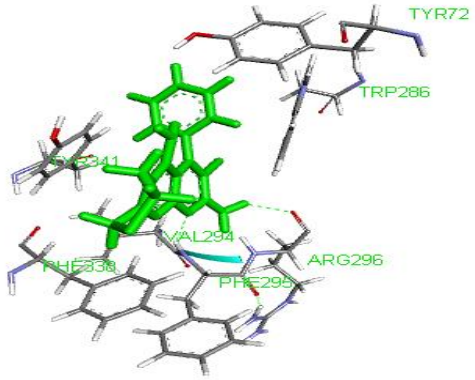
	Compounds/Models	3	5	6	8	10
	$CaCO_3$ (log Papp in 10^{-6} cm/s)	0.522	0.876	1.372	0.523	0.876
Absorption	Human Intestinal Absorption (% Absorbed)	90.268	90.836	92.722	90.608	90.836
	Skin permeability (log Kp)	-2.946	-2.949	-2.94	-2.941	-2.949
	VD_{ss} (human) (log L/kg)	0.063	0.052	0.184	-0.025	0.052
	Fraction unbound (human) (Fu)	0.152	0.157	0.138	0.163	0.157
	BBB permeability (log BB)	-0.422	-0.416	0.262	-0.464	-0.416
Distribution	CNS permeability (log PS)	-1.667	-1.719	-1.418	-1.734	-1.719
Excretion						
	Total clearance (log ml/min/kg)	0.116	0.124	0.248	0.157	0.100
	Renal OCT2 substrate (Yes/No)	No	No	No	No	No
Toxicity	AMEX toxicity (Yes/No)	2.837	2.836	0.252	0.175	0.165
	Oral rat acute toxicity (LD_{50}) (mol/kg)	-0.091	-0.029	2.83	2.827	2.836
	Minnor toxicity (log mM)	0.522	-0.029	-0.545	-0.041	-0.029



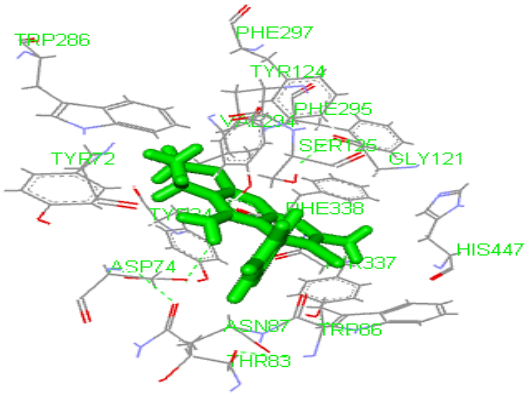
The authorized drug's three-dimensional Interaction with the receptor (the drug and the target



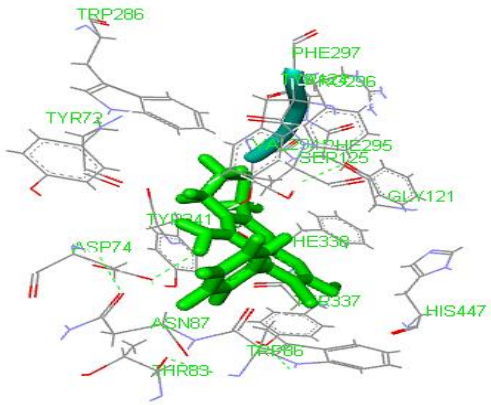
Docking Interaction between ligand B3 and receptor



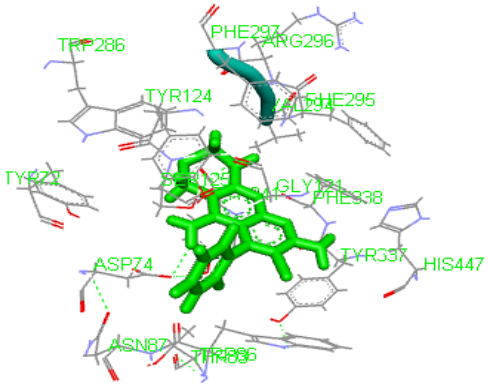
Docking Interaction between ligand B5 and receptor



Docking Interaction between ligand B6 and receptor

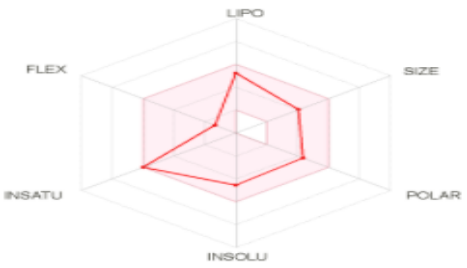


Docking Interaction between ligand B8 and receptor



Docking Interaction between ligand B10 and receptor

Figure 3: 3D interactions between protein targets and engineered ligands



A8

B3

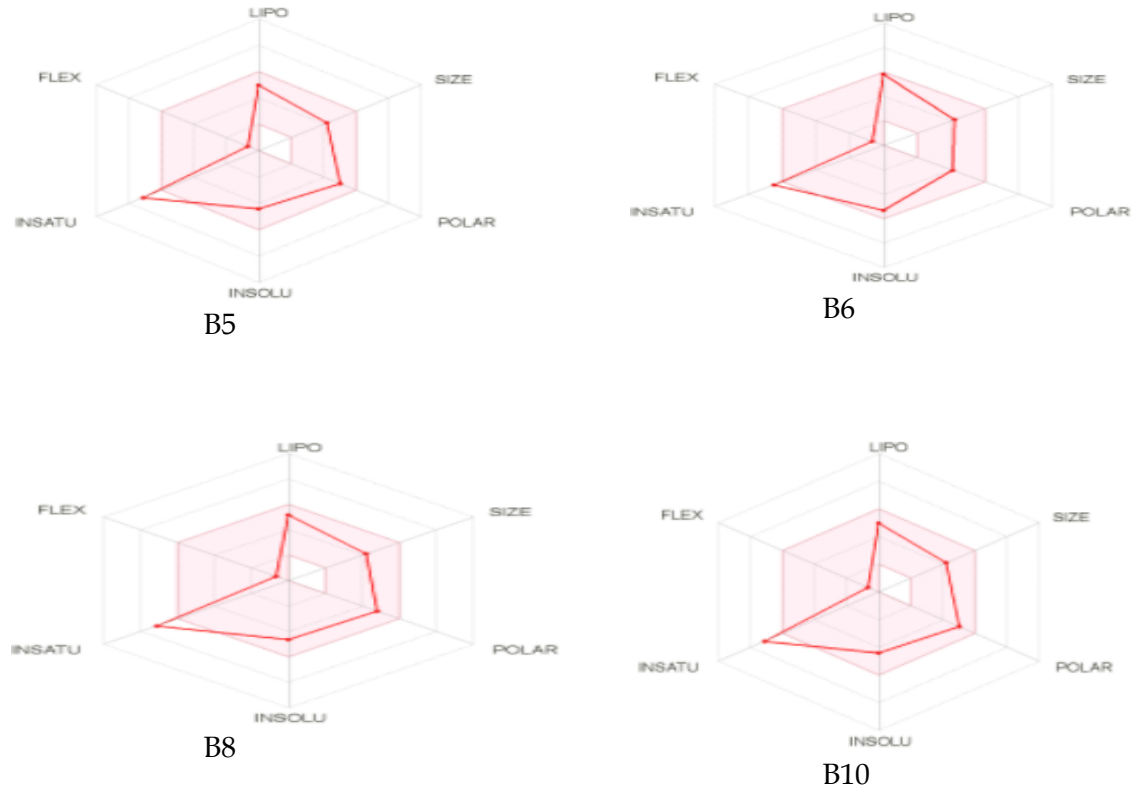


Figure 4. Plots of the oral bioavailability radar template and designed ligands

The Lipinski rule of five (RoF) for the ADMET analysis of the suggested compounds is shown in Table 4. All the designs adhered to Lipinski's rule of five, indicating that the compounds have drug-like characteristics and could be taken orally.

TABLE 4: Lipinski rule of five for ADMET analysis of our designed compounds

S/NO	MF	MW (g/mol)	MLogP	HBD	HBA	NRB	RVN	SA	GIA	MR	PGP
3	C17H15ClN4S	342.85	3.5	2	2	1	0	3.14	High	98.17	Yes
5	C17H15ClN4S	342.85	3.23	2	2	1	0	3.19	High	99.01	Yes
6	C18H16ClN3S	341.86	3.91	1	2	1	0	3.11	High	98.73	Yes
8	C17H14ClN3OS	343.83	3.23	2	3	1	0	3.12	High	96.63	Yes
10	C17H15ClN4S	342.85	3.23	2	2	1	0	3.19	High	99.01	Yes

The bioavailability radars for the five calculated theoretical substances are shown in Figure 5. B3, B5, B6, B8, B10, and so on. Orally administered chemicals are expected to exhibit little flexibility and polarity, be less toxic, have efficient absorption, and be physiologically active. The lengthened and updated version of the Edan–Egg model, known as the Brain or IntestinaL EstimateD, is an expanded transformed description of the Edan–Egg model. The BOILED egg (Fig. 5) below is an egg model.

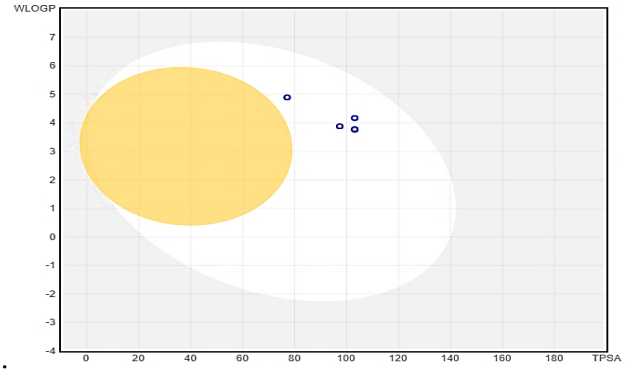


Figure 5: BOILED-Egg diagram.

Five compounds satisfied the Ghose (Ghose *et al*., 1999), Egan (Egan *et al*., 2000), Veber (Veber *et al*., 2002), and Muegge (Muegge *et al*., 2001) drug-likeness criteria in addition to the Lipinski rule of five (Lipinski, 2016) Table 5 displays these outcomes. Conversely, every suggested compound met the strict lead like requirement set out by Teague (Teague *et al*., 1999). High-affinity leads for high-throughput screens are generated by lead-likeness calculations, which enables the identification and usage of extra interfaces in the lead optimization stage. Lastly, there was no indication of the accessibility of the tacrine moiety in the result of the PAINS model (Teague *et al*., 1999), which was developed to filter out minute compounds that could avoid false positives in biological testing. In conclusion, there were no significant toxicity issues with the substances. The overall display of Table 5 indicates that every chemical may be an excellent therapy option or may provide recommendations for urgent management.

Table 5: Complexes' drug-likeness, lead-likeness and PAINS of designed compounds

		3	5	6	8	10
Drug-likeness	Lipinski violations	0	0	0	0	0
	Ghose violations	0	0	0	0	0
	Veber violations	0	0	0	0	0
	Egan violations	0	0	0	0	0
	Muegge violations	0	0	0	0	0
	Lead-Likeness violations	0	0	0	0	1
	PAINS alert	0	0	0	0	0

CONCLUSION

A molecular docking study determined that five Tacrine derivative chemicals form stable complexes with the human acetylcholinesterase receptor (PDB ID: 4EY7). The B3, B5, B6, and B8 values of the compounds are -10.3, -10.5, and -10.1 kcal/mol, respectively. Furthermore, every newly developed molecule has promising drug-like characteristics. The ADMET profiles show excellent oral bioavailability. Consequently, the research's findings will provide crucial information for synthesizing novel tacrine derivatives with improved anti-Alzheimer properties.

ABBREVIATION

Molecular weight (MW) and molecular formula (MF) HBA is a hydrogen bond acceptor, while HBD is a hydrogen bond donor. The number of rotatable bonds is NRB. AS: Artificial Sophistication, Gastrointestinal Absorption is GIA. Molar refractivity is MR. BBB stands for the blood-brain barrier, PGP for permeability glycoprotein, and CNS for central nervous system.

Declaration of Competing Interest

There are no interests to declare.

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