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In-Silico Design, Molecular Docking and Pharmacokinetics Studies of Some Tacrine Derivatives as Anti-Alzheimer Agents: Theoretical Investigation

Ajala Abduljelil *, Adamu Uzairu, Gideon A. Shallangwa, Stephen E. Abechi

Department of Chemistry, Faculty of Physical Sciences, Ahmadu Bello University, P.M.B. 1044, Zaria, Kaduna State, Nigeria

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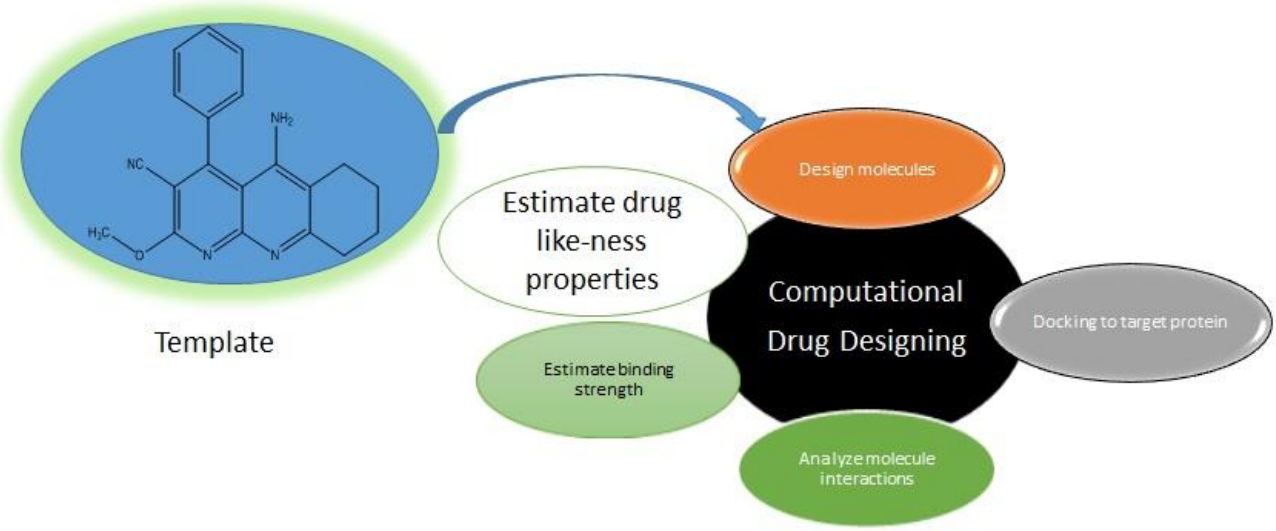
ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative ailment that affects many people worldwide. Its cause has yet to be determined. One of the symptoms of AD is the loss of cholinergic transmission, which is related to cognitive impairment and memory loss. Acetylcholinesterase (AChE) inhibitors like donepezil, galantamine, and rivastigmine are currently used in medicine, but they have been taken off the market due to their adverse side effects. Molecular docking simulation was used to simulate and design some tacrine derivatives because of the inhibitory ability of tacrine on the enzyme AChE. This study was tailored to theoretically calculate the tacrine derivatives binding scores and design some potent Alzheimer's inhibitors. After docking, molecule A8 has the highest binding scores of -9.8 kcal/mol, and it was chosen as a template for designing new compounds. Five new hypothetical molecules (B3, B5, B6, B8, and B10) were designed. ADMET prediction of the designed molecules and drug-likeness show good pharmacokinetic abilities. Moreover, the *in-silico* techniques used in this study could further design similar potent inhibitor compounds against AD.

GRAPHICAL ABSTRACT



* Corresponding author: Abduljelil, A.
✉ E-mail: abdulajala39@gmail.com

Introduction

Alzheimer's disease (AD) is an illness that results in the aggregate ruin of intelligent and psychological activities, characterized by loss of thinking capability commonly found in adults [1]. AD is characterized by a pronounced degradation of the cholinergic system andalteration in other neurotransmitter systems, and efforts are being made to explain the hallmarks of the disease [2]. The AD treatment has been considered and received significant attention using Acetylcholinesterase (AChE) as a drug design target. AChE is the single measure palliative drug provided for AD treatment in the market [3,4]. Regrettably, the presently available palliative drugs in the market have been restricted due to high toxic in tacrine [5], short half-life, and purpuric rash as rivastigmine [6] including high-cost are the most common AChE inhibitors therapeutic applications [5]. In a study carried out by some investigators, their attention was not only focused on developing effective the aiming inverse relationship between potency and toxicity of AChE inhibitors with their low toxicity and cost and high disponibility [6]. Due to several side effects such as hepatotoxicity and drug metabolism issues, all the drugs have been taken off the market. To identify more effective and targeted drugs, a CADD technique will be utilized [7].

In recent times, chemo-informatics study and Computer-Aided Drug Design (CADD) are critical trending procedures used by many pharmaceutical industries in drug discovery, design, and development tactics [8]. Therefore, for you to consolidate findings from the previous study [9], molecular docking analysis, pharmacokinetics study and bioactivity predictions, and structure-mainly based drug layout strategies have been hired as speedy and inexpensive 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 [9] and top-notch pharmacological houses as capacity anti-Alzheimer marketers.

Alzheimer Disease (AD) is highly multifactorial, suggesting that a multi-target/multi-drug strategy could be more effective than conventional monotherapy. This made some researchers utilize a computational approach to find combinations of approved drugs that are potentially more effective than single drugs in reducing microglial inflammation in AD. This novel approach exploits the distinct advantages of two computer programming languages, one imperative and the other declarative [10].

Moreover, multi-target AD drug discovery added extra challenges. These include the excellent binding affinity of ligands for multiple targets, optimal ADMET properties, no off-target side effects, and crossing the blood-brain barrier. These hurdles may be addressed by *in-silico* methods for an efficient solution in less time and cost as computational methods are successfully applied to single target drug discovery projects [11].

This research aims to get a molecular docking approach to a virtual screen of some tacrine derivatives with the AChE crystal structure as the receptor and highlight a possible lead ligand as a template for designing theoretical molecules with enhanced binding scores and improved performance molecular outstanding interactions with the receptor. Lastly, to evaluate the pharmacokinetic properties of the designed compounds.

Materials and Methods

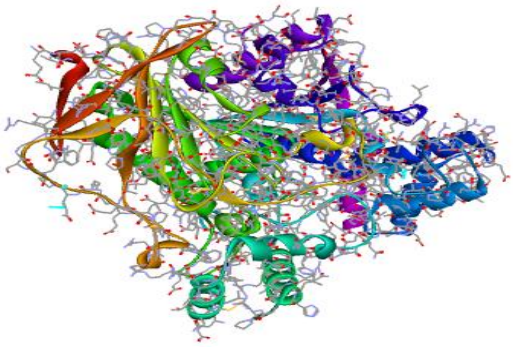
Experiment data sets and ligand preparation

All through the study, a workstation system with the following specifications was used: CPU Dual@2.30 GHz, Intel® Core i5-3210M, 6.00GB RAM. Nine potent dataset ligands (Table 1) were identified and selected from reliable literature

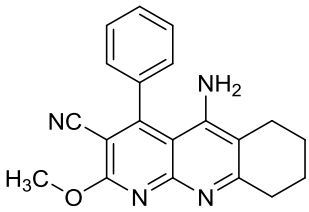
for this study [12]. 2D structures of tacrine products of the experimental dataset used were drawn by Chemdraw software ultra-version 16.0 and then transformed to 3D structures with the aid of Spartan 14 software [13]. The obtained 3D structures were subsequently optimized geometrically using the DFT approach with Spartan 14. The calculation was set to equilibrium geometry at the ground state using density functional theory at B3LYP [14–16] (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 [15,17]. After that, the optimized ligands were saved in PDB file format as prepared ligands for molecular docking simulations study [13].

Retrieval of receptor and preparation show

The receptor show was prepared by downloading the 3D structure of the protein complex (PDB: 4EY7) from Protein Databank. The heteroatoms and water molecules of the receptors were manually removed from the downloaded 3D structure of the amino acid and then saved in PDB file format as a refined/prepared receptor [14].



(a)



(b)

Figure 1. (a) 3D structure of the prepared receptor and (b) 2D structure of the designed Template compound

Binding energy calculations

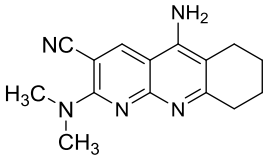
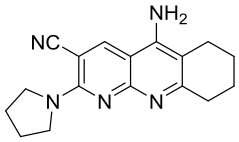
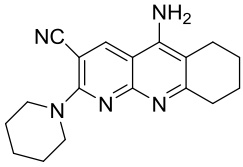
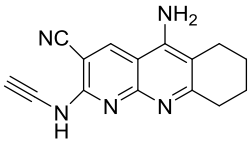
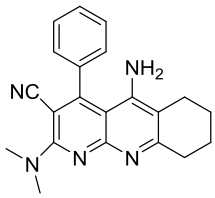
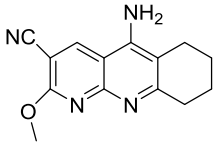
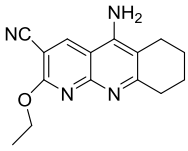
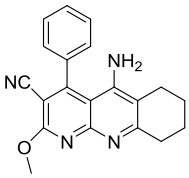
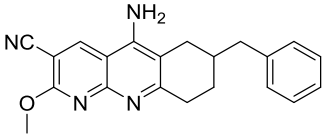
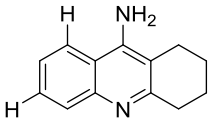
Molecular interaction study was conducted to compute the scoring function and research protein-ligand interactions in predicting the ligand's binding affinity and biochemical activity [9]. AutoDock Vina 4.2 of PyRx software was used to estimate the binding affinity. At the same time, visualization of protein-ligand interactions by non-bonding and hydrophobic interactions was explored, 2016 version of Discovery Studio Visualizer software [13]. The protein (PDB ID: 4EY7) structure in pdbqt format was opened using the virtual screening instrument PyRx. The molecules were selected and automatically transformed to pdbqt layout. The box centers were assigned for 4EY7 "(X =2.9286, Y = 40.538, Z = 31.022217)", the lattice box was automatically appearing, and the center of the mark site was allocated along with the dimensions after both of them were chosen. The docking was achieved with autodock vina to observe the precision of the docking situation.

ADMET properties of ligands used

On the nine molecules listed in Table 1, The SwissADME and pkcsm web platforms were used to conduct drug assessment evaluation. These stages' procedures accurately predict false-positive results in chemotherapeutic biochemical analyses [18]. The pharmacokinetic radar plots

demonstrate the oral bioavailability of our intended biosctive compounds (Figure 4), which provide a graphic picture of the molecule's drug-likeness yardstick.

Table 1. Molecular Binding Affinities of the Tacrine Derivatives 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

Results and Discussions

Molecular docking and virtual screening

The most desirable conformation is formed [19]. Table 1 shows the target conformations selected of the best pose, nine experimentally synthesized molecules, ordered by their score values. Because the binding affinity of complexes altered between - 8.3 and - 9.8 kcal/mol. The M8 molecule was chosen as the template with the top, binding score of - 9.8 kcal/mol, and structural changes were made to discover new theoretical molecules.

Five AChE inhibitors were structurally designed and presented in Figure 2 and Table 2 for their structures and IUPAC names, respectively. Their docking scores were calculated, and they were found to possess stable interactions (Figure 2) of the target receptor (AChE). From the results obtained, the five AChE inhibitors designed were found to have better docking energies than all the experimental compounds extracted from the literature [12]. Furthermore, the docking binding energy (-8.8 kcal/mol) for the AD commercially sold drug was found to have less docking binding energy than all the designed AChE inhibitors (Figure 2). 3D interactions of AD commercially sold drug with AChE receptor are presented in Figure 3. On the nine molecules (Table 1), we performed in silico ADMET and drug similarity variables of the tacrine derivatives; the parameters are demonstrated in Table 3.

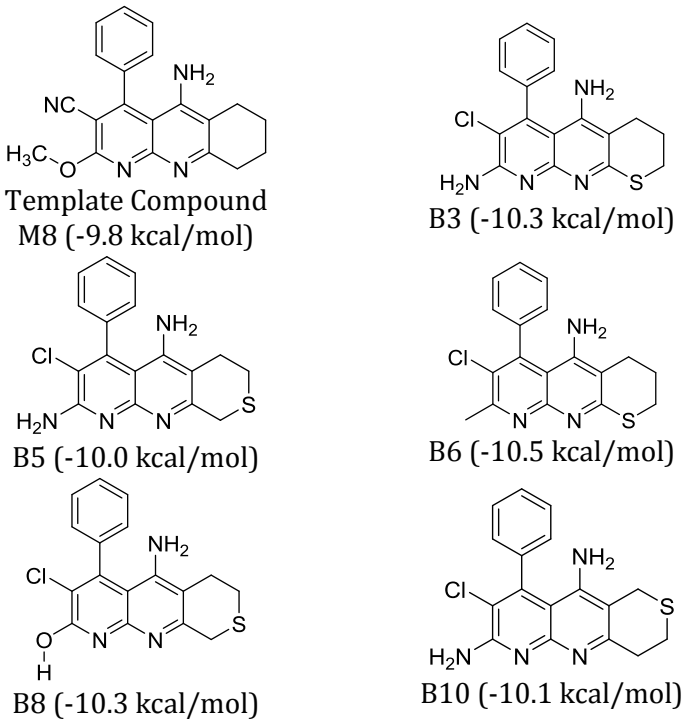
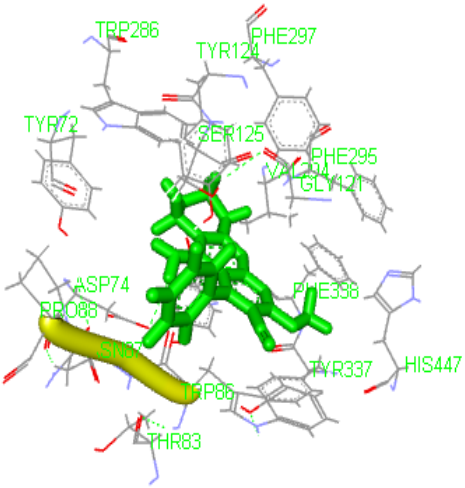


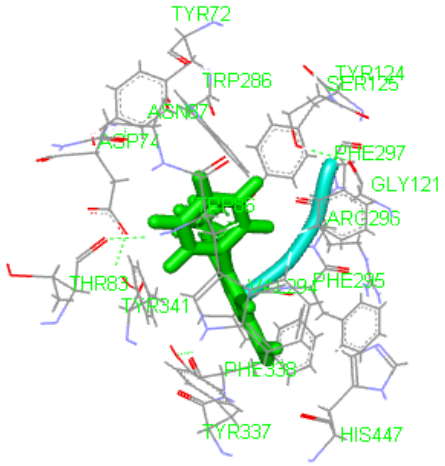
Figure 2. 2D structures of designed Tacrine derivatives from the template and their binding affinity

Table 2. The IUPAC names of designed molecules

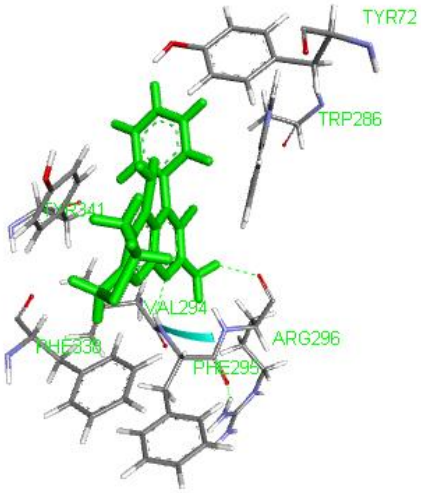
S/NO	Designed molecules
B3	7-chloro-6-phenyl-3,4-dihydro-2H-thiopyrano[2,3-b][1,8]naphthyridine-5,8-diamine
B5	3-chloro-4-phenyl-7,9-dihydro-6H-thiopyrano[3,4-b][1,8]naphthyridine-2,5-diamine
B6	7-chloro-8-methyl-6-phenyl-3,4-dihydro-2H-thiopyrano[2,3-b][1,8]naphthyridin-5-amine
B8	5-amino-3-chloro-4-phenyl-7,9-dihydro-6H-thiopyrano[3,4-b][1,8]naphthyridin-2-ol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



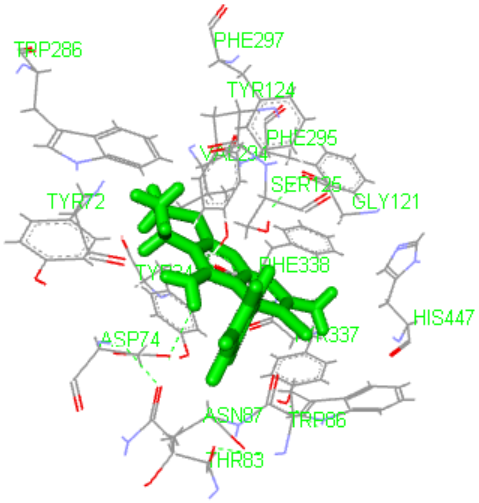
M8: 3D Interaction of the approved drug with a receptor (Approved drug and target)



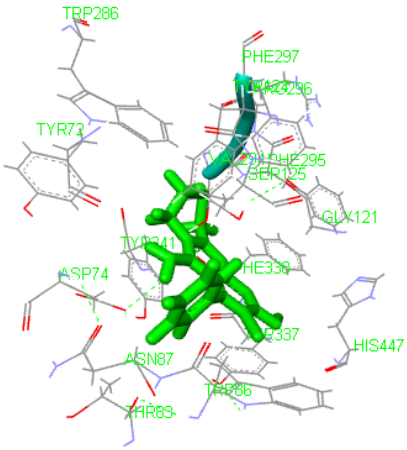
Docking Interaction of receptor and ligand B3



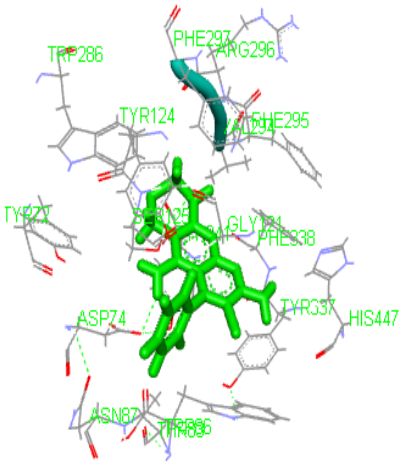
Docking Interaction of receptor and ligand B5



Docking Interaction of receptor and ligand B6



Docking Interaction of receptor and ligand B8



Docking Interaction of receptor and ligand B10

Figure 3. 3D interactions of designed ligands and protein target

Bioavailability Predictions of Experimental and Designed AChE Inhibitors

The SwissADME and pkcsm web platforms were used to conduct docking studies on the designed molecules in demand to evaluate their capability in the bioactive form to reach the targets. These stages' procedures accurately predict false-positive results in chemotherapeutic biochemical analyses [18]. The pharmacokinetic radar plots demonstrate the oral bioavailability of our intended bioactive compounds (Figure 4), which provide a graphic picture of the molecule's drug-likeness yardstick. Five compounds, specifically B3, B5, B6, B8, and B10, have been predicted to be orally bioavailable.

Table 3 shows the ADMET and drug-similarity belongings to the designed molecules, exposing them as BBB permeant, highly absorbable in the gastrointestinal tract, and containing P-glycoprotein (B3, B5, B6, B8, and B10). All the compounds have an excellent oral availability due to the extreme optimal CaCO2 cell permeability and HIA (>0.5 and >90 percent, respectively, Table 3) as replicated in the values shown in Table 3. Two of the key pharmacokinetic drug variables are the volume of distribution (VDss) and the unbound fraction, which display how the treatment will be distributed in tissue and plasma. The unbound fraction refers to the number of treated cells in plasma that could slowly add, whereas VDss refers to the amount of drug that has been dispersed. These outcomes show that the molecules are generally dispersed in plasma and have a large unbound fraction, coming in contact with the pharmacological target. The predicted total clearance values (Table 3), which measure the body's efficiency in removing a drug, designate that all compounds have a decent renal clearance and are not organic cation transporter 2 substrates in the kidney (OCT2).

Table 4 shows the Lipinski rule of five (RoF) for ADMET analysis of the designed compounds. All the designs obeyed Lipinski's rule of five, implying that the compounds are orally bioavailable and have drug-likeness properties.

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

	Compounds/Models	3	5	6	8	10
Absorption	$CaCO_3$ (log Papp in 10^{-6} cm/s)	0.522	0.876	1.372	0.523	0.876
	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
Distribution	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
	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

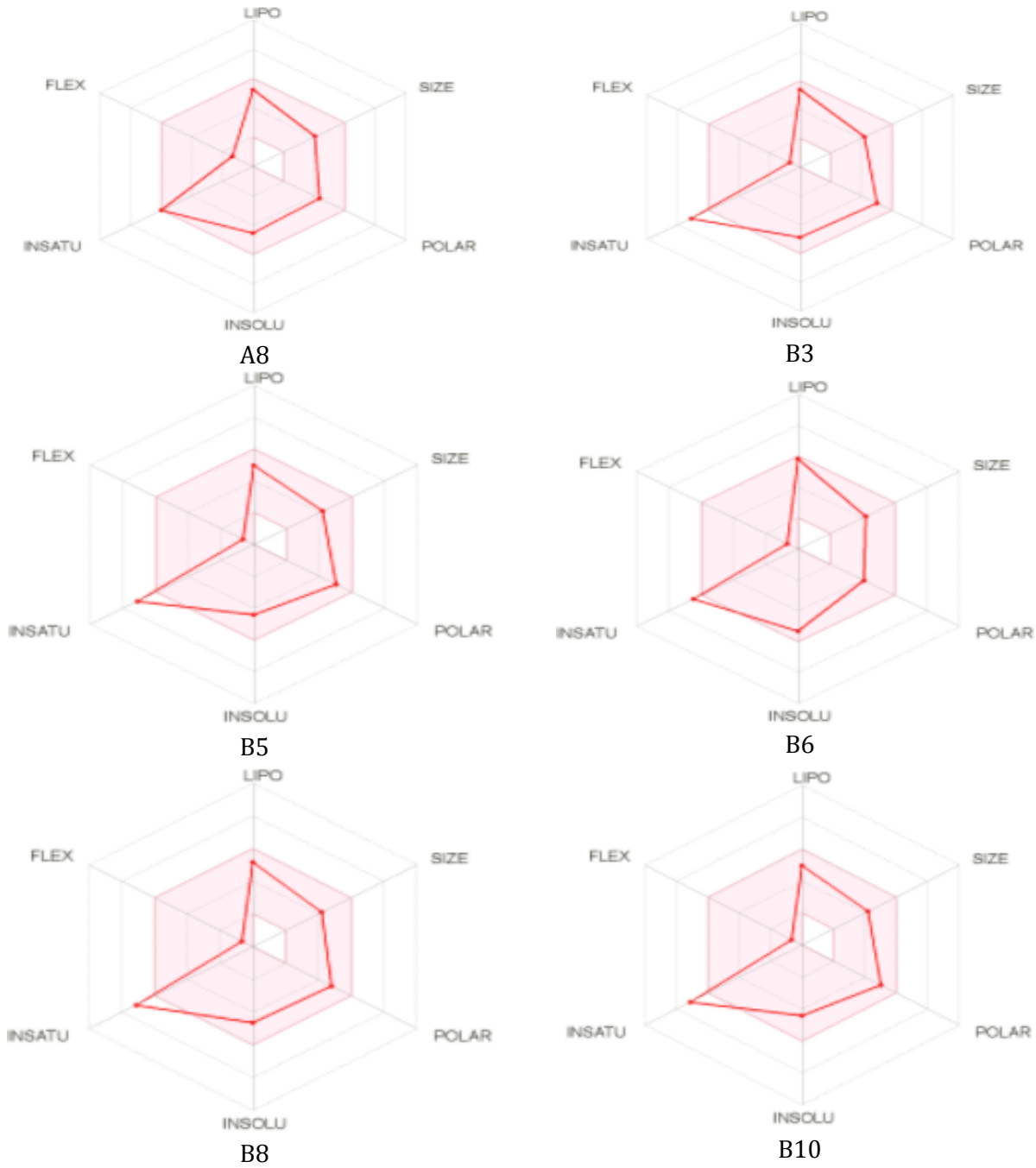


Figure 4. Radar plots of the template and the designed ligands of oral bioavailability

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

Figure 5 depicts the bioavailability radars of the five calculated theoretical molecules. (B3, B5, B6, B8, and B10). When occupied orally, the molecules are biologically active, include low flexibility and polarity, be less toxic, and have noble absorption. The extended transformed description of the Edan–Egg model, named the Brain or IntestinaL EstimateD, by the prolonged and renewed version of the Edan–Egg model, called the BOILED-egg (Figure 5) have been vividly observed [20].

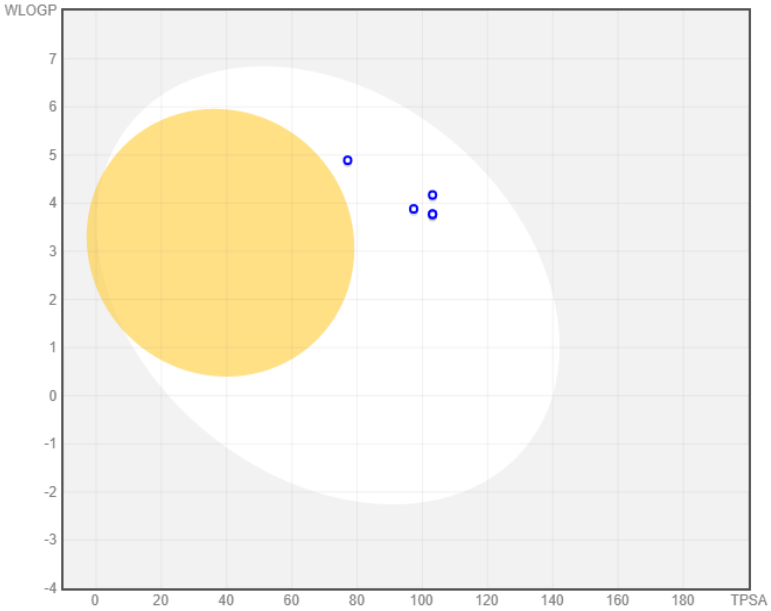


Figure 5. BOILED-Egg plot

Besides the Lipinski rule of five [21], five compounds met the Ghose [22], Egan [23], Veber [24], and Muegge [25] drug-likeness rules, as shown in Table 5. Instead, the designed molecules passed Teague's [26] tough lead-like criteria. Lead-likeness calculations are used to generate high-affinity leads for high-throughput screens, allowing for the finding and use of extra interfaces during the lead optimization stage. Finally, the product of the PAINS model [27], which was established to keep out small molecules that could avoid false positives in biological assays, displayed no evidence of the tacrine moiety's accessibility. Finally, there were no critical toxicity issues with the compounds. Table 5's overall lecture highlights that all compounds could be excellent drug candidates or suggest guidelines for imminent 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

Five Tacrine derivatives compounds were designed and subjected to molecular docking (B3: -10.3 kcal/mol, B5: -10.1 kcal/mol, B6: -10.5 kcal/mol, B8: -10.3 kcal/mol, and B10: -10.1 kcal/mol) which revealed the compounds form stable complexes with human Acetylcholinesterase receptor (PDB ID: 4EY7). In addition, all the newly designed compounds show good drug-like properties. The ADMET profiles indicated an excellent oral bioavailability. Therefore, the obtained results in this research will provide vital information to synthesize new Tacrine derivatives with enhanced anti-Alzheimer activity.

Abbreviation

MF=Molecular formula, MW= Molecular weight, HBD= Hydrogen bond donor, HBA= Hydrogen bond acceptor, NRB = Number of rotatable bond, AS= Synthetic accessibility, GIA= Gastrointestinal Absorption, MR= Molar refractivity, PGP= Permeability glycoprotein, BBB= blood-brain barrier, CNS= central nervous system

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Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Ajala Abduljelil: 0000-0002-9823-8847

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