chemistry proceedings

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Proceeding Paper

In Silico Exploration of a Symmetrical Acridine Derivative's Anti-Alzheimer Activity: Synthesis, AChE/BuChE Binding, and ADMET Prediction †

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† Presented at the 29th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-29); Available online: https://sciforum.net/event/ecsoc-29.

Abstract

Alzheimer's disease (AD) figures among the most triggering neurodegenerative disorders, constituting a constant subject of interest for medicinal chemistry researchers. The treatment of such disorders remains a challenge due to the complexity of their pathogenesis. Indeed, many factors are involved in the development of AD including different enzymes such as acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) which inhibition results in anti-AD activity, making the conception of novel AChE/BuChE inhibitors a possible way to manage Alzheimer's disease. Besides being a class of compounds that holds a various spectrum of biological applications, acridine compounds also figure among the most promising agents in the treatment of Alzheimer's disease through cholinesterase inhibition. The best example to mention is the well-known anti-AD agent Tacrine. However, the latter was found to have liver toxicity, which made the optimization of this acridine derivative a necessity. Our work was directed towards in silico evaluating a symmetrical acridine analogue as a potential cholinesterase inhibitor with controlled toxicity. The docking study was completed using Glide software (Schrodinger suites), and both AChE (pdb: 4EY6) and BuChE (4BDS) were utilized as drug targets. The molecular docking simulation resulted in satisfying docking score values alongside numerous significant interactions indicating the high stability of the investigated compound within the active sites of studied enzymes. Additionally, ADMET prediction was carried out for the assessed acridine derivative in order to explore its drug likeness through its pharmacokinetics and toxicity profiles employing SwissADME, MolSoft, and ProTox-II online servers.

Keywords: acridine; AChE/BuChE; molecular docking; ADMET; microwave synthesis

Academic Editor(s): Name

Published: date

Citation: Bouone, Y.O.; Bouzina, A.; Aouf, N.-E. In Silico Exploration of a Symmetrical Acridine Derivative's Anti-Alzheimer Activity: Synthesis, AChE/BuChE Binding, and ADMET Prediction. *Chem. Proc.* **2025**, *volume number*, x. https://doi.org/10.3390/xxxxx

1. Introduction

Brain-related diseases or neurodegenerative disorders (NDs) have been affecting health of millions of people all over the world. NDs results from a progressive deterioration of brain cells leading to different pathologic conditions such as Alzheimer disease, Parkinson's disease, amyotrophic lateral sclerosis, ataxia, and many others [1].

Drug design and development of an anti-Alzheimer drug is a challenging process since there is no complete treatment for Alzheimer and other neurological disorders. Synthesis of new agents in order to find new cures to this type of diseases is needed from pharmacological and medicinal perspectives [2].

Till know, most effective treatments of Alzheimer disease are acetylcholinesterase (AChE) inhibitors such as Donepezil and Galantamine, that's what made AChE the ideal drug target in the conception of new anti-AD agents [3].

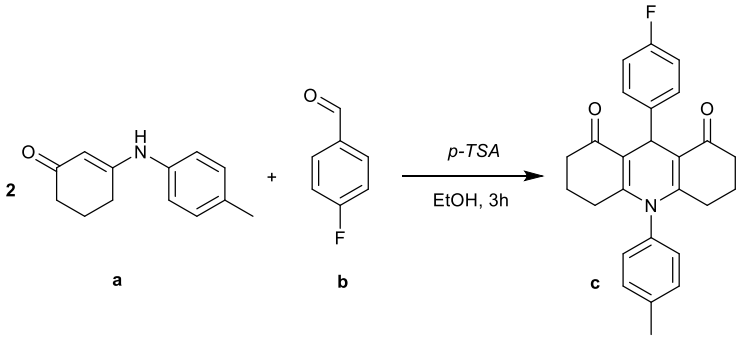
On the other hand, acridine and analogues are known for their beneficial biological activities including antibacterial [4], anticonvulsant [5], and analgesic [6] activities. Further, acridine derivatives were acknowledged for their efficiency in inhibiting cholinesterase enzymes resulting in anti-AD effect [7].

The ongoing need for AD treatments alongside the importance held by acridines prompted us to investigate the anticholinesterase effect of a symmetrical acridine compound through in silico studies involving molecular docking, in order to study the binding mode and stability of the prepared ligand inside the cavities of both acetylcholiesterase (AChE) and butyrylcholiesterase (BuChE). An ADMET prediction was also envisaged to evaluate the aptitude of our product in becoming a drug-candidate with acceptable ADME and toxicity profiles.

2. Materials and Methods

2.1. Synthesis

The synthesis of acridine derivative **c** was carried out using a previously described synthetic protocol [8] (Scheme 1).



Scheme 1. Synthesis of symmetrical acridine derivative.

*9-(4-fluorophenyl)-10-(p-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**Entry a**)*

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42–7.27 (m, 4H), 7.11 (d, *J* = 7.3 Hz, 2H), 6.91 (t, *J* = 8.7 Hz, 2H), 5.34 (s, 1H), 2.44 (s, 3H), 2.35 (dt, *J* = 16.2, 4.7 Hz, 2H), 2.29–2.12 (m, 4H), 2.04 (dt, *J* = 17.8, 4.6 Hz, 2H), 1.88 (dd, *J* = 13.4, 4.8 Hz, 2H), 1.75 (q, *J* = 11.8 Hz, 2H).

2.2. Molecular Docking

Molecular docking study was carried out using Schrodinger suite (glide) [9] and 3D visualization using Chimera software [10].

3. Results and Discussion

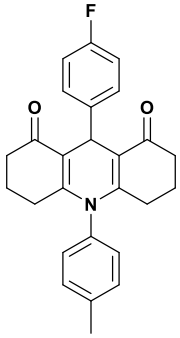
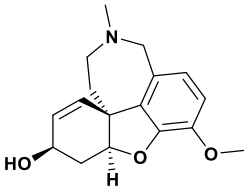
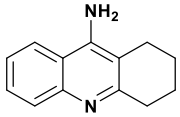
3.1. Molecular Docking

To evaluate the binding mode of the investigated acridine derivative within the active sites of both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), molecular docking simulations were performed using the PDB files 4EY6 [11] and 4BDS [12] respectively.

As a validation step, redocking of the co-crystallized ligands was carried out to ensure the reliability of the docking protocol. Protein structures were prepared using the Protein Preparation Wizard, and the co-crystallized ligands were redocked using extra precision (XP) for AChE and standard precision (SP) for BuChE. The obtained RMSD values were 0.3183 Å for AChE and 0.2266 Å for BuChE, confirming the validity of the adopted docking procedure.

The investigated acridine derivative exhibited stable binding within the active sites of both cholinesterase enzymes, with favorable docking scores of –8.704 kcal/mol for AChE and –8.620 kcal/mol for BuChE (Table 1).

Table 1. Docking scores of the studied ligand inside AChE and BuChE alongside the reference ligands.

Entry	Structure	Docking Score (kcal/mol)	
		AChE	BuChE
c		−8.704	−8.620
Galantamine		−11.057	-
Tacrine		-	−9.178

The investigated compound established significant interactions with key residues within the AChE active site. These included a prominent π–cation interaction between the backbone of Trp86 and the protonated nitrogen of the compound, along with multiple hydrophobic contacts involving residues such as Trp86, Leu130, Trp286, Ala127, and Phe297, and many others. While when docked with BuChE, investigated acridine derivative exhibited a water bridge as well as Pi-cation with Trp82 (Table 2).

3.2. ADMET Prediction

A potential drug candidate must undergo several evaluations to determine its ability to be absorbed and distributed within the body, including assessments of pharmacokinetic properties and toxicity profiles. In this study, a general in silico prediction of the ADMET parameters of the investigated acridine derivative was performed, and the results are summarized in Table 3.

Table 2. 2D visualization of acridine compound, galantamine, and tacrine inside the active sites of cholinesterase enzymes.

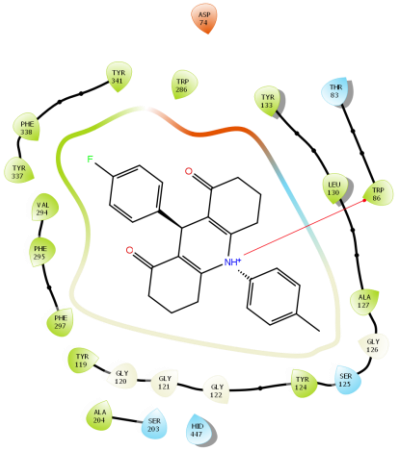
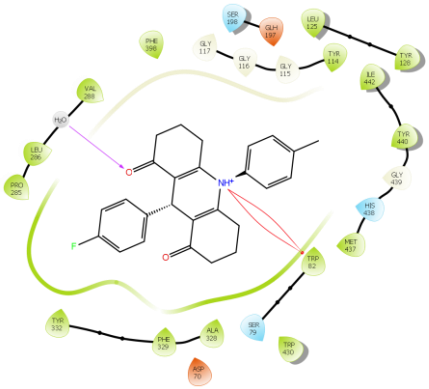
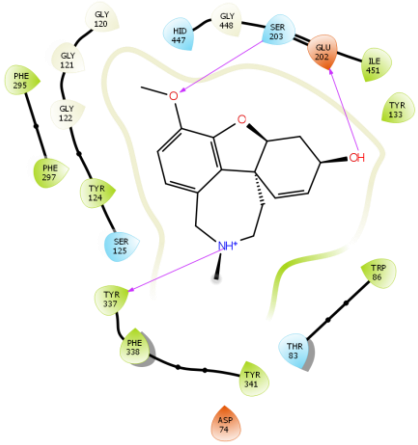
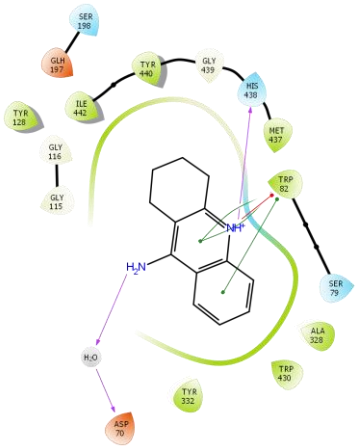
Entry	2D	
	AChE	BuChE
c		
Galantamine		-
Tacrine	-	

Table 3. ADMET predicted properties of compound **c**.

Properties	Compound c
Molecular weight (g per mole)	401.47
Rotatable bonds	2
H-bond donor	0
H-bond acceptor	3
Log $P_{o/w}$ iLOGP	3.60
Log S ESOL	−5.32
GI	High

BBB	Yes
Log Kp (cm/s)	−5.57
Bioavailability score	0.55
TPSA (Å²)	37.38
DLS score	−0.34
Predicted LD50 (mg/kg)	1200

According to the predicted parameters outlined in Table 3, compound **a** was found to respect the Lipinski's rule of five [13], exhibiting a molecular weight below 500, three hydrogen bond acceptors, no hydrogen bond donors, two rotatable bonds, and a LogP value of 3.6. The bioavailability radar further highlights the drug-like characteristics of the compound by evaluating parameters such as polarity, solubility, saturation, lipophilicity, flexibility, and size. As displayed in Figure 1, all evaluated properties of the molecule lie within the optimal range (depicted by the pink region). In addition, the drug-likeness score (DLS) provides a comparative measure of the compounds' potential as a drug candidate by comparing its features against those of approved drugs. The DLS plot depicted in Figure 2 shows that the score for compound **a** (–0.34) lies near the drug-like region (blue plot), supporting its potential as a promising lead molecule.

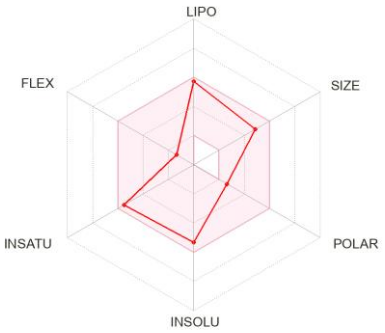


Figure 1. Bioavailability radar for compound **c**.

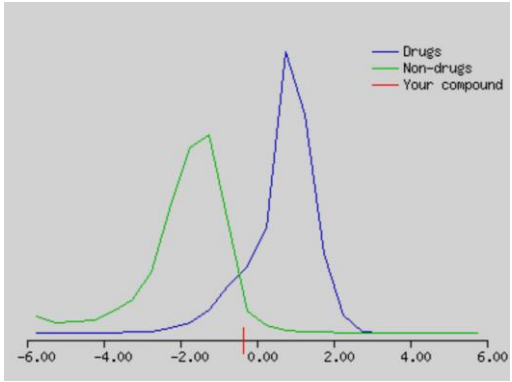


Figure 2. Drug likeness estimation curve for compound **c**.

4. Conclusions

A symmetrical acridine analogue was synthesized and evaluated through in silico studies to explore its potential as a drug candidate for Alzheimer's disease via cholinesterase inhibition. The ligand exhibited good stability within the active sites of both AChE and BuChE and established interactions with key residues associated with the inhibitory activity. Moreover, ADMET predictions yielded favorable results, suggesting that the compound possesses drug-like properties and promising pharmacokinetic characteristics.

Author Contributions: Conceptualization, Y.O.B. and A.B.; methodology, A.B.; software, Y.O.B.; validation, A.B., and N.-E.A.; investigation, Y.O.B.; resources, N.-E.A.; writing—original draft preparation, Y.O.B.; writing—review and editing, A.B.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement:

Informed Consent Statement:

Data Availability Statement:

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AChE	Acetylcholinesterase
AD	Alzheimer's disease
ADMET	Absorption, distribution, metabolism, excretion, toxicity
BuChE	Butyrylcholinesterase
DLS	Drug likeness score
NDs	Neurodegenerative disorders

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