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Exploration of New Inhibitors as Anti-Alzheimer Agents Through Molecular Modeling Methods †

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease that accounts for more than 80% of dementia cases worldwide. It is a neurological disorder that encompasses various stages of development (mild, moderate, or severe cognitive impairment), including certain psychological and behavioral syndromes such as depression, psychosis, and aggression. The main drug classes currently used to treat AD are acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitors. Advancements in bioinformatics and chemometrics have positioned the in silico approach as a pivotal tool in identifying novel therapeutic compounds. in contemporary pharmaceutical research. Therefore, we conducted a study to evaluate the effects of various newly developed N-substituted 5-chloro-2(3H)-benzoxazolone derivatives on AchE. The aim of this research paper is to utilize in-silico ADMET profiling to investigate the potential of natural analogues as inhibitors of the the AChE. using the computational techniques such as swissadme. Analysis of selected ligands with the highest affinity for the target was performed to evaluate ADME properties. The calculation of ADME properties proved that these ligands follow the rules: Lipinski, Veber and Egan and confirmed the docking results, this allowed us to select them as being probably the best inhibitors. Furthermore, they may be utilized to create novel pharmaceutical medicines to treat individuals with AD.

Keywords: Alzheimer's disease; inhibition; AChE; molecular modeling; ADME

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1. Introduction

Alzheimer's disease (AD), the major form of dementia, is a progressive neurodegenerative disease [1]. The disease manifests itself through numerous cognitive deficits, such as memory loss, cognitive impairment, difficulty thinking, and language impairment. However, the pathophysiology of the disease is not fully understood. Most approved medications can only treat the disease by alleviating its symptoms. The disease is accompanied by impaired cholinergic neurotransmission in the basal forebrain [2], leading to reduced cholinergic signaling. This impairment can be corrected with acetylcholinesterase inhibitors. Inhibition of acetylcholine (AChE) is a well-established therapeutic strategy that increases acetylcholine levels in the brain, thereby improving cognitive and memory function. This increase in AChE levels potentially improves cognitive function in individuals with AD. AChE is a key enzyme present primarily in cholinergic brain synapses and neuromuscular junctions.

For a candidate compound to become a drug, it must demonstrate appropriate pharmacokinetics, good pharmacological activity, and a low toxicity profile. It is also beneficial for molecules subjected to advanced bioactivity testing to demonstrate high bioavailability in addition to good activity. This ensures that only compounds with high potential and acceptable pharmacokinetic properties are selected for drug development [3].

In the context of Alzheimer's disease, pharmacokinetic properties were predicted using computational methods. This study examines a series of 2-hydroxy-N-phenylbenzamide derivatives as potential multitarget ligands for Alzheimer's disease. Selected compounds from the docking results were further evaluated for their physicochemical properties and ADMET characteristics. ADMET is a key element in drug development, assessing drug interactions with the body. A successful drug candidate should not only be effective against the therapeutic target but also exhibit appropriate ADMET properties at a therapeutic dose.

2. Materials and Methods

Many potential therapeutic agents are not subject to clinical trials due to their absorption, distribution, adverse metabolism, and elimination (ADME) parameters; moreover, they do not allow for verification of drug compatibility. Our study, based on the analysis of the properties of relevant pharmaceutical products, in particular: Lipinski's rule of five [4], Veber's rule [5], Egan's rule [6], surface polarity (TPSA), BBB permeability [7], gastrointestinal absorption [8], was calculated using the online property calculation tool SwissADME (http://www.swissadme.ch/) [9] by importing the chemical structure and then the SMILES format.

3. Results and Discussion

Based on the results obtained from molecular docking [10]. A computational study of 3 selected ligands that have the highest affinity for the target was carried out to evaluate the properties of ADME, and the results obtained are illustrated in Table 1.

Table 1. ADME properties for the three best AChE ligands.

	Physicochemical Properties					Lipophilicity		Pharmacokinetics		Druglikeness			
	TPSA Å²	MW g/mol	Num. Rotatable Bonds	Num. H-Bond Acceptors	Num. H-Bond Donors	MLOGP	WLOGP	GI Absorption	BBB Permeant	Lipinski	Ghose	Veber	Egan
AChE													
L18	49.33	351.01	3	2	2	4.48	5.07	High	Yes	Yes; 1 violation	Yes	Yes	Yes
L17	49.33	316.57	3	2	2	3.97	4.41	High	Yes	Yes; 0 violation	Yes	Yes	Yes
L6	49.33	351.01	3	2	2	4.48	5.07	High	Yes	Yes; 1 violation	Yes	Yes	Yes

Lipophilic is an important factor in the processes of solubility, absorption, distribution, metabolism, and excretion, as well as pharmacological activity. Hansch et al. [11] showed that highly lipophilic molecules are distributed and conserved within the lipid layers of cell membranes. For good oral bioavailability and optimal, the log P must be: $0 < \log P < 3$. Knowing that for a log P too high, the drug has low solubility, and for a log P too low, the drug has difficulties penetrating lipid membranes [12]. In light of the results obtained, all ligands L17,L18, and L6 have values between 3.97 and Log P 4.60; they possess values for log P that are positive, which indicate that these ligands are too lipophilic, but with low solubility and poor gastric tolerance [13].

According to the literature [14], a molecule has a surface area value (TPSA) below 140 Å^2, meaning it has a good prediction of oral bioavailability and ensures better transport across biological membranes. On the other hand, if the surface area (TPSA) is greater than 140, poor transport through the membranes has occurred (incomplete oral absorption). According to the values given in Table 1, it can be noted that all ligands have TPSA values = 49.33 Å^2 which means they possess excellent absorption and brain penetration of CNS drugs. On the other hand, the number of rotating bonds is also a topological parameter as a measure of molecular flexibility (threshold 10), and oral bioavailability indicates that these ligands, upon binding to a protein, only slightly change their conformation. This corresponds to the results of Table [15]. The HBAs that are in large numbers lead to low permeability through a bilayer membrane. The smaller number leads to a better permeability. From the results of Table 1, it is observed that all ligands have hydrogen acceptor numbers less than 10 (O, N) and hydrogen donor numbers less than 5 (OH, NH). Lipophilicity and the number of hydrogen bond donors appear to be key properties, as they have remained essentially constant in oral drugs over time [16]. In addition, the selected ligands have molecular weight values lower than 500 Da, so they pass through cell membranes easily and have a high level of gastrointestinal absorption, which contributes to good oral bioavailability.

Furthermore, it can be observed that compound L17 has a zero violation number, and the other compounds (L18, L6) have a violation number equal to 1 for the Lipinski rule. This justifies that all these molecules respect the rules of Lipinski, Ghose, Veber, and Egan.

4. Conclusions

Based on these results, we can confirm that these compounds do not cause any oral bioavailability problems and have good properties compared to the target drugs (native ligands), and can probably be selected as active oral drugs for this disease.

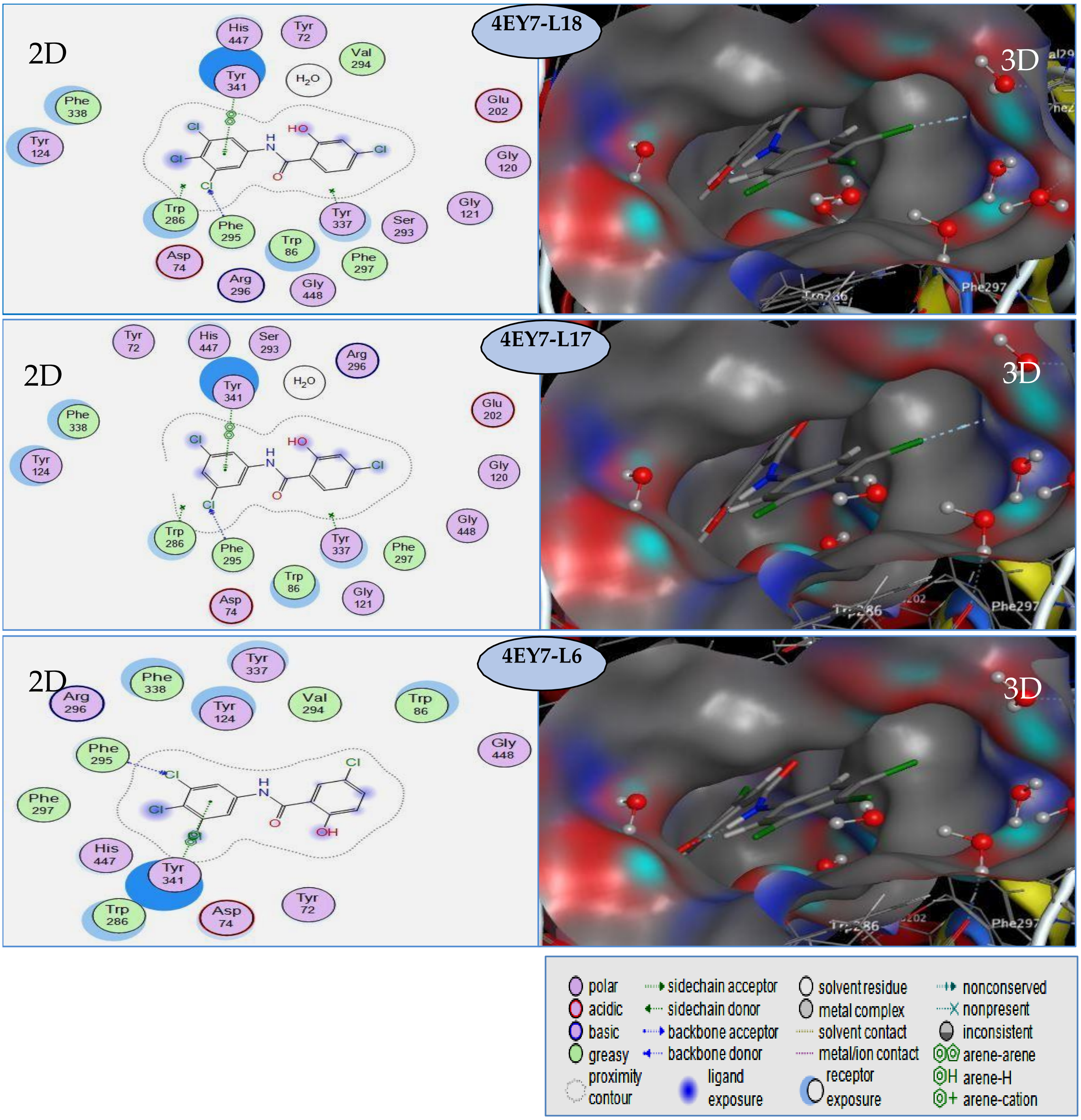

Figure 1. 2D and 3D representation of the best posed interactions of the complexes using molecular docking simulation: 4EY7-L18, 4EY7-L17 and 4EY7-L6.

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