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Review

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Comparison of *In Silico* AChE Inhibitory Potentials of Some Donepezil Analogues

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ABSTRACT

Cholinesterases are important in ensuring hemostasis in our body. Excessive increase in cholinesterase function causes various cholinergic dysfunctions. Alzheimer's is a disease characterized by loss of cholinergic activity, which is especially common in the elderly. One of the cholinesterase inhibitors most commonly used to stop the progression of Alzheimer's disease is donepezil. Due to some side effects of donepezil, the synthesis and design of new analogues that may be alternatives to donepezil are reported in the literature. In this study, molecular docking studies were performed to compare the *in silico* AChE inhibitory potential of some new structural analogs of donepezil. Molecular docking studies were performed using Autodock4.2 tools. In this study, the hypothesis emerges that especially compound 1 and compound 5 have the potential to inhibit AChE at least as much as donepezil. In silico docking studies showed that donepezil derivatives designed with bioisosteres of the piperidine ring in donepezil have high binding affinity towards acetylcholine esterase. These results need to be confirmed by synthesis of the donepezil analogues designed in the study and in vitro activity measurements.

Keywords: Acetylcholinesterase inhibitor, bioisostere, donepezil, molecular docking simulations, piperidine

INTRODUCTION

Acetylcholine is an important neurotransmitter that plays a role in the regulation of cardiac contractions, blood pressure, intestinal peristalsis and cognitive functions in the body.[1-3] Acetylcholine hydrolyzes to choline and acetate.[4] There are two basic choline esterases in humans: acetylcholine esterase and butyrylcholinesterase. In the central nervous system synapses, the amount of acetylcholine esterase is higher than the amount of butyrylcholine esterase, and the enzymes responsible for the breakdown of acetylcholine are AchEs.[5] Therefore, most of the studies in the literature on the treatment of pathophysiological conditions observed due to the decrease in the amount of acetylcholine in the central nervous system focus on AChE inhibition.[6-8]

Alzheimer's is a dementia disease characterized by a decrease in the amount of acetylcholine in the brain and loss of cognitive function. One of the most used drug groups to stop and slow down the progression of the disease is cholinesterase inhibitors. This treatment, based on the cholinergic hypothesis, aims to increase acetylcholine levels by reducing AChE activity in the brain.[9] Cholinesterase inhibitors prevent cholinesterase from hydrolyzing acetylcholine into acetate and choline components. Thus, the availability and duration of action of acetylcholine at neuromuscular junctions increases. As a result, acetylcholine stimulates the cholinergic receptors and ensures the continuation of cholinergic activity.[10]

Donepezil, rivastigmine, tacrine are FDA-approved cholinesterase inhibitors used in Alzheimer's disease.[11] Due to its significant hepatotoxic effects, tacrine is not widely used. Donepezil is safer than tacrine and rivastigmine in terms of side effect profile. However, donepezil also has some side effects such as nausea and vomiting that limit the use of the drug. There are many studies in the literature on the design of new molecules that can be bioequivalent to donepezil.[12]

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In a study in the literature on the structure-activity relationship of Donepezil, it was reported that various halogens, electron-withdrawing and electron-donating groups located in the ortho and meta positions in the phenyl part of Donepezil generally produced strong AChE inhibitors in the low nanomolar range.[13] Another study in the literature reported that Donepezil analogues made by replacing the piperidine moiety with piperazines or pyrrolidines exhibited high cholinesterase inhibitory activity.[14]

Structural analogs with similar chemical properties that maintain the same biological activity when used interchangeably are called bioisosteres. Bioisosteres make it possible to design and develop new compounds by making structural changes to reduce or eliminate undesirable properties of a compound.[15]

The piperidine ring can change the pharmacokinetic properties of the parent molecule, such as lipophilicity and stability against metabolism. Replacing the phenyl spacer that acts as a bridge in a drug backbone with an sp3-rich bioisostere such as piperidine reduces the molecular planarity of the drug and increases its solubility. While one of the enantiomers of substituted piperidine derivatives may exhibit higher biological activity as a eutomer, the other may not show biological activity as a distomer. In structures containing a piperidine ring instead of a phenyl ring Intramolecular π–π stacking interactions between aromatic phenyl rings are not observed and the lipophilicity of the molecule decreases.[16] Various cyclic structures (Figure 1) that may be bioisosteres to piperidine have been reported in the literature.[17-20] There are many drugs containing piperidine rings that have received FDA approval.

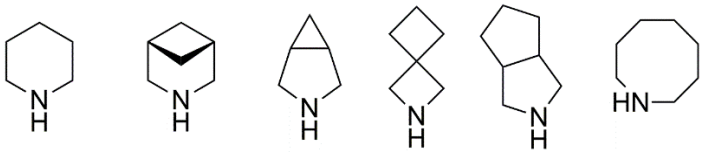

Figure 1. Some cyclic bioisosteres of piperidine

In silico molecular docking studies have an important place in the discovery of new drugs in terms of predicting the affinity of ligands to target proteins and their interactions with the target site. Molecular docking studies save both time and money in the discovery of new molecules.[21]

In this study, the in silico AChE inhibitor potentials of some structural analogues of donepezil (Figure 2), designed by replacing the piperidine ring in donepezil with bioisosteres, were compared.

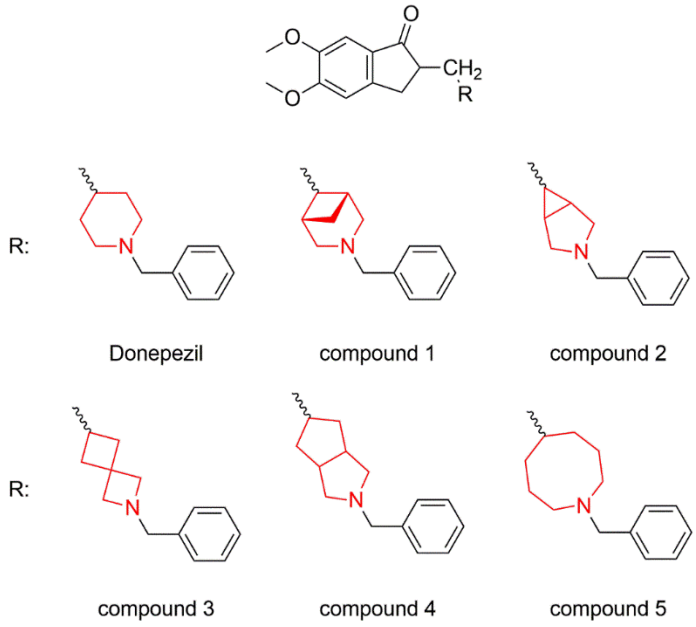

Figure 2. Some structural analogues of donepezil

METHODS

The crystal structure of AChE (1EVE) and was attained from the Protein Data Bank. Ligand and receptor structures were prepared for molecular docking using Autodock4.2 tools. The grid size was set to 60 × 60 × 60. The spacing between grid points was separated by 0.375 Å. Docking studies were performed on the binding sites of donepzil for the receptor. Grid center was designated at dimensions (x, y, and z): 2.12, 66.13, 67.41. The binding positions of the ligands were determined using the Lamarckian genetic algorithm. A maximum of 10 conformers were considered during the docking process for each compound. Clustering conformations were analyzed with RMSD tolerance of less than 2.0 Å. The binding free energy scores were ranked by the lowest energy representative of each cluster. Protein-ligand interactions were visualized by using Discovery Studio Visualize.[22]

RESULTS

According to the in silico results in Table 1, donepezil bound to 1EVE with a free binding energy (ΔG:) of -8.51 kcal/mol, while compound1 bound to 1EVE with the lowest binding energy (ΔG: -8.87). Additionally, other compounds showed high binding affinity for 1EVE (ΔG>-7.50). The lower the binding energy a ligand binds to an enzyme, the higher the binding affinity of that ligand to the relevant enzyme.[23]

Table 1. The binding affinity of the compounds and donepezil to AchE

Compounds	AChE (ΔG, kcal/mol).
Donepezil	-8,51
Compound 1	-8,87
Compound 2	-7,57
Compound 3	-8,07
Compound 4	-8,21
Compound 5	-8,59

Based on the docking results shown in Figure 2, In 1EVE and compound complex, two hydrogen bonds were formed. One of the hydrogen bond was between 6-methoxy group of the indanone and amine group (NH2) of ARG289. The other hydrogen bond was between carbonyl (C=O) group of the molecule and hydroxyl group (HO-Ph) of TYR121. Hydrophobic interactions occur between the catalytic residues of the protein (PHE330 and TRP84) and the azabicyclo[3.1.1]heptane ring of the compound 1. π-π stacking interaction was observed between aromatic benzene rings of the compound 1 and peripheral anionic site (PAS) residue TYR121.[24] Donepezil interacts primarily with residues Glu 199, His 440, Phe 330, Trp 84, Tyr 334, Tyr 121, Phe 331, Phe 288, Ser 286, Phe 290, Arg 289, Trp 279 and thus tightly binds to AchE.[25]

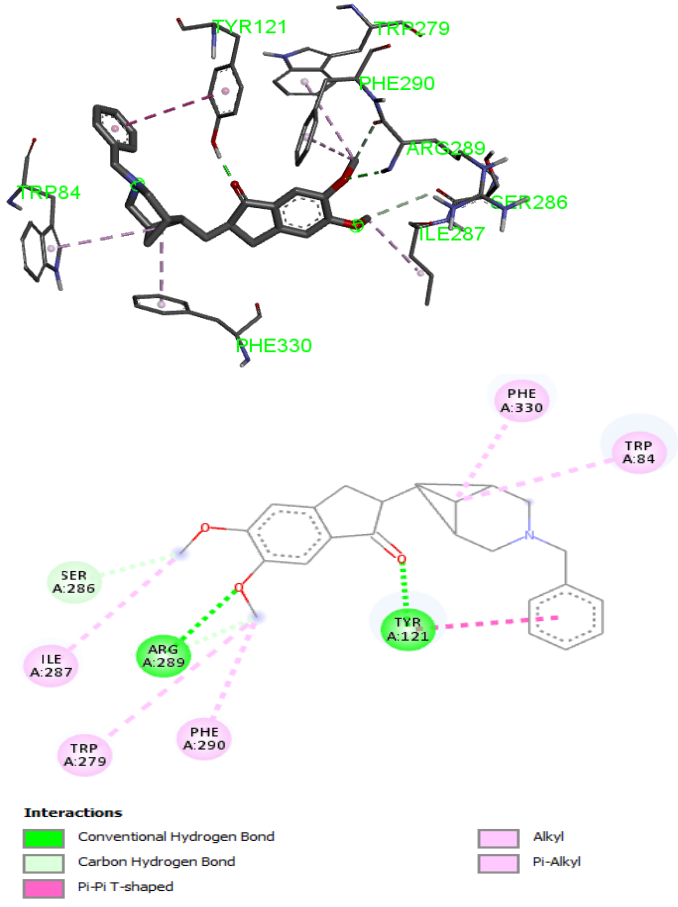

Figure 3. Docking pose and ligand interaction diagram of compound 1 with 1EVE.

DISCUSSION

In silico docking studies, donepezil derivatives designed with bioisosteres of the piperidine ring in donepezil were found to have high binding affinities towards acetylcholine esterase. In this study, the hypothesis emerges that especially compound 1 and compound 5 have the potential to inhibit AChE at least as much as donepezil. Of course, this hypothesis needs to be confirmed by synthesis of the donepezil analogues designed in the study and in vitro activity measurements.

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