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Review Article

Theoretical Study of Quinoline Derivatives Involved in Neurodegenerative Diseases

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ABSTRACT

Neurodegenerative diseases include more than 600 affections that alter the structures of the brain, the best-known being Alzheimer's disease and Parkinson's disease. These diseases can influence an individual's movement, speech, memory, intelligence, and much more; because neurodegenerative diseases are so complex. Although, it remains a mystery why only degeneration happens in neurodegenerative diseases. A series of quinoline derivative has been synthesized with a very high heterocyclic class in a wide range of biological activities. These derivatives have been shown to be selective inhibitors of Acetylcholinesterase (AChE) with IC50 values. This work is to study the inhibition of AChE enzyme involved in the Alzheimer's disease by computational methods for molecular modeling and simulation of macromolecule. These results will probably help in the development of an effective therapeutic tool to fight against the development of Alzheimer's disease.

Keywords: Acetylcholinesterase (AChE); Alzheimer's disease; Quinoline derivatives; Molegro Virtual Docker (MVD)

INTRODUCTION

Neurodegenerative diseases (NDDs) are described defined as disorders with selective loss of neurons and distinct involvement of functional systems defining clinical presentation [1]. Neurodegenerative diseases such as Alzheimer's and Parkinson's disease share a common pathogenetic mechanism involving aggregation and deposition of misfolded proteins which leads to progressive central nervous system disease [2]. Comprehensive biochemical, genetic and molecular pathological examinations have expanded this definition.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, clinically characterized by an impairment of cognitive function. Cholinergic deficit or the loss of cholinergic neurons associated with AD leads to the decreased activity of acetylcholine (ACh) [3]. Acetylcholinesterase (AChE) plays a key role in the regulation of the cholinergic system and secretory organs by rapid hydrolysis of the neurotransmitter acetylcholine (ACh) at an extremely fast turnover rate [4]. Particularly, the cholinergic system is altered and treatment strategies in AD are centered around the development of acetylcholinesterase (AChE) inhibitors that improve cholinergic transmitter activity. Hence, AChE is one of the plausible cause which is involved in the selective neuronal cell death observed in AD [5,6]. It has been demonstrated in earlier studies that the inhibition of AChE holds a key role not only to enhance cholinergic transmission in the brain but also to reduce the aggregation of β-amyloid and the formation of the neurotoxic fibrils in AD [7]. The use of natural compounds in drug discovery precedes recorded human history probably by thousands of years [8]. AChE inhibitors are important research topics because of their wide range of associated health implications, especially useful in the treatment of Alzheimer's disease. The finding of the novel AChE inhibitors is presented in this research.

Quinoline derivatives have represent an important class of nitrogen-containing heterocycles as they are useful in dyes and intermediates in organic synthesis for new drug development [9,10]. Therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activities in medicine. In recent years, high attention has been focused on their synthesis as they possess broad spectrum of biological and pharmacological activities as an antiviral, antimalarial, anti-inflammatory, antimicrobial, bactericidal, fungicidal and anti-cancer properties [11-13]. Because of their broad spectrum of biological and pharmacological properties and plays major role in the field of pharmaceuticals [14], the profiles of quinolines possess antitubercular property [15], anti-microbial, anti-cancer, anti-malarial and anti-inflammatory properties are documented [16,17].

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In this study, we investigated quinoline derivatives which could be synthesized and evaluated as acetylcholinesterase (AChE) inhibitor that may play an important role in the treatment of Alzheimer's disease (AD).

MATERIALS AND METHODS

Protein and ligands preparation

Data of acetylcholinesterase (AChE) was downloaded and done from Protein Data Bank (www.rcsb.org/pdb) (code 4BTL) with three-dimensional structure obtained by X-ray diffraction (resolution 2,5 Å) [18]. Molecular docking studies were performed with Molegro Virtual Docker 5.5 (MVD), to derive the affinity and mode of binding of the inhibitors to the active site of the AChE. The minimization is performed using a fairly simple force field (it useful in the Piecewise Linear Potential (PLP)) potentials for steric and hydrogen bonding interactions and the coulomb potential for the electrostatic forces. Initially the objectives proposed by Gehlhaar et al. [19] and later taken up and extended by Schulz et al. [20]. The enzyme contains water before the elimination and co-crystallization the dimer form with 543 groups, 4207 atoms, and 4411 bonds (Figure 1). The protein was prepared for the molecular docking by adding all hydrogen atoms using standard procedures, water molecules and other heteroatom of co-crystallization were deleted (Figure 2), the binding energy was observed in each ligand protein complex.

In this study, we used Quinoline derivatives which are synthesized (Table 1) [21]. The ligands used are drawn with Hyperchem 8.0.8 software [22]. To calculate a molecular optimization is done for the ligands, using the force field MM +, and the polka-ribiere algorithm (conjugate gradient), the optimization of inhibitors was performed with Hyperchem 8.0.8 to achieve the most stable conformation. For this, we applied the semi-empirical method (AM1) [23].

We have taken six ligands as an inhibitor of acetylcholinesterase to be considered in this study. The skeleton of Quinoline considered as main skeleton; and we have changed the radical (R1 and R2) according to the following which is shown in the Figure 3.

Docking and building complexes

Molecular docking is an efficient tool for investigating receptor-ligand interactions and for virtual screening, which plays a key role in rational drug design, especially when the crystal structure of a receptor or enzyme is available [24]. The atomic structures of protein molecules provide a healthy information for understanding the biological roles of proteins with geometric characterization, we can gain important insight on the structural basis of proteins [25].

Ligand docking studies were performed by MVD, which has recently been introduced and gained attention among medicinal chemists. MVD is a fast and flexible docking program that gives the most likely conformation of ligand binding to a macromolecule. The "MolDock Score" docking function used by MVD is a derivative of the PLP function [26]. This function contains additive terms for energies of hydrogen bonds, electrostatic interactions and hydrophobic interactions. MolDock Score is based on a new heuristic search algorithm that combines differential evolution with a cavity prediction algorithm [27]. Evolutionary algorithms are generic and iterative optimization methods.

MolDock Score automatically identifies potential binding sites (cavities) using a flexible cavity detection algorithm, as there is no dependence on the orientation of the target molecule, so an arbitrary number of directions may be used. The active site exploited in docking studies was defined through the calculated cavity. The fitness of a candidate solution is derived from the docking scoring function, E_{score} and is defined by the following energy terms: $E_{score}=E_{inter}+E_{intra}$

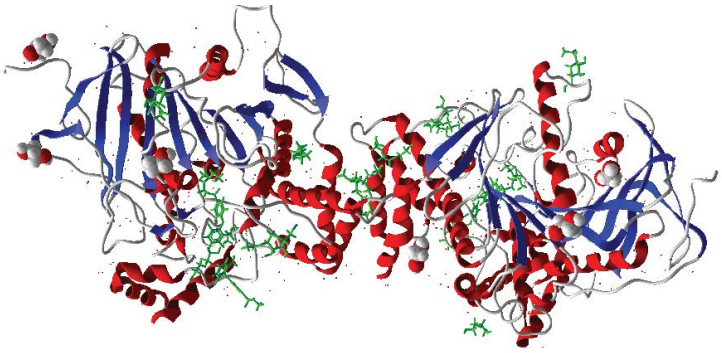

Figure 1: The dimerous form of AChE.

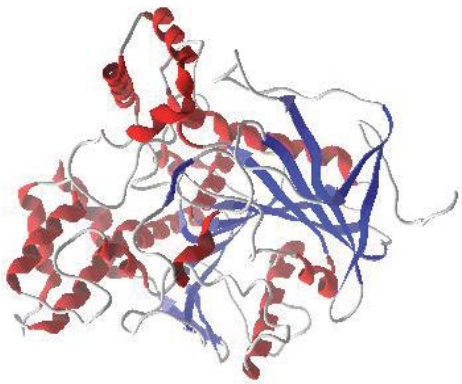

Figure 2: Simplified model AChE.

Table 1: The different ligands and their respective IC_{50} values.

Compounds	R_1	R_2	IC_{50} (µM)
Ligand -1	H	0	179
Ligand -2	CH_3	0	400
Ligand -3	H	$-C_2H_4NHC_2H_4NH_2$	172
Ligand -4	CH_3	$-C_2H_4NHC_2H_4NH_2$	142
Ligand -5	H	$-C_2H_4NHC_2H_4NHC_2H_4NH_2$	77.2
Ligand -6	CH_3	$-C_2H_4NHC_2H_4NHC_2H_4NH_2$	102

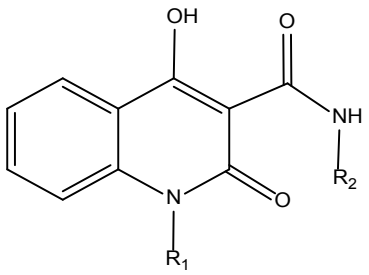

Figure 3: Skeleton of Quinoline.

Where E_{inter} is the ligand–protein interaction energy

E_{intra} is the internal energy of the ligand

In molecular docking, the evolutionary algorithm seeks to describe the interactions between the ligand and the protein target where the degrees of freedom correspond to the positions, orientations and conformation of the ligand and the receptor [28].

RESULTS AND DISCUSSION

Acetylcholinesterase is an important enzyme for developing a new drug against AD. Corresponding inhibitors are currently being explored as potential drugs for the clinical treatment of AD. Inhibitors of Acetylcholinesterase are used to relieve symptoms or slow the progression of AD. In this case several researchers suggest that the development of Acetylcholinesterase inhibitors leads to find new potent drugs for the treatment of AD [29-31].

To study the mode of interaction of different inhibitors with the active site of the AChE enzyme of Alzheimer's disease by molecular docking, we used the latest version of the Molegro (MDV) software [19,20] it shows hydrogen bonds, the latter are the most important among the strong bonds.

After ligand building, we proceed to positioning it in the active site of AChE. For this, we used the molecular docking module using Molegro (MDV) software. Once the ligand-receptor complex is formed, it will adopt the most stable conformation, i.e., the lowest energy level.

The purpose of the Dock application is to look after favorable conformational binding between medium size ligands and a semi soft macromolecular target, which is usually a protein. For each ligand, a number of conformations called poses were generated to identify favorable binding modes [32]. The search for binding modes is generally constrained to a small specific region of the receptor called the active site.

To obtain better potential link sites in acetylcholinesterase a maximum of five cavities have been detected using default parameters (Figure 4). The volume and area are presented in Table 2.

The best poses of the MVD score for the acetylcholinesterase host study with the different quinolines in the first cavity are listed in Table 3, which presents the energy of interaction between the ligand and the protein, marked by MolDock Score and the hydrogen binding energy of each ligand.

The formation of a stable complex depends on the binding of the inhibitor in the active site. Figure 5 shows that ligand-5 takes the form of the enzyme cavity formed by the residues of the active site (Table 3), which means that there are interactions that stabilize the complex and then better fixation of this inhibitor at the active site.

This ligand-5 reliability is confirmed by comparing the experimental values of IC50 in Table 1 with the energy values calculated by Moldock Score in Table 3, so it can be said that ligand-5 at the lowest value of IC50 = 77.2 µM and of energy -140.957 kcal/mol, so it represents a better inhibition compared to other inhibitors. Ligand-5 is the most potent and selective acetylcholinesterase inhibitor identified in this study; this is due to the length string. This experimental result has been confirmed in theory.

The MVD program allowed us to predict the interaction energy between ligand-5 and AChE, which is estimated at -140.957 kcal/mol. Figure 5 shows that ligand-5 penetrates well into the active site of the enzyme, forming 4 hydrogen bonds. The formed complex is stabilized within cavity 1 (Figure 6) of the AChE by hydrogen interactions by the residues His447, Tyr133, Asn87 and Thr83 (Figure 7).

According to the results obtained with the Molegro, we notice that ligand-5 has the lowest energy " -140.957 Kcal / mol " so it is the most stable.

We measured the distances between inhibitors of the chain groups responsible for the interaction of the different quinoline derivatives in cavity 1 (Table 4). The lengths and the spatial orientations of the various hydrogen bonds obtained are summarized in Table 4.

Interactions between 2.5 Å and 3.1 Å are considered very strong and those of 3, 1 Å and 3.55 Å are assumed to be average. Higher interactions of 3.55 Å are weak or absent [33].

Molecular docking with MDV of ligand-5 in the active site of acetylcholinesterase gives an energy -140,957Kcal/mol. This energy is reflected in the presence of four hydrogen bonds (Figure 5 & 7), the first two bonds of which are formed between ligand-5 hydrogen

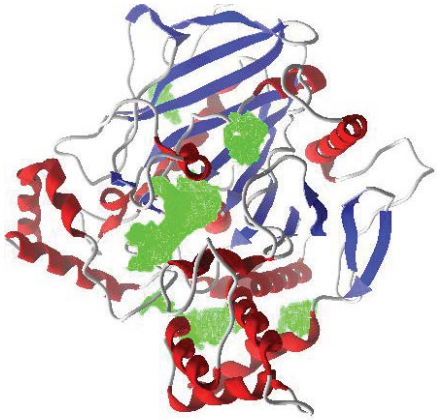

Figure 4: Cavity acetylcholinesterase.

Table 2: Chemical properties of our cavities.

Cavity of 4BTL	Volume (Å ^{3})	Surface area (Å ^{2})
Cavity 1	195.584	526.08
Cavity 2	155.136	500.48
Cavity 3	70.656	220.16
Cavity 4	53.248	202.08
Cavity 5	34.304	120.32

Table 3: Study of prevalence of oral lesion among the 304 HIV/AIDS patients.

Compounds	MolDock Score[a]	Interaction[b]	Hbond
Ligand -1	-83.983	-108.912	-2.158
Ligand -2	-83.783	-113.282	-3.629
Ligand -3	-114.492	-136.408	-7.273
Ligand -4	-115.81	-154.822	-6.825
Ligand -5	-140.957	-166.176	-9.601
Ligand -6	-138.617	-170.976	-8.32

Note: [a]: MolDock score calculated by the sum of external and internal ligand interaction (protein-ligand interaction) using the Virtual 1.2.0 molecular viewer.
[b]: Total interaction energy between the pose and the target molecules (s).

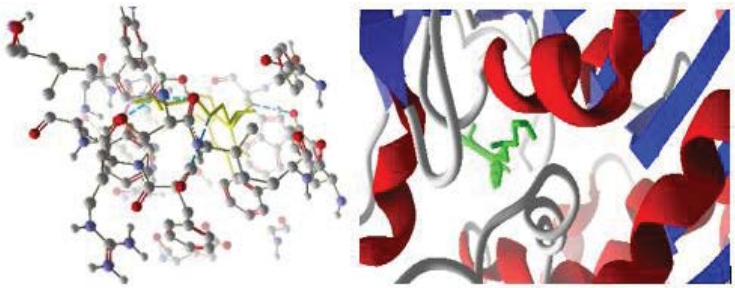

Figure 5: The predicted binding orientation of ligand-5 in the active site of acetylcholinesterase.

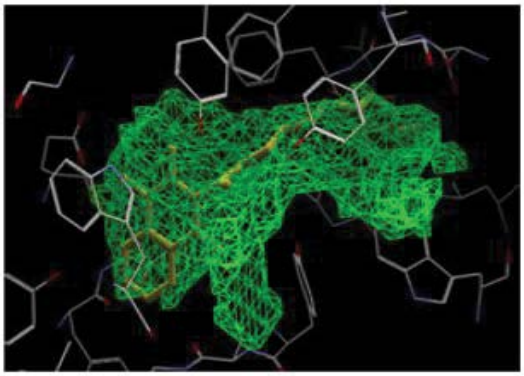

Figure 6: Positioning of ligand-5 (colored yellow) in cavity 1 (colored green).

Figure 7: The binding mode between ligand-5 and the acetylcholinesterase binding site in cavity 1.

Table 4: Representation of hydrogen bonds.

Compounds	Amino acids	Atom of the ligand	Distances Å
Ligand -1	Tyr133	N	3.08
	His447	N	2.59
Ligand -2	His447	N	2.97
	His447	N	3.23
Ligand -3	Tyr337	O	2.72
	Glu202	N	2.41
	His447	N	2.6
Ligand -4	Tyr337	O	2.95
	Glu202	N	3.16
	Tyr133	O	2.66
Ligand -5		N	3.11
	Asn87	N	3.1
	Thr83	N	2.77
	His447	N	3.1
Ligand -6	Tyr124	O	2.79
	Glu202	N	2.6

and nitrogen from the Tyr133 residue at a distance of 3.11 Å, and oxygen from the Tyr133 residue at a distance of 2.66 Å, the second is formed between ligand-5 hydrogen and nitrogen from the residue Asn87 separated by a distance of 3.10 Å and the third is formed between ligand-5 hydrogen and nitrogen from the residue Thr83 separated by a distance of 2.77 Å. We also observed that the increase in interactions between the inhibitor and the main residues improves inhibitory activity (inhibitor stability).

CONCLUSION

Computational Molecular Docking is a widely used technique to identify the theoretical free energy of the macromolecular complex. It has been clearly demonstrated that the approach used in this study has been successful in finding new inhibitors in ligand-5, in particular, showed a high affinity with a Moldock score of -140.957 kcal/mol against acetylcholinesterase.

After comparing the results of the theoretical study of acetylcholinesterase inhibition with those of the experimental study, it can be seen that the two results are compatible for the ligand-5 and this information can provide insight into the development of a new anti-Alzheimer's drug.

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