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Study of Acetylcholinesterase and Butyrylcholinesterase (AChE/BuChE) Inhibition Using Molecular Modelling Methods †

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disease that affects the majority of people worldwide. To date, there is no cure for the disease, so new therapeutic targets need to be identified and studied. Acetylcholinesterase (AChE) and Butyrylcholinesterase (BuChE) are the main targets of drugs for the treatment of AD. In order to identify new inhibitors, a newly synthesized series contained thirty seven 2-hydroxy-N-phenylbenzamide derivatives were tested for study the inhibition of enzymes associated with this disease. Our work focuses on the use of molecular modeling methods based on molecular docking, QSAR and ADME properties prediction. The molecular docking results discussion is based on a number of parameters. Analysis of these obtained results showed that the ligands L18, L17 and L6 have a high inhibitory effect in the case of the enzyme AChE, while the ligands L6′, L30′ and L4′ have a high inhibitory effect in the case of the enzyme BuChE. In addition, the ADME-T properties calculation proved that these ligands respects the rules: Lipinski, Veber and Egan, this allowed us to select them as being probably the best inhibitors of Alzheimer's disease (AD). Then, a QSAR model was developed to explain and predict the inhibitory activity of a series of compounds using different descriptors. This model has been validated by two methods: internal and external.

Keywords: AChE/BuChE; 2-hydroxy-N-phenylbenzamide derivatives; molecular docking; QSAR; ADME-T; interactions

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1. Introduction

Alzheimer's disease is characterized by progressive cognitive decline due to multiple pathological changes in the brain, primarily in cholinergic neurons of the basal forebrain [1]. This disease is the most common form of dementia and is associated with progressive and irreversible intellectual decline, resulting in impairment of mental performance and behavior, resulting in loss of autonomy [2]. Acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) are two different types of cholinesterases that hydrolyze acetylcholine (ACh) into acetate and choline, respectively [3]. AChE hydrolyzes ACh in normal brain. Therefore it is a major drug target [4]. To this end, we selected a series of recently synthesized derivatives 2-hydroxy-N-phenylbenzamide as inhibitors to study their effects on the two targets: AChE and BuChE, which are responsible for these diseases. It is to this approach of the treatment by inhibition of AChE and BuChE that we are interested in this

work in order to contribute to the development of new inhibitors using different molecular modelling techniques such as: Molecular docking, QSAR and ADME properties.

Molecular docking was performed to analyze the complex score and different types of interactions present between certain amino acids of the protein studied and that of ligands. On the other hand, the QSAR has become, at present, an indispensable tool in the field of drug design, especially in the absence of information on the active site of the enzyme. Technically, this approach is mainly based on the choice of descriptors and the learning algorithm [5].

Finally to reduce the failure rate of drug candidates the implementation of filters ADME (Absorption Distribution Metabolism and Elimination)-Tox (Toxicity) chemotherapies in any screening process gave good pharmacokinetic performance and bioavailability, as well as excellent results.

2. Materials and Methods

Molecular docking, QSAR and ADME were carried out in order to study 37 compounds that belong to the 2-hydroxy-N-phenylbenzamide derivatives and test their AChE and BuChE inhibitory activities, MOE [6], HyperChem software (Version 7.0, Hypercube, USA, http://www.hyper.com, accessed on), and others softwares were used to find the best compounds with high affinity.

3. Results and Discussion

The molecular docking simulation performed by keeping the main chain rigid, while the lateral chains remain flexible, and the best conformations of the ligands were classified according to the three parameters: score energy (S-score, kcal/mol), interactions (types and distances) and the RMSD values.

3.1. Interaction between Compounds and Targets (AChE/BuChE)

The results of the molecular docking of the three best compounds of 37 *2*-hydroxy-N-phenylbenzamide derivatives with active site residues of the AChE and BuChE targets are regrouped in Table 1.

We can see that the Based on the binding score energy values, compound L18 (−7.799 kcal/mol) was found to be the most potent inhibitor of the AChE target compared to the compounds L6 (−7.368 kcal/mol) and L17(−7.461 kcal/mol), these results confirmed by establish two interactions for each compounds with the binding site of AChE target

It can be observed that the complex formed by the compound L18 have a low score energy values of (−7.799 kcal/mol, which are very close to native ligand Donepezil (−11.247 kcal/mol). On the other hand, the RMSD value of the AChE-L18 complex is: 1.014, which are less than 2 A [7,8], implying that this compound fit well into the pocket of the AChE (Table 1).

It is also evident that compound L18 forms one strong hydrogen bond [9] with the active site residues of the AChE target, PHE295 was making hydrogen bond (bond distance = 3.40 Å) with the Cl18 atom of the compound L18. In addition, the same compound established one hydrophobic interaction with the binding site residues of AChE:

TYR341 was making Pi-Pi interaction with the 6-ring of the compound L18 with distances: 3.83 Å (Table 1 and Figure 1). This means that they have been detected the suitable active site of the enzyme for the study, which many recent papers [10,11] are located.

In the case of the BuChE, we found that compound L6′ (−6.603 kcal/mol) was present the most high affinity against to the BuChE target compared to the compounds L4′ (−5.250 kcal/mol) and L30′ (−5.590 kcal/mol).

It is also evident that compound L6′ forms two strong hydrogen bonds [9] with the active site residues of the BuChE target, HOH2153 was making hydrogen bond (bond distance = 2.97 Å) with the O16 atom of the compound L6′. The second, SER198 was establishing another hydrogen bond (bond distance = 3.08 Å) with Cl22 of the compound L6′

(Table 1 and Figure 1). In this regard, many recent studies [12,13] confirmed that SER198 and molecular water play a central role in inhibiting the BuChE target.

On the other hand, the RMSD value of the BuChE-L6′ complex is: 0.979, which are less than 2 A [7,8], implying that this compound fit well into BuChE binding site (Table 1).

Table 1. Docking score energy, RMSD values and interactions of studied compounds and clinical test with active site residues of AChE/BuChE.

Compds	IC_{50} Value(μM)	S-Score (kcal/mol)	RMSD (Å)	Bonds between Atoms of Compounds and Active Site Residues				
				Atom of Compound	Involved Receptor Atoms	Involved Receptor Residues	Type of Interaction Bond	Distance (Å)
AChE								
L6	51.06 ± 0.49	−7.368	2.115	Cl18	N	PHE295	H-acceptor	3.37
				6-ring	6-ring	TYR341	pi-pi	3.98
L17	50.15 ± 0.26	−7.461	0.726	Cl20	N	PHE295	H-acceptor	3.47
				6-ring	6-ring	TYR341	pi-pi	3.83
L18	57.78 ± 4.05	−7.799	1.014	Cl18	N	PHE295	H-acceptor	3.40
				6-ring	6-ring	TYR341	pi-pi	3.83
Donepezil	56.10 ± 1.41	**−11.247**	0.408	N-14	O	HOH931	H-donor	2.79
				C-15	6-ring	TYR337	H-Pi	4.11
				6-ring	6-ring	TRP286	Pi-Pi	3.73
BuChE								
L4′	186.47 ± 15.69	−5.250	4545	O16	O	HOH2153	H-donor	3.04
				Cl22	O	ALA328	H-donor	2.96
				Cl27	OE1	GLU197	H-donor	3.23
				6-ring	O	HOH2055	pi-H	3.62
L6′	102.72 ± 0.97	−6.603	0.979	O16	O	HOH2153	H-donor	2.97
				Cl22	OG	SER198	H-donor	3.08
L30′	140.07 ± 6.20	−5.590	1.930	O16	O	HOH2153	H-donor	2.93
				Br22	OG	SER198	H-donor	3.11
Tacrine	38.40 ± 1.97	**−6.193**	0.316	C1115	6-ring	TRP82	Pi-H	3.96
				6-ring	5-ring	TRP82	pi-pi	3.80

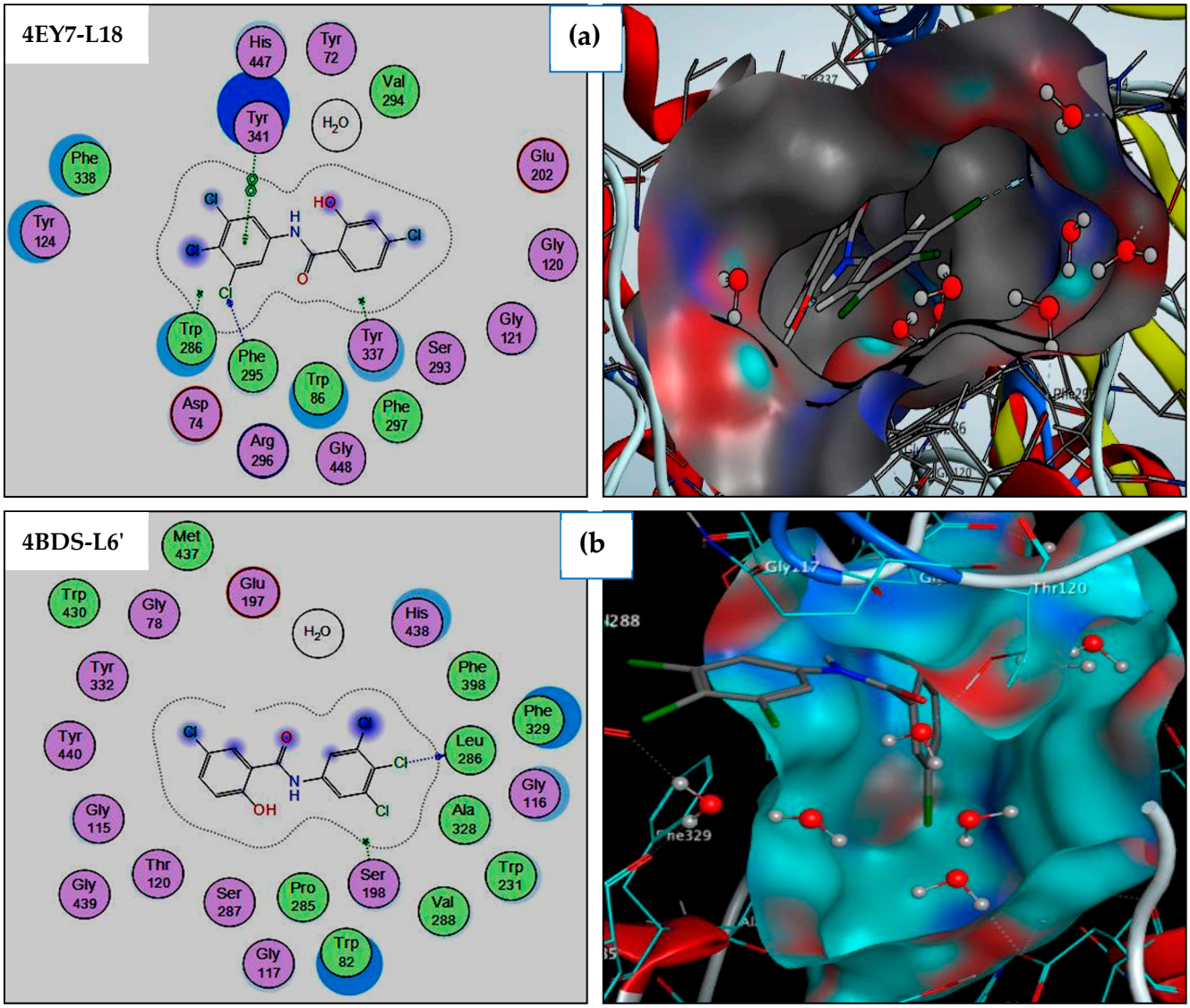

Figure 1. 2D and 3D representation of the best pose interactions of complexes: (**a**): 4EY7-L18, (**b**): 4BDS-L6′ using molecular docking simulation.

3.2. QSAR Modeling

Correlation between BuChE inhibitory activity and calculated descriptors given by the following relation:

$$\text{Log } (1/IC50) = 5.098 - 0.165\ \text{LogP} + 0.005\ \text{MW} - 0.037\ \text{MR} - 0.94\ qC3' - 0.566\ qC4'$$

$$n = 25;\ R = 0.869;\ R2 = 0.756;\ S = 0.0516;\ F = 11.749;\ Q = 6.470;\ p < 0.001$$

Our results suggest that the best QSAR model obtained is the one using the following descriptors: log p, MR, MW, qC3′, qC4′. Knowing that the reliability and predictive power of this QSAR model has been validated by the right values R^2adj, q^2, SPRESS.

In addition, a strong correlation was observed between experimental and predicted values of BuChE inhibitory biological activity, indicating the reliability and validity of the QSAR model obtained.

3.3. Evaluation of ADME Properties

The molecular structures of the best compounds L18 and L6′ were analyzed using the SwissADME server (http://www.swissadme.ch/, accessed on) to ensure adherence to compliance with Lipinski's, Veber's, and Egan's rules, which calculates diverse physicochemical properties of ligand molecules.

According to the drug-likeness property analysis, the tested compounds exhibit an important number of hydrogen bond donors < 7 (n-HD:(0~7)) and acceptors < 12 (n-HA: (0~12)). In addition, these compounds have molecular weights in the range of 100–500 g/mol, MLogP and WLogP values < 5, and also have an index of compound flexibility called a number of rotatable bonds (NRB); nROTB values < 11. On the other hand, the most significant feature of these compounds is their TPSA values, which are often used as a model to assess the ability of molecules to cross the blood–brain barrier (less than 140 A), as is the case here. Furthermore, the investigated compounds fully comply with the Lipinski, Veber, and Egan rule, which mean they represent a good drug-likeness profile. Finally, toxicity prediction results indicated that none of the compounds were toxicity.

4. Conclusions

The molecular docking study revealed that ligands: L18; L17; L6 are the best inhibitors in the case of AChE, and that ligands L6′; L30′ and L4′ in the case of BuChE, this is justified by the presence of different types of interactions (mainly hydrogen bonds with low energy score values).

We also note that the increase in interactions between inhibitors and residues of the active site improves affinity (Energie score), this means that these complexes have the lowest score energies compared to others, This is confirmed by the value of RMSD (root-mean-square deviation) that does not exceed 2 Å in most complexes formed by these inhibitors and the two enzymes AChE and BuChE.

In addition, a strong correlation was observed between experimental and predicted values of BuChE inhibitory biological activity, indicating the reliability and validity of the QSAR model obtained.

the combination of several molecular modelling methods may be useful in the interest of discovering new anti- drugs Alzheimer's, and these methods allow us to identify new inhibitors have raised potential against this disease and they can be suggested as new drugs.

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