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Original Research Paper

Molecular Docking of New Active Compounds Towards the Acetylcholinesterase Enzyme

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Abstract: Molecular docking is a key instrument in structural molecular biology and computer-assisted drug design. The objective of ligand-protein docking is to expect the main binding mode(s) of a ligand with a protein of known three-dimensional structure. Effective docking methods search high-dimensional spaces effectively and finding a scoring function that correctly ranks candidate dockings (Morris *et al*., 2008). In this study molecular docking study was performed for 54 Acetylcholinesterase Inhibitors compounds.

Keywords: Docking, Acetylcholinesterase Enzyme, Molecular Modeling

Introduction

Molecular docking is a computational process for the insertion of ligands (often small molecules) into the binding site of their receptor (macromolecular target). Docking algorithms and scoring functions can generate structures of receptor–ligand complexes, ranking compounds and estimating binding energies/affinities (Sousa *et al*., 2013). The objective of this work is to perform a molecular docking in order to determine the affinity of a total of DL0410 and its 49 DL0410 derivatives and four marketed molecules, tacrine, galantamine, donepezil and rivastigmine). Which were taken from the literature (Pang *et al*., 2017).

Molecular Docking Study

Protein Preparation, Grid Generation and Ligand Preparation

Protein enhancement and grid generation are required steps for suitable docking. The three-dimensional X-ray crystallographic structure of the acetylcholinesterase protein was taken from protein data bank. Protein was prepared by eliminating water molecules, needless atoms, removing the alternate conformations and adding hydrogen.

The grid generation describes a region in a receptor where binding interaction can happen. Before launching the molecular docking, the geometry of all molecules needs to be optimized (Vora *et al*., 2019).

All these steps were performed using (Schrodinger, Maestro) software.

Results and Discussion

Molecular docking study was performed for 56 Acetylcholinesterase Inhibitors compounds. The molecule 3.2 has the highest score (-13,681), the different types of interactions which may show the binding of the molecule 3.2 with the AChE are shown in (Fig. 1). The compound 3.2 was situated in the active site, interacting with four residues, the nitrogen 8403 interacts with TRP 279 by Pi -cation interaction, the aromatic structure of compound adopted a suitable orientation for its binding to PHE330 via Pi-cation interaction, carbonyl, Hydrogen 8451 forming hydrogen bonds with PHE288, SER122, respectively.

Compound 3.4.

The Nitrogen (8379) interacts with the Amino acid TRP279 assuring a pi-cation interaction, (PHE288, SER122) forming hydrogen bonds with (carbonyl 8387, Hydrogen 8460) respectively (Fig. 2).

Compound 2.3

Presence of hydrogen bond between the ARG289 and carbonyl8400, Pi-Pi staking between the aromatic ring of the compound and TRP 279, pi-cation between N8383 and TRP84. Three-dimensional docking model of compound 2.3 with AChE is shown in Fig. 3.

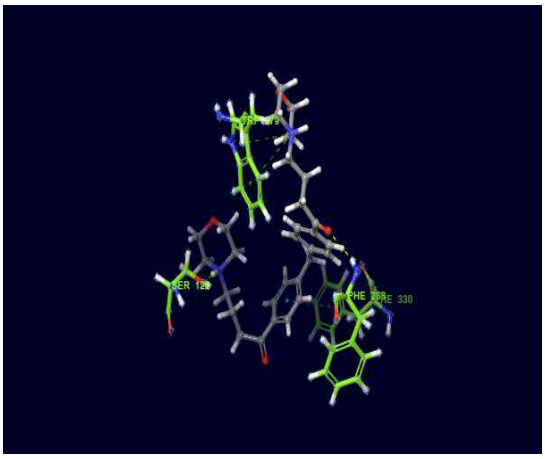

Fig. 1: Three-dimensional docking model of compound **3.2** with AChE

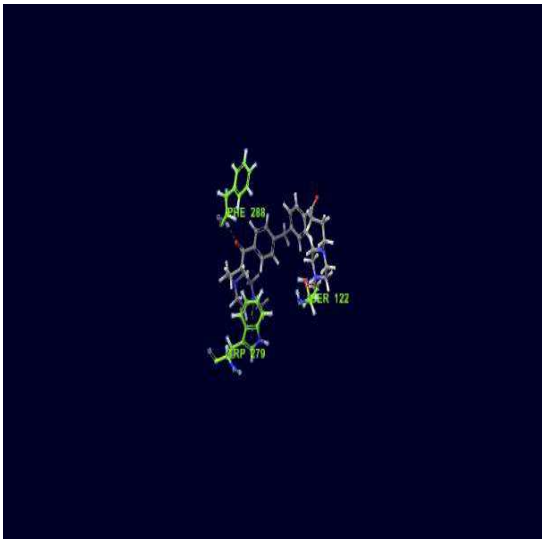

Fig. 2: Three-dimensional docking model of compound **3.4** with AChE

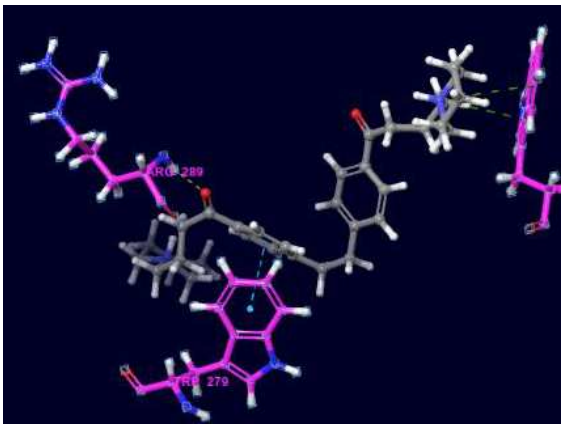

Fig. 3: Three-dimensional docking model of compound **2.3** with AChE

Compound 1.18

The aromatic ring of the compound interacts with TRP279 showing a pi-pi staking interaction, Nitrogen 8412 forming hydrogen bonds interaction with PHE330 and TRP 84, carbonyl8404 forms a hydrogen bond with PHE288, in addition to this interaction, there is another interaction between N8408 and TYR334 called pi-cation interaction. Three-dimensional docking model of compound **2.3** with AChE is shown in Fig. 3.

Donepezil (Marketed Molecule)

The nitrogen 8394 interacts with ASP72 by a salt bridg interaction. The aromatic structure of compound supposed a good orientation for its binding to 334TYR via Pi-cation interaction, carbonyl 8389 forms a hydrogen bonds with PHE288 and the aromatic ring interact with TRP279 by pi-pi staking interaction.

Table 1: Docking score of the investigated compounds

Compound	Docking score
3.2	-13,681
3.4	-13,549
2.3	-13,521
1.18	-13,421
Donepezil	-12,978
2.2	-12,902
6.2	-12,83
3.5	-12,353
2.1	-12,325
Galanthamine	-12,11
5.3	-12,1
6.4	-11,896
2.1	-11,29
7.7	-10,898
6.1	-10,633
1.15	-10,55
3.3	-10,531
1.7	-10,29
4.5	-10,151
2.6	-10,122
Rivastigmine	-10,013
2.7	-9,711
1.17	-9,535
1.14	-9,213
3.5	-8,716
3.1	-8,515
6.1	-8,191
5.2	-7,717
2.9	-7,629
4.4	-7,494
2.4	-6,509
2.8	-6,349
2.5	-6,213
7.4	-5,924
4.3	-5,918
4.1	-5,207
5.1	-5,189
4.2	-4,905
7.3	-4,842
2.9	-2,875

Docking Score

Table 1 represents the docking scores results of the investigated molecules; the scores are arranged in descending order from smallest the negative value to the major t negative value. It was found that ten molecules have no poses in the receptor site of AChE and four molecules with better scores when compared to the score of the marketed molecule (Donepezil).

Conclusion

In this work a docking study was carried out on 56 acetylcholinesterase inhibitory molecules, the results obtained indicate that most of these molecules have a very good affinity towards the acetylcholinesterase enzyme.

Acknowledgment

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Author's Contributions

Lemaoui Tarek: Work realization (calculation and redaction).

Hammoudi Nour El Houda: Provide ideas and some proposals.

Attoui Ayoub: Orientation and correction of the biological part.

Benguerba Yacine: Orientation and correction of the molecular modeling part.

Ethics

This research was subjected to ethical clearance from the faculty of technology, Ferhat ABBAS university setif-1, Setif/Algeria.

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