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Molecular docking investigation of *N*-Diphenylpiperazinyl-sulfonylamide compound as an acetylcholinesterase inhibitor against Alzheimer's disease

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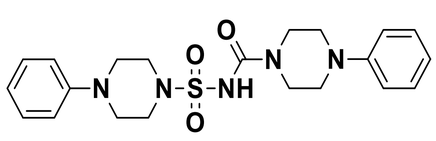
ABSTRACT

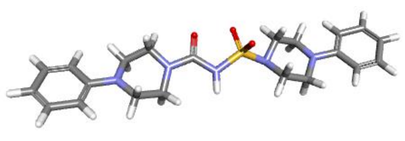
Cholinesterase inhibitors are promising drugs for the symptomatic treatment of mild to moderate forms of Alzheimer's disease. In our study, we exploited the inhibitory effect of the *N*-Diphenylpiperazinyl-sulfonylamide compound on anti-acetylcholinesterase activity. A molecular docking simulation method was applied to this compound to create stable complexes with protein targets (PDB ID: 7E3H) and (PDB ID: 6O4W). The result obtained highlighted interesting hydrophobic and hydrogen interactions of *N*-Diphenylpiperazinyl-sulfonylamide in comparison with the drug DONEPEZIL. These interactions cluster in the active pocket binding site of human acetylcholinesterase (AChE) 7E3H and 6O4W with residues Phe295, Tyr337 and Glu202 at interaction energies equal to -180.175 and -191.178 Kcal/mol, respectively. In addition, the pharmacokinetic parameters presenting to the invented compound were determined. As a result, the *N*-diphenylpiperazinyl-sulfonylamide compounds were found to have better pharmacokinetic properties and to form stable complexes with the acetylcholinesterase protein, which supports their use as drug candidates for Alzheimer's disease.

INTRODUCTION

Epidemiological studies have recently been demonstrated by Zhao et al. (2015) [1] to remove the doubt on the use of first-line antidiabetic sulfonylureas in the treatment of cancer progression in type II diabetic patients. These authors report that sulfonylureas exhibit in vitro inhibition of AKR1C (AKR1C1, AKR1C2, AKR1C3), which are essential enzymes in the metabolism of steroid hormones related to prostate cancer, breast cancer and endometrial diseases. **In this study**, the molecular docking technique was applied to predict the mode of inclusion and interaction of a sulfonylurea derivative (N-Diphenylpiperazinyl-sulfonylamide) within the macromolecular structure of human acetylcholinesterase (AChE), which is an essential protein in the metabolism related to Alzheimer's disease,



2D



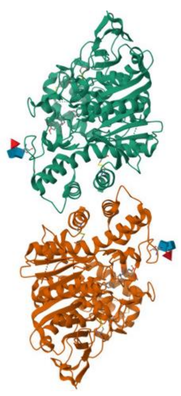
3D

N-Diphenylpiperazinyl-sulfonylamide

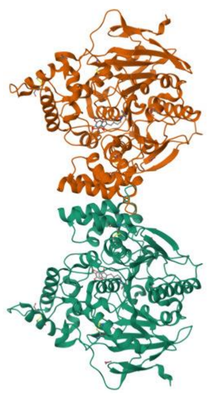
MATERIAL and METHODS

Download 3D (PDB ID: 7E3H) and (PDB ID: 6O4W). (http://www.pdb.org) (Resolution: 2.45 Å and 2.35 Å) Elimination of water molecules, co-crystallized ligand -To identify the active site using the cavity detection method using the Molegro Virtual Docker (MVD) v 5.5 program

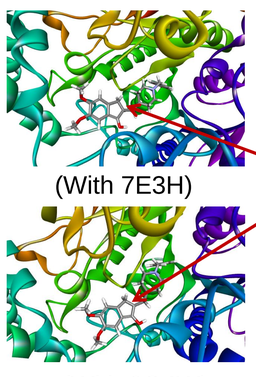
- ❑Searching for the best conformation
- ❑The energies of the scoring function "MolDock score" and the energies of the Protein-Ligand interactions
- ❑Evaluations and Analysis of the Results of the Formed Complexes
- ❑Prediction of interaction modes
- ❑Comparisons with ligands
- ❑ Re-docking the co-crystallized ligand



3D (PDB ID: 7E3H)

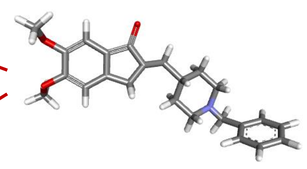


3D (PDB ID: 6O4W)



(With 7E3H)

(With 6O4W)



co-crystallized ligand (E20) DONEPEZIL

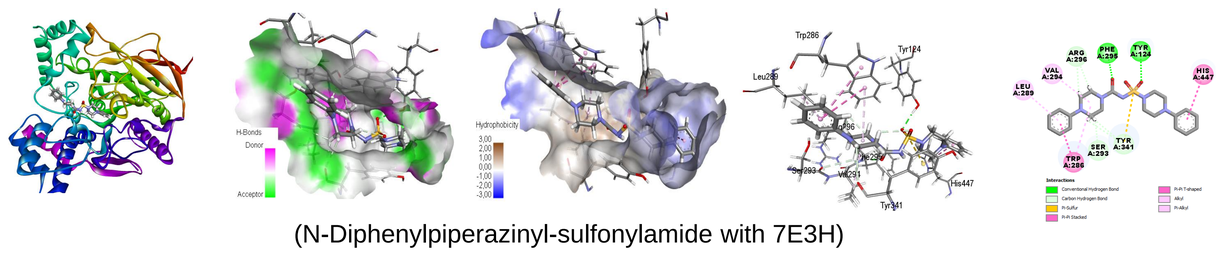
Re-docking the co-crystallized ligand **1-BENZYL-4-[(5,6-DIMETHOXY-1-INDANON-2-YL)METHYL]PIPERIDINE**

PDB	Postions	Surface Å²	Volume Å³
7E3H	**X=-5.6053 Y= -22.9126 Z=166.569**	**590.08**	**197.12**
6O4W	**X= 89,9369 Y= 83,9526 Z= -5.821**	**445,44**	**174,592**

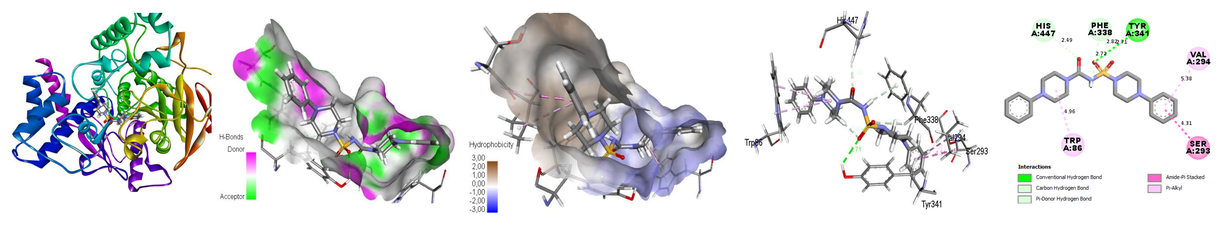
RESULTS and DISCUSSIONS

Once the Protein-ligand complex is formed, it will adapt the most stable conformation, with the lowest energy level (kcal/mol) for the best poses of the selected shapes

ID PDB	Ligands	MolDock Score	Energie d'interaction	Hbands
7E3H	Sulfonylurea	-159.576	-180.175	-2.5
	DONEPEZIL	-165.052	-178.211	-2.83233
6O4W	Sulfonylurea	-165.211	-191.178	-1.06264
	DONEPEZIL	-160.508	-176.999	-2.5



(N-Diphenylpiperazinyl-sulfonylamide with 7E3H)



(N-Diphenylpiperazinyl-sulfonylamide with 6O4W)

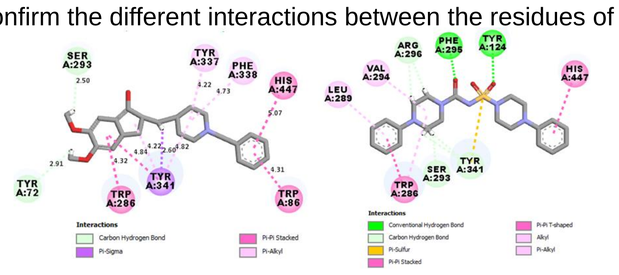
The ligand binding mode was regenerated to confirm the reliability of the molecular docking process. In particular, hydrogen and hydrophobic interactions. The MolDock score shows the ability of N-Diphenylpiperazinyl-sulfonylamide to find the right position in the active sites of macromolecular structure of human acetylcholinesterase (AChE), The strength of the H-bonds between the target and the structure of Sulfonylurea was considerably significant, as observed through the H-bond score (-2.5 kcal/mol for 7E3H and -1.06264 for 6O4W).

The structure of Sulfonylurea occupies a very favorable position in the center of the active site of the target which allows a certain similarity of intermolecular interactions:

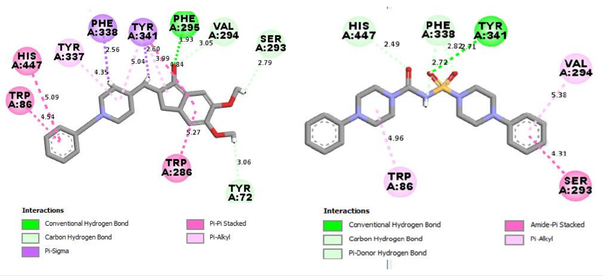
❑**By** providing the target human acetylcholinesterase (AChE), to form hydrogen bonds between the residues TYR 124 and SER293 a region of very powerful hydrophobic interaction with the residues HIS447 and TRP286. for PDB: 7E3H

❑By providing the target human acetylcholinesterase (AChE), to form hydrogen bonds between the residues TYR 341 and PHE338 a region of very powerful hydrophobic interaction with the residues SER293 and TRP86. for PDB: 6O4W

We confirm the different interactions between the residues of the active site of Sulfonylurea in the figures



2D interaction diagram for comparison DONEPEZIL with N-Diphenyl Piperazinyl-sulfonylamide (PDB: 7E3H)



2D interaction diagram for comparison DONEPEZIL with N-Diphenyl Piperazinyl-sulfonylamide (PDB: 6O4W)

CONCLUSION

We applied molecular docking based on N-Diphenyl Piperazinyl-sulfonylamide compound against the targets human acetylcholinesterase (AChE), which are recognized as one of the important targets for therapeutic intervention, these are (PDB: 7E3H and 6O4W), comparing with the drug DONEPEZIL. The study revealed that N-Diphenyl Piperazinyl-sulfonylamide presents better stable complexes in view of the requirements of interaction with active site residues, especially by hydrophobic interactions. We noted that the N-Diphenyl Piperazinyl-sulfonylamide inhibitor has been shown to be effective in therapy, significantly is potential future bioactive compounds against several Alzheimer's disease.

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