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Der Pharma Chemica, 2015, 7(8):181-186
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Theoretical study by molecular modeling methods the inhibition of acetylcholinesterase

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ABSTRACT

Alzheimer's disease (AD) is turning out to be one of the lethal diseases in older people. The etiology is multifactorial, and pathophysiology of the disease is complex. Data indicate an exponential rise in the number of cases of AD, emphasizing the need for developing an effective treatment. AD also imposes tremendous emotional and financial burden to the patient's family and community. The disease has been studied over a century, but acetylcholinesterase inhibitors is one drugs currently approved for it management. The multitarget approach is based on the unique structural properties of acetylcholinesterase and the interaction of the enzyme with the inhibitors; which could hold the key to treatment of AD in the near future. Posiphen is an experimental AD drug and it lacks acetylcholinesterase inhibitory activity. Where the objective of this work consists to use the molecular modeling methods as theoretical approach to study the inhibition of acetylcholinesterase.

Keywords: Acetylcholinesterase, posiphen drugs, molecular docking methods.

INTRODUCTION

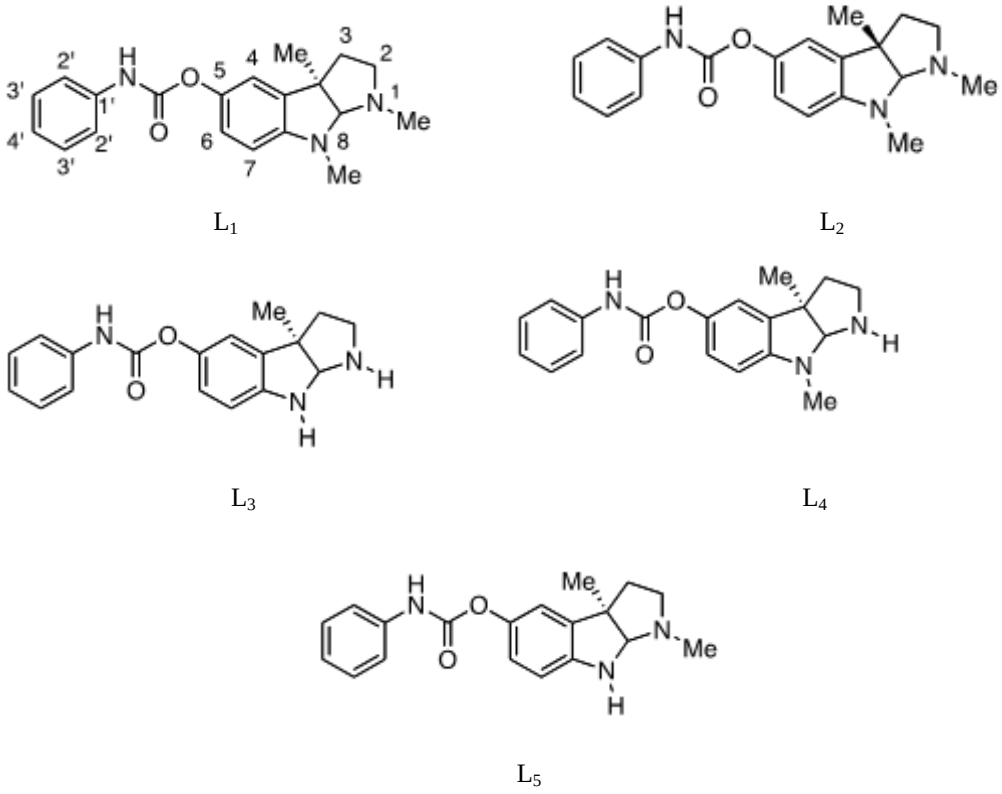
Alzheimer's disease (AD) is the major cause of dementia affecting approximately 10% of the population over the age of 65-year old and its incidence rises exponentially with age [1-2]. Alzheimer's disease is a common and severe neurodegenerative disorder among elderly patients that is characterized by a cascade of pathologic changes. These changes include abnormal amyloid β (Aβ) peptide aggregation with the consequent formation of senile plaques in the cerebrocortical and limbic regions and a reduction in the levels of acetylcholine (ACh) [3], together with progressive neuron loss [4]. The primary therapeutic approach to address cognitive loss associated with AD is based on acetylcholinesterase (AChE) [5]. Acetylcholinesterases, also known as acetyl-hydrolases and commonly abbreviated as AChE are hydrolase enzymes that function in hydrolyzing the neurotransmitter acetylcholine. Due to their function they are predominantly found in cholinergic synapsis of the brain and in the synapsis that serve as junction between the muscular system and nervous system [6]. Once a signal is passed via the acetylcholine neurotransmitter, the acetylcholinesterase breaks down the acetylcholine into its two component parts, acetic acid and choline. As a result, this mode of action halts the signaling process [7]. This allows the components to be recycled back into new neurotransmitters which will function in the next signal processing [8]. By administering a drug that inhibits the activity of acetylcholinesterase, the levels of the neurotransmitter can be heightened to normal. Thus acetylcholinesterase inhibitors have become popular for the treatment of the cognitive problems associated with Alzheimer's, by inhibiting the action of this enzyme [9-10]. As series of inhibitors of acetylcholinesterase we have Posiphen (**L_1**) and, its three major metabolic products, (+)-N^1-norPosiphen (**L_4**), (+)-N^8-norPosiphen (**L_3**) and (+)-N^1, N^8-bisnorPosiphen (**L_5**), were required in high chemical and optical purity [11]. Our work consists to study the inhibition of acetylcholisterase by molecular docking method.

MATERIALS AND METHODS

Molecular Docking:

a. Ligands structure:

The full geometrical of the ligands **L_{1-5}**are downloading from Pub Chem Project (Figure1).



L_1 L_2

L_3 L_4

L_5

Figure 1: chemical structure of ligands L_{1-5}

L_1	(+)-Posiphen
L_2	(-)-Phenserine
L_3	(+)-N^1,N^8-BisnorPosiphen
L_4	(+)-N^1-NorPosiphen
L_5	**(+)**-N^8-NorPosiphen

b. Enzyme structure:

The X-ray crystal structures of Acetylcholinesterase(PDB ID: 1EVE) [12]**,** were downloaded from RCSB Database (www.rcsb.org/pdb) [13]. 1EVE is a three dimensional structure of the anti-alzheimer drug, e2020 (aricept), complexed with its target Acetylcholinesterase with EC Number: 3.1.1.7 classified Serine Hydrolase under class of enzymes, complexed with a selective inhibitor E20 with 1 chains (A), with 2.50 Å resolution and 0.188 R-value respectively. Computational analysis was carried out on chain A of 1EVE. The five1EVEinhibitor molecules **L_{1-5}** were selected to study the associated physico-chemical parameters and protein-ligands interactions.

To obtain better potential binding sites in the 1EVE (PDB ID: 1EVE), a maximum of five cavities was detected using default parameters. The volume and surface of cavities are showed in Table 1.

Table 1: Chemical properties of five cavities

Cavities	Volume Å^3	Surface Å^2
Cavity1	**232.448**	**599.04**
Cavity2	177.152	704.00
Cavity3	76.800	275.20
Cavity4	27.648	111.36
Cavity5	23.552	83.20

It found that the reference selective inhibitor (E20) of 1EVE is fixed in cavity 1(V=232.448Å^3, S=599.04Å^2). Out of the detected cavities, cavity 1 was selected for further studies (Figure 2). The chosen cavity was further refined using

side chain minimization by selection of an add-visible option set at a maximum of 10,000 steps per residue and at a maximum of 10,000 global steps. The grid resolution was 0.30 Å; the max iterations were 1,500; the max population size was 50 and the energy threshold was 100.

Mol Dock Scoring function was employed to predict the binding energy for active site residue-ligand interactions and docking studies computed for all Ligands using MVD program that predicted interactions in terms of Dock score.

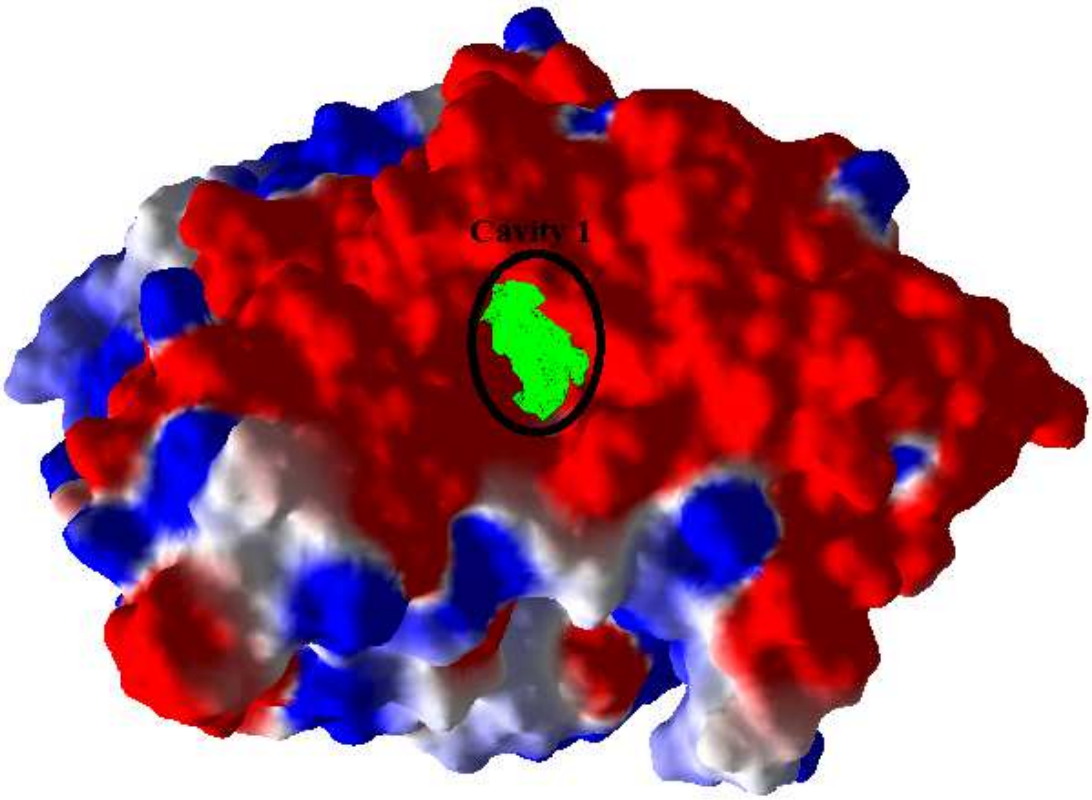


Figure 2: Graphical interface with the cavity1 indicated by ellipses identified by MolDock

c. Docking Protocol

The structure of the protein was corrected for missing atoms or unknown units using Molegro Virtual Docker (MVD2012) [14] program, graphical-automatic software (http://molegro.com/mvd-product.php). All solvent molecules and the co-crystallized inhibitor were removed from the structures to provide sterically unimpeded cavities for ligand docking.

Docking was performed by using Molegro Virtual Docker (MVD) software package. The identification of ligand binding modes is done by iteratively evaluating a number of candidate solutions (ligand conformations) and estimating the energy of their interactions with the macromolecule. MVD performs flexible ligand docking, so the optimal geometry of the ligand will be determined during the docking. The MolDock scoring function (MolDock Score) used by MVD is derived from the PLP scoring functions originally proposed by Gehlhaar et al. and later extended by Yang et al [15]. The MolDock scoring function further improves these scoring functions with a new hydrogen bonding term and new charge schemes.

RESULTS AND DISCUSSION

a. Active site residues

E20 reference ligand (Ref) with surrounding active site residues within 3.5 A°, hydrogen bonding interactions and the spatial orientation in binding pocket is given in Figure 3. The interactingresidues surrounding the ligand within 3.5 A° distance are Asp72, Tyr121, Phe330, His440, Gly441, Ser200, Trp84, Glu199, Ile287, Tyr334, Ile444, Tyr130, Phe290, Phe331, Phe288, Gly118, Trp279, Arg289, Gyl117, Leu282, Tyr70, Ser286.

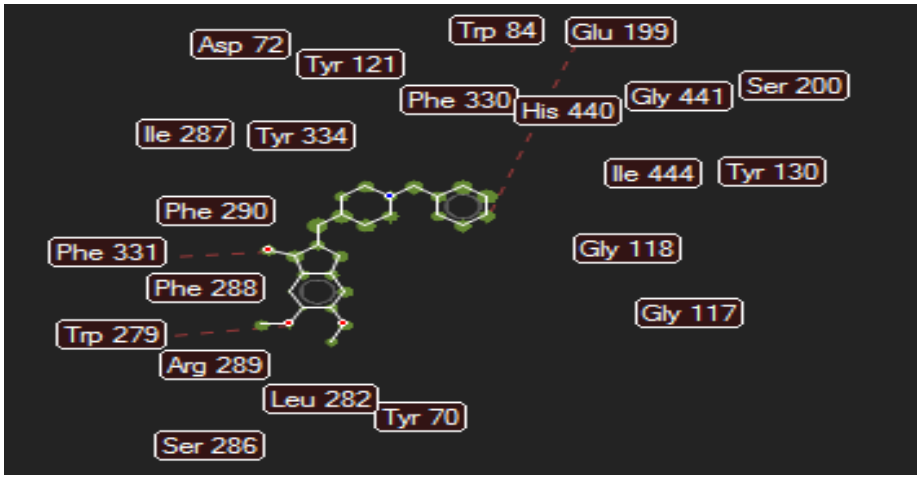


Figure 3: Spatial orientation of E20 crystal ligand within 3.5 A° active site residues

b. Study of Protein-Ligand Interaction

The scoring functions of the compounds were calculated from minimized ligand-protein complexes. In order to compare the binding affinity of the newly Ligands, we docked compounds $\mathbf{L_{1\text{-}5}}$into the empty binding active site of Acetylcholinesterase (1EVE).

c. Interaction of Ligands with the binding active site

Flexible docking of ligands selected in this study was carried out in the active site of Acetylcholinesterase. Five top poses for each ligand were returned in the simulation, out of which one best pose for each ligand was selected on the basis of their MolDock score. Table 3 presents the Interaction energy between the ligand and protein and Hydrogen Bond Energy for the selected alignment and conformation of each ligand.

The interaction of Ligands $\mathbf{L_{1\text{-}5}}$with the Acetylcholinesterasebinding site showed that they interacted with different amino acid residues at the active site (Figure4). Only a single H-bonding and steric interaction are showed in this figure.

The result from the Table 2 tells that the reference ligand E20 is having energy MolDock score -152.466 Kcal/Mol. In the other hand, the four selected molecules were having the lowest energy MolDock score as follows: Ligand $\mathbf{L_1}$is having minimum energy MolDock score -153.6090 Kcal/Mol and Ligand $\mathbf{L_5}$ is having -153.2800 Kcal/Mol.

Table 2: Docking results of Ligands $L_{1\text{-}5}$ with Acetylcholinesterase (1EVE) in the active site

	Cavity1				
	MolDockScore[a]	**Interaction[b]**	**H-bond**	**E-Intra(Steric)**	**E-Intra(vdw)**
Ref	**152.466**	-159.974	-1.3321	5.5063	-126.786
L_1	**-153.609**	-145.278	-4.5738	-9.89446	58.2314
L_2	-150.113	-143.74	-1.78136	-6.4516	60.6372
L_3	-149.123	-148.000	-2.244	-1.4355	59.7358
L_4	-151.9200	-152.239	-1.8054	-3.0736	59.6128
L_5	**-153.2800**	-149.3780	-1.4906	-3.9269	59.2859

[a]MolDock score calculated by summing the external ligand interaction (protein–ligand interaction) and internal ligand interaction score using Virtual Molecular Viewer 1.2.0.

[b] The total interaction energy between the pose and the target molecules(s).

The table 3 showed the exact hydrogen bond length between the selected ligans L_1 and $L_5$and the keys residues of Acetylcholinesterase (1EVE).

Table 3: Hydrogen bond lengths (Å)

	Glu199	**Phe331**
L_1	**3.1**	**2.6**
L_5	**3.2**	**3**
Ref	**3.4**	**3.2**

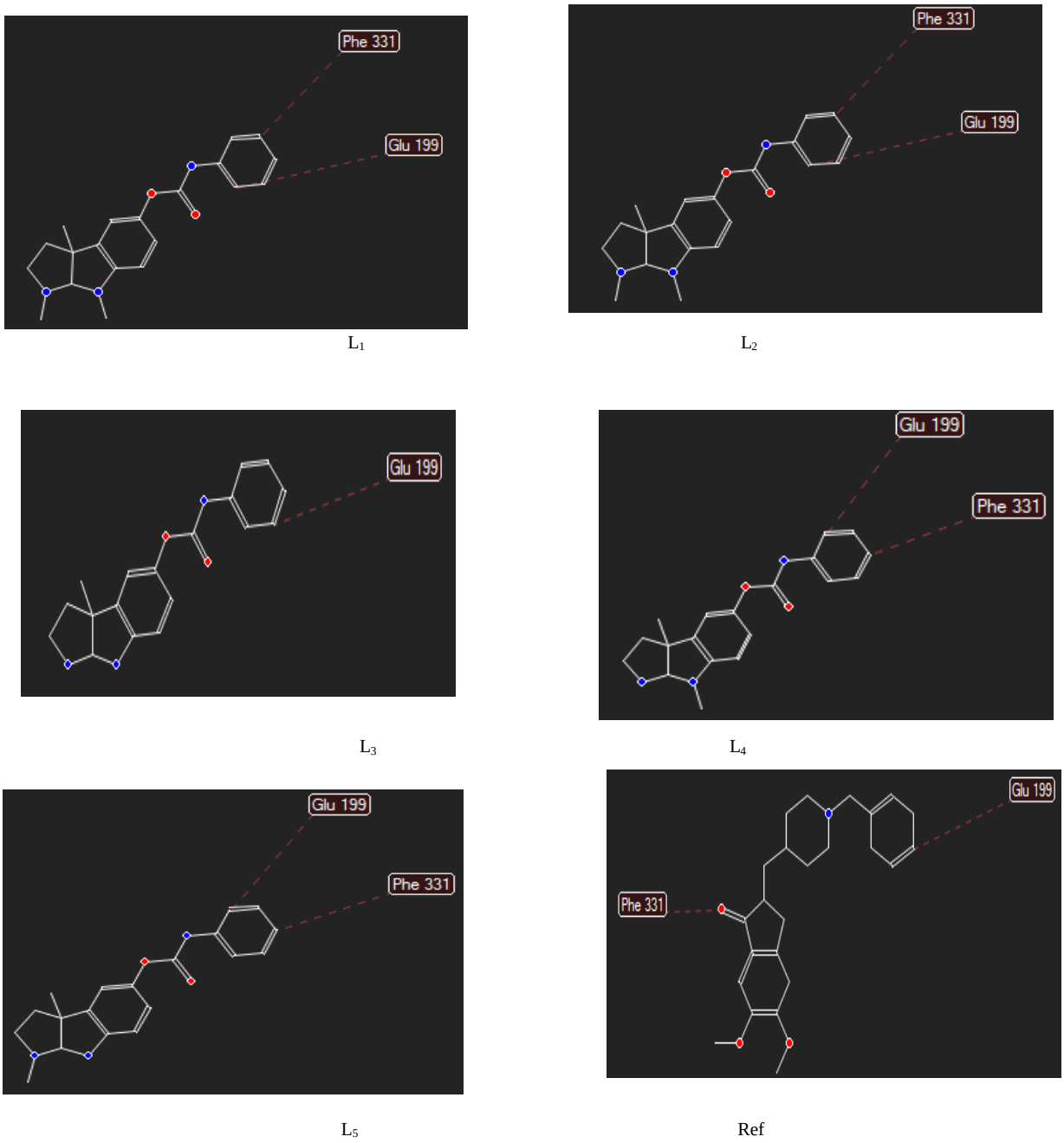


Figure 4: The interaction of the ligands with the protein

According to Anne Imberty et al, the interactions ranging between 2.5 **Å** and 3.1 **Å** are regarded as strong and those ranging between 3.1 **Å** and 3.55 **Å** are supposed to be average.The interactions higher than 3.55 **Å** are weak.

On table 3 we can easily note that the distances between the amino acids and the ligands (L_1 and L_5) change between 3.2**Å** and 2.6 **Å**, this shows that there is a strong interaction between these amino acids and the ligands **L_1, L_5**, thereafter a better fixing of these ligands with these residues, and consequently, it is probably best the ligands to inhibit the Acetylcholinesterase (1EVE).

CONCLUSION

The Protein-Ligand interaction plays a significant role in structural based drug discovery designing. In this study, molecular docking has been employed to identify the potential binding mode of a number of five ligands with Acetylcholinesterase (1EVE). The results obtain were compared with the reference ligand (E20). The study reveals

that, in the active site of the protein, the residues, Phe331 andGlu199seem to play crucial role in binding with the ligands.

It is noticed that the compounds $\mathbf{L_1}$and $\mathbf{L_5}$ have respectively the lowest values of energy MolDock score than the reference ligand (E20). These results indicate that four ligands act as potential binding sites for the design of highly selective and potent Acetylcholinesterase (1EVE) inhibitors in the active site.

Hence, it is concluded that $\mathbf{L_1}$ and $\mathbf{L_5}$ could be a potent ANTI-ALZHEIMER DRUG target molecule against Acetylcholinesterase(1EVE) which may be worth for further clinical trials.

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