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Molecular Docking Performance of Selective Organic Compounds with Target Protein

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Abstract: In this article, the docking analysis has been carried out to know some selective compounds' interaction to bind with a targeted protein. There are three approaches have been analyzed here with three different kinds of protein as the target species. They are 2-aminobenzimidazole (2ABZ) with Acetylcholinesterase receptor (AChE), Phenoxazine (POZ) with Penicillin-binding proteins (PBPs) receptor, and Phenothiazines with Calcium/calmodulin-dependent protein kinase IV (CAMK IV) receptor. All three studies showed that the binding is perfect at the binding site and explained with hydrogen bonding interaction via donor-acceptor interactions.

Keywords: organic compounds; AChE; PBPs; CAMKIV; molecular docking.

1. Introduction

In recent days, the computational approaches that ‘dock’ small molecules into the inner cavity and structures of macromolecular targets and ‘score’ their expected complementarity towards the binding sites are generally utilized in hit identification and lead optimization. To be sure, there are presently various drugs whose development was intensively influenced by or dependent on the structure-based design and screening techniques, for example, HIV protease inhibitors [1-6]. All things considered, there are considerable difficulties in the application of these approaches, precisely according to current scoring schemes. On a fundamental level, the docking process involves predicting the ligand conformation and orientation (or posing) inside a focused on a targeted binding site. In general, there are two significant aims of docking studies. The first one is accurate structural modeling, and the other one is the correct prediction of activity. However, the identification of molecular features that are responsible for specific biological recognition and its applications, or the prediction for the modifications/alteration of a compound that may be used to enhance ability, mostly creates complex issues that are frequently very tough and hard to understand easily and frequently [7].

Computational approaches have the potential to speed up the drug discovery process, thus reducing the costs and changing the way drugs are designed and formulated. Rational Drug Design (RDD) facilitates and speeds up the drug designing process, involving a variety of

methods to identify novel compounds [8-17]. One such method is the docking of the drug molecule with the receptor (target). The site of drug action, which is ultimately responsible for the pharmaceutical effect, is a receptor. Docking is the process by which two molecules fit together in 3D space.

Generally, plenty of inhibitors are available to study the binding ability with the targeted proteins [18-19]. Acetylcholinesterase (AChE), Penicillin-binding proteins (PBPs), and Calcium/calmodulin-dependent protein kinase type IV are the main and common receptors to study the binding interactions with the drugs or organic molecules. Acetylcholinesterase (AChE) is a key inhibitor involved in the termination of nerve signals through acetylcholine hydrolysis. It targets drug development to combat neuromuscular disorders such as myasthenia gravis, glaucoma, and Alzheimer's disease (AD) [20]. AChE is found in many types of conducting tissue: nerve and muscle, central and peripheral tissues, motor and sensory fibers, and cholinergic and noncholinergic fibers. The activity of AChE is higher in motor neurons than in sensory neurons [21-23]. AChE is also found on the red blood cell membranes, where different forms constitute the Yt blood group antigens [24]. AChE exists in multiple molecular forms, which possess similar catalytic properties but differ in their oligomeric assembly and attachment mode to the cell surface.

Penicillin-binding proteins (PBPs) are a group of proteins characterized by their affinity for and binding penicillin. They are a normal constituent of many bacteria; the name just reflects how the protein was discovered.

Calcium/calmodulin-dependent protein kinase type IV is an enzyme that in humans is encoded by the CAMK4 gene [25]. In biology, a gene is a sequence of nucleotides in DNA or RNA that encodes a gene product's synthesis, either RNA or protein. This gene's product belongs to the serine/threonine-protein kinase family and the Ca^{2+}/calmodulin-dependent protein kinase (CAMK) subfamily. This enzyme is a multifunctional serine/threonine-protein kinase with limited tissue distribution that has been implicated in transcriptional regulation in lymphocytes, neurons, and male germ cells [25].

Benzimidazole and its derivatives are regarded as important heterocyclic molecules that exhibit a wide range of pharmaceutical applications, including anti-microbial, anti-cancer, anti-hypertensive, anti-viral, anti-fungal, anti-HIV, anti-convulsant, and anti-diabetic. Given their wide-ranging activities and importance in the biological applications as novel compounds, the synthesis of benzimidazoles and their derivatives remains a primary goal for any synthetic chemistry communities [26].

Phenoxazine and its derivatives like phenothiazine compounds are the most important compounds in the class of nitrogen-oxygen heterocyclic compounds that are widely used as dyes and pigments [27]. We have to find to exhibit a broad spectrum of pharmacological activity such as CNS depressant, sedatives, antiepileptics, herbicidal, tranquilizers, antituberculosis, antitumor, antibacterial, spasmolytic, anthelminthic, and parasitical effects [28]. Phenothiazines belong to the oldest, synthetic antipsychotic drugs, which do not have their precursor in the world of natural compounds.

According to literature referenced data on relations between chemical structures of 2ABZ, PTZ, POZ, and their biological orientation, the main directions for molecular modeling studies can be carried out.

Therefore, docking is very useful for finding both the strength and type of signal produced during the process. In a structure-based drug design, molecular docking is one of the

most frequently used methods because of its ability to predict small-molecule ligands' binding-conformation to the appropriate target binding site.

2. Molecular Modeling

The objective of the study is to demonstrate that 2ABZ, PTZ, and POZ bind to Acetylcholinesterase Receptor (AChE), Penicillin-binding proteins (PBPs), and Calcium/calmodulin-dependent protein kinase IV (CAMK IV) Receptor enzyme (Figure 1), respectively and to evaluate whether these molecules can be used as a potential drug. The structural information and relevant data for the target were collected from the "Protein Data Bank" (PDB). The PDB ID: 1CEF [29], and PDB ID: 2W40 [30] were used as the template for our studies.

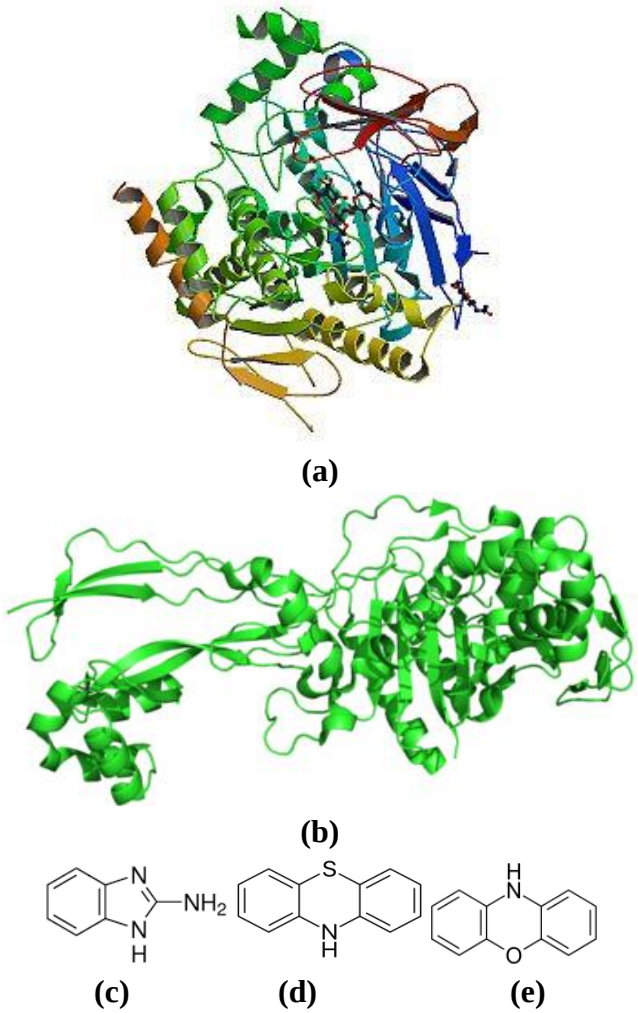

Figure 1. The structure of (**a**) Acetylcholinesterase (AChE) Receptor; (**b**) Penicillin binding proteins (PBPs) receptor; (**c**) 2-aminobenzimidazole (2ABZ); (**d**) Phenothiazine (PTZ); (**e**) Phenoxazine (POZ).

Calcium/calmodulin-dependent protein kinase IV (CAMKIV) is also one of the important receptors associated with many diseases, including cancer, neurodegenerative disorders, and so on. Thus, the receptor is being considered as a potential drug target.

In this study, molecular docking was performed using Auto-Dock software to predict the interaction mode and selectivity of the chosen molecules for AChE. Auto-Dock 4.2.0 was employed to perform the docking calculations [31]. Generate a grid box size of 20, 22, 24 $Å^3$ points was used, centered on the mass center of the crystallographic macromolecule encompassing all active-site atoms.

X-ray crystal structures of the TcAChE in complex with donepezil (PDB: 1EVE) was selected to build the starting model of AChE [32]. 2ABZ compound was chosen for molecular modeling as the most active compound of AChE inhibitor.

3. Results and Discussion

3.1. Molecular docking studies of 2-aminobenzimidazole with Acetylcholinesterase Receptor as the target protein.

The dock, glide energy, and hydrogen bonding interactions of the 2ABZ and co-crystallized ligand are given in Table 1. A view of the X-ray crystal structure of the 2ABZ in the AChE receptor active site showing the key hydrogen contacts between inhibitor and enzyme is depicted in Figure 2. The co-crystallized ligand in the AChE receptor active site showing the key hydrogen contacts between inhibitor and enzyme is depicted in Figure 3. The surface diagram showing the 2ABZ docked at the active site of the AChE receptor is depicted in Figure 4.

X-ray crystal structures confirmed the expected binding mode. Considering binding orientation and electronic properties enabled optimization to 2ABZ as a more potent second-generation lead.

Molecular docking studies are based on the fact that 2ABZ is an antibacterial drug, and it is proved to exert its action by the inhibition of AChE in trails. Based on the drug action, it has been performed docking simulation of the 2ABZ binding the AChE crystal structure's active site.

The docking result of the 2ABZ showed high binding energy with AChE targeted protein. 2ABZ showed excellent binding energy and compared co-crystal ligand with -6.8 and 6.6 kcal/mol, respectively for AChE enzyme. The binding energies and residues involved in H-bonding are tabulated in Table 1.

Table 1. Hydrogen bond interactions of 2ABZ with amino acids at the active site of AChE receptor.

Compound	Docking Score (kcal/mol)	Hydrogen Bonding Interactions		
		Donor	Acceptor	Distance (Å)
2ABZ	-6.8	N [SER80]	N*	**2.9**
		O [ASP71]	O*	**3.1**
		O [TYR333]	O*	**2.9**
Co-Crystal	-6.6	O [ASP71]	O-H*	3.3

* Ligand

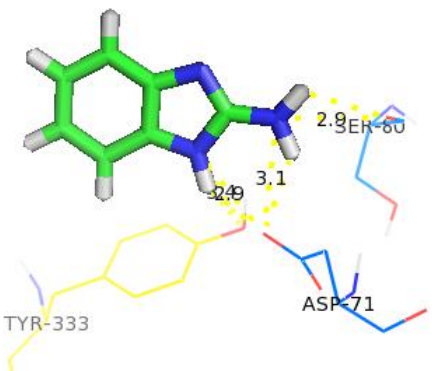

Figure 2. The 2ABZ in the AChE receptor active site showing the key hydrogen contacts between the 2ABZ inhibitor and enzyme.

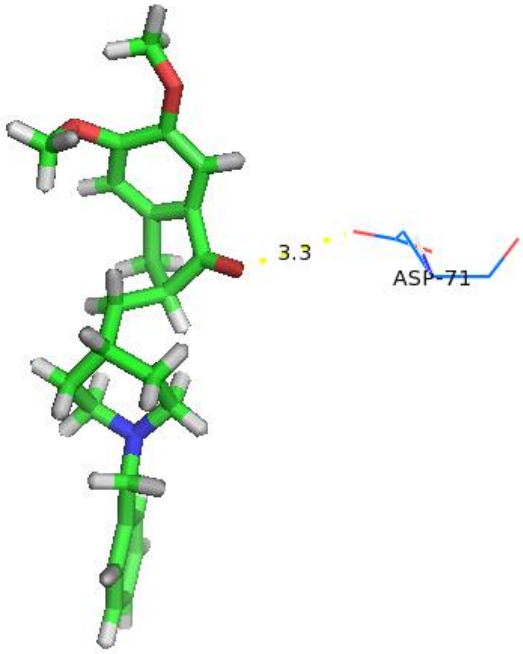

Figure 3. The co-crystallized ligand (dexamethasone) in the AChE receptor active site showing the key hydrogen contacts between inhibitor and enzyme.

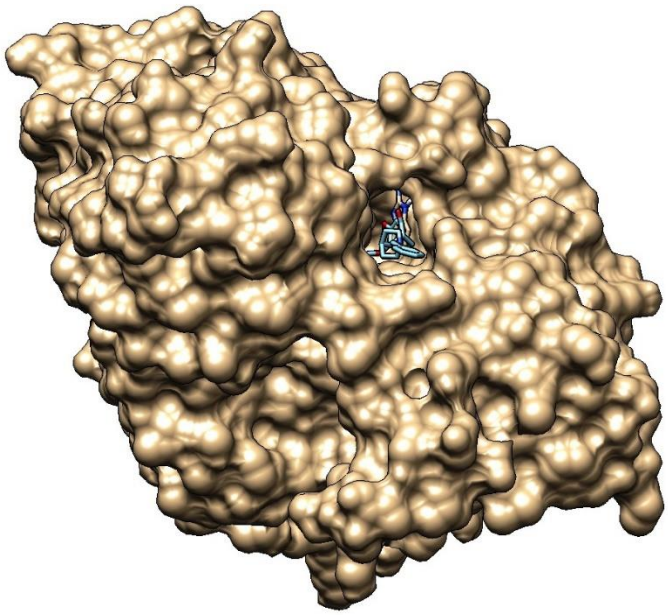

Figure 4. Surface diagram showing the 2ABZ docked at the active site of AChE receptor.

3.2. Molecular docking studies of Phenoxazine (POZ) with Penicillin-binding proteins (PBPs) receptor as the target protein.

The dock, glide energy, and hydrogen bonding interactions of the POZ and its co-crystallized ligand are provided in Table 2. A view of the X-ray crystal structure of the POZ in the PBPs receptor active site showing the key hydrogen contacts between inhibitor and enzyme is depicted in Figure 5. The co-crystallized ligand in the PBPs receptor active site showing the key hydrogen contacts between inhibitor and enzyme is depicted in Figure 6. The surface diagram showing the title compound docked at the PBPs receptor's active site is depicted in Figure 7.

X-ray crystal structures confirmed the expected binding mode. Considering binding orientation and electronic properties enabled optimization to POZ as a more potent second-generation lead.

The POZ is shown to be an effective inhibitor. The amide group in the THR301 interacts with the carbonyl group's oxygen atom at a distance of 3.1 Å. The co-crystallized ligand also docked well, and it shows better interactions with residues THR299, SER62, THR301, ASN161, and THR116, respectively [33-37]. The results show that the POZ has better binding energy, and the co-crystallized ligand has comparable interactions.

Table 2. Hydrogen bond interactions of POZ with amino acids at the active site of PBPs receptor.

Compound	Docking Score	Hydrogen Bonding Interactions		
		Donor	Acceptor	Distance (Å)
POZ	-6.1	O [THR301]	N-H*	3.4
Co-Crystal	-6.6	O [THR299]	N-H*	3.0
		O [SER62]	N-H*	3.3
		O [THR301]	N-H*	3.3
		O-H [ASN161]	O*	3.5
		O-H [THR116]	O*	3.5

* Ligand

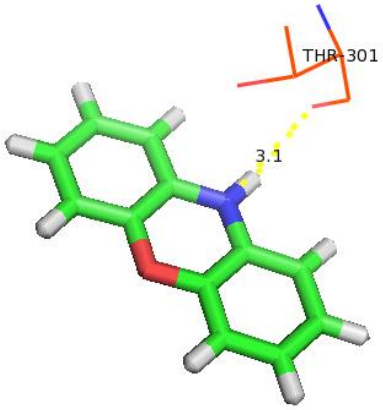

Figure 5. The POZ in the PBPs receptor active site showing the key hydrogen contacts between POZ inhibitor and enzyme.

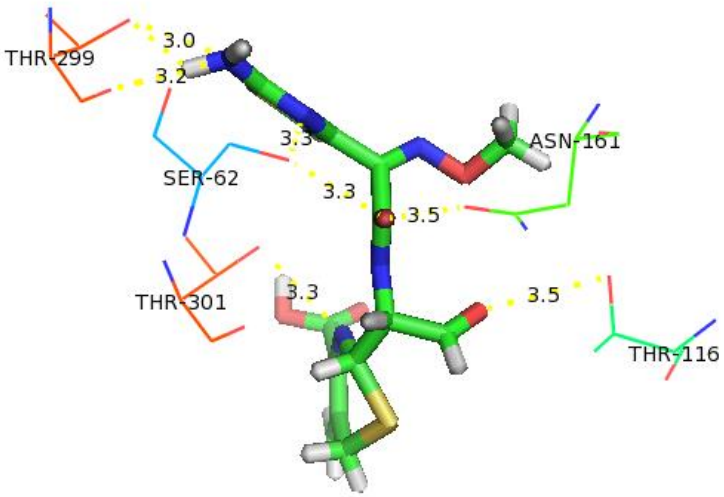

Figure 6. The co-crystallized ligand (dexamethasone) in the PBPs receptor active site showing the key hydrogen contacts between inhibitor and enzyme.

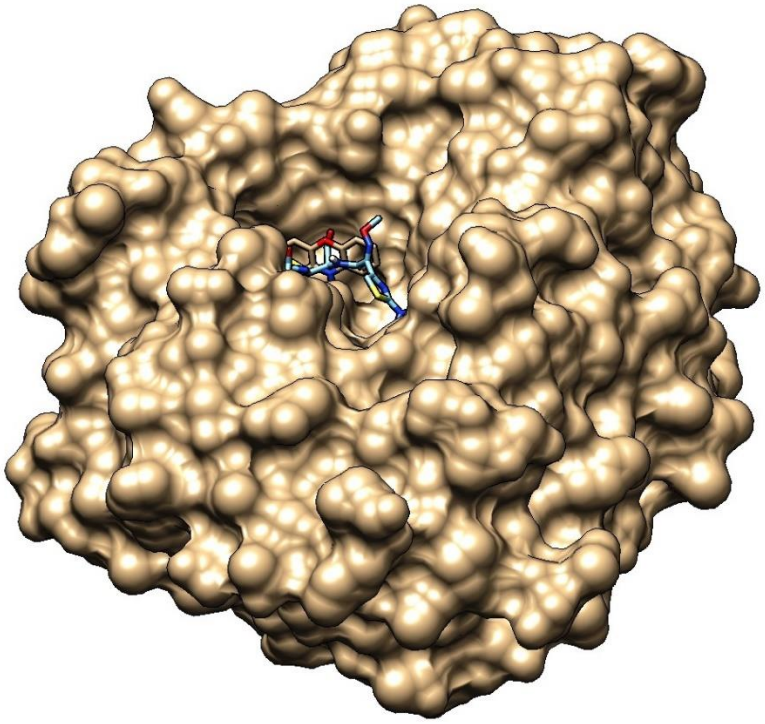

Figure 7. Surface diagram showing the POZ docked at the active site of PBPs receptor.

3.3. Molecular docking studies of Phenothiazines with Calcium/calmodulin-dependent protein kinase IV (CAMK IV) Receptor as the target protein.

The dock, glide energy, and hydrogen bonding interactions of the PTZ compound and co-crystallized ligand are given in Table 3. A view of the X-ray crystal structure of the PTZ in the CAMK IV Receptor active site showing the key hydrogen contacts between inhibitor and enzyme is depicted in Figure 8. The surface diagram showing the PTZ compound docked at the CAMK IV Receptor's active site is depicted in Figure 9.

Table 3. Hydrogen bond interactions of PTZ with amino acids at the active site of CAMK IV Receptor.

Compound	Docking Score	Hydrogen Bonding Interactions		
		Donor	Acceptor	Distance (Å)
PTZ	-5.6	O [SER360]	N-H*	2.9
		O [THR130]	O-H*	2.7
Co-Crystal	-3.9	N [TRP358]	O-H*	3.0

* Ligand

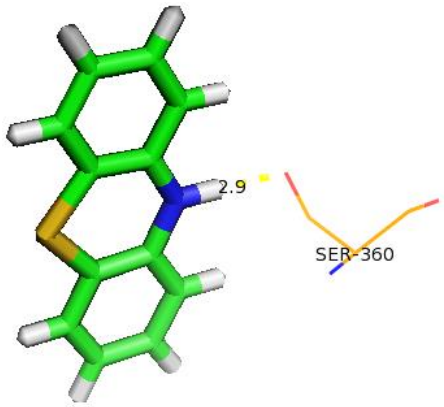

Figure 8. The PTZ in the CAMK IV Receptor active site showing the key hydrogen contacts between PTZ inhibitor and enzyme.

X-ray crystal structures confirmed the expected binding mode. Considering binding orientation and electronic properties enabled optimization to PTZ as a more potent second-generation lead.

The PTZ is shown to be an effective inhibitor. The amide group in the SER360 interacts with the carbonyl group's oxygen atom at a distance of 2.9Å. The co-crystallized ligand also docked well, and it shows better interactions. The results show that the PTZ has better binding energy, and the co-crystallized ligand has comparable interactions.

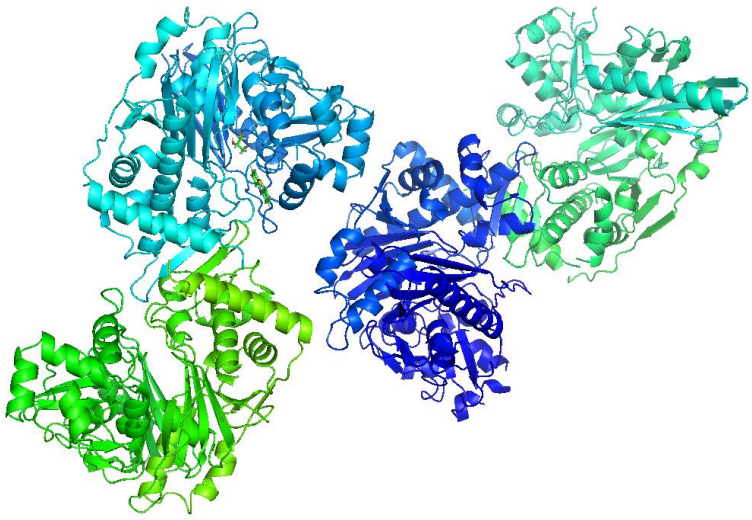

Figure 9. Cartoon diagram showing the PTZ docked at the active site of CAMK IV Receptor.

4. Conclusions

In this study, three chemically synthesized compounds were screened to find a new drug design by using the SBDD approach. These three different inhibitors were subjected to structure-based drug design (SBDD) to observe the docking score and hydrogen bond interactions. The active site of 2-aminobenzimidazole binds with Acetylcholinesterase Receptor, Phenoxazine (POZ) bind with Penicillin Penicillin-binding proteins (PBPs), and Phenothiazines bind with Calcium/calmodulin-dependent protein kinase IV (CAMK IV) Receptor as the target protein. These inhibitors were compared with re-docked complex protein using docking score, hydrogen bond and hydrophobic interactions, and binding free energy. All the SBDD have better docking scores and showed good binding free energy. Hydrogen and hydrophobic interactions were analyzed and revealed that having exhibited favorable interactions with the active site residues. The potential inhibition of SBDD could be revealed through *in-vivo* and *in-vitro* studies. It may be used to a new design of drugs against the targetted protein.

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Conflicts of Interest

The authors declare no conflict of interest.

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