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In Silico Analysis of Acetylcholinesterase Activity with Some Inhibitors

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Abstract

It is essential to comprehend how acetylcholinesterase (AChE) interacts with putative ligands in order to find and create drugs that will treat neurodegenerative illnesses. Using *in silico* molecular docking analysis, we examined the binding affinities of a number of substances to recombinant human acetylcholinesterase (PDB ID: 4EY6). These compounds included (-)-galantamine, a standard drug, pentachloronitrobenzene, sodium pentachlorophenate, Rogor (Dimethoate), trichloroacetic acid, trichlorphon, triterpenoid, saponin, and steroidal alkaloid. The results provide important new information about the possible pharmacological activity of these substances.

Keywords: Acetylcholinesterase Activity; inhibitors; *in silico* analysis; molecular docking

Introduction

By catalyzing the breakdown of acetylcholine, acetylcholinesterase (AChE) is an essential enzyme that contributes to the end of neurotransmission. Parkinson's and Alzheimer's diseases are among the neurological conditions where dysregulation of AChE activity is linked. Therefore, one common approach in the development of drugs for neurodegenerative illnesses has been to target AChE activity. Studies using *in silico* molecular docking offer an economical method for drug discovery by revealing important information about the interactions between putative ligands and target proteins.

Alzheimer's disease (AD) is a neurological illness that progresses with age and often affects those over 65. Cognitive impairment, a range of behavioral symptoms, and limitations in daily life tasks are the hallmarks of the disease. Between 65 and 85 years old, the prevalence of AD rises rapidly, doubling with each five-year age group [1]. Extracellular β-amyloid peptide deposition into amyloid plaques and intraneuronal formation of hyperphosphorylated τ-protein filaments into neurofibrillary tangles are two pathological hallmarks that are characteristically present. Both cause a progressive loss of neurons and the disintegration of neural circuits, especially in the cerebral cortex [2, 3]. The memory impairment observed in AD patients is caused by a decrease in the levels of the neurotransmitter acetylcholine (ACh) in the cortex and a deficiency in cholinergic activities [4]. In this sense, ACh is hydrolyzed and its activity is terminated by acetylcholinesterase (AChE, E.C. 3.1.1.7) and butyrylcholinesterase (BChE, E.C. 3.1.1.8) in later AD phases [5]. Cholinesterase inhibitors (ChEIs) are therefore therapeutically employed as AD treatments to sustain ACh levels in synapses [6-8].

The U.S. Food and Drug Administration has approved donepezil, galanthamine (Gal), and rivastigmine to treat the symptoms of mild to moderate AD [9]. The portfolio of ChEIs is limited. Pharmacologically speaking, rivastigmine functions as a dual cholinesterase inhibitor, whereas gal and donepezil are regarded as selective AChE inhibitors [6, 10, 11]. Moreover, China has made extensive use of

huperzine A (Hup A), an AChE selective inhibitor, in the treatment of AD [12]. In the search for novel and more potent treatments for AD, acetylcholinesterase inhibitors, or AChEIs, are still being thoroughly studied. Several of these drugs are already undergoing various stages of clinical studies [7, 8].

Apart from their impact on cognition, these substances frequently possess additional, frequently disease-modifying properties, primarily attributed to their neuroprotective properties. These include modifications to the metabolism of amyloid precursor protein, neuroprotection through agonizing nicotinic ACh receptors, inhibition of N-methyl-D-aspartate receptors, and modulation of muscarinic ACh receptors [4, 7, 12, 13]. ChEIs continue to offer a potential setting for the development of novel entities for AD therapy, as evidenced by the failure of certain recently produced medications based on anti-amyloid action in phase III clinical trials [7].

Strong AChEIs can be discovered in natural sources [14-16], and symptomatic AD therapy uses Gal and Hup A [9]. Natural-origin AChEIs are still being thoroughly studied to identify more effective molecules with superior pharmacotherapeutic properties. Recent research has isolated many ChEIs from Corydalis cava (L.) Schweigg. & Körte [17, 18], a plant used in Danish traditional medicine to enhance memory and cognition [19]. Using computational techniques in the process of creating novel and potent AChEIs with a wide biological profile is known as "computer-aided drug design" [20]. The understanding of AChE-ligand architecture of natural products is improved through the use of *in silico* approaches [21-25]. The development of novel AChEIs with a more accurately anticipated pharmacokinetic profile and reduced toxicity is another goal of molecular modeling techniques [26].

Lastly, a critical component of all possible drugs for the treatment of CNS-related illnesses is their ability to penetrate the blood-brain barrier (BBB), which must be demonstrated for compounds to be evaluated as therapeutic candidates for the treatment of AD. The blood-brain barrier (BBB) is a barrier made of endothelial cells with tight connections that keeps chemicals from entering the brain from the blood [27-29]. Lipid cell membranes allow molecules that are soluble in lipids to pass through the blood-brain barrier rather easily. Conversely, hydrophilic molecules only employ specific carrier-mediated transport processes to get beyond the barrier [30]. To measure penetration through the BBB, a model assay called a parallel artificial membrane permeability assay (PAMPA) is used. A high throughput technique called PAMPA was created to predict passive permeability through biological membranes [31, 32].

In this research work we used molecular docking as a method. A computational method known as "molecular docking" forecasts the orientation a molecule (usually a tiny ligand) would prefer when attached to another molecule (usually a protein) in order to form a stable complex. This approach is essential to drug design and discovery because it provides insight into the molecular interactions between ligands and target proteins. Molecular docking facilitates the identification of promising drug candidates and lead compound optimization by forecasting the binding affinity and interaction manner.

Potential inhibitors for molecular docking are mostly sourced from two sources: synthetic and natural substances. Man-made substances called synthetic compounds are intended to interact with particular biological targets. They have the benefit of exact control over their structure and characteristics, which makes it possible to create molecules with strong potency and specificity. Conversely, naturally occurring substances originating from flora, fauna, and microbes have traditionally provided an abundance of therapeutic agents. These substances frequently have intricate structures that allow them to interact with a variety of biological targets, providing distinct modes of action and minimal side effects.

Overall, molecular docking serves as a powerful tool in the rational design and discovery of new drugs. By leveraging both synthetic and natural compounds, researchers can explore a vast chemical space, enhancing the chances of identifying effective inhibitors that can be developed into safe and efficacious therapeutics.

All things considered, molecular docking is a highly useful technique for the logical design and discovery of novel medications. Through the utilization of both artificial and organic substances, scientists can delve into an extensive chemical space, increasing the likelihood of discovering potent inhibitors that can be transformed into secure and efficient medicines [33, 34].

Material and Methods

In this molecular docking analysis, Biovia discovery studio software 2023 was used for the molecular interaction analysis. The Recombinant Human Acetylcholinesterase in Complex with (-)-galantamine protein's X-ray crystal structures (PDB ID: 4EY6) were obtained from the Protein Data Bank. After adding hydrogen to the protein 4EY6 using the force field algorithm, the energy of the protein was reduced in Discovery Studio using the CHARM forcefield. The SDF file of the pentachloronitrobenzene, Rogor (Dimethoate), sodium pentachlorophenate, trichloroacetic acid, trichlorphon, triterpenoid, saponin, steroidal alkaloid molecules were obtained from the PubChem database at https://pubchem.ncbi.nlm.nih.gov. Using the ChemDraw programme, the phytochemical and conventional medications were transformed into three-dimensional coordinates. A torsion tree, sufficient non-polar hydrogen bonds, rotatable bonds, and all of the ligands and their complexes as flawless modules were produced. After that, the energy was decreased and saved in SDF file format for use in docking studies. The ligand binding affinity was determined using the CDOCKER interaction energy, CDOCKER interaction energy, hydrogen bonds, binding energies, protein energy, and ligand-protein complex energy. Negative values were mentioned for the CDOCKER interaction energy. A higher negative energy value signifies a higher molecule-target protein binding affinity.

Result and discussion

In this docking analysis Recombinant Human Acetylcholinesterase in Complex with (-)-galantamine (PDB ID: 4EY6) protein was for the pentachloronitrobenzene, Rogor (Dimethoate), sodium pentachlorophenate, trichloroacetic acid, trichlorphon, triterpenoid, saponin, steroidal alkaloid. The galantamine molecule was used as a standard drug. In the molecular docking results, due to the structure size of the saponin and steroidal alkaloid, they do not form any binding interaction with the active site of the Recombinant Human Acetylcholinesterase protein. The remaining molecules' docking energy is listed out in Table 1.

S. No	*Molecules*	*-CDOCKER interaction energy (kcal/mol)*
1	Galantamine	38.5931
2	Triterpenoid	33.5165
3	sodium pentachlorophenate	29.7655
4	Trichlorphon	29.5394
5	Rogor (Dimethoate)	29.1991
6	Pentachloronitrobenzene	26.0897
7	Trichloroacetic acid	21.7381

Table 1: The molecular docking energy of the molecules.

From the docking analysis, the standard drug Galantamine shows more binding interaction with the Recombinant Human Acetylcholinesterase than other molecules. The molecular docking energy is -38.5931 Kcal/mole. The Tyr 341 and Tyr 124 form the two strong Hydrogen bonds with the two oxygen atoms the Galantamine (Figure 1). Further, the Tyr 337 shows the Pi-Pi T-shaped integration with the target protein 4EY6. The other active site amino acids form the Van der Waals interaction with the Galantamine drug.

The OH group of the Triterpenoid molecule forms one strong Hydrogen bond with the 4EY6 active site. But it forms many alkyl, Pi-alkyl and van der Waals interactions with the active site amino acids. The binding energy of the Triterpenoid molecule is -33.5165 Kcal/mol (Figure 2). When these interactions come together, the triterpenoid molecule inside the 4EY6 enzyme's active site adopts a very stable binding shape. The triterpenoid molecule's predicted binding energy of -33.5165 Kcal/mol suggests a robust and energetically advantageous binding mechanism. A sustained and efficient inhibitor or substrate binding within an enzyme's active region is characterized by the release of energy, which is what this negative binding energy value indicates.

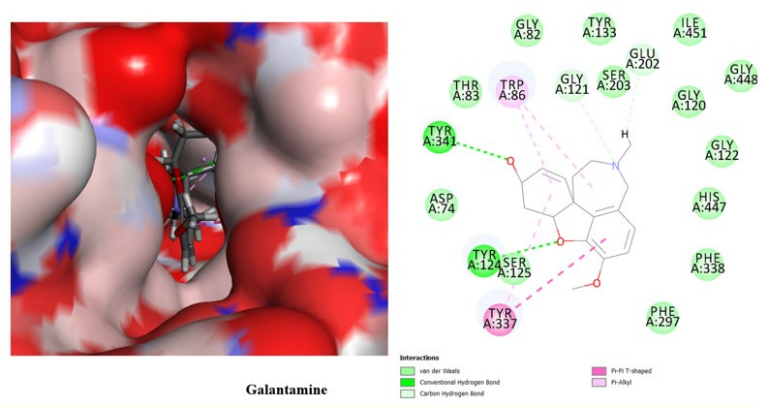

Figure 1: 3D and 2D binding interaction of the Galantamine with the 4EY6 target protein.

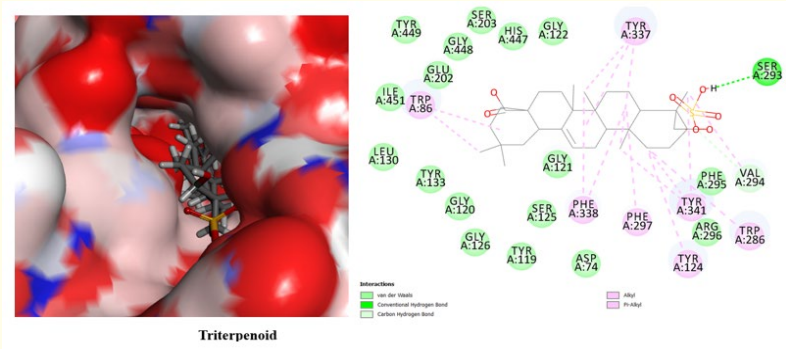

Figure 2: 3D and 2D binding interaction of the Triterpenoid with the 4EY6 target protein.

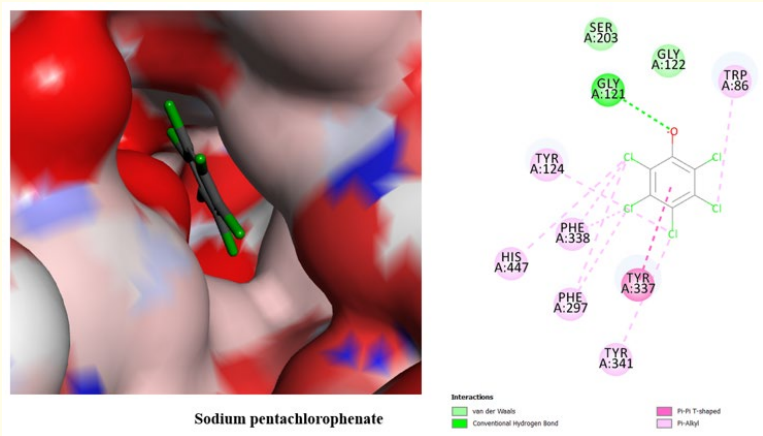

Figure 3: 3D and 2D binding interaction of the Sodium pentachlorophenate with the 4EY6 target protein.

The Sodium pentachlorophenate molecule shows the -29.7655 Kcal/mol docking energy with the 4EY6 target protein. The Oxygen atom of the Sodium pentachlorophenate forms a strong hydrogen bond with the Gly 121 amino acid. The aromatic benzene molecule shows the Pi-Pi-T-shaped interaction with the Tyr 337. Further, the Cl atoms show the Pi-Alkyl interaction with the active site amino acids (Figure 3). The specific interaction profile between sodium pentachlorophenate and the 4EY6 target protein demonstrates the substance's powerful binding capabilities. The variety of interactions guarantees the molecule's precise and stable binding inside the active site, which is essential for its biological activity and efficacy as a possible therapeutic agent.

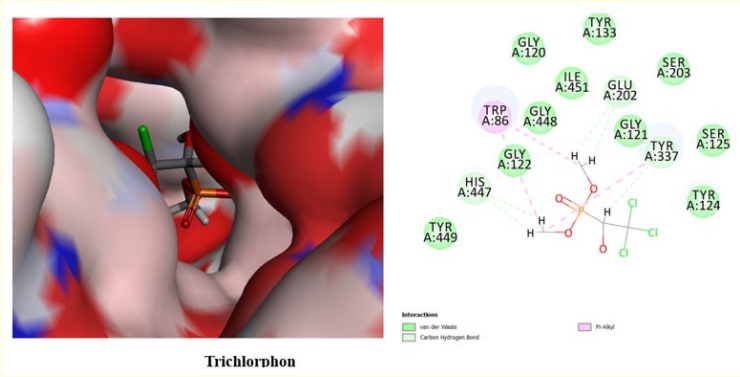

Figure 4: 3D and 2D binding interaction of the Trichlorphon with the 4EY6 target protein.

In figure 4, depicted the molecular interaction of the Trichlorphon with the 4EY6 target protein. In this analysis, the methyl group of the Trichlorphon forms the Pi-Alkyl interaction with the Tyr 337 and Trp 86 amino acids. The Glu 202 interacted with the one methyl group by carbon-hydrogen bond. The docking energy of the Trichlorphon with the 4EY6 target protein is -29.5394 Kcal/mol. Trichlorphon's intricate network of interactions with the 4EY6 target protein underpins both its binding affinity and stability, according to a thorough molecular interaction analysis. The selectivity and durability of the binding are demonstrated by the combination of Pi-Alkyl interactions with important aromatic residues and a carbon-hydrogen bond with Glu 202, underscoring Trichlorphon's potential utility as a bioactive chemical that targets the 4EY6 protein.

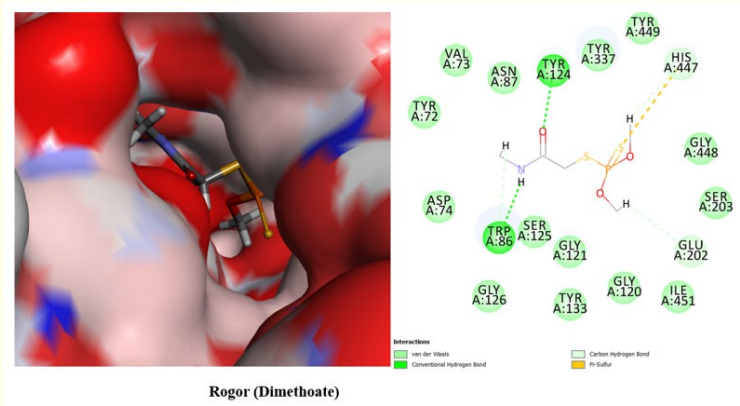

Figure 5: 3D and 2D binding interaction of the Rogor (Dimethoate) with the 4EY6 target protein.

The molecular docking energy of the Rogor (Dimethoate) is -29.1991 kcal/mol. The active site amino acids Tyr 124 and Trp 86 form two strong hydrogen bond interactions with the Oxygen and NH groups of the 4EY6 target protein. Additionally, the Glu 202 forms the conventional hydrogen bond with the methoxy group (Figure 5). A comprehensive and strong contact network is revealed by the thorough molecular interaction investigation of rogor (dimethoate) with the 4EY6 target protein. The high binding affinity and stability of Rogor within the active site are attributed to the strong hydrogen bonds with Tyr 124 and Trp 86, in addition to the usual hydrogen bond with Glu 202. The strength and favorability of these contacts are highlighted by the docking energy of -29.1991 kcal/mol, underscoring Rogor's potential efficacy as a bioactive chemical that targets the 4EY6 protein.

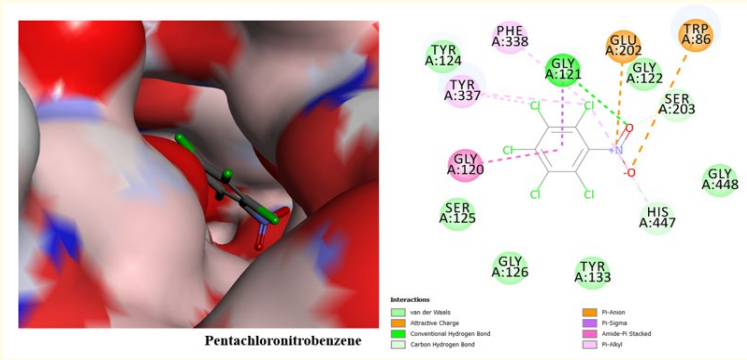

Figure 6: 3D and 2D binding interaction of the Pentachloronitrobenzene with the 4EY6 target protein.

The Pentachloronitrobenzene forms one strong hydrogen bond with the Gly 121 amino acids. The molecular docking energy of the Pentachloronitrobenzene is - 26.0897 Kcal/mol. Also this molecules forms Pi-anion, Pi-sigma, Amide-pi-Stacked and Pi-Alkyl interaction with respective amino acids (Figure 6). The aromatic benzene group of the Pentachloronitrobenzene forms the Amide-pi-Stacked interaction with the Gly 120 and Gly 121 amino acids. Pentachloronitrobenzene's complex network of interactions supporting its binding affinity and stability with the 4EY6 target protein is revealed by a thorough molecular interaction investigation. A very particular and persistent binding conformation is guaranteed by the combination of a strong hydrogen bond with Gly 121, Pi-anion, Pi-sigma, Amide-Pi stacking, and Pi-alkyl interactions. The strong and positive contact is highlighted by the docking energy of -26.0897 Kcal/mol, indicating Pentachloronitrobenzene's potential as a bioactive chemical that targets the 4EY6 protein. These interactions are detailed in Figure 6, which also highlights the molecular dynamics involved.

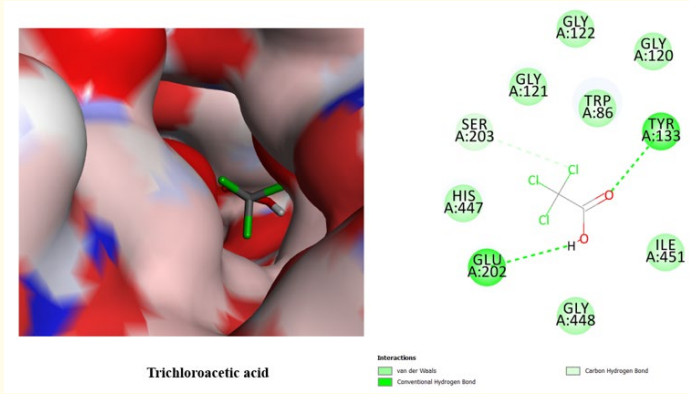

Figure 7: 3D and 2D binding interaction of the Trichloroacetic acid with the 4EY6 target protein.

Ketone and OH groups of the trichloroacetic acid form two strong hydrogen bond interactions with the Tyr 133 and Glu 202 amino acids. The other active site amino acid forms the van der Waals interaction with the trichloroacetic acid (Figure 7). The molecular docking energy of the trichloroacetic acid is - 21.7381 Kcal/mol. Trichloroacetic acid's intricate network of interactions with the 4EY6 target protein underpins both its binding affinity and stability, according to a thorough molecular interaction investigation. A very specific and stable binding conformation is ensured by several van der Waals interactions in addition to two strong hydrogen bonds with Tyr 133 and Glu 202. The strong and positive contact is highlighted by the docking energy of -21.7381 Kcal/mol, which also highlights the potential effectiveness of trichloroacetic acid as a bioactive chemical that targets the 4EY6 protein. A thorough understanding of the molecular dynamics at work is provided by the detailed illustrations of these interactions in Figure 7.

Summary

These chemicals' binding affinities and stabilities are partly attributed to a variety of intricate interaction networks, as shown by the molecular docking studies conducted with the 4EY6 target protein. The durability and specificity of these binds are highlighted by the strong hydrogen bonds and a variety of non-covalent interactions, including van der Waals forces, Pi-alkyl, Pi-Pi, and Pi-anion interactions. The compounds' potential efficacy as bioactive agents targeting the 4EY6 protein is highlighted by the computed binding energies, which demonstrate the energetically favorable nature of these interactions. The comprehensive interaction profiles offer insightful information for these drugs' continued research and optimization in therapeutic applications.

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