"Investigating the Potential Anti-Alzheimer's Agents via Molecular Docking of a 3,4 Dihydropyrimidinone Derivative"

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Abstract:

In this study, the focus was on the Ache active site as a target protein for Alzheimer activity. Pyrimidine compounds are used as cholinesterase inhibitors that also consist of pyrimidinone rings. Thirty-five novel 3,4 dihydropyrimidinone derivatives were subjected to molecular docking studies using AutoDock Vina Ver. 1.1.2 to investigate their binding to the AChE active site. The AChE active site with Protein Data Bank code 4EY7 was used as a reference for docking. The docking scores were analysed, and the interactions between the derivatives and the active site were studied. The results of this molecular docking study suggest that all the newly designed pyrimidinone derivatives have the potential to be synthesized and further evaluated for in vitro studies. These findings provide valuable insights for the development of novel antialzheimer's agents targeting the ACHE transporter. Further in vitro and in vivo research is required to validate the effectiveness of these substances as potential anti-Alzheimer's treatments.

Keyword: Anti-Alzheimer's,3,4 dihydropyrimidinone derivative,4EY7, AutoDock, vina, chem draw

1.INTRODUCTION:

A neurodegenerative condition that progresses over time is Alzheimer's disease (AD). The primary cause of dementia, Alzheimer's disease, is quickly overtaking all other chronic, fatal, and costly diseases in our century [1]. It is characterized by behavioural changes and a steady worsening of psychological features together with a decline in daily activities. Dementia is mostly caused by Alzheimer's disease (AD), a brain cell-damaging illness characterized by an impairment in thinking ability and independence with daily tasks. It is the most prevalent kind of pre-senile and demented state. The basic functions of the disease most likely interact with age-related, protective, and disease-promoting variables. As the illness worsens, symptoms such as behavioural issues, mood swings, self-neglect, motivational decline, difficulties with language, and confusion (including getting lost easily) might appear [2]. Worldwide,5% of men and 6% of women over 60 suffer from Alzheimer's type dementia, according to the World Health Organization (WHO) [3].

As the cause of AD there are many theories have consequently been proposed. Although the simultaneous presence of tau and amyloid is still required to diagnose Alzheimer's disease, the most common cause of dementia, scientists are now gradually shifting away from the basic linear causality assumption made in the very first amyloid hypothesis [4]. Three to twelve years is the average lifespan after diagnosis, though the rate of progression can vary. Amyloid is one of the proteins that is involved; deposits of this protein surround brain cells in the form of plaques. The other protein is known as tau, and deposits of it cause tangles in brain tissue. A reduction in the chemical messengers, or neurotransmitters, that are responsible for conveying signals or messages between brain

cells occurs when brain cells are impacted. The cholinergic hypothesis, which claims that reduced synthesis of acetylcholine, a neurotransmitter is the

cause of Alzheimer's disease, is one of the oldest theories and the foundation for the majority of pharmacological therapy [5]. It has been discovered that AD is characterized by cholinergic neuron degeneration, which results in changes in cognitive function and memory loss. It is thought that B-amyloid inhibits cholinergic neurotransmission, reducing choline absorption and releasing Ach [6].

Treatments now available, such as acetylcholinesterase inhibitors like galantamine, rivastigmine, and donepezil and N-methyl d-aspartate receptor antagonists like memantine, have minimal impact on the illness and only treat its advanced stages [7]. These medications help with symptoms and slow down the disease's progression, but they don't provide a permanent cure. The remaining Cholinesterase inhibitors used to treat Alzheimer's disease, such as galantamine, donepezil, and rivastigmine, have GI adverse effects and renal problems when taken continuously. Consequently, people experiencing various issues require an anti-Alzheimer medication that doesn't have any negative side effects.

In the field of medicinal chemistry, heterocyclic molecules represent a vast area of study. They have been significant in the development of many medicinal chemistry therapeutic compounds. These agents are generally found in nature and play a vital role in many aspects of daily existence. Heterocyclic compounds with sulphur, nitrogen, and oxygen in the heart of them serve as a unique and adaptable framework for the development of experimental drugs. Pyrimidine is one of these heterocyclic compounds having a varied range of pharmacological activity [8]. In 1893, Pietro Biginelli used an acidic ethanol-based one-pot three-component cyclo-condensation process using 3-hydroxyl benzaldehyde, ethyl acetoacetate, and urea to produce the first known synthesis of 3,4-

dihydropyrimidin-2(1H)-one [8]. 3, 4-Dihydropyrimidinone became a significant class in the field of medicinal chemistry. Other biological properties included antibacterial [9], antifungal [10], antiparasitic [11], antitubercular agent [12], antiviral [13], antimuscarinic [14], anticonvulsant activity [15], antithyroid [16],

antimalarial [17], calcium channel blockers [18,19], antihypertensive [20], hypolipidemic [21], antioxidant [22], anti-inflammatory [23], anticancer [24], and anti-parasitic [25]. Due to its numerous pharmacological and biological properties, including its ability to inhibit enzymes such as urease [26], acetylcholinesterase [27], and act as an agonist on the GABA receptor [28]. To identify the residues associated in the 3, 4-Dihydropyrimidinone regulatory action on Ache, docking analysis was also performed.

2.EXPERIMENTAL DETAILS:

2.1 Preparation of Target Protein X-ray Structure:

The X-ray crystal structure of the Ache, which was acquired from http://ww.pdb.org, showed the target protein to be donepezil bound at the active site (PDB ID: 4EY7).

2.2 Design of Novel 3,4 Dihydropyrimidinone Derivatives:

Identifying the pharmacophore, changing the pharmacophore's substituent, and generating a list of novel substituents are the three steps in the innovative drug development process. In this study 3,4 Dihydropyrimidinone are pharmacophores as the anti-Alzheimer agent. The several substituents designated for designing novel analogues contain -Cl, -CF3, -NO2, -CH3, -CH (CH3)2, -NH2, -OCH3 and so on.

2.3 Ligands Preparation:

Cambridge Soft's Chem Draw Ultra 8.0 program was utilized for creating the structures of 3, 4-Dihydropyrimidinone derivatives, such as DP-1 to DP-36. The Chem 3D Ultra 8.0

tool was utilized to transform the 2D structures of the suggested ligand into a 3D structure. Using the semi-empirical PM3 technique and a termination RMS gradient of 0.001 KCal/mol for extreme up to 1000 interactions, the proposed ligands were optimized and their energy was minimized. The results were saved as PDB arrangement, which the Auto Dock vina software could read. After that, the drug-likeness property was determined by Swiss ADME tool.

2.4 Molecular Docking Studies:

The computational simulation of a ligand interacting with a receptor or target protein is known as "molecular docking," and it helps forecast the ligand's binding to the target protein in order to see its affinity and activity. Efficient docking strategies use scoring functions to explore high-dimensional regions and prioritize molecules for further study. Docking enables the virtual screening of large chemical libraries, result rating, and the creation of structural hypotheses for ligand binding. Using molecular docking methods like AutoDock vina Version 1.1.2, the ache interaction and the study of 3, 4-Dihydropyrimidinone derivatives have been assessed. We used the Ache's X-ray crystal structure (PDB ID: 4EY7), which was obtained from http://www.pdb.org, as the target protein, where donepezil was bound at the active site. Redocking the ligand into its binding pocket of 4EY7 acted as an authentication of the docking process before the ligand examination.

3. RESULTS AND DISCUSSION

Molecular docking enables a computational method called virtual screening that finds new bioactive compounds in huge chemical libraries. By guiding drug-receptor interactions, these methods help designers of new medications by providing knowledge about the relationship between ligands and target proteins. Small compounds are

identified with the use of computer-aided drug design, which scores and aligns them in the target protein's active site.

The target protein for the docking simulation technique was Ache, and the tools used were 3, 4-Dihydropyrimidinone derivatives and AutoDock vina Version 1.1.2Based on two factors, such as the comparison of fitness function scores and the position of ligand binding, this software chose the best docked. The root-mean-square distance (RMSD) was the parameter used to determine the optimal ligand binding place. Table 1 displays the binding energy value of the derivatives of 3, 4-Dihydropyrimidinone.The approximate docking score of twenty- two 3, 4-Dihydropyrimidinone derivatives was between -9 and -10 kcal/mol. The DHP – 11 derivative showed higher docking scores compared to the standard compound donepezil.

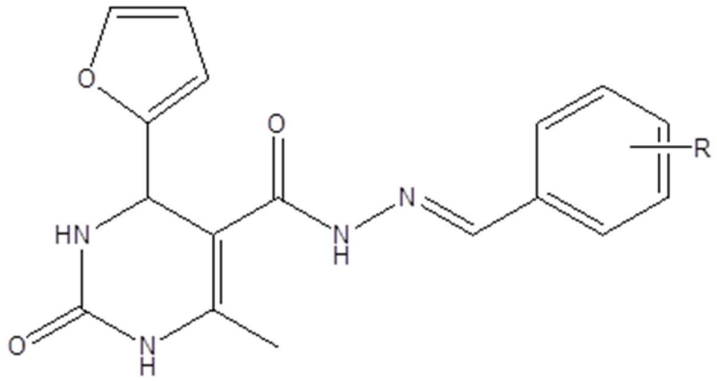

Figure 1: The general structure of 3,4 Dihydropyrimidinone Derivatives

Table 1. Docking Score of 3,4 Dihydropyrimidinone derivative with AChE

Active site

Ligand	Binding Affinity (kcal/cal)	Ligand	Binding Affinity (kcal/mol)	Ligands	Binding Affinity (kcal/mol)
DHP -1	-9.1	DHP-14	-8.7	DHP-28	-8.0
DHP-2	-9.0	DHP-15	-9.2	DHP-29	-9.5
DHP-3	-9.6	DHP-16	-9.1	DHP-30	-8.2
DHP-4	-8.5	DHP-17	-8.8	DHP-31	-8.1
DHP-5	-9.4	DHP-18	-9.4	DHP-32	-8.3
DHP-6	-9.1	DHP-19	-9.4	DHP-33	-8.7
DHP-7	-8.8	DHP-20	-8.0	DHP-34	-8.3
DHP-8	-9.0	DHP-21	-8.1	DHP -35	-9.0
DHP9	-9.2	DHP-22	-8.5	DHP-36	-8.8
DHP-10	-8.9	DHP-23	-9.0		
DHP-11	-8.4	DHP-24	-8.9		
DHP-12	-8.0	DHP-25	-9.0		
DHP-13	-8.8	DHP-27	-9.1		
STD-	-8.6				

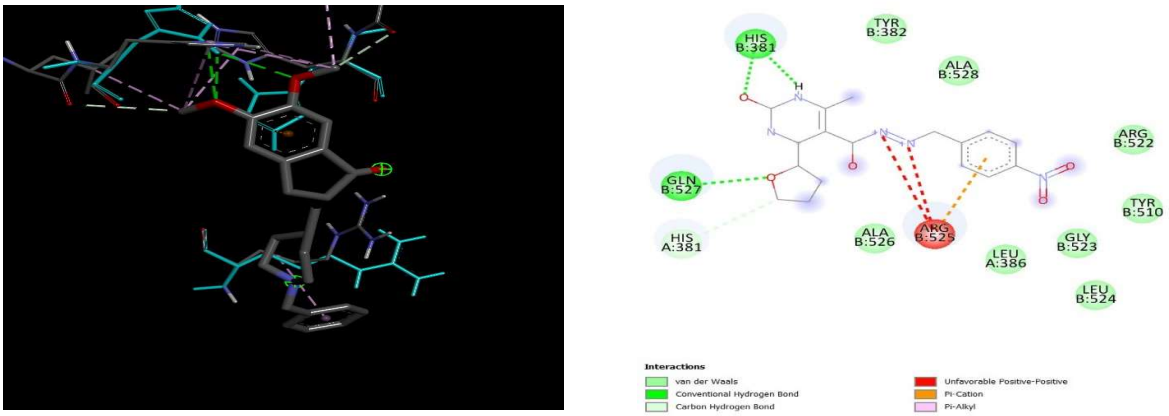

Figure 2: 3D &2D structure of donepezil interact with AChE active site

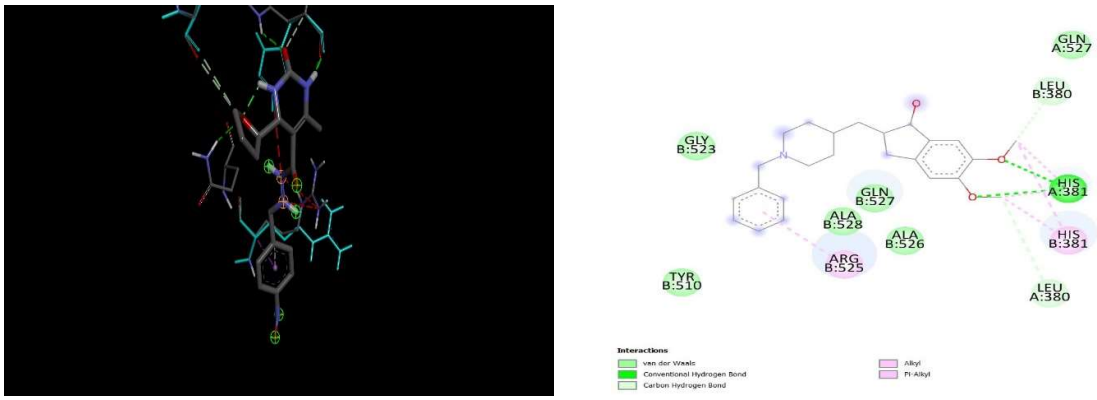

Figure 3:3D& 2D structure of DHP 3 interact with AChE active site

4.CONCLUSION:

In this research, the molecular structures of thirty-six novel pyrimidine-derived 3,4 dihydropyrimidinone derivatives with an aldehyde group on the ring were analysed. After that, docking tests were conducted on these compounds to determine how they interacted with the structure of the 4EY7 protein. High-affinity ligands for 4EY7 were found using the docking scores that were obtained. The result revealed that twenty-two derivative exhibited higher docking score compared to donepezil, indicating stronger binding energy and interaction with the target protein. However, further investigations involving

synthesis and in vitro evaluations are necessary to assess their actual anti-Alzheimer's activity.

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