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In-Silico Docking of Fused Ring Heterocyclic Compounds on Human Bace-1 and Amyloid Precursor Protein Receptors using Pyrex Docking for Predicting Anti-Alzheimer's Activity

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Thomas Kurian*

Associate Professor, College of Pharmacy Govt. Medical College, Alappuzha, Kerala

***Corresponding Author:** Thomas Kurian, Associate Professor, College of Pharmacy Govt. Medical College, Alappuzha, Kerala.

Abstract

Eight heterocyclic compounds with chalcone, isoquinoline, quinoline, coumarin, benzothiazole pyrazolopyridine, and a chondroitin derivative were tested in-silico using PyRX docking with auto dock vina tool; the docking of ligands was carried out on two receptors associated with Alzheimer's disease, Human BACE-1 complex with AYH011 and Alzheimer's disease amyloid precursor protein copper binding domain. The standard drugs tested for validation of the methods were donepezil and Resveratrol. The promising candidates selected for further studies were chondroitin 4,6 disulphate(,-7.3,-5,6), 4-chloro chalcone(-7.1,-6.8), 4-chloro-6-fluoro quinoline(-6.2,-5.8), 3-chloro iso coumarin (-6,1,-5.7) based on comparison to Donepezil(-8.3 ,-7.0) and Resveratrol (-6.9,-6.7).The Swiss-ADME parameters were found satisfactory. Lipinsky rule was followed (Swiss- ADME). Heterocyclic compounds have been widely used for the development of drugs for diseases like cancer and Alzheimer's. Further structural modification and clinical and animal studies are yet to be done for drug development. SAR techniques can be employed to develop better lead molecules.

Keywords: Alzheimer's; PyRX; Fused- Heterocyclics; Docking; Validation

Introduction

Alzheimer's disease is a neurodegenerative condition that worsens over time and impairs memory, thinking, and reasoning. The buildup of amyloid β plaques and other relevant variables causes the illness to start. The condition can be inherited up to 80% of the time. It is predicted to increase threefold in the upcoming years and is regarded as a global threat [1]. Cholinesterase inhibitors serve a critical role in preserving the cholinergic levels in the brain, which are necessary for memory and cognition, in the face of a steady loss in cholinergic activity. An increased level of extracellular senile plaques and intracellular neurofibrillary tangles with diminished cholinergic activity in the brain will lead to Alzheimer's disease [2]. It also affects how Aβ plaque develops in the brain. The primary goal of the AD treatment plan is to limit the disease's progression. Reducing Aβ plaque production or dissolving

pre-existing Aβ plaque in the brain can accomplish this. Tau phosphorylation is also caused by Aβ plaque. Aβ plaque causes neuronal death and neurofibrillary tangles in the brain [3]. The γ- and β-secretase enzymes also control Aβ production and neurofibrillary tangles formation. α-secretase inhibits Aβ plaque with the modulation of cholinergic activity. Cholinomimetics is the only approved medication for the treatment of AD because it suppresses the formation of Aβ plaque and γ secretase [4]. Their primary function is to boost brain cholinomimetic actions by acting as anticholinesterase agents. In AD, monoamine oxidase inhibitors help with cognitive deficiencies. They improve many of them and reverse the creation of Aβ plaque [5]. They show promise as therapy agents for AD. Another way to treat AD is to manage neuroinflammation and oxidative stress. The ring system of many medications that treat conditions like cancer, Alzheimer's, Parkinsonism, and inflammation contains heterocyclic molecules. Pyrazolo-pyridines, coumarin, chalcone, quinolones, dihydroisoquinolines, pyridine-oxadiazoles, and Benzothiazole scaffolds are frequently utilized [6]. In Alzheimer's disease medications, nitrogen plays a vital role. Heterocyclic compounds have a role in calcium homeostasis and trafficking, while mitochondrial calcium homeostasis and signaling have a role in AD [7].

Materials and Methods

Test Ligands

Chondroitin 4,6-disulfate, 4-Chlorochalcone, 3-chloroisochromen-1-one, 1,4-dichloroisoquinoline, 4-chloro-6-fluoroquinoline, 6-bromo-2-methyl-1,3-benzothiazole, 4-chloro-3-(2-chloroethyl) pyrazolo[4,3-b] pyridine, 1-(5-chloropyrazolo[3,4-c] pyridin-1-yl) ethenone [8-15].

Standard ligands

5-[(E)-2-(4-hydroxyphenyl) ethenyl] benzene-1, 3-diol (resveratrol), 2-[(1-benzylpiperidin-4-yl) methyl]-5, 6-dimethoxy-2, 3-dihydroinden-1-one (donepezil) [16-17].

Receptors (18-19)

3K5F - Human BACE - 1 COMPLEX AYH 011 (figure 1).

1OWT - Alzheimer's disease amyloid precursor protein copper binding domain (figure 2).

PyRX software

PyRX (0 .8) was utilized in the study, which is developed in Python and can be downloaded and run on any computer that meets the required configuration and specifications. The study used an HP Intel Core i5 5th Generation system with 8 GB RAM, running Windows 10 software and featuring HD Graphics. Input files were obtained by downloading the SD format of ligands from Pub Chem. Auto dock Vina, which PyRX provides, was used for docking. The receptor and ligand were loaded and prepared for docking by preparing PDBQT files. The grid box was established by selecting the protein and ligand and proceeding by clicking the forward button. The grid box was adjusted according to the docking requirements, and the level of docking exhaustiveness was specified by entering the relevant numerical value. Finally, the docking process was initiated by clicking the forward button, and the poses, affinities, and RMSD values were obtained. Analysis was performed using PYMOL, where PDB/PDBQT protein and vina output files were opened. The Swiss ADME bioavailability tool was used for drug-likeness to obtain RADAR predictions of compounds with good activity and ADME prediction. The same procedure was used for redocking, and the binding affinity was obtained [6-7].

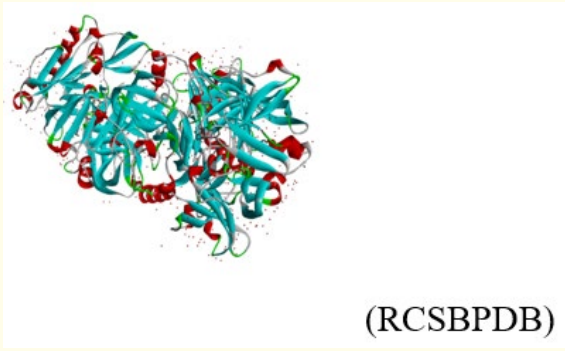

Figure 1: 3K5F -Human BACE - 1 COMPLEX AYH 011.

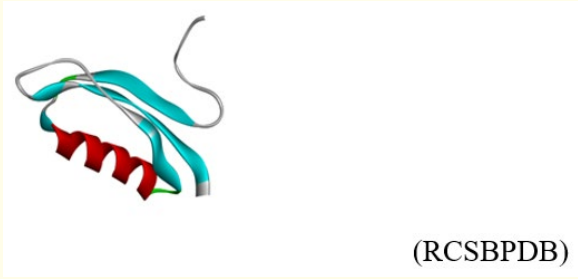

Figure 2: 1OWT- Alzheimer's disease amyloid precursor protein copper binding domain.

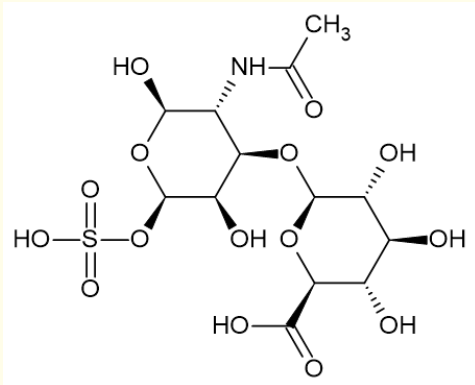

Figure 3: Chondroitin 4, 6-disulfate (348316420) (PubChem).

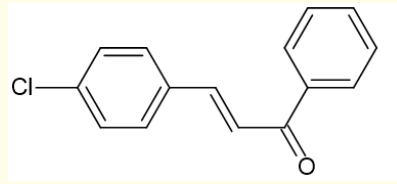

Figure 4: 4-chlorochalcone (5377022) (PubChem).

Results and discussion

Ligand name with Pub Chem ID	***Human BACE - 1 COMPLEX AYH 011*** ***Binding Energy***	***Alzheimer's disease amyloid precursor protein copper binding domain*** ***Binding Energy***
Donepezil (3152) standard drug	**-8.3**	**- 7.0**
Chondroitin 4,6-disulfate (348316420) **(figure :**3)	-7.3	-5.6
4-chlorochalcone (5377022**)** **(figure:** 4)	-7.1	-6.8
3-Chloro 150 coumarin (560737)	-6.1	-5.7
1, 4-dichloro quinoline (640955)	-6.3	-5.5
Resveratrol (445154) standard drug	**-6.9**	**-6.7**
4- Choro - 6 fluoroquinolone (2736583)	-6.2	-5.8
6- Bromo-2-methyl Benzothiazole (13848)	-5.5	-5.1
2-Chloroethyl-4-chloropyrazolo pyridine (129840414)	-5.8	-5.3
1- Acetyl -5- Chloro Pyrazolo-pyridine (12668483)	-6.5	-5.4

Table 1: Docking Results.

Table Swiss ADME Prediction-Chemo informatics of significant leads selected

Property	***Aromatic Compounds:***	***Score***	***Substituted aromatic Heterocyclic Compounds***	***Score***	***Polysaccharide derivative)***	***Score***
lipophilicity	4-Chlorochalcone	2.82	3-Chloroisochromen-1-one	1.98	Chondroitin 4,6-di-sulfate	-0.62
Water solubility		-4.81		-3.31		0.70
Absorption		high		high		low
Drug Likeliness		yes		yes		low
Synthetic accessibility		2.42		2.77		5.58
Lipinski Violations		0		0		2

The present study revealed that among the eight heterocyclic compounds selected for the survey of two targets about Alzheimer's disease, Chondroitin 4, 6-disulfate exhibited minimum binding energy, indicating a good predicted biological activity. [Table 1] The binding energies were calculated as (– 7.3) for the Base-1 receptor and (-6.1) for the amyloid precursor protein receptor. The following compound of interest found was 4-chlorochalcone (– 7.1) Base-1 receptor and (-6.8) for amyloid precursor protein receptor. The other compounds also showed promising activity 1, 4-dichloroquinoline. (– 6.3) Base-1 receptor and (-5.5) for amyloid precursor protein receptor, respectively. For other values, refer to Table). The remaining heterocyclic compounds gave comparable values, predicting their anti-Alzheimer activity on 3K5F -Human BACE - 1 complex AYH 011 and 1OWT- Alzheimer's disease amyloid precursor protein copper binding domain.

The compound of choice that gave a good score can be considered a lead compound for anti- Alzheimer's drug development. Further structural modifications and in vivo studies must be done for better drug development. The ADMET parameters of these compounds were found satisfactory and are represented in [Table 2]. Any discovery intended to improve human health is of high value. Molecular docking is an Insilco technique that predicts the mode of interaction of small molecules. Like drugs to macromolecular targets, the small molecule can be a phytochemical or a synthetic heterocyclic compound, a semisynthetic derivative, or a natural or marine chemical. This technique helps drug discovery, eliminating the non-significant compounds from further biological testing. It saves money and time in the research of drugs. Alpha-amyloid buildup and tau protein hyperphosphorylation are two hallmarks of Alzheimer's disease, a complex neurodegenerative illness. There are interrelated mechanisms at play in the disease. Nitrogen-containing heterocycles are crucial to biological processes because of their abundance in nature, their role as building blocks of biological molecules and/or macromolecular structures, and their biological activity. In the process of finding new drugs, nitrogen-containing heterocycles are essential. 60% or more of small-molecule medications. One crucial area of research is the creation of safe, affordable, and highly effective treatment medicines that use nitrogen-containing heterocycles to treat AD. The function of nitrogen heterocycles in drug discovery and development procedures for many human diseases is covered in several papers in the literature, along with a more in-depth analysis of triazole derivatives as anti-AD drugs. One of the most crucial heterocyclic building blocks for identifying substances with biological activity is pyridine. A five-membered aromatic nitrogen heterocycle, pyrazole, has various pharmacological, biological, and chemical characteristics. The pyrazole scaffold is present in several clinically FDA-approved medications, such as rimonabant, enpiprazole, celecoxib, and sulfathiazole. According to reports, the Pyrazolo [1, 5-a] pyrimidinone scaffold serves as the basis for the first-in-class histone deacetylases (HDACs) and phosphodiesterase-5 (PDE5) dual inhibitors used to treat AD.

Conclusion

The study concludes by showing the encouraging potential of heterocyclic compounds containing nitrogen as prospective anti-Alzheimer's medication candidates. Chondroitin 4, 6-disulfate showed the most favorable binding energy among the substances examined, suggesting substantial biological action against the amyloid precursor protein receptor and Base-1 receptor. The notion that these substances may have therapeutic relevance in the treatment of Alzheimer's disease is further supported by the promising binding affinities of other compounds, including 1, 4-dichloroquinoline and 4-chlorochalcone. The discovery of possible lead compounds that could be turned into potent medications was made easier by the molecular docking study, which offered vital insights into how these compounds interacted with essential targets. These results highlight the importance of nitrogen-containing heterocycles in developing new drugs, as they are necessary for biological activities. These findings highlight the importance of nitrogen-containing heterocycles in creating safe, affordable, and effective therapeutics for Alzheimer's disease, as they are essential to biological processes and drug discovery. To validate these compounds' safety and effectiveness and open the door for their possible usage in therapeutic settings, more structural optimization and in vivo research are necessary.

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Conflict of interest

There is no conflict of interest.

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