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Molecular Docking Study of Benzothiazole Derivatives for Anti-Alzheimer's Activity on Human BACE-1 Complex AYH- 011 Target

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Abstract

Benzothiazole derivatives have become a topic of interest in modern pharmacology due to their various pharmacological actions, such as their ability to fight cancer, bacteria, fungi, and HIV. This study investigated the potential of five benzothiazole derivatives with distinct functional groups as anti-Alzheimer's compounds. All derivatives, except Thiazoloquinazolinedione and ethionamide, have a pyrimidine ring in addition to the benzothiazole moiety. The study used molecular docking techniques to evaluate the binding affinity of these derivatives to the protein complex 3K5F - Human Bace-1, which is associated with Alzheimer's disease pathology. Thiazoloquinazolinedione had the highest docking score (-6.8) comparing the ligand AYH (-7.0) upon redocking. Specific interaction points were identified within chains A and B of the protein complex, indicating promising ligand-receptor interactions. The study highlights the significance of benzothiazole derivatives in Alzheimer's research, citing previous reports of their potential to reduce β-amyloid plaques, a hallmark of the disease. As SWISS-ADME predictions indicate, these compounds have weak base properties, unique methine centres in the thiazole ring, favourable blood-brain barrier penetration, and reduced toxicity. Further pharmacological, structure-activity relationship (SAR), and synthetic studies are necessary to elucidate their therapeutic usefulness and confirm their effectiveness in fighting Alzheimer's disease, thereby advancing the search for life-saving treatments in medicinal chemistry.

Keywords

Docking, Benzothiazole, Heterocyclic, Alzheimer's

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INTRODUCTION

Plaques and tangles of insoluble amyloid-b and tau proteins are formed in the brain during Alzheimer's disease. Amyloid-b and tau proteins, normally soluble, connect to form amyloid-like filaments that accumulate in the brain. Tau inclusions are also observed in various related disorders and Alzheimer's disease. Genetic studies have shown that either amyloid-b or tau dysfunction is enough to trigger the onset of dementia. The risk of Alzheimer's disease (AD) increases significantly as people age. Small plaques and tangles are typically observed over time and regarded as early disease indications. Tangles usually begin forming in the trans-entorhinal region before spreading to other parts, such as the hippocampus, amygdala, and neocortical regions.

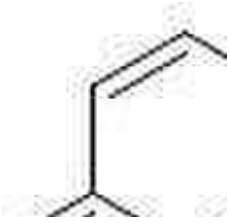
In contrast, amyloid-b deposits tend to appear first in the neocortex. It is fascinating to note that the formation of these two inclusions seems unrelated, with tangles appearing before amyloid-b deposits.

However, in the later stages of the illness, significant amyloid-b deposition in the neocortex has been reported to precede the development of severe tangle pathology. As a result, researchers have suggested that amyloid-b deposition may accelerate age-related tau pathology, which is consistent with the overproduction of amyloid-b seen in cases where APP gene mutations and duplications are present. [1-2]

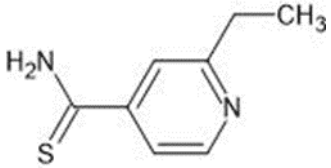
Benzothiazole is a heterocyclic aromatic compound that plays a crucial role in medicinal chemistry due to its organic structure, a combination of benzene and thiazole fused to form a bicyclic compound. Nowadays, various benzothiazoles have different pharmacological properties. The vitamin B group is the most critical natural compound containing a nitrogen heterocyclic ring. One of the examples of such a compound is Vitamin B6. Thiazole is structurally related to thiophene and pyridine, but its properties are more similar. The core structure of thiazole and many biologically active compounds contain nitrogen and sulphur atoms. In recent years, several benzothiazole-based anti-inflammatory agents have been synthesized. For instance, some novel derivatives of 2-amino benzothiazole were tested for anti-inflammatory activity. The test compounds showed significant anti-inflammatory activity, and it was observed that substituting 2-amino benzothiazole at 4 or 5 positions with electron-withdrawing groups such as Cl, NO2, and OCH3 resulted in increased anti-inflammatory activity. The antimalarial activity of 2-substituted-6-nitro and 6-amino benzothiazoles and their anthranilic acids were evaluated on W2 and 3D7 strains of P. falciparum. The results showed that these compounds are potent antimalarial agents for clinical and biological research. Various approaches have been made to investigate the role of the benzothiazole moiety as an antimicrobial agent since its discovery. A series of benzothiazoles were synthesized by conjugation addition to the Imino nitrogen of 2-amino benzothiazoles to the alkyne carbon atom of acetylenic acid, followed by ring closure, and the synthesized compounds were studied for antimicrobial activity against E. coli and Enterobacter as test organisms at a concentration. The synthesized compounds were also evaluated as an amyloid imaging agent in Alzheimer's disease, and they exhibited excellent features comparable to those of other agents, such as good affinity for amyloid plaques present in human Alzheimer's disease. Aryl-substituted benzothiazoles were synthesized by reacting o-amino phenols with substituted benzoic acid in the presence of polyphosphoric acid at a higher temperature and evaluated against human cervical cancer cell lines for their anticancer activity. [3-4]

The selected heterocyclic compounds share a common benzothiazole core and some similarities in their ring systems. Still, they differ significantly in the presence or absence of a pyrimidine ring, the nature of other substituents, and the functional groups they contain. These differences likely influence their chemical properties and biological activities.

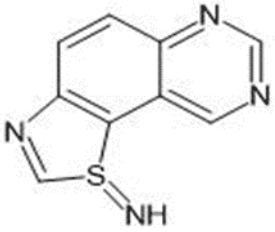
Figure:1 Thiazole Heterocyclic Compounds under study



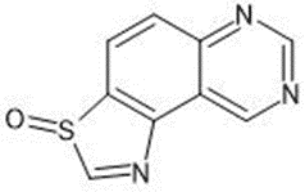
Thiazoloquinazolinedione



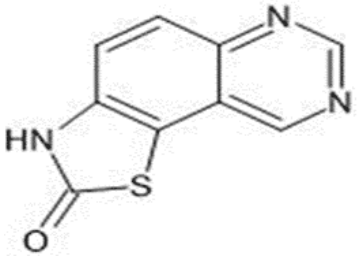
Ethionamide



Imino pyrimidobenzothiazole



Benzothiazolopyrimidone



MATERIALS AND METHODS

Receptor 3K5F human BACE - 1 COMPLEX AYH 011 (Figure 2)

Doi: https://doi.org/10.2210/pb. Classification: hydrolase/hydrolase inhibitor Organism(s): Hom sapiens. Expression system: Escherichia coli BL21 (DE3). AY Ligand of Interest in 3K5F designated by the RCSB.

AYH (IR 3S) -3-11 (1-acetylamino)-1-methyl ethyl)-N-(Is, 2S, 4R)-1-benzyl-5- (butyl amino)-2-hydroxy -4-methyl-5-isopentyl) cyclohexane carboxamide [5]

PyRX software was utilized for 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 Sdf 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] (figure3).

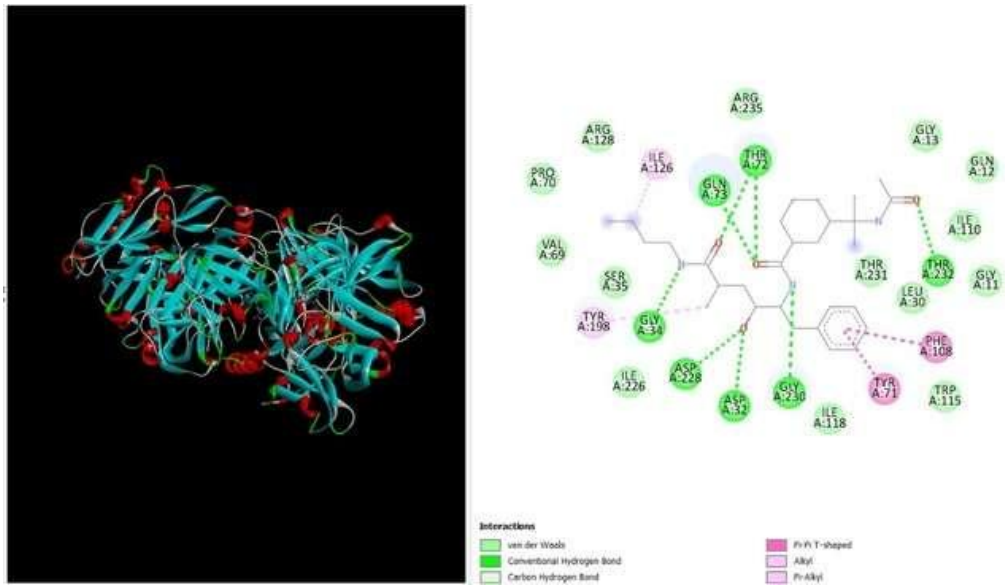


Figure: 2 Receptor 3K5F-Human BACE-1 COMPLEX WITH AYH011

RESULTS AND DISCUSSION

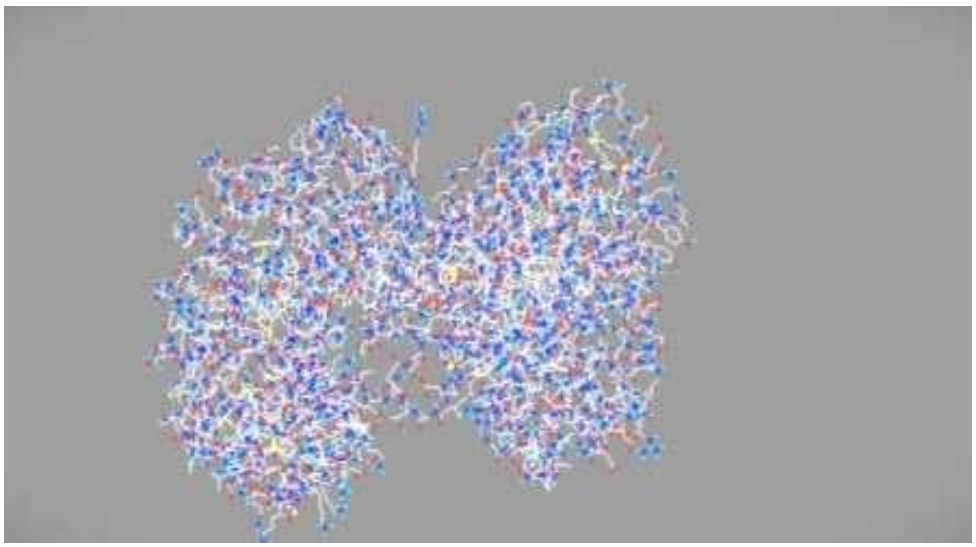


Figure :3 AYH ligand redocked image with 3k5f

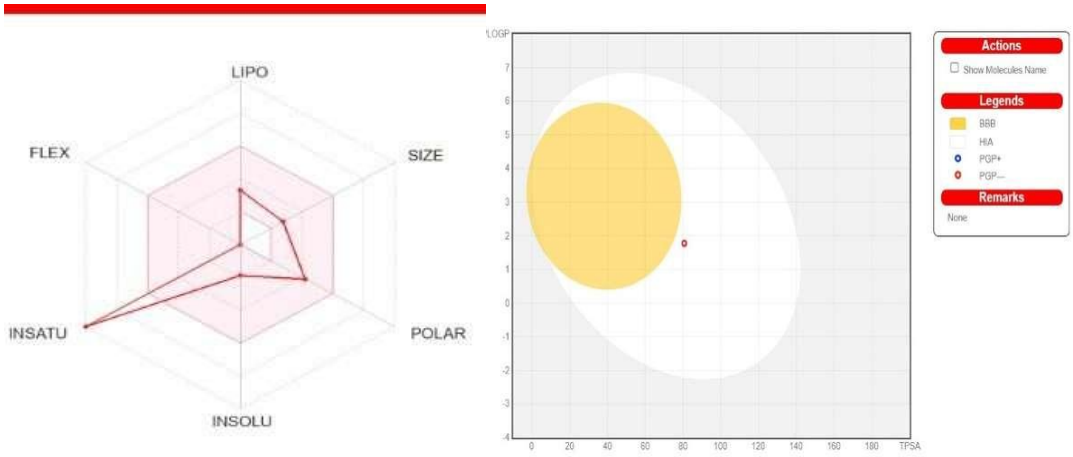


Fig:4 Bioavailability Radar & Boiled egg of Thiazoloquinazolinedione

Due to their diverse pharmacological actions, benzothiazole derivatives have gained importance in the modern era. In the present study, we have selected five Benzothiazole derivatives with different functional groups attached to them. Benzothiazole derivatives possess versatile biological activities like antitumor, antibiotic, antifungal, and HIV protease. Inhibitor, antiatherosclerosis, and anti-Alzheimer activity.[8] Among benzothiazole derivatives selected for this study, except for Thiazoloquinazolinedione and ethionamide, a pyrimidine ring coexists. (**Table 1**).

Thiazoloquinazolinedione possesses a quinazoline ring and benzothiazole, which has additional functional groups. The substitution positions are specific within the compound. This heterocyclic showed the best docking score (-6.8) compared to the reference ligand (AYH) -7.0 in redocking (Table2). The other Heterocyclic Benzthiazole derivatives with comparable docking scores are 2-oxopyrimidobenz thiazole (-6.5), Benzthiazolopyrimidine (-6.2), and Iminopyrimidine Benzthiazole (-6.2). Ethionamide gave the lowest score (-5.0). AYH was removed from the protein complex 3K5F-Human Bace-1-complex with AYH-011 and rocked as a reference ligand with a value of -7.0. The target possessed three chains, A, B, and C. Chain C was removed in cleaning Protein chains A and B, had maximum points of Ligand interaction, and was retained. Benzthiazole derivatives as anti-Alzheimer's compounds were reported in a previous article.[9] These Heterocyclic compounds cleaned the B amyloid plaques. Benzothiazole derivatives are weak bases with

unique methine centres in the Thiazole ring.[10] It is the component of many natural compounds that have versatile biological actions. They showed fewer toxic effects with good Blood-brain barrier penetration and less toxicity. The SWISS-ADME prediction revealed the synthetic utility and Hydrophilicity, Lipophilicity, and GIT absorption characteristics of these compounds. (**Figure 4**) (**Table 3**) Benzothiazole scaffold is a vital core group in Medicinal Chemistry. Various pharmacological, SAR and synthetic studies must be carried out to confirm the utility of these compounds as drugs that can save human lives.

Table:1 Structural Features of Compounds For The Study

Feature	Thiazoloquinazolinedione	Iminopyrimido Benzothiazole	Ethionamide	Benzothiazolo pyrimidone	2- Oxopyrimido benzothiazole
Core structure	Benzothiazole + quinazoline	Benzothiazole + pyrimidine	Benzothiazole	Benzothiazole + pyrimidine	Benzothiazole + pyrimidine
Pyrimidine ring	Yes	Yes	No	Yes	Yes
Additional rings	Quinazoline	-	-	-	-
Functional groups	Ketones, amides	Imine	Carboxamide	Amide	Ketone

Table:2 Docking Results

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
Benzothiazolopyrimidone	-6.2	0	0
IminopyrimidoBenzothiazole	-6.2	0	0
2- Oxopyrimidobenzothiazole	-6.5	0	0
Thiazoloquinazolinedione	-6.8	0	0
Ethionamide	-5	0	0
AYH	-7	0	0

Table :3 Swiss ADME Prediction

Property	Thiazoloquinazolinedione	Oxopyrimidobenzothiazole	Benzothiazolopyrimidone
lipophilicity	0.97	1.40	1.37
Water solubility	-1.87	-2.61	-2.03
Absorption	high	high	high
Drug Likeliness	Yes,0 violation	Yes,0 violation	Yes,0 violation
Synthetic accessibility	2.85	2.16	2.45

CONCLUSION

It has been deduced from the given data that specific Benzothiazole derivatives, which possess certain structural characteristics such as the presence of a pyrimidine ring, hold the potential to act as anti-Alzheimer's agents. These derivatives have displayed favourable docking scores compared to a reference ligand, indicating a strong binding affinity towards the target protein connected to Alzheimer's disease. They have also been reported to have proficiently cleared β-amyloid plaques, which are the hallmark of Alzheimer's pathology. Furthermore, Benzothiazole derivatives are renowned for their weak basic properties and unique methine centres, providing pharmacological versatility and potentially reduced toxicity. They can cross the blood-brain barrier, and their favourable ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties, as predicted by SWISS-ADME, further support their potential therapeutic use in Alzheimer's disease. Benzothiazole scaffold is an essential core group in Medicinal Chemistry. More pharmacological, structure-activity relationship (SAR), and synthetic analyses are required to thoroughly explore and validate the therapeutic usefulness of these compounds in treating Alzheimer's disease, which could offer significant benefits to human health. It can be inferred from the given data that certain Benzothiazole derivatives, which have specific structural characteristics like the presence of a pyrimidine ring, have the potential to act as anti-Alzheimer's agents. These derivatives have demonstrated favourable docking scores compared to a reference ligand, which suggests a strong binding affinity to the target protein linked with Alzheimer's disease. They are predicted to interfere with beta-amyloid plaques in the brain. Moreover, Benzothiazole derivatives are recognized for their weak basic properties and unique methine centres, contributing to their pharmacological versatility and

potentially lower toxicity. They cross the blood-brain barrier, and the favourable ADME (Absorption, Distribution, Metabolism, Excretion, and toxicity) features predicted by SWISS-ADME further support their potential as therapeutic agents for Alzheimer's disease.

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COMPETING INTEREST

There is no competing interest.

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