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ORIGINAL ARTICLE

Molecular Docking Study of Benzothiazole derivatives as Antidepressant agent

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ABSTRACT
Research into the creation of new antidepressants is still ongoing. This work is focused on the sodium-coupled leucine transporter (leuT) active site as an antidepressant target protein. Atypical antidepressant may be prescribed if your depression is resistant to other kind of antidepressant or you've had intolerable side effect to them. Atypical antipsychotics, a class of medications initially developed to treat schizophrenia, may also be helpful for some types of depression, either by themselves or in conjunction with more conventional antidepressants. In this research, we explored the potential of Benzothiazole derivatives as selective leuT inhibitors for the design of antidepressant agents. Molecular docking studies were conducted using AutoDock Vina Ver. 1.1.2 to investigate the binding of thirty-two Benzothiazole derivatives to the leuT active site. The LeuT active site with Protein Data Bank code 2Q72 was used as a reference for docking. The docking scores were analysed, and the interconnections between the derivatives and the active site were studied. Lurasidone was used as the reference standard for this study. The thirty-two Benzothiazole derivatives exhibited docking scores ranging from -8.1 to -9.1 kcal/mol. Thirteen Benzothiazole derivatives demonstrated higher docking scores compared to Lurasidone, which was used as the standard compound. Among the derivatives, BTZ25 displayed the highest binding energy, indicated by the lowest docking score. The outcomes of this molecular docking study suggest that all the newly designed Benzothiazole derivatives have the potential to be created and further evaluated for in vitro studies. These results provide valuable insights for the development of antidepressant agents targeting the sodium-coupled leucine transporter. Moreover in vitro and in vivo investigations are warranted to validate the activity of these derivatives as potential antidepressant candidates.
KEYWORDS: Benzothiazole, Antidepressant, Atypical, Docking, Lurasidone, leuT

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INTRODUCTION

A prevalent and pervasive illness, depression affects individuals of all ages, genders, and backgrounds. Suicidal thoughts, difficulty in concentration, changes in eating or weight, sleep difficulties, tiredness, prolonged depressive moods, and loss of interest or pleasure are some of its hallmarks. It can have a big effect on someone's relationships, day-to-day activities, and general well-being. Depression is one of the most common psychological health conditions in the world, affecting an estimated 300 million individuals worldwide.[1] About 7.5 crore individuals, or 5.66% of India's population, were considered by the World Health Organization (WHO) to be depressed in 2015.[2] Moreover, an investigation that was released in the 2020 issue of PLOS Medicine assessed that 36% of Indians overall suffer from depression. One of the main causes of years spent with a handicap is major depressive disorder (MDD), which is the most common psychological health disease in the world. Moreover, a significant percentage of suicide cases are linked to an MDD diagnosis.[3] Even with initiatives to raise healthcare personnel' knowledge and proficiency, MDD is still often misdiagnosed and managed insufficiently. A lot of strategies that could be very beneficial are still in the early stages of testing or are being approved by regulations, thus they are not yet prepared for general use.[4] Depression can arise from a number of variables, including fundamental abnormalities in brain chemistry, neurotransmitter malfunction (e.g., serotonin and dopamine), hormonal changes, and hereditary predisposition, though the exact origins of depression are

not entirely understood. The start of depression can also be attributed to psychological causes, including traumatic events, poor self-esteem, low self-esteem, negative thought patterns, and a personal or family history of depression. Depression is more common in people with certain medical conditions, such as disease, thyroid issues, hormone imbalances, and persistent pain. Addiction and substance abuse can alter brain chemistry, making a person more susceptible to depression. Atypical antidepressant may be prescribed if your depression is resistant to other kind of antidepressant or you've had intolerable side effect to them. Atypical antipsychotics, a class of medications initially developed to treat schizophrenia, may also be helpful for some types of depression, either by themselves or in conjunction with more conventional antidepressants. As some instances, consider: Bilify also known as Aripiprazole, Brexpiprazole (Rexulti), Lurasidone or Latuda, Combination olanzapine and fluoxetine (Symbyax), Seroquel also known as quetiapine. Atypical antipsychotics antidepressants can cause a range of side effects and the potential to induce symptoms such as headaches, dry mouth, nausea, anxiety, and insomnia. In contrast, some atypical antidepressants have the potential to alter appetite, induce sleeplessness or sleepiness, and cause insomnia, but they are not as likely to result in sexual dysfunction. Clinic depression therapy mostly focuses on antidepressants, which are often associated with slow acting and major adverse effects such weight gain, nausea, insomnia, or sexual dysfunction, along with loss of cognitive abilities. The alternatives for treating depression are somewhat limited. Therefore, it is critical to develop novel antidepressants with a brief half-life, minimal side effects, and improved cognitive function. The development of innovative dual- or multi-target antidepressants is an important field of research in the field. Benzothiazole is a bicyclic heterocyclic molecule which is made up of a fused benzene and thiazole moiety with structural elements of sulphur and nitrogen.[5] Since it has shown a extensive range of pharmacological actions, including antineoplastic[6,7,8] , antiviral agent [9] , antibacterial[7], antituberculosis[10], antimalarial[11], antimycotic[7,12], anthelminthic[13], antileishmanial[14], anti-inflammatory[15], anti-diabetic[16], anti-oxidant[17], anti-asthmatic[18] and immunomodulatory properties[19], the Benzothiazole essential has garnered ongoing attention for drug advance studies. In addition to these endeavors, research on the medication discovery of the central nervous system (CNS) has focused on the Benzothiazole moiety. The pharmacological actions of benzothiazole derivatives have been informed to include analgesic[20,21], antiepileptic[22,23], anti-Alzheimer[24,25], anticholinesterase[26,27], MAO inhibitory[28], adenosine receptor adversary[29] and neuroprotective properties.[30,31] There are currently too few effective medications for the pharmacotherapy of schizophrenia, and those that are available have a lot of negative side effects. Reducing adverse and cognitive symptoms appears to be an especially challenging issue. In order to achieve greater efficacy and fewer adverse effects, new therapeutic options are continually being searched.[32]

MATERIAL AND METHODS

Target Protein X-ray Structure Preparation:

The target protein was determined to be LeuT complexed with L-leucine, salt, and lurasidone (PDB ID: 2Q72). The Protein Data Bank (http://www.pdb.org) provided the structure.

Design of Benzothiazole Derivatives:

Figuring out the pharmacophore, adjusting the pharmacophore's substituents, and completing the list of new substituents are some of the processes involved in developing new medications. In this investigation, Benzothiazole was shown to be the unique pharmacophore for an antidepressant drug. To create novel derivatives, a variety of substituents were chosen. Various acetophenones and aldehydes were used to create a number of derivatives. Aromatic aldehydes with substitutions such as NO_2, CH_3, OH, OCH^3 etc, and substituted acetophenones such as NH_2 and Cl were used. Substituted derivatives were later converted into a Benzothiazole ring.

Ligand Preparation:

Using Chem Draw Ultra 8.0, the structures of Benzothiazole derivatives D1 to D32 (Figure 1) were created. Chem 3D Ultra 8.0 was used to transform the 2D structures into 3D structures. Density Functional Theory, or DFT, was used to optimize and minimize the shape of the ligands. For the AutoDock Vina program to work with the resultant ligand structures, they were saved in PDB format.

Molecular Docking Studies:

In computer-aided drug design (CADD) and structural molecular biology, molecular docking is an invaluable tool. It seeks to forecast a ligand's preferred binding modes given the target protein's known three-dimensional structure. In order to prioritize molecules for additional investigation, efficient docking techniques investigate high-dimensional spaces using scoring functions. Virtual screening of vast chemical libraries, result ranking, and structural hypothesis generation for ligand binding are all made

possible by docking. Molecular docking of Benzothiazole derivatives with the LeuT active site was performed in this work using AutoDock Vina Version 1.1.2. Target protein used in this study was the crystal structure 2Q72 from the Protein Data Bank. In order to determine the docked position and compute the root-mean-square distance (RMSD), the docking protocol [22] was verified by re-docking the ligands into their binding pocket of 2Q72.

RESULT AND DISCUSSION

Molecular docking enables a computational method called virtual screening that finds new bioactive compounds in huge chemical libraries. By comprehending the relationship between target proteins and ligands, these methods help to guide drug-receptor interactions and aid in the development of new medications. By placing and scoring tiny compounds in the active region of the target protein, computer-aided drug design helps identify them. In this work, benzothiazole derivatives were docked with the LeuT transporter as the target protein in molecular docking recreations carried out with AutoDock Vina Version 1.1.2. The ligand binding position and fitness function scores were used by the software to determine which docking poses were optimal. For ligand binding, the optimal site was determined using RMSD. Stable and suggestive of compound activity were the docking scores, which indicate the binding energy needed for the interface between the ligands and target protein. Table 1 displays the binding energy values of the derivatives of Benzothiazole. The thirty-two compounds showed docking scores between -8.1 and -9.1 kcal/mol. When compared to the reference chemical Lurasidone, the Benzothiazole derivatives displayed higher docking scores.

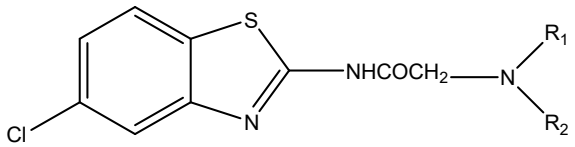


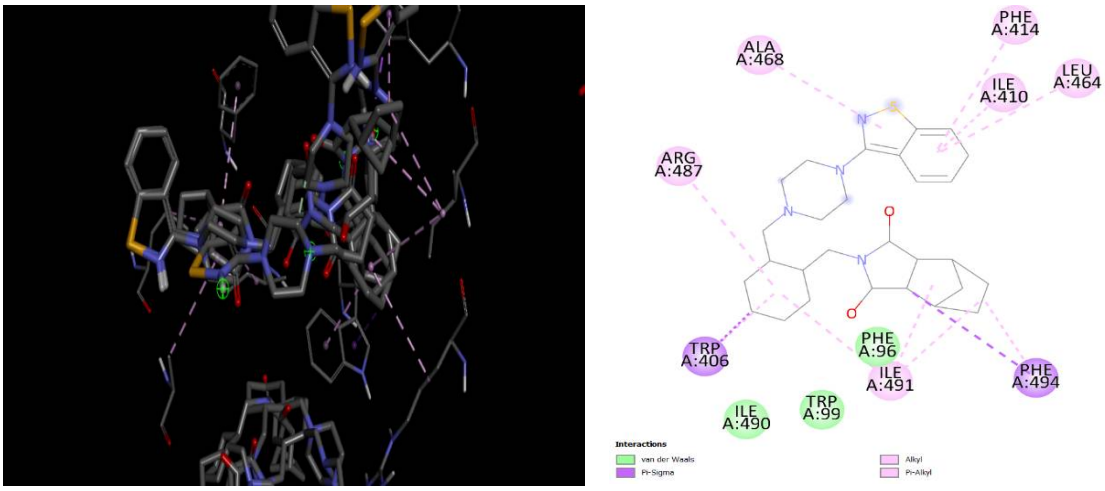
Figure1: General Structures of Benzothiazole Derivatives

Table 1. Docking Score of Benzothiazole derivatives with LeuT active site

Ligand	Binding Affinity (kcal/mol)	Ligand	Binding Affinity(kcal/mol)	Ligand	Binding Affinity(kcal/mol)
BTZ-1	-6.9	BTZ-14	-6.8	BTZ-27	-7.7
BTZ-2	-8.8	BTZ-15	-7.5	BTZ-28	-7.1
BTZ-3	-6	BTZ-16	-7.4	BTZ-29	-6.7
BTZ-4	-6.7	BTZ-17	-6.8	BTZ-30	-8.6
BTZ-5	-9	BTZ-18	-7.2	BTZ-31	-8.2
BTZ-6	-6.2	BTZ-19	-6.7	BTZ-32	-8.6
BTZ-7	-9	BTZ-20	-7.6	Lurasidone (STD)	-6.6
BTZ-8	-6.6	BTZ-21	-8.6		
BTZ-9	-6.5	BTZ-22	-7.8		
BTZ-10	-7	BTZ-23	-8.3		
BTZ-11	-6.8	BTZ-24	-7		
BTZ-12	-7.7	BTZ-25	-8.1		
BTZ-13	-9.1	BTZ-26	-6.4		

Interactions between the Leucine transporter protein and thirty-two benzothiazole derivatives were observed. Compound BTZ-3 shows a weaker affinity with a lower docking score. The following diagrams show the interactions of Lurasidone (Figure 3) and compound BTZ-25 (Figure 2) with the LeuT active site, along with the hydrogen bonds involved in the binding of Lurasidone. Studying these interactions shows that PHE A494 and LEU A464—common amino acid residues found in the LeuT active sites—are bound by both Lurasidone and compound BTZ-25.

Figure 2: 3D and 2D structures of Lurasidone (STD) interacting with LeuT active site



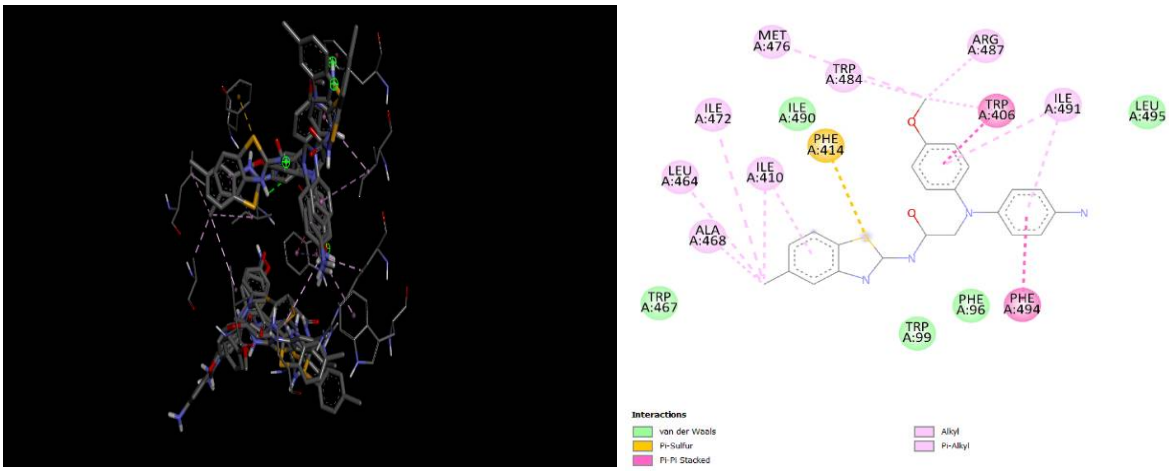


Figure 3: 3D and 2D structures of BTZ-25 interacting with LeuT active site

CONCLUSION

Thirty-two molecular structures of Benzothiazole derivatives with an aldehyde group bonded to the ring were analysed in this work. The interaction between these chemicals and the structure of the LeuT protein was subsequently investigated by docking experiments. The ligands with a high affinity for LeuT were found using the docking scores that were acquired. The findings showed that thirteen derivatives had larger binding energies and interactions with the target protein than lurasidone, as evidenced by their higher docking scores. This means that these substances could function as strong antidepressants. To determine their true antidepressant effectiveness, however, additional research involving synthesis and in vitro tests is required.

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