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Molecular Docking Study of Novel Chalcone-Derived Pyrazole Derivatives as Potential Antidepressant Agents

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ABSTRACT
The development of novel antidepressant agents remains an active area of research. In this study, the focus was on the sodium-coupled leucine transporter (leuT) active site as a target protein for antidepressant agents. Tricyclic antidepressants have been shown to inhibit various transporters, including those for glycine (glyt), GABA (GAT), dopamine (DAT), norepinephrine (NET), and serotonin (SERT), thereby preventing the reuptake of neurotransmitters like dopamine, serotonin, and norepinephrine. In this research, we explored the potential of Pyrazole derivatives as selective leuT inhibitors for the design of antidepressant agents. Molecular docking studies were conducted using AutoDock Vina Ver. 1.1.2. The LeuT active site with Protein Data Bank code 2Q72 was used as a reference for docking. The docking scores were analyzed, and the interactions between the derivatives and the active site were studied. Desipramine was used as the reference standard for this study. The thirty-seven Pyrazole derivatives exhibited docking scores ranging from -7.9 to -9.3 kcal/mol. Thirty-one Pyrazole derivatives demonstrated higher docking scores compared to Desipramine, which was used as the standard compound. Among the derivatives, PZ3 displayed the highest binding energy, indicated by the lowest docking score. The results of this molecular docking study suggest that all the newly designed Pyrazole derivatives have the potential to be synthesized and further evaluated for in vitro studies. These findings provide valuable insights for the development of novel antidepressant agents targeting the sodium-coupled leucine transporter.
Keywords: *Molecular docking, Antidepressant, PyRx, Computer-aided drug design, Tricyclic antidepressants, active site.*

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INTRODUCTION

Depression is a common and widespread condition that affects people of all ages, genders, and backgrounds, characterized by persistent feelings of sadness, loss of interest or pleasure, changes in appetite or weight, sleep disturbances, fatigue, feelings of worthlessness or guilt, difficulty concentrating, and thoughts of death or suicide. It can significantly impact a person's daily life, relationships, and overall well-being. It is estimated that over 300 million people worldwide experience depression, making it one of the most prevalent mental health disorders globally[1]. According to the World Health Organization (WHO), in 2015, India had an estimated 5.66% of its population (equivalent to approximately 7.5 crore people) suffering from depression[2]. Furthermore, a study published in the journal PLOS Medicine in 2020 estimated the prevalence of depression in India to be around 36% among the general population. Major depressive disorder (MDD) is the most prevalent mental health condition globally and a significant contributor to years lived with disability. Furthermore, a substantial portion of suicide cases are associated with a diagnosis of MDD[3]. Despite efforts to improve awareness and competence among healthcare providers, MDD continues to be frequently undetected and inadequately treated [4]. While the precise causes of depression are not fully understood, Various factors can contribute to the development of depression, including biological imbalances in brain chemistry, neurotransmitter dysfunction (e.g., serotonin and dopamine), hormonal changes, and genetic predisposition. Psychological factors such as personal or family history of depression, traumatic events, chronic stress, low self-esteem, and negative thinking patterns can also contribute to its onset. Certain medical conditions like chronic pain, illness, thyroid disorders, and hormonal imbalances increase the risk of depression[5]. Tricyclic antidepressants (TCAs) are a class of medications commonly used to treat depression. While newer antidepressants with different mechanisms of action have become more popular in recent years[6], TCAs are still prescribed in

certain cases when other treatments have been ineffective or when specific symptoms require their use. TCAs work by increasing the levels of certain neurotransmitters in the brain, particularly serotonin and norepinephrine[7]. They inhibit the reuptake of these neurotransmitters, allowing them to remain in the synaptic gap longer, which can help alleviate depressive symptoms. Some examples of TCAs include amitriptyline, nortriptyline, imipramine, desipramine, doxepin, and clomipramine TCAs are primarily used to treat major depressive disorder[8],but they may also be prescribed for other conditions such as generalized anxiety disorder, panic disorder, obsessive-compulsive disorder (OCD), and neuropathic pain. Tricyclic antidepressants can cause a range of side effects, including drowsiness, dry mouth, blurred vision, constipation, urinary retention, dizziness, weight gain, sexual dysfunction, and changes in heart rate.[9] Antidepressants, which are frequently linked to sluggish acting and significant side effects such as sexual dysfunction, nausea, insomnia, or weight gain, as well as loss of cognitive ability, are the main focus of depression therapy in clinics. There are relatively few options for treating depression[10]. Thus, it is crucial to create new antidepressants that have a quick onset, few adverse effects, and enhanced cognitive performance. A significant area of study in the discipline is the creation of novel dual- or multi-target antidepressants. The field of medicinal chemistry is working to improve novel derivatives. The pyrazole ring is vital in the thoughtful creation of drugs due to its widespread use in both business and medicine[11].The pyrazole moiety has sparked the development of new classes of pharmaceuticals as a preferred structure found in several medication classes.[12] The pyrazole ring is a five-membered heterocyclic ring composed of three carbon atoms and two adjacent nitrogen atoms, characterized by having a nitrogen atom at position 1 and a double bond between carbon atoms 2 and 3.[13] A common structural motif in many compounds with medicinal activity is the pyrazole ring. Some examples of marketed drugs containing pyrazole ring are Celecoxib, rimonabant, Phenylbutazone and fomepizole. Some of these compounds exhibit noteworthy properties and have substantial uses in material chemistry[14]. The biological activities associated with pyrazole derivatives are anti-inflammatory activity[15], antimicrobial activity[16], anti-cancer activity[17], antioxidant activity[18], analgesic activity[21], etc. We have designed and synthesized a number of derivatives of chalcone-derived pyrazoles with various combinations of substituents in the phenyl ring[21] on the basis of the studies we have mentioned and in consideration of the ongoing need to generate novel effective and selective antidepressant drugs[21]. The protein we have selected is LeuT protein. LeuT is the only member of the neurotransmitter sodium symporter family and is a stable sodium-coupled leucine transporter. Tricyclic antidepressants noncompetitively inhibit substrate uptake.

MATERIAL AND METHODS

Target Protein X-ray Structure Preparation

The crystal structure analysis of LeuT complexed with L-leucine, sodium, and imipramine (PDB ID: 2Q72) was chosen as the target protein. The structure was obtained from the Protein Data Bank (http://www.pdb.org/).

Design of Novel Pyrazole Derivatives

The development of new drugs involves several steps, including determining the pharmacophore, modifying substituents of the pharmacophore, and finalizing the list of new substituents. In this study, the novel pharmacophore for an antidepressant agent was identified as pyrazole. Various substituents were selected for designing new derivatives. Several chalcone derivatives were synthesized using different aldehydes and acetophenones. Aromatic aldehydes with substitutions such as 4-NO2, 4-NH2, 4-Cl, 4-Br, 4-Dimethylamino, 4-CF3, 4-OCH3, etc, and substituted acetophenones such as 4-NH_2 and 4-Cl were used. Substituted chalcone derivatives were later converted into a pyrazole ring.

Ligand Preparation

The structures of Pyrazole derivatives D1 to D37 (Figure 1) were drawn using Chem Draw Ultra 8.0. The 2D structures were converted to 3D structures using Chem 3D Ultra 8.0. The optimization and geometry minimization of the ligands were performed using the Density Functional Theory (DFT) method. The resulting ligand structures were saved in PDB format for compatibility with the AutoDock Vina program.

Molecular Docking Studies

Molecular docking is a valuable tool in structural molecular biology and computer-aided drug design. It aims to predict the preferred binding modes of a ligand with a known three-dimensional structure of the target protein. Effective docking methods explore high-dimensional spaces and employ scoring functions to rank molecules for further study. Docking enables virtual screening of large libraries of molecules, ranking the results, and proposing structural hypotheses for ligand binding. In this study, AutoDock Vina Version 1.1.2 was used for molecular docking of Pyrazole derivatives with the LeuT active site. The crystal structure 2Q72 from the Protein Data Bank was employed as the target protein. The docking protocol was

validated by re-docking the ligands into its binding pocket of 2Q72 to obtain the docked pose and calculate the root-mean-square distance (RMSD)[22].

RESULTS

Virtual screening, facilitated by molecular docking, is a computational technique used to identify novel bioactive molecules from large chemical libraries. These techniques aid in the design of new drugs by understanding the interaction between target proteins and ligands, thus guiding drug-receptor interactions. Computer-aided drug design assists in the identification of small molecules by positioning and scoring them in the target protein's active site. In this study, molecular docking simulations were performed using AutoDock Vina Version 1.1.2 with Pyrazole derivatives docked with the LeuT transporter as the target protein. The program selected the best docking poses based on ligand binding position and fitness function scores. RMSD was used to evaluate the best ligand binding position. The docking scores, representing the binding energy required for the interaction between the target protein and ligands, were stable and indicative of compound activity. The binding energy values of Pyrazole derivatives are presented in Table 1. The thirty-seven derivatives exhibited docking scores ranging from -7.9 to -9.3 kcal/mol. The Pyrazole derivatives showed higher docking scores compared to the standard compound Desipramine.

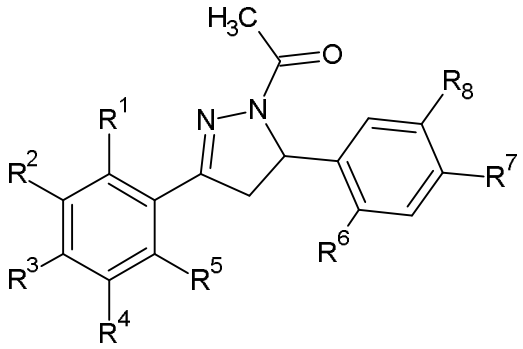

Figure1: General Structures of Pyrazole Derivatives

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

Ligand	Binding Affinity(kcal/mol)	Ligand	Binding Affinity(kcal/mol)	Ligand	Binding Affinity(kcal/mol)
PZ-1	-9.2	PZ-14	-8.6	PZ-27	-8.5
PZ-2	-8.3	PZ-15	-8.1	PZ-28	-8.6
PZ-3	-9.3	PZ-16	-8.9	PZ-29	-9.1
PZ-4	-8.7	PZ-17	-8.9	PZ-30	-8.1
PZ-5	-8.3	PZ-18	-7.8	PZ-31	-8.2
PZ-6	-8.7	PZ-19	-8.2	PZ-32	-8.2
PZ-7	-8.8	PZ-20	-7.9	PZ-33	-7.9
PZ-8	-9.1	PZ-21	-8.2	PZ-34	-8.2
PZ-9	-8.7	PZ-22	-8.3	PZ-35	-8.2
PZ-10	-8.5	PZ-23	-8	PZ-36	-8
PZ-11	-9	PZ-24	-8.1	PZ-37	-7.9
PZ-12	-8.4	PZ-25	-8.2		
PZ-13	-8.7	PZ-26	-8.2		

Thirty-seven novel chalcone-derived pyrazole derivatives showed interactions with the Leucine transporter protein. Compound Pz-3 demonstrates a lower docking score, indicating weaker affinity. To enhance its binding energy to the target receptor, compound Pz-3 was modified by substituting the R^7 group with a Bromine group. This modification increases the compound's ability to interact with the target receptor[23]. The interaction of Desipramine (Figure 3) and compound Pz-3 (Figure 2) with the active site of LeuT, as well as hydrogen bonds in Desipramine binding interactions, are depicted below. Analysis of these interactions reveals that both Desipramine and compound Pz-3 bind to common amino acid residues present in the LeuT active sites, such as Tyr A471 and Ile A245. Amino acids such as TRP A471, TYR A245 showed Pi-Pi T-shaped bonds.

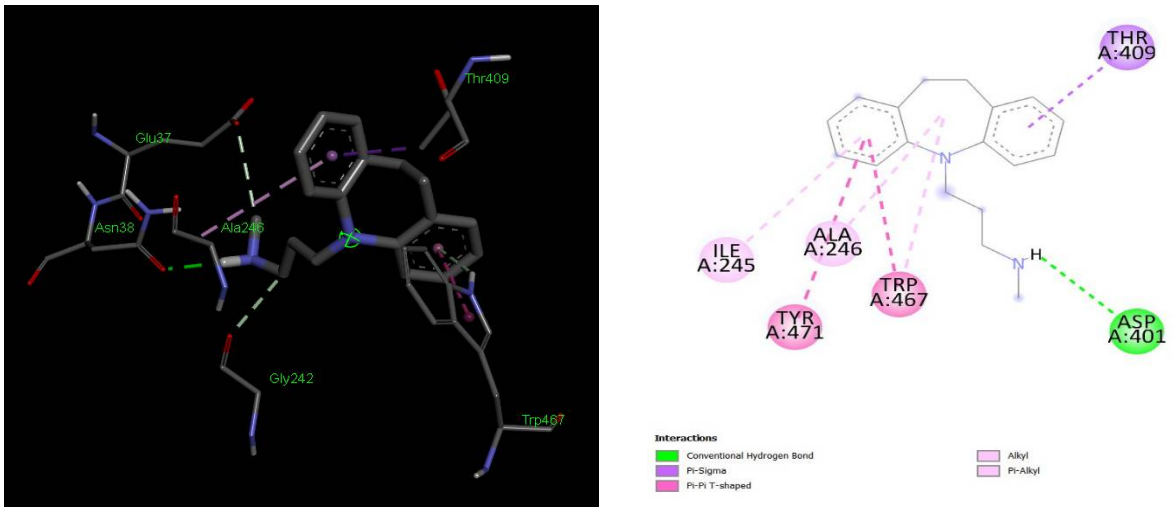

Figure 2: 3D and 2D structures of Desipramine interacting with LeuT active site

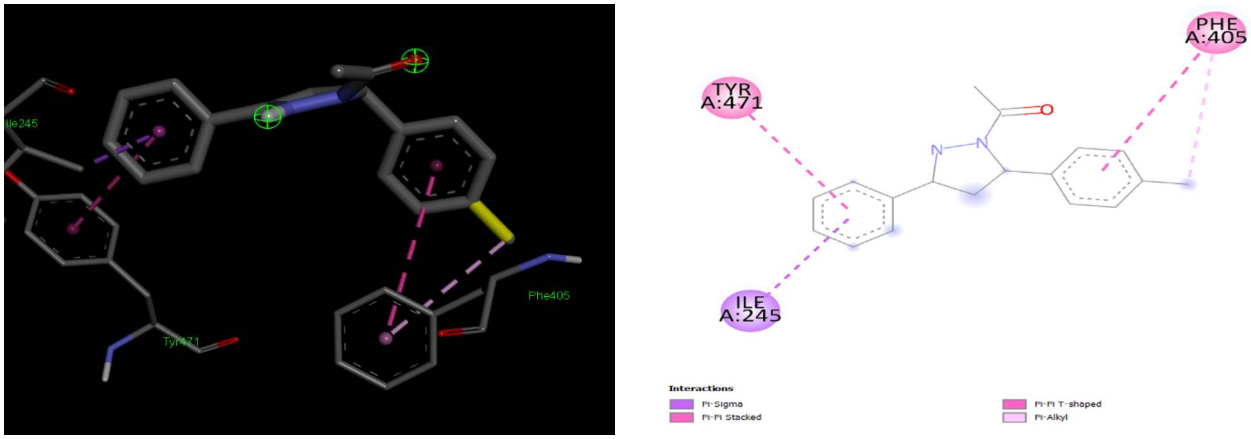

Figure 3: 3D and 2D structures of Pz-3 interacting with LeuT active site

DISCUSSION

In this study, a total of thirty-seven molecular structures of Novel Chalcone-derived Pyrazole derivatives, which featured an aldehyde group attached to the ring, were examined. These compounds were then subjected to docking studies to determine their interaction with the LeuT protein structure. The obtained docking scores were used to identify ligands with high affinity for LeuT. The results revealed that thirty-one derivatives exhibited higher docking scores compared to Desipramine, indicating stronger binding energy and interaction with the target protein. Consequently, these compounds have the potential to serve as potent antidepressant agents. However, further investigations involving synthesis and in vitro evaluations are necessary to assess their actual antidepressant activity.

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DECLARATION OF INTEREST STATEMENT

The products used for this research are commonly and predominantly use products in ourarea of research and country. There is absolutelyno conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded bythe producing company rather it was funded by personal efforts of the authors.

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