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Molecular modeling and docking on the 5HT1A receptor with small molecule drugs used in bipolar Disorder

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Abstract

Bipolar Disorder is a primary mental condition marked by recurrent episodes of manic and depressive states that affect thought, emotion, and social behaviour. It is a bipolar illness caused by periods of depression, mania, mixed mania, and hypomania. 5HT1A receptors are found in presynaptic and postsynaptic regions of neurons—anxiolytic, antidepressant, and antipsychotic medications work by activating this receptor. Serotonin receptors are proteins that play a role in various neurological and biological processes, including mood, sleep, hunger, cognition, learning, and memory. The aim of this current work Molecular docking analysis was used in this study to examine how 5-HT1A receptors are affected by antipsychotics and antidepressants in the case of bipolar disorder. This study was based on molecular docking using different tools for analyzing ligands-receptor interactions. There are many types of software included in molecular dockings, like Iterative Threading Assembly Refinement (I-TASSER), Discover Studio Visualizer, Schrodinger, Protein Structure Analysis (ProSA), SiteMap program, Swiss ADME online software, and Mol Inspiration software etc. 5-HT1A receptors are frequently linked to drug usage and addiction since they are a famous target population for various pharmaceutical and recreational drugs. We are using Iterative Threading Assembly Refinement (I-TASSER) software, and Discover Studio Visualizer was used to model the 5HT1A protein in this investigation. The protein preparation was used to add hydrogen to the simulated structure and improve the protonation states of the LYS, ASP, and PHE residues. The sitemap function of the Schrodinger package was used to determine the active site of the modeled protein. We also used Glide to conduct docking

tests with various ligands retrieved from the PubChem database. Potential ligands have been assessed, and their interactions with 5HT1A were discovered based on glide scores. The top hits were further examined for drug-likeliness according to Lipinski's rule, bioactivity rating, and ADME characteristics. The 5HT1A receptor protein was selected for the study because it has been suggested to be an appropriate target for the critical analysis. As a result, we present two compounds, risperidone and cariprazine, that successfully met all in silico criteria, requiring more in vitro and in vivo research. In the future, this work could be helpful in the drug design and development of novel and potentially effective 5HT1A inhibitors. Further, this study is expected to help create more specific and individualized treatment approaches for patients with bipolar disorder.

Key words : Serotonin receptor, 5HT1A, Discovery Studio Visualizer, Glide, Lipinski's rule, ADME, risperidone, and cariprazine.

Bipolar Disorder (BD) is among the world's leading public health problems today. In 2019, 40 million people will experience BD. People with BD experience alternating depressive episodes with periods of manic symptoms. It is an episodic behavioral illness in which episodes of depression, mania, mixed mania, and hypomania occur[35]. According to complicated phenotypes, the disease is likely caused by several genes and gene-environment interactions[31]. Monoamine neurotransmitters called serotonin interact with 14 serotonin receptors classified into seven different groups[26]. The 5HT1A receptor inhibits adenylate cyclase and other second messenger cascades, such as the MAPK pathway and NMDA receptor channels[16]. An essential neurotransmitter in the CNS (central nervous system), serotonin 5HT, has been linked to various mental disorders, including anxiety and affective disorders[19]. Since serotonin has a wide range of effects and interacts with several receptors, serotonin receptors (HTRs) have been the focus of significant studies into the pathophysiology of BD. Serotonin (5-HT) functions in both the CNS and PNS (peripheral nervous system). Compared to the PNS (95%), the CNS has a comparatively low (5%) concentration of 5-HT. Serotonergic neurons are found in the CNS in two relatively small dorsal and median raphe nuclei (DRN and MRN)[30]. The 5 HT1A receptor is among the 5HT receptors with the best characterization[29]. This receptor can be identified pharmacologically by its high attraction for5 HT[3]. Additionally, it has a robust relationship with second-generation antidepressants, antipsychotic and mood stabilizer drugs such as citalopram[9], risperidone[10], clozapine[22], buspirone[34], olanzapine[25], lithium, and valproate[28], as well as 8-OH-DPAT[38]. Physiology, medicine, and pharmacology studies indicate that the 5-HT1A receptor may play a part in neuroendocrine function and thermoregulation[1]. The 5HT1A receptor is one of the first GPCR proteins that play an essential role in bipolar Disorder signaling[7]. According to a hydropathicity investigation, the 5HT1A receptor has seven

hydrophilic areas that may come together to create membrane-spanning α-helices. The seven hydrophobic transmembrane sections are connected by three intracellular and extracellular loops of hydrophilic sequences[3]. Serotonin signaling has been recommended to play an essential role in the pathophysiology of BD[33]. The significance of monoamine signaling in the pathophysiology of BD means that both depressive and manic episodes can be treated via pharmacological changes in monoamine signaling[17]. Using either direct or indirect procedures, antidepressants, lithium, and valproate, all stimulate postsynaptic 5-HT1A signaling in individuals. Therefore, the purpose of the current work was to use molecular docking analysis to examine the antipsychotic and antidepressant actions of the drugs against the 5-HT1A receptor protein[16].

Protein modeling : The structure of the 5HT1A protein was obtained from the NCBI database, considering that the system was obtained using nuclear magnetic resonance (NMR) and X-ray crystallography. The amino acid chain for human 5HT1A was obtained from Uni Prot (P08908); it is suggested to contain 422 amino acids and is a serine/ threonine protein kinase. Using the Protein Data Bank database as a suitable template, BLAST was used to find the 5HT1A FASTA sequence. There was no full-length protein template found. We, therefore, modeled the protein using the I-TASSER server Discovery Studio Visualizer software. It's an integrated platform for predicting protein structure and function based on the sequence-to-structure concept (figure1). From various threading alignments, it produces three-dimensional atomic models. A prediction accuracy estimate was given based on the modeling confidence score, and the model with the highest score was chosen for model validation. The binding pockets of 5HT1A were located using the SiteMap program. A glide grid was used to create a grid for the site with a site score greater than 1. Studies on docking were conducted using Schrodinger Glide version 5.8 software.

Validation : In receptor-based drugs, design is essential to assess the accuracy of the 3D protein model created using ProSA (Protein Structure Analysis)[18]. ProSA is a program that provides the sequence based on the quality of the proteins and the quantity of energy in amino acid residues and is used to validate the energy-minimized 3D model of the protein[23].

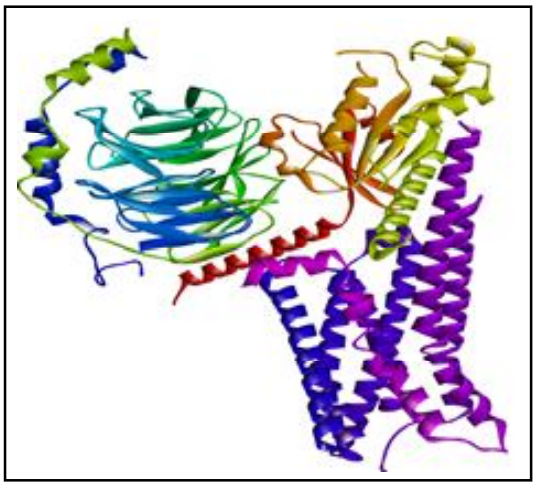


Fig 1: Modeled 5HT1A protein, using I-TASSER and Discovery Studio Visualizer software; Maestro visualization of the secondary structures of the protein 5HT1A, including helix, sheet, and loop.

Ligands selection : The ligands were obtained from various databases, including

ChemBridge, Maybridge, Pubchem, Sigma Aldrich, and Specs[27]. Ligprep, a product for Schrodinger ligand preparation, was utilized to create excellent, all-atom 3D structures. Thereby creating variants, correcting, validating, and optimizing the designs using all the parts of the ligands involved in the preparation process[14].

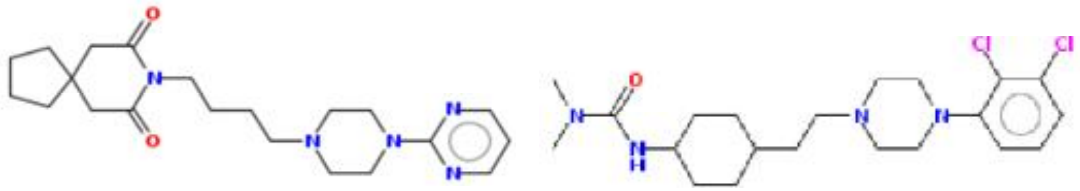
Active binding site analysis : The process of structure-based drug design involves finding the target protein's binding sites for docking. With the help of Sitemap, research in the literature, and manual correlation approaches, the binding site of the 5HT1A protein has been discovered[20]. Potential binding sites for the 5HT1A protein are listed in the Sitemap module of the Schrodinger suite, along with the surface area of their hydrophilic and hydrophobic regions, acceptors of hydrogen bonds, and donors of hydrogen bonds[6].

Molecular docking analysis : From the Protein Data Bank, the ligands from various databases was downloaded. Ligprep, a product for Schrodinger ligands preparation, was utilized to create excellent, all-atom 3D structures[5]. Creating variants, correcting, validating, and optimizing the designs involved in the ligands preparation process[4]. The Maestro Glide application's receptor grid-generating function created the receptor grid[2]. By identifying the residues that make up the binding (active) site, as determined by the SiteMap program, the receptor grid for 5HT1A was created[21]. The ligands were docked to the protein (5HT1A) once the receptor grid had been built with Glide version 5.8. This software uses a hierarchical method to predict protein structure. Iterative template fragment assembly simulations were used to construct full-length atomic models once structural templates were found using a multiple-threading approach. Protein preparation was applied to the model structure to fill in any missing hydrogen, improve the protonation state of the amino acid residues, and orient the hydroxyl groups[13].

ADME Analysis: Swiss ADME online software was used to analyze the ADME characteristics of a few selected ligands[12]. The tool makes predictions about the physiochemical properties after carefully examining: 1) the absorption of drug properties; 2) the digestion of drug processing; 3) the metabolic activity of drugs; and 4) the excretion process of drugs[37].

Chemical structure analysis of drugs:- ***Risperidone*** belongs to the pyridopyrimidines class and is a tetrahydropyran compound. A second ethylene group is present at position 2 of the compound pyrimidine. It functions as a prolyl oligopeptidase inhibitor, a serotonergic antagonist, an alpha-adrenergic antagonist, an H1-receptor antagonist, and a psychiatric medication. It belongs to the benzoxazole family and is a pyridopyrimidine, an organofluorine molecule, and heteroaryl piperidine. It is a second-generation antipsychotic (SGA) drug used to treat schizophrenia and bipolar Disorder, among other mood and mental health issues (Figure 2a).

Cariprazine is an N-alkyl piperazine with a 2, 3-chlorophenyl group substituted at position four on the piperazine ring. It functions as a serotonergic antagonist, an SGA, and a dopamine agonist. It is an N-alkyl piperazine, an N-aryl piperazine, and a dichlorobenzene, all of the urea family (Figure 2b).



2a. Risperidone **2b. Cariprazine**

Fig. 2. Molecular structure analyses of drugs from PubChem 2a. Risperidone, 2b. Cariprazine

Analysis of target active binding sites :

The Glide 5.8 XP scoring function and docking technique are revolutionary scoring functions to quantify protein-ligands binding affinities. Included are protein-ligands structural motifs that increase binding affinity: There are three charge-charged hydrogen bonds for analyzing active binding sites. The ligands docking were calculated using Glide's enhanced precision (XP) mode.

Modeling the 5HT1A receptor and drugs:

To assess and find suitable ligands that can fit into the most advantageous binding mode, against the 5HT1A protein, *in silico* docking studies were used in the present work. Using the Sitemap program, which offers a fast and effective means of finding possible binding sites for proteins, the active site of 5 HT1A was discovered. SiteMap assesses each binding site by evaluating its amino acid exposure, volume, size, contact, hydrophilicity, hydrophobicity, and donor/acceptor ratio. This was achieved using a particular search method to find the features of binding sites. The top 07 compounds' docking results are shown in Table-1 as a list. DB00734 has a docking score of -10.2; the compound forms a pi-pi interaction with PHE 403, Glu 292 and a pi-pi stack with Arg130**.** Figure 3a shows the interactions and binding mode. The compound DB06016 has a docking score of -8.9. This established an H-bond with LYS 405, LYS 349, and ASP 350. Figure 3b depicts the interaction and binding

Table-1. Analysis of docking scores for different compounds

S.No	compounds ID	compounds name	Docking score
1	DB00734	Risperidone	-10.2
2	DB06016	Cariprazine	-8.9
3	DB00490	Buspirone	-8.7
4	DB00334	Olanzapine	-7.3
5	DB00555	Lamotrigine	-6.5
6	DB00313	sodium valproate	-4.4
7	DB14509	Lithium carbonate	-3.4

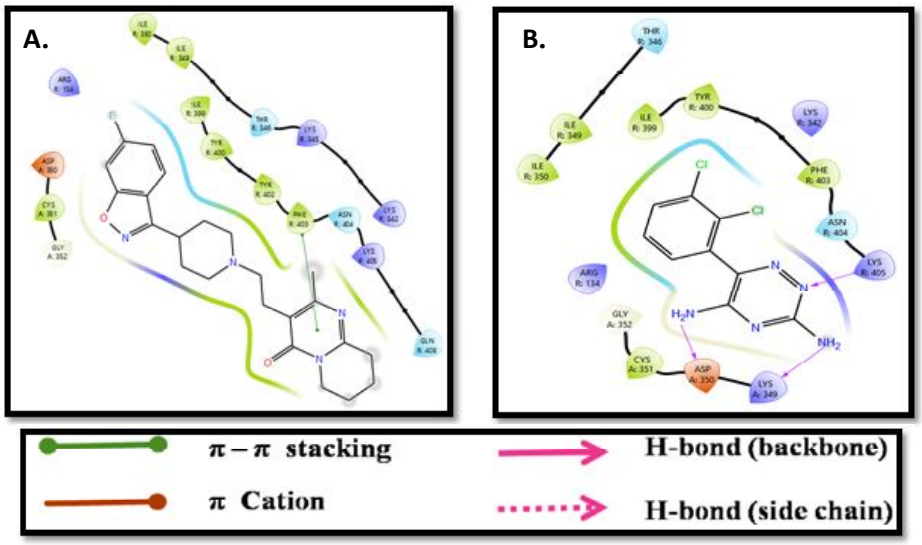


Fig. 3A. Risperidone compounds form pi-pi interactions with PHE 403 and B. The cariprazine compound established an H-bond with LYS 405, LYS 349, and ASP 350.

mode. Risperidone and Cariprazine exhibited the lowest binding energy and highest affinity with the 5HT1A receptor among all seven molecules. Despite comparatively high binding energy withRisperidone, and form the highest number of H-bond, indicating a stable complex.

Drug likeliness and bioactivity score: Lipinski's rule of five, essential to logical drug design, is satisfied by reading the molecular properties of the selected compound using the mol-inspiration software. No compound violated any of the five rules like not more than five hydrogen bond donors, not more than ten hydrogen bond acceptors, less than 500 g for compounds, less than five for partition coefficient (log P), less than ten for rotatable bonds, and not more than 140 for topologically polar in nature surface area (TPSA) (Table-2).

Table-2. Mol inspiration Calculation of Compounds

S. No.	Compound ID	No. of	Atoms H- Bond acceptor	H –Bond Donor	TPSA	log – P	N Violation
1.	DB00734	28	6	0	64.16	2.96	0
2.	DB06016	28	5	1	38.81	4.79	0
3.	DB00490	28	5	0	69.64	1.74	0
4.	DB00334	22	2	1	35.16	3.17	0
5.	DB00555	16	3	2	90.71	2.04	0
6.	DB00313	10	2	1	37.3	2.8	0
7.	DB14509	4	3	2	57.53	-1.09	0

Table-3. pharmacological activity parameter Calculation using Mol Inspiration software

S. No.	Compound Name	ompo-cund ID	GPCR Ligand	Ion channel modulator	Kinase inhibitors	Nuclear Receptors	Protease Inhibitors	Enzyme Inhibitors
1.	Risperidone	DB00734	0.44	-0.23	-0.13	-0.4	0.17	-0.04
2.	Cariprazine	DB06016	0.36	0.13	0.04	-0.2	0.06	0.07
3.	Buspirone	DB00490	0.41	0.09	0	-0.12	0.15	0.12
4.	Olanzapine	DB00334	0.17	-0.07	-0.28	-0.91	-0.5	-0.08
5.	Lamotrigine	DB00555	-0.16	-0.09	0.36	-1.12	-0.84	0.08
6.	sodium valproate	DB00313	-0.83	-0.3	-1.55	-0.78	-0.74	-0.39
7.	Lithium carbonate	DB14509	3.71	-3.65	-3.82	-3.89	-3.62	-3.51

Data was collected by mixing the sub-structure fragments in a molecule's activity contribution. Higher activity score of molecules with a highly active nature :

Cariprazine is identified as a potent ion channel modulator of bioactivity scoring (Table-3). The bioactivity contribution for each chemical will be determined by each structure of the fragment. The bioactivity for the whole molecule will be defined as the sum of the assistance from the entire molecule segment. This yields a molecular activity score, which is between -3 and 3. According to Molinspiration, a molecule with the highest activity score is most likely to be active.

We used a computational strategy in this investigation to find small chemical inhibitors of 5HT1A. The amount of intermolecular hydrogen bonding contacts and docking scores of the resulting receptor-ligands complex are used to evaluate the binding affinity of the ligands with 5 HT1A[15]. The DB06016 compound established three hydrogen bonds with amino acids that were present in the binding pockets. Pi-Pi stacking was visible in compound DB00734. Pi stacking is standard in the protein crystal structure and plays a significant role in the interactions between proteins and tiny molecules. The preferred interaction geometries were produced due to the form and electrical characteristics of the aromatic ring, which were responsible for their high polarizabilities and significant quadrupole moments. Electrostatic interaction may be a factor in the attraction between these stacks based on the geometry of their arrangement[32]. Additional research revealed that stacking interaction contributes to receptor-ligand binding energy. Other substances formed cation-Pi bonds with the amino acid in the active site. The stability and organization of proteins are significantly influenced by the interaction between ions and pi bonds[11]. The protein cation (PHE 403) and the small molecules aromatic ring provide the pi-pi interaction system. The cation-pi interaction is strong or more significant than the hydrogen bond. According to the studies, the cation-pi interaction is a potent force that helps proteins and ligands recognize one another and are a valuable indicator of drug-receptor interaction[8]. According to Lipinski's rule of five, which assesses if a substance has a specific pharmacological and biological activity that would make

it an orally effective medicine in humans, all the compounds in the current investigation that show good binding affinity additionally display drug-like features[39]. The examined drugs' pharmacokinetic analysis shows that their partition coefficient and water solubility are acceptable. The top two drugs also have strong serum protein binding capacity, good cell permeability, and bioavailability[36]. The two chosen ligands displayed favorable docking results that indicated drug-binding affinities with 5HT1A. All selected ligands showed good molecular characteristics by meeting Lipinski's rule of five and the ADME profile[24].

According to the NCBI data profile, several mental illnesses, direct or indirect, have been linked to 5HT1A in the case of human studies. Therefore, it is crucial to create a better BD pathophysiology involving important roles performed. This paper discusses the serotonin receptor targeting medicines for bipolar Disorder by utilizing the modern computer-aided modeling methods of the 5HT1A receptor. Risperidone and cariprazine are the two compounds that demonstrated a solid binding affinity and improved ADME properties. The findings of this work may be valuable in drug designing and conducting *in vivo* and *in vitro* to develop novel and potentially effective inhibitors of 5HT1A. Additionally, this study is expected to help create more specific and individualized treatment strategies for patients who have bipolar Disorder.

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