In Silico Evaluation of Tryptamine-Derived Schiff Bases as Modulators of the Serotonin 5-HT$_2$A Receptor

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Abstract: Serotonin receptors, also known as 5-hydroxytryptamine (5-HT) receptors, are a diverse family of G protein-coupled and ligand-gated ion channel receptors that mediate the physiological effects of the neurotransmitter serotonin. These receptors are widely distributed throughout the central and peripheral nervous systems, where they regulate numerous processes including mood, cognition, thermoregulation, appetite, and gastrointestinal function. To date, seven distinct receptor families (5-HT$_1$ to 5-HT$_7$) comprising multiple subtypes have been identified, each exhibiting unique pharmacological profiles, signal transduction mechanisms, and tissue-specific expression. Due to their broad functional relevance, serotonin receptors are key therapeutic targets in the treatment of neuropsychiatric disorders such as depression, anxiety, schizophrenia, and migraine. Continued investigation into their structure-function relationships, signaling pathways, and ligand specificity holds significant promise for the development of more selective and effective pharmacological agents.

The 5-HT$_2$A receptor is one of the most extensively studied subtypes of the serotonin receptor family due to its prominent role in both normal physiology and various neuropsychiatric conditions. The 5-HT$_2$A receptor is highly expressed in the cerebral cortex, especially in pyramidal neurons of the prefrontal cortex, where it plays a critical role in modulating perception, cognition, and mood. It has been implicated in the pathophysiology of disorders such as schizophrenia, depression, and anxiety, and is the principal target of many atypical antipsychotics and hallucinogenic compounds, including LSD and psilocybin. Activation of 5-HT$_2$A receptors by psychedelic agents is thought to underlie their profound effects on consciousness, suggesting a central role for this receptor in shaping subjective experience and higher-order cognitive functions. Ongoing research is exploring the therapeutic potential of selective 5-HT$_2$A modulation in treating mood disorders and facilitating psychotherapy, while also investigating the complex signaling pathwys and receptor interactions that influence its pharmacology.

In this study, molecular docking was performed to investigate the binding interactions of a series of tryptamine-based Schiff base compounds with the 5-HT$_2$A receptor. The three-dimensional structure of the receptor was obtained from available crystallographic data and prepared by refining the active site and removing any co-crystallized ligands. Ligands were constructed and energy-minimized using standard force fields to ensure accurate conformations for docking.

Docking simulations were conducted using AutoDock Vina, with a defined grid box centered on the orthosteric binding site known to accommodate serotonin and related ligands. The docking data were analyzed to identify key hydrogen bonding, π-π stacking, and hydrophobic contacts between the Schiff base ligands and crucial residues of the 5-HT$_2$A receptor in order to provide better insight into structure-activity relationships and offer a foundation for rational design of novel serotonergic ligands with potential psychoactive or therapeutic properties. The results have shown that quinoline-based Schiff base expressed the highest affinity towards the receptor, even greater than the known agonist serotonin, LSD and psilocybin.

Keywords: Serotonin, 5-HT$_2$A Receptor, Tryptamine, Schiff Base

1. Introduction

The serotonin 5-HT$_2$A receptor is a G protein-coupled receptor implicated in numerous neuropsychological processes, including perception, cognition, and mood regulation. It serves as a principal target for various psychoactive substances and antipsychotic agents. Tryptamine and its structural analogs are of particular interest due to their endogenous presence and pharmacological relevance in modulating serotonergic signaling [1].

Schiff bases, with their structural versatility and ease of synthesis, have made them valuable scaffolds in medicinal chemistry, where they exhibit a wide range of biological activities, including antimicrobial, anticancer, and CNS-modulating properties [2]. When derived from tryptamine, a natural indoleamine structurally related to serotonin, Schiff bases may retain affinity for serotonin receptors, potentially acting as modulators of serotonergic neurotransmission.

In this study, we employed molecular docking techniques to evaluate the binding affinity of a series of tryptamine-derived Schiff bases with the 5-HT$_2$A receptor and compare it to the known agonist and antagonist of this receptor. The aim was to identify structural features that may contribute to agonistic or antagonistic activity and provide insights into their potential as serotonergic modulators.

2. Methodology

Ligands were constructed and energy-minimized using standard molecular modeling tools embanded in SwissDock platform. The three-dimensional structures of the human serotonin 5-HT$_2$A receptor were obtained from the Protein Data Bank (PDB ID: 7vod, 6a93 and 7wc6) and prepared by refining the active site and removing any co-crystallized ligands. Ligand docking was performed using the SwissDock platform, which is based on AutoDock Vina as its docking engine [3]. The binding site was defined around the orthosteric region of the receptor. Binding affinities (ΔG, kcal/mol) were used as the primary metric for comparing ligand–receptor interactions. Molecular visualization and interaction analysis were carried out using UCSF ChimeraX 1.8.

3. Results and Discussion

Recently, a serie of tryptamine-derived Schiff bases was synthetized [2]. The biological potential of the Schiff bases was evaluated using the SwissTargetPrediction tool, which identified family A G protein-coupled receptors, particularly 5-HT$_2$A, as the most probable targets of the Schiff bases. Tryptamine-derived compounds can act as both agonists and antagonists of the 5-HT$_2$A receptor. Many classic psychedelic drugs are tryptamines (like LSD and psilocin) and are 5-HT$_2$A agonists (Figure 1). However, there are also tryptamine derivatives designed to be 5-HT$_2$A antagonists for potential therapeutic purposes. In this study we calculated and compared the binding affinities of synthesized Schiff bases **SB1-7** and known tryptamine agonist (LSD, Psilocin; Figure 1) and some antagonist (Riseridone, Katanserin; Figure 1) to this receptor. Three most common crystal structures of serotonin 2A receptors were used (PDB ID: 7vod, 6a93 and 7wc6). The data for this study are shown in Table 1.

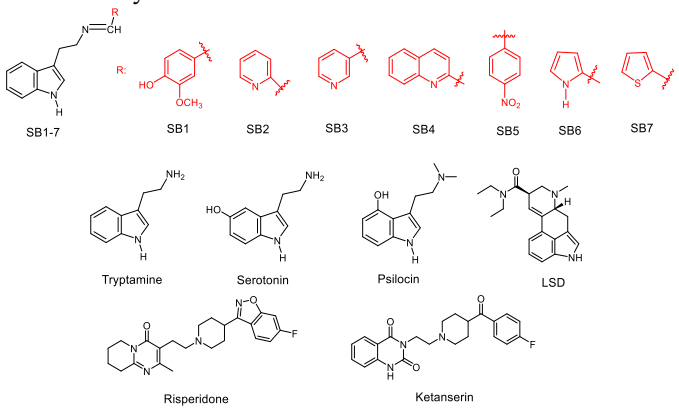

Figure 1. Structures of investigated compounds

Molecular docking simulations revealed that the synthesized tryptamine-derived Schiff bases exhibited consistently higher binding affinities toward the 5-HT$_2$A receptor compared to endogenous agonists tryptamine, serotonin, and the psychoactive compound psilocin. Notably, the majority of Schiff bases demonstrated binding affinities in the same range as lysergic acid diethylamide (LSD), a potent partial agonist of 5-HT$_2$A. While the affinities were slightly lower than those of the known antagonists risperidone and ketanserin, several Schiff bases approached their binding scores. Among the tested compounds, the Schiff base featuring a quinoline moiety (SB4) showed the highest binding affinity, suggesting that this scaffold may contribute favorably to receptor interaction and ligand stability within the binding pocket. Figure 2 shows the docked conformation of SB4 within the 5-HT$_2$A receptor and established interactions.

Table 1. Calculated binding affinities (kcal/mol) of the investigated compounds to the 5-HT$_2$A receptor

Compound PBD ID	SB1	SB2	SB3	SB4	SB5	SB6	SB7	Tryptamine	Serotonin	LSD	Psilocin	Risperidone	Ketanserin
7vod	-9.049	-8.567	-8.425	-9.746	-8.622	-8.292	-8.117	-6.506	-6.755	-8.895	-6.461	-11.562	-11.25
6a93	-8.866	-8.443	-8.441	-10.262	-8.785	-8.079	-8.122	-7.15	-6.474	-9.049	-6.724	-11.204	-10.668
7wc6	-8.312	-8.306	-8.295	-9.854	-8.477	-8.082	-7.838	-6.336	-6.644	-9.154	-6.417	-10.876	-9.995

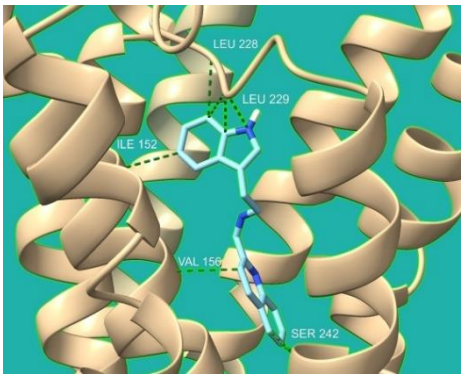

Figure 2. Molecular docking of 5-HT$_2$A receptor (PDB ID: 6a93) with ligand **SB4** and interactions with key residues.

4. Conclusions

The in-silico evaluation indicates that tryptamine-derived Schiff bases possess promising binding affinities for the 5-HT$_2$A receptor, exceeding those of common agonists and approaching those of established antagonists. The comparable affinity to LSD, particularly among derivatives with extended aromatic systems such as quinoline, suggests potential for further exploration as serotonergic modulators. These findings support the relevance of Schiff base scaffolds in the rational design of novel ligands targeting the 5-HT$_2$A receptor.

Acknowledgment

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