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Research Article

Direct and Indirect Drug Design Approaches for the Development of Novel Tricyclic Antipsychotics: Potential 5-HT_{2A} Antagonist

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Schizophrenia is a mental disorder manifested largely by disintegration of thought processes and emotional responsiveness. Given the therapeutic and toxic limitations of clinically available drugs, it is clear that there is still a need for the development of new generation antipsychotic agents with an improved clinical profile. Development of novel hybrid atypical tricyclic antipsychotic pharmacophore was achieved using direct (by measuring docking score of designed molecules on modelled 5-HT_{2A} receptor) and indirect (current, clinically available therapeutic agents' data) drug design approaches.

1. Introduction

Schizophrenia is a mental disorder which is manifested by the fragmentation of thought processes, auditory hallucinations, paranoid or bizarre delusions, and disorganized speech and is subsequently accompanied by significant social or occupational dysfunctions [1]. The onset of symptoms typically occurs during young adulthood with a global lifetime prevalence of about 0.3–0.7% [2]. The current mainstay for treatment is antipsychotic drugs, which are characterized as dopamine receptor antagonist, although many of them also act on other targets (particularly 5-HT receptors) which may contribute to their clinical efficacy [3]. The ability of selective 5-HT_{2A} receptor antagonists to modify the elevated level of dopamine, without interfering with neurotransmitter basal tone, demonstrate that such drugs possess antipsychotic activity and provide the baseline for the development of novel therapies for psychosis [4, 5].

The indirect approaches in drug design are used whenever the structure of the pharmaceutical target is unknown. In this case, as there is uncertainty regarding the active site, the discovery of new compounds with the desired characteristics for that target or the explication of some pharmaceutical properties has to be determined by studying series of known ligands for the same target. This approach comprises different techniques, of which the most used are quantitative structure activity relationship (QSAR), molecular similarity/diversity technique, and combinatorial chemistry. The direct approach in drug discovery, also known as structure based drug design, is applied whenever the 3D structural information for the biological target is known. This methodology combines information from several fields, such as X-ray crystallography and/or NMR, molecular modelling, synthetic organic chemistry, QSAR, and biological assays [6].

2. Limitations of Current Clinically Available Drugs

The drugs currently available for the treatment of schizophrenia are of limited use, as these agents are associated with potentially severe side effects such as extrapyramidal syndrome (EPS) [7] and tardive dyskinesia [8]. Furthermore,

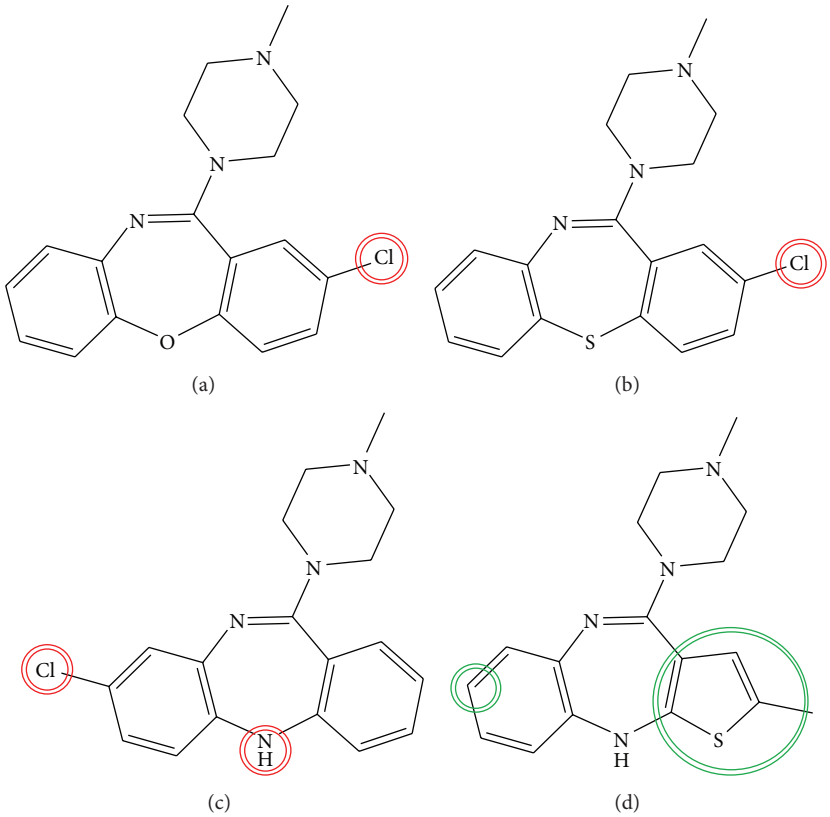


Figure 1: Limitations of current antipsychotic therapies (a) loxapine; (b) clothiapine; (c) clozapine; (d) olanzapine.

off-target effects associated with such therapies, namely, blockade of dopamine D_2-like receptors in the limbic and striatal regions of the brain, are assumed to be responsible for their neurological side effects [9]. Loxapine (Figure 1(a)) and clothiapine (Figure 1(b)) are well known antipsychotic agents prescribed in schizophrenia, but they have major extrapyramidal side effects (EPSE) and motor side effects, which can be attributed mainly to the electronegative chlorine atom on carbon number 2 (C-2) of their tricyclic ring, which is responsible for greater affinity of these drugs towards D_2 receptors. To minimize the side effects of the aforementioned drugs, clozapine (Figure 1(c)), the structural analogue of loxapine, was synthesized, where the chlorine on C-2 is shifted to C-8 atom and the oxygen at position 5 of tricyclic ring is replaced with nitrogen [10]. These modifications certainly improved clozapines' pharmacokinetic and pharmacodynamic profile and proved to be effective in reducing both positive and negative symptoms of schizophrenia. However, the potentially fatal blood disorder (agranulocytosis), detected in majority of patients, requires clozapine's clinical use to be accompanied by regular monitoring of white blood cell counts [11]. Subsequently, olanzapine (Figure 1(d)), which is structurally similar to clozapine, was developed with two major differences from than the previously mentioned drugs. The first modification was absence of a halogen substituent, and the second was a substituted thiophene ring in place of clozapine's benzene ring, which certainly improved the antipsychotic activity of olanzapine while minimizing side effects [12].

On the other hand, compounds such as quetiapine (Figure 2(a)) and zotepine (Figure 2(b)) exhibit low or no EPS and no signs of agranulocytosis, as the aliphatic side chains with heteroatom present in these compounds have a weaker affinity towards D_2 receptor with better antipsychotic potential. But the low bioavailability of these agents at receptor sites limits their clinical efficacy [13].

3. Development of Novel Potent Hybrid Tricyclic Atypical Antipsychotic with Minimal Side Effects

Considering the limitations and toxicities of clinically available drugs, it is clear that there is still an urgent need for the development of new generation antipsychotic agents with an improved clinical profile. Various attempts have been made to improve the clinical efficacy and to minimize the side effects of tricyclic atypical antipsychotics. Professor Ben Capuano and his research group studied different clozapine derivatives and reported that 4′-aryl substitution with an electron donating group gives more improved affinity towards D_4 and 5-HT_{2A} receptors than if electron withdrawing substituents are used [14, 15]. Further investigation on chain-extended series of clozapine analogues reported that the optimal length of the hydrocarbon linker between N4 and the introduced aryl system (phenyl) was three to five atoms [16]. These observations give us valuable insight into the spatial requirements in

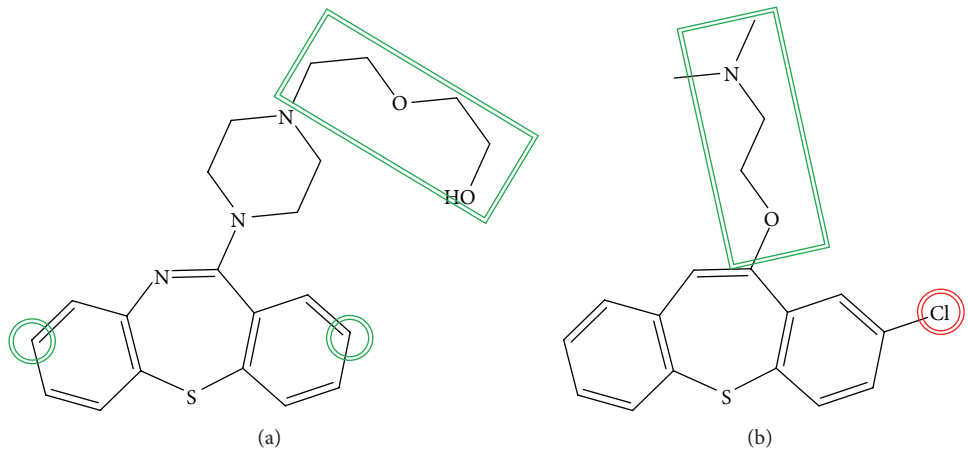


Figure 2: Limitations of current antipsychotic therapies (a) quetiapine; (b) zotepine.

the region of clozapine's distal nitrogen atom and thus will be useful in the ensuing study.

Given the aforementioned observations and pharmacological activity data of antipsychotic drugs, the following assumptions are made by our group for the development of new antipsychotic drugs.

(a) Chlorine at C-8 in clozapine could be responsible for its nonspecific action as well as hematological toxicities.

(b) The tricyclic ring is essential for atypical antipsychotic activity.

(c) The 4th atom from tricyclic ring should be a heteroatom (N or O) for D_4/5-HT_{2A} affinity.

With the help of the above assumptions, we attempted to use the molecular modelling approach to design and optimize new 5-HT_{2A} antagonists. The aim of the present study is to develop a hybrid tricyclic antipsychotic pharmacophore and to use this approach for the prediction of pharmacological activity of new molecules prior to their synthesis, with the hope that these molecules may be further explored as potent 5-HT_{2A} receptor antagonists. To achieve this objective, we applied the simple and predictive approach of direct and indirect drug design studies.

4. Materials and Methods

4.1. Indirect Drug Design Approach. In search of novel antipsychotic agents with maximum efficacy and minimal side effects, our group has worked on the various clinically available atypical tricyclic antipsychotic drugs, namely, clozapine, loxapine, and so forth. The first step in this search was to find out the energy minimized configurations of these derivatives and to refine the structures using molecular modelling techniques with the help of the LigPrep Module available in Schrödinger software [17].

4.1.1. Computational Methods

Data Set. The four well known drugs, namely, clozapine, loxapine, quetiapine, and olanzapine, were taken for the molecular modelling studies since these drugs belong to the atypical tricyclic antidepressant category with widely available clinical and toxicological data.

4.1.2. Molecular Modelling. All the structures for the study were drawn using Maestro and geometrically refined using LigPrep module. LigPrep is a robust collection of tools designed to prepare high quality 3D structures for large numbers of drug-like molecules. It produces low-energy, 3D molecular structures with correct chirality for each successfully proposed input structure. The conformations were generated by the Monte Carlo molecular modeling (MCMM) [18] method as implemented in MacroModel version 9.9 [19] using a maximum of 2,000 steps with a distance-dependent dielectric solvent model and an OPLS-2005 force field. All the conformers were subsequently minimized using truncated Newton conjugate gradient (TNCG) minimization up to 500 iterations. For each molecule, a set of conformers with a maximum energy difference of 30 kcal/mol related to the global energy minimum conformer were retained. The conformational search was conducted for aqueous solution using the generalized born/solvent accessible surface (GB/SA) continuum solvation model.

4.2. Direct Drug Design Approach. The direct drug design approach utilizes the X-ray crystallographic structure of the receptor for defining the binding mode of the ligand to the active site of the macromolecules. Results from the structural model obtained from indirect design encouraged us to corroborate the model using the direct drug design. But the restrained issues related to the X-ray crystallographic data of 5-HT_{2A} (such as difficulties in isolation, NMR solvent insolubilities) [20] forced our direction towards the development of (a) a 3D homology model of 5-HT_{2A} followed by (b) docking of the designed structural model into the active site of 3D receptor homology model. The general structure and organizations of GPCRs in the biomembrane are depicted in Figure 3.

To date, four different GPCR structures have been determined by X-ray crystallography, namely, β2 adrenergic receptor (PDB IDs: 3P0G, 3PDS, and 2RH1), β1 adrenergic

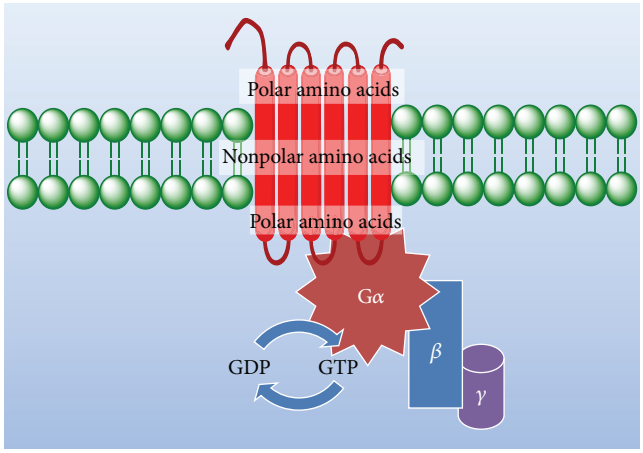


FIGURE 3: General structure and organization of GPCRs with distribution of amino acids within the structure.

>gi|46854843|gb|AAH69356.1| 5-hydroxytryptamine (serotonin) receptor 2A [Homo sapiens]
MDILCEENTSLSSTTNSLMQLNDDTRLYSNDFNSGEANTSDAFNWTVDSENRTNLSCEGCLSPSC
LSLLHLQEKNWSALLTAVVIILTIAGNILVIMAVSLEKKLQNATNYFLMSLAIADMLLGFLVMPVSML
TILYGYRWPLPSKLCAVWIYLDVLFSTASIMHLCAISLDRYVAIQNPIHHSRFNSRTKAFLKIIAVTISV
GISMPIPVFGLQDDSKVFKEGSCLLADDNFVLIGSFVSFFIPLTIMVITYFLTIKSLQKEATLCVSDLGT
RAKLASFSFLPQSSLSSEKLFQRSIHREPGSYTGRRTMQSISNEQKACKVLGIVFFLFVVMWCPFFI
TNIMAVICKESCNEDVIGALLNVFVWIGYLSSAVNPLVYTLFNKTYRSAFSRYIQCQYKENKKPLQLI
LVNTIPALAYKSSQLQMGQKKNSKQDAKTTDNDCSMVALGKQHSEEASKDNSDGVNEKVSCV

FIGURE 4: FASTA sequence of 5-HT$_{2A}$ receptor [Homo sapiens].

receptor (PDB IDs: 2Y00, 2Y01, 2Y02, 2Y03, 2Y04, and A2A), adenosine receptor (PDB ID: 3QAK) and rhodopsin (PDB ID: 1F88).

4.2.1. Homology Modeling of 5-HT$_{2A}$. The homology model of 5-HT$_{2A}$ receptor was achieved via the following steps.

(1) *Query sequence.* Homology modelling was used to build the 3D model for human 5-HT$_{2A}$ receptor using the Prime module present in the Schrödinger suite 2011. The protein sequence (>gi|46854843|gb|AAH69356.1| 5-hydroxytryptamine (serotonin) receptor 2A [Homo sapiens]) (470 amino acids) was retrieved from the National Centre for Biotechnology Information (http://www.ncbi.nlm.nih.gov/) (Figure 4).

(2) *Identification of structural templates.* The obtained protein sequence was further utilized to identify the 3D template using the Prime module [21] in Schrödinger suite 2011, a molecular modeling package installed in Windows XP platform. Blast search within the Prime was utilized to select the templates with PDB ID 2RH1. The template (PDB ID: 2RH1) was aligned with the target sequence of human 5-HT$_{2A}$ receptor (Figure 5). The aligned sequence was taken for model construction.

(3) *Building a homology model.* A homology model was constructed using Prime, based on the alignment obtained, and it generated a refined 3D homology model. A Ramachandran plot [22] was used to assess the quality of bond lengths, dihedral values, and angle distribution.

4.2.2. Molecular Docking Study. Molecular docking was carried out using the Glide module [23] present in Schrödinger suite 2011. Glide ligand docking jobs requires a set of previously calculated receptor grids and prepared ligand structures.

(1) *Dataset.* On the basis of results obtained from indirect drug design, we prepared a virtual library of molecules containing hybrid structural features of clozapine, loxapine, and quetiapine. The general structure of the designed molecules is depicted in Figure 7.

(2) *Ligand preparation.* All the structures for the study were drawn using Maestro and geometrically refined using the LigPrep module.

(3) *Receptor grid generation.* Glide searches for favourable interactions between one or more ligand molecules and a receptor molecule, usually a protein. The shape and properties of the receptor are represented on a grid by several different sets of fields that provide accurate progressive scoring of the various ligand poses. The binding site for ligands on modelled 5-HT$_{2A}$ receptor was generated by selecting a box centroid of selected residues; that is, it centres grid at a set of residues selected. With this we defined the active site (where grids should be centred using supplied X, Y and Z coordinates) with only the receptor in the workspace. The constraints are defined during grid generation setup and then applied during docking setup. For docking the ligands need to be prepared.

(4) *Molecular docking.* Glide ligand docking jobs require a set of previously calculated receptor grids and prepared ligand 3D structures. The docking score of all ligands was calculated automatically by using option dock flexibly and the ligands with maximum docking score are reported in Table 2.

5. Results and Discussion

5.1. Indirect Drug Design. Bearing in mind the assumptions made by us and carefully observing the energy minimized conformations of currently available antipsychotic agents, we calculated the distance between the N4 of a piperazine ring in the chair form (heteroatom) and C-2 and C-8 of tricyclic ring (Table 1), as both these groups are important as per our assumptions.

Based on the above observations, we have developed a structural skeleton depicted in Figure 6, which conceptualizes the collection of key structural features in atypical tricyclic antipsychotics. The envisaged assembly of aromatic rings (tricyclic nucleus), a nitrogen atom that is ionized at physiological pH, and a secondary aromatic or π-system separated by an aliphatic linker of designated length and

Table 1: The distance between N4 and C-2/C-8 of tricyclic ring.

Sr. no.	Molecule	Distance between N4 and C-2 of tricyclic ring (Å)	Distance between N4 and C-8 of tricyclic ring (Å)
(1)	Clozapine	6.256	8.660
(2)	Loxapine	6.301	8.717
(3)	Quetiapine	6.891	7.848
(4)	Olanzapine	6.354	8.667
(5)	Designed benzyl derivatives	6.659	7.544
(6)	Designed benzoyl derivatives	6.446	8.650

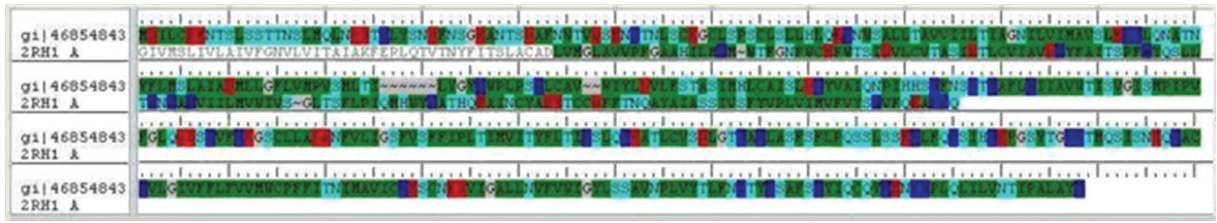


Figure 5: Alignment of FASTA sequence of 5-HT_{2A} receptor with template 2RH1.

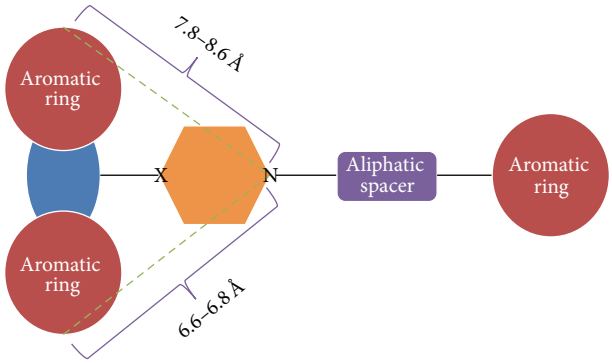


Figure 6: Structural model with detailed generic structural features that may afford potent antipsychotic activity.

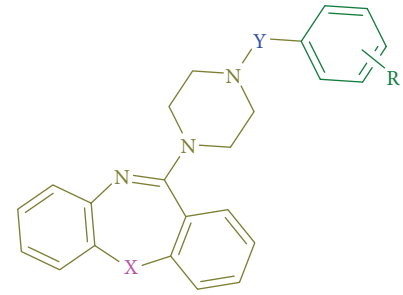


Figure 7: General structure of designed library used for further investigation.

nature from the nitrogen atom may provide comparatively potent and superior antipsychotic activity.

In addition to the above observations and indirect drug design approach, we analyzed various metabolic pathways of the atypical antipsychotic agents. In most related research articles, investigators have evaluated N4-methyl analogue of tricyclic derivatives for antipsychotic activity; however N4-demethylation is a prime metabolic process by which the tricyclic agents are eliminated from the body [24–26]; hence we attempted to modify N4 substitution via two possible approaches.

(1) *Substitution of methyl group by benzyl group*: this modification would change the conformation of the piperazine ring as well as lipophilic aryl group of benzyl and might adversely affect oxidation by the CYP3A4 enzyme.

(2) *Substituting the benzoyl group at N4*: such modification prevents the molecules from being metabolized by CYP3A4 enzyme due to delocalization of the nitrogen electron lone pair.

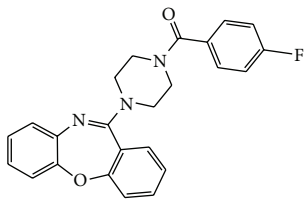
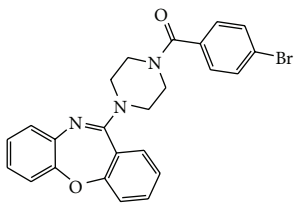
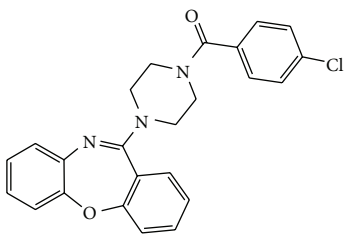
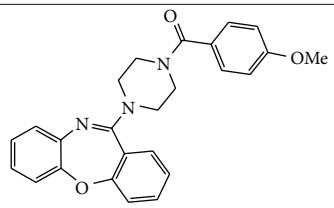
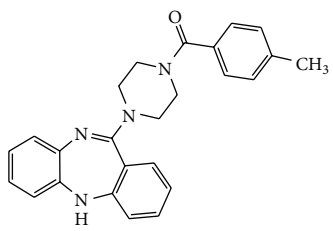
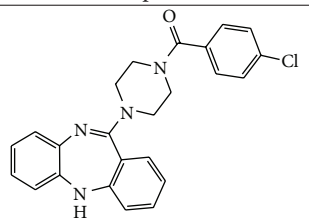
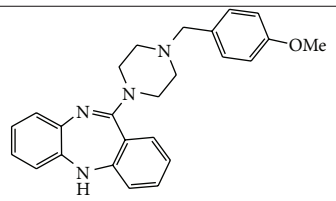
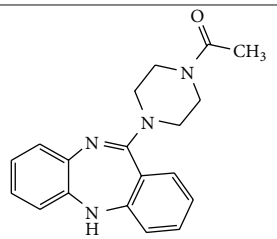
Substituted benzyl or benzoyl groups attached to the distal N4 atom of piperazine will be expected to improve selectivity of the compounds towards 5-HT_{2A} receptors which could be useful in treating negative symptoms of schizophrenia. An unsubstituted tricyclic nucleus may show improved efficacy and minimal side effects, like EPS and agranulocytosis.

The above mentioned replacements/substitutions may certainly increase the bioavailability as well as selectivity of the tricyclic derivatives at the receptor site. Considering the key structural features of the aforementioned model, the indirect drug design approach, and metabolic studies published on tricyclic antipsychotic agents, we prepared a library of molecules which would surely serve as potent, selective atypical antipsychotic agents with minimal side effects. The general structure of the designed molecules used for further investigation is depicted in Figure 7.

5.2. Direct Drug Design

5.2.1. Homology Modeling. The resulting Ramachandran plot (Figure 8) obtained of the modelled 5-HT_{2A} shows that about 98% of dihedrals fall within allowed regions and demonstrated that the constructed model can be used for docking

Table 2: Docking score of ligands.

Sr. no.	Compounds	Docking score
(1)	Clozapine	−5.842
(2)	Loxapine	−4.253
(3)	 MJ37	−6.489
(4)	 MJ40	−5.405
(5)	 MJ39	−5.346
(6)	 MJ41	−4.965
(7)	 MJ16	−5.735
(8)	 MJ18	−5.620
(9)	 MJ10	−4.759
(10)	 MJ13	−4.607

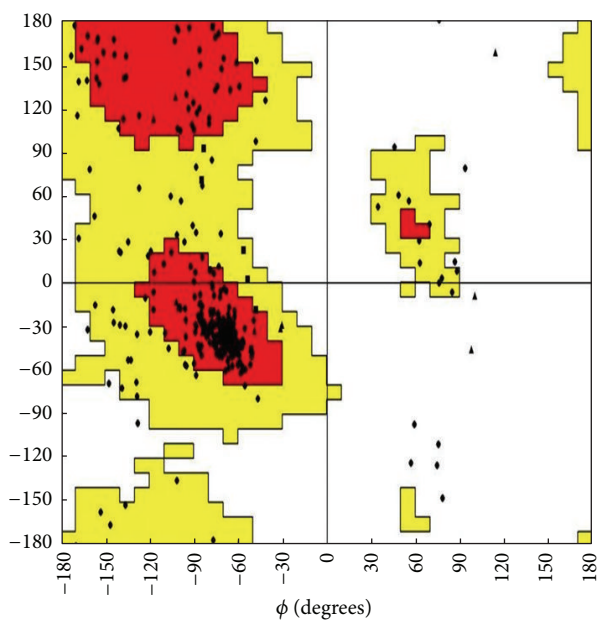
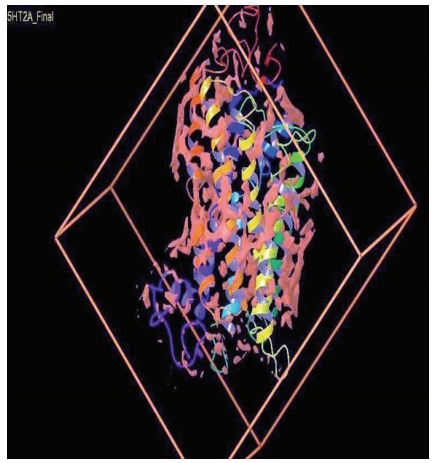
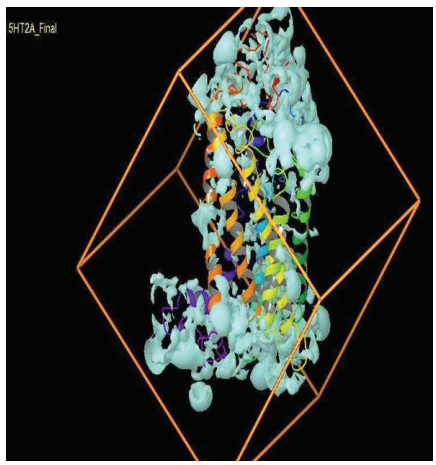


Figure 8: Ramachandran plot of modelled 5-HT_{2A} receptor; the dihedrals are 97.88% in allowed regions and 2.12% in disallowed regions.



(a)

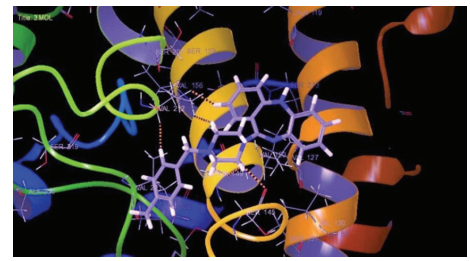


(b)

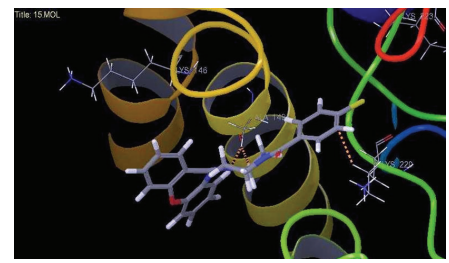
Figure 9: (a) Hydrophobic region and (b) hydrophilic region in modelled 5-HT_{2A} receptor.

and simulation purposes. The conservation of hydrogen bond network between the conserved residues was also taken into account as well as the hydrophobic and hydrophilic distribution (Figures 9(a) and 9(b)) by using GRID probe present in Prime module of Schrödinger suite 2011. Hydrophilic and hydrophobic probes revealed the correct orientation of alpha helixes within the structure.

5.2.2. Docking and Simulation. To study the molecular basis of interaction and binding affinities of designed hybrid atypical antipsychotic derivatives, all the designed ligands were docked into the active site of modelled 5-HT_{2A} receptor. The docking results of most active ligands are given in Table 2. The ranking of ligands was based on their Glide score. The docking results showed that the electron donating (–CH_3)/withdrawing (–F) group substitution at para position at the piperazinylbenzoyl/benzyl derivatives gives superior docking scores compared with loxapine and clozapine. The interactions of ligands are with Cys148, Val221, Phe222, Asp231, Cys353, Val156, Ser145, Ala149, and Phe222 amino



(a)



(b)

Figure 10: (a) Interaction of MJ 16 and (b) Interaction of MJ 37 with 5-HT_{2A} receptor.

acids. The interaction of MJ 16 and MJ 37 with 5-HT_{2A} receptor is depicted in Figures 10(a) and 10(b).

6. Conclusion

In the present investigation, we applied simple and productive direct and indirect drug design approaches for designing ideal antipsychotic agents. The theme for such designing was the unsubstituted tricyclic ring with modification at the N4 atom of 11-piperazinyl ring. From energy minimized structure analysis, we concluded that the distance between N4 of piperazine and C-2 and C-8 of tricyclic nucleus should be 6.3–6.8 Å and 7.8–8.6 Å, respectively, for improved activity. From the homology and docking studies we concluded that the electron donating (–CH_3)/withdrawing group (–F) substitution at para position at the benzoyl/benzyl derivatives gives superior docking scores compared with loxapine and clozapine. The present study investigates the indispensable molecular features of tricyclic derivatives which can be exploited for further structural modifications of these lead molecules in order to achieve improved antipsychotic activity for the management of schizophrenia.

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