International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Original Article **CODEN: IJPNL6**

DOCKING AND PHYSICOCHEMICAL SIMILARITY STUDIES ON INDOLE BASED ATYPICAL ANTIPSYCHOTICS

Alka Bali* and Umesh Sen

*University Institute of Pharmaceutical Sciences, UGC Centre of Advanced Study, Panjab University, Chandigarh, 160014, India.

***Corresponding author e-mail:** alka.bali@rediffmail.com

Received on: 14-01-2016; Revised on: 02-02-2016; Accepted on: 24-02-2016

ABSTRACT

A hypothetical binding model has been proposed based on *in silico* (docking studies) on a series of indole derivatives with atypical antipsychotic activity in order to investigate their hypothetical binding mode with respect to the dopaminergic D_3 receptors. The docking reproduced the established receptor binding profile of the standard drugs ziprasidone, risperidone, ketanserin, clozapine and eticlopride. The test compounds demonstrated a similar binding profile to the standard drugs. Salient interactions noted for the standard drugs as well as the test compounds were the hydrogen bonding interactions with the residues Asp110, Tyr373, Ser182, Ser192, Cys181 and π-π stacking with Phe345, Phe346 and His349. The D_3 docking scores of the compounds lacking the atypical profile were seen to be lower compared to those having an atypical profile. Further, the physicochemical similarity of the test compounds was assessed with respect to selected standard drugs and the test compounds were seen to possess very good similarity to ziprasidone.

Keywords: Docking, Antipsychotics, *In-silico*, Similarity studies; D_3-receptor; dopaminergic antagonists

INTRODUCTION

The application of computational methods to study the drug-target interactions has been a subject of intensive research during the last decade. The molecular binding of the ligand to the target proteins (or other macromolecules) translates into the observed biological activity. Molecular docking studies are routinely employed to study such interactions in order to predict the structure of the intermolecular complex formed as a result of collective 'binding modes' involved. These studies further highlight the probable affinity of the small molecules towards the endogenous macromolecular targets. The prediction of the intermolecular complex is vitally significant for the development of new therapeutics as docking can alter the chemical behaviour of the receptor macromolecule.

Schizophrenia is a complex, debilitating and severe mental illness characterized by impaired thought processes chronic, debilitating mental disorder affecting nearly 24 million people worldwide accounting for 1% of the world population irrespective of ethnic, economical, or cultural boundaries [1, 2]. The complexity of the etiology and pathophysiology of schizophrenia has led to development of a number of hypotheses for the development of antipsychotic drugs. The classical or 'typical' antipsychotic drugs such as chlorpromazine, haloperidol, fluphenazine are based on the dopaminergic hypothesis of schizophrenia which postulates an increased dopamine release and sensitization of the dopaminergic system as a major cause of schizophrenic manifestations [3]. However, these agents suffer from the drawbacks of severe mechanism related side effects including parkinsonism and akathesia (extrapyramidal symptoms), tardive dyskinesia and galactorrhoea (due to increased prolactin release) [4] and these are also ineffective against the negative symptoms of the

disease. The introduction of clozapine, a dibenzodiazepine derivative for treatment-resistant schizophrenia gave rise to a new group of atypical or non-classical antipsychotics, which have no extrapyramidal side effects (EPS) and are effective against negative symptoms [5]. It exhibits binding to multiple receptor subtypes including dopaminergic and serotonergic receptors. The atypical antipsychotic profile of clozapine is thought to result from its affinity for a multitude of receptors, including dopamine receptor subtypes, 5-HT_2 receptors, and others [6]. The dopamine hypothesis has dominated schizophrenia research for several decades now, although, modulation of other neurotransmitters, in particular glutamatergic, serotonergic, adrenergic and cholinergic receptor pathways is also seen to play an important role in schizophrenia [7].

Molecular biological techniques have seen the cloning of a number of different subtypes of dopamine receptors, which, on the basis of their pharmacology, can be divided into two classes, D_1-like (D_1 and D_5) and D_2- like (D_2, D_3 and D_4) [8]. The discovery of these subtypes mainly D_2, D_3 and D_4 has stimulated interest in the possibility of designing a new generation of antipsychotic drugs with a much lower propensity to induce the debilitating extrapyramidal side effects of current therapy [9]. The D_2 receptor subtype has a high density in the limbic region of the brain associated with cognitive and emotional functions as well as in the striatal areas of the brain associated with locomotor coordination and hence, D_2 receptor antagonists are classical antipsychotics. The dopamine D_3 receptor subtype has been hypothesized to play a fundamental role in the abuse related effects of cocaine and other drugs of abuse [10]. Further, there is greater abundance of D_3 receptor mRNAs and dopamine D_3 receptors in the mesocorticolimbic regions of the brain [11] in comparison to the nigrostriatal areas. Several literature reports suggest that antagonists with selectivity for D_3 receptors or D_3 antagonists possessing moderate D_2 affinity display an atypical antipsychotic profile [12-17].

We have recently reported a series of indole derivatives [18] with some of the lead molecules displaying good atypical antipsychotic profiles (Table 1) and docking studies were performed with respect to dopaminergic D_2 receptors and the serotonergic 5-HT_{2A} receptors. The present study has been carried out primarily to investigate the plausible role of selective D_3 *vs* D_2 affinity in the atypical antipsychotic activity of the investigated compound series. In our present paper, we report the *in silico* (docking studies) in order to investigate the hypothetical binding mode for the target compounds to the dopaminergic D_3 receptors. A binding model has been proposed based on the docking studies. The standard drugs ziprasidone, risperidone, ketanserin, clozapine and eticlopride (Figure 1) were also included in the studies in order to assess the ability of the *in silico* studies to reproduce established receptor binding profiles of the said drugs. The docking scores were compared to those previously obtained with D_2 receptors [18]. Further, the physicochemical similarity of the test compounds with respect to selected standard drugs was also assessed in order to authenticate the predictive capability of various computational approaches.

MATERIALS AND METHODS

The docking studies were carried out using Dell notebook PC, (Core 2 Duo Processor; 4GB RAM) running on Windows 7 using Maestro 9.3 (Schrodinger Inc.). The synthesized molecules were evaluated *in silico* (docking) using the crystallized D_3 receptor model obtained from protein data bank (PDB ID: 3PBL). The model of the dopaminergic D_2 receptors was obtained from ModBase by initial screening of the Swiss-Prot data base (UniProt ID: P14416). Various parameters including docking score, glide score and glide emodel were calculated. Similar data emphasizing the degree of interaction between the test compounds and receptor were deduced additionally. The physicochemical parameters utilized for the similarity studies were computed using ChemBio3D Ultra version12.0.

Selection of the Protein

Dopamine D_3 receptor structure: Dopamine D_3 receptors are G-protein coupled receptors consisting of seven transmembrane helices. The receptor consists of 481 amino acids and is not associated with any metal ion. The only crystallized D_3 receptor model was obtained from protein data bank (PDB ID: 3PBL). The retrieved protein structure consisted of two receptors in antiparallel orientation, co-crystallized with two molecules each of eticlopride and maltose. The crystal diffraction data for the crystallized complex was anisotropic extending 2.9A in the c* direction and 3.6Å in a* direction. Overall, the structure was determined at 3.15 Å and included all data up to 2.9 Å where an improvement in map quality was observed. The receptor consisted of single chain and harboured an active site for eticlopride and maltose.

Dopamine D_2 receptor structure: The model of the dopaminergic D_2 receptors employed for the in silico evaluation was obtained from ModBase by initial screening of the Swiss-Prot data base (UniProt ID:

P14416) was selected [19]. The model selected was based on human β_2-adrenergic receptor template (PDB ID: 2RH1), whose crystal structure was determined at 2.40 Å. The model contains net 414 residues, ranging from amino acids 30 to 442. The model was selected based on the notified reliability criteria and chain length.

Preparation of Protein

The pre-processing of the protein was carried out by assigning the bond orders, adding hydrogen atoms to the crystal structure, creating disulfide bonds, filling missing side chains and loops (using Prime). The water molecules beyond 5 Å were deleted straightaway. This was followed by reviewing and modifying the pre-processed protein, where the workspace protein was analyzed for multiple chains and associated ligands. In the next step (refinement), hydrogen bonds were optimized using PROPKA at pH of 7.0. The amino acids residues lying close to the active site were allowed to flip. Finally, the strain was minimized using OPLS2005. The quality of prepared protein was ascertained by Ramachandran plot.

Receptor grid generation

Dopamine D_3 receptor: In the Receptor Grid generation wizard, the receptor was defined as the workspace structure and the co-crystallized ligand (eticlopride) was selected in the workspace to exclude it from grid generation. The van der Waals radii were scaled by a factor of 1.0 for all those atoms carrying partial atomic charge. The docking ligand was confined to a box whose centre was defined by the centroid of workspace ligand, eticlopride. No constraints and excluded volumes were defined and the grid was generated with default settings.

Dopamine D_2 receptor: In the Receptor Grid generation wizard, the receptor was defined by default settings as the workspace structure. The van der Waals radii were scaled by a factor of 1.0 for all those atoms carrying partial atomic charge. Based on the previous literature reports, the receptor grid site was selected as the centroid of residues Asp114, Ser193 and Phe390. No constraints and excluded volumes were defined. The grid was generated retaining the default settings; dock ligands with less than 20 Å length and the diameter midpoint of each docked ligand was required to remain within a cube of edge length of 10 Å whose centroid overlapped with the centroid of mentioned residues.

Ligand Preparation

All ligand 2D structures were sketched in ChemBio3D Ultra version12.0 and were saved as .sdf files and then imported to Maestro 9.3. The ligands were selected as entries and were subjected to minimization using the OPLS_2005 force field and various ionization states between pH 7±2 were generated. The prepared ligands were saved in maestro format. The operation was performed under the LigPrep wizard.

Ligand Docking

Various conformations of the ligands generated by LigPrep were docked employing Ligand Docking tool under the Glide menu. The receptor grid and ligands were defined by browsing the respective files. Docking was performed using extra precision mode with generation of at most 10 poses per ligand. Besides, per residue interaction scores were also calculated during the run. Docking efficiency was evaluated on the basis of various parameters including Docking score, GScore, Glide emodel, potential energy, binding energy and complex energy.

Physicochemical similarity studies

Selected molecular parameters was computed for the test compounds as well as for four standard drugs clozapine, risperidone, ziprasidone and ketanserin using ChemBio3D Ultra version12.0 after carrying out MM2 minimization of the compound structures. The log BB values (indicative of BBB barrier penetration) were computed using an online software program based on topological descriptors [20]. The data obtained was then utilized to compute the physicochemical similarity of the test compounds to the standard drugs.

RESULTS AND DISCUSSION

D_3 receptor docking

Docking studies with D_3 receptor were carried out using the only available X-ray crystal structure for the receptor in the protein data bank (PDB ID: 3PBL) harbouring an active site each for eticlopride and maltose. In order to investigate the ability of molecular docking to reproduce an experimentally observed ligand-binding mode, the co-crystallized ligand, eticlopride (ETQ) was used as a reference ligand. The docking results have been given in Table 2 and the hypothetical binding mode depicted in Figures 2, 3 and 4. ETQ (5-chloro-3-ethyl-N-[[(2S)-1-ethylpyrrolidin-2-yl]methyl]-2-hydroxy-6-methoxybenzamide) is a dopamine antagonist with affinity towards both D_2 and D_3 receptors. Eticlopride (ETQ) docked well in the receptor pocket forming four hydrogen bonds. The anionic oxygen of Asp110 residue was involved in a strong charge reinforced hydrogen bond with the charged pyrrolidine and

another hydrogen bond was formed with the amide NH of the ligand. The protonated oxygen of amide functionality showed a backbone hydrogen bond with the NH of Ile183 and displayed another weaker hydrogen bonding interaction with His349 nitrogen. Among the docked drugs, ziprasidone possessed the best dock score (-9.182) quite interpretable by the strong π-π stacking and hydrogen bonding interactions with various amino acid residues. Similar to eticlopride, a strong charge reinforced hydrogen bond was seen between the charged piperazine and the Asp110 (1.584 Å) oxygen. A couple of similar interactions were seen between the indolinone NH and the backbone carbonyl of Cys181 and Ser182, at distances of 1.868 and 4.221 Å respectively. The benzisothiazole moiety accounted for strong π-π stacking interactions with residues Phe345, Phe346 and His349. A decent dock score of -8.897 was also obtained for risperidone accounted for by interactions almost parallel to those seen for ziprasidone, i.e., a charge reinforced hydrogen bond (1.598 Å) between charged piperidine NH with charged Asp110 residue and another hydrogen bond between the pyrimidinone carbonyl and the backbone NH of Ile183. The fluorophenyl part of benzoxazole ring was involved in π-π stacking with the phenyl ring and imidazole ring of Phe346 and His349. The oxazole ring showed similar stacking with Phe346, at a distance of 3.257 Å. Clozapine also showed a satisfactory docking profile. The NH of dibenzodiazepine ring formed a hydrogen bond (3.388 Å) with the oxygen of polar Ser192. Similarly, at a distance of 3.007 Å, the piperazine nitrogen formed a hydrogen bond with the backbone NH of the amino acid Ile183. The chlorophenyl ring of dibenzodiazepine moiety showed π-π stacking with Phe345, Phe346 and His349 at distances of 3.886, 3.185, 3.245 Å respectively. Similarly, the unsubstituted benzene ring of the moiety stacked (π-π stacking) well with the phenyl ring of Trp342 at a distance of 3.528 Å.

Among the test compounds **1**-**6**, a strong charge reinforced hydrogen bond was observed with the negatively charged oxygen of Asp110 only in case of compounds **2** and **5.** Interestingly, this interaction was not seen in the compounds **3** and **4** found most active in the in vivo assay for antipsychotic effect (and also possessing an atypical profile). However, both of these showed formation of another hydrogen bond with Tyr373.In addition to this strong hydrogen bonding interaction with Tyr373 interaction (between indole NH and Tyr373 OH), the compound **3** showed significant π-π stacking accounting for a very good dock score (-7.600) which was quite close to the score obtained for reference ligand eticlopride (-8.238). The terminal aromatic ring of **3** was involved in π-π stacking interactions with the phenyl ring of Phe345 and the imidazole ring of His349. Such π-π interactions contribute profoundly to the binding energy of the drug-receptor complex and magnitude wise, outweigh hydrogen bond interactions. The most active test ligand, i.e., compound **4** docked best (dock score -7.928) into the D_3 receptor pocket by forming two strong hydrogen bonds, one with Tyr373 OH (similar to **3**) and another between the phenylamine NH and the Ser192 OH. Further, the terminal chlorophenyl moiety of the molecule was involved in a π-π ring stacking interaction with the phenyl ring of Phe346 (3.159 Å). The compounds **1** and **2,** which had also shown good potency (albeit lower than **3** and **4**) as well as atypical profile also displayed satisfactory binding with the receptor. The absence of a hydrogen bond with Asp110 in case of 1was compensated by a strong hydrogen bonding interaction between the phenylamine NH of **1** (2.035 Å) with the carbonyl oxygen of Cys181 and the formation of another hydrogen bond with Ser182. The terminal chlorophenyl ring in both **1** and **2** was involved in π-π stacking with the phenyl ring of Phe346. The compound **2** additionally displayed another π-π stacking between the phenoxy moiety and Phe106 at a ring to ring distance of 3.446 Å. In compounds **5** and **6**, the phenylamine NH displayed hydrogen bonding interactions with residues Tyr373 and Ser192 respectively. Another back bone hydrogen bond seen between the propyloxy oxygen atom and the NH of Ile183 residue in case of **5** and two π-π stacking interactions were noted for **6** with residues Phe346 and His349.

Summarizing, the standard drugs as well as the test compounds displayed similar bonding interactions within the D_3 receptor pocket. The prominent amino acids involved in hydrogen bonding to the standard drugs were Asp110, Ile183, Ser182, Cys181 and Tyr373, all located within 3-4 Å distance. In case of the test compounds **1** to **6** also, important hydrogen bonding interactions were seen with Asp110, Tyr373, Ser182, Ser192 and Cys181. Salient π-π stacking interactions were noted for the standard drugs as well as test compounds with phenyl rings of Phe345and Phe346 and imidazole ring of His349. Their binding profile was also found to be quite similar to that displayed by the standard ligand eticlopride as well as by the standard drugs ziprasidone and ketanserin with similar hydrogen bonding interactions and π-π stacking.

D_2 receptor docking

We had recently compared the docking profiles of these test compounds with the $5HT_{2A}$ and D_2 receptors. As there was no crystal structure of the D_2 receptor lodged in the Protein Data bank (PDB),

hence, the model employed for the *in silico* evaluation was obtained from ModBase (Uniprot ID: P14416). Some standard drugs known to possess a good D_2 receptor affinity (ziprasidone and eticlopride) and a weak D_2 receptor affinity (ketanserin) were taken to assess the ability of the model to reproduce their binding profiles. As anticipated, ziprasidone showed good interactions with D_2 receptor including a strong charge reinforced hydrogen bonding interaction (1.561 Å) with the conserved residue Asp114. The docking model of eticlopride revealed a very good binding to the D_2 receptor involving five prominent hydrogen bonding interactions with the vicinity residues - the hydroxyl substituent on the penta-substituted phenyl ring and the amide oxygen hydrogen bonding to the donor OH moiety of Thr412 (1.962 Å and 2.949 Å respectively). The amide NH hydrogen of the molecule was involved in two hydrogen bonding interactions with the negatively charged oxygen of Asp114 (2.736 Å) and with the oxygen atom of Tyr416 (2.363 Å). A relatively weaker hydrogen bonding interaction (3.815 Å) was displayed by the methoxy oxygen atom with the backbone NH of Ile183 residue. Risperidone also showed good bonding *via* two prominent hydrogen bonds with amino acids Asp114 and Thr412. Ketanserin, as expected, showed the least affinity for the receptor. Though no π-π interactions were predicted for clozapine, it docked reasonably well in the binding pocket of D_2 receptor attributable to the two hydrogen bonding interactions with Ile183 and Thr412. The exposed chloro substituent of dibenzodiazepine system interacted hydrophobically with residues Asp114 (3.568 Å) and Phe389 (2.650 Å). The interaction of the test ligands **1-6** was recently reported and prominent interactions noted with Asp114, Cys118, Phe389 and Phe390 were in concordance with previous literature reports [21].

D_3 receptor docking and atypical antipsychotic profile

All the test compounds were seen to dock within the D_3 receptor pocket in a similar binding mode. We compared the D_3 docking scores with our previously reported results relating to their atypical antipsychotic profile. A comparatively lower D_3 dock score was seen for the compounds **5** and **6.** As shown in Table 1, both **5** and **6** possess a conventional antipsychotic profile, i.e., these cause the inhibition of apomorphine induced mesh climbing behaviour (indicative of antipsychotic effect) but additionally inhibit the apomorphine induced stereotypy (indicative of their potential to cause extrapyramidal side effects). In comparison, the compounds **1** to **4** showed higher docking scores. The compounds **1** to **4** possess an atypical antipsychotic profile, i.e., these cause the inhibition of apomorphine induced mesh climbing behaviour (indicative of antipsychotic effect) without causing the inhibition of apomorphine induced stereotypy, thus, indicating the absence of extrapyramidal side effects. Further, all these compounds have displayed higher docking scores with respect to the dopaminergic D_3 receptors compared to D_2 receptors. This preferential D_3 *vs* D_2 binding is an accepted receptor binding approach for the development of atypical antipsychotics. In our previous paper [18], docking studies of the test compounds had suggested a potential for combined 5-HT_{2A} / D_2 affinity, a profile exhibited by several standard atypical antipsychotic drugs as exemplified by risperidone and ziprasidone. Our present study further suggests that the activity profile of this compound series can be accounted for not only by their selective affinity for the serotonergic 5-HT_{2A} receptors, but also by the dopaminergic D_3 receptors. This is also in concordance with the current emphasis on multireceptor approaches being exploited in the design of atypical antipsychotics [22]. These approaches are quite perceivable considering the fact that most of the currently available atypical antipsychotic drugs are known to target multitude of receptors and a single receptor binding approach cannot account for their therapeutic activity.

Physicochemical similarity studies.

The physicochemical similarity of the target compounds was calculated with respect to four standard drugs clozapine, risperidone, ziprasidone and ketanserin. A set of eleven molecular parameters was computed for the test compounds as well as for the standard drugs using ChemBio3D Ultra version12.0 after carrying out MM2 minimization of the compound structures. The values obtained for selected molecular parameters computed for the test compounds and standard drugs are shown in Table 3. Considering the fact that antipsychotics are essentially intended to act on CNS target sites, the parameters selected were the ones that that could potentially have a bearing on the activity profiles of the CNS active compounds. These include the parameters important for blood-brain barrier (BBB) penetration including the theoretical log BB values, molecular surface area parameters (e.g., topological polar surface area TPSA), log P and volume parameters. Steric and molecular surface descriptors computed include Connolly Solvent Accessible Surface Area SAS (Angstroms^2), Connolly Molecular Surface Area MS (Angstroms^2), Connolly Solvent-Excluded Volume SEV (Angstroms^3) and Ovality. Global physicochemical properties computed were hydrophobic parameter log P and molecular weight

MW (atomic mass units). Other parameters were Molecular Topological Index MTI and Weiner Index WI.

The physicochemical and steric similarity of the target compounds was calculated with respect to the standard drugs. Firstly, the distance d_i of a particular target compound j to drug molecules e.g., clozapine was calculated by the formula:

$$d_i^2 = \sum_{j=1}^{n} (1 - X_{i,j} / X_{i,std})^2 / n$$

where, $X_{i,j}$ is the value of molecular parameter 'i' for compound 'j', $X_{i,std}$ is the value of the same molecular parameter for the standard drug, e.g., clozapine, risperidone, etc. Then, the similarity of compound 'j' to the standard drug was calculated as:

Similarity (%) = (1 – R) x 100

Where $R = \sqrt{d^2}$ is the quadratic mean (root mean square), a measure of central tendency. The calculation results obtained for assessment of the structural similarity of the prepared compounds to standard drugs are presented in Table 4. The table depicts that the test compounds **1-6** bear very little (practically insignificant) resemblance with clozapine. The similarity values with respect to ketanserin and risperidone are moderate ranging from 57.23 to 75.62%. However, with ziprasidone, it is found to be very high ranging from 85.71 to 89.67%. Ziprasidone is known to possess nanomolar affinity for the D_3 receptors and is also a potent D_2 receptor antagonist.

CONCLUSIONS

The present docking study has provided a hypothetical binding mode for the D_3 receptor binding of the indole based atypical antipsychotics **1-6**. The docking study effectively reproduced the receptor binding profiles of the established drugs. Inspite of possessing a novel structure seemingly different from standard drugs, the test compounds **1-6** demonstrated a similar binding profile to these. Salient interactions noted for the standard drugs as well as the test compounds were the hydrogen bonding interactions with the residues Asp110, Tyr373, Ser182, Ser192, Cys181 and π-π stacking with the phenyl rings of Phe345, Phe346 and imidazole ring of His349. Further, the D_3 docking scores of the compounds not possessing an atypical profile were seen to be lower compared to those having an atypical profile suggesting the involvement of D_3 receptors in their pharmacological activity. This study further endorses the multireceptor approaches currently being highlighted in the design of atypical antipsychotics. The results from the docking studies were further backed by the physicochemical similarity studies of the test compounds with respect to selected standard drugs as the test compounds were seen to possess very good similarity to ziprasidone, a potent D_3 antagonist also possessing good D_2 affinity.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Acknowledgments

The authors thank Schrodinger Inc. for providing us evaluation version of Maestro 9.3

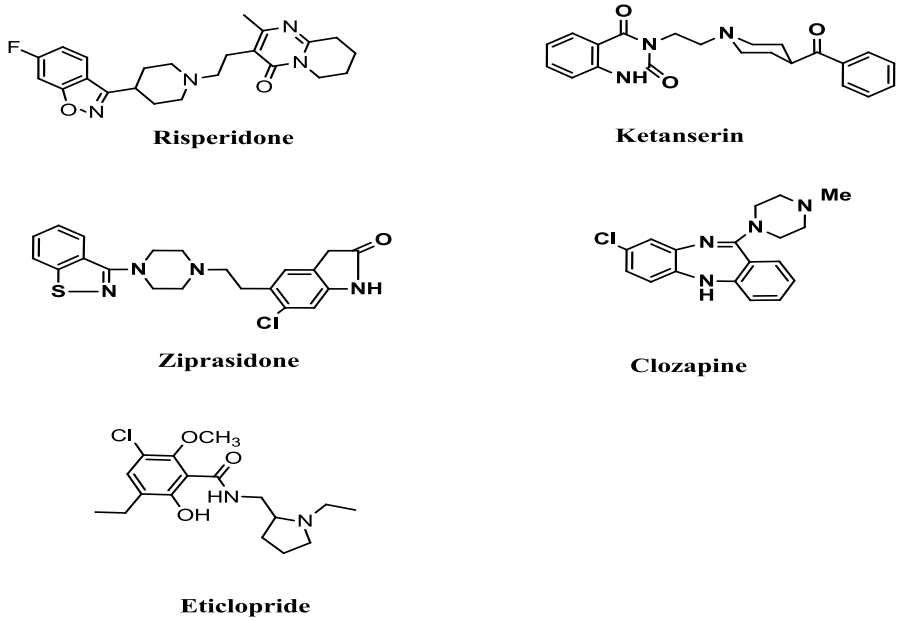


Figure 1: Chemical structures of the standard drugs included in the study.

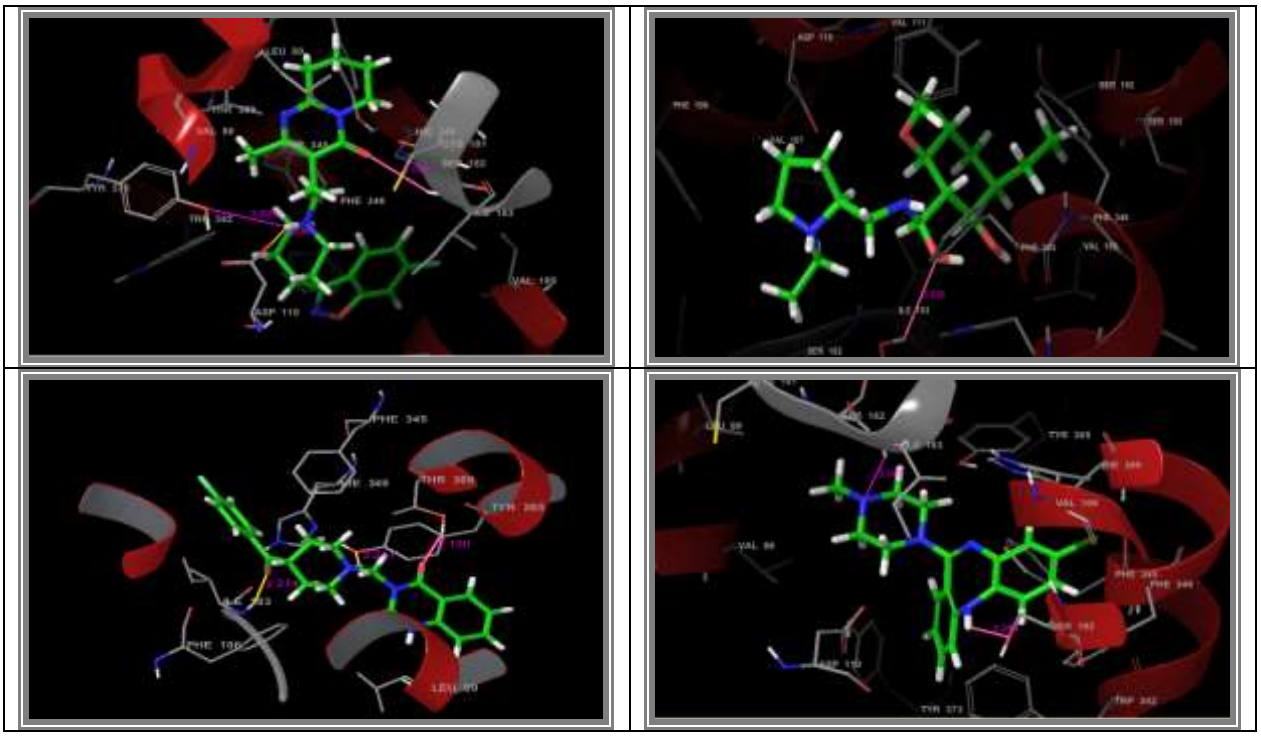
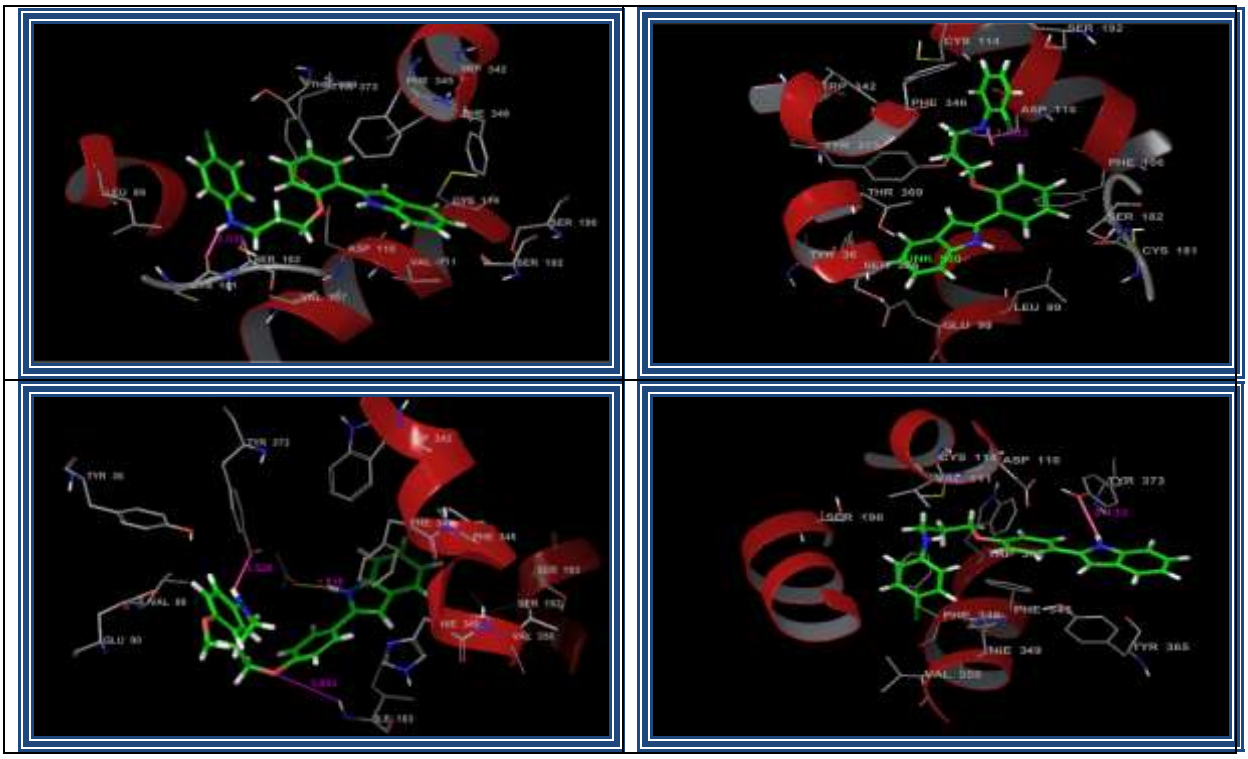


Figure 2: Docking model of risperidone, eticlopride, clozapine and ketanserin (clockwise from top left) with D_3 receptor.



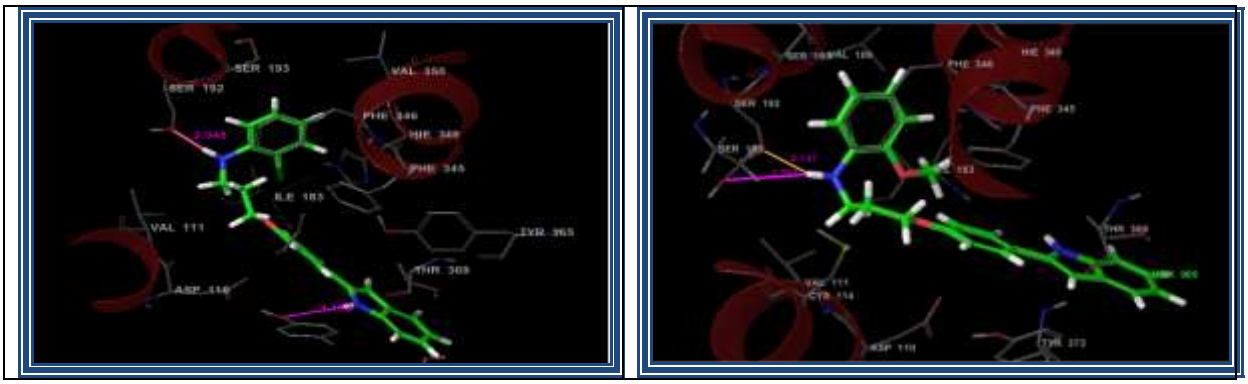


Figure 3: Docking model of compounds 1-6 (row-wise from top, left to right) with D_3 receptor.

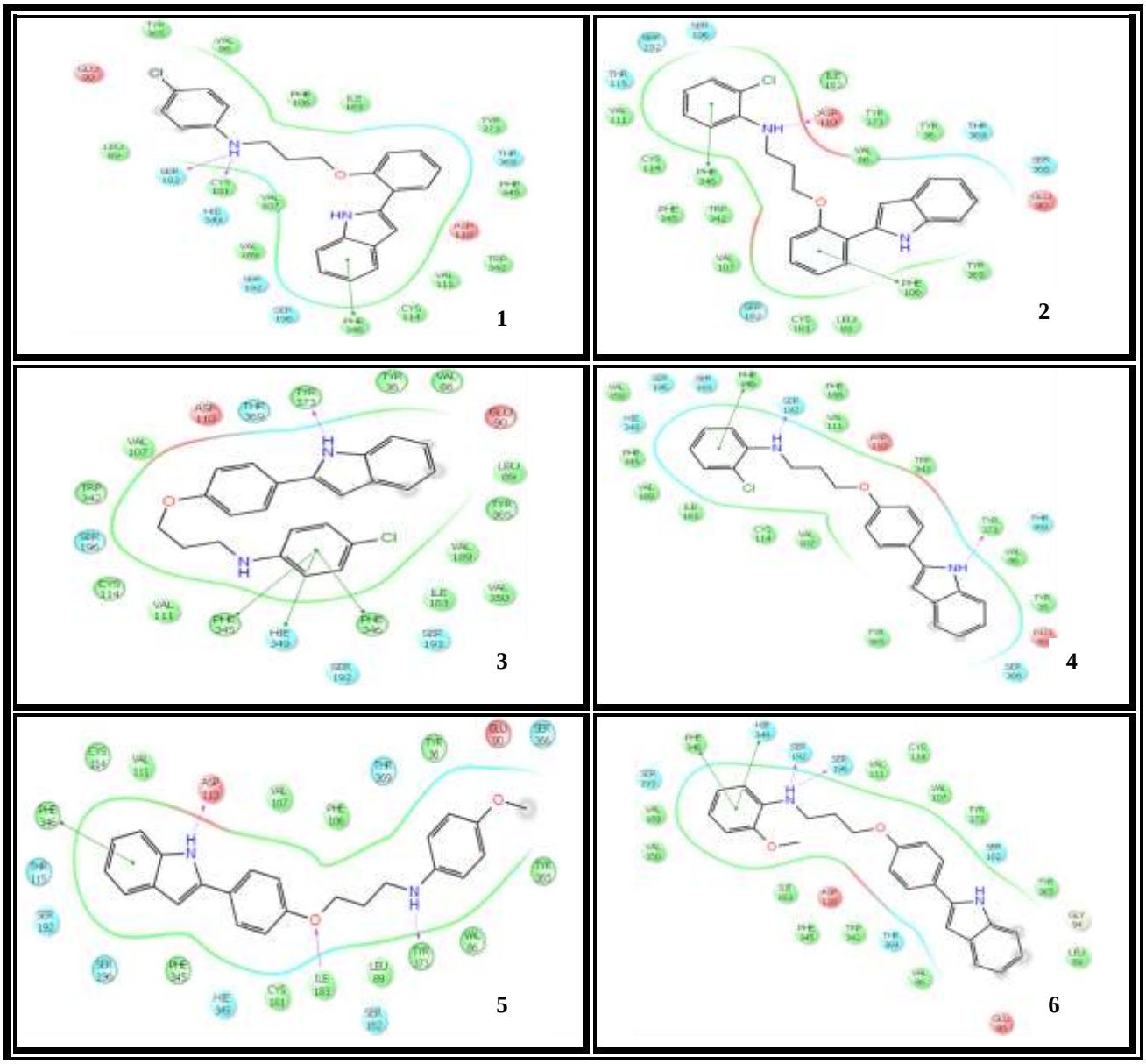
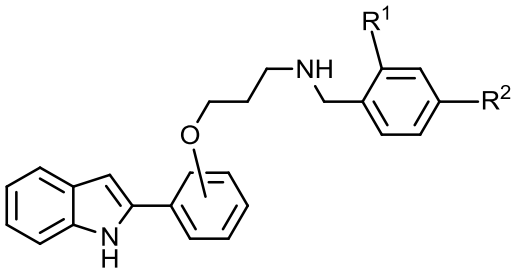


Figure 4: Ligand interaction diagrams of test compounds 1-6 (row-wise from top, left to right) with D_3 receptor.

Table 1: Chemical structures and activity profile of the test compounds



Compound	R^1	R^2	O-Pr	Atypical profile	ED_{50} (mg/kg) (mesh climbing)[b]
1	H	Cl	o-	+	7.23
2	Cl	H	o-	+	6.23
3	H	Cl	p-	+	1.80
4	Cl	H	p-	+	1.60
5	H	OCH_3	p-	-	1.90
6	OCH_3	H	p-	-	1.70
Clozapine	-	-	-	+	3.07

[a]Statistically significant reduction compared to control at $p < 0.05$ (One way ANOVA followed by Tukey test)
[b]Calculated from results for antipsychotic activity (mesh climbing assay) at three graded doses.

Table 2: DockScore of the active compounds

Compound No.	Glide Dock Score (D_3)	Rank Score (D_3)	Glide Dock Score (D_2)	Rank Score (D_2)
1	-7.571	4	-7.376	2
2	-7.601	2	-7.420	1
3	-7.600	3	-6.802	3
4	-7.928	1	-6.433	4
5	-5.482	6	-4.232	6
6	-7.307	5	-5.939	5
Ziprasidone	-9.182	Standard	-8.096	Standard
Ketanserin	-6.542	Standard	-3.471	Standard
Risperidone	-8.897	Standard	-7.387	Standard
Eticlopride	-8.238	Standard	-4.954	Standard
Clozapine	-5.50985	Standard	-4.310	Standard

Table 3: Calculation of various molecular properties of target compounds

Compound	Molecular Weight (MW)	Molar Refractivity (MR) cm^3/ mole	Connolly solvent Accessible surface Area ($Å^2$)	Connolly molecular surface Area ($Å^2$)	Connolly solvent excluded Volume ($Å^3$)	Ovality	LogP	Log BB	Topological polar Surface Area (TPSA) ($Å^2$)	Molecular Topological Index (MTI)	Wiener Index (WI)
1	376.87	112.570	586.28	334.76	328.32	1.454	5.133	0.43	29.66	16607	2207
2	376.87	112.570	585.68	333.67	327.44	1.452	5.133	0.50	29.66	16415	2167
3	376.87	112.57	674.64	353.22	299.20	1.632	5.13	0.70	33.29	18203	2423
4	376.87	112.57	666.76	350.83	298.99	1.622	5.13	0.46	33.29	18011	2383
5	372.45	114.23	698.73	366.45	310.27	1.653	4.445	0.38	42.52	20767	2715
6	372.45	114.23	686.83	362.99	310.77	1.635	4.445	0.48	42.52	20223	2635
Clozapine	326.82	95.22	534.29	284.76	262.33	1.436	3.707	0.75	30.87	8127	1082
Ketanserin	381.40	101.58	611.77	326.07	303.63	1.492	2.662	0.89	69.72	16231	2266
Ziprasidone	412.93	116.98	653.96	351.70	319.91	1.554	4.668	-0.08	47.94	16979	2344
Risperidone	410.48	114.65	668.72	364.57	352.73	1.510	2.1	-0.20	57.5	20311	2793

Table 4: Physicochemical similarity values of test compounds with respect to the standard drugs

Compd. No.	Similarity[a, b] (in %) to Clozapine	Ketanserin	Ziprasidone	Risperidone
1	50.50	58.40	85.80	41.79
2	51.79	58.31	86.26	50.45
3	22.78	69.52	88.98	57.29
4	22.31	69.78	89.67	57.23
5	05.07	74.33	85.71	67.54
6	05.07	75.62	88.17	67.71

[a](1-R) x 100 where R= Quadratic mean (Root mean square mean)
[b]Calcd. from the computed physicochemical properties.

REFERENCES

1. Jibson MD, Glick ID, Tandon R. Focus, 2004; 2(1): 17-30.
2. Saha S, Chant D, Welham J, McGrath J. PLoS Medicine, 2005; 2(5): e141.
3. Kapur S, Mamo D. Prog Neuro-Psychopharm Biol Psychiatry, 2003; 27: 1081-90.
4. Melkersson K, Dahl ML. Drugs, 2004; 64(7): 701-23.
5. Fitton A, Heel RC. Drugs, 1990; 40(5): 722-47.
6. Stahl SM. J Clin Psychiatry, 2003; 5(5): 9-13.
7. Lange JHM, Reinders JH, Tolboom TBM, Glennon JC, Coolen HKAC, Kruse CG. J Med Chem, 2007; 50(21): 5103-8.

8. Hartman DS, Civelli O. Prog Drug Res, 1997; 48: 173-94.
9. Mach RH, Huang Y, Freeman RA, Wu L, Blair S, Luedtke RR. Bioorg Med Chem, 2003; 11(2): 225-33.
10. Blaylock BL, Nader MA. Neuropsychopharmacology, 2012; 37(1): 297-98.
11. Joyce JN, Milian MJ. Drug Discov Today, 2005; 10(13): 917-25.
12. Millan MJ, Loiseau F, Dekeyne A, Gobert A, Filk G, Cremers TI, Rivet JM, Sicard D, Billiras R, Brocco M. J Pharm Exp Ther, 2008; 324(3): 1212-26.
13. Kiss B, Laszlovszky I, Horvath A, Nemethy Z, Schmidt E. Naunyn-Schmiedebergs Arch. Pharmacol, 2008; 378(5): 515-28.
14. Bettinetti L, Schlotter K, Hubner H, Gmeiner P. J Med Chem, 2002; 45(21): 4594-7.
15. Macdonald GJ, Branch CL, Hadley MS, Nash DJ, Austin NE, Boyfield I, Wood M, Parker SG. J Med Chem, 2003; 46(23): 4952-64.
16. Geneste H, Backwisch G, Braje W, Delzer J, Haupt A, Hutchins CW, King LL, Unger L, Wernet L. Bioorg Med Chem Lett, 2006; 16(7): 490-4.
17. Micheli F, Bonanomi G, Blaney FE, Braggio S. J Med Chem, 2007; 50(21): 5076-89.
18. Bali A, Sen U, Peshin T. Eur J Med Chem, 2014; 74: 477-90.
19. http://www.uniprot.org/uniprot/P14416.
20. http://www.chemsilico.com/CS_prBBB/BBBhome.html.
21. Aranda R, Villalba K, Ravina E, Masaguer CF, Brea J, Areias F, Domınguez E, Selent J, Lopez L, Sanz F, Pastor M. J Med Chem, 2008; 51(19): 6085–94.
22. Chen Y, Xu X, Liu X, Liu B, Zhang G. Archiv der Pharmazie, 2012; 345(11): 859-69.