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Computational Pharmacophore Modelling of 5-HT2a and D2 Receptor Inhibitors of Schizophrenia

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Authors' Contribution
SE, RZ, SK and AI conceived and designed the study and developed the pharmocophore structures. AK, DCH and ARS analyzed and verified the pharmocophore structures. MI, RA, FS and SN analyzed the data. RZ, AK, DCH and ARS wrote the article.

Key words
Pharmacophore, Schizophrenia, 5HT2a, D2, Receptors.

ABSTRACT

Schizophrenia is a chronic neurological disorder in which a person suffers from emotional and intellectual disturbances. First generation antipsychotics for Schizophrenia were replaced with by second generation ones with less side-effects like Parkinsonism and Hyperprolactinemia. A novel, computer-based drug designing technique, has emerged to develop more efficient drugs. One of the computational methods becoming increasingly popular to develop new drugs is relying on Pharmacophores. This method was utilized to develop pharmacophore models of Akt2 inhibitors and β2-Adrenoceptor agonists. A pharmacophore model is proposed, using fourteen second generation and one first generation antipsychotic drugs for Schizophrenia that are effective against both 5-HT2a and D2 receptors. Hydrogen bond acceptors (HBA), aromatic rings (AR ring) and positive ionizable (PI) groups were identified computationally as pharmacophore features by LigandScout. The distance range calculated by Visual Molecular Dynamics (VMD) between AR-HBA, AR-PI and HBA- PI was 3.68 A°-5.74 A°, 5.66 A°-7.64 A° and 3.77 A°-5.38 A°, respectively. This study should help finding specific and more efficient drugs for Schizophrenia in future.

INTRODUCTION

Schizophrenia causes emotional disturbances and distorted thought processes. According to World Health Organization (WHO), approximately 24 million people worldwide suffer from this disease (Mueser and Jeste, 2011). In a developing country like Pakistan, it is believed that a schizophrenic patient or someone with any mental disorder is suffering from demonic possessions (Karim *et al*., 2004). Therefore, owing to the lack of education, the attempts to find a cure from spiritual means is done. However, science explains a wide range of causes of schizophrenia e.g. genetic, environmental, drug abuse, inactive social life and chemical imbalance.

The chemical imbalance of Schizophrenia is due to alterations in the dopamine, serotonin, glutamate and other neurotransmitters pathways in the brain. Dopamine follows four pathways, namely the mesolimbic, mesocortical, nigrostriatal and tuberinfundibular pathways, to perform different functions in brain (Stahl, 2002). Mesolimbic pathway is involved in motivation, emotions, pleasure and reward. The hyperactivity of dopamine in the neurons in Mesolimbic pathway causes the positive symptoms of Schizophrenia. Mesocortical pathway is involved in emotions, executive function and cognition. The hypofunction of dopamine in this pathway leads to negative and cognitive symptoms of Schizophrenia (Lind *et al*., 2005). Motor planning and movement are the primary functions of nigrostriatal pathway. Tuberinfundibular pathway regulates the secretion of Prolactin from anterior Pituitary gland (Stahl, 2002).

Conventional or typical antipsychotics for the treatment of Schizophrenia are classified on the basis of their chemical structure and pharmacodynamics properties (Horacek *et al*., 2006). These first generation antipsychotics (FGAs) are dopamine antagonists which reduce the level of dopamine. D2 receptors are the most abundant in the

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brain. The affinity of dopamine antagonists depend upon the rate at which the binding to and dissociation from the D2 receptors occurs (Kapur and Seeman, 2000). The high affinity of these drugs causes a permanent blockade of D2 receptors in all the four pathways, instead of just the two required pathways, resulting in side-effects. The drug induced reduction of dopamine in nigrostriatal pathway leads to side effects like, Parkinsonism (Stahl, 2013). Whereas, the excess of dopamine leads to hyperkinetic movement disorders like, Tardive dyskinesia (Lind *et al*., 2005). The drug induced underactivity of dopamine in Tuberinfundibular pathway causes Hyperprolactinemia in which Prolactin is released more than normal.

Therefore, newer antipsychotic drugs, atypical or second generation antipsychotics, were introduced after it was realized that serotonin controls the release of dopamine (Stahl, 2003). New theories suggesting a role for serotonin in schizophrenia were proposed (Seeman, 2010). The primary action of these antipsychotics is on dopamine and serotonin receptors and their main targets are 5-HT2a and D2 receptors (Seeman and Kapur, 2000). The properties which made these drugs better than the typical ones were 5-HT2a antagonism, fast dissociation from D2 receptors and 5-HT1a agonism. Second generation antipsychotics were effective towards negative symptoms with lower risks of side effects (Lind *et al*., 2005). These drugs bound to dopamine receptors to cause an action but do not a side effect because of rapid dissociation (Stahl, 2003).

Drug development is a crucial and important process. However, many difficulties are encountered during drug development, such as the absence of appropriate laboratory tests, short time limits, difficulty in conducting early clinical trials and lack of new methods to predict accurately that which chemical will act against the diseased cells effectively (Yang, 2010).

Thanks to appropriate novel technologies, there has been a tremendous progress in the pharmaceutical industry which has proved successful in developing drugs. For instance, computer-based drug development has achieved high efficacy and specificity using the structure-based approach based on nucleic acids and proteins structures. One such computational method makes use of pharmacophores.

A pharmacophore is a three dimensional substructure or an active compound that is essential for bioactivity. This model provides the information about the active site of an enzyme indirectly from its electronic properties, shape, inhibitors, conformation of substrates or metabolic products (Yang, 2010; Fatima *et al*., 2018). The construction of a pharmacophore is only possible when all the substrates are sterically and electronically oriented in a similar way in the active site of an enzyme. Thus, a template can be derived from this model.

For the generation of pharmacophore, different computational tools exist such as HypoGen, HipHop, GALAHAD, DISCO, GASP, PHASE, MOE and LigandScout. These programs differ in the algorithms used for handling the flexibility of the ligands and for the alignment of molecules (Yang, 2010). The current study identifies the essential features of a pharmacophore of the individual ligands and generates a combined pharmacophore model against 5-HT2a and D2 receptor inhibitors by using the LigandScout software and distance calculation between the pharmacophore features by using the VMD software.

MATERIALS AND METHODS

Data set

Computer aided simulation (LigandScout software) was used to come up with a pharmacophore model. The primary input of variables was the data set consisting of fourteen atypical and one typical antipsychotic drugs acting on 5-HT2a and D2 receptors. 2D sdf structures were retrieved form PubChem, a database consisting chemical molecules and their responses in biological assays (Karthikeyan and Vyas, 2014). Sdf stands for 'structure-data file' containing chemical data file format displaying information on chemical structures (Karthikeyan and Vyas, 2014). Lowest Ki values of the drugs were obtained from PubChem and the literature. Ki value is equilibrium constant for the inhibitor binding to the enzyme which shows the binding affinity of a drug. Most of the drugs used are FDA approved and currently used.

Pharmacophore generation

Pharmacophore generation was done by using 3.1 version of LigandScout (http://www.inteligand.com/ligandscout/). This software is used to generate 3D pharmacophores based on the structures of the ligands or organic molecules. It provides the identification of 3D chemical features like, hydrogen bond acceptors, aromatic rings, hydrogen bond donors, hydrophobic rings, positive ionizable and negative ionizable groups *etc*. (Wolber and Langer, 2005). Formation of individual pharmacophores of the drugs was done and then a combined pharmacophore of all the fifteen drugs was established.

Distance triangle calculation

Pharmacophore features were identified. Sdf file formats of drugs were converted to Protein Data Bank (PDB) file formats by using free software, Open Babel (http://openbabel.org/wiki/Main_Page). Pdb is protein data bank file format was the textual file format demonstrating

the 3-D structures of molecules present in the protein data bank (Karthikeyan and Vyas, 2014). The distances between the selected features were measured by using the visual molecular dynamics (VMD) software. Distance triangles of each drug were calculated followed by the selection of the appropriate distance range for each drug.

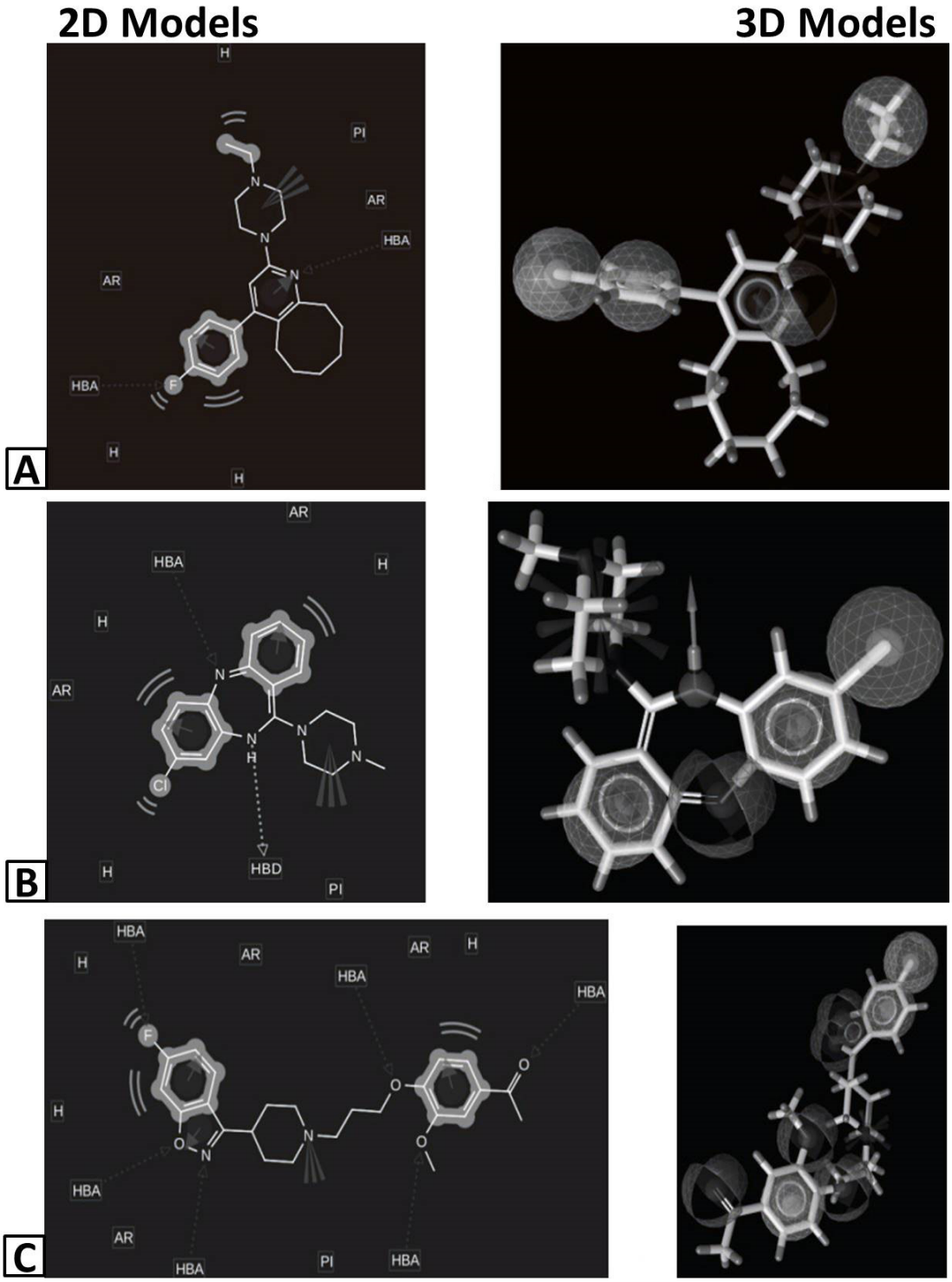

Fig. 1. Pharmacophore model of Blonanserin (A), Clozapine (B) and Iloperidone (C).

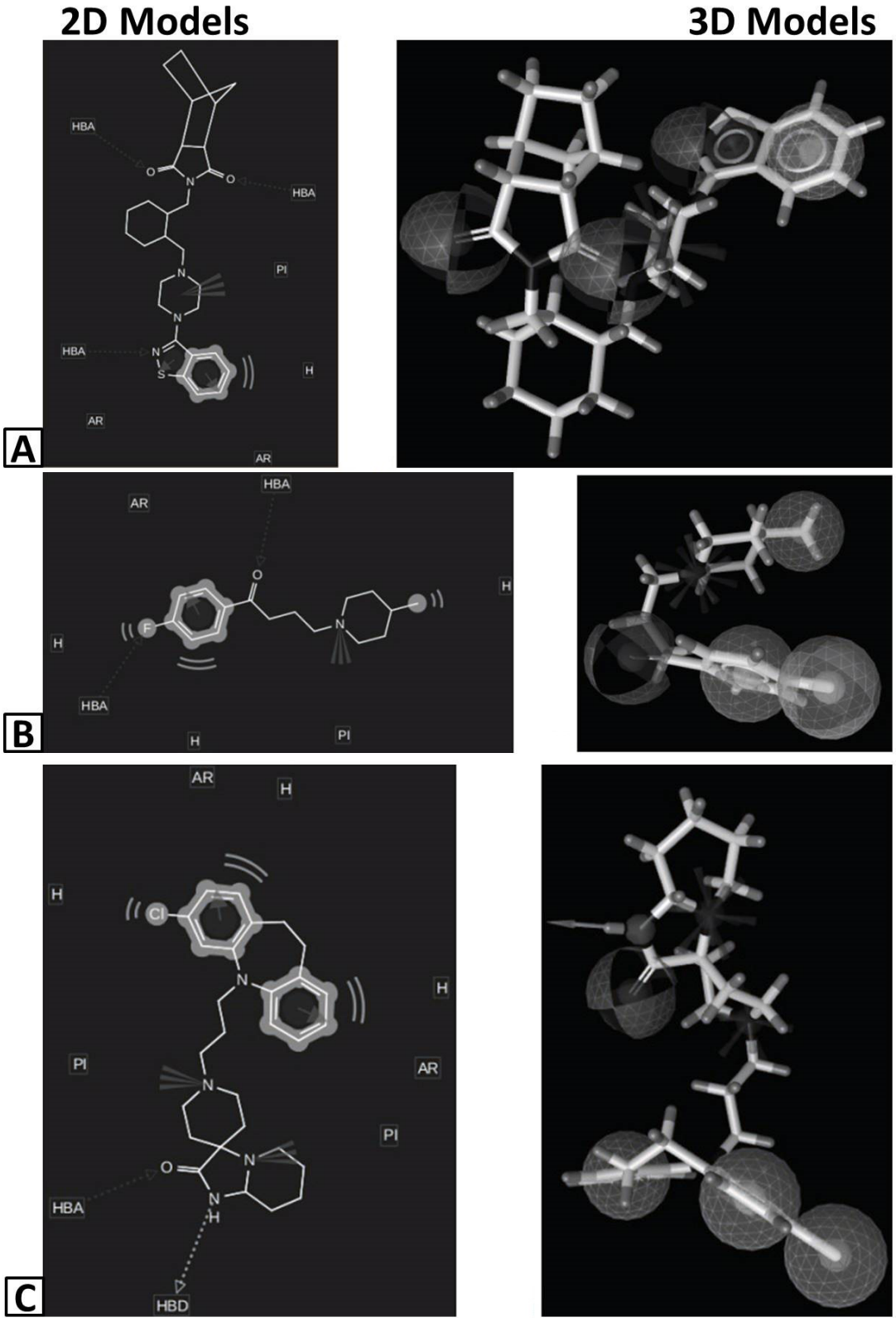

Fig. 2. Pharmacophore model of Lurasidone (A), Melperone (B) and Mosapramine (C).

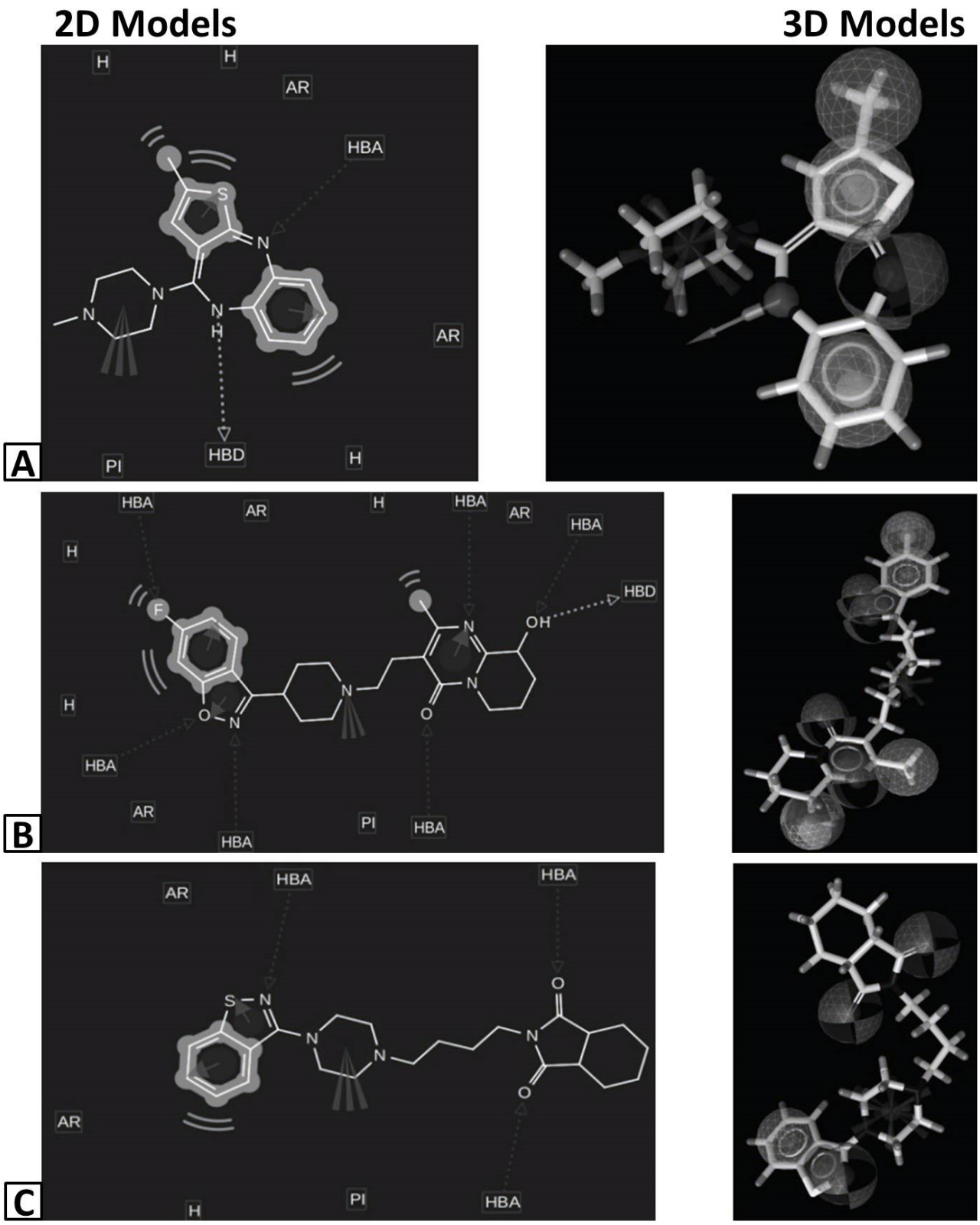

Fig. 3. Pharmacophore model of Olanzapine (A), Paliperidone (B) and Perospirone (C).

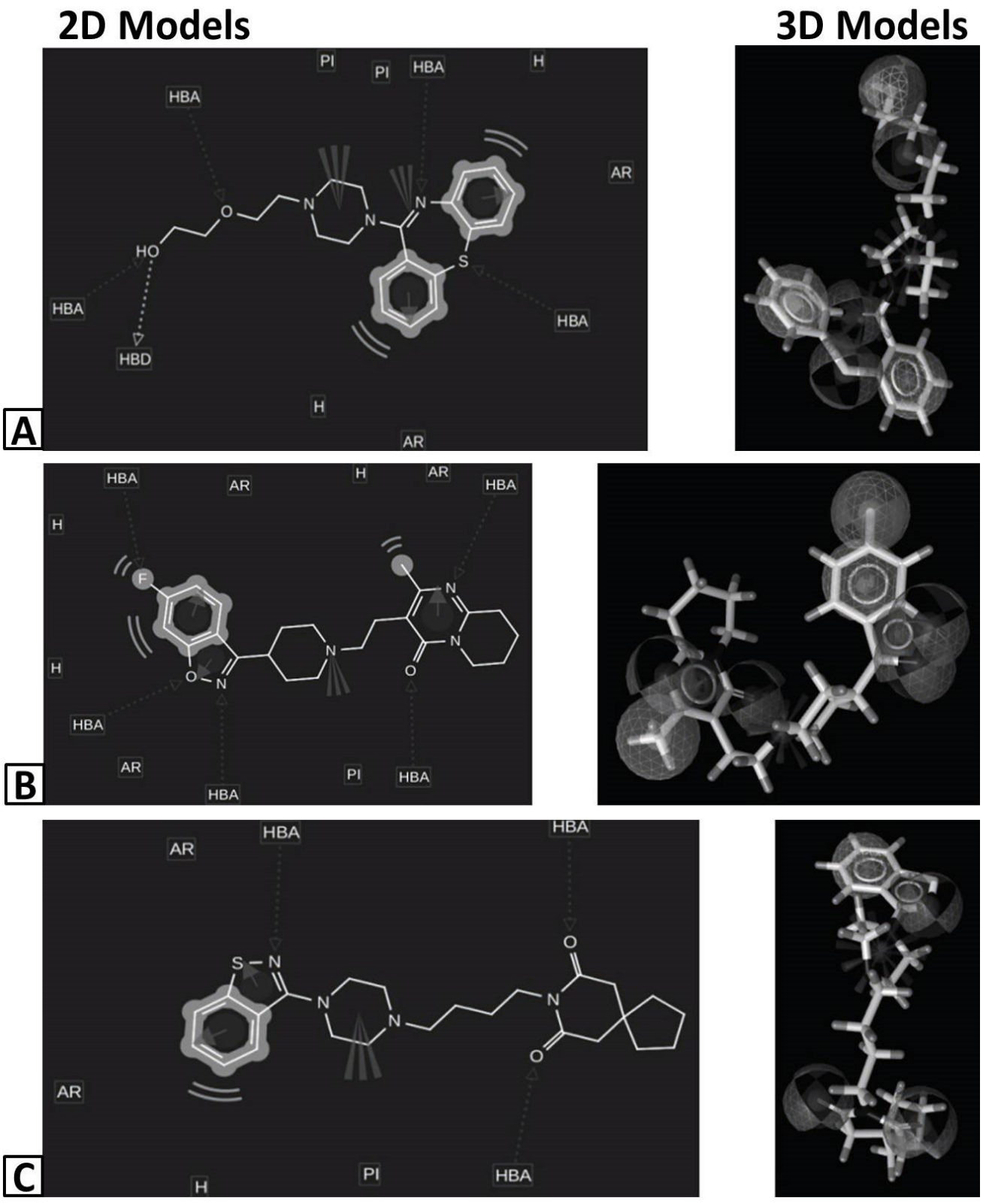

Fig. 4. Pharmacophore model of Quetiapine (A), Risperidone (B) and Tiospirone (C).

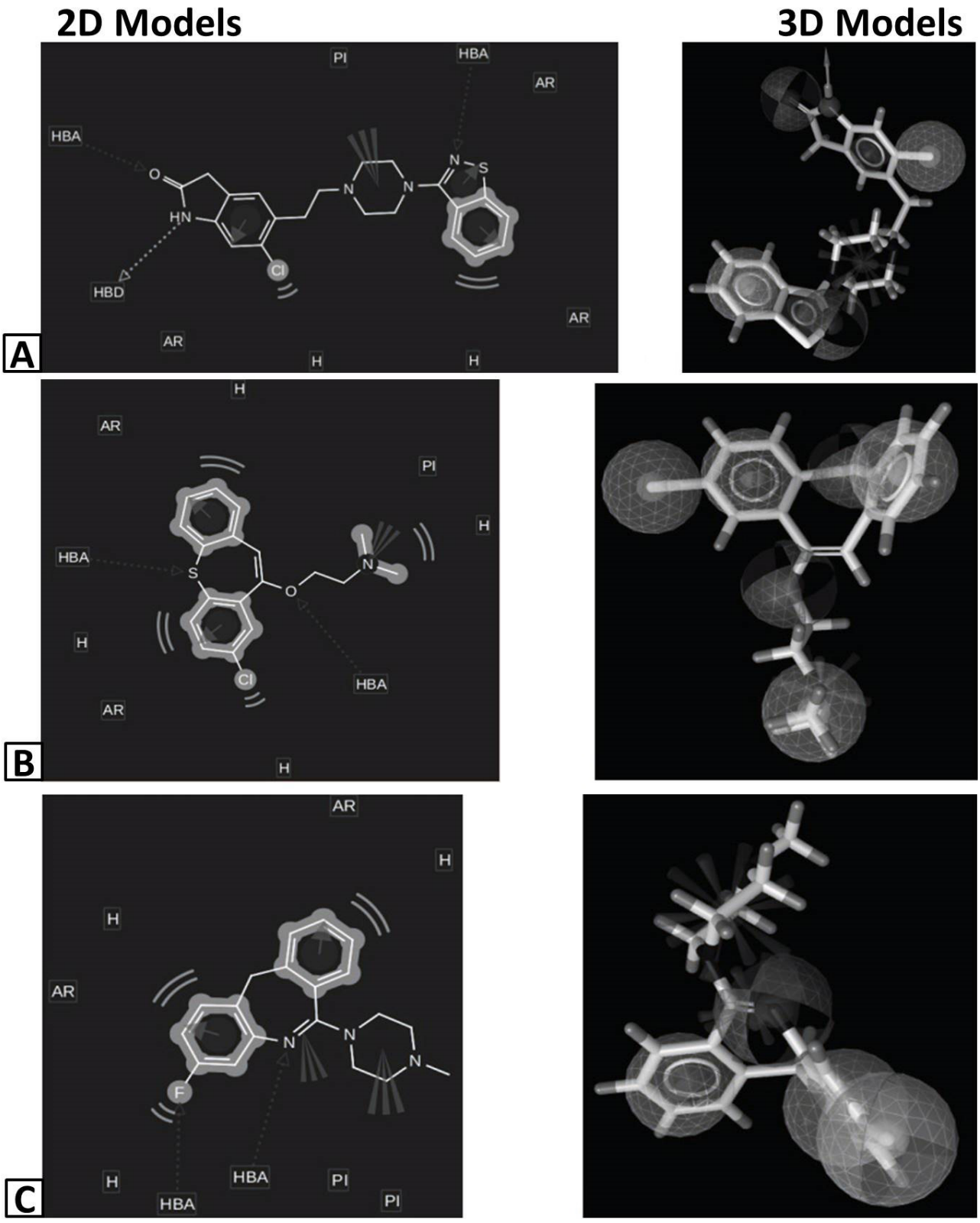

Fig. 5. Pharmacophore model of Ziprasidone (A), Zotepine (B) and Fluperlapine (C).

RESULTS AND DISCUSSION

2D and 3D Pharmacophore models of individual drugs obtained from LigandScout (Figs. 1, 2, 3, 4, 5).

Table I.- Pharmacophore features of each drug.

No.	Drug	AR Ring	HBA	PI	HBD	HP
1.	Blonanserin	2	2	1	0	3
2.	Clozapine	2	1	1	1	3
3.	Iloperidone	3	6	1	0	3
4.	Lurasidone	2	3	1	0	1
5.	Melperone	1	2	1	0	3
6.	Mosapramine	2	1	2	1	3
7.	Olanzapine	2	1	1	1	3
8.	Paliperidone	3	6	1	1	3
9.	Perospirone	2	3	1	0	1
10.	Quetiapine	2	4	2	1	2
11.	Risperidone	3	5	1	0	3
12.	Tiospirone	2	3	1	0	1
13.	Ziprasidone	3	2	1	1	2
14.	Zotepine	2	2	1	0	4
15.	Fluperlapine	2	2	2	0	3

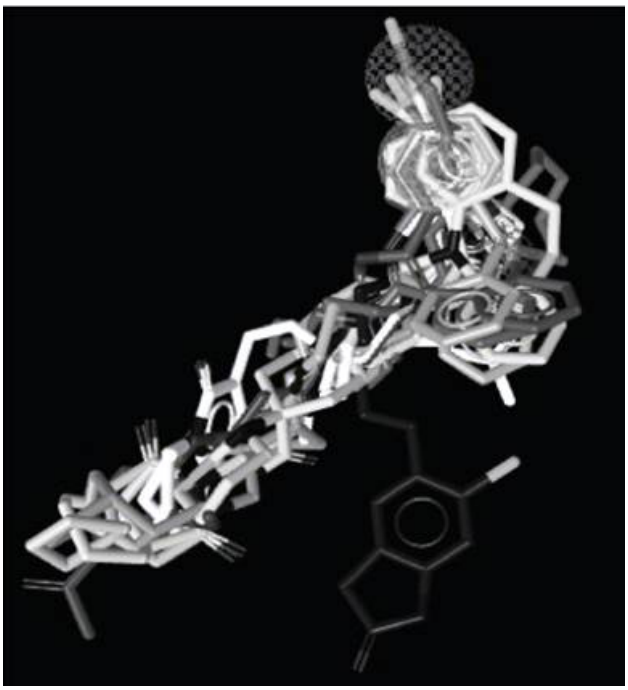

Fig. 6. Combined Pharmacophore model of all the 15 ligands.

Out of the total 5 features present in the selected ligands (see Table I), only three common features, *i.e.* aromatic ring (AR ring), hydrogen bond acceptor (HBA) and positive ionizable group (PI), were selected to form the distance triangles (Table II). A combined pharmacophore model was obtained by superimposing all the 15 ligands (Fig. 6).

All the possible distance triangles between the features were calculated using visual molecular dynamics (VMD). The range with the lower and upper limit of distances between the features was selected manually (see Table III) and visually represented (Fig. 7). The lower and upper limit of the features AR and HBA is 3.68 A° and 5.74 A°, shown by drugs Paliperidone and Mosapramine, respectively. For the features AR and PI, the lower and upper limit is 5.66 A° and 7.64 A°, indicated by drugs Melperone and Blonanserin, respectively. 3.77 A° and 5.38 A° is the lower and upper limit for the features HBA and PI, shown by the drugs Zotepine and Iloperidone, respectively.

Table II.- Selected distance triangles for the three pharmacophore features.

No.	Drug	AR-HBA	AR-PI	HBA-PI
1.	Blonanserin	4.24	7.64	4.98
2.	Clozapine	4.19	5.95	4.54
3.	Iloperidone	4.56	7.51	5.38
4.	Lurasidone	4.78	6.86	5.09
5.	Melperone	4.97	5.66	4.09
6.	Mosapramine	5.74	6.34	4.20
7.	Olanzapine	4.21	5.99	4.56
8.	Paliperidone	3.68	6.36	4.60
9.	Perospirone	3.75	5.72	5.09
10.	Quetiapine	4.51	6.78	5.27
11.	Risperidone	4.61	6.32	5.37
12.	Tiospirone	4.78	7.00	5.12
13.	Ziprasidone	4.78	7.17	4.42
14.	Zotepine	4.56	6.87	3.77
15.	Fluperlapine	4.46	7.05	4.36

Table III.- Minimum and maximum ranges between the three features.

Features	AR-HBA	AR-PI	HBA-PI
Ranges	3.68-5.74	5.66-7.64	3.77-5.38

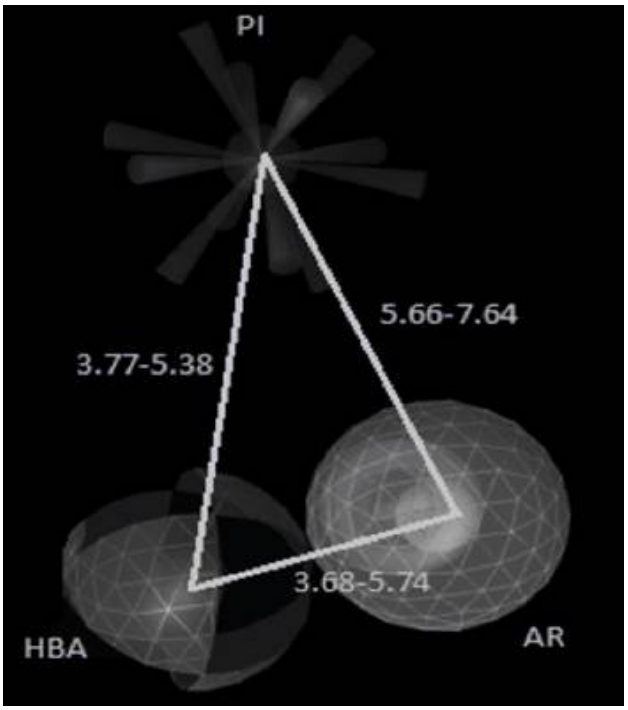

Fig. 7. Minimum and maximum distance ranges among all the features.

Public health is the biggest concern in today's world. The older methods to design a drug are expensive, time consuming with limited success rate. Moreover, there existed a lack of rationalism in the steps involving development of drug discovery. The complex procedures and commercial infeasibility to develop drugs by conventional methods led researchers to find new ways for drug designing, one of the new emerging methods being computational drug designing.

This research describes the *in silico* development of a pharmacophore model of 5-HT2a and D2 receptor inhibitors of schizophrenia. Ranked among the top 10 diseases causing disability, it affects 0.5-1% of the population of any country (López and Murray, 1996). Pharmacophore is a common skeleton of different drugs to treat a disease. Pharmacophore designing aims to improve the drug efficacy by refining its specificity and reducing its side effects. Use of computational tools for this purpose not only reduces the time required for drug designing but also reduce the cost substantially.

Seeman and Kapur (2000) considered D2 receptors as the primary targets for many antipsychotic drugs which act on this receptor with different potencies. Potency is determined by the drug's dissociation constant at D2. It shows how rapidly the drug dissociates from D2 receptor. A postmortem study states that D2 receptors are present in high levels in the striata of the patients with schizophrenia. Neuroimaging studies indicate that D2 receptor binding is associated with planning, visual processing, working memory and attention (Takahashi *et al*., 2007). Over activity of dopamine in schizophrenia can be explained because of two reasons; presynaptic overproduction of dopamine or an increase in D2 receptors in the postsynaptic part of the neuron or postreceptor action in the postsynaptic section (Seeman and Kapur, 2000).

The involvement of serotonin in schizophrenia was proposed for the first time by Wooley and Shaw (Berde and Schild, 2012). Serotonergic blockade by atypical antipsychotic drugs in schizophrenic patients causes an increase in the release of dopamine. In nigrostriatal pathway, this dopamine release reduces the risk of EPS (extrapyramidal symptoms) (Lind *et al*., 2005; Stahl, 2003).

The typical antipsychotics used for schizophrenia proved to be insignificant for treating this disorder. Due to permanent blockade of D2 receptors, side-effects like extra pyramidal symptoms, tardive dyskinesia and parkinsonism were apparent when using these drugs (Lind *et al*., 2005; Stahl, 2013). Researches to develop more effective drugs became the basis for development of atypical antipsychotics. The fast dissociation with the D2 receptors, 5-HT2a antagonism and 5-HT1a agonism are the unique features which make these drugs better than the conventional, standard antipsychotics (Lind *et al*., 2005). Atypical antipsychotics show both D2 and 5-HT2a antagonism. Antagonism at 5-HT2a receptors regulates the release of dopamine and thus, prevents permanent blockade of D2 receptors (Stahl, 2003).

Fourteen drugs used in this study are atypical antipsychotics while one drug, Mosapramine, is a typical antipsychotic drug (Fleischhacker and Stolerman, 2014). The inhibitory action against both the receptors, D2 and 5-HT2a, increased the efficiency and affectivity of atypical drugs. Both receptors have different binding affinities towards every drug. Blonanserin belongs to a series of 4-phenyl-2-(1-piperazinyl) pyridines. Although it is approved by Pharmaceuticals and Medical Devices Agency (PMDA) for use in South Korea and Japan for the treatment of Schizophrenia, it is not approved by Food and Drug Administration (FDA) for the same purpose (Tenjin *et al*., 2013; Wang *et al*., 2013). Clozapine is an FDA approved first atypical antipsychotic which is the only dibenzodiazepine available in the US (Li and Corey, 2013; Yagiela *et al*., 2010). Other FDA approved drugs for the treatment of Schizophrenia are Risperidone, Paliperidone, Iloperidone, Olanzapine, Quetiapine, Ziprasidone and Lurasidone. Risperidone, Paliperidone and Iloperidone are benzisoxazole derivatives (Albers *et al*., 2008;

Bruun and Budman, 1996). Risperidone was the second atypical antipsychotic (Li and Corey, 2013). Paliperidone is an active metabolite of Risperidone and both have similar pharmacologic profiles (Yagiela *et al*., 2010). Olanzapine is a Thienobenzodiazepine and Quetiapine is a dibenzothiazapine. Both have similar therapeutic and side-effects (Yagiela *et al*., 2010). Ziprasidone, a dihydroindolone, was the fifth atypical antipsychotic to be allowed for treatment of schizophrenia in the US (Caley and Cooper, 2002; Yagiela *et al*., 2010). Lurasidone is a benzoisothiazol derivative (Schatzberg and Nemeroff, 2013). Mosapramine is the only typical antipsychotic drug used in this study as research by Takahashi *et al*. (1999) showed that when the comparison of the effect of addition of risperidone and mosapramine was done in neuroleptic-treated schizophrenic patients, the results showed that both the drugs had similar effects in add-on design. Mosapramine is an iminodibenzyl typical antipsychotic drug which was approved in Japan for the treatment of Schizophrenia (Setoguchi *et al*., 1985). Perospirone and Tiospirone are atypical antipsychotic drugs which are azapirone derivatives (Kikuyama *et al*., 2006; Yevich *et al*., 1986). Perospirone is approved in Japan for the treatment of Schizophrenia (de Paulis, 2002). Zotepine is an atypical dibenzothiepine analogue of clozapine (Lieberman and Murray, 2012). Fluperlapine is a Morphanthridine atypical antipsychotic which showed efficacy in the treatment of schizophrenia but was never marketed (Fischer-Cornelssen, 1983; Ganellin and Triggle, 1996). Melperone and Zotepine are also atypical antipsychotics belonging to butyrophenone and dibenzothiepine drug classes, respectively.

Action of these drugs on D2 receptors reduces dopamine in the mesolimbic pathway and 5-HT2a antagonism causes dopamine release in the mesocortical pathway, thus, preventing secondary deficiency of dopamine. Moreover, 5-HT2a antagonism also inhibits any side-effects which arise in the nigrostriatal and tuberinfundibular pathway by using conventional antipsychotics.

Two of the range differences between the features AR ring, PI group and PI group, HBA were 1.98 A° and 1.61 A°, respectively. The maximum difference between the upper and lower limit of the range was 2.06 A° between the features, AR ring and HBA. In a study by Abro *et al*. (2013) the maximum difference between the two selected features was found out to be 2.05 A°. In a similar study by Haseeb and Hussain for the development of pharmacophore for anti-lung cancer drugs in 2015, the distances between the features that were obtained were 4.15-4.80, 7.03-8.66 and 5.85-6.97 between aromatic ring and HBD, aromatic rings to HBA and HBA to HBD (Haseeb and Hussain, 2015).

In a study by Salmas *et al*. (2016) top-scored pharmacophore models were made using 38 dopamine D2 receptor ligands (training set) using PHASE modeling. 15 test set compounds were used to validate the models.

CONCLUSION

More drugs can be added to the study. Docking studies can be done for further validation of the pharmacophore model. New drug design can be validated by virtual screening with the pharmacophore. To obtain more advanced results, other softwares like, MOE, CATALYST, HipHop and DISCO can be used. Pharmacophore of other targets of Schizophrenia can be designed using the same method. A single drug database containing structure and its biological activity is not available. Access to the licensed software was limited. Optimization and better biological evaluation obtained in this study will help in the discovery of more potent ligands against 5-HT2a and D2 receptors. The proposed pharmacophore will help in the development of more effective and efficient atypical antipsychotics for treating Schizophrenia. Hence, a new drug design can be validated by using the established pharmacophore model.

Statement of conflict of interest

Authors have declared no conflict of interest.

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