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Pharmacophore Hypothesis for Atypical Antipsychotics

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A three-dimensional pharmacophore hypothesis was developed for atypical antipsychotics in order to map common structural features of highly active compounds by using HipHop in CATALYST program. The pharmacophore hypotheses were generated using 12 compounds as training set and validated using 11 compounds as test set. The most predictive hypothesis (Hypo1) comprises five features *viz*. two hydrophobic regions, two hydrogen bond acceptor lipid and one aromatic ring. In the absence of information like crystallized structure of 5-HT_{2A} receptor and binding mode of antipsychotics with 5-HT_{2A} receptor, this hypothesis will serve as a potentially valuable tool in the design of novel atypical antipsychotics acting primarily at 5-HT_{2A} and D_2 receptors.

Key Words : Pharmacophore, Hypothesis, HipHop, Atypical antipsychotics, CATALYST

Introduction

Schizophrenia is a devastating mental disorder affecting 1% of the world's population with similar rates across different countries, cultural groups and sexes.[1,2] The disease is characterized by positive (hallucinations, delusions, disorganized speech, rambling monologues) and negative (alogia, avolition, anhedonia and flattened affect) symptoms.[3] Chlorpromazine was the first effective medicine discovered for schizophrenia followed by several agents, the so-called conventional antipsychotics. Conventional antipsychotics were found to cure only the positive symptoms, as they act as D_2 antagonists, and are characterized by undesirable effects, such as extra-pyramidal symptoms (EPS), hyperprolactinaemia, tardive dyskinesia (TD) and neuroleptic malignant syndrome.[4-7] The discovery of clozapine (**6**) later led to the development of "atypical antipsychotics". Second Generation Antipsychotics (SGAs) or the atypical antipsychotics represent a new class of therapeutic agents, which posses better clinical efficacy in treating negative symptoms apart from positive symptoms as most of these molecules were found to act at various receptors. These drugs are also associated with side effects like EPS, TD and hyperprolactinemia, but to a lesser extent when compared to the conventional ones. Other important examples of such atypical antipsychotics are iloperidone (**1**), ziprasidone (**2**), sertindole (**3**), risperidone (**4**), olanzapine (**5**), quetiapine (**7**), amisulpride (**8**), melperone (**9**), zotepine (**10**), tiosperone (**11**) and aripiprazole (**12**). But these compounds are also not completely devoid of side effects.

Side effects caused by SGAs are a result of their significant binding affinity to numerous receptors other than required for atypical antipsychotic activity. Side effects associated with SGAs include weight gain (Serotonergic 5-HT_{2C} and Histaminic H_1 receptors blockade)[8] postural or orthostatic hypotension, sedation, dizziness (α_1-adrenergic blockade)[8] somnolence (Histaminic H_1 receptor blockade), seizures (Muscarinic receptor blockade), new-onset type2 diabetes mellitus, exacerbation of pre-existing type2 diabetes mellitus,[8] hyperlipidemia (increase of triglycerides and leptin, a lipid regulatory hormone), atropine like side effects such as dry mouth, constipation, urinary retention (Muscarinic M_1 receptor blockade),[8] cardiac ventricular arrhythmias (prolongation of QT_C interval due to the blockade of Ikr channels), myocarditis, insomnia, headache and other possible secondary cardiovascular complications.[6] Not all the SGAs cause the above-mentioned adverse side effects.[4] Hence it can be concluded that there is still an unmet medical need for novel atypical antipsychotics that are devoid of these side effects. As part of the ongoing research in this direction in our laboratory[9] we thought it is worthwhile first to develop a suitable model based on the available drugs and then synthesize the new chemical entities accordingly.

In the absence of a 3D structure for a particular receptor protein of therapeutic interest, drug discovery and design efforts are often based on a model inferred from the different ligands that bind to it. Ligand-based drug design approach depends on a principle, which states that structurally similar compounds are more likely to exhibit similar properties. Atypical antipsychotics have affinity for both D_2 and 5-HT_{2A} receptors. Many currently available drugs in the market have affinities for these two receptors.[15] As very little information is known about the crystal structure of 5-HT_{2A} receptor, receptor based virtual screening cannot be performed efficiently. Thus, ligand based drug design appears the best choice for the design of novel atypical antipsychotics. It can aid the identification of the common 3D features present in diverse molecules that act at the same biological target. The aim of this work is to derive feature-based 3D model from a set of atypical antipsychotics using HipHop. In this paper, a

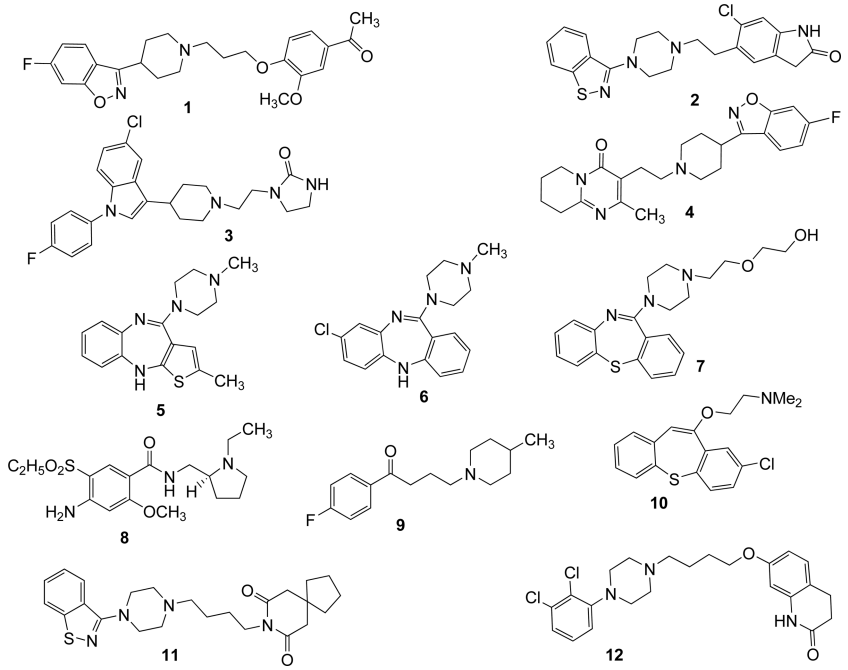


Figure 1. Structures of training set compounds.

pharmacophore model is developed based on the existing atypical antipsychotics.[10-13] As part of ligand based screening, we developed a pharmacophore hypothesis model using HipHop model in CATALYST 4.11[14] from 12 diverse compounds as training set and validated using 11 compounds as test set. HipHop generates hypotheses consisting only of identification and overlay of common features (without the use of activity data). The preliminary data set for pharmacophore generation included 125 antagonists (either D_2 or 5-HT_{2A}) retrieved from literature and respective inhibition constants (K_i). We selected the training set using chosen compounds with human binding data, defined stereochemistry and biological data (structures with $K_i > 300$ nM were excluded from the training set). 12 compounds with structural diversity and high activity were finally chosen to develop the model.

The most critical aspect in the generation of the pharmacophore hypothesis using CATALYST 4.11 is selection of the training set. Some basic guidelines have been followed for the selection of training set *e.g.* a minimum of 10-12 diverse compounds have been selected to avoid any chance correlation; the compounds are selected to provide clear, concise information to avoid redundancy or bias in terms of both structural features and activity range and the most of the highly active compounds are included so that they provide information on the most critical features required for a reliable/rational pharmacophore model. The series of marketed and preclinical atypical antipsychotics and typical antipsychotics consisting of 23 compounds was chosen as training and test sets for the present study.[14-17] The training set (Figure 1) consisting of 12 compounds was selected considering the above guidelines while 11 compounds were taken for test set (Figure 2) for further validation of the model (Table 1).

All molecular modeling studies were performed using CATALYST 4.11. All the structures were built and geometry optimized using CHARMm force field implemented in the program. The conformations were generated using the maximum limit of 255 conformations within a 20 kcal cutoff for the common feature pharmacophore generation using the HipHop module.[14,25,26]

Considering the prospects of atypical antipsychotics as potential agents for the treatment of schizophrenia, we have generated a pharmacophore model of atypical antipsychotics acting at $5HT_{2A}$ and D_2 receptors. HipHop, 3D pharmacophore generation, is a common feature based alignment. Here quantitative activity of the compounds is not taken into consideration for hypothesis generation, rather hypotheses are produced by comparing a set of conformational models and a number of 3D configurations of chemical features of training set compounds.[27]

CATALYST automatically generated conformational models for each compound. Conformation generating algorithms were adjusted to produce a diverse set of conformations, avoiding repetitious groups of conformations all representing local minima. The conformations generated were used to align common molecular features and generate pharmacophore hypotheses. HipHop used the generated conformations to align chemically important functional groups common to the compounds in the training set and generate a pharmacophore hypothesis from these aligned structures. The models showed a conformational diversity under the constraint of 20 kcal/mol energy threshold above the estimated global minimum based on the CHARMm force field. CATALYST provides two types of conformational analysis: fast and best quality. Best option was used, specifying 255 as the maximum number of conformers.[26,28] The compounds associated with the conformational model were submitted to

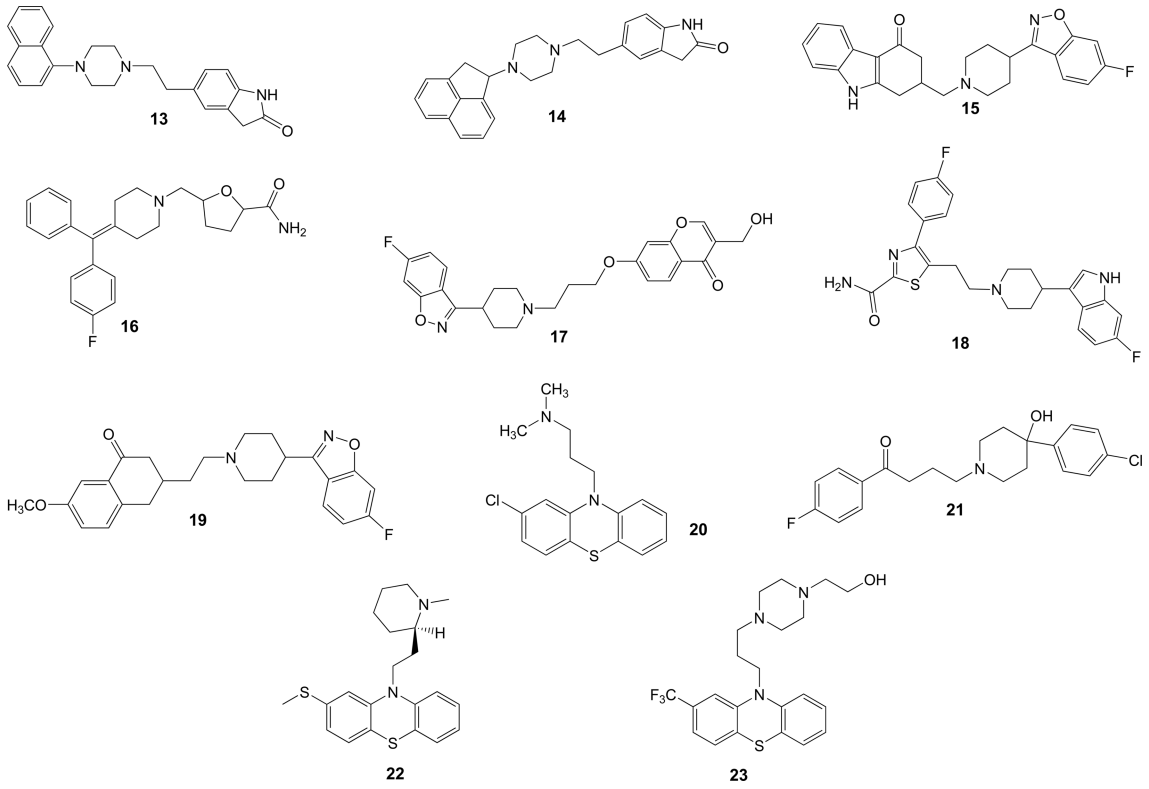


Figure 2. Structures of test set compounds.

Table 1. Receptor affinities of antipsychotics used as training and test sets

No.	Name/ Compound code	Receptor affinity (K_i, nM)		Reference
		D_2 Receptor	5-HT_{2A} Receptor	
1	Iloperidone	37	5.6	[15]
2	Ziprasidone	4.6	1.4	[15]
3	Sertindole	7	0.35	[15]
4	Risperidone	1.65	0.55	[15]
5	Olanzapine	31	3.5	[15]
6	Clozapine	187	130	[15]
7	Quetiapine	700	96	[15]
8	Amisulpride	1.3	2000	[15]
9	Melperone[a]	143	102	[15]
10	Zotepine	11	2.7	[17]
11	Tiosperone	1.59	0.063	[16]
12	Aripiprazole	2.3	4.6	[15]
13	**13**	38	20[c]	[18]
14	**14**	222	82	[19]
15	QF 2004B	141	1.58	[20]
16	**16**	98	32	[21]
17	**17**	17	6.2	[22]
18	NRA 0562	2.49	1.5	[23]
19	**19**	91	5.89	[24]
20	Chlorpromazine[b]	6.7	12	[15]
21	Haloperidol[b]	2.4	50	[15]
22	Thioridazine[b]	8.3	60	[15]
23	Fluphenazine[b]	0.6	80	[15]

[a]Melperone is classified as a conventional antipsychotic but its low affinity for D_2 receptors gives it a clinical profile similar to that of atypical agents. [b]Typical or Conventional or Classical antipsychotics. [c]Only 5-HT_2 activity is reported.

CATALYST hypothesis generation. Hypotheses approximating the pharmacophore were described as set of features distributed within 3D space. This process only considered surface accessible functions such as hydrogen-bond acceptor (HBA), hydrogen-bond acceptor lipid (HBAL), hydrogen-bond donor (HBD), hydrophobic (HY), ring aromatic (RA), and positive ionizable (PI).

HipHop provides feature-based alignment of a group of compounds without considering activity. It matches the chemical features of a molecule, against drug candidate molecules. HipHop utilizes a collection of conformational models of compounds and a selection of chemical features, and produces a series of molecular alignments. HipHop also maps partial features of compounds in the alignment set. This provision gives the option to use partial mapping during the alignment. Partial mapping allows to identify larger, more diverse, more significant hypotheses and alignment models without the risk of missing compounds that do not map to all of the pharmacophore features.[27,29,30]

In this paper, the generation of a pharmacophore model for atypical antipsychotics from training set of twelve compounds using HipHop method has been carried out. In the model generation methodology, the highest weight was assigned to the compound **1** (iloperidone, as it is the recent drug released in the market with less side effects compared to earlier drugs) in the training set, by assigning a value of **2** (which ensures that all of the chemical features in the compound will be considered in building hypothesis) and **0** (which forces mapping of all features of the compound) in the Principle and Maximum Omitting Features (Table 2),

Table 2. Characteristics for the common feature hypothesis run

Compound	Principal[a]	MaxOmitFeat[b]
1	2	0
2	2	1
3	1	1
4	2	0
5	2	0
6	2	1
7	2	1
8	2	1
9	1	0
10	2	1
11	2	0
12	2	1

[a]Principle = 1 means that this compound must map onto the hypotheses generated by the search procedure. Partial mapping is allowed. Principle = 2 means that this is a reference compound. The chemical feature space of the conformers of such a compound is used to define the initial set of potential hypotheses. [b]MaxOmitFeat = 1 means feature of a compound may not be mapped to hypothesis model. MaxOmitFeat = 0 means all features of a compound are mapped to hypothesis model.

respectively. A value of **1** for the principle column ensures that at least one mapping for each of generated hypotheses will be found, and a value of **1** for the maximum omitting features column ensures that all but one feature must map for all other compounds in the training set. All other parameters were kept at the default settings. In the absence of the activity data, all the features of the training set of compounds were taken as reference molecule data in such a way that it would satisfy features of all the compounds.[29,30]

Results and Discussion

From HipHop method, 10 hypotheses (Hypo) were generated based on test set of compounds and scores ranged from 130.613 to 117.05 (Table 3). This small range of ranking score and same features in all hypotheses suggests that the same five features are spatially arranged almost similarly in all hypotheses. Also the compounds of the training set were mapped on to each of the hypotheses and checked for fit values. Hypothesis model has five features, and hence, the maximum fit value of any ligand alignment with this model would be at most 5.0. As all the hypotheses had the same features, selection of best hypothesis was done based on the rank and fit value of test and training sets. Fit values and relative energies (energy in comparision to iloperidone) of compounds of training set are tabulated in (Table 4). Among the hypotheses, Hypothesis 1 (Hypo1) of rank 130.613 is the best hypothesis.

The selected pharmacophore model Hypo1 totally contained five chemical features namely two hydrophobic (HY-1 & HY-2), two hydrogen bond acceptors-lipid (HBAl-1 & HBAl-2) and one aromatic ring (RA) (Figure 3). The distances between these features in are tabulated (Table 5).

Alignment of Hypo1 with test set of compounds was performed and found to give fit scores ranging from 3.06 to 4.88 (Table 6). Compounds **15**, **16**, **17** and **19** showed mapping to all the features of the model generated by HipHop. Among the test set compounds, compound **17** has 4*H*-chromen-4-one ring, flouro and ethoxy groups and exhibited maximum fit value of 4.88. Compounds **13**, **18**, **20**, **21**, **22** and **23** didn't show mapping to the hydrogen bond acceptor feature while compound **14** didn't show mapping to hydrophobic feature (* in Table 6). According to Meltzer for atypical antipsychotic activity a compound should exhibit 5-

Table 3. Results of the common feature hypothesis run

Hypo	Feature[a]	Rank	Direct hit mask[b]	Partial hit mask[c]
1	**RZZHH**	130.613	111111011111	000000100000
2	**RZZHH**	127.432	111111011111	000000100000
3	**RZZHH**	123.901	111111011111	000000100000
4	**RZZHH**	122.775	111111011111	000000100000
5	**RZZHH**	120.592	111111011111	000000100000
6	**RZZHH**	119.758	111111011111	000000100000
7	**RZZHH**	119.102	111111011111	000000100000
8	**RZZHH**	119.027	111111011111	000000100000
9	**RZZHH**	117.050	111111011111	000000100000
10	**RZZHH**	117.050	111111011111	000000100000

[a]Feature; **H**, Hydrophobic (HY); **Z**, Hydrogen bond acceptor-lipid (HBAl); **R**, Ring aromatic (RA). [b]Direct hit mask, all the features of the hypothesis are mapped. (1) indicates every feature of training set compound is mapped; (0) indicates 1 or more features were not mapped. [c]Partial hit mask, partial mapping of the compounds. (0) indicates every feature of training set compound is mapped; (1) indicates 1 or more features were not mapped.

Table 4. Fit value and relative energy of compounds of training set (**1-12**)

Compound	Fit Value	Rel. Energy (k.cal/mol)
1	4.17	0
2	5	10.29
3	3.99	1.94
4	3.18	0.58
5	3.75	4.23
6	0	0.83
7	2.59	8.08
8	1.49	7.03
9	2.30	8.02
10	3.76	6.83
11	4.06	0.66
12	3.84	9.48

Table 5. The distances between various features in Å

Feature	HY-1	HY-2	HBAl-1	HBAl-2	RA
HY-1	-	8.630	3.539	6.844	8.630
HY-2	8.818	-	8.317	4.419	0.214
HBAl-1	3.539	8.317	-	6.547	8.136
HBAl-2	6.844	4.419	6.547	-	4.604
RA	8.630	0.214	8.136	4.604	-

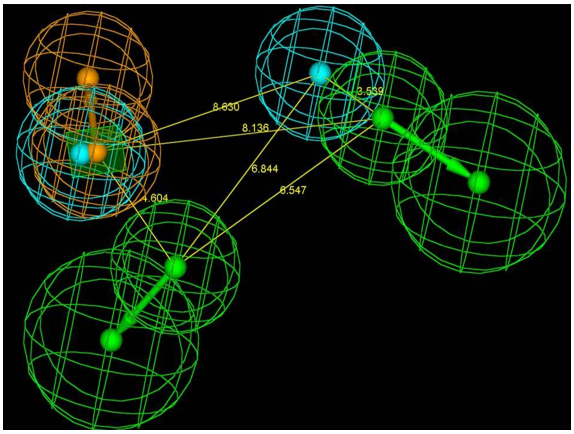


Figure 3. Common feature-based (HipHop) pharmacophore model Hypo1 for atypical antipsychotics.

Table 6[a]**.** Mapping of the Test Set compounds to the respective features in Hypo1 and fit values

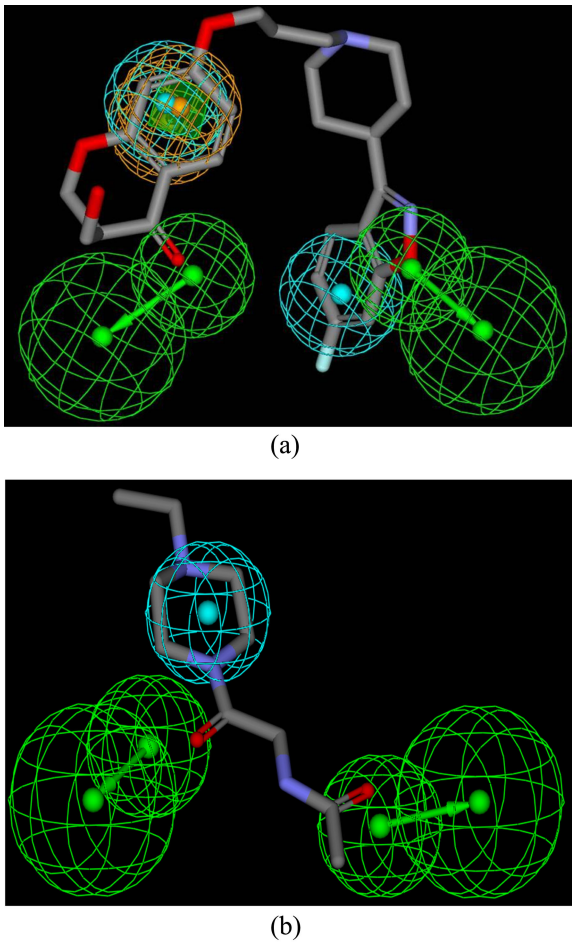
Name	Ring Aromatic	Hydro-phobic	Hydro-phobic	HBA-lipid	HBA-lipid	Fit Value
13	1	1	1	1	0[b]	3.06
14	1	1	0[b]	1	1	3.14
15	1	1	1	1	1	4.26
16	1	1	1	1	1	4.04
17	1	1	1	1	1	4.88
18	1	1	1	1	0[b]	3.87
19	1	1	1	1	1	4.45
20	1	1	1	1	0[b]	3.22
21	1	1	1	1	0[b]	3.49
22	1	1	1	1	0[b]	3.19
23	1	1	1	1	0[b]	3.31

[a]Mapping of the compound to the feature: 1 means Yes and 0 means No. [b]Compounds with no mapping to the particular feature

HT_{2A}/D_2 ratio greater than 1.12.[20] As reported in literature,[22] **17** has higher affinity for $5HT_{2A}$ receptors than D_2 receptors which an atypical antipsychotic should normally exhibit.[20] Also compounds **15**, **16** and **19** showed mapping to all the chemical features which is in accordance with their relative receptor affinities for 5-HT_{2A} and D_2 receptors. Fit values greater than 4.0 for compounds having greater affinity for $5HT_{2A}$ receptors than D_2 receptors in the test set namely **15**, **16**, **17** and **19** indicate the validity of the model. Also, conventional antipsychotics chlorpromazine, haloperidol, thioridazine and fluphenazine did not show mapping to hydrogen-bond acceptor feature, which is in accordance with their lesser affinity for 5-HT_{2A} receptors than D_2 receptors. This indicates the validity of the model exclusively for atypical antipsychotics but not to classical antipsychotics.

The Model (Hypo1) contains five features: two hydrophobic (cyan), two hydrogen bond acceptor-lipids (green), and one aromatic ring (yellow) & distance between chemical features in unit (for clarity, distances between hydrophobic group (HY-2) and other features are not shown).

Figure 4(a) represents compound **17** with a fit value of 4.88, in which the HBAL-1 maps the oxygen of isoxazole ring of benzisoxazole, HBAl-2 maps the carboxyl oxygen of 4*H*-chromen-4-one, the HY-1 feature maps theflouro group of benzisoxazyl ring attached to piperidine group, the HY-2 feature maps the phenyl group of 4*H*-chromen-4-one and aromatic ring (RA) feature maps the phenyl ring of 4*H*-chromen-4-one of compound **17**.



(a)

(b)

Figure 4. (a) Mapping of the active compound **17** and (b) inactive compound **P3** to the model Hypo1.

To further strengthen the proposed pharmacophore model as part of the ongoing research, we synthesized three series of molecules *viz*., 1,8-naphthyridine, quinoxaline and substituted piperazine derivatives and tested for mapping to model Hypo1 (Figure 5). All the above three series of compounds are synthesized, evaluated for their pharmacological activity along with receptor binding profiles and published.[9a-d] Summarized are the result whose fit scores range from 3.56 to 4.84 (Table 7). Compound NC1 and NC6 exhibited good response to every features of the proposed HipHop model. Out of these two compounds NC1 having fit value of 4.84 was found to be the most active compound in the pharmacological screening (5-HT_{2a}/D_2 ratio of 1.14).[9a] Compound P3 which doesn't have aromatic ring was found to be inactive in pharmacological screening (5-HT_{2a}/D_2 ratio of 0.44)[9c] and compound P4, QCMH1 and QCMH2[9d] didn't show mapping to hydrophobic feature (* in Table 7). Compounds P4, QCC3, QCC4, QCMO5 and QCMO6[9d]

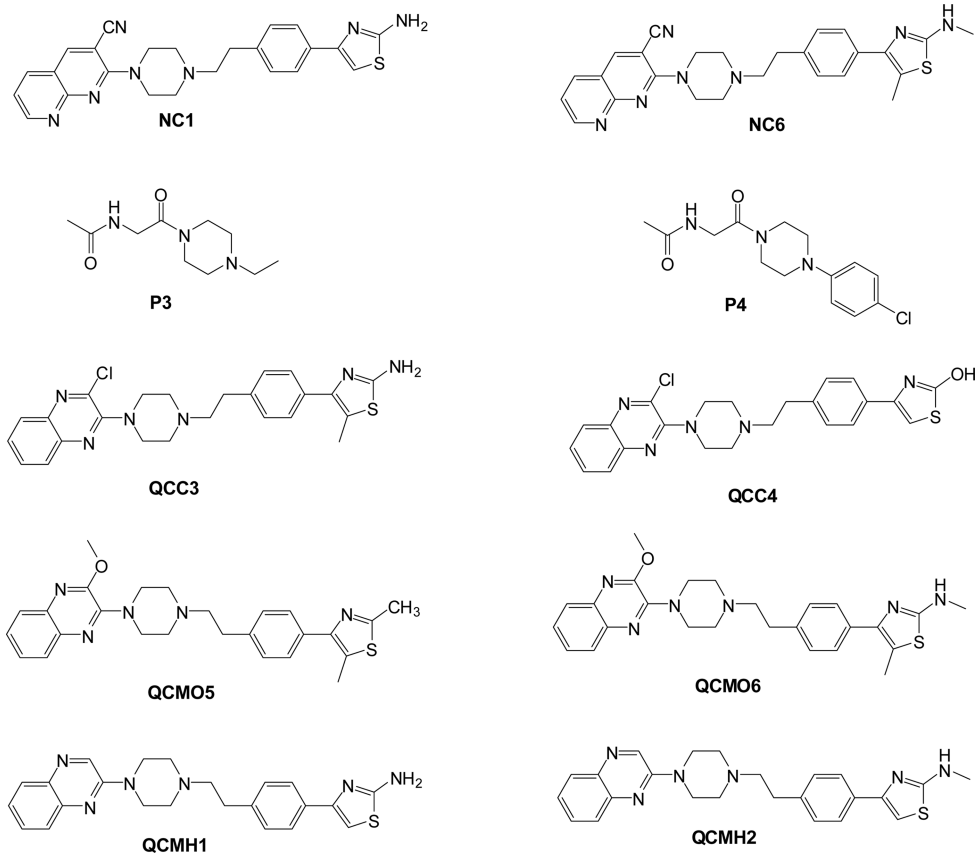


Figure 5. Structures of synthesized compounds to validate the model.

Table 7[a]**.** Mapping of the synthesized compounds to the respective features in Hypo1 and fit values

Name	Ring Aromatic	Hydro-phobic	Hydro-phobic	HBA-lipid	HBA-lipid	Fit Value
NC1	1	1	1	1	1	4.84
NC6	1	1	1	1	1	4.69
P3	0[b]	0[b]	1	1	1	2.39
P4	1	0[b]	1	1	0[b]	2.89
QCC3	1	1	1	1	0[b]	3.81
QCC4	1	1	1	1	0[b]	3.68
QCMO5	1	1	1	1	0[b]	3.95
QCMO6	1	1	1	1	0[b]	3.83
QCMH1	1	0[b]	1	1	1	3.56
QCMH2	1	0[b]	1	1	1	3.56

[a]Mapping of the compound to the feature: 1 means Yes and 0 means No. [b]Compounds with no mapping to the particular feature

didn't show mapping to the hydrogen bond acceptor feature. As we summarized earlier fit values greater than 4.0 for compounds have greater affinity for $5HT_{2A}$ receptors than D_2 receptors in the test set namely NC1 indicate the validity of the model.

Conclusions

In rational drug design process, it is common that the biological-activity data of a set of compounds acting upon a particular protein is known, while information on the three-dimensional structure of the protein active site is absent. A three-dimensional pharmacophore hypothesis that is consistent with existing compounds should be useful and predictive in evaluating new compounds and directing further synthesis. We have generated pharmacophore hypotheses for atypical antipsychotics using the HipHop model of CATALYST 4.11. The present work shows how a set of active compounds can uncover the molecular characteristics or features essential for activity. The results of the pharmacophore model revealed that 2 hydrogen bond acceptors (lipid), 2 hydrophobic features and an aromatic ring are significant for effective atypical antipsychotics acting primarily at 5-HT_{2A} and D_2 receptors. The model generated hypotheses (1-10) with rank scores ranging from 130-117 and results with training set led to the selection of Hypo1 as the best hypothesis. The mapping of compounds of test set to Hypo1 yielded considerable fit values with a maximum fit value of 4.88 for **17**. Also compounds **15**, **16** and **19** showed mapping to all the features of the developed pharmacophore model with fit values greater than 4.0. This result is in congruence with the reported literature, which shows the higher affinity of these compounds towards 5-HT_{2A} than D_2 receptors,[22] which an atypical antipsychotic should possess in order to show less extra-pyramidal side effects. The compounds **13**, **18**, **20**, **21**, **22** and **23** didn't show mapping to hydrogen bond acceptor (lipid) feature while compound **14** didn't show mapping to hydrophobic group feature. This result is in congruence with

the higher affinities for D_2 receptors than 5-HT_{2A} receptors of these compounds. Based on this, one can conclude that binding to both the hydrogen-bond acceptor groups is essential for atypical antipsychotic activity. Compounds **13**, **18**, **20**, **21**, **22** and **23** can be modified to incorporate a hydrogen bond acceptor-lipid in a specific 3D orientation, which satisfies the distance-criteria in Table 5. This study can be utilized in the design of new compounds with keeping in view the 3D orientation of the aforementioned five chemical features. Also, this study can be useful in the discovery of chemical features required but absent in various conventional antipsychotics and thus lead to incorporation of functional groups or moieties. Thus the model can prove an advantage for ligand based drug design of novel atypical antipsychotics. This study does not predict features required by compounds for binding to either of 5-HT_{2A} or D_2 receptors in particular but indicates the features significant to show antipsychotic activity akin to that of atypical antipsychotics.

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