'RESEARCH JOURNEY' International E- Research Journal
Impact Factor - (SJIF) – 6.261, (CIF) - 3.452(2015), (GIF)–0.676 (2013)
Special Issue 110 (B) : Chemistry
UGC Approved Journal
ISSN : 2348-7143
February -2019

Development of Pharmacophore Modelfor Antipsychotic Action of N-Substituted 2-Phenylcyclopropylmethylamines

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Abstract:

The present work is an attempt to develop a consensus pharmacophore model using common features that have correlation with antipsychotic action of N-Substituted 2-Phenylcyclopropylmethylamines. The dataset consists of thirty-one derivatives with moderate to high activity. The develop of consensus pharmacophore model consists of different steps like collection of dataset molecules, data curation, conversion to 3D-structure after drawing, optimization using force field, alignment of all molecules and then construction of consensus pharmacophore model. The analysis reveals that consensus pharmacophore model is a cluster of H-bond donor and acceptor groups as well as aromatic rings. The deductions could be useful for future optimizations of 6□ Hydroxypyridazinone derivatives as σ1 Receptor Ligands to treat pain.

Keywords: Pharmacophore modeling, antipsychotic, N-Substituted 2- Phenylcyclopropyl methylamines, GPCR

Introduction:

Gprotein-coupled receptors (GPCR) have been received high attention due to their crucial role as an attractive drug targets for obesity and many central nervous system (CNS) disorders, such as schizophrenia and drug addiction. Literature survey reveals that biased GPCR ligands could be very useful new generation therapeutic agents and have many benefits like improved efficacy and functionalselectivity, thereby, exhibiting reduced side effects [1-4].

Serotonin 2C (5-HT_{2C}) receptor, a GPCR, plays important role in many CNS related signaling mechanism and pathways. Hence, developing a drug using 5-HT_{2C} as a drug target is an attractive approach to solve many CNS related complications [1-4]. However, conventional procedure of drug development is very long and costly due to emphasis on repeated 'trial and errors' and animal testing. Hence, a novel method like Computer Aided Drug Designing (CADD) has appearedin the recent time to develop a new therapeutic agent or modify the exiting drug.

Computer Aided Drug Designing has many advantages like cheaper, easier, less timeconsuming, etc. QSAR, Pharmacophore modeling and many other branches of CADD are used for drug and lead optimizations. The results are very high quality and useful for medicinal chemists. In addition, deep understanding of drug action is also gained [5-7].

Recently, Zhanget al [1] identified many derivatives of 2-Phenylcyclopropylmethylamine as functionally selective 5-HT_{2C} agonists. The experimented2-Phenylcyclopropylmethylamine derivatives have good degree of difference in their biological profile because of extensive difference in substituents. In-depth structure-activity relationships (SAR) were discoursed to recognizeimportantfeatures. However, this is first attempt to rationalize the pharmacophoric features/pattern related with psychotic activity of substituted 2-Phenylcyclopropylmethylamine.

Therefore, in the present work, consensus pharmacophore modeling was performed to find the noteworthy structural features that decide the bio-activity of 2-Phenylcyclopropylmethylamine derivatives.

Experimental Methodology

Dataset:

The dataset consists of thirty-one2-Phenylcyclopropylmethylamine derivatives with a variety of substituents [1]. Therefore, the selected dataset is useful to develop a pharmacophore model. The compounds were tested for 5-HT_{2C} agonistactivity. The activity values described as EC_{50}(nM). The dataset has been tabulated in table 1.

Table-1.

Different 2-Phenylcyclopropylmethylamine derivatives (SMILES notation) along with reported EC_{50} used in the present work

Sr. No.	SMILES	EC_{50} (nM)
1	FC1=CC=C(OCCF)C([C@@H]2[C@H](C2)CNCC3=CC=CC=C3OC)=C1	2.4
2	FC1=CC=C(OCC=C)C([C@@H]2[C@H](C2)CNCC3=CC=CC=C3OC)=C1	9.2
3	FC1=CC=C(OCC=C)C([C@@H]2[C@H](C2)CNC)=C1	13
4	FC1=CC=C(OC)C([C@@H]2[C@H](C2)CNC)=C1	23
5	FC1=CC=C(OC)C([C@@H]2[C@H](C2)CNCC3=CC=CC=C3OC)=C1	23.5
6	FC1=CC=C(OC)C(C2C(C2)CNCC3=CC=CC=C3OCCF)=C1	28
7	FC1=CC=C(OC)C(C2C(C2)CNCC3CCCCC3)=C1	95
8	FC1=CC=C(OC)C([C@H]2[C@@H](C2)CNCC3=CC=CC=C3OC)=C1	103
9	FC1=CC=C(OC)C([C@@H]2[C@H](C2)CNCC3=CC=CS3)=C1	120
10	FC1=CC=C(OC)C(C2C(C2)CNCC3=C(OC)C=CS3)=C1	121
11	FC1=CC=C(OC)C(C2C(C2)CNCC3=CSC=C3OC)=C1	228
12	FC1=CC=C(OC)C([C@@H]2[C@H](C2)CNCC3=CC=CC(OC)=C3)=C1	231
13	FC1=CC=C(OC)C(C2C(C2)CNCC3=CC=CC=C3C#N)=C1	245
14	FC1=CC=C(OC)C(C2C(C2)CNCC3=CC=CC=C3O)=C1	304
15	FC1=CC=C(OC)C([C@H]2[C@@H](C2)CNCC3=CC=CS3)=C1	308
16	FC1=CC=C(OC)C(C2C(C2)CNC3CC3)=C1	399
17	FC1=CC=C(OC)C(C2C(C2)CNCC3=CC=CC=C3C(N)=O)=C1	409
18	FC1=CC=C(OC)C(C2C(C2)CNCC3=CC=CN=C3OC)=C1	433
19	FC1=CC=C(OC)C([C@@H]2[C@H](C2)CNCC3=CC=CC=C3F)=C1	502
20	FC1=CC=C(OC)C([C@@H]2[C@H](C2)CNCC3=CC=CC=C3Cl)=C1	529
21	FC1=CC=C(OC)C(C2C(C2)CNCC3=CC=CC4=C3N=CC=C4)=C1	530
22	FC1=CC=C(OC)C(C2C(C2)CNCC3=C(OC)SC=C3)=C1	556
23	FC1=CC=C(OC)C(C2C(C2)CNCCC3=C(OC)C=CC=C3)=C1	615
24	FC1=CC=C(OC)C(C2C(C2)CN(C)CC3=CC=CC=C3OC)=C1	670
25	FC1=CC=C(OC)C(C2C(C2)CNCC3=CC=CC4=C3SC=C4)=C1	777
26	FC1=CC=C(OC)C(C2C(C2)CNC3(CC3)C4=CC=CC=C4OC)=C1	874
27	FC1=CC=C(OC)C([C@@H]2[C@H](C2)CNCC3=CC=C(OC)C=C3)=C1	1200
28	FC1=CC=C(OC)C([C@H]2[C@@H](C2)CNCC3=CC=CC=C3F)=C1	1640
29	FC1=CC=C(OC)C([C@H]2[C@@H](C2)CNCC3=CC=CC=C3Cl)=C1	1860
30	FC1=CC=C(OC)C(C2C(C2)CNC(C)C3=CC=CC=C3OC)=C1	2550
31	FC1=CC=C(OC)C([C@H]2[C@@H](C2)CNCC3=CC=CC(OC)=C3)=C1	2600

Structure drawing, optimization and alignment [5-7]**:**

The standard procedure reported in literature has been followed to develop consensus pharmacophore modeling [5-7]. The different steps involved are:

Step-1: Drawing all structures (Chemsketch Freeware 12)

Step-2: Structure optimization of all the structures using MMFF94 force field (TINKER software) Step-3: Open3dAlign software gave alignment of all the optimized structures

Step-4: Consensus pharmacophore modeling was completed using LIQUID plugin (installed on PyMOl1.8.6) using the default settings

Results And Discussion

The present study reveals that the consensuspharmacophore model mainly consists of four regions. Of the four regions, three are hydrophobic and one is positively charged region. The cyclopropyl ring contributes as a hydrophobic region like its neighboring aromatic ring. The -NH- acts a linker and contributes as positively charged region. The aromatic ring in vicinity of -NH- acts as a hydrophobic moiety.

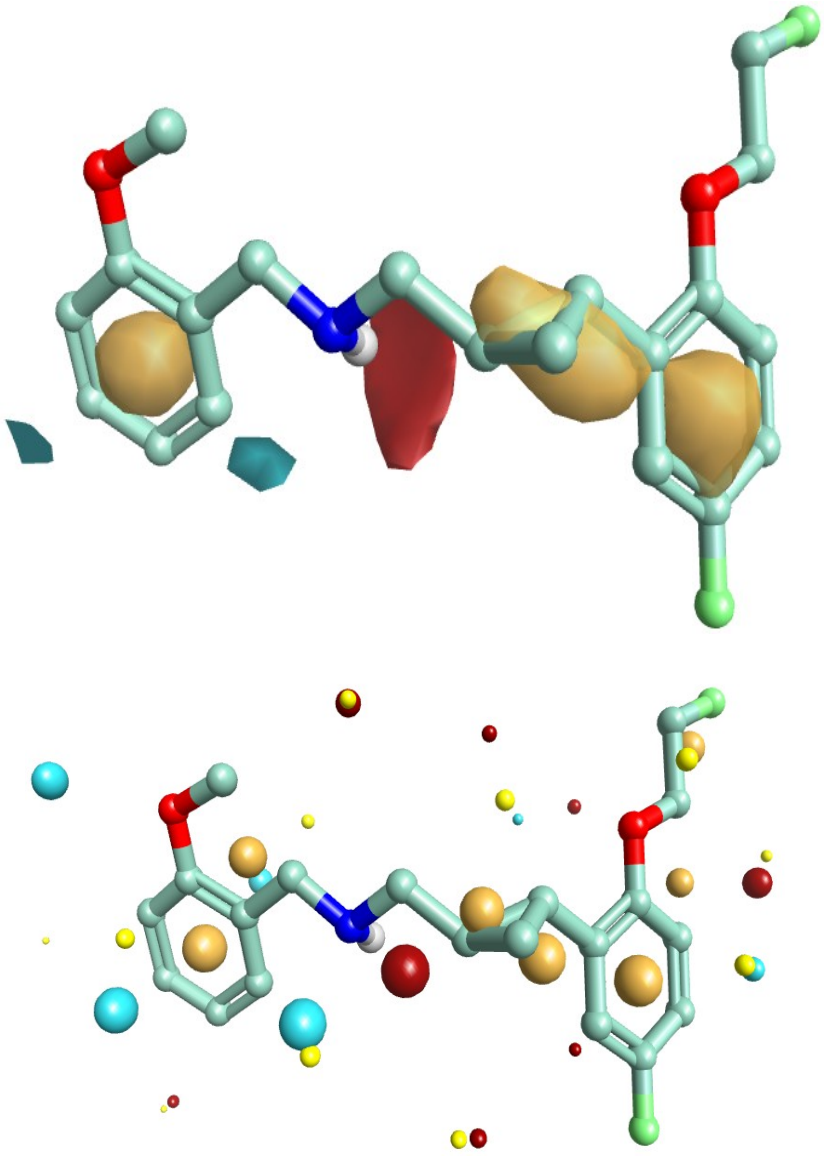

Figure-1. 3D- representation of consensus pharmacophoric pattern using the active molecule 1 as a representative only (Yellow: Hydrophobic, Blue: Negative and Red: Positive charged regions)

In future optimizations, this pharmacophoric pattern must be preserved for good antipsychotic action of N-Substituted 2-Phenylcyclopropylmethylamines.

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