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MOLECULAR DOCKING STUDIES OF PYRIDINE-CARBOXAMIDE DERIVATIVES AS POTENTIAL ANTIPSYCHOTIC DRUG: MULTI-TARGETED DRUG APPROACH

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ABSTRACT

Schizophrenia is a complex CNS disorder affecting 2 million people of the world's population. It is characterized by distortions in multiple domains inclusive of perception, thinking, emotions, self sense, and behaviour. The various symptoms associated with schizophrenia are positive symptoms (delusions, hallucinations, and thought disorder); negative symptoms (alogia, affective flattening, anhedonia, avolition, and apathy) and cognitive dysfunction. Schizophrenia is associated with many different symptoms, developing the multi-target drugs with more than one pharmacological activity is an effective approach. For this approach the receptors involved in atypical antipsychotics (5-HT2A and D2) are the best chosen targets. Molecular docking studies were performed using Molegro Virtual Docker 6.0 to estimate the inhibition potential of these compounds. A series of novel pyridinecarboxamides (22 compounds) were docked against two targets: Dopamine D2 [PDB: 6CM4 (2.86Å)] and Serotonin 5-HT2A [PDB: 5A93 (3Å)]. Out of which 2 compounds 17c and 7c showed the best docking result on both the receptor as compared to the standard drug Resperidone.

KEYWORDS: schizophrenia, molecular docking, dopamine (D2), serotonin (5-HT2A), multi- target drugs (MTDs).

INTRODUCTION

Schizophrenia is a chronic and severe mental disorder affecting 2 million people worldwide which is about 1% of the world's population.[1] It is a complicated psychiatric disorder

characterized by distortions in multiple domains inclusive of perception, thinking, emotions, self sense, and behaviour. The symptoms associated with schizophrenia are categorized into three: positive symptoms (delusions, hallucinations, and thought disorder); negative symptoms (alogia, affective flattening, anhedonia, avolition, and apathy) and cognitive dysfunction. Chlorpromazine and Haloperidol, the typical antipsychotics were found effective in reducing the positive symptoms by blocking dopamine D_2 receptors but were associated with severe adverse effects due to unavoidable inhibition of other dopamine pathways. The adverse effects include Extrapyramidal symptoms (EPS), Tardive dyskinesia (TD) and Hyperprolactinemia. Introduction of Clozapine imprints the importance to atypical antipsychotics. Later on Risperidone, Ziprasidone and Aripiprazole came in the market which block both serotonin 5-HT_{2A} and dopamine D_2 receptors at clinically effective doses. These help in the improvement of safety profile and adverse effects such as EPS and TD decreases considerably.[3]

It is generally accepted that the symptoms of schizophrenia arises due to disturbances in neurotransmission which involves a noteworthy receptors and enzymes, mainly within the dopaminergic, glutamerergic, serotonergic, and adrenergic systems. In context to this, blocking the dopamine pathway is still the main concept to treat schizophrenia and hence, all marketed antipsychotics target dopamine D_2 receptor.[4]

The “magic bullet” concept is not helpful in complex diseases such as schizophrenia which is associated with many different symptoms.[5] According to magic bullet concept, in drug discovery approach it is assumed that single target drugs are safer as they have fewer side effects due to their selectivity. Later it has seen that it is only true for single gene diseases. Therefore, “one-drug-one-target” model is replaced by multi-target drug (MTDs) which is also known as “magic shotgun”.[6] Schizophrenia is associated with many different symptoms, developing the multi-target drugs with more than one pharmacological activity is an effective approach. For this approach the receptors involved in atypical antipsychotics (5-HT_{2A} and D_2) are the best chosen targets. 5-HT_{2A} receptor antagonistic activity had been suggested to be responsible for reducing EPS. Antagonism of 5-HT_{2A} receptor counteracted the effect of D_2 receptor blockade in striatum, thus decreases the risk of EPS.[2]

Improved efficacy due to synergistic or additive effects, better distribution in the target tissue, accelerated therapeutic efficacy in terms of clinical onset and achievement of full effect,

predictable pharmacokinetic profile and fewer drug-drug interactions, lower risk of toxicity, improved patient compliance and tolerance and lower risk of target-based drug resistance due to modulation of a few targets are the advantages of MTDs over single-target drugs.[5]

A class of benzamide derivatives with potent antipsychotic activity were reported previously.[3] Using the concept of bioisosterism, a series of pyridine-carboxamide derivatives with dopamine (D_2) and serotonin (5-HT_{2A}) blocking ability were designed and docked against two PDBs: 6CM4 and 5A93.

MATERIAL AND METHODS

1. Platform for molecular docking

The computational investigations were performed using Molegro Virtual Docker v. 6.0.

2. Ligand preparation

A series of novel pyridinecarboxamides (22 compounds) were drawn on Chem Draw Ultra 8.0. The pubchem database was used to extract out 3D structure of selected molecules and then the energy minimization was taken out in Chem 3D Ultra 8.0 with minimum RMS Gradient 0.001.

3. Protein preparation

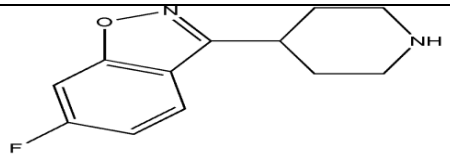
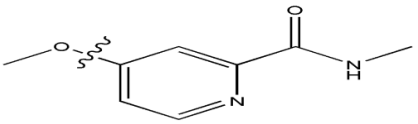
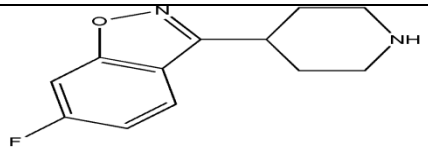
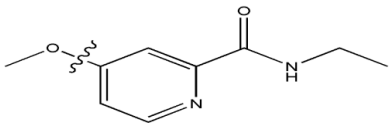
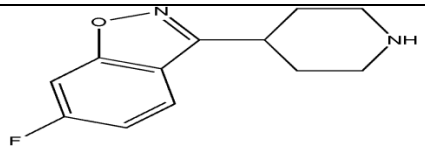
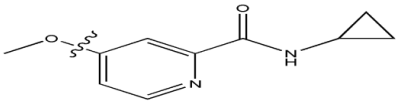
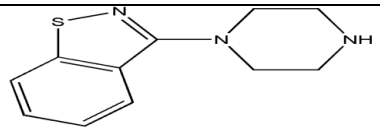
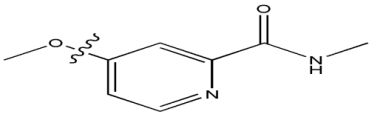
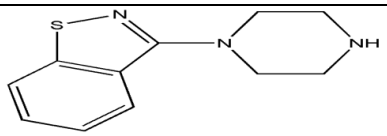
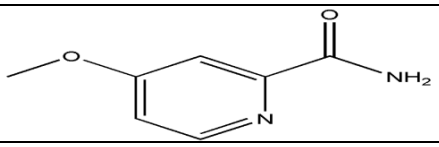
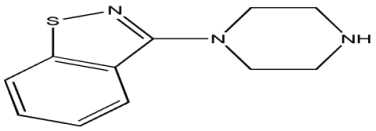
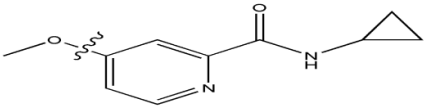
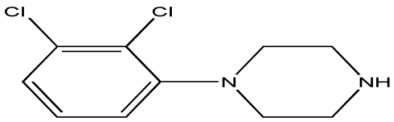
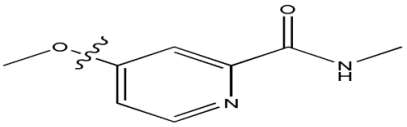
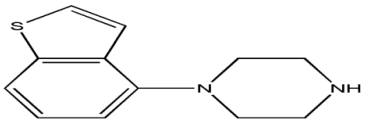
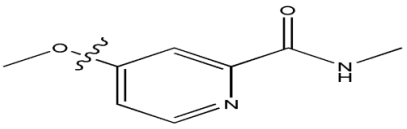
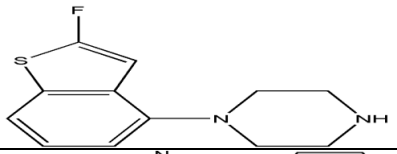
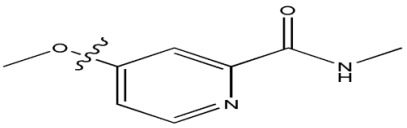
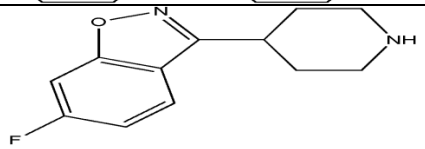
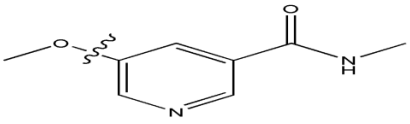
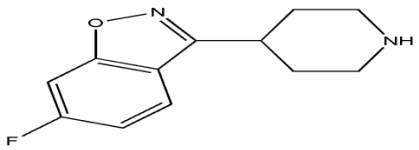
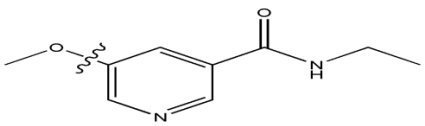
Protein structures for Dopamine D_2 and serotonin 5-HT_{2A} was downloaded from the protein data bank (RCSB PDB) for standard bioinformatics that contains X-ray crystal structures for proteins.

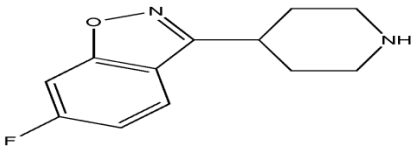
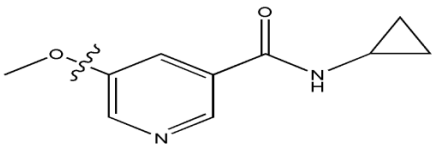
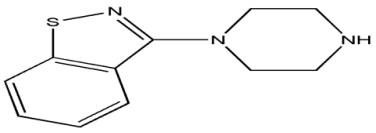
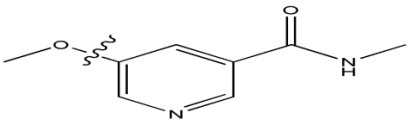
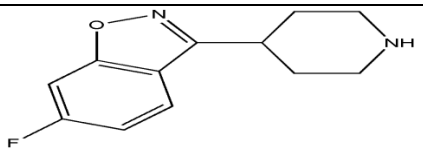
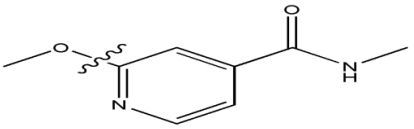
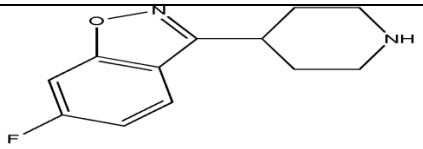
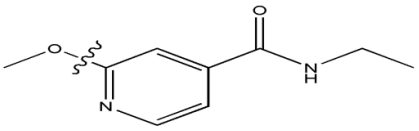
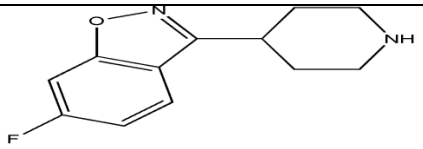
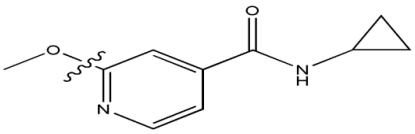
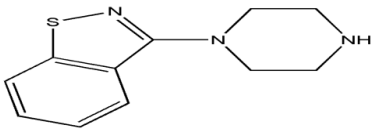
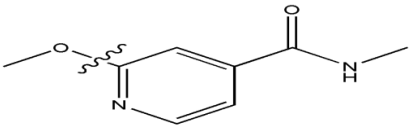
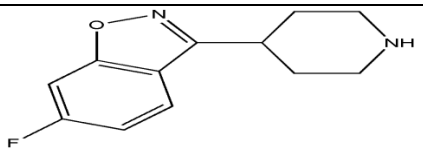
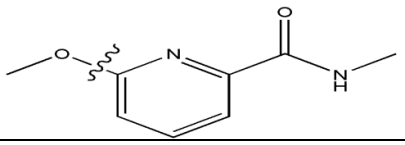
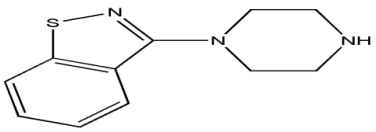
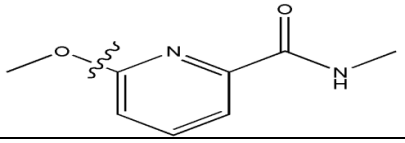
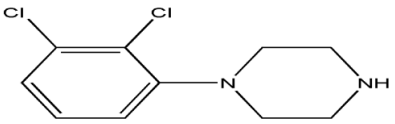
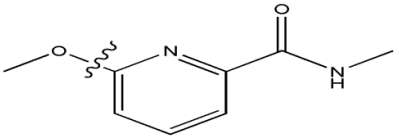
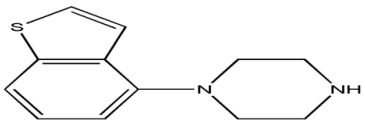
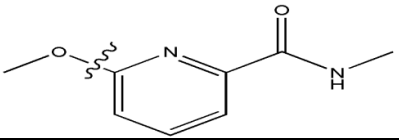
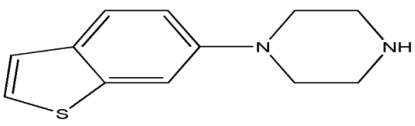
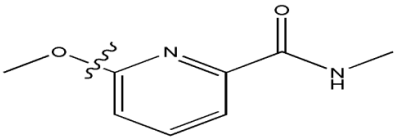
4. Molecular docking

Molecular docking is one of the most frequently used methods in SBDD because of its ability to predict, with a substantial degree of accuracy, the conformation of small- molecule ligands within the appropriate target binding site. The main objective of molecular docking is to attain ligand-receptor complex with optimized conformation and with the intention of possessing less binding free energy.

Molecular docking was performed on the respective proteins retrieved from the protein data bank and ligands in Molegro Virtual Docker ver. 6.0. using default parameters.Table1: showing series of compounds used in docking.

Table 1: Showing series of compounds used in docking.

Compound	R2N	Y
7a		
7b		
7c		
7d		
7e		
7f		
7g		
7h		
7i		
12a		
12b		

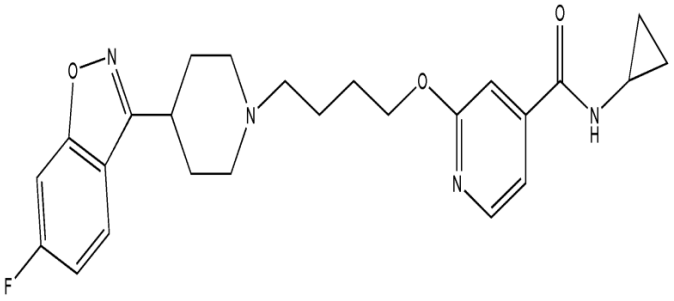
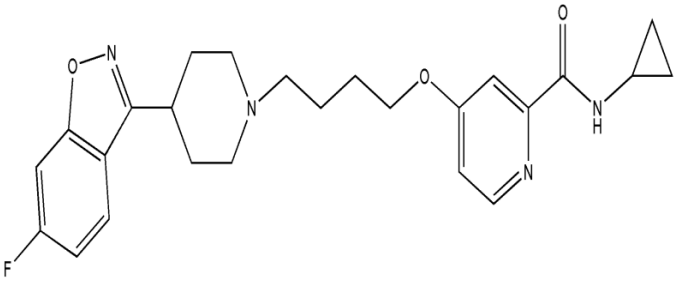
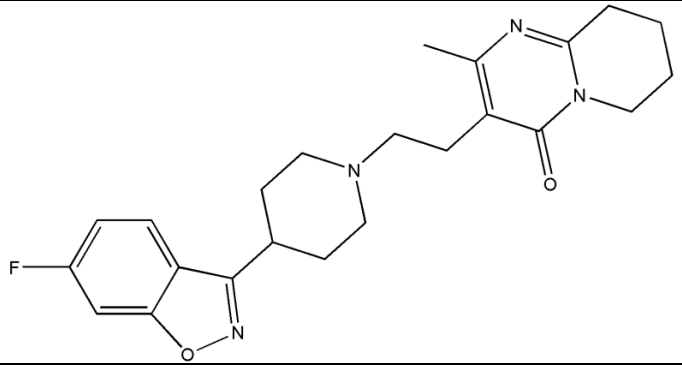
12c		
12d		
17a		
17b		
17c		
17d		
22a		
22b		
22c		
22d		
22e		

RESULTS

In order to find out the potential inhibitor on multi-receptor antipsychotic drugs, molecular studies were performed over 22 substituted pyridinecarboxamides on the binding pocket of Dopamine D2 [PDB: 6CM4 (2.86Å)] and Serotonin 5-HT2A [PDB:5A93(3Å)] to study the HITs identification.

Out of which 2 compounds 17c and 7c showed the best docking result on both the receptor as compared to the standard drug Resperidone. The docked conformations for both the compounds were analyzed and it was found that 17c ranked with less binding energy as compared to the standard drug.

Table 2: showed the standard drug and top two HITs on both the receptor with structure and Moldock score of both PDBs.

S. No.	Structure	Moldock Score (PDB-6A93) 5HT2A	Moldock Score (PDB-6CM4) D2
17c		-179.514	-174.218
7c		-175.828	-168.353
Resperidone		-146.196	-138.546

CONCLUSION

Schizophrenia being a complex disease associated with a large number of different symptoms requires a multi-target drug therapy for the treatment. As single-target drugs were causing various adverse effects. To combat this problem, a series of pyridine- carboxamide derivatives were designed and docked against the two targets: D2 and 5- HT2A. Out of which 17c and 7c shows the good docking score which can be used for further experimental strudies.

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