Olanzapine Derivatives as Inhibitors for 5-HT_{2A} Receptor

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ABSTRACT

Mental and behavioral disorders are found in peopleof all regions of countries. Among all the psychological well-being issues, schizophrenia is the one of the exceptionally extremeproblem with disturbance in thought, perception and feeling. To treat positive as well as negative symptoms of Schizophrenia antipsychotics drugs focused on 5-HT2A receptor to avoid side effects. In this work, we docked Olanzapine derivatives collected from literature with 5-HT_{2A}receptor using AutoDock 4.2 tool. After that docked protein - compound complex structure was optimized using molecular dynamics simulation for evaluatingthe stability of complex structure. Further,a quantitative structure activity relationship (QSAR) model was built using energy-based descriptors such as binding energy,intermol energy, vdW + Hbond + desolvenergy, electrostatic energy, internal energy and torsional energyobtained from docking as independent variables and experimental activity (pK_i) value as dependent variable of eleven known Olanzapine derivatives with 5-HT_{2A} Receptor, yielding correlation coefficient r^2 of 0.86. The predictive performance of QSAR model was assessed using different cross-validation procedures. Our results suggest that a ligand-receptor binding interaction for 5-HT_{2A} receptor using a QSAR model is promising approach to design more potent 5-HT_{2A} receptor inhibitors prior to their synthesis.

Keywords: *5-HT_{2A} receptor, Olanzapine derivatives, QSAR, Schizophrenia*

INTRODUCTION

Mental disorders have turned out to be very pervasive because of driven way of life, stressful environment and urbanization [1]. Mental disorders incorporate schizophrenia, depression, bipolar disorder, obsessive-compulsive disorder, Alzheimer's disease, anxiety and so on.

These scatters can create at any age and in people of any race, religion or wage gathering. A large portion of the general population don't have the foggiest idea about that they are experiencing symptoms of mental disorder because in the initial stage the symptoms is mild and later on it turn into a serious mental illness which is exceptionally hurtful for the general public. Schizophrenia is a serious mental disorder, described by significant interruptions in considering, observation influencing dialect, the feeling of self, influencing in excess of 21 million individuals around the world [2]. Schizophrenia is depicted as far as positive and negative indications. Positive symptoms are including the delusions disordered, thoughts, speech and tactile, sound-related visual olfactory and gustatory hallucinations. The negative symptoms are deficits of normal emotional responses. Schizophrenia etiology demonstrates that numerous elements are included, namely genetic factors, [3, 4] obstetrical complexities [5] and adjustments in substance transmission (serotonine, dopamine etc.) [6] and viral Infections [7].There is no satisfactory cure available for anticipation of the schizophrenia. At present accessible showcased drugs like chlorpromazine, clozapine, haloperidol, risperidone, and olanzapine have nanomolar affinities for dopamine D_2 and serotonin 5-HT_{2A} receptors [8] however have some serious antagonistic impacts such as dizziness, diabetes, neuroleptic malignant syndrome, weight gain, agitation, sexual dysfunction and sedation.

To treat positive as well as negative symptoms of Schizophrenia atypical antipsychotics drugs concentrated more on 5-HT_{2A} receptor rather than D_2 dopamine to avoid side effects called extrapyramidal symptoms (EPS). Neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) an old neurotransmitter, engaged with a few neurophysiological and behavioral functions, acts by interacting with numerous receptors (5-HT_1-5-HT_7) [9]. Changes in serotonergic signaling have likewise been involved in different psychiatric disorders [9]. Dold *et al.* [10] consolidated all randomized controlled trials that contrasted oral haloperidol and another oral unique antipsychotic cure (except for the low-strength antipsychotics chlorprothixene, mesoridazine, levopromazine, perazine, chlorpromazine, thioridazine and prochlorpromazine) in schizophrenia and schizophrenia-like psychosis. Data from all of these preliminaries is consolidated, as customary antipsychotics are useful for treatment of schizophrenia. Li *et al.* [11] looked into showcased normal and atypical antipsychotics and new therapeutic agents focusing on dopamine receptors and other neurotransmitters for the treatment of schizophrenia. Drug resistance in schizophrenic disorders treated with an antipsychotic medicine is exceedingly dangerous, lacking sound criteria to characterize it, and to discriminate between drug response and clinical abatement. A few neurochemical abnormalities have been accounted for to be applicable for the pathogenesis of schizophrenic disorders and have been related to clinical symptoms as well as to the quality of response to antipsychotics: the greater part of the discoveries originate from concentrates on DA and 5HT brain metabolism, yet more as of late, other non-dopaminergic pathways have been involved [12].

EXPERIMENTAL

Protein target structure: 3D structure model of 5-HT_{2A} Serotonin receptor in Homo sapiens was retrieved from our previous published paper [13].

Inhibitors dataset: ElevenOlanzapine derivatives with known pK_iwere obtained from literature [14]. The 3D structures of known elevenOlanzapine derivatives were built by using CORINA V3.6. CORINA is maintained for general usage by Molecular Networks GmbH Computerchemie. All thederivative were subjected to energy minimization using the HyperChem software [15].

Molecular docking: Docking of elevenOlanzapine derivatives screened from literature against 5-HT2A Receptor structure were done using molecular docking program AutoDock 4.2 [16]. Gasteiger charges are added to the ligand and maximum 6 numbers of active torsions are given to the lead compounds using AutoDock tool (http://autodock.scripps.edu/resources/adt). Kollman charges and the solvation term were added to the protein structure. The Lamarckian genetic algorithm implemented in Autodock was used for docking.

Molecular dynamics simulations: Molecular dynamics simulations were done using the NAMD (NAnoscale Molecular Dynamics program; v2.7) graphical interface module [17] incorporated visual molecular dynamics (VMD 1.9.2) [18].

2D QSAR: A QSAR based model was generated having correlation coefficient r^2 value 0.86 was developed using multiple linear regression analysis. An equation was developed for the inhibitory activities represented as pK_i values using the six types of energy values as variable descriptors such as Binding Energy (BE), Intermolecular Energy (IME), Internal Energy (IE), Torsional Energy (TorE), vdW + Hbond + desolv Energy (VdwE) and electrostatic energy (EE). A correlation coefficient (r2) of 0.86was obtained for 11Olanzapine derivatives as shown below in equation i.

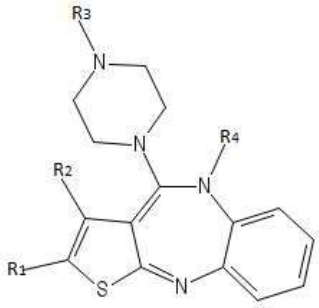
Predicted pK_i= 1.24211 -134.031(BE) + 44.1703(IME) + 1.24903(IE)
+134.952(TorE)+88.9773(VdwE) +91.0397(EE)
..……..(i)

Several cross-validation procedures were adopted to assess the predictive performance of the QSAR model. In leave-one-out strategy (LOOCV), one molecule was removed from the dataset
as a test compound and the remaining 10 molecules were used to build the model. This process was repeated 11 times with each inhibitor as a test molecule.

RESULTS AND DISCUSSION

Based on R1, R2, R3 and R4 groups at different positions, Olanzapine derivatives of 5-HT_{2A} Receptor were retrieved from literature [14] and are shown in table 1.

Table 1. Olanzapine derivatives of 5-HT_{2A} receptor on the basis of different R1, R2, R3 and R4 group



Olanzapine derivate	Group			
	R1	R2	R3	R4
1	CH3-CH2	H	CH3	H
2	CH3	CH3	CH3	H
3	CH3	C3H7	CH3	H
4	CH3	isobutyl	CH3	H

5	CH3	H	CH3	CH3
6	C6H5	H	CH3	H
7	CH3	H	H3C–CH2	H
8	CH3	H	C3H7	H
9	CH3	H	CH2F	H
10	CH3	H	CH2Cl	H
11	CH3	H	CH2OH	H

In docking studies of Olanzapine derivatives with 5-HT_{2A} Receptor, best autodock score was used as criteria to interpret the best conformation among the 30 conformations, generated by AutoDock 4.2 [16]. The docking results of the Olanzapine derivatives with 5-HT_{2A}receptor were shown in table 2. Further, the docked complexes were analyzed through Python Molecular Viewer software [19] for their interaction studies.Thus from the Complex scoring and binding ability it's deciphered that these compounds are promising inhibitors for 5-HT2A Receptor. MD simulation is a well-known theoretical technique and is mainly used for evaluating the stability of any predicted 3D model. Therefore, the constructed 3D model of protein-ligand complexes was processed for MD simulation in ps timescale with Langevin dynamics to control the kinetic energy, temperature, and/or pressure of the system.

Table 2. Docking results of Olanzapine derivatives with 5-HT_{2A} receptor structure with activity (pK_i = - logpK_i)

S.No.	Experimental pK_i	Predicted pK_i	BE	IME	IE	TorE	VdwE	EE
1.	8.15	7.93	-8.09	-8.69	-0.49	0.6	-8.24	-0.45
2.	8.27	8.44	-7.97	-8.27	0.50	0.3	-7.78	-0.49
3.	9.29	8.88	-7.9	-8.79	0.17	0.89	-8.23	-0.56
4.	9.19	9.40	-8.37	-9.27	0.47	0.89	-8.78	-0.48
5.	8.69	8.34	-8.38	-8.67	-0.49	0.3	-7.91	-0.76
6.	7.85	7.92	-8.99	-9.59	-0.84	0.6	-8.96	-0.63
7.	7.61	7.83	-8.09	-8.69	-0.42	0.6	-8.15	-0.54
8.	7.51	7.73	-8.29	-9.18	-0.72	0.89	-8.43	-0.75
9.	7.71	8.06	-7.68	-8.27	-0.47	0.6	-7.4	-0.87
10.	8.61	8.55	-8.17	-8.77	-0.1	0.6	-8.35	-0.42
11.	7.21	7.00	-7.95	-8.85	-0.36	0.89	-7.88	-0.96

BE = Binding Energy; IME: Intermolecular Energy; IE = Internal Energy; TorE= Torsional; Energy; VdwE = vdW + Hbond + desolv Energy; EE= Electrostatic energy.

Docked complexes showed stable interaction between ligand and receptor at microscopic level. Relationship between experimental and predicted pKi values of Olanzapine derivatives was shown in figure 1.

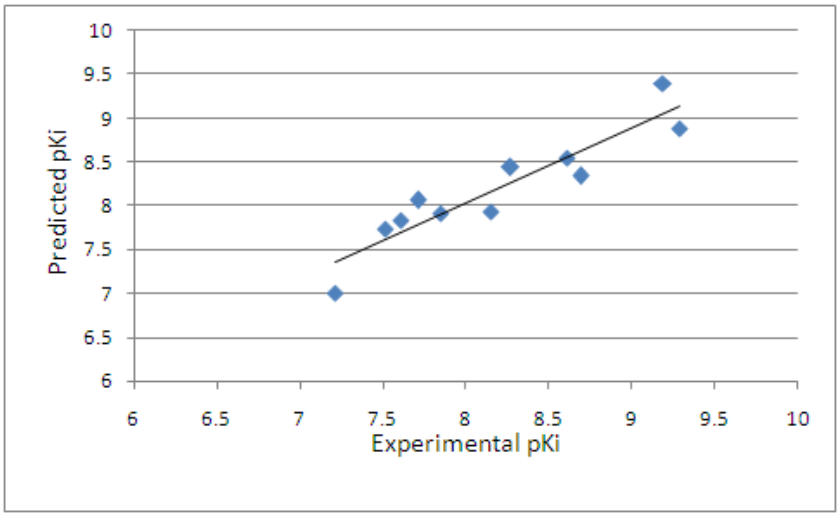


Fig 1. Relationship between experimental (x-axis) and predicted (y-axis) pK_i values with an r^2 value0.86 is shown in a QSAR model developed using multiple linear regression analysis.

Similar type work was performed by Chaudhary *et al.* [20] in 3D QSAR analysis using kNN-MFA method on a series of benzathaizapine and pyrrolobenzezapine derivatives as 5-HT2A inhibiters and found 5 potent novel 5-HT2A inhibitors. kNN-MFA methodology with simulating annealing was used for the model building. The selected best QSAR model has training set of 17 molecules and test set of 4 molecules. They reported significant values of the cross-validated correlation q2 (0.77) and the fitted correlation r^2 (0.95).

CONCLUSION

A QSAR model using pKi values for eleven known Olanzapine derivatives binding with 5-HT_{2A} receptor as dependent variable and six energy based descriptors independent variable had correlation coefficient r^2 value 0.86. This study may be useful in predicting the bioactivity of newly design inhibitors of 5-HT_{2A} receptors.

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