

QSAR modeling and docking analysis of D2 receptor with known olanzapine derivatives

Kiran Bhargava^{1*}, Prahlad Kishore Seth², Kamlesh Kumar Pant¹, Rakesh Kumar Dixit¹, Vivek Agarwal³, Kamal Kumar Sawlanid¹ & Rajendra Nath¹

¹Department of Pharmacology and Therapeutics, ²Biotech Park, Lucknow, ³Department of psychiatry, ⁴Department of Medicine, King George's Medical University Erstwhile CSMMU, Lucknow, UP, India; Kiren Bhargava - Email: kbhargavaphd@gmail.com; *Corresponding author

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Abstract:

Dopamine (D2) receptors are known drug targets for various antipsychotics used in Schizophrenia. Therefore, it is of interest to analyze the binding features of D2 receptors with known olanzapine derivatives for further consideration using molecular docking and QSAR analysis. A 2D QSAR model was built using energy-based descriptors generated by docking as independent variable and known K_i value of Olanzapine derivatives with D2 Receptor as dependent variable. QSAR model provided coefficient of determination of r^2 of 0.7 in multiple linear regression analysis. The predictive performance of QSAR model was assessed using different cross-validation procedures. Thus, data shows that a ligand-receptor binding interaction for D2 Receptor using a QSAR model is promising approach to design novel and potent inhibitors of D2 Receptor.

Keywords: Schizophrenia; Olanzapine derivatives; D2 receptor; QSAR, Antipsychotic agents.

Background:

In today world, mental disorders have become highly prevalent because of numerous reasons like urbanization, ambitious lifestyle and stressful environment [1]. A mental disorder is health conditions involving changes a person's normal thinking, feelings, mood, behaviour and that causes difficulty in person functioning. The majority of the people don't know that they are experiencing the side effects of mental issue on the grounds that in the underlying stage the side effects is mild and later on it become a serious mental disorder. Schizophrenia is a mental disorder characterized by distortions in thinking, perception, feels, behaviour and sense of self. People with schizophrenia often have problems doing well in society, at work, at school, and seeing someone [2]. They may feel alarmed and pulled back, and could seem to have put some distance with reality. Schizophrenia can't be cured but can be controlled with proper treatment. People with schizophrenia are 2-3 times more likely to die at a younger age than the normal one [3].

Worldwide, Schizophrenia affecting 20 million people [2] and is described in terms of positive and negative symptoms. Characteristics of schizophrenia typically include hallucinations or delusions as positive symptoms and negative symptoms as poverty of speech and impairments in cognition. Schizophrenia etiology shows that numerous variables are included, in particular genetic factors [4, 5] changes in chemical transmission [6], obstetrical complications [7] and viral Infections [8]. The prevalence of schizophrenia approaches 1% worldwide. The incidence is about 1.5 per 10,000 people [9].

The patho mechanism of schizophrenia is not fully understood and current antipsychotics had side effects. Second line antipsychotics treat mainly positive symptoms but negative and cognitive symptoms remain untreated [10]. D2 receptors [11] are widely expressed in the human brain and are very important from a

pharmacological point of view, as they constitute the target site of many centrally acting drugs. Therefore, it is of interest to analyze the binding features of D2 receptors with known olanzapine derivatives for further consideration using molecular docking and QSAR analysis.

Methodology:**Receptor and ligands preparation**

The 3D model structure of D2 receptor from *Homo sapiens* was retrieved from our previous published paper [12] for docking studies. Olanzapine and its derivatives with known K_i were obtained from literature [13]. Derivatives were building using PubChem Sketcher V2.4 [14] and after converted in 3D structures CORINA tool. All the ligands were subjected to energy minimization using the HyperChem software [15].

Molecular docking

Molecular docking is convenient tool utilized in the drug discovery process to investigate the binding compatibility of ligands to receptor [16]. Olanzapine and its 11 derivatives screened from literature against D2 Receptor structure was done by molecular docking program AutoDock 4.2 [17]. The Lamarckian genetic algorithm implemented in Autodock was used for docking process.

2D QSAR

A QSAR based model was developed using inhibitory activities of Olanzapine and its derivatives with D2 receptor represented as pK_i values and six types of energy value such as Binding Energy (BE), Intermolecular Energy (IME), Internal Energy (IE), Torsional Energy (TorE), vdW + Hbond + desolv Energy (VdwE) and electrostatic energy (EE) as descriptors. Several cross-validation systems were adopted to evaluate the predictive performance of the QSAR model.

Table 1: Olanzapine and its derivatives of D2 receptor based on different R1, R2, R3 and R4 group.

Compounds	Groups	R1	R2	R3	R4
Olanzapine		Methyl	Hydrogen	Methyl	Hydrogen
Olanza1		Ethyl	Hydrogen	Methyl	Hydrogen
Olanza2		Methyl	Methyl	Methyl	Hydrogen
Olanza3		Methyl	Isopropyl	Methyl	Hydrogen
Olanza4		Methyl	isobutyl	Methyl	Hydrogen
Olanza5		Methyl	Hydrogen	Methyl	Methyl
Olanza6		C6H5	Hydrogen	Methyl	Hydrogen
Olanza7		Methyl	Hydrogen	Ethyl	Hydrogen
Olanza8		Methyl	Hydrogen	Isopropyl	Hydrogen
Olanza 9		Methyl	Hydrogen	Fluoromethyl	Hydrogen
Olanza10		Methyl	Hydrogen	Chloromethyl	Hydrogen
Olanza11		Methyl	Hydrogen	Hydroxymethyl	Hydrogen

Table 2: Docking results of Olanzapine derivatives with D2 receptor structure with activity ($pK_i = -\log pK_i$).

Compound	Experimental pK_i	Predicted pK_i	BE	IME	IE	TorE	VdwE	EE
Olanzapine	7.46	7.12	-6.95	-7.24	-0.36	0.3	-6.68	-0.56
Olanza1	7.16	7.06	-7.27	-7.87	-0.56	0.6	-7.26	-0.61
Olanza2	7.52	7.69	-7.04	-7.34	0.5	0.3	-6.85	-0.5
Olanza3	7.46	7.41	-6.91	-7.8	0.21	0.89	-7.41	-0.39
Olanza4	7.46	7.27	-7.18	-8.08	0.02	0.89	-7.57	-0.51
Olanza5	6.48	6.65	-7.09	-7.39	-0.49	0.3	-6.85	-0.53
Olanza6	7.14	7.15	18.29	17.7	0.57	0.6	17.15	0.55
Olanza7	6.94	6.9	-2.99	-3.59	-0.4	0.6	-4.25	0.66
Olanza8	6.86	7.1	-7.43	-8.32	-0.57	0.89	-8	-0.32
Olanza9	7.06	7.2	-6.63	-7.22	-0.43	0.6	-6.55	-0.67
Olanza10	7.06	7.04	-7.18	-7.78	-0.57	0.6	-7.26	-0.52
Olanza11	6.58	7.51	-6.87	-7.76	-0.39	0.89	-7.38	-0.39

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

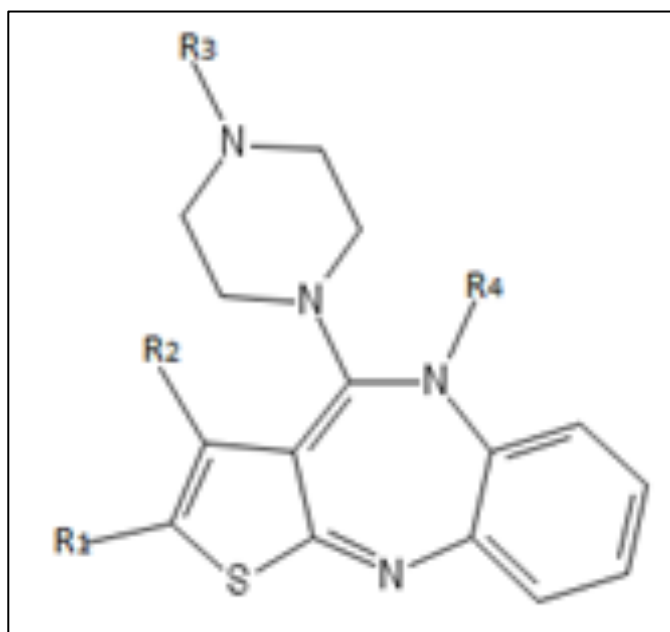


Figure 1: Olanzapine derivatives

Results & Discussion:

Olanzapine and its derivatives based on R1, R2, R3 and R4 groups in figure 1 at different positions was shown in table 1. Molecular docking study was carried out between Olanzapine derivatives and D2 receptor structure and best autodock score was used as criteria to interpret the best conformation among the 30 conformations, generated by AutoDock 4.2 program. Model structure of D2 receptor was shown in figure 2. All the derivatives were found to inhibit the receptor by occupying the active sites of D2 receptor. For

target protein, binding affinity values for all the compounds range from -2.99 to -7.43 kcal/mol as reported in Table 2.

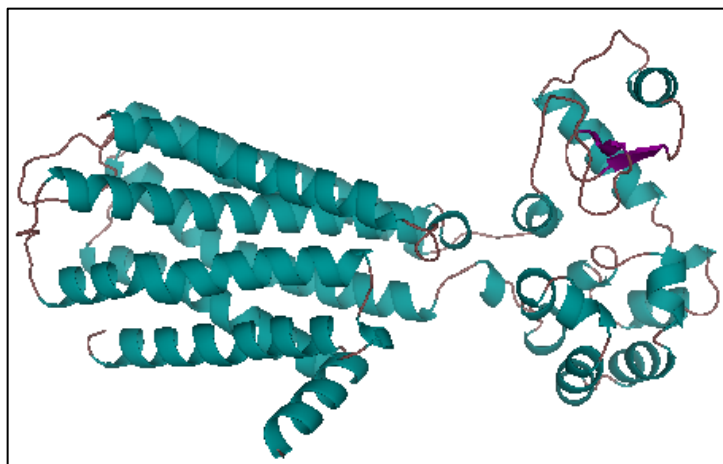


Figure 2: Model structure of D2 receptor

QSAR was performed to investigate the structure-activity relationship of Olanzapine derivatives as potent antipsychotics agents. A correlation coefficient (r^2) of 0.70283 was obtained for Olanzapine derivatives as shown below in equation 1.

$$\text{Predicted } pK_i = 6.929778 - 8.79967 (\text{BE}) + 41.70653 (\text{IME}) + 0.390359 (\text{IE}) + 9.09406 \rightarrow (1) \\ (\text{TorE}) - 32.9176 (\text{VdwE}) - 33.06 (\text{EE})$$

Experimental and predicted activities for Olanzapine derivatives were shown in Table 1. The low residual value between experimental and predicted activity indicates that the model is of high predictability. Relationship between experimental and predicted pK_i values of Olanzapine derivatives was shown in figure 3.

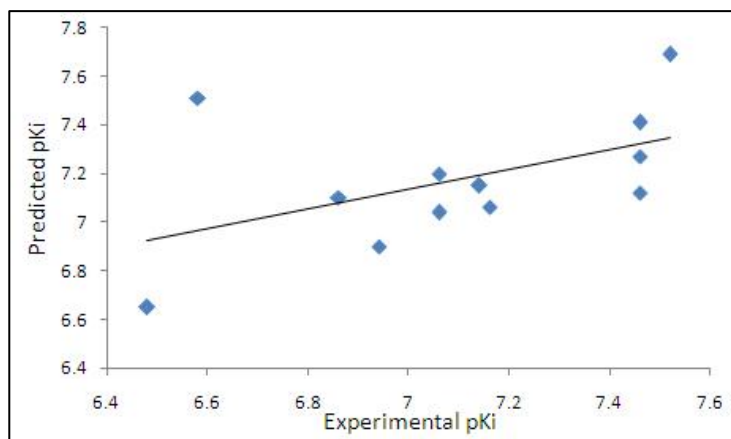


Figure 3: Relationship between experimental (x-axis) and predicted (y-axis) pK_i values with an r^2 value 0.70283 is shown in a QSAR model developed using multiple linear regression analysis.

The key accomplishment of the Quantitative structure-movement relationship (QSAR) strategy is the likelihood to anticipate the properties of new compound without the need to synthesize and test them. This strategy is comprehensively used for the prediction of physicochemical properties in the compound in pharmaceutical industry [18]. A lot of research works reported treatment of schizophrenia based on dopamine (D2) receptor as drug target. Such as de Haan et al., reported a level of D2 receptor occupancy between 60% and 70% is optimal for subjective experience of patients with recent-onset schizophrenia. A considerable interindividual variation in occupancy was resulted at fixed low level dose of olanzapine and haloperidol compounds [19]. Lavalaye et al., assessed striatal dopamine D2 receptor occupancy by olanzapine and risperidone in young patients with first episode schizophrenia and found that both drugs induce a high occupancy, depending on dose as well as group formation [20]. A selective antagonist (JNJ-37822681) of D2 receptor treatment in patients of schizophrenia was connected with more favorable results on weight and metabolic adverse effects compare to olanzapine [21]

Conclusion:

A QSAR model was developed using K_i value of known olanzapine derivatives with the D2 receptor as dependent variable. The six energy based descriptors namely binding energy, intermolecular energy, internal energy, torsion energy, vdW + H bond + desolv energy and electrostatic energy as independent variable. The coefficient of determination r^2 is 0.7. Thus, we document the QSAR modelling and docking analysis of D2 receptor with known olanzapine derivatives for further consideration.

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Conflict of interest:

The authors declare that they have no conflict of interest.

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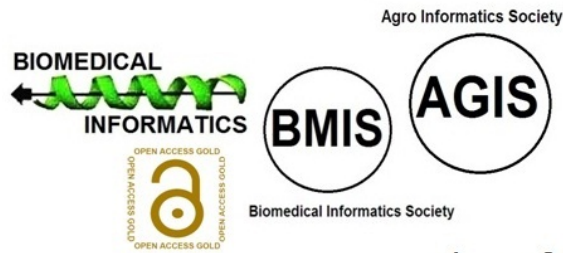
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