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3D QSAR, PHARMACOPHORE INDENTIFICATION STUDIES ON SERIES OF INDOLE DERIVATIVES AS DOPAMINE ANTAGONIST

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ABSTRACT

Dopamine receptors are of particular importance in the pathophysiology of CNS disorders and thus, serve as promising target proteins for the discovery of new chemical entities. For this purpose quantitative structure activity relationship (QSAR) modelling has been traditionally applied as an evaluative approach, with the focus on developing retrospective and explanatory models of existing data. To obtain a more detailed insight into the structure activity relationship for reported Dopamine D_2 antagonist, pharmacophore was identified through molecular alignment and employed in three-dimensional (3D) QSAR studies. 3D QSAR model developed considering training and test set approaches with step wise variable selection method. QSAR models which were further validated for statistical significance and predictive ability by internal and external validation. The selected best QSAR model A has training set of 18 molecules and test set of 9 molecules with the correlation coefficient of 0.9670. The predictive power of the derived model was demonstrated to be very high. Graphical interpretation of the results brings to the light, important structural features of the compound related to either low or high-affinity dopamine antagonism. Electrostatically favourable and unfavourable regions were identified. The results of the 3D QSAR studies indicate that bulky N-substituents decrease D_2 binding. Electrostatically favourable and unfavourable regions exclusive to D_2 receptor binding were identified. These observations may be exploited for the design of novel dopamine D_2 antagonists.

Keywords: Dopamine, D_2 receptor, 3D QSAR, PLS

INTRODUCTION

Alterations in dopaminergic function have found to be involved in a number of central nervous system (CNS) disorders. The dopamine function can be achieved through several mechanisms including direct receptor activation by agonist, partial agonist or antagonist such as benzodiazepines as anticonvulsants, Clozapine as antidepressants and Amisulpride as antipsychotics. These drugs act on specific family of dopamine receptors such as D_1- like (D_1 and D_5) and D_2-like (D_2, D_3 and D_4). The majority of the antipsychotic drugs are nonselective dopamine D_2 receptor antagonist.[1-8] To find novel D_2 receptor antagonist, computational studies are applied with the focus on developing retrospective and explanatory models of existing data with the help of Quantitative structure-activity (QSAR) method.[9-13] The goal of QSAR is to transform searches for compounds with desired

properties using chemical knowledge and express into a mathematically quantified form. Once a correlation between structure and activity is found, novel compounds with desired properties can be synthesised. The Partial least squares (PLS) regression is an extension of the multiple linear regression models.[14-18] We report the indentified pharmacophore using the existing data and 3D-QSAR studies using PLS method on training set of Indole derivatives as D_2 antagonist by considering the steric and electrostatic influences. The model derived from this investigation having high predictive ability, which could aid new D_2 antagonist prior to their synthesis.

Computational Details

Dataset

To obtain an equation a dataset of 28 compounds was taken from the published D_2 antagonist by Grundt et.al.[19] The structures and their D_2 antagonist activities are listed in table 1. The whole dataset was randomly divided into a training set of 18 compounds and a test set 9 of compounds. The training set was used to construct 3D-QSAR models and the test set was used for the models validation.

MATERIALS AND METHODS

Ligand Preparation

The template of indole was used to build the molecules in the dataset in Vlife MDS 4.1. All structures were minimized using the standard Merck molecular force field (MMFF) with distance dependant dielectric function and energy gradient of 0.001kcal/molÅ.

Molecular Alignment

The molecules of the dataset were aligned by the template based technique, using common structure of indole. The alignment of all the molecules on the template is shown in figure 2.

Descriptor Calculation

Like many 3D QSAR methods, a suitable alignment of given set of molecules was performed using the Vlife MDS 4.1 Engine. This was followed by generation of a common rectangular grid around the molecules. The hydrophilic, steric and electrostatic interaction energies which are computed at the lattice points of the grid using a methyl probe of charge +1.

3D QSAR Studies Using PLS Regression

A relationship between independent and dependent variables (3D fields and biological activities, respectively) were determined statistically using regression analysis. Linear regression is achieved by fitting a best-fit straight line to the data using the least squares method. The quality of fit for a regression equation was assessed relative to its correlation coefficient and standard deviation. The F value represents the level of statistical significance of the regression. Quality of selected models was further ascertained to select the best model from cross-validated squared correlation coefficient (q^2). For a regression model, r^2 was used to describe the fitness of data and fitness is considered to improve as r^2 approaches 1. Thus models having correlation coefficient above 0.9 were used to check the external predictivity while the significance of the model was decided on the basis of F value. Models showing q^2 below 0.7 were discarded. The selected models are shown in table 2.

Pharmacophore Modeling

Pharmacophore modeling was carried out using the mol sign module of Vlife MDS 4.1 software. Series of D_2 antagonist were first aligned on the active molecule. The software was set to generate minimum 4 pharmacophoric features obtained keeping the tolerance limit at 10 Å.

RESULT AND DISCUSSION

In the present study, 18 molecules were used in the training set (table 1) to derive 3D QSAR models with the number of field grid points being not more than five per model. To evaluate the predictive ability of generated 3D-QSAR models, and test set of 9 molecules with regularly distributed biological activities was used (table 1). On successful run of PLS two models were selected they are shown in table 2. The optimum structural properties of indole analogues for D_2 antagonist were obtained in the form of the 3D descriptors of model A. The r^2 value for model A was 0.9670 while that of model B was 0.9101.

Model A shows the first model which is selected on the basis of statistical coefficient like r^2 (0.9670). The contributing descriptor for model A are S_1587, S_1488, E_450, E_1366 which are nothing but the steric interaction (S) and electrostatic (E) at that lattice point. The derivatives which are having the halogen substitution on the aryl ring attached to amide bridge are showing more activity than other derivatives. The Electrostatic and steric interaction at the lattice point E_450, E_1366 S_1587, S_1488 are positively contributing. So the substitution favouring this interaction at that lattice point could yield active molecule.

A set of pharmacophore hypothesis was generated using the mole sign module of V life MDS 4.1 on the reported D_2 antagonist. Each hypothesis was found to contain common features like hydrogen bond acceptor, positive ionisable, aliphatic and aromatic.

The pharmacophore hypothesis generated in V life MDS 4.1 (figure 5) indicated the significance of presence of two aromatic features for the D_2 antagonist, these features are contributed by the Indole nucleus. The positive ionizable is also important feature for D_2 antagonist, in present data set of piperidine substituted at 3rd position in indole.

CONCLUSION

The present communication is an attempt to indentify the structural requirement of Indole analogs for D_2 antagonist. The pharmacophoric requirement of D_2 antagonist are also been identified by the generation of two different hypothesis, having similar results. Thus the model A derived from this investigation having good predictive ability, which could yield novel D_2 antagonist prior to their synthesis.

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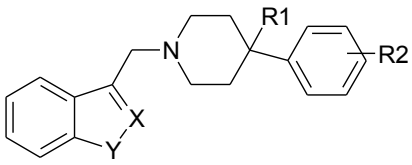


Table 1: Showing derivatives under study with observed and predicted activity

Sr. No.	Compound code	X-Y	R1	R2	Observed activity	Predicted activity
1.	5	CH-NH	OH	2'-Cl	382	382.2
2.	6	CH-NH	OH	2',3'-Cl	26.1	26.2
3.	7	CH-NH	OH	3'-Cl	129	129.2
4.	8	CH-NH	OH	3',4'-Cl	6.9	6.91
5.	9	CH-NH	OH	3'-CF_3	106	105.9
6.	10	CH-NH	OH	4'-F	127	126.1
7.	11	CH-NH	OH	4'-OH	5360	5361.2
8.	12	CH-NH	OH	4'-OMe	177	177.3
9.	13	CH-NH	OH	4'-OHex	159	159.4
10.	14	CH-NH	OH	4'-Ph	98.4	98.3
11.	18	CH-NH	Me	4'-Cl	992	992.1
12.	19	CH-NH	NH_2	4'-Cl	184	184.2
13.	20	CH-NH	NHAc	4'-Cl	83.1	83.2
14.	21	CH-NH	F	4'-Cl	120	120.5

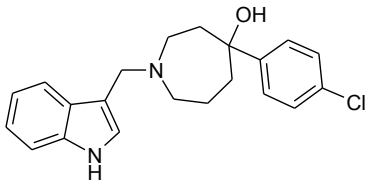
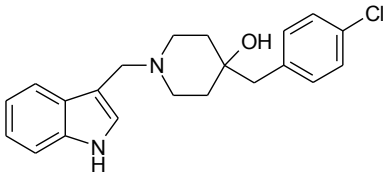
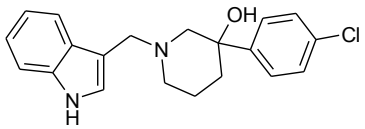
15.	22	CH-NH	CN	4'-Cl	199	199.1
16.	23	CH-NH	COOMe	4'-Cl	60	60.2
17.	24	CH-NH	COOEt	4'-Cl	58.8	58.8
18.	25	CH-NH	CH_2NH_2	4'-Cl	10000	10000
19.	26	CH-NH	CH_2NHAc	4'-Cl	2000	2000
20.	27	CH-NH	CH_2OH	4'-Cl	2370	2370
21.	28	CH-NH	OMe	4'-Cl	68.1	68.1
22.	29	CH-NH	OAllyl	4'-Cl	165	165
23.	30	CMe-NH	OH	4'-Cl	15.4	15.4
24.	31	N-NH	OH	3',4'-Cl	438	438
25.	32	N-NH	OH	4'-Cl	548	548
26.	15				201	199.1
27.	16				2890	2891.1
28.	17				4265	4266.2

Table 2: Showing the selected MLR QSAR equations along with statistical parameters employed for model selection

Model No.	QSAR model	N	r^2	q^2	F value
A	Ki= 3459.7 E_450 + 1523.81 S_1587 + 17.05 S_1488 + 24.83 E_1366 – 1.14	18	0.9670	0.9391	95.09
B	Ki = -5623.06 E_2047 + 475.19 E_1464 -6669.80 E_1000 - 1338.24 E_1343 + 542.92	20	0.9101	0.7162	37.97

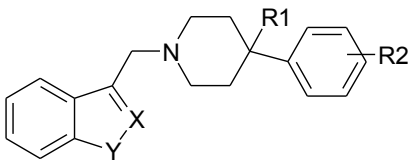


Figure 1: Showing molecules under study

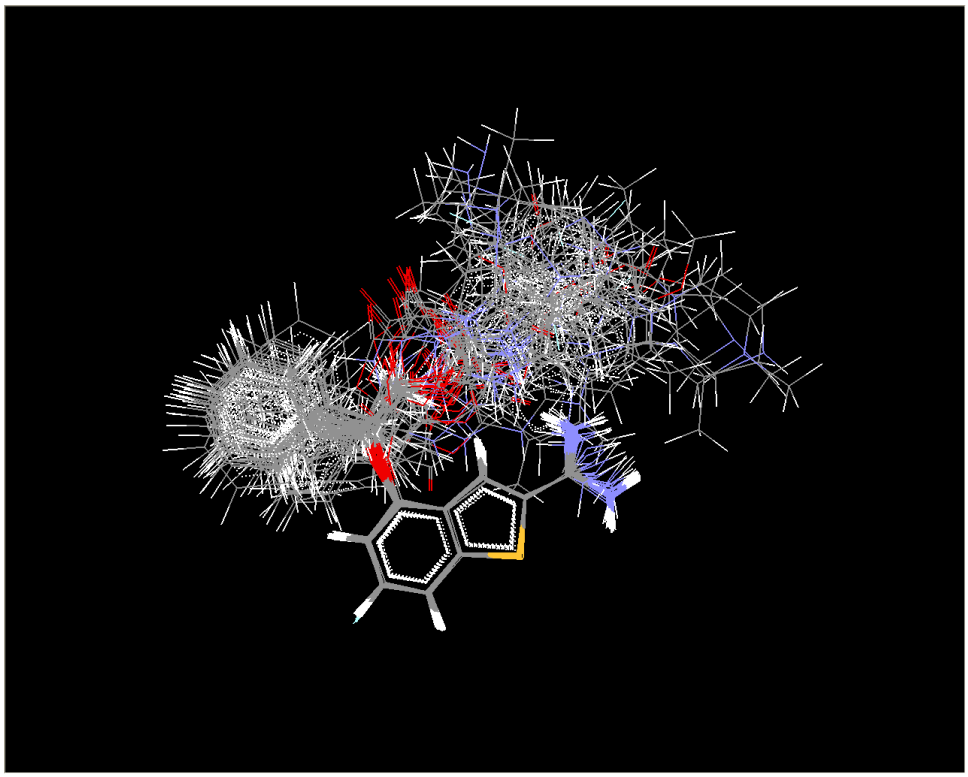


Figure 2: Showing the alignment of the molecules

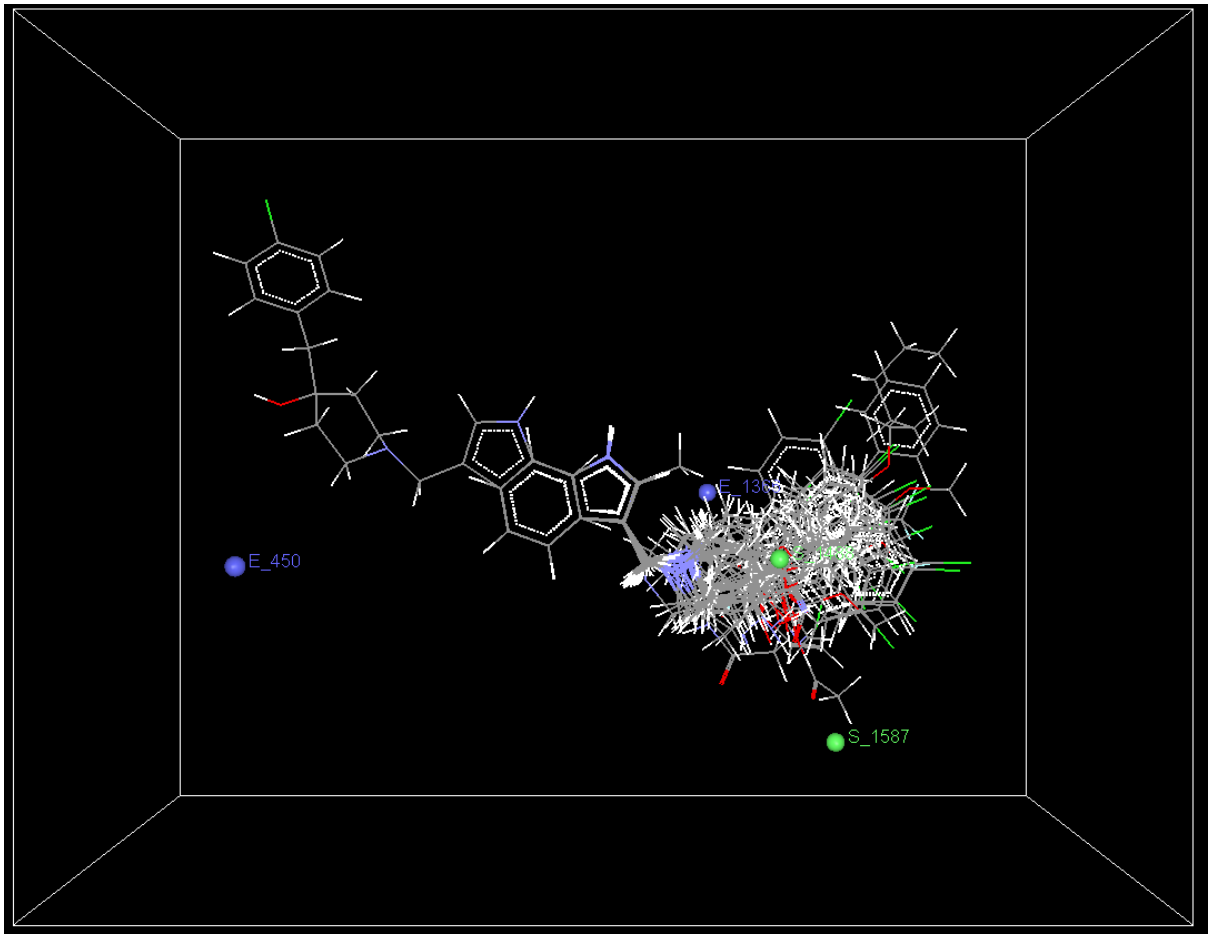


Figure 3: showing the field point of selected QSAR model A

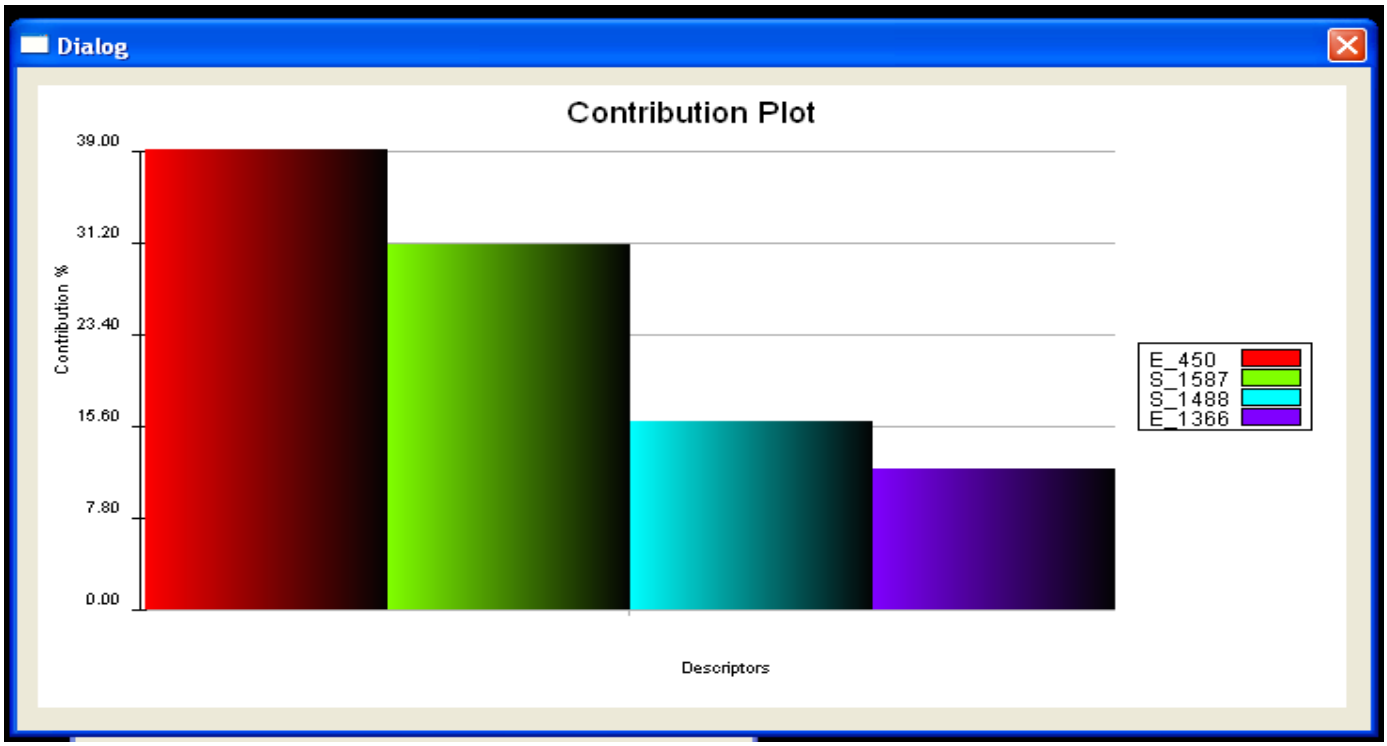


Figure 4: Showing contribution plot for selected QSAR model A

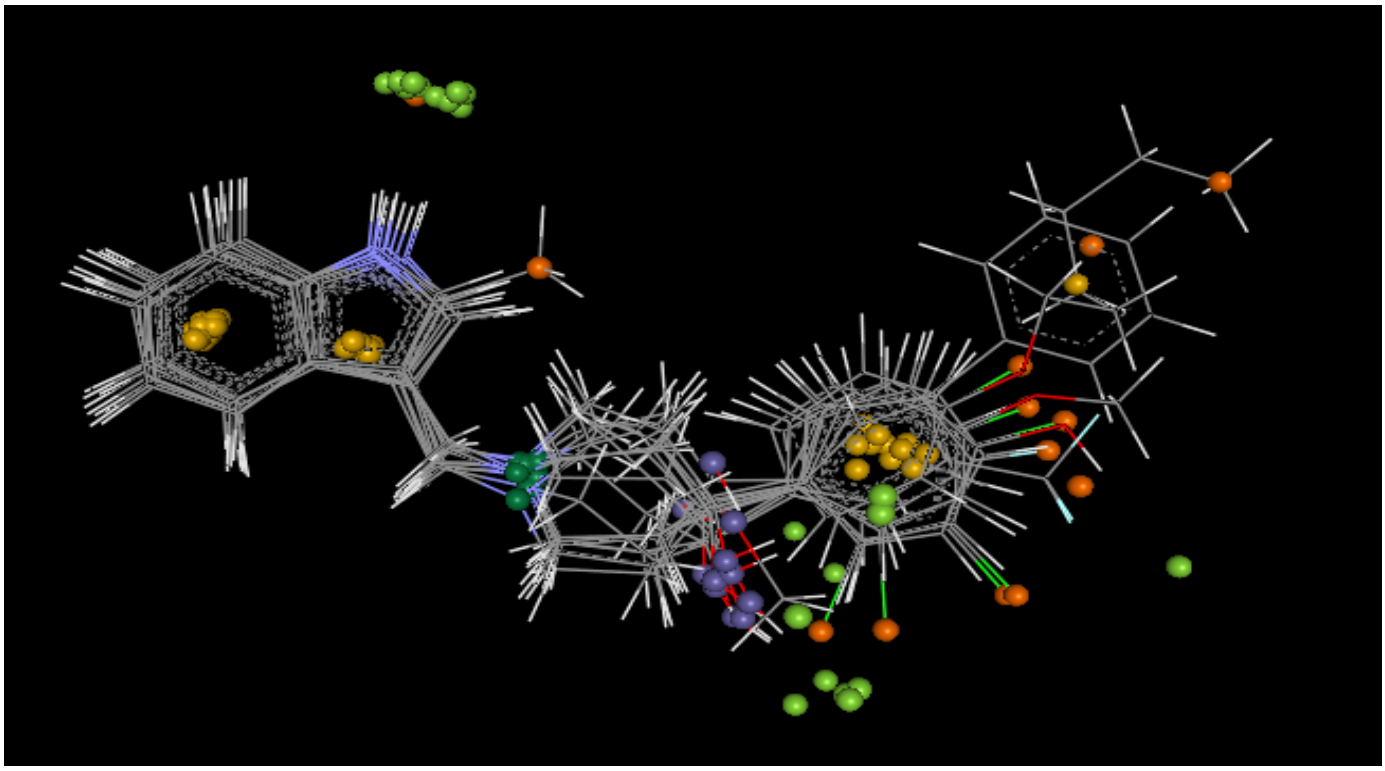


Figure 5: Showing selected pharmacophore model generated through Vlife MDS 4.1

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