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QSAR STUDIES IN 2-(5-BROMO-2, 3-DIMETHOXYPHENYL)-5-(AMINOMETHYL)-1H-PYRROLE ANALOGUES FOR THEIR BINDING AFFINITY AT D_2 AND D_3 RECEPTORS

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Research Article

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ABSTRACT

QSAR studies have been performed on thirty molecules of 2-(5-bromo-2,3-dimethoxyphenyl)-5-(aminomethyl)-1H-pyrrole analogues for identifying important physicochemical properties responsible for their binding affinity towards dopamine receptors (D_2 and D_3). All derived models display satisfactory fits to the experimental data (r>0.7) and have high statistical significance >99.9% for D_2 and >99.8% for D_3 subtype. Examinations of several statistically significant equations for both D_2 and D_3 receptors indicates that lipophilicity, molecular refractivity, indicator parameter, volume and hydration energy are important variance in the training and external test set

KEYWORDS: *QSAR, dopamine receptors, physicochemical parameters*

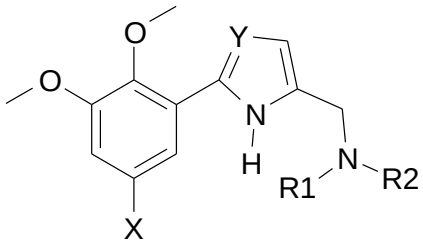
INTRODUCTION

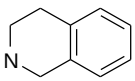
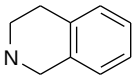
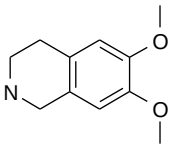
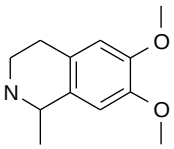
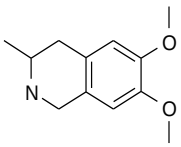
Dopamine receptors belong to the superfamily of seven transmembrane domain G-protein-coupled receptors[1,2]. Dopaminergic system and their associated receptors are important in modulating motor, endocrine, and emotional functions. Furthermore, both DA neuron and receptors are markedly reduced by normal aging and Parkinson's disease and have been implicated in a variety of other disorders, including schizophrenia and drug abuse[3-6]. There are two major pharmacological classes of receptors, that mediate dopaminergic neurotransmission, Dopamine D_1 like (D_1, D_5) and D_2 like (D_2, D_3, D_4) receptors[7-8]. Agonist stimulation of D_1 like receptors causes an increase in adenyl cyclase whereas activation of the D_2 like receptors results in an inhibition[9,10]. Dopamine antagonist have been of current interest because of their use in the treatment of neurological disorders particularly schizophrenia. The antipsychotic effects of neuroleptics are thought to be due to their action on the D_2 like receptors in the mesolimbic system, whereas extra-pyramidal side effects are thought to result from blockage of D_2 receptor in the striatum. The localization of D_3 receptor in limbic region of brain suggests that this receptor may be a target for the development of antipsychotic agents with reduced risk of extra-pyramidal side effects[11,12]. Therefore, the accurate determination of QSAR information concerning drug properties at DA receptors has great clinical significance[13]. QSAR has been a very useful tool in designing libraries of various ligands targeted towards particular receptors and to ensure the increase in probability of synthesizing therapeutically active drug[14-16]. Various DA ligands with different structural motifs have been designed and synthesized in order to develop specificity

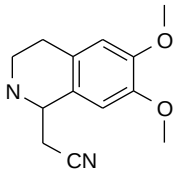
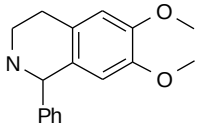
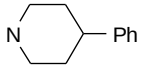
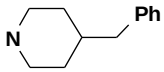
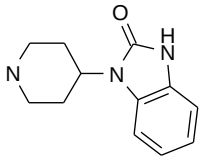
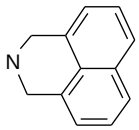
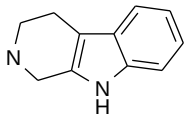
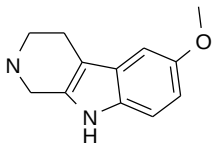
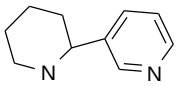
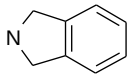
and potency. Robarge et al have reported piperazine analogs with good specificity for D_3 receptor subtype. Wittig et al developed D_5 specific heterocycles. A pyrazolopyridine analogs have been reported as complete D4 antagonist. Some highly potent D_3 analogs have been developed by systematic modification of benzothiophene nucleus. The pyrole analogs have been reported as potent dopamine receptor analogs. Since a few QSAR studies have been reported on pyroles as dopamine analogs. Therefore, to understand the influence of physicochemical and structural properties of pyrrole analogs (**Table 1**) for dopaminergic binding affinity and selectivity, 2D-QSAR studies have been carried out on 2-(5-Bromo-2,3-dimethoxyphenyl)-5-(aminomethyl)-1H pyroles[17,18] and the results are presented in this paper.

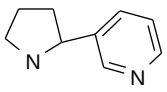
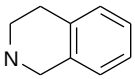
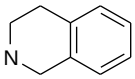
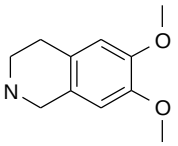
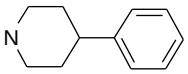
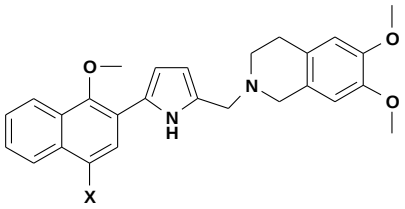
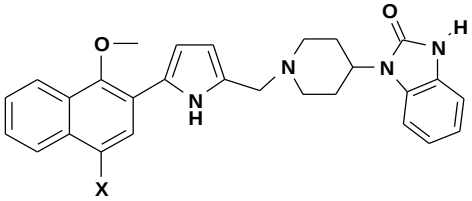
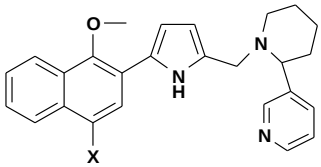
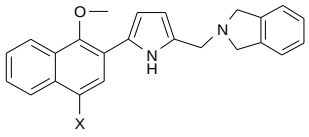
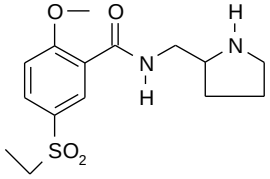
Table 1

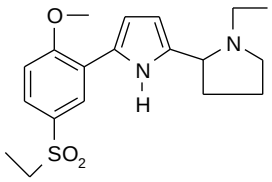
Structures and activity data (nM) for compounds of training set[a].



Compounds	Substituent			Binding affinity (nM)	
	X	**Y**	**NR1R2**	**D2**	D3
1.	H	CH		44.6	**99.4**
2.	Br	CH		29.5	**3.8**
3.	Br	CH		33.4	**3.9**
4.	Br	CH		26.3	**23.8**
5.	Br	CH		26.2	**8.6**

6.	Br	CH		373	**1560**
7.	Br	CH		6.6	**0.6**
8.	Br	CH		51.2	**12**
9.	Br	CH		13920	**5425**
10.	Br	CH		19	**1.9**
11.	Br	CH		10.9	**5.4**
12.	Br	CH		22.3	**14.1**
13.	Br	CH		27.8	**2.6**
14.	Br	CH		135	**98.4**
15.	Br	CH		31.5	**21**
16.	Br	CH		34.4	**14.5**
17.	Br	CH		86.8	**4.3**
18.	Br	CH		17.4	**1.7**

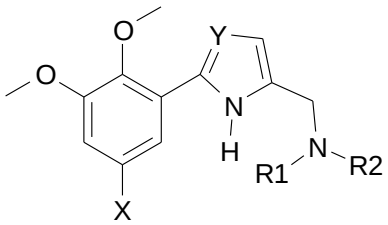
19.	Br	CH		169.1	**21.9**
20.	H	N		315.5	**664**
21.	Br	N		78.2	**23.8**
22.	Br	N		143	**21.2**
23.	Br	N		11.9	**10.8**
24.	Br	N		15.7	**40.5**
25.				303	**59.5**
26.				253	**20.1**
27.				354.2	**27.5**
28.				198.7	**35.2**
29.				6.3	**6.3**

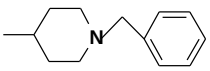
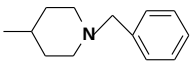
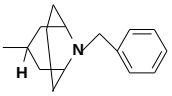
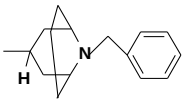
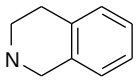
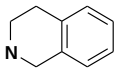
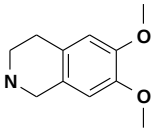
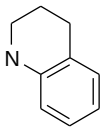
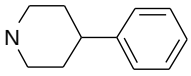
30.		25	5

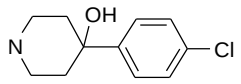
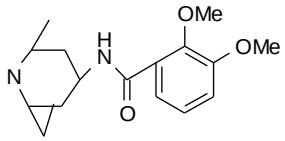
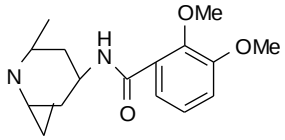
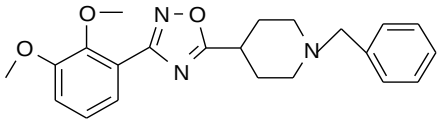
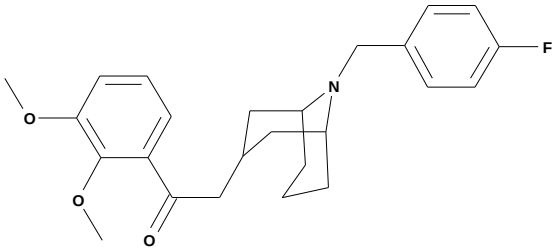
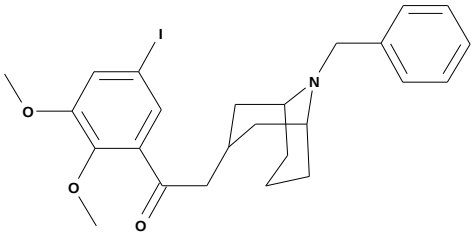
MATERIAL AND METHODS

The molecules of the series were drawn in Hyperchem, partial charges were calculated and geometry was minimized using steepest descent (Fletcher-Powell) followed by conjugate gradient (Polak-Ribiere) algorithm using MM2 force field. The molecules thus optimized were submitted for parameter calculation such as hydrophobicity, hydration energy, polarizability, volume and surface area using Hyperchem. Some other parameters were also calculated manually using Hansch table according to binding mode and symmetry. The analysis was performed into two steps i). Generation of QSAR equations for training set compounds. ii). External validation of the generated QSAR models using eighteen test compounds. The physicochemical parameters Lipophilicity, molar refractivity (for D_3), indicator parameter, volume, surface area and hydration energy were taken as independent and binding affinity (K_i) was taken as dependant parameter for derivation of QSAR equations. Hyperchem version 6.01 for the windows was used for calculation of parameters. The multiparameter linear regression analysis was carried out using SYSTAT (version 7.0) software. As some of the compounds had substitution at 4th position of the piperazine ring, therefore indicator variable was included and found to influence the activity negatively for D2 subtype than D3 (eq.1, eq.2 and eq.3). All the physicochemical parameters for both training and test set are given in table 4 and table 5.

Table 5: Test set (Huang *et.al*) [18] to evaluate the prediction capabilities of the eq.2 (for D2) and eq.7 (for D3) with various physicochemical and structural parameters.



C.	Substitution			-log ki (D2)[a]	-log ki (D3)[b]	D2	D3
	X	R^1	R^2			Pd. by eq.2[c]	pd. by eq.7[d]
1	H	Me	Benzyl	-0.96	-1.04	-2.4	-2.6
2	Br	Et	Et	-1.9	-1.95	-1.44	-1.1
3	H	H		-3.24	-3.23	-2.62	-2.1
4	Br	H		-2.45	-2.05	-2.64	-1.8
5	H	H		-2.9	-3.11	-1.65	-0.14
6	Br	H		-2.38	-2.16	-1.86	-2.0
		NR1R2					
7	H			-2.49	-2.82	-2.32	-2.5
8	Br			-1.9	-1.37	-2.4	-1.6
9	Br			-2.15	-1.32	-2.43	-1.25
10	Br			-2.6	-	-2.8	-
11	Br			-1.07	-1.03	-1.12	-1.61
12	Br			-1.19	-1.60	-1.7	-1.11

13	Br		-1.15	-1.56	-2.7	-2.5
14	H		-1.6	-1.76	-1.16	-0.35
15	Br		-1.8	-2.16	-1.13	-1.23
16			-2.77	-3.16	-3.1	-3.9
17			1.3	1.39	0.86	-1.3
18			0.69	0.39	1.3	-2.3

[a]*binding affinity data for D2 receptor,* [b]*binding affinity data for D3 receptor,* [c]*Pridicted activity via eq. 2,* [d]*Pridicted activity via eq. 7*

RESULTS AND DISCUSSION

Various physico-chemical descriptors such as lipophilicity, molar refractivity, indicator parameter, volume, surface area and hydration energy etc. were calculated using the software Hyperchem. The multiparameter regression analysis using the software Systat was carried out to correlate D2 and D3 binding affinity with the calculated physicochemical descriptors. Most of the descriptors showed reasonable correlations (r>0.4) with biological activity (**Table 2**).

Table 2:
Correlation matrix for intercorrelation among different physicochemical and structural parameters

	MR	π	π2	P	HE	In	SA	V	MR2	-log (D2)	log Pki (D3)
MR	1.0										
π	0.45	1.0									
π2	0.43	0.97	1.0								
P	0.99	0.47	0.47	1.0							
HE	-0.62	-.062	-.01	-0.61	1.0						
In	-0.06	-0.18	-0.03	-0.06	-0.11	1.0					
SA	0.56	0.08	0.07	0..50	-0.60	-0.10	1.0				
V	0.93	0.45	0.42	0.94	-0.71	-0.14	0.77	1.0			
MR2	0.99	0.52	0.50	0.98	-0.60	-0.47	0.57	0.92	1.0		
-log (D2)	-0.44	-0.41	-0.50	-0.47	0.43	-0.42	-0.04	-0.34	-0.43	1.0	
-log (D3)	-0.32	-0.36	-0.41	-0.34	-0.40	-0.22	-0.03	-0.26	-0.32		1.0

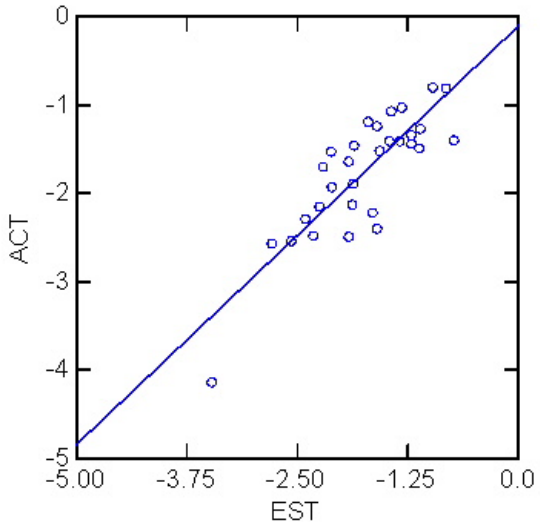
A no. of generated QSAR equations showed good correlation (r>0.75) of high statistical significance (eq. 1-8) (Table 3).

Table 3: Statistical significant equations obtained for both D2 and D3

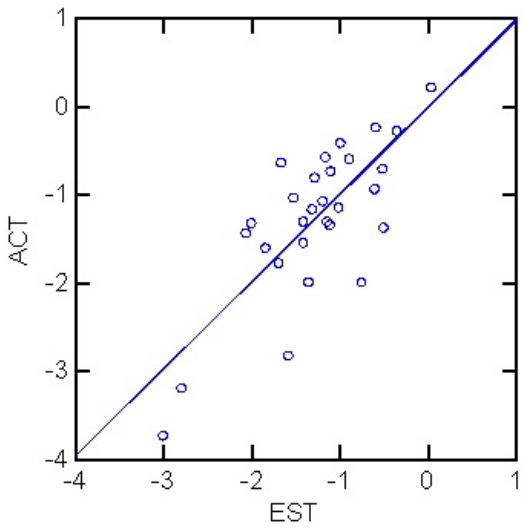
E.	Regression equations	n	r	S	f
1.	-log Ki (for D2) = 0.367 (±0.081) HE-0.565 (±0.180) In + 0.003 (±0.001) V – 0.264 (±0.07) $(\pi)^2$ + 0.88 (±0.40) π -3.365 (±1.116)	30	0.854	0.4	12.8
2.	-log Ki = 0.290 (±0.092) HE-0.44 (±0.21) In + 0.002 (±0.001) V – 0.483 (±0.122) π -1.498 (±1.106)	30	0.773	0.48	9.30
3.	-log Ki (for D2) = 0.39 (±0.078) HE-0.634 (±0.178) In + 0.003 (±0.001) V – 0.313 (±0.080 $(\pi)^2$ + 1.19 (±0.43) π -3.548 (±1.079)	29	0.871	0.39	14.45
4.	-log Ki (for D2) = 0.44 (±0.095) HE + 0.004 (±0.001) V – 0.237 (±0.093) $(\pi)^2$ + 1.09 (±0.50) π - 4.190 (±1.2)	29	0.790	0.47	10.1
5.	-log Ki (for D3) = 0.557 (±0.121) HE- 0.292 (±0.11) π^2 + 0.93 (±0.60) π + 0.005 (±0.002) SA + 0.075 (±0.041) P -4.963 (±1.548)	30	0.760	0.60	6.60
6.	-log Ki (for D3) = 0.46 (±0.12) HE - 0.56 (±0.20) π + 0.005 (±0.003) SA + 0.062 (±0.045) P – 2.77 (±1.42)	30	0.700	0.67	5.40
7.	-log Ki (for D3) = 0.585 (±0.125) HE- 0.052 (±0.016) MR + 1.089 (±0.60) π - 0.353 (±0.116) π^2 – 4.9 (±1.55)	29	0.760	0.60	8.38

8.	-log Ki (for D3) = 0.581 (±0.123) HE- 0.338 (±0.116) π^2 + 1.134 (±0.605) π + 0.006 (±0.002)V – 5.439 (±1.698)	29	0.760	0.60	8.36

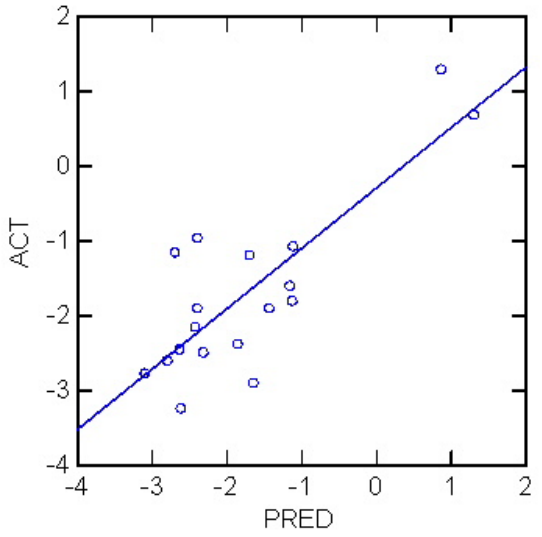
According to most of the equations table 3 lipophilicity was found to contribute positively in the determination of activity than MR. The parabolic model $logP^2$ fitted better than the linear log P (r=0.85) in defining activity. It indicates that the activity increases as π increases up to a certain point and decreases thereafter (Compare eq.1 and eq.2 for D2 and eq.5 and eq.6 for D3). These observations indicate that there is an optimum value for π required for pharmacological activity. This is reasonable as there is an optimum balance of lipophilicity and hydrophilicity to cross biological membranes. Hydration energy too requires attention as it is part of most of the significant equations and influence positively in favour of dopamine receptors binding affinity. Correlation matrix for intercorrelation among different physicochemical and structural parameters is given in Table 2. Critical inspection of the equations showed that is more important than MR in defining activity (see **plot 1 and 2 in fig. 1**).



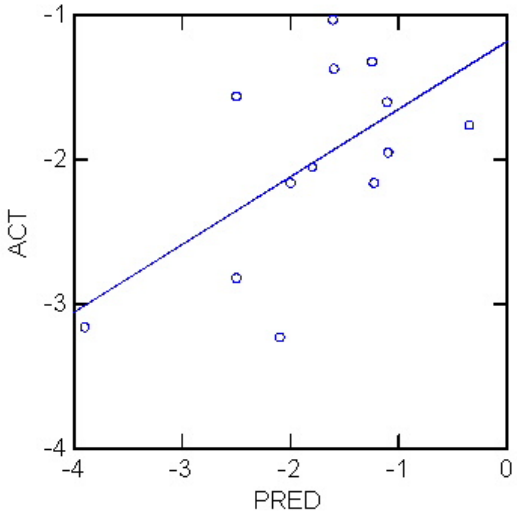
Plot 1



Plot 2



Plot 3



Plot 4

Figure 1: The plot of experimentally observed and estimated activity for D2 training set via equation 1 (Plot 1), for D3 training set via equation 7 (Plot 2). The plot of experimentally observed and predicted activity for D2 test set via equation 1 (plot3) and D3 test set via equation 7 (Plot 4).

Excluding the outliers (C. no.16 for D2 and C. no.15 for D3) resulted in decrease in the standard error significantly (more for D3), improved r-value (compare eq.1 and eq.3 for D2 and eq.5 and eq.7 for D3) with statistical significance more than 99.9% for D2 99.8% for D3 (F24, 5=12.9 for eq.1 and F23, 5=14.5 eq.3 for D2 and F24, 5=6.6 for eq.5 and F23, 4=8.3 for eq.7 for D3). In view of the earlier published work of the authors the test set of eighteen molecules having large variations in the biological activity with similar mode of binding and somewhat similar structural features was used to test the validity of the statistical significant equations. Equation 2 and equation 7 were used to predict the activity of D2 and D3 respectively. Critical observations of the results showed that prediction for D2 was quite good whereas for D3 it was satisfactory. Correlation coefficient r between observed and predicted activity is 0.74 for D2 and 0.6 for D3 receptor (after removing the outlier compounds 1,5,17 and 18; plot. 3 and 4 in fig.1). The reason for these observations may be the standard error in the generated equation itself, difference in the binding mode (D2 verses D3) and the high standard deviation in the biological data (more than 50% in most of the cases).

CONCLUSION

The MLR equations are statistically significant and they are also validated against an external data set and are predicting the activity quite well. Generally speaking the biological activity for D2 and D3 receptor antagonists depends largely on their lipophilicity as they have to cross blood brain barrier to reach the CNS. However this field requires further study in order to understand the

factors, which are prerequisite for good activity. Present study can serve as a useful tool for future development of new D2 and D3 receptor binding agents.

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