RESEARCH PAPER

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Binding of Phenylalkylamines at Serotonin Receptors: A Quantitative Analysis.

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A quantitative structure-activity relationship (QSAR) analysis of the binding activity data to the 5-HT1c and the 5-HT2 receptors for the congeneric series of phenylalkylamines was performed and the results thereof revealed that the pharmacophoric requirements for both are nearly similar with only likely difference at 5- position of the phenyl ring. Further, for both subtypes, moderately hydrophobic substituent at 4-ring and less bulky groups at X are predicted to cause enhancement in potency of the ligand. A substituents at 2-ring appears to have synergistic influence.
Key words: QSAR study, Phenylalkylamines, Serotonin receptors, Hydrophobic interaction, Van der Waals volume.

SEROTONIN (5-HT) has been shown to be a neurotransmitter involved in a wide range of pharmacological effects, and characterization of multiple 5-HT receptors has given impetus to the search for novel subtype-selective 5-HT ligands. The 5-HT subtype is most completely characterised due to the availability of more and more selective antagonists. With a view to drawing a distinction between the 5-HT2[1-3] and the 5HT1C[4] populations of 5- HT receptors, Glennon et al.[5] have examined 5-HT2 and 5- HT1C binding data of a series of phenylalkylamines shown in **Figure 1**. In this present study, a quantitative correlation between these binding data and appropriate structural and physicochemical parameters for the substituent as explaining variables are reported. The Hansch hydrophobic parameter[6], πa physicochemical parameter, and the van der Waals volume[7], Vw, a structural parameter, emerged as the best quantifying parameters for the present series. In a number of earlier studies too, these parameters have been found to correlate significantly with biological activities[8-12]. Multiple regression analysis (MRA) was used to obtain the best agreement between the observed data and the explaining variables.

***For Correspondence.**

RESULTS AND DISCUSSION

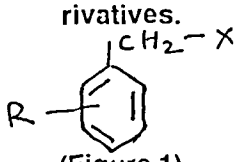
The binding affinity data, pKi, at the 5-HT2 and 5-HT1C receptors in **Table 1** were found to be mutually linearly correlated, $r^2 = 0.79$. The pKi data for the congeners included in this study were then separately correlated with π-values for the 4(para)-substituents, Vw for X substituent, and two dummy variables, I_2 and I_5 highlighting whether or not a substituent is present (I = 1 or 0 in that order) at the 2- or 5-position of the phenyl ring of ligand. The results of MRA are shown as Eq. (1) and (2).

$$pKi\ (5\text{-}HT1C) = 0.90(\pm0.12)\pi(p) + 0.94(\pm0.16)I_2 + 0.39\ (\pm0.15)I_5 - 3.52(\pm0.67)Vw(X) + 6.38$$

$$n = 29,\ R = 0.92,\ s = 0.37,\ EV = 0.82,\ F(4, 24) = 32.61 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ (1)$$

(Where n is data size, R, the multiple correlation coefficient, s, the standard error of estimates, EV, the explained variability, and F, the F-ratio between the variances of calculated to observed activities). Out of the compounds 1,2,6,19 and 27 with their uncertain activity values, only 19 showed outlier behaviour and was, therefore, not included in deriving Eq. (1). The

Table 1: Correlative parameters and observed and calculated binding data for phenylalkylamine derivatives.



(Figure 1)

S No.	X	R	Vw(X) (10^2A^3)	π(p)	I_2	I_3	pKi (M) (5-HT1C) Obsd[a]	pKi (M) (5-HT1C) Cald[b]	pKi (M) (5-HT2) Obsd[a]	pKi (M) (5-HT2) Cald[c]
1	$CH(Me)NH_2$	H	0.45	0.00	0	0	< 5.00	4.79	< 5.00	4.55
2	$CH(Me)NH_2$	4-Me	0.45	0.56	0	0	< 5.00	5.30	< 5.00	5.05
3	$CH(Me)NH_2$	4-Pr	0.45	1.55	0	0	5.90	6.19	5.63	5.92
4	CH(Me)NHMe	4-Pr	0.61	1.55	0	0	5.71	5.63	5.60	5.57
5	$CH(Me)NH_2$	4-Br	0.45	0.86	0	0	5.83	5.57	—	—
6	$CH(Me)NH_2$	4-OEt	0.45	0.38	0	0	< 5.00	5.14	< 5.00	4.89
7	$CH(Me)NH_2$	4-OBz	0.45	1.66	0	0	5.92	6.29	—	—
8	$CH(Me)NH_2$	2-OMe,4-Me	0.45	0.56	1	0	6.22	6.24	5.84	5.71
9	CH_2NH_2	2-OMe,4-Me	0.34	0.56	1	0	6.96	6.63	6.08	5.95
10	CH(Me)NHMe	2-OMe,4-Me	0.61	0.56	1	0	5.83	5.68	—	—
11	$CH(Me)NH_2$	2,4-$(OMe)_2$	0.45	-0.02	1	0	5.35	5.72	< 5.00	5.20
12	$CH(Me)NH_2$	2-OMe,4-Br	0.45	0.86	1	0	7.00	6.51	6.08	5.98
13	CH_2NH_2	2-OMe,4-Br	0.34	0.86	1	0	6.66	6.90	5.99	6.22
14	$CH(Me)NH_2$	2-OMe,6-Br	0.45	0.00	1	0	5.81	5.74	< 5.00	5.22
15	$CH(Me)NH_2$	2-OMe,4-I	0.45	1.12	1	0	6.89	6.75	6.24	6.21
16	$CH(Me)NH_2$	3,4,5-$(OMe)_3$	0.45	-0.02	0	1	5.24	5.17	4.78	5.35
17	$CH(Me)NH_2$	4,5-OCH_2O-	0.45	-0.03	0	1	5.64	5.17	5.66	5.34
18	$CH(Me)NH_2$	2,5-$(OMe)_2$	0.45	0.00	1	1	5.92	6.14	5.28	6.03
19	$CH(Me)NH_2$	2,5-$(OMe)_2$,4-COOPr	0.45	1.07	1	1	< 5.00	-d	5.61	-d
20	$CH(Me)NH_2$	2,4,5-$(OMe)_3$	0.45	-0.02	1	1	5.57	6.12	5.90	6.02
21	$CH(Me)NH_2$	2,5-$(OMe)_2$,4-OEt	0.45	0.38	1	1	5.64	6.48	5.66	6.37
22	$CH(Me)NH_2$	2,5-$(OMe)_2$,4-Me	0.45	0.56	1	1	6.71	6.64	7.00	6.53
23	$CH(Me)NH_2$	2,5-$(OMe)_2$,4-Et	0.45	1.02	1	1	7.00	7.05	7.00	6.94
24	$CH(Me)NH_2$	2,5-$(OMe)_2$,4-Pr	0.45	1.55	1	1	7.85	7.53	7.16	7.41
25	$CH(Me)NH_2$	2,5-$(OMe)_2$,4-Br	0.45	0.86	1	1	7.16	6.91	7.39	6.80
26	CH(Me)NHMe	2,5-$(OMe)_2$,4-Br	0.61	0.86	1	1	7.01	6.35	7.10	6.44
27	CH(Me)NHPr	2,5-$(OMe)_2$,4-Br	0.92	0.86	1	1	< 5.00	5.25	5.61	5.77
28	CH_2NH_2	2,5-$(OMe)_2$,4-Br	0.34	0.86	1	1	7.44	7.30	7.47	7.04
29	$CH(Me)NH_2$	2,5-$(OMe)_2$,4-I	0.45	1.12	1	1	7.52	7.14	7.72	7.03
30	$CH(Me)NH_2$	2,5-$(OMe)_2$,4-Bu	0.45	2.13	1	1	7.59	8.05	7.24	7.92

[a]Observed activity data taken from Ref. 5; [b]calculated using Eq. (1); [c]calculated using Eq. (2); [d]outlier compounds of Eq. (1) and Eq. (2) in the respective columns.

positive coefficients to π and I_2, which are of comparable magnitude, imply inter alia that the presence of a mildly hydrophobic substituent at 4-position and some non-hydrogen substituent, e.g., OMe at the 2-position would just enhance the binding of phenylalkylamines at the 5-HT1C receptor. The coefficient to I_5 is too small to be able to discriminate between the two alternatives, i.e., whether or not a substituent would be advantageous at 5-position of the ring. The large negative coefficient to Vw(X) suggests that the side chain, X, must not be a bulky one lest it reduces the potency of the ligand. The F-value, obtained for the above equation is significant at 99% level and R^2 (= 0.84) and EV both account for 82-84% of variance in the observed binding activity. The explaining variables of Eq. (1) are perfectly orthogonal with r_2- values approaching 0, except for I_2 vs I_5 (= 0.12).

Like Eq. (1), Eq. (2) shows the correlation between the pKi- values for these very ligands at the 5-HT2 receptor.

$$pKi(5HT2) = 0.89(\pm0.15)\ \pi\ (p) + 0.67(\pm0.21)I_2 + 0.82(\pm0.19)I_5 - 2.19(\pm0.85)\ Vw(X) + 5.53$$

$$n = 26,\ R = 0.89,\ s = 0.45,\ EV = 0.76,\ F(4, 21) = 20.69 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ (2)$$

The inferences that are derivable from this equation are similar to those derived from Eq. (1) above with the only difference that, for this receptor, a substituent at 5-position appears to be advantageous. The correlation with the 5-HT1C receptor using those same 26 data points as were used in deriving Eq. (2) yielded statistics that is quite similar to that of Eq. (1), i.e. R = 0.92, s = 0.39, EV = 0.82, and coefficients to π, Vw, I_2 and I_5 being 0.94, -3.65, 0.91, and 0.41. Consequently, it can be construed that similar structural features are involved at both 5-HT1C and 5-HT2 bindings. Using Eq. (1) and (2) the calculated activity values are given in Table 1. It can be noticed that there is agreement between observed and calculated values in majority data points, the exceptions being only those having trisubstitution in phenyl ring with a more bulky para-substituent, e.g., compounds 16, 26, 29 and 30. The explaining variables of Eq. (2) have also established their orthogonality.

Conclusively, this QSAR analysis has not only provided a convincing ground-work for the structural similarity of the 5-HT2 and 5-HT1C receptors but also highlighted the parametric requirements to enhance the activity of phenylalkylamines at these receptors. Additionally, the interactions exhibited by these congeners at the receptor level are similarly reflected through this study.

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