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Quantitative structure–activity relationship study of new potent and selective antagonists at the 5-HT_{1A} and adrenergic α_{1d} receptors: Derivatives of spiroethyl phenyl(substituted)piperazine

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Abstract

The antagonistic activities of derivatives of spiroethyl phenyl(substituted)piperazine at the 5-HT_{1A} and adrenergic α_{1d} receptors is quantitatively analyzed employing physicochemical and structural parameters. The derived correlation equation revealed that a substituent, other than 2-CH_3 in the phenyl ring, having higher molar refraction, *MR*, and a substituent producing higher positive field effect at the 3-position are beneficial in increasing the binding affinity at the 5-HT_{1A} receptor. In addition, a less hydrophobic substituent at the 4-position is also helpful in augmenting the binding affinity. The 5-*R* substituents which have higher *MR* values, however, elicit a detrimental effect. Two disubstituted compounds which are not present in the original data-set and have higher theoretical binding affinities are designed from the correlation equation. These compounds consisting of 2-$OCH(CH_3)_2$, 3-Cl and 2-C_3H_7, 3-Cl in the phenyl ring, have theoretical pK_i values 10.57 and 10.12 respectively. For the adrenergic α_{1d} receptor, a less bulky group at the 3-position with 5-Cl (or simply a 3-Cl) is advantageous in increasing the binding affinity. Likewise, a substituent exhibiting a less negative resonance effect at the 4-position and the substituent with low polarizability and showing more a negative resonance effect at the 5-position are suitable for enhancement of the binding affinity. The analysis provides the grounds for rationalizing substituent selection in designing better potency antagonists in the series.

Keywords: *Spiroethyl phenyl(substituted)piperazine compounds, antagonists, adrenergic and serotonergic receptors, QSAR analysis, physicochemical properties*

Introduction

Three subtypes of the human α_1 adrenergic receptor (AR) have been identified at the molecular level and are cloned as α_{1a}, α_{1b}, and α_{1d} which correlate with the pharmacologically defined receptors α_{1A}, α_{1B}, and α_{1D} [1,2]. The α_{1A} subtype is mainly present in rat submaxillary gland, human liver and different tissues namely, prostatic vas deferens, rabbit prostate and prostatic urethra [3–6]. The α_{1B} adrenoceptor is concerned with rat liver and spleen, on the other hand, the contractility of rat aorta is mediated through the α_{1D} subtype. However, the α_{1d} mRNA is shown to be the dominant α_1 subtype present in the human bladder detrusor [7]. In addition, it was reported [8–10] that the α_{1D} adrenergic receptor is involved in detrusor instability, secondary to bladder outlet obstruction and mediates constriction of rat skeletal muscles arterioles and protein synthesis by arterial smooth muscles. Therefore, the selective α_{1D} antagonists could be very useful in the treatment of urinary incontinence, vasoconstriction and atherosclerosis without affecting normal blood pressure. In this respect, among others, BMY 7378 first described in 1983 [11] was later shown to be a selective α_{1d} antagonist [12]. However, the selectivity profile of this compound is limited by high affinity for the 5-HT_{1A} serotonergic receptor.

More recently, a synthetic study was performed [13] with a view to identifing highly selective antagonists at the adrenergic receptor. These compounds were tested in radioreceptor binding assays and the most

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significant compounds were further investigated for functional activity at the three α_1 adrenoceptor subtypes and 5-HT_{1A} serotonergic receptor. The initial structure-activity relationship (SAR) study on these compounds was, however, directed only to alteration of the substituents at different positions of the structure but no rationale has been provided to reduce the trial-and-error factors. Hence, a quantitative SAR (QSAR) on these analogues was conducted since QSAR not only provides the rationale for drug design but also illuminates their possible mechanism of action at the molecular level.

Materials and methods

The QSAR analysis was made on a reported series of compounds [13], the derivatives of spiroethyl phenyl (substituted) piperazine, having the general structure shown in Figure 1. These compounds along with their activity values for 5-HT_{1A} and α_{1d} receptor subtype are compiled in Table I. The most appropriate physicochemical, structural and indicator variables are also listed in this Table. Amongst them, the physicochemical parameters such as molar refraction, *MR* (scaled to 0.1), Field, *F* and resonance, *R* are taken from the literature [14] whereas the structural parameter, the van der Waals volume for a given substituent was calculated according to the method discussed in one of our earlier publications [15] and the usefulness of this structural parameter has already previously been established [16–21]. Additionally, indicator variables are also employed to reflect upon some special structural features of a compound. The numerals, subscripted or within parentheses following these variables are indicative of the varying positions of title compounds. The affinities estimated were derived from displacement of [^{3}H]prazosin for the α_1 adrenoceptor and [^{3}H]8-hydroxy-2-(di-n-propylamino)tetraline (^{3}H-8-OH-DPAT) for the 5-HT_{1A} receptor. For the present work, the reported affinity constants K_i for 5-HT_{1A} and α_{1d} receptors are expressed as pK_i on a molar scale. The multiple regression analysis (MRA), employing the method of least squares, is used to derive significant correlation equations for further discussion. In addition, the final QSAR equations were also subjected to a validation test [22] by the leave-one-out (LOO) method. This method generates a number of modified data sets by taking away one compound from the parent data set in such a way that each observation is taken away once and once only. Then one model is developed for each reduced data set and the response values of the deleted observations are predicted from the model. The squared differences between predicted and actual values are added to give the predictive residual sum of squares (PRESS). In this way, PRESS will contain one contribution from each observation. The cross-validated, q^2 value may further be calculated as (SSY– PRESS)/SSY, where SSY denotes the variance of the observed activities of molecules around the mean value. For a reasonable QSAR model, q^2 should be greater than 0.6, and a value of this statistical index greater than 0.9 indicates an excellent model.

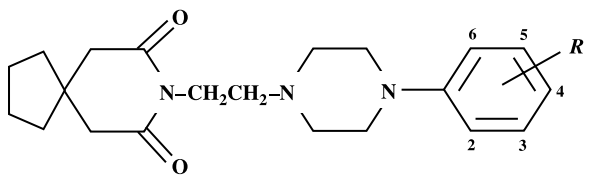

Figure 1. Structure of spiroethyl phenyl(substituted)piperazine derivatives.

Results and discussion

Table I lists the compounds where the alteration in substituents occurred at the phenyl ring linked to the piperazine ring. In order to account for effects produced by such substituents, a large number of descriptors related to hydrophobic, electronic and steric interactions were initially examined for the five varying positions of the phenyl ring in various possible permutations. The selected parameters for various substituents for each of these positions were hydrophobicity, π, hydrogen-bond donor, *HD*, electronic (*meta* and *para*), σ, field, *F*, resonance, *R*, dipole moment, μ, Taft's steric, E_S, molar refraction, *MR*, molecular weight, *MW* and van der Waals volume, V_w. This resulted into a large number of QSAR equations, which were then subjected to different statistical tests. The correlation equations, which returned the highest correlation coefficient, *r* and *F*-statistic and lowest standard deviation, *s* were finally retained for further discussion. The highest significant correlation as shown by equation (1) is finally obtained. The steps of its development are described through the correlation equation (i)–(iv) in Table II.

$$\begin{aligned} pK_i(\text{5-HT}_{1A}) = {} & 0.974(\pm 0.35)MR_2 \\ & + 1.986(\pm 1.14)F_3 \\ & - 1.401(\pm 0.68)\pi_4 \\ & - 1.419(\pm 0.50)MR_5 \\ & - 0.849(\pm 0.45)I_2 + 7.645 \end{aligned}$$

$$n = 34,\ r = 0.866,\ s = 0.486,\ F(5, 28) = 16.786,\ q^2 = 0.592 \quad (1)$$

As given above, *n* is the number of data points, *F*-statistic is the *F*-ratio between the variances of calculated and observed activities, and the ± data within the parentheses are the 90% confidence

Table I. QSAR parameters and antagonistic activities of substituted phenylpiperazine derivatives at the 5-HT$_{1A}$ and α_{1d} receptors (see Figure 1 for structure).

											pK_i(M)[a]							
											5-HT$_{1A}$				α_{1d}			
S. No.	R	MR_2	F_3	$V_w(3)$ (10^2Å^3)	π_4	R_4	MR_5	R_5	I_2	$I_{3,5}$	Obsd	Calcd equation (2)	Prctd LOO	Prctd EVM	Obsd	Calcd equation (4)	Prctd LOO	Prctd EVM
1	H	0.103	0.00	0.056	0.00	0.00	0.103	0.00	0	0	7.45	7.44	7.44	7.43	8.36	8.59	8.60	8.57
2	4-OCH_3	0.103	0.00	0.056	−0.02	−0.51	0.103	0.00	0	0	7.26	7.47	7.50	7.46	7.42	7.25	7.00	7.05
3	3-OCH_3	0.103	0.26	0.304	0.00	0.00	0.103	0.00	0	0	7.87	8.03	8.06	7.91	7.27	7.17	7.13	7.11
4	2-Cl	0.603	0.00	0.056	0.00	0.00	0.103	0.00	0	0	8.37	8.08	8.06	8.07	9.08	8.59	8.55	8.57
5	3-Cl	0.103	0.41	0.244	0.00	0.00	0.103	0.00	0	1	8.96	8.37	8.17	8.18	8.69	8.52	8.46	8.46
6	4-Cl	0.103	0.00	0.056	0.71	−0.15	0.103	0.00	0	0	6.22	6.51	6.66	6.58	7.45	8.20	8.26	8.26
7	4-F	0.103	0.00	0.056	0.14	−0.34	0.103	0.00	0	0	6.82	7.26	7.31	7.28	7.62	7.70	7.73	7.83
8	2-OCH $(CH_3)_2$	1.706	0.00	0.056	0.00	0.00	0.103	0.00	0	0	9.27	9.49	9.63	9.69	8.54	8.59	8.59	8.60
9	2-OH	0.285	0.00	0.056	0.00	0.00	0.103	0.00	0	0	8.87[b]	–	–	–	7.79[b]	–	–	–
10	2-F	0.092	0.00	0.056	0.00	0.00	0.103	0.00	0	0	7.49	7.43	7.42	7.43	9.04	8.59	8.55	8.60
11	2,3-Cl_2	0.603	0.41	0.244	0.00	0.00	0.103	0.00	0	1	8.47	9.01	9.23	9.22	7.90	8.52	8.69	8.68
12	2,4-$(CH_3)_2$	0.565	0.00	0.056	0.56	−0.13	0.103	0.00	1	0	5.63	6.45	6.94	6.86	7.13[b]	–	–	–
13	2-CH_3	0.565	0.00	0.056	0.00	0.00	0.103	0.00	1	0	7.60	7.18	7.01	7.41	8.67	8.59	8.58	8.59
14	3-CF_3	0.103	0.38	0.383	0.00	0.00	0.103	0.00	0	0	8.09	8.31	8.37	8.30	6.82	6.72	6.62	6.62
15	2-NO_2	0.736	0.00	0.056	0.00	0.00	0.103	0.00	0	0	7.95	8.25	8.28	8.26	7.81	8.59	8.64	8.59
16	2-CN	0.633	0.00	0.056	0.00	0.00	0.103	0.00	0	0	8.27	8.12	8.11	8.12	9.03	8.59	8.56	8.59
17	2-$COOC_2H_5$	1.747	0.00	0.056	0.00	0.00	0.103	0.00	0	0	8.39[b]	–	–	–	7.54[b]	–	–	–
18	2-Br	0.888	0.00	0.056	0.00	0.00	0.103	0.00	0	0	8.89	8.45	8.40	8.41	8.80	8.59	8.57	8.59
19	2,5-Cl_2	0.603	0.00	0.056	0.00	0.00	0.603	−0.15	0	1	7.44	7.39	7.38	7.36	9.89	9.57	9.49	9.45
20	2,4-Cl_2	0.603	0.00	0.056	0.71	−0.15	0.103	0.00	0	0	7.92	7.15	6.79	6.41	8.41	8.20	8.18	8.17
21	3,4-Cl_2	0.103	0.41	0.244	0.71	−0.15	0.103	0.00	0	1	7.70	7.44	7.24	6.64	8.27	8.12	8.07	8.00
22	2-CF_3	0.502	0.00	0.056	0.00	0.00	0.103	0.00	0	0	7.58	7.95	7.98	7.97	8.28	8.59	8.61	8.58
23	2-c-C_3H_7	1.353	0.00	0.056	0.00	0.00	0.103	0.00	0	0	8.92	9.04	9.08	9.12	8.87	8.59	8.57	8.58
24	2,5-F_2	0.092	0.00	0.056	0.00	0.00	0.092	−0.34	0	0	7.21	7.44	7.47	7.43	9.85	9.65	9.57	9.58
25	2-Cl,5-CF_3	0.603	0.00	0.056	0.00	0.00	0.502	0.19	0	0	NR[c]	–	–	–	7.41	7.62	7.66	7.71
26	2-Cl,5-CH_3	0.603	0.00	0.056	0.00	0.00	0.565	−0.13	0	0	7.16	7.44	7.46	7.44	8.54	8.55	8.55	8.57
27	2-F,5-CH_3	0.092	0.00	0.056	0.00	0.00	0.565	−0.13	0	0	7.28	6.78	6.72	6.75	8.62	8.55	8.54	8.57
28	2,5-$(CH3)_2$	0.565	0.00	0.056	0.00	0.00	0.565	−0.13	1	0	6.56	6.54	6.53	6.51	7.99	8.55	8.59	8.57
29	2-F,5-CF_3	0.092	0.00	0.056	0.00	0.00	0.502	0.19	0	0	6.80	6.87	6.88	6.84	8.12	7.62	7.52	7.41
30	2-F,5-NO_2	0.092	0.00	0.056	0.00	0.00	0.736	0.16	0	0	NR[c]	–	–	–	7.33	7.49	7.52	7.26
31	2-Cl,5-NO_2	0.603	0.00	0.056	0.00	0.00	0.736	0.16	0	0	NR[c]	–	–	–	7.74	7.49	7.43	7.26
32	2-CH_3,5-Cl	0.565	0.00	0.056	0.00	0.00	0.603	−0.15	1	1	6.87	6.48	6.33	6.44	9.43	9.57	9.61	9.60
33	2,5-Br_2	0.888	0.00	0.056	0.00	0.00	0.888	−0.17	0	0	7.21	7.35	7.39	7.52	8.43	8.36	8.35	8.31
34	2-CN,5-Cl	0.633	0.00	0.056	0.00	0.00	0.603	−0.15	0	1	7.53	7.42	7.41	7.51	9.70	9.57	9.54	9.55
35	2-Cl,5-F	0.603	0.00	0.056	0.00	0.00	0.092	−0.34	0	0	7.92	8.10	8.11	8.04	9.74	9.65	9.61	9.65
36	2-Cl,5-I	0.603	0.00	0.056	0.00	0.00	1.394	−0.19	0	0	6.09	6.28	6.46	6.60	7.82	7.94	8.04	7.96
37[d]	2-OCH_3	0.787	0.00	0.056	0.00	0.00	0.103	0.00	0	0	9.10	8.32	8.26	8.26	8.07	8.59	8.62	8.61

[a] K_i, expressed as negative logarithm on molar basis, represents the binding affinity that were derived from displacement of [^{3}H]prazosin binding [^{3}H] 8-hydroxy-2-(di-n-propylamino)tetraline for the 5-HT$_{1A}$ receptor and for α_{1d} adrenoceptor; taken from Ref. [13]. [b] "Outlier" compound in the present study. [c] Affinity is not reported. [d] Reference compound, BMY 7378.

Table II. Stepwise development of equation (1) $pK_i = a_0 + a_1MR_2 + a_2F_3 + a_3\pi_4 + a_4MR_5 + a_5I_2$ for $n = 34$.

a_0	a_1	a_2	a_3	a_4	a_5	r	s	$F_{k,n-k-1}$[a]	
7.234	0.852(±0.56)					0.414	0.828	6.630	(i)
6.944	1.112(±0.53)	2.789(±1.71)				0.580	0.753	7.844	(ii)
7.082	1.019(±0.51)	2.968(±1.63)	−1.201(±0.97)			0.648	0.715	7.256	(iii)
7.572	0.966(±0.40)	2.278(±1.30)	−1.574(±0.78)	−1.510(±0.57)		0.811	0.559	13.954	(iv)
7.645	0.974(±0.35)	1.986(±1.14)	−1.401(±0.68)	−1.419(±0.50)	−0.849(±0.45)	0.866	0.486	16.786	(v)

[a] The F statistics for n data points and k independent variable(s).

intervals. From above equation it appears that the substituents at the 4-positions are engaged in hydrophobic interaction while those at the 3-position are involved in electronic interaction. Furthermore, the *MR* variable, accounting for molecular bulk and/or polarizability, appears to be the important aspect for the substituents at the 2- and 5-positions. The arbitrarily chosen indicator variable, I_2, in addition, accounts for a methyl substituent at the 2-position. Its value, either 1 or 0 in that order, indicates the presence or absence of a 2-CH_3 in the phenyl ring. The statistical parameters, obtained for equation (1), do not indicate significant results as the r^2 value accounts for 75% of the variance and q^2 is nearer to a specified significant level. However, the F-value remained significant at 99% [$F_{5,28}(0.01) = 3.754$]. These observations reflect upon the parametric requirements for the subtituents in a compound that leads to binding affinity at the 5-HT_{1A} serotonergic receptor. In order to improve upon the significance levels of equation (1), all data points in Table I, were further analyzed for their deviation from a regular trend. Compounds that show large difference between observed and calculated pK_i values are underlined for this abnormality and are treated as 'outliers'. Compounds **9** and **17** are such congeners. Compound **9** having a 2-OH substituent seems to involved in hydrogen bonding with some site on to the receptor and elicits a higher observed binding affinity compared to the calculated value (= 7.68) using the QSAR equation (2). Similarly the 2-$COOC_2H_5$ substituent in compound **17** appears to undergo hydrolysis prior to reaching its receptor site and reveals lesser pK_i value than the calculated one (= 9.55) obtained from the model equation. Paying no attention to these two compounds, QSAR reveals correlation equation (2)

$$\begin{aligned} pK_i(5\text{-}HT_{1A}) = {} & 1.280(\pm 0.35)MR_2 \\ & + 2.270(\pm 0.98)F_3 \\ & - 1.308(\pm 0.58)\pi_4 \\ & - 1.394(\pm 0.43)MR_5 \\ & - 0.852(\pm 0.38)I_2 + 7.455 \end{aligned}$$

$$n = 32,\ r = 0.906,\ s = 0.411,\ F(5, 26) = 23.782,$$

$$q^2 = 0.679 \qquad (2)$$

Now both the r- and F-values were increased to account for 82% ($r^2 = 0.821$) of variance in the observed activities and 99% level of significance [$F_{5,26}(0.01) = 3.818$]. Also, the s-value and 90% confidence intervals (± data within parentheses) associated with regression coefficients were significantly lowered. Additionally, the higher value obtained for q^2 expressed a reasonable QSAR model. That the variables used in deriving equation (2) had no mutual correlation is shown in Table IV. The calculated activity values, using this equation and listed in Table I, are in close agreement with the observed ones. The predicted activity values from the data set of equation (2) and various model equations, discussed earlier, were also listed in this table for comparison sake. From equation (2), it appeared that a substituent, other than a methyl, present at 2-position and having a higher value of *MR* is advantageous to improve the pK_i value pertaining to the 5-HT_{1A} receptor. Similarly a substituent producing a higher positive field effect at the 3-position and a less hydrophobic substituent at

Table III. Stepwise development of equation (3) $pK_i = b_0 + b_1V_w(3) + b_2R_4 + b_3MR_5 + b_4R_5 + b_5I_{3,5}$ for $n = 37$.

b_0	b_1	b_2	b_3	b_4	b_5	r	s	$F_{k,n-k-1}$[a]	
8.586	−3.176(±2.67)					0.322	0.773	4.039	(i)
8.697	−3.342(±2.55)	2.505(±1.96)				0.460	0.736	4.575	(ii)
8.860	−3.725(±2.64)	2.791(±2.03)	−0.405(±0.71)			0.483	0.736	3.353	(iii)
8.733	−3.270(±2.09)	2.452(±1.60)	−0.570(±0.56)	−3.835(±1.41)		0.734	0.581	9.319	(iv)
8.811	−5.192(±1.77)	2.518(±1.25)	−0.769(±0.45)	−3.231(±1.13)	1.039(±0.38)	0.853	0.452	16.620	(v)

[a] See footnote under Table II.

Table IV. The intercorrelation matrix[a] amongst the independent variables of equation (2).

	MR_2	F_3	π_4	MR_5	I_2
MR_2	1.000	0.312	0.177	0.095	0.071
F_3		1.000	0.129	0.233	0.160
π_4			1.000	0.216	0.088
MR_5				1.000	0.092
I_2					1.000

[a] Matrix elements are the *r*-values.

the 4-position are also favorable to increase the binding affinity. The substituents which are present at the 5-position and have higher *MR* values, on the other hand, cause a detrimental effect. These guidelines may be used to design congeners which are more active than the compounds reported in the original data-set. Two such disubstituted compounds that possess 2-$OCH(CH_3)_2$, 3-Cl and 2-C_3H_7, 3-Cl in the phenyl ring have theoretical pK_i values of 10.57 and 10.12 respectively and may, therefore, be explored in the future.

As mentioned earlier, compounds which are selective antagonists at the α_{1d} adrenergic receptor could be very useful in the treatment of diseases such as urinary incontinence, vasoconstriction and atherosclerosis, with no effects on blood pressure. It is, therefore, pertinent to establish the quantitative relationship between binding affinity for the α_{1d} and the quantifying parameters. Employing data from Table I in MRA has revealed, through successive steps (Table III), correlation equation (3)

$$\begin{aligned} pK_i(\alpha_{1d}) = &-5.192(\pm1.77)V_W(3) + 2.518(\pm1.25)R_4 \\ &- 0.769(\pm0.45)MR_5 - 3.231(\pm1.13)R_5 \\ &+ 1.039(\pm0.38)I_{3,5} + 8.811 \\ n = 37,\ \ r = 0.853,\ \ s = 0.452,& \\ F(5,31) = 16.620,\ \ q^2 = 0.649& \end{aligned} \quad (3)$$

This equation analyzes the importance of 3-, 4- and 5-*R* substituents while the substituents at the 2-position make no contribution to $pK_i(\alpha_{1d})$. The indicator variable $I_{3,5}$ is selected to highlight the presence of a Cl group at the *meta*-position (3 or 5) of the phenyl ring (Table IV). Thus, for the presence of a 3-Cl or a 5-Cl, the value considered for $I_{3,5}$ is 1 and for its absence the value assigned to this variable is 0. Compound **12**, having 2,4-$(CH_3)_2$ substituents in the phenyl ring, has unusual behavior and, at present, there is no appropriate explaination. This compound, in addition to previously considered 'outlier' compounds **9** and **17**, is ignored to yield a more significant correlation equation (4)

$$\begin{aligned} pK_i(\alpha_{1d}) = &-5.712(\pm1.46)V_W(3) + 2.613(\pm1.04)R_4 \\ &- 0.958(\pm0.37)MR_5 - 3.091(\pm0.92)R_5 \\ &+ 1.003(\pm0.31)I_{3,5} + 9.006 \\ n = 34,\ \ r = 0.905,\ \ s = 0.368,& \\ F(5,28) = 25.297,\ \ q^2 = 0.759& \end{aligned} \quad (4)$$

All the statistical parameters, including 90% confidence intervals, of this equation have significantly improved over that of equation (3). The *r* value now accounts for 82% of the variance and the *s* value is lowered. In addition, the *F* value remained significant at 99% level, and the q^2 index, explaining a satisfactory statistical model, are both increased. The calculated pK_i values, using equation (4), and predicted pK_i values, using the LOO method, listed in Table I, are in close agreement with the observed ones. The required orthogonality conditions amongst the independent variables of this equation are evident in Table V. From equation (4), it appears that a less bulky group at the 3-position, while a Cl group at the 5-position (or simply a 3-Cl) are advantageous in increasing the activity of a compound. Similarly a substituent, exhibiting less polarizability and a more negative resonance effect at the 5-position, leads to higher antagonistic activity at α_{1d} receptor. Also, a substituent present at the 4-position and showing a less negative resonance effect is beneficial.

Equations (2) and (4) were further subjected to an external validation method (EVM). In this method, a few compounds were considered in the test set and were left out to derive a correlation equation on the remainder. The equation was then used to predict the activities of compounds in the test set. In this way, several equations were obtained and are listed in Table VI corresponding to the compounds left out of the test set. The predicted activities for these compounds are given in Table I for comparison. These activities were found in close agreement with the observed ones. The conclusions deduced from equations (2) and (4) may be used as guidelines to

Table V. The intercorrelation matrix[a] amongst the independent variables of equation (4).

	$V_w(3)$	R_4	MR_5	R_5	$I_{3,5}$
$V_w(3)$	1.000	0.050	0.264	0.115	0.336
R_4		1.000	0.233	0.102	0.057
MR_5			1.000	0.139	0.065
R_5				1.000	0.154
$I_{3,5}$					1.000

[a] See footnote under Table IV.

Table VI. QSAR model equations using external validation method.

Compounds in test set	Derived correlation equations from remaining compounds[a]	n	r	s	$F_{k,n-k-1}$[b]	
1, 2, 3, 4, 5	$pK_i(5\text{-HT}_{1A}) = 1.278(\pm 0.39)MR_2 + 1.829(\pm 0.20)F_3 - 1.223(\pm 0.64)\pi_4 - 1.378(\pm 0.47)MR_5 - 0.857(\pm 0.40)I_2 + 7.443$	27	0.909	0.425	19.871	2(i)
6, 7, 8, 10, 11	$pK_i(5\text{-HT}_{1A}) = 1.400(\pm 0.50)MR_2 + 2.618(\pm 1.27)F_3 - 1.218(\pm 0.70)\pi_4 - 1.461(\pm 0.45)MR_5 - 0.908(\pm 0.40)I_2 + 7.452$	27	0.898	0.412	17.407	2(ii)
12, 13, 14, 15, 16	$pK_i(5\text{-HT}_{1A}) = 1.315(\pm 0.33)MR_2 + 2.290(\pm 1.02)F_3 - 0.993(\pm 0.60)\pi_4 - 1.450(\pm 0.43)MR_5 - 0.620(\pm 0.51)I_2 + 7.439$	27	0.917	0.386	22.201	2(iii)
18, 19, 20, 21, 22	$pK_i(5\text{-HT}_{1A}) = 1.142(\pm 0.31)MR_2 + 1.945(\pm 0.96)F_3 - 2.350(\pm 0.74)\pi_4 - 1.453(\pm 0.39)MR_5 - 0.698(\pm 0.34)I_2 + 7.544$	27	0.941	0.352	32.355	2(iv)
23, 24, 26, 27, 28, 29	$pK_i(5\text{-HT}_{1A}) = 1.353(\pm 0.46)MR_2 + 2.282(\pm 1.12)F_3 - 1.310(\pm 0.65)\pi_4 - 1.452(\pm 0.50)MR_5 - 0.872(\pm 0.48)I_2 + 7.441$	26	0.897	0.445	16.517	2(v)
32, 33, 34, 35, 36, 37	$pK_i(5\text{-HT}_{1A}) = 1.270(\pm 0.36)MR_2 + 2.370(\pm 1.01)F_3 - 1.197(\pm 0.60)\pi_4 - 1.104(\pm 0.83)MR_5 - 0.987(\pm 0.45)I_2 + 7.371$	26	0.906	0.412	18.423	2(vi)
1, 2, 3, 4, 5	$pK_i(\alpha_{1d}) = -5.908(\pm 1.82)V_W(3) + 2.982(\pm 1.71)R_4 - 0.937(\pm 0.40)MR_5 - 3.110(\pm 0.97)R_5 + 1.000(\pm 0.35)I_{3,5} + 8.999$	29	0.902	0.383	20.103	4(i)
6, 7, 8, 10, 11	$pK_i(\alpha_{1d}) = -5.495(\pm 1352)V_W(3) + 2.271(\pm 1.09)R_4 - 1.008(\pm 0.35)MR_5 - 3.006(\pm 0.83)R_5 + 1.105(\pm 0.29)I_{3,5} + 9.016$	29	0.931	0.328	30.111	4(ii)
13, 14, 15, 16, 18	$pK_i(\alpha_{1d}) = -6.031(\pm 2.00)V_W(3) + 2.620(\pm 1.04)R_4 - 0.974(\pm 0.39)MR_5 - 3.065(\pm 0.91)R_5 + 1.033(\pm 0.33)I_{3,5} + 9.031$	29	0.912	0.357	22.819	4(iii)
19, 20, 21, 22, 23	$pK_i(\alpha_{1d}) = -5.627(\pm 1.61)V_W(3) + 2.739(\pm 1.14)R_4 - 0.960(\pm 0.40)MR_5 - 3.077(\pm 0.97)R_5 + 0.886(\pm 0.38)I_{3,5} + 8.997$	29	0.903	0.384	20.211	4(iv)
24, 25, 26, 27, 28	$pK_i(\alpha_{1d}) = -5.725(\pm 1.53)V_W(3) + 2.639(\pm 1.09)R_4 - 0.871(\pm 0.41)MR_5 - 2.866(\pm 1.23)R_5 + 0.989(\pm 0.34)I_{3,5} + 9.008$	29	0.900	0.382	19.504	4(v)
29, 30, 31, 32, 33	$pK_i(\alpha_{1d}) = -5.660(\pm 1.55)V_W(3) + 2.511(\pm 1.08)R_4 - 1.100(\pm 0.46)MR_5 - 3.675(\pm 1.22)R_5 + 1.058(\pm 0.35)I_{3,5} + 8.975$	29	0.905	0.378	20.880	4(vi)
34, 35, 36, 37	$pK_i(\alpha_{1d}) = -5.714(\pm 1.59)V_W(3) + 2.667(\pm 1.10)R_4 - 0.950(\pm 0.52)MR_5 - 3.014(\pm 1.12)R_5 + 0.959(\pm 0.36)I_{3,5} + 9.028$	30	0.891	0.380	18.499	4(vii)

[a] Previously considered "outliers" are not included in deriving above equations. [b] See footnote under Table II.

obtain more potency antagonists in the further synthesis of similar compounds.

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