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Research Article

Electronic structure and rat fundus serotonin receptor binding affinity of phenetylamines and indolealkylamines.

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ABSTRACT

We have studied the relationships between electronic structure and rat fundus serotonin receptor binding affinity in two groups of 22 phenetylamines and 31 indolealkylamines. The wave function of all molecules in their protonated form was calculated within the Density Functional Theory at the rmPW1PW91/DGDZVP level after full geometry optimization. For both groups of molecules we have discovered new requirements for specific atomic centers to enhance binding affinity. The associated pharmacophores should provide useful information for the synthesis of new molecules.

Keywords: Serotonin, rat stomach fundus, QSAR, DFT, receptor affinity, phenetylamines, indolealkylamines, KPG method.

INTRODUCTION

From a longtime our Quantum Pharmacology Unit has devoted its efforts to study the relationships between electronic structure and biological activities in phenetylamines and indolealkylamines[1-12]. Recently, we began to carry out some docking studies with the aim of relating both kinds of results [13]. In our first QSAR research the wave functions were obtained with semiempirical methods, the serotonin receptor affinities were measured in the rat stomach fundus preparation and the local atomic reactivity indices were a few ones (atomic net charges and superdelocalizabilities). Nevertheless, the results obtained were very significant. Based on these results, me and my collaborators were able to predict the hallucinogenic activity and human dose of (±)-2,5-dimethoxy-4-nitroamphetamine[8]. Regarding the molecules of the title, many QSAR studies were carried out[14-38]. After this studies, the formal method used here was extended by one of us (J.S. G.-J.) adding new local atomic indices obtained by a new analysis of the drug-site interaction energy. During year 2013 a totally new set of local atomic reactivity indices was discovered. Today, with the advent of faster and more powerful computers allowing the calculation of more complex wave functions and the advances in the theory providing more local atomic reactivity indices, it is interesting to explore again the relationships between electronic structure and rat fundus serotonin receptor binding affinity of phenetylamines and indolealkylamines. As fas as we know, no QSAR studies have been carried out with the use of more exact wavefunctions for calculating the electronic structure. This study is important because the molecules studied here can be considered part of the "first generation" of hallucinogenic drugs. With the coming of new and sometimes dangerous synthetic drugs, it is more necessary than ever to accumulate knowledge about the way these molecules bind to receptors. Here we present the results of such study.

METHODS, MODELS AND CALCULATIONS.

The method.

As the Klopman-Peradejordi-Gómez (KPG) model-based method linking biological activity with molecular structure has been presented in this Journal

and elsewhere, we shall discuss only the final results [39]. The receptor binding affinity, pA_2, is a linear function of several local atomic reactivity indices (LARIs) and has the following general form[40-44]:

$$pA_2 \cong a + bM_{D_i} + c\log\left[\sigma_{D_i}/(ABC)^{1/2}\right] + \sum_j \left[e_j Q_j + f_j S_j^E + s_j S_j^N\right] +$$

$$+ \sum_j \sum_m \left[h_j(m)F_j(m) + x_j(m)S_j^E(m)\right] + + \sum_j \sum_{m'} \left[r_j(m')F_j(m') + t_j(m')S_j^N(m')\right] +$$

$$+ \sum_j \left[g_j \mu_j + k_j \eta_j + o_j \omega_j + z_j \varsigma_j + w_j Q_j^{\max}\right]$$

where M is the drug's mass, σ its symmetry number and ABC the product of the drug's moment of inertia about the three principal axes of rotation, Q_i is the net charge of atom *i*, S_i^E and S_i^N are, respectively, the total atomic electrophilic and nucleophilic superdelocalizabilities of Fukui et al., $F_{i,m}$ is the Fukui index of atom i in occupied (empty) MO m (m'). $S_i^E(m)$ is the atomic electrophilic superdelocalizability of atom i in MO m, etc. The total atomic electrophilic superdelocalizability (ESD) of atom i is defined as the sum over occupied MOs of the $S_i^E(m)$'s and the total atomic nucleophilic superdelocalizability (NSD) of atom i is defined as the sum over empty MOs of the $S_i^N(m)$'s. The last bracket of the right side of Eq. 1 contains local atomic indices obtained by an approximate rearrangement of part of the remaining terms of the series expansion employed in the model. For example, μ_i is the total local atomic electronic chemical potential of atom i:

$$\mu_i = \frac{E_{oc}^* - E_{em}^*}{2} \qquad (2)$$

where E_{oc}^* is the upper occupied local MO with a non-zero Fukui index and E_{em}^* is the lowest empty local MO with a non-zero Fukui index. η_i is the local atomic hardness of atom i, ς_i, is the local atomic softness of atom i, ω_i is the local atomic electrophilic index of atom i, and $Q_i^{\max}$ is the maximal amount of electronic charge that atom i may accept.

The general meaning of these LARIs is: μ_i is a measure of the tendency of an atom to gain or lose electrons; a large negative value indicates a good electron acceptor atom while a small negative value implies a good electron donor atom. The local atomic hardness can be interpreted as the resistance of an atom to exchange electrons with the environment. The local atomic electrophilic index is associated with the electrophilic power of an atom and includes the tendency of the electrophile atom to receive extra electronic charge together with its resistance to exchange charge with the medium.

The moment of inertia term can be expressed in a first approximation as [42]:

$$\log\left[(ABC)^{-1/2}\right] \approx \sum_t \sum_t m_{i,t} R_{i,t}^2 = \sum_t O_t \qquad (3)$$

where the summation over t is over the different substituents of the molecule, $m_{i,t}$ is the mass of the i-th atom belonging to the t-th substituent, $R_{i,t}$ being its distance to the atom to which the substituent is attached. We have called them Orientation Parameters [42, 45, 46].

Then, for n (i=1, n) molecules we have a set of simultaneous equations 1. This system holds for the atoms of the molecule directly concerned in the interaction process. Combined with the habitual multiple-regression techniques, these equations can be practically applied to estimate the relative variation of the biological activities in the family of molecules analyzed. The application of this method provided significant results for a variety of molecular systems and biological activities ([10-13, 47-93] and references therein).

Selection of molecules and biological activities.

The rat fundus serotonin receptor binding affinities (pA_2) values were taken from the literature [94-101]. Figure 1 and Table 1 shows that selected phenetylamines. Figure 2 and Table 2 show the selected indolealkylamines.

Calculations.

The electronic structure of all molecules in their protonated form was calculated within the Density Functional Theory (DFT) at the rmPW1PW91/DGDZVP level with full geometry optimization. The Gaussian suite of programs was used [102]. All the information needed to calculate numerical values for the local atomic reactivity indices was obtained from the Gaussian results with the D-Cent-QSAR software [103]. All the electron populations smaller than or equal to 0.01 e were considered as zero. Negative electron populations coming from Mulliken Population Analysis were corrected as usual [104]. Orientational parameter values were taken from Tables [45, 46]. As the resolution of the system of linear equations is not possible because we have not sufficient molecules, we made use of Linear Multiple Regression Analysis (LMRA) techniques to find the best solution. It is hypothesized that there is a set of atoms, common to all molecules analyzed (the common skeleton), accounting for *almost* all the interactions leading to the expression of a given biological activity. The role of the substituents

consists in modifying the electronic structure of the common skeleton, influencing the correct alignment of the drug through the orientational parameters and sometimes directly interact with the receptor. The common skeletons are shown in Figs. 3 and 4. For each case, a matrix containing the dependent variable (the pA_2), the local atomic reactivity indices of all atoms of the common skeleton and the orientational parameter of the substituents as independent variables was built. The Statistica software was employed for LMRA [105].

RESULTS

Results for phenetylamines.

The best equation obtained was:

$$pA_2 = 0.45 - 0.22S_{11}^{E} + 1.17\omega_{10} + 1.13Q_{12}^{char} - 68.27F_7(HOMO)^* \quad (2)$$

with n=20, R=0.98, R^2=0.95, adj-R^2=0.94, F(4,15)=79.09 (p<0.000001) and SD=0.21. No outliers were detected and no residuals fall outside the ±2σ limits. Here, S_{11}^{E} is the total atomic electrophilic superdelocalizability of atom 11, ω_{10} is the total atomic electrophilicity of atom 10, Q_{12}^{char} is the total atomic charge capacity of atom 12 and F_7(HOMO)* is the Fukui index (the electron population) of the highest occupied MO localized on atom 7. Tables 3 and 4 show the beta coefficients, the results of the t-test for significance of coefficients and the matrix of squared correlation coefficients for the variables of Eq. 2. There are no significant internal correlations between independent variables (Table 4). Figure 5 displays the plot of observed *vs.* calculated pA_2.

The associated statistical parameters of Eq. 2 indicate that this equation is statistically significant and that the variation of the numerical values of a group of four local atomic reactivity indices of atoms of the common skeleton explains about 94% of the variation of the pA_2 in this group of molecules. Figure 5, spanning about 2.8 orders of magnitude, shows that there is a good correlation of observed *versus* calculated values and that almost all points are close or inside the 95% confidence interval. This can be considered as an indirect evidence that the common skeleton hypothesis works relatively well for this set of molecules.

Results for indole alkylamines

The best equation obtained was:

$$pA_2 = 3.88 + 1.6S_2^{E}(HOMO)^* + 5.87Q_7^{char} + 3.97S_{13}^{E} - 0.40S_6^{E}(HOMO)^* + 0.03S_{17}^{E} + 0.01\varphi_{R1} \quad (3)$$

with n=28, R=0.95, R^2=0.91, adj-R^2=0.88, F(6,21)=34.10 (p<0.000001) and SD=0.19. No outliers were detected and no residuals fall outside the ±2σ limits. Here, S_2^{E}(HOMO)* is the electrophilic superdelocalizability of the highest occupied MO localized on atom 2, Q_7^{char} is the local atomic charge capacity of atom 7, S_{13}^{E} is the total atomic electrophilic superdelocalizability of atom 13, S_6^{E}(HOMO)* is the Fukui index of the highest occupied MO localized on atom 6, S_{17}^{E} is the total atomic electrophilic superdelocalizability of atom 17 and φ_{R1} is the orientational parameter of the R_1 substituent. Tables 5 and 6 show the beta coefficients, the results of the t-test for significance of coefficients and the matrix of squared correlation coefficients for the variables of Eq. 3. There are no significant internal correlations between independent variables (Table 6). Figure 6 displays the plot of observed *vs.* calculated pA_2.

The associated statistical parameters of Eq. 3 indicate that this equation is statistically significant and that the variation of the numerical values of a group of six local atomic reactivity indices of atoms of the common skeleton explains about 88% of the variation of the pA_2 in this group of molecules. Figure 6, spanning about 2.4 orders of magnitude, shows that there is a good correlation of observed *versus* calculated values and that almost all points are close or inside the 95% confidence interval. This can be considered as an indirect evidence that the common skeleton hypothesis works relatively well for this set of molecules.

DISCUSSION

Discussion of the results for phenetylamines.

Table 3 shows that the importance of variables is S_{11}^{E} >> ω_{10} > Q_{12}^{char} > F_7(HOMO)*. A high pA_2 is associated with highly negative values of S_{11}^{E}, Q_{12}^{char} and ω_{10}, and with small values of F_7(HOMO)*. Atom 11 is the first atom of the substituent (R_2) attached to atom 5 (Fig. 3). A high value of S_{11}^{E} suggests that atom 11 is acting as an electron donor. The usual substituent at this position is OCH_3. Then for a high binding affinity any other substituent -O-X in which X contributes to increase the net charge of the oxygen atom should be a good candidate to test. Atom 10 is a hydrogen atom bonded to the side chain nitrogen atom (Fig. 3). A high value of ω_{10} suggests that this atom should be able to receive extra electronic charge. An interpretation consistent with this fact is that atom 10 is participating in a hydrogen bond. Atom 12 is the first atom of the substituent (R_3) attached to atom 4 (Fig. 3). A high value of Q_{12}^{char} strongly suggests that the ideal substituent is an atom or a group that can accept electronic charge. The

usual substituent is OMe but this result indicate that there are several more possibilities to explore. Atom 7 is the carbon atoms of the side chain directly bonded to the phenyl group (Fig. 3). A high pA_2 is associated with an almost zero electron density of the HOMO. All the suggestions are displayed in the partial 2D pharmacophore of Fig. 7.

It is interesting to note that all local atomic reactivity indices appearing in Eq. 2 do not belong to the phenyl ring. It is more or less obvious that this ring interacts with the receptor, probably through π-π MO interactions. What is important here is that our results presented here strongly suggest that some ring substituents also interact directly with the receptor. Besides the 2,5-dimethoxy-4-X substitution pattern, it appears that activity could be enhanced via a wise choice of the 3-substituent (12 in Fig. 8). In our earlier studies, the definition of the common skeleton was a very restrictive one, not allowing us to detect the role of the substituents of the phenyl ring. Very recently we studied the interaction of a group of N-benzylthenethylamines with the cloned rat 5-HT_{2C} receptor [12]. The results showed that several substituents of the phenyl ring interacted directly with the receptor. This fact was confirmed with our studies of the interaction of these same molecules with a cloned human 5-HT_{2B} receptor and a 5-HT_{2A} model receptor[10, 11]. In both papers docking studies showed the same phenomenon. Finally, the docking of some hallucinogens to 5-HT_{2A} receptor led to the same results. Now, the results obtained here provide more evidence that the substituents attached to the phenyl ring directly participate in the interaction with the receptor (the rat stomach fundus receptor in this case).

Discussion of the results for indole alkylamines.

Table 5 shows that the importance of variables is S_2^E(HOMO)*> S_6^E(HOMO)*> Q_7^{char}> S_{13}^E>> S_{17}^E> φ_{R1}. A high pA_2 is associated with high values of Q_7^{char} and φ_{R1}, large negative values of S_6^E(HOMO)* and small negative values of S_2^E(HOMO)*, S_{13}^E and S_{17}^E. Atom 7 is a nitrogen in ring B (Fig. 4). High values of Q_7^{char} suggests that this atom should be able to receive extra charge. If this is true, then a good way to drain electrons from N7 is by changing N7-H by N7-X, where X is an electron-attractor group. φ_{R1} is the orientational effect of the N7 substituent (see Figs. 2 and 3). Table 2 shows that only hydrogen and methyl were used to generate Eq. 3. As a large value of this substituent appears to be associated with a high pA_2, it is possible to substitute the methyl group by another with a greater OP value but fulfilling the condition for atom 7 (for OP numerical values of several substituents, see [45, 46]). Atom 6 is a carbon shared by rings A and B (Fig. 3). As large negative values of S_6^E(HOMO)* are associated with a high pA_2, the best possible situation is when the highest occupied local MO (HOMO*) coincides with the molecule's HOMO and has a large electron density. Atom 2 is a carbon of ring A (Figs. 2 and 3). A high pA_2 is associated with small negative values of S_2^E(HOMO)*. This suggests that the optimal R_5 substituent is one depleting electrons from atom 2, and that atom 2 seems to interact with an electron-rich site. Atom 13 is a hydrogen bonded to the nitrogen atom of the side chain. A high pA_2 is associated with a low negative value of S_{13}^E making this atom a poor electron donor. This is consistent with its participation in a hydrogen bond. Atom 17 is the first atom of the R_6 substituent (see Figs. 2 and 3). As a high pA_2 is associated with small negative values, this suggests that this atom is interacting as an electron acceptor. Therefore a substituent of the kind -A-X, where X drains electron from A, is a good choice to explore. All the suggestions are displayed in the partial 2D pharmacophore of Fig. 8.

In this case, the variation of the pA_2 is associated with the variation of reactivity indices belonging to the aromatic rings A and B and the substituents. Our results provide new conditions to be fulfilled by some atomic centers that may open the way for the synthesis of entirely new molecules with an increased receptor binding affinity. The equation for indolealkylamines provides data involving the direct interaction of only one substituent of the phenyl ring. Nevertheless, a docking study of psilocybin shows that this situation is possible [13].

In conclusion, the goal of reexamining the relationships between rat fundus serotonin receptor binding affinity and electronic structure for indolealkylamines and phenetylamines has been successful. For both families, more precise requirements for specific atomic centers are being proposed. This study confirmed our previous results on similar molecular systems and provides more evidence that the substituents of the phenyl ring directly interact with the receptor. Given the very general qualitative relationship between pA_2 and "hallucinogenic" activity it is possible that new psychoactive members be obtained.

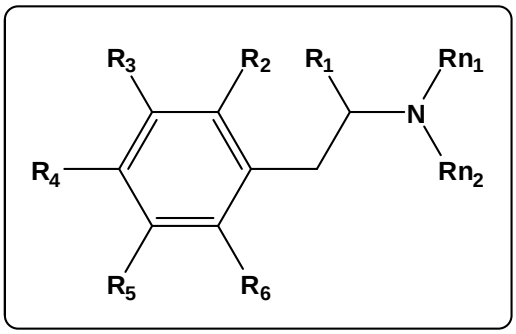

Figure 1
General formula of phenetylamines.

Table 1.
Phenetylamines derivatives and pA_2.

N°	R_1	R_2	R_3	R_4	R_5	R_{n1}	R_{n2}	pA_2
1	H	OH	H	H	OMe	H	H	7.10
2	H	$OCH_2C_6H_5$	H	H	OMe	Me	Me	5.44
3	H	OH	H	H	OMe	Me	Me	6.85
4	H	H	H	OH	H	H	H	5.07
5	Me	OMe	H	Br	OMe	H	H	6.93
6	Me	OMe	H	I	OMe	H	H	7.63
7	Me	OMe	H	NO_2	OMe	H	H	7.49
8	Me	H	H	OMe	H	H	H	5.38
9	H	H	H	H	H	H	H	5.26
10	Me	H	H	H	H	H	H	5.16
11	Me	H	H	H	H	H	H	5.35
12	H	OMe	H	H	H	H	H	5.52
13	H	H	OMe	H	H	H	H	5.89
14	H	H	H	OMe	H	H	H	5.10
15	Me	H	H	OMe	H	H	H	5.16
16	H	H	H	Me	H	H	H	5.51
17	H	OMe	H	H	OMe	H	H	6.85
18	H	OMe	H	H	OMe	Me	Me	6.52
19	H	H	OMe	OMe	H	H	H	5.36
20	H	H	3- OCH_2O-4		H	H	H	6.10
21	H	H	OMe	OMe	OMe	H	H	5.65
22	H	H	OMe	OMe	OMe	H	Me	5.28

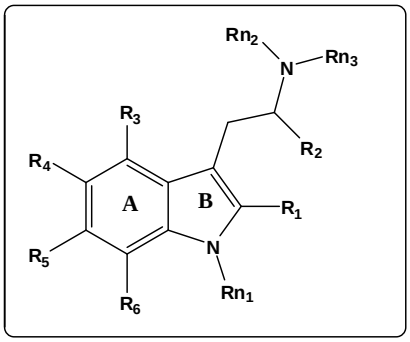

Figure 2.
General formula of indolealkylamines.

Table 2.
Indolealkylamines and pA_2.

N°	R_1	R_2	R_3	R_4	R_5	R_6	R_{n1}	R_{n2}	R_{n3}	pA_2
1	H	H	H	OH	H	H	H	Me	Me	7.41
2	H	H	H	OMe	H	H	H	Me	Me	7.08
3	H	H	H	OMe	H	H	H	Et	Et	6.94
4	H	H	H	Me	H	H	H	H	H	6.86
5	H	H	H	OMe	H	H	H	Me	Et	6.85
6	H	H	OH	H	H	H	H	Me	Me	6.84
7	H	H	H	OMe	H	H	H	Pr	Pr	6.53
8	H	H	H	Me	H	H	H	Me	Me	6.52
9	H	H	H	H	H	Me	H	Me	Me	6.29
10	H	H	NH_2	H	H	H	H	Me	Me	6.28
11	H	H	H	H	H	H	H	H	H	6.27
12	H	H	OMe	H	H	H	H	Me	Me	6.17
13	Me	H	H	H	H	H	H	Me	Me	6.04
14	H	H	H	H	H	H	Me	Me	Me	6.02
15	H	H	H	H	H	H	H	Me	Me	6.00
16	H	H	H	Ac	H	H	H	Me	Me	5.86
17	H	H	H	H	H	H	H	Et	ET	5.79
18	H	H	H	H	OMe	H	H	Me	Me	5.77
19	H	H	H	OMe	H	OMe	H	Me	Me	5.50
20	H	H	H	H	H	OMe	H	Me	Me	5.33
21	H	H	H	H	H	OH	H	Me	Me	4.88
22	H	Me	H	H	H	H	H	H	H	5.49
23	H	Me	H	H	H	H	H	H	H	6.46
24	H	H	H	H	H	Et	H	Me	Me	6.31
25	H	H	H	H	H	Br	H	Me	Me	6.51
26	H	H	H	OMe	H	Me	H	Me	Me	6.61
27	H	H	H	OMe	OMe	OMe	H	Me	Me	5.98
28	H	H	H	OMe	H	H	H	H	H	7.54
29	H	H	H	$OCOC(CH_3)_3$	H	H	H	Me	Me	7.42
30	H	H	OMe	H	H	H	H	H	H	6.58
31*	H	H	H	H	H	H	H	H	Me	5.97

* With a CH_2 group instead of N in ring B.

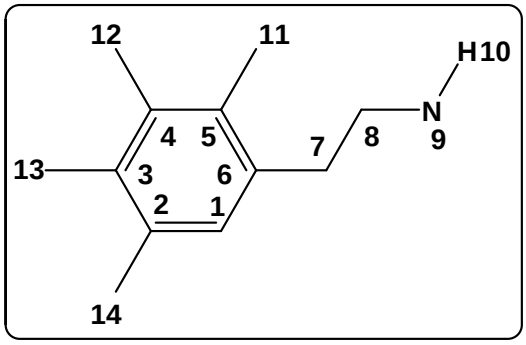

Figure 3.
Common skeleton of phenetylamines.

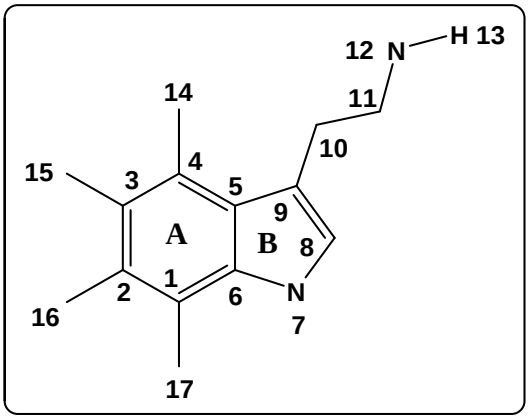

Figure 4.
Common skeleton of indolealkylamines.

Table 3
Beta coefficients and t-test for significance of coefficients in Eq. 2.

Var.	Beta	t(15)	p-level
S_{11}^{E}	-1.13	-17.37	<0.000001
ω_{10}	0.42	6.36	<0.00001
Q_{12}^{char}	0.23	4.15	<0.0009
F_7(HOMO)*	-0.20	-3.50	<0.003

Table 4
Matrix of squared correlation coefficients for the variables in Eq. 2.

	S_{11}^{E}	ω_{10}	Q_{12}^{char}
ω_{10}	0.28	1.00	
Q_{12}^{char}	0.03	0.05	1.00
F_7(HOMO)*	0.05	0.04	0.01

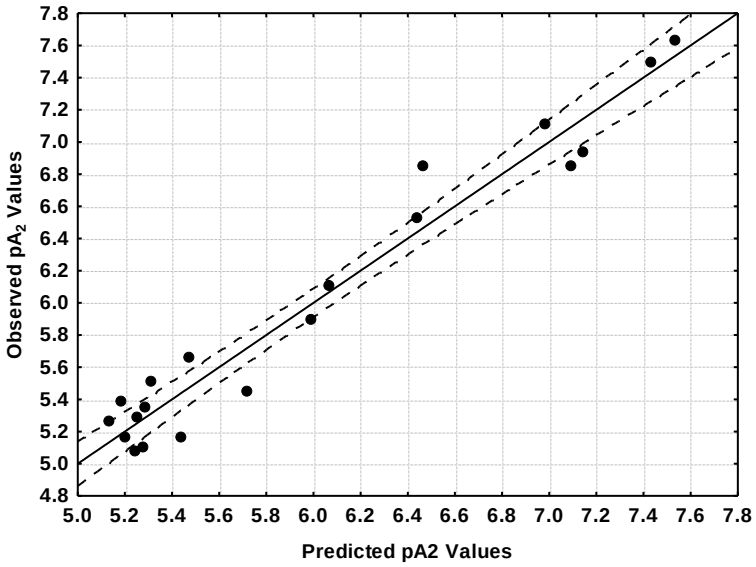

Figure 5
Plot of predicted *vs.* observed pA_2 values (Eq. 2). Dashed lines denote the 95% confidence interval.

Table 5
Beta coefficients and t-test for significance of coefficients in Eq. 3.

Var.	Beta	t(21)	p-level
S_2^E(HOMO)*	0.62	7.23	<0.000001
Q_7^{char}	0.35	4.95	<0.00007
S_{13}^E	0.30	4.32	<0.0003
S_6^E(HOMO)*	-0.41	-4.74	<0.0001
S_{17}^E	0.23	3.09	<0.006
φ_{R1}	0.18	2.49	<0.02

Table 6
Matrix of squared correlation coefficients for the variables in Eq. 3.

	S_2^E(HOMO)*	Q_7^{char}	S_{13}^E	S_6^E(HOMO)*	S_{17}^E
Q_7^{char}	0.00	1			
S_{13}^E	0.02	0.04	1.00		
S_6^E(HOMO)*	0.25	0.00	0.03	1.00	
S_{17}^E	0.00	0.01	0.04	0.12	1.00
φ_{R1}	0.12	0.03	0.01	0.02	0.01

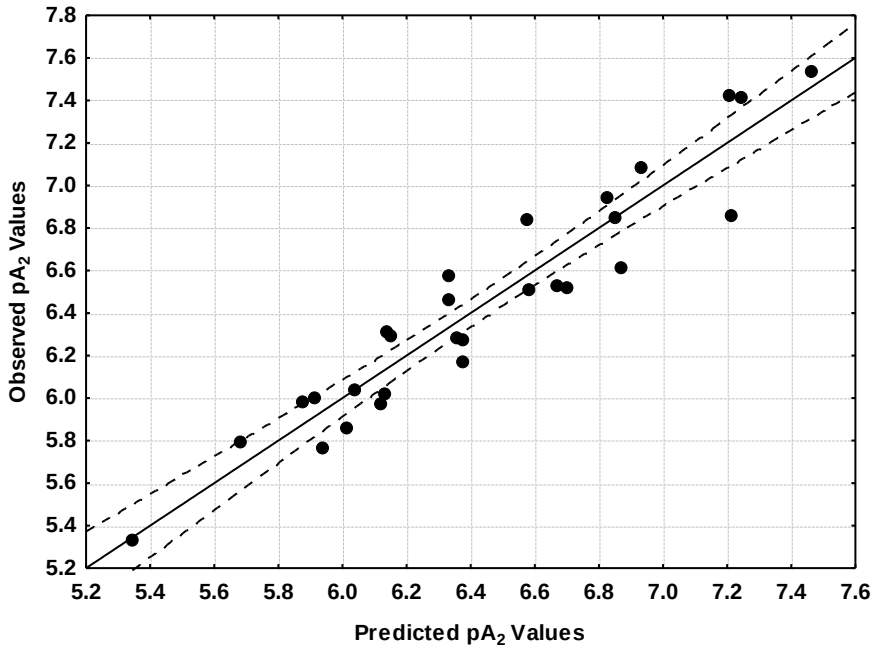

Figure 6
Plot of predicted *vs*. observed pA_2 values (Eq. 3). Dashed lines denote the 95% confidence interval.

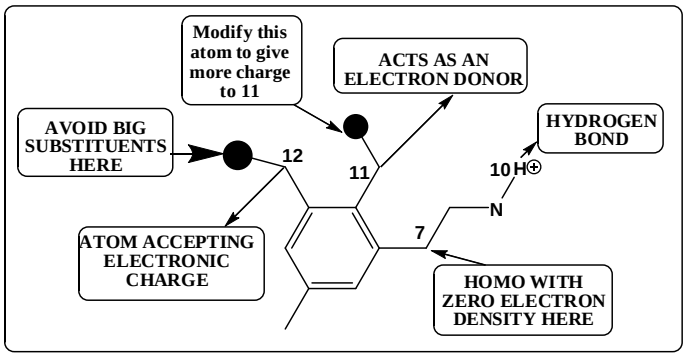

Figure 7
2D pharmacophore for phenetylamines.

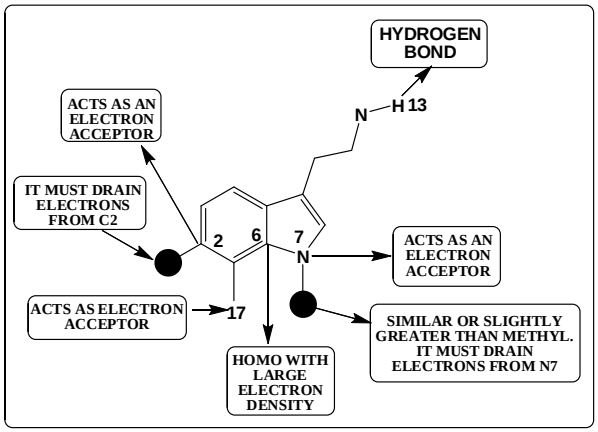

Figure 8
2D pharmacophore for indolealkylamines.

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