Quantum Chemical Approach to the Relationship Between Molecular Structure and Serotonin Receptor Binding Affinity

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Abstract □ We have analyzed the dependence of the serotonin receptor binding affinity on the atomic net charges, superdelocalizabilities, mass, and moment of inertia in a group of indole derivatives. The approaches employed are a new nonempirical quantitative structure-activity relationship (QSAR) method and multiple regression analyses. The results suggest that the indole derivatives interact with the receptor through a charge transfer between the phenyl ring and a counterpart in the receptor, plus some localized electrostatic interactions. Also, the fit of the equation obtained suggests that the indole derivatives have the aromatic ring placed in the same relative position during the interaction with the receptor.

Keyphrases □ Quantitative structure-activity relationships—perturbation theory, serotonin receptor binding affinity, quantum chemistry □ Serotonin—receptor binding affinity, perturbation theory, quantitative structure-activity relationship (QSAR) quantum chemistry

In recent years, there have been important advances toward a greater understanding of the activity of indole derivatives in terms of how their molecular structures might influence biological activity (1–16). It has been observed that there is a linear correlation between the potencies of tryptamine derivatives on the rat fundus and their ability to inhibit LSD (lysergide) binding to brain membranes (1, 2). This fact strongly supports the hypothesis that the conclusions based on the rat fundus receptor may hold also for the receptor in the brain.

A good correlation has been found between frontier orbital electron densities (FOED) and the ability of tryptamine derivatives to contract the rat fundus strip (3, 7). Also, it was observed (8, 9) that the position at which a high FOED was correlated with high biological potency corresponded to the sites at which the density of the highest occupied molecular orbital (HOMO) is localized in 5-hydroxytryptamine (serotonin, 5-HT), a fact that might explain the negative correlation between potency and FOED at certain atoms (1, 4). Also, the localization pattern of electron density for the HOMO and the next HOMO (NHOMO) of LSD is similar to that of 5-HT (10). These facts suggest that these molecules may interact with the receptor through a complex involving charge transfer from certain sites of the drug toward the receptor.

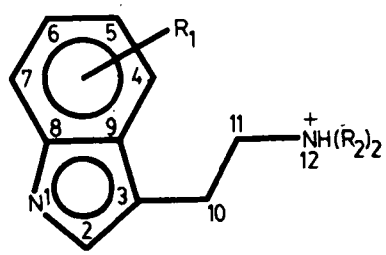
The patterns of the electrostatic potential maps of LSD and 5-HT show great similarities (10). The HOMO has a high influence on the electrostatic potential on the vicinities of the aromatic portion of the tryptamine derivatives (11).

Weinstein and co-workers (10, 12, 13) have suggested that a tryptamine congener attains a 5-HT-like recognition at the receptor by anchoring its side chain at the same place as 5-HT with its electrostatic vector (the vector connecting the minima through the area of the steepest change in the electrostatic potential) oriented parallel to the electrostatic vector in 5-HT. This matching is achieved by a conformational change in the side chain. For example, in the model of Weinstein and coworkers the aromatic rings of 5-HT and 6-HT are not in the same position during the interaction with the receptor (13). Also, on the basis of model complex calculations, these authors suggested that the interaction is mainly electrostatic (12), the transfer of charge being negligible.

The analysis of the photoelectron ionization potentials of LSD, some phenethylamines, and tryptamine derivatives (14, 15) has shown that not only the first ionization potential, but also the second ionization potential must be considered in order to correlate biological activity with the ionization potentials. This is consistent with the participation of the aromatic ring as an electron donor in the drug-receptor interaction, the ability of the stronger donor generally correlating with a greater activity. This study confirms the importance of the frontier orbitals, coinciding with the above points.

Glennon and Gessner (16) obtained a correlation between the binding affinities (pA_2) of some tryptamine derivatives in the 5-HT receptor of the rat stomach fundus and the ability to donate electrons in a localized charge transfer manner from the 4-position of the indole nucleus. Considering that the rat stomach fundus is an *in vitro* preparation (17, 18), the measured binding affinities will reflect only the binding energy between the drugs and the receptor. Also, as it seems that there is a certain similarity between the ability to interact with the rat fundus 5-HT receptor and 5-HT binding sites in the brain (1, 2), the study and analysis of the relations between pA_2 and the molecular electronic structure would be of a great help in a rational design of new tryptamine derivatives.

We report here the application of a new quantum-statistical approach, searching for a relationship between pA_2 and some reactivity indices.



EXPERIMENTAL SECTION

Consider the weak interaction of a drug, D_i, and a macromolecular receptor, R. The model is based on the following reasonable hypotheses (19):

1. The conformation of the receptor is so strongly preferred that the binding energy is accounted for entirely in terms of local atomic interactions.
2. The total molecular partition functions can be factorized in terms of independent and uncoupled translational, rotational, vibrational, and electronic partition functions.
3. Only the electronic ground state is important in the electronic partition function.

With this model, it is possible to show formally that the drug-receptor equilibrium constant, K_i may be expressed as (19):

$$\log K_i = q + b \cdot \log M_i + c \cdot \log \sigma_i/(\mathrm{ABC})_i^{3/2}) + d\Delta E_i \quad \text{(Eq. 1)}$$

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Table I—Experimental and Calculated pA_2 Values

Compound[a]	R_1	R_2	pA_2 Calculated[b]	pA_2 Observed[c]
I	5-OH	Me	7.39	7.41
II	5-OMe	Me	7.10	7.08
III	4-OH	Me	6.65	6.84
IV	5-Me	Me	6.31	6.52
V	7-Me	Me	5.84	6.29
VI	4-NH_2	Me	6.41	6.28
VII	5-Me	H	6.63	6.86
VIII	—H	H	6.54	6.25
IX	4-OMe	Me	6.19	6.17
X[d]	—H	Me	5.98	6.04
XI[e]	—H	Me	6.02	6.03
XII[f]	—H	Me	6.04	6.02
XIII	—H	Me	6.17	6.00
XIV	6-OMe	Me	6.01	5.77
XV	5,7-$(OMe)_2$	Me	5.44	5.50
XVI	7-OMe	Me	5.19	5.33
XVII	7-OH	Me	5.19	4.88
XVIII	5,6,7-$(OMe)_3$	Me	6.04	5.98
XIX	—H	H, Me	5.87	5.97
XX	5-OMe, 7-Me	Me	6.81	6.61
XXI	5-$OCOCH_3$	Me	7.59	7.71
XXII	5-$COCH_3$	Me	5.91	5.86
XXIII	5-$OCOCH_2CH_3$	Me	7.43	7.27
XXIV	5-$OCO(CH_2)_2CH_3$	Me	7.26	7.32

[a] See Fig. 1 for the substituent position. [b] Calculated using Eq. 5. [c] Taken from Ref. 26. [d] With a methyl group in position 2. [e] With S instead of N in position 1. [f] With a methyl group in position 1.

where a, b, c, and d are constants; M, σ, and (ABC) are, respectively, the mass, the symmetry number, and the product of the three moments of inertia about the three principal axes of rotation of the ith drug molecule; and ΔE_i is the difference between the ground state energy of the complex and the energies of D_i and R, *i.e.*:

$$\Delta E_i = E_{D_iR} - (E_{D_i} + E_R) \qquad \text{(Eq. 2)}$$

In a first approach, we shall accept that, among all the components of ΔE_i the most important is the change in the electronic energy ΔE_i^e (20). Considering the interaction of the indole derivatives with the receptor as weak (*i.e.*, without the formation of covalent bonds), a perturbation treatment (21) may be performed for the evaluation of ΔE_i^e. In this way, after some approximations as the molecular structure of the receptor is unknown (22, 23), ΔE_i^e can be expressed as:

$$E_i^e = q + \sum_p (f_p Q_p^i + g_p S_p^{E,i} + h_p S_p^{N,i}) \qquad \text{(Eq. 3)}$$

where q, f_p, g_p, and h_p are constants; and Q_p^i, $S_p^{E,i}$, and $S_p^{N,i}$ are, respectively, the net charge, the electrophilic superdelocalizability, and the nucleophilic superdelocalizability of atom p in molecule i (24).

Inserting Eq. 3 into Eq. 1, we get (19):

$$\log K_i = q' + b \cdot \log M_i + c \cdot \log [\sigma_i (\mathrm{ABC})_i^{-3/2}] + \sum_p (f_q Q_p^i + g_p S_p^{E,i} + h_p S_p^{N,i}) \qquad \text{(Eq. 4)}$$

The summation on p is over a set of atoms common to all the drugs that interact with the receptor. If Eq. 4 is to be satisfied, there must exist a common set of atomic reactivity indices in all the drugs interacting with the same receptor.

We have taken the pA_2 value as a good approximation to the affinity constant of the drug-receptor complex (25). These values were selected from the literature (26) (Table I).

We employed statistical analysis to determine the set of atomic properties in an attempt to find a group of variables whose variation better explains the variation of the pA_2 values in a series of molecules. A special case of Eq. 4 has been applied with success to very different kinds of drugs (22, 27–29).

The ring geometry is displayed in Fig. 1; this geometry is similar to the one used by Inoue *et al.* (30). The bond distances for the ring substituents were taken from the literature (31).

Considering that the structure of LSD possesses both the phenylalkylamine and the indolealkylamine molecular subfragments (32), we accepted as a working hypothesis that the phenethylamine and tryptamine derivatives mimic partially or totally the LSD structure during interaction with the receptor. With this consideration, and for the sake of simplicity, we placed the amine

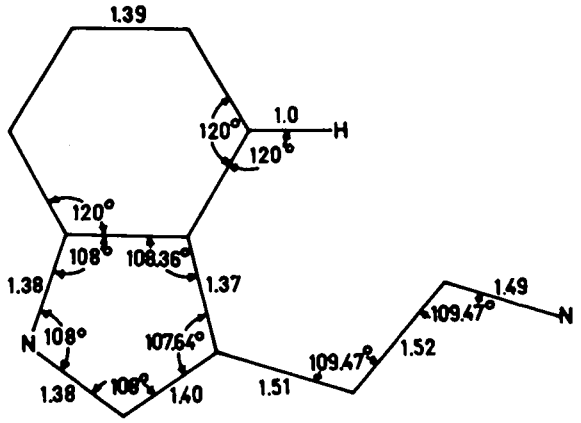

Figure 1—*Geometric parameters for the ring and the side chain.*

chain in the same plane as the phenyl ring. The net charges and the superdelocalizabilities were calculated from a CNDO/2 wave function (33).

RESULTS AND DISCUSSION

The statistical fitting of Eq. 4 was performed by means of a stepwise regression technique with pA_2 as the dependent variable. The net charges and the electrophilic superdelocalizabilities of the aromatic ring, plus the net charges and the nucleophilic superdelocalizabilities of the side-chain atoms, plus the mass and moment of inertia factors were used as independent variables (20 in all) (Table II). More than 500 combinations of variables were analyzed. The best expression found is:

$$pA_2 = 8.2812 + 3.1383Q_4 + 2.0529Q_7 + 4.8660S_5^E - 3.1825S_7^E - 2.2494S_8^E + 1.1416I \qquad \text{(Eq. 5)}$$

where $I = \log [\sigma_i/(\mathrm{ABC})_i^{3/2}]$.

This equation has a multiple correlation coefficient (r^2) of 0.97, which represents a significance of >94.1%, and a mean SD of 0.20. The analysis of variance (34) of Eq. 5 gives $F_{6,17} = 42.22$, showing the very high significance of this equation ($p < 0.0005$).

The results of the Student's t test for the significance of the coefficients are shown in Table III; the pA_2 values calculated with Eq. 5 are shown in Table I. The squared correlation matrix for the independent variables is presented in Table IV. The variables Q_4 and S_5^E appear with a relatively high r^2 value (Q_4 explaining the 62% of S_5^E). Nevertheless, considering that a certain degree of correlation between variables belonging to an aromatic system must be expected, and that these two variables have different physical meanings (the net charges representing electrostatic interactions and the electrophilic superdelocalizabilities being related to charge transfer), we think that they represent different physical processes.

Also, from the work of Topliss and Edwards (35), we can see that the relationship between the number of observations required to screen 18 variables, while keeping the probability of encountering a chance correlation with $r^2 \geq 0.9$ at the ≤1% level, is ~19. Therefore, the risk of chance correlation is very low.

The binding affinity is, therefore, related to a definite set of electronic indices. Considering the high significance of Eq. 5, we accepted that, within the accuracy of the approximations used for the determination of ΔE_i and pA_2, the results obtained suggest the existence of a direct dependence between the variation of pA_2 and those of the reactivity indices of Eq. 5.

The appearance of the total atomic electrophilic superdelocalizabilities in Eq. 5 indicates that the variation of pA_2 will depend on the relative reactivity of atoms 5, 7, and 9 toward the electrophilic components of the receptor. Also, their appearance suggests that the drug–receptor interaction has a strong orbital-controlled character (21). This is in perfect accord with the idea of a localized charge transfer from the drug to the receptor.

Remembering that S_5^E contains the contribution of the HOMO, the appearance of S_5^E is similar to that of the FOED at the 5-position. We cannot ensure that the frontier orbitals play a high significant role, because S^E, by including the other molecular orbitals, will obscure the contribution of the HOMO and NHOMO. The dependence of the variation of pA_2 on a variation of Q_4 and Q_7 indicates an electrostatic interaction between these atoms and one or more centers in the receptor.

The other index which contributes significantly is related to the molecular moment of inertia, and is defined as:

Table II—Variable Values Employed in the Statistical Analysis

Compound	Experimental pA_2	Q_4	Q_5	Q_6	Q_7	Q_8	Q_9	Q_{10}	Q_{11}	Q_{12}
I	6.2500	−0.0287	−0.0001	0.0073	−0.0244	0.1010	−0.0024	0.0028	0.1075	−0.0570
II	6.8600	−0.0528	0.0455	−0.0112	−0.0175	0.0923	0.0022	0.0032	0.1074	−0.0570
III	6.0000	−0.0285	−0.0033	0.0063	−0.0265	0.0998	−0.0027	0.0007	0.1057	0.0332
IV	7.4100	−0.0843	0.1717	−0.0511	−0.0044	0.0797	0.0157	0.0016	0.1053	0.0334
V	7.0800	−0.0864	0.1735	−0.0509	−0.0074	0.0801	0.0150	0.0016	0.1053	0.0333
VI	6.5200	−0.0519	0.0410	−0.0123	−0.0201	0.0909	0.0030	0.0021	0.0964	0.0752
VII	6.8400	0.1442	−0.0588	0.0251	0.0479	0.1158	−0.0392	−0.0085	0.0969	0.0263
VIII	6.2800	0.1400	−0.0714	0.0332	−0.0632	0.1214	−0.0524	−0.0151	0.1803	0.0089
IX	6.1700	0.1444	−0.0596	0.0231	−0.0471	0.1159	−0.0423	−0.0088	0.0989	0.0261
X	5.7700	−0.0089	−0.0537	0.1848	−0.0925	0.1174	−0.0225	0.0005	0.0964	0.0754
XI	6.2900	−0.0416	0.0028	−0.0180	0.0218	0.0808	0.0034	0.0019	0.0964	0.0750
XII	5.3300	−0.0555	0.0163	−0.0510	0.1551	0.0519	0.0154	0.0022	0.0962	0.0752
XIII	4.8800	−0.0540	0.0175	−0.0479	0.1521	0.0461	0.0168	0.0014	0.1056	0.0330
XIV	5.5000	−0.1133	0.1922	−0.1095	−0.1733	0.0319	0.0329	0.0031	0.0958	0.0754
XV	6.0400	−0.0339	−0.0020	0.0017	−0.0255	0.0949	0.0024	0.0055	0.1058	0.0331
XVI	6.0200	−0.0293	−0.0035	0.0041	−0.0251	0.0905	−0.0028	0.0016	0.1056	0.0331
XVII	6.0300	−0.0656	0.0454	−0.0282	0.0588	0.0145	0.0858	−0.0109	0.1049	0.0339
XVIII	5.9800	−0.0940	0.1471	0.0812	0.1165	0.0513	0.0140	0.0021	0.0958	0.0755
XIX	5.9700	−0.0284	−0.0022	0.0066	−0.0256	0.1001	−0.0018	0.0025	0.1045	−0.0287
XX	6.6100	−0.0992	0.1789	−0.0758	0.0402	0.0612	0.0209	0.0029	0.0960	0.0751
XXI	7.7100	−0.0939	0.1871	−0.1571	−0.0127	0.0797	0.0106	0.0032	0.1009	0.0003
XXII	5.8600	−0.0193	−0.0132	0.0225	−0.0332	0.1112	−0.0060	0.0016	0.1010	0.0007
XXIII	7.2700	−0.0939	0.1877	−0.5184	−0.0133	0.0792	0.0108	0.0033	0.1009	0.0002
XXIV	7.3200	−0.0942	0.1879	−0.1586	−0.0135	0.0790	0.0107	0.0033	0.1009	0.0002

Compound	S_4^E	S_5^E	S_6^E	S_7^E	S_8^E	S_9^E	S_{10}^N	S_{11}^N	S_{12}^N	Mass-Related Term	Moment of Inertia-Related Term
I	−4.4842	−4.4187	−4.4272	−4.4573	−4.1912	−4.3348	24.7255	21.0720	57.1031	−3.3112	−2.7062
II	−4.5953	−4.3449	−4.5129	−4.4552	−4.2362	−4.3398	24.4622	19.8324	54.6363	−3.3655	−2.8497
III	−4.5575	−4.4875	−4.4891	−4.5244	−4.2582	−4.4064	12.6679	4.4329	−37.7952	−3.4157	−2.9807
IV	−4.6877	−4.0953	−4.5876	−4.4436	−4.3075	−4.3531	20.1351	3.6279	−43.1664	−3.4685	−3.0987
V	−4.7027	−4.1367	−4.6365	−4.4630	−4.3147	−4.3632	19.5164	1.5388	−46.7765	−3.5116	−3.2093
VI	−4.6607	−4.4043	−4.5662	−4.5130	−4.2973	−4.4058	12.8513	−113.9695	−218.5616	−3.4622	−3.0917
VII	−4.1200	−4.5587	−4.4034	−4.5598	−4.1815	−4.4357	94.9910	7995.5313	15568.4297	−3.4685	−3.0082
VIII	−4.0844	−4.6561	−4.4170	−4.6543	−4.1987	−4.5106	23.9091	0.5264	−24.1683	−3.4654	−3.0058
IX	−4.1555	−4.6021	−4.4175	−4.5660	−4.1892	−4.4478	16.5885	304.8059	551.8584	−3.5116	−3.0765
X	−4.4798	−4.5784	−4.1217	−4.7075	−4.2129	−4.4580	10.1589	−77.9774	−155.0132	−3.5116	−3.2070
XI	−4.6234	−4.4846	−4.5956	−4.4391	−4.3428	−4.4111	6.9412	−176.9974	−320.2112	−3.4622	−3.0707
XII	−4.6350	−4.4200	−4.6129	−4.1407	−4.3671	−4.3477	−0.7368	−97.3377	−183.6725	−3.5086	−3.1400
XIII	−4.6367	−4.4215	−4.6052	−4.1151	−4.3493	−4.3421	17.4444	10.4940	−30.4729	−3.4685	−3.0736
XIV	−4.7826	−4.0756	−4.7632	−4.0857	−4.4261	−4.3078	16.6094	−173.3659	−315.2969	−3.5952	−3.3486
XV	−4.6018	−4.5098	−4.5304	−4.5450	−4.3035	−4.4261	42.9891	11.9697	−43.1691	−3.4622	−3.0983
XVI	−4.5798	−4.5055	−4.5108	−4.5419	−4.3104	−4.4331	25.6743	3.9224	−47.8569	−3.4622	−3.0878
XVII	−4.5536	−4.2837	−4.4861	−4.3542	−4.4048	−4.1529	29.7625	16.5035	26.0292	−3.4718	−3.0376
XVIII	−4.7039	−4.1612	−4.3536	−4.2226	−4.3643	−4.3479	18.1875	−109.3894	−210.1167	−3.6692	−3.4542
XIX	−4.5179	−4.4499	−4.4551	−4.4874	−4.2232	−4.3690	21.9919	42.8507	26.9736	−3.3655	−3.1653
XX	−4.7688	−4.1345	−4.7445	−4.3788	−4.3891	−4.3686	12.4215	−615.0073	−1042.3286	−3.5520	−3.2793
XXI	−4.7736	−4.1352	−5.3965	−4.6469	−4.4079	−4.4394	22.5130	29.9472	10.9827	−3.5872	−3.3674
XXII	−4.5132	−4.3936	−4.4493	−4.4701	−4.1739	−4.3431	20.8217	37.4708	22.6680	−3.5463	−3.2588
XXIII	−4.7839	−4.1432	−5.4065	−4.6520	−4.4140	−4.4454	22.2730	29.3867	10.2336	−3.6258	−3.4705
XXIV	−4.7894	−4.1478	−5.4149	−4.6567	−4.4182	−4.4493	22.1426	29.1086	9.8565	−3.6599	−3.5801

$$I = \log \sigma_i - (3/2)(\log A + \log B + \log C) \qquad \text{(Eq. 6)}$$

For explanatory purposes we shall examine the case where $A = Ixx$. In this case we have:

$$\log A = \log Ixx = \log \sum_i m_i(y_i^2 + z_i^2) \qquad \text{(Eq. 7)}$$

where m_i is the mass of atom i, whose coordinates are x_i, y_i, z_i. Inspection of Eq. 7 shows that these kinds of terms will appear in three cases: (*a*) when molecules differ in the nature of an atom at a certain position (m_i will be different); (*b*) when molecules differ in the position of an atom ($m_i y_i^2$ or $m_i z_i^2$ will be different); (*c*) a mixture of cases *a* and *b*. Therefore, this index can be associated with a purely positional effect and, in the case where all the molecules have a different substituent attached to the same place, with a steric effect.

Also, it is interesting to note that Eq. 5 does not include terms belonging to the side-chain atoms. There are two hypotheses explaining this fact:

1. The side chains used throughout this study are relatively constant, with the terminal amine position being primary or possessing a dimethyl group. In this case the contribution of the side chain will be almost constant, and it will be included in the constant term of Eq. 5.
2. The side chain, especially the charged nitrogen atom, only participates in the orientation and long-range recognition of these molecules by the receptor (36).

Table III—Student's *t* Test Values for Variables of Eq. 5

Variable	*t* Value	*p*
Q_4	3.20	<0.005
Q_7	3.11	<0.005
S_5^E	10.74	<0.0005
S_7^E	−9.06	<0.0005
S_9^E	−2.36	<0.025
I	4.73	<0.0005

Table IV—Squared Correlation Matrix for Varibles in Eq. 5

	Q_4	Q_7	S_5^E	S_7^E	S_9^E	I
Q_4	1.00					
Q_7	0.01	1.00				
S_5^E	0.62	0.0009	1.00			
S_7^E	0.12	0.18	0.07	1.00		
S_9^E	0.19	0.07	0.13	0.43	1.00	
I	0.19	0.0004	0.34	0.0004	0.02	1.00

Given that we are interested in the relative variation of the net charges, of the superdelocalizabilities, and of the inertia moment term, the position of the side chain will not be important if we place it in the same relative position in all the molecules considered. Also, as the pyrrole portion of the indole nucleus is relatively homogeneous in the molecules of Table I, it is not possible to determine its true importance in the regulation of the drug-receptor interaction.

Remembering that S^E is always negative, and considering only its absolute value, we may conclude that a high pA_2 is associated with: positive net charges for atoms 4 and 7; a low value of log $[\sigma/(ABC)^{3/2}]$ (which suggests a limit value for the size of the substituents); high S^E values for atoms 7 and 9, and a low S^E value for atom 5. This indicates that for atom 7 there must be an equilibrium between a positive (or slightly negative) net charge and an electronic density that participates in the interaction.

As an example of the predictive capacity of Eq. 5, we have considered the case of the 7-bromo-*N*,*N*-dimethyltryptamine. The experimental pA_2 for this compound is 6.51 (26), and Eq. 5 gives a pA_2 of 6.93.

Another problem is the solvation. It is clear that the charged groups of the drugs (*i.e.*, —$COCH_3$, —OH, *etc.*) are solvated. As we have shown[1], part of the solvation energy change calculated with the Born equation (37) is implicitly considered in the electrostatic terms of Eq. 5.

In conclusion, it seems well established that the 5-position in indole derivatives has a first-order importance in regulating pA_2, and that this regulation is associated with the availability of an electron density at this position. Our results agree with those of Weinstein and co-workers (8–10). Also, Eq. 5 shows that the ability of the ring to donate electrons is of great importance in the variation of pA_2; this agrees well with experimental (14, 15) and theoretical (10, 16) results. However, our results do not support suggestions that the charge transfer is negligible (12).

The derivation of Eq. 5 suggests very strongly that these molecules interact with the serotonergic receptor in a way such that their aromatic rings are in the same relative positions. This conclusion is in contrast with the previous suggestion that the main process in this drug-receptor interaction is the orientation of the electrostatic vector (10, 12, 13).

A question raised by this and other similar studies is why is it not possible to obtain equations with still higher multiple correlation coefficients without adding highly correlated variables. It seems that, experimental errors apart, the factors responsible are: (*a*) the method employed to obtain the reactivity indexes, especially the nucleophilic superdelocalizability (38) and (*b*) the quality of the approximations made to simplify the expression for ΔE_i^e given by perturbation theory[1].

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