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Abstract \square 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 structureactivity 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.
- 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):

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

Table I-Experimental and Calculated pA2 Values

			pA	2
Compound ^a	R ₁	R ₂	Calculated ^b	Observed ^c
1	5-OH	Me	7.39	7.41
11	5-OMe	Me	7.10	7.08
111	4-OH	Me	6.65	6.84
1V	5-Me	Me	6.31	6.52
v	7-Me	Me	5.84	6.29
VI	4-NH2	Me	6.41	6.28
VII	5-Me	н	6.63	6.86
VIII	—Н	н	6.54	6.25
IX	4-OMe	Me	6.19	6.17
Xď	—Н	Me	5.98	6.04
XI۲	—н	Me	6.02	6.03
XII	Н	Me	6.04	6.02
XIII	—н	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 ₂ CH ₃	Me	7.43	7.27
XXIV	5-OCO(CH ₂) ₂ CH 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. ^c 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 *i*th 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.*:

$$\Delta E_i = E_{\mathsf{D}_i\mathsf{R}} - (E_{\mathsf{D}_i} + E_{\mathsf{R}}) \tag{Eq. 2}$$

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:

$$E_{i}^{c} = q + \sum (f_{p}Q_{p}^{i} + g_{p}S_{p}^{\mathrm{E},i} + h_{p}S_{p}^{\mathrm{N},i})$$
(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):

$$\log K_{i} = q' + b \cdot \log M_{i} + c \cdot \log [\sigma_{i} (ABC)_{i}^{-3/2}] + \sum_{p} \{f_{q}Q_{p}^{i} + g_{p}S_{p}^{E,i} + h_{p}S_{p}^{N,i}\} \quad (Eq. 4)$$

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:

 $pA_2 = 8.2812 + 3.1383Q_4 + 2.0529Q_7 + 4.8660S_5^{E}$

$$-3.1825S_{\text{F}} - 2.2494S_{\text{F}} + 1.1416I$$
 (Eq. 5)

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

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^c appear with a relatively high r^2 value (Q_4 explaining the 62% of S_5^c). 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 $r^2 \ge 0.9$ at the $\le 1\%$ 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 - Tailable Talaça Linpidyea in the Statistical Analysis	Table II	-Variable	Values	Emplo	yed in	the S	Statistical	Analysis
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	Experi	mental										
Compound	l p.	A ₂	Q4	Q5	I	Q6	Q1	Q_8	Q9	Q10	<i>Q</i> 11	Q12
I	6.2	500	-0.0287	-0.00	01 0	.0073	-0.0244	0.1010	-0.0024	0.0028	0.1075	-0.0570
II	6.8	600	-0.0528	0.04	55 -0	.0112	-0.0175	0.0923	0.0022	0.0032	0.1074	-0.0570
III	6.0	000	-0.0285	-0.00	33 0	.0063	-0.0265	0.0998	-0.0027	0.0007	0.1057	0.0332
IV	7.4	100	-0.0843	0.17	17 -0	.0511	-0.0044	0.0797	0.0157	0.0016	0.1053	0.0334
v	7.0	800	-0.0864	0.17	35 -0	.0509	-0.0074	0.0801	0.0150	0.0016	0.1053	0.0333
VI	6.5	200	-0.0519	0.04	10 -0	.0123	-0.0201	0.0909	0.0030	0.0021	0.0964	0.0752
VII	6.8	400	0.1442	-0.05	88 0	.0251	0.0479	0.1158	-0.0392	-0.0085	0.0969	0.0263
V III	0.2	800	0.1400	-0.07	14 U	0332	-0.0632	0.1214	-0.0324	-0.0131	0.1803	0.0089
	0.1	700	-0.0080	-0.03	90 U 27 O	1949	-0.0471	0.1139	-0.0423	-0.0088	0.0767	0.0201
vî	5.7	000	-0.0009	0.05	28 –0	0180	0.0218	0.0808	0.0225	0.0005	0.0904	0.0750
Ŷ	5 3	300	-0.0555	0.00	20 0 63 _0	0510	0.1551	0.0500	0.0154	0.0012	0.0962	0.0752
	4.8	800	-0.0540	0.01	75 –0	0479	01521	0.0461	0.0168	0.0014	0 1056	0.0330
XIV	5 5	000	-0.1133	0 19	$\frac{1}{22}$ -0	1095	-0.1733	0.0319	0.0329	0.0031	0.0958	0.0754
xv	6.0	400	-0.0339	-0.00	20 0	.0017	-0.0255	0.0949	0.0024	0.0055	0.1058	0.0331
xvi	6.0	200	-0.0293	-0.00	35 0	.0041	-0.0251	0.0905	-0.0028	0.0016	0.1056	0.0331
XVII	6.0	300	-0.0656	0.04	54 -0	.0282	0.0588	0.0145	0.0858	-0.0109	0.1049	0.0339
XVIII	5.9	800	-0.0940	0.14	71 0	.0812	0.1165	0.0513	0.0140	0.0021	0.0958	0.0755
XIX	5.9	700	-0.0284	-0.00	22 0	.0066	-0.0256	0.1001	-0.0018	0.0025	0.1045	-0.0287
XX	6.6	100	-0.0992	0.17	89 -0	.0758	0.0402	0.0612	0.0209	0.0029	0.0960	0.0751
XXI	7.7	100	-0.0939	0.18	71 –0	.1571	-0.0127	0.0797	0.0106	0.0032	0.1009	0.0003
XXII	5.8	600	-0.0193	-0.01	32 0	.0225	-0.0332	0.1112	-0.0060	0.0016	0.1010	0.0007
XXIII	7.2	700	-0.0939	0.18	77 —0	.5184	-0.0133	0.0792	0.0108	0.0033	0.1009	0.0002
XXIV	7.3	200	-0.0942	0.18	79 -0	.1586	-0.0135	0.0790	0.0107	0.0033	0.1009	0.0002
										Mass-Related	Momen	t of Inertia-
Compound	~ F		- 5	~ F	c F	CE.	aN	CN .	- N1			. —
- surpound	S4	55	55	55	58	59	Siò	S_{11}	S_{12}^{11}	Term	Rela	ted Term
I	-4 4842	-4 4187	SE -4 4272	-4 4573	-4 1912	-4.3348	24,7255	21.0720	57.1031	Term -3.3112	Rela	ted Term
I	-4.4842 -4 5953	-4.4187 -4.3449	S ⁶ -4.4272 -4.5129	S ⁶ -4.4573 -4.4552	-4.1912 -4.2362	-4.3348 -4.3398	24.7255 24.4622	21.0720 19.8324	57.1031 54.6363	-3.3112 -3.3655	Rela –	ted Term
I II III	-4.4842 -4.5953 -4.5575	-4.4187 -4.3449 -4.4875	SE -4.4272 -4.5129 -4.4891	S ⁻ -4.4573 -4.4552 -4.5244	-4.1912 -4.2362 -4.2582	-4.3348 -4.3398 -4.4064	24.7255 24.4622 12.6679	21.0720 19.8324 4.4329	$\frac{S_{12}^{n}}{57.1031}$ 54.6363 -37.7952	Term -3.3112 -3.3655 -3.4157	Rela 	2.7062 2.8497 2.9807
I II III IV	-4.4842 -4.5953 -4.5575 -4.6877	-4.4187 -4.3449 -4.4875 -4.0953	SE -4.4272 -4.5129 -4.4891 -4.5876	S ⁻⁶ -4.4573 -4.4552 -4.5244 -4.4436	-4.1912 -4.2362 -4.2582 -4.3075	-4.3348 -4.3398 -4.4064 -4.3531	Siò 24.7255 24.4622 12.6679 20.1351	21.0720 19.8324 4.4329 3.6279	57.1031 54.6363 -37.7952 -43.1664	Term -3.3112 -3.3655 -3.4157 -3.4685	Rela	2.7062 2.8497 2.9807 3.0987
I II III IV V	-4.4842 -4.5953 -4.5575 -4.6877 -4.7027	-4.4187 -4.3449 -4.4875 -4.0953 -4.1367	<i>S</i> ⁶ -4.4272 -4.5129 -4.4891 -4.5876 -4.6365	S ^e -4.4573 -4.4552 -4.5244 -4.4436 -4.4630	-4.1912 -4.2362 -4.2582 -4.3075 -4.3147	-4.3348 -4.3398 -4.4064 -4.3531 -4.3632	Sib 24.7255 24.4622 12.6679 20.1351 19.5164	21.0720 19.8324 4.4329 3.6279 1.5388		Term -3.3112 -3.3655 -3.4157 -3.4685 -3.5116	Rela	2.7062 2.8497 2.9807 3.0987 3.2093
I II III IV V VI	-4.4842 -4.5953 -4.5575 -4.6877 -4.7027 -4.6607	-4.4187 -4.3449 -4.4875 -4.0953 -4.1367 -4.4043	<i>S</i> ⁶ -4.4272 -4.5129 -4.4891 -4.5876 -4.6365 -4.5662	S ^e -4.4573 -4.4552 -4.5244 -4.4436 -4.4630 -4.5130	-4.1912 -4.2362 -4.2582 -4.3075 -4.3147 -4.2973	-4.3348 -4.3398 -4.4064 -4.3531 -4.3632 -4.4058	Sib 24.7255 24.4622 12.6679 20.1351 19.5164 12.8513	21.0720 19.8324 4.4329 3.6279 1.5388 -113.9695	S_{12} 57.1031 54.6363 -37.7952 -43.1664 -46.7765 -218.5616	Term -3.3112 -3.3655 -3.4157 -3.4685 -3.5116 -3.4622	Rela 	ted Term 2.7062 2.8497 2.9807 3.0987 3.2093 3.0917
I II IV V VI VII	-4.4842 -4.5953 -4.5575 -4.6877 -4.7027 -4.6607 -4.1200	-4.4187 -4.3449 -4.4875 -4.0953 -4.1367 -4.4043 -4.5587	Se -4.4272 -4.5129 -4.4891 -4.5876 -4.6365 -4.5662 -4.4034	S ^e -4.4573 -4.4552 -4.5244 -4.4436 -4.4630 -4.5130 -4.5598	-4.1912 -4.2362 -4.2582 -4.3075 -4.3147 -4.2973 -4.1815	-4.3348 -4.3398 -4.4064 -4.3531 -4.3632 -4.4058 -4.4357	Sib 24.7255 24.4622 12.6679 20.1351 19.5164 12.8513 94.9910	21.0720 19.8324 4.4329 3.6279 1.5388 113.9695 7995.5313	<u>57.1031</u> 54.6363 -37.7952 -43.1664 -46.7765 -218.5616 15568.4297	Term -3.3112 -3.3655 -3.4157 -3.4685 -3.5116 -3.4622 -3.4685	Rela	ted Term 2.7062 2.8497 2.9807 3.0987 3.2093 3.0917 3.0082
I II IV V VI VII VII	<u>54</u> -4.4842 -4.5953 -4.5575 -4.6877 -4.7027 -4.6607 -4.1200 -4.0844	-4.4187 -4.3449 -4.4875 -4.0953 -4.1367 -4.4043 -4.5587 -4.6561	Se -4.4272 -4.5129 -4.4891 -4.5876 -4.6365 -4.5662 -4.4034 -4.4170	$\begin{array}{r} 5^{6}\\ -4.4573\\ -4.4552\\ -4.5244\\ -4.4436\\ -4.4630\\ -4.5130\\ -4.5598\\ -4.6543\end{array}$	5 k -4.1912 -4.2362 -4.2582 -4.3075 -4.3147 -4.2973 -4.1815 -4.1987	-4.3348 -4.3398 -4.4064 -4.3531 -4.3632 -4.4058 -4.4357 -4.5106	Sib 24.7255 24.4622 12.6679 20.1351 19.5164 12.8513 94.9910 23.9091	21.0720 19.8324 4.4329 3.6279 1.5388 -113.9695 7995.5313 0.5264	S12 57.1031 54.6363 -37.7952 -43.1664 -46.7765 -218.5616 15568.4297 -24.1683	Term -3.3112 -3.3655 -3.4157 -3.4685 -3.5116 -3.4622 -3.4685 -3.4654	Rela 	ted Term 2.7062 2.8497 2.9807 3.0987 3.2093 3.0917 3.0082 3.0058
I II III IV V VI VII VIII IX	Si -4.4842 -4.5953 -4.5575 -4.6877 -4.7027 -4.6607 -4.1200 -4.0844 -4.1555	$\begin{array}{r} -4.4187 \\ -4.3449 \\ -4.4875 \\ -4.0953 \\ -4.1367 \\ -4.4043 \\ -4.5587 \\ -4.6561 \\ -4.6021 \end{array}$	Se -4.4272 -4.5129 -4.4891 -4.5876 -4.6365 -4.5662 -4.4034 -4.4170 -4.4175	$\begin{array}{r} 5^{\circ}_{7} \\ -4.4573 \\ -4.4552 \\ -4.5244 \\ -4.4436 \\ -4.4630 \\ -4.5130 \\ -4.5598 \\ -4.6543 \\ -4.5560 \end{array}$	5 -4.1912 -4.2362 -4.2582 -4.3075 -4.3147 -4.2973 -4.1815 -4.1987 -4.1892	-4.3348 -4.3398 -4.4064 -4.3531 -4.3632 -4.4058 -4.4357 -4.5106 -4.4478	Siè 24.7255 24.4622 12.6679 20.1351 19.5164 12.8513 94.9910 23.9091 16.5885	21.0720 19.8324 4.4329 3.6279 1.5388 -113.9695 7995.5313 0.5264 304.8059	57.1031 54.6363 -37.7952 -43.1664 -46.7765 -218.5616 15568.4297 -24.1683 551.8584	Term -3.3112 -3.3655 -3.4157 -3.4685 -3.5116 -3.4622 -3.4685 -3.4654 -3.5116	Rela 	ted Term 2.7062 2.8497 2.9807 3.2093 3.0917 3.0082 3.0058 3.0755
I II III IV V VI VII VIII IX X	S4 -4.4842 -4.5953 -4.5575 -4.6877 -4.7027 -4.6607 -4.1200 -4.0844 -4.1555 -4.4798	-4.4187 -4.3449 -4.4875 -4.0953 -4.1367 -4.4043 -4.5587 -4.6561 -4.6021 -4.5784	$\begin{array}{r} S_6^{*} \\ \hline -4.4272 \\ -4.5129 \\ -4.4891 \\ -4.5876 \\ -4.6365 \\ -4.5662 \\ -4.4034 \\ -4.4170 \\ -4.4175 \\ -4.1217 \end{array}$	S ² -4.4573 -4.4552 -4.5244 -4.4436 -4.4630 -4.5130 -4.5598 -4.6543 -4.5660 -4.7075	$\begin{array}{r} S_{8}^{*} \\ \hline -4.1912 \\ -4.2362 \\ -4.2582 \\ -4.3075 \\ -4.3147 \\ -4.2973 \\ -4.1815 \\ -4.1987 \\ -4.1892 \\ -4.2129 \\ -4.2129 \end{array}$	$\begin{array}{r} -4.3348 \\ -4.3398 \\ -4.4064 \\ -4.3531 \\ -4.3632 \\ -4.4058 \\ -4.4357 \\ -4.5106 \\ -4.4478 \\ -4.4580 \end{array}$	Sib 24.7255 24.4622 12.6679 20.1351 19.5164 12.8513 94.9910 23.9091 16.5885 10.1589	21.0720 19.8324 4.4329 3.6279 1.5388 -113.9695 7995.5313 0.5264 304.8059 -77.9774	57.1031 54.6363 -37.7952 -43.1664 -46.7765 -218.5616 15568.4297 -24.1683 551.8584 -155.0132	Term -3.3112 -3.3655 -3.4157 -3.4685 -3.5116 -3.4685 -3.4654 -3.5116 -3.5116 -3.5116	Rela	ted Term 2.7062 2.8497 2.9807 3.0987 3.0917 3.0082 3.0058 3.0765 3.2070
I II III IV V VI VII VII IX X XI	S4 -4.4842 -4.5953 -4.5575 -4.6877 -4.7027 -4.6607 -4.1200 -4.0844 -4.1555 -4.4798 -4.6234	-4.4187 -4.3449 -4.4875 -4.0953 -4.1367 -4.4043 -4.5587 -4.6561 -4.6021 -4.5784 -4.4846	Se -4.4272 -4.5129 -4.4891 -4.5876 -4.6365 -4.5662 -4.4034 -4.4170 -4.4175 -4.1217 -4.5956	S ² -4.4573 -4.4552 -4.5244 -4.4436 -4.4630 -4.5130 -4.5598 -4.6543 -4.5660 -4.7075 -4.4391	$\begin{array}{r} S_{8}^{*} \\ \hline -4.1912 \\ -4.2362 \\ -4.2582 \\ -4.3075 \\ -4.3147 \\ -4.2973 \\ -4.1815 \\ -4.1987 \\ -4.1892 \\ -4.2129 \\ -4.2129 \\ -4.3428 \end{array}$	$\begin{array}{r} -4.3348 \\ -4.3398 \\ -4.4064 \\ -4.3531 \\ -4.4058 \\ -4.4058 \\ -4.457 \\ -4.5106 \\ -4.4478 \\ -4.4580 \\ -4.4111 \\ -4.4580 \\ -4.4111 \\ $	Sib 24.7255 24.4622 12.6679 20.1351 19.5164 12.8513 94.9910 23.9091 16.5885 10.1589 6.9412	21.0720 19.8324 4.4329 3.6279 1.5388 -113.9695 7995.5313 0.5264 304.8059 -77.9774 -176.9974	S12 57.1031 54.6363 -37.7952 -43.1664 -46.7765 -218.5616 15568.4297 -24.1683 551.8584 -155.0132 -320.2112	Term -3.3112 -3.3655 -3.4157 -3.4685 -3.5116 -3.4625 -3.4654 -3.5116 -3.5116 -3.5116 -3.5116	Rela	ted Term 2.7062 2.8497 2.9807 3.0987 3.097 3.0058 3.0058 3.0765 3.0707 3.007
I II III IV V VI VII VII IX X XI XII	-4.4842 -4.5953 -4.5575 -4.6877 -4.7027 -4.6607 -4.1200 -4.0844 -4.1555 -4.4798 -4.4798 -4.6350	-4.4187 -4.3449 -4.4875 -4.0953 -4.1367 -4.4043 -4.5587 -4.6561 -4.6561 -4.5784 -4.5784 -4.4846 -4.4200	Se -4.4272 -4.5129 -4.4891 -4.5876 -4.5652 -4.5662 -4.4034 -4.4170 -4.4170 -4.1217 -4.5956 -4.6129	$\begin{array}{r} -4.4573 \\ -4.4572 \\ -4.5244 \\ -4.4436 \\ -4.4630 \\ -4.5598 \\ -4.6543 \\ -4.5660 \\ -4.7075 \\ -4.4391 \\ -4.1407 \end{array}$	$\begin{array}{r} 5\frac{8}{8} \\ -4.1912 \\ -4.2362 \\ -4.2582 \\ -4.3075 \\ -4.3147 \\ -4.2973 \\ -4.1815 \\ -4.1987 \\ -4.1892 \\ -4.2129 \\ -4.2129 \\ -4.3671 \\ -4.3671 \\ \end{array}$	-4.3348 -4.3398 -4.4064 -4.3531 -4.3632 -4.4058 -4.4058 -4.4357 -4.5106 -4.4478 -4.4580 -4.4111 -4.3477	Sib 24.7255 24.4622 12.6679 20.1351 19.5164 12.8513 94.9910 23.9091 16.5885 10.1589 6.9412 -0.7368	21.0720 19.8324 4.4329 3.6279 1.5388 113.9695 7995.5313 0.5264 304.8059 77.9774 176.9974 97.3377	S12 57.1031 54.6363 -37.7952 -43.1664 -46.7765 -218.5616 15568.4297 -24.1683 551.8584 -155.0132 -320.2112 -183.6725 -183.6725	Term -3.3112 -3.3655 -3.4157 -3.4685 -3.5116 -3.4622 -3.4685 -3.4654 -3.5116 -3.5116 -3.5116 -3.5116 -3.5086	Rela	ted Term 2.7062 2.8497 2.9807 3.0987 3.0093 3.00917 3.0082 3.0058 3.0765 3.2070 3.2070 3.0707 3.1400
I II IV V VI VII VII VII IX X XI XII XII	-4.4842 -4.5953 -4.5575 -4.6877 -4.7027 -4.6607 -4.1200 -4.0844 -4.1555 -4.4798 -4.6234 -4.6350 -4.6350	-4.4187 -4.3449 -4.4875 -4.0953 -4.1367 -4.4043 -4.5587 -4.6561 -4.6021 -4.5784 -4.4846 -4.4200 -4.4215	S& -4.4272 -4.5129 -4.4891 -4.5876 -4.5652 -4.5662 -4.4034 -4.4170 -4.4175 -4.1217 -4.5956 -4.6129 -4.6052	S ⁴ -4.4573 -4.4552 -4.5244 -4.4436 -4.4630 -4.5130 -4.5598 -4.6543 -4.5660 -4.7075 -4.4391 -4.1407 -4.1151	5 % -4.1912 -4.2362 -4.2582 -4.3075 -4.3147 -4.2973 -4.1815 -4.1987 -4.1897 -4.1892 -4.2129 -4.3428 -4.3671 -4.3493	$\begin{array}{r} -4.3348 \\ -4.3398 \\ -4.4064 \\ -4.3531 \\ -4.3632 \\ -4.4058 \\ -4.4357 \\ -4.5106 \\ -4.4478 \\ -4.4580 \\ -4.4580 \\ -4.4111 \\ -4.3477 \\ -4.3421 \\ -2.3278 \end{array}$	Sib 24.7255 24.4622 12.6679 20.1351 19.5164 12.8513 94.9910 23.9091 16.5885 10.1589 6.9412 -0.7368 17.4444	21.0720 19.8324 4.4329 3.6279 1.5388 -113.9695 7995.5313 0.5264 304.8059 -77.9774 -176.9974 -97.3377 10.4940	S12 57.1031 54.6363 -37.7952 -43.1664 -46.7765 -218.5616 15568.4297 -24.1683 551.8584 -155.0132 -320.2112 -183.6725 -30.4729 -30.4729	Term -3.3112 -3.3655 -3.4157 -3.4685 -3.5116 -3.4622 -3.4654 -3.5116 -3.5116 -3.5116 -3.5086 -3.4685 -3.4685	Rela 	ted Term 2.7062 2.8497 2.9807 3.0987 3.0917 3.0082 3.0058 3.0705 3.2070 3.1400 3.0707 3.1400 3.036
I II IV VI VII VII IX XI XII XII XII XIV	-4.4842 -4.5953 -4.5575 -4.6877 -4.7027 -4.6607 -4.1200 -4.0844 -4.1555 -4.4798 -4.6234 -4.6350 -4.6367 -4.7826	-4.4187 -4.3449 -4.4875 -4.0953 -4.1367 -4.4043 -4.5587 -4.6561 -4.6021 -4.5784 -4.4846 -4.4200 -4.4215 -4.0756	Se -4.4272 -4.5129 -4.4891 -4.5876 -4.5662 -4.6365 -4.5662 -4.4034 -4.4170 -4.4170 -4.4175 -4.1217 -4.5956 -4.6052	5° -4.4573 -4.4552 -4.5244 -4.4436 -4.5430 -4.5598 -4.6543 -4.5660 -4.7075 -4.4391 -4.1077 -4.1151 -4.0857	5 % -4.1912 -4.2362 -4.2582 -4.3075 -4.3147 -4.2973 -4.1815 -4.1987 -4.1892 -4.2129 -4.3428 -4.3428 -4.3493 -4.3493 -4.4261 -4.305	$\begin{array}{r} -4.3348\\ -4.3398\\ -4.4064\\ -4.3531\\ -4.3632\\ -4.4058\\ -4.4357\\ -4.5106\\ -4.4478\\ -4.4478\\ -4.4478\\ -4.4478\\ -4.4580\\ -4.4111\\ -4.3477\\ -4.3421\\ -4.3078\\ -4.201$	Sib 24.7255 24.4622 12.6679 20.1351 19.5164 12.8513 94.9910 23.9091 16.5885 10.1589 10.1589 10.49412 -0.7368 17.4444 16.6094	21.0720 19.8324 4.4329 3.6279 1.5388 -113.9695 7995.5313 0.5264 304.8059 -77.9774 -176.9974 -97.3377 10.4940 -173.3659	S12 57.1031 54.6363 -37.7952 -43.1664 -46.7765 -218.5616 15568.4297 -24.1683 551.8584 -155.0132 -320.2112 -183.6725 -30.4729 -315.2969	Term -3.3112 -3.3655 -3.4157 -3.4685 -3.4685 -3.4622 -3.4685 -3.4654 -3.5116 -3.5116 -3.4622 -3.5086 -3.4685 -3.5086 -3.4685 -3.5952	Rela	ted Term .7062 .8497 .9807 .9807 .0987 .0987 .0082 .0017 .0082 .0058 .0765 .2070 .0707 .1400 .0736 .3486 .0082
I II IV V VI VII VII VII XX XII XII XIV XV	-4.4842 -4.5953 -4.5575 -4.6877 -4.7027 -4.6607 -4.1200 -4.0844 -4.1555 -4.4798 -4.6234 -4.6350 -4.6367 -4.7826 -4.6018	-4.4187 -4.3449 -4.4875 -4.0953 -4.1367 -4.4043 -4.5587 -4.6561 -4.6021 -4.6784 -4.4846 -4.4200 -4.4215 -4.0756 -4.0756 -4.5098	S& -4.4272 -4.5129 -4.4891 -4.5876 -4.5662 -4.6365 -4.5662 -4.4034 -4.4170 -4.4175 -4.1217 -4.5956 -4.6129 -4.6052 -4.6052 -4.7632 -4.5304	5° -4.4573 -4.4552 -4.5244 -4.4436 -4.5130 -4.5130 -4.5598 -4.6543 -4.5660 -4.7075 -4.4391 -4.1407 -4.1151 -4.0857 -4.5450 -4.5450	$\begin{array}{r} S_{8}^{*} \\ \hline -4.1912 \\ -4.2362 \\ -4.2582 \\ -4.3075 \\ -4.3147 \\ -4.2973 \\ -4.1815 \\ -4.1987 \\ -4.1892 \\ -4.2129 \\ -4.3428 \\ -4.3671 \\ -4.3493 \\ -4.4261 \\ -4.3035 \\ -4.305 \\ -4.305$	$\begin{array}{r} -4.3348\\ -4.3398\\ -4.4064\\ -4.3531\\ -4.3632\\ -4.4058\\ -4.4058\\ -4.5106\\ -4.4478\\ -4.4580\\ -4.4478\\ -4.4580\\ -4.4411\\ -4.3477\\ -4.3421\\ -4.3078\\ -4.261\\ -4.3078\\ -4.4261\\ -4.321\end{array}$	Sib 24.7255 24.4622 12.6679 20.1351 19.5164 12.8513 94.9910 23.9091 16.5885 10.1589 6.9412 -0.7368 17.4444 16.6094 42.9891	21.0720 19.8324 4.4329 3.6279 1.5388 -113.9695 7995.5313 0.5264 304.8059 -77.9774 -176.9974 -97.3377 10.4940 -173.3659 11.9697 11.9697	S12 57.1031 54.6363 -37.7952 -43.1664 -46.7765 -218.5616 15568.4297 -24.1683 551.8584 -155.0132 -320.2112 -183.6725 -30.4729 -315.2969 -43.1691 -47.9560	Term -3.3112 -3.3655 -3.4157 -3.4685 -3.5116 -3.4622 -3.4685 -3.4654 -3.5116 -3.5116 -3.4622 -3.5086 -3.4622 -3.5086 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4685 -3.5126 -3.5126 -3.5126 -3.5126 -3.4622 -3.5086 -3.4622 -3.462	Rela	ted Term .7062 .8497 .9807 .9807 .0987 .0987 .0082 .0058 .0058 .0058 .0705 .2070 .0058 .0705 .1400 .0736 .3486 .0983 .0975
I II III IV V VI VII VII VIII VIII XX XX XX XX XX XV XV XV XV	-4.4842 -4.5953 -4.6877 -4.7027 -4.1200 -4.0844 -4.1555 -4.4798 -4.6234 -4.6367 -4.7826 -4.6367 -4.7826 -4.6367 -4.7826 -4.6018 -4.5798	-4.4187 -4.3449 -4.4875 -4.0953 -4.1367 -4.4043 -4.5587 -4.6561 -4.6021 -4.5784 -4.4846 -4.4200 -4.4215 -4.0756 -4.5098 -4.5055 -4.2027	S_{6}^{*} -4.4272 -4.5129 -4.4891 -4.5876 -4.6365 -4.5662 -4.4034 -4.4170 -4.4175 -4.1217 -4.5956 -4.6129 -4.6052 -4.7632 -4.5304 -4.5108	$\begin{array}{r} 5^{\circ}_{7} \\ -4.4573 \\ -4.4552 \\ -4.5244 \\ -4.4436 \\ -4.4630 \\ -4.5130 \\ -4.5598 \\ -4.6543 \\ -4.5598 \\ -4.6543 \\ -4.7075 \\ -4.4391 \\ -4.1407 \\ -4.1151 \\ -4.0857 \\ -4.5450 \\ -4.5419 \\ -4.5419 \\ -4.5419 \end{array}$	$\begin{array}{r} 5\frac{8}{8} \\ -4.1912 \\ -4.2362 \\ -4.3075 \\ -4.3075 \\ -4.3147 \\ -4.2973 \\ -4.1815 \\ -4.1987 \\ -4.1892 \\ -4.3428 \\ -4.3428 \\ -4.3493 \\ -4.3493 \\ -4.3035 \\ -4.3104 \\ -4.3048 \\ -4.4049 \end{array}$	$\begin{array}{r} -4.3348\\ -4.3398\\ -4.4064\\ -4.3531\\ -4.3632\\ -4.4058\\ -4.45106\\ -4.4478\\ -4.45106\\ -4.4478\\ -4.4580\\ -4.4111\\ -4.3477\\ -4.3421\\ -4.3078\\ -4.4261\\ -4.431\\ -4.1529\end{array}$	Sib 24.7255 24.4622 12.6679 20.1351 19.5164 12.8513 94.9910 23.9091 16.5885 10.1589 6.9412 -0.7368 17.4444 16.6094 42.9891 25.6743 29.7625	21.0720 19.8324 4.4329 3.6279 1.5388 -113.9695 7995.5313 0.5264 304.8059 -77.9774 -176.9974 -97.3377 10.4940 -173.3659 11.9697 3.9224 4.6535	S12 57.1031 54.6363 -37.7952 -43.1664 -46.7765 -218.5616 15568.4297 -24.1683 551.8584 -155.0132 -320.2112 -183.6725 -30.4729 -315.2969 -43.1691 -47.8569 26.0292	Term -3.3112 -3.3655 -3.4157 -3.4685 -3.4685 -3.4622 -3.4654 -3.5116 -3.5116 -3.5116 -3.5116 -3.5116 -3.5086 -3.4685 -3.5952 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4685 -3.5952 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4685 -3.5952 -3.4622 -3.4622 -3.4622 -3.4685 -3.5952 -3.4622 -3.4622 -3.4622 -3.4685 -3.5952 -3.4622 -3.4622 -3.4622 -3.4685 -3.4622 -3.4685 -3.4622 -3.4685 -3.4622 -3.4685 -3.4622 -3.4685 -3.4622 -3.4685 -3.4622 -3.4685 -3.4622 -3.4685 -3.4622 -3.4685 -3.4622 -3.4685 -3.4622 -3.4685 -3.4622 -3.4685 -3.4622 -3.4685 -3.4622 -3.4685 -3.4622 -3.462	Rela	ted Term 2.7062 2.8497 2.9807 3.0987 3.0993 3.0917 3.0058 3.0058 3.0765 3.2070 5.0765 3.2070 5.0707 5.1400 5.0736 5.3486 5.0983 5.0878 5.0376 5.0376 5.0378 5.0376 5.0376 5.0378 5.0376 5.0378 5.0376 5.0376 5.0378 5.0376 5.0376 5.0378 5.0376 5.0376 5.0376 5.0376 5.0377 5.0377 5.0082 5.0058 5.075 5
I II IV V VI VII VII VII IX XI XII XII X	-4.4842 -4.5953 -4.5575 -4.6877 -4.7027 -4.1200 -4.0844 -4.1555 -4.4798 -4.6350 -4.6367 -4.7826 -4.6367 -4.7826 -4.6018 -4.5538 -4.5536	$\begin{array}{r} -4.4187 \\ -4.3449 \\ -4.4875 \\ -4.0953 \\ -4.1367 \\ -4.4043 \\ -4.5587 \\ -4.6561 \\ -4.6561 \\ -4.6521 \\ -4.5784 \\ -4.4215 \\ -4.756 \\ -4.2098 \\ -4.5055 \\ -4.2837 \\ -4.5055 \\ -4.2837 \\ -4.515$	S 6 -4.4272 -4.5129 -4.4891 -4.5876 -4.6365 -4.5662 -4.4034 -4.4170 -4.4175 -4.1217 -4.5956 -4.6129 -4.6052 -4.6052 -4.5304 -4.5304 -4.5304 -4.5304 -4.5304 -4.336	S ⁴ -4.4573 -4.4552 -4.6524 -4.4630 -4.5130 -4.5598 -4.6543 -4.5640 -4.7075 -4.4391 -4.1407 -4.1151 -4.0857 -4.5450 -4.5450 -4.5419 -4.3542 -4.2526	$\begin{array}{r} 5\frac{8}{8} \\ -4.1912 \\ -4.2362 \\ -4.2582 \\ -4.3075 \\ -4.3075 \\ -4.3075 \\ -4.1815 \\ -4.1892 \\ -4.2129 \\ -4.2129 \\ -4.3428 \\ -4.3671 \\ -4.3493 \\ -4.4261 \\ -4.3035 \\ -4.3104 \\ -4.4048 $	$\begin{array}{r} -4.3348\\ -4.3398\\ -4.4064\\ -4.3531\\ -4.3632\\ -4.4058\\ -4.4058\\ -4.45106\\ -4.4478\\ -4.4580\\ -4.4111\\ -4.3477\\ -4.3421\\ -4.3078\\ -4.4261\\ -4.4331\\ -4.1529\\ -4.3470\end{array}$	Sib 24.7255 24.4622 12.6679 20.1351 19.5164 12.8513 94.9910 23.9091 16.5885 10.1589 6.9412 -0.7368 17.4444 16.6094 42.9891 25.6743 29.7625 18.1875	21.0720 19.8324 4.4329 3.6279 1.5388 -113.9695 7995.5313 0.5264 304.8059 -77.9774 -176.9974 -97.3377 10.4940 -173.3659 11.9697 3.9224 16.5035 -109.3894	S12 57.1031 54.6363 -37.7952 -43.1664 -46.7765 -218.5616 15568.4297 -24.1683 551.8584 -155.0132 -320.2112 -183.6725 -30.4729 -315.2969 -43.1691 -47.8569 26.0092 -210.1167	Term -3.3112 -3.3655 -3.4157 -3.4655 -3.5116 -3.4622 -3.4685 -3.4654 -3.5116 -3.5116 -3.4622 -3.5086 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622	Rela 	ted Term 2.7062 2.8497 2.9807 3.0987 3.0987 3.0082 3.0075 3.0765 3.0765 3.0765 3.0765 3.076 3.0788 3.0878 3.0878 3.0376 3.4542
I II IV V VI VII VII VII VII VII VII X XI X X X X	54 -4.4842 -4.5953 -4.5575 -4.6877 -4.7027 -4.7027 -4.6607 -4.1200 -4.0844 -4.1555 -4.4798 -4.6350 -4.6367 -4.7826 -4.6018 -4.5798 -4.5536 -4.7039 -4.5179	$\begin{array}{r} -4.4187 \\ -4.3449 \\ -4.4875 \\ -4.0953 \\ -4.1367 \\ -4.4043 \\ -4.5587 \\ -4.6561 \\ -4.6561 \\ -4.6561 \\ -4.5784 \\ -4.4200 \\ -4.4215 \\ -4.0756 \\ -4.2008 \\ -4.2008 \\ -4.5055 \\ -4.2837 \\ -4.1612 \\ -4.499 \end{array}$	$\begin{array}{r} 5\% \\ -4.4272 \\ -4.5129 \\ -4.4891 \\ -4.5876 \\ -4.6365 \\ -4.5662 \\ -4.4034 \\ -4.4170 \\ -4.4170 \\ -4.4175 \\ -4.1217 \\ -4.5956 \\ -4.6052 \\ -4.6052 \\ -4.7632 \\ -4.5108 \\ -4.3536 \\ -4.4861 \\ -4.3536 \\ -4.4551 \end{array}$	S_{1}^{*} -4.4573 -4.4552 -4.5244 -4.4436 -4.4630 -4.5598 -4.6543 -4.5598 -4.6543 -4.5660 -4.7075 -4.4391 -4.1407 -4.1407 -4.1407 -4.5450 -4.5419 -4.3542 -4.3542 -4.3542 -4.42226	$\begin{array}{r} 5\frac{8}{4} \\ -4.1912 \\ -4.2362 \\ -4.2582 \\ -4.3075 \\ -4.3147 \\ -4.2973 \\ -4.1815 \\ -4.1987 \\ -4.1892 \\ -4.2129 \\ -4.2129 \\ -4.3428 \\ -4.3671 \\ -4.3493 \\ -4.3643 \\ -4.3643 \\ -4.2032 \end{array}$	$\begin{array}{r} -4.3348\\ -4.3398\\ -4.4064\\ -4.3531\\ -4.4058\\ -4.4058\\ -4.4357\\ -4.5106\\ -4.4478\\ -4.4580\\ -4.4111\\ -4.3477\\ -4.3421\\ -4.3078\\ -4.4261\\ -4.4331\\ -4.1529\\ -4.3479\\ -4.3479\\ -4.3479\end{array}$	Sib 24.7255 24.4622 12.6679 20.1351 19.5164 12.8513 94.9910 23.9091 16.5885 10.1589 6.9412 -0.7368 17.4444 16.6094 42.9891 25.6743 29.7625 18.1875 21.9919	21.0720 19.8324 4.4329 3.6279 1.5388 -113.9695 7995.5313 0.5264 304.8059 -77.9774 -176.9974 -97.3377 10.4940 -173.3659 11.9697 3.9224 16.5035 -109.3894 42.8507	$\begin{array}{r} S_{12}^{R} \\ \hline 57.1031 \\ 54.6363 \\ -37.7952 \\ -43.1664 \\ -46.7765 \\ -218.5616 \\ 15568.4297 \\ -24.1683 \\ 551.8584 \\ -155.0132 \\ -320.2112 \\ -183.6725 \\ -30.4729 \\ -315.2969 \\ -43.1691 \\ -47.8569 \\ 26.0292 \\ -210.1167 \\ 26.9736 \end{array}$	Term -3.3112 -3.3655 -3.4157 -3.4685 -3.5116 -3.4622 -3.4685 -3.4654 -3.5116 -3.5116 -3.5116 -3.5116 -3.5086 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4625 -3.4625 -3.4625 -3.4625 -3.5055 -3.4655 -3.5055 -3.4655 -3.5055 -3.4655 -3.5055 -3.4655 -3.5055 -3.4655 -3.5055 -3.4655 -3.5055 -3.4655 -3.5055 -3.4655 -3.5055 -3.4655 -3.5055 -3.4655 -3.5055 -3.4655 -3.4655 -3.5055 -3.4655 -3.4655 -3.4655 -3.5055 -3.4655 -3.4655 -3.5055 -3.4655 -3.4655 -3.5055 -3.4655 -3.4655 -3.4655 -3.5055 -3.465	Rela	ted Term 2.7062 2.8497 2.9807 1.0987 3.0093 3.00917 3.0082 3.0058 3.0765 3.2070 3.0707 3.1400 3.0707 3.1400 3.0766 3.3486 3.0983 3.0985 3.0983 3.0985 3.0
I II II V VI VII VII VII IX XI XII XII X	-4.4842 -4.5953 -4.5575 -4.6877 -4.7027 -4.6607 -4.1200 -4.0844 -4.1555 -4.4798 -4.6350 -4.6367 -4.7826 -4.6018 -4.6018 -4.5536 -4.5179 -4.5536	$\begin{array}{r} -4.4187 \\ -4.3449 \\ -4.4875 \\ -4.0953 \\ -4.1367 \\ -4.4043 \\ -4.5587 \\ -4.6561 \\ -4.6561 \\ -4.6561 \\ -4.5784 \\ -4.4846 \\ -4.4200 \\ -4.4215 \\ -4.0756 \\ -4.5098 \\ -4.5098 \\ -4.5098 \\ -4.5098 \\ -4.5098 \\ -4.2837 \\ -4.1612 \\ -4.4499 \\ -4.1345 \end{array}$	$\begin{array}{r} S_{6}^{*} \\ \hline -4.4272 \\ -4.5129 \\ -4.4891 \\ -4.5876 \\ -4.6365 \\ -4.5662 \\ -4.4034 \\ -4.4170 \\ -4.4175 \\ -4.1217 \\ -4.5956 \\ -4.6129 \\ -4.6052 \\ -4.6129 \\ -4.5304 \\ -4.5108 \\ -4.4861 \\ -4.3536 \\ -4.4551 \\ -4.7445 \end{array}$	S_{1}^{*} -4.4573 -4.4552 -4.5244 -4.4436 -4.4630 -4.5130 -4.5598 -4.6543 -4.5660 -4.7075 -4.4391 -4.1407 -4.1151 -4.0857 -4.5450 -4.5419 -4.5419 -4.3542 -4.2226 -4.4874 -4.3788	$\begin{array}{r} 5\frac{8}{8} \\ -4.1912 \\ -4.2362 \\ -4.2582 \\ -4.3075 \\ -4.3147 \\ -4.2973 \\ -4.1815 \\ -4.1987 \\ -4.1897 \\ -4.2129 \\ -4.2129 \\ -4.3428 \\ -4.3671 \\ -4.3493 \\ -4.3643 \\ -4.3643 \\ -4.2032 \\ -4.3643 \\ -4.2032 \\ -4.3891 \end{array}$	$\begin{array}{r} -4.3348\\ -4.3398\\ -4.4064\\ -4.3531\\ -4.3632\\ -4.4058\\ -4.4357\\ -4.5106\\ -4.4478\\ -4.4580\\ -4.4111\\ -4.3477\\ -4.3421\\ -4.3078\\ -4.4261\\ -4.4331\\ -4.1529\\ -4.3479\\ -4.3696\\ -4.3686\end{array}$	Sib 24.7255 24.4622 12.6679 20.1351 19.5164 12.8513 94.9910 23.9091 16.5885 10.1589 6.9412 -0.7368 17.4444 16.6094 42.9891 25.6743 29.7625 18.1875 21.9919 12.4215	Sii 21.0720 19.8324 4.4329 3.6279 1.5388 -113.9695 7995.5313 0.5264 304.8059 -77.9774 -176.9974 -97.3377 10.4940 -173.3659 11.9697 3.9224 16.5035 -109.3894 42.8507 -615.0073	S12 57.1031 54.6363 -37.7952 -43.1664 -46.7765 -218.5616 15568.4297 -24.1683 551.8584 -155.0132 -320.2112 -183.6725 -30.4729 -315.2969 -43.1691 -47.8569 26.0292 -210.1167 26.9736 -1042 3286	Term -3.3112 -3.3655 -3.4157 -3.4685 -3.5116 -3.4622 -3.4654 -3.5116 -3.5116 -3.5116 -3.5116 -3.4622 -3.4685 -3.4685 -3.4685 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.45520	Rela	ted Term 2.7062 2.8497 2.9807 3.0987 3.0917 3.0082 3.0058 3.0705 3.0707 3.1400 3.0736 3.3486 3.0376 3.4542 3.1653 3.2793
I II IV VI VII VII VII IX XX XII XVII XVII XVII XVII XXX XXX	St -4.4842 -4.5953 -4.5575 -4.6877 -4.7027 -4.6007 -4.1200 -4.0844 -4.1555 -4.4798 -4.6350 -4.6350 -4.6350 -4.6350 -4.6350 -4.6350 -4.6350 -4.6350 -4.6350 -4.6350 -4.6350 -4.6350 -4.7826 -4.7826 -4.7826 -4.7039 -4.5179 -4.7688 -4.7736	$\begin{array}{r} -4.4187 \\ -4.3449 \\ -4.4875 \\ -4.0953 \\ -4.1367 \\ -4.4043 \\ -4.5587 \\ -4.6561 \\ -4.6021 \\ -4.5784 \\ -4.4846 \\ -4.4200 \\ -4.4215 \\ -4.0756 \\ -4.5098 \\ -4.5055 \\ -4.2837 \\ -4.1612 \\ -4.4499 \\ -4.1345 \\ -4.1345 \\ \end{array}$	$\begin{array}{r} S_{6}^{*} \\ \hline -4.4272 \\ -4.5129 \\ -4.4891 \\ -4.5876 \\ -4.6365 \\ -4.5662 \\ -4.4034 \\ -4.4170 \\ -4.4175 \\ -4.1217 \\ -4.5956 \\ -4.6129 \\ -4.6052 \\ -4.7632 \\ -4.7632 \\ -4.5304 \\ -4.5108 \\ -4.4861 \\ -4.3536 \\ -4.4551 \\ -4.7445 \\ -5.3965 \end{array}$	S_{1}^{*} -4.4573 -4.4552 -4.5244 -4.4436 -4.4630 -4.5130 -4.5598 -4.6543 -4.5660 -4.7075 -4.4391 -4.1407 -4.1151 -4.0857 -4.5419 -4.5450 -4.5419 -4.3542 -4.2226 -4.4874 -4.3788 -4.669	$\begin{array}{r} 5\frac{8}{8} \\ -4.1912 \\ -4.2362 \\ -4.2582 \\ -4.3075 \\ -4.3147 \\ -4.2973 \\ -4.1815 \\ -4.1987 \\ -4.1892 \\ -4.2129 \\ -4.3428 \\ -4.3671 \\ -4.3493 \\ -4.3035 \\ -4.3044 \\ -4.4048 \\ -4.3643 \\ -4.2322 \\ -4.3891 \\ -4.4079 \end{array}$	$\begin{array}{r} -4.3348\\ -4.3398\\ -4.4064\\ -4.3531\\ -4.3632\\ -4.4058\\ -4.4580\\ -4.4580\\ -4.4357\\ -4.5106\\ -4.4478\\ -4.4357\\ -4.3477\\ -4.3421\\ -4.3078\\ -4.4261\\ -4.4331\\ -4.1529\\ -4.3479\\ -4.3686\\ -4.4394\end{array}$	Sib 24.7255 24.4622 12.6679 20.1351 19.5164 12.8513 94.9910 23.9091 16.5885 10.1589 6.9412 -0.7368 17.4444 16.6094 42.9891 25.6743 29.7625 18.1875 21.9919 12.4215 22.5130	21.0720 19.8324 4.4329 3.6279 1.5388 -113.9695 7995.5313 0.5264 304.8059 -77.9774 -176.9974 -97.3377 10.4940 -173.3659 11.9697 3.9224 16.5035 -109.3894 42.8507 -615.0073 29.9472	S12 57.1031 54.6363 -37.7952 -43.1664 -46.7765 -218.5616 15568.4297 -24.1683 551.8384 -155.0132 -320.2112 -183.6725 -30.4729 -315.2969 -43.1691 -47.8569 26.0292 -210.1167 26.9736 -1042.3286 10.9877	Term -3.3112 -3.3655 -3.4157 -3.4685 -3.5116 -3.4622 -3.4654 -3.5116 -3.5116 -3.5116 -3.5116 -3.4622 -3.4622 -3.4685 -3.5952 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4552 -3.45520 -3.5520 -3.5872	Rela	ted Term 2.7062 2.8497 2.9807 3.0987 3.0987 3.0917 3.0082 3.0058 3.0058 3.0078 3.0078 3.1400 3.0736 3.3486 3.0983 3.0376 3.4542 3.1653 3.2793 3.3674
I II IV V VI VII VII VII VII VII XX XX XVI XVI	-4.4842 -4.5953 -4.6877 -4.7027 -4.1200 -4.0844 -4.1555 -4.4798 -4.6367 -4.6367 -4.7826 -4.6367 -4.7826 -4.6367 -4.7826 -4.6018 -4.5536 -4.7039 -4.5179 -4.7786 -4.7736 -4.5132	$\begin{array}{r} -4.4187 \\ -4.3449 \\ -4.4875 \\ -4.0953 \\ -4.0953 \\ -4.1367 \\ -4.4043 \\ -4.5587 \\ -4.6561 \\ -4.6561 \\ -4.6021 \\ -4.5784 \\ -4.4846 \\ -4.4215 \\ -4.4215 \\ -4.0756 \\ -4.2037 \\ -4.4203 \\ -4.4203 \\ -4.4203 \\ -4.4215 \\ -4.1352 \\ -4.1352 \\ -4.3936 \end{array}$	$\begin{array}{r} 5\% \\ -4.4272 \\ -4.5129 \\ -4.4891 \\ -4.5876 \\ -4.6365 \\ -4.5662 \\ -4.4034 \\ -4.4170 \\ -4.4175 \\ -4.1217 \\ -4.5956 \\ -4.4175 \\ -4.6052 \\ -4.6052 \\ -4.6052 \\ -4.5304 \\ -4.5108 \\ -4.4861 \\ -4.3536 \\ -4.4551 \\ -4.7445 \\ -5.3965 \\ -5.44493 \end{array}$	$\begin{array}{r} 5^{\circ}_{7} \\ -4.4573 \\ -4.4552 \\ -4.4524 \\ -4.4436 \\ -4.4630 \\ -4.5130 \\ -4.5598 \\ -4.6543 \\ -4.5598 \\ -4.6543 \\ -4.7075 \\ -4.4391 \\ -4.1407 \\ -4.1151 \\ -4.0857 \\ -4.5450 \\ -4.5450 \\ -4.5450 \\ -4.54226 \\ -4.2226 \\ -4.4874 \\ -4.3788 \\ -4.6469 \\ -4.4701 \end{array}$	$\begin{array}{r} 5\frac{8}{4} \\ -4.1912 \\ -4.2362 \\ -4.3075 \\ -4.3075 \\ -4.3075 \\ -4.3075 \\ -4.1815 \\ -4.1987 \\ -4.1892 \\ -4.2129 \\ -4.3428 \\ -4.3671 \\ -4.3493 \\ -4.4261 \\ -4.3035 \\ -4.3104 \\ -4.4048 \\ -4.3643 \\ -4.2232 \\ -4.3891 \\ -4.3641 \\ -4.3071 \\ -4.3891 \\ -4.3643 \\ -4.2232 \\ -4.3891 \\ -4.3643 \\ -4.2322 \\ -4.3891 \\ -4.3643 \\ -4.2322 \\ -4.3891 \\ -4.3643 \\ -4.2732 \\ -4.3891 \\ -4.3643 \\ -4.2732 \\ -4.3891 \\ -4.3643 \\ -4.2732 \\ -4.3891 \\ -4.3643 \\ -4.2732 \\ -4.3891 \\ -4.3643 \\ -4.2732 \\ -4.3891 \\ -4.3643 \\ -4.2732 \\ -4.3891 \\ -4.3643 \\ -4.2732 \\ -4.3891 \\ -4.3643 \\ -4.2732 \\ -4.3891 \\ -4.3643 \\ -4.2732 \\ -4.3891 \\ -4.3643 \\ -4.2732 \\ -4.3891 \\ -4.3643 \\ -4.2732 \\ -4.3891 \\ -4.3671 $	$\begin{array}{r} -4.3348\\ -4.3398\\ -4.4064\\ -4.3531\\ -4.3632\\ -4.4058\\ -4.4058\\ -4.4058\\ -4.4580\\ -4.4111\\ -4.3477\\ -4.3421\\ -4.3078\\ -4.4261\\ -4.3078\\ -4.4261\\ -4.3421\\ -4.3686\\ -4.4341\\ -4.3680\\ -4.4394\\ -4.3431\\ \end{array}$	Sib 24.7255 24.4622 12.6679 20.1351 19.5164 12.8513 94.9910 23.9910 23.9910 23.9910 23.9910 23.9910 23.9910 16.5885 10.1589 6.9412 -0.7368 17.4444 16.6094 42.9891 25.6743 29.7625 18.1875 21.9919 12.4215 22.5130 20.8217	21.0720 19.8324 4.4329 3.6279 1.5388 -113.9695 7995.5313 0.5264 304.8059 -77.9774 -176.9974 -176.9974 -176.9974 0.4940 -173.3659 11.9697 3.9224 16.5035 -109.3894 42.8507 -615.0073 29.9472 37.4708	S12 57.1031 54.6363 -37.7952 -43.1664 -46.7765 -218.5616 15568.4297 -24.1683 551.8584 -155.0132 -320.2112 -183.6725 -30.4729 -315.2969 -43.1691 -47.8569 26.0292 -210.1167 26.9736 -1042.3286 10.9827 22.6680	Term -3.3112 -3.3655 -3.4157 -3.4685 -3.5116 -3.4622 -3.4654 -3.5116 -3.4622 -3.4654 -3.5116 -3.4622 -3.5086 -3.4622 -3.4685 -3.5952 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4655 -3.5952 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.5952 -3.4622 -3.4622 -3.5086 -3.5952 -3.5952 -3.4622 -3.4622 -3.4622 -3.5952 -3.5952 -3.4622 -3.4622 -3.4622 -3.5952 -3.5952 -3.4622 -3.4622 -3.4622 -3.5952 -3.5952 -3.4622 -3.4622 -3.4622 -3.5952 -3.5952 -3.4622 -3.4622 -3.4622 -3.4622 -3.5952 -3.4622 -3.4622 -3.5952 -3.4622 -3.4622 -3.5952 -3.4622 -3.4622 -3.5952 -3.4622 -3.4622 -3.4622 -3.5952 -3.4622 -3.4622 -3.4622 -3.5952 -3.4622 -3.5956 -3.5550 -3.5520 -3.55403	Rela	ted Term .7062 .8497 .9807 .9807 .0987 .0987 .0082 .0058 .0078 .0058 .0705 .1400 .0776 .1400 .0736 .3486 .0983 .0376 .0376 .0376 .1653 .0376 .1653 .2793 .3.3674 .2588
I II II V VI VII VII VII VII VII XXI XXI	-4.4842 -4.5953 -4.6877 -4.7027 -4.1200 -4.0844 -4.1555 -4.4798 -4.6350 -4.6350 -4.6367 -4.7826 -4.6367 -4.7826 -4.6018 -4.5798 -4.5798 -4.5798 -4.7736 -4.7736 -4.5132 -4.7738	$\begin{array}{r} -4.4187 \\ -4.3449 \\ -4.4875 \\ -4.0953 \\ -4.1367 \\ -4.6561 \\ -4.6021 \\ -4.6561 \\ -4.6021 \\ -4.5784 \\ -4.4846 \\ -4.4200 \\ -4.4215 \\ -4.0756 \\ -4.5055 \\ -4.2837 \\ -4.1612 \\ -4.4499 \\ -4.1345 \\ -4.1352 \\ -4.3936 \\ -4.1432 \end{array}$	$\begin{array}{r} 5\% \\ -4.4272 \\ -4.5129 \\ -4.6365 \\ -4.6365 \\ -4.5662 \\ -4.4034 \\ -4.4170 \\ -4.4175 \\ -4.1217 \\ -4.5956 \\ -4.4175 \\ -4.6129 \\ -4.6052 \\ -4.7632 \\ -4.5304 \\ -4.5108 \\ -4.4861 \\ -4.3536 \\ -4.4551 \\ -4.7445 \\ -5.3965 \\ -4.4493 \\ -5.4065 \end{array}$	$\begin{array}{r} 5^{\circ}_{7} \\ -4.4573 \\ -4.4552 \\ -4.4524 \\ -4.4436 \\ -4.5130 \\ -4.598 \\ -4.6543 \\ -4.5598 \\ -4.6543 \\ -4.5660 \\ -4.7075 \\ -4.4391 \\ -4.1407 \\ -4.1151 \\ -4.0857 \\ -4.5450 \\ -4.5419 \\ -4.3542 \\ -4.2226 \\ -4.4874 \\ -4.3788 \\ -4.6469 \\ -4.4701 \\ -4.6520 \\ \end{array}$	$\begin{array}{r} 5\frac{8}{8} \\ -4.1912 \\ -4.2362 \\ -4.2582 \\ -4.3075 \\ -4.3075 \\ -4.3075 \\ -4.1815 \\ -4.1892 \\ -4.2129 \\ -4.3428 \\ -4.3671 \\ -4.3493 \\ -4.4261 \\ -4.3035 \\ -4.3104 \\ -4.4048 \\ -4.3643 \\ -4.2232 \\ -4.3891 \\ -4.3643 \\ -4.2739 \\ -4.1739 \\ -4.1739 \\ -4.1440 \end{array}$	$\begin{array}{r} -4.3348\\ -4.3398\\ -4.4064\\ -4.3531\\ -4.4058\\ -4.4058\\ -4.45106\\ -4.44580\\ -4.45106\\ -4.4478\\ -4.4580\\ -4.4111\\ -4.3477\\ -4.3421\\ -4.3078\\ -4.4261\\ -4.4331\\ -4.4261\\ -4.3690\\ -4.3686\\ -4.394\\ -4.3431\\ -4.4454\end{array}$	Sib 24.7255 24.4622 12.6679 20.1351 19.5164 12.8513 94.9910 23.9091 16.5885 10.1589 6.9412 -0.7368 17.4444 16.6094 42.9891 25.6743 29.7625 18.1875 21.9919 12.4215 22.5130 20.8217 22.2730	Sii 21.0720 19.8324 4.4329 3.6279 1.5388 -113.9695 7995.5313 0.5264 304.8059 -77.9774 -176.9974 -97.3377 10.4940 -173.3659 11.9697 3.9224 16.5035 -109.3894 42.8507 -615.0073 29.9472 37.4708 29.3867	S ₁₂ 57.1031 54.6363 -37.7952 -43.166 15568.4297 -24.1683 551.8584 -155.0132 -320.2112 -183.6725 -30.4729 -43.1691 -47.8569 26.0292 -210.1167 26.9736 -1042.3286 10.9827 22.6680 10.2336	Term -3.3112 -3.3655 -3.4157 -3.4655 -3.5116 -3.4622 -3.4685 -3.4655 -3.5116 -3.5116 -3.4622 -3.5086 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4622 -3.4655 -3.5520 -3.552	Rela	ted Term 2.7062 2.8497 2.9807 3.0987 3.0997 3.0092 3.0058 3.0076 3.0705 3.0707 3.1400 3.0707 3.1400 3.0776 3.0386 4.0983 3.0878 3.0376 3.4542 3.1653 3.2793 3.2588 3.4705

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

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

$$\log A = \log Ixx = \log \sum_{i} m_i (y_i^2 + z_i^2)$$
 (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 $(m_i y_i^2 \text{ or } m_i z_i^2 \text{ will be different})$; (c) a mixture of cases *a* and *b*. Therefore, this index can be

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

Variable t Value р QA Q7ESE7E9 SE7E9 3.20 < 0.005 < 0.005 3.11 10.74 < 0.0005 < 0.0005 -9.06 -2.36 < 0.025 < 0.0005 I 4.73

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 IV-Square	l Correlation Matrix for	Varibles in Eq. 5
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	Q4	<i>Q</i> ₇	S ^E ₅	S ^E 7	S§	1
Q4	1.00					
\tilde{Q}_{7}	0.01	1.00				
ŠĘ	0.62	0.0009	1.00			
Sŧ	0.12	0.18	0.07	1.00		
SĘ	0.19	0.07	0.13	0.43	1.00	
Ĺ	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 shown¹, 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^{ϵ} given by perturbation theory¹.

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