

# Electronic Structure and Serotonin Receptor Binding Affinity of 7-Substituted Tryptamines

## QSAR of 7-Substituted Tryptamines

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### Abbreviations

QSAR	Quantitative Structure-Activity Relationships
$pA_2$	receptor affinity (rat stomach fundus)
HOMO	Highest Occupied Molecular Orbital
LEMO	Lowest Empty Molecular Orbital
MO	Molecular Orbital
CNDO	Complete Neglect of Differential Overlap
SD	Standard Deviation
PAA	Phenylalkylamines
IAA	Indolealkylamines
ESD	Electrophilic Superdelocalizability
NSD	Nucleophilic Superdelocalizability

### Abstract

A QSAR study was carried out seeking a relationship between the receptor binding affinities and the molecular-electronic structures of a group of 7-substituted tryptamines. The results suggest that these molecules interact with the rat stomach fundus serotonergic receptor by charge transfer from the aromatic nucleus and that there are pockets in the receptor which place limits on the sizes of acceptable *N*- and  $\alpha$ -carbon substituents. Also, the charge density available at carbon atom 7 and the size of the *C*-7 substituent as estimated by a calculated steric factor seem to make important contributions to an optimal interaction between the IAA and the receptor molecules.

**Key words:** Quantitative structure-activity relationships, substituted tryptamines, rat stomach fundus, affinities in, CNDO/2 method, serotonergic receptor, steric effect, perturbation theory, hallucinogens, reactivity indexes, frontier orbitals.

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### 1 Introduction

One of the approaches leading towards a complete understanding of the pharmacology of any type of drug is the obtainment of significant relationships between the molecular structures of these substances, and parameters involved in the pharmaceutical, pharmacokinetic and pharmacodynamic phases of their actions. Among the parameters regulating the pharmacodynamic phase, the affinity for appropriate receptors is of paramount importance. Glennon et al. [1–9] have measured the affinities of a fairly large sample of IAA and PAA hallucinogens for the rat stomach fundus serotonergic receptor, and have also obtained a set of correlations between these receptor affinities ( $pA_2$ ) and various reactivity indices [1]. Gupta, Singh and Bindal, in a recent critical review of QSAR studies on these molecules [10], concluded that none of the equations arrived at were highly significant, either because the data had been obtained using methods involving many approximations, or because only small numbers of data points had been employed. We may add that previous studies have usually examined a few individual parameters through the use of totally empirical approaches.

We have recently presented a general formal quantum- and statistical-mechanical method which relates receptor affinity to certain reactivity indices [11]. This procedure leads to so-called model-based equations which are more easily interpreted than those arising from empirical methods [12]. When applied to the study of the relationships between  $pA_2$  and electronic structure in groups of PAA [13] and IAA [14], it has given excellent results.

Nevertheless, excessive diversity in the structures of the molecules subjected to these analyses, as in references 1 and 14, makes it difficult to obtain a good equation accounting for the variation of  $pA_2$ . For this reason, we selected a group of 5-substituted tryptamines to carry out a QSAR study [15], including for the first time a non-empirical parameter to account for the steric effect of the substituents [16]. The results obtained in this way were the best until then (cf reference [10]).

As a further test of our method, and because of the interest that these compounds present, we have chosen a set of tryptamines bearing a substituent at position 7 of the benzene ring to study the relationships between the variation of  $pA_2$  and the variation of the atomic reactivity indices and steric factors (see Fig. 1). In this way, all the changes in the electron distribution in the indole nucleus can be ascribed to the group located at C-7. We should point out that, for the present purposes, we consider the hydrogen atom as a substituent, and include several analogues with a substituted amine nitrogen atom.

## 2 Methods, Models and Calculations

The formalism employed here has been presented and discussed elsewhere [11, 13, 16]. Its basic assumptions are a state of thermodynamic equilibrium and a 1:1 stoichiometry in the formation of the drug-receptor complex:



where D is the drug molecule, R is the receptor, and DR is the complex (i stands for the i-th drug species) [11]. The equilibrium constant is

$$K_i = (Q_{D_iR}/Q_{D_i}Q_R) \exp(-\Delta E_0^i/kT) \quad (2)$$

where  $\Delta E_0^i$  is the difference between the ground state energy of  $D_iR$  and the energies of the ground states of  $D_i$  and R:

$$\Delta E_i = E_{D_iR} - (E_{D_i} + E_R) \quad (3)$$

and the Q's are the total partition functions measured from the ground state in solution.

Considering that the mass of the receptor molecule is very much larger than the mass of the drug molecule, that the Boltzmann factors of the excited electronic states are negligible compared to those of the ground state, that the rotational and vibrational motions may be treated in a first approach as independent and uncoupled, and that at 37°C the vibrational partition function is close to one, we can approximate Eq. (2) as [11]:

$$\log K_i = a + b \log M_{D_i} + c \log [(Q_{D_i}/(I_1 I_2 I_3)^{1/2})] + d \Delta E_i \quad (4)$$

where a, b, c and d are constants,  $\sigma$  is the drug molecule's symmetry number and  $I_1 I_2 I_3$  is the product of its three moments of inertia around the three principal axes of rotation [11].

In general, the direct quantum-mechanical determination of  $\Delta E_i$  is not possible, either due to the size of the receptor or to the lack of knowledge of its structure. Nevertheless, in the case of a mechanism implying that the two molecules are sufficiently far apart (i.e. that there is molecular attraction rather than covalent bonding), we can employ the standard Rayleigh-Schrödinger perturbation theory up to the second order to evaluate  $\Delta E_i$  [17]. In this way, for a system involving pairs of interacting atoms, we obtain [18, 19]

$$\Delta E_i = \sum_{p \in D_i} \sum_{r \in R} \left\{ Q_{p_i} Q_r / R_{p_i r} + \sum_m \sum_{n'} C_{m p_i}^2 C_{n' r}^2 / (E_m - E_{n'}) \right\} + \sum_m \sum_{n'} C_{m p_i}^2 C_{n' r}^2 (E_m - E_{n'}) \quad (5)$$

where  $p_i$  and  $r$  refer, respectively, to atoms belonging to the drug and to the receptor. The summations on  $m(n)$  and  $m'(n')$  are, respectively, over the occupied and virtual molecular orbitals of the drug (receptor). We must note here that we have assumed that the resonance integral is dependent only on the atoms participating in the interaction; therefore, it is constant for a given group of compounds sharing a common skeleton.

The first term on the right hand side of Eq. (5) may be interpreted as an approximation to the electrostatic interaction energy of the unperturbed charge distributions of both molecules. The last two terms of Eq. (5) correspond to the polarisation energy of the interacting systems [20].

The problem at hand is related to the lack of knowledge of the occupied and virtual MO's of the receptor. Some authors have circumvented this difficulty by replacing the receptor's MO energies by average values [20, 21]. This procedure is not formally justified, however, and may shed some doubt on the formalism itself. We choose to avoid this approximation by considering a series expansion of the energy denominators of Eq. (5), as we have done before when determining polarizabilities using Perturbation Theory [22]. It can be shown [23] that this procedure leads to the following expression for  $\Delta E_i$ :

$$\Delta E_i = a + \sum_{p_i} \left\{ e_{p_i} Q_{p_i} + f_{p_i} S_{p_i}^E + g_{p_i} S_{p_i}^N \right\} + \sum_{p_i} \sum_{m=z}^{\infty} \left\{ h_{p_i}(m) D_{p_i}(m) + j_{p_i}(m) S_{p_i}^E(m) \right\} + \sum_{p_i} \sum_{m'=v}^x \left\{ r_{p_i}(m') D_{p_i}(m') + t_{p_i}(m') S_{p_i}^N(m') \right\} \quad (6)$$

where a, e, f, g, h, j, r, and t are constants,  $S_{p_i}^E(m)$ ,  $S_{p_i}^N(m')$ , and  $D_{p_i}(m)$  are respectively, the orbital ESD of MO m at atom  $p_i$  of the drug molecule, the orbital NSD of MO  $m'$ , and the orbital electron density of MO m at the same atom.  $S_{p_i}^E$ ,  $S_{p_i}^N$  and  $Q_{p_i}$  are, respectively, the atomic total ESD, the atomic total NSD, and the net charge of atom p in molecule i. The summation on m includes a group of MO's close to the HOMO, and the HOMO itself. The summation on  $m'$  includes the LEMO and a group of low-lying virtual MO's. These groups are determined with the help of statistical multiple regression analysis. Eq. (6) includes an approximate representation of the dispersion energy, which was not considered in the older treatments [18-21, 24].

The atoms  $p_i$  are those belonging to a skeleton which is common to all the drug molecules under consideration. For the physical meaning of the indices in Eq. (6), see reference [13].

It can be shown that, if we choose an appropriate coordinate system, the term related to the moments of inertia can be rewritten approximately as [16]:

$$\log(ABC) = \sum_t^{\text{subs atoms}} \sum_{j \in t} m_{ij} R_{ij}^2 = \sum_t^{\text{subs}} I_t \quad (7)$$

where the summation on t is over the different substituents and the summation on j is over the atoms belonging to the t-th substituent, m and R being, respectively, the mass of the atom and its distance to the origin of the chosen coordinate system. Eq. (7) allows, therefore, the separate analysis of the geometrical features of the substituent which may be important in the drug-receptor interaction. This steric factor

has already proven useful in another QSAR study on tryptamines [15].

**Table 1.** Experimental determined and calculated  $pA_2$ -values for 7-substituted tryptamines

Molecule	R <sup>7</sup>	R <sup>α</sup>	R <sup>N</sup>	Experimental $pA_2^a$	Calculated $pA_2$ Eq. (8)	$pA_2$ Eq. (9)
1	H	H	H	6.27	5.91	6.22
2	H	H	CH <sub>3</sub>	6.00	6.14	6.14
3	CH <sub>3</sub>	H	CH <sub>3</sub>	6.29	6.05	6.19
4	OCH <sub>3</sub>	H	CH <sub>3</sub>	5.33	5.36	5.20
5	OH	H	CH <sub>3</sub>	4.88	5.02	5.12
6 <sup>b</sup>	H	H	CH <sub>3</sub>	6.04	6.22	5.83
7 <sup>c</sup>	H	H	CH <sub>3</sub>	6.02	6.19	6.31
8 <sup>d</sup>	H	H	CH <sub>3</sub>	6.03	5.93	5.88
9	H	H	H and CH <sub>3</sub>	5.97	6.02	6.01
10	Br	H	CH <sub>3</sub>	6.51	6.49	6.37
11 <sup>e</sup>	H	H	CH <sub>3</sub>	5.68	5.55	5.64
12 <sup>f</sup>	H	CH <sub>3</sub>	H	5.49	5.49	5.49
13 <sup>g</sup>	H	CH <sub>3</sub>	H	6.46	6.44	6.55
14	H	H	C <sub>2</sub> H <sub>5</sub>	5.79	5.88	5.84
15	C <sub>2</sub> H <sub>5</sub>	H	CH <sub>3</sub>	6.31	6.33	6.24

<sup>a</sup> Ref. [1-9].

<sup>b</sup> With a CH<sub>3</sub> group at position 2.

<sup>c</sup> With a CH<sub>3</sub> group on the indole N.

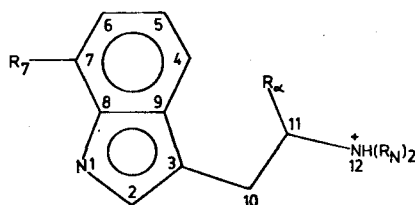
<sup>d</sup> With a S atom instead of the indole NH.

<sup>e</sup> With a CH<sub>2</sub> group instead of the indole NH.

<sup>f</sup> (S(+)) isomer.

<sup>g</sup> (R(-)) isomer.

The molecules selected for this study are presented in Table 1, together with their experimental  $pA_2$  values. The geometry employed is the same as in previous studies [14, 15]. The reactivity indices were obtained using Molecular Orbital Theory at the CNDO/2 level [25]. The steric factor was calculated with reference to the point X = -5.5 Å, Y = 1.2 Å, Z = 0.0 Å, of the coordinate system shown in Figure 1.



**Figure 1.** The 7-substituted tryptamines.

### 3 Results

The statistical fitting of Eq. (6) was performed by means of a stepwise regression technique with  $pA_2$  as the independent variable. To select the common skeleton for all the IAA we analysed two possibilities:

- The atoms of the two aromatic rings plus the side chain atoms.
- The atoms of the benzene ring plus the side chain atoms, considering that IAA and PAA interact with the same receptor [14, 15].

The choice of the variables to be used in the statistical analysis was carried out in the following way:

- Considering that an analysis of the electronic structure of these molecules strongly suggests that they can transfer charge from the aromatic ring to receptor, we did not use the NSD's or the virtual densities of the rings. We also neglected the ESD's corresponding to the side chain.
- To rule out errors resulting from the above simplification, we carried out a statistical analysis with all the variables. More than 250 equations were obtained and analysed.

The best one we found, considering all aspects of statistical analysis, is (see Figure 1 for the numbering of the atoms):

$$pA_2 = 7.78 - 2.92(0.773)D_8(H-2) - 3.291(0.4092)S_8^E + 0.00136(0.00029)I_7 - 0.00076(0.00017)I_\alpha \quad (8)$$

with  $R = 0.939$ ,  $R^2 = 0.882$ , mean SD = 0.181 and  $n = 15$ . The standard deviations of the coefficients are included in the formula in parentheses. The analysis of the variance of Eq. (8) gives  $F(10,4) = 18.75$  ( $p < 0.005$ ), showing that this equation is highly significant. The result of Student's test for the significance of the variables appearing in Eq. (8) are presented in Table 2.

The second best equation we obtained is:

$$pA_2 = -9.27 + 3.03(0.662)S_8^E(HOMO) - 3.60(0.446)S_7^E - 0.00084(0.00016)I_\alpha - 0.00015(0.00005)I_N \quad (9)$$

where  $S_8^E(HOMO)$  and  $I_N$  are, respectively, the HOMO orbital ESD of atom 8 and the steric factor (see Eq. (4)) corresponding to the N substituent. Eq. (9) has  $R = 0.945$ ,  $R^2 = 0.894$  and a mean SD of 0.172. The analysis of variance gave  $F(10,4) = 21.05$  ( $p < 0.0005$ ). The results of Student's t test for the variables appearing in Eq. (9) are presented in Table 3. The squared correlation coefficient matrix for the variables appearing in Eqs. (8) and (9) is displayed in Table 4; it shows clearly that there is no significant internal correlation between the variables considered. The variables employed in the statistical analysis are presented in Table 5. The calculated  $pA_2$  values, together with the experimental ones, are shown in Table 1.

**Table 2.** Results of the Student t test for the significance of the variables appearing in Eq. (8).

Variable	t value	p
$D_8(H-2)$	-3.78	<0.005
$S_8^E$	-8.04	<0.0005
$I_7$	-4.65	<0.0005
$I_\alpha$	-4.56	<0.0005

**Table 3.** Results of the Student t test for the significance of the variables appearing in Eq. (9).

Variable	t value	p
$S_8^E(HOMO)$	-4.57	<0.0005
$S_7^E$	-8.07	<0.0005
$I_\alpha$	-5.17	<0.0005
$I_N$	-2.92	<0.0005

**Table 4.** Squared correlation coefficient matrix for the variables appearing in Eqs. (8) and (9).

	$D_8(\text{H-2})$	$S_7^E$	$I_7$	$I_\alpha$	$S_7^E$ (HOMO)	$I_N$
$D_8(\text{H-2})$	1.0					
$S_7^E$	$4 \times 10^{-4}$	1.0				
$I_7$	0.13	0.16	1.0			
$I_\alpha$	0.16	0.03	0.02	1.0		
$S_7^E$ (HOMO)	0.04	0.38	0.46	$6 \times 10^{-4}$	1.0	
$I_N$	0.25	0.03	0.05	0.16	$9 \times 10^{-3}$	1.0

Before discussing the results, it must be mentioned that using these variables the probability of finding a chance correlation with  $R^2 > 0.9$  is 1% or less [26].

#### 4 Discussion

From Eq. (9) it can be appreciated that the  $pA_2$  value diminishes if the steric factor of the N substituent increases. This is in perfect agreement with the experimentalist's observations [3] and with our previous QSAR study on 5-substituted IAA [15], indicating that an unsubstituted amine nitrogen atom is conducive to high receptor affinity.

On the other hand, from Eqs. (8) and (9) it can be seen that if the steric factor of the  $\alpha$ -carbon substituent grows, the  $pA_2$  value falls. This result must be interpreted with caution because we have considered only one enantiomeric pair. Table 1 shows that the experimental  $pA_2$  value for the (*R*)(-)-isomer is greater than the value for the molecule with no  $\alpha$ -substituent, while the  $pA_2$  value for its enantiomer is lower. Before a firm opinion can be given it is necessary to wait for more receptor affinity measurements on individual optical isomers. Nevertheless, we may conjecture that the  $pA_2$  value increases in one case as a consequence of the substituent fitting into a hydrophobic pocket in the receptor, and decreases in the other due to the existence of steric repulsion with a neighbouring region of the receptor surface. As there are no data available for  $\alpha$ -substituents larger than  $\text{CH}_3$ , nothing can be said about the maximal size of this group.

The electron density of the (H-2) MO at C-8 and the atomic ESD at this position affect the  $pA_2$  value, as seen in Eqs. (8) and (9), respectively. In both cases,  $pA_2$  diminishes if these parameters increase, as  $D_p(m)$  is always positive and  $S_7^E$  is always negative. These results suggest that, for an optimal interaction, the electron density at C-8 should be low. Considering that this atom is part of an aromatic ring, the associated electron density will depend on the nature of the substituents attached to the neighbouring atoms, especially C-7.

The two equations show that  $pA_2$  values increase when the atomic ESD at C-7 increases. This fact may be explained by assuming that the receptor possesses an electrophilic centre that interacts directly with C-7.

The problem of the nature of the C-7 substituent seems to be more complex. In 1-phenyl-2-aminopropanes, where C-4 can be considered to be congruous with C-7 of the IAA, it has been suggested that the 4-substituent interacts directly with the receptor [6]. Also, in the case of a methyl group at this position, a hydrophobic interaction has been mentioned [2]. On the other hand, it is well known that the

substitution of a methyl or ethyl group or a bromine atom at the 4-position of hallucinogenic PAA enhances activity [4], and the aminopropanes bearing these substituents in addition to the 2,5-dimethoxy pattern are very potent hallucinogens.

Other researchers have found a parabolic dependence of potency on the net total atomic charge on C-7, such that an optimal charge can be calculated for this position [27]. According to these authors, the charge must be close to zero for high potency to be observed, a suggestion which contradicts the involvement of the atomic ESD at C-7 in our correlations. They postulated that the C-7 region may come into contact with a hydrophobic region of the receptor; and that a charge of either sign at C-7 would result in decreased hydrophobicity. Finally, they noted that this effect could not be quantitatively accounted for by including a term to estimate substituent volume (molar volume, polarisability, or Taft's steric coefficient). It is also pointed out that if a specific hydrophobic site exists, the introduction of a polar substituent at C-7 of an IAA should be expected to have a detrimental effect on the  $pA_2$  value. This is found to be the case, as 7-hydroxy-*N,N*-dimethyltryptamine (5 in Table 1) possesses the lowest affinity of any congener examined thus far [2, 3].

In a QSAR study based exclusively on electronic parameters [1], two of the statistical regression equations were found to improve when 7-methoxy-*N,N*-dimethyltryptamine (4 in Table 1, the only 7-substituted compound in Ref. [1]) was deleted. This immediately suggests that electronic properties alone are unable to account for the variation of  $pA_2$ . In fact, an older paper relating the contraction of rat stomach fundus strips to MO parameters and Hansch hydrophobicity coefficients [27] had already shown that inclusion of this constant for the C-7 substituent raises the significance level of half a dozen different equations.

To analyse the influence of the steric factor for the C-7 substituent appearing in Eq. (8), we shall order molecules 2, 3, 4, 5, 10 and 15 in the following way:

- $pA_2$  values:  $\text{Br} > \text{C}_2\text{H}_5 \approx \text{CH}_3 > \text{H} > \text{OCH}_3 > \text{OH}$
- $I_7$  values:  $\text{Br} > \text{OCH}_3 > \text{C}_2\text{H}_5 > \text{OH} > \text{CH}_3 > \text{H}$
- $S_7^E$  values:  $\text{H} > \text{Br} \approx \text{CH}_3 \approx \text{C}_2\text{H}_5 > \text{OCH}_3 \approx \text{OH}$

It can be seen immediately that the orders of the  $pA_2$ ,  $I_7$  and  $S_7^E$  values do not run parallel to each other. Nevertheless, if we neglect the molecules substituted at C-7 with the hydrophilic OH or  $\text{OCH}_3$  groups, an interesting fact emerges: the  $pA_2$  value parallels the value of  $I_7$  and the value of  $S_7^E$ , with the exception of the H-substituted molecule, for which  $S_7^E$  is highest. If we now consider only the deleted molecules, all three parameters are greater for the methoxy than for the hydroxy compound. All this clearly indicates that it is not the hydrophobicity that regulates  $pA_2$ , but the values of  $I_7$  and  $S_7^E$  taken together. The H-substituted molecule (2 in Table 1) is the most representative case. It has the highest value for  $S_7^E$  but the lowest for  $I_7$ , and its  $pA_2$  value lies between those of the molecules bearing hydrophobic substituents and those with hydrophilic ones. The OH and  $\text{OCH}_3$  derivatives, having fairly high  $I_7$  values, possess low receptor affinities because of their very low  $S_7^E$  values.

From these results, a tentative picture emerges for the serotonergic receptor, shown in Fig. (2). Now, from this study and others [13-15], the receptor appears to be a

highly complex structure interacting with the phenyl ring and the side chain, and with pockets that restrict the recognition of these moieties. Also, our results support the contention that IAA interact with the receptor in such a way that their aromatic ring always adopt the same orientation in contrast with other suggestions [28, 29].

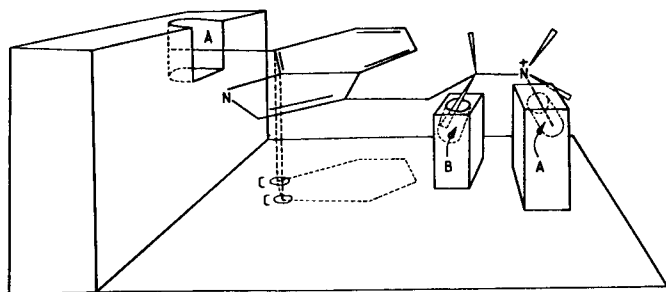


Figure 2. Some of the possible features of the rat stomach fundus serotonergic receptor:

- A) pockets controlling the size of substituents at the amine N and at C-7;  
 B) possible interaction area for one of the  $\alpha$ -carbon substituents;  
 C) areas interacting by charge transfer.

Our QSAR equations for IAA [14, 15] and PAA [13] are very similar for both kinds of compounds. If these different groups of drugs interact with the receptor by analogous mechanisms, then a PAA with a small hydrophilic group at C-4 but with a high  $I_4$  value (i.e. with a large mass) must have a high  $pA_2$  value if its  $S_4^E$  is high enough. If such a compound is able to pass through the blood-brain barrier, it may be hallucinogenic at low doses. These considerations apply perfectly to 1-(2,5-dimethoxy-4-nitrophenyl)-2-aminopropane (DON), with a  $pA_2$  value of 7.07 for the racemic mixture [6]. Our pharmacological studies, which will be published elsewhere, show that ( $\pm$ )-DON is a very potent hallucinogen, comparable to DOB (its 4-bromo analogue) and DOM (the 4-methyl analogue), which carry hydrophobic substituents at C-4 [30]. The same argument may be applied to 7-substituted IAA and, therefore, 7-nitrotryptamine would be expected to exhibit a high affinity for the rat stomach fundus serotonergic receptor.

The equations presented here can be refined in principle as more  $pA_2$  values become available. Also, it seems necessary to improve the term describing the steric factors by decomposing it into three terms accounting for the orientation of the substituent. Nevertheless, our correlations are the most significant obtained so far for IAA (cf. Ref. [10]).

These results, together with other reported previously [13-15], are convincing evidence that so-called theoretical equations [12] are much better than empirical ones (i.e., those derived by Hansch analysis and other similar techniques). Furthermore, they provide a deeper insight into the mechanism by which these molecules interact with their receptor.

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