

PARAMETRIZATION OF THE ORIENTATIONAL EFFECTS IN THE DRUG-RECEPTOR INTERACTION

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SUMMARY

We present a physically based treatment of the molecular rotational partition function for the case of the interaction of a macromolecular receptor with a small biologically active molecule.

This leads to the proposal of a new substituent parameter that we call the Orientational Parameter. Its physical interpretation is that it gives an account of the substituent's influence on the percentage of molecules achieving the correct orientation to interact with the receptor.

Finally we propose a universal way to calculate its values, avoiding the need of building long tables. A comparison between the old and new ways to calculate it is presented. We provide here an example to show its usefulness in QSAR studies

INTRODUCTION

Quantum pharmacology (QP) is now a well-established branch of quantum chemistry. Its scope is to study the electronic and conformational properties of biologically active molecules and to seek relationships between these properties and the action mechanisms of drugs.

Quantum pharmacology, through quantitative structure-activity relationships (QSAR), should provide a physical insight on the sequences of processes which form the basis of drug action: the pharmaceutical, pharmacokinetic and pharmacodynamic phases.

If we are able to obtain a QSAR for a given family of molecules possessing the same pharmacological activity, it is then possible to suggest new molecules with enhanced pharmacological activity and diminished side effects.

In the following we shall center our attention on the pharmacodynamic phase of drug action. This is because this step is well characterized by the drug-receptor equilibrium constant or related experimentally measurable data.

On the other hand, it has been proposed [1] that the space around the receptor can be divided into the following three zones. In zone I the drug-receptor interaction occurs through intermolecular forces. Zone II covers the first one and is defined as the space in which only ionic forces are acting. This is where an accumulation, recognition and guiding of the drug molecule towards the receptor occurs. This recognition process can be associated with a match between the molecular electrostatic potentials of the drug and the receptor. Zone III covers the remainder of the biophase. In this zone, thermal agitation will cause the passage of drug molecules to zone II.

A long time ago [2] we proposed a model-based method [3] to obtain quantitative structure-activity relationships for the case in which the receptor's structure is not known.

In this paper we shall show how, starting from a state of thermodynamic equilibrium and a 1:1 stoichiometry in the formation of the drug-receptor complex and by using the statistical-mechanical definition of the equilibrium constant, we may derive a new substituent parameter that is very important at the level of zone II of the receptor. This parameter has shown its utility in some QSAR studies [4] but its derivation

has never been published. In general, when a new parameter of this kind is proposed, tables of their values for a great number of substituents are built. In our case we propose an easy method to calculate it eliminating the need of those tables.

MODELS AND METHODS

1. The drug-receptor equilibrium constant.
Let us consider the equilibrium:



Where D, R and DR refer, respectively, to the drug, the receptor and the drug-receptor complex. The equilibrium constant for (1), K, is given by:

$$K = \left[\frac{Q_{DR}}{Q_D Q_R} \right] \quad (2)$$

where Q_D , Q_R and Q_{DR} are the total molecular partition functions for the three chemical species. The partition function is defined as:

$$Q = \sum_i g_i e^{-\varepsilon_i/kT} \quad (3)$$

Where index i represents the i -th molecular energy level with g_i degeneracy, ε is the total energy, κ the Boltzmann constant and T the temperature in Kelvin.

In a first approximation we may consider that the rotational, vibrational and translational movements are independent, their respective energies being therefore separable.

Nevertheless, as the vibrational and rotational states are not generally independent from the electronic states, Eq. (3) can be expressed as:

$$Q = Q^t \left[\left(\sum_i g_i^{el} e^{-\varepsilon_i^{el}/kT} Q_i^r Q_i^v \right) \right] \quad (4)$$

Where "el" refers to electronic states, Q^t is the translational partition function and Q_i^r and Q_i^v are, respectively, the rotational and vibrational partition functions for the i-th electronic state with degeneracy g_i .

As in almost all biological cases the three chemical species are in their fundamental electronic states we may rewrite Eq. (4) as:

$$Q = Q^t Q^{r0} Q^{v0} e^{-\varepsilon_0/kT} \quad (5)$$

Where now "0" indicates the ground electronic state of the molecule. Inserting Eq. (5) into Eq. (2) produces:

$$K = \left[\frac{Q_{DR}^{r0} Q_{DR}^{v0} Q_{DR}^{r0}}{Q_D^{r0} Q_D^{v0} Q_D^{r0} Q_R^{r0} Q_R^{v0} Q_R^{r0}} \right] e^{-\Delta\varepsilon_0/kT} \quad (6)$$

Where $\Delta\varepsilon_0$ is the drug-receptor energy:

$$\Delta\varepsilon_0 = (\varepsilon_D^0 + \varepsilon_R^0) - \varepsilon_{DR}^0 \quad (7)$$

If we consider the conditions under which the drug-receptor interaction occurs it is possible to apply some approximations to simplify Eq. (6). Usually, the receptors are macromolecules or parts of very complex molecular structures. On the other hand, drug molecules are very small in comparison to receptors. This fact will allow us to cancel the terms corresponding to the receptor and the drug-receptor complex obtaining:

$$K = \frac{e^{-\Delta\varepsilon_0/kT}}{Q_D^t Q_D^{r0} Q_D^{v0}} \quad (8)$$

or

$$\ln K = (-\Delta\varepsilon_0/kT) - \ln(Q_D^t Q_D^{r0} Q_D^{v0}) \quad (9)$$

For the first term on the right hand side of Eq. (9) a workable expression only in terms of the drug's electronic structure has been proposed earlier [5]. In the following we shall center our attention on the second term of the right side of Eq. (9). At body temperature ($\approx 37^\circ\text{C}$) the vibrational partition function for the ground state has a value of approximately 1 [6]. By using this fact, the expression for the translational partition function per volume unit in IS units, and some algebra we get:

$$\ln K = (-\Delta\varepsilon_0/kT) - \ln Q_D^{r0} - \frac{3}{2} \ln M_D - \frac{3}{2} \ln T - 152.992 \quad (10)$$

Where M_D is the drug's molecular mass. With the expression obtained earlier for the first term of the right side of Eq. (10) we may observe that no contribution from the receptor appears in Eq. (10).

2. The rotational partition function.

To find the expression for the rotational partition function for the case of a molecule rotating in three dimensions we must express the rotational kinetic energy in terms of the H(p,q) operator [7]. In terms of the Euler angles (δ, θ, ϕ) H(p,q) can be written as:

$$H(p, q) = \frac{\sin^2 \delta}{2A} \left[P_\theta - \frac{\cos \delta}{\sin \theta \sin \delta} (P_\phi - P_\delta \cos \phi) \right]^2 + \frac{\cos^2 \delta}{2B} \left[P_\theta + \frac{\sin \delta}{\sin \theta \cos \delta} (P_\phi - P_\delta \cos \theta) \right]^2 + \frac{1}{2C} P_\delta^2 \quad (11)$$

Where A, B and C are the moments of inertia around the principal axis of rotation.

Classically, the rotational partition function is defined as:

$$Q_r = \frac{1}{h^3} \int_0^\pi \int_0^{2\pi} \int_{-\infty}^\infty \int_{-\infty}^\infty \int_{-\infty}^\infty e^{-H(p,q)/kT} d\theta d\phi d\delta dP_\theta dP_\phi dP_\delta \quad (12)$$

Inserting Eq. (11) into Eq. (12) and carrying out the integration we arrive at the following expression:

$$Q_r = \frac{8\pi^2 (2\pi kT)^{3/2} (ABC)^{1/2}}{h^3 \sigma} \quad (13)$$

where the symmetry number σ has been added to take into account the number of identical configurations that the rotating molecule can adopt. Now we shall deal with the moments of inertia.

3. The moments of inertia.

The moments of inertia around the principal axes of rotation are defined as:

$$A \equiv I_{xx} = \sum_i m_i (y_i^2 + z_i^2) \quad (14)$$

$$B \equiv I_{yy} = \sum_i m_i (z_i^2 + x_i^2) \quad (15)$$

$$C \equiv I_{zz} = \sum_i m_i (x_i^2 + y_i^2) \quad (16)$$

Where m_i is the mass of atom i and, for example, x_i is the perpendicular distance from atom i to the x-axis of coordinates.

Now, let us consider a molecule (called hereafter "the skeleton") with a substituent attached to it. From Eq. (14) to (16) it is clear that we can formally separate the contribution of the skeleton from that of the substituent. We get the following general expression:

$$I_{ii} = I_{ii}^{SQ} + I_{ii}^S \quad (17)$$

Where ii stands for xx, yy or zz, SQ refers to the skeleton's contribution and S to the substituent's.

From Eq. (10) and (13) we may see that we have an expression of the form $\ln I_{xx} I_{yy} I_{zz} = \ln I_{xx} + \ln I_{yy} + \ln I_{zz}$. In a general way we may write any of the three terms as:

$$\ln I_{ii} = \ln \left[I_{ii}^{SQ} + I_{ii}^S \right] + \ln \frac{I_{ii}^{SQ}}{I_{ii}^{SQ}} = \ln \left[1 + \frac{I_{ii}^S}{I_{ii}^{SQ}} \right] + \ln I_{ii}^{SQ} \quad (18)$$

For the case in which the contribution of the skeleton is greater than the substituent's (a case that is normal in biologically active molecules) we may use a series expansion for the first term of the right side of Eq. (18). Doing this and keeping only the first term of the expansion (the series converges very fast) we get:

$$\ln I \equiv \ln I_{xx} + \ln I_{yy} + \ln I_{zz} = \left[\frac{I_{xx}^S}{I_{xx}^{SQ}} + \frac{I_{yy}^S}{I_{yy}^{SQ}} + \frac{I_{zz}^S}{I_{zz}^{SQ}} \right] + \ln(I_{xx}^{SQ} I_{yy}^{SQ} I_{zz}^{SQ}) \quad (19)$$

Now, by considering that within a family of biologically active molecules being subjected to a QSAR study the skeleton must be common (i.e., a constant) we may rearrange Eq. (19) as:

$$\ln I = k_0 \sum_l m_l r_l^2 - k_1 \sum_l m_l x_l^2 - k_2 \sum_l m_l y_l^2 - k_3 \sum_l m_l z_l^2 + k_4 \quad (20)$$

Where l runs only over the substituent atoms, $k_0 \neq k_1 \neq k_2 \neq k_3 \neq k_4$ are functions only of the skeleton and r_l^2 is the distance of atom l to the center of mass. From the mathematical form of the constants it follows that k_0 is greater than k_1 , k_2 and k_3 [8], k_4 being only an additive constant. Therefore, we shall approximate Eq. (20) as:

$$\ln I \approx k_0 \sum_l m_l r_l^2 \quad (21)$$

4. The practical calculation of $\ln I$.

To design a practical way to calculate $\ln I$ we start from the following fact. The main requirement for some of the above approximations is that the molecular skeleton must be heavier than the substituent. In the case of a family of molecules with a substituent attached to the same site in all them we expect that if we superimpose all the molecular skeletons, the centers of mass of all the molecules will occupy a small volume. Therefore, we shall change the calculation of $\ln I$ from the center of mass to a new coordinate system located on the atom to which the substituent is attached. This introduces a possible but negligible source of error but opens a way to create a set of standard substituent parameters for QSAR studies.

In the original study [8] $\ln I$ for a great group of possible substituents was calculated with Pople's standard geometry [9] with the substituent attached to an sp^3 carbon atom. This produced a very long list of Tables [8]. In these Tables values were provided for the most extended and the most folded configurations of the substituents if they existed.

With the rising capacity of personal computers and the appearance of new software we have modified the way to calculate $\ln I$. Now, we attach the substituent to a benzene molecule, perform a full AM1 geometry optimization with the Hyperchem Package [10] and calculate the substituent's contribution. We used benzene because almost all (but not all) biologically active molecules contain aromatic systems. In this way we avoid having to build long tables and replace this work by an

easy and universal way to get the values. Naturally, it is always convenient to publish in any QSAR paper the values of the parameters employed in the statistical analysis and the method used to obtain them. In Table I we present a comparison of values for some selected substituents calculated with both methods. We may see that there is no an apparent relationship between both sets of values. Another way to calculate $\ln I$ is the following. After a full geometry optimization of a molecule, we move the coordinate system from the center of mass to the atom to which the substituent is attached and we calculate directly. In this case, a Table containing the calculated OP values must be included in the paper.

Table I. A comparison of two methods to calculate the Orientational Parameter ($uma \cdot A^2$).

Substituent	Standard geometry ^a	AM1 geometry optimization
H	1.20	1.00
CF ₃	348.65	544.66
CH ₂ CH ₃	141.10	72.64
Cl	110.69	75.27
COCH ₃	231.01	185.31
COOH	228.80	174.95
CH ₂ OH	142.83	155.36
CONH ₂	142.81	181.74
COOH ₃	436.96	377.15
CH ₂ NH ₂	142.25	160.22

a. Ref. 8.

5. The physical meaning of $\ln I$.

What is the physical meaning of this parameter? If we remember that the moment of inertia tensor appears in the expression defining the rotational kinetic energy, an interpretation that is coherent with the classical treatment given to the rotational partition function is that this parameter gives an account of the substituent's influence on the percentage of molecules achieving the correct orientation to interact with the receptor.

In other words, the probability of the drug-receptor interaction rises when the molecule moves with a certain rotational velocity in such a way that it has the time to be recognized (probably through the matching of the molecular electrostatic potential of both partners) and attracted by the receptor. Using a classical analogy, if one molecule has a small substituent and another a big one and if they have the same rotational velocity, less energy will be necessary to stop the first one. For this reason we have called this parameter "Orientational Parameter" (OP). It is interesting to note that this orientational effect is associated with the molecular translational velocity in Eq. (10). The physical processes occurring in Zone II of the receptor depend on both velocities to get the drug-receptor interaction. We must remember that from the beginning of chemical kinetics the importance of proper mutual orientation of the reacting species was recognized. The appearance of the "steric factor" in the preexponential of the rate constant is related to the probability of achieving this proper orientation. It is possible then that this "steric factor" is related to our Orientational Parameter.

6. The relationship of $\ln I$ with other QSAR parameters.

It is interesting to examine if a relationship exists between this physically-based Orientational Parameter and some experimental and empirical QSAR parameters used to represent the elusive "steric effect".

For this purpose we studied the correlation between the OP values and the values of 74 parameters for a set of 35 substituents [8] taken from the literature [11,12]. We analyzed the most folded and the most extended configurations.

Table II shows the results for the best correlations obtained. The first parameter in Table I, κ_0 , is one of Kier's topological indices [13] related to the molecular shape. P_r , the parachor, is the surface tension adjusted molar volume. Specifically, it is the molecular weight of a liquid times the fourth root of its surface tension, divided by the difference between the density of the liquid and the density of the vapor in equilibrium with it; essentially constant over wide ranges of temperature. V_w is the van der Waals volume. X_{AR}^1 corresponds to the first-order valence molecular connectivity difference chi index. Finally, L is the length of the substituent along the direction of its bonding to the skeleton. We may see that, with the exception of parachor, all the other parameters correlating more or less well with the OP are geometrical and/or structural descriptors. The parachor could be related to intermolecular forces through the surface tension and the density and, for the case of apolar substances, to dispersion forces. No clear explanation of this intriguing correlation can be offered for the moment.

Table II. Square of the correlation coefficient between OP and other QSAR parameters.

Parameter	r_{ext}^2	r_{fol}^2
κ_0	0.89	0.91
P_r	0.85	0.80
V_w	0.82	0.81
X_{AR}^1	0.82	0.86
L	0.81	0.70

"ext" stands for extended and "fol" for folded configurations.

AN EXAMPLE OF APPLICATION

Despite the fact that until now the derivation of the OPs had not been published, their use in QSAR studies showed excellent results when applied to two cases: the inhibition of acetylcholinesterase by some phenyl-N-methylcarbamates [4] and the interaction of tryptamine derivatives with the rat stomach fundus serotonergic receptor [14,15]. Here we shall provide, as another example, the results of a study of the inhibition of monoamine oxidase (MAO) by a series of β -carbolines. This is an enzyme that is responsible for the metabolization (by oxidative deamination) of biogenic and related amines in the body. If this enzyme is not present, toxic amines, ingested with food or produced endogenously, cannot be metabolized. MAO inhibitors (IMAO), or drugs that block MAO, cause an increase in the concentrations of certain neurotransmitters (namely dopamine, norepinephrine, and serotonin) in the synapses of the nervous system.

MAO inhibitors have been used for the treatment of a wide spectrum of psychiatric disorders among which depression is a salient example. Some β -carbolines are good MAO inhibitors. The object of this study was to find an equation explaining the variation of the MAO inhibition constant in a family of β -carbolines (see Table III and Figure 1) in terms of the variation of the parameters appearing in Eq. 10, the rotational partition function contribution being replaced by the Orientational Parameter of the substituents. For the sake of brevity we refer the reader to a recent publication for more details about the

decomposition of $\Delta\epsilon_0$ [16]. The statistical fitting of Eq. 10 was performed by means of a stepwise regression technique with the MAO inhibition constants as the dependent variables and the static reactivity indices of the atoms belonging to a common skeleton and the Orientational Parameters of the substituents as the independent variables. The common skeleton is depicted in Fig. 1. Pople's standard geometry was employed [9]. The wave function was obtained within the Molecular Orbital Theory at the CNDO/2 level including the continuum solvent effects via an extended version of the generalized Born formula [17]. The MAO inhibition constant values (I_{50}) were taken from the literature [18-20]. They were transformed accordingly to $pI_{50} = -\log I_{50}$.

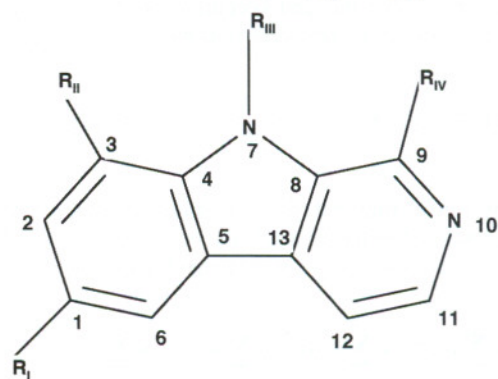


Fig. 1. β -carboline with the common skeleton numbering.

The best equation was the one obtained with the molecular wavefunctions calculated with a dielectric constant value for a low polarity medium ($\epsilon = 5$) [8]:

$$\log I_{50} = 2.0982 - 0.0018O_{III}^e - 0.0070O_{IV}^e + 2.6842D_5(HOMO-2) + 8.8883S_6^e(HOMO-1) + 0.8249S_6^e(HOMO) + 4.3733Q_7 \quad (22)$$

with $n = 24$, $R = 0.94$, $s = 0.22$ and $F(6,17) = 23.27$ ($p < 0.005$).

O_m^e and O_{IV}^e are, respectively, the orientational parameters of the substituents in their extended form [4,8] attached to atoms 3 and 9 of Fig. 1; $D_5(HOMO-2)$ is the electronic density of atom 5; Q_7 is the net charge of atom 7; and $S_6^e(HOMO)$ and $S_6^e(HOMO-1)$ are the orbital electrophilic superdelocalizabilities of the Highest Occupied Molecular Orbital (HOMO) and the next occupied MO below the HOMO (HOMO-1) at atom 6. The results of Student's t test for the variables appearing in Eq. 22 are shown in Table IV. The internal correlation matrix is presented in Table V. The values of pI_{50} calculated with Eq. 22 are shown in the right side of Table III.

Table III. Experimental and calculated values for b-carbolines.

Molecule	R_I	R_{II}	R_{III}	R_{IV}	Exp.	Calc.
1	H	H	H	H	1.5376	1.3372
2	H	H	H	Me	0.8539	1.0203
3	H	H	H	Et	0.3279	0.3113
4	H	H	Me	H	2.0000	1.7573
5	H	H	n-Pr	H	0.8239	1.0414
6	H	H	n-Bu	H	0.8539	0.3808
7	H	H	i-Pen	H	-0.2553	-0.0859
8	H	H	(CH ₂) ₃ OH	H	0.3188	0.3363
9	H	H	(CH ₂) ₂ OH	H	0.9586	1.0662
10	H	H	CH ₂ OH	H	1.4685	1.1934
11	H	H	CH ₂ OMe	H	0.3979	0.6080
12	H	H	COMe	H	0.8239	1.0757
13	H	H	H	NH ₂	0.8239	0.7166
14	Ome	H	H	H	1.3665	1.3371
15	Ome	H	Me	H	1.5528	1.6169
16	Me	H	H	H	0.9208	0.8445
17	Me	H	Me	H	1.1549	1.2963
18	Cl	H	H	H	1.6198	1.6169
19	NH ₂	H	H	H	0.2007	-0.0237
20	H	OMe	H	H	0.9298	1.0799
21	H	Me	H	H	1.1427	1.1650
22	H	Me	Me	H	1.6990	1.5952
23	H	NH ₂	H	H	0.2366	0.4792
24	H	H	Et	H	1.3188	1.3918

a. With Eq. 22

Table IV. Results of Student's t test for the significance of the variables appearing in Eq. 22.

Variable	t
O_{III}^r	-10.03 (p<0.0005)
O_{IV}^r	-4.12 (p<0.0005)
$D_3(HOMO-2)$	4.85 (p<0.0005)
$S_6^E(HOMO)$	6.35 (p<0.0005)
$S_6^E(HOMO-1)$	3.01 (p<0.005)
Q_7	2.84 (p=0.005)

Table V. Squared correlation coefficient matrix for the variables appearing in Eq. 22.

	O_{III}^r	O_{IV}^r	$D_3(HOMO-2)$	$S_6^E(HOMO-1)$	$S_6^E(HOMO)$
O_{IV}^r	0.04				
$D_3(HOMO-2)$	0.03	0.01			
$S_6^E(HOMO-1)$	0.01	0.08	0.34		
$S_6^E(HOMO)$	0.07	0.01	0.01	0.05	
Q_7	0.17	0.07	0.04	0.01	0.26

From the values of R, SD and F it is clear that a significant correlation exists between the variation of I_{50} and the variation of the variables appearing in Eq. 21.

The first thing to notice is that the b-carboline-MAO interaction is charge- and orbital-controlled [21], indicating its very high specificity. The fact that the best equation obtained is for a low polarizable medium is consistent with the fact that β -carbolines interact with MAO in their neutral form.

In general terms, we may say that the β -carboline-MAO interaction is controlled by the electron-donating capacity of atom 6, electrostatic interactions of atoms 5 and 7 with MAO complementary sites (atoms or residues) and the influence of the orientational parameters attached to atoms 7 and 9 (see Fig. 1). We must emphasize the following fact: the substituents attached to atom 1 show more variety in their OP values. Nevertheless, this variable does not appear in the final equation indicating that not all the substituents play equally important roles in the orientation of the molecules to interact with their partners.

As a final consideration we may say that the above example provides a new illustration of the utility of Orientational Parameters in QSAR studies. Naturally, there are cases in which these factors do not play an important role in the biomolecule-receptor interaction [see for example refs. 22 and 23].

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REFERENCES

- Ariens, E.J.; Simonis, A.M.; and van Rossum, J.M. 'Drug-receptor interaction: Interaction of one or more drugs with one receptor system' in E.J. Ariens Editor, Molecular Pharmacology, Vol. 1, pp. 119-286, Academic Press, NY, 1964.
- Gómez-Jeria, J.S. Int. J. Quant. Chem. 1983, 23, 1969.
- Martin, Y.C. Quantitative Drug Design. Marcel Dekker, NY, 1978.
- Gómez-Jeria, J.S.; Ojeda-Vergara, M. and Donoso-Espinoza, C. Molec. Eng. 1995, 5, 391.
- Gómez-Jeria, J.S. 'Modeling the drug-receptor interaction in Quantum Pharmacology' in J. Maruani Editor, Molecules in Physics, Chemistry and Biology, Vol. 4, pp. 231-251, Kluwer, Dordrecht, 1989.
- Knox, J.H. Molecular Thermodynamics, Wiley Interscience, New York, 1971.
- Glasstone, S. Theoretical Chemistry, D. Van Nostrand Inc., New York, 1950.
- Ojeda-Vergara, M. MSc. Thesis. University of Chile, Faculty of Sciences, 1991.
- Pople, J.A.; Beveridge, D.L. Approximate Molecular Orbital Theory, McGraw-Hill, New York, 1970.
- Hypercube Inc. 1115 NW 4th Street, Gainesville, FL, 32601, USA.
- Van de Waterbeemd, H. and Testa, B. J. Comp.-Aided Mol. Design 1989, 3, 111.
- Van de Waterbeemd, H. and Testa, B. 'The parametrization of lipophilicity and other structural properties' in B. Testa Editor, Drug Design, pp. 85-125, Academic Press, New York, 1987.
- Kier, L.B. Quant. Struct.-Act. Relat. 1986, 5, 1 and 7.
- Gómez-Jeria, J.S.; Morales-Lagos, D.; Rodríguez-Gatica, J.I. and Saavedra-Aguilar, J.C. Int. J. Quant. Chem. 1985, 28, 421.

15. Gómez-Jeria, J.S., Morales-Lagos, D., Cassels, B. and Saavedra-Aguilar, J.C. *Quant. Struct.-Act. Relat.* 1986, 5, 153.
16. Gómez-Jeria, J.S., Lagos-Arancibia, L. and Sobarzo-Sánchez, E. *J. Chil. Chem. Soc.* 2003, 48, 61.
17. Contreras, R. and Gómez-Jeria, J.S. *J. Phys. Chem.* 1984, 88, 1905.
18. Ho, B.T., McIsaac, W.M., Walker, K.E. and Estevez, V. *J. Pharm. Sci.* 1968, 57, 269.
19. Ho, B.T., McIsaac, W.M., Tansey, L.W. and Walker, K.E. *J. Pharm. Sci.* 1969, 58, 219.
20. Ho, B.T., Li, K., Walker, K.E., Tansey, L.W., Kralik, P.M. and McIsaac, W.M. *J. Pharm. Sci.* 1970, 59, 1445.
21. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions.* Wiley, New York, 1976.
22. Gómez-Jeria, J.S. and Ojeda-Vergara, M. *Int. J. Quant. Chem.* 1997, 61, 997.
23. Gómez-Jeria, J.S. and Lagos-Arancibia, L. *Int. J. Quant. Chem.* 1999, 71, 505.