Modeling the Drug-Receptor Interaction in Quantum Pharmacology

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1. Introduction

Quantum pharmacology (QP) is now a well-established branch of quantum chemistry. Its scope can be characterized by saying that QP studies the electronic and conformational properties of molecules possessing pharmacological activity, and seeks relationships between these properties and the drug's action mechanisms.

To study the electronic distribution and the spatial arrangement of nuclei, quantum pharmacology normally employs the now common methods of quantum chemistry used to obtain the wave function and the total energy of molecules: semiempirical [1—3] and *ab initio* [4—6] quantum-chemical methods.

Theoretical conformational studies can be of great help to the medicinal chemist due to the fact that they describe the whole conformational surface contrary to, for example, the NMR or the crystallographic studies that can reveal, respectively, only a section or one or several points of the surface.

It is also important to consider that a given molecule, in its crystalline form, may be in one or more conformations. The Quantum Pharmacologist can start from these conformations and explore only the surface available up to 7 Kcal mole^{-1}, without needing to analyze all the conformational space. In a family of molecules, it is therefore possible to create a conformational map of the common areas to select the most probable conformation(s) at the receptor level. This map can be improved by the inclusion of molecules with one or several degrees of restricted conformational freedom as shown in Figure 1 [7, 8].

From the electronic wave function, it is possible to calculate those electronic properties which depend on the electronic structure: atomic net charges, electronic densities at particular locations, electrophilic and nucleophilic superdelocalizabilities, dipole moments, etc. [9]. In the case of the total charge density, molecular orbital electronic density and molecular electrostatic potential, a visual picture is possible, permitting a fast analysis and comparison of the information presented [10—12]. In Figures 2 and 3 we present some of such examples.

Quantum pharmacology, through quantitative structure-activity relationships (QSAR), can provide a physical insight of the sequence of processes which form the basis of drug action: the pharmaceutical, pharmacokinetic and pharmacodynamic phases [13]. If we can establish a QSAR for a given family of molecules

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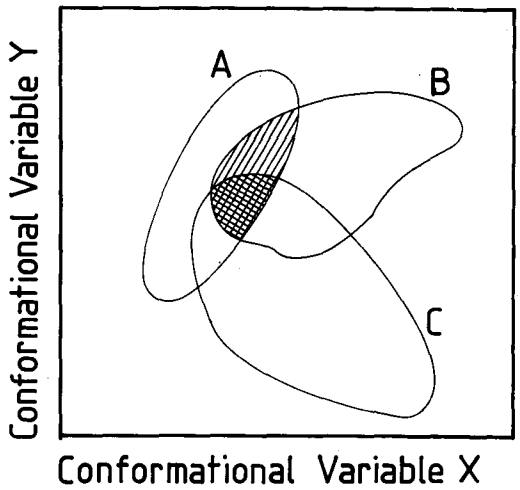

Fig. 1. Conformational map for molecules A, B, and C. The shaded areas show common conformational possibilities.

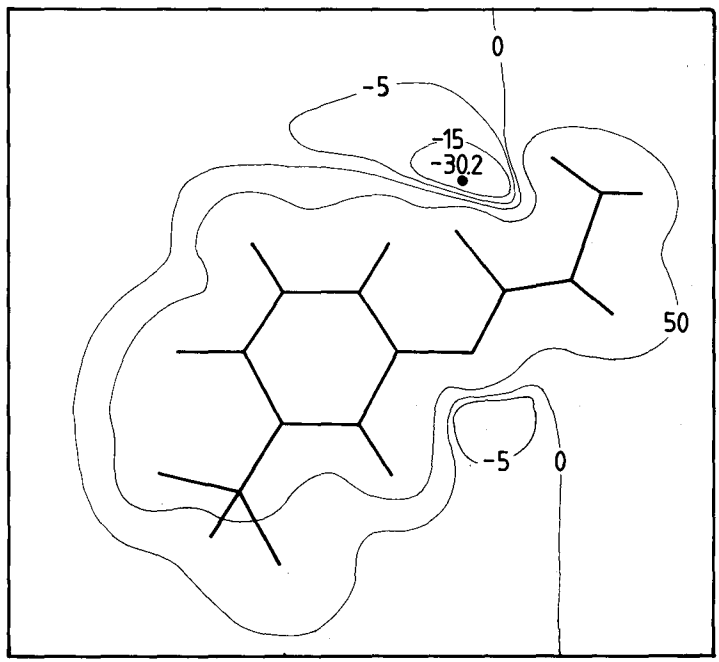

Fig. 2. Molecular electrostatic potential map for *m-t*-butyl-*N*-methylcarbamate. Values in kcal mol^{-1}.

possessing a similar effect, it is possible therefore to suggest new molecular structures with enhanced or diminished pharmacological activity. If we consider that, in general, it is necessary to synthetize, purify and test in animals and humans

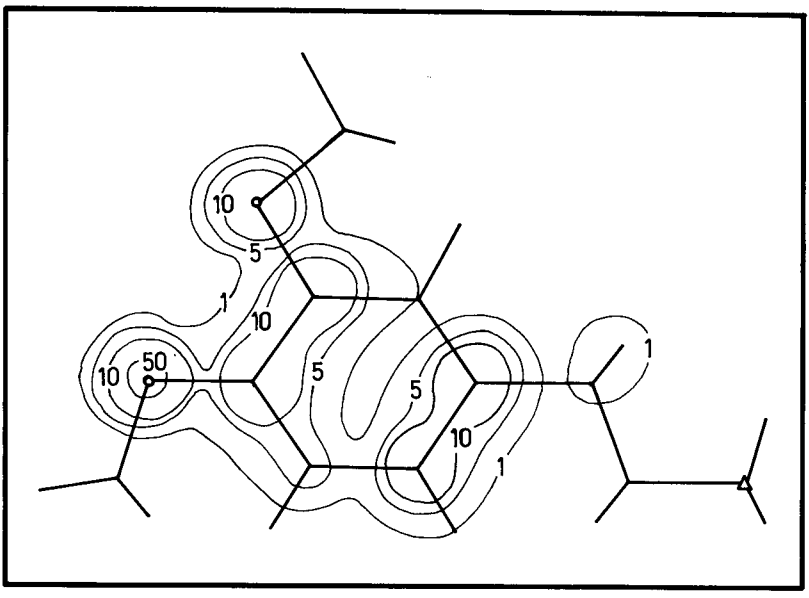

Fig. 3. Electronic density distribution map for the Highest Occupied Molecular Orbital of 3,4-dimethoxyphenylethylamine in the plane $z = 0.5$ Å. Values in 10^3 e.

several thousand molecules to get one useful for the market, we do not need to insist on the advantages (economical and time-saving) in using QP.

The usual way employed in QP to carry out a QSAR study is to use one of the two following approaches [14].

1. *Empirical methods*: they fit the experimental data and their main disadvantage is that they cannot provide a sure basis for a total theoretical understanding of the problem under study. The best examples of these methods are the Free-Wilson and the Hansch approaches [15—17].
2. *Model-based methods*: they start from a hypothesis of action and take into account the characteristics of the biological system. As the QSAR obtained were formally derived, it is expected that they will give a deep and physically correct insight of the underlying physics, and that they will be useful in predicting new active molecules.

With regard to the kind of parameters employed, the empirical methods may be divided into two groups.

1. Methods employing quantum-chemical reactivity indices (i.e., net charges, superdelocalizabilities, etc.).
2. Methods employing a mixture of quantum-chemical and classical (i.e., Hansch parameters, etc.) reactivity indices.

Hereafter, we shall center our attention on the model-based methods applied to

the drug-receptor interaction step of the pharmacodynamic phase of drug action. This is for at least two reasons.

1. The drug-receptor interaction is well characterized by the equilibrium constant. This quantity has been measured in vitro with different methods [18, 19] for a very large quantity of molecules interacting with a variety of receptors: opiates [20], serotonergic [21], GABAergic [22], dopaminergic [23], etc.
2. The advantages of the model, mentioned above.

To carry out our purpose, we shall present an analysis of the drug-receptor interaction and present a model-based expression for the equilibrium constant. Then we shall give a brief sketch of the decomposition of the intermolecular interaction energy through perturbation theory and present two approaches to deal with the fact that we do not know the electronic-conformational structure of one of the partners. Finally, we present an example showing the clear advantages of formal Quantum Pharmacology over other approaches.

2. The Drug-Receptor Interaction

2.1. THE DRUG-RECEPTOR INTERACTION CAUSES

The drug-receptor interaction is caused by intermolecular forces. Table I shows their classification according to the distance between partners.

TABLE I. Classification of intermolecular forces according to the distance between partners.

Small distances (Zone A of Figure 4)	Intermediate distances (Zone B of Figure 4)	Large distances (Zone C of Figure 4)
QUASIMOLECULE (Exchange and Coulomb integrals)	1. Electrostatic 2. Exchange-polarization 3. Exchange-repulsion 4. Polarization 5. Exchange-dispersion 6. Dispersion	1. Electrostatic 2. Polarization 3. Dispersion

The receptor may be defined as a pattern A of forces of different origin, forming part of a biological system and having approximately the same structure as a certain pattern B of forces exhibited by the drug, in such a way that among the patterns A and B there is a complementary relationship [24].

Ariens [25] has proposed dividing the space around the receptor in the following three zones.

Zone I: in this space, the drug-receptor interaction occurs through intermolecular forces.

Zone II: this covers the first zone, 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 through long-range interactions occurs [25]. The recognition process can be associated with the matching of the molecular electrostatic potentials of the drug and the receptor (for examples, see Refs. 26 and 27), to produce a correct geometrical alignment.

Zone III: it consists of the remainder of the biophase in which there is not an influence of the receptor. Here thermal agitation will cause the passing of drug molecules from this Zone to Zone II. We shall center our attention on Zone I.

The magnitude characterizing the drug-receptor interaction is the equilibrium constant, that is normally measured in vitro. In this preparation, we can assume that the influence of both the pharmaceutical and pharmacokinetic processes is reduced to a minimum, so that the concentration of the drug in the biophase is equal or proportional to the one in the vicinity of the receptor [25]. Also, as the number of drug molecules in the bath is greater than the ones reaching the receptor, it is possible to use the concentration of drug as the dose added.

If we consider a state of thermodynamic equilibrium and a 1 : 1 stoichiometry in the formation of the drug-receptor complex:

$$D + R \rightleftharpoons DR$$

where D is the drug molecule, R the receptor and DR is the drug-receptor complex (DR complex hereafter), the equilibrium constant is [28]:

$$K = (Q_{DR}/Q_D Q_R) \exp(-\Delta E/kT) \tag{1}$$

where ΔE is the difference between the ground-state energy of DR and the energies of the ground states of D and R: $\Delta E = E_{DR} - (E_D + E_R)$ and the Q's are the total partition functions measured from the ground state in solution [28].

We have shown that for the case where: (a) the receptor's mass is very much larger than the mass of the drug molecule, (b) the Boltzmann factors of the excited electronic states are negligible compared to those of the ground state, (c) the rotational and vibrational motions can be treated as independent and uncoupled, and (d) the temperature is 37 °C, we can approximate Eq. (1) as [28]:

$$\log(K) = a + b \log M_D + c \log(\sigma_D/(I_1 I_2 I_3) + d\Delta E \tag{2}$$

where a, b, c and d are constants, σ_D is the drug molecule's symmetry number and $I_1 I_2 I_3$ is the product of its three moments of inertia about the three principal axes of rotation [28]. To determine the constants, we carry out a linear multiple regression analysis for a given family of drugs whose equilibrium constant has been measured in the same experimental conditions. The resulting equation will indicate which are the relevant structural indices accounting for the variation of $\log(K)$ in the family.

The interaction energy, ΔE, cannot be determined directly, either due to the

size of the receptor or to the lack of knowledge of its molecular structure. Nevertheless, when we consider a drug-receptor interaction in which no covalent bonds are formed (i.e., a weak interaction), we can employ Perturbation Theory (PT) to evaluate ΔE.

Therefore, as a necessary step, we must model the interaction energy, maintaining the underlying physics in the interaction.

In the following, we shall give a brief sketch of the problems appearing in the application of Perturbation Theory to calculate ΔE.

2.2. THE INTERMOLECULAR INTERACTION ENERGY

Let us consider the interaction of a drug molecule D (with n_D electrons), with a receptor R (with n_R electrons). Our problem consists in solving the Schrödinger equation for the DR complex, for different intermolecular distances and relative orientations (r), remembering that our interest is mainly focused on the distances at which the DR complex is formed (Zone B of Figure 4).

At very large separations (Zone C in Figure 4), where the overlap of the charge distributions of the interacting molecules can be neglected, the straightforward application of the 'usual' Rayleigh-Schrödinger Perturbation Theory (RSPT) is valid. By 'usual' we mean that the unperturbed Hamiltonian, $\hat{H}^0$, is written as $\hat{H}^0 = \hat{H}^0_D + \hat{H}^0_R$, where $\hat{H}^0_D$ and $\hat{H}^0_R$ are, respectively, the Hamiltonian operators

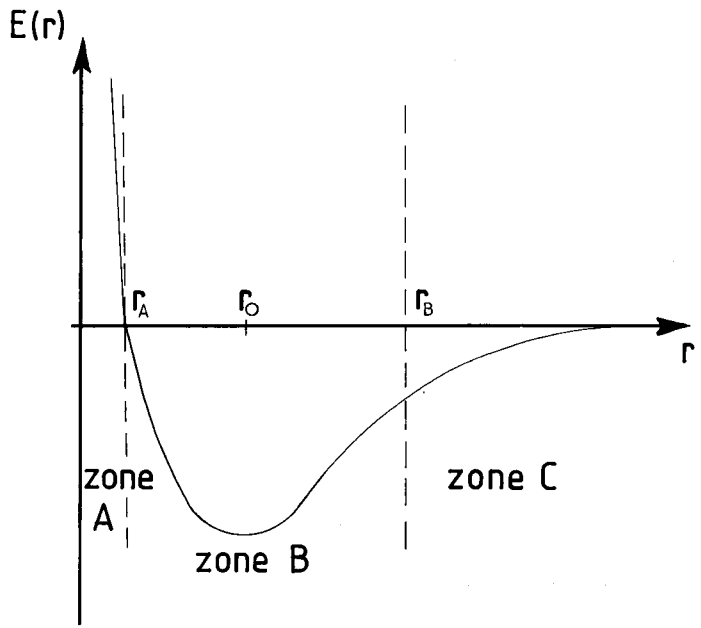

Fig. 4. Intermolecular potential. Zone A: small distances, Zone B: intermediate distances, Zone C: large distances.

of the drug and the receptor. This procedure, also called the 'polarization approximation', allots definite electrons to each partner. Up to second order, RSPT gives three contributions: the electrostatic (E(el)), polarization (E(pol)) and dispersion (E(disp)) energies (see Table II, first row). At large intermolecular separations we can employ the multipole expansion to express the electrostatic energy in terms of charge-charge, charge-dipole, dipole-dipole, . . . components [31].

TABLE II. Contributions to the intermolecular interaction energy for different wave functions.

Wave function	Perturbation contributions	
	First Order	Second Order
$\Psi_D\Psi_R + \cdots$	Electrostatic	Polarization, Dispersion
$A\Psi_D\Psi_R + \cdots$	Electrostatic Exchange-repulsion	Polarization, Dispersion, Exchange-dispersion, Exchange-polarization
$A\Psi_D\Psi_R + [A\Psi_D^+\Psi_R^- + A\Psi_D^-\Psi_R^+]^{(a)} + \cdots$	Electrostatic Exchange-repulsion	Polarization, Dispersion, Exchange-dispersion, Exchange-polarization, Charge transfer

Note: A is the antisymmetrizing operator.
[a] included to compensate for the incompleteness of the bases used for the separated molecules.

RSPT cannot be applied in its usual form to systems interacting very closely (Zone B of Figure 4). The reason can be briefly summarized as follows [32]. In the usual RSPT, $\hat{H}^0$ commutes with a group $G^0 = N \times S(n_D) \times S(n_R)$, where G^0 is the direct product of the symmetry group N of the nuclear configuration and of the groups $S(n_D)$ and $S(n_R)$ of permutations of the n_D and n_R electrons of the separate partners respectively.

On the other hand, the total spin-independent n-electron ($n = n_D + n_R$) Hamiltonian operator, $\hat{H}$, commutes with a group G, which is the direct product of the symmetry group N and of the group $S(n)$ of permutations of all n electrons of the DR complex. In other words, $\hat{H}^0$ has a lower symmetry than the perturbed Hamiltonian.

This fact has provided arguments against the direct use of RSPT for short intermolecular distances. Among these, the very clear analysis of Claverie is the most important contribution and it can be summarized by saying that RSPT would give, instead of the physical interaction energy corresponding to the physical ground state of the DR complex, some 'mathematical' interaction energy corresponding to some 'mathematical' ground state [33, 34]. It is necessary to add that in the region of weakly interacting systems (r = 7—8 Å or more, Zone C of Figure 4), the physical curve is not different from the mathematical one. The advantages of such a procedure is that the interaction energy can be calculated directly as the

sum of the first, second and higher order perturbation energies. This procedure can be applied to the study of the long-range interaction energy and of the best orientation (or recognition) of the drug by a receptor model.

At intermediate to small intermolecular distances, it becomes necessary to develop a perturbation formalism for the description at low orders of the effects of electron exchange between partners. A large number of exchange Perturbation Theories (or symmetry-adapted PT), have been suggested to treat this problem: the Murrel-Shaw-Musher-Amos [35, 36], the Eisenschitz-London-Hirschfelder-van der Avoid [37—39], the Hirschfelder-Silbey [40], etc., perturbation schemes.

This variety is due to the fact that there is a great deal of freedom available in the definition of the non-symmetric primitive function on which symmetry projection operators are applied to obtain one or more eigenvalues of $\hat{H}$ [41—43].

The second row of Table II shows, up to second-order, the different contributions to the interaction energy provided by symmetry-adapted PT. We avoided giving formulas, because of the diversity of exchange-perturbational schemes, but we can say that in order to model the short-range repulsive contributions it is necessary to introduce a proper term.

Therefore, we can conclude from this section that a correct modeling of the intermolecular interaction energy at short distances must take into account at least the electrostatic, polarization, dispersion and short-range repulsion (E(sr)) energies.

2.3. THE CLAVERIE *ET AL.* (CLETAL) APPROACH

In a series of papers, Claverie *et al.* [44—53] have developed formulas to evaluate the interaction energy as the sum of long-range contributions (electrostatic, polarization and dispersion), and a short-range repulsive contribution. Later, a charge-transfer contribution was added [49]. In their simplest form, these formulas can be summarized as follows:

1. *Electrostatic Energy* [45—47]

The simplest way to account for the electrostatic energy is to represent it as:

$$E(\text{el}) = \sum_i \sum_j Q_i Q_j / R_{ij} \tag{3}$$

where Q_i is the net charge of atom i, R_{ij} is the distance between atoms i and j, and the summation is over all the atoms of the partners. Now, considering that we are interested not in the values of the net charges per se, but in the charges whose variation can explain the variation of the equilibrium constant for a family of molecules interacting with the same receptor, E(el) may be represented by:

$$E(\text{el}) = \sum_i h_i Q_i \tag{4}$$

where h_i is a constant and the summation is now only over the atoms of the drug (hereafter represented by i).

A more refined way to compute $E(\text{el})$ is to employ the multipole expansion up to the quadrupoles of the electron distribution if necessary [31, 48]. The same above scheme can be applied, i.e., to consider the receptor terms as constants in order to get formulas involving only the drug's multipole terms.

2. *Polarization Energy* [47]

The polarization energy is calculated as a sum of atom polarization contributions:

$$E(\text{pol}) = -(1/2) \sum_i \alpha_i (\varepsilon_i)^2 \tag{5}$$

where ε_i is the electric field created at atom i of the drug molecule by the receptor, and α_i is the mean polarizability of atom i. With the same criteria employed for $E(\text{el})$, we get:

$$E(\text{pol}) = -(1/2) \sum_i t_i \alpha_i \tag{6}$$

with t_i constant.

3. *Dispersion and Short-Range Repulsion Energies* [47]

These contributions can be evaluated by using the semiempirical Kitaigorodsky formula which involves atom-atom terms [54—56]:

$$E(\text{disp}) + E(\text{sr}) = E(\text{KIT}) = \sum_i \sum_j E(i, j) \tag{7}$$

where $E(i, j)$ represents each atom-atom contribution and is the sum of a dispersion and a repulsion term:

$$E(i, j) = k_i k_j [-(A/z) + (1 - Q_i/N_i^{\text{val}})(1 - Q_j/N_j^{\text{val}}) C \exp(-\alpha z)] \tag{8}$$

where $z = R_{ij}/R_{ij}^0$ with $R_{ij}^0 = [(2R_i^\omega)(2R_j^\omega)]^{1/2}$, R_i^ω being the van der Waals radius of atom i. The parameters α, A and C are kept independent of the atomic species. The values used are, for example, $A = 0.214$ kcal mol^{-1}, $C = 47.10^3$ kcal mol^{-1}, and $\alpha = 12.35$. For the van der Waals radii, we can use the values reported in [57] or others. The factors $(1 - Q_i/N_i^{\text{val}})$ represent the influence of the electronic populations on the repulsion, N_i^{val} being the number of valence electrons of atom i. k_i and k_j are factors allowing the variation of the minimum of $E(i, j)$ accordingly to the kind of interacting atoms ($k_H = k_C = 1$, $k_N = 1.18$, $k_0 = 1.36$) [45].

This formula is reduced in our case to:

$$E(\text{KIT}) = \sum_i \{-p_i k_i (R_i^\omega)^{1/2} + s_i k_i (1 - Q_i/N_i^{\text{val}}) \exp[-q_i (R_i^\omega)^{-1/2}]\} \tag{9}$$

where p_i, s_i and t_i are constants.

There are other ways to compute these terms, and most of them can be similarly adapted.

The adaptation of the CLETAL approach to our purposes shows that it is not difficult to calculate the terms involved in Eqs. 4, 6 and 9. Within this approach, the drug-receptor interaction energy is represented by:

$$\Delta E = \sum_i \{h_i Q_i + t_i \alpha_i - p_i k_i (R_i^{\omega})^{1/2} + \\ + s_i k_i (1 - Q_i / N_i^{\text{val}}) \exp[-q_i (R_i^{\omega})^{-1/2}]\} \tag{10}$$

2.4. THE KLOPMAN-PERADEJORDI-GOMEZ (KPG) APPROACH

Klopman [58—61] has described a treatment, based on Perturbation Theory, in which allowance is made for ionic interactions. According to this method, the electronic energy change associated with the interaction of atoms i and j is:

$$\Delta E = \sum_p \left[Q_i Q_j / R_{ij} + (1/2)(\beta_{ij}^2) \sum_m \sum_{n'} D_{mi} D_{n'j} / (E_m - E_{n'}) - \right. \\ \left. - (1/2)(\beta_{ij}^2) \sum_{m'} \sum_n D_{m'i} D_{nj} / (E_{m'} - E_n) \right] \tag{11}$$

where Q_i is the net charge of atom i, $D_{mi} = \Sigma_\ell 2C_{j\ell}^2$ is the orbital charge of atom i in the Molecular Orbital (MO) m, $C_{i\ell}$ being the coefficients of the atomic orbitals (AO) of i, β_{ij} is the resonance integral; and E_m ($E_{m'}$) is the energy of the mth (m'th) occupied (virtual) MO of the drug, n and n' standing for the receptor. The value of β_{ij} is kept independent of the kind of AO because the drug-receptor complex does not involve covalent bonds. The summation on p is over all pairs of interacting atoms.

The first term of the right side of Eq. (11) represents the electrostatic interaction between two atoms having net charges Q_i and Q_j and is identical to the expression for the electrostatic energy in the CLETAL approach. The second and third terms introduce a partial electron transfer from MO m to MO n' and from MO n to MO m', respectively. It is clear that, for the last terms to be significant, a channel must be provided for the partial electron transfer. These terms do not appear in the CLETAL version above presented.

As we said before, the electronic-geometric structure of the receptor is not known in the great majority of cases, therefore we cannot directly evlauate Eq. (11).

Peradejordi *et al.* overcame this problem by replacing the MO energies of the

receptor by constant values [62]. This permits transformation of Eq. (11) into the following:

$$\Delta E = \sum_i [f_i Q_i + g_i S_i^E + h_i S_i^N] \tag{12}$$

where f_i, g_i and h_i are constants, S_i^E and S_i^N are, respectively, the total atomic electrophilic and nucleophilic superdelocalizabilities of atom i [63, 64], defined as:

$$S_i^E = 2 \sum_m \sum_r C_{mr}^2 / E_m \tag{13}$$

where the summation on m is over the occupied MO's and the one on r is over the AO's coefficients of atom i contributing to one MO, and:

$$S_i^N = 2 \sum_{m'} \sum_r C_{m'r}^2 E_{m'} \tag{14}$$

where the summation on m' is now over the virtual MO's.

These reactivity indices can be directly interpreted. Within a given molecule, S_i^E represents the relative capacity to transfer electrons to an electron-deficient center and S_i^N represents the relative capacity to accept electrons. When we are comparing a family of drugs sharing a common skeleton, these indices can be compared for similar atoms within the family.

The Peradejordi *et al.* approximation can be justified by assuming that the drug-receptor interaction is charge controlled [59, 62], but if the processus is not, the problem of the evaluation of the orbital energies of the receptor remains.

The last approximation can be improved by considering two facts.

1. The receptor is, in general, a macromolecule composed by thousands of atoms and the Molecular Orbitals can be considered as forming part of bands. In this case we can replace the set of the receptor's MO energies by another set composed by average values corresponding to the arithmetic media of the band energy.
2. The Frontier Molecular Orbitals are probably the ones involved in weak interactions.

These considerations, coupled to the fact that we can employ a series expansion of the energy denominators, permit to arrive to the following expression for E [11]:

$$\Delta E = a + \sum_i [e_i Q_i + f_i S_i^E + s_i S_i^N] + \sum_i \sum_m [h_i(m) D_i(m) + j_i(m) S_i^E(m)] +$$

$$+ \sum_i \sum_{m'} [r_i(m') D_i(m') + t_i(m') S_i^N(m')] \tag{15}$$

where a, e, f, g, h, j, r and t are constants, $S_i^E(m)$, $S_i^N(m')$ and $D_i(m)$ are, respectively, the orbital electrophilic superdelocalizability of MO m at atom i, the orbital nucleophilic superdelocalizability of MO m' and the orbital electron density of MO m at the same atom. The summation on m includes a group of MOs close to the Highest Occupied Molecular Orbital (HOMO), and the HOMO itself. The summation on m' includes the Lowest Empty Molecular Orbital (LEMO) and a group of low-lying virtual MOs. The other terms are the same as those appearing in Eq. (12).

Up to now, there are no comparative studies of the CLETAL and KPG approaches. The CLETAL modeling has shown that it works very well for crystals and nucleotides [44—53], but no applications to Quantum Pharmacology are known. In the next section, we shall present a summary of the KPG approach applied to a pharmacological problem.

3. A Practical Example: the Serotonin Receptor Binding Affinity

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter involved in a variety of actions: neuronal inhibition, smooth muscle contraction (rat stomach fundus) and relaxation (guinea pig ileum), tachycardia, hypotension, oedema, depolarization, etc. These actions are mediated through more than one 5-HT receptor [65].

The affinity for the 5-HT serotonin receptors of the rat stomach fundus has been measured by Glennon *et al.* for a very large quantity of indolealkylamines (Figure 5) and phenylalkylamines (Figure 6) ([66—74] and references therein). This system is of interest because there is experimental evidence showing that there is a linear correlation between the potencies of some indolealkylamines on the rat fundus and their capacity to inhibit Lysergic Acid Diethylamide (LSD) binding to brain membranes [75—76]. Therefore, the conclusions reached in the fundus preparation might also hold for one of the brain receptors.

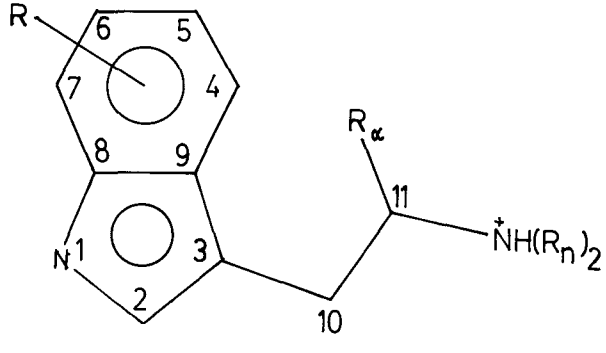

Fig. 5. General formula for indolealkylamines.

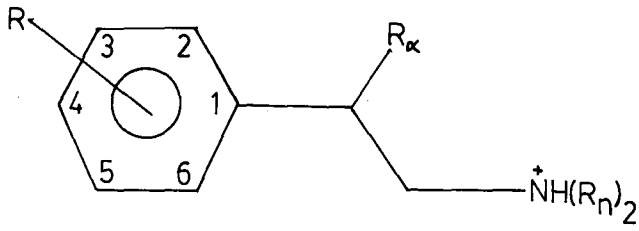

Fig. 6. General formula for phenylalkylamines.

QSAR studies on these molecules have been reviewed by Gupta *et al.* [77]. They concluded that none of the equations obtained were highly significant either because a small number of data points were employed, or because the data had been obtained using methods involving too many approximations [77]. To their criticism, we may add that the previous studies have normally examined a few individual parameters through the use of totally empirical methods.

Our first QSAR study with the KPG approach relating indolealkylamine serotonin receptor binding affinity (pA_2) to electronic structure indices obtained one equation explaining the variation of the pA_2 for 24 molecules, an equation that was the best one to that date [78]. Nevertheless, our study considered an excessive diversity in the structures of the molecules. For this reason, we carried out two more studies, one for 5-substituted tryptamines [79] and the other for 7-substituted tryptamines [80]. The results are presented in Tables III and IV

TABLE III. Experimental and calculated pA_2 for 5-substituted tryptamines.

Molecule	R_5	R_N	Experimental pA_2[a]	Calculated pA_2[b]	
1	Me	H	6.86	6.56	6.70
2	OH	Me	7.41	7.39	7.33
3	OMe	Me	7.08	7.40	7.35
4	Me	Me	6.52	6.29	6.29
5	OCOMe	Me	7.71	7.40	7.38
6	COMe	Me	5.86	6.01	5.98
7	OCOEt	Me	7.27	7.40	7.38
8	OCO-N-prop	Me	7.32	7.40	7.39
9	SMe	Me	6.84	6.65	6.59
10	OMe	Me, Et	6.85	6.91	7.03
11	OMe	Et	6.94	6.91	6.91
12	NH_2	Me	7.08	7.21	7.19
13	NH_2	H	7.53	7.38	7.53
14	OCO-*t*-but	Me	7.42	7.40	7.39
15	$OCOCH(Me)_2$	Me	7.40	7.40	7.39
16	H	H	6.27	6.24	6.38
17	H	Me	6.00	6.18	6.11
18	H	H, Me	5.97	6.16	6.11
19	H	Et	5.79	5.76	5.74

a. Refs. [66—75]; b. Ref. [79].

TABLE IV. Experimental and calculated pA_2 for 7-substituted tryptamines.

Molecule	R_7	R_α	R_N	Experimental pA_2[a]	Calculated pA_2[b]	
1	H	H	H	6.27	5.91	6.22
2	H	H	Me	6.00	6.14	6.14
3	Me	H	Me	6.29	6.05	6.19
4	OMe	H	Me	5.33	5.36	5.20
5	OH	H	Me	4.88	5.02	5.12
6[c]	H	H	Me	6.04	6.22	5.83
7[d]	H	H	Me	6.02	6.19	6.31
8[e]	H	H	Me	6.03	5.93	5.88
9	H	H	H, Me	5.97	6.02	6.01
10	Br	H	Me	6.51	6.49	6.37
11[f]	H	H	Me	5.68	5.55	5.64
12[g]	H	Me	H	5.49	5.49	5.49
13[h]	H	Me	H	6.46	6.44	6.55
14	H	H	Et	5.79	5.88	5.84
15	Et	H	Me	6.31	6.33	6.24

a. Refs. [66—75]; b. Ref. [80]; c. With a Me group at pos. 2; d. With a Me group on the indole N; e. With a S atom instead of the indole NH; f. With a CH_2 group instead of the indole NH; g. (*S*) (+) isomer; h. (*R*) (−) isomer.

respectively. Their inspection reveals that the predicted pA_2's are in excellent agreement with the experimental ones.

The results for the 7-substituted tryptamines were very striking because they suggested that the 7-substituent influenced the pA_2 through its steric effect (related to its size or to its influence in rising or diminishing the molecule's probability to reach the correct geometrical alignment permitting the DR interaction), and its effect on the total atomic electrophilic superdelocalizability of atom 7 ([80] see also Figure 5). Older theories suggested that it was the hydrophobicity of the 7-substituent the magnitude influencing the pA_2 [81].

On the other hand, a QSAR study employing the KPG model for the case of indolealkylamines [11] showed that the equations were very similar to the ones for indolealkylamines.

If indolealkylamines and phenylalkylamines interact with the rat stomach fundus serotonergic receptor by analogous mechanisms, our studies suggest that a phenylalkylamine carrying a small hydrophylic group at position 4 (see Figure 6), must have a high pA_2 value if its electrophilic superdelocalizability at C-4 is high enough. Moreover, if this compound is able to pass the blood-brain barrier it must be hallucinogenic at low doses. This is the case of the 1-(2,5-dimethoxy-4-nitrophenyl)-2-aminopropane (DON), having a pA_2 of 7.07 for the racemic mixture [82]. Our preliminary pharmacological studies showed that DON is a very potent hallucinogen [83].

This last result, obtained from a model-based study of the experimental

evidence, clearly indicates that these methods are much better than the empirical ones.

I would like to conclude this section by saying that with the computing facilities available now, the employ of the CLETAL KPG or any other model-based approach to design new drugs or to study the physics of the DR interaction must replace the older methods. Naturally, there are other problems that are still not modeled in a formal way (the pharmaceutical and pharmacokinetic steps of drug action), but we have the tools to do it.

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