Research Journal of Pharmaceutical, Biological and Chemical Sciences

Some Remarks on The Interpretation of The Local Atomic Reactivity Indices Within the Klopman-Peradejordi-Gómez (KPG) Method. I. Theoretical Analysis.

Juan S Gómez-Jeria[1]*, and Gaston A Kpotin[2].

[1]Quantum Pharmacology Unit, Department of Chemistry, Faculty of Sciences, University of Chile. Las Palmeras 3425, Santiago 7800003, Chile.
[2]Laboratory of Theoretical Chemistry and Molecular Spectroscopy, Faculty of Sciences and Technique, University of Abomey-Calavi, 03 BP 3409 Cotonou-Benin.

ABSTRACT

The Klopman-Peradejordi-Gómez method relates the variation of a biological activity, measured in vivo or in vitro, with the variation of the numerical values of a set of local atomic reactivity indices (LARIs). The introduction of local atomic reactivity indices within the Hartree-Fock scheme plus the orientational parameter of the substituents has produced excellent relationships between the electronic structure and the biological activity for many different molecules and biological measurements. Here we present a detailed analysis of how to modify the numerical values of the LARIs in order to increase the biological activity. The concept of local molecular orbital is central to this analysis.

Keywords: Klopman-Peradejordi-Gómez method, QSAR, local atomic reactivity indices, net charge, superdelocalizability, hardness, softness, charge capacity, electrophilicity, chemical reactivity.

*Corresponding author

INTRODUCTION

The Klopman-Peradejordi-Gómez method (KPG hereafter) seems to be the only member of the class of model-based methods[1-7]. As a paper presenting its scientific and philosophical foundations was recently published, here we shall present only a general description[8]. The method is employed to findsignificant relationships between the biological activity in a group of molecules and the values of a set of local atomic reactivity indices (LARIs) belonging to a partial molecular structure common to all of them (the common skeleton)[5, 6]. When needed, this set is complemented with the values of the Orientational Parameter (OP) of the substituents[4, 9,10].If we consider that an atom is described by about a dozen local atomic reactivity indices and that the smallest common skeleton we have employed has about ten atoms, in this simplest case approximately 121 constants must be found for each linear equation.As no paper publishes the experimental data for such a large number of molecules, we need another approach to solve this problem.The traditional technique employed is Linear Multiple Regression Analysis (LMRA).

The results appear in the form of a linear equation satisfying all necessary statistical tests. This equation shows a relationship between the variation of the value of a biological activity and the variation of the numerical values of a set of local atomic reactivity indices (plus one or more OPs if they appear). This implies that theequation does not contain those LARIs having a constant value in the set of molecules. Neither does the equation contain those LARIs the variation of whose numerical values is not statistically significant. Therefore, this equation showsthe importance of some atoms and some substituents.

The equation contains on its left side the logarithm of the biological activity considered (in vitro or in vivo data). A higher or lower value of this scalar is associated with a change in the biological activity.Onthe right side, we find a set of LARIs (plus one or more OPs) multiplied by a positive or negative scalar, plus a constant.The usual method for the study of the resulting equation is called the variable-by-variable (VbV) analysis: only the variation of the numerical value of one LARI is analyzed while the values of the remaining LARIs are kept frozen. This is a minor shortcoming of the method.

Until now no paper presenting a detailed way of analyzing each LARI has been published. After an analysis of the published papers employing the KPG method we feel that such a method issorelyneeded[11-32]. Therefore, in this paper we list all reactivity indices with their meaning and present a full analysis of the different situations in which they can appear and the way in which the results should be analyzed and presented.

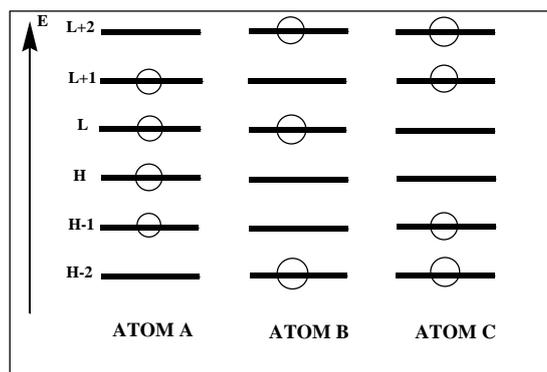**Local Molecular Orbitals (LMO).**

As we have said in several publications, the LARIs are intimately associated with the concept of local molecular orbital. Let us consider a series of molecules with several aromatic regions A, B, C and D separated by saturated chains (Fig. 1).
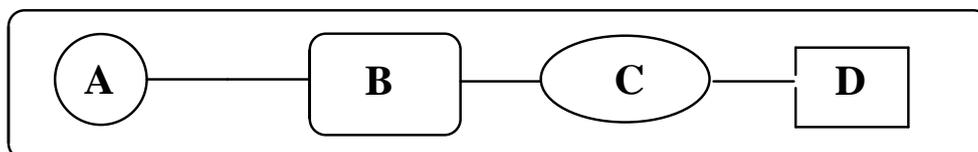
Figure 1: A molecular system with four aromatic regions A, B, C and D[8].

The analysis of the correspondingwave functions of the series shows that on different occasions theHOMO is localized on different regions: sometimes on A, sometimes on D, etc. What does that a given MO is localized on one specific atom mean? We have usually considered the results of a population analysis. Without entering into an endless discussion about the partition of the electron density or about what is the best (the concept of 'best' is not unanimous) population analysis we have simply stated that if a MO has a population of 0.01 electron or greater on a given atom, we consider it as being localized on that atom (see [6]). In this way we are able to find the local HOMO of atom i (i.e., the highest occupied MO having an electron population of 0.01 electron or greater on atom i) and the local LUMO (denoted usually by $HOMO_i^*$ and $LUMO_i^*$ respectively). It is clear that a different choice of electron population will lead to different local

MOs.Figure 2 shows three atoms A, B and C. Black lines denote the molecular orbitals of the molecule. The circles designate those MOs having a non-zero electron population on atoms A, B and C.

Figure 2: Examples of local molecular orbitals ('H' stands for HOMO, 'H-1' for the second highest occupied MO, 'H-2' for the third highest occupied MO, 'L' for LUMO, 'L+1' for the second lowest empty MO and 'L+2'for the third lowest empty MO).

Atatom A the local HOMO* and LUMO* correspond, respectively, to the molecule's HOMO and LUMO. Atatom B, the local HOMO* corresponds to the molecule's third highest occupied MO while the LUMO* isthe molecule's LUMO. Atatom C, the local HOMO* corresponds to the molecule's second highest occupied MO and the LUMO* to the molecule's second lowest empty MO. Figure 2 clearly shows that the inner MOs may play a substantial role in regulating biological activity and molecule-site interactions.Within this scheme, we may define several local atomic indices. It is very important to stress that the table of local molecular orbitals must be built for all atoms appearing in the resulting equation, even if the reactivity indices are independent of the MO structure (total atomic superdelocalizabilities and local atomic hardness for example)[5, 6].The role of the inner occupied MOs in chemical reactivity has been stressed many times. In the KPG method their participation in biological processes arises in a natural way through the concept of local MO.

The Local Atomic Reactivity Indices (LARIs).

In previous publications we have presented the definitions for the LARIs (aside fromthe net atomic charge)[6].The atomic net charge depends only on the LCAO/MO electronic structure. Net charges are associated with molecule-site electrostatic interactions. In the case of the electron population, the nature of the MOs (π, σ or lone pair) will determine the possible interactions in which they may participate.

The local orbital electrophilic superdelocalizability of the p-thoccupied localMO* localized on atom i, $S_i^{E*}(MO)_p^*$, is defined as:

$$S_i^{E*}(MO)_p^* = \frac{F_i(MO)_p^*}{E(MO)_p^*} \quad (1)$$

where $F_i(MO)_p^*$ is the electron population (Fukui index hereafter) of atom i in the p-thlocal MO* and $E(MO)_p^*$ is the corresponding MO* energy.Allorbital electrophilic superdelocalizabilities are negative because the Fukui indices are always positive and the eigenvalues of the occupied MOs are always negative (at least innormal molecules endowed with biological activities). This reactivity index is related to the electron-donating properties of atom i: if we shift the value of the MO* energy upwards (i.e., the energy approaches zero onthe energy axis) the MO* becomes more reactive.

The total local atomic electrophilic superdelocalizability of atom i, S_i^{E*}, is defined as:

$$S_i^{E*} = \sum_{p=1}^{occ} \frac{F_i(MO)_p^*}{E(MO)_p^*} = \sum_{p=1}^{occ} S_i^{E*}(MO)_p^* \quad (2)$$

where the summation on i runs over all occupied MO*s. The form of Eq. 2 indicates that the contribution of the highest local occupied MO* is the most important contribution.

The local orbital nucleophilic superdelocalizability of the q-th empty local MO* localized on atom i, $S_i^N(MO)_q^*$, is defined as:

$$S_i^{N*}(MO)_q^* = \frac{F_i(MO)_q^*}{E(MO)_q^*} \quad (3)$$

where $F_i(MO)_q^*$ is the Fukui index of atom i in the q-th MO* and $E(MO)_q^*$ isthe energy of the corresponding MO*. This reactivity index is related to the electron-accepting properties of atom i: if we shift the value of the MO* energy downwards (i.e., the energy approaches zero onthe energy axis) the MO* becomes more reactive. Now, in the resulting calculations (HF and DFT), many empty MO*s appear with negative eigenvalues. Below we shall discuss what to do in these cases.

The total atomic nucleophilic superdelocalizability of atom i, S_i^{N*}, is defined as:

$$S_i^{N*} = \sum_{q=1}^{empty} \frac{F_i(MO)_q^*}{E(MO)_q^*} = \sum_{q=1}^{empty} S_i^{N*}(MO)_q^* \quad (4)$$

where the summation if now over all empty local MO*s. Within a model in which all empty MO*s have a positive energy, Eq. 4 shows that the main contributions come from the first empty MO*s (because of the low value of the MO* energy). Unhappily, as we said before, the molecular wave function often has several empty MOs with negative energy. This situationproduces algebraic zeros around the Fermi Leveland incorrect numerical results. Therefore, the scientist must carefully examine the results of the quantum-chemical calculations searching for the possibility of numeric anomalies. If this is the case, it is better to use the orbital nucleophilic superdelocalizabilities.These four reactivity indices depend on the Fukui indices and the MO* energies.

Now we shall consider those local reactivity indices that are defined only in terms of the local HOMO* and LUMO* energies. The local atomic electronic chemical potentialis defined as:

$$\mu_i^* = (E(HOMO)_i^* + E(LUMO)_i^*)/2 \quad (5)$$

and it is considered to be a measure of the tendency of a system to gain or lose electrons: a large negative value indicates a good electron acceptor while a small negative value implies a good electron donor (see below).Within this model, μ_i^* is the midpoint between the local HOMO* and local LUMO* energies. This local index may have a value of zero in the case of metals and in some atoms of semimetals.

The local atomic hardness is defined as:

$$\eta_i^* = (E(HOMO)_i^* - E(LUMO)_i^*) \quad (6)$$

Within this model, η_i^* is the HOMO*-LUMO* energy gap. This index is interpreted as the resistance of atom i to exchange electrons with a site.

The local atomic softness of atom iis defined as:

$$s_i^* = \kappa_i^* = \frac{1}{\eta_i^*} \qquad (7)$$

The local atomic electrophilicity of atom i is defined as:

$$\omega_i^* = \frac{(\mu_i^*)^2}{2\eta_i^*} \qquad (8)$$

The local atomic electrophilic index is associated with the electrophilic power and includes the tendency of the electrophile to receive extra electronic charge together with its resistance to exchange charge with the medium.

The maximal amount of charge atom i may receive is defined as:

$$Q_i^{*max} = -\frac{\mu_i^*}{\eta_i^*} \qquad (9)$$

This index is interpreted as the maximal amount of electronic charge that atom i may receive from a donor site.

We must remark that the indices defined in Eqs. 5-9 were obtained within the Hartree-Fock LCAO/MO scheme and not from Density Functional Theory.

A standard interpretation of the LARIs.

Analysis of the local atomic reactivity indices.

Atomic net charges.

Atomic net charges are associated with the electrostatic interactions of atoms with positively or negatively charged sites (atoms or residues). Usually, the analysis of a certain equation leads to the following possibilities. For a positively charged atom a higher activity could be associated with a higher positive net charge or with a less positive one. For a negatively charged atom a higher activity could be associated with a higher negative net charge or with a less negative one. These cases are directly associated with enhanced or diminished electrostatic interactions.

Orbital superdelocalizabilities.

The analysis of these indices is more complex because it is related to the nature and relative 'position' of the local molecular orbitals. By 'position' we refer, in the case of frontier local MOs, to the coincidence or not of these MOs with the molecule's MOs. Figure 3 shows some possible cases.

Figure 3: Molecular eigenvalue distribution and possible combinations of the (HOMO)* and (LUMO)* local MOs.

The first column of Fig. 3 (marked '1') shows part of the eigenvalue distribution of a molecular system. For the sake of clarity we placed the zero in the midpoint between the molecule's HOMO and LUMO energies. Columns marked '2', '3', '4' and '5' show the four possible combinations of local MOs. For example,in case '2' the local HOMO* and LUMO* coincide with the molecule's HOMO and LUMO. In case '3', the local LUMO* coincides with the molecule's LUMO, while the local HOMO* coincides with the molecule's third highest occupied MO, and so on.

Orbital electrophilic superdelocalizabilities (Eq. 1).

Orbital electrophilic superdelocalizabilities values are always negative.The analysis of a QSAR equation may lead only to two possibilities: a need of more negative or less negative values of this index. Based on the definition given in Equation 1, we have the following cases:

1.Formorenegative values of $S_i^{E^*}(HOMO)^*$ we may, for example, raise the value of the Fukui index (Eq. 1). Note that the values of the Fukui index lie in the interval [0.1, 2.0]. If the Fukui index has a value of 2.0, we are in the presenceof a MO localized only on this atom and we cannot make the numerical value of this index any higher. An additional possibility is by shifting the MO energy toward zero (Eq. 1). Figure 4 shows the case in which the HOMO* coincides with the molecular HOMO (marked '2') and the case in which the HOMO* coincides with an inner molecular MO ((HOMO-2) in this case, marked '3').
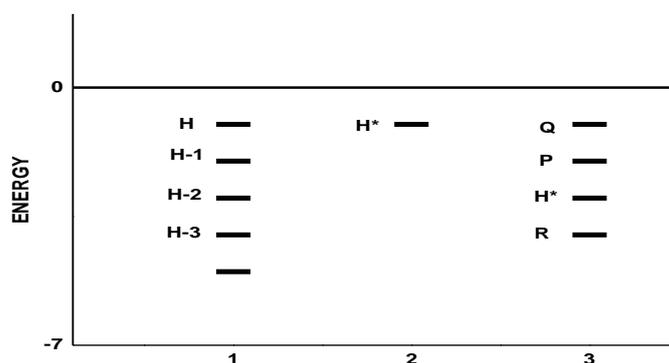
Figure 4:Two possible positions of the HOMO* in the energy axis.

In case '2' of Fig. 4, the HOMO* coincides with the molecule's HOMO. Therefore, it is not possible to find another local MO with less energy localized on atom i. To make this MO more reactive in this case, we may increase the value of the Fukui index up to 2.0 as said before, orwe may look for a substitution creating a degenerate or quasi degenerate HOMO* (by using substituents able to 'inject' π MOs such a NO_2 group for

example). In case '3' we may modify the localization of the molecule's (HOMO-1)* or HOMO* in such a way that now $HOMO_i^*$ coincides with P or Q (Fig. 4, right). This last procedure must be carefully analyzed case by case before usingit, because it may lead to changes of the whole electronic structure.The physical interpretation of the requirement of more negative values of this index (i.e., of a more reactive $HOMO_i^*$) is that atom i is interacting with an electron-deficient center. The specific nature of the MO-MO interaction(s) depends on the nature of the local MO (π, σ, or lone pair) and of the 'distance' of the Local Frontier MOs from the zero energy. Also, an interaction with a positively charged site may be suggested. Any list of molecular interactions can be used for this purpose.

2. To obtain smaller negative values of $S_i^{E^*}(HOMO)^*$ we may, for example, lower the value of the Fukui index.This method will produce a less reactive local MO. For the two cases shown in Fig. 4, the lowering of the MO energy can also be achieved simply by removing the localization of the actual $HOMO_i^*$ at center i, so that an inner MO, such as R in Fig. 4, becomes the local $HOMO_i^*$.This requirement is interpreted by suggesting that center i interacts with an electron-rich center or with a negatively-charged moiety (for, example, a carboxylate group). The nature of the MO must be taken into account for a more precise analysis.

Orbital nucleophilic superdelocalizabilities (Eq. 3).

For the ensuing analysis, orbital nucleophilic superdelocalizabilities will be considered as having positive numerical values. The analysis of a QSAR equation may lead only to two possibilities: a need of more positive or less positive values of this index. Based on the definition shown in Equation 1, we have the following cases:
1. For larger positive values of $S_i^{N^*}(LUMO)^*$ we may raise the corresponding Fukui index value if and only if its numerical value is less than 2.0.Also, we may lower the associated MO energy. In both cases the MO will become more reactive.
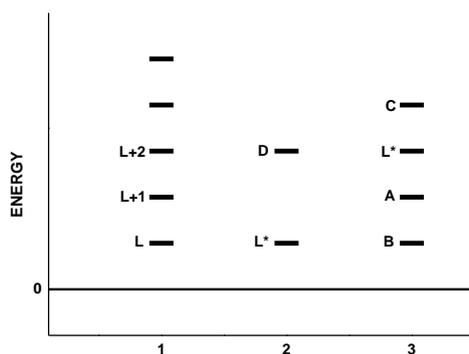

Figure 5:Two possible positions of LUMO* on the energy axis.

In case marked '2' in Fig. 5, we may induce quasi-degeneration of the LUMO* or 'inject' new empty σ MOs at center I (i.e., change the localization of a MO or create a new MO).In case marked '3' the task is theoretically easy: it consists inmodifying the structure of one or more MOs not localized on site i, such as A and B of Fig. 5, in such a way that their Fukui indices become non-null. This procedure is done by substituting at the correct site(s).This requirement is interpreted to suggest that atom i is interacting with an electron-rich center or with a negatively-charged site. The MO nature may help to make a more detailed suggestion.

2. Smaller positive numerical values of $S_i^{N^*}(LUMO)^*$ can be obtained by lowering the numerical value of the Fukui index or by shifting the MO energy upwards. In cases marked '2' and '3' in Fig. 5, the localization of the actual $LUMO_i^*$ is modified in such a way that now MO D or C become the new $LUMO_i^*$.Both cases produce a less reactive MO. This fact is interpreted to suggest that atom i interacts with an electron-deficient center.

The local atomic electronic chemical potential (ECP, Eq. 5).

In the case of large molecules possessing biological activity, we may safely consider that this reactivity index has a negative value. Case marked '1' in Fig. 6 shows a typical result of a DFT or HF calculation of a big molecule: some empty MOs have a negative energy.
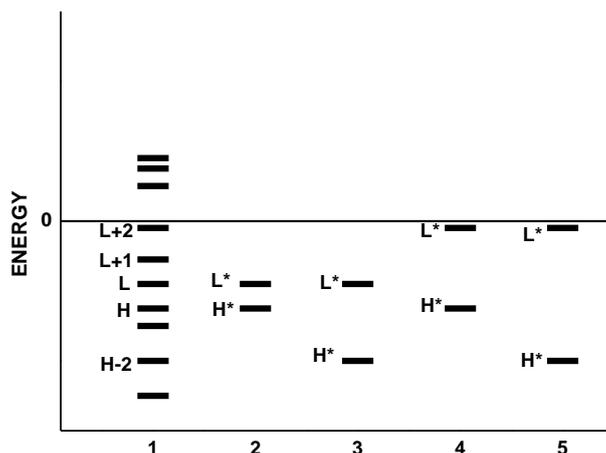
Figure 6: A pictorial representation of the calculated eigenvalue spectrum of a big molecule.

Four cases marked '2' to '5' in Fig. 6 can be distinguished. QSAR results may produce two opposite requirements for ECP: a need of more or less negative values.

A need of more negative values.

For cases '2' and '3' we need to make the Fukui index of the actual HOMO* zero, in such a way that an inner occupied MO of the molecule becomes the new HOMO* at i. This will make this occupied local frontier MO less reactive. For cases '4' and '5' we have two ways of obtaining the desired results. The first one is by modifying the MO localization in such a way that LUMO$_i$* coincides with the molecule's LUMO. This produces a more reactive LUMO*. The second one is by modifying HOMO$_i$* to match an even more internal molecular MO localized on atom i.

A need of less negative values.

In cases '2' and '4', as HOMO$_i$* coincides with the molecule's HOMO, the only way to get less negative values is that the LUMO$_i$* be replaced by a molecular MO with higher energy. This will produce a less reactive empty MO. For cases '3' and '5' we can proceed in two ways. The first one is by modifying HOMO$_i$* to match a more external molecular MO localized on atom i. This produces a more reactive HOMO$_i$*. The other one is by modifying the LUMO$_i$* replacing it by a molecular MO with higher energy. This produces a less reactive LUMO$_i$*.

The local atomic hardness (η$_i$, Eq. 6).

η$_i$ is the HOMO$_i$*-LUMO$_i$* gap and is always a positive number. For a given atom, the results of a QSAR analysis may require that the values of η$_i$ be greater or smaller for a enhanced biological activity. We shall discuss the four cases shown in Fig. 6.

A need of larger values.

This implies that the HOMO$_i$*-LUMO$_i$* gap should be increased. Theoretically speaking, we may increase this gap by changing the localization of the HOMO$_i$* replacing it with an inner MO, by changing the

localization of the LUMO$_i$* replacing it with a higher empty MO or by both procedures. We must note that when HOMO$_i$* coincides with the molecule's HOMO (cases '2' and '4' in Fig. 6) or when LUMO$_i$* coincides with the molecule's LUMO (cases '2' and '3' in Fig. 6) it is relatively easy to carry out the abovementioned procedures.Here, changing the localization of the HOMO$_i$* produces an atom with reduced electron-donating capacity. On the other hand, changing the localization of the LUMO$_i$* replacing it by a higher energy empty MO will produce a MO with reduced electron-accepting properties. What procedure should befollowed in a specific case?For case '2' we may use both of them. For case '3' one may modify LUMO$_i$*. For case '4' one may modify HOMO$_i$*. It is unusual for case '5' to appear in a QSAR equation because it corresponds to an almost unreactive atom.

A need of smaller values.

Here the HOMO$_i$*-LUMO$_i$* gap should be reduced. For case '2' of Fig. 6 there is no way to make the gap smaller because it involves the frontier MOs of the molecule. No such case has arisen during all the years of our work. In case '3' η_i can be decreased only by changing the localization of the actual HOMO$_i$* replacing it by an external MO (i.e., by an occupied MO with higher energy) because LUMO$_i$* coincides with the molecule's LUMO. This produces a more reactive HOMO$_i$*. For case '4' a decrease of η_i is obtained by changing the actual LUMO$_i$* replacing it by a molecular MO with reduced energy. This produces a more reactive LUMO$_i$*. In case '5' we may change the actual HOMO$_i$* replacing it by an occupied MO with higher energy, change the actual LUMO$_i$* replacing it by a molecular MO with reduced energy or carrying out both procedures simultaneously.

Considering that the local atomic softness is the inverse of η we feel it is unnecessary to discuss it.

Local atomic electrophilicity (Eq. 8).

$$\omega_i^* = \frac{(\mu_i^*)^2}{2\eta_i^*}$$

In Eq. 8, ω_i^* is always a positive number, as are both the numerator and denominator. We have only two possible cases: a high activity may be associated with either smaller or larger numerical values of ω_i^*.

A need of smaller positive values.

Smaller positive values may be obtained by raising the value of the local atomic hardness, by lowering the value of the ECP or by both procedures together.

A need of larger positive values.

Larger positive values may be obtained by lowering the value of the local atomic hardness, by raising the value of the ECP or by both procedures together.

The maximal amount of charge an atom may receive (Eq. 9).

$$Q_i^{*max} = -\frac{\mu_i^*}{\eta_i^*}$$

This index has a zero or positive value.

A need of small positive values.

A small value of can be obtained, for example, with a larger value of$\eta_i$keeping $\mu_i$constant. Also it is possible to shiftupwards the value of $\mu_i$in the energy axis.

A need of large positive values.

A small value of can be obtained, for example, with a smaller value of η_i keeping constant. Also it is possible to shiftdownwards the value of μ_i in the energy axis. A large value of this indexindicates that this atom is interacting with an electron-rich center and that is a good electron-receptor.

Finally, the experimentalist needs to ask this question: I need to modify this local atomic reactivity index in this way and this other index in that way. What doI have to do? This is the point where Quantum Chemistry shows its tremendous power. Before spending time and money synthesizing and testing many molecules, use quantum-chemical software to carry out an analysis of the wave function. As calculations run very fast on present-day computers and one may use software carrying out very fast analyses, one may test one or more substituents at several different positions and combinations of them. For medium sized molecules (about 40 heavy atoms plus the hydrogen atoms) about one hundred and fifty molecules may be analyzed in two weeks and one or more selected for synthesis.

REFERENCES

[1]   J. S. Gómez Jeria, La Pharmacologie Quantique, Bollettino Chimico Farmaceutico,1982 vol. 121, no. 12, pp. 619-625.
[2]   J. S. Gómez-Jeria, On some problems in quantum pharmacology I. The partition functions, International Journal of Quantum Chemistry,1983 vol. 23, no. 6, pp. 1969-1972.
[3]   J. S. Gómez-Jeria, Modeling the Drug-Receptor Interaction in Quantum Pharmacology, in Molecules in Physics, Chemistry, and Biology, J. Maruani Ed., vol. 4, pp. 215-231, Springer Netherlands, 1989.
[4]   J. S. Gómez-Jeria, and M. Ojeda-Vergara, Parametrization of the orientational effects in the drug-receptor interaction, Journal of the Chilean Chemical Society,2003 vol. 48, no. 4, pp. 119-124.
[5]   J. S. Gómez-Jeria, Elements of Molecular Electronic Pharmacology (in Spanish), Ediciones Sokar, Santiago de Chile, 2013.
[6]   J. S. Gómez-Jeria, A New Set of Local Reactivity Indices within the Hartree-Fock-Roothaan and Density Functional Theory Frameworks, Canadian Chemical Transactions,2013 vol. 1, no. 1, pp. 25-55.
[7]   J. S. Gómez-Jeria, and M. Flores-Catalán, Quantum-chemical modeling of the relationships between molecular structure and in vitro multi-step, multimechanistic drug effects. HIV-1 replication inhibition and inhibition of cell proliferation as examples., Canadian Chemical Transactions,2013 vol. 1, no. 3, pp. 215-237.
[8]   J. S. Gómez-Jeria, 45 Years of the KPG Method: A Tribute to Federico Peradejordi, Journal of Computational Methods in Molecular Design,2017 vol. 7, no. 1, pp. 17-37.
[9]   J. S. Gómez-Jeria, Tables of proposed values for the Orientational Parameter of the Substituent. II., Research Journal of Pharmaceutical, Biological and Chemical Sciences,2016 vol. 7, no. 4, pp. 2258-2260.
[10]   J. S. Gómez-Jeria, Tables of proposed values for the Orientational Parameter of the Substituent. I. Monoatomic, Diatomic, Triatomic, n-CnH2n+1, O-n-CnH2n+1, NRR', and Cycloalkanes (with a single ring) substituents, Research Journal of Pharmaceutical, Biological and Chemical Sciences,2016 vol. 7, no. 2, pp. 288-294.
[11]   J. S. Gómez-Jeria, and J. C. Surco-Luque, A Quantum Chemical Analysis of the Relationships between Electronic Structure and the inhibition of Botulinum Neurotoxin serotype A by a series of Derivatives possessing an 8-hydroxyquinoline core, Chemistry Research Journal,2017 vol. 2, no. 1, pp. 1-11.
[12]   J. S. Gómez-Jeria, and C. Moreno-Rojas, Dissecting the drug-receptor interaction with the Klopman-Peradejordi-Gómez (KPG) method. I. The interaction of 2,5-dimethoxyphenethylamines and their N-2-methoxybenzyl-substituted analogs with 5-HT1A serotonine receptors, Chemistry Research Journal,2017 vol. 2, no. 1, pp. 27-41.
[13]   J. S. Gómez-Jeria, P. Castro-Latorre, and G. Kpotin, Quantum Chemical Study of the Relationships between Electronic Structure and Antiviral Activities against Influenza A H1N1, Enterovirus 71 and Coxsackie B3 viruses of some Pyrazine-1,3-thiazine Hybrid Analogues, International Journal of Research in Applied, Natural and Social Sciences,2017 vol. 5, no. 2, pp. 49-64.
[14]   J. S. Gómez-Jeria, and P. Castro-Latorre, A Density Functional Theory analysis of the relationships between the Badger index measuring carcinogenicity and the electronic structure of a series of substituted Benz[a]anthracene derivatives, Chemistry Research Journal,2017 vol. 2, no. 3, pp. 112-126.

[15]   J. S. Gómez-Jeria, and M. B. Becerra-Ruiz, Electronic structure and rat fundus serotonin receptor binding affinity of phenetylamines and indolealkylamines, International Journal of Advances in Pharmacy, Biology and Chemistry,2017 vol. 6, no. 1, pp. 72-86.

[16]   J. S. Gómez-Jeria, and J. Abuter-Márquez, A Theoretical Study of the Relationships between Electronic Structure and 5-HT$_{1A}$ and 5- HT$_{2A}$ Receptor Binding Affinity of a group of ligands containing an isonicotinic nucleus, Chemistry Research Journal,2017 vol. 2, no. 4, pp. 198-213.

[17]   W. Anatovi, G. Kpotin, U. A. Kuevi, A. Houngue-Kpota, G. S. Atohoun, J.-B. Mensah, and J. S. Gómez-Jeria, A DFT study or the relationship between the electronic structure and the antiplasmodial activity of a series of 4-anilino-2-trichloromethylquinazolines derivatives, World Scientific News,2017 vol. 88, no. 2, pp. 138-151.

[18]   A. Robles-Navarro, and J. S. Gómez-Jeria, A Quantum-Chemical Analysis of the Relationships between Electronic Structure and Citotoxixity, GyrB inhibition, DNA Supercoiling inhibition and anti-tubercular activity of a series of quinoline–aminopiperidine hybrid analogues, Der Pharma Chemica,2016 vol. 8, no. 1, pp. 417-440.

[19]   G. A. Kpotin, G. S. Atohoun, U. A. Kuevi, A. Houngue-Kpota, J.-B. Mensah, and J. S. Gómez-Jeria, A quantum-chemical study of the relationships between electronic structure and anti-HIV-1 activity of a series of HEPT derivatives, Journal of Chemical and Pharmaceutical Research,2016   vol. 8, no. 8, pp. 1019-1026.

[20]   G. Kpotin, S. Y. G. Atohoun, U. A. Kuevi, A. Kpota-Hounguè, J.-B. Mensah, and J. S. Gómez-Jeria, A Quantum-Chemical study of the Relationships between Electronic Structure and Trypanocidal Activity against Trypanosoma Brucei Brucei of a series of Thiosemicarbazone derivatives, Der Pharmacia Lettre,2016 vol. 8, no. 17, pp. 215-222.

[21]   J. S. Gómez-Jeria, and R. Salazar, A DFT study of the inhibition of FMS-like tyrosine kinase 3 and the antiproliferative activity against MV4-11 cells by N-(5-(tert-butyl)isoxazol-3-yl)-N'-phenylurea analogs, Der Pharma Chemica,2016 vol. 8, no. 14, pp. 1-9.

[22]   J. S. Gómez-Jeria, and Í. Orellana, A theoretical analysis of the inhibition of the VEGFR-2 vascular endothelial growth factor and the anti-proliferative activity against the HepG2 hepatocellular carcinoma cell line by a series of 1-(4-((2-oxoindolin-3-ylidene)amino)phenyl)-3-arylureas, Der Pharma Chemica,2016 vol. 8, no. 2, pp. 476-487.

[23]   J. S. Gómez-Jeria, and C. Moreno-Rojas, A theoretical study of the inhibition of human 4-hydroxyphenylpyruvate dioxygenase by a series of pyrazalone-quinazolone hybrids, Der Pharma Chemica,2016 vol. 8, no. 1, pp. 475-482.

[24]   J. S. Gómez-Jeria, and M. Matus-Perez, A quantum chemical analysis of the inhibition of protein kinase A (PKA) and Rho-associated protein kinase-2 (ROCK2) by a series of urea-based molecules, Der Pharma Chemica,2016 vol. 8, no. 11, pp. 1-11.

[25]   J. S. Gómez-Jeria, and P. Latorre-Castro, On the relationship between electronic structure and carcinogenic activity in substituted Benz[a]anthracene derivatives, Der Pharma Chemica,2016 vol. 8, no. 16, pp. 84-92.

[26]   J. S. Gómez-Jeria, and G. A. Kpotin, A note on the inhibition of steroid 11β-hydroxylase, aldosterone synthase and aromatase by a series of coumarin derivatives Der Pharma Chemica,2016 vol. 8, no. 15, pp. 213-226.

[27]   J. S. Gómez-Jeria, and V. Gazzano, A quantum chemical study of the inhibition of α-glucosidase by a group of oxadiazole benzohydrazone derivatives, Der Pharma Chemica,2016 vol. 8, no. 11, pp. 21-27.

[28]   J. S. Gómez-Jeria, and R. Cornejo-Martínez, A DFT study of the inhibition of human phosphodiesterases PDE3A and PDE3B by a group of 2-(4-(1H-tetrazol-5-yl)-1H-pyrazol-1-yl)-4-(4-phenyl)thiazole derivatives, Der Pharma Chemica,2016 vol. 8, no. 4, pp. 329-337.

[29]   J. S. Gómez-Jeria, P. Castro-Latorre, and G. Kpotin, Quantum Chemical Analysis of the Relationships between Electronic Structure and Antiviral Activity against HIV-1 of some Pyrazine-1,3-thiazine Hybrid Analogues, Der Pharma Chemica,2016 vol. 8, no. 20, pp. 234-239.

[30]   J. S. Gómez-Jeria, and H. R. Bravo, A preliminary DFT analysis of phenolic acids in connection with their phytotoxic activity, Der Pharma Chemica,2016 vol. 8, no. 7, pp. 25-34.

[31]   J. S. Gómez-Jeria, and S. Abarca-Martínez, A theoretical analysis of the cytotoxicity of a series of β-carboline-dithiocarbamate derivatives against prostatic cancer (DU-145), breast cancer (MCF-7), human lung adenocarcinoma (A549) and cervical cancer (HeLa) cell lines, Der Pharma Chemica,2016 vol. 8, no. 2, pp. 507-526.

[32]   H. R. Bravo, B. E. Weiss-López, J. Valdebenito-Gamboa, and J. S. Gómez-Jeria, A theoretical analysis of the relationship between the electronic structure of indole derivatives and their phytotoxicity against

Lactuca Sativa seeds, Research Journal of Pharmaceutical, Biological and Chemical Sciences,2016 vol. 7, no. 2, pp. 792-798.