Research Article

Mathematical Analysis of a Series of 4-Acetylamino-2-(3,5-dimethylpyrazol-1-yl)-6-pyridylpyrimidines: A Simple Way to Relate Quantum Similarity to Local Chemical Reactivity Using the Gaussian Orbitals Localized Theory

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Molecular Quantum Similarity (MQS) descriptors and Density Functional Theory (DFT) based reactivity descriptors were studied for a series of 4-Acetylamino-2-(3,5-dimethylpyrazol-1-yl)-6-pyridylpyrimidines compounds used for Parkinson’s disease (PD) treatment. The quantification of the steric and electronic effects was shown through scales of quantitative convergence; such scales allow us to establish a methodology to quantify the similarity from the local chemical reactivity (Fukui Functions) point of view. This procedure provides new considerations in the local reactivity of the A2A Adenosine receptor antagonists in a disease of difficult control as PD. In addition, we present new considerations to the localized bonding theory and show a new methodology for quantum similarity on the Fukui Functions. Considering that the Fukui functions under a condensation scheme may have ambiguities in the (DFT) context.

1. Introduction

Parkinson’s disease (PD) is also known as idiopathic Parkinsonism or paralysis agitans [1]. PD is a chronic and degenerative disorder of the brain parts controlling the motor system. It occurs when nerve cells in the substantia nigra of the midbrain (a brain area that controls movement) die or suffer some deterioration [2]. PD is a chronic neurodegenerative disorder, which eventually leads to a progressive disability, for reasons still unknown [2–7]. PD is the second neurodegenerative disorder by their frequency, ranking behind only Alzheimer’s disease [2].

PD is not only a motor system disorder. It has a wider spectrum of affectedness such as emotional wellbeing, affecting sleep, cognition, visuospatial deficits, and sensation and perception [3–5]. For all these reasons there are also other aspects of PD to be considered such as social and economic cost, for instance, within families and work places of the PD affected patients.

In this study is presented a method to quantify the steric and electronic factors in a set of 4-Acetylamino-2-(3,5-dimethylpyrazol-1-yl)-6-pyridylpyrimidines as A2A adenosine receptor antagonists, reported by Zhang et al. [8] using the Molecular Quantum Similarity (MQS) [9–15]. Recently Bultinck and Carbó-Dorca have reported an analysis based on quantum similarity [16, 17], to define a link between quantum similarity and chemical reactivity. Taking into account this background, in this study we suggest a methodology for quantifying the steric and electronic effects of a series of A2A adenosine receptor antagonists [8]. Additionally, a series of global and local reactivity descriptors such as chemical potential (μ), hardness (η), softness (S), global electrophilic...
Table 1: Structures and inhibitory activity of compounds analyzed.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>pKa (^a)</th>
<th>hA(_{1A}) (^b)</th>
<th>hA(_{1B}) (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>-1.9395</td>
<td>2.4623</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3-pyridyl</td>
<td>-2.0792</td>
<td>-3.3222</td>
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</tr>
<tr>
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<td>-2.938</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3-MeO-Ph</td>
<td>0.0362</td>
<td>-1.8129</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2-F-3-MeO-Ph</td>
<td>0.2218</td>
<td>-2.0414</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3,5-di-MeO-Ph</td>
<td>0.7212</td>
<td>1.3424</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>5-MeO-3-pyridyl</td>
<td>-0.3617</td>
<td>2.2788</td>
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</tr>
<tr>
<td>8</td>
<td>5-OH-3-pyridyl8</td>
<td>-0.4623</td>
<td>2.2900</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>5-(2-methoxy-ethoxy)-3-pyridyl</td>
<td>-0.4914</td>
<td>-2.0414</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Exp: biological activity (nM) expressed as \(-\log_{10}\) K\(_{i}\). MCH-R1 antagonists.

\(^b\)Specific in the binding at hA\(_{1A}\) receptors expressed in HEK293 cells.

\(^c\)Specific in the binding at hA\(_{1B}\) receptors expressed in HEK293 cells.

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2. Theory and Computational Details

2.1. Molecular Set. A set of 4-Acetylamino-2-(3,5-dimethylpyrazol-1-yl)-6-pyridylpyrimidines reported by Zhang et al. [8] (Table 1) were studied. The adenosine plays an important role as a neuromodulator in the central nervous system through interaction with its receptors A\(_1\), A\(_2A\), A\(_2B\), and A\(_3\), that are widely distributed in body tissues causing vasodilatation, bronchoconstriction, immune suppression, among others effects [28]. Specifically, the compounds reported by Zhang et al. are associated with receptor antagonist activity A\(_2A\) [8].

2.2. Molecular Alignment and Computational Details. In the Molecular Quantum Similarity (MQS) field the molecular arrangement or alignment of the molecules has played a central role. Due of this dependence have been proposed by many alignment methods. Ranging from those used in CoMFA and CoMSIA methods which are in three dimensions (3D), allowing get maps steric, electronic and hydrophobic, among others [29, 30]. Gironés and Carbó-Dorca have implemented the alignment method based on the Topo-Geometrical Superposition Algorithm (TGSA) [31]. This method is based on the comparison of the types of atoms, distances between them, and the recognition of the largest common substructure in the aligned molecules; in this sense other alignment methods were presented in the quantum similarity [32].

In this study the similarity measures can be approximated as \(F_\text{a} = F_\text{m} + F_\text{si}\) and \(F_\text{b} = F_\text{m} + F_\text{ti}\) where \(F_\text{a}\) and \(F_\text{b}\) are density functions of two different molecules, \(F_\text{m}\) is the common part to both functions, and \(F_\text{si}\), \(F_\text{ti}\) represent the parties associated with the substituents of each compound analyzed (asymmetric carbon). The similarity provided by the partition of molecular space in this study is used to rationalize and quantify steric and electrostatic effects, through the proposition of scales of quantitative convergence, allowing us to obtain insights into atoms in molecules, aromaticity, among others [26, 27].

In this contribution all the molecular structures were optimized with the program Gaussian 03 [33] using DFT methods with the B3LYP exchange-correlation functional [34, 35], together with standard 6-31G* base set [36].

2.2.1. Theory and Computational Details. All the geometries were optimized using the Gaussian 03 suite of programs [33] by means of Becke’s three-parameter hybrid method with the Lee-Yang-Parr correlation functional [34, 35], and the split valence 6-31G(d) [36].

2.2.2. Similarity Indexes. The quantum similarity field was introduced by Carbó-Dorca and coworkers [9–15]; they defined the quantum similarity measurements \(Z_{AB}\) between molecules A and B with the electronic density \(\rho_\text{A}(r)\) and \(\rho_\text{B}(r)\) taking into account the minimization of the expression for the Euclidean distance as

\[
D_{AB}^2 = \int |\rho_\text{A}(r) - \rho_\text{B}(r)|^2 dr
= \int \rho_\text{A}^2(r) dr + \int \rho_\text{B}^2(r) dr - 2 \int \rho_\text{A}(r) \rho_\text{B}(r) dr
= Z_{AA} + Z_{BB} - 2Z_{AB}.
\]

Equation (1) involves the overlap integral ZAB, often called Molecular Quantum Similarity Measure (MQSM), between the electron densities of molecules A and B. ZAA and ZBB are called the Molecular Quantum Self-Similarity Measures of
molecules A and B [37]. Using the cosine of the angle between the density functions [15] can be expressed mathematically as

\[
I_{AB} = \frac{\int \rho_A(r) \rho_B(r) \, dr}{\sqrt{\int \rho_A(r) \rho_A(r) \, dr \int \rho_B(r) \rho_B(r) \, dr}} \tag{2}
\]
a simple manner using a general operator (\(\Omega\)) can be expressed as

\[
I_{AB} = \frac{Z_{AB}(\Omega)}{\sqrt{Z_{AA}(\Omega) Z_{BB}(\Omega)}} \tag{3}
\]
The range of this index in (3) is determined by the Schwartz integral inequality mathematically defined in the interval \((0, 1]\) that can be defined mathematically as

\[
\text{HR}(I_{AB}) = \frac{2Z_{AB}(\Omega)}{Z_{AA}(\Omega) + Z_{BB}(\Omega)}. \tag{4}
\]
Equation (4) is used in this study to obtain the Molecular Quantum Similarity Measurements (MQSM) and characterizations from the point of view of the atomic shells, described through the polarizability function in the B3LYP/6–31G* that characterize the electron density determined by steric and electronic effects in the local atomic shells; in this sense a convenient partition of the electronic density, such as the Hirshfeld Approach, is required.

2.2.3. Local Similarity Indexes (LSI)

(1) The Hirshfeld Approach. One of the techniques most used in quantum similarity to the partition of the electronic density was postulated by Hirshfeld [39]. This approach is based on partitioning of the electron density in a molecule by contributions \(\rho(r)\). These contributions are proportional to the weight \(w_A(r)\) of the electron density of the isolated molecule in the call promolecular density [40–42]; this weight is defined as the ratio of the electron density in the isolated atom constructed from the superposition of the density of all atoms isolated in the same position of the molecule (“the promolecular density”); this is obtained as

\[
\rho^\text{Prom}_A(r) = \sum_x \rho^0_A(x)(r). \tag{5}
\]
To calculate the contribution of atom \(A\), \(\rho_A(r)\) the electron density \(\rho(r)\) is obtained as

\[
\rho_A(r) = w_A(r) \rho(r). \tag{6}
\]
To obtain the weight \(w_A(r)\) the following equation is used:

\[
w_A(r) = \frac{\rho^0_A}{\sum_x \rho^0_x(r)}. \tag{7}
\]
where \(\rho^0_A(r)\) is the electronic density of the isolated atom \(A\). Recently, using the Hirshfeld partition in quantum similarity, the global similarity index (4) at local level [43] has been calculated. In this approximation the contribution of carbon atom (\(C^1\)) in the molecule \(A\) is given by

\[
\rho_{C_1,A}(r) = w_{C_1}(r) \rho_A(r), \tag{8}
\]
where

\[
w_{C_1,A} = \frac{\rho^0_{C_1,A}(r)}{\sum_x \rho^0_x(r)}, \tag{9}
\]
equally the contribution of carbon atom (\(C^2\)) in the molecule \(B\) is obtained as

\[
\rho_{C_2,B}(r) = w_{C_2}(r) \rho_B(r), \tag{10}
\]
where

\[
w_{C_2,B} = \frac{\rho^0_{C_2,B}(r)}{\sum_x \rho^0_x(r)}, \tag{11}
\]
so that the similarity by the product electron density in the asymmetric carbon \(\rho_A(r)\rho_B(r)\) is expressed as

\[
\rho_{C_{A+B}}(r) = w_{C_{A+B}}(r) \rho_A(r) \rho_B(r) \tag{12}
\]
getting the weighted total:

\[
w_{C_{A+B}}(r) = \frac{\rho^0_{C_1,A}(r) + \rho^0_{C_2,B}(r)}{\sum_x \rho^0_x(r) + \sum_y \rho^0_y(r)}, \tag{13}
\]
where \(\sum_x \rho^0_x(r) + \sum_y \rho^0_y(r)\) is the total promolecular density of the two molecules considered, so that we can express the numerator \(Z_{AB}\) Hodgkin-Richards index [38] (4) as

\[
Z_{AB}^{\text{Local,C}} = \int w_{C_{A+B}}(r) \rho_A(r) \rho_B(r) \, dr
\]
\[
= \int \left( \frac{\rho^0_{C_1,A}(r) + \rho^0_{C_2,B}(r)}{\sum_x \rho^0_x(r) + \sum_y \rho^0_y(r)} \right) \rho_A(r) \rho_B(r) \, dr, \tag{14}
\]
where the global index is partitioned in its atomic contributions; this Hirshfeld approach in this study is used taking into account the holographic electron density theorem postulated by Mezey [43]. To circumvent expensive computational calculations, promolecular ASA has been used routinely to compute density functions and fitted electronic density functions from \(H\) to \(Rn\) for use in quantum similarity measures [44].

3. Reactivity Indexes

In order to relate the MQS field and the local reactivity the Fukui functions are used. The Fukui function, \(f(\vec{r})\), was proposed as a tool to derive the relative reactivity of different positions on a molecule by Parr and Yang [45]; also see [46]. The electron density is calculated as

\[
\rho_A = \sum_{\nu} D_{\nu A} \phi_{\nu A} \phi_{\nu A}^*, \tag{15}
\]
where \((D)\) represents the charge and the binding order of the matrix and \(\varphi\) are the basis functions used in the iterative process of the self-consistent field (SCF). In this context the similarity measurements are obtained by the expression

\[
Z_{AB} = \sum_{\mu A, \nu B} \sum_{\delta A, \epsilon B} D_{\mu A} D_{\delta A} \int \varphi_{\mu A}^* (r) \varphi_{\nu B} (r) \varphi_{\delta A} (r) \varphi_{\epsilon B} (r) \, dr.
\]

(16)

To calculate the integral in (16) the classical approach of overlapping of Gaussian type orbitals is used. In this study is related the electron density with the call shape function \(\sigma_A(r)\) according to Bultinck and Carbó-Dorca [47], this can be obtained by the relation

\[
\sigma_A (r) = N_A^{-1} \rho_A (r),
\]

(17)

where \(N_A\) is the number of electrons in the molecule \(A\). The shape function determines each observable of the system and may give information about the number of electrons in the electron density, despite that is Minkowski normalized to unit in all molecules:

\[
\int \sigma_A (r) \, dr = 1.
\]

(18)

To use this shape function we considered the relationship with several indexes as was demonstrated by Bultinck and coworkers [16, 17, 38, 48]. Using this type of mathematical considerations from the point of view of overlapping in the electronic distribution (16) is low, increasing the fit between the electron densities of \(A\) with respect to \(B\).

The chemical potential \((\mu)\) can be interpreted as the measurement of the tendency of electrons to escape from the electron cloud, whose discontinuity for integer values of \(N\) was shown by Parr and Pearson [51]; the second term in (23) is called Hellmann-Feynman term [51] in the DFT context. From chemical reactivity point of view the first and second derivatives are important. The second order change in energy with respect to the number of electrons and the external potential through variations in the chemical potential is considered:

\[
d\mu [N, \nu_0 (r)] = \left( \frac{\partial \mu}{\partial N} \right)_{\nu_0 (r)} \, dN + \int \left( \frac{\delta \mu}{\delta \nu_0 (r)} \right)_N \delta \nu_0 (r) \, dr.
\]

(24)

and electron density

\[
\delta \rho [N, \nu_0 (r); r] = \left( \frac{\partial \rho (r)}{\partial N} \right)_{\nu_0 (r)} \, dN + \int \left( \frac{\delta \rho (r)}{\delta \nu_0 (r)} \right)_N \delta \nu_0 (r) \, dr.
\]

In (24) the first term relates to the chemical hardness \(\eta\), expressed mathematically as

\[
\eta \equiv \left( \frac{\partial \mu}{\partial N} \right)_{\nu_0 (r)} = \left( \frac{\delta^2 E}{\delta N^2} \right)_{\nu_0 (r)}.
\]

(26)

Using (26) can quantify the opposition that puts the system to deform its electron cloud [51], while the second term in (25) represents the term called linear response function \(\omega(r, r')\) [52]. Using the Maxwell relations in (23) is possible to define the Fukui functions [53] in (24) and (25):

\[
f(r) \equiv \left( \frac{\partial \rho (r)}{\partial N} \right)_{\nu_0 (r)} = \left( \frac{\delta \mu}{\delta \nu_0 (r)} \right)_N.
\]

(27)

from (19) we have

\[
\left( \frac{\delta E}{\delta \nu_0 (r)} \right)_N = \rho (r);
\]

(21)

using (20) it is possible to define the chemical potential, through the relationship

\[
\mu = \left( \frac{\delta E}{\delta N} \right)_{\nu_0 (r)}.
\]

(22)

Substituting (21) and (22) into (20) the following relationship is obtained:

\[
dE [N, \nu_0 (r)] = \mu dN + \rho (r) \delta \nu_0 (r) \, dr.
\]

(23)

The Fukui functions \((f(r))\) from (28) and (29), we return to the question of how to explain the similarity in the Fukui functions between two molecules \(A\) and \(B\), using the alignment method TGSAs. To answer this question we consider the case where the chemical potential of reagent \(A\) is larger than the one of reagent \(B\); in this case the similarity from the point of view of overlapping in the electronic distribution (16) is low, increasing the fit between the electron densities of \(A\) with respect to \(B\).

Now consider the case of the electronic overlap between molecules \(A\) and \(B\) when the electron density \(\rho_A (r)\) tends to increase the number of electrons, \(N_A\):

\[
f_A (r) = \left( \frac{\partial \rho_A (r)}{\partial N_A} \right)_{\nu_{A, 0} (r)} = \lim_{\varepsilon \to 0} \left[ \frac{\rho [N + \varepsilon, \nu_0 (r)] - \rho [N, \nu_0 (r)]}{2 \varepsilon} \right].
\]

(30)
This implies that \( f^+ \) is large in regions where there is high susceptibility to attack by nucleophilic species. Now consider the case of the electronic density \( B \) versus electron density \( A \) having few electrons:

\[
 f_B^\ast (r) = \left( \frac{\partial \rho_B(r)}{\partial N_B} \right)_{\nu_B(r)} = \lim_{\epsilon \to 0} \left[ \frac{\rho [N, \nu_B(r)] - \rho [N - \epsilon, \nu_B(r)]}{2\epsilon} \right]
\]

(31)

from which we can conclude that the molecule \( B \) donates electrons in regions where \( f^- \) is large, when the molecules \( A \) and \( B \) superimposed their similarity indexes in the molecular fragments depending on the similarity of chemical potential, which implies that the variations of electrons are \( (\Delta N_A \approx \Delta N_B \approx 0) \) and we can obtain high overlap values in the electronic population; this electronic similarity can be related to the overlap in the Fukui functions using the concept of lateral boundaries:

\[
f^0(r) = \lim_{\epsilon \to 0} \frac{\rho [N + \epsilon, \nu_B(r)] - \rho [N - \epsilon, \nu_B(r)]}{2\epsilon} = \frac{f^+(r) + f^-(r)}{2}.
\]

(32)

where we can get the following relations:

\[
 I = A, \quad B : f^0_I (r) = \frac{f^+_I (r) + f^-_I (r)}{2}.
\]

(33)

These expressions can be used to predict reactivity sites in neutral species.

4. Results and Discussions

In order to postulate a possible form to relate the MQS and local reactivity a MQS Indexes analysis, a global and local reactivity study and finally a mathematic analysis among the Fukui functions and Quantum similarity is developed.

4.1. Molecular Quantum Similarity Indexes Analysis. In Tables 3, 4, 5, and 6 the similarity matrixes used to quantify the steric and electronic effects on the different compounds studied are depicted. The similarity indexes are calculated using (1) for the Euclidean distances and (14) for the local Hodgkin-Richards index. This approach gives us information about the quantum similarity using shape function in the electron density of Gaussian type orbitals, taking into account the good correlation between the shape functions with the Hodgkin-Richards indexes demonstrated by Bultinck et al. [16, 17]. Such analysis was developed on the series of 4-Acetylamino-2-(3,5-dimethylpyrazol-1-yl)-6-pyridilpyrimidines as \( A_2A \) Adenosine receptor antagonists for the PD treatment reported by Zhang and coworkers [8].

The compounds 1 and 2 have the highest values of similarity with a value of 0.9904 (Table 2), whereas the comparison between compounds 1 and 5 give the smaller value 0.6262. So that effect of activation on para position in the compound 3 are more relevant that the activation of the substituent in the meta position 2, in agreement with the experimental values of the \( pK_i \) (see Table 1). Moreover, the lowest value of Euclidean distance is obtained in the substituent of compound 5 and compound 9, presenting difficulties in the structural alignment of the substituents of asymmetric carbon, to quantify the degree of alignment from the structural point of view the overlap index is displayed in Table 2.

In Table 3 is depicted the lowest Euclidean distance between the compounds 1 and 2 with a value of 0.5976, and presents a largest value in comparison with molecules 5 and 9 with a value of 4.1730. To quantify the similarity of the electronic orbital populations the values of Gaussian-Richards Hodgkin indexes in Table 4 with the corresponding Euclidean distance are calculated (Table 5).

In Table 4 are shown the Hodgkin-Richards Coulomb indexes; the higher value is found between the compounds 1 and 2 with a value of 0.9995, according to the similarity values of overlap shown in Tables 2 and 3. Moreover, Table 4 shows the high values of the electronic similarity in compounds that have low structural similarity as is the case of compounds 5 and 9 with the Hodgkin-Richards index of overlap 0.6417 (see Table 2) and for the Coulomb similarity 0.9322, through the alignment TGSA characterized by the Euclidean distances of Coulombs (Table 5).

In Table 5 are shown the values of the Euclidean distances computed under a Coulomb operator weight. The lower value is found between molecules 1 and 2 with a value of 1.3871, showing the higher similarity electronics reported (Table 4). The higher value in the Euclidean Distance is observed when we compared the compounds 5 and 9 with a value of 19.3302, in agreement with the greatest structural similarity shown in Table 2.

In order to quantify the steric and electronic similarity of the compounds, we used the compound 6 that is the most active of the series according to Table 1. Figure 1 shows the steric and electronic effects in form of similarity scales of the compound 6 with respect to the other compounds.

In Figure 1 are shown the Coulomb and overlap scales on the series of receptor antagonists 4-Acetylamino-2-(3,5-dimethylpyrazol-1-yl)-pyrimidines, using the most active compound of reference 6. Overlap and Coulomb scales show the same trends along of molecular set. Showing a good correlation in the quantitative method proposed for orbital similarity, allowing describe the structural and electronic similarity from the local perspective in the asymmetric carbon substituted. To determine the asymmetry from the point of view of the local chemical reactivity is calculated the global and local reactivity indexes.

4.2. Global and Local Reactivity Analysis. The global and local reactivity indexes such as Chemical potential (\( \mu \)), harness (\( \eta \)), and electrophilic (\( \omega \)) in units of electronvoltio (eV) are shown in Table 6.

The compound 6 has the higher chemical potential (\( \mu \)): \(-3.7105 \text{ eV} \) (Table 6) according to the experimental values of \( A_2A \) antagonist activity with a \( pK_i \): 0.7212; see Table 1.
Table 2: Molecular Quantum Similarity matrix using the overlap operator.

<table>
<thead>
<tr>
<th>Ca</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2</td>
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</tr>
<tr>
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<tr>
<td>4</td>
<td>0.8194</td>
<td>0.7941</td>
<td>0.9402</td>
<td>1.0000</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>5</td>
<td>0.6262</td>
<td>0.6291</td>
<td>0.7392</td>
<td>0.6939</td>
<td>1.0000</td>
<td></td>
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</tr>
<tr>
<td>6</td>
<td>0.7880</td>
<td>0.7699</td>
<td>0.8979</td>
<td>0.9526</td>
<td>0.6582</td>
<td>1.0000</td>
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<tr>
<td>7</td>
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<tr>
<td>8</td>
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<td>0.8414</td>
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<td>0.9011</td>
<td>0.7029</td>
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</tr>
<tr>
<td>9</td>
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<td>0.8721</td>
<td>0.8230</td>
<td>0.6417</td>
<td>0.8812</td>
<td>0.9398</td>
<td>0.9133</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

*C: compound (Table 1).

Table 3: Molecular Quantum Similarity matrix using the overlap Euclidean distances.

<table>
<thead>
<tr>
<th>Ca</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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*C: compound (Table 1).

Table 4: Molecular Quantum Similarity matrix using the Coulomb operator.

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*C: compound (Table 1).

Table 5: Molecular Quantum Similarity matrix using the Coulomb Euclidean distances.

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*C: compound (Table 1).
As the substituents R(6) with the R(4) differ only by the presence of methoxy (MeO–), this (dis)similarity in the asymmetric carbon between the two structures is due to the C33 carbon atom determinate by molecular alignment TGSA and is quantified with the overlap similarity index 0.9526, see Table 2, and with the electronic similarity 0.9898, see Table 4.

The consideration of the local chemical reactivity of the Fukui functions was derived taking into account the lateral equations ((30) and (31)) with 0.0552 to compound 6, and for the compound 4: 0.0196, these differences in the local reactivity were quantified through the (dis)similarity in the electronic population from the point of view of the Gaussian orbitals (16) and using the shape function in the ASA approach [54].

To establish the conditions of similarity in the chemical reactivity between the two structures 6 and 4 (see Table 1), we can use the relations

\[
\lim_{\varepsilon \to 0} \rho^E_6 \left[ N + \varepsilon, v_0(r) \right] = \lim_{\varepsilon \to 0} \rho^E_4 \left[ N - \varepsilon, v_0(r) \right],
\]

\[
\frac{f^+_{C33}(6) + f^-_{C33}(6)}{2} \approx \lim_{\varepsilon \to 0} \left\{ \frac{f^+_{C33}(4) + f^-_{C33}(4)}{2} \right\}
\]

where (IS) in (34) represents the Hodgkin-Richards indexes of overlap and Coulomb, respectively. On the other hand, the self-similarity in the Fukui functions occurs when (IS = 1) and in (37) the (Euclidean Distance = ED = 0) of Coulomb and overlap. From the point of view of the global reactivity descriptors the self-similarity occurs when

\[
\mu_A(6) \approx \mu_B(4) \quad \text{with} \quad \Delta N_A(6) \approx \Delta N_A(4).
\]

Equation (38) provides information about the local electronic population determined by steric considerations of the substituent groups (R), according to the methodology of alignment that is shown in Figure 2 in Table 7. Equation (38)

Moreover, the compound more stable is the compound 3 with \(\mu : -4.2797\) eV and a pK_a value: -1.6021. This Compound also has the higher hardness \(\eta : 4.3745\) eV, and allows understanding the greater tendency of the electrons to escape from the electron cloud with the substituent group 3,5-di-MeO-Ph, and the greatest opposition to distort the electron cloud in the common structural fragment in the test range. This relationship is also seen in the less reactive compound 3.

The stabilization energy of the system when it is saturated by electrons is calculated with the electrophilic index \(\omega : \mu^2/2\eta\), the compound 3 is the less reactive and it has the highest electrophilic, this is determined by the substituent group (4-pyridyl); see Table 1. These considerations are according to the reactivity and with the lower value in the hardness \(\eta : 2.0646\) eV allowing relating the degree of distortion of the electron cloud with a low energy needed by the system when it has electronic saturation according to equation \(\omega : \mu^2/2\eta\). Allowed us relate a low reactivity with a high electrophilicity in the Gaussian orbital, describing the asymmetry of the carbon atom and of the substituents studied. In this sense, the local indexes are calculated to determine this condition and the local reactivity through the Fukui functions that are shown in Table 7.

As the substituents R(6) with the R(4) differ only by the presence of methoxy (MeO–), this (dis)similarity in the asymmetric carbon between the two structures is due to the C33 carbon atom determinate by molecular alignment TGSA and is quantified with the overlap similarity index 0.9526, see Table 2, and with the electronic similarity 0.9898, see Table 4.

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\[
\frac{f^+_{C33}(6) + f^-_{C33}(6)}{2} \approx \lim_{\varepsilon \to 0} \left\{ \frac{f^+_{C33}(4) + f^-_{C33}(4)}{2} \right\}
\]

where (IS) in (34) represents the Hodgkin-Richards indexes of overlap and Coulomb, respectively. On the other hand, the self-similarity in the Fukui functions occurs when (IS = 1) and in (37) the (Euclidean Distance = ED = 0) of Coulomb and overlap. From the point of view of the global reactivity descriptors the self-similarity occurs when

\[
\mu_A(6) \approx \mu_B(4) \quad \text{with} \quad \Delta N_A(6) \approx \Delta N_A(4).
\]
Table 7: Fukui function, in the molecular fragment of the most reactive compound 6 with respect to the compound 4, of the substitute groups (R(n)) in Figure 2; see Table 1.

| Compound 6 | \( f(\vec{r}) \) \( f(\vec{r})^* \) \( f(\vec{r})^0 \) | Versus Comp. 4 | \( f(\vec{r}) \) \( f(\vec{r})^* \) \( f(\vec{r})^0 \) |
|------------|----------------|----------------|----------------|----------------|----------------|----------------|
| C30        | 0.0042         | 0.0652         | 0.0347         | C30            | 0.0181         | 0.0674         | 0.0428         |
| C31        | 0.2515         | 0.0686         | 0.1601         | C31            | 0.1536         | 0.0514         | 0.1025         |
| C32        | 0.2543         | 0.0680         | 0.1612         | C32            | 0.0468         | 0.0904         | 0.0686         |
| C33\*      | 0.0992         | 0.0112         | 0.0552         | C33\*          | 0.0230         | 0.0161         | 0.0196         |
| C35        | 0.1005         | 0.1005         | 0.0573         | C37            | 0.0879         | 0.0101         | 0.0490         |
| C36        | 0.0014         | 0.0846         | 0.0430         | C38            | 0.0872         | 0.1010         | 0.0941         |
| O38        | 0.1191         | 0.0035         | 0.0613         | O40            | 0.1151         | 0.0027         | 0.0589         |
| O44        | 0.1144         | 0.0028         | 0.0586         |                |                |                |                |

* Carbon asymmetric in the substituent R of compound 6 with respect to compound 4; see Table 1.

can be related con the Mulliken valence and in this sense understand the electronic population, according to Putz [55].

This measure is calculated taking the corresponding part of the squared norm of the density function belonging to the fragment of interest, so we can write

\[
Z_{AB}^X(\Omega) = \int \rho_A^X(r_1) \Omega(r_1,r_2) \rho_B^X(r_2) \, dr_1 dr_2,
\]

where \( X = \) Molecular Fragment, than can quantify the asymmetric carbon (see Table 1). This measure is based on the holographic theorem of the electronic density, which ensures that the information contained in the total electron density of a molecule is also present in the local density of any molecular fragment [55].

This method provides theoretical considerations about topological similarity analysis of the Fukui functions relating it to the local similarity and presenting new topological relationships, considering that the electron localization concept in the descriptive chemical is very important; due to the fact that the Hartree-Fock canonical orbitals are delocalized over the molecular space, this method can be complementary to any analysis proposed of the molecular topology as the developed by Bader [56].

Showing new considerations to the chemical bond theory located using Fukui function; considering that the structures (see Table 1) differ by only one substituent group and each electronic density has its own distinctive topology which provides information about the nature of chemical bonding to each fragment associated with the local molecular bond considered.

In this sense, this study presents new considerations on the local reactivity through Fukui function. Considering that Fukui functions under a condensation scheme may have ambiguities according to Bultinck et al. [57]. For this reason, a mathematic analysis among the Fukui functions and quantum similarity was made to search for new links in the molecular topology, aromaticity [25], and reactivity descriptors [46].

4.3. Mathematical Analysis among the Fukui Functions and Quantum Similarity. Taking in account the recent advances of atoms in molecules showing a closely relation between DFT and electron delocalization [24], in this section we study the similarity in the aromaticity. In this section was study the similarity in the aromaticity. In order to study 41 from the mathematic point of view the relation between quantum similarity and the Fukui function, the case of the self-similarity due to the equality of the chemical potential is considered in (38):

\[
\mu_A = \mu_B = \mu_{AB}.
\]
for the change of the electron population is considered the case:

\[ dN_A = dN_B = dN_{AB}. \] (41)

In this condition the external potential also has a (dis)similarity that we can see in the chemical potential according to (38); therefore using (28) we have

\[ d\mu = \eta_A dN_A + \int f_A(r) dv_A(r) dr \]
\[ = \eta_B dN_B + \int f_B(r) dv_B(r) dr = d\mu_B, \]

where

\[ dv_A(r) = \int \frac{\delta \rho_B(r)}{|r - r'|} dr' \] (43)

with

\[ \delta \rho_B(r) = \frac{\delta \rho_B(r)}{\delta N_B} \] (44)

Taking into account (27) and using the same analysis of (43) to \( dv_B \), is obtain for (42) through the Fukuii functions ((33) and (35)):

\[ \eta_A dN_A + \int f_A^0(r) dv_A(r) dr + \int \left[ \int \frac{f_A^0(r) f_B^0(r') dr dr'}{|r - r'|} \right] dN_B \]
\[ = \eta_B dN_B + \int f_B^0(r) dv_B(r) dr + \int \left[ \int \frac{f_B^0(r) f_A^0(r') dr dr'}{|r - r'|} \right] dN_A, \] (45)

Taking into account (41), with \( dv_A(r) = dv_B(r) \), we have for \( dN \)

\[ [(\eta_A - 1) + (\eta_B - 1)] dN = \int f_B^0(r) dv(r) dr - \int f_A^0(r) dv(r) dr, \] (46)

where

\[ J = \left[ \int \frac{f_A^0(r) f_A^0(r') dr dr'}{|r - r'|} \right]. \] (47)

Equation (47) is called coulomb equation and calculates the similarity determined by the quantum TGSA molecular alignment (see Table 4). Solving the equation for \( dN \) in (46) is obtained:

\[ dN = \left[ \frac{\int f_B^0(r) f_B^0(r') dv(r) dr}{(\eta_A + \eta_B) - 2J} \right]. \] (48)

In the case of the self-similarity we have for (48) \( dN = 0 \); this is due to the fact that \( A = B \), and therefore in the coulomb integral \( J = 1 \). This value for \( dN = 0 \) can be related to the value of the Euclidean distance \( D_{AB} = 0 \) (see Table 5) in terms of TGSA molecular alignment (see Figure 1). Thus, we can write a general equation for the Euclidean distance using (1):

\[ D_{AB} = \sqrt{Z_A + Z_B - 2Z_{AB}} = dN \]
\[ = \left[ \frac{\int f_B^0(r) f_B^0(r') dv(r) dr}{(\eta_A + \eta_B) - 2J} \right] \]
\[ = \left[ \frac{\int f_B^0(r) f_B^0(r') dv(r) dr}{(\eta_A + \eta_B) - 2\left( \int \left[ \left( f_A^0(r) f_B^0(r') dv(r) dr \right)^2 \right] \right)} \right]^{-1}, \] (49)

and in terms of the chemical \( P(\mu) \) and electrophilicity \( (\omega) \) as

\[ D_{AB} = \left[ \frac{\int f_B^0(r) f_B^0(r') dv(r) dr}{(\eta_A + \eta_B) - 2\left( \int \left[ \left( f_A^0(r) f_B^0(r') dv(r) dr \right)^2 \right] \right)} \right]^{-1} \]

where \( (\eta, \mu, \omega) \) were calculated in Table 6. Therefore, we can say that a high electronic similarity in the aromaticity between \( A \) and \( B \) determines a maximum molecular alignment, allowing getting the conditions of quantum similarity of the Fukui functions in terms of global reactivity descriptors and the coulomb functions. Finally, we can obtain the Carbó index, using (1) and (3):

\[ I_{AB} = \frac{D_{AB}^2 - (Z_{AA} + Z_{BB})}{-2} \left[ \frac{Z_{AB}}{\sqrt{Z_{AA} Z_{BB}}} \right] \]
\[ = \left[ \frac{\int f_B^0(r) f_B^0(r') dv(r) dr}{(\eta_A + \eta_B) - 2J} \right] \]
\[ \times \left[ \frac{\left( \frac{\mu_A^2}{2\omega_A} \right) + \left( \frac{\mu_B^2}{2\omega_B} \right)}{\left( \frac{Z_{AB}}{\sqrt{Z_{AA} Z_{BB}}} \right)} \right]^2 \] (51)

\[ - (Z_{AA} + Z_{BB}) \times 2^{-1} \left[ \frac{Z_{AB}}{\sqrt{Z_{AA} Z_{BB}}} \right] \]
and for the Hodgkin-Richards index (4), used in this study:

$$HR(I_{AB}) = \frac{D_{AB}^2 - (Z_{AA} + Z_{BB})}{2} \left[ \frac{2Z_{AB}(\Omega)}{Z_{AA}(\Omega) + Z_{BB}(\Omega)} \right]$$

$$= \left( \left\{ \int [f^0_B(r) - f^0_A(r)] \, dv(r) \, dr \right. \right.$$  

$$\times \left( \left( \frac{\mu^2}{2\omega} \right)_A + \left( \frac{\mu^2}{2\omega} \right)_B \right)$$  

$$- 2 \left\{ \left\{ f^0_A(r) \, f^0_B(r') \, dr \, dr' \right\} \right\}^{-1} \right) \right) \right)^2$$  

$$- (Z_{AA} + Z_{BB}) \times -2^{-1} \left[ \frac{2Z_{AB}}{Z_{AA} + Z_{BB}} \right] \right).$$

(52)

Using (51) and (52) we can obtain the global quantum similarity of the Fukui functions from the electronic point of view, through the Carbó and Hodgkin-Richards index, respectively. Due to the direct proportionality among the Coulomb and overlap operators is shows the similarity of the Fukui functions from point of view steric through the Dirac delta in (50) as

$$D_{AB} \equiv \int [f^0_B(r) - f^0_A(r)] \, dv(r) \, dr$$

$$\left( \left( \frac{\mu^2}{2\omega} \right)_A + \left( \frac{\mu^2}{2\omega} \right)_B \right) - 2 \left\{ \left\{ f^0_A(r) \, \delta(r - r') \, f^0_B(r') \, dr \, dr' \right\} \right\}^{-1} \right) \right)^2$$

obtaining for the Carbó index of (51):

$$I_{AB} = \left( \left\{ \int [f^0_B(r) - f^0_A(r)] \, dv(r) \, dr \right. \right.$$  

$$\times \left. \left( \left( \frac{\mu^2}{2\omega} \right)_A + \left( \frac{\mu^2}{2\omega} \right)_B \right) \right.$$

$$- 2 \left\{ \left\{ f^0_A(r) \, \delta(r - r') \, f^0_B(r') \, dr \, dr' \right\} \right\}^{-1} \right) \right)^2$$  

$$- (Z_{AA} + Z_{BB}) \times -2^{-1} \left[ \frac{Z_{AB}}{\sqrt{Z_{AA}Z_{BB}}} \right] \right).$$

(54)

and for the Hodgkin-Richards index (52)

$$HR(I_{AB})$$

$$= \left( \left\{ \int [f^0_B(r) - f^0_A(r)] \, dv(r) \, dr \right. \right.$$  

$$\times \left. \left( \left( \frac{\mu^2}{2\omega} \right)_A + \left( \frac{\mu^2}{2\omega} \right)_B \right) \right.$$  

$$- 2 \left\{ \left\{ f^0_A(r) \, \delta(r - r') \, f^0_B(r') \, dr \, dr' \right\} \right\}^{-1} \right) \right)^2$$

$$- (Z_{AA} + Z_{BB}) \times -2^{-1} \left[ \frac{2Z_{AB}}{Z_{AA} + Z_{BB}} \right] \right).$$

(55)

with the interval of (0, 1] according to the Schwartz integral inequality [58]:

$$\left\{ \int \rho_A(r) \, \rho_B(r) \, dr \right\}^2 \leq \int \rho_A^2(r) \, dr \int \rho_B^2(r) \, dr,$$

(56)

where $\rho_A(r)$ and $\rho_B(r)$ are the electron densities considered.

In this sense, new considerations on the quantum similarity field to relate the local selectivity from the electronic ((51) and (52)) and steric ((54) and (55)) point of view are presented. On the other hand, taking into account the role of the Fukui functions [58] in the chemistry reactivity and the mathematical approximations to compute such functions [57, 59] is necessary presents others mathematical methods that help to characterize the chemical bonds within the topological analysis.

Moreover, the coherence among the overlap and coulomb scales of quantitative convergence reported in this study (see Figure 2 in Table 7) is very important taking in account that the structures, their properties, and reactivity parameters in the compounds studies dependent strictly on the nature of covalent bond in the asymmetric carbon (see Table 1). These bonds provide a basic skeleton of the molecule easily modifiable by the repulsive forces in the case of bulky substituents. Therefore, complements with the electrostatic effects are involved, as for example induction, aromaticity, the molecular symmetry and the electrostatic interactions calculated by the coulomb operator.

5. Conclusions and Perspectives

A theoretical method to quantify the steric and electronic effects in a series of 4-Acetylamino-2-(3,5-dimethylpyrazol-1-yl)-6-pyridylpyrimidinides as $A_{2A}$ Adenosine receptor antagonists for the PD treatment, using Quantum Molecular similarity and global and local reactivity descriptors within of DFT context, was proposed. The overlap and Coulomb Hodgkin-Richards indexes are shown in form of quantitative convergence scales, obtaining the same trend of similarity in both scales, presenting a systematization method of steric and electronic effects in this type of inhibitors that can be
extended to a much larger series of inhibitors for the PD treatment.

To carry out the similarity in local reactivity, the TGS alignment method to solve the open problem of optimal alignment in quantum similarity is taken. Giving, new considerations on the Gaussian orbitals localized theory from the quantum similarity and the local reactivity, which can be applied in a much broader range of receptors antagonists A2A and understand from the electronic and structural point of view the experimental behavior of these compounds, that may be considered in drug design for the treatment of a disease of difficult control as the PD.

Presenting new considerations and alternatives for the characterization of the Fukui functions and taking into account that the Fukui function under a condensation scheme may have ambiguities according to Fukui [58]. In this sense, this contribution presents new insight to create systematic methodologies on the MQS analysis in the Quantitative Structural Activity Relationship (QSAR) methodology.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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