A Quantum-chemical Study of the Relationships Between Electronic Structure and Anti-proliferative Activity of Quinoxaline Derivatives on the HeLa Cell Line

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Abstract: A study of the relationships between electronic structure and anti-proliferative activity of quinoxaline derivatives on the HeLa cell line was carried out. For this QSAR study the technique employed is the Klopman-Peradejordi-Gómez (KPG) method. We obtain a statistically significant equation (R= 0.97 R²= 0.94 adj-R²= 0.91 F (8, 15)=29.50 p<0.000001 and SD=0.06). The results showed that the variation of the activity depends on the variation of the values of eight local atomic reactivity indices. The process seems to be charge and orbital-controlled. Based on the analysis of the result, a partial two-dimensional pharmacophore was built. The results should be useful to propose new molecules which higher activity.

Keywords: Quinoxaline, HeLa Cell Line, KPG Method, QSAR, Pharmacophore, DFT

1. Introduction

HeLa is the first immortalized cell line [1]. This cell line originates from a cervical cancer tumor of a patient named Henrietta Lacks, who later died of her cancer in 1951 [1]. One of the earliest uses of HeLa cells was to develop the vaccine against the polio virus [2]. The genomic and transcriptomic resource for a HeLa cell line based on deep DNA and RNA sequencing was created in 2013 [3]. Several studies are performed to found molecules that inhibit the proliferation of this cell line [4–28]. Theoretical studies were also done and are useful to explain the mechanism, the affinity and the activities of different compounds [26–29]. This work presents the results of the use of the KPG method [30] to obtain quantitative relationships between the electronic structure of quinoxaline derivatives and their anti-proliferative activities on the HeLa cell line.

2. Methods, Models and Calculations

2.1. Methods and Models

For this study we use the Klopman-Peradejordi-Gomez (KPG) method. In 1967, Klopman and Hudson presented a general perturbation model for chemical reactivity including ionic interactions and not restricted only to π electron [31–33]. In their model, the electronic energy change, ΔE, associated with the interaction of atom i of molecule A with atom j of molecule B is given by:

$$\Delta E = \sum_{p} Q_{i} Q_{j} / R_{ij} + (1/2)(\beta_{ij}) \sum_{m} F_{mi} F_{mj} / (E_{m} - E_{m'}) + (1/2)(\beta_{ij}) \sum_{m} \sum_{n} F_{mi} F_{nj} / (E_{m} - E_{n'})$$  

(1)
is the energy of the m-th occupied MO (m' for the empty MOs) of molecule A. n and n' refer to molecule B. The summation on p is over all interacting atom pairs. The first term of the right side of Equation 1 represents the electrostatic interaction between atom with net charges Q_i and Q_j. The next two terms introduce the interactions between occupied MOs of one molecule with the empty MOs of the other molecule and vice versa. As this model represents the interaction energy in terms of atom-atom interactions, it was only a matter of time that someone applied it for pharmacological/biological problems. Then, in 1971, Peradejordi et al published an article where they presented the results of a quantum-chemical study of the structure-activity relationships of tetracycline antibiotics [34]. The authors proposed that the inhibitory rate constants, \( K_i \), can be expressed as:

\[
\log K_i^f = \text{const} \tan t + \log K_i^r
\]  

(2)

where \( K_i^r \) is the ribosome-tetracycline equilibrium constant. Now, let us consider the state of thermodynamic equilibrium and a 1:1 stoichiometry in the formation of the drug-receptor complex:

\[
D_i + R \rightleftharpoons D_iR
\]  

(3)

where \( D_i \) is the drug, \( R \) the receptor and \( D_iR \) the drug-receptor complex. According to statistical thermodynamics the equilibrium constant \( K_i \) is written as:

\[
\log(\text{IC}_{50}) = a + bM_{D_i} + c \log \left[ \sigma_{D_i} / (ABC)^{\frac{1}{2}} \right] + \sum_j \left[ e_jQ_j + f_jS_j^E + g_jS_j^N \right] + \sum_j \left[ j_r(m_jF_j(m_j) + \eta_j \bar{\eta}_j + \omega_j \bar{\omega}_j + z_j \bar{z}_j + w_j \bar{w}_j) \right]
\]  

(7)

where \( a, b, c \) are constants, \( M_{D_i} \) is the drug’s mass, \( \sigma_{D_i} \) its symmetry number and \( ABC \) the product of the drug’s moments of inertia about the three principal axes of rotation. \( Q_j \) is the net charge of atom j, \( S_j^E \) and \( S_j^N \) are, respectively, the total atomic electrophilic and nucleophilic superdelocalizability of Fukui et al., \( F_j(m_j) \) (\( F_j(m_j) \)) is Fukui index of the occupied (vacant) MO \( m(m') \) located on atom j. \( S_j^E(m) \) is the atomic electrophilic superdelocalizability of MO m on atom j, etc. The total atomic electrophilic superdelocalizability of atom j corresponds to the sum over occupied MOs of the \( S_j^E(m) \)’s and the total atomic nucleophilic superdelocalizability of atom j is the sum over vacant MOs of \( S_j^N(m') \)’s. \( \mu_j \) is the local atomic electronic chemical potential of atom j, \( \eta_j \) is the local atomic hardness of atom j, \( \omega_j \) is the local atomic electrophilicity of atom j, \( S_j \) is the local atomic softness of atom j, and \( Q_j^{\text{max}} \) is the maximum amount of electronic charge that atom j may accept from another site. \( O_k \)'s are the orientational parameters of the substituents. Throughout this paper HOMO\(^\text{f} \) refers to the highest occupied molecular orbital localized on atom j and LUMO\(^\text{f} \) to the lowest empty MO localized on atom j.

\[
\Delta \epsilon_i^f = K_i \exp(-\Delta \epsilon_i^f / kT)
\]  

(4)

where \( Q_{D_iR}, Q_{D_i} \) and \( Q_R \) are respectively the total partition functions of the drug-receptor complex, the drug and the receptor; \( k \) is the Boltzmann’s constant and \( T \) is the absolute temperature. \( \Delta \epsilon_i^f \) is the difference between the ground-state energy of \( D_iR \) and the energies of the ground-states of \( D_i \) and \( R \):

\[
\Delta \epsilon_i^f = \epsilon_{D_iR} - (\epsilon_{D_i} + \epsilon_R)
\]  

(5)

Peradejordi et al consider that the partition function terms and the solvation energy are constant. After overs considerations and approximations (for details see [34]), the linear equations is obtained:

\[
\log K_i^f = A + \sum_p \left[ a_pQ_{b_p} + b_pS_{b_p}^E + c_pS_{b_p}^N \right]
\]  

(6)

where \( A, a_p, b_p, c_p \) are constant to be determined \( Q_{b_p} \) is the net charge \( S_{b_p}^E \) is the total atomic electrophilic superdelocalizability of atom p and \( S_{b_p}^N \) is the total atomic nucleophilic superdelocalizability of atom p. Gómez-Jeria continued working the drug-site interaction energy and published the results [35–43]. In 2013, he derived the following equation [44]:

\[
\log K_i^f = 1/2 \sum_t \left[ \log((ABC)^{1/2}) + \sum_j \left[ m_jh_j + x_jS_j^E(m_j) \right] + \sum_j \left[ r_jS_j^N(m_j) + t_jS_j^N(m_j) \right] \right]
\]  

(7)

where the summation over t is over the different substituents of the molecule, \( m_{i,t} \) is the mass of the i-th atom belonging to the t-th substituent, \( R_{i,t} \) being its distance to the atom to which the substituent is attached. This approximation allows him to transform a molecular property into a sum of substituent properties. He proposed that these terms represent...
the fraction of molecules attaining the proper orientation to interact with a given site. He called them Orientational Parameters (OP). The new local atomic reactivity indices (LARIs) of Eq. 7 are defined as follows:

Local atomic electronic chemical potential:

\[ \mu_i = \frac{\epsilon_{\text{HOMO}^*}}{2} + \frac{\epsilon_{\text{LUMO}^*}}{2} \]  

(9)

Local atomic hardness:

\[ \eta_i = \epsilon_{\text{HOMO}^*} - \epsilon_{\text{LUMO}^*} \]  

(10)

Local electrophilic superdelocalizability of the HOMO* of atom i and local nucleophilic superdelocalizability of the LUMO* of atom i:

\[ S_i^{E*} = \frac{F_i \text{HOMO}^*}{\epsilon_{\text{HOMO}}} \]  

(11)

\[ S_i^{N*} = \frac{F_i \text{LUMO}^*}{\epsilon_{\text{LUMO}}} \]  

(12)

The maximal amount of charge atom i may receive:

\[ Q_i^{\text{max}} = -\frac{\mu_i}{\eta_i} \]  

(15)

The physical meaning of these indices is summarized in Table 1.

| Index | Name | Physical meaning |
|-------|------|------------------|
| $Q_i$ | Net atomic charge of atom i | Electrostatic interaction |
| $S_i^E$ | Total atomic electrophilic superdelocalizability of atom i | Total atomic electron-donating capacity of atom i (MO-MO interaction) |
| $S_i^N$ | Total atomic nucleophilic superdelocalizability of atom i | Total atomic electron-accepting capacity of atom i (MO-MO interaction) |
| $S_i^{E*}(m)$ | Orbital atomic electrophilic superdelocalizability of atom i and occupied MO m | Electron-donating capacity of atom i at occupied MO m (MO-MO interaction) |
| $S_i^{N*}(m')$ | Orbital atomic nucleophilic superdelocalizability of atom i and empty MO m' | Electron-accepting capacity of atom i at empty MO m' (MO-MO interaction) |
| $F_i$ | Fukui index of atom i | Total electron population of atom i (MO-MO interaction) |
| $F_{mi}$ | Fukui index of atom i and occupied MO m | Electron population of occupied MO m at atom i (MO-MO interaction) |
| $F_{m'i}$ | Fukui index of atom i and empty MO m' | Electron population of empty MO m' at atom i (MO-MO interaction) |
| $\mu_i$ | Local atomic electronic chemical potential of atom i | Propensity of atom i to gain or lose electrons |
| $\eta_i$ | Local atomic hardness of atom i | Resistance of atom i to exchange electrons with a site |
| $\varsigma_i$ | Local atomic softness of atom i | The inverse of $\mu_i$ |
| $\omega_i$ | Local atomic electrophilicity of atom i | Propensity of atom i to receive extra electronic charge together with its resistance to exchange charge with a site |
| $Q_i^{\text{max}}$ | Maximal amount of electronic charge atom i may receive | Maximal amount of electronic charge that atom i may receive from a donor site |

The Klopman-Peradejordi-Gómez (KPG) method is also discussed in many previous papers [30, 35, 36, 38, 39, 42, 44–46]. From a conceptual perspective, the work presented here is a test of the hypothesis stating that the KPG model can provide a quantitative and formal relationship between the molecular structure and any biological activity. Nowadays, the KPG model produced excellent results in all its applications [35, 44, 46–53].

2.2. Selection of Molecules

For this study, a series of quinoxline derivatives were selected [23]. These molecules have an anti-proliferative activity on the HeLa cell line. The experimental data was taken from a recent study [23]. The structures of the
compounds are shown in Figure 1 and Table 2 which also summarizes the values of their median inhibitory concentrations expressed as log(IC₅₀).

![Figure 1. Structure of quinoxaline derivatives.](image)

Table 2. Quinoxalines and their experimental anti-proliferative activity.

| Mol. | R₁  | R₂  | R₃   | R₄   | R₅   | log(IC₅₀) |
|------|-----|-----|------|------|------|-----------|
| 1    | H   | H   | CH₃  | CH₃  | CH₃  | 1.66      |
| 2    | H   | H   | CH₃  | (CH₃)₂CHCH₂  | CH₃  | 1.35      |
| 3    | H   | H   | CH₃  | CH₃CH₂CH(CH₃)  | CH₃  | 1.58      |
| 4    | H   | Cl  | CH₃  | CH₃  | CH₃  | 1.42      |
| 5    | H   | Cl  | CH₃  | (CH₃)₂CHCH₂  | CH₃  | 1.51      |
| 6    | Cl  | H   | CH₃  | CH₃  | C₆H₄CH₂-  | 1.44      |
| 7    | Cl  | H   | CH₃  | (CH₃)₂CHCH₂  | CH₃  | 1.34      |
| 8    | H   | H   | CH₃  | CH₃  | H     | 1.45      |
| 9    | H   | H   | CH₃  | (CH₃)₂CHCH₂  | H     | 1.29      |
| 10   | H   | H   | CH₃  | CH₃CH₂CH(CH₃)  | H     | 1.48      |
| 11   | H   | Cl  | CH₃  | CH₃  | H     | 1.32      |
| 12   | H   | Cl  | CH₃  | (CH₃)₂CHCH₂  | H     | 1.33      |
| 13   | Cl  | H   | CH₃  | C₆H₄CH₂-  | H     | 1.33      |
| 14   | Cl  | H   | CH₃  | (CH₃)₂CHCH₂  | H     | 1.16      |
| 15   | H   | H   | NH(CH₃)₂  | C₆H₄CH₂-  | CH₃  | 1.48      |
| 16   | H   | H   | NH(CH₃)₂  | CH₃  | CH₃  | 1.43      |
| 17   | H   | H   | NH(CH₃)₂  | (CH₃)₂CHCH₂  | CH₃  | 1.49      |
| 18   | H   | H   | NH(CH₃)₂  | CH₃  | H     | 1.63      |
| 19   | H   | H   | NH(C(H₃)=CH₂)  | CH₃  | CH₃  | 1.59      |
| 20   | H   | H   | NH(C(H₃)=CH₂)  | C₆H₄CH₂-  | CH₃  | 1.01      |
| 21   | H   | H   | NH(CH₃)₂  | C₆H₄CH₂-  | H     | 0.87      |
| 22   | H   | H   | NH(CH₃)₂  | CH₃  | H     | 0.52      |
| 23   | H   | H   | NH(CH₃)₂  | (CH₃)₂CHCH₂  | H     | 1.33      |
| 24   | H   | H   | NH(CH₃)₂  | H     | H     | 1.42      |
| 25   | H   | H   | NH(C(H₃)=CH₂)  | CH₃  | H     | 1.26      |
| 26   | H   | H   | NH(C(H₃)=CH₂)  | CH₃CH₂CH(CH₃)- | H     | 1.63      |
| 27   | H   | H   | NH(C(H₃)=CH₂)  | C₆H₄CH₂-  | H     | 1.18      |

2.3. Calculations

The electronic structure of each fully optimized molecule was obtained using the Density Functional Theory (DFT) at the B3LYP/6-31G (d, p) level with the Gaussian software [54]. The local atomic reactivity indices were calculated from the single point results of Gaussian03 using the D-Cent-QSAR software [55] with a correction for Mulliken populations [56]. All populations of electrons less than or equal to 0.01e are considered null [56]. The orientational parameters of the substituents are calculated in the usual manner [57, 58]. We have used the concept of common skeleton defined as a set of atoms common to all the molecules analyzed. We hypothesize that the variation of the numerical values of the local atomic reactivity indices (LARIs) of the atoms of this common skeleton accounts for almost all the variation of the biological activity. As the number of LARIs involved is greater than the number of molecules, the solving of the linear systems of equations is not possible. For this reason we employed the technique of multiple linear regression analysis (LMRA) to determine the
atoms that are directly involved in the variation of the biological activity. The data matrix contains log (IC$_{50}$) as a dependent variable, and the local indices of atomic reactivity of all the atoms of the common skeleton as independent variables. The Statistica 10 software was used to perform LMRA studies [59]. The numbering of the common skeleton atoms is shown in Figure 2.

Figure 2. Common skeleton numbering.

3. Results

The best statistically significant equation obtained is the following:

$$\log(\text{IC}_{50}) = -33.32 + 1.69F_{21}(\text{HOMO})^* - 2.61S_{21}^E + 0.04S_{16}^N - 78.05Q_{16} - 0.12F_{23}(\text{HOMO})^* - 1.28F_{15}(\text{LUMO})^* + 0.69F_{20}(\text{HOMO})^* + 0.0015S_{22}^N(\text{LUMO})^*$$

(16)

with n=24, R= 0.97, R$^2$= 0.94, adj-R$^2$= 0.91, F(8.15)=29.50, (p<0.000001) and a standard error of estimate of 0.06. No outliers were detected and no residuals fall outside the ±2σ limits. Here $F_{21}(\text{HOMO})^*$ is the electron population (Fukui index) of the highest occupied MO localized on atom 21, $S_{21}^E$ is the total atomic electrophilic superdelocalizability of atom 21, $S_{16}^N$ is the total atomic nucleophilic superdelocalizability of atom 16, $Q_{16}$ is the net charge of atom 16, $F_{23}(\text{HOMO})^*$ is the Fukui index of the highest occupied MO localized on atom 23, $F_{15}(\text{LUMO})^*$ is the Fukui index of the first lowest vacant MO localized on atom 15, $F_{20}(\text{HOMO})^*$ is the electron population of the highest occupied MO localized on atom 20 and $S_{22}^N(\text{LUMO})^*$ is the atomic nucleophilic superdelocalizability of the first lowest vacant MO localized on atom 22. Table 3 shows the beta coefficients and the t-test results for the significance of coefficients of equation 1. Concerning independent variables, Table 4 shows that the highest internal correlation is $r^2[F_{20}(\text{HOMO})^*, F_{23}(\text{HOMO})^*]=0.43$. Figure 3 shows the plot of observed values vs. calculated values of log(IC$_{50}$). The associated statistical parameters of Eq.16 show that this equation is statistically significant and that the variation of the numerical values of eight LARIs explains about 91% of the variation of the biological activity.

Table 3. Beta coefficients and t-test for significance of coefficients in equation 1.

| Term            | Beta  | t(10) | p-level     |
|-----------------|-------|-------|-------------|
| $F_{21}(\text{HOMO})^*$ | 0.70  | 7.44  | <0.0000002  |
| $S_{21}^E$      | -1.11 | -10.08| <0.000000   |
| $S_{16}^N$      | 0.97  | 7.67  | <0.0000001  |
| $Q_{16}$        | -0.43 | -5.06 | <0.0001     |
| $F_{23}(\text{HOMO})^*$ | -0.26 | -3.51 | <0.003      |
| $F_{15}(\text{LUMO})^*$ | -0.31 | -3.26 | <0.005      |
| $F_{20}(\text{HOMO})^*$ | 0.34  | 3.23  | <0.006      |
| $S_{22}^N(\text{LUMO})^*$ | 0.28  | 2.61  | <0.02       |
Figure 3. Plot of predicted vs. observed log(IC50) values. Dashed lines denote the 95% confidence interval.

Table 4. Squared correlation coefficients for the variables appearing in equation 16.

|                   | $S_{21}^2$ | $S_{16}^2$ | $Q_{16}$ | $F_{23}(HOMO)^*$ | $F_{15}(LUMO)^*$ | $F_{20}(HOMO)^*$ |
|-------------------|------------|------------|----------|------------------|------------------|------------------|
| $S_{21}^2$        | 0.004      | 1.00       |          |                  |                  |                  |
| $S_{16}^2$        | 0.02       | 0.3        | 1.00     |                  |                  |                  |
| $Q_{16}$          | 0.002      | 0.034      | 0.2      | 1.00             |                  |                  |
| $F_{23}(HOMO)^*$  | 0.08       | 0.05       | 0.1      | 0.0001           | 1.00             |                  |
| $F_{15}(LUMO)^*$  | 0.001      | 0.03       | 0.4      | 0.07             | 0.03             | 1.00             |
| $F_{20}(HOMO)^*$  | 0.4        | 0.06       | 0.00004  | 0.03             | 0.01             | 0.002            |
| $S_{20}^2(LUMO)^*$| 0.01       | 0.3        | 0.3      | 0.2              | 0.04             | 0.19             |

Local Molecular Orbitals

Tables 5 and 6 show the Local Molecular Orbitals of atom 5, 10, 20, 21, 22 and 23 (see Figure 3). Nomenclature: Molecule (HOMO) / (HOMO-2)* (HOMO-1)* (HOMO)* - (LUMO)* (LUMO+1)* (LUMO+2)*.

Table 5. Local Molecular Orbitals of atoms 10, 15 and 20.

| Mol | Atom 10 (C) | Atom 15 (C) | Atom 20 (C) |
|-----|-------------|-------------|-------------|
| 1(96)| 92e93e96e-97e98e99e | 94e95e96e-97e98e100e | 86e90e94e-103e107e109 |
| 2(108)| 104e105e108e-109e110e111e | 106e107e108e-109e110e112e | 99e100e106e-114e115e118e |
| 3(116)| 113e115e116e-117e118e119e | 114e115e116e-117e118e120e | 107e112e114e-122e124e127e |
| 4(104)| 101e103e104e-105e106e107e | 102e103e104e-105e106e108e | 93e98e102e-112e115e118e |
| 5(116)| 113e115e116e-117e118e119e | 114e115e116e-117e118e120e | 107e111e114e-122e124e127e |
| 6(124)| 118e119e122e-125e126e127e | 120e121e122e-125e126e128e | 120e121e124e-130e132e134e |
| 7(116)| 112e113e116e-117e118e119e | 114e115e116e-117e118e120e | 108e111e115e-122e124e127e |
| 8(92)| 88e89e92e-93e94e95e | 90e91e92e-93e94e96e | 81e86e90e-96e100e106e |
| 9(104)| 100e101e104e-105e106e107e | 102e103e104e-105e106e108e | 97e98e102e-111e112e116e |
| 10(104)| 100e101e104e-105e106e107e | 102e103e104e-105e106e108e | 97e98e102e-111e112e116e |
| 11(100)| 97e99e100e-101e102e103e | 98e99e100e-101e102e104e | 89e94e98e-106e108e110e115e |
| 12(112)| 109e111e112e-113e114e115e | 110e111e112e-113e114e116e | 104e106e110e-118e120e121e |
| 13(120)| 114e115e118e-121e122e123e | 116e117e118e-121e122e124e | 110e112e116e-126e128e130 |
| 14(112)| 109e110e112e-113e114e115e | 110e111e112e-113e114e116e | 106e110e111e-118e120e122e |
| 15(164)| 160e162e164e-168e171e77e | 160e162e164e-165e166e167e | 158e159e163e-169e171e173e |
| 16(144)| 142e143e144e-148e150e159e | 142e143e144e-145e146e147e | 125e138e140e-151e157e163e |
| 17(156)| 154e155e156e-160e162e171e | 154e155e156e-157e158e159e | 145e153e154e-161e163e166e |
| 18(140)| 138e139e140e-144e146e167 | 138e139e140e-141e142e143e | 119e134e137e-147e154e161e |
| 19(112)| 109e111e112e-116e118e122e | 110e111e112e-113e114e115e | 106e110e110e-119e127e128e |
4. Discussion

The HeLa inhibition mechanism is unknown. We have stated that it is important to stress that our hypothesis covers multi-step (for example, in the n-th step molecules must cross a pore) and multimechanistic (for example, to cross the pore molecules must interact consecutively with j unknown sites) processes. Therefore it seems logical to state that a necessary condition to obtain good structure-activity relationships is that all the steps and all the mechanisms inside each step must be the same for all the group of molecules under study) [44]. If the molecules studied here employ multi-step and/or multimechanistic action mechanisms that are not exactly the same for all, we may expect that the linear multiple regression results contain sometimes variables whose interpretation seems contradictory.

The beta values shows that the importance of variables is $S_{21}^{E} > S_{16}^{N} > F_{21}(HOMO)^{*} > Q_{16} > F_{20}(HOMO)^{*} > F_{15}(LUMO)^{*} > S_{20}^{N}(LUMO)^{*} > F_{23}(HOMO)^{*}$. The process seems to be charge and orbital-controlled. A variable-by-variable analysis indicates that a good activity is associated with low negative numerical values of $S_{21}^{E}$ (they are always negative) and $Q_{16}$, with low numerical values of $F_{21}(HOMO)^{*}$ and $F_{20}(HOMO)^{*}$ (their values are always positive) and with high numerical values for $F_{15}(LUMO)^{*}$ and $F_{23}(HOMO)^{*}$. If $S_{22}^{N}(LUMO)^{*}$ is positive, a high inhibitory activity is associated with low numerical values. If $S_{16}^{N}$ is positive, a good activity is associated with low numerical values for this index.

Atom 21 is a carbon atom in the lateral chain of ring C (Figure 2). Table 6 shows that all local MO have $\sigma$ nature. A low value of $S_{21}^{E}$, with low negative numerical values of $S_{21}^{N}$ (they are always negative) and $Q_{16}$, with low numerical values of $F_{21}(HOMO)^{*}$ and $F_{20}(HOMO)^{*}$ (their values are always positive) and with high numerical values for $F_{15}(LUMO)^{*}$ and $F_{23}(HOMO)^{*}$. If $S_{22}^{N}(LUMO)^{*}$ is positive, a high inhibitory activity is associated with low numerical values. If $S_{16}^{N}$ is positive, a good activity is associated with low numerical values for this index.

4(160) 158s158106s164s168s174σ 156s158s160s161s162s163σ 152s154s155s163σ167σ169σ
22(140) 138s139s140s144s146s155σ 138s139s140s141s142s143σ 134s136s137s147s148s162σ
23(152) 150s151s152s156s158s168σ 150s151s152s153s154s155σ 146s148s149s157s159s160σ
24(136) 134s135s136s140s142s148σ 134s135s136s137s138s139σ 132s133s134s143s144s157σ
25(108) 106s107s108s112s114s119σ 106s107s108s109s110s111σ 102s104s105s110s115s123σ
26(120) 118s119s120s124s126s133σ 118s119s120s121s122s123σ 114s116s117s125s127s129σ
27(128) 124s126s128s132s136s141σ 124s126s128s129s130s131σ 120s122s123s133s135s137σ

Table 6. Local Molecular Orbitals of atoms 21, 22 and 23.
definition of \( S^N_{16} \), the dominant term is \( S^N_{16}(\text{LUMO})^* \). Low numerical values are obtained by shifting upwards the energy of the empty MOs, making this atom a bad electron acceptor. Therefore, we suggest that atom 16 is interacting with an electron deficient center. On the other hand, Eq. 16 shows that a high inhibitory activity is related with a positive value for \( Q_{16} \), fact that seems to be contradictory with the interaction with an electron deficient center. Examining Table II we may see that \( S^N_{16} \) is more significant than \( Q_{16} \). Therefore, and as a first approximation, we shall not consider \( Q_{16} \). Atom 20 is a carbon atom of the side chain of ring C (Figure 2). All local MOs have \( \sigma \) nature (Table 6). A low value for \( F_{20}(\text{HOMO})^* \) suggests that atom 20 is probably interacting with a center rich in \( \sigma \) electrons. Note that this condition is the same that the one for atom 21. Atom 22 is the carbon atom of the carboxylate moiety of the side chain of ring C (Figure 2). \( L(\text{LUMO})^* \) is a \( \pi \) MO in all molecules (Table 6). A low value for \( F_{22}(\text{LUMO})^* \) suggests that the lowest unoccupied local MO is interacting with an electron rich center. Atom 23 is an oxygen atom of the carboxylate moiety in the side chain of ring C (Figure 2). A high value for \( F_{23}(\text{HOMO})^* \) suggests that the highest occupied local MO is interacting with an electron deficient center. All the above suggestions are shown in the partial 2D pharmacophore of Figure 4.

5. Conclusion

We obtained a statistically significant relationship between the variation of the anti-proliferative activity of some quinoxaline derivatives and the variation of the numerical values of a set of local atomic reactivity indices. This allowed us to build the associated pharmacophore that should serve as a starting point for chemical modifications producing more active compounds. According to the obtained pharmacophore, it is not necessary to modify the indices of the atoms of the quinoxaline cycle. But the indices which would be modified to improve the anti-proliferative activity are those from the side chain.

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