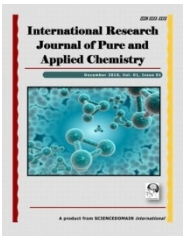

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A Theoretical Study of the Relationships between Electronic Structure and Anti-inflammatory and Anti-cancer Activities of a Series of 6,7-substituted-5,8-Quinolinequinones

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Author's contribution

This whole work was carried out by the author JSGJ.

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ABSTRACT

We report the results of the search of quantum-chemical model-based relationships between electronic structure and anti-inflammatory and antiproliferative activity against HL60 and T-cells of a group of 6,7-substituted-5,8-quinolinequinones. The wave functions and local atomic reactivity indices were obtained at the ab initio Hartree-Fock 6-311G (d,p) level of theory. We found and discussed several significant relationships explaining the variation of anti-inflammatory and anti-proliferative activity in terms of the variation of very definite and distinct sets of local atomic reactivity indices belonging to specific atoms of a common molecular skeleton. The variation of anti-inflammatory and anti-cancer activities seems to occur through very different mechanisms. It is shown that σ molecular orbitals localized on certain atoms could play an important function in controlling biological activity. The working hypothesis stating that a model built for in vitro drug-receptor interactions is useful for the study of other biological activities is supported by the results presented here.

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Keywords: *6,7-substituted-5; 8-quinolinequinones; QSAR; local atomic reactivity indices; anti-cancer activity; anti-inflammatory activity; anti-proliferative activity; Quantum Chemistry.*

1. INTRODUCTION

Human beings are the result of a very long evolutionary process. During this progression highly specific biological structures, such as receptors, were developed. These structures must recognize in a very specific way certain molecules (their endogenous ligands) to bind them and maintain the whole biological system working properly. Some synthetic ligands target these receptors, while others have anti-cancer, anti-influenza, anti-inflammatory, anti-fungal, etc. activities, being all them one of the great achievements of modern science. Structure-activity studies help to understand action mechanisms, the final goal being the production of enough knowledge to obtain molecules with more effective action and lacking unwanted side effects. Quantum chemistry, through the description of molecular/electronic structure, is one of the tools serving to accomplish these purposes. Quinoline is a heterocyclic aromatic nitrogen compound characterized by a double-ring structure containing a benzene ring fused to pyridine at two adjacent carbon atoms [1]. This basic skeleton, present in various pharmacologically active synthetic and naturally occurring compounds, is part of the building blocks for several antimalarial drugs. Apart from antimalarial activities, quinolines are also known for their antimicrobial, analgesic, cardiovascular, anticancer and anti-inflammatory activities [2-4]. Interestingly, these activities seem to be dependent on the nature and position of substitution present on the quinoline ring. Several derivatives of 5,8-quinolinequinones are endowed with biological properties including anti-bacterial, anti-tumor and anti-inflammatory activities [5-14] Streptonigrin, lavendamycin and ascidiathiazones A and B are good examples [15-25]. Lavendamycin is not appropriate for clinical use due to its toxicity but some of its analogs are less toxic and consequently have potential as antitumor agents. It is then of interest to try to find relationships between the electronic structure and the biological activities of these systems. Recently, Timmer, Stoker at al. synthesized a group of 6,7-substituted-5,8-quinolinequinones showing promising anti-tumor and anti-inflammatory activities [22]. To provide a first insight into the mechanisms underlying these activities, we present in this paper the results of a quantum-chemical study of the relationships between the electronic structure and anti-inflammatory activity, anti-proliferative activity against HL60 and T-cells of the above molecules.

2. METHODS, MODELS AND CALCULATIONS

2.1 Model

We have developed a formal model to correlate the drug-receptor affinity constant with the electronic and molecular structure of biological molecules [26-31]. This model has shown, beyond all reasonable doubt that it can shed light on the fine structure of the drug-receptor interaction [32-44]. Given that the last paper not belonging to our group, and using the model we are using here was published in 1979, we shall present in the following a comprehensive description of this model. We are doing so to distinguish it very clearly from the statistics-backed methodologies. Let us consider the state of thermodynamic equilibrium, and a 1:1 stoichiometry in the formation of the drug-receptor complex:

$$D_i + R \leftrightharpoons D_i R \quad (1)$$

where D_i is the drug, R is the receptor and D_iR is the drug-receptor complex. According to statistical thermodynamics the equilibrium constant, K_i, is written as [27]:

$$K_i = \frac{Q_{D_iR}}{Q_{D_i} Q_R} \exp(-\Delta\varepsilon_0^i / kT) \tag{2}$$

where $\Delta\varepsilon_0^i$ is the difference between the ground-state energy of D_iR and the energies of the ground states of D_i and R:

$$\Delta\varepsilon_0^i = \varepsilon_{D_iR} - (\varepsilon_{D_i} + \varepsilon_R) \tag{3}$$

and the Q's are the total partition functions (PF) measured from the ground state (in solution). T and k are the temperature and the Boltzmann constant, respectively. If we consider that for virtually all polyatomic molecules the Boltzmann factors of the excited electronic states are unimportant compared to those of the ground state, we may consider only the electronic ground state in the PF. Also we shall consider that the rotational and vibrational motions are independent and uncoupled and that at body temperature, the vibrational PFs have a value close to 1. Finally, we shall utilize the classical expression for the rotational PF together with the assumption that the rotational PFs of the receptor and the drug-receptor are comparable (this requires that the receptor molecule be much greater that the drug molecule). In logarithmic form, Eq. 2 transforms into:

$$\log K_i = a + bM_{D_i} + c\log\left[\sigma_{D_i} / (ABC)^{1/2}\right] + d\Delta\varepsilon_i \tag{4}$$

where a, b, c and d are constants, M is the drug's mass, σ its symmetry number and ABC the product of the drug's moment of inertia about the three principal axes of rotation. The interaction energy, $\Delta\varepsilon_0^i$, cannot be determined directly, either due to the dimension of the receptor or to the lack of information of its molecular structure. However, as we are dealing with a weak drug-receptor interaction, we can utilize Perturbation Theory in the Klopman-Hudson form to estimate $\Delta\varepsilon_0^i$ [45-47]. According to this scheme, the change in electron energy, ΔE, associated with the interaction of atoms i and j is [28]:

$$\Delta\varepsilon = \sum_p \left[Q_i Q_j / R_{ij} + (1/2)(\beta_{ij}^2) \sum_m \sum_n D_{mi} D_{n'j} / (E_m - E_{n'}) - (1/2)(\beta_{ij}^2) \sum_m \sum_{'n} D_{m'i} D_{nj} / (E_{m'} - E_n) \right] \tag{5}$$

where Q_i is the net charge of atom i, F_{mi} is the Fukui index of atom i in the MO m, β_{ij} is the resonance integral and E_m ($E_{m'}$) is the energy of the m-th (m'-th) occupied (virtual) MO of molecule A, n and n' standing for molecule B. The value of β_{ij} is kept independent of the kind of AO because the A-B complex does not involve covalent bonds. The summation on p is over all pairs of interacting atoms. A recent working on the expression for $\Delta\varepsilon$ allowed us to include new local atomic reactivity indices [30,31,48]. The final expression for $\Delta\varepsilon$ is:

$$\Delta\varepsilon = \sum_j \left[e_j Q_j + f_j S_j^E + s_j S_j^N \right] +$$
$$+ \sum_j \sum_m \left[h_j(m) F_j(m) + x_j(m) S_j^E(m) \right] + + \sum_j \sum_{m'} \left[r_j(m') F_j(m') + t_j(m') S_j^N(m') \right] +$$
$$+ \sum_j \left[g_j \mu_j + k_j \eta_j + o_j \omega_j + z_j \varsigma_j + w_j Q_j^{\max} \right] \quad (6)$$

where Q_i is the net charge of atom *i*, S_i^E and S_i^N are, respectively, the total atomic electrophilic and nucleophilic superdelocalizabilities of Fukui et al., $F_{i,m}$ is the Fukui index of atom i in occupied (empty) MO m (m') [48]. $S_i^E(m)$ is the atomic electrophilic superdelocalizability of atom i in MO m, etc. The total atomic electrophilic superdelocalizability (ESD) of atom i is defined as the sum over occupied MOs of the $S_i^E(m)$'s and the total atomic nucleophilic superdelocalizability (NSD) of atom i is defined as the sum over empty MOs of the $S_i^N(m')$'s. S_i^E is related with the total electron-donating capacity of atom i and S_i^N with its total electron-accepting capacity. These indices are very helpful to compare the reactivity of similar atomic positions through a series of molecules because they include the eigenvalue spectrum which is habitually different in each molecular system. The orbital components, $S_i^E(m)$ and $S_i^N(m')$, become important when fine aspects of the drug-receptor interaction are needed for a more comprehensive explanation. The last bracket of the right side of Eq. 6 contains the new local atomic indices obtained by an approximate rearrangement of part of the series expansion employed in the model . μ_i, η_i, ω_i, ς_i and $Q_i^{\max}$ are respectively, the local atomic electronic chemical potential of atom i, the local atomic hardness of atom i, the local electrophilicty of atom i, the local atomic softness of atom i and the maximal quantity of electronic charge atom i can receive It is important to notice that these new local atomic reactivity indices (LARIs) are similar to the ones used in Density Functional Theory (DFT), being their difference in that they are expressed in the same units (i.e., eV) than the global ones and not in eV·e as the projected local reactivity indices. For example, the total local atomic electronic chemical potential of atom i, μ_i, is defined as:

$$\mu_i = \frac{E_{oc}^* - E_{em}^*}{2} \quad (7)$$

where E_{oc}^* is the upper occupied MO located on atom i with a non-zero Fukui index (i.e., with a non-zero electron population) and E_{em}^* is the lowest empty MO located on atom i with a non-zero Fukui index (i.e., with a non-zero electron population). Physically, μ_i corresponds to the mid-point between E_{oc}^* and E_{em}^*. μ_i is then a measure of the propensity of an atom to gain or lose electrons; a large negative value indicates a good electron acceptor atom whereas a small negative value implies a good electron donor atom.

The total local atomic hardness of atom i, η_i, is defined as:

$$\eta_i = E_{em}^* - E_{oc}^* \quad (8)$$

and it corresponds to the distance between the energies of the local frontier molecular orbitals HOMO* and LUMO*. The local atomic hardness is simply the local HOMO-LUMO gap. A high value of this local reactivity index is interpreted as the resistance of an atom to exchange electrons with the milieu.

The total local atomic softness of atom i, ς_i, is defined as the inverse of the local atomic hardness. The local electrophilic index of atom i, ω_i, is defined as:

$$\omega_i = \frac{\mu_i^2}{2\eta_i} \tag{9}$$

The local atomic electrophilic index is related with the electrophilic power of an atom and includes the predisposition of the electrophile atom to receive extra electronic charge together with its resistance to exchange charge with the medium. The maximal amount of electronic charge that an electrophile may accept, Q_i^{max}, is defined as:

$$Q_i^{\max} = \frac{-\mu_i}{\eta_i} \tag{10}$$

The insertion of Eq. 6 into Eq. 4 lead to the master equation 11:

$$\begin{aligned}\log K_{i} = a + bM_{D_i} + c\log\left[\sigma_{D_i}/(ABC)^{1/2}\right] + \sum_j \left[e_j Q_j + f_j S_j^E + s_j S_j^N\right] + \\ + \sum_j \sum_m \left[h_j(m)F_j(m) + x_j(m)S_j^E(m)\right] + \sum_j \sum_{m'} \left[r_j(m')F_j(m') + t_j(m')S_j^N(m')\right] + \\ + \sum_j \left[g_j\mu_j + k_j\eta_j + o_j\omega_j + z_j\varsigma_j + w_j Q_j^{\max}\right]\end{aligned} \tag{11}$$

Then, for n molecules we have a system of n linear equations. *The most important attribute of this equation is that contains terms associated only to the drug molecule*.
It was shown that the moment of inertia term of Eq. 11 it can be transformed into the approximate form [29, 36]:

$$\log\left[(ABC)^{-1/2}\right] = \sum_t \sum_t m_{i,t} R_{i,t}^2 = \sum_t O_t \tag{12}$$

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 us to transform a molecular property into a sum of substituent properties. We proposed that these terms represent the fraction of molecules attaining the proper orientation to interact with a given site. We have called them Orientation Parameters.

On the other hand, there are several kinds of molecules exerting their biological actions through mechanisms that do not correspond to equilibrium constants (or receptor affinities). Two examples are anti-inflammatory and anti-tumoral activities. We face then the problem of

providing a scientific basis for the reliability of the use of equation 11 for other classes of systems such as drugs exerting their activity *in vitro* but throughout two or more steps, or drugs with pharmacological effects measured and reported *in vivo*. The general problem can be stated in this way: Let us consider a group of molecules whose final biological action (BA) occurs after two or more unknown steps that are the same for all molecules. These steps may be weak interactions with one or more sites, passage through one or more membranes, partition between two phases, etc. Cammarata et al. showed that the logarithm of the water/octanol partition coefficient (log P), that can be used in a first approximation as a good descriptor of membrane crossing, can be represented adequately in terms of net charges and superdelocalizabilities appearing in equation 11 [49-51]. Then, if on the one hand equation 11 represents a drug-site interaction and on the other hand Cammarata's model describes well the passage through membranes and given that both equations are linear functions of the same local atomic reactivity indices, a preliminary representation of the final biological action can be obtained simply by replacing log K_i *by* log (BA). This is the working hypothesis we shall test in this study. Several previous studies give some support to this hypothesis. More than two decades ago we combined results from a shorter version of equation 11 with an empirical relationship between receptor affinity and human hallucinogenic activity. With this combination we succeeded in predicting the hallucinogenic activity of (±)-1-(2,5-dimethoxy-4-nitrophenyl)-2-aminopropane and the approximate effective dose humans could take [52,53]. In the second study, interesting results were obtained for the relationship between accumulation data and molecular structure in a group of polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans and polychlorinated biphenyls in Gold Rush, Black Beauty and Patty Green zucchini subspecies [54]. In the third one, we obtained good results concerning structure-biological activity relationships for two different sets of molecules displaying inhibitory activity against some effects of HIV-1 (inhibition of HIV-induced cytopathicity, cytostatic effects and inhibitory activity against Reverse Transcriptase) and H1N1 (reduction of the H1N1-induced cytopathic effects) viruses [55]. A study of the inhibition of HIV-1 WT replication by some phenylaminopyridine derivatives and the inhibition of cell growth in various cell lines by several 1-azabenzanthrone derivatives provided an interesting insight on the action mechanisms [56]. Finally, solid structure-activity relationships were obtained for the relationships between electronic structure and pharmacokinetic profile, inhibitory strength toward hepatitis C virus NS5B polymerase and HCV replicons of several indole-based compounds [57]. These results seem to suggest that the approach employed here is suitable for our purposes.

2.2 Selected Molecular Systems

The molecules chosen for this study are shown in Fig. 1 and Table 1, together with the corresponding experimental biological activities (from left to right in Table 1, columns 4-6: anti-inflammatory activity, anti-proliferative activity against HL60-cells and anti-proliferative activity against T-cells).

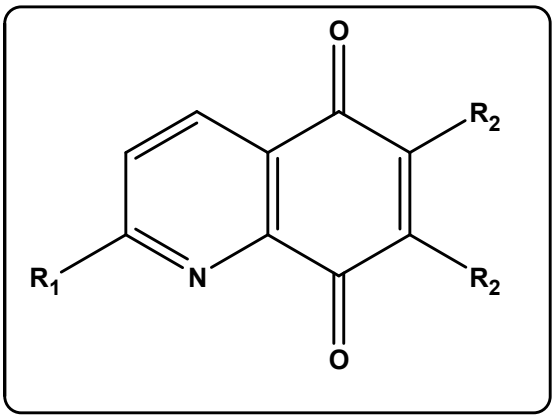

Fig. 1. General formula of the molecules employed in this study

Table 1. Molecules and their experimental biological activities

Molecule	R_1	R_2	R_3	Exp. log(AI_{50}) (μM)	Exp. log(IC_{50}) HL-60 (μM)	Exp. log(IC_{50}) T-cells (μM)
1	-H	-Cl	-Cl	0.11	1.50	1.52
2	-Me	-Cl	-Cl	0.53	1.27	1.65
3	-H	$-NH_2$	-Cl	----	0.5	0.31
4	-H	$-NH(CH)Phe_2$	-Cl	1.53	0.39	0.41
5	-H	-NHMe	-Cl	1.90	0.39	0.55
6	-H	-Cl	-NHMe	1.6	0.63	0.72
7	-H	$-NH(CH_2)_2Br$	-Cl	1.30	0.22	0.41
8	-H	-Cl	$-NH(CH_2)_2Br$	1.32	0.08	0.40
9	-H	$-NH(CH_2)_2Cl$	-Cl	1.57	0.21	0.36
10	-H	-Cl	$-NH(CH_2)_2Cl$	1.49	0.29	0.36
11	-Me	$-NH(CH_2)_2Br$	-Cl	1.53	0.11	0.35
12	-Me	-Cl	$-NH(CH_2)_2Br$	1.86	0.08	0.20
13	-H	$-NH_2$	-SMe	----	0.88	0.92
14	-H	-NHMe	-SMe	----	0.54	1.29
15	-H	-SMe	-NHMe	----	0.90	0.88
16	-H	-NHMe	-S-Ph	----	0.90	1.09
17	-H	-S-Ph	-NHMe	1.97	0.77	0.84
18*	-H	$-NH-CH_2-$	$-CH_2S-$	----	0.63	0.77
19*	-H	$-S-CH_2-$	$-CH_2-NH-$	----	0.55	0.78
20	-H	$-NH_2$	-SO-Me	----	0.11	0.29
21	-H	-NHMe	-SO-Me	----	1.08	1.07
22	-H	-SO-Me	-NHMe	----	1.52	1.13
23	-H	$-NH_2$	SO_2-Me	----	0.66	1.29
24	-H	$-SO_2$-Tol	-Cl	----	1.58	1.55
25	-H	-SMe	-SMe	-0.96	0.09	0.23
26	-H	-S-Ph	-S-Ph	1.39	0.57	0.89
27**	-H	-S-Ph	-S-Ph	0.36	0.84	1
28	-H	$-SO_2$-Tol	$-SO_2$-Tol	----	1.79	1.61

** – indicates that R_2 and R_3 are bonded forming a single substituent. **. With OH groups attached to atoms 11 and 12.*

2.3 Calculations

Molecular geometries were fully optimized at the ab initio HF/6-311G(d,p) level of theory. The Gaussian suite of programs was used [58]. With software written in our Laboratory all the necessary information was extracted from the above commercial software and the numerical values for the local atomic reactivity indices were calculated. All electron populations smaller than or equal to 0.01 e were considered as zero. In the case of the HF/6-311G (d,p) calculations, negative electron populations arising from Mulliken Population Analysis were corrected according to a recently proposed technique [59]. The orientational parameters were calculated as usual [29,36].

We worked within the common skeleton hypothesis which states that there is a definite group of atoms, common to all the molecules analyzed, that accounts for nearly all the variation of the biological action throughout the series. The effect of the substituents consists in modifying the electronic structure of this skeleton and/or influencing the correct alignment of the drug through the regulation of the molecular rotation about the three principal axes of rotation. For the case studied here the common skeleton is shown in Fig. 2.

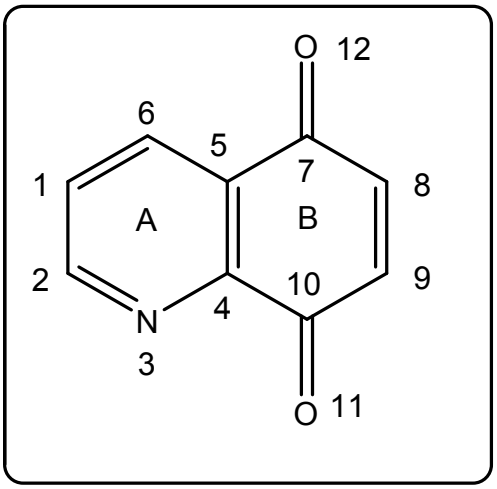

Fig. 2. Common skeleton with atom numbering

As solving the system of n linear equations requires at least n values of biological activities, a condition that is not generally satisfied in papers reporting experimental biological activities, we shall employ statistical techniques to find the best equation for each case. Linear multiple regression analysis (LMRA) was carried out with the Statistica software [60]. The dependent variable is the logarithm of the corresponding biological activity and the independent variables are the set of local atomic reactivity indices of the common skeleton, plus the orientational parameters of the substituents R_1-R_3 (see Fig. 1). Orientational parameters for the substituents were calculated as usual [34]. Here statistical analysis is used, not to see whether there is a structure-activity relationship, but to find the best one. For a full understanding of the results, we must comment on the variable ordering to form the matrix of independent variables. Fig. 3 shows the HOMO, HOMO-1, HOMO-2, LUMO, LUMO+1 and LUMO+2 of atoms I, II and III. The circles indicate non-zero electron populations on each atom/MO [30,44,56,61].

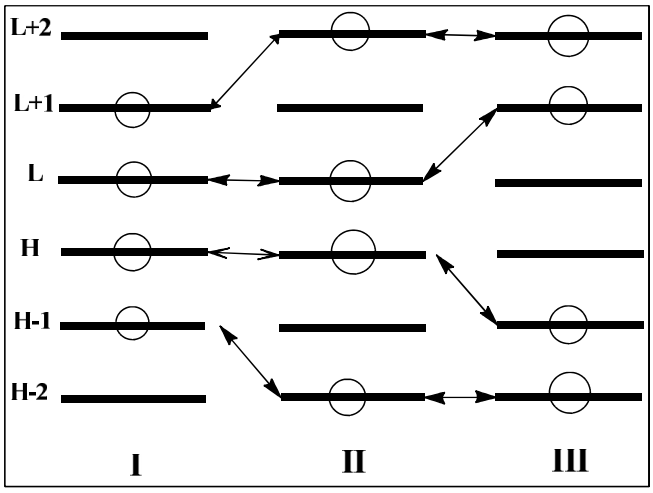

Fig. 3. MO's and electron populations for three atoms. Circles depict those MOs in which an atom has non-zero electron populations. H-2 means HOMO-2, H-1 means HOMO-1, L means LUMO, and so on

Atom I has non-zero electron populations only at the HOMO-1, HOMO, LUMO and LUMO+1 levels. Atom II has non-zero electron populations only at the HOMO-2, HOMO, LUMO and LUMO+2 levels. Atom III has non-zero electron populations only at the HOMO-2, HOMO-1, LUMO+1 and LUMO+2 levels. Note the very important fact that, for example, not all the highest MO localized on each of the three atoms is the same that the molecular HOMO. For this reason we called them the local HOMO and used an * to distinguish them from the molecular HOMO. Note that sometimes both MOs could be the same. These local MOs are the ones really participating in an interaction with a site. For that cause, we have prepared a matrix for LMRA containing only the non-zero values depicted above. This aspect must be taken into account in the analysis of results. The centre of Fig. 4 shows the matrix employed in the LMRA and the right side the new nomenclature used to avoid confusion with the molecular MOs.

$$\left\{\begin{array}{ccc} \text{I} & \text{II} & \text{III} \\ F_i(\text{L+1}) & F_i(\text{L+1}) & F_i(\text{L+1}) \\ F_i(\text{L}) & F_i(\text{L}) & F_i(\text{L}) \\ F_i(\text{H}) & F_i(\text{H}) & F_i(\text{H}) \\ F_i(\text{H-1}) & F_i(\text{H-1}) & F_i(\text{H-1}) \end{array}\right\} \rightarrow \left\{\begin{array}{ccc} \text{I} & \text{II} & \text{III} \\ F_i(\text{L+1}) & F_i(\text{L+2}) & F_i(\text{L+2}) \\ F_i(\text{L}) & F_i(\text{L}) & F_i(\text{L+1}) \\ F_i(\text{H}) & F_i(\text{H}) & F_i(\text{H-1}) \\ F_i(\text{H-1}) & F_i(\text{H-2}) & F_i(\text{H-2}) \end{array}\right\} \rightarrow \left\{\begin{array}{ccc} \text{I} & \text{II} & \text{III} \\ F_i(\text{L+1})^* & F_i(\text{L+1})^* & F_i(\text{L+1})^* \\ F_i(\text{L})^* & F_i(\text{L})^* & F_i(\text{L})^* \\ F_i(\text{H})^* & F_i(\text{H})^* & F_i(\text{H})^* \\ F_i(\text{H-1})^* & F_i(\text{H-1})^* & F_i(\text{H-1})^* \end{array}\right\}$$

Fig. 4. Left side: original matrix data for atom i built from Fig. 3. Centre: final matrix data for atoms containing only non-zero values. Right side: local atomic nomenclature.

3. RESULTS

3.1 Anti-inflammatory Activity (AI_{50})

A preliminary LMRA showed that for molecule 25 the resultant standard residual fell outside the ±2σ limit. We excluded this molecule from a new LMRA and the best equation obtained was:

$$\log(AI_{50}) = 15.72 - 2.23F_{10}(HOMO)^* + 2.91S_7^E(HOMO-2)^* \quad (13)$$

with n=14, R=0.98, R^2=0.97, F(3,10)=101.88 (p<0.000001), outliers>2σ=0 and SD=0.12. Here η_1 is the local hardness of atom 1, $F_{10}(HOMO-1)^*$ is the Fukui index (i.e., the electron population) of the second highest occupied MO with non-zero value localized on atom 10 and $S_7^E(HOMO-2)^*$ is the total local atomic electrophilic superdelocalizability of atom 7 at the third highest local occupied MO with non-zero electron population localized at that atom (see Fig. 2). Concerning independent variables, there are no significant internal correlations at p<0.05. The beta coefficients and t-test for significance of coefficients of Eq. 13 are shown in Table 2. Fig. 5 shows the plot of observed values *vs.* calculated ones. No outliers were detected and no residuals fall outside the ±2σ limits. The associated statistical parameters of Eq. 13 show that this equation is statistically significant, explaining about the 97% of the variation of anti-inflammatory activity.

Table 2. Beta coefficients and t-test for significance of coefficients in Eq. 13

Variable	Beta coefficients	t(10)	p-level
η_1	-1.12	-16.11	<0.0000001
F_{10} (HOMO-1)*	-0.25	-4.41	<0.001
S_7^E (HOMO-2)*	0.23	3.36	<0.007

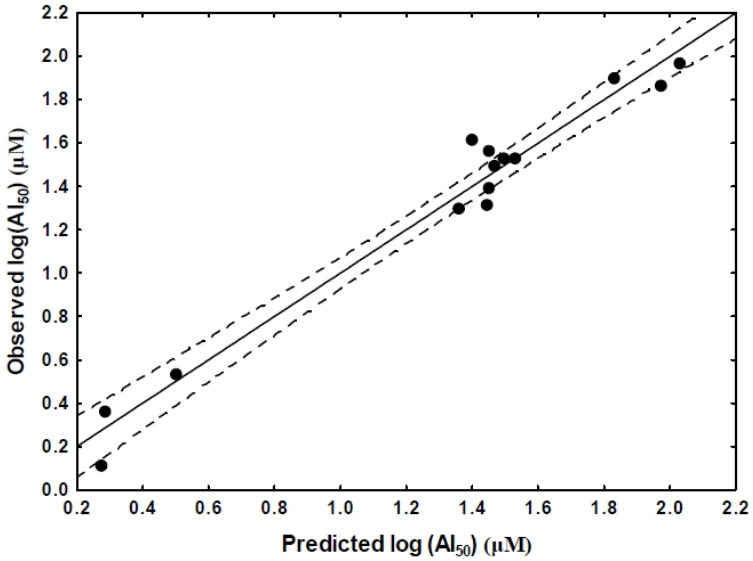

Fig. 5. Plot of predicted (with Eq. 13) vs. observed log AI_{50} values. Dashed lines indicate the 95% confidence interval

3.2 Anti-proliferative activity against HL60-cells (IC_{50})

A first LMRA study was carried out with all molecules. Examination of the results showed that the standard residual of molecule 20 falls outside the ±2σ limits. A new LMRA without molecule 20 provided the following equation:

$$\log(IC_{50}) = -1.24 + 0.47S_4^E(HOMO-1)^* + 2.3F_4(HOMO)^* - 10.19S_1^E - \\ -2.78F_7(HOMO)^* + 1.21F_9(LUMO+1)^* + 2.35F_{11}(HOMO)^* \quad (14)$$

with n=27, R=0.95, R^2=0.91, F(6,20)=32.027 (p<0.000001), outliers>2σ=0 and SD= 0.17. Here, the F's are the Fukui indices of different atoms/MO*s, the S^E_j (MO)* are the different local electrophilic superdelocalizabilities and $S_9^N(LUMO+1)^*$ is the nucleophilic superdelocalizability of atom 9 at the LUMO+1* (the next empty MO after the LUMO*) with non-zero electron population localized on atom 9. Table 3 shows the beta coefficients and the results of the t-test for significance of coefficients for the variables appearing in Eq. 14. No significant internal correlations exist at p<0.05 exist. Fig. 6 shows the plot of observed values *vs.* calculated ones. No outliers were detected and no residual fall outside the ±2σ limits. The associated statistical parameters of Eq. 14 show that this equation is statistically significant, explaining about the 91% of the variation of the anti-proliferative activity against HL60 cells.

Table 3. Beta coefficients and t-test for significance of coefficients in Eq. 14

Variable	Beta coefficients	t(20)	p-level
$S_4^E(HOMO-1)^*$	0.42	-5.04	0.00006
$F_4(HOMO)^*$	0.54	7.08	0.000001
S_1^E	-0.32	-4.15	0.0005
$F_7(HOMO)^*$	-0.35	-4.03	0.0007
$F_9(LUMO+1)^*$	0.23	2.74	0.012
$F_{11}(HOMO)^*$	0.20	2.57	0.018

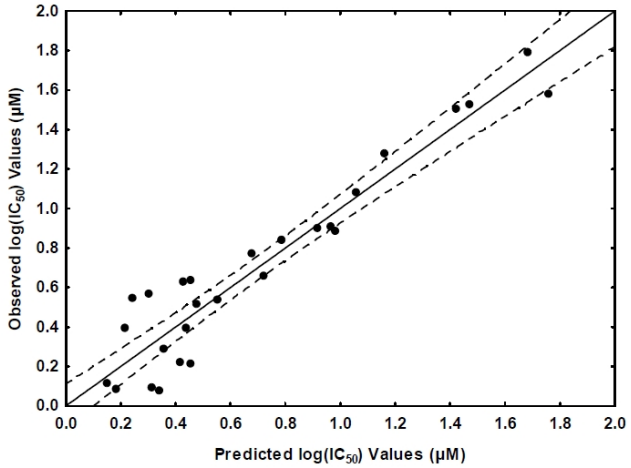

Fig. 6. Plot of predicted (with Eq. 14) vs. observed log IC_{50} values (HL-60 cells). Dashed lines denote the 95% confidence interval.

3.3 Anti-proliferative activity against T-cells (IC_{50}).

Three preliminary and consecutive LMRAs showed that for molecules 14, 20 and 23 the resultant standard residual fell outside the ±2σ limit. Consequently these molecules were excluded from the final LMRA. The best equation obtained was:

$$\log(IC_{50}) = 0.97 - 1.10S_4^E(HOMO)^* - 1.39F_5(HOMO-1)^* - 0.00007\Theta_2 \quad (15)$$

with n=25, R=0.93, R^2=0.86, F(3,21)=42.891 (p<0.000001), outliers>2σ=0 and SD.17.

Here, Θ_2 is the orientational effect of the substituent attached to atom 8 of the common skeleton, S_4^E (HOMO)* is the orbital electrophilic superdelocalizability of the highest occupied MO localized on atom 4 and F_5 (HOMO-1)* is the electron population (Fukui index) of the highest occupied MO localized on atom 5. Table 4 shows the beta coefficients and the results of the t-test for significance of coefficients for the variables appearing in Eq. 15. No significant internal correlations exist at p<0.05. Fig. 7 shows the plot of observed values *vs.* calculated ones. The associated statistical parameters of Eq. 15 show that this equation is statistically significant, explaining about the 86% of the variation of the antiproliferative activity against T-cells.

Table 4. Beta coefficients and t-test for significance of coefficients in Eq. 15

Variable	Beta coefficients	t(21)	p-level
S_4^E *(HOMO)**	-0.74	-9.03	<0.000001
F_5*(HOMO-1)**	-0.58	-6.82	<0.00001
Θ_2	-0.27	-3.17	<0.005

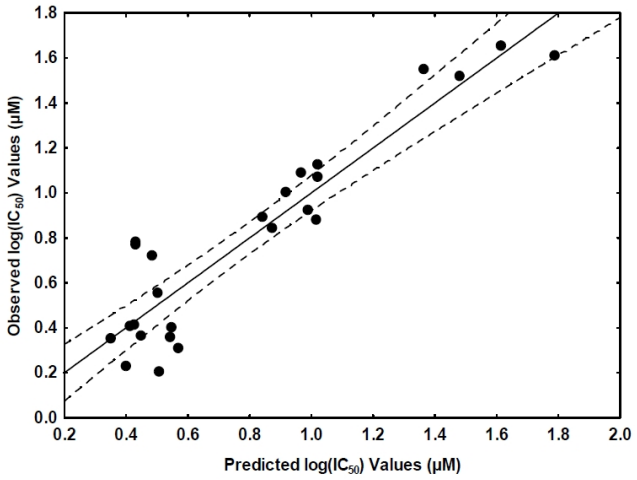

Fig. 7. Plot of predicted (with Eq. 15) vs. observed log IC_{50} values (T-cells). Dashed lines denote the 95% confidence interval

4. DISCUSSION

Our results indicate that, for the three cases analyzed, the variation of the biological activity is related to the variation of a definite set of local atomic reactivity indices belonging to the common skeleton. The results obtained are very good considering the approximations made to build the model [26-29,31]. It is important to point out that, as we are working with the variation of the reactivity indices, the contributions that are constant through the series will not appear in the final equations. For the understanding of the results we must consider the following detail. In the matrix containing the values of the independent variables only non zero values for local Fukui indices and local superdelocalizabilities were incorporated. Now, let us assume that only one of the indices belonging to an inner local occupied MO, for example F_5 *(HOMO-1)*,* appears in the final statistical equation. This means that F_5 *(HOMO)** should also take part in the process but its value does not appear in the equation because, or it is constant in all the molecules, or its *variation* through the series is not statistically significant.

The anti-inflammatory activity (AI_{50}, Eq. 13) was reported as the capacity to block the production of superoxide by activated human neutrophils, a process that seems to occur extracellularly [35,36]. Examining Eq. 13 and knowing that the hardness and the Fukui indices are always positive or zero, and that the electrophilic superdelocalizabilities are always negative [22], we propose that high anti-inflammatory activity is associated with high numerical values for η_1, F_{10}*(HOMO-1)** and S_7^E*(HOMO-2)*.* This statement is for the case when we analyze individually the contribution of each local atomic reactivity index. This is not fully correct because the variation of the biological activity throughout the series is related to the simultaneous variation of the local reactivity indices. This kind of analysis is similar to the ones found in hundreds of experimental Medicinal Chemistry papers ("if we change a methyl by an i-propyl substituent the activity raises", etc.). Nevertheless, and as a first approximation, this analysis might provide useful information for the experimentalist searching for new compounds with enhanced anti-inflammatory activity. As the hardness of atom 1 should be high we may associate this fact with the interaction of this atom with an apolar moiety, such as CH_2 groups. Beta coefficients and the t-test results indicate that hardness of atom 1 is the most important variable. A high numerical value for η_1 means that the distance between the local HOMO* and LUMO* must be great. To elaborate more on this we shall employ molecule 1 as an example. In this case the HOMO and LUMO are located on atom 1 (therefore, for atom 1 HOMO*=HOMO and LUMO*=LUMO). In Fig. 8 we display the HOMO (MO 57) of molecule 1 (see also Fig. 2 for atom numbering), that has π nature (MOs 56 and 55 also have a π nature).

The HOMO is located here in rings A and B (see Fig. 2). We may increase the HOMO-LUMO distance by finding a substitution that removes the localization of the HOMO (i.e., for atom 1 HOMO*≠HOMO) and/or LUMO on atom 1 (i.e., for atom 1 LUMO*≠LUMO), therefore increasing their local energy gap. Another way is by substituting the skeleton so that the HOMO keeps its actual localization but lowers its energy. On the other hand, atoms 7 and 10 are carbon atoms connected to oxygen atoms by double bonds. The requirement for atom 7 is that the local third highest occupied MO (HOMO-2*) should possess a high electron population. This implies that the local HOMO* and local HOMO-1*, having also a non-zero electron population, also participate in the interaction. In the case of molecule 1 and atom 7, HOMO-1*, HOMO-1* and HOMO* correspond, respectively, to molecular MOs 52, 53 and 54. Figs. 9-11 show, respectively, these three MOs.

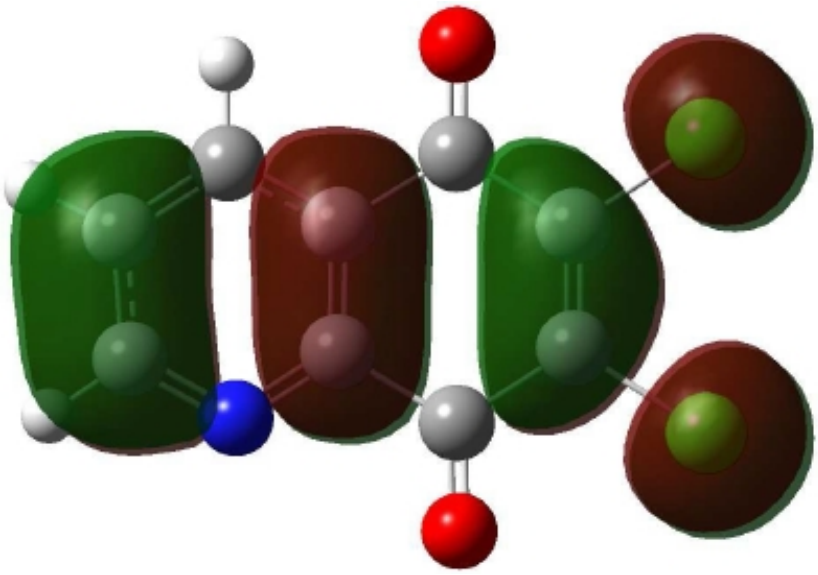

Fig. 8. Highest occupied MO (HOMO) of molecule 1

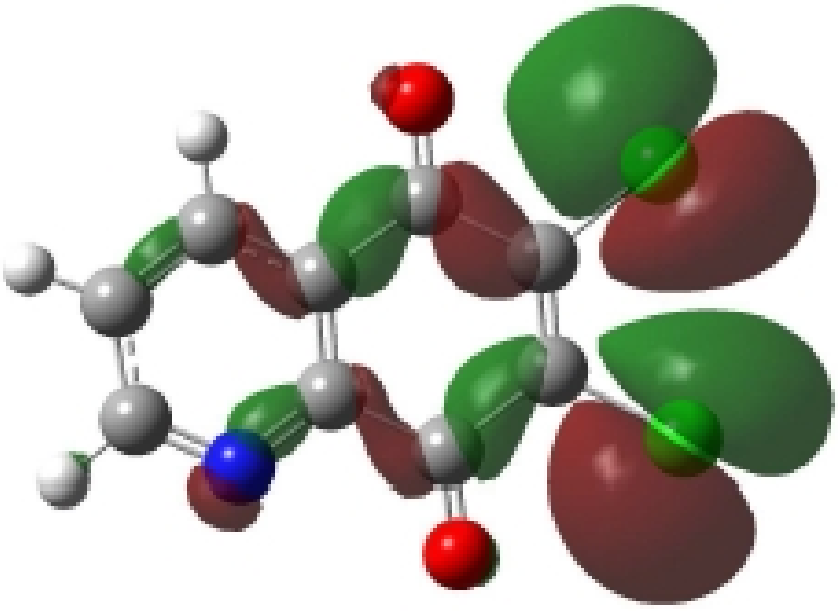

Fig. 9. MO 52 of molecule 1

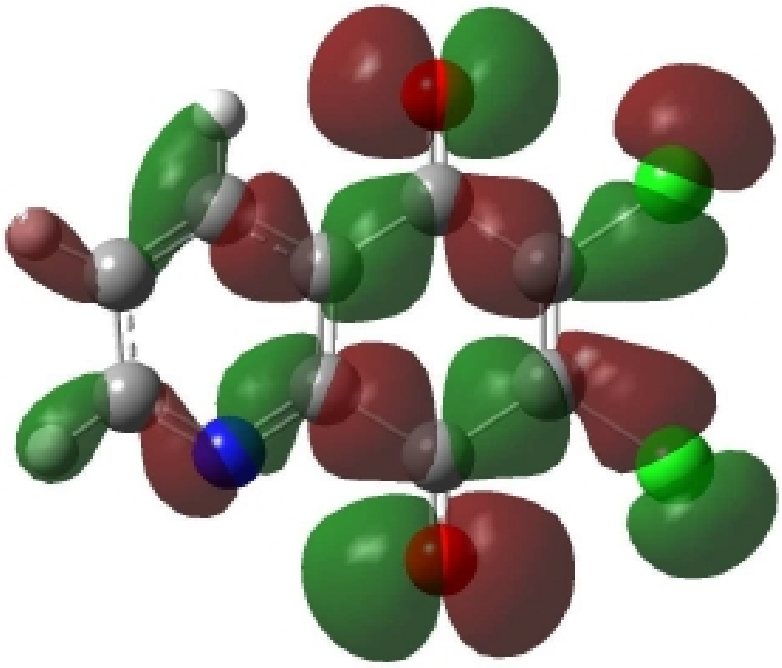

Fig. 10. MO 53 of molecule 1

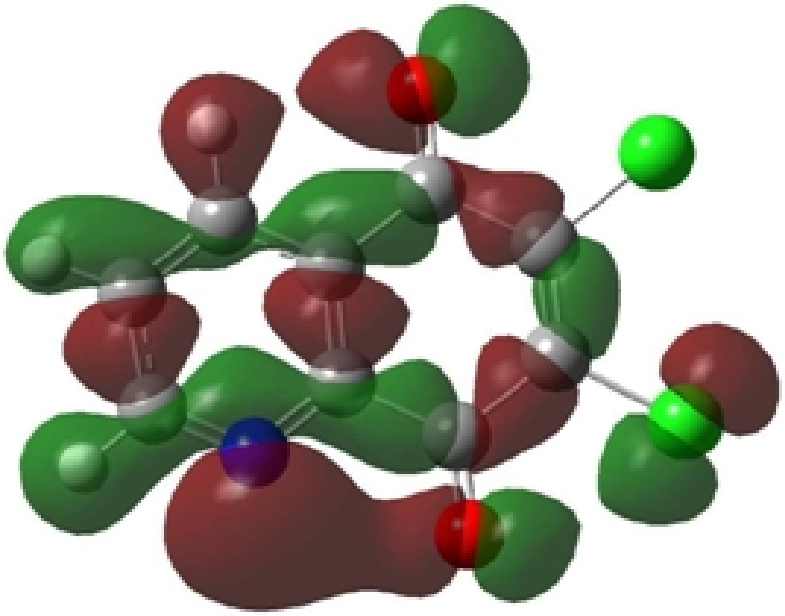

Fig. 11. MO 54 of molecule 1

Then, for atom 7, HOMO*=HOMO-4, HOMO-1*=HOMO-5 and HOMO-2*=HOMO-6 (see Fig. 2). These MOs are of σ nature. We need to find a substituent raising the negative numerical value of S_7^E *(HOMO-2)** by lowering the HOMO-2* energy (i.e. the MO energy moves closer

to the zero energy). The π nature of the three highest occupied molecular MOs, and their lack of localization on atom 7, strongly suggest that this atom is facing an electron-deficient centre. Atom 10 should have a high electron-donor capacity from (HOMO-2)*, indicating that this MO together with HOMO-1* and HOMO* also interact with an electron-deficient centre. Fig. 12 summarizes the associated anti-inflammatory pharmacophore in two dimensions.

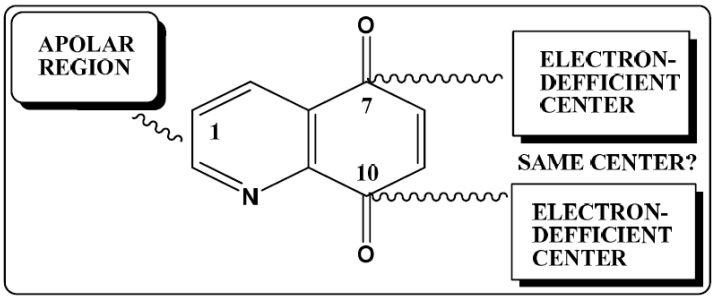

Fig. 12. Anti-inflammatory pharmacophore from Eq. 13

Eq. 14 shows that the variation of the anti-proliferative activity against HL60-cells is associated with the variation of six local atomic reactivity indices. The entire process seems to be orbital-controlled [37]. If we carry out a variable-by-variable analysis we may say that good anti-proliferative activity seems to be linked with high numerical values for S_4^E*(HOMO-1)** and F_7*(HOMO)*,* and with low numerical values for F_4*(HOMO)*, S_1^E, F_9*(LUMO+1)** and F_{11}*(HOMO)*. S_4^E*(HOMO-1)** and F_4*(HOMO)** have the highest beta coefficients (Table 3) indicating that these two variables are the most important ones. In atom 4 (HOMO)*=HOMO and (HOMO-1)*=HOMO-1, are both of π nature. The contradictory nature of the requirements for these variables could indicate that the anti-proliferative activity against HL60-cells is a rather complex process involving two or more steps, fact that make a full analysis not easy. Nevertheless, the low value required here for the numerical value of S_1^E is related to a high value for η_1 required for anti-inflammatory activity: S_1^E will be low if the highest occupied molecular MOs are not located on atom 1.

Eq. 15 shows that the variation of the anti-proliferative activity against T-cells is associated with the variation of only three local atomic reactivity indices. A one-by-one analysis of these variables indicate that high numerical values are needed for S_4^E *(HOMO)*, F_5 *(HOMO-1)** and Θ_2. Beta coefficients (Table 4) show that S_4^E (HOMO)* is the most important variable, Beta coefficients (Table 4) show that S_4^E (HOMO)* is the most important variable, Θ_2 being the least important. Θ_2 corresponds to the orientational parameter of the substituent attached to atom 8. The experimentalist should look for a substituent which raises the value of Θ_2 without altering the electronic structure of B ring. Suggested choices are alkyl chains or heavier substituents separated from B ring by two or more methylene groups that do not affect the electronic distribution on rings A and B. It is very important to mention here the following fact regarding. Θ_2. When experimental medicinal chemists substitute a site with analogous substituents that are longer and longer (for example, Me, Et, n-Pr, n-Bu, etc.), and notice that the activity (or binding) is diminishing, they interpret this fact by suggesting that a kind of pocket exists in the target molecule (receptor, enzyme, etc.). We do not fully agree with this. In fact, in the first studies of opiates it was shown that the binding affinity

diminished with the above mentioned substitutions, but after a certain longitude was attained the binding affinity raises again. The orientational parameter can explain these apparent anomalies because it gives an account of the percentage of rotating molecules attaining the right position to exert their activity. The above results suggest a different anti-proliferative mechanism for HL60 and T-cells. In atom 5 (like in atom 4) HOMO-1*=HOMO and HOMO*=HOMO. Fig. 13 shows the HOMO-1 of molecule 1 as an example (see Fig. 8 for the HOMO and Fig. 2 for atom numbering). Note also that Eq. 4 involves the two carbon atoms common to rings A and B. Variations on the electronic structure of atom 4 will affect the electronic structure of atom 5. The nature of the MOs involved in Eq. 3 suggests that atoms 4 and 5 interact with electron-deficient centers probably of π nature.

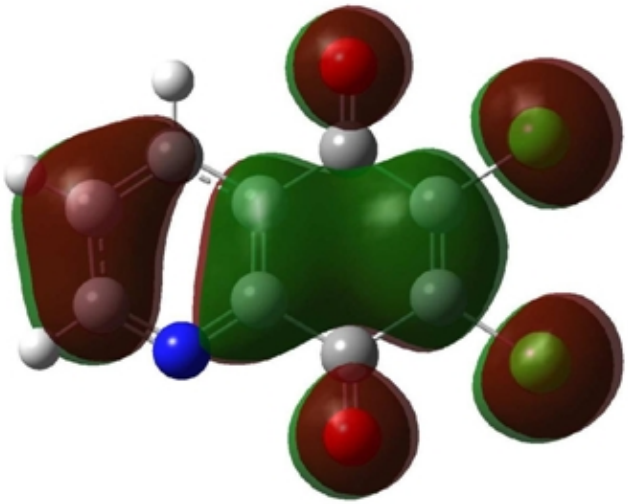

Fig. 13. MO 56 (HOMO-1) of molecule 1

Fig. 14 summarizes part of the T-cell anti-proliferative pharmacophore in two dimensions.

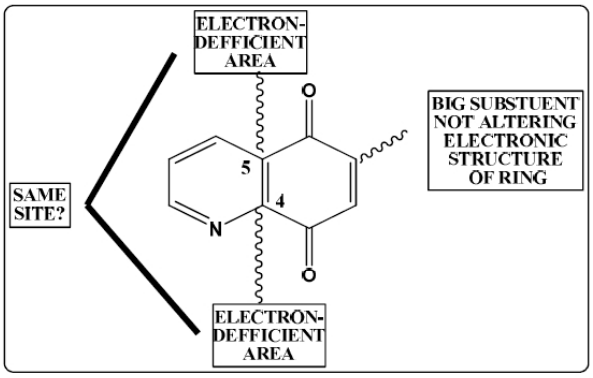

Fig. 14. Anti-proliferative pharmacophore against T-cells (in 2D) from Eq. 15

It is indispensable to comment about the appearance of molecular orbitals of σ nature in the resultant equations. The original equations from which this model was developed contained

terms corresponding to charge-charge (attractive or repulsive) and donor-MO/acceptor-MO interactions between two molecules. These equations do not contain a term giving an account of the occupied MOs repulsion. Then, the appearance of Fukui or electrophilic superdelocalizability indices related to a σ MO can be interpreted in two general ways remembering that the electronic density of these MOs is highly localized. If the value needs to be low we are in the presence of repulsion between σ electronic densities located on both interacting atoms. If the value needs to be high we could be in the presence of an interaction between the σ cloud and an atom with positive net charge located on the partner.

A final word. As computers become faster and more powerful, a formal method like this one could be easily incorporated as routine calculations because it seems to furnish valuable information about mechanisms of action. All the independent variables of this model come from the quantum chemical realm and have an unambiguous physical meaning. The total number of variables is entirely determined, contrary to the empirical QSAR methods that sometimes use hundreds or thousands variables coming from the classical and quantum realms.

5. CONCLUSIONS

The main conclusions of this work are: 1. We have been able to find statistically significant quantitative relationships between the electronic structure and three different biological activities for a group of 6,7-substituted-5,8-quinolinequinones. 2. The hypothesis that a model built for in vitro drug-receptor interactions is practical for the study of other biological activities is supported by the results presented here. 3. One of the new local atomic reactivity indices of the extended model appears in the resulting statistical equations, fact indicative of their utility. 4. The pharmacophores associated with the different biological activities are different suggesting different mechanisms of action. 5. For the first time in these kinds of studies it is clearly shown that the σ molecular orbitals could play a function in determining biological activities.

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COMPETING INTERESTS

The author has no financial and personal relationships with other people or organizations that could inappropriately influence his work.

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