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Electronic descriptors for the antimalarial activity of sulfonamides

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Abstract As an interesting class of materials for designing new antimalarial drugs, sulfonamides have shown potential for several pharmacological applications. In this study, multivariate data analyses were employed to correlate the antimalarial activity reported for a group of sulfonamide derivatives with electronic structure descriptors obtained through quantum mechanical calculations. A simple classification rule based on a discriminant function was obtained, which is able to correctly classify 94 % of the compounds as active or non-active. The obtained function combines only two electronic descriptors and provides valuable insights into the design of new derivatives with improved antimalarial potency, as well as identifies possible active sites on the structure of sulfonamides.

Keywords Sulfonamides · Antimalarial · Electronic structure calculations · Quantitative structure–activity relationship

Introduction

Malaria is an infectious disease caused by protozoa of the genus *Plasmodium* and is transmitted to humans by the *Anopheles* mosquito. Since this malady is mainly present in tropical regions and primarily affects poor people in developing countries, its occurrence is often associated with socioeconomic problems (World Health Organization, 2011). In spite of the recent progress, there are not yet vaccines available for clinical treatment against malaria and the problem is even greater due to increasing parasite resistance (Aguiar *et al.*, 2012; Flannery *et al.*, 2013; Jensen *et al.*, 2012).

In order to contain the epidemic, different technologies, methods and drugs are currently being used. Such procedures range from using nets treated with insecticides (Eisele *et al.*, 2011; Metropolis *et al.*, 2014) to employing a combination of drugs with distinct effects on the parasites (Desgrouas *et al.*, 2014; Guiguemde *et al.*, 2014; Mutabingwa, 2005; Santelli *et al.*, 2012). However, even with these actions tests indicate a continuous increase in the resistance of the parasites (Kümpornsin *et al.*, 2014; Mita *et al.*, 2014; Perakslis, 2014; Winzeler and Manary, 2014), evidencing the urgent need for new drugs.

In this context, we propose here a new study of a family of sulfonamides previously investigated by Elslager *et al.* (1984), and Agrawal and collaborators (Agrawal *et al.*, 2001a, b; Singh and Agrawal, 2008). Given the low cost of production and especially the versatility of the synthesis of these compounds, they can be an interesting option for malaria treatment (Kumar Parai *et al.*, 2008).

In general, the sulfonamide functional group has an impressive effectiveness and assuredness history in medicine. It usually presents interesting pharmacokinetic properties being well absorbed by several routes of administration, presenting good penetration into tissues and fluids, and being easily metabolized (Kahn, 2005; Spoo and Riviere, 2001). In particular, in the last decade it has been widely employed in the treatment of malaria (Barea *et al.*, 2011; Primas *et al.*, 2012; Salahuddin *et al.*, 2013), and

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currently there are more than 100 products containing this substance on the market (Smith and Jones, 2008).

In this report, we evaluate the possible relationships between the electronic structure and antimalarial activity of some molecules of the group 2,4-diamino-6-quinazoline sulfonamides. A quantitative structure–activity relationship (QSAR) study of a subset of these molecules was conducted by Agrawal and collaborators (Agrawal *et al.*, 2001a, b; Singh and Agrawal, 2008) by using topological parameters. In our study, we conducted an intensive investigation of the electronic structure by employing 65 descriptors derived solely from quantum mechanical calculations. We believe that the analysis of the electronic structure can bring a clearer explanation of the mechanisms associated with the antimalarial activity of these compounds and also delineate essential features for the design of new active compounds.

Statistical analyses were performed using simple and multiple linear regressions (SLR and MLR) and other
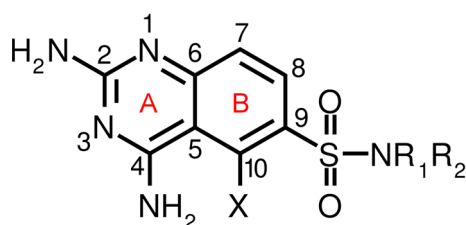
Fig. 1 Basic structure of 2,4-diamino-6-quinazoline sulfonamides. R_1, R_2, and X represent distinct substituents (Table 1)

multivariate methods such as principal component analysis (PCA) and linear discriminant analysis (LDA) (Hair *et al.*, 1998). No significant regression equation could be obtained via SLR and MLR studies. PCA data allow a clear separation of the compounds into two subgroups of molecules, according to the degree of activity. In addition, LDA provides a significant rule that allows the correct classification of a high percentage of the compounds as active or inactive. Finally, a simple rule for achieving new active compounds is proposed. Based on the proposed rules, some successful theoretical tests with substituents of known electronic influence on the common structure were carried out.

Materials and methods

A group of 16 sulfonamide derivatives with potential antimalarial activity was evaluated (Agrawal *et al.*, 2001a, b; Singh and Agrawal, 2008). Figure 1 presents the basic structure of 2,4-diamino-6-quinazoline sulfonamides, which is common to all the studied compounds.

Table 1 presents the chemical structure of the substituents attached to the basic structure of sulfonamide derivatives, as well as the experimental antimalarial activity associated with each. The activity index that we attempt to correlate with quantum descriptors of the compounds is given by the difference in lifetime, in days, of treated and untreated mice after infection (ΔMST) (Agrawal *et al.*, 2001a, b; Singh and Agrawal, 2008).

Table 1 Description of the structure of the sulfonamide derivatives and the activity index measured in days

ID	Substituents		Activity index *ΔMST*
	$-NR_1R_2$	X	
1	$N(C_2H_5)_2$	H	3.30
2	$N(C_2H_5)_2$	Cl	2.30
3	$N(CH_2CH_2CH_3)_2$	H	0.30
4	$N(CH_2CH_2OH)_2$	H	0.30
5	$N(CH_3)CH(CH_3)_2$	H	0.70
6	$N(CH_3)CH_2CH_2N(C_2H_5)_2$	H	0.10
7	$N(CH_2)_5$	H	4.40
8	$N(CH_2)_4$	H	5.00
9	$N[(CH_2)_2]_2O$	H	4.70
10	$N[(CH_2)_2]_2S$	H	2.50
11	$N[(CH_2)_2]_2NCH_3$	H	1.00
12	$N[(CH_2)_2]_2NC(=O)OC_2H_5$	H	0.20
13	$4Cl–C_6H_4NH$	H	0.70
14	$3Br–C_6H_4NH$	H	0.30
15	$3Cl–C_6H_4NCH_3$	H	0.30
16	$C_6H_5NCH_3$	H	0.50

All the calculations, including geometry optimization, were carried out via the semiempirical molecular orbital method Austin Model 1 (AM1) (Dewar *et al.*, 1985), which is implemented in the MOPAC package (Stewart, 1990). The choice of this approach was based on preliminary conformational studies employing varied methods (semiempiricals: MNDO, MNDO/d, PM3, and AM1; and DFT with B3LYP functional and 6-31G* basis set) carried out for the model molecule cyclohexanesulfonamide. AM1 was the semiempirical method that better reproduced the structural features of the model compounds (Malešič *et al.*, 1997; Ojala *et al.*, 2001), presenting an average deviation of 4.9 %, just a little bit superior to the DFT approach (3.7 %).

For QSAR studies, the geometry optimization was considered complete when achieving gradient norms below 0.01 and no negative force constants were observed. The calculations were performed *in vacuo* by employing a restricted Hartree–Fock (RHF) approach.

A collection of 65 electronic indexes, most of them related to the energy and electron density of the frontier molecular orbitals, was employed as molecular descriptors for each derivative. The descriptors are divided into two groups: (1) global indexes, related to the whole molecule: heat of formation (ΔH_F), total electric dipole moment (D_T), total energy (E_T), electronic energy (E_E), nuclear energy (E_N), the energies of the highest occupied molecular orbital (E_{HOMO}), the level below (E_{HOMO-1}), the lowest unoccupied molecular orbital (E_{LUMO}), the level above (E_{LUMO+1}), the difference in energy ($E_{LUMO} - E_{HOMO}$), and the chemical hardness ($E_{HOMO} + E_{LUMO}$)/2, and (2) local indexes, related to the *i*th atom or to the bond of all *i* and *j* chemically bonded atoms of the basic structure (Fig. 1): atomic charge ($CHAR_i$), total electron population (TEP_i) and partial electron population in the HOMO and LUMO (PEP_i^H and PEP_i^L, respectively), and bond orders (BO_{i-j}) (all originating from Mulliken population analysis).

Different statistical methods were employed to evaluate possible structure–activity correlations: simple and multiple linear regressions (SLR and MLR), principal component analysis (PCA), and linear discriminant analysis (LDA). In particular, PCA and LDA have shown to be interesting multivariate methods for pattern recognition and classification, having been successfully employed in QSAR studies of a variety of compounds (Autreto and Lavarda, 2008; Batagin-Neto and Lavarda, 2014; Naranjo-Montoya *et al.*, 2014).

SLR and MLR studies were performed with the aid of a proprietary software for statistical analyses. Combinations of up to three electronic descriptors (independent variables) were performed in MRL, involving the complete data set. The quality of the correlations was evaluated, first, by the

Pearson correlation parameter (R) between experimental and predicted values of the dependent variable. Distinct functional forms of ΔMST indexes were considered in the regressions: ΔMST, $1/\Delta MST$, and $\log(\Delta MST)$ (as a dependent variable). For each one of these cases, 45,825 combinations with up to three descriptors were performed.

Aiming to evaluate the similarities and differences between the electronic structures of the compounds, the PCA study was performed at two different levels: (1) full PCA, involving the whole data set (16 cases and 65 electronic descriptors) and (2) reduced PCA, involving subsets of descriptors (up to 5 independent variables). In reduced PCA, 45,825 distinct combinations of descriptors were considered. The calculations were automatically performed through specifically developed software. The compounds were divided into two subgroups based on their antimalarial potency for classification: (1) non-active compounds: with $\Delta MST < 2.0$. (compounds **3–6** and **11–16**) and (2) active compounds: with $\Delta MST \geq 2.0$. (compounds **1–2** and **7–10**). The choice of the threshold value (2 days) was based on the average value of the antimalarial potency of the data set that was 1.66 days.

LDA calculations were performed with the aid of the statistical package SPSS 11.0.1 (SPSS Inc., 2001). In order to obtain a minimum set of electronic indexes for the determination of the discriminant function (DF), the stepwise method with Mahalanobis distance criterion (validated by F statistics) was employed. Additionally, a cross-validation method (leave-one-out classification) was employed in order to critically evaluate the robustness of the obtained models. For this purpose, each molecule was tested by using the classification rule derived from a subset containing all the other molecules.

Results and discussion

Simple and multiple linear regressions

Despite the number of combinations evaluated, only low correlation parameters could be observed ($r < 0.9$) in the linear regressions studies that are not good enough to propose a significant prediction rule for the antimalarial potency of the compounds. However, even with the absence of a significant linear relationships, it is possible to obtain some interesting clues from the more representative results ($0.7 < r < 0.9$) that can help in the subsequent analyses. For example, it was noticed that the most relevant equations were often associated with local molecular indexes of ring B, what could indicate a potential reactive region on the sulfonamide's main structure.

Nevertheless, the absence of significant linear correlations suggests that exploratory and classificatory methods

could be more appropriate to propose a predictive rule for antimalarial activity of the molecules.

Principal component analysis

Figure 2 shows a plot of the first and second principal components (PC$_1$ and PC$_2$) coming from the full PCA study.

As shown, in spite of the PC$_1$ and PC$_2$ components determining around 70 % of the total variance, there is no evident separation between active and inactive subgroups. An interesting feature that deserves to be highlighted is the distinction of compound **2** with respect to the other molecules. As shown in Table 1, this derivative is the only one that presents a chlorine atom at position X (X = Cl), which
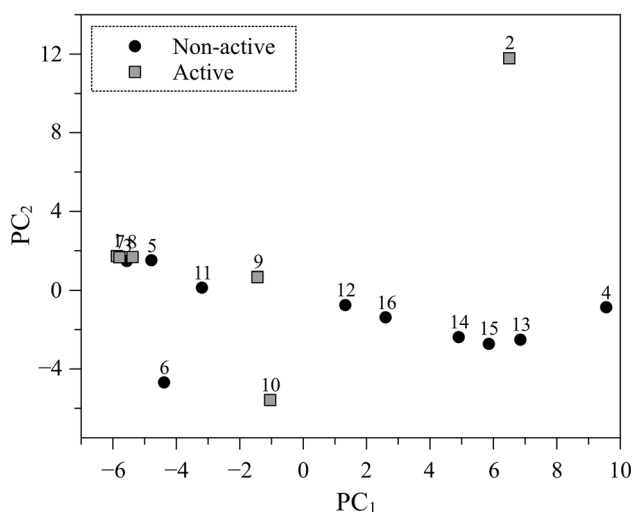
Fig. 2 PC$_1$ and PC$_2$ scores from the full PCA study
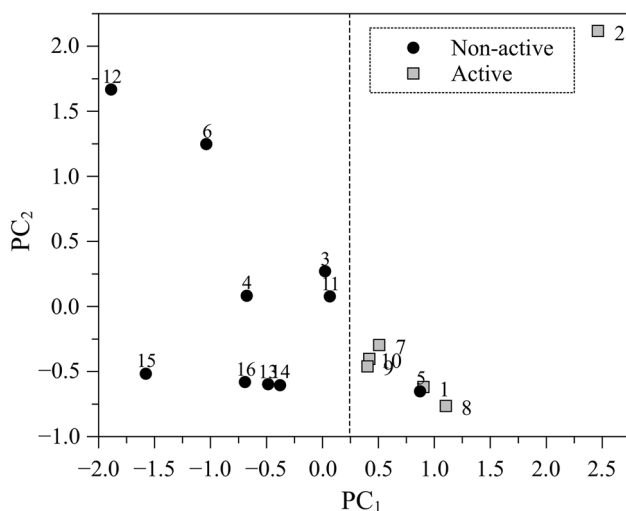
Fig. 3 Scores of PC$_1$ and PC$_2$ from the most significant reduced PCA. The involved descriptors are E_E and PEP$_9^L$

provides a distinct electronic structure to this molecule, evidenced in the PC$_2$ scores.

Reduced PCA was performed in order to investigate whether smaller sets of electronic descriptors could account for the antimalarial activity of the derivatives. Since it is based on few descriptors, the interpretation of the results via this approach is more direct than in full PCA.

Figure 3 shows a plot of PC$_1$ and PC$_2$, relative to the reduced PCA that better discriminates the two subgroups of molecules. The variables involved are the electronic energy (E_E), which represents the portion of the total energy due only to the electrons of the molecule, and the fraction of the lowest unoccupied molecular orbital (LUMO) that is located on atom 9, i.e., the partial electronic population, referred to as LUMO, on atom 9 (PEP$_9^L$).

As can be seen through PC$_1$ scores, it is possible to separate the molecules into two groups associated with the antimalarial potency of the compounds; only compound **5** is misclassified. As a matter of fact, this compound has already been considered an outlier in the work of Agrawal *et al.* (2001b), which is indeed reinforced by the results presented in Fig. 3.

Despite the fact that the PCA study does not allow for the proposition of a classification rule, it suggests that the antimalarial activity of the sulfonamide derivatives can be associated with the electronic descriptors E_E and PEP$_9^L$. Since these variables present similar loadings for PC$_1$ construction (~ 0.707), both are supposed to contribute with similar relevance to data dispersion and then to the clustering observed in Fig. 3.

Linear discriminant analysis

In LDA, the same criterion considered in the PCA studies was employed to define active and non-active subgroups of compounds. Equation 1 shows the discriminant function (DF), which provides better distinction between these subgroups. Similar to PCA, the descriptors involved are E_E and PEP$_9^L$.

$$DF = 3.07 \times 10^{-4}(E_E) + 143.814\left(PEP_9^L\right) - 11.984, \quad (1)$$

where E_E should be given in electron Volts (eV).

The DF presented has a statistical significance of 98.9 % (Wilk's Lambda = 0.497, $\chi^2 = 9.091$ with 2 degrees of freedom, and $p < 0.011$). Following the scores obtained from Eq. 1, a cutoff parameter of 0.243 can be defined for the classification of the compounds. This parameter defines the central value between the centroids of active and non-active groups and allows classifying the compounds according to their DF scores. So, compounds with DF scores higher than 0.243 can be classified as active molecules, while derivatives with DF < 0.243 can be identified
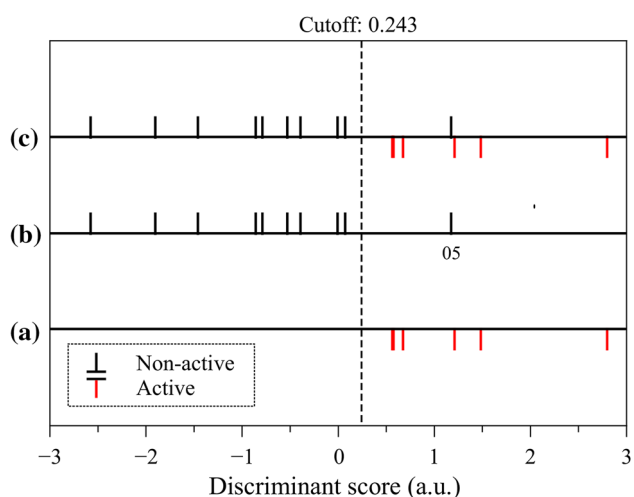
Fig. 4 Discriminant function scores of active, inactive, and the whole set of compounds. *Dotted line* indicates the cutoff parameter, 0.243

as non-active. By Eq. 1 and the cutoff parameter, using a leave-one-out classification it was possible to classify correctly around 94 % of the molecules, which indicates the relevance of the proposed rule.

Figure 4 illustrates the dispersion of the DF scores for (a) active, (b) non-active, and (c) the whole set of compounds; the cutoff parameter suggested for compound classification is also identified. The centroids of active and inactive subsets are located at 1.215 and −0.729, respectively.

As can be seen, similar to PCA, only compound **5** is misclassified, reinforcing the hypothesis that this derivative is in fact an outlier (Agrawal *et al.*, 2001b). Given this possibility, all the above-presented analyses were repeated, excluding compound **5** from the data set, and the same results were obtained.

Achieving high activity

Although the obtained DF is an interesting option for testing the activity tendency of already synthesized molecules, it would be more useful if it provided some clues regarding plausible substitutions on R_1 and R_2 ligands (Fig. 1), in order to obtain derivatives with improved biological properties.

Both, LDA and PCA, have indicated the relevance of the descriptors E_E and PEP_9^L in the distinction of active and non-active compounds. In particular, the DF (Eq. 1) suggests that active compounds must present high E_E and/or PEP_9^L values (since higher DF scores are associated with active derivatives). Such descriptors are associated with the molecular energy due to the electrons present in the systems (and their interactions), and the fraction of the LUMO's density located on atom 9 of the basic sulfonamide structure, respectively.

In order to identify the relevance of each one of these descriptors in the classification of the compounds, we have evaluated them individually. Figure 5 shows the relationship of E_E and PEP_9^L with the ΔMST values. The solid horizontal lines represent a guide to the eyes referring to the limit between active and inactive compounds (ΔMST ≥ 2.0: active derivatives and ΔMST < 2.0: non-active derivatives). As can be seen, the descriptor E_E plays a key role in explaining the antimalarial potency of the compounds, in such a way that active and non-active molecules can be discriminated just by considering the cutoff value $E_E^{cutoff} = -27,310$ eV (dashed vertical line presented in Fig. 5a). Note that molecule **5** is again the only misclassified molecule (it presents an electronic energy typical of an active molecule; however, it belongs to the non-active group).
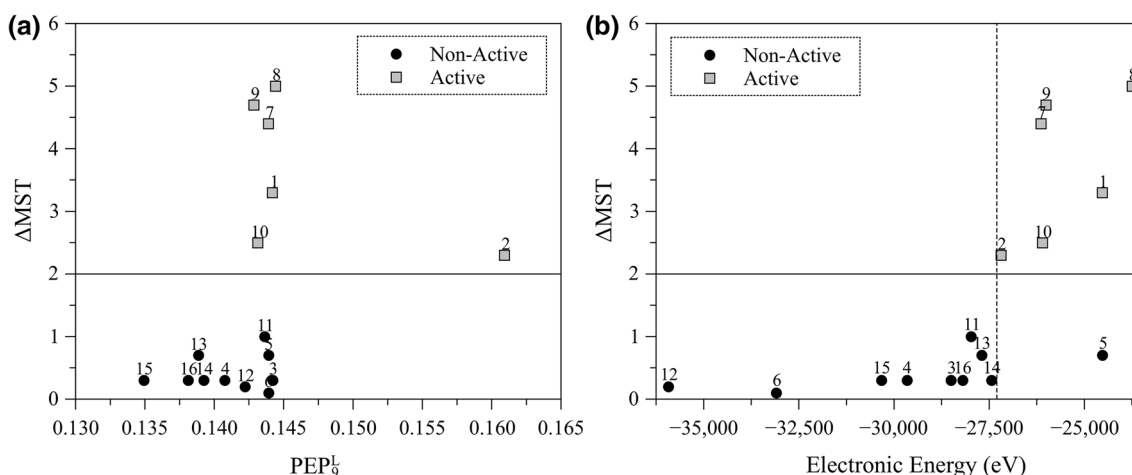

Fig. 5 Relationship between ΔMST parameter and the descriptors: **a** PEP_9^L and **b** E_E

In spite of subgroup separation observed in Fig. 5a, it is important to stress that both the descriptors, PEP_9^L and E_E, strongly contribute to construct the DF (Eq. 1), presenting similar standardized coefficients (0.821 for E_E and 0.706 for PEP_9^L). In general, it is noticed that the information provided by PEP_9^L descriptor (Fig. 5b) improves the statistical significance of the subgroups distinction provided by E_E (Fig. 5a). It suggests that the conjunction of these two parameters is relevant to distinguish between active and non-active compounds, and the best classification rule must be based on the DF and its cutoff value. Nevertheless, in order to get more information regarding the physical relevance of these parameters and its influence on the biological potency of the compounds, it could be interesting to evaluate them individually.

For the set of molecules considered in this study, as shown in Fig. 6, the larger is the number of electrons in the
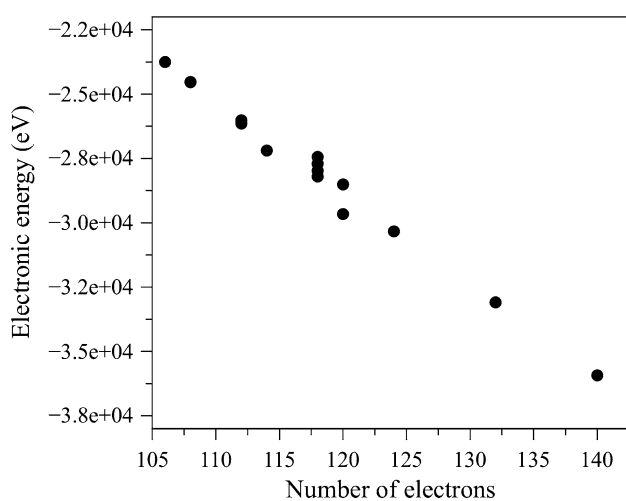
Fig. 6 Dependence of the electronic energy on the number of electrons in sulfonamide derivatives
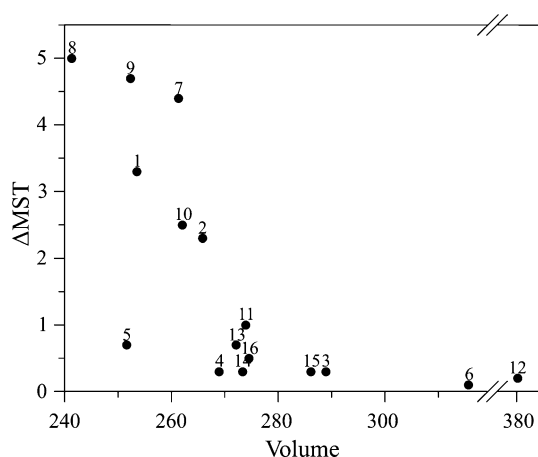
Fig. 7 Relationship between the substituent's volume and the antimalarial potency of sulfonamides

system, lower is the electronic energy of the compound. In general terms, it occurs because ground-state (and stable) molecules generally present occupied orbitals with negative energies (ε_i^{occ}). Since E_E predominantly depends on a summation of ε_i^{occ} values (subtracted by the twice counted coulomb and exchange contributions), each electron added to the system leads to a reduction in the E_E descriptor.

Indeed, as can be seen, higher values of E_E are typically associated with compounds presenting a reduced number of electrons in the valence shell. Given the fact that the set of molecules studied in this work presents a common basic structure (Fig. 1), a reduced number of electrons can be achieved by choosing appropriate substituents on sites R_1, R_2, and X.

This trend is in fact evidenced by comparing the molecules **8** and **6**, whose ΔMST are, respectively, the largest (5.00) and the lowest (0.10) in the whole set. The very active compound **8** contains 106 valence electrons and $N(CH_2)_4$ as the substituent group, while the potentially inactive compound **6** contains 132 electrons in the valence shell and $N(CH_3)CH_2CH_2N(C_2H_5)_2$ as the substituent group. Compound **8** does not just present the higher E_E value, but it also presents the smallest ligand. This fact can suggest that the substituent may play an important role in the antimalarial potency of the derivatives, in such a way that small ligands can be linked to a more efficient antimalarial effect (probably due to sterical effects). In this context, the electronic descriptor E_E is highlighted as relevant in the correlation studies, simply because it is the electronic index that best reflects the difference of the ligand's volume among the compounds.

Figure 7 shows the relationship between ΔMST and the volume of the substituents attached to each compound (Vol_{sub}) (obtained via VEGA ZZ package Pedretti et al., 2002; Pedretti et al., 2003; Pedretti et al., 2004) that reinforces this hypothesis.

As can be seen, compounds with smaller ligands generally present higher antimalarial potencies. Vol_{sub} is linked to the number of atoms present on the substituent and the van der Waals radius of these atoms (being this last associated with the electronic structure of the atom). In this sense, substituents with low Vol_{sub} tend to present a reduced number of atoms and/or atoms with lower van der Waals radius, and both of these features lead to molecules with a reduced number of electrons in the valence shell. As evidenced in Fig. 6, it leads to higher E_E values and then to active derivatives, suggesting that antimalarial potencies of the compounds can be mainly dominated by sterical effects.

Despite the relevance of the descriptors Vol_{sub} and E_E in describing the antimalarial potency of the compounds, as discussed before it is also important to address the physical meaning associated with the presence of PEP_9^L in Eq. 1

Table 2 PEP_9^L, E_E, and DF parameters obtained for distinct substituents at position X of sulfonamides derivatives

ID	Substituents	Dominant effect associated with X		Parameters			Predicted status
	$-NR_1R_2$	X		PEP_9^L	E_E	DF	
8	$N(CH_2)_4$	H	–	0.144	−23,747.650	1.487	Active
8A	$N(CH_2)_4$	CH_3	ERR^a and ERP^b	0.139	−26,185.139	−0.076	Non-active
8B	$N(CH_2)_4$	OH	ERR	0.118	−26,474.527	−3.137	Non-active
8C	$N(CH_2)_4$	NH_2	ERR	0.082	−26,333.040	−8.270	Non-active
8D	$N(CH_2)_4$	NO_2	EWP^c	0.174	−31,038.788	3.533	Active
8E	$N(CH_2)_4$	F	ERR and EWP^d	0.149	−26,675.258	1.273	Active
8F	$N(CH_2)_4$	CN	EWP	0.168	−27,047.573	3.878	Active

[a] Electron releasing by resonance; [b] electron releasing by polar effects; [c] electron withdrawing by resonance; [d] electron withdrawing by polar effects

(improving the quality of the DF obtained from LDA). In his theory about frontier orbitals, K. Fukui suggested that the electron density of the frontier orbitals carries information regarding local reactivity of the molecules. In this context, since electrophilic species tend to interact more efficiently with electrons located mainly in the HOMO of the molecules (most weakly bounded ones), Fukui proposed that sites with higher PEP^H values (higher contribution to the formation of the HOMO) could be considered the most reactive sites for reactions toward electrophiles (Fukui, 1982). Similarly, considering that nucleophilic agents tend to accommodate electrons preferentially in the LUMO of the molecule, the sites with higher PEP^L values can be considered as the most reactive toward these species. In Eq. 1, it is observed that active compounds (DF > 0.243) tend to present high values of PEP_9^L, which suggests that improved antimalarial activity can be achieved if site 9 is a good electron acceptor. Such a result indicates that the mechanism associated with the antimalarial activity of sulfonamides can be linked to chemical reactions on atom 9 (probably toward nucleophiles).

In contrast with the E_E parameter, it is not easy to propose substitutions that lead to the desired changes on the PEP_9^L index of the compounds. However, it is reasonable to consider that this parameter is directly affected by substitutions on the X position. So, in order to evaluate what changes could be induced by this substituent, some complementary calculations were performed by considering varied groups at position X. For this purpose, the R_1 and R_2 groups were kept the same, being chosen as the substituents present on the most active derivative, compound **8** ($NR_1R_2 = N(CH_2)_4$). The X substituents were chosen based on their polar and resonance effects on ring B (Hammett substituent constants Carey and Sundberg, 2007): (1) electron releasing (by resonance—ERR or polar effects—ERP) or (2) electron withdrawing (by resonance—EWR or polar effects—EWP). Table 2 illustrates

the substituents employed and the values obtained for the parameters PEP_9^L, E_E and DF (Eq. 1), as well as the status predicted for the derivatives based on the LDA classification rule. The indexes associated with compound **8** are also presented for comparison.

A decrease in the E_E value is observed for all the substituents (more negative values), in relation to the hydrogenated compound. On the other hand, distinct effects are observed on PEP_9^L. In general, higher values of this parameter are observed for substituents that present electron withdrawing as the dominant effect on ring B of sulfonamides (that were predicted as active derivatives), while lower values are obtained for substituents with ERR or ERP dominant effects (non-active derivatives). This result indicates that active compounds could be obtained by an appropriate choice of X substituent; in particular, electron-withdrawing groups are good candidates to achieve high activity.

In summary, our approach seems to be more comprehensive than the topological indices presented by Agrawal and collaborators (Agrawal *et al.*, 2001a, b; Singh and Agrawal, 2008). In their model, the compounds **5**, **9**, and **11** were considered as outliers, while in our case, only one outlier is identified (compound **5**). The misclassification of molecule **5** by the other studies can indicate that the electronic structure is related to the topology of the molecule, which is an expected finding. However, it seems that the electronic indexes bring more information than purely topological parameters.

Conclusions

The antimalarial properties of a group of sulfonamides were correlated with the electronic properties of these materials. Simple and multiple linear regressions (SLR and MLR), principal component analysis (PCA), and a linear discrimination analysis (LDA) were employed.

From LDA, we found a discriminant function with a statistical significance of 98.9 %. The function was obtained from the linear combination of only two electronic descriptors (among 65 indexes evaluated) and permits correct classifying of 94 % of the studied compounds, based on their antimalarial properties.

The obtained discriminant function indicates that active compounds must present high values of electronic energy and partial electronic population of the LUMO on atom 9 (this result is reinforced by PCA). The electronic energy plays a major role in determining the degree of activity of the compounds, which can be associated with the volume of the substituents. The simplest recommendation for new active compounds is employing substituents with the lowest possible volume. The presence of the descriptor PEP_9^L in the DF suggests that this region is a potential active site for the antimalarial action of the compounds. Complementary calculations indicate that the attachment of electron-withdrawing groups at the X position can improve PEP_9^L, leading also to new active compounds.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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