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The influence of electronic and steric effects in the structure–activity relationship (SAR) study of quinone compounds with biological activity against *Trypanosoma cruzi*

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Abstract

A set of 14 quinone compounds with anti-trypanocidal activity was studied by using the AM1 semi-empirical method in order to calculate atomic and molecular properties (variables or descriptors) to be correlated to the biological activity.

Principal component analysis (PCA), hierarchical cluster analysis (HCA), stepwise discriminant analysis (SDA) and the *K*th nearest neighbor (KNN) method were employed to obtain possible relationships between the calculated descriptors and the biological activity studied and to predict the anti-trypanocidal activity of new quinone compounds from a prediction set. The atomic and molecular descriptors responsible for the separation between the active and inactive compounds were: total energy (E_T), polarizability (α) and the charge on the R_1 atom (Q_4). These descriptors give information on the kind of interaction that can occur between the compounds and the biological receptor. The prediction study was done with a set of three new compounds by using the PCA, HCA, SDA and KNN methods and two of them were predicted as active against *T. cruzi*.

Keywords: Quinone; Anti-trypanocidal activity; AM1; Principal component analysis; Hierarchical cluster analysis; Stepwise discriminant analysis; *K*th nearest neighbor

1. Introduction

American trypanosomiasis (Chagas' disease), caused by the kinetoplastid protozoon *Trypanosoma cruzi* (*T. cruzi*), is considered by the World Health Organization as one of the most important tropical parasitic diseases worldwide together with malaria and schistosomiasis. This major health problem afflicts 16–18 million persons in Latin America, who are infected with *T. cruzi*. At the present time, it is esteemed that around of 2–3 million people present the typical symptoms that characterize the chronic stage of American trypanosomiasis producing

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45,000 deaths yearly [1]. The protozoan is transmitted to humans by contamination with insect feces during blood sucking. A particularly important portal of entry is the ocular conjunctiva that is put in contact with insect feces by involuntary scratching from nearby bites on a sleeping person's face. Other forms of transmission such as blood transfusion, congenital transmission and breast feeding are also important, particularly in northern hemisphere regions that received intense migratory currents from Ibero-Americam countries [2]. Therapy against Chagas' disease is unsatisfactory because of toxicity of currently available drugs together with the development of drug resistance [3].

Several compounds have been studied in last years against this illness and among these compounds are quinones, which present in their molecular skeleton an α,β-bisdienonic ring system that confers to them the capacity of reversible chemical reactivity of oxy-reduction and this characteristic is of fundamental importance in several biological processes. Among several naturally occurring quinones, the naphtoquinones are widely distributed in the plant kingdom and are involved in oxidative processes such as photosynthesis and electron transfer reactions [4]. The quinones present activity against several microorganisms [5–8], suppress HIV-1 replication in both acute and chronic infections [9] and have clinical utility against human leukemia and prostate cancer [10].

The attempt to rationalize the connection between the molecular structures of compounds and their biological activities comprises the field of structure–activity relationship (SAR) studies [11–15] and this field aids in the understanding of the nature of biological activity as well as the mechanism of interaction between quinones and the biological receptor. In this work, the main goal is to investigate the SAR of compounds listed in Fig. 1 using atomic and molecular descriptors (electronic, steric, hydrophobic and topological).

The present work employs the AM1 semi-empirical method [16] to calculate atomic and molecular descriptors for 14 quinones compounds (training set) reported in the literature as potent and selective trypanocidal agents [17,18]. The descriptors calculated were selected so that some steric, electronic, hydrophobic and topological characteristics of these compounds could be taken into account since each one of them can contribute to the biological activity and give information about the interactions between the compounds and the biological receptor. Additionally, chemometric techniques, namely, the principal component analysis (PCA), hierarchical cluster analysis (HCA), stepwise discriminant analysis (SDA) and *K*th nearest neighbor (KNN) were employed to analyze the data set and to obtain the relationship between the atomic and molecular descriptors and the biological activity. The results obtained with PCA, HCA, SDA and KNN were tested in three new quinone compounds (prediction set) [17,18] for activity prediction of these new compounds and validation of our models.

2. Methods

Initially, the chemical structure of each compound was obtained by using the molecular mechanic method MM + [19], as implemented in the Hyperchem 4.5 molecular package [20], and an additional conformational search was also performed making use the MM + method. Afterwards, a full optimization of the molecular structure was carried out by using the EF algorithm of the AM1 semi-empirical method [16] built-in the AMPAC 6.5 molecular package [21]. For some compounds (**11**–**14**) of the training set (Fig. 1), the initial structure used in the calculations was based on their X-ray structures, i.e. for the compounds **11**–**14** the initial geometry used in the calculations was their crystal structures determined by Malta et al. [22]. For the other compounds (**1**–**10** in Fig. 1), the initial structure was obtained by using the methodology initially described above.

The central structure, numbering used and the individual chemical structure of the fourteen compounds studied are presented in Fig. 1. The compounds showed in Fig. 1 consist of eight active molecules (1–8) and six inactive molecules (9–14) against *T. cruzi*.

For the calculations of atomic and molecular descriptors (variables) that have been utilized in SAR studies [11–15], we used four molecular packages:

- Ampac 6.5 [21], which calculated the following descriptors: ΔH_f (heat of formation), E_{HOMO}

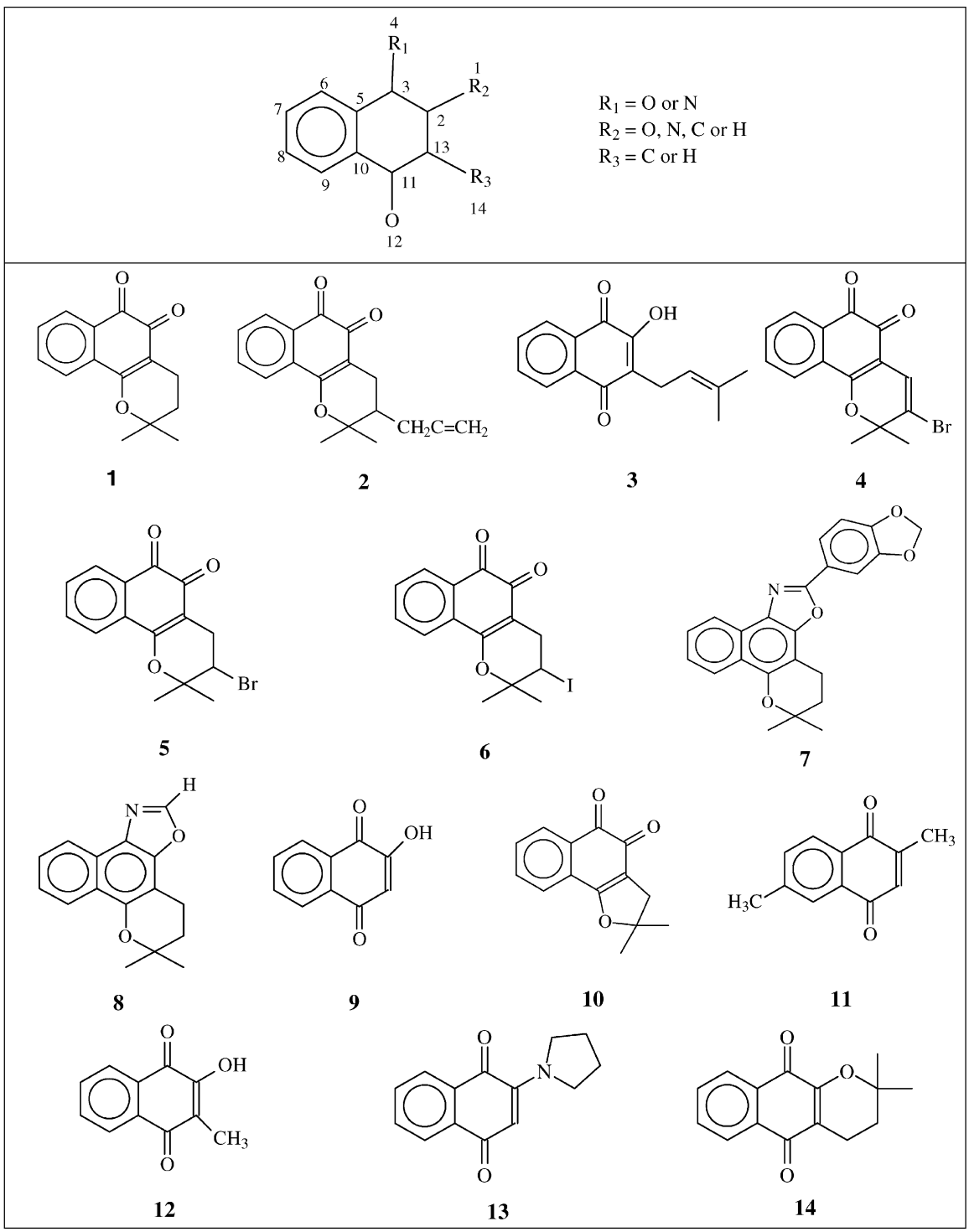


Fig. 1. The central chemical structure, numbering used and chemical structure of the 14 quinone compounds studied.

(the energy of the highest occupied molecular orbital), E_{LUMO} (the energy of the lowest unoccupied molecular orbital), E_T (total energy), Q_N (net atomic charge on atom N), α (molar polarizability), BO (bond order), T_N (torsion angle), A_N (bond angle), L_N (bond length) and μ (dipole moment);

- Spartan 5.0 [23], which calculated the log P (n-octanol/water partition coefficient);
- Chemplus 1.5 [24], which calculated HE (hydration energy), MR (molar refractivity), Vol (volume) and A (molecular surface area);
- WHIM/3D-QSAR [25], which calculated a large variety of topological descriptors. The WHIM descriptors contain information about the whole 3D molecular structure in terms of size, shape, symmetry and atom distribution [26].

The atomic charges were obtained by employing the electrostatic potential method of the Ampac 6.5 molecular package [21] and this method was used because the charges derived from the electrostatic potential method are physically more satisfactory than the Mulliken's charges [27], especially when related to biological activity.

All the statistical analysis (PCA, HCA, SDA and KNN) employed in this work were performed making use of the program MATLAB 6.0 [28].

3. Results and discussion

3.1. Principal component analysis

PCA is a exploratory data technique used to reduce the dimensionality of a multivariate data set. PCA employs a mathematical transformation to the original data with no assumptions about the form of the covariance matrix. The aim of this procedure is to determine a few linear combinations of the original variables which can be used to summarize the data set without losing much information [29]. This is achieved by linear transformation of the original data set of variables into a smaller number of uncorrelated principal components (PCs). Geometrically, this transformation represents the rotation of the original coordinate system and the direction of the maximum residual variance is given by the first principal component axis. The second principal component, orthogonal to the first one, has the second maximum variance and so on. In this way, projections conserving maximum amounts of statistical information can be plotted in order to show us a more detailed study of the data structure [30–32].

The first step for exploratory analysis of the data set is the autoscaling of the variables, i.e. each one of the variables is autoscaled so that they can be compared to each other on the same scale. Afterwards, several attempts to obtain a good classification of the compounds (separation between the active and inactive compounds against *T. cruzi*) were carried out and the best separation was obtained with three variables (E_T, α and Q_4, Table 1). This suggests that the other variables are not relevant for classifying these compounds according to their anti-trypanocidal activity.

The PCA results show that the first two PCs (PC_1 and PC_2) describe 96.43% of the overall variance as follows: $PC_1 = 63.84$ and $PC_2 = 32.59\%$. Since almost all of the variance is explained by the first two PCs, their score plot is a reliable representation of the spatial distribution of the points for the data set studied.

The score plots were examined and the most informative one is presented in Fig. 2 (PC_1 versus PC_2) and we can see that PC_1 alone is responsible for the separation between active and inactive compounds. Looking at Fig. 2, we can see that the 14 quinone compounds studied are separated into two

Table 1
Values obtained for the three most important properties (variables) that classify the 14 compounds studied

Compound	E_T (kcal/mol)	α (Å^3)	Q_4
1	−3073.490	21.189	−0.210
2	−3512.100	25.119	−0.215
3	−3058.360	22.216	−0.183
4	−3384.520	23.569	−0.210
5	−3412.890	22.685	−0.203
6	−3406.770	22.916	−0.432
7	−3924.020	34.947	−0.202
8	−3101.220	23.975	−0.222
9	−2322.820	14.443	−0.186
10	−2917.450	20.022	−0.209
11	−2313.990	16.636	−0.222
12	−2463.760	16.094	−0.207
13	−2802.990	13.531	−0.179
14	−3073.570	20.802	0.187

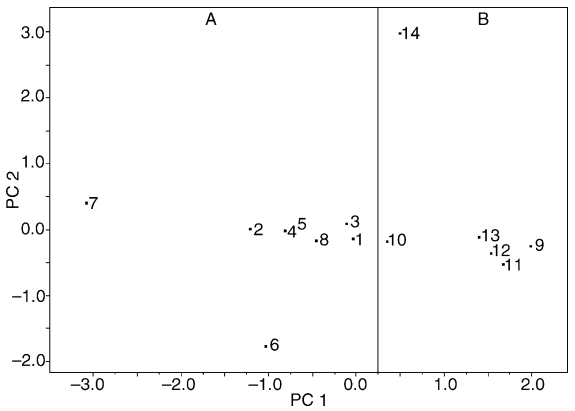


Fig. 2. PCA scores (PC_1 and PC_2) for the 14 compounds with anti-trypanocidal activity. The PCA methodology leads to a separation between two groups: active (Group A) and inactive (Group B) compounds.

groups: A (active compounds—compounds **1** to **8** in Fig. 1) and B (inactive compounds—compounds **9** to **14** in Fig. 1) where $PC_1 < 0$ for the active compounds and $PC1 > 0$ for the inactive ones.

Fig. 3 displays the plot of the loading vectors for the first two PCs (PC_1 and PC_2) and Table 2 shows the loading values of the selected variables in PC_1 and PC_2. According to Table 2, PC_1 can be expressed through the following equation:

$$PC_1 = 0.699[E_T] - 0.698[Pol] + 0.154[Q_4] \quad (1)$$

From Eq. (1), we can see that active molecules ($PC_1 < 0$) can be obtained when we have higher

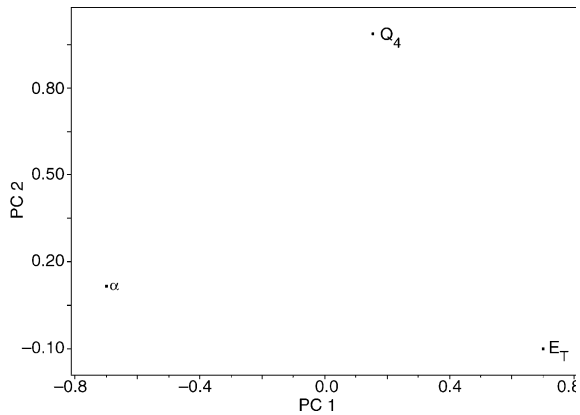


Fig. 3. PCA loading vectors (PC_1 and PC_2) for the three variables responsible for the separation between the active and inactive compounds: E_T is the total energy of the compound, α is the polarizability and Q_4 is the net atomic charge on atom R_1.

Table 2
Loading values for the first two principal components

Variable	PC_1	PC_2
E_T	0.699	−0.101
α	−0.698	0.117
Q_4	0.154	0.988

values for α (notice that α has negative coefficient in the PC_1 equation) combined with negative charges on atom at position 4 and negative values for the variable E_T.

Regarding the total energy (E_T), we can define it as the sum of the core–core repulsion and electronic energies. Thus, the smaller the total energy of a compound, the greater its chemical stability. For the active compounds studied, it is necessary that these compounds present negative values for E_T (since $PC_1 < 0$) and this means that the active compounds present high chemical stability.

For analysing the polarizability, we assumed that the molar polarization of a substance is given by the equation below

$$P_M = \left(\frac{\varepsilon - 1}{\varepsilon + 2}\right)\frac{MW}{d} \quad (2)$$

where ε represents the dielectric constant, MW is the molecular weight and d is the density. If $\varepsilon \approx n^2$, where n is the refractive index of a substance, $P_M =$ MR (molar refractivity) [33]. If a molecule with no permanent dipole is placed in a field of strength F, an induced dipole of magnitude M will develop. The magnitude is related to F by the equation

$$M = \alpha F \quad (3)$$

where α is the polarizability and α, in turns, is related to P_M and MR and is obtained by

$$P_M = \frac{4\pi N\alpha}{3} \quad (4)$$

where N is the Avogadro's number. Thus, α is a constant with dimensions of volume and, consequently, the polarizability of a molecule is a good measure of its volume [34]. As P_M can be equal to MR and α is directly related with P_M, we can consider that α is directly related with MR as well. The role of MR can be ambivalent, i.e. MR can represent dispersive

forces which help the interaction between substituents and the biological receptor and, in these cases, it is expected a positive coefficient for MR. The other MR character arises from the fact that MR can represent a measure of the molecular volume and, thereby, it can measure the capacity of the substituent in distorting the conformation of the receptor and, thus, avoiding the interaction receptor–substratum. So, a negative signal for MR coefficients reflects stereochemical hindrances [33,34].

For the active compounds studied, the polarizability must present high positive values and this indicates that some substituents in the active compounds can interact with polar groups of the biological receptor or some modifications on the receptor can occur due to the size of these substituents avoiding the interaction between the quinone compounds and the biological receptor.

On the charge at atom 4, we would like to pay attention to the fact that for the active compounds it is important to have atoms with negative charge at position 4, i.e. more electron-acceptor atoms at position 4 are required for the active compounds, as they could react with an electron-donor biological receptor.

These characteristics on the quinones studied in this work can be useful in the design of new quinone compounds with anti-trypanocidal activity. Here it is interesting to mention that the variables E_T, α and Q_4 are electronic descriptors (we must recall that α can represent steric effects as well) and we can suppose that a molecular association between active quinone compounds and the biological receptor can occur by electrostatic interaction and stereochemical effects can be relevant as well.

3.2. Hierarchical cluster analysis

In the HCA, each object (the 14 molecules studied) is initially assumed to be a lone cluster. One similarity matrix is built, generally calculating the Euclidean distance between all the objects, and scanned for the minor values. The corresponding objects are clustered together and treated as a single cluster, and successive iterations lead to the total clustering of all objects generating a dendrogram with the objects clustered together according to their similarity level [32].

Fig. 4 shows the results obtained from the HCA analysis. The horizontal lines in Fig. 4 represent the compounds and the vertical lines the similarity values between pairs of compounds, a compound and a group of compounds and between groups of compounds. The similarity value between the two classes of compounds was 0.237 and this means these two classes are distinct. From Fig. 4, we can see that HCA results are very similar to those obtained with the PCA analysis, i.e. the compounds studied were grouped into two categories: actives (compounds **1** to **8**—Group A in Fig. 4) and inactives (compounds **9** to **14**—Group B in Fig. 4) and only one inactive compound (compound **10**) was classified as active.

3.3. Stepwise discriminant analysis

Discriminant analysis is a multivariate technique that has two principal goals: (1) separate objects from distinct populations; (2) allocate new objects to populations previously defined [32,35]. In this work, we considered two groups: Group A, which contains the active compounds (compounds **1**–**8** in Fig. 1) and Group B, which contains the inactive compounds (compounds **9**–**14** in Fig. 1).

The SDA is a linear discriminant method based on the Fisher test (F-test) for the significance of the variables [35]. In each step, one variable is selected based on its significance and after some steps, the more significant variables are extracted from the variable set under investigation. In this work, the variables selected by SDA were: E_T, α and Q_4, and the discriminant functions are given as follows:

$$\text{Group A} : -83.779 - 0.053E_T - 0.967\alpha - 55.207Q_4$$

$$\text{Group B} : -52.461 - 0.045E_T - 1.171\alpha - 38.885Q_4$$

The three variables selected (E_T, α and Q_4) represent the strength of a molecular association by electrostatic interaction. By using the quantities given in the discriminant functions above, we can obtain the classification summary showed in Table 3.

The classification error rate was 0%, resulting in a satisfactory separation of the two groups. The allocation rule derived from the SDA results, when the anti-trypanocidal activity of a new quinone compound is investigated, is: (a) initially one

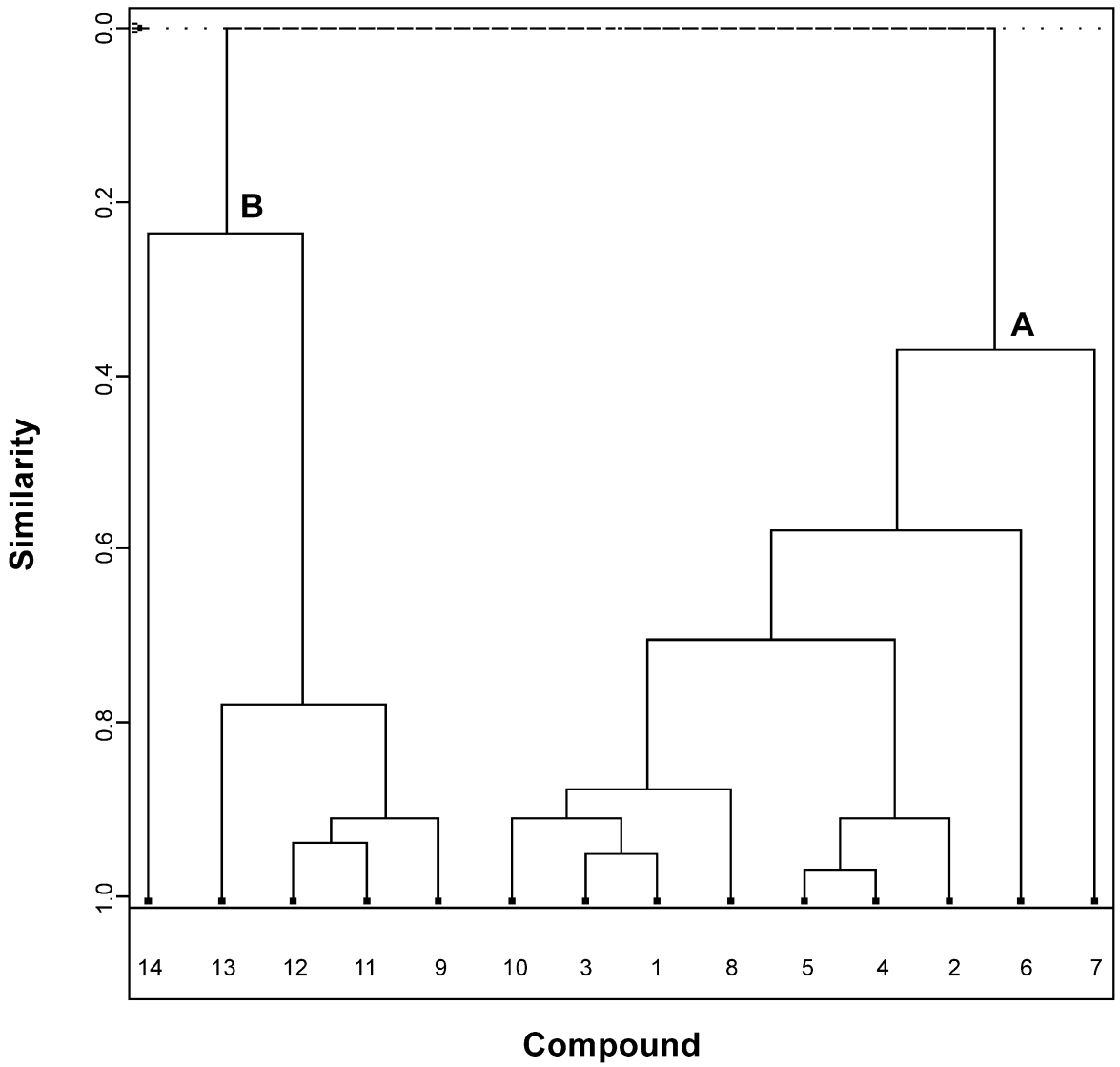


Fig. 4. Dendrogram obtained for the 14 quinone compounds studied. The compounds are grouped into two categories: A (actives) and B (inactives).

calculates, for the new quinone compound, the value of the more important variables obtained with the SDA methodology (E_T, α and Q_4); (b) substitute these values in the two discriminant functions obtained in this work; (c) check which discriminant function (Group A—anti-trypanocidal active compounds or Group B—anti-trypanocidal inactive compounds) presents the higher value. The new quinone compound is active if the higher value is related to the discriminant function of Group A and vice versa.

Table 3
Classification matrix obtained by using SDA

Classified group	True group	
	A	B
A	8	0
B	0	6
Total	8	6
Percentage	100	100

Table 4
Cross-validation matrix obtained by using SDA

Classified group	True group	
	A	B
A	8	0
B	0	6
Total	8	6
Percentage	100	100

Besides the classification matrix presented in Table 3, we also used a cross-validation test which uses the 'leave-one-out' methodology in order to determine if the model obtained is reliable. In this procedure, one compound is omitted of the data set and the classification functions are built based on the remaining compounds. Afterwards, the omitted compound is classified according the classification functions generated. In the next step, the omitted compound is included and a new compound is removed, and the procedure goes on until the last compound is removed. The results obtained with the cross-validation methodology are summarized in Table 4, and from these results we can verify that the model obtained with PCA, HCA and SDA is reliable once the cross-validation error is equal to 0%.

Comparing the results obtained with the PCA, HCA and SDA methodologies we can notice that the variables E_T, α and Q_4 are important in the three methodologies. Thus, combining the results obtained with PCA, HCA and SDA we can say that E_T, α and Q_4 are key variables for explaining the anti-trypanocidal activity of the quinone compounds studied in this work, mainly when one is trying to obtain (design) quinone compounds with anti-trypanocidal activity.

It is interesting to notice that the three variables (E_T, α and Q_4) found here as having an important role in anti-trypanocidal activity are predominantly electronic descriptors (and α can represent steric effects as well). Therefore, we can conclude that electronic and steric properties have an important role in the anti-trypanocidal activity of quinone compounds. Particularly, as the descriptors E_T, α and Q_4 represent the strength of a molecular association by electronic interaction, it is reasonable to suggest that electrostatic interactions play an important role in the mechanism of quinone compounds that present anti-trypanocidal activity.

3.4. Kth nearest neighbor

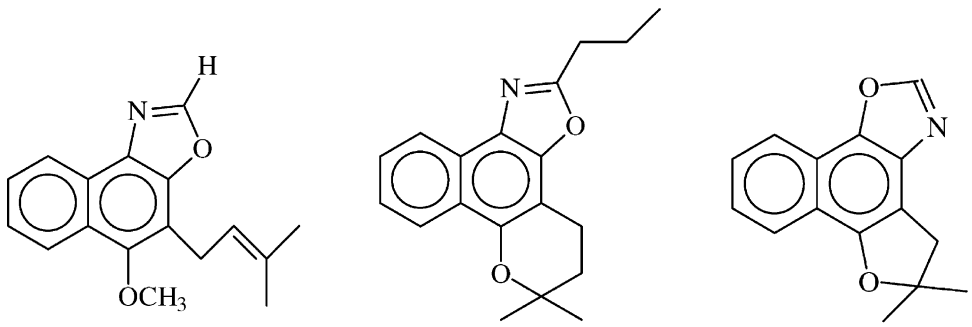
The KNN method classifies a new compound (object) according to its distance to an object of the training set. The closer neighbors of the training set are found and the object will be assigned into the class that have the majority of its nearest neighbors. This method is self-validating because in the training set each sample (object) is compared with all of the others in the set but not with itself. The best value of K can be chosen based on the results from the training set alone [36]. The classical KNN approach does not have outlier detection capability, i.e. a classification is always made whether or not the unknown object is a member of any class in the training set.

This method was used in this work for the validation of the initial data set and Table 5 presents the results obtained with 1 (1NN), 3 (3NN), 5 (5NN) and 7 (7NN) nearest neighbors. For all cases (1NN, 3NN, 5NN and 7NN), the percentage of correct information was 85.7%. We decided to use 7NN instead of 1NN, 3NN and 5NN because the greater the number of nearest neighbors, the better the reliability of the KNN method. The result obtained with the KNN method is similar to those obtained with the PCA, HCA and SDA.

After employing the four classification methods in the training set, we decided to apply them to a series of new quinone compounds which have similar chemical structure to the ones of our training set and whose activity against *T. cruzi* were well-known [17]. In fact, the opportunity of applying our methodology

Table 5
Classification obtained with the KNN method

Category	Number of compounds	Compounds incorrectly classified			
		1NN	3NN	5NN	7NN
Active	8	0	0	0	0
Inactive	6	2	2	2	2
Total	14	2	2	2	2
Percentage of correct information		85.7	85.7	85.7	85.7



1T(active) 2T (active) 3T (inactive)

Fig. 5. Chemical structure of the three new quinone compounds (test set).

Table 6
Values obtained for the properties (variables) of the three new quinone compounds (test set)

Compound	E_T (kcal/mol)	α (Å^3)	Q_4
1T	−3256.200	26.161	−0.200
2T	−3568.710	28.573	−0.233
3T	−2945.170	22.639	−0.017

in a new set of quinone compounds, whose activity against *T. cruzi* is already known previously, would be a good chance to validate the models we had obtained with our training set.

Fig. 5 shows the chemical structure of the three new quinone compounds (numbered as 1T to 3T). The calculated properties for the three new compounds are shown in Table 6. In order to verify if these new molecules would be active or inactive against *T. cruzi*, we had to apply the results obtained with the four pattern recognition methods, PCA, HCA, SDA and KNN, previously employed in our 14 molecules of the training set.

Table 7
The prediction results obtained with the four pattern recognition methods for the three new quinone compounds (test set): active compound (+) and inactive compound (−)

Compound	Activity			
	PCA	HCA	SDA	KNN
1T	+	+	+	−
2T	+	+	+	+
3T	−	−	−	−

From the results obtained, we can see that compound 2T was classified as active by using the four methods (PCA, HCA, SDA and KNN) and compound 1T was classified as active with PCA, HCA and SDA methodologies. The other compound (compound 3T) was classified as inactive by using all four methods. The prediction results are summarized in Table 7 and from it we can conclude that the models obtained for the training set with PCA, HCA, SDA and KNN can be applied to new quinone compounds whose biological activity is unknown, as the three new the quinone compounds were classified correctly according to our models, i.e. compounds 1T and 2T are active and compound 3T is inactive against *T. cruzi* [17].

4. Conclusions

The PCA and HCA showed that the quinone compounds studied in this work can be correctly classified into two groups according to their anti-trypanocidal activity: Group A (active compounds) and Group B (inactive compounds). The PCA results showed that the variables E_T, α and Q_4 are responsible for the separation between the compounds of the groups A and B.

The SDA showed that the two groups A (active compounds) and B (inactive compounds) were well separated and the same three variables, E_T, α and Q_4, are responsible for the separation between the active

and inactive compounds. The error rate was 0% and this suggests an allocation rule to classify new quinone compounds as active or inactive against *T. cruzi*.

Since E_T, α and Q_4 are electronic descriptors (and α can represent steric effects as well) we conclude that electronic and steric properties have an important role in anti-trypanocidal activity of quinone compounds. Particularly, as the descriptors E_T, α and Q_4 represent the strength of a molecular association by electronic interaction, it is reasonable to suggest that electrostatic interactions play an important role in the molecular mechanism of quinone compounds that present anti-trypanocidal activity.

The results obtained for the training set (the 14 compounds under study) with PCA, HCA, SDA and KNN methods were applied to three new quinone compounds with known activity against *T. cruzi*. Two of them were classified as active and the other one was classified as inactive against *T. cruzi*. These results corroborated the reliability of our models obtained by using the variables E_T, α and Q_4, as the three new quinone compounds were classified correctly according to our models, i.e. compounds 1T and 2T are active and compound 3T is inactive against *T. cruzi*.

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