Available online at www.sciencedirect.com
SCIENCE DIRECT
European Journal of Medicinal Chemistry 41 (2006) 616–623
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://france.elsevier.com/direct/ejmech

Original article

A density functional study of flavonoid compounds with anti-HIV activity

J. Lameira [a], C.N. Alves [a,*], V. Moliner [b], E. Silla [c]

[a] *Departamento de Química, Centro de Ciências Exatas e Naturais, Universidade Federal do Pará - UFPA, CP 11101, 66075-110 Belém, PA, Brazil*
[b] *Departament de Ciències Experimentals, Universitat Jaume I, 12071 Castellón, Spain*
[c] *Departament de Química Física, Universitat de Valencia, 46100 Burjasot, Valencia, Spain*

Received 10 October 2005; revised and accepted 24 January 2006
Available online 13 March 2006

Abstract

Quantum chemical calculations at the DFT/B3LYP theory level, with the 6-31G* basis set, was employed to calculate a set of molecular properties of 26 flavonoid compounds with anti-HIV activity. The correlation between biological activity and structural properties was obtained by using the multiple linear regression method. The model obtained showed not only statistical significance but also predictive ability. We demonstrate in this paper that the anti-HIV activity of compounds can be related with the molecular hydrophobicity (ClogP), the electronegativity (χ) and the charges on some key atoms, while that the toxicity can be related with the electronic affinities (EA), ClogP and charge on atom 8.

Keywords: Flavonoids; MLR; DFT; HIV; QSAR

1. Introduction

Flavonoids are a class of naturally occurring phenolic plant compounds that show biological and pharmacological activity coupled with low toxicity [1]. These compounds are widely distributed in the plant kingdom and ingested daily by humans. Therefore, their use as potential therapeutic compounds against a variety of diseases is of interest [2]. The biological activities of flavones have been extensively reviewed [2,3]. Some of them have demonstrated extensive biological activities such as anti-inflammatory and anti-allergic [4], mutagenic and carcinogenic [5,6] and anti-HIV [7].

In a previous work [8,9], we employ PM3 method to investigate which properties would be more effective for classifying 21 flavonoid compounds according to their anti-HIV activity. We found that five variables, namely χ (electronegativity) LUMO, and charges on atoms 2, 3 and 7, were responsible for activity of the 21 flavonoid compounds (Figs. 1 and 2). We found that higher values of χ were related with more active flavonoid. Similar results were found recently by Olivero-Verbel and Pacheco-Londoño [10] that divided 29 flavonoid compounds in three different groups to develop QSAR models but employing descriptors calculated by the semiempirical method AM1. In most QSAR studies the energy of the LUMO, negative of koopman's EA, have been considered to be a measure of EA. Nevertheless, semiempirical methods approximate certain properties up to a certain level, and it is obvious that variation in LUMO energy values of various congeners is very small, so an important error can be introduced if a low level quantum method is employed in the calculations.

In this work we employed density functional theory (DFT) using the B3LYP hybrid functional to explore and determine various electronic descriptors, with better accuracy, to make the necessary improvement in the QSAR models. Ionization potential (IP), electron affinity (EA), χ (electronegativity), hardness (η), softness (S), electrophilicity index (ω), charges and other properties were obtained for 26 flavonoid compounds, which do not have sugar in its structures (Fig. 2). The DFT-based reactivity descriptors such as χ, η, S and ω, that have an important role in many areas of research [11], were obtained through exact descriptions (for IP and EA). The multiple linear regression (MLR) method [12] was employed with the aim to obtain a correlation between these descriptors and the anti-HIV activity of these compounds.

* Corresponding author. Tel.: +55 91 211 1365; fax: +55 91 318 31635.
E-mail address: nahum@ufpa.br (C.N. Alves).

0223-5234/$ - see front matter © 2006 Elsevier SAS. All rights reserved.
doi:10.1016/j.ejmech.2006.01.008

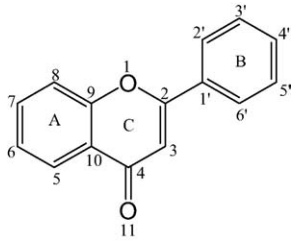

Fig. 1. Structural skeleton and numbering of the flavonoid compounds studied.

2. Calculation

2.1. Calculated properties

Quantum chemical calculations at the DFT/RB3LYP (restricted B3LYP) of level theory, together with the 6-31G* basis set, were used to determine the geometry and energies of the selected neutral compounds. The geometrical structures of the radicals studied were optimized independently from the neutral molecules prior to the calculations of energies, treated as open shell systems DFT/UB3LYP. All calculations were performed by using the Gaussian 03 package of programs [13].

In this work the more relevance electronic properties to anti-HIV activity were calculated such as: ionization potential (IP), electronic affinities (EA), electronegativity (χ), hardness (η), softness (S), electrophilicity index (ω) and charge on some key atoms. The calculated ionization potentials (IP) and electronic affinity (EA) were not corrected for zero-point energy, assuming a negligible error and thus saving computer-time. The IP was calculated as the energy differences between a radical cation (Ec) and the respective neutral molecule (En); IP = Ec – En. The EA was calculated as the energy differences between a radical anion (Ea) and the respective neutral molecule (En); EA = Ea – En. The DFT-based reactivity descriptors were obtained of Eqs. (1)–(4) [14–17].

$$\chi = -\mu = (\mathrm{IP}/\mathrm{EA})/2 \quad (1)$$

$$\eta = (\mathrm{IP} - \mathrm{EA})/2 \quad (2)$$

$$S = 1/(2\eta) \quad (3)$$

$$\omega = \mu^2/(2\eta) \quad (4)$$

Biological activities of molecules are highly influenced not only by their inherent electronic properties but also by their transportability. The transport of a compound through membranes can be modeled by molecular hydrophobicity, which can be described by octanol/water partition coefficients (CLogP). The value of this property was obtained by using the Chem-3D molecular package [18].

2.2. Statistical analysis

The more relevant properties were selected by stepwise multiple regression that was based on the forward-selection and backward-elimination methods. The independent variables were individually added or deleted from the model at each step of the regression depending on three criteria: the correlation coefficient (R), the Fisher ratio values (F) and the standard deviation (s). Variables were selected to enter or to remove until the "best" model is obtained. The Matlab software [19] was used in our statistical analyses.

The best equation was tested for their predictive power using a cross-validation procedure. Cross-validation is a practical and reliable method for testing this significance. In principle, the so-called "leave-one-out" approach consists in developing a number of models with one sample omitted at the time. After developing each model, the omitted data are predicted and the differences between actual and predicted y ($\mathrm{Log1/EC_{50}}$) values are calculated. The sum of squares of these differences is computed and finally the performance of the model (its predictive ability) can be given by the standard error of prediction (SEP) defined as:

$$\mathrm{SEP} = \sqrt{\frac{\sum_{i=1}^{n} (y_i - \hat{y}_i)^2}{n}} \quad (5)$$

where, y is the experimental $\mathrm{Log1/EC_{50}}$, $\hat{y}$ is the predicted value and n is the number of samples used for model building.

The predictive ability of the model was also quantified in terms of the Q^2 which is defined as:

$$Q^2 = 1.0 - \frac{\sum_{i=1}^{n} (y_i - {}^{y}{}_{i})^2}{\sum_{i=1}^{n} (y_i - -y^{-}{}_{i})^2} \mathit{where}, -y^{-} = y_{mean}. \quad (6)$$

2.3. Pharmacological data

Pharmacological data were taken from work of Hu et al. [7]. The biological evaluation of the flavonoids was done by using the log of the numerical indicator for activity, $\mathrm{EC_{50}}$, that indicates pharmacological potency (concentration which inhibits virus replication by 50%). The cytotoxic potencies of the compounds were measured as the concentration of flavonoid required to decrease uninfected lymphocyte cell growth to 50% of the untreated cell culture, $\mathrm{IC_{50}}$.

3. Results and discussion

3.1. QSAR models for the anti-HIV-1 activity

Fig. 1 shows the central chemical structure and numbering used in all 26 flavonoid compounds studied here (Fig. 2). Of 26 tested molecules two of them were not included in the model, those present, values reported as "greater than", therefore, in this work the MLR model was constructed with only 24 molecules (1–24), the two removed molecules (25 and 26) were used as test set (Fig. 2).

A number of models can be obtained using the log ($1/\mathrm{EC_{50}}$) as dependent variable and calculated properties as independent variables. In this work, the stepwise multiple regression procedure, based on the forward-selection and backward-elimination methods, was used for variable selection with the aim to obtain

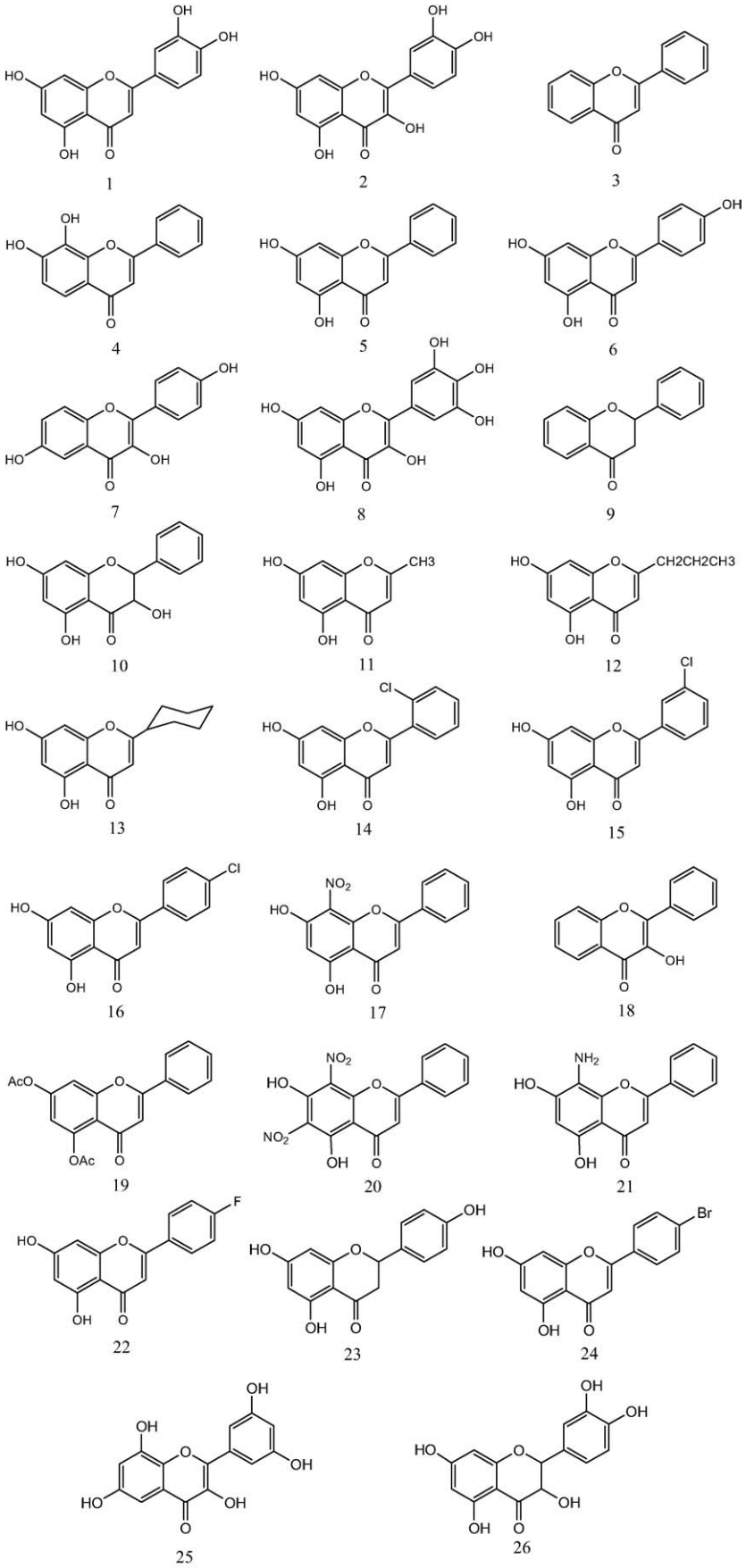

Fig. 2. Structure of the 26 flavonoids studied.

Table 1
Values of the five most important properties calculated and their respective values of activity (EC_{50})

Compounds	CLogP	χ (eV)	EA	C6	C7	C8	O11	log(1/IC_{50})	log(1/EC_{50})
1	2.310	3.337	–0.528	–0.254	0.380	–0.247	–0.594	4.796	5.000
2	1.304	3.158	–0.496	–0.256	0.382	–0.246	–0.631	3.879	3.879
3	3.480	3.686	–0.449	–0.131	-0.130	–0.18	–0.521	4.167	4.301
4	2.733	3.560	–0.320	–0.190	0.318	0.249	–0.526	4.854	5.000
5	3.563	3.451	–0.624	–0.253	0.380	–0.246	–0.591	4.328	5.301
6	2.906	3.414	–0.478	–0.254	0.379	–0.247	–0.594	4.456	5.046
7	1.640	3.658	–0.450	0.360	-0.189	–0.185	–0.563	3.804	3.914
8	0.637	3.128	–0.563	–0.217	0.380	–0.282	–0.632	4.161	4.456
9	3.475	3.953	0.050	–0.157	-0.124	–0.187	–0.471	4.347	4.237
10	2.035	3.742	–0.290	–0.257	0.387	–0.251	–0.572	4.357	4.553
11	1.964	3.978	0.170	–0.215	0.378	–0.279	–0.584	3.670	4.310
12	3.022	3.924	0.122	–0.215	0.378	–0.28	–0.586	4.137	4.569
13	4.085	3.904	0.141	–0.216	0.378	–0.28	–0.588	4.377	4.721
14	4.026	3.456	–0.689	–0.252	0.380	–0.243	–0.587	4.770	5.301
15	4.276	3.377	–0.884	–0.252	0.380	–0.245	–0.588	4.854	5.398
16	4.276	3.511	–0.567	–0.252	0.380	–0.246	–0.589	4.796	5.398
17	1.803	3.469	–1.016	–0.263	0.377	0.183	–0.588	4.921	4.921
18	2.843	3.349	–0.544	–0.136	-0.128	–0.179	–0.561	4.770	4.886
19	2.198	3.769	–0.131	–0.268	0.400	–0.274	–0.504	< 3.428	4.252
20	0.043	3.510	–1.577	0.157	0.338	0.222	–0.586	3.429	3.429
21	2.370	3.606	–0.387	–0.231	0.368	0.097	–0.589	4.469	4.959
22	3.706	3.443	–0.671	–0.253	0.380	–0.246	–0.59	4.886	5.398
23	2.445	3.849	0.068	–0.220	0.384	–0.289	–0.546	3.532	4.036
24	4.195	3.541	–0.654	–0.214	0.379	–0.283	–0.587	4.678	5.301
25	0.334	3.230	–0.674	0.374	-0.246	0.299	–0.556	< 3.480	< 3.480
26	0.771	3.767	0.103	–0.221	0.387	–0.570	–0.558	< 3.462	< 3.462

Table 2
Correlation matrix for descriptors included in the model, $N = 23$

	CLogP	χ	C6	C7	O11	log(1/EC_{50})
CLogP	1.000	0.105	–0.45	0.004	0.12	0.703
χ	0.105	1.000	0.067	–0.134	0.536	–0.45
C6	–0.449	0.067	1.000	–0.589	0.119	–0.63
C7	0.004	–0.134	–0.59	1.000	–0.545	0.359
O11	0.12	0.536	0.119	–0.545	1.000	–0.36
log(1/EC_{50})	0.703	–0.452	–0.63	0.359	–0.364	1.000

the best regression equation (in such a way that variables that swallow little increment or are redundant in the explanation of the dependent variable (log 1/EC_{50}) were not included). In order to avoid overfitting or difficulties in interpretation of the resulting models, pairs of variables with $r \geq 0.7$ were classified as intercorrelated ones, and only one of the variables was included in the model.

In a preliminary analyze, using all 24 molecules (1–24), the results indicated compound **2** to be an outlier. The standardized residual associated with molecule 2 was highest and greater than two (Table 3), values of standardized residual above of two are characteristic of outlier. It is common practice in QSAR studies to omit outliers in the spirit of exploratory data analysis. Hence, the compound **2** was excluded of model with the remaining 23 molecules. The omission of molecule 2 will be considered later in this section. After these considerations, the following forward-selection and backward-elimination models were obtained:

$$\mathrm{Log}(1/EC_{50}) = 7.74 + 0.75CLogP - 0.49\chi + 0.29C7 \quad (7)$$

$$R^2 = 0.86\ F = 37.75\ Q^2 = 0.80\ \mathrm{SEP} = 0.45\ N = 23.$$

Table 3
The anti-HIV activity predicted by using Eq. (1)

Compounds	Experimental Value	Predicted value	Residue residual	Research standard residual
1	5.000	4.930	0.070	0.315
2	3.879	4.591[a]	–0.712[a]	–2.539[a]
3	4.301	4.541	–0.240	–1.080
4	5.000	4.771	0.229	1.036
5	5.301	5.245	0.056	0.253
6	5.046	5.052	–0.006	–0.030
7	3.914	3.868	0.046	0.206
8	4.456	4.577	–0.121	–0.550
9	4.237	4.229	0.008	0.036
10	4.553	4.360	0.193	0.873
11	4.310	4.049	0.261	1.178
12	4.569	4.492	0.077	0.348
13	4.721	4.897	–0.176	–0.790
14	5.301	5.405	–0.104	–0.470
15	5.398	5.588	–0.190	–0.860
16	5.398	5.43	–0.032	–0.140
17	4.921	4.591	0.330	1.492
18	4.886	4.711	0.175	0.790
19	4.252	4.397	–0.145	–0.650
20	3.429	3.881	–0.452	–2.04
21	4.959	4.625	0.334	1.507
22	5.398	5.306	0.092	0.417
23	4.036	4.378	–0.342	–1.550
24	5.301	5.365	–0.064	–0.290

[a] Values obtained with the model for 24 molecules.

$$\mathrm{Log}(1/EC_{50}) = 7.95 + 0.61CLogP - 0.49\chi - 0.32C6 \quad (8)$$

$$R^2 = 0.86\ F = 37.90\ Q^2 = 0.75\ \mathrm{SEP} = 0.50\ N = 23.$$

$$\mathrm{Log}(1/EC_{50}) = 5.08 + 0.78C\mathrm{LogP} - 0.40\chi - 0.24O11 \quad (9)$$

$$R^2 = 0.82\ F = 27.91\ Q^2 = 0.75\ \mathrm{SEP} = 0.50\ N = 23.$$

$$\mathrm{Log}(1/EC_{50}) = 5.40 + 0.64CLogP - 0.39\chi - 0.30C6 - 0.19O11 \quad (10)$$

$$R^2 = 0.88\ F = 33.86\ Q^2 = 0.78\ \mathrm{SEP} = 0.47\ N = 23.$$

The respective log ($1/EC_{50}$) values for all the 26 flavonoid compounds studied are shown in Table 1. In previous equations CLogP is logarithm of partition coefficient, χ is the electronegativity and C6, C7, O11 are the charge on atoms 6, 7 and 11, respectively. The squared correlation coefficient, R^2, is a measure of the fit of the regression model, Q^2 is the cross-validation correlation coefficient, F the Fisher test, reflects the ratio of the variance explained by the model and variance due to the error in the model, high values of the F-test indicate the significance of the equation and SEP, as explained in previous section, is the SEP.

We obtained the correlation matrix between biological values and the respective calculated properties (Table 2). According to the principle of statistics, a regression equation is of no relevance when the variables are mutually interrelated by simple or multiple correlations (we considered correlated variables to those that possess correlation coefficients above 0.70), or either, they are no orthogonal. The correlation matrix shows that the properties in this study are independent.

Of the four models presented above, the Eq. (7) is the one that presents the best quality statistics, or either, the greater values for significance ($F = 37.75$) and previsibility ($Q^2 = 0.80$) and the lowest value for error of prediction (SEP = 0.45). Therefore, we will only argue this model. The fit of model 1 is shown in Fig. 3. The evaluation of the regression coefficients in the model—Eq. (7)—shows that CLogP has the highest contributions to the variation in log ($1/EC_{50}$). From Table 3, we can see the agreement between the observed and calculated values are satisfactory. It is interesting to mention that the variable CLogP is a measure of hydrophobicity; molecules with large value of CLogP have higher hydrophobicity and consequently better transport through membranes. In Table 1, we can observed that the compound with values of CLogP between 2 and 4 are the most active, while the compound with minor values of CLogP, such as, compounds **20**, **25** and **26** (with values of CLogP of 0.043, 0.334, 0.771, respectively) are less active. We can also observe that molecule 2 contains five OH groups in its structure, such as molecule 25. However, molecule 25 has a value of CLogP of 0.334, while molecule 2 has 1.304. This would explain the highest residue found for this compound; however, other methods of calculations of CLogP must be performed to prove this hypothesis.

On the other hand, also two electronic properties were important in the model 1; the electronegativity (χ) and charge on atom 7. According to Pearson's theory the absolute eletronegativity is a measure of the intrinsic donor–acceptor character of a species and determines the direction of electron transfer between two molecules when they react [15]. The eletronegativity varies from 3.128 to 3.978 eV. In principle, any molecules can act as an electron donor to all molecules with superior values to its [15]. These values are next to values found for the water molecule ($\chi = 3.1$ eV). Fesen et al. [20] have showed the inhibition of HIV-1 integrase by flavonoids and several works have hypothesized that the drugs could act by chelating the divalent metal (Mg^{2+}) in the integrase active site [21,22]. According to Pearson's HSAB theory metal ions such as Mg^{2+} can interact with bases such as water or flavonoids [20]. In accordance with the values observed in Table 1 and Eq (7) we can presume that in general more active flavonoid have minor value for χ. The charge in atoms 6 or 7 might be understood as a measure of extension of the electronic delocalization around the ring A. C7 and χ are all electronic descriptors;

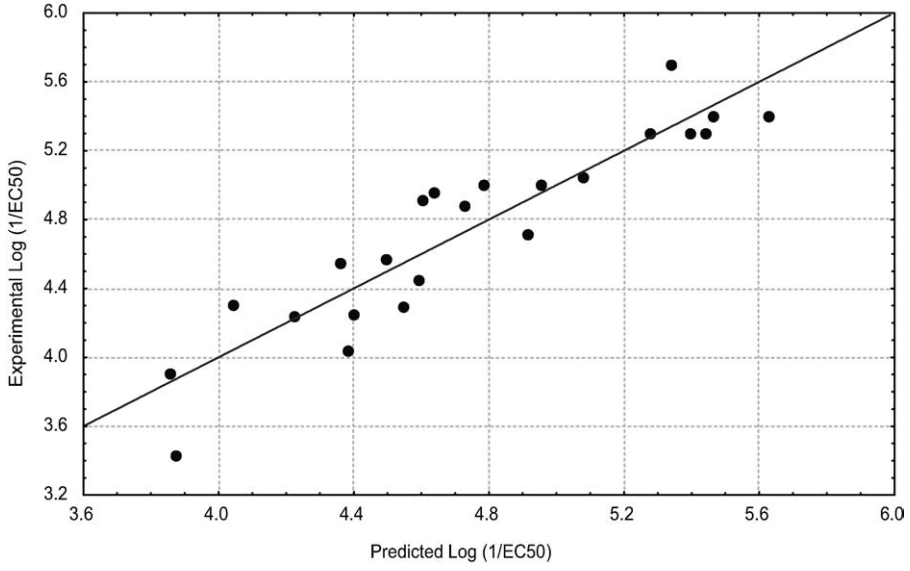

Fig. 3. Experimental versus predicted log($1/EC_{50}$) for Eq. (1).

Table 4
The anti-HIV activity predicted for test set by using Eqs. (7)–(10)

Compounds	Calc. Eq. (7)	Calc. Eq. (8)	Calc. Eq. (9)	Calc. Eq. (10)	Experimental
25	3.860	3.779	4.118	3.682	< 3.480
26	3.877	3.982	3.766	3.956	< 3.462

therefore we can conclude that electronic effects have a very important role when one is trying to understand the activity of flavonoid compounds with anti-HIV activity.

It can be observed that for the set of compounds studied in this work, lower values for the variable χ combined with high positive charges on atom 7 (C7) and higher values for the variable CLogP lead to an increasing of the anti-HIV activity. Here it is also important to mention that the descriptor χ is related to the strength of molecular association by charge transfer and the atomic charges (C7, C6 and O11) to the electrostatic interaction between the drug and a center of opposite charge on the receptor. Also the biological activity is highly influenced not only by their inherent electronic properties but also by their transportability represented by CLogP.

We apply the four models, along with the RML method, in the two flavonoid compounds (set test), whose activities well not were been defined. Table 4 shows the prediction values obtained for the test set with the Eqs. (7)–(10). We can observe a good prediction for these molecules.

3.2. QSAR models for the cytotoxicity against lymphocyte cells

The stepwise multiple regression procedure also was used to find the best models capable of the describer the toxicity of 23 studied compounds. The compounds **19**, **25** and **26** was excluded of model, because they not have accurate toxicity and were used as test set. Two models were obtained using the log ($1/IC_{50}$) as dependent variable and calculated properties as independent variables.

In first analysis, using the 23 molecules, the results indicated compounds **1** and **20** to be an outlier. Therefore, these compounds were excluded. After that the molecules 1 and 20 were excluded of the model, the following forward-selection and backward-elimination models were obtained:

$$\mathrm{Log}(1/IC_{50}) = 6.763 + 0.72CLogP - 0.48\chi + 0.51C8 \quad (11)$$

$$R^2 = 0.75\ F = 17.37\ Q^2 = 0.66\ \mathrm{SEP} = 0.57\ N = 21.$$

$$\mathrm{Log}(1/IC_{50}) = 3.70 + 0.56CLogP - 0.49EA + 0.39\mathrm{C}8 \quad (12)$$

$$R^2 = 0.75\ F = 16.88\ Q^2 = 0.68\ \mathrm{SEP} = 0.55\ N = 21.$$

The respective log ($1/IC_{50}$), electronic affinities (EA) and charge on atoms 8 (C8) values for all the 26 flavonoid compounds studied are shown in Table 1. We obtained the correlation matrix between log ($1/IC_{50}$) values and the respective calculated properties and log ($1/EC_{50}$) (Table 5). The correlation matrix shows that the properties in the same model described by the Eqs. (11) and (12) are independent. We can observe a correlation between EA and χ (correlation coefficient of 0.797), and also between the log ($1/IC_{50}$) and log ($1/EC_{50}$) (correlation coefficient of 0.844).

Table 5
Correlation matrix for descriptors included in the model of the toxicity, $N = 21$

	CLogP	χ	EA	C8	log($1/IC_{50}$)	log($1/EC_{50}$)
CLogP	1.000	0.197	–0.080	–0.207	0.515	0.653
χ	0.197	1.000	0.797	–0.078	–0.380	–0.320
EA	–0.080	0.797	1.000	–0.247	–0.630	–0.550
C8	–0.210	–0.078	–0.247	1.000	0.398	0.128
log($1/IC_{50}$)	0.515	–0.379	–0.627	0.398	1.000	0.844
log($1/EC_{50}$)	0.653	–0.319	–0.547	0.128	0.844	1.000

Table 6
The toxicity predicted by using Eq. (12)

Compounds	Experimental value	Predicted value	Residue residual	Research standard residual
1	4.796	4.268[a]	0.528	2.307
2	3.879	4.027	–0.150	–0.650
3	4.167	4.551	–0.380	–1.680
4	4.854	4.762	0.092	0.401
5	4.328	4.604	–0.280	–1.210
6	4.456	4.370	0.086	0.376
7	3.804	4.139	–0.330	–1.460
8	4.161	3.882	0.279	1.220
9	4.347	4.243	0.104	0.456
10	4.357	4.060	0.297	1.297
11	3.670	3.739	–0.070	–0.300
12	4.137	4.001	0.136	0.595
13	4.377	4.225	0.152	0.666
14	4.770	4.749	0.021	0.093
15	4.854	4.919	–0.060	–0.280
16	4.796	4.728	0.068	0.299
17	4.921	4.904	0.017	0.074
18	4.770	4.468	0.302	1.321
20	3.429	4.892[a]	–1.460	–6.400
21	4.469	4.561	–0.090	–0.400
22	4.886	4.664	0.222	0.971
23	3.532	3.896	–0.360	–1.590
24	4.678	4.723	–0.040	–0.200

[a] Values obtained with the model for 23 molecules.

Of the two models presented above, the Eq. (12) is the one that presents the best quality statistics, or either, the greater previsibility ($Q^2 = 0.68$) and the lower value for error of prediction (SEP = 0.55). The fit of model 12 is shown in Fig. 4. The evaluation of the regression coefficients in the model—Eq. (12)—shows also that CLogP has the highest contributions to the variation in log ($1/IC_{50}$). From Table 6, we can see the agreement between the observed and calculated values are relatively satisfactory. In Table 7 we can observe a good prediction for these molecules. Second the Eq. (12), more negatives values for the variable EA combined with high positive charges on atom 8 (C8) and higher values for the variable CLogP lead to an increasing of the toxicity of the set of compounds studied in this work.

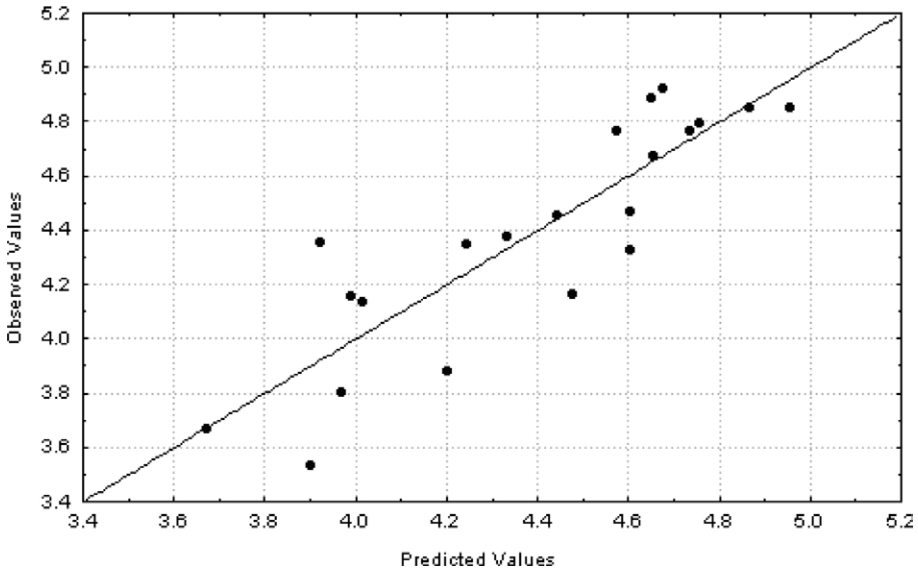

Fig. 4. Experimental versus predicted $\log(1/IC_{50})$ for Eq. (12).

Table 7
The anti-HIV toxicity predicted for test set by using Eqs. (11) and (12)

Compounds	Calc. Eq. (11)	Calc. Eq. (12)	Experimental
19	3.914	4.086	< 3.428
25	4.612	4.497	< 3.480
26	3.106	3.207	< 3.462

4. Conclusions

Significant regression equations were obtained by MLR for 23 flavonoid compounds according to their anti-HIV activity. The best regression equation obtained was based on the following descriptors: electronegativity (χ), atomic charge on atom C7 and CLogP. The model obtained showed not only statistical significance but also predictive ability and revealed that lower values for χ combined with high positive charges on C7 and higher values for CLogP lead to an increasing of the anti-HIV activity. These variables allowed a physical explanation of electronic molecular properties contributing to HIV inhibitory potency as the electronic character relates directly to the electron distribution of interacting molecules at the active site. Also the biological activity is highly influenced not only by their inherent electronic properties but also by their transportability represented by CLogP. We demonstrate that the toxicity of compounds can be related with the electronic affinities (EA), charge on atom 8 and CLogP. Second this model more negatives values for EA combined with high positive charges on C8 and higher values for CLogP lead to an increasing of the toxicity.

Acknowledgements

The authors would like to thank CNPq, FINEP and CAPES (Brazilian Agencies) for the financial support in this work.

References

[1] B. Havsteen, Biochem. Pharmacol. 23 (1983) 1141–1148.
[2] H.K. Wang, Y. Xia, Z.Y. Yang, S.L.M. Natschke, K.H. Lee, Adv. Exp. Med. Biol. 439 (1998) 191.
[3] B.H. Havsteen, Pharmacol. Ther. 96 (2002) 67–202.
[4] M. Gabor, Prog. Clin. Biol. Res. 213 (1986) 471–480.
[5] J.T. MacGregor, Prog. Clin. Biol. Res. 213 (1986) 411–424.
[6] A. Das, J.H. Wang, E.J. Lien, Prog. Drug Res. 42 (1994) 133–166.
[7] C. Hu, K. Chen, Q. Shi, R.E. Kilkuskie, Y. Cheng, K.H. Lee, K. H. J. Nat. Prod. 57 (1994) 42–51.
[8] C.N. Alves, J.C. Pinheiro, A.J. Camargo, A.J. Souza, R.B. Carvalho, A.B.F. da Silva, J. Mol. Struct. THEOCHEM 491 (1999) 123–131.
[9] C.N. Alves, J.C. Pinheiro, A.J. Camargo, M.C.C. Ferreira, R.A. Romero, A.B.F. da Silva, J. Mol. Struct. THEOCHEM 541 (2001) 81–88.
[10] J. Olivero-Verbel, L. Pacheco-Londoño, J. Chem. Inf. Comput. Sci. 42 (2002) 1241–1246.
[11] H. Chermette, J. Comput. Chem. 20 (1999) 129–154.
[12] B.R. Kowalski, Chemometrics "Mathematics and Statistics in Chemistry", D. Reidel Publ Comp, Dordrecht, 1984.
[13] Gaussian 03, Revision C.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian, Inc.; Wallingford, CT, 2004.
[14] W. Kohn, A.D. Becke, R.G. Parr, J. Phys. Chem. 10 (1996) 12974–12980.
[15] R.G. Parr, R.G. Pearson, J. Am. Chem. Soc. 105 (1983) 7512–7516.
[16] R.G. Parr, L.V. Szentpaly, S. Liu, J. Am. Chem. Soc. 121 (1999) 1922–1924.

[17] P.K. Chattaraj, H. Lee, R.G. Parr, J. Am. Chem. Soc. 113 (1991) 1855–1856.
[18] CS Chem 3D Ultra Molecular Modeling and Analyses, Cambridge soft, 2001.
[19] MATLAB, Mathworks Inc., Natick, MA, 1998.
[20] M.R. Fesen, F. Leteurtre, S. Hiroguchi, J. Yung, K.W. Kohn, Biochem. Pharmacol. 48 (1994) 595–608.
[21] N. Neamati, Z. Lin, R.G. Karki, A. Orr, K. Cowansage, D. Strumberg, G.C.G. Pais, J.H. Voigt, M.C. Nicklaus, H.E. Winslow, H. Zhao, J.A. Turpin, J. Yi, A.M. Skalka, T.R. Burke, J. Med. Chem. 45 (2002) 5661–5670.
[22] W.G. Virschueren, I. Dierynck, L.I.E. Amssoms, L. Hu, P.M.J. G. Boonants, G.M.E. Pille, F.F.D. Daeyaert, K. Hertogs, D.L.N. G. Surleraux, P.B.T.P. Wigerinck, J. Med. Chem. 48 (2005) 1930–1940.