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Simple criterion for selection of flavonoid compounds with anti-HIV activity

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Abstract—Flavonoid compounds represent an important natural source of antiretrovirals for AIDS therapy due to their significant anti-HIV-1 activity and low toxicity. Here we propose a simple theoretical criterion to discriminate active from inactive flavonoids that is suitable for rapid in silico screening of flavonoid libraries, and selection and optimization of lead compounds with anti-HIV-1 activity.

Over the past 25 years, since the first case of HIV/AIDS was identified, AIDS has become the largest and most devastating public health pandemic of our time, that has infected nearly 70 million people and left 25 million dead. Around the world, the number of people living with HIV is now 40.3 million. It is estimated that five million people will become newly infected with HIV in 2006 and that, during this same time period, more than three million people will likely die of AIDS-related illnesses.

The introduction of highly active antiretroviral therapy targeting HIV reverse transcriptase and protease (HAART) has dramatically improved survival and quality of life for HIV patients. Despite the effectiveness of HAART in controlling HIV-1 replication, the emergence of drug-resistant viruses in infected patients and the severe side effects caused by the currently used drug regimen necessitate continued search for new inhibitors targeted toward other viral proteins.

One viral protein that represents a promising target for antiretroviral therapy is HIV-1 integrase (IN). IN catalyzes the integration of viral cDNA into the host genomic DNA, a two-step process that is essential for the replication of HIV-1.[1] The recent demonstration that efficient IN inhibitors may possess a strong antiviral potency in vivo proved the pertinence of this approach.[2] The most potent compounds, now entering phase III clinical trial, are inhibitors of the strand transfer which constitutes the second step of the integration process.[3,4] Nevertheless, several lines of evidence suggest that inhibitors of the first integration step, or 3′ processing, may also represent an interesting lead.[5] Furthermore IN affects other steps in viral replication besides integration itself (viral particle formation, particle release, infectivity, the particle-associated reverse transcriptase activity, and nuclear localization of the preintegration complex (PIC)).[6–10] It is important to note that IN has no known counterpart or 'homolog' in mammalian cells. Because of the pleiotropic activity and specificity IN represents an attractive target for chemotherapy that could affect multiple steps in viral replication.[11,12]

In the last decade, many different classes of compounds have been reported to inhibit HIV-1 IN. An important one is that of the polyhydroxylated aromatics encompassing flavonoid compounds, naturally occurring phenolic plant compounds with anti-HIV-1 IN activity.[13] This class of compounds is a natural source for

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development of potent lead compounds of HIV-1 IN inhibitors.[14]

New technologies such as combinatorial chemistry and high-throughput screening (HTS) which allow synthesis of millions or possibly billions of compounds require chemists to confront an unimaginably large and diverse 'chemical landscape'. Attempts must therefore be made to introduce a variety of computational techniques that allow chemists to reduce by virtual screening (VS) huge molecular libraries to a more manageable size. For this reason, determination of the criterions that allow discrimination between anti-HIV-1 active and inactive flavonoids and their derivatives by in silico screening would represent an important step forward in selecting candidate flavonoid-based anti-HIV-1 compounds. Recently, two such theoretical criterions have been proposed.[15,16] Souza and co-workers using pattern recognition techniques, principal component analysis (PCA), hierarchical cluster analysis (HCA), stepwise discrimination analysis (SDA), and K-nearest neighbor (KNN) determined a criterion based on the partition coefficient, molecular volume, and electron affinity for classification of flavonoid compounds according to their degree of anti-HIV-1 activity.[15] Lemeira and co-workers used a similar approach to show that the molecular hydrophobicity, the charge on atom 11, and the electrophilic index represent properties which are responsible for the discrimination between anti-HIV-1 IN active and inactive flavonoid compounds.[16]

Here we propose a very simple and efficient criterion based on the electron–ion interaction potential (EIIP) and the average quasi valence number (AQVN) for selection of anti-HIV-1 active flavonoids.

The electron–ion interaction potential (EIIP). The intermolecular interactions in biological systems encompass two basic steps: (i) specific long-distance targeting of interacting molecules and (ii) chemical bond formation between interacting molecules. The first step is determined by selective long-range forces which are efficient at a distance longer than one linear dimension of the interacting macromolecules (10^2–10^3).[17–19] These forces directly influence the number of productive collisions between interacting molecules. Before covalent or non-covalent chemical bond formation takes place between interacting molecules (flavonoids can form both types of chemical bond with their targets), their reacting regions must be positioned close enough (at a distance of ~ 2 Å) for the reaction to follow, because the attractive forces involved in the recognition and binding of molecules include all the weak non-covalent forces (van der Waals, hydrogen bonding, ionic interactions, etc.) which operate over a very short distance range (< 10 Å).

It has been proposed that the number of valence electrons and the electron–ion interaction potential (EIIP), representing the main energy term of valence electrons, are important physical parameters which determine the long-range properties of biological molecules.[20] The EIIP can be calculated for organic molecules by the following simple equation,[20,21] derived from the 'general model pseudopotential':[22–24]

$$\mathrm{EIIP} = 0.25Z^* \sin(1.04\pi Z^*)/2\pi \quad (1)$$

where Z^* is the average quasivalence number (AQVN):

$$Z^* = \sum^{m} n_i Z_i / N \quad (2)$$

where Z_i is the valence number of the i-th atomic component, n_i is the number of atoms of the i-th component, m is the number of atomic components in the molecule, and N is the total number of atoms. The EIIP values calculated according to Eqs. (1) and (2) are in Rydbergs (Ry). A strong connection has been demonstrated between EIIP and AQVN of organic molecules and their biological activity (mutagenicity, carcinogenicity, toxicity, antibiotic and cytostatic activity, etc.).[20,21,25–28] It was shown that all these activities, which are usually conditioned by the ability of a molecule or its metabolites to interact covalently or non-covalently with various cellular or extra-cellular targets, are also influenced by the electronic properties EIIP and AQVN of molecules, which determine long-range interactions. It is of note that these parameters do not depend on the molecular structure (see Eqs. (1) and (2)) suggesting that long-distance recognition and targeting between interacting molecules are also structurally invariant. We will further use the parameters EIIP and AQVN for the analysis of flavonoid compounds with anti-HIV-1 activity.

Recently, Souza and co-workers, using as a selection criterion EC_{50} (concentration that inhibits the virus replication by 50%),[29] established the training set encompassing 22 flavonoid compounds with anti-HIV-1 activity (Table 1).[15] The compounds listed in Table 1 are divided into two groups: those that inhibit HIV-1 replication with an EC_{50} less than 100 μM were considered, active whereas those that produced weak or undetectable inhibitory activity at $\geqslant 100$ μM were considered inactive (this activity criterion was also used in analysis of other compounds in this work). By applying the pattern recognition techniques, the principal component analysis, the hierarchical cluster analysis, stepwise discrimination analysis, and the K-nearest neighbor analysis to this training set, Souza and co-workers proposed criterion for selection of flavonoid compounds with anti-HIV-1 activity.[15] They showed that log P (partition coefficient), molecular volume, and electron affinity represent the essential variables for discrimination between anti-HIV-1 active and inactive flavonoid compounds.

By employing density functional theory, Lameira and co-workers calculated a set of molecular properties of 32 flavonoid compounds with anti-HIV-1 IN activity.[16] Based on results of this analysis a criterion has been proposed for selection of flavonoid compounds with anti-HIV-1 IN activity which uses the molecular hydrophobicity, the charge on atom 11, and the electrophilic index as parameters for separation between active and inactive compounds. Of note the training set of flavonoid compounds used in this study encompassed all active compounds and 8 of 13 inactive compounds from the Souza's training set are presented in Table 1.

Table 1. Chemical name, activity indication, EIIP and AQVN values for the compounds used in this work as a training set[15]

Number	Chemical name	Activity	Compound (abbreviation)	EIIP [Ry]	AQVN	Lipinski[a]
1	3,3′,4′,5,6,7-Hexahydroxy flavone	Active	Quercetagetin	0.1100	3.576	3
2	3,3′,4′,5′,7-Pentahydroxy flavone	Active	Robinetin	0.1260	3.500	4
3	3,3′,4′,5,5′,7-Hexahydroxy flavone	Active	Myricetin	0.1100	3.576	3
4	3,3′,4′,5,7-Pentahydroxy flavone	Active	Quercetin	0.1100	3.576	4
5	3,3′,4′,7-Tetrahydroxy flavone	Active	Fisetin	0.1339	3.419	4
6	3,3′,4′,5-Tetrahydroxy-7-methoxy flavone	Active	Rhamnetin	0.1341	3.372	4
7	2′,3,4′,5,7-Pentahydroxy flavone	Active	Morin	0.1100	3.500	4
8	3′,4′,5,7-Tetrahydroxy-6-methoxy flavone	Active	6-MeO-Luteolin	0.1341	3.372	4
9	3,4′,5,7-Tetrahydroxy flavone	Active	Kaempferol	0.1339	3.419	4
10	4′,5,7-Trihydroxy flavone	Inactive	Apigenin	0.1319	3.333	4
11	3′,4′,5,6,7-Pentamethoxy flavone	Inactive	Sinensetin	0.0519	3.021	4
12	7-Hydroxy flavone	Inactive	7-OH flavone	0.0934	3.143	4
13	7-Hydroxy-3,4′-dimethoxy flavone	Inactive	7-OH-3,4′-MeO flavone	0.0835	3.111	4
14	4′,5,6,7-Tetramethoxy flavone	Inactive	4′,5,6,7-MeO flavone	0.0526	3.023	4
15	5,7-Dihydroxy-4′-methoxy flavone	Inactive	Acacetin	0.1121	3.212	4
16	5,7-Dihydroxy flavone	Inactive	5,7-OH flavone	0.1319	3.333	4
17	4′,5-Dihydroxy-7-methoxy flavone	Inactive	Genkwanin	0.1121	3.212	4
18	3′,4′,5,6-Tetramethoxy flavone	Inactive	3′,4′,5,6′-MeO flavone	0.0526	3.023	4
19	4′,5,6,7,8-Pentamethoxy flavone	Inactive	Tangeritin	0.0519	3.021	4
20	3′,4′-Dihydroxy flavone	Inactive	3′,4′-OH flavone	0.1185	3.241	4
21	6,7-Dihydroxy flavone	Inactive	6,7-OH flavone	0.1185	3.241	4
22	5-Hydroxy-5,7,3′,5′-tetramethoxy flavone	Inactive	Quercetin tetramethyl ether	0.0768	3.091	4

[a] Data were taken from the Anti-HIV/OI Chemical Compound Database (http://chemdb2.niaid.nih.gov).

The strong correlation between AQVN and EIIP values of organic molecules and their biological activities has been previously demonstrated.[20] Thus, it was interesting to investigate the possible relationship between these simple parameters of flavonoid compounds and their anti-HIV-1 activity. In Table 1 the values are given of AQVN and EIIP calculated for the training set proposed by Souza and co-workers.[15] As can be seen from the data presented in Table 1 and Figure 1, all active anti-HIV flavonoid compounds are grouped in the AQVN interval (3.34–3.59) and the EIIP interval (0.1100 and 0.1350 Ry) and all inactive flavonoids are outside of these intervals. According to these results, flavonoids with EIIP values between 0.1100 and 0.1350 Ry and AQVN values between 3.34 and 3.59 could be considered as compounds with anti-HIV activity. It should be noted that the EIIP interval ∈(0.0–0.14 Ry) and AQVN interval ∈(2.2–3.8) correspond to a homogeneous distribution of natural compounds.[20] All active, as well as inactive flavonoid compounds from the training set have the maximal values of the Lipinski's index (see Table 1). This indicates that properties of flavonoids from Table 1 which determine their specific anti-HIV activity differ from the features commonly found in active drugs.[30]

As proof of concept for application of the proposed EIIP/AQVN criterion for selection of flavonoids with anti-HIV activity, we analyzed 17 compounds selected from the set of 32 compounds which Lemeira and co-workers used as a training set.[16] Other 15 compounds from the Lameira's training set are included in the

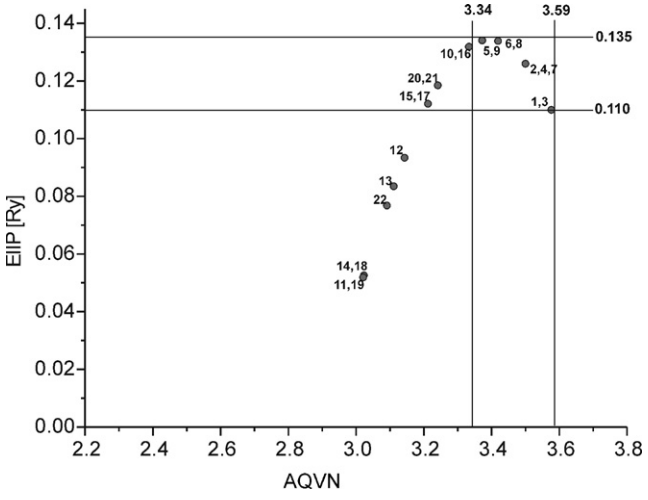


Figure 1. The relationship between AQVN and EIIP values of flavones listed in Table 1 and their anti-HIV activity.[15]

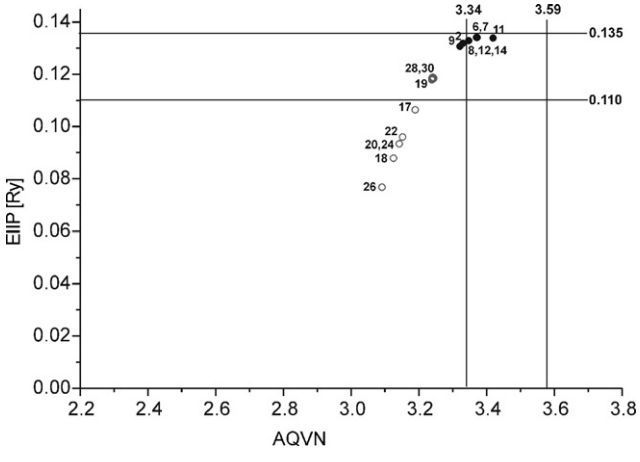
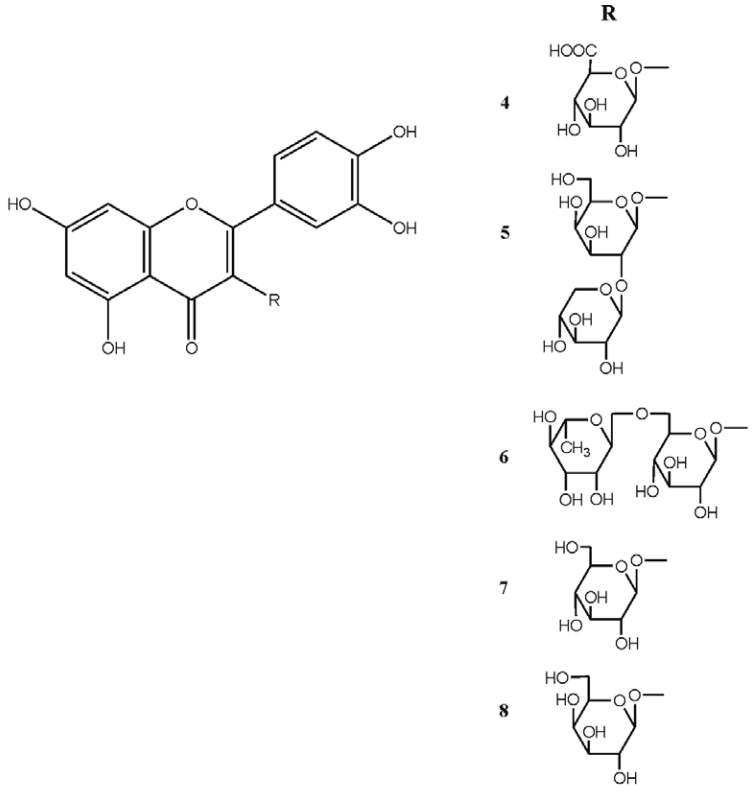


Figure 2. Separation of anti-HIV-1 active and inactive flavones by the EIIP/AQVN criterion (●—active, ○—inactive compounds). The abbreviation of compounds corresponds to their numbering in Ref. 16.

Souza's training set listed in Table 1. Results presented in Figure 2 demonstrate that 6 of 8 active and all 9 inactive compounds are in agreement with the proposed EIIP/AQVN criterion. The only exceptions are compounds **2** and **9** identified in this analysis as "false negative" anti-HIV flavonoid compounds. This result indicates that the predictive capacity of the EIIP/AQVN criterion is ≈ 90%.

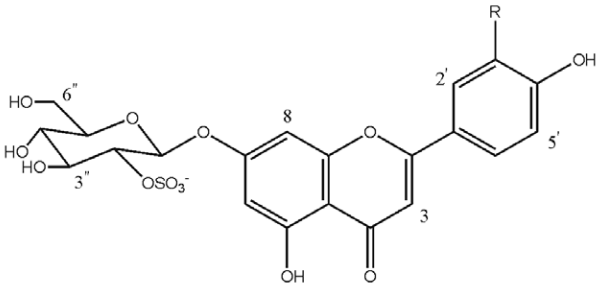
Further, we analyzed five flavonoid compounds isolated from the leaves of *Nelumbo nucifera*,[31] and three flavonoid compounds isolated from the Caribbean sea grass

a



Compound	EIIP [Ry]	AQVN	Predicted activity	Reported activity [31]
4	0.1310	3.462	active	active
5	0.1216	3.257	inactive	inactive
6	0.0979	3.158	inactive	inactive
7	0.1307	3.321	inactive	inactive
8	0.1307	3.321	inactive	inactive

b



Compound	EIIP [Ry]	AQVN	Predicted activity	Reported activity [32]
1	0.1245	3.509	active	active
2	0.1339	3.421	active	active
3	0.1308	3.463	active	active

Figure 3. The anti-HIV activity and EIIP and AQVN values of flavones isolated from (a) the leaves of *N. nucifera*[31] and (b) *T. testudinum*.[32]. The abbreviation of compounds corresponds to their numbering in Refs. 31 and 32.

Thalassia testudinum.[32] As can be seen from results presented in Figure 3, the predicted and reported anti-HIV-1 activities of all analyzed flavonoid compounds are in accord.

Finally, we compared the predictive capacity of our EIIP/AQVN criterion with the more complex criterion proposed by Souza and co-workers.[15] These authors performed a prediction study with a set of nine flavonoid compounds (Table 2) in order to verify which molecules of this set would be predicted to be active against HIV-1. According to this analysis, the compounds **I**, **II**, **III**, **IV**, **V**, **VI**, **VII** and **IX** were predicted as inactive and only the compound **VIII** was predicted as active against HIV-1.[15] According to the EIIP/AQVN criterion, only compound **VIII** can be predicted as active. These results demonstrate that the predictive capacities of our simple EIIP/AQVN criterion and the more complex criterion based on PCA, HCA, SDA, and KNN methods[15] are similar.

Over 4000 structurally unique flavonoids have been identified from plants.[33,34] Because of their high biological activity and low toxicity flavonoids represent a valuable natural source of molecules for identification of new anti-HIV drug candidates. There has been also increasing interest in the research of flavonoids from dietary sources, due to growing evidence of the versatile health benefits of flavonoids through clinical studies performed with HIV^+ patients. So, recently it has been demonstrated that ingestion of flavonoid-rich fruit juices might be favorable to HIV patients due to enhanced lymphocyte proliferation, which could restore disturbances in T-cell homeostasis.[35] Reliable values for the presence of flavonoids in food are needed to test the possible protective effects of flavonoids against different diseases including HIV infection. To address these needs, the United States Department of Agriculture (USDA) has developed a Special Interest Database of critically evaluated analytical data on selected compounds within five subclasses of dietary flavonoids. Twenty-five of the

Table 2. The abbreviation, AQVN and EIIP values and activities predicted by the EIIP/AQVN criterion and by the PCA, HCA, SDA and KNN methods[15] for the compounds used in this work as a prediction set

Number	Chemical name	AQVN	EIIP [Ry]	Predicted activity [EIIP/AQVN]	Predicted activity (Ref. 11)
I	3-Methoxy flavone	3.032	0.0560	Inactive	Inactive
II	4′,5-Dihydroxy-3′,5′–dimethoxy-6,7(2″, 2″-Dimethylpyran flavone)	3.061	0.0664	Inactive	Inactive
III	3′-Acetoxi-4′,7-dimethoxy flavone	3.123	0.0870	Inactive	Inactive
IV	4′,5,6-Trihydroxyflavone-3′,5′,7-trimethoxy flavone	3.238	0.1179	Inactive	Inactive
V	3′,4′,5′,6,7-Pentamethoxy flavone	3.021	0.0519	Inactive	Inactive
VI	5-hydroxy-3′,4′,5-Trimethoxy-6,7 (2″,2″Dimethylpyran) flavone	3.000	0.0439	Inactive	Inactive
VII	4′,5-Diacetate-3′,5′,6,7-tetramethoxy-flavone	3.164	0.0995	Inactive	Inactive
VIII	4′,5′,3,5,6,7-Hexahydroxy flavone	3.576	0.1100	Active	Active
IX	6,2,3,4-Tetramethoxy flavone	3.023	0.0526	Inactive	Inactive

Table 3. The AQVN and EIIP values and predicted anti-HIV-1 activity of the most abundant flavonoids in foods[36]

Nutr_No	Flavonoid	AQVN	EIIP [Ry]	Predicted activity
731	Cyanidin	3.344	0.1327	Active
741	Delphinidin	3.424	0.1337	Active
742	Malvidin	3.205	0.1104	Inactive
743	Pelargonidin	3.303	0.1158	Inactive
745	Peonidin	3.229	0.1158	Inactive
746	Petunidin	3.306	0.1290	Inactive
749	(+)-Catechin	3.143	0.0934	Inactive
750	(−)-Epigallocatechin	3.222	0.1144	Inactive
751	(−)-Epicatechin	3.143	0.0934	Inactive
752	(−)-Epicatechin 3-gallate	3.320	0.1310	Inactive
753	(−)-Epigallocatechin 3-gallate	3.373	0.1341	Active
755	Theaflavin	3.175	0.1026	Inactive
758	Eriodictyol	3.273	0.1240	Inactive
759	Hesperetin	3.167	0.1004	Inactive
762	Naringenin	3.188	0.1060	Inactive
770	Apigenin	3.333	0.1319	Inactive
773	Luteolin	3.419	0.1339	Active
785	Isorhamnetin	3.371	0.1341	Active
786	Kaempferol	3.419	0.1339	Active
788	Myrecetin	3.576	0.1100	Active
789	Quercetin	3.500	0.1260	Active
791	Theflavin-3,3′-digallate	3.464	0.1307	Active
792	Theflavin-3′-gallate	3.383	0.1344	Active
793	Theflavin-3-gallate	3.383	0.1344	Active
794	(+)-Gallocatetchin	3.222	0.1144	Inactive

most commonly occurring flavonoids in food over these five subclasses were included in this database.[36] Food containing some of these flavonoids could have positive effects in HIV patients. For this reason, we calculated the EIIP and AQVN values for these flavonoids and predicted their possible anti-HIV activity. According to results presented in Table 3, 11 of 25 analyzed flavonoids are predicted as active anti-HIV-1 compounds. The literature survey revealed that 8 of 11 flavonoids which are in Table 3 predicted as active (kaempferol, myrecetin, luteolin, quercetin, (−)-epigallocatechin 3-gallate, theaflavin-3,3′-digallate, theaflavin-3′-gallate, and heflavin-3-gallate) have been reported as anti-HIV-1 compounds.[15,37–45] Contrary, no one of 14 flavonoids predicted as inactive in Table 3 has been reported in the literature as an anti-HIV-1 compound. These results together with data from the USDA Database for the Flavonoid Content of Selected Foods (http://www.nal.usda.gov/fnic/foodcomp) can be used for selection of food which could have a beneficial effect for HIV patients.

The simple EIIP/AQVN criterion described in this paper can be used to discriminate flavonoids that are active or inactive in inhibiting HIV infection. The comparison with other more complex approaches for in silico selection of flavonoids with anti-HIV-1 activity shows a good correlation. As a corollary, the EIIP/AQVN approach can be used for powerful and rapid in silico screening of flavonoids and flavonoid-derived compounds, and for identification and optimization of new *lead* compounds with anti-HIV-1 activity.

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