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Efavirenz derivatives and marine natural compounds with anti-HIV activity: similarity, molecular modeling, and QSAR studies

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Abstract

The paper presents a theoretical study on the similarity between marine natural structures (avarol from *Dysidea cinerea*) and synthetically efavirenz derivatives with HIV-1 reverse transcriptase inhibitory activity. All compounds were molecular modeled and analyzed by conformational pint of view. The most stable conformations have very good superposition revealing similarities between these natural and synthetic compounds with anti-HIV activity. Further, quantitative structure-activity relationships analysis was performed for an efavirenz class consists of 43 compounds, and for other two subclasses with particular structures (31 and 16 structures, respectively). The best mono- and bilinear mathematical models were obtained in the case of efavirenz derivative subclasses by using autocorrelation descriptor, weighted by atomic polarizabilities descriptors for the first subclass, Broto-Moreau autocorrelation of a topological structure, weighted by atomic polarizabilities and with the leverage-weighted autocorrelation weighted by atomic polarizabilities descriptors for the second subclass (correlation coefficients >0.83).

Keywords: marine natural compounds, avarol, efavirenz, HIV-1 reverse transcriptase inhibitors, molecular modeling, QSAR

1. Introduction

Human Immunodeficiency Virus (HIV) is one of the major problems at the global level [1,2]. It is responsible for the AIDS syndrome (Acquired Immune Deficiency Syndrome), which is practically the final manifestation of this virus. The HIV virus attacks certain white blood cells (CD4+ T lymphocytes), which belong to the human immune system [2]. As the immune system begins to weaken, the white blood cells become unable to resist against diseases and fight against germs. Germs that normally would be rapidly neutralized remain in the body and multiply. AIDS is not caused by HIV itself, as with a common viral illness, but is due to the inability of the immune system to fight against infection. In medical terms, a series or group of symptoms and conditions that tend to act together is called a syndrome. Hence the name of disease is Acquired Immune Deficiency Syndrome (AIDS) [1-3]. Usually a person infected with HIV dies in about 10 years because of AIDS. WHO (World Health Organization) estimated that there are more than 34 million people worldwide living with HIV/AIDS, with 2.7 million new HIV infections per year and 1.8 million annual deaths due to this disease [3].

The main HIV virus characteristics are [4]: (1) it has many forms, from the biochemical structure point of view; the most spread are HIV-1 and HIV-2 forms; the first form is more spread in America and Western Europe, while the second one in Africa; (2) HIV-2 is little bit less virulent in comparison with HIV-1; HIV-1 can be grouped in the following classes: group M (major), with 8 subtypes (the most spread being B

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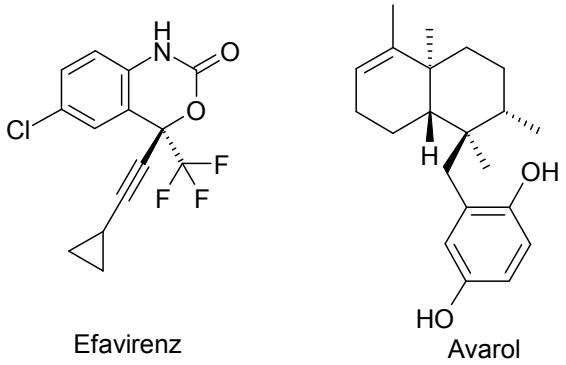
subtype), which is responsible for the most infections at a global level, group O (outlier), and group N (new), very rarely; (3) HIV attacks the most important cells from human immune system: monocytes/macrophages, Langerhans cells, T helper lymphocytes (they parasitize), affecting their function and leading to their premature destruction, so that in time leads to a lack of these cells and immunity. HIV also attack glial cells of the nervous system; (4) it is a slow-acting virus (HIV belongs of the genus *Lentivirus*, part of the family of *Retroviridae*). Evolution infection covers, on average, a period of 10 years.

The treatment against HIV virus is focused on the following directions: inhibitors of reverse transcriptase, inhibitors of HIV protease, and inhibitors of HIV integrase [4]. The first class is also grouped in nucleoside, nucleotide, and non-nucleoside reverse transcriptase inhibitors. The non-nucleoside reverse transcriptase inhibitors belong to several chemical classes and they imply different binding sites to the natural substrate. Non-nucleoside reverse transcriptase inhibitor class consists of more than 30 different classes of compounds, but only three drugs are approved for clinical use: nevirapine, delavirdine, and efavirenz [5-9].

Some natural compounds reveal also anti-HIV activity. Avarol and avarone derivatives (sesquiterpenoid class) were intensively studied as HIV-1 reverse transcriptase inhibitory activity [10-14]. These compounds were found in Red Sea fauna (mainly sponges and corals) and avarol was isolated from marine sponge *Dysidea cinerea* and was found to have potent *in vitro* inhibitory activity. Avarol derivatives have structures which resembling to efavirenz derivatives and could interact at the same site to the enzyme receptor.

In this paper the efavirenz and its derivatives, including resembling natural structures, were studied from the anti-HIV – structure relationship point of view. Forty three new efavirenz derivatives with HIV-1 reverse transcriptase inhibitory activity were correlated with a large number of structural descriptors and quantitative structure – activity relationships were developed.



Efavirenz Avarol

Figure 1. Structures of efavirenz and avarol (from marine source) with anti-HIV activity

2. Materials and methods

Structures and biological activities. A series of 43 benzo[d]oxazin-2-ones (efavirenz derivatives) resembling with avarol, having HIV-1 reverse transcriptase inhibitory activity were selected [6-8] and have structural variations at the C4-position of heterocyclic ring and in benzene ring (Figure 2). The biological activity (*A*) was considered the logarithm of the inverse of the molar concentration which inhibits the HIV-1 reverse transcriptase activity with 50%, $\log(1/IC_{50})$ (Table 1).

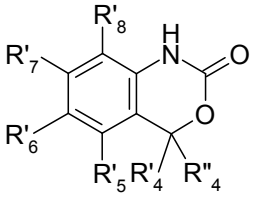


Figure 2. General structure of derivatives with anti-HIV activity

Table 1. Structures and HIV-1 reverse transcriptase inhibitory activity of efavirenz derivatives

No	R'$_4$	R"$_4$	R'$_5$	R'$_6$	R'$_7$	R'$_8$	log(1/IC_{50})
1	CF_3	C≡C-cPr	H	Cl	H	H	11.6990
2	CF_3	C≡C-Ph	H	Cl	H	H	11.0655
3	CF_3	Et	H	Cl	H	H	8.6383
4	CF_3	Ph	H	Cl	H	H	9.8386
5	CF_3	SPh	H	Cl	H	H	9.0655
6	CF_3	Allyl	H	Cl	H	H	9.6576
7	cPr	Pr	H	Cl	H	H	9.5129
8	Pr	Ph	H	Cl	H	H	8.2676
9	Et	Ph	H	Cl	H	H	9.5229
10	Et	Et	H	Cl	H	H	7.7825
11	Ph	C≡CH	H	Cl	H	H	9.1871
12	Et	Pr	H	Cl	H	H	10.2840
13	$CClF_2$	C≡C-Ph	H	Cl	H	H	10.9208
14	CF_3	C≡C-CH_2OMe	H	Cl	H	H	10.8239
15	CF_3	C≡C-CH_2OH	H	Cl	H	H	9.2596
16	Pr	C≡CH	H	Cl	H	H	8.7212
17	cPr	C≡C-CH_2OMe	H	Cl	H	H	9.3872
18	tBu	Pr	H	Cl	H	H	8.2757
19	CF_3	C≡C-cPr	H	H	H	H	9.3206
20	CF_3	C≡C-cPr	H	F	H	H	9.7212
21	CF_3	C≡C-cPr	H	iPr	H	H	8.7082
22	CF_3	C≡C-cPr	H	NMe_2	H	H	9.0883
23	CF_3	C≡C-cPr	H	OCF_3	H	H	8.9034
24	CF_3	C≡C-cPr	F	F	H	H	10.0757
25	CF_3	C≡C-cPr	F	H	H	F	9.0991
26	CF_3	C≡C-cPr	F	F	H	F	9.0969
27	CF_3	C≡C-cPr	F	F	F	H	9.3546
28	CF_3	C≡C-cPr	H	OMe	H	H	9.8827
29	CF_3	C≡C-cPr	H	Me	H	H	9.8761
30	CF_3	C≡C-cPr	F	H	H	H	10.1079
31	CF_3	C≡C-Et	F	H	H	H	9.8962
32	CF_3	C≡C-Pr	F	H	H	H	9.8069
33	CF_3	C≡C-iPr	F	H	H	H	9.9914
34	CF_3	C≡C-cPr	H	NO_2	H	H	9.6799
35	CF_3	C≡C-Et	H	NO_2	H	H	9.5591
36	CF_3	C≡C-Pr	H	NO_2	H	H	9.5171
37	CF_3	C≡C-iPr	H	NO_2	H	H	9.7011
38	CF_3	C≡C-cPr	H	NH_2	H	H	9.0958
39	CF_3	C≡C-Et	H	NH_2	H	H	8.7226
40	CF_3	C≡C-Pr	H	NH_2	H	H	8.8222
41	CF_3	C≡C-iPr	H	NH_2	H	H	9.0477
42	CF_3	C≡C-cPr	H	NHMe	H	H	9.2161
43	CF_3	C≡C-iPr	H	NHMe	H	H	9.3251

Molecular modeling. Molecular modeling of efavirenz derivative molecules was performed by using the molecular mechanics MM+ program from the HyperChem 5.1; a RMS of 0.01 kcal/mole and a Polak-Ribiere algorithm were used in the molecular modeling process.

Conformational analysis. In order to find the most stable conformations of efavirenz derivatives, a conformational analysis program (*Conformational Search* program, HyperChem 5.1) was used. Only the torsion angles corresponding to the C4 substituents were considered to the conformational analysis. The following conditions were set up for conformational search: variation of the flexible torsion angles ±60º ÷

±180º, energy criterion for acceptance of the conformation 4 kcal/mole above minimum, all conformations with atomic distances lower than 0.5 Å and differences between torsion angles lower than 15º were not considered as well as conformations with energy differences lower than 0.05 kcal/mole (duplicates); the maximum number of optimization and iterative calculations was 250 and maximum 20 conformations were retained. The hydrogen atoms were neglected.

Structural parameters. An exhaustive determination of a large number of structural descriptors was performed by using different *in house* programs, developed according to Todeschini *et al.* [15] and *QSAR Properties* program from HyperChem 5.1 package (total or polar/non-polar molecular surface and volume, hydration energy, log*P*, refractivity, polarizability). The other descriptor classes were following: constitutional (including total number of atoms, bonds, independent rings, flexible bonds, rigid bonds, heteroatoms, non-polar atoms, positive/negative ionization atoms, H-donor and H-acceptor atoms), topological, molecular walk, *BCUT* (descriptors derived from Burden matrix), *Galvez* (topological charge indices), 2D autocorrelation (autocorrelation descriptors, derived from topological descriptors), charge, aromaticity indices, *RDF* (radial distribution function descriptors), *3D-MoRSE*, *WHIM*, *Getaway*, functional groups, atom-centered fragments, empirical, and molecular property descriptors (Clog*P*, water solubility, log*Wsol* etc.) [15,16]. The minimum energy conformation for every compound was used for these determinations.

QSAR analysis. For the quantitative structure – activity relationships (QSAR) analysis in the efavirenz derivative compounds class with HIV-1 reverse transcriptase inhibitory activity the following mono- and bilinear mathematical models were used [16-23]:

$$\log(1/IC_{50})_i = a_0 + \sum_j b_{ij} \cdot P_{ij}$$

where P_{ij} represents the j parameter of the structure i, a_0 and b_{ij} are coefficients of the model.

Principal Component Analysis (PCA). The multivariate analysis of the descriptor data (descriptor classes) for efavirenz derivatives was achieved using the PCA analysis [24-28]. Principal component analysis (PCA) is the basis of the multivariate analysis of the data. PCA presumes an approximation of the *X* matrix (data) as a product of two reduced matrices, *T* and *P*, which retain only the useful information from *X*. The graphical representation of *T* columns conduct to the "object shape" images of *X*, and the graphical representation of *P* rows conduct to the "variable shape". Thus, the first direction (first principal component, PC_1) in the properties space, for which the data have maximum variance, conduct to the monodimensional representation of the data as projections on this PC_1; the second direction (named PC_2) has the same particularities, but it is perpendicular to PC_1. Other directions can be obtained in the same way, but only some of them will be PCs. The *X* matrix can be described as a sum of a useful matrix (**X*), which is a product of score matrix (**T*) and loadings matrix (**P*), and an error matrix (*E*). Representation of the *t* vectors (one to another) can conduct to information about similarities and possible grouping of the studied objects; the same representation of the *p* vectors can furnish the similarities between properties and the importance of these properties for the model.

3. Results and Discussion

In the benzo[d]oxazolin-2-one derivative series with HIV-1 reverse transcriptase inhibitory activity the standard compound, efavirenz, is used as approved anti-HIV drug. Molecular modeling and conformational analysis of these compounds revealed that the number of stable conformations was low due to the reduced number of flexible bonds. Thus, for the standard compounds efavirenz and avarol, the similar natural structure from marine sponge *Dysidea cinerea*, only two flexible bonds were selected for conformational analysis: cyclopropylalkynyl moiety from C4-position for efavirenz and benzyl moiety for avarol. In both cases a low number of stable conformations were identified and the most stable ones are superimposed; the bicyclic moieties as well as the cyclopropylalkynyl / arylalkyl moieties are in good superposition, this similarity suggesting a possible similar ligand-receptor interaction (Figure 3).

In order to evaluate the descriptor classes' similarities PCA analysis of all descriptor data for efavirenz derivatives was performed. PCA analysis was performed by sets of descriptor classes due to the large number of variables (almost 1500). Thus, for constitutional and topological descriptors conduct to

a good classification only for the first class. A better classification was obtained for *Randic*, aromaticity, and geometrical descriptor classes, the first and the second ones being clearly grouped in the PC_2 *vs.* PC_1 score plot. Similar behavior was observed in the case of *WHIM*, *Getaway*, and 2D-autocorrelation descriptor classes, but with a better classification for all these three classes. The same grouping was observed also for constitutional and the other properties descriptor classes.

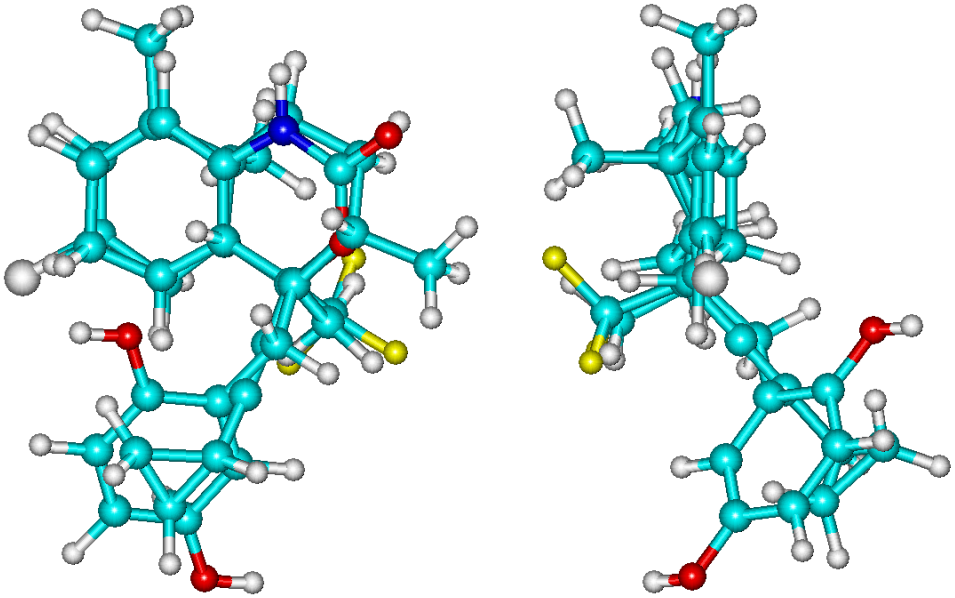


Figure 3. Superimposed most stable conformations of efavirenz and natural avarol

As a result, PCA analysis (Figure 4) suggests the use only one of every descriptor classes in the QSAR analysis, because the descriptors from every class generally intercorrelates. If it was used all compounds for QSAR studies, some statistically relevant correlation equations were obtained, but with low correlation coefficient. Thus, the best results were obtained in the case of topological or *Randic* descriptors *TI2* (second *Mohar* index), *VRA1* (*Randic*-type eigenvector-based index from adjacency matrix), *PCR* (ratio of multiple path counts to path counts), *T(F..Cl)* (sum of topological distances between F..Cl), for 2D-autocorrelational descriptor *ATS8v* (Broto-Moreau autocorrelation of a topological structure - lag 8 / weighted by atomic van der Waals volumes), for *3D-MoRSE* descriptor *Mor20m* (*3D-MoRSE* - signal 20 / weighted by atomic masses), *WHIM* descriptor *P1u* (first component shape directional *WHIM* index / unweighted), *Ku* (*K* global shape index / unweighted), and for constitutional descriptor *S* – van der Waals molecular surface. The main regression monolinear equations are presented below (Figure 5, Eqs. 1 and 2).

(Eq. 1)

$$A_i = 5.99(\pm 0.79) + 6.15(\pm 1.39) \cdot (P1u)_i$$

n = 43; r = 0.57

(Eq. 2)

$$A_i = 8.91(\pm 0.20) + 0.11(\pm 0.03) \cdot (RDF070m)_i$$

n = 43; r = 0.44

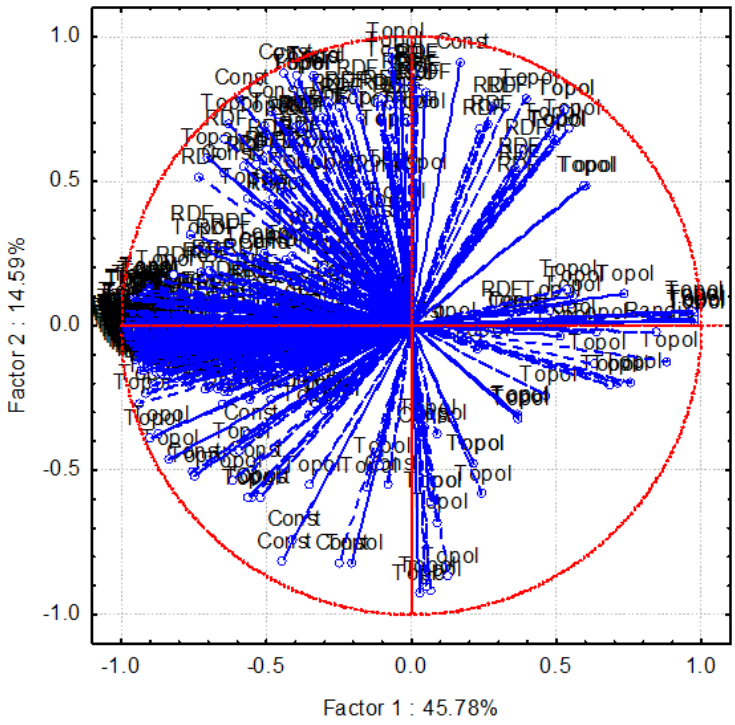


Figure 4. Score plot from PCA analysis of constitutional, *Randic*/topological, and *RDF* descriptor classes for anti-HIV efavirenz derivatives

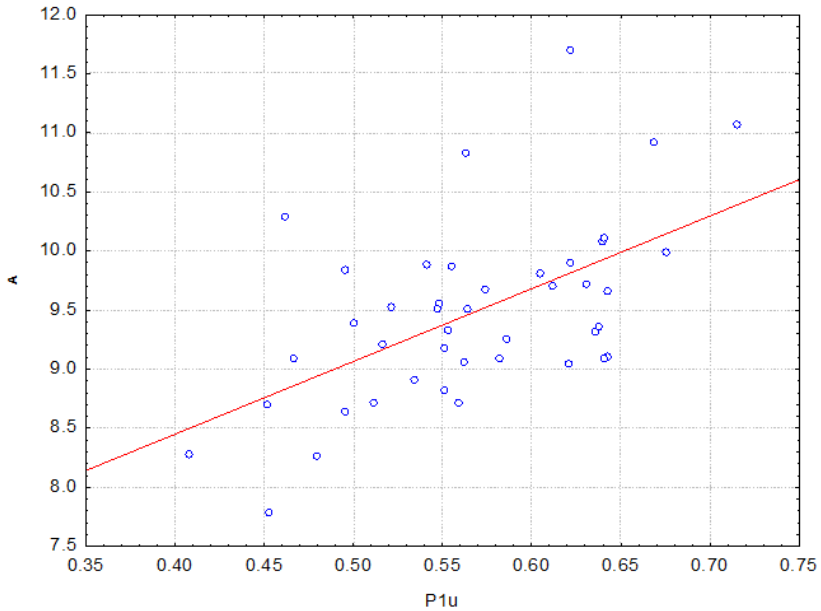


Figure 5. HIV-1 reverse transcriptase inhibitory activity (*A*) *versus P1u* descriptor for all efavirenz derivative class

A multilinear correlation conduct to a better equation if the *P1u* and *S* descriptors were used, the correlation coefficient being *r* = 0.61 (Eq. 3).

(Eq. 3)

$$A_i = 4.85(\pm 1.01) + 5.69(\pm 1.39) \cdot (P1u)_i + \\ + 0.0033(\pm 0.0019) \cdot (S)_i$$

n = 43; r = 0.61

Better results were obtained if the QSAR analysis was performed by using subsets of efavirenz derivatives. Thus, two types of subsets were selected: Set 1 - alkyl/cycloalkyl/aryl/arylalkyl-ethynyl derivatives (n = 31 compounds), and Set 2 - cyclopropylethynyl derivatives (n = 16).

For the first set topological *T(F..Cl)* (sum of topological distances between F and Cl) and *Getaway R5p+* (autocorrelation descriptor, weighted by atomic polarizabilities) descriptors conduct to the best results, both in mono- and bilinear attempt (Figure 6, Eq. 4 and 5).

(Eq. 4)

$$A_i = 5.44(\pm 0.86) + 47.47(\pm 9.62) \cdot (R5p+)_i$$

n = 31; r = 0.68

(Eq. 5)

$$A_i = 7.13(\pm 1.11) + 0.046(\pm 0.21) \cdot (T(F..Cl))_i + \\ + 26.94(\pm 12.92) \cdot (R5p+)_i$$

n = 31; r = 0.68

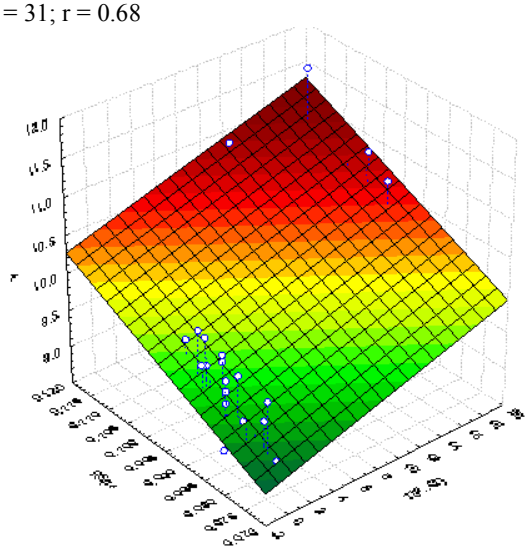


Figure 6. HIV-1 reverse transcriptase inhibitory activity (*A*) *versus T(F..Cl), R5p+* descriptors for subset 1 of efavirenz derivatives

In the case of subset 2, efavirenz cyclopropylethynyl derivatives, the use of 2D autocorrelation and *Getaway* descriptors conducts to a much better QSAR models, with correlation coefficient > 0.8. Thus, monolinear equations with *ATS5p* (Broto-Moreau autocorrelation of a topological structure - lag 5 / weighted by atomic polarizabilities) and with *HATS0p* (leverage-weighted autocorrelation of lag 0 / weighted by atomic polarizabilities) were obtained (Eq. 6 and Eq. 7).

(Eq. 6)

$$A_i = -8.77(\pm 3.33) + 41.76(\pm 7.59) \cdot (ATS5p)_i$$

n = 16; r = 0.83

(Eq. 7)

$$A_i = 5.91(\pm 0.61) + 33.17(\pm 5.44) \cdot (HATS0p)_i$$

n = 16; r = 0.85

A bilinear model with both descriptors doesn't increase significantly the quality of the model, the correlation coefficient being 0.87, but the cross validation of the model (leave-half-out) reveals a good correlation coefficient, q^2_{cv} 0.53 (Figure 7 and Eq. 8).

(Eq. 8)

$$A_i = -0.74 + 18.18(\pm 13.56) \cdot (ATS5p)_i + \\ + 21.09(\pm 10.46) \cdot (HATS0p)_i$$

n = 16; r = 0.87; q^2_{cv} = 0.53

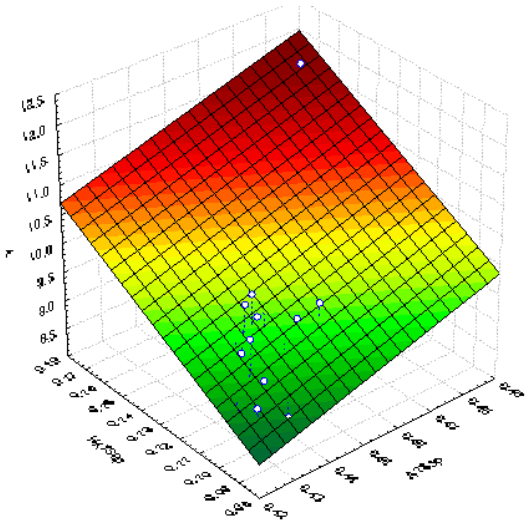


Figure 7. HIV-1 reverse transcriptase inhibitory activity (*A*) *versus ATS5p, HATS0p* descriptors for subset 2 of efavirenz derivatives

4. Conclusion

The following conclusions can be drawn among the molecular modeling and QSAR analysis of efavirenz derivatives and natural marine similar compounds (avarol) with HIV-1 reverse transcriptase inhibitory activity: (1) avarol type marine natural compounds have stable conformations very similar to efavirenz and derivatives and could have the same mechanism of action as HIV-1 reverse transcriptase inhibitors; (2) multivariate analysis of structural descriptors' data reveals that the descriptor classes are generally grouped and the best QSARs could be obtained by a rational selection of descriptors according to this analysis; (3) an exhaustive evaluation of quantitative structure-activity relationships for all efavirenz derivatives with HIV-1 reverse transcriptase inhibitory activity reveals statistically significant results with *WHIM* and molecular surface descriptors, but the quality of the mathematical models became better if the QSAR analysis is performed in specific subsets of efavirenz derivative compounds, *i.e.* alkyl/cycloalkyl/aryl/arylalkyl-ethynyl derivatives and further cyclopropylethynyl derivatives; the *Getaway* descriptors conduct to good models, with good predictive capacity, but only in these classes.

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