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Natural and synthetic HIV-1 non-nucleoside reverse transcriptase inhibitors: a theoretical approach

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Abstract

The paper presents a theoretical study on the similarities between some natural and synthetic HIV-1 non-nucleoside reverse transcriptase inhibitors. A lot of natural compounds from alkaloid, coumarin, flavonoid, lignan, phenolic, quinone, saponin, terpene, sterol, xanthone, carbohydrate, peptide, and protein classes reveal anti-HIV activity, some of them being with higher activity. Natural avarol and illimaquinone from the Red Sea sponges (*Dysidea cinerea* and *Smenospongia*, respectively), baicalin from *Scutellariae radix*, buchapine analogues from *Euodia roxburghiana*, depsidone from *Lichens* species, epiexcelsin from *Litsea verticillata*, magnoflorine from *Toddalia asiatica*, robustaflavone from *Rhus succedanea*, and especially 12-deoxyphorbol-13-(3*E*,5*E*-decadienoate) from *Excoecaria agallocha*, have anti-HIV activities and resembling to synthetic HIV-1 non-nucleoside reverse transcriptase inhibitors actually used to treat HIV infection: efavirenz, nevirapine, delavirdine, etravirine, and rilpivirine (the most recent approved by FDA, in May 2011). The most stable conformations of these compounds (obtained by molecular mechanics and conformational search analyses) are superimposed and similarities between them were identified. Furthermore, quantitative structure-activity relationships were obtained in the second generation of HIV-1 non-nucleoside reverse transcriptase inhibitors class, by using geometrical and *BCUT* descriptors (correlation coefficient of 0.96 for a bilinear model).

Keywords: anti-HIV-1 natural compounds, HIV-1 non-nucleoside reverse transcriptase inhibitors, efavirenz, nevirapine, delavirdine, etravirine, rilpivirine, molecular modelling, QSAR

1. Introduction

AIDS (Acquired immunodeficiency syndrome) is a degenerative disease of the immune and central nervous systems and its causative agent is the human immunodeficiency virus (HIV) [1]. Although no cure has been found for this disease, a lot of synthetic and natural inhibitors were developed and are used in chemotherapy [1-6]. The first case was identified in 1981 [7] and at the end of 2010, an estimated 34 million people were living with HIV worldwide, up to 17% from 2001, but in Eastern Europe and Central Asia, the number of people living with HIV rose 250% from 2001 to 2010 [8].

HIV virus has approximate 120 nm and is almost spherical. The outer part of the virus is formed by two lipid layers, which belong to the host cells. The virus membrane contains also proteins from the host cells and 72 copies of viral protein (Env); this protein consist of glycoprotein gp120 and a virus strain consist of three gp41 molecules which bond the structure to the viral membrane; this capside contains two copies of RNA chains and 2000 copies of p24 viral protein. RNA chain is strong bonded to the nucleocapside proteins and enzymes, used for replication. The main such enzymes are reverse transcriptase, protease and ribonuclease. A viral protein matrix surrounds the capsid ensuring their integrity [9].

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Three major classes of anti-HIV drugs exist: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors [4]. Now, all these therapies, including combined ones, are used [1]. The interaction of these anti-HIV compounds with receptor could be expressed in the following ways: inhibition constant, K_i, dissociation constant, K_d, minimum inhibitory concentration, *MIC*, inhibitory concentration 50%, IC_{50}, and half maximal effective concentration, EC_{50} [9].

The non-nucleoside reverse transcriptase inhibitors consist of five very important compounds (Figure 1): efavirenz, nevirapine, delavirdine, etravirine, and rilpivirine, the last being approved by the FDA in May 2011 [4,10].

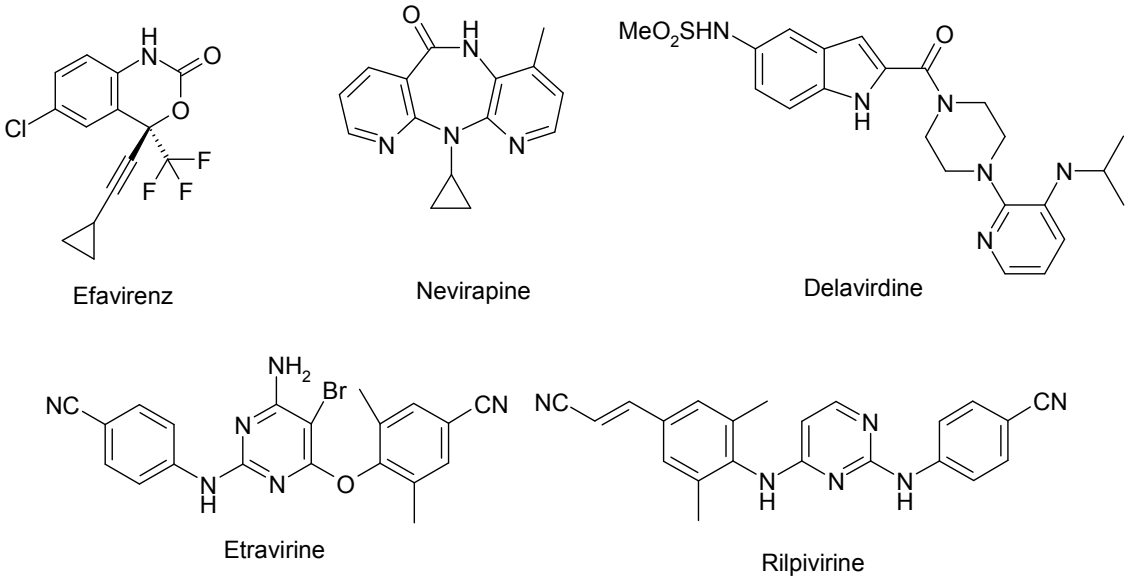

Figure 1. Approved HIV-1 non-nucleoside reverse transcriptase inhibitors

A great number of naturally occurring compounds from alkaloid, coumarin, flavonoid, lignan, phenolic, quinone, saponin, terpene, sterol, xanthone, carbohydrate, peptide, and protein classes, as well as their derivatives were studied (Figure 2), some of them having good anti-HIV activity [2-6,11,12]. Avarol and illimaquinone from the Red Sea sponges (*Dysidea cinerea* and *Smenospongia*, respectively) have been reported primarily to inhibit the reverse transcriptase activity of HIV-1, baicalin monohydrate (TJN-151) from *Scutellariae radix* inhibit the HIV-1 replication at an IC_{50} of 1.1 μM, buchapine and its analogue, 3-(3-methyl-but-2-enyl)-4-(3-methyl-but-2-enyloxy)-1*H*-quinolin-2-one, from *Euodia roxburghiana* have EC_{50} of 0.94 μM and 1.64 μM, respectively, depsidone from *Lichens* species with an anti-HIV activity of EC_{50} of 8.4 μM as well as an anti-integrase activity of IC_{50} 4.9 μM, epiexcelsin derivatives from *Litsea verticillata* with a low IC_{50} of 42.7 μM for 4'-demethoxy derivative, magnoflorine from *Toddalia asiatica* showed significant anti-HIV activity [4], robustaflavone, a biflavonoid from *Rhus succedanea*, showed strong inhibition of the polymerase of HIV-1 reverse transcriptase in *in vitro* assay, and especially 12-deoxyphorbol-13-(3*E*,5*E*-decadienoate) from *Excoecaria agallocha*, have anti-HIV activities (6 nM) [3].

In this paper the main natural compounds with anti-HIV activity were studied in comparison with the actual approved HIV-1 non-nucleoside reverse transcriptase inhibitors. Eleven new DPC derivatives with HIV-1 reverse transcriptase inhibitory activity were correlated with a large number of structural descriptors and quantitative structure – activity relationships were developed.

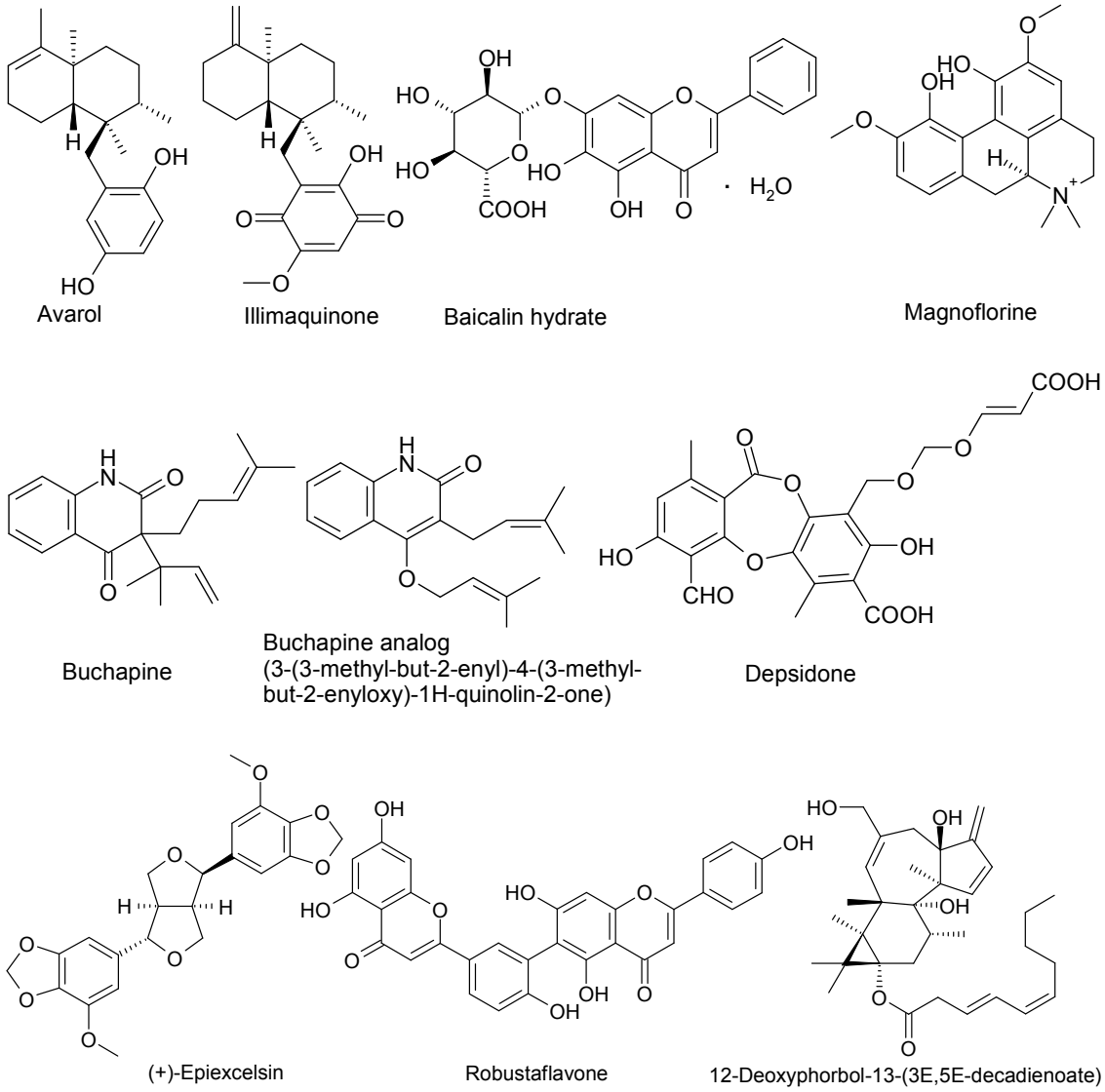

Figure 2. Natural occurring HIV-1 non-nucleoside reverse transcriptase inhibitors

2. Materials and methods

Structures and biological activities. Natural anti-HIV compounds, avarol, illimaquinone, baicalin, buchapine analogue, 3-(3-methyl-but-2-enyl)-4-(3-methyl-but-2-enyloxy)-1*H*-quinolin-2-one, depsidone, epiexcelsin, magnoflorine, robustaflavone, and 12-deoxyphorbol-13-(3*E*,5*E*-decadienoate) [3,4] as well as the approved synthetic anti-HIV compounds, efavirenz, nevirapine, delavirdine, etravirine, and rilpivirine [4,10], were selected in order to identify similarities between these two classes. A series of 11 benzo[d]diazin-2-ones (anti-HIV DPC phase III derivatives) resembling to natural avarol, illimaquinone, and synthetic efavirenz, having HIV-1 reverse transcriptase inhibitory activity were selected [13-15] and have structural variations at the C4-position of heterocyclic ring and in benzene ring (Figure 3). The biologial 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).

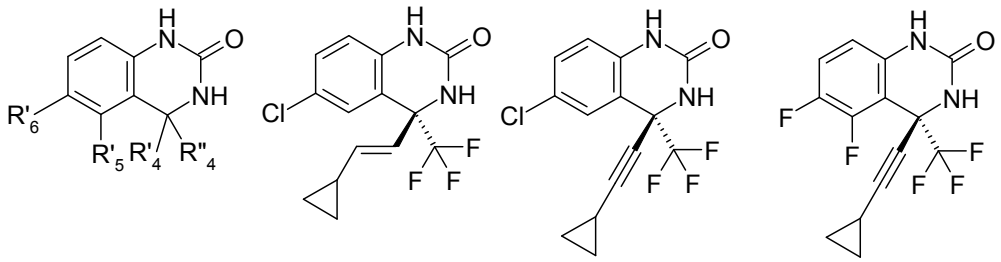

Figure 3. General structure of derivatives with anti-HIV activity (left) and the main DPC structures

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

No	R'_4	R''_4	R'_5	R'_6	$A = \log(1/IC_{50})$
1 (DPC-961)	CF_3	C≡C-cPr	H	Cl	7.5086
2	CF_3	C≡C-cPr	OMe	Cl	7.1549
3	CF_3	C≡C-Ph	OMe	Cl	6.8416
4	CF_3	C≡C-Py(3)	OMe	Cl	6.857
5	CF_3	C≡C-cPr	OH	Cl	7.2676
6	CF_3	C≡C-Ph	OH	Cl	6.7595
7	CF_3	CH=C(cPr)-O		Cl	7.0458
8	CF_3	CH=C(Ph)-O		Cl	6.6126
9	CF_3	CH=C(3-Py)-O		Cl	6.9136
10 (DPC-083)	CF_3	CH=CH-cPr	H	Cl	7.6383
11 (DPC-693)	CF_3	C≡C-cPr	F	F	7.7447

Molecular modeling. Molecular modeling of natural and synthetic anti-HIV compounds and DPC derivative molecules was performed by using the molecular mechanics MM+ program from the HyperChem 5.1; a RMS of 0.05 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 anti-HIV 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 of efavirenz and DPC derivatives; all other flexible bonds from natural and synthetic anti-HIV structures were also considered for this 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 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.) [16,17]. The minimum energy conformation for every compound was used for these determinations.

QSAR analysis. For the quantitative structure – activity relationships (QSAR) analysis in the DPC derivative compounds class with HIV-1 reverse transcriptase inhibitory activity the following mono- and bilinear mathematical models were used [16,18-25]:

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

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

3. Results and discussion

With some exceptions, many natural compounds with anti-HIV activity resembling to the synthetic approved drugs. Thus, avarol, illimaquinone, baicalin, and buchapine analogue resembling to efavirenz and DPC derivatives, the superimposing of the bicyclic moieties being successful (Figure 4). Other natural compounds with anti-HIV activity are superimposed on the approved synthetic nevirapine: magnoflorine and depsidone; the better superimposing of these compounds was obtained for tri- and tetracyclic moieties, while the exocyclic chain is oriented to the tricyclic rest for the depsidone case. Magnoflorine is a rigid structure and is better superimposed to nevirapine, having a good alignment for nitrogen and oxygen atoms (less than 0.8Å for the corresponding N-1 and N-6 atoms from nevirapine and magnoflorine, respectively, while O-6 and O-1 for these compounds are positioned at ~1Å) (Figure 5).

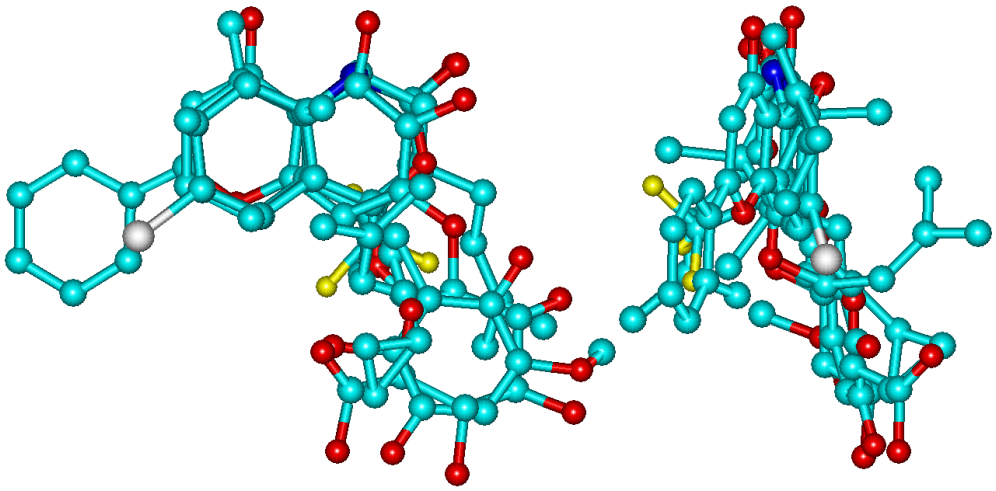

Figure 4. Superimposed of the most stable conformations of efavirenz and natural illimaquinone, baicalin, and buchapine analog

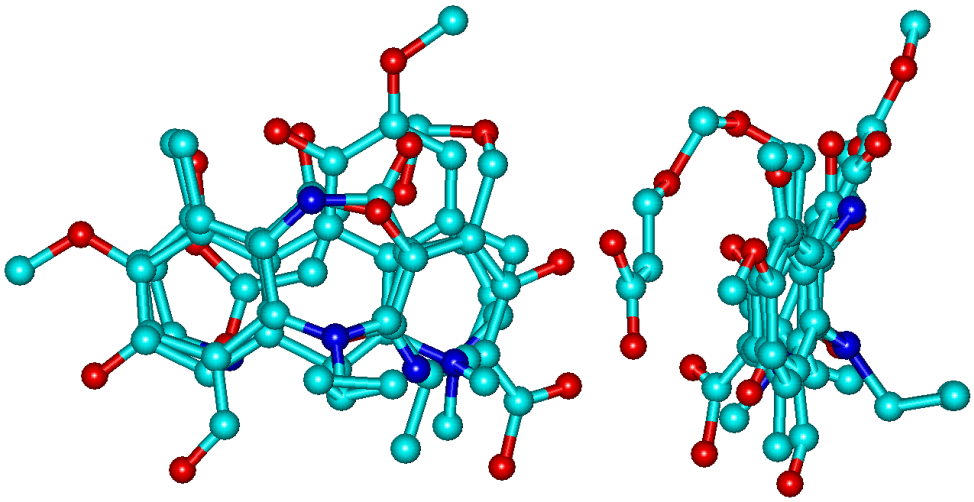

Figure 5. Superimposed of the most stable conformations of nevirapine and natural magnoflorine and depsidone

Superimposing of the very active phorbol derivative was realized on nevirapine with good results for the tricyclic moieties. These superposition suggests that the hydrophobic interaction of these anti-HIV compounds with the active site of HIV-1 reverse transcriptase is similar: for nevirapine ring A interact with Leu100, Tyr181, Trp229, and Leu234 from HIV-1 active site, ring B and the cyclopropyl moiety with Lys103, Val106, Gly190, Phe227, and Pro236, while ring C with Pro236 and Tyr319 [26]. Similar interactions could appear in the case of phorbol derivative, especially for B and C rings.

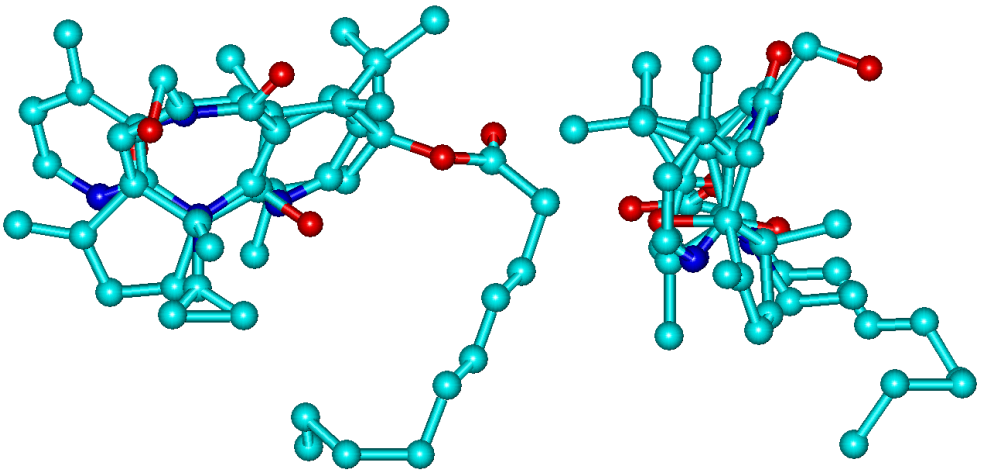

Figure 6. Superimposed of the most stable conformations of nevirapine and natural 12-deoxyphorbol-13-(3*E*,5*E*-decadienoate)

The attempt to superimpose robustaflavone and epiexcelsin derivatives (low anti-HIV activity) with the synthetic approved drugs was unsuccessful, even some similarities could be observed by superimposing robustaflavone with delarvidine (Figure 7).

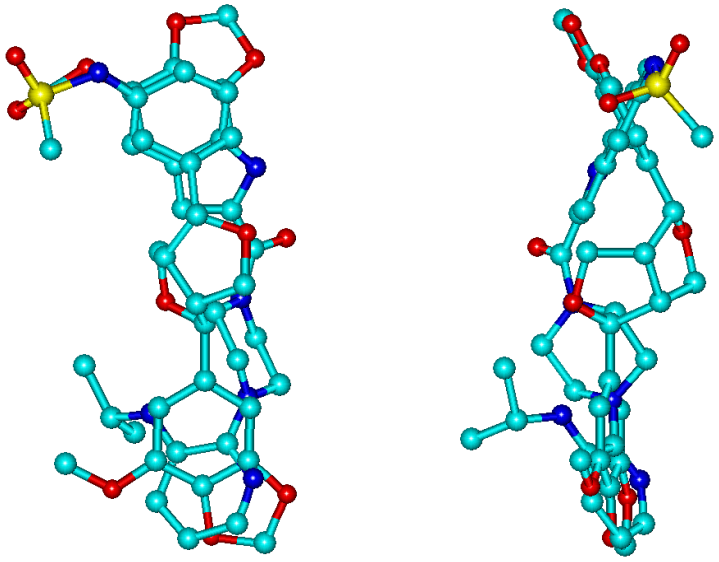

Figure 7. Superimposed of the most stable conformations of delarvidine and a natural biflavonoid, robustaflavone

No similarities were found in the case of the recent and highly active etravirine (TMC125), EC_{50} 3 nM, and rilpivirine (TMC278), EC_{50} 0.4 nM [27]; although, these two synthetic compounds are very similar and are better superimposed (Figure 8).

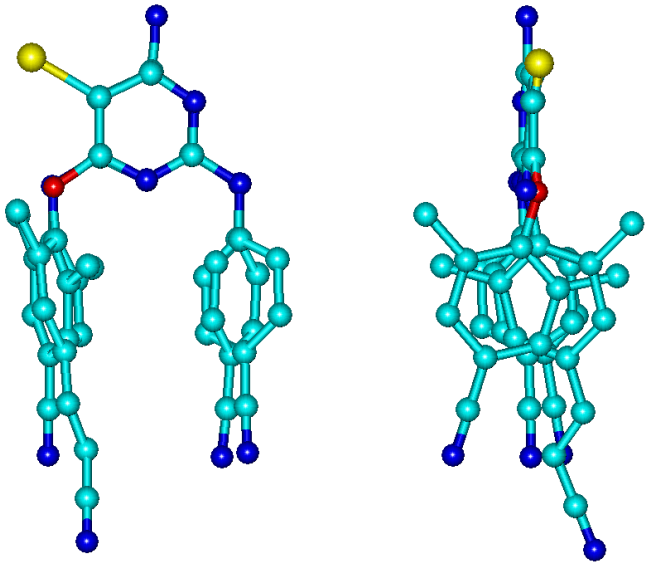

Figure 8. Superimposed of the most stable conformations of the most recent approved HIV-1 non-nucleoside reverse transcriptase inhibitors: etravirine (approved in 2008) and rilpivirine (approved in May 2011)

Even a monolinear or bilinear models were used, statistically significant QSARs were obtained in the case of anti-HIV DPC derivative class. Very good monolinear models with molecular weight (*MW*), as well as with *BCUT* and geometrical descriptors were obtained. Thus, in the case of the most simple descriptor (*MW*) the anti-HIV activity decrease with the increasing of *MW*, the correlation coefficient being almost 0.9 (Eq. 1 and Figure 9).

(Eq. 1)

$$A_i = 11.52(\pm 0.75) + 0.013(\pm 0.002) \cdot (MW)_i$$

n = 11; r = 0.891

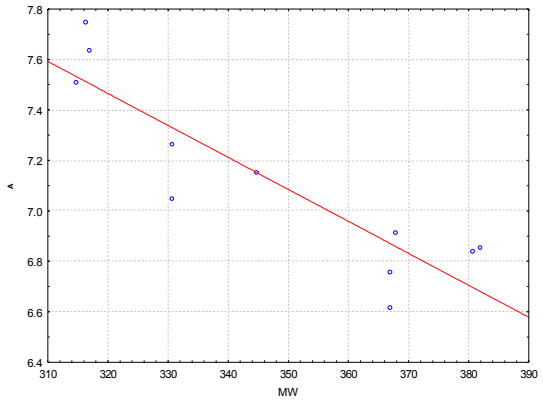

Figure 9. HIV-1 reverse transcriptase inhibitory activity (*A*) *versus MW* descriptor for DPC derivative class

In the case of geometrical descriptors, the asphericity (*ASP*) conducts to a very good monolinear model, the HIV-1 reverse transcriptase inhibitory activity of DPC derivatives increasing with the decrease of asphericity (Eq. 2 and Figure 10).

(Eq. 2)

$$A_i = 8.01(\pm 0.11) - 7.10(\pm 0.84) \cdot (ASP)_i$$

n = 11; r = 0.942

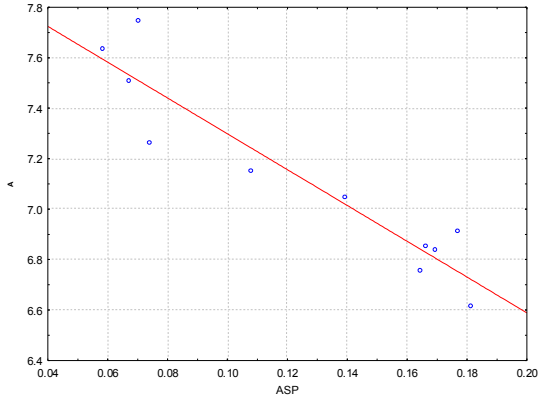

Figure 10. HIV-1 reverse transcriptase inhibitory activity (*A*) *versus ASP* descriptor for DPC derivative class

A multilinear correlation conduct to a better equation if the *BEHm6* (the highest eigenvalue n. 6 of Burden matrix / weighted by atomic masses, *BCUT* descriptor) and *ASP* descriptors were used, the correlation coefficient being $r = 0.96$, the model having a good predictability for DPC anti-HIV class, q^2 0.72 (Eq. 3 and Figure 11). Descriptor values and observed/predicted activities for HIV-1 reverse transcriptase inhibitory activity of DPC derivatives are presented in Table 2.

(Eq. 3)

$$A_i = 13.36(\pm 2.85) - 1.95(\pm 1.04) \cdot (BEHm6)_i - 3.72(\pm 1.95) \cdot (ASP)_i$$

n = 11; r = 0.960; s = 0.12; F = 47.4; $q_{cv}^2 = 0.72$

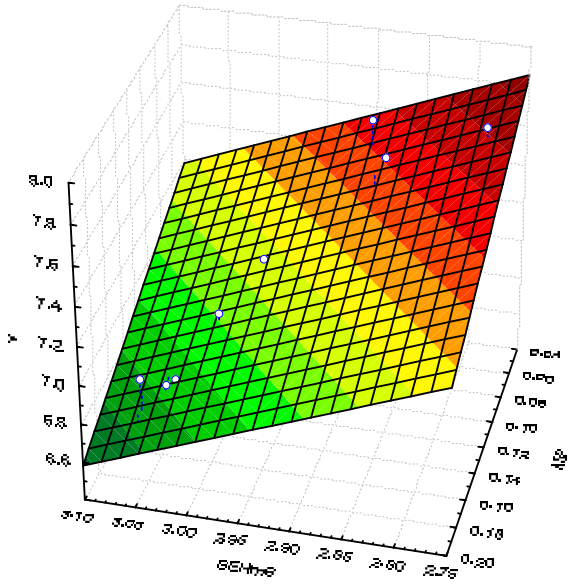

Figure 11. HIV-1 reverse transcriptase inhibitory activity (*A*) *versus BEHm6* and *ASP* descriptors for DPC derivative class

Table 2. Descriptor values and observed/predicted activities for HIV-1 reverse transcriptase inhibitory activity of DPC derivatives (according to Eq. 3)

No	*BEHm6*	*ASP*	*A* (observed)	*A* (predicted)	$\Delta A = A_{obs.} - A_{pred.}$
1	2.877	0.067	7.509	7.793	-0.285
2	2.976	0.108	7.155	7.113	0.041
3	3.038	0.169	6.842	6.772	0.070
4	3.030	0.166	6.857	6.953	-0.096
5	2.885	0.074	7.268	7.745	-0.478
6	3.038	0.164	6.760	6.927	-0.167
7	3.003	0.139	7.046	6.983	0.063
8	3.058	0.181	6.613	6.866	-0.254
9	3.057	0.177	6.914	6.646	0.268
10	2.895	0.058	7.638	7.363	0.275
11	2.777	0.070	7.745	8.516	-0.772

4. Conclusion

The following conclusions can be drawn among the molecular modeling and QSAR analysis of DPC derivatives and natural compounds with HIV-1 reverse transcriptase inhibitory activity: (1) a lot of natural compounds reveal HIV-1 reverse transcriptase inhibitory activity such as avarol and illimaquinone from the Red Sea sponges (*Dysidea cinerea* and *Smenospongia*, respectively), baicalin from *Scutellariae radix*, buchapine analogues from *Euodia roxburghiana*, depsidone from *Lichens* species, epiexcelsin from *Litsea verticillata*, magnoflorine from *Toddalia asiatica*, robustaflavone from *Rhus succedanea*, and especially 12-deoxyphorbol-13-(3*E*,5*E*-decadienoate) from *Excoecaria agallocha*; (2) some natural compounds resembling with the approved synthetic anti-HIV drugs, *i.e.* avarol, illimaquinone, baicalin, and buchapine analogue with efavirenz, magnoflorine, depsidone, and phorbol derivatives with nevirapine, but no structural correlations have been observed in the case of recently approved and highly active synthetic compounds from diarylaminopirimidine series (etravirine and rilpivirine); (3) statistically significant QSARs were obtained in the DPC class, especially if the molecular shape and dimensions were used. A bilinear model with good predictability power was obtained.

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