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Research Article

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A quantum-chemical study of the relationships between electronic structure and anti-HIV-1 activity of a series of HEPT derivatives

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ABSTRACT

A study of the relationships between electronic structure and anti HIV-1 activities of a series of 1-[2-hydroxyéthoxy-méthyl]-6-(phenylthio) thymine (HEPT) derivatives was carried out. The electronic structure was obtained at the B3LYP/6-311G(d,p) level after full geometry optimization. A linear multiple regression analysis was performed with the anti HIV activity as the dependent variable and a set of reactivity indices belonging to the atoms of a common skeleton as independent variables. A statistically significant equation (R= 0.98, R^2= 0.95, adj-R^2= 0.94, F(6,14)=49.02, p<0.00000 and SD=0.28) was obtained. The process seems to be charge and orbital-controlled. Based on the analysis of the results, a partial two-dimensional anti HIV-1 pharmacophore is proposed.

Keywords: Anti HIV-1, HEPT, pharmacophore, QSAR, DFT.

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is a pandemic immunosuppressive disease caused by the depletion of helper T lymphocytes. The causative agent, termed human immunodeficiency virus, which is in two types, type 1 (HIV-1) and type 2 (HIV-2) [1]. In fact, HIV continues to be a major global public health issue, having claimed more than 34 million lives so far. In 2014, 1.2 million people died from HIV- related caused globally. Also, there were approximately 36.9 million people living with HIV at the end of 2014 with 2.0 million people becoming newly infected with HIV in 2014 globally [2]. Various compounds have been reported to inhibit the replication of HIV-1 *in vitro* [3-22]. The HIV-1 Reverse Transcriptase (RT) enzyme shows both RNA- and DNA-dependent polymerase activities, and the lack of RT activity in the eukaryotic cells made RT as one of the most attractive target for the development of anti-VIH-1 agents [6,13]. The non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) can suppress the virus replication in cell cultures for at least 3 months [23-25]. The HEPT was the first NNRTI synthesized in 1989 [26] and has been considered as the lead compound [13] and most Quantitative Structure Activity Relationship (QSAR) studies have been carried out on HEPT derivatives [27-36].

In this paper we present the results of a quantum-chemical study of the relationships between electronic structure and anti-HIV-1 activities of a group of HEPT derivatives.

EXPERIMENTAL SECTION

Methods and calculations

The model

As the methodology employed here to find relationships between electronic structure and inhibition constants has been extensively discussed and applied in several papers, we present here a short standard summary [37-40]. The anti HIV activity, expressed as IC_{50}, can be expressed as a linear relationship of the form:

$$\log(IC_{50}) = a + \sum_j \left[e_j Q_j + f_j S_j^E + s_j S_j^N \right] + \sum_j \sum_m \left[h_j(m) F_j(m) + x_j(m) S_j^E(m) \right] +$$

$$+ \sum_j \sum_{m'} \left[r_j(m') F_j(m') + t_j(m') S_j^N(m') \right] + \sum_j \left[g_j \mu_j + k_j \eta_j + o_j \omega_j + z_j \varsigma_j + w_j Q_j^{\max} \right] + \sum_{k=1}^{U} O_k \qquad (1)$$

where Q_j is the net charge of atom j, S_j^E and S_j^N are, respectively, the total atomic electrophilic and nucleophilic superdelocalizabilities of Fukui et *al.*, $F_{j,m}(F_{j,m'})$ is Fukui index of the occupied (vacant) MO m(m') located on atom j [41]. $S_j^E(m)$ is the atomic electrophilic superdelocalizability of MO m on atom j, etc. The total atomic electrophilic superdelocalizability of atom j corresponds to the sum over occupied MOs of the $S_j^E(m)$'s and the total atomic nucleophilic superdelocalizability of atom j is the sum over vacant MOs of $S_j^N(m')$'s [37]. μ_j is the local atomic electronic chemical potential of atom j, η_j is the local atomic hardness of atom j, ω_j is the local atomic electrophilicity of atom j, ς_j is the local atomic softness of atom j, and $Q_j^{\max}$ is the maximum amount of electronic charge that atom j may accept from another site [37]. The O_k's are the orientational parameters of the substituents [38]. Through this paper $HOMO_j^*$ refers to the highest occupied molecular orbital localized on atom j and $LUMO_j^*$ to the lowest empty MO localized on atom j. They are called the local atomic frontier MOs. The application of this method (Eq. 1) has given excellent results for a great diversity of drug-receptor systems (see [42-51] and references within).

Selection of the experimental data

Molecules were selected from a set reported in Ref. [52]. The molecules are shown in Fig.1 and Table 1. The experimental data employed in this study is the anti-HIV-1 activity, measured as the effective concentration of compound required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1. The $HTLV\text{-}III_B$ strains of HIV-1 and MT-4 cells were used for the assay [18].

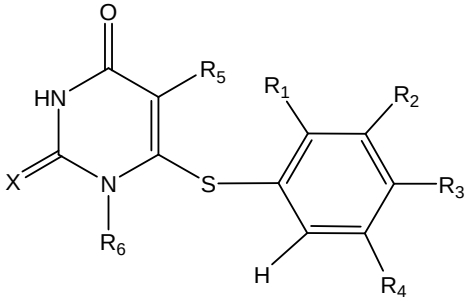

Figure 1: Structure of HEPT derivatives

Methods and calculations

The electronic structure of the molecules was obtained within the Density Functional Theory (DFT) at B3LYP/6-311G(d,p) level with full geometry optimization. The Gaussian package of programs was employed [53]. The numerical values of the reactivity indices were calculated from the single point log file with the D-Cent-QSAR software with correction of the anomalous electron populations that sometimes are produced by the Mulliken population analysis [54-55]. All electron populations smaller than or equal to 0.01e were considered as zero [37]. Orientational parameters of the substituents were calculated as accustomed [38]. We employed the common skeleton (CS) hypothesis stating that there is a particular set of atoms, common to all molecules, which accounts for nearly all the biological activity. The variation of the values of a set of local atomic reactivity indices of a group of atoms belonging to this CS should give an account of the variation of the anti HIV-1 activity throughout the series

analyzed. We made use of Linear Multiple Regression Analysis (LMRA) techniques to determine which atoms and reactivity indices are directly involved in the variation of the biological activity. The reason is that there is no enough experimental data to solve the system of linear equations 1. We built a matrix containing the dependent variable (log (EC_{50})), and the local atomic reactivity indices of all atoms of the common skeleton as independent variables. The Statistica software was used for LMRA [56]. The common skeleton numbering is shown in Fig. 2.

Table 1. Selected molecules and their anti-HIV-1 activities

Mol.	X	R1	R2	R3	R4	R5	R6	log(EC50)
1	O	H	CF_3	H	H	Me	$CH_2OC_2H_4OH$	1.65
2	O	H	NO_2	H	H	Me	$CH_2OC_2H_4OH$	1.53
3	O	OMe	H	H	H	Me	$CH_2OC_2H_4OH$	1.28
4	O	H	Cl	H	H	Me	$CH_2OC_2H_4OH$	1.11
5	O	H	CN	H	H	Me	$CH_2OC_2H_4OH$	1.00
6	S	H	H	H	H	Pr	$CH_2OC_2H_4OH$	1.00
7	O	H	COOMe	H	H	Me	$CH_2OC_2H_4OH$	0.90
8	O	H	COMe	H	H	Me	$CH_2OC_2H_4OH$	0.86
9	O	H	H	H	H	Me	$CH_2OC_2H_4OH$	0.85
10	O	H	Br	H	H	Me	$CH_2OC_2H_4OH$	0.76
11	O	H	H	H	H	Pr	$CH_2OC_2H_4OH$	0.53
12	O	H	F	H	H	Me	$CH_2OC_2H_4OH$	0.52
13	O	H	Et	H	H	Me	$CH_2OC_2H_4OH$	0.43
14	O	H	Me	H	H	Me	$CH_2OC_2H_4OH$	0.41
15	O	H	Cl	H	Cl	Me	$CH_2OC_2H_4OH$	0.11
16	O	H	Me	H	Me	Me	$CH_2OC_2H_4OH$	-0.59
17	S	H	Me	H	Me	Me	$CH_2OC_2H_4OH$	-0.66
18	O	H	H	H	H	Et	$CH_2OC_2H_4OH$	-0.92
19	S	H	H	H	H	Et	$CH_2OC_2H_4OH$	-0.96
20	O	H	H	H	H	iPr	$CH_2OC_2H_4OH$	-1.20
21	S	H	H	H	H	i-Pr	$CH_2OC_2H_4OH$	-1.23
22	S	H	Cl	H	Cl	Et	$CH_2OC_2H_4OH$	-1.37
23	O	H	Me	H	Me	Et	$CH_2OC_2H_4OH$	-1.89
24	S	H	Me	H	Me	iPr	$CH_2OC_2H_4OH$	-2.30
25	O	H	Me	H	Me	iPr	$CH_2OC_2H_4OH$	-2.57
26	O	H	H	Me	H	Me	$CH_2OC_2H_4OH$	2.34
27	O	H	OH	H	H	Me	$CH_2OC_2H_4OH$	1.91
28	S	H	H	H	H	Me	$CH_2OC_2H_4OH$	-0.02
29	O	H	Cl	H	Cl	Et	$CH_2OC_2H_4OH$	-1.85
30	S	H	Me	H	Me	Et	$CH_2OC_2H_4OH$	-2.11

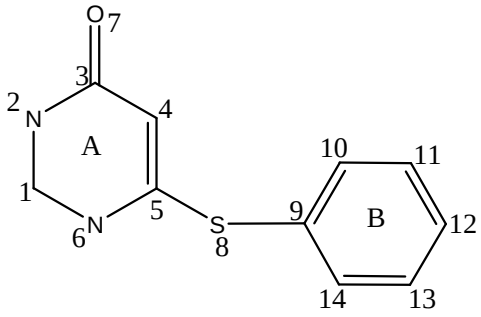

Figure 2: Common skeleton numbering.

RESULTS AND DISCUSSION

LMRA performed with all set (n=30) produced no statistically significant equation. We turned our attention to reported experimental values. The most active is EC_{50}=0.0027 M and the least active is EC_{50}=220 M, being their ratio 81481. Therefore we tested the hypothesis that molecules presenting a high antiviral activity may exert their

action through a different mechanism than those with low activity. We reduce the range by removing one by one the least active when we do not have a statistically significant equation. Molecules 1, 2, 3, 6, 11, 25, 26, 27 and 30 are suppressed. Finally, we get the following statistically significant equation with 21 molecules.

$$\log(EC_{50}) = 31.99 - 61.62Q_3 - 16.04\varsigma_1 - 1.88F_{14}(LUMO)^* + 5.58S_5^E(HOMO)^* + \\ +3.04F_{12}(HOMO)^* + 0.02S_5^N \quad (2)$$

with n=21, R= 0.98 R^2= 0.95, adj-R^2= 0.94, F(6,14)=49.02, p<0.00000 and a standard error of estimate of 0.28. No outliers were detected and no residuals fall outside the ±2σ limits. Here Q_3 is the net atomic charge of atom 3, ς_1 is the local softness of atom 1, $F_{14}(\mathrm{LUMO})^*$ is the electron population (Fukui index) of lowest vacant MO localized on atom 14, $S_5^E(\mathrm{HOMO})^*$ is the electrophilic superdelocalizability of atom 5 at (HOMO)* level, $F_{12}(\mathrm{HOMO})^*$ is the electron population of highest occupied MO localized on atom 12 and S_5^N total atomic nucleophilic superdelocalizability of atom 5.

Table 2 shows the beta coefficients and the *t*-test results for the significance of coefficients of Eq. 2. Concerning independent variables, Table 3 shows that the highest internal correlation is $r^2\{F_{12}(\mathrm{HOMO})^*, Q_3\}$=0.53. In π conjugated systems it is normal to find a certain degree of correlation between some "independent" variables. Fig. 3 shows the plot of observed *vs.* calculated values of log(IC_{50}). The associated statistical parameters of Eq.2 show that this equation is statistically significant and that the variation of a group of six local atomic reactivity indices belonging to the common skeleton explains about 94% of the variation of the anti HIV activity.

Table 2: Beta coefficients and t-test for significance of coefficients in equation 2

Variable	Beta coefficients	t(14)	p-Value
Q_3	-0.77	-8.22	0.000001
ς_1	-0.41	-6.39	0.00002
F_{14} (LUMO)*	-0.35	-5.04	0.0002
S_5^E(HOMO)*	0.28	3.86	0.002
F_{12}(HOMO)*	0.35	3.49	0.004
S_5^N	0.19	3.10	0.008

Table 3: Squared correlation coefficients for the variables appearing in equation 2

	Q_3	ς_1	F_{14}(LUMO)*	S_5^E(HOMO)*	F_{12}(HOMO)*
ς_1	0.12				
F_{14}(LUMO)*	0.04	0.00	1		
S_5^E(HOMO)*	0.03	0.04	0.17	1	
F_{12}(HOMO)*	0.53	0.21	0.01	0.17	1
S_5^N	0.00	0.02	0.00	0.07	0.01

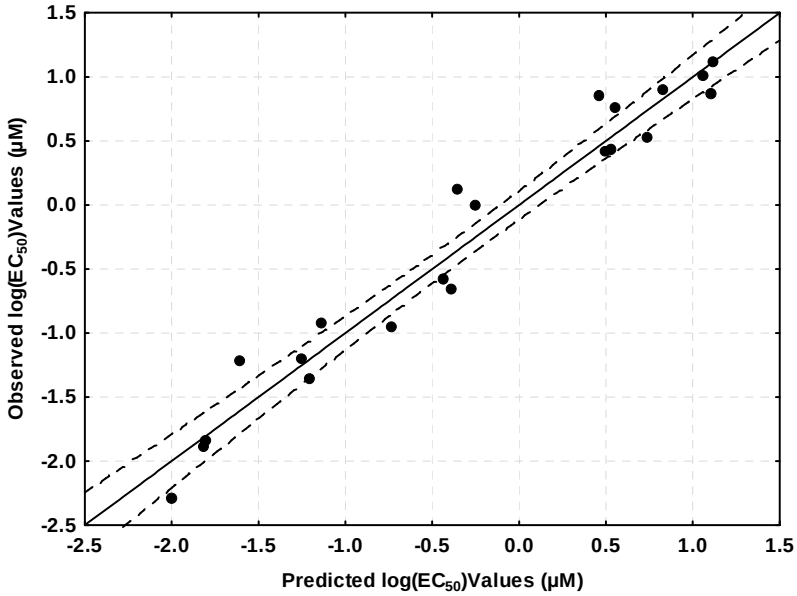

Figure 3: Plot of predicted vs. observed log(EC_{50}) values
Dashed lines denote the 95% confidence interval

The three first occupied and the first three vacant empty local MOs are of π nature. As an example, Fig. 4 shows the HOMO and LUMO of molecules 24 and 25.

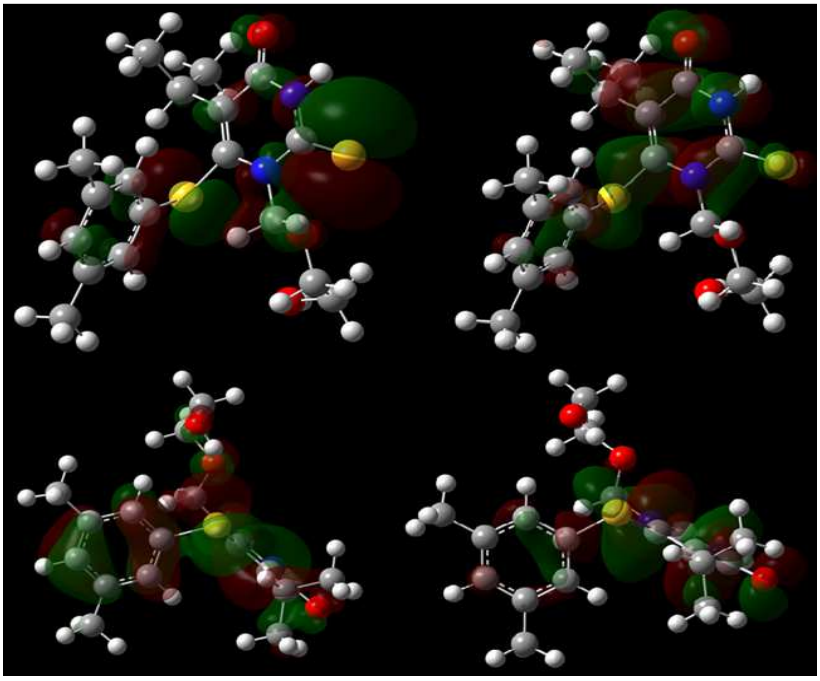

Figure 4. Frontier MOs of molecules 24 and 25
Upper left: HOMO of 24. Upper right: LUMO of 24. Lower, left: HOMO of 25. Lower right: LUMO of 25

We can see that in molecule 24 the HOMO has a mixed σ-π nature. The main electron-donor centers are at the sulphur atoms, -O- and O= atoms and ring B. The LUMO has the main electron-acceptor centers at the S= atom, the O= atom and ring A. In the case of molecule 25, the situation is analogous. Figure 5 shows the superimposition of the ten lowest conformations of molecule 24 obtained with MarvinView (Dreiding force field) [57]. Ring B (Fig. 2) was employed as the common element.

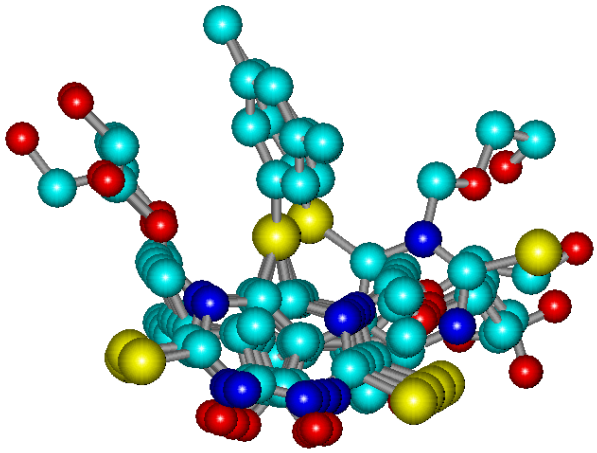

Figure 5: Superimposition of the ten lowest conformations on molecule 24

We can see that the molecule has not a high degree of conformational flexibility. We must remember that the active conformation is dependent on the microscopic composition of the *milieu*.

Our results indicate that for these molecules the variation of the anti-VIH-1 activity is related to the variation of the numerical values of a set of six local atomic reactivity indices belonging to the common skeleton. This result is very good considering the approximations made to build the model. The beta values (Table 2) show that the importance of the variables is $Q_3 > \varsigma_1 > F_{14}(LUMO)^* > F_{12}(HOMO)^* > S_5^E(HOMO)^* > S_5^N$. The process seems to be charge and orbital-controlled. The most important variables are Q_3, ζ_1 and $F_{14}(LUMO)^*$ (Table 2). Because ς_1 and $F_{14}(LUMO)^*$ have positive numerical values and are accompanied by minus sign in Eq. 2, high numerical values for them are associated with a good anti-VIH-1 activity. The net charge of atom 3, Q_3, can be positive, zero or negative. In this case a good anti HIV activity is associated with a positive value. Given that $F_{12}(HOMO)^*$ and S_5^N have positive numerical values and are accompanied by plus sign, a good anti HIV activity is associated with low numerical values for them. $S_5^E(HOMO)^*$ has always a negative value and it has a plus sign accompanying it in Eq. 1. Therefore a good anti-VIH-1 activity is associated with a negative value for this index. First, we shall analyze the MO-independent local atomic reactivity indices. Atom 3 is a carbon atom (Fig. 2) which should have a high positive charge for a good anti HIV activity. Therefore, we suggest that atom 3 is interacting with a negatively charged site or with the electrons of a delocalized π system. Atom 1 is carbon one (Fig. 2). A high value of the local atomic softness ς_1 corresponds to a low value of the local atomic hardness [37]. So the $(HOMO)_1^*$-$(LUMO)_1^*$ energy gap should be low. A smaller value for can ς_1 be theoretically obtained by lowering the $(LUMO)_1^*$ eigenvalue, rising the $(HOMO)_1^*$ eigenvalue or by both procedures simultaneously. In small molecules like the ones analyzed here it more likely to find a substitution lowering the $(LUMO)_1^*$ eigenvalue than to find one rising significantly the $(HOMO)_1^*$ eigenvalue. This suggests that atom 1 is probably interacting with an electron-rich center (π-π stacked, π-π T shaped, π-π stacking or π-anion interactions). Atom 5 is carbon atom one (Fig. 2). The low value of S_5^N means that atom 5 should act as a bad electron acceptor. This implies that atom 5 is interacting with an electron-deficient center (π-cation, π-alkyl or π-π). Now, we shall analyze the MO-dependent atomic reactivity indices. Atom 14 is a carbon atom of the phenyl moiety (Fig. 2). The high value of $F_{14}(LUMO)^*$ allow us to suggest that atom 14 is interacting with an electron-rich center through at least its first lowest vacant local MO. Atom 12 is a carbon atom of the phenyl moiety (Fig. 2). The low numerical value of $F_{12}(HOMO)^*$ indicates that atom 12 is interacting with an electron-rich center. Atom 5 is a carbon in ring A (Fig. 2). A high anti VIH-1 activity is associated with great negative values of $S_5^E(HOMO)^*$. This is a hint allowing us to suggest that atom 5 is acting as an electron donor through the interaction with an electron deficient center with at least its first highest occupied local MO.

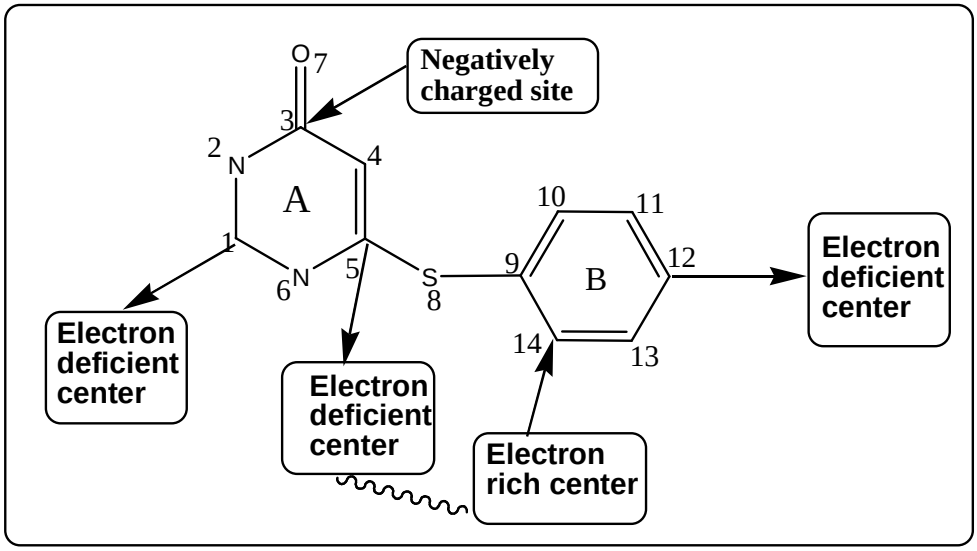

Figure 4: Proposed 2D pharmacophore for anti-HIV-1 activity of HEPT derivatives

CONCLUSION

We have obtained statistically significant results relating the variation of a definite set of local atomic reactivity indices to the variation of anti-HIV-1 activity for a series of HEPT derivatives. The whole process is charge and orbital-controlled. The results should be useful to propose new molecules which higher anti-HIV-1 activity.

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