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Theoretical aspects of some 4-[2,6-substituted-9*H*-purin-9-yl]-2-cyclopentene-1-methanol derivatives as anti-HIV agents

LEMI TÜRKER[1] and MERT SUDAĞIDAN[2]

[1]*Middle East Technical University, Department of Chemistry, Ankara, Turkey*
[2]*Institute of Technology, Department of Biotechnology, Izmir*

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Some (–)-(1*S*,4*R*) -4-[2-amino-6-(substituted)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol derivatives have been considered for semiempirical treatment at the level of AM1 type calculations. Certain theoretical structure–activity relationship were investigated.

Introduction

Human immunodeficiency virus-1 (HIV-1) has shown to be the causative agent of AIDS (acquired immunodeficiency syndrom) and AIDS-related diseases. HIV was first isolated in 1983 [1] and named as lympoadenopathy-associated virus (LAV). After that, it was shown that HIV causes AIDS and named as human-T lymphotropic virus type III (HTLV-III) [2, 3]. Human immunodeficiency virus type 2 (HIV-2) is related to simian immunodeficiency virus (SIV). According to studies, HIV-2 may be less virulent and pathogenic than HIV-1. Arya and Gallo reported that HIV-2 inhibits the replication of HIV-1 at the molecular level [4].

In recent years, carbocyclic nucleoside analogues have emerged as a promising group of compounds for antiviral and antitumour agents. Carbovir (CBV) **1** and other 2-cyclopentyl nucleoside analogues have been extensively investigated for their potential as anti-HIV agents [5–9].

Nucleoside-based inhibitors of HIV-1 reverse trascriptase (RT) were the first class of substances found to have activity against HIV-1 replication in cell-culture experiments. These inhibitors can have a dramatic effect in infected patients, as shown by the reduction of viral load and increase in counts of CD4 T-cells [10, 11]. In general, these effects exhibit certain correlation with the ability of the triphosphate form of the nucleosides to inhibit the polymerase activity of the viral RT by chain termination [12].

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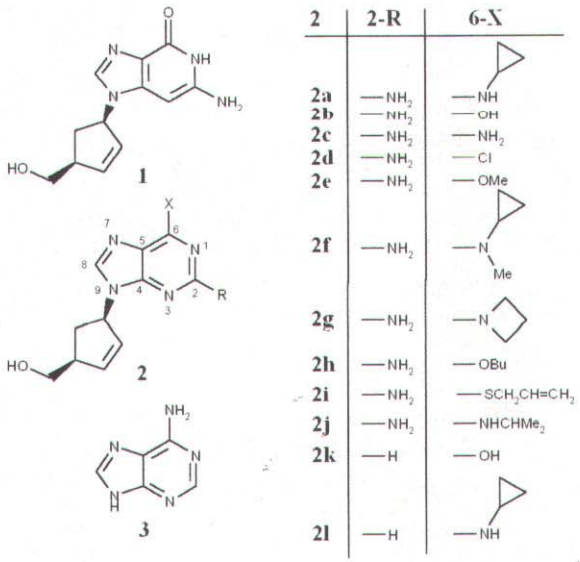

Fig. 1. Structure of the compounds considered

Two substances which have found some application in AIDS therapy are Zidovudine (3'-azidothymidine, AZT) and Lamivudine (3'-thiacytidine, 3-TC). Zidovudine is the drug that has been used most extensively and for longest period in AIDS therapy. Lamivudine has been introduced quite recently. Nucleoside human immunodeficiency virus (HIV) reverse transcriptase inhibitors continue to be the cornerstone of AIDS therapy. Side effects limit the use of AZT, ddI (2',3'-dideoxy-inosine), ddc (2',3'-dideoxycytidine) and d4T (2'3'-dideoxy-2',3'-didehydro-thymidine) [13–15].

In the present study, (–)-(1*S*,4*R*) -4-[2-amino-6-(substituted)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol derivatives (which are a series of carbocyclic nucleosides) were considered (Fig. 1). A semiempirical treatment at the level of AM1 type was employed for quantum chemical purposes. The biological data, based on anti-HIV-1 (III B) potency in MT4 cells of the above mentioned series of compounds were excerpted from the relevant literature [16], see Table I.

There were studies proving that some of these substances (**2c**, **2d** and **2e**) are relatively efficient substrates of mammalian adenosine deaminase while some others (**2a**, **2f**, **2g**, **2h**, and **2i**) are not [16, 27].

Table I

Calculated properties and measured in vitro anti-HIV-1 (III B) activities[a] of the purine derivatives investigated

Com-pound	Calculated properties						Measured activity	
	Total energy [kJ/mol]	Heat of formation [kJ/mol]	ε_{HOMO} [10^{-18} J]	ε_{LUMO} [10^{-18} J]	Dipole moment [10^{-12} Cm]	Overlay fit RMS error [10^{-12} m]	Mean IC_{50}	SD
2a	-346961	399	-1.31	0.00432	9.28	4.50	4.0	1.6
2b	-314340	96	-1.39	-0.03067	6.76	247	4.6	1.4
2c	-304755	259	-1.34	0.01488	4.78	3.48	10.0	6.0
2d	-318144	249	-1.41	-0.08077	3.86	6.10	7.6	4.4
2e	-327219	115	-1.38	-0.01940	9.34	0.00	3.0	0.1
2f	-361921	431	-1.32	0.01247	8.13	3.16	9.0	3.7
2g	-346953	408	-1.33	0.00346	10.58	7.49	6.1	1.9
2h	-374369	34	-1.37	-0.01388	9.22	9.87	6.6	3.5
2i	-344482	335	-1.32	-0.04721	8.25	6.11	7.3	1.6
2j	-349749	243	-1.33	0.00624	9.65	5.86	52.0	5.0
2k	-293064	69	-1.49	-0.07032	8.20	258	>200.0	-
2l	-325685	376	-1.39	-0.03139	9.53	258	>200.0	-
3	-167939	362	-1.40	-0.01787	7.26	-	12.0	3.0

[a] Data excerpted from ref. [16].

Method

In the present study, geometry optimizations and molecular orbital calculations were carried out using AM1 (Austin method-1 [17]) method at the level of restricted Hartree–Fock (RHF) approach and a conjugate gradient minimization, Polak–Ribiere technique was applied to get the optimized geometries. The conformational analyses of the structures were performed using the method of molecular mechanics on the already optimized structures then followed by reoptimization leading to global minima. Throughout the calculations convergence limit and gradient values (RMS) were maintained below 10^{-3} kcal/mol and 10^{-2} kcal/Åmol, respectively. All these calculations were carried out using the HyperChem (release 4.0) and ChemPlus (1.5) package programs [24]. The solvent accessible surfaces are drawn by using CSChem 3D Net program.

Results and discussion

It has been reported that 6-amino, 6-chloro and 6-methoxy-2-amino purine nucleoside analogs were relatively efficient substrates for mammalian adenosine deaminase [16]. On the other hand, although compounds **2a**, **2f**, **2i** and few other retain anti-HIV activity, they are not substrates of adenosine deaminase. Moreover, small modifications in the structure of the compounds of present interest results in significant reductions in anti-HIV activity.

Although, many factors intricately influence the biological activity, chemical ones, play undeniable role. In the present treatise, anti-HIV activities of the compounds listed in Table I have been tried to be correlated with certain quantum chemical and structural properties of them. For that purpose, using the Hansch approach [18, 19] to analyze the structure–activity relationship, various uni- and multivariable linear regression models (within the limitations of the degree of freedom) were employed between the dependent variable (anti-HIV activity) and various independent variables which included the highest occupied and lowest unoccupied molecular orbital energies (HOMO and LUMO energies, respectively), distances between certain heteroatoms, log*P* values, interfrontier energy gaps (HOMO, LUMO energy difference), dipole moments, molar volumes and polarizabilities (calculated by the methods of Bodor et al., [20] and Miller [21], respectively) and charges on heteroatoms. Unfortunately, in every combination of the independent variables, the regression statistics was found to be unacceptable (low goodness of fit, F and t-test values [22, 23]).

These results indicate that the simple quantum chemical quantities are not relevant descriptors in a linear correlation study as the Hansch approach is. At the present stage, the application of nonlinear methods is not promising because of the low number of items.

Anti-HIV activity vs. root-mean-square (RMS) overlay fit

RMS overlay fit is a method for overlaying molecules by minimizing the distances between the atoms. The RMS value of the residual distances is a measure of the similarity of the structures [24]. Compound **2e**, which is the most active one

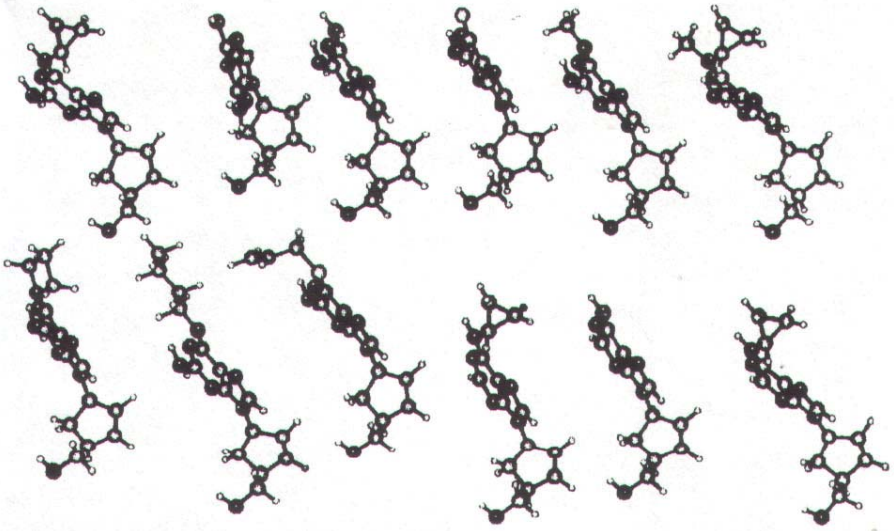

Fig. 2. σ-skeleton of AM1 geometry optimized structures of some of the compounds (**1**-**10**, **12**, **13**) studied (refer to Table I)

Fig. 3. Solvent accessible surfaces of compounds **1**, **2** and **5**

among the investigated set was chosen as the test structure and the others were overlayed on to it. Table I shows RMS errors in the overlaying process.

As we inspected the anti-HIV activities versus RMS overlay data, we classified the compounds in four groups:

(i) Compounds having RMS errors in the order of magnitude of 10^{-12} m and anti-HIV activities 3–10 (**2a**, **2c**, **2d**, **2e**, **2f**, **2g**, **2h**, and **2i**).

(ii) Compounds having RMS errors in the order of magnitude of 10^{-10} m and anti-HIV activities > 200 (**2k** and **2l**).

(iii) **2b** with RMS error in the order of magnitude of 10^{-10} m and anti-HIV activity of 4.6.

(iv) **2j** with RMS error in the order of magnitude of 10^{-12} m and anti-HIV activity of 52.

Groups (i) and (ii) suggest that the *in vitro* anti-HIV activity correlates well with the global shape of the molecules in the least-energy conformation, groups (iii) and (iv) represent the exceptions. We observed during the conformational analysis that group (i) molecules have similar least-energy conformations while in **2b** in the most stable conformer the orientation of the purine rings with respect to the cyclopentenyl moiety is very different. It is known that the biological effect is caused not necessarily by the least-energy conformer, any other one, energetically accessible under biological circumstances, may possess activity. We think that this is the case for **2b**.

Anti-HIV activity vs. chemical structure

It is known that in the timine-adenine pair the 6-NH_2 group of adenine is a H-donor and the nitrogen atom 1 is a H-acceptor. To inhibit nucleic acids one has to disturb this connecting pattern. Therefore, if the molecule has an NH_2 group at position 2 and no H-donor substituent at position 6, the adenine analogue connects with the 2-NH_2 group as H-donor and this way the angle of the purine moiety with respect to the other part of the nucleic acid chain changes, causing inhibition. Examining the structures and the activity data we observe that a 2-amino substituent is essential for the activity and it is advantegous if the heteroatom-connected substituent at position 6 has no hydrogen on the heteroatom.

Anti-HIV activity vs. logP values

Log*P* value is an important physicochemical parameter used in pharmacology. It reflects the distribution of a drug in between aqueous and lipid layers in living organisms.

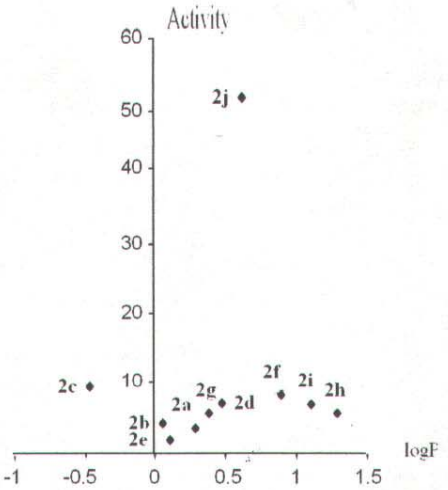

Fig. 4. Anti-HIV activity vs. log*P* graph of the compounds studied

In the present study, calculation of log*P* values is based on atomic parameters derived by Ghose et al. [25, 26]. Figure 4 shows anti-HIV acitivity vs. log*P* values of the compounds of present interest.

From the data points on Fig. 4 we concluded that there is no significant connection between the log*P* values and the *in vitro* anti-HIV activity. However, *in vivo* activity may depend on log*P* because this parameter is important for bio-availability and pharmacokinetic processes.

Conclusion

It has been reported that anti-HIV activities of (–)-(1*S*,4*R*)-4-[2-amino-6-(substituted)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol derivatives are highly dependent on structural variations. The compounds studied presently exhibit anti-HIV activity which cannot be explained simply relying on few quantum-chemical (within the limitations of AM1 method) parameters or merely on spatial configuration and conformations of the groups present on the molecules. However, certain deductions on qualitative structure-activity relationship basis still can be made. Presently, the root-mean-square overlay analysis was found to be effective on the (reported) anti-HIV activities of the above mentioned compounds. Maybe 3D-QSAR models using the 4D-QSAR analysis formalism in the structure-based design framework will be more instructive when the structures of the incorporative enzyme systems are available.

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