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The correlations between chemical structure properties and antiviral activities of HIV-1 inhibitors: The study of anti-AIDS

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ABSTRACT

In this work, we calculated the several physico chemical properties containing of solubility (by VCL), lipophilicity (by milinspiration), dipole and quadrupole moments (by Density Functional Theory) for 7 AZT analogs, and compared these parameters with inhibition assays of them. It is resulted; cytotoxicity of these drugs is related with their lipophilicity inversely. With using of this result, for 7 nucleoside analoges we predict, cytotoxicity addition arrangement are as following: CBV> d4T> ddI> AZT> ddC> ABC> 3TC

Keywords: HIV-1; Cytotoxicity; Lipophilicity; Solubility; Moments

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is the disease affecting a significant part of the population in recent years due to the epidemic spread of human immunodeficiency virus (HIV)[1]. Virtually all drugs that have been licensed for clinical use (or made available through expanded access programs) for the treatment of HIV-infections fall into one of the following three categories:(I) nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), e.g. zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), abacavir (ABC), act, as chain terminators, at the substrate binding site of the reverse transcriptase (RT); (II) non-nucleoside reverse transcriptase inhibitors (NNRTIs) that intract with the RT at an allosteric, non-substrate binding site e.g. nevirapine, delavirdine, efavirencz; and (III) protease inhibitors (PIs) that specifically inhibit, as peptidomimetics, the virus-associated protease e.g. saquinavir, ritonavir, indinavir, nelnavir[2].

Many of the nucleoside analogs (fig 1, 2) cause termination of the growing DNA chain. Because they closely resemble normal nucleosides, nucleoside analog inhibitors can be added to the newly synthesized DNA during reverse transcription. Elongation is blocked because the chain terminators lack the 3'-OH functional group essential for incorporation of additional group essential for incorporation of additional nucleotides [3]. All of the currently marketed AIDS drugs are selective for HIV-1 RT, they are not highly specific and can inhibit normal cellular polymerizes, causing serious side effects. Nucleoside analogs are also relatively expensive to synthesize [4]. The preliminary research of properties and antiviral activities basis for these drugs, with using of calculation, reduces a lot of expenses. To this meaning, we want find relationship between the antiretroviral activity and calculated chemical structural properties. Namely, by one of chemical property, we can predict cytotoxicity respect of nucleoside analogs. The usual structural properties that are related to bioactivity are lipophilicity, solubility [10], dipole and quadrupole moments [5,6].

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In this paper, we found one of these properties who related directly to antiviral activity of the nucleoside analogs and we use this property for predicting of respect inhibitor activity for other HIV-1 RTs, including of AZT, ddI, ddC, d4T, 3TC, ABC and CBV.

METHODOLOGY

Octanol-water partition coefficient (lipophilicity) for the drugs is obtained online service Molinspiration (miLogP1.2).

Solubility in water (IALogS) was obtained by the online software ALOGPS v 2.1 (Virtual Computational Laboratory, VCL).

Dipole and quadrupole moments of these drugs were performed at the Density Functional Theory, B3LYP/6-31G* level using the standard procedure in GUSSIAN 98.

RESULTS AND DISCUSSION

3-1 Process finding

For obtaining of the correlations between physico chemical properties and cytotoxicity, inhibition assays for 7 nucleoside analogs compared with their solubility, lipophilicity, dipole and quadrupole (show table1).

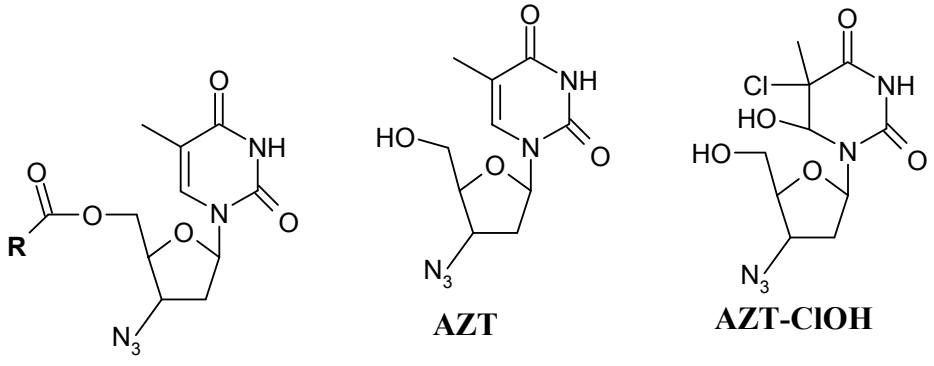
Inhibition assays for AZT analogs (figure 1) were by using from trypan blue (TB) dye methodology in peripherical blood mononuclear cells (PBMC) respectively as folowing:
AZT-Val> AZT-Ac> AZT-iLeu> AZT-Leu> AZT> AZT-Iso [9].

Method for lipophilicity (LogP, Octanol-water partition coefficient) developed at Molinspiration (miLogP1.2) is based on the group contributions. Group contributions of have been obtained by fitting calculated LogP with experimental LogP for a training set several thousands drug-like molecules.

Methodology for LogP calculation is very robust and is able to process practically all-organic and most organometallic molecules [17]. As the same method, the studied compounds have lipophilicity in the following order: AZT-Val< AZT-Ac< AZT-iLeu< AZT-Leu< AZT< AZT-ClOH<AZT-Iso.

Solubility in water (IALogS) was obtained by means of the online software ALOGPS V2.1 (Virtual Computational laboratory) as described by Tetko et al.[7,8]. By this software, the solubility arrangement of these AZT analogs is: AZT-iLeu< AZT-Leu< AZT-Ac< AZT-Val< AZT-Iso< AZT< AZT-ClOH.

Dipole (μ) and quadrupole moments (Q) of these drugs were performed at the Density Functional Theory (B3LYP) on 6-31G* using the standard procedure in GUSSIAN 98 [11]. μ is total dipole moment and the quantity $2Q_{ZZ}-(Q_{XX}+Q_{YY})$ of diogonalized matrix is often referred to as the quadrupole moment[13]. The B3LYP level a sufficient level for description of the total dipole moments of heterocycles also is used [12]. Since the number of atoms in these drugs are relatively high, 6-31g* basis set is explored and totally, B3LYP/6-31G* level is used for obtaining of dipole and quadrupole moments.



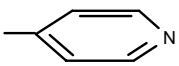
Drug	R
AZT -Iso	
AZT-Val	-CO-NH-CH (COOH) CH $(CH_3)_2$
AZT- iLeu	-CO-NH-CH (COOH) CH (CH_3) CH_2-CH_3
AZT-Leu	-CO-NH-CH (COOH) CH_2-CH $(CH_3)_2$
AZT- Ac	-COOH

Fig. 1. Chemical structures of representative AZT analogs

The dipole moment order for 7 AZT analogs are: AZT-ClOH< AZT-Iso< AZT-Ac< AZT-Val< AZT-Leu< AZT< AZT-iLeu and quadrupolr moment of these drugs are in following order: AZT-iLeu< AZT-ClOH< AZT-Val< AZT-Leu< AZT-Ac< AZT-Iso< AZT.

In table 1, process of cytotoxicity as inhibition assays are brought and compared with IALogS (solubility), LogP (lipophilicity), μ (total dipole), Q (quadrupole) and it is resulted that reductive process of 7 drugs cytotoxicity from up to down is agreement with additive process of lipophilicity only and completely. If addition of lipophilicity would be according with reduction of hydrophilicity then cytotoxicity changes are harmonies with hydrophilicity changes. This result will be generated to the other anti aids drugs in section 3-2.

3-2 cytotoxicity order of anti-AIDS drugs

In this section 7 nucleoside reverse transcriptase inhibitors (NRTIs), containing of Zidovudine (AZT or ZDV), Abacavir (ABC), Carbovir (CBV), Stavudine (d4T),

Lamivudine (3TC), Didanosine (ddI), Zalcitubine (ddC) are compaired together [14, 15,16]. These compounds are synthetic nucleoside analoges, and intracellularly are converted by cellular enzymes to the active metabolite, nucleoside analog triphosphate (N-TP). N-TP inhibits the activity of HIV-1 reverse transcriptase (RT) by its incorporation into viral DNA. The lack of the 3'-OH group incorporated nucleoside analog prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated.

Table 2, the lipophilicity of 7 noted anti-AIDS is shown. Since LogP amounts order is related with inhibition assay respect inversely, we predict cytotoxicity arrangement of 7 drugs would be as following: CBV> d4T> ddI> AZT> ddC> ABC> 3TC.

CONCLUSION

We found relationship between the antiretroviral activity and calculated chemical structural properties that it is relationship between the cytotoxicity of anti-AIDS drugs with lipophilicity inversely and consequently with hydrophilicity directly. With this respect, we can guess inhibition assays of the other anti-AIDs drugs in relation with together. Nucleoside analogs are relatively expensive to synthesize and the preliminary research of properties and antiviral activities basis for these drugs, with using of calculation, reduces a lot of expenses.

ACKNOWLEDGEMENT

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Table 1. Cytotoxicity, solubility, lipophilicity, dipole and quadrupole moments of studied AZT analogs

Drug	Cytotoxicity	IALogS	LogP	μ	Q
AZT-Val	6700	-5.74	-1.24	6.37	46.7
AZT-Ac	6000	-6.13	-1.16	4.59	50.2
AZT-iLeu	5700	-6.36	-0.80	6.49	39.2
AZT-Leu	2000	-6.33	-0.80	6.40	48.5
AZT	500	-2.67	-0.18	6.48	60.9
AZT-ClOH	ND	-2.36	0.25	1.16	41.9
AZT-Iso	400	-4.33	1.06	3.43	53.1

Table 2. Lipophilicity of studied anti-AIDS drugs

Drug	CBV	d4T	ddI	AZT	ddC	ABC	3TC
LogP	-0.38	-0.31	-0.29	-0.18	0.13	1.21	1.25

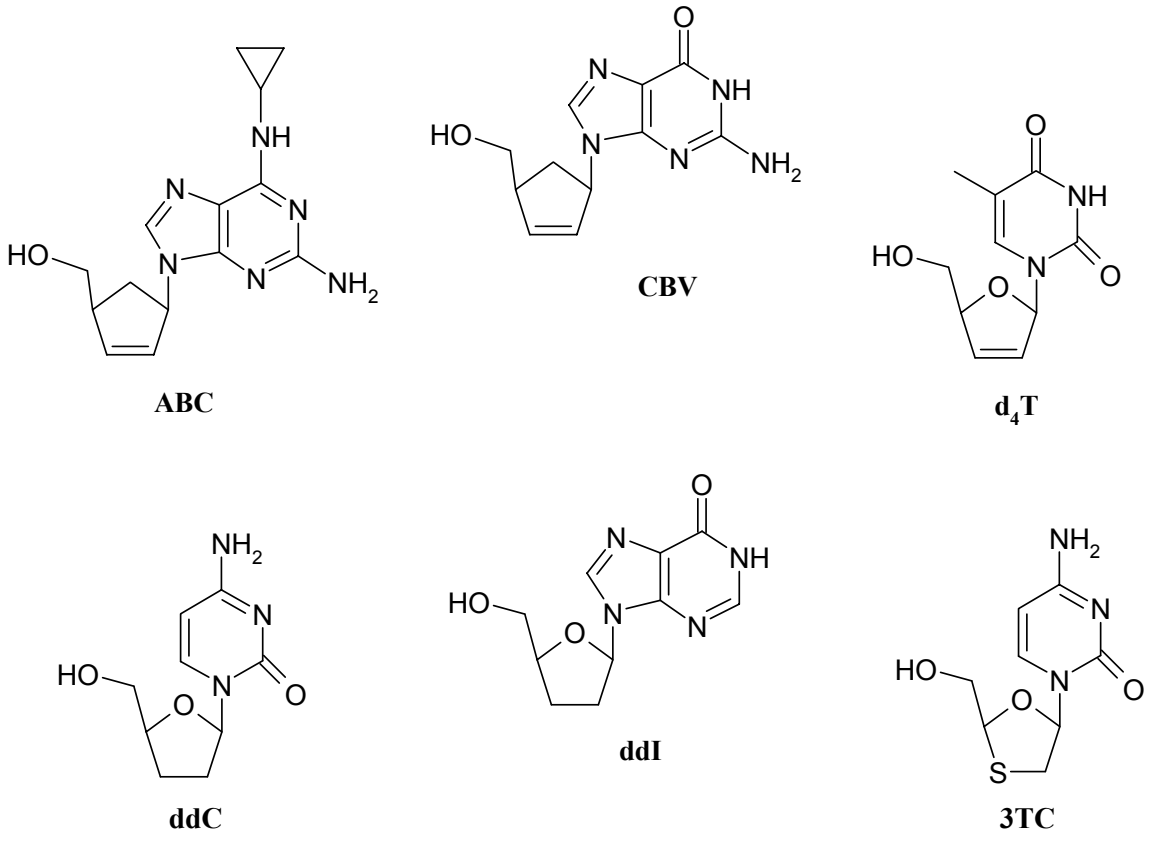

Fig. 2. Chemical structure of studied anti- AIDS drugs

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