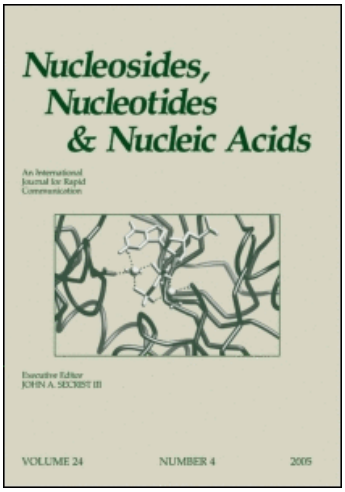

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ANTI-HIV ACTIVITY OF NOVEL PHOSPHONATE DERIVATIVES OF AZT, d4T, AND ddA

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ABSTRACT

Anti-HIV activity and cytotoxicity were tested for novel phosphonate derivatives of AZT, d4T and ddA. For d4T phosphonate derivatives the most active was 2′,3′-Dideoxy-2′,3′-didehydrothymidine 5′-isopropylphosphite and among the AZT phosphonate derivatives highest activity was shown by 2′,3′-Dideoxy-3′-azidothymidine 5′-cyclohexylphosphite.

INTRODUCTION

It has been shown that 5′-hydrogen phosphonate of AZT provides clear inhibition of HIV reproduction *in vitro* and *in vivo*. One of the general advantages of this compound is its low toxicity in comparison with the parent nucleoside analog [1,2]. Another advantage of 5′-hydrogen phosphonate of AZT is lower frequency of appearance of nucleoside-resistant mutants of HIV [3]. Phosphonate derivatives of other nucleoside analogs also provide inhibitory effect on the replication of HIV in several cell culture systems [4].

The goal of this work was the study of cytotoxicity and anti-HIV activity of novel phosphonate derivatives of AZT, d4T and ddA.

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EXPERIMENTAL

Cytotoxicity (CD_{50}) of the tested compounds was measured by determination of cell viability on MT-4 cells by trypan blue exclusion test. Anti-HIV activity of tested compounds (ID_{50} and ID_{90}) was assessed by means of a cell viability calculation as well as by measurement of p24 antigen by immunoenzyme method. The inhibitory effect on the replication of different HIV strains was evaluated in MT-4 cells infected by HIV-1/IIIB. Selectivity index (SI) was determined as the ratio of CD_{50} to ID_{50}.

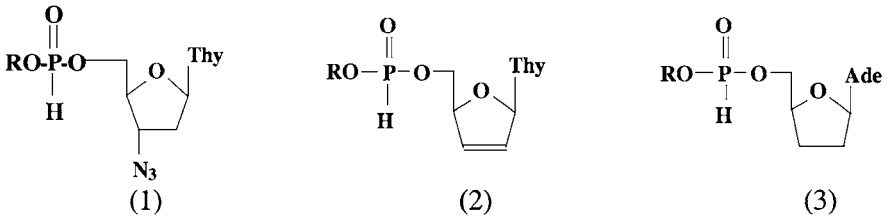
RESULTS AND CONCLUSIONS

Chemical structures of the tested compounds are shown on Figure 1.

New compounds were evaluated for their cytotoxicity and anti-HIV activity measured by inhibition of p24 antigen consumption. The data obtained are summarize in Table 1.

In general, phosphonate derivatives of the tested nucleosides showed low cytotoxicity in comparison with parent nucleoside analogs. This tendency most clearly was demonstrated for AZT and d4T phosphonate derivatives. Similar chemical modification of the different nucleosides resulted in the different biological activity. For example, in the case of ddA phosphonate derivatives cytotoxicity did not differ from that of the parent nucleoside.

All tested phosphonate AZT and d4T derivatives provided high anti-HIV activity. For AZT phosphonate derivatives, 2′,3′-dideoxy-3′-azidothymidine 5′-cyclohexylphosphite (1e) was the most active. In contrast, among d4T derivatives the highest SI value was shown for 2′,3′-dideoxy-2′,3′-didehydrothymidine 5′-isopropylphosphite (2b). The increase in the antiviral activity of the novel compounds appeared to be due to the presence of lipophilic groups. This may result in the higher membrane permeability and higher intracellular concentration of the tested derivatives. ID_{50} values for the parent nucleoside analogs (AZT and d4T) and their hydrogen phosphonates determined by measurement of cell protection did not differ from ID_{50} values detected by p24 antigen. For other compounds



1a - R=H; 1b - R=iPr, 1c - R=Adamantyl; 1d - R=Me_3CCH_2; 1e - R=cyclohexyl; 2a - R=H; 2b - R=iPr, 2c - R=Adamantyl; 2d - R=Me_3CCH_2; 2e - R=cyclohexyl; 3a - R=H; 3b - R=iPr, 3c - R=Adamantyl.

Figure 1. Structures of novel phosphonate derivatives of AZT (1), d4T (2) and ddA (3).

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Table 1. Inhibitory Activity of Phosphonate Derivatives of AZT, d4T, and ddA Against HIV-1 in MT-4 Cells

Tested Compound	CD_{50}, μM	ID_{50}, μM	HIV-1/IIIB ID_{90}, μM	SI
AZT	37.4	0.014	0.37	2671
1a	>262	0.13	2.62	2015
1b	134	0.013	2.68	10307
1c	>215	0.11	10.7	>1955
1d	>249	0.0249	124.6	12460
1e	121	0.0024	0.024	50417
d4T	73	0.22	2.7	332
2a	280	0.17	1.7	1647
2b	>304	0.15	15.2	>2027
2c	150	0.15	180	1000
2d	279	0.14	20	2000
2e	>289	1.4	16	>200
ddA	213	21	150	10
3a	>333	3.33	10.4	>100
3b	147	14.6	26.5	10
3c	120	60	>200	2

(1c–1e and 2c–2e) the two methods of anti-HIV activity determination do not correlate, however.

This discrepancy could possibly be attributed to differences in metabolism of the novel phosphonate derivatives (1c–1e and 2c–2e) in infected and in uninfected cells. The pathway of intracellular metabolism is unknown.

Nucleoside phosphonate esters may serve as depot forms of nucleosides or their phosphonates.

The obtained results are encouraging for designing of new anti-HIV compounds based on phosphonate derivatives of nucleoside analogs.

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