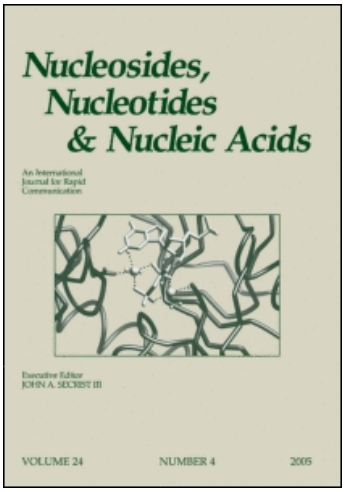

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BIS(S-ACYL-2-THIOETHYL)ESTERS OF 2',3'-DIDEOXYADENOSINE 5'-MONOPHOSPHATE ARE POTENT ANTI-HIV AGENTS IN CELL CULTURE

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Abstract. It is shown that ddA bis(SATE)phosphotriesters have potent anti-HIV activity in cell culture. Thus, compared with the parent nucleoside, a decrease of 3 or 4 orders of magnitude was observed in the EC_{50} values for the bis(S-acetyl-2-thioethyl)phosphotriester derivative, which makes this compound as active as AZT.

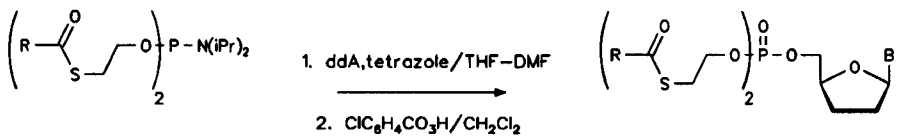
INTRODUCTION

We have previously demonstrated that neutral phosphotriester derivatives of nucleoside analogs which incorporate S-acyl-2-thioethyl [SATE] groups allow the intracellular release of the corresponding 5'-monophosphates (or phosphonates).[1,2] Here, we have applied the SATE pronucleotide approach to a well-known anti-HIV nucleoside analog, namely 2',3'-dideoxyadenosine (ddA) and we report the synthesis and the biological evaluation of the corresponding phosphotriester derivatives.[3]

RESULTS AND DISCUSSION

The synthesis of mononucleoside bis(SATE)phosphotriesters has been previously described.[1,2] Briefly, the appropriate diisopropyl aminophosphite diesters **1a-c** were condensed with ddA, followed by subsequent *in situ* oxidation (Scheme 1). The target compounds **2a-c** were characterized by UV, ^1H and ^{31}P NMR, FAB mass spectrometry, and HPLC, all data being consistent with their structure and purity.

When the antiviral activity of the ddA bis(SATE)phosphotriesters was evaluated on several HIV-1 infected T-cell lines, the bis(S-acetyl-2-thioethyl)ddAMP **2a** emerged as the most potent inhibitor. In peripheral blood mononuclear cells and in monocyte-derived macrophages, this compound is a more active HIV replication inhibitor than ddA by 3 or 4 orders of magnitude and is also more potent than AZT (Table).



1a R= CH_3
1b R= iPr
1c R= tBu

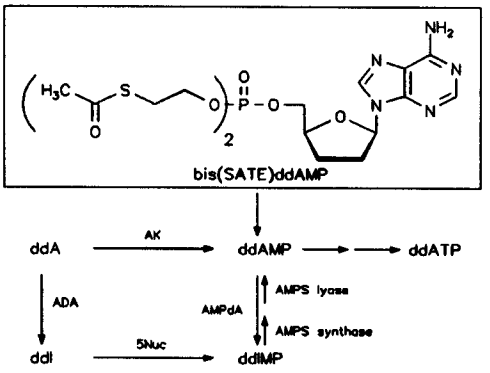
2a R= CH_3, B= adenin-9-yl
2b R= iPr, B= adenin-9-yl
2c R= tBu, B= adenin-9-yl

SCHEME 1

TABLE

	PBMC		Monocytes/Macrophages	
	EC_{50}[a]	CC_{50}[b]	EC_{50}[a]	CC_{50}[b]
2a	$2.3\ 10^{-10}$	$1.1\ 10^{-6}$	$1.0\ 10^{-11}$	$4.4\ 10^{-6}$
ddA	$9.0\ 10^{-8}$	$2.2\ 10^{-5}$	$1.7\ 10^{-7}$	$> 10^{-4}$
AZT	$1.2\ 10^{-9}$	$6.1\ 10^{-5}$	$4.9\ 10^{-10}$	$> 10^{-4}$

[a] 50% effective molar concentration or molar concentration required to inhibit the replication of HIV by 50%; [b] 50% cytotoxic molar concentration or molar concentration required to reduce the viability of the cells by 50%.



ADA, adenosine deaminase; AK, adenosine kinase; 5Nuc, 5'-nucleotidase; AMPdA, AMP deaminase; AMPS, adenylosuccinate

SCHEME 2

The antiviral data obtained with **2a** may be explained in relation to the well-established ddA/ddI cellular metabolic pathway[4,5] (Scheme 2).

Compared with ddA, the decrease in the EC_{50} values observed for the ddA bis(SATE)phosphotriesters could be related to the direct intracellular delivery of ddAMP, thus shunting the ddA/ddI pathway. This may result in an intracellular increase of ddAMP concentration, which is subsequently transformed to ddATP.

CONCLUSION

The present results show that the ddA bis(S-acetyl-2-thioethyl)phosphotriester **2a** is one of the most potent anti-HIV agents in cell culture. This can be tentatively explained if one considers that direct ddAMP intracellular delivery shunts the dda/ddI metabolism pathway, and work along these lines is in progress in our laboratory to corroborate this point.

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