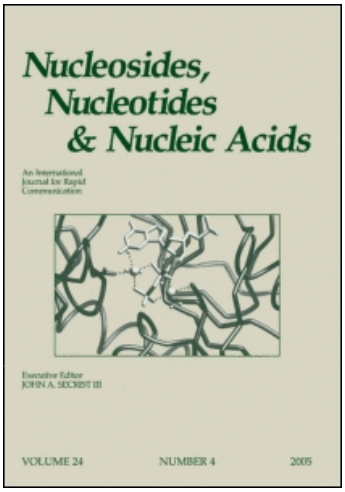

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Synthesis of Dioxolane Analogues of Dideoxynucleotides and Their Substrate Properties in DNA Synthesis Reactions

E. V. Efimtseva[a]; S. N. Mikhailov[a]; L. S. Victorova[a]; T. A. Rosovskaya[b]; R. Sh. Beabealashvilli[b]
[a] Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, Russia [b] Institute of Experimental Cardiology, National Cardiology Research Center, Russian Academy of Medical Sciences, Moscow, Russia

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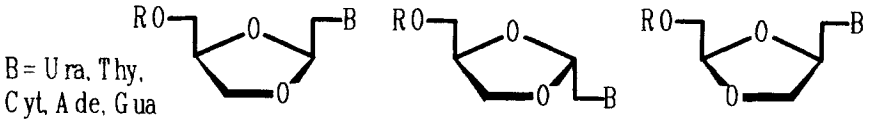
SYNTHESIS OF DIOXOLANE ANALOGUES OF DIDEOXYNUCLEOTIDES AND THEIR SUBSTRATE PROPERTIES IN DNA SYNTHESIS REACTIONS

E.V. Efimtseva*, S.N. Mikhailov, L.S. Victorova,
T.A. Rosovskaya[1], R.Sh. Beabealashvilli[1]

Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow 117984 Russia; [1] Institute of Experimental Cardiology, National Cardiology Research Center, Russian Academy of Medical Sciences, Moscow 121552 Russia.

Abstract. Dioxolane derivatives of dNTP were prepared and their substrate properties were investigated in DNA synthesis reactions.

The present work is a sequel to earlier experiments in which we synthesized dioxolane analogues of 2',3'-dideoxynucleosides and studied their physico-chemical properties[1-3]. Starting from nucleosides 1-3[2], the corresponding triphosphates 4-6 were prepared using standard procedures. Here we summarize the data on the substrate properties of 4-6 in the reactions of DNA synthesis catalyzed by DNA polymerases, AMV and HIV reverse transcriptases. The results are listed in the Table. The enzyme-catalysed reactions were carried out with an equimolar complex of M13 mp10 phage DNA and with [p^{32}]dCCCAGTCACGACGT as labeled primer. It should be noted that dNTP analogues with *cis* and *trans* configurations can be incorporated into a growing DNA chain by terminal deoxynucleotidyl transferase (TDT). The nucleosides 1-3 were found to be inactive against HIV-1 (CEM) and HSV, HCMV, VZV (HFF) at concentration up to 100 μg/ml and were nontoxic towards CEM and HFF cells[4]. The absence of antiviral activity of 1-3 is



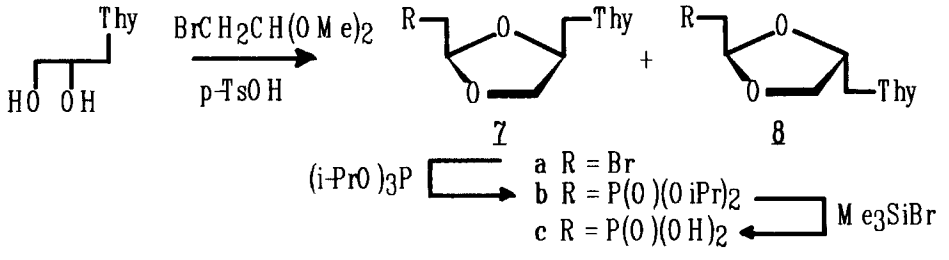
1 2 3

4 5 6

TABLE Substrate properties of nucleoside triphosphate analogues in DNA synthesis reactions.

Enzyme	4	5	6
Klenow fragment	*	*	terminator
RT HIV	terminator	*	terminator
RT AMV	*	*	terminator
TDT	terminator	terminator	*

* NTP analogs were not transformed.



Scheme

probably due to the fact that they are not recognized by cellular and viral kinases.

In order to overcome this enzymatic phosphorylation step we decided to prepare dioxolane phosphonate derivatives. The synthesis has been performed from 1-(2',3'-dihydroxypropyl)thymine[5] as shown in the Scheme. The *cis* and *trans* 7c and 8c isomers were separeted by HPLC reversed-phase chromatography. Their structures were confirmed by NMR spectroscopy.

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