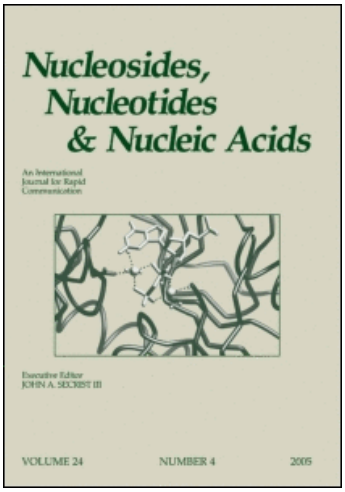

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Selective Inhibition of DNA Chain Elongation Catalyzed by DNA Polymerases

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SELECTIVE INHIBITION OF DNA CHAIN ELONGATION CATALYZED BY DNA POLYMERASES

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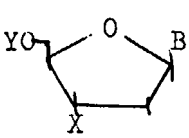
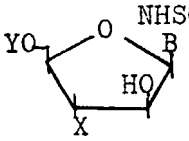
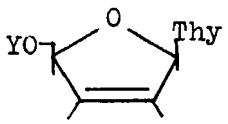
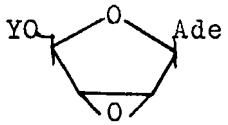
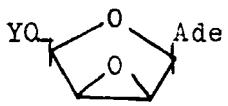
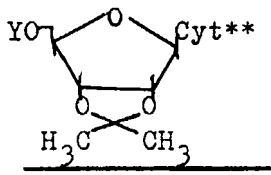
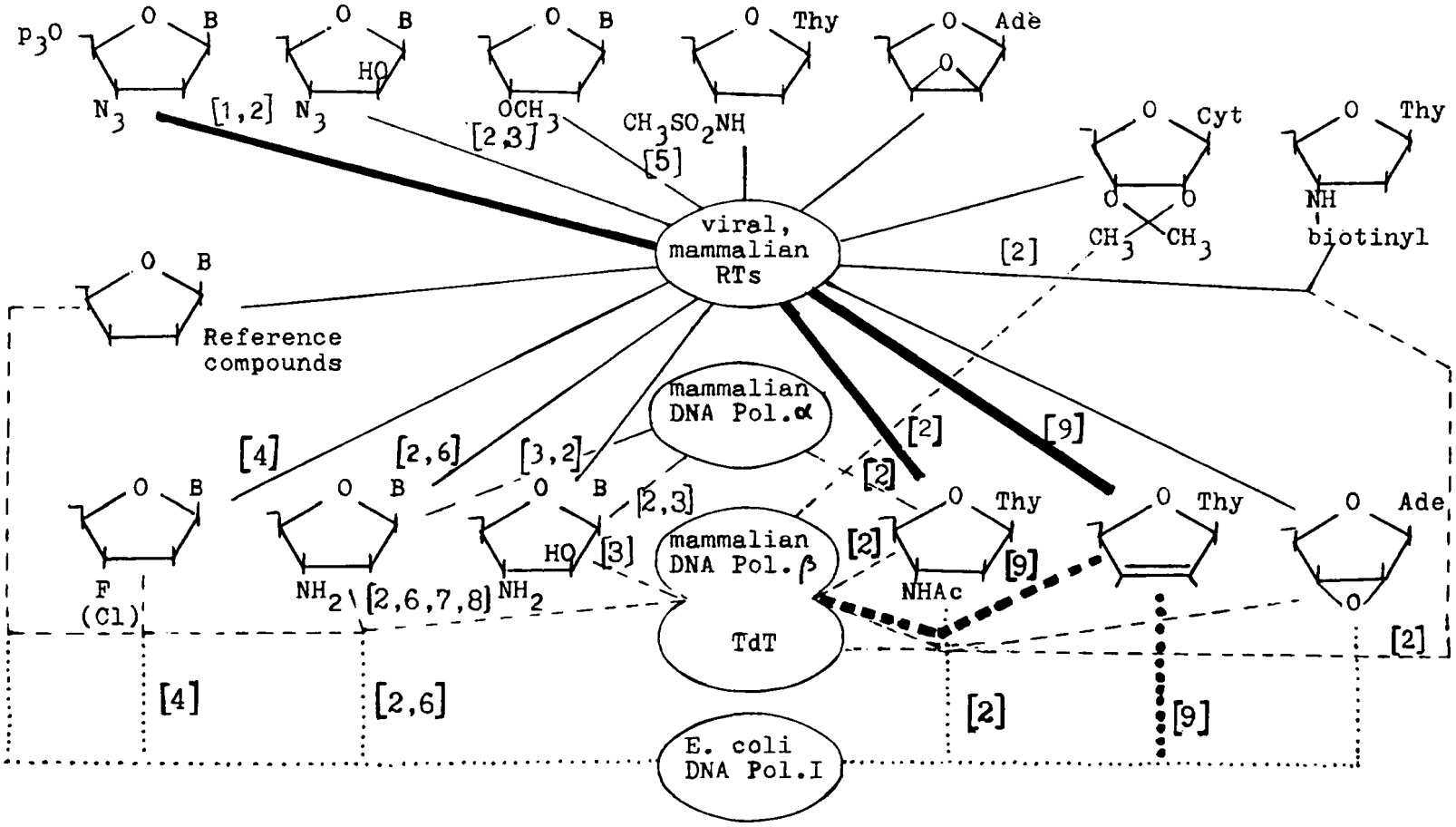
Abstract. The results of series of works on the properties of a large number of nucleoside 5'-triphosphates analogs in the reaction catalyzed by several DNA polymerases are summarized.

Molecular mechanisms of substrate selection by DNA polymerases are not studied in detail. Therefore we have undertaken a comparative analysis of DNA polymerases from different sources employing nucleoside 5'-triphosphate analogs capable of incorporating into DNA chains terminating these chains elongation. Synthesis of a large line of nucleoside 5'-triphosphate analogs with substitution at the sugar residue has been performed. DNA polymerases have been isolated, and the synthesis of DNA has been studied using phage M13 DNA or phage MS2 RNA with synthetic deoxyoligonucleotide primers. The molecular mechanism of the substrate action has been determined by PAG electrophoresis of the reaction

Table. Termination of DNA synthesis with pure enzymes

Compounds	DNA polymerases*						Ref.
	α	β	TdT	AMV	RSV	I	
 X=H	-	+	±	±	+	+	1,2,6-8
NH_2	+	+	+	+	+	+	
NHAc	+-	+	+	++		+	2
N_3	-	-	-	+	+	-	2
Cl	-	+	+	+	+	+	
X=NHbiotinyl	-	-	+	+		-	2
$NHSO_2CH_3$	-	-	-	+		-	
 $X=NH_2$	+	+	+	+		-	3,2
N_3	-	-	-	+	+	-	3,2
	-	+	++	++	++	++	9
	-	+	+	+		+	
	-	+	+	+		+	
	-	-	-	+		-	

Y = $Na_4P_3O_9$. * α -DNA polymerase α from calf thymus; β - DNA polymerase β from rat liver; TdT - terminal deoxynucleotidyl transferase from calf thymus; AMV and RSV - reverse transcripases; I from E.coli. ** Compounds of this nature with Ade, Gua and Thy bases were inactive.



Scheme of Nucleoside 5'-Triphosphate Analogs Action

products. The results of such experiments are given in the Table and Figure.

Basing on the data listed in the Table some conclusions can be made. (i) All DNA polymerases have different properties with respect to substrate analogs. (ii) Among the enzymes tested the most specific appears to DNA polymerase α and the least specific - viral reverse transcriptases. (iii) Some substrate analogs have been found to be specific inhibitors of viral reverse transcriptases only.

In addition, as is shown, some dNTP and araNTP analogs inhibit effectively the endogeneous reverse transcriptase from intracisternal A-type particles of regenerated rat liver[10]. Also, they block the reproduction of the hepatitis B virus isolated from sick humans (V.V.Tsibinogin, A.A.Krayevsky, R.Sh.Beabealashvilli, E.Ja.Gren and L.L.Kisselev, submitted for publication). In both cases the most active among the substances tested was dTTP($3'N_3$).

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