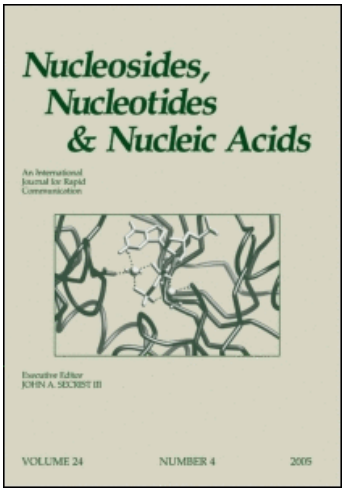

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Acyclic Nucleoside and Nucleotide Analogues with Amide Bond

E. V. Efimtseva[a]; S. N. Mikhailov[a]; M. V. Jasko[a]; D. V. Malakhov[a]; D. G. Semizarcv[a]; M. V. Fomicheva[a]; E. R. Kern[b]
[a] Engelhardt Institute of Molecular Biology, Russian Academy of Science, Moscow, Russia [b] Department of Pediatrics of, the University of Alabama, Birmingham, Alabama, USA

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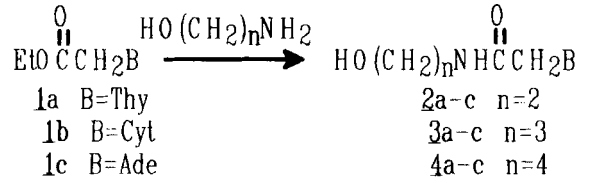
ACYCLIC NUCLEOSIDE AND NUCLEOTIDE ANALOGUES WITH AMIDE BOND

E.V. Efimtseva, S.N. Mikhailov*, M.V. Jasko, D.V. Malakhov,
D.G. Semizarov, M.V. Fomicheva, E.R. Kern[1]

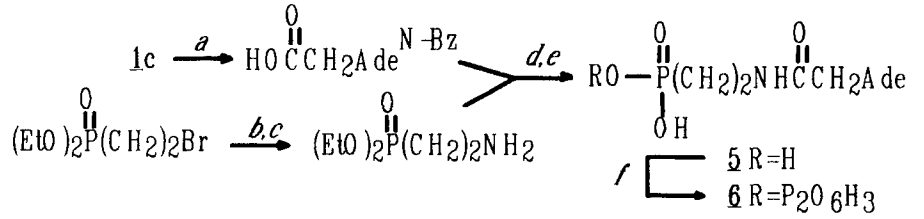
Engelhardt Institute of Molecular Biology, Russian Academy of Science, Vavilov str. 32, Moscow 117984 Russia; [1] Department of Pediatrics of the University of Alabama, 401 Volker Hall 1670, University Blvd., Birmingham, Alabama 35294 USA.

ABSTRACT: A series of acyclic nucleosides and related α-phosphonyl acyclic analogues of dNTP with an amide bond have been prepared. Their antiviral and substrate properties were investigated.

New acyclic nucleoside analogues with a rigid structural element, amide bond, have been synthesized in two stages. Alkylation of bis-trimethylsilylated thymine, cytosine and sodium salt of adenine by ethyl bromoacetate gave ethoxycarbonylmethyl derivatives 1a-c. Reaction of 1a-c with aminoalcohols afforded acyclic nucleosides 2-4 in good yields (Scheme 1). These analogues were found to be inactive against HIV-1 (CEM-SS cells) and HSV-1 , HSV-2, HCMV, VZV (HFF cells) at concentrations up to 100 μg/ml and were nontoxic towards CEM and HFF cells. However, it was shown that triphosphate of 2c is incorporated into the DNA chain by DNA polymerase from HSV-1[1]. The absence of antiviral activity and cytotoxicity is probably due to the fact that 2-4 are not recognized by cellular and viral kinases.

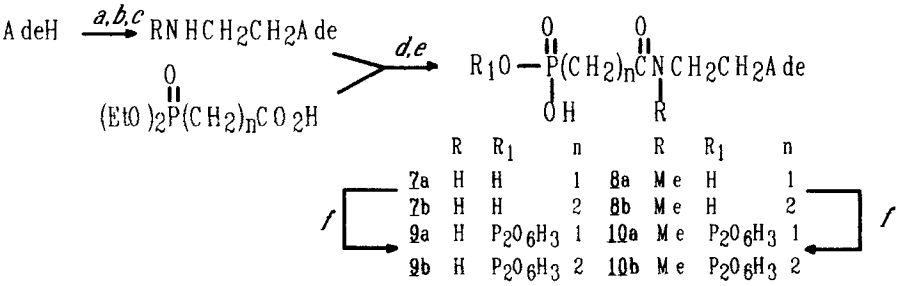


Scheme 1



a: BzCl/Py; KOH/EtOH; *b*: NaN_3; *c*: H_2/Pd/C; *d*: CDI; *e*: Me_3SiBr; NH_3/MeOH; *f*: CDI, $(Bu_3NH)_2H_2P_2O_7$

Scheme 2



	R	R_1	n		R	R_1	n
7a	H	H	1	8a	Me	H	1
7b	H	H	2	8b	Me	H	2
9a	H	$P_2O_6H_3$	1	10a	Me	$P_2O_6H_3$	1
9b	H	$P_2O_6H_3$	2	10b	Me	$P_2O_6H_3$	2

a: NaH, $BrCH_2CH_2Br$; *b*: NaN_3; *c*: PPh_3, NH_3 for R = H or $MeNH_2$ for R = Me; *d*: CDI; *e*: Me_3SiBr; *f*: CDI, $(Bu_3NH)_2H_2P_2O_7$

Scheme 3

To overcome this we decided to synthesize related phosphonyl acyclic derivatives 5, 7 and 8 (Scheme 2, 3). Their diphosphates 6 and 9, 10 were prepared by a standard procedure and were then investigated in DNA synthesis reactions catalyzed by DNA polymerases and reverse transcriptases in cell-free systems. These experiments showed that 6, 9 and 10 were incorporated into the 3'-end of the growing DNA chain by AMV RT and were not recognized by DNA polymerases α and β or by terminal deoxynucleotidyl transferase. The structures of all new compounds were confirmed by NMR and UV spectroscopy.

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