

This article was downloaded by:

On: 26 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

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

To cite this Article Efimtseva, E. V. , Mikhailov, S. N. , Jasko, M. V. , Malakhov, D. V. , Semizarcv, D. G. , Fomicheva, M. V. and Kern, E. R.(1995) 'Acyclic Nucleoside and Nucleotide Analogues with Amide Bond', *Nucleosides, Nucleotides and Nucleic Acids*, 14: 3, 373 – 375

To link to this Article: DOI: 10.1080/15257779508012386

URL: <http://dx.doi.org/10.1080/15257779508012386>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

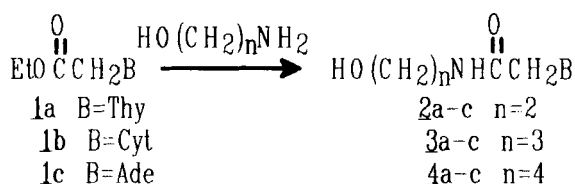
ACYCLIC NUCLEOSIDE AND NUCLEOTIDE ANALOGUES WITH AMIDE BOND

E.V. Efimtseva, S.N. Mikhailov*, M.V. Jasko, D.V. Malakhov,
D.G. Semizarov, M.V. Fomicheva, E.R. Kern¹

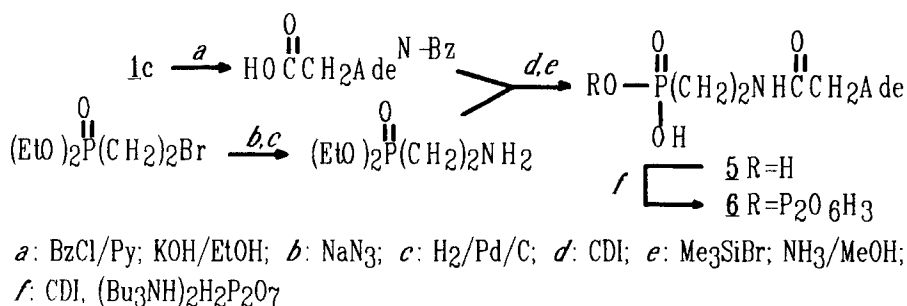
Engelhardt Institute of Molecular Biology, Russian Academy of Science, Vavilov str. 32, Moscow 117984 Russia; ¹ Department of Pediatrics of the University of Alabama, 401 Volker Hall 1670, University Blvd., Birmingham, Alabama 35294 USA.

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.

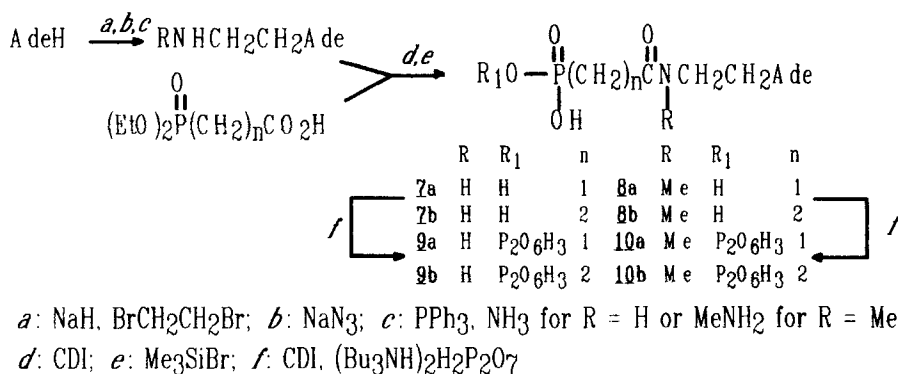
New acyclic nucleoside analogues with a rigid structural element, amide bond, have been synthesized in two stages. Alkylation of bis-trimethylsilylated thymine, cytosine and sodium salt of adenine by ethyl bromoacetate gave ethoxycarbonylmethyl derivatives 1a-c. Reaction of 1a-c with aminoalcohols afforded 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 μ g/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. 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



Scheme 2



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.

Acknowledgements: This research was supported by the International Science Foundation, grant MGA000 (S.N.M.). We are grateful to Dr. C.Tseng from the National Institute of Allergy and Infections Diseases (NIAID) and Dr. R.Schultz from the National Cancer Institute (NCI) for the antiviral screening.

REFERENCE

1. Kukhanova, M.K.; Kuznetsova, E.V.; Krayevsky, A.A; O'Hara, B.; Bekker, J; Morin, J.; Gluzman, Ya. *Molec. Biology (Russian)* 1994, 28, 999–1010.