Thematic Section: Preparative Research. **Full Paper**
Subsection: Biochemistry.
Reference Object Identifier – ROI: jbc-01/18-54-6-35
The Digital Object Identifier – DOI: 10.37952/ROI-jbc-01/18-54-6-35
Submitted on June 01, 2018.

Synthesis of pyrimidine nucleosides by method of enzymatic transglycosylation

© **Evgenia O. Dorinova**,[1,2+] **Kiryl S. Alexeev**,[1] **Mikhail S. Drenichev**,[1]
Nikolay N. Kurochkin,[1] and **Sergey N. Mikhailov**[1]*[+]
[1] *Laboratory of Design and Synthesis of Biologically Active Compounds. Engelhardt Institute of Molecular Biology, Russian Academy of Sciences. Vavilov St., 32. Moscow, 119991. Russia. Phone: +7 (499) 135-97-33. E-mail: smikh@eimb.ru, e_dorinova@mail.ru*
[2] *Department of Medical and Organic Chemistry. MIREA − Russian Technological University (M.V. Lomonosov Institute of Fine Chemical Technologies). Vernadsky Avenue, 86. Moscow, 119571. Russia.*

*Supervising author; [+] Corresponding author

Keywords: enzymes, nucleoside phosphorylases, nucleosides, transglycosylation.

Abstract

Nucleosides represent one the most important classes of natural compounds consisting of carbohydrate residue and heterocyclic base. Nucleosides are components of nucleic acids. More than 100 minor nucleosides were isolated from tRNA. About 100 drugs were developed on the basis of nucleosides, half of them being antiviral drugs and a quarter being anticancer drugs. Nucleosides can be synthesized by chemical or enzymatic methods. Chemical methods are based on the modification of natural compounds or on chemical synthesis of heterocyclic bases and monosaccharides with their subsequent condensation. To date, convenient and effective methods for producing of ribonucleosides based on trimethylsilyl derivatives of heterocyclic bases and fully acylated ribofuranose in the presence of Lewis acids have been developed. Enzymatic methods of synthesis significantly complement chemical ones and, in some cases, have undoubted advantages, such as high region- and stereoselectivity, the possibility to perform reactions in aqueous media, the use of environmentally friendly reagents. To obtain practically important nucleosides, a method based on the enzymatic transglycosylation reaction – the transfer of carbohydrate residue from one heterocyclic base to another – is actively elaborated and used.

In the course of the work, the method for nucleoside synthesis by the reaction of the enzymatic transglycosylation from 7-methyl-2'-deoxyguanosine and 7-methylguanosine as donors of carbohydrate residue in the presence of purine and various pyrimidine nucleoside phosphorylases has been optimized and the possibility of its application for the synthesis of various pyrimidine ribo- and 2'-deoxyribonucleosides has been shown. The optimal conditions for the enzymatic transglycosylation reaction leading to the production of practically important 5-substituted pyrimidine nucleosides in the presence of purine nucleoside phosphorylase and thymidine phosphorylase or uridine phosphorylase have been proposed.

References

[1] S. Mikhailov, V. Florentyev. Chemical synthesis of oligoribonucleotides. *Bioorganic Chemistry*. **1976**. Vol.2. P.1293-1317. (russian)
[2] M.S. Drenichev, V.E. Oslovsky, S.N. Mikhailov. Cytokinin Nucleosides - Natural Compounds with a Unique Spectrum of Biological Activities. *Curr. Top. Med. Chem.* **2016**. Vol.16. P.2562-2576.
[3] E. De Clercq, G. Li. Approved antiviral drugs over the past 50 years. Clinical microbiology reviews. **2016**. Vol.29. P.695-747.
[4] E.V. Efimtseva, I.V. Kulikova, S.N. Mikhailov. Disaccharide nucleosides and their incorporation into oligonucleotides. *Current Organic Chemistry.* **2007**. Vol.11. P.337-354.
[5] S.N. Mikhailov, Yu.P. Lysov, G.I. Yakovlev. The use of functionally competent nucleoside and nucleotide analogues for the study of enzyme-substrate interactions. *Molecular Biology.* **1999**. Vol.33. P.393-407. (russian)
[6] H. Vorbrüggen, C. Ruh-Pohlenz. Handbook of nucleoside synthesis. *John Wiley & Sons.* **2001**. Vol.60.
[7] R.N. Goldberg, Y.B. Tewari, T.N. Bhat. Thermodynamics of Enzyme-Catalyzed Reactions -a Database for Quantitative Biochemistry. *Bioinformatics.* **2004**. Vol.20. P.2874-2877.

[8] I.A. Mikhailopulo, A.I. Miroshnikov. Biologically important nucleosides: modern trends in biotechnology and application. *Mendeleev Commun.* **2011**. Vol.21. P.57-68.
[9] J.W. Jones, R.K. Robins. Purine nucleosides. III. Methylation studies of certain naturally occurring purine nucleosides. *J. Am. Chem. Soc.* **1963**. Vol.85. P.193-201.
[10] M.S. Drenichev, C.S. Alexeev, N.N. Kurochkin, S.N. Mikhailov. Use of nucleoside phosphorylases for the preparation of 2′-deoxynucleosides. *Advanced Synthesis & Catalysis.* **2018**. Vol.360. P.305-312.
[11] W.J. Hennen, C.H. Wong. A new method for the enzymic synthesis of nucleosides using purine nucleoside phosphorylase. *J. Org. Chem.* **1989**. Vol.54. P.4692-4695.
[12] C.H. Wong, W.J. Hennen. Process for the enzymatic synthesis of nucleosides. US Patent 5075225, Dec. 24, **1991**.
[13] D. Ubiali, C. Morelli, M. Rabuffetti, G. Cattaneo, I. Serra, T. Bavaro, G. Speranza. Substrate Specificity of a Purine Nucleoside Phosphorylase from Aeromonas hydrophila. Toward 6-Substituted Purines and its Use as a Biocatalyst in the Synthesis of the Corresponding Ribonucleosides. *Curr. Org. Chem.* **2015**. Vol.19. P.2220-2225.
[14] E. Kulikowska, A. Bzowska, J. Wierzchowski, D. Shugar. Properties of two unusual, and fluorescent, substrates of purine-nucleoside phosphorylase: 7-methylguanosine and 7-methylinosine. *Biochimica et Biophysica Acta.* **1986**. Vol.874. P.355-363.