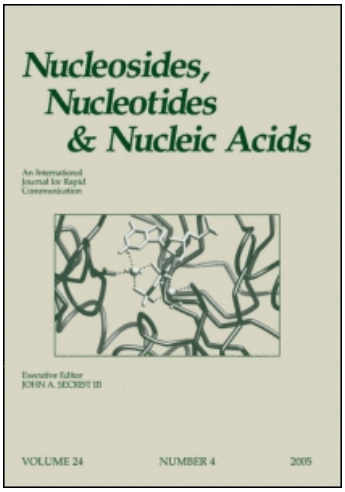

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Chemo-enzymatic Synthesis of 3-Deoxy-β-D-ribofuranosyl Purines and Study of Their Biological Properties

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ABSTRACT

9-(3-Deoxy-β-D-*erythro*-pentofuranosyl)-2,6-diaminopurine (**2**) was synthesized by an enzymatic transglycosylation of 2,6-diaminopurine using 3′-deoxycytidine (**1**) as a donor of the sugar moiety. Nucleoside **2** was transformed to 3′-deoxy guanosine (**3**), 9-(3-deoxy-β-D-*erythro*-pentofuranosyl)-2-amino-6-oxopurine (3′-deoxyisoguanosine; **4**), and 9-(3-deoxy-β-D-*erythro*-pentofuranosyl)-2-fluoroadenine (**5**). Compounds **2**–**5** were evaluated for their anti-HIV activity.

Key Words: Enzymatic transglycosylation; Purine nucleosides; Activity.

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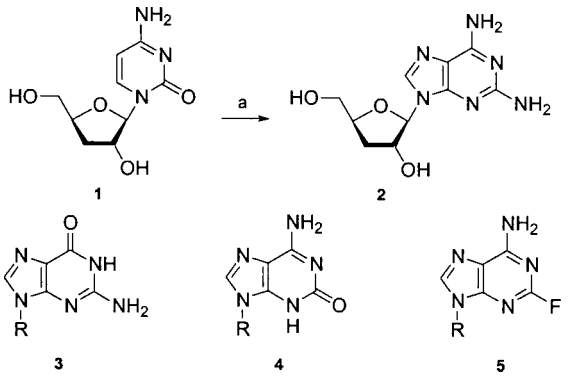

Scheme 1. Reagents and conditions: a) **1**/DAP (molar ratio = 1.5 : 1.0), the intact *E. coli* BMT- 4D/1A and BM-11 cells, K-phosphate buffer (60 mM; pH 7.0), 52°C, 26 h (**2**, 64%); b) **2** to **3**: ADase, r.t., 16 h (a + b, **3**, 68%; from **2**, **3** 85%); c) **2** to **4**: $NaNO_2$ (molar ratio = 1.0 : 4.5), AcOH, 50°C, 6 min, (71%); d) **2** to **5**: $HF/HBF_4/H_2O/THF$, $NaNO_2$, -10 / -12°C, 1 h (**5**, 43%; **4**, 7%).

9-(3-Deoxy-β-D-*erythro*-pentofuranosyl)-2,6-diaminopurine (**2**) was synthesized by the regio- and stereospecific enzymatic transglycosylation of 2,6-diaminopurine (DAP) using 3′-deoxycytidine (**1**)[1a,b] as a donor of the sugar moiety and the whole cells *E. coli* BM-11[2] and BMT-4D/1A[3] as biocatalysts. This transformation encompasses (*i*) deamination of **1** to 3′-deoxyuridine (3′dUrd) through the action of cytidine deaminase (CDase) of *E. coli* BM-11, (*ii*) phosphorolytic cleavage of 3′dUrd by uridine phosphorylase (UPase), thus giving rise to the formation of uracil and 3-deoxy-α-D-*erythro*-pentofuranose-1-*O*-phosphate, and (*iii*) coupling of the latter with DAP through the action of purine nucleoside phosphorylase (PNPase) of *E. coli* BMT-4D/1A. Deamination of **2** by adenosine deaminase (ADase) gave 3′-deoxyguanosine (**3**). Treatment of **2** with $NaNO_2$ afforded 3′-deoxyisoguanosine (**4**). Schiemann reaction of **2** ($HF/HBF_4 + NaNO_2$) gave **5** (Scheme 1). The compounds were evaluated for their inhibitory properties against HIV-1(III_B) and HIV-2(ROD) in CEM cell cultures. Whereas compound **5** was inactive at subtoxic concentrations [50% cytostatic concentration (CC_{50}) : 1.9 μg/ml], **2**–**4** were active against HIV-1 at a 50% effective concentration (EC_{50}) of 2.8, 4.8 and 12 μg/mL, respectively, and against HIV-2 at an EC_{50} of 10, 4 and 14 μg/mL, respectively. Their CC_{50} were 10, 5.8 and 30 μg/mL, respectively. Thus, the selectivity (ratio of CC_{50}/EC_{50}) of the compounds varied from only 1- to 3-fold, and therefore these compounds cannot be considered as specific anti-HIV agents.

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