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Chemical and Enzymatic Synthesis and Antiviral Properties of 2'-Deoxy-2'-fluoroguanosine

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CHEMICAL AND ENZYMATIC SYNTHESIS AND ANTIVIRAL PROPERTIES OF 2'-DEOXY-2'-FLUOROGUANOSINE

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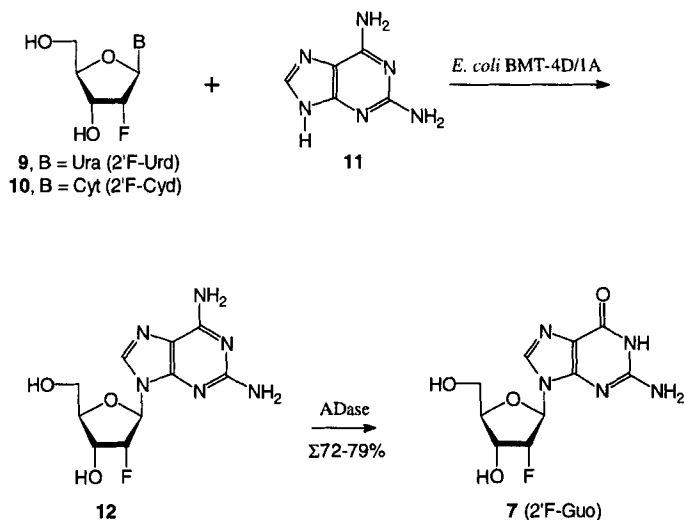
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ABSTRACT: Chemical and enzymatic methods were employed for the synthesis of the title compound, 2'-F-Guo **7**. High antiviral activity of 2'-F-Guo was established in chick embryo cells infected with influenza virus FPV/Rostock/34 (H7N1) and herpes simplex virus (HSV) type I (1C strain).

As a part of our continuing interest in fluorodeoxy nucleosides and nucleotides,¹ here we present the synthesis of 2'-F-Guo (*cf.*, *e.g.*^{2,3}) *via* chemical and enzymatic methods and data on its activity against influenza virus (*cf.*, *e.g.*^{2,4}) and HSV (type I) as well.

The condensation of 1-O-acetyl-2-deoxy-2-fluoro-3,5-di-O-benzoyl- β -D-ribofuranose (**1**)¹ with trimethylsilylated N²-palmitoylguanine (**2**) in the presence of TMS-TfI in anhydrous acetonitrile or 1,2-dichloroethane under reflux for 3–5 h afforded a mixture of the N⁷- β -D-glycoside **3** as principal product along with the formation of the N⁹- β - and - α -D-anomers **5** and **6**, respectively (**3/5/6** ratio *ca.* 5:2:1 according to the ¹H NMR data; 44–54%, combined). Deblocking of the above nucleosides gave the free N⁷- β -D-glycoside **4**, 2'-F-Guo **7** and its α -D-anomer **8**, respectively.

An enzymatic transglycosylation of 2,6-diaminopurine (**11**) using the glutaraldehyde-treated whole cells of *E. coli* BMT-4D/1A as a biocatalyst⁵ and 2'-deoxy-2'-fluoro-uridine (**9**) or -cytidine (**10**) as a donor of the glycosyl moiety followed by an enzymatic deamination of intermediate 2,6-diaminopurine glycoside **12** afforded the title compound 2'-F-Guo **7** in 72-79% combined yield.



Antiviral activity of 2'-F-Guo was tested in chick embryo cells infected with influenza virus FPV/Rostock/34 (H7N1) and herpes simplex virus (HSV) type I (1C strain). The 50% inhibitory concentration (IC₅₀) of 2'-F-Guo was found to be 0.42 µg/mL for FPV and 0.027 µg/mL for HSV. Rimantadine (xHCl), ribavirin (both against FPV) and acycloguanosine (HSV) were tested simultaneously for comparison and their IC₅₀ values were <0.1, 3.54 and 0.018 µg/mL, respectively.

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