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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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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-Tfl 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 -Dglycoside 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 μ g/mL for FPV and 0.027 μ g/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 μ g/mL, respectively.

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