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2'-Deoxy-2'-fluoropyrimidine Nucleosides with Antiviral Activity

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We have discovered that 2'-deoxy-2'-fluorocytidine has good activity against influenza *in vitro* (A and B strains). *In vivo*, it does not demonstrate an anti-influenza effect because it is rapidly metabolised to an inactive metabolite, 2'-deoxy-2'-fluorouridine. In the search for new, selective anti-influenza agents, we have prepared many derivatives of 2'-deoxy-2'-fluorocytidine and 2'-deoxy-2'-fluorouridine, modified in either the base or sugar moiety. This work has produced a number of selective, potent (IC_{50}, 2-5μM) anti-VZV agents. The synthesis and *in vitro* antiviral activity of these compounds will be reported.

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Novel 6-Alkoxypurine-2',3'-dideoxynucleosides as Inhibitors of the Human Immunodeficiency Virus. C. L. Burns, M. H. St. Clair, L. W. Frick, T. A. Spector, D. R. Averett, M. L. English, T. J. Holmes, T. A. Krenitsky, and G. W. Koszalka, Wellcome Research Laboratories, Research Triangle Park, NC 27709, U.S.A.

Seventeen 6-alkoxypurine-2',3'-dideoxynucleosides were enzymatically synthesized, and sixteen of these analogs had anti-HIV-1 activity in MT4 cells. The most active analog was 6-hexoxypurine-2',3'-dideoxynucleoside (**16**). It was as potent against HIV-1 as 2',3'-dideoxyinosine (ddI). Decreasing the length of the 6-alkoxy side chain to fewer than 6 carbons decreased the antiviral activity whereas increasing the chain length to 10 carbons resulted in cytotoxicity. The anti-HIV activities of **16** and ddI were not influenced when assayed in the presence of the adenosine deaminase (ADA) inhibitor *erythro*-9-(2-hydroxy-3-nonyl)adenine (EHNA). However, the addition of coformycin, an inhibitor of both ADA and adenylate deaminase, dramatically decreased the antiviral activity of **16** but not the antiviral activity of ddI. Neither EHNA nor coformycin was toxic to MT4 cells at the concentrations used in these studies. Compound **16** was administered to rats orally and intravenously at a dose of 10 mg/kg. Plasma samples obtained 40 minutes after the oral dose had at least 17 metabolites. **16** and ddI were both detected in the plasma; however, the plasma concentration of these nucleosides did not exceed 0.1 μM. After the IV dose, areas under the plasma concentration-time curves (AUC) for **16** and ddI were 68 and 38 μM·hr, respectively. The elimination of **16** followed biphasic kinetics with initial and terminal elimination rate half-lives of 7 and 40 minutes, respectively.