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N-3 DERIVATIVES OF AZIDO- OR FLUORO-DIDEOXYTHYMIDINE: SYNTHESIS AND BIOLOGICAL ACTIVIES.

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Of all the positions for modification in 2',3'-dideoxynucleosides the N-3 of the pyrimidine base has not been studied. We report the activity of several derivatives of AZT (1) and 3'-fluoro-dt (2) substituted at the N-3 position. These analogs were prepared either by reaction of the N-3 anion of (1) or (2) with an electrophile, or by reaction of 2,3'-anhydro-3'-deoxythymidine with the electrophile, followed by reaction of the resulting quaternary salt with azide ion. In vitro evaluation of the anti-HIV potential of these molecules identified the 3-NH_2 compound (RP-67042) to be the most potent, with an IC50 of 0.1μM compared to 0.01 for AZT and a selectivity index comparable to AZT. We observed less inhibitory effect for RP-67042 compared to AZT in both granulocytes-macrophages (CFU-GM) and erythrocytes (BFU-E) human bone marrow progenitors. The *in vivo* activity of this compound was also studied in mice infected with the friend complex virus. In this system, the 3-NH_2 derivatives reduced the spleenomegaly by 50% at 40 mg/Kg as compared to 4 mg/Kg for AZT. The plasma half-life of RP-67042 was found at 1.5 hours as compared to 40 minutes for AZT.

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Synthesis, anti-HIV activity and cytotoxicity of derivatives of 5-hydroxymethyl-deoxyuridine. Kumar, S.V.P., Stuart, A.L., Qualtiere, J., Tourigny, G., Qualtiere, L.F. and Gupta, V.S. Depts. Vet. Physiol. Sci., Chem. and Microbiol., Univ. of Saskatchewan, Saskatoon, Sk., Canada.

The naturally occurring nucleoside, 5-hydroxymethyldeoxyuridine (HMdUrd), inhibits HIV replication in cell culture and was effective in prolonging the survival of mice infected with FLV. In this presentation, we report the synthesis of some 3′-modified analogs of HMdUrd: 3′-azido, 3′-fluoro, 2′,3′-dideoxy, 2′,3′-dideoxydidehydro and 3′-*lyxo* derivatives. Thymidine-3′,5′-diacetate was brominated selectively at the 5-methyl position by a free radical process and hydrolysed in steps to HMdUrd.

Appropriate and selective 5- and 5′-protection followed by mesylation and cyclisation afforded the O^2,3′-anhydro intermediate. This was converted to 3′-azido, 3′-fluoro, 3′-*lyxo*, 2′,3′-dideoxy and 2′,3′-dideoxydidehydro analogs by different synthetic strategies. All the synthesised compounds were characterized and screened for anti-HIV activity using $CD4^+$ HeLa cells (plaque reduction assay) and cytotoxicity. Results of these studies will be presented.

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