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Synthesis and Anti-HSV-1 Activity of 5-Substituted 2'-Deoxyuridines

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A new series of 5-substituted 2'-deoxyuridine derivatives were synthesized. These compounds are substituted in the 5-position with an heteroaromatic substituent. They were synthesized starting from 5-iodo-2'-deoxyuridine making use of organo-tin chemistry. Yields were optimalized and a high-yield two-step synthesis method for the most active congeners was obtained. Several of these compounds [i.e. 5-(5-chlorothien-2-yl)-2'-deoxyuridine, 5-(5-bromothien-2-yl)-2'-deoxyuridine, 5-(thien-3-yl)-2'-deoxyuridine, 5-(5-chlorothien-2-yl)-2'-arauridine] showed high activity against HSV-1 and/or VZV. They were not inhibitory to other herpesviruses (HSV-2, TK$^-$ HSV-1, CMV), thus their antiviral activity spectrum appears similar to that of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU). 5-(5-Bromothienyl)-2'-deoxyuridine (BTDU) proved effective, when administered topically (as 0.2% eye drops) in an experimental HSV-1 keratitis model in rabbits.

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The Enzymatic Synthesis of Antiviral Nucleosides

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The enzyme-catalysed transfer of glycosyl residues from a donor nucleoside to an acceptor base is a convenient method for the synthesis of novel nucleosides. We have used a crude preparation of N-deoxyribosyltransferases from *Lactobacillus leichmannii* to catalyse the preparation of a number of antiviral nucleoside analogues. We find that addition of up to 10% (v/v) ethylene glycol or similar organic solvent to the transfer reaction has a highly beneficial effect on the transfer reaction. Side reactions such as hydrolysis or deamination of products and starting material are suppressed but glycosyl transfer is unaffected. Using these conditions, we have prepared, for example, 9-$\beta$-D-2',3'-dideoxyribofuranosyl 2-aminopurine in 60% yield in one step. The latter shows anti-HIV activity in JM cells. From variable temperature $^1$H NMR spectroscopy experiments (N. Hicks and D.W. Hutchinson, Carbohydrate Res., 1991, 216, 1) we deduce that for a nucleoside donor to be an effective glycosyl donor in reactions which are catalysed by N-deoxyribosyltransferases the sugar ring must be flexible. This allows it to achieve a planar conformation during the transfer reaction.