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3'-Heterocyclic Substituted 3'-Deoxythymidines: Synthesis and Anti-Retrovirus Activity

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In search for compounds that may be equally or more inhibitory than 3'-azido-3'-deoxythymidine (AZT) to the replication of human immunodeficiency virus (HIV), we synthesized a number of 3'-heterocyclic substituted 3'-deoxythymidines with the five-membered heterocyclic ring in the *erythro* conformation. By varying the position as well as the number of nitrogen atoms in the heterocyclic ring we obtained a variety of 3'-deoxythymidine analogues with different electronic properties. The goal was that one of these ring structures would mimic the azido group of AZT. Of all the compounds tested, only the 3'-(pyrrol-1-yl)-3'-deoxythymidine showed (marginal) inhibition of HIV-1 cytopathogenicity. To elucidate why these compounds are less active than AZT against HIV, we have studied their affinity for cellular kinases. Also, the interaction of the 5'-triphosphates of some of the newly synthesized compounds with HIV reverse transcriptase has been investigated. The synthesis and biochemical properties of these compounds will be presented.

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Synthesis and Anti-Retrovirus Properties of 5'-Isocyano- and 5'-Formamido Derivatives of AZT and the Corresponding Uridine Derivatives

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3'-Azido-3'-deoxythymidine and 3'-azido-2',3'-dideoxyuridine inhibit the replication of HIV. However, *in vivo*, AZT produces severe side effects. We and others have recently reported the synthesis of 3'-isocyano-3'-deoxythymidine and 3'-isocyano-2',3'-dideoxyuridine. As part of our program preparing new nucleoside analogues with more selective antiviral activity we synthesized 3'-azido-5'-formamido-3',5'-dideoxythymidine and 3'-azido-5'-isocyano-3',5'-dideoxythymidine and the corresponding uridine derivatives. After introduction of the azido function in the 5'-position we prepared the 2,3'-anhydronucleoside derivatives. Transformation of the azido group to the formamido group yielded the AZT derivative by a nucleophilic opening reaction with sodium azide. Dehydration using tosyl chloride and pyridine, afforded the 5'-isocyano derivative of AZT. Also, the corresponding uridine compounds were prepared using the same strategy. The anti-retrovirus properties of these new compounds will be reported.