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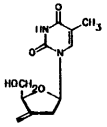
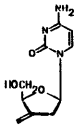
Synthesis of 2',3'-Dideoxy-3'-methylenepyrimidine Nucleosides as Potential Anti-AIDS Agents. M. Bobek and M. Sharma, Grace Cancer Drug Center, Roswell Park Memorial Institute, New York Department of Health, Buffalo, New York 14263, USA.





Among the various anti-HIV 2',3'-dideoxy nucleosides, 2',3'-dideoxy-2',3'-didehydrothymidine and its cytidine analog have been found both potent and selective agents. However, they are less stable than the corresponding 2',3'-saturated nucleosides due to spontaneous degradation. An analog of 2',3'-dideoxythymidine with an exocyclic methylene group at C-3' can be expected to be more stable, while retaining the conformational characteristics of 2',3'-dideoxy-2',3'-didehydrothymidine. The methylene analog was, therefore, prepared from 5'-triphenylmethylthymidine by oxidation with pyridinium dichromate followed by treatment with $Zn/CH_2Br_2/TiCl_4$ and aqueous acetic acid. 2',3'-Dideoxy-3'-methylene-uridine was prepared similarly, starting from 5'-trityl-2'-deoxyuridine. The corresponding cytidine derivatives were prepared by sequential treatment of the 5'-protected uridine analogs with trifluoromethanesulfonic anhydride, methanolic ammonia and deblocking.

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Anti-HIV drug activity in vitro: Impact of infection methodology and virus infectivity; O.Weislow, J.McMahon, J.Bader and M.Boyd Program Resources, Inc. and Developmental Therapeutics Program, DCT, NCI, Frederick Cancer Research Facility, Frederick Md. 21701 USA

The National Cancer Institute's in vitro anti-HIV drug screen depends on virus-induced cytolysis of T-lymphoblastoid, CEM-SS cells. Cytoprotection is estimated by metabolic reduction of the tetrazolium salt XTT to its soluble formazan by surviving cells. It was determined that antiviral activity was influenced by the quantity of virus input (MOI) and the status of virus replication at the time of drug addition. These factors were, in turn, influenced by infection methodology and the ratio of infectious to noninfectious material (infectivity ratio) in virus stocks. Use of virus stocks with low infectivity ratios, bulk infection of target cells or increasing MOI, temperature of infection or the interval between infection and drug exposure, decreased assay sensitivity, increasing effective drug concentrations (EC_{50}) required and reducing total antiviral protection. Employing virus stocks with high infectivity, infecting target cells directly in microculture wells, lowering MOI, reducing the temperature of infection and the interval between infection and drug exposure, decreased EC_{50} and improved overall antiviral protection. These data suggest that conclusions pertaining to in vitro drug-induced anti-viral protection or drug resistance (e.g. as with AZT) should take into account factors which impact both the rate and status of virus replication. Supported by contract #N01C074102 from the National Cancer Institute.