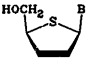
16

Synthesis and Anti-HIV Activity of 2',3'-Dideoxy-4'-thionucleosides. J. A. Secrist III, R. M. Riggs, K. N. Tiwari, W. M. Shannon, J. B. Kahlon, and J. A. Montgomery, Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, AL 35255-5305, USA.

Over the last few years many sugar-modified nucleosides have been prepared as potential anti-HIV agents. Because of the increased enzymatic stability imparted to the glycosidic linkage by the substitution of a sulfur for O-4' in certain ribofuranosyl nucleosides, we decided to prepare a series of 2',3'-dideoxynucleosides with this substitution. The lengthy routes necessary to get to either ribofuranosyl or 2-deoxyribofuranosyl carbohydrate precursors of the nucleosides caused us to look for a more direct route. The details of our chiral syntheses of a series of nucleosides containing the common bases, beginning with L-glutamic acid, will be presented. Initial anti-HIV data, showing some activity, will also be presented.



B = A, C, G, T, etc.

17

TIBO Derivatives Represent a New Lead of Potent and Selective HIV-1 Inhibitors that Interact with a Reverse Transcriptase-Associated Process

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Several tetrahydro-imidazo[4,5,1-jk][1,4]-benzodiazepin-2(1H)-thione (i.e. TIBO derivatives) have proved to be potent and selective inhibitors of HIV-1 replication in vitro. The 50% inhibitory concentration (IC_{50}) of these compounds for HIV-1 replication in MT-4 cells is 2 to 30 nM, while drug toxicity is observed only at 10,000- to 100,000-fold higher concentrations. Similar results were obtained in a variety of other cells including non-HTLV-I infected T-cells, peripheral blood lymphocytes and macrophages. Whereas at least 4 different HIV-1 strains proved sensitive to the TIBO compounds, no activity was observed with HIV-2, SIV and several other retroviruses. Since only one of the isomers of TIBO showed anti-HIV-1 activity, the interaction with the antiviral target(s) appears to be stereospecific. The compounds did not inhibit virion binding to the cells. Nor did they exert an inhibitory effect on chronically infected T-cell lines. Both virion-derived and recombinant reverse transcriptase (RT) proved sensitive toward TIBO compounds. No inhibition was observed with other human and murine reverse transcriptases. Investigation of the mode of RT inhibition suggested that TIBO compounds interact with a RT-associated process that is different from that of the known broad-spectrum RT inhibitors such as suramin, phosphonoformate and the 2',3'-dideoxynucleoside 5'-triphosphates.