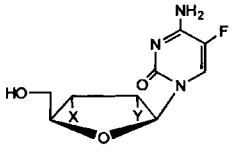
Oral Session I: Retrovirus Infections I

1

L-Enantiomers of 2'- and 3'-Azido-2',3'-Dideoxy-5-Fluorocytidine : Stereospecific Synthesis and Antiviral Activity. G. Gosselin,[1,2] J.-F. Griffon,[2] L. Hollecker,[2] J.-L. Imbach,[1,2] M. Bryant,[3] R.F. Schinazi,[4] and J.-P. Sommadossi[5]. [1]Laboratoire Coopératif Novirio-CNRS-Université Montpellier II ; [2]UMR 5625 CNRS-Université Montpellier II, France ; [3]Novirio Pharmaceuticals, [4]Emory University and VA Med Center, Decatur, USA, and [5]University of Alabama at Birmingham, USA.

Recently, nucleoside analogues with the unnatural β-L-configuration have emerged as a new class of sugar-modified derivatives with potential antiviral activity (Wang, P. ; Hong, J.H. ; Cooperwood, J.S. ; Chu, C.K. *Antiviral Res.* **1998**, 40, 19-44). For example, β-L-2',3'-dideoxy-5-fluorocytidine (L-5-FddC) exhibits activity against HIV and HBV, and β-L(-)-2',3'-dideoxy-3'-thiacytidine (3TC) has been approved as an anti-HIV and anti-HBV drug.

As a part of our current research program on L-sugar modified nucleoside analogs, we have discovered a stereospecific synthesis of 2'-azido- and 3'-azido-β-L-2',3'-dideoxy-5-fluorocytidine (2'-N_3-L-5-FddC and 3'-N_3-L-5-FddC, respectively), two hitherto unknown compounds.



L-5-FddC (X = Y = H)
2'-N_3-L-5-FddC (X = H, Y = N_3)
3'-N_3-L-5-FddC (X = N_3, Y = H)

The synthetic route and results of the antiviral evaluation of 2'-N_3-L-5-FddC and 3'-N_3-L-5-FddC will be presented.

2

Establishment of a CCR5-Expressing T-lymphoblastoid Cell Line Highly Susceptible to R5 HIV-1.

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The β-chemokine receptor CCR5 is considered to be an attractive target for inhibition of CCR5-using (R5 or macrophage-tropic) HIV-1. However, R5 HIV-1 cannot replicate in $CD4^+$ T-cell or monocyte lines due to the lack of CCR5 expression on their surface, which apparently hampers discovery and development of effective CCR5 antagonists against HIV-1 replication. In this study, we have established the CCR5-expressing T-cell line MOLT-4/CCR5 highly permissive to the replication of R5 HIV-1. The cells express a considerable amount of CCR5 on their surface. When the cells were infected with the R5 HIV-1 strains Ba-L and JR-FL, the virus-induced cytopathic effect (syncytium formation) was observed, and the cells produced large amounts of HIV-1 p24 antigen in the culture supernatants. The analyses of progeny viruses for their coreceptor use and gp120 V3 nucleotide sequence revealed that they were R5 HIV-1. The parental cell line MOLT-4 was much less susceptible to Ba-L and totally insusceptible to JR-FL. Furthermore, neither MOLT-4 nor MOLT-4/CCR5 cells could support the replication of a R5 clinical isolate. When TAK-779, a novel small-molecule non-peptide CCR5 antagonist, was examined for its inhibitory effect on R5 HIV-1 replication in MOLT-4/CCR5 cells, the compound displayed potent antiviral activity, as previously demonstrated in peripheral blood mononuclear cells. These results indicate that the established cell line will be an extremely useful tool for experiments with R5 HIV-1.