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Synthesis and Biological Evaluation of an Acyclic Thiosangivamycin. T.E. Renau, M.R. Nassiri, L.A. Coleman, S.R. Turk, D.E. Lopatin, E.E. Swayze, L.B. Townsend, and J. C. Drach. Department of Biologic and Materials Sciences, School of Dentistry and Department of Medicinal Chemistry, College of Pharmacy, University of Michigan, Ann Arbor, Michigan, 48109-1078, USA.

We have previously shown that a number of acyclic pyrrolopyrimidines are potent inhibitors of human cytomegalovirus (HCMV) replication both *in vitro* and *in vivo*. We now report the synthesis, antiviral activity, immunomodulating effects, and cytotoxicity of an active thioamide analog in this series: 4-amino-7-[(2-hydroxyethoxy)methyl]pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (compound UMJD 229). The compound was prepared from the known 5-cyano-6-bromo analog *via* catalytic hydrogenation to remove bromine followed by treatment with methanolic sodium hydrosulfide. In plaque reduction assays with HCMV, compound 229 gave a 50% inhibitory concentration (IC_{50}) of 9 μM compared to 8 μM for ganciclovir. No cytotoxicity was evident by visual examination of uninfected cells in virus-infected cultures treated with up to 100 μM of either compound. In yield reduction assays, ganciclovir was more potent, IC_{90}=2 μM vs. 40 μM, respectively. In contrast, compound 229 was inactive against HSV-1. In cytotoxicity tests, concentrations between 10 and 32 μM did not affect the growth of KB cells for incubation periods up to 72 hours. At 100 μM, a prolongation in population doubling time was noted from 19.3 hours (untreated) to 28.1 hours. This inhibition, however, was reversible upon removal of the compound indicating the inhibition was cytostatic. Flow cytometric studies measuring DNA content of uninfected cells showed no significant perturbations in the KB cell cycle up to a concentration of 32 μM. Similar concentrations were required to inhibit DNA synthesis in mitogen-stimulated lymphocytes. In contrast, significantly lower concentrations (0.1 to 1.0 μM) enhanced NK cell activity of peripheral blood mononuclear cells whereas ganciclovir did not affect this activity up to 10 μM. We conclude that acyclic pyrrolopyrimidines may have potential usefulness as antiviral or immunomodulating agents. This study was supported by NIH contracts N01-AI42554 and AI72641 and grant U01-AI25739.

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Activity of Tricyclic Nucleoside and Tricyclic Nucleoside 5' Phosphate (Triciribine) Against HIV and Other Retroviruses L. Kucera, N. Iyer, and S. Puckett; Bowman Gray Scool of Medicine of Wake Forest University, Winston-Salem, N.C., R.W. Buckheit, M. Hollingshead, L. Westbrook, B. Toyer, E.L. White, J. Germany, and W. Shannon; Southern Research Institute, Birmingham, AL, R.C.-S. Chen, J.C. Drach, and L.B. Townsend; University of Michigan, Ann Arbor, MI.

Tricylic nucleoside (TCN) and tricyclic nucleoside 5' monophosphate (TCN-P) are adenosine analogs with demonstrated anti-tumor activity in animals. They are presently in an anti-cancer Phase II clinical trial. We have investigated the activity of these compounds as anti-retroviral and anti- HIV agents *in vitro* and *in vivo*. Both TCN and TCN-P inhibited HIV-1 induced RT, p24 core antigen, and infectious virus production in a dose dependent manner using acutely infected H9 and chronically infected H9-IIIB and U1 cells. In a microtiter XTT assay. TCN exhibits an IC_{50} of 0.05ug/ml against $HIV\text{-}1_{RF}$, $HIV\text{-}1_{IIIB}$, and $HIV\text{-}1_{MN}$ while TCN-P has an IC_{50} of 0.01ug/ml against these isolates. These compounds also are active against a panel of HIV-1 and HIV-2 isolates measured by XTT assay. Activity was also demonstrated in fresh human peripheral blood lymphocytes and macrophages infected with clinical isolates of HIV-1. TCN and TCN-P inhibited HIV in chronically infected cells (U1 and CEM) as measured by a reduction in the number of syncytia formed in microtiter assays. HIV resistant to AZT inhibition did not show cross resistance to TCN or TCN-P. *In vitro* activity was similarly detected against Rauscher MuLV in an UV-XC plaque reduction assay with an observed IC_{50} of 0.12uM for TCN and 0.074 uM for TCN-P. RT inhibition assays utilizing TCN, TCN-monophosphate, and TCN-triphosphate have demonstrated that the compounds do not act via inhibition of this enzyme. We will report the results of our *in vitro* and *in vivo* assays, including combination therapy of TCN and TCNP with AZT, as well as the results of experiments examining the mechanism of action of these antivi ral compounds. Supported by 1 UO1 AI25739 from NIAID.