Poster Session III: Herpesvirus, Poxvirus Infections

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The Dendrimer BRI2999 inhibits the early stages of herpes simplex viruses replication. Y. Gong, C. Luscombe, D. Leung, P. Crosson, G. Holan, and S. L. Sacks, Viridae Clinical Sciences, Inc. and Starpharma Limited, Vancouver, BC, Canada.

Genital herpes simplex virus (HSV) is an important human sexually transmitted pathogen associated with significant morbidity and enhanced risk for transmission of HIV. Vaginal microbicides may represent one future method for prevention of STI's such as herpes. Dendrimers are a novel class of macromolecules with highly-branched, tree-like single molecular polymeric structures and the potential for broad-spectrum antimicrobial activity with minimal toxicity. Dozens of compounds with broad antiviral and antitumor activities have been synthesized and tested successfully against HIV, HSV, HBV and other viruses with good efficacy and minimal toxicity. BRI2999 has been successfully employed in mice as a preventive agent for intravaginal HSV infection. To investigate the antiviral mechanism of BRI2999 we modified plaque reduction assays as follows: (1) incubation of HSV-infected Vero cells; (2) pre-mixing of HSV, alone, with various doses; (3) pre-treatment of Vero cells with various doses; (4) binding of virus to the cells at 4°C, with uptake at 37°C, followed by stripping of uninternalized virus at low pH. Results indicate that BRI2999 inhibition is highly effective during early stages of replication, possibly at the virus adsorption or fusion stage. Addition of BRI2999 after this point in the life cycle fails to inhibit HSV replication in this assay. Inhibition of the viral life cycle in its early stages may explain the observed efficacy of this compound in animal models in preventing transmission of HSV. Further development of BRI2999 for use as a vaginal microbicide is indicated.

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A Thio Derivative of 5'-noraristeromycin: Enantiomeric Synthesis and Biological Properties

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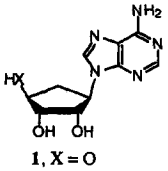

1, X = O
2, X = NH
3, X = S

5'-Noraristeromycin (**1**) and its enantiomer have been found to possess a wide range of biological properties, particularly antiviral activity against human cytomegalovirus, hepatitis B virus, measles, influenza B, vaccinia, vesicular stomatitis, reo Type 1, Junin, and Tacaribe. These properties have been attributed to the inhibition of *S*-adenosylhomocysteine hydrolase and, in turn, the inhibition of various macromolecular transmethylations. In the search for analogs of **1** that could act in a similar fashion, the nitrogen isostere (**2**) was also found to exhibit antiviral activity. Our attention now turned to the synthesis of 5'-deoxy-5'-mercapto-5'-noraristeromycin (**3**). The syntheses and biological activities of both enantiomers will be presented. This research was supported by funds from the Department of Health and Human Services U19-AI31718 and this is greatly appreciated.