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Selective Inhibition of Alpha-, Arena-, Bunya-, and Flaviviruses by 3'-Fluoro-3'-Deoxyadenosine. D. F. Smee, J. L. B. Morris, D. L. Barnard, and [1]A. Van Aerschot. Antiviral Program, Department of Animal, Dairy, and Veterinary Sciences, Utah State University, Logan, Utah, U.S.A. 84322-5600 and [1]Rega Institute, Catholic University of Leuven, Leuven, B-3000, Belgium.

3'-Fluoro-3'-deoxyadenosine (3'-FdAdo) was recently reported to inhibit several DNA and RNA viruses in cell culture, and to prevent lesion formation in mice infected with vaccinia virus. We evaluated 3'-FdAdo for antiviral activity in Vero cells against several RNA viruses, including Semliki Forest (SFV) and Venezuelan equine encephalitis (VEE) alphaviruses, lymphocytic choriomeningitis (LCMV) arenavirus, San Angelo (SAV) bunyavirus, and banzi (BV) flavivirus. Average plaque reduction 50% inhibitory concentrations of 3'-FdAdo (in μM) were 10.3 (SFV), 5.3 (VEE), 7.7 (LCMV), 1.6 (SAV), and 4.0 (BV). VEE virus yield was reduced in a dose-dependent manner by inhibitor treatment, with a 1,000-fold virus titer reduction achieved by 8 and 16 μM 3'-FdAdo for multiplicities of infection of 10^{-4} and 10^{-2}, respectively. 3'-FdAdo inhibited the proliferation of actively grown Vero cells by 50% at 35.8 μM, indicating selective inhibition of virus replication. The compound inhibited the incorporation of radioactive uridine and thymidine into acid-precipitable material (RNA and DNA, respectively) of uninfected cells by 50% at 8-16 μM. ^{3}H-leucine incorporation was not significantly inhibited by 64 μM. Up to 128 μM 3'-FdAdo failed to inhibit the uptake of 0.1 μM ^{3}H-adenosine and ^{3}H-deoxyadenosine into the acid-soluble (unincorporated) fractions of cells in 1 hour, indicating that 3'-FdAdo uses an alternative pathway other than nucleoside transport for cell entry. Because of the lack of effective antiviral agents to treat humans infected with the above families of viruses, 3'-FdAdo warrants further evaluation in animal infection models and in mode of action studies.

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Evaluation of Structure-Activity Relation Between (E)-5-(2-Bromovinyl)-and 5-Vinyl-1-B-D-Arabinofuranosyluracil (BV-araU, V-araU) in inhibition of Epstein-Barr Virus Replication. J.C. Lin, J. Reefschlager and G. Herrmann. Centers for Disease Control, Atlanta, Georgia, U.S.A., Pharma Research Center, Bayer AG, Wuppertal, F.R.G., Central Institute of Molecular Biology, Academy of Sciences Berlin-Buch, F.R.G.

The structure-activity between (E)-5-(2-bromovinyl)-and 5-vinyl-1-B-D-arabinofuranosyluracil(BV-araU and V-araU) in inhibition of Epstein-Barr virus(EBV) was evaluated. Both V-araU and BV-araU effectively inhibited EBV replication in virus producer P3HR-1(LS) cells, as determined by DNA-DNA hybridization. The 50% effective doses(ED_{50}) for viral DNA replication were 0.005 and 0.3 uM for V-araU and BV-araU, respectively. The relative efficacy on the basis of the in vitro therapeutic index was V-araU(4,000) > BV-araU(1,300). Synthesis of EBV-induced polypeptides with molecular weights of 145, 140, 130, and 110 kd were significantly inhibited by both drugs; synthesis of 85, 55, and 32 kd proteins were reduced approximately 50% by V-araU alone. Kinetic analysis of inhibition and reversibility of EBV DNA replication after removal of the drugs indicated that BV-araU has a more prolonged inhibitory effect than V-araU. These results indicate that the substitution of H with Br atom in 5-vinyl group results in marked reduction in anti-EBV activity while prolonged the drug effect and diminishing cytotoxicity.