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Antiviral (RNA) Evaluation and Synthesis of a Series of Amaryllidaceae Alkaloids and Related Substances; B. Gabrielsen, (USAMRIID), G.R. Pettit, S.B. Singh (Cancer Research Institute, Arizona State University, Tempe, AZ 85287), T.P. Monath, J.W. Huggins, M.J. Phelan, D. Kefauver (U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD 21701), E.M. Schubert (Pharm-Eco Laboratories, Simi Valley, CA 93065), J.H. Huffman, R.W. Sidwell (Dept. of Animal, Dairy and Veterinary Sciences, Utah State University, Logan, Utah 84322), and W.M. Shannon, J.J. Kirsi (Southern Research Institute, Birmingham, AL, 35255).

The following phenanthridone alkaloids were evaluated in vitro against the RNA-containing flaviviruses (Japanese encephalitis, yellow fever and dengue fever viruses), bunyaviruses (Punta Toro, sandfly fever and Rift Valley fever viruses), and alphavirus (Venezuelan equine encephalitis virus): narciclasine and 7-deoxynarciclasine (lycoricidine); the cis- and trans-dihydro analogues of narciclasine and lycoricidine; isonarciclasine, pancratistatin and their 7-deoxy analogues; and the related Amaryllidaceae alkaloids, lycorine and pseudolycorine. All of the above exhibited in vitro activity against the six flaviviruses and bunyaviruses while no activity was observed against the alphavirus. Additional structural analogues showed no antiviral activity.

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Selective Antiviral Agents for the Treatment of Arenavirus Infections

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Of the arenaviridae, four members are known to be pathogenic for humans: Lassa fever virus, lymphocytic choriomeningitis virus, Bolivian hemorrhagic fever (Machupo) virus and Argentinian hemorrhagic fever (Junin) virus. We have now investigated various antiviral compounds for their inhibitory effects on the replication of Junin virus (JV) and Tacaribe virus (TACV) in Vero cells. S-Adenosylhomocysteine (AdoHcy) hydrolase appears to be an adequate target enzyme for anti-arenavirus agents, since AdoHcy hydrolase inhibitors such as the acyclic and carbocyclic adenosine analogues [i.e. carbocyclic 3-deazaadenosine (C-c^{3}Ado), neplanocin A, 3-deazaneplanocin A, and the 2',3'-dihydroxycyclopentenyl derivatives of adenine and 3-deazaadenine] were found to inhibit the replication of JV and TACV within the concentration range of 1-10 μg/ml, while not being toxic to the host cells at a concentration of 100-400 μg/ml. Also, carbodine, cyclopentenyl cytosine, pyrazofurin and ribavirin inhibited viral CPE at a concentration that was more than 200-fold lower than the minimum cytotoxic concentration. The sulfated polysaccharides dextran sulfate, λ-carrageenan, fucoidan, heparin and pentosan polysulfate were active at concentrations of 0.2-2.8 μg/ml, and not cytotoxic up to a concentration of 400 μg/ml. That the antiviral effects of C-c^{3}Ado, carbodine, dextran sulfate and ribavirin truly reflect inhibition of virus multiplication was ascertained by virus yield reduction experiments. At concentrations of 10 and 100 μg/ml, these compounds significantly reduced both JV and TACV yield at 72 h post infection. It would now seem imperative to determine the efficacy of these compounds in experimental arenavirus infections *in vivo*, so as to obtain further evidence of their potential as candidate drugs for the treatment of arenavirus infections in humans.