I-14

Anti-RNA-Viral Activities of Phenanthridones Related to Narciclasine (I, R=H, R'=OH).
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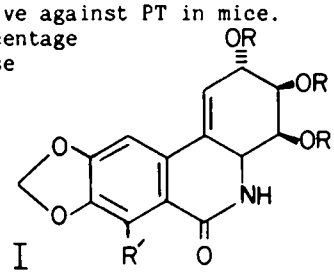
Viruses from the Bunyavirus family are important causes of human morbidity and mortality for which few current antiviral therapies exist. Phenanthridone alkaloid analogs related to I have been isolated or synthesized and tested against two Bunyaviruses, Punta Toro (PT) and Rift Valley fever (RVF). Therapeutic indices ranged from 4.0-7.6 against RVF in a plaque-reduction assay in Vero cells. 7-Deoxynarciclasine triacetate (I, R=$COCH_3$, R'=H), given b.i.d. for 5 days, was active against PT in mice. Treatment with 250 mg/Kg/day resulted in an increase in the percentage of survivors from 55-80% and a statistically significant increase in the mean survival time from 5.5 to 7.5 days ($P<0.01$). No in vivo toxicity was seen at 500 mg/Kg/day.



I

I-15

Effects and Mode of Action of Ribavirin Analog N3844 Against Semliki Forest Virus.
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An analog of ribavirin, designated N3844, was evalauated against classes of viruses of military importance. It was found to be inhibitory to Semliki Forest virus in Vero cells at $\geq$10 µM. This activity was unique since ribavirin itself showed no effect in this system at 1 mM. Further evaluation to define its mode of action and in vivo potential was undertaken. The nucleoside inhibited thymidine and amino acid incorporation into macromolecules of uninfected cells, but uridine incorporation was not affected. In infected cells treated with actinomycin D to suppress cellular RNA synthesis, N3844 decreased amino acid and uridine incorporation, indicating that viral RNA and protein syntheses were inhibited. SDS-PAGE of infected cell extracts showed that viral polypeptides were markedly inhibited whereas cell peptides were much less so. Viral RNA polymerase activity partially purified from cells was diminished in N3844-treated cells. Results of in vitro protein translation assays indicated N3844 to inhibit aminoacyl-tRNA synthetase reactions. Thus, the inhibition of Semliki Forest virus by N3844 was found to be due to an inhibition of virus RNA translation, which led to the decrease of the virus-specified RNA polymerase and other necessary proteins inside the infected cells. In animal studies, most mice treated with N3844 at 40 and 20 mg/kg/day for a week survived the infection, although some weight loss was associated with the treatment.