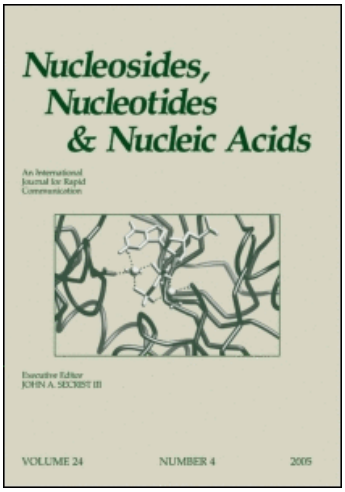


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# IN VITRO AND IN VIVO *PHLEBOVIRUS* INHIBITION BY NUCLEOSIDES RELATED TO RIBAVIRIN

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**Abstract**: Eleven compounds were compared to ribavirin for their in vitro and in vivo inhibition of Punta Toro virus (PTV), a *phlebovirus* in the Bunyaviridae virus family.

**Introduction**: These studies were done in an attempt to find compounds which might be used to overcome diseases due to *phlebovirus* infections of humans and animals.

**Materials and Methods**: Virus: The Adames strain of Punta Toro virus was prepared in cell culture for all experiments.

Cells: Continuous passaged Rhesus monkey kidney cells (LLC-$MK_2$ Derivative) were grown in Minimum Essential Medium (MEM) with fetal bovine serum (FBS) and $NaHCO_3$, without antibiotics. These cells were used to prepare virus pools and in all virus titrations. Gentamicin (50 µg/ml) was included in medium in which virus was prepared or titered.

Mice: C57BL/6 mice, 3-4 weeks old, were used for in vivo antiviral evaluations. They were infected by subcutaneous (s.c.) injection of the PTV preparations.

Compounds: The compounds used in these experiments were provided by the U.S. Army Medical Research Institute for Infectious Diseases.

Antiviral evaluations: In vitro experiments were evaluated by use of inhibition of viral cytopathogenic effect in 96-well microplates as previously described[1]. The 50% effective dose (ED50) was determined for each compound. The 50% cytotoxic dose (CD50) was also determined by microscopic examination of concomitantly run toxicity controls for cell anomalies. The therapeutic index (TI) of each compound was calculated

TABLE 1. COMPARATIVE IN VITRO AND IN VIVO ANTIVIRAL ACTIVITY OF 12 COMPOUNDS VS PUNTA TORO VIRUS

| Compound | Number | VR[a] | *In vitro* TI[b] | *In vivo* TI[c] |
|---|---|---|---|---|
| thioformycin B | 1 | 1.5 | 175 | 8 |
| ribavirin | 2 | 1.2 | 90 | 14 |
| 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamidine hydrochloride | 3 | 1.1 | 120 | 32 |
| selenazofurin | 4 | 1.0 | 16 | 8 |
| formycin A | 5 | 0.8 | 8 | 0 |
| tiazofurin | 6 | 0.8 | 2 | 8 |
| ribavirin 2',3',5'-triacetate | 7 | 0.4 | 4 | 32 |
| tiazofurin 2',3',5'-triacetate | 8 | 0.4 | 0.8 | ≥3 |
| 3-deazaguanine | 9 | 0.3 | 5 | 8 |
| formycin B | 10 | 0.3 | 3 | 8 |
| 9-(β-D-ribofuranosyl)purine-6-thiocarboxamide | 11 | 0.2 | 3 | 8 |
| 3-bromo-4-chloropyrazolo-[3,4-d]-pyrimidine | 12 | 0.05 | <1 | 2 |

[a]Virus Rating.

[b]Maximum TI obtained (TI = CD50 + ED50) (μg/ml).

[c]Maximum TI obtained (TI = Maximum Tolerated Dose + Minimum Statistically Effective Dose) (mg/kg/day).



as a measure of antiviral activity (TI = CD50 + ED50). The virus rating (VR) of each compound was also determined[1].

In vivo experiments were evaluated by use of several parameters, but only one (the statistically significant number of survivors 21-days post-virus injection) was utilized in calculations of the TIs shown.

**Results and Discussion**: The results, sorted by VR, are shown in Table 1. The compounds most active in vivo (2, 3, 6 and 7) were also among the most active compounds seen in vitro with the exception of 7, which had very low in vitro activity. Compound 1 had very low in vivo activity, even though it had the highest in vitro activity. Compounds 2, 3, 6 and 7 were all effective in vivo when given as a single inoculation as late as 48 hr after virus infection.

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