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Antiviral Activity of Triciribine and Triciribine Monophosphate Against Human Herpesvirus type 6. D. E. Ickes, C. Shipman, Jr., and J. C. Drach. University of Michigan, Ann Arbor, Michigan 48109, USA.

Triciribine (TCN) and its 5'-monophosphate (TCN-P) are novel nucleosides which we have recently shown to be potent and selective inhibitors of HIV-1 and HIV-2 (Kucera *et al.*, 1993, *AIDS Res. Human Retroviruses* **9**:307-314). We used a new ELISA to quantitate the antiviral activity of these compounds against the GS strain of human herpesvirus type 6 (HHV-6). Virus-infected HSB_2 cells were cocultured with uninfected cells for six days in the presence of various concentrations of TCN or TCNP. Aliquots of these samples were solubilized in Triton X-100, and crosslinked to an amine plate with bis(sulfosuccinimidyl) suberate. Primary murine monoclonal antibody to HHV-6 gp116 was added after the plate was washed and blocked. Following additional washing and blocking, horse radish peroxidase-conjugated rabbit anti-mouse antibody was added and the plate developed with TMB. The plate was read at 450/470 nm, and dose response curves were plotted to determine 50% inhibitory concentrations (IC_{50}) for each drug. TCN and TCNP were both potent inhibitors of HHV-6 with IC_{50} values of 8.3 μM and 1.2 μM, respectively. These values were well below the observed cytotoxicity of each of these compounds, as determined by inhibition of cell growth and incorporation of radiolabeled precursors in uninfected HSB_2 cells. Taken together, these data suggest that TCN and TCNP are potent and selective inhibitors of HHV-6 and may be especially useful in the treatment of AIDS patients. This study was supported by grants UO1-AI25739 and RO1-AI33332, and contract NO1-AI172641 from the National Institutes of Health.

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***In vitro* and *in vivo* Metabolism of HOE 961.**

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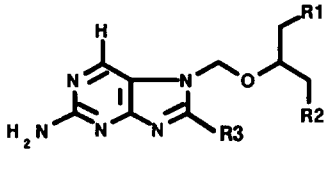
The metabolism of **HOE 961** (compound **I**), a prodrug ester of the active compound **II**, has been investigated. *In vitro*, by means of the S9 liver fractions of man, monkey, rat, dog, and rabbit, the prodrug **HOE 961** was almost completely degraded after 3 h incubation time. **HOE 961** was converted to **II** in large amounts passing the monoester intermediate **III**. Rabbit, monkey and rat formed a metabolite **IV** also in great portions. Compound **IV** could not be detected in dog liver fractions and was only formed in smaller quantities in human liver fractions. *In vivo* studies in rat, dog, monkey, and rabbit confirmed the results already obtained by the *in vitro* investigations. No or only smaller amounts of unchanged **HOE 961** were found in the urines of the respective animals. All species investigated showed large portions of the active compound **II** in plasma and/or urines. Metabolite **IV** was not found in dogs, but in all other species investigated. Compound **III**, the monoester derivative of compound **II**, was detected in minor quantities only (urines).



I: R1 = R2 = $OC(O)CH_3$, R3 = H (**HOE 961**)

II: R1 = R2 = OH, R3 = H

III: R1 = OC(O)CH3, R2 = OH, R3 = H

IV: R1 = R2 = R3 = OH