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Maturation of concatameric viral DNA in HCMV-infected cells is prevented by the benzimidazole riboside, 2- bromo- 5,6- dichloro- 1- β- D- ribofuranosyl benzimidazole (BDCRB).

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BDCRB and TCRB are respectively the 2- bromo and 2- chloro analogues of DRB, a molecule known to have marked activity against some viruses (influenza A and B, SV40, adeno 2 and 4) and to inhibit transcription (Segal and Tamm, *Antibiotics Chemother.* 27:93, 1980). BDCRB and TCRB have respective IC50's of 0.4-0.8 μM and 2-5 μM against HCMV. To characterize HCMV-specific transcription effects, RNA isolated from infected cells in the presence and absence of BDCRB was quantitated with probes for specific regions of the HCMV genome. Levels of immediate early mRNA and of mRNA encoding the structural proteins p154 (major capsid protein), p71 (upper matrix protein), and p67 (tegument protein) were unaffected by BDCRB. Drach *et al* previously showed that the level of HCMV DNA was not diminished by the presence of TCRB at 100 μM (March 1992 International Conference on Antiviral Research). Pulsed field gel electrophoresis was used in studies described here to examine the condition of intracellular HCMV DNA. The HCMV precursor DNA was at least 5 Mb in length. Normal maturation of this high molecular weight viral DNA to unit genomic length was prevented by BDCRB. Three independently selected BDCRB resistant HCMV mutants were generated by serial passage in increasing drug concentrations. One of these mutant virus had an IC50 of 20 μM for BDCRB and was cross resistant to TCRB. Concatameric DNA from BDCRB-resistant virus was processed in the presence of BDCRB. The mutant virus DNA is being mapped to identify the gene responsible for BDCRB resistance.

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Antiherpetic Activity, Cytotoxicity and Metabolism of Non-Nucleoside Analogs Related to Toyocamycin, Sangivamycin and Thiosangivamycin.

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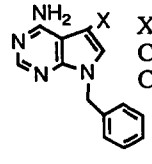

X= CN, **1**
$CONH_2$, **2**
$CSNH_2$, **3**

We have recently described the synthesis and antiviral activity of a number of 7-alkyl 4-aminopyrrolo[2,3-*d*]pyrimidine derivatives related to toyocamycin, sangivamycin and thiosangivamycin. We now have expanded our studies and report herein the antiviral activity, cytotoxicity and metabolism of a class of related compounds. Compounds **1-3** were synthesized in four or five steps from the known 5-amino-2-bromo-3,4-dicyanopyrrole. In HCMV plaque and HSV-1 ELISA assays, **1** and **2** were inactive. In contrast, **3** had an IC_{50} of 0.40 μM vs. HCMV and 1.1 μM against HSV-1. In cytotoxicity studies, **1** did not affect the growth of KB cells up to 100 μM, whereas **2** had an IC_{50} of 84 μM. Compound **3** was slightly more toxic (IC_{50}= 32 μM) and was similarly toxic in L1210 cells (IC_{50}= 70 μM). In uninfected KB and L1210 cells, the initial inhibition (24-48 h) of cell growth by **3** was more pronounced than at later times (48-96 h). This suggested that **3** was being converted *in vitro* to a less toxic metabolite. HPLC analysis demonstrated that under normal incubation conditions but without cells or serum **3** was converted to a single product which co-eluted with the nitrile, **1**. Synthesis of RNA was inhibited more than DNA by **3** in uninfected CEM cells, as shown by incorporation of [^{3}H]Urd and [^{3}H]dThd over a range of 0-4 h; however, inhibition of RNA and DNA synthesis was essentially the same at incubation times ≥ 6 h. Together, these data provide insights into a new class of non-nucleoside analogs with anti-herpetic activity.

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