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**Comparative Antiviral Activity of HPMPA, PMEA, HPMPG, HPMPC and Structurally Related Compounds Against African Swine Fever Virus.** P. La Colla^, A. Holy*, J. Jindrich*, H. Dvorakova*, L. Gelli^, M.E. Marongiu^, A. Pani^. *Czechoslovak Academy of Science, Praha and ^Dept. Biologia Sperimentale, Università di Cagliari, Italy.

Continuing our study on the comparative activity of nucleoside analogues against ASFV, we tested HPMPA, PMEA, HPMPG, HPMPC and a series of derivatives against the Lisbona 60 strain of ASFV, adapted to Vero cells. HPMPA, HPMPDAP, PMEDAP, HPMPG and HPMPC were the most active compounds and resulted more potent inhibitors of ASFV (TD50 range : 0.09 - 0.5 ug/mL) than of HSV-1 and vaccinia (TD50 range: 0.4-3.0 ug/mL), which were used as reference viruses. HPMPA and HPMPDAP showed the highest selectively index (S.I. > 200). The diisopropyl esters of PMEA, PMEDAP and HPMPC were totally inactive, but also non cytotoxic for uninfected cells at the maximum doses tested(250 ug/mL). The substitution, in the phosphonyl-methoxy-propyl chain of HPMPA, HPMPG or HPMPC of the 3-OH group for a fluorine or an amino group resulted in a consistent reduction or loss of antiviral activity. Also devoid of antiviral activity were HPMP-2-methylthioadenine, HPMP-2-methyladenine, HPMP-6-thiopurine, PME-6-methylthio-purine, PME-8-aza-7-deazaadenine and PME-8-aza-7-deaza-hypoxanthine. Of the PME-pyrimidine series, only PMET showed a selective, although not very potent activity against ASFV.
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Enhanced Inhibition of HIV-1 Protease by a Combination of Peptide and Non-Peptide Inhibitors: R.B. Luftig[1], M. Bu[1], C. Michejda[2] and J.J. Blumenstein[2,3]. Louisiana State University Medical Center[1], Frederick Cancer Center[2], and FDA[3]; USA.

Our laboratory has previously developed an immunoblotting assay that allows one to screen for HIV-1 protease inhibitors, based on inability of the protease to cleave "immature" $Pr65^{gag}$ murine leukemia virus particles (Bu, Oroszlan and Luftig; AIDS Res and Hum Retr; 5:259-268; 1989). We showed with this assay that pepstatin A and cerulenin, an antifungal antibiotic inhibited HIV protease cleavage by >50% at concentrations of 0.1-0.5 mM. A problem with use of cerulenin in vivo is it's toxicity at such high concentrations. We have now developed several non-toxic analogs of cerulenin. In particular, one of them, (2R-Cis)-Epoxydodecanoylproline methyl ester, when added together with pepstatin A at 0.1 mM or lower concentrations significantly inhibits cleavage than when either compound is used alone at the same concentration. Thus, a preferred modality of developing HIV-1 protease inhibitors could be to develop compounds that together enhance inhibition; in this way, reducing toxicity levels of either compound alone can be achieved.

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