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Potent Topical Anti-Herpes Activity of a Lipophilic Phosphorus Prodrug for the Antiviral Agent PMEA

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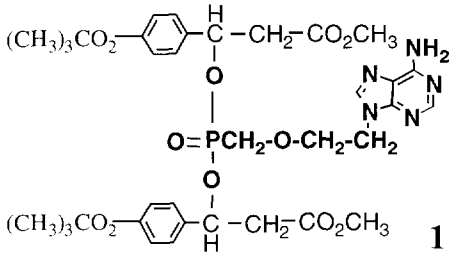
The lipophilic phosphorus prodrug (**1**) of the antiviral agent PMEA is based on a class of phospho-esters which undergo degradation via an elimination reaction following the unmasking of a para-hydroxy group.[1] This prodrug is 54,000 times more potent then PMEA against HSV 1 in a CPE inhibition assay. (EC_{50} **1.25 nanomolar** for 1 versus **68.5 micromolar** for PMEA). A cream containing 0.5% of prodrug 1 applied topically twice daily to mice with established HSV 1 vaginal infections resulted in ≅ 3-4 log reduction in vaginal HSV titers.



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Sulfated xylogalactans from marine algae useful as anti HSV-1 agents. E.B. Damonte*, M.C. Matulewicz**, A.S. Cerezo**, C.E. Coto*. *Laboratorio de Virología and **Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, 1428 Buenos Aires, Argentina.

During an investigation of the biological properties of natural products isolated from marine algae, the antiviral activity of F6, a xylomannan obtained from the red seaweed Nothogenia fastigiata,has been previously reported. In the present study, the antiherpetic activity of F1 and F7, two xylogalactans extracted from the seaweed, has been assayed. Both compounds achieved a dose-dependent inhibition of the multiplication of various strains of herpes simplex virus type 1 (HSV-1) in Vero cells without toxicity for the host cell. In a virus yield reduction assay, the ED50 values against HSV-1 strain F for F1 and F7 were 24 and 15 ug/ml, respectively, whereas concentrations greater than 200 ug/ml did not impair cell growth. The presence of sulfate groups in the molecule was essential for the antiviral properties of these compounds since the chemically desulfated xylogalactans F1D and F7D were totally inactive as HSV-1 inhibitors. Both F1 and F7 had no direct inactivating effect on virions by in vitro incubation in a virucidal test. F7 afforded significative inhibition in HSV-1 yield if added to the cell cultures simultaneously with virus inoculum but had no effect when it was added after 1 h of infection. The kinetics of infectious virus adsorption to Vero cells was highly altered in the presence of the compound whereas virus internalization was not impaired. These results demonstrate that the antiviral action of F1 and F7 on HSV-1 is a blockade on the initial virus attachment to the host cell mainly due to the negative charged groups present in the polysaccharide molecule.