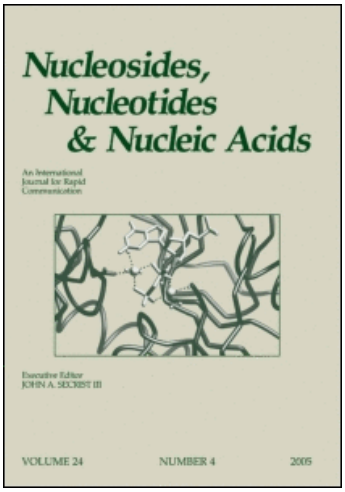

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Synthesis and Biological Application of a New Heterodinucleotide with Both Anti-HSV and Anti-HIV Activity

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SYNTHESIS AND BIOLOGICAL APPLICATION OF A NEW HETERODINUCLEOTIDE WITH BOTH ANTI-HSV AND ANTI-HIV ACTIVITY

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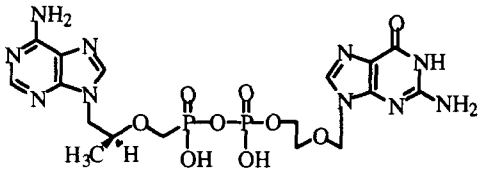
ABSTRACT: A new antiviral drug with both anti-HSV and anti-HIV activity was synthesized by coupling Acyclovir and the acyclic nucleoside phosphonate (*R*)PMPA. The heterodinucleotide ACVpPMPA encapsulated into autologous erythrocytes was added to human macrophages providing an effective *in vitro* protection from HSV-1 and HIV-1 replication.

Since human herpes viruses (HSVs) are among the most frequent causes of viral infection in HIV-1 immunocompromised patients, therapeutic strategies able to inhibit replication of both viruses are need.[1] The most common therapies against HSV-1 and HIV-1 infectivity are based on the administration of nucleoside analogues. Acyclovir (ACV) is among the drugs of choice against HSV-1 infection, while (*R*)PMPA is an acyclic nucleoside phosphonate analogue that has shown marked anti-HIV activity in a phase I clinical study.[2] As monocyte-derived macrophages are considered important *in vivo* reservoirs of both HSV-1 and HIV-1 infection, drugs able to inhibit replication of both viruses directly in macrophages would be ideal ones.[3,4] Prompted by these considerations, we designed and synthesized ACVpPMPA, a new heterodinucleotide consisting of both an antiherpetic and an antiretroviral drug bound by a phosphate bridge.



ACVpPMPA

The title compound was prepared by condensation of 9-((*R*)-2-phosphonomethoxypropyl)adenine [(*R*)PMPA] as morpholidate derivative with Acyclovir monophosphate as *n*-tributylammonium salt.

BIOLOGICAL EVALUATION

Metabolism and antiviral activity of ACVpPMPA were determined to evaluate its efficacy in different systems. Metabolism in human plasma was determined at different incubation times by HPLC. The compound was completely converted to ACV and (*R*)PMPA after 2 hours.

Antiviral activity of ACVpPMPA

ACVpPMPA was encapsulated into autologous erythrocytes (RBC) modified to increase their recognition and phagocytosis by human macrophages. Once inside macrophages, metabolic activation of the drug occurred.[4] The addition of ACVpPMPA-loaded erythrocytes to human macrophages provided an effective *in vitro* protection from HSV-1 and HIV-1 replications, respectively.

Anti-HSV-1 activity of ACVpPMPA: Human macrophages were cultured for 10 days before treatment with either ACVpPMPA-loaded RBC (approx. 1.0 mM ACVpPMPA inside erythrocytes) or control unloaded (UL) RBC in culture medium for 18 hours. A ratio RBC/macrophages 50/1 was used. After extensive washings, macrophages were infected for 2 hours with HSV-1 (3 p.f.u. $cell^{-1}$). As control, 15 μM ACVpPMPA added for the same time as RBC was used. The inhibitory effect of the compound was evaluated 48 hours after infection by plaque assay in Vero cells. The results obtained show that ACVpPMPA-loaded RBC were able to inhibit HSV-1 replication by 50 %. The addition of the drug at 15 μM concentration in the medium, reduced HSV-1 production by 40 %.

Anti-HIV activity of ACVpPMPA-loaded erythrocytes: Human macrophages were cultured for 10 days and then treated with ACVpPMPA (approx. 1.0 mM inside RBC) or unloaded RBC in culture medium for 18 hours before infection with a macrophage-tropic HIV-1_{BA-L} strain. Two different RBC/macrophages ratio (100/1 and 500/1) were tested. The production of p24 was determined at 14 days post infection. As control, the free drug ACVpPMPA was used. The results obtained show that ACVpPMPA-loaded RBC are able to efficiently protect macrophages from HIV-1 infection with percentage inhibitions ranging from 50 to 100 % of HIV-1 production. Addition of 1.0 μM ACVpPMPA to the medium for 18 hours was without effect on HIV-1 production.

In conclusion, the addition of ACVpPMPA-loaded erythrocytes to human macrophages provided an effective *in vitro* protection from HSV-1 and HIV-1 replications. Therefore, ACVpPMPA acts as an efficient antiviral prodrug following selective targeting to macrophages by means of loaded erythrocytes.

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