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Efficient Synthesis and Biological Properties of Base Substituted 2,4-Diamino-6-(*R*)-[3-hydroxy-2-(phosphonomethoxy) propoxy]pyrimidine (HPMPO-DAPy)

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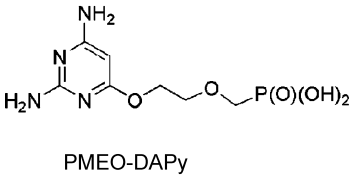
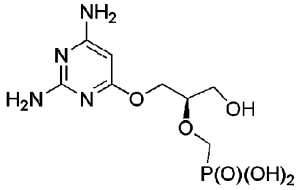
New generation of acyclic nucleoside phosphonates (ANPs) is derived from 2,4-diamino-6-hydroxypyrimidine (Holý et al., 2002; Balzarini et al., 2002). 2,4-Diamino-6-[(phosphonomethoxy)ethoxy]pyrimidine (PMEO-DAPy), its 4-hydroxy congener and 5-substituted derivatives possess pronounced antiviral activity against retroviruses (Hocková et al., 2003, 2004). 2,4-Diamino-6-(*R*)-[3-hydroxy-2-(phosphonomethoxy)propoxy]pyrimidine (HPMPO-DAPy) exhibited antiviral activity against various DNA viruses (adenovirus (Naesens et al., 2005), polyomavirus (Lebeau et al., 2007) and orf virus (Dal Pozzo et al., 2005)). To further study structure–activity relationship we decided to prepare base substituted derivatives bearing the 3-hydroxy-2-(phosphonomethoxy)propoxy (HPMPO) side chain. Various synthetic methods were developed for preparation of HPMPO-DAPy derivatives substituted at positions 2-, 4- and 5- of the pyrimidine base. Details of synthesis and biological activities will be discussed.



PMEO-DAPy



HPMPO-DAPy

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doi:10.1016/j.antiviral.2010.02.425

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A Single Intranasal Administration of DEF201 Protects Against Lethal Respiratory Challenge with Western Equine Encephalitis Viruses

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Objective: The aim of this study is to evaluate the prophylactic and treatment efficacy of DEF201 against lethal challenge of WEEV strains in a mouse model. DEF201 is a proprietary replication deficient adenovirus type 5 expressing mouse IFNα under development as a broad spectrum antiviral.

Method: Groups ($n = 10$) of female Balb/c mice were treated with a single dose intranasal administration of 1×10^7 pfu of DEF201 to each group up to 21 days prior to challenge. Groups of untreated mice were included as controls. On Day 0 all mice were challenged intranasally with a lethal dose of either WEEV California strain or WEEV CBA87 strain. A group of mice daily treated with a single intraperitoneal injection of 2×10^7 IU/kg IFNα recombinant protein served as a positive control group. Mice were monitored daily for clinical signs of disease during the 14 day post challenge period.

Results: Treatment of mice with DEF201 provided complete protection against otherwise lethal challenge with either WEEV California or CBA87 strains when given at Days 21, 14, 7 or 1 prior to challenge. In addition, when treatment was given 4 h post-challenge 100% protection was still conferred against WEEV California strain whereas 70% of mice survived the challenge with WEEV CBA87 strain. Protected mice demonstrated no drastic change in body weight with little to no clinical signs of WEEV infection which typically include ruffled hair, hunched posture, lethargy and ataxia.

Conclusion: This study demonstrated that DEF201 induced rapid and long-lasting protection against lethal WEEV infection of mice and could potentially be used as a prophylactic and possibly a therapeutic against biothreat agents and emerging pathogens. This work was funded by NIAID-DMID contract N01-AI-30063.

doi:10.1016/j.antiviral.2010.02.426

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Synthesis and Solution Structure of DNA Duplexes Containing the Potent Anti-poxvirus Agent Cidofovir

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Cidofovir (1-(S)-[3-hydroxy-2-(phosphonomethoxy)propyl]cytosine, CDV) is a potent inhibitor of poxvirus replication. Prior studies showed that the inhibitory mechanism involves (at least) two effects of the active intracellular metabolite of CDV, CDV diphosphate (CDVpp), on reactions catalyzed by vaccinia virus DNA polymerase: (1) after CDV and one more deoxynucleoside monophosphate are incorporated into a growing DNA strand, addition of the next base by the polymerase is greatly slowed, and the 3′-to-5′ exonuclease activity is completely blocked; and, (2) templates containing a CDV residue cannot be extended beyond the CDV base by the vaccinia DNA polymerase, effectively blocking further rounds of replication. As part of our studies to further characterize the mechanism of inhibition of vaccinia virus DNA