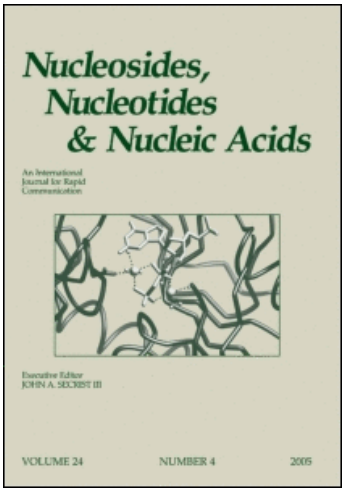

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Synthesis and Antiherpesvirus Activity of (S)-1-((3-Hydroxy-2-Phosphon-Ylmethoxy)Propyi.)Cytosine (HPMPC) and Related Nucleotide Analogues

John C. Martin[a]; Joanne J. Bronson[a]; Robert R. Webb II[a]; Michael M. J. Hitchcock[a]; Ismail Ghazzouli[a]
[a] Bristol-Myers Pharmaceutical Research and Development Division, Wallingford, Connecticut

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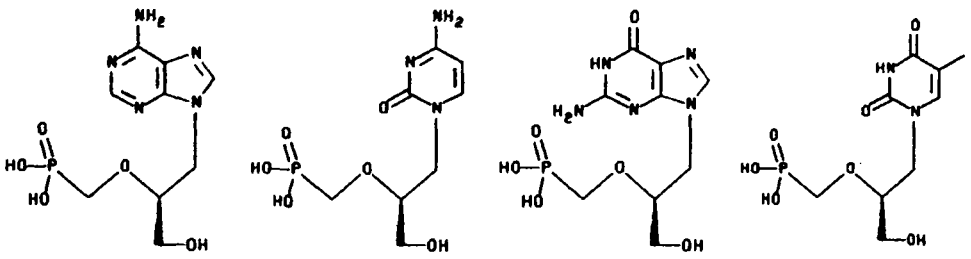
SYNTHESIS AND ANTIHERPESVIRUS ACTIVITY OF (S)-1-((3-HYDROXY-2-PHOSPHONYLMETHOXY)PROPYL)CYTOSINE (HPMPC) AND RELATED NUCLEOTIDE ANALOGUES

John C. Martin, Joanne J. Bronson, Robert R. Webb II,
Michael M. J. Hitchcock, and Ismail Ghazzouli
Bristol-Myers Pharmaceutical Research and Development Division,
5 Research Parkway, Wallingford, Connecticut 06492

Abstract. Of a series of phosphonate nucleotide analogues, HPMPC (2) showed the greatest in vivo therapeutic index against herpes simplex viruses.

The discovery by De Clercq and Holy of (S)-9-((3-hydroxy-2-phosphonylmethoxy)propyl)adenine (1, HPMPA) as a potent and broad spectrum antiviral agent provided a lead to a new class of nucleotide analogues which are structurally characterized as phosphonylmethyl ethers.[1] HPMPA was found to be active in vitro against a variety of DNA viruses including herpes simplex virus types 1 and 2 (HSV 1 and 2), cytomegalovirus (CMV), varicella-zoster virus (VZV), and adenovirus.[1] In addition, the activity of HPMPA against HSV 1 in mice indicated that this polar substance has sufficient penetration into cells to exert a beneficial effect in vivo.[1] Additional studies have further detailed the in vitro activity of HPMPA against herpes viruses,[2] Epstein-Barr virus,[3] adenovirus,[4] African swine fever virus,[5] and seal herpesvirus[6] and the in vivo efficacy in a rabbit model against a thymidine kinase deficient strain of HSV 1.[7] HPMPA has been proposed to be an analogue of 2'-deoxyadenylic acid, and it's mechanism of action to involve two phosphorylations to a triphosphate analogue which then inhibits the virus DNA polymerase.[8]

The in vitro antiviral activities of the other 2'-deoxynucleotide analogues, HPMPC (2), HPMPG (3), and HPMPT (4), have been reported.[2] Like HPMPA, HPMPC and HPMPG show activity against HSV 1, HSV 2, CMV, and VZV, but HPMPT is inactive. HPMPG has also been reported to be ten fold more potent than acyclovir in extending survival time in a mouse HSV 1 model.[9]

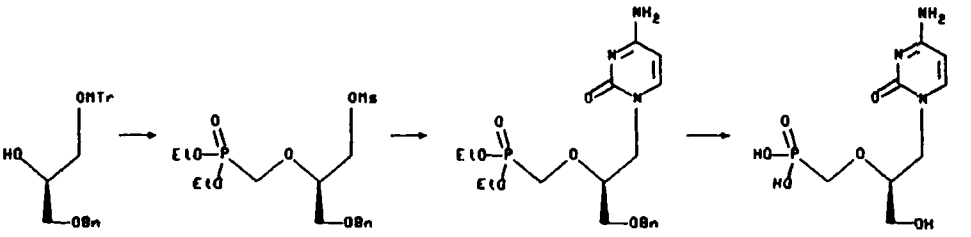


1, HPMPA 2, HPMPC 3, HPMPG 4, HPMPT

We have carried out multigram syntheses and comparative biological evaluation of the three active members of this series, HPMPA, HPMPC, and HPMPG.

RESULTS AND DISCUSSION

Holy and Rosenberg[10] and we[11] have published syntheses of HPMPA. The synthesis of HPMPC proceeded from (S)-1-O-benzylglycerol[12] which was protected to give alcohol **5** (90 %). Reaction of **5** with NaH/diethyl tosyloxymethylphosphonate/THF followed by aqueous acetic acid and then mesyl chloride/triethylamine/CH_2Cl_2 furnished mesylate **6** (50 %). Alkylation of cytosine cesium salt in DMF with **6** afforded **7** in 67 % yield. Deprotection of **7** by transfer hydrogenation (20 % $Pd(OH)_2$, cyclohexene, ethanol, reflux) and ester cleavage (TMS-bromide, DMF) gave a 52 % yield of HPMPC. HPMPG was prepared in an analogous manner, the key reaction being the alkylation of 6-O-benzylguanine with **6**.



5 6 7 2

HPMPC was the least toxic of this series of compounds showing no effect in mice dosed i.p. or p.o. with 200 mg/kg/day for five days. In

TABLE 1. % Survival of Treated Mice Infected with Herpes Simplex Virus Type 2[a]

Dose, mg/kg/day	HPMPC, i.p.	ACV, i.p.	HPMPC, p.o.	ACV, p.o.
200	100*	100*	90*	50*
100	100*	20	70*	10
10	100*	10	30	0
1	60*			
0.1	40*			
Placebo Control	0		5	

[a]Mice were inoculated i.p. with HSV 2 (G). Treatment was initiated 3 h post-infection and given twice a day for 5 days. * indicates a confidence of <.05 by the Fischer exact test. The i.p. data is a combination of two experiments.

contrast, HPMPA exhibited toxicity at a dose by the i.p. route of 100 mg/kg/day, and the toxic dose for HPMPG was 10 mg/kg/day. HPMPC was found to show exceptional in vivo potency against HSV 2, Table 1. When given i.p., this compound resulted in a significant reduction in mortality at a dose of 0.1 mg/kg/day and provided complete protection at 10 mg/kg/day. Complete protection with acyclovir was achieved at a much higher dose of 200 mg/kg/day. This high potency of HPMPC relative to acyclovir was surprising since HPMPC is 5-10 times less active than acyclovir against HSV 2 in vitro. Probably because of low absorption, HPMPC was less efficacious by the oral route but still showed a potency superior to that of acyclovir.

The utility of phosphonate nucleotide analogues as antiviral agents has been thought to be limited.[13] The anionic character of the phosphonate moiety could retard uptake by cells. The surprisingly high

potency of HPMPC in vivo relative to its in vitro activity demonstrate that these types of compounds have sufficient cellular penetration in vivo to merit evaluation for clinical utility.

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