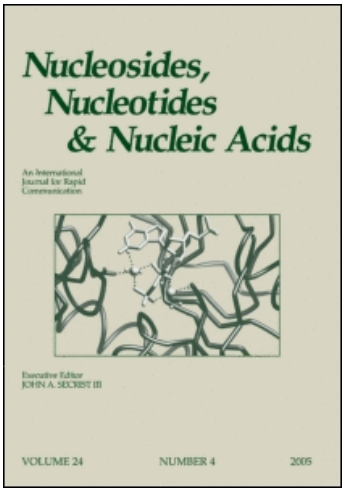

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Phosphate Modified Analogues of 5'-O-Phosphorylated 2',3'-Dideoxynucleosides: Synthesis and Anti-HIV Activity

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PHOSPHATE MODIFIED ANALOGUES OF 5'-O-PHOSPHORYLATED 2',3'-DIDEOXYNUCLEOSIDES: SYNTHESIS AND ANTI-HIV ACTIVITY

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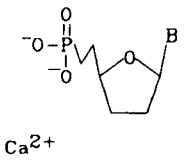
ABSTRACT: Phosphonate analogues of 5'-O-phosphoryl-2',3'-dideoxyribofuranosyl adenine, cytosine, hypoxanthine and thymine were synthesized. The hypoxanthine and thymine analogues were inactive against HIV induced cytopathy in the CEM-4 T-cell lines. The 2',3'-ddC and 2',3'-ddA analogues were marginally active.

The 2',3'-dideoxynucleosides are known inhibitors of the AIDS pathogen HIV. They act at the level of HIV reverse transcriptase, where they compete with the normal substrates for this enzyme. The dideoxynucleosides require conversion to the respective 5'-O-triphosphates by cellular kinases, which is know to occur slowly.[1] In hopes of promoting this conversion and thereby designing a more potent inhibitor of HIV, we have synthesized and tested the phosphonate analogues of 5'-O-phosphoryl-2',3'-dideoxyribofuranosyl adenine, cytosine, hypoxanthine and thymine; compounds **1-4**.



1 B = adenine
2 B = cytosine
3 B = hypoxanthine
4 B = thymine

Our synthetic methodologies paralleled those used by Moffatt *et al.* to synthesize 5'-deoxy-5'-(dihydroxyphosphinylmethyl)nucleosides.[2] Either a suitably protected dideoxynucleoside or the dideoxynucleoside itself was oxidized to 5'-aldehyde *in situ*, which was treated with diphenyl triphenylphosphoranylidenemethylphosphonate[3] to produce a mixture of olefins. This mixture was reduced by catalytic hydrogenation and the first phosphonyl phenyl ester was removed by hydrolysis with conc. NH_4OH or 0.2N NaOH. Removal of the second phenyl ester was accomplished with *C. atrox* phosphodiesterase. The liberated phosphonates **1-4** were precipitated as their calcium salts.

As seen below only the -ddA (1) and ddC (2) analogues showed any significant activity against HIV in T-lymphocyte cell culture.[4] Similar anionic nucleoside derivatives such as (S)-

HPMPA[5] have displayed potent antiviral activity, demonstrating the ability of such species to cross cell membranes. Lynn, *et al.*[6] have reported that T-cell membranes during HIV infection are disrupted and more permeable to ions. The low activity of compounds **1-4** suggests either poor penetration of these anionic species across the cell membrane of the infected cells, or more likely, that the 2',3'-dideoxynucleotide analogues may be poor substrates for the kinases responsible for conversion of nucleotides to di- and triphosphates.

Activity in CEM-4 T-Lymphocytes

Compound	Anti-HTLV-IIIB Activity - "RI_{50}"	Cytoxicity
1	60 μM	>200 μM
2	150 μM	>200 μM
3	>200 μM	>200 μM
4	>200 μM	>200 μM

$$RI_{50} = \frac{\text{p 24 at concentration x}}{\text{p 24 at concentration o}} = 50\%$$

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