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

Robert M. Rigs^a; Robert N. Comber^a; John A. Montgomery^a; John A. Secrist III^a; Janet M. Leeds^b; Sara Chaffee^b; Michael S. Hershfield^b

^a Organic Chemistry Research Department, Southern Research Institute, Birmingham, Alabama ^b Medical Center, Duke University, Durham, North Carolina

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

Robert M. Riggs, Robert N. Comber, John A. Montgomery,* and John A. Secrist III*

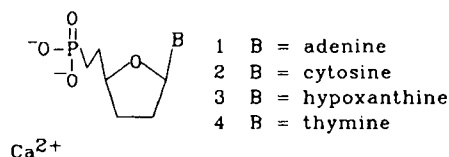
Southern Research Institute, Organic Chemistry Research Department,
Birmingham, Alabama 35255

Janet M. Leeds, Sara Chaffee, and Michael S. Hershfield

Medical Center, Duke University, Durham, North Carolina 27710

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 known 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.



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 triphenylphosphoranylidene methylphosphonate³ 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)-

HPMPA⁵ 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-III B Activity - "RI ₅₀ "	Cytotoxicity
1	60 μ M	>200 μ M
2	150 μ M	>200 μ M
3	>200 μ M	>200 μ M
4	>200 μ M	>200 μ M

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

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