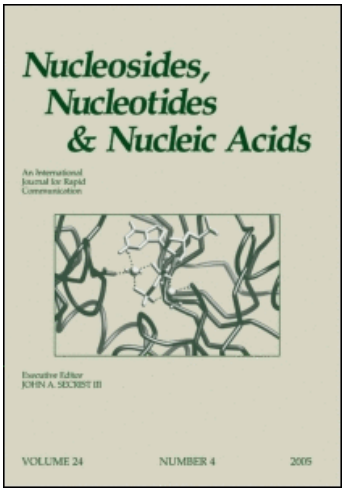

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Dinucleoside Monophosphates Containing AZT and 1-Methyladenosine or 7-Methylguanosine

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ABSTRACT

Dinucleoside monophosphates containing AZT and 1-methyladenosine or 7-methylguanosine were synthesized and their in vitro anti-HIV activity was determined.

A large number of 3′-azido-3′-deoxythymidine (AZT) masked phosphate derivatives were proposed and investigated as prodrugs possessing ability to by-pass the first phosphorylation step in the metabolic conversion of AZT to AZT-TP.[1] It is generally assumed that negatively charged nucleotides are unable to cross cell membranes and are easily dephosphorylated by phosphohydrolases. In an attempt to overcome these problems we decided to obtain a zwitterionic AZT-MP derivatives, containing 1-methyladenosine (m^1A) or 7-methylguanosine (m^7G). The starting adenylyl-(5′ → 5′)-AZT (ApAZT, **1)** and guanylyl-(5′ → 5′)-AZT (GpAZT, **2)** were

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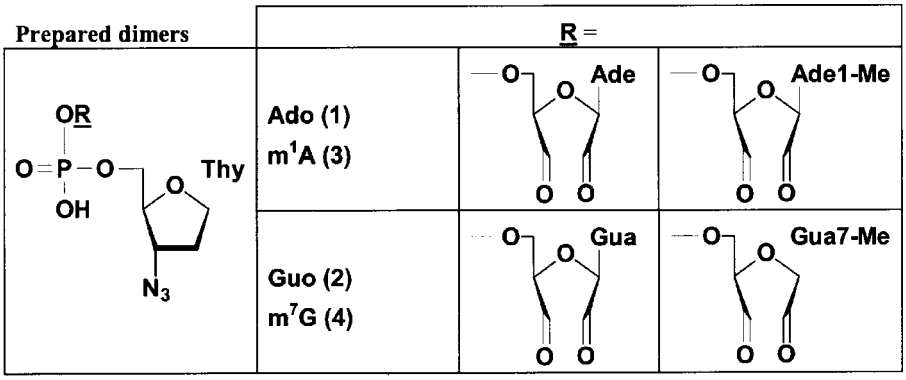
synthesized by standard methods. The dimers **1** and **2** were successively methylated[2,3] by a large excess of dimethylsulfate at pH 5.0 to give m^1ApAZT **3** and m^7GpAZT **4** in 85–90% yields.

The purity of thus obtained dimers **1–4** was checked by RP HPLC and NMR spectroscopy. The structure of **3** and **4** was also confirmed by enzymatic hydrolysis with bacterial alkaline phosphatase and snake venom phosphodiesterase. Dimers **3** and **4** were quantitatively degraded to AZT, m^1A and m^7G, respectively. Moreover, starting from **1–4** the corresponding periodate oxidized derivatives were prepared in high overall yield.



All dimers exhibited antiviral potency and cytotoxicity similar to that of AZT in CEM/0 cells. They were found completely inactive against HIV replication in CEM/TK$^-$ cell line at concentrations up to 250 μM. These dimers cannot be considered as pronucleotides of AZT-MP as they are unable to deliver the corresponding AZT-MP inside the cells.

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