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3' → 5' and 5' → 5' Uridine-AZT Phosphodiester Dimers: Synthesis and *In Vitro* Anti-HIV Activities

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The finding that uridine protects and reverses 3'-azido-3'-deoxythymidine (AZT) toxicity in human bone marrow progenitor cells[1] suggests that the combined use of AZT and uridine may have a therapeutic benefit in reducing anemia and neutropenia adverse effects of AZT administration to patients suffering from acquired immunodeficiency syndrome (AIDS).

In this regard, we have synthesized two phosphate diesters of uridine and AZT, namely the 3' → 5' phosphodiester dimer which is hitherto unknown and the 5' → 5' phosphodiester dimer which has been reported recently as possessing potential advantages over AZT due to higher therapeutic index and better pharmacokinetic properties.[2]

The chemical synthesis of these two dimers and the comparison results of their anti-human immunodeficiency virus (HIV) activity as well as toxicity evaluations will be discussed in detail.

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Synthesis, Anti-Human Immunodeficiency Virus Activities, Cytotoxicities, and decomposition pathways of the bis(SATE)phosphotriester derivatives of AZT

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For many years numerous attempts have been made to deliver mononucleotides intracellularly in order to bypass the first phosphorylation step in the activation of nucleosides. In this regard, we have previously demonstrated that those based on the use of neutral phosphotriester derivatives substitued with bioreversible protecting groups seem most promising.[1,2]

Here we report the synthesis, anti-human immunodeficiency virus (HIV) activities, cytotoxicities on progenitor cells, and decomposition pathways in several media including human serum of *O,O'*-bis(S-acyl-2-thioethyl)phosphotriester derivatives of AZT.

The anti-HIV activities particularly in thymidine kinase deficient cells as well as toxicities of these pronucleotides will be discussed in detail in relation to their decomposition pathways.

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