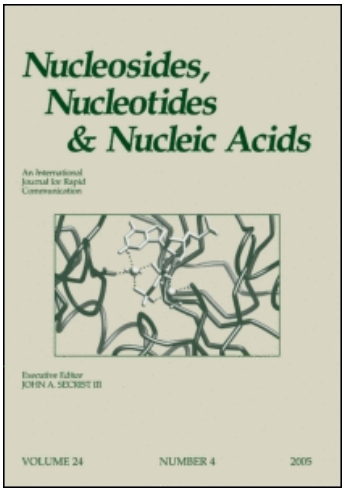

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Synthesis and In Vitro Antiviral Activity of Some Symmetrical Phosphoramidate Dimers of AZT

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SYNTHESIS AND *IN VITRO* ANTIVIRAL ACTIVITY OF SOME SYMMETRICAL PHOSPHORAMIDATE DIMERS OF AZT

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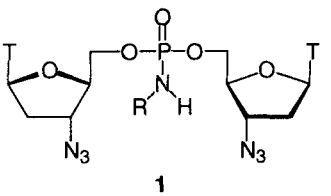
ABSTRACT: The synthesis of some symmetrical phosphoramidate dimers of AZT is presented. The synthetic scheme includes the formation of the symmetrical H-phosphonate diester of AZT, followed by its conversion to several dinucleoside phosphoramidate analogues. The compounds were evaluated for their anti-retroviral activity.

We have synthesized different phosphoramidates **1** (Fig. 1) as potential antiviral agents. These compounds were designed with the aim to act as prodrugs for both 3'-azido-3'-deoxythymidine (AZT) and its 5'-phosphorylated derivative (AZTMP)[1]. The synthetic



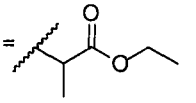
1

Fig. 1

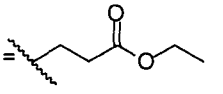
1a, R = H

1b, R = Bu

1c, R =

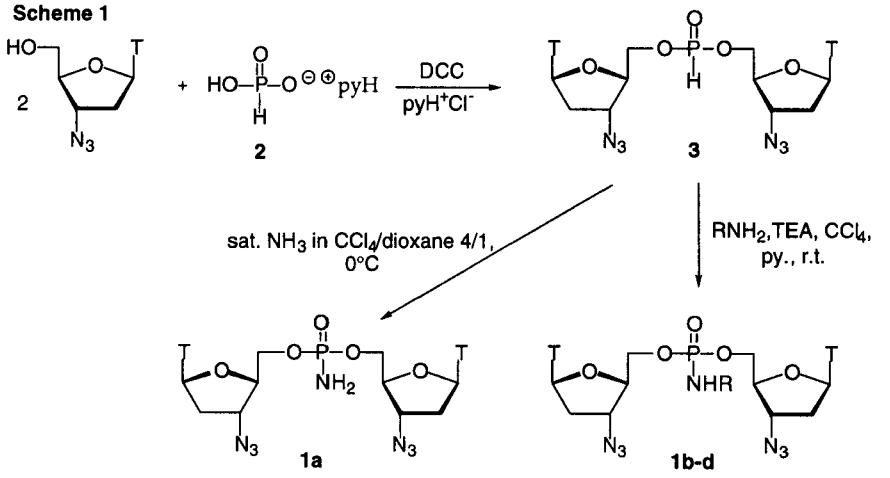


1d, R =



strategy used was based on H-phosphonate chemistry[2] and consisted of two steps: (i) the formation of the symmetrical H-phosphonate diester of AZT and (ii) its conversion into the desired phosphoramidates *via* oxidative coupling with a corresponding amine (Scheme 1). The symmetrical H-phosphonate diester **3** had been earlier prepared from phosphonic acid using pivaloyl chloride as a condensing agent[3]. To develop a more convenient procedure

for the synthesis of **3** we studied the dicyclohexylcarbodiimide (DCC) mediated condensation of phosphonic acid with AZT. We found that symmetrical H-phosphonate diester **3** could be produced practically quantitatively (^{31}P NMR) using pyridinium phosphonate **2** (1 equiv.), AZT (2 equiv.) and DCC (3 equiv.) in pyridine. The condensation was complete within one hour. The presence of pyridinium hydrochloride



(2 equiv.) was necessary to ensure reproducible results. The produced symmetrical H-phosphonate **3** could be used without purification for the subsequent oxidative couplings (Scheme 1) to afford target compounds **1** in 80-90% yield (after silica gel column purification).

The synthesized compounds were evaluated for their anti-retroviral activity in different cell cultures. They were found to be active in cells expressing thymidine kinase (comparable to AZT), but inactive in CEM/TK$^-$ cells (IC_{50} > 10 μM), thus suggesting that these compounds are not able to deliver AZTMP inside the cells.

Acknowledgements

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