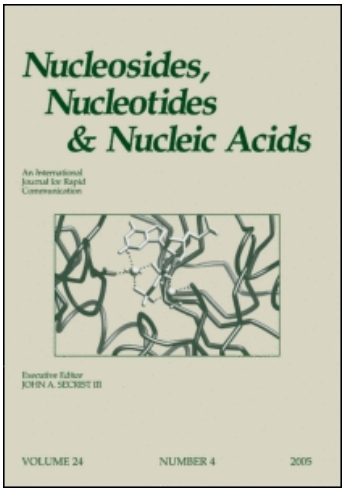

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SYNTHESIS OF THYMIDINE ANALOGUES WITH A CYANOIMIDO SUBSTITUENT

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Abstract. The synthesis of thymidine analogues with a N-cyanoimido substituent in the 3'- or 5'-position is described.

In our attempts to develop new nucleoside analogues with potential antiviral or antitumor activity, we synthesized a series of N-cyanoimido substituted thymidines starting from N-cyanoimido-S,S-dimethyldithiocarbonate **1**.

This reagent is easy to handle and reacts with aliphatic primary amines with formation of N-cyanoisothiourea derivatives in high yields. The S-Me-group can be easily reduced or replaced by an O-Me or NH-Me group with the formation of a N-cyanoamidino, N-cyanoisourea or a N-cyanoguanidino derivative, respectively. These substituents contain 3 conjugated nitrogen atoms and are devoid of basic properties, due to the presence of the electron withdrawing cyano group. The cyanoguanidino group is known to be part of important drugs such as cimetidine and pinacidil.

First, we introduced these substituents in the 3'-position of thymidine, as we reasoned that the lack of activity of 3'-amino-3'-deoxythymidine against HIV may be due to its basic properties (i.e. protonated at physiological pH). Therefore, 5'-O-trityl-3'-amino-3'-deoxythymidine **2** was reacted with 2 equivalents of **1** yielding **3**, which was detritylated with formic acid to **4a**. The other 3'-modified nucleosides **4b-d** could be synthesized readily from the same precursor **3**.

Since a potent inhibitory effect on herpetic thymidine kinase has been described for 5'-β-phenoxypropionamido derivatives, the 5'-modified thymidine analogues **7a-d** were synthesized as potential

thymidine kinase inhibitors. The starting product 5'-amino-5'-deoxythymidine 5 was prepared in 3 steps from thymidine by reaction with tri(isopropyl)benzenesulfonylchloride (82%), followed by introduction of the azido group (80%) and reduction with H_2 in the presence of Pd/C. The compounds 7a-c were synthesized using the same strategy as described above for 4b and 4c. The N-cyanoimidate 7d was obtained in one step from 5 using ethyl N-cyanoformimidate. The reaction of 6 with an excess of sodium phenolate gave 9 instead of the expected phenoxy derivative.

Compounds 4a-d, in which the N-cyanoimido group is linked to the 3'-position of thymidine, were devoid of anti-HIV activity in MT-4 cells at subtoxic concentrations. Among the 5'-substituted derivatives of thymidine, compounds 6 and 7b were also inactive against HIV.