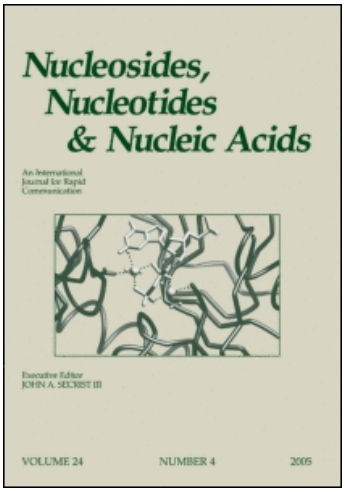

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Synthesis of 3'-Deoxy-3' and 5'-Deoxy-5'-[4-(Purin-9-yl/Pyrimidin-1-yl) methyl-1,2,3-Triazol-1-yl]thymidine via 1,3-Dipolar Cycloaddition

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NUCLEOSIDES & NUCLEOTIDES, 16(7-9), 1073-1077 (1997)

SYNTHESIS OF 3'-DEOXY-3' AND 5'-DEOXY-5'-[4-(PURIN-9-YL/PYRIMIDIN-1-YL)METHYL-1,2,3-TRIAZOL-1-YL]THYMIDINE *VIA* 1,3-DIPOLAR CYCLOADDITION

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ABSTRACT

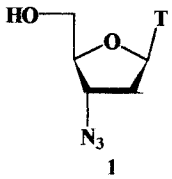
Synthesis of new 3'-deoxy-3' and 5'-deoxy-5'-[(4-(purin-9-yl/pyrimidin-1-yl)methyl-1,2,3-Triazol-1-yl]thymidine **8a-g**, **10a-g** from 3'-azido-3'-deoxy-5'-O-monomethoxytrityl-thymidine and 5'-azido-5'-deoxythymidine respectively are described. The key step is the 1,3-dipolar cycloaddition between the azido group and N-9/N-1-propargylpurine/pyrimidine derivatives.

INTRODUCTION

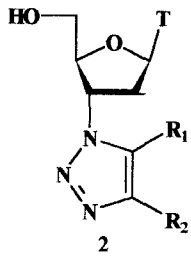
The search for clinically useful drugs for treatment of acquired immunodificiency syndrome (AIDS) was initially focused on inhibition of HIV reverse transcriptase. At present 3'-modified 2',3'-dideoxynucleosides such as 3'-azido-3'-deoxythymidine **1** (AZT) (Figure 1), 2',3'-dideoxyinosine (DDI), 2',3'-dideoxycytidine (DDC) are used as anti-AIDS agents[1-3]. However, these drugs are not free of undiserable side effects[4].This has prompted various attempts at 3' and 5'-modifications of the sugar moiety. Thus, a large number of 3' or 5'-deoxythymidine derivatives have indeed been synthesized and screened for anti-HIV activity[5,6]. For instance, Herdewijn et al.[7] have reported the synthesis of compounds, in which the N_3 unit of AZT is transformed to a triazole ring **2** (Figure 1), but these compounds did not show appreciable activity against HIV. On the other hand, Tittensor et al.[6] have used cycloadditions of 5'-azido-5'-deoxythymidine with carbonyl activated alkynes to synthesize 1,2,3-triazole as potential thymidylate kinase inhibitors.

In addition, Biserka et al.[8] have reported the synthesis of so called "double head" nucleosides **3** (Figure 1) bearing two heterocyclic bases on C-1' and C-5' positions of the single deoxyribose unit.

In connection with a project on the synthesis of bioisosters of 3'-azido-3'-deoxythymidine (AZT) and 5'-azido-5'-deoxythymidine and related 2',3'-deoxynucleosides, our goal was to prepare a series of nucleoside analogues bearing three heterocyclic bases at C-1' (thymine) and C-3'- or C-5' (nucleobase and 1,2,3-triazole).



1



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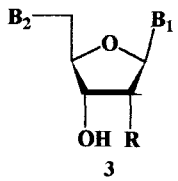


3

AZT

R_1 = H, R_2 = CO_2H

R_1 = CO_2Et, R_2 = H

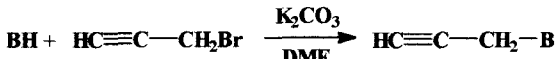
R_1 = CO_2Et, R_2 = CO_2Et

R = H, OH

B_1 = Purine, B_2 = Pyrimidine

B_1 = Pyrimidine, B_2 = Purine

Figure 1



3a : BH = Thymine	**4a**
3b : BH = Uracil	**4b**
3c : BH = 5-Chlorouracil	**4c**
3d : BH = 5-Bromouracil	**4d**
3e : BH = 5-Fluorouracil	**4e**
3f : BH = 5-Iodouracil	**4f**
3g : BH = Adenine	**4g**

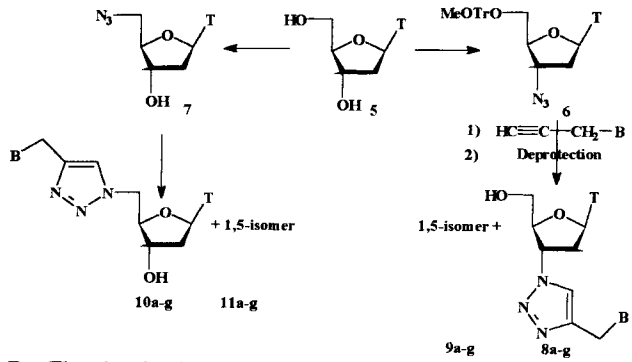
Scheme 1

RESULTS AND DISCUSSION

The starting material N-9/N-1-propargylpurine/pyrimidine **4a-g** (Scheme 1) were prepared regioselectively by a modification of known method (9). The synthesis was carried out by propargylbromide as alkylating agent, DMF as solvent and potassium carbonate (K_2CO_3) as base at room temperature for 4h to 24 h. The desired products 1-propargylpyrimidines **4a-f** and 9-propargyladenine **4g** were obtained in good yields

The second step of the synthesis was the preparation of 3'-azido-3'-deoxy-5'-O-monomethoxytritylthymidine **6**[10] and 5'-azido-5'-deoxythymidine **7**[6] by known procedures.

The cycloaddition reactions of the azidothymidine derivatives **6** and **7** respectively (5 eq.) with N-9/N-1-propargyl purine/pyrimidine **4a-g** in dry toluene under reflux, afforded a mixture of two regioisomers of which **8a-g** were the major component and **9a-g** turned up in minor amounts (Scheme 2). The ratio **8** / **9** was 90/10 as estimated from ^1H NMR spectra. After separtion by silica gel column



a: B = Thymine, **b** : B = Uracil, **c**: B = Adenine, **d** : B = 5-Chlorouracil, **e** : B = 5-Bromouracil, **f** : B = 5-Iodouracil, **g** : B = 5-Fluorouracil.

Scheme 2

TABLE 1 : 1,3-Dipolar cyloaddition of N-propargylpyrimidine/purine derivatives with azidonucleosides **6** and **7**

substrate	Acetylenic product	equivalent of azidonucleoside	Solvent	time (h)	yield %
6	**4a**	5	Toluene	66	85
	4b	5	Toluene	66	94
	4c	5	Toluene	36	90
	4d	5	Toluene	24	79
	4e	5	Toluene	24	77
	4f	5	Toluene	24	68
	4g	5	Toluene	24	75
7	**4a**	5	Toluene/DMF	24	70
	4b	5	Toluene/DMF	24	70
	4c	5	Toluene/DMF	24	78

chromatography, only the isomers **8a-g** were obtained as pure product (Table 1). It is known from the literature that addition of azides to unsymmetrical acetylenes is determined by steric and electronic factors. In general, such addition tends to give mainly the isomers with electron withdrawing groups at the 4-position[11-13]. On the other hand, the sterically less hindred isomers tend to be the major isomer 14,15.

The structure of new compounds were assigned on the basis of the corresponding analytical and spectroscopic data. A differenciation between 4- or 5-location of substitutent in triazolic regioisomers **8a-g** was determined on the basis of the chemical shifts of the triazole proton (H-5)[15-19]. Due to the effect of

the adjacent sugar the triazole proton in the 1,4-substituted 1,2,3-triazole isomers **8a-g** appeared at lower field (8.07-8.3 ppm) than in the isomeric 1,5-substituted 1,2,3-triazole derivatives **9a-g** (7.5-7.75 ppm).

The deprotection of the 5'-methoxytrityl group was smoothly performed upon treatment with 2% TFA in CH_2Cl_2/MeOH 4/1) to give **8a-g** (Scheme 2) in high yields.

In summary, we have successfuly synthesized by 1,3-dipolar cycloaddition new 3' or 5'-modified 2',3'-dideoxynucleosides containing three heterocyclic bases. Antiviral and antiretroviral evaluation of these new modified nucleosides are currently under investigation and complete results will be published in due course.

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