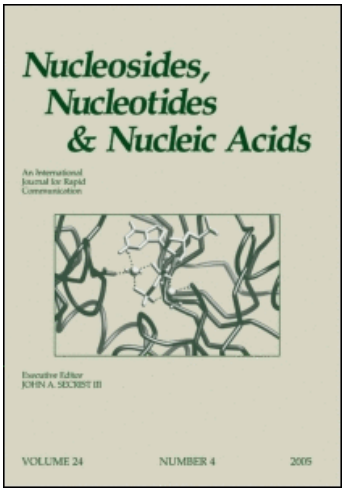

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SYNTHESIS OF NEW 1,2,3-TRIAZOLE ACYCLONUCLEOSIDE ANALOGUES OF ACV AND HBG.

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ABSTRACT

1,3-dipolar cycloaddition of N-9/N-1-propargylpurine/pyrimidine to the corresponding azido-compounds **9-10** produces acyclonucleoside analogues **13a-h**, **14a-h** in which the 4-methyl-1,2,3-triazole is used as spacer arm.

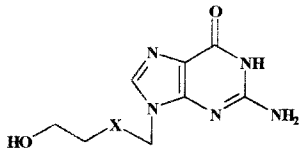
INTRODUCTION

In recent years, efforts in developing drugs targeted against the herpes virus family have resulted in the discovery of more selective compounds. Acyclovir [9-(2-hydroxyethoxy)methyl)guanine **1** (figure 1), (Zovirax)] is the first effective and highly selective antiviral drug used for the treatment of herpes simplex (HSV) virus infections and Varicella-Zoster[1]. The corresponding carba analogue HBG **2** (figure 1) have also demonstrated effective inhibition of herpes simplex virus (HSV) in cell cultures[2]. Sofar, the structure-activity studies have shown that the side chain of acyclonucleoside plays a main role in the antiviral activity (phosphorylation). However, the role of the nucleobase in the interaction between the acyclonucleoside and their antiviral target enzyme is yet unclear. Accordingly, many nucleoside chemists have directed their efforts toward the synthesis of analogues of ACV, HBG and other acyclonucleosides with various side chains and aglycons.

In order to determine the role of the modified nucleobase in the antiviral activity of ACV and HBG derivatives, we focused our attention on the replacement of guanine moiety by a series of 1,2,3-triazole substituted with groups that may be involved in the interaction of the ACV and HBG derivatives with the HSV thymidine kinase.

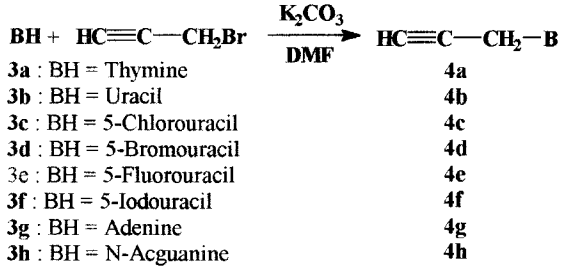
RESULTS AND DISCUSSION

For the synthesis of 1,2,3-triazole acyclonucleoside analogues of ACV and HBG, we employed the methodology of aglycon construction on the pseudo-sugar moiety using 1,3-dipolar cycloaddition. Thus, the reaction of heterocyclic bases **3a-h** with propargylbromide in the presence of potassium carbonate in



1 X = O Acyclovir
2 X = CH_2 HBG

Figure 1



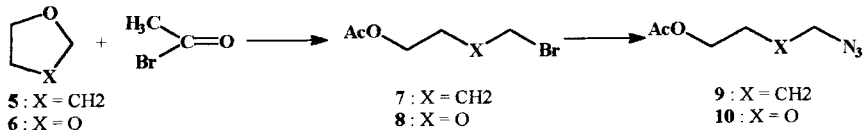
Scheme 1

DMF at room temperature for 4h to 24h gave the starting material N-1/N-9-propargylpyrimidine/purine **4a-g** (Scheme 1) in good yields[3].

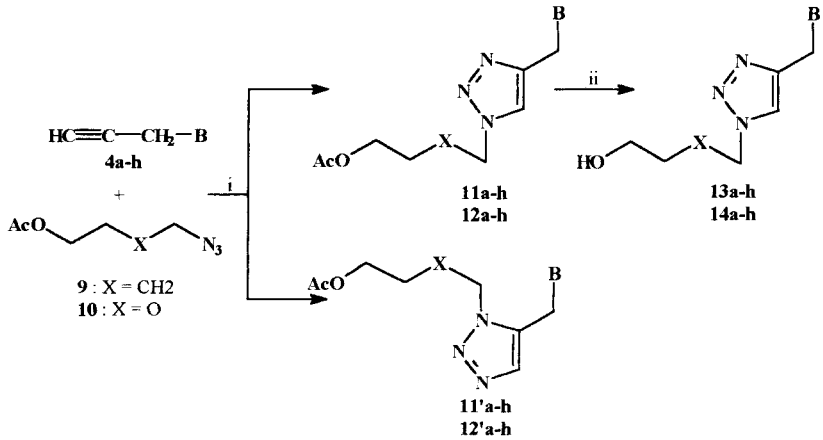
The second step of the synthesis was the preparation of the corresponding azido-compounds of acyclic portion that are found in ACV and HBG. Compounds **7** and **8** were reacted separately with sodium azide at 95 °C for 4h to give the corresponding azido-compounds **9** and **10** in high yields[4, 5] (Scheme 2).

The cycloaddition reaction of azido derivatives **9** (5 eq.) with N-9/N-1-propargylpurine/pyrimidine **4a-h** in dry toluene under reflux, afforded a mixture of two regioisomers **11a-h** and **11'a-h** (Scheme 3). The ratio of **11** / **11'** was determined from ^{1}H NMR spectra (Table 1). After separation on silica gel column chromatography, the only major isomers **11a-g** were obtained as pure products. It has been reported, that addition of azides to unsymetrical acetylenes is determined by steric and electronic factors. In general, such addition tends to give mainly the isomers with electron withdrawings groups at the 4-position and electron with releasing groups at the 5-position. On the other hand, the sterically less hindered isomers tends to be the major isomer[5-7].

Identical results were obtained in the case of **10** as azido-compound (Table 1). The structure of the two isomers were established by comparison of the chemical shift values for the triazole ring protons with those available from a known pair of 4-and 5-glycosyl-1,2,3-triazole derivatives[8-12]. In the case of the 4-substituted isomers **11** and **12** the signal of H5 proton appeared at lowerfield (8.2 ppm) than the signal of H4 proton (7.6 ppm) in the 5-substituted derivatives **11'** and **12'**.



Scheme 2



i = Toluene, reflux; ii = $MeOH/NH_3$.
a: B = Thymine, **b**: B = Uracil, **c**: B = 5-Chlorouracil, **d**: B = 5-Bromouracil, **e**: B = 5-Iodouracil, **f**: B = 5-Fluorouracil, **g**: B = Adenine, **h**: B = N-Acguanine.

Scheme 3

Table 1 : 1,3-dipolar cyloaddition of N-propargylpyrimidine/purine derivatives with azidoacyclic **9** and **10** :

substrate	azidoacyclic	equiv. of Azide	Reaction time (h)	yield %	Ratio **11/12***
4a	**9**	5	72	74	91/9
	10	5	72	67	89/11
4b	**9**	5	72	84	100
	10	5	72	75	84/16
4c	**9**	5	72	70	100
	10	5	72	57	100
4d	**9**	5	72	68	78/22
	10	5	72	52	86/14
4e	**9**	5	72	82	100
	10	5	72	80	67/23
4f	**9**	5	72	76	86/14
	10	5	72	73	91/9
4g	**9**	5	72	65	74/26
	10	5	72	79	70/30
4h	**9**	5	72	60	75/25
	10	5	72	69	75/25

* The ratio were determined from ^1H NMR spectra.

Treatment of the newly compounds **11a-h** and **12a-h** with ammonia in methanol at room temperature for 24h gave the corresponding deprotected products **13a-h** and **14a-h** in good yields (Scheme 3).

In conclusion, 1,3-dipolar cycloaddition has been used successfully to provide an easy entry into the 4- or 5-methylene-1,2,3-triazol-1-yl analogues of ACV and HBG. Extension of this methodology to the synthesis of other novel nucleosides or acyclonucleosides will be reported in due course.

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