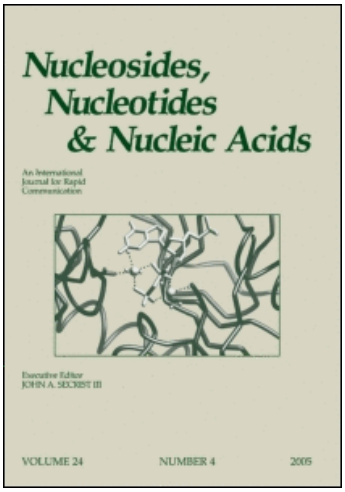

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SYNTHESIS OF SOME ACYCLONUCLEOSIDES α-(PYRAZOLO[3,4-d]PYRIMIDIN-4-YLTHIO)-ALKYLAMIDES

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ABSTRACT

The synthesis of some acyclic α-(pyrazolo[3,4-d]pyrimidin-4-ylthio)alkylamide nucleosides is described.

In the search for potent and selective chemotherapeutic agents, nucleosides and their derivatives are among the most widely explored types of compounds. The convenient general approach for their preparation involves the modification of the base and/or sugar residue of the nucleoside building blocks of desoxyribonucleic and ribonucleic acids (DNA and RNA respectively). Accordingly, the replacement of furanose ring by the appropriate pseudo-sugar moiety, e.g. (2-hydroxyethoxy)methyl, 4-hydroxybutyl or (2,3-dihydroxy-1-propoxy)methyl, is of particular interest since the resulting acyclovir (1) (ACV), HBG (2) or Iso-DHPG (3) (Fig. 1) have showed a potential anti-herpetic activity. In connection with our studies on acyclic nucleosides (4–6), we aimed through the synthesis of some acyclic α-(pyrazolo[3,4-d]pyrimidin-4-ylthio)alkylamide nucleosides (**14**–**16**)**a**-**c** (Fig. 1)

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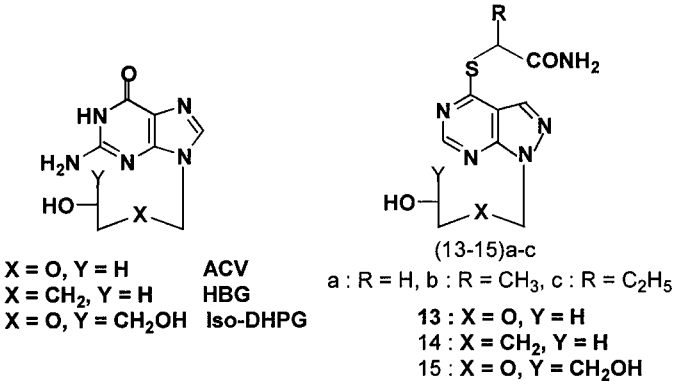


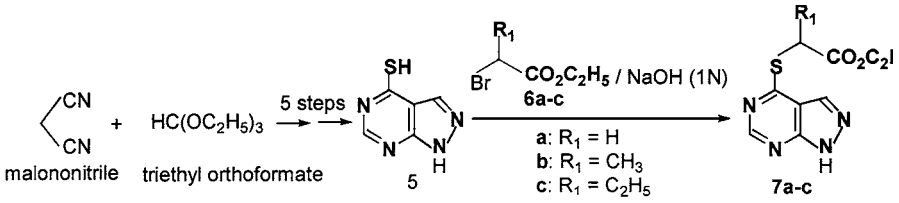
Figure 1.

in order to determine the biological activities of the resulting base-modified derivatives of acyclovir, HBG and Iso-DHPG.

The 4-mercaptopyrazolo[3,4-d]pyrimidine **5**, depicted in scheme 1, was prepared in five steps according to the literature procedure from malononitrile and triethyl orthoformate as starting materials (7,8). The C4 sulfur atom of the base was alkylated with ethyl bromoacetate **6a**, (DL)-ethyl-2-bromopropionate **6b** or (DL)-ethyl-2-bromobutyrate **6c** in a sodium hydroxide solution at room temperature to give α-(pyrazolo[3,4-d]pyrimidin-4-ylthio)ethylalkylates **7a-c**, in 85%, 83% and 82% yield, respectively.

Then the preparation of compounds (**11–13**)**a-c** (Scheme 2) was achieved using the same conditions previously described for the synthesis of the 4-substituted pyrazolo[3,4-d]pyrimidine N_1-acyclonucleosides (4–6). Thus, the alkylation of heterocycles **7a**, **7b** or **7c** with alkylating agents **8** (9), **9** (6,10), or **10** (4), using potassium carbonate as base and N,N-dimethylforamide (DMF) as solvent, afforded regioselectively the N_1-regioisomers (**11–13**)**a-c** in 89%, 80% and 80%, respectively. It was reported that N_2-nucleoside (acyclonucleoside) formation occurred during glycosylation (alkylation) of the pyrazolo[3,4-d]pyrimidines (4,11–15). In our case presumed N_2-regioisomers of (**11–13**)**a-c** were detected but not isolated.

Finally, the treatment of N1-protected acyclic nucleosides (**11–13**)**a-c** with methanol saturated with ammonia at room temperature gave the acyclic **nucleosides** (**14–16**)**a-c** (Scheme 2) in quantitative yield, through deprotection of the



Scheme 1.

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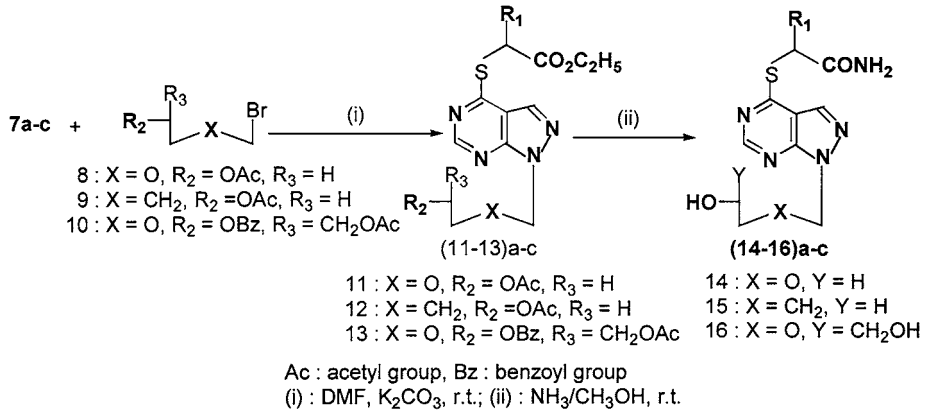

Scheme 2.

acetyl group and concomitant conversion of the ester into the amide moiety. All structures of the synthetic products were identified by ^{1}H-NMR, mass spectra, UV and elemental analysis.

Compounds (**14–16**)**a-c** were evaluated for their cytotoxycity and their inhibitory effect on HIV-1(III_B) and HIV-2(ROD) replication in MT-4 cells (16,17). No significant activity was found against the replication of HIV-1(III_B) and HIV-2(ROD) at subtoxic concentrations.

In conclusion, we have regioselectively synthesized some N1-acyclic α-(pyrazolo[3,4-d]pyrimidin-4-ylthio)alkylamide nucleosides with the alkyl chain of acyclovir, HBG and Iso-DHPG. They were characterized on the basis of their physical and spectroscopic properties. Their anti-tumor and anti-tuberculosis evaluations are in progress.

ACKNOWLEDGMENTS

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