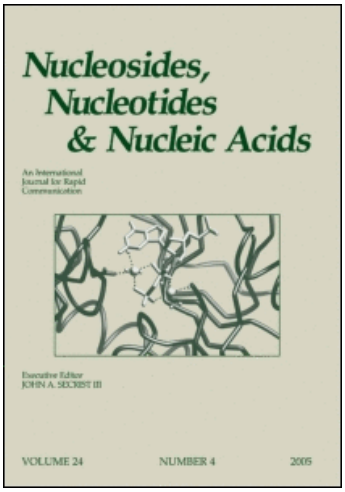

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Synthesis and Biological Activity of 5-Azacytosine Nucleosides Derived from 4-Thio-2-Deoxy-L-*threo*-Pentofuranose and 4-Thio-2-Deoxy-D-*erythro*-Pentofuranose

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 5-AZACYTOSINE NUCLEOSIDES DERIVED FROM 4-THIO-2-DEOXY-L-*threo*-PENTOFURANOSE AND 4-THIO-2-DEOXY-D-*erythro*-PENTOFURANOSE

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ABSTRACT: 1-*O*-Acetyl-2-deoxy-3,5-di-*O*-toluoyl-4-thio-D-*erythro*-pentofuranose and 2-deoxy-1,3,5-tri-*O*-acetyl-4-thio-L-*threo*-pentofuranose were coupled with 5-azacytosine to obtain α and β anomers of nucleosides.

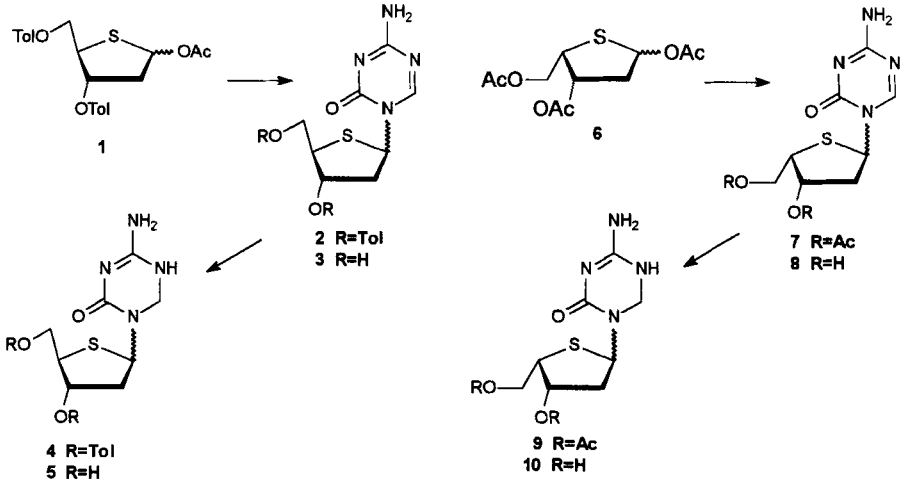
For some years we have been pursuing the synthesis of a variety of 4′-thionucleosides as anticancer and anti-infective agents. In that regard we have prepared 4′-thionucleosides with a variety of different carbohydrates attached to both the normal purine and pyrimidine bases as well as analogs of those bases.[1,2] One of our goals in this program is to gain a further understanding about the active site of deoxycytidine kinase, so that we are better able to prepare potential drugs that are activated by this enzyme.

As part of this program, we have prepared a series of 4′-thionucleosides incorporating both 5-azacytosine and 5,6-dihydro-5-azacytosine, in order to assess their anticancer activity, as well as to compare the saturated and unsaturated compounds in the same system. Specifically, we have prepared the α and β anomers of the nucleosides incorporating 5-azacytosine and 5,6-dihydro-5-azacytosine into 4-thio-2-deoxy-L-*threo*-pentofuranose and 4-thio-2-deoxy-D-*erythro*-pentofuranose. Chemical syntheses and biological data on these four compounds is presented.

The synthesis of 1-*O*-acetyl-2-deoxy-4-thio-3,5-di-*O*-p-toluoyl-D-*erythro*-pentofuranose **1** and 2-deoxy-1,3,5-*O*-acetyl-4-thio-L-*threo*-pentofuranose **6**, as 1:1 mixture of anomers have been performed as previously reported.[1]

Trimethylsilyl triflate catalyzed coupling of thiosugar **1** and **6** with silylated 5-azacytosine afforded the corresponding nucleosides (**2** and **7**) as anomeric mixtures (β:α

ratio ~ 1:1.8). Silica gel chromatography and fractional crystallization of **2** and **7** afforded pure anomers.



Reduction with sodium borohydride of compounds **2α**, **2β**, **7α**, **7β**, afforded **4α**, **4β**, **9α**, **9β**, respectively. Deprotection of compounds **2α**, **2β**, **4α**, **4β**, **7α**, **7β**, **9α**, **9β**, with sodium methoxide afforded **3α**, **3β**, **5α**, **5β**, **8α**, **8β**, **10α**, **10β**, respectively.

The assignment of the anomeric configurations of compounds were made by NOE difference spectroscopy. Only 2′-deoxy-4′-thio-5-azacytosine (**3β**) showed significant toxicity, as shown in Table 1. All the 2′-deoxy-4′-thiopyrimidine nucleoside analogues were evaluated against Hepatitis B virus (HBV) *in vitro* and no significant antiviral activity was observed.

Table 1. Cytotoxicity Data: IC50 (μM)

Compound	CCRF-CEM (leukemia)	CAKI-1 (renal)	DLD-1 (colon)	NCI-H23 (lung)	SNB-7 (CNS)
3β	0.001	0.4	7	4	9

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