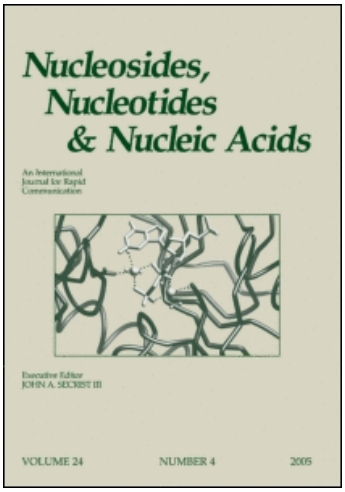

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Synthesis and Biological Activity of 4'-Thio-2'-deoxy Purine Nucleosides

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 4'-THIO-2'-DEOXY PURINE NUCLEOSIDES

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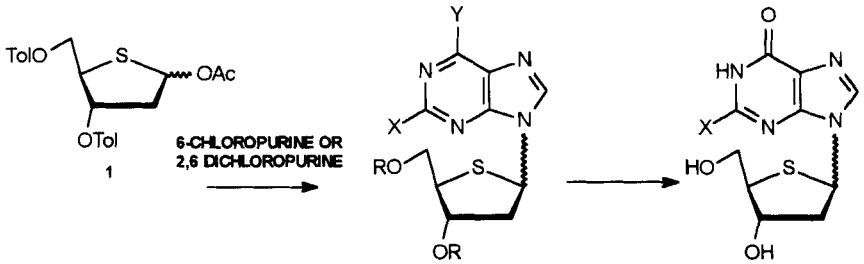
ABSTRACT: Coupling of 1-*O*-acetyl-2-deoxy-3,5-di-*O*-toluoyl-4-thio-D-ribofuranose with 6-chloropurine and 2,6-dichloropurine gave a mixture of 9α and 9β anomers as major products. These anomers were separated and converted to 2'-deoxy-4'-thio analogues of adenosine, inosine, guanosine, 2-amino-adenosine, and 2-chloro adenosine as well as their α-anomers.

Some years ago we reported our initial efforts on the synthesis of 2'-deoxy-4'-thio purine nucleosides. In that work, we found that formation of the α anomer was strongly favored (1β:9α), making the preparation of significant amounts of desired β nucleosides difficult. Herein we present a new coupling method for the synthesis of 2'-deoxy-4'-thio purine nucleosides, one that allows us to obtain reasonable quantities of both α and β anomers of the target nucleosides, which we then evaluated for their anticancer activity.[2]



2 R=Tol; X=H; Y=Cl
3 R=H; X=H; Y=NH_2
4 R=Tol; X,Y=Cl
5 R=H; Y=NH_2; X=Cl
6 R=Tol; X,Y=N_3
7 R=Tol; X,Y=NH_2
8 R=H; X,Y=NH_2

9 X=H
10 X=NH_2

Coupling of sugar **1** with 6-chloropurine was carried out using a mixture of $SnCl_4$ and TMSOTf in the following manner. In a typical experiment, to sugar **1** (1.1 mmol) and 6-chloropurine (1.37 mmol) in 20 mL of CH_2Cl_2 was added consecutively HMDS (1.3

mmol), TMSCl (3.77 mmol). The resulting mixture was stirred at R.T. for 0.5 h and then cooled to 0°C; TMSOTf (0.65 mmol) was added and the reaction mixture was stirred for 1 h at 0°C; then CH_3CN (20 mL) and $SnCl_4$ (0.65 mmol) were added to it. The reaction mixture was stirred at R.T. for 2 h and concentrated at reduced pressure. After standard work-up and flash chromatography (silica gel) **2α** and **2β** were obtained in 55% yield with a ratio of **2α:2β** (7:3). Treatment of **2α** and **2β** with ethanolic ammonia at 130°C in a bomb for 12 h gave compounds **3α** and **3β** respectively, which were purified on an XAD-4 resin column. Similarly, coupling of sugar **1** with 2,6-dichloropurine using the method described for 6-chloropurine gave **4α** and **4β** in 66% total yield (α:β ratio 7:3). Compounds **4α** and **4β** were treated with ethanolic ammonia at 130°C for 24 h in a pressure bomb to produce **5α** and **5β** respectively in approximately 85% yields. Compound **5β** was similar to the authentic sample made earlier in our laboratory by an alternative route.[3] Compounds **4α** and **4β** were converted to diazido compounds **6α** and **6β** using sodium azide in 95% ethanol in quantitative yields, which upon reaction with $SnCl_2$ in $MeOH:CH_2Cl_2$ (98:2) gave **7α** and **7β** respectively in about 80% yield after purification. Both **7α** and **7β** were deblocked with NaOMe in MeOH at R.T. for 6 h and after purification on an XAD-4 resin column[4] gave **8α** (85% yield) and **8β** (79% yield). Compound **3β** and **8β** upon treatment with adenosine deaminase at R.T. 16 h gave after purification **9β** (75% yield) and **10β** (80% yield) respectively. Compound **10β** has similar spectral data as reported earlier.[4] Similarly, **3α** and **8α** were converted to **9α** and **10α** (65% yield) respectively by adenosine deaminase at 37°C for 14 days. All the compounds were characterized by mass spectra, ^1H and ^{13}C NMR, UV spectra, and elemental analysis. Anomeric configuration and point of attachment of sugars to purines were derived from NOE experiments on compounds **2α**, **2β** and **5α**, **5β**.

The cell culture cytotoxicity of all ten target compounds was determined against four different human cell lines. Significant cytotoxicity was seen with **5β**, the 2-chloroadenine analog with the β configuration, as reported earlier.[3] This compound did not show any significant inhibition of tumor growth at the maximum tolerated doses using the murine colon 36 animal model.

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2. We wish to thank Prof. Grahame Mackenzie of the University of Hull for sharing with us several years ago a procedure from his laboratory those resulted in a β/α ratio comparable to that reported herein. His procedure employed a carbohydrate similar to **1** (with benzoyl groups at *O*-3 and *O*-5), used an excess of trimethylsilyl triflate, and was successful with 6-chloropurine. We were forced to search for an alternate method when that procedure did not work satisfactorily with 2,6-dichloropurine.

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