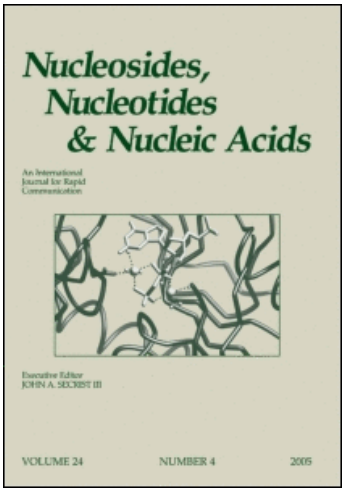

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Synthesis and Antitumor Activity of *N*-Sulfonyl Derivatives of Nucleobases and Sulfonamido Nucleoside Derivatives

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ABSTRACT

The introduction of sulfonamido group on the C-2 position of pyrimidine nucleosides was achieved by ring opening of 2,2′- and 2,3′-anhydronucleosides. *N*-sulfonyl derivatives of nucleobases and sulfonamido derivatives of nucleosides were assayed for in vitro antitumor activity.

Key Words: Anhydronucleosides; C-2 sulfonamido pyrimidine nucleosides; In vitro antitumor activity.

We have designed and synthesized *N*-sulfonyl derivatives of pyrimidine bases **I** as a new type of sulfonylcycloureas.[1] The compounds showed potent growth inhibitory activity (25–75%) against human tumor cell lines in vitro, at concentrations of $10^{-8} - 10^{-5}$ M and some of them showed the ability to induce apoptosis in treated tumor cells.[2] These results directed our interest toward *N*-sulfonyl

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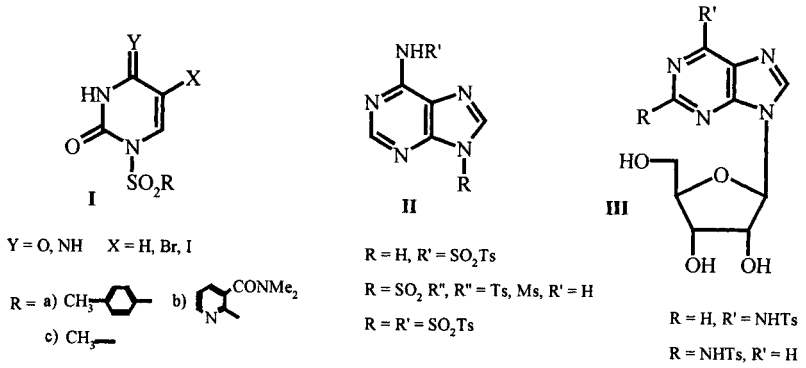
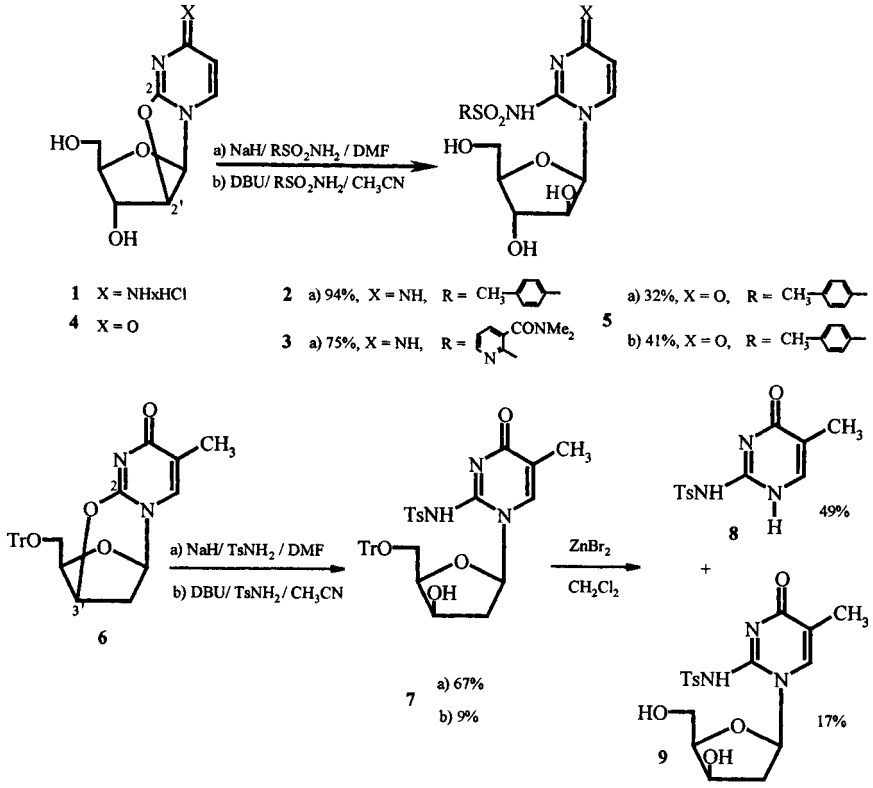


Figure 1.

derivatives of purine bases **II** and sulfonamido derivatives of purine nucleosides **III** (Fig. 1).[3]

The introduction of sulfonamido group on the C-2 position of pyrimidine nucleosides was achieved by ring opening of 2,2′- and 2,3′-anhydronucleosides with selected sulfonamide anion as nucleophile (Sch. 1).



Scheme 1.

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In the reaction of 2,2′-anhydrocytidine hydrochloride **1** with Na-salt of *p*-toluenesulfonamide, at room temperature, 4-imino-*N*2-tosylamino-1-(β-D-arabinofuranosyl) pyrimidine **2** was isolated in 94% yield. Pyridinesulfonamido derivative of araC **3**, was synthesized in the same way (75% yield) using 2-(aminosulfonyl)-*N,N*-dimethylnicotinamide as nucleophile.

Introduction of sulfonamido substituent on less reactive 2,2′-anhydrouridine **4** and 2,3′-anhydrothymidine **6** needs vigorous conditions (concentrated solutions and heating at 100–110°C, 1–4 days) and gave reasonable yields, 41% for **5** and 67% for **7**. These two anhydronucleosides does not react with weaker nucleophile such as 2-(aminosulfonyl)-*N,N*-dimethylnicotinamide. The action of acetic acid or $ZnBr_2/CH_2Cl_2$ on the 2-sulfonamido derivative **7** leads to the cleavage of both the protection group and the nucleoside bond.

The prepared derivatives were evaluated for their in vitro cytostatic activity against different human tumor cell lines (CaCo2, SW620, HT-29, HeLa2, and MIA-PACa2; MTT assay).

In comparison with 5-fluorouracil some of *N*-sulfonylpyrimidine derivatives **I** showed 10 times stronger activity and some of them showed the ability to induce apoptosis in treated tumor cells.

The *N*-sulfonylpurine and sulfonamido nucleoside derivatives showed lower activity.

REFERENCES

1. a) Kašnar, B.; Krizmanić, I.; Žinić, M. Synthesis of the sulfonylpyrimidine derivatives as a new type of sulfonylcycloureas. Nucleosides & Nucleotides **1997**, *16*, 1067–1071; b) Žinić, B.; Krizmanić, I.; Vikić-Topić, D.; Žinić, M. 5-Bromo- and 5-Iodo-N-1-sulfonylated cytosine derivatives. Exclusive formation of keto-imino tautomers. Croat. Chem. Acta **1999**, *72*, 957–966.
2. Glavaš-Obrovac, Lj.; Karner, I.; Žinić, B.; Pavelić, K. Antineoplastic activity of novel N-1-sulfonylpyrimidine derivatives. Anticancer Res. **2001**, *21*, 1979–1986.
3. Žinić, B.; Krizmanić, I.; Vikić-Topić, D.; Srzić, D.; Žinić, M. Synthesis, NMR and MS study of novel N-sulfonylated purine derivatives. Croat. Chem. Acta. **2001**, *74*, 399–414.

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