

This article was downloaded by:

On: 26 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

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

B. Žinić^a; I. Krizmanić^b; Lj. Glavaš-Obrovac^c; I. Karner^c; M. Žinić^a

^a Ruder Bošković Institute, Zagreb, Croatia ^b HERBOS Chem. Industry, Sisak, Croatia ^c Clinical Hospital Osijek, Osijek, Croatia

Online publication date: 09 August 2003

To cite this Article Žinić, B. , Krizmanić, I. , Glavaš-Obrovac, Lj. , Karner, I. and Žinić, M.(2003) 'Synthesis and Antitumor Activity of *N*-Sulfonyl Derivatives of Nucleobases and Sulfonamido Nucleoside Derivatives', *Nucleosides, Nucleotides and Nucleic Acids*, 22: 5, 1623 – 1625

To link to this Article: DOI: 10.1081/NCN-120023084

URL: <http://dx.doi.org/10.1081/NCN-120023084>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

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

B. Žinić,^{1,*} I. Krizmanić,² Lj. Glavaš-Obrovac,³
I. Karner,³ and M. Žinić¹

¹Ruder Bošković Institute, Zagreb, Croatia

²HERBOS Chem. Industry, Sisak, Croatia

³Clinical Hospital Osijek, Osijek, Croatia

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

*Correspondence: B. Žinić, Ruder Bošković Institute, Bijenička 54, 10 000 Zagreb, Croatia;
Fax: +1 313 832 7294; E-mail: bzinic@rudjer.irb.hr.



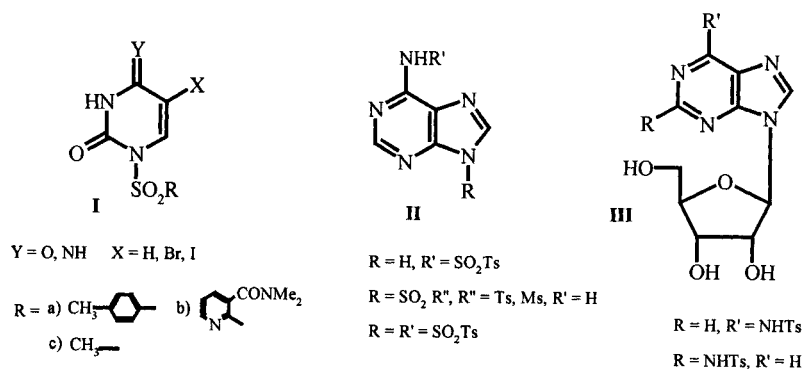
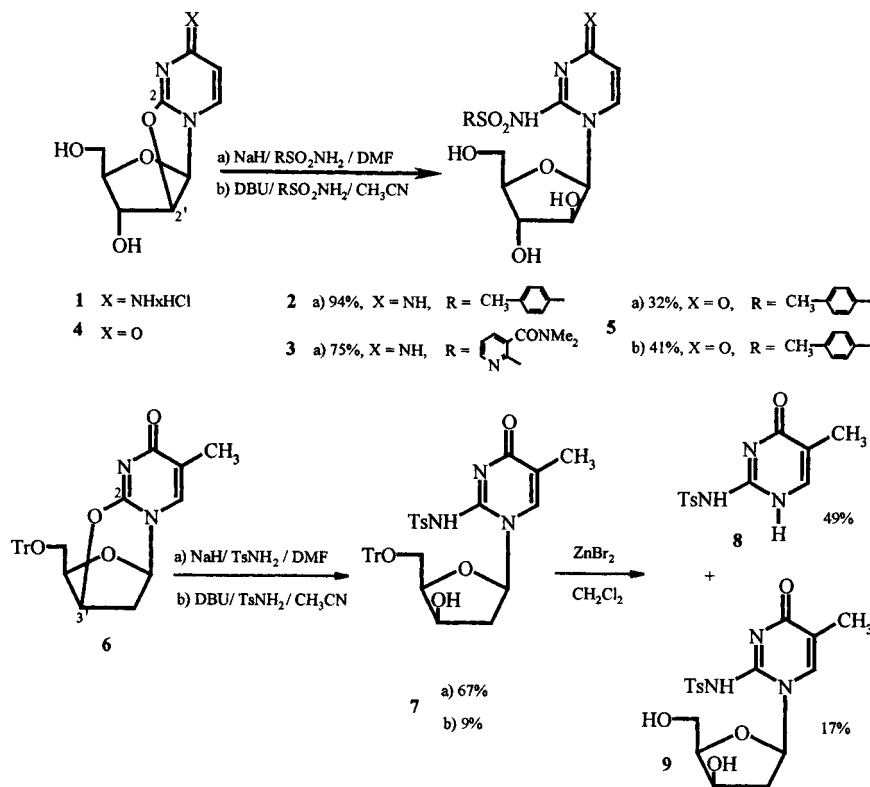


Figure 1.

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.

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 $\text{ZnBr}_2/\text{CH}_2\text{Cl}_2$ 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*-sulfonylpyrimidine 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.



