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# Nucleosides and Nucleotides

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lncn19

# Synthesis and Biological Activities of 2'-Modified 4'-Thionucleosides

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To cite this article: Yuichi Yoshimura , Kenji Kitano , Mikari Watanabe , Hiroshi Satoh , Shinji Sakata , Shinji Miura , Noriyuki Ashida , Haruhiko Machida & Akira Matsuda (1997) Synthesis and Biological Activities of 2'-Modified 4'-Thionucleosides, Nucleosides and Nucleotides, 16:7-9, 1103-1106, DOI: <u>10.1080/07328319708006142</u>

To link to this article: http://dx.doi.org/10.1080/07328319708006142

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#### SYNTHESIS AND BIOLOGICAL ACTIVITIES OF 2'-MODIFIED 4'-THIONUCLEOSIDES

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**ABSTRACT:** We have synthesized 4'-thioDMDC, 4'-thiogemcitabine, and 4'-thioarabinonucleosides, as potential antitumor and antiviral agents, originated from D-glucose. Biological activities of these compounds are also described.

Nucleoside antimetabolites play an important role in the field of chemotherapy for cancer and viral diseases. Finding of inhibitory activity of 3'-azidothymidine<sup>1</sup> (AZT, 1) against human immunodeficiency virus (HIV), a causative agent of acquired immunodeficiency syndrome (AIDS), further stimulates to synthesize various nucleoside analogues. Among such analogues, some sulfur containing nucleosides, 3'-thiacytidine (3TC, 2)<sup>2</sup> and 2'-deoxy-4'-thionucleosides 3,<sup>3</sup> are noteworthy. The former is a potent



anti-HIV agent and has recently been approved as a drug in US and other countries. The latter is considered as a new class of anti-herpesviral agents. We focused on unique biological activities of 4'-thionucleosides and envisaged to synthesize the 2'-modified derivatives 6-8, since some 2'-substituted nucleosides, e.g., DMDC 4<sup>4</sup> and gemcitabine 5,<sup>5</sup> have been known as promising antitumor agents. However, the classical methods for the preparation of 4'-thionucleosides were not practical,<sup>6</sup> thus, we planed to develop an

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alternative method. Here, we report a novel synthesis of potential antineoplastic and antiviral 2'-modified 4'-thionucleosides, started from D-glucose.<sup>7</sup>

Methyl 3-O-benzylxylofuranoside 9, readily derived from diisopropylideneglucose in 5 steps, was converted to a 1,4-anhydro-4-thioarabitol 12 in a 66 % yield (4 steps). (Scheme 1)

Protection of the primary alcohol of **12**, followed by oxidation, gave a 2-keto derivative **13**. The Wittig reaction or DAST treatment of **13** produced 2-deoxy-2-methylene (**14**, 74%) and 2-deoxy-2,2-difluoro (**16**, 48%) derivatives , respectively.

After transformation of 3'-protecting group, unique Pummerer type glycosylation between the corresponding sulfoxides and silylated acetylcytosine, followed by deprotection, produced 4'-thioDMDC 6 ( $\alpha$  :  $\beta$  = 2.5 : 1) and 4'-thiogemeitabine 7 ( $\alpha$  :  $\beta$  = 2.5 : 1). (Scheme 2) 4'-ThioDMDC was found to have potent antineoplastic activities *in vitro* (CCRF-HSB-2, IC<sub>50</sub> = 0.0091 µg/mL; KB cells, IC<sub>50</sub> = 0.12 µg/mL) and also





Table 1: Antiviral Activities of 4'-Thioarabinonucleosides

No	в	Antiviral Activities ED <sub>50</sub> (μg/ml)			Cytotoxicity IC <sub>50</sub> (μg/ml)	
		HSV-1 <sup>a,e</sup>	HSV-2 <sup>b,e</sup>	VZV <sup>c,e</sup>	HCMV <sup>d,e</sup>	CCRF-HSB-2f
8a	Thy	0.77	4.6	6.6	44	>100
8b	5-Et-Ura	0.43	6.5	>50	>50	>100
8c	5-BV-Ura	0.82	58	0.20	>50	>100
8d	Ade	18.4	13.5	1.85	1.36	14.8
8e	2,6-DAP	0.52	0.40	0.11	0.022	0.20
	BVaraU	0.036	62	0.0013	>50	>100
	Acyclovir	0.14	0.23	2.7	6.9	>100
	DHPG	0.016	0.039	0.21	0.21	17.0

<sup>a</sup>HSV-1 VR-3 strain, <sup>b</sup>HSV-2 MS strain, <sup>c</sup>VZV Oka strain, <sup>d</sup>HCMV AD 169 strain,

<sup>e</sup>plaque reduction assay, <sup>f</sup>MTT assay

showed antileukemic effect in mice bearing P388 leukemia (T/C = 133; 10 mg/kg/day × 4). On the other hand, 4'-thiogemcitabine only showed marginal activity against CCRF-HSB-2 (IC<sub>50</sub> =  $1.5 \mu$ g/mL).

The intermediate 1,4-anhydro-4-thioarabitol **12** was subjected to the Pummerer rearrangement after the free hydroxyl groups were benzylated. The obtained 1-O-acetyl-4-thioarabinose **18** was condensed with 5-substituted uracils and purines, followed by deprotection and HPLC purification, to furnish the corresponding 4'-thioarabino-nucleosides **8a-e**. (Scheme 3)

The separated  $\beta$ -isomers of 4'-thioarabinonucleosides showed potent antiviral activities ; 4'-thioaraT **8a** and 5-ethyl-4'-thioaraU **8b** showed anti-HSV-1 and HSV-2 activities, but the latter did not have any activity against VZV. (*E*)-5-Bromovinyl-4'-thioaraU **8c** revealed anti-HSV-1 and VZV activity. 2,6-Diaminopurine derivative **8e** exhibited antiherpesviral activity, particularly against HCMV, although **8e** had relatively high cytotoxicity. (Table 1).

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