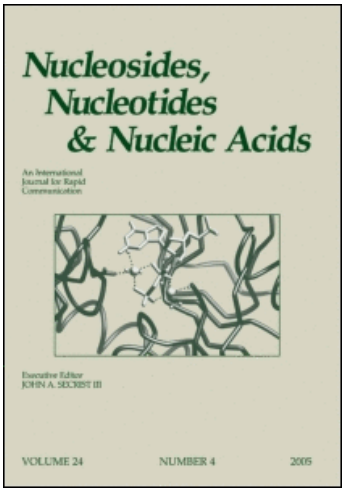

Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:
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To cite this Article Yoshimura, Yuichi , Kitano, Kenji , Watanabe, Mikari , Satoh, Hiroshi , Sakata, Shinji , Miura, Shinji , Ashida, Noriyuki , Machida, Haruhiko and Matsuda, Akira(1997) 'Synthesis and Biological Activities of 2'-Modified 4'-Thionucleosides', Nucleosides, Nucleotides and Nucleic Acids, 16: 7, 1103 — 1106

To link to this Article: DOI: 10.1080/07328319708006142

URL: http://dx.doi.org/10.1080/07328319708006142

NUCLEOSIDES & NUCLEOTIDES, 16(7-9), 1103-1106 (1997)

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

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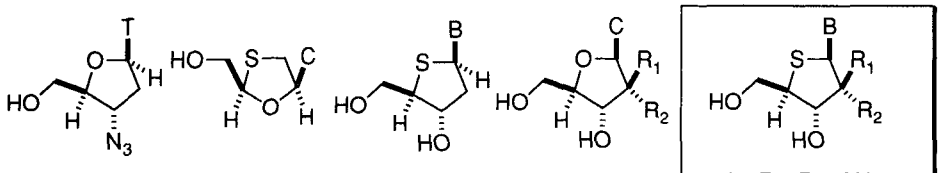
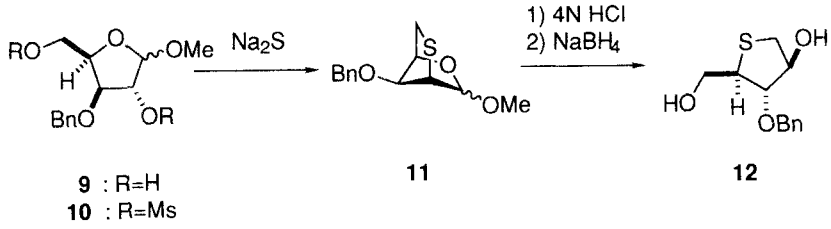
ABSTRACT: We have synthesized 4'-thioDMDC, 4'-thiogemcitabine, and 4'-thioarabinonucleosides, as potential antitumor and antiviral agents, originated from D-glucose. Biological activities of these compounds are also described.

Nucleoside antimetabolites play an important role in the field of chemotherapy for cancer and viral diseases. Finding of inhibitory activity of 3'-azidothymidine[1] (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**)[2] and 2'-deoxy-4'-thionucleosides **3**,[3] are noteworthy. The former is a potent



1 **2** **3** **4** : $R_1=R_2=CH_2$ **5** : $R_1=R_2=F$ **6** : $R_1=R_2=CH_2$ **7** : $R_1=R_2=F$ **8** : $R_1=OH$, $R_2=H$

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**[4] and gemcitabine **5**,[5] have been known as promising antitumor agents. However, the classical methods for the preparation of 4'-thionucleosides were not practical,[6] thus, we planed to develop an

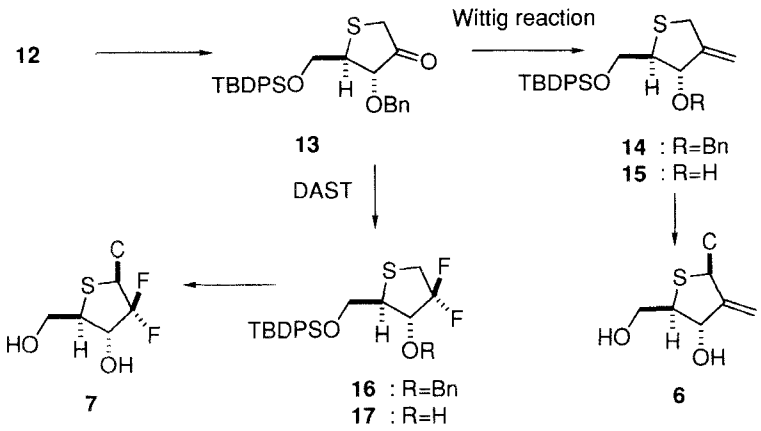


9 : R=H
10 : R=Ms

11

12

Scheme 1



13

14 : R=Bn
15 : R=H

16 : R=Bn
17 : R=H

7

6

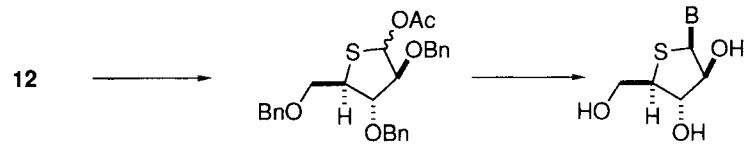
Scheme 2

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

Methyl 3-*O*-benzylxylofuranoside **9**, readily derived from diisopropylidene-glucose 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'-thiogemcitabine **7** ($\alpha : \beta = 2.5 : 1$). (Scheme 2) 4'-ThioDMDC was found to have potent antineoplastic activities *in vitro* (CCRF-HSB-2 , IC_{50} = 0.0091 μg/mL; KB cells , IC_{50} = 0.12 μg/mL) and also



8a : B = Thy
8b : B = 5-Et-Ura
8c : B = 5-BV-Ura
8d : B = Ade
8e : B = 2,6-diaminopurine

Scheme 3

Table 1: Antiviral Activities of 4'-Thioarabinonucleosides

No	B	Antiviral Activities ED_{50} (μg/ml)				Cytotoxicity IC_{50} (μg/ml)
		HSV-1[a,e]	HSV-2[b,e]	VZV[c,e]	HCMV[d,e]	CCRF-HSB-2[f]
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

[a]HSV-1 VR-3 strain, [b]HSV-2 MS strain, [c]VZV Oka strain, [d]HCMV AD 169 strain, [e]plaque reduction assay, [f]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_{50} = 1.5 μg/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 β-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 anti-herpesviral activity, particularly against HCMV, although **8e** had relatively high cytotoxicity. (Table 1).

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