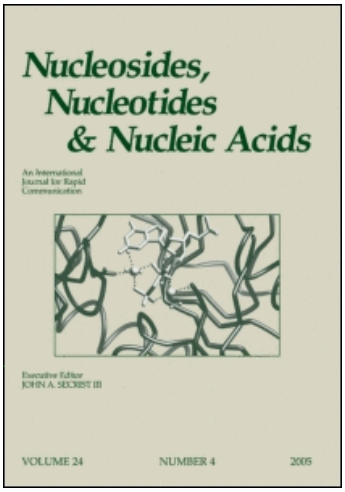

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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Online publication date: 09 August 2003

To cite this Article Kohgo, Satoru , Yamada, Kohei , Kitano, Kenji , Sakata, Shinji , Hayakawa, Hiroyuki , Nameki, Daisuke , Kodama, Eiichi , Matsuoka, Masao , Mitsuya, Hiroaki and Ohrui, Hiroshi(2003) 'Synthesis of 4'-*C*-Ethynyl and 4'-*C*-Cyano Purine Nucleosides from Natural Nucleosides and Their Anti-HIV Activity', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 887 — 889
To link to this Article: DOI: 10.1081/NCN-120022678
URL: http://dx.doi.org/10.1081/NCN-120022678

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 887–889, 2003

Synthesis of 4′-*C*-Ethynyl and 4′-*C*-Cyano Purine Nucleosides from Natural Nucleosides and Their Anti-HIV Activity

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ABSTRACT

Purine 2′-deoxynucleosides bearing an ethynyl or a cyano group at *C*-4′ of the sugar moiety were synthesized from the corresponding 2′-deoxynucleosides. These compounds exhibited very potent anti-HIV activity, and remained active against drug resistant HIV strains.

Key Words: 4′-*C*-Substituted nucleosides; Drug-resistant HIV; Anti-HIV activitiy.

From structure-activity relationship studies of series of 4′-*C*-substituted nucleosides,[1,2] we expected that purine 2′-deoxynucleosides bearing a smaller substituent

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DOI: 10.1081/NCN-120022678
1525-7770 (Print); 1532-2335 (Online)
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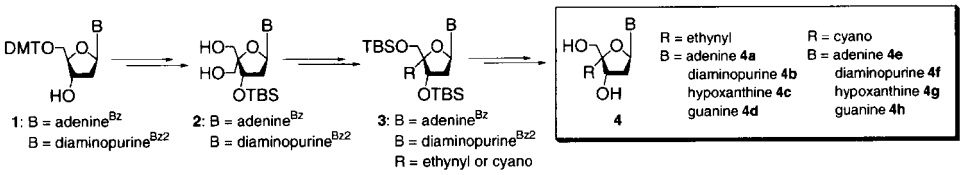

Scheme 1.

like an ethynyl or a cyano groups at *C*-4′ position would show more acceptable biological activity. However, preparation of 4′-*C*-cyano nucleosides by our previous method,[1] condensation of sugars with bases, is difficult as 4-*C*-cyano sugars have low reactivity. This problem encouraged us to develop a method for the preparation of 4′-*C*-substituted nucleosides from the corresponding nucleosides. In this report, we describe the synthesis of purine 2′-deoxynucleosides bearing an ethynyl or a cyano group at *C*-4′ position, and their anti-HIV activity.

4′-*C*-Hydroxymethyl nucleosides **2** were synthesized from 5′-*O*-dimethoxytrityl nucleosides **1** which were readily obtained from the corresponding nucleosides. After protection of the 5′-hydroxyl group of **2** in 3 steps, their 4′-*C*-hydroxymethyl group was converted to an ethynyl or a cyano group to afford compounds **3**. Target compounds **4** were obtained by deprotection and following enzymatic deamination of **3** (Sch. 1).

2,6-Diaminopurine and guanine derivatives showed remarkable cytotoxicity as well as very potent anti-HIV activity for both series, the 4′-*C*-ethynyl and 4′-*C*-cyano derivatives. While the adenine and hypoxanthine derivatives also showed potent

Table 1. Antiviral activity of 4′-*C*-substituted nucleosides against HIV and its drug resistant strains.

	MTT assay		MAGI assay[3]		
	HIV-1_{LAI}		HIV-1_{HXB2}	HIV-1_{MDR}[a]	HIV-1_{M184V}[a]
Compound no.	EC_{50} (μM)	IC_{50} (μM)	EC_{50} (μM)	EC_{50} (μM)	EC_{50} (μM)
4a	0.0098	16	0.008	0.0062	0.047
4b	0.00034	0.9	0.0014	0.001	0.0059
4c	0.13	137	0.81	0.51	16.6
4d	0.0015	1.4	0.007	0.0048	0.008
4e	0.137	10	0.043	0.083	2.28
4f	<0.03	<0.03	N.D.	N.D.	N.D.
4g	0.0278	23	0.242	0.296	6.06
4h	<0.03	<0.03	N.D.	N.D.	N.D.
AZT	0.0032	29.4	0.022	15.3	0.01
3TC	N.D.	N.D.	0.71	1.1	>100

[a]HIV-1_{MDR} and HIV-1_{M184V} strains show high levels of resistance against four nucleoside analogues (AZT, ddI, ddC and d4T) and 3TC, respectively.

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anti-HIV activity, their cytotoxicity was moderate compared with previous compounds. All derivatives displayed activity against drug resistant HIV strains (Table 1). Further investigations are in progress.

ACKNOWLEDGMENT

The authors are grateful to Dr. K. Kodama of Yamasa Corporation for his encouragement throughout this work.

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