

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 BIOLOGICAL ACTIVITY OF 4'-THIO-L-XYLOFURANOSYL NUCLEOSIDES

Kamal N. Tiwari^a; Lea Messini^a; John A. Montgomery^a; John A. Secrist III^a

^a Southern Research Institute, Birmingham, Alabama, U.S.A.

Online publication date: 31 March 2001

To cite this Article Tiwari, Kamal N. , Messini, Lea , Montgomery, John A. and Secrist III, John A.(2001) 'SYNTHESIS AND BIOLOGICAL ACTIVITY OF 4'-THIO-L-XYLOFURANOSYL NUCLEOSIDES', *Nucleosides, Nucleotides and Nucleic Acids*, 20: 4, 743 – 746

To link to this Article: DOI: 10.1081/NCN-100002420

URL: <http://dx.doi.org/10.1081/NCN-100002420>

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 BIOLOGICAL ACTIVITY OF 4'-THIO-L-XYLOFURANOSYL NUCLEOSIDES

Kamal N. Tiwari, Lea Messini, John A. Montgomery,
and John A. Secrist III*

Southern Research Institute, P.O. Box 55305,
Birmingham, Alabama 35255-5305

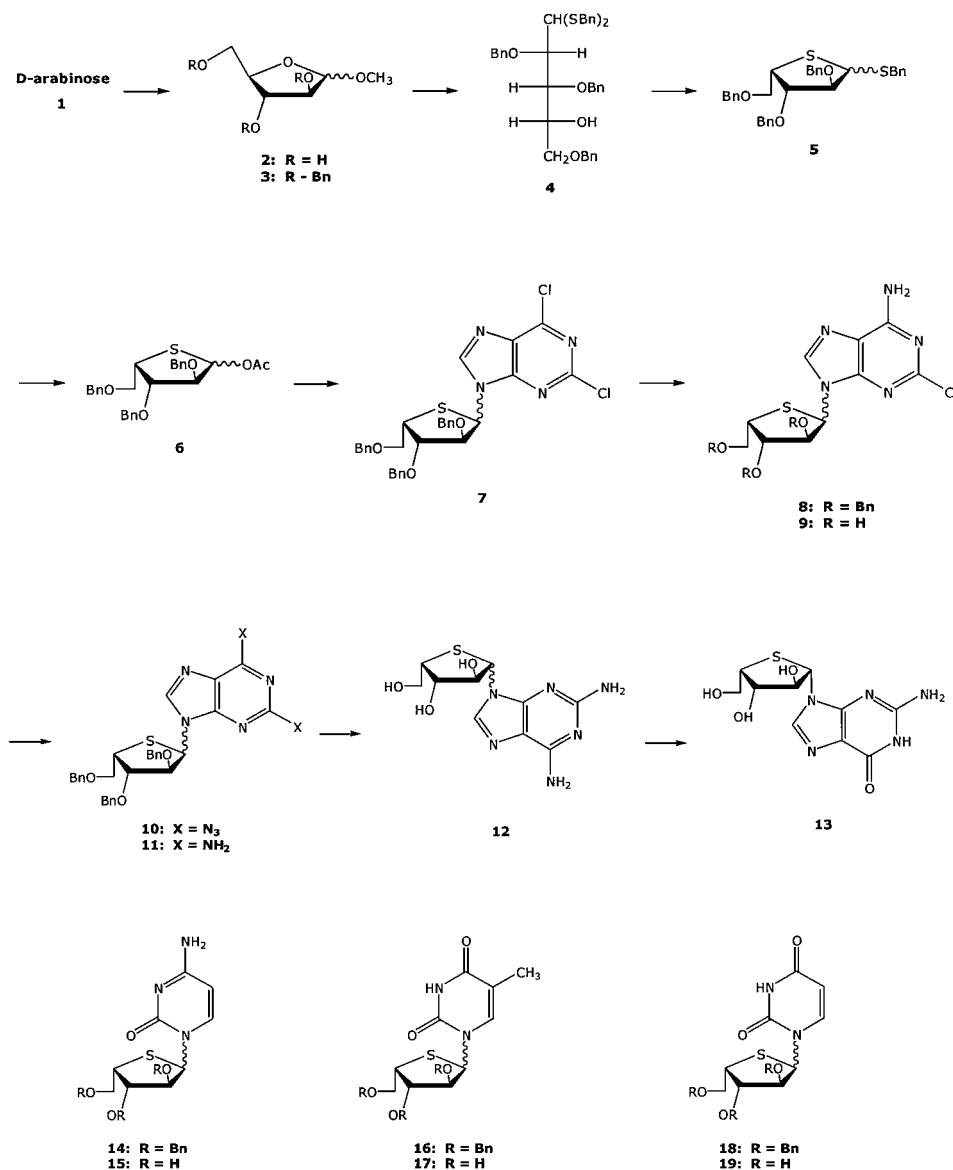
ABSTRACT

A series of 4'-thio-L-xylofuranosyl nucleosides were prepared and evaluated as potential anticancer and antiviral agents. The details of a convenient and high-yielding synthesis of the carbohydrate precursor 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-4-thio-L-xylofuranose (**6**) are presented. Proof of structure and configuration at all chiral centers of the nucleosides was obtained by proton and carbon NMR. All target compounds were evaluated in a series of human cancer cell lines in culture and as antiviral agents.

As a part of research in our laboratories to develop novel anticancer and antiviral agents we have been pursuing the synthesis of 4'-thionucleosides for the past several years (1–8). Based upon the significant activity in animals from certain arabinoside and 2'-deoxy thionucleosides (1,7,8), we have prepared a series of new purine and pyrimidine 4'-thio-L-xylofuranosyl nucleosides. All the sugar intermediates and the corresponding nucleosides have been characterized and the anomeric configuration was determined by PMR.

Our goal in this L-xylofuranose series, as with other 4'-thionucleoside analogs, was to prepare a series of compounds that included natural and modified purines and pyrimidines, chosen on the basis of biological evaluations within the series and biological information from our laboratories and others suggesting compounds with

*Corresponding author.



Scheme.

desirable properties. We have developed a five step sequence to the key intermediate **6**. Conversion of D-arabinose to methyl 2,3,5-tri-O-benzyl-D-arabinofuranoside (**3**) was accomplished in two steps by the usual method. Conversion to dibenzyl dithioacetal **4** employing benzyl mercaptan and stannic chloride proceeded in 63% yield after chromatographic purification. Cyclization at C-4 involving a single inversion, thus converting the D-arabino to the L-xylo configuration, was



accomplished employing triphenylphosphine, iodine, and imidazole in 72% yield. The final step, replacement of the benzylthio group at C-1 by an acetoxy group, involved treatment of **5** with mercuric acetate in acetic acid at room temperature. The overall yield of **6** from **1**, including four column purifications, was 32%, and afforded a *ca.* 1:1 mixture of α , β anomers.

A series of purine nucleoside analogs was prepared through the coupling of **6** and 2,6-dichloropurine. A Lewis acid catalyzed reaction utilizing stannic chloride (**6**) in acetonitrile was found to be an efficient method to achieve this coupling, and 30 and 25% yields of α and β anomers of **7** were obtained after chromatographic purification/separation. After treatment with ethanolic ammonia to produce the respective blocked 2-chloroadenine nucleosides **8 α** and **8 β** , removal of the *O*-benzyl groups was accomplished with boron trichloride in dichloromethane at -50°C to yield the final nucleoside targets **9 α** (55%) and **9 β** (45%). Treatment of **7 α** and **7 β** with sodium azide in 95% aqueous ethanol at reflux produced the corresponding 2,6-diazido intermediates **10 α** and **10 β** , which were subjected to reduction with stannous chloride in dichloromethane to afford the blocked diaminopurine nucleosides **11 α** (80%) and **11 β** (82%). Deblocking of **11 α** and **11 β** with boron trichloride in dichloromethane produced the target diamino nucleoside **12 α** (71%) and **12 β** (75%). The conversion of **12 β** to the corresponding guanine nucleoside **13** (45%) was accomplished by treatment with adenosine deaminase under standard conditions. Though the deamination was slow, it went to completion at room temperature in 72 hours. Cytosine, Thymine and Uracil were coupled (**8**) with thiosugar **5** to afford **14 α** (31%), **14 β** (30%), **16 $\alpha\beta$** (60%) and **18 $\alpha\beta$** (70%) respectively which were deblocked by boron trichloride to give the desired nucleosides **15 α** (70%), **15 β** (70%), **17 $\alpha\beta$** (65%) and **19 $\alpha\beta$** (65%) respectively.

In order to provide confirmatory evidence that the carbohydrate configuration and the anomeric configurations of our target compounds had been properly assigned, the NMR spectra of several compounds were examined by NOE difference spectroscopy.

BIOLOGICAL DATA

All the compounds were screened for cell culture cytotoxicity against several different human cancer cell lines and a variety of viruses HBV, RSV (Respiratory Syncytial), influenza, influenza A/PR/8, HHV8, and CMV for antiviral activity. None of the compounds have significant cytotoxicity and activity against any of the viruses tested except for compounds **12 α** , **15 α** , and **15 β** , which showed very good activity against CMV.

ACKNOWLEDGMENT

This investigation was supported by NIH Grant No. CA34200.

REFERENCES

1. Secrist, J.A., III; Tiwari, K.N.; Riordan, J.M.; Montgomery, J.A. *J. Med. Chem.*, **1991**, *34*, 2361–2366.
2. Tiwari, K.N.; Montgomery, J.A.; Secrist, J.A., III. *Nucleosides Nucleotides*, **1993**, *12*, 841–846.
3. Secrist, J.A., III; Riggs, R.M.; Tiwari, K.N.; Montgomery, J.A. *J. Med. Chem.*, **1992**, *35*, 533–538.
4. Tiwari, K.N.; Secrist, J.A., III; Montgomery, J.A. *Nucleosides Nucleotides*, **1994**, *13*, 1819–1828.
5. Secrist, J.A., III; Parker, W.B.; Tiwari, K.N.; Messini, L.; Shaddix, S.C.; Rose, L.M.; Bennett, L.L., Jr.; Montgomery, J.A. *Nucleosides Nucleotides*, **1995**, *14*, 675–686.
6. Secrist, J.A., III; Tiwari, K.N.; Shortnacy-Fowler, A.T.; Messini, L.; Riordan, J.M.; Montgomery, J.A. *J. Med. Chem.*, **1998**, *41*, 3865–3871.
7. Tiwari, K.N.; Shortnacy-Fowler, A.T.; Cappellacci, L.; Parker, W.B.; Waud, W.R.; Montgomery, J.A.; Secrist, J.A. III. *Nucleosides, Nucleotides & Nucleic Acids*, **2000**, *19*, 329–340.
8. Tiwari, K.N.; Shortnacy-Fowler, A.T.; Cappellacci, L.; Waud, W.R.; Parker, W.B.; Montgomery, J.A.; Secrist, J.A. III. *Nucleosides, Nucleotides & Nucleic Acids*, In Press **2000**.



Request Permission or Order Reprints Instantly!

Interested in copying and sharing this article? In most cases, U.S. Copyright Law requires that you get permission from the article's rightsholder before using copyrighted content.

All information and materials found in this article, including but not limited to text, trademarks, patents, logos, graphics and images (the "Materials"), are the copyrighted works and other forms of intellectual property of Marcel Dekker, Inc., or its licensors. All rights not expressly granted are reserved.

Get permission to lawfully reproduce and distribute the Materials or order reprints quickly and painlessly. Simply click on the "Request Permission/Reprints Here" link below and follow the instructions. Visit the [U.S. Copyright Office](#) for information on Fair Use limitations of U.S. copyright law. Please refer to The Association of American Publishers' (AAP) website for guidelines on [Fair Use in the Classroom](#).

The Materials are for your personal use only and cannot be reformatted, reposted, resold or distributed by electronic means or otherwise without permission from Marcel Dekker, Inc. Marcel Dekker, Inc. grants you the limited right to display the Materials only on your personal computer or personal wireless device, and to copy and download single copies of such Materials provided that any copyright, trademark or other notice appearing on such Materials is also retained by, displayed, copied or downloaded as part of the Materials and is not removed or obscured, and provided you do not edit, modify, alter or enhance the Materials. Please refer to our [Website User Agreement](#) for more details.

[Order now!](#)

Reprints of this article can also be ordered at

<http://www.dekker.com/servlet/product/DOI/101081NCN100002420>