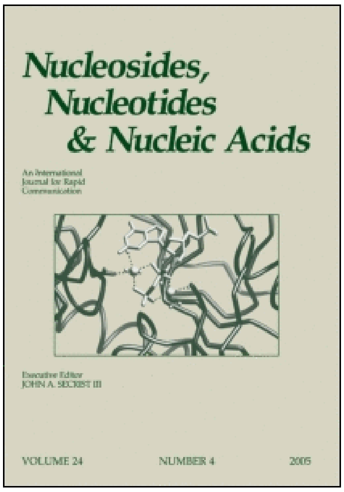


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

NOVEL NUCLEOSIDES WITH VINYL FLUORIDE OR VINYL BROMIDE MOIETY AS OPEN-CHAIN ANALOGS OF NEPLANOCIN A

Myung-Hee Choi[a]; Chong-Kyo Lee[b]; Lak Shin Jeong[c]; Moon Woo Chun[d]; Hee-Doo Kim[a]
[a] College of Pharmacy, Sookmyung Women's University, Seoul, Korea [b] Research Institute of Chemical Technology, Taejeon, Korea [c] College of Pharmacy, Ewha Womans University, Seoul, Korea [d] College of Pharmacy, Seoul National University, Seoul, Korea

To cite this Article Choi, Myung-Hee , Lee, Chong-Kyo , Jeong, Lak Shin , Chun, Moon Woo and Kim, Hee-Doo(2001) 'NOVEL NUCLEOSIDES WITH VINYL FLUORIDE OR VINYL BROMIDE MOIETY AS OPEN-CHAIN ANALOGS OF NEPLANOCIN A', Nucleosides, Nucleotides and Nucleic Acids, 20: 4, 681 — 684

To link to this Article: DOI: 10.1081/NCN-100002350

URL: http://dx.doi.org/10.1081/NCN-100002350

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 20(4–7), 681–684 (2001)

NOVEL NUCLEOSIDES WITH VINYL FLUORIDE OR VINYL BROMIDE MOIETY AS OPEN-CHAIN ANALOGS OF NEPLANOCIN A

Myung-Hee Choi,[1] Chong-Kyo Lee,[2] Lak Shin Jeong,[3]
Moon Woo Chun,[4] and Hee-Doo Kim[1,]*

[1]College of Pharmacy, Sookmyung Women's University,
Seoul 140-742, Korea
[2]Research Institute of Chemical Technology, Taejeon 305-606, Korea
[3]College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea
[4]College of Pharmacy, Seoul National University, Seoul 151-742, Korea

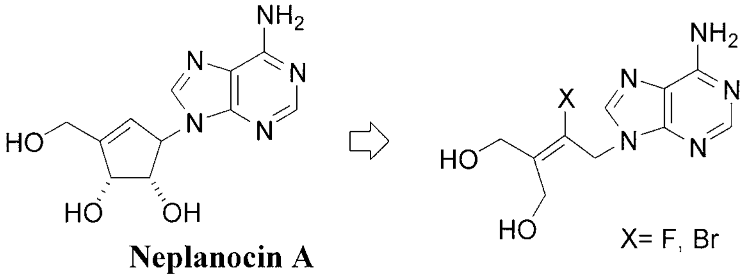
ABSTRACT

Novel nucleosides with vinyl fluoride and vinyl bromide were designed, synthesized and evaluated their antiviral activities against poliovirus, HSV, HIV, and HBV.

Neplanocin A and penciclovir are the most well known carbonucleosides to date. Because of the unusual presence of the double bond in neplanocin A and acyclic nature of penciclovir (1,2), these two compounds have stimulated extensive research in the synthesis of new cyclic and acyclic carbonucleoside analogues mimicking the sugar portion of naturally occurring nucleosides (3). In an effort to obtain more chemically and enzymatically stable carbonucleosides, while causing minimal structural disturbance, we designed the 2-halo-4-hydroxy-3-hydroxymethyl-2-butenyl nucelosides, which mimic both features of neplanocin A and penciclovir. The incorporation of halogen atoms into organic molecules has often been associated with profound changes in the biological profiles of the halogenated analogues compared to their hydrocarbon counterparts (4). It has also been suggested that

---

*Corresponding author.



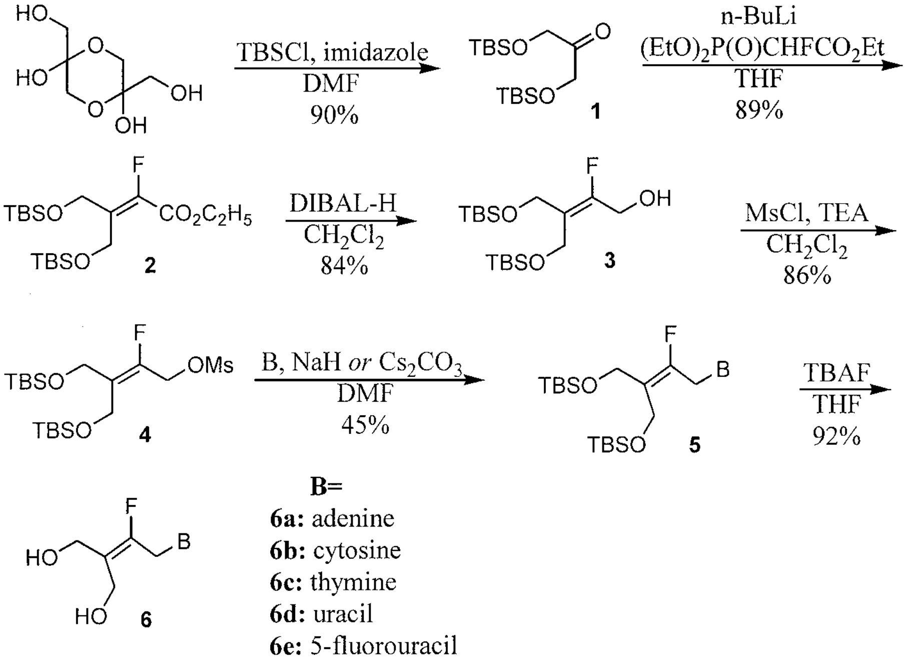
Neplanocin A

Figure 1.

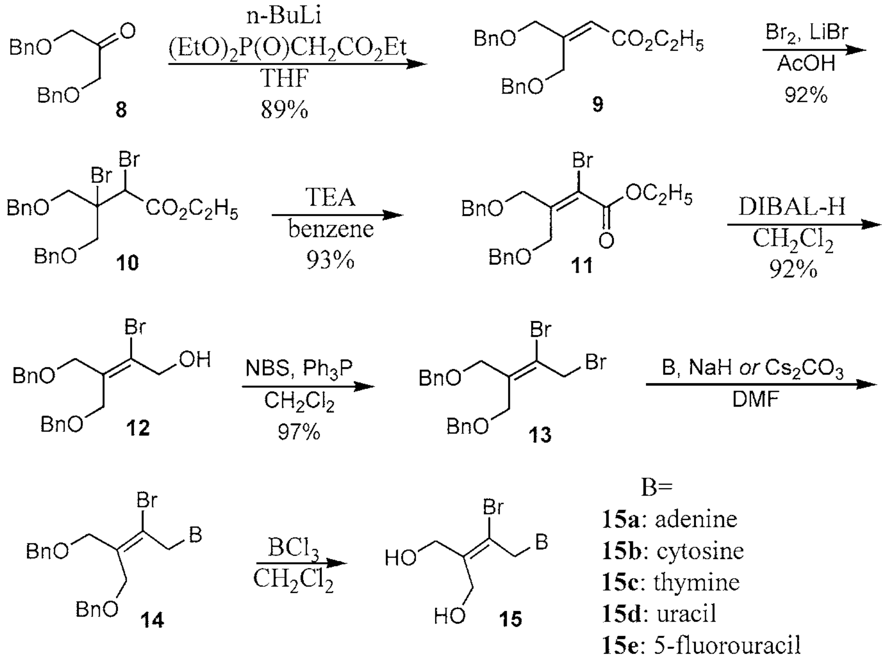
a fluoromethylene group is a better isostere of oxygen than the methylene group (5) and therefore carboacyclic derivatives substituted by halogen at the 1′a position were also attractive targets.

At first, our attention had been directed to the design and synthesis of nucleoside 6 in an attempt to mimic the natural nucleoside most closely by installing a fluorine at the 1′a position.

As shown in Scheme I, the key synthetic intermediate **3** for nucleoside **6** with vinyl fluoride was synthesized by Horner-Wadsworth-Emmons reaction using triethyl 2-fluoro-2-phosphonoacetate and **1**, followed by Dibal-H reduction. The fluorinated allyl alcohol **3** was, then, converted to the corresponding mesylates **4**,



Scheme I.



Scheme II.

which was used for the coupling with adenine (NaH, DMF) or pyrimidine bases (Cs_2CO_3, DMF) under basic conditions, followed by deprotection of silyl group with TBAF to afford the desired nucleosides **6a-e.** In a similar way, as shown in Scheme II, we were able to synthesize the corresponding bromonucleosides **15a-e.**

Horner-Wadsworth-Emmons reaction of ketone **8** with triethyl phosphonoacetate gave the α, β-unsaturated ester **9** in 89% yield. The bromination of ester **9** under basic conditions was unsuccessful, but did give dibromoester **10** with Br_2 and LiBr in acetic acid. Treatment of **10** with TEA followed by reduction with DIBAL-H afforded the allylic alcohol **12** *via* **11** in good yield. Conversion of **12** to **13** was accomplished by addition of NBS to a solution of the alcohol and triphenylphosphine in CH_2Cl_2 in 97% yield. The coupling of **13** with adenine or pyrimidine bases in basic conditions, followed by the removal of benzyl group with BCl_3 gave **15a**(58%), **15b**(88%), **15c**(83%), **15d**(62%), and **15e**(67%), respectively. The synthesized nucleosides (**15a-e**) were evaluated for their antiviral activity against poliovirus, HSV-1, HSV-2 and HIV. However, all compounds were found to be inactive in the assay.

ACKNOWLEDGMENT

This research was supported by the grant from STEPI (99-N6-02-01-A-05), Korea.

REFERENCES

1. De Clercq, E.; Cools, M.; Balzarini, J.; Marquez, V. E.; Bocherding, D. R.; Bochardt, R. T.; Drach, J. C.; Kitaoka, S.; Konno, T. *Antimicrob. Agents Chemother*., **1989**, 33, 1291–1297.
2. Harnden, M. R.; Jarvest, R. L.; Bacon, T. H., Boyd; M. R. *J. Med. Chem*., **1987**, 30, 1636–1642.
3. Marquez, V. E. *Carbocyclic nucleosides*. *In advances in antiviral drug design*, JAI Press, **1996**, Vol. **2**, pp 89–146, and references therein.
4. Pankiewicz, K. W. *Carbohydr. Res*., **2000**, 327, 87–105.
5. Blackburn, G. M.; Kent, D. E. *J. Chem. Soc. (Perkin I)*, **1986**, 913–917.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

Downloaded At: 12:05 26 January 2011

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/101081NCN100002350