

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>

A CYCLOBUTANE CARBONUCLEOSIDE WITH MARKED SELECTIVITY AGAINST TK AND TK⁻ VARICELLA ZOSTER VIRUS

C. López^a; C. Balo^a; J. M. Blanco^a; F. Fernández^a; E. De Clercq^b; J. Balzarini^b

^a Universidade de Santiago, Santiago de Compostela, Spain ^b Rega Institute for Medical Research, Katholieke Universiteit Leuven, Leuven, Belgium

Online publication date: 31 March 2001

To cite this Article López, C. , Balo, C. , Blanco, J. M. , Fernández, F. , De Clercq, E. and Balzarini, J.(2001) 'A CYCLOBUTANE CARBONUCLEOSIDE WITH MARKED SELECTIVITY AGAINST TK AND TK⁻ VARICELLA ZOSTER VIRUS', *Nucleosides, Nucleotides and Nucleic Acids*, 20: 4, 1133 — 1135

To link to this Article: DOI: 10.1081/NCN-100002505

URL: <http://dx.doi.org/10.1081/NCN-100002505>

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.

A CYCLOBUTANE CARBONUCLEOSIDE WITH MARKED SELECTIVITY AGAINST TK⁺ AND TK[−] VARICELLA ZOSTER VIRUS

C. López,^{1,*} C. Balo,¹ J. M. Blanco,¹ F. Fernández,¹
E. De Clercq,² and J. Balzarini²

¹Dpto. Química Orgánica, Universidade de Santiago, E-15706,
Santiago de Compostela, Spain

²Rega Institute for Medical Research, Katholieke Universiteit Leuven,
B-3000 Leuven, Belgium

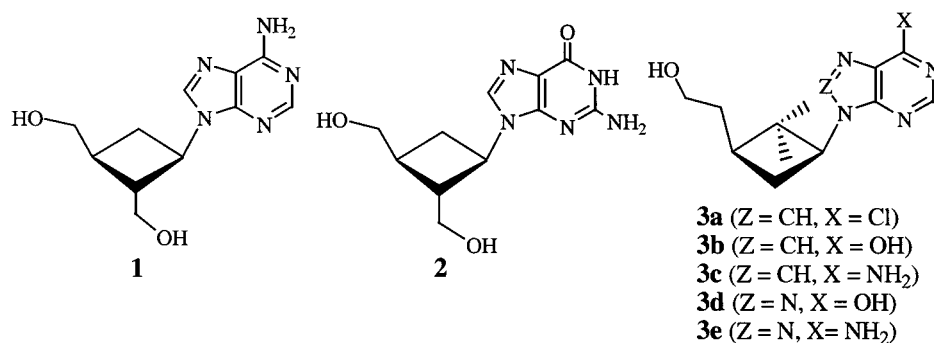
ABSTRACT

Several cyclobutyladenine and analogous carbonucleosides were synthesized from 1*R*- α -pinene and their anti-viral activity was tested. One of them (**3e**) showed interesting selectivity against both TK⁺ and TK[−] VZV.

The interesting antiviral properties of some carbocyclic nucleosides incorporating a cyclobutane ring in their pseudo-sugar moiety, such as the antiherpes activity of Cyclobut A (**1**) (**1**), and the antihepatitis activity of Lubocavir (**2**) (**2**), led us to explore several series of cyclobutane derivatives.

In this context several derivatives of adenine and of adenine analogues of type **3** were synthesized in enantiomerically pure form for the evaluation of their antiviral properties.

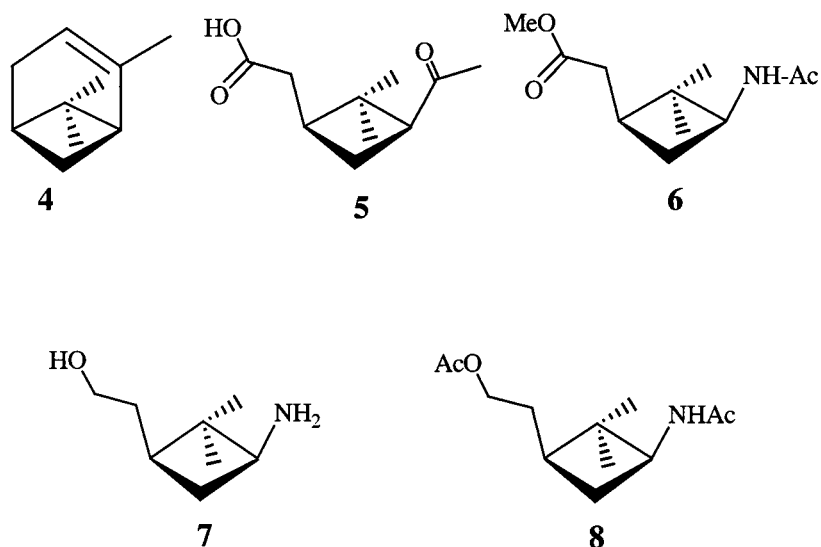
The starting material for the preparation of these compounds was easily available 1*R*- α -pinene (**4**), which upon permanganate oxidative cleavage gave (1*S*, *cis*)-pinonic acid (**5**). Beckmann rearrangement of **5** by means of H₂NOSO₃H, followed by esterification in MeOH/TsOH yielded acetamido ester **6**. Reduction of **6** by LiBH₄, followed by 2*N* HCl hydrolysis led to amino alcohol **7** in a 20–28% overall yield. Best yield was achieved when the crude product from the reduction of



Scheme 1.

6 was acetylated by Ac₂O/Pyr and the diacetyl derivative **8** was isolated previously to its hydrolysis to **7**. Synthesis of compounds **3** was then accomplished by constructing the adenine or 8-aza adenine moiety on the amino group of **7**, following well established procedures (3).

Compounds **3** were assayed against a variety of viruses. Most of them failed to show a noticeable activity against HIV-1 and HIV-2, cytomegalovirus, parainfluenza-3 virus, reovirus-1, sindbis virus, coxsackie virus B4, Punta Toro virus, herpes simplex virus types 1 and 2, vaccinia virus and vesicular stomatitis virus at subtoxic concentrations. However, compound **3e** showed a remarkable selective activity against both TK⁺ and TK⁻ strains of varicella zoster virus (see Table), thus



Scheme 2.



Table.

Compound	Antiviral Activity IC ₅₀ (μg/mL) ^a				Cytotoxicity (μg/mL)	
	TK ⁺ VZV		TK ⁻ VZV		Cell Morphology (MCC) ^b	Cell Growth (CC ₅₀) ^c
	YS Strain	OKA Strain	07/1 Strain	YS/R Strain		
3a	>50	50	>50	>50	>50	32
3b	>50	>50	>50	>50	>50	>50
3c	28	20	>20	20	≥50	45
3d	>50	>50	>50	>50	>50	>50
3e	3.5	3.2	9.3	3.5	50	>50
ACV^d	0.28	0.24	7.8	2.5	>50	>200
BVDU^e	0.0005	0.0004	8.7	20	>50	200

^aInhibitory concentration required to reduce virus plaque formation by 50%. Virus input was 20 plaque forming units (PFU). ^bMinimum cytotoxic concentration that causes a microscopically detectable alteration of cell morphology. ^cCytotoxic concentration required to reduce cell growth by 50%.). ^dAcyclovir. ^eBrivudine.

showing that its anti-VZV activity is independent from the VZV-encoded thymidine kinase.

REFERENCES

1. Bisacchi, G. S.; Braitman, A.; Cianci, C. W.; Clark, J. M.; Field, A. K.; Hagen, M. E.; Hockstein, D. R.; Malley, M. F.; Mitt, T.; Slusarchyk, W. A.; Sundeen, J. E.; Terry, B. J.; Tuomari, A. V.; Weaver, E. R.; Young, M. G.; Zahler, R. *J. Med. Chem.*, **1991**, *34*, 1415–1421.
2. Colacino, J. F.; Stachke, K. A. *Progress in Drug Research*, **1998**, *50*, 259–322.
3. Rodríguez-Borges, J. E.; Fernández, F.; García, X.; Rodríguez-Hergueta, A.; López, C.; Andrey, G.; Snoeck, R.; Witvrounw, M.; Balzarini, J.; De Clercq, E. *Nucleosides & Nucleotides*, **1998**, *17*, 1237–1253.



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/101081NCN100002505>