This article was downloaded by: [Nipissing University] On: 10 October 2014, At: 16:47 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 and Nucleotides

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lncn19

Synthesis and Biological Activity of Some 2-Aminopurine Carbonucleosides

L. Santana^a, M. Teijeira^a, E. Uriartea^a, C. Terán^b, G. Andrei^c, R. Snoeck^c & E. De Clercq^c

^a Facultad de Farmacia, Universidad de Santiago de Compostela, Spain

 $^{\rm b}$ Departamento de Química Pura y Aplicada , Universidad de Vigo , Spain

 $^{\rm c}$ Rega Institute for Medical Research , Katholieke Universiteit Leuven , Belgium

Published online: 16 Aug 2006.

To cite this article: L. Santana , M. Teijeira , E. Uriartea , C. Terán , G. Andrei , R. Snoeck & E. De Clercq (1997) Synthesis and Biological Activity of Some 2-Aminopurine Carbonucleosides, Nucleosides and Nucleotides, 16:7-9, 1337-1339, DOI: <u>10.1080/07328319708006183</u>

To link to this article: http://dx.doi.org/10.1080/07328319708006183

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME 2-AMINOPURINE CARBONUCLEOSIDES

L. Santana^a, M. Teijeira^a, E. Uriarte^a*, C. Terán^b, G. Andrei^c, R. Snoeck^c and E. De Clercq^c

a) Facultad de Farmacia, Universidad de Santiago de Compostela, Spain

b) Departamento de Química Pura y Aplicada, Universidad de Vigo, Spain

c) Rega Institute for Medical Research, Katholieke Universiteit Leuven, Belgium

Abstract. A series of new one two subtituted carbonucleoside analogues (OTC) of purine was synthesized and evaluated against cytomegalovirus and varicella-zoster virus in human embryonic lung (HEL) cells.

As part of an ongoing study of carbocyclic nucleoside analogues in which the standard 1,3- arrangement of the base and hydroxymethyl group is modified to a 1,2- arrangement, we prepared a series of analogues of the latter type that contain a modified 2-aminopurine base attached either directly, or via a methylene group, to the cyclopentane ring, and lying *cis* to the adjacent hydroxymethyl group.

Racemic mixtures of the 1,2-substituted (OTC) analogues 3 - 8 were obtained as shown in Scheme 1. Starting aminoalcohols 1 and 2 were prepared by selective reduction of 1-cyclopentene-1,2-dicarboxylic anhydride, followed by ring-opening of the resulting saturated lactone with ammonia, which afforded 2-hydroxymethylcyclopentane carboxamide, from which 1 was obtained by Hoffmann degradation and 2 by reduction with lithium aluminium hydride.¹ The purine base was then constructed about the primary amino group of these intermediates.² Each aminoalcohol was firstly reacted with 2-amino-4,6-dichloropyrimidine, and then a second amino group was introduced at position 5 of the pyrimidine ring by reaction with *p*-chlorobenzenediazonium chloride followed by reduction. The fused imidazole ring was then formed by reaction of this diamino compound with ethylorthoformate in acid medium, which afforded 2-aminochloropurines 3 and 4. The 2,6-diamino purines 5 and 6 were prepared in good yield by amination of 3 and 4 respectively in methanol,³ and similarly good yields of the guanosine analogues 7 and 8 were obtained by treatment of 3 and 4 with NaOH.



a) 2-amino-4,6-dichloropyrimidine, Et₃N, n-BuOH, reflux, 75-85 %; b) *p*-chlorobenzenediazonium chloride, NaOAc, AcOH, H₂O, room temp., 80-90%; c) Zn, AcOH, H₂O, EtOH, reflux, 86-98%; d) CH(OEt)₃, HCl (12M), 67-76%; e) NH₃, MeOH, reflux, 85%; f) NaOH (0.33M), reflux, 75%.

SCHEME 1.

Compound	Antiviral activity IC ₅₀ (µg/mL) ^a						Cytotoxicity CC ₅₀ (µg/mL) ^b
	CMV		TK ⁺ VZV		TK- VZV		
	AD-169 strain	Davis strain	OKA strain	YS strain	07/1 strain	YS/R strain	-
3	>5	>20	>20	>20	>20	>20	>50
4	>5	>5	>20	>20	>20	>20	20
5	>50	>50	>50	>50	>50	37	>50
6	>50	>50	>50	>50	>50	>50	>50
7	>50	>50	>50	>50	>50	>50	>50
8	>50	>50	>50	>50	>50	>50	>50
Ganciclovir	1.1	2	-	-	-	-	>50
Cidofovir	0.5	0.4	-	-	-	-	>50
Brivudin	-	-	0.0009	0.0015	>50	>50	>200
Acyclovir	-	-	0.5	1.2	20	14	>200

TABLE 1. Activity of compounds **3-8** against cytomegalovirus (CMV) and varicellazoster virus (VZV) in human embryonic lung (HEL) cells.

^a50% Inhibitory concentration, or concentration required to reduce virus plaque formation by 50%. Virus input was 100 plaque forming units (PFU) for cytomegalovirus and 20 PFU for varicella-zoster virus.

^b50% Cytotoxic concentration, or concentration required to reduce cell growth by 50%.

As shown in Table 1, compounds 3 - 8 did not exhibit appreciable activity against cytomegalovirus or varicella-zoster virus under conditions where for ganciclovir, cidofovir, brivudin and acyclovir the expected IC₅₀ (50% inhibitory concentration) was recorded.

Acknowledgement. We thank the Xunta de Galicia, Spain (XUGA 20306B95) for partial financial support.

REFERENCES

- 1. M. Teijeira. Doctoral Thesis, University of Santiago de Compostela, Spain, 1996.
- 2. R. Vince and M. Hua. J. Med. Chem. 1990, 33,17-21.
- 3. All compounds had spectral and analytical data consistent with their structures.