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# Synthesis and Biological Activity of Some 2-Aminopurine Carbonucleosides

L. Santana<sup>a</sup>; M. Teijeira<sup>a</sup>; E. Uriartea<sup>a</sup>; C. Terán<sup>b</sup>; G. Andrei<sup>c</sup>; R. Snoeck<sup>c</sup>; E. De Clercq<sup>c</sup>
<sup>a</sup> Facultad de Farmacia, Universidad de Santiago de Compostela, Spain <sup>b</sup> Departamento de Química
Pura y Aplicada, Universidad de Vigo, Spain <sup>c</sup> Rega Institute for Medical Research, Katholieke
Universiteit Leuven, Belgium

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## SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME 2-AMINOPURINE CARBONUCLEOSIDES

L. Santana<sup>a</sup>, M. Teijeira<sup>a</sup>, E. Uriarte<sup>a</sup>\*, C. Terán<sup>b</sup>, G. Andrei<sup>c</sup>, R. Snoeck<sup>c</sup> and E. De Clercq<sup>c</sup>

- 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. The purine base was then constructed about the primary amino group of these intermediates. 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-amino-6-chloropurines 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, and 3 and 4 with NaOH.

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HO 
$$(CH_2)_n$$
  $(CH_2)_n$   $(CH_2)$ 

a) 2-amino-4,6-dichloropyrimidine, Et $_3$ N, n-BuOH, reflux, 75-85 %; b) p-chlorobenzenediazonium chloride, NaOAc, AcOH, H $_2$ O, room temp., 80-90%; c) Zn, AcOH, H $_2$ O, EtOH, reflux, 86-98%; d) CH(OEt) $_3$ , HCl (12M), 67-76%; e) NH $_3$ , MeOH, reflux, 85%; f) NaOH (0.33M), reflux, 75%.

### SCHEME 1.

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

Compound	Antiviral activity IC <sub>50</sub> (μg/mL) <sup>a</sup>						Cytotoxicity CC <sub>50</sub> (µg/mL) <sup>b</sup>
	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

<sup>&</sup>lt;sup>a</sup>50% 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.

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 IC<sub>50</sub> (50% inhibitory concentration) was recorded.

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