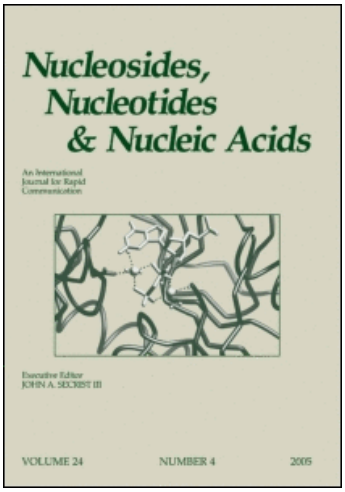

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME 2-AMINOPURINE CARBONUCLEOSIDES

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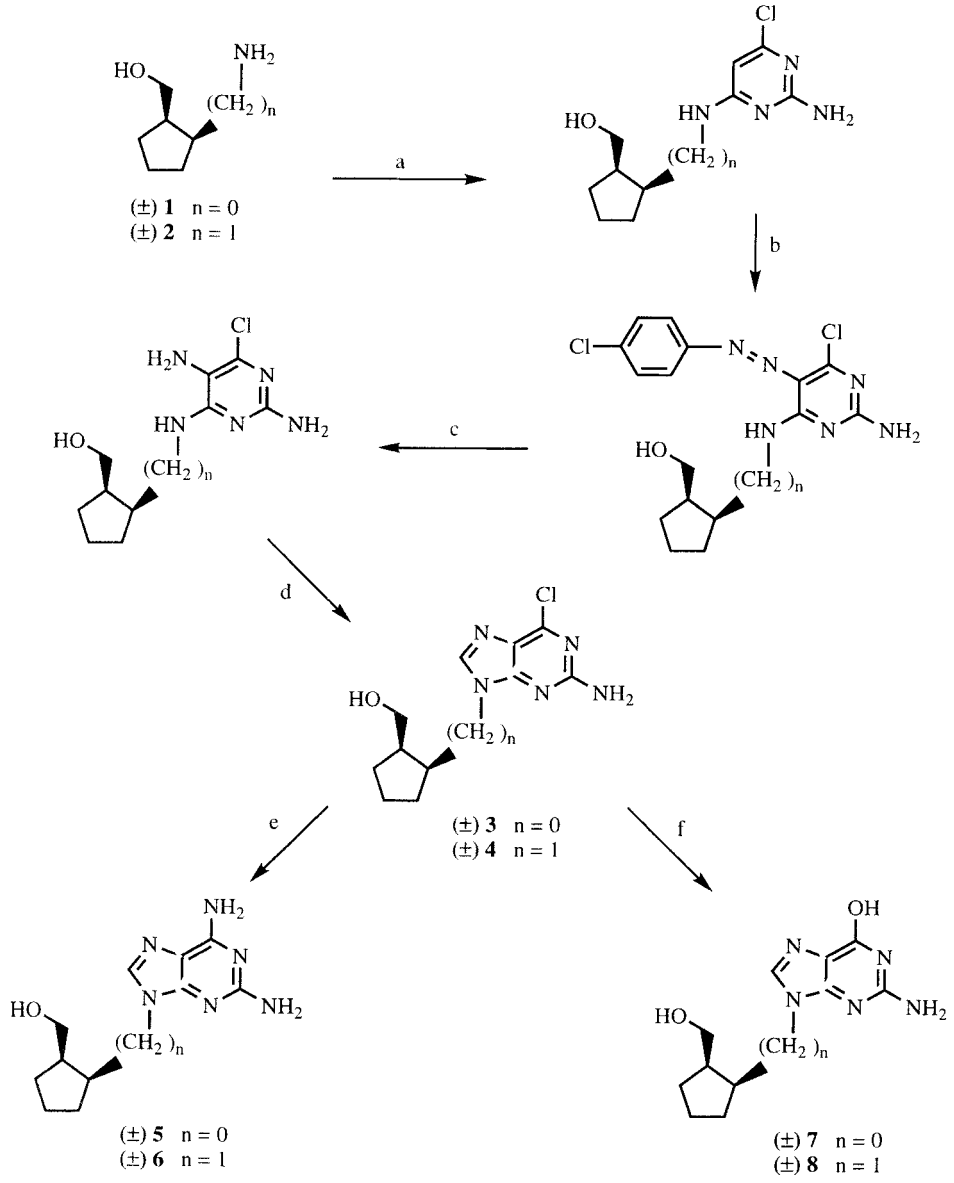
Abstract. A series of new one two subtituted carbonucleoside analogues (OTC) of purine was synthesized and evaluated against cytomegalovirus and varicella-zoster virus in human embryonic lung (HEL) cells.

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-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,[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, Et_3N, n-BuOH, reflux, 75-85 %; b) *p*-chlorobenzenediazonium chloride, NaOAc, AcOH, H_2O, room temp., 80-90%; c) Zn, AcOH, H_2O, 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 varicella-zoster virus (VZV) in human embryonic lung (HEL) cells.

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

[a]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.

[b]50% 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 IC_{50} (50% inhibitory concentration) was recorded.

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3. All compounds had spectral and analytical data consistent with their structures.