

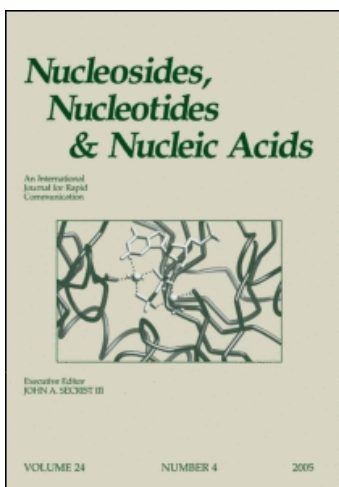
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## Nucleosides, Nucleotides and Nucleic Acids

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### Purine Derivatives of 1,2-Disubstituted Cyclohexane Analogues of Nucleosides

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## Purine Derivatives of 1,2-Disubstituted Cyclohexane Analogues of Nucleosides

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### ABSTRACT

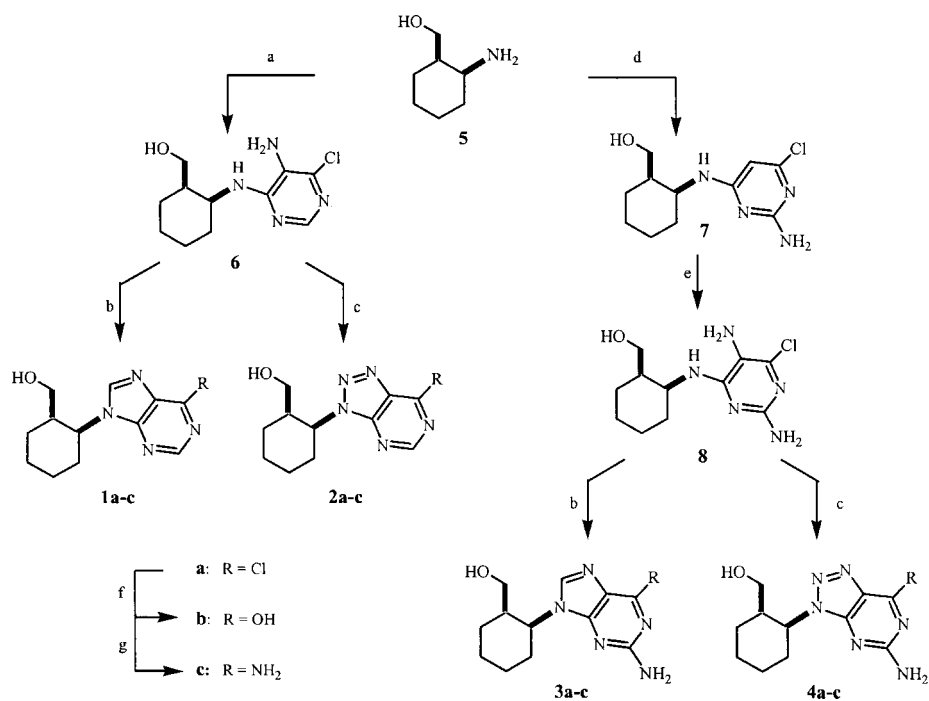
Starting from ( $\pm$ )-*cis*-2-hydroxymethylcyclohexylamine, a series of cyclohexane-derived *cis*-1,2-disubstituted carbonucleoside analogues with a 6- or 2,6-purine or 8-azapurine base were synthesized. The antiviral and antitumoral in vitro effects of the new compounds were evaluated.

As a follow-up to our work on one-two-disubstituted carbonucleosides (OTCs),<sup>[1]</sup> we describe herein the preparation of compounds **1–4**,<sup>a</sup> which were synthesized in racemic *cis* form starting from ( $\pm$ )-*cis*-2-hydroxymethylcyclohexylamine (**5**) and constructing the purine or 8-azapurine base on the primary amino group (Sch. 1).

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<sup>a</sup>All compounds had spectral and analytical data consistent with their structures.





**Scheme 1.** Reagents: a) 5-amino-4,6-dichloropyrimidine, Et<sub>3</sub>N, n-BuOH, reflux 24 h, 71%; b) CH(OEt)<sub>3</sub>, HCl 12M reflux 12 h, **1a**: 71%, **3a**: 60%; c) HCl 1M, NaNO<sub>2</sub>, 0°C, **2a**: 78%, **4a**: 80%; d) 2-amino-4,6-dichloropyrimidine, Et<sub>3</sub>N, nBuOH, reflux 24 h, 60%; e) p-chloroaniline, NaNO<sub>2</sub>, HCl 12M, 0°C; Zn, AcOH, EtOH, reflux 1 h, 30%; f) NaOH 0,33M, reflux 5 h, **1b**: 84%, **2b**: 72%, **3b**: 71%, **4b**: 90%; g) NH<sub>4</sub>OH, reflux 4 h, **1c**: 99%, **2c**: 78%, **3c**: 40%, **4c**: 40%.

**Table 1.** Antitumor activities of compounds 1–4.

Compound	IC <sub>50</sub> (µg/ml)		
	L1210	Molt4/C8	CEM/0
<b>1a</b>	45 ± 8	36 ± 3	47 ± 3
<b>1b</b>	>100	>100	>100
<b>1c</b>	>100	>100	>100
<b>2a</b>	ND	ND	ND
<b>2b</b>	>100	>100	>100
<b>2c</b>	>100	>100	>100
<b>3a</b>	37 ± 15	45 ± 2	42 ± 2
<b>3b</b>	>100	>100	>100
<b>3c</b>	>100	>100	>100
<b>4a</b>	7.6 ± 1.4	8.3 ± 1.2	7.7 ± 1.6
<b>4b</b>	64 ± 3	43 ± 3	49 ± 2
<b>4c</b>	>100	>100	>100

To obtain the 6-substituted compounds **1** and **2**, the amino alcohol **5** was first reacted with 5-amino-4,6-dichloropyrimidine to give the substituted diaminopyrimidine **6** as key compound. This afforded **1a** by reaction with ethylorthoformate in acidic medium, and **2a** (unstable) via the diazonium intermediate.

To obtain the 2-amino compounds **3a** and **4a**, the amino alcohol **5** was reacted with 2-amino-4,6-dichloropyrimidine to give **7**. Afterwards a second amino group was introduced at position 5 of the pyrimidine ring by reaction with *p*-chlorobenzene-diazonium chloride followed by reduction to afford the compound **8**, which was cyclized to obtain the compounds **3a** and **4a**.

Nucleophilic exchange of the 6-chloro atom to an hydroxy group (compounds **1b–4b**) was carried out by treatment with NaOH, whereas the 6-amino derivatives (compounds **1c–4c**) could be obtained by exchange with ammonium hydroxide.

Compounds **1–4** were evaluated, but found inactive, against a number of viruses. Their antitumor cell activities [expressed as 50% inhibitory concentration (IC<sub>50</sub> in µg/mL) required to inhibit tumor cell growth by 50%] are shown in Table 1.

#### REFERENCE

1. Estrada, E.; Uriarte, E.; Montero, A.; Teijeira, M.; Santana, L.; De Clercq, E. *J. Med. Chem.* **2000**, *43*, 1975–1985.



