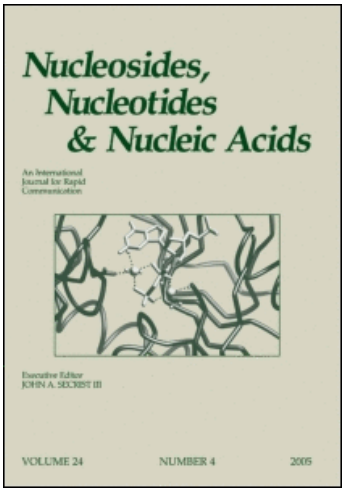

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Purine Derivatives of 1,2-Disubstituted Cyclohexane Analogues of Nucleosides

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ABSTRACT

Starting from (±)-*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),[1] we describe herein the preparation of compounds **1**–**4**,[a] which were synthesized in racemic *cis* form starting from (±)-*cis*-2-hydroxymethylcyclohexylamine (**5**) and constructing the purine or 8-azapurine base on the primary amino group (Sch. 1).

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[a]All compounds had spectral and analytical data consistent with their structures.

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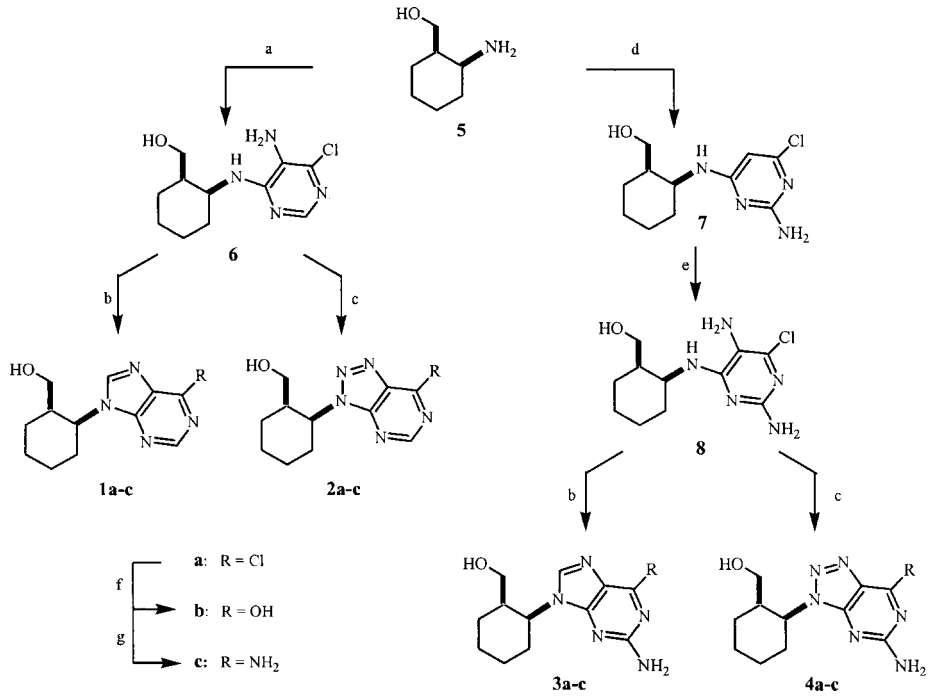

Scheme 1. Reagents: a) 5-amino-4,6-dichloropyrimidine, Et_3N, n-BuOH, reflux 24 h, 71%; b) $CH(OEt)_3$, HCl 12M reflux 12 h, **1a**: 71%, **3a**: 60%; c) HCl 1M, $NaNO_2$, 0°C, **2a**: 78%, **4a**: 80%; d) 2-amino-4,6-dichloropyrimidine, Et_3N, nBuOH, reflux 24 h, 60%; e) p-chloroaniline, $NaNO_2$, HCl 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_4OH, reflux 4 h, **1c**: 99%, **2c**: 78%, **3c**: 40%, **4c**: 40%.

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

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

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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*-chlorobenzenediazonium 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_{50} in μg/mL) required to inhibit tumor cell growth by 50%] are shown in Table 1.

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