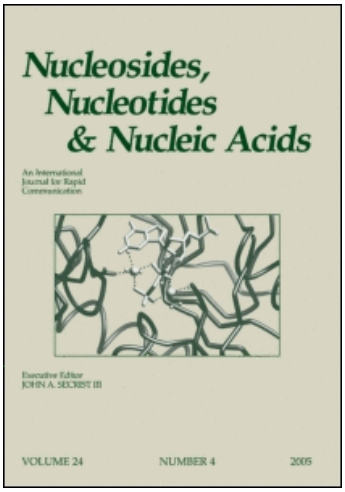

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BIOLOGICAL ACTIVITY

SYNTHESIS AND ANTIVIRAL ACTIVITY OF 1,2-CARBONUCLEOSIDES

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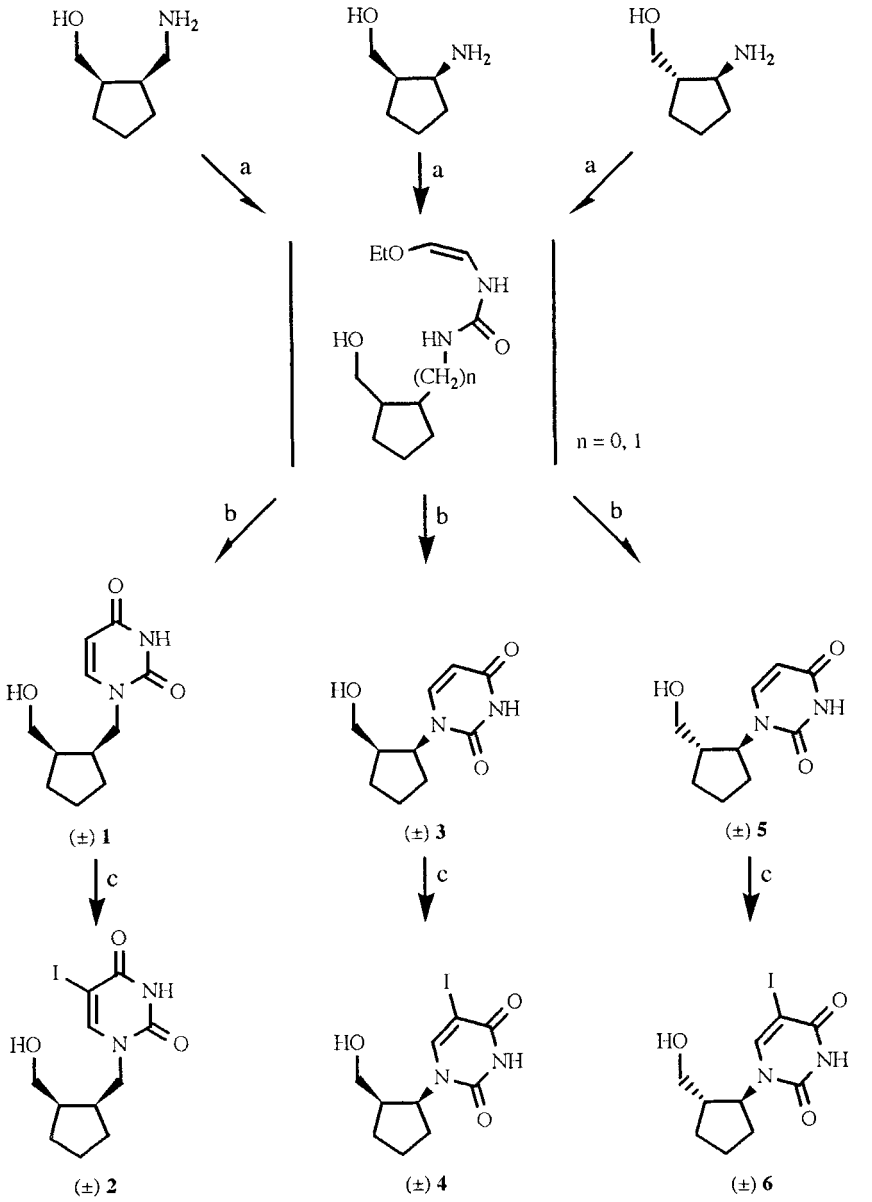
Abstract: Members of a new class of carbonucleoside analogues (OTC, one two substituted carbonucleosides) were synthesized and evaluated against HIV.

On the basis of our theoretical studies in the area of nucleoside analogues, we decided to prepare a series of new carbocyclic analogues in which the hydroxymethyl and pyrimidine base substituents on the cyclopentane ring are adjacent and in *cis* and *trans* position, with the base directly linked to the ring or separated from it by a methylene group (compounds **1-6**). The starting aminoalcohols were obtained by a simple, readily generalizable route from ethyl 2-oxocyclopentanecarboxylate; their stereochemistry was confirmed by NMR spectroscopy and alternative synthesis[1]. Compounds **1**, **3** and **5** were synthesized from racemic mixtures of the corresponding aminoalcohols by treatment with 3-ethoxy-2-propenoyl isocyanate[2] in dimethylformamide at room temperature[3], followed by cyclization of the resulting di-substituted urea in refluxing sulfuric acid medium (65 - 70% overall yield)[4]. Compounds **2**, **4** and **6** were synthesized by treatment of **1**, **3** or **5** with iodine - nitric acid in dioxane[5] (90% yield[6]); see Scheme 1.

In this series, only compound **4** showed antiviral activity at a concentration below 100 μg / mL, its EC_{50} for inhibiting both HIV-1- and HIV-2-induced giant cell formation in



a) 3-Ethoxy-2-propenoyl isocyanate, DMF b) Sulfuric acid (1M) c) Iodine, nitric acid, dioxane

SCHEME 1

TABLE 1. Anti-HIV-1 and -HIV-2 activity and cytotoxic properties of compounds **1** - **6** in human T-lymphocyte (CEM) cells

Compound	EC_{50}[a] (μg/mL)		CC_{50}[b] (μg/mL)
	HIV-1	HIV-2	
1	> 100	> 100	> 100
2	> 100	> 100	> 100
3	> 100	> 100	> 100
4	12.5 ± 3.5	12.5 ± 3.5	68.7 ± 44.3
5	> 100	> 100	> 100
6	> 100	> 100	> 100

[a]50% Effective concentration, or concentration required to protect CEM cells against the cytopathogenicity of HIV by 50%.

[b]50% Cytotoxic concentration, or concentration required to reduce CEM cell viability by 50%.

CEM cells being 12.5 μg / mL . The toxicity of this compound (CC_{50}) was 69 μg / mL in the same cell line (TABLE 1).

Acknowledgement

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6. All these compounds were purified by FC using 1:1 hexane/ethyl acetate, and had spectral and analytical data consistent with their structures.