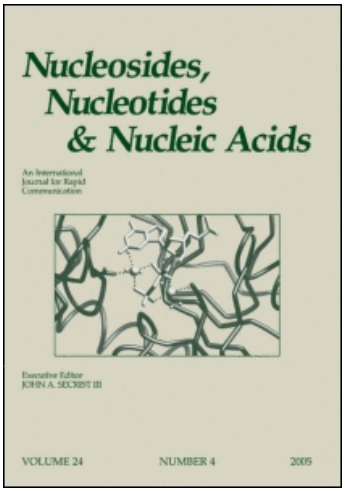

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1,2-Disubstituted Carbocyclic Analogues of Thymine Nucleosides

V. Escuredo[a]; B. Ferro[a]; L. Santana[a]; M. Teijeira[a]; E. Uriarte[a]
[a] Facultad de Farmacia, Universidad de Santiago de Compostela, Spain

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1,2-DISUBSTITUTED CARBOCYCLIC ANALOGUES OF THYMINE NUCLEOSIDES

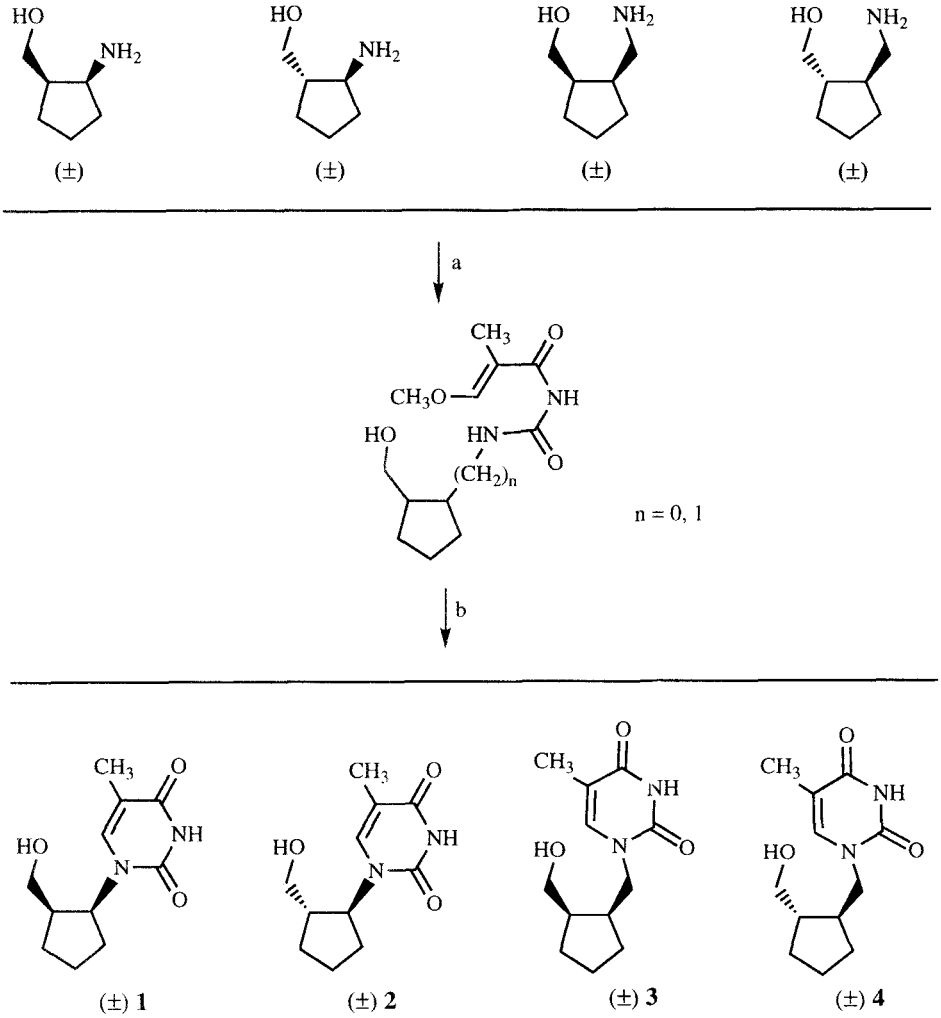
V. Escuredo, B. Ferro, L. Santana*, M. Teijeira and E. Uriarte
Facultad de Farmacia, Universidad de Santiago de Compostela, Spain

Abstract. A series of **o**ne **t**wo **c**arbonucleoside (OTC) analogues of thymine was synthetized and their conformation was studied by AM1 theoretical calculations. The low-energy conformations of Compound **1** and 2',3'-dideoxythymidine, showed a degree of steric congruity.

On the basis of our recent observation[1] that 1,3-disubstituted cyclopentane analogues of uracil nucleosides have similar configurations to the corresponding 1,2-disubstituted cyclopentanes, we prepared compounds of the latter type that are hybrids of 2',3'-dideoxy and carbocyclic analogues of nucleosides. These compounds contain a thymine base attached either directly, or via a methylene group, to a cyclopentane ring that bears a *cis* or *trans* hydroxymethyl group on the adjacent carbon (Scheme 1).

Compounds **1** - **4** were prepared in 45-50% overall yield[2] by constructing the pyrimidine ring about the primary amino group of racemic mixtures of suitable aminoalcohol precursors,[3] reacting these firstly with 3-methoxy-2-methylacryloyl isocyanate, and then cyclizing the product in acid[4] (Scheme 1).

The molecular geometries of analogues **1** - **4** were optimized by the AM1 semi-empirical quantum mechanical method[5] using the AMPAC program[6] on an SGI work station. Optimization focused on two angles χ and γ [see for analogue **1** in Fig. 1a; χ = C(2)-N(2)-C(6)-C(10) and γ = O(3)-C(11)-C(10)-C(6)] which were varied between 0° and 360° in 30° increments. For analogue **1**, χ showed two regions of minimum energy, one between -90° and -120°, corresponding to the *anti* conformation, and the other between 90° and 120°, corresponding to the less stable *syn* conformation (4 Kcal/mol higher in energy). For γ, there was a broad energy-minimum between 60° and 300°.



a) 3-methoxy-2-methyl-2-propenoyl isocyanate, DMF. b) 1M H_2SO_4 .

SCHEME 1

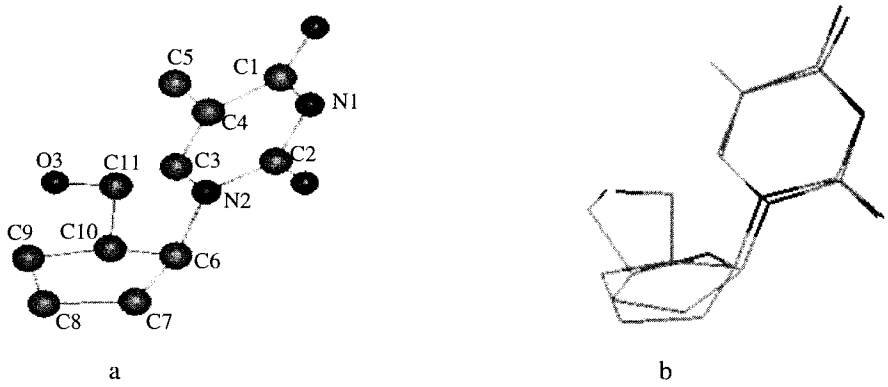


FIG. 1. a) Optimized molecular geometry of analogue **1** by AM1 theoretical calculation
b) Superposition of the analogue **1** on the low-energy conformation of 2', 3'-dideoxythymidine

Superposition of one preferred conformation of **1** on the low-energy conformer of 2',3'-dideoxythymidine (Fig. 1b) showed these compounds to have a high degree of steric congruity, as regards the heterocyclic base, the alicyclic ring and also the hydroxyl group. Both these compounds showed a strong preference for the *anti* conformation, which has also been observed for other nucleoside analogues and appears to be necessary for biological activity.[7]

There was less steric congruity between the preferred conformations of analogue **2** and the low-energy conformer of 2',3'-dideoxythymidine. Congruity as regards the rings, or the heterocyclic rings and the hydroxylic groups, was shown by some conformers of **2**, with barely appreciable energy differences separating the *syn* and *anti* conformations.

The high degree of steric freedom of analogues **3** and **4** meant that no preferred conformations could be identified for these compounds.

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