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1,2-DISUBSTITUTED CARBOCYCLIC ANALOGUES OF THYMINE NUCLEOSIDES

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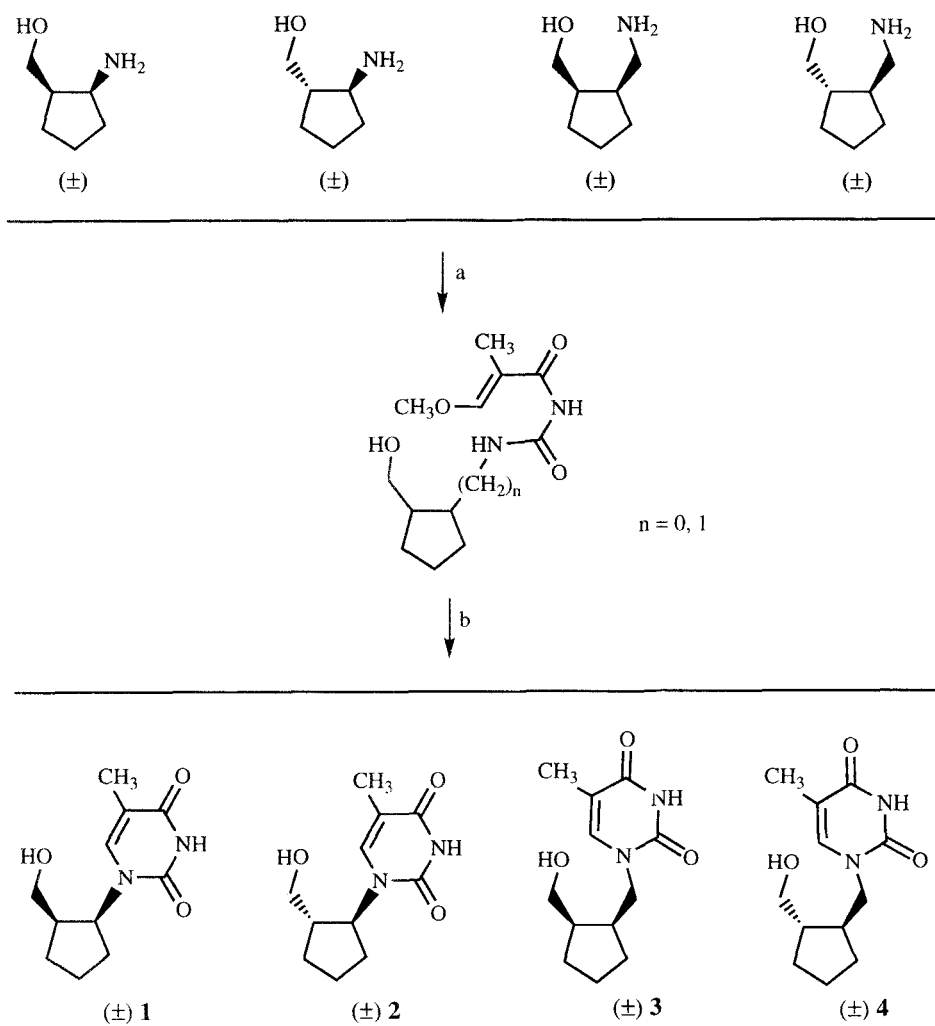
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Abstract. A series of one two carbonucleoside (OTC) analogues of thymine was synthesized and their conformation was studied by AM1 theoretical calculations. The low-energy conformations of Compound **1** and 2',3'-dideoxythymidine, showed a degree of steric congruity.

On the basis of our recent observation¹ 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 yield² 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 acid⁴ (Scheme 1).

The molecular geometries of analogues **1** - **4** were optimized by the AM1 semi-empirical quantum mechanical method⁵ using the AMPAC program⁶ on an SGI work station. Optimization focused on two angles χ and γ [see for analogue **1** in Fig. 1a; $\chi = \text{C}(2)\text{-N}(2)\text{-C}(6)\text{-C}(10)$ and $\gamma = \text{O}(3)\text{-C}(11)\text{-C}(10)\text{-C}(6)$] 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 H₂SO₄.

SCHEME 1

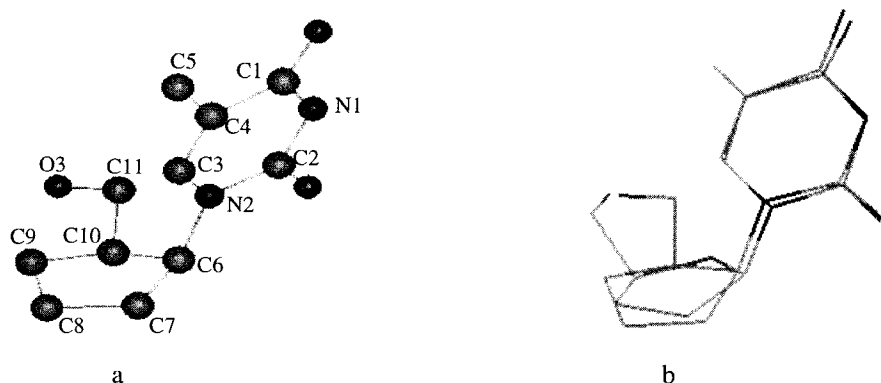


FIG. 1. a) Optimized molecular geometry of analogue **1** by AM1 theoretical calculation
b) Superposition of the analogue **1** on the low-energy conformation of 2',3'-dideoxythymidine

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.

REFERENCES

1. L. Santana, M. Teijeira, C. Terán, E. Uriarte, U. Cassellato and R. Graziani. *Nucleosides & Nucleotides*, 15(6), 1179, 1996.
2. All compounds were purified by FC using 98:2 methylene chloride/methanol as eluant and had spectral and analytical data consistent with their structures.
3. M. Teijeira. Ph. D. Thesis. University of Santiago de Compostela, Spain, 1996.
4. Y. F. Shealy, C. A. O'Dell and M. C. Thorpe. *J. Heterocyclic Chem.* 18, 383, 1981.

5. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart. *J. Am. Chem. Soc.* 107, 3902-3909, 1985.
6. BIOSYM Technologies, Inc. 10065 Barnes Canyon Road, San Diego, Ca 92121.
7. T. Kovacs, L. Parkanyi, I. Pelczer, F. Cervantes-Lee, K. H. Pannell and P. F. Torrence. *J. Med. Chem.* 34, 2595, 1991.