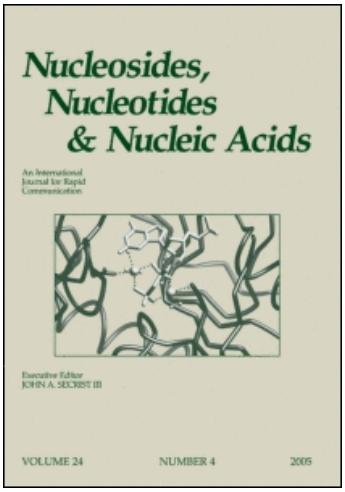

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SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,2-DISUBSTITUTED CARBONUCLEOSIDES OF 6-SUBSTITUTED PURINE AND 8-AZAPURINE

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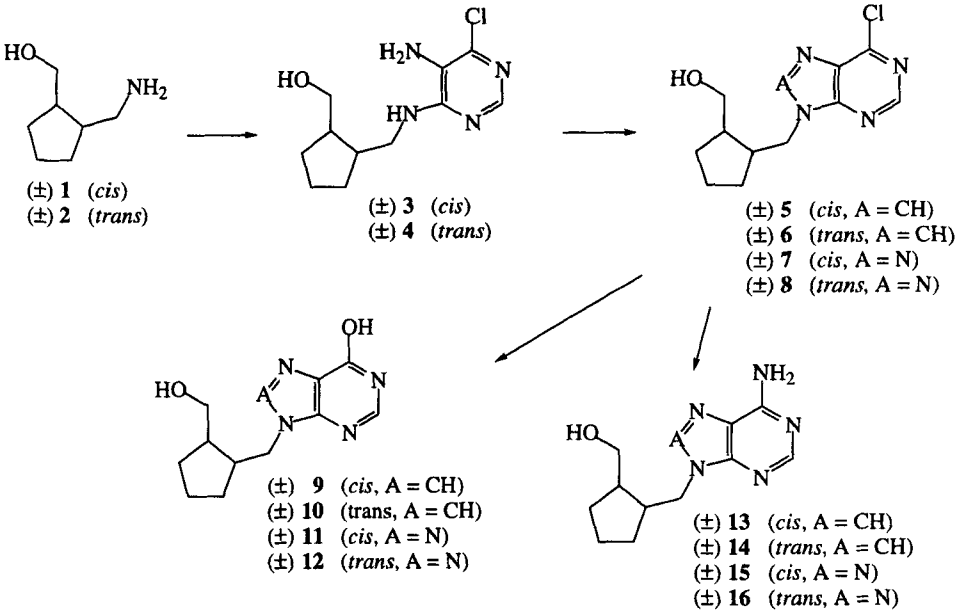
ABSTRACT. A series of new one two subtituted carbonucleoside analogues (OTC), with the purine and 8-azapurine base linked through a methylene group at the cyclopentane ring, were synthesized and evaluated for their activity against a number of viruses and tumor cells *in vitro*.

As part of an ongoing study of carbocyclic nucleoside analogues in which the standard 1,3- arrangement of the base and hydroxymethyl group is modified to a 1,2- arrangement, we prepared a series of analogues of the latter type that contain a 6-substituted purine or 8-azapurine base attached to the cyclopentane ring through a methylene group in *cis* or *trans* to the adjacent hydroxymethyl group. These are nucleoside analogues that contain four atoms between the hydroxyl group and the heterocyclic base.

Racemic mixtures of the 1,2-substituted (OTC) analogues **5** - **16** were obtained as shown in Scheme 1. The purine base was constructed about the primary amino group of the amino alcohol intermediates **1** and **2**.[1] Each aminoalcohol was firstly reacted with 5-amino-4,6-dichloropyrimidine to obtain the diaminopyrimidine **3** and **4**, and then these compounds afforded the chloropurines **5** and **6** by reaction with ethylortoformate in acid medium, or the 8-aza-6-chloropurines **7** and **8**, which were unstable, by formation of the diazonium intermediate. The 6-hydroxy analogues **9** - **12** were prepared in good yield by treatment of **5** - **8** respectively with NaOH, and similary good yields of the 6-amino analogues **13** - **16** were obtained by amination of **5** - **8** in methanol.[2]

The compounds **5**, **6** and **9** - **16** have been evaluated for their activity against a number of viruses and tumor cells *in vitro*. The antiviral activity was not appreciable and the antitumor activities [IC_{50} (μg/mL)] against murine leukaemia cells (L1210/0) and human T-lymphocytes (Molt4/C8 and CEM/0) is shown in Table 1.



SCHEME 1.

TABLE 1. Antitumor activities of compounds **5**, **6**, **9** - **16**.

Compound	L1210/0	Molt4/C8	CEM/0
5	14.0 ± 1.1	6.54 ± 0.47	16 ± 1
6	48.7 ± 0.8	22.3 ± 16.7	15 ± 2
9	> 200	> 200	> 200
10	> 200	> 200	> 200
11	61.8 ± 20.0	128 ± 101	124 ± 97
12	> 200	> 200	> 200
13	102±3	100 ± 18	108 ± 11
14	> 200	> 200	> 200
15	93.3 ± 12.2	98.8 ± 24.4	115 ± 14
16	152 ± 67	> 200	145 ± 0
ara A	14.2 ± 6.4	11.9 ± 7.3	24.8 ± 1.9

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1. M. Teijeira. Doctoral Thesis, University of Santiago de Compostela, Spain, 1996.
2. All compounds had spectral and analytical data consistent with their structures.