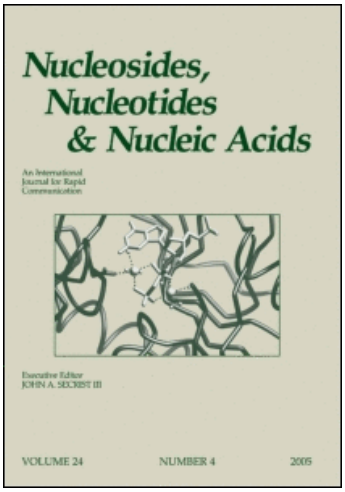

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RESOLUTION OF RACEMIC MIXTURES OF CARBOCYCLIC ANALOGUES OF NUCLEOSIDES AND ASSIGNMENT OF THEIR ABSOLUTE CONFIGURATION

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ABSTRACT

Racemic *trans*-6-chloro-9-[2-(hydroxymethyl)cyclopentyl]purine was resolved using HPLC with a chiral column. The absolute configurations of the enantiomers were determined by NMR studies of their (R)- and (S)-methoxyphenylacetates.

In our studies of 1,2-disubstituted carbocyclic analogues of nucleosides (OTCs) we have hitherto synthesized and tested only racemic mixtures. We have now developed methods for resolution of such mixtures using a chiral column, and for determination of the absolute configurations of the pure enantiomers by NMR analysis of appropriate derivatives (1). In this communication we describe the case of *trans*-6-chloro-9-[2-(hydroxymethyl) cyclopentyl]purine (Scheme 1), the preparation and anticancer activity of the racemic mixture of which have been reported previously (2).

Separation of the enantiomers was carried out using a semipreparative column of β-cyclodextrin (Cyclobond I 2000 RPS) with 9:1 water/acetonitrile as eluent. The separated enantiomers were then reacted with (R)- and (S)-methoxyphenylacetic acid (MPA), DCC and DMAP in methylene chloride at room temperature, and

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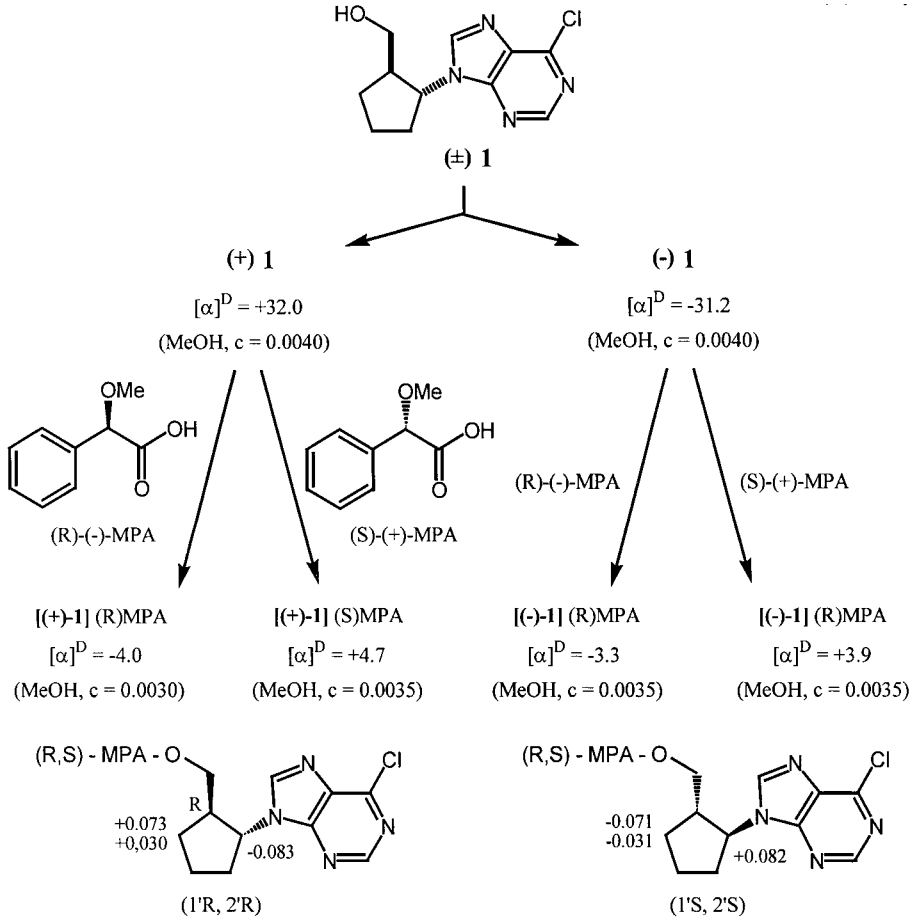

Scheme 1.

the resulting esters were purified by HPLC with 9:1 hexane/isopropanol as mobile phase. Unequivocal identification of the absolute configurations was achieved by comparison of the (R)-MPA and (S)-MPA esters as regards the chemical shifts of the protons on either side of the chiral centre nearest the substituted primary hydroxyl group (3), i.e. the protons on the carbons bearing the nitrogenated base and the hydroxymethyl group.

The same methods have been applied to other purine-based OTCs, and are currently being used on their pyrimidine-based analogues.

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3. δ^{RS} represents the difference between the chemical shift of determinated proton in the (R)- and (S)-derivatives ($\delta^{RS} = \delta R - \delta S$).

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