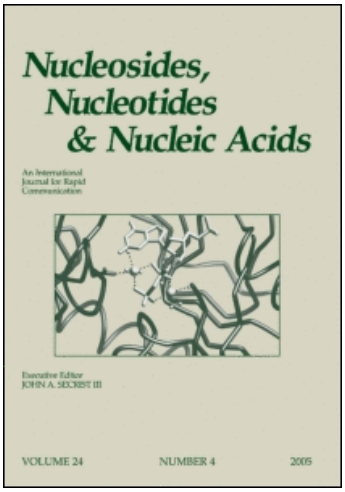

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Synthesis and Biological Activity of 2-Aminopurine Methylenecyclopropane Analogues of Nucleosides

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ABSTRACT

Synthesis and biological activity of 7- and 9-isomers ($Z+E$) of methylenecyclopropane analogues of 2-aminopurine nucleosides is described. The (S,Z)-9-isomer is a substrate for xanthine oxidase.

Key Words: Nucleoside analogues; Methylenecyclopropanes; 2-Aminopurine; Xanthine oxidase.

Purine Z-methylenecyclopropane analogues of nucleosides are antiviral agents strongly effective[1] against human cytomegalovirus (HCMV). Synguanol[1] is also a potent inhibitor of CMV in vivo.[2] The 6-deoxypurine analogues of antiviral agents acyclovir and penciclovir are efficient inhibitors of herpesviruses in vivo

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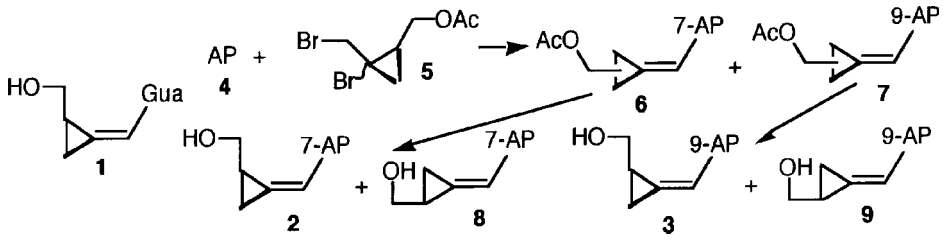
although they exhibit little activity in cell culture assays.[3,4] These analogues are converted in vivo to parent (guanine) antivirals by the action of xanthine oxidase. In addition, the 7-isomer of 6-deoxyganciclovir is an antiherpetic agent that does not require a similar activation in vivo.[5] It was therefore of interest to synthesize 7- and 9-isomers of 2-aminopurine (AP) methylenecyclopropanes **2** and **3** and investigate their biological activity.

Alkylation-elimination of 2-aminopurine (**4**) with dibromo derivative **5**[6] gave a mixture of four isomers which were smoothly resolved by a dual chromatography on



silica gel. The acetylated 7- and 9-isomers (*E,Z*) **6** and **7** were separated first. After deacetylation, the *E*- and *Z*-forms were resolved to give **2** and **3** as well as the respective *E*-isomers **8** and **9**. Because 2-amino-6-substituted purine *Z*-methylenecyclopropanes exhibit a strict *S* enantioselectivity of anti-CMV effect, the *S*-enantiomer of **3** was also prepared from (*S*)-6-chloro analogue[7] of synguanol (**1**) via the corresponding 6-thio derivative and subsequent desulfurization.

Compounds **2**, **3**, **8** and **9** were devoid of significant antiviral effect but the (*S*)-9-isomer **3** was readily oxidized by xanthine oxidase to the *S*-enantiomer of synguanol (**1**) as shown by UV spectra. Therefore, in vivo studies of anti-CMV effect of analogue **3** appear warranted. A full account of these results was published in Nucleosides, Nucleotides & Nucleic Acids.

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