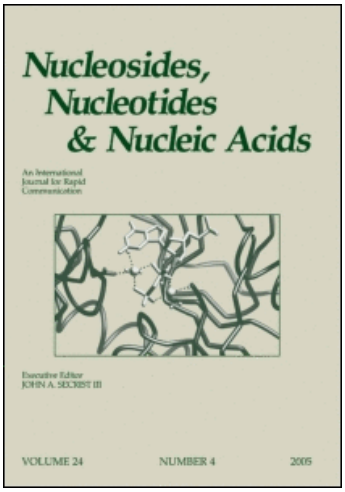

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Synthesis and Biological Evaluation of a Series of New Cyclohexenyl Nucleosides

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ABSTRACT

A series of cyclohexenyl nucleosides (**1–8**) were successfully prepared with moderate yield and their cytotoxicity and antiviral activity were investigated. Among the eight new compounds, only the diaminopurine analogue **8** showed pronounced activity against HSV-1, HSV-2.

INTRODUCTION

Carbocyclic nucleosides have taken a particular place in the design process of new antiviral agents because of their hydrolytic stability.[1] Indeed, introduction of a double bond into the cyclohexane ring could facilitate phosphorylation of the nucleoside analogue and, hence, lead to enhanced antiviral activity. Both *D*- and

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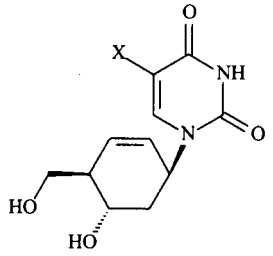
L-cyclohexenylguanine exhibited highly potent and selective activity against herpes viruses (HSV-1, HSV-2, VZV, CMV), similar to that of known antiviral drugs like acyclovir or ganciclovir.[2,3] These results prompted us to synthesize other cyclohexenyl nucleosides **1–8** in order to study the effects of different base substitutions on antiviral activity and toxicity.

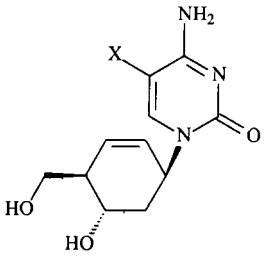
CHEMISTRY

Mitsunobu reaction conditions were chosen for coupling of the base moiety to the pseudosugar part, as it is generally done in carbocyclic pyrimidine nucleoside synthesis. Sodium benzoate was added as a catalyst which might probably accelerate the main SN_2 substitution reaction rather than the side reaction leading to formation of the *O*-substituted byproduct.[4,5]



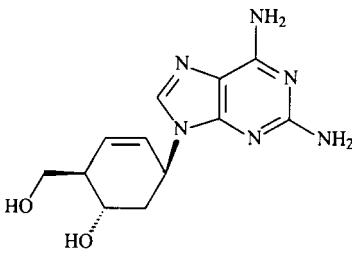
(±)

1 X= H
2 X= I
3 X= F
4 X= CH_3



(±)

5 X= H
6 X= F
7 X= CH_3



(±)

8

BIOLOGICAL ACTIVITY

Compounds **5–8** demonstrated marked activity against HSV-1 and HSV-2. Compound **8** effected a 50% reduction of the cytopathogenicity induced by HSV-1 at a concentration of 0.38 μg/mL. Compounds **1** and **4** exhibited no inhibitory effect on VZV or CMV in human embryonic lung (HEL) cells.

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