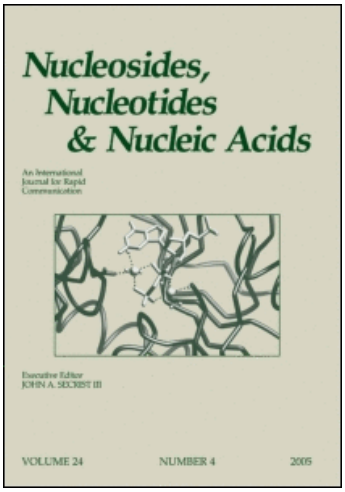

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A CYCLOBUTANE CARBONUCLEOSIDE WITH MARKED SELECTIVITY AGAINST TK^+ AND TK^- VARICELLA ZOSTER VIRUS

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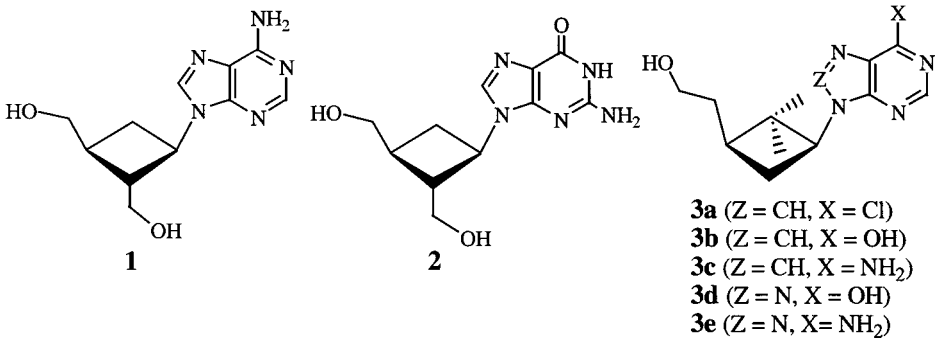
ABSTRACT

Several cyclobutyladenine and analogous carbonucleosides were synthesized from 1*R*-α-pinene and their anti-viral activity was tested. One of them (**3e**) showed interesting selectivity against both TK^+ and TK^- VZV.

The interesting antiviral properties of some carbocyclic nucleosides incorporating a cyclobutane ring in their pseudo-sugar moiety, such as the antiherpes activity of Cyclobut A (**1**) (1), and the antihepatitis activity of Lubocavir (**2**) (2), led us to explore several series of cyclobutane derivatives.

In this context several derivatives of adenine and of adenine analogues of type **3** were synthetized in enantiomerically pure form for the evaluation of their antiviral properties.

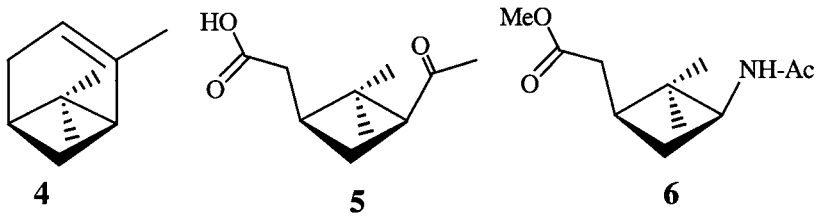
The starting material for the preparation of these compounds was easily available 1*R*-α-pinene (**4**), which upon permanganate oxidative cleavage gave (1*S*, *cis*)-pinonic acid (**5**). Beckmann rearrangement of **5** by means of H_2NOSO_3H, followed by esterification in MeOH/TsOH yielded acetamido ester **6**. Reduction of **6** by $LiBH_4$, followed by 2N HCl hydrolysis led to amino alcohol **7** in a 20–28% overall yield. Best yield was achieved when the crude product from the reduction of

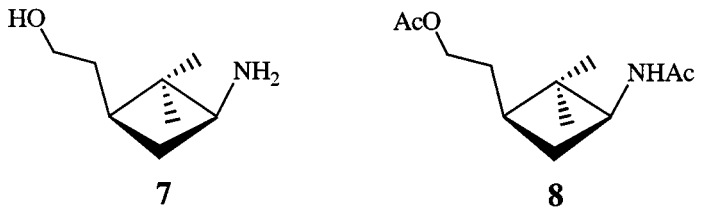


Scheme 1.

6 was acetylated by Ac_2O/Pyr and the diacetyl derivative **8** was isolated previously to its hydrolysis to **7**. Synthesis of compounds **3** was then accomplished by constructing the adenine or 8-aza adenine moiety on the amino group of **7**, following well established procedures (3).

Compounds **3** were assayed against a variety of viruses. Most of them failed to show a noticeable activity against HIV-1 and HIV-2, cytomegalovirus, parainfluenza-3 virus, reovirus-1, sindbis virus, coxsackie virus B4, Punta Toro virus, herpes simplex virus types 1 and 2, vaccinia virus and vesicular stomatitis virus at subtoxic concentrations. However, compound **3e** showed a remarkable selective activity against both TK^+ and TK^- strains of varicella zoster virus (see Table), thus





Scheme 2.

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Table.

Compound	Antiviral Activity IC_{50}(μg/mL)[a]				Cytotoxicity (μg/mL)	
	TK^+ VZV		TK^- VZV			
	YS Strain	OKA Strain	07/1 Strain	YS/R Strain	Cell Morphology (MCC)[b]	Cell Growth (CC_{50})[c]
3a	>50	50	>50	>50	>50	32
3b	>50	>50	>50	>50	>50	>50
3c	28	20	>20	20	≥50	45
3d	>50	>50	>50	>50	>50	>50
3e	3.5	3.2	9.3	3.5	50	>50
ACV[d]	0.28	0.24	7.8	2.5	>50	>200
BVDU[e]	0.0005	0.0004	8.7	20	>50	200

[a]Inhibitory concentration required to reduce virus plaque formation by 50%. Virus imput was 20 plaque forming units (PFU). [b]Minimum cytotoxic concentration that causes a microscopically detectable alteration of cell morphology. [c]Cytotoxic concentration required to reduce cell growth by 50%.). [d]Acyclovir. [e]Brivudine.

showing that its anti-VZV activity is independent from the VZV-encoded thimidine kinase.

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