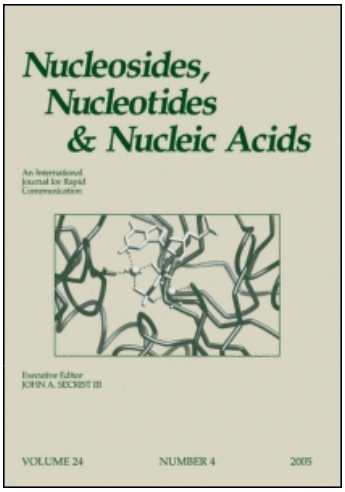

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Deaza- and Deoxyadenosine Derivatives: Synthesis and Inhibition of Animal Viruses as Human Infection Models

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ABSTRACT

N^6-Cycloalkyl-2′,3′-dideoxyadenosine derivatives and (2-chloro)-N^6-cycloheptyl-3-deazaadenosine have been synthesized and tested, along with other (deaza)purine (deoxy)nucleosides from our chemical library, as inhibitors of virus replication against Bovine Herpes Virus 1 (BHV-1) and sheep Maedi/Visna Virus (MVV). Most compounds demonstrated good antireplicative activity against MVV, showing also low cell toxicity.

Key Words: Deazaadenosine derivatives; Deoxyadenosine derivatives; Bovine Herpes Virus 1; Maedi Visna Virus; Antivirals.

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INTRODUCTION

Viral infections are life threatening and among the most common diseases both in developing and wealthy countries. Furthermore, emerging of new viral strains and increasing of resistance to known drugs push the needs for new antivirals.

In the last two decades the class of retrovirus has gained much attention, mostly because of human immunodeficiency virus (HIV), causative agent of acquired immunodeficiency disease (AIDS). Recently, it has been proposed that other viruses of the same class, in particular Maedi-Visna Virus (MVV), can be in vitro ed in vivo models for testing anti-HIV potential drugs.[1,2]

Another class of widespread viruses is that of herpes virus (HV), which cause severe infections both in humans and animals. Animal HV shows high degree of similarity to human one, being suitable models to study molecular biology and effective therapies of HV.[3] In particular, Bovine Herpes Virus type 1 (BHV-1), a neurotropic HV causing infectious rhinotracheitis in cattle, can be a suitable animal model for studying human HV.

Taking into account all the above, and also our long expertise in nucleoside medicinal chemistry, we started a program aimed at testing compounds on BHV and MVV.

In the present study we report on the synthesis of N^6-cycloalkylamino-2′,3′-dideoxyadenosine derivatives, bearing or not a chlorine atom in 2 position (**1–6**), and of 2-chloro-N^6-cyclopentyl-3-deazaadenosine (**18**).

Synthesized compounds, along with other purine nucleoside analogues previously prepared in our laboratory,[4–6] have been tested for their antiviral activity against BHV-1 and MVV, and for their cytotoxicity on the cell lines used for virus replication. Structures of tested compounds are shown in Fig. 1.

RESULTS AND DISCUSSION

Chemistry

The synthesis of the N^6-cycloalkyl-2′,3′-dideoxadenosine derivatives **1–6** was accomplished as reported in Sch. 1.

2,6-Dichloro-9-(2,3-dideoxy-β-D-*glycero*pentofuranosyl)-9H-purine (**33**)[7] was treated with the appropriate cycloalkylamine, and then deprotected with NH_3/MeOH, to give nucleosides **1**, **3**, and **5**. Dechlorination of the purified products with Pd/C under hydrogen atmosphere gave the corresponding 2′,3′-dideoxy-N^6-cycloalkyladenosine derivatives **2**, **4**, and **6**.

Synthesis of the 3-deazaadenosine derivative **18** was accomplished according to Scheme 2. 2,6-Dichloro-3-deazapurine[8] (**34**) was fused with tetraacetylribose (**35**) to give about 90% yield of the protected nucleoside **36**. This nucleoside has been already prepared, but with a different procedure and a much lower yield.[9] Treatement of **36** with cyclopentylamine at high temperature gave the desired nucleoside **18**.

Structures of synthesized compounds were confirmed using spectroscopic techniques; in particular, assignment of glycosilation site and anomeric configuration of compound **36** was performed using UV, [^{1}H] NMR and n.O.e. data.

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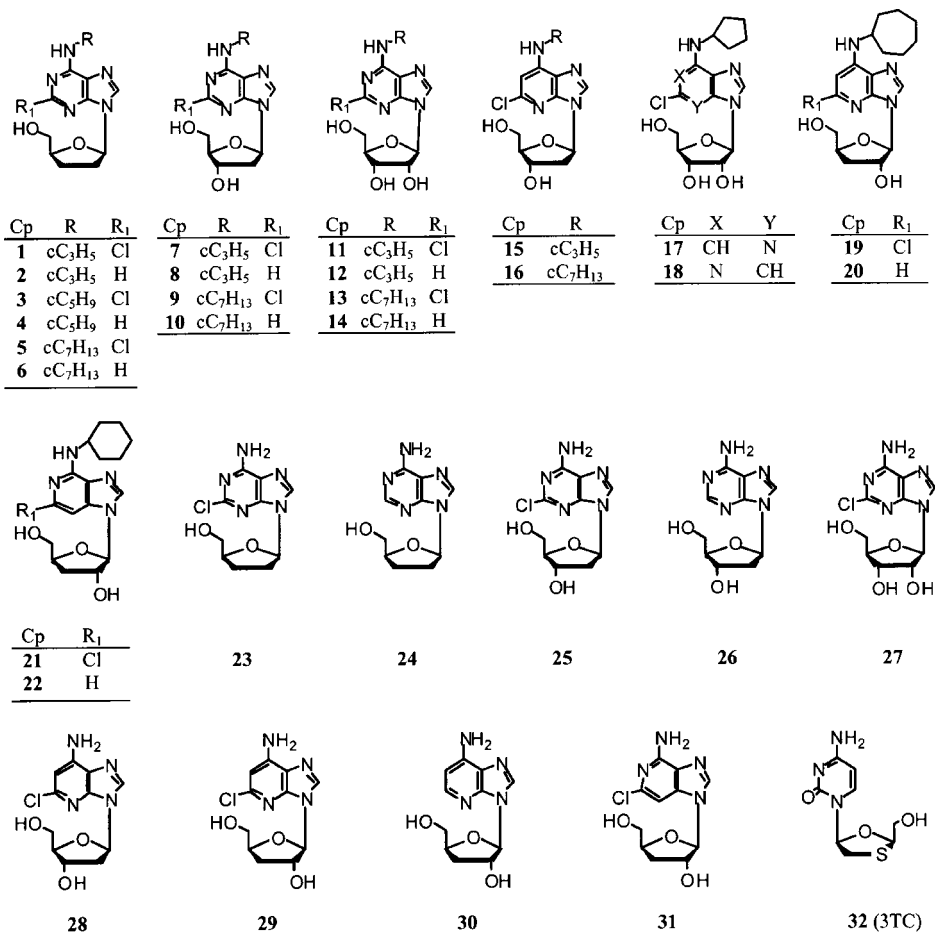
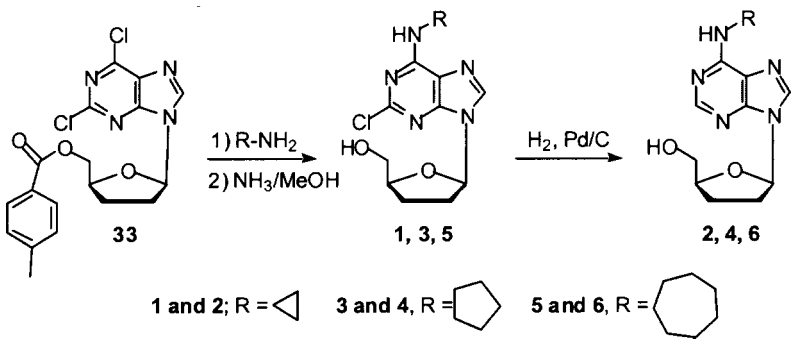


Figure 1. Structure of tested compounds.



Scheme 1. Synthesis of dideoxyadenosine derivatives.

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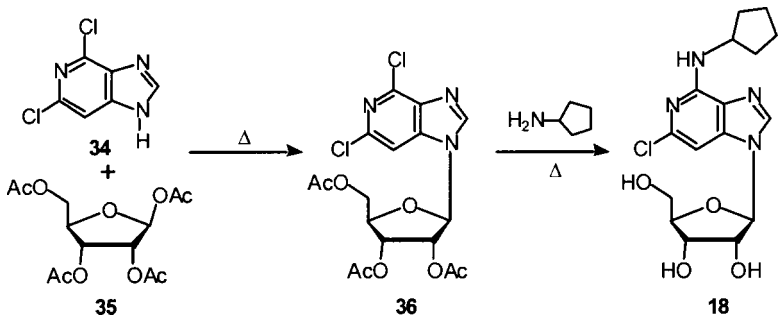

Scheme 2. Synthesis of 2-chloro-3-deazacyclopentyladenosine.

Table 1. AntiMVV activity and cytotoxicity of selected compounds.

Cp	CD_{50},[a] μM	Viral titre[b]	EC_{50},[c] μM	3-TC/Cp	CD_{50}/EC_{50}
2	280	2.50	0.15	33	1867
5	125	3.50	0.027	185	4630
7	234	3.75	0.15	33	1560
13	100	6.50	0.15	33	667
19	145	3.50	0.15	33	967
27	>400	3.50	0.15	33	>2667
3-TC	>300	<1	5	1	>60
Virus control		6.50			

[a]Concentration of compound able to give 50% of the maximal cytotoxic effect.
[b]Maximal dilution (negative log of concentration) at which the virus is still able to give cytopathic effect.
[c]Concentration of compound able to lower virus effects by 50%.

Biology

All compounds showed moderate activity against BHV-1, with EC_{50} averaging around 50 μM. Cytotoxicity of compounds ranged, with few exceptions, between 100 and 400 μM.

Regarding MVV, Table 1 shows data of compounds that are at least 20-fold more potent than the reference compound 3-thiacytidine (3-TC). In addition to the fact that 6 compounds out of 29 showed such a high activity, it is worth to note that a cycloheptyl substituent on N^6 (**5**, **13**, **19**) and a chlorine atom in 2 position (**5**, **7**, **13**, **19**, **27**) are important for high activity.

ACKNOWLEDGMENTS

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