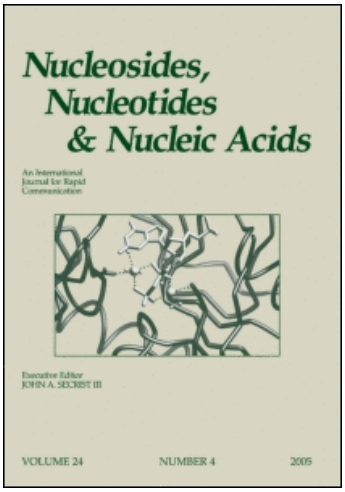

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INHIBITORY EFFECTS OF 1-DEAZAADENOSINE ANALOGUES ON HIV REPLICATION AND ADENOSINE DEAMINASE

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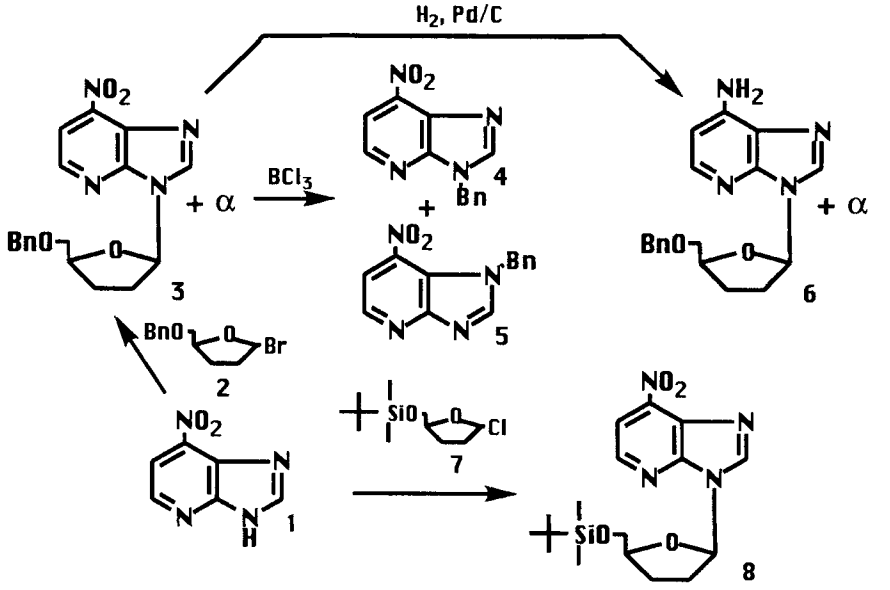
Abstract. A series of 2',3'-dideoxy-N^6-(cyclo)alkyl-1-deazaadenosine derivatives were synthesized starting from 2,6-dichloro-1-deazapurine (**9**). The new nucleosides proved to be good inhibitors of HIV-1 replication, the most active being the 2',3'-dideoxy-2-chloro-N^6-cycloctyl-1-deazaadenosine (**14h**, $ED_{50} = 0.4$ μM).

1-Deazaadenosine derivatives have been shown to possess cytotoxic activity,[1,2] adenosine receptor affinity,[3] and to inhibit adenosine deaminase[4,5] and platelet aggregation.[3,6] We have already reported the coupling of 7-nitro-3H-imidazo[4,5-b]pyridine (**1**)[1] and of 5-chloro-7-nitro-3H-imidazo[4,5-b]pyridine[7] with ribose and 2-deoxyribose derivatives to obtain 6-amino-[1] and 6-hydroxylamino-1-deazapurine nucleosides.[2,8] Moreover, 2',3'-dideoxynucleosides are good tools for inhibition of HIV replication.

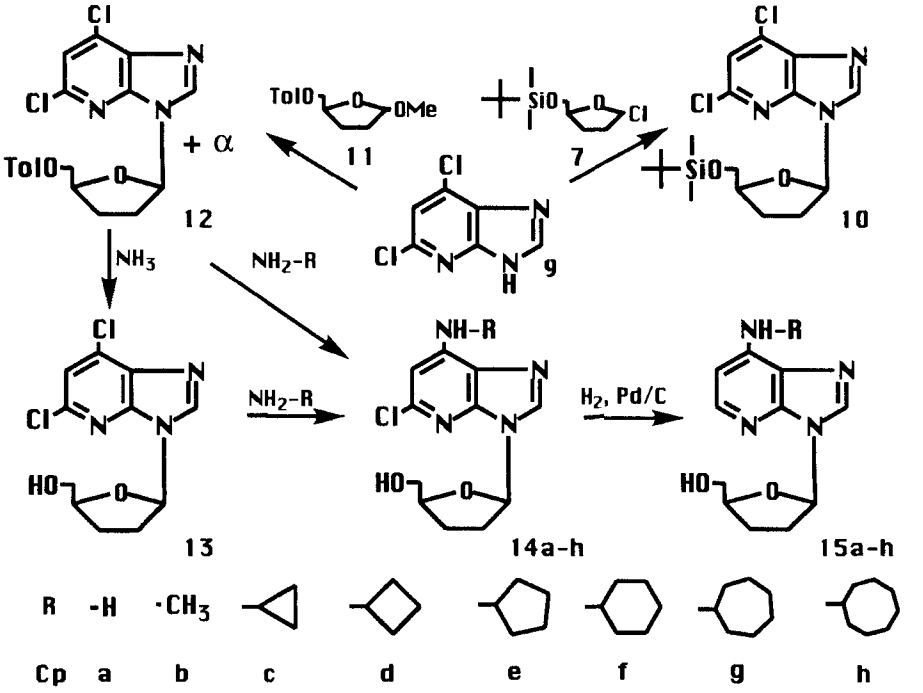
On this basis we attempted the synthesis of 2',3'-dideoxy-1-deazaadenosine by reaction of compound **1** with the benzyl derivative of dideoxy sugar **2** (Scheme 1). A mixture of α and β anomers (**3**) was obtained in 40% yield but attempts of deprotection failed leading to N-3 (**4**) and N-1 (**5**) benzyl derivatives. Catalytic reduction of compound **3** gave the still protected nucleoside **6** in low yield. Coupling of **1** with the *t*-butyldimethylsilyl derivative **7** led to the β anomer **8** in very low yield. Alternatively, we used the more versatile base 5,7-dichloro-3H-imidazo[4,5-b]pyridine,(**9**)[7,9] which was glycosylated using first the sugar **7**, to give small quantity of **10**, and then the toluoyl derivative **11**,[10] to give mixture of α and β anomers (**12**) in 70% yield (Scheme 2).

The anomeric and isomeric configuration of the new nucleosides was assigned on the basis of NMR and UV spectra.[11]

Substitution of chlorine in 6 position from compound **12** or from the deprotected derivative **13** with ammonia, methylamine and several



Scheme 1



Scheme 2

TABLE 1. Biological activity of 2',3'-dideoxy-N^6-(cyclo)alkyl-1-deazaadenosines.

Cp	R	EC_{50} (μM) HIV-1	CC_{50} (μM) C8166 cells	K_i (μM) ADA calf intest.
14a	H	>1000	>1000	>100
15a	H	500	>1000	2.5
14b	CH_3	400	800	11
15b	CH_3	50	100	2.2
14c	cC_3H_5	200	400	>100
15c	cC_3H_5	100	750	78
14d	cC_4H_7	4	250	>100
15d	cC_4H_7	50	400	92
14e	cC_5H_9	20	50	>100
15e	cC_5H_9	40	200	>100
14f	cC_6H_{11}	4	20	>100
15f	cC_6H_{11}	40	50	69
14g	cC_7H_{13}	0.8	9	>100
15g	cC_7H_{13}	8	40	53
14h	cC_8H_{15}	0.4	10	>100
15h	cC_8H_{15}	0.8	10	>100

cycloalkylamines gave nucleosides **14a-h**, whose reduction with Pd/C led to the dechlorinated products (**15a-h**).

BIOLOGICAL EVALUATION

The anti HIV-1 activities and toxicities of synthesized compounds were assessed in C8166 cells infected with HIV-1_{IIIB}. The results are reported on TABLE 1. While the parent compound **15a** was inactive, the presence of cycloalkyl substituents on N^6 brought about a good anti HIV activity, which increased with the dimension of the substituent; on the other hand, the presence of a chlorine atom in 2-position improved both activity and therapeutic index, the most active compound being 2',3'-dideoxy-2-chloro-N^6-cycloctyl-1-deazaadenosine (**14h**, EC_{50} = 0.4 μM).

The compounds were also tested for their ability to inhibit calf intestine adenosine deaminase (ADA). Results (TABLE 1) showed that none of the tested derivatives were substrate of the enzyme, and some of them were good inhibitors, with 2',3'-dideoxy-1-deazaadenosine (**15a**) and 2',3'-dideoxy-N^6-methyl-1-deazaadenosine (**15b**) being the most active compounds, with a Ki of 2.5 and 2.2 μM, respectively.

A considerable decrease in activity is produced by the presence of a chlorine atom

in the 2-position and of a cycloalkyl substituent in N^6. This is in agreement with our hypothesis that 1-deazaadenosine derivatives interact directly with the enzyme at the catalytic site, since the presence of a bulk, hydrophobic substituent on the exocyclic nitrogen is detrimental for the hydrogen bonding of the molecules.

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