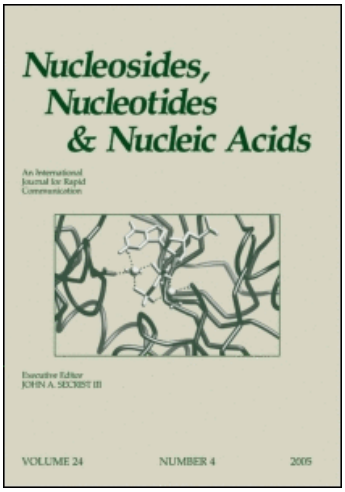

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BASE-MODIFIED PURINE 2',3'-DIDEOXYRIBONUCLEOSIDES: SYNTHESIS VIA DEOXYGENATION OR DIRECT NUCLEOBASE ANION GLYCOSYLATION

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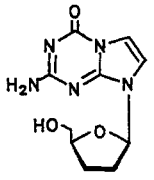
Abstract: 5-Aza-7-deazapurine, 5-aza-1,7-dideazapurine, and 8-azapurine 2',3'-dideoxy-D-ribonucleosides have been synthesized and inhibitory activity against HIV reverse transcriptase and DNA-polymerases has been evaluated.

Purine- and pyrimidine 2',3'-dideoxynucleosides show antiviral activity against human immunodeficiency virus (HIV).[1] Permeation through the cell membrane, phosphorylation at OH-5', and metabolic stability are necessary for their use as drugs during treatment of AIDS. Moreover, a high selectivity index of the corresponding triphosphates between HIV reverse transcriptase and DNA polymerases is required.

In the following we report on the synthesis of base-modified 2',3'-dideoxyribonucleosides (5-aza-7-deazapurine and 5-aza-1,7-dideazapurine as well as 8-azapurine and 7-deazapurine 2',3'-dideoxyribofuranosides). Moreover, inhibitory data of corresponding triphosphates against HIV reverse transcriptase (RT) and cellular DNA-polymerases are presented.

Apart from the 7-deazapurine compounds 2',3'-dideoxyribonucleosides have been prepared by anion glycosylation of corresponding nucleobases with an anomeric mixture of the halogenose 2 [2] according to the formula schemes A and B. The halogenose was prepared in-situ from the corresponding lactol affording the protected nucleosides. They were desilylated and converted into the final molecules. The glycosylation position as well as the anomeric configuration was determined from ^{13}C NMR in combination with 1D NOE difference spectroscopy.[3]



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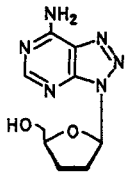

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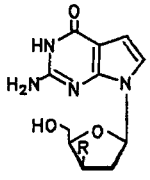
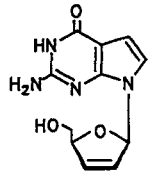


3a: R = H
3b: R = OH



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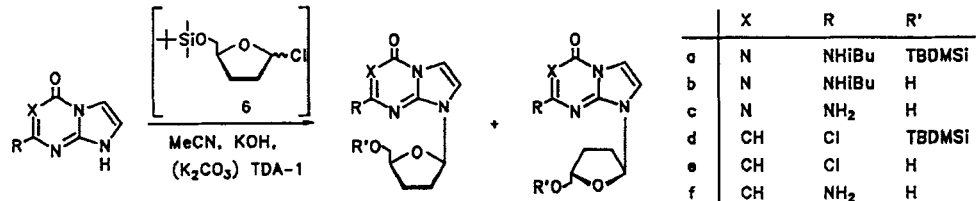
5-Aza-7-deazapurine- and 5-Aza-1,7-dideazapurine 2',3'-dideoxyribonucleosides (A)

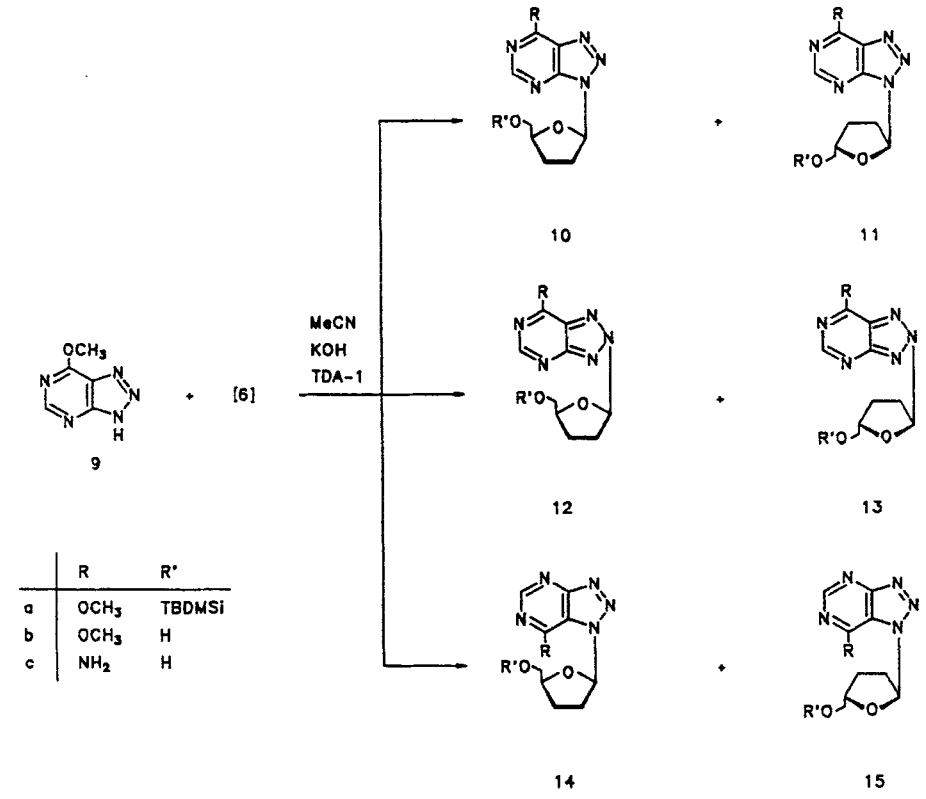


	X	R	R'
a	N	NHiBu	TBDMSi
b	N	NHiBu	H
c	N	NH_2	H
d	CH	Cl	TBDMSi
e	CH	Cl	H
f	CH	NH_2	H
g	CH	H	H

5a: R = Cl; X = CH
5b: R = NHiBu; X = N

7 8

8-Azapurine 2',3'-dideoxyribonucleoside (B)



9

	R	R'
a	OCH_3	TBDMSi
b	OCH_3	H
c	NH_2	H

10 11 12 13 14 15

7-Deazapurine 2',3'-didehydro-2',3'-dideoxynucleosides were prepared by deoxygenation via the elimination procedure depicted in the formula scheme C. Nucleophilic substitution of the 4-chloro

TABLE 1. ^{13}C NMR Data of Base-modified 2',3'-Dideoxyribonucleosides in DMSO-d_6 (rel. to int. TMS, purine numbering).

	C-1	C-2	C-4	C-5	C-6	C-7	C-8	C-1'	C-2'	C-3'	C-4'	C-5'
3a	-	152.6	150.3	100.1	158.7	102.9	116.9	83.0	31.5	26.5	80.6	63.4
3b	-	152.4	150.2	99.8	158.6	101.8	118.3	81.3	a)	69.3	84.0	59.9
7c	-	149.7	150.1	-	165.4	107.9	114.4	83.8	31.6	25.3	82.0	62.5
7e	97.3	156.1	144.0	-	155.9	107.3	117.3	84.9	32.0	25.0	82.4	62.3
4	-	152.6	150.5	100.1	158.6	102.2	116.9	87.4	126.1	133.6	87.0	63.6
8c	-	150.2	150.1	-	165.4	108.2	114.6	84.2	30.7	26.1	81.2	63.4
8e	97.4	156.1	144.2	-	155.9	107.6	117.5	85.3	31.0	26.0	81.5	63.4
10c	-	156.8	148.5	123.9	156.2	-	-	85.9	30.6	27.0	82.7	63.8
11c	-	156.9	148.5	124.0	156.1	-	-	86.3	30.1	26.5	81.7	63.1
12c	-	155.9	157.1	125.4	157.5	-	-	94.4	31.9	26.5	83.8	63.9
13c	-	156.7	157.1	125.5	157.5	-	-	94.7	31.3	25.6	82.3	63.1
14c	-	151.9	154.5	113.7	160.9	-	-	89.1	30.2	25.4	83.3	63.0
15c	-	151.8	154.6	113.6	160.9	-	-	89.5	29.4	25.3	81.8	63.0

a) superimposed by DMSO

substituent of **18** gave compound **4**. Catalytic hydrogenation of **4** opens a new access to the 2',3'-dideoxynucleoside **3a**. The threo-nucleoside **3b** was synthesized from **17a** as shown in the scheme.

7-Deazapurine 2',3'-Dideoxyribonucleosides (C)

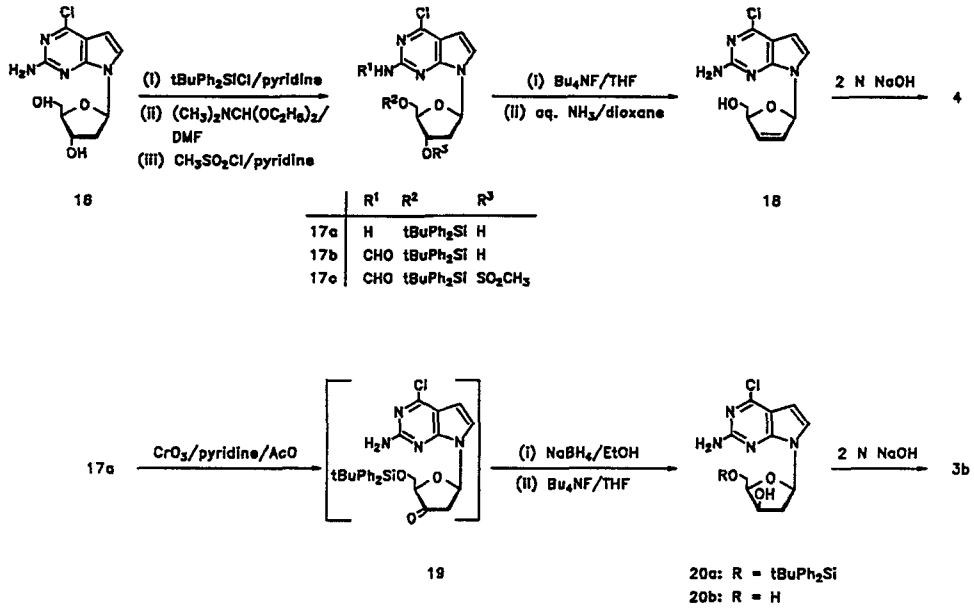
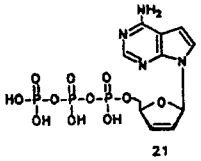


TABLE 2. Inhibitory Data (IC_{50}; μM) of 2',3'-Dideoxyribonucleoside Triphosphates against HIV Reverse Transcriptase (RT) and DNA Polymerases.

Compnd	IC_{50} (RT)	IC_{50} (DNA-Pol$_\alpha$)	IC_{50} (DNA-Pol$_\gamma$)
AZTTP	6.3	730	-
ddATP	0.45	-	-
ddGTP	0.2	-	-
21	0.53	970	-
22	0.12	680	1216
23	0.43	280	-
24	1000.		

From the series of base-modified dideoxynucleosides 5'-triphosphates were prepared in a one pot reaction.[4] Selected compounds are depicted in the formula scheme. They were tested as inhibitors of HIV reverse transcriptase or DNA-polymerases α and γ. Inhibitory data are summarized in Table 2. Compounds **21-23** are 10-50 times more potent than AZTTP. Compound **22** shows high selectivity between HIV RT and cellular DNA-polymerases. The inhibitory action of the 7-deazapurine 2',3'-dideoxyribonucleosides demonstrates that N-7 is not required for RT binding. On the other hand, inhibitory studies with **24** revealed that N-1 is an essential enzymic binding position.



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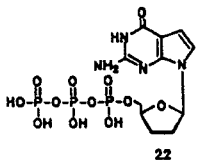

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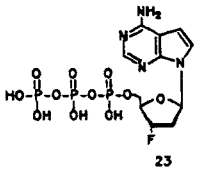

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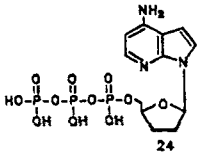

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