Synthesis and Biological Evaluation of N^6-Cycloalkyl Derivatives of 1-Deazaadenine Nucleosides: A New Class of Anti-Human Immunodeficiency Virus Agents

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A series of 1-deazaadenine nucleosides with the N^6 nitrogen unsubstituted or bearing methyl or cycloalkyl substituents, with or without a chloro group in the 2-position, and with the glycosylic moiety being ribose (**1**–**16**), 2′-deoxyribose (**17**-**32**), or 2′,3′-dideoxyribose (**33**–**48**) were designed and synthesized starting from 5,7-dichloro-3*H*-imidazo[4,5-*b*]pyridine (**50**). These compounds were evaluated for their *in vitro* activity against human immunodeficiency virus type-1 (HIV-1) and herpes simplex virus type-1 (HSV-1). In addition they were tested for their ability to inhibit adenosine deaminase (ADA) from calf intestine. While the parent compounds 1-deazaadenosine (**9**), 2′-deoxy-1-deazaadenosine (**25**), and 2′,3′-dideoxy-1-deazaadenosine (**41**) and the corresponding 2-chloro derivatives were inactive, nucleosides bearing cycloalkyl substituents on N^6 exhibited moderate to good anti-HIV-1 activity, compared to 2′,3′-dideoxyadenosine, with the degree and pattern of improvement depending on the structure of the sugar moiety. In general, 2′-deoxy- and 2′,3′-dideoxy derivatives were more potent compounds than the corresponding ribose nucleosides. Compounds bearing a 6-cycloheptyl or cyclooctylamine were the most active in every series. The presence of a chloro group in the 2-position improved both activity and therapeutic index in every series, the most active compound being 2′-deoxy-2-chloro-N^6-cycloheptyl-1-deazaadenosine (**23**; ED_{50} = 0.2 μM). On the other hand, most of these derivatives were inactive as anti-HSV-1 agents, showing a high degree of virus selectivity. The 1-deazaadenine derivatives were not substrates of adenosine deaminase, and some of them proved to be good inhibitors of the enzyme. However, the ADA inhibitory activity does not account for the antiviral potency since increased lipophilicity and steric hindrance of substituents resulted in derivatives much less active than the parent compounds.

Most of the antiviral drugs that have been world-wide licensed for clinical use belong to the class of purine and pyrimidine nucleoside analogues. Among the most promising inhibitors of human immunodeficiency virus (HIV) replication, which are targeted at the virus-specified reverse transcriptase, are the 2′,3′-dideoxy nucleoside analogues.[1] Several 6-(cycloalkylamino)-[2,3], 6-(cycloalkylthio)-,[2,3] and 6-(cycloalkyloxy)purine 2′,3′-dideoxy nucleosides[3] have been synthesized, and many of these analogues exhibit some anti-HIV activity. In our effort to synthesize N^6-substituted deaza nucleosides endowed with pharmacological activity, we selected 1-deazapurine derivatives since 1-deazaadenosine (**9**) has been shown to possess cytotoxic activity,[4] to inhibit platelet aggregation,[5] and to act as an agonist of adenosine receptors.[6] Interestingly, the 1-deaza analogues of adenosine exhibit good inhibitory activity on adenosine deaminase (ADA),[7,8] an enzyme involved in the pathogenesis of various diseases and particularly in the severe combined immunodeficiency disease (SCID).[9] This enzyme is also responsible for deamination, and concomitant loss of activity, of many potentially useful drugs with a nucleosidic structure.[10]

We have already reported the coupling of 7-nitro-3*H*-imidazo[4,5-*b*]pyridine,[4] 5-chloro-7-nitro-3*H*-imidazo[4,5-*b*]pyridine,[11] and the more versatile base 5,7-dichloro-3*H*-imidazo[4,5-*b*]pyridine (**50**)[11] with ribose and 2-deoxyribose derivatives to obtain 6-amino-,[4] 6-(hydroxyamino)-,[12,13] and 6-(cycloalkylamino)-1-deazapurine nucleosides.[6,14] Our approach is now to use **50**[11] as the starting base to obtain the new nucleoside 2′,3′-dideoxy-1-deazaadenosine (**41**) and a number of novel 2′,3′-dideoxy-6-(cycloalkylamino)-1-deazaadenosine analogues. In particular, the present study was aimed at direct comparison of the activity as anti-HIV-1 and anti-HSV-1 (herpes simplex virus type-1) agents and ADA inhibitors of a series of 1-deazapurine nucleosides with the N^6 nitrogen unsubstituted or bearing methyl or cycloalkyl substituents, with or without a chloro group in the 2-position, and with the glycosylic moiety being ribose (**1**–**16**), 2′-deoxyribose (**17**–**32**), or 2′,3′-dideoxyribose (**33**–**48**) (Figure 1).

Chemistry

The syntheses of 1-deazaadenosine (**9**),[4] 2-chloro-1-deazaadenosine (**1**),[11] and compounds **2**, **5**, **6**, **10**, **13**, and **14**[6] have already been described. Compounds **3**, **4**, **7**, **8**, **11**, **12**, **15**, and **16** were prepared starting from 2,6-dichloro-1-deazaadenosine[11] and are described elsewhere.[15] The synthesis of the 2′-deoxy nucleosides **17**, **18**, **21**, **22**, **25**, **26**, **29**, and **30** is reported in a preceding paper.[14] Preparation of the 7-(cycloalkylamino)-5-chloro-3-(2-deoxy-β-D-*glycero*-pentofuranosyl)-3*H*-imidazo[4,5-*b*]pyridines **19**, **20**, **23**, and **24** was accomplished by

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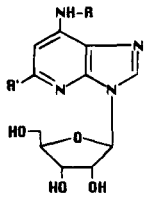
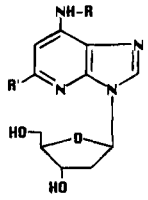
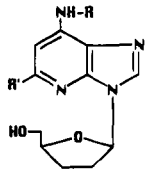


	R	R'		R	R'
1	H	Cl	9	H	H
2	CH_3	Cl	10	CH_3	H
3	cC_3H_5	Cl	11	cC_3H_5	H
4	cC_4H_7	Cl	12	cC_4H_7	H
5	cC_5H_9	Cl	13	cC_5H_9	H
6	cC_6H_{11}	Cl	14	cC_6H_{11}	H
7	cC_7H_{13}	Cl	15	cC_7H_{13}	H
8	cC_8H_{15}	Cl	16	cC_8H_{15}	H



	R	R'		R	R'
17	H	Cl	25	H	H
18	CH_3	Cl	26	CH_3	H
19	cC_3H_5	Cl	27	cC_3H_5	H
20	cC_4H_7	Cl	28	cC_4H_7	H
21	cC_5H_9	Cl	29	cC_5H_9	H
22	cC_6H_{11}	Cl	30	cC_6H_{11}	H
23	cC_7H_{13}	Cl	31	cC_7H_{13}	H
24	cC_8H_{15}	Cl	32	cC_8H_{15}	H



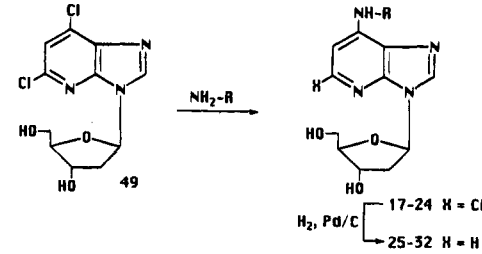
	R	R'		R	R'
33	H	Cl	41	H	H
34	CH_3	Cl	42	CH_3	H
35	cC_3H_5	Cl	43	cC_3H_5	H
36	cC_4H_7	Cl	44	cC_4H_7	H
37	cC_5H_9	Cl	45	cC_5H_9	H
38	cC_6H_{11}	Cl	46	cC_6H_{11}	H
39	cC_7H_{13}	Cl	47	cC_7H_{13}	H
40	cC_8H_{15}	Cl	48	cC_8H_{15}	H

Figure 1.

reacting 5,7-dichloro-3-(2-deoxy-β-D-*glycero*-pentofuranosyl)-3*H*-imidazo[4,5-*b*]pyridine **49**[14] with the appropriate cycloalkylamine (Scheme 1) under the reaction conditions listed in Table 1. Catalytic hydrogenolysis of the chloro group with 10% Pd/C in ethanol and 2 N NaOH afforded the corresponding derivatives **27**, **28**, **31**, and **32** (Scheme 1 and Table 1).

The synthesis of the 2′,3′-dideoxy nucleosides of 1-deazapurine was first attempted by coupling the sodium salt of **50**[11] with 2,3-dideoxy-5-*O*-(*tert*-butyldimethylsilyl)-D-*glycero*-pentofuranosyl chloride,[16] freshly

Scheme 1



prepared from the corresponding lactol.[17] This reaction gave a mixture of anomers **45** and **46** in very low yield.

Alternatively, the synthesis of the desired compounds was achieved by coupling the trimethylsilyl derivative of **50** with methyl 2,3-dideoxy-5-*O*-(4-methylbenzoyl)-D-*glycero*-pentofuranoside (**51**)[18] in the presence of trimethylsilyl triflate (TMS-TF) in dry methylene chloride to give the anomeric mixture of **52** and **53** (Scheme 2). Deprotection of nucleosides was attempted at room temperature both with potassium carbonate in methanol and with methanolic ammonia, the latter method giving the best yield of α- and β-anomers **54** and **55** which were separated from each other by flash chromatography.

The anomeric configuration of compounds **54** and **55** was assigned applying NOE difference spectroscopy. Saturation of H-1′ of **55** yielded 1.0% NOE of the H-4′ signal, establishing β-D-configuration, while saturation of H-1′ of **54** gave no effect at the H-4′ signal, establishing α-D-configuration. Moreover, this assignment is also in agreement with the empirical rule based on chemical shift differences of H-4′ and H-5′ ($\Delta\partial$), which should be smaller for the β-anomer than for the α-one.[19] In the case of the protected α-anomer **52**, $\Delta\partial$ was 0.38 ppm, and in the case of the β-anomer **53**, $\Delta\partial$ was 0 ppm. After deprotection, the $\Delta\partial$s of **54** and **55** were 0.95 and 0.58, respectively.

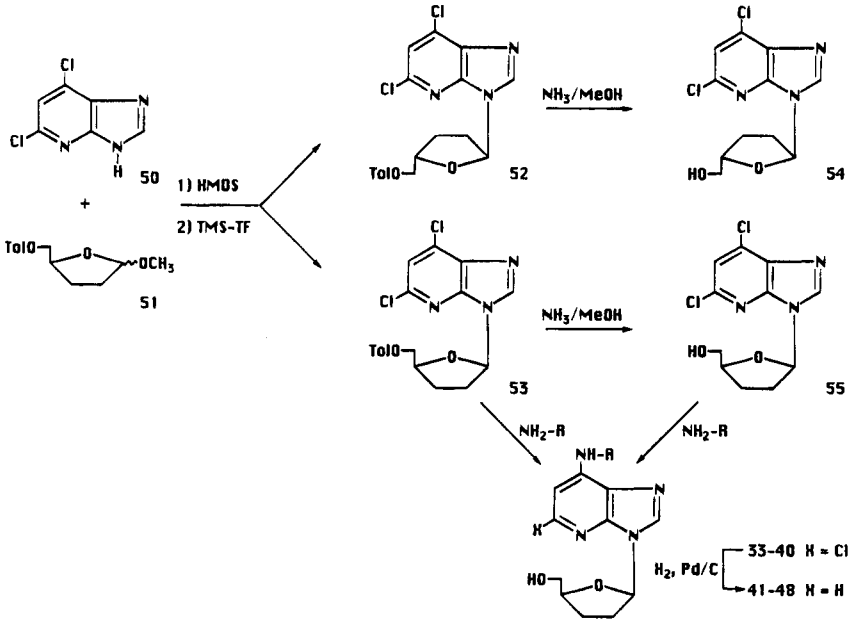
The site of dideoxyribosylation was assigned to be N-3 of the 3*H*-imidazo[4,5-*b*]pyridine ring by UV and ^{1}H NMR data. The UV spectra of compounds **54** and **55**, at different pH values, were essentially indistinguish-

Table 1. Preparation of Compounds in Schemes 1 and 2

compd no.[a]	method	*t* (°C)	time (h)	chromatography solvent	yield (%)	mp (°C)
19		110	8	$CHCl_3$–C_6H_6–CH_3OH (50:42:8)	46	173–175
20		110	24	$CHCl_3$–C_6H_6–CH_3OH (70:25:5)	51	112–115
23		130	20	$CHCl_3$–C_6H_6–CH_3OH (70:20:10)	44	94–97
24		130	36	$CHCl_3$–C_6H_6–CH_3OH (70:20:10)	48	144–147
33	A	120	16	$CHCl_3$–CH_3OH (98:2)[b]	61	179–181
34	A	120	16	$CHCl_3$–CH_3OH (97.5:2.5)[c]	49	240–243
35	B	120	8	$CHCl_3$–cC_6H_{12}–CH_3OH–CH_3CN (70:22:4:4)	40	135–138
36	B	110	16	$CHCl_3$–C_6H_{14}–CH_3OH (70:26:4)	93	125–127
37	A	120	20	$CHCl_3$–cC_6H_{12}–CH_3OH (70:28:2)[b]	86	130–132
38	A	130	24	$CHCl_3$–cC_6H_{12}–CH_3OH (70:25:5)	85	140–142
39	B	130	16	$CHCl_3$–cC_6H_{12}–CH_3OH (60:37:3)	45	122–125
40	B	130	16	$CHCl_3$–cC_6H_{12}–CH_3OH (60:36:4)	53	126–128

[a] The structure of compounds is shown in Figure 1. [b] Flash chromatography. [c] Preparative TLC.

Scheme 2



able and virtually identical with that of the corresponding 5,7-dichloro-3-(2-deoxy-β-D-*erythro*-pentofuranosyl)-3*H*-imidazo[4,5-*b*]pyridine and 5,7-dichloro-3-(2-deoxy-α-D-*erythro*-pentofuranosyl)-3*H*-imidazo[4,5-*b*]pyridine, previously characterized in our laboratory,[14] and with that of 5,7-dichloro-3-(β-D-ribofuranosyl)-3*H*-imidazo[4,5-*b*]pyridine.[20] On the other hand, the previously reported N-1-substituted derivative showed a completely different UV spectral profile.[14] Furthermore, a strong NOE effect was observed on H-2 when H-1′ was irradiated in compounds **54** and **55**, confirming N^3-glycosylation for both **52** and **53**. This observation is in agreement with the data for 3-deaza-2′-deoxyadenosine reported by Seela et al.[16] in the case of 3-deaza-2′-deoxyadenosine. On this basis, compounds **54** and **55** were identified as 5,7-dichloro-3-(2,3-dideoxy-α-D-*glycero*-pentofuranosyl)-3*H*-imidazo[4,5-*b*]pyridine and 5,7-dichloro-3-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-3*H*-imidazo[4,5-*b*]pyridine, respectively.

Reaction of **55** or the protected nucleoside **53** with the appropriate amine gave the corresponding 5-chloro-N^7-substituted derivatives **33**–**40** (Scheme 2 and Table 1). Catalytic hydrogenolysis of the chloro group in **33**–**40** with 10% Pd/C in ethanol and 2 N NaOH afforded the corresponding derivatives **41**–**48** (Scheme 2 and Table 2).

Table 2. Preparation of Compounds in Schemes 1 and 2

compd no.[a]	pressure (psi)	time (h)	chromatography solvent	yield (%)	mp (°C)
27	45	3	$CHCl_3$–C_6H_{14}–CH_3CN–CH_3OH (60:20:10:10)[b]	31	120–123
28	45	3	$CHCl_3$–C_6H_{14}–CH_3CN–CH_3OH (60:20:10:10)[b]	54	130 dec
31	60	24	$CHCl_3$–C_6H_{14}–CH_3CN–CH_3OH (70:10:10:10)[b]	37	80–83
32	60	48	$CHCl_3$–C_6H_{14}–CH_3CN–CH_3OH (70:10:10:10)[b]	44	135–138
41	55	10	EtOAc–CH_3OH (97:3)[b]	57	138–141
42	60	16	$CHCl_3$–cC_6H_{12}–CH_3OH (70:20:10)[b]	87	130–133
43	50	48	$CHCl_3$–C_6H_6–CH_3CN–CH_3OH (70:20:5:5)[b]	32	115–118
44	40	4	$CHCl_3$–C_6H_6–CH_3CN–CH_3OH (70:20:5:5)[b]	65	46–51
45	60	16	$CHCl_3$[c]	77	131–133
46	60	24	$CHCl_3$–C_6H_{14}–CH_3CN–CH_3OH (70:10:10:10)[b]	26	155–158
47	60	60	$CHCl_3$–C_6H_{14}–CH_3CN–CH_3OH (64:20:10:6)[b]	24	vetrous solid
48	40	48	$CHCl_3$–C_6H_{14}–CH_3OH (70:25:5)[b]	30	121–123

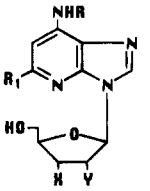
[a] The structure of compounds is shown in Figure 1. [b] Preparative TLC. [c] Flash chromatography.

Biological Evaluation

Anti-HIV-1 and Anti-HSV-1 Activity. The anti-HIV-1 activity and toxicity of compounds listed in Figure 1 were determined in C8166 cells infected with HIV-1_{IIIB}.[21] The results, listed in Table 3, showed that while the parent compounds 1-deazaadenosine (**9**), 2′-deoxy-1-deazaadenosine (**25**), and 2′,3′-dideoxy-1-deazaadenosine (**41**) and the corresponding 2-chloro derivatives were inactive, nucleosides bearing cycloalkyl substituents on N^6 exhibited moderate to good anti-HIV-1 activity, compared to 2′,3′-dideoxyadenosine (ddA), with the degree and pattern of improvement depending on the structure of the sugar moiety. In particular, compounds bearing a cycloheptyl- or cyclooctylamine were the most active in every series. However, the 2′-deoxy derivatives were the most potent compounds, and the 2′-deoxy-2-chloro-N^6-cyclobutyl-1-deazaadenosine was the most selective molecule, with a therapeutic index of 100 (**20**; ED_{50} = 4 μM vs TC_{50} = 400 μM). 2′,3′-Dideoxy derivatives were more active than the corresponding ribose nucleosides, with the highest activity once again shown by N^6-cycloalkyl substituents with larger ring size. In fact, 2′,3′-dideoxy-2-chloro-N^6-cycloheptyl- (**39**), 2′,3′-dideoxy-2-chloro-N^6-cyclooctyl- (**40**), and 2′,3′-dideoxy-N^6-cyclooctyl- (**48**) 1-deazaadenosine resulted as being slightly more potent, although less selective, than ddA itself.

Burns et al. reported that in a series of 6-alkoxypurine 2′,3′-dideoxy nucleosides and antiviral activity in MT4 cells increased as the length of the alkoxy carbon chain increased, the 6-hexyloxy and 6-heptyloxy analogues being the most active nucleosides in the series (ED_{50} = 18 and 25 μM, respectively).[3b] However, while the two derivatives in the alkoxy series were as active as the parent compound 2′,3′-dideoxyinosine (ddI), in the case of the 1-deaza derivatives the presence of a 6-cycloalkyl-

Table 3. Anti-HIV-1 and ADA Inhibitory Activity of 1-Deazapurine Nucleosides



compd no.	R	R_1	X	Y	anti-HIV-1 in C8166 cells ED_{50} (μM)[a]	cytotox in C8166 cells TC_{50} (μM)[b]	ADA inhibition K_i (μM)
1	H	Cl	OH	OH	>100	>100	30
9	H	H	OH	OH	>100	2	0.38
2	CH_3	Cl	OH	OH	>100	>100	69
10	CH_3	H	OH	OH	>100	>100	12
3	cC_3H_5	Cl	OH	OH	30	500	>100
11	cC_3H_5	H	OH	OH	>100	>100	38
4	cC_4H_7	Cl	OH	OH	100	400	97
12	cC_4H_7	H	OH	OH	>100	>100	100
5	cC_5H_9	Cl	OH	OH	10	100	>100
13	cC_5H_9	H	OH	OH	16	400	>100
6	cC_6H_{11}	Cl	OH	OH	20	50	>100
14	cC_6H_{11}	H	OH	OH	100	400	>100
7	cC_7H_{13}	Cl	OH	OH	8	50	>100
15	cC_7H_{13}	H	OH	OH	20	100	>100
8	cC_8H_{15}	Cl	OH	OH	2	40	71
16	cC_8H_{15}	H	OH	OH	4	50	80
17	H	Cl	OH	H	>100	>100	23
25	H	H	OH	H	>100	>100	0.19
18	CH_3	Cl	OH	H	>100	>100	4.2
26	CH_3	H	OH	H	>100	>100	0.25
19	cC_3H_5	Cl	OH	H	8	500	75
27	cC_3H_5	H	OH	H	>100	>100	5.9
20	cC_4H_7	Cl	OH	H	4	400	>100
28	cC_4H_7	H	OH	H	20	400	27
21	cC_5H_9	Cl	OH	H	0.8	7	>100
29	cC_5H_9	H	OH	H	40	400	22
22	cC_6H_{11}	Cl	OH	H	4	50	>100
30	cC_6H_{11}	H	OH	H	8	100	87
23	cC_7H_{13}	Cl	OH	H	0.2	5	>100
31	cC_7H_{13}	H	OH	H	30	80	42
24	cC_8H_{15}	Cl	OH	H	2	40	>100
32	cC_8H_{15}	H	OH	H	4	40	59
33	H	Cl	H	H	>100	>100	>100
41	H	H	H	H	>100	>100	2.5
34	CH_3	Cl	H	H	>100	>100	11
42	CH_3	H	H	H	50	100	2.2
35	cC_3H_5	Cl	H	H	>100	>100	>100
43	cC_3H_5	H	H	H	100	750	78
36	cC_4H_7	Cl	H	H	4	250	>100
44	cC_4H_7	H	H	H	50	400	92
37	cC_5H_9	Cl	H	H	20	50	>100
45	cC_5H_9	H	H	H	80	500	>100
38	cC_6H_{11}	Cl	H	H	4	20	>100
46	cC_6H_{11}	H	H	H	40	50	69
39	cC_7H_{13}	Cl	H	H	0.8	8	>100
47	cC_7H_{13}	H	H	H	8	40	53
40	cC_8H_{15}	Cl	H	H	0.4	10	>100
48	cC_8H_{15}	H	H	H	0.8	10	>100
ddA					2	>100	

[a] EC_{50} represents the concentration of drug which reduced HIV-1 gp120 plaque formation by 50% in infected cell cultures. [b] TC_{50} represents the concentration of drug which reduced cell growth by 50%. EC_{50} and TC_{50} values were not determined for those compounds showing antiviral activity at doses higher than 100 μM.

amino substituent seems to be crucial as the corresponding parent 6-amino compounds are completely inactive.

On the other hand, the presence of a 2-chloro group improved both activity and therapeutic index in every series, the most active compound being 2′-deoxy-2-chloro-N^6-cycloheptyl-1-deazaadenosine (**23**; ED_{50} = 0.2 μM). This finding seems to point out an additional difference between the purine and the 1-deazapurine moiety, since Rosowsky et al. reported that a 2-chloro substituent in 2′,3′-dideoxyadenosine (ddAdo) and 2′,3′-didehydro-2′,3′-dideoxyadenosine (ddeAdo) decreased antiretroviral activity and increased host cell toxicity.[22]

All compounds were also tested against HSV-1 strains MP in Vero cells.[23] 1-Deazaadenosine (**9**) and the 2′-deoxy derivatives **21**, **23**, and **30** exhibited anti-HSV-1 activity in the range 5−15 μM (ACV, ED_{50} = 0.1 μM), but no selectivity could be demonstrated. Most compounds were cytotoxic for Vero cells at concentrations comparable to those assessed for C8166 cells.

ADA Inhibitory Activity. The compounds were also tested for their ability to inhibit calf intestine ADA.[7] Results (Table 3) showed that none of the tested derivatives were substrates of the enzyme, and some of them were good inhibitors, 2′-deoxy-1-deazaadenosine (**25**) being the most potent in the series (K_i = 0.19 μM)

and apparently more active than 1-deazaadenosine itself (**9**; $K_i = 0.66\ \mu M$). Interestingly, 2',3'-dideoxy-1-deazaadenosine (**41**; $K_i = 2.5\ \mu M$) is the first dideoxy nucleoside reported so far to show ADA inhibitory activity in the micromolar range.

According to the fact that introduction of a chloro group in position 2 of substrates made the compounds more resistant to ADA,[24] the presence of a chloro group in the same position of our compounds produced a decrease in ADA inhibitory activity. Substitutions on the N^6 amino group did not produce a decrease in activity only when small groups such as methyl were introduced (**10**, $K_i = 12.0\ \mu M$; **26**, $K_i = 0.25\ \mu M$; **42**, $K_i = 2.2\ \mu M$). Increased lipophilicity and steric hindrance of substituents made derivatives much less active than the parent compounds. This is in agreement with our hypothesis that 1-deazaadenosine derivatives interact with the enzyme directly on the catalytic site, since the presence of a bulky, hydrophobic substituent on the exocyclic nitrogen is detrimental for the hydrogen bonding of the molecules.[8]

Conclusion

In conclusion a new class of nucleosides endowed with anti-HIV-1 activity is described. The 1-deazaadenine derivatives are not substrates of adenosine deaminase, and some of them are good inhibitors of the enzyme. However, the ADA inhibitory activity does not account for the antiviral potency, as already reported for other adenosine deaminase inhibitors.[25]

One can anticipate that the anti-HIV-1 activity of these nucleoside analogues generally rests on an inhibition of reverse transcriptase (RT). The observation that our compounds possess a modest anti-HSV-1 effect, which merely reflects cytotoxicity, argues against the possibility that they are selectively phosphorylated by the HSV-1 thymidine kinase or that they discriminate between cell DNA polymerase α and the herpes virus replicase. An interference with RT is certainly more likely to occur in view of both the therapeutic index of some of molecules (**20**, TI = 100) and the broad spectrum substrate specificity of the enzyme. The above considerations notwithstanding, we can not presently dissect the molecular nature of the antiretroviral action produced by our analogues. Studies are currently in progress to evaluate the metabolic conversion of these drugs and their *in vitro* anti-RT activity as well as the effect on the growth of HIV-1 strains carrying mutations on the RT gene. This kind of approach will certainly contribute to a better understanding of structure–activity relationships in N^6-cycloalkyl derivatives of 1-deazaadenine and, perhaps, lead to a tailored design of new congeners endowed with higher selectivity.

Experimental Section

Chemistry. Melting points were determined with a Büchi apparatus and are uncorrected. ^{1}H NMR spectra were obtained with a Varian VX 300 MHz spectrometer. UV spectra were recorded on a Perkin-Elmer Coleman 575 spectrophotometer. TLC was carried out on precoated TLC plates with silica gel 60 F-254 (Merck) and preparative TLC on precoated Whatman 60A TLC plates. For column chromatography, silica gel 60 (Merck) was used. Microanalytical results are within 0.4% of theoretical values.

Preparation of 7-(Cycloalkylamino)-5-chloro-3-(2-deoxy-β-D-*erythro*-pentofuranosyl)-3*H*-imidazo[4,5-*b*]pyridines 19, 20, 23, and 24. A mixture of 0.35 g (1.15 mmol) of 5,7-dichloro-3-(2-deoxy-β-D-*glycero*-pentofuranosyl)-3*H*-imidazo[4,5-*b*]pyridine (**49**)[14] and 10 mL of the appropriate amine was heated in a steel bomb at the temperature and for the time listed in Table 1. Compounds **23** and **24** were prepared by adding **49** to the mixture of 2 mL of the appropriate amine and 20 mL of ethanol. The reaction mixture was evaporated, and the residue was chromatographed on a silica gel column eluting with the suitable mixture of solvents (Table 1) to give **19**, **20**, **23**, and **24** as chromatographically pure solids.

19: ^{1}H NMR (Me_2SO-d_6) δ 0.58 (m, 2H, H cyclopropyl), 0.79 (m, 2H, H cyclopropyl), 2.26 (m, 1H, H-2'), 2.61 (m, 2H, H-1 cyclopropyl, H-2''), 3.56 (m, 2H, CH_2-5'), 3.87 (m, 1H, H-4'), 4.41 (m, 1H, H-3'), 6.332 (pt, 1H, J = 6.9, Hz, H-1'), 6.58 (s, 1H, H-6), 7.68 (m, 1H, NH), 8.35 (s, 1H, H-2). Anal. ($C_{14}H_{17}ClN_4O_3$) C, H, N.

20: ^{1}H NMR (Me_2SO-d_6) δ 1.74 (m, 2H, H cyclobutyl), 2.07 (m, 2H, H cyclobutyl), 2.33 (m, 3H, H cyclobutyl, and H-2'), 2.68 (m, 1H, H-2''), 3.57 (m, 2H, CH_2-5'), 3.88 (m, 1H, H-4'), 4.41 (m, 2H, H-1 cyclobutyl, H-3'), 6.32 (pt, 2H, J = 6.9 Hz, H-1', H-6), 7.49 (d, 1H, J = 7.4 Hz, NH), 8.35 (s, 1H, H-2). Anal. ($C_{15}H_{19}ClN_4O_3$) C, H, N.

23: ^{1}H NMR (Me_2SO-d_6) δ 1.60 (m, 10H, H cycloheptyl), 1.91 (m, 2H, H cycloheptyl), 2.27 (m, 1H, H-2'), 2.67 (m, 1H, H-2''), 3.58 (m, 2H, CH_2-5'), 3.87 (m, 1H, H-4'), 4.12 (bs, 1H, H-1 cycloheptyl), 4.40 (m, 1H, H-3'), 6.32 (pt, 1H, J = 6.4 Hz, H-1'), 6.36 (s, 1H, H-6), 6.98 (d, 1H, J = 8.6 Hz, NH), 8.33 (s, 1H, H-2). Anal. ($C_{18}H_{25}ClN_4O_3$) C, H, N.

24: ^{1}H NMR (Me_2SO-d_6) δ 1.52–1.83 (m, 14H, H cyclooctyl), 2.27 (m, 1H, H-2'), 2.68 (m, 1H, H-2''), 3.55 (m, 2H, CH_2-5'), 3.87 (m, 1H, H-4'), 4.15 (bs, 1H, H-1 cyclooctyl), 4.39 (m, 1H, H-3'), 6.31 (pt, 1H, H-1'), 6.35 (s, 1H, H-6), 6.97 (d, 1H, J = 8.7 Hz, NH), 8.33 (s, 1H, H-2). Anal. ($C_{19}H_{27}ClN_4O_3$) C, H, N.

Preparation of 7-(Cycloalkylamino)-3-(2-deoxy-β-D-*erythro*-pentofuranosyl)-3*H*-imidazo[4,5-*b*]pyridines 27, 28, 31, and 32. To a solution of **19**, **20**, **23**, and **24** (0.5 mmol) in 40 mL of ethanol and 1 mL of 2 N NaOH was added 0.1 g of 10% Pd/C, and the mixture was shaken with hydrogen at the pressure and for the time listed in Table 2. The catalyst was removed, and the filtrate was concentrated to dryness. The residue was chromatographed on a silica gel column eluting with the suitable mixture of solvents to give **27**, **28**, **31**, and **32** (Table 2) as chromatographically pure solids.

27: ^{1}H NMR (Me_2SO-d_6) δ 0.57 (m, 2H, H cyclopropyl), 0.78 (m, 2H, H cyclopropyl), 2.22 (m, 1H, H-2'), 2.58 (m, 1H, H-1 cyclopropyl), 2.79 (m, 1H, H-2''), 3.60 (m, 2H, CH_2-5'), 3.92 (m, 1H, H-4'), 4.43 (m, 1H, H-3'), 6.41 (pt, 1H, J = 7.2 Hz, H-1'), 6.67 (d, 1H, $J_{6,5}$ = 5.6 Hz, H-6), 7.23 (d, 1H, J = 1.6 Hz, NH), 7.94 (d, 1H, $J_{5,6}$ = 5.6 Hz, H-5), 8.29 (s, 1H, H-2). Anal. ($C_{14}H_{18}N_4O_3$) C, H, N.

28: ^{1}H NMR (Me_2SO-d_6) δ 1.75 (m, 2H, H cyclobutyl), 2.08 (m, 2H, H cyclobutyl), 2.36 (m, 3H, H cyclobutyl, and H-2') 2.71 (m, 1H, H-2''), 3.60 (m, 2H, CH_2-5'), 3.95 (m, 1H, H-4'), 4.44 (m, 2H, H-1 cyclobutyl, H-3'), 6.44 (m, 2H, J = 6.9 Hz, H-1', H-6), 7.36 (d, 1H, J = 7.4 Hz, NH), 7.93 (d, 1H, $J_{5,6}$ = 6.2 Hz, H-5), 8.42 (s, 1H, H-2). Anal. ($C_{15}H_{20}N_4O_3$) C, H, N.

31: ^{1}H NMR (Me_2SO-d_6) δ 1.60 (m, 10H, H cycloheptyl), 1.93 (m, 2H, H cycloheptyl), 2.21 (m, 1H, H-2'), 2.79 (m, 1H, H-2''), 3.60 (m, 2H, CH_2-5'), 3.92 (m, 1H, H-4'), 4.04 (bs, 1H, H-1 cycloheptyl), 4.43 (m, 1H, H-3'), 6.34 (d, 1H, $J_{6,5}$ = 5.8 Hz, H-6), 6.40 (pt, 1H, J = 7.2 Hz, H-1'), 6.55 (d, 1H, J = 8.6 Hz, NH), 7.84 (d, 1H, $J_{5,6}$ = 5.8 Hz, H-5), 8.28 (s, 1H, H-2). Anal. ($C_{18}H_{26}N_4O_3$) C, H, N.

32: ^{1}H NMR (Me_2SO-d_6) δ 1.52–1.84 (m, 14H, H cyclooctyl), 2.22 (m, 1H, H-2'), 2.76 (m, 1H, H-2''), 3.60 (m, 2H, CH_2-5'), 3.92 (m, 1H, H-4'), 4.13 (bs, 1H, H-1 cyclooctyl), 4.42 (m, 1H, H-3'), 6.35 (d, 1H, $J_{6,5}$ = 5.8 Hz, H-6), 6.38 (pt, 1H, J = 5.8 Hz, H-1'), 6.52 (d, 1H, J = 8.6 Hz, NH), 7.84 (d, 1H, $J_{5,6}$ = 5.8 Hz, H-5), 8.28 (s, 1H, H-2). Anal. ($C_{19}H_{28}N_4O_3$) C, H, N.

Preparation of 5,7-Dichloro-3-(2,3-dideoxy-5-*O*-*p*-toluoyl-α-D-*glycero*-pentofuranosyl)-3*H*-imidazo[4,5-*b*]pyridine (52) and 5,7-Dichloro-3-(2,3-dideoxy-5-*O*-*p*-toluoyl-β-D-*glycero*-pentofuranosyl)-3*H*-imidazo[4,5-*b*]-pyridine (53). A mixture of 2 g (10.5 mmol) of 5,7-dichloro-3*H*-imidazo[4,5-*b*]pyridine (**50**),[11] 50 mg of ammonium sulfate, and 20 mL of hexamethyldisilazane was refluxed for 5 h and then cooled to room temperature. The mixture was concentrated in vacuo and coevaporated three times with anhydrous

methylene chloride to give a residue to which a solution of 3.25 g (13 mmol) of **51**[18] in 40 mL of dry methylene chloride was added followed by dropwise addition of 1.75 mL of TMS-TF in 6 mL of dry methylene chloride. The reaction mixture was stirred for 4 h at room temperature and then slowly poured into a stirred ice-cooled mixture of methylene chloride and saturated sodium bicarbonate solution. The organic layer was washed with water, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was flash chromatographed on a silica gel column eluting with cC_6H_{12}–EtOAc (80:20) to give 2.9 g (68%) of a mixture of the α- and β-anomers **52** and **53** which was used without further purification for the next reaction. Analytical samples of **52** and **53** were obtained by flash chromatography eluting with C_6H_6–$CHCl_3$–CH_3CN (60:37:3).

52: ^{1}H NMR (Me_2SO-d_6) δ 2.05 (m, 1H, H-3′), 2.26 (m, 1H, H-3′), 2.39 (s, 3H, CH_3), 2.63 (m, 2H, H-2′), 4.41 (m, 2H, CH_2-5′), 4.79 (m, 1H, H-4′), 6.49 (dd, 1H, J = 1.6, 4.2 Hz, H-1′), 7.36 (d, 2H, H-Ph), 7.69 (s, 1H, H-6), 7.90 (d, 2H, H-Ph), 8.80 (s, 1H, H-2). Anal. ($C_{19}H_{17}Cl_2N_3O_3$) C, H, N.

53: ^{1}H NMR (Me_2SO-d_6) δ 2.26 (m, 2H, H-3′), 2.39 (s, 3H, CH_3), 2.63 (m, 2H, H-2′), 4.47 (m, 3H, CH_2-5′, H-4′), 6.38 (dd, 1H, J = 1.1, 3.6 Hz, H-1′), 7.29 (d, 2H, H-Ph), 7.65 (s, 1H, H-6), 7.73 (d, 2H, H-Ph), 8.75 (s, 1H, H-2). Anal. ($C_{19}H_{17}Cl_2N_3O_3$) C, H, N.

Preparation of 5,7-Dichloro-3-(2,3-dideoxy-α-D-*glycero*-pentofuranosyl)-3*H*-imidazo[4,5-*b*]pyridine (54) and 5,7-Dichloro-3-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-3*H*-imidazo[4,5-b]pyridine (55). To 4.3 g (10.3 mmol) of the mixture of **52** and **53** was added 50 mL of methanol saturated at 0 °C with ammonia, and the mixture was heated in a stainless steel bomb at 45 °C for 24 h. The reaction mixture was evaporated, and the residue was flash chromatographed over silica gel eluting with $CHCl_3$–C_6H_6–CH_3OH (94:5:1) to give 1.62 g (51%) of **54** and 1.07 g (35%) of **55**.

54: ^{1}H NMR (Me_2SO-d_6) δ 1.88 (m, 1H, H-3′), 2.23 (m, 1H, H-3′), 2.48 (m, 2H, H-2′), 3.43 (m, 2H, CH_2-5′), 4.38 (m, 1H, H-4′), 6.37 (dd, 1H, J = 1.8, 4.2 Hz, H-1′), 7.64 (s, 1H, H-6), 8.82 (s, 1H, H-2). Anal. ($C_{11}H_{11}Cl_2N_3O_2$) C, H, N.

55: mp 98–100 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.03 (m, 2H, H-3′), 2.45 (m, 2H, H-2′), 3.48 (m, 1H, CH_2-5′), 3.62 (m, 1H, CH_2-5″), 4.13 (m, 1H, H-4′), 6.30 (dd, 1H, J = 3.0, 3.3 Hz, H-1′), 7.63 (s, 1H, H-6), 8.82 (s, 1H, H-2). Anal. ($C_{11}H_{11}Cl_2N_3O_2$) C, H, N.

Preparation of 7-Amino- (33) and 7-(Alkylamino)- (34, 37, and 38) 5-Chloro-3-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-3*H*-imidazo[4,5-*b*]pyridines. General Method A. A solution of 0.432 g (1.5 mmol) of **55**, dissolved in 10 mL of the appropriate amine, was heated in a steel bomb at the temperature and for the time listed in Table 1. After cooling, the mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel eluting with the mixture of solvents listed in Table 1 to give **33**, **34**, **37**, and **38** as chromatographically pure solids.

Preparation of 7-(Alkylamino)-5-chloro-3-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-3*H*-imidazo[4,5-*b*]pyridines 35, 36, 39, and 40. General Method B. A mixture of 0.41 g (1.0 mmol) of **53** and 10 mL of the appropriate amine was heated in a steel bomb at the temperature and for the time listed in Table 1. Compounds **39** and **40** were prepared by adding **53** to the mixture of 3 mL of the appropriate amine and 30 mL of ethanol. The reaction mixture was evaporated, and the residue was chromatographed on a silica gel column eluting with the suitable mixture of solvents (Table 1) to give **35**, **36**, **39**, and **40** as chromatographically pure solids.

33: ^{1}H NMR (Me_2SO-d_6) δ 2.01 (m, 2H, H-3′), 2.35 (m, 2H, H-2′), 3.48 (m, 1H, CH_2-5′), 3.59 (m, 1H, CH_2-5″), 4.07 (m, 1H, H-4′), 6.15 (dd, 1H, J = 2.7, 4.2 Hz, H-1′), 6.35 (s, 1H, H-6), 6.73 (s, 2H, NH_2), 8.30 (s, 1H, H-2). Anal. ($C_{11}H_{13}ClN_4O_2$) C, H, N.

34: ^{1}H NMR (Me_2SO-d_6) δ 2.05 (m, 2H, H-3′), 2.40 (m, 2H, H-2′), 2.90 (d, 3H, J = 4.6 Hz, NCH_3), 3.51 (m, 1H, CH_2-5′), 3.61 (m, 1H, CH_2-5″), 4.12 (m, 1H, H-4′), 6.21 (dd, 1H, J = 2.2, 3.9 Hz, H-1′), 6.31 (s, 1H, H-6), 7.24 (d, 1H, J = 4.8 Hz, NH), 8.35 (s, 1H, H-2). Anal. ($C_{12}H_{15}ClN_4O_2$) C, H, N.

35: ^{1}H NMR (Me_2SO-d_6) δ 0.59 (m, 2H, H cyclopropyl), 0.79 (m, 2H, H cyclopropyl), 2.05 (m, 2H, H-3′), 2.40 (m, 2H, H-2′), 2.60 (m, 1H, H-1 cyclopropyl), 3.60 (m, 2H, CH_2-5′), 4.12 (m, 1H, H-4′), 6.22 (dd, 1H, J = 2.3, 4.1 Hz, H-1′), 6.58 (s, 1H, H-6), 7.61 (d, 1H, J = 2.1 Hz, NH), 8.37 (s, 1H, H-2). Anal. ($C_{14}H_{17}ClN_4O_2$) C, H, N.

36: ^{1}H NMR (Me_2SO-d_6) δ 1.71 (m, 2H, H cyclobutyl), 2.04 (m, 4H, H cyclobutyl, H-3′), 2.35 (m, 4H, H cyclobutyl, H-2′), 3.57 (m, 2H, CH_2-5′), 4.11 (m, 1H, H-4′), 4.60 (bs, 1H, H-1 cyclobutyl), 6.20 (dd, 1H, J = 2.4, 4.0 Hz, H-1′), 6.30 (s, 1H, H-6), 7.43 (d, 1H, J = 7.5 Hz, NH), 8.36 (s, 1H, H-2). Anal. ($C_{15}H_{19}ClN_4O_2$) C, H, N.

37: ^{1}H NMR (Me_2SO-d_6) δ 1.53 (m, 4H, H cyclopentyl), 1.68 (m, 2H, H cyclopentyl), 1.98 (m, 4H, H cyclopentyl, H-3′), 2.35 (m, 2H, H-2′), 3.47 (m, 1H, CH_2-5′), 3.60 (m, 1H, CH_2-5″), 4.08 (m, 1H, H-4′), 4.25 (bs, 1H, H-1 cyclopentyl), 6.16 (dd, 1H, J = 2.4, 4.0 Hz, H-1′), 6.34 (s, 1H, H-6), 6.99 (d, 1H, J = 7.2 Hz, NH), 8.31 (s, 1H, H-2). Anal. ($C_{16}H_{21}ClN_4O_2$) C, H, N.

38: ^{1}H NMR (Me_2SO-d_6) δ 1.34 (m, 4H, H cyclohexyl), 1.70 (m, 4H, H cyclohexyl), 1.93 (m, 2H, H cyclohexyl), 2.05 (m, 2H, H-2′), 2.38 (m, 2H, H-3′), 3.55 (m, 2H, CH_2-5′), 3.91 (bs, 1H, H-1 cyclohexyl), 4.11 (m, 1H, H-4′), 6.20 (dd, 1H, J = 2.4, 4.0 Hz, H-1′), 6.40 (s, 1H, H-6), 6.91 (d, 1H, J = 8.6 Hz, NH), 8.35 (s, 1H, H-2). Anal. ($C_{17}H_{23}ClN_4O_2$) C, H, N.

39: ^{1}H NMR (Me_2SO-d_6) δ 1.57 (m, 10H, H cycloheptyl), 1.94 (m, 2H, H cycloheptyl), 2.06 (m, 2H, H-3′), 2.41 (m, 2H, H-2′), 3.58 (m, 2H, CH_2-5′), 4.10 (m, 2H, H-4′, H-1 cycloheptyl), 6.20 (dd, 1H, J = 2.5, 3.7 Hz, H-1′), 6.35 (s, 1H, H-6), 6.92 (d, 1H, J = 8.7 Hz, NH), 8.35 (s, 1H, H-2). Anal. ($C_{18}H_{25}ClN_4O_2$) C, H, N.

40: ^{1}H NMR (Me_2SO-d_6) δ 1.50–1.83 (m, 14H, H cyclooctyl), 2.05 (m, 2H, H-3′), 2.39 (m, 2H, H-2′), 3.58 (m, 2H, CH_2-5′), 4.11 (m, 2H, H-4′, H-1 cyclooctyl), 6.20 (dd, 1H, J = 2.4, 4.0 Hz, H-1′), 6.34 (s, 1H, H-6), 6.92 (d, 1H, J = 8.7 Hz, NH), 8.35 (s, 1H, H-2). Anal. ($C_{19}H_{27}ClN_4O_2$) C, H, N.

Preparation of 7-Amino- (41) and 7-(Alkylamino)- (42–48) 3-(2,3-Dideoxy-β-D-*glycero*-pentofuranosyl)-3*H*-imidazo[4,5-*b*]pyridines. To a solution of **33**–**40** (0.5 mmol) in 40 mL of ethanol and 1 mL of 2 N NaOH was added 0.1 g of 10% Pd/C, and the mixture was shaken with hydrogen at the pressure and for the time listed in Table 2. The catalyst was removed, and the filtrate was concentrated to dryness. The residue was chromatographed on a silica gel column eluting with the suitable mixture of solvents to give **41**–**48** (Table 2) as chromatographically pure solids.

41: ^{1}H NMR (Me_2SO-d_6) δ 2.04 (m, 2H, H-3′), 2.38 (m, 2H, H-2′), 3.47 (m, 2H, CH_2-5′), 4.09 (m, 1H, H-4′), 6.22 (pt, 1H, J = 4.8 Hz, H-1′), 6.34 (m, 3H, NH_2, H-6), 7.69 (d, 1H, $J_{5,6}$ = 5.4 Hz, H-5), 8.24 (s, 1H, H-2). Anal. ($C_{11}H_{14}N_4O_2$) C, H, N.

42: ^{1}H NMR (Me_2SO-d_6) δ 2.08 (m, 2H, H-3′), 2.42 (m, 2H, H-2′), 2.91 (d, 3H, J = 5.1 Hz, NCH_3), 3.53 (m, 1H, CH_2-5′), 3.68 (m, 1H, CH_2-5″), 4.14 (m, 1H, H-4′), 6.25 (pt, 1H, J = 5.3 Hz, H-1′), 6.31 (d, 1H, $J_{6,5}$ = 5.6 Hz, H-6), 6.84 (m, 1H, NH), 7.92 (d, 1H, $J_{5,6}$ = 5.6 Hz, H-5), 8.30 (s, 1H, H-2). Anal. ($C_{12}H_{16}N_4O_2$) C, H, N.

43: ^{1}H NMR (Me_2SO-d_6) δ 0.58 (m, 2H, H cyclopropyl), 0.78 (m, 2H, H cyclopropyl), 2.09 (m, 2H, H-3′), 2.42 (m, 2H, H-2′), 2.59 (m, 1H, H-1 cyclopropyl), 3.59 (m, 1H, CH_2-5′), 3.67 (m, 1H, CH_2-5″), 4.14 (m, 1H, H-4′), 6.28 (pt, 1H, J = 5.3 Hz, H-1′), 6.61 (d, 1H, $J_{6,5}$ = 5.6 Hz, H-6), 7.18 (s, 1H, NH), 7.96 (d, 1H, $J_{5,6}$ = 5.6 Hz, H-5), 8.33 (s, 1H, H-2). Anal. ($C_{14}H_{18}N_4O_2$) C, H, N.

44: ^{1}H NMR (Me_2SO-d_6) δ 1.70 (m, 2H, H cyclobutyl), 2.08 (m, 4H, H cyclobutyl, H-3′), 2.37 (m, 4H, H cyclobutyl, H-2′), 3.51 (m, 1H, CH_2-5′), 3.66 (m, 1H, CH_2-5″), 4.13 (m, 1H, H-4′), 4.36 (m, 1H, H-1 cyclobutyl), 6.28 (m, 2H, H-1′, H-6), 6.99 (d, 1H, J = 7.4 Hz, NH), 7.86 (d, 1H, $J_{5,6}$ = 5.6 Hz, H-5), 8.33 (s, 1H, H-2). Anal. ($C_{15}H_{20}N_4O_2$) C, H, N.

45: ^{1}H NMR (Me_2SO-d_6) δ 1.54 (m, 4H, H cyclopentyl), 1.69 (m, 2H, H cyclopentyl), 1.98 (m, 2H, H cyclopentyl), 2.06 (m, 2H, H-3′), 2.36 (m, 2H, H-2′), 3.48 (m, 1H, CH_2-5′), 3.61 (m, 1H, CH_2-5″), 4.09 (m, 1H, H-4′), 4.20 (m, 1H, H-1 cyclopentyl), 6.23 (pt, 1H, J = 5.5 Hz, H-1′), 6.34 (d, 1H, $J_{6,5}$ = 5.6 Hz, H-6), 6.52 (d, 1H, J = 7.2 Hz, NH), 7.83 (d, 1H, $J_{5,6}$ = 5.6 Hz, H-5), 8.25 (s, 1H, H-2). Anal. ($C_{16}H_{22}N_4O_2$) C, H, N.

46: ^{1}H NMR (Me_2SO-d_6) δ 1.33 (m, 4H, H cyclohexyl), 1.70 (m, 4H, H cyclohexyl), 1.94 (m, 2H, H cyclohexyl), 2.07 (m, 2H, H-3′), 2.45 (m, 2H, H-2′), 3.51 (m, 1H, CH_2-5′), 3.66 (m, 1H, CH_2-5″), 3.83 (bs, 1H, H-1 cyclohexyl), 4.13 (m, 1H, H-4′),

6.26 (pt, 1H, H-1'), 6.40 (m, 2H, NH, H-6), 7.84 (d, 1H, $J_{5,6}$ = 5.5 Hz, H-5), 8.29 (s, 1H, H-2). Anal. ($C_{17}H_{24}N_4O_2$) C, H, N.

47: ^{1}H NMR (Me_2SO-d_6) δ 1.60 (m, 10H, H cycloheptyl), 1.93 (m, 2H, H cycloheptyl), 2.07 (m, 2H, H-3'), 2.41 (m, 2H, H-2'), 3.50 (m, 1H, CH_2-5'), 3.66 (m, 1H, CH_2-5''), 4.02 (bs, 1H, H-1 cycloheptyl), 4.13 (m, 1H, H-4'), 6.26 (pt, 1H, J = 5.7 Hz, H-1'), 6.32 (d, 1H, $J_{6,5}$ = 5.5 Hz, H-6), 6.44 (d, 1H, J = 9.0 Hz, NH), 7.86 (d, 1H, $J_{5,6}$ = 5.5 Hz, H-5), 8.29 (s, 1H, H-2). Anal. ($C_{18}H_{26}N_4O_2$) C, H, N.

48: ^{1}H NMR (Me_2SO-d_6) δ 1.54–1.90 (m, 14H, H cyclooctyl), 2.07 (m, 2H, H-3'), 2.40 (m, 2H, H-2'), 3.50 (m, 1H, CH_2-5'), 3.66 (m, 1H, CH_2-5''), 4.12 (m, 2H, H-4', H-1 cyclooctyl), 6.25 (pt, 1H, J = 5.6 Hz, H-1'), 6.32 (d, 1H, $J_{6,5}$ = 5.7 Hz, H-6), 6.41 (d, 1H, J = 8.6 Hz, NH), 7.84 (d, 1H, $J_{5,6}$ = 5.7 Hz, H-5), 8.28 (s, 1H, H-2). Anal. ($C_{19}H_{28}N_4O_2$) C, H, N.

Antiviral and Cytotoxicity Assays. The anti-HIV-1 activities and toxicities of compounds were assessed in C8166 cells infected with HIV-1_{IIIB} as described before.[21] The inhibitory activity against HIV-1 was determined by examining syncytia by XTT-Formazan assay for cell viability as reported by Weinslow et al.[26] and by measuring antigen gp120 ELISA as described previously.[27] The EC_{50} is the concentration of compound which reduces the production of viral antigen by 50%. The TC_{50} is the concentration of compound which reduces the viability of uninfected cells by 50%. The results shown in Table 3 are the mean of two different experiments performed in triplicate.

The anti-HSV-1 activity was assayed in Vero cells by a plaque reduction method as previously described.[28] Briefly, confluent monolayers of Vero cells (2×10^5 Vero cells in 24-well Costar plates) were infected with 100 plaque-forming units of HSV-1 wt.[23] Infected cells were fixed and stained at 48 h postinfection and plaques counted under an inverted microscope. Cytotoxicity was measured as reported for C8166 cells.

Enzyme Assay. The method used for the determination of activity against adenosine deaminase has been described in a preceding paper.[7]

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