Synthesis and Evaluation of the Anti-HIV Activity of Aza and Deaza Analogues of IsoddA and Their Phosphates as Prodrugs

Palmarisa Franchetti,*,† Loredana Cappellacci,† Mario Grifantini,† Lea Messini,† Ghassan Abu Sheikha,† Anna Giulia Loi,‡ Enzo Tramontano,‡ Antonella De Montis,‡ Maria Grazia Spiga,‡ and Paolo La Colla‡

Dipartimento di Scienze Chimiche, Università di Camerino, 62032 Camerino, Italy, and Dipartimento di Biologia Sperimentale, Università di Cagliari, 09124 Cagliari, Italy

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Some aza and deaza analogues of the anti-HIV agent 2′,3′-dideoxy-3′-oxoadenosine (isoddA) (8-aza-, 8-aza-1-deaza, 8-aza-3-deaza-, 1-deaza-, and 3-deaza-isoddA) were synthesized and found inactive against HIV *in vitro*. The hypothesis that the inactivity of these isonucleosides might be due to their poor affinity for cellular nucleoside kinases was checked by the synthesis of a series of 5′-[bis(2,2,2-trichloroethyl) phosphate] triesters and 5′-phenyl phosphoramidate derivatives which, acting as membrane soluble prodrugs, could release the free phosphate form inside the cell. The 5′-(phenylmethoxy)alananyl phosphate derived from 8-aza-isoddA was found active against HIV-1 and HIV-2 with a potency similar to that of isoddA, while the anti-HIV potency of 5′-(phenylmethoxy)alaninyl phosphate of isoddA proved remarkably higher than that of isoddA, in particular against HIV-2, being similar to that of AZT. Further evidence that 8-aza-isoddA could behave as anti-HIV agent, provided that it is activated as phosphate, was obtained by the synthesis of its 5′-triphosphate derivative, which proved to be an active inhibitor of HIV-1 recombinant reverse transcriptase.

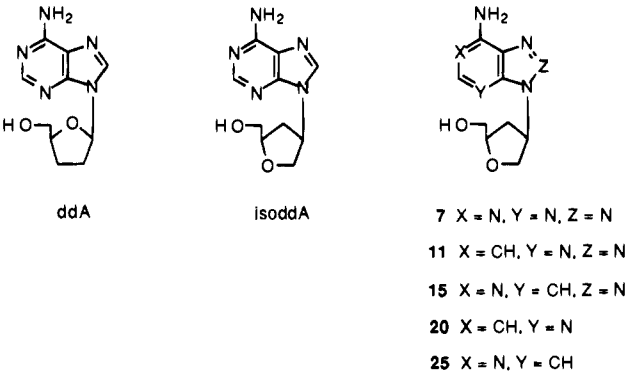
Introduction

Nucleoside reverse transcriptase inhibitors are the only drugs so far approved for the treatment of AIDS.[1] Among them is 2′,3′-dideoxyinosine (ddI), the deamination product of 2′,3′-dideoxyadenosine (ddA).[2] Following cellular uptake, both ddI and ddA are converted by cellular enzymes to 2′,3′-dideoxyadenosine triphosphate (ddATP), which then acts as a competitive inhibitor of reverse transcriptase (RT) and as a chain terminator.[3a-d]

The therapeutic use of ddA and ddI is limited by the instability of their glycosidic bond at low pH, by rapid adenosine deaminase (ADA)[4] metabolization, and by purine nucleoside phosphorylase (PNP).[5] This stimulated the search for more stable purine 2′,3′-dideoxynucleosides. Among them, 2′,3′-dideoxy-3′-oxoadenosine (isoddA), a nucleoside in which the C-3′ is transposed with the ring oxygen, was synthesized and found to have anti-HIV potency and selectivity comparable to those of ddA.[6a-b] The glycosidic bond in isoddA was more resistant to hydrolytic cleavage at low pH; furthermore, this isonucleoside proved to be resistant to degradation by ADA and PNP.[6b,7]

In this paper we explore the anti-HIV effects of isosteric substitutions in the purine ring of 2′,3′-dideoxy-3′-oxonucleosides. We synthesized a series of aza and deaza analogues of isoddA in which the nitrogen atoms at positions 1 or 3, and the methine group at position 8, were replaced by a CH group and a nitrogen atom, respectively, i.e. 8-aza- (**7**), 8-aza-1-deaza- (11), 8-aza-3-deaza- (**15**), 1-deaza- (**20**), and 3-deaza-isoddA (**25**).

In previous works we have introduced the above modifications in the purine ring of ddA, but the compounds have proven inactive as anti-HIV agents because



of inefficient phosphorylation by nucleoside kinase.[8a-c] However, when prepared as dialkyl monophosphate ester, 3-deaza-ddA proved to be as potent as ddA, although less selective.[8a] Therefore, some of the aza- and deaza-isoddA derivatives were prepared also as phosphate esters in order to overcome the putative inefficient phosphorylation (compounds **32–36**, **38–39**). Moreover, we also prepared 8-aza-isoddATP with the aim of directly testing its activity against the HIV-1 recombinant reverse transcriptase (rRT) in enzymatic assays.

Chemistry

The synthesis of compounds **7**, 11, **15** was accomplished by the method outlined in Scheme 1. Nucleophilic substitution of (3*S-trans*)-tetrahydro-5-(dimethoxymethyl)-3-furanol 4-methylbenzenesulfonate[6a] (4) with the appropriate heterocyclic bases **1–3** in DMF in the presence of K_2CO_3 and 18-crown-6 afforded in any case a mixture of regioisomers (**5–6**, **9–10**, **13–14**) which were separated by flash silica chromatography. Hydrolysis of the dimethyl acetals, followed by reduction with $NaBH_4$, yielded the isonucleosides **7**, **8**, 11, **12**, **15**, and **16**. In order to establish the substitution site spectroscopic data, particularly ^1H NMR, ^{13}C NMR, and

* Address for correspondence: Dipartimento di Scienze Chimiche, Università di Camerino, Via S. Agostino, 1, 62032 Camerino (MC), Italy. Tel (737)40336; FAX (737)37345.
† Università di Camerino.
‡ Università di Cagliari.
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Scheme 1

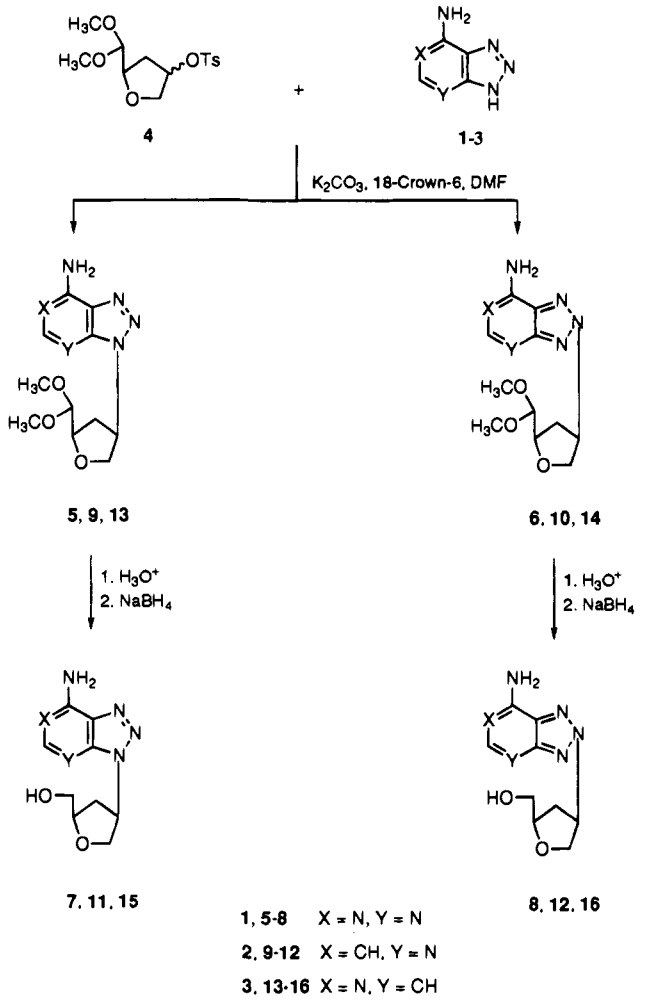


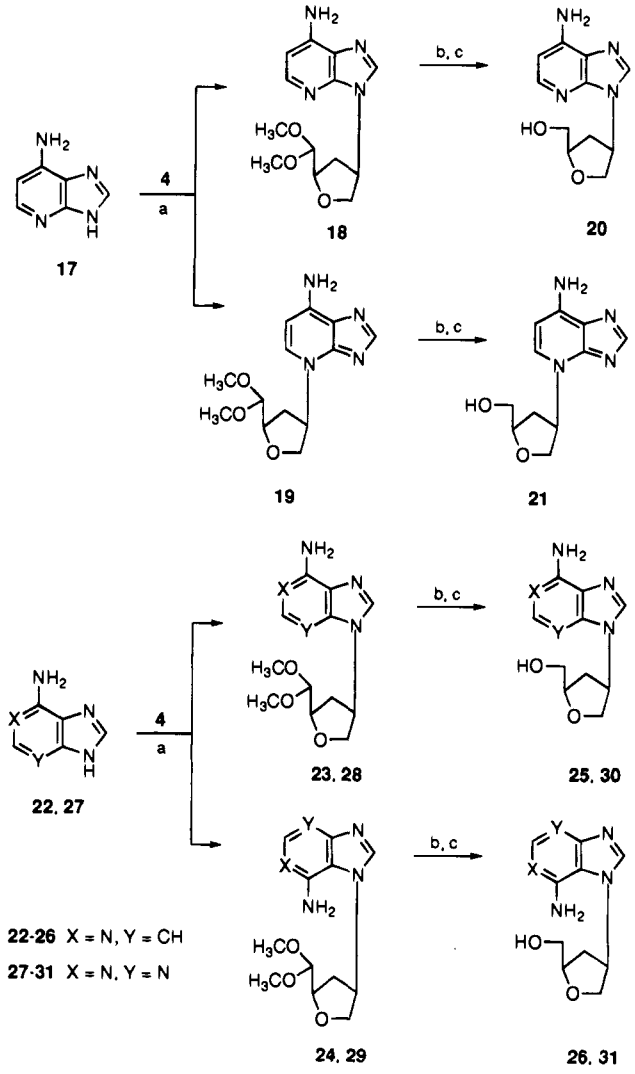
Table 1. ^{13}C NMR Chemical Shifts of IsoddA Derivatives and Bases 1–3[a,b]

compd	C-1	C-2	C-3	C-4	C-5	C-6	C-8
1	–	155.9	–	151.2	123.0	155.8	–
2	99.9	144.5	–	149.0	129.3	148.7	–
3	–	143.7	107.3	143.3	132.3	146.5	–
7	–	156.7	–	148.8	124.2	156.2	–
8	–	154.3	–	156.4	125.1	155.6	–
11	101.6	150.1	–	146.7	127.8	147.7	–
12	100.7	152.3	–	156.5	129.0	146.5	–
15	–	144.2	94.4	136.7	131.5	152.4	–
16	–	142.6	99.8	147.2	131.5	152.1	–
20	102.0	144.4	–	147.0	122.8	146.8	138.3
21	100.9	132.1	–	148.0	128.0	148.7	125.4
25	–	143.6	99.0	139.1	125.8	148.6	128.7
26	–	139.4	106.1	147.1	118.6	149.9	143.5
30	–	152.6	–	149.6	118.9	156.2	139.1
31	–	152.4	–	149.7	120.3	154.8	141.8

[a] Purine numbering. [b] DMSO-d_6.

UV of the above compounds were measured. In the following discussion the purine numbering is used while the systematic numbering is in brackets. The ^{13}C NMR spectra of compounds **7** and **11** showed an upfield shift of C(4) [C(3a)] compared to that of **1** and **3**, indicating that N^9 [N^3] carried a substituent (Table 1).[8a,b,9] A similar upfield shift was observed for C(4) [C(7a)] in the ^{13}C NMR spectrum of **15** as compared to that of **3**, indicating that N^9 [N^1] carried a substituent. In order to confirm the structure of 8-aza-3-deaza-isoddA (**15**), a difference NOE experiment was performed. With irradiation at δ 5.57 (H(4')), NOE peaks appeared at δ 2.62 (Hb(3'), 3%), 4.0 (H(2'), 1%), 4.15 (Ha(5'), Hb(5'), 2.2%) and 6.95 (H(3), [H(7)], 1.9%).

Scheme 2[a]



[a] Reagents: (a) K_2CO_3, 18-crown-6, DMF; (b) H_3O^+; (c) $NaBH_4$.

The presence of NOE on H(2') in compounds **7**, **11**, and **15** (2.4%, 1.3%, and 1%, respectively) when H(4') was irradiated attested that the nucleophilic reaction took place with inversion of configuration.[10] The absence of NOE effect on the amino group protons in 6 position (purine numbering) of compounds **8**, **12**, and **16** when H(4') was irradiated, indicated that the furan moiety is not attached to N^7 and thus must be attached to N^8. Confirmation of this substitution pattern was provided by UV experiment. In fact, it was found that the adsorbance maxima of these isonucleosides were similar to those of known 8-alkylated 8-aza-,[11] 8-aza-1-deaza-,[12] and 8-aza-3-deaza-purines.[8b]

The synthesis of 1-deaza-isoddA (**20**) was carried out in a similar way starting from 1-deazaadenine (**17**) (Scheme 2). The reaction with **4** gave two regioisomers (**18**, **19**) which were separated by flash chromatography. Hydrolysis and reduction of dimethyl acetals **18** and **19** gave isonucleosides **20** and **21**. The structure of compound **20** was deduced from a ^{13}C NMR spectrum which showed that the C(4) [C(3a)] signal was upfield shifted compared to that of **17**. In addition, the adsorbance maximum of this isonucleoside was similar to that reported for known 9-alkylated 1-deazaadenine.[13] The

structure of compound **21** was assigned on the basis of the presence of a NOE effect at δ 7.88 (H(2) [H(5)], 1.2%) when H(4') (δ 5.62) was irradiated. Confirmation of the structure of **21** was obtained by the UV spectrum which showed an absorbance maxima in NaOH 0.1 N at 278 (sh) and 292 nm, very similar to those reported for the 4-β-D-ribofuranosyl derivative of 1-deazaadenine.[14] The lack of alkylation at N^7 of **17** may be explained by the higher nucleophilicity of N^3 and N^9 as compared to that of N^7 in 1-deazapurine.[15]

The 3-deaza-isoddA (**25**) was synthesized in a similar way starting from 3-deazaadenine (**22**). The reaction with **4** gave, in this case as well, two regioisomers (**23** and **24**) which were separated by flash chromatography. Hydrolysis of dimethyl acetals **23** and **24**, followed by reduction with $NaBH_4$, gave isonucleosides **25** and **26**. The substitution pattern of these compounds was deduced from UV experiments by comparing their adsorbance maxima with those of known 7- and 9-alkylated 3-deazaadenine.[16] The structures were confirmed by ^{13}C NMR data which showed that the C(4) [C(7a)] signal of compound **25** was upfield shifted as compared to that of isomer **26**, indicating that N^9 carries a substituent. Conversely, the C(5) [C(3a)] signal of isomer **26** appeared upfield shifted, confirming N^7 substitution.

Finally, we synthesized isoddA (to be used as reference compound) starting from adenine (**27**) and 4, as described by Huryn and co-workers.[6a] The reaction gave a mixture of acetals (**28** and **29**) which were separated by flash chromatography and reduced with $NaBH_4$ to afford isoddA (**30**) (total yield 64%) and the N^7-substituted isomer **31**. The structure of this isomer was deduced by ^{13}C NMR spectrum which showed that the C(5) signal was upfield shifted as compared to that of isoddA, indicating that N^7 carried a substituent. In addition, the adsorbance maximum in the UV spectrum was similar to that reported for other N^7-alkylated adenines.[17]

Results and Discussion

The aza and deaza analogues of isoddA (compounds **7**, **11**, **15**, **20**, and **25**) were evaluated *in vitro* for cytotoxicity and inhibitory effect on the replication of HIV-1 and HIV-2 in MT-4 cells. The cytotoxicity of compounds for MT-4 cells was evaluated in parallel with their anti-HIV activity. The activity against HIV-1 and HIV-2 multiplication in acutely infected cells was based on inhibition of virus-induced cytopathogenicity in MT-4 cells and was determined by the MTT assay.[18]

None of the isonucleoside derivatives was active in protecting MT-4 cells against the HIV-1- and HIV-2-induced cytopathogenicity (Table 2), implying that isosteric substitutions in the purine moiety of isoddA are detrimental for the anti-HIV activity. The lack of antiviral effect could be due to the low affinity of compounds **7**, **11**, **15**, **20**, and **25** for the cellular kinases or for RT.

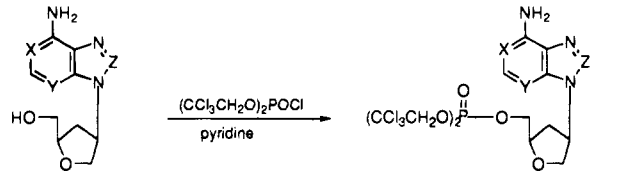
In order to examine the first possibility, we synthesized a series of bis(2,2,2-trichloroethyl) phosphates (compounds **32**–**37**). In fact, the introduction of bis(trihaloethyl) substituents at the phosphate site of nucleotide analogues has been reported to increase both lipophilicity and hydrolytic lability and, consequently, their biological activity.[19] In particular, the substitution of hydrogen atoms at ethyl group with halogens has been thought to induce a greater labilizing effect on the P—O—alkyl bond than on the more remote P—O—nucleoside bond, thus making easier the release of the unmasked nucleotide inside the cells.

Table 2. Cytotoxicity and Inhibitory Effect of Aza and Deaza Analogues of IsoddA (**7**, **11**, **15**, **20**, **25**), Their 5'-Alkyl Phosphates (**32**–**37**), and 5'-Phenyl Phosphoroamidates (**38**–**39**) on the HIV-Induced Cytopatogenicity in MT-4 Cells

		HIV-1		HIV-2	
compd	CC_{50}[a]	EC_{50}[b]	SI[c]	EC_{50}[b]	SI[c]
7	>425	>425		>425	
11	>425	>425		>425	
15	>425	>425		>425	
20	>425	>425		>425	
25	>425	>425		>425	
30 (isoddA)	>425	21	>20	32	>13
32	92	>92		>92	
33	>100	>100		>100	
34	>173	>173		>173	
35	>100	>100		>100	
36	34	>34		>34	
37	≥173	87	≥2	>173	
38	146	17	8.5	105	1.4
39	2.9	0.06	48	0.04	65
ddI	>425	10	>42	11	>38
AZT	>80	0.01	>8000	0.04	>2000

[a] Compound dose (μM) required to reduce the viability of mock-infected MT-4 cells by 50% (4 days). [b] Compound dose required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1 (4 days) and HIV-2 (8 days). [c] CC_{50}/EC_{50} ratio. Data are the mean of three independent experiments. Variation among duplicate samples was less than 15%.

Scheme 3



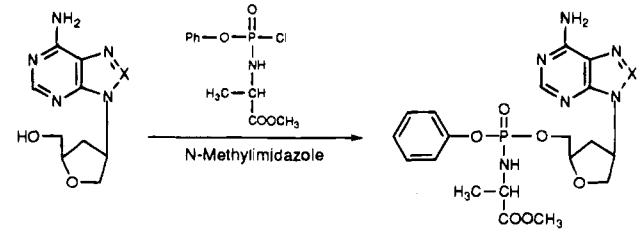
7, **11**, **15**, **20**, **25**, **30**

32 X = N, Y = N, Z = N
33 X = CH, Y = N, Z = N
34 X = N, Y = CH, Z = N
35 X = CH, Y = N, Z = CH
36 X = N, Y = CH, Z = CH
37 X = N, Y = N, Z = CH

Bis(2,2,2-trichloroethyl) phosphates of aza and deaza analogues of isoddA (compounds **32**–**36**) were obtained by reacting the appropriate isonucleosides with bis(2,2,2-trichloroethyl) phosphorochloridate (Scheme 3) and were fully characterized by spectroscopic and analytical data. When tested *in vitro* against HIV-1 and HIV-2, all the 5'-alkyl phosphates proved ineffective (Table 2). In particular, the very poor activity of the 5'-[bis(2,2,2-trichloroethyl) phosphate] of isoddA (**37**), which contrasted with the potent activity reported for the 5'-(alkyl phosphates) of AZT and ddC in C8166 cells,[20] raised the possibility of a greater resistance of 5'-alkylisonucleotides to esterases. It should be noted, however, that the cytotoxicity of the 8-aza- and 3-deaza-isoddA-5'-(alkyl phosphates) was higher than that of the corresponding nucleosides, which suggested a certain degree of metabolization of these derivatives by MT-4 cells.

In order to verify whether the use of a different type of masked nucleotide would afford better results, we

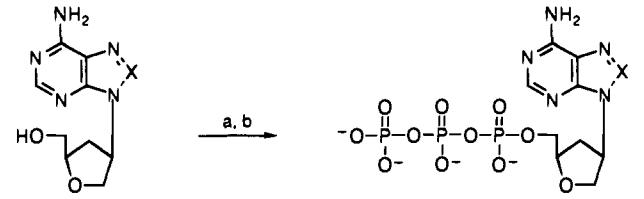
Scheme 4



7 X = N
IsoddA X = CH

38 X = N
39 X = CH

Scheme 5[a]



7 X = N
iso-ddA X = CH

40 X = N
41 X = CH

[a] Reagents: (a) $POCl_3$, $(CH_3O)_3PO$; (b) $(Bu_3N)_4P_2O_7$.

synthesized 5′-(phenyl phosphoramidate) derivatives of 8-aza-isoddA and of isoddA, based on the pronounced anti-HIV activity of the phenyl phosphoramidate derivative of AZT.[21] 5′-(Phenyl phosphoramidates) of 8-aza-isoddA (**38**) and isoddA (**39**) were obtained through reaction of the corresponding isonucleosides with (phenylmethoxy)alaninyl chlorophosphate[21] (Scheme 4). Reaction of this reagent with 8-aza-isoddA (**7**) and isoddA (**30**) in THF, in the presence of *N*-methylimidazole at room temperature, gave the target products. They were the mixture of the two diastereoisomers resulting from the mixed stereochemistry at the phosphate centre, as was evident from the phosphorus and ^1H NMR spectra; the ratio of diastereoisomers was approximately 1:1, as determined by HPLC. In this study the two 5′-(phenyl phosphoramidates) were tested as isomeric mixtures and were found active against both HIV-1 and HIV-2 (Table 2). The 5′-(phenyl phosphoramidate) of 8-aza-isoddA (**38**) showed a potency similar (against HIV-1) or slightly lower (against HIV-2) than that of isoddA, while the potency of the 5′-(phenyl phosphoramidate) of isoddA (**39**) was remarkably higher. This was particularly true in the case of HIV-2, against which the test compound was as potent as AZT. However, a considerable increase in cytotoxicity was also observed.

Evidence that 8-aza-isoddA targeted the RT, provided that it could be activated to triphosphate, was obtained through the chemical synthesis of its 5′-triphosphate derivative (**40**, Scheme 5) and the assay against the HIV-1 rRT (Table 3). Using activated calf thymus DNA as template primer, the IC_{50} of 8-aza-isoddATP (**40**) was 8-fold higher than that of ddATP but 8-fold lower than that of isoddATP (**41**).

Taken together, these results show that isosteric substitutions of the purine ring system of isoddA lead to compounds which are inactive against HIV because of their poor affinity for cellular kinases. As reported for other 2′,3′-dideoxynucleoside analogues, the use of suitable masked phosphates can overcome this obstacle and turn inactive purine-modified isonucleosides into active anti-HIV agents. However, in our hands, aryl phosphoramidate groups were endowed with a higher activating effect than trichloroethyl substituents.

Table 3. Inhibitory Effect of 8-Aza-isoddATP and IsoddATP on the HIV-1 Recombinant Reverse Transcriptase (rRT)

compd	IC_{50}[a]
8-aza-isoddATP (**40**)	4.3 ± 0.3
isoddATP (**41**)	35.0 ± 5.0
ddATP	0.5 ± 0.1

[a] Compound dose required to inhibit the HIV-1 rRT activity by 50%. Activated calf thymus DNA was used as template primer. Data represent mean values (±SD) for three separate experiments.

It was surprising that, besides isoddATP proved to be a weaker RT inhibitor than 8-aza-isoddATP in enzyme assays, it was a much more potent inhibitor of the HIV multiplication in acutely infected cells. Whether this could be due to a different uptake of the two compounds by infected cells remains to be proven.

Experimental Section

Melting points were determined on a Buchi SMP-20 apparatus and are uncorrected. Elemental analyses were determined on a Carlo Erba Model 1106 analyzer. Ultraviolet spectra were recorded on an HP 8452 A diode array spectrophotometer driven by an Olivetti M 24. Thin layer chromatography (TLC) was run on silica gel 60 F_{254} plates and RP-18 F_{254} S (Merck); silica gel 60 (Merck) (70–230 and 230–400 mesh) for column chromatography were used. Nuclear magnetic resonance ^1H, ^{13}C, and ^{31}P spectra were determined at 300, 75, and 121 MHz, respectively, with a Varian VXR-300 spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. All exchangeable protons were confirmed by addition of D_2O. Stationary NOE experiments were run on degassed solutions at 25 °C. A presaturation delay of 1 s was used, during which the decoupler low-power was set at 20 dB attenuation. Compounds were named following IUPAC rules as applied by AUTONOM, PC software for generating systematic names in organic chemistry (Beilstein-Institute and Springer-Verlag).

3-[(5*R*-*cis*)-5-(Dimethoxymethyl)tetrahydrofuran-3-yl]-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-ylamine (5) and 2-[(5*R*-*cis*)-5-(Dimethoxymethyl)tetrahydrofuran-3-yl]-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-ylamine (6). A mixture of 7-amino-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (**1**) (2.0 g, 14.68 mmol) in dry DMF (50 mL) and powdered K_2CO_3 (4.06 g, 29.36 mmol) was stirred at room temperature under N_2, and 18-crown-6 (1.94 g, 7.34 mmol) was added. After 30 min, (3*S*-*trans*)-tetrahydro-5-(dimethoxymethyl)-3-furanol 4-methylbenzenesulfonate[6a] (**4**) (4.64 g, 14.68 mmol) in DMF was added dropwise, and the resultant stirring mixture was heating at 75 °C for 17 h. After removal of the DMF, the residue was treated with EtOAc, filtered, and concentrated in vacuo. The crude mixture was purified by flash silica chromatography ($CHCl_3$–MeOH, 99:1) to afford **5** (400 mg, 23%), a first fraction, as a white solid: mp 161–163 °C; TLC R_f = 0.32 ($CHCl_3$–MeOH, 95:5); ^1H NMR (Me_2SO-d_6) δ 2.63 (m, 2H, H-4′), 3.32 (s, 6H, OCH_3), 4.10 (m, 2H, Ha-2′ and Hb-2′), 4.20 (dd, J = 9.3, 4.3 Hz, 1H, H-5′), 4.42 (d, J = 6.4 Hz, 1H, C*H*(OCH_3)$_2$), 5.41 (m, 1H, H-3′), 8.10, 8.43 (2 s, 2H, NH_2), 8.30 (s, 1H, H-5). Anal. ($C_{11}H_{16}N_6O_3$) C, H, N.

Compound **6** (800 mg, 45%) was separated as second eluate by the same chromatography as a white solid: mp 120–122 °C; TLC R_f = 0.23 ($CHCl_3$–MeOH, 95:5); ^1H NMR (Me_2SO-d_6) δ 2.55 (m, 1H, Ha-4′), 2.68 (m, 1H, Hb-4′), 3.32 (s, 6H, OCH_3), 4.04, 4.12 (AB of ABX, 2H, J_{AB} = 14, J_{AX} = 7.5, J_{BX} = 6.3 Hz, Ha-2′ and Hb-2′), 4.32 (dd, J = 10.2, 3.8 Hz, 1H, H-5′), 4.37 (d, J = 6.4 Hz, 1H, C*H*(OCH_3)$_2$), 5.54 (m, 1H, H-3′), 8.07–8.24 (2 br s, 2H, NH_2), 8.28 (s, 1H, H-5). Anal. ($C_{11}H_{16}N_6O_3$) C, H, N.

[(2*R-cis*)-4-(7-Amino[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)tetrahydrofuran-2-yl]methanol (7). A mixture of **5** (350 mg, 1.24 mmol) and trifluoroacetic acid/H_2O (10:1, 12 mL) was stirred at room temperature for 3.5 h. After coevaporation with H_2O (three times), the residue was solubilized in ethanol (10 mL) and added dropwise to a suspension of $NaBH_4$ (46.9 mg, 1.24 mmol) in ethanol. The reaction mixture was stirred for 1 h. After acidification with 10% HCl, the insoluble material was filtered off, and the filtrate was evaporated to dryness. The foam residue was crystallized from ethanol–ethyl ether to give **7** (160 mg, 54%) as a white solid: mp 193–195 °C; TLC R_f = 0.52 ($CHCl_3$–MeOH, 85:15); $[\alpha]_D$ +30.93° (*c* 0.097, MeOH); UV (H_2O, MeOH) λ_{max} 280 nm (ϵ 5800), (NaOH 0.1 N) 278 nm (ϵ 10 200); ^1H NMR (Me_2SO-d_6) δ 2.37 (m, 1H, Ha-3′), 2.62 (m, 1H, Hb-3′), 3.57 (m, 2H, CH_2OH), 4.06 (m, 1H, H-2′), 4.11, 4.19 (AB of ABX, 2H, J_{AB} = 10.3, J_{AX} = 6.7, J_{BX} = 4.7 Hz, Ha-5′ and Hb-5′), 4.80 (t, *J* = 5.7 Hz, 1H, OH), 5.43 (m, 1H, H-4′), 8.08, 8.42 (2 s, 2H, NH_2), 8.28 (s, 1H, H-5). Anal. ($C_9H_{12}N_6O_2$) C, H, N.

[(2*R-cis*)-4-(7-Amino[1,2,3]triazolo[4,5-*d*]pyrimidin-2-yl)tetrahydrofuran-2-yl]methanol (8). The title compound was prepared in 78% yield (490 mg) as white crystals from **6** (750 mg, 2.67 mmol) by a method entirely analogous to that used for **7**: mp 96–98 °C; TLC R_f = 0.35 ($CHCl_3$–MeOH, 85:15); UV (H_2O, MeOH) λ_{max} 256 nm (ϵ 2300), 294 nm (ϵ 4700), (NaOH 0.1 N) 254 nm (ϵ 2200), 290 nm (ϵ 4500); ^1H NMR (Me_2SO-d_6) δ 2.41 (m, 1H, Ha-3′), 2.67 (m, 1H, Hb-3′), 3.48 (m, 2H, CH_2OH), 4.03 (m, 1H, H-2′), 4.15 (dd, *J* = 6.6, 3.2 Hz, 1H, Ha-5′), 4.25 (dd, *J* = 5.9, 3.7 Hz, 1H, Hb-5′), 5.00 (br s, 1H, OH), 5.58 (m, 1H, H-4′), 8.35 (s, 1H, H-5), 8.65, 8.88 (2 s, 2H, NH_2). Anal. ($C_9H_{12}N_6O_2$) C, H, N.

3-[(5*R-cis*)-5-(Dimethoxymethyl)tetrahydrofuran-3-yl]-3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-7-ylamine (9) and 2-[(5*R-cis*)-5-(Dimethoxymethyl)tetrahydrofuran-3-yl]-2*H*-[1,2,3]triazolo[4,5-*b*]pyridin-7-ylamine (10). Compounds **9** and **10** were prepared from 7-amino-3*H*-[1,2,3]triazolo[4,5-*b*]pyridine[22] (**2**) (1 g, 7.34 mmol) as described for **5** (reaction time 6 h at 80 °C). By chromatographic purification of oil residue on silica gel column ($CHCl_3$–MeOH, 96:4), as first eluate **9** was obtained as white crystals (560 mg, 27%): mp 112–114 °C; TLC R_f = 0.31 ($CHCl_3$–MeOH, 96:4); ^1H NMR (Me_2SO-d_6) δ 2.62 (m, 2H, Ha-4′, Hb-4′), 3.35 (s, 6H, OCH_3), 4.15 (m, 3H, Ha-2′, Hb-2′ and H-5′), 4.43 (d, *J* = 6.4 Hz, 1H, C*H*(OCH_3)$_2$), 5.45 (m, 1H, H-3′), 6.38 (d, *J* = 5.5 Hz, 1H, H-6), 7.27 (s, 2H, NH_2), 8.05 (d, *J* = 5.5 Hz, 1H, H-5). Anal. ($C_{12}H_{17}N_5O_3$) C, H, N.

As second fraction of the same chromatography, compound **10** was obtained (650 mg, 32%) as white crystals: mp 104–106 °C; TLC R_f = 0.26 ($CHCl_3$–MeOH, 96:4); ^1H NMR (Me_2SO-d_6) δ 2.65 (m, 2H, Ha-4′, Hb-4′), 3.32 (s, 6H, OCH_3), 4.12 (m, 2H, Ha-2′, Hb-2′), 4.34 (dd, *J* = 9.4, 4.1 Hz, 1H, H-5′), 4.40 (d, *J* = 6.5 Hz, 1H, C*H*(OCH_3)$_2$), 5.58 (m, 1H, H-3′), 6.36 (d, *J* = 5.2 Hz, 1H, H-6), 6.98 (s, 2H, NH_2), 8.18 (d, *J* = 5.2 Hz, 1H, H-5). Anal. ($C_{12}H_{17}N_5O_3$) C, H, N.

[(2*R-cis*)-4-(7-Amino[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-tetrahydrofuran-2-yl]methanol (11). By the same procedure as for the preparation of **7**, compound **11** was prepared from **9** (550 mg, 1.97 mmol). After filtration of the mixture reaction, the filtrate was evaporated to dryness to give a foam residue which was crystallized from ethanol–ethyl ether. The title compound **11** was obtained (445 mg, 81%) as a white solid: mp 177–179 °C; TLC R_f = 0.46 ($CHCl_3$–MeOH–NH_4OH, 86:13:1); UV (H_2O) λ_{max} 260 nm (ϵ 2700); 304 nm (ϵ 4300), (NaOH 0.1 N) 260 nm (ϵ 3500), 266 nm (ϵ 3300), 306 nm (ϵ 5100); ^1H NMR (Me_2SO-d_6) δ 2.42 (m, 1H, Ha-3′), 2.61 (m, 1H, Hb-3′), 3.55 (m, 2H, CH_2OH), 4.10 (m, 3H, H-2′, Ha-5′, and Hb-5′), 4.82 (t, *J* = 5.7 Hz, 1H, OH), 5.48 (m, 1H, H-4′), 6.39 (d, *J* = 5.4 Hz, 1H, H-6), 7.28 (s, 2H, NH_2); 8.04 (d, *J* = 5.4 Hz, 1H, H-5). Anal. ($C_{10}H_{13}N_5O_2$) C, H, N.

[(2*R-cis*)-4-(7-Amino[1,2,3]triazolo[4,5-*b*]pyridin-2-yl)-tetrahydrofuran-2-yl]methanol (12). The title compound was prepared from **10** (600 mg, 2.14 mmol) as described for **11**. By crystallization from ethanol–ethyl ether, 440 mg (74%) of **12** was obtained as a white solid: mp 153–155 °C; TLC R_f = 0.35 ($CHCl_3$–MeOH–NH_4OH, 86:13:1); UV (H_2O) λ_{max} 270 nm (ϵ 9500), 278 nm (ϵ 7300), 316 nm (ϵ 11 100), (NaOH 0.1 N) 272 nm (ϵ 11 300), 278 nm (ϵ 11 100), 318 nm (ϵ 11 400); ^1H NMR (Me_2SO-d_6) δ 2.48 (m, 1H, Ha-3′), 2.74 (m, 1H, Hb-3′), 3.55 (t, *J* = 5.4 Hz, 2H, CH_2OH), 4.05 (m, 1H, H-2′), 4.16, 4.35 (AB of ABX, 2H, J_{AB} = 9.5, J_{AX} = 6.6, J_{BX} = 3.8 Hz, Ha-5′ and Hb-5′), 4.35 (m, 1H, H-2′), 4.83 (t, *J* = 5.7 Hz, 1H, OH), 5.58 (m, 1H, H-4′), 6.38 (d, *J* = 5.2 Hz, 1H, H-6), 7.03 (s, 2H, NH_2), 8.20 (d, *J* = 5.2 Hz, 1H, H-5). Anal. ($C_{10}H_{13}N_5O_2$) C, H, N.

1-[(5*R-cis*)-5-(Dimethoxymethyl)tetrahydrofuran-3-yl]-1*H*-[1,2,3]triazolo[4,5-*c*]pyridin-4-ylamine (13) and 2-[(5*R-cis*)-5-(Dimethoxymethyl)tetrahydrofuran-3-yl]-2*H*-[1,2,3]-triazolo[4,5-*c*]pyridin-4-ylamine (14). As described for **9** and **10**, compounds **13** and **14** were prepared from 4-amino-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine[23] (**3**) (1.5 g, 11.1 mmol) (reaction time 7 h, 80 °C). The chromatographic separation by silica gel column using $CHCl_3$–MeOH–NH_4OH (86:13:1) gave as first eluate compound **14**, which was recrystallized from methylene chloride–ethyl ether to yield 1 g (33%) as white crystals: mp 104–106 °C; TLC R_f = 0.45 ($CHCl_3$–MeOH–NH_4OH, 86:13:1); ^1H NMR (Me_2SO-d_6) δ 2.57 (m, 1H, Ha-4′), 2.68 (m, 1H, Hb-4′), 3.28 (s, 6H, OCH_3), 4.05 (dd, *J* = 6.4, 3.3 Hz, 1H, H-5′), 4.12, 4.30 (AB of ABX, 2H, J_{AB} = 13.8, J_{AX} = 7.2, J_{BX} = 5.6 Hz, Ha-2′ and Hb-2′), 4.35 (d, *J* = 6.0 Hz, 1H, C*H*(OCH_3)$_2$), 5.57 (m, 1H, H-3′), 6.83 (d, *J* = 6.1 Hz, 1H, H-7), 7.00 (s, 2H, NH_2), 7.67 (d, *J* = 6.1 Hz, 1H, H-6). Anal. ($C_{12}H_{17}N_5O_3$) C, H, N.

As second eluate from the same chromatography, compound **13** was separated (610 mg, 20%) as a white solid: mp 151–153 °C; TLC R_f = 0.40 ($CHCl_3$–MeOH–NH_4OH, 86:13:1); ^1H NMR (Me_2SO-d_6) δ 2.35 (m, 1H, Ha-4′), 2.70 (m, 1H, Hb-4′), 3.30 (s, 6H, OCH_3), 4.01–4.19 (m, 3H, Ha-2′, Hb-2′ and H-5′), 4.48 (d, *J* = 5.9 Hz, 1H, C*H*(OCH_3)$_2$), 5.53 (m, 1H, H-3′), 6.95 (d, *J* = 5.9 Hz, 1H, H-7), 7.18 (s, 2H, NH_2), 7.82 (d, *J* = 5.9 Hz, 1H, H-6). Anal. ($C_{12}H_{17}N_5O_3$) C, H, N.

[(2*R-cis*)-4-(4-Amino[1,2,3]triazolo[4,5-*c*]pyridin-1-yl)-tetrahydrofuran-2-yl]methanol (15). The title compound was prepared from **13** (600 mg, 2.18 mmol) as described for **7**. Recrystallization from ethanol–ethyl ether gave **15** (445 mg, 74%) as white solid: mp 170–172 °C; TLC R_f = 0.30 ($CHCl_3$–MeOH–NH_4OH, 90:9:1); UV (H_2O, MeOH) λ_{max} 294 nm (ϵ 4300), (NaOH 0.1 N) 290 nm (ϵ 4000); ^1H NMR (Me_2SO-d_6) δ 2.18 (m, 1H, Ha-3′), 2.62 (m, 1H, Hb-3′), 3.57 (pseudo t, 2H, CH_2OH), 4.0 (m, 1H, H-2′), 4.15 (m, 2H, Ha-5′, and Hb-5′), 4.86 (t, *J* = 5.5 Hz, 1H, OH), 5.57 (m, 1H, H-4′), 6.95 (d, *J* = 5.8 Hz, 1H, H-7), 7.10 (s, 2H, NH_2), 7.80 (d, *J* = 5.8 Hz, 1H, H-6). Anal. ($C_{10}H_{13}N_5O_2$) C, H, N.

[(2*R-cis*)-4-(4-Amino[1,2,3]triazolo[4,5-*c*]pyridin-2-yl)tetrahydrofuran-2-yl]methanol (16). Compound **16** was obtained from **14** (0.9 mg, 3.26 mmol), as described for **7**, as a white solid (740 mg, 82%): mp 135–138 °C; TLC R_f = 0.35 ($CHCl_3$–MeOH–NH_4OH, 90:9:1); UV (H_2O, MeOH) λ_{max} 310 nm (ϵ 3100), (NaOH 0.1 N) 312 nm (ϵ 3000); ^1H NMR (Me_2SO-d_6) δ 2.42 (m, 1H, Ha-3′), 2.68 (m, 1H, Hb-3′), 3.48 (m, 2H, CH_2OH), 4.02 (m, 1H, H-2′), 4.12, 4.30 (AB of ABX, 2H, J_{AB} = 9.5, J_{AX} = 6.5, J_{BX} = 3.8 Hz, Ha-5′ and Hb-5′), 4.80 (t, *J* = 5.6 Hz, 1H, OH), 5.58 (m, 1H, H-4′), 6.86 (d, *J* = 6.2 Hz, 1H, H-7), 7.00 (s, 2H, NH_2), 7.67 (d, *J* = 6.2 Hz, 1H, H-6). Anal. ($C_{10}H_{13}N_5O_2$) C, H, N.

3-[(5*R-cis*)-5-(Dimethoxymethyl)tetrahydrofuran-3-yl]-3*H*-imidazo[4,5-*b*]pyridin-7-ylamine (18) and 3-[(5*R-cis*)-5-(Dimethoxymethyl)tetrahydrofuran-3-yl]-4*H*-imidazo-[4,5-*b*]pyridin-7-ylamine (19). Compounds **18** and **19** were prepared from 7-amino-3*H*-imidazo[4,5-*b*]pyridine (**17**)[24] (1 g, 7.45 mmol) by essentially the same procedure as for the preparation of **5** and **6** (80 °C, 24 h). The residue was purified by flash chromatography, eluting with $CHCl_3$–MeOH (98:2) to give as first fraction compound **18** as a colorless gum (810 mg, 39%): TLC R_f = 0.19 ($CHCl_3$–MeOH, 98:2). ^1H NMR (Me_2SO-d_6) δ 2.18 (m, 1H, Ha-4′), 2.55 (m, 1H, Hb-4′), 3.35 (s, 6H, OCH_3), 4.03 (m, 3H, Ha-2′, Hb-2′, and H-5′), 4.43 (d, *J* = 5.6 Hz, 1H, C*H*(OCH_3)$_2$), 5.18 (m, 1H, H-3′), 6.30 (s, 2H, NH_2), 6.38 (d, *J* = 5.6 Hz, 1H, H-6), 7.80 (d, *J* = 5.6 Hz, 1H, H-5), 8.15 (s, 1H, H-2). Anal. ($C_{13}H_{18}N_4O_3$) C, H, N.

Compound **19** (second eluate) was obtained as yellow gum (760 mg, 37%): TLC R_f = 0.02 ($CHCl_3$–MeOH, 98:2); ^1H NMR (Me_2SO-d_6) δ 2.07 (m, 1H, Ha-4′), 2.62 (m, 1H, Hb-4′), 3.48 (s,

6H, OCH_3), 4.05 (m, 2H, Ha-2′, H-5′), 4.12 (dd, J = 5.8, 4.3 Hz, 1H, Hb-2′), 4.48 (d, J = 5.3 Hz, 1H, C*H*$(OCH_3)_2$), 5.60 (m, 1H, H-3′), 6.50 (d, J = 7.0 Hz, 1H, H-6), 7.56 (s, 2H, NH_2), 7.92 (d, J = 7.0 Hz, 1H, H-5), 8.05 (s, 1H, H-2). Anal. ($C_{13}H_{18}N_4O_3$) C, H, N.

[(2*R-cis*)-4-(7-Aminoimidazo[4,5-*b*]pyridin-3-yl)tetrahydrofuran-2-yl]methanol (20). As described for **7**, compound **20** was prepared from **18** (800 mg, 2.87 mmol) to yield 360 mg (45%) of a colorless foam. TLC R_f = 0.24 ($CHCl_3$–MeOH–NH_4OH, 90:9:1); UV (H_2O) λ_{max} 264 nm (ϵ 11 800), 278 nm (ϵ 9300), (NaOH 0.1 N) 264 nm (ϵ 15 100), 276 nm (ϵ 11 700); ^{1}H NMR (Me_2SO-d_6) δ 2.08 (m, 1H, Ha-3′), 2.53 (m, 1H, Hb-3′), 3.44 (m, 1H, H-2′), 3.52, 3.60 (AB of ABX, J_{AB} = 11.9, J_{AX} = 4.8, J_{BX} = 4.2 Hz, 2H, CH_2OH), 3.95 (m, 2H, Ha-5′, and Hb-5′), 4.95 (br s, 1H, OH), 5.20 (m, 1H, H-4′), 6.32 (s, 2H, NH_2), 6.35 (d, J = 5.5 Hz, 1H, H-6), 7.80 (d, J = 5.5 Hz, 1H, H-5), 8.18 (s, 1H, H-2). Anal. ($C_{11}H_{14}N_4O_2$) C, H, N.

[(2*R-cis*)-4-(7-Aminoimidazo[4,5-*b*]pyridin-4-yl)tetrahydrofuran-2-yl]methanol (21). As described for **7**, the title compound was prepared from **19** (700 mg, 2.51 mmol) to yield 315 mg (45%) of a colorless foam: TLC R_f = 0.11 ($CHCl_3$–MeOH–NH_4OH, 90:9:1); UV (H_2O) λ_{max} 290 nm (ϵ 5200), (NaOH 0.1 N) 278 (ϵ 13 500, sh), 292 (ϵ 15 200); ^{1}H NMR (Me_2SO-d_6) δ 2.04 (m, 1H, Ha-3′), 2.65 (m, 1H, Hb-3′), 3.52, 3.65 (AB of ABX J_{AB} = 12.0, J_{AX} = 4.6, J_{BX} = 3.6 Hz, 2H, CH_2OH), 3.92–4.06 (m, 3H, H-2′, Ha-5′, and Hb-5′), 4.38 (br s, 1H, OH), 5.62 (m, 1H, H-4′), 6.36 (d, J = 7.2 Hz, 1H, H-6), 7.20 (s, 2H, NH_2), 7.72 (s, 1H, H-2), 7.88 (d, J = 7.2 Hz, 1H, H-5). Anal. ($C_{11}H_{14}N_4O_2$) C, H, N.

1-[(5*R-cis*)-5-(Dimethoxymethyl)tetrahydrofuran-3-yl]-1*H*-imidazo[4,5-*c*]pyridin-4-ylamine (23) and 3-[(5*R-cis*)-5-(Dimethoxymethyl)tetrahydrofuran-3-yl]-3*H*-imidazo[4,5-*c*]pyridin-4-ylamine (24). Compounds **23** and **24** were obtained from 4-amino-1*H*-imidazo[4,5-*c*]pyridine (**22**)[25] (1 g, 7.46 mmol) by essentially the same procedure as used for the preparation of **5** and **6** (reaction time 24 h). The foam residue was purified by chromatography on silica gel column with $CHCl_3$–MeOH–NH_4OH (94:5:1) to give compound **23** (first eluate) as a white solid (760 mg, 37%): mp 168–170 °C; TLC R_f = 0.42 ($CHCl_3$–MeOH, 98:2); ^{1}H NMR (Me_2SO-d_6) δ 2.08 (m, 1H, Ha-4′), 2.56 (m, 1H, Hb-4′), 3.38 (s, 6H, OCH_3), 4.01 (m, 3H, Ha-2′, Hb-2′, and H-5′), 4.42 (d, J = 5.2 Hz, 1H, C*H*$(OCH_3)_2$), 5.11 (m, 1H, H-3′), 6.18 (s, 2H, NH_2), 6.85 (d, J = 5.8 Hz, 1H, H-7), 7.66 (d, J = 5.8 Hz, 1H, H-6), 8.10 (s, 1H, H-2). Anal. ($C_{13}H_{18}N_4O_3$) C, H, N.

Compound **24** was obtained as second eluate from the same chromatography column as a white foam (83 mg, 4%): TLC R_f = 0.32 ($CHCl_3$–MeOH–NH_4OH, 94:5:1); ^{1}H NMR (Me_2SO-d_6) δ 2.05 (m, 1H, Ha-4′), 2.62 (m, 1H, Hb-4′), 3.35 (s, 6H, OCH_3), 4.02 (m, 2H, Ha-2′, H-5′), 4.21 (dd, J = 9.9, 3.0 Hz, 1H, Hb-2′), 4.32 (d, J = 5.3 Hz, 1H, C*H*$(OCH_3)_2$), 5.51 (m, 1H, H-3′), 6.00 (s, 2H, NH_2), 6.92 (d, J = 5.7 Hz, 1H, H-7), 7.70 (d, J = 5.7 Hz, 1H, H-6), 8.25 (s, 1H, H-2). Anal. ($C_{13}H_{18}N_4O_3$) C, H, N.

[(2*R-cis*)-4-(4-Amino-1*H*-imidazo[4,5-*c*]pyridin-1-yl)tetrahydrofuran-2-yl]methanol (25). From **23** (750 mg, 2.69 mmol) was obtained as a white solid compound **25**, as described for **7**, which was recrystallized by ethanol–ethyl ether (365 mg, 58%): mp 198–200 °C; TLC R_f = 0.4 ($CHCl_3$–MeOH–NH_4OH, 85:14:1); UV (H_2O) λ_{max} 264 nm (ϵ 8000), (NaOH 0.1 N) 266 nm (ϵ 8100); ^{1}H NMR (Me_2SO-d_6) δ 2.01 (m, 1H, Ha-3′), 2.59 (m, 1H, Hb-3′), 3.52, 3.62 (AB of ABX, J_{AB} = 12.0, J_{AX} = 4.0, J_{BX} = 3.4 Hz, 2H, CH_2OH), 3.95 (m, 2H, Ha-5′, H-2′), 4.04 (dd, J = 2.6, 7.5 Hz, 1H, Hb-5′), 5.11 (br s, 1H, OH), 5.32 (m, 1H, H-4′), 7.35 (d, J = 7.0 Hz, 1H, H-7), 7.75 (d, J = 7.0 Hz, 1H, H-6), 8.54 (s, 2H, NH_2), 8.56 (s, 1H, H-2). Anal. ($C_{11}H_{14}N_4O_2$) C, H, N.

[(2*R-cis*)-4-(4-Amino-3*H*-imidazo[4,5-*c*]pyridin-3-yl)tetrahydrofuran-2-yl]methanol (26). Compound **26** was obtained from **24** (75 mg, 0.27 mmol), as described for **7**, as white foam (34 mg, 55%): TLC R_f = 0.35 ($CHCl_3$–MeOH–NH_4OH, 85:14:1); UV (H_2O) λ_{max} 242 nm (ϵ 4200), 286 nm (ϵ 7500), (NaOH 0.1 N) 246 nm (ϵ 4000), 286 nm (ϵ 5900); ^{1}H NMR (Me_2SO-d_6) δ 2.00 (m, 1H, Ha-3′), 2.65 (m, 1H, Hb-3′), 3.50 (m, 2H, CH_2OH), 3.95–4.19 (m, 3H, Ha-5′, Hb-5′, H-2′), 4.92 (t, 1H, OH), 5.55 (m, 1H, H-4′), 6.03 (s, 2H, NH_2), 6.95 (d, J = 5.7 Hz, 1H, H-7), 7.70 (d, J = 5.7 Hz, 1H, H-6), 8.35 (s, 1H, H-2). Anal. ($C_{11}H_{14}N_4O_2$) C, H, N.

9-[(5*R-cis*)-5-(Dimethoxymethyl)tetrahydrofuran-3-yl]-9*H*-purin-6-ylamine (28) and 7-[(5*R-cis*)-5-(Dimethoxymethyl)tetrahydrofuran-3-yl]-7*H*-purin-6-ylamine (29). From adenine (**27**) (1 g, 7.40 mmol), by a method entirely analogous to that described for **5** and **6** (reaction time 8 h), compounds **28** and **29** were prepared. The reaction residue was purified by flash chromatography using $CHCl_3$–MeOH (98:2) to give compound **28** (first eluate) as a white solid (830 mg, 80%): mp 144–146 °C (lit.[6a] mp 144–146 °C); TLC R_f = 0.53 ($CHCl_3$–MeOH–NH_4OH, 90:9:1); ^{1}H NMR (Me_2SO-d_6) δ 2.20 (m, 1H, Ha-4′), 2.57 (m, 1H, Hb-4′), 3.32 (s, 6H, OCH_3), 4.05 (m, 3H, Ha-2′, Hb-2′, and H-5′), 4.44 (d, J = 5.5 Hz, 1H, C*H*$(OCH_3)_2$), 5.13 (m, 1H, H-3′), 7.21 (br s, 2H, NH_2), 8.14, 8.21 (2 s, 2H, H-2 and H-8). Anal. ($C_{12}H_{17}N_5O_3$) C, H, N.

Compound **29** was obtained as second eluate from the same chromatographic column as a white foam (140 mg, 14%): TLC R_f = 0.39 ($CHCl_3$–MeOH–NH_4OH, 90:9:1); ^{1}H NMR (Me_2SO-d_6) δ 2.31 (m, 1H, Ha-4′), 2.61 (m, 1H, Hb-4′), 3.37 (s, 6H, OCH_3), 4.05 (m, 2H, Ha-2′ and H-5′), 4.30 (dd, J = 9.8, 3.9 Hz, 1H, Hb-2′), 4.53 (d, J = 5.2 Hz, 1H, C*H*$(OCH_3)_2$), 5.45 (m, 1H, H-3′), 7.77 (s, 1H, H-8), 7.95 (s, 2H, NH_2), 8.38 (s, 1H, H-2). Anal. ($C_{12}H_{17}N_5O_3$) C, H, N.

[(2*R-cis*)-4-(6-Aminopurin-9-yl)tetrahydrofuran-2-yl]methanol (30). From **28**, compound **30** was obtained (80%) as described for **7** (total yield 64%; lit.[6a] 35%).

[(2*R-cis*)-4-(6-Aminopurin-7-yl)tetrahydrofuran-2-yl]methanol (31). Compound **31** was obtained from **29** (140 mg, 0.50 mmol), as described for **7**, as a white solid (70 mg, 50%): mp >245 °C; TLC R_f = 0.17 ($CHCl_3$–MeOH–NH_4OH, 90:9:1); UV (H_2O) λ_{max} 274 nm (ϵ 11 800), (NaOH 0.1 N) 274 nm (ϵ 12 200); ^{1}H NMR (Me_2SO-d_6) δ 2.22 (m, 1H, Ha-3′), 2.62 (m, 1H, Hb-3′), 3.52, 3.70 (m, 2H, CH_2OH, dddd after exchange with D_2O), 4.03 (m, 2H, Ha-5′, H-2′), 4.23 (dd, J = 3.2, 9.9 Hz, 1H, Hb-5′), 5.10 (t, 1H, OH), 5.48 (m, 1H, H-4′), 7.75 (s, 1H, H-2), 7.90 (s, 2H, NH_2), 8.48 (s, 1H, H-8). Anal. ($C_{10}H_{13}N_5O_2$) C, H, N.

General Procedure for the Bis(2,2,2-trichloroethyl) Phosphates 32–37 of the Isonucleosides 7, 11, 15, 20, 25, 30. This synthesis was conducted in accordance with the procedure reported by McGuigan et al.[19] by reacting the appropriate isonucleoside with bis(2,2,2-trichloroethyl) phosphorochloridate (molar ratio 1:1).

8-Aza-isoddA-5′-[bis(2,2,2-trichloroethyl) phosphate] (32). Starting from **7**, the reaction was carried out for 24 h at room temperature. By chromatography on silica gel column ($CHCl_3$–MeOH, 96:4), **32** (28%) was separated as a white solid: mp 113–115 °C; TLC R_f = 0.33 ($CHCl_3$–MeOH, 96:4); UV (MeOH) λ_{max} 280 nm (ϵ 6100); ^{31}P NMR (Me_2SO-d_6) δ −3.40; ^{1}H NMR (Me_2SO-d_6) δ 2.48 (m, 1H, Ha-3′), 2.73 (m, 1H, Hb-3′), 4.18, 4.25 (AB of ABX, J_{AB} = 9.0, J_{AX} = 6.4, J_{BX} = 4.7 Hz, 2H, Ha-5′, and Hb-5′), 4.35 (m, 3H, H-2′, CH_2OP), 4.80 (m, 4H, CH_2Cl_3), 5.50 (m, 1H, H-4′), 8.08, 8.42 (2 s, 2H, NH_2), 8.28 (s, 1H, H-5). Anal. ($C_{13}H_{15}Cl_6N_6O_5P$) C, H, N.

8-Aza-1-deaza-isoddA-5′-[bis(2,2,2-trichloroethyl) phosphate] (33). Compound **33** was obtained starting from **11** at room temperature for 17 h and chromatographed by silica gel column eluting with $CHCl_3$–MeOH (93:7) as a white foam (30%): TLC R_f = 0.35 ($CHCl_3$–MeOH, 93:7); UV (MeOH) λ_{max} 260 nm (ϵ 3500), 304 (ϵ 4800); ^{31}P NMR (Me_2SO-d_6) δ −3.50; ^{1}H NMR (Me_2SO-d_6) δ 2.50 (m, 1H, Ha-3′), 2.75 (m, 1H, Hb-3′), 4.25 (m, 3H, H-2, Ha-5′, and Hb-5′), 4.82 (m, 6H, CH_2Cl_3, and CH_2OP), 5.57 (m, 1H, H-4′), 6.38 (d, J = 5.4 Hz, 1H, H-6), 7.28 (s, 2H, NH_2), 8.05 (d, J = 5.4 Hz, 1H, H-5). Anal. ($C_{14}H_{16}Cl_6N_5O_5P$) C, H, N.

8-Aza-3-deaza-isoddA-5′-[bis(2,2,2-trichloroethyl) phosphate] (34). This compound was obtained from **15** (reaction time 4 h) and purified by chromatographic silica gel column with $CHCl_3$–MeOH (97:3) as a white foam (43%): TLC R_f = 0.25 ($CHCl_3$–MeOH, 97:3); UV (MeOH) λ_{max} 294 nm (ϵ 6300); ^{31}P NMR (Me_2SO-d_6) δ −3.39; ^{1}H NMR (Me_2SO-d_6) δ 2.52 (m, 1H, Ha-3′), 2.77 (m, 1H, Hb-3′), 4.19 (A of ABX, J_{AB} = 9.8, J_{AX} = 6.2 Hz, 1H, Ha-5′), 4.32 (m, 4H, CH_2OP, H-2′, and Hb-5′), 4.79 (m, 4H, CH_2Cl_3), 5.62 (m, 1H, H-4′), 6.85 (d, J = 6.2 Hz,

1H, H-7), 7.00 (s, 2H, NH_2), 7.66 (d, J = 6.2 Hz, 1H, H-6). Anal. ($C_{14}H_{16}Cl_6N_5O_5P$) C, H, N.

1-Deaza-isoddA-5′-[bis(2,2,2-trichloroethyl) phosphate] (35). The title compound was obtained from **20** (reaction time 12 h). Chromatographic separation of the reaction mixture on silica gel column with $CHCl_3$–MeOH (90:10) gave **35** as white foam (48%): TLC R_f = 0.4 ($CHCl_3$–MeOH, 90:10); UV (MeOH) λ_{max} 264 nm (ϵ 12 000), 278 (ϵ 10 000); ^{31}P NMR (Me_2SO-d_6) δ −3.51; ^{1}H NMR (Me_2SO-d_6) δ 2.20 (m, 1H, Ha-3′), 2.62 (m, 1H, Hb-3′), 4.13 (m, 5H, CH_2OP, H-2′, Ha-5′, and Hb-5′), 4.80 (m, 4H, CH_2Cl_3), 5.40 (m, 1H, H-4′), 6.30 (s, 2H, NH_2), 6.50 (d, J = 5.5 Hz, 1H, H-6), 7.73 (d, J = 5.5 Hz, 1H, H-5), 8.15 (s, 1H, H-2). Anal. ($C_{15}H_{17}Cl_6N_4O_5P$) C, H, N.

3-Deaza-isoddA-5′-[bis(2,2,2-trichloroethyl) phosphate] (36). This compound was prepared from **24** (reaction time 3 h). Purification by chromatographic silica gel column with $CHCl_3$–MeOH (90:10) gave a white foam (68%): TLC R_f = 0.40 ($CHCl_3$–MeOH, 92:8); UV (MeOH) λ_{max} 264 nm (ϵ 8100); ^{31}P NMR (Me_2SO-d_6) δ −3.18; ^{1}H NMR (Me_2SO-d_6) δ 2.00 (m, 1H, Ha-3′), 2.63 (m, 1H, Hb-3′), 4.08 (m, 2H, Ha-5′, and Hb-5′), 4.32 (m, 3H, H-2′, and CH_2OP), 4.82 (m, 4H, CH_2Cl_3), 5.20 (m, 1H, H-4′), 6.23 (s, 2H, NH_2), 6.87 (d, J = 7.0 Hz, 1H, H-7), 7.66 (d, J = 7.0 Hz, 1H, H-6), 8.12 (s, 1H, H-2). Anal. ($C_{15}H_{17}Cl_6N_4O_5P$) C, H, N.

IsoddA-5′-[bis(2,2,2-trichloroethyl) phosphate] (37). This compound was obtained from **30** (reaction time 4 h, chromatography column with $CHCl_3$–MeOH, 90:10) as a white foam (57%): TLC R_f = 0.2 ($CHCl_3$–MeOH, 96:4); UV (MeOH) λ_{max} 260 nm (ϵ 14 800); ^{31}P NMR (Me_2SO-d_6) δ −4.25; ^{1}H NMR (Me_2SO-d_6) δ 2.18 (m, 1H, Ha-3′), 2.68 (m, 1H, Hb-3′), 4.07, 4.20 (AB of ABX, J_{AB} = 9.3, J_{AX} = 6.4, J_{BX} = 4.9 Hz, 2H, Ha-5′, and Hb-5′), 4.34 (m, 3H, H-2′, and CH_2OP), 4.84 (m, 4H, CH_2Cl_3), 5.20 (m, 1H, H-4′), 7.25 (s, 2H, NH_2), 8.12, 8.17 (2 s, 2H, H-2 and H-8). Anal. ($C_{14}H_{16}Cl_6N_5O_5P$) C, H, N.

General Procedure for the (Phenylmethoxy)alaninyl Phosphates 38 and 39 of IsoddA and 8-Aza-isoddA. This synthesis was conducted in accordance with the procedure reported by McGuigan et al.[21] from appropriate isonucleoside and (phenylmethoxy)alaninyl phosphorochloridate.

8-Aza-isoddA-5′-[(phenylmethoxy)alaninyl phosphate] (38). Compound **38** was prepared from **7** (0.2, 0.84 mmol) (reaction time 15 h at room temperature) and purified by flash chromatography ($CHCl_3$–MeOH, 90:10, R_f = 0.55) to give a white foam (48%): ^{31}P NMR ($CDCl_3$) δ 3.68, 3.48 (4:3); ^{1}H NMR ($CDCl_3$) δ (peaks labeled by an asterisk (*) are duplicated due to diastereoisomers) 1.38* (d, J = 7.2 Hz, 3H, Ala-Me), 2.70 (m, 2H, H-3′), 3.70* (s, 3H, OMe), 3.80 (m, 1H, NH), 4.12 (m, 1H, Ala-CH), 4.22–4.48 (m, 5H, H-2′, Ha-5′, Hb-5′, and CH_2-OP), 5.50 (m, 1H, H-4′), 6.10 (br s, 2H, NH_2), 7.10–7.33 (m, 5H, PhO), 8.45 (s, 1H, H-5). Anal. ($C_{19}H_{24}N_7O_6P$) C, H, N.

IsoddA-5′-[(phenylmethoxy)alaninyl phosphate] (39). From isoddA (**30**) (0.3 g, 1.27 mmol) in DMF (8 mL) for 2 h at room temperature was obtained **39**, which was purified by flash chromatography ($CHCl_3$–MeOH, 96:4, R_f = 0.08) as white foam (62%): ^{31}P NMR ($CDCl_3$) δ 3.36, 3.01 (4:3); ^{1}H NMR ($CDCl_3$): δ (peaks labeled by an asterisk (*) are duplicated due to diastereoisomers) 1.34* (d, J = 7.0 Hz, 3H, Ala-Me), 2.68 (2 m, 2H, H-3′), 3.67* (s, 3H, OMe), 3.98–4.40 (m, 7H, NH, H-2′, Ha-5′, Hb-5′, CH_2OP, and Ala-CH), 5.25 (m, 1H, H-4′), 5.82 (br s, 2H, NH_2), 7.00–7.38 (m, 5H, PhO), 8.10* (s, 1H, H-2), 8.33 (s, 1H, H-8). Anal. ($C_{20}H_{25}N_6O_6P$) C, H, N.

General Procedure for the Triethylammonium 5′-Triphosphates 40 and 41 of 8-Aza-isoddA and IsoddA. This synthesis was conducted in accordance with the procedure reported by Seela et al.[26] from appropriate isonucleoside with $PO(OMe)_3$, $POCl_3$, and $(Bu_3NH)_4P_2O_7$.

8-Aza-isoddA-5′-[tetrakis(triethylammonio) triphosphate] (40). From 8-aza-isoddA (**7**) (150 mg, 0.64 mmol) was obtained **40** as oil (10%): TLC R_f = 0.85 (H_2O–CH_3OH, 90:10); ^{31}P NMR ($CDCl_3$) δ −11.50 (d, J = 19 Hz, P α), −22.0 (t, J = 19.0 Hz, P β), −9.60 (d, J = 19.0 Hz, P γ). Anal. ($C_{33}H_{71}N_{10}O_{11}P_3$) C, H, N.

IsoddA-5′-[tetrakis(triethylammonio) triphosphate] (41). From IsoddA (**30**) (150 mg, 0.63 mmol) was obtained **41** as oil (12%): TLC R_f = 0.72 (H_2O–CH_3CN, 90:10); ^{31}P NMR ($CDCl_3$) δ −10.20 (d, J = 19 Hz, P α), −22.19 (t, J = 19.0 Hz, P β), −9.60 (d, J = 19.0 Hz, P γ). Anal. ($C_{34}H_{72}N_9O_{11}P_3$) C, H, N.

Viruses and Cells. H9/III_B, MT-4, and CEM cells were grown in RPMI-1640 containing 10% fetal calf serum (FCS), 100 IU/mL^{-1} penicillin G, and 100 μg/mL^{-1} streptomycin. Cell cultures were checked periodically for the absence of mycoplasma contamination with a MycoTect Kit (Gibco).

Human immunodeficiency virus type-1 (HIV-1, III_B strain) and type-2 (HIV-2, CBL 20 strain, kindly provided by MRC) were obtained from supernatants of persistently infected H9/III_B and CEM cells, respectively. HIV-1 and HIV-2 stock solutions had titers of 2 × 10^5 and 1.4 × 10^5 cell culture infectious dose fifty ($CCID_{50}$/mL^{-1}), respectively.

Inhibition of HIV-1- and HIV-2-Induced Cytopathicity in MT-4 Cells. Activity of compounds against the HIV-1 and HIV-2 multiplication in acutely infected cells was based on the inhibition of virus-induced cytopathogenicity in MT-4 cells. Briefly, 50 μL of culture medium (RPMI 10% FCS) containing 1 × 10^4 MT-4 cells were added to each well of flat bottomed microtiter trays containing 50 μL of medium with or without various concentrations of the test compounds; 20 μL of HIV-1 or HIV-2 suspensions containing 100 $CCID_{50}$ was then added. After a 4-day incubation at 37 °C, the number of viable MT-4 cells was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method.[18]

Reverse Transcriptase Assay. Assay was performed as previously described.[27] Briefly, highly purified HIV-1 recombinant reverse transcriptase (rRT) was assayed for its RNA-dependent DNA polymerase associated activity in a 50 μL volume containing: 50 mM Tris-HCl pH 7.8, 80 mM KCl, 6 mM $MgCl_2$, 1 mM DTT, 0.1 mg mL^{-1} BSA, 0.5 OD_{260} units mL^{-1} poly(rC)-oligo(dG)$_{12-18}$, 10 μM [^{3}H]dGTP (1 Ci mmol^{-1}). After incubation for 20 min at 37 °C, the samples were spotted on glass fiber filters (Whatman GF/A), and the acid-insoluble radioactivity was determined.

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References

(1) Powell, K. L.; Darby, G. HIV Reverse Transcriptase as a Target for Antiviral Drugs. In *Design of Anti-AIDS Drugs*; De Clercq, E., Ed.; Elsevier: Amsterdam, 1990; pp 123–140 and references cited therein.

(2) Fischl, M. A.; Richman, D. D.; Grieco, M. H.; Gottlieb, M. S.; Volberding, P. A.; Laskin, O. L.; Leedom, J. M.; Groopman, J. E.; Mildvan, D.; Schooley, R. T.; Jackson, G. G.; Durack, D. T.; King, D. The Efficacy of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-Related Complex. A Double-Blind, Placebo-Controlled Trial. *N. Engl. J. Med.* **1987**, *317*, 185–191.

(3) (a) Yarchoan, R.; Perno, C. F.; Thomas, R. V.; Klecker, R. W.; Allain, J. P.; Wills, R. J.; McAtee, N.; Fischl, M. A.; Dubinsky, R.; McNeely, M. C.; Mitsuya, H.; Pluda, J. M.; Lawley, T. J.; Leuther, M.; Safai, B.; Collins, J. M.; Myers, C. E.; Broder, S. Phase I Studies of 2′,3′-Dideoxycytidine in Severe Human Immunodeficiency Virus Infection as a Single Agent and Alternating with Zidovudine (AZT). *Lancet* **1988**, No. 1, 76–80. (b) Lambert, J. S.; Seidlin, M.; Reichman, R. C.; Plank, C. S.; Laverty, M.; Morse, G. D.; Knupp, C.; McLaren, C.; Pettinelli, C.; Valentine, F. T.; Dolin, R. 2′,3′-Dideoxyinosine (ddI) in Patients with the Acquired Immunodeficiency Syndrome or AIDS-Related Complex, A Phase I Trial *N. Engl. J. Med.* **1990**, *322*, 1333–1340. (c) Cooley, T. P.; Kunches, L. M.; Saunders, C. A.; Ritter, J. K.; Perkins, C. J.; McLaren, C.; McCaffrey, R. P.; Liebman, H. A. Once-Daily Administration of 2′,3′-Dideoxyinosine (ddI) in Patients with the Acquired Immunodeficiency Syndrome or AIDS-related Complex, Results of a Phase I Trial. *N. Engl. J. Med.* **1990**, *322*, 1340–1345. (d) Yarchoan, R.; Mitsuya, H.; Thomas, R. V.; Pluda, J. M.; Hartman, N. R.; Perno, C. F.; Marczyk, K. S.; Allain, J.-P.; Johns, D. G.; Broder, S. *In Vivo* Activity Against HIV and Favorable Toxicity Profile of 2′,3′-Dideoxyinosine. *Science* **1989**, *245*, 412–415.

(4) Johnson, M. A.; Ahluwalia, G.; Connelly, M. C.; Cooney, D. A.; Broder, S.; Johns, D. G.; Fridland, A. Metabolic Pathways for the Action of the Antiretroviral Agent 2',3'-Dideoxyadenosine in Human Lymphoid Cells. *J. Biol. Chem.* **1988**, *263*, 15354–15357.
(5) Stoeckler, J. D.; Cambor, C.; Parks, R. E. Human Erythrocytic Purine Nucleoside Phosphorilase: Reaction with Sugar-modified Nucleoside substrates. *Biochemistry* **1980**, *19*, 102–107.
(6) (a) Huryn, D. M.; Sluboski, B. C.; Tam, S. Y.; Todaro, L. J.; Weigele, M. Synthesis of Iso-ddA, Member of a Novel Class of Anti-HIV agents. *Tetrahedron Lett.* **1989**, *30*, 6259–6262. (b) Huryn, D. M.; Sluboski, B. C.; Tam, S. Y.; Weigele, M.; Sim, I.; Anderson, B. D.; Mitsuya, H.; Broder, S., Synthesis and Anti-HIV Activity of Isonucleosides. *J. Med. Chem.* **1992**, *35*, 2347–2354.
(7) Frank, K. B.; Connell, E. V.; Holman, M. J.; Huryn, D. M.; Sluboski, B. C.; Tam, S. Y.; Todaro, L. J.; Weigele, M.; Richman, D. D.; Mitsuya, H.; Broder, S.; Sim, I. S. Anabolism and Mechanism of action of Ro 24-5098, an Isomer of 2',3'-Dideoxyadenosine (ddA) with Anti-HIV Activity. *Ann. N. Y. Acad. Sci.* **1990**, *616*, 408–414.
(8) (a) Franchetti, P.; Cappellacci, L.; Cristalli, G.; Grifantini, M.; Pani, A.; La Colla, P.; Nocentini, G. Synthesis and Evaluation of Anti-HIV-1 and Antitumor Activity of 2',3'-Didehydro-2',3'-dideoxy-3-deazaadenosine, 2',3'-Dideoxy-3-deaza-adenosine and some 2',3'-Dideoxy-3-deazaadenosine 5'-Dialkyl Phosphates. *Nucleosides Nucleotides* **1991**, *10*, 1551–1562. (b) Franchetti, P.; Messini, L.; Cappellacci, L.; Grifantini, M.; Nocentini, G.; Guarracino, P.; Marongiu, M. E.; La Colla, P. 8-Aza Derivatives of 3-Deazapurine Nucleosides. Synthesis and in vitro Evaluation of Antiviral and Antitumor Activity. *Antiviral Chem. Chemother.* **1993**, *4*, 341–352. (c) Franchetti, P.; Messini, L.; Cappellacci, L.; Abu Sheikha, G.; Grifantini, M.; Guarracino, P.; De Montis, A.; Loi, A. G.; Marongiu, M. E.; La Colla, P. 8-Aza-1-deazapurine Nucleosides as Antiviral Agents. *Nucleosides Nucleotides* **1994**, *13*, 1739–1755.
(9) Kazimierczuk, Z.; Binding, U.; Seela, F. Synthesis of 8-Aza-2'-deoxy-adenosine and Related 7-Amino-3H-1,2,3-triazolo[4,5-d]-pyrimidine 2'-Deoxyribofuranosides: Stereoselective Glycosylation via Nucleobase Anion. *Helv. Chim. Acta* **1989**, *72*, 1527–1536.
(10) Rosemeyer, H.; Toth, G.; Seela, F. Assignment of Anomeric Configuration of D-ribo-, Arabino-, 2'-Deoxyribo-, and 2',3'-Dideoxyribofuranosides by NOE Difference Spectroscopy. *Nucleosides Nucleotides* **1989**, *8*, 587–597.
(11) Seela, F.; Mersmann, K. 8-Azaadenine 2',3'-Dideoxyribonucleosides: Synthesis via 1,2,3-Triazolo[4,5-*d*]pyrimidinyl Anions. *Helv. Chim. Acta* **1992**, *75*, 1885–1896.
(12) Franchetti, P.; Cappellacci, L.; Grifantini, M.; Lupidi, G.; Nocentini, G.; Barzi, A. 8-Aza analogues of deaza purine nucleosides. Synthesis and biological evaluation of 8-aza-1-deaazadenosine and 2'-deoxy-8-aza-1-deazaadenosine. *Nucleosides Nucleotides* **1992**, *11*, 1059–1076.
(13) Itoh, T.; Inaba, J.; Mizuno, Y. Synthesis Studies of Potential Antimetabolites. XXII. Synthesis of 5- and 6-Aminoimidazo-[4,5-b]pyridine Ribonucleosides (a new Type of Adenosine Analog) by Coupling Reaction. *Heterocycles* **1977**, *8*, 433–441.
(14) Itoh, T.; Kitano, S.; Mizuno, Y. Synthetic Studies of Potential Antimetabolites. XIII. Synthesis of 7-amino-3-β-D-ribofuranosyl-3H-imidazo[4,5-b]pyridine (1-deazaadenosine) and Related Nucleosides. *J. Heterocycl. Chem.* **1972**, *9*, 465–470.
(15) Lindon, J. C.; Williams, J. M.; Barraclough, P. ^{1}H, ^{13}C and ^{15}N NMR Observations on the protonation of 1- and 3-deazapurine. *Org. Magn. Reson.* **1986**, *24*, 55–58.
(16) Itoh, T.; Ishikura, T.; Mizuno, Y. Studies on the Chemical Synthesis of Potential Antimetabolites. XXXIV. Apparent Discrepancy among Reported Proton Nuclear Magnetic Resonance Spectra of 3-Deazaadenosine is Actually a Reflection of a Difference in Molecular Species. *Chem. Pharm. Bull.* **1983**, *31*, 4130–4134.
(17) Deneyer, R.; Cave, A.; Goutarel, R. 3-Substituted Adenines, Structure and Synthesis of Triacanthine. *Compt. Rend.* **1961**, *253*, 2994–2996.
(18) Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Schols, D.; Herdewijn, P.; Desmyter, J.; De Clercq, E. Rapid and automated tetrazolium-based colorimetric assay for the detection of anti-HIV compounds. *J. Virol. Methods* **1988**, *20*, 309–321.
(19) McGuigan, C.; Jones, B. C. N. M.; Tollerfield, S. M.; Riley, P. A. Synthesis and Biological Evaluation of Haloalkyl Phosphate Triester Derivatives of AraA and AraC. *Antiviral Chem. Chemother.* **1992**, *3*, 79–94.
(20) McGuigan, C.; O'Connor, T. J.; Nicholls, S. R.; Nickson, C.; Kinchngton, D. Synthesis and Anti-HIV Activity of Some Novel Substituted Dialkyl phosphate Derivatives of AZT and ddCyd. *Antiviral Chem. Chemother.* **1990**, *1*, 355–360.
(21) McGuigan, C.; Pathirana, R. N.; Mahmood, N.; Devine, K. G.; Hay, A. J. Aryl phosphate Derivatives of AZT Retain Activity Against HIV1 in Cell Lines which are Resistant to the Action of AZT. *Antiviral Res.* **1992**, *17*, 311–321.
(22) The 7-amino-3*H*-[1,2,3]triazolo[4,5-*b*]pyridine was obtained from 7-chloro-3*H*-[1,2,3]triazolo[4,5-*b*]pyridine (prepared as reported by De Roos, K. B.; Salemink, C. A. Deazapurine Derivatives IX. Synthesis of (7-Substituted-1,2- and 3-β-D-Ribofuranosyl-vic-triazolo[4,5-b]pyridine. 1-Deaza-8-azaadenosine and Related Compounds. *Recl. Trav. Chim. Pays Bas* **1971**, *90*, 1181–1196) with liquid ammonia at 160 °C for 13 h (yield 90%) (lit. 55%: Temple, C., Jr.; Smith, B. H.; Montgomery, J. A. Preparation and Properties of Some Isomeric v-Triazolopyridines. 1- and 3-Deaza-8-azapurines, *J. Org. Chem.* **1972**, *37*, 3601–3604).
(23) The 4-amino-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine was prepared from 4-chloro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine (Talik, Z.; Plazek, E. The Nitration of 2-Chloro-4-amino-pyridine. *Roczniki Chem.* **1956**, *30*, 1139–1149) with liquid ammonia at 150 °C for 24 h (yield 80%) (lit. 71%: Temple, C., Jr.; Smith, B. H.; Montgomery, J. A. Preparation and Properties of Some Isomeric v-Triazolopyridines. 1- and 3-Deaza-8-azapurines, *J. Org. Chem.* **1972**, *37*, 3601–3604).
(24) The 7-amino-3*H*-imidazo[4,5-*b*]pyridine was prepared from 7-chloroimidazo[4,5-*b*]pyridine (De Roos, K. B.; Salemink, C. A. Deazapurine derivatives V. A New Synthesis of 1- and 3-Deazaadenine and Related Compounds *Recl. Trav. Chim. Pays Bas* **1969**, *88*, 1263–1274) with liquid ammonia at 180 °C for 48 h (79%).
(25) The 4-amino-1*H*-imidazo[4,5-*c*]pyridine was prepared from 4-chloroimidazo[4,5-c]pyridine (De Roos, K. B.; Salemink, C. A. Deazapurine derivatives V. A New Synthesis of 1- and 3-Deazaadenine and Related Compounds *Recl. Trav. Chim. Pays Bas* **1969**, *88*, 1263–1274) with liquid ammonia at 150 °C for 48 h (80%).
(26) Seela, F.; Gumbiowski, R. 1,7-Dideaza-2',3'-dideoxy-adenosine: Syntheses of Pyrrolo[2,3-b]pyridine 2',3'-Dideoxyribofuranosides and Participation of Purine N(1) during HIV-1 Reverse Transcriptase Inhibition. *Helv. Chim. Acta* **1991**, *74*, 1048–1058.
(27) Tramontano, E.; Cheng, Y. C. HIV-1 Reverse Transcriptase Inhibition by a Dipyridodiazepinone Derivative: BI-RG-587. *Biochem. Pharmacol.* **1992**, *43*, 1371–1376.