

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

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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)alananyl 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.

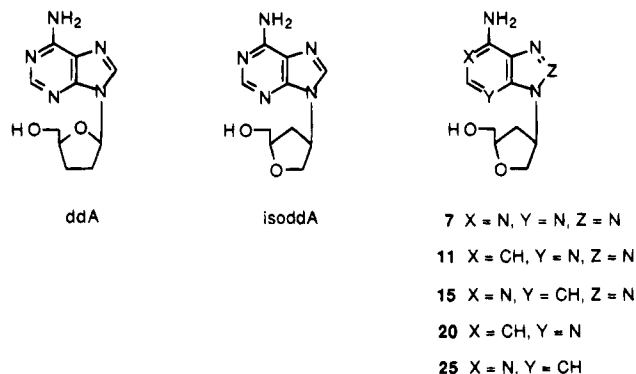
## Introduction

Nucleoside reverse transcriptase inhibitors are the only drugs so far approved for the treatment of AIDS.<sup>1</sup> Among them is 2',3'-dideoxyinosine (ddI), the deamination product of 2',3'-dideoxyadenosine (ddA).<sup>2</sup> 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.<sup>3a-d</sup>

The therapeutic use of ddA and ddI is limited by the instability of their glycosidic bond at low pH, by rapid adenosine deaminase (ADA)<sup>4</sup> metabolism, and by purine nucleoside phosphorylase (PNP).<sup>5</sup> 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.<sup>6a-b</sup> 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.<sup>6b,7</sup>

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.<sup>8a-c</sup> However, when prepared as dialkyl monophosphate ester, 3-deaza-ddA proved to be as potent as ddA, although less selective.<sup>8a</sup> 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<sup>6a</sup> (4) with the appropriate heterocyclic bases 1–3 in DMF in the presence of K<sub>2</sub>CO<sub>3</sub> 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<sub>4</sub>, yielded the isonucleosides 7, 8, 11, 12, 15, and 16. In order to establish the substitution site spectroscopic data, particularly <sup>1</sup>H NMR, <sup>13</sup>C NMR, and

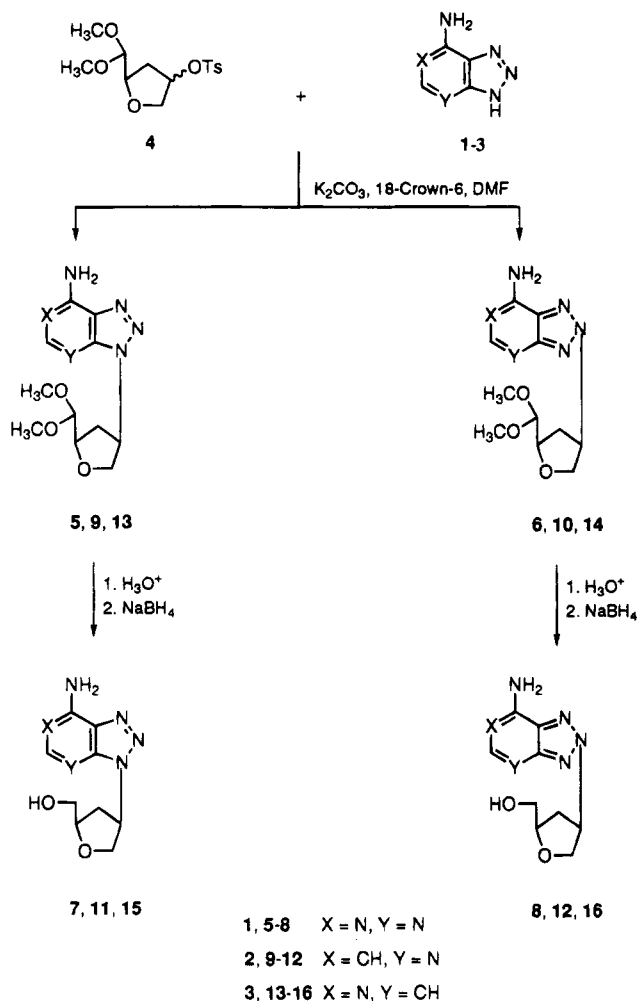
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## Scheme 1

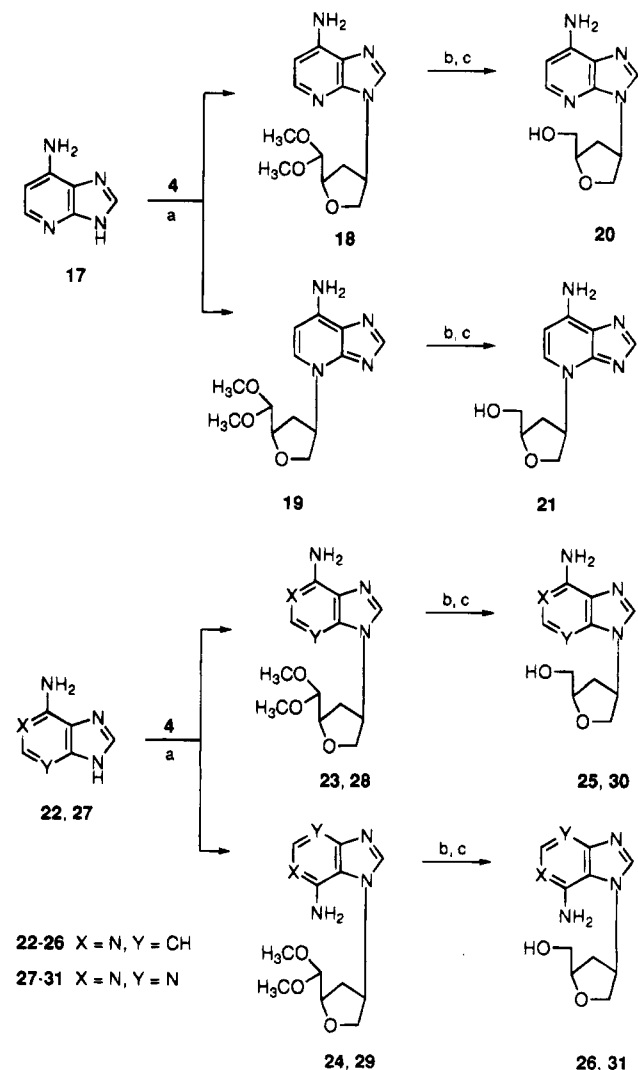


**Table 1.**  $^{13}\text{C}$  NMR Chemical Shifts of Isodda Derivatives and Bases 1-3<sup>a,b</sup>

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

<sup>a</sup> Purine numbering. <sup>b</sup> DMSO-*d*<sub>6</sub>.

UV of the above compounds were measured. In the following discussion the purine numbering is used while the systematic numbering is in brackets. The  $^{13}\text{C}$  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<sup>9</sup> [N<sup>3</sup>] carried a substituent (Table 1).<sup>8a,b,9</sup> A similar upfield shift was observed for C(4) [C(7a)] in the  $^{13}\text{C}$  NMR spectrum of 15 as compared to that of 3, indicating that N<sup>9</sup> [N<sup>1</sup>] 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  $\delta$  5.57 (H(4')), NOE peaks appeared at  $\delta$

Scheme 2<sup>a</sup>

<sup>a</sup> Reagents: (a)  $\text{K}_2\text{CO}_3$ , 18-crown-6, DMF; (b)  $\text{H}_3\text{O}^+$ ; (c)  $\text{NaBH}_4$ .

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%).

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.<sup>10</sup> 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<sup>7</sup> and thus must be attached to N<sup>8</sup>. 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,<sup>11</sup> 8-aza-1-deaza,<sup>12</sup> and 8-aza-3-deaza-purines.<sup>8b</sup>

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  $^{13}\text{C}$  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.<sup>13</sup> The

structure of compound **21** was assigned on the basis of the presence of a NOE effect at  $\delta$  7.88 (H(2) [H(5)], 1.2%) when H(4') ( $\delta$  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- $\beta$ -D-ribofuranosyl derivative of 1-deazaadenine.<sup>14</sup> The lack of alkylation at N<sup>7</sup> of **17** may be explained by the higher nucleophilicity of N<sup>3</sup> and N<sup>9</sup> as compared to that of N<sup>7</sup> in 1-deazapurine.<sup>15</sup>

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<sub>4</sub>, 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.<sup>16</sup> The structures were confirmed by <sup>13</sup>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<sup>9</sup> carries a substituent. Conversely, the C(5) [C(3a)] signal of isomer **26** appeared upfield shifted, confirming N<sup>7</sup> substitution.

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

## 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.<sup>18</sup>

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.

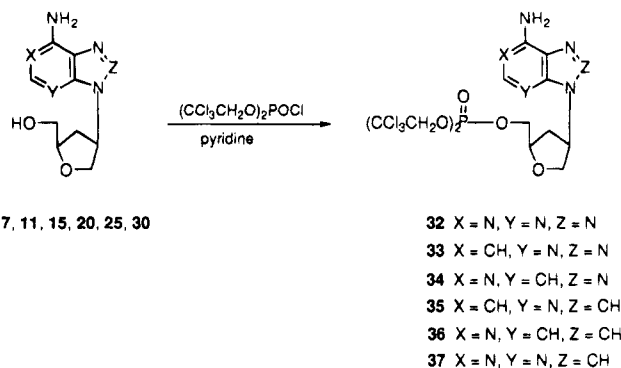
In order to examine the first possibility, we synthesized a series of bis(2,2,2-trichloroethyl) phosphates (compounds **32–37**). In fact, the introduction of bis-(trihaloethyl) substituents at the phosphate site of nucleotide analogues has been reported to increase both lipophilicity and hydrolytic lability and, consequently, their biological activity.<sup>19</sup> In particular, the substitution of hydrogen atoms at ethyl group with halogens has

**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 Phosphoramidates (**38–39**) on the HIV-Induced Cytopathogenicity in MT-4 Cells

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

<sup>a</sup> Compound dose ( $\mu$ M) required to reduce the viability of mock-infected MT-4 cells by 50% (4 days). <sup>b</sup> 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). <sup>c</sup> CC<sub>50</sub>/EC<sub>50</sub> ratio. Data are the mean of three independent experiments. Variation among duplicate samples was less than 15%.

## Scheme 3

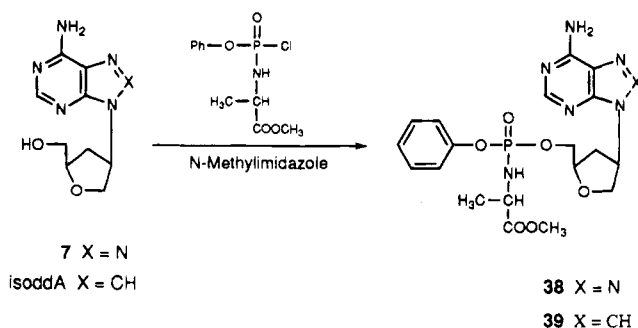
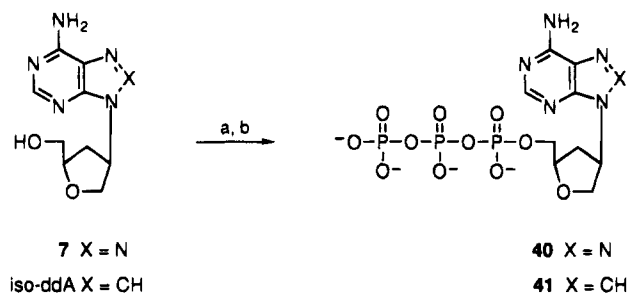


been thought to induce a greater labilizing effect on the P—O—alkyl bond than on the more remote P—O—nucleoside bond, thus making easier the release of the unmasked nucleotide inside the cells.

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,<sup>20</sup> raised the possibility of a greater resistance of 5'-alkylisnucleotides 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 metabolism 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

Scheme 5<sup>a</sup>

<sup>a</sup> Reagents: (a) POCl<sub>3</sub>, (CH<sub>3</sub>O)<sub>3</sub>PO; (b) (Bu<sub>3</sub>N)<sub>4</sub>P<sub>2</sub>O<sub>7</sub>.

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.<sup>21</sup> 5'-(Phenyl phosphoramidates) of 8-aza-isoddA (**38**) and isoddA (**39**) were obtained through reaction of the corresponding isonucleosides with (phenylmethoxy)alaninyl chlorophosphate<sup>21</sup> (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 <sup>1</sup>H 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<sub>50</sub> 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

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

compd	IC <sub>50</sub> <sup>a</sup>
8-aza-isoddATP ( <b>40</b> )	4.3 ± 0.3
isoddATP ( <b>41</b> )	35.0 ± 5.0
ddATP	0.5 ± 0.1

<sup>a</sup> 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.

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.

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<sub>254</sub> plates and RP-18 F<sub>254</sub> S (Merck); silica gel 60 (Merck) (70–230 and 230–400 mesh) for column chromatography were used. Nuclear magnetic resonance <sup>1</sup>H, <sup>13</sup>C, and <sup>31</sup>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<sub>2</sub>O. 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<sub>2</sub>CO<sub>3</sub> (4.06 g, 29.36 mmol) was stirred at room temperature under N<sub>2</sub>, 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<sup>6a</sup> (**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<sub>3</sub>–MeOH, 99:1) to afford **5** (400 mg, 23%), a first fraction, as a white solid: mp 161–163 °C; TLC R<sub>f</sub> = 0.32 (CHCl<sub>3</sub>–MeOH, 95:5); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.63 (m, 2H, H-4'), 3.32 (s, 6H, OCH<sub>3</sub>), 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, CH(OCH<sub>3</sub>)<sub>2</sub>), 5.41 (m, 1H, H-3'), 8.10, 8.43 (2 s, 2H, NH<sub>2</sub>), 8.30 (s, 1H, H-5). Anal. (C<sub>11</sub>H<sub>16</sub>N<sub>6</sub>O<sub>3</sub>) 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<sub>f</sub> = 0.23 (CHCl<sub>3</sub>–MeOH, 95:5); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.55 (m, 1H, Ha-4'), 2.68 (m, 1H, Hb-4'), 3.32 (s, 6H, OCH<sub>3</sub>), 4.04, 4.12 (AB of ABX, 2H, *J*<sub>AB</sub> = 14, *J*<sub>AX</sub> = 7.5, *J*<sub>BX</sub> = 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, CH(OCH<sub>3</sub>)<sub>2</sub>), 5.54 (m, 1H, H-3'), 8.07–8.24 (2 br s, 2H, NH<sub>2</sub>), 8.28 (s, 1H, H-5). Anal. (C<sub>11</sub>H<sub>16</sub>N<sub>6</sub>O<sub>3</sub>) 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<sub>2</sub>O (10:1, 12 mL) was stirred at room temperature for 3.5 h. After coevaporation with H<sub>2</sub>O (three times), the residue was solubilized in ethanol (10 mL) and added dropwise to a suspension of NaBH<sub>4</sub> (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<sub>f</sub>* = 0.52 (CHCl<sub>3</sub>–MeOH, 85:15); [α]<sub>D</sub><sup>20</sup> +30.93° (c 0.097, MeOH); UV (H<sub>2</sub>O, MeOH) λ<sub>max</sub> 280 nm (ε 5800), (NaOH 0.1 N) 278 nm (ε 10 200); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.37 (m, 1H, Ha-3'), 2.62 (m, 1H, Hb-3'), 3.57 (m, 2H, CH<sub>2</sub>OH), 4.06 (m, 1H, H-2'), 4.11, 4.19 (AB of ABX, 2H, *J*<sub>AB</sub> = 10.3, *J*<sub>AX</sub> = 6.7, *J*<sub>BX</sub> = 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<sub>2</sub>), 8.28 (s, 1H, H-5). Anal. (C<sub>9</sub>H<sub>12</sub>N<sub>6</sub>O<sub>2</sub>) 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<sub>f</sub>* = 0.35 (CHCl<sub>3</sub>–MeOH, 85:15); UV (H<sub>2</sub>O, MeOH) λ<sub>max</sub> 256 nm (ε 2300), 294 nm (ε 4700), (NaOH 0.1 N) 254 nm (ε 2200), 290 nm (ε 4500); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.41 (m, 1H, Ha-3'), 2.67 (m, 1H, Hb-3'), 3.48 (m, 2H, CH<sub>2</sub>OH), 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<sub>2</sub>). Anal. (C<sub>9</sub>H<sub>12</sub>N<sub>6</sub>O<sub>2</sub>) 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<sup>22</sup> (**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<sub>3</sub>–MeOH, 96:4), as first eluate **9** was obtained as white crystals (560 mg, 27%): mp 112–114 °C; TLC *R<sub>f</sub>* = 0.31 (CHCl<sub>3</sub>–MeOH, 96:4); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.62 (m, 2H, Ha-4', Hb-4'), 3.35 (s, 6H, OCH<sub>3</sub>), 4.15 (m, 3H, Ha-2', Hb-2' and H-5'), 4.43 (d, *J* = 6.4 Hz, 1H, CH(OCH<sub>3</sub>)<sub>2</sub>), 5.45 (m, 1H, H-3'), 6.38 (d, *J* = 5.5 Hz, 1H, H-6), 7.27 (s, 2H, NH<sub>2</sub>), 8.05 (d, *J* = 5.5 Hz, 1H, H-5). Anal. (C<sub>12</sub>H<sub>17</sub>N<sub>5</sub>O<sub>3</sub>) 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<sub>f</sub>* = 0.26 (CHCl<sub>3</sub>–MeOH, 96:4); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.65 (m, 2H, Ha-4', Hb-4'), 3.32 (s, 6H, OCH<sub>3</sub>), 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, CH(OCH<sub>3</sub>)<sub>2</sub>), 5.58 (m, 1H, H-3'), 6.36 (d, *J* = 5.2 Hz, 1H, H-6), 6.98 (s, 2H, NH<sub>2</sub>), 8.18 (d, *J* = 5.2 Hz, 1H, H-5). Anal. (C<sub>12</sub>H<sub>17</sub>N<sub>5</sub>O<sub>3</sub>) 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<sub>f</sub>* = 0.46 (CHCl<sub>3</sub>–MeOH–NH<sub>4</sub>OH, 86:13:1); UV (H<sub>2</sub>O) λ<sub>max</sub> 260 nm (ε 2700); 304 nm (ε 4300), (NaOH 0.1 N) 260 nm (ε 3500), 266 nm (ε 3300), 306 nm (ε 5100); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.42 (m, 1H, Ha-3'), 2.61 (m, 1H, Hb-3'), 3.55 (m, 2H, CH<sub>2</sub>OH), 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<sub>2</sub>); 8.04 (d, *J* = 5.4 Hz, 1H, H-5). Anal. (C<sub>10</sub>H<sub>13</sub>N<sub>5</sub>O<sub>2</sub>) 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<sub>f</sub>* = 0.35 (CHCl<sub>3</sub>–MeOH–NH<sub>4</sub>OH, 86:13:1); UV (H<sub>2</sub>O) λ<sub>max</sub> 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); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.48 (m, 1H, Ha-3'), 2.74 (m, 1H, Hb-3'), 3.55 (t, *J* = 5.4 Hz, 2H, CH<sub>2</sub>OH), 4.05 (m, 1H, H-2'), 4.16, 4.35 (AB of ABX, 2H, *J*<sub>AB</sub> = 9.5, *J*<sub>AX</sub> = 6.6, *J*<sub>BX</sub> = 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<sub>2</sub>), 8.20 (d, *J* = 5.2 Hz, 1H, H-5). Anal. (C<sub>10</sub>H<sub>13</sub>N<sub>5</sub>O<sub>2</sub>) 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<sup>23</sup> (**3**) (1.5 g, 11.1 mmol) (reaction time 7 h, 80 °C). The chromatographic separation by silica gel column using CHCl<sub>3</sub>–MeOH–NH<sub>4</sub>OH (86:13:1) gave as first eluate compound **14**, which was recrystallized from methylene chloride-ethyl ether to yield **14** (33%) as white crystals: mp 104–106 °C; TLC *R<sub>f</sub>* = 0.45 (CHCl<sub>3</sub>–MeOH–NH<sub>4</sub>OH, 86:13:1); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.57 (m, 1H, Ha-4'), 2.68 (m, 1H, Hb-4'), 3.28 (s, 6H, OCH<sub>3</sub>), 4.05 (dd, *J* = 6.4, 3.3 Hz, 1H, H-5'), 4.12, 4.30 (AB of ABX, 2H, *J*<sub>AB</sub> = 13.8, *J*<sub>AX</sub> = 7.2, *J*<sub>BX</sub> = 5.6 Hz, Ha-2' and Hb-2'), 4.35 (d, *J* = 6.0 Hz, 1H, CH(OCH<sub>3</sub>)<sub>2</sub>), 5.57 (m, 1H, H-3'), 6.83 (d, *J* = 6.1 Hz, 1H, H-7), 7.00 (s, 2H, NH<sub>2</sub>), 7.67 (d, *J* = 6.1 Hz, 1H, H-6). Anal. (C<sub>12</sub>H<sub>17</sub>N<sub>5</sub>O<sub>3</sub>) 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<sub>f</sub>* = 0.40 (CHCl<sub>3</sub>–MeOH–NH<sub>4</sub>OH, 86:13:1); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.35 (m, 1H, Ha-4'), 2.70 (m, 1H, Hb-4'), 3.30 (s, 6H, OCH<sub>3</sub>), 4.01–4.19 (m, 3H, Ha-2', Hb-2' and H-5'), 4.48 (d, *J* = 5.9 Hz, 1H, CH(OCH<sub>3</sub>)<sub>2</sub>), 5.53 (m, 1H, H-3'), 6.95 (d, *J* = 5.9 Hz, 1H, H-7), 7.18 (s, 2H, NH<sub>2</sub>), 7.82 (d, *J* = 5.9 Hz, 1H, H-6). Anal. (C<sub>12</sub>H<sub>17</sub>N<sub>5</sub>O<sub>3</sub>) 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<sub>f</sub>* = 0.30 (CHCl<sub>3</sub>–MeOH–NH<sub>4</sub>OH, 90:9:1); UV (H<sub>2</sub>O, MeOH) λ<sub>max</sub> 294 nm (ε 4300), (NaOH 0.1 N) 290 nm (ε 4000); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.18 (m, 1H, Ha-3'), 2.62 (m, 1H, Hb-3'), 3.57 (pseudo t, 2H, CH<sub>2</sub>OH), 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<sub>2</sub>), 7.80 (d, *J* = 5.8 Hz, 1H, H-6). Anal. (C<sub>10</sub>H<sub>13</sub>N<sub>5</sub>O<sub>2</sub>) 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<sub>f</sub>* = 0.35 (CHCl<sub>3</sub>–MeOH–NH<sub>4</sub>OH, 90:9:1); UV (H<sub>2</sub>O, MeOH) λ<sub>max</sub> 310 nm (ε 3100), (NaOH 0.1 N) 312 nm (ε 3000); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.42 (m, 1H, Ha-3'), 2.68 (m, 1H, Hb-3'), 3.48 (m, 2H, CH<sub>2</sub>OH), 4.02 (m, 1H, H-2'), 4.12, 4.30 (AB of ABX, 2H, *J*<sub>AB</sub> = 9.5, *J*<sub>AX</sub> = 6.5, *J*<sub>BX</sub> = 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<sub>2</sub>), 7.67 (d, *J* = 6.2 Hz, 1H, H-6). Anal. (C<sub>10</sub>H<sub>13</sub>N<sub>5</sub>O<sub>2</sub>) 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**)<sup>24</sup> (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<sub>3</sub>–MeOH (98:2) to give as first fraction compound **18** as a colorless gum (810 mg, 39%): TLC *R<sub>f</sub>* = 0.19 (CHCl<sub>3</sub>–MeOH, 98:2). <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.18 (m, 1H, Ha-4'), 2.55 (m, 1H, Hb-4'), 3.35 (s, 6H, OCH<sub>3</sub>), 4.03 (m, 3H, Ha-2', Hb-2', and H-5'), 4.43 (d, *J* = 5.6 Hz, 1H, CH(OCH<sub>3</sub>)<sub>2</sub>), 5.18 (m, 1H, H-3'), 6.30 (s, 2H, NH<sub>2</sub>), 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<sub>13</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>) C, H, N.

Compound **19** (second eluate) was obtained as yellow gum (760 mg, 37%): TLC *R<sub>f</sub>* = 0.02 (CHCl<sub>3</sub>–MeOH, 98:2); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.07 (m, 1H, Ha-4'), 2.62 (m, 1H, Hb-4'), 3.48 (s,

6H, OCH<sub>3</sub>), 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, CH(OCH<sub>3</sub>)<sub>2</sub>), 5.60 (m, 1H, H-3'), 6.50 (d,  $J = 7.0$  Hz, 1H, H-6), 7.56 (s, 2H, NH<sub>2</sub>), 7.92 (d,  $J = 7.0$  Hz, 1H, H-5), 8.05 (s, 1H, H-2). Anal. (C<sub>13</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>) 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<sub>3</sub>-MeOH-NH<sub>4</sub>OH, 90:9:1); UV (H<sub>2</sub>O)  $\lambda_{\max}$  264 nm ( $\epsilon$  11 800), 278 nm ( $\epsilon$  9300), (NaOH 0.1 N) 264 nm ( $\epsilon$  15 100), 276 nm ( $\epsilon$  11 700); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  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<sub>2</sub>OH), 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<sub>2</sub>), 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<sub>11</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>) 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<sub>3</sub>-MeOH-NH<sub>4</sub>OH, 90:9:1); UV (H<sub>2</sub>O)  $\lambda_{\max}$  290 nm ( $\epsilon$  5200), (NaOH 0.1 N) 278 ( $\epsilon$  13 500, sh), 292 ( $\epsilon$  15 200); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  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<sub>2</sub>OH), 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<sub>2</sub>), 7.72 (s, 1H, H-2), 7.88 (d,  $J = 7.2$  Hz, 1H, H-5). Anal. (C<sub>11</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>) 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)<sup>25</sup> (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<sub>3</sub>-MeOH-NH<sub>4</sub>OH (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<sub>3</sub>-MeOH, 98:2); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  2.08 (m, 1H, Ha-4'), 2.56 (m, 1H, Hb-4'), 3.38 (s, 6H, OCH<sub>3</sub>), 4.01 (m, 3H, Ha-2', Hb-2', and H-5'), 4.42 (d,  $J = 5.2$  Hz, 1H, CH(OCH<sub>3</sub>)<sub>2</sub>), 5.11 (m, 1H, H-3'), 6.18 (s, 2H, NH<sub>2</sub>), 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<sub>13</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>) 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<sub>3</sub>-MeOH-NH<sub>4</sub>OH, 94:5:1); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  2.05 (m, 1H, Ha-4'), 2.62 (m, 1H, Hb-4'), 3.35 (s, 6H, OCH<sub>3</sub>), 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, CH(OCH<sub>3</sub>)<sub>2</sub>), 5.51 (m, 1H, H-3'), 6.00 (s, 2H, NH<sub>2</sub>), 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<sub>13</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>) 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<sub>3</sub>-MeOH-NH<sub>4</sub>OH, 85:14:1); UV (H<sub>2</sub>O)  $\lambda_{\max}$  264 nm ( $\epsilon$  8000), (NaOH 0.1 N) 266 nm ( $\epsilon$  8100); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  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<sub>2</sub>OH), 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<sub>2</sub>), 8.56 (s, 1H, H-2). Anal. (C<sub>11</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>) 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<sub>3</sub>-MeOH-NH<sub>4</sub>OH, 85:14:1); UV (H<sub>2</sub>O)  $\lambda_{\max}$  242 nm ( $\epsilon$  4200), 286 nm ( $\epsilon$  7500), (NaOH 0.1 N) 246 nm ( $\epsilon$  4000), 286 nm ( $\epsilon$  5900); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  2.00 (m, 1H, Ha-3'), 2.65 (m, 1H, Hb-3'), 3.50 (m, 2H, CH<sub>2</sub>OH), 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<sub>2</sub>), 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<sub>11</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>) 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<sub>3</sub>-MeOH (98:2) to give compound 28 (first eluate) as a white solid (830 mg, 80%); mp 144-146 °C (lit.<sup>6a</sup> mp 144-146 °C); TLC  $R_f = 0.53$  (CHCl<sub>3</sub>-MeOH-NH<sub>4</sub>OH, 90:9:1); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  2.20 (m, 1H, Ha-4'), 2.57 (m, 1H, Hb-4'), 3.32 (s, 6H, OCH<sub>3</sub>), 4.05 (m, 3H, Ha-2', Hb-2', and H-5'), 4.44 (d,  $J = 5.5$  Hz, 1H, CH(OCH<sub>3</sub>)<sub>2</sub>), 5.13 (m, 1H, H-3'), 7.21 (br s, 2H, NH<sub>2</sub>), 8.14, 8.21 (2 s, 2H, H-2 and H-8). Anal. (C<sub>12</sub>H<sub>17</sub>N<sub>5</sub>O<sub>3</sub>) 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<sub>3</sub>-MeOH-NH<sub>4</sub>OH, 90:9:1); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  2.31 (m, 1H, Ha-4'), 2.61 (m, 1H, Hb-4'), 3.37 (s, 6H, OCH<sub>3</sub>), 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, CH(OCH<sub>3</sub>)<sub>2</sub>), 5.45 (m, 1H, H-3'), 7.77 (s, 1H, H-8), 7.95 (s, 2H, NH<sub>2</sub>), 8.38 (s, 1H, H-2). Anal. (C<sub>12</sub>H<sub>17</sub>N<sub>5</sub>O<sub>3</sub>) 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.<sup>6a</sup> 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<sub>3</sub>-MeOH-NH<sub>4</sub>OH, 90:9:1); UV (H<sub>2</sub>O)  $\lambda_{\max}$  274 nm ( $\epsilon$  11 800), (NaOH 0.1 N) 274 nm ( $\epsilon$  12 200); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  2.22 (m, 1H, Ha-3'), 2.62 (m, 1H, Hb-3'), 3.52, 3.70 (m, 2H, CH<sub>2</sub>OH, dddd after exchange with D<sub>2</sub>O), 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<sub>2</sub>), 8.48 (s, 1H, H-8). Anal. (C<sub>10</sub>H<sub>13</sub>N<sub>5</sub>O<sub>2</sub>) 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.<sup>19</sup> 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<sub>3</sub>-MeOH, 96:4), 32 (28%) was separated as a white solid: mp 113-115 °C; TLC  $R_f = 0.33$  (CHCl<sub>3</sub>-MeOH, 96:4); UV (MeOH)  $\lambda_{\max}$  280 nm ( $\epsilon$  6100); <sup>31</sup>P NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  -3.40; <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  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<sub>2</sub>OP), 4.80 (m, 4H, CH<sub>2</sub>Cl<sub>3</sub>), 5.50 (m, 1H, H-4'), 8.08, 8.42 (2 s, 2H, NH<sub>2</sub>), 8.28 (s, 1H, H-5). Anal. (C<sub>13</sub>H<sub>15</sub>Cl<sub>6</sub>N<sub>6</sub>O<sub>5</sub>P) 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<sub>3</sub>-MeOH (93:7) as a white foam (30%); TLC  $R_f = 0.35$  (CHCl<sub>3</sub>-MeOH, 93:7); UV (MeOH)  $\lambda_{\max}$  260 nm ( $\epsilon$  3500), 304 ( $\epsilon$  4800); <sup>31</sup>P NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  -3.50; <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  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<sub>2</sub>Cl<sub>3</sub> and CH<sub>2</sub>OP), 5.57 (m, 1H, H-4'), 6.38 (d,  $J = 5.4$  Hz, 1H, H-6), 7.28 (s, 2H, NH<sub>2</sub>), 8.05 (d,  $J = 5.4$  Hz, 1H, H-5). Anal. (C<sub>14</sub>H<sub>16</sub>Cl<sub>6</sub>N<sub>5</sub>O<sub>5</sub>P) 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<sub>3</sub>-MeOH (97:3) as a white foam (43%); TLC  $R_f = 0.25$  (CHCl<sub>3</sub>-MeOH, 97:3); UV (MeOH)  $\lambda_{\max}$  294 nm ( $\epsilon$  6300); <sup>31</sup>P NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  -3.39; <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  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<sub>2</sub>OP, H-2', and Hb-5'), 4.79 (m, 4H, CH<sub>2</sub>Cl<sub>3</sub>), 5.62 (m, 1H, H-4'), 6.85 (d,  $J = 6.2$  Hz,



1H, H-7), 7.00 (s, 2H, NH<sub>2</sub>), 7.66 (d, *J* = 6.2 Hz, 1H, H-6). Anal. (C<sub>14</sub>H<sub>16</sub>Cl<sub>6</sub>N<sub>5</sub>O<sub>5</sub>P) 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<sub>3</sub>-MeOH (90:10) gave **35** as white foam (48%): TLC *R<sub>f</sub>* = 0.4 (CHCl<sub>3</sub>-MeOH, 90:10); UV (MeOH) λ<sub>max</sub> 264 nm (ε 12 000), 278 (ε 10 000); <sup>31</sup>P NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ -3.51; <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.20 (m, 1H, Ha-3'), 2.62 (m, 1H, Hb-3'), 4.13 (m, 5H, CH<sub>2</sub>OP, H-2', Ha-5', and Hb-5'), 4.80 (m, 4H, CH<sub>2</sub>Cl<sub>3</sub>), 5.40 (m, 1H, H-4'), 6.30 (s, 2H, NH<sub>2</sub>), 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<sub>15</sub>H<sub>17</sub>Cl<sub>6</sub>N<sub>4</sub>O<sub>5</sub>P) 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<sub>3</sub>-MeOH (90:10) gave a white foam (68%): TLC *R<sub>f</sub>* = 0.40 (CHCl<sub>3</sub>-MeOH, 92:8); UV (MeOH) λ<sub>max</sub> 264 nm (ε 8100); <sup>31</sup>P NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ -3.18; <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) 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<sub>2</sub>OP), 4.82 (m, 4H, CH<sub>2</sub>Cl<sub>3</sub>), 5.20 (m, 1H, H-4'), 6.23 (s, 2H, NH<sub>2</sub>), 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<sub>15</sub>H<sub>17</sub>Cl<sub>6</sub>N<sub>4</sub>O<sub>5</sub>P) 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<sub>3</sub>-MeOH, 90:10) as a white foam (57%): TLC *R<sub>f</sub>* = 0.2 (CHCl<sub>3</sub>-MeOH, 96:4); UV (MeOH) λ<sub>max</sub> 260 nm (ε 14 800); <sup>31</sup>P NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ -4.25; <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.18 (m, 1H, Ha-3'), 2.68 (m, 1H, Hb-3'), 4.07, 4.20 (AB of ABX, *J<sub>AB</sub>* = 9.3, *J<sub>AX</sub>* = 6.4, *J<sub>BX</sub>* = 4.9 Hz, 2H, Ha-5', and Hb-5'), 4.34 (m, 3H, H-2', and CH<sub>2</sub>OP), 4.84 (m, 4H, CH<sub>2</sub>Cl<sub>3</sub>), 5.20 (m, 1H, H-4'), 7.25 (s, 2H, NH<sub>2</sub>), 8.12, 8.17 (2 s, 2H, H-2 and H-8). Anal. (C<sub>14</sub>H<sub>16</sub>Cl<sub>6</sub>N<sub>5</sub>O<sub>5</sub>P) 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.<sup>21</sup> 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<sub>3</sub>-MeOH, 90:10, *R<sub>f</sub>* = 0.55) to give a white foam (48%): <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 3.68, 3.48 (4:3); <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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<sub>2</sub>-OP), 5.50 (m, 1H, H-4'), 6.10 (br s, 2H, NH<sub>2</sub>), 7.10-7.33 (m, 5H, PhO), 8.45 (s, 1H, H-5). Anal. (C<sub>19</sub>H<sub>24</sub>N<sub>7</sub>O<sub>6</sub>P) 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<sub>3</sub>-MeOH, 96:4, *R<sub>f</sub>* = 0.08) as white foam (62%): <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 3.36, 3.01 (4:3); <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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<sub>2</sub>OP, and Ala-CH), 5.25 (m, 1H, H-4'), 5.82 (br s, 2H, NH<sub>2</sub>), 7.00-7.38 (m, 5H, PhO), 8.10\* (s, 1H, H-2), 8.33 (s, 1H, H-8). Anal. (C<sub>20</sub>H<sub>25</sub>N<sub>6</sub>O<sub>6</sub>P) 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.<sup>26</sup> from appropriate isonucleoside with PO(OMe)<sub>3</sub>, POCl<sub>3</sub>, and (Bu<sub>3</sub>NH)<sub>4</sub>P<sub>2</sub>O<sub>7</sub>.

**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<sub>f</sub>* = 0.85 (H<sub>2</sub>O-CH<sub>3</sub>OH, 90:10); <sup>31</sup>P NMR (CDCl<sub>3</sub>) 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<sub>33</sub>H<sub>71</sub>N<sub>10</sub>O<sub>11</sub>P<sub>3</sub>) 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<sub>f</sub>* = 0.72 (H<sub>2</sub>O-CH<sub>3</sub>CN, 90:10); <sup>31</sup>P NMR

(CDCl<sub>3</sub>) 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<sub>34</sub>H<sub>72</sub>N<sub>9</sub>O<sub>11</sub>P<sub>3</sub>) C, H, N.

**Viruses and Cells.** H9/III<sub>B</sub>, MT-4, and CEM cells were grown in RPMI-1640 containing 10% fetal calf serum (FCS), 100 IU/mL<sup>-1</sup> penicillin G, and 100 μg/mL<sup>-1</sup> streptomycin. Cell cultures were checked periodically for the absence of mycoplasma contamination with a MycoTest Kit (Gibco).

Human immunodeficiency virus type-1 (HIV-1, III<sub>B</sub> strain) and type-2 (HIV-2, CBL 20 strain, kindly provided by MRC) were obtained from supernatants of persistently infected H9/III<sub>B</sub> and CEM cells, respectively. HIV-1 and HIV-2 stock solutions had titers of 2 × 10<sup>5</sup> and 1.4 × 10<sup>6</sup> cell culture infectious dose fifty (CCID<sub>50</sub>/mL<sup>-1</sup>), 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<sup>4</sup> 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<sub>50</sub> 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.<sup>18</sup>

**Reverse Transcriptase Assay.** Assay was performed as previously described.<sup>27</sup> 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<sub>2</sub>, 1 mM DTT, 0.1 mg mL<sup>-1</sup> BSA, 0.5 OD<sub>260</sub> units mL<sup>-1</sup> poly(rC)-oligo(dG)<sub>12-18</sub>, 10 μM [<sup>3</sup>H]dGTP (1 Ci mmol<sup>-1</sup>). 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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