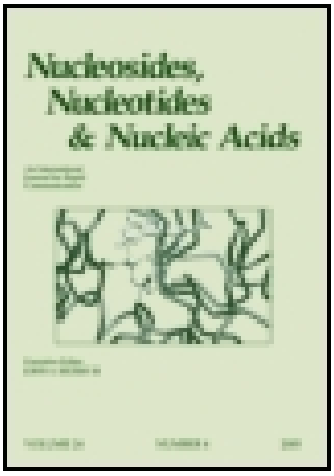

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Synthesis of 2′-Deoxyribonucleoside Derivatives of 1-Deazapurine

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SYNTHESIS OF 2'-DEOXYRIBONUCLEOSIDE DERIVATIVES OF 1-DEAZAPURINE.

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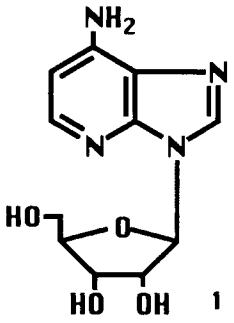
Abstract. 5,7-Dichloro-3H-imidazo[4,5-b]pyridine (**4**) is a versatile base which can be coupled with a variety of sugar moieties and transformed in a series of 7-alkyl(aryl)amino-derivatives by reacting with the corresponding amines. In this paper synthesis, structure elucidation and ADA inhibitory activity of 2'-deoxyribonucleoside derivatives of N^6-substituted 1-deazaapurines are described.

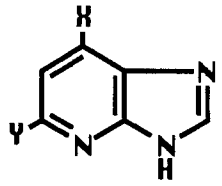
In our effort to synthesize deaza nucleosides endowed with pharmacological activity, we selected 1-deazapurine derivatives since 1-deazaadenosine (**1**) has been shown to possess cytotoxic activity,[1] to inhibit adenosine deaminase[2] and platelet aggregation,[3] and to act as an agonist of adenosine receptors.[4]

We have already reported the coupling of 7-nitro-3H-imidazo[4,5-b]pyridine (**2**)[1] and of 5-chloro-7-nitro-3H-imidazo[4,5-b]pyridine (**3**)[5] with ribose and 2-deoxyribose derivatives to obtain 6-amino-[1] and 6-hydroxyamino-1-deazapurine nucleosides.[6,7]

Our approach is now to use 5,7-dichloro-3H-imidazo[4,5-b]pyridine (**4**)[5] as a more versatile base which can be coupled with a

This paper is dedicated to the memory of Professor Roland K. Robins.





Compd	X	Y
2	NO_2	H
3	NO_2	Cl
4	Cl	Cl

Figure 1

variety of sugar moieties and transformed in a series of 7-alkyl(aryl)amino derivatives by reacting with the suitable amines.

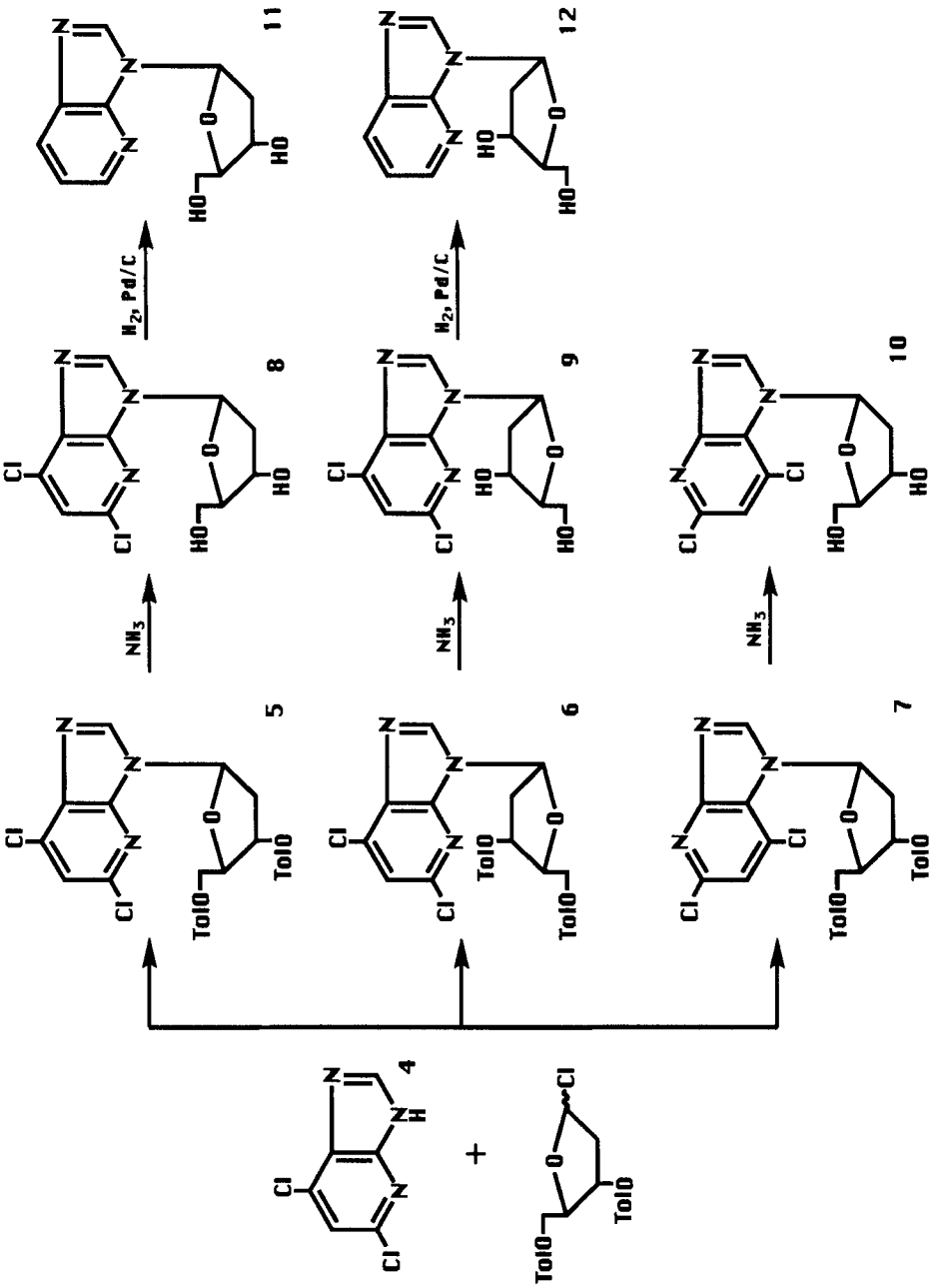
We previously reported on the synthesis of N^6-substituted 1-deazaadenosine[1,4] and in this paper the synthesis of the corresponding 2'-deoxyribonucleosides is described. The preparation of the corresponding 2',3'-dideoxyribonucleosides and their antiviral activity is reported elsewhere.[8]

CHEMISTRY

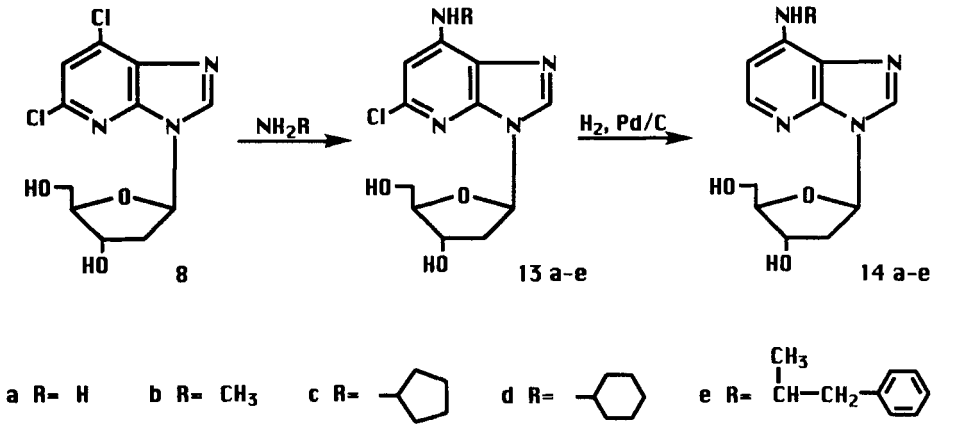
The synthesis of 5,7-dichloro-3-(2-deoxy-ß-D-*erythro*-pento furanosyl)-3H-imidazo[4,5-b]pyridine (**8**) was carried out according to Scheme I.

Reaction of freshly prepared 1-chloro-2-deoxy-3,5-di-O-p-toluoyl-α-D-*erythro*-pentofuranose[9] with the sodium salt of 5,7-dichloro-3H-imidazo[4,5-b]pyridine (**4**),[5] generated in situ by the treatment with sodium hydride in acetonitrile, gave compounds **5**, **6** and **7**. Deblocking of the mixture with methanolic ammonia yielded the dichloro derivatives **8**, **9** and **10** in 49%, 10% and 2% yield, respectively.

Reaction of 5,7-dichloro-3-(2-deoxy-ß-D-*erythro*-pentofurano syl)-3H-imidazo[4,5-b]pyridine (**8**) with the appropriate amine gave the N^7-substituted-5-chloro-3-(2-deoxy-ß-D-*erythro*-pentofurano syl)-3H-imidazo[4,5-b]pyridines **13a-e** (Scheme II).



Scheme I



Scheme II

Catalytic hydrogenolysis of the chlorine atom in **13a-e** with 10% Pd/C in ethanol and 2N NaOH afforded the corresponding derivatives **14a-e**.

Isomer identification

The site of deoxyribosylation was assigned by UV and ^{1}H NMR data. Since in the literature[10] were reported the UV spectra of 1-methyl-1H-imidazo[4,5-b]pyridine and 3-methyl-3H-imidazo[4,5-b]pyridine, compounds **8** and **9** were dehalogenated in a hydrogen atmosphere using 10% Pd/C in ethanol and 2N NaOH to give the corresponding imidazo[4,5-b]pyridine derivatives **11** and **12**. The UV spectra of compounds **11** and **12** were essentially indistinguishable and strictly similar to that of 3-methyl-3H-imidazo[4,5-b]pyridine (Table 1). The physical data of compound **11** are also in agreement with that of 9-β-D-2'-deoxyribofuranosyl-1-deazapurine obtained by Betbeder et al.[11] by enzymatic synthesis.

Moreover, the UV spectra of compounds **8** and **9** were very similar to that of 5,7-dichloro-3-(ß-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine, previously reported by Cline et al.[12], whereas compound **10** showed a spectral profile different from that observed for these three N-3 derivatives (Table 1).

Table 1. UV spectra of 1-deazapurine derivatives.

	UV λmax nm (ε)	
Compd	**pH 1.0**	**pH 12.0**
8	291 (14200) 252 (11500)	292 (11600) 266 (9000) 255 (7800) sh
9	290 (14100) 253 (11600)	292 (11400) 265 (9100) 254 (7900) sh
10	291 (11900) sh 286 (12000) 245 (8700) sh 237 (8900)	295 (12600) sh 288 (14500) 262 (10000)
5,7-dichloro-3-(β-D-ribofuranosyl)-3-H-imidazo[4,5-b]pyridine[12]	287 (9000) 254 (6000)	289 (8900) 259 (5900) 254 (5800) sh
11	282 (8900) 276 (14400) 236 (5500)	288 (7200) 282 (8900) 248 (5800)
12	282 (9000) 275 (10500) 236 (5400)	288 (7300) sh 282 (9200) 248 (5900)
3-Methyl-3H-imidazo[4,5-b] pyridine[10]	281 (8900) 275 (10600) 236 (4500)	288 (6900) sh 282 (9000) 252 (4500)
1-Methyl-1H-imidazo[4,5-b] pyridine[10]	289 (7600) sh 282 (8700) 277 (7900) 235 (2000)	288 (7900) sh 282 (9700)

Table 2. N.O.E.-data % of compounds **8**, **9** and **10** upon irradiation of H-1' (DMSO-d6, 25 °C, 300 MHz)

	H-2'a	H-2'b	H-3'	H-4'	H-2
8	a	3.0	a	1.3	3.0
9	3.0	a	1.0	a	3.4
10	a	3.0	a	1.0	<1

a: no detectable intensity enhancement (< 0.5%)

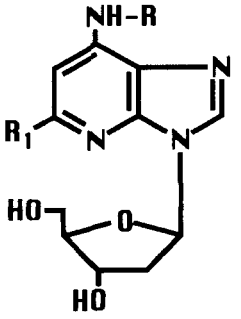
Furthermore standard criteria for assignment of regioisomers in purine 2'-deoxyribonucleosides are reported by Kazimierczuk et al. and by Hildebrand and Wright.[13,14] According to these authors, N-9 and N-7 purine 2'-deoxyribonucleosides (N-3 and N-1, respectively, in 1-deazapurines) are differentiated by ^{1}H NMR by the characteristic downfield chemical shifts for the anomeric H-1' and the purine H-8 resonances (H-2 in 1-deazapurines) of the N-7 (N-1) isomer relative to those of the N-9 (N-3) isomer. According to that, the 1-deaza derivatives **8** and **9** exhibited H-2 signal at δ 8.79 and 8.82 respectively and H-1' signal at δ 6.39 and 6.46 respectively, whereas compound **10** showed a singlet at δ 9.01 (H-2) and a triplet at δ 6.76 (H-1').

Anomer identification

The anomeric configuration of compounds **8**, **9** and **10** was assigned applying n.O.e. difference spectroscopy. Saturation of H-1' of **9** resulted in n.O.e.s of the H-2'a and H-3' signals (3.0 % and 1.0 %, respectively) while there was none at H-4' signal, establishing α-D-configuration (Table I). Saturation of H-1' of **8** and **10** yielded n.O.e.s of the H-2'b and H-4' signals (3.0 % and 1.3 %, respectively) while there was none at H-3' signal, establishing β-D-configuration (Table 2).

Furthermore a stronger n.O.e. effect was observed on H-2 when H-1' was irradiated in compounds **8** and **9** by comparison with **10**, confirming N^3-glycosylation for both **5** and **6**. This observation is in

Table 3. ADA inhibitory activity of 1-deazapurine derivatives.



n	R	R_1	Ki, μM
14a	H	H	0.19
13a	H	Cl	23
14b	CH_3	H	0.25
13b	CH_3	Cl	4.2
14c	cC_5H_9	H	100
13c	cC_5H_9	Cl	>1000
14d	cC_6H_{11}	H	130
13d	cC_6H_{11}	Cl	>1000
14e	$CH(CH_3)CH_2C_6H_5$	H	150
13e	$CH(CH_3)CH_2C_6H_5$	Cl	>1000

agreement with the data reported by Seela et al.[15] in the case of 3-deaza-2'-deoxyadenosine.

On these basis, compounds **8**, **9** and **10** were identified as 5,7-dichloro-3-(2-deoxy-ß-D-*erythro*-pentofuranosyl)-3H-imidazo[4,5-b]pyridine, 5,7-dichloro-3-(2-deoxy-α-D-*erythro*-pentofuranosyl)-3H-imidazo[4,5-b]pyridine and 5,7-dichloro-1-(2-deoxy-ß-D-*erythro*-pentofuranosyl)-1H-imidazo[4,5-b]pyridine, respectively

BIOLOGICAL EVALUATION

The synthesized nucleosides were evaluated as inhibitors of adenosine deaminase from calf intestine and the results are reported in Table 3.

None of the tested compounds proved to be substrate of ADA and some of them have good inhibitory activity. They showed the same structure activity relationships as the corresponding ribose derivatives.[17]

1-Deaza-2'-deoxyadenosine (**14a**) is the most potent in the series (K_i = 0.19 μM) and resulted to be more active than 1-deazaadenosine itself (K_i = 0.66 μM). The presence of a chlorine atom in position 2 produced a decrease in ADA inhibitory activity. Accordingly, the

introduction of a chlorine atom in the same position of substrates made the compounds more resistant to the enzyme. Substitution on the N^6 amino group did not produce a decrease in activity only when small groups are introduced (**13b** K_i = 4.2 μM and **14b** K_i = 0.25 μM). Increased lipophilicity and steric hindrance of substituents resulted in derivatives much less active than the parent compound **14a**.

EXPERIMENTAL SECTION

Chemistry.

Melting points were determined with a Buchi apparatus and are uncorrected. ^1H NMR spectra were obtained with a Varian VXR 300 MHz spectrometer. UV spectra were recorded on a Perkin-Elmer Coleman 575 spectrophotometer. TLC were carried out on pre-coated TLC plates with silica gel 60 F-254 (Merck). For column chromatography, silica gel 60 (Merck) was used. Elemental analyses were determined on Carlo Erba model 1106 analyser.

5,7-Dichloro-3-(2-deoxy-3,5-di-O-p-toluoyl-ß-D-*erythro*-pentofuranosyl)-3H-imidazo[4,5-b]pyridine (5), 5,7-dichloro-3-(2-deoxy-3,5-di-O-p-toluoyl-α-D-*erythro*-pentofuranosyl)-3H-imidazo[4,5-b]pyridine (6), 5,7-dichloro-1-(2-deoxy-3,5-di-O-p-toluoyl-ß-D-*erythro*-pentofuranosyl)-1H-imidazo[4,5-b]pyridine (7).

To a suspension of 1.2 g (6.28 mmol) of 5,7-dichloro-3H-imidazo[4,5-b]pyridine (**4**)[5] in 30 mL of dry acetonitrile under an atmosphere of dry N_2 was added 300 mg of 60% NaH and the mixture was stirred at room temperature for 30 min. To the ice-cooled mixture was added 3.6 g (9.25 mmol) of freshly prepared 1-chloro-2-deoxy-3,5-di-O-p-toluoyl-D-erythro-pentofuranose[9] and the suspension was stirred at 0 °C for 3 h. The reaction mixture was filtered through Celite to remove the insoluble material and the filtrate was concentrate to a residue which was used without further purification for the next reaction.

Analytical samples of **5** and **6** were obtained by flash chromatography eluting with C_6H_{12}-AcOEt from (90:10) to (50:50).
(**5**): mp 146-148 °C; ^1H NMR (Me_2SO-d6) δ 2.36 (s, 3H, CH_3), 2.40 (s,

3H, CH_3), 2.80 (m, 1H, H-2'), 3.26 (m, 1H, H-2"), 4.57 (m, 3H, CH_2-5' and H-4'), 5.79 (m,1H, H-3'), 6.59 (t, 1H, J= 6.9 Hz, H-1'), 7.26 (d, 2H, H-Ph), 7.36 (d, 2H, H-Ph), 7.68 (s, 1H, H-6), 7.78 (d, 2H, H-Ph), 7.95 (d, 2H, H-Ph), 8.80 (s, 1H, H-2). Anal. Calcd. for $C_{27}H_{23}Cl_2N_3O_5$: C, 60.01; H, 4.29; N, 7.78. Found: C, 60.37; H, 4.10; N, 7.47.

(**6**): ^{1}H NMR (Me_2SO-d6) δ 2.38 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.09 (m, 2H, H-2' and H-2"), 4.55 (m, 2H, CH_2-5'), 5.04 (m, 1H, H-4'), 5.66 (m,1H, H-3'), 6.70 ("t", 1H, H-1'), 7.28 (d, 2H, H-Ph), 7.38 (d, 2H, H-Ph), 7.60 (d, 2H, H-Ph), 7.67 (s, 1H, H-6), 7.95 (d, 2H, H-Ph), 8.85 (s, 1H, H-2). Anal. Calcd. for $C_{27}H_{23}Cl_2N_3O_5$: C, 60.01; H, 4.29; N, 7.78. Found: C, 60.32; H, 4.08; N, 7.45.

5,7-Dichloro-3-(2-deoxy-ß-D-*erythro*-pentofuranosyl)-3H-imidazo[4,5-b]pyridine (8), 5,7-dichloro-3-(2-deoxy-α-D-*erythro*-pentofuranosyl)-3H-imidazo[4,5-b]pyridine (9), 5,7-dichloro-1-(2-deoxy-ß-D-*erythro*-pentofuranosyl)-1H-imidazo[4,5-b]pyridine (10).

To the residue obtained from the above reaction was added 50 mL of methanol saturated at 0 °C with ammonia and the mixture was set aside at room temperature for 36 h. The reaction mixture was evaporated and the residue was flash chromatographed over silica gel eluting with $CHCl_3$-MeOH-NH_3 (96.5:3:0.5) to give 0.94 g (49%) of **8**, 0.19 g (10%) of **9** and 0.04 g (2%) of **10**. (Yields are based on **4**).

(**8**): mp 51-53 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.34 (m, 1H, H-2'), 2.71 (m, 1H, H-2"), 3.55 (m, 2H, CH_2-5'), 3.87 (m, 1H, H-4'), 4.41 (m,1H, H-3'), 6.39 (t, 1H, J= 6.8 Hz, H-1'), 7.66 (s, 1H, H-6), 8.79 (s, 1H, H-2). Anal. Calcd. for $C_{11}H_{11}Cl_2N_3O_3$: C, 43.44; H, 3.65; N, 13.82. Found: C, 43.12; H, 3.52; N, 14.11.

(**9**): ^{1}H NMR (Me_2SO-d_6) δ 2.44 (m, 1H, H-2'), 2.78 (m, 1H, H-2"), 3.48 (m, 2H, CH_2-5'), 4.19 (m, 1H, H-4'), 4.35 (m,1H, H-3'), 6.46 (dd, 1H, J= 5.5, 2.0 Hz, H-1'), 7.69 (s, 1H, H-6), 8.82 (s, 1H, H-2). Anal. Calcd. for $C_{11}H_{11}Cl_2N_3O_3$: C, 43.44; H, 3.65; N, 13.82. Found: C, 43.15; H, 3.51; N, 14.04.

(**10**): ^{1}H NMR (Me_2SO-d_6) δ 2.46 (m, 1H, H-2'), 2.67 (m, 1H, H-2"), 3.61 (m, 2H, CH_2-5'), 3.91 (m, 1H, H-4'), 4.41 (m,1H, H-3'), 6.76 (t, 1H,

J= 6.1 Hz, H-1'), 7.66 (s, 1H, H-6), 9.01 (s, 1H, H-2). Anal. Calcd. for $C_{11}H_{11}Cl_2N_3O_3$: C, 43.44; H, 3.65; N, 13.82. Found: C, 43.09; H, 3.48; N, 13.99.

3-(2-deoxy-ß-D-*erythro*-pentofuranosyl)-3H-imidazo[4,5-b]pyridine (11).

To 50 mg (0.16 mmol) of **8** in 10 mL of ethanol and 0.5 mL of 2 N NaOH was added 50 mg of 10% Pd/C, and the mixture was shaken with hydrogen at 60 psi for 6 h. The catalyst was removed, and the filtrate concentrated to dryness. The residue was chromatographed on a silica gel column eluting with $CHCl_3$-MeOH (90:10) to give 25 mg (67%) of **11** as a chromatographically pure solid.

(11): ^1H NMR (Me_2SO-d_6) δ 2.35 (m, 1H, H-2'), 2.78 (m, 1H, H-2"), 3.60 (m, 2H, CH_2-5'), 4.91 (m, 1H, H-4'), 4.46 (m,1H, H-3'), 6.54 (t, 1H, J= 6.8 Hz, H-1'), 7.34 (dd, 1H, $J_{6,7}$ = 7.9, $J_{6,5}$ = 4.7 Hz, H-6), 8.14 (d, 1H, $J_{7,6}$ = 7.8 Hz, H-7), 8.39 (d, 1H, $J_{5,6}$ = 4.7 Hz, H-5), 8.70 (s, 1H, H-2). Anal. Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.38; H, 5.71; N, 17.57.

3-(2-deoxy-α-D-*erythro*-pentofuranosyl)-3H-imidazo[4,5-b]pyridine (12).

The title compound was prepared following the same procedure as **11**, starting from 50 mg (0.16 mmol) of **9** to obtain 22 mg (58%) of **12** as a chromatographically pure solid.

(12): ^1H NMR (Me_2SO-d_6) δ 2.43 (m, 1H, H-2'), 2.81 (m, 1H, H-2"), 3.50 (m, 2H, CH_2-5'), 4.17 (m, 1H, H-4'), 4.36 (m,1H, H-3'), 6.54 (dd, 1H, J= 7.7, 3.1 Hz, H-1'), 7.34 (dd, 1H, $J_{6,7}$ = 8.1, $J_{6,5}$ = 4.7 Hz, H-6), 8.13 (d, 1H, $J_{7,6}$ = 8.1 Hz, H-7), 8.40 (d, 1H, $J_{5,6}$ = 4.7 Hz, H-5), 8.73 (s, 1H, H-2). Anal. Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.33; H, 5.69; N, 17.54.

Preparation of N^7-Substituted 5-chloro-3-(2-deoxy-ß-D-*erythro*-pentofuranosyl)-3H-imidazo[4,5-b]pyridines (13a-e).

A mixture of 0.45 g (1.5 mmol) of **8** and 30 mL of the appropriate amine was heated in a steel bomb at 135 °C for 20 h. Compound **13e** was prepared by heating a mixture of 0.45 g (1.5 mmol) of **8** in 30

mL of ethanol and 0.61 g (4.5 mmol) of L-amphetamine in a steel bomb at 135 °C for 60 h. The reaction mixture was evaporated and the residue was chromatographed on a silica gel column eluting with $CHCl_3$-C_6H_6-MeOH (70:20:10) to give **13a-e** as chromatographically pure solids

(**13a**) yield: 46%; mp 227-229 °C; ^1H NMR (Me_2SO-d_6) δ 2.22 (m, 1H, H-2'), 2.66 (m, 1H, H-2"), 3.54 (m, 2H, CH_2-5'), 3.84 (m, 1H, H-4'), 4.36 (m, 1H, H-3'), 6.28 (t, 1H, J= 6.9 Hz, H-1'), 6.36 (s, 1H, H-6), 6.78 (s, 2H, NH_2), 8.29 (s, 1H, H-2). Anal. Calcd. for $C_{11}H_{13}ClN_4O_3$: C, 46.41; H, 4.60; N, 19.68. Found: C, 46.12; H, 4.51; N, 19.92.

(**13b**) yield: 51%; mp 129-131 °C; ^1H NMR (Me_2SO-d_6) δ 2.23 (m, 1H, H-2'), 2.64 (m, 1H, H-2"), 2.87 (d, 3H, NCH_3), 3.54 (m, 2H, CH_2-5'), 3.83 (m, 1H, H-4'), 4.36 (m,1H, H-3'), 6.28 (m, 2H, H-1' and H-6), 7.24 (d, 1H, NH), 8.29 (s, 1H, H-2). Anal. Calcd. for $C_{12}H_{15}ClN_4O_3$: C, 48.25; H, 5.06; N, 18.75. Found: C, 47.95; H, 4.89; N, 18.96.

(**13c**) yield: 75%; mp 196-198 °C; ^1H NMR (Me_2SO-d_6) δ 1.57 (m, 4H, H cyclopent.), 1.69 (m, 2H, H cyclopent.), 1.97 (m, 2H, H cyclopent.), 2.26 (m, 1H, H-2'), 2.65 (m, 1H, H-2"), 3.54 (m, 2H, CH_2-5'), 3.84 (m,1H, H-4'),4.29 (m, 1H, H-1 cyclopent.), 4.38 (m,1H, H-3'), 6.29 (t, 1H, J= 6.9 Hz, H-1'), 6.36 (s, 1H, H-6), 7.05 (d, 1H, NH), 8.29 (s, 1H, H-2). Anal. Calcd. for $C_{16}H_{21}ClN_4O_3$: C, 54.47; H, 6.0; N, 15.88. Found: C, 54.71; H, 6.13; N, 15.54.

(**13d**) yield: 46%; mp 112-114 °C; ^1H NMR (Me_2SO-d_6) δ 1.13 and 1.29 (m, 5H, H cyclohexyl), 1.58, 1.70, and 1.87 (m, 5H, H cyclohexyl), 2.23 (m, 1H, H-2'), 2.63 (m, 1H, H-2"), 3.52 (m, 3H, CH_2-5' and H-1 cyclohexyl), 3.83 (m, 1H, H-4'), 4.37 (m, 1H, H-3'), 6.28 (t, 1H, J= 6.9 Hz, H-1'), 6.38 (s, 1H, H-6), 6.90 (d, 1H, NH), 8.29 (s, 1H, H-2). Anal. Calcd. for $C_{17}H_{23}ClN_4O_3$: C, 55.66; H, 6.32; N, 15.27. Found: C, 55.92; H, 6.18; N, 15.51.

(**13e**) yield: 50%; mp 260-262 °C; ^1H NMR (Me_2SO-d_6) δ 1.15 (d, 3H, $\underline{CH_3}$-CH), 2.23 (m, 1H, H-2'), 2.68 (m, 2H, H-2" and $\underline{CH_2}C_6H_5$), 2.95 (m, 1H, $\underline{CH_2}C_6H_5$), 3.73 (m, 2H, CH_2-5'), 3.84 (m, 1H, H-4'), 4.37 (m, 2H, H-3' and $\underline{CH}$NH), 6.28 (pt, 1H, J= 6.9 Hz, H-1') 6.36 (s, 1H, H-6), 7.04 (d, 1H, NH), 7.21 (m, 5H, H-Ph), 8.32 (s, 1H, H-2). Anal. Calcd. for $C_{20}H_{23}ClN_4O_3$: C, 59.63; H, 5.75; N, 13.91. Found: C, 59.98; H, 5.89; N, 13.63.

Preparation of N^7-Substituted 3-(2-deoxy-ß-D-*erythro*-pentofuranosyl)-3H-imidazo[4,5-b]pyridines (14a-e).

To a solution of **13a-e** (0.5 mmol) in 40 mL of ethanol and 1 mL of 2N NaOH was added 0.1 g of 10% Pd/C, and the mixture was shaken with hydrogen at 40 psi for 4 h. The catalyst was removed, and the filtrate concentrated to dryness. The residue was chromatographed on a silica gel column eluting with $CHCl_3$-C_6H_6-MeOH (70:20:10) to give **14a-e** as chromatographically pure solids.

(**14a**) yield: 65%; mp 205-207 °C (lit.[16] 207-208); ^1H NMR (Me_2SO-d_6) δ 2.22 (m, 1H, H-2'b), 2.75 (m, 1H, H-2'a), 3.54 (m, 2H, CH_2-5'), 3.89 (m, 1H, H-4'), 4.41 (m, 1H, H-3'), 6.37 (m, 2H, H-6 and H-1'), 6.47 (s, 2H, NH_2), 7.76 (d, 1H, J= 5.5 Hz, H-5), 8.29 (s, 1H, H-2). Anal. Calcd. for $C_{11}H_{14}N_4O_3$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.94; H, 5.45; N, 22.18.

(**14b**) yield: 80%; mp 162-164 °C; ^1H NMR (Me_2SO-d_6) δ 2.19 (m, 1H, H-2'), 2.75 (m, 1H, H-2"), 2.86 (d, 3H, N$\underline{CH_3}$), 3.54 (m, 2H, CH_2-5'), 3.88 (m, 1H, H-4'), 4.38 (m,1H, H-3'), 6.27 (d, 1H, J= 5.8 Hz, H-6), 6.36 (pt, 1H, J= 6.9 Hz, H-1'), 6.86 (m, 1H, NH), 7.86 (d, 1H, J= 5.8 Hz, H-5), 8.23 (s, 1H, H-2). Anal. Calcd. for $C_{12}H_{16}N_4O_3$: C, 54.54; H, 6.10; N, 21.20. Found: C, 54.87; H, 6.31; N, 19.94.

(**14c**) yield: 55%; mp 74-76 °C; ^1H NMR (Me_2SO-d_6) δ 1.53 (m, 4H, H cyclopent.), 1.68 (m, 2H, H cyclopent.), 1.95 (m, 2H, H cyclopent.),2.18 (m, 1H, H-2'), 2.74 (m, 1H, H-2"), 3.50 (m, 1H, CH_2-5'), 3.62 (m, 1H, CH_2-5"), 3.87 (m,1H, H-4'),4.20 (m, 1H, H-1 cyclopent.), 4.38 (m,1H, H-3'), 6.34 (d, 1H, J= 5.7 Hz, H-6), 6.36 (t, 1H, J= 7.5 Hz, H-1'), 6.61 (d, 1H, J= 7.5 Hz, NH), 7.81 (d, 1H, J= 5.7 Hz, H-5), 8.23 (s, 1H, H-2). Anal. Calcd. for $C_{16}H_{22}N_4O_3$: C, 60.39; H, 6.97; N, 17.60. Found: C, 60.80; H, 7.11; N, 17.29.

(**14d**) yield: 61%; mp 67-69 °C; ^1H NMR (Me_2SO-d_6) δ 1.14 and 1.30 (m, 5H, H cyclohexyl), 1.59, 1.70, and 1.90 (m, 5H, H cyclohexyl), 2.16 (m, 1H, H-2'), 2.74 (m, 1H, H-2"), 3.49 (m, 1H, CH_2-5'), 3.60 (m, 1H, CH_2-5"), 3.77 (m, 1H, H-1 cyclohexyl), 3.87 (m,1H, H-4'), 4.38 (m,1H, H-3'), 6.35 (m, 2H, H-1' and H-6), 6.48 (d, 1H, NH), 7.78 (d, 1H, J= 6.0 Hz, H-5), 8.23 (s, 1H, H-2). Anal. Calcd. for $C_{17}H_{24}N_4O_3$: C, 61.43; H, 7.28; N, 16.85. Found: C, 61.87; H, 7.39; N, 16.50.

(**14e**) yield: 23%; ^1H NMR (Me_2SO-d_6) δ 1.14 (d, 3H, $\underline{CH_3}$-CH), 2.16 (m, 1H, H-2'), 2.71 (m, 2H, H-2" and $\underline{CH_2}C_6H_5$), 2.96 (m, 1H, $\underline{CH_2}C_6H_5$), 3.54

(m, 2H, CH_2-5'), 3.87 (m, 1H, H-4'), 4.37 (m, 2H, H-3'and CHNH), 6.35 (m, 2H, H-1' and H-6), 6.60 (d, 1H, NH), 7.19 (m, 5H, H-Ph), 7.78 (d, 1H, J= 5.4 Hz, H-5), 8.24 (s, 1H, H-2). Anal. Calcd. for $C_{20}H_{24}N_4O_3$: C, 65.20; H, 6.57; N, 15.21. Found: C, 64.98; H, 6.76; N, 14.97.

Enzyme Assay.

The method used for the determination of activity against adenosine deaminase has been described in a preceding paper.[2]

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