

Synthesis and Adenosine Deaminase Inhibitory Activity of 3'-Deoxy-1-deazaadenosines

by Rosaria Volpini, Stefano Costanzi, Sauro Vittori and Gloria Cristalli*

Dipartimento di Scienze Chimiche

and Giulio Lupidi

Dipartimento di Biologia MCA, Università di Camerino, I-62032 Camerino (MC)

Dedicated to Prof. Dr. Frank Seela on the occasion of his 60th birthday

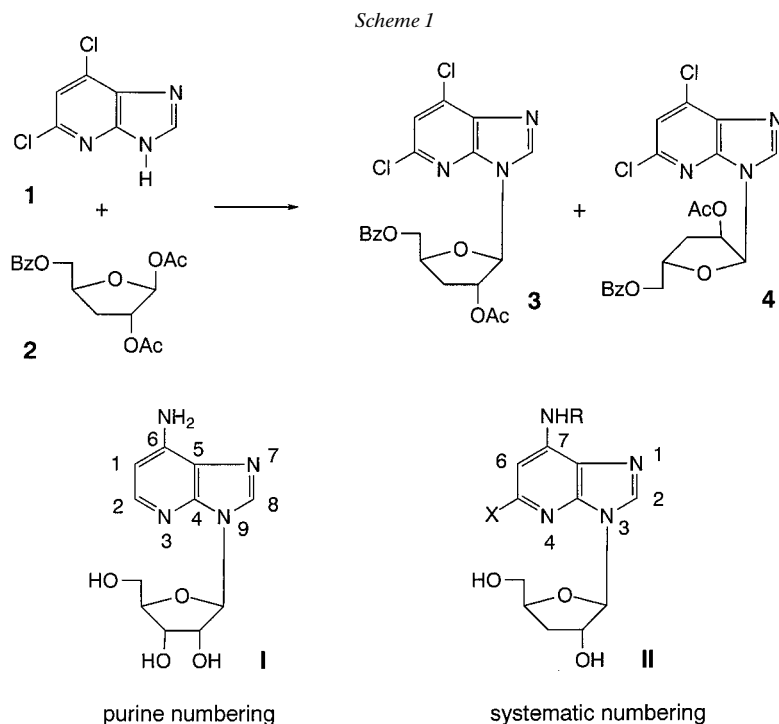
New 1-deazapurine nucleosides were synthesized by coupling 2,6-dichloro-1-deaza-9H-purine (= 5,7-dichloro-3H-imidazo[4,5-b]pyridine) with a 3-deoxyribose derivative by the acid-catalyzed fusion method. The condensation reaction gave an anomeric mixture of the *N*⁹-β-D- and *N*⁹-α-D-3'-deoxynucleosides, which were treated with methanolic ammonia at room temperature to obtain the deprotected derivatives. Reaction of the β-D-anomer with different amines gave 2-chloro-*N*⁶-substituted nucleosides, which were dechlorinated to give the corresponding 3'-deoxy-1-deazaadenosines. Biological studies on adenosine deaminase from calf intestine showed that the new compounds are inhibitors of the enzyme, the 3'-deoxy-1-deazaadenosine being the most potent one with a *K*_i of 2.6 μM.

1. Introduction. – 1-Deazaadenosine (c¹A, **I**) is a nucleoside endowed with a number of pharmacological properties: it has been shown to possess cytotoxic activity [1], to inhibit platelet aggregation [2], and to act as an agonist of adenosine receptors [3]. Furthermore, 1-deazaadenosine analogues exhibit good inhibitory activity against adenosine deaminase (ADA) [4][5], an enzyme involved in the pathogenesis of the severe combined immunodeficiency disease (SCID) [6–8], and responsible for deamination of potentially useful nucleoside-based drugs [9]. Elevated serum ADA activity has been described in various autoimmune and inflammatory diseases, including systemic lupus erythematosus [10].

Recently Seela *et al.* described the incorporation of 1-deazaadenosine into a hammerhead ribozyme and the resulting catalytic activity [11].

In recent years, a number of 1-deazapurine nucleosides were synthesized by coupling 5,7-dichloro-3H-imidazo[4,5-b]pyridine (**1**; *Scheme 1*) [12] with ribose, 2-deoxyribose, and 2,3-dideoxyribose derivatives [13–16]. Some of these molecules exhibited *in vitro* activity against human immunodeficiency virus type-1 (HIV-1); in particular compounds bearing an *N*⁶-cycloheptyl or a cyclooctyl ring were the most active ones in every series, while the *N*⁶-unsubstituted derivatives proved to be good inhibitors of adenosine deaminase (ADA).

In the present paper, we report for the first time the synthesis of a series of 1-deazaadenosine derivatives obtained by modifying the 3'-position of the sugar moiety. This goal was achieved by coupling 2,6-dichloro-1-deazapurine (**1**) with the 3-deoxy-β-D-ribose derivative **2** to obtain the 3'-deoxy-1-deazapurine nucleosides of the general formula **II**.



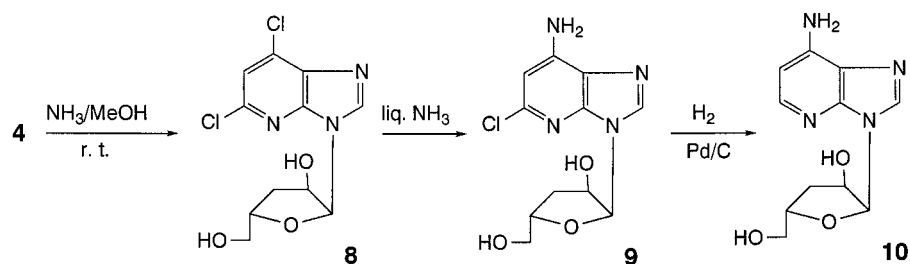
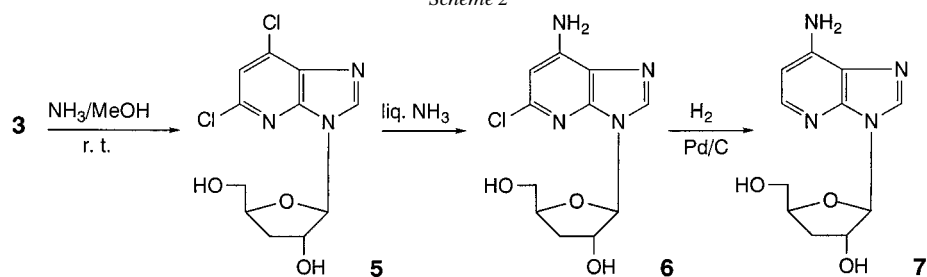
2. Results. – 5,7-Dichloro-3*H*-imidazo[4,5-*b*]pyridine (**1**) [12] was treated with 1,2-di-*O*-acetyl-5-*O*-benzoyl-3-deoxy- β -D-ribofuranose (**2**) [17] in the presence of a catalytic amount of TsOH at 160° *in vacuo* for 10 min. The coupling gave a mixture of the *N*-3- β -D-3' and *N*-3- α -D-3'-deoxyribonucleosides **3** and **4** with a total yield of 81% (*Scheme 1*). These protected nucleosides were reacted with NH₃/MeOH at room temperature to give the compounds **5** and **8**, respectively, from which the 1-deazaadenosine derivatives **6** and **9**, respectively, were obtained by treatment with liquid NH₃ at 120° in a steel bomb (*Scheme 2*). Catalytic hydrogenolysis of the Cl-atom in **6** or **9** with 10% Pd/C in absolute EtOH and in the presence of 1*N* NaOH afforded the corresponding derivatives **7** and **10** (*Scheme 2*).

Compound **5** was also reacted with cycloheptyl amine or cyclooctylamine, at 105° for 16 h, to provide the 5-chloro-7-(cycloheptylamino)-1-(3-deoxy- β -D-ribofuranosyl)-3*H*-imidazo[4,5-*b*]pyridine (**11**), and the 5-chloro-7-(cyclooctylamino)-1-(3-deoxy- β -D-ribofuranosyl)-3*H*-imidazo[4,5-*b*]pyridine (**13**), which were dechlorinated under the above-mentioned conditions to give **12** and **14** (*Scheme 3*), respectively.

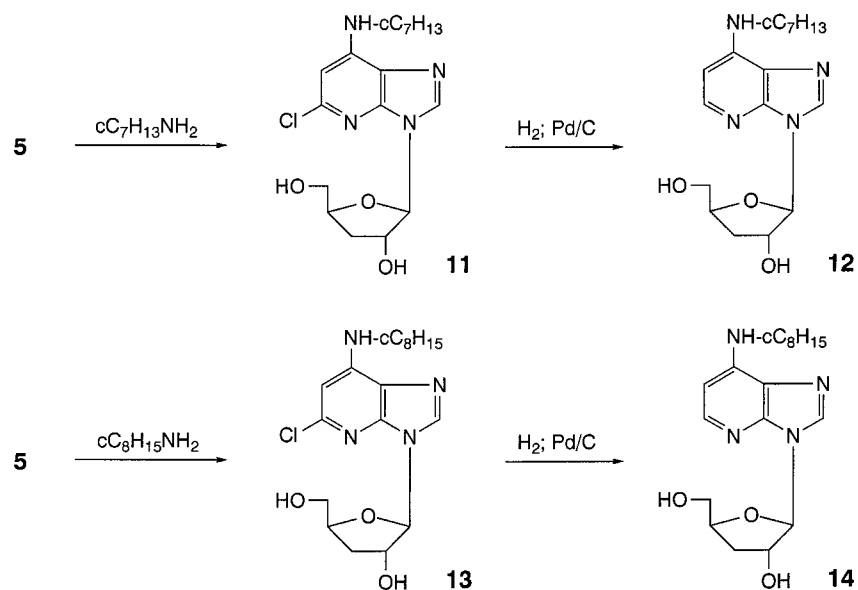
It is worth noting that previously reported coupling of the same sugar, **2**, with 2,6-dichloro-3-deazapurine afforded, in addition to the β -D- and α -D-anomers of the 3'-deoxyribonucleoside, the α -anomer of the 3'-deoxyarabino-nucleoside, derived from epimerization at C(2) of the sugar [18].

Structural Assignment. The glycosylation site and the anomeric configuration were assigned on the basis of UV data and ¹H-NMR spectra, including 1D-¹H-NOE difference spectra, of the deprotected nucleosides **5–9**.

Scheme 2



Scheme 3



The UV spectra of nucleosides **5** and **8** as **6** and **9** were essentially identical (see *Exper. Part*).

An NOE at the H-C(2) upon saturation of H-C(1') indicated N(1) or N(3) as glycosylation site in the case of all compounds **5–9** (see Table 1).

However, since no NOE was observed on the 7-NH₂ group in compounds **6** and **9**, the presence of N(1)-regioisomers can be excluded [19][20]. This assignment was also unequivocal for the chloro compounds **5** and **8**, as the amino compounds were obtained from the chloro derivatives. Furthermore, the lack of an NOE on H–C(5) upon irradiation of H–C(1') in compound **7** confirmed N(3) as glycosylation site, excluding the presence of N(4)-regioisomers.

Table 1. NOE Data [%] of Imidazo[4,5-b]pyridine Nucleosides in (*D*₆)DMSO at 23°

Compound	Irradiated proton	Observed NOE [%]
5	H–C(1')	H–C(2) (2.3), H–C(2') (1.7), H–C(4') (1.0), H _b –C(3') (0.4) H–C(4') H–C(2) (0.3), H–C(6) (1.4), H–C(1') (1.3), H _b –C(3') (3.1), H–C(5') (1.7), H–C(5') (1.7)
8	H–C(1')	H–C(2) (1.4), H–C(2') (and H–C(4')) (2.1), H _a –C(3') (0.7)
6	H–C(1')	H–C(2) (2.6), H–C(2') (1.2), H–C(4') (1.1), H _b –C(3') (0.4)
9	H–C(1')	H–C(2) (1.5), H–C(2') (and H–C(4')) (2.2), H _a –C(3') (0.7)
7	H–C(1')	H–C(2) (4.0), H–C(2') (2.0), H–C(4') (1.0)

The NOEs on H–C(4') upon irradiation of H–C(1') in compounds **5**, **6**, and **7** established the β -D-configuration in all three cases; NOEs on H_b–C(3') were observed in compounds **5** and **6** and not in **7**. On the other hand, irradiation of H–C(1') in compounds **8** and **9** gave NOEs on H_a–C(3') and none on H–C(4'), establishing the α -D-configuration [21].

Discussion. – The new compounds **6**, **7**, and **11–14** were evaluated as inhibitors of adenosine deaminase from calf intestine [22], and the results are listed in Table 2. The 2'-deoxy-1-deazaadenosine (**16**) and the corresponding 2-Cl derivative **15** were reported as reference compounds [14–16]. The results show that none of the tested compounds were substrates of the enzyme, and the 3'-deoxy-1-deazaadenosine (**7**), although less potent than the corresponding 2'-deoxy derivative **16** ($K_i = 0.19 \mu\text{M}$), was still a good ADA inhibitor with a K_i of $2.6 \mu\text{M}$. The presence of a Cl-atom at C(2) of 1-deazapurine produced a decrease of activity (**7**, $K_i = 2.6 \mu\text{M}$ vs. **6**, $K_i = 35 \mu\text{M}$) compared to 2'-deoxy-1-deazaadenosines **16** and **15** (Table 2) and the corresponding ribose- and 2',3'-dideoxyribose derivatives [16]. As expected, substitution at N(6) with bulky and hydrophobic cycloalkyl rings brought about a relevant decrease of ADA inhibitory activity (**11–14**, K_i from 38 to $115 \mu\text{M}$). In these cases, the Cl-atom at C(2) does not significantly affect the activity. All these findings are in agreement with our previous hypothesis of a direct interaction of the 1-deazaadenosine derivatives with the catalytic site of the enzyme, involving 6-NH₂ group as a H-bond donor [16]. Studies on human immunodeficiency virus type-1 (HIV-1) are in progress and will be reported elsewhere.

Experimental Part

General. TLC: precoated TLC plates with silica gel 60 F-254 (Merck). FC: silica gel 60 (Merck). M.p.: Büchi apparatus; uncorrected. UV Spectra: Perkin-Elmer Coleman 575 spectrophotometer. ¹H-NMR Spectra: Varian VXR 300-MHz spectrometer; δ in ppm, J in Hz. Elemental analyses were determined on a Carlo Erba model 1106 analyser, exper. values within $\pm 0.4\%$ of calc. values.

Glycosylation of 5,7-Dichloro-3H-imidazo[4,5-b]pyridine (1) with 1,2-O-Diacetyl-5-O-benzoyl-3-deoxy- β -D-ribofuranose (2). An intimate mixture of **1** [12] (100 mg, 0.53 mmol), **2** [17] (342 mg, 1.06 mmol), and TsOH (cat. amount) was heated at 160°; when the fusion started, vacuum from a water aspirator (25 mm) was applied until bubbling ceased (5–10 min). The resulting solid was submitted to FC (silica gel; cyclohexane AcOEt

Table 2. ADA Inhibitory Activity of 1-Deazapurine Nucleosides

6, 7, 11-14

15, 16

Compound	R	R ¹	K _i [μM]
6	H	Cl	35
7	H	H	2.6
1	cC ₇ H ₁₃	Cl	115
12	cC ₇ H ₁₃	H	93
13	cC ₈ H ₁₅	Cl	38
14	cC ₈ H ₁₅	H	89
15		Cl	23
16		H	0.19

70:30) to obtain a mixture of the two nucleosides **3** and **4** (195 mg; 81%). Anal. samples of **3** and **4** were obtained as amorphous solids by separating the mixture on prep. TLC (CHCl₃/MeOH 98:2).

3-(2-O-Acetyl-5-O-benzoyl-3-deoxy-β-D-ribofuranosyl)-5,7-dichloro-3H-imidazo[4,5-b]pyridine (3): Yield 52%. ¹H-NMR ((D₆)DMSO): 2.13 (s, MeCO); 2.28–2.42 (m, 1 H–C(3')); 2.72–2.89 (m, 1 H–C(3')); 4.40–4.78 (m, 2 H–C(5'), H–C(4')); 5.79 (d, *J* = 6.7, H–C(2')); 6.27 (s, H–C(1')); 7.53–7.43 (m, 2 arom. H); 7.69–7.60 (m, 1 arom. H); 7.70 (s, H–C(6)); 7.80–7.88 (m, 2 arom. H); 8.77 (s, H–C(2)). Anal. calc. for C₂₀H₁₇Cl₂N₃O₅ (450.27): C 53.35, H 3.81, N 9.33; found: C 53.50, H 3.92, N 9.12.

3-(2-O-Acetyl-5-O-benzoyl-3-deoxy-α-D-ribofuranosyl)-5,7-dichloro-3H-imidazo[4,5-b]pyridine (4): Yield 29%. ¹H-NMR ((D₆)DMSO): 1.78 (s, MeCO); 2.42–2.58 (m, 2 H–C(3')); 4.38–4.54 (m, 2 H–C(5')); 4.97–5.09 (m, H–C(4')); 5.59–5.70 (m, H–C(2')); 6.69 (d, *J* = 4.8, H–C(1')); 7.42–7.60 (m, 3 arom. H); 7.71 (s, H–C(6)); 7.99–8.10 (m, 2 arom. H); 8.76 (s, H–C(2)). Anal. calc. for C₂₀H₁₇Cl₂N₃O₅ (450.27): C 53.35, H 3.81, N 9.33; found: C 53.55, H 4.03, N 9.17.

5,7-Dichloro-3-(3-deoxy-β-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (5) and 5,7-Dichloro-3-(3-deoxy-α-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (8). To the mixture **3/4** (526 mg, 1.17 mmol) was added MeOH sat. at 0° with NH₃ (30 ml), and the mixture was allowed to stand at r.t. for 16 h. After evaporation, the residue was separated by FC (CHCl₃/MeOH 98:2) to obtain **5** (198 mg, 56%) and **8** (102 mg, 29%) as white solids.

Data of 5: M.p. 164–165°. UV (EtOH): 260 (9800), 287 (15500). ¹H-NMR ((D₆)DMSO): 1.75–2.00 (m, 1 H–C(3')); 2.17–2.36 (m, 1 H–C(3')); 3.49–3.66 (m, 1 H–C(5')); 3.68–3.83 (m, 1 H–C(5')); 4.35–4.50 (m, H–C(4')); 4.53–4.64 (m, H–C(2')); 6.00 (s, H–C(1')); 7.70 (s, H–C(6)); 8.89 (s, H–C(2)). Anal. calc. for C₁₁H₁₁Cl₂N₃O₃ (304.13): C 43.44, H 3.65, N 13.82; found: C 43.55, H 3.70, N 13.71.

Data of 8: M.p. 182–183°. UV (EtOH): 260 (6600), 287 (9800). ¹H-NMR ((D₆)DMSO): 2.04–2.29 (m, 2 H–C(3')); 3.38–3.63 (m, 2 H–C(5')); 4.49–4.64 (m, H–C(4'), H–C(2')); 6.33 (d, *J* = 4.4, H–C(1')); 7.68 (s, H–C(6)); 8.61 (s, H–C(2)). Anal. calc. for C₁₁H₁₁Cl₂N₃O₃ (304.13): C 43.44, H 3.65, N 13.82; found: C 43.48, H 3.72, N 13.70.

7-Amino-5-chloro-3-(3-deoxy-β-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (6) and 7-Amino-5-chloro-3-(3-deoxy-α-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (9). To compound **5** or **8** (100 mg, 0.33 mmol) liq. NH₃ (10 ml) was added, and the mixture was heated in a steel bomb at 120° for 12 h. After evaporation of the NH₃, the residue was chromatographed (silica gel; CHCl₃/MeOH 92:8) to obtain **6** (48 mg, 52%) or **9** (46 mg, 49%), as chromatographically pure solids.

Data of 6: M.p. 204–205°. UV (EtOH): 266 (19600). ¹H-NMR ((D₆)DMSO): 1.85–1.98 (m, 1 H–C(3')); 2.17–2.33 (m, 1 H–C(3')); 3.47–3.59 (m, 1 H–C(5')); 3.62–3.78 (m, 1 H–C(5')); 4.29–4.40 (m, H–C(4')); 4.50–4.60 (m, H–C(2')); 5.85 (d, *J* = 1.5, H–C(1')); 6.39 (s, H–C(6)); 6.79 (br. s, NH₂); 8.34 (s, H–C(2)). Anal. calc. for C₁₁H₁₃ClN₄O₃ (284.70): C 46.41, H 4.60, N 19.68; found: C 46.50, H 4.71, N 19.61.

Data of 9: M.p. 189–191°. UV (EtOH): 265 (14300). ¹H-NMR ((D₆)DMSO): 2.02–2.26 (*m*, 2 H–C(3′)); 3.38–3.60 (*m*, 2 H–C(5′)); 4.40–4.55 (*m*, H–C(4′), H–C(2′)); 6.18 (*d*, *J* = 4.3, H–C(1′)); 6.38 (*s*, H–C(6)); 6.76 (*br. s*, NH₂); 8.12 (*s*, H–C(2)). Anal. calc. for C₁₁H₁₃ClN₄O₃ (284.70): C 46.41, H 4.60, N 19.68; found: C 46.53, H 4.69, N 19.62.

7-Amino-3-(3-deoxy-β-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (7) and 7-Amino-3-(3-deoxy-α-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (10). To compound **6** or **9** (30 mg, 0.11 mmol) in abs. EtOH (10 ml), 1*N* NaOH (1 ml) and a cat. amount of 10% Pd/C were added. The mixture was hydrogenated at 40 psi for 6 h. The catalyst was removed by filtration and the filtrate evaporated. Purification by FC (CHCl₃/MeOH 94:6) gave **7** (20 mg, 73%) or **10** (16 mg, 55%) as colorless solids.

Data of 7: M.p. 183–185°. UV (H₂O): 262 (17000). ¹H-NMR ((D₆)DMSO): 1.87–2.03 (*m*, 1 H–C(3′)); 2.18–2.36 (*m*, 1 H–C(3′)); 3.42–3.58 (*m*, 1 H–C(5′)); 3.62–3.77 (*m*, 1 H–C(5′)); 4.27–4.42 (*m*, H–C(4′)); 4.57–4.70 (*m*, H–C(2′)); 5.87 (*d*, *J* = 2.9, H–C(1′)); 6.32–6.48 (*m*, H–C(6), NH₂); 7.80 (*d*, *J* = 5.5, H–C(5)); 8.27 (*s*, H–C(2)). Anal. calc. for C₁₁H₁₄N₄O₃ (250.25): C 52.79, H 5.64, N 22.39; found: C 52.91, H 5.70, N 22.22.

Data of 10: M.p. 177–179°. UV (H₂O): 261 (13400). ¹H-NMR ((D₆)DMSO): 2.02–2.25 (*m*, 2 H–C(3′)); 3.32–3.62 (*m*, 2 H–C(5′)); 4.38–4.56 (*m*, H–C(4′), H–C(2′)); 6.23–6.40 (*m*, H–C(1′), H–C(6), NH₂); 7.80 (*d*, *J* = 5.3, H–C(5)); 8.10 (*s*, H–C(2)). Anal. calc. for C₁₁H₁₄N₄O₃ (250.25): C 52.79, H 5.64, N 22.39; found: C 52.88, H 5.68, N 22.18.

5-Chloro-(cycloheptylamino)-3-(3-deoxy-β-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (11) and 5-Chloro-7-(cyclooctylamino)-3-(3-deoxy-β-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (13). To **5** (125 mg, 0.41 mmol), cycloheptylamine or cyclooctylamine (10 ml) was added, and the mixture was heated at 105° for 16 h. The excess amine was evaporated and the residue purified by FC (CHCl₃/MeOH 99:1) to give colorless solids which were crystallized from Et₂O to yield **11** (115 mg, 73%) and **13** (122 mg, 76%).

Data of 11: M.p. 140–142°. UV (EtOH): 271 (16000), 286 (15200). ¹H-NMR ((D₆)DMSO): 1.40–1.75 (*m*, 10 cycloheptyl H); 1.82–2.01 (*m*, 2 cycloheptyl H, 1 H–C(3′)); 2.16–2.32 (*m*, 1 H–C(3′)); 3.46–3.59 (*m*, 1 H–C(5′)); 3.62–3.77 (*m*, 1 H–C(5′)); 3.98–4.22 (*m*, 1 cycloheptyl H); 4.28–4.42 (*m*, H–C(4′)); 4.47–4.59 (*m*, H–C(2′)); 5.85 (*s*, H–C(1′)); 6.35 (*s*, H–C(6)); 6.93 (*d*, *J* = 8.4, NH₂); 8.35 (*s*, H–C(2)). Anal. calc. for C₁₈H₂₅ClN₄O₃ (380.87): C 56.76, H 6.62, N 14.71; found: C 56.88, H 6.79, N 14.60.

Data of 13: M.p. 131–132°. UV (EtOH): 271 (20100), 286 (19200). ¹H-NMR ((D₆)DMSO): 1.43–1.99 (*m*, 14 cyclooctyl H, 1 H–C(3′)); 2.16–2.32 (*m*, 1 H–C(3′)); 3.45–3.60 (*m*, 1 H–C(5′)); 3.64–3.79 (*m*, 1 H–C(5′)); 4.01–4.26 (*m*, 1 cyclooctyl H); 4.29–4.42 (*m*, H–C(4′)); 4.48–4.61 (*m*, H–C(2′)); 5.86 (*s*, H–C(1′)); 6.36 (*s*, H–C(6)); 6.95 (*d*, *J* = 8.4, NH₂); 8.36 (*s*, H–C(2)). Anal. calc. for C₁₉H₂₇ClN₄O₃ (394.90): C 57.79, H 6.89, N 14.19; found: C 57.91, H 6.97, N 14.28.

7-(Cycloheptylamino)-3-(3-deoxy-β-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (12) and 7-(Cyclooctylamino)-3-(3-deoxy-α-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (14). As described for **6** or **9**, with **11** or **13** (0.17 mmol), abs. EtOH (15 ml), 1*N* NaOH (2 ml) and a cat. amount of 10% Pd/C. Purification by FC (CHCl₃/MeOH 99:1) gave **12** (36 mg, 59%) or **14** (38 mg, 65%), both as colorless solids.

Data of 12: M.p. 140–142°. UV (EtOH): 267 (12100), 288 (14500). ¹H-NMR ((D₆)DMSO): 1.40–1.79 (*m*, 10 cycloheptyl H); 1.81–2.10 (*m*, 2 cycloheptyl H, 1 H–C(3′)); 2.19–2.39 (*m*, 1 H–C(3′)); 3.43–3.60 (*m*, 1 H–C(5′)); 3.62–3.80 (*m*, 1 H–C(5′)); 3.92–4.15 (*m*, 1 cycloheptyl H); 4.27–4.46 (*m*, H–C(4′)); 4.56–4.71 (*m*, H–C(2′)); 5.89 (*s*, H–C(1′)); 6.34 (*d*, *J* = 4.6, H–C(6)); 6.49 (*d*, *J* = 8.5, NH₂); 7.87 (*d*, *J* = 4.6, H–C(5)); 8.30 (*s*, H–C(2)). Anal. calc. for C₁₈H₂₆N₄O₃ (346.42): C 62.41, H 7.56, N 16.17; found: C 62.58, H 7.77, N 16.01.

Data of 14: M.p. 136–137°. UV (EtOH): 267 (15000), 288 (18000). ¹H-NMR ((D₆)DMSO): 1.48–2.06 (*m*, 14 cyclooctyl H, 1 H–C(3′)); 2.16–2.36 (*m*, 1 H–C(3′)); 3.42–3.59 (*m*, 1 H–C(5′)); 3.62–3.79 (*m*, 1 H–C(5′)); 3.98–4.22 (*m*, 1 cyclooctyl H); 4.28–4.34 (*m*, H–C(4′)); 4.55–4.71 (*m*, H–C(2′)); 5.88 (*s*, H–C(1′)); 6.34 (*d*, *J* = 4.5, H–C(6)); 6.48 (*d*, *J* = 8.5, NH₂); 7.86 (*d*, *J* = 4.5, H–C(5)); 8.29 (*s*, H–C(2)). Anal. calc. for C₁₉H₂₈N₄O₃ (360.45): C 63.31, H 7.83, N 15.54; found: C 63.42, H 7.94, N 15.25.

Enzyme Assay. The method used for determination of the activity against ADA has been described in a preceding paper [22].

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