Synthesis of Novel 2-Aryl AICAR Derivatives

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Received 7 June 2004; revised 14 July 2004

Abstract: Novel 2-aryl AICAR (5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamide) derivatives **8** were synthesized via the Suzuki–Miyaura cross-coupling reactions of 8-bromoadenosine. Following conversion of the adenine moiety of **4** to hypoxanthine (**5**) and the introduction of a MEM group, hydrolysis of **7** gave desired 2-aryl AICAR derivatives **8**.

Key words: nucleosides, cross-coupling, palladium, inosine, adenosine

A number of nucleotide analogues with modified purines have been known as potent biologically active compounds. Although 8-substituted purine derivatives are of great interest because of their capacity of changing the *syn*/*anti* conformation,[1] purine derivatives with C-linked substituents at position 8 were less reported than 2- or 6-substituted purines. Among them, Verlinde et al. synthesized 8-phenyladenosine and 8-(thien-2-yl)adenosine via the Stille-type cross-coupling reactions of tri-*O*-acetyl-8-bromoadenosine.[2] Very recently, 8-arylguanosine and 8-aryladenosines were synthesized via the Suzuki–Miyaura cross-coupling reaction.[3]

AMP-activated protein kinase (AMPK)[4] is considered to be a master switch, regulating key proteins in metabolic pathways, for example, hepatic fatty acid oxidation, lipogenesis, triglyceride synthesis and skeletal muscle fatty acid oxidation.[5] The activation of AMPK occurs under conditions such as hypoxia, ischemia, heat shock, inhibition of glycolysis and muscle contraction.[6] Because muscle contraction in exercise brings anti-diabetic effects, physical exercise is one of the most effective therapy in the patients of type 2 diabetes. AMPK is considered to be an important target for the treatment of type 2 diabetes since this kinase is activated during physical exercise.[7]

5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICAR; R^1 = H in **8**) is a constituent of AICA-ribotide, which is a biosynthetic precursor of purine nucleotides (AMP, GMP). AICAR is receiving great attention since it is an activatior of AMPK. In the course of exploring new AICAR analogues, we planned to synthesize 2-aryl AICAR derivatives that might provide a potential lead compound to new types of drugs. From the viewpoint of green chemistry, the Suzuki–Miyaura cross-coupling is more suitable than the Stille-type cross-coupling because boronic acid derivatives used in the Suzuki coupling are non-toxic in contrast to organotin compounds used in the Stille-type cross-coupling reactions.

Since we had already established the facile synthesis of AICAR from inosine,[8] we examined the Suzuki coupling reaction of 8-bromo-*N*-MEM-inosine first, but this reaction did not proceed. Next, we changed the strategy of introducing aryl groups to 8-bromoadenosine.

By the action of bromine in NaOAc buffer, 8-bromoadenosine (**2**) was obtained from adenosine (**1**) in 81% yield. The Suzuki coupling reaction of **2** was conducted using $Pd(Ph_3P)_4$ as the catalyst and K_2CO_3 as the base in DME–H_2O (2:1) at 90 °C (Scheme 1). The yields of 8-aryladenosines **3** from 8-bromoadenosine (**2**) and several boronic acids are given in Table 1.

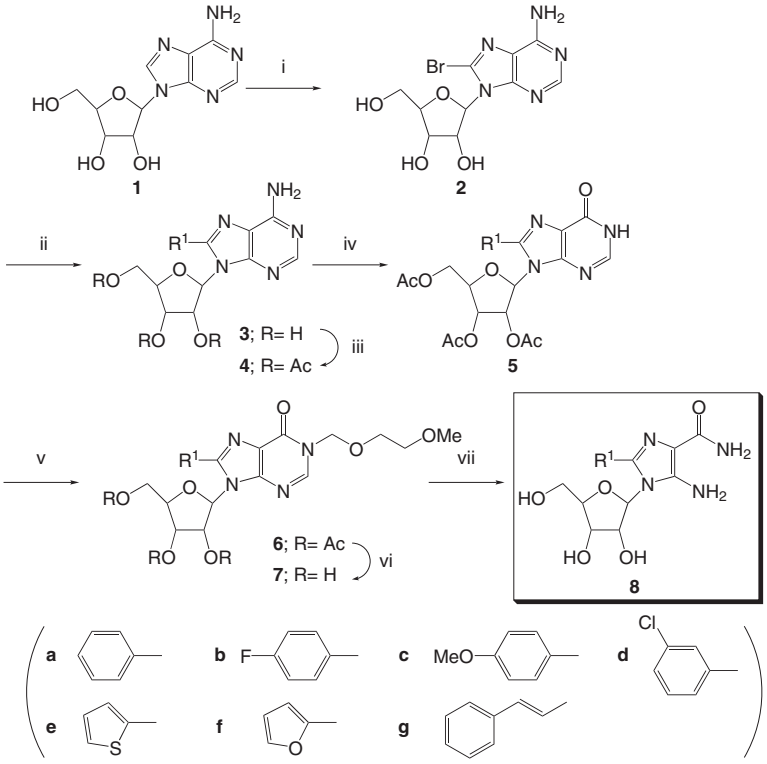
The yields with boronic acids having the electron-rich substituents (4-methoxyphenyl **3c**) are relatively higher than those with boronic acids having the electron-deficient substituents (3-chlorophenyl **3d**, phenylvinyl **3g**) and heterocyclic ones (thienyl **3e**, furyl **3f**). Due to the lower solubility of compounds **3e**–**3g** in $CHCl_3$ and MeOH, the column chromatography operation with them was more difficult than that with **3a**–**3d**. In order to increase the solubility of **3** in organic solvents, we conducted the acetylation of the sugar hydroxy groups in the next step.

Table 1 Yields of the Intermediates for the Syntheses of **8a**–**8g** (%)

R^1	**2** → **3**	**3** → **4**	**4** → **5**	**5** → **6**	**6** → **8**
a (Phenyl)	81	77	98	64	35
b (4-Fluorophenyl)	75	87	76	61	35
c (4-Methoxyphenyl)	73	91	79	75	22
d (3-Chlorophenyl)	63	82	90	68	50
e (2-Thienyl)	40	94	72	75	48
f (2-Furyl)	26	80	67	67	24
g (Phenylvinyl)	47	94	90	57	79

Acetylation of **3** with Ac_2O in pyridine gave more lipophilic tri-*O*-acetyladenosine derivatives **4** which were easily handled in organic solvents. The oxidation reaction, converting adenine moiety of **4** to hypoxanthine moiety, with $NaNO_2$ in HOAc gave tri-*O*-acetyl-8-arylinosines **5** without the deprotection of acetyl groups. In order to convert hypoxanthine moiety of **5** to the desired 5-amino-4-carboxamide-imidazole moiety, triacetate **5** was treated

SYNTHESIS 2004, No. 17, pp 2799–2804
Advanced online publication: 29.09.2004
DOI: 10.1055/s-2004-831249; Art ID: F08404SS



[a] Reagents and conditions: (i) Br_2, NaOAc buffer (81%); (ii) $R^1B(OH)_2$, K_2CO_3, $Pd(Ph_3P)_4$, DME–H_2O(2:1); (iii) Ac_2O, pyridine; (iv) $NaNO_2$, AcOH; (v) MEMCl, *i*Pr_2NEt, CH_2Cl_2; (vi) NH_3aq/MeOH; (vii) 0.2N-NaOHaq, reflux

Scheme 1

with 2-methoxyethoxymethyl chloride in the presence of *i*-Pr_2NEt in CH_2Cl_2.[8] Compounds **6** were deacetylated to increase the solubility in water since the final step reactions should be conducted homogeneously in an aqueous reaction medium. The hydrolysis reactions of **7** with 0.2 N NaOH gave desired 2-aryl AICAR derivatives **8**, which were purified by column chromatography except **8g**, which was purified by crystallization.

2-Aryl AICAR derivatives **8** of completely novel type nucleoside derivatives are expected to have interesting biological activities. The biological evaluation of these compounds will be reported elsewhere.

^{1}H NMR and ^{13}C NMR spectra were recorded with an JEOL alpha-500 (at 500 MHz for ^{1}H and 126 MHz for ^{13}C) and a JEOL-JNM-EX-270 (at 270 MHz for ^{1}H and 68 MHz for ^{13}C). Chemical shifts for ^{1}H and ^{13}C NMR are given in ppm (δ) relative to TMS as internal standard. *J* Values are given in Hz. Optical rotation was measured with a JASCO DIP-1030 (with a 1 dm cell). HRMS were done with a JEOL JMS-DX-300. TLC was carried out using Silica gel 60-F_{254} (Merck). Column chromatography was performed on silica gel (Wako Pure Chemical Industries, Ltd. Wakogel C-300). Almost all of reagents were purchased from Wako Pure Chemical Industries, Ltd., Nacalai Tesque, Aldrich Chemical Company, Inc.

8-Bromoadenosine (2); Typical Procedure

Saturated bromine–water (370 mL) was added slowly to a suspension of adenosine (10 g, 37.4 mmol) in NaOAc buffer (225 mL, 0.5 M, pH 4). The mixture was stirred at r.t. for 47 h. The solution was decolorized by the addition of 5 N $NaHSO_3$, and the pH of the solution was then adjusted to 7 with 2 N NaOH. The resulting solids were collected by filtration, successively washed with water and acetone, and dried in vacuo to yield **2** (10.5 g, 81%).

^{1}H NMR (270 MHz, DMSO-d_6): δ = 8.11 (s, 1 H, H-2), 7.56 (br s, 2 H, NH_2), 5.83 (d, *J* = 6.5 Hz, 1 H, 2′-OH), 5.52 (dd, *J* = 8.6, 4.0 Hz, 1 H, 5′-OH), 5.47 (d, H-1′, *J* = 6.3 Hz, 1 H), 5.24 (d, *J* = 4.6 Hz, 1 H, 3′-OH), 5.08 (dd, 1 H, H-2′), 4.22–4.16 (m, 1 H, H-3′), 3.98 (dd, *J* = 6.3, 4.0 Hz, 1 H, H-4′), 3.74–3.46 (m, 2 H, H-5′).

8-Phenyladenosine (3a), Coupling Reaction; Typical Procedure

A mixture of 1,2-dimethoxyethane–water (2:1, 11 mL) was added to a flask containing 8-bromoadenosine (1.0 g, 2.89 mmol), phenylboronic acid (545 mg, 4.33 mmol), and K_2CO_3 (2.4 g, 17.3 mmol). The mixture was stirred for 10 min at r.t. To the solution was added $Pd(PPh_3)_4$ (334 mg, 0.29 mmol) and the mixture was stirred for 16 h at 90 °C. The reaction mixture was cooled to r.t. and filtered through Celite. The solvent was evaporated and the residue was chromatographed on silica gel ($CHCl_3$–MeOH, 8:1) to give **3a** (808 mg, 81%).

^{1}H NMR (270 MHz, DMSO-d_6): δ = 8.16 (s, 1 H, H-2), 7.78–7.74 (m, 2 H, Ph), 7.61–7.58 (m, 3 H, Ph), 7.50 (br s, 2 H, NH_2), 5.83–5.73 (m, 2 H), 5.47 (d, *J* = 6.3 Hz, 1 H), 5.19 (dd, 1 H), 5.13 (d, *J* = 4.3 Hz, 1 H), 4.20–4.15 (m, 1 H), 3.94 (dd, 1 H), 3.74–3.66 (m, 1 H), 3.61–3.50 (m, 1 H).

8-(4-Fluorophenyl)adenosine (3b)

Prepared from **2** and 4-fluorophenylboronic acid in 75% yield according to the typical procedure for **3a**.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 8.15 (s, 1 H, H-2), 7.85–7.76 (dd, *J* = 8.9, 5.6 Hz, 2 H, Ph), 7.51 (br s, 2 H, NH_2), 7.49–7.40 (t, *J* = 8.9 Hz, 2 H, Ph), 5.79 (dd, *J* = 8.9, 3.3 Hz, 1 H), 5.72 (d, *J* = 7.3

Hz, 1 H), 5.47 (d, *J* = 6.6 Hz, 1 H), 5.21–5.12 (m, 2 H), 4.20–4.14 (m, 1 H), 3.95 (dd, 1 H), 3.75–3.65 (m, 1 H), 3.61–3.50 (m, 1 H).

8-(4-Methoxyphenyl)adenosine (3c)
Prepared from **2** and 4-methoxyphenylboronic acid in 73% yield according to the typical procedure for **3a**.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 8.13 (s, 1 H, H-2), 7.70 (d, *J* = 7.9 Hz, 2 H, Ph), 7.44 (br s, 2 H, NH_2), 7.14 (d, *J* = 8.2 Hz, 2 H, Ph), 5.82 (dd, *J* = 9.0, 3.1 Hz, 1 H), 5.76 (d, *J* = 6.9 Hz, 1 H), 5.45 (d, *J* = 6.3 Hz, 1 H), 5.18 (dd, 1 H), 5.12 (d, *J* = 4.3 Hz, 1 H), 4.22–4.14 (m, 1 H), 3.97–3.91 (m, 1 H), 3.75–3.64 (m, 1 H), 3.62–3.50 (m, 1 H), 3.32 (s, 3 H).

8-(3-Chlorophenyl)adenosine (3d)
Prepared from **2** and 3-chlorophenylboronic acid in 63% yield according to the typical procedure for **3a**.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 8.17 (s, 1 H, H-2), 7.82–7.59 (m, 4 H, Ph), 7.55 (br s, 2 H, NH_2), 5.82–5.71 (m, 2 H), 5.50 (d, *J* = 6.3 Hz, 1 H), 5.21–5.11 (m, 2 H), 4.20–4.13 (m, 1 H), 4.00–3.93 (m, 1 H), 3.75–3.65 (m, 1 H), 3.65–3.50 (m, 1 H).

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{16}H_{17}ClN_5O_4$: 378.0969; found: 378.0956.

8-(2-Thienyl)adenosine (3e)
Prepared from **2** and 2-thienylboronic acid in 40% yield according to the typical procedure for **3a**.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 8.14 (s, 1 H, H-2), 7.87 (d, *J* = 5.3 Hz, 1 H, thienyl), 7.65 (d, *J* = 3.6 Hz, 1 H, thienyl), 7.51 (br s, 2 H, NH_2), 7.29 (dd, *J* = 5.8, 4.5 Hz, 1 H, thienyl), 6.00 (d, *J* = 6.9 Hz), 5.79 (dd, *J* = 8.9, 3.6 Hz, 1 H), 5.52 (d, *J* = 6.3 Hz, 1 H), 5.25–5.15 (m, 2 H), 4.25–4.17 (m, 1 H), 3.99 (s, 1 H), 3.76–3.66 (m, 1 H), 3.65–3.51 (m, 1 H).

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{14}H_{16}N_5O_4S_1$: 350.0923; found: 350.0920.

8-(2-Furyl)adenosine (3f)
Prepared from **2** and 2-furylboronic acid in 26% yield according to the typical procedure for **3a**.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 8.14 (s, 1 H, H-2), 8.01 (d, *J* = 1.0 Hz, 1 H, furyl), 7.55 (br s, 2 H, NH_2), 7.14 (d, *J* = 3.3 Hz, 1 H, furyl), 6.77 (dd, *J* = 3.3, 2.0 Hz, 1 H), 6.11 (d, *J* = 6.9 Hz, 1 H), 5.74 (dd, *J* = 8.9, 3.6 Hz, 1 H), 5.43 (d, *J* = 6.6 Hz, 1 H), 5.25–5.07 (m, 2 H), 4.21 (dd, *J* = 6.6, 4.6 Hz, 1 H), 4.00 (d, *J* = 2.3 Hz, 1 H), 3.76–3.65 (m, 1 H), 3.61–3.47 (m, 1 H).

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{14}H_{16}N_5O_5$: 334.1151; found: 334.1151.

8-(2-Phenylvinyl)adenosine (3g)
Prepared from **2** and 2-phenylvinylboronic acid in 47% yield according to the typical procedure for **3a**.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 8.10 (s, 1 H, H-2), 7.80–7.72 (m, 3 H, Ph, PhC*H*=CH), 7.56 (d, *J* = 16.2 Hz, 1 H, PhCH=C*H*), 7.45–7.33 (m, 5 H, Ph, NH_2), 6.13 (d, *J* = 7.3 Hz, 1 H, H-1′), 5.81 (dd, *J* = 7.4, 3.5 Hz, 1 H, 5′-OH), 5.34 (d, *J* = 6.9 Hz, 1 H, 2′-OH), 5.24 (d, *J* = 4.3 Hz, 1 H, 3′-OH), 4.78–4.68 (m, 1 H, H-2′), 4.25–4.15 (m, 1 H, H-3′), 4.07–3.98 (m, 1 H, H-4′), 3.79–3.56 (m, 2 H, H-5′).

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{18}H_{20}N_5O_4$: 370.1515; found: 370.1521.

2′,3′,5′-Tri-*O*-acetyl-8-phenyladenosine (4a), Acetylation of Sugar Moiety; Typical Procedure
A suspension of 8-phenyladenosine (800 mg, 2.33 mmol) in pyridine (7 mL) was stirred at r.t., and then acetic anhydride (1.2 mL) was added. The reaction mixture was stirred at r.t. for 16 h and then the reaction was quenched by pouring into ice. The aqueous phase was extracted with EtOAc (2 × 30 mL), washed with water (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the crude product by flash chromatography (SiO_2, EtOAc) yielded **4a** (847 mg, 77%).

^{1}H NMR (270 MHz, $CHCl_3$): δ = 8.38 (s, 1 H, H-2), 7.78–7.73 (m, 2 H, Ph), 7.60–7.54 (m, 3 H, Ph), 6.49 (dd, *J* = 6.1, 4.4 Hz, 1 H, H-3′), 6.02 (t, *J* = 5.8 Hz, 1 H, H-2′), 5.96 (d, *J* = 4.3 Hz, 1 H, H-1′), 5.71 (s, 2 H, NH_2), 4.59–4.50 (m, 1 H, H-4′), 4.42–4.30 (m, 2 H, H-5′), 2.10 (s, 3 H, acetyl), 2.07 (s, 3 H, acetyl), 2.02 (s, 3 H, acetyl).

2′,3′,5′-Tri-*O*-acetyl-8-(4-fluorophenyl)adenosine (4b)
Prepared from **3b** in 87% yield according to the typical procedure for **4a**.

^{1}H NMR (270 MHz, $CHCl_3$): δ = 8.37 (s, 1 H, H-2), 7.79–7.72 (m, 2 H, Ph), 7.31–7.21 (m, 2 H, Ph), 6.48 (dd, *J* = 6.0, 4.3 Hz, 1 H, H-3′), 6.04 (t, *J* = 5.8 Hz, 1 H, H-2′), 5.87 (d, *J* = 4.3 Hz, 1 H, H-1′), 5.78 (s, 2 H, NH_2), 4.58–4.49 (m, 1 H, H-4′), 4.41–4.31 (m, 2 H, H-5′), 2.11 (s, 3 H, acetyl), 2.06 (s, 3 H, acetyl), 2.02 (s, 3 H, acetyl).

2′,3′,5′-Tri-*O*-acetyl-8-(4-methoxyphenyl)adenosine (4c)
Prepared from **3c** in 91% yield according to the typical procedure for **4a**.

^{1}H NMR (270 MHz, $CHCl_3$): δ = 8.34 (s, 1 H, H-2), 7.79 (d, *J* = 8.6 Hz, 2 H, Ph), 7.06(d, *J* = 8.6 Hz, 2 H, Ph), 6.50 (dd, *J* = 5.8, 4.5 Hz, 1 H, H-3′), 6.04 (t, *J* = 5.9 Hz, 1 H, H-2′), 5.95 (d, 1 H, H-1′), 5.94 (s, 2 H, NH_2), 4.60–4.49 (m, 1 H, H-4′), 4.42–4.30 (m, 2 H, H-5′), 3.90 (s, 3 H, OCH_3), 2.10 (s, 3 H, acetyl), 2.07 (s, 3 H, acetyl), 2.02 (s, 3 H, acetyl).

2′,3′,5′-Tri-*O*-acetyl-8-(3-chlorophenyl)adenosine (4d)
Prepared from **3d** in 82% yield according to the typical procedure for **4a**.

^{1}H NMR (270 MHz, $CHCl_3$): δ = 8.38 (s, 1 H, H-2), 7.78–7.46 (m, 4 H, phenyl), 6.47 (dd, *J* = 6.0, 4.3 Hz, 1 H, H-3′), 6.02 (t, *J* = 5.8 Hz, 1 H, H-2′), 5.92 (d, *J* = 4.3 Hz, 1 H, H-1′), 5.72 (s, 2 H, NH_2), 4.59–4.49 (m, 1 H, H-4′), 4.41–4.32 (m, 2 H, H-5′), 2.11 (s, 3 H, acetyl), 2.06 (s, 3 H, acetyl), 2.05 (s, 3 H, acetyl).

2′,3′,5′-Tri-*O*-acetyl-8-(2-thienyl)adenosine (4e)
Prepared from **3e** in 94% yield according to the typical procedure for **4a**.

^{1}H NMR (270 MHz, $CHCl_3$): δ = 8.35 (s, 1 H, H-2), 7.58 (d, 2 H), 7.22 (t, 1 H), 6.65 (dd, *J* = 5.6, 4.3 Hz, 1 H, H-3′), 6.16 (d, *J* = 4.3 Hz, 1 H, H-1′), 6.06 (t, *J* = 5.6 Hz, 1 H, H-2′), 5.98 (s, 2 H, NH_2), 4.57–4.47 (m, 1 H, H-4′), 4.44–4.32 (m, 2 H, H-5′), 2.12 (s, 3 H, acetyl), 2.05 (s, 3 H, acetyl), 2.04 (s, 3 H, acetyl).

2′,3′,5′-Tri-*O*-acetyl-8-(2-furyl)adenosine (4f)
Prepared from **3f** in 80% yield according to the typical procedure for **4a**.

^{1}H NMR (270 MHz, $CHCl_3$): δ = 8.35 (s, 1 H, H-2), 7.68 (s, 1 H), 7.14 (d, *J* = 3.6 Hz, 1 H), 6.66–6.62 (m, 1 H), 6.57 (dd, *J* = 6.0, 4.3 Hz, 1 H, H-3′), 6.42 (d, *J* = 4.0 Hz, 1 H, H-1′), 6.06 (t, *J* = 5.9 Hz, 1 H, H-2′), 5.78 (s, 2 H, NH_2), 4.56–4.47 (m, 1 H, H-4′), 4.45–4.30 (m, 2 H, H-5′), 2.14 (s, 3 H, acetyl), 2.08 (s, 3 H, acetyl), 2.02 (s, 3 H, acetyl).

2′,3′,5′-Tri-*O*-acetyl-8-phenylvinyladenosine (4g)
Prepared from **3g** in 94% yield according to the typical procedure for **4a**.

^{1}H NMR (270 MHz, $CHCl_3$): δ = 8.33 (s, 1 H, H-2), 7.85 (d, *J* = 15.8 Hz, 1 H, PhC*H*=CH), 7.65–7.53 (m, 2 H, Ph), 7.47–7.36 (m, 3 H, Ph), 7.11 (d, *J* = 15.5 Hz, 1 H, PhCH=C*H*), 6.42 (t, *J* = 5.3 Hz, 1 H,

H-3′), 6.18 (d, *J* = 4.9 Hz, 1 H, H-1′), 6.06 (t, *J* = 5.4 Hz, 1 H, H-2′), 5.59 (s, 2 H, NH_2), 4.55–4.33 (m, 3 H, H-4′, H-5′), 2.16 (s, 3 H, acetyl), 2.08 (s, 3 H, acetyl), 1.99 (s, 3 H, acetyl).

2′,3′,5′-Tri-*O*-acetyl-8-(2-phenylvinyl)inosine (5a): Oxidative Deamination; Typical Procedure

A solution of 2′,3′,5′-tri-*O*-acetyl-8-phenyladenosine (**4a**; 840 mg, 1.79 mmol) in HOAc (27 mL) was stirred at r.t., and then $NaNO_2$ (1.26 g) in H_2O (9 mL) was added. After the reaction mixture was stirred at r.t. for 19 h, the solvent was evaporated and water was added to the residue. The aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic layer was washed with sat. aq $NaHCO_3$ (2 × 30 mL) and sat. aq NaCl (2 × 30 mL), and dried ($MgSO_4$). Concentration in vacuo afforded **5a** (826 mg, 98%).

^{1}H NMR (270 MHz, $CHCl_3$): δ = 13.2 (br s, 1 H, 1-NH), 8.23 (s, 1 H, H-2), 7.77–7.62 (m, 2 H, Ph), 7.60–7.55 (m, 3 H, Ph), 6.42 (t, *J* = 5.3 Hz, 1 H, H-3′), 6.03 (d, *J* = 4.6 Hz, 1 H, H-1′), 5.88 (t, *J* = 5.6 Hz, 1 H, H-2′), 4.56–4.49 (m, 1 H, H-4′), 4.40–4.33 (m, 2 H, H-5′), 2.10 (s, 3 H, acetyl), 2.09 (s, 3 H, acetyl), 2.03 (s, 3 H, acetyl).

2′,3′,5′-Tri-*O*-acetyl-8-(4-fluorophenyl)inosine (5b)

Prepared from **4b** in 76% yield according to the typical procedure for **5a**.

^{1}H NMR (270 MHz, $CHCl_3$): δ = 13.1 (br s, 1 H, 1-NH), 8.27 (s, 1 H, H-2), 7.86–7.78 (m, 2 H, H-3″, H-5″), 7.30–7.22 (m, 2 H, H-2″, H-6″), 6.40 (dd, *J* = 6.1, 4.4 Hz, 1 H, H-3′), 5.94 (d, *J* = 4.6 Hz, 1 H, H-1′), 5.90 (t, *J* = 5.7 Hz, 1 H, H-2′), 4.56–4.47 (m, 1 H, H-4′), 4.40–4.31 (m, 2 H, H-5′), 2.11 (s, 3 H, acetyl), 2.06 (s, 3 H, acetyl), 2.04 (s, 3 H, acetyl).

2′,3′,5′-Tri-*O*-acetyl-8-(4-methoxyphenyl)inosine (5c)

Prepared from **4c** in 79% yield according to the typical procedure for **5a**.

^{1}H NMR (270 MHz, $CHCl_3$): δ = 12.9 (br s, 1 H, 1-NH), 8.15 (s, 1 H, H-2), 7.76 (d, *J* = 8.6 Hz, 2 H, H-3″, H-5″), 7.06 (d, *J* = 8.9 Hz, 2 H, Ph), 6.42 (dd, *J* = 5.9, 4.6 Hz, 1 H, H-3′), 6.01 (d, *J* = 5.0 Hz, 1 H, H-1′), 5.89 (t, *J* = 5.6 Hz, 1 H, H-2′), 4.56–4.47 (m, 1 H, H-4′), 4.40–4.31 (m, 2 H, H-5′), 3.90 (s, 3 H, OCH_3), 2.10 (s, 3 H, acetyl), 2.07 (s, 3 H, acetyl), 2.03 (s, 3 H, acetyl).

2′,3′,5′-Tri-*O*-acetyl-8-(3-chlorophenyl)inosine (5d)

Prepared from **4d** in 90% yield according to the typical procedure for **5a**.

^{1}H NMR (270 MHz, $CHCl_3$): δ = 13.0 (br s, 1 H, 1-NH), 8.19 (s, 1 H, H-2), 7.82 (t, 1 H), 7.81–7.71 (m, 1 H), 7.57–7.46 (m, 2 H), 6.38 (dd, *J* = 5.9, 4.6 Hz, 1 H, H-3′), 5.98 (d, *J* = 4.6 Hz, 1 H, H-1′), 5.87 (t, *J* = 5.6 Hz, 1 H, H-2′), 4.57–4.47 (m, 1 H, H-4′), 4.41–4.32 (m, 2 H, H-5′), 2.12 (s, 3 H, acetyl), 2.07 (s, 3 H, acetyl), 2.05 (s, 3 H, acetyl).

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{22}H_{22}ClN_4O_8$: 507.1126; found: 507.1107.

2′,3′,5′-Tri-*O*-acetyl-8-(2-thienyl)inosine (5e)

Prepared from **4e** in 72% yield according to the typical procedure for **5a**.

^{1}H NMR (270 MHz, $CHCl_3$): δ = 13.1 (br s, 1 H, 1-NH), 8.26 (s, 1 H, H-2), 7.62–7.58 (m, 2 H), 7.21 (dd, *J* = 5.0, 4.0 Hz, 1 H), 6.54 (dd, *J* = 5.9, 4.6 Hz, 1 H, H-3′), 6.23 (d, *J* = 4.6 Hz, 1 H, H-1′), 5.91 (t, *J* = 5.6 Hz, 1 H, H-2′), 4.54–4.46 (m, 1 H, H-4′), 4.44–4.31 (m, 2 H, H-5′), 2.13 (s, 3 H, acetyl), 2.07 (s, 3 H, acetyl), 2.05 (s, 3 H, acetyl).

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{20}H_{21}N_4O_8S_1$: 477.1080; found: 477.1085.

2′,3′,5′-Tri-*O*-acetyl-8-(2-furyl)inosine (5f)

Prepared from **4f** in 67% yield according to the typical procedure for **5a**.

^{1}H NMR (270 MHz, $CHCl_3$): δ = 12.9 (br s, 1 H, 1-NH), 8.17 (s, 1 H, H-2), 7.66–7.64 (m, 1 H), 7.31 (dd, 1 H), 6.67 (d, *J* = 4.3 Hz, 1 H, H-1′), 6.64–6.61 (m, 1 H), 6.35 (dd, *J* = 6.0, 4.3 Hz, 1 H, H-3′), 5.89 (t, *J* = 6.0 Hz, 1 H, H-2′), 4.55–4.48 (m, 1 H, H-4′), 4.44–4.28 (m, 2 H, H-5′), 2.15 (s, 3 H, acetyl), 2.09 (s, 3 H, acetyl), 2.05 (s, 3 H, acetyl).

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{20}H_{21}N_4O_9$: 461.1308; found: 461.1305.

2′,3′,5′-Tri-*O*-acetyl-8-(2-phenylvinyl)inosine (5g)

Prepared from **4g** in 90% yield according to the typical procedure for **5a**.

^{1}H NMR (270 MHz, $CHCl_3$): δ = 13.2 (br s, 1 H, 1-NH), 8.12 (s, 1 H, H-2), 8.09 (d, 1 H, PhC*H*=CH), 7.65–7.56 (m, 2 H, Ph), 7.47–7.35 (m, 3 H, Ph), 7.06 (d, *J* = 15.8 Hz, 1 H, PhCH=C*H*), 6.31 (t, *J* = 5.4 Hz, 1 H, H-3′), 6.19 (d, *J* = 5.3 Hz, 1 H, H-1′), 5.81 (t, *J* = 5.4 Hz, 1 H, H-2′), 4.53–4.32 (m, 3 H, H-4′, H-5′), 2.17 (s, 3 H, acetyl), 2.10 (s, 3 H, acetyl), 2.01 (s, 3 H, acetyl).

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{24}H_{25}N_4O_8$: 497.1672; found: 497.1677.

2′,3′,5′-Tri-*O*-acetyl-1-[(2-methoxyethoxy)methyl]-8-phenylinosine (6a): Introduction of MEM Group; Typical Procedure

To a solution of **5a** (1.09 g, 2.32 mmol) in CH_2Cl_2 (16 mL) was added *N*,*N*-diisopropylethylamine (605 μL, 3.48 mmol) at r.t,, and 2-methoxyethoxymethyl chloride (317 μL, 2.78 mmol) was added dropwise. The mixture was stirred at r.t. for 3.5 h, then quenched by pouring over water. The aqueous phase was extracted with $CHCl_3$ (2 × 30 mL), washed with 0.05 N HCl (2 × 30 mL) and sat. aq $NaHCO_3$ (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the crude product by flash chromatography (SiO_2, EtOAc–hexane, 4:1) yielded **6a** (820 mg, 64%).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.17 (s, 1 H, H-2), 7.79–7.74 (m, 2 H, Ph), 7.57–7.51 (m, 3 H, Ph), 6.36 (dd, *J* = 5.9, 4.6 Hz, 1 H, H-3′), 5.99 (d, *J* = 4.6 Hz, 1 H, H-1′), 5.86 (t, *J* = 5.4 Hz, 1 H, H-2′), 5.59 (s, 2 H, NCH_2O), 4.55–4.45 (m, 1 H, H-4′), 4.40–4.31 (m, 2 H, H-5′), 3.86–3.81 (m, 2 H, OCH_2CH_2O), 3.57–3.52 (m, 2 H, OCH_2CH_2O), 3.36 (s, 3 H, OCH_3), 2.10 (s, 3 H, acetyl), 2.09 (s, 3 H, acetyl), 2.03 (s, 3 H, acetyl).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 170.5, 169.4, 169.2 (CH_3CO), 156.6 (C-6), 148.1, 147.0 (C-2), 133.1, 130.5, 129.8, 128.9, 128.7, 124.8, 88.0 (C-1′), 80.0 (C-5′), 75.3 (NCH_2O), 72.3 (C-3′), 71.6 (OCH_2CH_2O), 70.6 (C-2′), 69.4 (OCH_2CH_2O), 63.3 (C-4′), 59.2 (OCH_3), 21.0, 20.7, 20.6 (CH_3CO).

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{26}H_{31}N_4O_{10}$: 559.2040; found: 559.2058.

2′,3′,5′-Tri-*O*-acetyl-8-(4-fluorophenyl)-1-[(2-methoxyethoxy)methyl]inosine (6b)

Prepared from **5a** in 61% yield according to the typical procedure for **6a**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.17 (s, 1 H, H-2), 7.77 (dd, *J* = 8.5 Hz, 2 H, Ph), 7.23 (t, *J* = 8.5 Hz, 2 H, Ph), 6.35 (dd, *J* = 6.1, 4.6 Hz, 1 H, H-3′), 5.90 (d, *J* = 4.3 Hz, 1 H, H-1′), 5.87 (t, *J* = 5.8 Hz, 1 H, H-2′), 5.59 (dd, 2 H, NCH_2O), 4.52–4.48 (m, 1 H, H-4′), 4.38–4.33 (m, 2 H, H-5′), 3.83 (dd, *J* = 3.7 Hz, 2 H, OCH_2CH_2O), 3.55–3.53 (m, 2 H, OCH_2CH_2O), 3.37 (s, 3 H, OCH_3), 2.11 (s, 3 H, acetyl), 2.09 (s, 3 H, acetyl), 2.03 (s, 3 H, acetyl).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.5, 169.5, 169.3 (CH_3CO), 165.1, 163.1, 156.6 (C-6), 150.7, 148.1, 147.1 (C-2), 131.9, 131.8 (Ph), 124.8, 116.2, 116.1 (Ph), 88.0 (C-1′), 80.0 (C-5′), 75.2

(NCH_2O), 72.3 (C-3′), 71.5 (OCH_2CH_2O), 70.5 (C-2′), 69.4 (OCH_2CH_2O), 63.1 (C-4′), 59.0 (OCH_3), 20.7, 20.5, 20.4 (CH_3CO).

HRMS (FAB): *m/z* [M + H] calcd for $C_{26}H_{30}N_4O_{10}F$: 577.1946; found: 577.1946.

2′,3′,5′-Tri-*O*-acetyl-1-[(2-methoxyethoxy)methyl]-8-(4-methoxyphenyl)inosine (6c)

Prepared from **5c** in 75% yield according to the typical procedure for **6a**.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.15 (s, 1 H, H-2), 7.72 (d, *J* = 8.9 Hz, 2 H, Ph), 7.04 (d, *J* = 8.9 Hz, 2 H, Ph), 6.36 (dd, *J* = 5.9, 5.0 Hz, 1 H, H-3′), 5.98 (d, *J* = 4.6 Hz, 1 H, H-1′), 5.87 (t, *J* = 5.6 Hz, 1 H, H-2′), 5.58 (s, 2 H, NCH_2O), 4.54–4.46 (m, 1 H, H-4–), 4.39–4.31 (m, 2 H, H-5′), 3.88 (s, 3 H, $PhOCH_3$), 3.84–3.81 (m, 2 H, OCH_2CH_2O), 3.56–3.52 (m, 2 H, OCH_2CH_2O), 3.36 (s, 3 H, OCH_3), 2.10 (s, 3 H, acetyl), 2.09 (s, 3 H, acetyl), 2.03 (s, 3 H, acetyl).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 170.5, 169.4, 169.2 (CH_3CO), 161.3, 156.6 (C-6), 151.6, 148.0, 146.7 (C-2), 131.3 (Ph), 124.7, 120.9, 114.3 (Ph), 87.9 (C-1′), 80.0 (C-5′), 75.2 (NCH_2O), 72.3 (C-3′), 71.6 (OCH_2CH_2O), 70.6 (C-2′), 69.4 (OCH_2CH_2O), 63.3 (C-4′), 59.1 (OCH_3), 55.6 ($PhOCH_3$), 20.9, 20.7, 20.6 (CH_3CO).

HRMS (FAB): *m/z* [M + H] calcd for $C_{27}H_{33}N_4O_{11}$: 589.2146; found: 589.2166.

2′,3′,5′-Tri-*O*-acetyl-8-(3-chlorophenyl)-1-[(2-methoxyethoxy)methyl]inosine (6d)

Prepared from **5d** in 68% yield according to the typical procedure for **6a**.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.18 (s, 1 H, H-2), 7.78–7.44 (m, 4 H, Ph), 6.33 (dd, *J* = 5.9, 4.6 Hz, 1 H, H-3′), 5.94 (d, *J* = 4.6 Hz, 1 H, H-1′), 5.85 (t, *J* = 5.6 Hz, 1 H, H-2′), 5.59 (s, 2 H, NCH_2O), 4.55–4.45 (m, 1 H, H-4′), 4.40–4.31 (m, 2 H, H-5′), 3.85–3.80 (m, 2 H, OCH_2CH_2O), 3.57–3.52 (m, 2 H, OCH_2CH_2O), 3.36 (s, 3 H, OCH_3), 2.11 (s, 3 H, acetyl), 2.09 (s, 3 H, acetyl), 2.07 (s, 3 H, acetyl).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 170.5, 169.4, 169.3 (CH_3CO), 156.5 (C-6), 150.0, 148.2, 147.3 (C-2), 134.8, 130.6, 130.3, 130.2, 129.9, 127.9, 87.9 (C-1′), 80.1 (C-5′), 75.3 (NCH_2O), 72.4 (C-3′), 71.6 (OCH_2CH_2O), 70.5 (C-2′), 69.5 (OCH_2CH_2O), 63.3 (C-4′), 59.2 (OCH_3), 20.9, 20.7, 20.6 (CH_3CO).

HRMS (FAB): *m/z* [M + H] calcd for $C_{27}H_{30}ClN_4O_{10}$: 593.1650; found: 593.1637.

2′,3′,5′-Tri-*O*-acetyl-1-[(2-methoxyethoxy)methyl]-8-(2-thienyl)inosine (6e)

Prepared from **5e** in 75% yield according to the typical procedure for **6a**.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.15 (s, 1 H, H-2), 7.59–7.54 (m, 2 H), 7.21 (dd, 1 H), 6.46 (dd, *J* = 5.9, 5.0 Hz, 1 H, H-3′), 6.19 (d, *J* = 4.6 Hz, 1 H, H-1′), 5.87 (t, *J* = 5.6 Hz, 1 H, H-2′), 5.58 (s, 2 H, NCH_2O), 4.51–4.30 (m, 3 H, H-4′, H-5′), 3.84–3.80 (m, 2 H, OCH_2CH_2O), 3.55–3.51 (m, 2 H, OCH_2CH_2O), 3.36 (s, 3 H, OCH_3), 2.16 (s, 3 H, acetyl), 2.12 (s, 3 H, acetyl), 2.07 (s, 3 H, acetyl).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 170.5, 169.4, 169.2 (CH_3CO), 156.4 (C-6), 148.2, 147.1 (C-2), 145.9, 130.2, 129.8, 129.7, 127.8, 124.9, 87.8 (C-1′), 80.2 (C-5′), 75.3 (NCH_2O), 72.2 (C-3′), 71.6 (OCH_2CH_2O), 70.7 (C-2′), 69.5 (OCH_2CH_2O), 63.3 (C-4′), 59.2 (OCH_3), 21.0, 20.8, 20.7 (CH_3CO).

HRMS (FAB): *m/z* [M + H] calcd for $C_{24}H_{29}N_4O_{10}S$: 565.1604; found: 565.1606.

2′,3′,5′-Tri-*O*-acetyl-8-(2-furyl)-1-[(2-methoxyethoxy)methyl]inosine (6f)

Prepared from **5f** in 67% yield according to the typical procedure for **6a**.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.14 (s, 1 H, H-2), 7.62(s, 1 H), 7.26 (d, *J* = 3.3 Hz, 1 H), 6.61 (m, 2 H), 6.30 (dd, *J* = 5.9, 4.3 Hz, 1 H, H-3′), 5.84 (t, *J* = 5.9 Hz, 1 H, H-2′), 5.57 (s, 2 H, NCH_2O), 4.49 (dd, 1 H, H-4′), 4.42–4.28 (m, 2 H, H-5′), 3.84–3.80 (m, 2 H, OCH_2CH_2O), 3.55–3.51 (m, 2 H, OCH_2CH_2O), 3.36 (s, 3 H, OCH_3), 2.14 (s, 3 H, acetyl), 2.09 (s, 3 H, acetyl), 2.06 (s, 3 H, acetyl).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 170.5, 169.4, 169.3 (CH_3CO), 156.4 (C-6), 147.9, 147.0 (C-2), 144.4, 144.1, 142.0, 141.1, 114.5, 112.3, 88.2 (C-1′), 80.0 (C-5′), 75.3 (NCH_2O), 72.8 (C-3′), 71.6 (OCH_2CH_2O), 70.5 (C-2′), 69.5 (OCH_2CH_2O), 63.5 (C-4′), 59.2 (OCH_3), 20.9, 20.8, 20.7 (CH_3CO).

HRMS (FAB): *m/z* [M + H]calcd for $C_{24}H_{30}N_4O_{11}$: 549.1833; found: 549.1821.

2′,3′,5′-Tri-*O*-acetyl-1-[(2-methoxyethoxy)methyl]-8-(2-phenylvinyl)inosine (6g)

Prepared from **5g** in 57% yield according to the typical procedure for **6a**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.11 (s, 1 H, H-2), 8.04 (d, *J* = 15.6 Hz, 1 H, PhC*H*=CH), 7.60–7.57 (m, 2 H, Ph), 7.43–7.35 (m, 3 H, Ph), 7.02 (d, *J* = 15.9 Hz, 1 H, PhCH=C*H*), 6.28 (t, *J* = 5.3 Hz, 1 H, H-2′), 6.15 (d, *J* = 4.9 Hz, 1 H, H-1′), 5.81 (t, *J* = 5.6 Hz, 1 H, H-3′), 5.58 (dd, 2 H, NCH_2O), 4.48 (dd, *J* = 3.7 Hz, 1 H, H-5′), 4.44–4.40 (m, 1 H, H-4′), 4.37–4.32 (m, 1 H, H-5′), 3.84–3.81 (m, 2 H, OCH_2CH_2O), 3.55–3.52 (m, 2 H, OCH_2CH_2O), 3.36 (s, 3 H, OCH_3), 2.17 (s, 3 H, acetyl), 2.10 (s, 3 H, acetyl), 2.03 (s, 3 H, acetyl).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.6, 169.7, 169.5 (CH_3CO), 156.6, 149.2, 147.9, 146.7 (C-2), 139.3 (Ph*C*H=CH), 135.8, 129.6 (Ph), 129.0 (Ph), 127.6 (Ph), 125.1, 111.9 (PhCH=*C*H), 86.5 (C-1′), 80.2 (C-4′), 75.2 (NCH_2O), 72.5 (C-2′), 71.6 (OCH_2CH_2O), 70.5 (C-3′), 69.5 (OCH_2CH_2O), 63.3 (C-5′), 59.2 (OCH_3), 20.8, 20.7, 20.6 (CH_3CO).

HRMS (FAB): *m/z* [M + H] calcd for $C_{28}H_{34}N_4O_{10}$: 585.2196; found: 585.2212.

5-Amino-2-phenyl-1-β-D-ribofuranosylimidazole-4-carboxamide (8a): Ring-Opening Reaction; Typical Procedure

A solution of **6a** (820 mg, 1.47 mmol) in MeOH (15 mL) was stirred at r.t., and then aq NH_3 (3 mL) was added. The reaction mixture was stirred at r.t. for 17 h and concentrated in vacuo to give white solid. Successively, the solid was suspended with 0.2 N aq NaOH and heated under reflux for 1 h. After cooling, the reaction mixture was neutralized with 3 N HCl, and concentrated in vacuo. The residue was extracted with hot EtOH, filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography (SiO_2, $CHCl_3$–MeOH, 7:1) yielded **1a** (171 mg, 35% for 2 steps); $[\alpha]_D^{25}$ –8.4 (*c* = 0.5, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.60–7.56 (m, 2 H, Ph), 7.49–7.42 (m, 3 H, Ph), 6.80 (br d, 2 H, $CONH_2$), 6.27 (s, 2 H, NH_2), 5.66 (s, 1 H, 5′-OH), 5.59 (d, *J* = 6.4 Hz, 1 H, 2′-OH), 5.53 (d, *J* = 5.8 Hz, 1 H, H-1′), 5.10 (s, 1 H, 3′-OH), 4.66 (dd, *J* = 9.2, 5.8 Hz, 1 H, H-2′), 4.07 (s, 1 H, H-3′), 3.85 (s, 1 H, H-4′), 3.68–3.60 (m, 2 H, H-5′).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.9 ($CONH_2$), 144.2 (C-4), 139.7 (C-2), 130.3 (Ph), 129.2 (Ph), 128.4 (Ph), 112.3 (C-5), 88.9 (C-1′), 85.5 (C-4′), 70.3 (C-3′), 69.6 (C-2′), 61.0 (C-5′).

HRMS (FAB): *m/z* [M + H] calcd for $C_{15}H_{19}N_4O_5$: 335.1355; found: 335.1349.

5-Amino-2-(4-fluorophenyl)-1-β-D-ribofuranosylimidazole-4-carboxamide (8b)
Prepared from **6b** in 35% yield (for 2 steps) according to the typical procedure for **8a**.

$[\alpha]_D^{25}$ –16 (*c* = 0.2, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.61 (dd, *J* = 8.6, 5.5 Hz, 2 H, Ph), 7.31 (t, *J* = 8.8 Hz, 2 H, Ph), 6.73 (br d, 2 H, $CONH_2$), 6.26 (s, 2 H, NH_2), 5.64 (s, 1 H, 5′-OH), 5.54 (s, 1 H, 2′-OH), 5.52 (s, 1 H, H-1′), 5.09 (s, 1 H, 3′-OH), 4.63 (dd, *J* = 6.9, 6.6 Hz, 1 H, H-2′), 4.06 (dd, 1 H, H-3′), 3.85 (d, 1 H, H-4′), 3.67–3.60 (m, 2 H, H-5′).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.8 ($CONH_2$), 161.2 (C-4″), 144.2 (C-4), 138.7 (C-2), 131.4 (Ph), 126.8 (C-1″), 115.4 (Ph), 112.2 (C-5), 88.8 (C-1′), 85.6 (C-4′), 70.2 (C-3′), 69.7 (C-2′), 60.9 (C-5′).

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{15}H_{18}FN_4O_5$: 353.1261; found: 353.1270.

5-Amino-2-(4-methoxyphenyl)-1-β-D-ribofuranosylimidazole-4-carboxamide (8c)
Prepared from **6c** in 22% yield (for 2 steps) according to the typical procedure for **8a**.

$[\alpha]_D^{25}$ –5.7 (*c* = 0.5, MeOH).

^{1}H NMR (270 MHz, DMSO-d_6): δ = 7.49 (d, *J* = 7.9 Hz, 2 H, Ph), 7.02 (d, *J* = 7.9 Hz, 2 H, Ph), 6.76 (br d, 2 H, $CONH_2$), 6.20 (s, 2 H, NH_2), 5.63 (s, 1 H, 5′-OH), 5.55 (d, *J* = 7.6 Hz, 1 H, H-1′), 5.49 (d, *J* = 6.3 Hz, 1 H, 2′-OH), 5.09 (d, *J* = 4.3 Hz, 1 H, 3′-OH), 4.63 (m, 1 H, H-2′), 4.07 (m, 1 H, H-3′), 3.85–3.81 (m, 1 H, H-4′), 3.80 (s, 3 H, O*CH*$_3$), 3.64 (m, 2 H, H-5′).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.9 ($CONH_2$), 159.5 (Ph), 144.0 (C-4), 140.0 (C-2), 130.7 (Ph), 122.6 (Ph), 113.8 (Ph), 112.0 (C-5), 88.8 (C-1′), 85.4 (C-4′), 70.2 (C-3′), 69.6 (C-2′), 61.0 (C-5′), 55.2 (OCH_3).

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{16}H_{21}N_4O_6$: 365.1461; found: 365.1467.

5-Amino-2-(3-chlorophenyl)-1-β-D-ribofuranosylimidazole-4-carboxamide (8d)
Prepared from **6d** in 50% yield (for 2 steps) according to the typical procedure for **8a**.

$[\alpha]_D^{25}$ –5.0 (c 0.6, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.65–7.48 (m, 4 H, Ph), 6.86 (br d, 2 H, $CONH_2$), 6.34 (s, 2 H, NH_2), 5.72 (d, *J* = 6.7 Hz, 1 H, 2′-OH), 5.69 (s, 1 H, 5′-OH), 5.59 (d, *J* = 7.6 Hz, 1 H, H-2′), 5.30–5.00 (m, 1 H, 3′-OH), 4.63 (t, *J* = 6.6 Hz, 1 H, H-2′), 4.07 (d, *J* = 3.6 Hz, 1 H, H-3′), 3.88 (d, *J* = 1.8 Hz, 1 H, H-4′), 3.70–3.60 (m, 2 H, H-5′).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.7 ($CONH_2$), 144.5 (C-4), 138.1 (C-2), 133.2, 132.2, 130.4, 128.7, 128.4, 127.6, 112.6 (C-5), 88.8 (C-1′), 85.7 (C-4′), 70.3 (C-3′), 69.8 (C-2′), 61.0 (C-5′).

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{15}H_{18}ClN_4O_5$: 369.0966; found: 369.0960.

5-Amino-1-β-D-ribofuranosylimidazole-2-(2-thienyl)-4-carboxamide (8e)
Prepared from **6e** in 48% yield (for 2 steps) according to the typical procedure for **8a**.

$[\alpha]_D^{25}$ +12 (*c* = 0.24, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.64 (d, *J* = 5.2 Hz, 1 H, thienyl), 7.36 (d, *J* = 3.7 Hz, 1 H, thienyl), 7.15 (t, *J* = 4.4 Hz, 1 H, thienyl), 6.79 (br d, 2 H, $CONH_2$), 6.34 (s, 2 H, NH_2), 5.80 (d, *J* = 7.6 Hz, 1 H, H-1′), 5.69 (t, *J* = 4.0 Hz, 1 H, 5′-OH), 5.59 (d, *J* = 6.1 Hz, 1 H, 2′-OH), 5.16 (d, *J* = 4.0, 1 H, 3′-OH), 4.58 (dd, *J* = 6.4 Hz, 1 H, H-2′), 4.09 (s, 1 H, H-3′), 3.89 (s, 1 H, H-4′), 3.68–3.63 (m, 2 H, H-5′).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.6 ($CONH_2$), 144.4 (C-4), 133.3 (C-2), 131.8(thienyl), 127.8(thienyl), 127.5 (thienyl), 127.4 (thienyl), 112.3 (C-5), 88.5 (C-1′), 85.7 (C-4′), 70.3 (C-3′), 70.1 (C-2′), 60.9 (C-5′).

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{13}H_{17}N_4O_5S_1$: 341.0920; found: 341.0912.

5-Amino-2-(2-furyl)-1-β-D-ribofuranosylimidazole-4-carboxamide (8f)
Prepared from **6f** in 24% yield (for 2 steps) according to the typical procedure for **8a**.

$[\alpha]_D^{25}$ –10 (*c* = 0.31, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.80 (s, 1 H, furyl), 6.90 (br d, 2 H, $CONH_2$), 6.76 (d, *J* = 3.0 Hz, 1 H, furyl), 6.62 (m, 1 H, furyl), 6.34 (s, 2 H, NH_2), 5.79 (d, *J* = 7.3 Hz, 1 H, H-1′), 5.66 (t, *J* = 4.1 Hz, 1 H, 5′-OH), 5.47 (d, *J* = 6.6 Hz, 1 H, 2′-OH), 5.15 (d, *J* = 4.3 Hz, 1 H, 3′-OH), 4.52 (dd, *J* = 6.6 Hz, 1 H, H-2′), 4.08 (s, 1 H, H-3′), 3.90 (s, 1 H, H-4′), 3.68–3.63 (m, 2 H, H-5′).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.6 ($CONH_2$), 144.1 (C-4), 143.8 (C-2), 143.6 (furyl), 130.6, 112.5, 111.4 (furyl), 110.9 (furyl), 88.8 (C-1′), 85.6 (C-4′), 70.2 (C-3′), 70.1 (C-2′), 60.8 (C-5′).

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{13}H_{17}N_4O_6$: 325.1148; found: 325.1146.

5-Amino-2-(2-phenylvinyl)-1-β-D-ribofuranosylimidazole-4-carboxamide (8g)
Prepared from **6g** in 79% yield (for 2 steps) according to the typical procedure for **8a**.

$[\alpha]_D^{25}$ +60 (*c* = 0.15, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.62, (d, 2 H, Ph), 7.38–7.18 (m, 5 H, Ph, PhC*H*=CH, PhCH=C*H*), 6.81 (br d, 2 H, $CONH_2$), 6.23 (s, 2 H, NH_2), 5.98 (br s, 2 H, OH), 5.82 (d, *J* = 7.3 Hz, 1 H, H-1′), 5.81 (br s, 1 H, OH), 4.30 (t, *J* = 6.8 Hz, 1 H, H-2′), 4.10 (dd, *J* = 6.2, 2.8, 1 H, H-3′), 3.93 (d, *J* = 2.4 Hz, 1 H, H-4′), 3.73–3.64 (m, 2 H, H-5′).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.5 ($CONH_2$), 144.3, 137.1, 136.7, 130.0, 128.7 (Ph), 127.8, 126.7 (Ph), 115.0, 112.5, 87.7 (C-1′), 86.0 (C-4′), 71.8 (C-2′), 69.6 (C-3′), 60.8 (C-5′).

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{17}H_{21}N_4O_5$: 361.1512; found: 361.1513.

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