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Synthesis of 6-(4,5-Dihydrofuran-2-yl)- and 6-(Tetrahydrofuran-2-yl)purine Bases and Nucleosides

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A novel approach to the synthesis of purine derivatives (bases and nucleosides) bearing 4,5-dihydrofuran-2-yl and tetrahydrofuran-2-yl substituents at the 6-position as partly and fully saturated analogues of biologically active 6-hetarylpurine nucleosides is reported. Palladium-catalyzed cross-coupling reactions of 6-iodopurines with new (4,5-dihydrofuran-2-yl)zinc chloride (**1**) gave 6-(4,5-dihydrofuran-2-yl)-purines in high yields. Their catalytic hydrogenation gave 6-(tetrahydrofuran-2-yl)purines. These modified purine bases and nucleosides did not exhibit any significant cytostatic or anti-HCV activity.

Introduction

Purine nucleosides bearing carbon substituents at the 6-position possess a broad spectrum of biological activities, including cytostatic[1] and antimicrobial[2] effects. Recently, we reported the synthesis and cytostatic activities of 6-(hydroxymethyl)-,[3] 6-(fluoromethyl)-,[4] 6-(difluoromethyl)-,[5] and 6-(trifluoromethyl)purine[6] ribonucleosides. 6-Aryl-, 6-hetaryl-, and 6-benzylpurine ribonucleosides[7] were also found to have significant cytostatic effects. Purine ribonucleosides bearing five-membered heterocycles at the 6-position exert strong anti-HCV activities.[8]

In some cases, purines bearing functionalized carbon substituents at the 6-position have been prepared by the direct cross-coupling[9] of 6-halopurines with functionalized organometallics. This approach has been successfully used to synthesize 6-(hydroxymethyl)purines by the coupling of (acyloxymethyl)zinc iodides,[3] 6-(ethoxycarbonylmethyl)-purines by coupling with the Reformatsky reagent,[10] and purin-6-yl amino acids by coupling with protected amino acid organometallics.[11] Other types of substituents have been prepared by functional-group transformation[4,5,12] of 6-(hydroxymethyl)purines or by conjugate addition of nucleophiles to 6-ethynyl- and 6-vinylpurines.[13]

In this work we have combined the structural features of the two above-mentioned types of biologically active compounds, cytostatic 6-(hydroxymethyl)purines and cytostatic,[7] antiviral[8] and antimicrobial[2] 6-(2-furyl)purines. We envisaged purines bearing a 4,5-dihydro- and tetrahydrofuran-2-yl residue at the 6-position (Figure 1) as partially and fully saturated analogues of anti-HCV 6-hetarylpurines[2,7,8] and cyclic (conformationally locked) derivatives of the cytostatic 6-(hydroxymethyl)purines.[3] Herein we report on the development of a synthetic methodology for the title purines bearing saturated five-membered oxygen heterocycles at the 6-position.

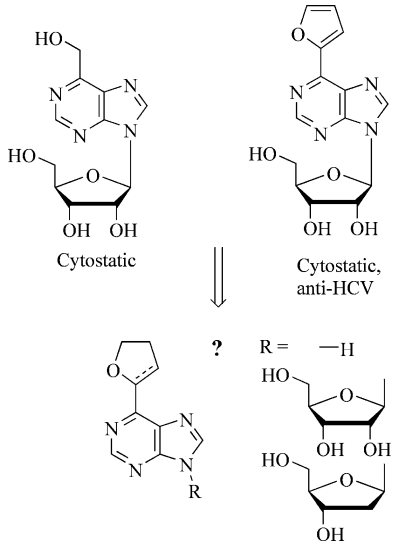

Figure 1. Structures of biologically active purine ribonucleosides and the title compounds.

Results and Discussion

The Negishi cross-coupling of halopurines with organozinc reagents is a very versatile method suitable for the introduction of diverse unfunctionalized and functionalized alkyl, alkenyl, aryl, and hetaryl groups.[14] Several hetaryl-

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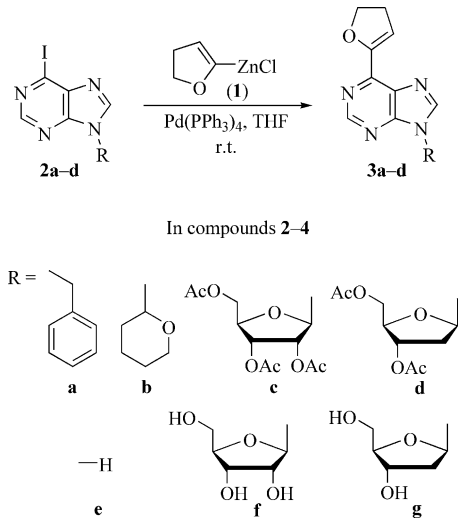
zinc halides generated by dehydrolithiation of five- or six-membered nitrogen heterocycles have been used in cross-coupling reactions with 6-iodopurine derivatives to give the corresponding 6-hetarylpurines in good yields.[15] Therefore, introduction of the 4,5-dihydrofuran-2-yl residue at the 6-position of the purine scaffold by the Neghishi cross-coupling reaction could be a method of choice. 2,3-Dihydrofuran is lithiated predominantly at the 5-position to give 2-lithio-4,5-dihydrofuran.[16] A few examples of the dehydrolithiation of 2,3-dihydrofuran, its further transmetalation to the corresponding organostannyl derivatives, and their use in Stille-type cross-coupling reactions have been described.[17] However, use of the corresponding organozinc derivatives for cross-coupling has not been reported.

We have tried to develop a practical new approach to the synthesis of novel 6-(4,5-dihydrofuran-2-yl)purines based on the cross-coupling reactions of 6-iodopurines with a new organozinc compound, (4,5-dihydrofuran-2-yl)zinc chloride (**1**). According to the literature,[16a] 2,3-dihydrofuran was deprotonated with *t*BuLi in a mixture of pentane and THF at –78 °C. Subsequent addition of $ZnCl_2$ in THF generated organozinc compound **1**. This organometallic reagent was used directly in the Pd-catalyzed cross-coupling with 6-iodopurines **2a**–**d** [9-benzyl-6-iodopurine (**2a**) was used as an example of 9-alkylated purines, 9-THP-6-iodopurine **2b** is a 9-protected purine base, and derivatives **2c** and **2d** are examples of an acyl-protected ribonucleoside and 2-deoxyribonucleoside, respectively; Scheme 1]. The reactions were carried out in THF at ambient temperature with [Pd(PPh_3)$_4$] as catalyst to give 6-(4,5-dihydrofuran-2-yl)purines **3a**–**d** in good yields (Table 1).

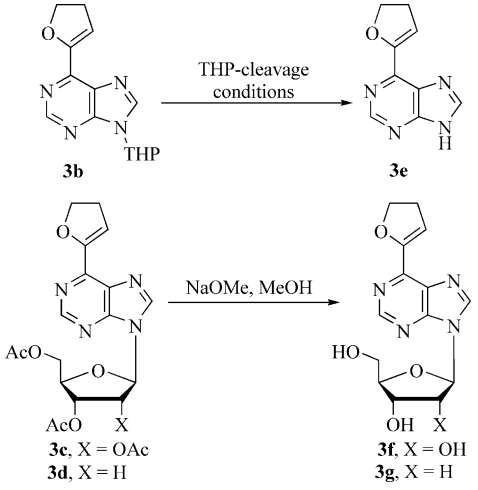


Scheme 1.

For deprotection of 9-THP-purine **3b** to the corresponding 9*H*-purine **3e** (Scheme 2), we first tried our standard methodology,[18] treatment with an acidic cation exchange resin (Dowex, H^+ form) in EtOH. However, no product was isolated, probably due to strong binding to the resin. Therefore, we tried some other acids to cleave the THP group (see Table 2, Entries 1–5). The use of HCl in EtOH led to decomposition to a complex mixture of degradation products. Treatment with trifluoroacetic or acetic acid was more promising and gave the desired purine in around 50% yield. The best yield of 54% was obtained when using TsOH in methanol. Moderate isolated yields were apparently caused by the limited stability of the 4,5-dihydrofuran-2-yl residue under acidic conditions. The acetyl-protected nucleosides **3c**,**d** were deprotected by standard treatment with NaOMe in methanol (Scheme 2) to give free 6-(4,5-dihydrofuran-2-yl)purine nucleosides **3f** and **3g** in good yields (Table 2, Entries 6 and 7).

Table 1. Cross-coupling of the organozinc compound **1** with iodopurine derivatives **2a**–**d**.

Entry	Iodopurine	Product	Yield [%]
1	**2a**	**3a**	78
2	**2b**	**3b**	93
3	**2c**	**3c**	70
4	**2d**	**3d**	70



Scheme 2.

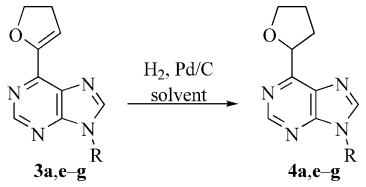
Table 2. Deprotection of purine base **3b** and the nucleosides **3c**,**d**.

Entry	Starting compound	Conditions	Time	Product	Yield [%]
1	**3b**	Dowex (H^+), EtOH	24 h	–	–[a]
2	**3b**	HCl, EtOH	3 h	–	–[b]
3	**3b**	TFA, CH_2Cl_2	1.5 h	**3e**	50
4	**3b**	AcOH, MeOH/H_2O	24 h	**3e**	49
5	**3b**	TsOH, MeOH	20 min	**3e**	54
6	**3c**	NaOMe, MeOH	6 h	**3f**	77
7	**3d**	NaOMe, MeOH	6 h	**3g**	99

[a] The starting compound/product strongly binds to the resin. [b] Decomposition occurred.

Having an efficient methodology for the synthesis of the 6-(4,5-dihydrofuran-2-yl)purines, we next explored the possibility of reducing the double bond of the 4,5-dihydrofuran-2-yl group to give the tetrahydrofuran-2-yl group. Catalytic hydrogenation of 9-benzyl-6-(4,5-dihydrofuran-2-yl)purine (**3a**) on Pd/C under atmospheric pressure proceeded smoothly to give the desired 9-benzyl-6-(tetrahydrofuran-2-yl)purine (**4a**) in a high yield of 92%

(Scheme 3, Table 3, Entry 1). The same conditions were then applied to the reduction of free purine base **3e** and nucleosides **3f**,**g** to give the 6-(tetrahydrofuran-2-yl)purine base **4e** and the nucleosides **4f**,**g** in good yields (Scheme 3, Table 3, Entries 2–4). A new stereogenic center is generated by this reaction at the 2-position of the tetrahydrofuran moiety. In the cases of the nucleosides **4f**,**g**, no diastereoselectivity due to the presence of the homochiral sugar unit was observed, and the compounds were characterized as epimeric mixtures.



Scheme 3.

Table 3. Catalytic hydrogenation of purines **6a**,**e**–**g**.

Entry	Starting compound	Solvent	Product	Yield [%]
1	**3a**	MeOH	**4a**	92
2	**3e**	EtOH/H_2O	**4e**	83
3	**3f**	EtOH/H_2O	**4f**	72
4	**3g**	EtOH/H_2O	**4g**	98

All the substituted purines and nucleosides **3** and **4** were subjected to biological-activity screening. The in vitro cytostatic activity (inhibition of cell growth) of the following cell cultures was studied: (i) Mouse leukemia L1210 cells (ATCC CCL 219), human promyelocytic leukemia HL60 cells (ATCC CCL 240), human cervix carcinoma HeLaS3 cells (ATCC CCL 2.2), and the human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119). Antiviral activities were tested in the HCV genotype 1b replicon.[19] None of the compounds showed any significant activity in any of these assays. This shows that the aromatic nature of the hetaryl substituent in cytostatic and antiviral 6-hetarylpurine nucleosides is crucial for biological activity.

Conclusion

A new organozinc reagent, (4,5-dihydrofuran-2-yl)zinc chloride (**1**), has been generated and used in Pd-catalyzed cross-coupling reactions with 6-iodopurines to afford efficiently the novel 6-(4,5-dihydrofuran-2-yl)purines. Their catalytic hydrogenation afforded fully saturated 6-(tetrahydrofuran-2-yl)purines. The organozinc reagent **1** can serve as a good building block for the attachment of di- and tetrahydrofuran to other types of compounds through a C–C bond.

Experimental Section

General Methods: Melting points were determined with a Kofler block. Optical rotations were measured at 25 °C; $[\alpha]_D^{20}$ values are given in 10^{-1} deg cm^2 g^{-1}. NMR spectra were measured at 400 MHz for ^{1}H and 100.6 MHz for ^{13}C nuclei, or at 500 MHz for ^{1}H and 125.7 MHz for ^{13}C in $CDCl_3$ and [D_6]DMSO. ^{1}H and ^{13}C NMR spectra were referenced to the signal of TMS or to the solvent residual signal. Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz. ^{1}H,^{13}C-HMBC experiments were performed for complete assignment of all signals. The starting compounds **2a**,[20] **2b**,[21] **2c**,[22] and **2d**[23] were prepared according to literature procedures. Mass spectra were measured using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol + thioglycerol matrix) or EI (electron energy 70 eV) techniques with a ZAB-EQ (VG Analytical) spectrometer.

Preparation of Organozinc Reagent 1 from 2,3-Dihydrofuran and Its Cross-Coupling with 6-Iodopurines 2a–d. General Pocedure. 9-Benzyl-6-(4,5-dihydrofuran-2-yl)purine (3a): THF (75 μL) was added to an argon-purged dried flask containing 2,3-dihydrofuran (153 μL, 2 mmol), and the mixture was cooled to –78 °C. Then *t*BuLi (1.3 mL, 2.2 mmol, 1.7 M solution in pentane) was added; after 30 min, a solution of $ZnCl_2$ (315 mg, 2.3 mmol) in THF (3 mL) was added. The mixture was stirred at –78 °C for 5 min and then warmed to room temp. during 1.5 h to generate **1**. Then, **2a** (504 mg, 1.5 mmol) and [$Pd(PPh_3)_4$] (87 mg, 0.075 mmol, 5 mol-%) in THF (2 mL) were added, and the reaction mixture was stirred at room temp. overnight. The solvents were removed in vacuo, and the crude product was diluted with EtOAc, washed with water and brine, dried with $MgSO_4$, and the solvent evaporated. The product was purified by chromatography on silica gel with a hexane/EtOAc gradient (2:1 to 1:2) to give pure **3a** (325 mg, 78%) as white crystals, m.p. 153–155 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.99 (td, $J_{4,5}$ = 9.7, $J_{4,3}$ = 3.2 Hz, 2 H, 4-H DHF), 4.64 (t, $J_{5,4}$ = 9.7 Hz, 2 H, 5-H DHF), 5.45 (s, 2 H, CH_2-Ph), 6.77 (t, $J_{3,4}$ = 3.2 Hz, 1 H, 3-H DHF), 7.26–7.38 (m, 5 H, Ph), 8.07 (s, 1 H, 8-H), 8.98 (s, 1 H, 2-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 31.12 (CH_2-4 DHF), 47.08 (CH_2-Ph), 69.89 (CH_2-5 DHF), 110.79 (CH-3 DHF), 127.61 (CH-*o* Ph), 128.42 (CH-*p* Ph), 128.96 (CH-*m* Ph), 129.69 (C-5), 134.91 (C-*i* Ph), 144.35 (CH-8), 147.00 (C-6), 151.62 (C-4), 152.35 (CH-2), 152.54 (C-2 DHF) ppm. FAB-MS: *m*/*z* (%) = 279 (100) [M + H]$^+$, 201 (10), 91 (80). HRMS: calcd. for $C_{16}H_{15}N_4O$ [M + H]$^+$ 279.1246; found 279.1250. IR (KBr): $\tilde{\nu}$ = 3098, 3060, 2927, 1622, 1580, 1501, 1319, 1211, 976 cm^{-1}.

6-(4,5-Dihydrofuran-2-yl)-9-(tetrahydropyran-2-yl)purine (3b): Compound **3b** was prepared according to the procedure described for **3a** starting from **2b** (1.65 g, 5 mmol); **3b** (1.23 g, 93%) was obtained as white crystals, m.p. 99–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.64–1.87 and 2.02–2.20 (2 m, 2 × 3 H, CH_2 THP), 3.00 (td, $J_{4,5}$ = 9.6, $J_{4,3}$ = 3.2 Hz, 2 H, 4-H DHF), 3.80 (td, J = 11.6, 2.8 Hz, 1 H, CH_aH_b-O THP), 4.19 (ddt, J = 12.0, 4.0, 2.0 Hz, 1 H, CH_aH_b-O THP), 4.65 (t, $J_{5,4}$ = 9.6 Hz, 2 H, 5-H DHF), 5.82 (dd, J = 10.4, 2.4 Hz, 1 H, CH-O THP), 6.77 (t, $J_{3,4}$ = 3.2 Hz, 1 H, 3-H DHF), 8.30 (s, 1 H, 8-H), 8.95 (s, 1 H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.69, 24.79 (CH_2 THP), 31.23 (CH_2-4 DHF), 31.79 (CH_2 THP), 68.81 (CH_2-O THP), 70.01 (CH_2-5 DHF), 81.94 (CH-O THP), 110.94 (CH-3 DHF), 129.99 (C-5), 142.36 (CH-8), 147.15 (C-6), 150.90 (C-4), 152.31 (CH-2), 152.64 (C-2 DHF) ppm. FAB-MS: *m*/*z* (%) = 273 (10) [M + H]$^+$, 189 (100), 85 (38). HRMS: calcd. for $C_{14}H_{17}N_4O_2$ [M + H]$^+$ 273.1352; found 273.1357. IR ($CHCl_3$): $\tilde{\nu}$ = 3125, 3062, 2953, 2858, 1625, 1587, 1493, 1410, 1334, 1325, 1146, 913 cm^{-1}.

6-(4,5-Dihydrofuran-2-yl)-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-purine (3c): Compound **3c** was prepared according to the procedure described for **3a** starting from **2c** (7.30 g, 14.48 mmol) to give **3c** (4.52 g, 70%) as a white foam, m.p. 83–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.09, 2.13, 2.16 (3 s, 3 × 3 H, CH_3CO), 3.02 (td, $J_{4,5}$

= 9.6, $J_{4,3}$ = 3.2 Hz, 2 H, 4-H DHF), 4.36–4.51 (m, 3 H, 4′-H and 5′-H), 4.67 (t, $J_{5,4}$ = 9.6 Hz, 2 H, 5-H DHF), 5.68 (t, $J_{3',2'}$ = $J_{3',4'}$ = 5.2 Hz, 1 H, 3′-H), 5.96 (t, $J_{2',1'}$ = $J_{2',3'}$ = 5.2 Hz, 1 H, 2′-H), 6.27 (d, $J_{1',2'}$ = 5.2 Hz, 1 H, 1′-H), 6.80 (t, $J_{3,4}$ = 3.2 Hz, 1 H, 3-H DHF), 8.29 (s, 1 H, 8-H), 8.98 (s, 1 H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.30, 20.47, 20.70 (3× *C*H_3CO), 31.24 (CH_2-4 DHF), 62.93 (CH_2-5′), 70.10 (CH_2-5 DHF), 70.53 (CH-3′), 73.07 (CH-2′), 80.38 (CH-4′), 86.38 (CH-1′), 111.64 (C-3 DHF), 130.38 (C-5), 142.93 (CH-8), 147.50 (C-6), 151.20 (C-4), 152.32 (C-2 DHF), 152.58 (CH-2), 169.29, 169.52, 170.25 (3× CH_3*C*O) ppm. FAB-MS: *m*/*z* (%) = 447 (20) $[M + H]^+$, 259 (45), 189 (48), 139 (100), 97 (85). HRMS: calcd. for $C_{20}H_{23}N_4O_8$ $[M + H]^+$ 447.1516; found 447.1521. IR ($CHCl_3$): $\tilde{\nu}$ = 3119, 1751, 1620, 1587, 1496, 1374, 1049, 937 cm^{-1}.

9-(3,5-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(4,5-dihydrofuran-2-yl)purine (3d): Compound **3d** was prepared according to the procedure described for **3a**. Starting from **2d** (1.10 g, 2.46 mmol), **3d** (0.67 g, 70%) was obtained as a white solid, m.p. 118–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.09, 2.15 (2 s, 2× 3 H, CH_3CO), 2.68 (ddd, J_{gem} = 14.0, $J_{2'b,1'}$ = 5.6, $J_{2'b,3'}$ = 2.4 Hz, 1 H, 2′b-H), 2.98 (ddd, J_{gem} = 14.0, $J_{2'a,1'}$ = 8.0, $J_{2'a,3'}$ = 6.4 Hz, 1 H, 2′a-H), 2.99 (td, $J_{4,5}$ = 9.6, $J_{4,3}$ = 3.2 Hz, 2 H, 4-H DHF), 4.35–4.45 (m, 3 H, 4′-H, 5′-H), 4.65 (t, $J_{5,4}$ = 9.6 Hz, 2 H, 5-H DHF), 5.46 (ddd, $J_{3',2'}$ = 6.4, 2.4, $J_{3',4'}$ = 2.0 Hz, 1 H, 3′-H), 6.53 (dd, $J_{1',2'a}$ = 8.0, $J_{1',2'b}$ = 5.6 Hz, 1 H, 1′-H), 6.78 (t, $J_{3,4}$ = 3.2 Hz, 1 H, 3-H DHF), 8.27 (s, 1 H, 8-H), 8.95 (s, 1 H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.71, 20.86 (2× *C*H_3CO), 31.25 (CH_2-4 DHF), 37.52 (CH_2-2′), 63.63 (CH_2-5′), 70.03 (CH_2-5 DHF), 74.39 (CH-3′), 82.65 (CH-1′), 84.65 (CH-4′), 111.29 (C-3 DHF), 130.52 (C-5), 142.59 (CH-8), 147.41 (C-6), 151.07 (C-4), 152.36 (CH-2), 152.51 (C-2 DHF), 170.19, 170.28 (2× CH_3*C*O) ppm. FAB-MS: *m*/*z* (%) = 389 (20) $[M + H]^+$, 279 (15), 189 (100), 81 (70). HRMS: calcd. for $C_{18}H_{21}N_4O_6$ $[M + H]^+$ 389.1461; found 389.1455. IR ($CHCl_3$): $\tilde{\nu}$ = 1745, 1625, 1587, 1493, 1410, 1233 cm^{-1}.

6-(4,5-Dihydrofuran-2-yl)-9*H*-purine (3e): TsOH (380 mg, 2 mmol) was added to a solution of **3b** (136 mg, 0.5 mmol) in MeOH (5 mL), and the mixture was stirred for 20 min. The solvent was then evaporated under vacuum, and the crude product was purified by chromatography on silica gel with a methanol/chloroform gradient (1:99 to 5:95) to give **3e** (51 mg, 54%) as a white solid, m.p. 206–208 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.87 (td, $J_{4,5}$ = 9.6, $J_{4,3}$ = 3.2 Hz, 2 H, 4-H DHF), 4.53 (t, $J_{5,4}$ = 9.6 Hz, 2 H, 5-H DHF), 6.47 (br. s, 1 H, 3-H DHF), 8.57 (s, 1 H, 8-H), 8.82 (s, 1 H, 2-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO): δ = 30.53 (CH_2-4 DHF), 70.08 (CH_2-5 DHF), 151.85 (C-4), 153.01 (CH-2 and C-2 DHF) ppm. The signals of C-5,6,8 and C-3 DHF were not detected due to N^7,N^9 tautomerism. EI-MS: *m*/*z* (%) = 188 (22) $[M]^+$, 159 (19), 149 (32), 119 (20), 69 (52). HRMS: calcd. for $C_9H_8N_4O$ 188.0698; found 188.0700. IR ($CHCl_3$): $\tilde{\nu}$ = 3444, 3118, 1646, 1602, 1567, 1458, 1385, 1146, 1009, 940 cm^{-1}.

6-(4,5-Dihydrofuran-2-yl)-9-(β-D-ribofuranosyl)purine (3f): NaOMe (1 M in MeOH, 500 μL, 0.5 mmol) was added dropwise to a solution of **3c** (670 mg, 1.5 mmol) in MeOH (15 mL), and the mixture was stirred for 6 h. The solvent was then evaporated under vacuum, and the crude product was purified by chromatography on silica gel with a methanol/chloroform gradient (2:98 to 5:95) to give **3f** (370 mg, 77%) as a white solid, m.p. 188–190 °C. $[\alpha]_D^{20}$= –45.9 (*c* = 2.64, DMSO). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.93 (td, $J_{4,5}$ = 9.6, $J_{4,3}$ = 3.2 Hz, 2 H, 4-H DHF), 3.58 (ddd, J_{gem} = 12.0, $J_{5'b,OH}$ = 5.6, $J_{5'b,4'}$ = 4.0 Hz, 1 H, 5′b-H), 3.70 (ddd, J_{gem} = 12, $J_{5'a,OH}$ = 5.6, $J_{5'a,4'}$ = 3.2 Hz, 1 H, 5′a-H), 3.98 (td, $J_{4',3'}$ = $J_{4',5'b}$ = 4.0, $J_{4',5'a}$ = 3.2 Hz, 1 H, 4′-H), 4.19 (ddd, $J_{3',OH}$ = 4.8, $J_{3',2'}$ = 4.4, $J_{3',4'}$ = 4.0 Hz, 1 H, 3′-H), 4.49 (t, $J_{5,4}$ = 9.6 Hz, 2 H, 5-H DHF), 4.62 (ddd, $J_{2',OH}$ = 6.0, $J_{2',1'}$ = 5.6, $J_{2',3'}$ = 4.4 Hz, 1 H, 2′-H), 5.12 (t, $J_{OH,5'}$ = 5.6 Hz, 1 H, 5′-OH), 5.24 (d, $J_{OH,3'}$ = 4.8 Hz, 1 H, 3′-OH), 5.54 (d, $J_{OH,2'}$ = 6.0 Hz, 1 H, 2′-OH), 6.05 (d, $J_{1',2'}$ = 5.6 Hz, 1 H, 1′-H), 6.78 (t, $J_{3,4}$ = 3.2 Hz, 1 H, 3-H DHF), 8.85, 8.88 (2 s, 2× 1 H, 2-H, 8-H) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 30.67 (CH_2-4 DHF), 61.14 (CH_2-5′), 69.01 (CH_2-5 DHF), 70.18 (CH-3′), 73.68 (CH-2′), 85.61 (CH-4′), 87.57 (CH-1′), 111.26 (C-3 DHF), 129.94 (C-5), 144.95 (CH-8), 146.05 (C-6), 151.10 (C-4), 151.58 (CH-2), 152.09 (C-2 DHF) ppm. FAB-MS: *m*/*z* (%) = 321 (24) $[M + H]^+$, 231 (33), 177 (62), 154 (100), 137 (83), 109 (28). HRMS: calcd. for $C_{14}H_{17}N_4O_5$ $[M + H]^+$ 321.1198; found 321.1192. IR ($CHCl_3$): $\tilde{\nu}$ = 3392, 3280, 3108, 1623, 1591, 1490, 1410, 1329, 1215, 1061, 977 cm^{-1}.

9-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-6-(4,5-dihydrofuran-2-yl)purine (3g): NaOMe (1 M in MeOH, 300 μL, 0.3 mmol) was added dropwise to a solution of **3d** (388 mg, 1.0 mmol) in MeOH (10 mL), and the mixture was stirred for 6 h. The solvent was evaporated in vacuo, and the crude product was purified by chromatography on silica gel with a methanol/chloroform gradient (1:99 to 5:95) to give **3g** (302 mg, 99%) as a white solid, m.p. 137–139 °C. $[\alpha]_D^{20}$ = –14.9 (*c* = 3.26, DMSO). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.31 (ddd, J_{gem} = 13.6, $J_{2'b,1'}$ = 6.4, $J_{2'b,3'}$ = 3.6 Hz, 1 H, 2′b-H), 2.73 (ddd, J_{gem} = 13.6, $J_{2'a,1'}$ = 6.8, $J_{2'a,3'}$ = 6.0 Hz, 1 H, 2′a-H), 2.87 (td, $J_{4,5}$ = 9.6, $J_{4,3}$ = 2.8 Hz, 2 H, 4-H DHF), 3.49 (ddd, J_{gem} = 11.6, $J_{5'b,OH}$ = 5.2, $J_{5'b,4'}$ = 4.8 Hz, 1 H, 5′b-H), 3.58 (ddd, J_{gem} = 11.6, $J_{5'a,OH}$ = 5.6, $J_{5'a,4'}$ = 4.4 Hz, 1 H, 5′a-H), 3.85 (ddd, $J_{4',5'}$ = 4.8, 4.4, $J_{4',3'}$ = 2.8 Hz, 1 H, 4′-H), 4.07 (dddd, $J_{3',2'}$ = 6.0, 3.2, $J_{3',OH}$ = 4.0, $J_{3',4'}$ = 2.8 Hz, 1 H, 3′-H), 4.35 (t, $J_{5,4}$ = 9.6 Hz, 2 H, 5-H DHF), 4.96 (dd, $J_{OH,5'}$ = 5.2, 5.6 Hz, 1 H, 5′-OH), 5.33 (d, $J_{OH,3'}$ = 4.0 Hz, 1 H, 3′-OH), 6.43 (dd, $J_{1',2'}$ = 6.8, 6.4 Hz, 1 H, 1′-H), 6.71 (t, $J_{3,4}$ = 2.8 Hz, 1 H, 3-H DHF), 8.75, 8.81 (2 s, 2× 1 H, 2-H, 8-H) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 30.67 (CH_2-4 DHF), 39.29 (CH_2-2′), 61.45 (CH_2-5′), 68.99 (CH_2-5 DHF), 70.52 (CH-3′), 83.66 (CH-1′), 87.95 (CH-4′), 111.14 (C-3 DHF), 129.96 (C-5), 144.86 (CH-8), 145.98 (C-6), 150.82 (C-4), 151.50 (CH-2), 152.14 (C-2 DHF) ppm. FAB-MS: *m*/*z* (%) = 305 (10) $[M + H]^+$, 279 (20), 217 (100), 189 (95), 119 (55), 71 (60). HRMS: calcd. for $C_{14}H_{17}N_4O_4$ $[M + H]^+$ 305.1249; found 305.1245. IR ($CHCl_3$): $\tilde{\nu}$ = 3339, 3103, 1592, 1577, 1491, 1408, 1327, 1216, 1098, 1056 cm^{-1}.

Hydrogenation of Compounds 3a,e–g. General Procedure. 9-Benzyl-6-(tetrahydrofuran-2-yl)purine (4a): 10% Pd/C (50 mg) was added to a solution of **3a** (188 mg, 0.676 mmol) in MeOH (20 mL) at room temp. The flask was evacuated, then filled with H_2 (100 kPa), and the mixture was stirred until the reaction was complete (TLC, ca. 4 h). The catalyst was filtered off, and the solvent was evaporated in vacuo. The crude product was purified by chromatography on silica gel with a hexane/ethyl acetate/methanol (1:1:0) to hexane/ethyl acetate/methanol (10:10:1) gradient to give the desired compound **4a** (175 mg, 92%) as a white solid, m.p. 97–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.08, 2.16 (2 m, 2 H, 4-H THF), 2.26, 2.52 (2 m, 2 H, 3-H THF), 4.07 (ddd, J_{gem} = 8.0, $J_{5b,4}$ = 7.6, 5.8 Hz, 1 H, 5b-H THF), 4.31 (dt, J_{gem} = 8.0, $J_{5a,4}$ = 7.1 Hz, 1 H, 5a-H THF), 5.45 (s, 2 H, CH_2-Ph), 5.58 (t, $J_{2,3}$ = 7.1 Hz, 1 H, 2-H THF), 7.28–7.39 (m, 5 H, Ph), 8.04 (s, 1 H, 8-H), 8.99 (s, 1 H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.20 (CH_2-4 THF), 32.14 (CH_2-3 THF), 47.23 (CH_2-Ph), 69.51 (CH_2-5 THF), 77.78 (CH-2 THF), 127.82 (CH-*o* Ph), 128.57 (CH-*p* Ph), 129.10 (CH-*m* Ph), 131.10 (C-5), 135.05 (C-*i* Ph), 144.11 (CH-8), 151.57 (C-4), 152.60 (CH-2), 161.61 (C-6) ppm. FAB-MS: *m*/*z* (%) = 281 (100) $[M + H]^+$, 191 (7), 128 (7), 91 (80). HRMS: calcd. for $C_{16}H_{17}N_4O$ [M +

H]$^+$ 281.1402; found 281.1410. IR ($CHCl_3$): $\tilde{\nu}$ = 3092, 3069, 3035, 1592, 1500, 1406, 1331, 1073 cm^{-1}.

6-(Tetrahydrofuran-2-yl)-9*H*-purine (4e): Compound **4e** was prepared according to the procedure described for **4a**. EtOH/H_2O (4:1) was used as the solvent, and the reaction time was 4 h. Starting from **3e** (50 mg, 0.27 mmol), **4e** (42 mg, 83%) was obtained as a white solid, m.p. 177–179 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO + DCl): δ = 1.8–2.04 (m, 2 H, 4-H THF), 2.12 (ddt, J_{gem} = 12.4, $J_{3b,2}$ = 8.1, $J_{3b,4}$ = 6.4 Hz, 1 H, 3b-H THF), 2.57 (dtd, J_{gem} = 12.4, $J_{3a,4}$ = 8.0, $J_{3a,2}$ = 6.4 Hz, 1 H, 3a-H THF), 3.93 (dt, J_{gem} = 8.0, $J_{5b,4}$ = 6.8 Hz, 1 H, 5b-H THF), 4.20 (ddd, J_{gem} = 8.0, $J_{5a,4}$ = 7.0, 6.1 Hz, 1 H, 5a-H THF), 5.56 (dd, $J_{2,3}$ = 8.1, 6.4 Hz, 1 H, 2-H THF), 9.17 (s, 1 H, 2-H), 9.33 (s, 1 H, 8-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]-DMSO + DCl): δ = 25.84 (CH_2-4 THF), 32.88 (CH_2-3 THF), 69.84 (CH_2-5 THF), 76.14 (CH-2 THF), 124.35 (C-5), 148.63 (CH-2), 149.54 (CH-8), 155.62 (C-4), 156.20 (C-6) ppm. FAB-MS: *m*/*z* (%) = 191 (100) [M + H]$^+$, 147 (5), 93 (8), 57 (6). HRMS: calcd. for $C_9H_{11}N_4O$ [M + H]$^+$ 191.0933; found 191.0935. IR ($CHCl_3$): $\tilde{\nu}$ = 3118, 3048, 2981, 2872, 1611, 1563, 1465, 1419, 1374, 1225, 1070 cm^{-1}.

9-(β-D-Ribofuranosyl)-6-[(*R*,*S*)-tetrahydrofuran-2-yl]purine (4f): Compound **4f** was prepared according to the procedure described for **4a**. EtOH/H_2O (4:1) was used as the solvent, and the reaction time was 3 h. Starting from **3f** (100 mg, 0.31 mmol), **4f** (72 mg, 72%) was obtained as a white foam, m.p. 81–82 °C. $[a]_D^{20}$ = –28.0 (*c* = 2.01, MeOH). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.99, 2.14 (2 m, 2× 2 H, 4-H THF), 2.20, 2.35 (2 m, 2× 2 H, 3-H THF), 3.57, 3.69 (2 dt, J_{gem} = 12.0, $J_{5',OH}$ = $J_{5',4'}$ = 4.4 Hz, 2× 2 H, 5′-H), 3.91 (td, J_{gem} = 7.6, $J_{5b,4}$ = 7.6, 5.6 Hz, 2 H, 5b-H THF), 3.98 (td, $J_{4',5'}$ = 4.4, $J_{4',3'}$ = 2.9 Hz, 2 H, 4′-H), 4.11, 4.12 (2 dt, J_{gem} = 7.6, $J_{5a,4}$ = 6.9 Hz, 2× 1 H, 5a-H THF), 4.19 (ddd, $J_{3',OH}$ = 5.1, $J_{3',2'}$ = 4.6, $J_{3',4'}$ = 2.9 Hz, 2 H, 3′-H), 4.63 (br. m, 2 H, 2′-H), 5.10 (br. t, $J_{OH,5'}$ = 4.4 Hz, 2 H, 5′-OH), 5.23 (d, $J_{OH,3'}$ = 5.1 Hz, 2 H, 3′-OH), 5.41, 5.42 (2 dd, $J_{2,3}$ = 7.8, 6.0 Hz, 2× 1 H, 2-H THF), 5.52 (d, $J_{OH,2'}$ = 5.9 Hz, 2 H, 2′-OH), 6.04 (d, $J_{1',2'}$ = 5.7 Hz, 1 H, 1′-H), 8.80 (s, 2 H, 8-H), 8.88 (s, 2 H, 2-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO): δ = 26.31 (CH_2-4 THF), 31.58, 31.65 (CH_2-3 THF), 61.45 (CH_2-5′), 68.97 (CH_2-5 THF), 70.51 (CH-3′), 73.84, 73.87 (CH-2′), 76.96, 77.00 (CH-2 THF), 85.89 (CH-4′), 87.80 (CH-1′), 131.56 (C-5), 144.87 (CH-8), 151.40 (C-4), 151.94 (CH-2), 161.24, 161.28 (C-6) ppm. FAB-MS: *m*/*z* (%) = 323 (8) [M + H]$^+$, 191 (100), 147 (18), 134 (14), 71 (16). HRMS: calcd. for $C_{14}H_{19}N_4O_5$ [M + H]$^+$ 323.1355; found 323.1345. IR ($CHCl_3$): $\tilde{\nu}$ = 3543, 3325, 2990, 2876, 1596, 1498, 1457, 1418, 1333, 1083, 909 cm^{-1}.

9-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-6-[(*R*,*S*)-tetrahydrofuran-2-yl]purine (4g): Compound **4g** was prepared according to the procedure described for **4a**. EtOH/H_2O (4:1) was used as the solvent, and the reaction mixture was stirred overnight. Starting from **3g** (150 mg, 0.5 mmol), **4g** (150 mg, 98%) was obtained as a colorless amorphous solid. $[a]_D^{20}$ = –10.0 (*c* = 1.95, DMSO). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.98, 2.14 (2 m, 4 H, 4-H THF), 2.19 (m, 2 H, 3b-H THF), 2.30–2.38 (m, 4 H, 3a-H THF and 2′b-H), 2.78, 2.79 (2 ddd, J_{gem} = 13.2, $J_{2'a,1'}$ = 7.2, $J_{2'a,3'}$ = 5.8 Hz, 2× 1 H, 2′a-H), 3.52, 3.53 (2× ddd, J_{gem} = 11.7, $J_{5'b,OH}$ = 5.6, $J_{5'b,4'}$ = 4.7 Hz, 2× 1 H, 5′b-H), 3.62, 3.63 (2 ddd, J_{gem} = 11.7, $J_{5'a,OH}$ = 5.6, $J_{5'a,4'}$ = 5.0 Hz, 2× 1 H, 5′a-H), 3.87–3.93 (m, 4 H, 4′-H and 5b-H THF), 4.10, 4.11 (2 dt, J_{gem} = 7.6, $J_{5a,4}$ = 6.9 Hz, 2× 1 H, 5a-H THF), 4.45 (m, 2 H, 3′-H), 4.98, 4.99 (2 t, $J_{OH,5'}$ = 5.6 Hz, 2× 1 H, 5′-OH), 5.36 (d, $J_{OH,3'}$ = 4.2 Hz, 2 H, 3′-OH), 5.40, 5.41 (2 dd, $J_{2,3}$ = 7.8, 6.1 Hz, 2× 1 H, 2-H THF), 6.47 (dd, $J_{1',2'a}$ = 7.2, $J_{1',2'b}$ = 6.3 Hz, 1 H, 1′-H), 8.76 (s, 2 H, 8-H), 8.87 (s, 2 H, 2-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO): δ = 26.31 (CH_2-4 THF), 31.58, 31.62 (CH_2-3 THF), 39.40, 39.45 (CH_2-2′), 61.74 (CH_2-5′), 68.95 (CH_2-5 THF), 70.82, 70.83 (CH-3′), 76.96, 77.00 (CH-2 THF), 83.91, 84.17 (CH-1′), 88.18 (CH-4′), 131.53, 131.55 (C-5), 144.78 (CH-8), 151.11 (C-4), 151.85 (CH-2), 161.12, 161.15 (C-6) ppm. FAB-MS: *m*/*z* (%) = 307 (22) [M + H]$^+$, 217 (50), 191 (100), 133 (25), 72 (25). HRMS: calcd. for $C_{14}H_{19}N_4O_4$ [M + H]$^+$ 307.1406; found 307.1402. IR ($CHCl_3$): $\tilde{\nu}$ = 3318, 2875, 1595, 1498, 1400, 1334, 1229, 1095, 1059 cm^{-1}.

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