CYTOSTATIC AND ANTIVIRAL 6-ARYLPURINE RIBONUCLEOSIDES VIII+. SYNTHESIS AND EVALUATION OF 6-SUBSTITUTED PURINE 3′-DEOXYRIBONUCLEOSIDES

Michal HOCEK[1,*], Peter ŠILHÁR and Radek POHL

Gilead Sciences & IOCB Research Center, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, CZ-16610 Prague 6, Czech Republic; e-mail: [1] hocek@uochb.cas.cz

Received September 29, 2006
Accepted October 3, 2006

A series of purine 3′-deoxyribonucleosides bearing diverse C-substituents (alkyl, aryl, hetaryl or hydroxymethyl) in the position 6 was prepared by Pd-catalyzed cross-coupling reactions of 6-iodo-9-[2,5-bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-β-D-ribofuranosyl]purine with the corresponding organometallics followed by deprotection by $(HF)_3 \cdot Et_3N$. None of the title 3′-deoxyribonucleoside showed any cytostatic activity or anti-HCV effect in replicon assay.
Keywords: Purines; Nucleosides; Cross-coupling reactions; Antivirals; HCV; Cordycepin.

Purine nucleosides bearing C-substituents in position 6 are biologically active compounds (Chart 1). 6-Methyl- and 6-ethylpurine nucleosides are cytotoxic[1]. Ribonucleosides bearing hydroxymethyl[2], fluoromethyl[3], difluoromethyl[4] or trifluoromethyl[5] and aryl or hetaryl[6] groups in position 6 of purine are all cytostatic. Moreover, some 6-hetarylpurine ribonucleosides have recently been reported to exert[7] strong anti-HCV activities. However, the cytotoxic or cytostatic side-effect prevents clinical applications as anti-HCV drugs. Therefore, in order to achieve selective inhibition of HCV RNA polymerase, some additional sugar modifications may be pursued. From the previous studies it is known that 2′- and 5′-deoxyribonucleosides[8], as well as 2′-methylribonucleosides[9] of the 6-aryl- or 6-hetarylpurine series are all inactive, while some carbocyclic homonucleosides still exert[10] cytostatic effects. Very recently, some L-ribonucleosides were found[11] to exert weak anti-HCV effect in replicon assay but their triphoshates did not inhibit HCV RNA polymerase.

+ Part VII see ref.[11]

Collect. Czech. Chem. Commun. 2006, Vol. 71, No. 10, pp. 1484–1496

doi:10.1135/cccc20061484

In this paper we report on the synthesis and evaluation of cytostatic and anti-HCV activity of novel 3′-deoxyribonucleosides derived from diverse 6-substituted purines. 3′-Deoxyribonucleosides possess broad spectrum of biological activities, e.g. antiviral[12], antitumor[13], antiparasitical[14], antifungal[15], etc. Incorporation of 3′-deoxyribonucleotides of natural nucleobases by RNA polymerase terminates[16] RNA synthesis.

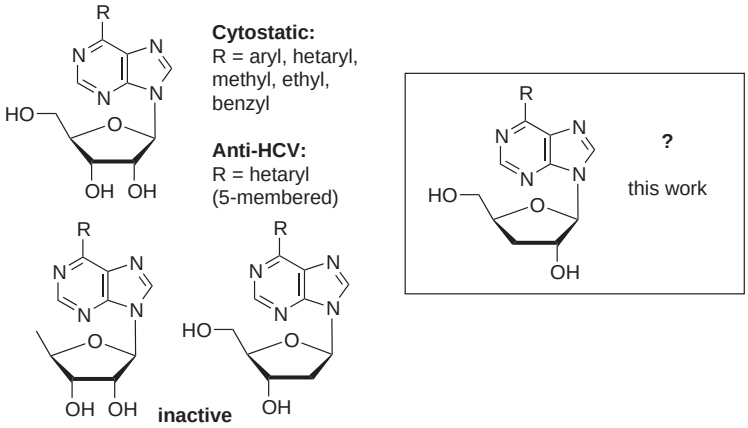
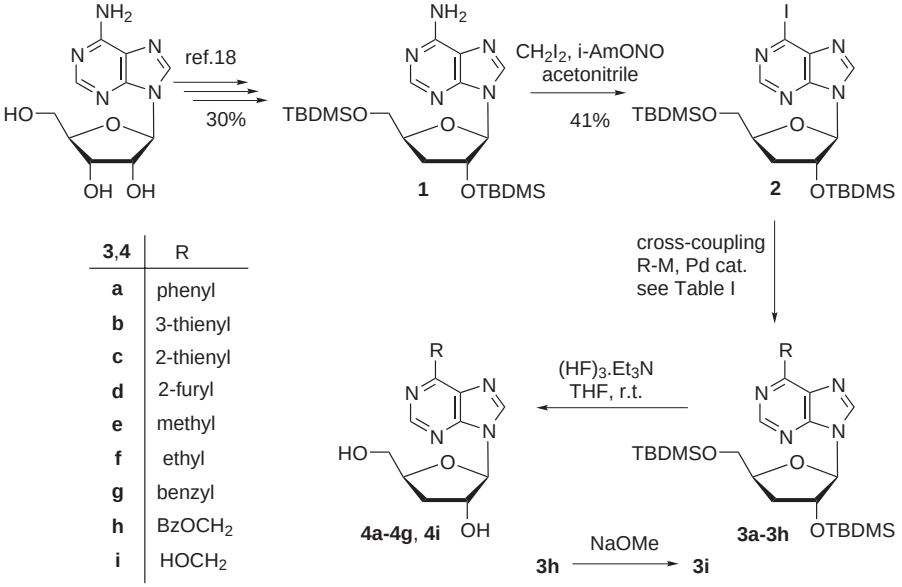


CHART 1
6-Substituted purine nucleosides

RESULTS AND DISCUSSION

Chemistry

A suitably protected cordycepin was an obvious starting compound of choice. There are many methods[17] for the preparation of 3′-deoxyribonucleosides but none of them is truly practical for larger scale synthesis. For our purpose we have chosen an approach recently published by Nair et al.[18] consisting in silylation of adenosine, separation of the two disilylated isomers, isomerization of the unwanted 3′,5′-di-TBDMS-adenosine to desired 2′,5′-isomer, followed by preparation of phenyl xanthate and radical deoxygenation using Bu_3SnH and AIBN (stoichiometric amount of this initiator has been used in contrast to catalytical amount reported[18] in the original paper). By this known sequence the disilylated cordycepin **1** was prepared in total yield of 30% in a 10-g scale. Then the adenine nucleoside **1** was converted to the corresponding 6-iodopurine nucleoside **2** by iododeamination (analogously to known[19] iododeamination of acetylated adenosine) using isoamyl nitrite and CH_2I_2 in 41% yield (Scheme 1).



3,4	R
a	phenyl
b	3-thienyl
c	2-thienyl
d	2-furyl
e	methyl
f	ethyl
g	benzyl
h	$BzOCH_2$
i	$HOCH_2$

SCHEME 1

TABLE I
Cross-coupling reactions of **2** with organometallics and deprotections

Entry	Reagent	Catalyst	Additive/Solvent	Product yield, %	Deprotection yield, %
1	$PhB(OH)_2$	$Pd(OAc)_2$, Cy_2Pbiphen[a]	K_3PO_4, dioxane	**3a** (76)	**4a** (93)
2	3-Thienyl$B(OH)_2$	$Pd(OAc)_2$, Cy_2Pbiphen	K_3PO_4, dioxane	**3b** (81)	**4b** (88)
3	2-ThienylSnBu_3	$PdCl_2(PPh_3)_2$	DMF	**3c** (91)	**4c** (79)
4	2-FurylSnBu_3	$PdCl_2(PPh_3)_2$	DMF	**3d** (75)	**4d** (93)
5	Me_3Al	$Pd(PPh_3)_4$	THF	**3e** (96)	**4e** (67)
6	Et_3Al	$Pd(PPh_3)_4$	THF	**3f** (41)	**4f** (75)
7	BnZnCl	$Pd(PPh_3)_4$	THF	**3g** (43)	**4g** (75)
8	$BzOCH_2ZnI$	$Pd(PPh_3)_4$	THF	**3h** (92)	**4i** (65)[b]

[a] Cy_2Pbiphen, 2-(dicyclohexylphosphino)biphenyl. [b] Overall yield of two steps: debenzoylation and desilylation.

TBDMS-protected iodopurine nucleoside **2** served as a versatile intermediate for further transformations by means of Pd-catalyzed cross-coupling reactions[20]. To avoid problems with partial desilylation during the Suzuki–Miyaura cross-coupling reactions with boronic acids in presence of stronger bases, we have applied a Lakshman's procedure[21] making use of a more reactive catalytical system based on $Pd(OAc)_2$ and 2-(dicyclohexylphosphino)biphenyl in presence of K_3PO_4 in anhydrous dioxane. Reactions of **2** with phenyl- and 3-thienylboronic acids under such conditions gave the desired 6-arylpurine nucleosides **3a** and **3b** in good yields (Scheme 1, Table I). The Stille coupling reactions of **2** with 2-thienyl- and 2-furylstannanes under standard conditions (analogy to ref.[6b]) gave the 6-hetarylpurines **3c** and **3d**. Cross-coupling reactions of **2** with trimethyl- and triethylaluminium (analogy to ref.[22]), as well as with benzylzinc chloride (analogy to ref.[6b]) under standard conditions in THF in presence of $Pd(PPh_3)_4$ also gave the desired 6-alkylpurine nucleosides **3e**–**3g**, though in the two latter cases in rather moderate yields. Cross-coupling of **2** with (benzoyloxymethyl)zinc iodide in presence of $Pd(PPh_3)_4$ in THF at room temperature (analogy to ref.[2]) gave 6-(benzoyloxymethyl)purine **4h** in excellent yield.

The deprotection of the silylated nucleoside intermediates **3** was performed using $(HF)_3{\cdot}Et_3N$ reagent[23] at room temperature in THF. All these reactions were quite clean and the corresponding title 6-substituted purine 3′-deoxyribonucleosides **4a**–**4g** were obtained in good yields. In case of the (benzoyloxymethyl)purine **4h**, the acyl protection was cleaved by treatment with NaOMe prior to desilylation to give the 6-(hydroxymethyl)purine nucleoside **4i** in 65%.

Biological Activity Evaluation

All the title 6-substituted purine 3′-deoxyribonucleosides **4a**–**4i** were subjected to biological activity screening. The cytostatic activity in vitro (inhibition of cell growth) was studied on the following cell cultures: (i) mouse leukemia L1210 cells (ATCC CCL 219); (ii) human promyelocytic leukemia HL60 cells (ATCC CCL 240); (iii) human cervix carcinoma HeLaS3 cells (ATCC CCL 2.2) and (iv) human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119). Antiviral activity of nucleosides **4a**–**4i** was evaluated in a HCV subgenomic replicon assay[24]. None of the compounds showed any considerable cytostatic or antiviral activity in these assays up to 10 μM concentration. Apparently, removal of the 3′-OH group from the biologically active 6-substituted purine ribonucleosides causes a complete loss of activ-

ity and, unlike biologically active 3′-deoxyribonucleosides[12–16] derived from canonical nucleobases, they are not promising antitumor or antiviral agents.

EXPERIMENTAL

NMR spectra were recorded on Bruker Avance 400 MHz (^{1}H at 400 MHz, ^{13}C at 100.6 MHz) and Bruker Avance 500 MHz (500 MHz for ^{1}H and 125.8 MHz for ^{13}C) spectrometers. Chemical shifts (in ppm, δ-scale) were referenced to TMS as internal standard. Coupling constants (*J*) are given in Hz. The assignment of carbons was based on C,H-HSQC and C,H-HMBC experiments. IR spectra (wavenumbers in cm^{-1}) were recorded on a Brucker IFS 88 spectrometer. Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured at 25 °C on an Autopol IV (Rudolph Research Analytical) polarimeter, $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol matrix). THF was dried and freshly distilled from sodium/benzophenone, anhydrous dioxane and DMF were purchased from Aldrich and used without further purification. Trimethylaluminium, triethylaluminium and benzylzinc chloride were commercial (Aldrich) solutions in THF. 9-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-β-D-ribofuranosyl]adenine (**1**) was prepared according to literature procedure[18] with the exception of the use of stoichiometric (instead of catalytic) amount of AIBN in the last step (total yield over three steps 30%). Cytostatic activity tests were performed as described in ref.[6a] and the HCV replicon assay as described in ref.[24]

9-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-β-D-ribofuranosyl]-6-iodopurine (**2**)

Isoamyl nitrite (20 ml, 150 mmol) was added to a solution of **1** (4.4 g, 9.2 mmol) and CH_2I_2 (10 ml, 125 mmol) in acetonitrile (150 ml). The mixture was irradiated by halogen lamp (250 W) for 10 min and then it was stirred at 90 °C for 8 h. After cooling to ambient temperature, the solvent was evaporated in vacuo, the residue was dissolved in chloroform (200 ml), and the organic phase was washed with saturated aqueous $Na_2S_2O_3$ and water (200 ml each), dried over anhydrous $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column (200 g, ethyl acetate/hexanes 1:4 to 1:1) to give the iodopurine **1** (2.2 g, 41%). Yellow powder, m.p. 48–52 °C, $[\alpha]_D$ –35.6 (*c* 0.20, $CHCl_3$). FAB MS, *m/z* (rel.%): 591 (13) [M + H], 533 (8), 345 (5), 213 (28), 73 (100). ^{1}H NMR (500 MHz, $CDCl_3$): 0.090, 0.128, 0.134 and 0.140 (4 × s, 4 × 3 H, CH_3Si); 0.90 and 0.94 (2 × s, 2 × 9 H, $(CH_3)_3C$); 1.88 (ddd, 1 H, J_{gem} = 13.0, $J_{3'b,4'}$ = 5.7, $J_{3'b,2'}$ = 2.3, H-3′b); 2.23 (ddd, 1 H, J_{gem} = 13.0, $J_{3'a,4'}$ = 9.7, $J_{3'a,2'}$ = 4.8, H-3′a); 3.78 (dd, 1 H, J_{gem} = 11.6, $J_{5'b,4'}$ = 2.7, H-5′b); 4.14 (dd, 1 H, J_{gem} = 11.6, $J_{5'a,4'}$ = 2.5, H-5′a); 4.59 (ddt, 1 H, $J_{4',3'}$ = 9.7, 5.7, $J_{4',5'}$ = 2.7, 2.5, H-4′); 4.66 (dt, 1 H, $J_{2',3'}$ = 4.8, 2.3, $J_{2',1'}$ = 1.5, H-2′); 6.05 (d, 1 H, $J_{1',2'}$ = 1.5, H-1′); 8.61 (s, 1 H, H-2); 8.64 (s, 1 H, H-8). ^{13}C NMR (100.6 MHz, $CDCl_3$): –5.38, –5.28, –5.02 and –4.75 (CH_3Si); 17.91 and 18.59 ($C(CH_3)_3$); 25.63 and 26.04 (($CH_3)_3C$); 33.52 (CH_2-3′); 63.56 (CH_2-5′); 77.33 (CH-2′); 81.67 (CH-4′); 92.20 (CH-1′); 121.75 (C-6); 139.25 (C-5); 143.02 (CH-8); 147.15 (C-4); 151.68 (CH-2). IR: 2956, 29231, 2859, 1578, 1552, 1472, 1331, 1257, 1134. Exact mass (HR FAB MS) found: 591.1699; for $C_{22}H_{40}IN_4O_3Si_2$ (M + H) calculated: 591.1684. For $C_{22}H_{39}IN_4O_3Si_2$ (590.6) calculated: 44.74% C, 6.66% H, 9.49% N; found: 45.05% C, 6.86% H, 9.37% N.

General Procedure for the Suzuki–Miyaura Cross-Coupling

Dioxane (4 ml) was added to an argon-purged flask containing the protected 6-iodopurine nucleoside **2** (295 mg, 0.5 mmol), K_3PO_4 (106 mg, 0.5 mmol), phenyl- or 3-thienylboronic acid (1 mmol), $Pd(OAc)_2$ (10 mg, 0.05 mmol) and (dicyclohexylphosphino)biphenyl (25 mg, 0.07 mmol). The mixture was then stirred at 100 °C for 10 h. After cooling to ambient temperature the mixture was evaporated in vacuo and the residue was chromatographed on a silica gel column (50 g, ethyl acetate/hexanes 1:2 to 9:1). Evaporation and drying of the product containing fractions afforded 6-arylpurines **3a** or **3b** as oils.

9-[2,5-Bis-O-(tert-butyldimethylsilyl)-3-deoxy-β-D-*ribofuranosyl]-6-phenylpurine* (**3a**). Yield 76%. Colorless oil. FAB MS, *m/z* (rel.%): 541 (25) [M + H], 483 (6), 213 (11), 197 (48), 73 (100). ^{1}H NMR (400 MHz, $CDCl_3$): 0.10, 0.14, 0.15 and 0.16 (4 × s, 4 × 3 H, CH_3Si); 0.91 and 0.95 (2 × s, 2 × 9 H, $(CH_3)_3C$); 1.91 (ddd, 1 H, J_{gem} = 13.0, $J_{3'b,4'}$ = 5.7, $J_{3'b,2'}$ = 2.4, H-3′b); 2.27 (ddd, 1 H, J_{gem} = 13.0, $J_{3'a,4'}$ = 9.5, $J_{3'a,2'}$ = 4.9, H-3′a); 3.80 (dd, 1 H, J_{gem} = 11.5, $J_{5'b,4'}$ = 3.0, H-5′b); 4.13 (dd, 1 H, J_{gem} = 11.5, $J_{5'a,4'}$ = 2.8, H-5′a); 4.60 (ddt, 1 H, $J_{4',3'}$ = 9.5, 5.7, $J_{4',5'}$ = 3.0, 2.8, H-4′); 4.73 (dt, 1 H, $J_{2',3'}$ = 4.9, 2.4, $J_{2',1'}$ = 1.6, H-2′); 6.13 (d, 1 H, $J_{1',2'}$ = 1.6, H-1′); 7.49–7.62 (m, 3 H, H-*m*,*p*-Ph); 8.61 (s, 1 H, H-8); 8.79 (m, 2 H, H-*o*-Ph); 8.99 (s, 1 H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): –5.39, –5.27, –5.00 and –4.70 (CH_3Si); 17.95 and 18.58 ($\mathbf{C}(CH_3)_3$); 25.61 and 26.05 (($\mathbf{C}H_3)_3C$); 33.88 (CH_2-3′); 63.87 (CH_2-5′); 77.19 (CH-2′); 81.38 (CH-4′); 91.94 (CH-1′); 128.63 (CH-*m*-Ph); 129.78 (CH-*o*-Ph); 130.83 (CH-*p*-Ph); 131.76 (C-5); 135.81 (C-*i*-Ph); 142.78 (CH-8); 151.81 (C-4); 152.15 (CH-2); 154.63 (C-6). Exact mass (HR FAB MS) found: 541.3020; for $C_{28}H_{45}N_4O_3Si_2$ (M + H) calculated: 541.3030.

9-[2,5-Bis-O-(tert-butyldimethylsilyl)-3-deoxy-β-D-*ribofuranosyl]-6-(3-thienyl)purine* (**3b**). Yield 81%. Colorless oil. FAB MS, *m/z* (rel.%): 547 (100) [M + H], 489 (25), 213 (6), 203 (11), 73 (60). ^{1}H NMR (400 MHz, $CDCl_3$): 0.10, 0.14, 0.15 and 0.16 (4 × s, 4 × 3 H, CH_3Si); 0.91 and 0.96 (2 × s, 2 × 9 H, $(CH_3)_3C$); 1.90 (ddd, 1 H, J_{gem} = 13.0, $J_{3'b,4'}$ = 5.7, $J_{3'b,2'}$ = 2.3, H-3′b); 2.28 (ddd, 1 H, J_{gem} = 13.0, $J_{3'a,4'}$ = 9.6, $J_{3'a,2'}$ = 4.9, H-3′a); 3.80 (dd, 1 H, J_{gem} = 11.5, $J_{5'b,4'}$ = 2.9, H-5′b); 4.14 (dd, 1 H, J_{gem} = 11.5, $J_{5'a,4'}$ = 2.6, H-5′a); 4.60 (ddt, 1 H, $J_{4',3'}$ = 9.6, 5.7, $J_{4',5'}$ = 2.9, 2.6, H-4′); 4.69 (dt, 1 H, $J_{2',3'}$ = 4.9, 2.3, $J_{2',1'}$ = 1.6, H-2′); 6.11 (d, 1 H, $J_{1',2'}$ = 1.6, H-1′); 7.45 (dd, 1 H, $J_{5'',4''}$ = 5.1, $J_{5'',2''}$ = 3.0, H-5″); 8.29 (dd, 1 H, $J_{4'',5''}$ = 5.0, $J_{4'',2''}$ = 1.2, H-4″); 8.62 (s, 1 H, H-8); 8.91 (s, 1 H, H-2); 8.93 (dd, 1 H, $J_{2'',5''}$ = 3.0, $J_{2'',4''}$ = 1.2, H-2″). ^{13}C NMR (100.6 MHz, $CDCl_3$): –5.42, –5.30, –5.02 and –4.71 (CH_3Si); 17.95 and 18.57 ($\mathbf{C}(CH_3)_3$); 25.69 and 26.05 (($\mathbf{C}H_3)_3C$); 33.74 (CH_2-3′); 63.77 (CH_2-5′); 77.27 (CH-2′); 81.38 (CH-4′); 91.88 (CH-1′); 125.74 (CH-5″); 127.78 (CH-4″); 130.61 (CH-2″); 130.79 (C-5); 138.35 (C-3″); 142.73 (CH-8); 150.56 (C-6); 151.49 (C-4); 152.29 (CH-2). Exact mass (HR FAB MS) found: 547.2579; for $C_{26}H_{42}N_4O_3SSi_2$ (M + H) calculated: 547.2594.

General Procedure for the Stille Cross-Coupling

DMF (2.5 ml) was added to an argon-purged flask containing the 6-iodopurine **2** (295 mg, 0.5 mmol), a 2-thienyl- or 2-furyl(tributyl)tin (1 mmol) and $PdCl_2(PPh_3)_2$ (20 mg, 0.03 mmol). The mixture was stirred at 110 °C for 12 h and the solvent was evaporated in vacuo. The residue was chromatographed on a silica gel column (50 g, ethyl acetate/hexanes 1:5 to 9:1) to give the 6-hetarylpurine nucleosides **3c** or **3d** as oils.

9-[2,5-Bis-O-(tert-butyldimethylsilyl)-3-deoxy-β-D-*ribofuranosyl]-6-(2-thienyl)purine* (**3c**). Yield 91%. Colorless oil. FAB MS, *m/z* (rel.%): 547 (23) [M + H], 489 (13), 213 (12), 203 (25), 73 (100). ^{1}H NMR (400 MHz, $CDCl_3$): 0.10, 0.14, 0.15 and 0.16 (4 × s, 4 × 3 H, CH_3Si); 0.91 and 0.96 (2 × s, 2 × 9 H, $(CH_3)_3C$); 1.90 (ddd, 1 H, J_{gem} = 13.0, $J_{3'b,4'}$ = 6.2, $J_{3'b,2'}$ = 2.3, H-3′b); 2.27

(ddd, 1 H, J_{gem} = 13.0, $J_{3'a,4'}$ = 9.6, $J_{3'a,2'}$ = 4.9, H-3′a); 3.80 (dd, 1 H, J_{gem} = 11.5, $J_{5'b,4'}$ = 3.0, H-5′b); 4.13 (dd, 1 H, J_{gem} = 11.5, $J_{5'a,4'}$ = 2.7, H-5′a); 4.60 (ddt, 1 H, $J_{4',3'}$ = 9.6, 6.2, $J_{4',5'}$ = 3.0, 2.7, H-4′); 4.69 (dt, 1 H, $J_{2',3'}$ = 4.9, 2.3, $J_{2',1'}$ = 1.6, H-2′); 6.10 (d, 1 H, $J_{1',2'}$ = 1.6, H-1′); 7.26 (dd, 1 H, $J_{4'',5''}$ = 5.0, $J_{4'',3''}$ = 3.7, H-4); 7.60 (dd, 1 H, $J_{5'',4''}$ = 5.0, $J_{5'',3''}$ = 1.2, H-5″); 8.61 (s, 1 H, H-8); 8.70 (dd, 1 H, $J_{3'',4''}$ = 3.7, $J_{3'',5''}$ = 1.2, H-3″); 8.85 (s, 1 H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): –5.41, –5.30, –5.02 and –4.71 (CH_3Si); 17.94 and 18.56 ($C(CH_3)_3$); 25.68 and 26.04 (($CH_3)_3C$); 33.78 (CH_2-3′); 63.80 (CH_2-5′); 77.24 (CH-2′); 81.40 (CH-4′); 91.92 (CH-1′); 128.81 (CH-4″); 129.58 (C-5); 130.41 (CH-5″); 132.80 (CH-3″); 140.21 (C-2″); 142.86 (CH-8); 149.87 (C-6); 151.30 (C-4); 152.20 (CH-2). Exact mass (HR FAB MS) found: 547.2588; for $C_{26}H_{42}N_4O_3SSi_2$ (M + H) calculated: 547.2594.

*9-[2,5-Bis-O-(tert-butyldimethylsilyl)-3-deoxy-*β*-D-ribofuranosyl]-6-(2-furyl)purine* (**3d**). Yield 75%. Colorless oil. FAB MS, *m/z* (rel.%): 531 (5) [M + H], 473 (2), 213 (8), 187 (10), 73 (100). ^{1}H NMR (400 MHz, $CDCl_3$): 0.10, 0.13, 0.14 and 0.15 (4 × s, 4 × 3 H, CH_3Si); 0.91 and 0.95 (2 × s, 2 × 9 H, $(CH_3)_3C$); 1.90 (ddd, 1 H, J_{gem} = 13.0, $J_{3'b,4'}$ = 5.7, $J_{3'b,2'}$ = 2.4, H-3′b); 2.26 (ddd, 1 H, J_{gem} = 13.0, $J_{3'a,4'}$ = 9.6, $J_{3'a,2'}$ = 5.0, H-3′a); 3.80 (dd, 1 H, J_{gem} = 11.5, $J_{5'b,4'}$ = 3.0, H-5′b); 4.13 (dd, 1 H, J_{gem} = 11.5, $J_{5'a,4'}$ = 2.7, H-5′a); 4.60 (ddt, 1 H, $J_{4',3'}$ = 9.6, 5.7, $J_{4',5'}$ = 3.0, 2.7, H-4′); 4.70 (dt, 1 H, $J_{2',3'}$ = 5.0, 2.4, $J_{2',1'}$ = 1.6, H-2′); 6.10 (d, 1 H, $J_{1',2'}$ = 1.6, H-1′); 6.67 (dd, 1 H, $J_{4'',3''}$ = 3.4, $J_{4'',5''}$ = 1.8, H-4″); 7.76 (dd, 1 H, $J_{5'',4''}$ = 1.8, $J_{5'',3''}$ = 0.8, H-5″); 7.89 (dd, 1 H, $J_{3'',4''}$ = 3.4, $J_{3'',5''}$ = 0.8, H-3″); 8.60 (s, 1 H, H-8); 8.93 (s, 1 H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): –5.41, –5.30, –5.01 and –4.72 (CH_3Si); 17.93 and 18.57 ($C(CH_3)_3$); 25.67 and 26.04 (($CH_3)_3C$); 33.79 (CH_2-3′); 63.82 (CH_2-5′); 77.20 (CH-2′); 81.41 (CH-4′); 91.93 (CH-1′); 112.60 (CH-4″); 117.49 (CH-3″); 129.07 (C-5); 143.06 (CH-8); 145.66 (CH-5″); 145.71 (C-6); 149.65 (C-2″); 151.29 (C-4); 152.36 (CH-2). Exact mass (HR FAB MS) found: 531.2835; for $C_{26}H_{42}N_4O_4Si_2$ (M + H) calculated: 531.2823.

General Procedure for the Cross-Coupling Reactions with Trialkylaluminium or Benzylzinc Chloride

THF (12 ml) was added to an argon-purged flask containing the 6-iodopurine **2** (295 mg, 0.5 mmol) and $Pd(PPh_3)_4$ (30 mg, 0.025 mmol). The mixture was stirred at ambient temperature for 10 min and, after dissolution of the solids, a commercial solution of trimethyl- or triethylaluminium or benzylzinc chloride in THF (2 mmol) was added dropwise (within 10 min) at ambient temperature. The stirring at ambient temperature was continued for 15 min followed by stirring at 70 °C for 8 h. Then the reaction mixture was allowed to stand at ambient temperature overnight and poured into saturated aqueous NH_4Cl (10 ml). To this mixture, saturated aqueous Na_2EDTA (10 ml) was added and the mixture was stirred for 10 min. Then the reaction mixture was extracted with ethyl acetate (3 × 20 ml) and the collected organic layers were washed with saturated aqueous Na_2EDTA (20 ml) and brine (20 ml), dried over anhydrous $MgSO_4$ and evaporated in vacuo. Column chromatography of the residue on silica gel (50 g, ethyl acetate/hexanes 1:2 to 9:1) afforded, after evaporation and drying, the 6-hetaryl- or 6-benzylpurines **3e**–**3g** as oils.

*9-[2,5-Bis-O-(tert-butyldimethylsilyl)-3-deoxy-*β*-D-ribofuranosyl]-6-methylpurine* (**3e**). Yield 96%. Colorless oil. FAB MS, *m/z* (rel.%): 479 (8) [M + H], 421 (2), 365 (3), 135 (40), 73 (100). ^{1}H NMR (400 MHz, $CDCl_3$): 0.101, 0.145, 0.150 and 0.166 (4 × s, 4 × 3 H, CH_3Si); 0.91 and 0.96 (2 × s, 2 × 9 H, $(CH_3)_3C$); 1.89 (ddd, 1 H, J_{gem} = 13.1, $J_{3'b,4'}$ = 5.5, $J_{3'b,2'}$ = 2.1, H-3′b); 2.27 (ddd, 1 H, J_{gem} = 13.1, $J_{3'a,4'}$ = 9.9, $J_{3'a,2'}$ = 4.7, H-3′a); 3.10 (s, 3 H, CH_3); 3.80 (dd, 1 H, J_{gem} = 11.8, $J_{5'b,4'}$ = 2.3, H-5′b); 4.21 (dd, 1 H, J_{gem} = 11.8, $J_{5'a,4'}$ = 2.3, H-5′a); 4.69 (dt, 1 H,

$J_{2',3'}$ = 4.7, 2.1, $J_{2',1'}$ = 1.3, H-2′); 4.64 (ddt, 1 H, $J_{4',3'}$ = 9.9, 5.5, $J_{4',5'}$ = 2.3, H-4′); 6.12 (d, 1 H, $J_{1',2'}$ = 1.3, H-1′); 8.92 (s, 1 H, H-8); 8.99 (s, 1 H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): –5.42, –5.33, –4.99 and –4.75 (CH_3Si); 17.28 (CH_3); 17.92 and 18.58 ($\mathbf{C}(CH_3)_3$); 25.62 and 26.02 (($\mathbf{C}H_3)_3C$); 33.16 (CH_2-3′); 63.26 (CH_2-5′); 77.63 (CH-2′); 82.03 (CH-4′); 92.36 (CH-1′); 133.30 (C-5); 145.45 (CH-8); 148.24 (CH-2); 150.74 (C-4); 156.23 (C-6). Exact mass (HR FAB MS) found: 479.2886; for $C_{23}H_{43}N_4O_3Si_2$ (M + H) calculated: 479.2874.

*9-[2,5-Bis-O-(tert-butyldimethylsilyl)-3-deoxy-*β*-D-ribofuranosyl]-6-ethylpurine* (**3f**). Yield 41%. Colorless oil. FAB MS, *m/z* (rel.%): 493 (4) [M + H], 435 (2), 149 (10), 73 (100). ^{1}H NMR (400 MHz, $CDCl_3$): 0.086, 0.123, 0.132 and 0.136 (4 × s, 4 × 3 H, CH_3Si); 0.90 and 0.94 (2 × s, 2 × 9 H, $(CH_3)_3C$); 1.44 (t, 3 H, J_{vic} = 7.6, $C\mathbf{H}_3CH_2$); 1.89 (ddd, 1 H, J_{gem} = 13.0, $J_{3'b,4'}$ = 5.7, $J_{3'b,2'}$ = 2.4, H-3′b); 2.26 (ddd, 1 H, J_{gem} = 13.0, $J_{3'a,4'}$ = 9.6, $J_{3'a,2'}$ = 5.0, H-3′a); 3.23 (q, 2 H, J_{vic} = 7.6, $C\mathbf{H}_2CH_3$); 3.78 (dd, 1 H, J_{gem} = 11.5, $J_{5'b,4'}$ = 2.9, H-5′b); 4.12 (dd, 1 H, J_{gem} = 11.5, $J_{5'a,4'}$ = 2.7, H-5′a); 4.58 (ddt, 1 H, $J_{4',3'}$ = 9.6, 5.7, $J_{4',5'}$ = 2.9, 2.7, H-4′); 4.69 (dt, 1 H, $J_{2',3'}$ = 5.0, 2.4, $J_{2',1'}$ = 1.6, H-2′); 6.07 (d, 1 H, $J_{1',2'}$ = 1.6, H-1′); 8.50 (s, 1 H, H-8); 8.85 (s, 1 H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): –5.41, –5.29, –5.04 and –4.74 (CH_3Si); 12.59 ($\mathbf{C}H_3CH_2$); 17.93 and 18.57 ($\mathbf{C}(CH_3)_3$); 25.67 and 26.03 (($\mathbf{C}H_3)_3C$); 26.41 ($\mathbf{C}H_2CH_3$); 33.79 (CH_2-3′); 63.76 (CH_2-5′); 77.20 (CH-2′); 81.33 (CH-4′); 91.85 (CH-1′); 132.90 (C-5); 142.08 (CH-8); 150.01 (C-4); 152.23 (CH-2); 163.61 (C-6). Exact mass (HR FAB MS) found: 493.3035; for $C_{24}H_{45}N_4O_3Si_2$ (M + H) calculated: 493.3030.

*9-[2,5-Bis-O-(tert-butyldimethylsilyl)-3-deoxy-*β*-D-ribofuranosyl]-6-benzylpurine* (**3g**). Yield 43%. Colorless oil. FAB MS, *m/z* (rel.%): 555 (3) [M + H], 211 (10), 73 (100). ^{1}H NMR (400 MHz, $CDCl_3$): 0.081, 0.120, 0.126 and 0.138 (4 × s, 4 × 3 H, CH_3Si); 0.89 and 0.94 (2 × s, 2 × 9 H, $(CH_3)_3C$); 1.87 (ddd, 1 H, J_{gem} = 13.0, $J_{3'b,4'}$ = 5.7, $J_{3'b,2'}$ = 2.2, H-3′b); 2.23 (ddd, 1 H, J_{gem} = 13.0, $J_{3'a,4'}$ = 9.7, $J_{3'a,2'}$ = 4.9, H-3′a); 3.78 (dd, 1 H, J_{gem} = 11.6, $J_{5'b,4'}$ = 2.9, H-5′b); 4.11 (dd, 1 H, J_{gem} = 11.6, $J_{5'a,4'}$ = 2.7, H-5′a); 4.47 and 4.57 (2 × d, 2 H, J_{gem} = 13.6, CH_2Ph); 4.58 (ddt, 1 H, $J_{4',3'}$ = 9.7, 5.7, $J_{4',5'}$ = 2.9, 2.7, H-4′); 4.68 (dt, 1 H, $J_{2',3'}$ = 4.9, 2.2, $J_{2',1'}$ = 1.5, H-2′); 6.05 (d, 1 H, $J_{1',2'}$ = 1.5, H-1′); 7.19 (m, 1 H, H-*p*-Ph); 7.27 (m, 1 H, H-*m*-Ph); 7.46 (m, 1 H, H-*o*-Ph); 8.54 (s, 1 H, H-8); 8.84 (s, 1 H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): –5.41, –5.32, –5.09 and –4.89 (CH_3Si); 17.83 and 18.49 ($\mathbf{C}(CH_3)_3$); 25.67 and 26.03 (($\mathbf{C}H_3)_3C$); 33.71 (CH_2-3′); 39.40 (CH_2Ph); 63.70 (CH_2-5′); 77.15 (CH-2′); 81.46 (CH-4′); 91.97 (CH-1′); 126.52 (CH-*p*-Ph); 128.48 (CH-*m*-Ph); 129.39 (CH-*o*-Ph); 133.09 (C-5); 137.97 (C-*i*-Ph); 142.56 (CH-8); 150.36 (C-4); 152.27 (CH-2); 160.40 (C-6). Exact mass (HR FAB MS) found: 555.3199; for $C_{29}H_{47}N_4O_3Si_2$ (M + H) calculated: 555.3187.

6-(Benzoyloxymethyl)-9-[2,5-bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-β-D-ribofuranosyl]-purine (**3h**)

A solution of 0.9 M (benzoyloxymethyl)zinc iodide in THF (1.6 ml, 1.44 mmol)[2] was added at room temperature to a solution of **2** (330 mg, 0.56 mmol), $Pd(PPh_3)_4$ (32 mg, 0.028 mmol) in THF (5 ml) under argon and stirred at room temperature for 6 h. The reaction was quenched with 1 M NaH_2PO_4 (20 ml) and extracted with $CHCl_3$ (4 × 20 ml). Collected organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. Column chromatography of the residue on silica gel (50 g, ethyl acetate/hexanes 1:2 to 9:1) afforded, after evaporation and drying, the product **3h** (308 mg, 92%) as oil. FAB MS, *m/z* (rel.%): 599 (6) [M + H], 255 (4), 132 (5), 115 (7), 105 (14), 59 (19). ^{1}H NMR (500 MHz, $CDCl_3$): 0.10, 0.11, 0.12 and 0.16 (4 × s, 4 × 3 H, CH_3Si); 0.91 and 0.92 (2 × s, 2 × 9 H, $(CH_3)_3C$); 1.85 (ddd, 1 H, J_{gem} = 13.0, $J_{3'b,4'}$ = 5.5, $J_{3'b,2'}$ = 1.9, H-3′b); 2.26 (ddd, 1 H, J_{gem} = 13.0, $J_{3'a,4'}$ =

10.0, $J_{3'a,2'}$ = 4.7, H-3′a); 3.78 (dd, 1 H, J_{gem} = 11.6, $J_{5'b,4'}$ = 2.6, H-5′b); 4.15 (dd, 1 H, J_{gem} = 11.6, $J_{5'a,4'}$ = 2.5, H-5′a); 4.60 (ddt, 1 H, $J_{4',3'}$ = 10.0, 5.5, $J_{4',5'}$ = 2.6, 2.5, H-4′); 4.64 (dt, 1 H, $J_{2',3'}$ = 4.7, 1.9, $J_{2',1'}$ = 1.3, H-2′); 5.85 and 5.89 (2 × d, 2 H, J_{gem} = 14.3, CH_2O); 6.10 (d, 1 H, $J_{1',2'}$ = 1.3, H-1′); 7.45 (m, 2 H, H-*m*-Ph); 7.57 (m, 1 H, H-*p*-Ph); 8.16 (m, 2 H, H-*o*-Ph); 8.66 (s, 1 H, H-8); 8.92 (s, 1 H, H-2). ^{13}C NMR (125.8 MHz, $CDCl_3$): –5.46 and –5.03 (CH_3Si); 17.93 and 18.53 ($C(CH_3)_3$); 25.67 and 25.99 ($(CH_3)_3C$); 33.38 (CH_2-3′); 63.25 (CH_2O); 63.44 (CH_2-5′); 77.44 (CH-2′); 81.62 (CH-4′); 92.00 (CH-1′); 128.32 (CH-*m*-Ph); 129.91 (C-*i*-Ph); 130.03 (CH-*o*-Ph); 132.44 (C-5); 133.03 (CH-*p*-Ph); 143.40 (CH-8); 150.91 (C-4); 152.07 (CH-2); 154.91 (C-6); 166.42 (CO). IR (CCl_4): 3124, 3066, 2899, 1731, 1595, 1492, 1472, 1463, 1331, 1272, 1211, 642. Exact mass (FAB HR MS) found: 599.3077; for $C_{30}H_{47}N_4O_5Si_2$ calculated: 599.3085.

General Procedure for Deprotection of Silylated Nucleosides

$(HF)_3{\cdot}Et_3N$ (250 µl, 1.9 mmol) was added to a solution of a TBDMS-protected nucleoside **3** (0.3–0.5 mmol) in THF (12 ml) in a PE vial and the mixture was stirred at room temperature overnight. Then the solvent was evaporated and the residue was chromatographed on a silica gel column (50 g, ethyl acetate/MeOH 1:0 to 4:1). The crude products **4** were crystallized from MeOH/ethyl acetate/heptane.

*9-(3-Deoxy-*β*-D-ribofuranosyl)-6-phenylpurine* (**4a**). Yield 93%. Colorless crystals, m.p. 181–184 °C, $[\alpha]_D$ –57.5 (*c* 0.24, DMF). FAB MS, *m/z* (rel.%): 313 (60) [M + H], 197 (100). ^{1}H NMR (400 MHz, DMSO-d_6): 1.95 (ddd, 1 H, J_{gem} = 13.2, $J_{3'b,4'}$ = 6.1, $J_{3'b,2'}$ = 2.5, H-3′b); 2.30 (ddd, 1 H, J_{gem} = 13.2, $J_{3'a,4'}$ = 9.4, $J_{3'a,2'}$ = 5.5, H-3′a); 3.58 (ddd, 1 H, J_{gem} = 12.0, $J_{5'b,OH}$ = 5.4, $J_{5'b,4'}$ = 3.8, H-5′b); 3.77 (dd, 1 H, J_{gem} = 12.0, $J_{5'a,OH}$ = 5.4, $J_{5'a,4'}$ = 3.3, H-5′a); 4.44 (ddt, 1 H, $J_{4',3'}$ = 9.4, 6.1, $J_{4',5'}$ = 3.8, 3.3, H-4′); 4.67 (m, 1 H, $J_{2',3'}$ = 5.5, 2.5, $J_{2',OH}$ = 4.0, $J_{2',1'}$ = 1.9, H-2′); 5.11 (t, 1 H, $J_{OH,5'}$ = 5.4, OH-5′); 5.77 (d, 1 H, $J_{OH,2'}$ = 4.0, OH-2′); 6.09 (d, 1 H, $J_{1',2'}$ = 1.9, H-1′); 7.55–7.64 (m, 3 H, H-*m*,*p*-Ph); 8.83 (m, 2 H, H-*o*-Ph); 8.93 (s, 1 H, H-8); 9.01 (s, 1 H, H-2). ^{13}C NMR (100.6 MHz, DMSO-d_6): 33.88 (CH_2-3′); 62.29 (CH_2-5′); 75.10 (CH-2′); 81.48 (CH-4′); 91.12 (CH-1′); 128.86 (CH-*m*-Ph); 129.53 (CH-*o*-Ph); 130.96 (C-5); 131.28 (CH-*p*-Ph); 135.50 (C-*i*-Ph); 144.56 (CH-8); 151.97 (C-4); 151.99 (CH-2); 152.92 (C-6). Exact mass (HR FAB MS) found: 313.1311; for $C_{16}H_{17}N_4O_3$ (M + H) calculated: 313.1301. For $C_{16}H_{16}N_4O_3$ (312.3) calculated: 61.53% C, 5.16% H, 17.94% N; found: 61.31% C, 5.21% H, 17.62% N.

*9-(3-Deoxy-*β*-D-ribofuranosyl)-6-(3-thienyl)purine* (**4b**). Yield 88%. Colorless crystals, m.p. 194–196 °C, $[\alpha]_D$ –60.8 (*c* 0.28, DMF). FAB MS, *m/z* (rel.%): 319 (60) [M + H], 203 (100). ^{1}H NMR (400 MHz, DMSO-d_6): 1.94 (ddd, 1 H, J_{gem} = 13.2, $J_{3'b,4'}$ = 6.1, $J_{3'b,2'}$ = 2.5, H-3′b); 2.30 (ddd, 1 H, J_{gem} = 13.2, $J_{3'a,4'}$ = 9.4, $J_{3'a,2'}$ = 5.5, H-3′a); 3.57 (ddd, 1 H, J_{gem} = 12.0, $J_{5'b,OH}$ = 5.4, $J_{5'b,4'}$ = 3.8, H-5′b); 3.76 (dd, 1 H, J_{gem} = 12.0, $J_{5'a,OH}$ = 5.4, $J_{5'a,4'}$ = 3.3, H-5′a); 4.43 (ddt, 1 H, $J_{4',3'}$ = 9.4, 6.1, $J_{4',5'}$ = 3.8, 3.3, H-4′); 4.66 (m, 1 H, $J_{2',3'}$ = 5.5, 2.5, $J_{2',OH}$ = 3.4, $J_{2',1'}$ = 1.9, H-2′); 5.10 (t, 1 H, $J_{OH,5'}$ = 5.4, OH-5′); 5.76 (d, 1 H, $J_{OH,2'}$ = 3.4, OH-2′); 6.07 (d, 1 H, $J_{1',2'}$ = 1.9, H-1′); 7.76 (dd, 1 H, $J_{5'',4''}$ = 5.1, $J_{5'',2''}$ = 3.0, H-5″); 8.24 (dd, 1 H, $J_{4'',5''}$ = 5.1, $J_{4'',2''}$ = 1.2, H-4″); 8.90 (s, 1 H, H-8); 8.93 (s, 1 H, H-2); 8.96 (dd, 1 H, $J_{2'',5''}$ = 3.0, $J_{2'',4''}$ = 1.2, H-2″). ^{13}C NMR (100.6 MHz, DMSO-d_6): 33.89 (CH_2-3′); 62.31 (CH_2-5′); 75.09 (CH-2′); 81.45 (CH-4′); 91.08 (CH-1′); 127.29 (CH-5″); 127.54 (CH-4″); 129.89 (C-5); 130.88 (CH-2″); 138.04 (C-3″); 144.48 (CH-8); 149.46 (C-6); 151.60 (C-4); 152.17 (CH-2). Exact mass (HR FAB MS) found: 319.0861; for $C_{14}H_{15}N_4O_3S$ (M + H) calculated: 319.0865. For $C_{14}H_{14}N_4O_3S$ (318.4) calculated: 52.82% C, 4.43% H, 17.60% N; found: 52.55% C, 4.50% H, 17.40% N.

9-(3-Deoxy-β-D-ribofuranosyl)-6-(2-thienyl)purine (**4c**). Yield 79%. Colorless crystals, m.p. 190–192 °C, $[\alpha]_D$ –61.5 (*c* 0.21, DMF). FAB MS, *m/z* (rel.%): 319 (60) [M + H], 203 (100). ^{1}H NMR (400 MHz, DMSO-d_6): 1.94 (ddd, 1 H, J_{gem} = 13.2, $J_{3'b,4'}$ = 6.1, $J_{3'b,2'}$ = 2.5, H-3′b); 2.29 (ddd, 1 H, J_{gem} = 13.2, $J_{3'a,4'}$ = 9.5, $J_{3'a,2'}$ = 5.5, H-3′a); 3.57 (ddd, 1 H, J_{gem} = 12.0, $J_{5'b,OH}$ = 5.5, $J_{5'b,4'}$ = 3.8, H-5′b); 3.76 (dd, 1 H, J_{gem} = 12.0, $J_{5'a,OH}$ = 5.4, $J_{5'a,4'}$ = 3.9, H-5′a); 4.43 (ddt, 1 H, $J_{4',3'}$ = 9.5, 6.1, $J_{4',5'}$ = 3.9, 3.8, H-4′); 4.65 (m, 1 H, $J_{2',3'}$ = 5.5, 2.5, $J_{2',OH}$ = 4.0, $J_{2',1'}$ = 1.9, H-2′); 5.10 (t, 1 H, $J_{OH,5'}$ = 5.5, 5.4, OH-5′); 5.76 (d, 1 H, $J_{OH,2'}$ = 4.0, OH-2′); 6.06 (d, 1 H, $J_{1',2'}$ = 1.9, H-1′); 7.34 (dd, 1 H, $J_{4'',5''}$ = 5.0, $J_{4'',3''}$ = 3.7, H-4″); 7.92 (dd, 1 H, $J_{5'',4''}$ = 5.0, $J_{5'',3''}$ = 1.2, H-5″); 8.63 (dd, 1 H, $J_{3'',4''}$ = 3.7, $J_{3'',5''}$ = 1.2, H-3″); 8.86 (s, 1 H, H-8); 8.90 (s, 1 H, H-2). ^{13}C NMR (100.6 MHz, DMSO-d_6): 33.86 (CH_2-3′); 62.29 (CH_2-5′); 75.12 (CH-2′); 81.51 (CH-4′); 91.13 (CH-1′); 128.69 (C-5); 129.26 (CH-4″); 131.91 (CH-5″); 132.57 (CH-3″); 139.84 (C-2″); 144.66 (CH-8); 148.72 (C-6); 151.41 (C-4); 152.08 (CH-2). Exact mass (HR FAB MS) found: 319.0879; for $C_{14}H_{15}N_4O_3S$ (M + H) calculated: 319.0865. For $C_{14}H_{14}N_4O_3S$ (318.4) calculated: 52.82% C, 4.43% H, 17.60% N; found: 52.58% C, 4.42% H, 17.29% N.

9-(3-Deoxy-β-D-ribofuranosyl)-6-(2-furyl)purine (**4d**). Yield 93%. Colorless crystals, m.p. 103–110 °C, $[\alpha]_D$ –54.4 (*c* 0.24, DMF). FAB MS, *m/z* (rel.%): 303 (35) [M + H], 187 (100). ^{1}H NMR (400 MHz, DMSO-d_6): 1.93 (ddd, 1 H, J_{gem} = 13.2, $J_{3'b,4'}$ = 6.1, $J_{3'b,2'}$ = 2.5, H-3′b); 2.29 (ddd, 1 H, J_{gem} = 13.2, $J_{3'a,4'}$ = 9.4, $J_{3'a,2'}$ = 5.4, H-3′a); 3.57 (ddd, 1 H, J_{gem} = 12.1, $J_{5'b,OH}$ = 5.5, $J_{5'b,4'}$ = 3.9, H-5′b); 3.75 (dd, 1 H, J_{gem} = 12.1, $J_{5'a,OH}$ = 5.4, $J_{5'a,4'}$ = 3.3, H-5′a); 4.42 (ddt, 1 H, $J_{4',3'}$ = 9.4, 6.1, $J_{4',5'}$ = 3.9, 3.3, H-4′); 4.64 (m, 1 H, $J_{2',3'}$ = 5.4, 2.5, $J_{2',OH}$ = 4.0, $J_{2',1'}$ = 1.9, H-2′); 5.10 (t, 1 H, $J_{OH,5'}$ = 5.5, 5.4, OH-5′); 5.76 (d, 1 H, $J_{OH,2'}$ = 4.0, OH-2′); 6.05 (d, 1 H, $J_{1',2'}$ = 1.9, H-1′); 6.82 (dd, 1 H, $J_{4'',3''}$ = 3.5, $J_{4'',5''}$ = 1.7, H-4″); 7.89 (dd, 1 H, $J_{3'',4''}$ = 3.5, $J_{3'',5''}$ = 0.9, H-3″); 8.07 (dd, 1 H, $J_{5'',4''}$ = 1.7, $J_{5'',3''}$ = 0.9, H-5″); 8.80 (s, 1 H, H-8); 8.90 (s, 1 H, H-2). ^{13}C NMR (100.6 MHz, DMSO-d_6): 33.86 (CH_2-3′); 62.28 (CH_2-5′); 75.09 (CH-2′); 81.48 (CH-4′); 91.08 (CH-1′); 113.07 (CH-4″); 117.57 (CH-3″); 128.34 (C-5); 144.59 (CH-8); 144.84 (C-6); 146.67 (CH-5″); 149.19 (C-2″); 151.30 (C-4); 152.10 (CH-2). Exact mass (HR FAB MS) found: 303.1078; for $C_{14}H_{15}N_4O_4$ (M + H) calculated: 303.1093. For $C_{14}H_{14}N_4O_4{\cdot}H_2O$ (320.3) calculated: 52.50% C, 5.03% H, 17.49% N; found: 52.21% C, 5.07% H, 16.98% N.

9-(3-Deoxy-β-D-ribofuranosyl)-6-methylpurine (**4e**). Yield 67%. Amorphous solid, $[\alpha]_D$ –42.8 (*c* 0.26, DMF). FAB MS, *m/z* (rel.%): 251 (10) [M + H], 115 (100). ^{1}H NMR (400 MHz, DMSO-d_6): 1.93 (ddd, 1 H, J_{gem} = 13.2, $J_{3'b,4'}$ = 6.1, $J_{3'b,2'}$ = 2.6, H-3′b); 2.27 (ddd, 1 H, J_{gem} = 13.2, $J_{3'a,4'}$ = 9.2, $J_{3'a,2'}$ = 5.5, H-3′a); 2.72 (s, 3 H, CH_3); 3.54 (ddd, 1 H, J_{gem} = 12.0, $J_{5'b,OH}$ = 5.5, $J_{5'b,4'}$ = 3.9, H-5′b); 3.71 (dd, 1 H, J_{gem} = 12.0, $J_{5'a,OH}$ = 5.4, $J_{5'a,4'}$ = 3.4, H-5′a); 4.40 (ddt, 1 H, $J_{4',3'}$ = 9.2, 6.1, $J_{4',5'}$ = 3.9, 3.4, H-4′); 4.61 (m, 1 H, $J_{2',3'}$ = 5.5, 2.6, $J_{2',OH}$ = 4.1, $J_{2',1'}$ = 2.0, H-2′); 5.09 (t, 1 H, $J_{OH,5'}$ = 5.5, 5.4, OH-5′); 5.76 (d, 1 H, $J_{OH,2'}$ = 4.1, OH-2′); 6.01 (d, 1 H, $J_{1',2'}$ = 2.0, H-1′); 8.76 (s, 1 H, H-8); 8.78 (s, 1 H, H-2). ^{13}C NMR (100.6 MHz, DMSO-d_6): 19.25 (CH_3); 34.02 (CH_2-3′); 62.39 (CH_2-5′); 74.98 (CH-2′); 81.32 (CH-4′); 91.02 (CH-1′); 132.94 (C-5); 143.58 (CH-8); 149.82 (C-4); 151.74 (CH-2); 158.26 (C-6). Exact mass (HR FAB MS) found: 251.1134; for $C_{11}H_{15}N_4O_3$ (M + H) calculated: 251.1144. For $C_{11}H_{14}N_4O_3$ (250.3) calculated: 52.79% C, 5.64% H, 22.39% N; found: 52.40% C, 5.26% H, 22.02% N.

9-(3-Deoxy-β-D-ribofuranosyl)-6-ethylpurine (**4f**). Yield 75%. Colorless crystals, m.p. 117–119 °C, $[\alpha]_D$ –34.9 (*c* 0.18, DMF). FAB MS, *m/z* (rel.%): 265 (35) [M + H], 149 (100). ^{1}H NMR (400 MHz, DMSO-d_6): 1.34 (t, 3 H, J_{vic} = 7.6, C**H**$_3$CH$_2$); 1.92 (ddd, 1 H, J_{gem} = 13.2, $J_{3'b,4'}$ = 6.2, $J_{3'b,2'}$ = 2.7, H-3′b); 2.27 (ddd, 1 H, J_{gem} = 13.2, $J_{3'a,4'}$ = 9.2, $J_{3'a,2'}$ = 5.7, H-3′a); 3.10 (q, 2 H, J_{vic} = 7.6, C**H**$_2$CH$_3$); 3.54 (ddd, 1 H, J_{gem} = 12.0, $J_{5'b,OH}$ = 5.4, $J_{5'b,4'}$ = 3.9, H-5′b); 3.72 (dd, 1 H, J_{gem} = 12.0, $J_{5'a,OH}$ = 5.4, $J_{5'a,4'}$ = 3.5, H-5′a); 4.40 (ddt, 1 H, $J_{4',3'}$ = 9.2, 6.2, $J_{4',5'}$ = 3.9, 3.5, H-4′); 4.63 (m, 1 H, $J_{2',3'}$ = 5.5, 2.7, $J_{2',OH}$ = 4.2, $J_{2',1'}$ = 2.0, H-2′); 5.06 (t, 1 H, $J_{OH,5'}$ = 5.4, OH-5′);

5.72 (d, 1 H, $J_{OH,2'}$ = 4.2, OH-2′); 6.01 (d, 1 H, $J_{1',2'}$ = 2.0, H-1′); 8.76 (s, 1 H, H-8); 8.83 (s, 1 H, H-2). ^{13}C NMR (100.6 MHz, DMSO-d_6): 12.39 (CH_3CH_2); 25.88 (CH_2CH_3); 34.02 (CH_2-3′); 62.42 (CH_2-5′); 74.95 (CH-2′); 81.28 (CH-4′); 91.00 (CH-1′); 132.26 (C-5); 143.58 (CH-8); 150.01 (C-4); 151.92 (CH-2); 162.60 (C-6). Exact mass (HR FAB MS) found: 265.1291; for $C_{12}H_{17}N_4O_3$ (M + H) calculated: 265.1301. For $C_{12}H_{16}N_4O_3 \cdot 1/2H_2O$ (273.3) calculated: 52.74% C, 6.27% H, 20.50% N; found: 52.93% C, 6.08% H, 20.31% N.

9-(3-Deoxy-β-D-ribofuranosyl)-6-benzylpurine (**4g**). Yield 75%. Colorless crystals, m.p. 167–170 °C, $[\alpha]_D$ –41.7 (*c* 0.18, DMF). FAB MS, *m/z* (rel.%): 327 (50) [M + H], 211 (100). ^{1}H NMR (400 MHz, DMSO-d_6): 1.92 (ddd, 1 H, J_{gem} = 13.1, $J_{3'b,4'}$ = 6.1, $J_{3'b,2'}$ = 2.7, H-3′b); 2.27 (ddd, 1 H, J_{gem} = 13.1, $J_{3'a,4'}$ = 9.1, $J_{3'a,2'}$ = 5.6, H-3′a); 3.54 (ddd, 1 H, J_{gem} = 12.0, $J_{5'b,OH}$ = 5.5, $J_{5'b,4'}$ = 3.9, H-5′b); 3.72 (dd, 1 H, J_{gem} = 12.0, $J_{5'a,OH}$ = 5.5, $J_{5'a,4'}$ = 3.4, H-5′a); 4.39 (ddt, 1 H, $J_{4',3'}$ = 9.1, 6.1, $J_{4',5'}$ = 3.9, 3.4, H-4′); 4.41 (s, 2 H, CH_2Ph); 4.63 (m, 1 H, $J_{2',3'}$ = 5.6, 2.7, $J_{2',OH}$ = 4.1, $J_{2',1'}$ = 2.1, H-2′); 5.06 (t, 1 H, $J_{OH,5'}$ = 5.5, OH-5′); 5.72 (d, 1 H, $J_{OH,2'}$ = 4.1, OH-2′); 6.01 (d, 1 H, $J_{1',2'}$ = 2.1, H-1′); 7.18 (m, 1 H, H-*p*-Ph); 7.26 (m, 2 H, H-*m*-Ph); 7.37 (m, 2 H, H-*o*-Ph); 8.81 (s, 1 H, H-8); 8.82 (s, 1 H, H-2). ^{13}C NMR (100.6 MHz, DMSO-d_6): 33.99 (CH_2-3′); 38.81 (CH_2Ph); 62.38 (CH_2-5′); 74.92 (CH-2′); 81.31 (CH-4′); 91.03 (CH-1′); 126.56 (CH-*p*-Ph); 128.57 (CH-*m*-Ph); 129.28 (CH-*o*-Ph); 132.46 (C-5); 138.18 (C-*i*-Ph); 144.17 (CH-8); 150.47 (C-4); 152.03 (CH-2); 159.75 (C-6). Exact mass (HR FAB MS) found: 327.1449; for $C_{17}H_{19}N_4O_3$ (M + H) calculated: 327.1457. For $C_{17}H_{18}N_4O_3 \cdot H_2O$ (344.4) calculated: 59.29% C, 5.85% H, 16.27% N; found: 59.00% C, 5.56% H, 16.88% N.

9-(3-Deoxy-β-D-ribofuranosyl)-6-(hydroxymethyl)purine (**4i**)

A 1 M methanolic MeONa (100 μl, 0.1 mmol) was added to a solution of **3h** (295 mg, 0.49 mmol) in methanol (30 ml) and the mixture was stirred at ambient temperature. After complete deacylation the solvent was evaporated and the residue was dissolved in ethyl acetate, filtered through silica gel and evaporated. Crude intermediate **3i** was dissolved in THF and $Et_3N \cdot 3HF$ (0.28 ml, 1.7 mmol) was added. After complete desilylation, the solvent was evaporated and the residue was chromatographed on silica gel (ethyl acetate/methanol). Product **4i** was crystallized from EtOH/heptane. Yield 65%. White hygroscopic solid, m.p. 160–161 °C, $[\alpha]_D^{20}$ –31.1 (*c* 0.31, H_2O). FAB MS, *m/z* (%): 267 (19) [M + H], 151 (100), 133 (17). ^{1}H NMR (400 MHz, DMSO-d_6): 1.93 (ddd, 1 H, J_{gem} = 13.2, $J_{3'b,4'}$ = 6.1, $J_{3'b,2'}$ = 2.6, H-3′b); 2.27 (ddd, 1 H, J_{gem} = 13.2, $J_{3'a,4'}$ = 9.3, $J_{3'a,2'}$ = 5.5, H-3′a); 3.54 (ddd, 1 H, J_{gem} = 12.1, $J_{5'b,OH}$ = 5.5, $J_{5'b,4'}$ = 3.9, H-5′b); 3.72 (dd, 1 H, J_{gem} = 12.1, $J_{5'a,OH}$ = 5.4, $J_{5'a,4'}$ = 3.3, H-5′a); 4.40 (ddt, 1 H, $J_{4',3'}$ = 9.3, 6.1, $J_{4',5'}$ = 3.9, 3.3, H-4′); 4.63 (ddt, 1 H, $J_{2',3'}$ = 5.5, 2.6, $J_{2',OH}$ = 4.1, $J_{2',1'}$ = 1.9, H-2′); 4.89 (d, 2 H, $J_{CH2,OH}$ = 6.2, C**H$_2$**OH); 5.08 (t, 1 H, $J_{OH,5'}$ = 5.5, 5.4, OH-5′); 5.44 (t, 1 H, $J_{OH,CH2}$ = 6.2, **H**OCH_2); 5.75 (d, 1 H, $J_{OH,2'}$ = 4.1, OH-2′); 6.03 (d, 1 H, $J_{1',2'}$ = 1.9, H-1′); 8.81 (s, 1 H, H-8); 8.90 (s, 1 H, H-2). ^{13}C NMR (100.6 MHz, DMSO-d_6): 33.96 (CH_2-3′); 60.14 (CH_2O); 62.37 (CH_2-5′); 75.02 (CH-2′); 81.38 (CH-4′); 91.05 (CH-1′); 131.51 (C-5); 144.10 (CH-8); 150.57 (C-4), 151.86 (CH-2); 159.70 (C-6). IR (KBr): 3433, 3251, 3111, 1605, 1581, 1491, 1405, 1335, 1218, 1091, 649. Exact mass (FAB HR MS) found: 267.1105; for $C_{11}H_{15}N_4O_4$ (M + H) calculated: 267.1093. For $C_{11}H_{14}N_4O_4 \cdot 1/2H_2O$ (275.3) calculated: 48.00% C, 5.49% H, 20.35% N; found: 47.87% C, 5.23% H, 19.87% N.

This work is a part of the research project Z4 055 0506. It was supported by the Centre for New Antivirals and Antineoplastics (1M0508), by the Programme of Targeted Projects of the Academy of Sciences of the Czech Republic (1QS400550501) and by Gilead Sciences, Inc. (Foster City, CA,

U.S.A.). Cytostatic activity was studied by Dr I. Votruba (IOCB) and anti-HCV activity by E. Mabery and Drs I. Shih and R. Mackman (Gilead). The contribution of these scientists is gratefully acknowledged.

REFERENCES

1. Montgomery J. A., Hewson K.: *J. Med. Chem.* **1968**, *11*, 48.
2. a) Šilhár P., Pohl R., Votruba I., Hocek M.: *Org. Lett.* **2004**, *6*, 3225; b) Šilhár P., Pohl R., Votruba I., Hocek M.: *Collect. Czech. Chem. Commun.* **2005**, *70*, 1669.
3. Šilhár P., Pohl R., Votruba I., Hocek M.: *Org. Biomol. Chem.* **2005**, *3*, 3001.
4. Šilhár P., Pohl R., Votruba I., Hocek M.: *Synthesis* **2006**, 1848.
5. Hocková D., Hocek M., Dvořáková H., Votruba I.: *Tetrahedron* **1999**, *55*, 11109.
6. a) Hocek M., Holý A., Votruba I., Dvořáková H.: *J. Med. Chem.* **2000**, *43*, 1817; b) Hocek M., Holý A., Votruba I., Dvořáková H.: *Collect. Czech. Chem. Commun.* **2001**, *66*, 483.
7. Hocek M., Nauš P., Pohl R., Votruba I., Furman P. A., Tharnish P. M., Otto M. J.: *J. Med. Chem.* **2005**, *48*, 5869.
8. Hocek M., Holý A., Votruba I., Dvořáková H.: *Collect. Czech. Chem. Commun.* **2000**, *65*, 1683.
9. Ding Y., Girardet J.-L., Hong Z., Lai V. C. H., An H., Koh Y.-H., Shaw S. Z., Zhong W.: *Bioorg. Med. Chem. Lett.* **2005**, *15*, 709.
10. Fernandez F., Garcia-Mera X., Morales M., Rodriguez-Borges J., De Clercq E.: *Synthesis* **2002**, 1084.
11. Hocek M., Šilhár P., Shih I., Mabery E., Mackman R.: *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5290.
12. Videll A., Hansson B. G., Oberg B., Nordenfelt E.: *Antiviral Res.* **1986**, *6*, 103.
13. a) Gitterman C. O., Burg R. W., Boxer G. E., Meltz D., Hitt J.: *J. Med. Chem.* **1965**, *8*, 664; b) Lin T.-S., Yang J.-H., Liu M.-C., Shen Z.-Y., Cheng Y.-C., Prusoff W. H., Birnbaum G. I., Giziewicz J., Ghazzouli I., Brankovan V., Feng J.-S., Hsiung G.-D.: *J. Med. Chem.* **1991**, *34*, 693.
14. Ghosal S., Krishnaprasad B. N., Khanna M., Dwivedi A. K., Singh S., Kumar A., Katti S. B.: *Int. J. Pharm.* **2000**, *194*, 15.
15. Kumar A., Khan S. I., Manglani A., Khan Z. K., Katti S. B.: *Nucleosides Nucleotides* **1994**, *13*, 1049.
16. Axelrod V., Kramer F. R.: *Biochemistry* **1985**, *24*, 5716.
17. a) Walton E., Holly F. W., Boxer G. E., Nutt R. F., Jenkins S. F.: *J. Med. Chem.* **1965**, *8*, 659; b) Bazin H., Chattopadhyaya J.: *Synthesis* **1985**, 1108; c) Hansske F., Robins M. J.: *Tetrahedron Lett.* **1985**, *26*, 4295; d) Norbeck D. W., Kramer J. B.: *J. Am. Chem. Soc.* **1988**, *110*, 7217; e) Dougherty J. P., Rizzo C. J., Breslow R.: *J. Am. Chem. Soc.* **1992**, *114*, 6254; f) Sheppard T. L., Rosenblatt A. T., Breslow R.: *J. Org. Chem.* **1994**, *59*, 7243; g) Robins M. J., Wilson J. S., Madej D., Low N. H., Hansske F., Wnuk S. F.: *J. Org. Chem.* **1995**, *60*, 7902; h) He G. X., Bischofberger N.: *Tetrahedron Lett.* **1995**, *36*, 6991; i) Cui Z., Zhang L., Zhang B.: *Tetrahedron Lett.* **2001**, *42*, 561.
18. Halligan K., Nair V.: *ARKIVOC* **2006**, 101.
19. Prasad A. S. B., Stevenson T. M., Citineni J. B., Nyzam V., Knochel P.: *Tetrahedron* **1997**, *53*, 7237.

20. Reviews: a) Hocek M.: *Eur. J. Org. Chem.* **2003**, 245; b) Agrofoglio L. A., Gillaizeau I., Saito Y.: *Chem. Rev.* **2003**, *103*, 1875.
21. a) Lakshman M. K., Hilmer J. H., Martin J. Q., Keeler J. C., Dinh Y. Q. V., Ngassa F. N., Russon L. M.: *J. Am. Chem. Soc.* **2001**, *123*, 7779; b) Lakshman M. K., Thomson P. F., Nuqui M. A., Hilmer J. H., Sevova N., Boggess B.: *Org. Lett.* **2002**, *4*, 1479; c) Gunda P., Russon L. M., Lakshman M. K.: *Angew. Chem., Int. Ed.* **2004**, *43*, 6372.
22. a) Hirota K., Kitade Y., Kanbe Y., Maki Y.: *J. Org. Chem.* **1992**, *57*, 5268; b) Česnek M., Hocek M., Holý A.: *Collect. Czech. Chem. Commun.* **2000**, *65*, 1357; c) Šilhár P., Pohl R., Votruba I., Klepetářová B., Hocek M.: *Collect. Czech. Chem. Commun.* **2006**, *71*, 788.
23. a) Čapek P., Pohl R., Hocek M.: *J. Org. Chem.* **2005**, *70*, 8001; b) Urban M., Pohl R., Klepetářová B., Hocek M.: *J. Org. Chem.* **2006**, *71*, 7322.
24. Lohmann V., Korner F., Koch J., Herian U., Theilmann L., Bartenschlager R.: *Science* **1999**, *285*, 110.