# CYTOSTATIC 6-ARYLPURINE NUCLEOSIDES IV+. SYNTHESIS OF 2-SUBSTITUTED 6-PHENYLPURINE RIBONUCLEOSIDES

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A series of 2-X-substituted-6-phenyl-9-(β-D-ribofuranosyl)purines (X = Cl, Br, I, $CH_3$, $CF_3$ and Ph) was prepared by halo-deaminations of protected 2-amino-6-phenylpurine ribonucleoside, by regioselective Suzuki–Miyaura reactions of 2,6-dihalopurines with phenylboronic acid or by cross-coupling reactions of the corresponding 2-halo-6-phenylpurines followed by deprotection. None of the title nucleosides exhibited any considerable cytostatic activity.
**Keywords**: Purines; Nucleosides; Cross-coupling reactions; Antineoplastic agents; Deaminations; Trifluoromethylation.

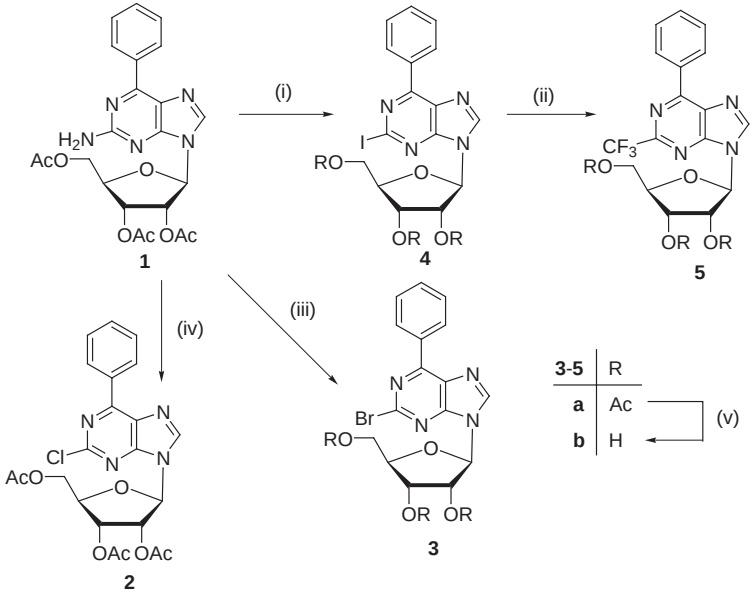
Recently, within the framework of our systematic studies of purines bearing *C*-substituents in positions 2, 6 and/or 8, a new efficient synthesis of arylpurines using the Suzuki–Miyaura cross-coupling methodology has been developed[1]. This method has been applied to the synthesis of purine bases and nucleosides[2,3], as well as of acyclic nucleotide analogues[4]. A significant cytostatic activity has been found with several 6-(substituted phenyl)purine ribonucleosides[2]. The SAR studies revealed a crucial influence of the presence of the β-D-ribofuranosyl moiety in the position N-9 and the effect of substitution at the purine and benzene rings on their biological activity. The 6-(4-substituted phenyl)purine ribonucleosides displayed[2] significant *in vitro* cytostatic activity (inhibition of the cell growth of L1210, HeLa S3 and CCRF-CEM cell cultures, $IC_{50}$ = 0.25–10 μmol $l^{-1}$), while the 6-phenylpurine bases and 2-amino-6-phenylpurine ribonucleosides were entirely inactive in these assays. Also several 6-hetaryl and 6-benzylpurine ribonucleosides

+ For Part III, see ref.[5]

showed[5] considerable activity. In contrast, sugar-modified 6-arylpurine nucleosides[6] (2′- or 5′-deoxyribosides and acyclonucleosides) as well as 6-(het)arylpurine acyclic nucleotide analogues[4,7] were devoid of any cytostatic activity. As an extension of the SAR study of this class of compounds, we report here on the synthesis of 6-phenylpurine ribonucleosides bearing diverse substituents (halo, alkyl and aryl) in position 2. In the selection of various types of 2-substituents, we took into account structural resemblance to some important biologically active purine derivatives (*e.g.* antiviral 2-(trifluoromethyl)adenines[8] or antitumor 2-chloroadenine nucleosides[9]).

There are two alternative approaches for the preparation of the target 2-substituted-6-phenylpurines: (i) selective Suzuki–Miyaura cross-coupling reactions of 2,6-dihalopurines[1b] with phenylboronic acid or (ii) deaminative transformations of easily available 2-amino-6-phenylpurine nucleosides. Both of these approaches have been advantageously used in this study depending on the nature of the 2-substituent required and on the efficiency of the synthesis.

Thus the known 2-amino-6-phenyl-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine[2] (**1**) was subjected to a series of halo-deamination reactions (Scheme 1, analogy to the known halo-deaminations[10] of chloro-

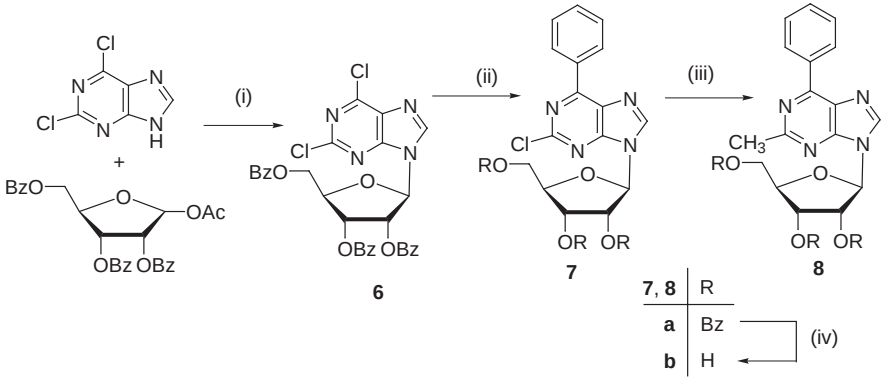



(i) $I_2$, CuI, $CH_2I_2$, i-AmONO, THF; (ii) $CF_3SiMe_3$, CuI, KF, DMF, NMP; (iii) $CHBr_3$, $NiBr_2$, i-AmONO, THF; (iv) $SbCl_3$, $ClCH_2CH_2Cl$, i-AmONO; (v) MeONa, MeOH

SCHEME 1

guanosines). The attempted chloro-deamination using $SbCl_3$ and $CCl_4$ in presence of isoamyl nitrite (i-AmONO) gave a complex mixture of products out of which the desired 2-chloro derivative **2** was isolated in moderate yield of 30% only. An analogous bromo-deamination using bromoform and i-AmONO under literature conditions[10] gave a complex mixture which did not contain the required 2-bromo-6-phenylpurine nucleoside **3a** (MS analysis of the crude reaction mixture). When using a combination of bromoform, $NiBr_2$ and i-AmONO, the 2-bromo derivative **3a** was isolated in the yield of 61%. The iodo-deamination using $CH_2I_2$, CuI and i-AmONO proceeded well to give 2-iodopurine **4a** in 54% yield. These halo-deamination reactions were not very clean and the 2-halopurine products **2**–**4a** had to be isolated by careful column chromatography. The 2-iodo-6-phenylpurine nucleoside **4a** was used as starting compound for the preparation of 6-phenyl-2-(trifluoromethyl)purine nucleoside **5a** (48% yield) using $CF_3Si(CH_3)_3$, KF and CuI (in analogy to the known[11] trifluoromethylation of 6-iodopurines).

As the preparation of 2-chloro-6-phenylpurine nucleoside **2** by chloro-deamination of the corresponding 2-aminopurine **1** was not efficient, we have used an alternative approach. Perbenzoylated 2,6-dichloropurine ribonucleoside[12] **6** was prepared by $SnCl_4$-mediated glycosidation of 2,6-dichloropurine with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose in 52% yield. The Suzuki–Miyaura reaction of the 2,6-dichloropurine nucleoside **6** with one equivalent of phenylboronic acid afforded selectively 2-chloro-6-phenylpurine **7a** in the yield of 80% (Scheme 2). This selectivity is in accord with the reported regioselective Suzuki[1b] and Stille[13] couplings of

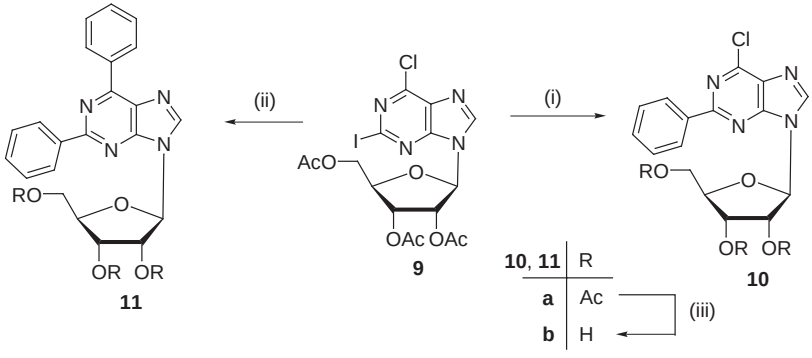



(i) $SnCl_4$, acetonitrile; (ii) $PhB(OH)_2$, $[Pd(PPh_3)_4]$, toluene; (iii) $(CH_3)_3Al$, $[Pd(PPh_3)_4]$,THF; (iv) MeONa, MeOH

SCHEME 2

2,6-dihalopurines. Reaction of compound **7a** with trimethylaluminium (in analogy to the known[14] methylation of 6-chloropurines) under [$Pd(PPh_3)_4$] catalysis afforded the 2-methyl-6-phenylpurine **8a** in a good yield (86%).

In contrast to the 2,6-dichloropurine **6**, an analogous reaction of the known[10] 6-chloro-2-iodopurine nucleoside **9** with one equivalent of phenylboronic acid gave selectively (in accord with previous results[1b,13]) the isomeric 6-chloro-2-phenylpurine **10a** in 76% yield (Scheme 3). Its reaction with 2 equivalents of phenylboronic acid led to the expected 2,6-diphenylpurine **11a**. Compounds **10a** and **11a** were previously prepared[15] less efficiently by a photochemical approach using irradiation of highly dilute solution of **9** in benzene.




(i) $PhB(OH)_2$ (1 eq.), [$Pd(PPh_3)_4$], toluene; (ii) $PhB(OH)_2$ (2.6 eq.), [$Pd(PPh_3)_4$], toluene; (iii) MeONa, MeOH

SCHEME 3

The acyl-protected ribonucleosides **3a**–**5a**, **7a**, **8a**, **10a** and **11a** were deprotected by the treatment with catalytic amount of sodium methoxide in methanol to give free nucleosides **3b**–**5b**, **7b**, **8b**, **10b** and **11b** in good yields (*ca* 90%).

All compounds were fully characterized by $^1H$ and $^{13}C$ NMR and mass spectra and by elemental analysis or HR MS. The structure of compound **6** was independently verified by means of COSY, HMBC, HMQC and NOE experiments. Assignment of the signals of the other products was based on analogy with our previous results[1,2,5].

In conclusion, the 2-substituted-6-phenylpurine ribonucleosides were prepared by halo-deaminations of 2-amino-6-phenylpurines, by the selective Suzuki–Miyaura cross-coupling reactions of 2,6-dihalopurines and by subsequent alkylation of the 2-halopurines followed by MeONa-mediated deprotection. The title nucleoside analogues **3b**–**5b**, **7b**, **8b**, **10b** and **11b**

were tested for their cytostatic activity (inhibition of cell growth of the following cell cultures: mouse leukemia L1210 cells (ATCC CCL 219), murine L929 cells (ATCC CCL 1), human cervix carcinoma HeLa S3 cells (ATCC CCL 2.2) and human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119)). In contrast to the significant *in vitro* activity of the corresponding 2-unsubstituted 6-phenylpurine ribonucleosides in these cell lines, neither the 2-substituted-6-phenylpurine nucleosides **3b**–**5b**, **7b**, **8b** and **11b** nor the 6-chloro-2-phenylpurine riboside **10b** exerted any considerable activity in any of these assays[16]. These results, together with the previous knowledge[2] of the inactivity of 2-amino-6-phenylpurines, show that the replacement of the hydrogen in position 2 of cytostatic 6-phenylpurine ribonucleosides by diverse types of substituents leads to the loss of activity[17].

## EXPERIMENTAL

Unless otherwise stated, solvents were evaporated at 40 °C/2 kPa and compounds were dried at 60 °C/2 kPa over $P_2O_5$. Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured at 25 °C on a Autopol IV (Rudolph Research Analytical) polarimeter, $[\alpha]_D$ values are given in $10^{-1}$ deg cm$^2$ g$^{-1}$. NMR spectra were measured on a Bruker AMX-3 400 (400 MHz for $^1$H, 100.6 MHz for $^{13}$C and 376.5 MHz for $^{19}$F), and on a Bruker DRX 500 (500 MHz for $^1$H, 125.8 MHz for $^{13}$C and 470.59 MHz for $^{19}$F). Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. TMS was used as internal standard for $^1$H and $^{13}$C NMR spectra; $CFCl_3$ was an internal standard for $^{19}$F spectra. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol matrix). Toluene was degassed *in vacuo* and stored over molecular sieves under argon. DMF was distilled from $P_2O_5$, degassed *in vacuo* and stored over molecular sieves under argon. THF was refluxed with Na and benzophenone under argon and freshly distilled prior to use. Cytostatic activity tests were performed as described in ref.[2]. 6-Chloro-2-iodo-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine[10] (**9**) and 2-amino-6-phenyl-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine[2] (**1**) were prepared according to literature procedures.

2-Chloro-6-phenyl-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine (**2**)

A solution of of 2-amino-6-phenylpurine nucleoside **1** (470 mg, 1 mmol) in 1,2-dichloroethane (10 ml) was stirred at –10 °C while a solution of $SbCl_3$ (350 mg, 1.5 mmol) in 1,2-dichloroethane (10 ml) was added dropwise followed by i-AmONO (1 ml, 7.5 mmol). Stirring at –10 °C was continued for 3 h, then the solvent was evaporated and the residue was chromatographed on a silica gel column (50 g, ethyl acetate–light petroleum 1 : 2) to give compound **2** as colourless oil; yield 145 mg (30%). EI MS, *m/z* (rel.%): 488 (7) [M], 259 (42), 138 (43), 43 (100). $^1$H NMR (500 MHz, $CDCl_3$): 2.10, 2.17 and 2.18 (3 × s, 3 × 3 H, 3 × $CH_3CO$); 4.43–4.50 (m, 3 H, H-4′ and 2 × H-5′); 5.62–5.64 (m, 1 H, H-3′); 5.85 (t, 1 H, *J* = 5.7, H-2′); 6.30 (d, 1 H, *J* = 5.7, H-1′); 7.55–7.57 (m, 3 H, H-arom.); 8.28 (s, 1 H, H-8); 8.76–8.78 (m, 2 H, H-arom.). $^{13}$C NMR (100.6 MHz, $CDCl_3$): 20.36, 20.54 and 20.78 (3 × $CH_3$); 63.02 ($CH_2$-5′); 70.69 (CH-3′); 73.18 (CH-2′); 80.66 (CH-4′); 85.91 (CH-1′); 128.73,

130.09 and 131.93 (CH-arom.); 130.53 and 134.21 (C-5 and C-*i*-arom.); 142.63 (CH-8); 153.71, 154.54 and 157.21 (C-4, C-2 and C-6); 169.38, 169.57 and 170.24 (3 × CO). HR MS (EI), calculated for $C_{22}H_{21}ClN_4O_7$ [M]: 488.1099; found: 488.1082.

2-Bromo-6-phenyl-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine (**3a**)

Isoamyl nitrite (2 ml, 15 mmol) was added to a stirred mixture of 2-amino-6-phenylpurine nucleoside **1** (490 mg, 1.04 mmol), $CHBr_3$ (6 ml, 69 mmol) and $NiBr_2$ (250 mg, 1.9 mmol) in THF (20 ml) at room temperature. Then the mixture was refluxed for 8 h and the solvent was evaporated. The residue was dissolved in chloroform (100 ml) and washed with water (2 × 100 ml). The organic layer was dried with $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column (100 g, ethyl acetate–light petroleum 1 : 2 to 1 : 1) to give compound **3a** as yellowish foam; yield 340 mg (61%). FAB MS, *m/z* (rel.%): 535/533 (30) [M + H], 277/275 (100). $^1$H NMR (400 MHz, $CDCl_3$): 2.11, 2.17 and 2.19 (3 × s, 3 × 3 H, 3 × $CH_3CO$); 4.42–4.51 (m, 3 H, H-4′ and 2 × H-5′); 5.62–5.66 (m, 1 H, H-3′); 5.85 (dd, 1 H, *J* = 5.6 and 5.7, H-2′); 6.30 (d, 1 H, *J* = 5.7, H-1′); 7.55–7.57 (m, 3 H, H-arom.); 8.26 (s, 1 H, H-8); 8.75–8.78 (m, 2 H, H-arom.). $^{13}$C NMR (100.6 MHz, $CDCl_3$): 20.36, 20.54 and 20.79 (3 × $CH_3$); 63.07 ($CH_2$-5′); 70.76 (CH-3′); 73.28 (CH-2′); 80.73 (CH-4′); 86.02 (CH-1′); 128.73, 130.15 and 131.93 (CH-arom.); 130.93 and 134.22 (C-5 and C-arom.); 142.45 (CH-8); 145.26, 153.58 and 157.20 (C-2, C-4 and C-6); 169.40, 169.57 and 170.25 (3 × CO). HR MS (FAB), calculated for $C_{22}H_{22}{}^{81}BrN_4O_7$ [M + H]: 535.0651; found: 535.0625.

2-Iodo-6-phenyl-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine (**4a**)

Isoamyl nitrite (2 ml, 15 mmol) was added to a stirred mixture of 2-amino-6-phenylpurine nucleoside **1** (1.4 g, 3 mmol), $I_2$ (750 mg, 3 mmol), CuI (600 mg, 3.2 mmol), $CH_2I_2$ (2.5 ml, 31 mmol) in THF (20 ml) at room temperature. Then the mixture was refluxed for 5 h and the solvent was evaporated. The residue was dissolved in chloroform (100 ml) and washed with saturated aqueous $Na_2S_2O_3$ (2 × 100 ml) and water (100 ml). The organic layer was dried with $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column (100 g, ethyl acetate–light petroleum 1 : 2 to 1 : 1) to give compound **4a** as yellowish foam; yield 940 mg (54%). FAB MS, *m/z* (rel.%): 581 (7) [M + H], 97 (100). $^1$H NMR (400 MHz, $CDCl_3$): 2.11, 2.15 and 2.18 (3 × s, 3 × 3 H, 3 × $CH_3CO$); 4.40–4.50 (m, 3 H, H-4′ and 2 × H-5′); 5.65 (m, 1 H, H-3′); 5.84 (dd, 1 H, *J* = 5.5 and 5.7, H-2′); 6.26 (d, 1 H, *J* = 5.5, H-1′); 7.53–7.55 (m, 3 H, H-arom.); 8.18 (s, 1 H, H-8); 8.72–8.75 (m, 2 H, H-arom.). $^{13}$C NMR (100.6 MHz, $CDCl_3$): 20.39, 20.54 and 20.83 (3 × $CH_3$); 63.07 ($CH_2$-5′); 70.74 (CH-3′); 73.33 (CH-2′); 80.70 (CH-4′); 86.19 (CH-1′); 119.74, 131.49 and 134.30 (C-2, C-5 and C-arom.); 128.70, 130.10 and 131.79 (CH-arom.); 142.06 (CH-8); 152.90 and 156.66 (C-4 and C-6); 169.37, 169.53 and 170.23 (3 × CO). HR MS (FAB), calculated for $C_{22}H_{22}IN_4O_7$ [M + H]: 581.0533; found: 581.0546.

6-Phenyl-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-(trifluoromethyl)purine (**5a**)

A mixture of 2-iodo-6-phenylpurine nucleoside **4a** (580 mg, 1 mmol), $CF_3SiMe_3$ (206 μl, 1.4 mmol), KF (82 mg, 1.4 mmol), CuI (304 mg, 1.6 mmol) in DMF (1 ml) and 1-methyl-2-pyrrolidinone (1 ml) was stirred in a sealed 5-ml glass vial at 60 °C for 24 h. After cooling to room temperature, the solvents were evaporated and the residue was chromatographed on a silica gel column (50 g, ethyl acetate–light petroleum 1 : 2) to give compound **5a** as

colourless oil; yield 250 mg (48%). FAB MS, *m/z* (rel.%): 523 (33) [M + H], 139 (100). $^1$H NMR (400 MHz, $CDCl_3$): 2.09, 2.12 and 2.18 (3 × s, 3 × 3 H, 3 × $CH_3CO$); 4.40–4.52 (m, 3 H, H-4′ and 2 × H-5′); 5.70 (m, 1 H, H-3′); 5.89 (dd, 1 H, *J* = 5.5 and 5.2, H-2′); 6.32 (d, 1 H, *J* = 5.2, H-1′); 7.56–7.58 (m, 3 H, H-arom.); 8.41 (s, 1 H, H-8); 8.85–8.88 (m, 2 H, H-arom.). $^{13}$C NMR (100.6 MHz, $CDCl_3$): 20.27, 20.49 and 20.65 (3 × $CH_3$); 63.04 ($CH_2$-5′); 70.72 (CH-3′); 73.52 (CH-2′); 80.79 (CH-4′); 86.86 (CH-1′); *ca* 120 (very weak q, $CF_3$); 128.79, 130.22 and 131.98 (CH-arom.); 132.33 and 134.38 (C-5 and C-arom.); 144.35 (CH-8); *ca* 150 (very weak q, C-2); 152.10 and 155.94 (C-4 and C-6); 169.39, 169.50 and 170.23 (3 × CO). $^{19}$F NMR (470.6 MHz, $CDCl_3$): –69.33. HR MS (FAB), calculated for $C_{23}H_{22}F_3N_4O_7$ [M + H]: 523.1441; found: 523.1442.

2,6-Dichloro-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)purine[12] (**6**)

$SnCl_4$ (2.4 ml, 20 mmol) was added to a stirred solution of 2,6-dichloropurine (1.89 g, 10 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (5.04 g, 10 mmol) in acetonitrile (50 ml), and the mixture was stirred at room temperature for 6 h. Then the solvent was evaporated and the residue was dissolved in chloroform (250 ml) and washed with saturated aqueous $NaHCO_3$ (2 × 200 ml) and water (200 ml). The organic layer was dried with $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column (250 g, ethyl acetate–light petroleum 1 : 2 to 1 : 1). The 9-substituted β-D-ribofuranosylpurine **9** was isolated in pure form as the major product along with a mixture of minor isomers; yield 3.32 g (52%), yellowish foam. FAB MS, *m/z* (rel.%): 633 (5) [M + H], 105 (100). $^1$H NMR (500 MHz, $CDCl_3$): 4.73 (dd, 1 H, *J* = 4.1 and 12.3, H-5′b); 4.88 (ddd, 1 H, *J* = 3.2, 4.1 and 5.5, H-4′); 4.93 (dd, 1 H, *J* = 3.2 and 12.3, H-5′a); 6.14 (dd, 1 H, $J_1 = J_2 = 5.5$, H-3′); 6.18 (dd, 1 H, $J_1 = J_2 = 5.5$, H-2′); 6.49 (d, 1 H, J = 5.5, H-1′); 7.36–7.39, 7.42–7.48, 7.54–7.62 and 7.92–8.07 (m, 15 H, H-arom.); 8.29 (s, 1 H, H-8). $^{13}$C NMR (100.6 MHz, $CDCl_3$): 63.46 ($CH_2$-5′); 71.53 (CH-3′); 74.28 (CH-2′); 81.50 (CH-4′); 86.97 (CH-1′); 128.58, 128.61, 128.72, 129.60, 129.85, 129.89, 133.63, 133.87 and 133.98 (CH-arom.); 128.07, 129.02 and 131.32 (C-5 and C-arom.); 143.80 (CH-8); 152.32 and 153.46 (C-2 and C-6); 152.60 (C-4); 165.12, 165.28 and 166.03 (C=O). HR MS (FAB), calculated for $C_{31}H_{23}Cl_2N_4O_7$ [M + H]: 633.0944; found: 633.0910.

The Suzuki–Miyaura Cross-Coupling of Phenylboronic Acid with Halopurines. General Procedure

Toluene (10 ml) was added to an argon-purged flask containing the protected halopurine nucleoside **6** or **9** (1 mmol), $K_2CO_3$ (200 mg, 1.5 mmol), phenylboronic acid (1.0-2.6 mmol) and [$Pd(PPh_3)_4$] (59 mg, 0.05 mmol) and the mixture was stirred under argon at 100 °C for 8 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–light petroleum 1 : 2 to 9 : 1). Evaporation and drying of the product containing fractions afforded the arylpurine nucleosides **7a**, **10a** or **11a** as foams or amorphous solids.

*2-Chloro-6-phenyl-9-(2,3,5-tri-O-benzoyl-*β*-D-ribofuranosyl)purine* (**7a**). This compound was prepared from 2,6-dichloropurine nucleoside **6** (1.267 g, 2 mmol) and $PhB(OH)_2$ (244 mg, 2 mmol); yield 1.08 g (80%); yellowish amorphous solid. FAB MS, *m/z* (rel.%): 675 (40) [M + H], 445 (100). $^1$H NMR (500 MHz, $CDCl_3$): 4.76 (dd, 1 H, *J* = 12.1 and 4.2, H-5′b); 4.86–4.89 (m, 1 H, H-4′); 4.93 (dd, 1 H, *J* = 12.1 and 3.1, H-5′a); 6.19 (t, 1 H, *J* = 5.6, H-3′); 6.24 (t, 1 H, *J* = 5.6, H-2′); 6.57 (d, 1 H, *J* = 5.5, H-1′); 7.35–7.62 (m, 12 H, H-arom.); 7.96 (d, 2 H, *J* = 7.5,

H-arom.); 8.04 (d, 2 H, *J* = 7.4, H-arom.); 8.09 (d, 2 H, *J* = 7.5, H-arom.); 8.29 (s, 1 H, H-8); 8.73–8.76 (m, 2 H, H-arom.). $^{13}$C NMR (100.6 MHz, $CDCl_3$): 63.70 ($CH_2$-5′); 71.58 (CH-3′); 74.28 (CH-2′); 81.24 (CH-4′); 86.48 (CH-1′); 128.57, 128.59, 128.70, 129.67, 129.88, 129.93, 130.11, 131.88, 133.53, 133.81 and 133.89 (CH-arom.); 128.24, 129.17, 130.57 and 134.25 (C-5 and C-arom.); 142.75 (CH-8); 153.76, 154.61 and 157.21 (C-2, C-4 and C-6); 165.17, 165.33 and 166.11 (C=O). HR MS (FAB), calculated for $C_{37}H_{28}ClN_4O_7$ [M + H]: 675.1647; found: 675.1667.

*6-Chloro-2-phenyl-9-(2,3,5-tri-O-acetyl-*β*-D-ribofuranosyl)purine*[15] (**10a**). This compound was prepared from 6-chloro-2-iodopurine nucleoside **9** (538 mg, 1 mmol) and $PhB(OH)_2$ (130 mg, 1.07 mmol); yield 370 mg (76%), yellowish amorphous solid. FAB MS, *m/z* (rel.%): 489 (29) [M + H], 97 (100). $^1$H NMR (500 MHz, $CDCl_3$): 1.96, 2.11 and 2.18 (3 × s, 3 × 3 H, 3 × $CH_3CO$); 4.31–4.35 and 4.43–4.49 (2 × m, 3 H, H-4′ and 2 × H-5′); 5.85 (dd, 1 H, *J* = 5.6 and 5.4, H-3′); 6.12 (dd, 1 H, *J* = 5.6 and 4.3, H-2′); 6.30 (d, 1 H, *J* = 4.3, H-1′); 7.49–7.52 (m, 3 H, H-arom.); 8.22 (s, 1 H, H-8); 8.50–8.53 (m, 2 H, H-arom.). $^{13}$C NMR (100.6 MHz, $CDCl_3$): 20.38, 20.50 and 20.54 (3 × $CH_3$); 62.54 ($CH_2$-5′); 70.03 (CH-3′); 73.13 (CH-2′); 80.07 (CH-4′); 87.22 (CH-1′); 128.65, 128.69 and 131.04 (CH-arom.); 130.74 (C-5); 136.26 (C-*i*-arom.); 143.66 (CH-8); 151.51, 151.94 and 159.93 (C-4, C-2 and C-6); 169.31, 169.44 and 170.26 (3 × CO). HR MS (FAB), calculated for $C_{22}H_{22}ClN_4O_7$ [M + H]: 489.1177; found: 489.1192.

*2,6-Diphenyl-9-(2,3,5-tri-O-acetyl-*β*-D-ribofuranosyl)purine*[15] (**11a**). This compound was prepared from 6-chloro-2-iodopurine nucleoside **9** (538 mg, 1 mmol) and $PhB(OH)_2$ (320 mg, 3 mmol); yield 440 mg (83%), yellowish amorphous solid. FAB MS, *m/z* (rel.%): 531 (30) [M + H], 273 (100). $^1$H NMR (500 MHz, $CDCl_3$): 1.98, 2.12 and 2.20 (3 × s, 3 × 3 H, 3 × $CH_3CO$); 4.33–4.37 (m, 1 H) and 4.47–4.52 (m, 2 H, H-4′ and 2 × H-5′); 5.95 (t, 1 H, *J* = 5.4, H-3′); 6.21 (dd, 1 H, *J* = 4.4 and 5.4, H-2′); 6.29 (d, 1 H, *J* = 4.4, H-1′); 7.48–7.62 (m, 6 H, H-arom.); 8.23 (s, 1 H, H-8); 8.68 (d, 2 H, *J* = 7.3, H-arom.); 8.91 (d, 2 H, *J* = 7.3, H-arom.). $^{13}$C NMR (125.8 MHz, $CDCl_3$): 20.48, 20.61 and 20.64 (3 × $CH_3$); 62.76 ($CH_2$-5′); 70.26 (CH-3′); 73.23 (CH-2′); 79.98 (CH-4′); 87.03 (CH-1′); 128.57, 128.61, 128.66, 129.91, 130.36 and 131.12 (CH-arom.); 130.43 (C-5); 135.89 and 138.04 (C-*i*-arom.); 142.97 (CH-8); 152.97 (C-4); 154.99 and 159.24 (C-2 and C-6); 169.44, 169.54 and 170.45 (3 × CO). HR MS (FAB), calculated for $C_{28}H_{27}N_4O_7$ [M + H]: 531.1880; found: 531.1873.

2-Methyl-6-phenyl-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)purine (**8a**)

Trimethylaluminium (2 M solution in toluene, 1.5 ml, 3 mmol) was added dropwise to a stirred solution of 2-chloro-6-phenylpurine nucleoside **10a** (675 mg, 1 mmol) and $[Pd(PPh_3)_4]$ (58 mg, 0.05 mmol) in THF (15 ml) under argon atmosphere at room temperature. The mixture was then stirred at 80 °C for 7 h and allowed to stand at room temperature overnight. Then the mixture was poured into a mixture of crushed ice (200 ml) and $NaHCO_3$ (1 g), and extracted with chloroform (2 × 100 ml). The organic layers were dried with $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column (100 g, ethyl acetate–light petroleum 1 : 2 to 1 : 1) to give compound **11a** as yellowish oil; yield 560 mg (86%). FAB MS, *m/z* (rel.%): 655 (7) [M + H], 105 (100). $^1$H NMR (400 MHz, $CDCl_3$): 2.85 (s, 3 H, $CH_3$); 4.73–4.78 (m, 1 H) and 4.85–4.95 (m, 2 H, H-4′ and H-5′); 6.40 (t, 1 H, *J* = 5.4, H-3′); 6.45 (dd, 1 H, *J* = 5.4 and 4.7, H-2′); 6.49 (d, 1 H, *J* = 4.7, H-1′); 7.35–7.60 (m, 12 H, H-arom.); 7.94–8.04 (m, 6 H, H-arom.); 8.20 (s, 1 H, H-8); 8.69–8.71 (m, 2 H, H-arom.). $^{13}$C NMR (100.6 MHz, $CDCl_3$): 26.13 ($CH_3$); 63.68 ($CH_2$-5′); 71.58 (CH-4′); 74.13 (CH-3′);

80.68 (CH-2′); 87.16 (CH-1′); 128.53, 128.57, 129.65, 129.78, 129.84, 129.87, 130.84, 133.36, 133.65 and 133.76 (CH-arom.); 128.85, 129.33 and 135.70 (C-5 and C-arom.); 142.20 (CH-8); 152.55, 155.16 and 162.67 (C-2, C-4 and C-6); 165.15, 165.28 and 166.13 (C=O). HR MS (FAB), calculated for $C_{38}H_{31}N_4O_7$ [M + H]: 655.2193; found: 655.2189.

Deacylation of Nucleosides **3a**–**5a**, **7a**, **8a**, **10a** and **11a**.
General Procedure

A 1 M methanolic MeONa (100 μl, 0.1 mmol) was added to a solution of a protected nucleoside **3a**–**5a**, **7a**, **8a**, **10a** or **11a** (0.5–0.8 mmol) in MeOH (20 ml) and the mixture was stirred at ambient temperature overnight. The solvent was evaporated and the residue was chromatographed on a silica gel column (50 g, ethyl acetate–MeOH 9 : 1). The crude products were recrystallized from EtOH/toluene/heptane to give free nucleosides **3b**–**5b**, **7b**, **8b**, **10b** or **11b**.

*2-Bromo-6-phenyl-9-(β-D-ribofuranosyl)purine* (**3b**). White crystals, yield 86%, m.p. 115–118 °C, $[\alpha]_D$ –22.4 (*c* 0.6, DMF). FAB MS, *m/z* (rel.%): 409/407 (25) [M + H], 277/275 (100). $^1$H NMR (500 MHz, DMSO-$d_6$): 3.60–3.63 (m, 1 H, H-5′b); 3.70–3.74 (m, 1 H, H-5′a); 4.00–4.03 (m, 1 H, H-4′); 4.20–4.22 (m, 1 H, H-3′); 4.59–4.61 (m, 1 H, H-2′); 5.12, 5.28 and 5.61 (3 × vbrs, 3 × OH); 6.03 (d, 1 H, *J* = 5.3, H-1′); 7.62–7.65 (m, 3 H, H-arom.); 8.74–8.77 (m, 2 H, H-arom.); 8.96 (s, 1 H, H-8). $^{13}$C NMR (125.8 MHz, DMSO-$d_6$): 60.97 ($CH_2$-5′); 70.08 (CH-3′); 73.84 (CH-2′); 85.71 (CH-4′); 87.61 (CH-1′); 128.87, 129.53 and 131.94 (CH-arom.); 130.51 and 133.96 (C-5 and C-*i*-arom.); 143.77 (C-2); 145.43 (C-8); 153.95 and 154.88 (C-4 and C-6). HR MS (FAB), calculated for $C_{16}H_{16}{}^{79}BrN_4O_4$ [M + H]: 407.0355; found: 407.0337. For $C_{16}H_{15}BrN_4O_4$ (407.2) calculated: 47.19% C, 3.71% H, 13.76% N; found: 47.38% C, 3.85% H, 13.42% N.

*2-Iodo-6-phenyl-9-(β-D-ribofuranosyl)purine* (**4b**). White crystals, yield 96%, m.p. 131–133 °C, $[\alpha]_D$ –8.8 (*c* 0.5, DMF). FAB MS, *m/z* (rel.%): 455 (52) [M + H], 323 (100). $^1$H NMR (400 MHz, DMSO-$d_6$): 3.57–3.63 (m, 1 H, H-5′b); 3.69–3.74 (m, 1 H, H-5′a); 3.98-4.02 (m, 1 H, H-4′); 4.18–4.22 (m, 1 H, H-3′); 4.58–4.63 (m, 1 H, H-2′); 5.05 (t, 1 H, *J* = 5.4, 5′-OH); 5.26 (d, 1 H, *J* = 5.1, 3′-OH); 5.56 (d, 1 H, *J* = 5.8, 2′-OH); 6.02 (d, 1 H, *J* = 5.5, H-1′); 7.60–7.63 (m, 3 H, H-arom.); 8.70–8.75 (m, 2 H, H-arom.); 8.86 (s, 1 H, H-8). $^{13}$C NMR (100.6 MHz, DMSO-$d_6$): 61.06 ($CH_2$-5′); 70.19 (CH-3′); 73.75 (CH-2′); 85.77 (CH-4′); 87.43 (CH-1′); 120.17 (C-2); 128.77, 129.43 and 131.69 (CH-arom.); 130.81 and 134.05 (C-5 and C-*i*-arom.); 144.85 (C-8); 153.30 and 154.34 (C-4 and C-6). HR MS (FAB), calculated for $C_{16}H_{16}IN_4O_4$ [M + H]: 455.0216; found: 455.0247. For $C_{16}H_{15}IN_4O_4$ (454.2) calculated: 42.31% C, 3.33% H, 12.33% N; found: 42.54% C, 3.48% H, 12.05% N.

*6-Phenyl-9-(β-D-ribofuranosyl)-2-(trifluoromethyl)purine* (**5b**). White crystals, yield 91%, m.p. 91–94 °C, $[\alpha]_D$ –35.9 (*c* 0.7, DMF). FAB MS, *m/z* (rel.%): 397 (100) [M + H]. $^1$H NMR (400 MHz, DMSO-$d_6$): 3.60–3.65 (m, 1 H, H-5′b); 3.70–3.75 (m, 1 H, H-5′a); 4.02–4.04 (brm, 1 H, H-4′); 4.24–4.26 (m, 1 H, H-3′); 4.66–4.71 (m, 1 H, H-2′); 5.04 (t, 1 H, *J* = 5.2, 5′-OH); 5.28 (d, 1 H, *J* = 5.1, 3′-OH); 5.57 (d, 1 H, *J* = 5.7, 2′-OH); 6.14 (d, 1 H, *J* = 5.2, H-1′); 7.60–7.70 (m, 3 H, H-arom.); 8.80–8.85 (m, 2 H, H-arom.); 9.16 (s, 1 H, H-8). $^{13}$C NMR (100.6 MHz, DMSO-$d_6$): 61.03 ($CH_2$-5′); 70.20 (CH-3′); 73.83 (CH-2′); 85.88 (CH-4′); 87.79 (CH-1′); 120.01 (q, $^1J_{CF}$ = 274.9, $CF_3$); 128.89, 129.58 and 131.94 (CH-arom.); 128.56 and 134.01 (C-5 and C-*i*-arom.); 147.40 (C-8); 148.23 (q, $^2J_{CF}$ = 35.6, C-2); 152.45 and 153.54 (C-4 and C-6). $^{19}$F NMR (470.6 MHz, DMSO-$d_6$): –66.91. For $C_{17}H_{15}F_3N_4O_4$ (396.3) calculated: 51.52% C, 3.81% H, 14.14% N; found: 51.24% C, 4.07% H, 13.89% N.

*2-Chloro-6-phenyl-9-(β-D-ribofuranosyl)purine* (**7b**). White crystals, yield 93%, m.p. 184–187 °C, $[\alpha]_D$ –38.0 (*c* 0.9, DMF). FAB MS, *m/z* (rel.%): 363 (40) [M + H], 231 (100). $^1$H NMR (400 MHz, DMSO-$d_6$): 3.58–3.65 (m, 1 H, H-5′b); 3.70–3.76 (m, 1 H, H-5′a); 3.99–4.03 (m, 1 H, H-4′); 4.19–4.22 (m, 1 H, H-3′); 4.57–4.62 (m, 1 H, H-2′); 5.08 (t, 1 H, *J* = 5.4, 5′-OH); 5.25 (d, 1 H, *J* = 5.2, 3′-OH); 5.58 (d, 1 H, *J* = 5.8, 2′-OH); 6.03 (d, 1 H, *J* = 5.2, H-1′); 7.60–7.64 (m, 3 H, H-arom.); 8.75–8.78 (m, 2 H, H-arom.); 8.97 (s, 1 H, H-8). $^{13}$C NMR (100.6 MHz, DMSO-$d_6$): 60.95 ($CH_2$-5′); 70.04 (CH-3′); 73.86 (CH-2′); 85.67 (CH-4′); 87.69 (CH-1′); 128.82, 129.50 and 131.89 (CH-arom.); 130.16 and 133.98 (C-5 and C-*i*-arom.); 145.59 (C-8); 152.69, 154.05 and 154.87 (C-2, C-4 and C-6). HR MS (FAB), calculated for $C_{16}H_{16}ClN_4O_4$ [M + H]: 363.0860; found: 363.0824. For $C_{16}H_{15}ClN_4O_4$ (362.7) calculated: 52.97% C, 4.17% H, 9.77% Cl, 15.44% N; found: 53.33% C, 4.33% H, 9.40% Cl, 15.09% N.

*2-Methyl-6-phenyl-9-(β-D-ribofuranosyl)purine* (**8b**). White crystals, yield 92%, m.p. 166–169 °C, $[\alpha]_D$ –50.1 (*c* 0.7, DMF). FAB MS, *m/z* (rel.%): 343 (80) [M + H], 211 (100). $^1$H NMR (400 MHz, DMSO-$d_6$): 2.77 (s, 3 H, $CH_3$); 3.58–3.64 (m, 1 H, H-5′b); 3.70–3.75 (m, 1 H, H-5′a); 3.99–4.03 (m, 1 H, H-4′); 4.19–4.23 (m, 1 H, H-3′); 4.64–4.69 (m, 1 H, H-2′); 5.20 (dd, 1 H, *J* = 6.2 and 5.1, 5′-OH); 5.23 (d, 1 H, *J* = 4.9, 3′-OH); 5.50 (d, 1 H, *J* = 6.0, 2′-OH); 6.07 (d, 1 H, *J* = 5.9, H-1′); 7.56–7.61 (m, 3 H, H-arom.); 8.79–8.81 (m, 2 H, H-arom.); 8.81 (s, 1 H, H-8). $^{13}$C NMR (100.6 MHz, DMSO-$d_6$): 25.68 ($CH_3$); 61.36 ($CH_2$-5′); 70.43 (CH-3′); 73.56 (CH-2′); 85.81 (CH-4′); 87.39 (CH-1′); 128.53, 129.30 and 130.93 (CH-arom.); 128.91 and 135.30 (C-5 and C-*i*-arom.); 144.27 (C-8); 152.69, 152.81 and 160.85 (C-2, C-4 and C-6). HR MS (FAB), calculated for $C_{17}H_{19}N_4O_4$ [M + H]: 343.1406; found: 343.1377. For $C_{17}H_{18}N_4O_4$ (342.3) calculated: 59.64% C, 5.30% H, 16.37% N; found: 59.82% C, 5.43% H, 16.03% N.

*6-Chloro-2-phenyl-9-(β-D-ribofuranosyl)purine* (**10b**). Yellowish crystals, yield 90%, slow decomp. >156 °C, $[\alpha]_D$ +32.5 (*c* 0.7, DMF). FAB MS, *m/z* (rel.%): 363 (12) [M + H], 93 (100). $^1$H NMR (400 MHz, DMSO-$d_6$): 3.60 (dd, 1 H, *J* = 11.8 and 3.9, H-5′b); 3.72 (dd, 1 H, *J* = 11.8 and 3.9, H-5′a); 4.00 (m, 1 H, H-4′); 4.25 (dd, 1 H, *J* = 4.7 and 3.6, H-3′); 4.70 (dd, 1 H, *J* = 5.2 and 4.7, H-2′); OH signals were exchanged; 6.12 (d, 1 H, *J* = 5.2, H-1′); 7.53–7.56 (m, 3 H, H-arom.); 8.39–8.42 (m, 2 H, H-arom.); 8.91 (s, 1 H, H-8). $^{13}$C NMR (125.8 MHz, DMSO-$d_6$): 61.12 ($CH_2$-5′); 70.19 (CH-3′); 73.83 (CH-2′); 85.70 (CH-4′); 88.03 (CH-1′); 128.00, 128.83 and 131.00 (CH-arom.); 130.12 (C-5); 136.06 (C-*i*-arom.); 146.14 (C-8); 149.44 (C-4); 152.55 and 157.87 (C-2 and C-6). HR MS (FAB), calculated for $C_{16}H_{16}ClN_4O_4$ [M + H]: 363.0860; found: 363.0802. For $C_{16}H_{15}ClN_4O_4$ (362.7) calculated: 52.97% C, 4.17% H, 9.77% Cl, 15.44% N; found: 53.24% C, 4.38% H, 9.45% Cl, 15.14% N.

*2,6-Diphenyl-9-(β-D-ribofuranosyl)purine* (**11b**). Yellowish crystals, yield 84%, m.p. 196–199 °C, $[\alpha]_D$ +12.5 (*c* 0.9, DMF). FAB MS, *m/z* (rel.%): 405 (34) [M + H], 273 (100). $^1$H NMR (500 MHz, DMSO-$d_6$): 3.60–3.65 and 3.72–3.77 (2 × m, 2 H, 2 × H-5′); 4.02 (m, 1 H, H-4′); 4.29 (m, 1 H, H-3′); 4.78 (m, 1 H, H-2′); 5.07 (t, 1 H, *J* = 5.1, 5′-OH); 5.30 (d, 1 H, *J* = 4.7, 3′-OH); 5.60 (d, 1 H, *J* = 5.7, 2′-OH); 6.20 (d, 1 H, *J* = 5.5, H-1′); 7.52–7.65 (m, 6 H, H-arom.); 8.59 (d, 1 H, *J* = 7.2, H-arom.); 8.91 (s, 1 H, H-8); 8.95 (d, 1 H, *J* = 7.1, H-arom.). $^{13}$C NMR (125.8 MHz, DMSO-$d_6$): 61.31 ($CH_2$-5′); 70.37 (CH-3′); 73.68 (CH-2′); 85.61 (CH-4′); 87.47 (CH-1′); 127.93, 128.69, 128.74 and 129.45 (CH-arom.); 129.78 (C-5); 130.36 and 131.20 (CH-arom.); 135.51 and 137.63 (C-*i*-arom.); 145.34 (C-8); 152.76 (C-4); 153.38 and 157.36 (C-2 and C-6). HR MS (FAB), calculated for $C_{22}H_{21}N_4O_4$ [M + H]: 405.1563; found: 405.1493. For $C_{22}H_{20}N_4O_4$ (404.4) calculated: 65.34% C, 4.98% H, 13.85% N; found: 65.62% C, 4.88% H, 13.52% N.

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