CYTOSTATIC 6-ARYLPURINE NUCLEOSIDES V.+ SYNTHESIS OF 8-SUBSTITUTED 6-PHENYLPURINE RIBONUCLEOSIDES

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Dedicated to the memory of Professor Otakar Červinka.

Regioselective Suzuki–Miyaura reaction of 8-bromo-6-iodo-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine with phenylboronic acid gave 8-bromo-6-phenylpurine derivative that was used for cross-coupling reactions (with $PhB(OH)_2$, Me_3Al, Et_3Al, BnZnCl) or nucleophilic substitutions (with NaOH, NaOMe, NH_3, $NHMe_2$ or thiourea). A series of 8-X-substituted 6-phenyl-9-(β-D-ribofuranosyl)purines (X = Ph, Me, Et, Bn, OH, OMe, NH_2, NMe_2, SH) was prepared in this way directly or after deprotection. None of the title nucleosides exhibited any considerable cytostatic activity.

Keywords: Purines; Nucleosides; Cross-coupling reactions; Nucleophilic substitutions; Suzuki–Miyaura reaction; Halodeaminations; Antineoplastic agents.

Recently, a significant cytostatic activity of 6-arylpurine ribonucleosides has been described[1]. 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. Thus 6-(4-substituted phenyl)purine ribonucleosides displayed 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), while the 6-phenylpurine bases and 2-amino-6-phenylpurine ribonucleosides were entirely inactive in these assays. Later, also several 6-hetaryl and 6-benzylpurine ribonucleosides were found to show[2] considerable activity. In contrast, sugar-modified 6-arylpurine nucleosides[3] (2′- or 5′-deoxyribosides and

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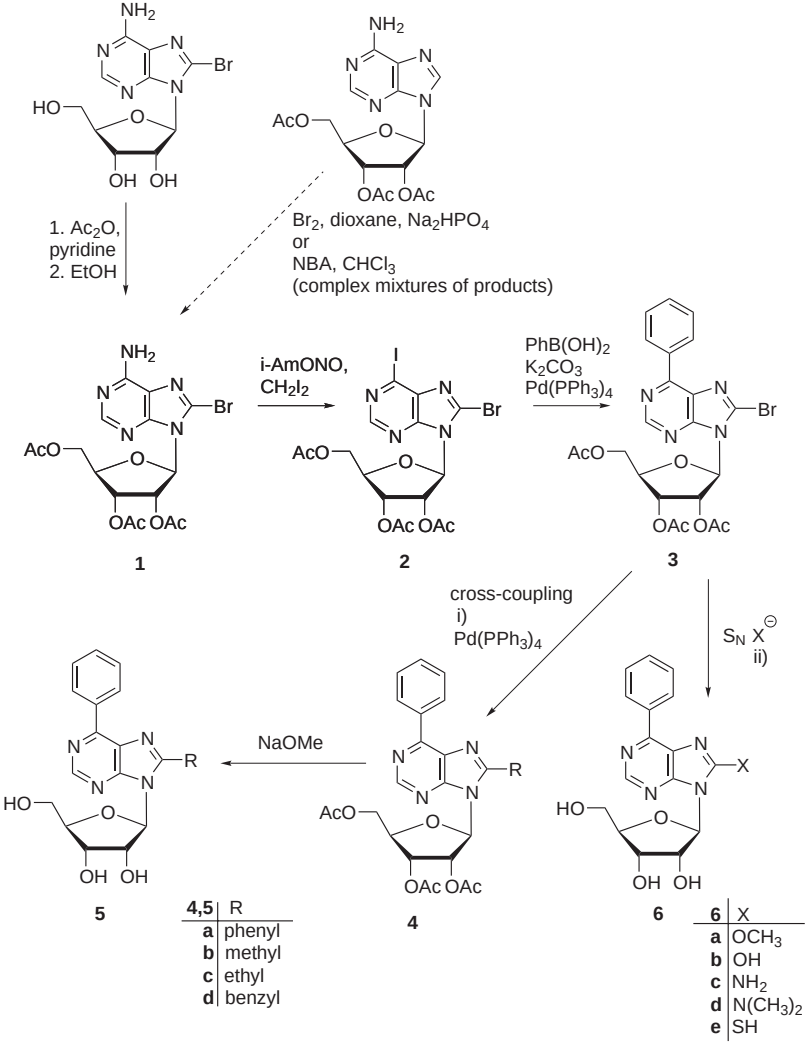
acyclonucleosides) as well as 6-(het)arylpurine acyclic nucleotide analogues[4,5] were devoid of any cytostatic activity. Also inactive were 2-substituted 6-phenylpurine nucleosides[6]. As an extension of the SAR study of this class of compounds, we report here on the synthesis of 6-phenylpurine ribonucleosides bearing diverse substituents in the position 8. Unlike in position 2, a substituent in position 8 does not interfere with hydrogen-bonding to a complementary nucleobase, but in principle could modulate a binding to an active site of the target cellular system.

Our synthetic strategy relied on regioselective Suzuki–Miyaura cross-coupling reactions of dihalopurines with phenylboronic acid[7–9] (for a comprehensive review on cross-couplings in purines, see ref.[10]). While the regioselectivity of this reaction was already extensively studied in 2,6-dihalopurines[6,8,11], in 6,8-dihalopurines only regioselectivities of analogous Stille couplings with organostannanes and Negishi reactions with organozinc reagents were described[12]. 6,8-Dichloropurines prefer the reaction in position 6, while 8-bromo- or 8-iodo-6-chloropurines react preferentially in position 8. Considering the regioselectivity rules, an acyl-protected 8-bromo-6-iodopurine ribonucleoside should be a good starting compound for this study: it should be easily available from known[13] 8-bromoadenosine and the Suzuki–Miyaura reaction should proceed preferentially in the position 6.

Our first goal was an efficient larger-scale synthesis of known[14,15] 2′,3′,5′-tri-*O*-acetyl-8-bromoadenosine (**1**) as a suitable precursor. In our hands, the published procedures for the bromination of 2′,3′,5′-tri-*O*-acetyladenosine making use of Br_2/dioxane[14] or *N*-bromoacetamide/chloroform[15] were not practical – both these reactions led to complex mixtures from which the required compound **1** was isolated by column chromatography in low yields. Therefore, we have prepared 8-bromoadenosine by a known[13] efficient bromination of adenosine with bromine in acetate buffer (pH 4). Its subsequent acetylation by acetic anhydride in pyridine followed by treatment with ethanol afforded the desired crystalline **1** in good yield without using chromatography. The protected 8-bromoadenosine **1** was easily converted to 8-bromo-6-iodo-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine (**2**) by means of iododeamination reaction using isopentyl nitrite (i-AmONO) and CH_2I_2 in 45% yield (analogously to the known[16] iododeamination of acetylated adenosine).

The next step was the regioselective Suzuki–Miyaura cross-coupling reaction (for a review on the use of this reaction in purines, see ref.[17]) of dihalopurine **2** with one equivalent of phenylboronic acid. Under standard

anhydrous conditions in toluene using K_2CO_3 as a base and $Pd(PPh_3)_4$ as catalyst, this reaction afforded regioselectively the 8-bromo-6-phenylpurine nucleoside **3** in 56% yield (27% of unreacted starting compound **2** was recovered). Analogous cross-coupling of **2** with 3.6 equivalents of phenylboronic acid gave the 6,8-diphenylpurine **4a** in a good yield of 83% (Scheme 1).



i) (a) $PhB(OH)_2$, (b) Me_3Al, (c) Et_3Al, (d) BnZnCl;
ii) (a) NaOMe, (b) NaOH, (c) NH_3/MeOH, (d) Me_2NH/EtOH; (e) 1. thiourea, 2. NaOMe

SCHEME 1

The 8-bromo-6-phenylpurine **3** was used as a key intermediate for further derivatizations in position 8 (for some recent examples of cross-coupling reactions in position 8, see ref.[18]). Cross-coupling reactions of **3** with trimethylaluminium[19] and triethylaluminium gave rise to the 8-methyl- and 8-ethylpurines **4b** (70% yield) and **4c** (55% yield), respectively. Similarly, the reaction of **3** with benzylzinc chloride[2] gave the 8-benzyl-6-phenylpurine **4d** in 52% yield. Treatment of the protected 6,8-disubstituted purines **4a**–**4d** with catalytic amount of sodium methoxide in methanol gave free ribonucleosides **5a**–**5d** in the yields of 58–83% after crystallization.

Nucleophilic substitutions of the 8-bromo-6-phenylpurine **3** were another possible approach for the derivatization as the bromine in position 8 of purine is very reactive[20–22]. Surprisingly, even the treatment of the 8-bromopurine **3** with catalytic amount of sodium methoxide in methanol at ambient temperature (originally meant to simply deprotect the bromopurine nucleoside) led to complete displacement of the bromine to give the 8-methoxy-6-phenylpurine ribonucleoside **6a** in 84% yield. This high reactivity of 8-bromo-6-phenylpurine is in contrast to that of 2-halo-6-phenylpurine nucleosides that were deprotected[6] under the same conditions without any nucleophilic substitution of the halogene (Cl, Br or I) in position 2. Analogously, treatment of compound **3** with aqueous NaOH gave the 8-hydroxypurine nucleoside **6b** in 65% yield (this simple reaction turned out to be more efficient than standard use of sodium acetate in acetic acid[20], which led to complex mixture). Reaction of compound **3** with saturated methanolic ammonia at ambient temperature gave a mixture of the desired 8-amino-6-phenylpurine nucleoside **6c** (54%) and 8-methoxypurine **6a** as side-product (15%). This very high reactivity is in contrast to that of 2′,3′,5′-tri-*O*-acetyl-8-bromoadenosine, which was deprotected[15] by methanolic ammonia without any substitution of the bromine. Ethanolic dimethylamine (analogously to ref.[21]) also reacted with **3** at ambient temperature to give the 8-dimethylamino derivative **6d** in 77% yield. In all the above nucleophilic substitutions, the acetyl protective groups were cleaved simultaneously to give directly the free ribonucleosides **6a**–**6d**. Treatment of **3** with thiourea (analogously to ref.[22]) gave 6-phenyl-8-sulfanyl-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine that was deprotected to the free nucleoside **6e** by NaOMe in methanol. Some of the final free nucleosides could not be crystallized directly from the crude products and had to be purified by preparative HPLC.

All compounds were completely characterized by NMR and mass spectra. Assignment of the signals was based on COSY, HMBC and HMQC experi-

ments, as well as on analogy with our previous results[1–7]. In most cases, the presence of the substituent in position 8 caused an up-field shift of the H-1′. Some of the final free nucleosides appeared to be quite hygroscopic. In compounds **6b** and **6e**, there is a possibility of tautomerism of 8-hydroxy- or 8-sulfanylpurine to 7*H*-purin-8(9*H*)-one or -thione, respectively. We have not studied this phenomenon thoroughly but, as the ^{13}C NMR spectral patterns were similar to the recently described analogous 8-substituted adenines[20,22], we suppose that also here the 8-(thi)oxo-tautomers prevail.

In conclusion, the 8-substituted 6-phenylpurine ribonucleosides were prepared by regioselective Suzuki–Miyaura cross-coupling reaction of 8-bromo-6-iodopurine nucleoside **2** with phenylboronic acid, followed by another cross-coupling or nucleophilic substitution and/or deprotection. The title nucleoside analogues **5a**–**5d**, **6a**–**6e** were tested for their cytostatic activity (inhibition of cell growth of the following cell cultures: 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 human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119)). In contrast to the significant *in vitro* activity of the corresponding 8-unsubstituted 6-phenylpurine ribonucleosides in these cell lines, none of the 8-substituted 6-phenylpurine nucleosides exerted any considerable activity in any of these assays[23].

EXPERIMENTAL

Unless otherwise stated, solvents were evaporated at 40 °C/2 kPa and compounds were dried at 60 °C/2 kPa. 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 ^1H and 100.6 MHz for ^{13}C nuclei), a Bruker DRX 500 (500 MHz for ^1H and 125.8 MHz for ^{13}C). Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. TMS was used as internal standard. 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. Preparative HPLC separations (*ca* 70 mg batches of mixtures) were performed on a column (20 × 100 mm) packed with 7 μm C18 reversed phase (Waters Delta 600 chromatograph) using a linear gradient MeOH/H_2O (1:4 to 9:1) as eluent. Preparative TLC was carried out on 40 × 17 × 0.4 cm loose layers of silica gel containing a UV indicator. Cytostatic activity tests were performed as described in ref.[1] 8-Bromoadenosine was prepared according to ref.[13]

8-Bromo-2′,3′,5′-tri-*O*-acetyladenosine (**1**)

Acetic anhydride (33 ml, 350 mmol) was added to a stirred solution of 8-bromoadenosine (9 g, 26 mmol) in pyridine (200 ml) at 0 °C. The stirred mixture was slowly allowed to reach ambient temperature and the stirring was contunued overnight. EtOH (10 ml) was added and the mixture was stirred for another 1 h. Then the solvents were evaporated *in vacuo* and the residue was co-distilled with EtOH (2 × 100 ml) and toluene (2 × 100 ml). The residue was re-crystallized from EtOH/toluene (1:1) to give 7.1 g (58%) of compound **1**; m.p. 188–189 °C (ref.[15] 187–188 °C).

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

A mixture of compound **1** (8 g, 17 mmol), CH_2I_2 (23.2 ml, 288 mmol), i-AmONO (24 ml, 178 mmol) and acetonitrile (130 ml) was refluxed for 8 h. Then the solvents were evaporated *in vacuo*, the residue was dissloved in chloroform (200 ml) and washed with 10% aqueous $Na_2S_2O_3$ (2 × 150 ml) and H_2O (150 ml). The organic phase was evaporated and the residue was chromatographed on a silica gel column (250 g, ethyl acetate/hexanes 1:3 to 3:1) to give the crude product which was recrystallized from CH_2Cl_2/heptane to yield **2** (4.4 g, 45%) as yellowish solid; m.p. 149–151 °C, $[\alpha]_D$ –0.3 (*c* 0.4, DMF). FAB MS, *m/z* (rel.%): 585/583 (50) [M + H], 327/325 (40), 92 (100). ^{1}H NMR ($CDCl_3$, 500 MHz): 2.03, 2.10 and 2.16 (3 × s, 3 × 3 H, CH_3CO); 4.31 (dd, 1 H, *J* = 12.0 and 5.8, H-5′a); 4.39–4.47 (m, 1 H, H-4′); 4.49 (dd, 1 H, *J* = 12.0 and 3.6, H-5′b); 5.86 (t, 1 H, *J* = 5.9, H-3′); 6.12 (d, 1 H, *J* = 4.5, H-1′); 6.32 (dd, 1 H, *J* = 5.9 and 4.5, H-2′); 8.62 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 125.8 MHz): 20.35, 20.48 and 20.62 (CH_3); 62.73 (CH_2-5′); 70.23 (CH-3′); 71.81 (CH-2′); 80.25 (CH-4′); 89.11 (CH-1′); 120.71 (C-5); 133.31, 139.39 and 148.32 (C-4, C-6 and C-8); 151.89 (CH-2); 169.34, 169.47 and 170.38 (CO). HR MS (FAB), calculated for $C_{16}H_{17}{}^{81}BrIN_4O_7$ [M + H]: 584.9305; found: 584.9326. For $C_{16}H_{16}BrIN_4O_7$ (583.1) calculated: 32.96% C, 2.77% H, 13.70% Br, 21.76% I, 9.61% N; found: 33.16% C, 2.87% H, 13.75% Br, 21.39% I, 9.29% N.

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

Toluene (20 ml) was added to an argon-purged flask containing **2** (1.162, 2 mmol), phenylboronic acid (270 mmol, 2.2 mmol), K_2CO_3 (400 mg, 2.9 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol). The mixture was stirred at 100 °C under argon for 8 h. Then the solvent was evaporated *in vacuo* and the residue was chromatographed on a silica gel column (100 g, ethyl acetate/hexanes 1:3 to 3:1) to give the product **3** (600 mg, 56%) followed by unreacted starting compound (320 mg, 27%). Compound **3** was isolated as a colorless foam. FAB MS, *m/z* (rel.%): 535/533 (15) [M + H], 377/375 (100). ^{1}H NMR ($CDCl_3$, 500 MHz): 2.05, 2.12 and 2.18 (3 × s, 3 × 3 H, CH_3CO); 4.36 (dd, 1 H, *J* = 12.0 and 5.7, H-5′a); 4.42–4.46 (m, 1 H, H-4′); 4.54 (dd, 1 H, *J* = 12.0 and 2.8, H-5′b); 5.98 (t, 1 H, *J* = 5.9, H-3′); 6.21 (d, 1 H, *J* = 4.0, H-1′); 6.42 (t, 1 H, *J* = 5.0, H-2′); 7.54–7.56 (m, 3 H, H-arom.); 8.70 (d, 2 H, *J* = 7.3, H-arom.); 8.98 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 125.8 MHz): 20.41, 20.51 and 20.65 (CH_3); 62.87 (CH_2-5′); 70.34 (CH-3′); 72.03 (CH-2′); 80.11 (CH-4′); 88.81 (CH-1′); 128.73, 129.74 and 131.34 (CH-arom.); 131.52, 132.61 and 134.84 (C-5, C-6 and C-*i*-arom.); 152.36 (CH-2); 152.84 and 154.20 (C-4 and C-8); 169.41, 169.54 and 170.52 (CO). HR MS (FAB), calculated for $C_{22}H_{22}{}^{81}BrN_4O_7$ [M + H]: 535.0651; found: 535.0647.

6,8-Diphenyl-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine (**4a**)

Toluene (10 ml) was added to an argon-purged flask containing **2** (290, 0.5 mmol), phenylboronic acid (224 mmol, 1.8 mmol), K_2CO_3 (200 mg, 1.5 mmol) and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol). The mixture was stirred at 100 °C under argon for 8 h. Then the solvent was evaporated *in vacuo* and the residue was chromatographed on a silica gel column (100 g, ethyl acetate/hexanes 1:3 to 3:1) to give the product **4a** (220 mg, 83%) as a colorless foam. FAB MS, *m/z* (rel.%): 531 (15) [M + H], 273 (100). ^{1}H NMR ($CDCl_3$, 400 MHz): 2.02, 2.07 and 2.12 (3 × s, 3 × 3 H, CH_3CO); 4.36–4.42 (m, 2 H) and 4.54–4.60 (m, 1 H, H-4′ and H-5′); 6.06–6.08 (m, 2 H, H-1′ and H-3′); 6.56–6.58 (m, 1 H, H-2′); 7.49–7.61 (m, 6 H, H-arom.); 7.88–7.89 (m, 2 H, H-arom.); 8.83 (d, 2 H, *J* = 6.7, H-arom.); 9.03 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 20.36, 20.49 and 20.69 (CH_3); 62.90 (CH_2-5′); 70.56 (CH-3′); 72.05 (CH-2′); 79.93 (CH-4′); 87.98 (CH-1′); 127.94, 128.62, 129.00, 129.87, 129.98 and 130.97 (CH-arom.); 128.83 and 131.22 (C-5 and C-*i*-arom.); 152.02 (CH-2); 153.33, 154.66 and 155.33 (C-4, C-6 and C-8); 169.30, 169.48 and 170.63 (CO). HR MS (FAB), calculated for $C_{28}H_{27}N_4O_7$ [M + H]: 531.1880; found: 531.1862.

8-Methyl-6-phenyl-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine (**4b**)

Trimethylaluminium (2 M solution in toluene, 1.5 ml, 3 mmol) was added dropwise to a stirred solution of **3** (356 mg, 0.66 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 into chloroform (2 × 100 ml). The organic layers were dried with $MgSO_4$ and evaporated. The residue was chromatographed on a column (100 g, ethyl acetate/hexanes 1:3 to 3:1) to give the product **4b** (220 mg, 70%) as a colorless foam. FAB MS, *m/z* (rel.%): 469 (32) [M + H], 211 (100). ^{1}H NMR ($CDCl_3$, 500 MHz): 2.04, 2.11 and 2.18 (3 × s, 3 × 3 H, CH_3CO); 2.77 (s, 3 H, CH_3); 4.36 (dd, 1 H, *J* = 12.0 and 5.5, H-5′a); 4.41–4.45 (m, 1 H, H-4′); 4.54 (dd, 1 H, *J* = 12.0 and 3.1, H-5′b); 5.98 (t, 1 H, *J* = 6.0, H-3′); 6.07 (d, 1 H, *J* = 4.4, H-1′); 6.31 (dd, 1 H, *J* = 4.4 and 6.0, H-2′); 7.50–7.58 (m, 3 H, H-arom.); 8.72 (d, 2 H, *J* = 7.3, H-arom.); 8.95 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 125.8 MHz): 14.84, 20.47, 20.54 and 20.64 (CH_3); 63.00 (CH_2-5′); 70.45 (CH-3′); 72.48 (CH-2′); 79.90 (CH-4′); 87.05 (CH-1′); 128.64, 129.62 and 130.74 (CH-arom.); 130.48 and 135.65 (C-5 and C-*i*-arom.); 151.65 (CH-2); 153.21, 153.56 and 153.65 (C-4, C-6 and C-8); 169.57 and 170.48 (CO). HR MS (FAB), calculated for $C_{23}H_{25}N_4O_7$ [M + H]: 469.1723; found: 469.1717.

8-Ethyl-6-phenyl-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine (**4c**)

This compound was prepared in the same manner as **4b** starting from **3** (270 mg, 0.5 mmol), Et_3Al (0.9 M solution in hexane, 2 ml, 1.8 mmol), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and THF (10 ml). Yield 135 mg (55%). Colorless foam. FAB MS, *m/z* (rel.%): 483 (10) [M + H], 225 (100). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.51 (t, 3 H, *J* = 7.4, C**H**$_3$CH$_2$); 2.03, 2.09 and 2.16 (3 × s, 3 × 3 H, CH_3CO); 3.03 (q, 2 H, *J* = 7.4, C**H**$_2$CH$_3$); 4.34–4.43 (m, 2 H, H-5′a and H-4′); 4.53 (dd, 1 H, *J* = 11.4 and 2.4, H-5′b); 5.97 (t, 1 H, *J* = 5.6, H-3′); 6.05 (d, 1 H, *J* = 4.3, H-1′); 6.38 (dd, 1 H, *J* = 4.3 and 5.6, H-2′); 7.49–7.57 (m, 3 H, H-arom.); 8.76 (d, 2 H, *J* = 7.3, H-arom.); 8.93 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 11.59 (**C**H$_3$CH$_2$); 20.43, 20.53 and 20.63 (CH_3); 21.55 (CH_3**C**H$_2$); 62.98 (CH_2-5′); 70.55 (CH-3′); 72.31 (CH-2′); 79.96 (CH-4′); 86.77

(CH-1′); 128.58, 129.72 and 130.71 (CH-arom.); 135.75 (C-*i*-arom.); 151.57 (CH-2); 153.35, 153.54 and 157.91 (C-4, C-6 and C-8); 169.46, 169.52 and 170.50 (CO). HR MS (FAB), calculated for $C_{24}H_{27}N_4O_7$ [M + H]: 483.1880; found: 483.1868.

8-Benzyl-6-phenyl-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine (**4d**)

THF (10 ml) was added to an argon-purged flask containing the **3** (420 mg, 0.8 mmol) and $Pd(PPh_3)_4$ (59 mg, 0.05 mmol). The mixture was stirred at ambient temperature for 10 min and, after dissolution of the solids, a solution of benzylzinc chloride (Rieke® organozinc reagent, 0.5 M solution in THF, 5 ml, 2.5 mmol) was added dropwise at ambient temperature (within 10 min). The stirring at ambient temperature was continued for 15 min followed by stirring at 60 °C for 8 h. Then the reaction mixture was allowed to stand overnight at ambient temperature 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 with anhydrous $MgSO_4$ and evaporated *in vacuo*. Column chromatography of the residue on silica gel (50 g, ethyl acetate/hexanes 1:3 to 3:1) afforded, after evaporation and drying, the product **4d** as amorphous solid (223 mg, 52%). FAB MS, *m/z* (rel.%): 545 (30) [M + H], 287 (100). ^{1}H NMR ($CDCl_3$, 500 MHz): 1.85, 2.05 and 2.10 (3 × s, 3 × 3 H, CH_3CO); 4.31–4.61 (m, 5 H, H-4′, H-5′ and CH_2Ph); 5.94–5.97 (m, 2 H, H-1′ and H-3′); 6.24 (dd, 1 H, *J* = 4.4 and 5.7, H-2′); 7.25–7.25 (m, 5 H, H-arom.); 7.52–7.63 (m, 3 H, H-arom.); 8.77 (d, *J* = 7.1, H-arom.); 9.05 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 125.8 MHz): 20.20, 20.44 and 20.66 (CH_3); 34.83 (CH_2Ph); 63.03 (CH_2-5′); 70.31 (CH-3′); 72.01 (CH-2′); 79.76 (CH-4′); 87.11 (CH-1′); 127.30, 128.42, 128.64, 128.95, 129.78 and 130.85 (CH-arom.); 135.35 and 135.65 (C-5 and C-*i*-arom.); 151.93 (CH-2); 153.24, 154.18 and 154.75 (C-4, C-6 and C-8); 168.89, 169.34 and 170.53 (CO). HR MS (FAB), calculated for $C_{24}H_{27}N_4O_7$ [M + H]: 545.2036; found: 545.2068.

Deprotection of Nucleosides **4a**–**4d**. General Procedure

A 1 M methanolic MeONa (100 μl, 0.1 mmol) was added to a solution of a protected nucleoside **4a**–**4d** (0.25–0.5 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 column (silica gel 50 g, ethyl acetate/MeOH 9:1). The crude products were recrystallized from EtOH (96% aq.)/toluene/heptane to give free nucleosides **5a**–**5d**.

6,8-Diphenyl-9-(β-D-ribofuranosyl)purine (**5a**). White solid; yield 83%; m.p. 112–116 °C; $[\alpha]_D$ –31.3 (*c* 0.5, DMF). FAB MS, *m/z* (rel.%): 405 (10) [M + H], 273 (100). ^{1}H NMR (DMSO-d_6, 400 MHz): 3.58–3.65 (m, 1 H, H-5′a); 3.74–3.80 (m, 1 H, H-5′b); 3.94–3.98 (m, 1 H, H-4′); 4.27–4.30 (m, 1 H, H-3′); 5.11 (dd, 1 H, *J* = 6.9 and 5.2, H-2′); 5.22 (d, 1 H, *J* = 4.6, 3′-OH); 5.36 (t, 1 H, *J* = 5.8, 5′-OH); 5.50 (d, 1 H, *J* = 6.1, 2′-OH); 5.88 (d, 1 H, *J* = 6.5, H-1′); 7.56–7.70 (m, 6 H, H-arom.); 7.89–7.92 (m, 2 H, H-arom.); 8.86 (d, 2 H, *J* = 7.6, H-arom.); 9.04 (s, 1 H, H-2). ^{13}C NMR (DMSO-d_6, 100.6 MHz): 61.91 (CH_2-5′); 70.52 and 70.62 (CH-2′ and CH-3′); 86.27 (CH-4′); 89.41 (CH-1′); 128.71, 128.86, 129.43, 129.86, 131.02 and 131.17 (CH-arom.); 130.69 and 135.21 (C-5 and C-*i*-arom.); 151.39 (CH-2); 152.91, 153.22 and 156.15 (C-4, C-6 and C-8). HR MS (FAB), calculated for $C_{22}H_{21}N_4O_4$ [M + H]: 405.1563; found: 405.1530. For $C_{22}H_{20}N_4O_4$ (404.4) calculated: 65.34% C, 4.98% H, 13.85% N; found: 65.23% C, 5.31% H, 13.56% N.

8-Methyl-6-phenyl-9-(β-D-ribofuranosyl)purine (**5b**). White solid; yield 71%; m.p. 149–151 °C; $[\alpha]_D$ –64.3 (*c* 0.5, DMF). FAB MS, *m/z* (rel.%): 343 (70) [M + H], 211 (100). ^{1}H NMR (DMSO-d_6, 500 MHz): 2.76 (s, 1 H, CH_3); 3.56–3.62 (m, 1 H, H-5′a); 3.73 (dd, 1 H, *J* = 4.5 and 12.0, H-5′b); 3.98–4.02 (brm, 1 H, H-4′); 4.24–4.27 (m, 1 H, H-3′); 4.97–5.02 (m, 1 H, H-2′); 5.18 (dd, 1 H, *J* = 4.8 and 7.0, 5′-OH); 5.29 (d, 1 H, *J* = 4.8, 3′-OH); 5.44 (d, 1 H, *J* = 6.5, 2′-OH); 5.98 (d, 1 H, *J* = 6.6, H-1′); 7.56–7.62 (m, 3 H, H-arom.); 8.79–8.82 (m, 2 H, H-arom.); 8.92 (s, 1 H, H-2). ^{13}C NMR (DMSO-d_6, 125.8 MHz): 15.49 (CH_3); 62.21 (CH_2-5′); 70.88 and 71.98 (CH-2′ and CH-3′); 86.55 (CH-4′); 88.87 (CH-1′); 129.10, 129.73 and 131.40 (CH-arom.); 130.53 (C-5); 135.79 (C-*i*-arom.); 151.28 (CH-2); 151.82, 153.72 and 155.77 (C-4, C-6 and C-8). HR MS (FAB), calculated for $C_{17}H_{19}N_4O_4$ [M + H]: 343.1406; found: 343.1437. For $C_{17}H_{18}N_4O_4$ (342.3) calculated: 59.64% C, 5.30% H, 16.37% N; found: 59.35% C, 5.45% H, 16.05% N.

8-Ethyl-6-phenyl-9-(β-D-ribofuranosyl)purine (**5c**). Yellowish hygroscopic solid; yield 68%; m.p. 133–136 °C; $[\alpha]_D$ –52.3 (*c* 0.4, DMF). FAB MS, *m/z* (rel.%): 357 (15) [M + H], 225 (100). ^{1}H NMR (DMSO-d_6, 400 MHz): 1.41 (t, 3 H, *J* = 7.1, C**H**$_3$CH$_2$); 3.09 (q, 2 H, *J* = 7.1, CH$_3$C**H**$_2$); 3.55–3.62 (m, 1 H, H-5′a); 3.70–3.76 (m, 1 H, H-5′b); 4.02 (br, 1 H, H-4′); 4.27 (br, 1 H, H-3′); 5.06 (br, 1 H, H-2′); 5.17, 5.26 and 5.43 (3 × brs, 3 × 1 H, OH); 5.96 (d, 1 H, *J* = 6.4, H-1′); 7.58–7.5 (m, 3 H, H-arom.); 8.80–8.84 (m, 2 H, H-arom.); 8.92 (s, 1 H, H-2). ^{13}C NMR (DMSO-d_6, 100.6 MHz): 11.68 (**C**H$_3$CH$_2$); 21.20 (CH$_3$**C**H$_2$); 61.87 (CH_2-5′); 70.56 (CH-3′); 71.35 (CH-2′); 86.20 (CH-4′); 88.33 (CH-1′); 126.62, 129.30 and 130.91 (CH-arom.); 130.19 (C-5); 135.38 (C-*i*-arom.); 150.78 (CH-2); 151.60, 153.25 and 159.49 (C-4, C-6 and C-8). HR MS (FAB), calculated for $C_{18}H_{21}N_4O_4$ [M + H]: 357.1563; found: 357.1516. For $C_{18}H_{20}N_4O_4 \cdot 2H_2O$ (392.4) calculated: 55.09% C, 6.16% H, 14.28% N; found: 54.80% C, 6.32% H, 13.89% N.

8-Benzyl-6-phenyl-9-(β-D-ribofuranosyl)purine (**5d**). Yellowish solid; yield 58%; m.p. 160–162 °C; $[\alpha]_D$ –117.7 (*c* 0.5, DMF). FAB MS, *m/z* (rel.%): 419 (8) [M + H], 287 (100). ^{1}H NMR (DMSO-d_6, 400 MHz): 3.56–3.62 (m, 1 H, H-5′a); 3.73 (dd, 1 H, *J* = 4.4 and 12.0, H-5′b); 3.95–3.98 (m, 1 H, H-4′); 4.24–4.29 (m, 1 H, H-3′); 4.53 (s, 2 H, CH_2Ph); 4.99 (dd, 1 H, *J* = 6.3 and 5.7, H-2′); 5.19 (dd, 1 H, *J* = 4.7 and 7.5, 5′-OH); 5.26 (d, 1 H, *J* = 4.8, 3′-OH); 5.37 (d, 1 H, *J* = 6.7, 2′-OH); 6.02 (d, 1 H, *J* = 6.6, H-1′); 7.34–7.36 and 7.57–7.61 (m, 8 H, H-arom.); 8.78–8.81 (m, 2 H, H-arom.); 8.95 (s, 1 H, H-2). ^{13}C NMR (DMSO-d_6, 100.6 MHz): 33.50 (CH_2Ph); 61.77 (CH_2-5′); 70.44 (CH-3′); 71.75 (CH-2′); 86.28 (CH-4′); 88.75 (CH-1′); 126.82, 128.62, 128.99, 129.35, 129.87 and 131.02 (CH-arom.); 130.31 (C-5); 135.28 and 135.88 (C-*i*-arom.); 151.03 (CH-2); 152.06, 153.07 and 156.49 (C-4, C-6 and C-8). HR MS (FAB), calculated for $C_{23}H_{23}N_4O_4$ [M + H]: 419.1719; found: 419.1724. For $C_{23}H_{22}N_4O_4$ (418.4) calculated: 66.02% C, 5.30% H, 13.39% N; found: 66.34% C, 5.52% H, 13.07% N.

8-Methoxy-6-phenyl-9-(β-D-ribofuranosyl)purine (**6a**)

This compound was obtained by treatment of **3** (190 mg, 0.36 mmol) with 1 M methanolic NaOMe (100 μl, 0.1 mmol) in methanol (10 ml) after analogous work-up as in the above general procedure. White solid; yield 84%; m.p. 102–104 °C; $[\alpha]_D$ –39.4 (*c* 0.5, DMF). FAB MS, *m/z* (rel.%): 359 (60) [M + H], 227 (100). ^{1}H NMR (DMSO-d_6, 500 MHz): 3.50–3.55 (brm, 1 H, H-5′a); 3.64–3.69 (brm, 1 H, H-5′b); 3.91–3.95 (brm, 1 H, H-4′); 4.21–4.24 (brm, 1 H, H-3′); 4.28 (s, 3 H, OCH_3); 4.95–5.03 (m, 2 H, H-2′ and 5′-OH); 5.21 (d, 1 H, *J* = 4.6, 3′-OH); 5.44 (d, 1 H, *J* = 5.6, 2′-OH); 5.89 (d, 1 H, *J* = 6.0, H-1′); 7.54–7.60 (m, 3 H, H-arom.); 7.72–7.74 (m, 2 H, H-arom.); 8.82 (s, 1 H, H-2). ^{13}C NMR (DMSO-d_6, 125.8 MHz): 58.02

(OCH_3); 61.87 (CH_2-5′); 70.49 and 70.71 (CH-2′ and CH-3′); 85.67 (CH-4′); 86.73 (CH-1′); 128.22 (C-5); 128.60, 128.88 and 130.55 (CH-arom.); 135.43 (C-*i*-arom.); 150.04 (CH-2); 148.72, 152.71 and 158.21 (C-4, C-6 and C-8). For $C_{17}H_{18}N_4O_5 \cdot 1/2H_2O$ (367.4) calculated: 55.58% C, 5.21% H, 15.25% N; found: 55.50% C, 5.10% H, 14.96% N.

8-Hydroxy-6-phenyl-9-(β-D-ribofuranosyl)purine (**6b**)

A solution of bromo derivative **3** (350 mg, 0.66 mmol) in 0.5 M sodium hydroxide (10 ml) was stirred at room temperature for 2 days. The mixture was neutralized by addition of 0.5 M acetic acid and evaporated *in vacuo*. The residue was subjected to preparative TLC (7% MeOH/EtOAc). After crystallization from water/methanol the product was obtained as white solid (160 mg, 65%); m.p. 233–235 °C; $[\alpha]_D$ –37.3 (*c* 0.6, DMF). FAB MS, *m/z* (rel.%): 345 (30) [M + H], 213 (100). ^{1}H NMR (DMSO-d_6, 500 MHz): 3.48–3.53 (m, 1 H, H-5′a); 3.66 (dd, 1 H, *J* = 4.7 and 11.8, H-5′b); 3.88–3.91 (m, 1 H, H-4′); 4.21–4.24 (m, 1 H, H-3′); 4.87 (dd, 1 H, *J* = 5.0 and 6.8, 5′-OH); 4.99 (dd, 1 H, *J* = 5.8 and 5.9, H-2′); 5.13 (d, 1 H, *J* = 5.0, 3′-OH); 5.32 (d, 1 H, *J* = 5.8, 2′-OH); 5.82 (d, 1 H, *J* = 5.9, H-1′); 7.52–7.57 and 7.97–7.99 (m, 6 H, H-arom. and OH); 8.69 (s, 1 H, H-2). ^{13}C NMR (DMSO-d_6, 100.6 MHz): 62.11 (CH_2-5′); 69.94 (CH-2′); 70.63 (CH-3′); 85.25 (CH-4′); 85.80 (CH-1′); 118.24 (C-5); 128.16, 128.76 and 130.10 (CH-arom.); 134.66 (C-*i*-arom.); 141.77 (C-6); 150.12 (CH-2); 150.23 (C-4); 152.97 (C-8). For $C_{16}H_{16}N_4O_5 \cdot 3/2H_2O$ (366.4) calculated: 51.75% C, 5.16% H, 15.09% N; found: 52.20% C, 5.24% H, 14.70% N.

8-Amino-6-phenyl-9-(β-D-ribofuranosyl)purine (**6c**)

Bromo derivative **3** (600 mg, 1.13 mmol) was dissolved in methanolic ammonia (25 ml) and stirred at room temperature overnight. The mixture was evaporated *in vacuo* and the residue was separated by preparative HPLC to obtain desired amino derivative **6c** (220 mg, 54%) followed by 8-methoxy derivative **6a** (60 mg, 15%) as a side product. Compound **6c**: white amorphous solid; $[\alpha]_D$ –41.6 (*c* 0.6, DMF). FAB MS, *m/z* (rel.%): 344 (90) [M + H], 212 (100). ^{1}H NMR (DMSO-d_6, 400 MHz): 3.67–3.70 (m, 2 H, H-5′); 4.02–4.04 (m, 1 H, H-4′); 4.15–4.19 (m, 1 H, H-3′); 4.71 (dd, 1 H, *J* = 6.3 and 7.4, H-2′); 5.18 (d, 1 H, *J* = 4.0, 3′-OH); 5.35 (d, 1 H, *J* = 6.3, 2′-OH); 5.67 (t, 1 H, *J* = 4.7, 5′-OH); 6.09 (d, 1 H, *J* = 7.4, H-1′); 7.50–7.55 (m, 3 H, H-arom.); 8.58 (s, 1 H, H-2); 8.71–8.75 (m, 2 H, H-arom.). ^{13}C NMR (DMSO-d_6, 100.6 MHz): 61.49 (CH_2-5′); 70.56 (CH-2′); 70.92 (CH-3′); 85.78 (CH-4′); 86.47 (CH-1′); 128.26, 128.49 and 129.47 (CH-arom.); 131.14 (C-5); 136.41 (C-*i*-arom.); 144.34 (C-6); 147.41 (CH-2); 154.00 and 155.31 (C-4 and C-8). HR MS (FAB), calculated for $C_{16}H_{18}N_5O_4$ [M + H]: 344.1359; found: 344.1320. For $C_{16}H_{17}N_5O_4 \cdot 1/2$MeOH (359.4) calculated: 55.15% C, 5.33% H, 19.49% N; found: 55.12% C, 5.37% H, 19.28% N.

8-Dimethylamino-6-phenyl-9-(β-D-ribofuranosyl)purine (**6d**)

Bromo derivative **3** (260 mg g, 0.52 mmol) was dissolved in a 33% solution of dimethylamine in ethanol (5 ml). The reaction mixture was stirred at room temperature for 2 days and evaporated *in vacuo*. The residue was purified by preparative HPLC and after crystallization from water/ethanol the product was obtained as white solid (150 mg, 77%); m.p. 173–174 °C; $[\alpha]_D$ –56.8 (*c* 0.9, DMF). FAB MS, *m/z* (rel.%): 372 (15) [M + H], 240 (100). ^{1}H NMR (DMSO-d_6, 400 MHz): 3.11 (s, 6 H, CH_3); 3.54–3.61 (m, 1 H, H-5′a); 3.73 (dd, 1 H, *J* = 4.8 and 11.8, H-5′b); 3.93–3.97 (m, 1 H, H-4′); 4.24–4.28 (m, 1 H, H-3′); 5.07 (dd, 1 H, *J* = 4.8

and 7.1, 5′-OH); 5.20 (d, 1 H, *J* = 4.9, 3′-OH); 5.25–5.30 (m, 1 H, H-2′); 5.42 (d, 1 H, *J* = 6.2, 2′-OH); 5.77 (d, 1 H, *J* = 6.7, H-1′); 7.50–7.60 (m, 3 H, H-arom.); 8.74 (s, 1 H, H-2); 8.77 (d, 2 H, *J* = 7.3, H-arom.). ^{13}C NMR (DMSO-d_6, 100.6 MHz): 41.83 (CH_3); 62.01 (CH_2-5′); 70.03 (CH-2′); 70.59 (CH-3′); 85.84 (CH-4′); 88.94 (CH-1′); 128.46, 128.83 and 130.19 (CH-arom.); 130.32 (C-5); 135.82 (C-*i*-arom.); 148.91 (CH-2); 147.63, 153.99 and 159.90 (C-4, C-6 and C-8). For $C_{18}H_{21}N_5O_5 \cdot 1/3H_2O$ (377.4) calculated: 57.29% C, 5.79% H, 18.56% N; found: 57.30% C, 5.80% H, 18.41% N.

6-Phenyl-8-sulfanyl-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine

Bromo derivative **3** (360 mg, 0.68 mmol) and thiourea (760 mg, 10 mmol) were dissolved in ethanol (10 ml) and the reaction mixture was stirred at 100 °C for 7 h. After cooling to room temperature, the white solid precipitate was filtered off and washed with ethanol to obtain crude product (220 mg, 67%) which was used for the next step without further purification. FAB MS, *m/z* (rel.%): 487 (25) [M + H], 229 (100). ^{1}H NMR ($CDCl_3$, 400 MHz): 2.00, 2.08 and 2.12 (3 × s, 3 × 3 H, CH_3CO); 4.23 (dd, 1 H, *J* = 12.0 and 5.7, H-5′a); 4.34–4.38 (m, 1 H, H-4′); 4.46 (dd, 1 H, *J* = 12.0 and 3.5, H-5′b); 5.83 (t, 1 H, *J* = 6.2, H-3′); 6.29 (dd, 1 H, *J* = 6.2 and 4.4, H-2′); 6.68 (d, 1 H, *J* = 4.4, H-1′); 7.56–7.59 (m, 3 H, H-arom.); 8.03–8.06 (m, 2 H, H-arom.); 8.88 (s, 1 H, H-2); 13.84 (brs, 1 H, SH). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 20.19, 20.31 and 20.45 (CH_3); 62.46 (CH_2-5′); 69.65 and 70.73 (CH-2′ and CH-3′); 78.89 (CH-4′); 86.18 (CH-1′); 120.50 (C-5); 128.74, 128.77 and 130.69 (CH-arom.); 134.00 (C-*i*-arom.); 144.51 (C-6); 151.05 (C-4); 151.38 (CH-2); 169.33, 169.34, 169.98 and 172.10 (3 × CO and C-8).

6-Phenyl-9-(β-D-ribofuranosyl)-8-sulfanylpurine (**6e**)

A 1 M methanolic MeONa (500 µl, 0.5 mmol) was added to a mixture of crude 6-phenyl-8-sulfanyl-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine (150 mg, 0.3 mmol) and methanol (10 ml). The resulting solution was stirred at room temperature for 1 h and then its pH adjusted to 6 by addition of 1 M acetic acid. Solvents were evaporated and the residue was chromatographed on preparative TLC (7% MeOH/EtOAc). The crude product was crystallized from water/methanol to give the title compound **6e** as white solid (80 mg, 72%); m.p. 262–263 °C; $[\alpha]_D$ –40.3 (*c* 0.5, DMF). FAB MS, *m/z* (rel.%): 361 (50) [M + H], 263 (100). ^{1}H NMR (DMSO-d_6, 500 MHz): 3.56 (dd, 1 H, *J* = 5.2 and 11.7, H-5′b); 3.72 (dd, 1 H, *J* = 4.3 and 11.7, H-5′b); 3.89–3.94 (m, 1 H, H-4′); 4.33–4.37 (m, 1 H, H-3′); 4.88 (brs, 1 H, 5′-OH); 5.13 (brs, 2 H, H-2′ and 3′-OH); 5.31 (brs, 1 H, 2′-OH); 6.48 (d, 1 H, *J* = 5.6, H-1′); 7.56–7.58 and 8.02–8.05 (m, 5 H, H-arom.); 8.83 (s, 1 H, H-2); 13.73 (s, 1 H, SH). ^{13}C NMR (DMSO-d_6, 100.6 MHz): 62.02 (CH_2-5′); 70.34 and 70.52 (CH-2′ and CH-3′); 85.34 (CH-4′); 88.90 (CH-1′); 120.50 (C-5); 128.73, 128.74 and 130.62 (CH-arom.); 134.09 (C-*i*-arom.); 144.20 (C-6); 151.13 (CH-2); 151.33 (C-4); 172.88 (C-8). For $C_{16}H_{16}N_4O_4S \cdot 1/3H_2O$ (366.4) calculated: 52.45% C, 4.58% H, 15.29% N; found: 52.51% C, 4.59% H, 14.98% N.

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