# Dichotomy in Regioselective Cross-Coupling Reactions of 6,8-Dichloropurines with Phenylboronic Acid and Methylmagnesium Chloride: Synthesis of 6,8-Disubstituted Purines

Michal Hocek,*[a] Dana Hocková,[a] Hana Dvořáková[b]

[a] Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nam. 2, 16610 Prague 6, Czech Republic
Fax +42(220)183559; E-mail: hocek@uochb.cas.cz

[b] NMR Laboratory, Prague Institute of Chemical Technology, 16628 Prague 6, Czech Republic

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**Abstract:** Pd-catalyzed cross-coupling reaction of 6,8-dichloro-9-(tetrahydropyran-2-yl)purine with one equivalent of phenylboronic acid proceeded regioselectively to give 8-chloro-6-phenylpurine, while the analogous Fe-catalyzed reaction with methylmagnesium chloride gave the 6-chloro-8-methylpurine derivative as major product. Both types of the monochloropurine intermediates were subjected to other cross-coupling reactions or nucleophilic substitutions affording the 9-(tetrahydropyran-2-yl)-6,8-disubstituted purines that were easily deprotected to 8-substituted 6-phenylpurines or 6-substituted 8-methylpurines. Attempted analogous reactions with benzylmagnesium chloride and phenylmagnesium bromide gave low conversions and little selectivity.

**Key words:** purines, nucleobases, cross-coupling reactions, iron, palladium

Purines bearing carbon substituents in the position 2, 6 and/or 8 are extensively studied as biologically active compounds and as tools in chemical biology. They are efficiently prepared[1] by cross-coupling reactions of halopurines with diverse organometallics. Also 2,6- and 6,8-disubstituted purines could be prepared by cross-coupling reactions of dihalopurines. General regioselectivity of these reactions differs by the type of the dihalopurines. While the 2,6-[2,3] and 6,8-dichloropurines[4] react with one equivalent of an organometallic reagent preferentially in the (more reactive) position 6, chloro- bromo- and iodopurines react in the position of the better leaving group (I > Br > Cl). In this way, by the selection of a proper starting dihalopurine, regioselective reactions can be accomplished either in position 2, 6 or 8, leaving the other halogen (Cl) available for another coupling or nucleophilic substitution. This approach has been recently used for the synthesis of 2- or 8-substituted 6-phenylpurine nucleosides,[5,6] 2-substituted 6-methylpurines[7] and carba-analogues of Myoseverin.[8]

As a continuation of the systematic study of regioselective cross-couplings of dihalopurines, we have focused on the synthesis of 8-substituted derivatives of important 6-phenyl- and 6-methylpurines. 6-Phenylpurine derivatives were found to exhibit cytostatic,[9] antimycobacterial and antibacterial[10] activity, while 6-methylpurine is a strongly cytotoxic compound considered for application in gene therapy in the form of its non-toxic 2′-deoxyribonucleoside prodrug.[11] The synthesis of 8-substituted derivatives of these purines should not only extend the knowledge of SAR (structure activity relationship) of this class of compounds but also complement the known regioselective cross-couplings of 6,8-dichloropurines with stannanes[4] by hitherto unpublished reactions with boronic acids and Grignard reagents.

9-(Tetrahydropyran-2-yl)-protected 6,8-dichloropurine (**1**)[12] was chosen as the starting compound for the regioselective cross-coupling reactions (Scheme 1, Table 1). The first reaction under study was the Suzuki–Miyaura coupling with phenylboronic acid.[13] The reaction of dichloropurine **1** with 1.1 equivalents of $PhB(OH)_2$ under $[Pd(PPh_3)_4]$ catalysis in toluene gave a mixture of the expected 8-chloro-6-phenylpurine **2a** in an acceptable yield of 60% followed by 6,8-diphenylpurine **2b** (11%) and traces of the unreacted starting compound **1** (6%). The analogous reaction of **1** with four equivalents of $PhB(OH)_2$ afforded the protected 6,8-diphenylpurine **2b** in 67% yield.

Fe-catalyzed reactions of aryl halides with Grignard reagents were recently developed[14] as an efficient cross-coupling methodology. It was also found[7] to be superior for regioselective methylation of 2,6-dichloropurines and our next goal was to study analogous reaction of 6,8-dichloropurines. Thus the reaction of **1** with 1.1 equivalents of methylmagnesium chloride in the presence of $Fe(acac)_3$ gave unexpectedly 6-chloro-8-methyl-9-tetrahydropyran-2-yl)purine (**3a**) in a moderate yield of 37%, followed by 6,8-dimethylpurine **3c** (14%) and unreacted starting compound **1** (34%). As the products were easily separable by column chromatography and the starting compound was recovered, despite the moderate yield, this reaction is still practical for the synthesis of **3a**. Reaction of **1** with 3–5 equivalents of MeMgCl gave mixtures of products, while finally the use of 9 equivalents of MeMgCl gave complete conversion to 6,8-dimethylpurine **3c** in 90% yield.

The dichotomy in regioselectivity of coupling reactions of **1** with phenylboronic acid (leading to 6-substitution) and with methylmagnesium chloride (leading to unexpected 8-substitution) is very interesting. Our next goal was to

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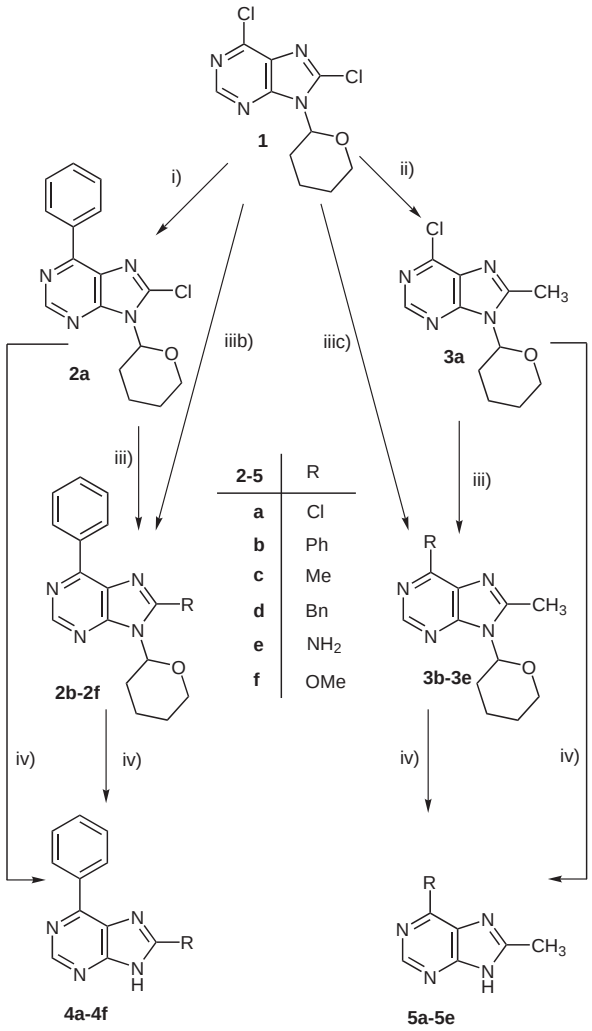
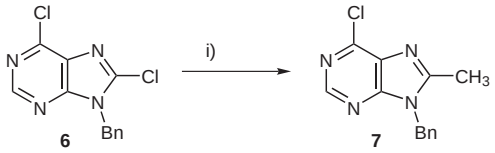



**Scheme 1** *Reagents and conditions*: i) $PhB(OH)_2$ (1.1 equiv), $K_2CO_3$, $Pd(PPh_3)_4$, toluene; ii) MeMgCl (1.1 equiv), $Fe(acac)_3$, THF/NMP; iii) b) $PhB(OH)_2$ (3–4 equiv), $K_2CO_3$, $Pd(PPh_3)_4$, toluene; c) MeMgCl (3 equiv), $K_2CO_3$, $Fe(acac)_3$, THF/NMP; d) BnZnCl, $Pd(PPh_3)_4$, THF; e) $NH_3$/EtOH; f) $NH_3$/MeOH; iv) Dowex 50WX8 ($H^+$ form), MeOH, $H_2O$

study the scope and to explain the course of the unexpected Fe-catalyzed reaction. Attempted reaction of **1** with one equivalent of phenylmagnesium bromide in the presence of $Fe(acac)_3$ gave only a very low conversion to a complex inseparable mixture of products. Also analogous Fe-catalyzed reaction of **1** with one equivalent of benzylmagnesium chloride afforded a complex mixture of products in which two products [6,8-dibenzyl-9-(tetrahydropyran-2-yl)purine and 6-benzyl-8-chloro-9-(tetrahydropyran-2-yl)purine] were identified (but not completely characterized).[15] Apparently, the scope of a synthetically useful application of this regioselective cross-coupling is limited to methylmagnesium chloride.

One of the possible explanations for the direction of the Fe-catalyzed reaction to position 8 was a complexation of either the Grignard reagent or the proposed catalytic species [$Fe(MgX)_2$] with the THP-oxygen. A model experiment reacting 9-benzyl-6,8-dichloropurine[4] (**6**, lacking the oxygen atom in proximity to the position 8) with one equivalent of methylmagnesium chloride was performed (Scheme 2). Major product of this reaction was 9-benzyl-6-chloro-8-methylpurine (**7**, 29%), accompanied by a minor amount (<10%) of an inseparable complex mixture of other products and recovered starting compound (45%). This result excludes the effect of the oxygen and thus the mechanism remains unclear.




**Scheme 2** i) MeMgCl (1.1 equiv), $Fe(acac)_3$, THF/NMP

Both protected monochloropurines **2a** and **3a** could be used in another cross-coupling or nucleophilic substitution reaction. Thus 8-chloro-6-phenyl-9-(tetrahydropyran-2-yl)purine (**2a**) was subjected to the Pd-catalyzed reaction with BnZnCl or to the Fe-catalyzed reaction with MeMgCl to give the corresponding 8-benzyl- **2d** or 8-methylpurines **2c** in good yields of 89 or 77%, respectively. Attempted ammonolysis of **2a** in methanolic ammonia gave a mixture of 8-methoxy- **2f** (58%) and 8-aminopurine **2e** (34%) derivatives. The use of ethanolic ammonia did not lead to any 8-ethoxypurine side-product and gave the 8-amino derivative **2e** in 69% yield. Analogously, the 6-chloro-8-methyl-9-(tetrahydropyrany-2-yl)purine (**3a**) was subjected to the Pd-catalyzed reactions with $PhB(OH)_2$ or BnZnCl to give the corresponding 6-phenyl-

**Table 1** Regioselective Cross-Coupling Reactions of 6,8-Dichloropurines

| Entry | Dichloropurine | Reagent | Ratio | Products, Yield (%) | | |
|---|---|---|---|---|---|---|
| 1 | **1** | $PhB(OH)_2$[a] | 1:1.1 | **2a** (60) | **2b** (11) | **1** (6) |
| 2 | **1** | $PhB(OH)_2$[a] | 1:4 | – | **2b** (67) | – |
| 3 | **1** | MeMgCl[b] | 1:1.1 | **3a** (37) | **3c** (14) | **1** (34) |
| 4 | **1** | MeMgCl[b] | 1:9 | – | **3c** (90) | – |
| 5 | **6** | MeMgCl[b] | 1:1.1 | **7** (29) | – | **6** (45) |

[a] Catalyzed by $Pd(PPh_3)_4$.
[b] Catalyzed by $Fe(acac)_3$.

**3b** (88%) or 6-benzylpurine **3d** (96%) derivatives in good yields. Ammonolysis of **3a** in ethanolic ammonia gave the protected 8-methyladenine **3e** in 59% yield accompanied by some polar easily separable by-products (no 6-ethoxy derivative was detected).

All the THP protected derivatives **2a**–**f** and **3a**–**e** were deprotected by reflux of their ethanolic solutions in the presence of a catalytic amount of wet Dowex 50WX8 ($H^+$ form)[16] to give the 8-substituted 6-phenylpurine bases **4a**–**f** and 6-substituted 8-methylpurine bases **5a**–**e** in good yields.

In order to verify the structures of the 6,8-disubstituted purines (in particular, the structure of unexpected 6-chloro-8-methylpurine **3a**), several NMR experiments were performed in several model compounds. For the key intermediate **3a**, $^1H$-$^{13}C$ HMBC showed clear cross-peaks of OCHN to C-4 and C-8 and of $CH_3$ to C-8. Moreover, significant NOE interactions between $CH_3$ and THP-methylenes were found as an independent evidence of 8-methyl substitution. In 6-phenyl-8-chloropurine derivative **2a**, HMBC cross-peaks were found for NCHO to C-4 and C-8 and for *o*-$CH_{arom}$ to C-6. NOE interaction from *o*-$CH_{arom}$ to CH-2 also confirmed the 6-phenyl substitution. Further proof was based on analogous independent HMBC assignments in 6-benzyl-8-methylpurine **3d** and 8-benzyl-6-phenylpurine **2d**. Due to tautomerism of free bases **4** and **5**, many purine (in particular quaternary) carbon signals were extremely weak and some even did not appear in their $^{13}C$ NMR spectra (albeit combinations of several experiments).

In conclusion, the Suzuki–Miyaura cross-coupling reaction of THP-protected 6,8-dichloropurine (**1**) with one equivalent of phenylboronic acid follows the same regioselectivity as reported[4] for the reactions of **1** with stannanes to give the 6-phenyl-8-chloropurine **2a** as the major product accompanied by minor amounts of the disubstituted derivative **2b**. On the other hand, Fe-catalyzed coupling of **1** with one equivalent of methylmagnesium chloride proceeded with lower conversion to give the 6-chloro-8-methylpurine **3a** in a moderate yield of 37%. As substantial amounts of the starting compound could be recovered, even this lower yielding reaction could be used for the practical synthesis of **3a**. Both monochloropurines **2a** and **3a** could be used for another cross-coupling or nucleophilic substitution to give, after deprotection, a series of 8-substituted-6-phenylpurines **4** or 6-substituted-8-methylpurines **5** in good yields. None of the purine bases **4** and **5** showed any considerable cytostatic activity (in vitro inhibition of the cell growth in the following cell cultures: mouse leukemia L1210 cells (ATCC CCL 219); human promyelocytic leukemia HL60 cells (ATCC CCL 240); human cervix carcinoma HeLa S3 cells (ATCC CCL 2.2); and human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119).[9a]

Unless otherwise stated, solvents were evaporated at 40 °C/2 kPa and compounds were dried at 60 °C/2kPa. Melting points were determined on a Kofler block and are uncorrected. NMR spectra were measured on Bruker AMX-3 400 (400 MHz for $^1H$ and 100.6 MHz for $^{13}C$ nuclei), and Bruker DRX 500 spectrometers (500 MHz for $^1H$ and 125.8 MHz for $^{13}C$). TMS was used as an internal standard. Mass spectra were measured on ZAB-SEQ (VG Analytical). Microanalyses were performed on a Perkin-Elmer 240-II CHN Analyzer. Silica gel (ICN SiliTech, 32–63) was used for column chromatography. Toluene was 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. Methylmagnesium chloride, benzylmagnesium chloride, phenylmagnesium bromide and benzylzinc chloride were commercial solutions in THF (Aldrich).

### Cross-Coupling Reaction of Chloropurines with Methylmagnesium Chloride

*Method A*: MeMgCl (3 M solution in THF, 0.33 mL, 1 mmol, 1 mL, 3 mmol or 3 mL, 9 mmol) was added dropwise to a stirred solution of a chloropurine (1 mmol) and $Fe(acac)_3$ (103 mg, 0.29 mmol) in THF (20 mL) and NMP (1 mL) under Ar and the resulting reaction mixture was stirred at r.t. for 8 h. Then the mixture was poured onto a mixture of ice (ca. 100 mL) and $NH_4Cl$ (1 g) and the products were extracted with $CHCl_3$ (3 × 100 mL). Evaporation of the organic phase followed by a column chromatography on silica gel (100 g, EtOAc–hexanes, 1:3 → EtOAc) afforded the products.

### Cross-Coupling Reaction of Chloropurines with Phenylboronic Acid

*Method B*: Toluene (10 mL) was added to an argon-purged flask containing a chloropurine (1 mmol), $K_2CO_3$ (300 mg, 2.2 mmol), phenylboronic acid (122 mg, 1 mmol, 366 mg, 3 mmol or 488 mg, 4 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 r.t., the solvent was evaporated in vacuo and the residue was chormatographed as in Method A.

### Cross-Coupling Reaction of Chloropurines with Benzylzinc Bromide

*Method C*: BnZnCl (0.5 M solution in THF, 6 mL, 3 mmol or 2.2 mL, 1.1 mmol) was added dropwise to a stirred solution of a chloropurine (1 mmol) and $Pd(PPh_3)_4$ (60 mg, 0.05 mmol) in THF (20 mL) and the mixture was stirred at 80 °C for 8 h. Then the mixture was cooled to rt and poured onto a mixture of ice (ca. 100 mL) and $NH_4Cl$ (1 g) and the products were isolated in the same way as in Method A.

### Ammonolysis of Chloropurines

*Method D*: A mixture of a chloropurine (1 mmol) in sat. methanolic or ethanolic ammonia (30 mL) was heated in a sealed tube at 80 °C for 15–24 h. The solvent was evaporated and the residue chromatographed as in Method A.

### Cleavage of the THP-Protected Purines

*Method E*: A mixture of a THP-protected base **2** or **3** (0.5–1.5 mmol), Dowex 50WX 8 ($H^+$) (ca. 300 mg), EtOH (50 mL) and $H_2O$ (1 mL) was refluxed for 1 h, then filtered while hot and the resin was washed with hot EtOH (2 × 50 mL). The combined filtrates were evaporated and the residue codistilled with toluene. Crystallization of the residue afforded the free bases **4** or **5**.

### 8-Chloro-6-phenyl-9-(tetrahydropyran-2-yl)purine (2a)[4]

Prepared from **1** (273 mg, 1 mmol) by Method B [1.1 equiv of $PhB(OH)_2$] in 60% yield (188 mg); colorless foam.

$^1H$ NMR ($CDCl_3$, 500 MHz): δ = 1.63–1.93, 2.13–2.15 and 3.00–3.10 (m, 6 H, $CH_2$), 3.57–3.63 (dt, 1 H, *J* = 11.9, 2.0 Hz, H-5′a), 4.21–4.25 (m, 1 H, H-5′b), 5.82 (dd, 1 H, *J* = 11.3, 2.3 Hz, H-1′), 7.51–7.56 and 8.69–8.72 (m, 5 $H_{arom}$), 9.00 (s, 1 H, H-2).

$^{13}C$ NMR (APT, $CDCl_3$, 125.8 MHz): δ = 23.3, 24.7 and 28.9 ($CH_2$), 69.4 ($CH_2O$), 83.9 (NCHO), 128.7, 129.7 and 131.1 ($CH_{arom}$), 129.9

(C-5), 135.1 ($C_{ipso}$), 142.6 (C-8), 152.4 (CH-2), 153.2 and 153.7 (C-4 and C-6).

HMBC cross-peaks: NCHO to C-4 and C-8, *o*-$CH_{arom}$ to C-6.

NOE: *o*-$CH_{arom}$ to CH-2.

EI-MS: *m*/*z* (%) = 314 (8), 231 (56), 85 (77), 41 (100).

EI-HRMS: *m*/*z* calcd for $C_{16}H_{15}ClN_4O$: 314.0934; found: 314.0922.

**6,8-Diphenyl-9-(tetrahydropyran-2-yl)purine (2b)[4]**
Prepared from **1** (273 mg, 1 mmol) by Method B [4 equiv of $PhB(OH)_2$] in 67% yield (239 mg) or by Method B [1.1 equiv of $PhB(OH)_2$] in 11% yield (39 mg); colorless foam.

$^1$H NMR ($CDCl_3$, 500 MHz): δ = 1.58–2.06 and 3.08–3.20 (m, 6 H, $CH_2$), 3.71 (br t, 1 H, *J* = 11.5 Hz, H-5′a), 4.28 (br d, 1 H, *J* = 9.5 Hz, H-5′b), 5.66 (d, 1 H, *J* = 11.0 Hz, H-1′), 7.50–7.59, 7.94–7.97 and 8.85–8.88 (m, 10 $H_{arom}$), 9.05 (s, 1 H, H-2).

$^{13}$C NMR (APT, $CDCl_3$, 127.8 MHz): δ = 23.5, 24.7 and 28.6 ($CH_2$), 69.0 ($CH_2O$), 84.2 (NCHO), 128.6, 128.7, 129.9, 130.0, 130.7 and 130.8 ($CH_{arom}$ and overlapped $C_{ipso}$), 135.9 (C-5), 151.9 (CH-2), 154.1, 154.2 and 155.4 (C-4, C-6 and C-8).

EI-MS: *m*/*z* (%) = 356 (8), 272 (100), 85 (28).

EI-HRMS: *m*/*z* calcd for $C_{22}H_{20}N_4O$: 356.1637; found: 356.1640.

**8-Methyl-6-phenyl-9-(tetrahydropyran-2-yl)purine (2c = 3b)**
Prepared from **2a** (314 mg, 1 mmol) by Method A (3 equiv of MeMgCl) in 77% yield (226 mg) or from **3a** (253 mg, 1 mmol) by Method B [3 equiv of $PhB(OH)_2$] in 88% yield (259 mg); colorless crystals; mp 89–92 °C ($CH_2Cl_2$–heptane).

$^1$H NMR ($CDCl_3$, 500 MHz): δ = 1.67–2.15 and 2.46–2.56 (m, 6 H, $CH_2$), 2.86 (s, 3 H, $CH_3$), 3.79 (dt, 1 H, *J* = 11.7, 2.3 Hz, H-5′a), 4.21 (br d, 1 H, *J* = 11.3 Hz, H-5′b), 5.91 (dd, 1 H, *J* = 11.3, 2.4 Hz, H-1′), 7.50–7.59 (m, 3 $H_{arom}$), 8.74–8.77 (m, 2 $H_{arom}$), 8.97 (s, 1 H, H-2).

$^{13}$C NMR (APT, $CDCl_3$, 100.6 MHz): δ = 16.4 ($CH_3$), 23.2, 25.0 and 30.4 ($CH_2$), 69.2 ($CH_2O$), 82.8 (NCHO), 127.9, 128.6 and 130.6 ($CH_{arom}$), 130.2 (C-5), 135.9 ($C_{ipso}$), 151.5 (CH-2), 153.1, 153.4 and 153.9 (C-8, C-4 and C-6). NOE: $CH_3$ to NCHO.

EI-MS: *m*/*z* (%) = 294 (19), 210 (100), 85 (26).

EI-HRMS: *m*/*z* calcd for $C_{17}H_{18}N_4O$: 294.1481; found: 294.1482.

Anal. Calcd for $C_{17}H_{18}N_4O$ (294.4): C, 69.37; H, 6.16; N, 19.03. Found: C, 69.13; H, 6.10; N, 18.79.

**8-Benzyl-6-phenyl-9-(tetrahydropyran-2-yl)purine (2d)**
Prepared from **2a** (314 mg, 1 mmol) by Method C (3 equiv of Bn-ZnCl) in 89% yield (330 mg); colorless oil.

$^1$H NMR ($CDCl_3$, 500 MHz): δ = 1.55–1.64, 1.70–1.78, 1.93–1.99 and 2.37–2.45 (m, 6 H, $CH_2$), 3.57–3.63 (m, 1 H, H-5′a), 4.15–4.20 (m, 1 H, H-5′b), 4.54 (dd, 2 H, *J* = 5.7, 14.4 Hz, C*H*$_2$Ph), 5.68 (dd, 1 H, *J* = 11.1, 2.0 Hz, H-1′), 7.24–7.35, 7.50–7.57 and 8.79–8.82 (m, 10$H_{arom}$), 8.97 (s, 1 H, H-2).

$^{13}$C NMR (APT, $CDCl_3$, 127.8 MHz): δ = 23.2, 24.8 and 29.9 ($CH_2$), 35.7 (*C*$H_2$Ph), 69.2 ($CH_2O$), 82.7 (NCHO), 127.0, 128.6, 128.7, 129.8, 130.6 ($CH_{arom}$ and overlapped C-5), 135.9 and 136.1 ($C_{ipso}$), 151.7 (CH-2), 153.5 (C-4 and C-6), 155.0 (C-8).

HMBC cross-peaks: $CH_2$Ph with C-8 and C-4, NCHO with C-4.

EI-MS: *m*/*z* (%) = 370 (11), 286 (100), 210 (25), 85 (40).

EI-HRMS: *m*/*z* calcd for $C_{23}H_{22}N_4O$: 370.1794; found: 370.1798.

**8-Amino-6-phenyl-9-(tetrahydropyran-2-yl)purine (2e)**
Prepared from **2a** (314 mg, 1 mmol) by Method D (ethanolic ammonia) in 69% yield (203 mg) or by Method D (methanolic ammonia) in 34% yield (100 mg); colorless foam.

$^1$H NMR ($CDCl_3$, 500 MHz): δ = 1.80–2.14 (m, 6 H, $CH_2$), 3.77–3.81 (m, 1 H, H-5′a), 4.23–4.27 (m, 1 H, H-5′b), 5.90 (dd, 1 H, *J* = 10.8, 2.3 Hz, H-1′), 6.18 (s, 2 H, $NH_2$), 7.45–7.55 and 8.53–8.55 (m, 5 $H_{arom}$), 8.74 (s, 1 H, H-2).

$^{13}$C NMR (APT, $CDCl_3$, 125.8 MHz): δ = 22.4, 25.1 and 29.8 ($CH_2$), 69.4 ($CH_2O$), 82.7 (NCHO), 128.4, 129.1 and 129.7 ($CH_{arom}$), 130.4 (C-5), 136.5 ($C_{ipso}$), 149.0 (CH-2), 148.1, 152.4 and 154.6 (C-4, C-6 and C-8).

EI-MS: *m*/*z* (%) = 295 (10), 211 (100), 184 (10), 85 (15).

EI-HRMS): *m*/*z* calcd for $C_{16}H_{17}N_5O$: 295.1433; found: 295.1414.

**8-Methoxy-6-phenyl-9-(tetrahydropyran-2-yl)purine (2f)**
Prepared from **2a** (314 mg, 1 mmol) by Method D (methanolic ammonia) in 58% yield (180 mg); colorless foam.

$^1$H NMR ($CDCl_3$, 500 MHz): δ = 1.59–1.86, 2.08–2.12 and 2.83–2.91 (m, 6 H, $CH_2$), 3.72–3.78 (m, 1 H, H-5′a), 4.17–4.20 (m, 1 H, H-5′b), 4.31 (s, 3 H, $CH_3$), 5.67 (d, 1 H, *J* = 11.3 Hz, H-1′), 7.45–7.55 and 8.71–8.75 (m, 5 $H_{arom}$), 8.87 (s, 1 H, H-2).

$^{13}$C NMR (APT, $CDCl_3$, 125.8 MHz): δ = 23.4, 24.8 and 28.7 ($CH_2$), 57.7 ($CH_3$), 69.1 ($CH_2O$), 81.6 (NCHO), 128.5, 129.3 and 130.2 ($CH_{arom}$), 128.6 (C-5), 136.0 ($C_{ipso}$), 150.6 (CH-2), 150.1, 153.0 and 157.9 (C-4, C-6 and C-8).

EI-MS: *m*/*z* (%) = 310 (9), 226 (100), 211 (24), 85 (26).

EI-HRMS): *m*/*z* calcd for $C_{17}H_{18}N_4O_2$: 310.1430; found: 310.1433

**6-Chloro-8-methyl-9-(tetrahydropyran-2-yl)purine (3a)[4]**
Prepared from **1** (273 mg, 1 mmol) by Method A (1.1 equiv of MeMgCl) in 37% yield (93 mg); colorless oil.

$^1$H NMR ($CDCl_3$, 400 MHz): δ = 1.63–2.15 and 2.45–2.53 (m, 6 H, $CH_2$), 2.81 (s, 3 H, $CH_3$), 3.74 (t, 1 H, *J* = 11.3 Hz, H-5′a), 4.21 (d, 1 H, *J* = 10.6 Hz, H-5′b), 5.79 (dd, 1 H, *J* = 11.2, 1.7 Hz, H-1′), 8.67 (s, 1 H, H-2).

$^{13}$C NMR (APT, $CDCl_3$, 100.6 MHz): δ = 16.3 ($CH_3$), 23.1, 24.8 and 30.1 ($CH_2$), 69.2 ($CH_2O$), 83.3 (NCHO), 130.7 (C-5), 149.0 (C-6), 151.0 (CH-2), 152.6 (C-4), 155.2 (C-8).

NOE interaction: $CH_3$ to NCHO.

HMBC cross-peaks: $CH_3$ with C-8 and C-5, NCHO with C-4 and C-8.

EI-MS: *m*/*z* (%) = 252 (8), 169 (26), 85 (100).

EI-HRMS): *m*/*z* calcd for $C_{11}H_{13}ClN_4O$: 252.0778; found: 252.0782.

**6,8-Dimethyl-9-(tetrahydropyran-2-yl)purine (3c)**
Prepared from **1** (273 mg, 1 mmol) by Method A (9 equiv of MeMgCl) in 90% yield (209 mg) or by Method A (1.1 equiv of MeMgCl) in 14% yield (32 mg); colorless oil.

$^1$H NMR ($CDCl_3$, 400 MHz): δ = 1.64–2.14 and 2.35–2.55 (m, 6 H, $CH_2$), 2.78 and 2.81 (2 s, 2 × 3 H, 2 × $CH_3$), 3.75 (dd, 1 H, *J* = 11.3, 9.5 Hz, H-5′a), 4.21 (br d, 1 H, *J* = 10.3 Hz, H-5′b), 5.80 (dd, 1 H, *J* = 11.1, 1.8 Hz, H-1′); 8.77 (s, 1 H, H-2).

$^{13}$C NMR (APT, $CDCl_3$, 100.6 MHz): δ = 16.2 and 19.3 ($CH_3$), 23.2, 24.9 and 30.2 ($CH_2$), 69.2 ($CH_2O$), 82.8 (NCHO), 131.9 (C-5), 151.4 (CH-2), 153.2 and 157.1 (C-8, C-4 and C-6).

EI-MS: *m*/*z* (%) = 232 (26), 149 (100), 85 (87).

EI-HRMS: *m*/*z* calcd for $C_{12}H_{16}N_4O$: 232.1324; found: 232.1326.

**6-Benzyl-8-methyl-9-(tetrahydropyran-2-yl)purine (3d)**
Prepared from **3a** (253 mg, 1 mmol) by Method C (3 equiv of Bn-ZnCl) in 96% yield (296 mg); colorless oil.

$^1$H NMR ($CDCl_3$, 500 MHz): δ = 1.62–1.67, 1.73–1.79, 1.87–1.96, 2.07–2.12 and 2.44–2.53 (m, 6 H, $CH_2$), 2.80 (s, 3 H, $CH_3$), 3.73 (dt,

1 H, *J* = 2.2, 11.7 Hz, H-5′a), 4.17–4.22 (m, 1 H, H-5′b), 4.48 (s, 2 H, C*H*$_2$Ph), 5.79 (dd, 1 H, *J* = 11.3, 2.3 Hz, H-1′), 7.16–7.70 (m, 5 H$_{arom}$), 8.80 (s, 1 H, H-2).

$^{13}$C NMR (APT, $CDCl_3$, 127.8 MHz): δ = 16.3 ($CH_3$), 23.2, 24.9 and 30.2 ($CH_2$), 39.0 (*C*H$_2$Ph), 69.2 ($CH_2O$), 82.8 (NCHO), 126.5, 128.4, 129.3 ($CH_{arom}$), 131.6 (C-5), 138.0 ($C_{ipso}$), 151.7 (CH-2), 152.1 (C-4), 153.6 (C-8), 158.6 (C-6).

HMBC cross-peaks: $CH_3$ to C-8, $CH_2$Ph to C-6 and C-5, NCHO to C-4 and C-8.

EI-MS: *m*/*z* (%) = 308 (51), 277 (56), 223 (100), 85 (20).

EI-HRMS): *m*/*z* calcd for $C_{18}H_{20}N_4O$: 308.1637; found: 308.1632.

**6-Amino-8-methyl-9-(tetrahydropyran-2-yl)purine (3e)**
Prepared from **3a** (253 mg, 1 mmol) by Method D (ethanolic ammonia) in 59% yield (137 mg); colorless oil.

$^1$H NMR ($CDCl_3$, 400 MHz): δ = 1.50–2.00 and 2.45–2.62 (m, 6 H, $CH_2$), 2.59 (s, 3 H, $CH_3$), 3.67 (br t, 1 H, *J* = 10.3 Hz, H-5′a), 4.04 (d, 1 H, *J* = 10.6 Hz, H-5′b), 5.62 (br d, 1 H, *J* = 10.4 Hz, H-1′), 7.07 (s, 2 H, $NH_2$), 8.09 (s, 1 H, H-2).

$^{13}$C NMR (APT, $CDCl_3$, 100.6 MHz): δ = 15.1 ($CH_3$), 22.7, 24.6 and 29.1 ($CH_2$), 68.0 ($CH_2O$), 82.2 (NCHO), 117.4 (C-5), 148.4, 150.3 and 155.0 (C-6, C-4 and C-8), 151.7 (CH-2).

EI-MS: *m*/*z* (%): 233 (7), 149 (100), 122 (10), 85 (10).

EI-HRMS: *m*/*z* calcd for $C_{11}H_{15}N_5O$: 233.1277; found: 233.1294.

**9-Benzyl-6-chloro-8-methylpurine (7)[4]**
Prepared from **6** (278 mg, 1 mmol) by Method A (1.1 equiv of MeMgCl) in 29% yield (75 mg); colorless foam.

$^1$H NMR ($CDCl_3$, 500 MHz): δ = 2.61 (s, 3 H, $CH_3$), 5.45 (s, 2 H, C*H*$_2$Ph), 7.17–7.35 (m, 5 H$_{arom}$), 8.72 (H-2).

$^{13}$C NMR (APT, $CDCl_3$, 100.6 MHz): δ = 14.8 ($CH_3$), 46.5 ($CH_2$), 127.1, 128.5 and 129.2 ($CH_{arom}$), 134.7 ($C_{ipso}$), 149.0 (C-6), 151.4 (CH-2), 153.3 (C-4), 155.3 (C-8).

HMBC cross-peaks: $CH_2$Ph with C-8 and C-4, Me with C-8.

FAB-MS: *m*/*z* (%) = 259 (45), 91 (100).

FAB-HRMS: *m*/*z* calcd for $C_{13}H_{12}ClN_4$: 259.0750; found: 259.0739 [M + H].

**8-Chloro-6-phenylpurine (4a)**
Prepared from **2a** (157 mg, 0.5 mmol) by Method E in 87% yield (100 mg); colorless crystals; mp 288–290 °C (MeOH–toluene).

$^1$H NMR ($CD_3OD$, 400 MHz): δ = 7.54–7.57 (m, 3 H$_{arom}$), 8.52–8.55 (br m, 2 H$_{arom}$), 8.86 (s, 1 H, H-2).

$^{13}$C NMR (APT; $CD_3OD$, 100.6 MHz): δ = 129.7, 130.6 and 132.3 ($CH_{arom}$), 135.9 ($C_{ipso}$), 152.7 (CH-2). Other quaternary carbon signals did not appear due to tautomerism.

EI-MS: *m*/*z* (%) = 230 (80), 195 (100).

EI-HRMS: *m*/*z* calcd for $C_{11}H_7ClN_4$: 230.0360; found: 230.0353.

**6,8-Diphenylpurine (4b)**
Prepared from **2b** (178 mg, 0.5 mmol) by Method E in 79% yield (107 mg); colorless crystals; mp >300 °C (MeOH–toluene).

$^1$H NMR ($CD_3OD$, 400 MHz): δ = 7.58–7.64 (m, 6 H$_{arom}$), 8.33–8.36 (m, 2 H$_{arom}$), 8.88–8.95 (br m, 2 H$_{arom}$), 8.94 (s, 1 H, H-2), 14.03 (br, 1 H, NH).

$^{13}$C NMR (APT; $CD_3OD$, 100.6 MHz): δ = 127.2, 128.6, 129.1, 129.2, 130.7 and 131.2 ($CH_{arom}$), 128.9 (C-5), 135.7 ($C_{ipso}$), 152.7 (CH-2), 151.2 and 153.6 (C-4, C-6 and/or C-8).

EI-MS: *m*/*z* (%) = 272 (100), 244 (8), 169 (10), 77 (30).

EI-HRMS): *m*/*z* calcd for $C_{17}H_{12}N_4$: 272.1062; found: 272.1071.

Anal. Calcd for $C_{17}H_{12}N_4$ (272.3): C, 74.98; H, 4.44; N, 20.58. Found: C, 74.64; H, 4.51; N, 20.30.

**8-Methyl-6-phenylpurine (4c = 5b)**
Prepared from **2c** (= **3b**) (170 mg, 0.58 mmol) by Method E in 82% yield (100 mg); colorless crystals; mp 224–226 °C (MeOH–toluene–heptane).

$^1$H NMR (DMSO-$d_6$, 400 MHz): δ = 2.62 (s, 3 H, $CH_3$), 7.53–7.60 (m, 3 H$_{arom}$), 8.70–8.80 (br m, 2 H$_{arom}$), 8.85 (s, 1 H, H-2), ca. 13.2 (br s, 1 H, NH).

$^{13}$C NMR (APT; DMSO-$d_6$, 100.6 MHz): δ = 15.1 ($CH_3$), 128.5, 129.0 and 130.4 ($CH_{arom}$), 135.8 (C), 151.0 (CH-2). Other quaternary carbon signals did not appear due to tautomerism.

$^{13}$C NMR (INVGATE, $CDCl_3$, 100.6 MHz): In addition to the above signals, very weak and broad signals of purine carbons were detected; δ = 149.9, and 154.8.

EI-MS: *m*/*z* (%) = 210 (100), 169 (53), 142 (15).

EI-HRMS): *m*/*z* calcd for $C_{12}H_{10}N_4$: 210.0905; found: 210.0901.

**8-Benzyl-6-phenylpurine (4d)**
Prepared from **2d** (300 mg, 0.81 mmol) by Method E in 85% yield (197 mg); colorless crystals; mp 244–246 °C (MeOH–toluene–heptane); colorless crystals.

$^1$H NMR ($CDCl_3$, 400 MHz): δ = 4.30 (s, 2 H, C*H*$_2$Ph), 7.23–7.60 (m, 8 H$_{arom}$), 8.74–8.82 (br m, 2 H$_{arom}$), 8.87 (s, 1 H, H-2), ca. 13.4 (br s, 1 H, NH).

$^{13}$C NMR (APT, $CDCl_3$, 100.6 MHz): δ = 35.1 (*C*H$_2$Ph), 126.7, 128.5, 128.6, 128.7, 129.1 and 130.6 ($CH_{arom}$), 135.7 and 136.6 ($C_{ipso}$), 151.3 (CH-2). Quaternary carbon signals did not appear due to tautomerism.

EI-MS: *m*/*z* (%) = 286 (100), 91 (25), 57 (31).

EI-HRMS): *m*/*z* calcd for $C_{18}H_{14}N_4$: 286.1218; found: 286.1221.

Anal. Calcd for $C_{18}H_{14}N_4$ (286.3): C, 75.50; H, 4.93; N, 19.57. Found: C, 75.25; H, 4.83; N, 19.26.

**8-Amino-6-phenylpurine (4e)**
Prepared from **2e** (148 mg) by Method E in 61% yield (64 mg); colorless crystals; mp >300 °C (MeOH–$H_2O$); colorless crystals.

$^1$H NMR (DMSO-$d_6$, 400 MHz): δ = 6.96 (s, 2 H, $NH_2$), 7.42–7.54 (m, 3 H$_{arom}$), 8.53 (s, 1 H, H-2), 8.50–8.70 (br m, 2 H$_{arom}$), 11.94 (br s, 1 H, NH).

$^{13}$C NMR (APT; DMSO-$d_6$, 100.6 MHz): δ = 128.2 and 129.1 ($CH_{arom}$), 136.7 (C). Other quaternary carbon signals did not appear due to tautomerism.

$^{13}$C NMR (INVGATE, $CDCl_3$, 100.6 MHz): In addition to the above signals, very weak and broad signals of purine carbons were detected; δ = 142.9, 148.2, and 156.9.

EI-MS: *m*/*z* (%) = 211 (80), 184 (35), 57 (95), 43 (100).

EI-HRMS: *m*/*z* calcd for $C_{11}H_9N_5$: 211.0858; found: 211.0860.

**8-Methoxy-6-phenylpurine (4f)**
Prepared from **2f** (155 mg, 0.5 mmol) by Method E in 69% yield (78 mg); colorless crystals; mp 201–203 °C (MeOH–$H_2O$).

$^1$H NMR (DMSO-$d_6$, 400 MHz): δ = 4.19 (s, 3 H, $CH_3$), 7.50–7.57 (m, 3 H$_{arom}$), 8.70 (br, 2 H$_{arom}$), 8.74 (s, 1 H, H-2).

$^{13}$C NMR (APT; DMSO-$d_6$, 100.6 MHz): δ = 57.2 ($CH_3$), 128.5, 128.7 and 130.2 ($CH_{arom}$), 135.8 ($C_{ipso}$), 150.2 (CH-2). Other quaternary carbon signals did not appear due to tautomerism.

EI-MS: *m*/*z* (%) = 226 (100) 211 (60).

EI-HRMS: *m*/*z* calcd for $C_{12}H_{10}N_4O$: 226.0855; found: 226.0848.

Anal. Calcd for $C_{12}H_{10}N_4O$ (226.2): C, 63.71; H, 4.46; N, 24.76. Found: C, 63.56; H, 4.54; N, 24.36.

**6-Chloro-8-methylpurine (5a)[17]**

Prepared from **3a** (270 mg, 1.1 mmol) by Method E in 75% yield (135 mg); colorless crystals; mp 195–200 °C (MeOH–toluene–heptane) [Lit.[17] mp 200 °C (dec.)].

$^1$H NMR (DMSO-$d_6$, 400 MHz): δ = 2.58 (s, 3 H, $CH_3$), 8.63 (s, 1 H, H-2).

$^{13}$C NMR (APT, DMSO-$d_6$, 100.6 MHz): δ = 15.0 ($CH_3$), 129.5 (C-5), 145.4 (C-8), 150.8 (CH-2), 155.2 and 156.4 (C-4 and C-6).

EI-MS: *m*/*z* (%) = 168 (100), 133 (45).

EI-HRMS: *m*/*z* calcd for $C_6H_5ClN_4$: 168.0203; found: 168.0205.

Anal. Calcd for $C_6H_5ClN_4$ (168.6): C, 42.75; H, 2.99; N, 33.23. Found: C, 42.49; H, 3.21; N, 32.89.

**6,8-Dimethylpurine (5c)**

Prepared from **3c** (350 mg, 1.5 mmol) by Method E in 78% yield (175 mg); colorless crystals; mp 204–208 °C (MeOH–toluene–heptane).

$^1$H NMR (DMSO-$d_6$, 400 MHz): δ = 2.54 and 2.64 (2 s, 2 × 3 H, 2 × $CH_3$), 8.63 (s, 1 H, H-2),

13.08 (br s, 1 H, NH).

$^{13}$C NMR (APT, DMSO-$d_6$, 100.6 MHz): δ = 14.9 ($CH_3$), 150.8 (CH-2). Quaternary carbon signals did not appear due to tautomerism.

EI-MS: *m*/*z* (%) = 148 (100).

EI-HRMS: *m*/*z* calcd for $C_7H_8N_4$: 148.0749; found: 148.0743.

**6-Benzyl-8-methylpurine (5d)**

Prepared from **3d** (300 mg, 0.97 mmol) by Method E and isolated by column chromatography on silica gel (100 g, EtOAc–hexanes, 1:1 → EtOAc → EtOAc–MeOH, 9:1) in 69% yield (150 mg); amorphous solid.

$^1$H NMR ($CDCl_3$, 400 MHz): δ = 2.70 (s, 3 H, $CH_3$), 4.53 (s, 2 H, $CH_2$Ph), 7.10–7.40 (m, 5 H, $H_{arom}$), 8.84 (s, 1 H, H-2), ca. 13.1 (br s, 1 H, NH).

$^{13}$C NMR (APT, $CDCl_3$, 100.6 MHz): δ = 15.5 ($CH_3$), 39.3 ($CH_2$Ph), 126.7, 128.5 and 129.2 ($CH_{arom}$), 137.7 ($C_{ipso}$), 151.0 (CH-2). Quaternary carbon signals did not appear due to tautomerism.

$^{13}$C NMR (H-decoupled, $CDCl_3$, 100.6 MHz): In addition to the above signals, very weak and broad signals of purine quaternary carbons were detected; δ = 133.1, 153.3, 153.7 and 160.0.

EI- MS: *m*/*z* (%) = 225 (100), 120 (7), 91 (6).

EI-HRMS: *m*/*z* calcd for $C_{13}H_{13}N_4$: 225.1140; found: 225.1126.

Anal. Calcd for $C_{13}H_{12}N_4$ (272.3): C, 69.62; H, 5.39; N, 24.98. Found: C, 69.99; H, 5.50; N, 24.51.

**6-Amino-8-methylpurine (5e)[18]**

Prepared from **3e** (140 mg, 0.6 mmol) by Method E in 89% yield (80 mg); colorless crystals; mp >300 °C (MeOH–toluene–heptane).

$^1$H NMR (DMSO-$d_6$, 400 MHz, 50 °C): δ = 2.44 (s, 3 H, $CH_3$), 6.70 (s, 2 H, $NH_2$), 8.04 (s, 1 H, H-2), 12.44 (br s, 1 H. NH).

$^{13}$C NMR (H-decoupl.; DMSO-$d_6$, 100.6 MHz): δ = 14.6 ($CH_3$), 147.9 (C), 151.6 (CH-2), 154.7 (C). Other quaternary carbon signals did not appear due to tautomerism.

EI-MS: *m*/*z* (%): 149 (100), 122 (29), 43 (83).

EI-HRMS: *m*/*z* calcd for $C_6H_7N_5$: 149.0701; found: 149.0699.

Anal. Calcd for $C_6H_7N_5$ (149.2): C, 48.32; H, 4.73; N, 46.95. Found: C, 48.20; H, 4.85; N, 46.63.

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