SYNTHESIS OF ACYCLIC NUCLEOTIDE ANALOGUES DERIVED FROM 6-(*sec*- OR *tert*-ALKYL)PURINES *via* COUPLING OF 6-CHLOROPURINE DERIVATIVES WITH ORGANOCUPRATES

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Coupling of 9-[2-(diisopropyloxyphosphonylmethoxy)ethyl]-6-chloropurine (**23**) (and (*R*)-9-[2-(diisopropyloxyphosphonylmethoxy)propyl]-6-chloropurine (**24**), respectively) with organocuprates derived from Grignard reagents afforded after deprotection 6-(*sec*- or *tert*-alkyl) substituted phosphonates **31**–**36**. As a model a series of 6-(*sec*- or *tert*-alkyl)purines **2**–**12** was also prepared.

Key words: Acyclic nucleoside phosphonates; Phosphonomethoxyalkylpurine derivatives; 6-Alkylpurines; Purines; Organocopper reagents; Cross-coupling reactions.

N-[(Phosphonomethoxy)alkyl] derivatives of purine bases are potent antivirals[1]. The structure–activity relationship study[2] of these compounds showed that the presence of an amino group at the purine moiety is necessary for the antiviral activity. However, recently it was found[3] that also 6-(alkylamino)- and 6-(dialkylamino)purine derivatives exhibit a strong antiviral, antitumor and immunomodulatory activity. To study the role of the unsubstituted or substituted amino function in the biological activity of these compounds the analogues bearing strongly basic 6-aminomethyl[4] and 6-(1-aminoethyl)[5] functions or nitrogen-containing heterocycles[6] on the purine ring were recently prepared. Antiviral activity tests of these compounds showed that several 6-(aminomethyl)purine derivatives still possess marginal activity against several strains of DNA viruses while the other compounds were inactive. As a continuation of those studies we report here on the synthesis of the acyclic nucleotide analogues derived from purine derivatives bearing secondary or tertiary alkyl group in the 6-position that could be

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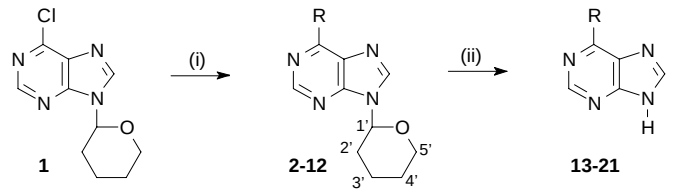
considered as isosteric (but not isopolar) analogues of the strongly active 6-(dialkylamino)purine derivatives. The study could bring some more information about the role of the basicity and hydrogen-bond-acceptor ability of the substituted amino function in the biological activity of this important class of compounds.

An attractive method for the introduction of the alkyl group into the 6 position of purine ring system is a transition metal (Pd, Ni) catalyzed cross-coupling of 6-halopurines with main group organometallics derived from tin[7], zinc[6,7b,7c] or aluminum[8]. Recently also reverse approach based on the reaction of purin-6-yl zinc halides with aryl halides has been reported[9]. These methods however work best for sp^2 (aryl, vinyl) organometallics, while cross couplings of sp^3 primary organometallics are known, but they generally suffer from a low reaction rate of the transmetallation step[10]. None of such reactions has been reported for secondary or tertiary organometallics.

In our preliminary report[11] we have already published a convenient route to 6-(*sec*- or *tert*-alkyl)purines *via* coupling of 6-chloropurines with organocuprates derived from Grignard reagents. Here we report the detailed extended form of that study as well as the application of the organocopper methodology for the preparation of 6-alkylpurine acyclic nucleotide analogues.

The model 6-chloro-9-(tetrahydropyran-2-yl)purine (**1**) reacts with excess (4 equivalents) of Gillman organocuprates derived from Grignard reagents under the formation of 6-alkylpurines **2**–**12** (Scheme 1) in low to modest yields (25–67%, Table I). The starting 6-chloro-9-(tetrahydropyran-2-yl)purine (**1**) was consumed quantitatively in all cases affording single product together with inseparable mixture of polar products of degradation. While in the case of secondary Grignard reagents the best results were achieved by using CuI, for the introduction of the *tert*-alkyl groups the cyanocuprates gave comparable results. The organocuprates containing primary alkyl and vinyl groups appeared to be unreactive under these conditions.

Allyl cuprate reacted differently from other cuprates. Its reaction with **1** proceeded rapidly even at –78 °C. However, 8-allyl-6-chloro-9-(tetrahydropyran-2-yl)purine (**22**)

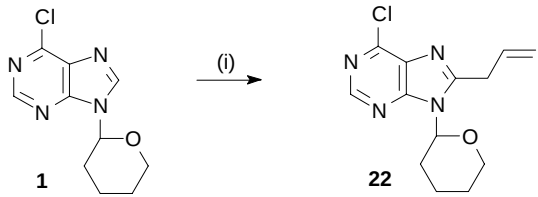


(i) 2 RMgX/CuI, THF
(ii) 0.25 M H_2SO_4

2, 13: R = 2-methylpropyl
3, 14: R = 2,2-dimethylpropyl
4, 15: R = isopropyl
5, 16: R = *tert*-butyl
6, 17: R = 1,1-dimethylpropyl
7, 18: R = 1,1-dimethyl-3-phenylpropyl
8, 19: R = cyclopentyl
9, 20: R = cyclohexyl
10, 21: R = cyclopropyl
11: R = methyl
12: R = phenyl

SCHEME 1

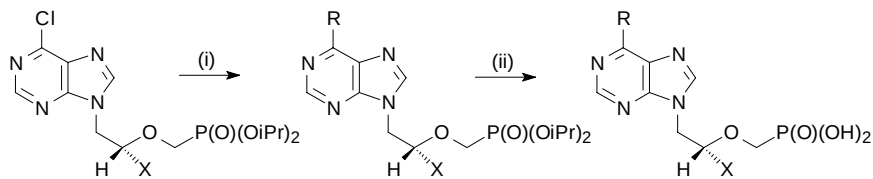
was isolated as the only product (Scheme 2), probably as a result of an addition–oxidation process[12].



(i) 2 CH_2=$CHCH_2MgX$/CuI, THF

SCHEME 2

The obtained 6-alkyl-9-(tetrahydropyran-2-yl)purines can be easily converted to free bases by hydrolysis under acidic conditions (**13**–**21**, Scheme 1) and can be further functionalized. However, an *N*-alkylation of purine bases usually does not offer high yields a formation of other regioisomers could be expected. Therefore, it is much more straightforward to use protected 6-chloropurine phosphonates **23** (ref.[5]) or **24** (ref.[13]) for the preparation of 6-alkylpurine phosphonates. The phosphonates 9-[2-(diisopropyloxyphosphonylmethoxy)ethyl]-6-chloropurine (**23**) (and (*R*)-9-[2-(diisopropyloxyphosphonylmethoxy)propyl]-6-chloropurine (**24**), respectively) that already contained protected phosphonate function at the N-9 position were chosen as key starting materials for the coupling reaction (Scheme 3). The reaction proceeded under the optimum



23: X = H
24: X = CH_3

(i) 2 RMgX/CuI, THF
(ii) TMSBr, CH_3CN

25-30

25, 31: X = H, R = 2,2-dimethylpropyl
26, 32: X = H, R = isopropyl
27, 33: X = H, R = *tert*-butyl
28, 34: X = H, R = 1,1-dimethylpropyl
29, 35: X = H, R = cyclopentyl
30, 36: X = CH_3, R = cyclohexyl

31-36

SCHEME 3

conditions described above (protected phosphonate **23** or **24** with excess (4 equivalents) of organocuprate derived from CuI and Grignard reagent in a 1 : 2 molar ratio). Although the starting compounds reacted quantitatively, the yields of the crude products **25**–**30** were rather low (20–25%, Table I). Without further isolation, the crude products **25**–**30** were treated with bromotrimethylsilane to cleave the isopropyl ester groups.

Standard purification by a combination of cation- and anion-exchange chromatography afforded pure products **31**–**36**. In spite of the lack of the amino function at the protected bases **2**–**12** or at the protected phosphonates **25**–**30** it was possible to use Dowex 50 X 8 for the isolation of free bases **13**–**21** or phosphonates **31**–**36**. This surprising behaviour may be explained by the hydrophobic aromatic interactions of the alkylated purine derivatives with Dowex 50 X 8.

Although the described method does not afford high yields and the purification of the products is quite difficult, the acyclic nucleotide analogues **31**–**36** as well as the deprotected purine bases **13**–**21** were prepared in amounts and purity sufficient for the biological activity tests.

Structure of all prepared compounds was proved by ^{1}H NMR spectra. They follow the same pattern as those of the 6-chloro-9-(tetrahydropyran-2-yl)purine (**1**, ref.[14]) and the phosphonates **23** (ref.[5]) and **24** (ref.[13]). In the ^{1}H NMR spectrum of the free base **14**, all the signals (except for the methyl) are doubled due to the 7H–9H tautomerism. This phenomenon has been already observed[15].

Compounds **13**–**21** and **31**–**36** were tested on their antiviral activity[16] (DNA viruses: HSV-1, HSV-2, CMV, VZV and vaccinia virus, and retroviruses: HIV-1, HIV-2 and MSV). None of the tested compounds exhibited any considerable activity in any of these assays.

EXPERIMENTAL

Methods: Unless otherwise stated, solvents were evaporated at 40 °C/2 kPa and compounds were dried at 2 kPa over P_2O_5. Melting points were determined on a Kofler block and are uncorrected. TLC was performed on Silufol UV_{254} plates (Kavalier Votice, Czech Republic). Preparative TLC was

TABLE I
Yields of the cross-coupling reactions of organocuprates with 6-chloro-9-(tetrahydropyran-2-yl)purine **1** and protected 6-chloropurine phosphonates **23** and **24**, respectively

R	Yields of **2**–**12** (%)	Yields of **25**–**30** (%)
2-Methylpropyl	**2** (25)	
2,2-Dimethylpropyl	**3** (33)	**25** (25)
Isopropyl	**4** (67)	**26** (23)
tert-Butyl	**5** (40)	**27** (25)
1,1-Dimethylpropyl	**6** (40)	**28** (25)
1,1-Dimethyl-3-phenylpropyl	**7** (37)	
Cyclopentyl	**8** (51)	**29** (21)
Cyclohexyl	**9** (67)	**30** (21)
Cyclopropyl	**10** (24)	
Methyl	**11** (19)	
Phenyl	**12** (10)	

carried out on 40 × 17 × 0.4 cm loose layer plates of silica gel containing UV indicator. Paper electrophoresis was performed on a Whatman No. 3 MM paper at 40 V/cm for 1 h in 0.05 M triethylammonium hydrogen carbonate (TEAB) at pH 7.5; the electrophoretical mobilities are referenced to uridine 3′-phosphate. NMR spectra were measured on a Varian Unity 500 spectrometer (500 MHz for ^{1}H) in hexadeuteriodimethyl sulfoxide referenced to the solvent signals (2.5 ppm for ^{1}H), or in deuterium oxide containing sodium deuteroxide with sodium 3-(trimethylsilyl)propane sulfonate (DSS) as internal standard for ^{1}H). Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol matrix).

Materials: 6-Chloropurine was purchased from Fluka (Switzerland), bromotrimethylsilane and CuI were obtained from Aldrich (Germany). DMF was distilled from P_2O_5 and stored over molecular sieves. Acetonitrile was refluxed with CaH_2 and distilled. THF was refluxed with Na and benzophenone under Ar atmosphere and freshly distilled *prior* to use.

General Method for Preparation of Compounds **2**–**12** and **25**–**30**

A mixture of CuI (0.76 g, 4 mmol), anhydrous THF (20 ml) and ethereal alkylmagnesium halide (8 mmol) was stirred under argon at –78 °C for 30 min. 6-Chloropurine **1**, **23** or **24** (1 mmol) in THF (4 ml) was added dropwise and the reaction mixture was stirred under argon for 2 h at –78 °C and then overnight at room temperature. Then the reaction mixture was quenched by a dropwise addition of a mixture of saturated solution of NH_4Cl and concentrated ammonia (4 : 1, 20 ml), diluted with water, extracted with ether and dried with $MgSO_4$. The solvent was evaporated to give a crude product, which was purified by preparative TLC on silica (chloroform–methanol 95 : 5 and 90 : 10, respectively) affording colorless oil.

6-(2-Methylpropyl)-9-(tetrahydropyran-2-yl)purine (**2**): Yield: 0.07 g (25%), R_F 0.42 (chloroform–methanol 95 : 5). Mass spectrum (FAB), *m/z*: 261.1 $[M + H]^+$. ^{1}H NMR spectrum ($(CD_3)_2SO$): 8.83 and 8.72 2 × s, 2 × 1 H (H-2 and H-8); 5.75 dd, J = 2.2 and 11.0 (H-1′); 4.00 m, 1 H (H-5′); 3.70 m, 1 H (H-5′); 2.95 d, 2 H, J(1″,2″) = 7.1 (H-1″); 2.28–2.38 m, 2 H (THP and H-2″); 1.98 m, 2 H (THP); 1.74 m, 1 H (THP); 1.60 m, 2 H (THP); 0.89 d, 6 H, $J(CH_3,CH)$ = 6.6 (CH_3).

6-(2,2-Dimethylpropyl)-9-(tetrahydropyran-2-yl)purine (**3**): Yield: 0.09 g (33%), R_F 0.30 (chloroform–methanol 95 : 5). Mass spectrum (FAB), *m/z*: 275.4 $[M + H]^+$. ^{1}H NMR spectrum ($(CD_3)_2SO$): 8.84 and 8.71 2 × s, 2 × 1 H (H-2 and H-8); 5.76 dd, J = 2.0 and 11.0 (H-1′); 4.01 m, 1 H (H-5′); 3.71 m, 1 H (H-5′); 2.99 s, 2 H (H-1″); 2.35 m, 1 H (THP); 2.00 m, 2 H (THP); 1.76 m, 1 H (THP); 1.59 m, 2 H (THP); 0.97 s, 9 H (CH_3).

6-Isopropyl-9-(tetrahydropyran-2-yl)purine (**4**): Yield: 0.16 g (67%), R_F 0.54 (chloroform–methanol 95 : 5). Mass spectrum (FAB), *m/z*: 247.3 $[M + H]^+$. ^{1}H NMR spectrum ($CDCl_3$): 8.90 and 8.22 2 × s, 2 × 1 H (H-2 and H-8); 5.78 dd, 1 H, J = 3.1 and 9.5 (H-1′); 4.15 m, 1 H (H-5′); 3.79 m, 2 H (H-5′ and CH); 2.09 m, 1 H (THP); 1.72 m, 2 H (THP); 1.74 m, 1 H (THP); 1.58 m, 2 H (THP); 1.43 d, 6 H, J(Me,CH) = 6.9 (Me).

6-tert-Butyl-9-(tetrahydropyran-2-yl)purine (**5**): Yield: 0.10 g (40%), R_F 0.51 (chloroform–methanol 95 : 5). Mass spectrum (FAB), *m/z*: 261.0 $[M + H]^+$. ^{1}H NMR spectrum ($(CD_3)_2SO$): 8.84 and 8.72 2 × s, 2 × 1 H (H-2 and H-8); 5.77 dd, 1 H, J = 2.0 and 11.0 (H-1′); 4.01 m, 1 H (H-5′); 3.71 m, 1 H (H-5′); 2.33 m, 1 H (THP); 1.99 m, 2 H (THP); 1.75 m, 1 H (THP); 1.58 m, 2 H (THP); 1.53 s, 9 H (CH_3).

6-(1,1-Dimethylpropyl)-9-(tetrahydropyran-2-yl)purine (**6**): Yield: 0.11 g (40%), R_F 0.48 (chloroform–methanol 95 : 5). Mass spectrum (FAB), *m/z*: 275.0 $[M + H]^+$. ^{1}H NMR spectrum ($(CD_3)_2SO$): 8.84 and 8.71 2 × s, 2 × 1 H (H-2 and H-8); 5.77 dd, J = 2.2 and 11.0 (H-1′); 4.05 m, 1 H (H-5′); 3.71 m, 1 H (H-5′); 2.33 m, 1 H (THP); 2.05 q, 2 H, $J(CH_2,CH_3)$ = 7.3 (CH_2); 1.95 m, 2 H (THP); 1.76 m, 1 H (THP); 1.58 m, 2 H (THP); 1.48 s, 6 H (CH_3); 0.61 t, 3 H, $J(CH_3,CH_2)$ = 7.3 (CH_3).

6-(1,1-Dimethyl-3-phenylpropyl)-9-(tetrahydropyran-2-yl)purine (**7**): Yield: 0.13 g (37%), R_F 0.55 (chloroform–methanol 95 : 5). Mass spectrum (FAB), *m/z*: 351.4 $[M + H]^+$. ^{1}H NMR spectrum

($(CD_3)_2SO$): 8.87 and 8.74 2 × s, 2 × 1 H (H-2 and H-8); 7.30–7.00 m, 5 H (arom.); 5.78 dd, J = 2.2 and 11.0 (H-1′); 4.02 m, 1 H (H-5′); 3.71 m, 1 H (H-5′); 2.32 m, 5 H (THP and H-2″ and H-3″); 2.00 m, 2 H (THP); 1.76 m, 1 H (THP); 1.59 m, 2 H (THP); 1.56 s, 6 H (CH_3).

6-Cyclopentyl-9-(tetrahydropyran-2-yl)purine (**8**): Yield: 0.14 g (51%), R_F 0.50 (chloroform–methanol 95 : 5). Mass spectrum (FAB), *m/z*: 273.0 $[M + H]^+$. ^1H NMR spectrum ($(CD_3)_2SO$): 8.71 and 8.23 2 × s, 2 × 1 H (H-2 and H-8); 5.75 dd, 1 H, J = 2.0 and 11.0 (H-1′); 4.01 m, 1 H (H-5′); 3.70 m, 1 H (H-5′); 3.77 pent, 1 H (H-1″); 2.35 m, 1 H (THP); 2.04 m, 2 H (THP); 1.97 m, 4 H and 1.83 m, 2 H (cyclopentyl); 1.70 m, 3 H (THP and cyclopentyl); 1.58 m, 2 H (THP).

6-Cyclohexyl-9-(tetrahydropyran-2-yl)purine (**9**): Yield: 0.19 g (67%), R_F 0.60 (chloroform–methanol 95 : 5). Mass spectrum (FAB), *m/z*: 287.3 $[M + H]^+$. ^1H NMR spectrum ($(CD_3)_2SO$): 8.83 and 8.71 2 × s, 2 × 1 H (H-2 and H-8); 5.75 dd, 1 H, J = 2.2 and 11.0 (H-1′); 4.01 m, 1 H (H-5′); 3.70 m, 1 H (H-5′); 3.32 m, 1 H (H-1″); 2.35 m, 1 H (THP); 1.98 m, 2 H (THP); 1.90–1.70 m, 8 H (THP and cyclohexyl); 1.58 m, 2 H (THP); 1.43 m, 2 H and 1.30 m, 1 H (cyclohexyl).

6-Cyclopropyl-9-(tetrahydropyran-2-yl)purine (**10**): Yield: 0.06 g (24%), R_F 0.39 (chloroform–methanol 95 : 5). Mass spectrum (FAB), *m/z*: 245.3 $[M + H]^+$. ^1H NMR spectrum ($(CD_3)_2SO$): 8.69 and 8.67 2 × s, 2 × 1 H (H-2 and H-8); 5.74 dd, 1 H, J = 2.0 and 11.0 (H-1′); 4.02 m, 1 H (H-5′); 3.71 m, 1 H (H-5′); 2.68 m, 1 H (H-1″); 2.33 m, 1 H (THP); 1.98 m, 2 H (THP); 1.76 m, 1 H (THP); 1.60 m, 2 H (THP); 1.27 m, 2 H and 1.19 m, 2 H (cyclopropyl).

6-Methyl-9-(tetrahydropyran-2-yl)purine (**11**): Yield: 0.04 g (19%), R_F 0.44 (chloroform–methanol 95 : 5). Mass spectrum (FAB), *m/z*: 219.3 $[M + H]^+$. ^1H NMR spectrum ($(CD_3)_2SO$): 8.78 and 8.73 2 × s, 2 × 1 H (H-2 and H-8); 5.75 brdd, 1 H, J = 1.0 and 10.3 (H-1′); 4.01 m, 1 H (H-5′); 3.70 m, 1 H (H-5′); 2.72 s, 1 H (Me); 2.35 m, 1 H (THP); 1.97 m, 2 H (THP); 1.74 m, 1 H (THP); 1.58 m, 2 H (THP).

6-Phenyl-9-(tetrahydropyran-2-yl)purine (**12**): Yield: 0.03 g (10%), R_F 0.60 (chloroform–methanol 95 : 5). Mass spectrum (FAB), *m/z*: 281.3 $[M + H]^+$. ^1H NMR spectrum ($(CD_3)_2SO$): 9.01 and 8.89 2 × s, 2 × 1 H (H-2 and H-8); 8.83 m, 2 H and 8.30 m, 1 H and 7.60 m, 2 H (phenyl); 5.83 dd, 1 H, J = 2.0 and 11.0 (H-1′); 4.04 m, 1 H (H-5′); 3.74 m, 1 H (H-5′); 2.38 m, 1 H (THP); 2.02 m, 2 H (THP); 1.78 m, 1 H (THP); 1.60 m, 2 H (THP).

8-Allyl-6-chloro-9-(tetrahydropyran-2-yl)purine (**22**): Yield: 0.08 g (30%), R_F 0.65 (chloroform–methanol 95 : 5). Mass spectrum (FAB), *m/z*: 279.2 $[M + H]^+$. ^1H NMR spectrum ($(CD_3)_2SO$): 8.72 s, 1 H (H-2); 6.10 ddt, 1 H, J(2″,1″) = 6.3, J(2″,3″*cis*) = 10.5, J(2″, 3″*trans*) = 17.3 (H-2″); 5.72 dd, 1 H, J = 2.2 and 11.2 (H-1′); 5.25 dq, 1 H, J(3″*trans*,1″) = J(gem) = 1.5, J(3″*trans*,2″) = 17.3 (H-3″*trans*); 5.22 dq, 1 H, J(3″*cis*,1″) = J(gem) = 1.5, J(3″*cis*,2″) = 10.5 (H-3″*cis*); 4.03 m, 1 H and 3.71 m, 1 H (H-5′); 3.91 brd, 2 H, J(1″,2″) = 6.3 (H-1″); 2.75 m, 1 H and 1.97 m, 1 H and 1.88 m, 1 H and 1.76–1.54 m, 3 H (THP).

6-(2,2-Dimethylpropyl)-9-[2-(diisopropyloxyphosphonylmethoxy)ethyl]purine (**25**): Yield: 0.10 g (25%), R_F 0.42 (chloroform–methanol 9 : 1). Mass spectrum (FAB), *m/z*: 413.0 $[M + H]^+$. ^1H NMR spectrum ($(CD_3)_2SO$): 8.81 s, 1 H (H-2); 8.45 s, 1 H (H-8); 4.46 t, 2 H, J(1′,2′) = 5.1 (H-1′); 4.43 m, 2 H (P-OCH); 3.95 t, 2 H, J(2′,1′) = 5.1 (H-2′); 3.78 d, 2 H, J(P,CH) = 8.3 (P-CH_2); 2.98 s, 2 H (H-1″); 1.12 d, 6 H and 1.06 d, 6 H, J(CH_3,CH) = 6.1 (CH_3); 0.98 s, 9 H (CH_3).

6-Isopropyl-9-[2-(diisopropyloxyphosphonylmethoxy)ethyl]purine (**26**): Yield: 0.09 g (23%), R_F 0.40 (chloroform–methanol 9 : 1). Mass spectrum (FAB), *m/z*: 385.1 $[M + H]^+$. ^1H NMR spectrum ($(CD_3)_2SO$): 8.82 s, 1 H (H-2); 8.46 s, 1 H (H-8); 4.45 t, 2 H, J(1′,2′) = 5.0 (H-1′); 4.43 m, 2 H (P-OCH); 3.94 t, 2 H, J(2′,1′) = 5.0 (H-2′); 3.78 d, 2 H, J(P,CH) = 8.3 (P-CH_2); 3.64 sept, 1 H, J(CH,CH_3) = 6.8 (H-1″); 1.36 d, 6 H, J(CH_3,CH) = 6.8 (CH_3); 1.12 d, 6 H and 1.05 d, 6 H, J(CH_3,CH) = 6.1 (CH_3).

6-tert-Butyl-9-[2-(diisopropyloxyphosphonylmethoxy)ethyl]purine (**27**): Yield: 0.10 g (25%), R_F 0.61 (chloroform–methanol 9 : 1). Mass spectrum (FAB), *m/z*: 399.3 $[M + H]^+$. ^1H NMR spectrum

($(CD_3)_2SO$): 8.81 s, 1 H (H-2); 8.46 s, 1 H (H-8); 4.45 t, 2 H, J(1′,2′) = 5.0 (H-1′); 4.43 dsept, 2 H, J(CH,CH_3) = 6.1, J(P,CH) = 7.6 (P-OCH); 3.94 t, 2 H, J(2′,1′) = 5.0 (H-2′); 3.78 d, 2 H, J(P,CH) = 8.3 (P-CH_2); 1.53 s, 9 H (CH_3); 1.12 d, 6 H and 1.05 d, 6 H, J(CH_3,CH) = 6.1 (CH_3).

6-(1,1-Dimethylpropyl)-9-[2-(diisopropyloxyphosphonylmethoxy)ethyl]purine (**28**): Yield: 0.10 g (25%), R_F 0.47 (chloroform–methanol 9 : 1). Mass spectrum (FAB), *m/z*: 413.5 $[M + H]^+$. ^{1}H NMR spectrum ($(CD_3)_2SO$): 8.81 s, 1 H (H-2); 8.44 s, 1 H (H-8); 4.46 t, 2 H, J(1′,2′) = 5.0 (H-1′); 4.44 dsept, 2 H, J(CH,CH_3) = 6.1, J(P,OCH) = 7.6 (P-OCH); 3.96 t, 2 H, J(2′,1′) = 5.0 (H-2′); 3.79 d, 2 H, J(P,CH) = 8.3 (P-CH_2); 2.05 q, 2 H, J(CH_2,CH_3) = 7.1 (CH_2); 1.48 s, 6 H (CH_3); 1.12 d, 6 H and 1.05 d, 6 H, J(CH_3,CH) = 6.1 (CH_3); 0.62 t, 3 H, J(CH_3,CH_2) = 7.3 (CH_3).

6-Cyclopentyl-9-[2-(diisopropyloxyphosphonylmethoxy)ethyl]purine (**29**): Yield: 0.09 g (21%), R_F 0.50 (chloroform–methanol 9 : 1). Mass spectrum (FAB), *m/z*: 411.0 $[M + H]^+$. ^{1}H NMR spectrum ($(CD_3)_2SO$): 8.80 s, 1 H (H-2); 8.44 s, 1 H (H-8); 4.44 t, 2 H, J(1′,2′) = 5.1 (H-1′); 4.42 dsept, 2 H, J(CH,CH_3) = 6.1, J(P,OCH) = 7.6 (P-OCH); 3.93 t, 2 H, J(2′,1′) = 5.1 (H-2′); 3.77 d, 2 H, J(P,CH) = 8.6 (P-CH_2); 3.76 pent, 1 H, J = 8.3 (H-1″); 2.05 m, 2 H and 1.98 m, 2 H and 1.85 m, 2 H and 1.70 m, 2 H (cyclopentyl); 1.12 d, 6 H and 1.05 d, 6 H, J(CH_3,CH) = 6.1 (CH_3).

(R)-6-Cyclohexyl-9-[2-(diisopropyloxyphosphonylmethoxy)propyl]purine (**30**): Yield: 0.90 g (21%), R_F 0.40 (chloroform–methanol 9 : 1). Mass spectrum (FAB), *m/z*: 439.1 $[M + H]^+$. ^{1}H NMR spectrum ($(CD_3)_2SO$): 8.80 s, 1 H (H-2); 8.41 s, 1 H (H-8); 4.45 m, 2 H (P-OCH); 4.37 dd, 1 H, J(1′a,2′) = 3.4, J(gem) = 14.7 (H-1′a); 4.26 dd, 1 H, J(1′b,2′) = 7.1, J(gem) = 14.7 (H-1′b); 4.02 m, 1 H (H-2′); 3.81 dd, 1 H, J(P,CHa) = 9.5, J(gem) = 13.9 (P-CHa); 3.70 dd, 1 H, J(P,CHb) = 9.5, J(gem) = 13.2 (P-CHb); 3.37 m, 1 H (H-1″); 1.90–1.60 m, 5 H and 1.50–1.20 m, 3 H and 1.15 m, 2 H (cyclohexyl); 1.16 d, 3 H and 1.13 d, 3 H and 1.10 d, 6 H and 1.04 d, 3 H, J(CH_3,CH) = 6.1 (CH_3).

General Method for Preparation of Compounds **13**–**21**

The hydrolysis of **2**–**10** (1 mmol) was carried out in 0.25 M H_2SO_4 (10 ml) at room temperature for 24 h. The reaction mixture was then deionized on a column of Dowex 50 X 8 (H^+-form, 20 ml) and the column was washed with water until the UV absorption of the eluate dropped to the original value. The column was then washed with 2.5% aqueous ammonia and the UV-absorbing eluate was collected and evaporated *in vacuo*. The crude product was purified by preparative thin layer chromatography on silica ($CHCl_3$–MeOH 8 : 2).

6-(2-Methylpropyl)purine (**13**): Yield: 0.13 g (76%), R_F 0.43 (chloroform–methanol 9 : 1). Mass spectrum (FAB), *m/z*: 177.4 $[M + H]^+$. For $C_9H_{12}N_4$ (176.18) calculated: 61.35% C, 6.87% H, 31.78% N; found: 60.94% C, 6.71% H, 31.16% N. ^{1}H NMR spectrum ($(CD_3)_2SO$): 13.40 br, 1 H (NH); 8.78 s, 1 H (H-2); 8.52 s, 1 H (H-8); 2.93 d, 2 H, J(1′,2′) = 7.3 (H-1′); 2.29 sept, 1 H (H-2′); 0.90 d, 6 H, J(CH_3,CH) = 6.6 (CH_3).

6-(2,2-Dimethylpropyl)purine (**14**): Yield: 0.13 g (70%), R_F 0.76 (chloroform–methanol 8 : 2). Mass spectrum (FAB), *m/z*: 191.1 $[M + H]^+$. For $C_{10}H_{14}N_4 \cdot 1/2\ H_2O$ (199.2) calculated: 60.29% C, 7.08% H, 28.11% N; found: 60.20% C, 7.34% H, 27.63% N. ^{1}H NMR spectrum ($(CD_3)_2SO$): 13.36 and 13.31 2 × brs, 2 × 1 H (NH); 8.77 and 8.84 2 × s, 2 × 1 H (H-2); 8.44 and 8.65 2 × s, 2 × 1 H (H-8); 2.98 and 2.92 2 × s, 2 × 2 H (CH_2); 0.97 s, 9 H (*t*-Bu).

6-Isopropylpurine (**15**): Yield: 0.12 g (75%), R_F 0.76 (chloroform–methanol 8 : 2). Mass spectrum (FAB), *m/z*: 163.0 $[M + H]^+$. For $C_8H_{10}N_4$ (162.16) calculated: 59.25% C, 6.22% H, 34.53% N; found: 58.89% C, 6.06% H, 34.33% N. ^{1}H NMR spectrum ($(CD_3)_2SO$): 13.40 br, 1 H (NH); 8.79 s, 1 H (H-2); 8.47 brs, 1 H (H-8); 3.63 m, 1 H (CH); 1.34 d, 6 H, J(CH_3,CH) = 7.0 (CH_3).

6-tert-Butylpurine (**16**): Yield: 0.14 g (79%), R_F 0.76 (chloroform–methanol 8 : 2). Mass spectrum (FAB), *m/z*: 177.1 $[M + H]^+$. For $C_9H_{12}N_4 \cdot 1/2\ H_2O$ (185.2) calculated: 58.36% C, 7.07% H, 30.23% N;

found: 58.58% C, 6.82% H, 30.69% N. ^{1}H NMR spectrum ($(CD_3)_2SO$): 13.40 br, 1 H (NH); 8.78 s, 1 H (H-2); 8.46 brs, 1 H (H-8); 1.52 s, 9 H (*t*-Bu).

6-(1,1-Dimethylpropyl)purine (**17**): Yield: 0.13 g (71%), R_F 0.73 (chloroform–methanol 85 : 15). Mass spectrum (FAB), *m/z*: 191.2 $[M + H]^+$. For $C_{10}H_{14}N_4 \cdot 1/2\ H_2O$ (199.2) calculated: 60.28% C, 7.08% H, 28.11% N; found: 60.23% C, 7.37% H, 27.88% N. ^{1}H NMR spectrum ($(CD_3)_2SO$): 13.40 br, 1 H (NH); 8.78 s, 1 H (H-2); 8.47 s, 1 H (H-8); 2.02 q, 2 H, $J(CH_2,CH_3)$ = 7.3 (2′-CH_2); 1.47 s, 6 H (Me); 0.60 t, 3 H, $J(CH_3,CH_2)$ = 7.3 (3′-CH_3).

6-(1,1-Dimethyl-3-phenylpropyl)purine (**18**): Yield: 0.22 g (82%), R_F 0.66 (chloroform–methanol 85 : 15). Mass spectrum (FAB), *m/z*: 267.2 $[M + H]^+$. For $C_{16}H_{18}N_4 \cdot 1/2\ H_2O$ (275.4) calculated: 69.79% C, 6.96% H, 20.34% N; found: 69.50% C, 6.68% H, 19.97% N. ^{1}H NMR spectrum ($(CD_3)_2SO$): 13.45 br, 1 H (NH); 8.82 s, 1 H (H-2); 8.50 s, 1 H (H-8); 7.19 t, 2 H and 7.10 t, 1 H and 7.03 d, 2 H (arom.); 2.30 m, 4 H (2″-CH_2 and 3″-CH_2); 1.56 s, 6 H (CH_3).

6-Cyclopentylpurine (**19**): Yield: 0.14 g (72%), R_F 0.69 (chloroform–methanol 8 : 2). Mass spectrum (FAB), *m/z*: 189.2 $[M + H]^+$. For $C_{10}H_{12}N_4 \cdot 1/2\ H_2O$ (197.2) calculated: 60.90% C, 6.64% H, 28.40% N; found: 60.99% C, 6.29% H, 28.62% N. ^{1}H NMR spectrum ($(CD_3)_2SO$): 13.39 br, 1 H (NH); 8.78 s, 1 H (H-2); 8.48 brs, 1 H (H-8); 3.55 m, 1 H (H-1′); 2.10–1.60 m, 8 H (cyclopentyl).

6-Cyclohexylpurine (**20**): Yield: 0.16 g (80%), R_F 0.76 (chloroform–methanol 8 : 2). Mass spectrum (FAB), *m/z*: 203.1 $[M + H]^+$. For $C_{11}H_{14}N_4$ (202.2) calculated: 65.34% C, 6.98% H, 27.70% N; found: 64.95% C, 6.98% H, 27.23% N. ^{1}H NMR spectrum ($(CD_3)_2SO$): 15.00 br, 1 H (NH); 8.78 s, 1 H (H-2); 8.50 s, 1 H (H-8); 3.28 m, 1 H (H-1′); 1.90–1.68 m, 7 H and 1.41 m, 2 H and 1.28 m, 1 H (cyclohexyl).

6-Cyclopropylpurine (**21**): Yield: 0.12 g (75%), R_F 0.34 (chloroform–methanol 9 : 1). Mass spectrum (FAB), *m/z*: 161.2 $[M + H]^+$. For $C_8H_8N_4 \cdot 1/2\ H_2O$ (169.15) calculated: 56.80% C, 5.36% H, 33.10% N; found: 58.50% C, 4.90% H, 32.97% N. ^{1}H NMR spectrum ($(CD_3)_2SO$): 13.40 br, 1 H (NH); 8.66 s, 1 H (H-2); 8.49 brs, 1 H (H-8); 2.65 m, 1 H (CH); 1.24 m, 2 H and 1.175 m, 2 H (CH_2).

General Method for Cleavage of the Phosphonate Esters **31**–**36**

The protected phosphonate 2**5–30** (1 mmol) was dissolved in acetonitrile (10 ml), bromotrimethylsilane (1 ml) was added and the mixture was set aside in a stoppered flask at 20 °C for 24 h. After evaporation, the residue was codistilled with acetonitrile (3 × 20 ml), mixed with water (20 ml) and adjusted to pH 8 with triethylamine. The mixture was allowed to stand for 1 h, then evaporated *in vacuo* and the residue was deionized on Dowex 50 X 8 (H^+-form, 40 ml) as described above. The crude product was purified by chromatography on a column of Dowex 1 X 2 (acetate form, 40 ml). The product was stirred batchwise with hot acetic acid (2 mol l^{-1}, 250 ml), the residue was filtered off, the filtrate evaporated, codistilled with water (3 × 20 ml) and ethanol (3 × 20 ml) to afford yellowish foam.

6-(2,2-Dimethylpropyl)-9-(2-phosphonomethoxyethyl)purine (**31**): Yield: 0.12 g (39%), E_{Up} = 0.69. Exact mass (FAB HRMS) calculated for $C_{13}H_{22}N_4O_4P$: 329.1379; found: 329.1413. ^{1}H NMR spectrum (D_2O): 9.12 s, 1 H (H-2); 8.90 s, 1 H (H-8); 4.67 t, 2 H, $J(1',2')$ = 5.0 (H-1′); 4.04 t, 2 H, $J(2',1')$ = 5.1 (H-2′); 3.66 d, 2 H, $J(P,CH)$ = 8.8 (P-CH_2); 3.26 s, 2 H (H-1″); 1.05 s, 9 H (CH_3).

6-Isopropyl-9-(2-phosphonomethoxyethyl)purine (**32**): Yield: 0.17 g (56%), E_{Up} = 0.80. Exact mass (FAB HRMS) calculated for $C_{11}H_{18}N_4O_4P$: 301.1066; found: 301.1147. ^{1}H NMR spectrum (D_2O): 9.06 s, 1 H (H-2); 8.56 s, 1 H (H-8); 4.66 t, 2 H, $J(1',2')$ = 4.8 (H-1′); 4.03 t, 2 H, $J(2',1')$ = 4.8 (H-2′); 3.86 sept, 1 H, $J(CH,CH_3)$ = 7.1 (H-1″); 3.65 d, 2 H, $J(P,CH)$ = 8.8 (P-CH_2); 1.52 d, 6 H, $J(CH_3,CH)$ = 7.1 (CH_3).

6-tert-Butyl-9-(2-phosphonomethoxyethyl)purine (**33**): Yield: 0.11 g (35%), E_{Up} = 0.71. Exact mass (FAB HRMS) calculated for $C_{12}H_{20}N_4O_4P$: 315.1222; found: 315.1191. ^{1}H NMR spectrum (D_2O): 9.09 s, 1 H (H-2); 8.92 s, 1 H (H-8); 4.69 t, 2 H, J(1′,2′) = 5.0 (H-1′); 4.03 t, 2 H, J(2′,1′) = 5.0 (H-2′); 3.67 d, 2 H, J(P,CH) = 9.0 (P-CH_2); 1.70 s, 9 H (CH_3).

6-(1,1-Dimethylpropyl)-9-(2-phosphonomethoxyethyl)purine (**34**): Yield: 0.12 g (38%), E_{Up} = 0.75. For $C_{13}H_{21}N_4O_4P{\cdot}2\ H_2O$ (364.3) calculated: 42.85% C, 6.91% H, 15.37% N, 8.50% P; found: 43.01% C, 6.67% H, 15.67% N, 8.13% P. Mass spectrum (FAB), *m/z*: 329.1 $[M + H]^+$. ^{1}H NMR spectrum ($(CD_3)_2SO$): 8.82 s, 1 H (H-2); 8.50 s, 1 H (H-8); 4.43 t, 2 H, J(1′,2′) = 5.1 (H-1′); 3.92 t, 2 H, J(2′,1′) = 5.1 (H-2′); 3.62 d, 2 H, J(P,CH) = 8.8 (P-CH_2); 2.05 q, 2 H, J(CH_2,CH_3) = 7.3 (CH_2); 1.48 s, 6 H (CH_3); 0.62 t, 3 H, J(CH_3,CH_2) = 7.3 (CH_3).

6-Cyclopentyl-9-(2-phosphonomethoxyethyl)purine (**35**): Yield: 0.13 g (40%), E_{Up} = 0.78. For $C_{13}H_{19}N_4O_4P{\cdot}H_2O$ (344.3) calculated: 45.34% C, 6.14% H, 16.26% N, 9.00% P; found: 45.45% C, 5.71% H, 15.90% N, 9.33% P. Mass spectrum (FAB), *m/z*: 327.3 $[M + H]^+$. ^{1}H NMR spectrum (D_2O): 9.00 s, 1 H (H-2); 8.80 s, 1 H (H-8); 4.64 t, 2 H, J(1′,2′) = 5.4 (H-1′); 4.02 t, 2 H, J(2′,1′) = 5.4 (H-2′); 3.87 pent, 1 H, J = 8.5 (H-1″); 3.65 d, 2 H, J(P,CH) = 8.8 (P-CH_2); 2.29 m, 2 H and 2.06–1.92 m, 4 H and 1.84 m, 2 H (cyclopentyl).

(R)-6-Cyclohexyl-9-(2-phosphonomethoxypropyl)purine (**36**): Yield: 0.14 g (40%), E_{Up} = 0.75. Exact mass (FAB HRMS) calculated for $C_{15}H_{24}N_4O_4P$: 355.1535; found: 355.1554. ^{1}H NMR spectrum (D_2O): 9.06 s, 1 H (H-2); 8.87 s, 1 H (H-8); 4.64 dd, 1 H, J(1′a,2′) = 2.9, J(gem) = 14.7 (H-1′a); 4.64 dd, 1 H, J(1′b,2′) = 7.1, J(gem) = 14.7 (H-1′b); 4.05 m, 1 H (H-2′); 3.72 dd, 1 H, J(P,CHa) = 9.3, J(gem) = 13.2 (P-CHa); 3.55 m, 1 H (H-1″); 3.50 dd, 1 H, J(P,CHb) = 9.5, J(gem) = 13.2 (P-CHb); 2.08 m, 2 H and 1.96 m, 2 H and 1.83 m, 3 H and 1.52 m, 2 H and 1.39 m, 1 H (cyclohexyl); 1.23 d, 3 H, J(CH_3,CH) = 6.1 (CH_3).

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