SYNTHESIS OF ACYCLIC NUCLEOTIDE ANALOGUES DERIVED FROM 6-HETARYLPURINES *via* CROSS-COUPLING REACTIONS OF 9-[2-(DIETHOXYPHOSPHONYLMETHOXY)ETHYL]-6-IODOPURINE WITH HETARYL ORGANOMETALLIC REAGENTS

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The title acyclic nucleotide analogues derived from 6-hetarylpurines were prepared by Pd(0)-catalysed cross-coupling reactions of 9-[2-(diethoxyphosphonylmethoxy)ethyl]-6-iodopurine (**1**) with hetaryl-organometallics: (pyridin-2-yl)-, (imidazol-2-yl)- and (pyrrol-2-yl)zinc chlorides or (imidazol-5-yl)- stannanes, followed by deprotection in fair to good yields. The starting 6-iodopurine derivative **1** was prepared by iododeamination of the adenine derivative.

Key words: Acyclic nucleoside phosphonates; Phosphonomethoxyethylpurine derivatives; PMEA; Organozinc reagents; Organotin reagents; Palladium; Antivirals.

N-Phosphonomethoxyalkyl 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 in the purine moiety is a prerequisite for the antiviral activity. To study the role of the amino function in the antiviral activity, their analogues bearing strongly basic aminoalkyl functions on the purine ring were prepared[3]. Antiviral activity tests of these compounds have shown that some 6-(aminomethyl)purine derivatives still possess moderate activity against several strains of viruses while the other compounds are inactive. As a continuation of that study we report here on the synthesis of acyclic nucleotide analogues based on 6-hetarylpurines bearing a nitrogen atom in α-position of the heterocyclic ring.

Cross-coupling reactions of organometallics[4] with hetaryl halides represent a convenient route for the preparation of C-substituted heterocycles. This methodology has been widely used for the synthesis of 6-alkyl(aryl)purine derivatives by the cross-coupling reactions of 6-halopurine derivatives with alkyl(aryl)zinc or tin reagents[5a–5c], trialkylaluminum[5d] or alkylcuprates[5e]. These methods, however, have not yet been used for the attachement of a nitrogen containing heterocycle to purine. Recently the "reverse" approach based on the reactions of purine-6-zinc halides with aryl halides was reported[6].

The protected 6-iodopurine derivative **1** that already contained the 2-phosphonomethoxyethyl function in the N-9 position was chosen as a key starting compound for the cross-coupling reactions. It was prepared by iododeamination of 9-[2-(diethoxyphosphonylmethoxy)ethyl]adenine[7] using isoamyl nitrite and diiodomethane in 44% yield (analogy to a reported procedure[8]).

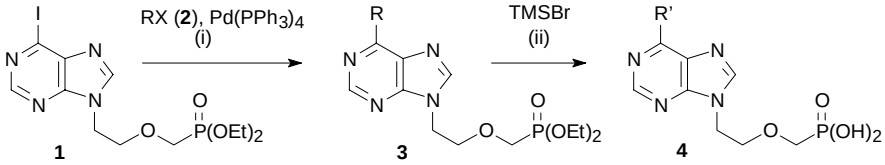
The results of the cross-coupling reactions of compound **1** with hetarylzinc chlorides and hetarylstannanes catalyzed by tetrakis(triphenylphosphine)palladium (Scheme 1) are summarized in Table I.

Reaction of (pyridin-2-yl)zinc chloride **2a** generated[9] from 2-bromopyridine with the compound **1** under Pd(0) catalysis gave the 6-(pyridin-2-yl)purine derivative **3a** in good yield. However, an analogous reaction with (pyrimidin-2-yl)zinc chloride was unsuccessful even with the use of additional two equivalents of $ZnCl_2$. Deprotection of compound **3a** was accomplished using bromotrimethylsilane (TMSBr) in acetonitrile to afford the pure phosphonate **4a** in the yield of 80% after isolation by anion exchange chromatography.

(Imidazol-2-yl)zinc reagents **2c** and **2d** were generated from 1-methylimidazole or 1-(methoxymethyl)imidazole using butyllithium followed by zinc chloride[10]. Their reaction with the compound **1** was performed under analogous conditions but additional two equivalents of $ZnCl_2$ were used to reach acceptable yields of compounds **3c** and **3d** (73 and 74%, respectively). Deprotection using TMSBr cleaved both the phosphonate ethyl ester and methoxymethyl (MOM) groups to give **4c** in good (82%) and **4d** in lower yield (36%).

A known method[11] was used for the synthesis of imidazol-5-yl substituted derivatives. Reaction of both 1-methyl and 1-MOM substituted imidazoles with butyllithium followed by tributyl(chloro)stannane gives a mixture of mono- and distannyl substituted imidazoles. Since the 2-stannyl group is very unstable[11], hydrolysis of the reaction mixture gave a mixture of starting imidazole and (imidazol-5-yl)stannanes **2e** and **2f**. Their reaction with compound **1** in dimethylformamide under Pd(0)-catalysis gave the 6-(imidazol-5-yl)purine derivatives **3e** and **3f** in the yields of 66% and 31%, respectively. Deprotection in the same manner as above afforded the pure phosphonates **4e** and **4f** in good yields.

N,N,N′,N′-Tetramethylethylenediamine (TMEDA) is used as an additive for the ortho-lithiation of 1-methylpyrrole by butyllithium[12] to increase the strength of the base[13] and to avoid formation of products of nucleophilic addition[14]. The recently reported method[12] for the cross-coupling reactions of (1-methylpyrrol-2-yl)zinc chloride had to be modified using a twofold excess of 1-methylpyrrole to avoid reaction of the excessive butyllithium with iodopurine **1**. This modified procedure (*Method A2*) afforded the compound **3g** in the yield of 60%. Since the standard deprotection and isolation was unsuccessful, milder reaction conditions were used and the product was isolated on a cation exchanger (*Method B*) to avoid the use of concentrated acetic acid



SCHEME 1

TABLE I
Reactions of the 6-iodopurine **1** with hetaryl-organometallics **2a–2i**

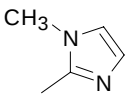
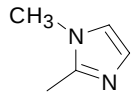
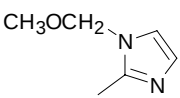
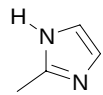
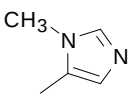
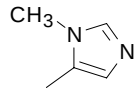
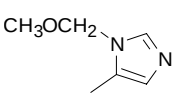
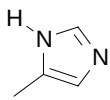
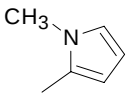
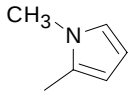
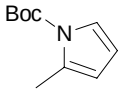
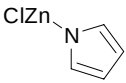
Entry	*R*	X	Method step (i)	Yield of **3** %	*R′*	Method step (ii)	Yield of **4** %
a		ZnCl	*A*	84		*A*	80
b		ZnCl	*A* *A1*	0 0			
c		ZnCl	*A1*	74		*A*	82
d		ZnCl	*A1*	73		*A*	36
e		$SnBu_3$	*B*	66		*A*	60
f		$SnBu_3$	*B*	31		*A*	71

TABLE I
(*Continued*)

Entry	*R*	X	Method step (i)	Yield of **3** %	*R′*	Method step (ii)	Yield of **4** %
g		ZnCl	*A2*	60		*B*	61
h		ZnCl	*A2*	0			
i[a]		ZnCl	*C*	83		*B*	0

[a] Compound **2i** = 

for the elution of the product from the anion exchanger column. This method gave the pure phosphonate **4g** in 61% yield.

In order to prepare the *N*-unsubstituted pyrrole derivative **4i** our efforts focused first on protection of the pyrrole nitrogen with a suitable protecting group. The known[15] procedure for the synthesis of 1-MOM-pyrrole was irreproducible in our hands. The pyrrole *N*-trimethylsilyl group is reported[16] to migrate under the lithiation conditions. The *N*-Boc group is easily introduced[17] and the *N*-Boc-pyrrole is known[18] to undergo lithiation followed by stannylation. However, our attempt on analogous lithiation of 1-Boc-pyrrole using butyllithium/TMEDA was unsuccessful. Further efforts focused on the reactions of *N*-unprotected pyrrole derivatives. Unlike *N*-alkali metal salts of pyrrole, (pyrrol-1-yl)magnesium halides are known[19] to undergo alkylation by alkyl halides to the 2 (major) and 3 (minor) positions. We have tried to transmetallate (pyrrol-1-yl)magnesium bromide to zinc chloride **2i** and utilize this reagent in the cross-coupling reaction with iodopurine **1**. Thus, pyrrole was treated consecutively with vinylmagnesium bromide, zinc chloride and compound **1** under Pd(0)-catalysis to give regioselectively the 6-(pyrrol-2-yl)purine **3i** in high yield (*Method C*). Efforts to cleave the phosphonate ethyl ester groups with TMSBr led to a complex mixture of of pyrrole

ring degradation products (^{1}H NMR spectrum exhibited no signals of the pyrrole moiety). This observation is in accord with the known[20] unstability of pyrroles in acid medium.

The conjugation of the two heteroaromatic rings manifests itself in strong bathochromic shifts of the UV maxima of the 6-hetarylpurine nucleotide analogues **4** compared to the adenine or aminoalkylpurine derivatives. The 6-(pyridin-2-yl)purine derivative **4a** is characterized by a bathochromic shift at pH 2 caused by *N*-protonation in strongly acid medium. The imidazole derivatives **4c–4f**, on the other hand, exhibit bathochromic shifts at pH 12 that may indicate protonation of the imidazole moiety at pH 7 and, in compounds **4d** and **4f**, also deprotonation of the imidazole in alkali. The 6-(imidazol-5-yl)purine **4f** exhibited a double maximum due probably to the 1H-3H tautomerism and intramolecular H-bonds. The *N*-methylpyrrole derivative **4g** exhibited a strong bathochromic shift at pH 2 which was caused by the degradation of the pyrrole moiety (this was supported by the measurement of ^{1}H NMR spectrum of compound **4g** in the presence of sulfuric acid which did not contain the pyrrole proton signals).

The structure of compounds **3** and **4** was determined by ^{1}H and ^{13}C NMR spectra. The 2- and 5-linked imidazoles were differentiated using a combination of proton-coupled and APT ^{13}C NMR techniques. While the NMR data of 2-linked imidazoles **3c**, **3d** and **4c**, **4d** are in accord with those reported for (imidazol-2-yl)pyridine derivatives[21], a downfield shift of imidazole proton signals was observed in the spectra of compounds **3e**, **3f** and **4e**, **4f**. Proton-coupled ^{13}C NMR spectrum of the compound **3e** exhibited the following signals of the imidazole carbon atoms: δ 143.30 (ddq, ^1J(C-2″,H-2″) = 208.7, ^2J(C-2″,H-4″) = 11.0, ^3J(C-2″,CH$_3$) = 4.2 (C-2″)); δ 137.65 (dd, ^1J(C-4″,H-4″) = 192.4, ^3J(C-4″,H-2″) = 10.7 (C-4″)) and δ 126.71 (ddq, ^2J(C-5″,H-4″) = 14.0, ^3J(C-5″,H-2″) = 5.0, ^3J(C-5″,CH$_3$) = 3.0 (C-5″)). The observed shifts and interaction constants are in good accord with the values reported for 5-linked imidazoles[22]. Some heteroaromatic proton and carbon signals of the *N*-unsubstituted imidazole derivatives **4d** (H-2, H-8, H-2″, H-4″, C-2″, C-4″ and C-8) and **4f** (all aromatic except for C-2) were broad due to the H-tautomerism and H-bonding.

Compounds **4a** and **4c–4g** were tested for their cytostatic[23] activity (inhibition of the cell growth on the following cell cultures: (i) mouse leukemia L1210 cells (ATCC CCL 219); (ii) murine L929 cells (ATCC CCL 1) and (iii) human cervix carcinoma HeLaS3 cells (ATCC CCL 2.2)) and antiviral activity[24] (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; neither of them was cytotoxic under the experimental conditions.

EXPERIMENTAL

Unless otherwise stated, solvents were evaporated at 40 °C/2kPa and compounds were dried at 60 °C/2kPa 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) in the following systems:

(A) ethyl acetate–MeOH (3 : 1); (B) i-PrOH–H_2O–35% aq. NH_3 (7 : 2 : 1). Paper electrophoresis was performed on Whatman No. 3 MM paper at 40 V/cm for 1 h in 0.05 M triethylammonium hydrogencarbonate at pH 7.5. Electrophoretical mobilities (E_{Up}) are referenced to uridine 3′-phosphate. NMR spectra (δ, ppm; *J*, Hz) were measured on a Varian Unity 500 spectrometer (500 MHz for ^1H and 125.7 MHz for ^{13}C NMR) in hexadeuteriodimethyl sulfoxide referenced to the solvent signals at 2.5 ppm for ^1H and 39.7 ppm for ^{13}C NMR, or in deuterium oxide containing sodium deuteroxide with sodium disilapentasulfonate as internal standard for ^1H and dioxane as external standard for ^{13}C NMR (δ(dioxane) = 66.86). Some simple ^1H NMR spectra were recorded on a Varian Unity 200 spectrometer at 200 MHz in $CDCl_3$ (TMS as internal standard) or in hexadeuteriodimethyl sulfoxide. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol matrix) or EI (electron energy 70 eV) techniques. UV absorption spectra (λ_{max}, nm; ε, $l\ mol^{-1}\ cm^{-1}$) were measured on a Beckman DU-65 spectrometer in aqueous solutions. DMF was distilled from P_2O_5 under reduced pressure, degassed *in vacuo* and stored over molecular sieves under Ar. Acetonitrile was refluxed with CaH_2 and distilled. THF was refluxed with Na and benzophenone under Ar atmosphere and freshly distilled *prior* to use.

Preparation of 1-Substituted-5-(tributylstannyl)imidazoles **2e** and **2f**

To a stirred solution of 1-substituted imidazole (19 mmol) in THF (10 ml) 2.5 M BuLi in hexane (7 ml, 17.5 mmol) was added dropwise (10 min.) at –78 °C under Ar atmosphere and the cooling bath was removed. After stirring for 1 h at room temperature the solution was cooled to –78 °C and tributyltin chloride (3.9 ml, 14.4 mmol) was added dropwise. The mixture was then stirred 4 h at room temperature, poured into a saturated aqueous NH_4Cl (100 ml) and extracted with diethyl ether (2 × 50 ml). The combined organic layers were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (30 g, light petroleum–ethyl acetate) afforded the stannanes.

1-Methyl-5-(tributylstannyl)imidazole (**2e**); yield 26%; colourless viscous liquid. Its FAB MS and ^1H NMR spectra are in accord with the reported ones (ref.[11]).

1-(Methoxymethyl)-5-(tributylstannyl)imidazole (**2f**); yield 24%; colourless viscous liquid. FAB MS, *m/z* (rel.%): 403 (100) $[M + H]^+$. ^1H NMR (500 MHz, $(CD_3)_2SO$): 0.83-1.60 m, 27 H (H-Bu); 3.08 s, 3 H (OCH_3); 5.19 s, 2 H (NCH_2O); 6.92 d, 1 H, *J* = 0.9 and 7.93 d, 1 H, *J* = 0.9 (H-imidazole). For $C_{17}H_{34}N_2OSn$ (402.2) calculated: 50.77% C, 8.52% H, 6.97% N; found: 50.33% C, 8.75% H, 7.19% N.

9-[2-(Diethoxyphosphonylmethoxy)ethyl]-6-iodopurine (**1**)

Method A: A mixture of 9-[2-(diethoxyphosphonylmethoxy)ethyl]adenine[7] (0.92 g, 2.8 mmol), isoamyl nitrite (1.8 ml, 13.4 mmol), diiodomethane (3.6 ml, 44.7 mmol) and acetonitrile (20 ml) was refluxed for 8 h. The solvents were evaporated, the residue was treated with saturated aqueous $Na_2S_2O_3$ (100 ml) and extracted with chloroform (3 × 100 ml). The combined organic phases were evaporated and the residue was chromatographed on a silica gel column (30 g, ethyl acetate–methanol) to give crude 6-iodopurine derivative **1** (540 mg, 44%) which was crystallized from ethyl acetate–ether.

Yellow powder; m.p. 112–113 °C; R_F (A) 0.30. FAB MS, *m/z* (rel.%): 441 (68) $[M + H]^+$. ^1H NMR (500 MHz, $(CD_3)_2SO$): 1.10 t, 6 H, $J(CH_3,CH_2)$ = 7.1 (CH_3); 3.84 d, 2 H, *J*(P,CH) = 8.3 (PCH_2); 3.87 m, 4 H ($POCH_2$); 3.93 t, 2 H, $J(2',1')$ = 5.1 (H-2′); 4.46 t, 2 H, $J(1',2')$ = 5.1 (H-1′); 8.61 s, 1 H and 8.63 s, 1 H (H-2 and H-8). ^{13}C NMR (125 MHz, $(CD_3)_2SO$): 16.29 d, *J*(P,C) = 5.9 (CH_3); 43.38 (C-1′); 61.79 d, *J*(P,C) = 6.8 ($POCH_2$); 63.87 d, *J*(P,C) = 163.1 (PCH_2); 70.00 d, *J*(P,C) = 11.7 (C-2′); 122.62 (C-5); 138.12 (C-6); 146.90 (C-8); 148.29 (C-4); 151.88 (C-2). For $C_{12}H_{18}IN_4O_4P$ (440.2) calculated: 32.74% C, 4.12% H, 12.73% N, 7.04% P, 28.83% I; found: 32.59% C, 4.24% H, 13.05% N, 7.09% P, 29.07% I.

Method B: The reaction followed the same procedure as above except that iodine (0.77 g, 3.04 mmol) and CuI (0.61, 3.2 mmol) were also added to the reaction mixture *prior* to reflux. Yield 260 mg (21%). M.p. and ^{1}H NMR spectrum were identical with the data of compound **1** above.

Coupling of the Iodopurine **1** with Hetaryl Organometallics **2** – General Methods

Method A: To a stirred solution of 2-bromopyridine or 2-chloropyrimidine (4 mmol) in THF (20 ml) under Ar at –78 °C 1.6 M *t*-BuLi in pentane (3.13 ml, 5 mmol) was added dropwise (20 min) and the stirring at –78 °C was continued for 1 h. Then 1 M $ZnCl_2$ in ether (5 ml, 5 mmol) was added dropwise, the mixture was allowed to warm up to room temperature and stirred for 1 h. A solution of compound **1** (440 mg, 1 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in THF (10 ml) was then added, the mixture was refluxed for 6 h and poured into saturated aqueous NH_4Cl (50 ml). After addition of EDTA (2 g) the mixture was extracted with chloroform (3 × 30 ml). The combined organic layers were evaporated and the residue was chromatographed on a silica gel column (40 g, ethyl acetate–methanol) to afford the oily TLC-pure product which was used in further step without additional purification.

Method A1: To a stirred solution of *N*-methylimidazole or *N*-MOM-imidazole (8 mmol) in THF (20 ml) under Ar at –78 °C 2.5 M BuLi in hexane (2.8 ml, 7 mmol) was added dropwise (20 min) and the mixture was slowly (2 h) allowed to warm up to –40 °C, recooled to –78 °C and then 1 M $ZnCl_2$ in ether (7 ml, 7 mmol) was added dropwise (20 min). The mixture was then stirred at room temperature for 30 min and a solution of compound **1** (440 mg, 1 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in THF (10 ml) was added. The mixture was refluxed for 14 h and worked-up in the same manner as above (*Method A*).

Method A2: To a solution of TMEDA (604 μl, 4 mmol) and 1-methylpyrrole or 1-Boc-pyrrole (8 mmol) in THF (20 ml) 1.5 M *t*-BuLi in pentanes (2.7 ml, 4 mmol) was added dropwise at –70 °C. The solution was then slowly warmed up and stirred at room temperature for 1 h, recooled to –70 °C, and 1 M $ZnCl_2$ in ether (4 ml, 4 mmol) was added dropwise. The mixture was then stirred for 1 h at room temperature and a solution of compound **1** (440 mg, 1 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in THF (10 ml) was added. The mixture was refluxed for 14 h and worked-up in the same manner as above (*Method A*).

Method B: A mixture of compound **1** (440 mg, 1 mmol), stannane **2e** or **2f** (1.5 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in DMF (10 ml) was refluxed under Ar for 8 h. The solvent was evaporated *in vacuo*, the residue was treated with saturated aqueous EDTA (20 ml) and 35% aqueous NH_3 (1 ml) and extracted with chloroform (3 × 20 ml). The collected organic layers were worked-up in the same manner as above (*Method A*).

9-[2-(Diethoxyphosphonylmethoxy)ethyl]-6-(pyridin-2-yl)purine (**3a**). Brownish oil; R_F (A) 0.05. FAB MS, *m/z* (rel.%): 392 (100) $[M + H]^+$. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): 1.09 t, 6 H, $J(CH_3,CH_2)$ = 7.1 (CH_3); 3.87 d, 2 H, J(P,CH) = 8.3 (PCH_2); 3.88 m, 4 H ($POCH_2$); 3.98 t, 2 H, $J(2',1')$ = 5.0 (H-2′); 4.54 t, 2 H, $J(1',2')$ = 5.0 (H-1′); 7.56 ddd, 1 H, $J(5'',3'')$ = 1.2, $J(5'',6'')$ = 4.9, $J(5'',4'')$ = 7.6 (H-5″); 8.05 td, 1 H, $J(4'',6'')$ = 1.7, $J(4'',3'')$ = $J(4'',5'')$ = 7.8 (H-4″); 8.63 brd, 1 H, $J(3'',4'')$ = 8.0 (H-3″); 8.83 ddd, 1 H, $J(6'',5'')$ = 4.9, $J(6'',4'')$ = 1.7, $J(6'',3'')$ = 0.9 (H-6″); 8.65 s, 1 H and 9.05 s, 1 H (H-2 and H-8). ^{13}C NMR (125 MHz, $(CD_3)_2SO$): 16.28 d, J(P,C) = 4.9 (CH_3); 42.99 (C-1′); 61.84 d, J(P,C) = 5.9 ($POCH_2$); 63.94 d, J(P,C) = 163.1 (PCH_2); 70.19 d, J(P,C) = 10.7 (C-2′); 125.17 and 125.62 (C-3″ and C-5″); 131.09 (C-5); 137.10 (C-4″); 147.69 (C-8); 150.10 (C-6″); 151.88 (C-2); 152.90, 153.20 and 153.75 (C-6, C-4 and C-2″).

9-[2-(Diethoxyphosphonylmethoxy)ethyl]-6-(1-methylimidazol-2-yl)purine (**3c**). Colourless oil. FAB MS, *m/z* (rel.%): 395 (100) $[M + H]^+$. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): 1.10 t, 6 H, $J(CH_3,CH_2)$ = 7.1 (CH_3); 3.89 m, 6 H (PCH_2 and $POCH_2$); 3.95 t, 2 H, $J(2',1')$ = 5.0 (H-2′); 3.86 brs and 4.04 brs

(3 H, CH_3N); 4.50 t, 2 H, *J*(1′,2′) = 5.0 (H-1′); 7.18 brs, 1 H and 7.48 brs, 1 H (H-4″ and H-5″); 8.54 s, 1 H and 8.98 s, 1 H (H-2 and H-8). ^{13}C NMR (125 MHz, $(CD_3)_2SO$): 16.31 d, *J*(P,C) = 5.9 (CH_3); 43.00 (C-1′); 61.84 d, *J*(P,C) = 5.9 ($POCH_2$); 63.90 d, *J*(P,C) = 162.1 (PCH_2); 70.14 d, *J*(P,C) = 10.7 (C-2′); 129.27 (C-5″); 132.27 (C-4″); 132.54 (C-5); 137.71 (C-2″); 142.41 (C-6); 147.38 (C-8); 151.50 (C-2); 152.57 (C-4).

9-[2-(Diethoxyphosphonylmethoxy)ethyl]-6-[1-(methoxymethyl)imidazol-2-yl]purine (**3d**). Colourless oil. FAB MS, *m/z* (rel.%): 425 (62) $[M + H]^+$. ^1H NMR (500 MHz, $(CD_3)_2SO$): 1.10 t, 6 H, *J*(CH_3,CH_2) = 7.1 (CH_3); 3.15 s, 3 H (CH_3O); 3.88 m, 6 H (PCH_2 and $POCH_2$); 3.98 t, 2 H, *J*(2′,1′) = 5.0 (H-2′); 4.54 t, 2 H, *J*(1′,2′) = 5.0 (H-1′); 5.98 brs, 2 H (OCH_2N); 7.20 brs, 1 H and 7.40 brs, 1 H (H-4″ and H-5″); 8.54 s, 1 H and 9.02 s, 1 H (H-2 and H-8). ^{13}C NMR (125 MHz, $(CD_3)_2SO$): 16.33 d, *J*(P,C) = 4.9 (CH_3); 43.16 (C-1′); 56.02 (CH_3O); 61.90 d, *J*(P,C) = 6.9 ($POCH_2$); 63.96 d, *J*(P,C) = 162.1 (PCH_2); 70.10 d, *J*(P,C) = 10.7 (C-2′); 78.17 (NCH_2O); 129.15 (C-5″); 132.01 (C-4″); 132.55 (C-5); 139.40 (C-2″); 141.00 (C-6); 148.00 (C-8); 151.50 (C-2); 152.64 (C-4).

9-[2-(Diethoxyphosphonylmethoxy)ethyl]-6-(1-methylimidazol-5-yl)purine (**3e**). Colourless oil. FAB MS, *m/z* (rel.%): 395 (100) $[M + H]^+$. ^1H NMR (500 MHz, $(CD_3)_2SO$): 1.10 t, 6 H, *J*(CH_3,CH_2) = 7.1 (CH_3); 3.35 s, 3 H (CH_3N); 3.85 dd, 1 H, *J*(P,CHb) = 9.8, *J*(gem) = 12.7 (PCHb); 3.88 dd, 1 H, *J*(P,CHa) = 9.8, *J*(gem) = 12.7 (PCHb); 3.89 m, 4 H ($POCH_2$); 3.95 t, 2 H, *J*(2′,1′) = 5.0 (H-2′); 4.49 t, 2 H, *J*(1′,2′) = 5.0 (H-1′); 7.94 d, 1 H, *J*(5″,4″) = 1.2 (H-4″); 8.38 d, 1 H, *J*(4″,5″) = 1.2 (H-2″); 8.56 s, 1 H and 8.89 s, 1 H (H-2 and H-8). ^{13}C NMR (125 MHz, $(CD_3)_2SO$): 16.30 d, *J*(P,C) = 5.9 (CH_3); 35.46 (CH_3N); 42.87 (C-1′); 61.85 d, *J*(P,C) = 6.8 ($POCH_2$); 63.91 d, *J*(P,C) = 162.1 (PCH_2); 70.21 d, *J*(P,C) = 11.7 (C-2′); 126.71 (C-5″); 128.72 (C-5); 137.65 (C-4″); 143.30 (C-2″); 146.31 (C-8); 147.03 (C-6); 151.41 (C-4); 151.66 (C-2).

9-[2-(Diethoxyphosphonylmethoxy)ethyl]-6-[1-(methoxymethyl)imidazol-5-yl]purine (**3f**). Colourless oil. FAB MS, *m/z* (rel.%): 425 (100) $[M + H]^+$. ^1H NMR (500 MHz, $(CD_3)_2SO$): 1.10 t, 6 H, *J*(CH_3,CH_2) = 7.1 (CH_3); 3.19 s, 3 H (CH_3O); 3.86 d, 1 H, *J*(P,CH) = 8.1 (PCH_2); 3.88 brpent, 4 H, *J*(CH_2,CH_3) = *J*(P,OCH) = 7.1 ($POCH_2$); 3.96 t, 2 H, *J*(2′,1′) = 5.1 (H-2′); 4.50 t, 2 H, *J*(1′,2′) = 5.1 (H-1′); 6.07 s, 2 H (OCH_2N); 8.18 d, 1 H, *J*(5″,4″) = 1.2 (H-4″); 8.42 d, 1 H, *J*(4″,5″) = 1.2 (H-2″); 8.58 s, 1 H and 8.89 s, 1 H (H-2 and H-8). ^{13}C NMR (125 MHz, $(CD_3)_2SO$): 16.27 d, *J*(P,C) = 4.9 (CH_3); 42.88 (C-1′); 55.56 (CH_3O); 61.83 d, *J*(P,C) = 5.9 ($POCH_2$); 63.90 d, *J*(P,C) = 162.1 (PCH_2); 70.18 d, *J*(P,C) = 11.7 (C-2′); 77.21 (NCH_2O); 125.98 (C-5″); 128.80 (C-5); 136.13 (C-4″); 143.67 (C-2″); 146.58 (C-6); 146.59 (C-8); 151.53 (C-4); 151.62 (C-2).

9-[2-(Diethoxyphosphonylmethoxy)ethyl]-6-(1-methylpyrrol-2-yl)purine (**3g**). Colourless oil. FAB MS, *m/z* (rel.%): 394 (100) $[M + H]^+$. ^1H NMR (500 MHz, $(CD_3)_2SO$): 1.11 t, 6 H, *J*(CH_3,CH_2) = 7.1 (CH_3); 3.86 d, 2 H, *J*(P,CH) = 8.3 (PCH_2); 3.89 m, 4 H ($POCH_2$); 3.94 t, 2 H, *J*(2′,1′) = 5.1 (H-2′); 4.15 s, 3 H (CH_3N); 4.46 t, 2 H, *J*(1′,2′) = 5.1 (H-1′); 6.24 dd, 1 H, *J*(4″,5″) = 2.4, *J*(4″,3″) = 3.9 (H-4″); 7.12 brt, 1 H, *J* = 2.2 (H-5″); 7.78 dd, 1 H, *J*(3″,4″) = 3.9, *J*(3″,5″) = 2.0 (H-3″); 8.47 s, 1 H and 8.80 s, 1 H (H-2 and H-8). ^{13}C NMR (125 MHz, $(CD_3)_2SO$): 16.30 d, *J*(P,C) = 4.9 (CH_3); 38.21 (NCH_3); 42.72 (C-1′); 61.84 d, *J*(P,C) = 6.9 ($POCH_2$); 63.92 d, *J*(P,C) = 162.1 (PCH_2); 70.26 d, *J*(P,C) = 10.7 (C-2′); 108.70 (C-4″); 119.24 (C-5″); 126.68 (C-2″); 128.26 (C-5); 130.01 (C-3″); 145.39 (C-8); 148.76 (C-6); 151.22 (C-4); 151.37 (C-2).

9-[2-(Diethoxyphosphonylmethoxy)ethyl]-6-(pyrrol-2-yl)purine (**3i**)

Method C: To a stirred solution of pyrrole (345 μl, 5 mmol) in THF (5 ml) 1 M vinylmagnesium bromide solution in THF (5 ml, 5 mmol) was added dropwise at ambient temperature under Ar atmosphere. The mixture was stirred 30 min at 50 °C, cooled to –78 °C and $ZnCl_2$ (1 M solution in ether, 7 ml, 7 mmol) was added dropwise. The resulting heavy suspension was stirred at room temperature for 1 h and a solution of compound **1** (110 mg, 0.25 mmol), $Pd(PPh_3)_4$ (14.5 mg, 0.013 mmol)

in THF (5 ml) was added. The mixture was then refluxed for 5 h and allowed to stand overnight at room temperature. The work-up was performed in the same manner as above to yield compound **3i** (80 mg, 84%) as greenish oil. FAB MS, *m/z* (rel.%): 380 (100) $[M + H]^+$. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): 1.11 t, 6 H, $J(CH_3,CH_2)$ = 7.1 (CH_3); 3.86 d, 2 H, J(P,CH) = 8.3 (PCH_2); 3.89 dq, 4 H, $J(CH_2,CH_3)$ = 7.1, J(P,OCH) = 8.1 ($POCH_2$); 3.95 t, 2 H, $J(2',1')$ = 5.1 (H-2′); 4.46 t, 2 H, $J(1',2')$ = 5.1 (H-1′); 6.31 dt, 1 H, $J(4'',5'')$ = $J(4'',NH)$ = 2.4, $J(4'',3'')$ = 3.9 (H-4″); 7.09 ddd, 1 H, $J(5'',3'')$ = 1.5, $J(5'',4'')$ = 2.4, $J(5'',NH)$ = 3.0 (H-5″); 7.54 ddd, 1 H, $J(3'',4'')$ = 3.7, $J(3'',5'')$ = 1.5, $J(3'',NH)$ = 2.4 (H-3″); 8.49 s, 1 H and 8.76 s, 1 H (H-2 and H-8); 11.85 brs, 1 H (NH). ^{13}C NMR (125 MHz, $(CD_3)_2SO$): 16.32 d, J(P,C) = 5.9 (CH_3); 42.75 (C-1′); 61.83 d, J(P,C) = 5.9 ($POCH_2$); 63.93 d, J(P,C) = 162.1 (PCH_2); 70.26 d, J(P,C) = 10.7 (C-2′); 110.61 (C-4″); 115.49 (C-5″); 123.82 (C-3″); 127.27 and 127.64 (C-5 and C-2″); 145.68 (C-8); 147.19 (C-6); 151.43 (C-4); 151.97 (C-2).

Deprotection of Phosphonates **3** – General Procedure

Method A: To a solution of compound **3** (0.26–1.2 mmol) in acetonitrile (5–10 ml) TMSBr (5 ml, 38 mmol) was added. The solution was stirred for 4 h at 80 °C and then allowed to stand overnight at room temperature. After evaporation of the solvents the residue was dissolved in water (10 ml) and 35% aqueous NH_3 (1 ml) was added. The solution was washed with ether (10 ml) and the aqueous layer was applied onto a column of Dowex 1 X 2 (50 ml, acetate form). The column was washed with water and the products were eluted with a gradient of 0.01–1 M acetic acid; the eluents were evaporated and the residue was crystallized from water–ethanol–ether mixture.

Method B: The reaction was performed similarly as above but at room temperature. After addition of ammonia it was allowed to stand for 10 min. and aqueous HCl was added to pH 3. This solution was applied to a column of Dowex 50 X 8 (50 ml, H^+ form); the column was washed with water and the products eluted with 1% aqueous NH_3, evaporated and crystallized from water–ethanol–ether mixture.

9-[2-(Phosphonomethoxy)ethyl]-6-(pyridin-2-yl)purine (**4a**). Yellowish powder, m.p. 215–218 °C (dec.); R_F (B) 0.18; E_{Up} 0.78. FAB MS, *m/z* (rel.%): 336 (100) $[M + H]^+$. ^{1}H NMR (500 MHz, D_2O): 3.72 d, 2 H, J(P,CH) = 8.8 (PCH_2); 4.08 t, 2 H, $J(2',1')$ = 5.0 (H-2′); 4.66 t, 2 H, $J(1',2')$ = 5.0 (H-1′); 8.14 m, 1 H (H-5″); 8.68 td, 1 H, $J(4'',6'')$ = 1.0, $J(4'',3'')$ = $J(4'',5'')$ = 7.8 (H-4″); 8.96 brd, 1 H, $J(6'',5'')$ = 4.5 (H-6″); 8.65 s, 1 H and 9.05 s, 1 H (H-2 and H-8); 9.09 brd, 1 H, $J(3'',4'')$ = 8.0 (H-3″). ^{13}C NMR (125 MHz, D_2O): 44.16 (C-1′); 67.04 d, J(P,C) = 157.2 (PCH_2); 70.26 d, J(P,C) = 11.7 (C-2′); 128.19 and 128.60 (C-3″ and C-5″); 130.55 (C-5); 144.38 (C-4″); 144.45 and 145.82 (C-6 and C-2″); 145.96 (C-8); 150.36 (C-6″); 151.65 (C-2); 153.60 (C-4). UV, pH 7: 293 (12 500), 237 sh (5 600); pH 2: 317 (13 000), 240 sh (5 400); pH 12: 292 (13 400). For $C_{13}H_{14}N_5O_4P$. 1.5 H_2O (362.3) calculated: 43.09% C, 4.73% H, 19.33% N, 8.54% P; found: 43.48% C, 4.59% H, 19.09% N, 8.23% P.

6-(1-Methylimidazol-2-yl)-9-[2-(phosphonomethoxy)ethyl]purine (**4c**). Greenish solid; m.p. 219–222 °C; R_F (B) 0.13; E_{Up} 0.81. FAB MS, *m/z* (rel.%): 339 (100) $[M + H]^+$. ^{1}H NMR (500 MHz, D_2O): 3.67 d, 2 H, J(P,CH) = 8.3 (PCH_2); 4.07 t, 2 H, $J(2',1')$ = 5.0 (H-2′); 4.27 s, 3 H (CH_3N); 4.67 t, 2 H, $J(1',2')$ = 5.0 (H-1′); 7.76 brs, 1 H and 7.77 brs, 1 H (H-4″ and H-5″); 8.80 brs, 1 H and 9.14 brs, 1 H (H-2 and H-8). ^{13}C NMR (125 MHz, D_2O): 36.50 (CH_3N); 43.50 (C-1′); 66.59 d, J(P,C) = 156.4 (PCH_2); 69.74 d, J(P,C) = 11.7 (C-2′); 121.12 (C-5″); 126.28 (C-4″); 130.84 (C-5); 137.42 and 138.83 (C-6 and C-2″); 149.85 (C-8); 151.39 (C-2); 152.64 (C-4). UV, pH 7: 304 (18 700); pH 2: 303 (18 700); pH 12: 312 (19 500). For $C_{12}H_{15}N_6O_4P$. 1.5 H_2O (365.3) calculated: 39.45% C, 4.96% H, 23.00% N; found: 39.13% C, 4.67% H, 22.59% N.

6-(Imidazol-2-yl)-9-[2-(phosphonomethoxy)ethyl]purine (**4d**). Greenish solid, slowly decomposing above 170 °C; R_F (B) 0.16; E_{Up} 0.76. FAB MS, *m/z* (rel.%): 325 (13) $[M + H]^+$. ^{1}H NMR (500 MHz, D_2O): 3.61 d, 2 H, J(P,CH) = 8.6 (PCH_2); 4.01 t, 2 H, $J(2',1')$ = 5.0 (H-2′); 4.61 t, 2 H, $J(1',2')$ = 5.0

(H-1′); 7.53 brs, 2 H (H-2″ and H-4″); 8.67 s, 1 H and 9.05 s, 1 H (H-2 and H-8). ^{13}C NMR (125 MHz, D_2O): 43.69 (C-1′); 66.54 d, *J*(P,C) = 158.3 (PCH_2); 69.59 d, *J*(P,C) = 10.7 (C-2′); 124.00 (C-5″); 127.91 (C-4″); 129.62 (C-5); 137.07 (C-2″); 139.41 (C-6); 149.66 (C-8); 152.08 (C-2); 152.50 (C-4). UV, pH 7: 315 (18 100); pH 2: 313 (16 800); pH 12: 321 (17 000). For $C_{11}H_{13}N_6O_4P$. H_2O (342.3) calculated: 38.59% C, 4.42% H, 24.19% N; found: 38.15% C, 4.21% H, 24.23% N.

6-(1-Methylimidazol-5-yl)-9-[2-(phosphonomethoxy)ethyl]purine (**4e**). Colourless crystals, m.p. 247–250 °C (dec.); R_F (B) 0.23; E_{Up} 0.73. FAB MS, *m/z* (rel.%): 339 (35) $[M + H]^+$. ^{1}H NMR (500 MHz, D_2O): 3.56 d, 2 H, *J*(P,CH) = 8.2 (PCH_2); 3.88 s, 3 H (CH_3N); 3.98 t, 2 H, *J*(2′,1′) = 4.9 (H-2′); 4.45 t, 2 H, *J*(1′,2′) = 4.9 (H-1′); 7.72 brs, 1 H and 7.77 brs, 1 H (H-2″ and H-4″); 8.46 brs, 1 H and 8.56 brs, 1 H (H-2 and H-8). ^{13}C NMR (125 MHz, D_2O): 34.93 (CH_3N); 43.68 (C-1′); 68.84 d, *J*(P,C) = 150.6 (PCH_2); 70.06 d, *J*(P,C) = 10.0 (C-2′); 126.29 (C-5″); 128.63 (C-5); 135.19 (C-4″); 143.01 (C-2″); 146.49 (C-6); 147.11 (C-8); 150.58 (C-4); 151.14 (C-2). UV, pH 7: 294 (13 400); pH 2: 291 (13 600); pH 12: 309 (18 000). For $C_{12}H_{15}N_6O_4P$. 0.5 H_2O (347.3) calculated: 41.50% C, 4.64% H, 24.20% N, 8.91% P; found: 41.51% C, 4.56% H, 24.25% N, 8.86% P.

6-(Imidazol-5-yl)-9-[2-(phosphonomethoxy)ethyl]purine (**4f**). Colourless crystals; m.p. 255–260 °C (dec.); R_F (B) 0.12; E_{Up} 0.69. FAB MS, *m/z* (rel.%): 325 (45) $[M + H]^+$. ^{1}H NMR (500 MHz, D_2O): 3.54 d, 2 H, *J*(P,CH) = 8.3 (PCH_2); 3.97 t, 2 H, *J*(2′,1′) = 5.0 (H-2′); 4.42 t, 2 H, *J*(1′,2′) = 5.0 (H-1′); 7.90 brs, 2 H (H-2″ and H-4″); 8.44 s, 1 H and 8.59 s, 1 H (H-2 and H-8). ^{13}C NMR (125 MHz, D_2O): 43.13 (C-1′); 68.64 d, *J*(P,C) = 150.3 (PCH_2); 69.53 d, *J*(P,C) = 9.8 (C-2′); 127.52 (C-5); 132.00 (C-5″); 137.95 (C-4″); 143.00 (C-2″); 146.69 (C-8); 147.66 (C-6); 150.47 (C-4); 151.12 (C-2). UV, pH 7: 304 sh (15 200), 298 (16 500); pH 2: 304 sh (12 300), 296 (16 100), 241 sh (6 400); pH 12: 337 (19 700), 262 sh (4 200), 236 (9 300). For $C_{11}H_{13}N_6O_4P$. H_2O (342.3) calculated: 38.59% C, 4.42% H, 24.19% N; found: 38.09% C, 4.05% H, 24.19% N.

6-(1-Methylpyrrol-2-yl)-9-[2-(phosphonomethoxy)ethyl]purine (**4g**). Yellow crystalls, m.p. 227–229 °C; R_F (B) 0.33; E_{Up} 0.75. FAB MS, *m/z* (rel.%): 338 (100) $[M + H]^+$. ^{1}H NMR (500 MHz, D_2O): 3.68 d, 2 H, *J*(P,CH) = 8.8 (PCH_2); 3.87 s, 3 H (NCH_3); 3.96 t, 2 H, *J*(2′,1′) = 5.1 (H-2′); 4.40 t, 2 H, *J*(1′,2′) = 5.1 (H-1′); 6.29 t, 1 H, *J*(4″,3″) = *J*(4″,5″) = 3.5 (H-4″); 7.04 d, 2 H, J= 3.5 (H-3″ and H-5″); 8.55 s, 1 H and 8.37 s, 1 H (H-2 and H-8). ^{13}C NMR (125 MHz, D_2O): 36.23 (CH_3N); 43.04 (C-1′); 66.58 d, *J*(P,C) = 156.3 (PCH_2); 69.83 d, *J*(P,C) = 12.0 (C-2′); 108.67 (C-4″); 118.12 (C-5″); 125.28 (C-2″); 127.48 (C-5); 130.37 (C-3″); 145.84 (C-8); 147.70 (C-6); 149.82 (C-4); 150.16 (C-2). UV, pH 7: 340 (24 300), 269 (4 100), 237 (9 500); pH 2: 370 (26 700), 244 (7 200); pH 12: 339 (24 600), 270 (4 200), 236 (9 600). For $C_{13}H_{16}N_5O_4P$ (337.3): 46.29% C, 4.87% H, 20.77% N, 9.16% P; found: 45.87% C, 4.64% H, 20.30% N, 9.18% P.

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