SYNTHESIS OF ACYCLIC NUCLEOTIDE ANALOGUES DERIVED FROM 2-AMINO-6-*C*-SUBSTITUTED PURINES *via* CROSS-COUPLING REACTIONS OF 2-AMINO-9-{2-[(DIISOPROPOXYPHOSPHORYL)METHOXY]ETHYL}-6-HALOPURINES WITH DIVERSE ORGANOMETALLIC REAGENTS

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Cross-coupling reactions of 2-amino-6-chloro-9-{2-[(diisopropoxyphosphoryl)methoxy]-ethyl}purine (**1**) and 2-amino-9-{2-[(diisopropoxyphosphoryl)methoxy]ethyl}-6-iodopurine (**2**) with diverse types of organometallic reagents have been studied. Arylboronic acids reacted with **1** to give the corresponding 2-amino-6-arylpurines **3a**–**3d** in good yields. Analogously, trialkylaluminium reagents were used for the preparation of 6-alkyl-2-aminopurines **3k** and **3l** from **1**. Hetarylzinc halides and hetarylstannanes required the use of 2-amino-6-iodopurine **2** to give the corresponding 2-amino-6-hetarylpurines **3e**–**3j** in fair to good yields. A CuI/KF mediated coupling of perfluoroalkylsilanes with **2** afforded the 2-amino-6-perfluoroalkylpurines **3m** and **3n** in moderate yields. Cleavage of the esters **3** with bromo(trimethyl)silane gave the target free phosphonates **4** that were purified by ion-exchange chromatography. The title compounds were tested on antiviral and cytostatic activity.

Key words: Purines; Phosphonates; Cross-coupling reactions; Nucleosides; Nucleotides; Acyclic Analogs; Stannanes; Boronic acids; Organozinc reagents; Trialkylaluminum reagents; Perfluoroalkylations; Antivirals.

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 in 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], as well as simple 6-*sec*- or 6-*tert*-alkyl[7] or 6-perfluoroalkyl[8] groups 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. Since most of these modifications were made on 2-unsubstituted purine system only[6–8], and considering the crucial role of the amino group, a logical continuation of those studies should be the preparation of acyclic nucleotide analogues derived from 2-amino-6-*C*-substituted purines, which is the subject of this paper.

Cross-coupling methodology is the most versatile and efficient approach to the synthesis of 6-*C*-substituted purines. Thus, reactions of arylmagnesium halides[9], alkyl(aryl)zinc or tin reagents[5,6,10], trialkylaluminiums[11] or alkylcuprates[12] and recently also arylboronic acids[13,14] with 6-halopurines give the corresponding 6-*C*-substituted purine derivatives usually in good yields. In contrast, the reaction of 6-halopurines with Michael acceptors under the conditions of the Heck reaction leads[15] to 1-substituted hypoxanthine derivatives. A reverse approach based on the reaction of purine-6-zinc iodide with aryl or vinyl halides has also been described[16]. 6-*C*-Substituted purines display diverse types of biological activity, *e.g.* 6-methylpurine derivatives are cytotoxic[17]; 6-(trifluoromethyl)purine[18] and 6-phenylpurine[14] ribonucleosides display cytostatic activity; 6-(arylalkynyl)- and 6-(arylalkenyl)-purines show cytokinin activity[19], while 9-benzyl-6-arylpurines exhibit antimycobacterial activity[20].

Cross-coupling reactions of 2-amino-6-halopurines with diverse types of organometallic reagents was the methodology of choice for the introduction of various carbon substituents into the position 6 of the 2-aminopurine ring. Since *N*-alkylation of purines usually leads to mixtures of regioisomers, 2-amino-6-halopurines bearing already the protected 2-(phosphonomethoxy)ethyl moiety in the position 9 were chosen as starting compounds for the coupling reactions. The known 2-amino-6-chloropurine phosphonate[2b] **1** was easily transformed to the 6-iodo derivative **2** by treatment with hydroiodic acid in analogy to published procedure[21].

The Suzuki–Miyaura cross-coupling reactions of the 2-amino-6-chloropurine **1** with a series of arylboronic acids was the first approach studied (Scheme 1, Table I). The reaction of **1** with phenyl-, 2-tolyl- and 4-fluorophenylboronic acid in toluene at 100 °C under $Pd(PPh_3)_4$ catalysis proceeded smoothly to give the corresponding 6-arylpurines **3a**–**3c** in good yields (76, 80 and 84%, respectively). For the reaction with 2-thienylboronic acid the conditions had to be modified: using water–1,2-dimethoxyethane (1 : 3) as solvent, the product **3d** was obtained in a good yield of 91%.

The Negishi reactions with hetarylzinc halides were selected for the introduction of hetaryl substituents. Thus (pyridin-2-yl)-, (1-methylpyrrol-2-yl)-, (1-methylimidazol-2-yl)- and [1-(methoxymethyl)imidazol-2-yl]zinc chlorides were generated *in situ* and reacted with the 2-amino-6-halopurines **1** and **2** in THF under conditions analogous to the procedures published for the 2-unsubstituted purines[6]. (Pyridin-2-yl)zinc chloride was generated[22] from 2-bromopyridine using *t*-BuLi followed by the addition of one equivalent of $ZnCl_2$. (1-Methylpyrrol-2-yl)zinc chloride was prepared[6,23] by lithiation of 1-methylpyrrole using BuLi in presence of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) followed by transmetallation with $ZnCl_2$. Both (1-substituted imidazol-2-yl)zinc chlorides were generated[6,24] analogously from the corresponding 1-substituted imidazoles using BuLi followed by addition of 3 equivalents of $ZnCl_2$. The reactions of these hetarylzinc halides with the 2-amino-6-iodopurine **2** proceeded well to give the desired 6-hetarylpurines **3e**–**3h** in good yields (85, 65, 94 and 76%, respectively), while analogous reactions of 2-amino-6-chloropurine **1** gave very low conversions and complex mixtures of products.

The Stille coupling reactions with known[6,25] (1-methylimidazol-5-yl)- and [1-(methoxymethyl)imidazol-5-yl]tributylstannanes, prepared by successive double lithiation, stannylation and hydrolysis of the corresponding imidazoles, were used for the introduction of the imidazol-5-yl moiety. While the reaction of these stannanes with the 2-amino-6-iodopurine **2** in DMF at 120 °C gave the desired 6-(imidazol-5-yl)purines **3i** and **3j** in fair yields of 61 and 45%, respectively, analogous reaction with the 2-amino-6-chloropurine **1** led to complex mixtures.

Cross-coupling reactions of 6-halopurines with trialkylaluminium reagents were described as a good method for the preparation of 6-alkylpurines[11]. In our study, reactions of trimethyl- and triethylaluminium with the 2-amino-6-chloropurine **1** in refluxing THF catalyzed by $Pd(PPh_3)_4$ gave the corresponding 2-amino-6-alkylpurines **3k** and **3l** in good yields of 67 and 78%, respectively. This approach to the known compound **3k** was more efficient than the recently described procedure[2b] based on analogous methylation of 2-amino-9-benzyl-6-chloropurine followed by debenzylation and alkylation with protected 2-(phosphonomethoxy)ethyl chloride.

Cross-coupling reactions of 6-chloropurines with alkyl cuprates generated *in situ* from the corresponding Grignard reagents were recently used[7,12b] for the introduction of *sec*- and *tert*-alkyl groups into the position 6 of purine derivatives. However, analogous reactions of a cuprate generated from isobutylmagnesium bromide and CuI with both 2-amino-6-halopurines **1** and **2** led to complex mixtures of products with no traces of the desired

Scheme 1:

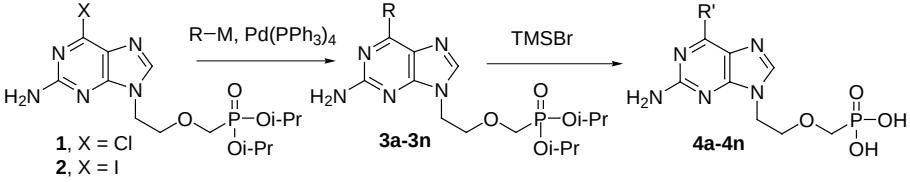


TABLE I
Reactions of the 2-amino-6-halopurines **1** and **2** with organometallics

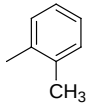
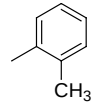
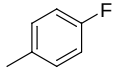
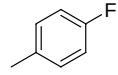
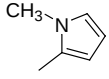
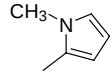
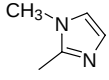
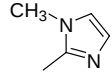
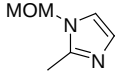
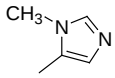
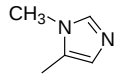
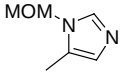
Entry	Starting halopurine	R	M	Yield of **3**	R'	Yield of **4**
a	**1**		$B(OH)_2$	76 %		84 %
b	**1**		$B(OH)_2$	80 %		92 %
c	**1**		$B(OH)_2$	84 %		66 %
d	**1**		$B(OH)_2$	91 %		95 %
e	**2**		ZnCl	85 %		90 %
f	**2**		ZnCl	65 %		61 %
g	**2**		ZnCl	94 %		83 %
h	**2**		ZnCl	76 %		55 %

TABLE I
(*continued*)

Entry	Starting halopurine	R	M	Yield of **3**	R'	Yield of **4**
i	**2**		$SnBu_3$	61 %		61 %
j	**2**		$SnBu_3$	45 %		78 %
k	**1**	CH_3	$AlMe_2$	67 %	CH_3	89 %
l	**1**	CH_2CH_3	$AlEt_2$	78 %	CH_2CH_3	89 %
m[a]	**2**	CF_3	$SiMe_3$	28 %	CF_3	65 %
n[a]	**2**	$CF_2CF_2CF_3$	$SiMe_3$	21 %	$CF_2CF_2CF_3$	59 %

[a] without Pd catalysis - mediated by CuI and KF

2-amino-6-isobutylpurine (FAB MS analysis of the crude mixture). Recently we have developed a facile synthesis[8] of 6-(perfluoroalkyl)purines making use of reactions of perfluoroalkyl cuprates generated from trimethyl(perfluoroalkyl)silanes by the use of KF and CuI with 6-iodopurines. Analogous reactions of trimethyl(trifluoromethyl)silane and (heptafluoropropyl)trimethylsilane with the 2-amino-6-iodopurine **2** in the presence of KF and CuI at room temperature (heating caused decomposition of the starting compound) was sluggish and gave the corresponding 2-amino-6-perfluoroalkylpurines **3m** and **3n** after prolonged reaction times in moderate yields of 28 and 21%, respectively.

Standard transesterification protocol was used for the cleavage of the phosphonate esters **3a**–**3n**. Thus the reaction of esters **3a**–**3n** with bromo(trimethyl)silane (TMSBr) in acetonitrile at ambient temperature or at 80 °C followed by the hydrolysis of the intermediate silyl esters using aqueous ammonia or triethylamine gave the free phosphonates **4a**–**4n**. In

the MOM-protected compounds **3h** and **3j**, the MOM-groups were cleaved simultaenously to give the 2-amino-6-(1-unsubstituted imidazolyl)purine phosphonates **4h** and **4j**. The crude products **4a**–**4n** were deionized and purified using a combination of cation [Dowex 50X8 (H^+ form)] and anion [Dowex 1X2 (acetate form)] exchange chromatography. In some cases, when dilute acetic acid was insufficient for the elution of the products from Dowex 1X2 and the use of concentrated acetic acid led to partial acetylation of the compounds (MS analysis of the impure products), elution was accomplished by the use of dilute aqueous formic acid. In several cases even the deionization on Dowex 50X8 was sufficient for the purification of the products and the anion exchange chromatography could have been omitted. Generally, the conditions must have been modified case by case and the free phosphonates were isolated in the yields varying from 55 to 95%.

All compounds were fully characterized by NMR and MS. Most of the free phosphonates **4** were also characterized by elemental analysis. The assignment of the ^1H and ^{13}C NMR signals of the compounds **3k**, **4a** and **4l** was based on COSY, HMBC and HMQC experiments. Assignment of signals of all other compounds was made in analogy to these compounds and to the analogous 2-unsubstituted purine derivatives described previsously[6]. UV spectra showed strong substituent effect depending on the nature of the substituent in the position 6: the maxima varied from 373 nm (6-(1-methylpyrrol-2-yl) derivative **4f**) to 310 nm (6-methyl derivative **4k**).

In conclusion, cross-coupling reactions of diverse types of organometallic reagents with 2-amino-6-halopurines **1** and **2** were used for the preparation of the corresponding protected 2-amino-6-*C*-substituted purine derivatives **3a**–**3n**. Each type of organometallic reagent turned out to be superior for the introduction of different types of *C*-substituents: arylboronic acids were used for the introduction of aryl groups, hetarylzinc chlorides or hetarylstannanes for the introduction of hetaryl functions, trialkylaluminium reagents for simple alkyl groups and perfluoroalkylsilanes for the introduction of perfluoroalkyl substituents. Except for cuprates, all the organometallic reagents used well tolerated the presence of the unprotected amino group. Cleavage of the phosphonate esters **3a**–**3n** with TMSBr afforded the target acyclic nucleotide analogues **4a**–**4n**. The title compounds **4a**–**4n** were tested *in vitro* for cytostatic activity (inhibition of cell growth in the following cell cultures: mouse leukemia L1210 cells, murine L929 cells and human cervix carcinoma HeLaS3 cells) and for antiviral activity (inhibitory effect on DNA viruses: HSV-1, HSV-2, CMV, VZV and vaccinia virus, and on retroviruses: MSV, HIV-1 and HIV-2). Only the 2-amino-6-(hepta-

fluoropropyl)purine **4n** showed[26] antiviral activity against HSV-1 (KOS) (MIC_{50} 21.8 μmol/l), HSV-2 (F) (MIC_{50} 7.3 μmol/l) and HSV-1 TK^- (VMW 1837) (MIC_{50} 4.4 μmol/l) in E_6SM cells and against CMV (Davis strain) (MIC_{50} 3.6 μmol/l) and VZV (TK^- and TK^+ mutants) (MIC_{50} 0.6–1.3 μmol/l) in HEL cells. Compound **4n** was cytotoxic for the host cells at concentrations above 45 μmol/l. None of the other compounds showed any considerable activity in these assays. The absence of antiviral and cytostatic activity in this series of compounds is interesting in comparison with the high activity of the aforementioned acyclic nucleotide analogues derived from 2-amino-6-[(di)alkylamino]purines[3].

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. Paper electrophoresis was performed on a paper Whatman No.3 MM at 40 V/cm for 1 h in 0.05 M triethylammonium hydrogencarbonate (TEAB) at pH 7.5 and the electrophoretical mobilities (E_{Up}) are referenced to uridine 3′-phosphate. TLC was performed on Silufol UV_{254} plates (Kavalier Votice, Czech Republic) in the following solvent systems: MeOH-EtOAc (1 : 9) (A); MeOH-EtOAc (2 : 8) (B); MeOH-$CHCl_3$ (1 : 9) (C); MeOH-$CHCl_3$ (3 : 20) (D); isopropyl alcohol-water-35% aqueous NH_3 (7 : 2 : 1) (E). NMR spectra (*J*, Hz; δ, ppm) were measured on a Bruker AMX-3 400 (400 MHz for ^1H, 100.6 MHz for ^{13}C and 376.5 MHz for ^{19}F nuclei), Bruker DRX 500 (500 MHz for ^1H, 125.7 MHz for ^{13}C and 470.59 MHz for ^{19}F) and Varian Gemini 300HC (300.075 MHz for ^1H and 75.462 MHz for ^{13}C). TMS was used as internal standard for ^1H and ^{13}C NMR spectra; $CFCl_3$ was an internal standard for ^{19}F spectra. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol matrix) or EI (electron energy 70 eV) techniques. UV absorption spectra (λ_{max}, nm; ε, l mol^{-1} cm^{-1}) were measured on a Shimadzu UVmini 1240 spectrometer in aqueous solutions. DMF was distilled from P_2O_5, degassed *in vacuo* and stored over molecular sieves under Ar. THF was refluxed with Na and benzophenone under Ar atmosphere and freshly distilled *prior* to use. Toluene was degassed *in vacuo* and stored over molecular sieves under Ar. Acetonitrile was refluxed with CaH_2 and distilled. All non-hydrolytic reactions were performed under argon atmosphere using vacuum-line techniques.

2-Amino-6-iodo-9-{2-[(diisopropoxyphosphoryl)methoxy]ethyl}purine (**2**)

Compound **1** (1.2 g, 3 mmol) was added to stirred 55% aqueous HI (10 ml) at 0 °C and the resulting suspension was stirred at 0 °C for 2 h. After addition of water (10 ml) the mixture was neutralized with 1 M aqueous NaOH until the suspension dissolved. The solution was then extracted with ethyl acetate (3 × 30 ml). The collected organic layers were washed with saturated aqueous NaS_2O_3 (30 ml), dried with $MgSO_4$ and evaporated *in vacuo*. Crystallization of the residue from ethyl acetate yielded the iodo derivative **2** (1.2 g, 81%) as yellowish crystals; m.p. 116–117 °C, R_F (C) 0.48. FAB MS, *m/z* (rel. %): 484 (100) [M + H]. ^1H NMR (400 MHz, $CDCl_3$): 1.26 and 1.30 (2 × d, 2 × 6 H, $J(CH,CH_3)$ = 6.2, CH_3); 3.73 (d, 2 H,

J(P,CH) = 8.1, PCH_2); 3.92 (t, 2 H, *J*(1′,2′) = 5.0, H-2′); 4.25 (t, 2 H, *J*(2′,1′) = 5.0, H-1′); 4.69 (sept, 2 H, *J*(CH_3,CH) = 6.2, POCH); 5.35 (s, 2 H, NH_2); 7.89 (s, 1 H, H-8). ^{13}C NMR (75 MHz, $CDCl_3$): 24.60 and 24.64 (2 × d, *J*(P,C) = 3.5, CH_3); 44.00 (C-1′); 66.69 (d, *J*(P,C) = 167.3, PCH_2); 71.39 (d, *J*(P,C) = 9.7, C-2′); 71.86 (d, *J*(P,C) = 6.3, POCH); 123.19 (C-5); 132.76 (C-6); 143.20 (C-8); 150.46 (C-4); 159.42 (C-2). For $C_{14}H_{23}IN_5O_4P$ (483.2) calculated: 34.80% C, 4.80% H, 26.26% I, 14.49% N, 6.41% P; found: 35.20% C, 4.83% H, 26.15% I, 14.52% N, 6.62% P.

Cross-Coupling Reactions of the 2-Amino-6-chloropurine **1** with Boronic Acids - General Procedure

Method A: Toluene (10 ml) was added through a septum to an Ar purged 50 ml flask with a mixture of compound **1** (195 mg, 0.5 mmol), a boronic acid (1 mmol), K_2CO_3 (100 mg, 0.75 mmol) and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol). The mixture was stirred at 100 °C until the starting compound **1** was consumed (TLC). The solvent was then evaporated and the residue chromatographed on a column of silica gel (50 g) to get the products **3a**–**3d**.

Method B: The same procedure as method *A*; only a mixture DME–water (3 : 1) (10 ml) was used as solvent instead of toluene.

2-Amino-9-{2-[(diisopropoxyphosphoryl)methoxy]ethyl}-6-phenylpurine (**3a**). Method *A*; reaction time 24 h; chromatographed in ethyl acetate/methanol (98 : 2); yield 76%; colourless oil; R_F (A) 0.42. EI MS, *m/z* (rel. %): 433 (36) [M]; 254 (100). ^{1}H NMR (400 MHz, $CDCl_3$): 1.25 (d, 3 H, *J*(CH_3,CH) = 6.2, CH_3); 1.28 (d, 3 H, *J*(CH_3,CH) = 6.2, CH_3); 3.73 (d, 2 H, *J*(CH_2,P) = 8.3, PCH_2); 3.93 (t, 2 H, *J*(2′,1′) = 4.9, CH_2-2′); 4.32 (t, 2 H, *J*(2′,1′) = 4.9, CH_2); 4.68 (m, 1 H, POCH); 5.09 (s, 2 H, NH_2); 7.46-7.53 (m, 3 H, H-arom.); 7.92 (s, 1 H, H-8); 8.63 (m, 2 H, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): 23.91 (d, *J*(P,C) = 4.0, CH_3); 42.94 (C-1′); 66.03 (d, *J*(P,C) = 167.2, PCH_2); 70.96 (d, *J*(P,C) = 9.7, C-2′); 71.13 (d, *J*(P,C) = 6.9, POCH); 125.40 (C-5); 128.38, 129.51, 130.57 (5 × CH-arom); 135.70 (C-1″); 142.60 (C-8); 154.26 a 155.55 (C-6 a C-4); 159.43 (C-2). For $C_{20}H_{28}N_5O_4P$ (433.4) calculated: 55.42% C, 6.51% H, 16.16% N; found: 55.06% C, 6.54% H, 15.82% N.

2-Amino-9-{2-[(diisopropoxyphosphoryl)methoxy]ethyl}-6-(2-tolyl)purine (**3b**). Method *A*; reaction time 5 h; chromatographed in $CHCl_3$–methanol (98 : 2); yield 80%; crystallized from ethanol–diethyl ether; colourless crystals; m.p. 107–110 °C; R_F (C) 0.60. FAB MS, *m/z* (rel. %): 448 (100) [M + H]. ^{1}H NMR (300 MHz, $CDCl_3$): 1.26 (d, 3 H, *J*(CH_3, CH) = 6.1, CH_3); 1.29 (d, 3 H, *J*(CH_3,CH) = 6.1, CH_3); 2.40 (s, 3 H, CH_3); 3.75 (d, 2 H, *J*(CH_2,P) = 8.8, PCH_2); 3.96 (t, 2 H, *J*(2′,1′) = 5.0, CH_2-2′); 4.33 (t, 2 H, *J*(1′,2′) = 5.0, CH_2-1′); 4.70 (m, 1 H, POCH); 5.08 (s, 2 H, NH_2); 7.34 (m, 3 H, H-arom.); 7.58 (m, 1 H, H-arom.); 7.86 (s, 1 H, H-8). ^{13}C NMR (75.5 MHz, $CDCl_3$): 20.33 (CH_3, tolyl); 23.93 (CH_3); 42.93 (C-1′); 66.02 (d, *J*(P,C) = 167.8, PCH_2); 70.90 (C-2′); 71.11 (d, *J*(P,C) = 6.3, POCH); 126.29 (C-5); 125.66, 129.34, 129.92, 130.88 (4 × CH-arom); 135.10, 136.61 (C-1″,C-2″); 142.78 (C-8); 153.54 (C-4); 159.33, 159.59 (C-6,C-2). For $C_{21}H_{30}N_5O_4P$ (447.5) calculated: 56.37% C, 6.76% H, 15.65% N; found: 56.29% C, 6.51% H, 15.43% N.

2-Amino-9-{2-[(diisopropoxyphosphoryl)methoxy]ethyl}-6-(4-fluorophenyl)purine (**3c**). Method *A*; reaction time 6 h; chromatographed in ethyl acetate-methanol (98 : 2); yield 84%; colourless oil; R_F (A) 0.36. FAB MS, *m/z* (rel. %): 452 (96) [M + H]. ^{1}H NMR (300 MHz, $CDCl_3$): 1.26 (d, 3 H, *J*(CH_3, CH) = 6.1, CH_3); 1.29 (d, 3 H, *J*(CH_3, CH) = 6.1, CH_3); 3.73 (d, 2 H, *J*(CH_2,P) = 8.3, PCH_2); 3.94 (t, 2 H, *J*(2′,1′) = 5.0, CH_2-2′); 4.32 (t, 2 H, *J*(1′,2′) = 5.0, CH_2-1′); 4.68 (m, 1 H, POCH); 5.01 (s, 2 H, NH_2); 7.19 (t, 2 H, *J*(H_o,H_m) = 8.8, H-*o*-FPh); 7.92 (s, 1 H, H-8); 8.73 (dd, 2 H, *J*(H_m,H_o) = 8.8, *J*(F,H_m) = 6.0, H-*m*-FPh). ^{13}C NMR (75.5 MHz, $CDCl_3$): 23.94 (CH_3);

42.99 (C-1′); 66.03 (d, *J*(P,C) = 167.2, PCH_2); 70.92 (d, *J*(P,C) = 10.3, C-2′); 71.15 (d, *J*(P,C) = 6.3, POCH); 115.51 (d, *J*(F,C) = 21.2, C-3″); 125.04 (C-5); 131.43 (C-1″); 131.82 d, *J*(F,C) = 8.6 (C-2″); 142.99 (C-8); 153.82, 154.43 (C-6, C-4); 159.06 (C-2). 164.49 d, *J*(F,C) = 252 (C-4″). For $C_{20}H_{27}FN_5O_4P$ (451.4) calculated: 53.21% C, 6.03% H, 4.21% F, 15.51% N; found: 53.36% C, 6.20% H, 4.02% F, 14.89% N.

2-Amino-9-{2-[(diisopropoxyphosphoryl)methoxy]ethyl}-6-(2-thienyl)purine (**3d**). Method *B*; reaction time 6 h; chromatographed in $CHCl_3$–methanol (95 : 5); yield 91%; yellow oil; R_F (A) 0.27. FAB MS, *m/z* (rel. %): 440 (100) [M + H]; ^{1}H NMR (300 MHz, $CDCl_3$): 1.26 (d, 3 H, *J*(CH_3, CH) = 6.1, CH_3); 1.29 (d, 3 H, *J*(CH_3,CH) = 6.1, CH_3); 3.72 (d, 2 H, *J*(CH_2,P) = 8.2, PCH_2); 3.93 (t, 2 H, *J*(2′,1′) = 4.9, CH_2-2′); 4.31 (t, 2 H, *J*(1′,2′) = 5.0, CH_2-1′); 4.69 (m, 1 H, POCH); 4.99 (s, 2 H, NH_2); 7.21 (dd, 1 H, *J* = 5.0, 3.8, H-arom.); 7.54 (dd, 1 H, *J* = 5.0, 1.1, H-arom.); 7.90 (s, 1 H, H-8); 8.58 (dd, 1 H, *J* = 3.8, 1.1, H-arom). ^{13}C NMR (75.5 MHz, $CDCl_3$): 23.93 (d, *J*(P,C) = 4.3, CH_3); 42.93 (C-1′); 66.03 (d, *J*(P,C) = 167.2, PCH_2); 70.98 (d, *J*(P,C) = 9.7, C-2′); 71.14 (d, *J*(P,C) = 6.9, POCH); 123.49 (C-5); 128.42, 130.05, 132.21 (3 × CH-arom); 139.96 (C-2″); 142.64 (C-8); 150.43 (C-6); 153.90 (C-4); 159.27 (C-2). Exact mass (FAB HRMS, *m/z*) found 440.1513; calculated for $C_{18}H_{27}N_5O_4PS$ [M + H] 440.1521.

2-Amino-9-{2-[(diisopropoxyphosphoryl)methoxy]ethyl}-6-(pyridin-2-yl)purine (**3e**).

A solution of 2-bromopyridine (0.38 ml, 8 mmol) in THF (40 ml) was stirred at –78 °C under Ar atmosphere and *t*-BuLi (1.5 M solution in pentane, 6.2 ml, 10 mmol) was added dropwise. After stirring for 1 h at –78 °C, $ZnCl_2$ (0.5 M solution in THF, 20 ml, 10 mmol) was added dropwise and the resulting mixture was allowed to warm up to ambient temperature and stirred for additional 1 h. To this mixture, a solution of compound **2** (960 mg, 2 mmol) and $Pd(PPh_3)_4$ (110 mg, 0.1 mmol) in THF (14 ml) was added and the mixture was refluxed for 6 h, cooled to ambient temperature and poured into a saturated aqueous NH_4Cl (100 ml). To this mixture, 3% aqueous NH_3 (20 ml) and saturated aqueous Na_2EDTA (20 ml) were added and the mixture was extracted with ethyl acetate (4 × 40 ml). The collected organic layers were washed with a mixture of saturated aqueous NH_4Cl, 3% aqueous NH_3 and sat aqueous Na_2EDTA (60 ml, 1 : 1 : 1, v/v/v) and dried with $MgSO_4$. After evaporation of the solvents, the residue was chromatographed on a column of silica gel [100 g, ethyl acetate–methanol–saturated methanolic ammonia (94 : 3 : 3)] to give compound **3e** (730 mg, 85 %) as yellowish oil, R_F (E) 0.79. FAB MS, *m/z* (rel. %): 435 (100) [M + H]. ^{1}H NMR (300 MHz, $CDCl_3$): 1.25 (d, 3 H, *J*(CH_3,CH) = 6.1, CH_3); 1.29 (d, 3 H, *J*(CH_3,CH) = 6.1, CH_3); 3.73 (d, 2 H, *J*(CH_2,P) = 8.2, PCH_2); 3.95 (t, 2 H, *J*(2′,1′) = 4.7, CH_2-2′); 4.34 (t, 2 H, *J*(1′,2′) = 4.7, CH_2-1′); 4.69 (m, 1 H, POCH); 5.20 (brs, 2 H, NH_2); 7.39 (m, 1 H, H-5″); 7.88 (dt, 1 H, *J*(4″,6″) = 1.1, *J*(4″,3″) = (4″,5″) = 7.7, H-4″); 7.98 (s, 1 H, H-8); 8.81 (d, 1 H, *J*(3″,4″) = 7.7, H-3″); 8.91 (m, 1 H, H-6″). ^{13}C NMR (75.5 MHz, $CDCl_3$): 23.94 (CH_3); 43.01 (C-1′); 66.06 (d, *J*(P,C) = 167.2, PCH_2); 70.98 (d, *J*(P,C) = 9.7, C-2′); 71.15 (d, *J*(P,C) = 6.7, POCH); 124.58 (C-3″); 125.83 (C-5); 126.07 (C-5″); 136.60 (C-4″); 143.46 (C-8); 150.23 (C-6″); 153.54 (C-6); 154.26 (C-4); 159.73 (C-2). Exact mass (FAB HRMS, *m/z*) found 435.1938; calculated for $C_{19}H_{28}N_6O_4P$ [M + H] 435.1909.

2-Amino-9-{2-[(diisopropoxyphosphoryl)methoxy]ethyl}-6-(1-methylpyrrol-2-yl)purine (**3f**).

t-BuLi (1.5 M solution in pentane, 2.2 ml, 3.5 mmol) was dropwise added to a stirred solution of TMEDA (0.6 ml, 4 mmol) and 1-methylpyrrole (0.7 ml, 8 mmol) in THF (20 ml) at –70 °C under Ar atmosphere and the mixture was allowed to warm up to ambient tempera-

ture. After stirring for 1 h at room temperature, the mixture was re-cooled to –70 °C and $ZnCl_2$ (0.5 M solution in THF, 8 ml, 4 mmol) was added dropwise. The mixture was allowed to warm up to room temperature and after stirring for 1 h, a solution of compound **2** (340 mg, 0.7 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in THF (7 ml) was added dropwise. The mixture was then refluxed for 10 h, cooled to ambient temperature and poured into saturated aqueous NH_4Cl (50 ml). After addition of 3% aqueous NH_3 (10 ml) and saturated aqueous EDTA (20 ml), the mixture was extracted with $CHCl_3$ (3 × 40 ml). The collected organic layers were dried with $MgSO_4$ and the solvents were evaporated *in vacuo*. Column chromatography on silica gel [50 g, ethyl acetate–methanol (95 : 5)] afforded compound **3f** (200 mg, 65%) as brownish oil, R_F (A) 0.30. FAB MS, *m/z* (rel. %): 437 (100) [M + H]. ^{1}H NMR (300 MHz, $CDCl_3$): 1.25 (d, 3 H, *J*(CH_3,CH) = 6.1, CH_3); 1.29 (d, 3 H, *J*(CH_3,CH) = 6.1, CH_3); 3.72 (d, 2 H, *J*(CH_2,P) = 8.2, PCH_2); 3.92 (t, 2 H, *J*(2′,1′) = 5.0, CH_2-2′); 4.12 (s, 3 H, NCH_3); 4.28 (t, 2 H, *J*(1′,2′) = 5.0, CH_2-1′); 4.67 (m, 1 H, POCH); 4.90 (brs, 2 H, NH_2); 6.26 (dd, 1 H, *J*(4″,5″) = 2.2, *J*(4",3″) = 3.8, H-4″); 6.81 (t, 1 H, *J* = 2.2, H-5″); 7.70 (dd, 1 H, *J*(3″,5″) = 1.7, *J*(3″,4″) = 3.9, H-3″); 7.83 (s, 1 H, H-8). ^{13}C NMR (75.5 MHz, $CDCl_3$): 23.95 (CH_3); 37.96 (NCH_3); 42.83 (C-1′); 66.01 (d, *J*(P,C) = 167.7, PCH_2); 71.03 (C-2′); 71.17 (d, *J*(P,C) = 6.9, POCH); 108.73, 119.04 (2 × CH-arom); 123.71 (C-5); 127.08 (C-2″); 128.94 (CH-arom); 141.52 (C-8); 150.29 (C-6); 152.94 (C-4); 158.64 (C-2). Exact mass (FAB HRMS, *m/z*) found 437.2096; calculated for $C_{19}H_{30}N_6O_4P$ [M + H] 437.2066.

2-Amino-9-{2-(diisopropoxyphosphoryl)methoxy]ethyl}-6-(1-methylimidazol-2-yl)purine (**3g**).

BuLi (2.5 M solution in hexane, 3.2 ml, 8 mmol) was added to a stirred solution of 1-methylimidazole (660 mg, 8 mmol) in THF (20 ml) at –78 °C under Ar. The mixture was slowly (2 h) allowed to warm up to –40 °C and re-cooled to –78 °C. Then $ZnCl_2$ (1 M solution in THF, 22 ml, 22 mmol) was added and the mixture was allowed to warm up to ambient temperature and stirred for 30 min. A solution of compound **2** (960 mg, 2 mmol) and $Pd(PPh_3)_4$ (110 mg, 0.1 mmol) in THF (20 ml) was then added and the mixture was refluxed for 10 h, cooled to room temperature and poured into saturated aqueous NH_4Cl (50 ml). To this mixture, saturated aqueous EDTA (20 ml) was added and the mixture was extracted with $CHCl_3$ (4 × 40 ml). The collected organic layers were dried with $MgSO_4$ and the solvents were evaporated. The residue was chromatographed on a silica gel column [100 g, ethyl acetate–saturated methanolic ammonia (90 : 10)] to give compound **3g** (820 mg, 94 %) as yellow oil; R_F (D) = 0.51. FAB MS, *m/z* (rel. %): 438 (100) [M + H]. ^{1}H NMR (300 MHz, $CDCl_3$): 1.29 (t, 6 H, *J*(CH_3,CH) = 6.6, CH_3); 3.73 (d, 2 H, *J*(CH_2,P) = 8.2, PCH_2); 3.92 (t, 2 H, *J*(2′,1′) = 5.0, CH_2-2′); 4.12 (s, 3 H, NCH_3); 4.31 (t, 2 H, *J*(1′,2′) = 5.0, CH_2-1′); 4.71 (m, 1 H, POCH); 4.96 (s, 2 H, NH_2); 7.03 and 7.34 (s, 1 H, H-4″, H-5″); 7.95 (s, 1H, H-8). ^{13}C NMR (75.5 MHz $CDCl_3$): 23.90 (d, *J*(P,C) = 4.0, CH_3); 36.11 (NCH_3); 42.86 (C-1′); 66.07 (d, *J*(P,C) = 167.7, PCH_2); 71.05 (C-2′); 71.13 (d, *J*(P,C) = 6.3, POCH); 124.61 (C-5″); 125.10 (C-5); 130.246 (C-4″); 141.83 (C-2″); 143.29 (C-8); 148.12 (C-6); 154.32 (C-4); 158.82 (C-2). Exact mass (FAB HRMS, *m/z*) found 438.2077; calculated for $C_{18}H_{29}N_7O_4P$ [M + H] 438.2019.

2-Amino-9-{2-[(diisopropoxyphosphoryl)methoxy]ethyl}-6-[1-(methoxymethyl)imidazol-2-yl]purine (**3h**)

This compound was prepared in a similar manner as described for compound **3g**. [1-(Methoxymethyl)imidazol-2-yl]zinc chloride was generated from 1-(methoxymethyl)-

imidazole (1.78 g, 16 mmol), BuLi (2.5 M solution in hexane, 5.6 ml, 14 mmol) and $ZnCl_2$ (1 M solution in THF, 32 ml, 32 mmol) and reacted with compound **2** (960 mg, 2 mmol) and $Pd(PPh_3)_4$ (110 mg, 0.1 mmol) in THF at reflux for 14 h. After analogous work up the resudie was chromatographed on a preparative loose layer of silica gel [40 × 17 × 0.4 cm, ethyl acetate–methanolic ammonia (85 : 15)] to give compound **3h** (660 mg, 76%) as yellow oil; R_F (E) 0.76. FAB MS, *m/z* (rel. %): 468 (100) [M + H]; ^{1}H NMR (300 MHz, $CDCl_3$): 1.26 (t, 6 H, *J*(CH_3,CH) = 6.1, CH_3); 1.29 (t, 6 H, *J*(CH_3,CH) = 6.1, CH_3); 3.26 (s, 3H, CH_3O); 3.72 (d, 2 H, *J*(CH_2,P) = 8.2, PCH_2); 3.92 (t, 2 H, *J*(2′,1′) = 5.0, CH_2-2′); 4.30 (t, 2 H, *J*(1′,2′) = 5.2, CH_2-1′); 4.69 (m, 1 H, POCH); 5.02 (brs, 2 H, NH_2); 5.99 (s, 2 H, NCH_2O); 7.26 (m, 1 H, H-4″); 7.38 (s, 1 H, H-5″); 7.97 (s, 1 H, H-8). ^{13}C NMR (75.5 MHz $CDCl_3$): 23.91 (CH_3); 42.87 (C-1′); 56.32 (CH_3O); 66.01 (d, *J*(P,C) = 167.7, PCH_2); 70.99 (C-2′); 71.15 (d, *J*(P,C) = 6.7, POCH); 78.58 (NCH_2O); 122.73 (C-5″); 125.05 (C-5); 130.64 (C-4″); 141.82 (C-2″); 143.58 (C-8); 147.69 (C-6); 154.48 (C-4); 158.85 (C-2). Exact mass (FAB HRMS, *m/z*) found 468.2126; calculated for $C_{19}H_{31}N_7O_5P$ [M + H] 468.2124.

Cross-Coupling Reactions of 2-Amino-6-iodopurine **2** with Stannanes. General Procedure

A mixture of compound **2** (480 mg, 1 mmol), 1-methyl- or 1-(methoxymethyl)-5-(tributylstannyl)imidazole (1.9 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and DMF (10 ml) was refluxed under Ar for 8 h. The solvent was evaporated *in vacuo*, the residue co-distilled with toluene and treated with saturated aqueous Na_2EDTA (20 ml) and 35 % aqueous NH_3 (1 ml). The mixture was extracted with $CHCl_3$ (4 × 30 ml). The collected organic layers were dried with $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (50 g) to give product **3i** or **3j**.

2-Amino-9-{2-[(diisopropoxyphosphoryl)methoxy]ethyl}-6-(1-methylimidazol-5-yl)purine (**3i**). Chromatographed in $CHCl_3$–methanol (96 : 4); yield 61 %; yellow oil; R_F (C) 0.21. FAB MS, *m/z* (rel. %): 438 (100) [M + H]. ^{1}H NMR (300 MHz, $CDCl_3$): 1.25 (d, 3 H, *J*(CH_3,CH) = 6.6, CH_3); 1.29 (d, 3 H, *J*(CH_3,CH) = 6.6, CH_3); 3.72 (d, 2 H, *J*(CH_2,P) = 8.2, PCH_2); 3.92 (t, 2 H, *J*(2′,1′) = 5.0, CH_2-2′); 4.12 (s, 3 H, NCH_3); 4.29 (t, 2 H, *J*(1′,2′) = 5.0, CH_2-1′); 4.68 (m. 1 H, POCH); 4.92 (s, 2 H, NH_2); 7.57 (s, 1 H, CH); 7.87 (s, 1 H, H-8); 8.46 (s, 1 H, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): 23.90 (m, *J*(P,C) = 4.0, CH_3); 35.40 (NCH_3); 42.80 (C-1′); 65.97 (d, *J*(P,C) = 167.8, PCH_2); 70.98 (d, *J*(P,C) = 10.3, C-2′); 71.15 (d, *J*(P,C) = 6.9, POCH); 123.93 (C-5″); 127.09 (C-5); 137.71 (C-4″); 141.88 (C-2″); 142.05 (C-8); 148.59 (C-6); 153.14 (C-4); 158.97 (C-2). Exact mass (FAB HRMS, *m/z*) found 438.2050; calculated for $C_{18}H_{29}N_7O_4P$ [M + H] 438.2019.

2-Amino-9-{2-[(diisopropoxyphosphoryl)methoxy]ethyl}-6-[1-(methoxymethyl)imidazol-5-yl]purine (**3j**). Chromatographed in ethyl acetate–methanol (90 : 10); crystallized from methanol-toluene–petroleum ether; yield 45%; m.p. 106–109 °C. R_F (B) 0.11. FAB MS, *m/z* (rel. %): 490 (31) [M+Na]; 468 (100) [M + H]. ^{1}H NMR (300 MHz, $CDCl_3$): 1.26 (d, 3 H, *J*(CH_3,CH) = 6.6, CH_3); 1.29 (d, 3 H, *J*(CH_3,CH) = 6.6, CH_3); 3.31 (s, 3 H, CH_3O); 3.73 (d, 2 H, *J*(CH_2,P) = 8.2, PCH_2); 3.92 (t, 2 H, *J*(2′,1′) = 5.0, CH_2-2′); 4.30 (t, 2 H, *J*(1′,2′) = 5.0, CH_2-1′); 4.69 (m, 1 H, POCH); 4.92 (s, 2 H, NH_2); 6.03 (s, 2 H, NCH_2O); 7.81 (s, 1 H, H-4″); 7.89 (s, 1 H, H-8); 8.51 (s, 1 H, H-2″). ^{13}C NMR (75.5 MHz, $CDCl_3$): 23.93 (CH_3); 42.85 (C-1′); 56.27 (OCH_3); 65.99 (d, *J*(P,C) = 167.7, PCH_2); 70.97 (d, *J*(P,C) = 9.7, C-2′); 71.17 (d, *J*(P,C) = 6.3, POCH); 77.92 (NCH_2O); 124.05 (C-5″); 126.51 (C-5); 138.31 (C-4″); 141.70 (C-2″); 142.35 (C-8); 148.19 (C-6); 153.30 (C-4); 158.97 (C-2). For $C_{19}H_{30}N_7O_5P$ (467.5) calculated: 48.82% C, 6.47% H, 20.97% N; found: 48.95% C, 6.70% H, 20.90% N.

Cross-Coupling Reactions of 2-Amino-6-chloropurine **1** with Trialkylaluminiums. General Procedure

A trialkylaluminium solution in toluene or cyclohexane (2 mmol) was dropwise added to a stirred solution of compound **1** (390 mg, 1 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in THF (20 ml) at room temperature under Ar and the mixture was refluxed for 6 h. The solvent was then evaporated and the residue was treated with methanol (10 ml) and evaporated. The residue was chromatographed on a column of silica gel [50 g, ethyl acetate–methanol (93 : 7)] to give product **3k** or **3l**.

2-Amino-9-{2-[(diisopropoxyphosphoryl)methoxy]ethyl}-6-methylpurine (**3k**). Yield 67%; colourless oil; R_F (C) 0.32. FAB MS, *m/z* (rel. %): 372 (100) [M + H]. ^{1}H NMR (300 MHz, $CDCl_3$): 1.25 (d, 3 H, $J(CH_3,CH)$ = 6.6, CH_3); 1.28 (d, 3 H $J(CH_3,CH)$ = 6.6, CH_3); 2.65 (s, 3 H, CH_3); 3.71 (d, 2 H, $J(CH_2,P)$ = 8.2, PCH_2); 3.89 (t, 2 H, $J(2',1')$ = 5.0, CH_2-2′); 4.26 (t, 2 H, $J(1',2')$ = 5.0, CH_2-1′); 4.67 (m, 1 H, POCH); 5.13 (s, 2 H, NH_2); 7.82 (s, 1 H, H-8). Exact mass (FAB HRMS, *m/z*) found 372.1889; calculated for $C_{15}H_{27}N_5O_4P$ [M + H] 372.1801.

2-Amino-9-{2-[(diisopropoxyphosphoryl)methoxy]ethyl}-6-ethylpurine (**3l**). Yield 78%; colourless oil; R_F (A) 0.12. FAB MS, *m/z* (rel. %): 408 (11) [M+Na]; 386 (100) [M + H]. ^{1}H NMR (300 MHz, $CDCl_3$): 1.25 (d, 3 H, $J(CH_3,CH)$ = 6.6, CH_3); 1.29 (d, 3 H, $J(CH_3,CH)$ = 6.6, CH_3); 1.37 (t, 3 H, $J(CH_3,CH_2)$ = 7.7, CH_3); 3.02 (q, 2 H, $J(CH_3,CH_2)$ = 7.7, CH_2); 3.72 (d, 2 H, $J(CH_2,P)$ = 8.3, PCH_2); 3.90 (t, 2 H, $J(2',1')$ = 5.3, CH_2-2′); 4.28 (t, 2 H, $J(1',2')$ = 5.0, CH_2-1′); 4.68 (m, 1 H, POCH); 4.93 (s, 2 H, NH_2); 7.80 (s, 1 H, H-8). Exact mass (FAB HRMS, *m/z*) found 386.1952; calculated for $C_{16}H_{29}N_5O_4P$ [M + H] 386.1957.

Perfluoroalkylation of 2-Amino-6-iodopurine **2**. General Procedure

A mixture of compound **2** (480 mg, 1 mmol), R_FSiMe_3 (2 mmol), KF (82 mg, 1.4 mmol), CuI (304 mg, 1.6 mmol), DMF (1 ml) and *N*-methylpyrrolidone (1 ml) was stirred at 25 °C for 4 days. To this solution, saturated aqueous $Na_2S_2O_3$ (10 ml) was added and the mixture was extracted with ethyl acetate (3 × 10 ml). The collected organic layers were dried and evaporated under low pressure (*ca* 100 Pa, bath temperature *ca* 40 °C) and the residue was chromatographed on a column of silica gel [50 g, ethyl acetate–methanol (90 : 10)] to give the product **3m** or **3n**.

2-Amino-9-{2-[(diisopropoxyphosphoryl)methoxy]ethyl}-6-(trifluoromethyl)purine (**3m**). Yield 28%; yellowish oil. FAB MS, *m/z* (rel. %): 426 (100) [M + H], 384 (15) [M – C_3H_6], 342 (36) [M – $2C_3H_6$]. ^{1}H NMR (400 MHz, $CDCl_3$): 1.25 and 1.29 (2 × d, 2 × 6 H, $J(CH,CH_3)$ = 6.2, CH_3); 3.73 (d, 2 H, $J(P,CH)$ = 8.1, PCH_2); 3.94 (t, 2 H, $J(1',2')$ = 4.9, H-2′); 4.33 (t, 2 H, $J(2',1')$ = 4.9, H-1′); 4.68 (sept, 2 H, $J(CH_3,CH)$ = 6.2, POCH); 5.35 (s, 2 H, NH_2); 8.02 (s, 1 H, H-8). ^{19}F NMR (376.5 MHz, $CDCl_3$): –67.89 (s, CF_3). Exact mass (FAB HRMS, *m/z*) found 426.1530; calculated for $C_{15}H_{24}F_3N_5O_4P$ [M + H] 426.1518.

2-Amino-9-{2-[(diisopropoxyphosphoryl)methoxy]ethyl}-6-(heptafluoropropyl)purine (**3n**). Yield 21 %; yellowish oil. FAB MS, *m/z* (rel. %): 526 (100) [M + H], 484 (12) [M – C_3H_6], 442 (62) [M – $2C_3H_6$]. ^{1}H NMR (400 MHz, $CDCl_3$): 1.24 and 1.28 (2 × d, 2 × 6 H, $J(CH,CH_3)$ = 6.2, CH_3); 3.74 (d, 2 H, $J(P,CH)$ = 8.2, PCH_2); 3.94 (t, 2 H, $J(1',2')$ = 4.8, H-2′); 4.34 (t, 2 H, $J(2',1')$ = 4.9, H-1′); 4.68 (sept, 2 H, $J(CH_3,CH)$ = 6.2, POCH); 5.22 (s, 2 H, NH_2); 8.03 (s, 1 H, H-8). ^{19}F NMR (376.5 MHz, $CDCl_3$): –80.62 (t, J= 9.0, CF_2); –115.30 (brd, J= 8.3, CF_2), –126.65 (s, CF_3). Exact mass (FAB HRMS, *m/z*) found 526.1542; calculated for $C_{17}H_{24}F_7N_5O_4P$ [M + H] 526.1454.

Cleavage of the Phosphonate Esters **3a**–**3n**. General Procedure

Method A: Ester **3** (0.5 mmol) was dissolved in acetonitrile (10 ml) and to this solution, TMSBr (2 ml, 15.2 mmol) was added dropwise. The mixture was stirred overnight at room temperature. After evaporation of the solvent and reagent and co-distillation with acetonitrile (10 ml) and toluene (10 ml), the residue was treated with water (10 ml) and 35% aqueous NH_3 (1 ml) for 5 min and evaporated. The residue was dissolved in water, acidified with one drop of conc. aqueous HCl and applied onto a column of Dowex 50X8 (H^+ form). The column was washed with water and eluted with 3% aqueous NH_3. The product containing UV-absorbing fractions were evaporated, the residue was dissolved in 35% aqueous NH_3 and applied onto a column of Dowex 1X2 (acetate form), washed with water and eluted with a linear gradient of aqueous acetic or formic acid (0–1 M). The product containing fractions were evaporated, codistilled with water (5 × 30 ml) and the residue was crystallized to give pure free phosphonate **4**.

Method B: A mixture of ester **3** (0.5 mmol), TMSBr (2 ml, 15.2 mmol) and acetonitrile (10 ml) was stirred at 80 °C for 2 h and then allowed to stand at room temperature overnight. The quenching of the reaction and isolation of the products was performed in the same manner as in method *A*.

Method C: Ester **3** (0.5 mmol) was dissolved in acetonitrile (10 ml) and to this solution, TMSBr (2 ml, 15.2 mmol) was added dropwise. The mixture was stirred overnight at room temperature. After evaporation of the solvent and reagent and co-distillation with acetonitrile (10 ml) and toluene (10 ml), the residue was treated with water (10 ml) and triethylamine (1 ml) for 5 min and evaporated. The residue was dissolved in water, acidified with one drop of conc. aqueous HCl and applied onto a column of Dowex 50X8 (H^+ form). The product was eluted with water. The product-containing fractions were evaporated and the residue was crystallized from water-ethanol–diethyl ether.

2-Amino-6-phenyl-9-[2-(phosphonomethoxy)ethyl]purine (**4a**). Method *A*; eluted by a gradient of aqueous formic acid; yield 84%, crystallized from water; m.p. 284–286 °C (dec.); E_{Up} 0.68. FAB MS, *m/z* (rel. %): 350 (100) [M + H]. ^{1}H NMR (400 MHz, DMSO-d_6): 3.62 (d, 2 H, $J(CH_2,P)$ = 8.7, PCH_2); 3.88 (t, 2 H, $J(2',1')$ = 5.2, CH_2-2′); 4.27 (t, 2 H, $J(1',2')$ = 5.2, CH_2-1′); 6.51 (brs, 2 H, NH_2); 7.52 (m, 3 H, H-arom); 8.15 (s, 1 H, H-8); 8.71 (m, 2 H, H-arom). ^{13}C NMR (100.6 MHz, DMSO-d_6): 42.06 (C-1′); 66.35 (d, J(P,C) = 160.0, PCH_2); 69.92 (d, J(P,C) = 10.4, C-2′); 123.87 (C-5); 128.24, 129.07, 130.40 (3 × CH-arom); 135.95 (C-1″) 142.87 (C-8); 153.34 (C-6); 154.47 (C-4); 160.01 (C-2). For $C_{14}H_{16}N_5O_4P$ (349.3) calculated: 48.14% C, 4.62% H, 20.05% N, 8.87% P; found: 47.81% C, 4.72% H, 19.91% N, 9.03% P. UV spectrum: (pH 2) λ_{max} 259 (ε_{max} 10 700), λ_{max} 340 (ε_{max} 11 800).

2-Amino-9-[2-(phosphonomethoxy)ethyl]-6-(2-tolyl)purine (**4b**). Method *A*, eluted by a gradient of aqueous formic acid; yield 92%; crystallized from water–ethanol; colourless crystals; m.p. 154–157 °C (dec.); E_{Up} 0.72. FAB MS, *m/z* (rel. %): 364 (100) [M + H]. ^{1}H NMR (400 MHz, DMSO-d_6): 2.35 (s, 3 H, CH_3); 3.62 (d, 2 H, $J(CH_2,P)$ = 8.6, PCH_2); 3.89 (t, 2 H, $J(2',1')$ = 5.3, CH_2-2′); 4.26 (t, 2 H, $J(1',2')$ = 5.3, CH_2-1′); 6.51 (vbrs, 2 H, NH_2); 7.32 (m, 3 H, H-arom.); 7.54 (m, 1 H, H-arom.); 8.07 (s, 1H, H-8). ^{13}C NMR (100.6 MHz, DMSO-d_6): 20.21 (CH_3-tolyl); 42.03 (C-1′); 66.35 (d, J(P,C) = 160.2, PCH_2); 69.89 (d, J(P,C) = 10.1, C-2′); 124.77 (C-5); 125.19, 128.87, 130.16, 130.33 (4 × CH-arom); 135.77, 136.28 (C-1″, C-2″); 142.80 (C-8); 153.59 (C-6); 157.93 (C-4); 159.88 (C-2). Exact mass (FAB HRMS, *m/z*) found 364.1222; calculated for $C_{15}H_{18}N_5O_4P$ [M + H] 364.1175. UV spectrum: (pH 2) λ_{max} 253 (ε_{max} 5 700), λ_{max} 327 (ε_{max} 9 300).

2-Amino-6-(4-fluorophenyl)-9-[2-(phosphonomethoxy)ethyl]purine (**4c**). Method *A*; eluted by a gradient of aqueous formic acid; yield 66%; crystallized from water; colourless crystals; m.p. 145–150 °C. E_{Up} 0.68. FAB MS, *m/z* (rel. %): 368 (100) [M + H]. ^{1}H NMR (400 MHz, DMSO-d_6): 3.62 (brs, 2 H, PCH_2); 3.88 (brs, 2 H, CH_2-2′); 4.27 (brs, 2 H, CH_2-1′); 6.54 (brs, 2 H, NH_2); 7.32 (t, 2 H, *J* = 8.9, H-arom.); 8.16 (s, 1 H, H-8); 8.80 (dd, 2 H, *J* = 6.0, *J* = 8.5, H-arom.). ^{13}C NMR (100.6 MHz, DMSO-d_6): 42.07 (C-1′); 69.88 (C-2′); 115.23 (d, *J*(F,C) = 21.4, C-3″); 123.59 (C-5); 131.37 (d, *J*(F,C) = 7.7, C-2″); 132.44 (C-1″); 142.95 (C-8); 152.10 (C-6); 154.47 (C-4); 159.97 (C-2); 163.47 *J*(F,C) = 248.5 (C-4″). For $C_{14}H_{15}FN_5O_4P{\cdot}H_2O$ (385.3) calculated: 43.64% C, 4.45% H, 4.93%F, 18.18% N, 8.04% P; found: 43.53% C, 4.16% H, 4.79%F, 18.21% N, 8.44% P. UV spectrum: (pH 2) λ_{max} 261 (ε_{max} 9 000), λ_{max} 341 (ε_{max} 11 300).

2-Amino-9-[2-(phosphonomethoxy)ethyl]-6-(2-thienyl)purine (**4d**). Method *A*; eluted by a gradient of aqueous formic acid; yield 95%, crystallized from water; yellowish crystals; m.p. 260–264 °C. E_{Up} 0.67. FAB MS, *m/z* (rel. %): 356 (95) [M + H]. ^{1}H NMR (400 MHz, DMSO-d_6): 3.62 (d, 2 H, *J*(CH_2,P) = 8.6, PCH_2); 3.88 (t, 2 H, *J*(2′,1′) = 5.2, CH_2-2′); 4.25 (t, 2 H, *J*(1′,2′) = 5.2, CH_2-1′); 6.50 (vbrs, 2 H, NH_2); 7.27 (dd, 1 H, *J* = 4.8, 3.9, H-arom.); 7.80 (m, 1 H, H-arom.); 8.14 (s, 1 H, H-8); 8.54 (m, 1 H, H-arom). ^{13}C NMR (100.6 MHz, DMSO-d_6): 42.06 (C-1′); 66.31 (d, *J*(P,C) = 160.2, PCH_2); 69.93 (d, *J*(P,C) = 10.5, C-2′); 121.93 (C-5); 128.49, 130.28, 131.57 (3 × CH-arom); 140.50 (C-2″); 143.01 (C-8); 149.01 (C-6); 153.98 (C-4); 159.90 (C-2). For $C_{12}H_{14}N_5O_4PS$ (355.3) calculated: 40.57% C, 3.97% H, 19.71% N, 8.72% P; found: 40.18% C, 4.01% H, 19.45% N, 8.81% P. UV spectrum: (pH 2) λ_{max} 235 (ε_{max} 17 600), λ_{max} 292 (ε_{max} 6 500), λ_{max} 369 (ε_{max} 13 800).

2-Amino-9-[2-(phosphonomethoxy)ethyl]-6-(pyridin-2-yl)purine (**4e**). Method *B*; eluted by a gradient of aqueous acetic acid; yield 90%; crystallized from water; yellow crystals; m.p. 240 °C (dec). E_{Up} 0.70. FAB MS, *m/z* (rel. %): 351 (100) [M + H]. ^{1}H NMR (400 MHz, DMSO-d_6): 3.61 (d, 2 H, *J*(CH_2,P) = 8.6, PCH_2); 3.89 (t, 2 H, *J*(2′,1′) = 5.1, CH_2-2′); 4.28 (t, 2 H, *J*(1′,2′) = 5.1, CH_2-1′); 6.75 (brs, 2 H, NH_2); 7.52 (m, 1 H, H-5″); 7.99 (m, 1 H, H-4″); 8.23 (s, 1 H, H-8); 8.58 (d, 1 H, *J*(3″,4″) = 7.9, H-3″); 8.77 (d, 1 H, *J*(6″,5″) = 4.2, H-6″). ^{13}C NMR (100.6 MHz, DMSO-d_6): 42.35 (C-1′); 66.64 (d, *J*(P,C) = 159.9, PCH_2); 69.93 (d, *J*(P,C) = 10.3, C-2′); 124.25 (C-5); 124.92 (C-3″); 125.52 (C-5″); 136.78 (C-4″); 144.04 (C-8); 149.61 (C-6″); 153.05 (C-6); 153.33 (C-2″); 155.11 (C-4); 159.98 (C-2). For $C_{13}H_{15}N_6O_4P$ (350.3) calculated: 44.58% C, 4.32% H, 23.99% N; found: 44.24% C, 4.35% H, 23.69% N. UV spectrum: (pH 2) λ_{max} 276 (ε_{max} 8 500), λ_{max} 360 (ε_{max} 7 900).

2-Amino-6-(1-methylpyrrol-2-yl)-9-[2-(phosphonomethoxy)ethyl]purine (**4f**). Method *A*; eluted by a gradient of aqueous formic acid; yield 61%; crystallized from water-ethanol–diethyl ether; greenish crystals; m.p. 141–146 °C. E_{Up} 0.67. FAB MS, *m/z* (rel. %): 353 (100) [M + H]. ^{1}H NMR (400 MHz, DMSO-d_6): 3.61 (d, 2 H, *J*(CH_2,P) = 8.6, PCH_2); 3.86 (t, 2 H, *J*(2′,1′) = 5.2, CH_2-2′); 4.12 (s, 3 H, NCH_3); 4.22 (t, 2 H, *J*(1′,2′) = 5.1, CH_2-1′); 6.16 (m, 1 H, H-4″); 6.33 (brs, 2 H, NH_2); 7.00 (s, 1 H, H-3″); 7.63 (m, 1 H, H-5″); 8.01 (s, 1 H, H-8). ^{13}C NMR (100.6 MHz, DMSO-d_6): 37.81 (NCH_3); 41.87 (C-1′); 66.31 (d, *J*(P,C) = 160.2, PCH_2); 70.03 (d, *J*(P,C) = 10.8, C-2′); 107.83 (C-4″); 117.92 (C-5″); 121.89 (C-2″); 126.87 (C-5); 128.72 (C-3″); 141.36 (C-8); 149.37 (C-6); 152.99 (C-4); 159.34 (C-2). For $C_{13}H_{17}N_6O_4P{\cdot}0.5H_2O$ (361.3) calculated: 43.22% C, 5.02% H, 23.26% N, 8.57% P; found: 43.52% C, 5.06% H, 23.11% N, 8.95% P. UV spectrum: (pH 2) λ_{max} 235 (ε_{max} 16 000), λ_{max} 258 sh. (ε_{max} 4 500), λ_{max} 310 (ε_{max} 4 200), λ_{max} 373 (ε_{max} 20 100).

2-Amino-6-(1-methylimidazol-2-yl)-9-[2-(phosphonomethoxy)ethyl]purine (**4g**). Method *B*; eluted by a gradient of aqueous acetic acid; yield 83%; crystallized from water–ethanol; yel-

low crystals; m.p. 252 °C (dec). E_{Up} 0.67. FAB MS, *m/z* (rel. %): 354 (85) [M + H], 99 (100). ^{1}H NMR (400 MHz, DMSO-d_6): 3.59 (d, 2 H, J(CH_2,P) = 8.6, PCH_2); 3.87 (t, 2 H, J(2′,1′) = 5.1, CH_2-2′); 4.00 (s, 3 H, CH_3); 4.26 (t, 2 H, J(1′,2′) = 5.1 CH_2-1′); 6.64 (brs, 2 H, NH_2); 7.20 and 7.43 (s, 1 H, H-4″ and H-5″); 8.16 (s, 1 H, H-8). ^{13}C NMR (100.6 MHz, DMSO-d_6): 35.42 (CH_3); 42.10 (C-1′); 66.57 (d, J(P,C) = 159.8, PCH_2); 69.78 (d, J(P,C) = 9.9, C-2′); 123.76 (C-5); 124.91 (C-5″); 127.43 (C-4″); 141.15 (C-6); 143.50 (C-8); 146.55 (C-2″); 154.38 (C-4); 159.66 (C-2). For $C_{12}H_{16}N_7O_4P{\cdot}0.5H_2O$ (362.3) calculated: 39.78% C, 4.73% H, 27.06% N, 8.55% P; found: 39.74% C, 4.78% H, 26.91% N, 8.57% P. UV spectrum: (pH 2) λ_{max} 229 (ε_{max} 20 300), λ_{max} 265 (e_{max} 10 300), λ_{max} 351 (ε_{max} 7 600).

2-Amino-6-(imidazol-2-yl)-9-[2-(phosphonomethoxy)ethyl]purine (**4h**). Method *B*; eluted by a gradient of aqueous acetic acid; yield 55%; crystallized from water–ethanol; yellow crystals; m.p. 234 °C (dec); E_{Up} 0.68. FAB MS, *m/z* (rel. %): 340 (15) [M + H], 99 (100). ^{1}H NMR (400 MHz, DMSO-d_6): 3.60 (d, 2 H, J(CH_2,P) = 8.7, PCH_2); 3.88 (t, 2 H, J(2′,1′) = 5.1, CH_2-2′); 4.27 (t, 2 H, J(1′,2′) = 5.2, CH_2-1′); 6.53 (brs, 2 H, NH_2); 7.35 (m, 2 H, H-4″ and H-5″); 8.23 (s, 1 H, H-8). ^{13}C NMR (100.6 MHz, DMSO-d_6): 42.15 (C-1′); 66.53 (d, J(P,C) = 160.0, PCH_2); 69.78 (d, J(P,C) = 10.1, C-2′); 122.45 (C-5); 124.75 (CH-arom); 142.11 (C-6); 143.49 (C-8); 144.74 (C-2″); 154.22 (C-4); 160.21 (C-2). Exact mass (FAB HRMS, *m/z*) found 340.0887; calculated for $C_{11}H_{14}N_7O_4P$ [M + H] 340.0923. UV spectrum: (pH 2) λ_{max} 231 (ε_{max} 21 100), λ_{max} 272 (ε_{max} 13 600), λ_{max} 360 (ε_{max} 8 800).

2-Amino-6-(1-methylimidazol-5-yl)-9-[2-(phosphonomethoxy)ethyl]purine (**4i**). Method *B*; eluted by a gradient of aqueous acetic acid; yield 61%; crystallized from water; colourless crystals; m.p. 325 °C (dec); E_{Up} 0.68. FAB MS, *m/z* (rel. %): 354 (15) [M + H]. ^{1}H NMR (400 MHz, D_2O): 3.70 (d, 2 H, J(CH_2,P) = 8.9, PCH_2); 3.91 (s, 3 H, NCH_3); 3.95 (t, 2H, J(2′,1′) = 4.7, CH_2-2′); 4.24 (t, 2 H, J(1′,2′) = 4.8, CH_2-1′); 7.75 and 7.95 (s, 1 H, H-4″and H-5″); 8.16 (s, 1 H, H-8). ^{13}C NMR (100.6 MHz, D_2O): 39.20 (NCH_3); 45.72 (C-1′); 69.90 (d, J(P,C) = 117.3, PCH_2); 73.09 (d, J(P,C) = 8.8, C-2′); 125.22 (C-5); 129.40 (C-5″); 132.08 (C-4″); 142.96 (C-8); 146.78 (C-2″); 148.53 (C-6); 155.42 (C-4); 161.61 (C-2). For $C_{12}H_{16}N_7O_4P{\cdot}0.5H_2O$ (362.3) calculated: 39.78% C, 4.73% H, 27.06% N, 8.55% P; found: 40.02% C, 4.71% H, 27.02% N, 8.80% P. UV spectrum: (pH 2) λ_{max} 336 (ε_{max} 7 500).

2-Amino-6-(imidazol-5-yl)-9-[2-(phosphonomethoxy)ethyl]purine (**4j**). Method *B*; eluted by a gradient of aqueous acetic acid; yield 78%; crystallized from water–ethanol; yellow crystals; m.p. 207–212 °C; E_{Up} 0.63. FAB MS, *m/z* (rel. %): 340 (100) [M + H]. ^{1}H NMR (400 MHz, D_2O): 3.79 (d, 2 H, J(CH_2,P) = 8.8, PCH_2); 3.95 (m, 2 H, CH_2-2′); 4.13 (m, 2 H, CH_2-1′); 7.52 and 7.81 (s, 1 H, H-2″ and H-4″); 8.55 (s, 1 H, H-8). ^{13}C NMR (100.6 MHz, D_2O): 37.88 (CH_3); 44.16 (C-1′); 68.15 (d, J(P,C) = 157.0, PCH_2); 71.27 (d, J(P,C) = 11.9, C-2′); 122.08 (C-5); 122.90 (C-5″); 128.50 (C-4″); 136.65 (C-2″); 142.87 (C-6); 145.98 (C-8); 154.32 (C-4); 159.26 (C-2). Exact mass (FAB HRMS, *m/z*) found 340.0866; calculated for $C_{11}H_{14}N_7O_4P$ [M + H] 340.0923. UV spectrum: (pH 2) λ_{max} 229 (ε_{max} 19 400), λ_{max} 345 (ε_{max} 7 900).

2-Amino-6-methyl-9-[2-(phosphonomethoxy)ethyl]purine (**4k**). Method *A*; eluted by a gradient of aqueous acetic acid; yield 89%; crystallized from water; colourless crystals; m.p. 287–290 °C (ref.[2b] >270 °C); E_{Up} 0.83. FAB MS, *m/z* (rel. %): 288 (80) [M + H], 57 (100). ^{1}H NMR (300 MHz, D_2O): 2.70 (s, 3 H, CH_3) 3.61 (d, 2 H, J(CH_2,P) = 8.8, PCH_2); 3.91 (t, 2 H, J(2′,1′) = 5.0, CH_2-2′); 4.33 (t, 2 H, J(1′,2′) = 5.0, CH_2-1′); 8.40 (s, 1 H, H-8). For $C_9H_{14}N_5O_4P$ (287.2) calculated: 37.64% C, 4.91% H, 24.38% N, 10.78% P; found: 37.31% C, 4.94% H, 23.99% N, 10.89% P. UV spectrum: (pH 2) λ_{max} 248 (ε_{max} 3 700), λ_{max} 310 (ε_{max} 5 000).

2-Amino-6-ethyl-9-[2-(phosphonomethoxy)ethyl]purine (**4l**). Method *A*; eluted by a gradient of aqueous acetic acid; yield 89%; crystallized from water–ethanol; colourless crystals; m.p.

139–144 °C; E_{Up} 0.78. FAB MS, *m/z* (rel. %): 302 (44) [M + H], 115 (100). ^{1}H NMR (400 MHz, DMSO-d_6): 1.26 (t, 3 H, $J(CH_2,CH_3)$ = 7.6, CH_3); 2.84 (q, 2 H, $J(CH_3,CH_2)$ = 7.6, CH_2); 3.48 (d, 2 H, J(P,CH) = 8.5, PCH_2); 3.80 (t, 2 H, J(1′,2′) = 5.3, H-2′); 4.18 (t, 2 H, J(2′,1′) = 5.3, H-1′); 6.37 (brs, 2 H, NH_2); 8.02 (s, 1 H, H-8). ^{13}C NMR (100 MHz, DMSO-d_6): 12.33 (CH_3); 25.66 (CH_2CH_3); 42.01 (C-1′); 67.49 (d, J(P,CH_2) = 157.1 CH_2P); 69.67 (C-2′); 124.67 (C-5); 141.80 (C-8); 152.45 (C-4); 160.09 (C-2); 162.86 (C-6). For $C_{10}H_{16}N_5O_4P$ (301.2) calculated: 39.87% C, 5.35% H, 23.25% N, found: 39.66% C, 5.52% H, 22.97 %N. UV spectrum: (pH 2) λ_{max} 246 (ε_{max} 4 100), λ_{max} 311 (ε_{max} 5 200).

2-Amino-9-[2-(phosphonomethoxy)ethyl]-6-(trifluoromethyl)purine (**4m**). Method *C*; yield 65%; yellowish crystals; m.p. 138–141 °C; E_{Up} 0.83. FAB MS, *m/z* (rel. %): 342 (100) [M + H]. ^{1}H NMR (400 MHz, DMSO-d_6): 3.56 (d, 2 H, J(P,CH) = 7.6, PCH_2); 3.85 (brs, 2 H, H-2′); 4.26 (brs, 2 H, H-1′); 7.03 (brs, 2 H, NH_2); 8.30 (s, 1 H, H-8). ^{19}F NMR (376.5 MHz, DMSO-d_6): –65.06 (s, CF_3). For $C_9H_{11}F_3N_5O_4P$ (341.2) calculated: 31.68% C, 3.25% H, 20.53% N; found: 31.37% C, 3.32% H, 20.29% N.

2-Amino-6-(heptafluoropropyl)-9-[2-(phosphonomethoxy)ethyl]purine (**4n**). Method *C*; yield 59%; yellowish crystals; m.p. 166–168 °C; E_{Up} 0.77. FAB MS, *m/z* (rel. %): 442 (100) [M + H]. ^{1}H NMR (400 MHz, DMSO-d_6): 3.56 (d, 2 H, J(P,CH) = 8.5, PCH_2); 3.86 (t, 2 H, J(1′,2′) = 5.0, H-2′); 4.26 (t, 2 H, J(2′,1′) = 5.0, H-1′); 7.03 (brs, 2 H, NH_2); 8.30 (s, 1 H, H-8). ^{19}F NMR (376.5 MHz, DMSO-d_6): –79.42 (brs, CF_2); -113.09 (brs, CF_2), –125.43 (s, CF_3). For $C_{11}H_{11}F_7N_5O_4P$ (441.2) calculated: 29.95% C, 2.51% H, 15.87% N; found: 29.86% C, 2.74% H, 15.83% N.

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