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Synthesis of Acyclic Nucleotide Analogues Derived from N-Substituted 6-(1-Aminoethyl)purines *via* 6-Acetylpurine Derivatives[1]

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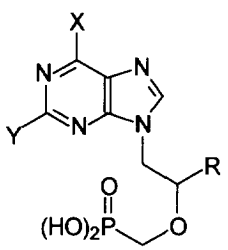
Abstract: The Stille coupling of 9-{2-[bis(2-propoxy)phosphonylmethoxy]ethyl}-6-chloropurines with 1-(ethoxyvinyl)tributyltin afforded 6-(1-ethoxyvinyl)purine derivatives. Their acid hydrolysis gave 6-acetylpurine derivatives that after reductive amination using various primary and secondary amine hydrochlorides and sodium cyanoborohydride followed by deprotection afforded the title N-substituted 6-(1-aminoethyl)-9-(2-phosphonomethoxyethyl)purine derivatives.

INTRODUCTION

N-Phosphonomethoxyalkyl derivatives of purine bases **1** are potent antivirals.[2] The structure-activity relationship study[3] of these compounds showed that the presence of an amino group at the purine moiety is necessary for the antiviral activity. However, recently[4] it was found, that several 6-alkylamino or 6-dialkylaminopurine derivatives **2** also exhibit a strong antiviral effect. To study the role of the amino function in the antiviral activity of these compounds the analogues bearing strongly basic 2- or 6-aminomethyl or 6-carboxamidine functions **3-5** were prepared.[5,6] While the 2-aminomethyl[5] **3** and 6-carboxamidinio[6] **5** derivatives were inactive against all viruses tested, the 6-(aminomethyl)purine analogues **4** still exert certain activity against several strains of VZV, HSV and MSV viruses.[6]



1 X and/or Y = NH_2; R = H, CH_3, CH_2OH

2 X = (di)alkylamino; Y = H, H_2N; R = H, CH_3, CH_2

3 Y = H_2NCH_2; X = NH_2, OH; R = H, CH_3, CH_2OH

4 Y = H, H_2N; X = CH_2NH_2; R = H, CH_2OH

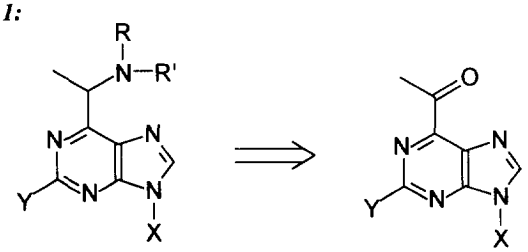
5 X = $C(=NH)NH_2$; Y = H, H_2N; R = H

As a continuation of the above study we have designed the N-substituted 6-(1-aminoethyl)purine analogues that superpose the structural features of the active types of compounds **2** and **4**. The N-substituents were chosen as representative examples of primary and secondary amines that were most active in the 6-(di)alkylaminopurine series **2**. Evaluation of the antiviral activity of such analogues may provide more information about the mechanism of action of these drugs.

RESULTS AND DISCUSSION

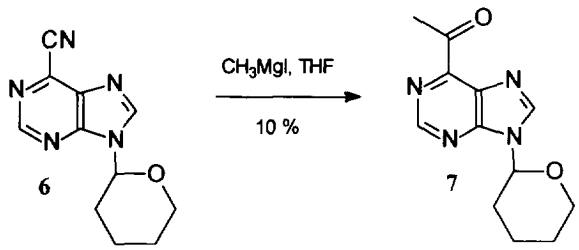
The 6-acetylpurines were the proposed key starting compounds for the synthesis of this group of compounds ***(Scheme 1)***. Three approaches for the synthesis of acetyl (or acyl) purines have been reported so far: (a) reaction[7,8] of 6-cyanopurines with Grignard reagents (the yields varied from 4-18 % for 6-cyanopurines[7] to 22-51 % for 2-cyanopurines[8]); (b) alkylation[9] of 6-halopurine with trimethylsilylacetylene followed by Hg^{2+} catalysed hydration (the yields: 13 % for 6-chloropurine, 38 % for 6-iodopurine) and (c) the Stille coupling[10] of the 6-chloropurines with (1-ethoxyvinyl)tributyltin under $Pd(PPh_3)_4$ catalysis, which gives[11,12,13] 6-(1-ethoxyvinyl)purines in the yields of 58-81 %, followed by hydrolysis. Other general methods for the synthesis of arylmethylketones (not yet used on purines) *via* S_NAr substitution are: (d) Heck reaction[14] of vinylethers (or vinylesters) with aryl halides followed by hydrolysis and (e) coupling[15] of (1-ethoxyvinyl)zinc halide reagents with aryl halides followed by hydrolysis.

Scheme 1:

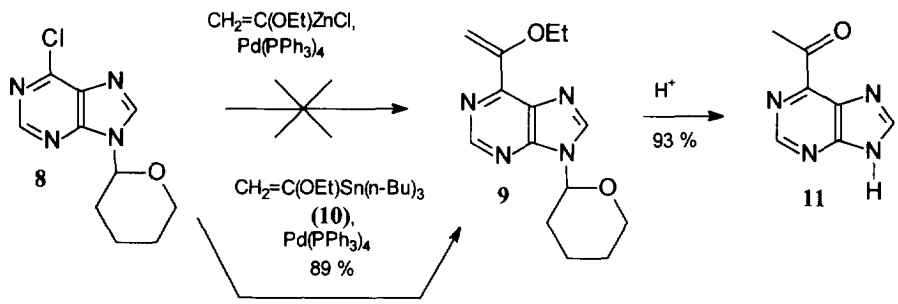


Several methods have been evaluated in this study in order to elaborate facile and efficient preparation of hitherto unknown 6-acetylpurine **11**: (a) Reaction of the tetrahydropyran-2-yl (THP)-protected 6-cyanopurine[16] **6** with methylmagnesium iodide ***(Scheme 2)*** afforded the 6-acetylpurine derivative **7** in an unsatisfactory yield of 10 %. (b) Reaction of (1-ethoxyvinyl)zinc chloride, formed[15] *in situ* from ethyl vinyl ether and *tert*-BuLi followed by treatment with zinc chloride, with the protected 6-chloropurine **8** under $Pd(PPh_3)_4$ catalysis gave a complex mixture of products which did not contain the expected product **9** at all ***(Scheme 3)***. (c) The Stille coupling of the 6-chloropurine **8** with (1-ethoxyvinyl)tributyltin[17] **(10)** under $Pd(PPh_3)_4$ catalysis gave the 6-(1-ethoxyvinyl)purine **9** in the yield of 89 %. The unstable compound **9** was immediately hydrolyzed using acetone / aq. HCl mixture at reflux temperature to afford 6-acetylpurine **(11)** in 93 % yield (82 % overall yield from **8**) ***(Scheme 3)***.

Scheme 2:



Scheme 3:

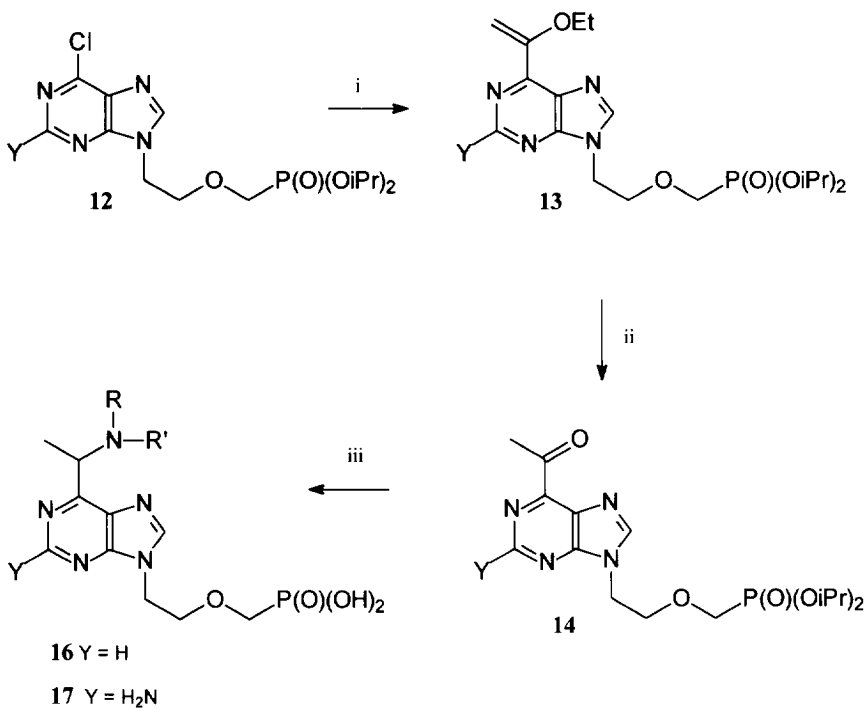


An N-alkylation of purine bases usually does not give high yields and in the case of compound **11** a number of possible regioisomers could be expected. Therefore further effort focused on the analogous Stille coupling of the protected 6-chloropurine derivatives **12a,b**[18] that already contained protected phosphonomethoxyethyl moiety in the N-9 position ***(Scheme 4)***.

The 6-chloropurine derivative **12a** reacted with the stannane **10** under the above conditions to give the 6-(1-ethoxyvinyl)purine **13a** in 83 % yield. This compound was very unstable and quickly darkened. Therefore it was without characterization hydrolyzed using DMF / aq. HCl mixture at reflux temperature to afford after column chromatography the 6-acetylpurine derivative **14a** in 76 % yield (63 % overall yield from **12a**). This compound was also unstable and had to be freshly prepared for each reaction and directly used in further steps. It was characterized as its stable 2,4-dinitrophenylhydrazone derivative.

Similarly, the 2-amino-6-chloropurine derivative **12b** reacted with the stannane **10** in the same way to give the 6-(1-ethoxyvinyl)purine **13b** in the yield of 61 %. While this compound was sufficiently stable itself, its hydrolysis by refluxing in DMF / aq. HCl mixture gave a complex mixture of products with mere traces of the desired 6-acetyl derivative **14b**. However, reflux in acetone / aq. HCl mixture afforded the 6-acetyl-2-aminopurine **14b** in an acceptable yield of 65 % after column chromatography.

Scheme 4:



In the formulae **12-14**:
a) Y = H
b) Y = H_2N

In the formulae **15-17**:
a) R = R' = H
b) R = H, R' = CH_3
c) R = H, R' = allyl
d) R = H, R' = cyclopropyl
e) R = H, R' = cyclohexyl
f) R = R' = CH_3
g) R, R' = -$(CH_2)_4$-

i CH_2=C(OEt)Sn(n-Bu)$_3$ **(10)**, $Pd(PPh_3)_4$, DMF
ii HCl, H_2O, DMF or acetone
iii 1. $RR'NH_2^+ Cl^-$ **(15)**, $NaBH_3CN$, MeOH
2. TMSBr, CH_3CN

Ketones can be easily converted to amines by reductive amination[19] using an amine and a reducing agent (HCOOH, H_2-cat., $NaBH_4$, $NaBH_3CN$ etc.). Among these methods the use[20] of amine hydrochlorides and $NaBH_3CN$ is reported to proceed under the mildest conditions and to give the best yields of amines.

Application of this method to the reductive amination of the 6-acetylpurine **14a** using ammonium chloride, as well as primary and secondary amine hydrochlorides **15** afforded the corresponding protected 6-(1-aminoethyl)purine derivatives that were without isolation deprotected using bromotrimethylsilane (TMSBr) to afford the title acyclic nucleotide analogues **16** in the yields of 20-50 %. The products were easily purified by anion exchange chromatography and characterized as pure amorphous solids. With the only exception for the cyclopropyl derivative **16d**, that slowly darkened, these compounds were stable on storage.

Three representative examples - compounds **17a,c,f** were prepared by this method to prove its applicability for the synthesis of N-substituted 2-amino-6-(1-aminoethyl)purine analogues. The reactions of

compound **14b** with amine hydrochlorides **15a,c,f** were performed in the same manner as for the compounds **14a** and after analogous work-up the compounds **17** were obtained in the yields of 11-42 %; all compounds in this series were stable on storage.

Despite the fact, that in some cases the yields are rather moderate, the 6-(1-aminoethyl)purine analogues **16** and **17** could be prepared by this method in sufficient amount and purity for the biological activity tests. NMR and UV spectra of the compounds **16** and **17** follow the same pattern as those[6] of the 6-(aminomethyl)purine analogues **4**. Electrophoretical mobilities of the compounds **16** and **17** are, similarly to those[6] of compounds **4**, substantially lower compared to those of adenine derivatives **1**.

Compounds **16** and **17** were tested on their cytostatic[21] (inhibition of the cell growth on the following cell cultures: (a) mouse leukemia L1210 cells (ATCC CCL 219); (b) murine L929 cells (ATCC CCL 1) and (c) human cervix carcinoma HaLaS3 cells (ATCC CCL 2.2)) and antiviral[22] (DNA viruses: HSV-1, HSV-2, CMV, VZV and vaccinia virus, and retroviruses: HIV-1, HIV-2 and MSV) activity. None of the tested compounds exhibited any considerable activity in any of these assays; neither was any of them 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) $CHCl_3$/ MeOH (90:10); (B) ethyl acetate; (C) i-PrOH / H_2O / 35% aq. NH_3 (70:20:10). Paper electrophoresis was performed on a paper Whatman No.3 MM at 40 V/cm for 1 h in 0.05 M triethylammonium hydrogen carbonate at pH 7.5 and the electrophoretical mobilities are referenced to uridine 3'-phosphate. NMR spectra were measured on Varian Unity 500 (500 MHz for ^1H and 125.7 MHz for ^{13}C NMR) in hexadeuteriodimethyl sulfoxide referenced to the solvent signals 2.5 ppm for ^1H and 39.7 ppm for ^{13}C NMR, or in deuterium oxide containing sodium deuteroxide with sodium disilapentasulfonate (DSS) 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 Varian Unity 200 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 were measured on a Beckman DU-65 spectrometer in aqueous solutions. DMF was distilled from P_2O_5, 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.

6-Acetyl-9-(tetrahydropyran-2-yl)purine (7)

To a stirred solution of the THP-protected 6-cyanopurine **6**[16] (920 mg, 4 mmol) in THF (30 ml) at -78 °C 0.9M methylmagnesium iodide solution in ether (13.3 ml, 12 mmol) was added dropwise (10 min.) under Ar atmosphere. The cooling bath was then removed and the solution was stirred for 2 h at r.t. The solvents were evaporated and the residue was treated with H_2O/ 35% aq. NH_3/ NH_4Cl (4:1:1; v/v/w) solution (20 ml) and extracted with $CHCl_3$ (3 x 30 ml). The collected organic phases were evaporated and the residue was chromatographed on a column of silica gel (40 g, $CHCl_3$) to afford the acetylpurine **7** as yellow oil. Yield 100 mg (10%). $C_{12}H_{14}N_4O_2$ (246.3); FABMS, *m/z* (rel.%): 247 (20) $[M+H]^+$. ^1H NMR ($(CD_3)_2SO$): 1.60, 1.76, 2.00 and 2.35 (4 x m, together 6 H, CH_2); 2.80 (s, 3 H, CH_3); 3.73 and 4.03 (2 x m, 2 x 1 H, H-5'); 5.83 (dd, 1 H, J= 2.2, 11.0, H-1'); 8.99 and 9.10 (2 x s, 2 x 1 H, H-2 and H-8).

6-(1-Ethoxyvinyl)-9-(tetrahydropyran-2-yl)purine (9)

To a stirred solution of compound **8**[23] (0.5 g, 2.1 mmol) and $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) in dry degassed DMF (5 ml) under Ar atmosphere (1-ethoxyvinyl)tri(n-butyl)tin[17] **(10)** (1.08 g, 3 mmol) was added and the mixture was stirred at 100 °C for 5 h. The solvent was evaporated, the residue dissolved in water (20 ml) and extracted with $CHCl_3$ (3 x 20 ml). Column chromatography of the residue after evaporation of the organic phase (silica gel, 20 g, ethyl acetate) afforded rather unstable compound **9** as yellow oil that quickly darkened. Yield 510 mg (89 %); R_F(B) 0.29. $C_{14}H_{18}N_4O_2$ (274.3); FABMS, *m/z* (rel.%): 275 (15) $[M+H]^+$. ^{1}H NMR (200 MHz, $CDCl_3$): 1.53 (t, 3 H, $J(CH_3,CH_2)$= 7.0, CH_3CH_2); 1.75 and 2.10 (2 x m, 2 x 3 H, CH_2); 3.80 and 4.22 (2 x m, 2 x 1 H, H-5'); 4.10 (q, 2 H, $J(CH_2,CH_3)$= 7.0, CH_2CH_3); 4.98 (d, 1 H, J_{gem}= 2.4, CH_2=); 5.84 (dd, 1 H, J= 2.2, 11.0, H-1'); 6.15 (d, 1 H, J_{gem}= 2.4, CH_2=); 8.31 and 9.02 (2 x s, 2 x 1H, H-2 and H-8).

6-Acetylpurine (11)

A solution of compound **9** (510 mg, 1.86 mmol) in a mixture of acetone (5 ml), water (2 ml) and 35% aq. HCl (1 ml) was refluxed for 1 h, cooled to room temperature, neutralized with triethylamine (pH 7) and taken down *in vacuo*. Column chromatography of the residue (silica gel (20 g), ethyl acetate) afforded compound **11** as white solid. Yield 280 mg (93 %). An analytical sample was crystallized from water; colourless crystals; dec. 240-250 °C; R_F(B) 0.16. EIMS, *m/z* (rel.%): 162 (100) $[M]^+$, 149 (20), 134 (88), 120 (80), 93 (65), 83 (22), 69 (30), 57 (37), 43 (60), 28 (62). ^{1}H NMR ($(CD_3)_2SO$): 2.76 (s, 3 H, 2"-CH_3); 8.81 and 9.14 (2 x s, 2 x 1 H, H-2 and H-8); 12.0 (br, 1 H, NH). ^{13}C NMR ($(CD_3)_2SO$): 25.71 (2"-CH_3); 129.00 (C-5); 150.94 (C-8); 151.63 (C-2); 151.76 and 151.80 (C-6 and C-4); 200.75 (1"-CO). UV; pH 7: λ_{max} 300 nm (ε 7500), pH 2: λ_{max} 294 nm (ε 6300), pH 12: λ_{max} 310 nm (ε 5600). Anal.: Calcd. for $C_7H_6N_4O$. 0.5 H_2O (171.2): C, 49.12; H, 4.20; N, 32.73. Found: C, 49.54; H, 3.90; N, 32.33.

Attempted Reaction of the Protected 6-Chloropurine 8 with (1-Ethoxyvinyl)zinc Chloride.

To a stirred solution of ethyl vinyl ether (1 ml, 10.5 mmol) in THF (30 ml) at -70 °C under Ar 1.6M *tert*-BuLi in pentane (3.12 ml, 5 mmol) was added dropwise over period of 10 min. and stirring at -70 °C was continued for another 10 min. The solution was then stirred at 0 °C for 45 min., 1M $ZnCl_2$ solution in hexanes (5 ml, 5 mmol) was added dropwise, the stirring was continued for 10 min at 0 °C and 30 min. at r.t.. A solution of 6-chloropurine **8** (250 mg, 1.05 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in THF (10 ml) was added and the mixture was refluxed for 5 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (20 ml) and the solvents were evaporated. The residue was distributed between water (100 ml) and $CHCl_3$ (100 ml). The complex mixture obtained after evaporation of the organic phase did not contain the desired product **9** (MS and ^{1}H NMR detection).

6-Acetyl-9-{2-[bis(2-propoxy)phosphonylmethoxy]ethyl}purine (14a)

To a stirred solution of **12a**[18] (440 mg, 1.17 mmol) and $Pd(PPh_3)_4$ (75 mg, 0.065 mmol) in DMF (4 ml) under Ar atmosphere (1-ethoxyvinyl)tri(n-butyl)tin **(10)** (650 μl, 1.95 mmol) was added dropwise. The mixture was

then refluxed for 8 h at 120 °C. The solvent was evaporated *in vacuo* and the residue was dissolved in H_2O (10 ml) and extracted with chloroform (3 x 10 ml). The collected organic layers were dried with $MgSO_4$ and evaporated. Column chromatography (silica gel (30 g), ethyl acetate) of the residue afforded the ethoxyvinylpurine derivative **13a** as yellow oil, that slowly darkened. Yield 350 mg (73 %); R_F(A) 0.53. FABMS, *m/z* (rel.%): 413 (100) $[M+H]^+$. ^{1}H NMR (200 MHz, $CDCl_3$): 1.07 and 1.13 (2 x d, 2 x 6 H, J(CH_3,CH)= 6.3, C**H**$_3$CH); 1.38 (t, 3 H, J(CH_3,CH_2)= 7.0, C**H**$_3$CH$_2$); 3.78 (d, 2 H, J(P,CH_2)= 8.2, P**C**H$_2$); 3.95 (t, 2 H, J(2',1')= 5.0, 2'-CH_2); 3.98 (q, 2 H, J(CH_2,CH_3)= 7.0, C**H**$_2$CH$_3$); 4.35-4.55 (m, 4 H, 1'-CH_2 and POCH); 4.96 (d, 1 H, J_{gem}= 2.4, CH_2=); 6.10 (d, 1 H, J_{gem}= 2.4, CH_2=); 8.56 and 8.90 (2 x s, 2 x 1 H, H-2 and H-8). Due to the unstability of this compound it was immediately deprotected: A solution of compound **13a** (350 mg, 0.85 mmol) in a mixture of DMF (2 ml), H_2O (2 ml) and 35% aq. HCl (0.2 ml) was heated at 100 °C for 1 h. After cooling to room temperature the solvents were evaporated, the residue was dissolved in H_2O (10 ml) and neutralized with 1M NaOH (pH 7) and extracted with chloroform (3 x 10 ml). The residue after evaporation of the combined organic layers was chromatographed on a column of silica gel (20 g, ethyl acetate) to afford the acetylpurine derivative **14a** as yellow oil, that slowly darkened. Yield 240 mg (74 %; 54 % overall from **12a**); R_F(A) 0.40. FABMS, *m/z* (rel.%): 407 (100) $[M+Na]^+$, 385 (92) $[M+H]^+$. Exact mass (HREIMS); found: 384.1549, $C_{16}H_{25}N_4O_5P$ requires: 384.1535. ^{1}H NMR ($(CD_3)_2SO$): 1.07 and 1.13 (2 x d, 2 x 6 H, J(CH_3,CH)= 6.1, C**H**$_3$CH); 2.80 (s, 3 H, 2"-CH_3); 3.78 (d, 2 H, J(P,CH_2)= 8.3, P**C**H$_2$); 3.96 (t, 2 H, J(2',1')= 5.0, 2'-CH_2); 4.53 (t, 2 H, J(1',2')= 5.0, 1'-CH_2); 4.44 (dsept, 2 H, J(CH,CH_3)= 6.1, J(P,OCH)= 7.6, POCH); 8.74 and 9.08 (2 x s, 2 x 1 H, H-2 and H-8). Due to its unstability this compound was characterized as its 2,4-dinitrophenylhydrazone; yellow amorphous solid, m.p. 130-134 °C (dec.) (EtOH / H_2O). Anal.: Calcd. for $C_{22}H_{29}N_8O_8P$ (564.5): C, 46.81; H, 5.18; N, 19.85; P, 5.45. Found: C, 47.09; H, 5.09; N, 19.90; P, 5.47.

Reductive Amination of the Acetylpurine 14a Followed by Cleavage of Phosphonate Ester Functions - General Procedure.

A mixture of the 6-acetylpurine **14a** (0.75 mmol), ammonium chloride **15** (7.5 mmol), $NaBH_3CN$ (47 mg, 0.75 mmol) and methanol (10 ml) was stirred at room temperature for 72 h. The solvent was then evaporated, the residue was dissolved in water (10 ml) and 1M aq. NaOH (1 ml) was added. The solution was extracted with $CHCl_3$ (3 x 10 ml), the collected organic layers were dried with $MgSO_4$, the solvent was evaporated and the oily residue was dried for 1 h at 25 °C/100 Pa. The residue was dissolved in acetonitrile (10 ml) and TMSBr (4 ml, 30.4 mmol) was added. The solution was stirred for 4 h at 80 °C and then allowed to stand overnight at r.t. After evaporation of the solvents the residue was dissolved in water (10 ml) and Et_3N (1 ml) was added. The solution was washed with ether (10 ml) and the aq. layer was applied to a column of Dowex 1 X 2 (acetate form). The column was washed with water and the products were eluted with 0.01 M acetic acid. After evaporation of the appropriate fractions and codistillation with water (20 ml) the pure compounds **16** were obtained as amorphous solids.

6-(1-Aminoethyl)-9-[2-(phosphonomethoxy)ethyl]purine (16a); yield 31 %; E_{Up} 0.73; R_F(C) 0.14. FABMS, *m/z* (rel.%): 302 (45) $[M+H]^+$. ^{1}H NMR (D_2O): 1.79 (d, 3 H, J(CH_3,CH)= 7.1, 2"-CH_3); 3.62 (d, 2 H, J(P,CH_2)= 8.8, PCH_2); 4.02 (t, 2 H, J(2',1')= 5.0, 2'-CH_2); 4.59 (t, 2 H, J(1',2')= 5.0, 1'-CH_2); 5.24 (q, 1 H, J(CH,CH_3)= 7.1, 1"-CH); 8.63 and 8.96 (2 x s, 2 x 1 H, H-2 and H-8). ^{13}C NMR (D_2O): 17.84 (C-2"); 43.31 (C-1'); 47.24 (C-1"); 66.60 (d, J= 156.3, P-CH_2); 69.85 (d, J= 10.7, C-2'); 129.48 (C-5); 147.66 (C-8); 151.01 (C-4); 151.39 (C-2); 154.97 (C-6). UV; pH 7 and pH 2: λ_{max} 265 nm (ε 9400), pH 12: λ_{max} 263 nm (ε 9200). Anal.: Calcd. for $C_{10}H_{16}N_5O_4P$. 3.5 H_2O (364.3): C, 32.97; H, 6.36; N, 19.22. Found: C, 33.14; H, 5.89; N, 19.17.

6-[1-(Methylamino)ethyl]-9-[2-(phosphonomethoxy)ethyl]purine (16b); yield 21%, amorph. glass; E_{Up} 0.67; R_F(C) 0.19. FABMS, *m/z* (rel.%): 316 (100) $[M+H]^+$. ^{1}H NMR (D_2O): 1.77 (d, 3 H, J(CH_3,CH)= 6.8, 2"-CH_3); 2.79 (s, 3 H, NCH_3); 3.62 (d, 2 H, J(P,CH_2)= 8.6, PCH_2); 4.01 (t, 2 H, J(2',1')= 5.0, 2'-CH_2); 4.59 (t, 2 H, J(1',2')= 5.0, 1'-CH_2); 5.10 (q, 1 H, J(CH,CH_3)= 6.8, 1"-CH); 8.65 and 8.98 (2 x s, 2 x 1 H, H-2 and H-8). ^{13}C NMR (D_2O): 16.52 (C-2"); 30.80 (NCH_3); 43.32 (C-1'); 54.87 (C-1"); 66.57 (d, J= 156.3, P-CH_2); 69.83 (d, J= 11.7, C-2'); 130.13 (C-5); 147.96 (C-8); 151.19 (C-4); 151.57 (C-2); 153.68 (C-6). UV; pH 7 and pH 2: λ_{max} 266 nm (ε 8200), pH 12: λ_{max} 264 (ε 8100). Anal.: Calcd. for $C_{11}H_{18}N_5O_4P$. 0.5 H_2O (324.3): C, 40.74; H, 5.91; N, 21.59. Found: C, 40.54; H, 5.75; N, 21.16.

6-[1-(Allylamino)ethyl]-9-[2-(phosphonomethoxy)ethyl]purine (16c); yield 48 %, amorph. solid. E_{Up} 0.70. R_F(C) 0.29. FABMS, *m/z* (rel.%): 342 (100) $[M+H]^+$. ^{1}H NMR (D_2O): 1.80 (d, 3 H, J(CH_3,CH)= 6.8, 2"-CH_3); 3.67 (d, 2 H, J(P,CH_2)= 8.8, PCH_2); 3.76 (m, 2 H, NCH_2); 4.05 (t, 2 H, J(2',1')= 5.0, 2'-CH_2); 4.63 (t, 2 H, J(1',2')= 5.0, 1'-CH_2); 5.22 (q, 1 H, J(CH,CH_3)= 6.8, 1"-CH); 5.47 (brd, 1 H, J_{trans}(H,H)= 17.1, =CH-H_{cis}); 5.50 (brd, 1 H, J_{cis}(H,H)= 10.3, =CH-H_{trans}); 5.97 (ddt, J= 6.8, 10.3, 17.1, -CH=); 8.69 and 9.02 (2 x s, 2 x 1 H, H-2 and H-8). ^{13}C NMR (D_2O): 17.49 (C-2"); 43.88 (C-1'); 48.28 ($NHCH_2$); 53.33 (C-1"); 67.15 (d, J= 157.2, P-CH_2); 70.38 (d, J= 11.7, C-2'); 124.31 (CH_2=); 127.31 (CH=); 130.62 (C-5); 148.51 (C-8); 151.74 (C-4); 152.16 (C-2); 154.23 (C-6). UV; pH 7 and pH 2: λ_{max} 266 nm (ε 9900), pH 12: λ_{max} 264 nm (ε 9500). Anal.: Calcd. for $C_{13}H_{20}N_5O_4P$. 0.75 H_2O (354.8): C, 44.00; H, 6.10; N, 19.73. Found: C, 44.14; H, 6.00; N, 19.81.

6-[1-(Cyclopropylamino)ethyl]-9-[2-(phosphonomethoxy)ethyl]purine (16d); yield 39 %, yellow heavy oil, that slowly darkened. It did not give satisfactory microanalysis. E_{Up} 0.76; R_F(C) 0.28. FABMS, *m/z* (rel.%): 342 (100) $[M+H]^+$. Exact mass (FAB HRMS) calcd. for $C_{13}H_{21}N_5O_4P$ $[M+H]^+$: 342.1331; found: 342.1277. ^{1}H NMR (D_2O): 0.60-0.75 (m, 4 H, CH_2-cyclopropyl); 1.69 (d, 3 H, J(CH_3,CH)= 6.8, 2"-CH_3); 2.40 (m, 1 H, CH-cyclopropyl); 3.60 (d, 2 H, J(P,CH_2)= 8.8, PCH_2); 4.04 (t, 2 H, J(2',1')= 5.0, 2'-CH_2); 4.61 (t, 2 H, J(1',2')= 5.0, 1'-CH_2); 5.01 (q, 1 H, J(CH,CH_3)= 6.8, 1"-CH); 8.70 and 8.97 (2 x s, 2 x 1 H, H-2 and H-8). ^{13}C NMR (D_2O): 3.91 and 4.28 (CH_2-cyclopropyl); 18.32 (C-2"); 28.61 (CH-cyclopropyl); 43.87 (C-1'); 58.68 (C-1"); 68.08 (d, J= 154.3, P-CH_2); 70.22 (d, J= 11.7, C-2'); 130.97 (C-5); 148.27 (C-8); 151.47 (C-4); 152.04 (C-2); 158.36 (C-6). UV; pH 7: λ_{max} 265 nm, pH 2: λ_{max} 266 nm, pH 12: λ_{max} 264 nm.

6-[1-(Cyclohexylamino)ethyl]-9-[2-(phosphonomethoxy)ethyl]purine (16e); yield 28%, amorph. glass; E_{Up} 0.61; R_F(C) 0.33. FABMS, *m/z* (rel.%): 384 (100) $[M+H]^+$. ^{1}H NMR (D_2O): 1.10-1.30 (m, 3 H), 1.43 (m, 2 H) and 1.62 (m, 1 H, all H-cyclohexyl); 1.75 (d, 3 H, J(CH_3,CH)= 6.8, 2"-CH_3); 1.82 (m, 2 H), 2.15 (m, 2 H) and 3.11 (m, 1 H, all H-cyclohexyl); 3.65 (d, 2 H, J(P,CH_2)= 8.8, PCH_2); 4.03 (t, 2 H, J(2',1')= 4.5, 2'-CH_2); 4.61 (t, 2 H, J(1',2')= 4.5, 1'-CH_2); 5.33 (q, 1 H, J(CH,CH_3)= 6.8, 1"-CH); 8.66 and 9.00 (2 x s, 2 x 1 H, H-2 and H-8). ^{13}C NMR (D_2O): 17.33 (C-2"); 23.48, 23.56, 24.00, 28.25 and 28.99 (all C-cyclohexyl); 43.33 (C-1'); 50.10 (NCH<); 55.45 (C-1"); 66.57 (d, J= 157.2, P-CH_2); 69.84 (d, J= 11.7, C-2'); 129.97 (C-5); 147.94 (C-8); 151.21 (C-4); 151.57 (C-2); 153.89 (C-6). UV; pH 7 and pH 2: λ_{max} 266 nm (ε 8000), pH 12: λ_{max} 264 nm (ε 8000). Anal.: Calcd. for $C_{16}H_{26}N_5O_4P$. H_2O (401.4): C, 47.87; H, 7.03; N, 17.45. Found: C, 48.25; H, 6.98; N, 17.35.

6-[1-(Dimethylamino)ethyl]-9-[2-(phosphonomethoxy)ethyl]purine (16f); yield 28%, amorph. glass; E_{Up} 0.70; R_F(C) 0.22. FABMS, *m/z* (rel.%): 330 (100) $[M+H]^+$. ^{1}H NMR (D_2O): 1.84 (d, 3 H, J(CH_3,CH)= 6.8, 2"-CH_3); 2.99 (brs, 6 H, 2 x NCH_3); 3.64 (d, 2 H, J(P,CH_2)= 8.8, PCH_2); 4.03 (t, 2 H, J(2',1')= 5.0, 2'-CH_2); 4.62 (t, 2 H, J(1',2')= 5.0, 1'-CH_2); 5.20 (q, 1 H, J(CH,CH_3)= 6.8, 1"-CH); 8.68 and 9.02 (2 x s, 2 x 1 H, H-2 and H-8). ^{13}C NMR (D_2O): 14.82 (C-2"); 41.00 (br, 2 C, NCH_3); 43.35 (C-1'); 61.41 (C-1"); 66.57 (d, J= 157.2, P-CH_2); 69.80 (d, J= 11.7, C-2'); 130.84 (C-5); 148.36 (C-8); 151.60 (C-4); 151.61 (C-2); 152.54 (C-6). UV; pH 7 and pH 2: λ_{max} 267 nm (ε 7700), pH 12: λ_{max} 266 nm (ε 7800). Anal.: Calcd. for $C_{12}H_{20}N_5O_4P$. 0.5 H_2O (338.3): C, 42.60; H, 6.25; N, 20.70. Found: C, 42.66; H, 6.28; N, 20.38.

9-[2-(Phosphonomethoxy)ethyl]-6-[1-(pyrrolidin-1-yl)ethyl]purine (16g); yield 37 %, amorph. solid; E_{Up} 0.55; R_F(C) 0.25. FABMS, *m/z* (rel.%): 356 (100) $[M+H]^+$. ^{1}H NMR (D_2O): 1.81 (d, 3 H, J(CH_3,CH)= 6.8, 2"-CH_3); 2.10 (m, 4 H, CCH_2CH_2C); 3.03 (m, 1 H) and 3.48 (m, 2 H, $N(CH_2)_2$); 3.65 (d, 2 H, J(P,CH_2)= 8.8, PCH_2); 3.92 (m, 1 H, $N(CH_2)_2$); 4.03 (t, 2 H, J(2',1')= 4.5, 2'-CH_2); 4.61 (t, 2 H, J(1',2')= 4.5, 1'-CH_2); 5.18 (q, 1 H, J(CH,CH_3)= 6.8, 1"-CH); 8.68 and 9.01 (2 x s, 2 x 1 H, H-2 and H-8). ^{13}C NMR (D_2O): 17.00 (C-2"); 22.43 (2 C, CCH_2CH_2C); 43.34 (C-1'); 53.56 and 53.59 ($N(CH_2)_2$); 60.52 (C-1"); 66.58 (d, J= 156.3, P-CH_2); 69.81 (d, J= 11.7, C-2'); 130.17 (C-5); 148.24 (C-8); 151.55 (C-4); 151.74 (C-2); 153.74 (C-6). UV; pH 7 and pH 2: λ_{max} 267 nm (ε 8100), pH 12: λ_{max} 265 nm (ε 7800). Anal.: Calcd. for $C_{14}H_{22}N_5O_4P.H_2O$ (373.4): C, 45.04; H, 6.47; N, 18.75. Found: C, 45.21; H, 6.45; N, 18.31.

2-Amino-9-{2-[bis(2-propoxy)phosphonylmethoxy]ethyl}-6-(1-ethoxyvinyl)purine (13b).

To a stirred solution of compound **12b**[18] (600 mg, 1.53 mmol) and $Pd(PPh_3)_4$ (90 mg, 0.08 mmol) in DMF (5 ml) under Ar atmosphere the stannane **10** was added dropwise and the solution was stired at 120 °C for 7 h. The solvent was evaporated, water (20 ml) was added to the residue and the mixture was extracted with chloroform (3 x 20 ml). The collected organic layers were dried and taken down *in vacuo*. Column chromatography of the residue furnished compound **13b** as yellow amorph. solid. Yield 400 mg (61 %); R_F(A) 0.41. Exact mass (EIHRMS) calcd. for $C_{18}H_{30}N_5O_5P$: 427.1986; found: 427.1966. FABMS, *m/z* (rel.%): 428 (100) $[M+H]^+$. ^{1}H NMR (200 MHz, $(CD_3)_2SO$): 1.12 and 1.17 (2 x d, 2 x 6 H, J(CH_3,CH)= 6.1, C**H**$_3$CH); 1.33 (t, 3 H,

J(CH_3,CH_2)= 7.1, C**H**$_3$C**H**$_2$); 3.77 (d, 2 H, J(P,CH_2)= 8.2, PCH_2); 3.86 (t, 2 H, J(2',1')= 5.0, 2'-CH_2); 3.91 (q, 2 H, J(CH_2,CH_3)= 7.1, C**H**$_2$C**H**$_3$); 4.23 (t, 2 H, J(1',2')= 5.0, 1'-CH_2); 4.48 (dsept, 2 H, J(CH,CH_3)= 6.1, J(P,OCH)= 7.3, POCH); 4.82 (brd, 1 H, J_{gem}= 1.8, CH_2=); 5.91 (d, 1 H, J_{gem}= 1.8, CH_2=); 6.48 (brs, 2 H, NH_2); 8.01 (s, 1 H, H-8). ^{13}C NMR ($(CD_3)_2SO$): 14.51 (**C**H$_3$CH$_2$); 23.75 and 23.89 (2 x d, 2 x 2 C, J= 3.9, **C**H$_3$CH); 42.22 (C-1'); 62.95 (**C**H$_2$CH$_3$); 64.76 (d, J= 164.1, PCH_2); 70.21 (d, J= 11.7, C-2'); 70.34 (d, 2 C, J= 5.9, POCH); 93.46 (C-2"); 123.56 (C-5); 142.75 (C-8); 151.93 (C-4); 154.19 (C-6); 155.85 (C-1"); 159.96 (C-2). Anal.: Calcd. for $C_{18}H_{30}N_5O_5P$ (427.4): C, 50.58; H, 7.07; N, 16.39. Found: C, 51.06; H, 7.13; N, 16.24.

6-Acetyl-2-amino-9-{2-[bis(2-propoxy)phosphonylmethoxy]ethyl}purine (14b)

A solution of the 6-(1-ethoxyvinyl)purine derivative **13b** (660 mg, 1.55 mmol) in a mixture of acetone (20 ml), water (10 ml) and 35% HCl (1 ml) was stirred at 100 °C for 1.5 h, after cooling to r.t. Et_3N (2 ml) was added and the solution was taken down in vacuo. Column chromatography (silica gel, 30 g, ethyl acetate) of the residue afforded compound **14b** as oil which solidified after drying. Yield 400 mg (65 %); yellow amorph. solid; R_F(B) 0.33. FABMS, *m/z* (rel. %): 401 (100) $[M+2H]^+$, 400 (68) $[M+H]^+$. ^{1}H NMR (200 MHz, $(CD_3)_2SO$): 1.12 and 1.16 (2 x d, 2 x 6 H, J(CH_3,CH)= 6.1, C**H**$_3$CH); 2.70 (s, 3 H, 2"-CH_3); 3.77 (d, 2 H, J(P,CH_2)= 8.3, PCH_2); 3.88 (t, 2 H, J(2',1')= 5.0, 2'-CH_2); 4.27 (t, 2 H, J(1',2')= 5.0, 1'-CH_2); 4.48 (dsept, 2 H, J(CH,CH_3)= 6.1, J(P,OCH)= 7.6, POCH); 6.76 (brs, 2 H, NH_2); 8.17 (s, 1 H, H-8). ^{13}C NMR (500 MHz, $(CD_3)_2SO$): 23.74 and 23.88 (2 x d, 2 x 2 C, J= 3.9, **C**H$_3$CH); 28.89 (C-2"); 42.39 (C-1'); 64.75 (d, J= 164.1, PCH_2); 70.11 (d, J= 10.7, C-2'); 70.33 (d, 2 C, J= 6.8, POCH); 124.15 (C-5); 145.14 (C-8); 150.53 (C-4); 156.27 (C-6); 160.23 (C-2); 198.72 (C-1"). Anal.: Calcd. for $C_{16}H_{26}N_5O_5P$ (399.4): C, 48.11; H, 6.56; N, 17.54. Found: C, 48.17; H, 6.59; N, 17.40.

Reductive Amination of the 6-Acetyl-2-aminopurine 14b Followed by Cleavage of the Phosphonate Ester Protecting Functions - General Procedure.

The reductive amination of compound **14b** (350 mg, 0.88 mmol) with $NaBH_3CN$ (60 mg, 0.97 mmol) and amine hydrochloride **15a,c** or **f** (14 mmol) in methanol (10 ml) was performed in the same manner as for **42a**; after analogous work-up the intermediates were treated with TMSBr (7 ml, 53 mmol) in acetonitrile (10 ml) in the same manner as described above. Anion exchange chromatography afforded the 6-(aminoethyl)purine derivatives **17** on elution with 0.01 M aq. acetic acid.

2-Amino-6-(1-aminoethyl)-9-[2-(phosphonomethoxy)ethyl]purine (17a); yield 11 %; amorph. glass; R_F(C) 0.13; E_{Up} 0.59. FABMS, *m/z* (rel.%): 317 (38) $[M+H]^+$. ^{1}H NMR (D_2O): 1.72 (d, 3 H, J(CH_3,CH)= 6.8, 2"-CH_3); 3.62 (d, 2 H, J(P,CH_2)= 8.8, PCH_2); 3.96 (t, 2 H, J(2',1')= 4.9, 2'-CH_2); 4.38 (t, 2 H, J(1',2')= 4.9, 1'-CH_2); 5.02 (q, 1 H, J(CH,CH_3)= 6.8, 1"-CH); 8.22 (s, 1 H, H-8). ^{13}C NMR (D_2O): 18.33 (C-2"); 43.24 (C-1'); 47.56 (C-1"); 67.23 (d, J= 156.3, P-CH_2); 70.52 (d, J= 10.7, C-2'); 123.46 (C-5); 145.02 (C-8); 153.52 (C-4); 156.96 (C-6); 160.06 (C-2). UV; pH 7: λ_{max} 307 nm (ε 6500), λ_{max} 244 nm (ε 3800); pH 2: λ_{max} 313 nm (ε 5700), λ_{max}

240 nm sh (ε 3800); pH 12: λ_{max} 303 nm (ε 6600), λ_{max} 243 nm (ε 4200). Anal.: Calcd. for $C_{10}H_{17}N_6O_4P$. 0.75 H_2O (329.8): C, 36.42; H, 5.65; N, 25.48. Found: C, 36.51; H, 5.64; N, 25.07.

6-[1-(Allylamino)ethyl]-2-amino-9-[2-(phosphonomethoxy)ethyl]purine (17c); yield 42 %; amorph. solid; R_F(C) 0.24; E_{Up} 0.61. FABMS, *m/z* (rel.%): 357 (100) $[M+H]^+$. ^{1}H NMR (D_2O): 1.73 (d, 3 H, J(CH_3,CH)= 6.8, 2"-CH_3); 3.66 (d, 2 H, J(P,CH_2)= 8.6, PCH_2); 3.73 (d, 2 H, J(CH_2,CH)= 6.8, NCH_2); 3.98 (t, 2 H, J(2',1')= 4.9, 2'-CH_2); 4.40 (t, 2 H, J(1',2')= 4.9, 1'-CH_2); 4.97 (q, 1 H, J(CH,CH_3)= 6.8, 1"-CH); 5.47 (brd, 1 H, J_{trans}(H,H)= 17.1, =CH-H_{cis}); 5.50 (brd, 1 H, J_{cis}(H,H)= 10.3, =CH-H_{trans}); 5.96 (ddt, J= 6.8, 10.3, 17.1,-CH=); 8.24 (s, 1 H, H-8). ^{13}C NMR (D_2O): 17.43 (C-2"); 43.21 (C-1'); 48.21 (NHCH_2); 53.09 (C-1"); 67.18 (d, J= 156.3, P-CH_2); 70.48 (d, J= 11.7, C-2'); 124.05 (C-5); 124.21 (CH_2=); 127.41 (CH=); 145.28 (C-8); 153.72 (C-4); 155.56 (C-6); 160.20 (C-2). UV; pH 7: λ_{max} 309 nm (ε 6600), λ_{max} 243 nm (ε 4000); pH 2: λ_{max} 316 nm (ε 6100), λ_{max} 241 nm sh (ε 4900); pH 12: λ_{max} 304 nm (ε 6700), λ_{max} 243 nm (ε 4200). Anal.: Calcd. for $C_{13}H_{21}N_6O_4P$. 0.5 H_2O (365.3): C, 42.73; H, 6.07; N, 23.01. Found: C, 42.79; H, 6.15; N, 22.61.

2-Amino-6-[1-(dimethylamino)ethyl]-9-[2-(phosphonomethoxy)ethyl]purine (17f); yield 36 %; amorph. glass; R_F(C) 0.20; E_{Up} 0.55. FABMS, *m/z* (rel.%): 345 (26) $[M+H]^+$. ^{1}H NMR (D_2O): 1.76 (d, 3 H, J(CH_3,CH)= 6.8, 2"-CH_3); 2.98 (brs, 6 H, 2 x NCH_3); 3.63 (d, 2 H, J(P,CH_2)= 8.6, PCH_2); 3.97 (t, 2 H, J(2',1')= 5.0, 2'-CH_2); 4.40 (t, 2 H, J(1',2')= 5.0, 1'-CH_2); 4.93 (q, 1 H, J(CH,CH_3)= 6.8, 1"-CH); 8.26 (s, 1 H, H-8). ^{13}C NMR (D_2O): 15.58 (C-2"); 41.60 (2 C, NCH_3); 43.24 (C-1'); 62.01 (C-1"); 67.29 (d, J= 157.2, P-CH_2); 70.45 (d, J= 10.7, C-2'); 124.62 (C-5); 145.69 (C-8); 154.11 (C-4); 154.80 (C-6); 160.26 (C-2). UV; pH 7: λ_{max} 311 nm (ε 6400), λ_{max} 243 nm (ε 3800); pH 2: λ_{max} 320 nm (ε 5900), λ_{max} 240 nm sh (ε 4500); pH 12: λ_{max} 306 nm (ε 6800), λ_{max} 242 nm sh (ε 4200). Anal.: Calcd. for $C_{12}H_{21}N_6O_4P$. H_2O (362.3): C, 39.78; H, 6.40; N, 23.20. Found: C, 40.18; H, 6.57; N, 23.02.

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