SYNTHESIS OF N^9- AND N^7-[2-HYDROXY-3-(PHOSPHONOMETHOXY)-PROPYL] DERIVATIVES OF N^6-SUBSTITUTED ADENINES, 2,6-DIAMINOPURINES AND RELATED COMPOUNDS

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Dedicated with due respect to Professor Miloslav Černý on the occasion of his 75th birthday in recognition of his outstanding contributions to carbohydrate chemistry.

Base-catalyzed reactions of diethyl [(oxiranylmethoxy)methyl]phosphonate (**2**) with purine bases (adenine, 2,6-diaminopurine, 6-chloropurine and 2-amino-6-chloropurine) gave corresponding 9- or 7-[2-hydroxy-3-(phosphonomethoxy)propyl] purines. The adenine and 2,6-diaminopurine derivatives cyclize to cyclic phosphonates **4** and **6**. The 9-[2-hydroxy-3-(phosphonomethoxy)propyl] derivatives of N^6-substituted adenine and 2,6-diaminopurine (**15**–**27**) were prepared by the treatment of diethyl {[3-(6-chloropurin-9-yl)-2-hydroxypropoxy]methyl}phosphonate (**11**) or diethyl {[3-(2-amino-6-chloropurin-9-yl)-2-hydroxypropoxy]methyl}phosphonate (**13**) with primary or secondary amines. The reaction of 6-chloro- or 2-amino-6-chloropurine derivatives (**11**, **13**) with thiourea gave the corresponding diethyl purine-6-thiol or 2-aminopurine-6-thiol phosphonates **47**, **48**. The guanine derivative **49** was prepared by the treatment of compound **13** with 80% acetic acid. All diethyl phosphonates were transformed to free phosphonic acids (**31**–**43**, **50**–**52**) by the action of bromotrimethylsilane and subsequent hydrolysis.

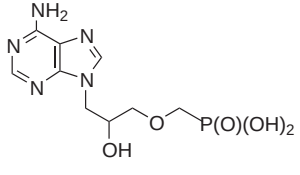
Keywords: Acyclic nucleotide analogues; Phosphonates; Purines; Oxirane ring opening; Epoxides; Nucleotides; Nucleosides; Antivirals; HPMPA.

In the course of systematic studies of various types of acyclic nucleotide analogues we paid considerable attention to a group of the so-called HPMP derivatives, i.e. (*S*)-9-[3-hydroxy-2-(phosphonomethoxy)propyl] derivatives of purine and pyrimidine bases[1]. Some of these compounds exhibit significant antiviral activity, in particular the adenine and diaminopurine derivatives (HPMPA, HPMPDAP)[1,2], their guanine counterpart HPMPG [3] and the cytosine derivative HPMPC (cidofovir[4]), an active constituent of Vistide™, the

drug used for the treatment of CMV retinitis in AIDS patients and papillomatosis caused by HPV and other viral diseases[5].

Several approaches to the preparation of HPMP derivatives have been elaborated, most of them using attachment of the phosphonomethoxy group to the 3′-protected 9-(2,3-dihydroxypropyl) derivatives by the action of a [(tosyloxy)methyl]phosphonic acid diester in the presence of alkali[6–8]. The starting *N*-(2,3-dihydroxypropyl) derivatives are easily accessible either by reaction of an appropriate nucleobase with (*R*)-glycidol butyrate (in the case of *R* enantiomers), or by reaction of a nucleobase with (*R*)-2,2-dimethyl-4-[(tosyloxy)methyl]-1,3-dioxolane (in the case of *S* enantiomers). Both types of reactions are catalyzed by cesium carbonate[4].

In spite of numerous studies dealing with HPMP derivatives, there is only a limited knowledge about their structural isomers bearing a phosphonomethyl ether group at the 3′-position, i.e. 9-[2-hydroxy-3-(phosphonomethoxy)propyl] derivatives of nucleobases. Several years ago, we described a first representative of this group, 9-[2-hydroxy-3-(phosphonomethoxy)propyl]adenine[8] (**1**). Unfortunately, it proved to be biologically inactive[1a]. Later, we also described mixtures of 2-hydroxy-3-(phosphonomethoxy)propyl and 3-hydroxy-2-(phosphonomethoxy)propyl analogues derived from cytosine and 5-methylcytosine, as well as their deaminated products uracil and thymine[9]. The formation of such compounds was observed in the course of studies of esterification reactions of 9-(2,3-dihydroxypropyl)purine derivatives, e.g. 9-(2,3-dihydroxypropyl)adenine (DHPA) with (chloromethyl)phosphonic acid derivatives[8–10]. Such reactions afford always a mixture of 2′- and 3′-(chloromethyl)phosphonates, which undergo intramolecular cyclization in aqueous alkali to corresponding cyclic phosphonates and subsequent ring opening to give a mixture of both nucleotide analogues: HPMPA from 3′-(chloromethyl)phosphonate and 3′-phosphonomethoxy derivative **1** from 2′-(chloromethyl)phosphonate. Both free acids (HPMPA and **1**) are separable only by HPLC technique, so this method is useful only for micro and semimicro scale. In some cases the difference in HPLC mobilities of 2′- and 3′-phosphonates is so small that their separation is impossible[9].



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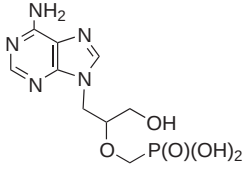
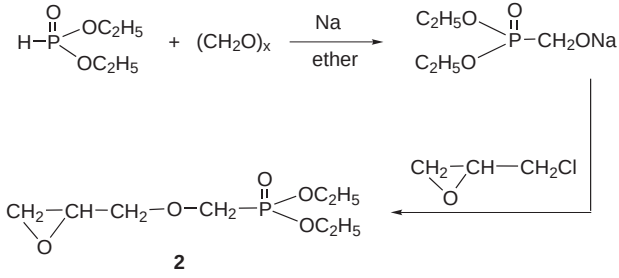


HPMPA

In order to verify the general validity of the rule according to which the biological activity is associated with the 2′-phosphonomethyl isomers only, we have performed the present study; its aim is the elaboration of preparative synthesis of a large group of racemic 9-[2-hydroxy-3-(phosphonomethoxy)propyl] derivatives of various purine bases: 2,6-diaminopurine, guanine, 2-amino-6-chloropurine, N^6-(alkylamino)purines, 2-amino-N^6-(alkylamino)purines, purine-6-thiol and 2-aminopurine-6-thiol. Special care is paid to N^6-substituted adenine and 2,6-diaminopurine derivatives with respect to the fact that the N^6-substitution can considerably increase antiviral and cytostatic activity of some acyclic nucleoside phosphonates. This effect is most evident with 2,6-diamino-9-[2-(phosphonomethoxy)ethyl]-purine (PMEDAP), where the *N*-substitution of 6-amino group leads to numerous compounds with a high cytostatic and antiviral activity[11]. The best results were obtained with 2,2,2-trifluoroethyl, allyl, 2-(dimethylamino)-ethyl, cyclopropyl and dimethyl N^6-derivatives.

Our syntheses of 2-hydroxy-3-(phosphonomethoxy)propyl derivatives are based on the oxirane ring opening of racemic diethyl [(oxiranylmethoxy)-methyl]phosphonate (**2**) with nucleobases. The synthon **2** was prepared according to a literature procedure[12] starting from epichlorohydrin and a sodium salt of diethyl (hydroxymethyl)phosphonate, accessible by the Arbuzov reaction of diethyl phosphite and paraformaldehyde[13] (Scheme 1).

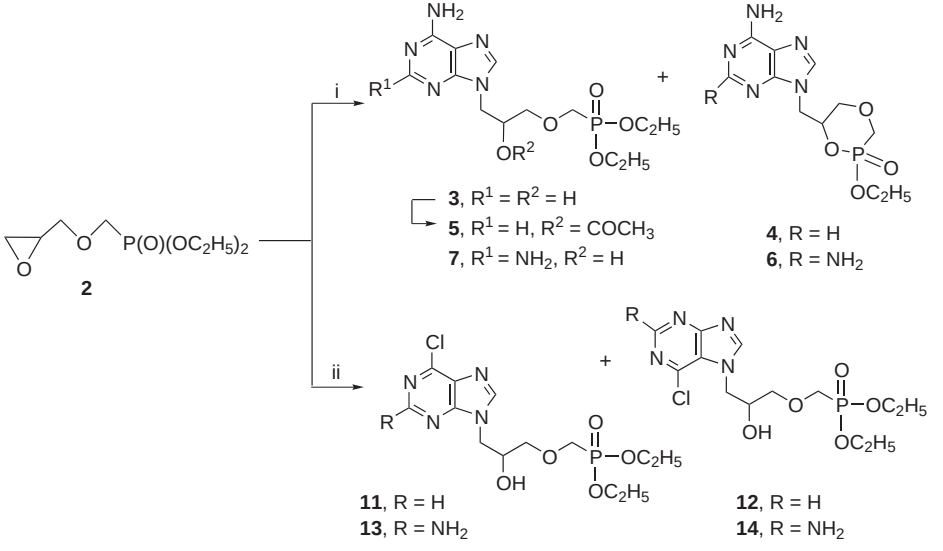


SCHEME 1

Reactivity of diethyl [(oxiranylmethoxy)methyl]phosphonate (**2**) towards various nucleobases was studied. The reaction was carried out with adenine, 2,6-diaminopurine, 6-chloropurine and 2-amino-6-chloropurine under standard conditions: DMF as a solvent, temperature 120 °C and cesium carbonate as a base catalyst. As expected, the nucleophilic opening of oxirane ring in **2** took place always at the terminal C-3 position giving regiospecifically 9-[2-hydroxy-3-(phosphonomethoxy)propyl] derivatives. Some of these compounds underwent an intramolecular nucleophilic attack of

2-hydroxy group at the phosphorus atom forming six-membered cyclic phosphonates. Such situation occurs especially when the reaction is carried out with adenine and 2,6-diaminopurine.

Thus, the reaction of oxirane **2** with adenine afforded a mixture of diethyl ester of 9-[2-hydroxy-3-(phosphonomethoxy)propyl]adenine (**3**) and the cyclization product **4** in the ratio of 1:1. The cyclic phosphonate **4** was an equimolar mixture of two chromatographically easily separable diastereoisomers (**4a** and **4b**); both of them were fully characterized. On the other hand, the chromatographic mobilities of the uncyclized compound **3** and cyclic phosphonate **4a** are practically the same and their separation was possible only by acetylation of the mixture transforming compound **3** to the faster moving acetate **5** (Scheme 2).

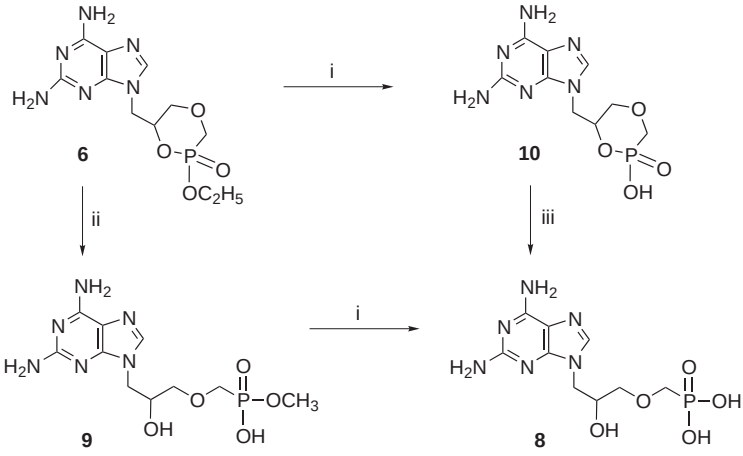


(i) adenine or 2,6-diaminopurine; (ii) 6-chloropurine or 2-amino-6-chloropurine in both cases: DMF, 110 °C, Cs_2CO_3, 2 h

SCHEME 2

With 2,6-diaminopurine, oxirane **2** affords the cyclic phosphonate **6** practically as a single reaction product. Compound **7** was present only in trace amounts. In order to prepare the required 9-[2-hydroxy-3-(phosphonomethoxy)propyl]purine-2,6-diamine (**8**), cyclic phosphonate **6** was utilized. It was treated first with sodium methoxide to give 9-{2-hydroxy-3-[(hydroxymethoxyphosphoryl)methoxy]propyl}purine-2,6-diamine (**9**). Removal of the methyl ester group in **9** with bromotrimethylsilane gave

free acid **8** as final product. Another method for the preparation of **8** consists in transformation of cyclic phosphonate **6** to free cyclic phosphonic acid **10** and its treatment with aqueous sodium hydroxide (Scheme 3). However, this method is not so advantageous as the above mentioned procedure because of partial deamination of the product.

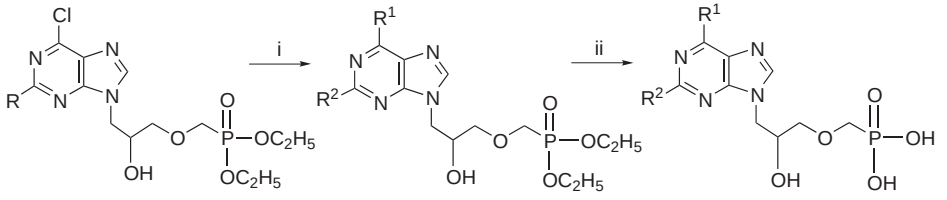


(i) $(CH_3)_3SiBr$, CH_3CN, r.t.; (ii) CH_3ONa/CH_3OH, reflux; (iii) 1 M NaOH, 80 °C, 3 h

SCHEME 3

The treatment of diethyl [(oxiranylmethoxy)methyl]phosphonate (**2**) with 6-chloropurine gave a mixture of N^9- and N^7-alkylated products: 6-chloro-9-{2-hydroxy-3-[(diethoxyphosphoryl)methoxy]propyl}purine (**11**) and 6-chloro-7-{2-hydroxy-3-[(diethoxyphosphoryl)methoxy]propyl}purine (**12**) in the ratio 3:1. Both isomers can be separated chromatographically. In this case, no formation of cyclic phosphonate was observed. Similarly, no cyclization product was formed in the treatment of oxirane **2** with 2-amino-6-chloropurine; also in this case only the N^9- and N^7-alkylated products **13** and **14** were isolated (in the ratio 7:2). It can be speculated that in both cases the electron-withdrawing effect of chlorine in the purine moiety decreases the nucleophilic character of 2-hydroxy group and makes its attack on phosphorus difficult.

9-[2-Hydroxy-3-(phosphonomethoxy)propyl] derivatives of N^6-substituted adenine and 2,6-diaminopurine derivatives were synthesized by the reaction of primary or secondary amines with 6-chloropurine derivative **11** or 2-amino-6-chloropurine derivative **13** (Table I, Scheme 4). The reaction was performed in boiling acetonitrile under exclusion of CO_2, except for



11, R = H
13, R = NH_2

15-27

31-43

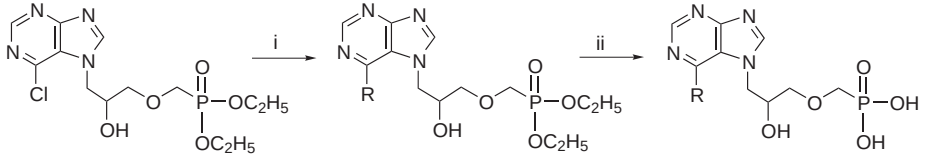
(i) primary and secondary amines or dimethylammonium *N,N*-dimethylcarbamate, CH_3CN, reflux;
(ii) $(CH_3)_3SiBr$, CH_3CN, r.t.

SCHEME 4

TABLE I
Transformation of 6-chloro- and 2-amino-6-chloropurine derivatives of N^9-[2-hydroxy-3-(phosphonomethoxy)propyl] series (**11**, **13**) to corresponding N^6-substituted analogues

Starting compound	Phosphonate ester	R^1	R^2	Yield of ester, %	Phosphonic acid	Yield of phosphonic acid, %
11	**15**	$-N(CH_3)_2$	H	88	**31**	77
11	**16**		H	98	**32**	77
11	**17**		H	58	**33**	42
11	**18**	$-NHCH_2CH_2OCH_3$	H	91	**34**	76
11	**19**	$-NHCH_2CH_2OH$	H	86	**35**	72
11	**20**	$-NHCH_2CH{=}CH_2$	H	96	**36**	52
11	**21**	$(CH_3)_2NCH_2CH_2NH-$	H	87	**37**	65
11	**22**	$-NHCH_2CF_3$	H	57	**38**	74
13	**23**	$-N(CH_3)_2$	NH_2	95	**39**	77
13	**24**		NH_2	95	**40**	52
13	**25**	$-NHCH_2CF_3$	NH_2	93	**41**	62
13	**26**	$-NHCH_2CH{=}CH_2$	NH_2	94	**42**	52
13	**27**	$(CH_3)_2NCH_2CH_2NH-$	NH_2	97	**43**	69

2,2,2-trifluoroethylamine, where it was performed in an autoclave, and for dimethylamine which was replaced by dimethylammonium *N*,*N*-dimethylcarbamate. The thus obtained intermediate diethyl phosphonates **15**–**27** were purified by column chromatography on silica gel with the exeption of compounds with a low chromatographic mobility, i.e. N^6-[2-(dimethylamino)ethyl] derivatives **21** and **27**, which were desalted by ion exchange chromatography. Analogously, we prepared also some N^6-substituted adenine derivatives of the 7-[2-hydroxy-3-(phosphonomethoxy)propyl] series (**28**–**30**) by the treatment of 6-chloropurine derivative **12** with various amines under the above described conditions (Table II, Scheme 5). All diethyl phosphonates were subsequently converted to free phosphonic acids by the action of bromotrimethylsilane in acetonitrile followed by deionization and ion exchange chromatography on Dowex 50 resin. Thus, we obtained a series of free 2-hydroxy-3-(phosphonomethoxy)propyl derivatives of N^6-substituted adenine and diaminopurine **31**–**43** and **44**–**46** as final products.



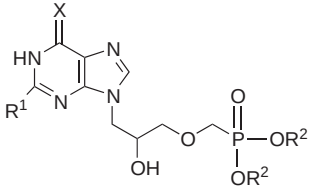
(i) amines or dimethylammonium *N*,*N*-dimethylcarbamate, CH_3CN, reflux; (ii) $(CH_3)_3SiBr$, CH_3CN, r.t.

SCHEME 5

TABLE II
Preparation of some N^6-substituted adenine derivatives of N^7-[2-hydroxy-3-(phosphonomethoxy)propyl] series from compound **12**

Phosphonate ester	R	Yield of ester, %	Phosphonic acid	Yield of phosphonic acid, %
28	$-N(CH_3)_2$	63	**44**	55
29		65	**45**	49
30	$-NHCH_2CH{=}CH_2$	87	**46**	53

Another transformation of chlorine atom in position 6 of purine consists in its conversion to thiol group. Thus, the treatment of diethyl phosphonates **11** and **13** with thiourea in ethanol afforded the corresponding thiol derivatives **47** and **48**. Transformation of chlorine atom in 2-amino-6-chloropurine compound **13** to guanine derivative **49** was performed by heating with 80% acetic acid. Also diethyl phosphonates **47**–**49** were treated with bromotrimethylsilane to give a series of free phosphonic acids **50**–**52**.



47, X = S, R^1 = H, R^2 = C_2H_5
48, X = S, R^1 = NH_2, R^2 = C_2H_5
49, X = O, R^1 = NH_2, R^2 = C_2H_5
50, X = S, R^1 = R^2 = H
51, X = S, R^1 = NH_2, R^2 = H
52, X = O, R^1 = NH_2, R^2 = H

In conclusion, we developed a novel synthetic approach leading selectively to 9- or 7-[2-hydroxy-3-(phosphonomethoxy)propyl] derivatives of purine nucleobases, the structural isomers of biologically active HPMP compounds.Using the method based on utilization of diethyl [(oxiranylmethoxy)methyl]phosphonate as an easily accessible synthon bearing a phosphonomethyl group, we have prepared a large series of racemic 9- or 7-[2-hydroxy-3-(phosphonomethoxy)propyl]purine derivatives for biological screening. All final products were tested for cytostatic activity in vitro. In contrast to N^6-substituted adenines and 2,6-diaminopurines of *N*-[2-(phosphonomethoxy)ethyl] series prepared earlier[11], no cytostatic activity was found for these compounds. The antiviral screening is under way.

EXPERIMENTAL

Unless stated otherwise, solvents were evaporated at 40 °C/2 kPa and compounds were dried at 13 Pa. Melting points were determined on a Kofler block and are uncorrected. Analytical TLC were performed on Silufol UV_{254} plates (Kavalier, Votice, Czech Republic) in systems ethyl acetate–acetone–ethanol–water (18:3:1:1, system S1; 18:3:2:2, system S2 or 15:3:4:3, system S3). Other chromatographic systems are described in text. Column chromatography was performed on silica gel 60 μm (Fluka). ^{1}H NMR spectra were measured on a Varian Unity 500 instrument (at 500 MHz) in DMSO-d_6 solutions (referenced to the solvent signal at δ 2.50) or in D_2O solutions with internal standard sodium 3-(trimethylsilyl)propane-1-sulfonic acid (DSS). ^{1}H NMR chemical shifts (δ, ppm) and coupling constants (*J*, Hz) were obtained by first-order analysis of the spectra. ^{13}C NMR spectra were recorded on the same instrument (at 125.7 MHz) using APT pulse sequence in DMSO-d_6 (referenced to the solvent

signal δ 39.70). The numbering system for assignment of NMR signals is outlined in Fig. 1. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using FAB (ionization with xenon, accelerating voltage 8 kV, glycerol matrix).

Materials and Solvents

Most of chemicals and ion-exchange resin (Dowex 50WX8-200) were purchased from Sigma–Aldrich (Czech Republic). 2,2,2-Trifluoroethylamine was a product of Fluka. Dimethylformamide and acetonitrile were dried by distillation from CaH_2 (DMF in vacuo) and stored over molecular sieves (4 Å).

Diethyl [(Oxiranylmethoxy)methyl]phosphonate (**2**)

The compound was prepared by published procedure[12] from diethyl phosphite (27.6 g, 0.2 mol). Yield 30 g (67%) of a colorless liquid, b.p. 130 °C/133 Pa. ^{1}H NMR (DMSO-d_6): 4.05 dq, 2 H and 4.03 dq, 2 H, J(CH_2,CH_3) = 7.1, J(P,OCH) = 7.6 (P-OCH_2); 3.85 d, 2 H, J(P,CH) = 8.3 (PCH_2); 3.82 dd, 1 H, J(3a,2) = 3.7, J(gem) = 11.6 (H-3a); 3.35 dd, 1 H, J(3b,2) = 6.6 (H-3b); 3.12 m, 1 H (H-2); 2.73 dd, 1 H, J(1b,2) = 4.4, J(gem) = 5.0 (H-1b); 2.55 dd, 1 H, J(1a,2) = 2.7 (H-1a); 1.24 t, 6 H (CH_3). ^{13}C NMR ((DMSO-d_6): 73.56 d, J(P,C) = 11.7 (C-3); 64.40 d, J(P,C) = 163.6 (PCH_2); 61.92 d, 2 C, J(P,C) = 6.3 (P-OCH_2); 50.12 (C-2); 43.45 (C-1); 16.98 d, 2 C, J(P,C) = 5.4 (CH_3).

Reaction of Diethyl [(Oxiranylmethoxy)methyl]phosphonate (**2**) with Adenine

A suspension of adenine (270 mg, 2 mmol) and Cs_2CO_3 (65 mg, 0.2 mmol) in dry DMF (10 ml) was heated to 120 °C. Oxirane **2** (448 mg, 2 mmol) was added and the reaction mixture was stirred at 120 °C for 1 h. After cooling to room temperature, the mixture was neutralized with acetic acid to pH 7, taken down in vacuo, the residue codistilled with xylene (2 × 10 ml) and then applied onto a column of silica gel (150 ml) in system S2. The chromatography gave, in elution sequence, a non-separable mixture of **4b** and **3** as a white solid (330 mg together) and pure diastereoisomer **4a**.

9-[(2-Ethoxy-2-oxo-2λ^5-1,4,2-dioxaphosphinan-6-yl)methyl]-9H-purin-6-amine (**4a**). Isolated as white crystals (113 mg, 18%), m.p. 172–174 °C (ethanol). FAB MS, *m/z* (%): 314 (100) [M + H], 136 (11) [adenine + H]. ^{1}H NMR (DMSO-d_6): 8.16 s, 1 H and 8.10 s, 1 H (H-2, H-8); 7.30 br s, 2 H (NH_2); 4.99 m, 1 H, ΣJ = 28.7, J(2′,P) = 8.0 (H-2′); 4.47 ddd, 1 H, J(1′a,P) = 0.9, J(1′a,2′) = 7.3, J(gem) = 14.6 (H-1′a); 4.43 ddd, 1 H, J(1′b,P) = 1.6, J(1′b,2′) = 4.8 (H-1′b); 4.06 m, 2 H

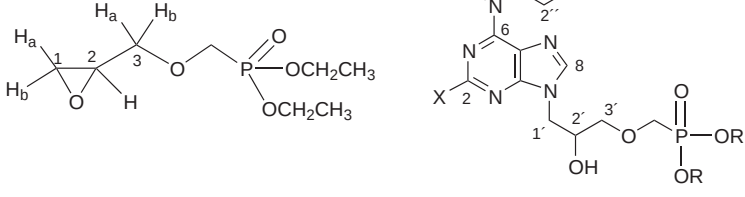


FIG. 1
General numbering scheme for assignment of NMR signals

(P-OCH_2); 4.01 d, 2 H, *J*(P,CH) = 5.0 (PCH_2); 3.94 dd, 1 H, *J*(3′a,2′) = 1.8, *J*(gem) = 12.8 (H-3′a); 3.56 dd, 1 H, *J*(3′b,2′) = 6.7 (H-3′b); 1.22 t, 3 H, *J*(CH_3,CH_2) = 7.1 (CH_3). ^{13}C NMR (DMSO-d_6): 156.20 (C-6); 152.75 (C-2); 149.875 (C-4); 141.72 (C-8); 118.72 (C-5); 78.33 d, *J*(P,C) = 8.3 (C-2′); 67.67 d, *J*(P,C) = 5.4 (C-3′); 63.94 d, *J*(P,C) = 141.6 (P-C); 62.84 d, *J*(P,C) = 5.9 (P-OCH_2); 43.84 d, *J*(P,C) = 2.9 (C-1′); 16.47 d, *J*(P,C) = 4.9 (CH_3).

Diethyl {[3-(6-amino-9H-purin-9-yl)-2-hydroxypropyloxy]methyl}phosphonate (***3***) *and 9-[(2-ethoxy-2-oxo-2*λ^5*-1,4,2-dioxaphosphinan-6-yl)methyl]-9H-purin-6-amine* (**4b**). FAB MS, *m/z* (%): 360 (40) [M + H, **3**], 314 (55) [M + H, **4b**]. Separation and characterization of both compounds after acetylation.

Acetylation of a Mixture of Compounds **3** and **4b**. Separation of Products

A mixture of **3** and **4b** (330 mg) in acetonitrile (20 ml) was stirred with acetic anhydride (178 mg, 1.8 mmol) and 4-(dimethylamino)pyridine (10 mg, 0.08 mmol) at ambient temperature for 1 h, then diluted with methanol (5 ml) and taken down. The residue was chromatographed on a column of silica gel (100 ml) in system S3. Two products were obtained in the following elution sequence.

2-(6-Amino-9H-purin-9-yl)-1-{[(diethoxyphosphoryl)methoxy]methyl}ethyl acetate (**5**). Yield 250 mg (31%, based on adenine), white solid, m.p. 87–88 °C. For $C_{15}H_{24}N_5O_6P$ (401.4) calculated: 44.89% C, 6.03% H, 17.45% N, 7.72% P; found: 44.33% C, 6.30% H, 17.61% N, 7.33% P. FAB MS, *m/z* (%): 402 (100) [M + H], 136 (28) [adenine + H]. ^{1}H NMR (DMSO-d_6): 8.16 s, 1 H and 8.10 s, 1 H (H-2, H-8); 7.31 br s, 2 H (NH_2); 5.29 m, 1 H (H-2′); 4.41 dd, 1 H, *J*(1′a,2′) = 3.9, *J*(gem) = 14.7 (H-1′a); 4.34 dd, 1 H, *J*(1′b,2′) = 7.2 (H-1′b); 4.04 m, 4 H (P-OCH_2); 3.89 dd, 1 H, *J*(P,CH_a) = 7.9, *J*(gem) = 14.2 (PCH_a); 3.85 dd, 1 H, *J*(P,CH_b) = 7.9 (PCH_b); 3.72 dd, 1 H, *J*(3′a,2′) = 4.0, *J*(gem) = 10.9 (H-3′a); 3.62 dd, 1 H, *J*(3′b,2′) = 6.1 (H-3′b); 1.90 s, 3 H (acetyl); 1.23 t, 3 H and 1.225 t, 3 H, *J*(CH_3,CH_2) = 7.1 (CH_3). ^{13}C NMR (DMSO-d_6): 169.69 (COCH_3); 155.97 (C-6); 152.49 (C-2); 149.97 (C-4); 141.395 (C-8); 118.63 (C-5); 71.36 d, *J*(P,C) = 10.7 (C-3′); 70.33 (C-2′); 64.58 d, *J*(P,C) = 162.1 (P-C); 62.00 d, 2 C, *J*(P,C) = 6.3 (P-OCH_2); 43.26 (C-1′); 20.77 (COCH_3); 16.46 d, 2 C, *J*(P,C) = 5.4 (CH_3).

9-[(2-Ethoxy-2-oxo-2λ^5*-1,4,2-dioxaphosphinan-6-yl)methyl]-9H-purin-6-amine* (**4b**). Isolated as white crystals, m.p. 183–184 °C (ethanol). Yield 107 mg (16%). For $C_{11}H_{16}N_5O_4P{\cdot}0.5C_2H_5OH$ (336.3) calculated: 42.86% C, 5.69% H, 20.83% N, 9.21% P; found: 42.72% C, 5.90% H, 20.32% N, 8.82% P. FAB MS, *m/z* (%): 314 (100) [M + H], 136 (12) [adenine + H]. ^{1}H NMR (DMSO-d_6): 8.165 s, 1 H and 8.11 s, 1 H (H-2, H-8); 7.33 br s, 2 H (NH_2); 4.91 m, 1 H, Σ*J* = 24.9, *J*(2′,P) = 2.0 (H-2′); 4.39 ddd, 1 H, *J*(1′a,2′) = 4.3, *J*(gem) = 15.6, *J*(1′a,P) = 1.8 (H-1′a); 4.35 ddd, 1 H, *J*(1′b,P) = 1.4, *J*(1′b,2′) = 6.7 (H-1′b); 4.17 dd, 1 H, *J*(P,CH_a) = 10.0, *J*(gem) = 14.9 (PCH_a); 3.99 dt, 1 H, *J*(3′a,P) = *J*(3′a,2′) = 1.8, *J*(gem) = 12.8 (H-3′a); 3.90 m, 2 H (P-OCH_2); 3.75 d, 1 H, *J*(gem) = 14.9 (PCH_b); 3.40 dd, 1 H, *J*(3′b,2′) = 10.1 (H-3′b); 1.08 t, 3 H, *J*(CH_3,CH_2) = 7.1 (CH_3). ^{13}C NMR (DMSO-d_6): 156.145 (C-6); 152.68 (C-2); 149.84 (C-4); 141.56 (C-8); 118.72 (C-5); 79.37 d, *J*(P,C) = 8.3 (C-2′); 67.92 d, *J*(P,C) = 4.4 (C-3′); 62.54 d, *J*(P,C) = 141.1 (P-C); 61.36 d, *J*(P,C) = 6.3 (P-OCH_2); 43.69 d, *J*(P,C) = 5.4 (C-1′); 16.16 d, *J*(P,C) = 5.4 (CH_3).

9-[(2-Ethoxy-2-oxo-2λ^5-1,4,2-dioxaphosphinan-6-yl)methyl]-9*H*-purine-2,6-diamine (**6**)

A suspension of 2,6-diaminopurine (500 mg, 3.33 mmol) and Cs_2CO_3 (130 mg, 0.4 mmol) in DMF (18 ml) was heated to 120 °C. Oxirane **2** (747 mg, 3.33 mmol) was added and the heating continued for 3 h. The reaction mixture was worked up in the same manner as de-

scribed for adenine derivatives **3**, **4**. The crude mixture of products was chromatographed on a silica gel column (300 ml) in system chloroform–methanol (4:1) giving **6** as a white solid (700 mg, 64%) contaminated by a chromatographically non-separable compound **7** (ca. 10% according to NMR spectrum). For characterization of **6**, acetylation of such obtained product was performed: A mixture of crude **6** (700 mg, 2.1 mmol), acetonitrile (25 ml) and 4-(dimethylamino)pyridine (20 mg, 0.16 mmol) was stirred with acetic anhydride (80 mg, 0.8 mmol) at 25 °C for 2 h. After addition of methanol (5 ml), the mixture was evaporated and the residue chromatographed on silica gel (200 ml) in the system chloroform–methanol (4:1). A mixture of chromatographically faster moving acetates was eluted first, followed by a pure compound **6** which is a mixture of two diastereoisomers (**6a** and **6b**, 3:1), yield 500 mg (46%), white crystals, m.p. 218–220 °C (CH_3OH). HR MS (FAB): For $C_{11}H_{18}N_6O_4P$ [M + H] calculated: 329.1127; found: 329.1147. FAB MS, *m/z* (%): 329 (85) [M + H]. ^{1}H NMR (DMSO-d_6), major diastereoisomer **6a**: 7.66 s, 1 H (H-8); 6.74 br s, 2 H (NH_2); 5.85 br s, 2 H (NH_2); 4.94 m, 1 H (OCH); 4.27 br dd, 1 H, *J*(1′a,P) ≤ 1.0, *J*(1′a,2′) = 7.2, *J*(gem) = 14.6 (H-1′a); 4.22 ddd, 1 H, *J*(1′b,P) = 1.6, *J*(1′b,2′) = 5.1 (H-1′b); 4.07 m, 2 H (P-OCH_2); 4.03 dd, 1 H, *J*(P,CH) = 5.5, *J*(gem) = 14.3 and 4.00 dd, 1 H, *J*(P,CH) = 4.5 (PCH_2); 3.88 dd, 1 H, *J*(3′a,2′) = 2.8, *J*(gem) = 12.9 (H-3′a); 3.54 dd, 1 H, *J*(3′b,2′) = 6.8 (H-3′b); 1.24 t, 3 H, *J*(CH_3,CH_2) = 7.1 (CH_3). ^{13}C NMR (DMSO-d_6): 160.56 (C-2); 156.34 (C-6); 152.09 (C-4); 137.93 (C-8); 113.15 (C-5); 78.16 d, *J*(P,C) = 8.3 (C-2′); 67.72 d, *J*(P,C) = 4.9 (C-3′); 64.01 d, *J*(P,C) = 142.1 (P-C); 62.81 d, *J*(P,C) = 5.9 (P-OCH_2); 43.41 d, *J*(P,C) = 2.9 (C-1′); 16.49 d, *J*(P,C) = 5.4 (CH_3). ^{1}H NMR (DMSO-d_6), minor diastereoisomer **6b**: 7.67 s, 1 H (H-8); 6.74 br s, 2 H (NH_2); 5.85 br s, 2 H (NH_2); 4.88 m, 1 H (OCH); 4.18 dd, 1 H, *J*(P,CH) = 10.0, *J*(gem) = 14.9 and 3.76 d, 1 H, *J*(P,CH) = 0, *J*(gem) = 14.9 (PCH_2); 4.16 m, 2 H (H-1′); 3.95 m, 2 H (P-OCH_2); 3.93 dt, 1 H, *J*(3′a,P) = *J*(3′a,2′) = 1.8, *J*(gem) = 12.9 (H-3′a); 3.40 dd, 1 H, *J*(3′b,2′) = 10.1 (H-3′b); 1.13 t, 3 H, *J*(CH_3,CH_2) = 7.1 (CH_3). ^{13}C NMR (DMSO-d_6): 160.56 (C-2); 156.34 (C-6); 152.06 (C-4); 138.07 (C-8); 113.15 (C-5); 79.26 d, *J*(P,C) = 8.3 (C-2′); 68.02 d, *J*(P,C) = 4.2 (C-3′); 62.58 d, *J*(P,C) = 141.1 (P-C); 61.365 d, *J*(P,C) = 5.4 (P-OCH_2); 43.25 d, *J*(P,C) = 5.4 (C-1′); 16.17 d, *J*(P,C) = 5.4 (CH_3).

Methyl {[3-(2,6-Diamino-9*H*-purin-9-yl)-2-hydroxypropoxy]methyl}phosphonate (**9**)

A solution of **6** (390 mg, 1.2 mmol) in 1 M sodium methoxide in methanol (25 ml) was refluxed for 6 h, then left to cool to room temperature and neutralized with Dowex 50 (H^+ form). Hydrochloric acid (36%) was added until the precipitated product dissolved. The mixture was applied onto a column of Dowex 50 (H^+ form, 100 ml). Elution was carried out with water (1200 ml) and then continued with 2.5% aqueous ammonia. The UV absorbing ammonia eluate was collected and evaporated in vacuo. Yield 307 mg (69.5%) of white crystals, m.p. 235–238 °C (ethanol). For $C_{10}H_{17}N_6O_5P{\cdot}2H_2O$ (368.3) calculated: 32.61% C, 5.75% H, 22.82% N, 8.41% P; found: 32.75% C, 5.55% H, 23.30% N, 8.32% P. HR MS (FAB): for $C_{10}H_{18}N_6O_5P$ [M + H] calculated: 333.1076; found: 333.1066. FAB MS, *m/z* (%): 333 (40) [M + H]. ^{1}H NMR (D_2O + NaOD): 7.81 s, 1 H (H-8); 4.19 dd, 1 H, *J*(1′a,2′) = 4.2, *J*(gem) = 13.4 (H-1′a); 4.15 m, 1 H (H-2′); 4.06 dd, 1 H, *J*(1′b,2′) = 6.7 (H-1′b); 3.72 dd, 1 H and 3.69 dd, 1 H, *J*(P,CH) = 8.4, *J*(gem) = 10.4 (P-CH_2); 3.62 d, 3 H, *J*(P,OCH) = 10.4 (P-OCH_3); 3.61 dd, 1 H, *J*(3′a,2′) = 4.5, *J*(gem) = 10.3 (H-3′a); 3.54 dd, 1 H, *J*(3′b,2′) = 5.2 (H-3′b). ^{13}C NMR (D_2O + NaOD): 159.96 (C-2); 156.04 (C-6); 151.28 (C-4); 140.75 (C-8); 112.82 (C-5); 74.60 d, *J*(P,C) = 11.2 (C-3′); 68.28 (C-2′); 65.56 d, *J*(P,C) = 157.72 (PCH_2); 51.93 d, *J*(P,C) = 5.9 (P-OCH_3); 46.44 (C-1′).

{[3-(2,6-Diamino-9*H*-purin-9-yl)-2-hydroxypropoxy]methyl}phosphonic Acid (**8**)

Method A. From 2,6-diaminopurine (550 mg, 3.66 mmol) and oxirane **2** (830 mg, 3.7 mmol) in the same manner as described for compound **6**. The crude product (containing small amount of **7**) was dried in vacuo at 60 °C and treated with bromotrimethylsilane (4.05 ml, 30 mmol) in acetonitrile (30 ml) at room temperature for 48 h. The reaction mixture was then poured to 1 M triethylammonium hydrogencarbonate (100 ml), evaporated to dryness and the residue coevaporated with water (3 × 100 ml). 1 M NaOH (25 ml) was added, the solution heated to 80 °C for 4 h, then cooled to room temperature, neutralized with acetic acid to pH 6 and evaporated to ca. quarter of its original volume. Hydrochloric acid (36%) was added until the product dissolved and the solution was applied onto a column of Dowex 50 (H^+ form, 300 ml). Elution was carried out first with water (3.5 l; thorough washing with water is necessary to remove contaminating guanine derivatives) and then continued with 1.5% ammonia. The UV absorbing ammonia eluate was taken down to give a crude **8** together with a small amount of **10**. Purification of this product by HPLC was performed on C-18 reverse phase with elution with water. The phosphonate **8** was eluted first, followed by compound **10**. Fractions of **8** were evaporated to dryness and the residue was crystallized from 80% aqueous ethanol. Yield 600 mg (48%) of white crystals, m.p. 222–225 °C (decomp.). For $C_9H_{15}N_6O_5P \cdot 1.5H_2O$ (345.3) calculated: 31.31% C, 5.25% H, 24.34% N, 8.97% P; found: 31.42% C, 4.97% H, 24.02% N, 9.02% P. FAB MS, *m/z* (%): 319 (10) [M + H]. ^{1}H NMR (D_2O): 7.78 s, 1 H (H-8); 4.20 dd, 1 H, *J*(1′a,2′) = 3.7, *J*(gem) = 14.2 (H-1′a); 4.18 m, 1 H (H-2′); 4.10 dd, 1 H, *J*(1′b,2′) = 9.2 (H-1′b); 3.69 dd, 1 H, *J*(3′a,2′) = 3.7, *J*(gem) = 10.6 (H-3′a); 3.57 dd, 1 H, *J*(3′b,2′) = 5.6 (H-3′b); 3.64 dd, 1 H, *J*(P,CH) = 8.8, *J*(gem) = 12.7 and 3.61 dd, 1 H, *J*(P,CH) = 8.7 (P-CH_2). ^{13}C NMR (D_2O): 159.59 (C-2); 155.98 (C-6); 150.69 (C-4); 140.56 (C-8); 112.63 (C-5); 73.71 d, *J*(P,C) = 11.2 (C-3′); 68.56 d, *J*(P,C) = 154.8 (P-C); 68.29 (C-2′); 45.86 (C-1′).

Method B. A solution of **6** (390 mg, 1.2 mmol) in 1 M sodium methoxide in methanol (25 ml) was refluxed for 6 h, then left standing at room temperature overnight and neutralized with Dowex 50 (H^+ form). Hydrochloric acid (36%) was added to dissolution of precipitated product. The mixture was applied onto a column of Dowex 50 (H^+ form, 100 ml), the elution was performed with water (1.2 l) and then with 2.5% aqueous ammonia. The UV absorbing eluate was evaporated in vacuo and the residue stirred with a mixture of ethanol and acetone (1:1, 10 ml). The solid product was filtered off and dried in vacuo. Yield 130 mg (68%) of white solid (anhydrous).

6-[(2,6-Diamino-9*H*-purin-9-yl)methyl]-2-hydroxy-2λ^5-1,4,2-dioxaphosphinan-2-one (**10**)

The compound was isolated as a side product in preparation of **8**. Yield 250 mg (22%) of white crystals, m.p. > 300 °C. For $C_9H_{13}N_6O_4P \cdot 0.5H_2O$ (309.2) calculated: 34.96% C, 4.56% H, 27.18% N, 10.02% P; found: 34.76% C, 4.39% H, 26.77% N, 9.79% P. FAB MS, *m/z* (%): 301 (70) [M + H]. ^{1}H NMR (D_2O + NaOD): 7.80 s, 1 H (H-8); 4.71 m, 1 H (H-2′); 4.16 m, 2 H (H-1′); 3.98 br dt, 1 H, *J*(3′a,2′) ≈ *J*(3′a,P) ≤ 1.0, *J*(gem) = 12.2 (H-3′a); 3.92 dd, 1 H, *J*(P,CH) = 8.7, *J*(gem) = 13.9 and 3.61 dd, 1 H, *J*(P,CH) = 1.8 (P-CH_2); 3.32 dd, 1 H, *J*(3′b,2′) = 10.2, *J*(gem) = 12.2 (H-3′b). ^{13}C NMR (D_2O + NaOD): 159.86 (C-2); 155.83 (C-6); 150.94 (C-4); 140.51 (C-8); 112.51 (C-5); 76.34 d, *J*(P,C) = 6.4 (C-2′); 68.40 d, *J*(P,C) = 3.0 (C-3′); 65.51 d, *J*(P,C) = 143.5 (P-C); 43.95 d, *J*(P,C) = 5.4 (C-1′).

Reaction of Diethyl [(Oxiranylmethoxy)methyl]phosphonate (**2**) with 6-Chloropurine and 2-Amino-6-chloropurine. General Procedure

A suspension of an appropriate nucleobase (21 mmol) and Cs_2CO_3 (652 mg, 2 mmol) in dry DMF (100 ml) was evaporated to half of its volume and then heated to 115 °C. Compound **2** (4.42 g, 19.7 mmol) was added and the reaction mixture stirred at 115 °C for 2 h. After cooling to room temperature the mixture was neutralized with acetic acid to pH 7, evaporated in vacuo and the residue codistilled with xylene (2 × 50 ml). The crude mixture of products was chromatographed on a silica gel column (1000 ml) in system S1 in separation of **11** and **12** or S2 in separation of **13** and **14**. In both cases the N^9-isomers are chromatographically faster then the N^7-isomers.

Diethyl {[3-(6-chloro-9H-purin-9-yl)-2-hydroxypropoxy]methyl}phosphonate (**11**). Yield 4.2 g (56%) of a colorless syrup. For $C_{13}H_{20}ClN_4O_5P$ (378.8) calculated: 41.23% C, 5.32% H, 9.36% Cl, 14.79% N, 8.18% P; found: 41.24% C, 5.63% H, 9.26% Cl, 14.89% N, 7.85% P. FAB MS, *m/z* (%): 379 (100) [M + H], 155 (20) [6-chloropurine + H]. ^{1}H NMR (DMSO-d_6): 8.77 s, 1 H and 8.62 s, 1 H (H-2, H-8); 5.36 d, 1 H, *J*(OH,2′) = 5.6 (OH); 4.40 dd, 1 H, *J*(1′a,2′) = 3.6, *J*(gem) = 13.9 (H-1′a); 4.21 dd, 1 H, *J*(1′b,2′) = 8.4 (H-1′b); 4.07 m, 1 H (H-2′); 4.06 br pent, 4 H, *J*(CH_2,CH_3) ≈ *J*(P,CH_2) = 7.1 (P-OCH_2); 3.87 d, 2 H, *J*(P,CH) = 7.8 (P-CH_2); 3.56 dd, 1 H, *J*(3′a,2′) = 5.2, *J*(gem) = 10.0 (H-3′a); 3.52 dd, 1 H, *J*(3′b,2′) = 5.9 (H-3′b); 1.24 t, 6 H (CH_3). ^{13}C NMR (DMSO-d_6): 152.41 (C-4); 151.56 (C-2); 148.99 (C-6); 148.36 (C-8); 130.94 (C-5); 74.66 d, *J*(P,C) = 10.3 (C-3′); 67.31 (C-2′); 64.70 d, *J*(P,C) = 162.1 (P-C); 61.97 d and 61.92 d, *J*(P,C) = 5.9 (P-OCH_2); 47.31 (C-1′); 16.51 d, 2 C, *J*(P,C) = 5.4 (CH_3).

Diethyl {[3-(6-chloro-7H-purin-7-yl)-2-hydroxypropoxy]methyl}phosphonate (**12**). Yield 1.4 g (19%) of white crystals, m.p. 98–100 °C (ethanol–acetone 1:1). For $C_{13}H_{20}ClN_4O_5P$ (378.8) calculated: 41.23% C, 5.32% H, 9.36% Cl, 14.79% N, 8.18% P; found: 41.53% C, 5.21% H, 9.30% Cl, 15.25% N, 7.82% P. FAB MS, *m/z* (%): 379 (100) [M + H], 155 (17) [6-chloropurine + H]. ^{1}H NMR (DMSO-d_6): 8.80 s, 1 H and 8.71 s, 1 H (H-2, H-8); 5.36 d, 1 H, *J*(OH,2′) = 5.6 (OH); 4.67 dd, 1 H, *J*(1′a,2′) = 3.1, *J*(gem) = 14.3 (H-1′a); 4.31 dd, 1 H, *J*(1′b,2′) = 9.1 (H-1′b); 4.06 br pent, 4 H, *J*(CH_2,CH_3) = *J*(P,CH_2) = 7.1 (P-OCH_2); 4.00 m, 1 H (H-2′); 3.62 dd, 1 H, *J*(3′a,2′) = 5.0, *J*(gem) = 10.0 (H-3′a); 3.57 dd, 1 H, *J*(3′b,2′) = 5.9 (H-3′b); 1.25 t, 6 H (CH_3). ^{13}C NMR (DMSO-d_6): 161.84 (C-4); 151.97 (C-8); 151.54 (C-2); 142.25 (C-6); 122.445 (C-5); 74.57 d, *J*(P,C) = 10.7 (C-3′); 68.47 (C-2′); 64.75 d, *J*(P,C) = 162.5 (P-C); 61.91 d, 2 C, *J*(P,C) = 5.9 (P-OCH_2); 50.04 (C-1′); 16.50 d, 2 C, *J*(P,C) = 5.4 (CH_3).

Diethyl {[3-(2-amino-6-chloro-9H-purin-9-yl)-2-hydroxypropoxy]methyl}phosphonate (**13**). Yield 4.5 g (58%) of a colorless syrup. For $C_{13}H_{21}ClN_5O_5P$ (393.8) calculated: 39.65% C, 5.38% H, 9.00% Cl, 17.79% N, 7.87% P; found: 39.66% C, 5.43% H, 9.06% Cl, 17.72% N, 7.78% P. FAB MS, *m/z* (%): 394 (100) [M + H], 170 (50) [2-amino-6-chloropurine + H]. ^{1}H NMR (DMSO-d_6): 8.03 s, 1 H (H-8); 6.91 br s, 2 H (NH_2); 5.33 d, 1 H, *J*(OH, 2′) = 5.3 (2′-OH); 4.05 dq, 4 H, *J*(CH_2,CH_3) = 7.1, *J*(P,OCH) = 8.2 (P-OCH_2); 4.13 dd, 1 H, *J*(1′a,2′) = 3.0, *J*(gem) = 13.2 (H-1′a); 3.95 dd, 1 H, *J*(1′b,2′) = 8.5 (H-1′b); 4.02 m, 1 H (H-2′); 3.86 d, 2 H, *J*(P,CH) = 7.8 (PCH_2); 3.53 dd, 1 H, *J*(3′a,2′) = 5.1, *J*(gem) = 10.0 (H-3′a); 3.49 dd, 1 H, *J*(3′b,2′) = 5.4 (H-3′b); 1.24 t, 6 H (CH_3). ^{13}C NMR (DMSO-d_6): 159.91 (C-2); 154.50 (C-4); 149.37 (C-6); 144.20 (C-8); 123.46 (C-5); 74.97 d, *J*(P,C) = 9.8 (C-3′); 67.19 (C-2′); 64.75 d, *J*(P,C) = 162.1 (P-C); 61.94 d, 2 C, *J*(P,C) = 6.4 (P-OCH_2); 46.59 (C-1′); 16.52 d, 2 C, *J*(P,C) = 5.4 (CH_3).

Diethyl {[3-(2-amino-6-chloro-7H-purin-7-yl)-2-hydroxypropoxy]methyl}phosphonate (**14**). Yield 1.3 g (17%) of a white solid, m.p. 70–72 °C. For $C_{13}H_{21}ClN_5O_5P·0.5H_2O$ (402.8) calculated:

38.77% C, 5.51% H, 8.80% Cl, 17.38% N, 7.69% P; found: 38.94% C, 5.55% H, 8.86% Cl, 17.11% N, 7.30% P. FAB MS, *m/z* (%): 394 (100) [M + H], 170 (20) [2-amino-6-chloropurine + H]. ^{1}H NMR (DMSO-d_6): 8.24 s, 1 H (H-8); 6.16 br s, 2 H (NH_2); 5.33 d, 1 H, *J*(OH,2′) = 5.4 (2′-OH); 4.47 dd, 1 H, *J*(1′a,2′) = 3.2, *J*(gem) = 14.2 (H-1′a); 4.11 dd, 1 H, *J*(1′b,2′) = 9.0 (H-2′b); 4.05 br pent, 4 H, *J*(CH_2,CH_3) ≈ *J*(P,OCH) ≈ 7.2 (P-OCH_2); 3.93 m, 1 H (H-2′); 3.87 d, 2 H, *J*(P,CH) = 7.8 (PCH_2); 3.57 dd, 1 H, *J*(3′a,2′) = 5.1, *J*(gem) = 10.0 (H-3′a); 3.52 dd, 1 H, *J*(3′b,2′) = 5.7 (H-3′b); 1.24 t, 6 H, *J*(CH_3,CH_2) = 7.1 (CH_3). ^{13}C NMR (DMSO-d_6): 164.47 (C-4); 160.00 (C-2); 150.54 (C-8); 142.29 (C-6); 115.20 (C-5); 74.71 d, *J*(P,C) = 10.7 (C-3′); 68.31 (C-2′); 64.73 d, *J*(P,C) = 162.1 (P-C); 61.92 d, 2 C, *J*(P,C) = 6.4 (P-OCH_2); 49.75 (C-1′); 16.51 d, 2 C, *J*(P,C) = 5.4 (CH_3).

Diethyl Esters of N^6-Substituted 9- and 7-[2-Hydroxy-3-(phosphonomethoxy)propyl] Derivatives of Adenine and 2,6-Diaminopurine. General Procedure

A mixture of an appropriate 6-chloro derivative **11**, **12** or **13** (1 mmol), primary or secondary amine, or dimethylammonium *N*,*N*-dimethylcarbamate (5 mmol) in acetonitrile (10 ml) was refluxed for 0.5–4 h. The reaction course was monitored by TLC in system S1, S2 or S3. The mixture was evaporated to dryness in vacuo and the residue chromatographed on a silica gel column (100 ml) in the system described below.

Diethyl ({3-[6-(dimethylamino)-9H-purin-9-yl]-2-hydroxypropoxy}methyl)phosphonate (**15**). Chromatographed in system S2. Yield 342 mg (88%) of a colorless syrup. For $C_{15}H_{26}N_5O_5P$ (387.4) calculated: 46.51% C, 6.76% H, 18.08% N, 8.00% P; found: 46.32% C, 6.98% H, 17.97% N, 7.66% P. FAB MS, *m/z* (%): 388 (100) [M + H], 164 (15) [6-(dimethylamino)purine + H]. ^{1}H NMR (DMSO-d_6): 8.20 s, 1 H and 8.06 s, 1 H (H-2, H-8); 5.33 d, 1 H, *J*(OH,2′) = 5.4 (2′-OH); 4.26 dd, 1 H, *J*(1′a,2′) = 3.4, *J*(gem) = 13.4 (H-1′a); 4.04 dd, 1 H, *J*(1′b,2′) = 8.0 (H-1′b); 4.06 br pent, 4 H, *J*(CH_2,CH_3) ≈ *J*(P,CH_2) = 7.1 (P-OCH_2); 4.00 m, 1 H (H-2′); 3.86 d, 2 H, *J*(P,CH) = 7.7 (PCH_2); 3.50 d, 2 H, *J*(3′,2′) = 5.4 (H-3′); 3.45 br, 6 H (NCH_3); 1.24 t, 6 H, *J*(CH_3,CH_2) = 7.0 (CH_3). ^{13}C NMR (DMSO-d_6): 154.405 (C-6); 151.77 (C-2); 150.59 (C-4); 140.56 (C-8); 119.25 (C-5); 74.86 d, *J*(P,C) = 10.2 (C-3′); 67.60 (C-2′); 64.72 d, *J*(P,C) = 162.1 (P-C); 61.91 d, *J*(P,C) = 5.9 (P-OCH_2); 61.90 d, *J*(P,C) = 5.9 (P-OCH_2); 46.42 (C-1′); 39.95, 2 C (NCH_3); 16.46 d, 2 C, *J*(P,C) = 5.4 (CH_3).

Diethyl ({3-[6-(cyclopropylamino)-9H-purin-9-yl]-2-hydroxypropoxy}methyl)phosphonate (**16**). Chromatographed in system S3. Yield 397 mg (98%) of a white solid. For $C_{16}H_{26}N_5O_5P\cdot 0.25H_2O$ (403.9) calculated: 47.58% C, 6.61% H, 17.34% N, 7.67% P; found: 47.58% C, 6.91% H, 17.18% N, 7.29% P. FAB MS, *m/z* (%): 400 (100) [M + H], 176 (12) [6-(cyclopropylamino)purine + H]. ^{1}H NMR (DMSO-d_6): 8.23 s, 1 H and 8.04 s, 1 H (H-2, H-8); 7.83 br s, 1 H (NH); 5.32 d, 1 H, *J*(OH,2′) = 5.4 (2′-OH); 4.26 dd, 1 H, *J*(1′a,2′) = 2.8, *J*(gem) = 13.2 (H-1′a); 4.05 br pent, 4 H, *J*(CH_2,CH_3) ≈ *J*(P,CH_2) = 7.1 (P-OCH_2); 4.03 overlay, 1 H (H-1′b); 4.01 m, 1 H (H-2′); 3.51 dd, 1 H, *J*(3′a,2′) = 5.1, *J*(gem) = 11.1 (H-3′a); 3.48 dd, 1 H, *J*(3′b,2′) = 5.4 (H-3′b); 3.05 m, 1 H (CH-cyclopropyl); 1.24 t, 6 H, *J*(CH_3,CH_2) = 7.0 (CH_3); 0.72 m, 2 H and 0.61 m, 2 H (CH_2-cyclopropyl). ^{13}C NMR (DMSO-d_6): 155.66 (C-6); 153.94 (C-4); 152.31 (C-2); 141.515 (C-8); 119.10 (C-5); 74.84 d, *J*(P,C) = 10.2 (C-3′); 67.62 (C-2′); 64.70 d, *J*(P,C) = 161.6 (P-C); 61.89 d and 61.87 d, *J*(P,C) = 6.4 (P-OCH_2); 46.42 (C-1′); 29.80 (cyclopropyl); 16.46 d, 2 C, *J*(P,C) = 5.4 (CH_3); 6.55 (cyclopropyl).

Diethyl {[2-hydroxy-3-(6-piperidino-9H-purin-9-yl)propoxy]methyl}phosphonate (**17**). Chromatographed in system S1. Yield 249 mg (58%) of a white solid. For $C_{18}H_{30}N_5O_5P\cdot 0.25H_2O$ (431.9) calculated: 50.05% C, 7.12% H, 16.21% N, 7.17% P; found: 49.99% C, 7.30% H,

16.22% N, 7.28% P. FAB MS, *m/z* (%): 428 (100) [M + H], 204 (17) [6-piperidinopurine + H]. ^{1}H NMR (DMSO-d_6): 8.20 s, 1 H and 8.06 s, 1 H (H-2, H-8); 5.32 d, 1 H, *J*(OH,2′) = 5.4 (2′-OH); 4.26 dd, 1 H, *J*(1′a,2′) = 3.3, *J*(gem) = 13.4 (H-1′a); 4.20 m, 4 H (NCH_2-piperidinyl); 4.06 d pent, 4 H, *J*(CH_2,CH_3) = 7.1, *J*(P,OCH) = 8.2 (P-OCH_2); 4.03 dd, 1 H, *J*(1′b,2′) = 8.2 (H-1′b); 4.00 m, 1 H (H-2′); 3.87 d, 2 H, *J*(P,CH) = 7.8 (PCH_2); 3.51 dd, 1 H, *J*(3′a,2′) = 5.2, *J*(gem) = 10.4 (H-3′a); 3.49 dd, 1 H, *J*(3′b,2′) = 5.4 (H-3′b); 1.67 m, 2 H and 1.57 m, 4 H (CH_2-piperidinyl); 1.24 t, 6 H (CH_3). ^{13}C NMR (DMSO-d_6): 153.31 (C-6); 151.89 (C-2); 150.87 (C-4); 140.56 (C-8); 118.97 (C-5); 74.89 d, *J*(P,C) = 9.8 (C-3′); 67.59 (C-2′); 64.72 d, *J*(P,C) = 161.6 (P-C); 61.95 d and 61.92 d, *J*(P,C) = 6.4 (P-OCH_2); 47.20 br, 2 C (NCH_2); 46.49 (C-1′); 25.88, 2 C (C-CH_2); 24.49 (C-CH_2); 16.51 d, 2 C, *J*(P,C) = 5.4 (CH_3).

Diethyl [(2-hydroxy-3-{6-[(2-methoxyethyl)amino]-9H-purin-9-yl}propoxy)methyl]phosphonate (**18**). Chromatographed in system S1. Yield 386 mg (91%) of a white solid. For $C_{16}H_{28}N_5O_6P\cdot 0.25H_2O$ (421.9) calculated: 45.55% C, 6.81% H, 16.60% N, 7.34% P; found: 45.65% C, 6.90% H, 16.65% N, 7.24% P. FAB MS, *m/z* (%): 418 (100) [M + H]. ^{1}H NMR (DMSO-d_6): 8.20 s, 1 H and 8.05 s, 1 H (H-2, H-8); 7.60 br s, 1 H (NH); 5.33 d, 1 H, *J*(OH,2′) = 5.3 (2′-OH); 4.25 dd, 1 H, *J*(1′a,2′) = 3.0, *J*(gem) = 13.2 (H-1′a); 4.06 dq, 4 H, *J*(CH_2,CH_3) = 7.0, *J*(P,OCH) = 8.2 (P-OCH_2); 4.04 dd, 1 H, *J*(1′b,2′) = 8.0 (H-1′b); 4.01 m, 1 H (H-2′); 3.86 d, 2 H, *J*(P,CH) = 7.8 (PCH_2); 3.64 m, 2 H (NCH_2); 3.52 t, 2 H, *J*(CH_2,CH_2) = 5.9 (OCH_2); 3.50 dd, 1 H and 3.48 dd, 1 H, *J*(3′a,2′) = *J*(3′b,2′) = 5.0, *J*(gem) = 10.5 (H-3′); 3.26 s, 3 H (OCH_3); 1.24 t, 6 H, *J*(CH_3,CH_2) = 7.0 (CH_3). ^{13}C NMR (DMSO-d_6): 154.60 (C-6); 152.13 (C-2); 149.50 (C-4); 141.34 (C-8); 118.88 (C-5); 74.36 d, *J*(P,C) = 9.8 (C-3′); 70.63 (OCH_2); 67.58 (C-2′); 64.68 d, *J*(P,C) = 162.1 (P-C); 61.71 d, 2 C, *J*(P,C) = 6.4 (P-OCH_2); 57.86 (OCH_3); 46.31 (C-1′); 45.70 (NCH_2); 16.24 d, 2 C, *J*(P,C) = 5.4 (CH_3).

Diethyl [(2-hydroxy-3-{6-[(2-hydroxyethyl)amino]-9H-purin-9-yl}propoxy)methyl]phosphonate (**19**). Chromatographed in system S3. Yield 348 mg (86%) of a colorless syrup. For $C_{15}H_{26}N_5O_6P$ (403.4) calculated: 44.66% C, 6.50% H, 17.36% N, 7.68% P; found: 44.37% C, 6.51% H, 17.48% N, 7.49% P. FAB MS, *m/z* (%): 404 (100) [M + H]. ^{1}H NMR (DMSO-d_6): 8.20 br s, 1 H and 8.05 s, 1 H (H-2, H-8); 7.54 br s, 1 H (NH); 5.34 d, 1 H, *J*(OH,2′) = 5.4 (2′-OH); 4.78 br t, 1 H, *J*(OH,CH_2) = 5.0 (OH); 4.25 dd, 1 H, *J*(1′a,2′) = 3.2, *J*(gem) = 13.2 (H-1′a); 4.06 dq, 4 H, *J*(CH_2,CH_3) = 7.1, *J*(P,OCH) = 8.1 (P-OCH_2); 4.03 overlay, 1 H (H-1′b); 4.01 m, 1 H (H-2′); 3.86 d, 2 H, *J*(P,CH) = 7.8 (PCH_2); 3.57 m, 4 H (NCH_2 and OCH_2); 3.51 dd, 1 H and 3.48 dd, 1 H, *J*(3′a,2′) = *J*(3′b,2′) = 5.0, *J*(gem) = 10.5 (H-3′); 1.24 t, 6 H (CH_3). ^{13}C NMR (DMSO-d_6): 154.72 (C-6); 152.14 (C-2); 150.0 (C-4); 141.325 (C-8); 118.89 (C-5); 74.73 d, *J*(P,C) = 10.3 (C-3′); 67.59 (C-2′); 64.75 d, *J*(P,C) = 162.1 (P-C); 61.72 d, 2 C, *J*(P,C) = 6.3 (P-OCH_2); 60.06 (OCH_2); 46.32 (C-1′); 45.0 (NCH_2); 16.25 d, 2 C, *J*(P,C) = 5.4 (CH_3).

Diethyl ({3-[6-(allylamino)-9H-purin-9-yl]-2-hydroxypropoxy}methyl)phosphonate (**20**). Chromatographed in system S1. Yield 385 mg (96%) of a yellow solid. For $C_{16}H_{26}N_5O_5P$ (399.4) calculated: 48.12% C, 6.56% H, 17.54% N, 7.76% P; found: 47.76% C, 6.65% H, 17.36% N, 7.57% P. FAB MS, *m/z* (%): 400 (100) [M + H]. ^{1}H NMR (DMSO-d_6): 8.19 br s, 1 H and 8.05 s, 1 H (H-2, H-8); 7.89 br s, 1 H (NH); 5.95 ddt, 1 H, *J*(2″,1″) = 5.1, *J*(2″,3″) = 10.3 (cis) and 17.3 (trans) (H-2″); 5.34 d, 1 H, *J*(OH,2′) = 5.3 (2′-OH); 5.15 br dq, 1 H, *J*(3″,1″) ≈ *J*(gem) = 1.6, *J*(3″,2″) = 17.3 (H-3″trans); 5.04 dq, 1 H, *J*(3″,1″) ≈ *J*(gem) = 1.7, *J*(3″,2″) = 10.3 (H-3″cis); 4.26 dd, 1 H, *J*(1′a,2′) = 2.7, *J*(gem) = 12.9 (H-1′a); 4.11 m, 2 H (H-1″); 4.06 br pent, 4 H, *J*(CH_2,CH_3) = 7.1, *J*(P,OCH) = 7.8 (P-OCH_2); 4.02 m, 1 H (H-1′b); 4.02 m, 1 H (H-2′); 3.87 d, 2 H, *J*(P,CH) = 7.8 (PCH_2); 3.51 dd, 1 H, *J*(3′a,2′) = 5.0, *J*(gem) = 10.0 (H-3′a); 3.49 dd, 1 H, *J*(3′b,2′) = 5.4 (H-3′b); 1.24 t, 6 H (CH_3). ^{13}C NMR (DMSO-d_6): 154.50 (C-6);

152.37 (C-2); 149.23 (C-4); 141.59 (C-8); 136.02 (C-2″); 119.05 (C-5); 115.095 (C-3″); 74.86 d, *J*(P,C) = 10.2 (C-3′); 67.64 (C-2′); 64.70 d, *J*(P,C) = 162.1 (P-C); 61.91 d, 2 C, *J*(P,C) = 6.4 (P-OCH_2); 46.47 (C-1′); 42.16 (C-1″); 16.49 d, 2 C, *J*(P,C) = 5.4 (CH_3).

Diethyl {[3-(6-{[2-(dimethylamino)ethyl]amino}-9H-purin-9-yl)-2-hydroxypropoxy]methyl}phosphonate (**21**). Instead of chromatography, the crude reaction product was dissolved in 20% aqueous methanol (30 ml) and Dowex 50 (H^+ form) was added until the solution was acid. The mixture was applied onto a column of the same ion exchanger (60 ml), elution performed first with 20% methanol (1.5 l) and then with 2.5% ammonia in 20% methanol. The UV absorbing fractions were collected and taken down to give **21** as a yellowish syrup. Yield 373 mg (87%). The product of ca. 90% purity was used for subsequent preparation of **37** without further purification. FAB MS, *m/z* (%): 431 (30) [M + H].

Diethyl [(2-hydroxy-3-{6-[(2,2,2-trifluoroethyl)amino]-9H-purin-9-yl}propoxy)methyl]phosphonate (**22**). Prepared with 5% solution of 2,2,2-trifluorethylamine in ethanol (20 ml) in an autoclave at 100 °C for 6 h. Chromatography in system S1 gave 250 mg (57%) of **22** as a yellowish syrup. For $C_{15}H_{23}F_3N_5O_5P$ (441.4) calculated: 40.82% C, 5.25% H, 12.91% F, 15.87% N, 7.02% P; found: 40.74% C, 5.45% H, 12.82% F, 15.85% N, 7.31% P. FAB MS, *m/z* (%): 442 (100) [M + H]. ^{1}H NMR (DMSO-d_6): 8.32 br s, 1 H (NH); 8.30 s, 1 H and 8.16 s, 1 H (H-2, H-8); 5.34 d, 1 H, *J*(OH,2′) = 5.5 (2′-OH); 4.35 m, 2 H (NCH_2); 4.29 dd, 1 H, *J*(1′a,2′) = 3.4, *J*(gem) = 13.6 (H-1′a); 4.06 dq, 4 H, *J*(CH_2,CH_3) = 7.1, *J*(P,CH) = 8.2 (P-OCH_2); 4.05 m, 1 H (H-2′); 4.02 dd, 1 H, *J*(1′b,2′) = 7.0 (H-1′b); 3.87 d, 2 H, *J*(P,CH) = 7.8 (PCH_2); 3.52 dd, 1 H, *J*(3′a,2′) = 5.2, *J*(gem) = 10.0 (H-3′a); 3.50 dd, 1 H, *J*(3′b,2′) = 5.4 (H-3′b); 1.24 t, 6 H (CH_3). ^{13}C NMR (DMSO-d_6): 154.16 (C-6); 152.05 (C-2); 150.0 (C-4); 142.59 (C-8); 125.61 (C-5); 125.30 q, *J*(C,F) = 280.3 (CF_3); 74.83 d, *J*(P,C) = 10.2 (C-3′); 67.565 (C-2′); 64.70 d, *J*(P,C) = 161.6 (P-C); 61.93 d, 2 C, *J*(P,C) = 6.4 (P-OCH_2); 43.08 q, *J*(C,F) = 31.3 (NCH_2); 16.48 d, 2 C, *J*(P,C) = 5.4 (CH_3).

Diethyl ({3-[2-amino-6-(dimethylamino)-9H-purin-9-yl]-2-hydroxypropoxy}methyl)phosphonate (**23**). Chromatography in system S3. Yield 384 mg (95%) of a colorless syrup. For $C_{15}H_{27}N_6O_5P$ (402.4) calculated: 44.77% C, 6.76% H, 20.89% N, 7.70% P; found: 44.36% C, 6.83% H, 20.37% N, 7.68% P. FAB MS, *m/z* (%): 403 (100) [M + H]. ^{1}H NMR (DMSO-d_6): 7.64 s, 1 H (H-8); 5.83 br s, 2 H (NH_2); 5.38 br, 1 H (OH); 4.06 dd, 1 H, *J*(1′a,2′) = 3.5, *J*(gem) = 13.2 (H-1′a); 4.05 dq, 4 H, *J*(CH_2,CH_3) = 7.1, *J*(P,OCH) = 8.2 (P-OCH_2); 3.945 m, 1 H (H-2′); 3.86 dd, 1 H, *J*(1′b,2′) = 7.3 (H-1′b); 3.86 d, 2 H, *J*(P,CH) = 7.7 (PCH_2); 3.47 d, 2 H, *J*(3′,2′) = 5.0 (H-3′); 3.35 br s, 6 H (N-CH_3); 1.24 t, 6 H (CH_3). ^{13}C NMR (DMSO-d_6): 159.42 (C-2); 154.83 (C-6); 152.85 (C-4); 137.55 (C-8); 113.65 (C-5); 75.035 d, *J*(P,C) = 9.8 (C-3′); 67.63 (C-2′); 64.74 d, *J*(P,C) = 162.1 (P-CH_2); 61.945 d, 2 C, *J*(C,P) = 6.4 (P-OCH_2); 46.08 (C-1′); 37.84, 2 C (NCH_3); 16.54 d, 2 C, *J*(C,P) = 5.9 (CH_3).

Diethyl ({3-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-hydroxypropoxy}methyl)phosphonate (**24**). Chromatographed in system S3. Yield 392 mg (95%) of a yellow syrup. For $C_{16}H_{27}N_6O_5P$ (414.4) calculated: 46.37% C, 6.57% H, 20.28% N, 7.47% P; found: 45.99% C, 6.55% H, 20.01% N, 7.25% P. FAB MS, *m/z* (rel.%): 415 (100) [M + H]. ^{1}H NMR (DMSO-d_6): 7.61 s, 1 H (H-8); 7.28 d, 1 H, *J*(NH,CH) = 4.5 (NH); 5.84 br s, 2 H (NH_2); 5.38 d, 1 H, *J*(OH,2′) = 5.0 (2′-OH); 4.05 dq, 4 H, *J*(CH_2,CH_3) = 7.1, *J*(P,OCH) = 8.3 (P-OCH_2); 4.02 m, 3 H (H-1′, H-2′); 3.86 d, 2 H, *J*(P,CH) = 7.7 (PCH_2); 3.50 dd, 1 H, *J*(3′a,2′) = 3.8, *J*(gem) = 10.0 (H-3′a); 3.44 dd, 1 H, *J*(3′b,2′) = 5.0 (H-3′b); 3.02 m, 1 H (H-1″); 1.23 t, 6 H (CH_3); 0.62 m, 2 H and 0.58 m, 2 H (H-2″). ^{13}C NMR (DMSO-d_6): 160.31 (C-2); 156.11 (C-6); 151.64 (C-4); 138.29 (C-8); 113.48 (C-5); 75.07 d, *J*(C,P) = 10.0 (C-3′); 67.715 (C-2′); 64.75 d, *J*(C,P) = 161.9

(P-CH_2); 62.01 d, 2 C, *J*(C,P) = 6.7 (P-OCH_2); 46.10 (C-1′); 24.06 (cyclopropyl); 16.575 d, 2 C, *J*(C,P) = 5.6 (CH_3); 6.69, 2 C (cyclopropyl).

Diethyl [(3-{2-amino-6-[(2,2,2-trifluoroethyl)amino]-9H-purin-9-yl}-2-hydroxypropoxy)methyl]-phosphonate (**25**). Prepared with a 5% solution of 2,2,2-trifluorethylamine in ethanol (20 ml) in an autoclave at 100 °C for 12 h. Chromatography in system S2 gave 423 mg (93%) of **25** as a white foam. For $C_{15}H_{24}F_3N_6O_5P$ (456.4) calculated: 39.48% C, 5.30% H, 12.49% F, 18.42% N, 6.79% P; 39.31% C, 5.17% H, 12.59% F, 18.13% N, 6.67% P. FAB MS, *m/z* (%): 457 (100) [M + H], 233 (40) [M + H of 2-amino-6-[(trifluoroethyl)amino]purine]. ^{1}H NMR (DMSO-d_6): 7.78 br, 1 H (NH); 7.70 s, 1 H (H-8); 6.02 br s, 2 H (NH_2); 5.35 d, 1 H, *J*(OH,2′) = 4.8 (2′-OH); 4.29 m, 2 H (H-1″); 4.05 dq, 4 H, *J*(CH_2,CH_3) = 7.1, *J*(P,OCH) = 8.2 (P-OCH_2); 4.03 overlay, 1 H (H-1′a); 3.97 m, 1 H (H-2′); 3.89 dd, 1 H, *J*(1′b,2′) = 7.6, *J*(gem) = 13.2 (H-1′b); 3.86 d, 2 H, *J*(P,CH) = 7.7 (PCH_2); 3.49 d, 2 H, *J*(3′,2′) = 4.6 (H-3′); 1.24 t, 6 H (CH_3). ^{13}C NMR (DMSO-d_6): 160.07 (C-2); 154.51 (C-6); 152.36 (C-4); 139.12 (C-8); 125.40 q, *J*(C,F) = 280.1 (CF_3); 113.315 (C-5); 75.055 d, *J*(C,P) = 9.8 (C-3′); 67.57 (C-2′); 64.74 d, *J*(C,P) = 161.6 (P-C); 61.95 d, 2 C, *J*(C,P) = 6.3 (P-OCH_2); 46.37 q, *J*(C,F) = 29.0 (NCH_2); 46.13 (C-1′); 16.53 d, 2 C, *J*(C,P) = 5.4 (CH_3).

Diethyl ({3-[6-(allylamino)-2-amino-9H-purin-9-yl]-2-hydroxypropoxy}methyl)phosphonate (**26**). Chromatographed in system S2. Yield 391 mg (94%) of a colorless syrup. For $C_{16}H_{27}N_6O_5P$ (414.4) calculated: 46.37% C, 6.57% H, 20.28% N, 7.47% P; found: 45.86% C, 6.65% H, 20.08% N, 7.26% P. FAB MS, *m/z* (%): 415 (100) [M + H]. ^{1}H NMR (DMSO-d_6): 7.63 s, 1 H (H-8); 7.32 br s, 1 H (NH); 5.93 ddt, 1 H, *J*(2″,1″) = 5.1, *J*(2″,3″cis) = 10.4, *J*(2″,3″trans) = 17.3 (H-2″); 5.83 br s, 2 H (NH_2); 5.37 d, 1 H, *J*(OH,2′) = 5.4 (2′-OH); 5.14 dq, 1 H, *J*(3″,1″) ≈ *J*(gem) = 1.8 (H-3″trans); 5.03 dq, 1 H, *J*(3″,1″) = 1.8 (H-3″cis); 4.06 dd, 1 H, *J*(1′a,2′) = 3.8, *J*(gem) = 13.8 (H-1′a); 4.05 dq, 4 H, *J*(CH_2,CH_3) = 7.1, *J*(P,OCH) = 8.2 (P-OCH_2); 4.05 m, 2 H (H-1″); 3.96 m, 1 H (H-2′); 3.87 dd, 1 H (1′b,2′) = 7.8 (H-1′b); 3.86 d, 2 H, *J*(P,CH) = 7.7 (PCH_2); 3.49 dd, 1 H, *J*(3′a,2′) = 5.4, *J*(gem) = 10.0 (H-3′a); 3.46 dd, 1 H, *J*(3′b,2′) = 5.2 (H-3′b); 1.24 t, 6 H (CH_3). ^{13}C NMR (DMSO-d_6): 160.25 (C-2); 154.91 (C-6); 150.0 (C-4); 138.225 (C-8); 136.52 (C-2″); 114.85 (C-3″); 113.285 (C-5); 75.02 d, *J*(C,P) = 9.8 (C-3′); 67.68 (C-2′); 64.74 d, *J*(C,P) = 162.1 (P-C); 61.92 d and 61.90 d, *J*(C,P) = 6.4 (P-OCH_2); 46.07 (C-1′); 43.33 (C-1″); 16.50 d, 2 C, *J*(C,P) = 5.4 (CH_3).

Diethyl {[3-(2-amino-6-{[2-(dimethylamino)ethyl]amino}-9H-purin-9-yl)-2-hydroxypropoxy]methyl}-phosphonate (**27**). The crude reaction product was desalted on Dowex 50 (H^+ form) in the same way as described for compound **21**. Yield 434 mg (97%) of a foam. HR MS (FAB): For $C_{17}H_{33}N_7O_5P$ [M + H] calculated: 446.2278; found: 446.2281. FAB MS, *m/z* (%): 446 (8) [M + H]. ^{1}H NMR (DMSO-d_6): 7.64 s, 1 H (H-8); 6.85 br s, 1 H (NH); 5.86 br s, 2 H (NH_2); 4.04 dd, 1 H, *J*(1′a,2′) = 3.2, *J*(gem) = 12.8 (H-1′a); 3.90 m, 1 H (H-2′); 3.85 dd, 1 H, *J*(H-1′b,2′) = 8.1 (H-1′b); 3.76 pent, 4 H, *J*(CH_2,CH_3) = *J*(P,OCH) = 7.1 (P-OCH_2); 3.50 m, 2 H, *J*(CH_2,CH_2) = 6.4 (NCH_2); 3.44 dd, 1 H, *J*(3′a,2′) = 5.4, *J*(gem) = 10.4 (H-3′a); 3.43 dd, 1 H and 3.40 dd, 1 H, *J*(P,CH) = 8.2, *J*(gem) = 13.4 (PCH_2); 3.39 dd, 1 H, *J*(3′b,2′) = 5.4 (H-3′b); 2.81 t, 2 H (NCH_2); 2.19 s, 6 H (NCH_3); 1.05 t, 6 H (CH_3). ^{13}C NMR (DMSO-d_6): 160.29 (C-2); 154.96 (C-6); 152.75 (C-4); 138.36 (C-8); 113.25 (C-5); 75.065 d, *J*(C,P) = 9.3 (C-3′); 68.42 d, *J*(C,P) = 153.3 (P-C); 68.02 (C-2′); 59.20 d, 2 C, *J*(C,P) = 6.4 (P-OCH_2); 58.36 and 47.02 (NCH_2); 45.90 (C-1′); 45.27 and 45.13 (NCH_3); 17.20 d, 2 C, *J*(C,P) = 5.4 (CH_3).

Diethyl ({3-[6-(dimethylamino)-7H-purin-7-yl]-2-hydroxypropoxy}methyl)phosphonate (**28**). Chromatographed in system S3. Yield 244 mg (63%) of a colorless syrup. For $C_{15}H_{26}N_5O_5P$ (387.4) calculated: 46.51% C, 6.76% H, 18.08% N, 8.00% P; found: 46.66% C, 6.78% H, 17.87% N, 8.25% P. FAB MS, *m/z* (%): 388 (100) [M + H]. ^{1}H NMR (DMSO-d_6): 8.42 s, 1 H

and 8.37 s, 1 H (H-2, H-8); 5.25 d, 1 H, *J*(OH,2′) = 5.7 (2′-OH); 4.51 dd, 1 H, *J*(1′a,2′) = 3.2, *J*(gem) = 14.4 (H-1′a); 4.19 dd, 1 H, *J*(1′b,2′) = 9.2 (H-1′b); 4.06 br pent, 4 H, *J*(P,OCH) = *J*(CH_2,CH_3) = 7.1 (P-OCH_2); 3.89 m, 1 H (H-2′); 3.85 d, 2 H, *J*(P,CH) = 8.1 (PCH_2); 3.49 dd, 1 H, *J*(3′a,2′) = 5.0, *J*(gem) = 10.9 (H-3′a); 3.43 dd, 1 H, *J*(3′b,2′) = 6.3 H-3′b); 3.01 s, 6 H (NCH_3); 1.25 t, 6 H, *J*(CH_3,CH_2) = 7.0 (CH_3). ^{13}C NMR (DMSO-d_6): 161.53 (C-4); 155.64 (C-6); 150.975 (C-2); 148.69 (C-8); 114.66 (C-5); 74.79 d, *J*(C,P) = 10.7 (C-3′); 68.30 (C-2′); 64.63 d, *J*(C,P) = 162.6 (P-C); 61.86 d, 2 C, *J*(C,P) = 6.4 (P-OCH_2); 50.94 (C-1′); 16.47 d, 2 C, *J*(C,P) = 5.4 (CH_3).

Diethyl ({3-[6-(cyclopropylamino)-7H-purin-7-yl]-2-hydroxypropoxy}methyl)phosphonate (**29**). Chromatographed in system S3. Yield 264 mg (65%) of a white solid. For $C_{16}H_{26}N_5O_5P\cdot 0.5H_2O$ (408.4) calculated: 47.06% C, 6.66% H, 17.15% N, 7.58% P; found: 47.26% C, 6.74% H, 16.91% N, 7.45% P. FAB MS, *m/z* (%): 400 (100) [M + H]. ^{1}H NMR (DMSO-d_6): 8.33 s, 1 H and 8.14 s, 1 H (H-2, H-8); 7.31 br d, 1 H, *J*(NH,CH) = 2.8 (NH); 6.01 d, 1 H, *J*(OH,2′) = 4.9 (2′-OH); 4.48 dd, 1 H, *J*(1′a,2′) = 2.6, *J*(gem) = 15.0 (H-1′a); 4.23 dd, 1 H, *J*(1′b,2′) = 7.7 (H-1′b); 4.07 dq, 4 H, *J*(CH_2,CH_3) = 7.1, *J*(P,OCH) = 8.2 (P-OCH_2); 3.92 m, 1 H (H-2′); 3.88 d, 2 H, *J*(P,CH) = 7.7 (PCH_2); 3.53 dd, 1 H, *J*(3′a,2′) = 5.5, *J*(gem) = 10.2 (H-3′a); 3.49 dd, 1 H, *J*(3′b,2′) = 5.6 (H-3′b); 2.90 m, 1 H (CH-cyclopropyl); 1.25 t, 6 H (CH_3); 0.77 m, 2 H and 0.52 m, 2 H (CH_2-cyclopropyl). ^{13}C NMR (DMSO-d_6): 159.00 (C-4); 152.04 (C-6); 151.84 (C-2); 146.23 (C-8); 112.64 (C-5); 73.96 d, *J*(C,P) = 9.8 (C-3′); 68.64 (C-2′); 64.815 d, *J*(C,P) = 162.1 (P-C); 61.75 d, 2 C, *J*(C,P) = 6.3 (P-OCH_2); 49.38 (C-1′); 23.81 (cyclopropyl); 16.26 d, 2 C, *J*(C,P) = 5.4 (CH_3); 6.59 and 6.33 (cyclopropyl).

Diethyl ({3-[6-(allylamino)-7H-purin-7-yl]-2-hydroxypropoxy}methyl)phosphonate (**30**). Chromatographed in system chloroform–methanol 8:1. Yield 347 mg (87%) of a white solid. For $C_{16}H_{26}N_5O_5P$ (399.4) calculated: 48.12% C, 6.56% H, 17.54% N, 7.76% P; found: 48.05% C, 6.76% H, 17.38% N, 7.78% P. FAB MS, *m/z* (%): 400 (100) [M + H]. ^{1}H NMR (DMSO-d_6): 8.26 s, 1 H and 8.16 s, 1 H (H-2, H-8); 7.22 t, 1 H, *J*(NH,CH_2) = 5.6 (NH); 5.97 ddt, 1 H, *J*(2″,1″) = 5.1, *J*(2″,3″) = 10.4 (cis) and 17.2 (trans) (H-2″); 5.90 d, 1 H, *J*(OH,2′) = 5.0 (2′-OH); 5.22 dq, 1 H, *J*(3″trans,1″) ≈ *J*(gem) = 1.7 (H-3″trans); 5.08 dq, 1 H, *J*(3″cis,1″) ≈ *J*(gem) = 1.7 (H-3″cis); 4.52 dd, 1 H, *J*(1′trans,2′) = 2.8, *J*(gem) = 15.0 (H-1′trans); 4.28 dd, 1 H, *J*(1′cis,2′) = 7.9 (H-1′cis); 4.13 m, 2 H (H-1″); 4.07 dq, 4 H, *J*(CH_2,CH_3) = 7.1, *J*(P,OCH) = 8.2 (P-OCH_2); 3.95 dqd, 1 H (H-2′); 3.89 d, 2 H, *J*(P,CH) = 7.8 (PCH_2); 3.55 dd, 1 H, *J*(3′a,2′) = 5.4, *J*(gem) = 10.0 (H-3′a); 3.52 dd, 1 H, *J*(3′b,2′) = 5.5 (H-3′b); 1.25 t, 6 H (CH_3). ^{13}C NMR (DMSO-d_6): 159.24 (C-4); 151.92 (C-2); 150.89 (C-6); 146.45 (C-8); 135.545 (C-2″); 115.30 (C-3″); 112.43 (C-5); 74.115 d, *J*(C,P) = 9.8 (C-3′); 68.82 (C-2′); 64.805 d, *J*(C,P) = 162.6 (P-CH_2); 61.94 d, 2 C, *J*(C,P) = 6.4 (P-OCH_2); 49.47 (C-1′); 42.64 (C-1″); 16.49 d, 2 C, *J*(C,P) = 5.4 (CH_3).

Preparation of Free 9- and 7-[2-Hydroxy-3-(phosphonomethoxy)propyl] Derivatives of N^6-Substituted Adenines and 2,6-Diaminopurines **31**–**37**, **39**–**43** and **44**–**46**. General Procedure

Bromotrimethylsilane (1.35 ml, 10 mmol) was added to a solution (or suspension) of an appropriate diethyl phosphonate **15**–**28** (1 mmol) in acetonitrile (10 ml). The mixture was stirred at room temperature in the dark for 24 h, the reaction was then quenched by addition of a mixture of ethanol, water and $(C_2H_5)_3N$ (15:15:2; 32 ml), the resulting solution evaporated to dryness and codistilled with water (2 × 30 ml). The residue was dissolved in water (5 ml) and applied onto a column of Dowex 50X8 (H^+ form, 50 ml) equilibrated in

water and the column was washed with water until the UV absorption of the eluate (254 nm) dropped to the original value (1000 ml). The column was then washed with 2.5% aqueous ammonia, the UV absorbing fractions were collected and evaporated to dryness. The amorphous residue was dissolved in water (3–5 ml), applied onto a column of Dowex 50X8 (Na^+ form, 30 ml) and the column was washed with water. The UV absorbing eluate was evaporated to dryness, the residue stirred with a mixture of ethanol (20 ml) and petroleum ether (5 ml) for 1 h and then left standing in a refrigerator overnight. The obtained sodium salt of the product was filtered off, washed with ethanol and ether and dried in vacuo. The following compounds were obtained as disodium salts.

({3-[6-(Dimethylamino)-9H-purin-9-yl]-2-hydroxypropoxy}methyl)phosphonic acid (**31**). Yield 303 mg (77%). For $C_{11}H_{16}N_5Na_2O_5P{\cdot}H_2O$ (393.2) calculated: 33.60% C, 4.61% H, 17.81% N, 7.88% P; found: 33.27% C, 4.78% H, 17.79% N, 7.66% P. FAB MS, *m/z* (%): 376 (9) [M + H, sodium salt], 332 (14) [M + H, free acid]. ^{1}H NMR (D_2O): 7.98 s, 2 H (H-2, H-8); 4.30 m, 1 H and 4.21 m, 2 H (H-1′, H-2′); 3.72 dd, 1 H, *J*(3′a,2′) = 3.0, *J*(gem) = 10.5 (H-3′a); 3.67 dd, 1 H, *J*(P,CH_a) = 9.0, *J*(gem) = 12.9 (PCH_a); 3.63 dd, 1 H, *J*(P,CH_b) = 8.8 (PCH_b); 3.59 dd, 1 H, *J*(3′b,2′) = 5.2 (H-3′b); 3.26 br s, 6 H (NCH_3). ^{13}C NMR (D_2O): 154.00 (C-6); 151.48 (C-2); 148.99 (C-4); 140.86 (C-8); 118.43 (C-5); 73.81 d, *J*((P,C) = 11.7 (C-3′); 68.39 d, *J*(P,C) = 154.3 (P-C); 68.28 (C-2′); 46.20 (C-1′); 38.81, 2 C (NCH_3).

({3-[6-(Cyclopropylamino)-9H-purin-9-yl]-2-hydroxypropoxy}methyl)phosphonic acid (**32**). Yield 303 mg (77%). For $C_{12}H_{17}N_5NaO_5P{\cdot}1.5H_2O$ (392.3) calculated: 36.74% C, 5.14% H, 17.85% N, 7.90% P; found: 36.66% C, 5.06% H, 18.32% N, 7.40% P. FAB MS, *m/z* (%): 366 (19) [M + H, sodium salt], 344 (20) [M + H, free acid]. ^{1}H NMR (D_2O): 8.18 s, 1 H and 8.07 s, 1 H (H-2, H-8); 4.38 dd, 1 H, *J*(1′a,2′) = 3.3, *J*(gem) = 13.7 (H-1′a); 4.28 dd, 1 H, *J*(1′b,2′) = 8.2 (H-1′b); 4.24 m, 1 H (H-2′); 3.72 dd, 1 H, *J*(3′a,2′) = 3.7, *J*(gem) = 10.5 (H-3′a); 3.68 dd, 1 H and 3.65 dd, 1 H, *J*(P,CH) = 8.8, *J*(gem) = 12.9 (PCH_2); 3.59 dd, 1 H, *J*(3′b,2′) = 5.2 (H-3′b); 2.80 m, 1 H, 0.92 m, 2 H and 0.68 m, 2 H (cyclopropyl). ^{13}C NMR (D_2O): 155.37 (C-6); 152.14 (C-2); 148.03 (C-4); 142.48 (C-8); 118.53 (C-5); 73.73 d, *J*(P,C) = 10.7 (C-3′); 68.29 (C-2′); 68.01 d, *J*(P,C) = 153.8 (P-C); 46.23 (C-1′); 23.26 and 6.56, 2 C (cyclopropyl).

{[2-Hydroxy-3-(6-piperidino-9H-purin-9-yl)propoxy]methyl}phosphonic acid (**33**). Yield 181 mg (42%). For $C_{14}H_{20}N_5Na_2O_5P{\cdot}H_2O$ (433.3) calculated: 38.81% C, 5.12% H, 16.16% N, 7.15% P; found: 39.32% C, 5.32% H, 15.99% N, 6.89% P. FAB MS, *m/z* (%): 416 (60) [M + H, sodium salt], 372 (5) [M + H, free acid]. ^{1}H NMR (D_2O): 8.03 s, 1 H and 8.02 s, 1 H (H-2, H-8); 4.33 m, 1 H and 4.24 m, 2 H (H-1′, H-2′); 3.90 m, 4 H (NCH_2-piperidine); 3.73 dd, 1 H, *J*(3′a,2′) = 2.7, *J*(gem) = 10.5 (H-3′a); 3.67 dd, 1 H and 3.63 dd, 1 H, *J*(P,CH) = 8.8, *J*(gem) = 12.9 (PCH_2); 3.60 dd, 1 H, *J*(3′b,2′) = 5.1 (H-3′b); 1.70 m, 2 H and 1.58 m, 4 H (CH_2-piperidine). ^{13}C NMR (D_2O): 153.02 (C-6); 151.67 (C-2); 149.36 (C-4); 140.71 (C-8); 118.30 (C-5); 73.75 d, *J*(P,C) = 11.2 (C-3′); 68.59 d, *J*(P,C) = 153.3 (P-C); 68.25 (C-2′); 46.935, 2 C (piperidine); 46.15 (C-1′); 25.55, 2 C and 23.91 (piperidine).

[(2-Hydroxy-3-{6-[(2-methoxyethyl)amino]-9H-purin-9-yl}propoxy)methyl]phosphonic acid (**34**). Yield 310 mg (76%). FAB MS, *m/z* (%): 406 (15) [M + H, sodium salt], 362 (95) [M + H, free acid]. ^{1}H NMR (D_2O): 8.12 s, 1 H and 8.065 s, 1 H (H-2, H-8); 4.36 m, 1 H and 4.26 m, 2 H (H-1′, H-2′); 3.75 m, 4 H (NCH_2, OCH_2); 3.75 overlay (H-3′a); 3.73 dd, 1 H and 3.70 dd, 1 H, *J*(P,CH) = 8.8, *J*(gem) = 13.1 (PCH_2); 3.62 dd, 1 H, *J*(3′b,2′) = 5.4, *J*(gem) = 10.6 (H-3′b); 3.45 s, 3 H (OCH_3). ^{13}C NMR (D_2O): 154.51 (C-6); 152.33 (C-2); 148.24 (C-4); 142.52 (C-8); 118.62 (C-5); 73.98 d, *J*(P,C) = 11.7 (C-3′); 70.725 (OCH_2); 68.49 (C-2′); 68.03 d, *J*(P,C) = 155.8 (P-C); 58.37 (OCH_3); 46.45 (C-1′); 40.27 (NCH_2).

[(2-Hydroxy-3-{6-[(2-hydroxyethyl)amino]-9H-purin-9-yl}propoxy)methyl]phosphonic acid (**35**). Yield 295 mg (72%). For $C_{11}H_{16}N_5Na_2O_6P \cdot H_2O$ (409.3) calculated: 32.28% C, 4.43% H, 17.11% N, 7.56% P; found: 32.36% C, 4.65% H, 16.86% N, 7.46% P. FAB MS, *m/z* (%): 392 (37) [M + H, sodium salt], 348 (5) [M + H, free acid]. ^{1}H NMR (D_2O): 8.08 s, 1 H and 8.06 s, 1 H (H-2, H-8); 4.34 m, 1 H and 4.25 m, 2 H (H-1′, H-2′); 3.86 t, 2 H, *J*(CH_2,CH_2) = 5.5 and 3.67 m, 2 H (NCH_2, OCH_2); 3.74 dd, 1 H, *J*(3′a,2′) = 3.3, *J*(gem) = 10.6 (H-3′a); 3.66 dd, 1 H and 3.64 dd, 1 H, *J*(P,CH) = 8.8, *J*(gem) = 12.7 (PCH_2); 3.61 dd, 1 H, *J*(3′b,2′) = 5.4 (H-3′b). ^{13}C NMR (D_2O): 154.29 (C-6); 152.025 (C-2); 148.00 (C-4); 142.25 (C-8); 118.35 (C-5); 73.69 d, *J*(P,C) = 11.7 (C-3′); 68.72 d, *J*(P,C) = 152.8 (P-C); 68.31 (C-2′); 60.71 (OCH_2); 46.22 (C-1′); 42.78 (NCH_2).

({3-[6-(Allylamino)-9H-purin-9-yl]-2-hydroxypropoxy}methyl)phosphonic acid (**36**). Yield 200 mg (52%). For $C_{12}H_{16}N_5Na_2O_5P$ (387.2) calculated: 37.22% C, 4.16% H, 18.09% N, 8.00% P; found: 37.21% C, 4.58% H, 17.69% N, 8.10% P. FAB MS, *m/z* (%): 388 (16) [M + H]. ^{1}H NMR (D_2O): 8.05 s, 2 H (H-2, H-8); 6.01 ddt, *J*(2″,1″) = 4.9, *J*(2″,3″cis) = 10.4, *J*(2″,3″trans) = 17.3 (H-2′); 5.24 dq, 1 H, *J*(3″trans,1″) = *J*(gem) = 1.6 (H-3″trans); 5.19 dq, 1 H, *J*(3″cis,1″) = 1.6 (H-3′cis); 4.34 m, 1 H and 4.25 m, 2 H (H-1′, H-2′); 4.09 m, 2 H (H-1″); 3.74 dd, 1 H, *J*(3′a,2′) = 3.3, *J*(gem) = 10.4 (H-3′a); 3.70 dd, 1 H and 3.66 dd, 1 H, *J*(P,CH) = 8.8, *J*(gem) = 12.8 (PCH_2); 3.61 dd, 1 H, *J*(3′b,2′) = 5.3 (H-3′b). ^{13}C NMR (D_2O): 154.04 (C-6); 152.13 (C-2); 147.91 (C-4); 142.24 (C-8); 134.00 (C-2″); 118.23 (C-5); 115.54 (C-3″); 73.72 d, *J*(P,C) = 11.7 (C-3′); 68.28 (C-2′); 68.23 d, *J*(P,C) = 154.1 (P-C); 46.22 (C-1′); 42.77 (C-1″).

{[3-(6-{[2-(Dimethylamino)ethyl]amino}-9H-purin-9-yl)-2-hydroxypropoxy]methyl}phosphonic acid (**37**). Yield 273 mg (65%). FAB MS, *m/z* (%): 419 (1) [M + H, sodium salt], 375 (5) [M + H, free acid]. ^{1}H NMR (D_2O): 8.20 s, 1 H and 8.13 s, 1 H (H-2, H-8); 4.39 dd, 1 H, *J*(1′a,2′) = 3.6, *J*(gem) = 14.2 (H-1′a); 4.31 dd, 1 H, *J*(1′b,2′) = 8.1 (H-1′b); 4.25 m, 1 H (H-2′); 3.97 t, 2 H, *J*(CH_2,CH_2) = 6.1 (NCH_2); 3.72 dd, 1 H, *J*(3′a,2′) = 3.5, *J*(gem) = 10.5 (H-3′a); 3.60 dd, 1 H, *J*(3′b,2′) = 6.0 (H-3′b); 3.60 dd, 1 H and 3.56 dd, 1 H, *J*(P,CH) = 8.8, *J*(gem) = 12.2 (PCH_2); 3.41 t, 2 H, *J*(CH_2,CH_2) = 6.1 (NCH_2); 2.92 s, 6 H (NCH_3). ^{13}C NMR (D_2O): 154.20 (C-6); 152.095 (C-2); 148.42 (C-4); 142.83 (C-8); 118.61 (C-5); 73.65 d, *J*(P,C) = 11.7 (C-3′); 69.53 d, *J*(P,C) = 150.9 (P-C); 68.375 (C-2′); 56.91 (NCH_2); 50.51 (NCH_3); 46.32 (C-1′); 43.225 (NCH_3); 36.31 (NCH_2).

({3-[2-Amino-6-(dimethylamino)-9H-purin-9-yl]-2-hydroxypropoxy}methyl)phosphonic acid (**39**). Yield 290 mg (77%). FAB MS, *m/z* (%): 391 (45) [M + H]. ^{1}H NMR (D_2O): 7.68 s, 1 H (H-8); 4.18 dd, 1 H, *J*(1′a,2′) = 3.3, *J*(gem) = 14.0 (H-1′a); 4.14 m, 1 H (H-2′); 4.06 dd, 1 H, *J*(1′b,2′) = 8.8 (H-1′b); 3.71 dd, 1 H, *J*(3′a,2′) = 3.0, *J*(gem) = 10.6 (H-3′a); 3.55 d, 2 H, *J*(P,CH) = 8.6 (PCH_2); 3.54 dd, 1 H, *J*(3′b,2′) = 5.5 (H-3′b); 3.21 s, 6 H (CH_3). ^{13}C NMR (D_2O): 159.61 (C-2); 155.06 (C-6); 151.69 (C-4); 138.95 (C-8); 113.60 (C-5); 74.20 d, *J*(P,C) = 11.7 (C-3′); 70.02 d, *J*(P,C) = 150.8 (P-C); 68.77 (C-2′); 46.275 (C-1′); 38.775, 2 C (CH_3).

({3-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-hydroxypropoxy}methyl)phosphonic acid (**40**). Yield 208 mg (52%). For $C_{12}H_{17}N_6Na_2O_5P$ (402.3) calculated: 35.83% C, 4.26% H, 20.89% N, 7.70% P; found: 35.80% C, 4.53% H, 20.62% N, 7.48% P. FAB MS, *m/z* (%): 403 (10) [M + H, sodium salt], 359 (17) [M + H, free acid]. ^{1}H NMR (D_2O): 7.76 s, 1 H (H-8); 4.20 m, 2 H (H-1′a, H-2′); 4.10 dd, 1 H, *J*(1′b,2′) = 8.0, *J*(gem) = 14.2 (H-1′b); 3.69 dd, 1 H, *J*(3′a,2′) = 3.4, *J*(gem) = 10.6 (H-3′a); 3.56 d, 2 H, *J*(P,CH) = 8.8 (PCH_2); 3.54 dd, 1 H, *J*(3′b,2′) = 5.6 (H-3′b); 2.81 m, 1 H, 0.88 m, 2 H and 0.65 m, 2 H (cyclopropyl). ^{13}C NMR (D_2O): 160.35 (C-2); 156.475 (C-6); 150.51 (C-4); 140.385 (C-8); 113.42 (C-5); 74.25 d, *J*(P,C) = 11.6 (C-3′); 69.99 d, *J*(P,C) = 150.4 (P-C); 68.825 (C-2′); 46.35 (C-1′); 23.63 and 7.155, 2 C (cyclopropyl).

[(3-{2-Amino-6-[(2,2,2-trifluoroethyl)amino]-9H-purin-9-yl}-2-hydroxypropoxy)methyl]phosphonic acid (**41**). Yield 300 mg (62%). For $C_{11}H_{14}F_3N_6Na_2O_5P \cdot 2H_2O$ (480.2) calculated: 11.86% F, 17.50% N, 6.45% P; found: 12.16% F, 17.16% N, 6.33% P. FAB MS, *m/z* (%): 445 (80) [M + H, sodium salt]. ^{1}H NMR (D_2O): 7.83 s (H-8); 4.34 br q, 2 H, *J*(H,F) = 9.5 (NCH_2); 4.24 dd, 1 H, *J*(1′a,2′) = 3.5, *J*(gem) = 13.2 (H-1′a); 4.21 m, 1 H (H-2′); 4.14 dd, 1 H, *J*(1′b, 2′) = 7.1 (H-1′b); 3.70 dd, 1 H, *J*(3′a,2′) = 3.3, *J*(gem) = 10.5 (H-3′a); 3.60 dd, 1 H and 3.56 dd, 1 H, *J*(P,CH) = 8.7, *J*(gem) = 12.4 (PCH_2); 3.57 dd, 1 H, *J*(3′b,2′) = 4.9 (H-3′b). ^{13}C NMR (D_2O): 159.95 (C-2); 154.88 (C-6); 151.23 (C-4); 140.655 (C-8); 124.68 q, *J*(C,F) = 278.8 (CF_3); 113.19 (C-5); 73.68 d, *J*(C,P) = 11.3 (C-3′); 69.24 d, *J*(C,P) = 151.4 (P-C); 68.39 (C-2′); 45.85 (C-1′); 41.37 q, *J*(C,F) = 29.0 (NCH_2).

({3-[6-(Allylamino)-2-amino-9H-purin-9-yl]-2-hydroxypropoxy}methyl)phosphonic acid (**42**). Yield 220 mg (52%). For $C_{12}H_{17}N_6Na_2O_5P \cdot H_2O$ (420.3) calculated: 34.29% C, 4.56% H, 19.99% N, 7.37% P; found: 34.42% C, 4.38% H, 19.70% N, 7.37% P. FAB MS, *m/z* (%): 403 (30) [M + H]. ^{1}H NMR (D_2O): 7.79 s, 1 H (H-8); 6.02 ddt, 1 H, *J*(2″,1″) = 5.0, *J*(2″,3″cis) = 10.4, *J*(2″,3″trans) = 17.3 (H-2″); 5.26 dq, 1 H, *J*(3″trans,1″) ≈ *J*(gem) = 1.6 (H-3″trans); 5.19 dq, 1 H, *J*(3″cis,1″) = 1.6 (H-3″cis); 4.23 dd, 1 H, *J*(1′a,2′) = 3.7, *J*(gem) = 14.6 (H-1′a); 4.21 m, 1 H (H-2′); 4.14 m, 2 H (H-1″); 4.13 dd, 1 H, *J*(1′b,2′) = 9.8 (H-1′b); 3.69 dd, 1 H, *J*(3′a,2′) = 3.2, *J*(gem) = 10.5 (H-3′a); 3.55 dd, 1 H, *J*(3′b,2′) = 5.0 (H-3′b); 3.57 dd, 1 H and 3.53 dd, 1 H, *J*(P,CH) = 8.8, *J*(gem) = 12.4 (PCH_2). ^{13}C NMR (D_2O): 160.14 (C-2); 155.11 (C-6); 150.10 (C-4); 140.04 (C-8); 134.61 (C-2″); 115.41 (C-3″); 112.995 (C-5); 73.70 d, *J*(P,C) = 11.7 (C-3′); 69.62 d, *J*(P,C) = 150.9 (P-C); 68.45 (C-2′); 45.84 (C-1′); 42.66 (C-1″).

{[3-(2-Amino-6-{[2-(dimethylamino)ethyl]amino}-9H-purin-9-yl)-2-hydroxypropoxy]methyl}phosphonic acid (**43**). Yield 300 mg (69%), white solid. HR MS (FAB): For $C_{13}H_{23}N_7Na_2O_5P$ [M + H] calculated: 434.1294; found: 434.1267. FAB MS, *m/z* (%): 434 (12) [M + H]. ^{1}H NMR (D_2O): 7.785 s, 1 H (H-8); 4.23 dd, 1 H, *J*(1′a,2′) = 3.8, *J*(gem) = 14.8 (H-1′a); 4.21 m, 1 H (H-2′); 4.13 dd, 1 H, *J*(1′b,2′) = 9.2 (H-1′b); 3.70 dd, 1 H, *J*(3′a,2′) = 3.3, *J*(gem) = 10.7 (H-3′a); 3.66 m, 2 H (NCH_2); 3.58 dd, 1 H and 3.55 dd, 1 H, *J*(P,CH) = 8.7, *J*(gem) = 12.4 (PCH_2); 3.56 dd, 1 H, *J*(3′b,2′) = 5.3 (H-3′b); 2.70 t, 2 H, *J*(CH_2,CH_2) = 6.7 (NCH_2); 2.33 s, 6 H (CH_3). ^{13}C NMR (D_2O): 160.11 (C-2); 155.13 (C-6); 150.445 (C-4); 139.99 (C-8); 113.10 (C-5); 73.74 d, *J*(P,C) = 11.2 (C-3′); 69.65 d, *J*(P,C) = 149.9 (P-C); 68.46 (C-2′); 57.36 (NCH_2); 45.87 (C-1′); 44.045, 2 C (NCH_3); 37.93 (NCH_2).

({3-[6-(Dimethylamino)-7H-purin-7-yl]-2-hydroxypropoxy}methyl)phosphonic acid (**44**). Yield 206 mg (55%). Hygroscopic material. FAB MS, *m/z* (%): 376 (10) [M + H, sodium salt], 332 (100) [M + H, free acid]. ^{1}H NMR (D_2O): 8.37 s, 1 H and 8.30 s, 1 H (H-2, H-8); 4.69 dd, 1 H, *J*(1′a,2′) = 3.7, *J*(gem) = 14.9 (H-1′a); 4.47 dd, 1 H, *J*(1′b,2′) = 8.8 (H-1′b); 4.32 m, 1 H (H-2′); 3.64 d, 2 H, *J*(P,CH) = 8.8 (PCH_2); 3.63 dd, 1 H, *J*(3′a,2′) = 4.1, *J*(gem) = 10.5 (H-3′a); 3.52 dd, 1 H, *J*(3′b,2′) = 5.4 (H-3′b); 3.15 s, 6 H (NCH_3). ^{13}C NMR (D_2O): 159.50 (C-4); 156.19 (C-6); 151.18 (C-2); 148.69 (C-8); 114.30 (C-5); 73.67 d, *J*(P,C) = 11.2 (C-3′); 69.01 (C-2′); 67.88 d, *J*(P,C) = 155.8 (P-C); 51.07 (C-1′); 40.98, 2 C (NCH_3).

({3-[6-(Cyclopropylamino)-7H-purin-7-yl]-2-hydroxypropoxy}methyl)phosphonic acid (**45**). Yield 200 mg (49%). For $C_{12}H_{16}N_5Na_2O_5P \cdot H_2O$ (405.3) calculated: 35.56% C, 4.48% H, 17.28% N, 7.64% P; found: 35.61% C, 4.70% H, 17.11% N, 7.49% P. FAB MS, *m/z* (%): 388 (12) [M + H]. ^{1}H NMR (D_2O): 8.22 s, 1 H and 8.18 s, 1 H (H-2, H-8); 4.55 dd, 1 H, *J*(1′a,2′) = 2.9, *J*(gem) = 15.5 (H-1′a); 4.40 dd, 1 H, *J*(1′b,2′) = 5.3 (H-1′b); 4.19 m, 1 H (H-2′); 3.68 dd, 1 H and 3.65 dd, 1 H, *J*(P,CH) = 8.2, *J*(gem) = 12.8 (PCH_2); 3.65 dd, 1 H, *J*(3′a,2′) = 5.5, *J*(gem) = 10.4 (H-3′a); 3.60 dd, 1 H, *J*(3′b,2′) = 6.2 (H-3′b); 2.78 m, 1 H, 0.94 m, 2 H and 0.67 m, 2 H (cyclopropyl). ^{13}C NMR (D_2O): 156.675 (C-4); 152.36 (C-6); 151.93 (C-2); 146.64 (C-8);

112.09 (C-5); 73.11 d, *J*(P,C) = 10.7 (C-3′); 68.84 (C-2′); 68.37 d, *J*(P,C) = 153.3 (P-C); 49.74 (C-1′); 23.52, 6.62 and 6.49 (cyclopropyl).

({3-[6-(Allylamino)-7H-purin-7-yl]-2-hydroxypropoxy}methyl)phosphonic acid (**46**). Yield 205 mg (53%). FAB MS, *m/z* (%): 388 (72) [M + H]. ^{1}H NMR (D_2O): 8.28 s, 1 H and 8.25 s, 1 H (H-2, H-8); 6.07 ddt, 1 H, *J*(2″,1″) = 4.6, *J*(2″,3″cis) = 10.4, *J*(2″,3″trans) = 17.3 (H-2″); 5.26 dq, 1 H, *J*(3″trans,1″) ≈ *J*(gem) = 1.6 (H-3″trans); 5.22 dq, 1 H, *J*(3″cis,1″) ≈ *J*(gem) = 1.6 (H-3″cis); 4.68 dd, 1 H, *J*(1′a,2′) = 3.1, *J*(gem) = 15.4 (H-1′a); 4.53 dd, 1 H, *J*(1′b,2′) = 7.6 (H-1′b); 4.27 m, 1 H (H-2′); 4.20 dt, 2 H (H-1″); 3.72 dd, 1 H, *J*(3′a,2′) = 4.4, *J*(gem) = 10.4 (H-3′a); 3.63 dd, 1 H, *J*(3′b,2′) = 6.5 (H-3′b); 3.61 dd, 1 H and 3.57 dd, 1 H, *J*(P,CH) = 8.7, *J*(gem) = 12.4 (PCH_2). ^{13}C NMR (D_2O): 157.02 (C-4); 152.21 (C-2); 151.40 (C-6); 146.69 (C-8); 133.92 (C-2″); 115.295 (C-3″); 112.16 (C-5); 73.13 d, *J*(P,C) = 11.2 (C-3′); 69.37 d, *J*(P,C) = 150.9 (P-C); 69.07 (C-2′); 49.75 (C-1′); 42.87 (C-1″).

Preparation of 6-Thioxo Derivatives **47** and **48**. General Procedure

Thiourea (152 mg, 2 mmol) was added to a solution of an appropriate 6-chloro derivative **11** or **13** (1.5 mmol) in absolute ethanol (15 ml). The reaction mixture was refluxed for 3 h, then cooled to room temperature and taken down. The residue was applied onto a column of silica gel (150 ml) and chromatographed in system chloroform–methanol 4:1 (compound **47**) or in system S3 (compound **48**). Product-containing fractions were evaporated and the thus obtained solid residue further recrystallized. The following compounds were obtained.

Diethyl {[2-hydroxy-3-(6-thioxo-1,6-dihydro-9H-purin-9-yl)propoxy]methyl}phosphonate (**47**) was prepared from compound **11**. Yield 460 mg (81%), white crystals, m.p.137–138 °C (ethyl acetate). HR MS (FAB): For $C_{13}H_{22}N_4O_5PS$ [M + H] calculated: 377.1049; found: 377.1032. FAB MS, *m/z* (%): 377 (100) [M + H]. ^{1}H NMR (DMSO-d_6): 13.70 br s, 1 H (NH); 8.195 s, 1 H and 8.19 s, 1 H (H-2, H-8); 5.36 br s, 1 H (2′-OH); 4.26 dd, 1 H, *J*(1′a,2′) = 3.7, *J*(gem) = 13.8 (H-1′a); 4.07 dd, 1 H, *J*(1′b,2′) = 7.2 (H-1′b); 4.05 br pent, 4 H, *J*(CH_2,CH_3) ≈ *J*(P,OCH) = 7.2 (P-OCH_2); 4.00 m, 1 H (H-2′); 3.86 d, 2 H, *J*(P,CH) = 7.8 (PCH_2); 3.53 dd, 1 H, *J*(3′a,2′) = 5.2, *J*(gem) = 10.0 (H-3′a); 3.49 dd, 1 H, *J*(3′b,2′) = 5.7 (H-3′b); 1.24 t, 6 H (CH_3). ^{13}C NMR (DMSO-d_6): 175.86 (C-6); 144.94 (C-2); 144.57 (C-4); 143.93 (C-8); 135.03 (C-5); 74.69 d, *J*(P,C) = 10.3 (C-3′); 67.62 (C-2′); 64.70 d, *J*(P,C) = 162.1 (P-C); 61.94 d, 2 C, *J*(P,C) = 6.4 (P-OCH_2); 46.90 (C-1′); 16.51 d, 2 C, *J*(P,C) = 5.4 (CH_3).

Diethyl {[3-(2-amino-6-thioxo-1,6-dihydro-9H-purin-9-yl)-2-hydroxypropoxy]methyl}phosphonate (**48**) was prepared from compound **13**. Yield 437 mg (74%), white crystals, m.p. 146–148 °C (ethanol). For $C_{13}H_{22}N_5O_5PS$ (391.4) calculated: 39.89% C, 5.66% H, 17.89% N, 7.91% P, 8.19% S; found: 39.52% C, 5.62% H, 17.77% N, 7.84% P, 8.37% S. FAB MS, *m/z* (%): 392 (100) [M + H]. ^{1}H NMR (DMSO-d_6): 11.85 br s, 1 H (NH); 7.80 s, 1 H (H-8); 6.78 br s, 2 H (NH_2); 5.31 d, 1 H, *J*(OH,2′) = 5.5 (2′-OH); 4.05 dq, 4 H, *J*(CH_2,CH_3) = 7.1, *J*(P,CH) = 8.3 (P-OCH_2); 4.04 dd, 1 H, *J*(1′a,2′) = 3.4, *J*(gem) = 13.6 (H-1′a); 3.95 m, 1 H (H-2′); 3.86 dd, 1 H, *J*(1′b,2′) = 8.4 (H-1′b); 3.85 d, 2 H, *J*(P,CH) = 7.6 (PCH_2); 3.51 dd, 1 H, *J*(3′a,2′) = 5.4, *J*(gem) = 10.0 (H-3′a); 3.47 dd, 1 H, *J*(3′b,2′) = 5.4 (H-3′b); 1.24 t, 6 H (CH_3). ^{13}C NMR (DMSO-d_6): 174.88 (C-6); 153.065 (C-2); 148.22 (C-4); 141.50 (C-8); 128.32 (C-5); 74.97 d, *J*(P,C) = 9.8 (C-3′); 67.42 (C-2′); 64.735 d, *J*(P,C) = 161.6 (P-C); 61.91 d, 2 C, *J*(P,C) = 6.4 (P-OCH_2); 46.30 (C-1′); 16.50 d, 2 C, *J*(P,C) = 5.4 (CH_3).

Diethyl {[3-(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)-2-hydroxypropoxy]methyl}-phosphonate (**49**)

A mixture of 2-amino-6-chloro derivative **13** (825 mg, 2.1 mmol) and 80% acetic acid (20 ml) was heated to reflux for 2 h, then cooled to room temperature and taken down. The residue was coevaporated with toluene (3 × 20 ml) and then chromatographed on a silica gel column (100 ml) in system chloroform–methanol (4:1). Yield 580 mg (74%), white crystals, m.p. 139–142 °C (ethanol). For $C_{13}H_{22}N_5O_6P$ (375.3) calculated: 41.60% C, 5.91% H, 18.66% N, 8.25% P; found: 41.11% C, 5.97% H, 18.36% N, 8.25% P. FAB MS, *m/z* (%): 376 (100) [M + H], 152 (58) [guanine + H]. ^{1}H NMR (DMSO-d_6): 10.75 br s, 1 H (NH); 7.60 s, 1 H (H-8); 6.44 br s, 2 H (NH_2); 5.50 d, 1 H, *J*(OH,2′) = 5.4 (2′-OH); 4.03 br pent, 4 H, *J*(CH_2,CH_3) = 7.1, *J*(P,OCH) = 8.0 (P-OCH_2); 3.99 dd, 1 H, *J*(1′a,2′) = 2.9, *J*(gem) = 13.8 (H-1′a); 3.92 m, 1 H (H-2′); 3.86 dd, 1 H, *J*(1′b,2′) = 8.2 (H-2′b); 3.82 d, 2 H, *J*(P,CH) = 7.8 (PCH_2); 3.46 d, 2 H, *J*(3′,2′) = 5.0 (H-3′); 1.21 t, 6 H (CH_3). ^{13}C NMR (DMSO-d_6): 158.08 (C-6); 154.39 (C-2); 152.30 (C-4); 139.75 (C-8); 116.715 (C-5); 75.57 d, *J*(P,C) = 10.7 (C-3′); 68.44 (C-2′); 65.25 d, *J*(P,C) = 162.6 (P-C); 63.26 d, 2 C, *J*(P,C) = 6.4 (P-OCH_2); 46.90 (C-1′); 17.06 d, 2 C, *J*(P,C) = 5.4 (CH_3).

{[2-Hydroxy-3-(6-thioxo-1,6-dihydro-9*H*-purin-9-yl)propoxy]methyl}-phosphonic Acid (**50**)

Bromotrimethylsilane (0.79 ml, 6 mmol) was added to a suspension of thioxo derivative **47** (346 mg, 0.92 mmol) in acetonitrile (10 ml). The reaction mixture was stirred in the dark at room temperature for 20 h, taken down in vacuo at 30 °C and the residue coevaporated with toluene (2 × 20 ml). The residue was dissolved in water (10 ml) and neutralized dropwise with 5% LiOH to pH 7. The neutral solution was evaporated to a smaller volume (ca. 2–3 ml), applied onto a column of Dowex 50 (Li^+ form, 50 ml) and eluted with water. Combined UV-absorbing fractions were evaporated, the solid residue mixed with acetone (20 ml) and set aside. The acetone solution (containing LiBr) was removed, the sediment treated three times more with acetone (20 ml) to remove all LiBr. The solid residue was then filtered with suction, washed thoroughly with acetone and finally with ether and dried in vacuo. Yield 255 mg (83%) of dilithium salt of **50**. Yellowish solid. FAB MS, *m/z* (%): 333 (30) [M + H of lithium salt]. ^{1}H NMR (D_2O): 8.30 s, 1 H and 8.29 s, 1 H (H-2, H-8); 4.46 dd, 1 H, *J*(1′a,2′) = 3.5, *J*(gem) = 14.4 (H-1′a); 4.35 dd, 1 H, *J*(1′b, 2′) = 8.3 (H-1′b); 4.28 m, 1 H (H-2′); 3.73 dd, 1 H, *J*(3′a,2′) = 3.5, *J*(gem) = 10.5 (H-3′a); 3.63 d, 2 H, *J*(P,CH) = 8.9 (PCH_2); 3.62 dd, 1 H, *J*(3′b,2′) = 6.0 (H-3′b). ^{13}C NMR (D_2O): 174.685 (C-6); 145.57 (C-2); 145.05 (C-8); 144.53 (C-4); 134.51 (C-5); 73.62 d, *J*(P,C) = 11.2 (C-3′); 68.69 d, *J*(P,C) = 152.8 (P-C); 68.35 (C-2′); 46.74 (C-1′).

Conversion of Esters **22**, **48** and **49** to Free Acids

A mixture of an appropriate diethyl phosphonate (1 mmol), acetonitrile (10 ml) and bromotrimethylsilane (1.35 ml, 10 mmol) was treated and then worked up analogously as described in the preparation of compounds **31**–**37** or **39**–**43**. The crude product was desalted on a column of Dowex 50X8 (H^+ form, 50 ml) by elution with water. Elution of the product began after ca. 700–1000 ml of eluate. UV-absorbing fractions containing the product were evaporated to dryness and the residue was crystallized from aqueous ethanol. The following compounds were obtained as free acids.

[(2-Hydroxy-3-{6-[(2,2,2-trifluoroethyl)amino]-9H-purin-9-yl}propoxy)methyl]phosphonic acid (**38**). Yield 300 mg (74%), m.p. 99–101 °C. For $C_{11}H_{15}F_3N_5PO_5 \cdot H_2O$ (403.3) calculated: 32.76% C, 4.25% H, 14.13% F, 17.36% N, 7.68% P; found: 32.74% C, 4.24% H, 14.07% F, 17.66% N, 7.89% P. FAB MS, *m/z* (%): 386 (100) [M + H]. ^{1}H NMR (D_2O): 8.48 s, 1 H and 8.44 s, 1 H (H-2, H-8); 4.60 m, 2 H (NCH_2); 4.54 dd, 1 H, *J*(1′a,2′) = 3.9, *J*(gem) = 14.7 (H-1′a); 4.44 dd, 1 H, *J*(1′b,2′) = 7.8 (H-1′b); 4.28 m, 1 H (H-2′); 3.73 dd, 1 H and 3.70 dd, 1 H, *J*(P,CH) = 8.7, *J*(gem) = 12.4 (PCH_2); 3.71 dd, 1 H, *J*(3′a,2′) = 3.4, *J*(gem) = 10.5 (H-3′a); 3.66 dd, 1 H, *J*(3′b,2′) = 5.0 (H-3′b). ^{13}C NMR (D_2O): 153.20 (C-6); 151.25 (C-2); 148.30 (C-4); 144.67 (C-8); 123.99 q, *J*(C,F) = 278.8 (CF_3); 117.92 (C-5); 73.59 d, *J*(P,C) = 11.7 (C-3′); 68.08 (C-2′); 67.25 d, *J*(P,C) = 157.2 (P-C); 46.935 (C-1′); 42.72 q, *J*(C,F) = 30 (NCH_2).

{[3-(2-Amino-6-thioxo-1,6-dihydro-9H-purin-9-yl)-2-hydroxypropoxy]methyl}phosphonic acid (**51**). Yield 230 mg (69%) of white crystals, m.p. 232–234 °C. For $C_9H_{14}N_5O_5PS$ (335.3) calculated: 32.24% C, 4.21% H, 20.89% N, 9.24% P, 9.56% S; found: 31.94% C, 4.23% H, 20.53% N, 8.90% P, 9.81% S. FAB MS, *m/z* (rel.%): 336 (6) [M + H]. ^{1}H NMR (D_2O + NaOD): 7.87 s, 1 H (H-8); 4.21 dd, 1 H, *J*(1′a,2′) = 4.0, *J*(gem) = 14.8 (H-1′a); 4.20 m, 1 H (H-2′); 4.09 dd, 1 H, *J*(1′b,2′) = 9.2 (H-1′b); 3.66 dd, 1 H, *J*(3′a,2′) = 3.5, *J*(gem) = 10.6 (H-3′a); 3.54 dd, 1 H, *J*(3′b,2′) = 5.6 (H-3′b); 3.56 dd, 1 H and 3.52 dd, 1 H, *J*(P,CH) = 8.8, *J*(gem) = 12.4 (PCH_2). ^{13}C NMR (D_2O + NaOD): 177.925 (C-6); 158.75 (C-2); 148.06 (C-4); 141.17 (C-8); 129.42 (C-5); 74.13 d, *J*(P,C) = 11.2 (C-3′); 69.66 d, *J*(P,C) = 150.4 (P-C); 68.46 (C-2′); 46.16 (C-1′).

{[3-(2-Amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-2-hydroxypropoxy]methyl}phosphonic acid (**52**). Yield 202 mg (55%). For $C_9H_{14}N_5O_6P \cdot 2.5H_2O$ (364.3) calculated: 29.68% C, 5.26% H, 19.23% N, 8.50% P; found: 29.61% C, 4.98% H, 19.23% N, 8.24% P. FAB MS, *m/z* (%): 320 (30) [M + H], 152 (5) [guanine + H]. ^{1}H NMR (D_2O + NaOD): 7.75 s, 1 H (H-8); 4.16 m, 1 H (H-2′); 4.16 dd, 1 H, *J*(1′a,2′) = 5.6, *J*(gem) = 14.6 (H-1′a); 4.00 dd, 1 H, *J*(1′b,2′) = 8.8 (H-1′b); 3.58 dd, 1 H, *J*(3′a,2′) = 3.8, *J*(gem) = 10.0 (H-3′a); 3.51 d, 2 H, *J*(P,CH) = 8.8 (PCH_2); 3.47 dd, 1 H, *J*(3′b,2′) = 5.6 (H-3′b). ^{13}C NMR (D_2O + NaOD): 160.39 (C-6); 155.21 (C-2); 150.87 (C-4); 138.68 (C-8); 116.73 (C-5); 74.57 d, *J*(P,C) = 11.2 (C-3′); 68.78 d, *J*(P,C) = 150.4 (P-C); 67.73 (C-2′); 46.31 (C-1′).

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