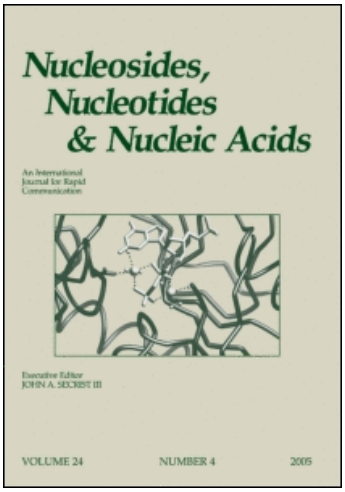

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Synthesis of Base Substituted 2-Hydroxy-3-(purin-9-yl)-propanoic Acids and 4-(Purin-9-yl)-3-butenoic Acids[#]

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ABSTRACT

Alkylation of 6-chloropurine and 2-amino-6-chloropurine with bromoacetaldehyde diethyl acetal afforded 6-chloro-9-(2,2-diethoxyethyl)purine (**3a**) and its 2-amino congener (**3b**). Treatment of compounds **3** with primary and secondary amines gave the N^6-substituted adenines (**5a–5c**) and 2,6-diaminopurines (**5d–5f**). Hydrolysis of **3** resulted in hypoxanthine (**6a**) and guanine (**6b**) derivatives, while their reaction with thiourea led to 6-sulfanylpurine (**7a**) and 2-amino-6-sulfanylpurine (**7b**) compounds. Treatment with diluted acid followed by potassium cyanide treatment and acid hydrolysis afforded 6-substituted 3-(purin-9-yl)- and 3-(2-aminopurin-9-yl)-2-hydroxypropanoic acids (**8–10**). Reaction of compounds **3** with malonic acid in aqueous solution gave exclusively the product of isomerisation, 6-substituted 4-(purin-9-yl)-3-butenoic acids (**15**).

Key Words: Purines; Purine alkylation; Acyclic nucleosides; Malonic acid; 3-(Purin-9-yl)-2-hydroxypropanoic acids.

[#]In honor and celebration of the 70th birthday of Professor Leroy B. Townsend.

[‡]Part of the Diploma Thesis (P.D.), Faculty of Sciences, Charles University Prague (Czech Republic).

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INTRODUCTION

3-(Adenin-9-yl)-2-hydroxypropanoic acid (AHPA) (**1a**) is a powerful inactivator of S-adenosyl-L-homocysteine hydrolase.[1] Hence it is endowed with a capacity to interfere with proliferating cells and systems which require massive SAM-mediated methylation reactions catalyzed by methyl transferases.[2] Thus, it manifested strong chemosterilizing effect on certain insects,[3] on differentiation of plant root cells[4] and, also, an antiviral effect directed against minus stranded RNA viruses and poxviruses. The antiviral activity was enhanced by esterification, which increased the lipophilic character and penetrability of the compounds through the cell membranes.[5] 2-Methylpropyl ester of AHPA (**1b**) was selected as the optimum candidate for detailed investigation.[6] Its activity against vaccinia virus was higher compared to the parent acid, which formed therefrom in the cell pool by cytosolic enzymes. As expected, the target for AHPA action was the capping process (methylation of 5′-end-guanine of viral mRNA).[7]

With the growing interest in compounds active against poxviruses we decided to look more closely on the structure∼activity relationship in this field to find out whether there is not any additional mechanism of antiviral action besides the above-mentioned inhibition of methylation.

RESULTS

This article describes synthesis of racemic base-modified 3-(purin-9-yl)-2-hydroxypropanoic acids, mainly 6-substituted purine and 2-aminopurine derivatives. Recently, we have prepared several optically active compounds of this type by enantiospecific synthesis based on the alkylation of the bases with chiral oxiranecarboxylic acid esters.[8] In the present case, we are applying the cyanohydrin synthesis from the appropriate 2-(purin-9-yl)ethanals, under the conditions used for the original preparation of AHPA and its congeners.[9] The two key-compounds, the 6-chloropurine (**3a**) and the 2-amino-6-chloropurine (**3b**) derivatives were synthesized by treatment of the respective purine base with bromoacetaldehyde diethyl acetal in the presence of NaH, Cs_2CO_3 or DBU in DMF. Under these conditions, the alkylation was directed predominantly to the N9 position. The thus obtained key-intermediates (**3a**) and (**3b**) were treated with the appropriate amine solution (dimethylamine was replaced with dimethylammonium N,N-dimethylcarbamate). The N6-substituted 9-(2,2-diethoxyethyl) adenines (**5a–5c**) or-2,6-diaminopurines (**5d–5f**) were isolated and fully characterized. The DABCO-catalyzed alkaline hydrolysis of the 6-chloro derivatives (**3a**) and (**3b**) gave hypoxanthine (**6a**) and guanine derivative (**6b**), while their treatment with thiourea afforded the 6-sulfanylpurine (**7a**) and 2-amino-6-sulfanylpurine (**7b**) derivatives.[10]

To perform the cyanohydrin synthesis, the 2,2-diethoxyethyl derivatives (**5a–5f**, **6a–6b**, **7a–7b**) were first heated with dilute inorganic acid to form the free aldehydes and the reaction mixtures were treated directly with KCN at neutral pH. Subsequent hydrolysis with dilute HCl afforded the base-modified 2-hydroxy-3-(purin-9-yl)propanoic acids (**8a–8f**, **9a–9b**, **10a–10b**). The deionized reaction products were finally purified by anion exchange chromatography (Sch. 1).

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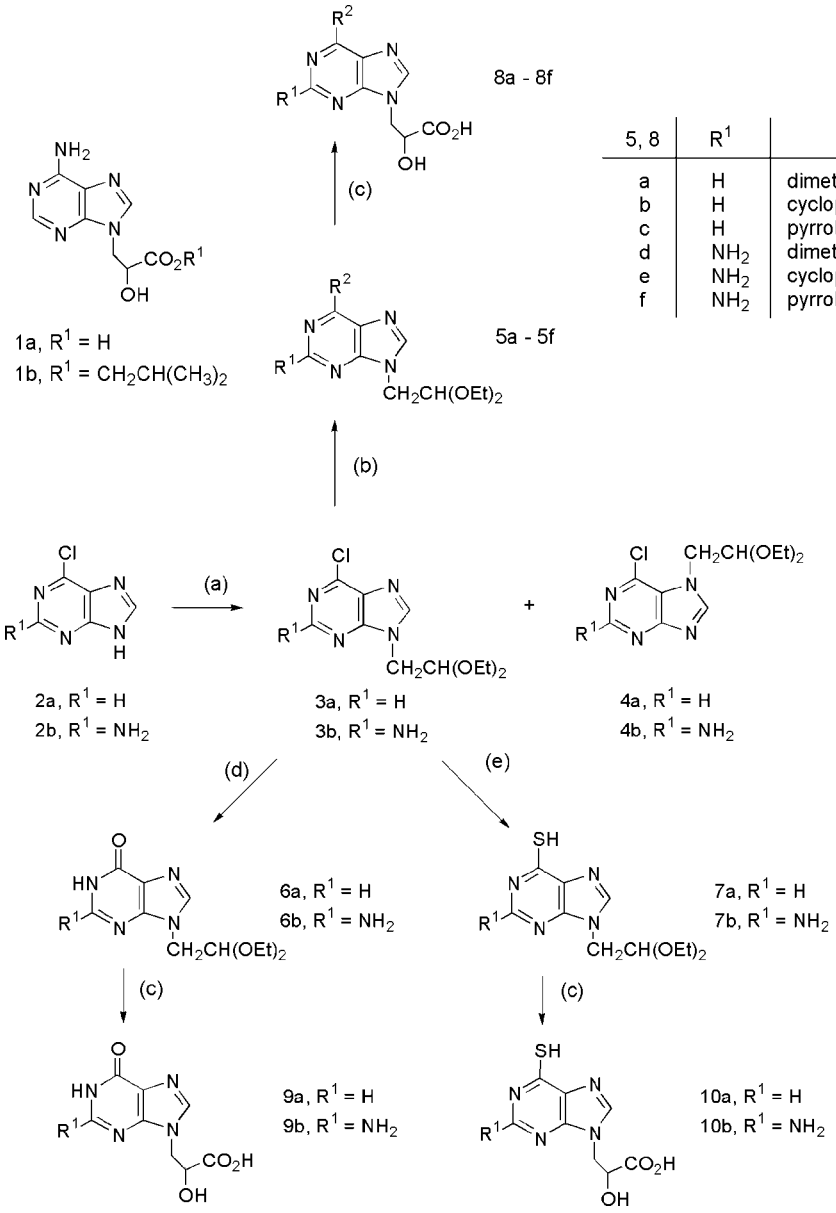

5, 8	R^1	R^2
a	H	dimethylamino
b	H	cyclopropylamino
c	H	pyrrolidin-1-yl
d	NH_2	dimethylamino
e	NH_2	cyclopropylamino
f	NH_2	pyrrolidin-1-yl

Scheme 1. (a) $BrCH_2CH(OEt)_2$,Cs_2CO_3/DMF, 100°C; (b) R_1R_2NH or R_1NH_2, [or $(CH_3)_2NH^+(CH_3)_2N\text{-}COO^-$]; (c) (1) H^+, (2) KCN (3) H^+; (d) DABCO, aq. K_2CO_3; (e) thiourea.

In our earlier article,[9] we have discovered that the treatment of 9-(2,2-diethoxyethyl)adenine (**11a**) with malonic acid in boiling aqueous solution does not afford the expected 4-(adenin-9-yl)-2-butenoic acid (**12**) but gives exclusively the isomeric 4-(adenin-9-yl)-3-butenoic acid (**13**). We have postulated the mechanism of this

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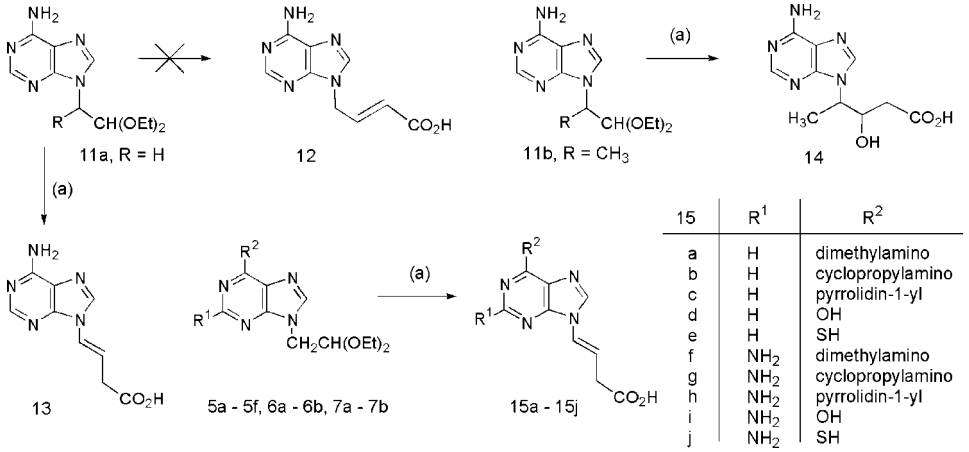
isomerisation based on addition of water to the primary reaction product and its subsequent elimination in either direction. It was considered plausible that the markedly low water solubility of compound (**13**) could shift this equilibrium in favor of this isomer. This speculation was supported by the fact that the homologue, 2-(adenin-9-yl)-1,1-diethoxypropane (**11b**) gives with malonic acid in water the postulated intermediate, 4-(adenin-9-yl)-3-hydroxypropanoic acid (**14**) as the only reaction product. Having in hand the above series of 2,2-diethoxyethyl purines (**5a–5f**, **6a–6b**, **7a–7b**) we have further investigated this reaction. However, in all cases examined solely the 6-substituted 4-(purin-9-yl)-3-butenoic acids (**15a–15j**) were obtained, disregarding the solubility of the product in the course of the reaction. Removal of excess malonic acid and final purification were performed by ion exchange chromatography.

Untypical formation of β,γ-unsaturated acids from malonic acid and aldehydes was already described in the literature.[11] However, in all such cases the reaction was performed in non-aqueous solvents in the presence of the tertiary base or, in the neat tertiary base. Thus, to explain the formation of the β,γ-unsaturated acids from 2,2-diethoxyethyl purines and malonic acid in water we are suggesting the above water addition-elimination mechanism. The driving force of this reaction could well be the formation of the enamine product with extended π-orbital overlap involving the heteroaromatic system (Sch. 2).

In conclusion, we have synthesized a series of base-substituted 2-hydroxy-3-(purin-9-yl)propanoic acids by cyanohydrin synthesis from 3-(purin-9-yl)ethanals. The latter compounds were obtained by transformations of 9-(2,2-diethoxyethyl)-6-chloropurine or 2-amino-6-chloropurine prepared by alkylation of the bases with bromoacetaldehyde diethyl acetal. The 2,2-diethoxyethyl derivatives give with aqueous malonic acid 6-substituted 4-(purin-9-yl)-3-butenoic acids.

The biological examination of these compounds is not yet finished. However, we have not encountered in this group any compound with prominent cytostatic activity and/or antiviral activity against vaccinia virus.



15	R^1	R^2
a	H	dimethylamino
b	H	cyclopropylamino
c	H	pyrrolidin-1-yl
d	H	OH
e	H	SH
f	NH_2	dimethylamino
g	NH_2	cyclopropylamino
h	NH_2	pyrrolidin-1-yl
i	NH_2	OH
j	NH_2	SH

Scheme 2. (a) $CH_2(COOH)_2$, H_2O reflux.

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EXPERIMENTAL

Unless otherwise stated, solvents were evaporated at 40°C/2 kPa and compounds were dried overnight at 2 kPa over P_2O_5. Melting points were determined on a Büchi Melting Point B-545 aparatus and are uncorrected. TLC was performed on plates of kieselgel 60 F254 (Merck) in systems S1 (chloroform-methanol 95:5), S2 (chloroform-methanol 9:1), S3 (ethyl acetate-acetone-ethanol-water 4:1:1:1) and S4 (ethyl acetate-petroleum ether 1:1). Paper electrophoresis was performed on a Whatman No. 3 MM paper at 40 V/cm for 1 h in 0.05 M triethylammonium hydrogencarbonate, pH 7.5; the electrophoretical mobilities were referenced to uridine 3′-phosphate. NMR spectra were measured on an FT NMR spectrometer Varian UNITY 500 (^{1}H at 500 MHz and ^{13}C at 125.7 MHz) in dimethyl sulfoxide-d_6. Chemical shifts (δ ppm) and coupling constants (J, Hz) were obtained by the first-order analysis of the spectra. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol matrix).

General Methods

Deionization of the Reaction Mixture. The solution of reaction products in water (20–25 mL) was applied on a column of Dowex 50 × 8 (100 mL, H^+ form), and the column was washed with water until the drop of the UV absorption (254 nm) and acid reaction of the eluate. The standard elution rate was 3 mL/min. Elution was continued with 10% ammonia, and the UV-absorbing eluate was collected and evaporated.

Purification by Column Chromatography on Dowex 1 × 2. Unless stated otherwise, 100 mL columns of Dowex 1 × 2 (acetate form) were used. The sample was dissolved in water (20–25 mL), alkalified with concentrated aqueous ammonia to pH 9–9.5, and applied on the column. Elution with water (3 mL/min) was continued until the drop of the initial UV absorption (254 nm) of the eluate. The column was then eluted with a linear gradient of acetic acid.

6-Chloro-9-(2,2-diethoxyethyl)purine (3a) and 6-Chloro-7-(2,2-diethoxyethyl)purine (4a). To the stirred mixture of (**2a**) (7.7 g, 50 mmol) and cesium carbonate (8.1 g, 25 mmol) in DMF (150 mL) was added bromoacetaldehyde diethylacetal (11.6 mL, 75 mmol). The mixture was heated under stirring at 100°C for 24 h with exclusion of moisture. The reaction mixture was filtered while hot through Celite, taken down at 50°C/13 Pa and codistilled with toluene (3 × 50 mL) and ethanol (2 × 50 mL). The residue was extracted with boiling chloroform (500 mL), filtered through Celite and evaporated. The residue in methanol (200 mL) was treated with silica gel (150 mL), evaporated and applied on a column of silica gel (600 mL) in ethyl acetate-petroleum ether mixture (1:2). The column was eluted with ethyl acetate-petroleum ether mixture (1:2–1:1). The crystallization from ethyl acetate-petroleum ether afforded 5.6 g (42%) of compound (**3a**), white crystals, mp 85°C, $R_F = 0.66$ (S1). ^{1}H NMR: 8.79 (s, 1H, H–2); 8.62 (s, 1H, H–8); 4.89 (t, 1H, $J(2',1') = 5.0$, H-2′); 4.40 (d, 2H,

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$J(1',2') = 5.0$, H-1′); 3.64 and 3.45 (dq, 2H, $J(CH_2, CH_3) = 7.1$, $J(gem) = 9.6$, O-CH_2); 1.01 (t, 6H, $J(CH_3,CH_2) = 7.1$, CH_3). ^{13}C NMR: 152.32 (C-4); 151.74 (C-2); 149.15 (C-6); 148.04 (C-8); 130.64 (C-5); 99.26 (C-2′); 62.59 (2C, O-CH_2); 46.01 (C-1′); 15.21 (2C, CH_3). FAB MS, m/z: 271.2 [M + H]. For $C_{11}H_{15}N_4O_2Cl$ calcd: C, 48.80; H, 5.58; N, 20.70; Cl, 13.10; O, 11.82%; found: C, 48.93; H, 5.60; N, 20.60; Cl, 13.19; O, 11.68%. Further elution of the column with ethyl acetate-petroleum ether (1:1) gave, after crystallization from ethyl acetate-petroleum ether, compound (**4a**) (0.73 g, 5.5%), white crystals, mp = 60°C, $R_F = 0.54$. ^1H NMR: 8.78 (s, 1H, H-2); 8.72 (s, 1H, H–8); 4.82 (t, 1H, $J(2',1') = 5.0$, H-2′); 4.59 (d, 2H, $J(1',2') = 5.0$, H-1′); 3.64 and 3.42 (dq, 2H, $J(CH_2, CH_3) = 7.1$, $J(gem) = 9.6$, O-CH_2); 0.99 (t, 6H, $J(CH_3,CH_2) = 7.1$, CH_3). ^{13}C NMR: 161.57 (C-4); 151.87 (C-2); 151.63 (C-8); 142.51 (C-6); 122.45 (C-5); 100.40 (C-2′); 63.23 (2C,O-CH_2); 48.85 (C-1′); 15.20 (2C, CH_3). FAB MS, m/z: 271 [M + H]. For $C_{11}H_{15}N_4O_2Cl$ calcd: C, 48.80; H, 5.58; N, 20.70; Cl, 13.10; O, 11.82%; found: C, 48.72; H, 5.54; N, 20.54; Cl, 13.18; O, 12.02%.

2-Amino-6-chloro-9-(2,2-diethoxyethyl)purine (3b) and 2-Amino-6-chloro-7-(2,2-diethoxyethyl)purine (4b). These compounds were prepared from 2-amino-6-chloropurine (**2b**) (8.5 g, 50 mmol) by the same procedure as compounds (**3a**) and (**4a**). The silica gel column was eluted with chloroform (1 L) and then with chloroform-methanol mixture (98:2). The crystallization from ethyl acetate-petroleum ether afforded 8.5 g (59%) of compound (**3b**), white crystals, mp = 139.2°C, $R_F = 0.54$ (S1). ^1H NMR: 8.04 (s, 1H, H–8); 6.94 (s, 2H, NH_2); 4.80 (t, 1H, $J(2',1') = 5.4$, H-2′); 4.13 (d, 2H, $J(1',2') = 5.4$, H-1′); 3.63 and 3.42 (dq, 2H, $J(CH_2, CH_3) = 7.1$, $J(gem) = 9.6$, O-CH_2); 1.025 (t, 6H, $J(CH_3,CH_2) = 7.1$, CH_3). ^{13}C NMR: 160.00 (C-2); 154.43 (C-4); 149.45 (C-6); 143.73 (C-8); 123.14 (C-5); 99.37 (C-2′); 62.48 (2C, O-CH_2); 45.44 (C-1′); 15.28 (2C, CH_3). FAB MS, m/z: 286 [M + H]. For $C_{11}H_{16}N_5O_2Cl$ calcd: C, 46.24; H, 5.64; N, 24.51; Cl, 12.41; O, 11.20%; found: C, 46.22; H, 5.75; N, 24.29; Cl, 12.25. O, 11.49%. Further elution of the column, and crystallization from ethyl acetate-petroleum ether, afforded 1.7 g (12%) of compound (**4b**), white crystals, mp = 163°C, $R_F = 0.41$ (S1). ^1H NMR: 8.28 (s, 1H, H–8); 6.64 (brs, 2H, NH_2); 4.76 (t, 1H, $J(2',1') = 5.4$, H-2′); 4.37 (d, 2H, $J(1',2') = 5.4$, H-1′); 3.63 and 3.39 (dq, 2H, $J(CH_2, CH_3) = 7.1$, $J(gem) = 9.6$, O-CH_2); 1.01 (t, 6H, $J(CH_3,CH_2) = 7.1$, CH_3). ^{13}C NMR: 164.24 (C-4); 160.02 (C-2); 150.45 (C-8); 143.66 (C-6); 115.21 (C-5); 100.49 (C-2′); 63.12 (2C, O-CH_2); 48.64 (C-1′); 15.27 (2C, CH_3). FAB MS, m/z: 286 [M + H]. For $C_{11}H_{16}N_5O_2Cl$ calcd: C, 46.24; H, 5.64; N, 24.51; Cl, 12.41; O, 11.20%; found: C, 46.32; H, 5.75; N, 24.61; Cl, 12.42; O, 10.90%.

9-(2,2-Diethoxyethyl)-6-(dimethylamino)purine (5a). The solution of compound (**3a**) (4.1 g, 15 mmol) and dimethylamonium N,N-dimethylcarbamate (5.8 mL, 45 mmol) in acetonitrile (120 mL) was refluxed for 0.5 h with exclusion of moisture. The mixture was evaporated and the residue codistilled with ethanol (2 × 50 mL). The residue was dissolved in chloroform (100 mL) and washed with water (3 × 50 mL) and the water was washed with chloroform (2 × 50 mL). Organic phase was dried with $MgSO_4$ and evaporated. The crystallization from ethyl acetate-petroleum ether afforded 4.54 g (95%) of compound (**5a**), white crystals, mp = 65°C,

$R_F = 0.75$ (S1). ^{1}H NMR: 8.22 (s, 1H, H–2); 8.07 (s, 1H, H–8); 4.83 (t, 1H, $J(2',1') = 5.4$, H-2′); 4.23 (d, 2H, $J(1',2') = 5.4$, H-1′); 3.63 and 3.41 (dq, 2H, $J(CH_2, CH_3) = 7.1$, $J(gem) = 9.6$, O-CH_2); 3.44 (brs, 6H, N-CH_3); 1.02 (t, 6H, $J(CH_3,CH_2) = 7.1$, CH_3). ^{13}C NMR: 154.34 (C-6); 151.95 (C-2); 150.60 (C-4); 140.22 (C-8); 119.03 (C-5); 99.56 (C-2′); 62.36 (2C, O-CH_2); 45.40 (C-1′); 39.00 (br, N-CH_3); 38.00 (br, N-CH_3); 15.22 (2C, CH_3). FAB MS, m/z: 280 [M + H]. For $C_{13}H_{21}N_5O_2$ calcd: C, 55.90; H, 7.58; N, 25.07; O, 11.45%; found: C, 55.74; H, 7.69; N, 24.91; O, 11.66%.

2-Amino-9-(2,2-diethoxyethyl)-6-(dimethylamino)purine (5d). This compound was prepared from compound (**3b**) (4.3 g, 15 mmol) by the procedure described for compound (**5a**). Yield 4.07 g (92%), white crystals, mp = 108–109°C, $R_F = 0.86$ (S3). ^{1}H NMR: 7.64 (s, 1H, H–8); 5.84 (brs, 2H, NH_2); 4.76 (t, 1H, $J(2',1') = 5.5$, H-2′); 4.04 (d, 2H, $J(1',2') = 5.5$, H-1′); 3.63 and 3.39 (dq, 2H, $J(CH_2, CH_3) = 7.0$, $J(gem) = 9.6$, O-CH_2); 3.37 (brs, 6H, N-CH_3); 1.04 (t, 6H, $J(CH_3,CH_2) = 7.0$, CH_3). ^{13}C NMR: 159.70 (C-2); 154.85 (C-6); 153.03 (C-4); 137.05 (C-8); 113.41 (C-5); 99.67 (C-2′); 62.31 (2C, O-CH_2); 45.08 (C-1′); 43.20 and 37.90 (N-CH_3); 15.35, 2C (CH_3). FAB MS, m/z: 295.2 [M + H]. For $C_{13}H_{22}N_6O_2$ calcd: C, 53.05; H, 7.53; N, 28.55; O, 10.87%; found: C, 53.00; H, 7.75; N, 28.51; O, 10.74%.

***N*^{6}-Substituted 6-Amino-9-(2,2-diethoxyethyl)purines and 2,6-Diamino-9-(2,2-diethoxyethyl)purines.** *General procedure*. A mixture of compound (**3a**) (2.17 g, 8 mmol) [for preparation of *N*^{6}-substituted 6-amino-9-(2,2-diethoxyethyl)purines] or compound (**3b**) (2.28 g, 8 mmol) [for preparation of *N*^{6}-substituted 2,6-diamino-9-(2,2-diethoxyethyl)purines], ethanol (80 mL) and primary or secondary amine (4 equivalents) was refluxed for 1–6 h with exclusion of moisture. The course of the reaction was checked with TLC in systems S1 and S3. After completion, the mixture was evaporated and the residue codistilled with ethanol (2 × 50 mL). The residue was dissolved in chloroform (50 mL), washed with water (2 × 50 mL) and the water was washed with chloroform (2 × 50 mL). Organic phase was dried with $MgSO_4$ and evaporated. The following compounds were prepared by this procedure:

6-(Cyclopropylamino)-9-(2,2-diethoxyethyl)purine (5b). Crystallized from ethyl acetate-petroleum ether, yield 2.0 g (86%) of white crystals, mp = 96.6°C, $R_F = 0.46$ (S2). ^{1}H NMR: 8.25 (brs, 1H, H-2); 8.05 (s, 1H, H–8); 7.89 (brs, 1H, NH); 4.84 (t, 1H, $J(2',1') = 5.4$, H-2′); 4.23 (d, 2H, $J(1',2') = 5.4$, H-1′); 3.63 and 3.41 (dq, 2H, $J(CH_2, CH_3) = 7.1$, $J(gem) = 9.6$, O-CH_2); 3.04 (m, 1H, N-CH); 1.02 (t, 6H, $J(CH_3,CH_2) = 7.1$, CH_3); 0.72 and 0.61 (m, 2H, C-CH_2). ^{13}C NMR: 155.65 (C-6); 152.56 (C-2); 149.50 (C-4); 141.28 (C-8); 118.91 (C-5); 99.61 (C-2′); 62.38 (2C, O-CH_2); 45.40 (C-1′); 27.88 (N-CH); 15.28 (2C, CH_3); 6.57 (2C, CH_2). FAB MS, m/z: 292.1 [M + H]. For $C_{14}H_{21}N_5O_2$ calcd: C, 57.72; H, 7.26; N, 24.04; O, 10.98%; found: C, 57.63; H, 7.22; N, 23.96; O, 11.19%.

9-(2,2-Diethoxyethyl)-6-(pyrrolidin-1-yl)purine (5c). Crystallized from petroleum ether, yield 2.46 g (96%), white crystals, mp = 59–61°C, $R_F = 0.56$ (S1). ^{1}H NMR: 8.20 (s, 1H, H–2); 8.04 (s, 1H, H–8); 4.83 (t, 1H, $J(2',1') = 5.4$ (H-2′); 4.22 (d, 2H, $J(1',2') = 5.4$, H-1′); 4.05 and 3.60 (m, 2H, N-CH_2); 3.63 and 3.41

(dq, 2H, $J(CH_2, CH_3) = 7.1$, $J(gem) = 9.6$, O-CH_2); 1.97 and 1.91 (m, 2H, C-CH_2); 1.025 (t, 6H, $J(CH_3,CH_2) = 7.1$, CH_3). FAB MS, m/z: 306 [M + H]. For $C_{15}H_{23}N_5O_2$ calcd: C, 59.00; H, 7.59; N, 22.93; O, 10.48; found: C, 58.93; H, 7.74; N, 22.83; O, 10.50%.

2-Amino-6-(cyclopropylamino)-9-(2,2-diethoxyethyl)purine (5e). Crystallized from ethanol-ether, yield 1.92 g (78%), white crystals, mp = 164.2°C, $R_F = 0.49$ (S2). ^{1}H NMR: 7.61 (s, 1H, H–8); 7.28 (brs, 1H, NH); 5.87 (brs, 2H, NH_2); 4.76 (t, 1H, $J(2',1') = 5.4$, H-2′); 4.03 (d, 2H, $J(1',2') = 5.4$, H-1′); 3.63 and 3.39 (dq, 2H, $J(CH_2, CH_3) = 7.1$, $J(gem) = 9.6$, O-CH_2); 3.03 (m, 1H, N-CH); 1.04 (t, 6H, $J(CH_3,CH_2) = 7.1$, CH_3); 0.65 and 0.58 (m, 2H, C-CH_2). ^{13}C NMR: 160.41 (C-2); 156.02 (C-6); 150.00 (C-4); 137.78 (C-8); 113.21 (C-5); 99.74 (C-2′); 62.32 (2C, O-CH_2); 45.06 (C-1′); 27.00 (N-CH); 15.34 (2C, CH_3); 6.55 (2C, CH_2). FAB MS, m/z: 307.1 [M + H]. For $C_{14}H_{22}N_6O_2$ calcd: C, 54.89; H, 7.24; N, 27.43; O, 10.44%; found: C, 54.73; H, 7.37; N, 27.32; O, 10.58%.

2-Amino-9-(2,2-diethoxyethyl)-6-(pyrrolidin-1-yl)purine (5f). Crystallized from ethyl acetate-petroleum ether, yield 2.2 g (88%) of white crystals, mp = 110.4°C, $R_F = 0.88$ (S3), $R_F = 0.14$ (S4). ^{1}H NMR: 7.61 (s, 1H, H–8); 5.80 (brs, 2H, NH_2); 4.76 (t, 1H, $J(2',1') = 5.5$, H-2′); 4.03 (d, 2H, $J(1',2') = 5.5$, H-1′); 3.96 and 3.55 (m, 2H, N-CH_2); 3.63 and 3.39 (dq, 2H, $J(CH_2, CH_3) = 7.1$, $J(gem) = 9.6$, O-CH_2); 1.89 (m, 4H, C-CH_2); 1.04 (t, 6H, $J(CH_3,CH_2) = 7.1$, CH_3). ^{13}C NMR: 160.06 (C-2); 153.21 (C-6); 152.60 (C-4); 137.48 (C-8); 113.64 (C-5); 99.69 (C-2′); 62.28 (2C, O-CH_2); 48.20 and 47.00 (N-CH_2); 45.02 (C-1′); 25.15 a 24.00 (C-CH_2); 15.35 (2C, CH_3). FAB MS, m/z: 321.1 [M + H]. For $C_{15}H_{24}N_6O_2$ calcd: C, 56.23; H, 7.55; N, 26.23; O, 9.98%; found: C, 56.06; H, 7.65; N, 25.97; O, 10.32%.

9-(2,2-Diethoxyethyl)hypoxanthine (6a). The solution of (**3a**) (2.17 g, 8 mmol), K_2CO_3 (4.43 g, 32 mmol) and DABCO (1.8 g, 16 mmol) in water (25 mL) was stirred at reflux for 2 h, neutralized by addition of Dowex 50 × 8, alkalified with 10% ammonia and filtered. The resin was washed with water (200 mL) and 10% ammonia (200 mL). The filtrate was evaporated. The residue was extracted with boiling ethyl acetate, filtered, evaporated and applied on a silica gel column. The column was eluted with ethyl acetate-methanol (90:10). The crystallization from ethyl acetate-petroleum ether afforded 1.5 g (74%) of compound (**6a**), white solid, mp = 172.3–173.8°C, $R_F = 0.51$ (S2). ^{1}H NMR: 7.85 (s, 1H, H-2); 7.60 (s, 1H, H–8); 4.74 (t, 1H, $J(2',1') = 5.6$, H-2′); 4.07 (d, 2H, $J(1',2') = 5.6$, H-1′); 3.62 and 3.39 (dq, 2H, $J(CH_2, CH_3) = 7.1$, $J(gem) = 9.6$, O-CH_2); 1.03 (t, 6H, $J(CH_2,CH_3) = 7.1$, CH_3). ^{13}C NMR: 167.22 (C-6); 153.57 (C-2); 150.00 (C-4); 137.16 (C-8); 124.05 (C-5); 99.95 (C-2′); 62.26 (2C, O-CH_2); 45.33 (C-1′); 15.33 (2C, CH_3). FAB MS, m/z: 253 [M + H]. For $C_{11}H_{16}N_4O_3$ calcd: C, 52.37; H, 6.39; N, 22.21; O, 19.03%; found: C, 52.15; H, 6.49; N, 21.90; O, 19.46%.

9-(2,2-Diethoxyethyl)guanine (6b). The compound (**3b**) (1.7 g, 6 mmol), K_2CO_3 (3.32 g, 24 mmol) and DABCO (1.34 g, 12 mmol) were dissolved in water (20 mL) and stirred at reflux for 1.5 h, neutralized with Dowex 50 × 8, alkalified with 10% ammonia and filtered. The resin was washed with water (200 mL) and 10% ammonia

(200 mL). The filtrate was evaporated. The crude product was crystallized from water to afford 1.21 g (73%) of compound (**6b**), white solid, mp = 277.7°C (dec.), $R_F = 0.75$ (S3). ^{1}H NMR: δ10.58 (s, 1H, NH); 7.60 (s, 1H, H–8); 6.46 (brs, 2H, NH_2); 4.73 (t, 1H, $J(2',1') = 5.4$, H-2′); 4.01 (d, 2H, $J(1',2') = 5.4$, H-1′); 3.63 a 3.39 (dq, 2H, $J(CH_2, CH_3) = 7.1$, J(gem) = 9.6, O-CH_2); 1.04 (t, 6H, $J(CH_3,CH_2) = 7.1$, CH_3). ^{13}C NMR: δ157.01 (C-2); 153.77 (C-6); 151.54 (C-4); 138.06 (C-8); 116.35 (C-5); 99.78 (C-2′); 62.40 (2C, O-CH_2); 45.32 (C-1′); 15.31 (2C, CH_3). FAB MS, m/z: 268.2 [M + H]. For $C_{11}H_{17}N_5O_3 \cdot 1/2H_2O$ calcd: C, 47.82; H, 6.57; N, 25.35; O, 20.27%; found: C, 47.73; H, 6.44; N, 25.16; O, 20.67%.

9-(2,2-Diethoxyethyl)-6-sulfanylpurine (7a). A solution of compound (**3a**) (2.17 g, 8 mmol) and thiourea (1.9 g, 24 mmol) in ethanol (120 mL) was stirred at reflux for 1.5 h, cooled and made basic with triethylamine. The crystalline product was filtered, washed with ethanol and ether and dried. Yield 1.85 g (86%), white crystals, mp = 241-243°C (dec.), $R_F = 0.54$ (S2). ^{1}H NMR: δ13.75 (brs, 1H, SH); 8.215 (s, 1H, H-2); 8.21 (s, 1H, H–8); 4.82 (t, 1H, $J(2',1') = 5.3$, H-2′); 4.26 (d, 2H, $J(1',2') = 5.3$, H-1′); 3.62 and 3.43 (dq, 2H, $J(CH_2, CH_3) = 7.0$, J(gem) = 9.6, O-CH_2); 1.03 (t, 6H, $J(CH3,CH_2) = 7.0$, CH_3). ^{13}C NMR: δ175.95 (C-6); 145.17 (C-2); 144.48 (C-4); 143.69 (C-8); 134.81 (C-5); 99.53 (C-2′); 62.53 (2C, O-CH_2); 45.74 (C-1′); 15.26 (2C, CH_3). FAB MS, m/z: 269.1 [M + H]. For $C_{11}H_{16}N_4O_2S$ calcd: C, 49.24; H, 6.01; N, 20.88; O, 11.92; S, 11.95%; found: C, 49.03; H, 6.07; N, 20.73; O, 12.25%; S, 11.92%.

2-Amino-9-(2,2-diethoxyethyl)-6-sulfanylpurine (7b). This compound was prepared from compound (**3b**) (1.71 g, 6 mmol) according to the above described procedure for compound (**7a**). Yield 1.56 g (89%) of white crystals, not melting below 300°C, $R_F = 0.54$ (S2). ^{1}H NMR: δ11.88 (s, 1H, SH); 7.80 (s, 1H, H–8); 6.81 (brs, 2H, NH_2); 4.75 (t, 1H, $J(2',1') = 5.2$, H-2′); 4.03 (d, 2H, $J(1',2') = 5.2$, H-1′); 3.63 and 3.41 (dq, 2H, $J(CH_2, CH_3) = 7.0$, J(gem) = 9.6, O-CH_2); 1.04 (t, 6H, $J(CH_3,CH_2) = 7.0$, CH_3). ^{13}C NMR: 175.01 (C-6); 153.19 (C-2); 148.22 (C-4); 141.13 (C-8); 128.06 (C-5); 99.57 (C-2′); 62.45 (2C, O-CH_2); 45.29 (C-1′); 15.32 (2C, CH_3). FAB MS, m/z: 284 [M + H]. For $C_{11}H_{17}N_5O_2S.1/2H_2O$ calcd: C, 45.19; H, 6.21; N, 23.96; O, 13.68; S, 10.97%; found: C, 45.02; H, 6.11; N, 23.77; O, 13.99; S, 11.11%.

***N*^{6}-Substituted 3-(6-Aminopurin-9-yl)-2-hydroxypropanoic acids and 3-(2,6-Diaminopurin-9-yl)-2-hydroxypropanoic Acids.** *General procedure*. A mixture of *N*^{6}-substituted 6-amino- or 2,6-diamino-9-(2,2-diethoxyethyl)purine (5–7) (6 mmol), water (30 mL) and conc. hydrochloric acid (1.2 mL) was heated for 4–8 h at 60°C until the reaction was complete (S2). After cooling to −5°C (ice-salt mixture), potassium cyanide (1.95 g, 30 mmol) was added under stirring, the mixture was rapidly adjusted to pH 6–6.5 with acetic acid and stirred at 0°C for 5 h and at room temperature overnight. Concentrated hydrochloric acid (20 mL) was added, the mixture was refluxed for 6 h, cooled, and evaporated. The residue was deionized on Dowex 50 × 8 (see above), and purified by Dowex 1 × 2 column chromatography (see above). Unless otherwise stated, the column was eluted with gradient of acetic

acid (2 L, 0–0.5 M). The crude product was crystallized from water. The following compounds were prepared by this procedure:

3-[6-(Dimethylamino)purin-9-yl]-2-hydroxypropanoic Acid (8a). Pale brown solid, yield 76%, mp = 232°C (dec.), $E_{Up} = 0.61$. ^{1}H NMR: 12.90 (brs, 1H, COOH); 8.22 (s, 1H, H–2); 8.07 (s, 1H, H–8); 5.90 (brs, 1H, OH); 4.46 (dd, 1H, $J(1'a,2') = 3.9$, J(gem) = 13.7, H-1′a); 4.39 (dd, 1H, $J(2',1'a) = 3.9$, $J(2',1'b) = 8.2$, H-2′); 4.27 (dd, 1H, $J(1'b,2') = 8.2$, J(gem) = 13.7, H-1′b); 3.46 (brs, 6H, N-CH_3). FAB MS m/z: 252 [M + H]. For $C_{10}H_{13}N_5O_3 \cdot 1/2H_2O$ calcd: C, 46.15; H, 5.42; N, 26.91; O, 21.52%; found: C, 46.11; H, 5.39; N, 26.69; O, 21.81%.

3-[6-(Cyclopropylamino)purin-9-yl]-2-hydroxypropanoic Acid (8b). Crystallized from water-acetone mixture, white solid, yield 80%, mp = 245°C (dec.), $E_{Up} = 0.50$. ^{1}H NMR: 12.80 (brs, 1H, COOH); 8.24 (s, 1H, H–2); 8.04 (s, 1H, H–8); 7.90 (brs, 1H, NH); 5.90 (brs, 1H, OH); 4.46 (dd, 1H, $J(1'a,2') = 3.6$, J(gem) = 13.7, H-1′a); 4.40 (dd, 1H, $J(2',1'a) = 3.6$, $J(2',1'b) = 8.0$, H-2′); 4.27 (dd, 1H, $J(1'b,2') = 8.0$, J(gem) = 13.7, H-1′b); 3.05 (m, 1H, N-CH); 0.71 and 0.60 (m, 2H, C-CH_2). ^{13}C NMR: 173.36 (C=O); 155.66 (C-6); 152.44 (C-2); 149.30 (C-4); 141.56 (C-8); 68.72 (C-2′); 46.39 (C-1′); 24.02 (N-CH); 6.64 (2C, CH_2). FAB MS m/z: 264 [M + H]. For $C_{11}H_{13}N_5O_3$ calcd: C, 50.19; H, 4.98; N, 26.60; O, 18.23%; found: C, 49.86; H, 4.98; N, 26.47; O, 18.69%.

2-Hydroxy-3-[6-(pyrrolidin-1-yl)purin-9-yl]propanoic Acid (8c). Pale brown solid, yield 81%, mp = 236°C (dec.), $E_{Up} = 0.54$. ^{1}H NMR: 12.80 (brs, 1H, COOH); 8.21 (s, 1H, H-2); 8.04 (s, 1H, H-8); 5.80 (brs, 1H, OH); 4.46 (dd, 1H, $J(1'a,2') = 3.9$, J(gem) = 13.8, H-1′a); 4.39 (dd, 1H, $J(2',1'a) = 3.9$, $J(2',1'b) = 8.1$, H-2′); 4.27 (dd, 1H, $J(1'b,2') = 8.1$, J(gem) = 13.8, H-1′b); 4.05 and 3.62 (m, 2H, N-CH_2); 1.97 and 1.93 (m, 2H, C-CH_2). ^{13}C NMR: 173.28 (C=O); 152.42 (C-6); 152.01 (C-2); 150.08 (C-4); 141.10 (C-8); 119.30 (C-5); 68.67 (C-2′); 48.52 and 47.19 (N-CH_2); 46.33 (C-1′); 25.91 and 24.02 (C-CH_2). FAB MS m/z: 278 [M + H]. For $C_{12}H_{15}N_5O_3$ calcd: C, 51.98; H, 5.45; N, 25.26; O, 17.31%; found: C, 51.90; H, 5.44; N, 25.02; O, 17.64%.

3-[2-Amino-6-(dimethylamino)purin-9-yl]-2-hydroxypropanoic Acid (8d). The resin, after the elution by acetic acid, was stirred with boiling water (1 L), filtered and the water was evaporated. The residue was crystallized from water to afford white solid, yield 67%, mp = 272°C (dec.), $E_{Up} = 0.47$. ^{1}H NMR: 7.63 (s, 1H, H-8); 5.87 (brs, 2H, NH_2); 4.33 (dd, 1H, $J(2',1'a) = 3.9$, $J(2',1'b) = 8.4$, H-2′); 4.29 (dd, 1H, $J(1'a,2') = 3.9$, J(gem) = 13.8, H-1′a); 4.06 (dd, 1H, $J(1'b,2') = 8.4$, J(gem) = 13.8, H-1′b); 3.35 (brs, 6H, N-CH_3). FAB MS m/z: 267 [M + H]. For $C_{10}H_{14}N_6O_3 \cdot H_2O$ calcd: C, 42.25; H, 5.67; N, 29.56; O, 22.51%; found: C, 42.16; H, 5.75; N, 29.20; O, 22.89%.

3-[2-Amino-6-(cyclopropylamino)purin-9-yl]-2-hydroxypropanoic Acid (8e). White solid, yield 82%, mp = 258 – 260°C (dec.), $E_{Up} = 0.45$. ^{1}H NMR: 7.61 (s, 1H, H-8); 7.36 (brs, 1H, NH); 6.00 (brs, 1H, OH); 5.95 (brs, 2H, NH_2); 4.33 (dd, 1H, $J(2',1'a) = 3.8$, $J(2',1'b) = 8.4$, H-2′); 4.28 (dd, 1H, $J(1'a,2') = 3.8$, J(gem) = 13.9,

H-1′a); 4.06 (dd, 1H, $J(1'b,2') = 8.4$, $J(gem) = 13.9$, H-1′b); 3.01 (m, 1H, N-CH); 0.65 and 0.57 (m, 2H, C-CH_2). ^{13}C NMR: 173.59 (C=O); 160.11 (C-2); 155.97 (C-6); 150.00 (C-4); 138.21 (C-8); 113.32 (C-5); 68.91 (C-2′); 46.11 (C-1′); 28.45 (N-CH); 6.66 (2C, CH_2). FAB MS m/z: 279 [M + H]. For $C_{11}H_{14}N_6O_3 \cdot 1/3H_2O$ calcd: C, 46.48; H, 5.20; N, 29.56; O, 18.76%; found: C, 46.54; H, 5.22; N, 29.73; O, 18.51%.

3-[2-Amino-6-(pyrrolidin-1-yl)purin-9-yl]-2-hydroxypropanoic Acid (8f). The Dowex 1 × 2 resin, after the elution with acetic acid, was stirred with boiling water (1 L), filtered and the filtrate evaporated. The crude product was crystallized from water. White solid, yield 51%, mp = 275°C (dec.), $E_{Up} = 0.44$. ^1H NMR: 7.61 (s, 1H, H-8); 5.84 (brs, 2H, NH_2); 4.30 and 4.05 and 4.00 (m, 1H, H-1′and H-2′); 3.70 (m, 4H, N-CH_2); 1.90 (m, 4H, C-CH_2). ^{13}C NMR: 173.49 (C=O); 159.87 (C-2); 153.20 (C-6); 152.40 (C-4); 137.82 (C-8); 113.78 (C-5); 68.85 (C-2′); 46.03 (C-1′). FAB MS m/z: 293 [M + H]. For $C_{12}H_{16}N_6O_3$ calcd: C, 49.31; H, 5.52; N, 28.75; O, 16.42%; found: C, 49.04; H, 5.57; N, 28.60; O, 16.79%.

2-Hydroxy-3-[hypoxanthin-9-yl]propanoic Acid (9a). The Dowex 1 × 2 column was eluted with gradient of acetic acid (2 L, 0–1 M). The resin was then stirred with boiling water (1 L), filtered and stirred with hot acetic acid (1 L, 1.5 M). The aqueous solutions were joined, evaporated and the residue has crystallized from water. White crystals, yield 25%, mp = 112.6°C, $E_{Up} = 0.72$. ^1H NMR: 12.60 (brs, 1H, COOH); 12.30 (brs, 1H, NH); 8.05 (s, 1H, H–2); 7.99 (s, 1H, H–8); 5.90 (brs, 1H, OH); 4.44 (dd, 1H, $J(1'a,2') = 3.8$, $J(gem) = 13.7$, H-1′a); 4.37 (dd, 1H, $J(2',1'a) = 3.8$, $J(2',1'b) = 8.3$, H-2′); 4.26 (dd, 1H, $J(1'b,2') = 8.3$, $J(gem) = 13.7$, H-1′b). ^{13}C NMR: 173.20 (C=O); 156.85 (C-6); 148.67 (C-4); 145.69 (C-2); 141.15 (C-8); 123.90 (C-5); 68.87 (C-2′); 46.66 (C-1′). FAB MS m/z: 225 [M + H]. For $C_8H_8N_4O_4 \cdot H_2O$ calcd: C, 39.67; H, 4.16; N, 23.13; O, 33.03; found: C, 39.53; H, 4.23; N, 22.93; O, 33.31%.

3-[Guanin-9-yl]-2-hydroxypropanoic Acid (9b). The Dowex 1 × 2 column was eluted with gradient of acetic acid (2 L, 0–1.5 M). White solid, yield 27%, mp = 292°C (dec.), $E_{Up} = 0.66$. ^1H NMR: 12.50 (brs, 1H, COOH); 10.60 (brs, 1H, NH); 7.61 (s, 1H, H-8); 6.49 (brs, 2H, NH_2); 5.90 (brs, 1H, OH); 4.31 (dd, 1H, $J(2',1'a) = 3.9$, $J(2',1'b) = 8.8$, H-2′); 4.25 (dd, 1H, $J(1'a,2') = 3.9$, $J(gem) = 13.9$, H-1′a); 4.04 (dd, 1H, $J(1'b,2') = 8.8$, $J(gem) = 13.9$, H-1′b). ^{13}C NMR: 173.39 (C=O); 157.01 (C-2); 153.74 (C-6); 151.42 (C-4); 138.38 (C-8); 116.43 (C-5); 68.83 (C-2′); 46.14 (C-1′). FAB MS m/z: 240 [M + H]. For $C_8H_9N_5O_4 \cdot 1/3H_2O$ calcd: C, 39.19; H, 3.79; N, 28.56; O, 28.28; found: C, 39.30; H, 4.04; N, 28.18; O, 28.48%.

2-Hydroxy-3-[6-sulfanylpurin-9-yl]propanoic Acid (10a). DMF (5 mL) was added to the reaction mixture to improve solubility. Crystallization from water afforded yellow solid, yield 89%, mp = 220°C (dec.), $E_{Up} = 0.88$. ^1H NMR: 13.74 (brs, 1H, SH); 12.50 (brs, 1H, COOH); 8.21 (s, 1H, H–2); 8.19 (s, 1H, H–8); 5.90 (brs, 1H, OH); 4.46 (dd, 1H, $J(1'a,2') = 3.9$, $J(gem) = 13.7$, H-1′a); 4.38 (dd, 1H, $J(2',1'a) = 3.9$, $J(2',1'b) = 8.2$, H-2′); 4.30 (dd, 1H, $J(1'b,2') = 8.2$, $J(gem) = 13.7$, H-1′b). ^{13}C NMR: 175.90 (C-6); 173.08 (C=O); 145.11 (C-2); 144.47 (C-4); 143.88

(C-8); 134.99 (C-5); 68.72 (C-2′); 46.72 (C-1′). FAB MS m/z: 241 [M + H]. For $C_8H_8N_4O_3S.H_2O$ calcd: C, 37.21; H, 3.90; N, 21.69; O, 24.78; S, 12.41%; found: C, 37.59; H, 3.77; N, 21.74; O, 24.51; S, 12.39%.

3-[2-Amino-6-sulfanylpurin-9-yl]-2-hydroxypropanoic Acid (10b). DMF (5 mL) was added to the reaction mixture to improve solubility. The resin was, after the elution by acetic acid, stirred with boiling water (1 L), filtered and then stirred with hot acetic acid (1 L, 1 M) and filtered. Water and acetic acid were evaporated. The residue has crystallized from water to afford yellow solid, yield 27%, mp = 284°C (dec.), $E_{Up} = 0.63$. ^{1}H NMR: 12.90 (brs, 1H, SH); 11.88 (brs, 1H, COOH); 7.79 (s, 1H, H-8); 6.82 (brs, 2H, NH_2); 5.90 (brs, 1H, OH); 4.32 (dd, 1H, $J(2',1'a) = 3.9$, $J(2',1'b) = 8.7$, H-2′); 4.26 (dd, 1H, $J(1'a,2') = 3.9$, J(gem) = 14.0, H-1′a); 4.07 (dd, 1H, $J(1'b,2') = 8.7$, J(gem) = 14.0, H-1′b). ^{13}C NMR: 174.95 (C-6); 173.24 (C=O); 153.15 (C-2); 148.14 (C-4); 141.37 (C-8); 128.20 (C-5); 68.60 (C-2′); 46.12 (C-1′). FAB MS m/z: 256 [M + H]. For $C_8H_9N_5O_3S.1/3H_2O$ calcd: C, 36.78; H, 3.73; N, 26.81; O, 20.41; S, 12.27%; found: C, 37.19; H, 3.70; N, 26.51; O, 20.49; S, 12.11%.

***N*^{6}-Substituted 4-(6-Aminopurin-9-yl)-3-butenoic Acids.** *General procedure*. A mixture of *N*^{6}-substituted 6-amino-9-(2,2-diethoxyethyl)purine (**5a–5c**) (2 mmol) and malonic acid (8 mmol) in water (15 mL) was stirring at reflux for 24–32 h. The course of the reaction was checked by TLC in S1 and by electrophoresis. The reaction mixture was cooled to r.t. and the crystalline product was filtered, washed with water and ether and dried over P_2O_5. The following compounds were prepared:

4-[6-(Dimethylamino)purin-9-yl]-3-butenoic Acid (15a). White crystals, yield 0.28 g (60%), mp = 222.8°C, $E_{Up} = 0.57$. ^{1}H NMR: 12.43 (brs, 1H, COOH); 8.46 (s, 1H, H-2); 8.25 (s, 1H, H–8); 7.20 (dt, 1H, $J(1',2') = 14.5$, $J(1',3') = 1.3$, H-1′); 6.63 (dt, 1H, $J(2',1') = 14.5$, $J(2',3') = 7.4$, H-2′); 3.24 (dd, 2H, $J(3',2') = 7.4$, $J(3',1') = 1.3$, H-3′); 3.37 (brs, 6H, CH_3). ^{13}C NMR: 172.64 (C=O); 154.36 (C-6); 152.49 (C-2); 149.44 (C-4); 137.48 (C-8); 123.19 (C-1′); 119.62 (C-5); 113.70 (C-2′); 43.50 and 37.55 (N-CH_3); 35.12 (C-3′). FAB MS, m/z: 248 [M + H]. For $C_{11}H_{13}N_5O_2$ calcd: C, 53.44; H, 5.30; N, 28.32; O, 12.94%; found: C, 53.33; H, 5.37; N, 28.15; O, 13.15%.

4-[6-(Cyclopropylamino)purin-9-yl]-3-butenoic Acid (15b). Pale yellow crystals, yield 0.36 g (70%), mp = 239°C (dec.), $E_{Up} = 0.52$. ^{1}H NMR: 12.47 (brs, 1H, COOH); 8.44 (s, 1H, H-2); 8.30 (s, 1H, H–8); 8.01 (brs, 1H, N-H); 7.20 (dt, 1H, $J(1',2') = 14.5$, $J(1',3') = 1.3$, H-1′); 6.66 (dt, 1H, $J(2',1') = 14.5$, $J(2',3') = 7.4$, H-2′); 3.24 (dd, 2H, $J(3',2') = 7.4$, $J(3',1') = 1.3$, H-3′); 3.02 (m, 1H, N-CH); 0.73 and 0.62 (m, 2H, C-CH_2). ^{13}C NMR: 172.66 (C=O); 156.02 (C-6); 153.14 (C-2); 149.50 (C-4); 138.74 (C-8); 123.41 (C-1′); 119.62 (C-5); 113.63 (C-2′); 35.15 (C-3′); 27.00 (N-CH); 6.61 (C-CH_2). FAB MS, m/z: 260 [M + H]. For $C_{12}H_{13}N_5O_2$ calcd: C, 55.59; H, 5.05; N, 27.01; O, 12.34%; found: C, 55.33; H, 5.17; N, 27.39; O, 12.11%.

4-[6-(Pyrrolidin-1-yl)purin-9-yl]-3-butenoic Acid (15c). White crystals, yield 0.37 g (64%), mp = 213°C (dec.), $E_{Up} = 0.58$. ^{1}H NMR: 12.45 (brs, 1H, COOH); 8.42 (s, 1H, H-2); 8.24 (s, 1H, H–8); 7.20 (dt, 1H, $J(1',2') = 14.5$, $J(1',3') = 1.3$,

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H-1′); 6.64 (dt, 1H, $J(2',1') = 14.5$, $J(2',3') = 7.4$, H-2′); 4.01 and 3.62 (m, 2H, N-CH_2); 3.24 (dd, 2H, $J(3',2') = 7.4$, $J(3',1') = 1.3$, H-3′); 1.95 and 1.91 (m, 2H, C-CH_2). ^{13}C NMR: 172.68 (C=O); 152.90 (C-2); 152.62 (C-6); 149.12 (C-4); 137.99 (C-8); 123.30 (C-1′); 119.80 (C-5); 113.53 (C-2′); 48.64 and 47.21 (N-CH_2); 35.14 (C-3′); 25.96 and 23.90 (C-CH_2). FAB MS, m/z: 274 [M + H]. For $C_{13}H_{15}N_5O_2.2H_2O$ calcd: C, 50.48; H, 6.19; N, 22.64; O, 20.69%; found: C, 50.77; H, 6.23; N, 22.64; O, 20.36%.

4-(Hypoxanthin-9-yl)-3-butenoic Acid (15d). The mixture of compound (**6a**) (1.13 g, 4.5 mmol) and malonic acid (1.89 g, 18 mmol) in water (30 mL) was refluxed for 24 h and cooled to r.t. The crystalline product was filtered, washed with water and acetone. Recrystallization from water afforded 0.59 g (59%) of white solid, mp = 294°C (dec.), $E_{Up} = 0.63$. ^{1}H NMR: 12.47 (brs, 2H, COOH and N-H); 8.42 (s, 1H, H-2); 8.11 (s, 1H, H–8); 7.16 (dt, 1H, $J(1',2') = 14.5$, $J(1',3') = 1.5$, H-1′); 6.58 (dt, 1H, $J(2',1') = 14.5$, $J(2',3') = 7.4$, H-2′); 3.25 (dd, 2H, $J(3',2') = 7.4$, $J(3',1') = 1.5$, H-3′). ^{13}C NMR: 172.49 (C=O); 156.69 (C-6); 147.35 (C-4); 146.43 (C-2); 138.13 (C-8); 124.67 (C-5); 122.99 (C-1′); 115.00 (C-2′); 35.00 (C-3′). FAB MS, m/z: 221 [M + H]. For $C_9H_8N_4O_3$ calcd: C, 49.09; H, 3.66; N, 25.45; O, 21.80%; found: C, 48.97; H, 3.65; N, 25.28; O, 22.10%.

4-(6-Sulfanylpurin-9-yl)-3-butenoic Acid (15e). The solution of compound (**7a**) (1.9 g, 7 mmol) and malonic acid (3 g, 28 mmol) in water (40 mL) was refluxed for 5 h. The reaction mixture was evaporated and deionized on a column of Dowex 50 × 8 (see above). The crude solid was dissolved in water (10 mL), alkalified with ammonia and applied on a column of Dowex 1 × 2 (acetate form). The column was eluted with water (500 mL), gradient of acetic acid (2 L, 0–1 M) and then with formic acid (500 mL, 1 M). The UV absorbing fraction of the last eluate was evaporated and codistilled with water (3 × 50 mL). The crystallization from water afforded 0.52 g (30%) of compound (**15e**). Yellow solid, mp = 225°C (dec.), $E_{Up} = 0.86$. ^{1}H NMR: 13.90 (brs, 1H, SH); 12.50 (brs, 1H, COOH); 8.62 (s, 1H, H-2); 8.25 (s, 1H, H–8); 7.18 (dt, 1H, $J(1',2') = 14.5$, $J(1',3') = 1.5$, H-1′); 6.61 (dt, 1H, $J(2',1') = 14.5$, $J(2',3') = 7.4$, H-2′); 3.26 (dd, 2H, $J(3',2') = 7.4$, $J(3',1') = 1.5$, H-3′). ^{13}C NMR: 176.18 (C-6); 172.46 (C=O); 145.80 (C-2); 143.02 (C-4); 140.83 (C-8); 135.61 (C-5); 122.68 (C-1′); 115.79 (C-2′); 35.00 (C-3′). FAB MS, m/z: 237 [M + H]. For $C_9H_8N_4O_2S.2/3H_2O$ calcd: C, 43.54; H, 3.79; N, 22.57; O, 17.19; S, 12.91%; found: C, 43.37; H, 3.69; N, 22.77; O, 17.08; S, 13.09%.

***N*^{6}-Substituted 4-(2,6-Diaminopurin-9-yl)-3-butenoic Acids.** *General procedure*. A mixture of N^6-substituted 2,6-diamino-9-(2,2-diethoxyethyl)purine (**5f–5h**) (6 mmol) and malonic acid (24 mmol) in water (35 mL) was refluxed for 19–25 h, the course of the reaction was checked on TLC (S2) and by electrophoresis. The reaction mixture was evaporated, deionized on Dowex 50 × 8 (see above). The crude product was purified by Dowex 1 × 2 column chromatography (see above), the column was eluted with gradient of acetic acid (2 L, 0–0.5 M). The UV absorbing eluate was evaporated and codistilled with water (3 × 50 mL). The subsequent

crystallization afforded these compounds:

4-[2-Amino-6-(dimethylamino)purin-9-yl]-3-butenoic Acid (15f). White solid, crystallized from water, yield 0.95 g (54%), mp = 241°C (dec.), $E_{Up} = 0.47$. ^{1}H NMR: 12.30 (brs, 1H, COOH); 8.06 (s, 1H, H-8); 7.00 (dt, 1H, $J(1',2') = 14.5$, $J(1',3') = 1.2$, H-1′); 6.44 (dt, 1H, $J(2',1') = 14.5$, $J(2',3') = 7.4$, H-2′); 6.00 (brs, 2H, NH_2); 3.36 (brs, 6H, N-CH_3); 3.18 (dd, 2H, $J(3',2') = 7.4$, $J(3',1') = 1.2$, H-3′). ^{13}C NMR: 172.74 (C=O); 159.68 (C-2); 154.62 (C-6); 151.83 (C-4); 134.09 (C-8); 123.39 (C-1′); 113.86 (C-5); 111.90 (C-2′); 40.29 and 37.90 (N-CH_3); 35.22 (C-3′). FAB MS, m/z: 263 [M + H]. For $C_{11}H_{14}N_6O_2$ calcd: C, 50.38; H, 5.38; N, 32.04; O, 12.20%; found: C, 50.21; H, 5.35; N, 31.92; O, 12.52%.

4-[2-Amino-6-(cyclopropylamino)purin-9-yl]-3-butenoic Acid (15 g). White solid, crystallized from water-acetone mixture, yield 0.9 g (50%), mp = 247°C (dec.), $E_{Up} = 0.41$. ^{1}H NMR: 12.43 (brs, 1H, COOH); 8.18 (s, 1H, H-8); 7.50 (brs, 3H, N-H); 7.00 (d, 1H, $J(1',2') = 14.4$, H-1′); 6.49 (dt, 1H, $J(2',1') = 14.4$, $J(2',3') = 7.4$, H-2′); 3.19 (d, 2H, $J(3',2') = 7.4$, H-3′); 2.95 (m, 1H, N-CH); 0.80 and 0.68 (m, 2H, C-CH_2). ^{13}C NMR: 172.63 (C=O); 157.5 (C-2); 153.00 (C-6); 149.99 (C-4); 123.14 (C-1′); 113.26 (C-5); 112.84 (C-2′); 35.19 (C-3′); 24.11 (N-CH); 7.08 (2C, CH_2). FAB MS, m/z: 275 [M + H]. For $C_{12}H_{14}N_6O_2.3/2H_2O$ calcd: C, 47.84; H, 5.69; N, 27.89; O, 18.58%; found: C, 48.15; H, 5.33; N, 27.76; O, 18.76%.

4-[2-Amino-6-(pyrrolidin-1-yl)purin-9-yl]-3-butenoic Acid (15 h). White solid, crystallized from water-ethanol mixture, yield 0.6 g (35%), mp = 259°C, $E_{Up} = 0.39$. 0.39. ^{1}H NMR: 12.40 (brs, 1H, COOH); 8.01 (s, 1H, H-8); 7.00 (dt, 1H, $J(1',2') = 14.5$, $J(1',3') = 1.0$, H-1′); 6.44 (dt, 1H, $J(2',1') = 14.5$, $J(2',3') = 7.1$, H-2′); 5.92 (brs, 2H, NH_2); 3.95 and 3.55 (m, 2H, N-CH_2); 3.17 (d, 2H, $J(3',2') = 7.1$, H-3′); 1.91 (m, 4H, C-CH_2). ^{13}C NMR: 172.78 (C=O); 160.27 (C-2); 153.13 (C-6); 151.54 (C-4); 134.48 (C-8); 123.51 (C-1′); 114.14 (C-5); 111.61 (C-2′); 48.60 and 47.50 (N-CH_2); 35.25 (C-3′); 25.50 and 25.0 (C-CH_2). FAB MS, m/z: 289 [M + H]. For $C_{13}H_{16}N_6O_2 \cdot 1/2H_2O$ calcd: C, 52.52; H, 5.76; N, 28.27; O, 13.45%; found: C, 52.79; H, 5.73; N, 28.17; O, 13.31%.

4-(Guanin-9-yl)-3-butenoic Acid (15i). This compound was prepared by the same procedure as compound (**15d**) from compound (**6b**) (1.2 g, 4.5 mmol), white solid, yield 0.63 g (60%), mp = 306°C (dec.), $E_{Up} = 0.52$. ^{1}H NMR: 12.45 (brs, 1H, COOH); 10.71 (s, 1H, N-H); 8.02 (s, 1H, H-8); 6.93 (dt, 1H, $J(1',2') = 14.5$, $J(1',3') = 1.5$, H-1′); 6.56 (brs, 2H, NH_2); 6.41 (dt, 1H, $J(2',1') = 14.5$, $J(2',3') = 7.4$, H-2′); 3.17 (dd, 2H, $J(3',2') = 7.4$, $J(3',1') = 1.5$, H-3′). ^{13}C NMR: 172.69 (C=O); 156.85 (C-2); 154.11 (C-6); 150.31 (C-4); 135.08 (C-8); 123.19 (C-1′); 117.06 (C-5); 113.03 (C-2′); 35.17 (C-3′). FAB MS, m/z: 236 [M + H]. For $C_9H_9N_5O_3$ calcd: C, 45.96; H, 3.86; N, 29.78; O, 20.41%; found: C, 45.61; H, 3.89; N, 29.74; O, 20.76%.

4-(2-Amino-6-sulfanylpurin-9-yl)-3-butenoic Acid (15j). This compound was prepared from compound (**7b**) (0.98 g, 7 mmol) by the same procedure as the compound (**15e**). Crystallization from water afforded 0.76 g (42%) of yellow solid, mp = 259°C (dec.), $E_{Up} = 0.67$. ^{1}H NMR: 12.48 (brs, 1H, COOH); 12.01 (s, 1H, SH);

8.21 (s, 1H, H-8); 6.94 (dt, 1H, $J(1',2') = 14.5$, $J(1',3') = 1.0$, H-1′); 6.88 (brs, 2H, NH_2); 6.46 (dt, 1H, $J(2',1') = 14.5$, $J(2',3') = 7.4$, H-2′); 3.19 (dd, 2H, $J(3',2') = 7.4$, $J(3',1') = 1.0$, H-3′). ^{13}C NMR: 175.30 (C-6); 172.55 (C=O); 153.43 (C-2); 146.80 (C-4); 138.13 (C-8); 128.65 (C-5); 122.84 (C-1′); 113.86 (C-2′); 35.14 (C-3′). FAB MS, m/z: 252 [M + H]. For $C_9H_9N_5O_2S.1/2H_2O$ calcd: C, 41.53; H, 3.87; N, 26.91; O, 15.37; S, 12.32%; found: C, 41.87; H, 3.83; N, 26.53; O, 15.34; S, 12.43%.

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