SYNTHESIS OF RACEMIC 9-(6- AND 2,6-SUBSTITUTED 9*H*-PURIN-9-YL)-5-OXATRICYCLO[4.2.1.$0^{3,7}$]NONANE-3-METHANOLS, NOVEL CONFORMATIONALLY LOCKED CARBOCYCLIC NUCLEOSIDES

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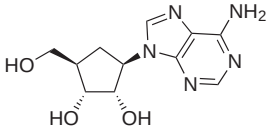
(1*R**,3*R**,6*R**,7*S**,9*S**)- and (1*R**,3*R**,6*R**,7*S**,9*R**)-9-Amino-5-oxatricyclo[4.2.1.$0^{3,7}$]nonane-3-methanols (**16a** and **17a**) were prepared from 2-(hydroxymethyl)bicyclo[2.2.1]hept-5-ene-2-methanol (**10**) in five easy steps. The amines **16a** and **17a** were used to construct 6-chloro-9*H*-purine **20** and **21**, 2-amino-6-chloro-9*H*-purine **30** and **31**, and 6-chloro-8-methyl-9*H*-purine analogues **34** and **35**. Ammonolysis of these compounds led to 6-amino-9*H*-purine **22a** and **23a**, 2,6-diamino-9*H*-purine **32** and **33**, and 6-amino-8-methyl-9*H*-purine derivatives of 5-oxatricyclo[4.2.1.$0^{3,7}$]nonane-3-methanol **36** and **37**. (1*R**,3*R**,6*R**,7*S**,9*S**)- and (1*R**,3*R**,6*R**,7*S**,9*R**)-9-[6-(Dimethylamino)-9*H*-purin-9-yl]-5-oxatricyclo[4.2.1.$0^{3,7}$]nonane-3-methanols (**22b** and **23b**), and (1*R**,3*R**,6*R**,7*S**,9*S**)- and (1*R**,3*R**,6*R**,7*S**,9*R**)-9-[6-(cyclopropylamino)-9*H*-purin-9-yl]-5-oxatricyclo[4.2.1.$0^{3,7}$]nonane-3-methanols (**22c** and **23c**) were prepared by aminolysis of **20** and **21**.

Keywords: Amines; Oximes; Nucleosides; Carbocyclic nucleosides; Norbornanes; Purines; Carbanucleosides; LNA; Antivirals.

The search for new modified nucleosides as antivirals has become a promising field of research. Carbocyclic nucleosides, in which the ring oxygen of the hemiacetal moiety is replaced by a methylene group, possess enhanced biostability due to the absence of acid-labile hemiacetal group. The discovery of the antibiotic and antitumor activity of the natural carbocyclic nucleosides aristeromycin[1] (**1**) and neplanocin A[2] (**2**) stimulated the search for novel carbocyclic nucleoside analogues with biological activity; indeed, additional synthetic carbocyclic nucleosides with important therapeutic properties were discovered. Particularly carbovir[3] (**3**), the structurally related abacavir[4] (**4**) as well as BCA[5] (**5**) are potent inhibitors of HIV. Lobucavir[6] (**6**) inhibits herpes simplex virus type 1 (HSV-1), type 2 (HSV-2), varicella-zoster virus (VZV), and human cytomegalovirus (HCMV). Compound **7** (lit.[7]) is a potent inhibitor of Epstein–Barr virus (EBV) and HCMV and its

thymine analogue[8] inhibits HSV-1 and HSV-2 replication. Cyclohexene nucleoside analogues **8** and **9** have been found[9] to be inhibitors of HSV-1, HSV-2, VZV, and HCMV.



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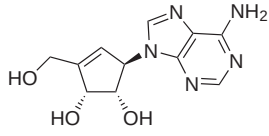

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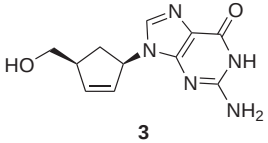

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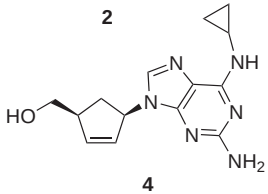

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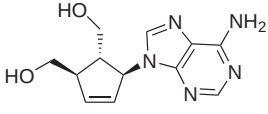

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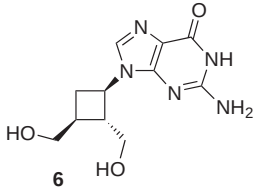

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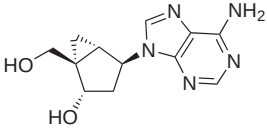

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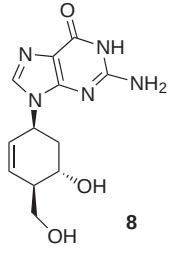

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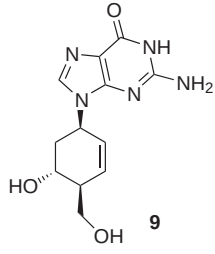

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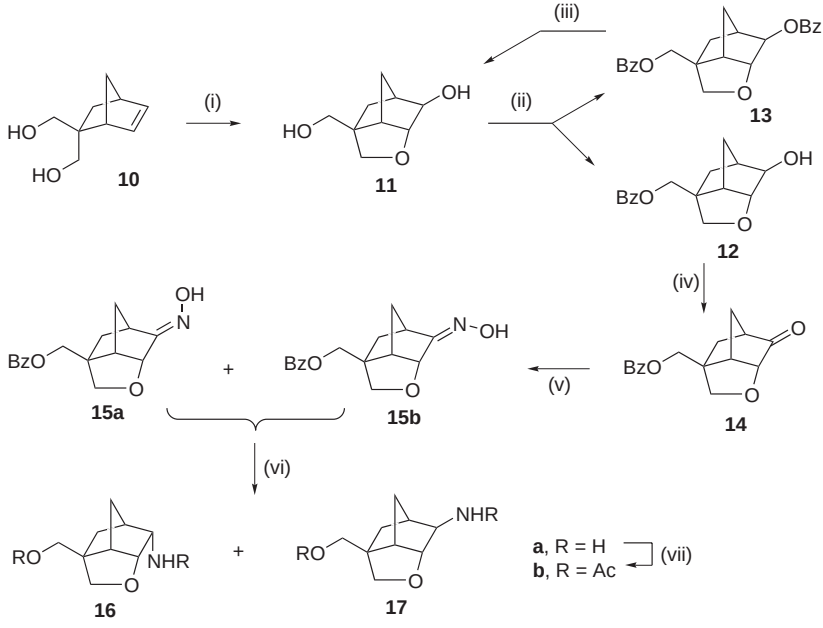
The carbocyclic nucleoside **2**–**5** and **7** are conformationally restricted analogues of natural nucleosides. Compound **6** (lobucavir) is a conformationally locked analogue of the antiviral acyclic nucleoside ganciclovir[6]. Conformational analysis[9] of cyclohexenyl nucleosides **8** and **9** led to the conclusion that this sacharide-modified nucleoside might be the best mimic of a natural furanose nucleoside. Synthesis of novel conformationally locked carbocyclic nucleosides with an oxabicyclo[2.2.1]heptane ring system (as precursors of carbocyclic locked nucleic acids) was recently described[10].

The bicyclo[2.2.1]heptane (norbornane) ring, like the oxabicyclo[2.2.1]-heptane ring system, represents conformationally locked carbapentofuranose and/or carbahexopyranose ring systems. This study concerns syntheses of novel purines substituted with 5-oxatricyclo[4.2.1.$0^{3,7}$]nonane-3-methanols which are conformationally locked carbocyclic hexopyranosyl nucleosides. Commercially available 2-(hydroxymethyl)bicyclo[2.2.1]hept-5-ene-2-methanol (**10**) was chosen as a starting compound for syntheses of the target compounds (Scheme 1).



(i) mCPBA/$CHCl_3$, 86%; (ii) BzCl/pyridine, 6 % of **12**, 15% of **13**; (iii) MeONa/MeOH; (iv) a) Dess–Martin's reagent /CH_2Cl_2, 77%, b) PDC/CH_2Cl_2, 79%; (v) $NH_2OH{\cdot}HCl/CH_3COONa$/MeOH, 45% of **15a**, 43% of **15b**; (vi) LAH/THF, 77% of **16a** + **17a**; (vii) Ac_2O/pyridine, 55% of **16**, 20% of **17**

SCHEME 1

Treatment of alcohol **10** with 3-chloroperoxybenzoic acid led to epoxidation and immediate cyclization to give cyclic ether **11**. Similar treatment of *endo*-bicyclo[2.2.1]hept-5-ene-2-methanol affording a cyclic ether was reported[11]. Benzoylation of **11** with benzoyl chloride in a dilute pyridine solution gave monobenzoate **12** (68%) together with a small amount of dibenzoate **13** (15%). Methanolysis of **13** with methanolic sodium methoxide recovered compound **11**. Oxidation of the secondary hydroxy group was performed by treatment with Dess–Martin's reagent[12] or with

pyridinium dichromate (PDC)[13]. Both the methods gave similar yields (77 and 79%, respectively) but, in our opinion, oxidation with PDC is more convenient and cheaper. Reaction of the obtained ketone **14** with hydroxylamine afforded a mixture of *E*-oxime **15a** (43%) and *Z*-oxime **15b** (45%). Both the isomers were separated by chromatography. Assignment of the configurations was performed by ^{13}C NMR. NMR study[14] of oximes found that signal of the carbon atom adjacent to the oxime hydroxy group is upfield-shifted. In ^{13}C NMR spectrum of *E*-isomer **15a**, the signal of the carbon atom C-1 is upfield-shifted, while the upfield shift of C-6 was found in ^{13}C NMR spectrum of *E*-isomer **15b**, as shown in Fig. 1. Reduction of the oxime mixture with $LiAlH_4$ yielded a mixture of amines **16a** and **17a**. Because the isomers could not be separated by chromatography, the amines were acetylated, separated by chromatography on silica gel and characterized as acetates **16b** (55%) and **17b** (20%).

The amino derivatives were converted to the 6-chloropurine derivatives by described procedures[15]. Coupling of the mixture of amines **16** and **17** with 4,6-dichloropyrimidin-5-amine in ethanol in the presence of triethylamine gave a mixture of pyrimidinylamino derivatives **18** (57%) and **19** (20%). The mixture was separated by chromatography on a silica gel column. Ring closure of **18** or **19** with triethyl orthoformate in the presence of concentrated hydrochloric acid gave 6-chloropurine derivative **20** (85%) or **21** (86%). Chloropurine **20** or **21** was ammonolyzed with liquid ammonia at 75 °C to give adenine derivative **22a** (90%) or **23a** (88%), treated with dimethylammonium *N*,*N*-dimethylcarbamate to afford (dimethylamino)-purine **22b** (80%) or **23b** (79%) and aminolyzed with cyclopropylamine to yield (cyclopropylamino)purine **22c** (88%) or **23c** (82%) (Scheme 2).

Using modification of the described procedures[15b,15c,16] 2,6-diaminopurine analogues **32** and **33** were prepared (Scheme 3) from a mixture of amines **16** and **17**. It was condensed with 4,6-dichloropyrimidin-2-amine to afford, after chromatography, pyrimidinylamino derivatives **24** (45%) and

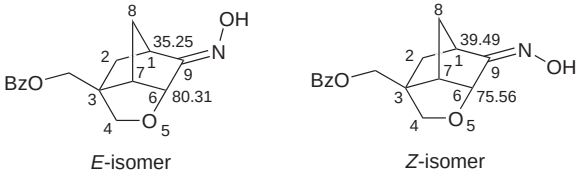
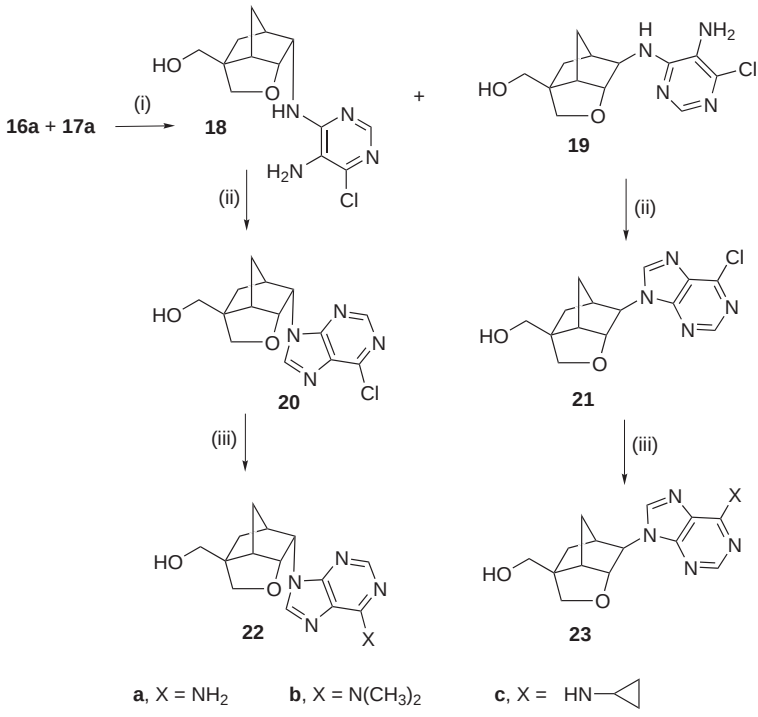


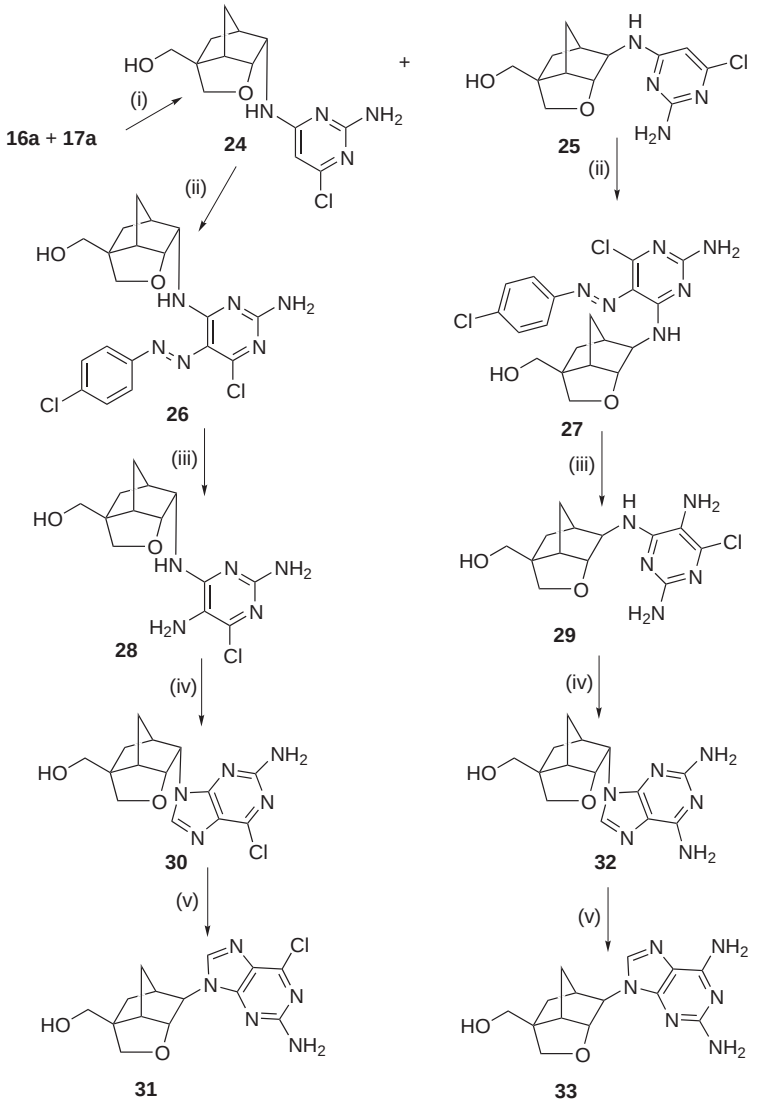
FIG. 1
Chemical shifts of signals of carbons C-1 and C-6 in ^{13}C NMR spectra of oximes **15a** and **15b**



(i) 4,6-dichloropyrimidin-5-amine/TEA/EtOH, 100 °C, 57% of **18**, 20% of **19**; (ii) 1. $CH(OEt)_3$/HCl, 2. THF/H_2O/HCl, 85% of **20**, 86% of **21**; (iii) a) NH_3 (l), 75 °C, 90% of **22a**, 88% of **23a**; b) $(CH_3)_2NCOO^-$ $(CH_3)_2NH_2^+$, 80% of **22b**, 87.5% of **23b**; c) cyclopropylamine, 88% of **22c**, 82% of **23c**

SCHEME 2

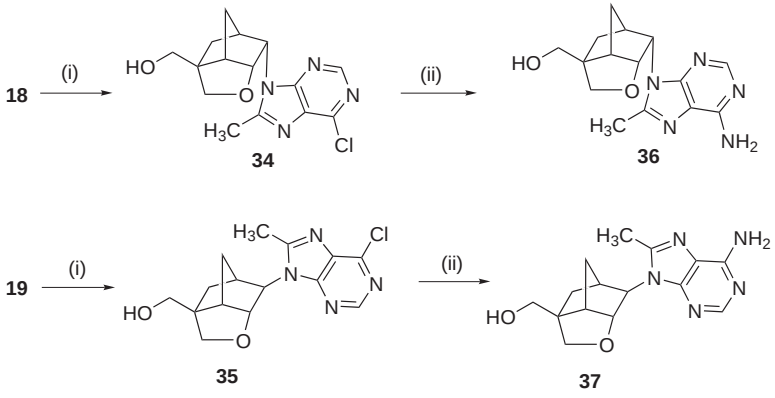
25 (16%). Treatment of **24** or **25** with 4-chlorobenzenediazonium chloride under standard conditions[15b,15c,16] led to very low yields of azopyrimidines **26** or **27**. This reaction proceeds slowly and diazonium chloride decomposes. Therefore, 4-chlorobenzenediazonium chloride was added to the reaction mixture at 0 °C in four portions over two days. Azo derivative **26** was obtained in 60% yield. Due to low solubility of pyrimidine **25**, the preparation of **27** was performed in a mixture of acetic acid and dimethyl sulfoxide. The yield of **27** was 69%. Reduction of **26** or **27** with zinc in the presence of acetic acid gave diaminopyrimidine **28** (45%) or **29** (51%) and subsequent cyclization with triethyl orthoformate and concentrated hydrochloric acid yielded chloropurine derivative **30** (64%) or **31** (73%). Ammonolysis of **30** or **31** with liquid ammonia at 75 °C afforded diaminopurine **32** (87%) or **33** (88%).



(i) 4,6-dichloropyrimidin-2-amine/TEA/EtOH, 100 °C, 45% of **24**, 16% of **25b**; (ii) 4-chloroaniline/ $HCl/NaNO_2/AcOH/NaOAc$, 60% of **26**, 76% of **27**; (iii) $Zn/EtOH/H_2O/AcOH$, 45% of **28**, 51% of **29**; (iv) 1. $CH(OEt)_3/HCl$, 2. $THF/H_2O/HCl$, 64% of **30**, 73% of **31**; (v) NH_3 (l), 75 °C, 87% of **32**, 88% of **33**

SCHEME 3

8-Methyl-6-aminopurine analogues **36** and **37** were obtained by ammonolysis of corresponding chloropurines **34** and **35**. Since coupling of **18** or **19** with triethyl orthoacetate in presence of strong acid (HCl, H_2SO_4, benzenesulfonic acid, or methanesulfonic acid) failed, compounds **34** and **35** were synthesized by cyclization of pyrimidine **18** or **19** with acetaldehyde promoted by $FeCl_3$–SiO_2 (cf. lit.[17]) in dioxane at 100 °C. While chloropurine **35** was obtained in a satisfactory yield (74%), the yield of compound **34** was low (35%), apparently due to formation of a strong iron complex (Scheme 4).



(i) CH_3CHO/1,4-dioxane/$FeCl_3$–SiO_2, 35% of **34**, 74% of **35**; (ii) NH_3 (l), 75 °C, 86% of **36**, 91% of **37**

SCHEME 4

The structure of the prepared compounds was determined by ^1H and ^{13}C NMR spectroscopy. The following values of coupling constants $J(2,3)$ of 2,3-substituted norbornanes could be found in the literature[18]: J(2-*exo*,3-*exo*) = 6–7 Hz, J(2-*endo*,3-*endo*) = 9–10 Hz, and J(2-exo,3-*endo*) = 2.5–5 Hz. Values of the corresponding coupling constants $J(6,9)$ of 5-oxatricyclo[4.2.1.$0^{3,7}$]nonane-3-methanols were 6.5–7.3 Hz for the compounds with the base in the "*endo*" position and ≈0 Hz for the analogues with the "*exo*" oriented base. Also chemical shifts of carbons C-2 and C-3 of 2,3-substituted norbornanes depend on configuration[19]. For example, ^{13}C NMR spectra of 3-methylbicyclo[2.2.1]heptan-2-ols exhibits chemical shifts for 2-*endo*,3-*endo* isomer 71.2 ppm (C-2) and 36.5 ppm (C-3), and for 2-*endo*,3-*exo* isomer 81.8 ppm (C-2) and 45.8 ppm (C-3). ^{13}C NMR spectra of the prepared compounds exhibit corresponding chemical shifts 77.11–78.19 ppm (C-6) and 53.47–62.83 ppm (C-9) for "*endo*" isomers and 83.77–87.53 ppm (C-6), and 60.8–69.71 ppm (C-9) for "*exo*" isomers.

In conclusion, novel racemic conformationally locked carbocyclic nucleoside analogues of adenine, 6-(dimethylamino)purine, 6-(cyclopropylamino)purine, 2,6-diaminopurine, and 6-amino-8-methyl-9*H*-purine derived from 5-oxatricyclo- [4.2.1.$0^{3,7}$]nonane-3-methanol were prepared from commercially available 2-(hydroxymethyl)bicyclo[2.2.1]hept-5-ene-2-methanol. The analogues **22a**–**22c**, **23a**–**23c**, **32**, **33**, **36**, and **37** were tested for inhibition of cell growth of the following cell cultures: mouse leukemia L1210 cells (ATCC CCL 240), human cervix carcinoma HeLaS3 cells (ATCC CCL 2.2), human promyelocytic leukemia HL60 cells (ATCC CCL 240), and human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119). None of the compounds exhibited considerable activity[20]. The compounds were also tested for anti-HIV-1 and -HIV-2 activity in human T-lymphocyte (CEM) cells. The only chloropurine (**21**) and (cyclopropylamino)purine (**23c**) derivatives exhibit low activity which corresponds with their cytotoxicity[21].

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Mass spectra were recorded on a ZAB-EQ (VG Analytical) spectrometer using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol matrix). NMR spectra (δ, ppm; *J*, Hz) were measured on a Varian UNITY 500 instrument (500 MHz for ^{1}H and 125.7 MHz for ^{13}C) in hexadeuteriodimethyl sulfoxide (referenced to the solvent signal). Column chromatography was performed on Silica gel 60 (Fluka) and thin-layer chromatography (TLC) on Silufol UV 254 foils (Kavalier, Votice). Solvents were evaporated at 2 kPa and bath temperature 36–60 °C; the compounds were dried at 13 Pa and 50 °C.

(1*R**,2*R**,3*R**,6*R**,7*S**)-6-(Hydroxymethyl)-4-oxatricyclo[4.2.1.$0^{3,7}$]nonan-2-ol (**11**)

A) A solution of 3-chloroperoxybenzoic acid (70%, 16.3 g, 66 mmol) in chloroform (200 ml) was dried over anhydrous sodium sulfate. The sulfate was filtered off and washed with chloroform. Norbornene **10** (7.71 g, 50 mmol) was added to the stirred and ice-cooled collected filtrates and washings. The mixture was then stirred at room temperature for 2 h and evaporated. Column chromatography on silica gel (500 g) in ethyl acetate–acetone–ethanol–water (100:15:6:4) followed by crystallization from toluene–ethyl acetate (1:1) afforded 7.28 g (86%) of compound **11**, m.p. 96–98 °C. For $C_9H_{14}O_3$ (170.2) calculated: 63.51% C, 8.29% H; found: 63.53% C, 8.34% H. FAB MS, *m/z* (%): 171 (100) [M + H], 153 (21), 135 (19). ^{1}H NMR: 0.97 dd, 1 H, *J*(9b,8a) = 2.2, J_{gem} = 12.7 (H-9b); 1.38 dq, 1 H, *J*(8b,1) = 1.2, *J*(8b,7) = *J*(8b,2) = 1.6, J_{gem} = 10.2 (H-8b); 1.45 ddd, 1 H, *J*(9a,5a) = 0.5, *J*(9a,1) = 4.5 (H-9a); 1.74 brdq, 1 H, *J*(8a,1) = 1.2, *J*(8a,7) = 1.6 (H-8a); 1.94 dm, 1 H, *J*(1,8) = *J*(1,2) = 1.2, *J*(1,7) = *J*(1,3) = 1.4 (H-1); 2.27 dq, 1 H, *J*(7,3) = 5.1 (H-7); 3.24 brdt, 1 H, *J*(2,OH) = 3.2 (H-2); 3.31 dd, 1 H and 3.33 dd, 1 H, *J*(CH,OH) = 5.3, J_{gem} = 11.0 (CH_2O); 3.50 d, 1 H and 3.64 d, 1 H, J_{gem} = 7.8 (2 × H-5); 3.80 dd, 1 H (H-3); 4.68 t, 1 H (CH_2O**H**); 4.69 d, 1 H (2-OH). ^{13}C NMR:

32.08 (C-9); 36.81 (C-8); 41.63 (C-1); 45.66 (C-7); 49.37 (C-6); 64.06 (CH_2O); 76.76 (C-6); 80.18 (C-3); 88.30 (C-2).

B) Dibenzoate **13** (11.35 g, 30 mmol) was dissolved under stirring at 50 °C in 0.1 M methanolic sodium methoxide (100 ml), the solution was set aside at room temperature overnight and neutralized with Dowex 50 (H^+). The resin was filtered off, washed with methanol and the collected filtrates were evaporated. Crystallization of the residue from toluene–ethyl acetate afforded 4.75 g (93%) of **11**.

((1*R**,3*R**,6*R**,7*S**,9*S**)-9-Hydroxy-5-oxatricyclo[4.2.1.$0^{3,7}$]nonan-3-yl)methyl Benzoate (**12**) and ((1*R**,3*R**,6*R**,7*S**,9*S**)-9-(Benzoyloxy)-5-oxatricyclo[4.2.1.$0^{3,7}$]-nonan-3-yl)methyl Benzoate (**13**)

A solution of benzoyl chloride (2.7 ml, 23 mmol) in pyridine (25 ml) was added dropwise at room temperature during 6 h to a solution of alcohol **11** (3.40 g, 20 mmol) in pyridine (70 ml) and the solution was set aside overnight. Methanol (3 ml) was then added and, after 10 min, the mixture was evaporated and the residue was partitioned between ethyl acetate (100 ml) and water (50 ml). The organic phase was washed with water (2 × 50 ml), dried over anhydrous sodium sulfate, and the solvent was taken down. Crystallization of the residue from an acetate–toluene (1:1) mixture afforded 2.57 g (47%) of benzoate **12**. Chromatography of the mother liquors on a silica gel column (150 g) in ethyl acetate–toluene (18:7) gave 1.14 g (21%) of benzoate **12** and 1.13 g (15%) of dibenzoate **13**.

Compound **12**: M.p. 129–130.5 °C. For $C_{16}H_{18}O_4$ (274.3) calculated: 70.06% C, 6.61% H; found: 70.26% C, 6.70% H. FAB MS, *m/z*: 275 [M + H]. ^{1}H NMR: 1.16 dd, 1 H, *J*(2b,8a) = 2.2, J_{gem} = 12.8 (H-2b); 1.53 dq, 1 H, *J*(8b,1) = 1.2, *J*(8b,7) = *J*(8b,9) = 1.6, J_{gem} = 10.5 (H-8b); 1.64 dd, 1 H, *J*(2a,1) = 4.6 (H-2a); 1.83 brdq, 1 H, *J*(8a,1) = *J*(8a,7) = 1.6 (H-8a); 2.02 dm, 1 H, *J*(1,7) = 1.2, *J*(1,9) = *J*(1,6) =1.6 (H-1); 2.42 dq, 1 H, *J*(7,6) = 5.1 (H-7); 3.30 brdt, 1 H, *J*(9,OH) = 3.0 (H-9); 3.68 d, 1 H and 3.71 d, 1 H, J_{gem} = 7.8 (2 × H-4); 3.89 dd, 1 H (H-6); 4.26 s, 2 H (CH_2O); 4.80 d, 1 H (9-OH); 7.53 t, 2 H, 7.66 t, 1 H, and 7.95 d, 2 H (H-arom.).

Compound **13**: M.p. 153.5–154.5 °C. For $C_{23}H_{22}O_5$ (378.4) calculated: 73.00% C, 5.86% H; found: 73.12% C, 5.91% H. FAB MS, *m/z*: 379 [M + H]. ^{1}H NMR: 1.39 dd, 1 H, *J*(2b,8a) = 1.8, J_{gem} = 13.2 (H-2b); 1.76 dm, 1 H, *J*(8b,1) ≈ *J*(8b,7) ≈ *J*(8b,9) = 1.5, J_{gem} = 10.5 (H-8b); 1.81 dd, 1 H, *J*(2a,1) = 4.6 (H-2a); 1.90 dm, 1 H, *J*(8a,1) ≈ *J*(8a,7) = 1.7 (H-8a); 2.37 dm, 1 H, *J*(1,7) ≈ *J*(1,9) ≈ *J*(1,6) = 1.2 (H-1); 2.62 brdq, 1 H, *J*(7,6) = 5.1 (H-7); 3.80 d, 1 H and 3.84 d, 1 H, J_{gem} = 7.8 (2 × H-4); 4.23 dt, 1 H, *J*(6,9) = 1.2 (H-6); 4.32 s, 2 H (CH_2O); 4.56 q, 1 H (H-9); 7.54 m, 4 H, 7.65 m, 2 H, and 7.97 m, 4 H (H-arom.).

((1*R**,3*S**,6*R**,7*S**)-9-Oxo-5-oxatricyclo[4.2.1.$0^{3,7}$]nonan-3-yl)methyl Benzoate (**14**)

A) A solution of monobenzoate **12** (5.49 g, 20 mmol) in dichloromethane (50 ml) was added to a stirred solution of Dess–Martin's reagent (9.33 g, 22 mmol) in dichloromethane (100 ml). After 30 min, the mixture was evaporated and the residue was disolved in ethyl acetate (50 ml). The insoluble portion was filtered off with a Celite pad and washed with ethyl acetate. The collected filtrates were washed with 10% aqueous potassium hydrogencarbonate (2 × 50 ml), dried over anhydrous sodium sulfate and evaporated. Chromatography of the residue on a silica gel column (200 g) in ethyl acetate–toluene (7:18) afforded 4.19 g (77%) of compound **14**, m.p. 85–86 °C. For $C_{16}H_{16}O_4$ (272.3) calculated: 70.57% C, 5.92% H; found: 70.51% C, 5.95% H. FAB MS, *m/z*: 273 [M + H]. ^{1}H NMR: 1.51 ddd, 1 H,

J(2b,1) = 0.6, J(2b,8b) = 2.1, J_{gem} = 13.1 (H-2b); 1.75dtd, 1 H, J(8b,1) = 1.4, J(8b,7) = 2.1, J_{gem} = 11.3 (H-8b); 1.91 ddd, 1 H, J(8a,1) = 1.4, J(8a,7) = 2.1 (H-8a); 1.96 brdd, 1 H, J(2a,4a) = 0.5, J(2a,1) = 4.3 (H-2a); 2.46 brdpent, 1 H, J(1,7) = J(1,6) = 1.4 (H-1); 2.90 dq, 1 H, J(7,6) = 5.5 (H-7); 3.84 d, 1 H and 3.94 d, 1 H, J_{gem} = 7.8 (2 × H-4); 3.95 dd, 1 H (H-6); 4.41 s, 2 H (CH_2O); 7.54 t, 2 H, 7.67 t, 1 H, and 7.98 d, 2 H (H-arom.). ^{13}C NMR: 28.48 (C-2); 35.80 (C-8); 46.07 (C-1); 46.44 (C-7); 47.89 (C-3); 67.03 (CH_2O); 77.38 (C-4); 81.31 (C-6); 129.07, 2 C, 129.43, 2 C, 129.64, and 133.72 (arom.); 165.89 (C=O); 213.45 (C-9).

B) A mixture of pyridinium dichromate (11.29 g, 30 mmol), molecular sieves (3A, powder, 12 g) and dichloromethane (120 ml) was stirred at room temperature for 15 min. A solution of monobenzoate **12** (5.49 g, 20 mmol) in dichloromethane (45 ml) was added to the mixture. After 3 h stirring at room temperature, the mixture was filtered and the filtrates were evaporated. The residue was stirred with ethyl acetate (90 ml), the mixture was filtered with a Celite pad and the filtrates were taken down. Chromatography of the residue, performed as above, afforded 4.30 g (79%) of **14**.

((6*E*,1*R**,3*S**,6*R**,7*S**)-9-(Hydroxyimino)-5-oxatricyclo[4.2.1.0^{3,7}]nonan-3-yl)methyl Benzoate (**15a**) and ((6*Z*,1*R**,3*S**,6*R**,7*S**)-9-(Hydroxyimino)-5-oxatricyclo[4.2.1.0^{3,7}]-nonan-3-yl)methyl Benzoate (**15b**)

Anhydrous sodium acetate (1.89 g, 23 mmol) and hydroxylamine hydrochloride (1.60 g, 23 mmol) were added to a solution of ketone **14** (5.45 g, 20 mmol) in methanol (45 ml). The mixture was stirred at room temperature for 30 min and then evaporated. The residue was partitioned between ethyl acetate (270 ml) and water (80 ml). The organic layer was separated, washed with water (60 ml), dried over anhydrous sodium sulfate and evaporated. Crystallization of the residue from an ethyl acetate–toluene (1:1) mixture afforded 5.07 g (88%) of a mixture of *E*- and *Z*-oximes **15a** and **15b**, respectively. The mixture was used in the next reaction step. Chromatography of the mixture (200 mg) on a silica gel column (40 g) in ethyl acetate–toluene (1:1) gave 90 mg of oxime **15a** and 85 mg of oxime **15b**.

Compound **15a**: M.p. 172–174 °C. For $C_{16}H_{17}NO_4$ (287.3) calculated: 66.89% C, 5.96% H, 4.88% N; found: 66.92% C, 5.88% H, 4.75% N. FAB MS, *m/z*: 288 [M + H]. ^{1}H NMR: 1.40 brdq, 1 H, J(8b,7) ≈ J(8b,1) = 1.7, J_{gem} = 11.0 (H-8b); 1.42 ddd, 1 H, J(2b,1) = 0.6, J(2b,8b) = 1.8, J_{gem} = 12.7 (H-2b); 1.73 dtd, 1 H, J(8a,6) = 0.6, J(8a,7) = J(8a,1) = 1.6 (H-8a); 1.86 brdd, 1 H, J(2a,4a) = 0.7, J(2a,1) = 4.2 (H-2a); 2.72 dq, 1 H, J(7,1) = 1.5, J(7,6) = 5.4 (H-7); 3.30 brdpent, 1 H, J(1,6) = 1.2 (H-1); 3.78 d, 1 H, J_{gem} = 7.8 (H-4a); 3.88 d, 1 H (H-4b); 4.34 s, 1 H (CH_2O); 4.47 dd, 1 H (H-6); 7.54 t, 2 H, 7.67 t, 1 H, and 7.98 d, 2 H (H-arom.); 10.49 s, 1 H (N-OH). ^{13}C NMR: 32.33 (C-2); 35.25 (C-1); 37.98 (C-8); 47.52 (C-7); 48.43 (C-3); 67.24 (CH_2O); 76.72 (C-4); 80.31 (C-6); 129.08, 2 C, 129.41, 2 C, 129.70, and 133.70 (arom.); 162.91 (C-9); 165.93 (C=O).

Compound **15b**: M.p. 155–157 °C. For $C_{16}H_{17}NO_4$ (287.3) calculated: 66.89% C, 5.96% H, 4.88% N; found: 66.72% C, 5.92% H, 4.73% N. FAB MS, *m/z*: 288 [M + H]. ^{1}H NMR: 1.42 brdt, 1 H, J(8b,7) ≈ J(8b,1) = 1.7, J_{gem} = 10.7 (H-8b); 1.49 brdd, 1 H, J(2b,1) = 0.5, J(2b,8b) = 2.0, J_{gem} = 12.4 (H-2b); 1.75 brdt, 1 H, J(8a,6) = 1.0, J(8a,7) ≈ J(8a,1) = 1.7 (H-8a); 1.89 brdd, 1 H, J(2a,4a) = 0.5, J(2a,1) = 3.8 (H-2a); 2.66 dm, 1 H, J(1,6) = 0.5, J(1,7) ≈ J(1,8) = 1.5 (H-1); 2.71 dq, 1 H, J(7,1) = 1.3, J(7,8) = 1.6, J(7,6) = 5.2 (H-7); 3.76 d, 1 H and 3.87 d, 1 H, J_{gem} = 8.0 (2 × H-4); 4.34 s, 2 H (CH_2O); 4.77 brd, 1 H (H-6); 7.54 t, 2 H, 7.67 t, 1 H, and 7.98 d, 2 H (H-arom.); 10.30 s, 1 H (N-OH). ^{13}C NMR: 32.26 (C-2); 39.45 (C-8); 39.49

(C-1); 47.45 (C-7); 48.08 (C-3); 67.26 (CH_2O); 75.56 (C-6); 76.80 (C-4); 129.08, 2 C, 129.40, 2 C, 129.69, and 133.70 (arom.); 162.41 (C-9); 165.91 C=O).

Mixture of (1*R**,3*R**,6*R**,7*S**,9*S**)- and (1*R**,3*R**,6*R**,7*S**,9*R**)-9-Amino-5-oxatricyclo-[4.2.1.$0^{3,7}$]nonane-3-methanols (**16a** and **17a**)

A solution of the mixture of oximes **15a** and **15b** (5.75 g, 20 mmol) in tetrahydrofuran (40 ml) was added dropwise under stirring to a boiling 1 M solution of lithium aluminium hydride (40 ml) in argon atmosphere. The mixture was refluxed for 1 h, cooled and ethyl acetate (20 ml) was added, followed after 15 min by water (20 ml). The mixture was taken down and the residue was extracted with 90% aqueous methanol (4 × 50 ml). The collected extracts were concentrated to a small volume and applied on a column filled with Dowex 50 (H^+, 180 ml). The column was washed with water (300 ml) and methanol (300 ml) and then eluted with methanolic 2 M ammonia. Evaporation of the UV absorbing fraction afforded 2.16 g (77%) of a mixture of **16a** and **17a**. For $C_9H_{15}NO_2$ (169.2) calculated: 63.88% C, 8.93% H, 8.28% N; found: 63.59% C, 8.90% H, 7.99% N. FAB MS, *m/z*: 170 [M + H].

((1*R**,3*R**,6*R**,7*S**,9*S**)-9-Acetamido-5-oxatricyclo[4.2.1.$0^{3,7}$]nonan-3-yl)methyl Acetate (**16b**) and ((1*R**,3*R**,6*R**,7*S**,9*R**)-9-Acetamido-5-oxatricyclo[4.2.1.$0^{3,7}$]nonan-3-yl)methyl Acetate (**17b**)

Acetic anhydride (0.5 ml) was added to a stirred ice-cooled solution of amines **16a** and **17a** (254 mg, 1.5 mmol) in pyridine (4 ml) and the mixture was set aside overnight. Methanol (0.5 ml) was added and, after 10 min, the mixture was evaporated. The residue was co-distilled with toluene and chromatographed on a silica gel column (30 g) in ethyl acetate–acetone–ethanol–water (100:15:6:4) to give, after crystallization from toluene, 209 mg (55%) of acetate **16b** and 75 mg (20%) of acetate **17b**.

Compound **16b**: M.p. 126–127 °C. For $C_{13}H_{19}NO_4$ (253.3) calculated: 61.64% C, 7.56% H, 5.53% N; found: 61.67% C, 7.61% H, 5.50% N. FAB MS, *m/z* (%): 254 (100) [M + H], 212 (30). ^{1}H NMR: 1.33 brdq, 1 H, *J*(8b,7) ≈ *J*(8b,1) ≈ *J*(8b,2b) = 1.5, J_{gem} = 10.9 (H-8b); 1.43 brddd, 1 H, *J*(2a,9) = 2.0, *J*(2a,1) = 4.0, J_{gem} = 12.8 (H-2a); 1.50 m, 2 H (H-8a, H-2b); 1.87 s, 3 H and 2.02 s, 3 H (2 × $COCH_3$); 2.08 m, 1 H (H-1); 2.47 brdq, 1 H, *J*(7,1) = 1.2, *J*(7,8a) = *J*(7,8b) = 1.5, *J*(7,6) = 5.2 (H-7); 3.60 d, 1 H and 3.72 d, 1 H, J_{gem} = 7.4 (2 × H-4); 3.62 tdd, 1 H, *J*(9,1) = 3.3, *J*(9,6) = 7.3 (H-9); 3.98 d, 1 H and 4.01 d, 1 H, J_{gem} = 11.2 (CH_2O); 4.12 dd, 1 H (H-6); 7.20 d, 1 H, *J*(NH,9) = 7.7 (NH). ^{13}C NMR: 20.81 (CH_3); 22.89 (CH_3); 31.78 (C-2); 34.50 (C-8); 38.06 (C-1); 58.32 (C-3); 48.71 (C-7); 53.47 (C-9); 66.09 (CH_2O); 75.26 (C-4); 77.53 (C-6); 169.60 (C=O); 170.76 (C=O).

Compound **17b**: M.p. 147–148 °C. For $C_{13}H_{19}NO_4$ (253.3) calculated: 61.64% C, 7.56% H, 5.53% N; found: 61.68% C, 7.65% H, 5.41% N. FAB MS, *m/z* (%): 254 (100) [M + H], 212 (16). ^{1}H NMR: 1.21 dd, 1 H, *J*(2b,8a) = 2.2, J_{gem} = 12.7 (H-2b); 1.51 brdq, 1 H, *J*(8b,9) = 1.6, *J*(8b,7) ≈ *J*(8b,1) = 1.6, J_{gem} = 11.0 (H-8b); 1.60 dd, 1 H, *J*(2a,1) = 4.5 (H-2a); 1.68 brdq, 1 H, *J*(8a,7) ≈ *J*(8a,1) ≈ *J*(8a,2b) = 1.8 (H-8a); 1.78 s, 3 H and 2.02 s, 3 H (2 × $COCH_3$); 2.02 dm, 1 H (H-1); 2.36 dq, 1 H, *J*(7,1) = 1.3, *J*(7,8a) = *J*(7,8b) = 1.5, *J*(7,6) = 5.1 (H-7); 3.24 dd, 1 H, *J*(9,NH) = 6.7 (H-9); 3.62 d, 1 H and 3.65 d, 1 H, J_{gem} = 7.8 (2 × H-4); 3.96 dd, 1 H, *J*(6,1) = 1.2 (H-6); 3.99 s, 2 H (CH_2O); 7.77 d, 1 H (NH). ^{13}C NMR: 20.82 (CH_3); 22.79 (CH_3); 32.86 (C-2); 38.61 (C-8); 39.75 (C-1); 46.88 (C-7); 47.28 (C-3); 60.80 (C-9); 66.32 (CH_2O); 76.23 (C-4); 86.94 (C-6); 168.74 (C=O); 170.70 (C=O).

(1*R**,3*R**,6*R**,7*S**,9*S**)-9-[(5-Amino-6-chloropyrimidin-4-yl)amino]-5-oxatricyclo[4.2.1.$0^{3,7}$]-nonane-3-methanol (**18**) and (1*R**,3*R**,6*R**,7*S**,9*R**)-9-[(5-Amino-6-chloropyrimidin-4-yl)-amino]-5-oxatricyclo[4.2.1.$0^{3,7}$]nonane-3-methanol (**19**)

A solution of amines **16a** and **17a** (508 mg, 3 mmol), 4,6-dichloropyrimidin-5-amine (984 mg, 6 mmol), and triethylamine (1.8 ml) in ethanol (18 ml) was heated in a pressure vessel at 100 °C for 7 days and, after cooling, was taken down. Crystallization of the residue from methanol (10 ml) afforded 360 mg (40%) of compound **18**.The mother liquors were evaporated and the residue was chromatographed on a column of silica gel (100 g) in ethyl acetate–acetone–toluene–ethanol–water (85:15:15:7:3) to give 150 mg (17%) of **18** and 190 mg (20%) of **19**.

Compound **18**: M.p. 225–228 °C. For $C_{13}H_{17}ClN_4O_2$ (296.8) calculated: 52.62% C, 5.77% H, 11.95% Cl, 18.88% N; found: 52.45% C, 5.88% H, 11.89% Cl, 18.68% N. FAB MS, *m/z* (%): 299/297 (34/100) [M + H]. ^{1}H NMR: 1.36 brdq, 1 H, *J*(8b,7) ≈ *J*(8b,1) ≈ *J*(8b,2b) = 1.5, J_{gem} = 10.6 (H-8b); 1.38 ddd, 1 H, *J*(2a,9) = 2.1, *J*(2a,1) = 4.0, J_{gem} = 12.8 (H-2a); 1.50 dt, 1 H, *J*(8a,7) = *J*(8a, 1) = 1.7 (H-8b); 1.54 dd, 1 H, *J*(2b,8b) = 2.2 (H-2b); 2.27 m, 1 H (H-1); 2.49 m, 1 H (H-7); 3.34 dd, 1 H, *J*(CH,OH) = 5.5 and 3.37 dd, 1 H, *J*(CH,OH) = 5.3, J_{gem} = 12.0 (CH_2O); 3.68 d, 1 H and 3.72 d, 1 H, J_{gem} = 7.4 (2 × H-4); 3.78 tdd, 1 H, *J*(9,1) = 3.3, *J*(9,6) ≈ *J*(9,NH) = 7.0 (H-9); 4.23 dd, 1 H, *J*(6,7) = 5.1, *J*(6,9) = 7.3 (H-6); 4.75 t, 1 H, *J*(OH,CH_2) = 5.4 (CH_2O**H**); 5.22 brs, 2 H (NH_2); 6.04 d, 1 H, *J*(NH,9) = 6.6 (NH); 7.74 s, 1 H (H-2′). ^{13}C NMR: 31.80 (C-2); 34.42 (C-8); 37.65 (C-1); 48.25 (C-7); 50.67 (C-3); 55.76 (C-9); 63.74 (CH_2O); 75.76 (C-4); 77.41 (C-6); 123.83 (C-4′); 136.85 (C-5′); 145.69 (C-2′); 151.14 (C-6′).

Compound **19**: M.p. 226–228.5 °C. For $C_{13}H_{17}ClN_4O_2 \cdot H_2O$ (314.8) calculated: 49.60% C, 6.08% H, 11.26% Cl, 17.80% N; found: 49.87% C, 6.04% H, 11.40% Cl, 17.76% N. FAB MS, *m/z* (%): 299/297 (47/100) [M + H], 171 (65), 157 (44). ^{1}H NMR: 1.20 dd, 1 H, *J*(2b,8a) = 2.2, J_{gem} = 12.6 (H-2b); 1.50 brdq, 1 H, *J*(8b,7) ≈ *J*(8b,1) ≈ *J*(8b,9) = 1.5, J_{gem} = 10.9 (H-8b); 1.59 dd, 1 H, *J*(2a,1) = 4.5 (H-2a); 1.75 brdq, 1 H, *J*(8a,7) ≈ *J*(8a,1) = 1.5 (H-8a); 2.18 brdm, 1 H (H-1); 2.39 brdq, 1 H, *J*(7,1) = 1.2, *J*(7,2a) = *J*(7,2b) = 1.5, *J*(7,6) = 5.1 (H-7); 3.36 d, 2 H, *J*(CH_2,OH) = 5.3 (CH_2O); 3.52 brdd, 1 H, *J*(9,1) = 1.0, *J*(9,8b) = 1.3, *J*(9,NH) = 5.8 (H-9); 3.63 d, 1 H and 3.72 d, 1 H, J_{gem} = 7.6 (2 × H-4); 4.08 dd, 1 H, *J*(6,1) = 1.1 (H-6); 4.76 t, 1 H (CH_2O**H**); 5.12 brs, 2 H (NH_2); 6.48 d, 1 H (NH); 7.72 s, 1 H (H-2′). ^{13}C NMR: 32.95 (C-2); 38.69 (C-8); 39.58 (C-1); 46.52 (C-7); 49.68 (C-3); 63.19 (C-9); 63.96 (CH_2O); 76.65 (C-4); 86.70 (C-6); 123.83 (C-4′); 136.85 (C-5′); 145.69 (C-2′); 151.14 C-6′).

(1*R**,3*R**,6*R**,7*S**,9*S**)-9-(6-Chloro-9*H*-purin-9-yl)-5-oxatricyclo[4.2.1.$0^{3,7}$]nonane-3-methanol (**20**) and (1*R**,3*R**,6*R**,7*S**,9*R**)-9-(6-Chloro-9*H*-purin-9-yl)-5-oxatricyclo-[4.2.1.$0^{3,7}$]nonane-3-methanol (**21**)

Concentrated hydrochloric acid (1 ml) was added to a stirred mixture of compound **18** (594 mg, 2 mmol) or **19** (629 mg, 2 mmol) and triethyl orthoformate (20 ml), the resulting solution was set aside at room temperature for 3 days and then evaporated. The residue was dissolved in tetrahydrofuran (12 ml). To the stirred solution, 0.5 M hydrochloric acid (12 ml) was added, the mixture was stirred at room temperature for 2.5 h and then neutralized with solid sodium hydrogencarbonate. The organic layer was separated and the aqueous layer was extracted with tetrahydrofuran (3 × 10 ml). The combined organic layers were evaporated.

Compound **20**: Chromatography of the residue on a silica gel column (50 g) in ethyl acetate–acetone–ethanol–water (180:30:13:7) and following crystallization from water. Yield 520 mg (85%). M.p. 171–173 °C. For $C_{14}H_{15}ClN_4O_2$ (306.8) calculated: 54.82% C, 4.93% H,

11.56% Cl, 18.26% N; found: 54.58% C, 4.95% H, 11.61% Cl, 18.05% N. FAB MS, *m/z* (%): 309/307 (47/100) [M + H], 171 (26), 157 (74). ^{1}H NMR: 1.48 dd, 1 H, *J*(2b,8b) = 2.4, J_{gem} = 13.6 (H-2b); 1.58 brdq, 1 H, *J*(8b,1) = 1.5, J_{gem} = 10.9 (H-8b); 1.67 brddd, 1 H, *J*(2a,9) = 1.8, *J*(2a,1) = 4.2 (H-2a); 1.70 dt, 1 H, *J*(8a,1) = 1.7 (H-8a); 2.68 brdq, 1 H, *J*(7,1) = 1.2, *J*(7,8a) = *J*(7,8b) = 1.5, *J*(7,6) = 5.4 (H-7); 2.85 m, 1 H (H-1); 3.36 dd, 1 H and 3.41 dd, 1 H, J_{gem} = 11.2 (CH_2O); 3.45 d, 1 H and 3.63 d, 1 H, J_{gem} = 7.7 (2 × H-4); 4.43 ddd, 1 H, *J*(9,1) = 3.2, *J*(9,6) = 6.8 (H-9); 4.73 ddd, 1 H, *J*(6,1) = 0.7 (H-6); 4.82 t, 1 H, *J*(OH,CH_2) = 5.4 (CH_2O**H**); 8.67 s, 1 H and 8.75 s, 1 H (H-2′, H-8′). ^{13}C NMR: 32.52 (C-2); 35.54 (C-8); 37.59 (C-1); 48.46 (C-7); 50.43 (C-3); 60.41 (C-9); 63.11 (CH_2O); 75.43 (C-4); 77.13 (C-6); 130.52 (C-5′); 147.20 (C-8′); 149.02 (C-6′); 151.42 (C-2′); 152.98 (C-4′).

Compound **21**: Crystallization of the residue from aqueous ethanol. Yield 532 mg (87%). M.p. 197–198 °C. For $C_{14}H_{15}ClN_4O_2$ (306.8) calculated: 54.82% C, 4.93% H, 11.56% Cl, 18.26% N; found: 54.79% C, 5.05% H, 11.47% Cl, 18.01% N. FAB MS, *m/z* (%): 309/307 (36/100) [M + H]. ^{1}H NMR: 1.40dd, 1 H, *J*(2b,8a) = 2.3, J_{gem} = 12.8 (H-2b); 1.68 brdq, 1 H, *J*(8b,1) ≈ *J*(8b,7) = 1.7, J_{gem} = 11.6 (H-8b); 1.75 dd, 1 H, *J*(2a,1) = 4.5 (H-2a); 1.76 brdq, 1 H, *J*(8a,1) = 1.7 (H-8a); 2.57 brdq, 1 H, *J*(7,1) = 1.3, *J*(7,6) = 5.0, *J*(7,8) = 1.7 (H-7); 2.63 dm, 1 H (H-1); 3.42 d, 2 H, *J*(CH_2,OH) = 5.4 (CH_2O); 3.75 d, 1 H and 3.81 d, 1 H, J_{gem} = 7.7 (2 × H-4); 4.20 d, 1 H, *J*(9,8b) = 1.8 (H-9); 4.82 dd, 1 H, *J*(6,1) = 1.3 (H-6); 4.84 t, 1 H (CH_2O**H**); 8.765 s, 1 H and 8.77 s, 1 H (H-2′ and H-8′). ^{13}C NMR: 31.54 (C-2); 36.57 (C-8); 37.95 (C-1); 45.155 (C-7); 47.60 (C-3); 61.60 (CH_2O); 64.86 (C-9); 74.72 (C-4); 83.00 (C-6); 129.23 (C-5′); 143.68 (C-8′); 147.17 (C-6′); 149.48 (C-2′); 150.25 (C-4′).

(1*R**,3*R**,6*R**,7*S**,9*S**)-9-[6-(Dimethylamino)-9*H*-purin-9-yl]-5-oxatricyclo[4.2.1.$0^{3,7}$]-nonane-3-methanol (**22b**) and (1*R**,3*R**,6*R**,7*S**,9*R**)-9-[6-(Dimethylamino)-9*H*-purin-9-yl]-5-oxatricyclo[4.2.1.$0^{3,7}$]nonane-3-methanol (**23b**)

Chloropurine **20** or **21** (153 mg, 0.5 mmol) was dissolved under stirring in dimethylammonium *N*,*N*-dimethylcarbamate (1.5 ml), the solution was set aside at room temperature for 5 h and then evaporated.

Compound **22b**: Crystallization of the residue from water. Yield 134 mg (80%). M.p. 145 °C (hydrate), 166–167 °C. For $C_{16}H_{21}N_5O_2 \cdot H_2O$ (333.4) calculated: 57.64% C, 6.95% H, 21.01% N; found: 57.70% C, 7.06% H, 20.96% N. FAB MS, *m/z* (%): 316 (100) [M + H], 164 (12). ^{1}H NMR: 1.51 dd, 1 H, *J*(2b,8b) = 2.2, J_{gem} = 12.8 (H-2b); 1.53 dm, 1 H, J_{gem} = 10.6 (H-8b); 1.62 ddd, 1 H, *J*(2a,1) = 3.7, *J*(2a,9) = 2.0 (H-2a); 1.65 dt, 1 H, *J*(8a,1) = *J*(8a,7) = 1.7 (H-8a); 2.63 m, 1 H (H-1); 2.66 brdq, 1 H, *J*(7,1) = 1.0, *J*(7,6) = 5.2 (H-7); 3.39 dd, 1 H, *J*(CH_2,OH) = 5.5 and 3.41 dd, 1 H, *J*(CH_2,OH) = 5.2, J_{gem} = 11.2 (CH_2O); 3.40 brs, 6 H ($N(CH_3)_2$); 3.54 d, 1 H and 3.67 d, 1 H, J_{gem} = 7.7 (2 × H-4); 4.37 ddd, 1 H, *J*(9,1) = 2.9, *J*(9,6) = 6.8 (H-9); 4.61 dd, 1 H (H-6); 4.82 t, 1 H (CH_2O**H**); 8.16 s, 1 H and 8.19 s, 1 H (H-2′, H-8′). ^{13}C NMR: 32.54 (C-2); 35.47 (C-8); 38.01 (C-1); 39.05 ($N(CH_3)_2$); 48.67 (C-7); 50.45 (C-3); 59.33 (C-9); 63.22 (CH_2O); 75.25 (C-4); 77.28 (C-6); 118.84 (C-5′); 139.13 (C-8′); 151.31 (C-4′); 151.64 (C-2′); 154.37 (C-6′).

Compound **23b**: Chromatography of the residue on a silica gel column (10 g) in ethyl acetate–toluene–acetone–ethanol–water (85:15:15:7:3) and following crystallization from ether. Yield 138 mg (87.5%). M.p. 167–169 °C. For $C_{16}H_{21}N_5O_2$ (315.4) calculated: 60.93% C, 6.71% H, 22.21% N; found: 60.90% C, 6.83% H, 22.07% N. FAB MS, *m/z* (%): 316 (100) [M + H], 164 (17). ^{1}H NMR: 1.37 dd, 1 H, *J*(2b,8a) = 2.2, J_{gem} = 12.8 (H-2b); 1.62 brdq, 1 H, *J*(8b,1) ≈ *J*(8b,7) = 1.5, J_{gem} = 10.7 (H-8b); 1.71 dd, 1 H, *J*(2a,1) = 4.4 (H-2a); 1.73 dm, 1 H (H-8a);

2.45 dm, 1 H (H-1); 2.55 brdq, 1 H, *J*(7,1) = 1.7, *J*(7,6) = 5.0 (H-7); 3.40 brs, 6 H ($N(CH_3)_2$); 3.41 d, 2 H, *J*(CH_2,OH) = 5.3 (CH_2O); 3.74 d, 1 H and 3.80 d, 1 H, J_{gem} = 7.8 (2 × H-4); 4.08 brd, 1 H, *J*(9,8b) = 1.2 (H-9); 4.76 brd, 1 H (H-6); 4.83 t, 1 H (CH_2O**H**); 8.19 s, 1 H and 8.20 s, 1 H (H-2′, H-8′). ^{13}C NMR: 33.345 (C-2); 38.725 (C-8); 39.90 ($N(CH_3)_2$); 40.065 (C-1); 47.065 (C-7); 49.59 (C-3); 63.68 (CH_2O); 65.89 (C-9); 76.69 (C-4); 85.16 (C-6); 119.56 (C-5′); 137.685 (C-8′); 150.58 (C-4′); 151.82 (C-2′); 154.43 (C-6′).

(1*R**,3*R**,6*R**,7*S**,9*S**)-9-[6-(Cyclopropylamino)-9*H*-purin-9-yl]-5-oxatricyclo[4.2.1.0^{3,7}]-nonane-3-methanol (**22c**) and (1*R**,3*R**,6*R**,7*S**,9*R**)-9-[6-(Cyclopropylamino)-9*H*-purin-9-yl]-5-oxatricyclo[4.2.1.0^{3,7}]nonane-3-methanol (**23c**)

A solution of chloropurine **20** or **21** (153 mg, 0.5 mmol) in cyclopropylamine (1.5 ml) was set aside at room temperature overnight and then was taken down. Chromatography of the residue on a silica gel column (10 g) in ethyl acetate–acetone–ethanol–water (90:15:11:9) afforded, after treatment with ether, crystalline **22c** or **23c**.

Compound **22c**: Yield 88%. M.p. 196–198 °C. For $C_{17}H_{21}N_5O_2$ (327.4) calculated: 62.37% C, 6.47% H, 21.39% N; found: 62.21% C, 6.67% H, 21.27% N. FAB MS, *m/z*: 328 [M + H]. ^{1}H NMR: 0.60 m, 2 H, 0.70 m, 2 H, and 3.05 m, 1 H (cyclopropyl); 1.50 dd, 1 H, *J*(2b,8b) = 2.2, J_{gem} = 13.2 (H-2b); 1.54 dm, 1 H, J_{gem} = 10.7 (H-8b); 1.63 ddd, 1 H, *J*(2a,1) = 3.7, *J*(2a,9) = 1.8 (H-2a); 1.65 dt, 1 H, *J*(8a,1) = *J*(8a,7) = 1.7 (H-8a); 2.66 brdq, 1 H, *J*(7,1) = 1.0, *J*(7,6) = 6.0, *J*(7,8b) = 1.7 (H-7); 2.67 m, 1 H (H-1); 3.39 dd, 1 H, *J*(CH_2,OH) = 5.5 and 3.42 dd, 1 H, *J*(CH_2,OH) = 5.3, J_{gem} = 11.1 (CH_2O); 3.54 d, 1 H and 3.68 d, 1 H, J_{gem} = 7.7 (2 × H-4); 4.36 ddd, 1 H, *J*(9,1) = 2.9, *J*(9,6) = 6.8 (H-9); 4.62 dd, 1 H (H-6); 4.81 t, 1 H (CH_2O**H**); 7.81 brs, 1 H (NH); 8.14 s, 1 H and 8.22 s, 1 H (H-2′, H-8′).^{13}C NMR: 6.59, 2 C and 35.37 (cyclopropyl); 32.50 (C-2); 35.48 (C-8); 38.03 (C-1); 48.66 (C-7); 50.46 (C-3); 59.35 (C-9); 63.23 (CH_2O); 75.27 (C-4); 77.32 (C-6); 118.665 (C-5′); 140.13 (C-8′); 152.20 (C-2′); 152.84 (C-4′); 155.62 (C-6′).

Compound **23c**: Yield 82%. M.p. 190–191 °C. For $C_{17}H_{21}N_5O_2$ (327.4) calculated: 62.37% C, 6.47% H, 21.39% N; found: 62.12% C, 6.50% H, 21.20% N. FAB MS, *m/z* (%): 328 (100) [M + H], 176 (25). ^{1}H NMR: 0.60 m, 2 H, 0.71 m, 2 H, and 3.05 m, 1 H (cyclopropyl); 1.37 dd, 1 H, *J*(2b,8a) = 2.2, J_{gem} = 12.8 (H-2b); 1.63 brdq, 1 H, *J*(8b,1) ≈ *J*(8b,7) ≈ *J*(8b,9) = 1.7, J_{gem} = 11.2 (H-8b); 1.71 dd, 1 H, *J*(2a,1) = 4.4 (H-2a); 1.74 dm, 1 H (H-8a); 2.48 dm, 1 H (H-1); 2.56 brdq, 1 H, *J*(7,1) ≈ *J*(7,8a) ≈ *J*(7,8b) = 1.5, *J*(7,6) = 4.8 (H-7); 3.41 d, 2 H, *J*(CH_2,OH) = 5.4 (CH_2O); 3.74 d, 1 H and 3.80 d, 1 H, J_{gem} = 7.8 (2 × H-4); 4.08 brs, 1 H (H-9); 4.79 brd, 1 H, *J*(6,1) = 1.0 (H-6); 4.83 t, 1 H (CH_2O**H**); 7.86 brs, 1 H (NH); 8.20 s, 1 H and 8.23 s, 1 H (H-2′, H-8′). ^{13}C NMR: 6.60, 2 C and 37.54 (cyclopropyl); 33.39 (C-2); 38.72 (C-8); 40.21 (C-1); 47.07 (C-7); 49.59 (C-3); 63.68 (CH_2O); 66.00 (C-9); 76.68 (C-4); 85.14 (C-6); 119.45 (C-5′); 138.79 (C-8′); 152.38 (C-2′); 152.70 (C-4′); 155.74 (C-6′).

(1*R**,3*R**,6*R**,7*S**,9*S**)-9-[(2-Amino-6-chloropyrimidin-4-yl)amino]-5-oxatricyclo-[4.2.1.0^{3,7}]nonane-3-methanol (**24**) and (1*R**,3*R**,6*R**,7*S**,9*R**)-9-[(2-Amino-6-chloropyrimidin-4-yl)amino]-5-oxatricyclo[4.2.1.0^{3,7}]nonane-3-methanol (**25**)

A solution of amines **16a** and **17a** (508 mg, 3 mmol), 4,6-dichloropyrimidin-2-amine (984 mg, 6 mmol), and triethylamine (1.8 ml) in ethanol (18 ml) was heated in a pressure vessel at 100 °C for 7 days and, after cooling, was taken down. The residue was chromatographed on a column of silica gel (200 g) in ethyl acetate–acetone–toluene–ethanol–water

(85:15:15:7:3) to give 805 mg (45%) of **24** as solid foam and 310 mg (16%) of **25** after crystallization from methanol.

Compound **24**: Solid foam. For $C_{13}H_{17}ClN_4O_2$ (296.8) calculated: 52.62% C, 5.77% H, 11.95% Cl, 18.88% N; found: 52.47% C, 5.90% H, 11.76% Cl, 18.61% N. FAB MS, *m/z* (%): 299/297 (36/100) [M + H], 263 (11). ^{1}H NMR: 1.27 brd, 1 H, J_{gem} = 12.6 (H-2b); 1.34 brd, 1 H, J_{gem} = 10.5 (H-8b); 1.38 brddd, 1 H, *J*(2a,9) = 1.6, *J*(2a,1) = 4.2 (H-2a); 1.47 brd, 1 H (H-8a); 2.24 m, 1 H (H-1); 2.47 brdq, 1 H, *J*(7,1) ≈ *J*(7,8a) ≈ *J*(7,8b) = 1.5, *J*(7,6) = 5.4 (H-7); 3.34 d, 2 H, *J*(CH_2,OH) = 5.4 (CH_2O); 3.64 d, 1 H and 3.69 d, 1 H, J_{gem} = 7.6 (2 × H-4); 3.76 m, 1 H (H-9); 4.18 dd, 1 H, *J*(6,9) = 7.1 (H-6); 4.74 t, 1 H (CH_2O**H**); 6.09 s, 1 H (H-5′); 6.36 brs, 2 H (NH_2); 6.56 brd, 1 H, *J*(NH,9) = 7.3 (NH). ^{13}C NMR: 31.67 (C-2); 34.55 (C-8); 37.67 (C-1); 48.14 (C-7); 50.68 (C-3); 54.56 (C-9); 63.62 (CH_2O); 75.83 (C-4); 77.67 (C-6); 93.73 (C-5′); 157.34 (C-4′); 163.13 (C-6′); 164.12 (C-2′).

Compound **25**: M.p. 213.5–214.5 °C. For $C_{13}H_{17}ClN_4O_2 \cdot H_3OH$ (328.8) calculated: 51.14% C, 6.44% H, 10.78% Cl, 17.04% N; found: 50.97% C, 6.55% H, 10.89% Cl, 16.82% N. FAB MS, *m/z* (%): 299/297 (33/100) [M + H], 263 (10). ^{1}H NMR: 1.15 brd, 1 H, J_{gem} = 12.6 (H-2b); 1.47 brdq, 1 H, *J*(8b,1) ≈ *J*(8b,9) = 1.6, J_{gem} = 10.9 (H-8b); 1.56 dd, 1 H, *J*(2a,1) = 4.5 (H-2a); 1.68 brdm, 1 H (H-8a); 2.09 m, 1 H (H-1); 2.36 brdq, *J*(7,1) = 1.1, *J*(7,6) = 4.9, *J*(7,8a) = *J*(7,8b) = 1.5 (H-7); 3.35 d, 2 H, *J*(CH_2,OH) = 5.4 (CH_2O); 3.50 m, 1 H (H-9); 3.61 d, 1 H and 3.71 d, 1 H, J_{gem} = 7.7 (2 × H-4); 3.95 brd, 1 H, *J*(6,1) = 1.0 (H-6); 4.74 t, 1 H (CH_2O**H**); 5.71 brs, 1 H (H-5′); 6.34 brs, 2 H (NH_2); 7.06 brd, 1 H, *J*(NH,9) = 5.0 (NH). ^{13}C NMR: 32.92 (C-2); 38.66 (C-8); 40.12 (C-1); 46.45 (C-7); 49.575 (C-3); 61.20 (C-9); 63.925 (CH_2O); 76.66 (C-4); 87.04 (C-6); 99.07 (C-5′); 157.53 (C-4′); 163.05 (C-6′); 163.53 (C-2′).

(1*R**,3*R**,6*R**,7*S**,9*S**)-9-({2-Amino-6-chloro-5-[(4-chlorophenyl)azo]pyrimidin-4-yl}-amino)-5-oxatricyclo[4.2.1.0^{3,7}]nonane-3-methanol (**26**)

A cold diazonium salt solution was prepared from 4-chloroaniline (111 mg, 0.9 mmol) in 3 M HCl (1.9 ml) and sodium nitrite (69 mg, 1 mmol). This solution was added to a mixture of **24** (445 mg, 1.5 mmol), acetic acid (12 ml), water (9 ml), and anhydrous sodium acetate (1 g) and the mixture was stirred at 0 °C. The three additional portions of diazonium salt and sodium acetate were added in 5 h intervals. After 5 h, the precipitate was filtered and washed with cold water until neutral and then air-dried. Yield 395 mg (60%) of azo compound **26**. M.p. 262–265.5 °C. For $C_{19}H_{20}Cl_2N_6O_2$ (435.3) calculated: 52.42% C, 4.63% H, 16.29% Cl, 19.31% N; found: 52.39% C, 4.75% H, 16.17% Cl, 19.02% N. FAB MS, *m/z* (%): 437/435 (73/100) [M + H], 403/401 (11/21), 310/308 (29/58). ^{1}H NMR: 1.15 dd, 1 H, *J*(2b,8b) = 2.2, J_{gem} = 12.7 (H-2b); 1.38 dm, 1 H, J_{gem} = 10.7 (H-8b); 1.42 ddd, 1 H, *J*(2a,1) = 3.4, *J*(2a,9) = 2.2 (H-2a); 1.58 dt, 1 H, *J*(8a,1) = *J*(8a,7) = 1.7 (H-8a); 2.50 m, 1 H (H-1); 2.56 brdq, 1 H, *J*(7,1) = 1.2, *J*(7,6) = 5.1, *J*(7,8b) = 1.7 (H-7); 3.35 d, 2 H, *J*(CH_2,OH) = 5.4 (CH_2O); 3.66 d, 1 H and 3.89 d, 1 H, J_{gem} = 7.7 (2 × H-4); 3.92 dddd, 1 H, *J*(9,1) = 3.4, *J*(9,6) = 7.3, *J*(9,NH) = 6.3 (H-9); 4.31 dd, 1 H (H-6); 4.77 t, 1 H (CH_2O**H**); 7.52 brs, 2 H (NH_2); 7.59 d, 2 H and 7.71 d, 2 H (arom.); 10.62 d, 1 H (NH). ^{13}C NMR: 31.90 (C-2); 35.16 (C-8); 37.61 (C-1); 48.06 (C-7); 50.78 (C-3); 55.21 (C-9); 63.43 (CH_2O); 76.43 (C-4); 78.19 (C-6); 119.33 (C-5′); 122.72, 2 C, 129.72, 2 C, 133.56, and 150.99 (arom.); 154.59 (C-4′); 161.34 (C-6′); 164.82 (C-2′).

(1*R**,3*R**,6*R**,7*S**,9*R**)-9-({2-Amino-6-chloro-5-[(4-chlorophenyl)azo]pyrimidin-4-yl}-amino)-5-oxatricyclo[4.2.1.$0^{3,7}$]nonane-3-methanol (**27**)

A cold diazonium salt solution, prepared from 4-chloroaniline (111 mg, 0.9 mmol) in 3 M HCl (1.9 ml) and sodium nitrite (69 mg, 1 mmol), was added to a mixture of **25** (493 mg, 1.5 mmol), acetic acid (12 ml), dimethyl sulfoxide (11 ml), and anhydrous sodium acetate (1 g) and the mixture was stirred at 0 °C. The three additional portions of diazonium salt and sodium acetate were added in the course of 15 h. After 5 h, the precipitate was filtered off and washed with cold water until neutral and then air-dried. Yield 498 mg (76%) of azo compound **27**. M.p. >310 °C. For $C_{19}H_{20}Cl_2N_6O_2$ (435.3) calculated: 52.42% C, 4.63% H, 16.29% Cl, 19.31% N; found: 52.28% C, 4.70% H, 16.14% Cl, 19.04% N. ^{1}H NMR: 1.22 dd, 1 H, *J*(2b,8b) = 2.2, J_{gem} = 12.8 (H-2b); 1.62 brdq, 1 H, *J*(8b,1) ≈ *J*(8b,7) ≈ *J*(8b,9) = 1.7, J_{gem} = 11.2 (H-8b); 1.65 dd, 1 H, *J*(2a,1) = 4.8 (H-2a); 1.70 brdq, 1 H, *J*(8a,1) ≈ *J*(8a,7) = 1.7 (H-8a); 2.24 dm, 1 H (H-1); 2.49 brdq, 1 H, *J*(7,1) ≈ *J*(7,8a) ≈ *J*(7,8b) = 1.2, *J*(7,6) = 5.1 (H-7); 3.39 d, 2 H, *J*(CH_2,OH) = 5.3 (CH_2O); 3.64 d, 1 H and 3.73 d, 1 H, J_{gem} = 7.7 (2 × H-4); 3.85 brd, 1 H, *J*(9,8b) = 1.2, *J*(9,NH) = 7.8 (H-9); 4.07 dd, 1 H, *J*(6,1) = 1.0 (H-6); 4.79 t, 1 H (CH_2O**H**); 7.58 d, 2 H and 7.68 d, 2 H (arom.); 7.60 brs, 2 H (NH_2); 10.42 d, 1 H (NH). ^{13}C NMR: 33.33 (C-2); 38.41 (C-8); 40.09 (C-1); 46.66 (C-7); 49.36 (C-3); 61.35 (C-9); 63.79 (CH_2O); 76.69 (C-4); 87.53 (C-6); 118.69 (C-5′); 122.90, 2 C, 129.71, 2 C, 133.56, and 150.71 (arom.); 154.23 (C-4′); 161.23 (C-6′); 165.00 (C-2′).

(1*R**,3*R**,6*R**,7*S**,9*S**)-9-[(2,5-Diamino-6-chloropyrimidin-4-yl)amino]-5-oxatricyclo-[4.2.1.$0^{3,7}$]nonane-3-methanol (**28**) and [(1*R**,3*R**,6*R**,7*S**,9*R**)-9-[(2,5-Diamino-6-chloropyrimidin-4-yl)amino]-5-oxatricyclo[4.2.1.$0^{3,7}$]nonane-3-methanol (**29**)

A mixture of azo compound **26** or **27** (435 mg, 1 mmol), ethanol (30 ml), water (13 ml), acetic acid (0.33 ml), and zinc dust (655 mg) was refluxed under argon for 3 h. The insoluble material was filtered off, washed with ethanol and combined filtrates and washings were evaporated. The residue was chromatographed on a silica gel column in ethyl acetate–acetone–toluene–ethanol–water (85:15:15:7:3) and crystallized from ethanol.

Compound **28**: Yield 45%. M.p. 255.5–257.5 °C. For $C_{13}H_{18}ClN_5O_2$ (311.8) calculated: 50.08% C, 5.82% H, 11.37% Cl, 22.46% N; found: 49.72% C, 5.70% H, 11.09% Cl, 22.15% N. FAB MS, *m/z* (%): 314/312 (33/100) [M + H]. ^{1}H NMR: 1.30 brdq, 1 H, *J*(8b,1) = 1.2, J_{gem} = 10.7 (H-8b); 1.36 ddd, 1 H, *J*(2a,1) = 3.8, *J*(2a,9) = 2.1, J_{gem} = 12.8 (H-2a); 1.42 dd, 1 H, *J*(2b,8b) = 2.0 (H-2b); 1.50 dt, 1 H, *J*(8a,1) = *J*(8a,7) = 1.7 (H-8a); 2.34 brtm, 1 H (H-1); 2.49 brdq, 1 H, *J*(7,1) = 1.2, *J*(7,6) = 5.3, *J*(7,8b) = 1.7 (H-7); 3.33 dd, 1 H and 3.36 dd, 1 H, *J*(CH_2,OH) = 5.4, J_{gem} = 11.2 (CH_2O); 3.68 d, 1 H and 3.72 d, 1 H, J_{gem} = 7.6 (2 × H-4); 3.70 dddd, 1 H, *J*(9,1) = 3.3, *J*(9,NH) = 6.6 (H-9); 3.82 brs, 2 H and 5.74 brs, 2 H (2 × NH_2); 4.21 dd, 1 H, *J*(6,9) = 7.4 (H-6); 4.75 t, 1 H (CH_2O**H**); 5.99 d, 1 H (NH). ^{13}C NMR: 31.585 (C-2); 34.405 (C-8); 39.53 (C-1); 48.02 (C-7); 50.76 (C-3); 54.75 (C-9); 63.61 (CH_2O); 75.97 (C-4); 77.705 (C-6); 112.61 (C-5′); 144.145 (C-4′); 149.13 (C-6′); 156.90 (C-2′).

Compound **29**: Yield 51%. M.p. 241.5–243.5 °C. For $C_{13}H_{18}ClN_5O_2$ (311.8) calculated: 50.08% C, 5.82% H, 11.37% Cl, 22.46% N; found: 49.70% C, 5.75% H, 11.07% Cl, 22.13% N. FAB MS, *m/z* (%): 314/312 (34/100) [M + H], 278 (12). ^{1}H NMR: 1.17 dd, *J*(2b,8a) = 2.2, J_{gem} = 12.6 (H-2b); 1.48 dq, 1 H, *J*(8b,1) = *J*(8b,7) = 1.5, J_{gem} = 10.8 (H-8b); 1.59 dd, 1 H, *J*(2a,1) = 4.3 (H-2a); 1.75 brdq, 1 H, *J*(8a,1) ≈ *J*(8a,7) = 1.7 (H-8a); 2.14 dm, 1 H (H-1); 2.38 brdq, 1 H, *J*(7,1) = 1.5, *J*(7,6) = 5.1 (H-7); 3.37 d, 2 H, *J*(CH_2,OH) = 5.0 (CH_2O); 3.54 dd, 1 H, *J*(9,8b) = 1.2, *J*(9,NH) = 6.5 (H-9); 3.62 d, 1 H and 3.73 d, 1 H, J_{gem} = 7.7 (2 × H-4);

4.00 brs, 2 H (NH_2); 4.09 dd, 1 H, *J*(6,1) = 1.1 (H-6); 4.72 t, 1 H (CH_2O**H**); 5.53 brs, 2 H (NH_2); 6.11 d, 1 H (NH). ^{13}C NMR: 32.78 (C-2); 38.71 (C-8); 39.78 (C-1); 46.49 (C-7); 49.56 (C-3); 62.425 (C-9); 63.93 (CH_2O); 76.60 (C-4); 86.97 (C-6); 113.65 (C-5′); 140.90 (C-4′); 154.11 (C-6′); 155.62 (C-2′).

(1*R**,3*R**,6*R**,7*S**,9*S**)-9-(2-Amino-6-chloro-9*H*-purin-9-yl)-5-oxatricyclo[4.2.1.$0^{3,7}$]-nonane-3-methanol (**30**) and (1*R**,3*R**,6*R**,7*S**,9*R**)-9-(2-Amino-6-chloro-9*H*-purin-9-yl)-5-oxatricyclo[4.2.1.$0^{3,7}$]nonane-3-methanol (**31**)

A mixture of triethyl orthoformate (10 ml), pyrimidine **28** or **29** (312 mg, 1 mmol), and concentrated hydrochloric acid (0.54 ml) was stirred at room temperature for 3 days and then evaporated. The residue was dissolved in tetrahydrofuran (10 ml). To the stirred solution, 0.5 M hydrochloric acid (10 ml) was added, the mixture was stirred at room temperature for 2.5 h and then neutralized with solid sodium hydrogencarbonate. The organic layer was separated and the aqueous layer was extracted with tetrahydrofuran (3 × 5 ml). The collected organic layers were evaporated. The residue was crystallized from water.

Compound **30**: Yield 64%. M.p. 239–243 °C. For $C_{14}H_{16}ClN_5O_2$ (321.8) calculated: 52.26% C, 5.01% H, 11.02% Cl, 21.77% N; found: 51.98% C, 5.11% H, 10.81% Cl, 21.50% N. FAB MS, *m/z* (%): 324/322 (36/100) [M + H]. ^{1}H NMR: 1.47 dd, 1 H, *J*(2b,8b) = 2.2, J_{gem} = 12.6 (H-2b); 1.47 dm, 1 H, J_{gem} = 10.7 (H-8b); 1.62 ddd, 1 H, *J*(2a,1) = 3.8, *J*(2a,9) = 2.0 (H-2a); 1.65 dt, 1 H, *J*(8a,1) ≈ *J*(8a,7) = 1.7 (H-8a); 2.65 m, 1 H (H-1); 2.66 brdq, 1 H, *J*(7,1) ≈ *J*(7,8b) = 1.5, *J*(7,6) = 5.4 (H-7); 3.38 dd, 1 H, *J*(CH,OH) = 5.5 and 3.41 dd, 1 H, *J*(CH,OH) = 5.1, J_{gem} = 11.6 (CH_2O); 3.56 d, 1 H and 3.67 d, 1 H, J_{gem} = 7.8 (2 × H-4); 4.22 dddd, 1 H, *J*(9,1) = 3.0 (H-9); 4.59 dd, 1 H, *J*(6,9) = 6.7 (H-6); 4.82 t, 1 H, *J*(OH, CH_2) = 5.3 (CH_2O**H**); 6.84 brs, 1 H (NH_2); 8.14 s, 1 H (H-8′). ^{13}C NMR: 32.47 (C-2); 35.34 (C-8); 37.82 (C-1); 48.60 (C-7); 50.43 (C-3); 59.49 (C-9); 63.125 (CH_2O); 75.22 (C-4); 77.11 (C-6); 122.95 (C-5′); 142.66 (C-8′); 149.33 (C-6′); 155.16 (C-4′); 159.72 (C-2′).

Compound **31**: Yield 73%. M.p. 242–246 °C. For $C_{14}H_{16}ClN_5O_2$ (321.8) calculated: 52.26% C, 5.01% H, 11.02% Cl, 21.77% N; found: 51.97% C, 5.23% H, 10.79% Cl, 21.51% N. FAB MS, *m/z* (%): 324/322 (37/100) [M + H]. ^{1}H NMR: 1.31 dd, 1 H, *J*(2b,8a) = 2.3, J_{gem} = 12.7 (H-2b); 1.64 dq, 1 H, *J*(8b,1) = 1.5, *J*(8b,7) ≈ *J*(8b,9) = 1.7, J_{gem} = 11.4 (H-8b); 1.715 dd, 1 H, *J*(2a,1) = 4.4 (H-2a); 1.72 dm, 1 H (H-8a); 2.47 dm, 1 H (H-1); 2.56 dq, 1 H, *J*(7,1) = 1.2, *J*(7,8a) = 1.7, *J*(7,6) = 5.1 (H-7); 3.41 d, 2 H, *J*(CH_2,OH) = 5.3 (CH_2O); 3.72 d, 1 H and 3.80 d, 1 H, J_{gem} = 7.8 (2 × H-4); 3.96 brd, 1 H (H-9); 4.73 brdd, 1 H, *J*(6,1) = 2.2 (H-6); 4.82 t, 1 H (CH_2O**H**); 6.90 brs, 2 H (NH_2); 8.14 s, 1 H (H-8′). ^{13}C NMR: 33.45 (C-2); 38.72 (C-8); 39.80 (C-1); 47.04 (C-7); 49.55 (C-3); 63.66 (CH_2O); 65.93 (C-9); 76.67 (C-4); 85.02 (C-6); 123.55 (C-5′); 141.21 (C-8′); 149.58 (C-6′); 154.37 (C-4′); 159.84 (C-2′).

(1*R**,3*R**,6*R**,7*S**,9*S**)-9-(6-Chloro-8-methyl-9*H*-purin-9-yl)-5-oxatricyclo[4.2.1.$0^{3,7}$]-nonane-3-methanol (**34**) and (1*R**,3*R**,6*R**,7*S**,9*R**)-9-(6-Chloro-8-methyl-9*H*-purin-9-yl)-5-oxatricyclo[4.2.1.$0^{3,7}$]nonane-3-methanol (**35**)

A mixture of silica gel (particle size 0.06 mm, 4 g) and anhydrous $FeCl_3$ (4 mmol) was stirred at 150 °C under argon for 2 h. After cooling, 1,4-dioxane (20 ml), pyrimidine **18** (593 mg, 2 mmol) or **19** (630 mg, 2 mmol), and a solution of acetaldehyde (176 mg, 4 mmol) in 1,4-dioxane (2 ml) were added and the mixture was stirred under argon at room temperature for 2 h and at 100 °C for 45 h. Then, after cooling, silica gel was filtered off and eluted with ethyl acetate–acetone–ethanol–water (30:5:4:3). The elution was followed by TLC. The col-

lected filtrates and eluates were evaporated. Powdered $NaHCO_3$ (1.5 g) was added to a solution of the residue in methanol (10 ml) and the mixture was stirred at room temperature for 2 h. The solid was filtered off and washed with methanol. The combined filtrates and washings were taken down.

Compound **34**: Crystallization from water and chromatography of mother liquors on a silica gel column (30 g) in ethyl acetate–acetone–ethanol–water (30:5:4:3). Yield 224 mg (35%). M.p. 247–249.5 °C. For $C_{15}H_{17}ClN_4O_2$ (320.8) calculated: 56.16% C, 5.34% H, 11.05% Cl, 17.47% N; found: 55.81% C, 5.32% H, 10.88% Cl, 17.18% N. FAB MS, *m/z* (%): 323/321 (38/100) [M + H]. ^{1}H NMR: 1.49 brdq, 1 H, *J*(8b,1) = 1.3, J_{gem} = 10.7 (H-8b); 1.62 dd, 1 H, *J*(2b,8b) = 2.4, J_{gem} = 13.4 (H-2b); 1.73 dt, 1 H, *J*(8a,1) = *J*(8a,7) = 1.7 (H-8a); 1.78 ddd, 1 H, *J*(2a,9) = 1.7, *J*(2a,1) = 4.0 (H-2a); 2.66 dq, 1 H, *J*(7,1) = 1.2, *J*(7,6) = 5.4, *J*(7,8b) = 1.7 (H-7); 2.69 s, 3 H (CH_3); 3.18 d, 1 H and 3.58 d, 1 H, J_{gem} = 7.4 (2 × H-4); 3.35 dd, 1 H, *J*(CH,OH) = 5.5 and 3.39 dd, 1 H, *J*(CH,OH) = 5.2, J_{gem} = 11.1 (CH_2O); 3.49 m, 1 H (H-1); 4.22 ddd, 1 H, *J*(9,1) = 2.1, *J*(9,6) = 6.5 (H-9); 4.72 t, *J*(OH,CH_2) = 5.3 (CH_2O**H**); 4.78 brdd, 1 H (H-6); 8.61 s, 1 H (H-2′). ^{13}C NMR: 16.66 (CH_3); 32.49 (C-2); 37.60 (C-1); 37.86 (C-8); 47.72 (C-7); 49.77 (C-3); 62.83 (C-9); 63.08 (CH_2O); 75.88 (C-4); 77.80 (C-6); 130.36 (C-5′); 147.21 (C-6′); 150.06 (C-2′); 154.66 (C-4′); 158.49 (C-8′).

Compound **35**: Chromatography on a silica gel column (60 g) in ethyl acetate–acetone–ethanol–water (30:5:4:3) and crystallization from aqueous ethanol. Yield 475 mg (74%). M.p. 208–209.5 °C. For $C_{15}H_{17}ClN_4O_2$ (320.8) calculated: 56.16% C, 5.34% H, 11.05% Cl, 17.47% N; found: 55.82% C, 5.31% H, 10.89% Cl, 17.16% N. FAB MS, *m/z* (%): 323/321 (35/100) [M + H]. ^{1}H NMR: 1.41 brd, 1 H, J_{gem} = 11.6 (H-2b); 1.68 m, 2 H (H-2a, H-8a); 2.03 brd, 1 H, J_{gem} = 10.5 (H-8a); 2.63 m, 1 H (H-1); 2.65 m, 1 H (H-7); 2.67 s, 3 H (CH_3); 3.43 brd, 2 H (CH_2O); 3.76 d, 1 H and 3.82 d, 1 H, J_{gem} = 7.6 (2 × H-4); 4.08 m, 1 H (H-9); 4.81 m, 1 H (H-6); 5.43 brt, 1 H, *J*(OH,CH_2) = 5.0 (CH_2O**H**); 8.62 s, 1 H (H-2′). ^{13}C NMR: 15.315 (CH_3); 34.61 (C-2); 40.10 (C-8); 40.79 (C-1); 47.24 (C-7); 49.71 (C-3); 63.81 (CH_2O); 69.71 (C-9); 76.685 (C-4); 84,15 (C-6); 130.26 (C-5′); 147.59 (C-6′); 150.27 (C-2′); 153.38 (C-4′); 157.34 (C-8′).

Ammonolysis of Chloropurines **20**, **21**, **30**, **31**, **34**, and **35**

Liquid ammonia (10 ml) was added to a stirred suspension of a 6-chloropurine (0.5 mmol) in methanol (2 ml) at –70 °C and the mixture was heated in an autoclave at 75 °C for 48 h. Ammonia was evaporated and a crystalline product was filtered off, washed with water and crystallized from aqueous methanol.

(1R,3R*,6R*,7S*,9S*)-9-(6-Amino-9H-purin-9-yl)-5-oxatricyclo[4.2.1.0^{3,7}]nonane-3-methanol* (**22a**): Yield 90%. M.p. 265–267.5 °C. For $C_{14}H_{17}N_5O_2$ (287.3) calculated: 58.52% C, 5.96% H, 24.37% N; found: 58.23% C, 5.72% H, 24.08% N. FAB MS, *m/z*: 288 [M + H]. ^{1}H NMR: 1.51 dd, 1 H, *J*(2b,8b) = 2.2, J_{gem} = 13.2 (H-2b); 1.54 brdq, 1 H, *J*(8b,1) = 1.5, *J*(8b,7) = 1.7, J_{gem} = 10.7 (H-8b); 1.63 ddd, 1 H, *J*(2a,1) = 3.9, *J*(2a,9) = 2.1 (H-2a); 1.66 dt, 1 H, *J*(8a,1) = *J*(8a,7) = 1.7 (H-8a); 2.67 brdm, 1 H, *J*(7,1) = 1.5, *J*(7,6) = 5.9 (H-7); 2.67 m, 1 H (H-1); 3.40 dd, 1 H, *J*(CH,OH) = 5.6 and 3.42 dd, 1 H, *J*(CH,OH) = 5.3, J_{gem} = 11.1 (CH_2O); 3.56 d, 1 H and 3.69 d, 1 H, J_{gem} =7.8 (2 × H-4); 4.35 ddd, 1 H, *J*(9,1) = 2.7, *J*(9,6) = 6.8 (H-9); 4.61 brdd, 1 H (H-6); 4.80 t, 1 H, *J*(CH_2,OH) = 5.5 (CH_2O**H**); 7.13 brs, 2 H (NH_2); 8.12 s, 1 H and 8.14 s, 1 H (H-2′, H-8′). ^{13}C NMR: 32.48 (C-2); 35.46 (C-8); 38.03 (C-1); 48.66 (C-7); 50.46 (C-3); 59.33 (C-9); 63.21 (CH_2O); 75.25 (C-4); 77.31 (C-6); 118.28 (C-5′); 140.30 (C-8′); 150.54 (C-4′); 152.29 (C-2′); 156.015 (C-6′).

(1R,3R*,6R*,7S*,9R*)-9-(6-Amino-9H-purin-9-yl)-5-oxatricyclo[4.2.1.0^{3,7}]nonane-3-methanol* (**23a**): Yield 88%. M.p. 265.5–268 °C. For $C_{14}H_{17}N_5O_2$ (287.3) calculated: 58.52% C, 5.96% H, 24.37% N; found: 58.20% C, 5.71% H, 24.06% N. FAB MS, *m/z*: 288 [M + H]. ^{1}H NMR: 1.37 dd, 1 H, *J*(2b,8a) = 2.3, J_{gem} = 12.7 (H-2b); 1.63 brdq, 1 H, *J*(8b,1) = 1.3, *J*(8b,7) = 1.7, J_{gem} = 11.2 (H-8b); 1.72 dd, 1 H, *J*(2a,1) = 4.4 (H-2a); 1.75 dm, 1 H (H-8a); 2.48 dm, 1 H (H-1); 2.56 brdq, 1 H, *J*(7,1) = 1,0, *J*(7,6) = 5.0, *J*(7,8a) = 1.7 (H-7); 3.41 d, 2 H, *J*(CH_2,OH) = 5.4 (CH_2O); 3.74 d, 1 H and 3.81 d, 1 H, J_{gem} = 7.8 (2 × H-4); 4.07 brd, 1 H, *J*(9,8b) = 1.6 (H-9); 4.80 brdd, 1 H, *J*(6,1) = 1.0 (H-6); 4.82 t, 1 H (CH_2O**H**); 7.19 brs, 1 H (NH_2); 8.13 s, 1 H and 8.19 s, 1 H (H-2′, H-8′). ^{13}C NMR: 33.39 (C-2); 38.71 (C-8); 39.10 (C-1); 47.06 (C-7); 49.57 (C-3); 63.86 (CH_2O); 66.01 (C-9); 76.67 (C-4); 85.12 (C-6); 119.05 (C-5′); 138.95 (C-8′); 149.83 (C-4′); 152.48 (C-2′); 156.18 (C-6′).

(1R,3R*,6R*,7S*,9S*)-9-(2,6-Diamino-9H-purin-9-yl)-5-oxatricyclo[4.2.1.0^{3,7}]nonane-3-methanol* (**32**): Yield 87%. M.p. 288–291 °C. For $C_{14}H_{18}N_6O_2$ (302.3) calculated: 55.62% C, 6.00% H, 27.80% N; found: 55.33% C, 6.10% H, 27.51% N. FAB MS, *m/z*: 303 [M + H]. ^{1}H NMR: 1.45 dm, 1 H, J_{gem} = 10.7 (H-8b); 1.49 dd, 1 H, *J*(2b,8b) = 2.2, J_{gem} = 13.2 (H-2b); 1.59 ddd, 1 H, *J*(2a,1) = 3.8, *J*(2a,9) = 2.0 (H-2a); 1.62 dt, 1 H, *J*(8a,1) = *J*(8a,7) = 1.7 (H-8a); 2.50 m, 1 H (H-1); 3.41 d, 2 H, *J*(CH_2,OH) = 5.1 (CH_2O); 3.63 d, 1 H and 3.72 d, 1 H, J_{gem} =7.8 (2 × H-4); 4.21 ddd, 1 H, *J*(9,1) = 2.8, *J*(9,6) = 6.7 (H-9); 4.51 brdd, 1 H, *J*(6,7) = 5.3 (H-6); 4.81 t, 1 H (CH_2O**H**); 5.76 brs, 2 H (NH_2); 6.68 brs, 2 H (NH_2); 7.79 s, 1 H (H-8′). ^{13}C NMR: 32.46 (C-2); 35.29 (C-8); 38.31 (C-1); 48.84 (C-7); 50.53 (C-3); 58.67 (C-9); 63.26 (CH_2O); 75.14 (C-4); 77.375 (C-6); 112.58 (C-5′); 136.50 (C-8′); 152.82 (C-4′); 156.09 (C-6′); 160.08 (C-2′).

(1R,3R*,6R*,7S*,9R*)-9-(2,6-Diamino-9H-purin-9-yl)-5-oxatricyclo[4.2.1.0^{3,7}]nonane-3-methanol* (**33**): Yield 88%. M.p. 284–287 °C. $C_{14}H_{18}N_6O_2$ (302.3) calculated: 55.62% C, 6.00% H, 27.80% N; found: 55.39% C, 6.09% H, 27.59% N. FAB MS, *m/z*: 303 [M + H]. ^{1}H NMR: 1.30 dd, 1 H, *J*(2b,8a) = 2.3, J_{gem} = 12.7 (H-2b); 1.60 brdq, 1 H, *J*(8b,1) = 1.5, *J*(8b,7) = 1.7, J_{gem} = 11.4 (H-8b); 1.69 dd, 1 H, *J*(2a,1) = 4.4 (H-2a); 1.73 brdq, 1 H, *J*(8a,1) = 1.6 (H-8a); 2.36 dm, 1 H (H-1); 2.55 dq, 1 H, *J*(7,1) = 1.2, *J*(7,6) = 5.1, *J*(7,8a) = 1.5 (H-7); 3.40 d, 2 H, *J*(CH_2,OH) = 5.3 (CH_2O); 3.71 d, 1 H and 3.80 d, 1 H, J_{gem} =7.8 (2 × H-4); 3.90 brd, 1 H, *J*(9,8b) = 1.7 (H-9); 4.72 brdd, 1 H, *J*(6,1) = 1.0 (H-6); 4.82 t, 1 H (CH_2O**H**); 5.77 brs, 2 H (NH_2); 6.65 brs, 2 H (NH_2); 7.75 s, 1 H (H-8′). ^{13}C NMR: 33.29 (C-2); 38.85 (C-8); 40.17 (C-1); 46.90 (C-7); 49.56 (C-3); 63.69 (CH_2O); 65.24 (C-9); 76.65 (C-4); 85.26 (C-6); 113.36 (C-5′); 135.41 (C-8′); 152.10 (C-4′); 156.82 (C-6′); 160.36 (C-2′).

(1R,3R*,6R*,7S*,9S*)-9-(6-Amino-8-methyl-9H-purin-9-yl)-5-oxatricyclo[4.2.1.0^{3,7}]nonane-3-methanol* (**36**): Yield 86%. M.p. 297–298.5 °C. For $C_{15}H_{19}N_5O_2$ (301.4) calculated: 59.79% C, 6.36% H, 23.24% N; found: 59.45% C, 6.24% H, 22.95% N. FAB MS, *m/z*: 302 [M + H]. ^{1}H NMR: 1.44 dm, 1 H, J_{gem} = 10.7 (H-8b); 1.67 dt, *J*(8a,1) = *J*(8a,7) = 1.7 (H-8a); 1.72 m, 2 H (2 × H-2); 2.54 s, 3 H (CH_3); 2.62 dq, 1 H, *J*(7,1) = 1.3, *J*(7,6) = 5.4, *J*(7,8b) = 1.7 (H-7); 3.18 d, 1 H and 3.59 d, 1 H, J_{gem} =7.4 (2 × H-4); 3.35 dd, 1 H, *J*(CH,OH) = 5.6 and 3.38 dd, 1 H, *J*(CH,OH) = 5.1, J_{gem} = 11.1 (CH_2O); 3.46 m, 1 H (H-1); 4.04 dd, 1 H, *J*(9,1) = 2.1, *J*(9,6) = 6.5 (H-9); 4.70 t, 1 H, *J*(OH,CH_2) = 5.4 (CH_2O**H**); 4.71 dd, 1 H (H-6); 6.87 brs, 2 H (NH_2); 8.00 s, 1 H (H-2′). ^{13}C NMR: 16.24 (CH_3); 32.53 (C-2); 37.62 (C-1); 38.05 (C-8); 47.72 (C-7); 49.74 (C-3); 62.17 (C-9); 63.21 (CH_2O); 75.81 (C-4); 78.045 (C-6); 118.16 (C-5′); 150.90 (C-4′); 151.025 (C-2′); 152.23 (C-8′); 155.14 (C-6′).

(1R,3R*,6R*,7S*,9R*)-9-(6-Amino-8-methyl-9H-purin-9-yl)-5-oxatricyclo[4.2.1.0^{3,7}]nonane-3-methanol* (**37**): Yield 91%. M.p. 284.5–287 °C. For $C_{15}H_{19}N_5O_2$ (301.4) calculated: 59.79% C, 6.36% H, 23.24% N; found: 59.50% C, 6.29% H, 22.97% N. FAB MS, *m/z*: 302 [M + H]. ^{1}H NMR: 1.38 dd, 1 H, *J*(2b,8a) = 2.2, J_{gem} = 12.7 (H-2b); 1.58 dm, 1 H, J_{gem} = 11.1 (H-8b);

1.67 dd, 1 H, *J*(2a,1) = 4.4 (H-2a); 2.11 dm, 1 H (H-8a); 2.48 dm, 1 H (H-1); 2.51 s, 3 H (CH_3); 2.59 brdq, 1 H, *J*(7,1) = 1.2, *J*(7,6) = 5.1, *J*(7,8) = 1.5 (H-7); 3.40 dd, 1 H, *J*(CH,OH) = 5.6 and 3.43 dd, 1 H, *J*(CH,OH) = 5.0, J_{gem} = 11.7 (CH_2O); 3.74 d, 1 H and 3.81 d, 1 H, J_{gem} = 7.8 (2 × H-4); 3.94 brs, 1 H (H-9); 4.78 t, *J*(OH,CH_2) = 5.3 (CH_2O**H**); 5.56 brd, 1 H, *J*(6,1) = (H-6); 6.99 brs, 1 H (NH_2); 8.02 s, 1 H (H-2′). ^{13}C NMR: 14.74 (CH_3); 34.39 (C-2); 38.99 (C-8); 41.35 (C-1); 47.37 (C-7); 49.63 (C-3); 63.98 (CH_2O); 69.09 (C-9); 76.65 (C-4); 83.77 (C-6); 117.87 (C-5′); 149.60 (C-4′); 150.92 (C-8′); 151.35 (C-2′); 155.34 (C-6′).

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