SYNTHESIS OF NOVEL RACEMIC CARBOCYCLIC NUCLEOSIDE ANALOGUES DERIVED FROM 4,8-DIOXATRICYCLO[4.2.1.0^{3,7}]NONANE-9-METHANOL AND 4-OXATRICYCLO[4.3.1.0^{3,7}]DECANE-10-METHANOL, COMPOUNDS WITH ACTIVITY AGAINST *COXSACKIE* VIRUSES

Hubert HŘEBABECKÝ[a1,*], Martin DRAČÍNSKÝ[a2], Armando M. De PALMA[b1], Johan NEYTS[b2] and Antonín HOLÝ[a3]

[a] *Centre for New Antivirals and Antineoplastics, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, v.v.i., 166 10 Prague 6, Czech Republic; e-mail: [1] hubert@uochb.cas.cz, [2] dracinsky@uochb.cas.cz, [3] holy@uochb.cas.cz*

[b] *Katholieke Universiteit Leuven, Rega Institute for Medical Research, Minderbroedersstraat 10, BE-3000, Leuven, Belgium; e-mail: [1] armando.depalma@rega.kuleuven.be, [2] johan.neyts@rega.kuleuven.ac.be*

Received October 2, 2008
Accepted October 24, 2008
Published online March 11, 2009

(1*R**,2*R**,3*R**,4*S**)-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dimethanol (**10**) and (1*R**,2*R**,3*R**,4*S**)-bicyclo[2.2.2]oct-5-ene-2,3-dimethanol (**14**), which were prepared by the Diels–Alder reaction and subsequent reduction with lithium aluminium hydride, were treated with benzyl azidoformate to give benzyl *N*-[(1*R**,2*R**,3*S**,6*S**,7*S**,9*S**)-9-(hydroxymethyl)-4,8-dioxatricyclo[4.2.1.0^{3,7}]nonan-2-yl]carbamate (**11**) and benzyl *N*-[(1*R**,2*R**,3*R**,6*R**,7*S**,10*S**)-10-(hydroxymethyl)-4-oxatricyclo[4.3.1.0^{3,7}]decan-2-yl]carbamate (**15**). Hydrogenolysis of carbamates **11** or **15** afforded (1*R**,2*R**,3*S**,6*S**,7*S**,9*S**)-2-amino-4,8-dioxatricyclo[4.2.1.0^{3,7}]-nonane-9-methanol (**12**) or (1*R**,2*R**,3*R**,6*R**,7*S**,10*S**)-2-amino-4-oxatricyclo[4.3.1.0^{3,7}]-decane-10-methanol (**16**). The amines **12** and **16** were transformed to thymine and purine nucleoside analogues. The target compounds were tested for the activity against *Coxsackie* virus.

Keywords: Amines; Nucleosides; Carbocyclic nucleosides; Purines; Adenine; Thymine; 5-Methylpyrimidine-2,4(1*H*,3*H*)-dione; 6-(Dimethylamino)purine; 6-(Cyclopropylamino)purine; 9*H*-Purine-6-thiol; *Coxsackie* virus; Antivirals.

The search for new nucleoside analogues, in which the furan ring of natural nucleosides is replaced by a carbocycle, is a promising field of research. A number of synthetic carbocyclic nucleosides with important therapeutic properties were discovered. U.S. Food and Drug Administration approved abacavir (Ziagen™; **1**)[1] for the treatment of HIV-1 infections and entecavir (Baraclude; **2**)[2] for the treatment of chronic hepatitis B virus (HBV) infections (Chart 1).

doi:10.1135/cccc2008193

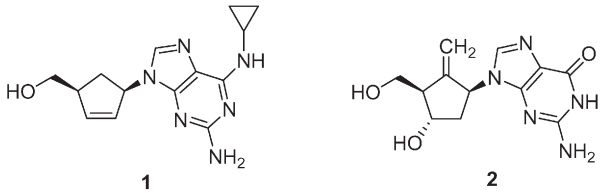


CHART 1

Also analogues containg bicyclic and tricyclic systems exhibit a biological activity. The recently described[3] bisphosphate of the 2-iodo-(6-methylamino)purine analogue containing the oxabicyclo[2.2.1]heptane moiety displayed a potent binding affinity to the human $P2Y_1$ receptor[4]. We reported the synthesis of novel racemic conformationally-locked carbocyclic purine nucleoside analogues derived from 4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-6-methanol[5], 4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-9-methanol and their Pro-Tides[6], 5,5- and 6,6-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ols[7], 3-(hydroxymethyl)bicyclo[2.2.1]heptane-2,5-diol[8], 5- and 6-(hydroxymethyl)bicyclo[2.2.1]heptane-2-methanols[9], 5- and 6-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ols[10], and analogues[11] with a bicyclo[2.2.1]heptene or -heptane ring-substituted with nucleobase at position 7. Nucleoside analogues **3**–**8** (Chart 2) exhibit a weak activity in tests for anti-HIV-1 and anti-HIV-2 activity in human T-lymphocyte (CEM) cells.

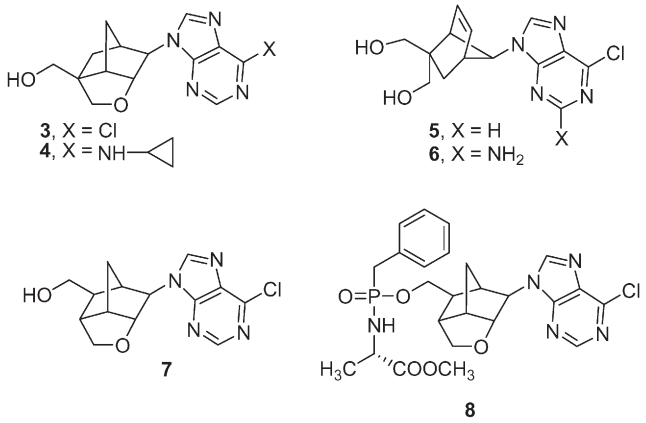


CHART 2

Recently, we discovered, that some 6-chloro- and 2,6-dichloropurines bearing in the position 9 substituted bicyclic hydrocarbons show activity against the *Coxsackie* virus (CVB3)[9,10,12]. The virus is a cytolytic virus, be-

longing to the genus enterovirus within the family of *Picornaviridae*[13]. The enteroviruses (polioviruses, coxsackieviruses, echoviruses) are associated with several human and mammalian diseases. Enteroviruses are the second most common viral infectious agents in humans (after rhinoviruses). In most cases infection is asymptomatic or causes only mild symptoms, but can sometimes also lead to acute haemorrhagic conjunctivitis, herpangina, aseptic meningitis, infectious myocarditis, infectious pericarditis, and pleurodynia. Currently there is no approved therapy for the treatment of picornaviral infections[14].

This study concerns synthesis and anti-coxsackievirus assay of novel racemic nucleoside analogues containg 4,8-dioxatricyclo[4.2.1.$0^{3,7}$]nonane-9-methanol and 4-oxatricyclo[4.3.1.$0^{3,7}$]decane-10-methanol. Chart 3 describes the target compounds.

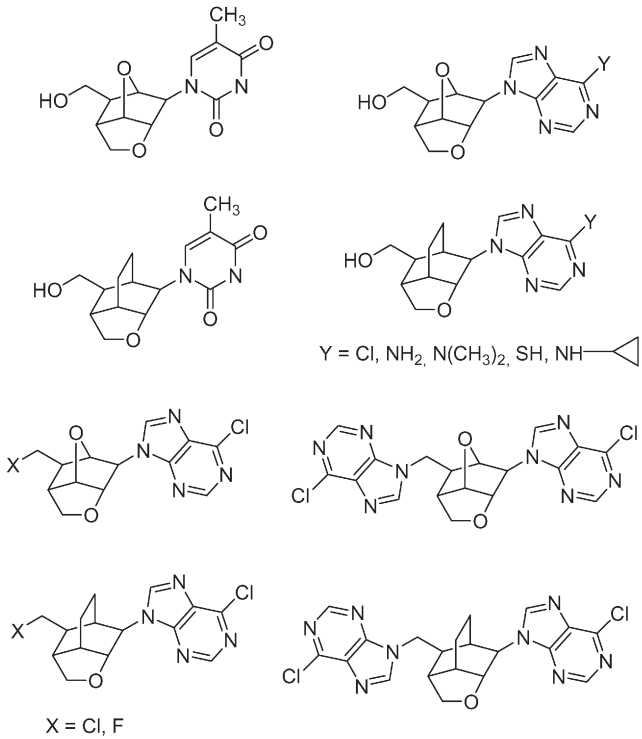
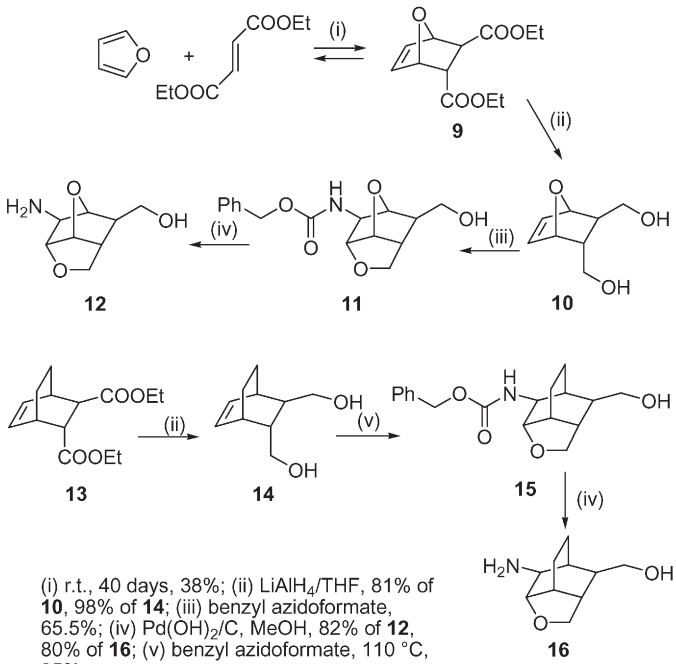


CHART 3

Diols **10** and **14** were used as the key starting materials. Diol **10** was prepared by the Diels–Alder reaction of furan and diethyl fumarate and subsequent reduction with lithium aluminium hydride (Scheme 1). A mixture of furan, fumarate, and a small amount of hydroquinone was left under argon at room temperature for 40 days. The product was, after chromatography on silica gel, immediately reduced without complete characterization to prevent decomposition of the adduct. Due to the aromatic character of furan and the strain of the bicyclo[2.2.1]heptane ring system[15], the cycloadducts are rather sensitive to reverse decomposition to starting materials. Inokuma and co-workers[16] used fumaryl dichloride as dienophile for reaction with furan; the reaction is finished within 48 h. The used dienophile, however, is a potent lachrymator. Diol **14** was obtained by lithium aluminium hydride reduction of diester **13** [17].



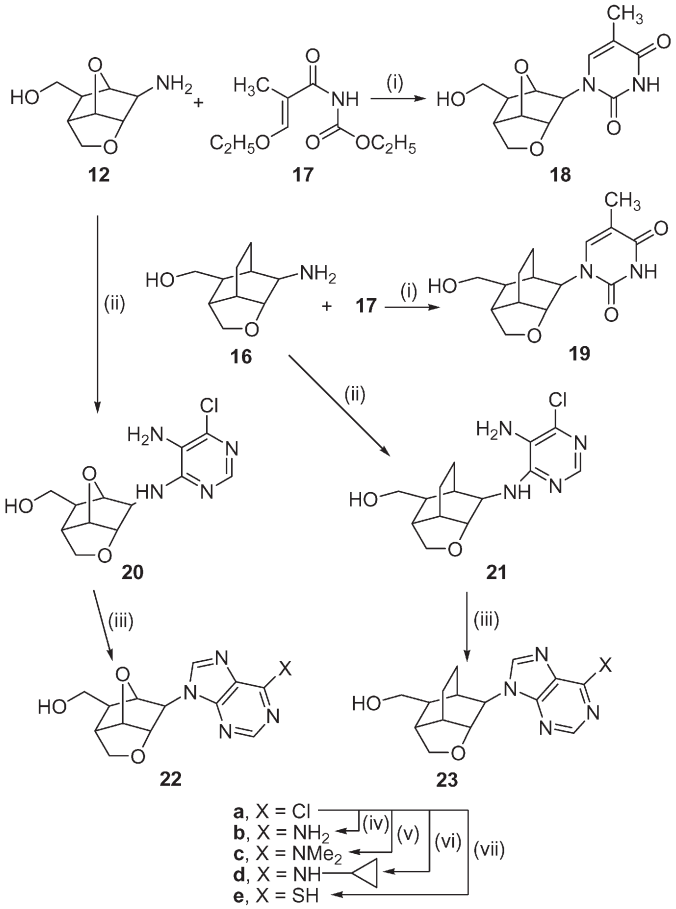
(i) r.t., 40 days, 38%; (ii) $LiAlH_4$/THF, 81% of **10**, 98% of **14**; (iii) benzyl azidoformate, 65.5%; (iv) $Pd(OH)_2$/C, MeOH, 82% of **12**, 80% of **16**; (v) benzyl azidoformate, 110 °C, 35%

SCHEME 1

Treatment of diols **10** and **14** with benzyl azidoformate[18] afforded carbamates **11** (81%) and **15** (35%), respectively. Recently, we prepared carbamate derived from 4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-9-methanol[6] using a similar reaction. Whereas the reaction of 4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-

9-methanol or diol **10** with benzyl azidoformate is exothermic and proceeds readily, the reaction mixture of compound **14** and the azidoformate had to be heated at 110 °C for 5 h. Hydrogenolysis of the carbamates **11** and **15** led to amines **12** (82%) and **16** (80%), respectively.

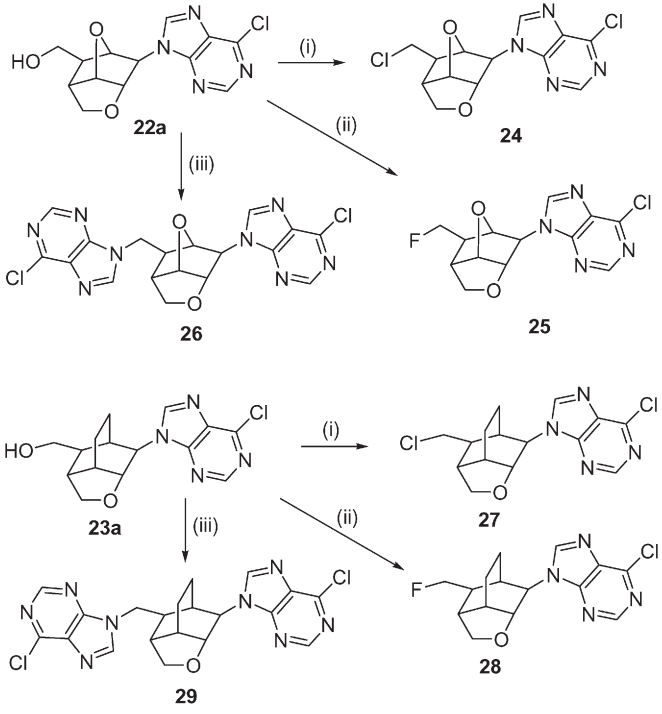
The reaction of amine **12** or **16** with ethyl [(2*E*)-3-ethoxy-2-methylprop-2-enoyl]carbamate[7] (Scheme 2) in 1,4-dioxane at 100 °C followed by treatment with Dowex 50 (H^+) afforded thymine derivative **18** (48%) or **19** (26%).



(i) 1. 1,4-dioxane, 100 °C, 2. Dowex 50 (H^+), 100 °C, 48% of **18**, 31% of **19**; (ii) 4,6-dichloropyrimidin-5-amine/TEA/EtOH, 100 °C, 68% of **20**, 85.5% of **21**; (iii) 1. $CH(OEt)_3$/HCl, 2. THF/H_2O/HCl, 98% of **22a**, 97% of **23a**; (iv) NH_3 (l), 70 °C, 81% of **22b**, 80% of **23b**; (v) $Me_2NCOO^-Me_2NH_2^+$, r.t., 78% of **22c**, 83% of **23c**; (vi) cyclopropylamine, r.t., 73% of **22d**, 79% of **23d**; (vii) thiourea/EtOH, reflux, 95% of **22e**, 82% of **23e**

SCHEME 2

Conversion of amines **12** and **16** to the 6-chloropurine derivatives **22a** and **23a**, respectively, was performed by previously described procedures[5–8,11a,19,20]. Coupling of amine **12** or **16** with 4,6-dichloropyrimidin-5-amine in ethanol in the presence of triethylamine gave pyrimidinylamino derivative **20** (68%) or **21** (85.5%). Ring closure of **20** or **21** with triethyl orthoformate in the presence of concentrated hydrochloric acid afforded 6-chloropurine derivative **22a** (98%) or **23a** (97%). The chloropurine derivatives **22a** and **23a** were ammonolysed with liquid ammonia at 70 °C to give adenine derivatives **22b** (81%) and **23b** (80%), respectively. Treatment of **22a** or **23a** with dimethylammonium dimethylcarbamate afforded 6-(dimethylamino)purine derivative **22c** (78%) or **23c** (83%). Aminolysis of **22a** or **23a** with cyclopropylamine led to cyclopropylamino derivative **22d** (73%) or **23d** (79%). The purine-6-thiol derivatives **22e** and **23e** were prepared by reaction of **22a** and **23a**, respectively, with thiourea in refluxing ethanol.



(i) $SOCl_2$/HMPA, 80 °C, 77% of **24**, 75% of **27**; (ii) DAST/pyridine/CH_2Cl_2, 33% of **25**, 31% of **28**; (iii) 6-chloropurine, PPh_3, DIAD, THF, 79% of **26**, 84% of **29**

SCHEME 3

Also compounds **24**–**29** with modified 9-(hydroxymethyl) group were prepared (Scheme 3) to determine the effect of the hydroxy group on antiviral activity and find out whether the presence of an aditional 6-chloropurine ring in molecule increases their antiviral activity. The chloro derivatives **24** and **27** were prepared by the treatment of **22a** or **23a** with thionyl chloride in hexamethylphosphoramide (HMPA) at 80 °C in 77 and 75% yields, respectively. Treatment of **22a** or **23a** with (diethylamino)-sulfur trifluoride (DAST) and pyridine in dichloromethane led to the fluoro derivative **25** (33%) or **28** (31%). Reaction of **22a** or **23a** with 6-chloropurine under Mitsunobu's conditions afforded bis(6-chloropurine) derivative **26** (79%) or **29** (84%).

The structures of the prepared compounds were confirmed by NMR spectroscopy. Complete assignment of all ^{1}H and ^{13}C resonances is based on combination of ^{1}H, ^{13}C APT, H,H-COSY, H,C-HSQC, and H,C-HMBC experiments.

In conclusion, novel racemic carbocyclic nucleoside analogues of thymine, 6-chloropurine, adenine, 6-(dimethylamino)purine, 6-(cyclopropylamino)purine, and 9*H*-purine-6-thiol derived from 4,8-dioxatricyclo[4.2.1.$0^{3,7}$]nonane-9-methanol and 4-oxatricyclo[4.3.1.$0^{3,7}$]decane-10-methanol. The target compounds were tested for the activity against *Coxsackie* virus (CVB3). Some of the analogues exhibit the activity (**22a**: EC_{50} 1.86 μM and CC_{50} 50 μM; **23a**: EC_{50} 1.28 μM and CC_{50} 50 μM; **24**: EC_{50} 0.88 μM and CC_{50} 50 μM; **25**: EC_{50} 1.05 μM and CC_{50} 50 μM; **27**: EC_{50} 1.45 μM and CC_{50} 50 μM; **28**: EC_{50} 0.95 μM and CC_{50} 50 μM). The antiviral activity will be discussed in detail in a separate paper.

EXPERIMENTAL

Melting points were determined on a Kofler block and are not corrected. NMR spectra (δ, ppm; *J*, Hz) were measured on a Varian Unity 500 or Bruker Avance-500 instruments (500 MHz for ^{1}H and 125.7 MHz for ^{13}C) in hexadeuterated dimethyl sulfoxide and the chemical shifts were referenced to the solvent signal (δ 2.50 and 39.70, respectively). Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using the FAB (ionization with Xe, accelerating voltage 8 kV, thioglycerol–glycerol 3:1 mixture or bis(2-hydroxyethyl) disulfide were used as a matrix) or LTQ Orbitrap XL (Thermo Fischer Scientific) using the ESI. Column chromatography was performed on Silica gel 60 (Fluka) and thin-layer chromatography (TLC) on Silufol Silica gel 60 F_{254} foils (Merck). Solvents were evaporated at 2 kPa and bath temperature 30–60 °C; compounds were dried at 13 Pa and 50 °C.

Diethyl (1*R**,2*S**,3*S**,4*S**)-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (**9**)

A mixture of diethyl fumarate (50 ml, 305 mmol), furan (250 ml), and hydroquinone (1 g) was left standing under argon at room temperature for 40 days and then evaporated. Chro-

matography of the residue on a silica gel column (1.5 kg) in toluene–ethyl acetate (23:2) afforded 27.96 g (38%) of diester **9** as thick oil. HR MS (ESI): For $C_{12}H_{16}NaO_5$ [M + Na] calculated 263.0890, found 263.0891.

(1*R**,2*R**,3*R**,4*S**)-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dimethanol (**10**) and (1*R**,2*R**,3*R**,4*S**)-Bicyclo[2.2.2]oct-5-ene-2,3-dimethanol (**14**)

A solution of diester **9** or **13** [17] (100 mmol) in tetrahydrofuran (100 ml) was added dropwise to a stirred mixture of lithium aluminium hydride (6.07 g, 160 mmol) in tetrahydrofuran (200 ml) at 0 °C under argon atmosphere. The mixture was stirred at room temperature for 3 h, the hydride excess was decomposed by slow addition of water. Then solid CO_2 was added to adjust pH of the mixture to ~8. The thick suspension was filtered with a Celite pad, the filter was washed with methanol (5 × 100 ml) and the combined filtrates were evaporated. The residue was chromatographed on a silica gel column (1 kg) in ethyl acetate–acetone–ethanol–water (100:15:6:4) for compound **10** and (50:15:6:2) for compound **14**.

Compound **10**: Yield 12.51 g (81%) as a syrup. For $C_8H_{12}O_3$ (156.2) calculated: 61.52% C, 7.74% H; found: 61:23% C, 7.82% H. ESI MS, *m/z* (%): 178.9 (100) [M + Na], 110.9 (18). ^{1}H NMR: 1.07 ddd, 1 H, *J*(3,CH_2) = 9.5 and 5.7, *J*(3,2) = 4.1 (H-3); 1.65 ddt, 1 H, *J*(2,CH_2) = 10.5 and 6.3, *J*(2,1) = *J*(2,3) = 4.2 (H-2); 2.97 ddd, 1 H, J_{gem} = 10.6, *J*(CH_2,2) = 9.5, *J*(CH_2,OH) = 5.2 (2-CH^{a}H); 3.24–3.31 m, 2 H (2-CH^{b}H and 3-CH^{a}H); 3.47 m, 1 H (3-CH^{b}H); 4.55 t, 1 H, *J*(OH,CH_2) = 5.1 (2-CH_2-O**H**); 4.66 dd, 1 H, *J*(4,5) = 1.8, *J*(4,1) = 0.9 (H-4); 4.69 t, 1 H, *J*(OH,CH_2) = 5.4 (3-CH_2-O**H**); 4.79 ddd, 1 H, *J*(1,2) = 4.4, *J*(1,6) = 1.6, *J*(1,4) = 0.9 (H-1); 6.29 dd, 1 H, *J*(6,5) = 5.9, *J*(6,1) = 1.6 (H-6); 6.42 dd, 1 H, *J*(5,6) = 5.9, *J*(5,4) = 1.8 (H-5). ^{13}C NMR: 45.01 (C-3); 45.67 (C-2); 63.38 (2-CH_2); 63.75 (3-CH_2); 79.25 (C-1); 79.38 (C-4); 135.58 (C-6); 136.46 (C-5).

Compound **14**: Yield 16.48 g (98%). M.p. 72–73 °C (ethyl acetate). For $C_{10}H_{16}O_2$ (168.2) calculated: 71.39% C, 9.59% H; found: 71.59% C, 9.68% H. neg ESI MS, *m/z* (%): 168.1 (12) [M], 167.0 (100) [M – H]. ^{1}H NMR: 0.89 m, 1 H (H-2); 0.95 m, 1 H (H-7); 1.07 m, 1 H (H-3); 1.17 tt, 1 H, J_{gem} = *J*(8a,7a) = 12.0, *J*(8a,7b) = *J*(8a,4) = 3.8 (H-8a); 1.33 m, 1 H (H-8b); 1.63 m, 1 H (H-7b); 2.49 m, 1 H (H-1); 2.53 m, 1 H (H-4); 2.94 m, 1 H and 3.01 m, 1 H (3-CH_2); 3.26 m, 1 H and 3.44 m, 1 H (2-CH_2); 4.49 t, 1 H, *J*(OH,CH_2) = 5.2 (3-CH_2O**H**); 4.52 t, 1 H, *J*(OH,CH_2) = 5.1 (2-CH_2O**H**); 6.08 m, 1 H (H-5); 6.32 ddd, 1 H, *J*(6,5) = 8.1, *J*(6,1) = 6.8, *J*(6,4) = 1.1 (H-6). ^{13}C NMR: 18.82 (C-7); 25.69 (C-8); 30.24 (C-1); 31.12 (C-4); 43.38 (C-2); 45.19 (C-3); 63.40 (2-CH_2); 65.81 (3-CH_2); 132.51 (C-5); 135.71 (C-6).

Benzyl [(1*R**,2*R**,3*S**,6*S**,7*S**,9*S**)-9-(Hydroxymethyl)-4,8-dioxatricyclo[4.2.1.0^{3,7}]nonan-2-yl]-carbamate (**11**)

A mixture of compound **10** (1.56 g, 10 mmol), benzyl azidoformate (1.77 g, 10 mmol), and toluene (2 ml) was stirred at 68 °C (bath temperature). The bath was removed when an exothermic reaction commenced. After termination of the reaction, the mixture was heated to 95 °C for 2 h. Chromatography of the mixture on a silica gel column (150 g) in ethyl acetate–acetone–ethanol–water (105:15:3:2) and following crystallization from ether afforded 2.00 g (65.5%) of compound **11**, m.p. 117–119 °C. For $C_{16}H_{19}NO_5$ (305.3) calculated: 62.94% C, 6.27% H, 4.59% N; found: 62.87% C, 6.34% H, 4.51% N. ESI MS, *m/z* (%): 328.2 (100) [M + Na], 306.0 (34), 288.4 (40). ^{1}H NMR: 1.72 m, 1 H (H-9); 1.94 m, 1 H (H-6); 3.22–3.26 m, 3 H (H-2 and CH_2O); 3.75 m, 2 H (H-5); 3.98 dd, 1 H, *J*(3,7) = 4.8, *J*(3,2) = 1.3

(H-3); 4.15 bs, 1 H (H-1); 4.76 t, 1 H, *J*(OH,CH_2) = 5.3 (OH); 4.86 bt, 1 H, *J*(7,3) = *J*(7,6) = 4.8 (H-7); 5.02 bs, 2 H (CH_2Ph); 7.29–7.39 m, 6 H (NH and Ph). ^{13}C NMR: 41.06 (C-6); 50.99 (C-9); 61.91 (CH_2O); 62.61 (C-2); 65.48 (CH_2Ph); 71.82 (C-5); 80.09 (C-1); 81.05 (C-7); 82.86 (C-3); 127.95 (C-2´); 128.01 (C-4´); 128.58 (C-3´); 137.33 (C-1´); 155.79 (C=O).

Benzyl [(1*R**,2*R**,3*R**,6*R**,7*S**,10*S**)-10-(Hydroxymethyl)-4-oxatricyclo[4.3.1.0^{3,7}]decan-2-yl]-carbamate (**15**)

A mixture of diol **14** (6.73 g, 40 mmol), benzyl azidoformate (7.79 g, 44 mmol), and toluene (10 ml) was stirred at 110 °C (bath temperature) for 5 h. The mixture was then diluted with ethyl acetate (200 ml) and washed with water (3 × 100 m), dried over anhydrous sodium sulfate and evaporated. Chromatography of the residue on a silica gel column (1 kg) with ethyl acetate–toluene (22:3) afforded 4.49 g (35%) of carbamate **15** as a foam. For $C_{18}H_{23}NO_4$ (317.4) calculated: 68.12% C, 7.30% H, 4.41% N; found: 67.87% C, 7.30% H, 4.28% N. ESI MS, *m/z* (%): 340.1 (100) [M + Na], 335.0 (35), 318.0 [M + H]. ^{1}H NMR: 1.26 m, 2 H (H-9); 1.41 m, 1 H (H-10); 1.52 m, 1 H (H-8a); 1.65 m, 1 H (H-8b); 1.65 td, 1 H, *J*(6,10) = 2.0, *J*(6,5b) = *J*(6,7) = 3.9 (H-6); 1.76 m, 1 H (H-1); 1.78 m, 1 H (H-7); 3.17 dd, 1 H, *J*(2,NH) = 7.2, *J*(2,1) = 4.1 (H-2); 3.32 d, 1 H, J_{gem} = 7.3 (H-5a); 3.35–3.47 m, 2 H (CH_2O); 3.59 dd, 1 H, J_{gem} = 7.3, *J*(5b,6) = 3.8 (H-5b); 3.67 d, 1 H, *J*(3,7) = 5.2 (H-3); 4.59 t, 1 H, *J*(OH,CH_2) = 5.2 (OH); 5.02 s, 2 H (CH_2Ph); 7.30–7.39 m, 5 H (Ph); 7.43 d, 1 H, *J*(NH,2) = 7.0 (NH). ^{13}C NMR: 11.63 (C-9); 14.52 (C-8); 27.43 (C-1); 34.92 (C-7); 37.32 (C-6); 44.50 (C-10); 58.71 (C-2); 63.44 (CH_2OH); 65.48 (CH_2Ph); 75.35 (C-5); 79.35 (C-3); 128.07 (C-4´); 128.10 (C-2´); 128.63 (C-3´); 137.42 (C-1´); 155.79 (C=O).

(1*R**,2*R**,3*S**,6*S**,7*S**,9*S**)-2-Amino-4,8-dioxatricyclo[4.2.1.0^{3,7}]nonane-9-methanol (**12**) and (1*R**,2*R**,3*R**,6*R**,7*S**,10*S**)-2-Amino-4-oxatricyclo[4.3.1.0^{3,7}]decane-10-methanol (**16**)

Palladium(II) hydroxide on carbon (20% Pd, 300 mg) was added to a solution of protected amine **11** or **15** (30 mmol) in methanol (80 ml) and the mixture was stirred under hydrogen atmosphere at room temperature for 24 h. The catalyst was filtered off with a Celite pad, washed with methanol and the filtrate was evaporated. The residue was crystallized from propan-2-ol.

Compound **12**: Yield 4.21 g (82%). M.p. 113–115 °C. For $C_8H_{13}NO_3$ (171.2) calculated: 56.13% C, 7.65% H, 8.18% N; found: 55.94% C, 7.73% H, 7.94% N. FAB MS, *m/z* (%): 172 (100) [M + H]. ^{1}H NMR: 1.60 ddd, 1 H, *J*(9,CH_2) = 9.3 and 6.8, *J*(9,6) = 2.1 (H-9); 1.89 m, 1 H (H-6); 2.53 s, 1 H (H-2); 3.21 dd, 1 H, *J*(CH_2,9) = 6.8 and 3.25 dd, 1 H, J_{gem} = 10.5, *J*(CH_2,9) = 9.3 (CH_2O); 3.69 m, 3 H (H-3 and H-5); 3.90 s, 1 H (H-1); 4.80 t, 1 H, *J*(7,3) = *J*(7,6) = 4.8 (H-7). ^{13}C NMR: 41.13 (C-6); 51.27 (C-9); 62.16 (CH_2O); 62.99 (C-2); 71.61 (C-5); 80.90 (C-7); 82.84 (C-1); 85.75 (C-3).

Compound **16**: Yield 4.40 g (80%). M.p. 145–147 °C. For $C_{10}H_{17}NO_2$ (183.3) calculated: 65.54% C, 9.35% H, 7.64% N; found: 65.65% C, 9.46% H, 7.44% N. ^{1}H NMR: 1.16 m, 1 H (H-9a); 1.34 m, 1 H (H-10); 1.47–1.60 m, 4 H (H-1, 8a, 8b and H-9b); 1.61 m, 1 H (H-6); 1.75 m, 1 H (H-7); 2.50 m, 1 H (H-2); 3.25 d, 1 H, J_{gem} = 7.1 (H-5a); 3.40 d, 1 H, *J*(3,7) = 5.3 (H-3); 3.44 m, 2 H (CH_2O); 3.55 dd, 1 H, J_{gem} = 7.1, *J*(5b,6) = 3.7 (H-5b). ^{13}C NMR: 11.17 (C-9); 15.04 (C-8); 29.86 (C-1); 34.97 (C-7); 37.53 (C-6); 45.21 (C-10); 58.70 (C-2); 63.70 (CH_2OH); 75.39 (C-5); 82.01 (C-3).

1-[(1*R**,2*R**,3*S**,6*S**,7*S**,9*S**)-9-(Hydroxymethyl)-4,8-dioxatricyclo[4.2.1.0^{3,7}]nonan-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**18**) and
1-[(1*R**,2*R**,3*R**,6*R**,7*S**,10*S**)-10-(Hydroxymethyl)-4-oxatricyclo[4.3.1.0^{3,7}]decan-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**19**)

A solution of amine **12** or **16** (2 mmol) and ethyl *N*-[(2*E*)-3-ethoxy-2-methylprop-2-enoyl]-carbamate (402 mg, 2 mmol) in 1,4-dioxane (15 ml) was heated at 100 °C for 3 h. Dowex 50 (H^+; 6 ml) was washed with 1,4-dioxane and then added to the solution. The mixture was heated at 100 °C for 4 h, the resin was filtered off, washed with dioxane and the combined filtrates were evaporated. The residue was crystallized from methanol.

Compound **18**: Yield 242 mg (43%). M.p. 243–244 °C. For $C_{13}H_{16}N_2O_5$ (280.3) calculated: 55.71% C, 5.75% H, 9.99% N; found: 55.56% C, 5.85% H, 9.92% N. FAB MS, *m/z* (%): 281 (100) [M + H], 127 (36). ^{1}H NMR: 1.74 d, 3 H, $J(CH_3,6)$ = 1.2 (5-CH_3); 1.86 ddd, 1 H, J(9′,6′) = 2.0, $J(9',CH_2)$ = 7.0 and 9.0 (H-9′); 2.07 m, 1 H (H-6′); 3.26 m, 2 H (CH_2O); 3.83 dd, 1 H, J_{gem} = 8.7, J(5′a,6′) = 4.2 (H-5′a); 3.87 d, 1 H, J_{gem} = 8.6 (H-5′b); 4.27 s, 1 H (H-1′); 4.32 dd, 1 H, J(3′,7′) = 4.8, J(3′,2′) = 1.5 (H-3′); 4.38 t, 1 H, J(2′,3′) = J(2′,1′) = 1.3 (H-2′); 4.80 bt, 1 H, $J(OH,CH_2)$ = 5.3 (OH); 5.03 td, 1 H, J(7′,3′) = J(7′,6′) = 4.9, J(7′,1′) = 0.8 (H-7′); 7.33 q, 1 H, $J(6,CH_3)$ = 1.2 (H-6); 11.30 bs, 1 H (NH). ^{13}C NMR: 12.44 (5-CH_3); 41.00 (C-6′); 51.76 (C-9′); 61.63 (CH_2O); 64.32 (C-2′); 72.06 (C-5′); 80.06 (C-1′); 81.28 (C-7′); 83.33 (C-3′); 108.76 (C-5); 137.96 (C-6); 151.18 (C-2); 163.89 (C-4).

Compound **19**: Yield 181 mg (31%). M.p. 226–228.5 °C. For $C_{15}H_{20}N_2O_4$ (292.3) calculated: 61.63% C, 6.90% H, 9.58% N; found: 61.39% C, 6.97% H, 9.31% N. FAB MS, *m/z* (%): 293 (100) [M + H], 127 (100). ^{1}H NMR: 0.93 m, 1 H (H-9′a); 1.39 m, 1 H (H-9′b); 1.52 m, 1 H (H-10′); 1.61–1.84 m, 4 H (H-1′, H-6′ and H-8′); 1.80 d, 3 H, $J(CH_3,6)$ = 1.1 (5-CH_3); 1.98 m, 1 H (H-7′); 3.38–3.50 m, 3 H (H-5′a and CH_2O); 3.67 dd, 1 H, J_{gem} = 7.5, J(5′b,6′) = 4.0 (H-5′b); 3.99 bd, 1 H, J(2′,1′) = 3.8 (H-2′); 4.31 d, 1 H, J(3′,7′) = 5.1 (H-3′); 4.69 bt, 1 H, $J(OH,CH_2)$ = 5.0 (OH); 7.28 d, 1 H, $J(6,CH_3)$ = 0.8 (H-6); 11.31 bs, 1 H (H-3). ^{13}C NMR: 11.30 (C-9′); 12.35 (5-CH_3); 15.13 (C-8′); 27.74 (C-1′); 35.10 (C-7′); 37.77 (C-6′); 44.69 (C-10′); 63.06 (CH_2O); 63.39 (C-2′); 74.93 (C-5′); 75.75 (C-3′); 108.57 (C-5); 139.07 (C-6); 151.15 (C-2); 163.99 (C-4).

(1*R**,2*R**,3*S**,6*S**,7*S**,9*S**)-2-[(5-Amino-6-chloropyrimidin-4-yl)amino]-4,8-dioxatricyclo-[4.2.1.0^{3,7}]nonane-9-methanol (**20**) and
(1*R**,2*R**,3*R**,6*R**,7*S**,10*S**)-2-[(5-Amino-6-chloropyrimidin-4-yl)amino]-4-oxatricyclo-[4.3.1.0^{3,7}]- decane-10-methanol (**21**)

A solution of amine **12** or **16** (8 mmol), 4,6-dichloropyrimidin-5-amine (1.31 g, 8 mmol), and triethylamine (2.4 ml) in ethanol (24 ml) was heated in a pressure vessel at 100 °C for 144 h and, after cooling, was evaporated. The residue was crystallized from ethanol and the mother liquor was chromatographed on a silica gel column (25 g) in ethyl acetate–acetone–ethanol–water (50:7:3:2) for compound **20** or (100:15:6:4) for compound 21.

Compound **20**: Yield 1.63 g (68%). M.p. 260–262 °C. For $C_{12}H_{15}ClN_4O_3$ (298.7) calculated: 48.25% C, 5.06% H, 11.87% Cl, 18.76% N; found: 48.21% C, 5.07% H, 11.79% Cl, 18.67% N. FAB MS, *m/z* (%): 301/299 (35/100) [M + H], 265 (41). ^{1}H NMR: 1.82 ddd, 1 H, J(9,6) = 2.0, $J(9,CH_2)$ = 7.0 and 9.1 (H-9); 2.01 dt, 1 H, J(6,7) = J(6,5a) = 4.6, J(6,9) = 1.9 (H-6); 3.24–3.32 m, 2 H (CH_2O); 3.78 d, 1 H, J(2,NH) = 6.5 (H-2′); 3.80 dd, 1 H, J_{gem} = 8.5, J(5a,6) = 4.1 (H-5a); 3.83 brd, 1 H, J_{gem} = 8.5 (H-5b); 4.02 dd, 1 H, J(3,7) = 4.8, J(3,2) = 1.3 (H-3); 4.24 brs, 1 H (H-1); 4.77 t, 1 H, $J(OH,CH_2)$ = 5.4 (OH); 4.96 t, 1 H, J(7,3) = J(7,6) = 4.7 (H-7); 5.18 brs, 2 H

(NH_2); 6.76 d, 1 H (NH); 7.74 s, 1 H (H-2´). ^{13}C NMR: 41.25 (C-6); 51.16 (C-9); 61.99 (CH_2O); 62.88 (C-2); 71.88 (C-5); 80.05 (C-1); 81.24 (C-7); 83.25 (C-3); 123.96 (C-5´); 136.93 (C-4´); 145.54 (C-2´); 150.98 (C-6´).

Compound **21**: Yield 2.13 g (85.5%). M.p. 253–254 °C. For $C_{14}H_{19}ClN_4O_2$ (310.8) calculated: 54.11% C, 6.16% H, 11.41% Cl, 18.03% N; found: 53.96% C, 6.15% H, 11.43% Cl, 17.83% N. FAB MS, *m/z* (%): 313/311 (55/100) [M + H]. ^{1}H NMR: 1.26 m, 2 H (H-9); 1.50 m, 1 H (H-10); 1.63 m, 1 H (H-8a); 1.71 m, 1 H (H-6); 1.74 m, 1 H (H-8b); 1.88 m, 1 H (H-7); 2.00 m, 1 H (H-1); 3.38 d, 1 H, J_{gem} = 7.2 (H-5a); 3.43 ddd, 1 H, J_{gem} = 10.7, J(CH_2,10) = 8.6, J(CH_2,OH) = 5.3 (CH^aH-O); 3.48 ddd, 1 H, J_{gem} = 10.7, J(CH_2,10) = 7.4, J(CH_2,OH) = 5.3 (CH^bH-O); 3.65 dd, 1 H, J_{gem} = 7.4, J(5b,6) = 3.8 (H-5b); 3.70 dd, 1 H, J(2,NH) = 6.6, J(2,1) = 4.0 (H-2); 3.85 d, 1 H, J(3,7) = 5.2 (H-3); 4.59 t, 1 H, J(OH,CH_2) = 5.3 (OH); 5.21 bs, 2 H (NH_2); 6.49 bd, 1 H, J(NH,2) = 6.6 (NH); 7.71 s, 1 H (H-2´). ^{13}C NMR: 11.80 (C-9); 14.78 (C-8); 26.45 (C-1); 35.06 (C-7); 37.50 (C-6); 44.56 (C-10); 58.96 (C-2); 63.54 (CH_2O); 75.32 (C-5); 79.47 (C-3); 123.83 (C-5´); 136.95 (C-6´); 145.66 (C-2´); 151.27 (C-4´).

(1*R**,2*R**,3*S**,6*S**,7*S**,9*S**)-2-(6-Chloro-9*H*-purin-9-yl)-4,8-dioxatricyclo[4.2.1.0^{3,7}]nonane-9-methanol (**22a**) and
(1*R**,2*R**,3*R**,6*R**,7*S**,10**S*)-2-(6-Chloro-9*H*-purin-9-yl)-4-oxatricyclo[4.3.1.0^{3,7}]decane-10-methanol (**23a**)

Concentrated hydrochloric acid (1.8 ml) was added to a stirred mixture of compound **20** or **21** (2.5 mmol) and triethyl orthoformate (39 ml), the resulting solution was left aside at room temperature for 3 days and then evaporated. The residue was dissolved in tetrahydrofuran (23 ml). To the stirred solution, 0.5 M hydrochloric acid (23 ml) was added, the mixture was stirred at room temperature for 3 h and then neutralized with solid sodium hydrogencarbonate. The organic layer was separated and the aqueous layer was extracted with tetrahydrofuran (4 × 20 ml). The combined organic layers were evaporated and the residue was crystallized from water.

Compound **22a**: Yield 756 mg (98%). M.p. 205.5–206.5 °C. For $C_{13}H_{13}ClN_4O_3$ (308.7) calculated: 50.58% C, 4.24% H, 11.48% Cl, 18.15% N; found: 50.43% C, 4.29% H, 11.66% Cl, 18.01% N. FAB MS, *m/z* (%): 311/309 (37/100) [M + H]. ^{1}H NMR: 2.05 ddd, 1 H, J(9,6) = 2.0, J(9,CH_2) = 7.3 and 8.8 (H-9); 2.16 dt, 1 H, J(6,7) = J(6,5a) = 4.5, J(6,9) = 2.0 (H-6); 3.33 m, 2 H (CH_2O); 3.88 dd, 1 H, J_{gem} = 8.6, J(5a,6) = 4.2 (H-5a); 3.96 d, 1 H, J_{gem} = 8.5 (H-5b); 4.51 dd, 1 H, J(3,7) = 4.8, J(3,2) = 1.5 (H-3); 4.59 m, 2 H (H-1 and H-2); 4.86 t, 1 H, J(OH,CH_2) = 5.3 (OH); 5.18 t, 1 H, J(7,3) = J(7,6) = 4.8 (H-7); 8.54 s, 1 H (H-8´); 8.80 s, 1 H (H-2´). ^{13}C NMR: 41.06 (C-6); 50.92 (C-9); 61.66 (CH_2O); 64.53 (C-2); 72.29 (C-5); 80.06 (C-1); 81.86 (C-7); 83.25 (C-3); 130.76 (C-5´); 145.24 (C-8´); 149.16 (C-6´); 151.69 (C-2´); 151.85 (C-4´).

Compound **23a**: Yield 778 mg (97%). M.p. 183.5–184.5 °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: 55.88% C, 5.35% H, 11.03% Cl, 17.24% N. FAB MS, *m/z* (%): 323/321 (39/100) [M + H], 157/155 (35/73). ^{1}H NMR: 0.62 m, 1 H (H-9a); 1.35 m, 1 H (H-9b); 1.69–1.78 m, 2 H (H-8a and H-10); 1.82 m, 1 H (H-6); 1.99 m, 1 H (H-8b); 2.08 m, 1 H (H-1); 2.10 m, 1 H (H-7); 3.45 m, 1 H (CH^aH-O); 3.51 d, 1 H, J_{gem} = 7.5 (H-5a); 3.53 m, 1 H (CH^bH-O); 3.74 dd, 1 H, J_{gem} = 7.5, J(5b,6) = 3.9 (H-5b); 4.38 bd, 1 H, J(2,1) = 4.0 (H-2); 4.69 bd, 1 H, J(3,7) = 5.0 (H-3); 4.72 t, 1 H, J(OH,CH_2) = 4.9 (OH); 8.77 s, 1 H (H-2´); 8.78 s, 1 H (H-8´). ^{13}C NMR: 11.65 (C-9); 14.45 (C-8); 28.91 (C-1);

35.12 (C-7); 37.52 (C-6); 44.25 (C-10); 63.08 (CH_2O); 63.49 (C-2); 75.28 (C-5); 76.23 (C-3); 130.99 (C-5´); 146.29 (C-8´); 149.44 (C-6´); 151.67 (C-2´); 152.19 (C-4´).

(1*R**,2*R**,3*S**,6*S**,7*S**,9*S**)-2-(6-Amino-9*H*-purin-9-yl)-4,8-dioxatricyclo[4.2.1.$0^{3,7}$]nonane-9-methanol (**22b**) and
(1*R**,2*R**,3*R**,6*R**,7*S**,10*S**)-2-(6-Amino-9*H*-purin-9-yl)-4-oxatricyclo[4.3.1.$0^{3,7}$]decane-10-methanol (**23b**)

A solution of chloropurine derivative **22a** or **23a** (0.5 mmol) in liquid ammonia (15 ml) was heated in an autoclave at 70 °C for 48 h and then ammonia was evaporated. The residue was crystallized from water.

Compound **22b**: Yield 117 mg (81%). M.p. 257–258.5 °C. For $C_{13}H_{15}N_5O_3$ (289.3) calculated: 53.97% C, 5.23% H, 24.21% N; found: 53.69% C, 5.09% H, 23.96% N. FAB MS, *m*/*z* (%): 290 (100) [M + H], 136 (100) [adenine + H]. ^{1}H NMR: 2.00 ddd, 1 H, *J*(9,6) = 2.0, *J*(9,CH_2) = 7.1 and 9.1 (H-9); 2.14 dt, 1 H, *J*(6,7) = *J*(6,5a) = 4.6, *J*(6,9) = 2.0 (H-6); 3.30–3.34 m, 2 H (CH_2O); 3.88 dd, 1 H, J_{gem} = 8.6, *J*(5a,6) = 4.1 (H-5a); 3.94 d, 1 H, J_{gem} = 8.6 (H-5b); 4.41 dd, 1 H, *J*(3,7) = 4.7, *J*(3,2) = 1.2 (H-3); 4.43 m, 1 H (H-1); 4.44 bs, 1 H (H-2); 4.86 bs, 1 H (OH); 5.15 t, 1 H, *J*(7,3) = *J*(7,6) = 4.9 (H-7); 7.26 bs, 2 H (NH_2); 7.99 s, 1 H (H-8´); 8.15 s, 1 H (H-2´). ^{13}C NMR: 41.09 (C-6); 51.13 (C-9); 61.76 (CH_2O); 63.73 (C-2); 72.29 (C-5); 80.51 (C-1); 81.73 (C-7); 83.66 (C-3); 118.45 (C-5´); 138.56 (C-8´); 149.38 (C-4´); 152.72 (C-2´); 156.22 (C-6´).

Compound **23b**: Yield 121 mg (80%). M.p. 282–285 °C. For $C_{15}H_{19}N_5O_2$ (301.4) calculated: 59.79% C, 6.36% H, 23.24% N; found: 59.53% C, 6.45% H, 22.98% N. EI MS, *m*/*z* (%): 301 (71) [M], 136 (100) [adenine + H]. ^{1}H NMR: 0.62 m, 1 H (H-9a); 1.33 m, 1 H (H-9b); 1.68 m, 1 H (H-10); 1.72 m, 1 H (H-8a); 1.80 dt, 1 H, *J*(6,5b) = *J*(6,7) = 3.9, *J*(6,10) = 1.6 (H-6); 1.94 m, 1 H (H-8b); 2.01 m, 1 H (H-1); 2.07 m, 1 H (H-7); 3.44 m, 1 H (CH^aH-O); 3.49 d, 1 H, J_{gem} = 7.5 (H-5a); 3.52 m, 1 H (CH^bH-O); 3.73 dd, 1 H, J_{gem} = 7.5, *J*(5b,6) = 3.9 (H-5b); 4.23 dd, 1 H, *J*(2,1) = 4.2, *J*(2,9b) = 1.2 (H-2); 4.60 bd, 1 H, *J*(3,7) = 5.1 (H-3); 4.71 t, 1 H, *J*(OH,CH_2) = 4.9 (OH); 7.25 bs, 2 H (NH_2); 8.12 s, 1 H (H-2´); 8.21 s, 1 H (H-8´). ^{13}C NMR: 11.60 (C-9); 14.64 (C-8); 28.87 (C-1); 35.18 (C-7); 37.58 (C-6); 44.41 (C-10); 62.41 (C-2); 63.22 (CH_2O); 75.30 (C-5); 76.64 (C-3); 118.82 (C-5´); 139.60 (C-8´); 149.79 (C-4´); 152.68 (C-2´); 156.29 (C-6´).

(1*R**,2*R**,3*S**,6*S**,7*S**,9*S**)-2-[6-(Dimethylamino)-9*H*-purin-9-yl]-4,8-dioxatricyclo[4.2.1.$0^{3,7}$]-nonane-9-methanol (**22c**) and
(1*R**,2*R**,3*R**,6*R**,7*S**,10*S**)-2-[6-(Dimethylamino)-9*H*-purin-9-yl]-4-oxatricyclo[4.3.1.$0^{3,7}$]-decane-10-methanol (**23c**)

A solution of chloropurine derivative **22a** and **23a** (0.5 mmol) in dimethylammonium dimethylcarbamate (2.5 ml) was left standing at room temperature overnight and then evaporated. The residue was crystallized from water (**22c**) or chromatographed on a silica gel column (20 g) in ethyl acetate–acetone–ethanol–water (95:15:8:7) and then crystallized from ethyl acetate (**23c**).

Compound **22c**: Yield 124 mg (78%). M.p. 209–210 °C. For $C_{15}H_{19}N_5O_3$ (317.4) calculated: 56.77% C, 6.03% H, 22.07% N; found: 56.71% C, 6.18% H, 21.88% N. FAB MS, *m*/*z*: 318 [M + H]. ^{1}H NMR: 2.01 ddd, 1 H, *J*(9,6) = 2.1, *J*(9,CH_2) = 7.0 and 9.1 (H-9); 2.14 dt, 1 H, *J*(6,7) = *J*(6,5a) = 4.5, *J*(6,9) = 2.0 (H-6); 3.32 m, 2 H (CH_2O); 3.44 bs, 6 H (N-CH_3); 3.88 dd,

1 H, J_{gem} = 8.6, *J*(5a,6) = 4.2 (H-5a); 3.94 d, 1 H, J_{gem} = 8.6 (H-5b); 4.38 dd, 1 H, *J*(3,7) = 4.8, *J*(3,2) = 1.5 (H-3); 4.44 m, 1 H (H-1); 4.47 bs, 1 H (H-2); 4.84 t, 1 H, *J*(OH,CH_2) = 5.4 (OH); 5.15 t, 1 H, *J*(7,3) = *J*(7,6) = 4.9 (H-7); 8.00 s, 1 H (H-8´); 8.22 s, 1 H (H-2´). ^{13}C NMR: 41.07 (C-6); 51.13 (C-9); 61.71 (CH_2O); 63.68 (C-2); 72.26 (C-5); 80.39 (C-1); 81.69 (C-7); 83.67 (C-3); 118.96 (C-5´); 137.35 (C-8´); 150.10 (C-4´); 152.00 (C-2´); 154.42 (C-6´).

Compound **23c**: Yield 137 mg (83%). M.p. 180–181 °C. For $C_{17}H_{23}N_5O_2$ (329.4) calculated: 61.99% C, 7.04% H, 21.26% N; found: 61.72% C, 6.91% H, 21.23% N. FAB MS, *m/z* (%): 330 (100) [M + H], 164 (19). ^{1}H NMR: 0.60 m, 1 H (H-9a); 1.32 m, 1 H (H-9b); 1.68 m, 1 H (H-10); 1.74 m, 1 H (H-8a); 1.80 dt, 1 H, *J*(6,5b) = *J*(6,7) = 3.9, *J*(6,10) = 1.8 (H-6); 1.92 m, 1 H (H-8b); 2.02 m, 1 H (H-1); 2.07 m, 1 H (H-7); 3.44 ddd, 1 H, *J*(CH^{a}H,10) = 9.0, *J*(CH^{a}H,OH) = 5.3, J_{gem} = 10.7 (CH^{a}H-O); 3.49 d, 1 H, J_{gem} = 7.4 (H-5a); 3.5 vbs, 6 H (N-CH_3); 3.52 ddd, 1 H, 1 H, *J*(CH^{b}H,10) = 7.2, *J*(CH^{b}H,OH) = 5.1, J_{gem} = 10.7 (CH^{b}H-O); 3.73 dd, 1 H, J_{gem} = 7.5, *J*(5b,6) = 3.9 (H-5b); 4.26 bd, 1 H, *J*(2,1) = 4.1 (H-2); 4.59 bd, 1 H, *J*(3,7) = 5.0 (H-3); 4.68 t, 1 H, *J*(OH,CH_2) = 5.2 (OH); 8.20 s, 1 H (H-2´); 8.22 s, 1 H (H-8´). ^{13}C NMR: 11.51 (C-9); 14.58 (C-8); 28.61 (C-1); 35.13 (C-7); 37.55 (C-6); 44.36 (C-10); 62.25 (C-2); 63.17 (CH_2OH); 75.26 (C-5); 76.63 (C-3); 119.31 (C-5´); 138.31 (C-8´); 150.48 (C-4´); 151.95 (C-2´); 154.49 (C-6´).

(1*R**,2*R**,3*S**,6*S**,7*S**,9*S**)-2-[6-(Cyclopropylamino)-9*H*-purin-9-yl]-4,8-dioxatricyclo-[4.2.1.0^{3,7}]nonane-9-methanol (**22d**) and
(1*R**,2*R**,3*R**,6*R**,7*S**,10*S**)-2-[6-(Cyclopropylamino)-9*H*-purin-9-yl]-4-oxatricyclo-[4.3.1.0^{3,7}]decane-10-methanol (**23d**)

A solution of chloropurine derivative **22a** or **23a** (0.5 mmol) in cyclopropylamine (2 ml) was left standing at room temperature overnight and then evaporated. The residue was crystallized from water (**22d**) or chromatographed on a silica gel column (20 g) in ethyl acetate–acetone–ethanol–water (95:15:8:7) (**23d**).

Compound **22d**: Yield 120 mg (73%). M.p. 209–210°C. For $C_{16}H_{19}N_5O_3$ (329.4) calculated: 58.35% C, 5.81% H, 21.26% N; found: 58.37% C, 5.74% H, 21.09% N. FAB MS, *m/z*: 330 [M + H]. ^{1}H NMR: 0.60 m, 2 H and 0.71 m, 2 H and 3.00 bs, 1 H (cyclopropane); 2.01 ddd, 1 H, *J*(9,6) = 2.0, *J*(9,CH_2) = 7.0 and 9.1 (H-9); 2.14 dt, 1 H, *J*(6,7) = *J*(6,5a) = 4.5, *J*(6,9) = 2.0 (H-6); 3.31 m, 2 H (CH_2O); 3.87 dd, 1 H, J_{gem} = 8.6, *J*(5a,6) = 4.2 (H-5a); 3.94 d, 1 H, J_{gem} = 8.6 (H-5b); 4.41 dd, 1 H, *J*(3,7) = 4.8, *J*(3,2) = 1.4 (H-3); 4.44 m, 1 H (H-1); 4.46 bs, 1 H (H-2); 4.84 t, 1 H, *J*(OH,CH_2) = 5.4 (OH); 5.15 t, 1 H, *J*(7,3) = *J*(7,6) = 4.8 (H-7); 7.95 bs, 1 H (NH); 8.00 s, 1 H (H-8´); 8.25 bs, 1 H (H-2´). ^{13}C NMR: 6.53, 2 C (CH_2 of cyclopropane); 23.85 (CH of cyclopropane); 41.07 (C-6); 51.11 (C-9); 61.73 (CH_2O); 63.66 (C-2); 72.27 (C-5); 80.47 (C-1); 81.71 (C-7); 83.66 (C-3); 118.84 (C-5´); 138.36 (C-8´); 148.68 (C-4´); 152.61 (C-2´); 155.72 (C-6´).

Compound **23d**: Yield 135 mg (79%) as a foam. For $C_{18}H_{23}N_5O_2$ (341.4) calculated: 63.32% C, 6.79% H, 20.51% N; found: 63.22% C, 6.90% H, 20.32% N. FAB MS, *m/z* (%): 342 (100) [M + H], 176 (37). ^{1}H NMR: 0.61 m, 3 H (CH_2 of cyclopropane and H-9a); 0.72 m, 2 H (CH_2 of cyclopropane); 1.33 m, 1 H (H-9b); 1.69 m, 1 H (H-10); 1.74 m, 1 H (H-8a); 1.80 m, 1 H (H-6); 1.94 m, 1 H (H-8b); 2.02 m, 1 H (H-1); 2.07 m, 1 H (H-7); 3.02 bs, 1 H (CH of cyclopropane); 3.47 m, 2 H (CH_2O); 3.49 d, 1 H, J_{gem} = 7.4 (H-5a); 3.73 dd, 1 H, J_{gem} = 7.5, *J*(5b,6) = 3.9 (H-5b); 4.25 d, 1 H, *J*(2,1) = 4.0 (H-2); 4.61 d, 1 H, *J*(3,7) = 5.1 (H-3); 4.68 t, 1 H, *J*(OH,CH_2) = 5.2 (OH); 7.90 bs, 1 H (NH); 8.21 s, 1 H (H-8´); 8.23 bs, 1 H (H-2´). ^{13}C NMR: 6.57 (CH_2 of cyclopropane); 11.56 (C-9); 14.61 (C-8); 28.85 (C-1); 35.15 (C-7);

37.56 (C-6); 44.39 (C-10); 62.38 (C-2); 63.19 (CH_2O); 75.25 (C-5); 76.61 (C-3); 119.16 (C-5´); 139.38 (C-8´); 149.20 (C-4´); 152.51 (C-2´); 155.79 (C-6´).

(1*R**,2*R**,3*S**,6*S**,7*S**,9*S**)-2-(6-Sulfanyl-9*H*-purin-9-yl)-4,8-dioxatricyclo[4.2.1.$0^{3,7}$]nonane-9-methanol (**22e**) and
(1*R**,2*R**,3*R**,6*R**,7*S**,10*S**)-2-(6-Sulfanyl-9*H*-purin-9-yl)-4-oxatricyclo[4.3.1.$0^{3,7}$]decane-10-methanol (**23e**)

A solution of chloropurine derivative **22a** or **23a** (0.5 mmol) and thiourea (42 mg, 0.55 mmol) in ethanol (5 ml) was refluxed for 2.5 h. The precipitated product was filtered off and washed with ethanol and ether.

Compound **22e**: Yield 145 mg (95%). M.p. 321–324 °C. For $C_{13}H_{14}N_4O_3S$ (306.4) calculated: 50.97% C, 4.61% H, 18.29% N, 10.47% S; found: 50.72% C, 4.40% H, 18.08% N, 10.51% S. FAB MS, *m*/*z* (%): 307 (100) [M + H], 153 (84) [9*H*-purine-6-thiol + H]. ^{1}H NMR: 2.00 ddd, 1 H, *J*(9,6) = 2.1, *J*(9,CH_2) = 7.1 and 9.1 (H-9); 2.14 dt, 1 H, *J*(6,7) = *J*(6,5a) = 4.5, *J*(6,9) = 1.9 (H-6); 3.28–3.35 m, 2 H (CH_2O); 3.87 dd, 1 H, J_{gem} = 8.7, *J*(5a,6) = 4.1 (H-5a); 3.93 d, 1 H, J_{gem} = 8.6 (H-5b); 4.42 dd, 1 H, *J*(3,7) = 4.8, *J*(3,2) = 1.4 (H-3); 4.43 bs, 1 H (H-2); 4.50 m, 1 H (H-1); 5.16 bt, 1 H, *J*(7,3) = *J*(7,6) = 4.8 (H-7); 8.12 s, 1 H (H-8´); 8.21 s, 1 H (H-2´); 13.74 bs, 1 H (SH). ^{13}C NMR: 41.05 (C-6); 51.06 (C-9); 61.69 (CH_2O); 64.22 (C-2); 72.33 (C-5); 80.28 (C-1); 81.81 (C-7); 83.53 (C-3); 134.81 (C-5´); 140.78 (C-8´); 143.96 (C-4´); 145.23 (C-2´); 176.08 (C-6´).

Compound **23e**: Yield 131 mg (82%). M.p. 323–326 °C. For $C_{15}H_{18}N_4O_2S$ (318.4) calculated: 56.58% C, 5.70% H, 17.60% N, 10.07% S; found: 56.29% C, 5.45% H, 17.33% N, 10.18% S. FAB MS, *m*/*z* (%): 319 (40) [M + H], 153 (89) [9*H*-purine-6-thiol + H]. ^{1}H NMR: 0.62 m, 1 H (H-9a); 1.36 m, 1 H (H-9b); 1.67 m, 1 H (H-10); 1.73 m, 1 H (H-8a); 1.80 m, 1 H (H-6); 1.93 m, 1 H (H-8b); 2.00 m, 1 H (H-1); 2.07 m, 1 H (H-7); 3.44 m, 1 H (CH^aH-O); 3.49 d, 1 H, J_{gem} = 7.5 (H-5a); 3.52 dd, 1 H, J_{gem} = 10.8, *J*(CH^bH,10) = 7.1, J_{gem} = 10.8 (CH^bH-O); 3.72 dd, 1 H, J_{gem} = 7.5, *J*(5b,6) = 3.8 (H-5b); 4.43 bd, 1 H, *J*(2,1) = 4.2 (H-2); 4.58 bd, 1 H, *J*(3,7) = 5.1 (H-3); 8.19 d, 1 H, *J*(2´,SH) = 3.8 (H-2´); 8.37 s, 1 H (H-8´); 13.73 bs, 1 H (SH). ^{13}C NMR: 11.52 (C-9); 14.48 (C-8); 29.09 (C-1); 35.10 (C-7); 37.49 (C-6); 44.32 (C-10); 62.98 (C-2); 63.08 (CH_2O); 75.30 (C-5); 76.40 (C-3); 135.09 (C-5´); 141.83 (C-8´); 144.32 (C-4´); 145.14 (C-2´); 176.17 (C-6´).

6-Chloro-9-[(1*R**,2*R**,3*R**,6*S**,7*S**,9*S**)-9-(chloromethyl)-4-oxatricyclo[4.2.1.$0^{3,7}$]-nonan-2-yl]-9*H*-purine (**24**) and
6-Chloro-9-[(1*R**,2*R**,3*R**,6*S**,7*S**,10*S**)-10-(chloromethyl)-4-oxatricyclo[4.3.1.$0^{3,7}$]-decan-2-yl]-9*H*-purine (**27**)

Thionyl chloride (0.15 ml) was added to a stirred solution of chloropurine derivative **22a** or **23a** (0.5 mmol) in hexamethylphosphoramide (1 ml), the mixtue was heated to 80 °C for 2 h and then poured into saturated aqueous solution of sodium hydrogencarbonate (10 ml). The mixture was extracted with ethyl acetate (10 ml) and the extract was washed with water (2 × 5 ml), dried over anhydrous sodium sulfate and evaporated. The residue was crystallized from methanol (**24**) or chromatographed of on silica gel (15 g) in ethyl acetate–toluene (22:3) and crystallized from acetone–ether (**27**).

Compound **24**: Yield 126 mg (77%). M.p. 176–177 °C. For $C_{13}H_{12}Cl_2N_4O_2$ (327.2) calculated: 47.72% C, 3.70% H, 21.67% Cl, 17.12% N; found: 47.67% C, 3.85% H, 21.85% Cl, 16.95% N. FAB MS, *m*/*z* (%): 329/327 (64/100) [M + H], 157/155 (5/15) [6-chloropurine + H].

^{1}H NMR: 2.34 dt, 1 H, *J*(6′,7′) = *J*(6′,5′a) = 4.7, *J*(6′,9′) = 2.0 (H-6′); 2.41 dt, 1 H, *J*(9′,6′) = 2.1, *J*(9′,CH_2) = 8.1 (H-9′); 3.61 d, 2 H, *J*(CH_2,9′) = 8.1 (CH_2Cl); 3.92 dd, 1 H, J_{gem} = 8.8, *J*(5′a,6′) = 4.4 (H-5′a); 4.01 d, 1 H, J_{gem} = 8.7 (H-5′b); 4.53 dd, 1 H, *J*(3′,7′) = 4.7, *J*(3′,1′) = 1.4 (H-3′); 4.67 m, 2 H (H-1′ and H-2′); 5.25 t, 1 H, *J*(7′,3′) = *J*(7′,6′) = 4.7 (H-7′); 8.55 s, 1 H (H-8); 8.80 s, 1 H (H-2). ^{13}C NMR: 43.43 (C-6′); 45.81 (CH_2Cl); 50.80 (C-9′); 64.10 (C-2′); 71.96 (C-5′); 80.70 (C-1′); 82.17 (C-7′); 83.07 (C-3′); 130.77 (C-5); 145.25 (C-8); 149.18 (C-6); 151.72 (C-2); 151.89 (C-4).

Compound **27**: Yield 127 mg (75%). M.p. 192–193.5 °C. For $C_{15}H_{16}Cl_2N_4O$ (339.2) calculated: 53.11% C, 4.75% H, 20.90% Cl, 16.52% N; found: 53.32% C, 4.82% H, 21.05% Cl, 16.25% N. FAB MS, *m/z* (%): 337/339 (59/100) [M + H], 157/155 (15/55) [6-chloropurine + H]. ^{1}H NMR: 0.67 m, 1 H (H-9′a); 1.33 m, 1 H (H-9′b); 1.83 m, 1 H (H-8′a); 1.95–2.03 m, 3 H (H-6′, 8′b and H-10′); 2.14–2.18 m, 2 H (H-1′ and H-7′); 3.58 d, 1 H, J_{gem} = 7.7 (H-5′a); 3.74–3.78 m, 2 H (CH^{a}H-Cl and H-5′b); 3.88 dd, 1 H, J_{gem} = 10.9, *J*(CH,10) = 7.3 (CH^{b}H-Cl); 4.53 dd, 1 H, *J*(2′,1′) = 4.1, *J*(2′,9′b) = 1.5 (H-2′); 4.73 d, 1 H, *J*(3′,7′) = 5.2 (H-3′); 8.79 s, 1 H (H-2); 8.80 s, 1 H (H-8). ^{13}C NMR: 11.19 (C-9′); 14.01 (C-8′); 29.76 (C-1′); 35.15 (C-7′); 39.25 (C-6′); 44.16 (C-10′); 47.44 (CH_2Cl); 62.92 (C-2′); 74.86 (C-5′); 75.91 (C-3′); 131.01 (C-5); 146.30 (C-8); 149.47 (C-6); 151.72 (C-2); 152.19 (C-4).

6-Chloro-9-[(1*R**,2*R**,3*S**,6*S**,7*S**,9*R**)-9-(fluoromethyl)-4,8-dioxatricyclo[4.2.1.0^{3,7}]-nonan-2-yl]-9*H*-purine (**25**) and
6-Chloro-9-[(1*R**,2*R**,3*R**,6*S**,7*S**,10*S**)-10-(fluoromethyl)-4-oxatricyclo[4.3.1.0^{3,7}]-decan-2-yl]-9*H*-purine (**28**)

(Diethylamino)sulfur trifluoride (DAST) (0.7 ml, 5 mmol) was added under argon to a stirred solution of chloropurine derivative **22a** or **23a** (1 mmol) and pyridine (1.3 ml) in dichloromethane (12 ml). The mixture was refluxed for 4 h and then it was poured under stirring into an aqueous saturated solution of potassium hydrogencarbonate (60 ml). The mixture was extracted with ethyl acetate (2 × 25 ml) and the combined extracts were washed with 10% aqueous solution of potassium hydrogencarbonate (20 ml), 5% hydrochloric acid (10 ml), and 10% aqueous potassium hydrogencarbonate (10 ml), dried over anhydrous sodium sulfate and evaporated. The residue was crystallized from ethyl acetate–ether (**25**) or chromatographed on silica gel (30 g) with ethyl acetate–toluene (22:3) (**28**) and subsequently crystallized from methanol.

Compound **25**: Yield 102 mg (33%). M.p. 176–179 °C. For $C_{13}H_{12}ClFN_4O_2$ (310.7) calculated: 50.25% C, 3.89% H, 11.41% Cl, 18.03% N; found: 50.01% C, 4.00% H, 11.51% Cl, 17.89% N. ESI MS, *m/z* (%): 313.1/311.0 (33/100) [M + H]. ^{1}H NMR: 2.24 dt, 1 H, *J*(6′,7′) = *J*(6′,5′a) = 4.6, *J*(6′,9′) = 2.1 (H-6′); 2.47 m, 1 H (H-9′); 3.90 ddd, 1 H, J_{gem} = 8.7, *J*(5′a,6′) = 4.3, *J*(5′a,F) = 1.5 (H-5′a); 4.02 d, 1 H, J_{gem} = 8.7 (H-5′b); 4.32 dt, 1 H, J_{gem} = *J*(CH,9′) = 9.3, *J*(CH,F) = 47.7 (CH^{a}H-F); 4.38 ddd, 1 H, J_{gem} = 9.1, *J*(CH,9′) = 6.5, *J*(CH,F) = 46.8 (CH^{b}H-F); 4.53 dd, 1 H, *J*(3′,7′) = 4.8, *J*(3′,1′) = 1.5 (H-3′); 4.67 s, 1 H (H-2′); 4.70 m, 1 H (H-1′); 5.23 m, 1 H (H-7′); 8.55 s, 1 H (H-8); 8.79 s, 1 H (H-2). ^{13}C NMR: 40.06 d, *J*(6′,F) = 7.2 (C-6′); 48.06 d, *J*(9′,F) = 19.1 (C-9′); 64.31 (C-2′); 71.85 (C-5′); 79.31 d, *J*(1′,F) = 4.8 (C-1′); 81.97 (C-7′); 82.87 d, *J*(CH_2,F) = 167.8; 83.19 (C-3′); 130.79 (C-5); 145.30 (C-8); 149.16 (C-6); 151.71 (C-2); 151.91 (C-4).

Compound **28**: Yield 101 mg (31%). M.p. 169–170 °C. For $C_{15}H_{16}ClFN_4O$ (322.8) calculated: 55.82% C, 5.00% H, 10.98% Cl, 17.36% N; found: 55.76% C, 5.11% H, 11.14% Cl, 17.21% N. FAB MS, *m/z* (%): 325/323 (37/100) [M + H], 157/155 (5/15) [6-chloropurine + H].

^{1}H NMR: 0.69 m, 1 H (H-9′a); 1.36 m, 1 H (H-9′b); 1.80 m, 1 H (H-8′a); 1.92 dt, 1 H, *J*(6′,5′b) = *J*(6′,7′) = 3.9, *J*(6′,3′) = 1.8 (H-6′); 2.00 m, 1 H (H-8′b); 2.03–2.10 m, 2 H (H-1′ and H-10′); 2.15 m, 1 H (H-7′); 3.58 d, 1 H, J_{gem} = 7.7 (H-5′a); 3.75 ddd, 1 H, J_{gem} = 7.7, *J*(5′b,6′) = 3.9, *J*(5′b,F) = 0.8 (H-5′b); 4.44 dd, 1 H, *J*(2′,1′) = 4.0, *J*(2′,9′b) = 1.5 (H-2′); 4.48–4.65 m, 2 H (CH_2F); 4.75 d, 1 H, *J*(3′,7′) = 5.2 (H-3′); 8.78 s, 1 H (H-2); 8.81 s, 1 H (H-8). ^{13}C NMR: 11.82 (C-9′); 14.19 (C-8′); 28.53 d, *J*(1′,F) = 5.0 (C-1′); 34.95 (C-7′); 36.09 d, *J*(6′,F) = 7.4 (C-6′); 41.75 d, *J*(10′,F) = 17.8 (C-10′); 63.04 (C-2′); 74.81 (C-5′); 75.99 (C-3′); 84.50 d, *J*(CH_2,F) = 166.9 (CH_2F); 131.02 (C-5); 146.33 (C-8); 149.46 (C-6); 151.70 (C-2); 152.22 (C-4).

6-Chloro-9-{[(1*R**,2*R**,3*S**,6*S**,7*S**,9*S**)-2-(6-chloro-9*H*-purin-9-yl)-4,8-dioxatricyclo-[4.2.1.0^{3,7}]nonan-9-yl]methyl}-9*H*-purine (**26**) and
6-Chloro-9-{[(1*R**,2*R**,3*S**,6*S**,7*S**,9*S**)-2-(6-chloro-9*H*-purin-9-yl)-4-oxatricyclo-[4.3.1.0^{3,7}]decan-10-yl]methyl}-9*H*-purine (**29**)

A solution of diisopropyl azodicarboxylate (0.2 ml) in tetrahydrofuran (1 ml) was added dropwise to a stirred suspension of chloropurine derivative **22a** or **23a** (0.5 mmol), 6-chloropurine (116 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) in tetrahydrofuran (5 ml). The resulting solution was left standing at room temperature overnight. The precipitated crystalline product was separated by filtration and washed with methanol and ether.

Compound **26**:Yield 176 mg (79%). M.p. 291 °C (decomp.). For $C_{18}H_{14}Cl_2N_8O_2$ (445.3) calculated: 48.55% C, 3.17% H, 15.92% Cl, 25.17% N; found: 48.35% C, 3.15% H, 16.02% Cl, 24.94% N. FAB MS, *m/z* (%): 447/445 (43/61) [M + H], 157/155 (18/40) [6-chloropurine + H]. ^{1}H NMR: 2.45 m, 1 H (H-6); 2.76 ddd, 1 H, *J*(9,6) = 2.1, *J*(9,CH_2) = 8.7 and 6.8 (H-9); 3.87 dd, 1 H, J_{gem} = 8.9, *J*(5a,6) = 4.3 (H-5a); 3.94 d, 1 H, J_{gem} = 8.8 (H-5b); 4.29 dd, 1 H, J_{gem} = 14.1, *J*(CH_2,9) = 6.7 and 4.37 dd, 1 H, *J*(CH_2,9) = 8.7 (CH_2N); 4.49 dd, 1 H, *J*(3,7) = 4.8, *J*(3,1) = 1.3 (H-3); 4.28 s, 1 H (H-2); 4.64 bs, 1 H (H-1); 5.28 t, 1 H, *J*(7,3) = *J*(7,6) = 4.8 (H-7); 8.49 s, 1 H and 8.80 s, 1 H (H-8′, H-8′′); 8.76 s, 1 H and 8.79 s, 1 H (H-2′, H-2′′). ^{13}C NMR: 42.50 (C-6); 45.44 (CH_2N); 48.05 (C-9); 64.21 (C-2); 71.97 (C-5); 80.58 (C-1); 82.23 (C-7); 83.11 (C-3); 130.67 and 131.00 (C-5′, C-5′′); 145.17 and 147.87 (C-8′, C-8′′); 149.09 and 149.14 (C-6′, C-6′′); 151.66 and 151.76 (C-2′, C-2′′); 151.82 and 152.55 (C-4′, C-4′′).

Compound **29**: Yield 127 mg (84%). M.p. 360 °C (decomp.). For $C_{20}H_{18}Cl_2N_8O$ (457.3) calculated: 52.53% C, 3.97% H, 15.50% Cl, 24.50% N; found: 52.27% C, 3.89% H, 15.75% Cl, 24.32% N. FAB MS, *m/z* (%): 501/459/457 (2/8/13) [M + H], 157/155 (25/100) [6-chloropurine + H]. ^{1}H NMR: 0.75 m, 1 H (H-9a); 1.28 m, 1 H (H-1); 1.66 m, 1 H (H-9b); 1.98 m, 1 H (H-8a); 2.06–2.13 m, 2 H (H-6 and H-8b); 2.20 m, 1 H (H-7); 2.46 m, 1 H (H-10); 3.38 m, 1 H (H-5a); 3.65 dd, 1 H, J_{gem} = 7.9, *J*(5b,6) = 3.9 (H-5b); 4.40 bd, 1 H, *J*(2,1) = 3.9 (H-2); 4.47 dd, 1 H, J_{gem} = 14.0, *J*(CH,10) = 8.0 and 4.52 dd, 1 H, *J*(CH,10) = 8.5 (CH_2N); 4.73 d, 1 H, *J*(3,7) = 5.1 (H-3); 8.74 s, 1 H and 8.81 s, 1 H (H-2′, H-2′′); 8.76 s, 1 H and 8.86 s, 1 H (H-8′, H-8′′). ^{13}C NMR: 9.72 (C-9); 14.14 (C-8); 29.67 (C-1); 35.21 (C-7); 38.07 (C-6); 41.60 (C-10); 46.82 (CH_2N); 63.10 (C-2); 74.75 (C-5); 75.95 (C-3); 130.97 and 131.03 (C-5′, C5′′); 146.43 and 147.85 (C-8′, C-8′′); 149.32 and 149.43 (C-6′, C-6′′); 151.66 and 151.83 (C-2′, C-2′′); 152.21 and 152.34 (C-4′, C-4′′).

The authors are indebted to Ms J. Sklenářová for excellent technical assistance and to the staff of the Analytical Laboratory of the Institute for elemental analyses. This study, a part of the research project Z4 055 0506, was supported by the Ministry of Education, Youth and Sports of the Czech Republic (Centre for New Antivirals and Antineoplastics No. 1M0508), the Programme of Targeted Projects of Academy of Sciences of the Czech Republic (1QS400550501), and Gilead Sciences, Inc. (Foster City, CA, U.S.A.).

REFERENCES

1. a) Crimmins M. T., King B. W.: *J. Org. Chem.* **1996**, *61*, 4192; b) Daluge S. M., Good S. S., Faletto M. B., Miller W. H., StClair M. H., Boone L. R., Tisdale M., Parry N. R., Reardon J. E., Dornsife R. E., Averett D. R., Krenitski T. A.: *Antimicrob. Agents Chemother.* **1997**, *41*, 1082; c) Hervey P. S., Perry C. M.: *Drugs* **2000**, *60*, 447.
2. Bisacchi G. S., Chao S. T., Bachard C., Daris J. P., Innaimo S., Jacobs G. A., Kocy O., Lapointe P., Martel A., Merchant Z., Slusarchyk W. A., Sundeen J. E., Young M. G., Colonno R., Zahler B.: *Bioorg. Med. Chem. Lett.* **1997**, *7*, 127.
3. Kim H. S., Jacobson K. A.: *Org. Lett.* **2003**, *5*, 1665.
4. Ohno M., Costanzi S., Kim H. S., Kempeneers V., Vastmans K., Herdewijn P., Maddileti S., Gao Z.-G., Harden T. K., Jacobson K. A.: *Bioorg. Med. Chem.* **2004**, *12*, 5619.
5. Hřebabecký H., Masojídková M., Holý A.: *Collect. Czech. Chem. Commun.* **2005**, *70*, 103.
6. Hřebabecký H., Dračínský M., Holý A.: *Collect. Czech. Chem. Commun.* **2007**, *71*, 1331.
7. Hřebabecký H., Masojídková M., Holý A.: *Collect. Czech. Chem. Commun.* **2005**, *70*, 519.
8. Hřebabecký H., Masojídková M., Dračínský M., Holý A.: *Collect. Czech. Chem. Commun.* **2006**, *71*, 871.
9. Dejmek M., Hřebabecký H., Dračínský M., Holý A.: *Collect. Czech. Chem. Commun.* **2007**, *72*, 1523.
10. Hřebabecký H., Dračínský M., Holý A.: *Collect. Czech. Chem. Commun.* **2008**, *73*, 44.
11. a) Šála M., Hřebabecký H., Masojídková M., Holý A.: *Collect. Czech. Chem. Commun.* **2006**, *71*, 635; b) Šála M., Hřebabecký H., Dračínský M., Holý A.: *Conference Book IRT-17 International Roundtable on Nucleosides, Nucleotides and Nucleic Acids*, p. 217. DCB University of Bern, Bern 2006.
12. Šála M., Hřebabecký H., Dračínský M., De Palma A., Neyts J., Holý A.: *Antiviral Res.* **2007**, *74*, A52.
13. Yin-Murphy M., Almond J. W. in: *Medicinal Microbiology* (S. Baron, Ed.), 4th ed., Section 2, http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=mmed.chapter.2833. The University of Texas, Medical Branch at Galveston 1996.
14. De Palma A. M., Vliegen I., De Clercq E., Neyts J.: *Med. Res. Rev.* **2008**, *28*, 823.
15. Kappe O. C., Murphree S. S., Padwa A.: *Tetrahedron* **1997**, *53*, 14179.
16. Inokuma S., Sugie A., Moriguchi K., Katsube J.: *Heterocycles* **1983**, *20*, 1109.
17. Koch H.: *Monatsh. Chem.* **1962**, *93*, 1343.
18. Patil R. T., Parveen G., Gumaste V. K., Bhawal B. H., Deshmukh A. R. A. S.: *Synlett* **2002**, 1455.
19. Hřebabecký H., Masojídková M., Holý A.: *Collect. Czech. Chem. Commun.* **2004**, *69*, 435.
20. a) Greenberg S. M., Ross L. O., Robins R. K.: *J. Org. Chem.* **1959**, *24*, 1314; b) Bhushan R. S., Vince R.: *Bioorg. Med. Chem.* **2002**, *10*, 2325; c) Legraverend M., Boumchita H., Bisagni E: *Synthesis* **1990**, 587.