# SYNTHESIS OF NOVEL CARBOCYCLIC NUCLEOSIDES AND PRO-TIDES DERIVED FROM 4-OXATRICYCLO[4.2.1.0$^{3,7}$]NONANE-9-METHANOL

Hubert HŘEBABECKÝ[1,*], Martin DRAČÍNSKÝ[2] and Antonín HOLÝ[3]

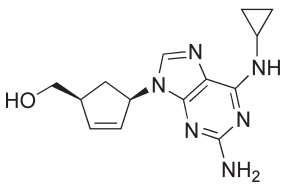
*Centre for New Antivirals and Antineoplastics, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, v. v. i., 166 10 Prague 6, Czech Republic; e-mail: [1] hubert@uochb.cas.cz, [2] dracinsky@uochb.cas.cz, [3] holy@uochb.cas.cz*

Received June 7, 2007
Accepted August 13, 2007

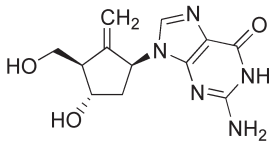
(1*R**,2*R**,3*R**,6*R**,7*S**)-2-Amino-4-oxatricyclo[4.2.1.0$^{3,7}$]nonane-9-methanol (**9**) was prepared from (1*R**,2*R**,3*R**,4*S**)-bicyclo[2.2.1]hept-5-ene-2,3-dimethanol by treatment with benzyl azidoformate followed by hydrogenolysis. The amine **9** was transformed to thymine and purine nucleoside analogues. The prepared analogues were converted to corresponding Pro-Tides by treatment with methyl *N*-[chloro(phenoxy)phosphoryl]-L-alaninate in the presence of 1-methylimidazole or *tert*-butylmagnesium chloride.

**Keywords**: Nucleosides; Purines; Pyrimidines; Pro-drugs; Pro-nucleotides; Phosphoramidates; Antiviral activity.

Various structural modifications of natural nucleosides have led to analogues with important biological activities[1]. Carbocyclic nucleosides, in which a methylene unit replaces the furanose oxygen atom, are potentially active therapeutic agents. U.S. Food and Drug Administration approved abacavir (Ziagen™)[2] (**1**) for the treatment of HIV-1 infections and entecavir (Baraclude)[3] (**2**) for the treatment of chronic hepatitis B virus (HBV) infections (Chart 1).




**1**




**2**

CHART 1

Collect. Czech. Chem. Commun. 2007, Vol. 72, No. 10, pp. 1331–1349

doi:10.1135/cccc20071331

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[4]. Bisphosphate of the 2-iodo-(6-methylamino)purine analogue containing this ring system displayed potent binding affinity to the human $P2Y_1$ receptor[5]. The bicyclo[2.2.1]-heptane (norbornane) ring is conformationally locked carbapentofuranose and/or carbahexopyranose ring system. Recently, 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[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], and analogues[9] with a bicyclo[2.2.1]heptene or -heptane ring substituted with nucleobase at position 7. Nucleoside analogues **3**–**6** (Chart 2) exhibit certain activity in tests for anti-HIV-1 and anti-HIV-2 activity in human T-lymphocyte (CEM) cells.

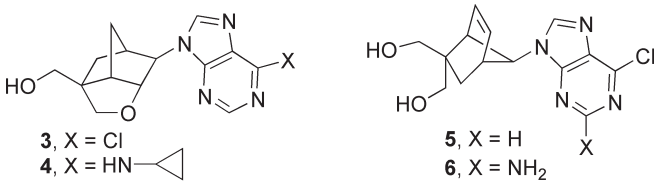



CHART 2

The antiviral or anticancer effect of chemotherapeutic nucleoside analogues is exerted only after intracellular phosphorylation to related nucleotides. The efficiency of intracellular phosphorylation can limit therapeutic potential of nucleoside analogues. Also preformed phosphates have a limited utility due to their poor membrane permeation. Therefore, a wide variety of phosphate pro-drug approaches[10], known as ′Pro-Tide′ methods, was elaborated. One such approach based on aryl phosphoramidates was introduced by McGuigan and co-workers[11].

This study concerns syntheses of novel racemic carbocyclic nucleosides derived from 4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-9-methanol and preparation of the corresponding McGuigan's Pro-Tides. The Pro-Tides with a 4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-6-methanol scaffold[6] were also prepared (Chart 3).

Treatment of bis(hydroxymethyl) derivative **7**, which was obtained by reduction of diethyl *trans*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate[12] with lithium aluminium hydride[13], with benzyl azidoformate[14] afforded carba-

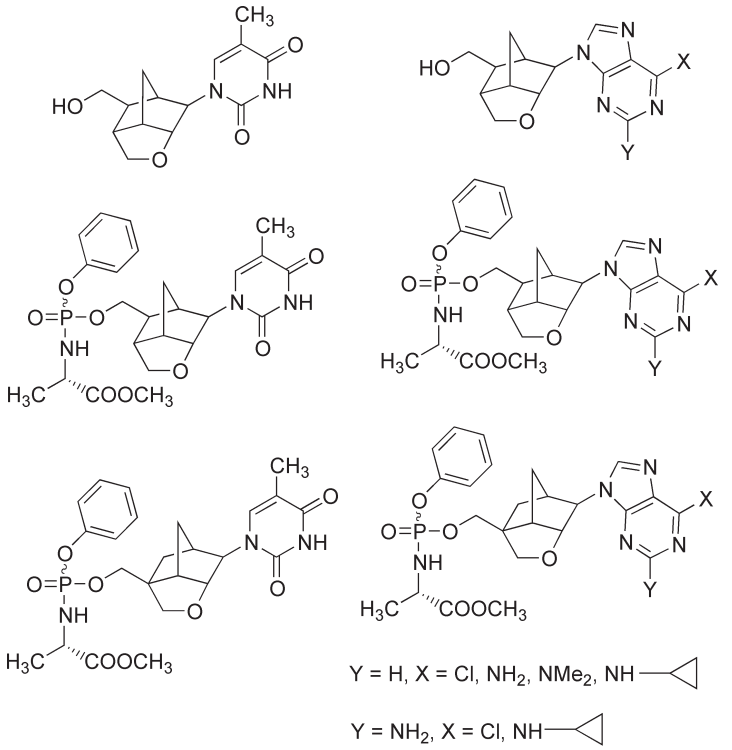
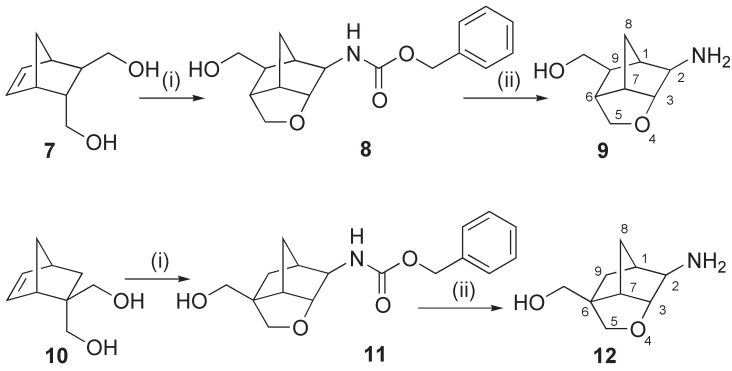



CHART 3

mate **8**. Oakland and Scheinmann[15] obtained (4-oxatricyclo[4.2.1.$0^{3,7}$]non-2-yl)carbamate by vacuum destilation of *exo*-adducts of ethyl azidoformate with 5-*endo*-(hydroxymethyl)norborn-2-ene. Hydrogenolysis of the carbamate **8** led to amine **9**. Using of the same procedure, compound **10** afforded amine **12**, which was recently prepared in an alternative way[6] (Scheme 1). Reaction of norbornene derivatives **7** and/or **10** with benzyl azidoformate, which is initiated by heating to ~68 °C, is strongly exothermic. Carbamates **8** and **11** were obtained in 88 and 83% yields, respectively.

The reaction of amines **9** or **12** with *N*-acylcarbamate[7–9] **13** (Scheme 2) in 1,4-dioxane at 100 °C followed by treatment with Dowex 50 ($H^+$ form) afforded thymine derivatives **14** (48%) or **15** (55%).

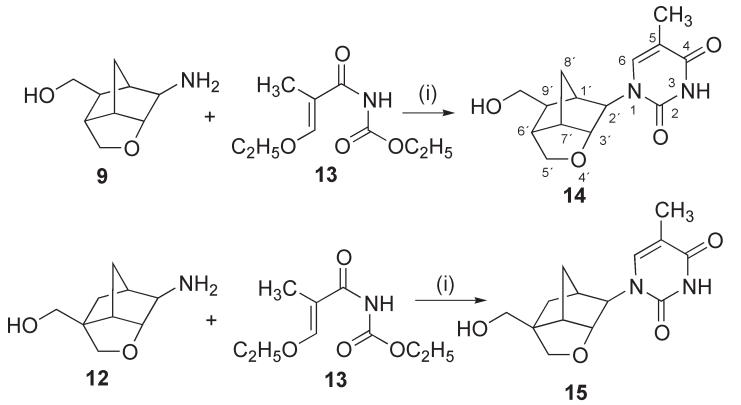
Conversion of amines **9** and **12** to the 6-chloropurine derivatives was performed by the described procedures[6–9,16,17] (Scheme 3). Coupling of amine **9** with 4,6-dichloropyrimidin-5-amine or 4,6-dichloropyrimidin-2,5-diamine[17c] in ethanol and triethylamine gave pyrimidinylamino derivatives **16** (91%)




(i) $N_3COOBn$, 88% of **8**, 83% of **11**; (ii) $H_2$, $Pd(OH)_2/C$, 92% of **9**, 93% of **12**

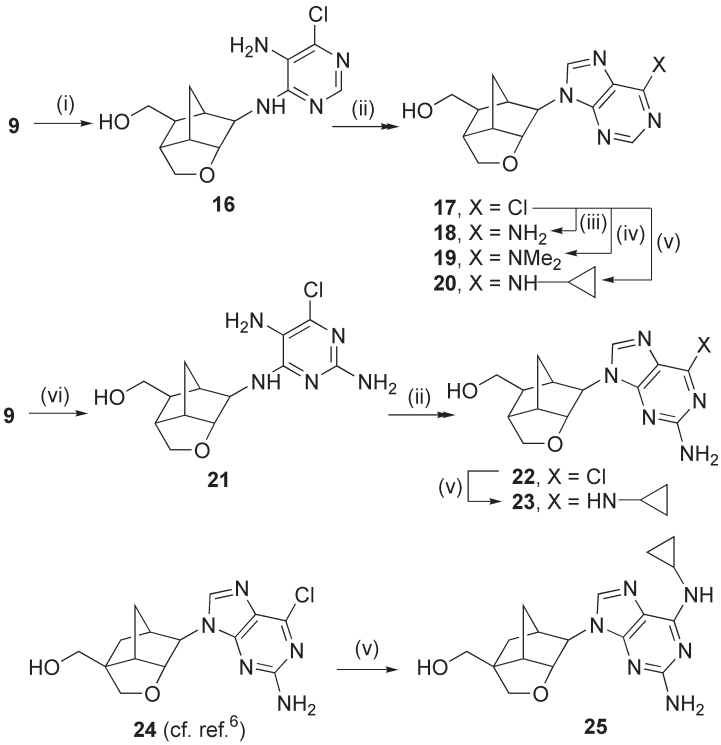
SCHEME 1

or **21** (73%). Ring closure of **16** or **21** with triethyl orthoformate in the presence of concentrated hydrochloric acid afforded 6-chloropurine derivative **17** (80%) or **22** (71%). The chloropurine **17** was ammonolyzed with liquid ammonia at 70 °C to give adenine derivative **18** (87%). Treatment of **17**




(i) 1. 1,4-dioxane, 100 °C, 2. Dowex 50 ($H^+$), 100 °C, 48% of **14**, 55% of **15**

SCHEME 2



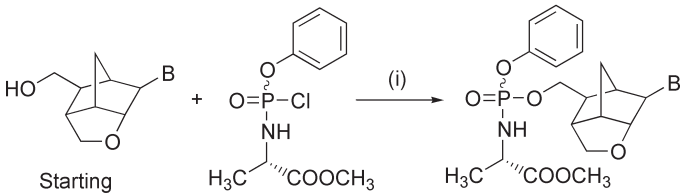

(i) 4,6-dichloropyrimidin-5-amine/TEA/EtOH, 100 °C, 91%; (ii) 1. $CH(OEt)_3$/HCl, 2. THF/$H_2O$/HCl, 80%; (iii) $NH_3$(l), 87%; (iv) $Me_2NCOO^-Me_2NH_2^+$, 82%; (v) cyclopropylamine, 85% of **20**, 84% of **23**, 78% of **25**; (vi) 4,6-dichloropyrimidine-2,5-diamine/TEA/EtOH, 100 °C, 73%

SCHEME 3

with dimethylammonium dimethylcarbamate afforded 6-(dimethylamino)-purine derivative **19** (82%). Aminolysis of **17**, **22** or **24** with cyclopropylamine led to cyclopropylamino derivative **20** (85%), **23** (84%) or **25** (87%).

The prepared compounds were converted to the corresponding Pro-Tides by reaction of a nucleoside with *N*-[chloro(phenoxy)phosphoryl]-L-alaninate[18] **26** using two diferent methods. The reaction of compounds **14**, **15**, **17**, **19**, **27**, and **29**, which do not contain any primary or secondary amino group, with **26** in tetrahydrofuran was mediated by 1-methylimidazole[18] (method *A*, Schemes 4 and 5). The analogues **18**, **20**, **23**, **25**, **28**, and

**30** bearing amino or cyclopropylamino group were treated with *tert*-butylmagnesium chloride in tetrahydrofuran[19] and then with phosphorochloridate **26** (method *B*, Schemes 4 and 5). Phosphate derivatives were obtained in 59–81% yields. The reactions yielded a 1:1:1:1 mixture of diastereomers (determined by NMR) because of the chiral phosphorus. Attempts to separate the mixtures were not successful. McGuigan and co-workers[18] described separation of diastereomeric abacavir 5′-[phenyl-(methoxy-L-alaninyl)]phosphate using supercritical fluid chromatography with a Chiralpak AS column and methanol in carbon dioxide as eluent. The authors found that the diastereomeric mixtures showed the some activity (within experimental deviation) as the more potent of the purified isomers since the chirality at phosphorus is removed in the first step of conversion of the Pro-Tide to monophosphate. Therefore, we used the prepared mixtures of diastereomers in tests for antiviral activity.



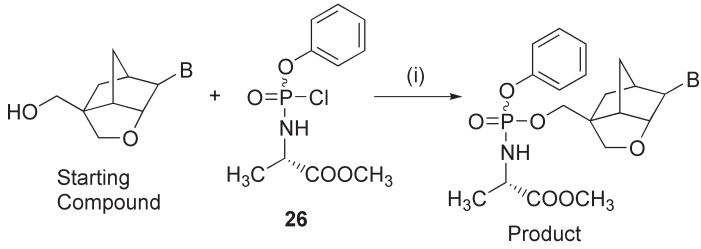

B = nucleoside base

(i) method *A*, 1-methylimidazole/THF; method *B*, *t*-BuMgCl/THF

| Starting compound | Product | Nucleoside base | Method | Yield, % |
|---|---|---|---|---|
| **14** | **31** | thymin-1-yl | *A* | 68 |
| **17** | **32** | 6-chloropurin-9-yl | *A* | 75 |
| **18** | **33** | adenin-9-yl | *B* | 64 |
| **19** | **34** | 6-(dimethylamino)-purin-9-yl | *A* | 63 |
| **20** | **35** | 6-(cyclopropylamino)-purin-9-yl | *B* | 74 |
| **23** | **36** | 2-amino-6-(cyclopropylamino)purin-9-yl | *B* | 63 |

SCHEME 4

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.




B = nucleoside base

(i) method *A*, 1-methylimidazole/THF; method *B*, *t*-BuMgCl/THF

| Starting compound | Product | Nucleoside base | Method | Yield, % |
|---|---|---|---|---|
| **15** | **37** | thymin-1-yl | *A* | 76 |
| **25** | **38** | 2-amino-6-(cyclopropylamino)purin-9-yl | *B* | 64 |
| **27**[a] | **39** | 6-chloropurin-9-yl | *A* | 81 |
| **28**[a] | **40** | adenin-9-yl | *B* | 59 |
| **29**[a] | **41** | 6-(dimethylamino)-purin-9-yl | *A* | 65 |
| **30**[a] | **42** | 6-(cyclopropylamino)-purin-9-yl | *B* | 67 |

[a] Ref.[6]

SCHEME 5

In conclusion, novel racemic conformationally locked carbocyclic nucleoside analogues of thymine, 6-chloropurine, adenine, 6-(dimethylamino)purine, 6-(cyclopropylamino)purine, and 2-amino-6-chloropurine derived from 4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-9-methanol and their phenyl *N*-[(*S*)-1-(methoxycarbonyl)ethyl]phosphoramidates were prepared. 4-Oxatricyclo[4.2.1.$0^{3,7}$]nonane-6-methanol analogues bearing the same bases were also synthesized. The target compounds were tested for anti-HIV-1 and anti-HIV-2 activities in human T-lymphocyte (CEM) cells. Preliminary data showed that only compound **17** and its Pro-Tide derivatives exhibit a weak activity almost comparable with their cytotoxicity (**17**: $EC_{50}$ 13 μM and $CC_{50}$ 28.3 ± 3.6 μM; **32**: $EC_{50}$ 7.3 μM and $CC_{50}$ 16.9 ± 0.35 μM)[20].

## 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 and/or Bruker Avance-500 instruments (500 MHz for $^1$H and 125.7 MHz for $^{13}$C) in hexadeuterated dimethyl sulfoxide and 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). 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.

Benzyl *N*-[(1*R**,2*R**,3*R**,6*R**,7*S**,9*S**)-9-(Hydroxymethyl)-4-oxatricyclo[4.2.1.0$^{3,7}$]non-2-yl]carbamate (**8**)

A mixture of alcohol **7** (6.17 g, 40 mmol), benzyl azidoformate (8.68 g, 49 mmol), and toluene (10 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 applied onto a silica gel column (300 g) and eluted with ethyl acetate. 10.65 g (88%) of compound **8** was obtained as syrup. For $C_{17}H_{21}NO_4$ (303.4) calculated: 67.31% C, 6.98% H, 4.62% N; found: 67.01% C, 7.12% H, 4.39% N. FAB MS, *m/z* (rel.%): 304 (4) [M + H], 91 (100). $^1$H NMR: 1.31 brtd, 1 H, *J*(9,1) ~ *J*(9,8a) = 1.0, *J*(9,6) = 2.4, *J*(9,$CH_2$) = 7.3 (H-9); 1.54 dm, 1 H, $J_{gem}$ = 11.0 (H-8b); 1.61 dm, 1 H (H-8a); 1.87 td, 1 H, *J*(6,5a) = *J*(6,7) = 4.0 (H-6); 1.99 m, 1 H (H-1); 2.43 ddq, 1 H, *J*(7,1) ~ *J*(7,8a) ~ *J*(7,8) = 1.2, *J*(7,3) = 4.9 (H-7); 2.96 brdd, 1 H, *J*(2,1) ~ *J*(2.3) = 1.0, *J*(2,8b) = 1.2, *J*(2,NH) = 6.5 (H-2); 3.25 ddd, 1 H and 3.29 ddd, 1 H, *J*(CH,9) = 7.3, *J*(CH,OH) = 5.5, $J_{gem}$ = 10.7 ($CH_2O$); 3.58 d, 1 H, $J_{gem}$ = 7.8 (H-5b); 3.64 d, 1 H (H-5a); 3.91 brd, 1 H, *J*(3,1) = 1.2 (H-3); 5.01 s, 2 H (Ph$CH_2$O); 7.30–7.35 m, 6 H (NH, arom.). $^{13}$C NMR: 31.18 (C-8); 41.37 (C-6); 44.41 (C-7); 44.41 (C-1); 50.55 (C-9); 62.97 ($CH_2O$); 63.03 (C-2); 65.38 (Ph$CH_2$O); 73.91 (C-5); 85.34 (C-3); 127.92, 128.04, 2 C, 128.54, 2 C, 137.35 (arom.); 155.59 (C=O).

(1*R**,2*R**,3*R**,6*R**,7*S**,9*S**)-2-Amino-4-oxatricyclo[4.2.1.0$^{3,7}$]nonane-9-methanol (**9**)

Palladium(II) hydroxide on carbon (20% Pd, 500 mg) was added to a solution of protected amine **8** (9.10 g, 30 mmol) in methanol (200 ml) and the mixture was stirred under hydrogen atmosphere at room temperature for 7 h. The catalyst was filtered off with a Celite pad, washed with methanol and the filtrates were evaporated. The residue was mixed with ether and the resulting crystalline compound was filtered off. It was obtained 4.62 g (92%) of amine **9**, m.p. 102–104 °C. For $C_9H_{15}NO_2$ (169.2) calculated: 63.88% C, 8.93% H, 8.28% N; found: 63.93% C, 8.98% H, 8.21% N. FAB MS, *m/z*: 170 [M + H]. $^1$H NMR: 1.23 brddd, 1 H, *J*(9,1) ~ *J*(9,8a) = 1.0, *J*(9,6) = 2.4, *J*(9,$CH_2$) = 7.2 and 8.6 (H-9); 1.46 dq, 1 H, *J*(8b,1) = *J*(8b,2) = *J*(8b,7) = 1.5, $J_{gem}$ = 10.4 (H-8b); 1.77 m, 1 H (H-1); 1.78 dm, 1 H (H-8a); 1.85 td, 1 H, *J*(6,5a) = *J*(6,7) = 4.0 (H-6); 2.38 brt, 1 H, *J*(2,1) = 1.2 (H-2); 2.38 ddq, 1 H, *J*(7,1) = *J*(7,8a) = 1.5, *J*(7,3) = 5.0 (H-7); 3.26 dd, 1 H, *J*(CH,9) = 7.2 and 3.30 dd, 1 H, *J*(CH,9) = 8.6, $J_{gem}$ = 10.6 ($CH_2O$); 3.52 d, 1 H, *J*(5b,8a) = 1.0, $J_{gem}$ = 7.7 (H-5b); 3.61 dd, 1 H (H-5a); 3.63 brd, 1 H, *J*(3,1) = 1.2, *J*(3,8b) = 0.5 (H-3); 4.50 brs, 3 H ($NH_2$, OH). $^{13}$C NMR: 30.83 (C-8); 41.49 (C-6); 43.64 (C-1); 44.38 (C-7); 50.99 (C-9); 63.27 ($CH_2O$); 63.52 (C-2); 73.69 (C-5); 87.28 (C-3).

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

A mixture of alcohol **10** (6.17 g, 40 mmol), benzyl azidoformate (8.68 g, 49 mmol), and toluene (10 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 stirred at 75 °C for 0.5 h. After cooling, ethyl acetate (10 ml) was added and the mixture was set aside at room temperature for 2 h. The deposited crystals were filtered off, washed with toluene–ethyl acetate (1:1) and ether. It was obtained 9.52 g (78%) of protected amine **11**, m.p. 145–146 °C. The combined mother liquors were evaporated. Chromatography of the residue on a silica gel column (50 g) with ethyl acetate followed by crystallization from toluene–ethyl acetate (1:1) gave another crop (620 mg, 5%) of **11**. For $C_{17}H_{21}NO_4$ (303.4) calculated: 67.31% C, 6.98% H, 4.62% N; found: 67.27% C, 6.97% H, 4.63% N. FAB MS, *m/z* (rel.%): 304 (15) [M + H], 91 (100). $^1$H NMR: 1.10 dd, 1 H, *J*(9b,8a) = 2.0, $J_{gem}$ = 12.6 (H-9b); 1.41 dq, 1 H, *J*(8b,1) ~ *J*(8b,2) ~ *J*(8b,7) = 1.4, $J_{gem}$ = 10.9 (H-8b); 1.52 dd, 1 H, *J*(9a,1) = 4.4 (H-9a); 1.65 dm, 1 H (H-8a); 2.03 dm, 1 H, *J*(1,7) ~ *J*(1,8a) ~ *J*(1,8b) = 1.0 (H-1); 2.30 dq, 1 H, *J*(7,1) ~ *J*(7,8a) ~ *J*(7,8b) = 1.2, *J*(7,3) = 5.1 (H-7); 3.05 dd, 1 H, *J*(2,8b) = 1.6, *J*(2,NH) = 6.5 (H-2); 3.32 d, 1 H, *J*($CH_2$,OH) = 5.4 ($CH_2O$); 3.58 d, 1 H and 3.68 d, 1 H, $J_{gem}$ = 7.8 (2 × H-2); 3.97 brd, 1 H, *J*(3,1) = 1.0 (H-3); 4.71 t, 1 H (OH); 4.99 d, 1 H and 5.02 d, 1 H, $J_{gem}$ = 12.6 (Ph$CH_2$O); 7.28 d, 1 H (NH); 7.35–7.40 m, 5 H (arom.). $^{13}$C NMR: 32.66 (C-9); 38.56 (C-8); 46.33 (C-1); 46.335 (C-7); 49.45 (C-6); 62.66 (C-2); 63.91 ($CH_2O$); 65.39 (Ph$CH_2$O); 76.60 (C-5); 86.74 (C-3); 127.98, 128.05, 2 C, 128.54, 2 C, 137.33 (arom.); 155.59 (C=O).

(1*R**,2*R**,3*R**,6*R**,7*S**)-2-Amino-4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-6-methanol (**12**)

Carbamate **11** (9.10 g, 30 mmol) was hydrogenolyzed in the same way as compound **9**. The catalyst was filtered off with a Celite pad, washed with methanol and the filtrates were evaporated. The residue was applied onto a column of Dowex 50 ($H^+$ form, 120 ml)). Elution was carried out with water (500 ml), methanol (500 ml), and then continued with 5% aqueous ammonia. 4.72 g (93%) of amine **12** was obtained as syrup. For $C_9H_{15}NO_2$ (169.2) calculated: 63.88% C, 8.93% H, 8.28% N; found: 64.01% C, 9.01% H, 8.09% N. FAB MS, *m/z*: 170 [M + H]. $^1$H NMR: 1.01 dd, 1 H, $J_{gem}$ = 12.4, *J*(9a,1) = 2.6 (H-9a); 1.33 dm, 1 H, $J_{gem}$ = 10.2 (H-8a); 1.48 ddd, 1 H, $J_{gem}$ = 12.4, *J*(9b,1) = 4.3, *J*(9b,5b) = 0.9 (H-9b); 1.78–1.84 m, 2 H (H-1, H-8b); 2.24 dq, 1 H, *J*(7,3) = 5.0, *J*(7,8a) = *J*(7,8b) = *J*(7,1) = 1.4 (H-7); 2.46 m, 1 H (H-2); 3.31 s, 2 H ($CH_2O$); 3.50 d, 1 H, $J_{gem}$ = 7.6 (H-5a); 3.65 dd, 1 H, $J_{gem}$ = 7.6, *J*(5b,9b) = 0.9 (H-5b); 3.68 dd, 1 H, *J*(3,7) = 5.0, *J*(3,8a) = 1.3 (H-3). $^{13}$C NMR: 32.17 (C-8); 39.03 (C-9); 42.15 (C-1); 46.28 (C-7); 49.39 (C-6); 63.12 (C-2); 64.15 ($CH_2O$); 76.47 (C-5); 88.84 (C-3).

1-[(1*R**,2*R**,3*R**,6*R**,7*S**,9*S**)-9-(Hydroxymethyl)-4-oxatricyclo[4.2.1.$0^{3,7}$]nonan-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**14**) and
1-[(1*R**,2*R**,3*R**,6*R**,7*S**)-6-(Hydroxymethyl)-4-oxatricyclo[4.2.1.$0^{3,7}$]nonan-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**15**)

A solution of amine **9** or **12** (169 mg, 1 mmol) and *N*-acylcarbamate **13** (201 mg, 1 mmol) in 1,4-dioxane (9 ml) was heated at 100 °C for 3 h. Dowex 50 ($H^+$ form, 3 ml) was washed with 1,4-dioxane and then added to the mixture. The mixture was heated at 100 °C for 3 h, the resin was filtered off, washed with dioxane and the collected filtrates were evaporated.

*1-[(1R*,2R*,3R*,6R*,7S*,9S*)-9-(Hydroxymethyl)-4-oxatricyclo[4.2.1.0$^{3,7}$]nonan-2-yl]-5-methylpyrimidine-2,4(1H,3H)-dione* (**14**): Yield after crystallization from ether 134 mg (48%), m.p. 234.5–237 °C. For $C_{14}H_{18}N_2O_4$ (278.3) calculated: 60.42% C, 6.52% H, 10.07% N; found: 60.19% C, 6.62% H, 9.80% N. FAB MS, *m/z* (rel.%): 279 (100) [M + H], 127 (70). $^1$H NMR: 1.77 s, 3 H ($CH_3$); 1.44 tm, 1 H, *J*(9′,1′) ~ *J*(9′,8′a) = 1.2, *J*(9′,6′) = 2.4, *J*(9′,$CH_2$) = 7.8 (H-9′); 1.53 dm, 1 H, $J_{gem}$ = 11.0 (H-8′b); 1.73 dm, 1 H (H-8′a); 1.97 td, 1 H, *J*(6′,5′a) ~ *J*(6′,7′) = 4.0 (H-6′); 2.27 m, 1 H (H-1′); 2.57 ddq, 1 H, *J*(7′,1′) ~ *J*(7′,8′a) ~ *J*(7′,8′b) = 1.5, *J*(7′,3′) = 5.0 (H-7′); 3.34 m, 2 H ($CH_2O$); 3.61 brd, 1 H, *J*(2′,1′) ~ *J*(2′,3′) = 1.0, *J*(2′,8′b) = 1.6 (H-2′); 3.65 d, 1 H, $J_{gem}$ = 7.8 (H-5′b); 3.70 dd, 1 H, *J*(5′a,6′) = 3.8 (H-5′a); 4.36 brd, 1 H, *J*(3′,1′) ~ *J*(3′,2′) = 1.0 (H-3′); 4.67 brs, 1 H (OH); 7.43 s, 1 H (H-6); 11.25 s, 1 H (NH). $^{13}$C NMR: 12.32 ($CH_3$); 31.86 (C-8′); 40.21 (C-1′); 41.55 (C-6′); 44.99 (C-7′); 51.05 (C-9′); 62.75 ($CH_2O$); 68.12 (C-2′); 73.87 (C-5′); 83.79 (C-3′); 108.11 (C-5); 138.26 (C-6); 151.26 (C-2); 163.95 (C-4).

*1-[(1R*,2R*,3R*,6R*,7S*)-6-(Hydroxymethyl)-4-oxatricyclo[4.2.1.0$^{3,7}$]nonan-2-yl]-5-methylpyrimidine-2,4(1H,3H)-dione* (**15**): Yield after crystallization from ethanol 153 mg (55%), m.p. 231.5–233 °C. For $C_{14}H_{18}N_2O_4$ (278.3) calculated: 60.42% C, 6.52% H, 10.07% N; found: 60.25% C, 6.61% H, 9.99% N. FAB MS, *m/z*: 279 [M + H]. $^1$H NMR: 1.23 d, 1 H, $J_{gem}$ = 12.7 (H-9′b); 1.59 m, 2 H (2 × H-8′); 1.65 dd, 1 H, *J*(9′a,1) = 4.4, $J_{gem}$ = 12.8 H-9′a); 1.77 s, 3 H ($CH_3$); 2.31 brd, 1 H, *J*(1′,9′a) = 4.1 (H-1′); 2.45 brd, 1 H, *J*(7′,3′) = 4.8 (H-7′); 3.36 m, 2 H ($CH_2O$); 3.65 d, 1 H, $J_{gem}$ = 7.7 (H-5′a); 3.72 s, 1 H (H-2′); 3.73 d, 1 H (H-5′b); 4.42 d, 1 H (H-3′); 4.80 t, 1 H, *J*(OH,$CH_2$) = 5.3 (OH); 7.43 s, 1 H (H-6); 11.24 s, 1 H (NH). $^{13}$C NMR: 12.26 ($CH_3$); 33.31 (C-8′); 38.84 (C-1′); 39.06 (C-9′); 46.94 (C-7′); 49.71 (C-6′); 63.68 ($CH_2O$); 67.56 (C-2′); 76.44 (C-5′); 85.24 (C-3′); 108.13 (C-5); 138.20 (C-6); 151.26 (C-2); 163.95 (C-4).

(1*R**,2*R**,3*R**,6*R**,7*S**,9*S**)-2-[(5-Amino-6-chloropyrimidin-4-yl)amino]-4-oxatricyclo[4.2.1.0$^{3,7}$]nonane-9-methanol (**16**)

A solution of amine **9** (1.015 g, 6 mmol), 4,6-dichloropyrimidin-5-amine (1.48 g, 9 mmol), and triethylamine (1.8 ml) in ethanol (18 ml) was heated in a pressure vessel at 100 °C for 6 days and, after cooling, was taken down. Chromatography on a silica gel column (100 g) in ethyl acetate–acetone–ethanol–water (95:15:9:6) followed by crystallization from ethanol–ether afforded 1.62 g (91%) of compound **16**, m.p. 217–218 °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: 52.47% C, 5.83% H, 11.76% Cl, 18.65% N. FAB MS, *m/z* (rel.%): 299/297 (38/100) [M + H], 263 (84). $^1$H NMR: 1.42 brtd, 1 H, *J*(9,1) ~ *J*(9,8a) = 1.0, *J*(9,6) = 2.4, *J*(9,$CH_2$) = 7.4 (H-9); 1.63 dq, 1 H, *J*(8b,1) ~ *J*(8b,2) ~ *J*(8b,7) = 1.4, $J_{gem}$ = 11.0 (H-8b); 1.72 dm, 1 H (H-8a); 1.94 td, 1 H, *J*(6,5a) ~ *J*(6,7) = 4.0 (H-6); 2.13 m, 1 H (H-1); 2.51 ddq, 1 H, *J*(7,1) ~ *J*(7,8a) ~ *J*(7,8b) = 1.2, *J*(7,3) = 4.9 (H-7); 3.30 ddd, 1 H, *J*(CH,9) = 7.2, *J*(CH,OH) = 5.5 and 3.33 ddd, 1 H, *J*(CH,9) = 7.6, *J*(CH,OH) = 5.3, $J_{gem}$ = 10.7 ($CH_2O$); 3.44 brdd, 1 H, *J*(2,1) ~ *J*(2,3) = 1.0, *J*(2,8b) = 1.2, *J*(2,NH) = 5.9 (H-2); 3.64 d, 1 H, $J_{gem}$ = 7.8 (H-5b); 3.69 dd, 1 H, *J*(5a,6) = 3.9 (H-5a); 4.02 brd, 1 H, *J*(3,1) = 1.0 (H-3); 4.61 t, 1 H, *J*(OH,$CH_2$) = 5.4 (OH); 5.13 brs, 2 H ($NH_2$); 6.47 d, 1 H (NH); 7.73 s, 1 H (H-2′).$^{13}$C NMR: 31.53 (C-8); 41.00 (C-1); 41.59 (C-6); 44.56 (C-7); 50.66 (C-9); 63.10 ($CH_2O$); 63.47 (C-2); 73.94 (C-5); 85.32 (C-3); 123.80 (C-5′); 136.83 (C-4′); 145.64 (C-2′); 151.10 (C-6′).

(1*R**,2*R**,3*R**,6*R**,7*S**,9*S**)-2-(6-Chloro-9*H*-purin-9-yl)-4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-9-methanol (**17**) and
(1*R**,2*R**,3*R**,6*R**,7*S**,9*S**)-2-(2-Amino-6-chloro-9*H*-purin-9-yl)-4-oxatricyclo-[4.2.1.$0^{3,7}$]nonane-9-methanol (**22**)

Concentrated hydrochloric acid (1.8 ml) was added to a stirred mixture of compound **16** 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. The residue was crystallized from water.

*(1R*,2R*,3R*,6R*,7S*,9S*)-2-(6-Chloro-9H-purin-9-yl)-4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-9-methanol* (**17**): Yield 615 mg (80%), m.p. 190.5–192 °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: 54.69% C, 4.94% H, 11.55% Cl, 18.08% N. $^1$H NMR: 1.62 brtd, 1 H, *J*(9,1) ~ *J*(9,8a) = 1.0, *J*(9,6) = 2.6, *J*(9,$CH_2$) = 7.9 (H-9); 1.72 dm, 1 H, $J_{gem}$ = 11.7 (H-8a); 1.82 dq, 1 H, *J*(8b,1) ~ *J*(8b,2) ~ *J*(8b,7) = 1.4 (H-8b); 2.07 td, 1 H, *J*(6,5a) ~ *J*(6,7) = 4.0 (H-6); 2.58 m, 1 H (H-1); 2.69 ddq, 1 H, *J*(7,1) ~ *J*(7,8a) ~ *J*(7,8b) = 1.2, *J*(7,3) = 5.0 (H-7); 3.39 dd, 2 H, *J*($CH_2$,OH) = 5.3 ($CH_2$O); 3.75 d, 1 H, $J_{gem}$ = 7.8 (H-5b); 3.78 dd, 1 H, *J*(5a,6) = 3.6 (H-5a); 4.12 brd, 1 H, *J*(2,1) ~ *J*(2,3) = 1.0, *J*(2,8b) = 1.6 (H-2); 4.12 t, 1 H (OH); 4.78 brd, 1 H, *J*(3,1) = 1.2, *J*(3,8b) = 1.0 (H-3); 8.77 s, 1 H and 8.78 s, 1 H (H-2′, H-8′). $^{13}$C NMR: 32.05 (C-8); 41.10 (C-1); 41.35 (C-6); 45.24 (C-7); 50.67 (C-9); 62.75 ($CH_2$O); 67.27 (C-2); 74.16 (C-5); 83.56 (C-3); 131.24 (C-5′); 145.76 (C-8′); 149.18 (C-6′); 151.50 (C-2′); 152.28 (C-4′).

*(1R*,2R*,3R*,6R*,7S*,9S*)-2-(2-Amino-6-chloro-9H-purin-9-yl)-4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-9-methanol* (**22**): Yield 575 mg (71%), m.p. 238–241 °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: 52.19% C, 5.10% H, 10.94% Cl, 21.50% N. FAB MS, *m/z* (rel.%): 324/322 (35/100) [M + H], 288 (37). $^1$H NMR: 1.52 brddd, 1 H, *J*(9,1) ~ *J*(9,8a) = 1.0, *J*(9,6) = 2.4, *J*(9,$CH^a$) = 7.2, *J*(9,$CH^b$) = 8.4 (H-9); 1.70 dm, 1 H, $J_{gem}$ = 11.7 (H-8a); 1.79 dq, 1 H, *J*(8b,1) ~ *J*(8b,2) ~ *J*(8b,7) = 1.4 (H-8b); 2.04 td, 1 H, *J*(6,5a) ~ *J*(6,7) = 4.0 (H-6); 2.37 m, 1 H (H-1); 2.67 ddq, 1 H, *J*(7,1) ~ *J*(7,8a) ~ *J*(7,8b) = 1.2, *J*(7,3) = 5.0, *J*(7,6) = 4.0 (H-7); 3.35 ddd, 1 H, *J*(CH,5a) = 7.2, *J*(CH,OH) = 5.4 and 3.38 ddd, 1 H, *J*(CH,5a) = 8.4, *J*(CH,OH) _ 5.0, $J_{gem}$ = 10.6 ($CH_2$O); 3.72 d, 1 H, $J_{gem}$ = 7.8 (H-5b); 3.76 dd, 1 H, *J*(5a,6) = 3.9 (H-5a); 3.88 brd, 1 H, *J*(2,8b) = 1.6 (H-2); 4.67 dd, 1 H, *J*(3,1) = 1.2 (H-3); 4.73 t, 1 H, *J*(OH,$CH_2$) = 5.2 (OH); 6.94 brs, 2 H ($NH_2$); 8.19 s, 1 H (H-8′). $^{13}$C NMR: 31.97 (C-8); 41.25 (C-1); 41.33 (C-6); 45.13 (C-7); 50.83 (C-9); 62.80 ($CH_2$O); 66.23 (C-2); 74.09 (C-5); 83.74 (C-3); 123.50 (C-5′); 141.27 (C-8′); 149.61 (C-6′); 154.38 (C-4′); 159.85 (C-2′).

(1*R**,2*R**,3*R**,6*R**,7*S**,9*S**)-2-(6-Amino-9*H*-purin-9-yl)-4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-9-methanol (**18**)

A solution of chloropurine derivative **17** (158 mg, 0.5 mmol) in liquid ammonia (15 ml) was heated in an autoclave at 70 °C for 48 h and then ammonia was evaporated. Crystallization of the residue from water gave 129 mg (87%) of adenine derivative **18**, m.p. 234–236 °C. For $C_{14}H_{17}N_5O_2 \cdot 0.5H_2O$ (296.3) calculated: 56.74% C, 6.12% H, 23.63% N; found: 56.92% C, 6.16% H, 23.70% N. FAB MS, *m/z* (rel.%): 288 (100) [M + H], 136 (68). $^1$H NMR: 1.59 tm,

1 H, *J*(9,1) ~ *J*(9,8a) = 1.0, *J*(9,6) = 2.7, *J*(9,$CH_2$) = 7.5 (H-9); 1.71 dm, 1 H, $J_{gem}$ = 11.6 (H-8a); 1.77 dm, 1 H (H-8b); 2.04 td, 1 H, *J*(6,5a) = *J*(6,7) = 3.8 (H-6); 2.41 m, 1 H (H-1); 2.68 ddq, 1 H, *J*(7,1) ~ *J*(7,8a) ~ *J*(7,8b) = 1.0, *J*(7,3) = 5.0, *J*(7,6) = 3.8 (H-7); 3.36 ddd, 1 H, *J*(CH,OH) = 5.2, *J*(CH,9) = 7.5 and 3.39 ddd, 1 H, *J*(CH,OH) = 5.2, *J*(CH,9) = 7.5, $J_{gem}$ = 10.6 ($CH_2O$); 3.74 d, 1 H, $J_{gem}$ = 7.8 (H-5b); 3.77 dd, 1 H, *J*(5a,6) = 3.8 (H-5a); 3.98 brd, 1 H, *J*(2,8b) = 1.6 (H-2); 4.72 t, 1 H, *J*(OH,$CH_2$) = 5.2 (OH); 4.76 brd, 1 H, *J*(3,1) = 1.0, *J*(3,7) = 5.0 (H-3); 7.22 brs, 2 H ($NH_2$); 8.14 s, 1 H and 8.20 s, 1 H (H-2′, H-8′). $^{13}$C NMR: 31.89 (C-8); 41.35 (C-1); 41.56 (C-6); 45.15 (C-7); 50.78 (C-9); 62.85 ($CH_2O$); 66.44 (C-2); 74.11 (C-5); 83.68 (C-3); 119.04 (C-5′); 139.08 (C-8′); 149.84 (C-4′); 152.50 (C-2′); 156.17 (C-8′).

(1*R**,2*R**,3*R**,6*R**,7*S**,9*S**)-2-[6-(Dimethylamino)-9*H*-purin-9-yl]-4-oxatricyclo-[4.2.1.$0^{3,7}$]nonane-9-methanol (**19**)

Chloropurine **17** (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. Chromatography of the residue on a silica gel column (10 g) in ethyl acetate–acetone–ethanol–water (90:15:11:9) followed by crystallization from ethyl acetate gave 130 mg (82%) of purine **19**, m.p. 178–180 °C. For $C_{16}H_{21}N_5O_2$ (315.4) calculated: 60.93% C, 6.71% H, 22.21% N; found: 60.70% C, 6.73% H, 22.07% N. FAB MS, *m/z* (rel.%): 316 (100) [M + H], 164 (20). $^1$H NMR: 1.54 brdt 1 H, *J*(9,1) ~ *J*(9,8a) = 1.0, *J*(9,6) = 2.3, *J*(9,$CH_2$) = 7.6 (H-9); 1.69 dm, 1 H, $J_{gem}$ = 11.7 (H-8a); 1.76 dm, 1 H (H-8b); 2.03 brtd, 1 H, *J*(6,5a) ~ *J*(6,7) = 4.0 (H-6); 2.40 m, 1 H (H-1); 2.66 brt, 1 H, *J*(7,6) = 4.0, *J*(7,3) = 4.0 (H-7); 3.36 dd, 2 H, *J*($CH_2$,OH) = 5.2 ($CH_2O$); 3.40 brs, 6 H ($N(CH_3)_2$); 3.74 d, 1 H, $J_{gem}$ = 7.8 (H-5b); 3.76 dd, 1 H, *J*(5a,6) = 3.5 (H-5a); 3.99 brs, 1 H (H-2); 4.72 t, 1 H (OH); 8.18 s, 1 H and 8.20 s, 1 H (H-2′, H-8′). $^{13}$C NMR: 31.85 (C-8); 34.50 ($N(CH_3)_2$); 41.38 (C-1); 41.40 (C-6); 45.15 (C-7); 50.81 (C-9); 62.84 ($CH_2O$); 66.30 (C-3); 74.11 (C-5); 83.77 (C-3); 119.54 (C-5′); 137.73 (C-8′); 150.59 (C-4′); 151.84 (C-2′); 154.40 (C-6′).

(1*R**,2*R**,3*R**,6*R**,7*S**,9*S**)-2-[6-(Cyclopropylamino)-9*H*-purin-9-yl]-4-oxatricyclo-[4.2.1.$0^{3,7}$]nonane-9-methanol (**20**)

A solution of chloropurine **17** (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 140 mg (85%) of compound **20** as solid foam. For $C_{17}H_{21}N_5O_2$ (327.4) calculated: 62.37% C, 6.47% H, 21.39% N; found: 62.09% C, 6.42% H, 21.24% N. FAB MS, *m/z* (rel.%): 328 (100) [M + H], 127 (22). $^1$H NMR: 0.57 m, 2 H, 0.65 m, 2 H, and 3.02 m, 1 H (cyclopropyl); 1.51 brdd, 1 H, *J*(9,1) ~ *J*(9,8a) = 1.0, *J*(9,6) = 2.2, *J*(9,$CH^a$) = 7.1, *J*(9,$CH^b$) = 8.5 (H-9); 1.71 dm, 1 H, $J_{gem}$ = 11.5 (H-8a); 1.75 dq, 1 H, *J*(8b,1) ~ *J*(8b,2) ~ *J*(8b,7) = 1.2 (H-8b); 2.02 td, 1 H, *J*(6,5a) = *J*(6,7) = 4.0, *J*(6,9) = 2.2 (H-6); 2.25 m, 1 H (H-1); 2.66 ddq, 1 H, *J*(7,1) ~ *J*(7,8a) = 1.2, *J*(7,3) = 5.0 (H-7); 3.33 ddd, 1 H, *J*(CH,OH) = 5.5 and 3.38 ddd, 1 H, *J*(CH,OH) = 5.0, $J_{gem}$ = 10.6 ($CH_2O$); 3.70 d, 1 H, $J_{gem}$ = 7.8 (H-5b); 3.76 dd, 1 H, *J*(5a,6) = 3.9 (H-5a); 3.83 brd, 1 H, *J*(2,8b) = 1.4 (H-2); 4.64 brdd, 1 H, *J*(3,1) = 1.2 (H-3); 4.72 t, 1 H, *J*(OH,$CH_2$) = 5.3 (OH); 5.86 brs, 2 H ($NH_2$); 7.28 brs, 1 H (NH); 7.74 s, 1 H (H-8′). $^{13}$C NMR: 6.61, 2 C, 28.13 (cyclopropyl); 31.81 (C-8); 41.73 (C-6); 41.63 (C-1); 45.04 (C-7); 50.91 (C-9); 62.91 ($CH_2O$); 65.47 (C-2); 74.09 (C-5); 84.06 (C-3); 113.53 (C-5′); 135.23 (C-8′); 150.20 (C-4′); 156.10 (C-6′); 160.30 (C-2′).

(1*R**,2*R**,3*R**,6*R**,7*S**,9*S**)-2-[(2,5-Diamino-6-chloropyrimidin-4-yl)amino]-4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-9-methanol (**21**)

A solution of amine **9** (508 mg, 3 mmol), 4,6-dichloropyrimidine-2,5-diamine (537 mg, 3 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 evaporated. Chromatography of the residue on a silica gel column (100 g) in ethyl acetate–acetone–ethanol–water (90:15:11:9) followed by crystallization from ethanol afforded 628 mg (73%) of pyrimidine **21**, m.p. 231–233 °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: 50.07% C, 5.91% H, 11.19% Cl, 22.20% N. FAB MS, *m/z* (rel.%): 314/312 (34/100) [M + H]. $^1$H NMR: 1.39 dt, 1 H, *J*(9,$CH_2$) = 7.8, *J*(9,6) = 2.2 (H-9); 1.62 dm, 1 H, $J_{gem}$ = 11.2 (H-8a); 1.73 brd, 1 H, $J_{gem}$ = 10.9 (H-8b); 1.95 m, 1 H (H-6); 2.04 brs, 1 H (H-1); 2.51 m, 1 H (H-7); 3.29 ddd, 1 H, $J_{gem}$ = 10.7, *J*($CH_2$,OH) = 5.5 ($CH^aH$-O); 3.35 m, 1 H ($CH^bH$-O); 3.50 brd, 1 H, *J*(2,NH) = 6.2 (H-2); 3.62 d, 1 H, $J_{gem}$ = 7.8 (H-5a); 3.69 dd, 1 H, $J_{gem}$ = 7.8, *J*(5b,6) = 3.9 (H-5b); 4.00 brd, 1 H, *J*(3,7) = 4.9 (H-3); 4.02 brs, 2 H (2′-$NH_2$); 4.61 t, 1 H, *J*(OH,$CH_2$) = 5.3 (OH); 5.56 brs, 2 H (5′-$NH_2$); 6.11 d, 1 H, *J*(NH,2) = 6.7 (NH). $^{13}$C NMR: 31.52 (C-8); 41.40 (C-1); 41.61 (C-6); 44.62 (C-7); 50.68 (C-9); 62.55 (C-2); 63.16 ($CH_2$O); 73.96 (C-5); 85.79 (C-3); 113.67 (C-5′); 140.88 (C-4′); 154.06 (C-6′); 155.62 (C-2′).

(1*R**,2*R**,3*R**,6*R**,7*S**,9*S**)-2-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-9-methanol (**23**) and
(1*R**,2*R**,3*R**,6*R**,7*S**)-2-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-6-methanol (**25**)

A suspension of chloropurine derivative **22** or **24** (161 mg, 0.5 mmol) in cyclopropylamine (4 ml) was stirred at room temperature overnight and the resulting solution was evaporated. The residue was crystallized from water.

*(1R*,2R*,3R*,6R*,7S*,9S*)-2-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-4-oxatricyclo-[4.2.1.$0^{3,7}$]nonane-9-methanol* (**23**): Yield 148 mg (84%), m.p. 147–149 °C (hydrate). For $C_{17}H_{22}N_6O_2 \cdot 0.5H_2O$ (351.4) calculated: 58.10% C, 6.60% H, 23.92% N; found: 58.31% C, 6.55% H, 23.98% N. FAB MS, *m/z* (rel.%): 343 (100) [M + H], 191 (15). $^1$H NMR: 0.57 m, 2 H, 0.65 m, 2 H, and 3.01 brs, 1 H (cyclopropyl); 1.51 dt, 1 H, *J*(9,$CH_2$) = 7.8, *J*(9,6) = 2.3 (H-9); 1.69–1.76 m, 2 H (H-8); 2.02 m, 1 H (H-6); 2.25 brs, 1 H (H-1); 2.66 m, 1 H (H-7); 3.32–3.40 m, 2 H ($CH_2$O); 3.72 d, 1 H, $J_{gem}$ = 7.9 (H-5a); 3.76 dd, 1 H, $J_{gem}$ = 8.0, *J*(5b,6) = 3.9 (H-5b); 3.84 brs, 1 H (H-2); 4.64 brd, 1 H, *J*(3,7) = 5.0 (H-3); 4.72 t, 1 H, *J*(OH,$CH_2$) = 5.3 (OH); 5.87 brs, 2 H ($NH_2$); 7.30 brs, 1 H (NH); 7.74 s, 1 H (H-8′). $^{13}$C NMR: 6.64, 2 C ($CH_2$ cyclopropyl); 23.96 (CH cyclopropyl); 31.82 (C-8); 41.38 (C-6); 41.65 (C-1); 45.07 (C-7); 50.92 (C-9); 62.92 ($CH_2$O); 65.46 (C-2); 74.11 (C-5); 84.09 (C-3); 113.53 (C-5′); 135.25 (C-8′); 151.56 (C-4′); 156.11 (C-6′); 160.32 (C-2′).

*(1R*,2R*,3R*,6R*,7S*)-2-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-4-oxatricyclo[4.2.1.$0^{3,7}$]-nonane-6-methanol* (**25**): Yield 137 mg (78%), m.p. 138–140 °C (hydrate). For $C_{17}H_{22}N_6O_2 \cdot H_2O$ (360.4) calculated: 56.65% C, 6.71% H, 23.32% N; found: 56.96% C, 6.79% H, 23.42% N. FAB MS, *m/z* (rel.%): 343 (100) [M + H], 242 (85), 191 (47). $^1$H NMR: 0.56–0.68 m, 4 H and 3.04 brs, 1 H (cyclopropyl); 1.31 dd, 1 H, *J*(6b,1) = 2.3, $J_{gem}$ = 12.6 (H-6b); 1.61 dm, 1 H, $J_{gem}$ = 11.4 (H-7b); 1.70 dd, 1 H, *J*(6a,1) = 4.4 (H-6a); 1.73 m, 1 H (H-7a); 2.37 m, 1 H (H-1); 2.55 m, 1 H (H-4); 3.41 d, 2 H, *J*($CH_2$,OH) = 5.3 ($CH_2$O); 3.71d, 1 H and 3.79 d, 1 H, $J_{gem}$ = 7.5 (2 × H-9); 3.91 d, 1 H, *J*(2,1) = 2.0 (H-2); 4.72 brd, 1 H, *J*(3,4) = 5.0 (H-3); 4.78 t, 1 H (OH); 5.78 brs, 2 H ($NH_2$); 7.20 brs, 1 H (NH); 7.73 s, 1 H (H-8′). $^{13}$C NMR: 6.54, 2 C, 23.97

(cyclopropyl); 33.25 (C-7); 38.80 (C-6); 40.11 (C-1); 46.94 (C-4); 49.50 (C-5); 63.67 (C-8); 65.18 (C-2); 76.61 (C-9); 85.23 (C-3); 113.61 (C-5′); 135.10 (C-8′); 151.67 (C-4′); 156.02, 160.15 (C-2′, C-6′).

Preparation of Compounds **31**, **32**, **34**, **37**, **39** and **41** (Method *A*)

1-Methylimidazole (250 μl, 3 mmol) was added dropwise over 1 min to a stirred solution of **26** (420 mg, 1.5 mmol) and compound **14**, **15**, **17**, **19**, **27**[6] or **29**[6] (0.5 mmol) in tetrahydrofuran (5 ml). The mixture was stirred under argon at room temperature overnight and then was evaporated. A solution of the residue in chloroform (10 ml) was washed with 1 M HCl (2 × 10 ml), saturated aqueous solution of sodium hydrogencarbonate (10 ml) and water (5 ml). The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column (40 g) in ethyl acetate–acetone–ethanol–water (100:15:6:4). The products were obtained as solid foams.

*Methyl N-({[(1R*,2R*,3R*,6R*,7S*,9S*)-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-oxatricyclo[4.2.1.0$^{3,7}$]nonan-9-yl]methoxy}phenoxyphosphoryl)-L-alaninate* (**31**): Yield 177 mg (68%). For $C_{24}H_{30}N_3O_8P$ (519.5) calculated: 55.49% C, 5.82% H, 8.09% N, 5.96% P; found: 55.20% C, 5.81% H, 7.93% N, 6.17% P. FAB MS, *m/z* (rel.%): 520 (100) [M + H], 261 (32), 200 (58). $^1$H NMR: 1.21–1.26 m, 3 H ($CH_3$); 1.54–1.80 m, 3 H (2 × H-8, H-9); 1.78–1.79 m, 3 H (5′-$CH_3$); 2.05–2.11 m, 1 H (H-6); 2.206 brs, 2.231 brs, 2.238 brs and 2.275 brs, 1 H (H-1); 2.59–2.64 m, 1 H (H-7); 3.599 s, 1.5 H, 3.601 s, 0.75 H, and 3.606 s, 0.75 H ($OCH_3$); 3.56–3.72 m, 3 H and 3.80–4.00 m, 3 H (2 × H-5, H-2, CH, $OCH_2$); 4.390 brs, 0.25 H, 4.400 brs, 0.5 H, and 4.410 brs, 0.25 H (H-3); 5.90–6.02 m, 1 H (NH); 7.13–7.22 m, 3 H (arom.); 7.34–7.42 m, 3 H (H-6′, arom.); 11.28 (H-3′). $^{13}$C NMR: 12.24 (5′-$CH_3$); 19.28 ($CH_3$); 31.28 (C-8); 40.20, 41.21, 48.46 (C-1, C-6); 45.08 (C-7); 48.41, 48.46 (C-9); 49.87, 50.04 (CH); 52.03 ($OCH_3$); 66.94 ($OCH_2$); 67.78 (C-2); 73.51 (C-5); 83.58 (C-3); 108.18 (C-5′); 120.43, 120.47, 124.67, 129.77, 2 C, 150.83 (arom.); 138.16, 138.20 (C-6′); 151.21 (C-2′); 163.92 (C-4′); 173.69, 173.73, 173.80, 173.84 (C=O). $^{31}$P NMR: 4.00, 4.04, 4.46, 4.51.

*Methyl N-({[(1R*,2R*,3R*,6R*,7S*,9S*)-2-(6-chloro-9H-purin-9-yl)-4-oxatricyclo[4.2.1.0$^{3,7}$]-nonan-9-yl]methoxy}phenoxyphosphoryl)-L-alaninate* (**32**): Yield 205 mg (75%). For $C_{24}H_{27}ClN_5O_6P$ (547.9) calculated: 52.61% C, 4.97% H, 6.47% Cl, 12.78% N, 5.65% P; found: 52.34% C, 5.08% H, 6.59% Cl, 12.52% N, 5.82% P. FAB MS, *m/z* (rel.%): 550/548 (17/43) [M + H], 214 (39), 200 (100). $^1$H NMR: 1.23 m, 3 H ($CH_3$); 1.75–1.93 m, 3 H (H-8a, H-8b, H-9); 2.16 m, 1 H (H-6); 2.51 brs, 2.54 brs, 2.56 brs and 2.60 brs, 1 H (H-1); 2.73 m, 1 H (H-7); 3.57 s, 3.58 s, 3.59 s and 3.59 s, 3 H ($OCH_3$); 3.77 m, 2 H (H-5); 3.88 m, 1 H (CH); 4.00 m, 2 H ($CH_2O$); 4.15 m, 1 H (H-2); 4.81 m, 1 H (H-3); 5.93–6.06 m, 1 H (NH); 7.09–7.22 m, 3 H (H-2 phenyl, H-4 phenyl); 7.30–7.36 m, 2 H (H-3 phenyl); 8.75 s, 8.76 s, 8.77 s and 8.78 s, 1 H (H-8′); 8.78 s and 8.79 s, 1 H (H-2′). $^{13}$C NMR: 19.82, 19.88, 19.94 ($CH_3$); 32.05 (C-8); 40.92–41.13 m, 2 C (C-1, C-6); 45.35 (C-7); 48.10 m (C-9); 49.89, 50.04 (CH); 52.05 ($OCH_3$); 66.88–67.01 m, 2 C (C-2, $CH_2O$); 73.83 (C-5); 83.44 (C-3); 120.43 m, 2 C (C-2 phenyl); 124.65, 124.69 (C-4 phenyl); 129.74, 129.78, 2 C (C-3 phenyl); 131.26 (C-5′); 145.75 (C-8′); 149.24 (C-6′); 150.93 m (C-1 phenyl); 151.56 (C-2′); 152.28 (C-4′); 173.85, 173.87, 173.97, 174.00 (C=O). $^{31}$P NMR: 3.99, 4.10, 4.39, 4.49.

*Methyl N-[({(1R*,2R*,3R*,6R*,7S*,9S*)-2-[6-(dimethylamino)-9H-purin-9-yl]-4-oxatricyclo[4.2.1.0$^{3,7}$]-nonan-9-yl}methoxy)phenoxyphosphoryl]-L-alaninate* (**34**): Yield 189 mg (68%). For $C_{26}H_{33}N_6O_6P$ (556.6) calculated: 56.11% C, 5.98% H, 15.10% N, 5.57% P; found: 55.93% C, 6.06% H,

14.91% N, 5.34% P. FAB MS, *m/z* (rel.%): 557 (100) [M + H], 298 (28), 200 (40), 164 (95). $^1$H NMR: 1.20–1.26 m, 3 H ($CH_3$); 1.72–1.90 m, 3 H (2 × H-8, H-9); 2.13–2.19 m, 1 H (H-3); 2.367 brs, 0.25 H, 2.396 brs, 0.5 H, and 2.434 brs, 0.25 H (H-1); 2.70–2.75 m, 1 H (H-7); 3.34 brs, 6 H ($N(CH_3)_2$); 3.567 s, 3.584 s, 3.587 s and 3.589 s, 3 H ($OCH_3$); 3.72–4.05 m, 6 H (2 × H-5, H-2, CH, $OCH_2$); 4.73–4.76 m, 1 H (H-3); 5.90–6.02 m, 1 H (NH); 7.08–7.22 m, 3 H and 7.30–7.37 m, 2 H (arom.); 8.176 s, 8.184 s, 8.188 s and 8.198 s, 1 H, 8.213 s, 0.5 H, 8.216 s, 0.25 H, and 8.219 s, 0.25 H (H-2′, H-8′). $^{13}$C NMR: 19.85 ($CH_3$); 31.87 (C-8); 38.00, 2 C ($N(CH_3)_2$); 41.11, 41.14, 41.20, 41.24 (C-1, C-6); 45.24 (C-7); 48.20 (C-9); 49.87, 50.02 (CH); 52.02 ($OCH_3$); 66.02 (C-2); 67.03 ($OCH_2$); 73.78 (C-5); 83.63 (C-3); 119.54 (C-5′); 120.43, 2 C, 124.65, 129.75, 2 C, 150.60 (arom.); 137.76, 137.78 (C-8′); 150.94 (C-4′); 151.88 (C-2′); 154.45 (C-6′); 173.83, 173.94 (C=O). $^{31}$P NMR: 4.00, 4.08, 4.41, 4.48.

*Methyl N-({[(1R*,2R*,3R*,6R*,7S*)-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-oxatricyclo[4.2.1.0$^{3,7}$]nonan-6-yl]methoxy}phenoxyphosphoryl)-L-alaninate* (**37**): Yield 198 mg (76%). For $C_{24}H_{30}N_3O_8P$ (519.5) calculated: 55.49% C, 5.82% H, 8.09% N, 5.96% P; found: 55.18% C, 5.83% H, 7.87% N, 6.18% P. FAB MS, *m/z* (rel.%): 520 (17) [M + H], 261 (68), 200 (100). $^1$H NMR: 1.22–1.26 m, 3 H ($CH_3$); 1.26–1.34 m, 1 H, 1.60–1.65 m, 2 H, and 1.70–1.80 m, 1 H (2 × H-2, 2 × H-8); 1.77–1.78 m, 3 H (5′-$CH_3$); 2.34–2.39 m, 1 H and 2.48–2.54 m, 1 H (H-1, H-7); 3.605 s, 1.5 H, 3.619 s, 0.75 H, and 3.622 s, 0.75 H ($OCH_3$); 3.65–3.75 m, 3 H, 3.80–3.89 m, 1 H, and 3.93–4.06 m, 2 H (2 × H-4, H-9, CH, $OCH_2$); 4.43–4.48 m, 1 H (H-6); 5.94–6.05 m, 1 H (NH); 7.16–7.22 m, 3 H and 7.35–7.40 m, 2 H (arom.); 7.42–7.44 m, 1 H (H-6′); 11.25 brs, 1 H (H-3′). $^{13}$C NMR: 12.25 (5′-$CH_3$); 19.79 ($CH_3$); 33.28 (C-8); 38.62 (C-1); 47.03, 47.14 (C-7); 48.31 (C-3); 49.87, 50.02 (CH); 52.06 ($OCH_3$); 67.38 (C-9); 68.04 ($OCH_2$); 75.86, 75.96 (C-4); 85.32, 85.35 (C-9); 108.18 (C-5′); 120.41, 120.45 124.75, 129.76, 129.79, 150.91 (arom.); 138.13 (C-6′); 151.25 (C-2′); 163.93 (C-4′); 173.90 (C=O). $^{31}$P NMR: 3.80, 2 P, 4.31, 4.43.

*Methyl N-({[(1R*,2R*,3R*,6R*,7S*)-2-(6-chloro-9H-purin-9-yl)-4-oxatricyclo[4.2.1.0$^{3,7}$]nonan-6-yl]-methoxy}phenoxyphosphoryl)-L-alaninate* (**39**): Yield 222 mg (81%). For $C_{24}H_{27}ClN_5O_6P$ (547.9) calculated: 52.61% C, 4.97% H, 6.47% Cl, 12.78% N, 5.65% P; found: 52.40% C, 5.09% H, 6.23% Cl, 12.50% N, 5.46% P. FAB MS, *m/z* (rel.%): 550/548 (13/34) [M + H], 214 (100), 200 (90). $^1$H NMR: 1.23–1.26 m, 3 H ($CH_3$); 1.43–1.51 m, 1 H, 1.68–1.75 m, 1 H, and 1.78–1.90 m, 2 H (2 × H-2, 2 × H-8); 2.59–2.66 m, 1 H (H-1); 2.69 brs, 1 H (H-7); 3.611 s, 1.5 H, 3.625 s, 0.75 H, and 3.628 s, 0.75 H ($OCH_3$); 3.75–3.91 m, 3 H (2 × H-4, CH); 3.39–4.11 m, 2 H ($OCH_2$); 4.231 brs and 4.243 brs, 1 H (H-9); 4.85–4.89 m, 1 H (H-6); 5.96–6.08 m, 1 H (NH); 7.16–7.23 m, 3 H and 7.36–7.41 m, 2 H (arom.); 8.784 s and 8.786 s, 1 H, and 8.790 s and 8.794 s, 1 H (H-2′, H-8′). $^{13}$C NMR: 19.81 ($CH_3$); 33.57 (C-8); 38.26 (C-2); 39.95 (C-1); 47.40 (C-7); 48.24 (C-3); 49.87, 50.03 (CH); 52.07 ($OCH_3$); 66.61 (C-9); 68.32 ($OCH_2$); 76.11, 76.12 (C-4); 85.02 (C-6); 120.43, 120.46, 124.77, 129.78, 129.80, 150.73 (arom.); 131.27 (C-5′); 145.73 (C-8′); 149.18 (C-4′); 151.52 (C-2′); 152.29 (C-6′); 173.75 (C=O). $^{31}$P NMR: 3.82, 3.83, 4.38, 4.45.

*Methyl N-[({(1R*,2R*,3R*,6R*,7S*)-9-[6-(dimethylamino)-9H-purin-9-yl]-5-oxatricyclo[4.2.1.0$^{3,7}$]-nonan-6-yl}methoxy)phenoxyphosphoryl]-L-alaninate* (**41**): Yield 253 mg (65%). For $C_{26}H_{33}N_6O_6P$ (556.6) calculated: 56.11% C, 5.98% H, 15.10% N, 5.57% P; found: 55.89% C, 5.91% H, 14.80% N, 5.48% P. FAB MS, *m/z* (rel.%): 557 (100) [M + H], 298 (41), 200 (28), 164 (83). $^1$H NMR: 1.23–1.27 m, 3 H ($CH_3$); 1.40–1.49 m, 1 H, 1.64–1.71 m, 1 H, and 1.75–1.86 m, 2 H (2 × H-2, 2 × H-8); 2.51–2.54 m, 1 H and 2.59–2.65 m, 1 H (H-1, H-7); 3.44 brs, 6 H ($N(CH_3)_2$); 3.614 s, 3.628 s and 3.630 s, 3 H ($OCH_3$); 3.74–3.91 m, 3 H (2 × H-4, CH); 3.98–4.13 m, 3 H (H-9, $OCH_2$); 4.79–4.83 m, 1 H (H-6); 5.93–6.05 m, 1 H (NH); 7.16–7.23 m,

3 H and 7.36–7.40 m, 2 H (arom.); 8.194 s and 8.197 s, 1 H, and 8.207 s and 8.210 s, 1 H (H-2′, H-8′). $^{13}$C NMR: 19.75 ($CH_3$); 33.35 (C-8); 37.99 ($N(CH_3)_2$); 39.94 (C-1); 38.30, 38.50 (C-2); 47.24, 47.31 (C-7); 48.20 (C-3); 49.85, 50.00 (CH); 51.96 ($OCH_3$); 65.66 (C-9); 68.30 ($OCH_2$); 76.07, 76.17 (C-4); 85.14 (C-6); 119.57 (C-5′); 120.38, 2 C, 124.66, 129.68, 129.70, 150.85 (arom.); 137.67 (C-8′); 150.57 (C-4′); 151.78 (C-2′); 154.44 (C-6′); 173.77 (C=O). $^{31}$P NMR: 3.83, 2 P, 4.37, 4.44.

Preparation of Compounds **33**, **35**, **36**, **38**, **40** and **42** (Method *B*)

Compound **18**, **20**, **23**, **25**, **28** [6] or **30** [6] (0.7 mmol) was azeotropically dried with anhydrous pyridine (3 × 5 ml) and suspended in THF (4 ml). To the stirred suspension was added *t*-BuMgCl (1 ml, 1.0 M solution in THF) and then dropwise a solution of compound **26** (390 mg, 1.4 mmol) in THF (4 ml). The mixture was stirred under argon at room temperature for 3 days and then evaporated. A solution of the residue in chloroform (20 ml) was washed with water (3 × 10 ml), dried over anhydrous sodium sulfate and the solvent was evaporated. The residue was chromatographed on a silica gel column (40 g) in ethyl acetate–acetone–ethanol–water (100:15:6:4). The products were obtained as solid foams.

*Methyl N-({[(1R*,2R*,3R*,6R*,7S*,9S*)-2-(6-amino-9H-purin-9-yl)-4-oxatricyclo[4.2.1.0$^{3,7}$]-nonan-9-yl]methoxy}phenoxyphosphoryl)-L-alaninate* (**33**): Yield 237 mg (64%). For $C_{24}H_{29}N_6O_6P$ (528.5) calculated: 54.54% C, 5.53% H, 15.90% N, 5.86% P; found: 54.54% C, 5.70% H, 15.68% N, 5.72% P. FAB MS, *m/z* (rel.%): 529 (100) [M + H], 438 (49), 200 (64). $^1$H NMR: 1.20–1.26 m, 3 H ($CH_3$); 1.74–1.90 m, 3 H (2 × H-8, H-9); 2.12–2.18 m, 1 H (H-6); 2.39 brs, 2.42 brs, 2.43 brs and 2.46 brs, 1 H (H-1); 2.70–2.75 m, 1 H (H-7); 3.568 s, 3.587 s, 3.590 s and 3.592 s, 3 H ($OCH_3$); 3.71–3.80 m, 2 H and 3.84–4.04 m, 4 H (2 × H-5, H-3, CH, $OCH_2$); 4.77–4.81 m, 1 H (H-3); 5.88–6.00 m, 1 H (NH); 7.10–7.22 m, 5 H ($NH_2$, arom.); 7.30–7.37 m, 2 H (arom.); 8.13–8.19 m, 2 H (H-2′, H-8′). $^{13}$C NMR: 19.76 ($CH_3$); 31.85 (C-8); 41.12, 41.35 (C-1, C-6); 45.17 (C-7); 48.14 (C-9); 49.82, 49.97 (CH); 51.89 ($OCH_3$); 66.13 (C-2); 67.03 ($OCH_2$); 73.69 (C-5); 83.48 (C-3); 119.02 (C-5′); 120.34, 2 C, 124.54, 129.61, 129.64, 150.91 (arom.); 138.98 (C-8′); 149.81 (C-4′); 152.45 (C-2′); 156.14 (C-6′); 173.84 (C=O). $^{31}$P NMR: 4.00, 4.07, 4.41, 4.49.

*Methyl N-[({(1R*,2R*,3R*,6R*,7S*,9S*)-2-[6-(cyclopropylamino)-9H-purin-9-yl]-4-oxatricyclo-[4.2.1.0$^{3,7}$]nonan-9-yl}methoxy)phenoxyphosphoryl]-L-alaninate* (**35**): Yield 294 mg (74%). For $C_{27}H_{33}N_6O_6P$ (568.6) calculated: 57.04% C, 5.85% H, 14.78% N, 5.45% P; found: 56.82% C, 5.93% H, 14.53% N, 5.38% P. FAB MS, *m/z* (rel.%): 569 (100) [M + H], 200 (31), 176 (34). $^1$H NMR: 0.60–0.63 m, 2 H, 0.70–0.74 m, 2 H, and 3.08 brs, 1 H (cyclopropyl); 1.21–1.26 m, 3 H ($CH_3$); 1.74–1.90 m, 3 H (2 × H-8, H-9); 2.13–2.19 m, 1 H (H-6); 2.393 brs, 2.423 brs, 2.429 brs and 2.464 brs, 1 H (H-1); 2.70–2.75 m, 1 H (H-7); 3.570 s, 3.588 s, 3.591 s and 3.594 s, 3 H ($OCH_3$); 3.72–3.80 m, 2 H and 3.83–4.05 m, 4 H (2 × H-5, H-2, CH, $OCH_2$); 4.77–4.80 m, 1 H (H-3); 5.88–6.00 m, 1 H (NH); 7.10–7.22 m, 3 H and 7.30–7.37 m, 2 H (arom.); 7.81 brd, 1 H, 8.154 s, 8.167 s and 8.181 s, 1 H, and 8.24 brs, 1 H (H-2′, H-8′, NH cyclopropyl). $^{13}$C NMR: 6.48, 2 C, 24.14 (cyclopropyl); 19.76 ($CH_3$); 31.84 (C-8); 41.11, 41.33 (C-1, C-6); 45.17 (C-7); 48.14 (C-9); 49.82, 49.96 (CH); 51.89 ($OCH_3$); 66.11 (C-2); 67.03 ($OCH_2$); 73.68 (C-5); 83.49 (C-3); 119.37 (C-5′); 120.33, 2 C, 124.53, 129.61, 129.64 (arom.); 138.79 (C-8′); 150.94, 2 C (C-4′, arom.); 152.34 (C-2′); 155.72 (C-6′); 173.84 (C=O). $^{31}$P NMR: 4.00, 4.08, 4.41, 4.49.

*Methyl N-[({(1R*,2R*,3R*,6R*,7S*,9S*)-2-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-4-oxatricyclo-[4.2.1.0$^{3,7}$]nonan-9-yl}methoxy)phenoxyphosphoryl]-L-alaninate* (**36**): Yield 302 mg (74%). For

$C_{27}H_{34}N_7O_6P$ (583.6) calculated: 55.57% C, 5.87% H, 16.80% N, 5.31% P; found: 55.59% C, 6.04% H, 16.52% N, 5.29% P. FAB MS, *m/z* (rel.%): 584 (100) [M + H], 200 (47), 191 (53). $^1$H NMR: 0.57–0.68 m, 4 H and 3.04 m, 1 H (cyclopropyl); 1.21–1.26 m, 3 H ($CH_3$); 1.72–1.82 m, 3 H (2 × H-8, H-9); 2.12–2.18 m, 1 H (H-6); 2.25 brs, 2.28 brs, 2.30 brs and 2.33 brs, 1 H (H-1); 2.68–2.73 m, 1 H (H-7); 3.573 s, 0.75 H, 3.589 s, 1.5 H, and 3.593 s, 0.75 H ($OCH_3$); 4.65–4.69 m, 1 H (H-3); 3.68–3.77 m and 3.83–4.06 m, 6 H (2 × H-5, H-2, CH, $OCH_2$); 5.76–5.82 m, 2 H ($NH_2$); 5.88–6.00 m, 1 H (NH); 7.11–7.22 m, 4 H (6′-NH, arom.); 7.71 s, 7.72 s, 7.725 s and 7.73 s, 1 H (H-8′). $^{13}$C NMR: 6.53, 2 C, 23.99 (cyclopropyl); 19.74, 19.79 ($CH_3$); 31.84 (C-8); 41.17, 41.37 (C-1, C-6); 45.09 (C-7); 48.26, 48.32 (C-9); 49.84, 49.99 (CH); 51.93 ($OCH_3$); 65.25 (C-2); 67.13 ($OCH_2$); 73.66 (C-5); 83.79, 83.84 (C-3); 113.57 (C-5′); 120.33, 120.37, 124.59, 129.68, 2 C, 150.91 (arom.); 135.13 (C-8′); 151.67 (C-4′); 156.07 (C-6′); 160.22 (C-2′); 173.76, 173.86 (C=O). $^{31}$P NMR: 4.07, 4.10, 4.50, 4.56.

*Methyl N-[({(1R*,2R*,3R*,6R*,7S*)-2-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-4-oxatricyclo-[4.2.1.0$^{3,7}$]nonan-6-yl}methoxy)phenoxyphosphoryl]-L-alaninate* (**38**): Yield 261 mg (64%). For $C_{27}H_{34}N_7O_6P$ (583.6) calculated: 55.57% C, 5.87% H, 16.80% N, 5.31% P; found: 55.28% C, 5.86% H, 16.55% N, 5.33% P. FAB MS, *m/z* (rel.%): 584 (100) [M + H], 325 (26), 200 (37), 191 (69). $^1$H NMR: 0.55–0.67 m, 4 H and 3.02 brs, 1 H (cyclopropyl); 1.22–1.26 m, 3 H ($CH_3$); 1.35 m, 1 H (H-9a); 1.63 m, 1 H (H-8a); 1.73–1.83 m, 2 H (H-8b, H-9b); 2.40 m, 1 H (H-1); 2.56–2.62 m, 1 H (H-7); 3.61 s, 3.62 s and 3.63 s, 3 H ($OCH_3$); 3.71–3.79 m, 2 H (H-5); 3.82–3.90 m, 1 H (CH); 3.92 m, 1 H (H-2); 3.96–4.08 m, 2 H ($CH_2O$); 4.75 m, 1 H (H-3); 5.83 brs, 2 H ($NH_2$); 5.98–6.10 m, 1 H (NH); 7.16–7.23 m, 3 H (H-2 phenyl, H-4 phenyl); 7.28 brs, 1 H (2′-NH); 7.38 m, 2 H (H-3 phenyl); 7.76 s and 7.761 s, 1 H (H-8′). $^{13}$C NMR: 6.62, 2 C, 24.04 m (cyclopropyl); 19.85 m ($CH_3$); 33.30 (C-8); 38.45 m (C-9); 40.05 m (C-1); 47.17, 47.26 (C-7); 48.20 m (C-6); 49.90, 50.05 (CH); 52.10, 52.12 ($OCH_3$); 64.99 (C-2); 68.19 m ($CH_2O$); 76.05, 76.19 (C-5); 85.30 (C-3); 113.63 (C-5′); 120.44, 120.48, 2 C (C-2 phenyl); 124.80 (C-4 phenyl); 129.80, 129.83, 2 C (C-3 phenyl); 135.16 (C-8′); 150.90 m (C-1 phenyl); 151.65 (C-4′); 156.10 (C-6′); 160.29 (C-2′); 173.92 m (C=O). $^{31}$P NMR: 3.79, 3.81, 4.32, 4.42.

*Methyl N-({[(1R*,2R*,3R*,6R*,7S*)-9-(6-amino-9H-purin-9-yl)-4-oxatricyclo[4.2.1.0$^{3,7}$]nonan-6-yl]-methoxy}phenoxyphosphoryl)-L-alaninate* (**40**): Yield 218 mg (59%). For $C_{24}H_{29}N_6O_6P$ (528.5) calculated: 54.54% C, 5.53% H, 15.90% N, 5.86% P; found: 54.25% C, 5.62% H, 15.69% N, 5.77% P. FAB MS, *m/z* (rel.%): 529 (100) [M + H], 200 (63), 136 (94). $^1$H NMR: 1.23–1.27 m, 3 H ($CH_3$); 1.40–1.48 m, 1 H, 1.64–1.71 m, 1 H, and 1.77–1.86 m, 2 H (2 × H-2, 2 × H-8); 2.51–2.56 m, 1 H and 2.59–2.65 m, 1 H (H-1, H-7); 3.614 s, 1.5 H, 3.628 s, 0.75 H, and 3.630 s, 0.75 H ($OCH_3$); 3.74–3.90 m, 3 H (2 × H-4, CH); 3.98–4.11 m, 3 H (H-9, $OCH_2$); 4.83–4.87 m, 1 H (H-6); 5.93–6.05 m, 1 H (NH); 7.15 brs, 2 H ($NH_2$); 7.15–7.23 m, 3 H and 7.36–7.41 m, 2 H (arom.); 8.134 s and 8.136 s, 1 H, and 8.190 s and 8.193 s, 1 H (H-2′, H-8′). $^{13}$C NMR: 17.73 ($CH_3$); 33.37 (C-8); 36.26, 38.34 (C-2); 40.00 (C-1); 47.22, 47.31 (C-7); 48.11, 48.17 (C-3); 49.84, 49.98 (CH); 51.95 ($OCH_3$); 65.77 (C-9); 68.07 ($OCH_2$); 76.04, 76.17 (C-4); 85.07 (C-6); 119.04 (C-5′); 120.32, 120.34, 120.36, 120.38, 124.65, 129.66, 129.69, 150.91 (arom.); 138.94 (C-8′); 149.79 (C-4′); 152.42 (C-2′); 156.13 (C-6′); 173.77 (C=O). $^{31}$P NMR: 3.82, 2 P, 4.37, 4.44.

*Methyl N-[({(1R*,2R*,3R*,6R*,7S*)-2-[6-(cyclopropylamino)-9H-purin-9-yl]-4-oxatricyclo[4.2.1.0$^{3,7}$]-nonan-6-yl}methoxy)phenoxyphosphoryl]-L-alaninate* (**42**): Yield 267 mg (67%). For $C_{27}H_{33}N_6O_6P$ (568.6) calculated: 57.04% C, 5.85% H, 14.78% N, 5.45% P; found: 56.81% C, 5.79% H, 14.62% N, 5.54% P. FAB MS, *m/z* (rel.%): 569 (100) [M + H], 200 (42), 176 (54). $^1$H NMR: 0.59–0.74 m, 4 H and 3.07 m, 1 H (cyclopropyl); 1.237 s, 0.75 H, 1.250 s, 1.5 H, and

1.265 s, 0.75 H ($CH_3$); 1.40–1.48 m, 1 H, 1.63–1.70 m, 1 H, and 1.76–1.86 m, 2 H (2 × H-2, 2 × H-8); 2.50–2.65 m, 2 H (H-1, H-7); 3.614 s, 1.5 H, 3.628 s, 0.75 H, and 3.630 s, 0.75 H ($OCH_3$); 3.75–3.90 m, 3 H (2 × H-4, CH); 3.38–4.12 m, 3 H (H-9, $OCH_2$); 4.82–4.87 m, 1 H (H-6); 5.93–6.04 m, 1 H (NH); 7.16–7.23 m, 3 H and 7.36–7.40 m, 2 H (arom.); 7.80 brd, 1 H (6′-NH); 8.187 s, 0.5 H, 8.192 s, 0.5 H, and 8.23 s, 1 H (H-2′, H-8′). $^{13}$C NMR: 6.51, 2 C, 23.99 (cyclopropyl); 19.73 ($CH_3$); 33.37 (C-8); 38.27, 38.36 (C-2); 39.99 (C-1); 47.23, 47.29 (C-7); 48.18, 48.22 (C-3); 49.84, 49.98 (CH); 51.96 ($OCH_3$); 65.76 (C-9); 68.16 ($OCH_2$); 76.04, 76.15 (C-4); 85.09 (C-6); 119.40 (C-5′); 120.36, 2 C, 124.65, 129.69, 2 C, 150.91 (arom.); 138.75 (C-8′); 152.32 (C-2′); 155.71 (C-6′); 173.77 (C=O). $^{31}$P NMR: 3.82, 2 P, 4.36, 4.44.

*Antiviral activity of the prepared compounds was tested by Dr J. Balzarini (Rega Institut, Katholieke Universiteit Leuven, Belgium). His contribution is gratefully acknowledged. 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) and by the Programme of Targeted Projects of Academy of Sciences of the Czech Republic (1QS400550501).*

## REFERENCES

1. a) Balzarini J.: *J. Pharm. World Sci.* **1994**, *16*, 113; b) De Clercq E.: *Nature Rev. Drug Discovery* **2002**, *1*, 13.
2. 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.
3. 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.
4. Kim H. S., Jacobson K. A.: *Org. Lett.* **2003**, *5*, 1665.
5. 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.
6. Hřebabecký H., Masojídková M., Holý A.: *Collect. Czech. Chem. Commun.* **2005**, *70*, 103.
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. Šála M., Hřebabecký H., Masojídková M., Holý A.: *Collect. Czech. Chem. Commun.* **2006**, *71*, 635.
10. a) Jochum A., Schlienger N., Egron D., Peyrottes S., Périgaud C.: *J. Organomet. Chem.* **2005**, *690*, 2614; b) Calogeropoulou T., Detsi A., Lekkas E., Koufaki M.: *Curr. Top. Med. Chem.* **2003**, *3*, 1467.
11. McGuigan C., Pathirana R. N., Mahmood N., Hay A.: *J. Bioorg. Med. Chem. Lett.* **1992**, *2*, 701.
12. Koch H.: *Monatsh. Chem.* **1962**, *93*, 1343.
13. Naemura K., Nakazuki M.: *Bull. Chem. Soc. Jpn.* **1973**, *46*, 888.

14. Patil R. T., Parveen G., Gumaste V. K., Bhawal B. H., Deshmukh A. R. A. S.: *Synlett* **2002**, 1455.
15. Oakland J. S., Scheinmann F.: *J. Chem. Soc., Perkin Trans. 1* **1973**, 800.
16. Hřebabecký H., Masojídková M., Holý A.: *Collect. Czech. Chem. Commun.* **2004**, *69*, 435.
17. 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.
18. McGuigan C., Pathirana R. N., Mahmood N., Devine K. G., Hay A. J.: *Antiviral Res.* **1992**, *17*, 311.
19. McGuigan C., Harris S. A., Daluge S. M., Gudmundsson K. S., McLean E. W., Burnette T. C., Marr H., Hazen R., Condreay L. D., Johnson L., De Clercq E., Balzarini J.: *J. Med. Chem.* **2005**, *48*, 3504.
20. Balzarini J.: Unpublished results.