SYNTHESIS OF NOVEL CARBOCYCLIC NUCLEOSIDE ANALOGUES DERIVED FROM 7-OXABICYCLO[2.2.1]HEPTANE-2-METHANOL

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Hydroboration of [(1*R**,2*R**,4*R**)-7-oxabicyclo[2.2.1]hept-5-en-2-yl]methyl benzoate (**5**), which was prepared by Diels–Alder reaction of furan with acrolein and subsequent reduction and benzoylation of the Diels–Alder product, afforded [(1*R**,2*S**,4*S**,6*S**)-6-hydroxy-7-oxabicyclo[2.2.1]heptan-2-yl]methyl benzoate (**6**) and [(1*R**,2*R**,4*R**,5*S**)-5-hydroxy-7-oxabicyclo[2.2.1]heptan-2-yl]methyl benzoate (**7**). The key intermediates, [(1*R**,2*S**,4*S**,6*R**)-6-hydroxy-7-oxabicyclo[2.2.1]heptan-2-yl]methyl benzoate (**10**) and [(1*R**,2*R**,4*R**,5*R**)-5-hydroxy-7-oxabicyclo[2.2.1]heptan-2-yl]methyl benzoate (**11**), were prepared from **6** and **7**, respectively, by oxidation with pyridinium dichromate and subsequent reduction of the thus obtained ketones. The Mitsunobu reaction of **10** and **11** with 6-chloropurine and subsequent reductive deprotection with diisobutylaluminium hydride afforded 6-chloropurine derivatives, which were converted to other purine analogues. Thymine analogues were prepared by Mitsunobu reaction of **10** and **11** with 3-benzoyl-5-methylpyrimidine-2,4(1*H*,3*H*)-dione and subsequent methanolysis. The target compounds were tested for the activity against *Coxsackie* virus.

Keywords: Nucleosides; Carbocyclic nucleosides; Purines; Adenine; Thymine; 5-Methylpyrimidine-2,4(1*H*,3*H*)-dione; 6-Chloropurine; 6-(Dimethylamino)purine; 6-(Cyclopropylamino)purine; Mitsunobu reaction; *Coxsackie* virus.

Extensive modifications of naturally occurring nucleosides led to discovery of a great deal of compounds with remarkable biological activity. The most important are the effects on various severe diseases such as cancer or viral infection. A disadvantage of analogues of natural nucleosides is cleavage of N-glycosidic bond by phosphorylases. One of modifications, which were examined to overcome this difficulty, is substitution of the furanose ring of

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the sugar moiety by hydrocarbon ring. Many of such modified analogues – carbocyclic nucleosides[1] – exhibit interesting antiviral activity. U.S. Food and Drug Administration approved abacavir (Ziagen™; **1**)[2] for the treatment of HIV-1 infections and entecavir (Baraclude; **2**)[3] for the treatment of chronic hepatitis B virus (HBV) infections (Chart 1).

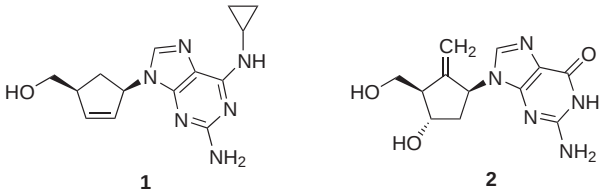


CHART 1

The analogues containg bicyclic or tricyclic skeleton were also synthesized. Jacobson and co-workers[4] described bisphosphate of the 2-iodo- and 2-chloro-6-(methylamino)purine analogues containing the oxabicyclo-[2.2.1]heptane moiety which are the most potent known antagonists of the $P2Y_1$ receptor. Recently, we reported the syntheses of novel racemic conformationally-locked carbocyclic purine nucleoside analogues[5] derived from bicyclo[2.2.1]heptane, 4-oxa- and 4,8-dioxatricyclo[4.2.1.$0^{3,7}$]nonane, and 4-oxatricyclo[4.3.1.$0^{3,7}$]decane. Some of the prepared compounds ex-

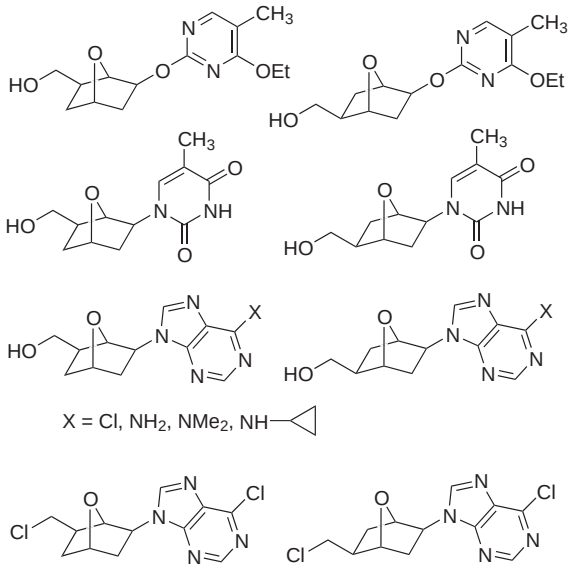
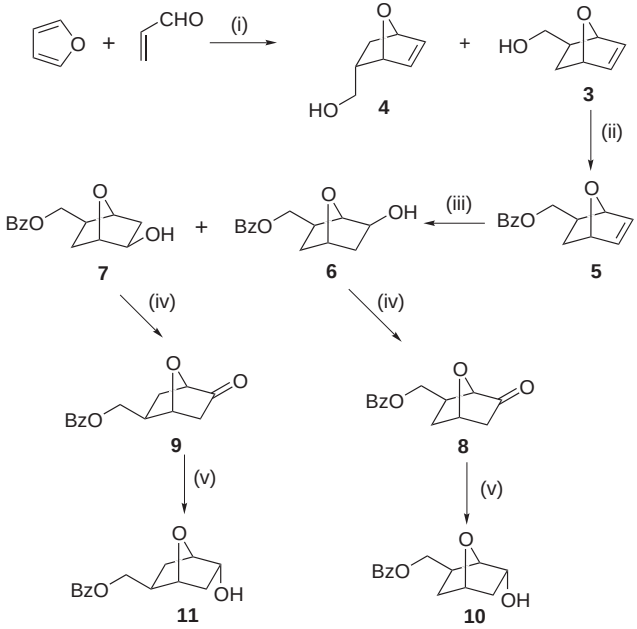


CHART 2

hibit a weak activity[5a,5c,5f] in tests for anti-HIV-1 and anti-HIV-2 in human T-lymphocyte (CEM) cells and an activity[5g–5i,6] against the *Coxsackie* virus (CVB3). The virus is a small cytolytic virus, belonging to the genus Enterovirus within the family of *Picornaviridae*. The clinical manifestations associated with enteroviruses range from mild illnesses, such as fever, rash, hand-foot-mouth syndrome, and herpangina, to serious life-threatening infections, such as meningitis, encephalitis, myocarditis, pancreatitis, acute paralysis, or neonatal sepsis. There is currently no approved therapy for treatment of enteroviral infections[7].

This study concerns synthesis and anti-coxsackievirus assay of novel racemic nucleoside analogues contaning 7-oxabicyclo[2.2.1]heptane-2-methanol. Chart 2 describes the target compounds.

Alcohol **3**, which was prepared by Diels–Alder reaction between furan and acrolein and subsequent reduction with lithium aluminium hydride, was used as the key starting material (Scheme 1). The Diels–Alder products

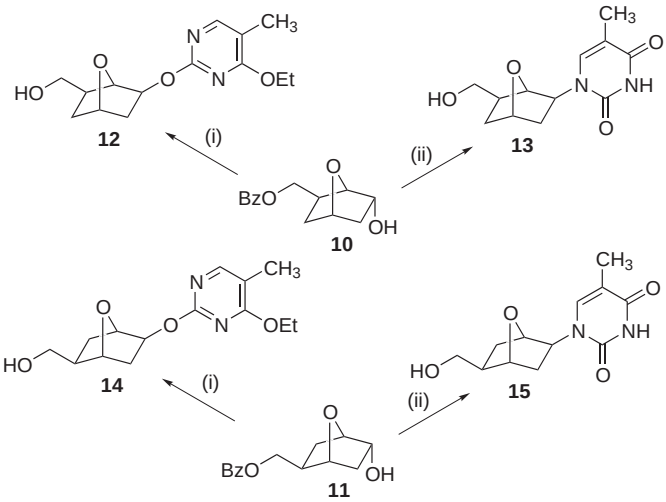


(i) 1. 100 °C, pressure, 2. $LiAlH_4$/THF, 0 °C,16.5% of **3**, 8.5% of **4**, both based on acrolein; (ii) benzoyl chloride/pyridine, 89%; (iii) 1. BF_3·THF, 0 °C, 2. $NaBO_3$, 48% of **6**, 46% of **7**; (iv) PDC/CH_2Cl_2, 75% of **8**, 85% of **9**; (v) $NaBH_4$/MeOH/THF, 0 °C, 84% of **10**, 79% of **11**

SCHEME 1

were immediately reduced without isolation to prevent the back reaction leading to starting materials[8]. *Exo*-**3** (16.5% based on acrolein) and *endo*-**4** (8.5% based on acrolein) were separated by chromatography on silica gel and isomer **3** was benzoylated. Hydroboration of the protected norbornene derivative **5** with the borane-tetrahydrofuran complex afforded a mixture of hydroxy derivatives **6** and **7** which were separated by chromatography on silica gel. The desired 2-*endo*-hydroxy derivatives **10** and **11** were prepared by oxidation of **6** and **7** with pyridinium dichromate and subsequent reduction of the thus obtained ketones **8** or **9** with sodium borohydride, respectively.

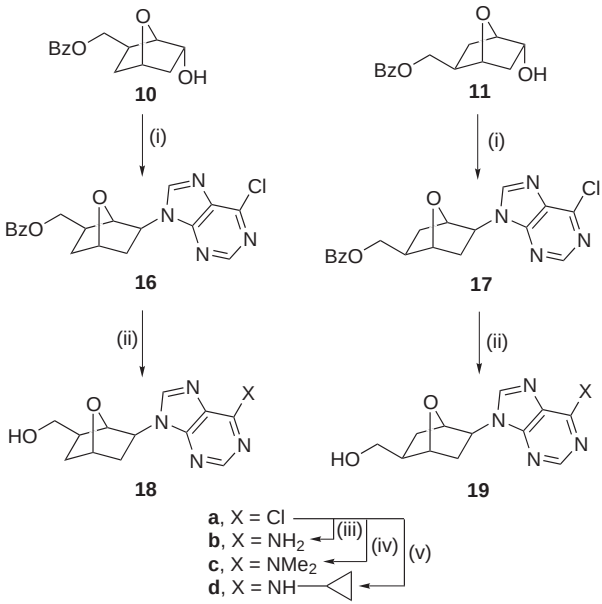
The reaction of alcohols **10** and **11** with 4-ethoxy-5-methylpyrimidin-2(1*H*)-one was performed under Mitsunobu conditions[9] and afforded, after treatment with methanolic sodium methoxide, pyrimidinyloxy derivatives **12** (85%) and **14** (77%), respectively (Scheme 2). The same reaction of **10** and **11** with 3-benzoyl-5-methylpyrimidine-2,4(1*H*,3*H*)-dione gave, after deprotection, the expected thymine derivative **13** (59%) and **15** (60%), respectively.



(i) 1. 4-ethoxy-5-methylpyrimidin-2(1*H*)-one, PPh_3, DIAD, THF, 2. MeONa/MeOH, 85% of **12** based on **10**, 77% of **14** based on **11**; (ii) 3-benzoyl-5-methylpyrimidine-2,4(1*H*,3*H*)-dione, PPh_3, DIAD, THF, 2. MeONa/MeOH, 59% of **13** based on **10**, 60% of **15** based on **11**

SCHEME 2

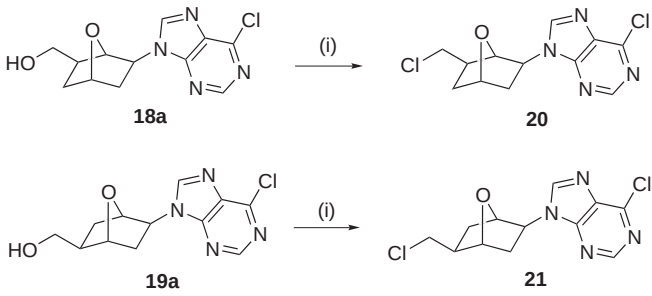
The Mitsunobu reaction of **10** and **11** with 6-chloro-9*H*-purine afforded 6-chloropurine derivatives **16** (59%) and **17** (56%), respectively, which were deprotected with diisobutylaluminium hydride in dichloromethane at –78 °C (Scheme 3). Chloropurine derivatives **18a** and **19a** were converted to adenine derivatives **18b** (72%) and **19b** (80%), respectively, by ammonolysis with liquid ammonia at 75 °C. Treatment of **18a** and **19a** with dimethylammonium dimethylcarbamate led to 6-(dimethylamino)purine analogues **18c** (79%) and **19c** (80%), respectively. Aminolysis of **18a** and **19a** with cyclopropylamine afforded 6-(cyclopropylamino)purine derivatives **18d** (83%) and **19d** (79%), respectively.



(i) 6-chloro-9*H*-purine, PPh_3, DIAD, THF, 59% of **16**, 56% of **17**; (ii) DIBAL-H/CH_2Cl_2, - 78 °C, 71% of **18a**, 88% of **19a**; (iii) NH_3 (l), 70 °C, 72% of **18b**, 80% of **19b**; (iv) $Me_2NCOO^-Me_2NH_2^+$, r.t., 79% of **18c**, 80% of **19c**; (v) cyclopropylamine, r.t., 83% of **18d**, 79% of **19d**

SCHEME 3

Substitution of the hydroxymethyl group for the chloromethyl group led, in some cases, to increasing antiviral activity[5i]. Therefore, the chloromethyl derivatives **20** and **21** were prepared by the treatment of **18a** or **19a** with thionyl chloride in hexamethylphosphoramide (HMPA) at 80 °C in 77 and 82% yields, respectively (Scheme 4).



(i) $SOCl_2$/HMPA, 80 °C, 77% of **20**, 82% of **21**

SCHEME 4

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

In conclusion, novel racemic conformationally-locked carbocyclic nucleoside analogues of thymine, 6-chloropurine, adenine, 6-(dimethylamino)purine, and 6-(cyclopropylamino)purine derived from (1*R**,2*R**,4*S**)-7-oxabicyclo[2.2.1]heptane-2-methanol substituted with a base in the position 5-*exo* or 6-*exo* were prepared. The target compounds were tested for the activity against *Coxsackie* virus (CVB3). Preliminary data showed that the 6-chloropurine analogues **18a**, **19a**, **20**, and **21** exhibit some activity (**18a**: EC_{50} 1.40 μM and CC_{50} > 50 μM; **19a**: EC_{50} 2.21 μM and CC_{50} > 50 μM; **20**: EC_{50} 0.84 μM and CC_{50} > 50 μM; **21**: EC_{50} 5.08 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 a Büchi B-540 apparatus 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 ^1H 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 (Xe, accelerating voltage 8 kV, thioglycerol–glycerol 3:1 or bis(2-hydroxyethyl) disulfide matrix) and 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.

(1*R**,2*R**,4*R**)-7-Oxabicyclo[2.2.1]hept-5-ene-2-methanol (**3**) and (1*R**,2*S**,4*R**)-7-Oxabicyclo[2.2.1]hept-5-ene-2-methanol (**4**)

A mixture of furan (50 ml), acrolein (10 ml), and hydroquinone (300 mg) was kept at room temperature under argon for 15 days and then evaporated. A solution of the residue in tetrahydrofuran (18 ml) was added dropwise to a stirred 1 M solution of lithium aluminium hydride in tetrahydrofuran (20 ml) at 0 °C under argon. The mixture was stirred at room temperature for 3 h and excess of the hydride 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 tetrahydrofuran (3 × 30 ml) and the combined filtrates were evaporated. Chromatography of the residue on a silica gel column in ethyl acetate–toluene (22:3) afforded 4.46 g (16.5%) of **3** and 2.26 g (8.5%) of **4**, both as a syrup.

Compound **3**: For $C_7H_{10}O_2$ (126.2) calculated: 66.64% C, 7.99% H; found: 66.45% C, 8.10% H. ESI MS, *m/z*: 149.1 [M + Na]. ^{1}H NMR: 1.05 ddd, 1 H, J_{gem} = 11.4, *J*(3ex,4) = 4.6, *J*(3ex,2) = 3.5 (H-3ex); 1.23 dd, 1 H, J_{gem} = 11.3, *J*(3en,2) = 8.0 (H-3en); 1.58 dddd, 1 H, *J*(2,3en) = 7.9, *J*(2,3ex) = 3.5, *J*(2,CH_2) = 9.5 and 4.8 (H-2); 3.24 m, 1 H and 3.41 m, 1 H (CH_2O); 4.68 t, 1 H, *J*(OH,CH_2) = 5.4 (OH); 4.74 m, 1 H (H-1); 4.84 m, 1 H (H-4); 6.30–6.33 m, 2 H (H-5 and H-6). ^{13}C NMR: 28.37 (C-3); 40.48 (C-2); 64.21 (CH_2O); 77.14 (C-4); 78.64 (C-1); 135.08 (C-6); 135.97 (C-5).

Compound **4**: For $C_7H_{10}O_2$ (126.2) calculated: 66.64% C, 7.99% H; found: 66.37% C, 8.13% H. ESI MS, *m/z* (%): 149 (100) [M + Na], 150 (9) [M + Na + H]. ^{1}H NMR: 0.56 dd, 1 H, J_{gem} = 11.1, *J*(3en,2) = 4.2 (H-3en); 1.79 ddd, 1 H, J_{gem} = 11.1, *J*(3ex,2) = 9.1, *J*(3ex,4) = 4.8 (H-3ex); 2.21 m, 1 H (H-2); 2.92 td, 1 H, J_{gem} = *J*(CH_2,2) = 10.1, *J*(CH_2,OH) = 5.0 and 3.27 ddd, 1 H, J_{gem} = 10.5, *J*(CH_2,OH) = 6.1, *J*(CH_2,2) = 4.5 (CH_2O); 4.54 t, 1 H, *J*(OH,CH_2) = 5.1 (OH); 4.83 m, 1 H (H-4); 4.85 m, 1 H (H-1); 6.24 d, 1 H, *J*(6,5) = 5.9, *J*(6,1) = 1.6 (H-6); 6.37 dd, 1 H, *J*(5,6) = 5.9, *J*(5,4) = 1.7 (H-5). ^{13}C NMR: 27.97 (C-3); 40.83 (C-2); 63.74 (CH_2O); 77.66 (C-4); 78.98 (C-1); 132.36 (C-6); 136.42 (C-5).

[(1*R**,2*R**,4*R**)-7-Oxabicyclo[2.2.1]hept-5-en-2-yl]methyl Benzoate (**5**)

Benzoyl chloride (20.9 ml, 18 mmol) was added at 0 °C to a stirred solution of alcohol **3** (18.91 g, 150 mmol) in pyridine (200 ml) and the mixture was allowed to stand at room temperature overnight. Pyridine was then evaporated and the residue was partitioned between ethyl acetate (600 ml) and water (300 ml). The organic phase was washed with water (300 ml), 5% hydrochloric acid (to acidic reaction of the aqueous phase), 10% sodium hydrogencarbonate solution (3 × 300 ml), dried over anhydrous sodium sulfate and evaporated. Chromatography of the residue on silica gel (1 kg) in toluene–ethyl acetate (22:3) afforded 30.74 g (89%) of benzoate **5** as a thick sirup. For $C_{14}H_{14}O_3$ (230.3) calculated: 73.03% C, 6.13% H; found: 72.89% C, 6.10% H. ^{1}H NMR: 1.31 ddd, 1 H, J_{gem} = 11.5, *J*(3ex,4) = 4.6, *J*(3ex,2) = 3.4 (H-3exo); 1.39 dd, 1 H, J_{gem} = 11.5, *J*(3en,2) = 7.9 (H-3en); 1.95 dddd, 1 H, *J*(2,CH_2O) = 9.4 and 6.2, *J*(2,3en) = 7.9, *J*(2,3ex) = 3.6 (H-2); 4.12 dd, 1 H, J_{gem} = 10.8, *J*(CH_2,2) = 9.4 and 4.32 dd, 1 H, *J*(CH_2,2) = 6.2 (CH_2O); 4.85 m, 1 H (H-1); 4.95 dm, 1 H, *J*(4,3ex) = 4.5 (H-4); 6.37 dd, 1 H, *J*(5,6) = 5.8, *J*(5,4) = 1.7 (H-5); 6.39 dd, 1 H, *J*(6,5) = 5.8, *J*(6,1) = 1.6 (H-6); 7.54 m, 2 H, 7.67 m, 1 H and 8.01 m, 2 H (arom.). ^{13}C NMR: 28.49 (C-3); 36.95 (C-2); 67.43 (CH_2O); 77.38 (C-4); 78.82 (C-1); 128.99, 2 C, 129.45, 2 C, 129.97 and 133.58 (arom.); 134.79 (C-6); 136.52 (C-5); 165.94 (C=O).

[(1*R**,2*S**,4*S**,6*S**)-6-Hydroxy-7-oxabicyclo[2.2.1]heptan-2-yl]methyl Benzoate (**6**) and
[(1*R**,2*R**,4*R**,5*S**)-5-Hydroxy-7-oxabicyclo[2.2.1]heptan-2-yl]methyl Benzoate (**7**)

A 1 M solution of borane in tetrahydrofuran (20 ml) was added dropwise under argon to a stirred solution of alkene **5** (9.21 g, 40 mmol) in tetrahydrofuran (10 ml) cooled to 0 °C. The reaction mixture was stirred at 0 °C for 3 h. Excess of borane was decomposed by addition of water (0.5 ml) and then a suspension of sodium perborate tetrahydrate (18.5 g, 120 mmol) in water (70 ml) was added in one portion. The reaction mixture was stirred at room temperature overnight and then diluted with ethyl acetate (300 ml). The organic phase was separated, dried over anhydrous sodium sulfate, and evaporated. The residue was chromatographed on silica gel (1.3 kg) in toluene–ethyl acetate (1:1).

Compound **6**: Yield 4.80 g (48%) of a sirup. For $C_{14}H_{16}O_4$ (248.3) calculated: 67.73% C, 6.50% H; found: 67.72% C, 6.64% H. FAB MS, *m/z* (%): 249 (48) [M + H], 105 (100) [benzoyl]. ^{1}H NMR: 1.13 m, 1 H (H-3ex); 1.36 m, 1 H (H-5ex); 1.49 dd, 1 H, J_{gem} = 11.9, *J*(3en,2) = 8.5 (H-3en); 1.81 dd, 1 H, J_{gem} = 12.4, *J*(5en,6) = 7.1 (H-5en); 2.05 m, 1 H (H-2); 3.82 ddd, 1 H, *J*(6,5en) = 7.0, *J*(6,OH) = 4.7, *J*(6,5ex) = 2.5 (H-6); 4.00 dd, 1 H, J_{gem} = 10.7, *J*(CH_2,2) = 9.3 and 4.06 dd, 1 H, J_{gem} = 10.7, *J*(CH_2,2) = 6.4 (CH_2O); 4.09 bs, 1 H (H-1); 4.50 t, 1 H, *J*(4,3ex) = *J*(4,5ex) = 5.3 (H-4); 4.78 d, 1 H, *J*(OH,6) = 4.7 (OH); 7.54 m, 2 H (H-3´); 7.67 m, 1 H (H-4´); 7.98 m, 2 H (H-2´). ^{13}C NMR: 32.76 (C-3); 37.25 (C-2); 41.98 (C-5); 66.52 (CH_2O); 72.49 (C-6); 74.67 (C-4); 83.64 (C-1); 129.00 (C-3´); 129.37 (C-2´); 129.93 (C-1´); 133.59 (C-4´); 165.89 (C=O).

Compound **7**: Yield 4.57 g (46%) of a sirup. For $C_{14}H_{16}O_4$ (248.3) calculated: 67.73% C, 6.50% H; found: 67.56% C, 6.69% H. FAB MS, *m/z* (%): 249 (41) [M + H], 105 (100) [benzoyl]. ^{1}H NMR: 1.14 bddd, 1 H, J_{gem} = 12.6, *J*(3ex,4) = 5.7, *J*(3ex,2) = 3.6 (H-3ex); 1.40 dddd, 1 H, J_{gem} = 12.6, *J*(6ex,1) = 5.7, *J*(6ex,5) = 2.4, $J_{l.r.}$ = 0.9 (H-6ex); 1.47 dd, 1 H, J_{gem} = 12.6, *J*(3en,2) = 8.5 (H-3en); 1.83 dd, 1 H, J_{gem} = 12.5, *J*(6en,5) = 7.0 (H-6en); 2.03 m, 1 H (H-2); 3.78 ddd, 1 H, *J*(5,6en) = 7.0, *J*(5,OH) = 4.8, *J*(5,6ex) = 2.4 (H-5); 3.97 dd, 1 H, J_{gem} = 10.8, *J*(CH_2,2) = 9.3 and 4.02 dd, 1 H, J_{gem} = 10.8, *J*(CH_2,2) = 6.4 (CH_2O); 4.20 d, 1 H, *J*(4,3ex) = 5.7 (H-4); 4.38 d, 1 H, *J*(1,6ex) = 5.6 (H-1); 4.77 d, 1 H, *J*(OH,5) = 4.8 (OH); 7.53 m, 2 H (H-3´); 7.66 m, 1 H (H-4´); 7.97 m, 2 H (H-2´). ^{13}C NMR: 28.52 (C-3); 40.92 (C-2); 41.31 (C-6); 66.74 (CH_2O); 72.85 (C-5); 75.94 (C-1); 81.88 (C-4); 128.97 (C-3´); 129.38 (C-2´); 129.93 (C-1´); 133.54 (C-4´); 165.90 (C=O).

[(1*R**,2*S**,4*S**)-6-Oxo-7-oxabicyclo[2.2.1]heptan-2-yl]methyl Benzoate (**8**) and
[(1*R**,2*R**,4*R**)-5-Oxo-7-oxabicyclo[2.2.1]heptan-2-yl]methyl Benzoate (**9**)

A solution of alcohol **6** or **7** (2.48 g, 10 mmol) in dichloromethane (20 ml) was added to a suspension of powdered molecular sieves (5.5 g) and pyridinium dichromate (5.83 g, 15.5 mmol) in dichloromethane (60 ml). The reaction mixure was stirred at room temperature for 3 days. Solids were filtered off and washed with ethyl acetate. The filtrate was evaporated, the residue was dissolved in ethyl acetate (100 ml), filtered and the filtrate evaporated. The residue was chromatographed on silica gel (150 g) in toluene–ethyl acetate (4:1) and crystallized from methanol.

Compound **8**: Yield 1.85 g (75%). M.p. 105–106 °C. For $C_{14}H_{14}O_4$ (246.3) calculated: 68.28% C, 5.73% H; found: 68.26% C, 5.78% H. ^{1}H NMR: 1.56 dddd, 1 H, J_{gem} = 12.4, *J*(3ex,4) = 5.4, *J*(3ex,2) = 4.3, *J*(3ex,5ex) = 2.5 (H-3ex); 1.97 dd, 1 H, J_{gem} = 12.4, *J*(3en,2) = 8.7 (H-3en); 2.14 d, 1 H, J_{gem} = 15.5 (H-5en); 2.37–2.45 m, 2 H (H-2 and H-5ex); 4.12 dd, 1 H, J_{gem} = 10.8, *J*(CH_2,2) = 9.1 and 4.20 dd, 1 H, *J*(CH_2,2) = 6.3 (CH_2O); 4.35 bs, 1 H (H-1);

4.93 t, 1 H, *J*(4,3ex) = *J*(4,5ex) = 5.6 (H-4); 7.54 m, 2 H, 7.67 m, 1 H and 7.99 m, 2 H (arom.). ^{13}C NMR: 31.97 (C-3); 36.93 (C-2); 43.87 (C-5); 65.32 (CH_2O); 76.31 (C-4); 80.70 (C-1); 129.03, 2 C, 129.47, 2 C, 129.75 and 133.70 (arom.); 165.85 (C=O); 211.80 (C-6).

Compound **9**: Yield 2.09 (85%). M.p. 103–104 °C. For $C_{14}H_{14}O_4$ (246.3) calculated: 68.28% C, 5.73% H; found: 68.33% C, 5.82% H. FAB MS, *m/z* (%): 247 (8) [M + H], 105 (100) [benzoyl]. ^{1}H NMR: 1.58 dddm, 1 H, J_{gem} = 13.4, *J*(3ex,4) = 6.4, *J*(3ex,2) = 4.2 (H-3ex); 1.82 dd, 1 H, J_{gem} = 13.4, *J*(3en,2) = 8.6 (H-3en); 2.17 d, 1 H, J_{gem} = 17.5 (H-6en); 2.45 ddm, 1 H, J_{gem} = 17.5, *J*(6ex,1) = 6.1 (H-6ex); 2.52 m, 1 H (H-2); 4.11 dd, 1 H, J_{gem} = 10.9, *J*(CH_2,2) = 9.1 and 4.18 dd, 1 H, J_{gem} = 10.9, *J*(CH_2,2) = 6.3 (CH_2O); 4.41 bd, 1 H, *J*(4,3ex) = 6.3 (H-4); 4.80 bd, 1 H, *J*(1,6ex) = 6.0 (H-1); 7.54 m, 2 H (H-3′); 7.67 m, 1 H (H-4′); 8.00 m, 2 H (H-2′). ^{13}C NMR: 27.80 (C-3); 40.34 (C-2); 42.90 (C-6); 66.23 (CH_2O); 77.55 (C-1); 78.96 (C-4); 128.97 (C-3′); 129.45 (C-2′); 129.83 (C-1′); 133.62 (C-4′); 165.87 (C=O); 211.79 (C-5).

[(1*R**,2*S**,4*S**,6*R**)-6-Hydroxy-7-oxabicyclo[2.2.1]heptan-2-yl]methyl Benzoate (**10**) and [(1*R**,2*R**,4*R**,5*R**)-5-Hydroxy-7-oxabicyclo[2.2.1]heptan-2-yl]methyl Benzoate (**11**)

Sodium borohydride (760 mg, 20 mmol) was added to a stirred solution of ketone **8** or **9** (4.93 g, 20 mmol) in methanol (75 ml) and tetrahydrofuran (25 ml) at 0 °C. The mixture was stirred at 0 °C for 30 min and then a saturated aqueous solution of ammonium chloride was slowly added. The mixture was extracted with ethyl acetate (400 ml), the ethyl acetate solution was dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on a silica gel column (450 g) in toluene–ethyl acetate (1:1) and compound **10** was then crystallized from diethyl ether–cyclohexane.

Compound **10**: Yield 4.17 g (84%). M.p. 117–118 °C. For $C_{14}H_{16}O_4$ (248.3) calculated: 67.73% C, 6.50% H; found: 67.53% C, 6.59% H. FAB MS, *m/z* (%): 249 (17) [M + H], 105 (100) [benzoyl]. ^{1}H NMR: 1.04 dd, 1 H, J_{gem} = 12.2, *J*(5en,6) = 3.3 (H-5en); 1.30 dtd, 1 H, J_{gem} = 11.8, *J*(3ex,2) = *J*(3ex,4) = 5.0, *J*(3ex,5ex) = 2.6 (H-3ex); 1.73 dd, 1 H, J_{gem} = 11.9, *J*(3en,2) = 8.7 (H-3en); 1.96 dddd, 1 H, J_{gem} = 12.2, *J*(5ex,6) = 10.0, *J*(5ex,4) = 5.7, *J*(5ex,3ex) = 2.6 (H-5ex); 2.90 tdd, 1 H, *J*(2,CH_2) = *J*(2,3en) = 8.9, *J*(2,CH_2) = 6.7, *J*(2,3ex) = 4.5 (H-2); 4.05 dd, 1 H, J_{gem} = 10.6, *J*(CH_2,2) = 9.2 and 4.10 dd, 1 H, J_{gem} = 10.6, *J*(CH_2,2) = 6.6 (CH_2O); 4.10 m, 1 H (H-6); 4.18 d, 1 H, *J*(1,6) = 5.0 (H-1); 4.42 t, 1 H, *J*(4,3ex) = *J*(4,5ex) = 5.4 (H-4); 5.09 d, 1 H, *J*(OH,6) = 4.0 (OH); 7.53 m, 2 H (H-3′); 7.66 m, 1 H (H-4′); 7.98 m, 2 H (H-2′). ^{13}C NMR: 33.81 (C-2); 34.26 (C-3); 39.11 (C-5); 66.62 (CH_2O); 69.95 (C-6); 77.22 (C-4); 79.91 (C-1); 128.95 (C-3′); 129.38 (C-2′); 130.02 (C-1′); 133.53 (C-4′); 165.94 (C=O).

Compound **11**: Yield 3.92 g (79%) as a solid foam. For $C_{14}H_{16}O_4$ (248.3) calculated: 67.73% C, 6.50% H; found: 67.57% C, 6.66% H. ESI MS, *m/z* (%): 271.1 (100) [M + Na], 249 (5) [M + H]. ^{1}H NMR: 1.04 dd, 1 H, J_{gem} = 12.3, *J*(6en,5) = 3.4 (H-6en); 1.10 m, 1 H (H-3en); 2.01 ddd, 1 H, J_{gem} = 12.3, *J*(6ex,5) = 10.0, *J*(6ex,1) = 6.0 (H-6ex); 2.24 tdd, 1 H, *J*(2,3en) = *J*(2,CH_2) = 8.8, *J*(2,CH_2) = 6.5, *J*(2,3ex) = 3.8 (H-2); 2.32 dd, 1 H, J_{gem} = 12.1, *J*(3en,2) = 8.7 (H-3en); 3.99 dd, 1 H, J_{gem} = 10.7, *J*(CH_2,2) = 8.9 and 4.02 dd, 1 H, J_{gem} = 10.8, *J*(CH_2,2) = 6.5 (CH_2O); 4.07 m, 1 H (H-5); 4.26–4.30 m, 2 H (H-1 and H-4); 5.03 d, 1 H, *J*(OH,5) = 4.1 (OH); 7.53 m, 2 H (H-3′); 7.66 m, 1 H (H-4′); 7.98 m, 2 H (H-2′). ^{13}C NMR: 25.78 (C-3); 38.55 (C-6); 42.28 (C-2); 66.82 (CH_2O); 70.15 (C-5); 78.14 (C-4); 78.35 (C-1); 128.98 (C-3′); 129.39 (C-2′); 129.95 (C-1′); 133.54 (C-4′); 165.94 (C=O).

(1*R**,2*S**,4*S**,6*S**)-6-[(4-Ethoxy-5-methylpyrimidin-2-yl)oxy]-7-oxabicyclo[2.2.1]heptane-2-methanol (**12**) and
(1*R**,2*R**,4*R**,5*S**)-5-[(4-Ethoxy-5-methylpyrimidin-2-yl)oxy]-7-oxabicyclo[2.2.1]heptane-2-methanol (**14**)

A solution of diisopropyl azodicarboxylate (1.18 ml, 6 mmol) in tetrahydofuran (8 ml) was added dropwise to a stirred solution of 4-ethoxy-5-methylpyrimidin-2(1*H*)-one (924 mg, 6 mmol), triphenylphosphine (2.10 g, 8 mmol), and alcohol **10** or **11** (1.24 g, 5 mmol) in tetrahydrofuran (20 ml). The mixture was then heated to reflux for 4 h and evaporated. The residue was chromatographed on a silica gel column (250 g) in toluene–ethyl acetate (18:7) and the fractions containing pyrimidine derivative were evaporated. A solution of the residue in methanolic 0.1 M sodium methoxide (75 ml) was kept at room temperature overnight. Dowex 50 (H^+) was then added until UV-absorption of the solution disappeared; **12** or **14** was adsorbed on the resin. The resin was filtered off and washed with methanol–aqueous 25% ammonia (8:2; 150 ml). The washings were evaporated and the residue was crystallized from water (**12**) or chromatographed on silica gel (100 g) in ethyl acetate–toluene (4:1) (**14**).

Compound **12**: Yield 1.19 g (85%). M.p. 90–91 °C. For $C_{14}H_{20}N_2O_4$ (280.3) calculated: 59.98% C, 7.19% H, 9.99% N; found: 59.85% C, 7.18% H, 9.83% N. ESI MS, *m/z* (%): 304.1 (16) [M + Na + H], 303.1 (100) [M + Na], 281.0 (53) [M + H], 155.1 (6) [base + H]. ^{1}H NMR: 0.99 dm, 1 H, J_{gem} = 11.8 (H-3ex); 1.30 t, 3 H, J(CH_3,CH_2) = 7.1 ($CH_2C\mathbf{H}_3$); 1.51 dd, 1 H, J_{gem} = 11.9, J(3en,2) = 8.5 (H-3en); 1.62 dm, 1 H, J_{gem} = 13.1 (H-5ex); 1.89 m, 1 H (H-2); 1.96 d, 3 H, J(CH_3,5´) = 0.9 (5´-CH_3); 2.07 dd, 1 H, J_{gem} = 13.1, J(5en,6) = 7.2 (H-5en); 3.12–3.18 m, 2 H (CH_2O); 4.28 q, 2 H, J(CH_2,CH_3) = 7.1 (OC$\mathbf{H}_2CH_3$); 4.43 bs, 1 H (H-1); 4.55 bt, 1 H, J(4,3ex) = J(4,5ex) = 5.2 (H-4); 4.74 bt, 1 H, J(OH,CH_2) = 5.4 (OH); 5.02 dd, 1 H, J(6,5en) = 7.1, J(6,5ex) = 2.6 (H-6); 8.08 q, 1 H, J(6´,CH_3) = 0.9 (H-6´). ^{13}C NMR: 11.59 (5´-CH_3); 14.57 ($CH_2\mathbf{C}H_3$); 32.44 (C-3); 39.84 (C-5); 40.80 (C-2); 62.70 (O$\mathbf{C}H_2CH_3$); 63.41 (CH_2O); 74.77 (C-4); 78.44 (C-6); 80.81 (C-1); 110.46 (C-5´); 157.99 (C-6´); 163.10 (C-4´); 168.16 (C-2´).

Compound **14**: Yield 1.08 g (77%) as a thick sirup. For $C_{14}H_{20}N_2O_4$ (280.3) calculated: 59.98% C, 7.19% H, 9.99% N; found: 59.91% C, 7.30% H, 9.75% N. ESI MS, *m/z* (%): 304.1 (15), 303.1 (100) [M + Na]. ^{1}H NMR: 1.05 ddd, 1 H, J_{gem} = 12.6, J(3ex,4) = 6.0, J(3ex,2) = 4.0 (H-3ex); 1.30 t, 3 H, J(CH_3,CH_2) = 7.1 ($CH_2C\mathbf{H}_3$); 1.57 dd, 1 H, J_{gem} = 12.6, J(3en,2) = 8.5 (H-3en); 1.66 dddd, 1 H, J_{gem} = 13.1, J(6ex,1) = 5.6, J(6ex,5) = 2.6, $J_{l.r.}$ = 0.8 (H-6ex); 1.82 m, 1 H (H-2); 1.96 d, 3 H, J(CH_3,6´) = 0.9 (5´-CH_3); 2.04 dd, 1 H, J_{gem} = 13.1, J(6en,5) = 7.2 (H-6en); 3.09–3.17 m, 2 H (C$\mathbf{H}_2$OH); 4.27 q, 2 H, J(CH_2,CH_3) = 7.1 (OC$\mathbf{H}_2CH_3$); 4.44 bd, 1 H, J(1,6ex) = 5.7 (H-1); 4.49 bd, 1 H, J(4,3ex) = 5.9 (H-4); 4.68 bt, 1 H, J(OH,CH_2) = 5.3 (OH); 5.00 dd, 1 H, J(5,6en) = 7.1, J(5,6ex) = 2.6 (H-5); 8.08 q, 1 H, J(6´,CH_3) = 0.9 (H-6´). ^{13}C NMR: 11.61 (5´-CH_3); 14.54 ($CH_2\mathbf{C}H_3$); 28.44 (C-3); 39.09 (C-6); 44.42 (C-2); 62.64 (O$\mathbf{C}H_2CH_3$); 63.69 (CH_2OH); 76.09 (C-1); 78.64 (C-5); 79.07 (C-4); 110.59 (C-5´); 157.83 (C-6´); 163.06 (C-4´); 168.26 (C-2´).

1-[(1*R**,2*S**,4*S**,6*S**)-6-(Hydroxymethyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**13**) and
1-[(1*R**,2*S**,4*R**,5*R**)-5-(Hydroxymethyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**15**)

A solution of diisopropyl azodicarboxylate (0.59 ml, 3 mmol) in tetrahydofuran (4 ml) was added dropwise to a stirred solution of 3-benzoyl-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (805 mg, 3.5 mmol), triphenylphosphine (1.05 g, 4 mmol), and alcohol **10** or **11** (620 mg, 2.5 mmol) in tetrahydrofuran (10 ml). The mixture was heated to reflux for 4 h and then evaporated. The residue was chromatographed on a silica gel column (120 g) in toluene–ethyl acetate (18:7) and the fractions containing the pyrimidine derivative were evaporated. A solution of the residue in methanolic 0.1 M sodium methoxide (40 ml) was left at room temperature overnight. The solution was neutralized with Dowex 50 (H^+), filtered, and evaporated. The residue was crystallized from diethyl ether.

Compound **13**: Yield 372 mg (59%). M.p. 179–181 °C. For $C_{12}H_{16}N_2O_4$ (252.3) calculated: 57.13% C, 6.39% H, 11.10% N; found: 56.96% C, 6.32% H, 10.89% N. ESI MS, *m/z* (%): 275.0 (100) [M + Na], 253.1 (18) [M + H]. ^{1}H NMR: 1.02 m, 1 H (H-5′ex); 1.57 dd, 1 H, J_{gem} = 12.0, *J*(5′en,6′) = 8.5 (H-5′en); 1.65 m, 1 H (H-3′ex); 1.76 d, 3 H, *J*(CH_3,6) = 1.2 (CH_3); 1.91 m, 1 H (H-6′); 2.08 dd, 1 H, J_{gem} = 13.1, *J*(3′en,2′) = 8.7 (H-3′en); 3.10–3.14 m, 2 H (CH_2O); 4.34 s, 1 H (H-1′); 4.64 bt, 1 H, *J*(4′,3′ex) = *J*(4′,5′ex) = 5.2 (H-4′); 4.69 dd, 1 H, *J*(2′,3′en) = 8.6, *J*(2′,3′ex) = 3.9 (H-2′); 4.74 bs, 1 H (OH); 7.48 q, 1 H, *J*(6,CH_3) = 1.2 (H-6); 11.25 bs, 1 H (NH). ^{13}C NMR: 12.60 (CH_3); 32.72 (C-5′); 39.32 (C-3′); 43.40 (C-6′); 56.15 (C-2′); 63.40 (CH_2O); 75.36 (C-4′); 81.61 (C-1′); 109.51 (C-5); 137.27 (C-6); 151.27 (C-2); 163.97 (C-4).

Compound **15**: Yield 380 mg (60%). M.p. 249–251 °C. For $C_{12}H_{16}N_2O_4$ (252.3) calculated: 57.13% C, 6.39% H, 11.10% N; found: 57.00% C, 6.41% H, 10.91% N. ESI MS, *m/z*: 275.0 [M + Na]. ^{1}H NMR: 1.05 m, 1 H (H-6′ex); 1.59 dd, 1 H, J_{gem} = 12.6, *J*(6′en,5′) = 8.5 (H-6′en); 1.70 m, 1 H (H-3′ex); 1.76 d, 3 H, *J*(CH_3,6) = 1.2 (CH_3); 1.87 m, 1 H (H-5′); 2.06 dd, 1 H, J_{gem} = 13.2, *J*(3′en,2′) = 8.7 (H-3′en); 3.08–3.15 m, 2 H (CH_2O); 4.48 d, 1 H, *J*(1′,6′ex) = 5.7 (H-1′); 4.52 d, 1 H, *J*(4′,3′ex) = 5.6 (H-4′); 4.66 dd, 1 H, *J*(2′,3′en) = 8.6, *J*(2′,3′ex) = 3.8 (H-2′); 4.73 bt, 1 H, *J*(OH,CH_2) = 5.2 (OH); 7.49 q, 1 H, *J*(6,CH_3) = 1.2 (H-6); 11.24 bs (NH). ^{13}C NMR: 12.63 (CH_3); 30.96 (C-6′); 38.51 (C-3′); 44.80 (C-5′); 56.57 (C-2′); 63.68 (CH_2O); 76.73 (C-4′); 79.97 (C-1′); 109.30 (C-5); 137.38 (C-6); 151.28 (C-2); 163.98 (C-4).

[(1*R**,2*R**,4*S**,6*S**)-6-(6-Chloro-9*H*-purin-9-yl)bicyclo[2.2.1]heptan-2-yl]methyl Benzoate (**16**) and
[(1*R**,2*R**,4*R**,5*S**)-5-(6-Chloro-9*H*-purin-9-yl)-7-oxabicyclo[2.2.1]heptan-2-yl]methyl Benzoate (**17**)

A solution of diisopropyl azodicarboxylate (8.9 ml, 45 mmol) in tetrahydrofuran (50 ml) was slowly added to a solution of alcohol **10** or **11** (7.45 g, 30 mmol), triphenylphosphine (15.74 g, 60 mmol), and 6-chloropurine (6.96 g, 45 mmol) in THF (250 ml). The reaction mixture was then heated to reflux for 6 h and evaporated. The residue was chromatographed on silica gel (1 kg) in ethyl acetate–toluene (1:1) and crystallized from butyl acetate.

Compound **16**: Yield 6.86 g (59%). M.p. 186.5–188.5 °C. For $C_{19}H_{17}ClN_4O_3$ (384.8) calculated: 59.30% C, 4.45% H, 9.21% Cl, 14.56% N; found: 59.21% C, 4.51% H, 9.29% Cl, 14.42% N. ESI MS, *m/z* (%): 794.5 (15), 793.5 (24), 792.5 (64), 790.5 (100), 789.7 (16), 409.1/407.1 (27/79) [M + Na], 387/385.2 (9/26) [M + H]. ^{1}H NMR: 1.37 dm, 1 H, J_{gem} = 12.0

(H-3ex); 1.84 dd, 1 H, J_{gem} = 12.1, *J*(3en,2) = 8.6 (H-3en); 2.08 dm, 1 H, J_{gem} = 13.3 (H-5ex); 2.35 dd, 1 H, J_{gem} = 13.3, *J*(5en,6) = 8.4 (H-5en); 2.54 m, 1 H (H-2); 4.06 dd, 1 H, J_{gem} = 10.9, *J*(CH_2,2) = 9.2 and 4.14 dd, 1 H, J_{gem} = 10.9, *J*(CH_2,2) = 6.3 (CH_2O); 4.71 bs, 1 H (H-1); 4.86 bt, 1 H, *J*(4,5ex) = *J*(4,3ex) = 5.2 (H-4); 5.05 dd, 1 H, *J*(6,5en) = 8.4, *J*(6,5ex) = 3.3 (H-6); 7.50 m, 2 H, 7.64 m, 1 H, and 7.97 m, 2 H (arom.); 8.66 s, 1 H (H-8´); 8.77 s, 1 H (H-2´). ^{13}C NMR: 33.03 (C-3); 38.82 (C-2); 39.46 (C-5); 56.92 (C-6); 66.09 (CH_2O); 75.79 (C-4); 81.81 (C-1); 128.90, 129.44, 129.85, and 133.54 (C-4´´); 130.96 (C-5´); 145.22 (C-8´); 149.10 (C-6´); 151.54 (C-2´); 151.87 (C-4´); 165.89 (C=O).

Compound **17**: Yield 6.50g (56%). M.p. 183–185 °C. For $C_{19}H_{17}ClN_4O_3$ (384.8) calculated: 59.30% C, 4.45% H, 9.21% Cl, 14.56% N; found: 59.10% C, 4.44% H, 9.42% C, 14.33% N. ESI MS, *m/z* (%): 409.1/407.1 (27/78) [M + Na], 391.3 (100), 387.2/385.1 (22/66) [M + H]. ^{1}H NMR (DMSO): 1.43 dm, 1 H, J_{gem} = 12.9 (H-3ex); 1.96 dd, 1 H, J_{gem} = 12.9, *J*(3en,2) = 8.6 (H-3en); 2.14 dddd, 1 H, J_{gem} = 13.4, *J*(6ex,1) = 5.6, *J*(6ex,5) = 5.6, $J_{l.r.}$ = 0.9 (H-6ex); 2.38 dd, 1 H, J_{gem} = 13.4, *J*(6en,5) = 8.4 (H-6en); 2.38 m, 1 H (H-2); 4.06–4.14 m, 2 H (CH_2O); 4.73 m, 2 H (H-1 and H-4); 5.01 dd, 1 H, *J*(5,6en) = 8.4, *J*(5,6ex) = 3.1 (H-5); 7.55 m, 2 H (H-3´´); 7.68 m, 1 H, 8.01 m, 2 H, and 8.66 s, 1 H (arom.); 8.79 s, 1 H (H-2´). ^{13}C NMR (DMSO): 29.87 (C-3); 38.58 (C-6); 41.24 (C-2); 57.21 (C-5); 66.36 (CH_2O); 76.96 (C-1); 80.25 (C-4); 128.99, 129.42, 129.89, and 133.60 (arom.); 130.92 (C-5´); 145.34 (C-8´); 149.12 (C-6´); 151.60 (C-2´); 151.85 (C-4´); 165.92 (C=O).

(1*R**,2*S**,4*S**,6*S**)-6-(6-Chloro-9*H*-purin-9-yl)-7-oxabicyclo[2.2.1]heptane-2-methanol (**18a**) and
(1*R**,2*R**,4*R**,5*S**)-5-(6-Chloro-9*H*-purin-9-yl)-7-oxabicyclo[2.2.1]heptane-2-methanol (**19a**)

A 1 M solution of DIBAL-H in dichloromethane (42 ml) was added dropwise to a solution of compound **16** or **17** (5.45 g, 14 mmol) in dichloromethane (100 ml) at –78 °C under argon. The reaction mixture was stirred for 1 h, excess DIBAL-H was decomposed by addition of methanol and temperature was allowed to rise to room temperature. Then water (3 ml) and methanol (400 ml) were added and the mixture was filtered with a Celite pad. The filter was washed with methanol and the filtrate was evaporated. The residue was crystallized from methanol.

Compound **18a**: Yield 2.8 g (71%). M.p. 191.5–193 °C. For $C_{12}H_{13}ClN_4O_2$ (280.7) calculated: 51.34% C, 4.67% H, 12.63% Cl, 19.96% N; found: 51.15% C, 4.74% H, 12.85% Cl, 19.81% N. ESI MS, *m/z* (%): 305.1/303.1 (10/25) [M + Na], 288.3 (60), 283.1/281.1 (36/100) [M + H]. HR ESI MS (M + H) calculated 281.0800, found 281.0796. ^{1}H NMR (DMSO): 1.11 dtd, 1 H, J_{gem} = 11.9, *J*(3ex,4) = *J*(3ex,2) = 4.9, *J*(3ex,5ex) = 2.6 (H-3ex); 1.67 dd, 1 H, J_{gem} = 11.9, *J*(3en,2) = 8.5 (H-3en); 2.06 dm, 1 H, J_{gem} = 13.3 (H-5ex); 2.11 m, 1 H (H-2); 2.30 dd, 1 H, J_{gem} = 13.3, *J*(5en,6) = 8.4 (H-5en); 3.13–3.22 m, 2 H (CH_2O); 4.47 s, 1 H (H-1); 4.75 t, 1 H, *J*(OH,CH_2) = 5.4 (OH); 4.77 t, 1 H, *J*(4,3ex) = *J*(4,5ex) = 5.2 (H-4); 4.97 dd, 1 H, *J*(6,5en) = 8.4, *J*(6,5ex) = 3.2 (H-6); 8.63 s, 1 H (H-8´); 8.78 s, 1 H (H-2´). ^{13}C NMR (DMSO): 33.00 (C-3); 39.62 (C-5); 42.34 (C-2); 57.04 (C-6); 63.41 (CH_2O); 75.59 (C-4); 82.00 (C-1); 130.89 (C-5´); 145.19 (C-8´); 149.14 (C-6´); 151.60 (C-2´); 151.77 (C-4´).

Compound **19a**: Yield 3.47 g (88%). M.p. 182–183.5 °C. For $C_{12}H_{13}ClN_4O_2$ (280.7) calculated: 51.34% C, 4.67% H, 12.63% Cl, 19.96% N; found: 51.15% C, 4.60% H, 12.59% Cl, 19.80% N. negESI MS, *m/z* (%): 281.1/279 (31/88) [M – H], 155/153 (32/100) [6-chloropurine – H]. ^{1}H NMR (DMSO): 1.15 ddd, 1 H, J_{gem} = 12.7, *J*(3ex,4) = 5.8, *J*(3ex,2) = 3.8 (H-3ex); 1.78 dd, 1 H, J_{gem} =

12.7, *J*(3en,2) = 8.6 (H-3en); 1.97 m, 1 H (H-2); 2.10 dddd, 1 H, J_{gem} = 13.3, *J*(6ex,1) = 5.7, *J*(6ex,5) = 3.2, $J_{l.r.}$ = 0.8 (H-6ex); 2.27 dd, 1 H, J_{gem} = 13.3, *J*(6en,5) = 8.4 (H-6en); 3.14 dd, 1 H, J_{gem} = 10.5, *J*(CH_2,2) = 6.1 and 3.19 dd, 1 H, J_{gem} = 10.5, *J*(CH_2,2) = 9.6 (CH_2O); 4.60 d, 1 H, *J*(4,3ex) = 5.8 (H-4); 4.65 d, 1 H, *J*(1,6ex) = 5.7 (H-1); 4.78 bs, 1 H; 4.94 dd, 1 H, *J*(5,6en) = 8.4, *J*(5,6ex) = 3.2 (H-5); 8.64 s, 1 H (H-8´); 8.76 s, 1 H (H-2´). ^{13}C NMR (DMSO): 29.93 (C-3); 38.82 (C-6); 44.94 (C-2); 57.45 (C-5); 63.61 (CH_2O); 76.83 (C-1); 80.23 (C-4); 130.95 (C-5´); 145.29 (C-8´); 149.14 (C-6´); 151.62 (C-2´); 151.87 (C-4´).

(1*R**,2*S**,4*S**,6*S**)-6-(6-Amino-9*H*-purin-9-yl)-7-oxabicyclo[2.2.1]heptane-2-methanol (**18b**) and
(1*R**,2*R**,4*R**,5*S**)-5-(6-Amino-9*H*-purin-9-yl)-7-oxabicyclo[2.2.1]heptane-2-methanol (**19b**)

A solution of chloropurine derivative **18a** or **19a** (281 mg, 1 mmol) in liquid ammonia (20 ml) was heated in an autoclave at 75 °C for 48 h and then ammonia was evaporated. The residue was crystallized from water.

Compound **18b**: Yield 188 mg (72%). M.p. 268–269.5 °C. For $C_{12}H_{15}N_5O_2$ (261.3) calculated: 55.16% C, 5.79% H, 26.80% N; found: 54.98% C, 5.76% H, 26.62% N. ESI MS, *m/z* (%): 284.1 (57) [M + Na], 262.1 (100) [M + H]. ^{1}H NMR: 1.08 m, 1 H (H-3ex); 1.64 dd, 1 H, J_{gem} = 11.8, *J*(3en,2) = 8.5 (H-3en); 1.94 dm, 1 H, J_{gem} = 13.1 (H-5ex); 2.06 m, 1 H (H-2); 2.25 dd, 1 H, J_{gem} = 13.1, *J*(5en,6) = 8.6 (H-5en); 3.12–3.21 m, 2 H (CH_2O); 4.35 s, 1 H (H-1); 4.72–4.77 m, 2 H (H-4 and OH); 4.80 dd, 1 H, *J*(6,5en) = 8.4, *J*(6,5ex) = 3.2 (H-6); 7.22 bs, 2 H (NH_2); 8.08 s, 1 H (H-8´); 8.14 s, 1 H (H-2´). ^{13}C NMR: 32.95 (C-3); 39.97 (C-5); 42.51 (C-2); 55.52 (C-6); 63.47 (CH_2O); 75.47 (C-4); 82.35 (C-1); 118.61 (C-5´); 138.39 (C-8´); 149.40 (C-4´); 152.60 (C-2´); 156.19 (C-6´).

Compound **19b**: Yield 193 mg (74%). M.p. 225–226.5 °C. For $C_{12}H_{15}N_5O_2$ (261.3) calculated: 55.16% C, 5.79% H, 26.80% N; found: 54.97% C, 5.77% H, 26.69% N. ESI MS, *m/z* (%): 285.1 (39) [M + Na + H], 284.1 (100) [M + Na], 262.2 (81) [M + H]. ^{1}H NMR: 1.12 ddd, 1 H, J_{gem} = 12.6, *J*(3ex,4) = 5.8, *J*(3ex,2) = 3.8 (H-3ex); 1.73 dd, 1 H, J_{gem} = 12.6, *J*(3en,2) = 8.5 (H-3en); 1.92–2.02 m, 2 H (H-2 and H-6ex); 2.23 dd, 1 H, J_{gem} = 13.1, *J*(6en,5) = 8.4 (H-6en); 3.11–3.20 m, 2 H (CH_2O); 4.49 d, 1 H, *J*(4,3ex) = 5.7 (H-4); 4.62 d, 1 H, *J*(1,6ex) = 5.6 (H-1); 4.76 bt, 1 H, *J*(OH,CH_2) = 5.3 (OH); 4.78 dd, 1 H, *J*(5,6en) = 8.4, *J*(5,6ex) = 3.3 (H-5); 7.24 bs, 2 H (NH_2); 8.10 s, 1 H (H-8´); 8.14 s, 1 H (H-2´). ^{13}C NMR: 30.12 (C-3); 39.12 (C-6); 44.92 (C-2); 56.38 (C-5); 63.66 (CH_2O); 76.72 (C-1); 80.55 (C-4); 118.69 (C-5´); 138.46 (C-8´); 149.47 (C-4´); 152.59 (C-2´); 156.20 (C-6´).

(1*R**,2*S**,4*S**,6*S**)-6-[6-(Dimethylamino)-9*H*-purin-9-yl]-7-oxabicyclo[2.2.1]heptane-2-methanol (**18c**) and
(1*R**,2*R**,4*R**,5*S**)-5-[6-(Dimethylamino)-9*H*-purin-9-yl]-7-oxabicyclo[2.2.1]heptane-2-methanol (**19c**)

A solution of chloropurine derivative **18a** and **19a** (140 mg, 0.5 mmol) in dimethylammonium dimethylcarbamate (2.5 ml) was left standing at room temperature overnight and then evaporated. The residue was chromatographed on a silica gel column (20 g) in ethyl acetate–acetone–ethanol–water (95:15:8:7) and then crystallized from ether.

Compound **18c**: Yield 114 mg (79%). M.p. 137–139 °C. For $C_{14}H_{19}N_5O_2$ (289.3) calculated: 58.12% C, 6.62% H, 24.21% N; found: 58.13% C, 6.64% H, 24.10% N. ESI MS, *m/z* (%): 291.2 (15) [M + 2 H], 290.2 (100) [M + H]. ^{1}H NMR: 1.08 m, 1 H (H-3ex); 1.64 dd, 1 H,

J_{gem} = 11.9, *J*(3en,2) = 8.5 (H-3en); 1.92 dm, 1 H, J_{gem} = 13.1 (H-5ex); 2.06 m, 1 H (H-2); 2.25 dd, 1 H, J_{gem} = 13.1, *J*(5en,6) = 8.5 (H-5en); 3.12–3.20 m, 2 H (CH_2O); 3.4 vbs, 6 H (CH_3); 4.34 s, 1 H (H-1); 4.73 t, 1 H, *J*(4,3ex) = *J*(4,5ex) = 5.2 (H-4); 4.78 t, 1 H, *J*(OH,CH_2) = 5.4 (OH); 4.83 dd, 1 H, *J*(6,5en) = 8.5, *J*(6,5ex) = 3.4 (H-6); 8.09 s, 1 H (H-8´); 8.21 s, 1 H (H-2´). ^{13}C NMR: 32.94 (C-3); 40.00 (C-5); 42.57 (C-2); 55.93 (C-6); 63.48 (CH_2O); 75.49 (C-4); 82.30 (C-1); 119.16 (C-5´); 137.24 (C-8´); 150.18 (C-4´); 151.94 (C-2´); 154.45 (C-6´).

Compound **19c**: Yield 116 mg (80%). M.p. 162–163.5 °C. For $C_{14}H_{19}N_5O_2$ (289.3) calculated: 58.12% C, 6.62% H, 24.21% N; found: 57.97% C, 6.64% H, 24.13% N. ESI MS, *m/z* (%): 291.2 (16) [M + 2 H], 290.2 (100) [M + H]. ^{1}H NMR: 1.12 ddd, 1 H, J_{gem} = 12.6, *J*(3ex,4) = 5.8, *J*(3ex,2) = 3.8 (H-3ex); 1.73 dd, 1 H, J_{gem} = 12.6, *J*(3en,2) = 8.6 (H-3en); 1.92–1.99 m, 2 H (H-2 and H-6ex); 2.23 dd, 1 H, J_{gem} = 13.2, *J*(6en,5) = 8.5 (H-6en); 3.11–3.20 m, 2 H (CH_2O); 3.4 vbs, 6 H (CH_3); 4.48 d, 1 H, *J*(4,3ex) = 5.7 (H-4); 4.62 d, 1 H, *J*(1,6ex) = 5.7 (H-1); 4.76 t, 1 H, *J*(OH,CH_2) = 5.3 (OH); 4.80 dd, 1 H, *J*(5,6en) = 8.4, *J*(5,6ex) = 3.3 (H-5); 8.10 s, 1 H (H-8´); 8.20 s, 1 H (H-2´). ^{13}C NMR: 30.15 (C-3); 38.47 (CH_3); 39.07 (C-6); 44.91 (C-2); 56.38 (C-5); 63.67 (CH_2O); 76.73 (C-1); 80.52 (C-4); 119.23 (C-5´); 137.30 (C-8´); 150.22 (C-4´); 151.90 (C-2´); 154.44 (C-6´).

(1*R**,2*S**,4*S**,6*S**)-6-[6-(Cyclopropylamino)-9*H*-purin-9-yl]-7-oxabicyclo[2.2.1]heptane-2-methanol (**18d**) and
(1*R**,2*R**,4*R**,5*S**)-5-[6-(Cyclopropylamino)-9*H*-purin-9-yl]-7-oxabicyclo[2.2.1]heptane-2-methanol (**19d**)

A solution of chloropurine derivative **18a** or **19a** (140 mg, 0.5 mmol) in cyclopropylamine (2 ml) was left standing at room temperature overnight and then evaporated. The residue was chromatographed on a silica gel column (20 g) in ethyl acetate–acetone–ethanol–water (90:15:11:9) and then crystallized from ether.

Compound **18d**: Yield 125 mg (83%). M.p. 171–173 °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, 6.43% H, 22.99% N. negESI MS, *m/z* (%): 623 (28) [2 × (M – H) + Na], 301.1 (17) [M], 300 (100) [M – H], 270 (25), 174.1 (43) [6-(cyclopropylamino)purine – H]. ^{1}H NMR: 0.59 m, 2 H, 0.71 m, 2 H, and 3.00 bs, 1 H (cyclopropyl); 1.08 m, 1 H (H-3ex); 1.64 dd, 1 H, J_{gem} = 11.9, *J*(3en,2) = 8.5 (H-3en); 1.94 m, 1 H (H-5ex); 2.07 m, 1 H (H-2); 2.25 dd, 1 H, J_{gem} = 13.1, *J*(5en,6) = 8.5 (H-5en); 3.12–3.20 m, 2 H (CH_2O); 4.35 s, 1 H (H-1); 4.73 t, 1 H, *J*(4,3ex) = *J*(4,5ex) = 5.2 (H-4); 4.77 t, 1 H, *J*(OH,CH_2) = 5.4 (OH); 4.82 dd, 1 H, *J*(6,5en) = 8.5, *J*(6,5ex) = 3.3 (H-6); 7.91 bs, 1 H (NH); 8.09 s, 1 H (H-8´); 8.25 bs, 1 H (H-2´). ^{13}C NMR: 6.63 (cyclopropyl CH_2); 32.97 (C-3); 40.02 (C-5); 42.54 (C-2); 55.93 (C-6); 63.50 (CH_2O); 75.50 (C-4); 82.38 (C-1); 119.02 (C-5´); 138.26 (C-8´); 149.78 (C-4´); 152.55 (C-2´); 155.76 (C-6´).

Compound **19d**: Yield 119 mg (79%). M.p. 199–201 °C. For $C_{15}H_{19}N_5O_2$ (301.4) calculated: 59.79% C, 6.36% H, 23.24% N; found: 59.55% C, 6.51% H, 22.98% N. ESI MS, *m/z* (%): 324.1 (23), 302.2 (100) [M + H]. ^{1}H NMR: 0.59 m, 2 H, 0.71 m, 2 H, and 3.02 bs, 1 H (cyclopropyl); 1.13 ddd, 1 H, J_{gem} = 12.6, *J*(3ex,4) = 5.7, *J*(3ex,2) = 3.9 (H-3ex); 1.74 dd, 1 H, J_{gem} = 12.6, *J*(3en,2) = 8.5 (H-3en); 1.92–2.02 m, 2 H (H-2 and H-6ex); 2.23 dd, 1 H, J_{gem} = 13.1, *J*(6en,5) = 8.4 (H-6en); 3.11–3.22 m, 2 H (CH_2O); 4.49 d, 1 H, *J*(4,3ex) = 5.7 (H-4); 4.62 d, 1 H, *J*(1,6ex) = 5.3 (H-1); 4.75 t, 1 H, *J*(OH,CH_2) = 5.3 (OH); 4.79 dd, 1 H, *J*(5,6en) = 8.4, *J*(5,6ex) = 3.3 (H-5); 7.87 bs, 1 H (NH); 8.09 s, 1 H (H-8´); 8.23 bs, 1 H (H-2´). ^{13}C NMR: 6.66 (cyclopropyl CH_2); 24.30 (cyclopropyl CH); 30.12 (C-3); 39.10 (C-6); 44.91 (C-2); 56.37

(C-5); 63.66 (CH_2O); 76.73 (C-1); 80.55 (C-4); 119.06 (C-5′); 138.29 (C-8′); 148.92 (C-4′); 152.47 (C-2′); 155.74 (C-6′).

6-Chloro-9-[(1*R**,2*S**,4*S**,6*R**)-6-(chloromethyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-9*H*-purine (**20**) and
6-Chloro-9-[(1*R**,2*S**,4*R**,5*S**)-5-(chloromethyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-9*H*-purine (**21**)

Thionyl chloride (0.13 ml, 1.8 mmol) was added to a solution of hydroxymethyl derivative **18a** or **19a** (140 mg, 0.5 mmol) in hexamethylphosphoramide (1.8 ml). The solution was heated to 80 °C for 2.5 h and then poured into a saturated solution of sodium hydrogencarbonate (10 ml). The resulting 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 ethyl acetate.

Compound **20**: Yield 115 mg (77%). M.p. 193–195 °C. For $C_{12}H_{12}Cl_2N_4O$ (299.2) calculated: 48.18% C, 4.04% H, 23.70% Cl, 18.73% N; found: 47.91% C, 3.91% H, 23.95% Cl, 18.48% N. ESI MS, *m/z* (%): 316.4 (56), 303.1/301.1/299.1 (10/40/67) [M + H]. ^{1}H NMR: 1.31 dtd, 1 H, J_{gem} = 12.2, J(5′ex,4′) = J(5′ex,6′) = 4.9, J(5′ex,3′ex) = 2.6 (H-5′ex); 1.85 dd, 1 H, J_{gem} = 12.2, J(5′en,6′) = 8.4 (H-5′en); 2.07 dm, 1 H, J_{gem} = 13.3 (H-3′ex); 2.32 dd, 1 H, J_{gem} = 13.3, J(3′en,2′) = 8.5 (H-3′en); 2.44 m, 1 H (H-6′); 3.44 dd, 1 H, J_{gem} = 10.7, J(CH_2,6′) = 7.2 and 3.51 dd, 1 H, J_{gem} = 10.7, J(CH_2,6′) = 8.7 (CH_2Cl); 4.52 s, 1 H (H-1′); 4.84 t, 1 H, J(4′,3′ex) = J(4′,5′ex) = 5.1 (H-4′); 5.04 dd, 1 H, J(2′,3′en) = 8.4, J(2′,3′ex) = 3.3 (H-2′); 8.63 s, 1 H (H-8); 8.78 s, 1 H (H-2). ^{13}C NMR: 35.38 (C-5′); 39.25 (C-3′); 42.61 (C-6′); 47.47 (CH_2Cl); 56.74 (C-2′); 76.14 (C-4′); 82.63 (C-1′); 130.92 (C-5); 145.20 (C-8); 149.17 (C-6); 151.64 (C-2); 151.83 (C-4).

Compound **21**: Yield 123 mg (82%). M.p. 162–163 °C. For $C_{12}H_{12}Cl_2N_4O$ (299.2) calculated: 48.18% C, 4.04% H, 23.70% Cl, 18.73% N; found: 47.90% C, 3.99% H, 23.95% Cl, 18.46% N. ESI MS, *m/z* (%): 303.2/301.1/299.0 (13/68/100) [M + H], 288.3 (50). ^{1}H NMR: 1.36 dm, 1 H, J_{gem} = 13.1 (H-6′ex); 1.96 dd, 1 H, J_{gem} = 13.0, J(6′en,5′) = 8.5 (H-6′en); 2.15 dddd, 1 H, J_{gem} = 13.5, J(3′ex,4′) = 5.7, J(3′ex,2′) = 3.1, $J_{l.r.}$ = 0.9 (H-3′ex); 2.26 m, 1 H (H-5′); 2.34 dd, 1 H, J_{gem} = 13.5, J(3′en,2′) = 8.4 (H-3′en); 3.43 dd, 1 H, J_{gem} = 10.7, J(CH_2,5′) = 7.0 and 3.52, dd, 1 H, J_{gem} = 10.7, J(CH_2,5′) = 9.0 (CH_2Cl); 4.66 d, 1 H, J(4′,3′ex) = 5.7 (H-4′); 4.69 d, 1 H, J(1′,6′ex) = 5.8 (H-1′); 4.98 dd, 1 H, J(2′,3′en) = 8.4, J(2′,3′ex) = 3.1 (H-2′); 8.64 s, 1 H (H-8); 8.77 s, 1 H (H-2). ^{13}C NMR: 32.04 (C-6′); 38.31 (C-3′); 45.04 (C-5′); 47.64 (CH_2Cl); 57.01 (C-2′); 77.56 (C-4′); 80.50 (C-1′); 130.92 (C-5); 145.26 (C-8); 149.13 (C-6); 151.60 (C-2); 151.85 (C-4).

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