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Norbornane as the novel pseudoglycone moiety in nucleosides

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ABSTRACT

Novel nucleoside analogues based on bicyclo[2.2.1]heptene/heptane were prepared by linear synthesis starting from commercially available 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene **1**. The crucial step of the synthesis was insertion of the amino group to the position 7 of the substituted bicyclo[2.2.1]heptene with *anti*-configuration by a Ritter reaction (H_2SO_4, AcOH, CH_3CN). All nucleobases were constructed at this amino function. The prepared family of the target nucleosides was tested for cytostatic and antiviral activity.

1. Introduction

Nucleosides and nucleotides are of fundamental importance for all living systems. Therefore, nucleoside analogues play an important role, mainly as antiviral and antitumor drugs. A disadvantage of analogues of natural nucleosides is cleavage of the *N*-glycosidic bond by phosphorylases. A modification, which increases resistance against enzymatic degradation, is substitution of the furanose ring of the sugar moiety by a hydrocarbon ring. Many of such modified analogues – carbocyclic nucleosides[1] – exhibit interesting antiviral activity. Analogues containing conformationally locked tricyclic systems were also synthesised. Well known are carbocyclic nucleosides with a fused cyclopropane moiety[2] (bicyclo[3.1.0]hexane). Recently, novel conformationally locked carbocyclic nucleosides based on 2-oxabicyclo[2.2.1]heptane ring system were described[3] (as precursors for carbocyclic locked nucleic acids). Bisphosphate of the 2-iodo-(6-methylamino)-purine analogue of this ring system displayed a potent binding affinity to the human $P2Y_1$ receptor. Recently, a series of carbocyclic analogues containing bicycloalkanes,[4] bicycloheteroalkanes[5] or tricycloheteroalkanes[6] with activity against Coxsackie viruses was prepared in our laboratory. Also, we have reported a synthesis of analogues[4b] with a bicyclo[2.2.1]heptene or heptane ring system substituted with nucleobase at position 7 with *syn*-configuration. This study concerns the synthesis of novel racemic conformationally locked nucleosides with bicyclo[2.2.1]hept-2-ene or heptane ring system substituted with nucleobase at position 7 with the *anti*-configuration (Fig. 1). These bicyclo systems (norbornene or norbornane), like the oxabicyclo[2.2.1]heptane, represent conformationally locked carbapentofuranose ring systems. Simple tricyclic derivatives of the original compounds were also prepared.

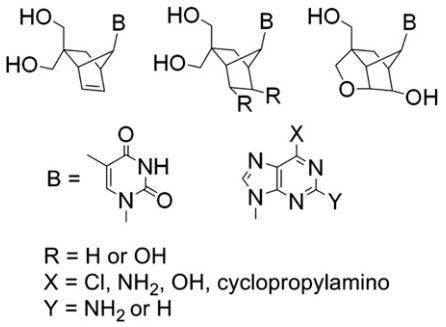

Figure 1.

2. Chemistry

The crucial compound for the synthesis of all the prepared nucleosides was amine **7** (Scheme 1), because our synthetic strategy was based on construction of the nucleobases at the amino group.[4a,7,8]

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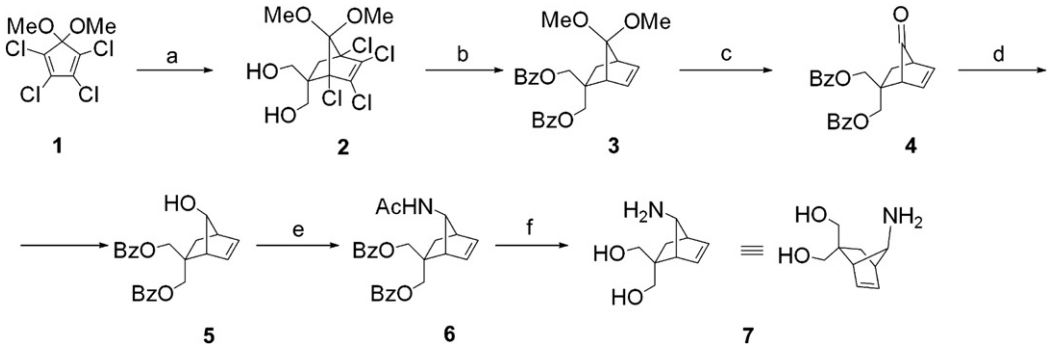
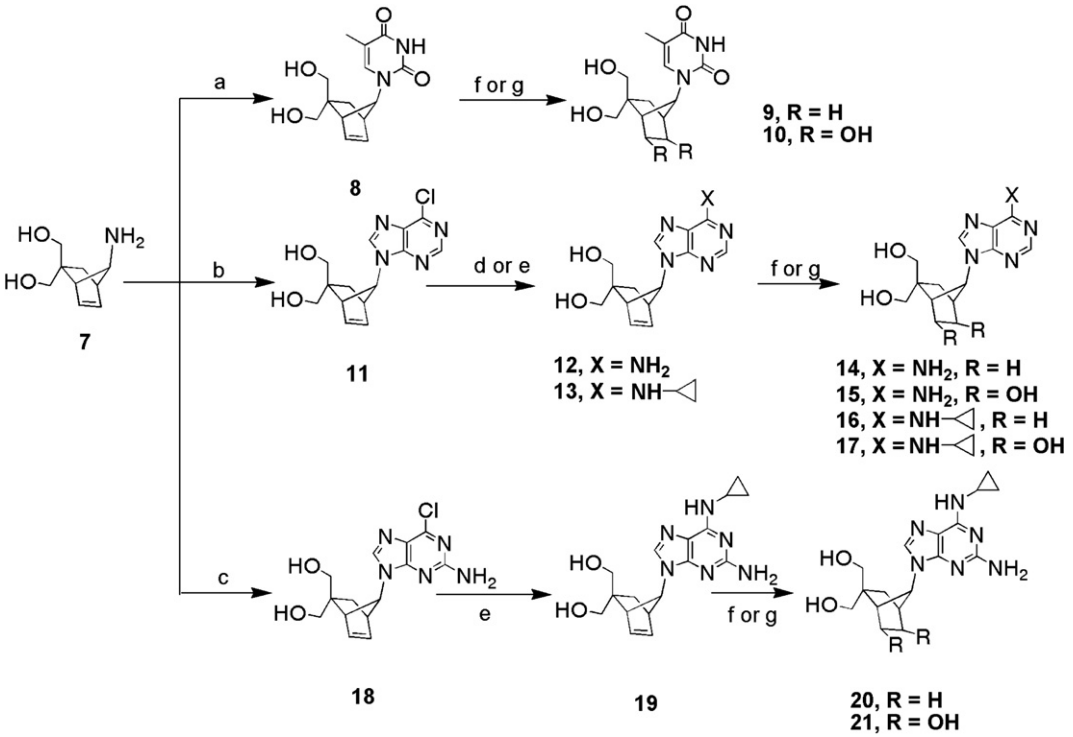


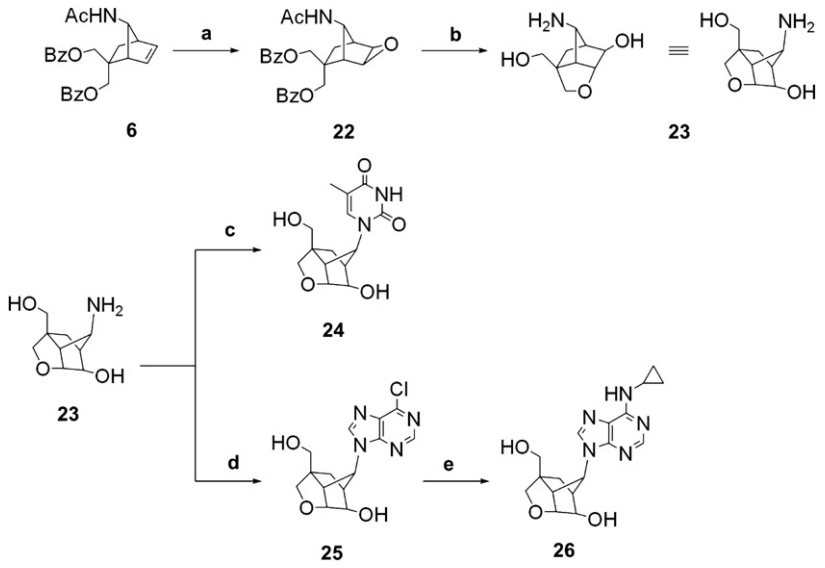
Scheme 1. Reagents and conditions: a) 1. acrolein, 55 °C, 8 h 2. aq HCHO, 55 °C, 4 h, 3. $NaBH_4$, MeOH, overnight, 82%; b) 1. Na, liq NH_3, THF–EtOH, −45 °C, 2 h, 2. BzCl, pyridine, overnight, 78%; c) Dowex 50 (H^+ form), dioxane–water, reflux, 10 h, 75%; d) $NaBH_4$, THF–H_2O, 0 °C, 30 min, 88%; e) CH_3CN, H_2SO_4–AcOH, rt 1 h, 84%; f) KOH, EtOH–H_2O, 100 °C, 9 h, 90%.

Amine **7** was prepared in six steps, starting from commercially available 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene **1**. The cyclopentadiene **1** was treated with acrolein[9] and the Diels–Alder intermediate – formyl derivative – was reacted with formaldehyde under basic conditions (NaOH) to yield, after reduction, the dihydroxymethyl derivative **2** (82%, overall yield from **1**). The chlorine atoms were removed with sodium in liquid ammonia,[10] and the free hydroxy groups were immediately protected by benzoylation (78%). Ketone **4** was then prepared by deketalization (Dowex 50, H^+ cycle) in refluxing mixture of dioxane–water. For satisfactory yield (75%), it was necessary to continuously remove methanol from the reaction mixture. Reduction of the keto group was achieved by reaction with sodium borohydride in mixture of tetrahydrofuran and water. Due to the steric hindrance (hydroxymethyl group against double bond) only one isomer (*anti*) was obtained in very good yield (88%). The configuration of the alcohol **5** was confirmed by 2DROESY spectrum where cross-peaks between hydrogen H-7 and hydrogens of the double bond (H-5 and H-6) and between OH and H-3*exo* were observed. The s*yn*-isomer was not observed in reaction mixture. Finally, the protected amino group was inserted by a Ritter reaction (84%, acetonitrile/acetic acid/sulfuric acid) with retention of the configuration.[11] The free amine **7** was finally released by basic deprotection (90%, KOH, ethanol–water). Many attempts to prepare the amino derivative directly from the protected ketone **4** were not successful. For example, we used reductive amination[12] (benzylamine/$NaBH_3CN$), oximation (NH_2OH) and reduction of the oxime ($LiAlH_4$),[13] insertion of the amino group by selective monoalkylation of ammonia method[14] (NH_4Cl/$Ti(OiPr)_4$). None of these methods gave any or satisfactory yield.

Amine **7** was then used for construction of the nucleosides (Scheme 2). The amine **7** was coupled with ethyl[(2E)-3-ethoxy-2-methylprop-2-enoyl]carbamate[4a,8] in dioxane and acyclic intermediate was closed under acidic conditions (Dowex 50, H^+ cycle) in dioxane giving thymine nucleoside **8** (Scheme 2). Purine nucleosides **11** and **18** were prepared by coupling with 4,6-dichloropyrimidin-5-amine[4a,15] and with 4,6-dichloropyrimidin-2,5-diamine,[7] respectively and the purine ring was then obtained by ring closure (triethyl orthoformate, HCl). Position 6 at the purine ring was further



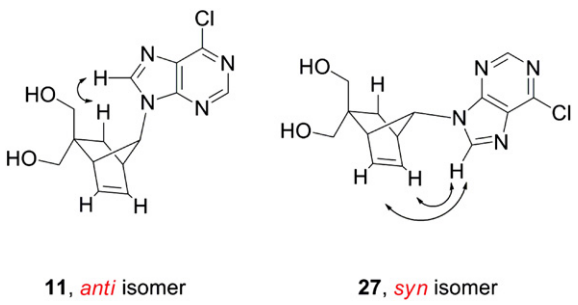
Scheme 2. Reagents and conditions: a) 1. ethyl [(2*E*)-3-ethoxy-2-methylprop-2-enoyl]carbamate, dioxane, 100 °C, 3 h, 2. Dowex 50 (H^+ form), dioxane, 100 °C, 2.5 h, 55%; b) 1. 4,6-dichloropyrimidin-5-amine, Et_3N, EtOH, 100 °C, 144 h, 2. $CH(OEt)_3$, HCl, 48 h, 3. HCl, THF–H_2O, 3 h, 63%; c) 1. 4,6-dichloropyrimidine-2,5-diamine, Et_3N, EtOH, 100 °C, 6 d, 2. $CH(OEt)_3$, HCl, 120 h, 3. HCl, THF–H_2O, 4 h, 67%; d) NH_3 (l), 75 °C, 48 h, 91%; e) cyclopropylamine, MeOH, for **13**: 10 h, 92%, for **18**: 10 h, 80%; f) H_2, $Pd(OH)_2$/C, MeOH–H_2O; g) OsO_4, NMMO, acetone–water.



Scheme 3. Reagents and conditions: a) mCPBA, CH_2Cl_2, overnight, quant; b) 1. K_2CO_3, MeOH, 2. KOH, EtOH–H_2O, 100 °C, 9 h, 85%; c) 1. ethyl [(2*E*)-3-ethoxy-2-methylprop-2-enoyl]carbamate, dioxane, 100 °C, 3 h, 2. Dowex 50 (H^+ form), dioxane, 100 °C, 2.5 h, 56%; d) 1. 4,6-dichloropyrimidin-5-amine, Et_3N, EtOH, 100 °C, 144 h, 2. $CH(OEt)_3$, HCl, 48 h, 3. HCl, THF–H_2O, 3 h, 30%; e) cyclopropylamine, MeOH, overnight, 61%.

derivatised. Reaction with ammonia in an autoclave afforded the adenine derivative **12** in excellent yield (91%). Both of the chloropurine derivatives were treated with cyclopropylamine in methanol to obtain cyclopropyl derivatives **13** and **19** in very good yields (92% resp. 80%). The double bond in each of the nucleosides **8**, **12**, **13**, **19** was utilized in two ways. Saturated compounds **9**, **14**, **16**, **20** were obtained after hydrogenation over palladium hydroxide on charcoal. Lower yields (79% for **9**, 40% for **14**, 67% for **16**, 65% for **20**) of the hydrogenation step are caused by the poor solubility of the starting compounds and products (difficult isolation from reaction mixture). The compounds **10**, **15**, **17**, and **21** with two *cis*-hydroxy groups were prepared by osmium tetroxide catalyzed *cis*-hydroxylation in an acetone–water mixture with *N*-methylmorpholine-*N*-oxide (NMMO) as a recovering agent for osmium catalytic cycle.

Compounds with a tricyclic skeleton were synthesised starting from the protected amide **6** (Scheme 3). This compound was treated with *m*-chloroperbenzoic acid in dichloromethane and after extraction of the reaction mixture the epoxide **22** was obtained in nearly quantitative yield. The amine **23** was obtained by intramolecular opening of the oxirane ring (mild deprotection of the benzoyl groups by potassium carbonate) followed by basic deprotection of the amidic group with potassium hydroxide in refluxing water–ethanol mixture (85%). Starting from amine **23**, using the same procedures as described above, nucleosides **24**, **25**, **26** were prepared. The structures of the prepared compounds were determined by ^1H and ^{13}C NMR spectroscopies. The relative configuration (*anti*) at the position **7** was also confirmed by NOE experiment. The NOE experiment with the 6-chloropurine derivative **11** showed correlation between the proton H-8′ (8.76 ppm) and proton H-3*exo* (1.85 ppm) indicating *anti*-position of the nucleobase (Fig. 2). No NOE correlation between H-8′ and H-5 and H-6 was observed. These correlations were observed in a previously prepared compound **27**.[4b]



11, *anti* isomer **27**, *syn* isomer

Figure 2.

3. Conclusion

We have synthesized a novel series of conformationally locked carbocyclic nucleosides based on the norbornene or norbornane skeleton. The target compounds were tested for inhibition of cell growth of the following cell cultures: mouse leukemia L1210 cells (ATCC CCL 240), human cervix carcinoma HeLaS3 cells (ATCC CCL 2.2), human promyelocytic leukemia HL60 cells (ATCC CCL 240), and human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119). None of the compounds exhibited considerable activity.[16] The compounds were also tested for anti-HIV-1 and anti-HIV-2 activity in human T-lymphocyte (CEM) cells and for the activity against Coxsackievirus (CVB3) in Vero cells. Preliminary data showed that only compound **11** exhibits a weak activity (EC_{50} 46.9 μM, TC_{50}>326 μM) against Coxsackievirus.

4. Experimental

4.1. General

Melting points were determined on a Büchi B-540 apparatus and are uncorrected. NMR spectra (δ, ppm; *J*, Hz) were measured on a Bruker Avance II-600 and/or Bruker Avance II-500 instruments (600.1 or 500.0 MHz for ^1H and 150.9 or 125.7 MHz for ^{13}C) in hexadeuterodimethyl 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 (ionization with Xe, accelerating voltage 8 kV, thioglycerol–glycerol 3:1 or bis-(2-hydroxyethyl) disulfide matrix) or LTQ Orbitrap XL (Thermo Fisher Scientific) for ESI. IR spectra were obtained on an FTIR Bruker Equinox IFS 55 spectrometer in $CHCl_3$, CCl_4 or KBr pellets. Column chromatography was performed on Silica gel 60 (Fluka) and thin-layer chromatography (TLC) on Silufol Silica gel 60 F254 foils (Merck). Solvents were evaporated at 2 kPa and bath temperature 30–60 °C; the compounds were dried at 13 Pa and 50 °C. 5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene **1** was purchased from Sigma–Aldrich.

4.1.1. [(1R,4S*)-1,4,5,6-Tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-ene-2,2-diyl]dimethanol (**2**).* A mixture of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene **1** (5.54 g, 21 mmol) and acrolein (8 mL, 120 mmol) was heated to reflux for 8 h. The reaction mixture was evaporated and codistilled with toluene (3×10 mL). To the residue aqueous formaldehyde (10 mL, 37%) was added and reaction mixture was stirred vigorously at 0 °C. Then an aqueous solution of sodium hydroxide (25%, 3.6 mL) was added dropwise. The resulting mixture was heated at 55 °C for 4 h and evaporated to half volume. The residue was partitioned between ether (120 mL) and water (80 mL). The water layer was extracted with diethyl ether (2×120 mL) and the combined organic phases were dried over anhydrous sodium sulfate and evaporated. The residue was dissolved in methanol (80 mL), cooled to 0 °C and sodium borohydride (600 mg, 16 mmol) was added in portions and the solution was stirred overnight at rt and then evaporated. The residue was codistilled with methanol (2×50 mL) and partitioned between water (80 mL) and ethyl acetate (120 mL). The water phase was extracted with ethyl acetate (120 mL). The combined organic phases were dried over anhydrous sodium sulfate and evaporated. Column chromatography of the residue on silica gel (400 g) in toluene–ethyl acetate (6:1→1:1) afforded 6.09 g (82.4%) of dihydroxymethyl derivative as a white powder. A sample was crystallized from hexanes–ether. Mp=106.5–107.5 °C. IR ($CHCl_3$): 3623 (m), 3521 (br), 2953 (m), 2847 (w), 1648 (w), 1463 (w), 1439 (w), 1069 (m), 835 (m). ^{1}H NMR: 4.71 (1H, t, *J* 5.6 Hz, OH), 4.61 (1H, t, *J* 5.8 Hz, OH), 3.83 (1H, dd, *J* 10.4, 5.8 Hz, C*H*HO), 3.74 (1H, dd, *J* 10.4, 5.6 Hz, C*H*HO), 3.52 (3H, s, OCH_3), 3.42 (3H, s, OCH_3), 3.42 (1H, dd, *J* 11.1, 5.8 Hz, C*H*HO), 3.03 (1H, dd, *J* 11.1, 4.9 Hz, C*H*HO), 2.37 (1H, d, *J* 12.1 Hz, H-3*exo*), 1.45 (1H, d, *J* 12.1 Hz, H-3*endo*). ^{13}C NMR: 131.58 (C-6), 128.01 (C-5), 112.51 (C-7), 79.76 (C-1), 74.37 (C-4), 62.34 (CH_2O), 59.91 (CH_2O), 53.09 (C-2), 52.22 (OCH_3), 51.34 (OCH_3), 40.27 (C-3). FABMS, *m*/*z* (rel%): 353 (10), 352 (8), 322 (50), 321 (100), 319 (90), 285 (60), 251 (45). For $C_{11}H_{14}Cl_4O_4$ (352) calculated: 37.53% C, 4.01% H, 40.28% Cl; found: 37.67% C, 4.03% H, 40.12% Cl.

4.1.2. [(1R,4R*)-7,7-Dimethoxybicyclo[2.2.1]hept-5-ene-2,2-diyl]dimethyl dibenzoate (**3**).* A solution of tetrachloro derivative **2** (6.55 g, 17.9 mmol) in THF (86 mL) and EtOH (10 mL) was dropwise added to a blue solution of sodium (7.63 g, 0.33 mol) in liquid ammonia (160 mL) and the mixture was stirred at −40 °C for 2 h. The excess sodium was decomposed with a saturated solution of NH_4Cl and then the ammonia was allowed to evaporate. The residue was extracted with ethyl acetate (3×150 mL), the combined organic phases were dried over anhydrous sodium sulfate and evaporated. Residue was coevaporated with pyridine, dissolved in pyridine (100 mL), benzoylchloride (6.5 mL, 56 mmol) was added and the mixture was left at rt overnight. Water (5 mL) was then added and, after 15 min, the solvent was evaporated. The residue was partitioned between ethyl acetate (250 mL) and water (100 mL). The organic phase was washed with water (150 mL), 5% hydrochloric acid (120 mL), saturated aqueous $NaHCO_3$ (3×150 mL), dried over anhydrous sodium sulfate and evaporated. Column chromatography of the residue on silica gel (400 g) in toluene–ethyl acetate (7:1) afforded 5.90 g (78%) of benzoylated ketal as an oil. IR (CCl_4): 3092 (w), 3071 (w), 3035 (w), 2981 (m), 2957 (m), 2941 (m), 2907 (w), 2874 (w), 2832 (w), 1724 (vs) 1604 (w), 1586 (w), 1492 (w), 1470 (w), 1451 (m), 711 (vs). ^{1}H NMR: 7.97–7.93 (4H, m, Bz-2), 7.65–7.61 (2H, m, Bz-4), 7.50–7.44 (4H, m, Bz-3), 6.23 (1H, ddd, 6.2, 3.4, 1.1 Hz, H-5), 6.18 (1H, ddd, *J* 6.2, 3.4, 1.1 Hz, H-6), 4.88 (1H, d, *J* 10.8 Hz, C*H*HO), 4.62 (1H, d, *J* 10.8 Hz, C*H*HO), 4.24 (1H, d, *J* 11.0 Hz, C*H*HO), 4.01 (1H, d, *J* 11.0 Hz, C*H*HO), 3.17 (3H, s, OCH_3), 3.06 (3H, s, OCH_3), 3.07–3.04 (1H, m, H-1), 2.96–2.92 (1H, m, H-4), 1.86 (1H, dd, *J* 12.0, 3.8 Hz, H-3*exo*), 1.02 (1H, d, *J* 12.0 Hz, H-3*endo*). ^{13}C NMR: 165.72 and 165.58, 2 C (2×BzCO), 133.90 (C-5), 133.42, 2 C (Bz-4), 132.94 (C-6), 129.89 and 129.74, 2 C (Bz-1), 129.33 and 129.24, 4 C, 128.84 and 128.82, 4 C (Bz-3, Bz-2), 118.99 (C-7), 67.94 (CH2O), 67.36 (CH_2O), 51.60 (OCH_3), 49.40 (OCH_3), 48.16 (C-1), 45.45 (C-2), 44.88 (C-4), 30.02 (C-3). FABMS, *m*/*z* (rel%): 423 (2) [M+H], 391 (5), 105 (100) [PhCO]. For $C_{25}H_{26}O_6$ (422.5) calculated: 71.07% C, 6.20% H; found: 70.97% C, 6.22% H.

4.1.3. (1R,4R*)-7-Oxobicyclo[2.2.1]hept-5-ene-2,2-diyl]dimethyl dibenzoate (**4**).* Benzoylated ketal **3** (5.80 g, 13.7 mmol) was dissolved in a dioxane–water mixture (100 mL, 4:1). To this mixture Dowex 50 (H^+ form, 20 mL) was added, the reaction mixture was stirred overnight. The solvents were slowly distilled off at atmospheric pressure in the course of 10 h to remove methanol. The dioxane–water mixture was continuously added to retain the same reaction mixture volume. Dowex was filtered off and the residue was evaporated. Column chromatography of the residue on silica gel (400 g) in toluene–ethyl acetate (12:1) afforded 3.87 g (75%) of benzoylated keto compound as an oil. IR (CCl_4): 3093 (w), 3073 (w), 3066 (w), 3036 (w), 3010 (w), 2954 (w), 2875 (w), 1785 (s), 1728 (vs), 1645 (vw), 1604 (w), 1586 (w), 1492 (w), 1468 (w), 1452 (w), 1279 (sh), 1265 (vs), 710 (vs). ^{1}H NMR: 8.27–7.92 (4H, m, Bz-2), 7.68–7.62 (2H, m, Bz-4), 7.53–7.41 (4H, m, Bz-3), 6.82 (1H, ddd, *J* 6.8, 3.8, 1.2 Hz, H-5), 6.65 (1H, ddd, *J* 6.8, 3.7, 1.2 Hz, H-6), 4.45 (1H, d, *J* 11.5 Hz, C*H*HO), 4.40 (1H, d, *J* 11.5 Hz, CHHO), 4.22 (1H, d, *J* 11.4 Hz, C*H*HO), 4.11 (1H, d, *J* 11.4 Hz, C*H*HO), 3.15 (1H, dt, *J* 3.7, 1.2, 1.2 Hz, H-1), 3.01 (1H, tt, *J* 3.8, 3.8, 1.2, 1.2 Hz, H-4), 2.02 (1H, dd, *J* 12.8, 3.8 Hz, H-3*exo*), 1.25 (1H, d, *J* 12.8 Hz, H-3*endo*). ^{13}C NMR: 201.79 (C-7), 165.72 and 165.60, 2 C (2×BzCO), 135.13 (C-5), 133.61, 2 C (Bz-4), 131.26 (C-6), 129.55, 2 C (Bz-1), 129.47, 2 C, 128.88 and 128.84, 2 C (Bz-3, Bz-2), 66.70 (CH_2O), 66.03 (CH_2O), 51.25 (C-1), 46.27 (C-8), 42.40 (C-2), 29.23 (C-3). FABMS, *m*/*z* (rel%): 377 (1) [M+H], 105 (100) [PhCO]. For $C_{23}H_{20}O_5$ (376) calculated: 73.39% C, 5.36% H; found: 73.16% C, 5.20% H.

4.1.4. [(1R,4R*,7R*)-7-Hydroxybicyclo[2.2.1]hept-5-ene-2,2-diyl]dimethyl dibenzoate (**5**).* A solution of the ketone **4** (5.26 g, 14 mmol) in a tetrahydrofuran–water mixture (8:1, 180 mL) was cooled and stirred at 0 °C, sodium borohydride (330 mg, 8.8 mmol) was added in portions and the mixture was then stirred for 30 min. The reaction mixture was evaporated to half volume and partitioned between ether (120 mL) and brine (50 mL). The water phase was then extracted with ether (150 mL) and the combined organic phases were dried over anhydrous sodium sulfate and evaporated. Column chromatography of the residue on silica gel (350 g) in toluene–ethyl acetate (6:1) afforded 4.67 g (88.3%) as a clear oil. IR ($CHCl_3$): 3624 (m), 3488 (m), 3092 (w), 3065 (w), 3028 (w), 1715 (vs), 1646 (w), 1603 (m), 1585 (w), 1492 (w) 1471 (m), 1451 (s), 1335 (m), 1316 (s), 1287 (vs), 1271 (vs). ^{1}H NMR: 7.96–7.93 (4H, m, Bz-2), 7.66–7.61 (2H, m, Bz-4), 7.51–7.46 (4H, m, Bz-3), 6.18 (1H, ddd, 6.2, 3.5, 1.0 Hz, H-5), 6.10 (1H, ddd, *J* 6.2, 3.5, 1.0 Hz, H-6), 5.62 (1H, br s, OH), 4.96 (1H, d, *J* 10.6 Hz, C*H*HO), 4.72 (1H, d, *J* 10.6 Hz, C*H*HO), 4.28 (1H, d, *J* 10.9 Hz, C*H*HO), 3.96 (1H, d, *J* 10.9 Hz, C*H*HO), 3.61 (1H, br s, H-7), 2.73–2.71 (1H, m, H-1), 2.64–2.60 (1H, m, H-4), 2.02 (1H, dd, *J* 12.1, 3.7 Hz, H-3*exo*), 1.12 (1H, d, *J* 12.1 Hz, H-3*endo*). ^{13}C NMR: 165.82 and 165.63, 2 C (2×CO), 135.37 (C-5), 133.64 (C-6), 133.39 and 133.30, 2 C (Bz-4), 130.05 and 129.85, 2 C (Bz-1), 129.26 and 129.19, 4 C (Bz-2), 128.85 and 128.82, 4 C (Bz-3), 84.13 (C-7), 68.54 (CH2O), 67.14 (CH_2O), 49.93 (C-1), 46.97 (C-4), 46.23 (C-2), 30.24 (C-3). FABMS, *m*/*z* (rel%): 379 (1) [M+H], 361 (15) [M+H–H_2O], 105 (100) [PhCO]. For $C_{23}H_{22}O_5$ (378.4) calculated: 73.00% C, 5.86% H; found: 72.96% C, 5.81% H.

4.1.5. [(1R,4R*,7R*)-7-(Acetylamino)bicyclo[2.2.1]hept-5-ene-2,2-diyl]dimethyl dibenzoate (**6**).* A solution of the hydroxy compound **5** (2.03 g, 5.4 mmol) in acetonitrile (40 mL) was dropwise added over 20 min at rt to a mixture of glacial acetic acid (11 mL) and sulfuric acid (6.5 mL) and the resulting reaction mixture was stirred for a further 40 min at rt. The reaction was quenched by pouring on the ice (100 g), the water phase was then extracted with ethyl acetate (500 mL). The organic phase was separated and washed with

saturated solution of potassium hydrogen carbonate (3×150 mL), dried over anhydrous sodium sulfate and evaporated. The residue was crystallized from toluene–ethylacetate (2:1) to give 1.88 g (83.7%) of the amide **6** as white crystals. Mp=188.5–193 °C. IR ($CHCl_3$): 3434 (w), 3365 (w), 3091 (w), 3067 (w), 1715 (s), 1671 (s), 1602 (w), 1585 (w), 1527 (m), 1508 (m), 1493 (w), 1468 (w), 1452 (w), 1372 (m), 1328 (w), 1316 (m), 1268 (s). ^{1}H NMR: 8.07 (1H, d, *J* 4.7 Hz, NH), 7.96–7.93 (4H, m, Bz-2), 7.66–7.61 (2H, m, Bz-4), 7.50–7.46 (4H, m, Bz-3), 6.31 (1H, ddd, *J* 6.0, 3.3, 1.0 Hz, H-5), 6.19 (1H, ddd, *J* 6.0, 3.4, 0.8 Hz, H-6), 4.63 (1H, d, *J* 10.6 Hz, C*H*HO), 4.54 (1H, d, *J* 10.6 Hz, C*H*HO), 4.31 (1H, d, *J* 10.9 Hz, C*H*HO), 3.93 (1H, d, *J* 10.9 Hz, C*H*HO), 3.43–3.40 (1H, m, H-7), 3.12–3.10 (1H, m, H-1), 2.77–2.75 (1H, m, H-4), 2.24 (1H dd, *J* 12.8, 3.6 Hz, H3-*exo*), 1.81 (3H, s, CH_3), 1.16 (1H, d, *J* 12.8 Hz, H-3*endo*). ^{13}C NMR: 169.83 (AcCO), 165.73 and 165.58, 2 C (2×BzCO), 134.65 (C-6), 136.61 (C-5), 133.45 and 133.41, 2 C (Bz-4), 129.90 and 129.76, 2 C (Bz-1), 129.29 and 129.27, 4 C (Bz-2), 128.88 and 128.83, 4 C (Bz-3), 69.08 (CH_2O), 66.83 (CH_2O), 65.88 (C-7), 48.53 (C-1), 45.65 (C-2), 43.91 (C-4), 30.45 (C-3), 22.77 (CH3). FABMS, *m*/*z* (rel%): 420 (30) [M+H], 105 (100) [PhCO]. For $C_{25}H_{25}NO_5$ (419.5) calculated: 71.58% C, 6.01% H, 3.34% N; found: 71.45% C, 5.95% H, 3.08% N.

4.1.6. [(1R,4R*,7R*)-7-Aminobicyclo[2.2.1]hept-5-ene-2,2-diyl]dimethanol (**7**).* To a solution of amide **6** (3.03 g, 7.2 mmol) in ethanol–water (40 mL, 1:1) was added potassium hydroxide (3.8 g, 68 mmol) and reaction mixture was refluxed for 9 h in an argon atmosphere. The reaction mixture was neutralized with 6 M hydrochloric acid and applied onto a Dowex 50 (H^+ form, 100 mL). The column was eluted with methanol–water (1:1, 300 mL), water (300 mL), methanol (300 mL) and then with 3.5 M methanolic ammonia. The fractions containing product were evaporated to yield 1.1 g (90.2%) of amine **7**. Crude amine solidifies upon storage in refrigerator. IR (KBr): 3391 (vs), 3285 (s), 3058 (s), 1632 (m), 1597 (m), 1026 (s). ^{1}H NMR: 6.09 (1H, ddd, *J* 6.0, 3.3, 1.0 Hz, H-6), 6.01 (1H, ddd, *J* 6.0, 3.2, 1.0 Hz, H-5), 4.19 (4H, br s, NH2, 2×OH), 3.84 (1H, d, *J* 10.8 Hz, C*H*HO), 3.74 (1H, d, *J* 10.8 Hz, C*H*HO), 3.21 (1H, d, *J* 10.1 Hz, C*H*HO), 3.00 (1H, d, *J* 10.1 Hz, C*H*HO), 2.80 (1H, br s, H-7), 2.41–2.38 (1H, m, H-4), 2.34–2.32 (1H, m, H-1), 1.88 (1H, dd, *J* 12.1, 3.7 Hz, H-3*exo*), 0.57 (1H, d, *J* 12.1 Hz, H-3*endo*). ^{13}C NMR: 136.81 (C-6), 134.84 (C-5), 69.32 (C-7), 67.46 (CH_2O), 64.83 (CH_2O), 51.53 (C-1), 49.62 (C-2), 47.37 (C-4), 28.14 (C-3). ESI MS, *m*/*z* (rel%): 210 (100), 192 (10) [M+Na], 170 (15) [M+H]. ESI HRMS: calculated: 170.1181, found: 170.1176. For C9H15NO2 (169.2) calculated: 63.88% C, 8.93% H, 8.28% N; found: 63.52% C, 8.75% H, 8.02% N.

4.1.7. 1-[(1R,4R*,7R*)-5,5-Bis(hydroxymethyl)bicyclo[2.2.1]hept-2-en-7-yl]-5-methylpyrimidine-2,4(1H,3H)-dione (**8**).* A solution of amine **7** (650 mg, 3.8 mmol) and ethyl[(2*E*)-3-ethoxy-2-methylprop-2-enoyl]carbamate [4a,8] (720 mg, 3.86 mmol) in 1,4-dioxane (25 mL) was heated at 100 °C for 3 h. Dowex 50 (H^+ form, 10 mL) was washed with 1,4-dioxane and then added to the mixture. The mixture was heated at 100 °C for 2.5 h, the resin was filtered off, washed with methanol and the collected filtrates were evaporated. The residue was crystallized from ethanol to yield 340 mg (31.5%) of the thymine nucleoside as a white powder. A second crop (241 mg, 22.3%) of the product was obtained by column chromatography of the mother liquor on silica gel (25 g) in ethyl acetate–acetone–ethanol–water (100:15:6:4). Mp=231–237 °C. IR (KBr): 3426 (s), 3190 (s), 3062 (s), 1685 (s), 1464 (s), 1362 (m), 1043 (s), 1031 (s) 1024 (s), 761 (m). ^{1}H NMR: 11.16 (1H, br s, NH), 7.38 (1H, q, *J* 1.0 Hz, H-6), 6.25 (1H, bdd, *J* 6.0, 3.4 Hz, H-3′), 6.21 (1H, ddd, *J* 6.0, 3.4, 1.1 Hz, H-2′), 4.36 (1H, t, *J* 4.7 Hz, CH_2OH), 4.27 (1H, t, *J* 5.1 Hz, CH_2OH), 3.47 (1H, br s, H-7′), 3.42–3.37 (2H, m, OCH_2), 3.26–3.24 (1H, m, H-1′), 3.24–3.22 (1H, m, H-4′), 3.04 (1H, dd, *J* 9.8, 4.7 Hz, C*H*HO), 2.94 (1H, dd, *J* 10.2, 5.1 Hz, C*H*HO), 1.80 (3H, d, *J* 1.0 Hz, CH_3), 1.71 (1H, dd, *J* 13.5, 3.4 Hz, H-6′*exo*), 0.72 (1H, d, *J* 13.5 Hz, H-6′*endo*). ^{13}C NMR: 164.20 (C-4), 151.47 (C-2), 138.89 (C-6), 136.53 (C-3′), 134.00 (C-2′), 108.48 (C-5), 70.657 (C-7′), 64.92 (CH_2O), 62.23 (CH_2O), 48.76 (C-5′), 47.82 (C-4′), 42.16 (C-1′), 29.62 (C-6′), 12.23 (CH_3). FABMS, *m*/*z* (rel%): 279 (45) [M+H], 127 (100). For $C_{14}H_{18}N_2O_4$ .1/2 H_2O (287) calculated: 58.53% C, 6.67% H, 9.75% N; found: 58.69% C, 6.90% H, 9.41% N.

4.1.8. [(1R,4R*,7R*)-7-(6-Chloro-9H-purin-9-yl)bicyclo[2.2.1]hept-5-ene-2,2-diyl]dimethanol (**11**).* A mixture of amine **7** (1.01 g, 6 mmol), 4,6-dichloropyrimidin-5-amine[15] (1.44 g, 9 mmol), and triethylamine (3.6 mL) in ethanol (18 mL) was heated in a pressure vessel at 105 °C for 6 days and, after cooling, was evaporated. The residue was chromatographed on a column of silica gel (200 g) in ethyl acetate–acetone–ethanol–water (100:15:6:4) to afford 1.27 g (71%) of product as a foam. To a suspension of pyrimidine (1.27 g, 4.3 mmol) in triethyl orthoformate (130 mL) concentrated hydrochloric acid (2.3 mL) was added and the reaction mixture was vigorously stirred for 3 days at room temperature (suspension dissolved). The solution was evaporated and the residue was dissolved in a mixture of tetrahydrofuran (17 mL) and 0.5 M hydrochloric acid (17 mL) and the solution was stirred at room temperature for 4 h. After neutralization with solid sodium hydrogen carbonate, the mixture was evaporated to a one fourth of the original volume and, after adsorbtion on silica gel, applied on a silica gel column (200 g). Elution with ethyl acetate–acetone–ethanol–water (150:15:3:2) gave 1.15 g (63%) of the chloropurine nucleoside **11**. A sample was crystallized from water to obtain white crystals. Mp=166–169.5 °C (decomp.). IR (KBr): 3355 (s), 3318 (s), 3091 (m), 3064 (m), 1642 (w), 1591 (s), 1574 (s), 1561 (s), 1489 (m), 1335 (s), 1210 (s), 1034 (s), 1018 (s), 647 (m). ^{1}H NMR: 8.79 (1H, s, H-2′), 8.76 (1H, s, H-8′), 6.30–6.40 (2H, m, H-5, H-6), 4.35 (1H, t, *J* 5.2 Hz, CH_2OH), 4.16 (1H, t, *J* 5.2 Hz, CH_2OH), 4.07–4.04 (1H, m, H-7), 3.75–3.73 (1H, m, H-4), 3.59 (1H, dq, *J* 2.6, 1,7, 1.7, 1.7 Hz, H-1), 3.38 (1H dd, *J* 10.3, 5.2 Hz, C*H*HO), 3.01 (1H dd, *J* 10.3, 5.2 Hz, C*H*HO), 2.83 (1H dd, *J* 10.3, 5.2 Hz, C*H*HO), 2.22 (1H dd, *J* 10.3, 4.8 Hz, C*H*HO), 1.85 (1H, dd, *J* 13.2, 3.4 Hz, H-3*exo*), 0.85 (1H, d, J 13.2 Hz, H-3*endo*). ^{13}C NMR: 152.64 (C-4′), 151.76 (C-2′), 149.23 (C-6′), 146.61 (C-8′), 135.56 (C-5), 134.74 (C-6), 131.13 (C-5′), 68.81 (C-7), 64.76 (CH_2O), 62.07 (CH_2O), 49.40 (C-2), 47.92 (C-1), 43.12 (C-4), 29.54 (C-3). FABMS, *m*/*z* (rel%): 309/307 (10/30) [M+H], 155 (100). For $C_{14}H_{15}ClN_4O_2$ .1/4 H_2O (311.2) calculated: 54.02% C, 5.02% H, 11.39% Cl, 18.00% N; found: 54.03% C, 4.89% H, 11.54% Cl, 18.11% N.

4.1.9. [(1R,4R*,7R*)-7-(6-Amino-9H-purin-9-yl)bicyclo[2.2.1]hept-5-ene-2,2-diyl]dimethanol (**12**).* Chloropurine derivative 11 (650 mg, 2.12 mmol) was heated with liquid ammonia (40 mL) and methanol (6 mL) in an autoclave at 75 °C for 48 h. Ammonia was then evaporated and the residue was crystallized from water to give 552 mg (91%) adenine nucleoside **12** as white crystals. Mp=282–283.5 °C (decomp.). IR (KBr): 3429 (s), 3323 (s), 3261 (s), 3178 (s), 3150 (s), 3112 (s), 1666 (s), 1638 (m), 1604 (s), 1567 (s), 1512 (w), 1484 (s), 1417 (s), 1344 (s), 1303 (s), 1047 (s), 1031 (s), 1024 (s), 1214 (m), 798 (m), 648 (s). ^{1}H NMR: 8.14 (1H, s, H-8′), 8.12 (1H, s, H-2′), 7.16 (1H, br s, NH_2), 6.25–6.35 (2H, m, H-5, H-6), 4.28 (1H, t, *J* 5.3 Hz, CH_2OH), 4.11 (1H, t, *J* 5.0 Hz, CH_2OH), 3.66–3.63 m, 1H, (H-4), 3.65 (1H, br s, H-7), 3.55–3.53 (1H, m, H-1), 3.42 (1H, dd, *J* 10.3, 5.5 Hz, C*H*HO), 2.98 (1H, dd, *J* 10.0, 5.4 Hz, C*H*HO), 2.97 (1H, dd, *J* 10.3, 5.3 Hz, C*H*HO), 2.25 (1H, dd, *J* 10.3, 4.9 Hz, C*H*HO), 1.92 (1H, dd, *J* 13.1, 3.5 Hz, H-3*exo*), 0.79 (1H, d, *J* 13.1 Hz, H-3*endo*). ^{13}C NMR: 156.10 (C-6′), 152.60 (C-2′), 150.30 (C-4′), 139.50 (C-8′), 135.66 (C-6), 134.73 (C-5), 119.12 (C-5′), 67.53 (C-7), 64.81 (CH_2O), 62.06 (CH_2O), 49.26 (C-2), 48.10 (C-1), 43.12 (C-4), 29.79 (C-3). FABMS, *m*/*z* (rel%): 288 (33) [M+H], 136 (100) [base+H]. For $C_{14}H_{17}N_5O_2$ .H_2O (294) calculated: 57.33% C, 6.07% H, 23.88% N; found: 57.40% C, 5.95% H, 24.05% N.

4.1.10. {(1R,4R*,7R*)-7-[6-(Cyclopropylamino)-9H-purin-9-yl]bicyclo[2.2.1]hept-5-ene-2,2-diyl}dimethanol (**13**).* A mixture of

chloropurine derivative **11** (310 mg, 1 mmol), cyclopropylamine (2 mL) and methanol (3 mL) was left overnight and evaporated. The product was purified by chromatography on silica gel (80 g) in ethyl acetate–acetone–ethanol–water (95:15:9:6). It was obtained 300 mg (92%) of compound **13**. A sample was crystallized from ethanol to obtain a white powder. Mp=212–216.5 °C (decomp.). IR (KBr): 3408 (s), 3316 (m), 3231 (s), 3096 (m), 1613 (s), 1582 (s), 1566 (s), 1529 (w), 1482 (m), 1417 (m), 1337 (s), 1299 (s), 1217 (m), 1043 (s), 1033 (s), 1021 (m), 796 (m), 646 (m). ^{1}H NMR: 8.23 (1H, s) and 8.15 (1H, s, H-2′, H-8′), 7.83 (1H, br s, NH_2), 6.33–6.28 (2H, m, H-5, H-6), 4.28 (1H, t, *J* 5.3 Hz, CH_2OH), 4.10 (1H, t, *J* 5.0 Hz, CH_2OH), 3.89 (1H, br s, H-7), 3.67–3.63 (1H, m, H-4), 3.56–3.53 (1H, m, H-1), 3.42 (1H, dd, *J* 10.2, 5.4 Hz, C*H*HO), 3.05 (1H, br s, cyclopropyl), 2.99 (1H, dd, *J* 10.1, 5.2 Hz, C*H*HO), 2.97 (1H, dd, *J* 10.2, 5.3 Hz, C*H*HO), 2.25 (1H, dd, *J* 10.2, 4.9 Hz, C*H*HO), 1.91 (1H, dd, *J* 12.8, 3.6 Hz, H-3*exo*), 0.79 (1H, d, *J* 13.2 Hz, H-3*endo*), 0.74–0.70 (2H, m, cyclopropyl CH_2), 0.64–0.60 (2H, m, cyclopropyl CH_2). ^{13}C NMR: 155.61 (C-6′), 152.51 (C-2′), 149.67 (C-4′), 139.32 (C-8′), 135.67 (C-6), 134.72 (C-5), 119.66 (C-5′), 67.55 (C-7), 64.81 (CH_2O), 62.08 (CH_2O), 49.26 (C-2), 48.11 (C-1), 43.13 (C-4), 29.81 (C-3), 23.95 (NCH), 6.51, 2 C (2×CH2). FABMS, *m*/*z* (rel%): 328 (100) [M+H], 207 (50). For $C_{17}H_{21}N_5O_2$ .1/3 H_2O (332) calculated: 61.52% C, 6.53% H, 21.10% N; found: 61.64% C, 6.57% H, 21.18% N.

4.1.11. [(1R,4R*,7R*)-7-(2-Amino-6-chloro-9H-purin-9-yl)bicyclo[2.2.1]hept-5-ene-2,2-diyl]dimethanol (**18**).* A mixture of amine **7** (510 mg, 3 mmol), 2,5-diamino-4,6-dichloropyrimidine[7] (600 mg, 3.35 mmol), and triethylamine (2.4 mL) in ethanol (18 mL) was heated in a pressure vessel at 105 °C for 6 days and, after cooling, was evaporated. The residue was chromatographed on a column of silica gel (200 g) in ethyl acetate–acetone–ethanol–water (105:15:3:2) to afford 734 mg (78.5%) of pyrimidine intermediate, which was immediately used in the next step. Concentrated hydrochloric acid (1.5 mL) was added to a suspension of pyrimidine intermediate in triethyl orthoformate (100 mL) and the reaction mixture was vigorously stirred for 5 days at room temperature. The mixture was evaporated and the residue was dissolved in a mixture of tetrahydrofuran (15 mL) and 0.5 M hydrochloric acid (15 mL) and stirred at room temperature for 4 h. After neutralization with solid sodium hydrogen carbonate, the mixture was evaporated to one fourth of the original volume, absorbed on silica gel and applied on a silica gel column (200 g). Chromatography in ethyl acetate–acetone–ethanol–water (105:15:3:2) gave 650 mg (67% based on **7**) of compound **18**. The compound was recrystallized from water–methanol (95:5) to obtain a brownish powder. Mp=221–222 °C. IR (KBr): 3493 (m), 3407 (m), 3350 (s), 3215 (m), 1658 (w), 1615 (s), 1577 (m), 1565 (s), 1511 (m), 1406 (m), 1215 (m), 1045 (m), 1034 (m), 638 (w). ^{1}H NMR: 8.15 (1H, s, H-8′), 6.88 (2H, br s, NH_2), 6.30–6.28 (2H, m, H-5, H-6), 4.31 (1H, t, *J* 5.2 Hz, CH2OH), 4.18 (1H, t, *J* 5.0 Hz, CH_2OH), 3.82 (1H, br s, H-7), 3.59 (1H, br s, H-4), 3.51–3.48 (1H, m, H-1), 3.42 (1H, dd, *J* 10.3, 5.2 Hz, C*H*HO), 3.03 (1H, dd, *J* 10.2, 5.3 Hz, C*H*HO), 2.97 (1H, dd, *J* 10.3, 5.3 Hz, C*H*HO), 2.35 (1H, dd, *J* 10.2, 4.4 Hz, C*H*HO), 1.90 (1H, dd, *J* 13.1, 3.5 Hz, H-3*exo*), 0.79 (1H, d, *J* 13.1 Hz, H-3*endo*). ^{13}C NMR: 159.85 (C-2′), 154.84 (C-4′), 149.44 (C-6′), 141.80 (C-8′), 135.52 (C-6), 134.74 (C-5), 123.62 (C-5′), 67.36 (C-7), 64.73 (CH_2O), 62.00 (CH_2O), 49.23 (C-2), 47.78 (C-1), 42.99 (C-4), 29.66 (C-3). FABMS, *m*/*z* (rel%): 322/324 (15/10) [M+H], 170 (27) [base+H], 100 (100), 57 (70). For $C_{14}H_{16}ClN_5O_2$ .1/3 H_2O (327.8) calculated: 51.30% C, 5.13% H, 10.82% Cl, 21.37% N; found: 51.45% C, 4.94% H, 10.65% Cl, 21.08% N.

4.1.12. {(1R,4R*,7R*)-7-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]bicyclo[2.2.1]hept-5-ene-2,2-diyl}dimethanol (**19**).* A mixture of chloropurine derivative **18** (350 mg, 1.09 mmol), cyclopropylamine (6 mL) and methanol (8 mL) was vigorously stirred overnight and evaporated. Crystallization of the residue from water–methanol (9:1) afforded 290 mg (80%) of cyclopropyl derivative as ochre crystals. An additional crop of the product (45 mg, 12%) was obtained by chromatography of the mother liquor on silica gel (50 g) in ethyl acetate–acetone–ethanol–water (36:6:5:3). Mp=252–253 °C (decomp.). IR (KBr): 3479 (m), 3393 (s), 3361 (s), 3279 (m), 3162 (m), 3097 (m), 1628 (s), 1600 (s), 1522 (w), 1479 (s), 1405 (m), 1216 (m), 1037 (m), 1030 (m), 1023 (m), 788 (w), 647 (w), 638 (w). ^{1}H NMR: 7.69 (1H, s, H-8′), 7.22 (1H, bd, *J* 3.8 Hz, NH), 6.30–6.25 (2H, m, H-5, H-6), 5.79 (2H, br s, NH_2), 4.27 (1H, t, *J* 5.3 Hz, CH_2OH), 4.09 (1H, t, *J* 5.1 Hz, CH_2OH), 3.70 (1H, br s, H-7), 3.53–3.48 (2H, m, H-1, H-4), 3.42 (1H, dd, *J* 10.3, 5.1 Hz, C*H*HO), 3.08 (1H, dd, *J* 10.2, 5.2 Hz, C*H*HO), 3.03 (1H, br s, cyclopropyl), 2.97 (1H, dd, *J* 10.3, 5.5 Hz, C*H*HO), 2.40 (1H, dd, *J* 10.2, 4.9 Hz, C*H*HO), 1.93 (1H, dd, *J* 13.1, 3.5 Hz, H-3*exo*), 0.76 (1H, d, *J* 13.1 Hz, H-3*endo*), 0.68–0.57 (4H, m, cyclopropyl). ^{13}C NMR: 160.32 (C-2′), 155.95 (C-6′), 152.17 (C-4′), 135.72 (C-6), 135.51 (C-8′), 134.83 (C-5), 113.79 (C-5′), 67.37 (C-7), 64.74 (CH_2O), 61.99 (CH_2O), 49.27 (C-2), 48.02 (C-1), 43.13 (C-4), 29.97 (C-3), 23.71 (NCH), 6.57, 2 C (2×CH_2). FABMS, *m*/*z* (rel%): 343 (40) [M+H], 255 (12), 191 (35) [base+H], 93 (100). For $C_{17}H_{22}N_6O_2$ .1/4 H_2O (346.9) calculated: 58.86% C, 6.54% H, 24.23% N; found: 58.94% C, 6.58% H, 24.61% N.

4.2. General method for preparation of saturated compounds 9, 14, 16, 20

A mixture of unsaturated compound **8**, **12**, **13** or **19** (160 mg) and $Pd(OH)_2$ (20% on charcoal, 80 mg) in the appropriate solvent was stirred in an atmosphere of hydrogen for 3 days. The catalyst was filtered off and washed with methanol and filtrate was evaporated. Residue was crystallized or chromatographed on silica gel column and crystallized.

4.2.1. 1-[(1R,4S*,7R*)-2,2-Bis(hydroxymethyl)bicyclo[2.2.1]hept-7-yl]-5-methylpyrimidine-2,4(1H,3H)-dione (**9**).* Solvent: methanol–water (11 mL, 10:1). Chromatography on silica gel (10 g) in ethyl acetate–acetone–ethanol–water (100:15:6:4) afforded 128 mg (79%) of the oily product, which was crystallized from ethanol as a white powder. Mp=255–257 °C. IR (KBr): 3509 (s), 3415 (m), 3353 (s), 1692 (s), 1675 (s), 1635 (s), 1475 (s), 1362 (m), 1048 (s), 1031 (s), 760 (m). ^{1}H NMR: 11.16 (1H, s, NH), 7.41 (1H, q, *J* 1.1 Hz, H-6), 4.33 (1H, t, *J* 5.1 Hz, CH_2OH), 4.31 (1H, t, *J* 4.9 Hz, CH_2OH), 3.69 (1H, br s, H-7′), 3.61 (1H, dd, *J* 10.6, 5.1 Hz, C*H*HO), 3.27 (1H, dd, *J* 9.8, 5.1 Hz, C*H*HO), 3.15 (1H, dd, *J* 10.6, 5.4 Hz, C*H*HO), 2.79 (1H, dd, *J* 9.8, 4.6 Hz, C*H*HO), 2.67–2.64 (1H, m, H-1′), 2.62–2.59 (1H, m, H-4′), 1.78 (3H, d, *J* 1.1 Hz, CH_3), 1.73–1.66 (3H, m, H-3′*exo*, H-5′*exo*, H-6′*endo*), 1.51–1.47 (1H, m, H-6′*exo*), 1.21–1.18 (1H, m, H-5′*endo*), 0.80 (1H, d, *J* 13.6 Hz, H-3*endo*). ^{13}C NMR: 164.23 (C-4), 151.60 (C-2), 139.97 (C-6), 108.17 (C-5), 67.67 (C-7′), 63.57 (CH_2O), 63.03 (CH_2O), 46.90 (C-2′), 42.60 (C-1′), 36.82 (C-4′), 35.52 (C-3′), 26.35 (C-5′), 22.55 (C-6′′), 12.23 (CH_3). FABMS, *m*/*z* (rel%): 281 (100) [M+H], 239 (80), 127 (72) [base+H]. For $C_{14}H_{18}N_2O_4$ .1/3 H_2O (286.3) calculated: 58.73% C, 7.28% H, 9.78% N; found: 58.54% C, 7.27% H, 9.56% N.

4.2.2. [(1R,4S*,7R*)-7-(6-Amino-9H-purin-9-yl)bicyclo[2.2.1]-heptane-2,2-diyl]dimethanol (**14**).* Solvent: methanol–dimethylformamide (20 mL, 1:1). Crystallization from water afforded 65 mg (40.3%) of the saturated compound as a white powder. Mp=293.5–296 °C (decomp.). IR (KBr): 3302 (s), 3143 (s), 1671 (s), 1613 (s), 1564 (s), 1510 (m), 1489 (s), 1418 (m), 1336 (s), 1313 (s), 1215 (s), 1046 (s), 1029 (s), 798 (m), 648 (m). ^{1}H NMR: 8.14 (1H, s, H-8′), 8.12 (1H, s, H-2′), 7.18 (2H, br s, NH_2), 4.40 (1H, t, *J* 4.7 Hz, CH_2OH), 4.10 (1H, t, *J* 4.9 Hz, CH_2OH), 4.08 (1H, br s, H-7), 3.60 (1H, dd, *J* 10.6, 4.6 Hz, C*H*HO), 3.17 (1H, dd, *J* 10.6, 4.6 Hz, C*H*HO), 3.05–3.02 (1H, m, H-4), 2.97–2.95 (1H, m, H-1), 2.90 (1H, dd, *J* 10.2, 5.1 Hz, C*H*HO), 1.99 (1H, dd, *J* 10.1, 4.6 Hz, C*H*HO), 1.89–1.75 (3H, m, H-3*exo*, H-5*exo*, H-6*endo*), 1.61–1.59 (1H, m, H-6*exo*), 1.26–1.24 (1H, m, H-5*endo*), 0.84 (1H, d, *J* 13.6 Hz, H-3*endo*). ^{13}C NMR: 156.14 (C-6′), 152.59 (C-2′), 150.60 (C-4′), 140.49 (C-8′), 119.32 (C-5′), 64.22 (C-7), 63.43 (CH_2O), 62.73

(CH_2O), 47.41 (C-2), 43.27 (C-1), 38.00 (C-4), 35.87 (C-3), 26.62 (C-5), 22.77 (C-6). ESI MS, *m*/*z* (rel%): 312 (5) [M+Na], 290 (100) [M+H]. For $C_{14}H_{19}N_5O_2$ .0.5 H_2O (298.3) calculated: 56.36% C, 6.76% H, 23.47% N; found: 56.37% C, 6.63% H, 23.34% N.

4.2.3. {(1R,4S*,7R*)-7-[6-(Cyclopropylamino)-9H-purin-9-yl]bicyclo[2.2.1]heptane-2,2-diyl}dimethanol (**16**).* Solvent: methanol (10 mL). Crystallization from ethanol afforded 108 mg (67%) of the saturated compound as a white powder. Mp=212–213 °C. IR (KBr): 3297 (s), 3093 (m), 1617 (s), 1581 (s), 1534 (m), 1491 (m), 1417 (s), 1405, 1335 (s), 1299 (s), 1216 (s), 1047 (s), 1035 (s), 799 (m), 648 (m). ^{1}H NMR: 8.23 (1H, s, H-8′), 8.13 (1H, s, H-2′), 7.79 (1H, br s, NH), 4.34 (1H, t, *J* 4.9 Hz, CH_2OH), 4.10 (1H, br s, H-7), 4.04 (1H, t, *J* 4.9 Hz, CH_2OH), 3.61 (1H, dd, *J* 10.1, 4.8 Hz, C*H*HO), 3.19 (1H, dd, *J* 10.5, 5.1 Hz, C*H*HO), 3.07–3.04 (2H, m, H-4, cyclopropyl), 2.89 (1H, dd, *J* 10.1, 5.0 Hz, C*H*HO), 2.04 (1H, dd, *J* 9.8, 4.6 Hz, C*H*HO), 2.01–3.97 (1H, m, H-1), 1.89–1.76 (3H, m, H-3*exo*, H-5*exo*, H-6*endo*), 1.62–1.59 (1H, m, H-6*exo*), 1.28–1.26 (1H, m, H-5*endo*), 0.86 (1H, bd, *J* 13.2 Hz, H-3*endo*), 0.74–0.70 (2H, m, cyclopropyl), 0.64–0.60 (2H, m, cyclopropyl). ^{13}C NMR: 155.63 (C-6′), 152.47 (C-2′), 149.93 (C-4′), 140.28 (C-8′), 119.66 (C-5′), 64.19 (C-7), 63.36 (CH_2O), 62.68 (CH_2O), 47.39 (C-2), 43.26 (C-1), 37.98 (C-4), 35.84 (C-3), 26.58 (C-5), 22.76 (C-6), 6.57, 2 C (2×CH_2). FABMS, *m*/*z* (rel%): 330 (100) [M+H], 176 (55) [base+H]. For $C_{17}H_{23}N_5O_2$ .1/3 H_2O (335.4) calculated: 60.88% C, 7.11% H, 20.88% N; found: 60.83% C, 7.00% H, 20.65% N.

4.2.4. (1R,4S*,7R*)-7-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]bicyclo[2.2.1]heptane-2,2-diyl}dimethanol (**20**).* Solvent: methanol–water (15 mL, 3:2). Crystallization from ethanol afforded 105 mg (65%) of the saturated compound as a white powder. Mp=252–255.5 °C (decomp.). IR (KBr): 3483 (m), 3398 (m), 3359 (m), 3275 (m), 3160 (m), 3100 (m), 1627 (s), 1617 (s), 1599 (s), 1524 (w), 1480 (s), 1391 (m), 1233 (w), 1040 (m), 1029 (m), 792 (m), 641 (w). ^{1}H NMR: 7.68 (1H, s, H-8′), 7.24 (1H, br s, NH), 5.78 (2H, br s, NH_2), 4.38 (1H, br s, CH_2OH), 4.07 (1H, t, *J* 4.8 Hz, CH_2OH), 3.90 (1H, br s, H-7), 3.62 (1H, dd, *J* 10.3, 3.3 Hz, C*H*HO), 3.16 (1H, dd, *J* 10.3, 3.5 Hz, C*H*HO), 3.00 (1H, dd, *J* 10.2, 4.9 Hz, C*H*HO), 2.97 (1H, br s, cyclopropyl), 2.95–2.91 (2H, m, H-1, H-4), 2.16 (1H, dd, *J* 10.2, 4.5 Hz, C*H*HO), 1.87 (1H, dm, *J* 13.6 Hz, H-3*exo*), 1.82–1.71 (2H m, H-5*exo*, H-6*endo*), 1.56–1.53 (1H, m, H-6*exo*), 1.23–1.20 (1H, m, H-5*endo*), 0.81 (1H, d, *J* 13.3 Hz, H-3*endo*), 0.68–0.64 (2H, m, cyclopropyl), 0.60–0.56 (2H, m, cyclopropyl). ^{13}C NMR: 160.25 (C-2′), 155.96 (C-6′), 152.37 (C-4′), 136.61 (C-8′), 114.00 (C-5′), 63.76 (C-7), 63.39 (CH_2O), 62.74 (CH_2O) 47.41 (C-2), 42.87 (C-1), 37.98 (C-4), 36.01 (C-3), 26.68 (C-5), 23.95 (cyclopropyl), 22.80 (C-6), 6.66 (cyclopropyl). ESI MS, *m*/*z* (rel%): 367 (5) [M+Na], 345 (100) [M+H]. For $C_{17}H_{24}N_6O_2 \cdot H_2O$ (362.4) calculated: 56.34% C, 7.23% H, 23.19% N; found: 56.70% C, 7.08% H, 22.89% N.

4.3. General method for preparation of the *cis*-hydroxylated compounds 10, 15, 17, 21

Unsaturated analogues **8**, **12**, **13** or **19** (170 mg) were dissolved in a mixture of water–acetone (10 mL, 1:1). A solution of NMMO (50% in water, 1.5 mL) and a water solution of osmium tetroxide (50 μl, 20 mg/mL) were added and the reaction mixture was stirred at rt for 2 days and then evaporated. The product was isolated by column chromatography on silica gel and crystallization.

4.3.1. 1-[(1R,4S*,5R*,6S*,7R*)-5,6-Dihydroxy-2,2-bis(hydroxymethyl)bicyclo[2.2.1]hept-7-yl]-5-methylpyrimidine-2,4(1H,3H)-dione (**10**).* Chromatography on silica gel (25 g) in ethyl acetate–acetone–ethanol–water (36:5:5:3) afforded 100 mg (79%) of the product, which was crystallized from ethanol to give 85 mg as a white powder. Mp=267–270 °C (decomp.). IR (KBr): 3385 (s), 3255 (s), 1691 (s), 1638 (s), 1467 (s), 1373 (m), 1059 (s), 1038 (s), 1027 (s), 761 (m). ^{1}H NMR: 11.13 (1H, s, NH), 7.37 (1H, q, *J* 1.1 Hz, H-6), 4.93 (1H, d, *J* 4.4 Hz, 5-O*H*), 4.67 (1H, d, *J* 5.8 Hz, 5-OH), 4.48 (1H, t, *J* 4.7 Hz, CH_2OH), 4.38 (1H, t, *J* 4.9 Hz, CH_2OH), 4.15 (1H, br s, H-7′), 4.13 (1H, dd, *J* 7.0, 4.4 Hz, H-5′), 3.64 (1H, t, *J* 6.2, 6.2 Hz, H-5′), 3.54 (1H, dd, *J* 10.8, 4.3 Hz, C*H*HO), 3.27 (1H, dd, *J* 10.0, 5.1 Hz, C*H*HO), 3.03 (1H, dd, *J* 10.8, 4.9 Hz, C*H*HO), 2.76 (1H, dd, *J* 10.0, 4.6 Hz, C*H*HO), 2.63–2.61 (1H, m, H-1′), 2.49–2.47 (1H, m, H-4′), 1.78 (3H, d, *J* 1.1 Hz, CH_3), 1.61 (1H, dd, *J* 13.7, 3.5 Hz, H-3′*exo*), 0.78 (1H, d, *J* 13.7 Hz, H-3′*endo*). FABMS, *m*/*z* (rel%): 313 (100) [M+H], 295 (7), 181 (27), 127 (39) [base+H]. For $C_{14}H_{20}N_2O_6$ .1/3 H_2O (318.3) calculated: 52.82% C, 6.54% H, 8.80% N; found: 52.86% C, 6.45% H, 8.58% N.

4.3.2. (1R,2S*,3R*,4S*,7S*)-7-(6-Amino-9H-purin-9-yl)-5,5-bis(hydroxymethyl)bicyclo[2.2.1]heptane-2,3-diol (**15**).* Chromatography on silica gel (25 g) in ethyl acetate–acetone–ethanol–water (17:3:3:3) afforded 154 mg (86%) of the product, which was crystallized from ethanol (125 mg) as a greyish powder. Mp=239.5–242 °C (decomp.). IR (KBr): 3465 (s), 3414 (s), 3353 (s), 3275 (s), 3169 (s), 3108 (s), 1668 (s), 1648 (s), 1608 (s), 1569 (s), 1513 (w), 1414 (s), 1331 (s), 1322 (s), 1213 (m), 1066 (s), 1045 (s), 1032 (s), 1026 (s), 799 (m), 791 (m), 649 (m), 645 (m). ^{1}H NMR: 8.13 (1H, s) and 8.12 (1H, s, H-2′, H-8′), 7.13 (1H, br s, NH_2), 5.03 (1H, d, *J* 4.4 Hz, 3-O*H*), 4.76 (1H, d, *J* 5.6 Hz, 2-OH), 4.51 (1H, br s, H-7), 4.48 (1H, t, *J* 4.7 Hz, CH_2OH), 4.22 (1H, dd, *J* 6.4, 4.4 Hz, H-3), 4.12 (1H, t, *J* 4.7 Hz, CH_2OH), 3.55 (1H, dd, *J* 10.0, 5.5 Hz, C*H*HO), 3.54 (1H, t, *J* 6.2, 6.2 Hz, H-2), 3.06 (1H, dd, *J* 10.0, 5.4 Hz, C*H*HO), 2.922.87 (3H, m, H-1, H-4, C*H*HO), 2.00 (1H, dd, *J* 10.2, 5.1 Hz, C*H*HO), 1.78 (1H, dd, *J* 13.6, 3.5 Hz, H-6*exo*), 0.84 (1H, d, *J* 13.6 Hz, H-6*endo*). ^{13}C NMR: 156.08 (C-6′), 152.46 (C-2′), 150.55 (C-4′), 140.43 (C-8′), 119.40 (C-5′), 72.07 (C-2), 67.77 (C-3), 62.59 (CH_2O), 61.37 (CH_2O), 60.01 (C-7), 50.12 (C-4), 46.14 (C-1), 45.79 (C-5), 31.20 (C-6). FABMS, *m*/*z* (rel%): 362 (100) [M+H]. For $C_{14}H_{197}N_5O_4$ .2/3 H_2O (373.4) calculated: 48.27% C, 6.37% H, 20.10% N; found: 48.33% C, 6.46% H, 19.89% N.

4.3.3. (1R,2S*,3R*,4S*,7S*)-7-[6-(Cyclopropylamino)-9H-purin-9-yl]-5,5-bis(hydroxymethyl)bicyclo[2.2.1]heptane-2,3-diol (**17**).* Chromatography on silica gel (25 g) in ethyl acetate–acetone–ethanol–water (36:5:5:3) afforded 149 mg (84%) of the product, which was crystallized from ethanol (120 mg) as a greyish powder. Mp=179–182 °C. IR (KBr): 3555 (w), 3415 (m), 3300 (s), 3240 (s), 3197 (m), 1620 (s), 1578 (m), 1526 (w), 1484 (m), 1415 (m), 1402 (m), 1327 (s), 1223 (m), 1068 (m), 1047 (m), 1038 (m), 1028 (m), 795 (m), 646 (m). ^{1}H NMR: 8.23 (1H, s, H-2′), 8.12 (1H, s, H-8′), 7.78 (1H, br s, NH), 5.03 (1H, d, *J* 4.5 Hz, 3-OH), 4.76 (1H, d, *J* 5.8 Hz, 2-OH), 4.51 (1H, br s, H-7), 4.48 (1H, t, *J* 4.7 Hz, CH_2OH), 4.22 (1H, dd, *J* 6.5, 4.6 Hz, H-3), 4.11 (1H, t, *J* 5.0 Hz, CH_2OH), 3.73 (1H, t, *J* 6.2, 6.2 Hz, H-2), 3.55 (1H, dd, *J* 10.8, 4.3 Hz, C*H*HO), 3.07 (1H, dd, *J* 10.9, 5.1 Hz, C*H*HO), 3.05 br s, 1H (cyclopropyl), 2.93–2.87 (3H, m, H-1, H-4, C*H*HO), 2.00 (1H, dd, *J* 9.8, 4.8 Hz, C*H*HO), 1.78 (1 H, dd, *J* 13.5, 4.2 Hz, H-6*exo*), 0.84 (1 H, d, *J* 13.5 Hz, H-6*endo*), 0.74–0.70 (2H, m, cyclopropyl), 0.64–0.60 (2H, m, cyclopropyl). ^{13}C NMR: 156.08 (C-6′), 152.46 (C-2′), 150.55 (C-4′), 140.43 (C-8′), 119.40 (C-5′), 72.07 (C-2), 67.77 (C-3), 62.59 (CH_2O), 61.36 (CH_2O), 60.03 (C-7), 50.13 (C-4), 46.15 (C-1), 45.78 (C-5), 31.30 (C-6), 23.81 (NCH), 6.49, 2 C (2×CH_2). FABMS, *m*/*z* (rel%): 362 (100) [M+H], 176 (95) [base+H]. For $C_{17}H_{23}N_5O_4$ .1/2 H_2O (370.4) calculated: 55.12% C, 6.53% H, 18.91% N; found: 55.04% C, 6.60% H, 18.65% N.

4.3.4. (1R,2S*,3R*,4S*,7S*)-7-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-5,5-bis(hydroxymethyl)bicyclo[2.2.1]heptane-2,3-diol (**21**).* Chromatography on silica gel (25 g) in ethyl acetate–acetone–ethanol–water (95:15:9:6) afforded 85 mg (37%) of the product, which was crystallized from ethanol (59 mg) as a greyish powder. Mp=194–196 °C (decomp.). IR (KBr): 3490 (s), 3402 (s), 3363 (s), 3237 (m), 1657 (m), 1617 (s), 1597 (s), 1535 (w), 1491 (s), 1406 (m), 1226 (w), 1063 (m), 1042 (m), 1032 (m), 788 (w), 637 (w). ^{1}H NMR:

7.67 (1H, s, H-8′), 7.24 (1H, br s, NH), 5.74 (2H, br s, NH2), 4.96 (1H, d, *J* 4.7 Hz, 3-OH), 4.80 (1H, d, *J* 5.8 Hz, 2-OH), 4.51 (1H, t, *J* 4.6 Hz, CH_2OH), 4.31 (1H, br s, H-7), 4.19–4.17 (1H, m, H-3), 4.14 (1H, t, *J* 5.1 Hz, CH_2OH), 3.69 (1H, t, *J* 6.1, 6.1 Hz, H-2), 3.55 (1H, dd, *J* 10.8, 4.0 Hz, CHHO), 3.05–2.98 (3H, m, cyclopropyl, C*H*HO), 2.88–2.86 (1H, m, H-4), 2.83–2.81 (1H, m, H-1), 2.15 (1H, dd, *J* 10.4, 5.1 Hz, C*H*HO), 1.76 (1H, dd, *J* 13.6, 4.4 Hz, H-6*exo*), 0.78 (1H, d, *J* 13.4 Hz, H-6*endo*), 0.68–0.64 (2H, m, cyclopropyl), 0.60–0.56 (2H, m, cyclopropyl). ^{13}C NMR: 160.18 (C-2′), 155.95 (C-6′), 152.47 (C-4′), 136.88 (C-8′), 114.16 (C-5′), 72.09 (C-2), 67.94 (C-3), 62.65 (CH_2O), 61.32 (CH_2O), 59.52 (C-7), 49.62 (C-4), 46.23 (C-1), 45.89 (C-5), 31.52 (C-6), 23.91 (cyclopropane–CH), 6.44 (cyclopropane–CH_2). ESI MS, *m*/*z* (rel%): 399 (10) [M+Na], 377 (100) [M+H], 316 (10), 288 (15), 191 (5). For $C_{17}H_{24}N_6O_4$ .1.5 H_2O (403.5) calculated: 50.61% C, 6.75% H, 20.83% N; found: 50.46% C, 6.81% H, 20.47% N.

4.4. Synthesis of tricyclic derivatives

4.4.1. (1R,2R*,4S*,5S*,8R*)-8-(Acetylamino)-3-oxatricyclo[3.2.1.0^{2,4}]-octane-6,6-diyl]dimethanediyl dibenzoate (**22**).* *m*-Chloroperbenzoic acid (1.7 g, 7.6 mmol, 70%) was added to a solution of amide **8** (1.77 g, 4.05 mmol) in dichloromethane (50 mL) and the solution was stirred at rt overnight. The precipitated chlorobenzoic acid was removed by filtration and the filtrate was washed with saturated aqueous $Na_2S_2O_3$ (30 mL), saturated $NaHCO_3$ (3×30 mL), dried over anhydrous sodium sulfate and evaporated. Epoxide **22** was obtained in quantitative yield (1.75 g) as a white powder. Mp=180.5–183.5 °C. IR (KBr): 3300 (s), 3070 (w), 3036 (w), 3007 (w), 1723 (s), 1717 (s), 1667 (s), 1649 (s), 1601 (m), 1584 (m), 1551 (s), 1491 (w), 1473 (m), 1451 (s), 1371 (s), 1316 (s), 1273 (s), 1178 (s), 1111 (s), 1071 (s), 1026 (s), 1003 (w), 980 (m), 941 (w), 690 (m), 676 (m), 618 (w), 413 (w). ^{1}H NMR: 7.99–7.95 (2H, m, H-2′), 7.93–7.88 (2H, m, H-2′), 7.93 (1H, br s, NH), 7.66–7.61 (2H, m, H-4′), 7.51–7.44 (4H, m, H-3′), 4.58 (1H, d, *J* 11.5 Hz), (C*H*HO), 4.44 (1H, d, *J* 11.2 Hz), (C*H*HO), 4.38 (1H, d, *J* 11.2 Hz), (C*H*HO), 4.33 (1H, d, *J* 11.5 Hz), (C*H*HO), 3.66–3.64 (1H, m, H-8), 3.55 (1H, dd, *J* 3.9, 1.6 Hz, H-4), 3.47 (1H, dd, *J* 3.9, 1.5 Hz, H-2), 2.80 (1H, t, *J* 1.6, 1.6 Hz, H-5), 2.53–2.51 (1H, m, H-1), 2.16 (1H, dd, *J* 13.6, 4.1 Hz, H-7*exo*), 1.81 (3H, s, CH_3), 1.41 (1H, dd, *J* 13.6, 1.4 Hz, H-7*endo*). ^{13}C NMR: 170.15 (CH_3–CO), 165.77 and 165.67 (Ph-CO), 133.64 and 133.60 (C-4′), 129.81 and 129.76 (C-1′), 129.52 and 129.39 (C-2′), 129.01 and 128.95 (C-3′), 66.73 (CH_2O), 66.17 (CH_2O), 51.06 (C-4), 50.65 (C-2), 49.87 (C-8), 46.27 (C-6), 41.43 (C-5), 40.34 (C-1), 31.55 (C-7), 22.88 (CH_3). FABMS, *m*/*z* (rel%): 436 (7) [M+H], 272 (8), 150 (7), 105 (100) [Bz], 77 (30) [Ph]. For $C_{25}H_{25}NO_6$ (435.5) calculated: 68.95% C, 5.79% H, 3.22% N; found: 69.01% C, 5.91% H, 3.03% N.

4.4.2. (1R,2R*,3R*,6R*,7S*,8R*)-8-Amino-6-(hydroxymethyl)-4-oxatricyclo[4.2.1.0^{3,7}]nonan-2-ol (**23**).* Potassium carbonate (150 mg, 1.5 mmol) was added to a solution of the epoxide **22** (1.75 g, 4 mmol) in methanol (75 mL) and reaction mixture was stirred for 5 h. The reaction mixture was evaporated. Potassium hydroxide (6.5 g, 116 mmol) was added to a solution of the residue in ethanol–water (40 mL, 1:1) and the reaction mixture was refluxed for 9 h in an argon atmosphere. The reaction mixture was neutralized with 6 M hydrochloric acid and applied onto a Dowex 50 (H^+ form, 100 mL). The column was eluted with methanol–water (1:1, 300 mL), water (300 mL), methanol (300 mL) and then with 3.5 M methanolic ammonia. The fractions containing product were evaporated to yield 600 mg (81%) of amine **23** as a white solid. Mp=155.5–158 °C. IR (KBr): 3300 (s), 3277 (s), 3191 (m), 2657 (w), 2533 (w), 1618 (m), 1551 (w), 1430 (w), 1076 (s), 1057 (s). ^{1}H NMR: 4.86 (1H, br s, 2-OH), 3.85 (1H, dd, *J* 5.0, 1.5 Hz, H-3), 3.55 (1H, d, *J* 7.9 Hz, H-5b), 3.47 (1H, d, *J* 7.9 Hz, H-5a), 3.46–3.48 (1H, m, H-8), 3.40 (1H, d, *J* 10.6 Hz), (C*H*HO), 3.29 (1H, d, *J* 10.6 Hz), (C*H*HO), 3.25 (1H, br s, H-2), 2.22 (1H, dd, *J* 12.6, 4.6 Hz, H-9*exo*), 2.11 (1 H, dt, *J* 5.0, 1.5, 1.5 Hz, H-7), 1.86–1.82 (1H, m, H-1), 0.92 (1H, d, *J* 12.6 Hz, H-9*endo*). ^{13}C NMR: 88.69 (C-3), 80.31 (C-2), 77.85 (C-5), 63.02 (CH_2OH), 55.35 and 55.32 (C-7 and C-8), 50.35 (C-6), 47.60 (C-1), 32.35 (C-9). ESI MS, *m*/*z* (rel%): 186 (100) [M+H], 187 (10) [M+2H], 180 (5). For $C_9H_{15}NO_3$ (185.2) calculated: 58.36% C, 8.16% H, 7.56% N; found: 58.09% C, 8.10% H, 7.24% N.

4.4.3. (1R,2R*,3R*,6R*,7S*,8R*)-1-[2-Hydroxy-6-(hydroxymethyl)-4-oxatricyclo[4.2.1.0^{3,7}]non-8-yl]-5-methylpyrimidine-2,4(1H,3H)-dione (**24**).* A solution of amine **23** (300 mg, 1.62 mmol) and ethyl [(2*E*)-3-ethoxy-2-methylprop-2-enoyl]carbamate][4a,8] (331 mg, 1.64 mmol) in 1,4-dioxane (15 mL) was heated at 100 °C for 3 h. Dowex 50 (H^+ form, 5 mL) was washed with 1,4-dioxane and then added to the mixture. The mixture was heated at 100 °C for 2.5 h, the resin was filtered off, washed with methanol and the collected filtrates were evaporated. The residue was crystallized from ethanol to yield 266 mg (56%) of the thymine nucleoside **24** as a white powder. Mp=258.5–259.5 °C. IR (KBr): 3390 (s), 3355 (s), 3307 (s), 3202 (m), 3178 (m), 1714 (s), 1693 (s), 1672 (s), 1663 (s), 1468 (s), 1366 (m), 1271 (s), 1055 (s), 1049 (s), 1035 (m), 1026 (m), 759 (w). ^{1}H NMR: 11.24 (1H, s, NH), 7.47 (1H, q, *J* 1.3 Hz, H-6), 5.23 (1H, d, *J* 3.3 Hz, 2′-OH), 4.76 (1H, t, *J* 4.8 Hz, CH_2OH), 4.16 (1H, br s, H-8′), 3.94 (1H, dd, *J* 5.2, 1.4 Hz, H-3′), 3.68 (1H, d, *J* 7.9 Hz, H-5b), 3.64 (1H, d, *J* 7.9 Hz, H-5a), 3.38 (1H, dd, *J* 3.3, 1.3 Hz, H-2′), 3.16 (1H, dd, *J* 10.5, 4.8 Hz, CHHO), 3.10 (1H, dd, *J* 10.5, 4.9 Hz, CHHO), 3.07 (1H, dt, *J* 5.2, 1.5, 1.5 Hz, H-7′), 2.66–2.63 (1H, m, H-1′), 1.89 (1H, dd, *J* 13.9, 4.3 Hz, H-9′*exo*), 1.79 (3H, d, *J* 1.2 Hz, CH_3), 1.25 (1H, d, *J* 13.9 Hz) (H-9′*endo*). ^{13}C NMR: 164.41 (C-4), 151.71 (C-2), 139.95 (C-6), 108.39 (C-5), 86.88 (C-3′), 78.81 (C-2′), 78.54 (C-5′), 64.78 (CH_2OH), 63.49 (C-8′), 49.78 (C-6′), 48.24 (C-7′), 43.40 (C-1′), 35.12 (C-9′), 12.32 (CH_3). FABMS, *m*/*z* (rel%): 295 (100) [M+H], 277 (10), 127 (35), 127 (35). For $C_{14}H_{18}N_2O_5$ .0.5 EtOH (317.4) calculated: 56.77% C, 6.67% H, 8.83% N; found: 56.83% C, 6.69% H, 8.54% N.

4.4.4. (1R,2R*,3R*,6R*,7S*,8R*)-8-(6-Chloro-9Hpurin-9-yl)-6-(hydroxymethyl)-4-oxatricyclo[4.2.1.0^{3,7}]nonan-2-ol (**25**).* A mixture of amine **23** (555 mg, 3 mmol), 4,6-dichloropyrimidin-5-amine[15] (720 mg, 4.4 mmol), and triethylamine (1.2 mL) in ethanol (9 mL) was heated in a pressure vessel at 105 °C for 6 days and, after cooling, was evaporated. The residue was chromatographed on a column of silica gel (200 g) in ethyl acetate–acetone–ethanol–water (105:15:3:2) to afford 472 mg (50%) of pyrimidine intermediate, which was immediately used in the next step. Concentrated hydrochloric acid (1 mL) was added to a suspension of pyrimidine intermediate in triethyl orthoformate (60 mL) and the reaction mixture was vigorously stirred for 5 days at room temperature. The mixture was evaporated and the residue was dissolved in a mixture of tetrahydrofuran (10 mL) and 0.5 M hydrochloric acid (10 mL) and stirred at room temperature for 4 h. After neutralization with solid sodium hydrogen carbonate, the mixture was evaporated to one fourth of the original volume, absorbed on silica gel and applied on a silica gel column (200 g). Chromatography in ethyl acetate–acetone–ethanol–water (105:15:3:2) gave 294 mg (30% based on **23**) of compound **25**. The compound was recrystallized from water as an ochre powder. Mp=231.5–233 °C (decomp.). IR ($CHCl_3$): 3609 (m), 1602 (s), 1591 (s), 1561 (s), 1492 (w), 1404 (w), 1341 (s), 1058 (m), 1075 (w). ^{1}H NMR: 8.79 (1H, s, H-2′), 8.78 (1H, s, H-8′), 5.36 (1H, d, *J* 3.2 Hz, 2-OH), 4.71 (1H, br s, H-8), 4.53 (1H, t, *J* 4.9 Hz, CH_2OH), 4.10 (1H, bd, *J* 5.2 Hz, H-3), 3.73 (1H, d, *J* 7.9 Hz, H-5b), 3.66 (1H, d, *J* 8.1 Hz, H-5a), 3.52–3.50 (1H, m, H-2), 3.48 (1H, dm, *J* 5.2 Hz, H-7), 3.27–3.25 (1H, m, H-1), 2.67 (1H, dd, *J* 10.8, 4.8 Hz, C*H*HO), 2.52 (1H, dd, *J* 10.8, 5.0 Hz, C*H*HO), 1.86 (1H, dd, *J* 13.9, 4.4 Hz, H-9*exo*), 1.33 (1H, d, *J* 13.9 Hz, H-9*endo*). ^{13}C NMR: 152.91 (C-4′), 151.69 (C-2′), 149.28 (C-6′), 147.45 (C-8′), 131.28 (C-5′), 87.01 (C-3), 78.90 (C-2), 78.37 (C-5), 64.31 (CH_2OH), 61.18 (C-8), 50.05 (C-6), 48.41 (C-7), 44.38 (C-1), 34.83 (C-9). FABMS, *m*/*z* (rel%): 323/325 (100/35) [M+H], 289 (20), 93 (30). For

$C_{14}H_{15}ClN_4O_3$ .1/3 H_2O (328.8) calculated: 51.15% C, 4.80% H, 10.78% Cl, 17.04% N; found: 51.12% C, 4.49% H, 10.62% Cl, 16.80% N.

4.4.5. (1R,2R*,3R*,6R*,7S*,8R*)-8-[6-(Cyclopropylamino)-9H-purin-9-yl]-6-(hydroxymethyl)-4-oxatricyclo[4.2.1.0^{3,7}]nonan-2-ol (**26**).* A mixture of chloropurine derivative **23** (260 mg, 0.76 mmol), cyclopropylamine (2 mL) and methanol (3 mL) was vigorously stirred overnight and evaporated. The pure derivative **26** (169 mg, 61%) was obtained by chromatography on silica gel (30 g) in ethyl acetate→ethyl acetate–acetone–ethanol–water (95:15:9:6). The compound was crystallized from ethanol–water (9:1) as a white powder. Mp=246–247 °C. IR (KBr): 3411 (s), 3349 (s), 3236 (s), 3095 (s), 1621 (s), 1595 (m), 1578 (s), 1528 (m), 1487 (m), 1408 (m), 1335 (s), 1300 (s), 1212 (m), 1072 (s), 1048 (s), 1042 (s), 1025 (s), 800 (m), 642 (m). ^{1}H NMR: 8.24 (1H, br s, H-2′), 8.20 (1H, s, H-8′), 7.89 (1H, br s, NH), 5.30 (1H, d, *J* 3.2 Hz, 2-OH), 4.57 (1H, br s, H-8), 4.54 (1H, t, *J* 4.9 Hz, CH_2OH), 4.06 (1H, dd, *J* 5.1, 1.4 Hz, H-3), 3.72 (1H, d, *J* 8.1 Hz, H-5b), 3.67 (1H, d, *J* 8.0 Hz, H-5a), 3.48–3.46 (1H, m, H-2), 3.42 (1H, dt, *J* 5.1, 1.6, 1.6 Hz, H-7), 3.20–3.18 (1H, m, H-1), 2.98 (1H, br s, cyclopropyl), 2.79 (1H, dd, *J* 10.6, 4.6 Hz, C*H*HO), 2.46 (1H, dd, *J* 10.6, 5.0 Hz, C*H*HO), 1.91 (1H, dd, *J* 13.7, 4.5 Hz, H-9*exo*), 1.30 (1H, d, 13.7 Hz, H-9*endo*), 0.74–0.70 (2H, m, cyclopropyl), 0.62–0.59 (2H, m, cyclopropyl). ^{13}C NMR: 155.72 (C-6′), 152.59 (C-2′), 149.92 (C-4′), 140.42 (C-8′), 119.58 (C-5′), 87.04 (C-3), 79.06 (C-2), 78.71 (C-5), 65.00 (CH_2OH), 60.40 (C-8), 50.09 (C-6), 48.61 (C-7), 44.41 (C-1), 35.32 (C-9), 23.50 (cyclopropyl), 6.61 (cyclopropyl). FABMS, *m*/*z* (rel%): 344 (100) [M+H], 176 (55), 147 (25), 93 (35). For $C_{17}H_{21}N_5O_3$ (343.4) calculated: 59.46% C, 6.16% H, 20.40% N; found: 59.15% C, 6.04% H, 20.11% N.

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