Synthesis of Novel Purinyl-1′-homocarbanucleosides Based on a Cyclopenta[*b*]pyrazine System

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Received November 29, 2007; accepted February 2, 2008; published online February 14, 2008

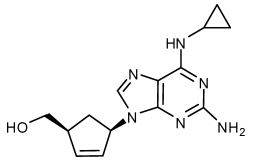
***cis*-2,3-Diphenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyrazine-5,7-dimethanol, prepared by Diels–Alder reaction from cyclopentadiene and appropriately protected 2-imidazolone—followed by dihydroxylation, glycol protection, diamine deprotection, condensation with benzyl, glycol deprotection, oxidative cleavage and reduction—, was used to synthesize (±)-*cis*-{[7-(6-chloro-9*H*-purin-9-yl)methyl]-2,3-diphenyl-6,7-dihydro-5*H*-cyclopenta[*b*]-pyrazin-5-yl}methanol, a key intermediate for novel 1′-homocarbanucleosides based on a cyclopenta[*b*]pyrazine scaffold as shown by its conversion into several 6-substituted purinyl derivatives.**

Key words imidazolone; oxidative cleavage; hydroxylation; dihydropyrazine; epimerization; homocarbanucleoside

The success of abacavir (**1**) as reverse transcriptase inhibitor in human immunodeficiency (HIV) clinical trials,[1—4] which led to its approval by FDA for treatment of HIV infection in 1998, has been attributed in large part to the rigidity afforded by its double bond between C2′ and C3′[5,6] and to its cyclopropylamino group, which increases its lipophilicity and its ability to penetrate into the central nervous system, an important reservoir of the HIV and other viruses.[7]

Inspired on that, our research group has been investigating the biological properties of other carbanucleosides as well as their 1′-homo-counterparts, in which the planar region of the carbocyclic double bond present in abacavir is replaced by a benzene ring[8—10] or by an aromatic heterocycle,[11—13] seeking to modify the lipophilicity and polar interactions of this region of the molecule while preserving its rigidity. Most of the new compounds showed little if any antiviral activity against HIV, but in a broader antiviral survey some of them in which there is a pyrazol ring fused to the cyclopentene ring such as in **2**, proved to be highly active against varicella-zoster virus and cytomegalovirus at subcytotoxic concentration,[12] while an important number of both indan and cyclopenta[*c*]pyrazole derivatives were found to have considerable cytostatic activity against human T lymphocytes (Molt4/C8 and CEM/0 cells).[8,9,13]

These results pushed us to further explore the field of compounds in which an heterocycle is fused to the cyclopentene moiety of the carbanucleoside. Here we report a synthetic way that leads to 1′-homonucleoside analogues of the type A, based on a 6,7-dihydro-5*H*-cyclopenta[*b*]pyrazine scaffold.



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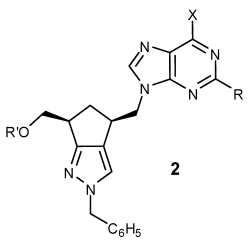

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Results and Discussion

Our work was initially planned on a convergent synthesis (Chart 1) that brings together the preformed main blocs of the final structure through a Mitsunobu coupling, as in some previous analogues.[13] Now, while several purine derivatives are commercially available, this strategy compelled us to achieve a properly functionalised cyclopenta[*b*]pyrazine derivative, and a dimethanol derivative of the type B was envisaged as the key synthetic intermediate. B would be available through a sequence based on the retrosynthetic pathway B⇒E depicted in Chart 1.

Following 1,3-diacetylation of 2-imidazolone, compound **3** (Chart 2) was obtained as per Whitney.[14] Hydroxylation with OsO_4 and methylmorpholine *N*-oxide[15] in acetone/water afforded a 74% yield of glycol **4**, which upon treatment with dimethoxypropane gave acetonide **5**. An attempt to convert **5** into diamine **7** in one step by heating with KOH in methanol at 155 °C afforded a complex mixture including only traces of the desired product, while a two-steps process, heating of compound **5** with KOH in methanol at 65 °C, isolation of the resulting imidazolone **6**, and heating of **6** with KOH in methanol at 155 °C in a sealed tube,[16] afforded a good yield of a product that could be by identified as **7** by ^{1}H-NMR spectroscopy. Due to the lability and volatility of this kind of compounds,[16] **7** was used in the next step without further pu-

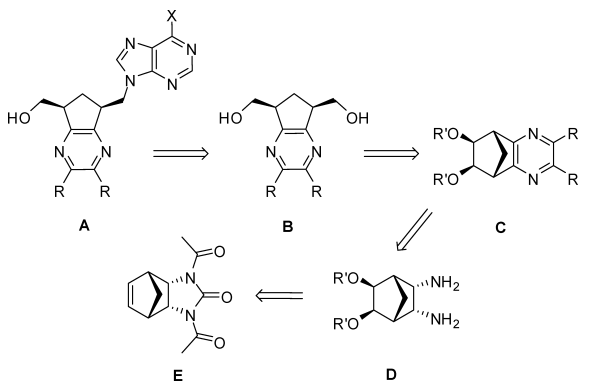

Chart 1

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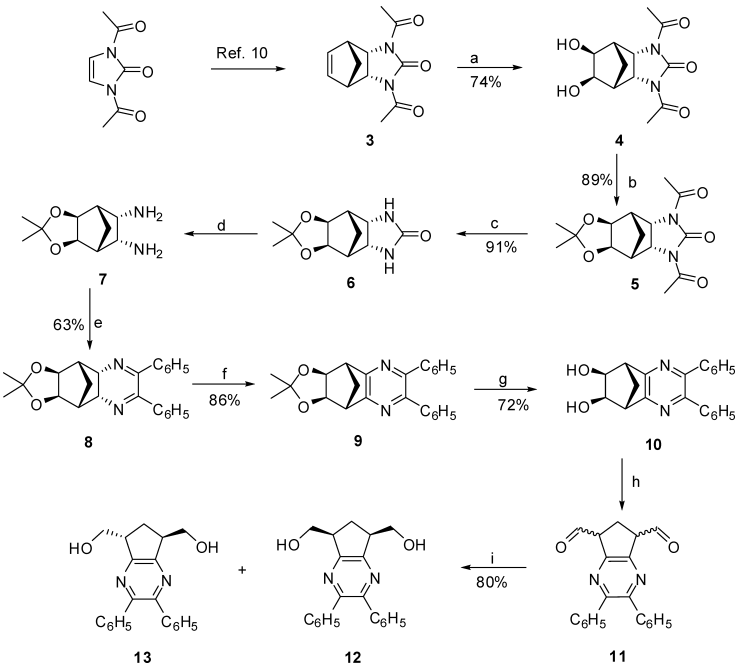


Reaction conditions: a) OsO_4, NMO, 40 °C; b) 2,2-dimethoxypropane/H^+, r.t.; c) KOH/MeOH, reflux. 5 h; d) KOH/MeOH, 155 °C, 48 h; e) benzil/THF/H^+, reflux; f) DDQ/toluene, reflux. 2.5 h; g) HCl/EtOH, 70 °C, 10 h; h) $NaIO_4$/silica gel CH_2Cl_2, r.t.; i) $NaBH_4$/MeOH, r.t.

Chart 2

rification. Thus, crude **7** was condensed with benzil in THF with acetic acid as catalyst, and the resulting dihydropyrazine (**8**) was aromatized in 86% yield by refluxing with 4,5-dichloro-3,6-dioxo-1,4-cyclohexadiene-1-2-dicarbonitrile (DDQ) in toluene for 2.5 h. Attempts to achieve mild cleavage of the acetonide moiety of compound **9** (treatment with 60% AcOH or HCO_2H, at r.t. or under reflux, or with $HClO_4$ or $BF_3 \cdot OEt_2$ at r.t.) were all unsuccessful, the starting material being recovered or intractable mixtures of unidentified products being obtained. Finally diol **10** was prepared in good yield by moderate heating of **9** in EtOH in presence of HCl.

Oxidative cleavage of **10** with sodium periodate on silica gel[17] then gave dialdehyde **11** (as identified by IR spectroscopy), and reduction of crude **11** with $NaBH_4$ in methanol finally afforded an approximately 2 : 1 mixture of the desired *cis*-diol **12** and its diastereomer **13**; partial epimerization is presumed to have occurred during these last two steps.

Diastereomers **12** and **13** were clearly distinguished and *cis*/*trans* relative configurations initially assigned to them on the basis of their ^{1}H-NMR spectra: each of the chemically unequivalent C6 protons of *cis*-diol **12** gives rise to a doublet of triplets, at δ 1.61 (J=9.3, 13.1 Hz) and δ 2.51 (J=8.3, 13.1 Hz), while the two chemically equivalent C6 protons of *trans*-diol **13** give rise to a single triplet at δ 2.18 (J=7.3 Hz). Compound **13** was then conclusively identified by X-ray crystallography (Fig. 1).[18]

Several attempts to perform Mitsunobu processes with 6-chloropurine on **12** or monoprotected derivatives of it were fruitless and we then turned to more classical nuecleophilic displacements. Esterification of **12** with acetic anhydride and pyridine afforded a mixture including the starting compound, its diacetate, and the monoacetate **14**, which was converted into mesylate **15** in 69% yield by treatment with mesyl chloride, triethylamine and 4-(dimethylamino)pyridine (DMAP) at 0 °C (Chart 2). Coupling **15** with 6-chloropurine by reaction in DMF in the presence of NaH and 18-crown-6 ether[11] finally afforded nucleoside analogue **16** in 37% yield; an alkene, thought to be **17** (two singlets at 5.36 and 6.17 ppm in the ^{1}H-NMR spectra) and formed from **15**, presumably through a dehydromesyloxylation promoted by the basic medium,[11] was also detected as the main by-product (in an estimated 25% yield).

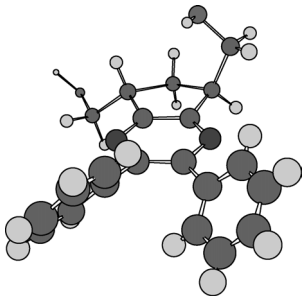
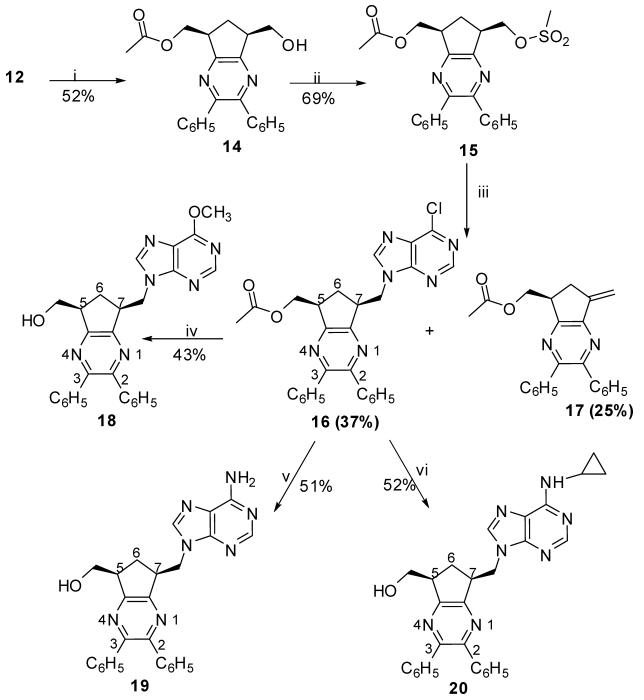


Fig. 1. ORTEP Projection of the Molecular Structure of Compound **13**

Suitability of chloropurine **16** to serve as an appropriate key intermediate for the preparation of nucleoside analogues of this new class was shown through its smooth conversion into methoxypurine analogue **18** by treatment with methanol and aqueous HCl at room temperature (r.t.), and into amino derivatives **19** and **20**, by reaction with liquid ammonia and cyclopropylamine, respectively.

In conclusion, this paper describes a convenient synthetic procedure for the preparation of novel purinyl-1′-homocarbanucleoside derivatives **16**, **18**, **19** and **20**, as examples of an interesting new template in which the double bond of the cyclopentenyl nucleosides is embedded in a pyrazine ring, thus opening a route to a wide variety of other purinyl derivatives



Reaction conditions: i) Ac_2O/Pyr, r.t.; ii) $MeSO_2Cl$, NEt_3/DMAP; iii) 6-chloropurine, NaH, 18-crow-6 ether; HCl, MeOH, r.t.; iv) MeOH/HCl, r.t.; v) MeOH/NH_3, 75 °C; vi) cyclopropylamine/EtOH, reflux.

Chart 3

with similar cyclopenta[*b*]pyrazine scaffolds.

Experimental

All chemical used were of reagent grade and were obtained from Aldrich Chemical Co. and used without further purification. Melting points were measured in a Reichert Kofler Thermopan and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1640 FT-IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded in a Bruker AMX-300 spectrometer at 300 and 75 MHz, respectively, using TMS as internal standard (chemical shifts in δ values, J in Hz). Microanalyses were performed in a LECO CHNS-932 Elemental Analyser at the University of Santiago Microanalysis Service. Analyses indicated by the symbols of elements were within ±0.4% of the theoretical values. Flash chromatography was performed on silica gel (Merck 60, 230—240 mesh) and analytical TCL on pre-coated silica gel plates (Merck 60, F_{254}, 0.25 mm). MPLC separations were carried out using a Biotage Flash 4Di system with a Biotage column (Si-40B, silica gel). X-Ray diffraction data were collected in an Enraf-Nonius CAD4 automatic diffractometer using the programme CAD4-EXPRESS.

(3a*R*,4*R*,5*R*,6*S*,7*S*,7a*S*)-1,3-Diacetyl-5,6-dihydroxyperhydro-4,7-methanobenzo-imidazol-2-one (4) A solution of **3** (4.0 g, 17 mmol) in (4 : 1 acetone/water) (35 ml) was heated to 40 °C and methylmorpholine *N*-oxide (2.2 g, 18.9 mmol) was added, followed after 5 min at the same temperature by a 4% (w/w) solution of OsO_4 in water (0.5 ml), which immediately caused the mixture to turn brown. After 90 min stirring at 40 °C the reaction mixture was filtered through celite, concentrated, and treated with saturated NH_4Cl solution. This mixture was extracted with EtOAc, the organic phase was washed with brine and dried over Na_2SO_4, the solvent was removed under reduced pressure, and purification of the residue by chromatography on silica gel with 1 : 1 hexane/EtOAc as eluent afforded **4** as a white solid (3.55 g, yield 74%). A sample was recrystallized from toluene for analysis, mp 178—179 °C. IR (KBr) cm^{-1}: 3479, 2957, 1755, 1683, 1274, 1239. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (1H, d, J=11.7 Hz, 8-HH), 2.04 (1H, d, J=11.7 Hz, 8-HH), 2.53 (6H, s, 2×CH_3), 2.69 (2H, s, 2×OH, D_2O exch.), 2.83 (2H, s, 4H+7H), 3.76 (2H, s, 5H+6H), 4.27 (2H, s, 3aH+7aH). ^{13}C-NMR ($CDCl_3$) δ: 24.80 (CH_3), 31.16 (CH_2), 46.76 (CH), 54.16 (CH), 68.99 (CH), 152.55 (CO), 172.00 (CO). *Anal.* Calcd for $C_{12}H_{16}N_2O_5$ (268.27): C, 53.73; H, 6.01; N, 10.44. Found: C, 53.70, H, 5.99, N, 10.43.

(3a*R*,4*R*,4a*R*,7a*S*,8*S*,8a*S*)-5,7-Diacetyl-2,2-dimethylperhydro-4,8-methano[1,3]dioxolo[4,5-*f*]benzoimidazol-6-one (5) A solution of diol **4** (3.18 g, 11.9 mmol) in 2,2-dimethoxypropane (8 ml) containing a small amount of *p*-toluenesulphonic acid was stirred at r.t. until reaction was judged to be complete on the basis of TLC monitoring (12 h). The reaction mixture was then washed with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2, and the organic phase was dried with Na_2SO_4 and concentrated to dryness under reduced pressure, affording **5** as a white solid (3.23 g, yield 89%) from which a sample was taken and recrystallized from toluene for analysis, mp 176—177 °C. IR (KBr) cm^{-1}: 2991, 2944, 1746, 1691, 1368, 1322, 1277, 1238, 1056. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, s, CH_3), 1.24—1.29 (1H, m, 9-HH), 1.42 (3H, s, CH_3), 1.87 (1H, d, J=11.6 Hz, 9-HH), 2.52 (6H, s, 2×CH_3), 2.92—2.94 (2H, m, 4-H+8-H), 3.98 (2H, d, J=1.4 Hz, 3a-H+8a-H), 4.29 (2H, t, J=2.3 Hz, 4a-H+7a-H). ^{13}C-NMR ($CDCl_3$) δ: 24.33 (CH_3), 24.73 (CH_3), 25.73 (CH_3), 30.84 (CH_2), 43.55 (CH), 53.60 (CH), 76.81 (CH), 109.45 (C), 152.41 (CO), 171.12 (CO). *Anal.* Calcd for $C_{15}H_{20}N_2O_5$ (308.33): C, 58.43; H, 6.49; N, 9.09. Found: C, 58.67, H, 6.69, N, 10.13.

(3a*R*,4*R*,4a*R*,7a*S*,8*S*,8a*S*)-2,2-Dimethylperhydro-4,8-methano[1,3]-dioxolo[4,5-*f*]benzoimidazol-6-one (6) A suspension of **5** (3.05 g, 9.9 mmol), methanol (12 ml) and 50% KOH (4.5 ml) was refluxed for 5 h with TLC monitoring, and the solids were then filtered out, washed repeatedly with water, and dried to constant mass (1.67 g) in a vacuum desiccator. The filtrate was neutralized and extracted with $CHCl_3$, and the $CHCl_3$ phase was dried and concentrated to dryness under reduced pressure, yielding a solid (0.32 g) with the same chromatographic *Rf* as the filtration residue. Total yield, 91%. A sample was taken and recrystallized from toluene for analysis, mp 310—312 °C. IR (KBr) cm^{-1}: 3358, 3236, 2977, 1693, 1379, 1249, 1213, 1039, 860. ^{1}H-NMR (DMSO-d_6) δ: 1.05 (1H, d, J=10.7 Hz, 9-HH), 1.20 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.53 (1H, d, J=10.7 Hz, 9-HH), 2.24 (2H, s, 4-H+8-H), 3.84 (2H, s, 3a-H+8a-H), 4.29 (2H, s, 4a-H+7a-H), 6.37 (2H, 2×NH, exch. D_2O). ^{13}C-NMR (DMSO-d_6) δ: 24.13 (CH_3), 25.78 (CH_3), 30.13 (CH_2), 44.06 (CH), 53.68 (CH), 77.13 (CH), 107.85 (C), 162.48 (CO). *Anal.* Calcd for $C_{11}H_{16}N_2O_3$ (224.25): C, 58.91; H, 7.19; N, 12.49. Found: C, 59.08; H, 7.32, N, 12.61.

(3a*R*,4*R*,5*R*,6*S*,7*S*,7a*S*)-2,2-Dimethylperhydro-4,7-methano-1,3-benzodioxole-5,6-diamine (7) A suspension of **6** (1.9 g, 8.5 mmol) in methanol (8.6 ml) and 50% KOH (21 ml) was heated at 155 °C in a sealed tube for 48 h, allowed to cool to r.t., concentrated, and extracted with $CHCl_3$. The $CHCl_3$ phase was dried over Na_2SO_4, and removal of the solvent under reduced pressure left a yellow solid (1.63 g) that was used in the next step without further purification. ^{1}H-NMR (DMSO-d_6) δ: 1.03—1.08 (1H, m, 8-HH), 1.20—1.58 (11H, m, 2×CH_3+8-HH+2×NH_2, exch. four with D_2O), 2.64 (2H, s, 4-H+7-H), 3.34 (2H, s, 3a-H+7a-H), 4.32 (2H, s, 5-H+6-H).

(3a*R*,4*R*,4a*R*,8a*S*,9*S*,9a*S*)-2,2-Dimethyl-6,7-diphenyl-3a,4,4a,8a,9,9a-hexahydro-4,9-methano[1,3]dioxolo[4,5-*g*]quinoxaline (8) A solution of benzil (1.72 g, 8.2 mmol) in THF (6 ml) was added to a solution of crude **7** (1.63 g, 8.2 mmol) in the same solvent (20 ml), a catalytic amount of acetic acid was added, and the mixture was refluxed until reaction was deemed complete on the basis of TLC monitoring (4 h). Concentration to dryness left a yellow solid that was purified by chromatography on silica gel with (2 : 1) hexane/EtOAc as eluent followed by recrystallization from ethanol (1.92 g, yield 63%), mp 166—167 °C. IR (KBr) cm^{-1}: 2984, 2912, 1570, 1461, 1206, 1057. ^{1}H-NMR ($CDCl_3$) δ: 1.16—1.20 (4H, m, CH_3+10-HH), 1.39 (3H, s, CH_3), 1.73 (1H, d, J=10.7 Hz, 10-HH), 2.98 (2H, m, 4-H+9-H), 4.19—4.21 (2H, m, 3a-H+9a-H), 4.22 (2H, d, J=1.2 Hz, 4a-H+8a-H), 7.03—7.21 (10H, m, arom). ^{13}C-NMR ($CDCl_3$) δ: 24.29 (CH_3), 25.80 (CH_3), 27.18 (CH_2), 47.05 (CH), 54.69 (CH), 78.04 (CH), 108.90 (C), 128.24 (CH), 128.44 (CH), 129.39 (CH), 139.37 (C), 156.76 (C). *Anal.* Calcd for $C_{24}H_{24}N_2O_2$ (372.46): C, 77.39; H, 6.49; N, 7.52. Found: C, 77.18; H, 6.75, N, 7.33.

(3a*R*,4*R*,9*S*,9a*S*)-2,2-Dimethyl-6,7-diphenyl-3a,4,9,9a-tetrahydro-4,9-methano[1,3]-dioxolo[4,5-*g*]quinoxaline (9) A solution of DDQ (1.09 g, 4.8 mmol) in toluene (20 ml) was added to a solution of **8** (1.79 g, 4.8 mmol) in the same solvent (28 ml), and the mixture was refluxed under argon for 2.5 h, vacuum filtered, and concentrated to dryness, leaving a reddish solid that was recrystallized from EtOH/EtOAc (1.53 g, yield 86%), mp 237—239 °C. IR (KBr) cm^{-1}: 2984, 2907, 1454, 1360, 960. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, s, CH_3), 1.51 (3H, s, CH_3), 2.19 (1H, dd, J=1.4, 10.1 Hz, 10-HH), 2.48 (1H, d, J=10.1 Hz, 10-HH), 3.50 (2H, s, 4-H+9-H), 4.47 (2H, d, J=1.2 Hz, 3a-H+9a-H), 7.16—7.32 (10H, m, arom.). ^{13}C-NMR ($CDCl_3$) δ: 24.75 (CH_3), 26.15 (CH_3), 41.61 (CH_2), 48.77 (CH), 80.86 (CH), 114.20 (C), 128.55 (CH), 128.68 (CH), 130.15 (CH), 139.39 (C), 150.50 (C), 158.89 (C). *Anal.* Calcd for $C_{24}H_{22}N_2O_2$ (370.45): C, 77.81; H, 5.99; N, 7.56. Found: C, 77.53, H, 6.11, N, 7.38.

(5*R*,6*R*,7*S*,8*S*)-2,3-Diphenyl-5,6,7,8-tetrahydro-5,8-methanoquinoxaline-6,7-diol (10) 12 N HCl (1.5 ml) was added to a suspension of **9**

(1.31 g, 3.54 mmol) in ethanol (60 ml) at 0 °C, and the mixture was heated at 70 °C until TLC showed no starting compound (10 h). Following removal of the solvent under reduced pressure, the residue was taken into methanol and passed through an ion-exchange column (Amberlite IRA 400 OH^-), and the methanolic eluate was concentrated to dryness. Column chromatography of the residue on silica gel with 3 : 1 hexane/EtOAc as eluent afforded a solid (0.84 g, yield 72%), a sample of which was recrystallized from hexane/EtOAc for analysis, mp 185—187 °C. IR (KBr) cm^{-1}: 3384, 1449, 1364, 1222, 1144, 949. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (1H, d, J=10.1 Hz, 9-HH), 2.44 (1H, d, J=10.1 Hz, 9-HH), 3.42 (2H, s, 5-H+8-H), 3.97 (2H, s, 6-H+7-H), 4.37 (2H, br s, 2×OH, exch. D_2O), 7.26—7.19 (10H, m, arom.). ^{13}C-NMR ($CDCl_3$) δ: 42.22 (CH_2), 51.59 (CH), 70.41 (CH), 128.44 (CH), 128.68 (CH), 130.13 (CH), 138.42 (C), 146.78 (C), 157.77 (C). *Anal.* Calcd for $C_{21}H_{18}N_2O_2$ (330.38): C, 76.34; H, 5.49; N, 8.48. Found: C, 76.00, H, 5.68, N, 8.81.

2,3-Diphenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyrazine-5,7-dicarbaldehyde (mixture of *cis* and (±)-*trans*) (11) A 0.65 M aqueous solution of $NaIO_4$ (6.06 ml) was added to a suspension of silica gel (5.9 g) in CH_2Cl_2 (50 ml), and the mixture was shaken vigorously by hand and, following the formation of a flaky precipitate, added to a solution of **10** (1.0 g, 3.03 mmol) in CH_2Cl_2 (6.0 ml). This mixture was stirred at room temperature until TLC showed no starting compound (15 min), and was then filtered through Na_2SO_4 and concentrated under reduced pressure, affording a vivid orange solid that was identified as compound **11** (on the basis of the strong carbonyl band at 1723 cm^{-1} in its IR spectrum) and was used without further purification in the next step.

***cis*-2,3-Diphenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyrazine-5,7-dimethanol (12) and (±)-*trans*-2,3-Diphenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyrazine-5,7-dimethanol (13)** $NaBH_4$ (56.74 mg, 1.5 mmol) was added to a solution of **10** (90 mg, 0.27 mmol) in MeOH (15 ml) and the mixture was left stirring (colour change). When TLC showed no remaining starting compound (30 min), water (10 ml) was added and stirring was continued for 15 min, after which the methanol was removed under reduced pressure and the remaining aqueous solution was extracted with EtOAc. The organic phase was dried with Na_2SO_4 and concentrated to dryness, leaving a solid that following chromatography on a silica gel column with (1 : 2) hexane/EtOAc as eluent afforded a solid foam (81 mg, yield 80%) with two components. Further chromatography on an MPLC column with (98 : 2) CH_2Cl_2/MeOH as eluent afforded the **12** (52 mg) followed by the **13** (29 mg).

Compound **12**: mp 126—128 °C (from EtOAc/Et_2O). IR (KBr) cm^{-1}: 3411, 2899, 1594, 1449, 1386, 1238, 1059, 950. ^{1}H-NMR ($CDCl_3$) δ: 1.61 (1H, dt, J=9.3, 13.1 Hz, 6-HH), 2.51 (1H, dt, J=8.3, 13.1 Hz, 6-HH), 3.51—3.71 (4H, m, 5-H+7-H+2×OH (two of them D_2O exch.), 3.92 (2H, dd, J=7.9, 10.8 Hz, 2×CHHOH), 4.05 (2H, dd, J=4.9, 10.8 Hz, 2×CHHOH), 7.24—7.41 (10H, m, arom.). ^{13}C-NMR ($CDCl_3$) δ: 28.09 (CH_2), 44.10 (CH), 66.07 (CH_2), 128.63 (CH), 128.94 (CH), 130.19 (CH), 139.04 (C), 151.56 (C), 158.63 (C). *Anal.* Calcd for $C_{21}H_{20}N_2O_2$ (332.40): C, 75.88; H, 6.06; N, 8.43. Found: C, 76.08, H, 6.18, N, 8.69.

Compound **13**: mp 207—209 °C (from EtOAc/Et_2O). IR (KBr) cm^{-1}: 3380, 3225, 2921, 2864, 1459, 1387, 1141, 772. ^{1}H-NMR ($CDCl_3$) δ: 1.65 (1H, br s, OH, D_2O exch.), 2.18 (2H, t, J=7.3 Hz, 6-HH), 3.08 (1H, br s, OH, D_2O exch.) 3.51—3.61 (2H, m, 5-H+7-H), 3.91 (2H, dd, J=7.8, 10.5 Hz, 2×CHHOH), 4.02 (2H, dd, J=5.9, 10.5 Hz, 2×CHHOH), 7.13—7.52 (10H, m, arom.). ^{13}C-NMR ($CDCl_3$) δ: 27.38 (CH_2), 43.89 (CH), 65.84 (CH_2), 128.12 (CH), 128.40 (CH), 128.68 (CH), 138.53 (C), 151.15 (C), 157.62 (C). Single crystals suitable for X-ray diffractometry were obtained by dissolving a sample of **13** in the least possible quantity of cold EtOAc in an open vial that was then placed in a larger container with a little hexane at the bottom; the container was closed, and after a few days in a cool, dark place free from vibrations some single crystals were formed, one of which was analysed by X-ray diffractometry.

(±)-*cis*-[7-(Hydroxymethyl)-2,3-diphenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyrazin-5-yl]methyl Acetate (14) Acetic anhydride (180 mg, 1.8 mmol) was added to a solution of **12** (60 mg, 0.18 mmol) in pyridine (2 ml), the mixture was stirred under argon at r.t. for 12 h, water was added, and following extraction with AcOEt the organic phase yielded a residue from which chromatography on silica gel with hexane/EOtAc (3 : 1) as eluent separated the diester (12 mg), the desired monoester **14** (as oil) (53 mg, yield 52%), and starting diol **12** (10 mg). IR (film) cm^{-1}: 3360, 1738, 1443, 1247, 1038, 782. ^{1}H-NMR ($CDCl_3$) δ: 1.76 (1H, dt, J=8.8, 13.2 Hz, 6-HH), 2.07 (3H, s, CH_3), 2.62 (1H, dt, J=8.6, 13.3 Hz, 6-HH), 3.53 (1H, dq, J=5.3, 8.6 Hz, 7-H), 3.63—3.72 (2H, m, CHHOH+5-H), 3.93 (1H, dd, J=8.1, 10.6 Hz, CHHOH), 4.03 (1H, br s, OH, exch. D_2O), 4.39 (1H, dd, J=7.1, 11.1 Hz, CHHOAc), 4.72 (1H, dd, J=4.6, 11.1 Hz, CHHOAc), 7.25—7.40 (10H, m, arom.). ^{13}C-NMR ($CDCl_3$) δ: 21.35 (CH_3), 29.39 (CH_2), 42.14 (CH), 43.63 (CH), 66.19 (CH_2), 66.32 (CH_2), 128.60 (CH), 128.87 (CH), 128.92 (CH), 130.22 (CH), 139.08 (C), 139.26 (C), 155.85 (C), 158.41 (C), 171.53 (CO). *Anal.* Calcd for $C_{23}H_{22}N_2O_3$ (374.44): C, 73.78; H, 5.94; N, 7.48. Found: C, 73.69; H, 6.05; N, 7.22.

(±)-*cis*-{[7-(Methanesulfonyloxymethyl)-2,3-diphenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyrazin-5-yl]}methyl Acetate (15) To a solution of **14** (400 mg, 1.07 mmol) in dry chloroform (5 ml) in an ice bath were added Et_3N (0.5 ml) and a catalytic amount of DMAP. Following dropwise addition of mesyl chloride (0.25 ml, 3.2 mmol), the mixture was stirred at r.t. for 2 h, refluxed for 12 h with TLC monitoring, poured over ice-water, and left stirring for 1 h, after which the organic phase was drawn off, washed with 1 N NaOH and brine, dried with Na_2SO_4 and concentrated under reduced pressure, affording compound **15** as an oil that was purified by column chromatography with (2 : 1) hexane/AcOEt as eluent (330 mg, yield 69%). IR (film) cm^{-1}: 3450, 3025, 2989, 1735, 1456, 1285, 1250, 1045, 977, 879, 755. ^{1}H-NMR ($CDCl_3$) δ: 1.94—2.04 (1H, m, 6-HH), 2.08 (3H, s, CH_3CO), 2.77 (1H, dt, J=8.8, 13.5 Hz, 6-HH), 2.99 (3H, s, CH_3SO_3), 3.65—3.73 (2H, m, 5-H+7-H), 4.40 (1H, dd, J=6.8, 9.8 Hz, CHH), 4.62 (1H, dd, J=6.8, 10.0 Hz, CHH), 4.71—4.81 (2H, m, 2×CHH), 7.26—7.54 (10H, m, arom.). ^{13}C-NMR ($CDCl_3$) δ: 21.35 (CH_3), 28.35 (CH_2), 38.01 (CH_3SO_3), 40.21 (CH), 42.57 (CH), 67.90 (CH_2), 68.85 (CH_2), 128.01 (CH), 128.77 (CH), 129.33 (CH), 138.26 (C), 138.97 (C), 155.60 (C), 158.32 (C), 171.50 (CO). *Anal.* Calcd for $C_{24}H_{24}N_2O_5S$ (452.52): C, 63.70; H, 5.35; N, 6.18; S, 7.08. Found: C, 63.98; H, 5.55; N, 6.34; S, 6.89.

(±)-*cis*-{[7-(6-Chloro-9*H*-purin-9-yl)methyl]-2,3-diphenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyrazin-5-yl]}methyl Acetate (16) A solution of 6-chloropurine (148 mg, 0.96 mmol), NaH (24 mg, 0.96 mmol) and 18-crown-6 ether (170 mg, 0.66 mmol) in DMF (8 ml) was heated to 55 °C, a solution of mesylate **15** (300 mg, 0.66 mmol) in the same solvent (4 ml) was added, and heating was continued for 20 h. The solvent was removed under reduced pressure, and chromatography of the residue on silica gel with (1 : 1) hexane/EtOAc as eluent finally afforded compound **16** as a white solid (180 mg, yield 37%), mp 196—198 °C. IR (KBr) cm^{-1}: 3323, 2990, 1739, 1594, 1336, 1044, 768. ^{1}H-NMR ($CDCl_3$) δ: 1.86 (1H, dt, J=8.8, 13.2 Hz, 6-HH), 1.99 (3H, s, CH_3), 2.72 (1H, dt, J=8.4, 13.2 Hz, 6-HH), 3.60—3.67 (1H, m, 5-H), 3.85—3.93 (1H, m, 7-H), 4.36 (1H, dd, J=6.6, 11.0 Hz, 5-CHH), 4.64 (1H, dd, J=4.2, 11.1 Hz, 5-CHH), 4.87 and 4.78 (2H, AB part of an ABX system, J_{AX}=6.0, J_{BX}=6.2, J_{AB}=14.1 Hz, 7-CH_2), 7.26—7.50 (10H, m, arom.), 8.29 and 8.72 (2H, 2s, 2′-H+8′-H). ^{13}C-NMR ($CDCl_3$) δ: 20.89 (CH_3), 30.86 (CH_2), 41.17 (CH), 42.25 (CH), 46.31 (CH_2), 65.15 (CH_2), 128.12 (CH), 128.18 (CH), 128.55 (CH), 128.89 (C), 129.50 (CH), 129.66 (CH), 129.77 (C), 138.30 (C), 138.39 (C), 146.01 (CH), 151.32 (C), 151.81 (CH), 152.02 (C), 152.22 (C), 154.36 (C), 154.93 (C), 170.73 (CO). *Anal.* Calcd for $C_{26}H_{21}ClN_6O$ (464.94): C, 66.82; H, 4.54; N, 17.45. Found: C, 66.59, H, 4.51, N, 17.92.

(±)-*cis*-{[7-(6-Methoxy-9*H*-purin-9-yl)methyl]-2,3-diphenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyrazin-5-yl]}methanol (18) A solution of **16** (305 mg, 0.59 mmol), MeOH (4 ml) and HCl 1 N (4 ml) was stirred at r.t. for 14 h, and after removal of the solvent the resulting residue was dissolved in EtOAc (20 ml). This solution was washed with brine (20 ml) and the solvent removed under reduced pressure, leaving a oil (260 mg) that after chromatography on silica gel with CH_2Cl_2–MeOH (92 : 8) as eluent afforded **18** as a oil (120 mg; 43% yield). IR (film) cm^{-1}: 3400, 2989, 2869, 1602,1486, 1414, 1285, 1045, 977, 879, 755. ^{1}H-NMR ($CDCl_3$) δ: 1.71 (1H, dt, J=13.3 Hz, 6-HH), 2.48 (1H, dt, J=13.3 Hz, 6-HH), 3.42 (3H, s, OCH_3), 3.55—3.62 (1H, m, 5-H), 3.78—3.84 (2H, m, 5-CH_2), 3.98—4.04 (1H, m, 7-H), 4.13 (1H, br s, OH, D_2O exch), 4.55—4.61 (part A of an ABX system J_{AX}=5.7, J_{AB}=14.3 Hz, CHHN) 4.75—4.86 (part B of an ABX system J_{BX}=7.7, J_{BA}=14.3 Hz, CHHN), 7.19—7.34 (10H, m, arom.), 7.88 and 8.01 (2H, 2s, 2′-H+8′-H). ^{13}C-NMR ($CDCl_3$) δ: 32.8 (CH_2), 35.2 (CH), 44.2 (CH), 45.8 (CH_3), 46.3 (CH_2), 62.1 (CH_2), 121.1 (C), 127.8 (CH), 128.7 (CH), 128.9 (CH), 129.8 (C), 136.3 (CH), 136.8 (C), 142.0 (CH), 146.5 (C), 151.4 (C), 152.3 (CH), 158.4 (C), 160.2 (C), 162.3 (C). *Anal.* Calcd for $C_{27}H_{24}N_6O_2$ (464.52): C, 69.81; H, 5.21; N, 18.09. Found: C, 69.98, H, 5.52, N, 17.86.

(±)-*cis*-{[7-(6-Amino-9*H*-purin-9-yl)methyl]-2,3-diphenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyrazin-5-yl]}methanol (19) A solution of **16** (150 mg, 0.32 mmol) in MeOH (4 ml) and liquid NH_3 (3 ml) was heated in a bomb at 75 °C for 60 h. Once the reaction mixture had cooled to r.t., the solvent was evapored under reduced pressure and **19** was isolated as a white solid (0.07 g, 51% yield), mp 224—226 (Et_2O). IR (film) cm^{-1}: 3353, 1653, 1556, 1418, 1319, 1238, 1074, 798, 776. ^{1}H-RMN ($CDCl_3$) δ: 1.73 (1H, dt,

J=8.5, 13.1 Hz, 6-HH), 2.34 (1H, dt, J=8.3, 13.3 Hz, 6-HH), 3.54—3.60 (1H, m, 5-H), 3.70—3.79 (2H, m, 5-CH_2), 3.88 (1H, br s, OH, D_2O exch.), 4.03—4.12 (1H, m, 7-H), 4.34—4.50 (part A of an ABX system J_{AX}=5.2, J_{AB}=13.3 Hz, CHHN) 4.55—4.68 (part B of an ABX system J_{BX}=7.5, J_{BA}=13.3 Hz, CHHN), 6.76 (2H, NH_2, D_2O exch). 7.11—7.44 (10H, m, arom.), 7.80 and 7.89 (2H, 2s, 2′-H+8′-H). ^{13}C-NMR ($CDCl_3$) δ: 31.6 (CH_2), 34.2 (CH), 44.5 (CH), 47.3 (CH_2), 61.2 (CH_2), 120.1 (C), 128.0 (CH), 128.9 (CH), 129.6 (C), 135.4 (CH), 135.7 (C), 141.2 (CH), 145.5 (C), 150.4 (C), 151.8 (CH), 158.4 (C), 158.2 (C), 160.3 (C). *Anal.* Calcd for $C_{26}H_{23}N_7O$ (449.51). C, 69.47; H, 5.16; N, 21.81.Found: C, 69.32; H, 5.23; N, 22.00.

(±)-*cis*-{[7-(6-Cyclopropylamino-9*H*-purin-9-yl)methyl]-2,3-diphenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyrazin-5-yl]}methanol (20) A solution of **16** (150 mg, 0.31 mmol) and cyclopropylamine (127 mg, 2.22 mmol) in EtOH (10 ml) was refuxed for 22 h. Removal of the solvent under reduced pressure left a brown oil from which, following chromatography on silica gel with CH_2Cl_2–MeOH (95 : 5) as eluent, **20** (78 mg, 52%) was isolated as a ligh oil. IR (film) cm^{-1}: 3410, 2360, 1740, 1635, 1476, 1377, 1298, 1074, 768, 676. ^{1}H-NMR ($CDCl_3$) δ: 0.54—0.58 (m, 2H, cyclopropyl), 0.80—0.93 (m, 2H, cyclopropyl), 1.73 (1H, dt, J=8.5, 13.1 Hz, 6-HH), 2.34 (1H, dt, J=7.3, 13.1 Hz, 6-HH), 2.93—2.98 (m, 1H, $1_{cyclopropyl}$H), 3.54—3.60 (1H, m, 5-H), 3.79—3.97 (2H, m, 5-CH_2), 4.11 (1H, br s, OH, D_2O exch.), 4.18—4.22 (1H, m, 7-H), 4.35—4.51 (part A of an ABX system J_{AX}=5.7, J_{AB}=13.3 Hz, CHHN), 4.55—4.68 (part B of an ABX, J_{BX}=7.5, J_{BA}=13.3 Hz, CHHN), 7.11—7.44 (10H, m, arom.), 7.80 and 7.89 (2H, 2s, 2′-H=8′-H). ^{13}C-NMR ($CDCl_3$) δ: 7.2 (2×CH_3), 29.6 (CH), 31.6 (CH_2), 34.2 (CH), 44.5 (CH), 47.3 (CH_2), 61.2 (CH_2), 120.1 (C), 128.0 (CH), 128.9 (CH), 129.6 (CH), 135.4 (CH), 135.7 (C), 141.2 (CH), 145.5 (C), 150.4 (CH), 151.8 (C), 158.4 (C), 158.2 (C), 160.3 (C). *Anal.* Calcd for $C_{29}H_{27}N_7O$ (489.58). C, 71.15; H, 5.56; N, 20.03. Found: C, 71.3; H, 5.76; N, 19.88.

Acknowledgements Authors thank Xunta de Galicia for financial support under project PGIDIT02BTF20305PR.

References and Notes

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18) Crystallographic data (excluding structure factors) for the structures **13** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication, no. CCDC 242738. Empirical formula: $C_{21}H_{20}N_2O_2$ formula weight: 332.39; crystal size: 0.88×0.08×0.04; crystal system: monoclinic; unit cell dimensions: a=14.6253(13) Å, b=6.2834(5) Å, c=18.6333(7) Å; α=90°, α=92.811(8)°, γ=90°; V=1710.3(2) Å^3; space group: $P_2(1)/n$; D_{calc}=1.291 Mg/m^3; $F(000)$=704; R1=0.0569, wR2=0.1624. Diffractometer: Smart-1000 BRUKER.