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Synthesis and Antiviral Activities of Novel Purinyl- and Pyrimidinylcarbanucleosides Derived from Indan[1]

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Abstract: Starting from (±)-*trans*- and (±)-*cis*-3-hydroxymethyl-1-indanol, novel 6-substituted purinylcarbanucleoside derivatives of indan (**5**, **6**, **9**, **10**, **15** and **17**) were synthesized through a key coupling reaction with 6-chloropurine under Mitsunobu conditions. Suzuki–Miyaura reactions of the protected 6-chloropurine derivative with different arylboronic acids afforded the corresponding 6-arylpurinylcarbanucleoside derivatives. Finally, three new 5-halouracilcarbanucleosides (**19**, **20** and **21**) were prepared by reaction of uracilcarbanucleoside **18** with different *N*-halosuccinimides. All of the new analogues were evaluated for antiviral activity against a wide variety of viruses.

Keywords: Synthesis; Indan carbanucleosides; Mitsunobu reaction; Suzuki–Miyaura reaction; Antiviral activity.

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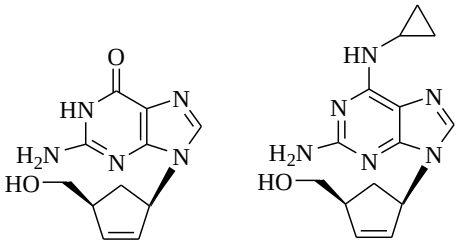
Introduction

Carbocyclic nucleosides (carbanucleosides) are analogues of nucleosides in which a methylene group has replaced the oxygen atom in the furanose ring.[2] These analogues show similar biological activities to the parent nucleosides and have higher metabolic and chemical stability against different phosphorylases, hydrolases and cleaving agents.[3] Of the different carbanucleosides prepared to date, carbovir[4] has shown significant anti-HIV activity through the selective inhibition of *HIV-1 reverse transcriptase*. Its derivative abacavir[5] is equally potent but is less toxic, has greater bioavailability and has been approved by the FDA for the treatment of HIV infection. Both of these compounds are cyclopentenyl carbanucleosides and their anti-HIV capacity has stimulated the development of new carbanucleosides in which the carbocycle is a cyclopentane ring.



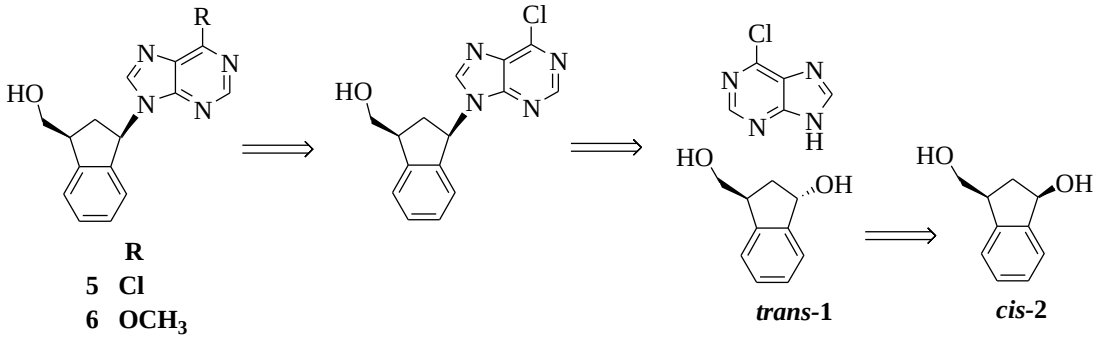
Carbovir **Abacavir**

In the last two years our research group has prepared different series' of carbanucleosides derived from indan and these bear purine and pyrimidine bases and are of the type 1'-homoderivative[6] and 5'-nor-1'-homoderivative.[7] These were synthesised with the aim of increasing the liposolubility of the compounds and to facilitate their access to the central nervous system, a significant reservoir of HIV and other viruses.[8] Some of these compounds showed interesting cytostatic activity, particularly the 6-arylpurinyl derivatives (which is in keeping with reports concerning 6-arylpurinylribonucleosides).[9]

As a logical continuation of our research into the preparation and pharmacological evaluation of novel carbanucleosides derived from indan, we report here the synthesis of a new series of nucleosides in which the link between the carbacycle bearing the base (purine or pyrimidine) and the hydroxyl group is the same as in natural nucleosides. More specifically, we report the synthesis and antiviral and cytostatic activities of a series of indanylcarbanucleosides bearing purine and pyrimidine bases.

Results and discussion

Retrosynthetic analysis (Scheme 1) led to the choice of diol *trans*-**1** as the starting material for the prepatration of the different purine derivatives. Appropriate functionalization of *trans*-**1** enables the coupling with 6-chloropurine under Mitsunobu conditions. This reaction leads to inversion of the configuration at the carbon bearing the secondary hydroxyl group and gives the key intermediate with a *cis* disposition. Acid hydrolysis of this compound gave analogue **5**, which on replacement of the chloro-substituent of the purine ring gave the 6-substituted purinylcarbanucleosides **6**, **15** and **17**, while Suzuki–Miyaura cross-coupling with appropriate boronic acids would give 6-arylpurinylcarbanucleosides **9** and **10**.



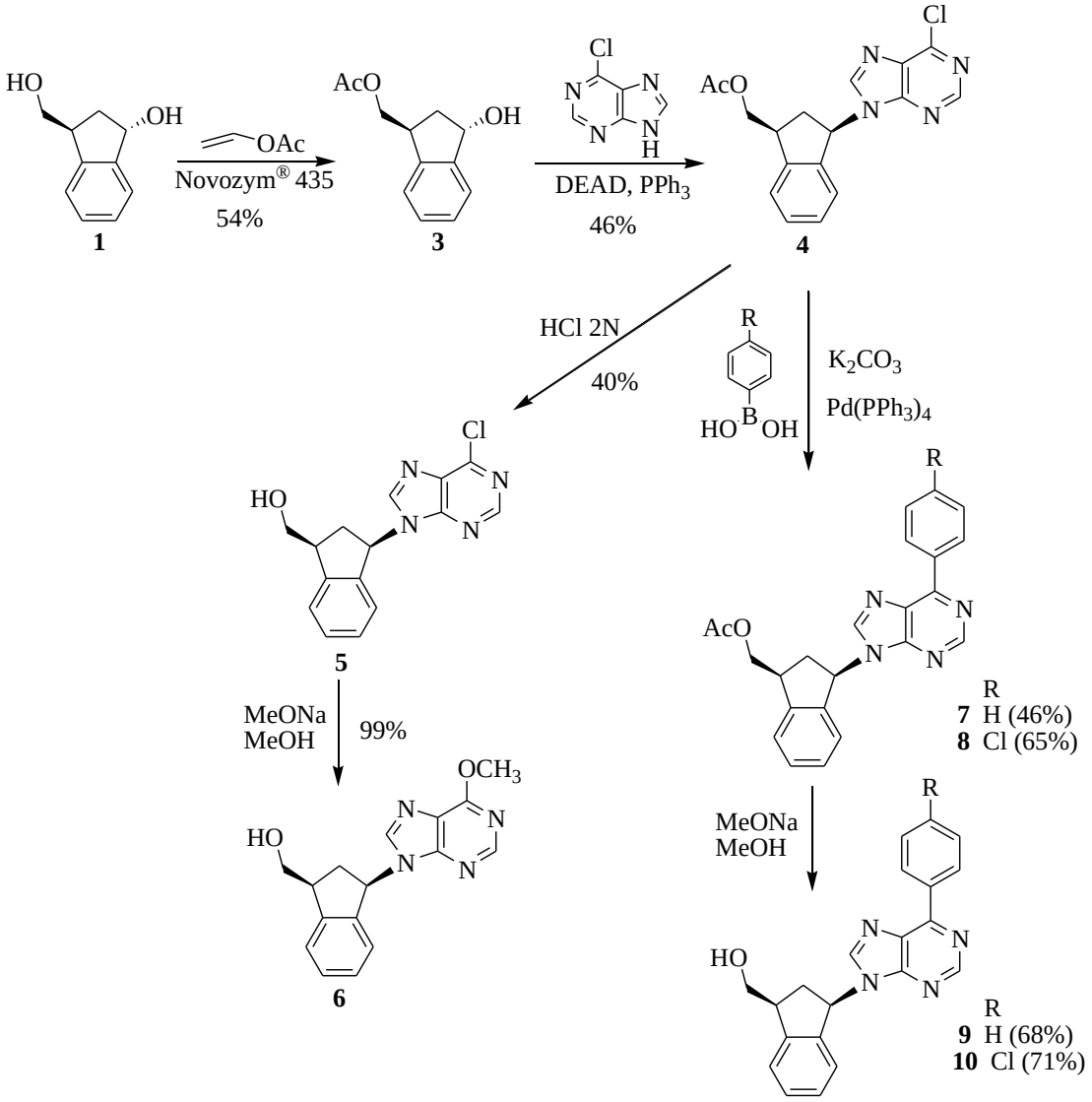
R
5 **Cl**
6 **OCH_3**
9 **Ph**
10 ***p*-ClPh**
15 **OH**
17 **NH-^{c}Pr**

***trans*-1** ***cis*-2**

Scheme 1

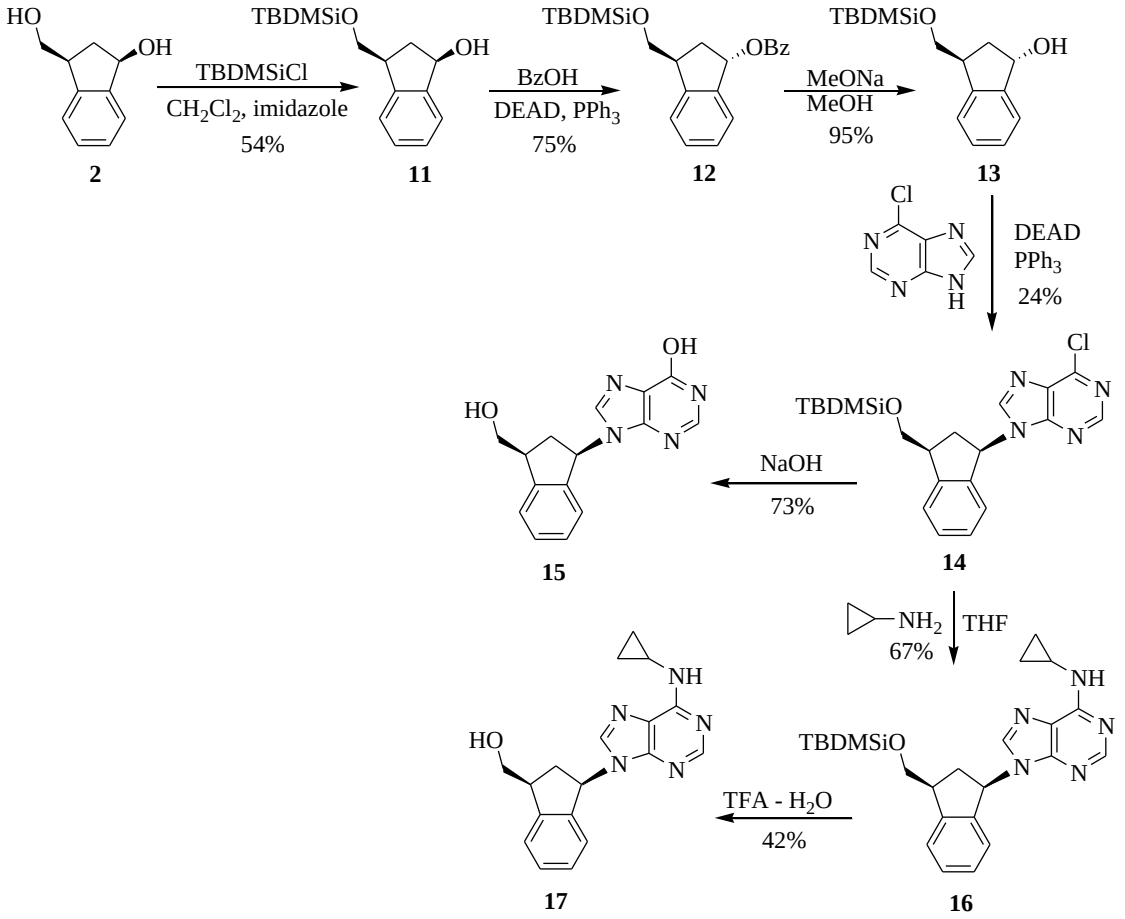
Diol *trans*-**1** was obtained from phenylsuccinic anhydride by Friedel–Crafts reaction with aluminium trichloride in 1,2-dichloroethane followed by esterification with methanol in sulphuric acid[10] and treatment with lithium borohydride in tetrahydrofuran. In this way a 17:83 mixture of (±)-*trans*-**1** and (±)-*cis*-**2** was obtained and this was efficiently resolved by chromatography on silica gel.[7a] Diol (±)-*trans*-**1** is the starting material required to obtain analogues with a *cis* disposition, but this compound was only obtained in small quantities. As a result, we decided to use the diol (±)-*cis*-**2** as a starting material as this could be transformed into (±)-*trans*-**1** through a Mitsunobu reaction with benzoic acid. Protection of the primary alcohol in *trans*-**1** was achieved by enzymatic transesterification with vinyl acetate using *Candida antarctica* lipase (Novozym® 435)[11] to give the monoacetylated derivative **3** as the only product in 93% yield. 6-Chloropurine was condensed with **3** by a standard Mitsunobu reaction,[12] in the presence of triethylphosphine and diethyl azodicarboxylate, to give the key intermediate

4 in 46% yield. Treatment of **4** with 2N hydrochloric acid in tetrahydrofuran gave 6-chloropurinylcarbanucleoside **5** in 40% yield. Subsequent treatment of **5** with MeONa in MeOH gave 6-methoxypurinylcarbanucleoside **6** in 99% yield. On the other hand, on following the conditions reported by Hocek and co-workers,[13] the chloro-substituent in position 6 of the purine was replaced in a Suzuki–Miyaura cross coupling reaction with **4** and different arylboronic acids in dry toluene containing tetrakis(triphenylphospine)palladium as a catalyst and potassium carbonate as a base.[14] This procedure gave 46–65% yields of compounds **7** and **8**. Deprotection of these compounds with MeONa in MeOH afforded the 6-arylpurinylcarbanucleosides **9** and **10** in yields of 68–71% (Scheme 2).



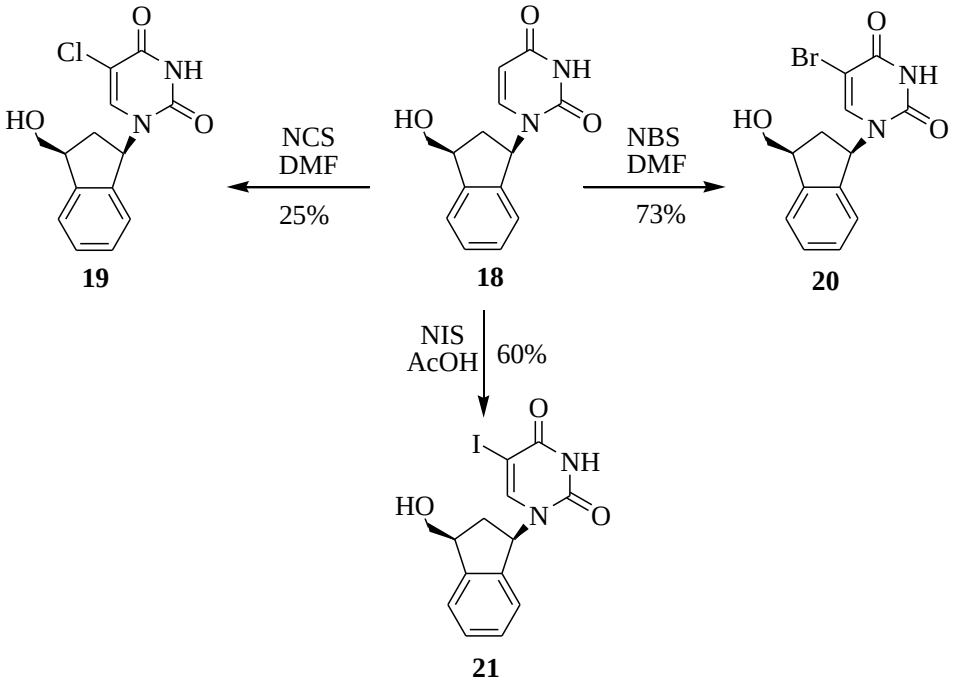
Scheme 2

The primary alcohol of *cis*-**2** was protected by reaction with *tert*-butyldimethylsilyl chloride and imidazole in dichloromethane,[15] and the secondary alcohol of the resulting compound **11** was reacted with benzoic acid under Mitsunobu conditions to give compound **12** in 75% yield. Compound **12** had the required *trans* disposition. Deprotection of the secondary alcohol using MeONa in MeOH gave the key intermediate **13** in 95% yield. Compound **13** was used in the coupling with 6-chloropurine, through a Mitsunobu reaction, to give 6-chloropurinylcarbanucleoside **14** in 24% yield (with a *cis* disposition). Treatment of **14** with 0.25 N NaOH in 1,4-dioxane afforded the 6-hydroxypurinylcarbanucleoside **15** in one step and in 73% yield, while treatment with *N*-cyclopropylamine in tetrahydrofuran followed by deprotection with a 3:1 mixture of trifluoroacetic acid/water gave the 6-methoxypurinylcarbanucleoside **17** in an overall yield of 28% (Scheme 3).



Scheme 3

Finally, the 5-halouracilcarbanucleosides **19**, **20** and **21** (Scheme 4) were obtained by reaction of uracilcarbanucleoside **18**, previously reported by ourselves,[16] with the corresponding *N*-halosuccinimide in DMF (**19**; 25% and **20** 73%) or AcOH (**21**; 60%).[17]



Scheme 4

Compounds **5**, **6**, **9**, **10**, **15**, **17**, **19**, **20** and **21** were evaluated for antiviral activity[18] against a wide variety of viruses, including Cytomegalovirus (AD 169 and Davis strains), Varicella-zoster virus (OKA and 07/1 strains), Herpes simplex virus type 1 (strain KOS), Herpes simplex virus type 2 (strain G), Vaccinia virus and Vesicular stomatitis virus in HEL cell cultures; Coxsackie virus B4, Respiratory syncytial virus and Vesicular stomatitis virus in HeLa cell cultures; Para-influenza-3 virus, Sindbis, Coxsackie virus B4 and Punta Toro virus in Vero cell cultures; Influenza A virus (H1N1 and H3N2 subtypes) and Influenza B virus in MDCK cell cultures; and Feline Corona virus and Feline Herpes Virus in CRFK cell cultures. The most outstanding results were obtained for compound **10**, which showed moderate antiviral effects against Varicella-zoster virus (OKA strain), Vaccinia virus, Herpes simplex virus-1 (KOS) and Herpes simplex virus-2 (G) in HEL cell cultures with EC_{50} values of 6.0, 12, 12 and 12 μg/mL, respectively, and compounds **5** and **9**, which showed moderate antiviral effects against Coxsackie virus B4 in Vero cell cultures with EC_{50} values of 12 μg/mL.

Conclusions

In summary, we have described the synthesis of nine novel carbocyclic nucleosides that are indan derivatives (**5**, **6**, **9**, **10**, **15**, **17**, **19**, **20** and **21**) with a pseudosugar based on indanol, a template in which the double bond of the cyclopentenyl nucleosides is embedded in a benzene ring. Evaluation of the antiviral activity of these compounds showed that compounds **5**, **9** and **10** had moderate antiviral effects.

Experimental Section

General Methods

Silica gel (230 mesh) was purchased from Merck. All other chemicals used were of reagent grade and were obtained from Aldrich Chemical Co. Melting points were determined using a Reichert Kofler Thermopan or in capillary tubes on a Büchi 510 apparatus, and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1640-FT spectrophotometer. ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75.47 MHz) were recorded on a Bruker AMX spectrometer, using TMS as internal standard (chemical shifts (δ) in ppm, *J* in Hz). Elemental analyses were obtained on a Perkin-Elmer 240B microanalyser by the Microanalysis Service of the University of Santiago de Compostela. Flash chromatography was performed on silica gel (Merck 60, 230–240 mesh) and analytical TLC on pre-coated silica gel plates (Merck 60 F254, 0.25 mm).

(±)-*trans*-3-Hydroxymethyl-1-indanol, 1,and (±)-*cis*-3-hdroxymethyl-1-indanol, 2.

A solution of methyl-3-oxo-1-indanecarboxylate[6a] (12.48 g, 70.61 mmol) in dry THF was added dropwise under argon to a suspension of $LiBH_4$ (8.09 g, 353.06 mmol) in the same solvent. The mixture was stirred for 12 h and saturated aqueous (40 mL) was added dropwise at 0°C. The resulting mixture was filtered through Celite and the aqueous and organic phases were separated. The aqueous phase was extracted with AcOEt (3 × 100 mL) and the combined organic phases were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Chromatography of the resulting yellow oil on a column of silica gel (295 g) with 40:1 CH_2Cl_2/^{i}PrOH as eluent afforded *cis*-**2** in the early fractions [as an oil that spontaneously solidified; 8.22 g, 50.06 mmol, yield 78%; M.p. 78-80 °C (Et_2O/cyclohexane)] and *trans*-**1** in the late fractions (as a yellow oil; 1.76 g, 10.71 mmol, yield 15%).

(±)-*cis*-2.

IR (KBr): ν = 3250, 2984, 2933, 1461, 1407, 1379, 1281, 1263, 1211, 1173, 1067, 1051, 1025, 777, 743, 577 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.74-1.81 (m, 1H, 2β-H), 2.20-2.40 (m, 1H, -OH, exchangeable with D_2O), 2.49-2.57 (m, 1H, 2α-H), 3.20-3.50 (m, 1H, 3β-H), 3.40-3.50 (b.s., 1H, -OH, exchangeable with D_2O), 3.72-3.83 (m, 2H, C<u>H</u>$_2$OH), 4.91-5.01 (m, 1H, 1β-H), 7.18-7.35 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ = 39.37 (CH_2), 45.63 (CH), 65.60 (CH_2), 74.83 (CH), 124.56, 125.24, 128.02 and 129.17 (CH), 143.77 and 146.43 (C). Anal. calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.41; H, 7.17.

(±)-*trans*-1.

IR (NaCl): ν = 3265, 2922, 1455, 1409, 1372, 1267, 1205, 1169, 1054, 1045, 768, 745, 573 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.02-2.13 (m, 1H, 2β-H), 2.24-2.34 (m, 1H, 2α-H), 3.43-3.50 (m, 1H, 3β-H), 3.68-3.70 (m, 2H, C<u>H</u>$_2$OH), 5.22-5.26 (m, 1H, 1α-H), 7.23-7.40 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ = 47.06 (CH_2), 52.87 (CH), 73.73 (CH_2), 82.85 (CH), 132.20, 132.38, 135.36 and 136.31 (CH), 151.12 and 153.27 (C). Anal. calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.36; H, 7.13.

(±)-*trans*-3-Hydroxy-1-indanylmethyl acetate, 3.

A suspension of the lipase Novozym® 435 (0.140 g; 0.321 mmol) and diol **1** (0.550 g; 3.35 mmol) in THF (25 mL), at 0º C under an argon atmosphere, was added a solution of vinyl acetate (0.32 mL; 3.35 mmol) in THF (30 mL). The mixture was stirred for 4 h at 0ºC and then at room temperature for 68 h. The mixture was filtered through Celite and the solvent was removed under reduced pressure to give a yellow oil, which was purified by column chromatography on silica gel (30.4 g), using hexane/AcOEt (8:1) as eluent, to give **3** as a colourless oil (0.300 g; Yield 54%). IR (NaCl): υ = 3385, 1734, 1556, 1458, 1349, 1259, 1134, 1034, 832, 738 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.06 (s, 3H, CH_3), 2.17-2.27 (m, 2H, 2β-H + 2α-H), 3.64-3.70 (m, 1H, 1β-H), 4.10-4.25 (m, 2H, C<u>H</u>$_2$OAc), 5.28-5.33 (m, 1H, 3α-H), 7.26-7.45 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ = 21.38 (CH_3), 40.10 (CH_2), 42.24 (CH), 67.82 (CH_2), 75.46 (CH), 124.98, 125.14, 128.29 and 129.14 (CH), 143.40, 145.61, 171.54 (C). Anal. calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.03; H, 6.99.

(±)-*cis*-3-(6-Chloro-9*H*-purin-9-yl)indanylmethyl acetate, 4.

To a solution of **3** (0.42 g; 2.03 mmol), PPh_3 (1.07 g; 4.06 mmol) and 6-chloropurine (0.63 g; 4.06 mmol) in THF (20 mL), under an argon atmosphere at 0ºC, was added dropwise a solution of DEAD (1.86 mL; 4.06 mmol) in THF (15 mL). The mixture was stirred at 0ºC for 1 h and at room temperature for 65 h. The solvent was removed under reduced pressure to give a solid, which was purified by column chromatography on silica gel (113 g), using hexane/AcOEt (2:1) as eluent, to give an oil that crystallised spontaneously to give a colourless solid (0.17 g; Yield 46%). This product was identified as (±)-*cis*-3-(6-chloro-9*H*-purin-9-yl)indanylmethyl acetate, **4**. M.p.: 35-38ºC (pentane). IR (KBr): υ = 2979, 1731, 1591, 1578, 1557, 1497, 1436, 1402, 1354, 1336, 1236, 1040, 941, 859 763 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.05 (s, 3H, CH_3), 2.06-2.17 (dt, 1H, $J_{(t)}$ = 13.64 Hz, $J_{(d)}$ = 7.75 Hz, 2β-H), 3.05-3.17 (dt, 1H, $J_{(t)}$ = 13.64 Hz, $J_{(d)}$ = 8.29 Hz, 2α-H), 3.60-3.71 (m, 1H, 1β-H), 4.26-4.34 (Part A of an ABM system, 1H, J_{AB} = 11.72 Hz, J_{AM} = 6.90 Hz, -C<u>H</u>HOAc), 4.38-4.45 (Part B of an ABM system, 1H, J_{BA} = 11.72 Hz, J_{BM} = 6.62 Hz, -CH<u>H</u>OAc), 6.24-6.31 (t, 1H, *J* = 8.29 Hz, 3β-H), 7.05-7.08 (d, 1H, *J* = 8.0 Hz, ArH), 7.26-7.44 (m, 3H, ArH), 7.99 (s, 1H, 8'-H), 8.77 (s, 1H, 2'-H). ^{13}C NMR ($CDCl_3$): δ = 20.34 (CH_3), 37.12 (CH_2), 41.50 (CH), 57.76 (CH), 65.93 (CH_2), 123.88, 124.26, 127.99 and 129.17 (CH), 131.28 (C), 138.88 (C), 142.66 (C), 143.20 (CH), 150.66 (C), 151.44 (CH), 156.21 (C) and 170.40 (C). Anal. calcd. for $C_{17}H_{15}ClN_4O_2$: C, 59.57; H, 4.41; N, 16.34. Found: C, 59.36; H, 4.73; N, 16.56.

(±)-*cis*-3-(6-Chloro-9*H*-purin-9-yl)-1-indanylmethanol, 5.

To a solution of **4** (0.175 g; 0.510 mmol) in THF was added 2N HCl (10 mL) and the mixture was stirred for 20 h at 40ºC. The mixture was neutralised with 2N NaOH (12 mL) and the solvent was removed under reduced pressure followed by several coevaporations with toluene and ethanol. This process gave a colourless solid, which was purified by column chromatography on silica gel (50 g), using hexane/AcOEt (1:3) as eluent, to give compound **5** as a colourless solid (0.06 g; Yield 40%). IR (KBr): υ = 3285, 2887, 1594, 1561, 1446, 1396, 1339, 1259, 927, 763, 653, 548 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.27-2.36 (dt, 1H, $J_{(t)}$ = 13.97 Hz, $J_{(d)}$ = 6.53 Hz, 2β-H), 3.03-3.13 (dt, 1H, $J_{(t)}$ = 13.98 Hz, $J_{(d)}$ = 8.81 Hz, 2α-H), 3.52-3.60 (m, 1H, 1β-H), 3.95-4.12 (m, 2H, C<u>H</u>$_2$OH), 6.25-6.30 (t, 1H, $J_{(t)}$ = 6.81 Hz, 3β-H), 7.02-7.05 (d, 1H, $J_{(d)}$ = 7.61 Hz, ArH), 7.24-7.29 (m, 1H, ArH), 7.37-7.42 (t, 1H, $J_{(t)}$ = 7.56 Hz, ArH), 7.43-7.47 (t, 1H, $J_{(t)}$ =

7.45 Hz, ArH), 8.12 (s, 1H, 8'-H), 8.75 (s, 1H, 2'-H). ^{13}C NMR ($CDCl_3$): δ = 36.19 (CH_2), 45.28 (CH), 58.63 (CH), 64.81 (CH_2), 124.47, 124.68, 128.23 and 129.66 (CH), 131.71 (C), 140.11 (C), 144.02 (C), 144.52 (CH), 150.99 (C), 151.81 (CH). Anal. calcd. for $C_{15}H_{13}ClN_4O$: C, 59.91; H, 4.36; N, 18.63. Found: C, 60.15; H, 4.11; N, 18.40.

(±)-*cis*-3-(6-Methoxy-9*H*-purin-9-yl)-1-indanylmethanol, 6.

To a solution of **5** (0.030 g; 0.101 mmol) in MeOH (10 mL) was added, under an argon atmosphere, MeONa (0.11 mL; 0.11 mmol) and the mixture was stirred for 6 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (3.15 g), using CH_2Cl_2/isopropanol (30:1) as eluent, to give **6** as a colourless solid (0.030 g; Yield 99%). IR (NaCl): υ = 3394, 1602, 1480, 1316, 1229, 1056, 760, 649 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.65 (s, 3H, CH_3CO), 2.33-2.42 (dt, 1H, $J_{(t)}$ = 13.96 Hz, $J_{(d)}$ = 6.98 Hz, 2β-H), 3.00-3.11 (dt, 1H, $J_{(t)}$ =13.94 Hz, $J_{(d)}$ = 8.82 Hz, 2α-H), 3.52-3.60 (m, 1H, 1β-H), 3.90-4.01 (m, 2H, C$\underline{H}_2$OAc), 4.19 (s, 3H, OCH_3), 6.17-6.22 (t, 1H, $J_{(t)}$ = 7.87 Hz, 3β-H), 7.01-7.04 (d, 1H, $J_{(d)}$ = 7.58 Hz, ArH), 7.23-7.31 (m, 1H, ArH), 7.36-7.46 (m, 2H, ArH), 7.88 (s, 1H, 2'-H), 8.51 (s, 1H, 8'-H). ^{13}C NMR ($CDCl_3$): δ = 35.84 (CH_2), 45.16 (CH), 54.08 (CH_3), 58.41 (CH), 64.82 (CH_2), 124.40, 124.83, 127.92 and 129.22 (CH), 140.34 (CH), 140.58 (CH), 143.59 (C), 144.06 (C), 151.73 (CH), 160.99 (C). Anal. calcd. for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 65.16; H, 5.29; N, 19.13.

(±)-*cis*-3-(6-Phenyl-9*H*-purin-9-yl)-1-indanylmethyl acetate, 7.

A mixture of **4** (0.154 g; 0.83 mmol), K_2CO_3 (0.085 g; 0.675 mmol), 6-phenylboronic acid (0.094 g; 0.675 mmol) and $Pd(PPh_3)_4$ (0.046 g) in anhydrous toluene (80 mL) under an argon atmosphere was stirred for 12 h at 100ºC. The solvent was removed by vacuum distillation and the residue was purified by column chromatography on silica gel (48 g), using hexane/AcOEt (4:1) as eluent, to give **7** as a yellow oil, which crystallised spontaneously as a colourless solid (0.08 g; Yield 46%). M.p.: 38-41ºC ($CHCl_3$/Hexane). IR (KBr): υ = 3418, 2919, 1734, 1649, 1560, 1536, 1457, 1351, 1223, 1021, 765, 694 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.05 (s, 3H, CH_3), 2.09-2.21 (dt, 1H, $J_{(t)}$ = 13.52 Hz, $J_{(d)}$ = 7.77 Hz, 2β-H), 3.08-3.20 (dt, 1H, $J_{(t)}$ = 13.52 Hz, $J_{(d)}$ = 8.18 Hz, 2α-H), 3.62-3.73 (m, 1H, 1β-H), 4.35-4.42 (Part A of an ABM system, 1H, J_{AB} = 11.11 Hz, J_{AM} = 6.30 Hz, -C$\underline{H}$HOAc), 4.44-4.51 (Part B of an ABM system, 1H, J_{BA} = 11.11 Hz, J_{BM} = 5.59 Hz, -CH$\underline{H}$OAc), 6.31-6.38 (t, 1H, J = 7.89 Hz, 3β-H), 7.10-7.13 (d, 1H, J =

7.62 Hz, ArH), 7.26-7.61 (m, 6H, ArH), 7.98 (s, 1H, 8'-H), 8.78-8.81 (d, 2H, *J* = 7.63 Hz, ArH), 9.06 (s, 1H, 2'-H). ^{13}C NMR ($CDCl_3$): δ = 21.31 (CH_3), 38.29 (CH_2), 42.46 (CH), 58.02 (CH), 66.97 (CH_2), 124.94, 125.15, 128.83, 129.10, 129.88 and 130.20 (CH), 131.43 (C), 136.08 (C), 143.06 (CH), 143.61 (C), 152.83 (CH) and 171.34 (C). Anal. calcd. for $C_{23}H_{20}N_4O_2$: C, 71.86; H, 5.24; N, 14.57. Found: C, 71.61; H, 5.03; N, 14.80.

(±)-*cis*-3-[6-(4'-Chloro)phenyl-9*H*-purin-9-yl)-1-indanylmethyl acetate, 8.

Reaction of **4** with 6-chlorophenylboronic acid, following an identical procedure to that described in section **5.7**, gave **8** as a clear oil that spontaneously crystallised to a colourless solid. (Yield 65%). M.p. 60-63ºC ($CHCl_3$/Hexane). IR (KBr): υ = 3412, 1734, 1649, 1578, 1514, 1496, 1469, 1445, 1325, 1221, 1014, 843, 803, 747, 646 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.04 (s, 3H, CH_3), 2.09-2.19 (dt, 1H, $J_{(t)}$ = 13.58 Hz, $J_{(d)}$ = 7.70 Hz, 2β-H), 3.07-3.17 (dt, 1H, $J_{(t)}$ = 13.58 Hz, $J_{(d)}$ = 8.10 Hz, 2α-H), 3.64-3.71 (m, 1H, 1β-H), 4.35-4.41 (Part A of an ABM system, 1H, J_{AB} = 11.11 Hz, J_{AM} = 6.30 Hz, -C<u>H</u>HOAc), 4.43-4.48 (Part B of an ABM system, 1H, J_{BA} = 11.11 Hz, J_{BM} = 5.58 Hz, -CH<u>H</u>OAc), 6.30-6.35 (t, 1H, *J* = 7.85 Hz, 3β-H), 7.09-7.11 (d, 1H, *J* = 7.60 Hz, ArH), 7.26-7.49 (m, 3H, ArH), 7.50-7.53 (d, 2H, *J* = 8.57 Hz, ArH), 7.97 (s, 1H, 8'-H), 8.78-8.81 (d, 2H, *J* = 8.57 Hz, ArH), 9.02 (s, 1H, 2'-H). ^{13}C NMR ($CDCl_3$): δ = 21.27 (CH_3), 38.21 (CH_2), 42.47 (CH), 58.07 (CH), 66.96 (CH_2), 124.91, 125.17, 128.83, 129.31, 129.91 and 131.52 (CH), 131.58 (C), 134.56 (C), 137.67 (C), 140.37 (C), 143.22 (CH), 143.63 (C), 152.76 (CH), 153.19 (C), 154.02 (C) and 171.30 (C). Anal. calcd. for $C_{23}H_{19}ClN_4O_2$: C, 65.95; H, 4.57; N, 13.38. Found: C, 66.22; H, 4.35; N, 13.57.

(±)-*cis*-3-(6-Phenyl-9*H*-purin-9-yl)-1-indanylmethanol, 9.

To a solution of **7** (0.05 g; 0.13 mmol) in MeOH (5 mL), under an argon atmosphere, was added powdered 95% MeONa (0.015 g; 0.264 mmol) and the mixture was stirred for 20 h. The solution was neutralised by the addition of Dowex 50 × 8 (H^+) resin (*ca*. 100 mg) and the mixture was stirred for 20 min. The resin was filtered off and washed with MeOH saturated with ammonia (10 mL) and MeOH (10 mL). The filtrates were combined and concentrated to dryness. The resulting colourless solid was purified by column chromatography on silica gel (6 g), using hexane/AcOEt (1:2) as eluent, to give **9** as a colourless solid. (0.034 g; Yield 68%). M.p. 53-56ºC ($CHCl_3$/Hexane). IR (KBr): υ = 3378, 2921, 1654, 1562, 1499, 1488, 1457, 1416, 1399, 1350, 1325, 1265, 1218,

1131, 1030, 828, 764, 694, 647 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.28-2.40 (dt, 1H, $J_{(t)}$ = 13.85 Hz, $J_{(d)}$ = 7.10 Hz, 2β-H), 2.95-3.07 (dt, 1H, $J_{(t)}$ = 13.85 Hz, $J_{(d)}$ = 8.70 Hz, 2α-H), 3.44-3.54 (m, 1H, 1β-H), 3.88-3.94 (Part A of an ABM system, 1H, J_{AB} = 10.74 Hz, J_{AM} = 4.12 Hz, -CHHOH), 3.99-4.05 (Part B of an ABM system, 1H, J_{BA} = 10.74 Hz, J_{BM} = 6.377 Hz, -CHHOH), 6.19-6.26 (t, 1H, *J* = 7.56 Hz, 3β-H), 6.97-7.01 (d, 1H, *J* = 7.56 Hz, ArH), 7.08-7.53 (m, 6H, ArH), 8.03 (s, 1H, 8'-H), 8.67-8.71 (d, 2H, *J* = 7.68 Hz, ArH), 8.93 (s, 1H, 2'-H). ^{13}C NMR ($CDCl_3$): δ = 36.00 (CH_2), 45.16 (CH), 58.09 (CH), 64.84 (CH_2), 124.36 (CH), 124.48 (C), 128.01, 128.11, 128.58, 128.93, 129.32 and 129.70 (CH), 130.91 (C), 135.52 (C), 140.60 (C), 143.36 (CH), 143.68 (C), 152.06 (CH), 154.98 (C). Anal. calcd. for $C_{21}H_{18}N_4O$: C, 73.67; H, 5.30; N, 16.36. Found: C, 73.30; H, 5.51; N, 16.61.

(±)-*cis*-3-[(6-(4'-Chloro)phenyl-9*H*-purin-9-yl)-1-indanylmethanol, 10.

The same procedure as described in section **5.9** was used to prepare **10** from **8**. (Yield 71%). M.p. 56-59ºC ($CHCl_3$/Hexane). IR (KBr): υ = 2922, 1582, 1518, 1497, 1485, 1447, 1416, 1386, 1344, 1261, 1240, 1086, 802, 757, 649 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.19-1.23 (b.s., 1H, OH exchangeable with D_2O), 2.33-2.45 (dt, 1H, $J_{(t)}$ = 13.85 Hz, $J_{(d)}$ = 7.02 Hz, 2β-H), 3.05-3.17 (dt, 1H, $J_{(t)}$ = 13.85 Hz, $J_{(d)}$ = 7.67 Hz, 2α-H), 3.59-3.64 (m, 1H, 1β-H), 3.99-4.15 (m, 2H, CH_2OH), 6.28-6.35 (m, 1H, 3β-H), 7.05-7.08 (d, 1H, *J* = 7.55 Hz, ArH), 7.26-7.47 (m, 3H, ArH), 7.51-7.53 (d, 2H, *J* = 8.66 Hz, ArH), 8.12 (s, 1H, 8'-H), 8.78-8.81 (d, 2H, *J* = 8.66 Hz, ArH), 8.99 (s, 1H, 2'-H). ^{13}C NMR ($CDCl_3$): δ = 36.09 (CH_2), 42.23 (CH), 58.26 (CH), 64.97 (CH_2), 124.47, 124.58, 128.19, 128.93, 129.50 and 131.11 (CH), 131.43 (C), 134.13 (C), 137.27 (C), 140.66 (C), 143.56 (CH), 143.70 and 152.17 (C). Anal. calcd. for $C_{21}H_{17}ClN_4O$: C, 66.93; H, 4.55; N, 14.87. Found: C, 67.19; H, 4.76; N, 14.59.

(±)-*cis*-3-(*tert*-Butyldimethylsilyloxy)methylindanol, 11.

To a suspension of diol **2** (1.6 g; 8.37 mmol) and imidazole (1.13 g; 16.74 mmol) in anhydrous dichloromethane (60 mL) was added, at 0ºC under an argon atmosphere, a solution of *tert*-butyldimethylsilyl chloride (1.35 g; 9.21 mmol) in anhydrous dichloromethane (20 mL). The mixture was cooled to 0-5ºC and stirred for 24 h. The mixture was allowed to warm up to room temperature and stirred for 1 h. Dichloromethane (60 mL) was added and the solution was extracted $NaHCO_3$ (80 mL). The aqueous phase was extracted with dichloromethane (3 × 50 mL) and the combined

organic phases were washed with saturated aqueous NH_4Cl (100 mL) and dried (Na_2SO_4). The solvent was evaporated to give a yellow oil, which was purified by column chromatography on silica gel (84 g), using hexane/AcOEt (12:1) as eluent, to give **11** as a colourless oil (1.25 g; Yield 54%). IR (NaCl): υ = 3383, 3030, 2738, 1918, 1736, 1607, 1467, 1387, 1329, 1254, 1200, 1156, 1020, 968, 776, 667 cm^{-1}. ^1H NMR ($CDCl_3$): δ = - 0.12 (s, 3H, CH_3), - 0.04 (s, 3H, CH_3), 0.76 (s, 9H, $C(CH_3)_3$), 1.84-1.90 (m, 1H, 2β-H), 2.57-2.66 (m, 1H, 2α-H), 3.28-3.33 (m, 1H, 3β-H), 3.36-3.39 (d, 1H, $J_{(d)}$ = 3.45 Hz, exchangeable with D_2O), 3.88-3.89 (d, 2H, $J_{(d)}$ = 3.36 Hz, C<u>H</u>$_2$OSi-), 4.99-5.05 (m, 1H, 1β-H), 7.24-7.31 (m, 3H, ArH), 7.42-7.45 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$): δ = - 5.38 (CH_3), - 5.24 (CH_3), 18.78 (C), 26.16 ($C(CH_3)_3$), 39.81 (CH_2), 45.97 (CH), 67.19 (CH_2), 74.98 (CH), 124.51, 125.14, 127.83 and 128.82 (CH), 144.05 (C), 146.69 (C). Anal. calcd. for $C_{16}H_{26}O_2Si$: C, 69.01; H, 9.41. Found: C, 69.35; H, 9.19.

(±)-*trans*-3-[(*tert*-Butyldimethylsilyloxy)methyl]-1-indanyl benzoate, 12.

To a solution of **11** (1.0 g; 3.59 mmol), benzoic acid (0.62 g; 5.02 mmol) and triphenylphosphine (1.10 g; 3.95 mmol) in THF (40 mL) was added dropwise, under an argon atmosphere at 0ºC, a solution of DEAD (1.56 mL) in THF (5 mL). The mixture was stirred at 0ºC for 1 h and at room temperature for 25 h. Dichloromethane (80 mL) and saturated aqueous $NaHCO_3$ (60 mL) were added. The aqueous phase was extracted with dichloromethane (3 × 60 mL) and the solvent was removed under reduced pressure to give a colourless solid, which was purified by column chromatography on silica gel (130 g), using hexane/AcOEt (60:1) as eluent, to give **12** as a colourless liquid (1.03 g; Yield 75%). IR (NaCl): υ = 3068, 2857, 1603, 1462, 1351, 1175, 1109, 1024, 941, 838, 758, 712 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.01 (s, 3H, CH_3Si-), 0.05 (s, 3H, CH_3Si-), 0.89 (s, 9H, $C(CH_3)_3$), 2.33-2.51 (m, 2H, 2α-H and 2β-H), 3.57-3.65 (m, 1H, 3β-H), 3.70-3.76 (m, 1H, CH<u>H</u>OSi-), 3.83-3.88 (m, 1H, C<u>H</u>HOSi-), 6.48-6.52 (m, 1H, 1β-H), 7.26-7.57 (m, 2H, ArH), 8.04-8.06 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ = - 0.51 (CH_3), - 4.98 (CH_3), 18.68 (C), 26.29 (CH_3), 36.90 (CH_2), 46.11 (CH), 67.23 (CH_2), 78.53 (CH), 125.10, 126.02, 127.77, 128.68, 129.28, 130.09, 130.91 and 133.27 (CH), 142.15 (C), 145.80 (C), 167.02 (C). Anal. calcd. for $C_{23}H_{30}O_3Si$: C, 72.21; H, 7.90. Found: C, 71.91; H, 8.17.

(±)-*trans*-3-[(*tert*-Butyldimethylsilyloxy)methyl]-1-indanol, 13.

A solution of **12** (0.5 g; 1.307 mmol) and MeONa (0.5 g; 1.43 mmol) in methanol (20 mL) was stirred for 16 h under an argon atmosphere at room temperature. The solvent was removed under reduced pressure to give a colourless solid, which was purified by column chromatography on silica gel (45 g), using hexane/AcOEt (18:1) as eluent, to give **13** as a colourless oil (0.280 g; Yield 95%). IR (NaCl): υ = 3345, 3030, 2930, 2857, 1720, 1466, 1385, 1254, 1103, 939, 837, 775 cm^{-1}. ^1H NMR ($CDCl_3$): δ = - 0.06 (s, 3H, CH_3), - 0.09 (s, 3H, CH_3), 0.83 (s, 9H, $C(CH_3)_3$), 2.02-2.10 (m, 1H, 2β-H), 2.28-2.34 (m, 1H, 2α-H), 3.42-3.48 (m, 1H, 3β-H), 3.60-3.63 (m, 1H, C<u>H</u>HOSi-), 3.70-3.74 (m, 1H, CH<u>H</u>OSi-), 5.26-5.29 (m, 1H, 1β-H), 7.23-7.31 (m, 3H, ArH), 7.36-7.39 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$): δ = 5.50 (CH_3), 18.24 (C), 25.84 (CH_3), 39.74 (CH_2), 45.39 (CH), 66.91 (CH_2), 75.45 (CH), 124.21, 124.91, 127.36 and 128.28 (CH), 144.27 (C), 145.49 (C). Anal. calcd. for $C_{16}H_{26}O_2Si$: C, 69.01; H, 9.41. Found: C, 69.29; H, 9.21.

(±)-*cis*-3-(6-Chloro-9*H*-purin-9-yl)-1-[(*tert*-butyldimethylsilyloxy)methyl]indan, 14.

To a solution of **13** (0.280 g; 1.006 mmol), triphenylphosphine (0.300 g; 1.107 mmol) and 6-chloropurine (0.220 g; 1.41 mmol) in THF (20 mL), under an argon atmosphere and at 0ºC, was added dropwise a solution of DEAD (0.440 mL; 1.107 mmol) in THF (10 mL). The mixture was stirred for 1 h at 0ºC and for 39 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (50 g), using hexane/AcOEt (18:1) as eluent, to give **14** as a yellow oil (0.100 g; Yield 24%). IR (NaCl): υ = 2928, 1562, 1391, 1254, 1066, 837, 776 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.0016-0.03 (2s, 6H, $2CH_3$), 0.84 (1s, 9H, $C(CH_3)_3$), 2.11-2.21 (dt, 1H, $J_{(t)}$ = 13.65 Hz, $J_{(d)}$ = 7.36 Hz, 2β-H), 2.98-3.04 (dt, 1H, $J_{(t)}$ = 13.64 Hz, $J_{(d)}$ = 8.41 Hz, 2α-H), 3.46-3.54 (m, 1H, 1β-H), 4.023-4.13 (m, 2H, CH_2OSi-), 6.31-6.34 (m 1H, 3β-H), 7.01-7.04 (d, 1H, J = 7.51 Hz, ArH), 7.26-7.47 (m, 3H, ArH), 8.00 (s, 1H, 8'-H), 8.79 (s, 1H, 2'-H). ^{13}C NMR ($CDCl_3$): δ = 26.25 (CH_3), 37.45 (CH_2), 45.83 (CH), 58.69 (CH), 66.05 (CH_2), 124.62, 125.41, 128.44 and 129.70 (CH), 132.14 (C) 132.15 (C *trans*), 140.28 (C), 144.33 (CH), 144.95 (C), 151.46 (C), 152.32 (CH), 152.47 (C). Anal. calcd. for $C_{21}H_{27}ClN_4OSi$: C, 60.78; H, 6.56; N, 13.50. Found: C, 61.09; H, 6.38; N, 13.67.

(±)-*cis*-3-(6-Hydroxy-9*H*-purin-9-yl)-1-indanylmethanol, 15.

A solution of **14** (0.060 g; 0.145 mmol) in 1,4-dioxane (15 mL) and 0.25 N NaOH (8 mL) was stirred for 4 h at room temperature. The solvent was removed under reduced pressure and successive coevaporations with toluene were carried out to remove any residual solvent. A colourless oil was obtained and this was purified by column chromatography on silica gel (12 g), using CH_2Cl_2/MeOH (30:1) as eluent, to give **15** as a colourless solid (0.030 g; Yield 73%). M.p. 168-170ºC. IR (KBr): υ = 3417, 2923, 1693, 1586, 1459, 1379, 1212, 1032, 650 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.21-2.31 (dt, 1H, $J_{(t)}$ = 13.43 Hz, $J_{(d)}$ = 7.62 Hz, 2β-H), 2.93-3.03 (dt, 1H, $J_{(t)}$ = 13.43 Hz, $J_{(d)}$ = 8.31 Hz, 2α-H), 3.45-3.49 (m, 1H, 1β-H), 3.84-3.98 (m, 2H, C<u>H</u>$_2$O), 6.16-6.21 (t, 1H, $J_{(t)}$ = 8.01 Hz, 3β-H), 7.01-7.03(d, 1H, $J_{(d)}$ = 7.58 Hz, ArH), 7.23-7.28 (t, 1H, $J_{(t)}$ = 7.42 Hz, ArH), 7.34-7.39 (t, 1H, $J_{(t)}$ = 7.44 Hz, ArH), 7.46-7.49 (m, 1H, ArH), 7.91 (s, 1H, 2'H), 8.05 (s, 1H, 8'H). ^{13}C NMR ($CDCl_3$): δ = 37.99 (CH_2), 46.56 (CH), 59.77 (CH), 65.53 (CH_2), 66.18 (CH_2), 125.11 (CH), 125.30 (C), 125.77, 128.87 and 130.11 (CH), 140.71 (CH), 142.19 (C), 145.63 (C), 146.55 (CH), 150.45 (C). Anal. calcd. for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.66; H, 5.24; N, 19.55.

(±)-*cis*-3-(6-*N*-Cyclopropylamino-9*H*-purin-9-yl)-1-[(*tert*-butyldimethylsilyloxy)methyl]indan, 16.

In a pressure reactor, previously purged with argon, was placed a solution of **14** (0.100 g; 0.241 mmol) and *N*-cyclopropylamine (0.027 mL; 0.265 mmol) in THF (15 mL) and the mixture was stirred for 150 h a 50ºC. The solvent was removed under reduced pressure to give a yellow oil, which was purified by column chromatography on silica gel (8 g), using $CHCl_3$/isopropanol (60:1) as eluent, to give **16** as a yellow oil (0.070 g; Yield 67%). IR (NaCl): υ = 3387, 1732, 1560, 1350, 1242, 1066 cm^{-1}. ^1H NMR ($CDCl_3$): δ = - 0.01 (s, 3H, CH_3), 0.03 (s, 3H, CH_3), 0.83 (s, 9H, $C(CH_3)_3$), 1.03-1.05 (m, 4H, cyclopropyl-$(CH_2)_2$), 2.08-2.18 (dt, 1H, $J_{(t)}$ = 13.71 Hz, $J_{(d)}$ = 7.10 Hz, 2β-H), 2.97-3.07 (dt, 1H, $J_{(t)}$ = 13.71 Hz, $J_{(d)}$ = 8.43 Hz, 2α-H), 3.45-3.54 (m, 3H, 1β-H + 1α-H + -CH-cyclopropyl), 3.87-3.92 (Part A of an ABM system, 1H, J_{AB} = 11.13 Hz, J_{AM} = 5.28 Hz, -C<u>H</u>HOSi-), 3.92-3.97 (Part B of an ABM system, 1H, J_{BA} = 11.13 Hz, J_{BM} = 5.27 Hz, -CH<u>H</u>OSi-), 6.18-6.23 (t, 1H, $J_{(t)}$ = 7.62 Hz, 3β-H), 7.04-7.07 (d, 1H, $J_{(d)}$ = 7.56 Hz, ArH), 7.29-7.42 (m, 3H, ArH), 7.67 (s, 1H, 2'H), 7.82 (s, 1H, 8'H), 8.31 (b.s., 1H, NH, exchangeable with D_2O). ^{13}C NMR ($CDCl_3$): δ = 25.82 (CH_2), 26.09 (CH_3),

37.07 (CH_2), 45.45 (CH_3), 58.36 (CH_2), 65.59 (CH), 124.25, 124.44, 125.01 and 125.34 (ArH), 128.06 (CH), 128.20 (C), 129.44 (CH), 129.61 (C), 137.37 (C), 154.35 (C). Anal. calcd. for $C_{24}H_{33}N_5OSi$: C, 66.17; H, 7.64; N, 16.08. Found: C, 65.81; H, 7.45; N, 16.38.

(±)-*cis*-3-(6-*N*-Cyclopropylamino-9*H*-purin-9-yl)-1-indanylmethanol, 17.

To a solution of **16** (0.06 g; 0.147 mmol) in THF (10 mL) was added a mixture of TFA/H_2O (3:1) (6 mL) and the mixture was stirred for 21 h at room temperature. The solvent was removed under reduced pressure and several coevaporations with toluene were carried out to remove residual solvent. A yellow oil was obtained and this was purified by column chromatography on silica gel (5 g), using CH_2Cl_2/isopropanol (30:1) as eluent, to give **17** as a colourless solid (0.020 g; Yield 42%). IR (KBr): υ = 3394, 1618, 1458, 1198, 1038, 785, 649 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.85-0.97 (m, 4H, cyclopropyl-$(CH_2)_2$), 2.30-2.40 (dt, 1H, $J_{(t)}$ = 13.94 Hz, $J_{(d)}$ = 7.00 Hz, 2β-H), 2.99-3.10 (dt, 1H, $J_{(t)}$ = 13.94 Hz, $J_{(d)}$ = 8.87 Hz, 2β-H), 3.14 (m, 1H, cyclopropyl-CH), 3.51-3.59 (m, 1H, 1β-H), 3.98-4.04 (part A of an ABM system, 1H, J_{AB} = 10.90 Hz, J_{AM} = 4.03 Hz, -C<u>H</u>HOH), 4.06-4.11 (part B of an ABM system, 1H, J_{BA} = 10.90 Hz, J_{BM} = 4.65 Hz, -CH<u>H</u>OH), 6.12-6.17 (t, 1H, $J_{(t)}$ = 7.85 Hz, 3β-H), 6.24-6.29 (t, 1H, $J_{(t)}$ = 5.89 Hz, 3α-H), 7.02-7.05 (d, 1H, $J_{(d)}$ = 7.60 Hz, ArH), 7.22-7.31 (m, 1H, ArH), 7.36-7.47 (m, 2H, ArH), 7.74 (s, 1H, 8'-H), 8.39 (s, 1H, 2'-H). ^{13}C NMR ($CDCl_3$): δ = 7.51 (CH_2), 29.76 (CH), 36.08 (CH_2), 45.37 (CH), 58.48 (CH), 64.97 (CH_2), 119.96 (C), 124.62, 125.07, 128.10 and 129.41 (CH), 138.67 (C), 139.38 (C), 140.90 (CH), 143.81 (CH), 144.37 (C). Anal. calcd. for $C_{18}H_{19}N_5O$: C, 67.27; H, 5.96; N, 21.79. Found: C, 67.45; H, 6.19; N, 21.46.

(±)-*cis*-5-Chloro-1-(3-hydroxymethyl-1-indanyl)-1,2,3,4-tetrahydropyrimidino-2,4-dione, 19.

A solution of **18**[16] (32 mg; 0.124 mmol) and NCS (17.5 mg; 0.129 mmol) in DMF (10 mL) was stirred, under an argon atmosphere, for 1 h at room temperature. The DMF was removed under reduced pressure with the aid of repeated coevaporations with toluene. The residue was purified by column chromatography on silica gel (16 g), using dichloromethane/methanol (40:1) as eluent, to give **19** as a colourless solid (15 mg; Yield 25%). M.p. 248ºC (decomposition). IR (KBr): υ = 3546, 3262, 3036, 1689, 1454, 1376, 1259, 1069, 766 cm^{-1}. ^1H NMR (DMSO): δ = 1.86-1.98 (dt, 1H, $J_{(t)}$ = 13.67 Hz,

$J_{(d)}$ = 7.55 Hz, 2'β-H), 2.76-2.89 (dt, 1H, $J_{(t)}$ = 13.67 Hz, $J_{(d)}$ = 8.59 Hz, 2'α-H), 3.30-3.39 (m, 1H, 3'β-H), 3.85-3.91 (part A of an ABM system, J_{AB} = 10.96 Hz, J_{AM} = 4.29 Hz, C<u>H</u>HO), 3.94-4.01 (part B of an ABM system, J_{BA} = 10.96 Hz, J_{BM} = 4.79 Hz, CH<u>H</u>O), 4.65-5.01 (s, 1H, OH exchangeable with D_2O), 6.07-6.14 (t, 1H, $J_{(t)}$ = 7.99 Hz, 1'β-H), 7.13-7.16 (d, 1H, *J* = 7.21 Hz, ArH), 7.28-7.46 (m, 3H, ArH), 7.58 (s, 1H, 6-H), 11.65-12.09 (s, 1H, NH exchangeable with D_2O). ^{13}C NMR (DMSO): δ = 34.75 (CH_2), 44.52 (CH), 59.02 (C), 63.57 (CH_2), 107.25 (C), 124.33, 124.97, 127.78 and 128.90 (CH), 139.80 (CH), 140.99 (C), 145.66 (C), 150.92 (C), 159.55 (C). Anal. calcd. for $C_{14}H_{13}ClN_2O_3$: C, 57.44; H, 4.48; N, 9.57. Found: C, 57.67; H, 4.73; N, 9.69.

(±)-*cis*-5-Bromo-1-(3-hydroxymethyl-1-indanyl)-1,2,3,4-tetrahydropyrimidino-2,4-dione, 20.

The same procedure as described in section **5.18** was used to prepare compound **20** from **18** by reaction with NBS. (Yield 73%). M.p. 246ºC (decomposition). IR (KBr): υ = 3037, 1858, 1687, 1502, 1446, 1326, 1262, 910, 768 cm^{-1}. ^{1}H NMR (DMSO): δ = 1.83-1.94 (dt, 1H, $J_{(t)}$ = 13.68 Hz, $J_{(d)}$ = 7.52 Hz, 2'β-H), 2.72-2.84 (dt, 1H, $J_{(t)}$ = 13.68 Hz, $J_{(d)}$ = 8.60 Hz, 2'α-H), 3.27-3.34 (m, 1H, 3'β-H), 3.81-3.87 (part A of an ABM system, J_{AB} = 10.98 Hz, J_{AM} = 4.16 Hz, C<u>H</u>HO), 3.90-3.97 (part B of an ABM system, J_{BA} = 10.98 Hz, J_{BM} = 4.72 Hz, CH<u>H</u>O), 6.03-6.10 (t, 1H, $J_{(t)}$ = 7.96 Hz, 1'β-H), 7.09-7.12 (d, 1H, *J* = 7.45 Hz, ArH), 7.24-7.42 (m, 3H, ArH), 7.63 (s, 1H, 6-H), 11.90-12.03 (s, 1H, NH exchangeable with D_2O). ^{13}C NMR (DMSO): δ = 34.74 (CH_2), 44.52 (CH), 59.02 (CH_2), 63.51 (CH), 95.48 (C), 123.98, 124.64, 127.45 and 128.57 (CH), 140.69 (C), 141.88 (CH), 145.33 (C), 150.78 (C), 159.35 (C). Anal. calcd. for $C_{14}H_{13}BrN_2O_3$: C, 49.87; H, 3.89; N, 8.31. Found: C, 50.11; H, 3.71; N, 8.46.

(±)-*cis*-5-Iodo-1-(3-hydroxymethyl-1-indanyl)-1,2,3,4-tetrahydropyrimidino-2,4-dione, 21.

A solution of **18** (32 mg; 0.124 mmol) and NIS (27 mg; 0.129 mmol) in acetic acid (10 mL) was stirred, under an argon atmosphere, for 36 h at room temperature. The acetic acid was removed under reduced pressure and the residue was dissolved in 0.5 M NaOH and neutralised with 0.5 M HCl. The material was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (11 g), using dichloromethane/methanol (25:1) as eluent, to give **21** as a colourless solid (25 mg; Yield 60%). M.p. 225-227ºC. IR (KBr): υ = 3505, 1681, 1492, 1443, 1327, 1261, 1025,

911, 756 cm^{-1}. ^{1}H NMR (DMSO): δ = 1.75-1.86 (dt, 1H, $J_{(t)}$ = 13.45 Hz, $J_{(d)}$ = 7.61 Hz, 2'β-H), 2.54-2.66 (dt, 1H, $J_{(t)}$ = 13.45 Hz, $J_{(d)}$ = 8.63 Hz, 2'α-H), 3.21-3.39 (m, 1H, 3'β-H), 3.70 (b.s., 2H, C$\underline{H_2}$OH), 4.75 (s, 1H, OH exchangeable with D_2O), 5.87-5.93 (t, 1H, $J_{(t)}$ = 8.07 Hz, 1'β-H), 7.06-7.09 (d, 1H, *J* = 7.25 Hz, ArH), 7.17-7.29 (m, 2H, ArH), 7.34-7.37 (d, 1H, *J* = 7.25 Hz, ArH), 7.61 (s, 1H, 6-H), 10.80 (s, 1H, NH exchangeable with D_2O). ^{13}C NMR (DMSO): δ = 35.08 (CH_2), 44.87 (CH), 59.21 (CH), 63.79 (CH_2), 69.49 (C), 124.20, 124.97, 127.75 and 128.85 (CH), 141.09 (C), 145.63 (C), 146.82 (CH), 151.43 (C), 160.98 (C). Anal. calcd. for $C_{14}H_{13}IN_2O_3$: C, 43.77; H, 3.41; N, 7.29. Found: C, 44.01; H, 3.59; N, 7.13.

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