Synthesis of New 1′(*N*)-Homocarbanucleosides Based on 1-Methylcyclopenta[*c*]pyrazole Scaffold

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Abstract: A series of 1′-homocarbanucleosides was prepared by coupling a purine or pyrimidine to, or constructing it on, a protected 1-methylcyclopenta[*c*]pyrazole pseudosugar synthesized from (±)-(*exo*,*exo*)-1-methyl-4,5,6,7-tetrahydro-4,7-methanoindazole-5,6-diol by oxidative cleavage of the starting glycol, reduction of the resulting dialdehyde with $NaBH_4$, and the protective monosilylation of the bis(hydroxymethyl) reduction product.

Key words: methanoindazoles, 1′(*N*)-homocarbanucleosides, nucleoside analogues, methylcyclopenta[*c*]pyrazol, glycol cleavage, silyl ethers

Nucleoside analogues in which the furanose ring has been replaced by carbocyclic or non-furanose heterocyclic systems are of interest because of their biological actions. Carbocyclic nucleoside analogues (carbanucleosides, or CANs)[1] are classified as nucleoside reverse transcriptase inhibitors,[2] and certain members of this family are clinically important antiviral agents, particularly for use against HIV infection. Furthermore, the CAN family appears to offer sufficient variety to allow solution to current limitations due to low polymerase selectivity and the susceptibility of glycoside linkages to enzymatic hydrolysis. For example, in 1′(*N*)-homocarbanucleosides increased resistance to enzymatic degradation has been sought by inclusion of a methylene group between the heterocyclic base and C1 of the pseudosugar moiety.[3]

To explore the dependence of the biological activity of CANs on their structural characteristics and liposolubility (enhancing liposolubility facilitates access to the central nervous system, an important reservoir of HIV[4]), our research group has in recent years prepared a number of trimethylcyclopentyl 1′(*N*)-homocarbanucleosides (**1**, **2**; Figure 1),[5–7] and also a series of cyclopentenyl 1′(*N*)-homocarbanucleosides in which the cyclopentene ring is incorporated in an indan system (**3**).[8–10] Some of these compounds have shown considerable cytostatic activity.[8]

With a view to further modify the lipophilicity and polar interactions while retaining the structural rigidity of the pseudosugar, we have also prepared analogues of **3** in which the benzene ring of indan is replaced by a heterocycle.[11–14] Preliminary tests of these compounds have shown certain purinylmethyl derivatives of a 2-benzyl cyclopenta[*c*]pyrazole to be highly active against varicella-zoster virus and cytomegalovirus at subtoxic concentrations.[14] Here we report a more efficient synthesis of purinylmethyl and pyrimidinylmethyl derivatives of an analogous 1-substituted cyclopenta[*c*]pyrazole.

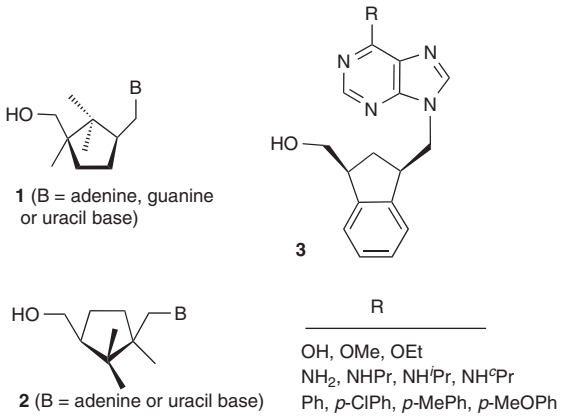

Figure 1

Key intermediate **5** was prepared from (±)-(*exo*,*exo*)-1-methyl-4,5,6,7-tetrahydro-4,7-methanoindazole-5,6-diol (**4**)[12] by oxidative cleavage with sodium periodate and silica gel, followed immediately by reduction of the resulting crude dialdehyde with $NaBH_4$ in MeOH (Scheme 1). The desired monoprotected derivatives **6** and **7** were obtained by treating **5** with NaH and TBDPSCl under conditions similar to those described by McDougal for monoprotection with TBDMSCl.[15] Clean separation of **6** (58%) and **7** (25%) was achieved via chromatography, and a small proportion of unreacted **5** was recovered.

Although the popular Mitsunobu condensation reaction[16] is often used for direct coupling of heterocyclic bases to primary alcohols, it requires laborious subsequent work-up[17] and in our experience has failed to couple certain alcohols similar to **6** or **7**.[14] In order to couple purines to compound **6**, we accordingly opted in the first instance for an indirect approach via its mesylate **8**, which was obtained in almost quantitative yield by treatment of **6** with methanesulfonyl chloride, Et_3N and DMAP (Scheme 1).

Reaction of crude **8** with adenine in DMF in the presence of NaH[18] gave the displacement product **9a** in 41% yield, and the desired deprotected product **9b** was then obtained by treating a THF solution of **9a** with TBAF (1 M in THF) for one hour. Similarly, reaction of **8** with 2-amino-6-

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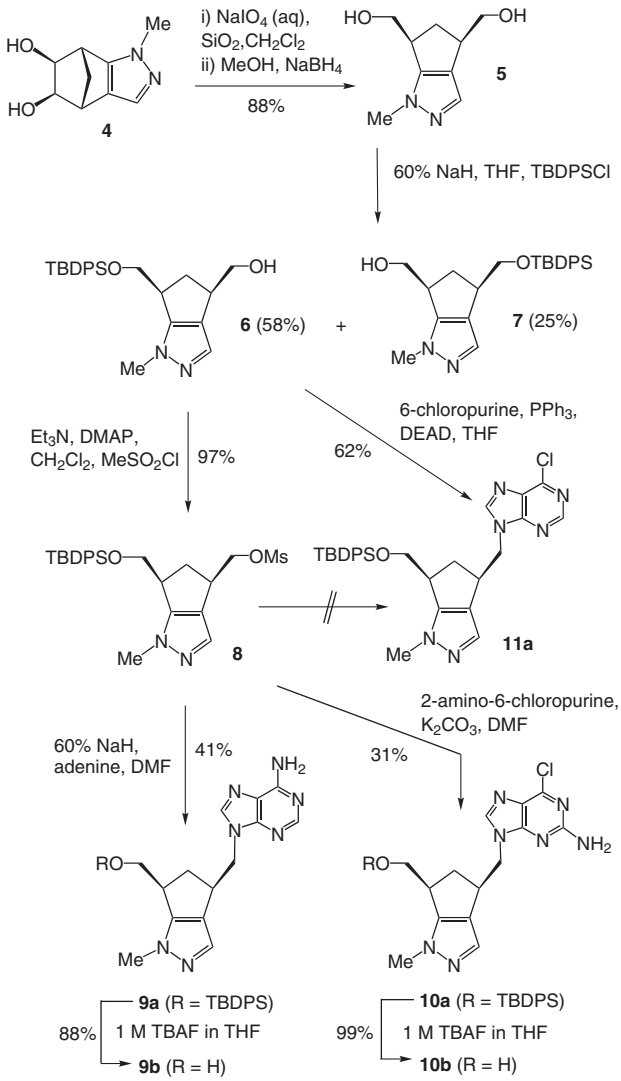


Scheme 1

chloropurine afforded **10a**, from which **10b** was obtained by unproblematic desilylation. However, an attempt to couple **8** to 6-chloropurine produced a complex mixture in which the desired displacement product **11a** was not obtained. In this case, a standard Mitsunobu reaction[19] between 6-chloropurine and **6** afforded **11a** with an estimated overall yield of 62%; 45% as a pure **11a** fraction obtained by repeated chromatography and the remainder as an unresolved fraction shown by its ^{1}H NMR spectrum to be a 2.5:1 mixture of **11a** and triphenylphosphine oxide.

Figure 2[20] shows an ORTEP representation of the asymmetric unit of adenine derivative **9b**. Note that the position of the hydroxyl group linked to the C19 has some degree of indeterminacy, as has that of the molecule of water of crystallization, the H atoms of which could not be refined. While the disorder of these atoms prevents complete elucidation of intermolecular interactions, the connectivity and *cis*-configuration of adenine **9b** is nevertheless unequivocally established. This structural information also

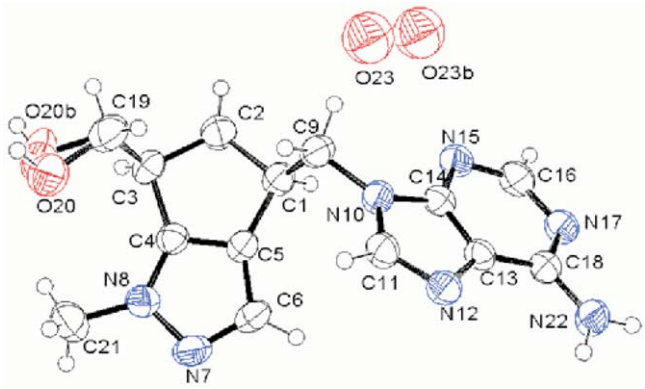


Figure 2 ORTEP projection of the molecular structure of compound **9b**, showing atomic numbering sheme.

determined the configurations of purine derivatives **9a** and **10**.

Compound **11a** was also prepared by construction of the base on protected aminoalcohol **13**,[21] which was obtained from mesylate **8** by treatment with NaN_3 and reduction of the resulting azide, **12** (Scheme 2). Condensation of **13** with 5-amino-4,6-dichloropyrimidine afforded diamine **14**, and cyclization of the latter with triethyl orthoformate gave **11a** in 34% overall yield from **6**. Desilylation of **11a** gave a 66% yield of the unprotected carbanucleoside. By contrast, desilylation of compound **15a**, obtained in 97% yield by refluxing **11a** with cyclopropylamine, afforded a 94% yield of **15b**.

Finally, uracil was constructed on the protected aminoalcohol **13** by condensation with 3-methoxy-2-propenoyl isocyanate[22] and cyclization of the resulting urea, **16**, with NH_4OH. Deprotection of the resulting uracil derivative, **17a**, afforded the desired carbanucleoside **17b**, the structure of which was unequivocally determined by single-crystal X-ray crystallography (Figure 3 shows one of the enantiomers present in the racemic crystal).[20] This structural information also determined the configurations of **11**, **15** and **16**.

The above-described syntheses of purine and pyrimidine 1′(*N*)-homocarbanucleosides with 1-methylcyclopenta[*c*]pyrazole scaffold are practical and should be extend-

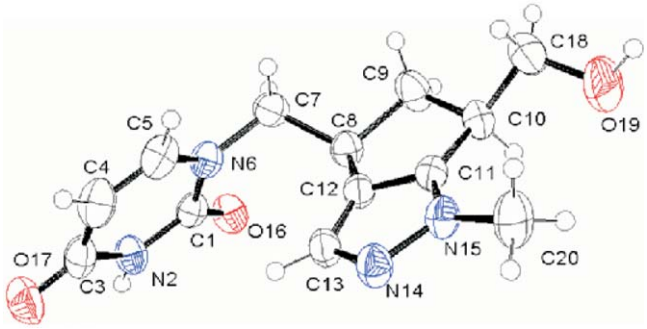
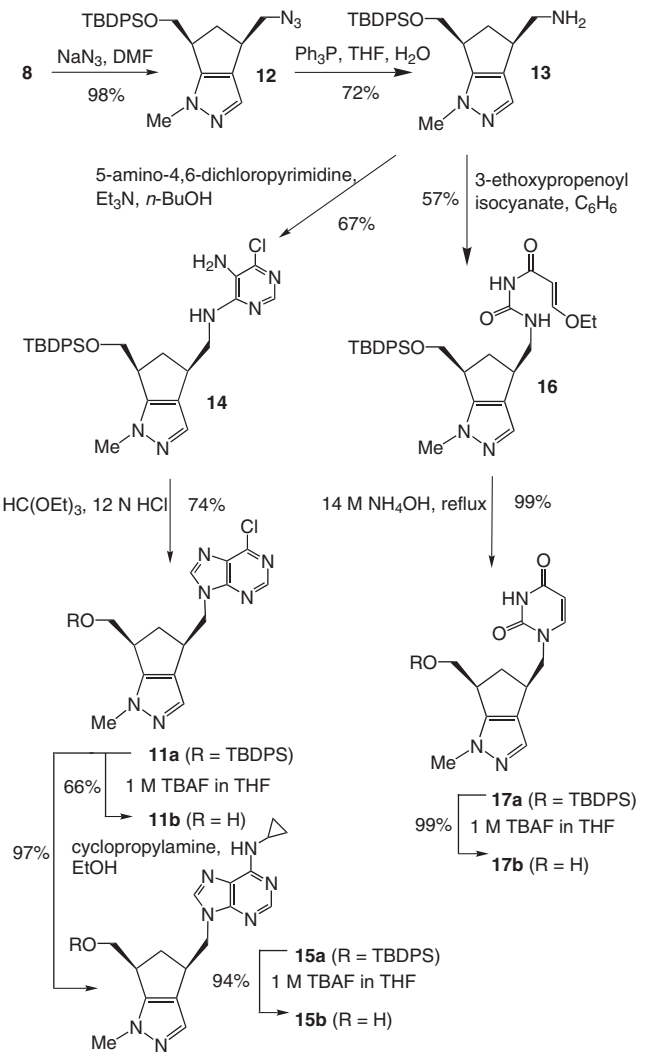


Figure 3 ORTEP projection of the molecular structure of compound **17b**, showing atomic numbering scheme.



Scheme 2

able to the preparation of a variety of other nucleoside analogues. The stereochemistry of the new compounds and intermediates was confirmed by X-ray crystallographic determination of the structure of two of the end products.

All chemicals used were of reagent grade and were obtained from Aldrich Chemical Co and used without further purification. Melting points were measured with a Reichert Kofler Thermopan and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1640 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 300 spectrometer at 300 MHz and 75.47 MHz, respectively, using TMS as internal standard (chemical shifts in δ values, *J* in Hz). Mass spectra were recorded on a Kratos MS-59 spectrometer. Microanalyses were performed on a Perkin-Elmer 240B Elemental Analyser at the University of Santiago Microanalysis Service; all results shown are within ± 0.4% of the theoretical values. All air-sensitive reactions were carried out under Ar. Flash chromatography was performed on silica gel (Merck 60, 230–240 mesh) and analytical TLC on pre-coated silica gel plates (Merck 60 F_{254}, 0.25 mm). X-ray diffraction data were collected on an Enraf-Nonius CAD4 automatic diffractometer using the program CAD4-EXPRESS.

(±)-*cis*-1-Methylcyclopenta[*c*]pyrazol-4,6-dimethanol (5)

A 0.65 M aqueous solution of $NaIO_4$ (1.42 mL, 0.92 mmol) was added dropwise to a vigorously stirred suspension of chromatography grade silica gel (1.42 g) in CH_2Cl_2 (15 mL). After addition of compound **4** (0.36 g, 2 mmol) in CH_2Cl_2 (10 mL) to the resulting flaky suspension, stirring was continued for another 5 min and the solution was then passed through a filter pad onto a small quantity of Na_2SO_4; the retained silica gel was washed with CH_2Cl_2 (50 mL) and the washings were pooled with the filtrate. Removal of the solvent left the dialdehyde as an oily reddish residue, which was dissolved in MeOH (25 mL). $NaBH_4$ (0.45 g, 10 mmol) was added in a single portion, stirring was continued for 30 min, the reaction was cooled in an ice bath and water (10 mL) was added. MeOH was removed under reduced pressure, and the residue left was dissolved in NH_4Cl (25 mL). This solution was extracted with EtOAc (3 × 50 mL), and removal of the solvent from the pooled extracts under reduced pressure afforded a white solid (0.9 g) that was further purified by chromatography on silica gel using CH_2Cl_2–MeOH (5:1) as eluent.

Compound 5

Yield: 0.15 g (88%); white solid. An analytical sample was obtained by repeatedly washing a small quantity of **5** with Et_2O and EtOAc; mp 111–112 °C.

IR (KBr): 3332, 3149, 2937, 2910, 2863, 1522, 1473, 1438, 1378, 1336, 1313, 1067, 1029, 1002, 793, 750 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 7.03 (s, 1 H, 3-H), 4.93 (t, *J* = 5.1 Hz, 1 H, D_2O exchange, OH), 4.64 (t, *J* = 5.1 Hz, 1 H, D_2O exchange, OH), 3.72 (s, 3 H, NCH_3), 3.55–3.50 (m, 1 H, OC*H*H), 3.49–3.44 (m, 1 H, OCH*H*), 3.41–3.37 (m, 1 H, OC*H*H), 3.31–3.28 (m, 1 H, OCH*H*), 3.14–3.05 (m, 1 H), 2.94–2.85 (m, 1 H), 2.64 (dt, *J* = 13.5, 8.7 Hz, 1 H, 5-*H*H), 1.89 (dt, *J* = 13.5, 4.2 Hz, 1 H, 5-H*H*).

^{13}C NMR [DEPT (DMSO-d_6)]: δ = 150.83 (C), 132.45 (CH), 128.23 (C), 66.68 (CH_2), 64.96 (CH_2), 39.68 (CH), 38.87 (CH), 38.00 (CH_2), 37.65 (CH_3).

EI–MS: *m*/*z* (%) = 182 (13) [M], 152 (11), 151 (100), 137 (9), 133 (19), 123 (20), 121 (11), 119 (7), 95 (13), 92 (9), 66 (8), 65 (7), 52 (6).

Anal. Calcd for $C_9H_{14}N_2O_2$ (182.22): C, 59.32; H, 7.74; N, 15.37. Found: C, 59.54; H, 7.90; N, 15.24.

(±)-*cis*-6-(*tert*-Butyldiphenylsilyloxymethyl)-1-methylcyclopenta[*c*]pyrazol-4-methanol (6) and (±)-*cis*-4-(*tert*-Butyldiphenylsilyloxymethyl)-1-methylcyclopenta[*c*]pyrazol-6-methanol (7)

NaH (60%, 0.40 g, 9.78 mmol) was added in one portion under Ar to a solution of **5** (1.62 g, 8.89 mmol) in THF (350 mL) at 0 °C. The resulting suspension was stirred at 0 °C for 10 min, after which a mixture of TBDPSCl (2.53, 9.78 mmol) and THF (150 mL) was added dropwise over 1.5 h. After stirring at r.t. for 6 h, this reaction mixture was partitioned between sat. $NaHCO_3$ solution (150 mL) and EtOAc (150 mL). The aqueous phase was extracted with EtOAc (2 × 150 mL), and the organic phases were dried over Na_2SO_4. Removal of the solvent under reduced pressure left an oily residue (4.35 g) that was fractionated by column chromatography on silica gel with hexane–EtOAc (2:1), hexane–EtOAc (1:2) and CH_2Cl_2–MeOH (5:1) as successive eluents. The monosilylated compounds **6** and **7** were obtained from hexane–EtOAc fractions (2:1 and 1:2), and unreacted diol **5** (0.17 g, 10%) from CH_2Cl_2–MeOH (5:1).

Compound 6

Yield: 2.18 g (58%); transparent oil.

IR (film): 3335, 3071, 2931, 2858, 1522, 1472, 1438, 1428, 1388, 1112, 1073, 999, 823, 741 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.64–7.61 (m, 4 H), 7.46–7.36 (m, 6 H), 7.19 (s, 1 H, 3-H), 3.79 (dd, *J* = 9.9, 6.8 Hz, 1 H), 3.73–3.69 (m, 1 H),

3.71 (s, 3 H, NCH_3), 3.59 (dd, *J* = 10.5, 6.6 Hz, 1 H), 3.53 (dd, *J* = 10.2, 6.5 Hz, 1 H), 3.28–3.21 (m, 1 H), 3.15–3.09 (m, 1 H), 2.80 (dt, *J* = 13.9, 8.9 Hz, 1 H, 5-*H*H), 2.04 (dt, *J* = 13.9, 4.4 Hz, 1 H, 5-H*H*), 1.74 (br s, 1 H, D_2O exchange, OH), 1.06 (s, 9 H, $3 \times CH_3$).

^{13}C NMR [DEPT ($CDCl_3$)]: δ = 150.55 (C), 135.59 (CH), 135.53 (CH), 133.29 (C), 133.15 (C), 132.80 (CH), 129.86 (CH), 129.83 (CH), 127.80 (CH), 127.77 (CH), 127.61 (C), 66.98 (CH_2), 66.96 (CH_2), 39.66 (CH), 38.58 (CH), 37.92 (CH_2), 37.57 (CH), 26.91 ($3 \times CH_3$), 19.20 (C).

FAB–MS: *m*/*z* (%) = 421.2 (100) [M + 1].

HRMS: *m*/*z* calcd for $C_{25}H_{32}N_2O_2Si$: 420.2233; found: 420.2251.

Compound 7
Yield: 0.93 g (25%); transparent oil.

IR (film): 3420, 3159, 3069, 2928, 2891, 2855, 1472, 1427, 1378, 1089, 1054, 1029, 999, 821, 805, 741 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.67–7.61 (m, 4 H), 7.42–7.33 (m, 6 H), 7.18 (s, 1 H, 3-H), 3.81 (s, 3 H, NCH_3), 3.73–3.66 (m, 2 H), 3.63–3.57 (m, 2 H), 3.23–3.17 (m, 2 H), 2.80 (dt, *J* = 13.8, 8.9 Hz, 1 H, 5-*H*H), 1.98 (dt, *J* = 13.8, 4.3 Hz, 1 H, 5-*H*H), 1.79 (br s, 1 H, D_2O exchange, OH), 1.07 (s, 9 H, $3 \times CH_3$).

^{13}C NMR [DEPT ($CDCl_3$)]: δ = 149.94 (C), 135.58 (CH), 135.52 (CH), 133.65 (C), 133.09 (C), 133.20 (CH), 129.56 (CH), 129.52 (CH), 127.57 (C), 127.55 (CH), 68.42 (CH_2), 65.79 (CH_2), 39.59 (CH), 38.62 (CH), 37.67 (CH_2), 37.65 (CH), 26.99 ($3 \times CH_3$), 19.38 (C).

HRMS: *m*/*z* calcd for $C_{25}H_{32}N_2O_2Si$: 420.2233; found: 420.2256.

(±)-*cis*-{6-(*tert*-Butyldiphenylsilyloxymethyl)-1-methylcyclopenta[*c*]pyrazol-4-yl}methyl Methanesulfonate (8)
Mesyl chloride (182 μL, 2.38 mmol) was added under Ar, with stirring, to a solution of **6** (0.66 g, 1.57 mmol), Et_3N (0.33 mL) and a catalytic amount of DMAP in anhyd CH_2Cl_2 (10 mL) at 0 °C. This solution was stirred at r.t. for 1 h and washed successively with sat. $NaHCO_3$ solution (2×30 mL), H_2O (2×30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4, and concentration under reduced pressure then afforded **8**.

Compound 8
Yield: 0.76 g (97%); transparent viscous oil.

IR (film): 3071, 2933, 2858, 1472, 1438, 1428, 1356, 1175, 1113, 952, 824, 743, 704 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.60–7.57 (m, 4 H), 7.46–7.35 (m, 6 H), 7.20 (s, 1 H, 3-H), 4.14–4.12 (m, 2 H), 3.79 (dd, *J* = 10.3, 6.6 Hz, 1 H), 3.73 (dd, *J* = 10.3, 5.1 Hz, 1 H), 3.68 (s, 3 H, NCH_3), 3.35 (ddd, *J* = 11.5, 7.2, 4.3 Hz, 1 H), 3.29–3.23 (m, 1 H), 2.97–2.83 (m, 1 H, 5-*H*H), 2.90 (s, 3 H, OCH_3), 2.08 (dt, *J* = 13.9, 4.5 Hz, 1 H 5-H*H*), 1.06 (s, 9 H, $3 \times CH_3$).

^{13}C NMR [DEPT ($CDCl_3$)]: δ = 149.97 (C), 135.43 (CH), 135.39 (CH), 132.99 (C), 132.83 (CH), 129.86 (CH), 129.82 (CH), 127.79 (CH), 127.76 (CH), 126.16 (C), 73.32 (CH_2), 66.39 (CH_2), 39.52 (CH), 37.98 (CH_2), 37.58 (CH), 37.36 (CH), 35.56 (CH), 26.99 ($3 \times CH_3$), 19.31 (C).

FAB–MS: *m*/z (%) = 499.2 (100) [M + 1].

HRMS: *m*/*z* calcd for $C_{26}H_{34}N_2O_4SSi$: 498.2009; found: 498.2034.

(±)-*cis*-4-[(6-Amino-9*H*-purin-9-yl)methyl]-6-(*tert*-butyldiphenylsilyloxymethyl)-1-methylcyclopenta[*c*]pyrazole (9a)
A suspension of adenine (0.11 g, 0.82 mmol) and 60% NaH (26 mg, 0.82 mmol) in anhyd DMF (15 mL) was heated at 80 °C under Ar, with stirring for 45 min. After cooling to r.t., a solution of **8** (0.32 g, 0.64 mmol) in anhyd DMF (10 mL) was added via a cannula and this mixture was heated at 80 °C for 48 h. The solvent was then removed under reduced pressure and the crude residue was taken up in NH_4Cl (50 mL). The resulting solution was extracted with CH_2Cl_2 (3×100 mL), the pooled extract was dried over Na_2SO_4, and concentration under reduced pressure then afforded a yellow oil (0.30 g) that was chromatographed on a column of silica gel using CH_2Cl_2–MeOH (40:1) as eluent.

Compound 9a
Yield: 0.14 g (41%); white solid; mp 218–220 °C.

IR (KBr): 3251, 3141, 2960, 2934, 2897, 1676, 1604, 1572, 1470, 1441, 1427, 1412, 1326, 1306, 1240, 1034, 747, 707, 696, 690 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.34 (s, 1 H, 2_{purine}-H), 7.60–7.56 (m, 4 H), 7.53 (s, 1 H, 8_{purine}-H), 7.47–7.37 (m, 6 H), 6.79 (s, 1 H, 3-H), 5.69 (br s, 2 H, D_2O exchange, NH_2), 4.27 (dd, *J* = 13.5, 6.4 Hz, 1 H, NC*H*H), 4.06 (dd, *J* = 13.5, 8.5 Hz, 1 H, NCH*H*), 3.76–3.68 (m, 2 H), 3.67 (s, 3 H, NCH_3), 3.61–3.59 (m, 1 H), 3.25–3.22 (m, 1 H), 2.90–2.86 (m, 1 H, 5-H*H*), 2.08 (dt, *J* = 13.9, 4.2 Hz, 1 H, 5-*H*H), 1.06 (s, 9 H, $3 \times CH_3$).

^{13}C NMR [DEPT ($CDCl_3$)]: δ = 155.80 (C), 153.36 (CH), 150.40 (C), 141.22 (CH), 135.96 (CH), 135.92 (CH), 130.41 (CH), 130.36 (C), 128.31 (CH), 127.75 (C), 120.08 (C), 66.82 (CH_2), 50.07 (CH_2), 39.88 (CH), 39.31 (CH_2), 37.87 (CH), 36.55 (CH), 27.36 ($3 \times CH_3$), 19.66 (C).

EM–BAR: *m*/*z* (%) = 538.15 (58) [M].

Anal. Calcd for $C_{30}H_{35}N_7OSi$ (537.73): C, 67.01; H, 6.56; N, 18.23. Found: C, 67.32; H, 6.76; N, 18.52.

(±)-*cis*-4-[(2-Amino-6-chloro-9*H*-purin-9-yl)methyl]-6-(*tert*-butyldiphenylsilyloxymethyl)-1-methylcyclopenta[*c*]pyrazole (10a)
A mixture of crude **8** (0.4 g, 0.8 mmol), K_2CO_3 (0.16 g, 1.2 mmol) and 2-amino-6-chloropurine (0.2 g, 1.2 mmol) in anhyd DMF (25 mL) was heated for 24 h at 80 °C, after which the solvent was removed under reduced pressure and the resulting residue was dissolved in CH_2Cl_2 (100 mL). This solution was washed with water (50 mL), dried over Na_2SO_4 and concentrated to dryness. When the resulting solid residue (0.65 g) was chromatographed on silica gel with hexane–EtOAc (1:2) and hexane–EtOAc (1:3) as successive eluents, the initial fractions afforded unreacted **8** (0.22 g, 55%) and the product-bearing fractions **10a**.

Compound 10a
Yield: 0.14 g (31%); white solid; mp 79–81 °C.

IR (KBr): 3324, 3197, 2930, 2857, 1616, 1560, 1541, 1521, 1508, 1458, 1406, 1112, 703 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.61–7.56 (m, 4 H), 7.53 (s, 1 H, 8_{purine}-H), 7.45–7.36 (m, 6 H), 6.87 (s, 1 H, 3-H), 4.97 (br s, 2 H, D_2O exchange, NH_2), 4.13–4.10 (m, 1 H, NC*H*H), 4.02 (dd, *J* = 21.6, 13.7 Hz, 1 H, NC*H*H), 3.83 (dd, *J* = 10.3, 6.1 Hz, 1 H, OC*H*H), 3.69 (dd, *J* = 10.3, 5.6 Hz, 1 H, OC*H*H), 3.68 (s, 3 H, NCH_3), 3.67–3.49 (m, 1 H), 3.25–3.19 (m, 1 H), 2.84 (dt, *J* = 13.9, 8.9 Hz, 1 H, 5-*H*H), 2.08–2.02 (m, 1 H, 5-H*H*), 1.04 (s, 9 H, $3 \times CH_3$).

^{13}C NMR [DEPT ($CDCl_3$)]: δ = 158.94 (C), 153.82 (C), 151.34 (C), 149.95 (C), 142.49 (CH), 135.52 (CH), 135.48 (CH), 133.06 (C), 132.99 (C), 132.66 (CH), 130.03 (CH), 129.99 (CH), 127.92 (CH), 127.89 (CH), 127.09 (C), 125.28 (C), 66.36 (CH_2), 49.47 (CH_2), 39.43 (CH), 38.89 (CH_2), 37.45 (CH), 35.99 (CH), 26.94 ($3 \times CH_3$), 19.25 (C).

FAB–MS: *m*/*z* (%) = 572.2 (100) [M + 1].

Anal. Calcd for $C_{30}H_{34}ClN_7OSi$ (572.17): C, 67.97; H, 5.99; N, 17.14. Found: C, 68.22; H, 6.07; N, 17.31.

(±)-*cis*-{6-(*tert*-Butyldiphenylsilyloxymethyl)-1-methylcyclopenta[*c*]pyrazol-4-yl}methyl Azide (12)

NaN_3 (0.5 g, 7.85 mmol) was added in one portion to a solution of **8** (0.78 g, 1.56 mmol) in anhyd DMF (50 mL) stirred under Ar at r.t. This mixture was heated for 20 h at 90 °C, the DMF was removed under reduced pressure, and the residue was partitioned between water (150 mL) and Et_2O (100 mL). The aqueous phase was extracted with Et_2O (2 × 100 mL), and the pooled organic phases were washed with sat. NaCl solution (50 mL). Removal of the solvent afforded azide **12**.

Compound 12

Yield: 0.68 g (98%); faintly yellowish oil.

IR (film): 3071, 2932, 2858, 2097, 1472, 1438, 1428, 1264, 1113, 998, 823, 702, 689 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.65–7.58 (m, 4 H), 7.47–7.36 (m, 6 H), 7.22 (s, 1 H, 3-H), 3.90–3.84 (m, 1 H), 3.80 (dd, *J* = 10.2, 6.2 Hz, 1 H, N_3CHH), 3.72 (dd, *J* = 10.2, 5.9 Hz, 1 H, N_3CHH), 3.69 (s, 3 H, NCH_3), 3.32–3.23 (m, 2 H), 3.21–3.11 (m, 1 H), 2.91–2.84 (m, 1 H, 5-*H*H), 2.02 (t, *J* = 4.6 Hz, 1 H, 5-H*H*), 1.06 (s, 9 H, 3 × CH_3).

^{13}C NMR [DEPT ($CDCl_3$)]: δ = 150.22 (C), 135.99 (CH), 135.93 (CH), 133.44 (C), 133.30 (C), 130.33 (CH), 130.29 (CH), 128.26 (CH), 128.23 (CH), 66.91 (CH_2), 57.33 (CH_2), 40.03 (CH), 39.50 (CH_2), 37.91 (CH), 36.34 (CH), 27.23 (3 × CH_3), 19.62 (C).

FAB–MS: *m*/*z* (%) = 446.2 (100) [M + 1].

HRMS: *m*/*z* calcd for $C_{25}H_{31}N_5OSi$: 445.2298; found: 445.2309.

(±)-*cis*-6-(*tert*-Butyldiphenylsilyloxymethyl)-1-methylcyclopenta[*c*]pyrazol-4-methanamine (13)

Triphenylphosphine (0.84 g, 3.2 mmol) was added to a solution of **12** (0.68 g, 1.53 mmol) in THF–H_2O (25:1, 24 mL), and the mixture was refluxed for 6 h. The THF was removed under reduced pressure, and the oily residue was dissolved in CH_2Cl_2 (25 mL). This solution was dried over Na_2SO_4 and condensed to dryness, leaving a yellowish oil (1.56 g) that was chromatographed on silica gel using mixtures of CH_2Cl_2 and MeOH (20:1 and 1:1) as successive eluents. Removal of solvent from the first CH_2Cl_2–MeOH (1:1) fractions yielded amine **13**.

Compound 13

Yield: 0.46 g (72%); thick whitish oil.

IR (film): 3278, 3128, 3070, 2930, 2879, 2858, 1654, 1608, 1559, 1428, 1112, 703, 675 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.63–7.60 (m, 4 H), 7.44–7.35 (m, 6 H), 7.21 (s, 1 H, 3-H), 3.78 (dd, *J* = 10.1, 6.7 Hz, 1 H, H_2NCHH), 3.71 (s, 3 H, NCH_3), 3.69 (dd, *J* = 10.1, 5.9 Hz, 1 H, H_2NCHH), 3.25–3.16 (m, 3 H, 2 × D_2O exchange, NH_2), 3.05–2.96 (m, 1 H), 2.87–2.65 (m, 3 H), 1.97–1.89 (m, 1 H, 5-H*H*), 1.05 (s, 9 H, 3 × CH_3).

^{13}C NMR [DEPT ($CDCl_3$)]: δ = 150.52 (C), 135.98 (CH), 135.93 (CH), 133.65 (C), 133.52 (C), 133.05 (C), 130.28 (CH), 130.24 (CH), 129.06 (C), 128.22 (CH), 128.19 (CH), 67.37 (CH_2), 48.08 (CH_2), 40.14 (CH_2), 39.51 (CH), 39.18 (CH), 37.99 (CH), 27.31 (3 × CH_3), 19.60 (C).

FAB–MS: *m*/*z* (%) = 420.2 (100) [M + 1].

HRMS: *m*/*z* calcd for $C_{25}H_{33}N_3OSi$: 419.2393; found: 419.2419.

(±)-*cis*-*N*-[(5-Amino-6-chloropyrimidin-4-yl)-6-(*tert*-butyldiphenylsilyloxymethyl)]-1-methylcyclopenta[*c*]pyrazol-4-methanamine (14)

A solution of **13** (0.46 g, 1.1 mmol) and 5-amino-4,6-dichloropyrimidine (0.27 g, 1.95 mmol) in anhyd *n*-BuOH (20 mL) and anhyd Et_3N (1 mL) was refluxed under Ar for 24 h. Evaporation of the solvents under vacuum left a residue (1.0 g) that was purified by column chromatography on silica gel with hexane–EtOAc (1:1) as eluent.

Compound 14

Yield: 0.4 g (67%); white solid that was recrystallized twice from hexane–EtOAc (4:1); mp 120–122 °C.

IR (KBr): 3343, 3242, 3070, 3048, 2930, 2857, 1581, 1470, 1427, 1361, 1336, 1112, 823, 741, 703 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.02 (s, 1 H, $2_{pyrimidine}$-H), 7.61–7.58 (m, 4 H), 7.43–7.34 (m, 6 H), 7.17 (s, 1 H, 3-H), 5.07 (t, *J* = 5.4 Hz, D_2O exchange, 1 H, NH), 3.79 (dd, *J* = 10.1, 6.8 Hz, 1 H, NHC*H*H), 3.73–3.61 (m, 1 H), 3.72 (s, 3 H, NCH_3), 3.40–3.24 (m, 4 H, 2 × D_2O exchange, NH_2), 2.85 (dt, *J* = 13.9, 8.6 Hz, 1 H, 5-*H*H), 1.99 (dt, *J* = 13.9, 4.7 Hz, 1 H, 5-H*H*), 1.05 (s, 9 H, 3 × CH_3).

^{13}C NMR [DEPT ($CDCl_3$)]: δ = 155.73 (C), 150.87 (C), 150.18 (CH), 143.84 (C), 135.94 (CH), 135.91 (CH), 133.61 (C), 133.06 (C), 130.33 (CH), 130.30 (CH), 128.58 (C), 128.25 (CH), 128.23 (CH), 121.97 (C), 67.31 (CH_2), 47.0 (CH_2), 40.11 (CH), 39.32 (CH_2), 38.04 (CH), 35.96 (CH), 27.32 (3 × CH_3), 19.63 (C).

FAB–MS: *m*/*z* (%) = 547.2 [M] (100).

Anal. Calcd for $C_{29}H_{35}ClN_6OSi$ (547.17): C, 63.66; H, 6.45; N, 15.36. Found: C, 63.89; H, 6.66; N, 15.56.

(±)-*cis*-6-(*tert*-Butyldiphenylsilyloxymethyl)-4-[(6-chloro-9*H*-purin-9-yl)methyl]-1-methylcyclopenta[*c*]pyrazole (11a)

Method A: DEAD (0.87 mL, 1.9 mmol) was added dropwise under Ar to a solution of **6** (0.44 g, 0.95 mmol), triphenylphosphine (0.50 g, 1.91 mmol) and 6-chloropurine (0.29 g, 1.91 mmol) in anhyd THF (30 mL), and the mixture was stirred for 24 h at r.t. Removal of the solvents under reduced pressure left a yellow oil (1.72 g) that when chromatographed on silica gel with mixtures of hexane and EtOAc (1:2, 1:3 and 1:4) as successive eluents afforded a mixture of **11a** and triphenylphosphine oxide. Chromatography of this mixture was performed on silica gel with mixtures of CH_2Cl_2 and MeOH (150:1 and 40:1) as successive eluents.

Compound 11a

Yield: 0.26 g (45%); white solid; mp 104–106 °C after washing with pentane.

IR (KBr): 3070, 2930, 2856, 1590, 1559, 1427, 1401, 1332, 1112, 938, 703 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.71 (s, 1 H, 2_{purine}-H), 7.83 (s, 1 H, 8_{purine}-H), 7.59–7.55 (m, 4 H), 7.46–7.36 (m, 6 H), 6.78 (s, 1 H, 3-H), 4.35 (dd, *J* = 13.6, 6.7 Hz, 1 H, NC*H*H), 4.18 (dd, *J* = 13.6, 8.3 Hz, 1 H, NCH*H*), 3.80 (dd, *J* = 10.3, 5.8 Hz, 1 H, OC*H*H), 3.71 (dd, *J* = 10.3, 5.5 Hz, 1 H, OC*H*H), 3.65 (s, 3 H, NCH_3), 3.61–3.58 (m, 1 H), 3.27–3.23 (m, 1 H), 2.90 (dt, *J* = 13.9, 8.7 Hz, 1 H, 5-*H*H), 2.12 (dt, *J* = 13.9, 4.3 Hz, 1 H, 5-H*H*), 1.07 (s, 9 H, 3 × CH_3).

^{13}C NMR [DEPT ($CDCl_3$)]: δ = 152.33 (CH), 151.54 (C), 150.31 (C), 145.73 (CH), 135.93 (CH), 135.90 (CH), 133.4 (C), 132.93 (C), 132.0 (C), 130.47 (CH), 130.44 CH), 128.32 (CH), 127.29 (C), 66.62 (CH_2), 50.48 (CH_2), 39.81 (CH), 39.37 (CH_2), 37.83 (CH), 36.53 (CH), 27.37 (3 × CH_3), 19.70 (C).

FAB–MS: *m*/*z* (%) = 557.3 (82) [M + 1].

Anal. Calcd for $C_{30}H_{33}ClN_6OSi$ (557.16): C, 64.67; H, 5.97; N, 15.08. Found: C, 64.92; H, 6.12; N, 15.34.

Method B: A mixture of **14** (0.4 g, 0.73 mmol), triethyl orthoformate (4.1 mL, 39.20 mmol) and 12 N HCl (0.25 mL) was stirred at r.t. for 24 h and then concentrated under vacuum to obtain a residue that was treated with 0.5 N HCl (15 mL) and THF (5 mL) for 2 h at r.t. The resulting solution was brought to pH 7 with 1 N NaOH, and evaporation of the solvents under reduced pressure left a solid residue (1.28 g) that upon purification by column chromatography on

silica gel using hexane–EtOAc (1:3) as eluent afforded **11a** as a white solid (0.30 g, 74%).

(±)-*cis*-9-{[6-(*tert*-Butyldiphenylsilyloxymethyl)-1-methylcyclopenta[*c*]pyrazol-4-yl]methyl}-6*N*-cyclopropyl-9*H*-purin-6-amine (15a)

Cyclopropylamine (0.12 g, 0.2 mL, 2.88 mmol) was added to a stirred solution of chloropurine **11a** (0.12 g, 0.22 mmol) in EtOH (3 mL). The mixture was refluxed for 6 h, and after cooling to r.t., the solvent was evaporated under reduced pressure. Chromatography of the solid residue (0.14 g) was performed on silica gel using hexane–EtOAc (1:5) and CH_2Cl_2–MeOH (10:1) as successive eluents.

Compound 15a

Yield: 0.12 g (97%); a white, waxy solid.

IR (KBr): 3261, 2930, 2856, 1617, 1475, 1427, 1354, 1297, 1112, 703 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.47 (s, 1 H, 2_{purine}-H), 7.59–7.57 (m, 4 H), 7.48 (s, 1 H, 8_{purine}-H), 7.45–7.36 (m, 6 H), 6.77 (s, 1 H, 3-H), 5.93 (br, 1 H, D_2O exchange, NH), 4.26 (dd, *J* = 13.5, 6.3 Hz, 1 H, NC*H*H), 4.04 (dd, *J* = 13.5, 8.5 Hz, 1 H, NCH*H*), 3.74–3.70 (m, 2 H), 3.65 (s, 3 H, NCH_3), 3.61–3.53 (m, 1 H), 3.28–3.17 (m, 1 H), 3.06–3.03 (m, 1 H), 2.88 (dt, *J* = 13.9, 8.7 Hz, 1 H, 5-*H*H), 2.07 (dt, *J* = 13.9, 4.2 Hz, 1 H, 5-H*H*), 1.06 (s, 9 H, 3 × CH_3), 0.99–0.88 (m, 2 H, cyclopropyl), 0.69–0.64 (m, 2 H, cyclopropyl).

^{13}C NMR [DEPT ($CDCl_3$)]: δ = 156.18 (C), 153.59 (CH), 150.41 (C), 140.58 (CH), 135.96 (CH), 135.91 (CH), 133.52 (C), 133.42 (C), 133.17 (CH), 130.40 (CH), 130.34 (CH), 128.30 (CH), 128.28 (CH), 127.81 (C), 120.33 (C), 66.85 (CH_2), 50.03 (CH_2), 39.89 (CH), 39.30 (CH_2), 37.88 (CH), 36.57 (CH), 27.36 (3 × CH_3), 24.10 (CH), 19.66 (C), 7.79 (CH_2), 7.76 (CH_2).

EM: *m*/*z* (%) = 578 (3), 577 (6) [M], 520 (5), 519 (12), 404 (7), 403 (20), 347 (9), 346 (32), 345 (100), 199 (8), 197 (4), 183 (6).

HRMS: *m*/*z* calcd for $C_{33}H_{39}N_7OSi$: 577.2985; found: 577.3006.

(±)-*cis*-1-{[6-(*tert*-Butyldiphenylsilyloxymethyl)-1-methylcyclopenta[*c*]pyrazol-4-yl]methyl}-3-(3-ethoxypropenoyl)urea (16)

Silver cyanate (12.0 g, 80 mmol), previously dried at 100 °C under vacuum over P_2O_5, was added to anhyd benzene (80 mL) in the dark under Ar, and the suspension was refluxed with vigorous stirring for 0.5 h. A solution of 3-ethoxypropenoyl chloride (4.82 g, 40 mmol) in anhyd benzene (15 mL) was then added dropwise, and the resulting suspension was refluxed for a further 0.5 h with vigorous stirring and then allowed to settle at r.t. for 3 h. A sample of the supernatant (8.53 mL, theoretically containing 5.97 mmol of 3-ethoxypropenoyl isocyanate) was transferred to a dry dropping funnel and added dropwise to a solution of **13** (0.50 g, 1.19 mmol) in anhyd DMF (10 mL) at –25 °C. The mixture was allowed to warm to r.t. over 1 h, stirred overnight at r.t., and concentrated under reduced pressure (oil pump) at a temperature below 40 °C by driving off the solvent by repeated co-evaporation with toluene (3 × 10 mL) and EtOH (3 × 10 mL). The residue (1.3 g) was chromatographed on silica gel with hexane–EtOAc (1:1 and 1:2) as successive eluents, and the product-bearing fractions were pooled to obtain **16**.

Compound 16

Yield: 0.38 g (57%); greenish solid, a sample of which was washed with pentane resulting in a white solid of low mp.

IR (KBr): 2931, 1705, 1677, 1616, 1551, 1243, 1167, 1112, 703 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.76 (br s, 1 H, D_2O exchange, CONHCO), 8.23 (br s, 1 H, D_2O exchange, CON*H*CH_2), 7.65–60 (m, 5 H), 7.46–7.35 (m, 6 H), 5.22 (d, *J* = 12.2 Hz, 1 H, COCH), 3.95 (q, *J* = 7.1 Hz, 2 H, CH_3CH_2), 3.78 (dd, *J* = 10.1, 6.9 Hz, 1 H, OC*H*H), 3.72–3.67 (m, 1 H, OCH*H*), 3.71 (s, 3 H, NCH_3), 3.69–3.67 (m, 1 H), 3.42–3.32 (m, 1 H), 3.28–3.16 (m, 3 H), 2.83 (dt, *J* = 13.7, 8.4 Hz, 1 H, 5-*H*H), 1.92 (dt, *J* = 13.7, 4.6 Hz, 1 H, 5-H*H*), 1.34 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.05 (s, 9 H, 3 × CH_3).

^{13}C NMR [DEPT ($CDCl_3$)]: δ = 167.96 (C), 163.47 (CH), 154.85 (C), 150.43 (C), 135.97 (CH), 135.92 (CH), 133.65 (C), 133.50 (C), 133.20 (CH), 130.27 (CH), 128.83 (C), 128.23 (CH), 128.20 (CH), 98.19 (CH), 68.13 (CH_2), 67.33 (CH_2), 46.04 (CH_2), 40.19 (CH), 39.59 (CH_2), 38.01 (CH), 36.33 (CH), 27.31 (3 × CH_3), 19.61 (C), 14.93 (CH).

FAB–MS: *m*/*z* (%) = 561.4 (100) [M + 1].

HRMS: *m*/*z* calcd for $C_{31}H_{40}N_4O_4Si$: 560.2819; found: 560.2832.

(±)-*cis*-1-{[6-(*tert*-Butyldiphenylsilyloxymethyl)-1-methylcyclopenta[*c*]pyrazol-4-yl]methyl}-1,2,3,4-tetrahydropyrimidine-2,4-dione (17a)

A solution of **16** (0.20 g, 0.36 mmol) in a mixture of 14 M NH_4OH (20 mL) and dioxane (5 mL) was refluxed for 48 h, after which removal of the solvents left a brown solid (0.20 g) that was partitioned between NH_4Cl (50 mL) and CH_2Cl_2 (100 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL), and the organic phases were dried over Na_2SO_4. Removal of the solvent left a residue that when chromatographed on silica gel with hexane–EtOAc (1:4) as eluent yielded the pure product.

Compound 17a

Yield: 0.18 g (99%); white solid. An analytical sample was obtained by washing a small quantity of this solid with pentane; mp 78–80 °C.

IR (KBr): 3447, 3049, 2930, 2856, 1684, 1458, 1427, 1388, 1112, 704 cm^{-1}.

^1H NMR [DEPT ($CDCl_3$)]: δ = 9.14 (s, 1 H, D_2O exchange, $2_{pyrimidine}$-H), 7.59–7.54 (m, 4 H), 7.47–7.35 (m, 6 H), 7.0 (s, 1 H, 3-H), 6.79 (d, *J* = 7.9 Hz, 1 H, $6_{pyrimidine}$-H), 5.56 (dd, *J* = 7.9, 2.04 Hz, 1 H, $5_{pyrimidine}$-H), 3.99 (dd, *J* = 12.9, 5.5 Hz, 1 H, NC*H*H), 3.85–3.75 (m, 1 H), 3.80 (dd, *J* = 5.8, 3.5 Hz, 1 H, OC*H*H), 3.69 (s, 3 H, CH_3), 3.45–3.37 (m, 1 H, OCH*H*), 3.30–3.21 (m, 2 H), 2.90 (dt, *J* = 13.9, 8.7 Hz, 1 H, 5-*H*H), 1.99 (dt, *J* = 13.9, 4.2 Hz, 1 H, 5-H*H*), 1.07 (s, 9 H, 3 × CH_3).

^{13}C NMR [DEPT ($CDCl_3$)]: δ = 163.96 (C) 151.18 (C), 150.38 (C), 145.78 (CH), 135.93 (CH), 135.89 (CH), 133.43 (CH), 130.44 (CH), 130.39 (CH), 128.32 (CH), 128.30 (CH), 127.94 (C), 101,67 (CH), 66.75 (CH_2), 55.38 (CH_2), 39.77 (CH), 39.10 (CH_2), 37.84 (CH), 35.25 (CH), 27.37 (3 × CH_3), 19.91 (C).

FAB–MS: *m*/*z* (%) = 515.27 (16) [M + 1].

Anal. Calcd for $C_{29}H_{34}N_4O_3Si$ (514.69): C, 67.67; H, 6.66; N, 10.89. Found: C, 67.89; H, 6.78; N, 11.09.

Cleavage of the *tert*-Butyldiphenylsilyl Group from Compounds 9a–11a, 15a, and 17a; General Procedure

A 1 M solution of TBAF in THF (1.1 mmol) was added under Ar to a stirred solution of the compound to be deprotected (1 mmol) in anhyd THF (10 mL) in an ice bath. This mixture was allowed to reach r.t., and stirring was continued for 1 h, after which the solvent was removed under reduced pressure and the residue so obtained was chromatographed on silica gel with an appropriate eluent. Finally, product-bearing fractions were concentrated to dryness.

(±)-*cis*-4-[(6-Amino-9*H*-purin-9-yl)methyl]-1-methylcyclopenta[*c*]pyrazol-6-methanol (9b)

Eluent: CH_2Cl_2–MeOH (20:1). Yield: 86%; white solid; mp 262.5–264 °C.

IR (KBr): 3143, 1670, 1643, 1603, 1573, 1474, 1448, 1416, 1304, 1247, 1068, 1009, 721 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 8.12 (s, 1 H, 2_{purine}-H), 8.05 (s, 1 H, 8_{purine}-H), 7.19 (br s, 2 H, D_2O exchange, NH_2), 6.60 (s, 1 H, 3-H), 5.0 (t, *J* = 5.03 Hz, 1 H, D_2O exchange, OH), 4.18 (d, *J* = 7.4 Hz, 2 H, NCH_2), 3.73 (s, 3 H, NCH_3), 3.59–3.35 (m, 3 H), 3.15–3.11 (m, 1 H), 2.69 (dt, *J* = 13.7, 8.7 Hz, 1 H, 5-*H*H), 1.95 (dt, *J* = 13.7, 4.3 Hz, 1 H, 5-H*H*).

^{13}C NMR [DEPT (DMSO-d_6)]: δ = 156.33 (C), 152.75 (CH), 150.98 (C), 149.98 (C), 141.28 (CH), 131.97 (CH), 127.09 (C), 119.05 (C), 64.35 (CH_2), 48.88 (CH_2), 39.65 (CH), 38.5 (CH_2), 37.67 (CH), 36.1 (CH).

FAB–MS: *m*/*z* (%) = 300.2 [M + 1] (40).

Anal. Calcd for $C_{14}H_{17}N_7O$ (299.33): C, 56.18; H, 5.72; N, 32.76. Found: C, 56.42; H, 5.97; N, 33.03.

(±)-*cis*-4-[(2-Amino-6-chloro-9*H*-purin-9-yl)methyl]-1-methylcyclopenta[*c*]pyrazol-6-methanol (10b)

Eluents: CH_2Cl_2–MeOH (60:1, 40:1, 20:1). Yield: 99%; white solid washed with Et_2O–pentane; mp 185–187 °C.

IR (KBr): 3364, 2993, 2934, 1617, 1585, 1562, 1537, 1520, 1496, 1467, 1428, 1407, 1162, 1002, 914 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 8.23 (s, 1 H, 8_{purine}-H), 6.91 (br s, 2 H, D_2O exchange, NH_2), 6.63 (s, 1 H, 3-H), 5.0 (t, *J* = 5.0 Hz, 1 H, D_2O exchange, OH), 4.10 (dd, *J* = 7.2 Hz, 2 H, NCH_2), 3.72 (s, 3 H, NCH_3), 3.60–3.52 (m, 1 H, OC*H*H), 3.52–3.42 (m, 2 H), 3.19–3.12 (m, 1 H), 2.70 (dt, *J* = 13.7, 8.7 Hz, 1 H, 5-*H*H), 1.94 (dt, *J* = 13.7, 4.5 Hz, 1 H, 5-H*H*).

^{13}C NMR [DEPT (DMSO-d_6)]: δ = 160.13 (C), 154.53 (C), 150.95 (C), 149.72 (C), 143.74 (CH), 131.98 (CH), 126.92 (C), 123.63 (C), 64.18 (CH_2), 48.97 (CH_2), 39.62 (CH), 38.50 (CH_2), 37.67 (CH), 35.58 (CH).

FAB–MS: *m*/*z* (%) = 334.1 (50) [M + 1].

Anal. Calcd for $C_{14}H_{16}ClN_7O$ (333.77): C, 50.38; H, 4.83; N, 29.38. Found: C, 50.67; H, 4.99; N, 29.56.

(±)-*cis*-4-[(6-Chloro-9*H*-purin-9-yl)methyl]-1-methylcyclopenta[*c*]pyrazol-6-methanol (11b)

Purification required serial chromatography on three columns with the following eluents: first column, CH_2Cl_2–MeOH (30:1); second column, CH_2Cl_2–MeOH (15:1, 10:1 and 5:1); third column, EtOAc–MeOH (15:1). Yield: 66%; white solid recrystallized from acetone–hexane; mp 133–134 °C.

IR (KBr): 3261, 2932, 1592, 1577, 1562, 1443, 1403, 1337, 1217, 1178, 1018, 940 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.74 (s, 1 H, 2_{purine}-H), 8.05 (s, 1 H, 8_{purine}-H), 6.87 (s, 1 H, 3-H), 4.5 (dd, *J* = 13.8, 7.7 Hz, 1 H, NC*H*H), 4.38 (dd, *J* = 13.8, 7.2 Hz, 1 H, NCH*H*), 3.88–3.84 (m, 1 H), 3.81 (s, 3 H, NCH_3), 3.72–3.67 (m, 1 H), 3.64–3.56 (m, 1 H), 3.30–3.25 (m, 1 H), 3.05 (br s, 1 H, D_2O exchange), 2.92 (dt, *J* = 14.0, 9.0 Hz, 1 H, 5-*H*H), 2.08 (dt, *J* = 14.0, 3.2 Hz, 1 H, 5-H*H*).

^{13}C NMR [DEPT ($CDCl_3$)]: δ = 152.33 (CH), 151.74 (C), 150.44 (C), 145.92 (CH), 132.9 (CH), 131.97 (CH), 130.07 (C), 127.45 (C), 64.59 (CH_2), 49.94 (CH_2), 39.69 (CH_3), 38.96 (CH_2), 37.84 (CH), 36.97 (CH).

FAB–MS: *m*/*z* (%) = 319.1 (43) [M + 1].

Anal. Calcd for $C_{14}H_{15}ClN_6O$ (318.76): C, 52.75; H, 4.74; N, 26.36. Found: C, 52.48; H, 4.91; N, 26.52.

(±)-*cis*-4-[(6-Cyclopropylamino-9*H*-purin-9-yl)methyl]-1-methylcyclopenta[*c*]pyrazol-6-methanol (15b)

Eluent: CH_2Cl_2–MeOH (30:1 and 15:1). Yield: 95%; white solid recrystallized from acetone–hexane; mp 195–196 °C.

IR (KBr): 3383, 2985, 2930, 1621, 1506, 1480, 1381, 1354, 1234, 1120, 1047, 922 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.44 (s, 1 H, 2_{purine}-H), 7.63 (s, 1 H, 8_{purine}-H), 6.96 (s, 1 H, 3-H), 6.20 (br s, 1 H, D_2O exchange, NH), 4.43 (dd, *J* = 13.9, 9.2 Hz, 1 H, NC*H*H), 4.22 (dd, *J* = 13.9, 6.6 Hz, 1 H, NCH*H*), 3.86 (dd, *J* = 11.5, 4.2 Hz, 1 H, OC*H*H), 3.79 (s, 3 H, NCH_3), 3.75 (dd, *J* = 11.5, 4.6 Hz, 1 H, OC*H*H), 3.51–3.48 (m, 1 H), 3.24–3.20 (m, 1 H), 3.05 (br s, 1 H, D_2O exchange, OH), 2.82 (dt, *J* = 14.1, 9.0 Hz, 1 H, 5-*H*H), 2.12 (dt, *J* = 14.1, 2.7 Hz, 1 H, 5-H*H*), 1.0–0.92 (m, 2 H), 0.91–0.87 (m, 1 H), 0.69–0.63 (m, 2 H).

^{13}C NMR [DEPT ($CDCl_3$)]: δ = 156.61 (CH), 153.56 (C), 150.41 (C), 149.95 (C), 140.50 (CH), 132.96 (CH), 127.88 (C), 120.23 (C), 64.11 (CH_2), 49.25 (CH_2), 40.03 (CH), 38.68 (CH_2), 37.75 (CH), 37.68 (CH), 24.84 (CH), 7.79 (2 × CH_2).

FAB–MS: *m*/*z* (%) = 340.14 (100) [M + 1].

Anal. Calcd for $C_{17}H_{21}N_7O$ (339.39): C, 60.16; H, 6.24; N, 28.89. Found: C, 60.41; H, 6.50; N, 29.04.

(±)-*cis*-1-{[6-(Hydroxymethyl)-1-methylcyclopenta[*c*]pyrazol-4-yl]methyl}-1,2,3,4-tetrahydropyrimidine-2,4-dione (17b)

Eluent: CH_2Cl_2–MeOH (15:1). Yield: 99%; white solid (recrystallized from EtOAc–EtOH); mp 196–197 °C.

IR (KBr): 3434, 2956, 2765, 1703, 1690, 1670, 1439, 1389, 1354, 1292, 1242, 1012, 806, 767 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 11.22 (br s, 1 H, D_2O exchange, $2_{pyrimidine}$-H), 7.53 (d, *J* = 7.8 Hz, 1 H, $6_{pyrimidine}$-H), 6.88 (s, 1 H, 3-H), 5.52 (d, *J* = 7.8 Hz, 1 H, $5_{pyrimidine}$-H), 4.97 (t, *J* = 5.0 Hz, 1 H, D_2O exchange, OH), 3.80–3.76 (m, 1 H, NC*H*H), 3.73 (s, 3 H, NCH_3), 3.72–3.47 (m, 3 H), 3.29–3.24 (m, 1 H), 3.18–3.11 (m, 1 H), 2.70 (dt, *J* = 13.6, 8.7 Hz, 1 H, 5-*H*H), 1.88 (dt, *J* = 13.6, 4.2 Hz, 1 H, 5-H*H*).

^{13}C NMR [DEPT (DMSO-d_6)]: δ = 164.02 (C), 151.43 (C), 150.96 (C), 146.47 (CH), 132.30 (CH), 126.90 (C), 100.75 (CH), 64.31 (CH_2), 53.29 (CH_2), 39.61 (CH_3), 38.25 (CH_2), 37.67 (CH), 34.99 (CH).

FAB–MS: *m*/*z* (%) = 300.09 (100) [(M + 1) + Na].

Anal. Calcd for $C_{13}H_{16}N_4O_3$ (276.29): C, 56.51; H, 5.84; N, 20.28. Found: C, 56.79; H, 6.03; N, 20.45.

Crystal Structure Determination of 9b (see Figure 2)

Crystal Data: $C_{15}H_{18}N_2O_2$, M_r = 315.35, Monoclinic, P 21/c, a = 14.456(5) Å, b = 8.260(5) Å, c = 12.908(5) Å, α = 90.000(5)°, β = 93.825(5)°, γ = 90.000(5)°, T = 293(2) K, V = 1537.9(12) Å^3, Z = 4, *D*x (calculated) = 1.362 Mg/m^3, μ = 0.097 mm^{-1}, F(000) = 664.

Date Collection and Reduction: Crystal size: 0.31 × 0.27 × 0.05 mm^3, θ-range 2.82–26.02°, index ranges: –17 ≤ h ≤ 17, 0 ≤ k ≤ 10, 0 ≤ l ≤ 15, reflections collected: 15648, independent reflections: 3012 [*R*(int) = 0.0462], absorption correction: semi-empirical from equivalents, refinement method: full-matrix least-squares on F^2, data/restraints/parameters: 3012/0/228, goodness-of-fit on F^2: 1.047, final *R* indices [I > 2σ (I)]: *R*1 = 0.0580, *wR*2 = 0.1570, *R* indices (all data): *R*1 = 0.0974, *wR*2 = 0.1740, largest diff. peak and hole: 0.470 and –0.363 e·Å^{-3}. Enraf Nonius FR590, computing data collection: CAD4 Express (Enraf Nonius, 1994), computing cell refinement: CAD4 Express (Enraf Nonius, 1994), computing data reduction: XCAD4 (Harms & Wocadlo, 1995), computing structure solution: SIR-97 (Altomare et al., 1999), computing structure refinement: SHELXL-97 (Sheldrick, 1997), computing molecular graphics: Ortep-3 for Windows (Farrugia, 1997), computing publication material: WinGX publication routines (Farrugia, 1999).

Crystal Structure Determination of 17b (see Figure 3)

Crystal Data: $C_{13}H_{16}N_4O_3$, M_r = 276.30, monoclinic, P 21/c, *a* = 5.107(5) Å, *b* = 11.483(5) Å, *c* = 22.499(5) Å, α = 90.000(5)°, β =

90.361(5)°, γ = 90.000(5)°, T = 293(2) K, V = 1319.4(14) Å^3, Z = 4, *D*x (calculated) = 1.391 Mg/m^3, μ = 0.102 mm^{-1}, F(000) = 584.

Date Colletion and Reduction: Crystal size: 0.54 × 0.51 × 0.03 mm^3, θ-range 1.81–28.28°, index ranges: $-6 \le h \le 6$, $0 \le k \le 15$, $0 \le l \le 29$, reflections collected: 3174, independent reflections: 3174 [*R*(int) = 0.0000], absorption correction: semi-empirical from equivalents, refinement method: full-matrix least-squares on F^2, data/restraints/parameters: 3174/0/198, goodness-of-fit on F^2: 1.027, final *R* indices [I > 2σ (I)]: *R*1 = 0.0511, *wR*2 = 0.1200, *R* indices (all data): *R*1 = 0.0988, *wR*2 = 0.1423, largest diff. peak and hole: 0.196 and –0.203 e·Å^{-3}. Enraf Nonius FR590, computing data collection: CAD4 Express (Enraf Nonius, 1994), computing cell refinement: CAD4 Express (Enraf Nonius, 1994), computing data reduction: XCAD4 (Harms & Wocadlo, 1995), computing structure solution: SIR-97 (Altomare et al., 1999), computing structure refinement: SHELXL-97 (Sheldrick, 1997), computing molecular graphics: Ortep-3 for Windows (Farrugia, 1997), computing publication material: WinGX publication routines (Farrugia, 1999).

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