A Convenient Synthesis of New Purinyl-*homo*-carbonucleosides on a Cyclopentane Ring Fused with Pyridazine

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Abstract: The new purinyl *homo*-carbonucleosides **10** and **17a** were prepared from 1,4-diphenyl-5,8-dihydro-5,8-methanophthalazine by one-pot ozonolysis and reductive cleavage, followed by monoprotection with an Ac or TBDMS group, mesylation of the resulting diol and replacement of the mesyl group with 6-chloropurine in the presence of NaH and 18-crown-6 ether. *Homo*-carbonucleosides **12** and **13** were then obtained from **10** by substitution of the chlorine in purine position 6. Compounds **17b** and **19** were obtained from **17a** in the same way.

Key words: ozonolysis, acylation, diols, carbocyclic nucleosides, heterocycles, pyridazine

In keeping with the general antineoplastic and antileukemic properties of purine bases and their nucleosides,[1] natural and synthetic carbocyclic nucleosides can have significant antitumour and/or antiviral activity.[2] In particular, carbovir[3] (**1**) and abacavir[4] (**2**) have potent anti-HIV activity. In previous work, our research group synthesized several abacavir analogues with structures of type **3** (Figure 1),[5] some of which have shown marked cytostatic activity against human T lymphocytes (Molt4/C8 and CEM/0 cells).[6]

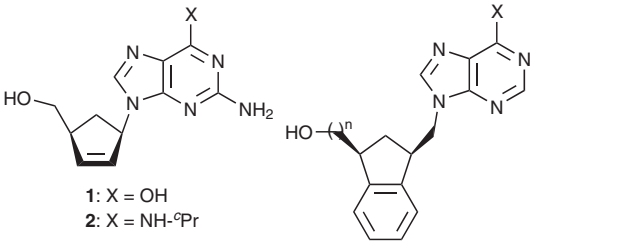

Figure 1

Most of these analogues have had an oxo or amino group at purine position 6 so as to maintain the ability of the natural nucleobase to form hydrogen bonds with polymerases and other key enzymes of nucleic acid metabolism.[7] In order to modify the lipophilicity and polar interactions of the pseudosugar moiety while retaining its rigidity, we have also begun to explore a class of analogues in which the benzene ring of **3** is replaced by an aromatic heterocycle.[8] Here we describe the synthesis of a number of compounds of this kind in which the heterocycle is pyridazine.

The key intermediate **6** was prepared from 1,4-diphenyl-5,8-dihydro-5,8-methanophthalazine (**4**, obtained[9] from 2,3-dibenzoylbicyclo[2.2.1]hepta-2,5-diene). Initially, this was achieved by a method which parallels that previously employed[8b] to prepare 1- and 2-alkyl derivatives of *exo*,*exo*-5,6-dihydroxy-4,5,6,7-tetrahydro-4,7-methanoindazoles. In this method (Method A), hydroxylation of the 'exposed' double bond of **4** was followed by oxidative cleavage of the resulting diol **5** (with sodium periodate and silica gel)[8,10] and reduction of the dialdehyde product by $NaBH_4$ in MeOH (Scheme 1). Subsequently, we discovered that **4** can be transformed cleanly into **6** in high yield (93%) in a one-pot process consisting of ozonolysis followed by reductive cleavage of the resulting ozonide (Method B).

To monoprotect compound **6** in readiness for its coupling with the nucleobase, and in the light of previous experience,[5] we first attempted to acetylate it by enzymatic transesterification from vinyl acetate in dimethylformamide with Novozym® 435 as catalyst. However, several attempts under various reaction conditions (temperatures of 20–50 °C and reaction times of 1–18 h) failed to provide acetylated products, so chemical acetylation was resorted to. Refluxing a 1:1.06:2.3 mixture of compound **6**, acetic anhydride and pyridine in anhydrous THF for 8 hours afforded a 58% yield of **7** accompanied by a 32% yield of the diacetylate **8**.

Although Mitsunobu coupling[11] of purines to indans analogous to **7** only provides yields of around 40%,[5] and the present substrate was expected to be even less reactive, we nevertheless attempted to couple **7** with 6-chloropurine in THF containing triphenylphosphine and diethyl azodicarboxylate. Not unexpectedly, these attempts failed and the desired compound **10** was not detected despite careful separation of the products of reaction. We therefore tried an indirect route via mesylate **9**, which was obtained from **7** by treatment with methanesulphonyl chloride, Et_3N and DMAP at 0 °C. Heating crude **9** for 24 hours at 55 °C with

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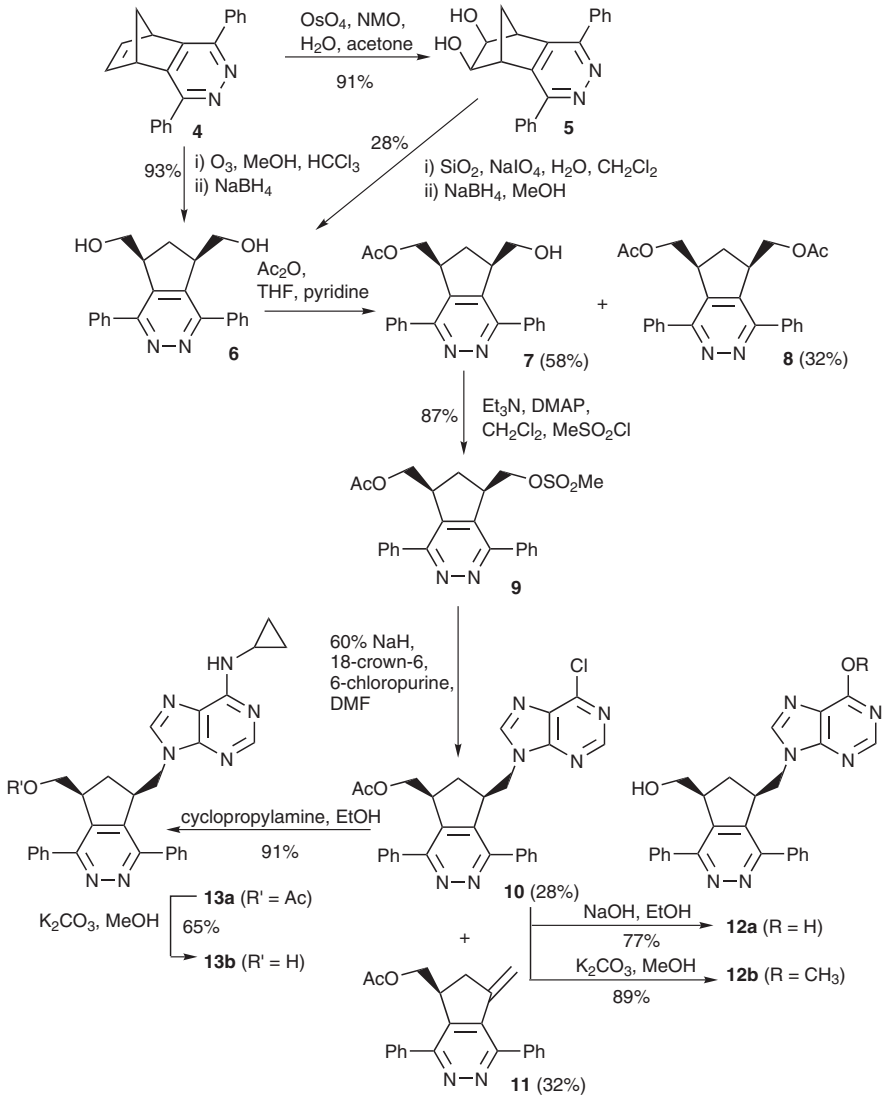


Scheme 1

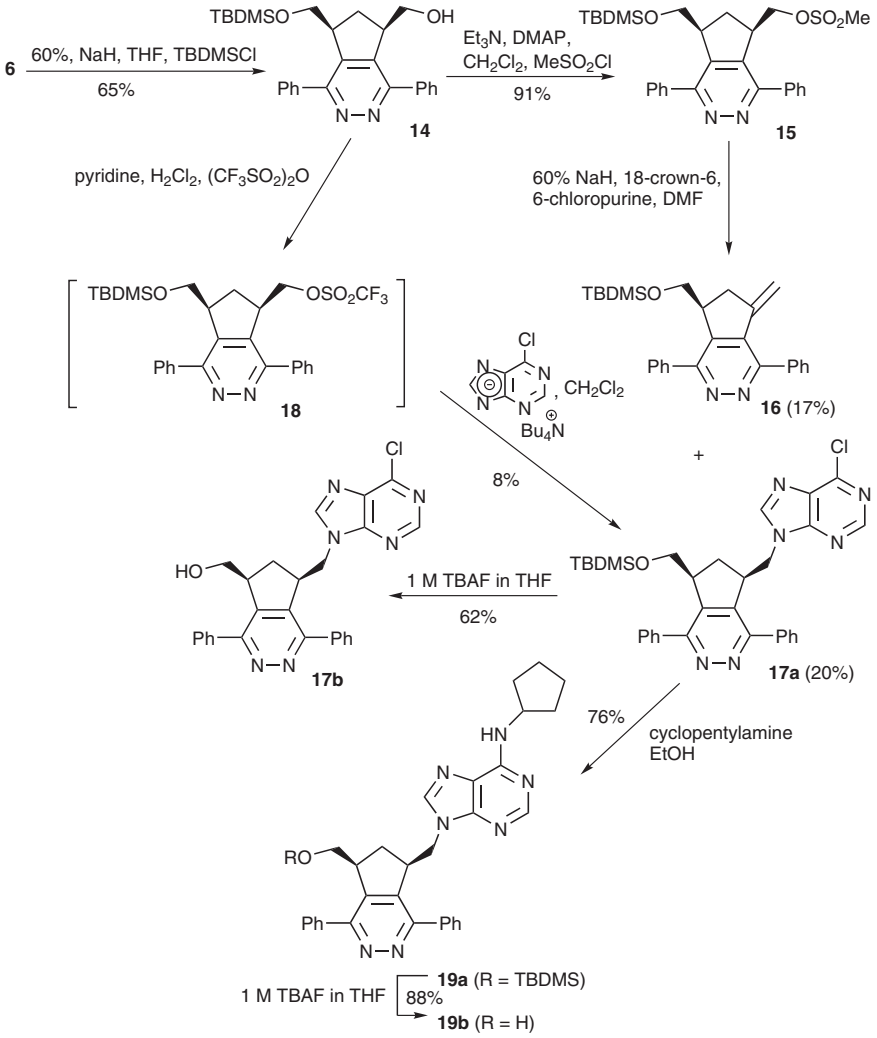
6-chloropurine, NaH and 18-crown-6 ether in DMF afforded a 28% yield of **10** (lower temperatures and shorter reaction times gave lower yields) together with a 32% yield of **11**. The latter compound is the product of a competing elimination reaction shown by TLC monitoring (with 1:1 hexane–EtOAc as eluent) which produced detectable amounts of **11** within just a few minutes of the start of the reaction.

Purinyl carbonucleosides in which purine position 6 bears a OH (**12a**), OMe (**12b**) or cyclopropylamino group (**13a**) were obtained directly from **9** by treatment with the corresponding nucleophiles, with simultaneous deprotection in the cases of **12a** and **12b**. Thus reaction of **10** with NaOH and EtOH for 48 hours at room temperature afforded **12a** directly, while stirring **10** with Na_2CO_3 in MeOH for 40 hours gave the methyl ether **12b**. Refluxing **10** with cyclopropylamine in EtOH gave **13a**, basic hydrolysis of which then afforded the deprotected product **13b**.

Since direct deprotection of **10** resulted in simultaneous replacement of the chlorine by an hydroxyl group under all the ester hydrolysis conditions that were tried, the chloropurinyl carbonucleoside **17b** (Scheme 2) was obtained from the TBDMS-protected analogue **17a** by treatment with a 1 M solution of TBAF in THF. Compound **17a** was prepared by TBDMS-protection of diol **6**, mesylation of the resulting compound **14**, and replacement of the mesyl group of **15** with chloropurinyl in analogy to the preparation of **10** from **9**. In view of the reported preparation of methylene-linked nucleoside analogues by reaction between the tetrabutylammonium salt of 6-chloropurine and a primary triflate,[12] we also tried to obtain **17a** by generating the triflate of pseudosugar **14** (compound **18**) and treating it with the Bu_4N^+ salt in question, but the yield of **17a** obtained by this method never exceeded 8%.

Finally, reaction of **17a** with cyclopentylamine and subsequent deprotection of the resulting compound **19a** with a 1 M solution of TBAF in THF afforded the new purinyl carbonucleoside **19b**.

Compounds **12a**, **12b**, **13b**, **17a**, **17b** and **19b** were evaluated for antiviral activity[13] against a wide variety of virus-



Scheme 2

es, including herpes simplex virus type 1 (strain KOS), herpes simplex virus type 2 (strain G), vaccinia virus, a thymidine kinase-deficient HSV-1 strain (KOS, ACV^R) and vesicular stomatitis virus (VSV) in HEL cell cultures; respiratory syncytial virus, Coxsackie virus B4 and vesicular stomatitis virus in HeLa cell cultures; and type 3 parainfluenza virus, type 1 reovirus, Sindbis virus, Coxsackie virus B4 and Punta Toro virus in Vero cell cultures. None of the compounds showed inhibitory activity against any of the virus strains at 400 μg/mL.

All chemicals used were of reagent grade and were obtained from Aldrich Chemical Co and used without further purification. Melting points were measured in a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a MIDAC Prospect spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 300 spectrometer at 300 MHz and 75.47 MHz, respectively, using tetramethylsilane as internal standard (chemical shifts, δ , in ppm; *J* in Hz). Mass spectra were recorded on a Fisons VG Autoespec M spectrometer. Ozonolysis was performed with Erwin Sander ozone generator. All air-sensitive reactions were carried out under Ar. 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).

***endo,endo*-1,4-Diphenyl-5,6,7,8-tetrahydro-5,8-methanophthalazine-6,7-diol (5)**

A solution of phthalazine **4** (2.65 g, 8.78 mmol) in acetone–water mixture (4:1, 60 mL) at 40 °C was treated with *N*-methylmorpholine *N*-oxide (1.13 g, 9.65 mmol) followed by a 4% solution of osmium tetraoxide (0.25 mL) in water. After 5 h at this temperature the mixture was allowed to cool to r.t., and **5** was filtered out as a white solid (2.48 g). The filtrate was concentrated to dryness, the resulting residue was taken up in sat. NH_4Cl solution (130 mL), and this solution was extracted with EtOAc (3 × 100 mL). The pooled organic phases were dried over Na_2SO_4, and evaporation of the solvent left another small amount of **5** (0.22 g,) as a white solid; yield: 91%. An analytical sample was obtained by recrystallization from EtOH; mp 210–211 ºC.

IR (KBr): 3420, 3063, 3008, 2918, 1646, 1576, 1558, 1417, 1382, 1071, 972, 774, 683, 658 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.60, and 1.69 (AB system, *J* = 16.8, 10.3 Hz, 2 H, 9-HH), 3.65 (virtual s, 2 H, 5-H, 8-H), 4.54 (virtual s, 2 H, 6-H, 7-H), 4.88 (d, D_2O exchange, *J* = 5.2 Hz, 2 H, 2 × OH), 7.44–7.57 (m, 6 H), 8.09–8.11 (m, 4 H).

^{13}C NMR (DMSO-d_6): δ = 154.8 (C), 143.9 (C), 136.5 (C), 128.9 (CH), 128.7 (CH), 128.3 (CH), 68.7 (CH), 47.9 (CH), 42.83 (CH_2).

EIMS: *m*/*z* (%) = 331 (24) [M + 1], 330 (M, 100), 299 (16), 283 (12), 272 (23), 271 (85), 270 (55), 242 (29), 241 (55), 239 (31), 215 (16), 165 (33), 128 (16), 115 (33), 77 (17).

HRMS: *m*/*z* calcd for $C_{21}H_{18}N_2O_2$: 330.1368; found: 330.1347.

cis-1,4-Diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazine-5,7-dimethanol (6)

Method A: A 0.65 M aq solution of $NaIO_4$ (4.28 mL, 2.77 mmol) was added dropwise to a vigorously stirred suspension of chromatography grade silica gel (4.28 g) in CH_2Cl_2 (175 mL). After addition of compound **5** (0.50 g, 1.5 mmol) in CH_2Cl_2 (10 mL) to the resulting flaky solution stirring was continued for another 5 min and the mixture 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). $NaBH_4$ (0.23 g, 2.34 mmol) was added in a single portion and stirring was continued for 30 min. After cooling with an ice bath, water (5 mL) was added. MeOH was removed under reduced pressure and the resulting residue was dissolved in NH_4Cl (25 mL). This solution was extracted with EtOAc (3 × 100 mL), and removal of the solvent from the pooled extracts under reduced pressure afforded a greenish solid (0.17 g). Upon purification by chromatography on silica gel using CH_2Cl_2–MeOH (40:1) as eluent **6** (0.14 g, 28%) was obtained as a white solid; mp 217–218 ºC (dec).

IR (KBr): 3296, 2938, 2877, 1739, 1569, 1447, 1395, 1092, 1046, 1021, 763, 701, 672 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.14–2.18 (m, 1 H, 6-*H*H), 2.44–2.49 (m, 1 H, 6-H*H*), 3.03–3.10 (m, 2 H, CH_2OH), 3.18–3.22 (m, 2 H, CH_2OH), 3.96–3.91 (m, 2 H, 5-H, 7-H), 4.57 (t, D_2O exchange, *J* = 5.0 Hz, 2 H, 2 OH), 7.51–7.59 (m, 6 H), 7.79–7.81 (m, 4 H).

^{13}C NMR (DMSO-d_6): δ = 157.4 (C), 143.4 (C), 137.2 (C), 128.9 (CH), 128.5 (CH), 128.2 (C), 128.1 (CH), 61.9 (CH_2), 45.7 (CH), 29.2 (CH_2).

EIMS: *m*/*z* (%) = 333 (24) [M + 1], 332 (100) [M], 331 (16), 315 (39), 302 (24), 301 (10), 289 (16), 283 (23), 274 (16), 272 (14), 271 (57), 241 (11), 239 (14), 165 (14), 128 (12), 115 (17), 91 (10), 77 (10).

HRMS: *m*/*z* calcd for $C_{21}H_{20}N_2O_2$: 332.1525; found: 332.1517.

Method B: Ozone was bubbled for 15 min through a vigorously stirred solution of phthalazine **4** (4.32 g, 14.4 mmol) in MeOH–$CHCl_3$ (1:1, 200 mL) at –78 °C. $NaBH_4$ (2.43 g, 64.2 mmol) was added in small portions over 1 h at the same temperature, and after further 15 min at –78 °C the mixture was allowed to reach r.t. Removal of the solvents under reduced pressure left an oily yellow residue from which compound **6** precipitated as a white solid (4.47 g, 93%) upon addition of water (600 mL). The spectroscopic data of this product were identical to those of the compound obtained by Method A.

(±)-*cis*-[7-(Hydroxymethyl)-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-yl]methyl Acetate (7) and *cis*-(1,4-Diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazine-5,7-diyl)bis(methylene) Diacetate (8)

A stirred suspension of diol **6** (2.0 g, 6.02 mmol) in THF (50 mL) was refluxed for 1 h under Ar. Anhydrous pyridine (1.1 g, 13.7 mmol) and acetic anhydride (0.65 g, 6.37 mmol) were added, and refluxing was continued for further 8 h. The solvent was removed under reduced pressure and the residue was taken into sat. $NaHCO_3$ solution (100 mL). This solution was extracted with EtOAc (3 × 150 mL), and the pooled organic phases were dried over Na_2SO_4 and concentrated to dryness, leaving an oily residue (3 g) that was fractionated on a silica gel column using CH_2Cl_2–MeOH (99:1 and then 49:1) eluent. From the early fractions, diacetate **8** (0.8 g, 32%) was isolated as a brown solid whereas the middle fractions yielded compound **7** (1.3 g, 58%), likewise as a brown solid. From the fractions eluted with MeOH, unreacted compound **6** (0.2 g) was obtained.

Compound 8

Mp 73–74 ºC.

IR (KBr): 3055, 2993, 1738, 1553, 1444, 1383, 1252, 1024, 906, 763, 699 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.84 (s, 6 H, 2 × OCOCH_3), 1.91 (dt, *J* = 14.3, 5.6 Hz, 1 H, 6-*H*H), 2.66 (dt, *J* = 14.3, 5.6 Hz, 1 H, 6-H*H*), 3.78 (dd, *J* = 11.1, 7.4 Hz, 2 H, 5-H, 7-H), 3.90 (dd, *J* = 11.1, 4.4 Hz, 2 H, OCH_2), 4.10–4.17 (m, 2 H, OCH_2), 7.47–7.55 (m, 6 H), 7.78–7.80 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 170.6 (C), 157.9 (C), 141.9 (C), 136.6 (C), 128.5 (CH), 128.9 (CH), 128.3 (CH), (CH), 64.9 (CH_2), 42.6 (CH), 30.2 (CH_2), 20.6 (3 CH_3).

EIMS: *m*/*z* (%) = 416 (100) [M], 373 (19), 356 (18), 355 (17), 314 (11), 313 (45), 298 (11), 297 (49), 296 (28), 295 (72), 285 (20), 284 (10), 283 (42), 271 (20), 268 (28), 267 (20), 253 (13), 252 (18), 241 (10), 239 (17), 215 (10), 202 (11), 180 (12), 165 (10), 128 (21), 127 (13), 91 (12), 77 (28), 71 (13), 69 (11).

HRMS: *m*/*z* calcd for $C_{25}H_{24}N_2O_4$: 416.1736; found: 416.1946.

Compound 7

Mp 165 ºC.

IR (KBr): 3378, 2945, 1738, 1538, 1447, 1383, 1234, 1030, 770, 700 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.87 (s, 3H, OCOCH_3), 2.05 (dt, *J* = 14.2, 7.8 Hz, 1 H, 6-*H*H), 2.62 (dt, *J* = 14.2, 5.5 Hz, 1 H, 6-H*H*), 3.30 (dd, *J* = 9.5, 5.8 Hz, 1 H, 5-H), 3.50 (dd, *J* = 9.4, 5.1 Hz, 1 H, 7-H), 3.81 (dd, *J* = 11.0, 4.7 Hz, 1 H, HOC*H*H), 3.99 (dd, *J* = 7.5, 4.3 Hz, 1 H, HOCH*H*), 4.00–3.98 (m, 1 H, AcOC*H*H), 4.11–4.17 (m, 1 H, AcO-CH*H*), 7.47–7.55 (m, 6 H), 7.77–7.80 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 171.0 (C), 158.0 (C), 157.9 (C), 142.7 (C), 142.1 (C), 136.9 (C), 136.8 (C), 129.4 (CH), 129.3 (CH), 128.9 (CH), 128.8 (CH), 128.4 (CH), 128.3 (CH), 65.1 (CH_2), 63.2 (CH_2), 46.0 (CH), 42.9 (CH), 29.8 (CH_2), 20.7 (3 × CH_3).

EIMS: *m*/*z* (%) = 375 (28) [M + 1], 374 (100) [M], 331 (35), 315 (36), 314 (20), 297 (13), 285 (29), 284 (16), 283 (58), 271 (33), 255 (31), 128 (13), 115 (12), 73 (12).

HRMS: *m*/*z* calcd for $C_{23}H_{22}N_2O_3$: 374.1630; found: 374.1629.

(±)-*cis*-[7-(Mesyloxymethyl)-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-yl]methyl Acetate (9)

Mesyl chloride (0.24 mL, 2.09 mmol) was added dropwise to a solution of **7** (0.23 g, 0.61 mmol), Et_3N (0.28 mL) and a cat. amount of DMAP in anhyd $CHCl_3$ (3 mL) stirred under Ar at 0 °C. After stirring for 5 h at r.t., the mixture was diluted with $CHCl_3$ (15 mL) and washed successively with water (15 mL), 1 M NaOH (15 mL) and brine (15 mL). The organic phase was then dried over Na_2SO_4 and concentrated under reduced pressure, leaving a brown residue (0.31 g) that following chromatography on a silica gel column with CH_2Cl_2–MeOH (99:1) as eluent afforded **9** (0.24 g, 87%) as a light brown solid; mp 63–65 ºC.

IR (KBr): 3446, 2956, 1739, 1448, 1384, 1358, 1237, 1175, 1035, 955, 921, 830, 771, 701 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.85 (s, 3 H, OCOCH_3), 2.06 (dt, *J* = 14.3, 7.1 Hz, 1 H, 6-*H*H), 2.63–2.73 (m, 1 H, 6-H*H*), 2.71 (s, 3 H, SO_2CH_3), 3.74 (dd, *J* = 11.02, 7.0 Hz, 1 H, 7-H), 3.86–3.92 (m, 2 H, AcOC*H*H, 5-H), 3.99 (dd, *J* = 9.8, 3.4 Hz, 1 H, AcOC*H*H), 4.09–4.23 (m, 2 H, SO_2OCH_2), 7.49–7.59 (m, 6 H), 7.76–7.81 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 181.1 (C), 170.6 (C), 157.9 (C), 157.6 (C), 142.3 (C), 140.5 (C), 136.3 (C), 129.8 (CH), 129.7 (CH), 129.0 (CH), 128.9 (CH), 128.3 (CH), 69.1 (CH_2), 64.5 (CH_2), 43.2 (CH), 42.7 (CH), 36.9 (CH_3), 29.9 (CH_2), 20.6 (CH_3).

EIMS: *m*/*z* (%) = 452 (2) [M], 357 (8), 356 (20), 355 (6), 298 (7), 297 (29), 296 (49), 295 (100), 283 (14), 281 (8), 267 (8), 266 (7), 253 (12), 252 (23), 239 (7), 165 (6), 127 (11), 126 (71), 115 (6), 78 (6), 77 (10).

HRMS: *m*/*z* calcd for $C_{24}H_{24}N_2O_5S$: 452.1405; found: 452.1419.

(±)-*cis*-{7-[(6-Chloro-9*H*-purin-9-yl)methyl]-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-yl}methyl Acetate (10) and (±)-(7-Methylidene-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-yl)methyl Acetate (11)

A solution of 6-chloropurine (0.16 g, 1.03 mmol), 60% NaH (40 mg, 1.6 mmol) and 18-crown-6 ether (0.16 g, 0.59 mmol) in anhyd DMF (10 mL) was stirred at 55 °C for 1.5 h. A solution of **9** (0.27 g, 0.59 mmol) in DMF (6 mL) was added, and stirring at 55 °C was continued for further 24 h, after which the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with H_2O (4 × 25 mL). The organic phase was dried over Na_2SO_4, and removal of the solvent left a solid residue (0.31 g) that was fractionated on a silica gel column using hexane–EtOAc (1:1) as eluent. The early fractions afforded **11** (0.11 g, 32%) as an oil that slowly crystallized. The middle fractions gave unreacted **9** (42 mg) and the late fractions provided **10** (84 mg, 28%) as a pale yellow solid.

Compound 11

Mp 113–115 ºC (after washing with hexane).

IR (KBr): 3056, 2939, 1732, 1685, 1534, 1491, 1445, 1424, 1375, 1364, 1266, 1244, 1219, 1037, 914, 903, 769, 705 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.80 (s, 3 H, $OCOCH_3$), 2.69 (dd, *J* = 16.2, 1.7 Hz, 1 H, 6-*H*H), 3.09 (ddt, *J* = 13.7, 8.5, 2.6 Hz, 1 H, 6-H*H*), 3.72–3.78 (m, 1 H, OCOC*H*H), 3.85–3.91 (m, 1 H, OCOCH*H*), 4.01–4.09 (m, 1 H, 5-H), 5.20 (s, 1 H, =C*H*H), 5.26 (s, 1 H, =CH*H*), 7.49–7.56 (m, 6 H), 7.69–7.71 (m, 2 H), 7.79–7.82 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 170.5 (C), 158.6 (C), 144.3 (C), 142.5 (C), 137.5 (C), 136.7 (C), 136.5 (C), 129.3 (CH), 129.2 (CH), 128.9 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 114.5 (CH_2), 64.8 (CH_2), 40.5 (CH), 36.0 (CH_2), 20.6 (CH_3).

EIMS: *m*/*z* (%) = 357 (9) [M + 1], 356 (38) [M], 357 (21), 313 (16), 295 (100), 284 (6), 283 (23), 281 (14), 267 (12), 253 (13), 252 (24), 239 (6), 207 (6).

HRMS: *m*/*z* calcd for $C_{23}H_{20}N_2O_2$: 356.1525; found: 356.1742.

Compound 10

Mp 195–196 ºC.

IR (KBr): 3450, 2893, 2360, 1736, 1594, 1558, 1384, 1349, 1243, 1107, 966, 938, 769, 696 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.91 (s, 3 H, $OCOCH_3$), 1.92–1.96 (m, 1 H, 6-*H*H), 2.57 (dt, *J* = 14.3, 5.2 Hz, 1 H, 6-H*H*), 3.83–3.91 (m, 2 H), 4.08–4.21 (m, 3 H), 4.54–4.60 (m, 1 H), 7.44–7.58 (m, 6 H), 7.68 (s, 1 H, 8_{purine}-H), 7.78–7.85 (m, 4 H), 8.67 (s, 1 H, 2_{purine}-H).

^{13}C NMR ($CDCl_3$): δ = 170.5 (C), 158.2 (C), 157.6 (CH), 151.9 (CH), 151.8 (C), 151.2 (C), 144.7 (CH), 141.6 (C), 136.3 (C), 136.0 (C), 131.4 (C), 129.8 (CH), 129.1 (CH), 129.0 (CH), 128.4 (CH), 128.3 (CH), 64.5 (CH_2), 47.4 (CH_2), 43.9 (CH), 42.9 (CH), 30.4 (CH_2), 20.8 (CH_3).

HRMS: *m*/*z* calcd for $C_{28}H_{23}ClN_6O_2$; 510.1571; found: 510.1552.

(±)-*cis*-9-{[7-(Hydroxymethyl)-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-yl]methyl}-1,9-dihydropurin-6-one (12a)

A solution of **10** (0.10 g, 0.20 mmol) and NaOH (7.8 mg, 0.20 mmol) in EtOH (6 mL) was stirred at r.t. for 48 h, and after removal of the solvent the resulting residue was dissolved in EtOAc (10 mL). This solution was washed with brine (2 × 10 mL) and the solvent was removed under reduced pressure, leaving a solid (96 mg) that upon recrystallization from MeOH afforded **12a** (60 mg, 77%) as a white solid; mp 236–238 ºC.

IR (KBr): 3183, 2929, 2869, 1595, 1496, 1444, 1046, 1380, 1332, 1286, 1256, 1117, 1022, 942, 767, 697, 678, 640 cm^{-1}.

^{1}H NMR ($DMSOd_6$): δ = 1.93–1.96 (m, 1 H, 6-*H*H), 2.53 (dt, *J* = 13.7, 9.8 Hz, 1 H, 6-H*H*), 3.18 (dd, *J* = 10.7, 6.4 Hz, 1 H, 7-H), 3.29 (dd, *J* = 10.7, 3.1 Hz, 1 H, HOC*H*H), 4.29–4.21 (m, 1 H, HOC*H*H), 4.25–4.27 (m, 1 H, 5-H), 4.56–4.58 (m, 1 H, NC*H*H), 4.66–4.68 (m, 1 H, NCH*H*), 4.80 (br s, 1 H D_2O exchange, OH), 7.21–7.35 (m, 3 H), 7.45–7.56 (m, 5 H), 7.77–7.82 (m, 2 H), 8.25, 8.60 (2 × s, 2 H, 2_{purine}-H, 8_{purine}-H), 11.15 (br s, 1 H, D_2O exchange, 1_{purine}-H).

^{13}C NMR ($CDCl_3$): δ = 157.3 (C), 156.8 (C), 151.5 (C), 151.0 (CH), 148.7 (C), 146.7 (CH), 143.5 (C), 142.8 (C), 136.8 (C), 136.0 (C), 130.6 (C), 129.0 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 61.12 (CH_2), 47.6 (CH_2), 45.4 (CH), 42.0 (CH), 30.0 (CH_2).

EIMS: *m*/*z* (%) = 450 (4) [M], 449 (17), 441 (17), 440 (22), 439 (46), 438 (29), 315 (20), 314 (41), 313 (55), 297 (22), 296 (14), 295 (18), 285 (25), 284 (69), 283 (100), 272 (13), 271 (57), 255 (16), 253 (12), 252 (12), 239 (15), 153 (11), 142 (14), 128 (25), 127 (13), 115 (23), 89 (11), 74 (11), 73 (19).

HRMS: *m*/*z* calcd for $C_{26}H_{22}N_6O_2$: 450.1804; found: 450.1802.

(±)-*cis*-{7-[(6-Methoxy-9*H*-purin-9-yl)methyl]-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]-pyridazin-5-yl}methanol (12b)

A solution of chloropurine **10** (100 mg, 0.20 mmol) and K_2CO_3 (40.6 mg, 0.7 mmol) in MeOH (7 mL) was stirred at r.t. for 40 h. The solvent was evaporated under reduced pressure, leaving a solid residue (175 mg) that after chromatography on silica gel with CH_2Cl_2–MeOH (97:3) as eluent afforded **12b** as a white solid (80 mg, 89%); mp 156–157 ºC.

IR (KBr): 3308, 2941, 2869, 1602, 1484, 1447, 1414, 1379, 1342, 1227, 1060, 1011, 767, 700, 644 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.81–1.89 (m, 1 H, 6-*H*H), 2.38–2.46 (m, 1 H, 6-H*H*), 3.37–3.41 (m, 1 H, 5-H), 3.59 (dd, *J* = 11.8, 2.7 Hz, 1 H), 3.82–3.84 (d, *J* = 8.7 Hz, 1 H, NC*H*H), 3.92–3.94 (m, 1 H, NCH*H*), 4.15 (s, 3 H, OCH_3), 4.3–4.36 (m, 2 H, OCH_2), 4.78 (br s, 1 H, D_2O exchange, OH), 7.46–7.57 (m, 7 H), 7.74–7.77 (m, 2 H), 7.85–7.87 (m, 2 H), 8.44 (s, 1 H, 2_{purine}-H).

^{13}C NMR ($CDCl_3$): δ = 161.3 (C), 158.4 (C), 157.3 (C), 152.1 (C), 152.0 (CH), 143.4 (C), 142.1 (C), 142.0 (CH), 136.7 (C), 136.6 (C), 129.7 (CH), 129.5 (C), 129.3 (CH), 129.0 (CH), 128.8 (CH), 128.4 (CH), 128.3 (CH), 121.4 (C), 62.2 (CH_2), 54.4 (CH), 46.4 (CH), 45.3 (CH_2), 45.2 (CH), 29.3 (CH_2).

EIMS: *m*/*z* (%) = 466 (34) [M + 2], 465 (100) [M + 1], 464 (4) [M], 435 (10), 316 (9), 315 (33), 313 (6), 307 (9), 285 (11), 284 (7), 283 (17), 271 (9), 155 (10), 154 (36).

HRMS: *m*/*z* calcd for $C_{27}H_{25}N_6O_2$: 465.2039; found: 465.2046.

(±)-*cis*-{7-[(6-Cyclopropylamine-9*H*-purin-9-yl)methyl]-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-yl}methyl Acetate (13a)

A solution of **10** (114 mg, 0.22 mmol) and cyclopropylamine (127 mg, 2.22 mmol) in EtOH (10 mL) was refluxed for 22 h. Removal of the solvent under reduced pressure left a solid from which, fol-

lowing chromatography on silica gel with CH_2Cl_2–MeOH (95:5) as eluent, **13a** (108 mg, 91%) was isolated as a white solid; mp 137–138 ºC.

IR (KBr): 3413, 2362, 1738, 1616, 1476, 1382, 1296, 1235, 1039, 767, 699, 646 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.59–0.63 (m, 2 H, cyclopropyl), 0.86–0.91 (m, 2 H, cyclopropyl), 1.84 (s, 3 H, $OCOCH_3$), 2.04 (dt, *J* = 14.3, 3.1 Hz, 1 H, 6-*H*H), 2.51 (dt, *J* = 14.3, 9.8 Hz, 1 H, 6-H*H*), 2.96–2.99 (m, 1 H, $1_{cyclopropyl}$-H), 3.57 (dd, *J* = 11.2, 7.2 Hz, 1 H, 5-H), 3.81 (dd, *J* = 11.2, 4.3 Hz, 1 H, 7-H), 4.00–4.06 (m, 2 H), 4.10–4.12 (m, 1 H), 4.47–4.53 (m, 1 H, C*H*HO), 5.92 (br s, 1 H, D_2O exchange, NH), 7.22 (s, 1 H, 8_{purine}-H), 7.43–7.53 (m, 6 H), 7.74–7.76 (m, 2 H), 7.86–7.88 (m, 2 H), 8.35 (s, 1 H, 2_{purine}-H).

^{13}C NMR ($CDCl_3$): δ = 170.4 (C), 158.0 (C), 157.6 (C), 155.7 (C), 153.1 (CH), 141.9 (C), 141.8 (C), 139.3 (CH), 136.4 (C), 136.2 (C), 129.6 (CH), 129.5 (CH), 128.9 (CH), 128.4 (CH), 128.2 (CH), 119.6 (C), 64.6 (CH_2), 46.1 (CH_2), 44.2 (CH), 42.7 (CH), 30.0 (CH_2), 20.6 (CH_3), 7.8 (2 × CH_2).

EIMS: *m*/*z* (%) = 532 (21) [M + 1], 531 (56) [M], 516 (14), 505 (10), 504 (30), 502 (21), 471 (14), 444 (23), 358 (16), 357 (59), 298 (22), 297 (100), 296 (36), 295 (58), 284 (14), 283 (53), 281 (13), 253 (11), 252 (18), 236 (11), 188 (11), 187 (12), 175 (22), 174 (44), 160 (27), 77 (10).

HRMS: *m*/*z* calcd for $C_{31}H_{29}N_7O_2$: 531.2382; found: 531.2401.

(±)-*cis*-{7-[(6-Cyclopropylamino-9*H*-purin-9-yl)methyl]-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-yl}methanol (13b)

A solution of **13a** (0.1 g, 0.19 mmol) and K_2CO_3 (39 mg, 0.28 mmol) in anhyd MeOH (5 mL) was refluxed under Ar for 24 h. Removal of the solvent under reduced pressure left a residue from which, following chromatography on silica gel with CH_2Cl_2–MeOH (97:3) as eluent, **13b** (60 mg, 65%) was isolated as a white solid; mp 191–192 ºC.

IR (KBr): 3354, 2362, 1628, 1540, 1483, 1446, 1354, 1303, 1235, 1071, 761, 701, 646 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.54–0.58 (m, 2 H, cyclopropyl), 0.80–0.93 (m, 2 H, cyclopropyl), 2.13–2.20 (m, 1 H, 6-*H*H), 2.26–2.33 (m, 1 H, 6-H*H*), 2.93–2.98 (m, 1 H, $1_{cyclopropy}$-H), 3.36 (dd, *J* = 11.1, 5.1 Hz, 1 H, 5-H), 3.48 (dd, *J* = 11.1, 3.3 Hz, 1 H, 7-H), 3.72 (dd, *J* = 8.1, 3.6 Hz, 1 H, NCH*H*), 3.93, 4.02 (ABM system, *J* = 13.9, 8.7, 5.2 Hz, 2 H, HOCH_2), 4.43–4.50 (m, 1 H, CH*H*N), 6.24 (br s, 1 H, D_2O exchange, NH), 7.06 (s, 1 H, 8_{purine}-H), 7.41–7.43 (m, 6 H), 7.54–7.56 (m, 2 H), 7.68–7.70 (m, 2 H), 8.34 (s, 1 H, 2_{purine}-H).

^{13}C NMR ($CDCl_3$): δ = 158.1 (C), 157.6 (C), 155.5 (C), 153.2 (CH), 143.2 (C), 142.6 (C), 138.9 (CH), 136.6 (C), 136.3 (C), 129.5 (CH), 129.4 (CH), 128.8 (CH), 128.7 (CH), 128.4 (CH), 128.4 (CH), 119.1 (C), 62.8 (CH_2), 46.3 (CH_2), 45.3 (CH), 44.2 (CH), 32.0 (CH_2), 29.6 (CH), 7.2 (2 × CH_2).

EIMS: *m*/*z* (%) = 490 (11) [M + 1], 316 (27), 315 (100), 313 (18), 299 (10), 298 (15), 297 (45), 295 (11), 285 (17), 284 (15), 283 (46), 281 (10), 272 (11), 271 (26), 189 (15), 188 (14), 176 (36), 174 (13), 165 (11), 160 (10).

HRMS: *m*/*z* calcd for $C_{29}H_{28}N_7O$: 490.2355; found: 490.2337.

(±)-*cis*-{7-[(*tert*-Butyldimethylsilyloxy)methyl]-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-yl}methanol (14)

A suspension of diol **6** (0.60 g, 1.81 mmol) and 60% NaH (72.32 mg, 1.81 mmol) in anhyd THF (40 mL) was stirred under Ar at r.t. for 50 min, after which a solution of *tert*-butyldimethylsilyl chloride (0.27g, 1.81 mmol) in 5 mL of the same solvent was added dropwise and stirring was continued for further 16 h. THF was removed under reduced pressure, the crude was dissolved in EtOAc (50 mL) and washed successively with 10% K_2CO_3 solution (2 × 50 mL) and water (50 mL). After removal of the solvent under reduced pressure the resulting residue was fractionated on a silica gel column with hexane–EtOAc (1:1) and EtOAc–MeOH (95:5) as successive eluents. Compound **14** (0.52 g, 65%) was isolated as a white solid from the fractions eluted with hexane–EtOAc, and unreacted **6** (115 mg) was recovered from those eluted with EtOAc–MeOH.

Compound 14

Mp 168–169 ºC.

IR (KBr): 3433, 2927, 2855, 1555, 1446, 1386, 1252, 1121, 1030, 1002, 834, 769, 700 cm^{-1}.

^1H NMR ($CDCl_3$): δ = –0.26 [s, 3 H, Si(CH_3)$_2$], –0.22 [s, 3 H, Si(CH_3)$_2$], 0.68 [s, 9 H, C(CH_3)$_3$], 1.90 (br s, 1 H, D_2O exchange, OH), 2.14 (dt, *J* = 14.2, 3.6 Hz, 1 H, 6-*H*H), 2.64 (dt, *J* = 14.2, 10.3 Hz, 1 H, 6-H*H*), 3.34–38. (m, 2 H, 5-H, 7-H), 3.46–3.49 (m, 2 H), 3.90–3.97 (m, 2 H), 7.43–7.55 (m, 6 H), 7.75–7.79 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 158.0 (C), 157.8 (C), 143.1 (C), 143.0 (C), 137.2 (C), 137.1 (C), 129.2 (CH), 128.8 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 64.1 (CH_2), 63.9 (CH_2), 46.1 (CH), 46.0 (CH), 29.9 (CH_2), 25.8 [C(CH_3)$_3$], 18.23 (C), -5.7 (CH_3), –5.8 (CH_3).

EIMS: *m*/*z* (%) = 446 (10) [M], 432 (14), 431 (40), 415 (31), 390 (28), 389 (100), 388 (11), 387 (33), 298 (10), 297 (44), 285 (11), 283 (23), 282 (12), 281 (19), 253 (10), 252 (12), 194 (53), 75 (14).

HRMS: *m*/*z* calcd for $C_{27}H_{34}N_2O_2Si$: 446.2390; found: 446.2383.

(±)-*cis*-{7-[(*tert*-Butyldimethylsilyloxy)methyl]-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-yl]methyl Mesylate (15)

Mesyl chloride (0.77 g, 6.72 mmol) was added to a solution of **14** (1.0 g, 2.24 mmol), Et_3N (0.94 mL) and a catalytic amount of DMAP in anhyd CH_2Cl_2 (15 mL) stirred under Ar at –10 °C. After stirring for 1 h at r.t., the mixture was diluted with CH_2Cl_2 (60 mL) and washed successively with water (2 × 80 mL), 1 M NaOH (2 × 40 mL) and brine (80 mL). The organic phase was then dried over Na_2SO_4 and concentrated under reduced pressure, leaving a residue that following chromatography on a silica gel column with CH_2Cl_2–MeOH (99:1) as eluent afforded **15** (1.07 g, 91%) as a white solid; mp 56–57 ºC.

IR (KBr): 2928, 2856, 2360, 2341, 1540, 1494, 1471, 1449, 1360, 1256, 1176, 1095, 956, 834, 770, 699, 669 cm^{-1}.

^1H NMR ($CDCl_3$): δ = –0.27 [s, 3 H, Si(CH_3)$_2$], –0.21 [s, 3 H, Si(CH_3)$_2$], 0.65 [s, 9 H, C(CH_3)$_3$], 2.11 (dt, *J* = 14.2, 3.2 Hz, 1 H, 6-*H*H), 2.65–2.73 (m, 1 H, 6-H*H*), 2.68 (s, 3 H, SO_2CH_3), 3.31 (dd, *J* = 10.0, 5.5 Hz, 1 H, 5-H), 3.47 (dd, *J* = 10.0, 2.8 Hz, 1 H, 7-H), 3.91–4.00 (m, 3 H, CH_3SO_2CHH + TBDMSiOCH_2), 4.15–4.20 (m, 1 H, CH_3SO_2CHH), 7.49–7.57 (m, 6 H), 7.80–7.82 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 158.0 (C), 157.4 (C), 143.3 (C), 140.8 (C), 136.7 (C), 129.6 (CH), 129.4 (CH), 129.1 (CH), 128.8 (CH), 128.5 (CH), 128.3 (CH), 70.4 (CH_2), 63.5 (CH_2), 46.3 (CH), 43.5 (CH), 36.7 (CH), 30.4 (CH_2), 25.8 [C(CH_3)$_3$], 18.1 (C), –5.7 (CH_3), –5.8 (CH_3).

EIMS: *m*/*z* (%) = 526 (38) [M + 1], 525 (100) [M], 468 (8), 467 (24), 429 (7), 297 (10), 285 (5), 283 (10), 271 (5).

HRMS calcd. for $C_{28}H_{37}N_2O_4SSi$, 525.2243; found, 525.2240.

(±)-*cis*-5-[(*tert*-Butyldimethylsilyloxy)methyl]-7-methylidene-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazine (16) and (±)-*cis*-5-[(*tert*-Butyldimethylsilyloxy)methyl]-7-[(6-chloro-9*H*-purin-9-yl)methyl]-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazine (17a)

Method A: A solution of 6-chloropurine (0.16 g, 0.98 mmol), 60% NaH (39.14 mg, 0.98 mmol) and 18-crown-6 ether (93.54 mg, 0.35 mmol) in anhyd DMF (12 mL) was stirred at 55 °C for 1.5 h and

then allowed to cool to r.t. A solution of **15** (0.30 g, 0.57 mmol) in anhyd DMF (8 mL) was added via a cannula, and stirring was continued for further 24 h at 55 °C, after which the reaction mixture was allowed to cool, diluted with CH_2Cl_2 (50 mL) and washed with H_2O (4 × 50 mL). The organic phase was concentrated to dryness, leaving a solid residue (0.35 g) that was fractionated on a silica gel column using hexane–EtOAc (1:1) as eluent. The early fractions afforded **16** (43 mg, 17%) as a white solid. The middle fractions gave unreacted **15** (120 mg) whereas and the late fractions yielded **17a** (65 mg, 20%) as a pale yellow solid.

Compound 16
Mp 116–118 ºC.

IR (KBr): 3080, 2926, 2854, 1542, 1492, 1465, 1382, 1253, 1109, 1003, 923, 835, 768, 697 cm^{-1}.

^1H NMR ($CDCl_3$): δ = –0.27 [s, 3 H, $Si(CH_3)_2$], –0.20 [s, 3 H, $Si(CH_3)_2$], 0.68 [s, 9 H, $C(CH_3)_3$], 2.81–2.86 (m, 1 H, 6-*H*H), 3.02 (ddd, *J* = 16.4, 8.5, 2.7 Hz, 1 H, 6-H*H*), 3.17 (dd, *J* = 9.9, 6.7 Hz, 1 H, TBSOC*H*H), 3.41 (dd, *J* = 9.9, 3.4 Hz, 1 H, TBDMSiOCH*H*), 3.77–3.82 (m, 1 H, 5-H), 5.12–5.14 (m, 1 H, =C*H*H), 5.20–5.21 (m, 1 H, =CH*H*), 7.45–7.53 (m, 6 H), 7.66–7.69 (m, 2 H), 7.77–7.80 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 158.8 (C), 156.3 (C), 145.7 (C), 143.9 (C), 138.3 (C), 137.1 (C), 137.0 (C), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 113.7 (CH_2), 63.4 (CH_2), 43.8 (CH), 35.6 (CH_2), 25.6 [$C(CH_3)_3$], 18.0 (C), -5.7 (CH_3), –5.8(CH_3).

EIMS: *m*/*z* (%) = 430 (38) [M + 2], 429 (100) [M + 1], 428 (5) [M], 427 (6), 372 (6), 371 (15), 297 (13), 295 (7), 285 (7), 284 (7), 283 (26).

HRMS: *m*/*z* calcd for $C_{27}H_{33}N_2Osi$: 429.2373; found: 429.2362.

Compound 17a
Mp 87–89 ºC.

IR (KBr): 3059, 2951, 2929, 2856, 1592, 1559, 1496, 1443, 1381, 1334, 1254, 1214, 1178, 1142, 1102, 937, 835, 771, 699, 637 cm^{-1}.

^1H NMR ($CDCl_3$): δ = –0.28 [s, 3 H, $Si(CH_3)_2$], –0.22 [s, 3 H, $Si(CH_3)_2$], 0.63 [s, 9 H, $C(CH_3)_3$], 1.99–2.03 (m, 1 H, 6-*H*H), 2.58 (ddd, *J* = 14.1, 10.0, 4.1 Hz, 1 H, 6-H*H*), 3.35 (dd, *J* = 10.2, 4.5 Hz, 1 H, OC*H*H), 3.52 (dt, *J* = 10.2, 2.8 Hz, 1 H, OCH*H*), 3.96–3.99 (m, 1 H, 5-H), 4.12 (dd, *J* = 13.8, 5.8 Hz, 1 H, NC*H*H), 4.25 (dd, *J* = 13.8, 8.6 Hz, 1 H, NCH*H*), 4.49–4.54 (m, 1 H, 7-H), 7.34–7.43 (m, 3 H), 7.47–7.52 (m, 3 H), 7.56 (s, 1 H, 8_{purine}-H), 7.75–7.80 (m, 4 H), 8.64 (s, 1 H, 2_{purine}-H).

^{13}C NMR ($CDCl_3$): δ = 157.9 (C), 157.3 (C), 151.8 (C), 151.7 (CH), 151.0 (C), 144.7 (CH), 142.8 (C), 142.2 (C), 136.6 (C), 136.2 (C), 131.4 (C), 129.5 (CH), 129.4 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 63.5 (CH_2), 47.7 (CH_2), 46.2 (CH), 43.5 (CH), 31.1 (CH_2), 25.8 [(CH_3)$_3$], 18.2 [$C(CH_3)_3$], –5.6 [$(CH_3)_2$].

EIMS: *m*/*z* (%) = 585 (45) [M + 2], 584 (44) [M + 1], 583 (100) [M], 528 (5), 527 (14), 526 (30), 430 (9), 429 (24), 297 (7), 285 (5), 284 (4), 283 (15), 271 (5).

HRMS: *m*/*z* calcd for $C_{32}H_{36}ClSiN_6O$: 583.2408; found: 583.2114.

Method B: To a solution of anhyd pyridine (0.13 mL, 1.66 mmol) in anhyd CH_2Cl_2 (5 mL) at –40 ºC was slowly added a solution of $(CF_3SO_2)_2O$ (0.16 mL, 0.96 mmol) in anhyd CH_2Cl_2 (5 mL). After the mixture had been stirred for 50 min, **14** (0.27 g, 0.61 mmol) in CH_2Cl_2 (5 mL) was added dropwise, the temperature was allowed to rise to –20 ºC over 2 h, and stirring was continued at this temperature for another 19 h. The resulting solution was diluted with anhyd CH_2Cl_2 (35 mL), ice (5 g) was added, and the organic phase was washed successively with 3% aq HCl (10 mL), sat. aq $NaHCO_3$ (30 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated to ca. 20 mL in vacuo. This concentrate was stirred with 4 Å molecular sieves (ca. 2.5 g) for 1 h at 0 ºC, and then treated with the tetrabutylammonium salt of 6-chloropurine (0.27 mg, 0.68 mmol), previously prepared from 6-chloropurine as described Franzyk et al.[12] Stirring was continued for 64 h at –10 ºC, after which the mixture was filtered and the filtrate was concentrated to dryness, leaving a residue (0.57 g) that was fractionated on a silica gel column using hexane–EtOAc (1:1), hexane–EtOAc (1:3) and 2% MeOH–EtOAc as successive eluents. The middle fractions afforded **17a** (27 mg, 8%) as a white solid with spectroscopic data identical to those of the compound obtained by Method A.

(±)-*cis*-{7-[(6-Chloro-9*H*-purin-9-yl)methyl]-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-yl}methanol (17b)
A 1 M solution of TBAF in THF (0.4 mL, 0.40 mmol) was added dropwise to a solution of **17a** (0.11 g, 0.20 mmol) in the same solvent (4 mL) stirred under Ar in an ice bath. The solution was allowed to reach r.t., and stirring was continued for a further 30 min. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column using EtOAc–hexane (9:1) as eluent. Concentration to dryness of the non-void fractions afforded **17b** (55 mg, 62%) as a white solid; mp 217–219 ºC.

IR (KBr): 3178, 2924, 2867, 1595, 1567, 1497, 1443, 1379, 1332, 1292, 1254, 1215, 1175, 1074, 1021, 941, 911, 766, 696, 638 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.91–1.98 (m, 1 H, 6-*H*H), 2.54–2.64 (m, 1 H, 6-H*H*), 3.14–3.19 (m, 1 H, 5-H), 3.28–3.36 (m, 1 H, 7-H), 3.98–4.04 (m, 1 H, OC*H*H), 4.18 (dd, *J* = 13.8, 7.9 Hz, 1 H, OCH*H*), 4.28 (dd, *J* = 13.8, 7.5 Hz, 1 H, NC*H*H), 4.65–4.70 (m, 1 H, NCH*H*), 4.81 (t, D_2O exchange, *J* = 4.9 Hz, 1 H, OH), 7.23–7.33 (m, 4 H), 7.52–7.67 (m, 4 H), 7.84–7.86 (m, 2 H), 8.25 (s, 1 H, 8_{purine}-H), 8.69 (s, 1 H, 2_{purine}-H).

^{13}C NMR (DMSO-d_6): δ = 157.4 (C), 156.9 (C), 151.5 (C), 151.0 (CH), 148.7 (C), 146.7 (CH), 143.6 (C), 142.8 (C), 136.8 (C), 136.0 (C), 130.6 (C), 129.0 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 61.1 (CH_2), 47.6 (CH_2), 42.0 (CH), 30.6 (C), 30.1 (CH_2).

EIMS: *m*/*z* (%) = 471 (22) [M + 2], 470 (18), 469 (59) [M], 453 (20), 439 (17), 316 (19), 315 (75), 297 (7), 286 (20), 285 (100), 284 (26), 283 (89), 271 (26).

HRMS: *m*/*z* calcd for $C_{26}H_{22}ClSiN_6O$: 471.1530; found: 471.1508.

(±)-*cis*-9-({7-[(*tert*-Butyldimethylsilyloxy)methyl]-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-yl}methyl)-*N*-cyclopentyl-9*H*-purin-6-amine (19a)
A solution of **17a** (133 mg, 0.24 mmol) and cyclopentylamine (0.13 mL, 0.12 mg, 1.37 mmol) in anhyd EtOH (10 mL) was refluxed under Ar for 8 h. Removal of the solvent under reduced pressure left a solid residue that after chromatography on a silica gel column with hexane–EtOAc (1:2) as eluent afforded **19a** (109 mg, 76%) as a white solid; mp 110–112 ºC.

IR (KBr): 3338, 2952, 2858, 2362, 1616, 1475, 1382, 1296, 1252, 1103, 925, 836, 771, 698 cm^{-1}.

^1H NMR ($CDCl_3$): δ = –0.27 [s, 3 H, $Si(CH_3)_2$], –0.22 [s, 3 H, $Si(CH_3)_2$], 0.67 [s, 9 H, $C(CH_3)_3$], 1.52–1.55 (m, 2 H), 1.65–1.76 (m, 5 H), 2.03–2.14 (m, 3 H, 6-*H*H + C*HH*$_{cyclopentyl}$), 2.55 (dd, *J* = 14.1, 10.0 Hz, 1 H, 6-H*H*), 3.24 (dd, *J* = 10.1, 5.2 Hz, 1 H, 7-H), 3.48 (dd, *J* = 10.1, 2.9 Hz, 1 H, 5-H), 3.94 (dd, *J* = 7.4, 2.5 Hz, 1 H, OC*H*H), 4.06–4.08 (m, 2 H, OCH*H* + NC*H*H), 4.55–4.59 (m, 2 H, NCH*H*), 5.57 (d, D_2O exchange, *J* = 6.78 Hz, 1 H, NH), 7.16 (s, 1 H, 8_{purine}-H), 7.36–7.53 (m, 6 H), 7.79–7.85 (m, 4 H), 8.30 (s, 1 H, 2_{purine}-H).

^{13}C NMR (DMSO-d_6): δ = 157.8 (C), 157.5 (C), 154.3 (C), 153.0 (CH), 142.9 (C), 142.6 (C), 139.1 (CH), 136.8 (C), 136.3 (C), 129.3 (CH), 129.2 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.4

(CH), 119.5 (C), 63.5 (CH_2), 47.0 (CH_2), 46.2 (CH), 43.6 (CH), 33.5 (CH_2), 30.8 (CH_2), 25.8 [$(CH_3)_3$], 23.6 (CH_2), 18.20 [$C(CH_3)_3$], –5.7 [$(CH_3)_2$], –5.9 [$(CH_3)_2$].

EIMS: *m*/*z* (%) = 633 (30) [M + 1], 632 (88) [M], 631 (10), 602 (11), 583 (11), 575 (10), 574 (22), 451 (11), 431 (11), 430 (36), 429 (100), 297 (14), 283 (28), 202 (10), 154 (12).

HRMS: *m*/*z* calcd for $C_{37}H_{46}SiN_7O$: 632.3507; found: 632.3482.

(±)-*cis*-{7-[(6-Cyclopentylamino-9*H*-purin-9-yl)methyl]-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-yl}methanol (19b)

A 1 M solution of TBAF in THF (0.51 mL, 0.51 mmol) was added dropwise to a solution of **19a** (0.16 g, 0.25 mmol) in the same solvent (6 mL) stirred under Ar in an ice bath. The solution was allowed to reach r.t., and stirring was continued for a further 4.5 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column using CH_2Cl_2–MeOH (95:5) as eluent. Concentration to dryness of the non-void fractions afforded **19b** (114 mg, 88%) as a white solid; mp 158–160 ºC.

IR (KBr): 3187, 2941, 2865, 1626, 1483, 1448, 1381, 1319, 1231, 770, 698, 643 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.25–1.32 (m, 1 H), 1.48–1.59 (m, 2 H), 1.61–1.64 (m, 3 H, one exchanging with D_2O, OH + C*H*$H_{cyclopentyl}$), 1.67–1.72 (m, 2 H), 1.90 (d, *J* = 14.4 Hz, 1 H), 2.03–2.10 (m, 2 H, 6-*H*H + 1$H_{cyclopentyl}$), 2.34–2.43 (m, 1 H, 6-H*H*), 3.37 (dd, *J* = 12.0, 3.6 Hz, 1 H, 5-H), 3.56 (dd, *J* = 12.0, 7.1 Hz, 1 H, 7-H), 3.71–3.74 (m, 1 H, HOC*H*H), 3.87–3.90 (m, 1 H, HOCH*H*), 4.19–4.28 (m, 1 H, NC*H*H), 4.46–4.60 (m, 1 H, NCH*H*), 6.16 (d, D_2O exchange, *J* = 7.1 Hz, 1 H, NH), 7.32 (s, 1 H, 8_{purine}-H), 7.42–7.55 (m, 6 H), 7.72–7.75 (m, 2 H), 7.83–7.85 (m, 2 H), 8.21 (s, 1 H, 2_{purine}-H).

^{13}C NMR ($CDCl_3$): δ = 158.4 (C), 157.3 (C), 154.5 (C), 152.9 (CH), 143.6 (C), 142.3 (C), 139.1 (CH), 136.7 (C), 136.6 (C), 129.5 (CH), 129.2 (CH), 128.9 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 119.1 (C), 62.0 (CH_2), 52.4 (CH_2), 46.6 (CH), 45.4 (CH), 44.9 (CH_2), 29.2 (CH_2), 23.7 (CH_2).

EIMS: *m*/*z* (%) = 518 (100) [M + 1], 517 (10) [M], 516 (8), 488 (18), 316 (15), 315 (62), 313 (8), 307 (8), 285 (17), 284 (8), 283 (20), 271 (9), 243 (9), 242 (47), 204 (13), 186 (57), 155 (18), 154 (52).

HRMS: *m*/*z* calcd for $C_{31}H_{32}N_7O$: 518.2667; found: 518.2624.

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