Synthesis of Purinyl and Pyrimidinyl 1’(N)-Homocarbanucleosides Based on a 1-Methylcyclopenta[c]pyrazole Scaffold; Part 2

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Abstract: Two new 6-aryl-substituted 1’(N)-homocarbanucleosides were prepared by Suzuki–Miyaura reactions of the protected 6-halopurine derivatives with phenylboronic acids. Additionally, 1’(N)-homocarbanucleosides of 6-chloropurine, 2-amino-6-chloropurine and 3-benzoyluracil were prepared by Mitsunobu reaction with a protected diol. From the uracil derivative, the corresponding 5-bromo- and 5-iodouracil compounds were also obtained.

Key words: synthesis, 1’(N)-homocarbanucleosides, methylcyclopenta[c]pyrazole, Mitsunobu reaction, Suzuki–Miyaura cross-coupling reaction.

The search for new therapies against human immunodeficiency virus has involved prodigious chemical efforts leading to the synthesis of large numbers of nucleoside variants featuring modifications of the heterocyclic base and/or the sugar moiety. Although initially spurred by the need for anti-HIV agents, this work has also resulted in the discovery of compounds that are active against other viral infections.1 In a number of the antiviral agents so-discovered, the furanose ring has been replaced by a carbocyclic or non-furanose heterocyclic system. Of particular interest are 1’(N)-homocarbanucleosides, which are especially resistant to enzymatic degradation because of the methylene group between their heterocyclic base and pseudosugar moieties.2

In recent years our research group3–6 has prepared several carbanucleoside and homocarbanucleosides analogues of carbovir (1a) and abacavir (1b) in which the cyclopentene ring is incorporated in an indan system, as in 2 (Figure 1). Some show significant cytostatic activity against human T lymphocytes (Molt4/C8 and CEM/0 cells).4 We have also begun to explore the effects of replacing the benzene ring of 2 with an aromatic heterocycle in order to modify the lipophilicity and polar interactions of the pseudosugar moiety while retaining its rigidity.5–11 The finding that, in preliminary evaluation studies, certain purinylimethyl derivatives of 2-benzylcyclopenta[c]pyrazole-6-methanol (3) proved active against varicella-zoster virus and cytomegalovirus at subtoxic concentrations10 encouraged us to prepare other cyclopenta[c]pyrazole derivatives with a view to correlating activity with structure. We started11 with a series of 1-methylcyclopenta[c]pyrazole-6-methanol (4) (Figure 1), including a number of 6-substituted purine derivatives; substituents in position 6 of purinyl nucleoside analogues are known to affect cytostatic activity, and 6-methylpurine derivatives have already been used for anticancer therapy.12–15

In the present work we explored the effect of placing an aryl group at purine position 6 of purinyl compounds of type 4, and we also prepared a number of analogues of 4 in which the positions of the hydroxymethyl group and heteroarylmethyl groups on the cyclopentane ring have been exchanged.

Type 4 6-arylpurine derivatives were prepared by Suzuki–Miyaura cross-coupling (palladium-catalyzed reaction of a halide or triflate electrophile with a boronic acid or an ester thereof).16 In the first instance, treatment of 5a11 with phenylboronic acid under Suzuki–Miyaura conditions, using potassium carbonate as base, tetrakis(triphenylphosphine)palladium as catalyst and toluene as solvent, afforded an 87% yield of 6, which upon deprotection gave carbanucleoside 7 (Scheme 1). However, an attempt to obtain carbanucleoside 9 by reaction of compound 5a with p-methoxyphenylboronic acid under the same conditions was unsuccessful. Since 6-iodopurines have been reported to be more reactive than 6-chloropurinines in Pd-catalyzed coupling reactions,17 we therefore prepared intermediate 8, by treatment of 5a with NaI and CF3CO2H.

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in ethyl methyl ketone at –50 °C. Suzuki–Miyaura coupling of 8 with p-methoxyphenylboronic acid proceeded as expected, giving a 46% yield of 9. Finally, the projected series of 6-substituted purine derivatives of type 4 was completed by preparation of 10, which was obtained by first converting 5a to 5b as previously described, and then refluxing 5b in aqueous 0.33 N NaOH for one hour (yield of 10: 67% from 5b).

For the synthesis of 1¢(N)-homocarbanucleosides with 1-methylcyclopenta[c]pyrazole-4-methanol as their pseudosugar, the key intermediate 12 was prepared from (±)-(exo,exo)-1-methyl-4,5,6,7-tetrahydro-4,7-methanoindazole-5,6-diol (11) by oxidative cleavage with sodium periodate and silica gel, followed immediately by reduction of the resulting crude dialdehyde with NaBH4 (Scheme 2). The desired monoprotected derivative 13 was obtained by treating 12 with NaH and TBDPSCl, subsequent chromatography achieving clean separation of 13 (25%), 14 (58%) and a small proportion of unreacted 12.11 Mitsunobu couplings11,18 of 13 with 6-chloropurine, 2-amino-6-chloropurine and 3-benzoyl-1,3-dihydropyrimidine-2,4-dione gave 15 (in 72% yield), 16 (75%) and 18 (92%), respectively (Scheme 3). Deprotection of 16 and 18 then afforded the expected carbanucleosides 17 and 20. Finally, the iodo derivative 21 was obtained in 47% yield by reaction of 20 with I2 in a 0.75 N solution of HNO3 in dioxane; and the bromo derivative 22 by reaction of 20 with NBS in DMF (yield 48%).

Compounds 5, 7, 10, 15–17 and 19–22 were evaluated for cytostatic activity, with positive results in the cases of 5a, 15, 16 and 19, which inhibited the proliferation of tumor cell lines at concentrations of 1–10 μg/mL (Table 1).

All purchased chemicals were of reagent grade and were obtained from Aldrich Chemical Co. and used without further purification. 3-Benzoyl-1,3-dihydropyrimidine-2,4-dione, was prepared as per Márquez et al. Melting points were measured in a Reichert Kofler Thermopan and are uncorrected. IR spectra were recorded on a
a Perkin-Elmer 240B Elemental Analyzer at the University of Santiago Microanalysis Service; all values were within ±0.4% of the theoretical values. All air-sensitive reactions were carried out under argon. 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).

(2R,6S)-cis-6-(tert-Butyldiphenylsilyloxy)methyl]-4-[6-iodo-9H-purin-9-yl][methyl]-1-methylcyclopent[a][pyrazole] (6)

A mixture of 5a (100 mg, 0.18 mmol), phenylboronic acid (33 mg, 0.27 mmol), Pd(PPh3)4 (9.4 mg, 8.46 mmol) and K2CO3 (37.7 mg, 0.27 mmol) in toluene (10 mL) was stirred under argon at 100 °C for 24 h. Once at r.t., the solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel using 2:1 and 1:4 hexane–EtOAc as successive eluents; yield: 94 mg (87%); thick whitish oil.

IR (film): 3327, 3117, 3070, 3005, 2926, 2881, 2856, 1568, 1506, 1493, 1437, 1414, 1326, 1182, 1112, 823, 767, 743, 700, 677, 638 cm–1.

1H NMR (CDCl3): δ = 9.0 (s, 1 H, 2-pyrazine-H), 8.80–8.77 (m, 2 H), 7.90 (s, 1 H, 8-pyrazine-H), 7.70–7.63 (m, 2 H), 7.59–7.53 (m, 5 H), 7.49–7.35 (m, 6 H), 6.85 (s, 1 H, 3-H), 4.40 (dd, J = 13.6, 6.5 Hz, 1 H, NCH=H), 4.21 (dd, J = 13.6, 8.3 Hz, 1 H, NCH=H), 3.79 (dd, J = 10.2, 6.0 Hz, 1 H, OCH=H), 3.68 (dd, J = 10.2, 5.5 Hz, 1 H, OCH=H), 3.67 (s, 3 H, CH3), 3.66–3.58 (m, 1 H), 3.29–3.21 (m, 1 H), 2.92 (dt, J = 13.9, 8.9 Hz, 1 H, 5-HH), 2.15 (dt, J = 13.9, 4.1 Hz, 1 H, 5-HH), 1.07 (s, 9 H, 3 CH3).

13C NMR [DEPT (CDCl3)]: δ = 155.37 (C), 152.91 (C), 152.78 (CH), 150.53 (C), 144.91 (CH), 135.94 (CH), 135.90 (CH), 133.45 (CH), 133.37 (C), 133.01 (CH), 132.56 (C), 132.43 (CH), 131.40 (CH), 130.43 (CH), 129.09 (CH), 129.04 (CH), 128.88 (C), 128.31 (CH), 128.30 (CH), 127.59 (CH), 66.70 (CH), 50.0 (CH), 39.88 (CH), 39.34 (CH), 37.85 (CH), 36.58 (CH), 27.36 (3 CH3), 19.67 (C).

FABMS: m/z = 599.14 (100%, [M + 1]).

HRMS: m/z calc for C38H48N10O4Si: 598.2876; found: 598.2890.

(1R,14S,18S)-cis-6-(tert-Butyldiphenylsilyloxy)methyl]-4-[6-iodo-9H-purin-9-yl][methyl]-1-methylcyclopent[a][pyrazole] (8)

Trifluoroacetic acid (1 mL, 11.95 mmol) was added dropwise under argon to a well-stirred suspension of NaI (3.58 g, 23.9 mmol) and 5a (0.27 g, 0.48 mmol) in anhyd ethyl methyl ketone (10 mL) at –40 to –50 °C. This temperature was maintained for 48 h, and when the mixture had returned to r.t. it was treated with aq sat. NaHCO3 solution (20 mL). The aqueous phase was extracted with CH2Cl2 (3 x 50 mL), and the pooled organic phases were washed with aq sat. NaHCO3 solution (20 mL) followed by brine (20 mL). The halogenated phase was then dried (Na2SO4) and removal of the solvent under reduced pressure afforded virtually pure 8; yield: 0.18 g (57%). An analytical sample was obtained by column chromatography on silica gel with 90:1 CH2Cl2–MeOH as eluent; white solid; mp 72–75 °C.

IR (KBr): 3416, 2929, 2875, 2857, 1580, 1549, 1426, 1329, 1167, 1110, 742, 704 cm–1.

1H NMR (CDCl3): δ = 8.59 (s, 1 H, 2-pyrazine-H), 7.86 (s, 1 H, 8-pyrazine-H), 7.59–7.57 (m, 5 H), 7.47–7.36 (m, 6 H), 6.79 (s, 1 H, 3-H), 4.32 (dd, J = 13.6, 6.6 Hz, 1 H, NCH=H), 4.14 (dd, J = 13.6, 8.3 Hz, 1 H, NCH=H), 3.80 (dd, J = 10.2, 5.7 Hz, 1 H, OCH=H), 3.70 (dd, J = 10.3, 5.5 Hz, 1 H, OCH=H), 3.64 (s, 3 H, CH3), 3.60–3.57 (m, 1 H), 3.27–3.22 (m, 1 H), 2.90 (dt, J = 13.9, 8.9 Hz, 1 H, 5-HH), 2.11 (dt, J = 13.9, 4.0 Hz, 1 H, 5-HH), 1.06 (s, 9 H, 3 CH3).

13C NMR [DEPT (CDCl3)]: δ = 152.34 (CH), 150.30 (C), 148.48 (C), 145.02 (CH), 139.00 (C), 135.93 (CH), 135.90 (CH), 133.41 (C), 132.95 (C), 130.47 (CH), 130.43 (CH), 128.34 (CH), 127.31 (C),

Table 1 Inhibitory Effects of Compounds 5a,14,15,18 on the Proliferation of Murine Leukemia Cells (L1210) and Human T-Lymphocyte (Molt4/C8) and CEM Cells

<table>
<thead>
<tr>
<th>Cell line</th>
<th>5a IC50 (µg/mL)</th>
<th>14 IC50 (µg/mL)</th>
<th>15 IC50 (µg/mL)</th>
<th>18 IC50 (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1210/00</td>
<td>3.7 ± 0.1</td>
<td>5.9 ± 3.5</td>
<td>6.9 ± 1.4</td>
<td>8.9 ± 3.7</td>
</tr>
<tr>
<td>Molt4/C8</td>
<td>3.2 ± 0.0</td>
<td>11 ± 7</td>
<td>6.5 ± 0.3</td>
<td>7.1 ± 1.9</td>
</tr>
<tr>
<td>CEM</td>
<td>3.4 ± 0.1</td>
<td>6.4 ± 2.2</td>
<td>8.3 ± 5.3</td>
<td>5.6 ± 0.2</td>
</tr>
</tbody>
</table>

*a IC50 = concentration required to inhibit cell proliferation during the linear growth phase by 50%.
was refluxed for 1 h. Subsequent evaporation of the solvent afforded a yellow solid that upon purification by column chromatography on silica gel with successive 20:1, 10:1 and 5:1 mixtures of CHCl₃–MeOH as eluents, followed by concentration of the product-bearing fractions to dryness, afforded white solid (washed with Et₂O); mp 51–52 °C.

Synthesis 2006, No. 23, 3967–3972 © Thieme Stuttgart · New York
IR (KBr): 3070, 2956, 2894, 1683, 1448, 1427, 1329, 1243, 1112, 823, 804, 704 cm⁻¹.

1H NMR (CDCl₃, J in Hz): δ = 9.33 (s, 1 H, exchangeable with D₂O, 2-pyrimidine-H), 7.63 (dd, d J = 7.7, 1.5 Hz, 2 H), 7.57 (dd, d J = 7.7, 1.4 Hz, 2 H), 7.45–7.74 (m, 6 H), 7.23 (s, 1 H, 3-H), 6.58 (d, d J = 7.9 Hz, 1 H, 5-pyrimidine-H), 5.54 (dd, d J = 7.9, 1.1 Hz, 1 H, 5-pyrimidine-H), 3.83–3.78 (m, 2 H), 3.74–3.68 (m, 1 H), 3.71 (s, 3 H, CH₃), 3.58–3.47 (m, 2 H), 3.25–3.17 (m, 1 H), 2.87 (dt, d J = 13.9, 8.6 Hz, 1 H, 5-HH), 2.07–2.02 (m, 1 H, 5-HH), 1.07 (s, 9 H, 3 CH₃).

13C NMR (CDCl₃, J in Hz): δ = 163.89 (C), 151.22 (C), 149.41 (CH), 145.23 (C), 135.98 (CH), 134.12 (CH), 133.95 (C), 130.27 (C), 128.49 (C), 128.22 (CH), 128.16 (CH), 102.44 (CH), 68.45 (CH₂), 54.61 (CH₂), 39.09 (CH₂), 39.06 (CH), 37.47 (CH), 35.73 (CH), 27.37 (3 CH₃), 19.76 (C).

FABMS: m/z = 515.20 (100%, [M + 1]).


Cleavage of the tert-Butyldiphenylsilyle Group from Compounds 6, 16, and 19; General Procedure

A 1 M solution of TBAF in THF (1.1 mmol) was added under argon 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 stand for 1 h, after which the solvent was removed under reduced pressure. The residue obtained was chromatographed on silica gel with an appropriate eluent. Finally, product-bearing fractions were concentrated to dryness.

(±)-cis-1-[(6-Phenyl-9H-purin-9-yl)methyl]-1-methylcyclopentane[pyrazole-6-ylmethyl]-1,2,3,4-tetrahydropryrimidin-2,4-dione (20)

A mixture of 20 (57 mg, 0.21 mmol), I₄ (105 mg, 0.42 mmol), 0.75 mL N NHO (0.3 mL) and dioxane (2 mL) was refluxed for 2 h. The solvent was removed in vacuo, and any residual H₂O was eliminated by repeated dissolution of the residue in EtOH and evaporation to dryness. The solid brown crude was purified by chromatography on a column of silica gel with 25:1 CH₂Cl₂–MeOH as eluent, and concentration of the product-containing fractions to dryness afforded 21; yield: 39 mg (47%); white solid (recrystallized from EtOAc–MeOH); mp 250–251 °C.

IR (KBr): 3479, 3099, 2928, 1758, 1523, 1504, 1481, 1440, 1400, 1349, 1325, 1215, 1054, 929, 862, 725, 695, 675, 643 cm⁻¹.

1H NMR (CDCl₃): δ = 8.90 (s, 1 H, 3-pyrazole-H), 8.30–8.20 (m, 1 H), 7.65 (d, d J = 13.9, 8.3 Hz, 1 H, NCH₂), 4.53 (dd, d J = 13.9, 6.9 Hz, 1 H, 1 H, NCH₂), 3.78–3.82 (m, 1 H, OCH₂), 3.80 (s, 3 H, CH₃), 3.73 (dd, d J = 11.5, 5.1 Hz, 1 H, OCH₂), 3.62–3.58 (m, 1 H, 3.26–3.22 (m, 1 H), 2.89 (dt, d J = 14.0, 3.9 Hz, 1 H, 5-HH), 2.11 (dt, d J = 14.0, 3.0 Hz, 1 H, 5-HH).

13C NMR (CDCl₃): δ = 156.55 (C), 153.07 (C), 152.64 (CH), 150.47 (C), 145.04 (CH₂), 135.89 (C), 132.97 (CH), 131.57 (CH), 131.45 (C), 130.25 (CH), 129.12 (CH), 127.70 (C), 64.55 (CH₃), 49.40 (CH), 39.82 (CH₃), 38.93 (CH₂), 37.78 (CH), 37.39 (CH₂).

FABMS: m/z = 361.14 (100%, [M + 1]).


(±)-cis-1-[(4-Hydroxyethyl)-1-methylcyclopentane[pyrazol-6-ylmethyl]-5-ido-1,2,3,4-tetrahydropryrimidine-2,4-dione (21)

A mixture of 20 (57 mg, 0.21 mmol), I₄ (105 mg, 0.42 mmol), 0.75 mL N NHO (0.3 mL) and dioxane (2 mL) was refluxed for 2 h. The solvent was removed in vacuo, and any residual H₂O was eliminated by repeated dissolution of the residue in EtOH and evaporation to dryness. The solid brown crude was purified by chromatography on a column of silica gel with 25:1 CH₂Cl₂–MeOH as eluent, and concentration of the product-containing fractions to dryness afforded 21; yield: 39 mg (47%); white solid (recrystallized from EtOAc–MeOH); mp 250–251 °C.
was removed under reduced pressure. When the brown residue was taken into EtOAc, 22 precipitated as a yellowish solid that was collected by filtration; yield: 34 mg (48%); yellow solid; mp 221–222 °C.

IR (KBr): 3426, 3114, 2954, 1697, 1662, 1441, 1242, 1013 cm⁻¹.

¹H NMR (CD₃OD): δ = 11.85 (br s, 1 H D₂O exchange, NH), 8.14 (s, 1 H, 6-pyrimidine-H), 7.32 (s, 1 H, 3-H), 4.22 (dd, J = 13.7, 5.6 Hz, 1 H, NC₃H), 3.94 (dd, J = 13.8, 8.7 Hz, 1 H, NCH₂), 3.92–3.87 (m, 1 H), 3.85 (s, 3 H, CH₃), 3.71–3.63 (m, 3 H), 3.20–3.16 (m, 1 H), 2.91–2.81 (m, 1 H, 5-H).

¹³C NMR [DEPT (CD₃OD)]: δ = 161.99 (C), 152.42 (C), 147.49 (C), 146.79 (CH), 146.74 (C), 134.02 (CH), 128.97 (C), 66.92 (CH₂), 53.38 (CH₂), 39.98 (CH₂), 39.36 (CH₃), 37.25 (CH), 37.27 (CH).

FABMS: m/z = 355.04 (6%, [M]).

Anal. Calcd for C₁₃H₁₅BrN₄O₃ (355.18): C, 43.96; H, 4.26; N, 15.77. Found: C, 44.12; H, 4.53; N, 15.89.

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References