Synthesis and Biological Evaluation of 6-Substituted Purinylcarbanucleosides with a Cyclopenta[*b*]thiophene Pseudosugar

Paula Abeijón,[a] José M. Blanco,*[a] Olga Caamaño,[a] Franco Fernández,[a] Marcos D. García,[b] Xerardo García-Mera,[a] José E. Rodríguez-Borges,[c] Jan Balzarini,[d] Erik De Clercq[d]

[a] Departamento de Química Orgánica, Facultade de Farmacia, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain
Fax +34(981)594912; E-mail: jm.blanco@usc.es

[b] Departmento de Química Fundamental, Facultade de Ciencias, Campus da Zapateira s/n, 15701 A Coruña, Spain

[c] CIQ, Departamento de Química, Facultade de Ciencias do Porto, Rua do Campo Alegre, 687-4169007 Porto, Portugal

[d] Rega Institute for Medical Research, Katholieke Universiteit Leuven, 3000 Leuven, Belgium

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Abstract: The first members of a new family of heterocarbobicyclic nucleoside analogues have been synthesized from the *cis*/*trans* mixture of (4-amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl)methanols (*cis*/*trans*-**7**). The separation of the *cis* and *trans* intermediates during the preparation of the 6-chloropurine derivatives allowed a separate preparation of the purine heterocarbanucleosides *cis*-**10** and *trans*-**11**, from which *cis*-**12**–**14** and *trans*-**16**–**18** were obtained by replacement of the 6-chloro substituent with amino, hydroxy, and cyclopropylamino groups. Additionally, the 6-phenylpurinyl analogues *cis*-**15** and *trans*-**19** were prepared from *cis*-**10** and *trans*-**11** using Suzuki–Miyaura methodology. In tests of antiviral and cytostatic activities, compound **11** showed cytostatic activity against Molt4/C8 human T lymphoblastic leukemia cells. Antiviral activity was shown by compounds **15** and **19** against Punta Toro virus and Coxackie virus B4 (compound **11**).

Key words: heterobicyclic amino alcohol, cyclopenta[*b*]thiophene, Suzuki–Miyaura cross-coupling reaction, purinylcarbanucleoside, biological activity

The development of new antiviral drugs is a dynamic process driven by the identification of new molecular targets and the emergence of problems associated with drugs in current clinical use (resistance, toxicity, etc.).[1] In recent decades, many research programs have sought nontoxic antiviral drugs that act by selective inhibition of kinases or polymerases.[2] Among the most extensively and intensively studied compounds are the nucleoside analogues, which become active when acted upon by kinases after entry into a target cell. A number of these prodrugs have been found to have antiviral activity and/or antitumoral activity, and some are in clinical use.[3]

The many structural modifications that have been made to natural nucleosides in the search for desired biological properties include the introduction of a double bond between positions 2′ and 3′ of the sugar ring. The seminal work of Balzarini et al.[4] showed that when the parent compound is a pyrimidine nucleoside the resulting cytosine and thymidine analogues [d4C (**1**) and d4T (**2**), respectively; see Figure 1] are active against human immunodeficiency virus (HIV), and d4T is still in clinical use under the commercial name Stavudine®.[5] The antiviral activity of these compounds is thought to be related to the conformational restriction imposed on the pseudosugar moiety by its double bond,[6] which also increases the lipophilicity of the molecule and thereby facilitate its access to the central nervous system, a major reservoir of the HIV virus.[7]

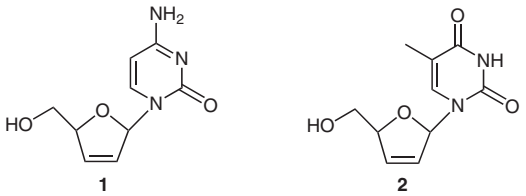

Figure 1 Modified pyrimidine nucleosides d4C (**1**) and d4T (**2**)

In carbanucleosides (CNs),[8] the D-ribose moiety of the natural nucleosides is replaced by an aliphatic or aromatic carbocycle. Carbanucleosides include the well-known anti-HIV agents carbovir (**3**)[9] and abacavir (**4**, marketed as Ziagen®);[10] the purine derivative BMS-200475 (**5**),[11] which is active against hepatitis B virus (HBV); and the pyrimidine derivative carba-BVDU (**6**), which is active *in vitro* against herpes simplex virus 1 (HSV-1) (Figure 2).[12] Once in a cell, they are active for a longer period than the analogues with the endocyclic oxygen of natural nucleosides because they resist the phosphorylases and hydrolases that cleave the glycoside bonds of the latter. Furthermore, replacement of the endocyclic furanose oxygen by a methylene group makes CNs less toxic than their parent compounds.

In previous papers our research group reported the synthesis of abacavir analogues in which a purine or pyrimidine base was linked to an indane system.[13] Some of these compounds showed considerable cytostatic activity against human T lymphoblastic leukemia cell lines (Molt4/C8 and CEM/0) and murine leukemia cells (L1210/0),[14] and many of the active purine derivatives featured an oxo or amino group at position 6 that would allow hydrogen bonding between the nucleobase and the polymerases and other enzymes involved in nucleic acid metabolism.[15]

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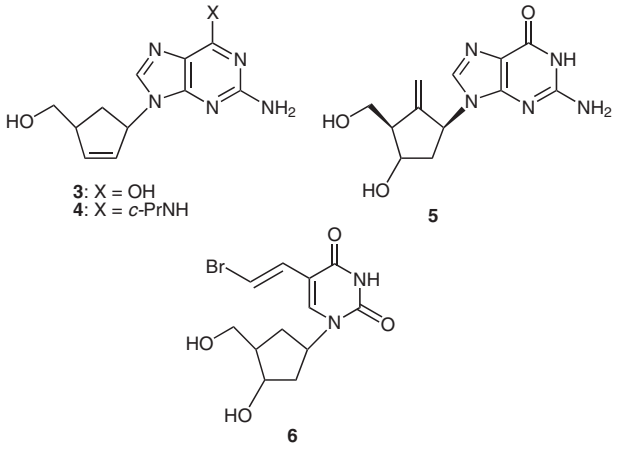
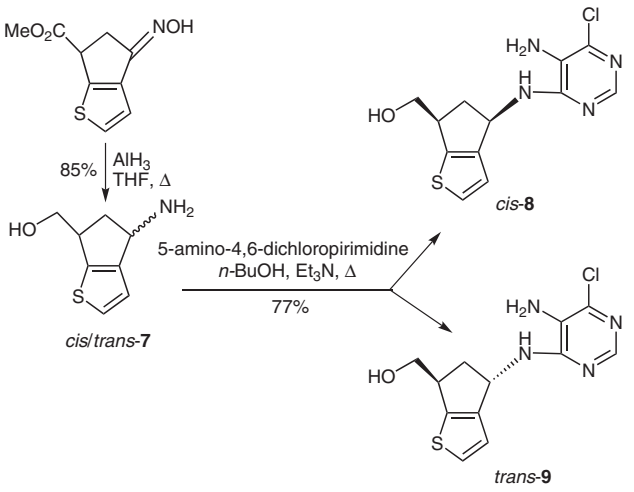


Figure 2 Carbanucleosides **3**–**6**



Scheme 1

In the search for ways of increasing the lipophilicity and polar interactions of the pseudosugar while maintaining the rigidity of this moiety, our group has now begun to explore a new class of analogues in which the aromatic ring of the indane system has been replaced by a heterocyclic aromatic ring system.[16] The results have been encouraging: for example, preliminary biological assays of purinylmethyl derivatives of 2-benzylcyclopenta[*c*]pyrazoles have found them to possess high activity against varicella zoster virus and cytomegalovirus at subcytotoxic concentrations,[17] and derivatives of 1-methylcyclopenta[*c*]pyrazoles have cytostatic activity.[18] We are currently exploring the case in which the pseudosugar is cyclopenta[*b*]thiophene; in the work reported here, we examined the dependence of the biological activity of some members of this family on the stereochemistry of the pseudosugar-nucleobase linkage.

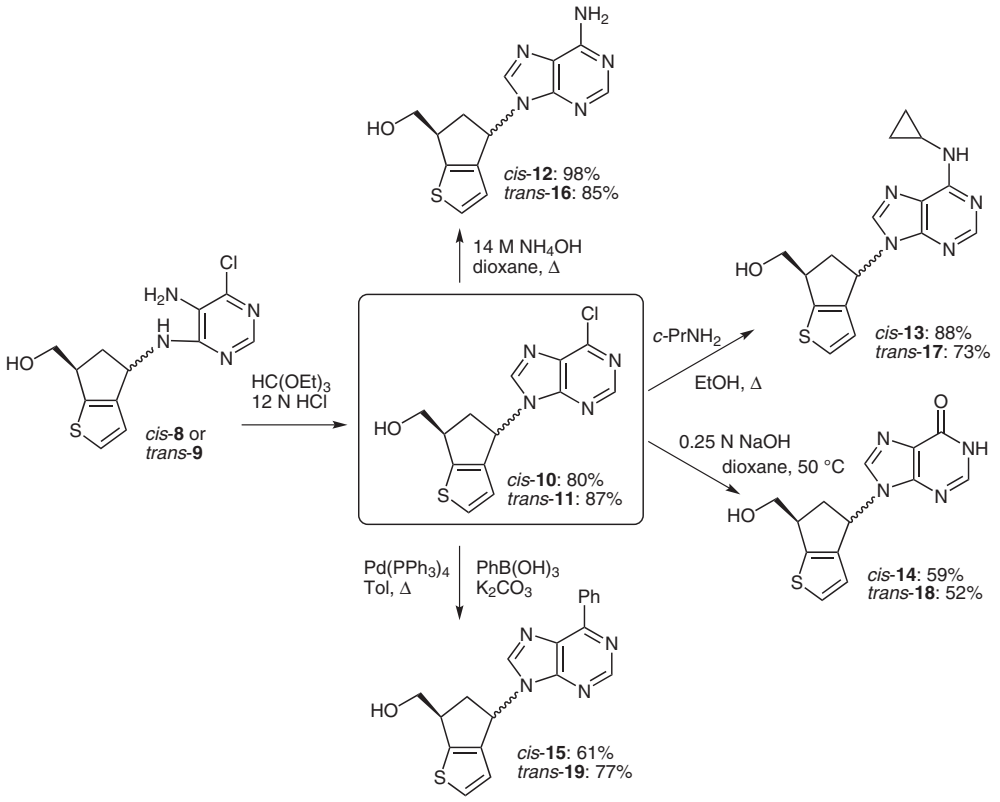
Carbanucleosides are generally prepared either by constructing the nucleobase on the amino group of a suitable amino alcohol,[19] or by direct coupling of the heterocyclic base with an appropriately functionalized carbocyclic system[16a,b,17] (e.g., by means of the Mitsunobu reaction).[13c,14a] In this work, we chose the former approach not only because it allows divergent synthesis of multiple CNs from a single pseudosugar intermediate, but also because it would hopefully allow easy separation of stereoisomers with *cis* and *trans* pseudosugar-nucleobase linkages (whereas in previous work[20] direct separation of the mixture of amino pseudosugar isomers *cis*/*trans*-**7** had been found to afford only moderate combined yields). Our hopes in this respect were fulfilled; thus, flash column chromatography of the heterocarbanucleoside precursors *cis*-**8** and *trans*-**9** (Scheme 1) was accomplished more efficiently (96%). These CNs have been synthesized in its racemic form, so the resolution of the enantiomers was planned for a later work, once the biological activities of the racemic mixtures were known.

The amino alcohol mixture *cis*/*trans*-**7** was synthesized as before,[20] in spectroscopically determined 1:1 isomer ratio and 55% combined yield, by reduction of the corresponding hydroxy iminoester in refluxing THF with AlH_3 that had been freshly prepared in quantitative yield from $LiAlH_4$ and H_2SO_4.[21] Reaction of *cis*/*trans*-**7** for 45 hours with 5-amino-4,6-dichloropyrimidine and Et_3N in refluxing *n*-BuOH afforded a mixture of *cis*-**8** and *trans*-**9** in 41% and 36% yield, respectively (the combined yield of 77% was less with shorter reaction times), and flash column chromatography of this mixture using 40:1 $CHCl_3$–MeOH as eluent efficiently separated *cis*-**8** from *trans*-**9** (in addition, a small amount of starting material was recovered and traces of 5-amino-4-chloro-6-hydroxypyrimidine were detected).

Treatment of *cis*-**8** and *trans*-**9** with triethyl orthoformate, for the synthesis of the five-membered ring of purine[22] afforded the corresponding 6-chloropurines, *cis*-**10** and *trans*-**11**, in 80% and 87% yield, respectively (Scheme 2). In turn, these heterocarbanucleosides were directly converted into the corresponding 6-amino, 6-cyclopropylamino, and 6-hydroxy derivatives by reaction with the appropriate nucleophile: reaction with NH_4OH in dioxane afforded *cis*-**12** and *trans*-**16** in 98% and 85% yield, respectively; reaction with cyclopropylamine in refluxing EtOH, *cis*-**13** (88%) and *trans*-**17** (73%); and reaction with 0.25 N NaOH in dioxane for 24 hours at 50 °C, *cis*-**14** (59%) and *trans*-**18** (52%).

The relative configuration of the heterocarbanucleoside *trans*-**18** was confirmed by means of X-ray crystallographic analysis of a single crystal obtained by recrystallization of a pure sample from 9:1 EtOAc–MeOH (Figure 3).[23]

In view of the high antineoplastic activities of certain 6-arylpurinyl nucleosides[15] and related acyclic nucleotide analogues[24] (including previous products of our group),[14a,b] we also synthesized the 6-arylpurinyl heterocarbanucleosides *cis*-**15** and *trans*-**19**, using Hocek's protocol[25] to achieve Suzuki–Miyaura cross-coupling[26] between 6-halopurines and boronic acids. Heating compounds *cis*-**10** and *trans*-**11** at 100 °C with phenylboronic acid, tetrakis(triphenylphosphine)palladium, and potassi-



Scheme 2

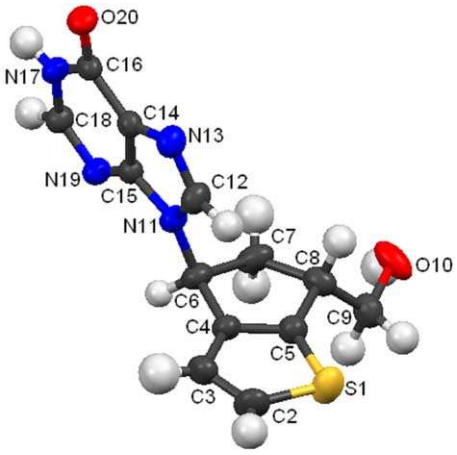


Figure 3 MERCURY projection (with 40% probability ellipsoids) of the molecular structure of *trans*-**18** (the atomic numbering is arbitrary)

um carbonate in anhydrous toluene afforded the 6-phenyl derivatives *cis*-**15** and *trans*-**19** in good yields. Attempts to improve these results by using the Buchwald methodology[27] were unsuccessful.

Previously established procedures[28] were employed to determine the *in vitro* antiviral activities of compounds **10**–**19** against a variety of DNA and RNA viruses. In human embryonic lung (HEL) cells: cytomegalovirus (CMV; strains AD-169 and Davis), herpes simplex virus 1 (HSV-1; strain KOS and the thymidine-kinase-deficient strain KOS ACVr), herpes simplex virus 2 (HSV-2; strain G), vaccinia virus, vesicular stomatitis virus (VSV), and both thymidine kinase-positive (TK^+) and thymidine kinase-deficient (TK^-) strains of varicellazoster virus (VZV). In HeLa cells: VSV, Coxsackie virus B4, and respiratory syncytial virus. In Vero cells: reovirus 1, Sindbis virus, Coxsackie virus B4, and Punta Toro virus. In HEL cells, compound **10** had an EC_{50} of 52 μM against a TK^+ VZV (OKA); compounds **15** and **19** had EC_{50}'s of 69 μM [eight times less than their MCCs (MCC = minimum cytotoxic concentration)] against vaccinia virus; and EC_{50}'s of 115 and 122 μM (five times less than their MCCs) were shown by compounds **13** and **19**, respectively, against HSV-2 G. Also, compounds **10** and **11** were both strong inhibitors of HEL cell growth, with CC_{50}'s of 32 and 4 μM, respectively.

In Vero cells, EC_{50}'s of 23 μM (compounds **15** and **19**) and 26 μM (compound **11**) (five times less than their MCCs) were shown against Punta Toro virus and by compound **11** against Coxsackie virus B4.

Compounds **10**–**19** were evaluated for their cytostatic activities against murine leukemia cells (L1210/0) and human T lymphoblastic leukemia cells (Molt4/C8 and CEM/0). Activity was quantified as IC_{50}, the concentration required to inhibit cell proliferation during the linear growth phase by 50%.[28] Against Molt4/C8 cells, compound **11** had an IC_{50} of 26 μM, and compounds **15** and **19** activities of 46 and 37 μM, respectively. Against CEM/0 cells, compounds **11** and **19** had IC_{50}'s of 42 and 40 μM, respectively. No compound had an IC_{50} of less than 40–50 μM against L1210/0 cells.

In conclusion, we have reported the synthesis of the new 6-substituted purinyl heterocarbanucleosides *cis*-**10**, **12**–**15** and *trans*-**11**, **16**–**19**, which like the well-known biologically active purinyl heterocarbanucleosides carbovir and abacavir have a pseudosugar (in this case cyclopenta[*b*]thiophenylmethanol) that features an endocyclic double bond. The *cis* and *trans* isomers were efficiently separated by flash column chromatography during construction of the nucleobase on the pseudosugar, and their relative stereochemistry was elucidated by X-ray crystallography of the inosine derivative *trans*-**18**. Greatest cytostatic activity was shown by compound **11**, with an IC_{50} of 26 μM against Molt4/C8 cells, followed by compounds **15** and **19**. Greatest antiviral activity was shown by compounds **11**, **15**, and **19**, which in Vero cells had EC_{50}'s of 26 μM (**11**) and 23 μM (**15** and **19**) (five times less than their MCCs) against Punta Toro virus and (in the case of compound **11**) Coxsackie virus B4.

Melting points are uncorrected and were determined in a Reichert Kofler Thermopan or in capillary tubes in a Büchi 510 apparatus. IR spectra were recorded on a Perkin-Elmer 1640 FTIR spectrophotometer. ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded in a Bruker AMX 300 spectrometer using TMS as internal reference (chemical shifts in δ values, *J* in Hz). EI and FAB mass spectra were recorded on HP5988A and Micromass Autospec spectrometers, respectively. Microanalyses were performed using a Perkin-Elmer 240B elemental analyzer by the Microanalysis Service of the University of Santiago. X-ray diffraction data were collected with an Enraf-Nonius CAD4 automatic diffractometer using the program CAD4-EXPRESS. Most reactions were monitored by TLC on precoated silica gel plates (Merck 60 F254, 0.25 mm). Synthesized products were purified by flash column chromatography on silica gel (Merck 60, 230–240 mesh), and were crystallized, if necessary. Solvents were dried by distillation prior to use.

(±)-{*cis*-4-[(5-Amino-6-chloropyrimidin-4-yl)amino]-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl}methanol (8) and (±)-{*trans*-4-[(5-Amino-6-chloropyrimidin-4-yl)amino]-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl}methanol (9)

5-Amino-4,6-dichloropyrimidine (1.04 g, 6.38 mmol) was added to a solution of the amino alcohol mixture (±)-*cis*/*trans*-**7** (0.6 g, 3.55 mmol) in anhyd *n*-BuOH (60 mL) and Et_3N (4 mL). This mixture was refluxed under argon for 45 h, cooled to r.t., and the solvents were removed under reduced pressure. Chromatography of the solid residue on silica gel (60 g) using 40:1 $CHCl_3$–MeOH as eluent afforded first (±)-*cis*-**8** (0.43 g, 41%) and then (±)-*trans*-**9** (0.38 g, 36%).

(±)-*cis*-8

An analytical sample was obtained by recrystallization from EtOAc; white solid; mp 197-198 °C; R_f = 0.23 ($CHCl_3$–MeOH, 20:1).

IR (KBr): 3256, 2991, 2934, 1582, 1505, 1482, 1425, 1059 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.77 (s, 1 H, pyrimidine 2-H), 7.35 (d, *J* = 4.9 Hz, 1 H, 2-H), 7.00 (d, *J* = 7.3 Hz, 1 H, D_2O exch., NH), 6.83 (d, *J* = 4.9 Hz, 1 H, 3-H), 5.48–5.46 (m, 1 H, 4-H), 5.09 (br s, 2 H, D_2O exch., NH_2), 4.98-4.95 (m, 1 H, D_2O exch., OH), 3.69–3.59 (m, 1 H, 6-H), 3.43–3.41 (m, 1 H, OCHH), 3.35–3.25 (m, 1 H, OCHH), 3.02–2.97 (m, 1 H, 5-H), 1.90–1.86 (m, 1 H, 5-H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 151.60 (pyrimidine C-6), 146.67 (pyrimidine C-4), 146.02 (pyrimidine C-5), 145.84 (pyrimidine C-2), 137.43 (C-6a), 129.46 (C-3), 123.88 (C-3a), 122.19 (C-2), 65.74 (CH_2O), 51.81 (C-4), 43.51 (C-6), 41.16 (C-5).

EIMS: *m*/*z* (%) = 297 (4, [M + 1]$^+$), 296 (11, [M$^+$]), 266 (3, [M$^+$ – CH_2O]), 153 (100, [M$^+$ – $C_4H_4ClN_4$]), 135 (90, [M$^+$ – $C_4H_6ClN_4O$]), 125 (28), 121 (34).

Anal. Calcd for $C_{12}H_{13}ClN_4OS$: C, 48.56; H, 4.42; Cl, 11.95; N, 18.88; S, 10.80. Found: C, 48.41; H, 4.51; Cl, 12.03; N, 18.72; S, 11.02.

(±)-*trans*-9

An analytical sample was obtained by recrystallization from EtOAc; white solid; mp 89–91 °C; R_f = 0.17 ($CHCl_3$–MeOH, 20:1).

IR (KBr): 3442, 3346, 3245, 2924, 1649, 1575, 1466, 1421, 1089 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.78 (s, 1 H, pyrimidine 2-H), 7.35 (d, *J* = 5.1 Hz, 1 H, 2-H), 7.01 (d, *J* = 7.2 Hz, 1 H, D_2O exch., NH), 6.86 (d, *J* = 4.9 Hz, 1 H, 3-H), 5.50–5.44 (m, 1 H, 4-H), 5.07 (br s, 2 H, D_2O exch., NH_2), 4.95–4.92 (m, 1 H, D_2O exch., OH), 3.59–3.50 (m, 1 H, 6-H), 3.48–3.41 (m, 2 H, OCH_2), 2.61–2.52 (m, 1 H, 5-H), 2.39–2.31 (m, 1 H, 5-H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 151.54 (pyrimidine C-6), 146.85 (pyrimidine C-4), 146.60 (pyrimidine C-5), 145.83 (pyrimidine C-2), 136.88 (C-6a), 129.49 (C-3), 123.91 (C-3a), 122.39 (C-2), 65.47 (CH_2O), 51.64 (C-4), 43.46 (C-6), 41.44 (C-5).

EIMS: *m*/*z* (%) = 296 (1, [M$^+$]), 278 (1, [M$^+$ – H_2O]), 153 (65, [M$^+$ – $C_4H_4ClN_4$]), 135 (100, [M$^+$ – $C_4H_6ClN_4O$]), 125 (38), 121 (60), 97 (31).

Anal. Calcd for $C_{12}H_{13}ClN_4OS$: C, 48.56; H, 4.42; Cl, 11.95; N, 18.88; S, 10.80. Found: C, 49.02; H, 4.38; Cl, 12.14; N, 18.67; S, 11.05.

(±)-[*cis*-4-(6-Chloro-9*H*-purin-9-yl)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl]methanol (10)

A mixture of (±)-*cis*-**8** (0.23 g, 0.78 mmol), triethyl orthoformate (4.3 mL, 38.3 mmol), dioxane (10 mL), and aq 12 N HCl (0.27 mL) was stirred at r.t. for 22 h. Once the reaction was judged to have terminated, the solvents were removed under reduced pressure. The resulting residue was dissolved in dioxane (5 mL) and treated with aq 0.5 N HCl (16 mL) for 2 h. The organic solvent was evaporated under reduced pressure, the aqueous layer was brought to pH 8 by the addition of aq 2 N NaOH (8 mL), and the resulting mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to dryness. Column chromatography of the residue on silica gel (8 g) using 80:1 CH_2Cl_2–MeOH as eluent yielded (±)-*cis*-**10** (0.19 g, 80%) as a white solid; mp 162–164 °C; R_f = 0.25 ($CHCl_3$–MeOH, 40:1).

IR (KBr): 3373, 3277, 1595, 1564, 1445, 1397, 1341, 1126, 1089 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.74 (s, 1 H, purine 8-H), 8.10 (s, 1 H, purine 2-H), 7.36 (d, *J* = 5.0 Hz, 1 H, 2-H), 6.74 (d, *J* = 5.0 Hz, 1 H, 3-H), 6.12 (dd, *J* = 8.6, 4.1 Hz, 1 H, 4-H), 3.95 and 3.77 (AB part of an ABM system, J_{AB} = 10.5, J_{AM} = 5.4 and J_{BM} = 4.4 Hz, 2 H, OCH_2), 3.66–3.59 (m, 1 H, 6-H), 3.51–3.41 (m, 1 H, 5-H), 2.95 (t, *J* = 4.5 Hz, 1 H, D_2O exch., OH), 2.47 (dt, *J* = 14.2, 4.3 Hz, 1 H, 5-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.16 (purine C-2), 151.88 (purine C-6), 151.22 (purine C-4), 148.93 (purine C-5), 144.82 (purine C-8), 142.35 (C-6a), 132.18 (C-3a), 131.94 (C-3), 121.26 (C-2), 65.74 (CH_2O), 55.51 (C-4), 43.79 (C-6), 41.70 (C-5).

FABMS: *m*/*z* (%) = 307 (15, [M + 1]$^+$), 306 (1, [M$^+$]), 288 (11, [M$^+$ – H_2O]), 155 (35), 154 (100, [M$^+$ – C_5HClN_4]), 153 (14), 137 (99, [M$^+$ – $C_5H_2ClN_4O$]), 109 (24).

Anal. Calcd for $C_{13}H_{11}ClN_4OS$: C, 50.90; H, 3.61; Cl, 11.56; N, 18.26; S, 10.45. Found: C, 50.68; H, 3.69; Cl, 11.70; N, 18.23; S, 10.52.

(±)-[*cis*-4-(6-Amino-9*H*-purin-9-yl)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl]methanol (12)

Concd NH_4OH (40 mL) was added to a solution of (±)-*cis*-**10** (0.06 g, 0.196 mmol) in dioxane (5 mL) and the mixture was refluxed for 42 h. After cooling to r.t., the solvents were evaporated under reduced pressure and the residue was chromatographed on silica gel (9 g) using 20:1 CH_2Cl_2–MeOH as eluent to give (±)-*cis*-**12** (0.055 g, 98%) as a yellowish solid. An analytical sample was obtained by recrystallization from EtOH; mp 213–215 °C; R_f = 0.11 (CH_2Cl_2–MeOH, 30:1).

IR (KBr): 3097, 2923, 2821, 1687, 1608, 1526, 1468, 1299, 1080 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.14 (s, 1 H, purine 8-H), 7.85 (s, 1 H, purine 2-H), 7.46 (d, *J* = 4.95 Hz, 1 H, 2-H), 7.22 (br s, 2 H, D_2O exch., NH_2), 6.76 (d, *J* = 5.0 Hz, 1 H, 3-H), 5.96 (dd, *J* = 8.1, 5.7 Hz, 1 H, 4-H), 5.01 (t, *J* = 4.8 Hz, 1 H, D_2O exch., OH), 3.66–3.60 (m, 1 H, OCHH), 3.54–3.47 (m, 1 H, OCHH), 3.45–3.39 (m, 1 H, 6-H), 3.25–3.15 (m, 1 H, 5-H), 2.33–2.24 (m, 1 H, 5-H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 156.00 (purine C-6), 152.36 (purine C-2), 149.36 (purine C-4), 147.47 (purine C-5), 143.03 (C-6a), 138.64 (purine C-8), 130.62 (C-3), 120.96 (C-2), 119.01 (C-3a), 64.63 (CH_2O), 53.82 (C-4), 43.29 (C-6), 40.34 (C-5).

FABMS: *m*/*z* (%) = 288 (19, $[M + 1]^+$), 287 (1, $[M^+]$), 155 (35, $[C_8H_{11}OS]^+$), 154 (95, $[C_8H_{10}OS]^+$), 137 (100, $[C_8H_9S]^+$), 135 (11, $[C_5H_5N_5]^+$), 109 (26), 105 (11).

Anal. Calcd for $C_{13}H_{13}N_5OS$: C, 54.34; H, 4.56; N, 24.37; S, 11.16. Found: C, 54.21; H, 4.65; N, 24.59; S, 11.01.

(±)-[*cis*-4-(6-Cyclopropylamino-9*H*-purin-9-yl)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl]methanol (13)

A mixture of (±)-*cis*-**10** (0.06 g, 0.20 mmol) and *c*-$PrNH_2$ (0.14 mL, 2.02 mmol) in anhyd EtOH (5 mL) was refluxed under argon for 3 h and then concentrated to dryness. The residue was chromatographed on silica gel (9 g) using 30:1 CH_2Cl_2–MeOH as eluent, yielding (±)-*cis*-**13** as a white solid (0.056 g, 88%). An analytical sample was obtained by recrystallization from EtOAc; mp 135–137 °C; R_f = 0.18 (CH_2Cl_2–MeOH, 30:1).

IR (KBr): 3242, 1738, 1618, 1474, 1309, 1265, 1053 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.44 (s, 1 H, purine 8-H), 7.62 (s, 1 H, purine 2-H), 7.32 (d, *J* = 5.0 Hz, 1 H, 2-H), 6.72 (d, *J* = 5.0 Hz, 1 H, 3-H), 6.11 (br s, 1 H, D_2O exch., NH), 5.99 (dd, *J* = 8.6, 4.7 Hz, 1 H, 4-H), 3.94–3.89 (m, 1 H, OCHH), 3.77–3.71 (m, 1 H, OCHH), 3.61–3.55 (m, 2 H, one of them D_2O exch., 6-H + OH), 3.46–3.35 (m, 1 H, *c*-Pr CH), 3.02–3.01 (m, 1 H, 5-H), 2.49 (dt, *J* = 14.1, 4.8 Hz, 1 H, 5-H), 0.94–0.88 (m, 2 H, *c*-Pr CH_2), 0.66–0.60 (m, 2 H, *c*-Pr CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.23 (purine C-6), 153.42 (purine C-2), 149.18 (purine C-4), 148.12 (purine C-5), 143.21 (C-6a) 138.97 (purine C-8), 131.46 (C-3), 121.44 (C-2), 120.87 (C-3a), 66.10 (CH_2O), 55.26 (C-4), 43.90 (C-6), 41.45 (C-5), 30.05 (*c*-Pr CH_2), 24.67 (*c*-Pr CH), 7.79 (*c*-Pr CH_2).

FABMS: *m*/*z* (%) = 328 (50, $[M + 1]^+$), 327 (4, $[M^+]$), 309 (23), 278 (27), 263 (15), 231 (68), 176 (16, $[C_8H_{10}N_5]^+$), 156 (11), 155 (37, $[C_8H_{11}OS]^+$), 154 (98, $[C_8H_{10}OS]$), 137 (100, $[C_8H_9S]$), 135 (10, $[C_5H_5N_5]$), 109 (23), 105 (10).

Anal. Calcd for $C_{16}H_{17}N_5OS$: C, 58.70; H, 5.23; N, 21.39; S, 9.79. Found: C, 58.51; H, 5.36; N, 21.48; S, 9.98.

(±)-6,9-Dihydro-9-[*cis*-(6-hydroxymethyl)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-4-yl)]-1*H*-purin-6-one (14)

Aq 0.25 N NaOH (8 mL) was added to a solution of (±)-*cis*-**10** (0.1 g, 0.33 mmol) in dioxane (15 mL). The mixture was heated at 50 °C for 24 h and cooled to r.t. The solvents were removed under reduced pressure and the solid residue (0.23 g) was purified by column chromatography on silica gel (10 g) using 30:1 CH_2Cl_2–MeOH as eluent to give (±)-*cis*-**14** (0.055 g, 59%) as a white solid; mp 219–221 °C; R_f = 0.08 (CH_2Cl_2–MeOH, 20:1).

IR (KBr): 3108, 2923, 2875, 1705, 1607, 1584, 1506, 1348, 1206, 1137, 1039 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.30 (br s, 1 H, D_2O exch., purine OH), 8.05 (s, 1 H, purine 8-H), 7.80 (s, 1 H, purine 2-H), 7.47 (d, *J* = 5.0 Hz, 1 H, 2-H), 6.77 (d, *J* = 5.0 Hz, 1 H, 3-H), 5.95 (dd, *J* = 8.1, 5.7 Hz, 1 H, 4-H), 5.01 (t, *J* = 4.9 Hz, 1 H, D_2O exch., CH_2OH), 3.66–3.59 (m, 1 H, 6-H), 3.53–3.36 (m, 2 H, OCH_2), 3.25–3.15 (m, 1 H, 5-H), 2.27 (dt, *J* = 13.6, 5.6 Hz, 1 H, 5-H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 157.21 (purine C-6), 148.54 (purine C-4), 148.10 (purine C-5), 145.89 (purine C-2), 142.88 (C-6a), 138.43 (purine C-8), 131.10 (C-3), 124.75 (C-3a), 121.29 (C-2), 64.93 (CH_2O), 54.65 (C-4), 43.64 (C-6), 40.96 (C-5).

FABMS: *m*/*z* (%) = 289 (35, $[M + 1]^+$), 288 (3, $[M^+]$), 262 (11), 231 (53), 156 (10), 155 (32, $[C_8H_{11}OS]^+$), 154 (90, $[C_8H_{10}OS]^+$), 137 (100, $[C_8H_9S]^+$), 135 (13, $[C_5H_3N_4O]^+$), 109 (32), 105 (13).

Anal. Calcd for $C_{13}H_{12}N_4O_2S$: C, 54.15; H, 4.20; N, 19.43; S, 11.12. Found: C, 54.25; H, 4.31; N, 19.24; S 11.08.

(±)-[*cis*-4-(6-Phenyl-9*H*-purin-9-yl)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl]methanol (15)

A mixture of (±)-*cis*-**10** (0.068 g, 0.22 mmol), phenylboronic acid (0.041 g, 0.33 mmol), $Pd(PPh_3)_4$ (0.012 g, 0.011 mmol), and K_2CO_3 (0.046 g, 0.33 mmol) in anhyd toluene (10 mL) was stirred under argon at 100 °C for 48 h, after which it was allowed to reach r.t. and the solvent was removed under reduced pressure. The solid residue was chromatographed on silica gel (13 g) using 2:1 hexane–EtOAc as eluent, and the product obtained after removal of the solvent was washed with Et_2O, yielding (±)-*cis*-**15** (0.047 g, 61%) as a white solid; mp 138–140 °C; R_f = 0.38 (hexane–EtOAc, 1:1).

IR (KBr): 3322, 2925, 1683, 1566, 1438, 1317, 1208, 1026 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.01 (s, 1 H, purine 8-H), 8.77 (dd, *J* = 7.9, 1.7 Hz, 2 H, 2′ + 6′-H_{arom}), 8.07 (s, 1 H, purine 2-H), 7.59–7.52 (m, 3 H, 3′ + 4′ + 5′-H_{arom}), 7.37 (d, *J* = 5.1 Hz, 1 H, 2-H), 6.78 (d, *J* = 5.0 Hz, 1 H, 3-H), 6.18 (dd, *J* = 8.5, 4.7 Hz, 1 H, 4-H), 3.97 and 3.77 (AB part of an ABM system, J_{AB} = 10.4, J_{AM} = 5.3 and J_{BM} = 4.7 Hz, 2 H, OCH_2), 3.67–3.61 (m, 1 H, 6-H), 3.53–3.42 (m, 1 H, 5-H), 2.51 (dt, *J* = 14.1, 4.8 Hz, 1H, 5-H), 2.42–2.35 (m, 1 H, D_2O exch., OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.88 (purine C-6), 152.56 (purine C-2), 148.23 (purine C-4), 143.56 (C-6a), 142.94 (purine C-8), 136.04 (purine C-5), 132.01 (C-1′$_{arom}$), 131.74 (CH_{arom}), 131.40 (C-3), 130.19 and 129.08 (4 × CH_{arom}), 121.41 (C-2), 120.93 (C-3a), 66.15 (CH_2O), 55.20 (C-4), 43.83 (C-6), 41.50 (C-5).

FABMS: *m*/*z* (%) = 349 (19, $[M + 1]^+$), 348 (1, $[M^+]$), 309 (17), 278 (26), 263 (16), 231 (74), 197 (17, $[C_{11}H_9N_4]^+$), 156 (11), 155 (36, $[C_8H_{11}OS]^+$), 154 (94, $[C_8H_{10}OS]^+$), 137 (100, $[C_8H_9S]^+$), 109 (26), 105 (12).

Anal. Calcd for $C_{19}H_{16}N_4OS$: C, 65.50; H, 4.63; N, 16.08; S, 9.20. Found: C, 65.34; H, 4.78; N, 15.91; S, 9.44.

(±)-[*trans*-4-(6-Chloro-9*H*-purin-9-yl)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl]methanol (11)

A mixture of (±)-*trans*-**9** (0.2 g, 0.68 mmol), triethyl orthoformate (3.8 mL, 33.8 mmol), dioxane (10 mL), and aq 12 N HCl (0.23 mL)

was stirred at r.t. for 3.5 h. Once the reaction was judged to have terminated, the mixture was concentrated to dryness under reduced pressure, and the residue was dissolved in dioxane (10 mL) and treated for 1.5 h with aq 0.5 N HCl (14 mL). (±)-*trans*-**11** was obtained as a white solid (0.18 g, 87%) in the same way as (±)-*cis*-**10**. An analytical sample was obtained by recrystallization from EtOAc; mp 134–136 °C; R_f = 0.24. ($CHCl_3$–MeOH, 40:1).

IR (KBr): 3372, 2926, 1590, 1560, 1485, 1395, 1334, 1202, 1042 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.75 (s, 1 H, purine 8-H), 7.82 (s, 1 H, purine 2-H), 7.37 (d, *J* = 5.0 Hz, 1 H, 2-H), 6.82 (d, *J* = 5.0 Hz, 1 H, 3-H), 6.17 (dd, *J* = 7.9, 2.4 Hz, 1 H, 4-H), 3.93–3.89 (m, 1 H, OCHH), 3.79–3.72 (m, 2 H, OCHH + 6-H), 3.05–2.96 (m, 1 H, 5-H), 2.75–2.67 (m, 1 H, 5-H), 2.28 (br s, 1 H, D_2O exch., OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.30 (purine C-2), 151.90 (purine C-6), 151.45 (purine C-4), 149.14 (purine C-5), 143.78 (purine C-8), 142.19 (C-6a), 132.43 (C-3a), 131.91 (C-3), 121.36 (C-2), 66.22 (CH_2O), 55.82 (C-4), 43.84 (C-6), 42.44 (C-5).

FABMS: *m*/*z* (%) = 307 (61, $[M + 1]^+$), 306 (2, $[M^+]$), 288 (2, $[M^+ – H_2O]$), 155 (51), 154 (100, $[M^+ – C_5HClN_4]$), 153 (45), 137 (91, $[M^+ – C_5H_2ClN_4O]$), 109 (25).

Anal. Calcd for $C_{13}H_{11}ClN_4OS$: C, 50.90; H, 3.61; Cl, 11.56; N, 18.26; S, 10.45. Found: C, 50.72; H, 3.57; Cl, 11.74; N, 18.18; S, 10.54.

(±)-[*trans*-4-(6-Amino-9*H*-purin-9-yl)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl]methanol (16)

Concd NH_4OH (22 mL) was added to a solution of (±)-*trans*-**11** (0.07 g, 0.23 mmol) in dioxane (5 mL), and the mixture was refluxed for 23 h. (±)-*trans*-**16** (0.055 g, 85%) was obtained as a beige solid by a procedure similar to that used for (±)-*cis*-**12**; mp 100–102 °C; R_f = 0.22 (CH_2Cl_2–MeOH, 20:1).

IR (KBr): 3319, 3172, 2923, 2854, 1646, 1579, 1471, 1409, 1369, 1329, 1299, 1207, 1037 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.14 (s, 1 H, purine 8-H), 7.83 (s, 1 H, purine 2-H), 7.43 (d, *J* = 4.9 Hz, 1 H, 2-H), 7.20 (br s, 2 H, D_2O exch., NH_2), 6.81 (d, *J* = 5.0 Hz, 1 H, 3-H), 5.98–5.95 (m, 1 H, 4-H), 5.03 (t, *J* = 4.7 Hz, 1 H, D_2O exch., OH), 3.75–3.61 (m, 2 H, OCH_2), 3.50–3.41 (m, 1 H, 6-H), 2.80–2.66 (m, 2 H, 5-H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 157.01 (purine C-6), 152.79 (purine C-2), 149.88 (purine C-4), 148.01 (purine C-5), 144.06 (C-6a), 139.07 (purine C-8), 130.84 (C-3), 121.38 (C-2), 118.93 (C-3a), 65.07 (CH_2O), 54.32 (C-4), 43.78 (C-6), 41.02 (C-5).

FABMS: *m*/*z* (%) = 288 (12, $[M + 1]^+$), 287 (1, $[M^+]$), 155 (36, $[C_8H_{11}OS]^+$), 154 (100, $[C_8H_{10}OS]^+$), 137 (99, $[C_8H_9S]^+$), 135 (10, $[C_5H_5N_5]^+$), 109 (22), 105 (10).

Anal. Calcd for $C_{13}H_{13}N_5O_5$: C, 54.34; H, 4.56; N, 24.37; S, 11.16. Found: C, 54.40; H, 4.62; N, 24.17; S, 11.08.

(±)-[*trans*-4-(6-Cyclopropylamino-9*H*-purin-9-yl)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl]methanol (17)

A solution of (±)-*trans*-**11** (0.084 g, 0.27 mmol) and *c*-$PrNH_2$ (0.2 mL, 2.89 mmol) in anhyd EtOH (7 mL) was refluxed under argon for 6 h. (±)-*trans*-**17** (0.056 g, 73%) was obtained as a white solid by a method similar to that used for (±)-*cis*-**13**. An analytical sample was obtained by recrystallization from 1:1 hexane–EtOAc; mp 73–75 °C; R_f = 0.16 (CH_2Cl_2–MeOH, 30:1).

IR (KBr): 3256, 2923, 1619, 1469, 1354, 1314, 1297, 1220, 1042 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.48 (s, 1 H, purine 8-H), 7.39 (s, 1 H, purine 2-H), 7.32 (d, *J* = 4.9 Hz, 1 H, 2-H), 6.81 (d, *J* = 4.9 Hz, 1 H, 3-H), 6.31 (br s, 1 H, D_2O exch., NH), 6.07 (dd, *J* = 7.5, 2.6 Hz, 1 H, 4-H), 3.91–3.84 (m, 1 H, OCHH), 3.73–3.69 (m, 2 H, OCHH + 6-H), 3.02–2.82 (m, 3 H, one of them D_2O exch., OH + 5-H + *c*-Pr CH), 2.69–2.62 (m, 1 H, 5-H), 1.05–0.84 (m, 2 H, *c*-Pr CH_2), 0.66–0.60 (m, 2 H, *c*-Pr CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.20 (purine C-6), 153.59 (purine C-2), 148.95 (purine C-4), 148.84 (purine C-5), 142.90 (C-6a), 138.25 (purine C-8), 131.35 (C-3), 121.63 (C-2), 120.48 (C-3a), 66.15 (CH_2O), 54.90 (C-4), 43.85 (C-6), 42.73 (C-5), 24.10 (*c*-Pr CH), 7.77 (2 × *c*-Pr CH_2).

FABMS: *m*/*z* (%) = 328 (25, $[M + 1]^+$), 327 (2, $[M^+]$), 309 (16), 278 (16), 263 (12), 231 (59), 176 (11, $[C_8H_{10}N_5]^+$), 156 (10), 155 (33, $[C_8H_{11}OS]^+$), 154 (100, $[C_8H_{10}OS]^+$), 137 (98, $[C_8H_9S]^+$), 135 (10, $[C_5H_5N_5]^+$), 109 (23), 105 (9).

Anal. Calcd for $C_{16}H_{17}N_5OS$: C, 58.70; H, 5.23; N, 21.39; S, 9.79. Found: C, 58.77; H, 5.42; N, 21.32; S, 9.68.

(±)-6,9-Dihydro-9-[*trans*-(6-hydroxymethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-4-yl)]-1*H*-purin-6-one (18)

Aq 0.25 N NaOH (7 mL) was added to a solution of (±)-*trans*-**11** (0.1 g, 0.33 mmol) in dioxane (15 mL), and the mixture was heated at 50 °C for 24 hours. (±)-*trans*-**18** (0.049 g, 52%) was isolated as a white solid following a procedure similar to that used for (±)-*cis*-**14**. An analytical sample was obtained by recrystallization from 9:1 EtOAc–MeOH; mp 225–227 °C; R_f = 0.10 (CH_2Cl_2–MeOH, 20:1).

IR (KBr): 3747, 3662, 2923, 1857, 1694, 1581, 1543, 1459, 1206, 1099, 1039 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 12.29 (br s, 1 H, D_2O exch., purine OH), 8.03 (s, 1 H, purine 8-H), 7.78 (s, 1 H, purine 2-H), 7.44 (d, *J* = 4.9 Hz, 1 H, 2-H), 6.81 (d, *J* = 5.0 Hz, 1 H, 3-H), 5.96 (dd, *J* = 7.3, 3.2 Hz, 1 H, 4-H), 5.03 (t, *J* = 4.5 Hz, 1 H, D_2O exch., CH_2OH), 3.73–3.60 (m, 2 H, OCH_2), 3.45–3.37 (m, 1 H, 6-H), 2.81–2.66 (m, 2 H, 5-H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 156.88 (purine C-6), 148.43 (purine C-4), 148.22 (purine C-5), 145.85 (purine C-2), 143.86 (C-6a), 138.55 (purine C-8), 130.96 (C-3), 124.78 (C-3a), 121.31 (C-2), 65.02 (CH_2O), 54.81 (C-4), 43.72 (C-6), 41.07 (C-5).

FABMS: *m*/*z* (%) = 289 (5, $[M + 1]^+$), 288 (5, $[M^+]$), 263 (13), 231 (65), 156 (10), 155 (37, $[C_8H_{11}OS]^+$), 154 (81, $[C_8H_{10}OS]^+$), 137 (100, $[C_8H_9S]^+$), 135 (11, $[C_5H_3N_4O]^+$), 110 (11), 109 (25), 105 (11).

Anal. Calcd for $C_{13}H_{12}N_4O_2S$: C, 54.15; H, 4.20; N, 19.43; S, 11.12. Found: C, 53.97; H, 4.28; N, 19.31; S, 11.30.

(±)-[*trans*-4-(6-Phenyl-9*H*-purin-9-yl)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl]methanol (19)

A mixture of (±)-*trans*-**11** (0.125 g, 0.41 mmol), phenylboronic acid (0.075 g, 0.62 mmol), $Pd(PPh_3)_4$ (0.023 g, 0.02 mmol), and K_2CO_3 (0.086 g, 0.62 mmol) in anhyd toluene (17 mL) was stirred under argon at 100 °C for 38 h. (±)-*trans*-**19** (0.11 g, 77%) was isolated as a white solid by a procedure similar to that used for (±)-*cis*-**15**; mp 166–168 °C; R_f = 0.21 (hexane–EtOAc, 1:1).

IR (KBr): 3321, 2916, 1567, 1496, 1407, 1323, 1206, 1127, 1024 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.99 (s, 1 H, purine 8-H), 8.83–8.81 (m, 2 H, 2′ + 6′-H_{arom}), 8.42 (s, 1 H, purine 2-H), 7.59–7.57 (m, 3 H, 3′ + 4′ + 5′-H_{arom}), 7.44 (d, *J* = 4.9 Hz, 1 H, 2-H), 6.85 (d, *J* = 4.9 Hz, 1 H, 3-H), 6.20–6.17 (m, 1 H, 4-H), 5.07 (t, *J* = 4.9 Hz, 1 H, D_2O exch., OH), 3.81–3.79 (m, 1 H, OCHH), 3.70–3.66 (m, 1 H, OCHH), 3.50–3.45 (m, 1 H, 6-H), 2.85–2.81 (m, 2 H, 5-H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 153.02 (purine C-6), 152.40 (purine C-4), 152.11 (purine C-2), 149.07 (C-6a), 145.02 (purine C-8), 143.16 (purine C-5), 135.80 (C-1′$_{arom}$), 131.37 (C-3), 131.13 (CH_{arom}), 131.00 (C-3a), 129.70 and 129.01 (4 × CH_{arom}), 121.39 (C-2), 65.07 (CH_2O), 54.89 (C-4), 43.89 (C-6), 40.79 (C-5).

FABMS: *m/z* (%) = 349 (40, $[M + 1]^+$), 348 (1, $[M^+]$), 309 (13), 278 (17), 263 (13), 231 (68), 197 (37, $[C_{11}H_9N_4]^+$), 156 (9), 155 (27, $[C_8H_{11}OS]^+$), 154 (89, $[C_8H_{10}OS]^+$), 137 (100, $[C_8H_9S]^+$), 109 (30), 105 (12).

Anal. Calcd for $C_{19}H_{16}N_4OS$: C, 65.50; H, 4.63; N, 16.08; S, 9.20. Found: C, 65.28; H, 4.81; N, 16.18; S, 9.31.

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