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# A convenient synthesis of new 6-substituted purinylcarbanucleosides on cyclopenta[b]thiophene

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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 *cis* and *trans* intermediates during preparation of the 6-chloropurine derivatives allowed 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-phenyl-purinyl analogues *cis*-**15** and *trans*-**19** were prepared from *cis*-**10** and *trans*-**11** using Suzuki-Miyaura methodology.

## Introduction

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 non-toxic 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]

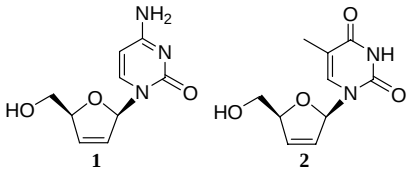



**Figure 1**

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 (respectively d4C (**1**) and d4T (**2**); 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]

In carbanucleosides (CNs),[8] the D-ribose moiety of the natural nucleosides is replaced by an aliphatic or aromatic carbocycle. CNs 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 longer than 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.

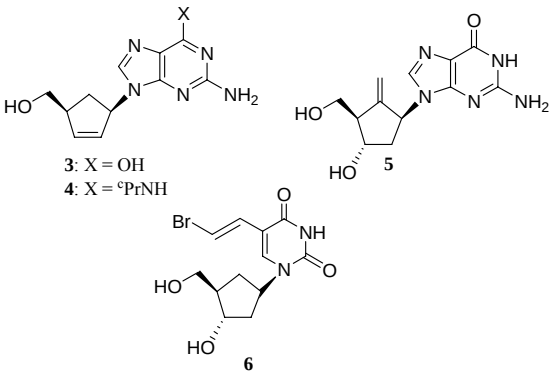



**Figure 2**

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 leukaemia cell lines (Molt4/C8 and CEM/0) and murine leukaemia 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]

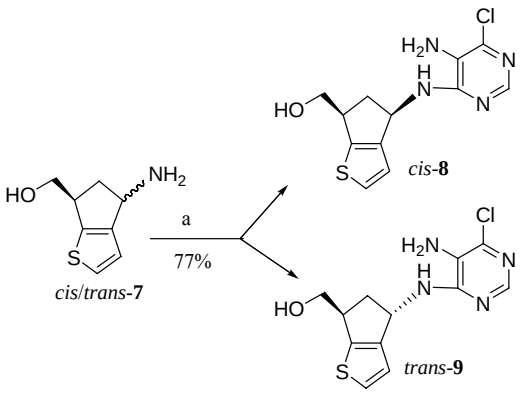
In the search for ways of increasing the lipophilicity and polar interactions of the pseudosugar while maintaining the rigidity of this moiety, our group has now begun to explore a new class of analogues in which the aromatic ring of the indane system has been replaced by a heterocyclic aromatic ring 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*]thiopene; 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.

CNs are generally prepared either by constructing the nucleobase on the amino group of a suitable aminoalcohol,[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, flash column chromatography of the heterocarbanucleoside precursors *cis*-**8** and *trans*-**9** (Scheme 1) was accomplished more eficiently (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.

## Results and discussion

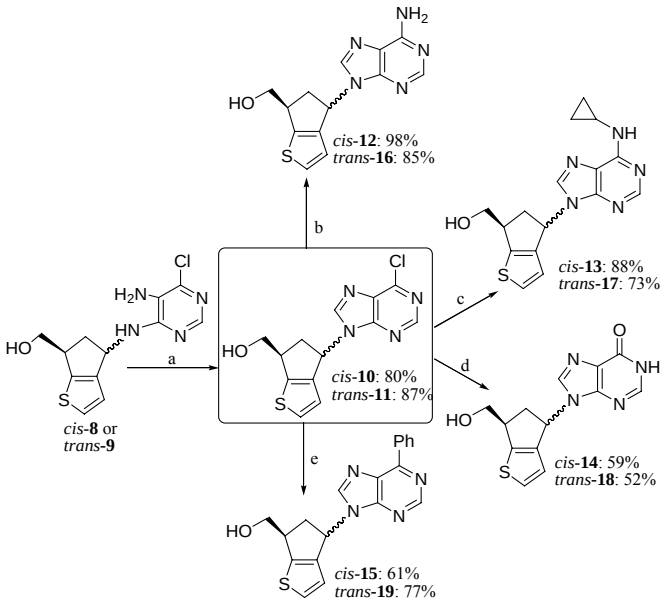
The aminoalcohol mixture *cis*/*trans*-**7** was synthesized as before,[20] in spectroscopically determined 1:1 isomer ratio and 55% combined yield, by reduction of the corresponding hydroxyiminoester in refluxing THF with $AlH_3$ that had been freshly prepared in quantitative yield from $LiAlH_4$ and $H_2SO_4$.[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).




**Scheme 1.** *a*) 5-Amino-4,6-dichloropyrimidine,$^n$BuOH, $Et_3N$, Δ.

Treatment of *cis*-**8** and *trans*-**9** with triethyl orthoformiate under the classical conditions for synthesis of the 5-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-cyclopropyl-amino 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 50ºC, *cis*-**14** (59%) and *trans*-**18** (52%).




**Scheme 2**. (*a*) $HC(OEt)_3$, 12 N HCl; (*b*) 14 M $NH_4OH$, dioxane, Δ; (*c*) $^{c}PrNH_2$, EtOH, Δ; (*d*) 0.25 N NaOH, dioxane, 50$^{o}$C; (*e*) $PhB(OH)_3$, $K_2CO_3$, $Pd(PPh_3)_4$.

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]

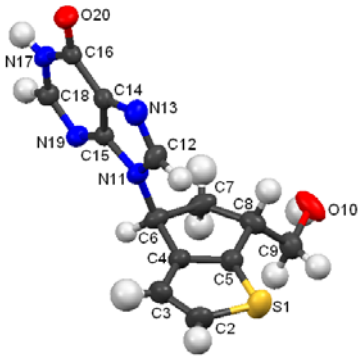



**Figure 3.** MERCURY projection (with 40% probability ellipsoids) of the molecular structure of *trans*-**18** (the atomic numbering is arbitrary).

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 100ºC with phenylboronic acid, tetrakis(triphenylphosphine)-palladium and potassium carbonate in dry 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.

## Experimental

### 3.1 General

Melting points are uncorrected and were determined in a Reichert Kofler Thermopan or in capillary tubes in a Büchi 510 apparatus. Infrared spectra were recorded in 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 in a Perkin-Elmer 240B elemental analyser 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 pre-coated silicagel plates (Merck 60 F254, 0.25 mm). Synthesized products were purified by flash column chromatography on silicagel (Merck 60, 230-240 mesh), and were crystallized if necessary. Solvents were dried by distillation prior to use.

**3.1.1 (±)-{*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 aminoalcohol mixture (±)-*cis*/*trans*-**7** (0.6 g, 3.55 mmol) in dry *n*-butanol (60 mL) and triethylamine (4 mL). This mixture was refluxed under Ar for 45 hours, and once cool, 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. M.p. 197−198°C. $R_f$ (20:1 $CHCl_3$/MeOH) = 0.23. IR (KBr): $\tilde{\nu}$ = 3256, 2991, 2934, 1582, 1505, 1482, 1425 and 1059 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ: 7.77 (s, 1H, pyrimidine 2-H), 7.35 (d, 1H, *J* = 4.9 Hz, 2-H), 7.00 (d, 1H, *J* = 7.3 Hz, $D_2O$ exch., NH), 6.83 (d, 1H, *J* = 4.9 Hz, 3-H), 5.48-5.46 (m, 1H, 4-H), 5.09 (br s, 2H, $D_2O$ exch., $NH_2$), 4.98−4.95 (m, 1H, $D_2O$ exch., OH), 3.69−3.59 (m, 1H, 6-H), 3.43−3.41 (m, 1H, OC<u>H</u>H), 3.35−3.25 (m, 1H, OCH<u>H</u>), 3.02−2.97 (m, 1H, 5-H), 1.90−1.86 (m, 1H, 5-H) ppm. $^{13}C$ 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) ppm. 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). $C_{12}H_{13}ClN_4OS$ (296.05): calcd. 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. M.p. 89−91°C. $R_f$ (20:1 $CHCl_3$/MeOH) = 0.17. IR (KBr): $\tilde{\nu}$ = 3442, 3346, 3245, 2924, 1649, 1575, 1466, 1421 and 1089 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ: 7.78 (s, 1H, pyrimidine 2-H), 7.35 (d, 1H, *J* = 5.1 Hz, 2-H), 7.01 (d, 1H, *J* = 7.2 Hz, $D_2O$

exch., NH), 6.86 (d, 1H, *J* = 4.9 Hz, 3-H), 5.50−5.44 (m, 1H, 4-H), 5.07 (br s, 2H, $D_2O$ exch., $NH_2$), 4.95−4.92 (m, 1H, $D_2O$ exch., OH), 3.59−3.50 (m, 1H, 6-H), 3.48−3.41 (m, 2H, $OCH_2$), 2.61−2.52 (m, 1H, 5-H), 2.39−2.31 (m, 1H, 5-H) ppm. $^{13}C$ 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) ppm. 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). $C_{12}H_{13}ClN_4OS$ (296.05): calcd. 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.

**3.1.2 (±)-[*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 orthoformiate (4.3 mL, 38.3 mmol), dioxane (10 mL) and 12 N HCl (0.27 mL) was stirred at room temperature for 22 hours. 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 0.5 N HCl (16 mL) for 2 hours. The organic solvent was evaporated under reduced pressure, the aqueous layer was brought to pH 8 by addition of 2 N NaOH (8 mL), and the resulting mixture was extracted with EtOAc (3×50 mL), dried over $Na_2SO_4$ 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. M.p. 162−164ºC. $R_f$ (40:1 $CHCl_3$/MeOH) = 0.25. IR (KBr): ν̃ = 3373, 3277, 1595, 1564, 1445, 1397, 1341, 1126 and 1089 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ: 8.74 (s, 1H, purine 8-H), 8.10 (s, 1H, purine 2-H), 7.36 (d, 1H, *J* = 5.0 Hz, 2-H), 6.74 (d, 1H, *J* = 5.0 Hz, 3-H), 6.12 (dd, 1H, *J* = 8.6 and 4.1 Hz, 4-H), 3.95 and 3.77 (the AB part of an ABM system, 2H, $J_{AB}$ = 10.5, $J_{AM}$ = 5.4 and $J_{BM}$ = 4.4 Hz, $OCH_2$), 3.66−3.59 (m, 1H, 6-H), 3.51−3.41 (m, 1H, 5-H), 2.95 (t, 1H, *J* = 4.5 Hz, $D_2O$ exch., OH), 2.47 (dt, 1H, *J* = 14.2 and 4.3 Hz, 5-H) ppm. $^{13}C$ 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) ppm. 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). $C_{13}H_{11}ClN_4OS$ (306.03): calcd. 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.

**3.1.3 (±)-[*cis*-4-(6-Amino-9*H*-purin-9-yl)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl]methanol (12).** Concentrated $NH_4OH$ (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 hours. Once cool, the solvents were evaporated under reduced pressure and chromatography of the residue on silica gel (9 g) using 20:1 $CH_2Cl_2$ as eluent yielded (±)-*cis*-**12** (0.055 g, 98%) as a yellowish solid. An analytical sample was obtained by recrystallization from EtOH. M.p. 213−215ºC. $R_f$ (30:1 $CH_2Cl_2$/MeOH) = 0.11. IR (KBr): $\tilde{\nu}$ = 3097, 2923, 2821, 1687, 1608, 1526, 1468, 1299 and 1080 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ: 8.14 (s, 1H, purine 8-H), 7.85 (s, 1H, purine 2-H), 7.46 (d, 1H, *J* = 4.95 Hz, 2-H), 7.22 (br s, 2H, $D_2O$ exch., $NH_2$), 6.76 (d, 1H, *J* = 5.0 Hz, 3-H), 5.96 (dd, 1H, *J* = 8.1 and 5.7 Hz, 4-H), 5.01 (t, 1H, *J* = 4.8 Hz, $D_2O$ exch., OH), 3.66−3.60 (m, 1H, OC<u>H</u>H), 3.54−3.47 (m, 1H, OCH<u>H</u>), 3.45−3.39 (m, 1H, 6-H), 3.25−3.15 (m, 1H, 5-H), 2.33−2.24 (m, 1H, 5-H) ppm. $^{13}C$ 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) ppm. 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). $C_{13}H_{13}N_5OS$ (287.08): calcd. 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.

**3.1.4 (±)-[*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 cyclopropylamine (0.14 mL, 2.02 mmol) in dry EtOH (5 mL) was refluxed under Ar for 3 hours and then concentrated to dryness. The residue was chromatrographed 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. M.p. 135−137ºC. $R_f$ (30:1 $CH_2Cl_2$/MeOH) = 0.18. IR (KBr): $\tilde{\nu}$ = 3242, 1738, 1618, 1474, 1309, 1265 and 1053 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ: 8.44 (s, 1H, purine 8-H), 7.62 (s, 1H, purine 2-H), 7.32 (d, 1H, *J* = 5.0 Hz, 2-H), 6.72 (d, 1H, *J* = 5.0 Hz, 3-H), 6.11 (br s, 1H, $D_2O$ exch., NH), 5.99 (dd, 1H, *J* = 8.6 and 4.7 Hz, 4-H), 3.94−3.89 (m, 1H, OC<u>H</u>H), 3.77−3.71 (m, 1H, OCH<u>H</u>), 3.61−3.55 (m, 2H, one of them $D_2O$ exch., 6-H + OH), 3.46−3.35 (m, 1H, cyclopropyl CH), 3.02−3.01 (m, 1H, 5-H), 2.49 (dt, 1H, *J* = 14.1 and 4.8 Hz, 5-H), 0.94−0.88 (m, 2H, cyclopropyl $CH_2$), 0.66−0.60 (m, 2H, cyclopropyl $CH_2$) ppm. $^{13}C$ 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 (cyclopropyl $CH_2$), 24.67 (cyclopropyl CH), 7.79 (cyclopropyl $CH_2$) ppm. 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). $C_{16}H_{17}N_5OS$ (327.12): calcd. 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.

**3.1.5. (±)-6,9-Dihydro-9-[*cis*-(6-hydroxymethyl)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-4-yl)]-1*H*-purin-6-one (14).** 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 then cooled, 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. From the non-void fractions, (±)-*cis*-**14** (0.055 g, 59%) was obtained as a white solid. M.p. 219−221ºC. $R_f$ (20:1 $CH_2Cl_2$/MeOH) = 0.08. IR (KBr): ν̃ = 3108, 2923, 2875, 1705, 1607, 1584, 1506, 1348, 1206, 1137 and 1039 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ: 12.30 (br s, 1H, $D_2O$ exch., purine OH), 8.05 (s, 1H, purine 8-H), 7.80 (s, 1H, purine 2-H), 7.47 (d, 1H, *J* = 5.0 Hz, 2-H), 6.77 (d, 1H, *J* = 5.0 Hz, 3-H), 5.95 (dd, 1H, *J* = 8.1 and 5.7 Hz, 4-H), 5.01 (t, 1H, *J* = 4.9 Hz, $D_2O$ exch., $CH_2O\underline{H}$), 3.66−3.59 (m, 1H, 6-H), 3.53−3.36 (m, 2H, $OCH_2$), 3.25−3.15 (m, 1H, 5-H), 2.27 (dt, 1H, *J* = 13.6 and 5.6 Hz, 5-H) ppm. $^{13}C$ 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) ppm. 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). $C_{13}H_{12}N_4O_2S$ (288.07): calcd. 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.

**3.1.6 (±)-[*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 dry toluene (10 mL) was stirred under Ar at 100°C for 48 hours, after which it was allowed to reach room temperature 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 from the non-void fractions after removal of the solvent was washed with diethyl ether, yielding (±)-*cis*-**15** (0.047 g, 61%) as a white solid. M.p. 138−140ºC. $R_f$ (1:1 hexane/EtOAc) = 0.38. IR (KBr): ν̃ = 3322, 2925, 1683, 1566, 1438, 1317, 1208 and 1026 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ: 9.01 (s, 1H, purine 8-H), 8.77 (dd, 2H, *J* = 7.9 and 1.7 Hz, 2' + 6'-$H_{arom}$), 8.07 (s, 1H, purine 2-H), 7.59−7.52 (m, 3H, 3' + 4' + 5'-$H_{arom}$), 7.37 (d, 1H, *J* = 5.1 Hz, 2-H), 6.78 (d, 1H, *J* = 5.0 Hz, 3-H), 6.18 (dd, 1H, *J* = 8.5 and 4.7 Hz, 4-H), 3.97 and 3.77 (the AB part of an ABM system, 2H, $J_{AB}$ = 10.4, $J_{AM}$ = 5.3 and $J_{BM}$ = 4.7 Hz, $OCH_2$), 3.67−3.61 (m, 1H, 6-H), 3.53−3.42 (m, 1H, 5-H), 2.51 (dt, 1H, *J* = 14.1 and 4.8 Hz, 5-H), 2.42−2.35 (m, 1H, $D_2O$ exch., OH) ppm. $^{13}C$ 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) ppm. 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). $C_{19}H_{16}N_4OS$ (348.10): calcd. 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.

**3.1.7 (±)-[*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 orthoformiate (3.8 mL, 33.8 mmol), dioxane (10 mL) and 12 N HCl (0.23 mL) was stirred at room temperature for 3.5 hours. 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 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. M.p. 134−136ºC. $R_f$ (40:1 $CHCl_3$/MeOH) = 0.24. IR (KBr): ν̃ = 3372, 2926, 1590, 1560, 1485, 1395, 1334, 1202 and 1042 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ: 8.75 (s, 1H, purine 8-H), 7.82 (s, 1H, purine 2-H), 7.37 (d, 1H, *J* = 5.0 Hz, 2-H), 6.82 (d, 1H, *J* = 5.0 Hz, 3-H), 6.17 (dd, 1H, *J* = 7.9 and 2.4 Hz, 4-H), 3.93−3.89 (m, 1H, OC<u>H</u>H), 3.79−3.72 (m, 2H, OCH<u>H</u> + 6-H), 3.05−2.96 (m, 1H, 5-H), 2.75−2.67 (m, 1H, 5-H), 2.28 (br s, 1H, $D_2O$ exch., OH) ppm. $^{13}C$ 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) ppm. 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). $C_{13}H_{11}ClN_4OS$ (306.03): calcd. 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.

**3.1.8 (±)-[*trans*-4-(6-Amino-9*H*-purin-9-yl)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl]methanol (16).** Concentrated $NH_4OH$ (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 hours. (±)-*trans*-**16** (0.055 g, 85%) was obtained as a beige solid by a procedure similar to that used for (±)-*cis*-**12**. M.p. 100−102°C. $R_f$ (20:1 $CH_2Cl_2$/MeOH) = 0.22. IR (KBr): $\tilde{\nu}$ = 3319, 3172, 2923, 2854, 1646, 1579, 1471, 1409, 1369, 1329, 1299, 1207 and 1037 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ: 8.14 (s, 1H, purine 8-H), 7.83 (s, 1H, purine 2-H), 7.43 (d, 1H, *J* = 4.9 Hz, 2-H), 7.20 (br s, 2H, $D_2O$ exch., $NH_2$), 6.81 (d, 1H, *J* = 5.0 Hz, 3-H), 5.98−5.95 (m, 1H, 4-H), 5.03 (t, 1H, *J* = 4.7 Hz, $D_2O$ exch., OH), 3.75−3.61 (m, 2H, $OCH_2$), 3.50−3.41 (m, 1H, 6-H), 2.80−2.66 (m, 2H, 5-H) ppm. $^{13}C$ 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) ppm. 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). $C_{13}H_{13}N_5O_5$ (287.08): calcd. 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.

**3.1.9 (±)-[*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 cyclopropylamine (0.2 mL, 2.89 mmol) in dry EtOH (7 mL) was refluxed under Ar for 6 hours. (±)-*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. M.p. 73−75°C. $R_f$ (30:1 $CH_2Cl_2$/MeOH) = 0.16. IR (KBr): $\tilde{\nu}$ = 3256, 2923, 1619, 1469, 1354, 1314, 1297, 1220 and 1042 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ: 8.48 (s, 1H, purine 8-H), 7.39 (s, 1H, purine 2-H), 7.32 (d, 1H, *J* = 4.9 Hz, 2-H), 6.81 (d, 1H, *J* = 4.9 Hz, 3-H), 6.31 (br s, 1H, $D_2O$ exch., NH), 6.07 (dd, 1H, *J* = 7.5 and 2.6 Hz, 4-H), 3.91−3.84 (m, 1H, OC<u>H</u>H), 3.73−3.69 (m, 2H, OCH<u>H</u> + 6-H), 3.02−2.82 (m, 3H, one of them $D_2O$ exch., OH + 5-H + cyclopropyl CH), 2.69−2.62 (m, 1H, 5-H), 1.05−0.84 (m, 2H, cyclopropyl $CH_2$), 0.66−0.60 (m, 2H, cyclopropyl $CH_2$) ppm. $^{13}C$

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 (cyclopropyl CH), 7.77 (2 × cyclopropyl $CH_2$) ppm. 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). $C_{16}H_{17}N_5OS$ (327.12): calcd. 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.

**3.1.10. (±)-6,9-Dihydro-9-[*trans*-(6-hydroxymethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-4-yl)]-1*H*-purin-6-one (18).** 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. M.p. 225−227°C. $R_f$ (20:1 $CH_2Cl_2$/MeOH) = 0.10. IR (KBr): ν̃ = 3747, 3662, 2923, 1857, 1694, 1581, 1543, 1459, 1206, 1099 and 1039 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ: 12.29 (br s, 1H, $D_2O$ exch., purine OH), 8.03 (s, 1H, purine 8-H), 7.78 (s, 1H, purine 2-H), 7.44 (d, 1H, *J* = 4.9 Hz, 2-H), 6.81 (d, 1H, *J* = 5.0 Hz, 3-H), 5.96 (dd, 1H, *J* = 7.3 and 3.2 Hz, 4-H), 5.03 (t, 1H, *J* = 4.5 Hz, $D_2O$ exch., $CH_2O\underline{H}$), 3.73−3.60 (m, 2H, $OCH_2$), 3.45−3.37 (m, 1H, 6-H), 2.81−2.66 (m, 2H, 5-H) ppm. $^{13}C$ 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) ppm. 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). $C_{13}H_{12}N_4O_2S$ (288.07): calcd. 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.

**3.1.11 (±)-[*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 dry toluene (17 mL) was stirred under Ar at 100°C for 38 hours. (±)-*trans*-**19** (0.11 g, 77%) was isolated as a white solid by a procedure similar to that used for (±)-*cis*-**15**. M.p. 166−168°C. $R_f$ (1:1 hexane/EtOAc) = 0.21. IR (KBr): ν̃ = 3321, 2916, 1567, 1496, 1407, 1323, 1206, 1127 and 1024 $cm^{-1}$. $^1H$ NMR (300 MHz,

DMSO-$d_6$) δ: 8.99 (s, 1H, purine 8-H), 8.83−8.81 (m, 2H, 2' + 6'-$H_{arom}$), 8.42 (s, 1H, purine 2-H), 7.59−7.57 (m, 3H, 3' + 4' + 5'-$H_{arom}$), 7.44 (d, 1H, *J* = 4.9 Hz, 2-H), 6.85 (d, 1H, *J* = 4.9 Hz, 3-H), 6.20−6.17 (m, 1H, 4-H), 5.07 (t, 1H, *J* = 4.9 Hz, $D_2O$ exch., OH), 3.81−3.79 (m, 1H, OCHH), 3.70−3.66 (m, 1H, OCHH), 3.50−3.45 (m, 1H, 6-H), 2.85−2.81 (m, 2H, 5-H) ppm. $^{13}C$ 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) ppm. 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). $C_{19}H_{16}N_4OS$ (348.10): calcd. 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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**References**

[1] a) K. Vermeire, D. Schols, T. W. Bell, *Curr. Med. Chem*. **2006**, *13*, 731. b) E. De Clercq, *J. Med. Chem.* **2005**, *48*, 1297. c) E. De Clercq, *Front. Med. Chem*. **2004**, *1*, 543. d) A. Lazzarin, B. Clotet, D. Cooper, J. Reynes, K. Arastéh, M. Nelson, C. Katlama, H.-J. Stellbrink, J.-F. Delfraissy, J. Lange, L. Huson, R. DeMasi, C. Wat, J. Delehanty, C. Drobnes, M. Salgo, *N. Engl. J. Med*. **2003**, *348*, 2186.

[2] T. S. Mansour, R. Storer, *Curr. Pharm. Des.* **1997**, *3*, 227.

[3] a) B. D. Cheson, M. J. Keating, W. Plunkett, eds., *Nucleoside Analogs in Cancer Therapy*, Marcel Dekker, New York, **1997**. b) E. De Clercq, *Clin. Microb. Rev.* **1997**, *10*, 674. c) E. De Clercq, *Curr. Med. Chem*. **2001**, *8*, 1543. d) J. Ena, F. Pasquau, *Clin. Infect. Dis*. **2003**, *36*, 1186. e) M. Louie, C. Hogan, M. Di Mascio, A. Hurley, V. Simon, J. Rooney, N. Ruiz, S. Brun, E. Sun, A. S. Perelson, D. D. Ho, M. Markowitz, *J. Infect. Dis*. **2003**, *187*, 896.

[4] J. Balzarini, G.-J. Kang, M. Dala, P. Herdewijn, E. De Clercq, S. Broker, D. G. Johns, *Mol. Pharmacol*. **1987**, *32*, 162.

[5] A. P. Lea, D. Faulds, *Drugs* **1996**, *51*, 846.

[6] A. A. Krayevsky, K. A. Watanabe, *Modified Nucleosides as Anti-AIDS Drugs: Current Status and Perspectives,* Bioinform, Moscow, **1993.**

[7] S. Thomas, J. E. McDowall, V. Cheah, A. Bye, M. B. Segal, *The entry of Abacavir into the Guinea-pig Brain: Comparison with Other Reverse Transcriptase Inhibitors,* presented at the 12th World AIDS Conference, Geneva, **1998**.

[8] For recent reviews of the biological properties of CNs, see: a) J. H. Cho, D. L. Bernard, R. W. Sidwell, E. R. Kern, C. K. Chu, *J. Med. Chem.* **2006**, *49*, 1140. b) S. W. Schneller, *Curr. Top. Med. Chem.* **2002**, *2*, 1087. c) J. B. Rodríguez, M. J. Comin, *Mini Rev. Med. Chem*. **2003**, *3*, 95. d) E. Ichicawa, K. Kato, *Curr. Med. Chem*. **2001**, *8*, 385. e) X.-F. Zhu, *Nucleosides, Nucleotides & Nucleic Acids* **2000**, *19*, 651. f) L. Agrofoglio, S. R. Challand, *Acyclic, Carbocyclic and L-Nucleosides,* Klewer Academic, Dordrecht, The Netherlands, **1998**.

[9] M. T. Crimmins, B. W. King, *J. Org. Chem.* **1996**, *61*, 4192.

[10] a) R. H. Foster, D. Faulds, *Drugs* **1998**, *55*, 729. b) S. M. Daluge, M. T. Martín, B. R. Sickles, D. A. Livingston, *Nucleosides, Nucleotides & Nucleic Acids* **2000**, *19*, 297. c) W. B. Mahony, B. A. Domin, S. M. Daluge, T. P. Zimmerman, *Biochemical Pharmacology* **2004**, *68*, 1797. d) M. Opravil, B. Hirschel, A. Lazzarin, H. Furrer, J.-P. Chave, S. Yerly, L. R. Bisset, M. Fischer, P. Vernazza, E. Benasconi, M. Battegay, B. Ledergerber, H. Günthard, C. Howe, R. Weber, L. Perrin, *J. Infect. Dis*. **2002**, *185*, 1251.

[11] G. S. Bisacchi, S. T. Chao, C. Bachard, J. P. Daris, S. Innaimo, G. A. Jacobs, O. Kocy, P. Lapointe, A. Martel, Z. Merchant, W. A. Slusarchyk, J. E. Sundeen, M. G. Young, R. Colonno, R. Zahler, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 127.

[12] P. G. Wyatt, A. S. Anslow, B. A. Coomber, R. P. C. Cousins, D. N. Evans, V. S. Gilbert, D. C. Humber, I. L. Paternoster, S. L. Sollis, D. J. Tapolczay, G. G. Weingarten, *Nucleosides & Nucleotides* **1995**, *14*, 2039.

[13] a) F. Fernández, X. García-Mera, M. Morales, J. E. Rodríguez-Borges, *Synthesis* **2001**, 239. b) F. Fernández, X. García-Mera, M. Morales, L. Vilariño, O. Caamaño, E. De Clercq, *Tetrahedron* **2004**, *60*, 9245. c) F. Fernández, X. García-Mera, C. López, M. Morales, J. E. Rodríguez-Borges, *Synthesis* **2005**, 3549.

[14] a) F. Fernández, X. García-Mera, M. Morales, J. E. Rodríguez-Borges, E. De Clercq, *Synthesis* **2002**, 1084. b) S.-W. Yao, V. H. C. Lopes, F. Fernández, X. García-Mera, M. Morales, J. E. Rodríguez-Borges, M. N. D. S. Cordeiro, *Bioorganic & Medicinal Chemistry* **2003**, *11*, 4999.

[15] M. Hocek, A. Hol, I. Votruba, H. Dvoráková, *J. Med. Chem.* **2000**, *43*, 1817.

[16] a) M. D. García, O. Caamaño, F. Fernández, P. Abeijón, J. M. Blanco, *Synthesis* **2006**, 73. b) O. Caamaño, G. Gómez, F. Fernández, M. D. García, X. García-Mera, E. De Clercq, *Synthesis* **2004**, 2855. c) A. R. Hergueta, C. López, X. García-Mera, F. Fernández, *Tetrahedron* **2004**, *60*, 10343. d) M. D. García, O. Caamaño, F. Fernández, M. J. Figueira, G. Gómez, *Synthesis* **2003**, 2138. e) C. López, O. Caamaño, A. R. Hergueta, M. D. García, F. Fernández, *Tetrahedron Letters* **2002**, *43*, 5311.

[17] M. D. García, O. Caamaño, F. Fernández, C. López, E. De Clercq, *Synthesis* **2005**, 925.

[18] M. D. García, O. Caamaño, F. Fernández, X. García-Mera, I. Pérez-Castro, *Synthesis* **2006**, 3967.

[19] a) J. M. Blanco, O. Caamaño, F. Fernández, J. E. Rodríguez-Borges, J. Balzarini, E. De Clercq, *Chem. Pharm. Bull.* **2003**, *51*, 1060. b) H.-P. Guan, M. B. Ksebati, Y. Ch. Cheng, J. C. Drach, E. R. Kern, J. Zemlicka, *J. Org. Chem.* **2000**, *65*, 1280.

[20] P. Abeijón, J. M. Blanco, F. Fernández, M. D. García, C. López, *Eur. J. Org. Chem.* **2006**, 759.

[21] N. M. Yoon, H. C. Brown, *J. Am. Chem. Soc.* **1968**, *90*, 2927.

[22] a) S. Daluge, R. Vince, *J. Org. Chem.* **1978**, *43*, 2311. b) S. D. Patil, S. W. Schneller, M. Hosoya, R. Snoeck, G. Andrei, J. Balzarini, E. De Clercq, *J. Med. Chem.* **1992**, *35*, 3372.

[23] CCDC-636456 (**18)** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[24] M. Cesnek, M. Hocek, A. Holy, *Collect. Czech. Chem. Commun.* **2000**, *65*, 1357.

[25] a) M. Hocek, *Eur. J. Org. Chem.* **2003**, 245. b) M. Havelková, D. Dvorak, M. Hocek, *Synthesis* **2001**, 1704. c) M. Havelková, M. Hoces, M. Cesnek, D. Dovorák, *Synlett* **1999**, 1145.

[26] A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147, and references cited therein.

[27] S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871.