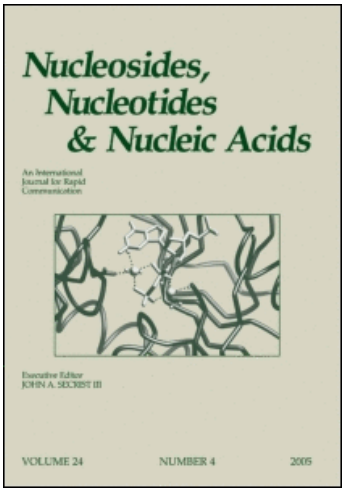

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Synthesis and Antiviral Properties of New Cycloalkanol Derivatives of Guanine

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SYNTHESIS AND ANTIVIRAL PROPERTIES OF NEW CYCLOALKANOL DERIVATIVES OF GUANINE.

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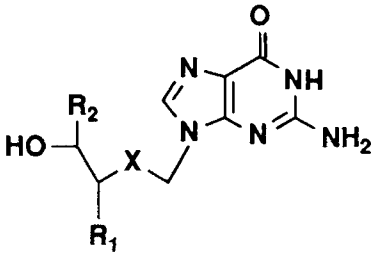
Abstract : New conformationaly constrained cycloalkanol derivatives of guanine have been prepared as potential anti-herpetic agents. None of these compounds was found to inhibit HSV or CMV replication in cell culture but some of them show some antagonism or synergism towards acyclovir protecting effect.

Introduction

The search for therapeutically useful nucleoside analogs lacking the ribose moiety has been considerably stimulated by the discovery of acyclovir[1] (ACV) 1 which is a marketed, potent and selective anti-herpetic agent. Numerous acyclic nucleoside analogs of ACV have then been reported as for example ganciclovir[2] (DHPG) 2, HBG[3] 3, DHBG[4] 4 bucyclovir[5] (BCV) 5 and i-NDG[6] 6 (scheme 1). These compounds (1-6) prevent herpes viruses replication by inhibiting ultimately viral DNA polymerases. This inhibition is due to the triphosphate derivatives of the parent nucleosides 1-6. It is noteworthy that an important part of the selectivity of action of ACV is due to the fact that the first phosphorylation step (producing the acyclic nucleoside monophosphate) is only catalyzed by viral encoded thymidine kinases which means that formation of the acyclic nucleoside triphosphates only takes place in infected cells.

More recently, it has been discovered that some conformationally constrained analogs of acyclovir as the cyclohexyl derivative 7 (L-653-180) could function as selective and potent inhibitor of HSV-TK (IC_{50} = 0,05 μM)[8]. HSV thymidine kinase has recently been recognized[9] to be important for the reactivation of the virus from latently infected ganglia and it has been demonstrated[10] that potent HSV-TK inhibitors like L-653-180 do effectively diminish reactivation of latent virus in vitro. Such compounds are therefore considered as potential new candidates for antiviral therapy, since in humans, reactivation

SCHEME 1



1: X = O; R_1 = H ; R_2 = H (ACV)

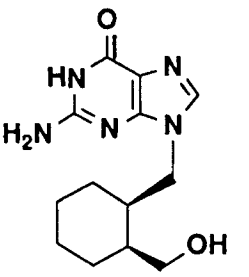
2: X = O; R_1 = CH_2OH; R_2 = H (DHPG)

3: X = CH_2; R_1 = H; R_2 = H (HBG)

4: X = CH_2; R_1 = CH_2OH; R_2 = H (DHBG)

5: X = CH_2; R_1 = OH; R_2 = H (BCV)

6: X = O; R_1 = H; R_2 = CH_2OH (i-NDG)



7 (L-653-180)

of virus from latent infections is responsible for recurrent episodes of disease and latent infections cannot be cured by currently available antiviral drugs including acyclovir. As viral thymidine kinase is not essential in viral replication, potent and selective HSV-TK inhibitors are not expected to exhibit antiviral activity in a plaque reduction assay but are expected to prevent the protective effect of acyclovir in HSV infected cells since ACV absolutely requires HSV-TK to show antiviral activity.

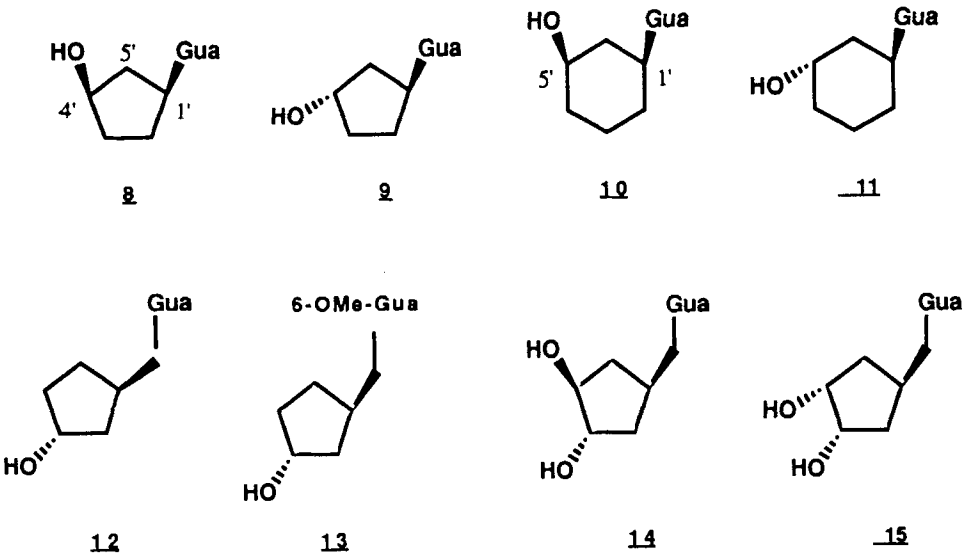
Considering these two possible mechanisms of action (i.e. inhibition of HSV-DNA polymerase or inhibition of HSV-TK), we have designed, prepared and evaluated a series of new cyclic secondary alcohol derivatives of guanine 8-15 as potential HSV replication inhibitors.

Results and discussion

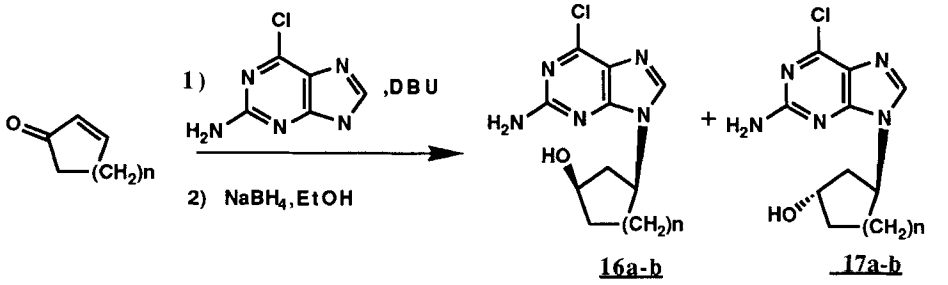
Chemistry

The cycloalkanol derivatives of guanine 8-11 have been prepared by acid aqueous hydrolysis (HCl 1N, 80°C) of the corresponding 2-amino-6-chloropurine derivatives 16 and 17 obtained as described in scheme 3 : 2-amino-6-chloro-purine is first condensed with excess 2-cyclopenten-1-one (n=1) or 2-cyclohexen-1-one (n=2) in the presence of a

SCHEME 2

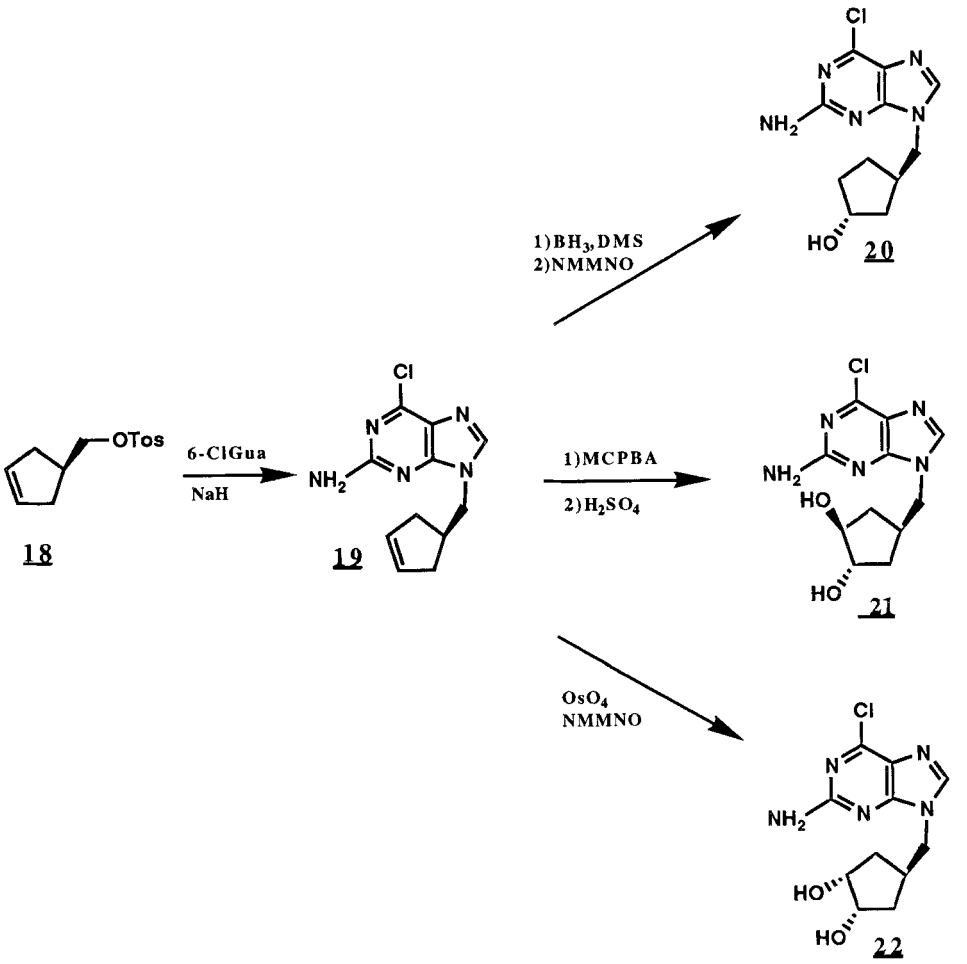


SCHEME 3



entry	n	Yield	cis/trans ratio
a	1	66%	78/22
b	2	73%	95/5

Scheme 4



catalytic amount of 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) in acetonitrile or dimethylformamide to give the expected unstable" 1,4 adducts" which, after evaporation of excess enones, are directly reduced into the desired alcohols 16 and 17 by reaction with excess sodium borohydride in ethanol at -15°C. The cis and trans isomers 16 and 17 have been separated by flash chromatography on silica gel in both series (n = 1 or n = 2). In the case of the five membered rings (n = 1) the stereochemistry of the major isomer 16a has been demonstrated by ^1H NMR analysis : 2D NOESY experiments show that both $H_{1'}$ and $H_{4'}$ present a strong NOE effect only with the same $H_{5'}$ (δ = 2.65 ppm) and no effect with

the $H_{5'}$ appearing at 2.15 ppm. In the case of the six membered rings (n = 2), ^1H NMR study of the major isomer 16b shows that both purinyl and hydroxyl groups are equatorial while in the minor isomer 17b, the purinyl group is equatorial and the hydroxyl group is axial. It is also noteworthy that ^1H and ^{13}C NMR studies show only traces of the N^7 isomers.

The cyclopentanol derivatives of guanine 12-15 have all been prepared from the common key intermediate 19 which is obtained in 56% yield by nucleophilic substitution of the tosylate 18[12] with the sodium salt of 2-amino-6-chloro-purine (scheme 4). Hydroboration of 19 with the boron hydride-dimethylsulfide complex followed by oxidation of the resulting borane with N-methyl morpholine-N-oxide (NMMNO) produces the alcohol 20 in 76 % yield contaminated by 15 % of the cis stereoisomer. It is noteworthy that oxidation of the intermediary borane with hydrogen peroxide as usually described leads to the formation of more polar compounds which are probably formed by the concommitant oxidation of the purine moiety under these conditions. NMMNO thus appears as a reagent of choice to selectively oxidize a borane in the presence of a purine residue.

Acid-aqueous hydrolysis of the intermediate 20 gives the expected guanine derivative 12 while reaction of 20 with excess sodium methoxide leads to the formation of the 6-O-methyl analog 13 in 77% yield. Oxidation of the cyclopentene derivative 19 with m-chloro perbenzoic acid in dichloromethane produces a mixture of stereoisomeric epoxides which upon sulfuric acid hydrolysis are transformed into the expected trans diol 21 in 40% global yield for both steps. Finally, when the intermediate 19 is submitted to a catalytic amount of osmium tetroxide in the presence of NMMNO, the expected diols are obtained in 88 % yield as a 7/3 mixture of isomers. Crystallization from methanol lead to the isolation of the pure major isomer 22 in 60 % yield as shown by 1H NMR analysis. Aqueous acidic work-up of 22 gives the expected final product 15.

Antiviral activities

These compounds were tested for in vitro antiviral activity by the cytopathic endpoint methods described previously[13]. There was no inhibitory activity (IC50 > 500 μM) against the DNA viruses herpes simplex types (HSV) 1 and 2, human cytomegalovirus, vaccinia or adenovirus type 4 or against the RNA viruses rhinovirus type 2, coxsackie virus A21, reovirus type 1, parainfluenza virus type 2, respiratory syncytial virus, influenza virus A/PR/8/34 or influenza virus A/NWS/33.

In a separate series of experiments, the ability of the test compounds to modulate the anti-HSV type 1 activity of acyclovir was investigated (Table).

Table : Effects of cycloakanol derivatives of guanine on the anti-HSV type 1 activity of acyclovir.

	Percent reduction in Virus CPE at 22 µM acyclovir (1)				
Test compound (µM)	0	62,5	125	250	500
8	64	15	42	11	4
9	62	62	61	39	25
10	64	68	68	68	69
11	52	32	46	18	12
12	70	69	65	41	24
13	41	32	55	86	NT(2)
14	47	89	91	93	NT
15	52	68	67	64	64

(1) Optimal concentration for demonstration of antagonistic or synergistic responses. Based on checkerboard titrations utilizing 4.4, 22 and 110 µM acyclovir in HSV type 1-infected HeLa cells.
(2) Not tested

The lack of activities of the cycloalkanol derivatives of guanine 8-15 against DNA or RNA viruses can probably be attributed to a lack of phosphorylation of these derivatives since, some acyclic secondary alcohols have been reported[7] to be poorly phosphorylated by HSV1 thymidine kinase. Moreover, in the case of i-NDG 6 (scheme 1) it has been demonstrated[7] that HSV-TK catalyzes preferentially the phosphorylation of the primary alcohol although the number of atoms between the secondary alcohol and the nucleobase moiety is the same as in acyclovir.

Combination studies with acyclovir (see table) have revealed some interesting properties of the new reported cycloalkanol derivatives of guanine : Compound 8 and, to a lesser extent, compound 11 were shown to clearly antagonize the protective effect of acyclovir in HSV-1 infected cells while their stereoisomers 9 and 10 have almost no effect. In contrast, the trans-diol derivative 14 was found to strongly potentiate the antiviral effect of ACV while the cis-diol 15 didn't show any synergism with ACV. The antagonism effects towards ACV due to 8 and 11 are tentatively explained by the ability of these compounds to inhibit HSV-TK ; this hypothesis as well as the mechanism of potentiation of ACV by compound 14 are currently under studies in our laboratories.

Experimental

Nuclear magnetic resonance spectra were recorded on Bruker instruments (200 and 360 MHz) and chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Mass spectra were recorded on a Finnigan TSQ 46 apparatus. Thin-layer chromatography was performed on Silica gel 60F-254 plates (Merck, 0.2 mm layer). Flash column chromatography utilized silica gel 60 as the solid phase (230-400 mesh) from E. Merck laboratories. UV spectra have been recorded in methanol.

Synthesis of 2-amino-6-chloro-9-(3-hydroxycyclopentyl)purines 16a and 17a

1,8-diazabicyclo[5.4.0]undec-7-ene (250 mg) is added to a stirred suspension of 5 g (29,5 mmoles) of 2-amino-6-chloro-purine and 10 g (119 mmoles) of cyclopenten-2-one in 50 mL of anhydrous DMF at 20°C under argon. The reaction mixture is stirred for 48 hours and evaporated to dryness under reduced pressure. The residue is suspended in ethanol (100 mL) and cooled to -15°C before sodium borohydride (1.5 g ; 40 mmoles) is added portionwise. The reaction mixture is stirred at 20°C for 20 hours, quenched by addition of excess acetone containing acetic acid, evaporated and purified by flash chromatography on silica gel using chloroform and increasing amounts of methanol as eluents to give 3.6 g of 16a (48 % yield) and 1.4 g of 17a (18 % yield).

16a : ^{1}H NMR (CD_3OD): 8.3 (1, 8-H) ; 4.95 (m, CH-N) 4.45 (m, CHOH) ; 1.8-2.65 (m, 6Hcycl.) ; MS (CI, NH_3) : 254 (MH^+)

17a : ^{1}H NMR (CD_3OD) : 8.15 (s, 8-H) ; 5.15 (m, CHN) ; 4.55 (m, CHOH) : 1,35-2,5 (m, 6Hcycl.) ; MS (CI, NH_3) : 254 (MH^+)

Synthesis of 2-amino-6-chloro-9-(3-hydroxycyclohexyl)purines 16b and 17b

DBU (150 mg), 2-amino-6-chloropurine (3 g ; 17,75 mmoles), 4 g of cyclohexenone and 1 g of sodium borohydride have been used according to the method described above to give 3.35 g of product 16b (70 % yield) and 150 mg of product 17b (3 % yield)

16b : ^{1}H NMR ($CDCl_3$) : 8.15 (s, 8-H) ; 4.8 (s, NH_2 + OH) ; 4.4 (m, CHN) ; 3.7 (m, CHOH 2.3 (m, H_6) ; 1.75-2.1 (m, 5Hcycl.) ; 1.3-1.6 (m, 2Hcycl.). MS (CI, NH_3) : 268 (MH^+)

17b : ^{1}H NMR ($CDCl_3$) : 8.15 (s, 8-H) ; 4.8 (s, NH_2 + OH) ; 4.75 (m, CHN) ; 4.25 (s, CHOH) 1.6-2,3 (m, 8Hcycl.) ; MS (CI, NH_3) : 268 (MH^+).

Synthesis of 2-Amino-6-chloro-9-(3-cyclopenten-1-yl-methyl)purine 19

2-amino-6-chloropurine (10 g ; 59 mmoles) is added portionwise to a vigorously stirred suspension of NaH (2.36 g of a 60 % suspension in oil freshly washed with anhydrous hexane) in 100 ml of DMF at 20°C under argon. After stirring for 30 min, the tosylate derivative 18 (14.86 g ; 59 mmoles) dissolved in 20 ml of DMF is added to the reaction

mixture which is stirred at 50°C for 23 hours, evaporated under reduced pressure and purified by flash chromatography on silica gel to give 8.14 g of expected product 19 (56 % yield) and 2.46 g of unreacted tosylate derivative 18 (16 % yield).

19 : ^{1}H NMR ($CDCl_3$) : 7.8 (s, 8-H) ; 56.7 (s, CH=CH) ; 5.15 (m, NH_2) ; 4.0 (d, N-CH2) ; 2.9 (m, CHcycl) ; 2.5 (m, 2CHallyl) 2.15 (m, 2CH allyl) ; MS (CI, NH_3) : 250 (MH^+) ; 267 (MNH_4^+)

Synthesis of (±)-(1α,3β)-2-amino-6-chloro-9-[(3-hydroxycyclopentyl)-methyl]purine 20 :

A 10 N solution of borane dimethylsulfide in 2 ml THF is slowly added to a stirred solution of 19 (2.49 g ; 10 mmoles) in 15 ml of anhydrous THF at 0°C under argon. The reaction mixture is stirred at 20°C for 18 hours and N-methyl morpholine-N-oxide (4.05 g ; 30 mmoles) is added portionwise. The reaction mixture is stirred at 40°C for 4.5 hours, evaporated to dryness and directly purified by flash chromatography on silica gel to give 2.02 g of expected product 20 (76 % yield) as a mixture of 85/15 isomers.

20 : ^{1}H NMR ($CDCl_3$) : 8.15 (s,8-H) ; 4.4 (d,OH) ; 4.15 (m, CHOH) ; 3.95 (d, CH_2N) ; 2.65 (m, CH cycl.) ; 1.2-1,8 (m,6H cycl.). The minor isomer is essentially distinguished by the following signals : 4,1 (m, CHOH) 4.05 (d,CH2N) ; 2.4 (m,CH cycl.). MS (CI, NH_3) : 268 (MH^+) ; 285 (MNH_4^+)

Synthesis of (±)-(1α,3α,4β)-2-amino-6-chloro-9-[(3,4 dihydroxycyclo-pentyl)methyl] purine 21 :

MCPBA (1.14 g ; 3.3 mmoles) is added portionwise to a stirred suspension of 19 (0.747 g ; 3 mmoles) in 20 ml of water at 0°C. The reaction mixture is stirred at 20°C for 1 hr and 0.5 ml of 10 % sulfuric acid is added to the reaction mixture which is stirred at 20°C for 5 hours, quenched at 0°C by careful addition of sodium bicarbonate, evaporated under reduced pressure and purified by flash chromatography on silica gel (by using chloroform and increasing amounts of methanol as eluents) to give 0.33 g of product 21 (40 % yield)

21 : ^{1}H NMR (D_2O) : 8.75 (s, 8-H) ; 4.1 (d, CH_2N) ; 3.85 (m, CHOH) ; 2.6 (q, CH cycl.) ; 2.05 (m, 1H cycl) ; 1.6 (m, 2H cycl.) ; 1.2 (m, 1H cycl.). MS (CI, NH_3) : 284 ($MNH4^+$), 186.

Synthesis of (±)-(1α,3β,4β)-2-amino-6-chloro-9-[(3,4 dihydroxycyclo-pentyl)methyl]purine 22 :

N-Methylmorpholine-N-oxide (0.6 g ; 4,4 mmoles) and 12 mg of osmium tetroxide are added to a stirred suspension of 19 (1 g, 4 mmoles) in 5 ml of water and 15 ml of acetone. The reaction mixture is stirred at 70°C for 2 hours, evaporated under reduced pressure and purified by flash chromatography on silica gel to give 1.0 g of expected diols (88 % yield) as a 7/3 mixture of isomers. Crystallization of the mixture from methanol gives 0.7 g of 22.

22 (^{1}H NMR,$CDCl_3$) : 8.1 (8-H, s) ; 4.9 (m, NH_2, 2OH) ; 3.85-4.15 (m, CH_2N, $2CHO^-$) ; 2.9 (m, CHcycl) ; 1.45-2.05 (m, 4Hcycl). The minor isomer is essentially distinguished by a signal at 2.5 pm (CH cycl).

MS (CI, NH_3) : 284 (MH+).

Synthesis of (±)-(1α,3β)-2-amino-6-methoxy-9-[(3-hydroxycyclopentyl)-methyl]purine 13 :

Sodium methoxide (137 mg ; 2.53 mmoles) is added to a stirred suspension of 20 (0,45 g ; 1.68 mmole) in 5 ml of anhydrous methanol at 20°C under argon. The reaction mixture is stirred for 40 hours, and 190 mg of sodium methoxide are added. After stirring for 70 hours, the reaction mixture is evaporated to dryness and purified by flash chromatography on silica gel (using chloroform and increasing amounts of methanol as eluants) to give 340 mg of expected product 13 (77 %).

13 (^{1}H NMR, CD_3OD) : 7.85 (s, 8-H) ; 4.3 (m, CHO^-) 4.05 (s, OCH_3) ; 4.02 (d, CH_2N) ; 2.75 (m, CH cycl) ; 1.3-1.95 (m, 6H cycl.). The minor isomer is essentially distinguished by signals at 4.2 (m, CHOH) ; 4.1 (d, CH_2N) and 2.5 (m, CHcycl.).

MS (CI, NH_3) : 264 (MH+)

Anal. ($C_{12}H_{17}N_5O_2$, 0.25 H_2O) : calc : C: 53.82 ; H : 6.59; N : 26.15

found : C : 53.41 ; H : 6,55 ; N : 26,24.

UV (λ max, ε) : 279.8 (9100) ; 249.2 (7300) ; 213.2 (22000)

Synthesis of (±)-(1α,3β)-9-[3-hydroxycyclopentyl)methyl]guanine 12 :

A solution of 20 (1.52 g ; 5.7 mmoles) in 10 ml of 1N aqueous HCl and 2.5 ml of THF is heated for 10 hours at 80°C. The reaction mixture is evaporated under reduced pressure. The residue is dissolved in hot water and crystallized on cooling to give 1, 15 g of product 12 (80 % yield) as a cis-trans mixture of isomers (75/25).

12 : ^{1}H NMR (DMSO) : 12.0 (s,OH) ; 9.35 (s, 8-H) ; 7.5 (m, NH_2) 4.3 (m, CHO^-) ; 4.1 (d, CH_2N) ; 2.8 (m, CH cycl.) ; 1.25-1.95 (m, 6Hcycl). The minor cis isomer is distinguished by signals at 4.2 ppm (d, CH_2N) and 2.55 (m, CHcycl.)

MS (NH_3, CI) : 250 (MH+)

Anal. ($C_{11}H_{15}N_5O_2$, 1.75 HCl) : calc : C : 42,20 ; H : 5.39 ; N : 22.37

found : C : 41.46 ; H : 5.45 ; N : 21,86.

UV [λ max (ε)] : 267.4 (9200) ; 252.6 (11900) ; 206.5 (16400) 194.5 (17300).

Synthesis of (±)-(1α,3α,4β)-9-[(3,4-dihydroxycyclopentyl)methyl] guanine 14

14 is obtained in 70 % yield from 21 according to the method described above for the preparation of 12.

14 : ^{1}H NMR (D_2O) : 7.85 (s, 8-H) :; 4.1 (d, CH_2N) ; 4.05 (m, $2CHO^-$)

2.7 (m, CHcycl) : 2.2 (m, Hcycl.) ; 1.8 (m, Hcycl.) 1.7 (m, Hcycl.) ; 1.3 (m, H cycl.).

MS (CI, NH3) : 266 (MH+)

UV [λ max (ε)] : 267.5 (6900) ; 252.0 (9200) ; 203.1 (13400) 193.0 (15300).

Synthesis of (±)-(1α,3β,4β)-9-[(3,4 dihydroxycyclopentyl)methyl]guanine 15 :

Compound 15 is obtained in 80 % yield from 22 according to the method described above for the preparation of 12.

15 : (^{1}H NMR, DMSO) : 10.7 (s, 6-OH) ; 7.85 (s, 8-H) ; 6.55 (s, NH_2) 4.45 (s, 2OH) ; 4.0 (m,2CHOH) ; 3.9 (d, CH_2N) ; 2.75 (m,CH cycl.) ; 1.4-1.8 (m, 4H cycl.).

MS (CI, NH_3) : 266 (MH^+)

Anal. ($C_{11}H_{15}N_5O_3$, 0.5 H_2O) : calc : C : 48.17 ; H : 5.88 ; N : 25.53

Found : C : 47.83 ; H : 5.50 ; N : 25.15.

UV [λ max (ε)] : 268.6 (9800) ; 252.10 (13000) ; 203.40 (20300) 191.0 (26200)

Synthesis of (±)-(1α,3α)-9-(3-hydrocycyclopentyl)guanine 8 :

Compound 8 has been obtained in 75 % yield from 16a according to the method described above for the preparation of 12.

8 : ^{1}H NMR (D_2O) : 8.85 (s, 8-H) ; 5.0 (m, CHN) ; 4.5 (m, CHO^-) ; 2.6 (m, 1Hcycl) ; 2.45 (m, 1Hcycl); 2.2 (m, 1Hcycl) 2.0 (m, CH2 cycl.).

MS (CI, NH_3) : 236 (MH^+)

Anal ($C_{10}H_{13}H_5O_2$, 1.1 HCl) : Calc : C : 43.62 ; H : 5.16 ; H : 25.43

found : C : 43.44 ; H : 5.09 ; N : 25.63.

UV [λ max (ε)] : 270.9 (9290) ; 252.2 (12600) ; 205.7 (18200)

Synthesis of (±)-(1α,3β)-9-(3-hydroxycyclopentyl)guanine 9 :

Compound 9 has been prepared in 60 % yield from 17a according to the method described for the preparation of 12.

9 : ^{1}H NMR (D_2O) : 8.8 (s, 8-H) ; 5.1 (m, CHN) ; 4.65 (m, CHO^-) ; 2.5 (m, 1H cycl.) ; 2.3 (m ^{2}H cycl.) ; 2.05 (m, ^{1}H cycl.) ; 1.8 (m, ^{1}H cycl.).

MS (CI, NH3) : 236 (MH+)

Anal. ($C_{10}H_{13}N_5O_2$, HCl) : calc : C : 44.21 ; H : 5.19 ; H : 25.77

found : C : 44.16 ; H : 5.23 ; H : 25.92.

UV [λ max (ε)] : 270.1 (9700) ; 252.9 (12900) ; 209.5 (14600).

Synthesis of (±)-(1α,3α)-9-(3-hydrocycyclohexyl)guanine 10 :

Compound 10 has been prepared in 72 % yield from 16b according to the method described for 12.

10 : ^{1}H NMR (D_2O) : 8.85 (s, 8-H) ; 4.5 (m, CHN) ; 3.85 (m, CHO^-) 2.5 (d, Hcycl.) ; 1.3-2.2 (m, 7H cycl).

Anal. ($C_{11}H_{15}N_5O_2$,HCl) ; Calc : C : 46,24 ; H : 5,64 ; N : 24.51

found : C : 45.80 ; H : 5.61 ; N : 24.60

UV [λ max (ε)] : 269.5 (9600) ; 252.1 (12800) ; 204.9 (18600) ; 194.0 (21000).

Synthesis of (±)-(1α,3β)-9-(3-hydrocycyclohexyl)guanine 11 :

Compound 11 has been obtained in 80 % yield from 17b according to the method described for the preparation of 12.

11 : ^{1}H NMR (D_2O) : 8.85 (S, 8-H) ; 4.8 (m, CHN) ; 4.3 (m, CHO^-) 2.25 (m, 2H cycl) ; 2.05 (dt ; H6 axial) ; 1.7-1.9 (m, 4H cycl) 1.65 (m, H cycl).

Anal. ($C_{11}H_{15}N_5O_2$,HCl,H_2O) : Calc : C : 43.50; H : 5.97 ; N : 23,06

found : C : 43.74 ; H : 5.69 ; N : 22.43.

UV [λ max (ε)] : 269.6 (9000) ; 252.3 (12100) ; 206.2 (16900) 199.1 (16700).

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