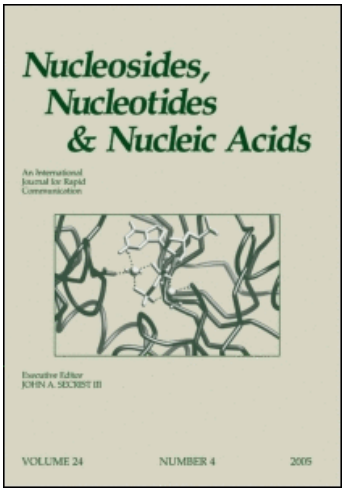

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C-1'-BRANCHED ACYCLOVIR DERIVATIVES. SYNTHESIS AND ANTIVIRAL EVALUATION

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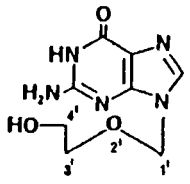
ABSTRACT: The synthesis of 9-[1-(2-hydroxyethoxy)-3-hydroxypropyl]guanine (3a), its thia-congener (3b) and prodrugs (4a,b) was accomplished by paths involving Michael-type addition. The new compounds were found to be inactive against herpes simplex type 1 (HSV-1) and type 2 (HSV-2), human cytomegalovirus (CMV) and varicella-zoster virus (VZV), and unreactive as substrates for HSV-1 thymidine kinase phosphorylation.

The selective activity of acyclovir (1)[1] against herpes simplex virus has stimulated the synthesis and evaluation of many related compounds.[2] Several of these derivatives eg. ganciclovir[3] retain potent antiviral activity. The essential features of their common biochemical mechanism have been elucidated and structure-activity relationships have emerged. Acyclovir and its active derivatives[2] are acyclic analogs of 2'-deoxyguanosine (2). Initially phosphorylated at the C-4' hydroxyl (corresponding to C-5' of 2) by viral thymidine kinase,[4]



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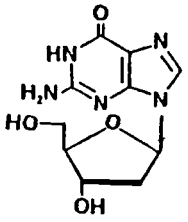

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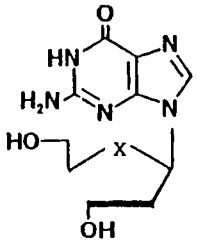
these compounds are subsequently converted to triphosphates by host cell kinases.[5] The triphosphates may then inhibit viral DNA polymerase or, following incorporation, function as viral DNA chain terminators.

Apart from metabolic precursors (prodrugs) of the guanine structure,[6] replacement of the 9-guanyl residue with other bases [2,7] results in substantial or complete loss of activity. On the other hand, modifications of the aliphatic portion of 1 have shown that antiherpes activity is associated with guanines substituted in the 9-position with 4-atom straight chains terminating in hydroxyl groups. Thus replacement of the 2'-oxygen of 1 by S,[8] saturated C,[9] or cis-2',3'-unsaturation[10] affords active compounds, as does incorporation of an additional hydroxyl at C-3',[9] or a hydroxymethyl at C-2',[11] C-3',[3] or C-4'.[12]

Since acyclovir-type antivirals are analogs of 2'-deoxyguanosine (2), it appeared possible that 9-[1-(2-hydroxyethoxy)-3-hydroxypropyl]guanine (3a) might display significant antiherpes activity. Previously, Keller et al have described three other C-1'-branched acyclovir derivatives as inactive.[8] But those compounds lacked the structural features of 3a. Compound 3a possesses the requisite 4-atom acyclovir chain and differs from 2'-deoxyguanosine only in scission of the C-3',4' bond. As depicted, easily attainable conformations of 3a closely resemble the natural nucleoside. Thus 3a was an intriguing synthetic target, along with its S-congener (3b) and the potential prodrugs 4a,b. This paper reports the preparation of these compounds and their in vitro evaluation against herpes simplex virus type 1 and type 2, cytomegalovirus and varicella-



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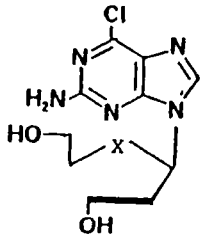

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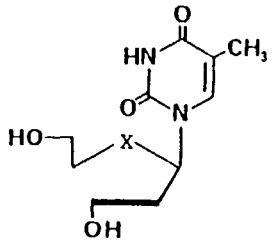

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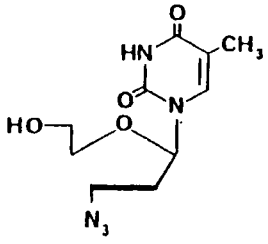

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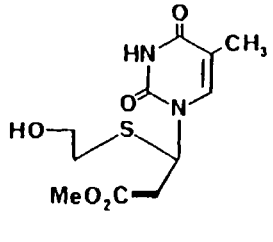
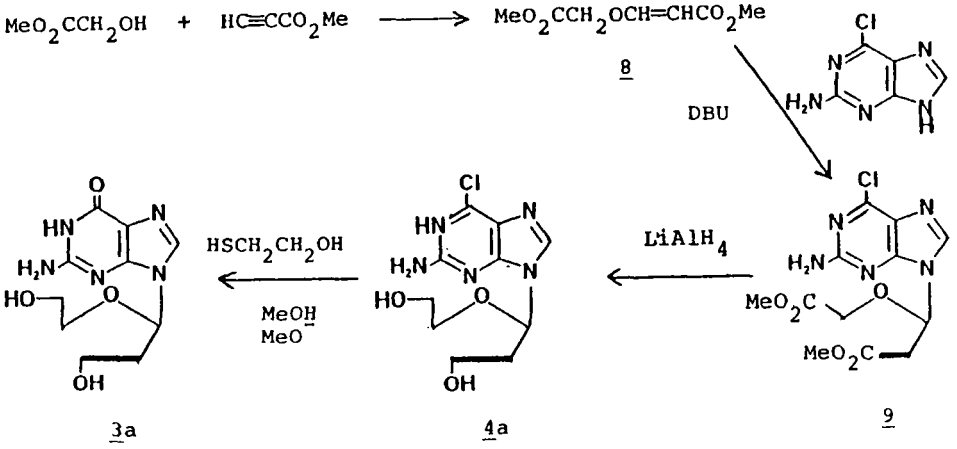


7

zoster virus. For comparative purposes acyclothymidine derivatives 5a,b, 6 and 7 were similarly tested, and K_i values were determined with viral (HSV-1) thymidine kinase.

CHEMISTRY. Methods recently described for the preparation of compounds 5-7[13] were successfully employed for the synthesis of 3a and 4a (Scheme 1). Methyl E-3-(methoxycarbonyl)methoxy propenoate (8), obtained by addition of methyl glycolate to

SCHEME 1

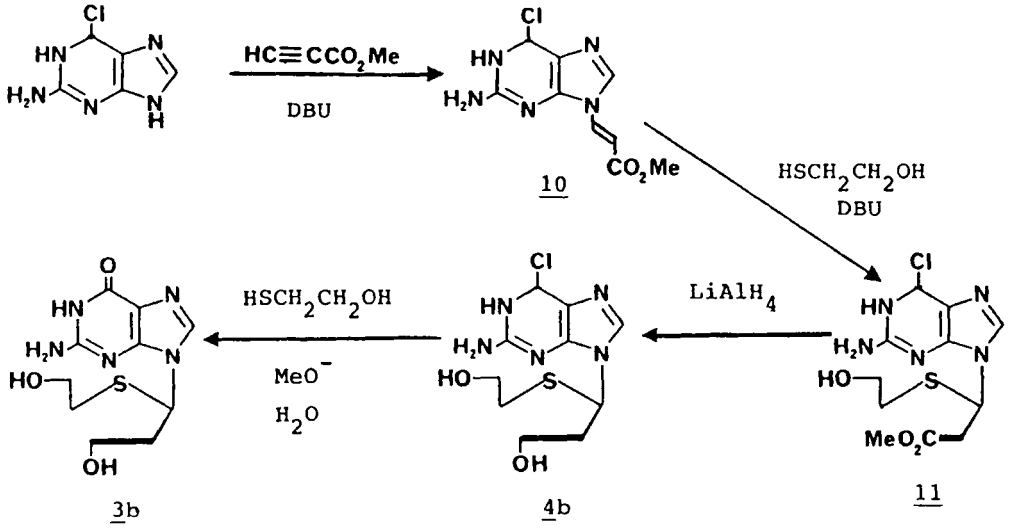


methyl propiolate, underwent Michael-type addition with 2-amino-6-chloropurine to give 9 in satisfactory yield (47%, after chromatographic purification). For this and similar Michael-type additions 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) served as the basic catalyst. Lithium aluminum hydride reduction of 9 gave 4a which was subsequently converted to the guanine derivative 3a under basic conditions.

The sulfur analogs 3b and 4b were prepared as shown in Scheme 2. Conjugate addition of 2-amino-6-chloropurine to methyl propiolate afforded methyl 3-(2-amino-6-chloro-9-purinyl) propenoate (10, mainly E by NMR). Compound 10, in turn, served as a Michael acceptor for 2-mercaptoethanol, giving the acyclovir derivative 11. Competing nucleophilic displacement of the 6-chloro substituent was unimportant under the conditions used to obtain 11. Ester reduction ($LiAlH_4$) gave 4b and conversion to 3b completed the sequence. The site of alkylation (N-9) in 3a and 3b was established from the UV spectra;[14] by inference precursor compounds were assigned as N-9 substituted. A preference for N-9

substitution in Michael-type additions with adenine[15] and 6-chloropurine[16] has been previously noted.

SCHEME 2



ANTIVIRAL TESTING. The new C-1'-branched acyclovir derivatives (3a,b, 4a,b,11) and the acyclothymidine compounds (5a,b, 6, 7) were tested in vitro for activity against HSV-1, HSV-2, CMV and VZV using human foreskin host cells. Results are tabulated in Table 1. The compounds were found to be completely devoid of activity against HSV-1 and HSV-2; only weak activity against CMV (4a, 11) and VZV (3b, 4a, 4b, 5a, 11) was observed.

TABLE 1. Antiviral Activity of C-1'-Branched Nucleoside Analogs.

	ED_{50}, μM			
Compound	HSV-1	HSV-2	CMV	VZV
3a	>200	>200	>200	>200
3b	>200	>200	>200	149
4a	>200	>200	88	90
4b	>200	>200	>200	131
11	>200	>200	179	147
5a	>200	>200	>200	127
5b	>200	>200	>200	>200
6	>200	>200	>200	>200
7	>200	>200	>200	>200

To further probe their lack of antiherpes activity, inhibition constant values (K_i) with HSV-1 thymidine kinase were determined. The K_m for thymidine in the system employed was 0.6

TABLE 2. Cell-Free Phosphorylation by HSV-1 Thymidine Kinase.

Compound	K_i, μM
3a	1311
3b	602
4a	1777
4b	667
11	477
5a	219
5b	256
6	155
7	406
Thymidine(K_m)	0.6

μM, in agreement with published values. K_i values for the nucleoside analogs are given in Table 2. Lipid solubility, a measure of the ease of passive transport across cell membranes and consequent possible bioavailability within host cells, was also assessed. Octanol-water partition coefficients are given in Table 3.

TABLE 3. Octanol-Water Partition Coefficients

Compound	$K_{octanol/H_2O}$
3a	0.014
3b	0.033
4a	0.377
4b	0.986
11	0.106
6	0.484
7	0.324

As anticipated, the 2-amino-6-chloropurine derivatives 4a,b (potential prodrugs) were considerably more lipid soluble than the corresponding acycloguanosines 3a,b. Although lipid solubility may contribute the low levels of anti-VZV and CMV activity (Table 1), no effect was observed on herpes simplex virus. None of the compounds investigated showed HSV-1 or HSV-2 activity. The HSV-1 thymidine kinase K_i values (Table 2) show the C-1'-branched acyclovir derivatives (3a,b, 4a,b, 11) to be poor substrates for the enzyme. Compounds 3a and 4a (K_i = 1311 and 1777 μM respectively) are particularly notable in this respect. Despite more favorable charateristics (K_i = 155 μM; $K_{octanol/H_2O}$ = 0.484) acyclothymidine derivative 6 was similarly inactive.

DISCUSSION. The observed inactivity (Table 1) of the thymine compounds (5a,b, 6, 7) accords with previous results for acyclovir derivatives substituted with bases other than guanine.[2] For the acycloguanosines (3a,b, 4a,b, 11) it is apparent that

their structural similarity to 2'-deoxyguanosine is insufficient for antiherpes activity. As suggested earlier,[8] and verified in the present study, C-1'-branched derivatives of acyclovir are inactive against HSV-1 and HSV-2.

Several factors contribute to the antiherpes (HSV) efficacy of acycloguanosines.[17] Bioavailability of the analog within the host cell is critical, as is phosphorylation by viral thymidine kinase. Subsequent cellular phosphorylations must occur at a rate sufficient to produce effective levels of the triphosphate, and the latter must function efficiently as a substrate or inhibitor of viral DNA polymerase. The data in Table 2 show the C-1'-branched acycloguanosines to be poor substrates for HSV-1 thymidine kinase phosphorylation. This behavior contributes to their lack of activity.

In comparison with thymidine itself the acyclothymidine compounds (5a,b, 6, 7) are also poor substrates for HSV-1 TK (Table 2). Thus an effect of C-1'-branching on both acyclothymidine and acycloguanosine derivatives appears to be inhibition of viral TK phosphorylation. Such compounds may be poorly accomodated at the active site of HSV-1 thymidine kinase.

EXPERIMENTAL

General Methods. Melting points (uncorrected) were taken with an Electrothermal apparatus. NMR (^{1}H) spectra were obtained with a Varian 360 instrument (60MHz) using tetramethylsilane as an internal standard. UV spectra were recorded with a Carey 2300 spectrophotometer. Thin layer chromatography used silica gel plates (EK-F254) and Merck silica gel (230-400 mesh) was employed for column chromatography. Elemental analyses were performed by Atlantic Micro Lab, Norcross, GA, USA.

(R,S) Methyl 3-(2-amino-6-chloro-9-purinyl)-3-(methoxycarbonylmethoxy)propanoate (9). A suspension of 2-amino-6-chlorpurine (1.70 g, 10.0 mmol), methyl 3-(methoxycarbonyl)-methoxypropenoate (8)[13] (13.0 g, 75.0 mmol), methyl glycolate (0.90 g, 10.0 mmol), DBU (0.152 g, 1.00 mmol) in acetonitrile (200 mL) was refluxed 16 h. After addition of glacial acetic acid (12 drops) the solvent was removed under reduced pressure and the resulting semisolid was chromatographed. Elution with petroleum ether-EtOAc (1:1) gave 9 (2.10 g) slightly contaminated with 10. This material was rechromatographed to give pure 9 (1.61 g, 47%), mp 122-124°C (from Et_2O). NMR ($CDCl_3$): δ 7.98 (s, 1, C(8)H); 6.13 (t, 1,

J=6.5Hz, C(1')H); 5.80 (s, 2, D_2O exch., NH_2); 4.13 (s, 2, CH_2O); 3.68 (s, 6, CH_3); 3.35 (d, 2, J=6.5 Hz, C(2')H). Anal. Calcd for $C_{12}H_{14}ClN_5O_5 \cdot 3/4H_2O$: C, 40.35; H, 4.37; Cl, 9.92; N, 19.60. Found: C, 40.37; H, 4.06; Cl, 9.49; N, 19.55.

(R,S)-2-Amino-6-chloro-9-[1-(2-hydroxyethoxy)-3-hydroxypropyl]purine (4a). Under a N_2 atmosphere a solution of 9 (1.61 g, 4.96 mmol) in anhydrous THF (140 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (0.510 g, 13.4 mmol) in dry THF (60 mL). After stirring 0.5 h. at room temperature water (0.970 mL, 53.9 mmol) was cautiously added, and the resulting suspension was stirred for an additional 0.5 h. The mixture was filtered and the residual solids washed with several portions of THF. Evaporation of the combined filtrates gave 4a (0.752 g, 53%), mp 131-132°C (from EtOAc). NMR (DMSO-D_6): δ 8.23 (s, 1, C(8)H); 6.87 (s, 2, D_2O exch., NH_2); 5.72 (t, 1, J=6 Hz, C(1')H); 4.6 (m 2, D_2O exch.; OH); 3.7-3.2 (m, 7, CH_2O and ½ H_2O); 2.25 (m, 2, C(2')H). Anal. Calcd for $C_{10}H_{14}ClN_5O_3 \cdot$ ½ H_2O): C, 40.48; H, 5.10; Cl, 11.95; N, 23.60. Found: C, 40.31; H, 4.85; Cl, 11.89; N, 23.32.

(R,S)-9-[1-(2-Hydroxyethoxy)-3-hydroxypropyl]guanine (3a). A solution of 4a (0.436 g, 1.47 mmol), 2-mercaptoethanol (0.49 g, 6.3 mmol), water (0.084 g, 4.7 mmol), 1.0 M NaOMe in MeOH (5 mL, 5 mmol) and MeOH (15 mL) was refluxed 18 h, then concentrated to about one-half the orginal volume under reduced pressure. After dilution with water (7 mL) the pH was adjusted to ca. 6 with glacial acetic acid and the mixture cooled (4°C) for several hours. The precipitated white solid was collected and washed with acetone (0.402 g, 98%). Recrystallization from MeOH-acetone, mp >300°C dec. UV (MeOH): max = 252 nm; sh 272 nm. NMR (D_2O, TSP ref.): δ 7.88 (s, 1, C(8)H); 5.75 (t, 1, J=6 Hz, C(1')H); 3.8-3.3 (m, 6, CH_2O); 2.5-2.2 (m, 2, C(2')H). Anal. Calcd for $C_{10}H_{15}N_5O_4 \cdot$½H_2O: C, 43.16; H, 5.80; N, 25.17. Found: C, 42.99; H, 5.65; N, 25.06.

Methyl E-3-(2-amino-6-chloro-9-purinyl)propenoate (10). A suspension of 2-amino-6-chloropurine (1.69 g, 10.0 mmol), methyl propiolate (3.78 g, 45.0 mmol), DBU (0.05 g, 0.3 mmol) and acetonitrile (120 mL) was stirred at room temperature for 3 weeks. Filtration gave 10 (1.01 g, 39%), a white solid after crystallization from EtOAc, mp 247-249°C dec. NMR (DMSO-D_6): δ 8.57 (s, 1, C(8)H); 8.17 (d, 1, J=14 Hz, C(1')H); 7.27 (s, 2,D_2O exch., NH_2); 7.03 (d, 1, J=14 Hz C(2')H); 3.77 (s, 3, CH_3). Satisfactory elemental analysis was not obtained; compound 10 partially decomposes on standing. Freshly crystallized material was used for the NMR and to prepare 11.

Evaporation of the filtrate (above) and chromatography of the residue (1% MeOH in chloroform) gave the Z-isomer of 10 0.56 g) followed by additional 10 (0.34 g). NMR of the Z-isomer (DMSO-D_6): δ 8.73 (s,1, C(8)H); 7.30 (d, 1, J=10 Hz, C(1')H); 7.12 (s, 2, D_2O exch., NH_2); 5.92 (d, 1, J=10 Hz, C(2')H); 3.72 (s, 3, CH_3).

(R,S) Methyl 3-(2-amino-6-chloro-9-purinyl-3-(2-hydroxyethylthio)propanoate (11). A solution of 10 (0.762 g, 3.00 mmol), 2-mercaptoethanol (1.0 mL, 15.0 mmol), DBU (15 mg. 0.1 mmol) in THF (8 mL) was stirred at room temperature for 2 days. Glacial acetic acid (3 drops) was added and volatile material was removed under reduced pressure. The residue was chromatogrphed and 11 (0.435 g, 44%) was eluted with petroleum ether-EtOAc (1:1), mp 160-162°C (from EtOAc). NMR (DMSO-D_6): δ 8.42 (s, 1, C(8)H); 7.03 (s, 1, D_2O exch., NH_2); 5.97 (t, 1, J=8 Hz, C(1')H); 4.83 (s, 1, D_2O exch., OH); 3.63 (s) and 3.7-3.2 (m) (7, CH_3, CH_2O, C(2')H); 2.63 (t, 2, J = 6 Hz, CH_2S). Anal. Calcd for $C_{11}H_{14}ClN_5O_3S$: C, 39.82; H, 4.25; Cl, 10.69; N, 21.11; S, 9.66. Found: C, 39.85; H, 4.28; Cl, 10.75; N, 21.06; S. 9.62.

(R,S)-2-Amino-6-chloro-9-(2-hydroxyethylthio)-3-hydroxypropyl]guanine (4b). Lithium aluminum hydride reduction of 11 as described for 4a gave 4b, (66%) after chromatography (3% MeOH in CH_2Cl_2). Recrystallized from EtOAc, mp 132-133°C. NMR (DMSO-D_6): δ 8.34 (s, 1, C(8)H); 6.97 (s, 2, D_2O exch., NH_2); 5.74 (t, 1, J=7 Hz, C(1')H); 4.6 (s, v. broad, OH); 3.5-3.2 (m, 4, CH_2O); 2.50 (m, 2, CH_2S); 2.35 (m, 2, C(2')H).

(R,S)-9-[1-(2-Hydroxyethylthio)-3-hydroxypropyl]guanine (3b). A solution of 4b (0.699 g, 2.31 mmol), 2-mercaptoethanol (0.741g, 9.48 mmol), 1.0 M NaOMe in MeOH (7.8 mL, 7.8 mmol), water (72 mg. 4.0 mmol) and MeOH (23 mL) was refluxed 16 h, then concentrated to a few mL under reduced pressure. After addition of water (5 mL) the pH was adjusted to about 6 with glacial acetic acid and the mixture evaporated to dryness. Chromatography (5% MeOH in CH_2Cl_2) gave 3b (0.565 g, 82%), mp>200°C dec. (from EtOH). NMR (DMSO-D_6): δ 10.67 (s, 1, NH); 7.68 (s, 1, C(8)H); 6.55 (s, 2, NH_2); 5.62 (t, 1, J=7 Hz, C(1')H); 4.80 and 4.68 (t's, 2, OH); 3.36 (m, ca.6, CH_2O and H_2O); 2.50 (m, 2, CH_2S); 2.23 (m, 2, C(2')H). Anal. Calcd for $C_{10}H_{15}N_5O_3S \cdot 3/4H_2O$: C, 40.19; H, 5.57; N, 23.43; S, 10.73. Found: C, 39.92; H, 5.23; N, 23.22; S, 10.63.

Determination of ED_{50} values. (Table 1). The antiviral efficacies were determined in an antiviral assay as previously described.[18] Briefly, 10-fold dilutions of the compounds were tesed against HSV-1, HSV-2, CMV, and VZV in human foreskin

fibroblasts. The medium was replenished every 3 or 4 days and ED_{50} values were determined by scoring the inhibition of cytopathic effect. Toxicity of the compounds was assessed by monitoring uninfected cell monolayers.

Determination of Ki values (Table 2). K_i values were determined at 3 concentrations of the compounds and 5 concentrations of thymidine ranging from 0.0625 μM to 1 μM in a buffer pH 7.6 consisting of 10 mM ATP, 200 mM tris, 5 μM $MgCl_2$, 10 μM NaF, and ^3H-thymidine. Reactions were run for 15 minutes at 37°C and reactants then separated using DE-81 paper disks. The paper disks were washed 3 x 5 minutes in 1 mM ammonium formate and dried before counting. K_i values were determined by a Lineweaver Burke plot.

Determination of partition coefficients (Table 3). An initial drug concentration of 100 μM in 25 μM phosphate buffer, pH 7.4, was mixed with an equal volume of 1-octanol for 3 hours and the phases separated by centrifugation. Determination of the concentrations of compounds in the phases was done by HPLC (isocratic conditions) on a C-18 column .

ACKNOWLEDGEMENT

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