The growth inhibition data were then used to calculate the ID_{50} values (the drug concentration required to inhibit cell growth by 50% of control).

LOVO[48] and LOVO/DOXO[49] were cultured at 37 °C by using Ham's F12 medium supplemented with 20% fetal calf serum and maintained at 37 °C in an atmosphere of 5% carbon dioxide. LOVO and LOVO/DOXO were plated at concentrations of 2.5×10^3 cells/dish. After 144 h of continuous drug exposure, growth inhibition was evaluated (ID_{50}) via an MTT assay.

In Vivo Efficacy Studies. L1210, P388, and P388/DOXO murine leukemia cells are maintained in vivo by weekly intraperitoneal (ip) injections of 10^6 cells, respectively, in BDF_1, DBA_2, and CDF_1 mice. For test purposes, mice were inoculated ip with 10^6 tumor cells and treatment was initiated 24 h later. The desired dose of drug was administered on days 1, days 1 and 5, or days 1, 5, and 9 as reported in the tables. Mice were observed daily for signs of toxicity and survival. The day of death was recorded for all animals that died or were sacrificed during the 60-day study group. The mean survival time (MST) for each treatment group was calculated and the percent T/C was determined by using the following formula:

$$\%T/C = [(\text{MST treated})/(\text{MST control})]100$$

Registry No. 1, 64862-96-0; 2, 65271-80-9; 3, 28736-42-7; 4, 131401-54-2; 5a, 2944-12-9; 5b, 134529-39-8; 5e, 4471-41-4; 5d, 19853-95-3; 5e, 69895-68-7; 5f, 134529-40-1; 5g, 134529-43-4; 6c, 70476-63-0; 7a, 134529-36-5; 6b, 134529-44-5; 7c, 134529-45-6; 7d, 134529-46-7; 7e, 134529-47-8; 7f, 134529-48-9; 8, 134529-37-6; 9a, 129732-44-1; 9b, 121498-41-7; 9c, 102650-22-6; 9d, 134529-41-2; 10a, 134566-65-7; 10b, 134529-42-3; 11, 134529-38-7; $PhNH_2$, 62-53-3; $HOCH_2CH_2NH_2$, 141-43-5; $NH_2CH_2CH_2NH_2$, 107-15-3; $NH_2CH_2CH_2N(CH_3)_2$, 108-00-9; $CH_3NHCH_2CH_2N(CH_3)_2$, 142-25-6; $NH_2CH_2CH_2NHCH_2CH_2OH$, 111-41-1; $NH_2(CH_2)_4NH_2$, 110-60-1; cyclopropylamine, 765-30-0; 1-(2-aminoethyl)aziridine, 4025-37-0; aziridine, 151-56-4.

Supplementary Material Available: In vivo antitumor activity of 10a evaluated against P388 murine leukemia (Table VI), P388/DOXO resistant murine leukemia (Table VII), and on human mammary carcinoma (MX-1) transplanted in nude mice (Table VIII) (3 pages). Ordering information is given on any current masthead page.

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Synthesis and Antiviral Activity of 3-Substituted Derivatives of 3,9-Dihydro-9-oxo-5*H*-imidazo[1,2-*a*]purines, Tricyclic Analogues of Acyclovir and Ganciclovir

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9-[(2-Hydroxyethoxy)methyl]guanine (acyclovir, 1a) and 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG, ganciclovir, 1b) were transformed to their respective tricyclic derivatives, 3-substituted 3,9-dihydro-9-oxo-5*H*-imidazo[1,2-*a*]purines **2b**, **3a**, and **3b**. The 6-methyl-substituted compound **2b** was obtained following reaction of **1b** with bromoacetone. A two-step approach via 1-(2,2-diethoxyethyl) intermediates **4a,b** was the most effective for the preparation of the derivatives unsubstituted in the appended ring (**3a,b**). The novel acyclonucleosides, in particular ganciclovir derivative **2b**, proved markedly active against herpes simplex virus type 1 and 2, varicella-zoster virus, and cytomegalovirus.

During our previous work on the antiviral activity of novel N-substituted derivatives of acyclovir, 9-[(2-hydroxyethoxy)methyl]guanine (**1a**), we found that the tricyclic 3,9-dihydro-3-[(2-hydroxyethoxy)methyl]-6-methyl-9-oxo-5*H*-imidazo[1,2-*a*]purine (**2a**)[1] exhibited marked and selective activity against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). We have now extended these studies to additional tricyclic analogues bearing either a 3-[(1,3-dihydroxy-2-propoxy)methyl] side chain (**2b**) or a 6-unsubstituted appended imidazole ring (**3a**), or both (**3b**).

The discussed tricyclic ring system is frequently referred to in the literature as 1,*N*-2-ethenoguanine to indicate its relation to the parent, naturally occuring heterocycle.

Chemistry

The tricyclic analogue of ganciclovir, 3,9-dihydro-3-[(1,3-dihydroxy-2-propoxy)methyl]-6-methyl-9-oxo-5*H*-imidazo[1,2-*a*]purine (**2b**), was obtained upon reaction of the 1-sodium derivative of **1b** in dimethylformamide with bromoacetone (yield 84%) according to a previously reported method for the preparation of the analogously modified guanosine (**2c**)[2-4] and acyclovir (**2a**) (Scheme I).[1]

Literature data on the formation of 1,*N*-2-etheno derivatives of guanine have been limited to the report of Sattsangi et al.[5] The authors obtained 1,*N*-2-ethenoguanosine (**3c**) in 7% yield after reacting guanosine with aqueous chloroacetaldehyde under physiological conditions. Three approaches toward a more efficient synthesis of **3c** have been recently developed.[6] They are based upon the reaction of guanosine with (i) aqueous chloroacetaldehyde at pH 10, (ii) anhydrous haloacetaldehydes, or (iii) bromoacetaldehyde diethyl acetal.

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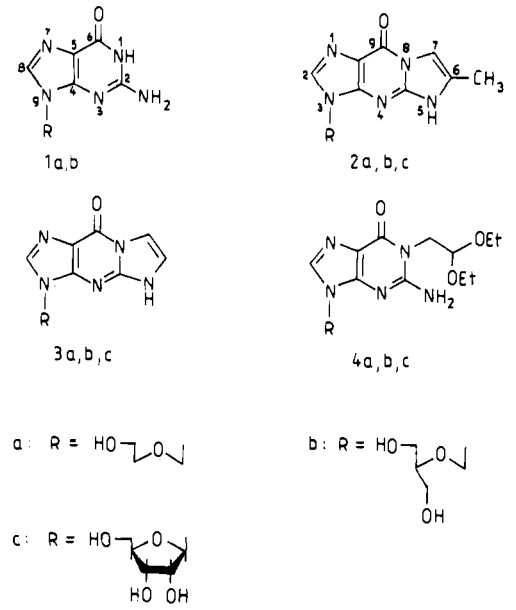
0022-2623/91/1834-2380$02.50/0

Scheme I[a]



Reactions: **1b** $\xrightarrow{i}$ **2b**; **1a** $\xrightarrow{ii}$ **3a**; **1ab** $\xrightarrow{iii}$ **4ab** $\xrightarrow{iv}$ **3ab**

[a] Reagents: (i) NaH, DMF, then $BrCH_2COCH_3$; (ii) NaH, DMF, room temperature, then 90% $ClCH_2CHO$, Et_2O; (iii) K_2CO_3, DMF, then $BrCH_2CH(OEt)_2$; (iv) 40% aqueous AcOH or 1.2 N HCl.

In the present work treatment of the 1-sodium derivative of acyclovir (**1a**) in dimethylformamide with an ethereal solution of chloroacetaldehyde followed by alkaline hydrolysis afforded 1,*N*-2-ethenoacyclovir (**3a**) only in 18% yield.

As in the case of guanosine,[6] the two-step procedure employing bromoacetaldehyde diethyl acetal as a means of introducing the etheno unit proved to be advantageous. Both the 1,*N*-2-etheno compounds, ethenoacyclovir **3a** and its (1,3-dihydroxy-2-propoxy)methyl derivative ethenoganciclovir (**3b**), were prepared via this route. Thus alkylation of the acyclic guanosine analogues **1a** and **1b** with 2-bromo-1,1-diethoxyethane (bromoacetaldehyde diethyl acetal) in dimethylformamide in the presence of solid potassium carbonate gave the 1-(2,2-diethoxyethyl)-guanines **4a** and **4b**, accompanied by small amounts (ca. 8%) of isomeric side products, *O*-6-(2,2-diethoxyethyl) compounds. The formation of O-6-substituted products during reaction of guanosine with alkylating agents in the presence of potassium carbonate has already been described.[6,7] The desired 1-substituted products **4a** and **4b** were isolated from the reaction mixture, by using silica gel short-column chromatography, in yields of 41% and 33%, respectively.

The compounds **4a** and **4b** were then subjected to acidic hydrolysis: **4a** was refluxed in 40% acetic acid for 40 min, and **4b** was hydrolyzed in 1.2 N hydrochloric acid at room temperature for 18 h. This gave the respective etheno compounds **3a** and **3b** in quantitative yields.

Of additional interest is that this approach provided as intermediates the 1-(2,2-diethoxyethyl) derivatives **4a** and **4b**, which can be considered as close analogues of 1-methylacyclovir, a compound that has been found to be inhibitory to HSV-1 and HSV-2.[1]

The structures of newly synthesized acyclonucleosides were confirmed by elemental analyses, proton magnetic resonance spectra, ultraviolet spectra, and thin-layer chromatography (Table I).

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Table I. Ultraviolet Spectral and Thin-Layer Chromatography Data

compd	H_2O λ_{max}, nm (ϵ)[b]	R_f values × 100 in system[a] A	B	C
1a	253 (14500), 269 (sh, 11700)	65	49	09
1b	254 (14600), 270 (sh, 11900)	61	40	03
2a	231 (27300), 285 (10100)	73	54	45
2b	231 (28500), 284 (10700)	68	52	25
2c	231 (34400), 284 (12100)	68	55	32
3a	227 (28100), 284 (11000)	72	53	32
3b	228 (28600), 283 (11200)	70	48	21
3c	227 (34600), 285 (12000)	65	50	23
4a	253 (12600), 270 (sh, 9700)	79	61	70
4b	253 (12600), 270 (sh, 9600)	76	60	54
4c	254 (12300), 271 (sh, 9500)	72	61	59

[a] See the Experimental Section. [b] Shoulder, sh.

Antiviral Activity

All the compounds were examined for their inhibitory effects on the replication of a wide variety of DNA viruses including HSV-1 (strains KOS, F and McIntyre), HSV-2 (strains G, Lyons and 196), vaccinia virus (VV), thymidine kinase deficient (TK^-) HSV-1 mutants (B2006 and VMW 1837), varicella-zoster virus (VZV) (strains YS and Oka), TK^- VZV mutants (YSR and 07-01), and cytomegalovirus (CMV) (strains Davis and AD-169) (Table II). Of the newly synthesized acyclonucleosides, compound **2b** exhibited the most pronounced antiviral activity. It proved inhibitory to HSV-1, HSV-2, VZV, and CMV, whereas VV was not inhibited. The second most effective was compound **2a**, which showed marked activity against HSV-1, HSV-2, and, to a lesser extent, VZV, whereas CMV and VV were not inhibited. Third was **3b**, which was as active as **2a** against HSV-1 and HSV-2, but did not affect VZV, CMV, or VV. Compounds **4a** and **4b** were only weakly inhibitory to HSV-1 and HSV-2, but not any of the other viruses. The guanosine derivatives **2c**, **3c**, and **4c** were totally inert as antiviral agents.

The compounds were also examined and found inactive at the highest concentration tested (400 μg/mL), against the following RNA viruses: vesicular stomatitis virus, Coxsackie virus type B4, poliovirus type 1, parainfluenza virus type 3, reovirus type 1, Sindbis virus, and Semliki forest virus (data not shown). Furthermore, all compounds were subjected to cytotoxicity measurements based on either of the following parameters: alteration of cell morphology, inhibition of host cell DNA synthesis, or inhibition of cell growth (Table II). None of the test compounds affected any of these parameters at concentrations up to 200 or 400 μg/mL.

From our findings it is clear that compounds **2a**, **2b**, and **3b** should be considered as selective antiherpesvirus agents: i.e. **2b** inhibits HSV, VZV, and CMV replication at concentrations which are at least 100-fold (VZV, CMV) to 10000-fold (HSV) lower than the cytotoxic concentrations. The fact that **2a**, **2b**, and **3b**, akin to acyclovir (**1a**) and ganciclovir (**1b**), are less inhibitory to the TK^- mutants of HSV and VZV than to their TK^+ wild-type HSV and VZV strains (Table II) indicates that the antiviral activity of these compounds depends at least in part on a specific phosphorylation by the virus-induced thymidine kinase.

The potential of acyclovir and ganciclovir as antiherpetic agents[8] and their role in the chemotherapy of HSV, VZV, and CMV infections[9,10] have been well-established. The

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Table II. Antiviral Activity and Cytotoxicity of Novel N-Substituted Derivatives of Acyclovir (1a), Ganciclovir (1b), and Guanosine

virus	cells	minimum inhibitory concentration,[a] μg/mL										
		1a	1b	2a	2b	2c	3a	3b	3c	4a	4b	4c
Antiviral Activity												
HSV-1 (KOS)	ESM	0.02	0.004	0.7	0.07	>400	20	0.7	>400	>400	70	>400
HSV-1 (F)	ESM	0.007	0.004	0.7	0.07	>400	4	0.7	>400	70	20	100
HSV-1 (McIntyre)	ESM	0.007	0.004	1	0.07	>400	20	0.7	>400	>400	20	100
HSV-2 (G)	ESM	0.02	0.004	2	0.07	>400	20	2	>400	>400	70	>400
HSV-2 (Lyons)	ESM	0.01	0.004	0.4	0.02	>400	10	0.7	>400	20	20	100
HSV-2 (196)	ESM	0.07	0.004	0.7	0.07	>400	70	2	>400	20	70	>400
VV	ESM	>200	20	>400	>400	>400	>400	>400	>400	>400	>400	>400
TK⁻ HSV-1 (B2006)	ESM	100	7	>400	200	>400	>400	>400	>400	>400	>400	>400
TK⁻ HSV-1 (VMW2837)	ESM	40	1	>400	20	>400	>400	150	>400	>400	>400	>400
VZV (YS)	HEL	0.3	ND[b]	25	10	>200	>400	>400	>400	>400	>400	>200
VZV (Oka)	HEL	0.2	ND	20	4	>200	>400	400	>400	>400	>400	>200
TK⁻ VZV (YSR)	HEL	10	ND	>400	50	>200	>400	300	>400	>400	>400	>200
TK⁻ VZV (07-1)	HEL	5	ND	400	15	>200	>400	400	>400	>400	>400	>200
CMV (Davis)	HEL	15	1	>400	5	>200	>400	200	400	>400	>400	>400
CMV (AD-169)	HEL	15	1	200	4	>200	>400	150	400	>400	>400	>400
Cytotoxicity												
cell morphology	ESM	400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400
cellular DNA synthesis	ESM	>200	>200	>200	>200	150	>200	>200	150	>200	>100	>200
cell growth	HEL	200	90	>200	>200	>200	>200	>200	>200	>200	>200	>200

[a] Required to inhibit virus-induced cytopathogenicity in ESM cells or viral plaque formation in HEL cells by 50%. Virus input was 100 $CCID_{50}$ (1 $CCID_{50}$ being the infective dose for 50% of the cell cultures) in the cytophatogenicity assays and 20 PFU (plaque-formings units) in the plaque-formation assays. In the cytotoxicity experiments, the minimum inhibitory concentration corresponded to the concentration required to cause either (i) a microscopically detectable alteration of normal cell morphology or (ii) 50% reduction in cellular DNA synthesis (monitored by the incorporation of [*methyl*-^{3}H]dThd) or (iii) 50% reduction in cell growth. For abbreviations, see the text. [b] Not determined.

present results suggest that some novel acyclovir or ganciclovir derivatives (**2a**, **2b**, and **3b**) also offer promise, and deserve further pursuit, as antiherpes agents.

Experimental Section

General Methods. Melting points were determined on a micromelting point apparatus in open capillaries and are uncorrected. The ultraviolet spectra were measured in water on a Zeiss Specord UV–vis and on a Zeiss VSU-2P spectrophotometer. The ^{1}H NMR spectra were recorded on a JEOL FX 90Q FT NMR spectrometer in DMSO-d_6 at 89.55 MHz. Chemical shifts are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. Thin-layer chromatography (TLC) conducted on Merck precoated silica gel F_{254} Type 60 plates in the following solvent systems (measured by volume): A, 2-propanol–concentrated aqueous ammonia–water (7:1:2), B, 1-butanol–glacial acetic acid–water (5:3:2), C, chloroform–methanol (4:1). For a preparative short-column chromatography, Merck TLC gel HF_{254} Type 60 was used. Elemental analyses were performed on a Perkin-Elmer 240 elemental analyzer, and the results are within 0.4% of the theoretical values.

The following compounds tested in this work were synthesized as described previously: **2a**,[1] **2c**,[3] **3c**,[6] **4c**.[6] The 90% solution of chloroacetaldehyde in ethyl ether was prepared from commercial 50–55% aqueous chloroacetaldehyde (Fluka AG), as reported.[6]

3,9-Dihydro-3-[(1,3-dihydroxy-2-propoxy)methyl]-6-methyl-9-oxo-5*H*-imidazo[1,2-*a*]purine (2b). Sodium hydride (14.4 mg, 0.6 mmol) in 50% suspension in oil was added to a suspension of **1b** (127.6 mg, 0.5 mmol) in anhydrous dimethylformamide (4 mL). The mixture was stirred with exclusion of moisture for 45 min, and a resulting cloudy solution was treated with bromoacetone (82 mg, 0.6 mmol). After 90 min the dark red reaction mixture was made alkaline by addition of concentrated aqueous ammonia (3 mL) and left at room temperature for 2 h. The solution thus obtained was evaporated to an oil, which was redissolved in 50% aqueous ethanol and adsorbed on a portion of silica gel (ca. 3 g, 70–230 mesh) by evaporation of the solvent. The dried gel was applied onto a silica gel short column (3.5 × 6 cm) and the product was eluted with chloroform–ethanol (4:1). Fractions 21–42 (at 12 mL) containing the homogeneous by TLC product **2b** were pooled and evaporated to give 122.6 mg (84%) of a crystallizing oil. An analytical sample was recrystallized from ethanol: mp 235 °C dec; ^{1}H NMR δ 2.26 (3, d, CH_3), 3.45 (m, 4, 3′H and 5′H), 3.62 (p, 1, 4′H), 4.58 (t, 2, OH), 5.58 (s, 2, 1′H), 7.35 (d, 1, HC=), 8.00 (s, 1, 8-H), 12.38 (br s, 1, NH). Anal. ($C_{12}H_{15}N_5O_4 \cdot H_2O$) C, H, N.

1-(2,2-Diethoxyethyl)-9-[(2-hydroxyethoxy)methyl]guanine (4a). Well-powdered potassium carbonate (898 mg, 6.5 mmol) was added at 80 °C to a stirred suspension of **1a** (676 mg, 3.0 mmol) in dimethylformamide (20 mL), followed by bromoacetaldehyde diethyl acetal (1.182 g, 6.0 mmol). Stirring was continued at this temperature for 32 h, and the next portions of potassium carbonate (276 mg, 2.0 mmol) and the acetal (394 mg, 2.0 mmol) were added after 16 h. The reaction mixture was then evaporated to a solid, which was powdered and extracted with a warm mixture of chloroform and methanol (9:1). The extracts were concentrated in vacuo to a small volume and chromatographed on a silica gel short column in a chloroform–ethanol gradient (95:5 to 9:1), and 12-mL fractions were collected. Fractions 64–71 contained a small amount of the O-6-alkylated side product (R_f 0.74 in solvent C, λ_{max} (H_2O) 210, 249 and 281 nm), 81 mg (8%) an oil after evaporation. The next fractions (73–109) containing the chromatographically pure product **4a** were evaporated to give 418 mg (41%) of a white solid. An analytical sample was crystallized from water: mp 203–204 °C; ^{1}H NMR δ 1.07 (t, 6, CH_3), 3.30–3.79 (m, 8, OCH_2), 4.06 (d, 2, NCH_2), 4.66 (t, 1, OH), 4.72 (t, 1, OCHO), 5.36 (s, 2, 1′H), 6.86 (br s, 2, NH_2), 7.84 (s, 1, 8H). Anal. ($C_{14}H_{23}N_5O_5$) C, H, N.

1-(2,2-Diethoxyethyl)-9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (4b). The alkylation reaction was performed as described for the preparation of **4a**, using 255 mg (1.0 mmol) of **1b**, 415 mg (3.0 mmol) of potassium carbonate, and 591 mg (3.0 mmol) of bromoacetaldehyde diethyl acetal, in 10 mL of dimethylformamide. The reaction mixture thus obtained was filtered through a layer of Celite and the insoluble material was washed with dimethylformamide. The filtrate was evaporated to a brown oil, which was then chromatographed on a silica gel short column (2.5 × 9 cm) in chloroform–methanol (9:1). Evaporation of fractions containing the main product afforded 123 mg (33%) of **4b** as a crystalline solid. An analytical sample was recrystallized from 2-propanol: mp 172–173 °C; ^{1}H NMR δ 1.07 (t, 6, CH_3), 3.21–3.76 (m, 9, OCH_2 and 4′H), 4.05 (d, 2, NCH_2), 4.56 (t, 2, OH), 4.72 (t, 1, OCHO), 5.44 (s, 2, 1′H), 6.80 (br s, 2, NH_2), 7.82 (s, 1, 8H). Anal. ($C_{15}H_{25}N_5O_6$) C, H, N.

3,9-Dihydro-3-[(2-hydroxyethoxy)methyl]-9-oxo-5*H*-imidazo[1,2-*a*]purine (3a). Method A. Sodium hydride (12.7 mg, 0.53 mmol) in 50% suspension in oil was added to an an-

(10) De Clercq, E. *Verh. K. Acad. Geneeskd. Belg.* **1990**, *52*, 69.

hydrous suspension of **1a** (112.6 mg, 0.5 mmol) in dimethylformamide (3 mL). After being stirred with exclusion of moisture for 45 min, the resulting solution was treated with 90% chloroacetaldehyde in ethyl ether (50 μL, ca. 0.6 mmol). Stirring was continued at room temperature for 45 min, then at 45 °C for 1 h. The reaction mixture was made basic by addition of concentrated aqueous ammonia (2 mL), and after 1 h the obtained solution was evaporated to dryness. The residue after evaporation was dissolved in 50% aqueous ethanol and adsorbed on a portion of silica gel (ca. 3 g, 70–230 mesh) by repeated coevaporation with ethanol. The dried gel was applied onto a silica gel short column (2.8 × 9 cm) and the product was eluted with chloroform–methanol (6:1). Fractions 34–47 (at 6 mL) containing the TLC-homogeneous **3a** were evaporated to give 22.4 mg (18%) of a white solid. The ultraviolet and ^{1}H NMR spectra were identical with those described in method B.

Method B. Acetal derivative **4a** (400 mg, 1.17 mmol) was gently refluxed in 40% acetic acid (25 mL) with a slow distillation of solvent in order to remove ethanol formed in the reaction. During the reaction time ca. 10 mL of a distillate (bp 92–94 °C) were collected. The rest of solvent was then evaporated under diminished pressure and a resulting white residue was coevaporated twice with 2-propanol, which gave the chromatographically pure **3a** as a white powder (yield 286 mg, 98%). An analytical sample was crystallized from water: mp 248.5 °C dec; ^{1}H NMR δ 3.50 (s, 4, 4'H and 5'H), 4.67 (t, 1, OH), 5.50 (s, 2, 1'H), 7.45 and 7.63 (2 d, J = 2.6 Hz, 2, HC=CH), 8.04 (s, 1, 8H), 12.48 (br s, 1, NH). Anal. ($C_{10}H_{11}N_5O_3$) C, H, N.

3,9-Dihydro-3-[(1,3-dihydroxy-2-propoxy)methyl]-9-oxo-5*H*-imidazo[1,2-*a*]purine (3b). Acetal derivative **4b** (100 mg, 0.269 mmol) was hydrolyzed in 1.2 N hydrochloric acid (6 mL) at room temperature for 18 h. At this time TLC in solvent C showed that substrate **4b** had completely disappeared, and the reaction mixture was made alkaline by addition of concentrated aqueous ammonia (5 mL). An excess of ammonia was gently evaporated after 1 h, and a resulting colorless solution was adsorbed on a portion of silica gel (ca. 3 g, 70–230 mesh) by evaporation. The dried gel was applied onto a silica gel short column (2.5 × 7 cm) and the product was eluted with chloroform–methanol (6:1). Fractions 35–45 (at 6 mL) contained chromatographically pure **3b** and were evaporated to a crystalline solid (yield 58.4 mg, 78%). An analytical sample was recrystallized from 90% aqueous ethanol: mp 250–251 °C dec; ^{1}H NMR δ 3.41 (m, 4, 3'H and 5'H), 3.64 (p, 1, 4'H), 4.60 (t, 2, OH), 5.59 (s, 2, 1'H), 7.42 and 7.61 (2 d, J = 2.6 Hz, 2, HC=CH), 8.03 (s, 1, 8H), 12.46 (br s, 1, NH). Anal. ($C_{11}H_{13}N_5O_4$) C, H, N.

Antiviral Activity and Cytotoxicity Evaluation. The methods for measuring virus-induced cytopathogenicity,[11] viral plaque formation,[12] host cell DNA synthesis,[11] and cell growth,[12] as well as the sources of the different virus strains,[11,13,14] have been described previously.

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Registry No. **1a**, 59277-89-3; **1b**, 82410-32-0; **2a**, 114199-19-8; **2b**, 134287-58-4; **2c**, 59327-60-5; **3a**, 134287-59-5; **3b**, 134287-60-8; **3c**, 62462-38-8; **4a**, 134287-61-9; **4b**, 134287-62-0; **4c**, 132131-58-9.

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5-(5-Bromothien-2-yl)-2'-deoxyuridine and 5-(5-Chlorothien-2-yl)-2'-deoxyuridine Are Equipotent to (*E*)-5-(2-Bromovinyl)-2'-deoxyuridine in the Inhibition of Herpes Simplex Virus Type I Replication

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2'-Deoxyuridines with a five-membered heterocyclic substituent in the 5-position were synthesized by palladium-catalyzed coupling reactions of 5-iodo-2'-deoxyuridine with the activated heteroaromatics. Further modification of the compound with the 5-thien-2-yl substituent gave 5-(5-bromothien-2-yl)-2'-deoxyuridine and 5-(5-chlorothienyl-2-yl)-2'-deoxyuridine. Both compounds show potent and selective activity against herpes simplex virus type 1 and varicella-zoster virus.

Introduction

Several 5-substituted pyrimidine nucleosides show potent anti herpes virus activity.[1] Among them, 5-iodo-2'-deoxyuridine (IdUrd) and 5-(trifluoromethyl)-2'-deoxyuridine have been in clinical use for years. The most active congeners among the 5-substituted 2'-deoxyuridine derivatives are (*E*)-5-(2-halogenovinyl)-2'-deoxyuridines.[2] These compounds are particularly active against herpes simplex virus type 1 (HSV-1) and varicella-zoster virus. Their antiviral selectivity is primarily due to a preferential phosphorylation by the virus-encoded thymidine kinase and a greater inhibitory effect of the 5'-triphosphates on the viral DNA polymerase than the cellular DNA polymerases.[1]

From a structure–activity relationship study of some 30 5-substituted 2'-deoxyuridine analogues, the following features for the ideal 5-substitutent were proposed:[3] the substituent should be unsaturated, in conjugation with the pyrimidine base, not more than four carbon atoms long, it should possess *E* stereochemistry, and include an electronegative hydrophobic function.

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