S-Glucosylated Hydantoins as New Antiviral Agents

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S-Glycosylation took place on reaction of 5-alkylidene- and 5-arylidene-3-aryl-2-thiohydantoins with glycosyl halides under alkaline conditions. Bisglucosylation also took place when N-3 unsubstituted hydantoins were reacted. The bisglucosylated hydantoins produced N-3 glucosylated hydantoins on treatment with ammonia in methanol. In antiviral studies the most active compounds against both HSV-1 and HSV-2 were 5-(2-thienylmethylene)-3-phenyl-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin and 5-(2-thienylmethylene)-3-(4-chlorophenyl)-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin.

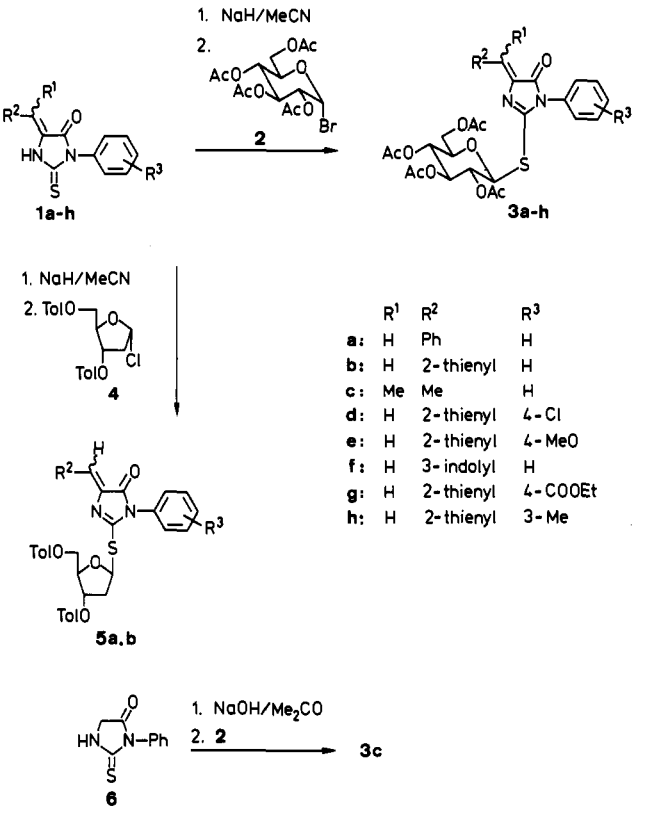
Introduction

Some acyclic nucleoside analogues have achieved considerable success as antiviral agents[1] because of their low toxicity for normal cells while having an inhibitory activity against herpes simplex virus (HSV). One of the most potent compounds is 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir).[2,3] Recently, novel phosphonate isosteres of acyclovir and ganciclovir monophosphates have also been found selective antiherpes virus agents.[4] Among pyrimidine nucleosides,[5] 5-iodo-2′-deoxyuridine (IdUrd) has been in clinical use as a drug for years. The most active congeners among the 5-substituted 2′-deoxyuridine derivatives are (*E*)-5-(2-halogenovinyl)-2′-deoxyuridines.[6] These compounds are particularly active against herpes simplex virus type 1 (HSV-1) and varicella-zoster virus. The structure activity relationship of 5-substituted 2′-deoxyuridine analogues has been studied.[7,8] Many examples of new nucleoside analogues have been described that show broad spectrum antiviral activity.[9] On the contrary, non-nucleosides are expected to interact with very specific targets, hence a narrow spectrum and a good chance of a high therapeutic index could be the result.[9] As a part of our program to find new antiviral agents, we report our results on the synthesis and evaluation of the antiherpes virus activity of the 5-arylidene-3-phenyl-2-[3,5-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-2-thiohydantoins and 5-arylidene-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoins. Our interest in 2-glucosylated hydantoin derivatives has been outlined in an earlier publication.[10]

Chemistry

For the synthesis of hydantoins **5a,b** (Scheme 1), compounds **1a,b** were treated with 1.1 equiv of NaH in anhydrous acetonitrile followed by 1.1 equiv of the 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl chloride, **4**, prepared from 2-deoxy-D-ribose according to the published methods.[11–13] For the synthesis of glucosyl hydantoins **3a–h**, compounds **1a–h** were likewise treated with 1.1 equiv of NaH in anhydrous acetonitrile followed by 1.1 equiv of the 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **2**. Alternatively, the isopropylidene derivative **3c** could be synthesized by treatment of 3-phenyl-2-thiohydantoin **6**

Scheme 1



	R¹	R²	R³
a:	H	Ph	H
b:	H	2-thienyl	H
c:	Me	Me	H
d:	H	2-thienyl	4-Cl
e:	H	2-thienyl	4-MeO
f:	H	3-indolyl	H
g:	H	2-thienyl	4-COOEt
h:	H	2-thienyl	3-Me

with aqueous NaOH in acetone followed by **2**. In all cases the yields were in the range of 72–95%.

When the N-3 unsubstituted compounds **7a–c** were reacted with **2** in aqueous acetone, both mono- and bisglucosylation reactions took place with formation of the compounds **8** and **9**, respectively (Scheme 2). Upon deprotection of **9a,b** with ammonia in methanol, the glucosylthio group was most likely replaced by a methoxide group in a nucleophilic substitution reaction. Subsequent demethylation afforded the N-3 glucosyl hydantoin derivatives **10a,b**. However, formation of the 2-oxo derivative directly from moisture cannot be excluded. This type of cleavage also explains why we were not successful in the deprotection of the compounds **3**, **5**, or **8** in saturated methanolic ammonia.

The ^{1}H-NMR (Me_2SO-d_6) spectrum of 5-(phenylmethylene)-3-methylhydantoin has been reported to show N^1-H at 10.72 ppm whereas 5-(phenylmethylene)-1-methylhy-

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Scheme 2

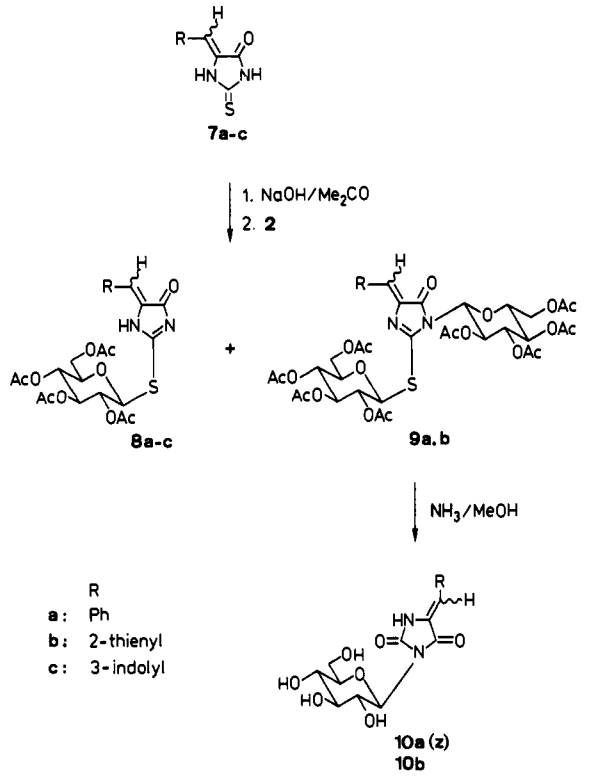

Table 1. Antiviral Activity of 3-Aryl-2-glucopyranosyl-2-thiohydantoin Derivatives **3a–h** against HSV-1 in Vero Cells

	ED_{50},[a] μM			SI[c]	
compd	HSV-1	HSV-2	CD_{50}[b] μM	HSV-1	HSV-2
3a	>100	100	>100		
3b	0.4	0.7	24	60	34
3c	119	100	>200	>1.6	>2
3d	0.6	1	20	33	20
3e	27	27	35	1.3	1.3
3f	46	40	>100	>2.2	>2.5
3g	32	46	46	1.4	1
3h	10	19	25	2.5	1.3
BVDU	0.3	6.8	>100	>333	>15
Acyclovir	0.5	0.5	>50	>100	>100

[a] Effective dose of compound, achieving 50% protection of Vero cells against either HSV-1 or HSV-2. [b] Cytotoxic dose of compound, required to reduce the viability of normal uninfected Vero cells by 50%. [c] Selectivity index: ratio CD_{50}/ED_{50}. ED_{50} and CD_{50} are expressed as the mean values of three independent determinations.

dantoin showed N^3-H at 11.38 ppm.[14] The ^{1}H-NMR (DMSO-d_6) spectra of **10a,b** showed NH at 10.91 and 10.70 ppm, respectively, corresponding to N^1-H, proving N-3 glycosylation. N-3 glucosylation was further confirmed by nuclear Overhauser effect (NOE) experiments on compound **10a**. On irradiation of the NH resonance 10.91 ppm a large NOE enhancement was found for the ortho protons of the phenyl group (9%) and on irradiation of the ortho protons a small NOE enhancement was found for NH (2%). Actually, this also proves *Z* configuration of the exocyclic double bond in compound **10a**.

Antiviral Activity

The glucopyranosylthiohydantoin derivatives **3a–h** were tested for their activity against herpes simplex virus, type 1 (HSV-1) and type 2 (HSV-2) in Vero cells. As shown in Table 1, only **3a** was devoid of any activity against HSV-1 at 100 μM whereas **3b–h** were active; inhibitory concentrations (ED_{50}) ranged from 0.4 to 119 μM. Most compounds, however, had an *in vitro* therapeutic index of only 1–3. Compounds **3b** and **3d** were found to be interesting, having activities against HSV-1 comparable to those of acyclovir and BVDU. However, their selectivity index (SI) was in the range of 33–60 and was lower than the one of acyclovir. Since **3b** and **3d** belong to a new class of active compounds and also were active against HSV-2, further investigations are needed in order to determine the mechanism of their action against herpes virus.

None of the 3-unsubstituted 2-glucopyranosyl-2-thiohydantoin derivatives **8a–c**, the 3-phenyl-2-(2-deoxy-D-pentofuranosyl)hydantoin derivatives **5a,b**, or the bis-glucosyl derivative **9b** showed any selectivity and/or antiviral activity against HSV-1 or HIV-1. Nor were any of the 3-aryl-2-glucopyranosyl-2-thiohydantoins **3a–h** endowed with substantial anti-HIV activity in MT-4 cells.

Experimental Section

The ^{1}H-NMR spectra were recorded on a Bruker A 250 FT NMR spectrometer with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). Mass spectra (MS) were recorded using electron ionization (EI) on a Varian Mat 311A spectrometer or using fast atom bombardment (FAB) on a Kratos MS 50 spectrometer. The silica gel (0.040–0.063 mm) used for column chromatography was purchased from Merck. IR spectra were recorded with a Perkin-Elmer 1720 spectrometer.

3-Aryl-2-thiohydantoin Derivatives. These compounds were prepared according to the published method[15] for the preparation of 3-phenyl-2-thiohydantoin.

3-[4-(Ethoxycarbonyl)phenyl]-2-thiohydantoin. Glycine (0.75 g, 10 mmol) was dissolved in a mixture of water (25 mL) and pyridine (25 mL), and the pH was adjusted to 9 by addition of 1 M NaOH. The solution was heated at 40 °C during addition of 4-(ethoxycarbonyl)phenyl isothiocyanate (3.9 g) under vigorous stirring. NaOH (1 M) was added portionwise to keep the pH at 9. The reaction was complete when the alkali consumption ceased after 30 min. Pyridine and excess of 4-(ethoxycarbonyl)phenyl isothiocyanate were then removed by repeated extractions with equal volumes of benzene. A volume of 1 M HCl equivalent to the total volume of 1 M NaOH was added. The solvent was removed under reduced pressure, and the residue was suspended in 30 mL of a saturated solution of HCl in EtOH and refluxed for 4 h. The reaction mixture was concentrated to dryness *in vacuo*. The residue was triturated with water, and the solid product was filtered off and recrystallized from methanol to give 0.89 g (30%) of 3-[4-(ethoxycarbonyl)phenyl]-2-thiohydantoin: mp 164 °C; MS (EI) *m/z* 264 (M^+); ^{1}H NMR (DMSO-d_6) δ 1.32 (3H, t, J = 6.8 Hz, CH_3), 3.86 (2H, q, J = 6.4 Hz, CH_2), 7.46 (2H, d, J = 8.0 Hz, aryl), 8.05 (2H, d, J = 8.1 Hz, aryl), 10.42 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ 13.99 (CH_3), 49.11 (C-5), 60.79 (CH_2), 128.99, 129.29, 129.67, 137.45 (aryl), 165.00 (C=O), 171.72 (C-4), 182.51 (C-2).

5-Arylidene-3-aryl-2-thiohydantoins (1a–h) and 5-Arylidene-2-thiohydantoins 7a–c. The standard procedure was used.[16]

3-(4-Chlorophenyl)-5-(2-thienylmethylene)-2-thiohydantoin (1d): yield 2.28 g (71%); mp 275 °C; MS (EI) *m/z* 320 (M^+); ^{1}H NMR (DMSO-d_6) δ 6.84 (1H, s, =CH), 7.23–7.95 (7H, m, aryl); ^{13}C NMR (DMSO-d_6) δ 105.79 (=CH), 124.27, 128.78, 129.17, 130.59, 130.79, 131.03, 132.09, 133.32, 135.31 (C-5, aryl), 163.35 (C-4), 177.57 (C-2).

3-(4-Methoxyphenyl)-5-(2-thienylmethylene)-2-thiohydantoin (1e): yield 2.34 g (74%); mp 274 °C; MS (EI) *m/z* 316 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.81 (3H, s, CH_3), 7.02–7.80 (8H, m, =CH, aryl), 12.47 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ 55.27 (CH_3), 112.04 (=CH), 113.88, 125.07, 125.60, 127.71, 129.85, 131.86, 135.02, 135.56, 159.16 (C-5, aryl), 161.31 (C-4), 174.81 (C-2).

5-(3-Indolylmethylene)-3-phenyl-2-thiohydantoin (1f): yield 2.5 g (78%); mp 300 °C; MS (EI) *m/z* 319 (M^+); ^{1}H NMR

(DMSO-d_6) δ 7.10–9.1 (11H, m, aryl), 12.00 (2H, s, 2 NH); ^{13}C NMR (DMSO-d_6) δ 108.96, 112.40, 117.35, 120.80, 122.57, 123.21, 127.44, 128.48, 128.64, 128.83, 130.58, 133.60, 135.90 (=CH, C-5, aryl), 161.50 (C-4), 172.14 (C-2).

3-[4-(Ethoxycarbonyl)phenyl]-5-(2-thienylmethylene)-2-thiohydantoin (1g). To a mixture of 3-[4-(ethoxycarbonyl)-phenyl]-2-thiohydantoin (0.89 g, 3 mmol) and piperidine (0.26 g, 3 mmol) in absolute ethanol (20 mL), was added 2-thiophenecarboxaldehyde (0.34 g, 3 mmol). The reaction mixture was stirred at room temperature for 6 h until the starting material was consumed (TLC). The reaction mixture was poured into water, and the yellow solid obtained was filtered off. Recrystallization from ethanol gave 0.9 g (84%) of 1g: mp 200 °C dec; MS (EI) m/z 358 (M^+); ^{1}H NMR (DMSO-d_6) δ 1.35 (3H, t, J = 6.9 Hz, CH_3), 4.36 (2H, q, J = 6.8 Hz, CH_2), 7.06 (1H, s, =CH), 7.11–8.11 (8H, m, aryl), 12.50 (1H, s, NH); ^{13}C NMR (Me_2SO-d_6) δ 14.05 (CH_3), 60.91 (CH_2), 105.95 (=CH), 124.25, 128.87, 129.06, 129.17, 129.48, 130.85, 131.12, 135.31, 137.30 (C-5, aryl), 163.25 (C=O), 165.02 (C-4), 177.27 (C-2).

3-(3-Methylphenyl)-5-(2-thienylmethylene)-2-thiohydantoin (1h): yield 1.2 g (80%); mp 152 °C; MS (EI) m/z 300 (M^+); ^{1}H NMR (DMSO-d_6) δ 2.35 (3H, s, CH_3, 6.79–7.90 (8H, m, =CH, aryl), 12.35 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ 20.67 (CH_3), 105.37 (=CH), 125.48, 125.72, 128.44, 128.97, 129.16, 130.44, 130.75, 133.36, 135.69, 138.11 (C-5, aryl), 163.90 (C-4), 178.01 (C-2).

5-Arylidene- and 5-Isopropylidene-3-phenyl-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin (3a–h). General Procedure. The hydantoin 1 (5 mmol) was suspended in anhydrous MeCN (25 mL) at room temperature. To this suspension was added NaH (50%, 0.26 g, 5 mmol), and the mixture was stirred at room temperature for 30 min. The mixture became clear after 15 min. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2, 2.26 g, 5.5 mmol) was added, and the mixture was stirred at room temperature for 12 h until the starting material was consumed (TLC) and then filtered. The residue from evaporation of the filtrate under reduced pressure was purified by silica gel column chromatography with Et_2O/petroleum ether (1:1, v/v) to give the products **3a–h**.

5-Benzylidene-3-phenyl-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin (3a): yield 3.1 g (91%); mp 182 °C (lit.[10] mp 180 °C).

3-Phenyl-5-(2-thienylmethylene)-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin (3b): yield 2.75 g (89%); mp 189–190 °C; MS (EI) m/z 616 (M^+), 286 (base), 331 (glycon + 1); IR (KBr) 1752 (C=O); ^{1}H NMR ($CDCl_3$) δ 1.87 (3H, s, CH_3), 2.02 (6H, s, $2CH_3$), 2.07 (s, 3H, CH_3), 4.04 (1H, m, 5′-H), 4.23 (m, 2H, 6′-H), 5.17 (t, J = 9.7 Hz, 1H, 4′-H), 5.27 (t, J = 9.9 Hz, 1H, 2′-H), 5.41 (t, J = 9.3 Hz, 1H, 3′-H), 5.91 (d, J = 10.5 Hz, 1H, 1′-H), 7.12–7.70 (m, 8H, aryl); ^{13}C NMR ($CDCl_3$) δ 20.22, 20.33 (4 Ac), 61.51 (C-6′), 67.88 (C-2′), 68.86 (C-3′), 73.88 (C-4′), 76.84 (C-5′), 81.27 (C-1′), 119.52 (=CH), 126.81, 127.34, 129.12, 129.45, 131.76, 133.54, 134.08, 135.33, 137.65 (C-5, aryl), 159.29 (C-2), 167.46 (C-4), 169.11, 169.17, 170.38 (4 C=O). Anal. ($C_{28}H_{28}N_2O_{10}S_2$) C, H, N.

5-Isopropylidene-3-phenyl-2-(2,3,4,6,tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin (3c): yield using the general procedure 2.4 g (85%); mp 167–168 °C; MS (EI) m/z 562 (M^+), 232 (base), 331 (glycon + 1); IR (KBr) 1757, 1718 (C=O); ^{1}H NMR (DMSO-d_6) δ 1.94 (s, 3H, CH_3), 197 (s, 6H, 2 CH_3), 1.99 (s, 3H, CH_3), 2.29, 2.34 (2 s, 6H, $(CH_3)_2CH$=), 4.04 (m, 1H, 6′-H), 4.16 (m, 2H, 5′-H, 6′-H), 4.97 (1H, t, J = 9.2 Hz, 4′-H), 5.10 (1H, t, J = 9.8 Hz, 2′-H), 5.50 (t, J = 9.8 Hz, 1H, 3′-H), 5.90 (d, J = 10.4 Hz, 1H, 1′-H), 7.27–7.55 (m, 5H, aryl); ^{13}C NMR (DMSO-d_6) δ 18.51, 21.74 (2 Me), 20.11, 20.17, 20.23 (4 Ac), 61.50 (C-6′), 67.78 (C-2′), 68.93 (C-3′), 72.80 (C-4′), 74.99 (C-5′), 80.16 (C-1′), 127.42, 128.99, 129.31, 132.08, 135.32 (C-5, aryl), 147.17 (=CH), 153.34 (C-2), 165.64 (C-4), 169.06, 169.30, 169.75 (4 C=O). Anal. ($C_{28}H_{30}N_2O_{10}S$) C, H, N.

Synthesis of 3c from 6. 3-Phenyl-2-thiohydantoin (6, 0.96 g, 5 mmol) was suspended in aqueous NaOH (4.4%, 5 mL) at room temperature. To this suspension was added acetone (25 mL), and the mixture became clear after stirring at room temperature for 5 min. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2, 2.26 g, 5.5 mmol) was added, and the mixture was stirred overnight at room temperature. After filtration and evaporation of the filtrate under reduced pressure, the residue was chromatographed on a silica gel column with ether/petroleum ether (1:1, v/v) to obtain 1.3 g (67%) of **3c**.

3-(4-Chlorophenyl)-5-(2-thienylmethylene)-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin (3d): yield 3.0 g (92%); mp 183–185 °C; MS (FAB) m/z 651 (M + H^+), 331 (glycon + 1), 321 (base + 1); IR (KBr) 1752 (C=O); ^{1}H NMR (DMSO-d_6) δ 1.81 (s, 3H, Ac), 1.96 (s, 3H, Ac), 1.99 (s, 3H, Ac), 2.02 (s, 3H, Ac), 4.07 (d, J = 11.1 Hz, 1H, 6′-H), 4.22 (m, 2H, 5′-H, 6′-H), 5.15 (t, J = 9.5 Hz, 1H, 4′-H), 5.37 (t, J = 9.7 Hz, 1H, 2′-H), 5.55 (t, J = 9.3 Hz, 1H, 3′-H), 5.87 (d, J = 10.2 Hz, 1H, 1′-H), 7.19–7.94 (m, 7H, aryl); ^{13}C NMR (DMSO-d_6) δ 20.18, 20.21, 20.29 (4 Ac), 61.49 (C-6′), 67.67 (C-2′), 68.60 (C-3′), 72.85 (C-4′), 75.57 (C-5′), 80.63 (C-1′), 119.34 (=CH), 127.73, 129.39, 129.58, 130.78, 133.99, 134.75, 135.10, 137.41 (C-5, aryl), 158.31 (C-2), 166.59 (C-4), 169.23, 169.26, 169.46, 169.85 (4 C=O).

3-(4-Methoxyphenyl)-5-(2-thienylmethylene)-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin (3e): yield 2.95 g (91%); mp 190–192 °C; MS (EI) m/z 646 (M^+), 331 (glycon + 1), 316 (base); IR (KBr) ν(C=O) 1752; ^{1}H NMR (DMSO-d_6) δ 1.82 (s, 3H, Ac), 1.96 (s, 3H, Ac), 1.99 (s, 3H, Ac), 2.03 (s, 3H, Ac), 3.82 (s, 3H, OMe), 4.07 (d, J = 10.1 Hz, 1H, 6′-H), 4.22 (m, 2H, 5′-H, 6′-H), 5.13 (t, J = 9.7 Hz, 1H, 4′-H), 5.37 (d, J = 9.8 Hz, 1H, 2′-H), 5.53 (t, J = 9.3 Hz, 1H, 3′-H), 5.85 (d, J = 10.3 Hz, 1H, 1′-H), 7.05–7.93 (=CH, m, 7H, Aryl); ^{13}C NMR (DMSO-d_6) δ 20.13, 20.16, 20.24 (4 Ac), 55.35 (OMe), 61.44 (C-6′), 67.66 (C-2′), 68.59 (C-3′), 72.86 (C-4′), 75.53 (C-5′), 80.47 (C-1′), 114.65 (=CH), 118.79, 124.20, 127.63, 128.98, 134.46, 134.79, 134.99, 137.44, 159.50 (C-5, aryl), 159.71 (C-2), 166.96 (C-4), 169.14, 169.19, 169.38, 169.78 (4 C=O). Anal. ($C_{29}H_{30}N_2O_{11}S_2$) C, H, N.

5-(3-Indolylmethylene)-3-phenyl-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin (3f): yield 5.07 g (78%); mp 215 °C; MS 651 (M^+); ^{1}H NMR (DMSO-d_6) δ 1.71 (3H, s, Ac), 1.98 (3H, s, Ac), 2.01 (3H, s, Ac), 2.04 (3H, s, Ac), 4.06 (1H, d, J = 10.7 Hz, 6′-H), 4.18 (1H, dd, J = 5.6, 12.5 Hz, 6′-H), 4.40 (1H, m, 5′-H), 5.02 (1H, t, J = 9.7 Hz, 4′-H), 5.11 (1H, t, J = 9.8 Hz, 2′-H), 5.72 (1H, t, J = 9.3 Hz, 3′-H), 6.27 (1H, d, J = 10.5 Hz, 1′-H), 7.19–8.78 (11H, m, =CH, aryl), 12.16 (1H, d, J = 1.8 Hz, NH); ^{13}C NMR (DMSO-d_6) δ 20.00, 20.23, 20.35 (4 Ac), 61.66 (C-6′), 67.96 (C-2′), 69.09 (C-3′), 72.81 (C-4′), 75.34 (C-5′), 80.15 (C-1′), 110.82, 112.21, 119.00, 119.84, 120.92, 122.52, 126.90, 127.43, 129.04, 129.47, 132.42, 132.52, 133.96, 136.32 (=CH, C-5, aryl), 154.65 (C-2), 167.02 (C-4), 169.26, 169.52, 169.85 (4 C=O).

3-[4-(Ethoxycarbonyl)phenyl]-5-(2-thienylmethylene)-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin (3g): yield 0.4 g (72%); mp 187 °C; MS (EI) m/z 688 (M^+), 358 (base), 331 (glycon); IR (KBr) 1757, 1725 (C=O); ^{1}H NMR (DMSO-d_6) δ 1.34 (3H, t, J = 7.1 Hz, CH_3), 1.82, 1.96, 2.00, 2.03 (12H, 4 s, 4 Ac), 4.10 (1H, d, J = 10.9 Hz, 6′-H), 4.16–4.29 (2H, m, 5′-H, 6′-H), 4.37 (2H, q, J = 7.1 Hz, CH_2), 5.14 (1H, t, J = 9.5 Hz, 4′-H), 5.36 (1H, t, J = 9.7 Hz, 2′-H), 5.55 (1H, t, J = 9.3 Hz, 3′-H), 5.90 (1H, d, J = 10.2 Hz, 1′-H), 7.21–8.13 (8H, m, =CH, aryl); ^{13}C NMR (DMSO-d_6) δ 14.00 (CH_3), 20.17, 20.28 (4 Ac), 61.00 (CH_2), 61.48 (C-6′), 67.68 (C-2′), 68.58 (C-3′), 72.83 (C-4′), 75.55 (C-5′), 80.67 (C-1′), 119.56 (=CH), 127.55, 127.76, 130.27, 130.37, 134.62, 134.89, 135.23, 135.94, 137.35 (C-5, aryl), 157.76 (C-2), 164.79 (*C*OOEt), 166.35 (C-4), 169.22, 169.42, 169.81 (4 C=O).

3-(3-Methylphenyl)-5-(2-thienylmethylene)-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin (3h): yield 1.0 g (95%); mp 177 °C; MS (EI) m/z 630 (M^+), 300 (base), 331 (glycon); IR (KBr) 1757 (C=O); ^{1}H NMR (DMSO-d_6) δ 1.82, 1.96, 2.00, 2.03 (12H, 4s, 4Ac), 2.36 (3H, s, CH_3), 4.10 (1H, d, J = 10.2 Hz, 6′-H), 4.26 (2H, m, 5′-H, 6′-H), 5.14 (1H, t, J = 9.6 Hz, 4′-H), 5.37 (1H, t, J = 9.7 Hz, 2′-H), 5.54 (1H, t, J = 9.3 Hz, 3′-H), 5.86 (1H, d, J = 10.3 Hz, 1′-H), 7.14–7.94 (8H, m, =CH, aryl); ^{13}C NMR (DMSO-d_6) δ 20.16, 20.27, 20.61 (4 Ac + CH_3), 61.47 (C-6′), 67.67 (C-2′), 68.59 (C-3′), 72.84 (C-4′), 75.54 (C-5′), 80.55 (C-1′), 119.04 (=CH), 124.50, 127.68, 127.86, 129.26, 129.99, 131.76, 134.61, 134.89, 134.95, 137.42, 139.16 (C-5, aryl), 158.86 (C-2), 166.70 (C-4), 169.14, 169.21, 169.40, 169.79 (4 C=O).

5-Benzylidene-3-phenyl-2-(3,5-di-*O*-4-toluoyl-β-D-*erythro*-pentofuranosyl)-2-thiohydantoin (5a). Typical Procedure. 5-Benzylidene-3-phenyl-2-thiohydantoin (1a, 2.80 g, 10 mmol) was suspended in anhydrous MeCN (50 mL) at room temperature. To this suspension was added NaH (50%, 0.53 g,

11 mmol), and the mixture was stirred at room temperature for 30 min. The mixture became clear after 15 min. 2-Deoxy-3,5-di-*O*-4-toluoyl-α-D-*erythro*-pentofuranosyl chloride (4, 4.27 g, 11 mmol) was added, and the mixture was stirred at room temperature for 4 h until the starting material was consumed (TLC). Evaporation of the filtrate gave a dry residue which was purified by silica gel column chromatography with Et_2O/petroleum ether (1:1, v/v) to give 4.5 g (71%) of **5a**: mp 163–165 °C; MS (FAB, MeOH + 3-nitrobenzyl alcohol) *m/z* 633 ($M + H^+$), 281 (BH^+), 353 (glycon + H^+); IR (KBr) 1744, 1719 (C=O); ^1H NMR ($CDCl_3$) δ 2.38 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.77 (m, 1H, 2′-H), 2.93 (m, 1H, 2′-H), 4.56 (m, 2H, 5′-H), 4.64 (m, 1H, 4′-H), 5.65 (m, 1H, 3′-H), 6.70 (t, *J* = 5.5 Hz, 1H, 1′-H), 7.08 (s, 1H, =CH), 7.12–8.49 (m, 18H, aryl); ^{13}C NMR ($CDCl_3$) δ 21.48 (CH_3), 21.55 (CH_3), 39.56 (C-2′), 63.74 (C-5′), 74.95 (C-3′), 83.44 (C-4′), 83.79 (C-1′), 125. 32 (=CH), 126.39, 126.54, 126.96, 127.97, 128.45, 128.93, 129.09, 129.33, 129.58, 129.83, 131.86, 132.02, 134.12, 137.60, 143.68, 144.24 (C-5, aryl), 162.37 (C-2), 165.75 (C=O), 165.96 (C=O), 168.44 (C-4). Anal. ($C_{37}H_{32}N_2O_6S \cdot 0.5H_2O$) C, H, N.

3-Phenyl-5-(2-thienylmethylene)-2-(3,5-di-*O*-4-toluoyl-β-D-*erythro*-pentofuranosyl)-2-thiohydantoin (5b): yield 1.4 g (88%); mp 168–170 °C; MS (FAB, DMSO + 1% CH_3COOH + 3-nitrobenzyl alcohol) *m/z* 639 ($M + H^+$), 353 (glycon + H^+), 287 (BH^+); IR (KBr) 1719 (C=O); ^1H NMR ($CDCl_3$) δ 2.38 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.78 (td, *J* = 7.0, 14.1 Hz, 1H, 2′-H), 3.11 (ddd, *J* = 3.1, 6.1, 14.4 Hz, 1H, 2-H), 4.51 (d, *J* = 4.3 Hz, 2H, 5′-H), 4.63 (m, 1H, 4′-H), 5.67 (m, 1H, 3′-H), 6.66 (t, *J* = 6.6 Hz, 1H, 1′-H), 7.12–8.00 (m, 17H, =CH, aryl); ^{13}C NMR ($CDCl_3$) δ 21.48 (CH_3), 21.55 (CH_3), 40.04 (C-2′), 63.78 (C-5′), 75.11 (C-3′), 83.41 (C-4′), 84.40 (C-1′), 118.86 (=CH), 126.60, 126.65, 126.83, 127.19, 128.87, 128.94, 129.09, 129.33, 129.61, 129.67, 132.14, 132.91, 133.62, 135.58, 138.02, 143.66, 144.19 (C-5, aryl), 160.96 (C-2), 165.66 (C=O), 165.95 (C=O). Anal. ($C_{35}H_{30}N_2O_6S_2 \cdot 1.5H_2O$) C, H, N.

5-(3-Indolylmethylene)-2-thiohydantoin (7c): yield 1.97 g (81%); mp 312 °C; MS (EI) *m/z* 243 (M^+); ^1H NMR (DMSO-d_6) δ 6.91 (=CH), 7.15–8.93 (5H, m, aryl), 12.05 (3H, s, 3 NH); ^{13}C NMR (DMSO-d_6) δ 105.52, 108.32, 112.10, 118.04, 120.69, 122.63, 123.30, 127.13, 128.90, 135.92 (=CH, C-5, aryl), 165.50 (C-4), 176.76 (C-2).

5-Benzylidene-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin (8a) and 5-Benzylidene-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin (9a). 5-Benzylidene-2-thiohydantoin (**7a**, 1.02 g, 5 mmol) was suspended in aqueous NaOH (4.4%, 5 mL) at room temperature. To this suspension was added acetone (25 mL), and the mixture became clear after stirring at room temperature for 5 min. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**2**, 2.26 g, 5.5 mmol) was added, and the mixture was stirred overnight at room temperature. After filtration and evaporation of the filtrate under reduced pressure, the residue was chromatographed on a silica gel column with ether/petroleum ether (6:4, v/v) to obtain 1.07 g (40%) of **8a** (mp 171–172 °C) and 0.86 g (20%) **9a** (mp 111–112 °C). **8a**: MS (EI) *m/z* 534 (M^+, 331 (glycon + 1), 204 (base); IR (KBr) 3436 (NH), 1757 (C=O); ^1H NMR ($CDCl_3$) δ 1.93 (s, 3H, Ac), 2.04 (s, 3H, 2Ac), 2.08 (s, 6H, 2Ac), 4.00 (m, 1H, 5′-H), 4.22 (d, *J* = 3.4 Hz, 2H, 6′-H), 5.15 (t, *J* = 9.6 Hz, 1H, 4′-H), 5.27 (t, *J* = 9.7 Hz, 1H, 3′-H), 5.41 (t, *J* = 9.2 Hz, 1H, 2′-H), 5.68 (d, *J* = 10.3 Hz, 1H, 1′-H), 7.03 (1H, s, =CH), 7.42–8.14 (m, 5H, aryl), 9.98 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 20.37, 20.42 (4Ac), 61.83 (C-6′), 67.97 (C-2′), 69.15 (C-3′), 73.43 (C-4′), 76.60 (C-5′), 81.04 (C-1′), 126.25 (=CH), 128.60, 130.33, 132.03, 133.74, 138.10 (C-5, aryl), 158.56 (C-2), 169.28 (C-4), 169.41, 169.99, 170.58, 171.14 (4 C=O). Anal. ($C_{24}H_{26}N_2O_{10}S \cdot 0.25H_2O$) C, H, N. **9a**: MS (FAB, MeOH + 3-nitrobenzyl alcohol) *m/z* 865 ($M + H^+$); IR (KBr) 1757 (C=O); ^1H NMR ($CDCl_3$) δ 1.85, 1.91, 2.02, 2.04, 2.05, 2.07, 2.12 (7s, 24H, 8Ac), 3.86–3.91 (m, 2H, 5′-H, 5″-H), 4.11–4.31 (m, 4H, 6′-H, 6″-H), 5.15–5.25 (m, 2H, 4′-H, 4″-H), 5.30–5.42 (m, 4H, 3′-H, 3″-H, 2″-H, 1″-H), 5.64 (t, *J* = 9.3 Hz, 1H, 2′-H), 5.84 (d, *J* = 10.1 Hz, 1H, 1′-H), 7.04 (s, 1H, =CH), 7.43–8.14 (m, 5H, aryl); ^{13}C NMR ($CDCl_3$) δ 19.97, 20.20, 20.30, 20.35, 20.41 (8Ac), 61.31 (C-6′), 61.73 (C-6″), 67.40 (C-2′), 68.09 (C-2″), 69.01 (C-3′, C-3″), 72.78 (C-4′), 73.83 (C-4″), 75.97 (C-5′), 76.40 (C-5″), 79.60 (C-1′), 81.56 (C-1″), 126.76 (=CH), 128.62, 130.48, 131.99, 133.62, 136.47 (C-5, aryl), 158.30 (C-2), 167.80 (C-4), 168.61, 169.08, 169.11, 169.20, 169.80, 169.97, 170.42, 170.49 (8 C=O). Anal. ($C_{38}H_{43}N_2O_{19}S$) C, H, N.

5-(2-Thienylmethylene)-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin (8b) and 5-(2-Thienylmethylene)-3-(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl)-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin (9b). The reaction of **7b** with **2** under the same conditions as for preparation of **8a**: yield 1.55 g (57%) of **8b**, mp 180–182 °C, and 0.80 g (18%) of **9b**, mp 120–122 °C. **8b**: MS (FAB, DMSO + 1% CH_3COOH + 3-nitrobenzyl alcohol) *m/z* 541 ($M + H^+$), 331 (glycon + 1); ^1H NMR (DMSO)-d_6) δ 1.81 (3H, s, Ac), 1.98 (s, 3H, Ac), 2.03 (s, 6H, 2 Ac), 4.07 (m, 1H, 6′-H), 4.18 (m, 2H, 5′-H, 6′-H), 5.13 (t, *J* = 9.5 Hz, 1H, 4′-H), 5.34 (t, *J* = 10.2 Hz, 1H, 3′-H), 5.52 (t, *J* = 9.4 Hz, 1H, 2′-H), 5.85 (d, *J* = 10.2 Hz, 1H, 1′-H), 7.17 (dd, *J* = 3.9, 4.9 Hz, 1H, 4″-H), 7.21 (s, 1H, =CH), 7.69 (d, *J* = 3.5 Hz, 1H, 3″-H), 7.85 (d, *J* = 5.0 Hz, 1H, 5″-H), 11.78 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ 20.10, 20.17, 20.21, 20.27 (4 Ac), 61.47 (C-6′), 67.75 (C-2′), 68.76 (C-3′), 72.87 (C-4′), 75.49 (C-5′), 80.16 (C-1′), 117.04 (=CH), 127.51, 133.81, 134.13, 136.34, 137.58 (C-5 and aryl), 158.59 (C-2), 169.16, 169.20, 169.41, 169.78 (C-4 and 4 C=O). **9b**: MS (EI) *m/z* 870 (M^+); IR (KBr) 1763, 1742 (2 C=O); ^1H NMR ($CDCl_3$) δ 1.89, 1.91, 2.02, 2.03, 2.04, 2.05, 2.07, 2.11 (s, 24H, 8 Ac), 3.86–3.91 (m, 2H, 5′-H, 5″-H), 4.11–4.28 (m, 4H, 2 × 6′-H, 2 × 6″-H), 5.20–5.42 (m, 4H, 3′-H, 3″-H, 2″-H, 1″-H), 5.64 (t, *J* = 9.3 Hz, 1H, H-2′), 5.84 (d, *J* = 10.1 Hz, 1H, H-1′), 7.11–7.73 (m, 4H, =CH, aryl); ^{13}C NMR ($CDCl_3$) δ 20.09, 20.31, 20.40, 20.47 (8 × Ac), 61.31 (C-6′), 61.67 (C-6″), 67.45 (C-2′), 68.09 (C-2″), 68.95, 69.01 (C-3′, C-3″), 72.92 (C-4′), 74.05 (C-4″), 75.01 (C-5′), 76.91 (C-5″), 79.64 (C-1′), 81.78 (C-1″), 120.30 (=CH), 127.43, 134.23, 134.39, 137.45 (aryl, C-5), 156.85 (C-2), 166.99 (C-4), 168.61, 169.11, 169.20, 169.26, 169.86, 170.10, 170.55 (8 C=O).

5-(3-Indolylmethylene)-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin (8c). The reaction of **7c** with **2** under the same conditions as for preparation of **8a** gave 3.95 g (69%) of **8c**: mp 150 °C; MS (EI) *m/z* 573 (M^+), 243 (base), 331 (glycon); ^1H NMR (DMSO-d_6) δ 1.74 (3H, s, Ac), 1.99 (3H, s, Ac), 2.05 (6H, s, 2Ac), 4.06 (1H, d, *J* = 10.7 Hz, 6′-H), 4.14–4.33 (2H, m, 5′-H and 6′-H), 5.05 (1H, t, *J* = 9.7 Hz, 4′-H), 5.14 (1H, t, *J* = 9.8 Hz, 3′-H), 5.67 (1H, t, *J* = 9.3 Hz, 2′-H), 6.18 (1H, d, *J* = 10.4 Hz, 1′-H), 7.16–8.61 (6H, m, Aryl), 11.56 (1H, s, NH hydantoin), 12.02 (1H, d, *J* = 2.3 Hz, NH indole); ^{13}C NMR (DMSO-d_6) δ 20.03, 20.25, 20.27, 20.35 (4 Ac), 61.66 (C-6′), 68.02 (C-2′), 69.15 (C-3′), 72.77 (C-4′), 75.27 (C-5′), 79.80 (C-1′), 110.69 (=CH), 112.10, 117.56, 118.94, 120.64, 122.32, 126.80, 133.11, 134.16, 136.25 (C-5, aryl), 154.59 (C-2), 169.25 (C-4), 169.32, 169.49, 169.53, 169.83 (4 C=O).

(*Z*)-5-Benzylidene-3-D-glucopyranosylhydantoin (10a). The protected nucleoside **9a** (0.5 g, 0.58 mmol) was stirred in saturated NH_3/MeOH (25 mL) at room temperature for 1 day. The solvent was removed *in vacuo*, and the residue was chromatographed on silica gel with a gradient of 5–10% MeOH in $CHCl_3$ to afford 100 mg (49%) of **10a** as a white foam. **10**: MS (EI) *m/z* 350 (M^+), 188 (base), 162 (glycon); IR (KBr) 3408 (OH, NH), 1770 (C=O); ^1H NMR (DMSO-d_6) δ 3.12 (m, 1H, 4′-H), 3.26 (m, 1H, 3′-H), 3.43 (m, 1H, 5′-H, 6′-H), 3.71 (dd, 3.72 (dd, *J* = 4.0, 11.4 Hz, 1H, 6′-H), 4.20 (m, 1H, 2′-H), 4.52 (m, 1H, 6′-OH), 4.85 (d, *J* = 9.0 Hz, 1H, 1′-H), 5.00 (1H, d, *J* = 5.0 Hz, 4′-OH), 5.06 (d, *J* = 3.7 Hz, 1H, 3′-OH), 5.28 (d, *J* = 4.8 Hz, 1H, 2′-OH), 6.55 (s, 1H, =CH), 7.35–7.66 (m, 5H, aryl), 10.91 (s, 1H, NH); ^{13}C NMR (CD_3OD-d_6) δ 62.71 (C-6′), 69.79 (C-4′), 71.20 (C-2′), 79.04 (C-5′), 80.92 (C-3′), 82.20 (C-1′), 112.57 (=CH), 127.04 (C-5), 130.03, 130.33, 134.24 (aryl), 156.50 (C-2), 165.85 (C-4).

3-D-Glucopyranosyl-5-(2-thienylmethylene)hydantoin (10b). The protected nucleoside **9b** (0.5 g, 0.92 mmol) was treated similarly as described for the preparation of the deprotected nucleosides **10a**. Yield 95 mg (29%) of **10b** as a yellow solid: mp 215 °C; MS (EI) *m/z* 356 (M^+), 194 (base), 162 (glycon); ^1H NMR (DMSO-d_6) δ 3.09 (m, 1H, 4′-H), 3.20 (m, 1H, 3′-H), 3.38 (m, 2H, 5′-H, 6′-H), 3.71 (dd, *J* = 5.8, 11.0 Hz, 1H, 6′-H), 4.20 (m, 1H, 2′-H), 4.58 (t, *J* = 5.7 Hz, 1H, 6′-OH), 4.83 (d, *J* = 9.4 Hz, 1H, 1′-H), 5.00 (d, *J* = 5.2 Hz, 1H, 4′OH), 5.06 (d, *J* = 4.7 Hz, 1H, 3′-OH), 5.28 (d, *J* = 5.0 Hz, 2′-OH), 6.72 (s, 1H, =CH), 7.19 (dd, *J* = 3.9, 4.9 Hz, 1H, 4″-H), 7.64 (d, *J* = 3.6 Hz, 1H, 3″-H), 7.74 (d, *J* = 4.8 Hz, 1H, 5″-H), 10.70 (s, 1H, NH); ^{13}C NMR (DMSO-

d_6) δ 61.01 (C-6'), 67.82 (C-4'), 69.93 (C-2'), 77.37 (C-5'), 79.96 (C-3'), 80.72 (C-1'), 102.95 (=CH), 128.52 (C-5), 128.69, 129.02, 129.50, 135.60 (thienyl), 153.61 (C-2), 166.83 (C-4).

Virus and Cells. The HIV-1 strain HTLV-IIIB[17] was propagated in H9 cells[18] at 37 °C using RPMI 1640 with 10% heat-inactivated Fetal Calf Serum (FCS) and antibiotics (growth medium). Culture supernatant was filtered (0.45 nm), aliquotted, and stored at −80 °C until use. HSV-1 strain McIntyre (American Type Culture Collection, VR-539) and HSV-2 strain MS (American Type Culture Collection, VR-540) were propagated in the African green monkey kidney cell line Vero (American Type Culture Collection, CRL-1587) using Eagle medium with 10% FCS and antibiotics (growth medium). Culture supernatants were filtered (0.45 nm), aliquotted, and stored at −80 °C until use.

Drugs. Acyclovir was a gift from The Wellcome Research Laboratories, Beckenham, Kent, and (*E*)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) was purchased from Sigma Chemical Co., St. Louis, MO. Stock solutions of these drugs were prepared in H_2O and stored at −80 °C until use.

Inhibition of HSV-1 and HSV-2 Replication. Nucleoside analogues were examined for possible antiviral activity against HSV-1 and HSV-2 using Vero cells as target cells. For screening studies Vero cells were incubated with virus for 2.5 h, washed, and thereafter added in a proportion of 1:50 to uninfected Vero cells, which had been preincubated in growth medium containing the test compound for 2.5 h. Cultures were maintained with the test compound for 5 days in parallel with virus-infected control cultures without compound added. Expression of HSV-1 and HSV-2 in the culture medium was quantiated by HSV-1 and HSV-2 antigen detection ELISA.[19] Compounds mediating less than 30% reduction of antigen expression were considered without biological activity. Compounds mediating a reduction of 30% or more were examined for cytotoxic potential using concentration-dependent inhibition of Vero cell proliferation as measure of cytoxicity. A 30% inhibition of cell growth relative to control cultures was considered significant.

Inhibition of HIV-1 Replication. Nucleoside analogues were examined for possible antiviral activity against HIV-1 using MT-4 cells as target cells. For screening studies MT-4 cells were incubated with virus for 2 h, washed, and thereafter added in a proportion of 1:10 to uninfected cells, which had been preincubated in growth medium containing the test compound for 2 h. Cultures were maintained with the test compound for 7 days in parallel with virus-infected control cultures without compound added. Expression of HIV in the culture medium was quantiated by HIV antigen detection ELISA.[20] Compounds mediating less than 30% reduction of antigen expression were considered without biological activity. Compounds mediating a reduction of 30% or more were examined for cytotoxic potential using concentration-dependent inhibition of MT-4 cell proliferation as measure of cytoxicity. A 30% inhibition of cell growth relative to control cultures was considered significant.

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