Structure−Activity Relationships among 2-Substituted 5,6-Dichloro-, 4,6-Dichloro-, and 4,5-Dichloro-1-[(2-hydroxyethoxy)methyl]- and -1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazoles

Sunita Saluja,[†] Ruiming Zou,[‡] John C. Drach, and Leroy B. Townsend*

Department of Medicinal Chemistry, College of Pharmacy, Department of Chemistry, College of Literature, Science and Arts, and Department of Biologic and Materials Sciences, School of Dentistry, The University of Michigan, Ann Arbor, Michigan 48109-1065

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The sodium salt of 2,5,6-trichlorobenzimidazole (**8a**) was condensed with [2-(benzyloxy)ethoxy]-methyl chloride (**9**) and [1,3-bis(benzyloxy)-2-propoxy]methyl chloride (**18**) to provide the corresponding protected acyclic nucleosides **10a** and **19a**, which on debenzylation afforded 2,5,6-trichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (**11a**) and 2,5,6-trichloro-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (**20a**), respectively. A similar condensation of 2,4,6-trichlorobenzimidazole (**2a**) and 2,4,5-trichlorobenzimidazole (**7a**) followed by debenzylation yielded **11b**, **20b**, **11c**, and **20c**, respectively. A nucleophilic displacement of the 2-chloro group of **11a**−**c** and **20a**−**c** with liquid ammonia, methylamine, dimethylamine, and thiourea furnished several interesting 2-substituted compounds in good yields, e.g., **12**−**14**(**a**−**e**), **21**−**23**(**a**−**e**), **15**−**17**, and **24**−**26**. Alkylation of the 2-thio analogs **15**−**17** and **24**−**26** with benzyl chloride furnished the 2-alkylthio acyclic nucleosides **12d**−**14d** and **21d**−**23d**. Desulfurization of **15** and **24** with Raney Ni furnished 5,6-dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (**12e**) and 5,6-dichloro-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (**21e**), respectively (acyclic analog of 5,6-dichloro-1-β-D-ribofuranosylbenzimidazole). Similarly the dihalo compounds **13e**, **14e**, and **23e** were prepared in moderate yields from the 2-thio analogs **16**, **17**, and **26**. Treatment of 2-bromo-5,6-dichlorobenzimidazole (**8b**) with **27** and **30** gave the protected acyclic compounds **28a** and **31a**, which on deacetylation with sodium carbonate and potassium cyanide yielded 2-bromo-5,6-dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (**29a**) and 2-bromo-5,6-dichloro-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (**32a**), respectively, in moderate yields. The 2-bromo-4,6-dichlorobenzimidazole and 2-bromo-4,5-dichlorbenzimidazole analogs **29b**,**c** and **32b**,**c** were prepared in a similar manner. Compounds were tested for activity against human cytomegalovirus (HCMV) and herpes simplex virus type 1 (HSV-1) and for cytotoxicity. In marked contrast to the ribosylbenzimidazoles, none of the acyclic analogs were specific and potent inhibitors of HCMV. Only the 2-thiobenzyl analogs **12d**, **13d**, **14d**, and **23d** and the 2-Br analogs **32a**,**b** were active, but activity was not well separated from cytotoxicity. The lack of specific and potent antiviral activity strongly suggests that these acyclic nucleoside analogs are not phosphorylated by HCMV or HSV-1 gene products and that the ribosylbenzimidazoles do not require phosphorylation for antiviral activity.

Introduction

Acyclic nucleoside analogs are an important class of compounds having potent and selective antiviral activity.[1] Acyclovir[2] (ACV) and ganciclovir[3] (GCV, DHPG) are two important acyclic drugs whose discovery led to an extensive search for novel nucleosides with improved properties. Although a number of nucleoside analogs such as vidarabine,[4] ACV,[4] (bromovinyl)deoxyuridine (BVDU),[5] and (fluoroiodoaracytosine (FIAC)[6] are active against herpes simplex virus type 1 (HSV-1), it has been more difficult to find drugs active against human cytomegalovirus (HCMV). GCV[7] and foscarnet[8] are the only effective drugs for HCMV infections even though the drugs produce certain adverse toxicological effects and have poor oral bioavailability. The deficiencies of these drugs have emphasized the need for more effective agents against HCMV infections, especially in immunocompromised and acquired immune deficiency syndrome (AIDS) patients.[9]

The mode of antiviral action of GCV against HSV-1 and HCMV is similar to that of ACV in that both compounds are phosphorylated to a greater extent in virus-infected cells than in uninfected cells.[10] Both drugs are initially phosphorylated by a virus-encoded pyrimidine deoxynucleoside kinase (thymidine kinase) in HSV-1-infected cells.[4] HCMV, however, does not code this enzyme, and therefore ACV is relatively inactive against this virus.[11] In contrast, GCV is active against HCMV because it is phosphorylated in infected cells by a kinase specified by HCMV gene *UL97*.[12] It is inactive or less active in HCMV strains with a mutated gene which consequently fail to phosphorylate GCV.[13,14] Once formed in infected cells, ACV and GCV monophosphates are metabolized to their triphosphates which then act as potent and selective inhibitors of the virus-encoded DNA polymerases.[15]

The success of ACV and GCV as antiviral drugs has prompted intensive efforts by several groups to prepare and evaluate many structurally related acyclic nucleoside analogs (e.g., see refs 16 and 17). As a part of our

[†] Present address: Department of Chemistry, Hunter College of the University of New York, New York, NY 10021.
[‡] Present address: Gilead Sciences, 346 Lakeside Dr., Foster City, CA 94404.
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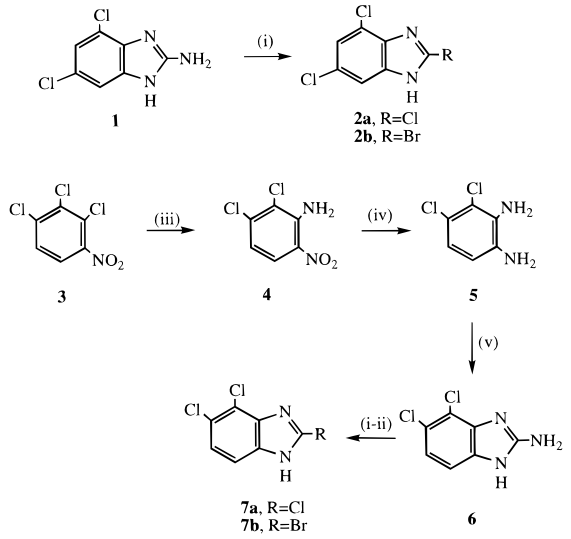
Scheme 1[a]



[a] Reagents: (i) $CuBr_2/CH_3COCH_3$; (ii) $CuCl_2/CH_3COCH_3$; (iii) $MeOH-NH_3$; (iv) Raney Ni; (v) $CNBr/MeOH/H_2O$.

search for new antiviral drugs, we have been exploring benzimidazole nucleosides as potential drugs to treat HCMV infections. In 1954, Tamm, Folkers, and coworkers first reported the synthesis and antiviral activity of halogenated benzimidazole nucleosides.[18,19] They found that 5,6-dichloro-1-β-D-ribofuranosylbenzimidazole (DRB) has multiple biological activities including activity against RNA[19] and DNA[20] viruses. DRB inhibits viral[21] and cellular[22] RNA synthesis most likely as a consequence of inhibiting cellular RNA polymerase II.[23] Thus DRB affects multiple cellular processes so that its antiviral activity is poorly separated from cytotoxicity. Consequently it has little potential as an antiviral drug.[19,24] The early studies by Tamm and coworkers prompted us to synthesize a series of 2-substituted benzimidazole ribonucleosides as potential anticancer agents.[25] More recently, we have examined the 2-chloro analog of DRB [2,5,6-trichloro-1-β-D-ribofuranosylbenzimidazole (TCRB)] for activity against HCMV based in part on its low cytotoxicity and lack of activity in anticancer tests.[26] We found that TCRB and its 2-Br analog (BDCRB) are potent and selective inhibitors of HCMV replication at noncytotoxic concentrations.[27] Both compounds act by a unique mechanism which does not involve inhibition of DNA synthesis[27,28] but does involve inhibition of DNA processing.[28] The potent and new activity of TCRB and the known efficacy of ACV and GCV prompted us to initiate a program designed to elucidate structure−activity relationships among some halogenated acyclic benzimidazole nucleosides; the results of the study are presented herein.

Results and Discussion

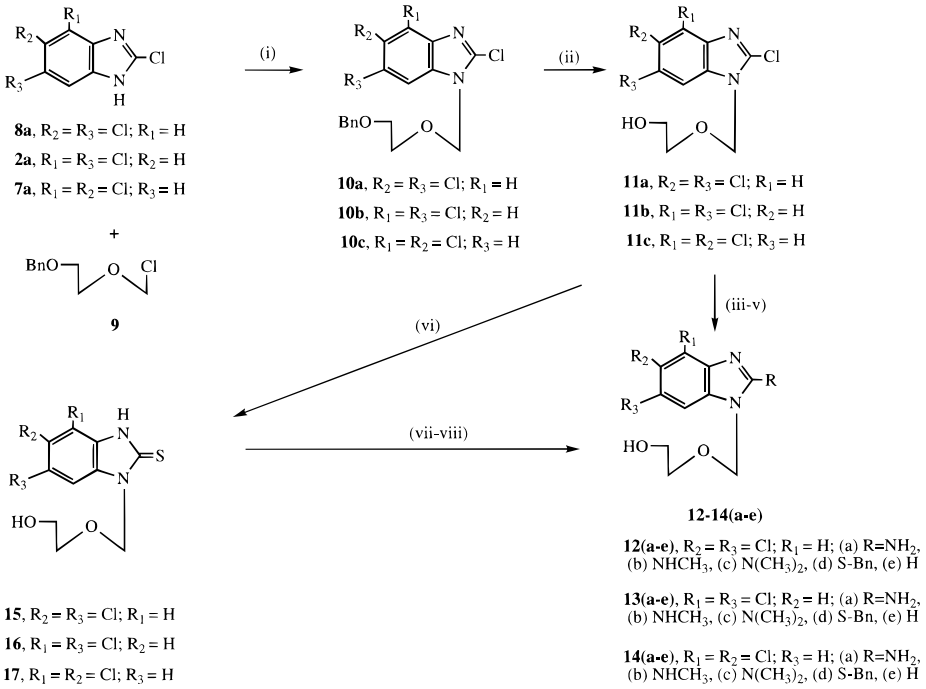
Chemistry. The requisite heterocycle 2-bromo-4,6-dichlorobenzimidazole (**2b**) (Scheme 1) was prepared[32] by a nonaqueous diazotization of 2-amino-4,6-dichlorobenzimidazole (**1**)[29] with *tert*-butyl nitrite and cupric bromide in acetone. Similarly, 2,4,5-trichlorobenzimidazole and 2-bromo-4,5-dichlorobenzimidazole (**7a**,**b**) (Scheme 1) were prepared[32] in the same fashion from 2-amino-4,5-dichlorobenzimidazole (**6**). Compound **6** was obtained, by a modified literature procedure, in three steps from commercially available 2,3,4-trichloronitrobenzene (**3**). In the present work we elected to use the sodium salt glycosylation method,[30] which has been used for the synthesis of various 2′-deoxynucleosides of several heterocycles. Sodium salts of the halogenated benzimidazoles **8a**,[31] **2a**,[32] and **7a** have been generated by treatment of the free base with sodium hydride in acetonitrile. These salts were then condensed with [2-(benzyloxy)ethoxy]methyl chloride (**9**)[33] and 1-[1,3-bis(benzyloxy)-2-propoxy]methyl chloride (**18**)[34] (Scheme 2) to give the blocked acyclic nucleosides **10a**−**c** and **19a**−**c** (Scheme 3). These compounds were deblocked with boron trichloride in methylene chloride at −78 °C using a literature procedure,[35] followed by column chromatography, to yield desired alcohol and diol derivatives in 30−40% yields. The site of alkylation of **11b**,**c**, and **20b**,**c** was confirmed to be at N-1 on the basis of difference NOE spectroscopic experiments,[36] which provided qualitative and semiquantitative information about the configurational and conformational parameters. Thus, when H-1′ of compound **11b** was irradiated, a 14.1% enhancement was observed for H-7, while a 4.6% enhancement was observed for H-5. Similar results were obtained for compounds **11c** and **20b**,**c**.

It has been previously reported[37] that a nucleophilic displacement of the 2-chloro group from 2-chlorobenzimidazole is greatly facilitated by a substituent residing at N-1. Amination of 2,5,6-trichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (**11a**) (Scheme 2) was achieved with liquid ammonia in a sealed reaction vessel at 70 °C. Amination of the compounds **11b**,**c** and **20a**−**c** was achieved under similar conditions. Compounds **11a**−**c** and **20a**−**c** were also aminated with methylamine and dimethylamine to determine if alkyl substitution on the 2-amino group would have any influence on biological activity. The compounds **12b**,**c**, **13b**,**c**, **14b**,**c**, **21b**,**c**, **22b**,**c**, and **23b**,**c** were obtained in good yields by treating the compounds **11a**−**c** and **20a**−**c** with methylamine and dimethylamine (33% in alcohol) at room temperature.

Displacement of the 2-chloro group of **11a** was also accomplished with thiourea in ethanol to furnish 5,6-dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole-2-thione (**15**). There was observed an absorption band in the infrared spectrum (potassium bromide) at 1605 cm^{-1} which was assigned as C═S stretching and part of a −N−C═S system[37,38] which indicated that **15** exists in the thione rather than the thiol form. There was an absence of a band at 2550−2600 cm^{-1} usually attributable to −SH stretching, and there was observed an absorption peak in the ^1H NMR spectrum at δ 13.16 (1 proton) which was assigned to N-3 of **15** and provided additional support for the thione form. A similar displacement reaction was accomplished with the compounds **11b**,**c** and **20a**−**c**. Alkylation of **15** with benzyl chloride in aqueous ammonia solution yielded 2-(benzylthio)-5,6-dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (**12d**) in excellent yield. A similar alkylation reaction produced compounds **13d**, **14d**, **21d**, **22d**, and **23d**. Desulfurization of **15** with Raney Ni afforded the acyclic analog of DRB, 5,6 dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (**12e**), in 48% yield. Desulfurization of **16**, **17**, **24**, and **26** under similar conditions afforded **13e**, **14e**, **21e**, and **23e** in moderate yields.

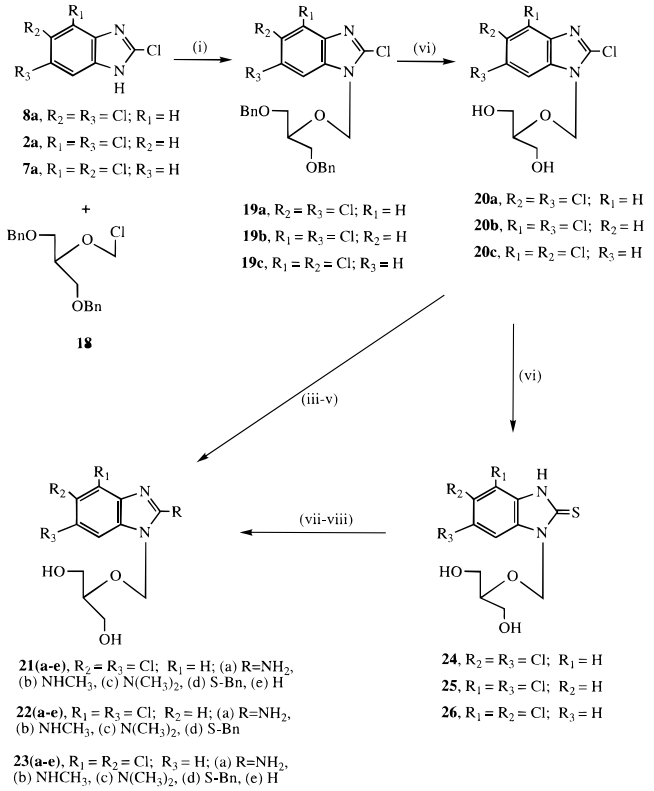
The sodium salt of **8b**[32] was condensed with (2-acetoxyethoxy)methyl bromide (**27**)[39] and (1,3-diacetoxy-

Scheme 2[a]



[a] Reagents: (i) NaH/CH_3CN; (ii) BCl_3/CH_2Cl_2; (iii) liquid NH_3; (iv) $NHCH_3$; (v) $NH(CH_3)_2$; (vi) NH_2CSNH_2; (vii) $BnCl/NH_4OH$; (viii) Raney Ni. Bn = $CH_2C_6H_5$.

Scheme 3[a]



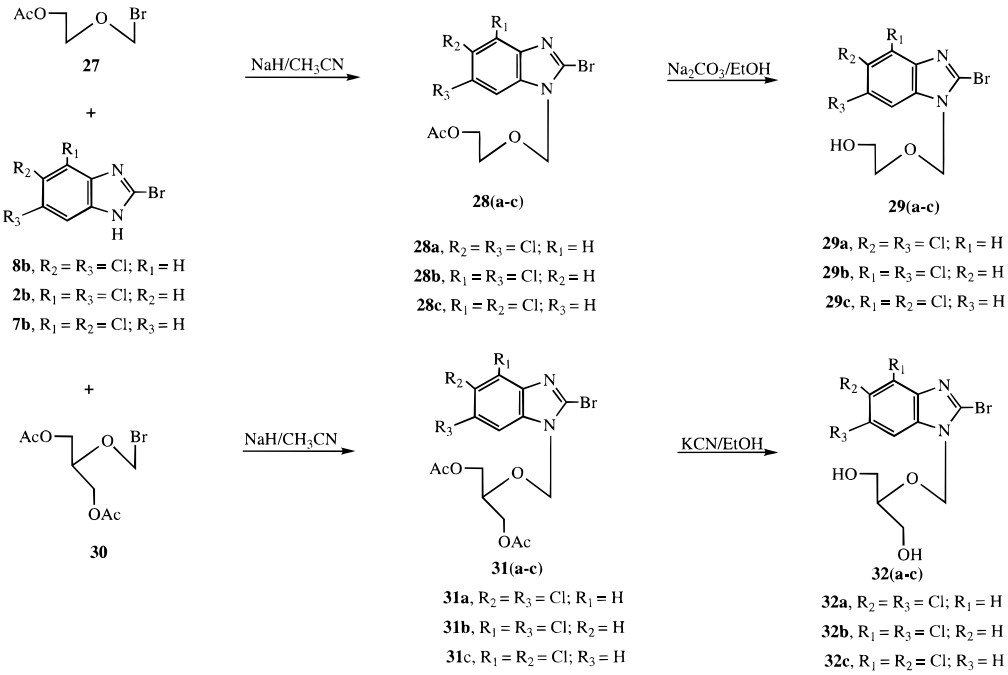
[a] Reagents: (i) NaH/CH_3CN; (ii) BCl_3/CH_2Cl_2; (iii) liquid NH_3; (iv) $NHCH_3$; (v) $NH(CH_3)_2$; (vi) NH_2CSNH_2; (vii) $BnCl/NH_4OH$; (viii) Raney Ni. Bn = $CH_2C_6H_5$.

2-propoxy)methyl bromide (**30**)[40] (Scheme 4) by using essentially the same reaction conditions as were used for the preparation of compound **10a**. These condensations were followed by silica gel column chromatography to yield 2-bromo-5,6-dichloro-1-[(2-acetoxyethoxy)methyl]benzimidazole (**28a**) and 2-bromo-5,6-dichloro-1-[(1,3-diacetoxy-2-propoxy)methyl]benzimidazole (**31a**) in 75% and 64% yields, respectively. In a similar fashion, compounds **28b**,**c** and **31b**,**c** were prepared. Treatment of compound **28a** with sodium carbonate in aqueous ethanol (90%) at room temperature afforded 2-bromo-5,6-dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (**29a**) in 62% yield. In a similar fashion, compounds **29b**,**c** were prepared and characterized. Deblocking of **31a**−**c** with potassium cyanide in aqueous ethanol (90%) at room temperature followed by column chromatography furnished **32a**−**c** in 40−50% yields.

Biology. Unlike the benzimidazole ribonucleosides which are potent and selective inhibitors of HCMV,[27] the acyclic analogs were either inactive or weakly active against HCMV and HSV-1. The analogs also were not cytotoxic or were weakly cytotoxic in both stationary or growing cells. Of the (hydroxyethoxy)methyl derivatives (Table 1), only the 2-thiobenzyl analogs **12d**, **13d**, and **14d** showed any activity against HCMV. This activity, however, was poorly separated from cytotoxicity and may not represent specific antiviral activity. We observed similar weak activity which was not well separated from cytotoxicity in a series of ribosyl 2-thiobenzyl benzimidazoles.[41] All of the other compounds in the series were inactive and noncytotoxic including the direct analogs (**11a** and **29a**) of the very active ribosides TCRB and BDCRB.

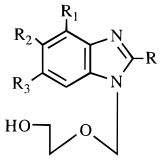
Likewise, compounds in the (dihydroxypropoxy)methyl series (Table 2) were inactive except for the thiobenzyl analog **23d** which had weak activity against HCMV in the plaque reduction assay and the BDCRB analogs **32a**,**b** which were weakly active in the yield reduction assay. In the case of **23d**, the activity was, at best, poorly separated from cytotoxicity. In contrast, the activity of **32a**,**b** in yield reduction assays appeared to be separated from cytotoxicity. Together with the fact that the 2-Br analog is the most active compound in the ribosyl series,[27] this result suggests that the weak activity of **32a**,**b** may be from an interaction with the

Scheme 4[a]



[a] Ac = acetyl.

Table 1. Antiviral Activity and Cytotoxicity of Dichloro 2-Substituted 1-[(Hydroxyethoxy)methyl]benzimidazoles



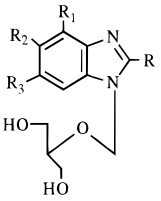
					50% or 90% inhibitory concentration (μM)				
					antiviral activity				
					HCVM[a]		HSV-1[b]	cytotoxicity[c]	
no.	R_1	R_2	R_3	R	plaque	yield	ELISA	visual	growth
11a	H	Cl	Cl	Cl	>320[d]		>100	>320	>320
11b	Cl	H	Cl	Cl	>100			>100	
11c	Cl	Cl	H	Cl	>100		>100	>100	>100
12a	H	Cl	Cl	NH_2	>100		>100	>100	>100
12b	H	Cl	Cl	$NHCH_3$	>100		>100	>100	>100
12c	H	Cl	Cl	$N(CH_3)_2$	>100		>100	>100	>100
12d	H	Cl	Cl	$SCH_2C_6H_5$	40		45	32	55
12e	H	Cl	Cl	H	>100		>100	>100	>100
13a	Cl	H	Cl	NH_2	>100			100	>100
13b	Cl	H	Cl	$NHCH_3$	>100		>100	>100	>100
13c	Cl	H	Cl	$N(CH_3)_2$	>100			>100	
13d	Cl	H	Cl	$SCH_2C_6H_5$	50		>100	32	>100
13e	Cl	H	Cl	H	>100		>100	>100	>100
14a	Cl	Cl	H	NH_2	>100		>100	>100	>100
14b	Cl	Cl	H	$NHCH_3$	>100		>100	>100	>100
14d	Cl	Cl	H	$SCH_2C_6H_5$	30		>100	32	35
14e	Cl	Cl	H	H	>100		>100	>100	>100
15	H	Cl	Cl	SH	>100		>100	100	>100
16	Cl	H	Cl	SH	>100		>100	>100	>100
17	Cl	Cl	H	SH	>100		>100	>100	>100
29a	H	Cl	Cl	Br	>100		>100	>100	>100
29b	Cl	H	Cl	Br	>100		>100	>100	>100
29c	Cl	Cl	H	Br	>100		>100	>100	>100
TCRB[e]	H	Cl	Cl	Cl	2.9	1.4	102	238	210
BDCRB[e]	H	Cl	Cl	Br	0.7	0.2	130	118	>100

[a] Plaque and yield reduction assays were performed in duplicate as described in the text. Results from plaque assays are reported as IC_{50}'s, those for yield reduction experiments as IC_{90}'s. [b] All compounds were assayed by ELISA in quadruplicate wells. [c] Visual cytotoxicity was scored on HFF cells at time of HCMV plaque enumeration. Inhibition of KB cell growth was determined as described in the text in quadruplicate assays. Results are presented as IC_{50}'s. [d] A greater than sign (>) indicates IC_{50} or IC_{90} was not reached at the noted (highest) concentration tested. [e] Data also reported in ref 27; average derived from three to six experiments.

viral target of the ribosylbenzimidazoles. The alternative hypothesis that the weak activity of **32a**,**b** was a consequence of phosphorylation by the *UL97* gene product (and subsequent inhibition of HCMV DNA polymerase) is less attractive because the ribosylbenzimidazoles do not inhibit DNA synthesis.[27] Furthermore, all of the compounds in Table 2 might be considered analogs of GCV but almost all were inactive.

This interpretation also is consistent with the lack of activity against HSV-1 of the compounds in Table 1. Because these compounds could be considered analogs of ACV, phosphorylation by HSV-1 deoxypyrimidine

Table 2. Antiviral Activity and Cytotoxicity of Dichloro 2-Substituted 1-[(Dihydroxypropoxy)methyl]benzimidazoles



					50% or 90% inhibitory concentration (μM)				
					antiviral activity				
					HCVM[a]		HSV-1[b]	cytotoxicity[c]	
no.	R_1	R_2	R_3	R	plaque	yield	ELISA	visual	growth
20a	H	Cl	Cl	Cl	>100[d]		>100	>100	>100
20b	Cl	H	Cl	Cl	>100			>100	
20b	Cl	Cl	H	Cl	>100		100	>100	>100
21a	H	Cl	Cl	NH_2	>100		>100	>100	>100
21b	H	Cl	Cl	$NHCH_3$	>100		>100	>100	>100
21c	H	Cl	Cl	$N(CH_3)_2$	>100		>100	>100	>100
21d	H	Cl	Cl	$SCH_2C_6H_5$	>100		>100	>100	>100
21e	H	Cl	Cl	H	>100		>100	>100	>100
22a	Cl	H	Cl	NH_2	>100			100	
22b	Cl	H	Cl	$NHCH_3$	>100			100	
22c	Cl	H	Cl	$N(CH_3)_2$	>100		>100	>100	>100
23a	Cl	Cl	H	NH_2	>100		>100	>100	>100
23b	Cl	Cl	H	$NHCH_3$	>100		>100	>100	>100
23c	Cl	Cl	H	$N(CH_3)_2$	>100		>100	>100	>100
23d	Cl	Cl	H	$SCH_2C_6H_5$	35		55	32	60
23e	Cl	Cl	H	H	>100		>100	>100	>100
24	H	Cl	Cl	SH	>100		55	>100	>100
25	Cl	H	Cl	SH	>100		>100	>100	>100
26	Cl	Cl	H	SH	>100		>100	>100	>100
32a	H	Cl	Cl	Br	>100	25	100	>100	>100
32b	Cl	H	Cl	Br	136	50		161	>100
32c	Cl	Cl	H	Br	>100		>100	>100	>100
ganciclovir[e]					7.4 ± 6.5	1.6 ± 1.2	3.5 ± 2.1	>100	>100

[a] See Table 1 for footnotes a−d. [e] Average ± standard deviation from 108, 33, and 3 experiments, respectively, in which ganciclovir was used as a positive control.

kinase in infected cells would lead to activity against the virus—which was not observed. Thus, the weak or lack of antiviral activity against either herpes virus argues that these compounds are not phosphorylated by the *UL97* gene product in HCMV-infected cells nor by a deoxypyrimidine kinase in HSV-1-infected cells. Alternatively, if the corresponding nucleotide analogs are formed in virus-infected cells, they are not active and do not interfere with viral replication. This possibility, however, does not seem likely on an *a priori* basis.

Experimental Section

General Procedures. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H NMR) spectra were determined at 270 MHz with an IBM WP 270-SY spectrometer, at 300 MHz with an IBM AM-300 spectrometer, or at 360 MHz with an IBM WM-360 spectrometer. The chemical shift values are expressed in δ values (part per million) relative to the standard chemical shift of TMS. Ultraviolet spectra were recorded on a Hewlett-Packard 8450 A spectrophotometer. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Thin-layer chromatography (TLC) was performed on silica gel GHLF-254 plates (Merck Reagents). E. Merck silica gel (230−400 mesh) was used for flash column chromatography. Detection of components on TLC was made by UV light (254 nm). Evaporations were carried out under reduced pressure (water aspiration) with the bath temperature below 50 °C unless specified otherwise.

2-Bromo-4,6-dichlorobenzimidazole (2b). A mixture of acetone (112 mL), *tert*-butyl nitrite (4.0 mL), and $CuBr_2$ (12.7 g, 56.85 mmol) was stirred at room temperature for 15 min. **1**[29] (5.98 g, 29.6 mmol) was added slowly to the above solution, and the reaction mixture was stirred at 60 °C for 0.5 h. An additional quantity of *t*-BuNO (2 × 4.0 mL) was added every 0.5 h, and the mixture was stirred at 60 °C for an additional 2 h. The reaction mixture was cooled to room temperature, concentrated to 30 mL, and poured into a mixture of EtOAc/2 N HBr (48% aqueous) (35/20). The EtOAc layer was washed with 2 N HBr (200 mL). During this process, a yellow solid appeared in the organic layer, and it was collected by filtration and discarded. The filtrate was washed with $NaHCO_3$ (aqueous) (2 × 100 mL) and NaCl (aqueous) (2 × 100 mL), dried (Na_2SO_4), and then evaporated to dryness. The resulting solid was purified by flash column chromatography (2 × 24 cm) (230−400 mesh). Elution of the column with hexane:EtOAc (9:1, v/v) and evaporation of the appropriate fractions gave 3.02 g (38%) of **2b**: mp 212 °C (MeOH−H_2O); ^{1}H NMR (DMSO-d_6) δ 13.80 (bs, 1 H, exchanges with D_2O, NH), 7.56 (bs, 1 H, H-7), 7.39 (d, 1 H, J = 1.5 Hz, H-5). Anal. ($C_7H_3N_2Cl_2Br$) C, H, N.

2-Amino-3,4-dichloro-1-nitrobenzene (4). A mixture of 1-nitro-2,3,4-trichlorobenzene. (**3**) (10.0 g, 44.15 mmol) (Aldrich) and MeOH−NH_3 (120 mL) was heated in a steel reaction vessel at 120 °C for 24 h. The reaction mixture was cooled to 0 °C, and the solid which had separated was collected by filtration. The solid was crystallized from MeOH. The filtrate was evaporated to dryness, extracted with EtOAc (200 mL), washed with water (200 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue thus obtained was recrystallized from MeOH to give 7.31 g (80%) of **4**: mp 161−163 °C; ^{1}H NMR (DMSO-d_6) δ 8.00 (d, 1 H, J = 9.5 Hz, H-6), 7.53 (bs, 2 H, exchanges with D_2O, NH_2), 6.88 (d, 1 H, J = 9.5 Hz, H-5). Anal. ($C_6H_4N_2Cl_2O_2$) C, H, N.

1,2-Diamino-3,4-dichlorobenzene (5). A mixture of **4** (1.41 g, 6.8 mmol), EtOH (100 mL), and Raney Ni (0.90 g, wet) was hydrogenated at 40 psi at room temperature for 10 h. The reaction mixture was filtered through a Celite pad and washed with EtOH (50 mL). The filtrate and washings were combined, evaporated, and coevaporated with EtOH gave 0.94 g (78%) of **5**: mp 81−83 °C; ^{1}H NMR (DMSO-d_6) δ 6.58 and 6.55 (dd, 2 H, J = 7.2 Hz, H-6, H-5), 4.95 and 4.93 (bs, 4 H, exchanges with D_2O, 2 × NH_2). Anal. ($C_6H_6N_2Cl_2$) C, H, N.

2-Amino-4,5-dichlorobenzimidazole (6). A 5 M solution of BrCN/CH_3CN (1.0 mL) was added to H_2O (10 mL). Com-

pound **5** (0.94 g, 5.3 mmol) in MeOH (10 mL) was then slowly added, and the reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was concentrated (10 mL) under reduced pressure. The product was partitioned between EtOAc and H_2O (10/5), and the EtOAc layer was discarded. The pH of the aqueous layer was adjusted to pH 8 with a saturated aqueous solution of $NaHCO_3$, and the resulting suspension was extracted with EtOAc (100 mL), washed with H_2O (50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting solid was purified by a flash chromatography column (SiO_2, 2 × 24 cm) prepared with wet $CHCl_3$. Elution of the column with $CHCl_3$:MeOH (85:15, v/v) and evaporation of the appropriate fractions gave 0.98 g (92%) of **6**: mp 239−240 °C; ^{1}H NMR (DMSO-d_6) δ 11.05 (bs, 1 H, exchanges with D_2O, NH), 7.04−6.97 (m, 2 H, H-7, H-6), 6.62 (bs, 2 H, exchanges with D_2O, NH_2). Anal. ($C_7H_5N_3Cl_2$) C, H, N.

2,4,5-Trichlorobenzimidazole (7a). A mixture of acetone (15 mL), *tert*-butyl nitrite (0.8 mL), and $CuCl_2$ (1.07 g, 7.9 mmol) was stirred at room temperature for 15 min. Compound **6** (0.8 g, 3.9 mmol) was added slowly to the above solution, and the reaction mixture was stirred at 60 °C for 0.5 h. Fresh *t*-BuNO (2 × 0.8 mL) was added every 0.5 h, and the stirring was continued for an additional 2 h. The reaction mixture was cooled to room temperature, concentrated to 8 mL, and poured into a mixture of EtOAc/2N HCl (15/10). The EtOAc layer was washed with 2 N HCl (100 mL). During this process, the yellow solid which separated was collected by filtration and discarded. The filtrate was washed with $NaHCO_3$ (100 mL) and NaCl (100 mL), dried (Na_2SO_4), and then evaporated to dryness. The resulting solid was purified by flash column chromatography (2 × 20 cm) (230−400 mesh), and elution of the column with hexane:EtOAc (9:1, v/v) and evaporation of the appropriate fractions gave 0.29 g (33%) of **7a**: mp 252 °C (MeOH−H_2O); ^{1}H NMR (DMSO-d_6) δ 13.80 (bs, 1 H, exchanges with D_2O, NH), 7.48 (d, 1 H, J = 8.6 Hz, H-7), 7.42 (d, 1 H, J = 8.6 Hz, H-6). Anal. ($C_7H_3N_2Cl_3$) C, H, N.

2-Bromo-4,5-dichlorobenzimidazole (7b). Compound **7b** (3.73 g, 47%) was prepared from **6** (5.98 g, 29.6 mmol) using $CuBr_2$ (12.7 g, 56.85 mmol), acetone (112 mL), and *t*-BuNO (3 × 4.0 mL) by the method described for **7a**. **7b**: mp 225 °C (MeOH−H_2O); ^{1}H NMR (DMSO-d_6) δ 13.80 (bs, 1 H, exchanges with D_2O, NH), 7.48 (d, 1 H, J = 8.6 Hz, H-7), 7.42 (d, 1 H, J = 8.6 Hz, H-6). Anal. ($C_7H_3N_2Cl_2Br$) C, H, N.

2,5,6-Trichloro-1-[[2-(benzyloxy)ethoxy]methyl]benzimidazole (10a). NaH (0.32 g, 8.0 mmol, 60% oil disperson) was added to a stirred suspension of 2,5,6-trichlorobenzimidazole[31] (**8a**) (1.5 g, 6.7 mmol) in dry CH_3CN (150 mL) under a N_2 atmosphere. The solution was stirred until H_2 evolution had ceased and a clear solution was obtained (20 min). [2-(Benzyloxy)ethoxy]methyl chloride[33] (**9**) (2.03 g, 10.66 mmol) in CH_3CN (20 mL) was then added dropwise. The reaction mixture was stirred for an additional 20 h. The resulting mixture was concentrated under reduced pressure, diluted with H_2O (100 mL), extracted with EtOAc (250 mL), washed with H_2O (100 mL), and dried (anhydrous Na_2SO_4), and the solvent was removed under reduced pressure to yield the oil **10a** (3.2 g). This oil was used as such without further purification.

2,5,6-Trichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (11a). To a solution of **10a** (4.10 g, 11.0 mmol) in dry CH_2Cl_2 (70 mL) at −78 °C under a N_2 atmosphere was added BCl_3 (5 M solution in CH_2Cl_2, 30 mL) dropwise while maintaining the bath temperature at −78 °C. The reaction mixture was stirred for an additional 4 h, MeOH (25 mL) was added at 0 °C, and the cold solution was immediately neutralized (pH 7) with NH_4OH. The solution was allowed to warm up to room temperature and then concentrated at 40 °C to yield an oil. The mixture was diluted with H_2O (100 mL), extracted with EtOAc (250 mL), washed with H_2O (100 mL), dried (anhydrous Na_2SO_4), and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (2 × 20 cm) (230−400 mesh), prepared with wet SiO_2 in $CHCl_3$. Elution of the column with $CHCl_3$:MeOH (95:5, v/v) and evaporation of the appropriate fractions gave a solid which was recrystallized from EtOAc to afford 1.0 g (51%) of **11a**: mp 144−146 °C; ^{1}H NMR (DMSO-d_6) δ 8.12 and 7.95 (2 s, 2 H, H-7, H-4), 5.68 (s, 2 H, H-1′). Anal. ($C_{10}H_9N_2Cl_3O_2$) C, H, N.

2-Amino-5,6-dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (12a). A mixture of **11a** (0.09 g, 0.3 mmol) and liquid ammonia (condensed at −70 °C, 20 mL) was heated at 70 °C for 12 h in a sealed steel reaction vessel. The resulting mixture was cooled to 0 °C, and the NH_3 was removed. The resulting mixture was redissolved in hot MeOH (20 mL) and concentrated *in vacuo* (5 mL), SiO_2 (2 g) was added, and the solvent was removed under reduced pressure. The SiO_2 gel powder was placed on the top of a SiO_2 column (2 × 14 cm) prepared with wet SiO_2 in $CHCl_3$. Elution of the column with $CHCl_3$:MeOH (8:2, v/v) and evaporation of the appropriate fractions gave 0.065 g (70%) of **12a**: mp 206−208 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 7.50 and 7.29 (2 s, 2 H, H-7, H-4), 6.89 (s, 2 H, exchanges with D_2O, NH_2), 5.44 (s, 2 H, H-1′). Anal. ($C_{10}H_{11}N_3Cl_2O_2$) C, H, N.

5,6-Dichloro-2-(methylamino)-1-[(2-hydroxyethoxy)methyl]benzimidazole (12b). A mixture of **11a** (0.09 g, 0.3 mmol) and NH_2CH_3 (33% solution in absolute ethanol, 10 mL) was stirred at room temperature for 6 h or until the reaction was complete as monitored by TLC. The excess EtOH and NH_2CH_3 was removed under reduced pressure; the mixture was coevaporated with EtOH (20 mL) and crystallized from MeOH−H_2O to give 0.068 g (77%) of **12b**: mp 146−148 °C; ^{1}H NMR (DMSO-d_6) δ 7.54 and 7.37 (2 s, 2 H, H-7, H-4), 7.06 (q, 1 H, exchanges with D_2O, NH), 5.41 (s, 2 H, H-1′). Anal. ($C_{11}H_{13}N_3Cl_2O_2 \cdot 0.5H_20$) C, H, N.

2-(Dimethylamino)-5,6-dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (12c). Compound **12c** (0.08 g, 84%) was prepared from **11a** (0.09 g, 0.3 mmol) using $NH(CH_3)_2$ (33% solution in absolute ethanol, 12 mL) by the method described for the preparation of **12b**. **12c**: mp 89−90 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 7.71 and 7.51 (2 s, 2 H, unsymmetrical H-7, H-4), 5.43 (s, 2 H, H-1′), 4.74 (t, 1 H, exchanges with D_2O, OH), 3.51−3.50 (m, 4 H, H-3′, H-4′), 3.04 (s, 6 H, $N(CH_3)_2$). Anal. ($C_{12}H_{15}N_3Cl_2O_2$) C, H, N.

5,6-Dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole-2-thione (15). A mixture of **11a** (0.5 g, 1.7 mmol), EtOH (80 mL), and thiourea (0.26 g, 3.3 mmol) was heated at reflux for 12 h or until the reaction was complete as monitored on TLC. The excess EtOH was removed under reduced pressure, and trituration of the resulting solid with ice cold water gave a crystalline solid. This solid was collected by filtration, dried, and recrystallized from MeOH−H_2O to yield 0.46 g (93%) of **15**: mp 174−176 °C; ^{1}H NMR (DMSO-d_6) δ 13.16 (bs, 1 H, exchanges with D_2O, NH), 7.70 and 7.37 (2 s, 2 H, H-7, H-4), 5.67 (s, 2 H, H-1′). Anal. ($C_{10}H_{10}N_2Cl_2O_2S$) C, H, N.

2-(Benzylthio)-5,6-dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (12d). Compound **15** (0.09 g, 0.3 mmol) was dissolved in a mixture of CH_3CN:H_2O (1:1) containing NH_4OH (aqueous, 0.01 mL). Benzyl chloride (0.08 mL) was added to the above solution, and stirring was continued for an additional 12 h. The resulting mixture was concentrated to remove CH_3CN. The white solid which had separated from the solution was collected by filtration, washed with H_2O (10 mL), and recrystallized from MeOH−H_2O to give 0.09 g (75%) of **12d**: mp 103−105 °C; ^{1}H NMR (DMSO-d_6) δ 7.96 and 7.88 (2 s, 2 H, H-7, H-4), 7.46−7.34 (m, 2 H, C_6H_5), 7.31−7.23 (m, 3 H, C_6H_5), 5.53 (s, 2 H, H-1′). Anal. ($C_{17}H_{16}N_2Cl_2O_2S$) C, H, N.

5,6-Dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (12e). Raney Ni (0.3 g, wet) was added to a solution of compound **15** (0.12 g, 0.4 mmol) in EtOH (30 mL). The reaction mixture was heated at reflux temperature for 3 days, at which time TLC showed no starting material. The reaction mixture was filtered through a Celite pad and washed with ETtOH (20 mL), the filtrate and washings were combined, and the solvent was removed *in vacuo*. The resulting solid was redissolved in MeOH (10 mL), SiO_2 (2 g) was added, and the solvent was removed under reduced pressure. The SiO_2 gel powder was placed on the top of a SiO_2 column (2 × 14 cm), prepared with wet SiO_2 in $CHCl_3$. Elution of the column with $CHCl_3$:MeOH (9:1, v/v) gave 0.05 g (58%) of **12e**: mp 119−121 °C (hexane−EtOAc); ^{1}H NMR (DMSO-d_6) δ 8.49 (s, 1 H,

C-2), 8.03 and 7.97 (2 s, 2 H, H-7, H-4), 5.68 (s, 2 H, H-1′). Anal. ($C_{10}H_{10}N_2Cl_2O_2$) C, H, N.

2,4,6-Trichloro-1-[[2-(benzyloxy)ethoxy]methyl]benzimidazole (10b). Compound **10b** was prepared from **2a**[32] (1.5 g, 6.7 mmol) using NaH (0.32 g, 8.0 mmol, 60% oil dispersion), CH_3CN (120 mL), and **9** (1.6 g, 8.1 mmol) in CH_3CN (20 mL) by the method described for **10a**. This oil (product) (4.24 g) was used as such without further purification.

2,4,6-Trichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (11b). Compound **11b** was prepared from **10b** (4.24 g, 11.0 mmol), BCl_3 (5 M solution in CH_2Cl_2, 30 mL), CH_2Cl_2 (70 mL), and MeOH (25 mL) by the method described for **11a** to give 1.0 g (50%) of **11b**: mp 100−101 °C (EtOAc); ^{1}H NMR (DMSO-d_6) δ 7.92 (d, 1 H, J = 1.6 Hz, H-7), 7.52 (d, 1 H, J = 1.2 Hz, H-5), 5.69 (s, 2 H, H-1′). Anal. ($C_{10}H_9N_2Cl_3O_2$) C, H, N.

2-Amino-4,6-dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (13a). Compound **13a** (0.069 g, 92%) was prepared from **11b** (0.08 g, 0.27 mmol) and liquid ammonia (10 mL) by the method described for **12a**. **13a**: mp 218 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 7.34 (d, 1 H, J = 1.85 Hz, H-7), 7.09 (d, 1 H, J = 1.82 Hz, H-5), 7.00 (bs, 2 H, exchanges with D_2O, NH_2), 5.44 (s, 2 H, H-1′). Anal. ($C_{10}H_{11}N_3Cl_2O_2$) C, H, N.

4,6-Dichloro-2-(methylamino)-1-[(2-hydroxyethoxy)methyl]benzimidazole (13b). Treatment of **11b** (0.08 g, 0.27 mmol) with NH_2CH_3 (33% solution in absolute ethanol, 10 mL) by the method described for **12b** gave 0.064 g (83%) of **13b**: mp 168 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 7.37 (d, 1 H, J = 1.7 Hz, H-7), 7.12 (d, 1 H, exchanges with D_2O, NH), 7.09 (d, 1 H, J = 1.7 Hz, H-5), 5.44 (s, 2 H, H-1′). Anal. ($C_{11}H_{13}N_3Cl_2O_2$) C, H, N.

4,6-Dichloro-2-(dimethylamino)-1-[(2-hydroxyethoxy)methyl]benzimidazole (13c). Compound **13c** (0.069 g, 85%) was prepared from **11b** (0.08 g, 0.27 mmol) and $NH(CH_3)_2$ (33% solution in absolute ethanol, 10 mL) by the method described for **12b**. **13c**: mp 141−143 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 7.53 (d, 1 H, J = 1.7 Hz, H-7), 7.20 (d, 1 H, H-5), 5.43 (s, 2 H, H-1′). Anal. ($C_{12}H_{15}N_3Cl_2O_2$) C, H, N.

4,6-Dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole-2-thione (16). Compound **16** (0.41 g, 79%) was prepared from **11b** (0.53 g, 1.8 mmol), EtOH (80 mL), and thiourea (0.26 g, 3.3 mmol) by the method described for **15**. **16**: mp 181−182 °C; ^{1}H NMR (DMSO-d_6) δ 13.60 (bs, 1 H, NH), 7.50 (d, 1 H, J = 1.42 Hz, H-7), 7.41 (d, 1 H, J = 1.37 Hz, H-5), 5.68 (s, 2 H, H-1′). Anal. ($C_{10}H_{10}N_2Cl_2O_2S$) C, H, N.

2-(Benzylthio)-4,6-dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (13d). Compound **13d** (0.09 g, 80%) was prepared from **16** (0.09 g, 0.3 mmol), CH_3CN:H_2O (1:1), NH_4OH (aqueous, 0.01 mL), and benzyl chloride (0.08 mL) by the method described for **12d**. **13d**: mp 84−85 °C; ^{1}H NMR (DMSO-d_6) δ 7.76 (d, 1 H, J = 1.8 Hz, H-7), 7.50−7.47 (m, 2 H, C_6H_5), 7.40 (d, 1 H, J = 1.7 Hz, H-5), 7.33−7.23 (m, 3 H, C_6H_5), 5.50 (s, 2 H, H-1′). Anal. ($C_{17}H_{16}N_2Cl_2O_2S$), C, H, N.

4,6-Dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (13e). Compound **13e** (0.04 g, 49%) was prepared from **16** (0.09 g, 0.3 mmol), Raney Ni (0.2 g, wet), and EtOH (25 mL) by the method described for **12e**. **13e**: mp 112−113 °C (hexane−EtOAc); ^{1}H NMR (DMSO-d_6) δ 8.51 (s, 2 H, H-2), 7.82 (d, 1 H, J = 1.8 Hz, H-7), 7.45 (d, 1 H, J = 1.8 Hz, H-5), 5.69 (s, 2 H, H-1′). Anal. ($C_{10}H_{10}N_2Cl_2O_2$) C, H, N.

2,4,5-Trichloro-1-[[2-(benzyloxy)ethoxy]methyl]benzimidazole (10c). Compound **10c** was prepared from **7a** (1.5 g, 6.7 mmol) using NaH (0.35 g, 8.8 mmol, 60% oil dispersion), CH_3CN (120 mL), and **9** (1.6 g, 8.1 mmol) in CH_3CN (20 mL) by the method described for **10a**. Compound **10c** (4.10 g) was used as such without further purification.

2,4,5-Trichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (11c). Compound **11c** was prepared from **10c** (4.10 g, 11.0 mmol), BCl_3 (5 M solution in CH_2Cl_2, 30 mL), CH_2Cl_2 (50 mL), and MeOH (25 mL) by the method described for **11a** to give 0.90 g (45%) of **11c**: mp 82−85 °C; ^{1}H NMR (DMSO-d_6) δ 7.74 (d, 1 H, J = 8.65 Hz, H-7), 7.57 (d, 1 H, J = 8.65 Hz, H-6), 5.70 (s, 2 H, H-1′). Anal. ($C_{10}H_9N_2Cl_3O_2$) C, H, N.

2-Amino-4,5-dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (14a). Compound **14a** (0.081 g, 87%) was prepared from **11c** (0.1 g, 0.3 mmol) and liquid NH_3 (10 mL) by the method described for **12a**. **14a**: mp 220−221 °C (MeOH−H_2O); ^{1}H NMR (DMSO-d_6) δ 7.21 (d, 1 H, J = 8.4 Hz, H-7), 7.07 (d, 3 H, J = 10.8 Hz, exchanges with D_2O, NH_2, H-6), 5.44 (s, 2 H, H-1′). Anal. ($C_{10}H_{11}N_3Cl_2O_2$) C, H, N.

4,5-Dichloro-2-(methylamino)-1-[(2-hydroxyethoxy)methyl]benzimidazole (14b). Compound **14b** (0.047 g, 81%) was prepared from **11c** (0.06 g, 0.2 mmol) and NH_2CH_3 (33% solution in absolute ethanol, 6 mL) by the method described for **12b**. **14b**: mp 199−200 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 7.23 (d, 1 H, J = 8.39 Hz, C-7), 7.09 (m, 2 H, exchanges with D_2O, NH, H-6), 5.42 (s, 2 H, H-1′), 2.93 (d, 3 H, J = 4.8 Hz, $NHCH_3$). Anal. ($C_{11}H_{13}N_3Cl_2O_2$) C, H, N.

4,5-Dichloro-2-(dimethylamino)-1-[(2-hydroxyethoxy)methyl]benzimidazole (14c). Compound **14c** (0.056 g, 78%) was prepared from **11c** (0.07 g, 0.23 mmol) and $NH(CH_3)_2$ (33% solution in absolute ethanol, 6 mL) by the method described for **12b**. **14c**: mp 88−90 °C; ^{1}H NMR (DMSO-d_6) δ 7.39 (d, 1 H, J = 8.46 Hz, H-7), 7.22 (d, 1 H, J = 8.46 Hz, H-6), 5.45 (s, 2 H, H-1′), 3.0 (s, 6 H, $N(CH_3)_2$). Anal. ($C_{12}H_{15}N_3Cl_2O$) C, H, N.

4,5-Dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole-2-thione (17). Compound **17** (0.48 g, 96%) was prepared from **11c** (0.50 g, 1.7 mmol), EtOH (80 mL), and thiourea (0.26 g, 3.3 mmol) by the method described for **15**. **17**: mp 162−164 °C; ^{1}H NMR (DMSO-d_6) δ 13.50 (bs, 1 H, exchanges with D_2O, NH), 7.43 (d, 1 H, J = 8.5 Hz, H-7), 7.37 (d, 1 H, J = 8.59 Hz, H-6), 5.69 (s, 2 H, H-1′). Anal. ($C_{10}H_{10}N_2Cl_2O_2S$) C, H, N.

2-(Benzylthio)-4,5-dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (14d). Compound **14d** was prepared from **17** (0.09 g, 0.3 mmol), CH_3CN:H_2O (1:1), NH_4OH (aqueous, 0.01 mL), and benzyl chloride (0.09 mL) by the method described for **12d** to give 0.09 g (80%) of **14d**: mp 109−111 °C; ^{1}H NMR (DMSO-d_6) δ 7.59 (d, 1 H, J = 8.43 Hz, H-7), 7.49 (d, 2 H, C_6H_5), 7.43 (d, 1 H, J = 8.3 Hz, H-6), 7.29−7.23 (m, 3 H, C_6H_5), 5.54 (s, 2 H, H-1′). Anal. ($C_{17}H_{16}N_2Cl_2O_2S$) C, H, N.

4,5-Dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (14e). Compound **14e** was prepared from **17** (0.14 g, 0.48 mmol), Raney Ni (0.2 g, wet), and EtOH (30 mL) by the method described for **12e** to give 0.053 g (43%) of **14e**: mp 116−117 °C (hexane−EtOAc); ^{1}H NMR (DMSO-d_6) δ 8.53 (s, 1 H, H-2), 7.69 (d, 1 H, J = 8.6 Hz, H-7), 7.50 (d, 1 H, J = 8.6 Hz, H-6), 5.70 (s, 2 H, H-1′). Anal. ($C_{10}H_{10}N_2Cl_2O_2$) C, H, N.

2,5,6-Trichloro-1-[[1,3-bis(benzyloxy)-2-propoxy]methyl]benzimidazole (19a). Compound **19a** was prepared from **8a** (1.0 g, 4.5 mmol), CH_3CN (200 mL), NaH (0.21 g, 5.2 mmol, 60% oil dispersion), and [1,3-bis(benzyloxy)-2-propoxy]methyl chloride (**18**)[34] (2.2 g, 6.7 mmol) in CH_3CN (25 mL) by the method described for **10a**. The resulting oil was purified by flash column chromatography (2 × 28 cm) 230−400 mesh), prepared with wet SiO_2 in hexane. Elution with hexane:EtOAc (8:2, v/v) and evaporation of the appropriate fractions gave **19a** (2.77 g) as an oil. Although the ^{1}H NMR spectra revealed a small amount of an impurity (**18**), it was used without further purification for the next step.

2,5,6-Trichloro-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (20a). Compound **20a** (0.62 g, 41%) was prepared from **19a** (2.36 g, 4.6 mmol), BCl_3 (5 M solution in CH_2Cl_2, 21 mL), CH_2Cl_2 (50 mL), and MeOH (20 mL) by the method described for **11a**. **20a**: mp 142−144 °C (EtOAc); ^{1}H NMR (DMSO-d_6) δ 8.05 and 7.93 (2 s, 2 H, H-7, H-4), 5.74 (s, 2 H, H-1′). Anal. ($C_{11}H_{11}N_2Cl_3O_3$) C, H, N.

2-Amino-5,6-dichloro-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (21a). Compound **21a** was prepared from **20a** (0.1 g, 0.3 mmol) and liquid NH_3 (10 mL) by the method described for **12a** to give 0.069 g (74%) of **21a**: mp 159−161 °C (MeOH−H_2O); ^{1}H NMR (DMSO-d_6) δ 7.49 and 7.29 (2 s, 2 H, H-7, C-4), 6.83 (s, 2 H, exchanges with D_2O, NH_2), 5.49 (s, 2 H, H-1′). Anal. ($C_{11}H_{13}N_3Cl_2O_3$) C, H, N.

5,6-Dichloro-2-(methylamino)-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (21b). Compound **21b** was prepared from **20a** (0.1 g, 0.3 mmol) and NH_2CH_3 (33% solution in absolute ethanol, 10 mL) by the method described for **12b** to give 0.087 g (85%) of **21b**: mp 185−186 °C (MeOH−

H_2O); ^1H NMR (DMSO-d_6) δ 7.51 and 7.36 (2 s, 2 H, H-7, H-4), 6.97 (d, 1 H, exchanges with D_2O, NH), 5.48 (s, 2 H, H-1′), 2.89 (d, 3 H, $NHCH_3$). Anal. ($C_{12}H_{15}N_3Cl_2O_3$) C, H, N.

5,6-Dichloro-2-(dimethylamino)-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (21c). Compound **21c** (0.098 g, 94%) was prepared from **20a** (0.1 g, 0.3 mmol) and $NH(CH_3)_2$ (33% solution in absolute ethanol, 10 mL) by the method described for **12b**. **21c**: mp 175−176 °C (MeOH−H_2O); ^1H NMR (DMSO-d_6) δ 7.68 and 7.50 (2 s, 2 H, H-7, H-4), 5.50 (s, 2 H, H-1′), 3.15 (d, 3 H, $N(CH_3)_2$). Anal. ($C_{13}H_{17}N_3Cl_2O_3$) C, H, N.

5,6-Dichloro-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole-2-thione (24). Compound **24** was prepared from **20a** (0.05 g, 0.15 mmol), EtOH (10 mL), and thiourea (0.034 g, 3.3 mmol) by the method described for **15** to give 0.04 g (76%) of **24**: mp 175−176 °C; ^1H NMR (DMSO-d_6) δ 13.20 (bs, 1 H, exchanges with D_2O, NH), 7.69 and 7.36 (2 s, 2 H, H-7, H-4), 5.70 (s, 2 H, H-1′). Anal. ($C_{11}H_{12}N_2Cl_2O_3S$) C, H, N.

2-(Benzylthio)-5,6-dichloro-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (21d). Compound **21d** was prepared from **24** (0.09 g, 0.3 mmol) using CH_3CN:H_2O (1:1), NH_4OH (aqueous, 0.01 mL), and benzyl chloride (0.05 mL) by the method described for **12d** to give 0.10 g (87%) of **21d**: mp 128−129 °C (MeOH−H_2O); ^1H NMR (DMSO-d_6) δ 7.90 and 7.86 (2 s, 2 H, H-7, H-4), 7.45 (d, 2 H, C_6H_5), 7.33−7.25 (m, 3 H, C_6H_5), 5.60 (s, 2 H, H-1′), 4.60 (s, 2 H, $CH_2C_6H_5$). Anal. ($C_{18}H_{18}N_2Cl_2O_3S$) C, H, N.

5,6-Dichloro-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (21e). Compound **21e** was prepared from **24** (0.15 g, 0.46 mmol) using Raney Ni (0.2 g, wet) and EtOH (30 mL) by the method described for **12e** to give 0.093 g (69%) of **21e**: mp 160−162 °C (hexane−EtOAc); ^1H NMR (DMSO-d_6) δ 8.47 (bs, 1 H, H-2), 8.01 and 7.95 (2 s, 2 H, H-7, H-4), 5.75 (s, 2 H, H-1′). Anal. ($C_{11}H_{12}N_2Cl_2O_3$) C, H, N.

2,4,6-Trichloro-1-[[1,3-bis(benzyloxy)-2-propoxy]methyl]benzimidazole (19b). Compound **19b** (2.73 g) was prepared from **2a** (0.59 g, 2.69 mmol), NaH (0.11 g, 2.7 mmol, 60% oil dispersion), CH_3CN (72 mL), and **18** (1.03 g, 3.2 mmol) in CH_3CN (10 mL) by the method described for **19a**. **19b**: oil. The ^1H NMR spectrum showed a small impurity (**18**), but the mixture was used without further purification for the next step.

2,4,6-Trichloro-1-[(1,3-dihydroxy-2-propoxy)methyl]-benzimidazole (20b). Compound **20b** was prepared from **19b** (2.53 g, 5.0 mmol) using BCl_3 (5 M solution in CH_2Cl_2, 23 mL), CH_2Cl_2 (49 mL), and MeOH (20 mL) by the method described for **11a** to give 0.22 g (14%) of **20b**: mp 135−137 °C (EtOAc); ^1H NMR (DMSO-d_6) δ 7.84 (bs, 1 H, H-7), 7.49 (bs, 1 H, H-5), 5.75 (s, 2 H, H-1′). Anal. ($C_{11}H_{11}N_2Cl_3O_3$) C, H, N.

2-Amino-4,6-dichloro-1-[(1,3-dihydroxy-2-propoxy)-methyl]benzimidazole (22a). Compound **22a** was prepared from **20b** (0.27 g, 0.83 mmol) and liquid NH_3 (20 mL) by the method described for **12a** to give 0.24 g (95%) of **22a**: mp 181−183 °C (MeOH); ^1H NMR (DMSO-d_6) δ 7.32 (d, J = 1.4 Hz, 1 H, H-7), 7.09 (d, J = 1.4 Hz, 1 H, H-5), 6.98 (bs, 2 H, exchanges with D_2O, NH_2), 5.50 (s, 2 H, H-1′). Anal. ($C_{11}H_{13}N_3Cl_2O_3$) C, H, N.

4,6-Dichloro-2-(methylamino)-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (22b). Compound **22b** was prepared from **20b** (0.11 g, 0.34 mmol) and NH_2CH_3 (33% solution in absolute ethanol, 15 mL) by the method described for **12b** to give 0.11 g (80%) of **22b**: mp 152 °C (MeOH−H_2O); ^1H NMR (DMSO-d_6) δ 7.33 (d, J = 1.5 Hz, 1 H, H-7), 7.09 (d, J = 1.2 Hz, 1 H, H-5), 6.97 (d, 1 H, exchanges with D_2O, NH), 5.48 (s, 2 H, H-1′), 2.89 (d, 3 H, $NHCH_3$). Anal. ($C_{12}H_{15}N_3Cl_2O_3$·0.25H_20) C, H, N.

4,6-Dichloro-2-(dimethylamino)-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (22c). Compound **22c** (0.068 g, 88%) was prepared from **20b** (0.076 g, 0.23 mmol) and $NH(CH_3)_2$ (33% solution in absolute ethanol, 10 mL) by the method described for **12b**. **22c**: mp 156−158 °C (EtOH); ^1H NMR (DMSO-d_6) δ 7.50 (d, J = 0.9 Hz, 1 H, H-7), 7.21 (d, J = 1.2 Hz, 1 H, H-5), 5.51 (s, 2 H, H-1′), 3.06 (d, 6 H, $N(CH_3)_2$). Anal. ($C_{13}H_{17}N_3Cl_2O_3$) C, H, N.

4,6-Dichloro-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole-2-thione (25). Compound **25** was prepared from **20b** (0.35 g, 1.0 mmol), EtOH (70 mL), and thiourea (0.51 g, 6.8 mmol) by the method described for **15** to give 0.29 g (84%) of **25**: mp 218−220 °C; ^1H NMR (DMSO-d_6) δ 13.55 (bs, 1 H, exchanges with D_2O, NH), 7.49 (d, J = 1.5 Hz, 1 H, H-7), 7.40 (d, J = 1.4 Hz, 1 H, H-5), 5.74 (s, 2 H, H-1′), 4.55 (t, 2 H, exchanges with D_2O, 2 × OH), 3.66−3.60 (m, 1 H, H-3′), 3.48−3.42 (m, 2 H, H-4′), 3.34−3.32 (m, 2 H, H-5′). Anal. ($C_{11}H_{12}N_2Cl_2O_3S$) C, H, N.

2-(Benzylthio)-4,6-dichloro-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (22d). Compound **22d** was prepared from **25** (0.09 g, 0.3 mmol) using CH_3CN:H_2O (1:1), NH_4OH (aqueous, 0.01 mL), and benzyl chloride (0.05 mL) by the method described for **12d** to give 0.086 g (75%) of **22e**: mp 117 °C; ^1H NMR (DMSO-d_6) δ 7.70 (bs, 1 H, H-7), 7.50−7.37 (m, 2 H, C_6H_5), 7.34 (s, 1 H, H-5), 7.31−7.24 (m, 3 H, C_6H_5), 5.61 (s, 2 H, H-1′), 4.62 (bs, 4 H, exchanges with D_2O, 2 × OH, $CH_2C_6H_5$), 3.48−3.38 (m, 3 H, H-3′, H-4′), 3.30−3.26 (m, 2 H, H-5′). Anal. ($C_{18}H_{18}N_2Cl_2O_3S$) C, H, N.

2,4,5-Trichloro-1-[[1,3-bis(benzyloxy)-2-propoxy]methyl]benzimidazole (19c). Compound **19c** (1.6 g) was prepared as an oil from **7a** (0.6 g, 2.7 mmol), NaH (0.13 g, 3.2 mmol, 60% oil dispersion), CH_3CN (200 mL), and **18** (1.04 g, 3.2 mmol) in CH_3CN (20 mL) by the method described for **10a**. The ^1H NMR spectrum showed a small impurity (**18**), but the oil was used without further purification for the next step.

2,4,5-Trichloro-1-[[1,3-dihydroxy-2-propoxy]methyl]-benzimidazole (20c). Compound **20c** was prepared as an oil from **19c** (1.56 g, 3.0 mmol) using (5 M solution in CH_2Cl_2, 14 mL), CH_2Cl_2 (30 mL), and MeOH (14 mL) by the method described for **11a** to give 0.32 g (32%) of **20c**: mp 162−164 °C (EtOAc); ^1H NMR (DMSO-d_6) δ 7.74 (d, 1 H, J = 8.7 Hz, H-7), 7.57 (d, 1 H, J = 8.7 Hz, H-6), 5.70 (s, 2 H, H-1′). Anal. ($C_{11}H_{11}N_2Cl_3O_3$) C, H, N.

2-Amino-4,5-dichloro-1-[(1,3-dihydroxy-2-propoxy)-methyl]benzimidazole (23a). Compound **23a** (0.073 g, 90%) was prepared from **20c** (0.088 g, 0.27 mmol) and liquid ammonia (10 mL) by the method described for **12a**. **23a**: mp 181−183 °C; ^1H NMR (DMSO-d_6) δ 7.20 (d, 1 H, J = 8.2 Hz, H-7), 7.08 (d, 1 H, J = 8.23 Hz, H-6), 6.96 (bs, 2 H, exchanges with D_2O, NH_2), 5.51 (s, 2 H, H-1′). Anal. ($C_{11}H_{13}N_3Cl_2O_3$) C, H, N.

4,5-Dichloro-2-(methylamino)-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (23b). Compound **23b** (0.068 g, 93%) was prepared from **20c** (0.08 g, 0.23 mmol), EtOH (5 mL), and NH_2CH_3 (33% solution in absolute ethanol, 6 mL) by the method described for **12b**. **23b**: mp 164−165 °C (hexane−EtOAc); ^1H NMR (DMSO-d_6) δ 7.21 (d, 1 H, J = 8.4 Hz, H-7), 7.10 (d, 1 H, J = 8.3 Hz, H-6), 7.01 (d, 1 H, exchanges with D_2O, NH), 5.49 (s, 2 H, H-1′), 2.93 (d, 3 H, $NHCH_3$). Anal. ($C_{12}H_{15}N_3Cl_2O_3$) C, H, N.

4,5-Dichloro-2-(dimethylamino)-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (23c). Compound **23c** was prepared from **20c** (0.076 g, 0.23 mmol), EtOH (5 mL), and $NH(CH_3)_2$ (33% solution in absolute ethanol, 6 mL) by the method described for **12b**. **23c** (0.07 g, 91%): mp 149−150 °C (hexane−EtOAc); ^1H NMR (DMSO-d_6) δ 7.38 (d, 1 H, J = 8.40 Hz, H-7), 7.22 (d, 1 H, J = 8.34 Hz, H-6), 5.53 (s, 2 H, H-1′), 3.08 (d, 6 H, $N(CH_3)_2$). Anal. ($C_{13}H_{17}N_3Cl_2O_3$) C, H, N.

4,5-Dichloro-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole-2-thione (26). Compound **26** (0.081 g, 83%) was prepared from **20c** (0.1 g, 0.3 mmol), EtOH (15 mL), and thiourea (0.069 g, 0.9 mmol) by the method described for **15**. **26**: mp 155−156 °C; ^1H NMR (DMSO-d_6) δ 13.57 (bs, 1 H, exchanges with D_2O, NH), 7.43 and 7.37 (dd, 2 H, J = 9.5 Hz, H-6, H-7), 5.76 (s, 2 H, H-1′). Anal. ($C_{11}H_{12}N_2Cl_2O_3S$) C, H, N.

2-(Benzylthio)-4,5-dichloro-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (23d). Compound **23d** was prepared from **26** (0.09 g, 0.3 mmol), CH_3CN:H_2O (1:1), NH_4OH (aqueous, 0.01 mL), and benzyl chloride (0.05 mL) by the method described for **12d**. **23d** (0.10 g, 89%): mp 118−120 °C; ^1H NMR (DMSO-d_6) δ 7.56 (d, 1 H, J = 8.5 Hz, H-7), 7.49 (d, 1 H, J = 8.7 Hz, H-6), 7.42 (d, 2 H, C_6H_5), 7.33−7.25 (m, 3 H, C_6H_5), 5.62 (s, 2 H, H-1′). Anal. ($C_{18}H_{18}N_2Cl_2O_3S$) C, H, N.

4,5-Dichloro-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (23e). Compound **23e** was prepared from **26** (0.14 g, 0.43 mmol) using Raney Ni (0.1 g, wet) and EtOH (15 mL) by the method described for **12e** to give 0.08 g (64%) of **23e**: mp 156−158 °C (MeOH−H_2O); ^{1}H NMR (DMSO-d_6) δ 8.50 (s, 1 H, H-2), 7.67 (d, 1 H, J = 8.6 Hz, H-7), 7.49 (d, 1 H, J = 8.6, 1 Hz, H-6), 5.77 (s, 2 H, H-1′). Anal. ($C_{11}H_{12}N_2Cl_2O_3$) C, H, N.

2-Bromo-5,6-dichloro-1-[(2-acetoxyethoxy)methyl]benzimidazole (28a). To a stirred suspension of 2-bromo-5,6-dichlorobenzimidazole[20a] (**8b**) (0.3 g, 1.1 mmol) in dry CH_3CN (60 mL) was added NaH (0.066 g, 60% oil dispersion, 1.6 mmol) under a N_2 atmosphere. The solution was stirred until H_2 evolution had ceased and a clear solution was obtained (20 min). At that time, (2-acetoxyethoxy)methyl bromide[39] (**27**) (0.26 g, 1.3 mmol) in CH_3CN (10 mL) was added dropwise. The reaction mixture was stirred for an additional 5 h. The resulting mixture was concentrated under reduced pressure, diluted with H_2O (100 mL), extracted with EtOAc (150 mL), washed with H_2O (50 mL), and dried (anhydrous Na_2SO_4) and the solvent removed under reduced pressure. The resulting oil was purified by flash column chromatography (2 × 20 cm) (230−400 mesh), prepared with wet SiO_2 in hexane. Elution with hexane:EtOAc (8:2, v/v) gave the desired product which was recrystallized from MeOH to afford 0.32 g (75%) of **28a** which was used as such without further purification: mp 110−111 °C; ^{1}H NMR (DMSO-d_6) δ 8.14 and 7.96 (2s, 2 H, H-7, H-4), 5.67 (s, 2 H, H-1′).

2-Bromo-5,6-dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (29a). A mixture of **28a** (0.48 g, 1.2 mmol), Na_2CO_3 (0.3 g, 2.8 mmol), and EtOH (10% aqueous, 100 mL) was stirred at room temperature for 12 h or until the reaction was complete as determined by TLC. The excess ethanol was removed under reduced pressure to dryness. The resulting mixture was diluted with H_2O (100 mL), extracted with EtOAc (250 mL), washed with H_2O (50 mL), and dried (anhydrous Na_2SO_4) and the solvent removed under reduced pressure. The resulting product was purified by flash column chromatography (2 × 20 cm) (230−400 mesh), prepared with wet SiO_2 in $CHCl_3$. Elution of the column with $CHCl_3$:MeOH (95:5, v/v) gave the desired product which was recrystallized from a mixture of hexane:EtOAc to afford 0.26 g (62%) of **29a**: mp 154−155 °C; ^{1}H NMR (DMSO-d_6) δ 8.12 and 7.95 (2, 2 H, H-7, H-4), 5.67 (s, 2 H, H-1′). Anal. ($C_{10}H_9N_2Cl_2O_2Br$) C, H, N.

2-Bromo-4,6-dichloro-1-[(2-acetoxyethoxy)methyl]benzimidazole (28b). Compound **28b** was prepared from **2b** (0.53 g, 1.9 mmol), NaH (0.12 g, 2.9 mmol, 60% oil dispersion), CH_3CN (100 mL), and **27** (0.46 g, 2.3 mmol) in CH_3CN (20 mL) by the method described for **28a**. **28b** (0.56 g, 75%): mp 103−105 °C; ^{1}H NMR (DMSO-d_6) δ 7.85 (d, 1 H, J = 1.7 Hz, H-5), 7.48 (d, 1 H, J = 1.8 Hz, H-7), 5.75 (s, 2 H, H-1′). Anal. ($C_{12}H_{11}N_2Cl_2O_3Br$) C, H, N.

2-Bromo-4,6-dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (29b). Compound **29b** was prepared from **28b** (0.49 g, 1.2 mmol) using Na_2CO_3 (0.3 g, 2.8 mmol) and EtOH (10% aqueous, 100 mL) by the method described for **29a** to give 0.24 g (55%) of **29b**: mp 128−130 °C; ^{1}H NMR (DMSO-d_6) δ 7.91 (d, H, J = 1.7 Hz, H-7), 7.48 (d, 1 H, J = 1.7 Hz, H-5), 5.67 (s, 2 H, H-1′). Anal. ($C_{10}H_9N_2Cl_2O_2Br$) C, H, N.

2-Bromo-4,5-dichloro-1-[(2-acetoxyethoxy)methyl]benzimidazole (28c). Compound **28c** was prepared from **7b** (0.53 g, 1.9 mmol), NaH (0.12 g, 2.9 mmol, 60% oil dispersion), CH_3CN (100 mL), and **27** (0.46 g, 2.3 mmol) in CH_3CN (10 mL) by the method described for **28a**. **28c** (0.63 g, 83%): mp 123−125 °C; ^{1}H NMR (DMSO-d_6) δ 7.75 (d, H, J = 8.8 Hz, H-7), 7.56 (d, 1 H, J = 8.8 Hz, H-6), 5.70 (s, 2 H, H-1′). Anal. ($C_{12}H_{11}N_2Cl_2O_3Br$) C, H, N.

2-Bromo-4,5-dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole (29c). Compound **29c** was prepared from **28c** (0.39 g, 1.0 mmol), Na_2CO_3 (0.21 g, 2.0 mmol), and EtOH (10% aqueous, 100 mL) by the method described for **29a**. **29c** (0.24 g, 69%): mp 128−130 °C; ^{1}H NMR (DMSO-d_6) δ 7.74 (d, 1 H, J = 8.7 Hz, H-7), 7.55 (d, 1 H, J = 8.6 Hz, H-6), 5.69 (s, 2 H, H-1′). Anal. ($C_{10}H_9N_2Cl_2O_2Br$) C, H, N.

2-Bromo-5,6-dichloro-1-[(1,3-diacetoxy-2-propoxy)methyl]benzimidazole (31a). Compound **31a** (0.34 g, 61%) was prepared from **8b** (0.33 g, 1.23 mmol), NaH (0.048 g, 1.2 mmol, 60% oil dispersion), CH_3CN (40 mL), and **30** (0.49 g, 1.85 mmol) in CH_3CN (10 mL) by the method described for **28a**. **31a**: mp 110−112 °C; ^{1}H NMR (DMSO-d_6) δ 8.10 and 7.96 (2 s, 2 H, H-7, H-4), 5.74 (s, 2 H, H-1′). Anal. ($C_{15}H_{15}N_2Cl_2O_5Br$) C, H, N.

2-Bromo-5,6-dichloro-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (32a). A mixture of **31a** (0.2 g, 0.44 mmol), KCN (0.086 g, 2.8 mmol), and EtOH (10% aqueous, 18 mL) was stirred at room temperature for 4 h or until the reaction was complete. The excess ethanol was removed under reduced pressure to dryness. The resulting mixture was diluted with H_2O (50 mL), extracted with EtOAc (50 mL), washed with H_2O (50 mL), and dried (anhydrous Na_2SO_4) and the solvent removed under reduced pressure to dryness. The resulting solid was dissolved in $CHCl_3$ (20 mL) and filtered. The residue was recrystallized with MeOH−H_2O to afford 0.087 g (47%) of **32a**: mp 149−150 °C; ^{1}H NMR (DMSO-d_6) δ 8.05 and 7.93 (2 s, 2 H, H-7, H-4), 5.73 (s, 2 H, H-1′). Anal. ($C_{11}H_{11}N_2Cl_2O_3Br$) C, H, N.

2-Bromo-4,6-dichloro-1-[(1,3-diacetoxy-2-propoxy)methyl]benzimidazole (31b). Compound **31b** was prepared from **2b** (0.31 g, 1.1 mmol), NaH (0.49 g, 1.1 mmol, 60% oil dispersion), CH_3CN (40 mL), and **30** (0.62 g, 2.3 mmol) in CH_3CN (10 mL) by the method described for **28a**. **31b** (0.34 g, 64%): mp 125 °C; ^{1}H NMR (DMSO-d_6) δ 7.89 (d, 1 H, J = 1.77 Hz, H-7), 7.50 (d, 1 H, J = 1.77 Hz, H-5), 5.75 (s, 2 H, H-1′). Anal. ($C_{15}H_{15}N_2Cl_2O_5Br$) C, H, N.

2-Bromo-4,6-dichloro-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (32b). Compound **32b** was prepared from **31b** (0.19 g, 0.34 mmol), KCN (0.083 g, 1.3 mmol), and EtOH (10% aqueous, 12 mL) by the method described for **32a**. **32b** (0.70 g, 55%): mp 148−150 °C; ^{1}H NMR (DMSO-d_6) δ 7.84 (d, 1 H, J = 1.7 Hz, H-6), 7.47 (d, 1 H, J = 1.8 Hz, H-4), 5.74 (s, 2 H, H-1′). Anal. ($C_{11}H_{11}N_2Cl_2O_2Br$) C, H, N.

2-Bromo-4,5-dichloro-1-[(1,3-diacetoxy-2-propoxy)methyl]benzimidazole (31c). Compound **31c** (0.47 g, 69%) was prepared from **7b** (0.4 g, 1.5 mmol), NaH (0.072 g, 1.8 mmol, 60% oil dispersion), CH_3CN (60 mL), and **30** (0.67 g, 1.8 mmol) in CH_3CN (10 mL) by the method described for **28a**. **31c**: mp 135−137 °C; ^{1}H NMR (DMSO-d_6) δ 7.72 (d, 1 H, J = 8.2 Hz, H-7), 7.53 (d, 1 H, J = 8.3 Hz, H-6), 5.76 (s, 2 H, H-1′). Anal. ($C_{15}H_{15}N_2Cl_2O_5Br$) C, H, N.

2-Bromo-4,5-dichloro-1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazole (32c). Compound **32c** was prepared from **31c** (0.3 g, 0.66 mmol), KCN (0.128, 1.9 mmol), and EtOH (10% aqueous, 18 mL) by the method described for **32a**. **32c** (0.094 g, 38%): mp 148−150 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 7.69 (d, 1 H, J = 8.5 Hz, H-7), 7.53 (d, 1 H, J = 8.7 Hz, H-6), 5.75 (s, 2 H, H-1′). Anal. ($C_{11}H_{11}N_2Cl_2O_3Br$) C, H, N.

Cell Culture Procedures. The routine growth and passage of KB, BSC-1, and HFF cells was performed in monolayer cultures using minimal essential medium (MEM) with either Hanks salts [MEM(H)] or Earle salts [MEM(E)] supplemented with 10% calf serum or 10% fetal bovine serum (HFF cells). The sodium bicarbonate concentration was varied to meet the buffering capacity required. Cells were passaged at 1:2−1:10 dilutions according to conventional procedures by using 0.05% trypsin plus 0.02% EDTA in a HEPES-buffered salt solution.

Virological Procedures. The Towne strain, plaque-purified isolate P_O, of HCMV was kindly provided by Dr. Mark Stinski, University of Iowa. The KOS strain of HSV-1 was used in most experiments and was provided by Dr. Sandra K. Weller, University of Connecticut. Stock HCMV was prepared by infecting HFF cells at a multiplicity of infection (moi) of <0.01 plaque-forming units (PFU)/cell as detailed previously.[43] High-titer HSV-1 stocks were prepared by infecting KB cells at an moi of <0.1 also as detailed previously.[43] Virus titers were determined using monolayer cultures of HFF cells for HCMV and monolayer cultures of BSC-1 cells for HSV-1 as described earlier.[43] Briefly, HFF or BSC-1 cells were planted as described above in 96-well cluster dishes and incubated overnight at 37 °C. The next day cultures were inoculated with HCMV or HSV-1 and serially diluted 1:3 across the remaining 11 columns of the 96-well plate. After virus adsorption the inoculum was replaced with fresh medium, and

cultures were incubated at 7 days for HCMV, 2 or 3 days for HSV-1. Plaques were enumerated under 20-fold magnification in wells having the dilution which gave 5−20 plaques/well. Virus titers were calculated according to the following formula: titer (PFU/mL) = no. of plaques × 5 × 3^n, where n represents the nth dilution of the virus used to infect the well in which plaques were enumerated.

HCMV Plaque Reduction Assay. HFF cells in 24-well cluster dishes were infected with ca. 100 PFU of HCMV/cm^2 cell sheet using the procedures detailed above. Following virus adsorption, compounds dissolved in growth medium were added to duplicate wells in four to eight selected concentrations. After incubation at 37 °C for 7 days, cell sheets were fixed and stained with crystal violet and microscopic plaques enumerated as described above. Drug effects were calculated as a percentage of reduction in the number of plaques in the presence of each drug concentration compared to the number observed in the absence of drug.

HCMV Yield Assay. HFF cells were planted as described above in 96-well cluster dishes and incubated overnight, medium was removed, and the cultures were inoculated with HCMV at a moi of 0.5−1 PFU/cell as reported[44] elsewhere. After virus adsorption, inoculum was replaced with 0.2 mL of fresh medium containing test compounds. The first row of 12 wells was left undisturbed and served as virus controls. Each well in the second row received an additional 0.1 mL of medium with test compound at 3 times the desired final concentration. The contents of the 12 wells were mixed by repeated pipetting and then serially diluted 1:3 along the remaining wells. In this manner, six compounds could be tested in duplicate on a single plate with concentrations from 100 to 0.14 μM. Plates were incubated at 37 °C for 7 days and subjected to one cycle of freezing and thawing; aliquots from each of the eight wells of a given column were transferred to the first column of a fresh 96-well monolayer culture of HFF cells. Contents were mixed and serially diluted 1:3 across the remaining 11 columns of the secondary plate. Each column of the original primary plate was diluted across a separate plate in this manner. Cultures were incubated, plaques were enumerated, and titers were calculated as described above.

HSV-1 ELISA An ELISA was employed[45] to detect HSV-1. Ninety-six-well cluster dishes were planted with 10 000 BSC-1 cells/well in 200 μL/well of MEM(E) plus 10% calf serum. After overnight incubation at 37 °C, selected drug concentrations in quadruplicate and HSV-1 at a concentration of 100 PFU/well were added. Following a 3 day incubation at 37 °C, medium was removed, plates were blocked and rinsed, and horse radish peroxidase-conjugated rabbit anti-HSV-1 antibody was added. Following removal of the antibody-containing solution, plates were rinsed and then developed by adding 150 μL/well of a solution of tetramethylbenzidine as substrate. The reaction was stopped with H_2SO_4, and absorbance was read at 450 and 570 nm. Drug effects were calculated as a percentage of the reduction in absorbance in the presence of each drug concentration compared to absorbance obtained with virus in the absence of drug.

Cytotoxicity Assays. Two different assays were used to explore cytotoxicity of selected compounds using methods we have detailed previously. (i) Cytotoxicity produced in stationary HFF cells was determined by microscopic inspection of cells not affected by the virus used in plaque assays.[43] (ii) The effect of compounds during two population doublings of KB cells was determined by crystal violet staining and spectrophotometric quantitation of dye eluted from stained cells as described earlier.[46] Briefly, 96-well cluster dishes were planted with KB cells at 3000−5000 cells/well. After overnight incubation at 37 °C, test compound was added in quadruplicate at six to eight concentrations. Plates were incubated at 37 °C for 48 h in a CO_2 incubator, rinsed, fixed with 95% ethanol, and stained with 0.1% crystal violet. Acidified ethanol was added, and plates were read at 570 nm in a spectrophotometer designed to read 96-well ELISA assay plates.

Data Analysis. Dose−response relationships were constructed by linearly regressing the percent inhibition of parameters derived in the preceding sections against log drug concentrations. Fifty percent inhibitory (IC_{50}) concentrations were calculated from the regression lines. Samples containing positive controls (ACV for HSV-1, GCV for HCMV, and 2-acetylpyridine thiosemicarbazone for cytotoxicity) were used in all assays.

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