

# Design, Synthesis, and Biological Evaluation of Tricyclic Nucleosides (Dimensional Probes) as Analogues of Certain Antiviral Polyhalogenated Benzimidazole Ribonucleosides

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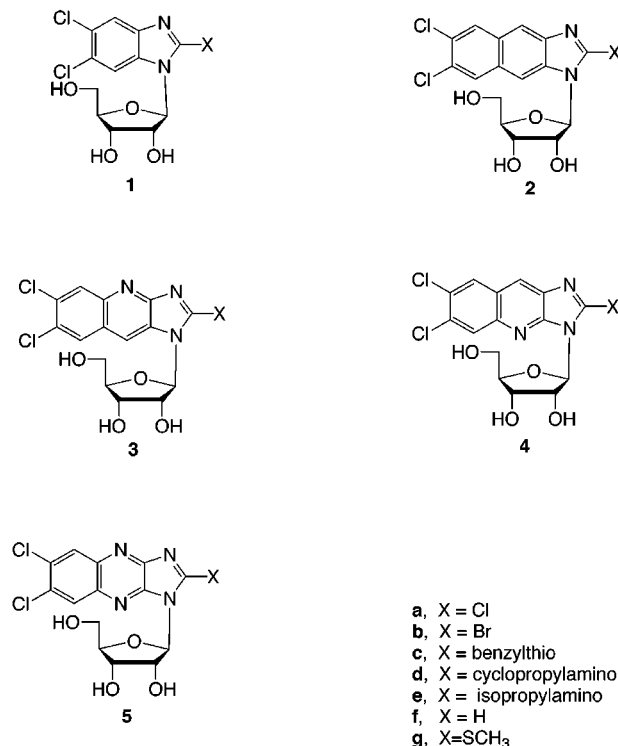
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The polyhalogenated benzimidazole nucleosides 2,5,6-trichloro-1-( $\beta$ -D-ribofuranosyl)benzimidazole (TCRB) and the 2-bromo analogue (BDCRB) were synthesized in our laboratory and established as potent and selective inhibitors of human cytomegalovirus (HCMV) with a novel mode of action. In an effort to study the behavior of the key substructure in a dimensionally extended manner and probe the spatial limitation of the target enzyme(s), a series of 2-substituted 6,7-dichloro-1-( $\beta$ -D-ribofuranosyl)naphtho[2,3-*d*]imidazoles and the N1- and N3-ribonucleosides of 2-substituted 6,7-dichloroimidazo[4,5-*b*]quinolines were prepared. The nucleosides 6,7-dichloro-1-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one and 6,7-dichloro-3-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one were selected and used as the key synthetic intermediates in the imidazo[4,5-*b*]quinoline series. Evaluation of the compounds for activity against HCMV and herpes simplex virus type 1 revealed that the trichloro analogues of TCRB (**2a**, **3a**) were nearly as active against HCMV as TCRB but were more cytotoxic. The results suggest that extending the heterocycle of TCRB affected the affinity for the HCMV target only slightly but increased the affinity for cellular enzymes.

## Introduction

Human cytomegalovirus<sup>1</sup> (HCMV) is a significant pathogen for immunocompromised individuals<sup>2</sup> such as bone marrow<sup>3</sup> and organ transplant<sup>4</sup> patients and individuals with AIDS.<sup>5</sup> Ganciclovir, foscarnet, and cidofovir have been approved by the Food and Drug Administration for the systemic treatment of HCMV infections in these patient populations.<sup>6–8</sup> However, their use is limited by low oral bioavailability, in vivo toxicity, and the development of resistance.<sup>9</sup> These deficiencies demonstrate the need for new compounds to treat HCMV infections. As part of our antiviral drug discovery program, we have reported that 2,5,6-trichloro-1-( $\beta$ -D-ribofuranosyl)benzimidazole (TCRB, **1a**) and the 2-bromo analogue (BDCRB, **1b**) (Chart 1) are potent and selective inhibitors of HCMV.<sup>10</sup> Furthermore, both TCRB and BDCRB act by a unique mechanism which does not involve inhibition of DNA synthesis but does involve inhibition of viral DNA processing.<sup>11</sup> Genotypic characterization of HCMV resistant to TCRB and BDCRB has identified two viral genes, UL56 and UL89, which mutate to give drug-resistant virus.<sup>11,12</sup> Thus, the proteins encoded by these two genes must be the target(s) for TCRB and related analogues. However, little is known about these proteins, and nothing is known regarding their overall three-dimensional structure nor of benzimidazole binding pocket(s) on the proteins.

Chart 1

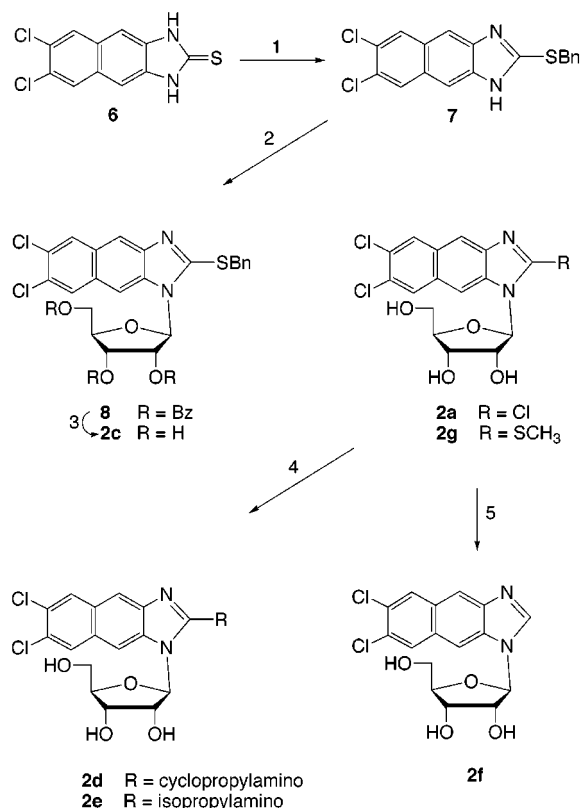


Because the actual target binding pocket is unknown, we have elected to probe the putative pocket by synthesizing and testing a series of TCRB analogues in which the heterocycle is extended in a dimensionally extended manner. We have already reported the synthesis and initial evaluation of a limited number of

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Scheme 1<sup>a</sup>

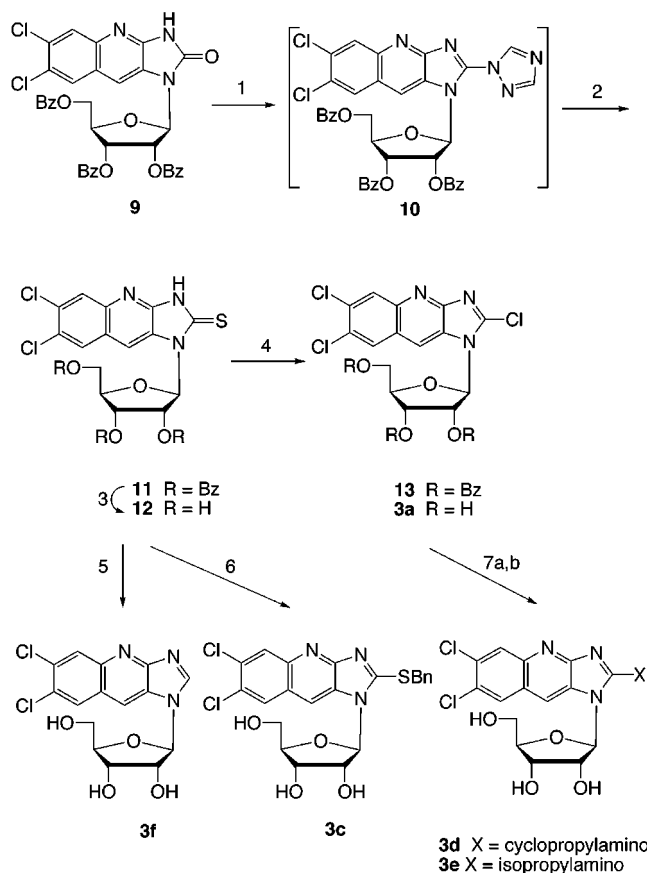
<sup>a</sup> (1) BnBr, DMF, rt, 90%; (2) (a) BSA, ClCH<sub>2</sub>CH<sub>2</sub>Cl, rt, (b) TBAR, TMSOTf, 65 °C, 64%; (3) NH<sub>3</sub>, MeOH, rt, 61%; (4) cyclopropylamine (**2d**), isopropylamine (**2e**); (5) W-4 Raney Ni, EtOH (from **2g**).

trisubstituted naphtho[2,3-*d*]imidazo- and imidazo[4,5-*b*]quinoxaline ribonucleosides<sup>13,14</sup> as linear dimensional probes of TCRB. We now report the synthesis and evaluation of some additional 2-substituted 6,7-dichloro-1-(β-D-ribofuranosyl)naphtho[2,3-*d*]imidazoles, a series of 6,7-dichloro-1-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinolines (**3**), and a series of 6,7-dichloro-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinolines (**4**), with different substituents at the 2-position, which also were designed as dimensional analogues<sup>15</sup> of **1a**.

## Results and Discussion

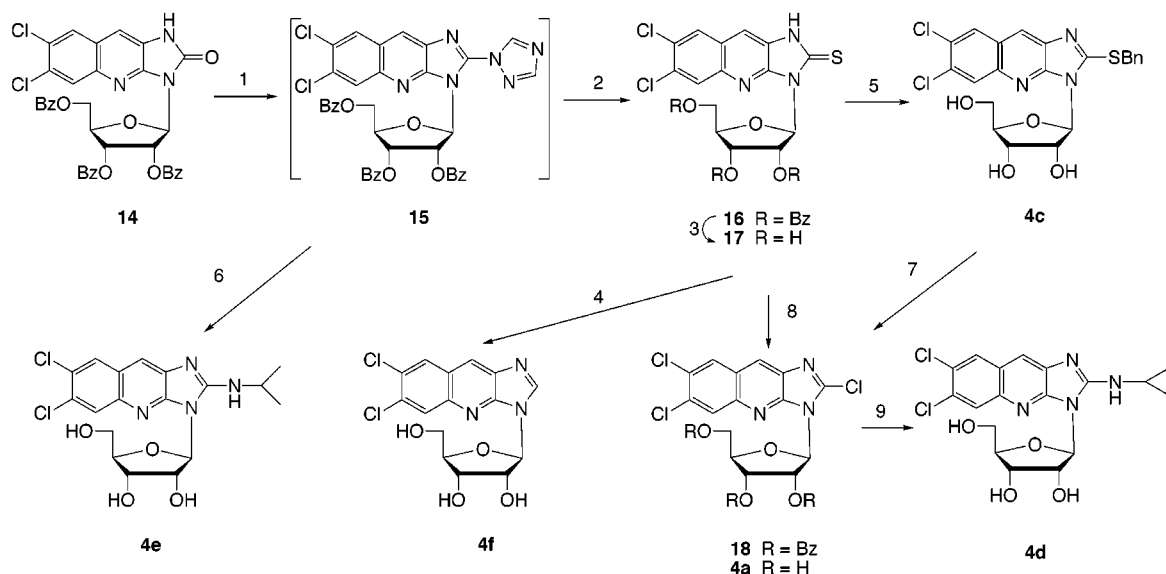
**Chemistry.** Compound 6,7-dichloronaphtho[2,3-*d*]imidazole-2-thione<sup>13</sup> (**6**) was used as the starting material for the synthesis of 2-benzylthio-6,7-dichloro-1-(β-D-ribofuranosyl)naphtho[2,3-*d*]imidazole (**2c**) (Scheme 1). Benzylation of **6** with benzyl bromide in DMF at room temperature gave the 2-benzylthio derivative **7** in a 90% yield. Ribosylation under Vorbruggen conditions<sup>16</sup> with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (TBAR) gave the benzoyl-protected ribonucleoside **8** in 63% yield. Deprotection of **8** with methanolic ammonia gave **2c** in 61% yield. Compounds **2d** and **2e** were prepared by the treatment of 2,6,7-trichloro-1-(β-D-ribofuranosyl)naphtho[2,3-*d*]imidazole<sup>13</sup> (**2a**) with cyclopropylamine and isopropylamine, respectively, in 75% and 88% yields. Compound **2f** was obtained in 52% yield by Raney nickel desulfurization of 6,7-dichloro-2-methylthio-1-(β-D-ribofuranosyl)naphtho[2,3-*d*]imidazole<sup>13</sup> (**2g**).

The N1-ribonucleosides of the targeted imidazo[4,5-*b*]quinolines **3** were prepared starting from 6,7-dichloro-

Scheme 2<sup>a</sup>

<sup>a</sup> (1) POCl<sub>3</sub>, triazole, Et<sub>3</sub>N, CH<sub>3</sub>CN; (2) H<sub>2</sub>S, 83% from **9**; (3) NH<sub>3</sub>, MeOH, 98%; (4) Cl<sub>2</sub>, MeOH, 44%; (5) Raney Ni, 26%; (6) BnBr, NH<sub>4</sub>OH, 71%, (7) (a) cyclopropylamine (**3d**), isopropylamine (**3e**), (b) NH<sub>3</sub>, MeOH, 59% for **3d** and 37% for **3e** from **11**.

1-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one<sup>17</sup> (**9**) (Scheme 2). Compound **9** was first treated with POCl<sub>3</sub>/1,2,4-triazole/Et<sub>3</sub>N<sup>18</sup> in acetonitrile to obtain the corresponding 2-triazolyl derivative **10**. Compound **10** was converted in one pot to the corresponding 2-thio derivative **11** by using H<sub>2</sub>S. Removal of the benzoyl protecting groups with methanolic ammonia gave 6,7-dichloro-1-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinoline-2-thione (**12**) in 98% yield. Compound **12** was converted to 2,6,7-trichloro-1-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinoline (**3a**) with chlorine in methanol<sup>13,19</sup> at temperatures between -40 and -78 °C. A small amount of the deprotected derivative of compound **9** was also isolated in the generation of **3a**, presumably due to a hydrolysis of the 2-chloro group in the reaction or during the workup. 2-Benzylthio-6,7-dichloro-1-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinoline (**3c**) was prepared in 71% yield by benzylation of **12** with benzyl bromide in the presence of ammonium hydroxide. 6,7-Dichloro-1-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinoline (**3f**) was obtained in 26% yield by desulfurization of **12** with Raney nickel. To avoid extensive hydrolysis of the 2-chloro group in **3a**, the introduction of cyclopropylamino and isopropylamino groups to the 2-position was carried out on the benzoyl-protected nucleoside **13**, which was generated by the treatment of **11** with chlorine in methanol. Compound **13** was treated with cyclopropylamine and isopropylamine, followed by deprotection with methanolic ammonia, to give 6,7-dichloro-2-cyclopropylamino-

Scheme 3<sup>a</sup>

<sup>a</sup> (1) POCl<sub>3</sub>, triazole, Et<sub>3</sub>N, CH<sub>3</sub>CN; (2) H<sub>2</sub>S, 94% from **14**; (3) NH<sub>3</sub>, MeOH, quantitative; (4) Raney Ni, 52%; (5) BnBr, NH<sub>4</sub>OH, quantitative; (6) (a) isopropylamine (**3e**), (b) NH<sub>3</sub>, MeOH, 58% from **14**; (7) Cl<sub>2</sub>, MeOH, 46% (from **4c** to **4a**); (8) Cl<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> (from **16** to **18**); (9) (a) cyclopropylamine, (b) NH<sub>3</sub>, MeOH, 84% from **16**.

1-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline (**3d**) and 6,7-dichloro-2-isopropylamino-1-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline (**3e**) in overall yields of 59% and 37%, respectively.

The N3-ribonucleosides of the targeted imidazo[4,5-*b*]quinolines **4** were prepared from 6,7-dichloro-3-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one<sup>17</sup> (**14**) (Scheme 3). Compound **14** was converted into 6,7-dichloro-3-(2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline-2-thione (**16**) through the 2-triazolyl derivative **15** in an overall 94% yield. This was followed by removal of the benzoyl groups to give the nucleoside **17**, which was subsequently converted to 2-benzylthio-6,7-dichloro-3-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline (**4c**). The synthesis of 6,7-dichloro-3-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline (**4f**) was accomplished by desulfurization of **17** with Raney nickel. A direct conversion of the 2-thio group of **17** to a chloro group by using chlorine gave a complicated mixture under various conditions. However, treatment of **4c** with an excess amount of chlorine in methanol at  $-78$  °C gave the 2-chloro derivative **4a** in 46% yield without any major complications. 2-Cyclopropylamino-6,7-dichloro-3-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline (**4d**) was prepared in an overall 84% yield through replacement of the 2-chloro group of the protected nucleoside **18** with cyclopropylamine followed by deprotection. 6,7-Dichloro-2-isopropylamino-1-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline (**4e**) was obtained in an overall 58% yield directly from **15** by using isopropylamine followed by deprotection.

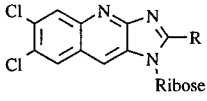
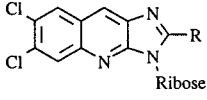
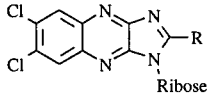
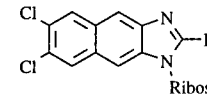
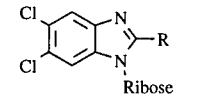
**Biological Evaluations.** All new imidazo[4,5-*b*]quinoline ribonucleosides were tested for activity against HCMV and herpes simplex virus type 1 (HSV-1) and for cytotoxicity in stationary human foreskin fibroblasts (HFF) and growing KB cells. In the N1-nucleoside series, the chloro and benzylthio analogues (**3a**, **3c**) were nearly as active as TCRB in the HCMV plaque assay, but **3a** was not as active in the more stringent yield assay (Table 1). However, both compounds were more cytotoxic in HFF and KB cells than was TCRB (**1a**) or

the benzylthio analogue of TCRB, **1c**. The unsubstituted compound and both amine analogues (**3f**, **3d**, **3e**) were less active or inactive against HCMV and less cytotoxic. These results are similar to those observed for the cyclopropylamine analogue **1d** but differ from those of the 2-unsubstituted benzimidazole DRB (**1f**) in that **1f** was weakly active against HCMV and HSV-1 but probably as a consequence of cytotoxicity (Table 1).

In the N3 series, only the trichloro analogue **4a** was active against against HCMV and HSV-1 but at concentrations which also were cytotoxic in both HFF and KB cells suggesting that the apparent antiviral activity was due to cytotoxicity. The lower activity of **4a** compared to **3a** in the plaque assay but the apparently greater activity in the yield assay is consistent with a cytotoxic mechanism. Regardless of mechanism, the data imply that the N1 analogues interact with greater affinity to a putative binding pocket than the N3 analogues.

Together, these results suggest that the trichloro dimensional analogues of TCRB in the N1 and N3 imidazo[4,5-*b*]quinoline series and in the previously reported<sup>13</sup> naphtho[2,3-*d*]imidazole series (compounds **2a**, **3a**, **4a**) may fit a putative benzimidazole binding site on the HCMV target UL56/UL89 protein(s). However, based on the lower activity in both plaque and yield reduction assays, the fit must be poorer or binding is with less affinity than for TCRB. Other mechanisms unrelated to UL56/UL89, of course, are also possible. The activity of two of the benzylthio analogues (**3c**, **5c**)<sup>14</sup> against HCMV and the inactivity of the other two benzylthio analogues (**2c**,<sup>13</sup> **4c**) is more difficult to explain but may be related to the cytotoxicity of the compounds (Table 1). Nonetheless, the activity of these two compounds and that of the 2-benzylthiobenzimidazole **1c** occurred at concentrations below cytotoxic concentrations suggesting some affinity for a viral protein binding site. The isopropylamine and cyclopropylamine analogues in all the series were weakly active against HCMV and weakly cytotoxic or inactive

**Table 1.** Comparison of the Antiviral Activity and Cytotoxicity of Imidazo[4,5-*b*]quinoline Ribonucleosides to That of Imidazo[4,5-*b*]quinoxaline, Naphtho[2,3-*d*]imidazole, and Benzimidazole Ribonucleosides

	compound no.	substituent R	50 or 90% inhibitory concentration ( $\mu\text{M}$ ) <sup>a</sup>				
			antiviral activity		cytotoxicity <sup>b</sup>		
			HCMV <sup>c</sup> plaque	HCMV <sup>c</sup> yield	HSV-1 <sup>d</sup> ELISA	HFF cells visual	KB cells growth
<b>N-1 imidazo[4,5-<i>b</i>]quinolines</b> 	<b>3a</b>	Cl	2 <sup>e</sup>	45 <sup>e</sup>	70	21 <sup>e</sup>	11
	<b>3c</b>	BnS	4.2		>100	20	40
	<b>3f</b>	H	>100	85	>100	>100	85
	<b>3d</b>	<i>c</i> -PrNH	>100		>100	>100	>100
	<b>3e</b>	<i>i</i> -PrNH	32		>100	100	90
<b>N-3 imidazo[4,5-<i>b</i>]quinolines</b> 	<b>4a</b>	Cl	18 <sup>e</sup>	9.2	90 <sup>e</sup>	18 <sup>e</sup>	8.0
	<b>4c</b>	BnS	>10		>100	>10	>100
	<b>4f</b>	H	>10		>100	>10	>100
	<b>4d</b>	<i>c</i> -PrNH	>100		>100	>100	100
	<b>4e</b>	<i>i</i> -PrNH	32		>100	32	90
<b>imidazo[4,5-<i>b</i>]quinoxalines<sup>f</sup></b> 	<b>5c</b>	BnS	4.2		30	20	20
	<b>5f</b>	H	32		>100	45	>100
	<b>5d</b>	<i>c</i> -PrNH	32		>100	>100	90
	<b>5e</b>	<i>i</i> -PrNH	32		100	100	70
	<b>naphtho[2,3-<i>d</i>]imidazoles<sup>g</sup></b> 	<b>2a</b>	Cl	2.0 <sup>e</sup>	2.3 <sup>e</sup>	26 <sup>e</sup>	3.2 <sup>e</sup>
<b>2c</b>		BnS	>100 <sup>e</sup>		>100	>100 <sup>e</sup>	>100 <sup>e</sup>
<b>2f</b>		H	>100 <sup>e</sup>	17	>100	>100 <sup>e</sup>	>100 <sup>e</sup>
<b>2d</b>		<i>c</i> -PrNH	32 <sup>e</sup>		80	32 <sup>e</sup>	55 <sup>e</sup>
<b>2e</b>		<i>i</i> -PrNH	32 <sup>e</sup>		80	32 <sup>e</sup>	146 <sup>e</sup>
<b>benzimidazoles</b> 	<b>1a</b> (TCRB) <sup>h</sup>	Cl	2.9	1.4	102	238	210
	<b>1c</b> <sup>i</sup>	BnS	22 <sup>e</sup>	7	25	100 <sup>e</sup>	>100
	<b>1f</b> (DRB) <sup>h,j</sup>	H	42	19	30	24	36
	<b>1d</b>	<i>c</i> -PrNH	>100 <sup>e</sup>	21 <sup>e</sup>	20	>100 <sup>e</sup>	>100
<b>ganciclovir<sup>k</sup></b>			7.4	1.6	3.5	>100	>100

<sup>a</sup> All data given as IC<sub>50</sub>'s except for HCMV yield results which are IC<sub>90</sub>'s. <sup>b</sup> Visual cytotoxicity scored on HFF cells at time of HCMV plaque enumeration. Inhibition of KB cell growth determined as described in the text in quadruplicate wells. <sup>c</sup> Plaque and yield reduction assays were performed in duplicate wells using the Towne strain of HCMV as described in the text. <sup>d</sup> Assayed by ELISA in quadruplicate wells. <sup>e</sup> Average of 2–3 separate experiments. <sup>f</sup> Data published previously in ref 14. <sup>g</sup> Data for compound **2a** published previously in ref 13. <sup>h</sup> Data for TCRB and DRB published previously as compounds **9** and DRB in ref 10. <sup>i</sup> Data for compound **1c** published previously as compound **7** in ref 25. <sup>j</sup> Compound referred to as DRB by Tamm and co-workers.<sup>26</sup> <sup>k</sup> Average of 108, 33, and 3 experiments, respectively.

against HCMV and not cytotoxic suggesting there is little, if any, specificity for viral targets. Furthermore, the greater cytotoxicity observed with the new compounds suggests that they bind with more affinity than TCRB to a cellular target of benzimidazoles, possibly the cellular protein kinase inhibited by DRB.<sup>20</sup> Thus, changing the benzimidazole heterocycle to the dimensionally extended N1 imidazo[4,5-*b*]quinoline ribonucleosides gave properties opposite those desired for a more active and less cytotoxic HCMV drug.

## Experimental Section

**General Chemical Procedures.** Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. The silica gel used for chromatography was silica gel 60 230–400 mesh (E. Merck, Darmstadt, West Germany). Thin Layer Chromatography (TLC) was performed on prescored SilicAR 7GF plates (Analtech, Newark, DE). Compounds were visualized by illumination under UV light (254 nm). Evaporations were carried out under reduced pressure (water aspirator) with the bath temperature below 40 °C, unless specified otherwise. UV spectra were performed on a Hewlett-Packard 8450-A UV/

VIS spectrophotometer. Nuclear magnetic resonance (NMR) spectra were determined at 360 MHz with a Bruker WP 360 SY. The chemical shift values are expressed in  $\delta$  values (parts per million) relative to the standard chemical shift of TMS or the solvent used. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

**2-Benzylthio-6,7-dichloro-1-( $\beta$ -D-ribofuranosyl)naphtho[2,3-*d*]imidazole (2c).** Benzyl bromide (0.16 mL, 1.3 mmol) was added dropwise to a solution of 6,7-dichloronaphtho[2,3-*d*]imidazole-2-thione<sup>13</sup> (**6**; 0.3 g, 1.1 mmol) in dry DMF (6.0 mL) and the solution was stirred at room temperature for 24 h to give a brown suspension. The suspension was diluted with ethyl acetate (200 mL), washed with a saturated sodium bicarbonate solution (3  $\times$  50 mL) and a saturated sodium chloride solution and then dried over anhydrous sodium sulfate. The solution was removed under reduced pressure to give 2-benzylthio-6,7-dichloronaphtho[2,3-*d*]imidazole (**7**; 0.36 g, 90%) as a brown solid. This solid was used directly in the next step without further purification.

BSA (0.396 mL, 1.6 mmol) was added to a suspension of compound **7** (0.29 g, 0.8 mmol) in dry 1,2-dichloroethane (24 mL) under an atmosphere of argon and the mixture was stirred at room temperature for 1 h to give a clear brown solution. 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranose (0.61 g, 1.2 mmol) was added to the solution followed by TMSOTf (0.25 mL, 1.28 mmol). The reaction solution was then stirred at 65 °C for 7 h and diluted with chloroform (100 mL). The chloroform solution was washed with a saturated sodium bicarbonate solution (3  $\times$  50 mL) and a saturated sodium chloride solution and then dried over anhydrous sodium sulfate. The solution was evaporated and the residue was subjected to silica gel chromatography (2.5  $\times$  15 cm) and eluted with chloroform. The appropriate fractions containing the protected nucleosides, as followed by TLC, were collected. The solvent was removed under reduced pressure and the residue was again subjected to silica gel chromatography (2.5  $\times$  15 cm) with elution by dichloromethane. The appropriate fractions were collected, the solvent was removed under reduced pressure and the solid was dried under vacuum at 78 °C to give 2-benzylthio-6,7-dichloro-1-(2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)naphtho[2,3-*d*]imidazole (**8**; 0.41 g, 63%) as a slightly brown solid. This solid was used directly in the deprotection step without further purification.

Compound **8** (0.3 g) was added to saturated methanolic ammonia (100 mL) and the mixture was stirred at room temperature for 20 h. The solvent was evaporated and the residue was subjected to silica gel chromatography (3  $\times$  10 cm) with elution by 5% methanol in chloroform. The appropriate fractions, as determined by TLC, were collected and the solvent was evaporated to give a white solid (0.146 g). The solid was recrystallized from ethanol (4 mL) to give **2c**, 0.112 g, 61.2% as a white solid: mp 238–240 °C; UV [ $\lambda_{\max}$  nm ( $\epsilon$ )] (MeOH) 347.0 (19800), 331.5 (14800), 271.5 (62200), 263.5 (55800), 239.0 (44600). Anal. (C<sub>23</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S·H<sub>2</sub>O) C, H, N.

**6,7-Dichloro-2-cyclopropylamino-1-( $\beta$ -D-ribofuranosyl)naphtho[2,3-*d*]imidazole (2d).** Cyclopropylamine (6 mL, large excess) was added to a solution of 2,6,7-trichloro-1-( $\beta$ -D-ribofuranosyl)naphtho[2,3-*d*]imidazole<sup>13</sup> (**2a**) (0.17 g, 0.42 mmol) in dry THF (12 mL) and stirred at room temperature for 3 days. The solvent was evaporated under reduced pressure, the residue was subjected to silica gel chromatography (3  $\times$  5 cm) and eluted by 5% to 10% of methanol in chloroform. The appropriate fractions, as determined by TLC, were collected and the solvent was evaporated to give a slightly brown solid. The solid was dried under vacuum at 56 °C for 24 h to give **2d** (0.134 g, 75%): mp 140–145 °C; UV [ $\lambda_{\max}$  nm ( $\epsilon$ )] (MeOH) 349.5 (14500), 266.0 (76900), 231.5 (33800). Anal. (C<sub>19</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>4</sub>·H<sub>2</sub>O) C, H, N.

**6,7-Dichloro-2-isopropylamino-1-( $\beta$ -D-ribofuranosyl)naphtho[2,3-*d*]imidazole (2e).** Trichloro-1-( $\beta$ -D-ribofuranosyl)naphtho[2,3-*d*]imidazole<sup>13</sup> (**2a**) (0.19 g, 0.47 mmol) was treated with isopropylamine (using a similar procedure as for **2d**) to give **2e** (0.176 g, 88%): mp 122–126 °C; UV [ $\lambda_{\max}$  nm

( $\epsilon$ )] (MeOH) 349.5 (16200), 266.5 (87500), 231.5 (35600). Anal. (C<sub>19</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>4</sub>·H<sub>2</sub>O) C, H, N.

**6,7-Dichloro-1-( $\beta$ -D-ribofuranosyl)naphtho[2,3-*d*]imidazole (2f).** 6,7-Dichloro-2-methylthio-1-( $\beta$ -D-ribofuranosyl)naphtho[2,3-*d*]imidazole<sup>13</sup> (**2g**) (0.15 g) was dissolved in ethanol (30 mL) and ethyl acetate (3 mL) by heating. After the solution was cooled to room temperature, W-4 Raney nickel (about 3 g as a wet paste) was washed into the flask by ethanol (20 mL). The reaction mixture was heated at reflux for 3.5 h and then cooled to room temperature. The solution was decanted, ethanol (2  $\times$  50 mL) was added to the Raney nickel residue and the mixture was heated at reflux again for about 10 min. The mixture was cooled to room temperature and the solution was again decanted. The combined organic solutions (decantations) were first centrifuged and the clear solution was evaporated. The solid residue was then subjected to silica gel chromatography (5  $\times$  2 cm) with elution by 10% methanol in chloroform. The appropriate fractions, as determined by TLC, were collected and the solvent was evaporated to give a white solid (0.085 g). This solid was recrystallized from ethanol to give **2f** (0.069 g, 52%) as a white solid: mp 245–247 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  8.78 (s, 1H), 8.40 (s, 1H), 8.34 (s, 1H), 8.33 (s, 1H), 8.32 (s, 1H), 5.96 (d, *J* = 6.42 Hz, 1H, H1'), 5.53 (d, *J* = 6.33 Hz, 1H, O*H*), 5.28 (d, *J* = 4.46 Hz, 1H, O*H*), 5.21 (t, *J* = 4.92 Hz, 1H, O*H*), 4.51 (q, *J* = 6.19 Hz, 1H, H2'), 4.17 (q, 1H, H3'), 4.02 (q, 1H), 3.70 (m, 2H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>)  $\delta$  147.75, 145.10, 134.33, 129.14, 128.77, 128.56, 128.52, 126.61, 125.77, 116.01, 107.07, 88.70, 85.60, 73.08, 70.23, 61.28; UV [ $\lambda_{\max}$  nm ( $\epsilon$ )] (MeOH) 325.5 (7610), 247.0 (102000). Anal. (C<sub>16</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>4</sub>·H<sub>2</sub>O) C, H, N.

**6,7-Dichloro-1-(2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline-2-thione (11).** POCl<sub>3</sub> (0.8 mL, 8.6 mmol) was added to a solution of triazole (2.78 g, 37.2 mmol) in dry acetonitrile (120 mL) under an argon atmosphere to give a white suspension. The suspension was placed in an ice bath and dry triethylamine (5.2 mL, 40.1 mmol) was added dropwise for a period of 5 min. The reaction mixture was then removed from the ice bath and 6,7-dichloro-1-(2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one<sup>17</sup> (**9**; 1.0 g, 1.4 mmol) was added under argon. The suspension was stirred at room temperature for 7 days. Triethylamine (0.6 mL) was again added to the yellow suspension and hydrogen sulfide was bubbled into the reaction for 10 min. The flask was sealed and stirred at room temperature for an additional 30 min. The reaction suspension was evaporated and the solid was redissolved in chloroform (300 mL). The chloroform solution was washed sequentially with water (6  $\times$  100 mL), a saturated sodium bicarbonate solution (100 mL), and a saturated sodium chloride solution (50 mL) and dried over anhydrous sodium sulfate. The chloroform was evaporated and the solid was recrystallized from a mixture of chloroform (25 mL) and methanol (5 mL) to give **11** (0.588 g, 57%) as a slightly yellow solid. The mother liquor was then subjected to silica gel flash chromatography (2  $\times$  10 cm) and eluted with 1% methanol in chloroform to give an additional 0.26 g of **11** (25%) as a slightly yellow solid. The total combined yield was 83%. Anal. (C<sub>36</sub>H<sub>25</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>7</sub>S·H<sub>2</sub>O) C, H, N.

**6,7-Dichloro-1-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline-2-thione (12).** Compound **11** (0.485 g, 0.68 mmol) was treated with a saturated methanolic ammonia solution (see procedure for **2c**) to give **12** (0.267 g, 97.8%) as a yellow solid: mp dec above 200 °C. Anal. (C<sub>15</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>4</sub>S·H<sub>2</sub>O) C, H, N.

**2,6,7-Trichloro-1-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline (3a).** Chlorine in carbon tetrachloride (1.44 M, 0.42 mL, 0.6 mmol) was added to a suspension of 6,7-dichloro-1-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline-2-thione (**12**; 0.17 g, 0.41 mmol) in methanol (17 mL) at –78 °C. The reaction was stirred at –78 °C for 40 min followed by the addition of another portion of chlorine in carbon tetrachloride (1.44 M, 0.42 mL, 0.6 mmol). The slightly cloudy reaction solution was allowed to slowly warm to –40 °C over a period of 40 min to give a clear solution. The reaction solution was diluted with ethyl acetate (170 mL), washed sequentially with a mixture of saturated sodium chloride solution and saturated sodium

bicarbonate solution ( $2 \times 100$  mL, 1/1 v/v), a saturated sodium bicarbonate solution ( $2 \times 100$  mL), and a saturated sodium chloride solution (50 mL) and then dried over anhydrous sodium sulfate. The solvent was evaporated to dryness. The residue was then subjected to silica gel flash chromatography ( $5 \times 11$  cm) and eluted with methanol in chloroform (6%). The appropriate fractions were collected and evaporated to dryness to give **3a** (0.075 g, 43.9%): mp dec above  $190^\circ\text{C}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  9.04 (s, 1H), 8.36 (s, 1H), 8.34 (s, 1H), 6.01 (d,  $J = 7.54$  Hz, 1H), 5.58 (d, 1H), 5.48 (t, 1H), 5.35 (d, 1H), 4.54 (m, 1H), 4.19 (m, 1H), 4.07 (m, 1H), 3.81 (m, 2H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  151.71, 146.32, 139.67, 126.86, 125.43, 124.95, 123.56, 122.28, 120.44, 114.30, 85.57, 82.39, 67.64, 65.95, 57.25; UV [ $\lambda_{\text{max}}$ , nm ( $\epsilon$ )] (MeOH) 343.2 (22500), 328.8 (16300), 247.6 (66900); MS (FAB)  $m/z$  404 (M + H, 100%); HRMS (FAB) calcd for  $m/z$  [ $\text{C}_{15}\text{H}_{12}\text{N}_3\text{O}_4\text{Cl}_3 + \text{H}$ ] $^+$  403.9972, found 404.0001. Anal. ( $\text{C}_{15}\text{H}_{12}\text{Cl}_3\text{N}_3\text{O}_4 \cdot \text{H}_2\text{O}$ ) C, H, N.

**2-Benzylthio-6,7-dichloro-1-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline (3c).** Benzyl bromide (0.075 mL, 6.3 mmol) was added to a solution of 6,7-dichloro-1-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline-2-thione (**12**; 125 mg, 0.31 mmol) in methanol (9 mL) in the presence of concentrated ammonium hydroxide (0.5 mL) and stirred at room temperature for 1 h to give a white suspension. The solid was collected by filtration and washed with a small amount of methanol. The solid was redissolved in ethyl acetate (100 mL) which was washed sequentially with a saturated ammonium chloride solution (20 mL), water (20 mL), and a saturated sodium chloride solution (10 mL) and then dried over anhydrous sodium sulfate. Evaporation of the solvent gave a white solid which was recrystallized from ethanol (4 mL) to give **3c** (0.109 g, 71.3%) as white needles: mp  $208\text{--}210^\circ\text{C}$ ; UV [ $\lambda_{\text{max}}$ , nm ( $\epsilon$ )] (MeOH) 356.4 (31200), 270.2 (40400), 234.0 (53500), 204.0 (20900). Anal. ( $\text{C}_{22}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_4\text{S} \cdot \text{H}_2\text{O}$ ) C, H, N.

**6,7-Dichloro-2-cyclopropylamino-1-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline (3d).** Chlorine in carbon tetrachloride (0.676 M, 1.45 mL, 1.0 mmol) was added dropwise to a solution of 6,7-dichloro-1-(2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline-2-thione (**11**; 0.35 g, 0.5 mmol) in dry dichloromethane (40 mL) at  $-78^\circ\text{C}$ . The reaction solution was stirred for an additional 2 h at  $-78^\circ\text{C}$  and then diluted with chloroform (100 mL). The solution was washed sequentially with a mixture of a saturated sodium chloride solution and a saturated sodium bicarbonate solution ( $3 \times 50$  mL, 1/1), water (50 mL), and a saturated sodium chloride solution (20 mL) and then dried over anhydrous sodium sulfate. The solution was concentrated to about 50 mL. A small amount of 4 Å molecular sieves and cyclopropylamine (0.34 mL, 5 mmol) were added to the solution. The mixture was stirred at room temperature for 3 days. The molecular sieves were removed by filtration through Celite and the solid paste was washed with chloroform. This filtrate was then washed with a saturated sodium bicarbonate solution ( $2 \times 20$  mL) and a saturated sodium chloride solution (10 mL) and then dried over anhydrous sodium sulfate. The solvent was evaporated and the resulting solid was subjected to silica gel flash chromatography ( $2 \times 10$  cm). The column was eluted by 1% methanol in chloroform to give compound **13** (0.24 g, 66.7%) as a slightly yellow solid. This compound (0.24 g) was stirred in saturated methanolic ammonia (120 mL) at room temperature for 24 h. The solvent was evaporated and the solid was triturated with hot hexane ( $3 \times 30$  mL). The hexane was decanted and the resulting solid was subjected to silica gel flash chromatography ( $3 \times 5$  cm). The column was eluted by 1% to 10% methanol in chloroform to give **3d** (0.122 g, 88.4%) as a white solid: mp  $192\text{--}194^\circ\text{C}$ ; UV [ $\lambda_{\text{max}}$ , nm ( $\epsilon$ )] (MeOH) 355.6 (25200), 340.0 (18700, shoulder), 264.8 (39700), 229.8 (39800). Anal. ( $\text{C}_{18}\text{H}_{18}\text{Cl}_2\text{N}_4\text{O}_4 \cdot 0.25\text{H}_2\text{O}$ ) C, H, N.

**6,7-Dichloro-2-isopropylamino-1-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline (3e).** Using the same procedure as for **3d** but with isopropylamine, compound **11** (0.305 g, 0.43 mmol) was converted into **3e** (0.1 g, 37% overall) as a white solid: mp dec above  $240^\circ\text{C}$ ; UV [ $\lambda_{\text{max}}$ , nm ( $\epsilon$ )] (MeOH) 357.6

(29200), 342.0 (23100, shoulder), 265.8 (46000), 258.0 (47300). Anal. ( $\text{C}_{18}\text{H}_{20}\text{Cl}_2\text{N}_4\text{O}_4 \cdot \text{H}_2\text{O}$ ) C, H, N.

**6,7-Dichloro-1-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline (3f).** Compound **12** (0.145 g) was treated with W-4 Raney nickel (see procedure for **2f**) to give **3f** (0.035 g, 26%) as a slightly yellow solid: mp  $138\text{--}140^\circ\text{C}$ ; UV [ $\lambda_{\text{max}}$ , nm ( $\epsilon$ )] (MeOH) 341.4 (15000), 331.4 (13400), 243.8 (63200). Anal. ( $\text{C}_{15}\text{H}_{13}\text{Cl}_2\text{N}_3\text{O}_4 \cdot 0.5\text{H}_2\text{O}$ ) C, H, N.

**6,7-Dichloro-3-(2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline-2-thione (16).** Using the same procedure as for **11**,  $\text{POCl}_3$  (1.2 mL, 12.9 mmol) was added in one portion to a solution of triazole (3.86 g, 55.9 mmol) in dry acetonitrile (150 mL) to give a white suspension. The suspension was then cooled in an ice bath and triethylamine (8.39 mL, 60.2 mmol) was added dropwise. The suspension was brought to room temperature and compound **17** (**14** (1.5 g, 2.15 mmol) was added to give **16** (1.44 g, 94%) as a slightly yellow solid. Anal. ( $\text{C}_{36}\text{H}_{25}\text{Cl}_2\text{N}_3\text{O}_7\text{S} \cdot \text{H}_2\text{O}$ ) C, H, N.

**6,7-Dichloro-3-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline-2-thione (17).** Compound **16** (0.4 g, 0.56 mmol) was stirred with sodium methoxide (0.106 g 1.96 mmol) in methanol (90 mL) at room temperature for 5 h. Acetic acid (0.11 mL, 1.96 mmol) was added and the reaction was stirred for another 10 min. The solvent was removed by evaporation and the residue was redissolved in saturated methanolic ammonia (50 mL) and evaporated to dryness again. The solid was dried under vacuum (0.01 mmHg/ $78^\circ\text{C}$ ) overnight. The solid was then triturated with water ( $2 \times 100$ ), collected by filtration, and washed with water. The solid was dried under vacuum at  $78^\circ\text{C}$  to give **17** (0.23 g, quantitative) as a slightly yellow solid. A small sample was recrystallized from ethanol for analysis: mp dec above  $200^\circ\text{C}$ . Anal. ( $\text{C}_{15}\text{H}_{13}\text{Cl}_2\text{N}_3\text{O}_4\text{S} \cdot \text{H}_2\text{O}$ ) C, H, N.

**2,6,7-Trichloro-3-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline (4a).** Chlorine in carbon tetrachloride (1.3 M, 0.67 mL, 0.86 mmol) was added to a solution of **4c** (141 mg, 0.29 mmol) in a mixture of dry tetrahydrofuran (25 mL) and dry methanol (11 mL) at  $-78^\circ\text{C}$ . The reaction was stirred at  $-78^\circ\text{C}$  for 1 h. Another portion of chlorine in carbon tetrachloride (1.3 M, 0.44 mL, 0.57 mmol) was added and the reaction was stirred at  $-78^\circ\text{C}$  for an additional hour to give a clear colorless solution. The solution was then diluted with ethyl acetate (200 mL), washed sequentially with a mixture of a saturated sodium chloride solution and a saturated sodium bicarbonate solution ( $2 \times 100$  mL, 1/1) and a saturated sodium chloride solution (40 mL), and then dried over anhydrous sodium sulfate. The solvent was removed and the residue was then subjected to silica gel flash chromatography ( $5 \times 6$  cm) and eluted by methanol in chloroform (3%). The appropriate fractions, as identified by TLC, were collected and evaporated to give a solid (63 mg) which was recrystallized from ethanol (2.5 mL) to give **4a** (53.5 mg, 46%) as a white solid: mp dec above  $170^\circ\text{C}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  8.75 (s, 1H), 8.54 (s, 1H), 8.24 (s, 1H), 6.04 (d,  $J = 6.44$  Hz, 1H), 5.53 (d,  $J = 5.94$  Hz, 1H), 5.31 (d,  $J = 4.80$  Hz, 1H), 5.27 (m, 1H), 5.18 (dd,  $J = 4.81, 7.07$  Hz, 1H), 4.35 (m, 1H), 4.02 (m, 1H), 3.81 (m, 1H), 3.62 (m, 1H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  148.91, 147.99, 142.48, 134.36, 131.75, 129.64, 128.24, 127.29, 125.34, 124.79, 89.44, 86.35, 70.69, 70.34, 61.93; HRMS  $m/z$  calcd for  $\text{C}_{15}\text{H}_{12}\text{N}_3\text{O}_4\text{Cl}_3$  402.9893, found 402.9873; MS  $m/z$  403 ( $\text{M}^+$ , 1.4%); UV [ $\lambda_{\text{max}}$ , nm ( $\epsilon$ )] (MeOH) 344.0 (10800), 330.8 (14900), 316.6 (13300), 246.8 (63200). Anal. ( $\text{C}_{15}\text{H}_{12}\text{Cl}_3\text{N}_3\text{O}_4 \cdot \text{H}_2\text{O}$ ) C, H, N.

**2-Benzylthio-6,7-dichloro-1-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline (4c).** Benzyl bromide (0.15 mL, 1.2 mmol) was added to a solution of **17** (0.25 g, 0.6 mmol) in methanol (25 mL) in the presence of concentrated ammonium hydroxide (about 20 drops). The reaction was stirred at room temperature for 4 h to give a white suspension. The suspension was concentrated to about 3 mL and then diluted with ethyl acetate (150 mL). The reaction mixture was washed with a saturated sodium bicarbonate solution ( $2 \times 50$  mL), water (40 mL), and a saturated sodium chloride solution (20 mL) and then dried over anhydrous sodium sulfate. The solvent was evaporated and the solid was dried under  $0.01$  mmHg/ $78^\circ\text{C}$  to give **4c** (0.3 g, quantitative) as a white solid. A small amount of sample

(80 mg) was recrystallized from ethanol (15 mL) for analysis: mp dec above 200 °C; UV [ $\lambda_{\max}$ , nm ( $\epsilon$ )] (MeOH) 372.0 (6820), 353.0 (36900), 337.4 (25300), 267.6 (39700), 232.6 (54900). Anal. (C<sub>22</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>4</sub>S·H<sub>2</sub>O) C, H, N.

**6,7-Dichloro-2-cyclopropylamino-3-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline (4d).** Using a procedure similar to that used for the preparation of **3d**, compound **16** (0.2 g, 0.28 mmol) was converted into **4d** for a total combined yield of **4d** of 84% from **16** in three steps: mp dec above 190 °C; UV [ $\lambda_{\max}$ , nm ( $\epsilon$ )] (MeOH) 351.6 (23200), 335.0 (15900, shoulder), 262.6 (38800), 229.6 (39000). Anal. (C<sub>18</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>4</sub>·0.5H<sub>2</sub>O) C, H, N.

**6,7-Dichloro-2-isopropylamino-3-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline (4e).** POCl<sub>3</sub> (0.16 mL, 1.7 mmol) was added in one portion to a solution of triazole (0.52 g, 7.5 mmol) in dry acetonitrile (17 mL) to give a white suspension. The suspension was then cooled in an ice bath and triethylamine (1.12 mL, 8.03 mmol) was added dropwise. The suspension was brought to room temperature and compound **14** (0.2 g, 0.29 mmol) was added. The suspension was then stirred at room temperature for 24 h to give another white suspension which was diluted with dry dichloromethane (15 mL) to give a clear brown solution. Isopropylamine (4 mL) was then added and the reaction solution was stirred at room temperature for 9 h. The solvent was evaporated and the residue was subjected to silica gel chromatography (5 × 8 cm). The column was eluted by chloroform. The appropriate fractions were collected and the solvent was evaporated to give 6,7-dichloro-2-isopropylamino-3-(2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline (0.202 g) as a syrup. This syrup (0.202 g) was deprotected by a procedure similar to that used for **3d** to provide a total yield of **4e** of 58% from **14** in three steps: mp dec above 220 °C; UV [ $\lambda_{\max}$ , nm ( $\epsilon$ )] (MeOH) 353.4 (26700), 340.2 (19800), 264.6 (44900), 229.0 (42600). Anal. (C<sub>18</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>4</sub>·H<sub>2</sub>O) C, H, N.

**6,7-Dichloro-3-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*b*]quinoline (4f).** Compound **17** (80 mg.) was treated with W-4 Raney nickel using a procedure similar to that used for **2f** to give **4f** (37 mg, 52%) as a white solid: UV [ $\lambda_{\max}$ , nm ( $\epsilon$ )] (MeOH) 346.0 (19000), 332.2, (19800), 318.0 (19400), 243.6 (108000). Anal. (C<sub>15</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>4</sub>·H<sub>2</sub>O) C, H, N.

**Biological Methods. Cell culture and virological procedures:** The routine growth and passage of KB, BSC-1, and HFF cells was performed in monolayer cultures as detailed previously.<sup>21</sup> The Towne strain, plaque-purified isolate P<sub>0</sub>, 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, high-titer HSV-1, and methods for determining virus titers also have been described earlier.<sup>21,22</sup>

**Antiviral assays:** HCMV was assayed by two methods. In plaque assays, HFF cells in 24-well cluster dishes were infected with approximately 100 PFU of HCMV/cm<sup>2</sup> cell sheet, compounds dissolved in growth medium were added to duplicate wells in 4–8 selected concentrations, and drug effects were determined as detailed previously.<sup>21</sup> For yield assays, HFF cells were plated as described above in 96-well cluster dishes, incubated overnight, and inoculated with HCMV at a MOI of 0.5–1 PFU/cell, drug was added, and cultures were assayed as reported elsewhere.<sup>21,22</sup> An ELISA was employed to detect HSV-1. Ninety-six-well cluster dishes were planted with 10 000 BSC-1 cells/well and incubated overnight, selected drug concentrations in quadruplicate and HSV-1 at a concentration of 100 PFU/well were then added. Other details have been published.<sup>23</sup>

**Cytotoxicity assays:** Two different assays were used. (i) Cytotoxicity produced in stationary HFF cells was determined by microscopic inspection of cells not affected by the virus used in plaque assays.<sup>24</sup> (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.<sup>24</sup>

**Data analysis:** Dose–response relationships were used to quantitate drug effects by linearly regressing the percent

inhibition of parameters derived in the preceding assays against log drug concentrations except for yield assays in which log, log plots were used. Fifty-percent inhibitory concentrations (IC<sub>50</sub>'s) or IC<sub>90</sub>'s (yield assay) were calculated from the linear portion of regression lines. Samples containing positive controls (acyclovir for HSV-1, ganciclovir for HCMV, and 2-acetylpyridine thiosemicarbazone for cytotoxicity) were used in all assays.

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**Supporting Information Available:** Additional experimental data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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