Synthesis and Anti-Herpes Virus Activity of 2′-Deoxy-4′-thiopyrimidine Nucleosides

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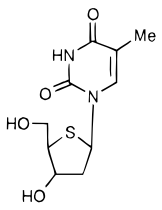
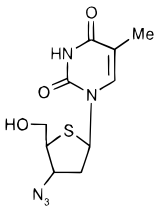
A series of 5-substituted 2′-deoxy-4′-thiopyrimidine nucleosides was synthesized and evaluated as potential antiviral agents. A number of analogues such as 2′-deoxy-5-propyl-4′-thiouridine (**3ii**), 2′-deoxy-5-isopropyl-4′-thiouridine (**3iii**), 5-cyclopropyl-2′-deoxy-4′-thiouridine (**3iv**), 2′-deoxy-4′-thio-5-vinyluridine (**3viii**), and 5-(2-chloroethyl)-2′-deoxy-4′-thiouridine (**3xx**) were found to be highly active against herpes simplex virus type-1 (HSV-1) and varicella zoster virus (VZV) *in vitro* with no significant cytotoxicity. The compound with the broadest spectrum of activity was 2′-deoxy-5-ethyl-4′-thiouridine (**3i**) which showed significant activity against HSV-1, HSV-2, and VZV.

The susceptibility of 2′-deoxynucleosides to degradation by nucleoside phosphorylases, thus limiting their biological activity, has been recognized for some time. Furthermore, chemical modification, such as replacement of the 4′-oxygen by a methylene group, has given rise to carbocyclic nucleosides which are resistant to such degradation and which are highly active as anticancer and antiviral agents.[1] Replacement of the 4′-oxygen by sulfur has also conferred resistance to nucleoside cleavage as in the case of 4′-thioadenosine[2] and 4′-thioinosine[3] and other 4′-thioribonucleosides have shown biological activity, particularly as anticancer agents.[2,4−8]

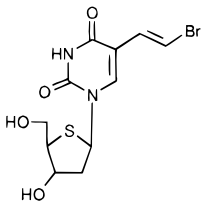
Examples of 2′-deoxy-4′-thionucleosides have been scarce in the literature with 2′-deoxy-5-fluoro-4′-thiouridine,[9] 4′-thiothymidine (4′-S-Thd)[10,11] (*E*)-5-(2-bromovinyl)-2′-deoxy-4′-thiouridine (4′-S-BVDU),[10−12] and the nucleosides of the other naturally occurring pyrimidine bases[13] being the few analogues reported. The



4′-S-Thd



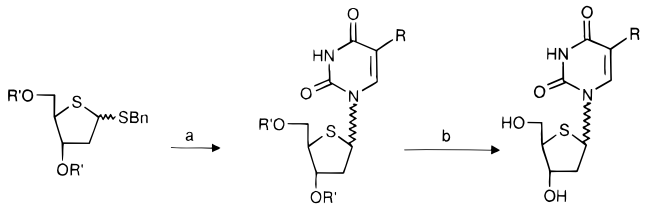
4′-S-AZT



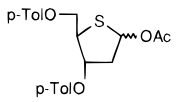
4′-S-BVDU

analogues of the naturally occurring bases were found to be cytotoxic at different levels to a variety of cell lines and 4′-S-Thd was claimed to have antiviral activity against herpes simplex virus type 1(HSV-1) and human cytomegalovirus (HCMV).[13] However, it is likely that this activity is due to the severe cytotoxicity of the compound in the cell lines used and is not an intrinsic effect. Recently synthesized 4′-S-BVDU was found to be highly active against HSV-1, HSV-2, and varicella zoster virus (VZV).[12] We have also reported the synthesis of 3′-azido-3′-deoxy-4′-thiothymidine (4′-S-AZT), the 4′-thio analogue of the anti-human immunodeficiency virus agent, 3′-azido-3′-deoxythymidine, which, interestingly, has appeared inactive against this virus.[12] Two other groups have subsequently described the synthesis of 4′-S-AZT but no biological data was provided.[13,14] To fulfill the need for further analogues in this relatively unexplored area, we have embarked on a program to synthesize a wide range of 2′-deoxy-4′-thiopyrimidine nucleosides with a variety of substituents at the C-5 position. This has been made possible due to the ready access of a key thiosugar starting material.[16]

Scheme 1[a]



1a R'= Benzyl
1b R'= Acetyl
1c R'= Pivaloyl
1d R'= p-Toluoyl
1e R'= p-Nitrobenzoyl



1f

[a] a: Sugar/base condensation (see text);

b: R' =Bn: BCl_3, CH_2Cl_2, -78°C; R'= acyl: NaOMe, MeOH

Chemistry

In our recent reports[11,12] we described the synthesis of 4′-S-Thd by a coupling reaction of benzyl 3,5-di-*O*-benzyl-2-deoxy-1,4-dithio-D-*erythro*-pentofuranoside (**1a**)[16] with 2,4-bis-*O*-(trimethylsilyl)-5-methyluracil in the presence of mercuric bromide and cadmium carbonate according to the method of Horton and Markovs[17] (Scheme 1, R = CH=CHBr). For the synthesis of

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Table 1. Compounds Synthesized Using Sugar/Base Condensation

compd	R	anomer comp	sugar used	uracil ref	mp, °C	^{1}NMR H-6 (ppm)	MS: mol ion	anal.
3i	Et	α[c]	**1a**	20		8.12	M + 272	CHN
	Et	β[c]	**1a**	20	205−7	7.77	M + 272	CHN
3iii	*i*-Pr	β	**1a**	21	164−6	7.78	MH + 287	CHN
3iv	c-Pr	β	**1a**	21	183−4	7.67	MH + 285	C[o]HN[p]
3v	CH(Me)Et[a]	α/β[d]	**1b**	22		7.76(d);8.1	M + 300	CHN
3vi	*t*-Bu	β	**1a**	21	140−2	7.73	MH + 301	CHN
3vii	adamantyl	β	**1a**	21	196−7	7.59	M + 378	
3x	(*E*)-CH=CHMe	β[c]	**1f**	I	170−5	8.03	M + 284	
3xi	ethynyl	β[c,e]	**1f**	23	>195[b]	8.4	M + 268	
3xii	propynyl	β[c,e]	**1f**	24	265d	8.2	M + 282	
3xiii	CH_2CH_2OMe	β	**1a**	25	133−5	7.85	MH + 303	
3xiv	CH(OH)Me[a]	α/β[f]	**1f**	26		7.8(s); 8.2(d)	M + 288	CHN
3xviii	CF_3	α	**1e**		194−5	8.99	M + 312	CHN
	CF_3	β	**1e**		220−2	8.83	M + 312	CHN
3xix	CH_2CH_2F	β	**1f**	27	192−5	7.9	M + 290	CHN
3xx	CH_2CH_2Cl	α/β[g]	**1f**	28		7.93;8.2	M + 306	CHN
3xxi	CH_2CF_3	β	**1b**	m	158−9	8.14	MH + 327	CHN
3xxii	$CH=CF_2$	β	**1e**	29	168−9	8.12	M + 306	CHN
3xxiii	(*E*)-CH=CHCl	β	**1f**	30	219[b]	8.18	MH + 305	
3xxiv	$CF=CCl_2$	β	**1a**	31		8.65	M + 357	
3xxv	CH_2SMe	α/β[h]	**1c**	32		7.94; 8.22	MH + 305	CHN
3xxvi	OMe	α/β[i]	**1f**	33	90	7.63; 8.02	M + 274	
3xxvii	F	α/β[c,j]	**1f**		181−2	8.25; 8.37	M + 262	
3xxix	Br	β	**1e**		221−4	8.49	MH + 324	CHN
3xxx	I	β[c,e]	**1a**		225−6	8.48	M + 370	CHN
3xxxi	CN	β[c,e]	**1f**		>197[b]	9.03		
3xxxii	NO_2	α[c]	**1f**			9.8	K	
	NO_2	β[c]	**1f**		*n*	9.54	K	
3xxxiii	5,6-$[CH_2]_3$	α/β[c,k]	**1f**	34	*n*	N/A	MH + 285	

[a] Diastereoisomeric mixture. [b] Decomposed on melting. [c] Anomeric composition confirmed by reversed-phase HPLC. [d] 1.4:1 α/β. [e] Contains <5% α-anomer. [f] 1:1 α/β. [g] 1.25:1 α/β. [h] 0.4:1 α/β. [i] 1.4:1 α/β. [j] 1.2:1 α/β. [k] EI MS fragmentation consistent with structure. [l] See Experimental Section for synthesis. [m] 5-(2,2,2-Trifluoroethyl)uracil was prepared according to an analogous procedure to that in ref 16 starting with ethyl 4,4,4-trifluorobutanoate. [n] Freeze-dried solid. [o] C: calcd, 50.69; found, 49.9. [p] N: calcd, 9.85; found, 9.3.

additional analogues, we have modified this methodology and replaced the mercury and cadmium reagents with alternative thiophilic promoters such as *N*-bromo- or *N*-iodosuccinimide in the presence of molecular sieves, as exemplified by Sugimura and co-workers,[18,19] but using acetonitrile as solvent instead of dichloromethane. In some cases where R′ was an acyl group such as acetyl (**1b**), pivaloyl (**1c**), *p*-toluoyl (**1d**),[12] or *p*-nitrobenzoyl (**1e**), the *N*-iodosuccinimide/trimethylsilyl trifluoromethanesulfonate system[19] was found to be more effective. These reagents allowed the use of milder conditions accompanied by faster reactions and cleaner product mixtures. The ester-protected sugars such as benzyl 2-deoxy-3,5-di-*O*-*p*-toluoyl-1,4-dithio-D-*erythro*-pentofuranoside (**1d**) and its *p*-nitrobenzoyl derivative (**1e**) were obtained by boron trichloride-mediated debenzylation of **1a** in dichloromethane at −78 °C followed by acylation of the resulting diol with the appropriate acyl chloride in pyridine.

In other instances where 1-acetyl-2-deoxy-3,5-di-*O*-*p*-toluoyl-4-thio-D-*erythro*-pentofuranoside (**1f**)[15] was used, glycosylation was carried out under standard Lewis acid-catalyzed conditions in the presence of trimethylsilyl trifluoromethanesulfonate in acetonitrile. The thiosugar **1f** was generated by treatment of **1d** with mercuric acetate in acetic acid. The anomeric ratios of the coupled nucleosides, **2**, were typically 2:1 α/β. Deprotection of **2** was carried out either with boron trichloride in dichloromethane at −78 °C (R′ = Bn) or sodium methoxide in methanol (R′ = acyl). The required β-nucleoside (**3**) was obtained by fractional crystallization or chromatographic separation of **2** or its deprotected product. In cases where total separation could not be achieved, the desired product was tested as an anomeric mixture. The compounds synthesized by this method together with their physical data are listed in Table 1. The 5-substituted uracils used were commercially available or were generated according to literature procedures as indicated in Table 1, which also shows the starting thiosugars. In cases where the preformed uracil bases were not available, the required 5-substituted nucleosides were prepared by appropriate modification or functionalization at C-5 of a β-nucleoside precursor. The compounds prepared by this method are listed together with their physical properties in Table 2. Standard room temperature catalytic hydrogenation of 2′-deoxy-5-propynyl-4′-thiouridine (**3xii**) with 5% Pd/C readily afforded the 5-propyl analogue, **3ii**. An excess of catalyst was used to overcome poisoning by the sulfur of the thiosugar. 5-Acetyl-2′-deoxy-4′-thiouridine (**3xvii**) was obtained as a hydrolysis byproduct during purification of a sample of 2′-deoxy-5-ethynyl-4′-thiouridine (**3xi**) (Scheme 2).

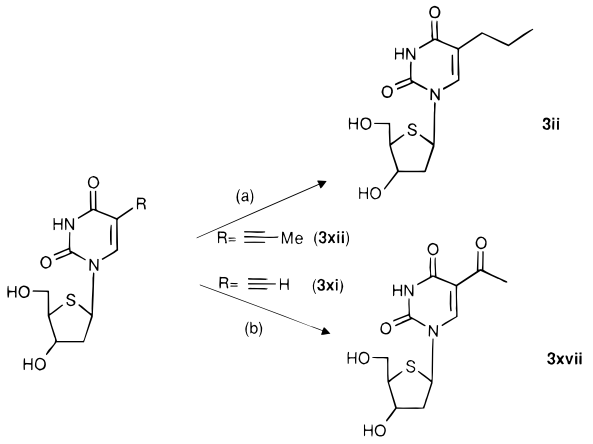
For the synthesis of the 2′-deoxy-5-(methoxymethyl)-4′-thiouridine (**3xv**), 5-(chloromethyl)uracil[32] was condensed with the thiosugar, **1f**, as above. Deprotection

Table 2. Compounds Synthesized from Thionucleoside Starting Materials

compd	R	anomer comp	^{1}NMR H-6 (ppm)	MS: mol ion	anal.
3ii	*n*-Pr	β[a]	7.78	M + 286	
3viii	$CH=CH_2$[f]	β	8.19	MH + 271	CHN
3ix	$C(=CH_2)Me$	β	8.03	M + 284	CHN
3xv	CH_2OMe	1.3:1[a,b]	8.0; 8.29	M + 288	
3xvi	CH(OMe)Me[c]	1:4.5[a,d]	7.9; 8.28	M + 302	CHN
3xvii	COMe	1:10[a,e]	8.71; 9.15	*h*	
3xxviii	Cl[g]	β	8.42	M + 278	CHN

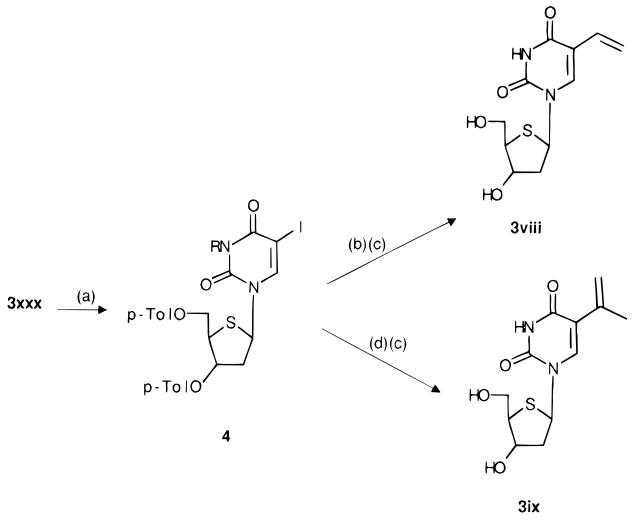
[a] Anomeric composition confirmed by reversed-phase HPLC. [b] α/β 1.3:1. [c] Diastereoisomeric mixture. [d] α/β 1:4.5. [e] α/β 1:10. [f] mp 246 °C. [g] mp 221−222 °C. [h] EI MS fragmentation consistent with structure.

Scheme 2[a]



[a] (a) H_2, 5% Pd/C, MeOH, r.t.; (b) Hydrolysis

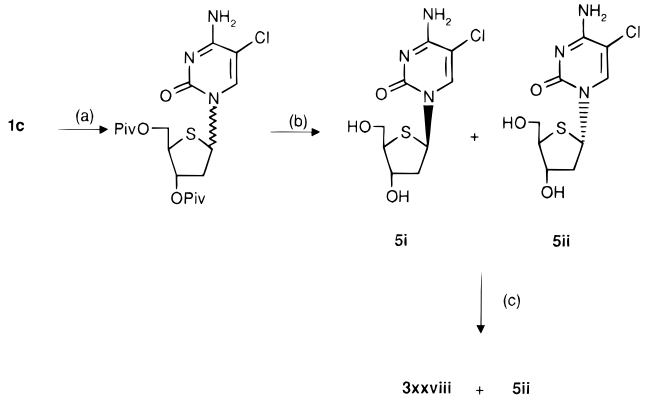
Scheme 3[a]



[a] (a) P-Toluoylchloride, pyridine, N,N-dimethylaminopyridine, 0°C-r.t.; (b) $(CH_2{=}CH)_4Sn$, $(PPh_3)_4Pd$, HMPA, 60-75°C; (c) NaOMe, MeOH, r.t.; (d) $Me(C{=}CH_2)SnMe_3$, $(PPh_3)_4Pd$, HMPA, 100°C.

of the intermediate nucleoside, **2** (R = CH_2Cl; R′ = *p*-toluoyl) with sodium methoxide in methanol, also resulted in concomitant chloride substitution to give the required methoxymethyl product. Using organotin methodology as developed by Herdewijn and co-workers for the synthesis of thymidine from 5-iodo-2′-deoxyuridine,[35] 2′-deoxy-4′-thio-5-vinyluridine (**3viii**) and 2′-deoxy-5-isopropenyl-4′-thiouridine (**3ix**) were prepared analogously from 2′-deoxy-5-iodo-4′-thiouridine (**3xxx**) via its 3′,5′-bis-toluoylated intermediate, **4** (Scheme 3). Interestingly, while it was found necessary to acylate the 3-N position of **4** (R = *p*-toluoyl) for the synthesis of **3viii** to avoid complex mixtures, the synthesis of **3ix** was performed without 3-N protection (R = H). Deprotection of the coupling product between **4** (R = H) and isopropenyltrimethyltin with sodium methoxide gave a relatively low yield of the required compound, the major byproduct being 4′-thiothymidine (4′-S-Thd). Presumably this resulted from methyl abstraction from the same tin reagent in the high-temperature coupling reaction. This reagent was generated according to the literature synthesis of trimethylphenylstannanes[36] from

Scheme 4[a]



[a] (a) Silylated 5-chlorocytosine, N-iodosuccinimide, TMSOTf, ACN, r.t.; (b) n-$Bu_3N^+OH^-$, MeOH; (c) Cytidine deaminase, H_2O, 37°C

isopropenylmagnesium bromide and trimethyltin bromide in refluxing ether. The methyl ether, 2′-deoxy-5-(1-methoxyethyl)-4′-thiouridine (**3xvi**) was prepared as a 1:1 diastereoisomeric mixture by standard methylation of 2′-deoxy-3′,5′-di-*O*-*p*-toluoyl-5-(1-hydroxymethyl)-4′-thiouridine, **2** (R = CH(OH)Me, R′ = *p*-toluoyl), with methanol in the presence of *p*-toluenesulfonic acid followed by deprotection with sodium methoxide. Finally, to obtain 5-chloro-2′-deoxy-4′-thiouridine (**3xxviii**) in pure β-anomeric form, a useful method of synthesis was developed which avoids unpredictable fractional recrystallization or column chromatography for achieving anomer separation.

5-Chlorocytosine[37] was silylated and condensed with benzyl 2-deoxy-3′,5′-di-*O*-pivaloyl-1,4-dithio-D-*erythro*-pentofuranoside (**1c**) to give, after deprotection, 5-chloro-2′-deoxy-4′-thiocytidine as an anomeric mixture (**5i** and **5ii**) (Scheme 4). Deamination of this mixture with cytidine deaminase at 37 °C afforded the required β-uridine (**3xxviii**) and the unreacted α-cytidine (**5ii**) which were easily separated by column chromatography and recrystallization from methanol. Since this process takes advantage of the differential rate of deamination between the two anomers, allowing the reaction to proceed for prolonged periods of time caused partial deamination of the α-cytidine, **5ii**, as well.

Biological Evaluation

The antiviral activity and cytotoxicity of the 5-substituted thionucleosides synthesized are presented in Table 3.

In general, the activities of the pure β-anomers are quoted but in some cases, where the anomer separation was not achieved, the activity of an α/β mixture is given. However, the activities of the examples of pure α anomers obtained were found to be significantly less than their β counterparts, paralleling results obtained in the normal oxygen series. Therefore, the activities observed for the anomer mixtures most likely reside in the β component.

The 5-substituents giving the highest activity against HSV-1 and VZV include small alkyl-, substituted alkyl-, vinyl-, and 2-halovinyl groups, although some 5-substituted 2′-deoxyuridines active against HSV-1 and HSV-2 appeared less active in the 4′-thio series.

For instance, the most potent ($IC_{50} < 5\ \mu M$) and least toxic ($CCID_{50} > 500\ \mu M$) analogues against HSV-1 were

Table 3. Antiviral Activities and Cytotoxicities of 5-Substituted 2′-Deoxy-4′-thiouridines

			IC_{50}[a] (μM)				
compd	R	α/β	HSV-1	HSV-2	VZV	HCMV	$CCID_{50}$[b] (μM)
3i	Et	α		>100	>100	>100	>100
3i[c]	Et	β	0.17−0.5	2−5	0.99	138	>500
3ii	*n*-Pr	β	6.8	>10	3	>100	>100
3iii	*i*-Pr	β	2.2	>100	4.1	>100	>500
3iv	c-Pr	β	1.6	>100	0.5	>100	>500
3v	CH(Me)Et	α/β		>100		>100	>500
3vi	*t*-Bu	β		>100		>100	475
3vii	adamantyl	β	>100	>100	T40[d]	>100	>125
3viii	$CH{=}CH_2$	β	1.4	>100	1.1	93	>500
3ix	$C(=CH_2)Me$	β	3.4	>100	<40	>100	>500
3x	(*E*)-CH=CHMe	β	>2	>20	0.46	>100	>100
3xi	ethynyl	β	6.6	>10	5.5	9.3	33
3xii	propynyl	β	>100	>100	1.4	>100	492
3xiii	CH_2CH_2OMe	β		>100	>10	>100	
3xiv	CH(OH)Me	α/β	40	>100	12	>100	>500
3xv	CH_2OMe	α/β	>10	>10	>10	>100	
3xvi	CH(OMe)Me	α/β	>100	>100	>40	>100	>500
3xvii	COMe	α/β	>10	>10	>10	>100	351
3xviii	CF_3	α		>100		>100	>500
3xviii	CF_3	β	<1.6	15		>10	139
3xix	CH_2CH_2F	β	0.7	>100	0.12	>100	>500
3xx	CH_2CH_2Cl	α/β	0.15	>100	0.3		>200
3xxi	CH_2CF_3	β		>100	>40	>100	>500
3xxii	$CH{=}CF_2$	β		>100	<10	>100	>500
3xxiii	(*E*)-CH=CHCl	β	0.5	>100	>10	>100	>500
3xxiv	$CF{=}CCl_2$	β	>50		>100	>100	>500
3xxv	CH_2SMe	α/β		>100		>100	>500
3xxvi	OMe	α/β	>100	>100	>100	>100	
3xxvii	F	α/β	>10	>10	>100	>100	92
3xxviii	Cl	β	>100	>100	>40	0.2	59
3xxix	Br	β	5.3	>100	>40	0.44	>500
3xxx	I	β	0.8−1	10	3.5	4	>100
3xxxi	CN	β	>100	>100	>100	>100	>500
3xxxii	NO_2	α	>100	>100	>100		
3xxxii	NO_2	β	18	27	9−13		476
3xxxiii	5,6-$[CH_2]_3$	α/β		>100	>40	>100	>500
BVDU		β	1.4	10.0	<1	>100	>250
acyclovir[e,f]			1.8	1.7	46.8	85	>500
pencyclovir[e,g]			3.9	12.8	78.7	>100	

[a] Minimum inhibitory concentration (μM) required to reduce the number of virus plaques by 50%. [b] Inhibitory dose required to reduce the growth of Vero cells by 50% over a 4 day period. HSV-1 and HSV-2 assays were carried out in Vero or MRC-5 cells while VZV and HCMV assays were carried out in MRC-5 cells. [c] IC_{50}'s in MRC-5 cell line: HSV-1 0.15 μM HSV-2 1.12 μM, $CCID_{50}$ >500 μM. [d] Unable to calculate an IC_{50} value due to severe toxicity in the virus assay at 40 μM. [e] Average for a range of clinical isolates (10 for HSV-1, 10 for HSV-2, 20 for VZV, and 5 for HCMV). [f] IC_{50}'s in MRC-5 cell line: HSV-1 0.7 μM, HSV-2 1.6 μM, $CCID_{50}$ >500 μM. [g] IC_{50}'s in MRC-5 cell line: HSV-1 2.7 μM, HSV-2 8.9 μM.

the 5-ethyl (**3i**), 5-isopropyl (**3iii**), 5-cyclopropyl (**3iv**), 5-vinyl (**3viii**), 5-isopropenyl (**3ix**), 5-(2-fluoroethyl) (**3xix**), 5-(2-chloroethyl) (**3xx**) ($CCID_{50}$ > 200 μM), and (*E*)-5-(2-chlorovinyl) (**3xxiii**) 2′-deoxy-4′-thiouridines. Furthermore, these analogues displayed similar or higher activities against HSV-1 than standard antivirals such as BVDU (IC_{50} 1.4 μM), acyclovir (IC_{50} 1.8 μM) and pencyclovir (IC_{50} 3.9 μM). Compared with their oxy counterparts,[38] the 5-fluoro (**3xxvii**), 5-chloro (**3xxviii**), 5-methoxymethyl (**3xv**), (*E*)-5-(1-propenyl) (**3x**), and 5-prop-1-ynyl (**3xii**) analogues were much less active or showed no significant activity against this virus. The compounds highly active against HSV-1 were in general also active against VZV, the exception being **3xxiii**. Activity selective for VZV was seen with the 5-propynyl nucleoside, **3xii**, which had an IC_{50} of 1.4 μM and a $CCID_{50}$ of 492 μM. The 5-ethynyl analogue, **3xi**, was somewhat less active (IC_{50} 5.5 μM) but much more toxic ($CCID_{50}$ 33 μM) although the toxicity is less severe than for the oxy analogue, 2′-deoxy-5-ethynyluridine ($CCID_{50}$ 1.6 μM).[39] Interestingly, such a reduced level of cytotoxicity associated with a 4′-thionucleoside compared with its oxy counterpart was also observed with 2′-deoxy-4′-thio-5-vinyluridine (**3viii**). This appeared to show no significant cytotoxicity in Vero cells, whereas 2′-deoxy-5-vinyluridine is known to exhibit a number of toxic properties including toxicity to murine leukemia cells.[40,41] However, the compound was nontoxic *in vivo*, an observation attributed to degradation by nucleoside phosphorylase;[41] curiously the more stable thio analogue, **3viii**, showed less cytotoxicity. Those compounds showing activity against VZV were generally more active than acyclovir (IC_{50} 46.8 μM) and pencyclovir (IC_{50} 78.7 μM), and the most potent showed equivalent activity to BVDU (IC_{50} <1 μM).

The only compound that showed significant activity against HSV-2 was 2′-deoxy-5-ethyl-4′-thiouridine (**3i**) (4′-S-EtdU) which gave an IC_{50} in the range 2−5 μM. This level of activity is equivalent to that of acyclovir (IC_{50} 1.7 μM) but higher than that of BVDU (IC_{50} 10 μM) and pencyclovir (IC_{50} 12.8 μM). Such paucity of potent activity against HSV-2 is surprising since a number of 5-substituted 2′-deoxyuridines are known to have potent activity against this virus, *e.g.* the vinyl, (2-chlorovinyl), (2-chloroethyl), and (methylthio)methyl derivatives (IC_{50} 0.2−3.0 μM).[38] A possible explanation for the reduced activity of the thionucleosides is that they may be poor substrates for the HSV-2 encoded

thymidine kinase and, hence, are not converted to phosphorylated derivatives to the extent necessary to exert an antiviral effect.

The only compounds showing reasonable activity against HCMV (IC_{50} < 5 μM) with no significant cytotoxicity ($CCID_{50}$ > 100 μM) were 5-bromo-2′-deoxy-4′-thiouridine (**3xxix**) and 2′-deoxy-5-iodo-4′-thiouridine (**3xxx**). The anti-HCMV activity by the 5-ethynyl (**3xi**) and 5-Cl (**3xxviii**) analogues is almost certainly due to their cytotoxicity, as exemplified in Vero cells.

The development of this new series of 4′-thiopyrimidine nucleosides has produced a number of analogues with potent *in vitro* antiviral activity, particularly against HSV-1, HSV-2, and VZV coupled with relatively low levels of cytotoxicity in Vero cells. Some of these compounds, particularly those with higher activities than BVDU, acyclovir or pencyclovir, have potential as clinically useful chemotherapeutic agents. However, the realization of this potential depends upon further extensive biological evaluation to establish safety and efficacy *in vivo*.

Experimental Section

General Procedures. *N*-Bromo- and *N*-iodosuccinimide, trimethylsilyl trifluoromethanesulfonate, 1 M solution of boron trichloride in dichloromethane, mercuric acetate, isopropenyl bromide, and trimethyltin bromide were purchased from Aldrich Chemical Company. Cytidine deaminase with a specific activity of 102 units/mg (isolated and purified from *Escherichia coli*) was used as an aqueous suspension at a concentration of 2550 units/mL. Acetonitrile was dried by refluxing and distilling from calcium hydride; dichloromethane, by refluxing and distilling from phosphorus pentoxide. Anhydrous methanol was prepared by the magnesium drying procedure, and ether was dried by storing over freshly prepared sodium wire. Thin-layer chromatography was performed on E. Merck 60 F254 no. 5719 glass-backed plates eluting with methanol/dichloromethane or ethyl acetate/cyclohexane solvent mixtures with sample detection under short-wave UV light. Flash column chromatography was conducted using E. Merck silica gel 60 (230−400 mesh). High-field ^{1}H NMR spectra were obtained on a Brucker 200 MHz, AC300 (300 MHz), or AMX400 (400 MHz) spectrometer in d_6-DMSO or $CDCl_3$ relative to an internal tetramethylsilane reference. Electron impact mass spectra were recorded on a Kratos Concept 1S spectrometer and FAB mass spectra were recorded on Kratos MS50 or MS80 spectrometers using 3-nitrobenzyl alcohol or thioglycerol matrices. Melting points were obtained using a Gallenkamp or Electrothermal apparatus.

Benzyl 2-Deoxy-3,5-di-*O*-*p*-toluoyl-1,4-dithio-D-*erythro*-pentofuranoside (1d). To a stirred 1 M solution of boron trichloride (100 mL, 100 mmol) in dichloromethane at −78 °C under nitrogen was added a solution of benzyl 3,5-di-*O*-benzyl-2-deoxy-1,4-dithio-D-*erythro*-pentofuranoside (**1a**) (10 g, 22.9 mmol) in 50 mL of dichloromethane over 25 min and stirring was maintained at −78 °C for 4.5 h. The mixture was then quenched by the slow addition of 100 mL of a 1:1 mixture of methanol and concentrated ammonium hydroxide. After allowing the mixture to warm up to room temperature, the aqueous phase was separated and extracted with 4 × 300 mL of dichloromethane. The organic phases were then combined, dried (sodium sulfate), and evaporated to dryness. The residue was dissolved in 50 mL of dry pyridine, treated at 0 °C with *p*-toluoyl chloride (7.3 mL, 55 mmol), stirred at 0 °C for 15 min and then room temperature overnight. The solution was quenched with *N*,*N*-dimethylethylenediamine (7.5 mL, 68.1 mmol) in 200 mL of dichloromethane with external cooling; the mixture was washed with 200 mL of 2 N hydrochloric acid, 200 mL of saturated sodium carbonate solution, and 200 mL of water, dried, and evaporated to dryness. Residual pyridine was coevaporated with toluene and the remaining residue was purified by silica gel column chromatography eluting with 7% ethyl acetate/cyclohexane to give the title compound (**1a**): (7.9 g; 70%; ^{1}NMR ($CDCl_3$) 2.6−2.3 (m, 2H, H-2), 2.35 (s, 3H, CH_3-Ph), 2.38 (s, 3H, CH_3Ph), 3.87 (m, 2H, PhCH_2S), 3.85−4.12 (m, 1H, H-4), 4.45−4.5 (m, 2H, H-5), 4.4−4.62 (m, 1H, H-1), 5.05−5.8 (m, 1H, H-3), 7.1−8 (m, 13H, aromatic H's); MS *m*/*z* 493 $(M + 1)^+$.

Benzyl 2-Deoxy-3,5-di-*O*-*p*-nitrobenzoyl-1,4-dithio-D-*erythro*-pentofuranoside (1e). This compound was prepared using an identical procedure to that used for the preparation of **1d** but using *p*-nitrobenzoyl chloride as the acylating agent: ^{1}NMR ($CDCl_3$) 2.3−2.7 (m, 2H, H-2), 3.8−4.1 (m, 3H, H-4 and S-CH_2Ph), 4.35−4.6 (m, 3H, H-1 and H-5), 5.6−5.8 (m, 1H, H-3), 7.1−7.4 (m, 6H, aromatic H), and 8.0−8.3 (m, 7H, aromatic H); MS *m*/*z* 554 M^+.

Condensation Reaction with *N*-Iodosuccinimide Catalysis. 1-(3,5-Di-*O*-benzyl-2-deoxy-4-thio-β-D-*erythro*-pentofuranosyl)-5-ethyluracil (2β, R = ethyl; R′ = Benzyl) and 1-(3,5-Di-*O*-benzyl-2-deoxy-4-thio-α-D-*erythro*-pentofuranosyl)-5-ethyluracil (2α, R = Ethyl; R′ = benzyl). To a suspension of 5-ethyluracil (1.57 g, 11.2 mmol) in hexamethyldisilazane (30 mL) were added chlorotrimethylsilane (0.3 mL, 2.4 mmol) and ammonium sulfate (0.003 g) and the mixture was heated at reflux for 2 h. The resulting clear solution was evaporated to remove all volatiles, and the remaining clear syrup of the silylated base was taken up in 50 mL of dry acetonitrile. The solution was added to **1a** (3.97 g, 9.1 mmol) and 4A molecular sieves (0.5 g), and the mixture was stirred at room temperature for 10 min. To this was added *N*-iodosuccinimide (2.5 g, 11.1 mmol), stirring was maintained for 2 h, and the resulting dark mixture was filtered. The filtrate was diluted with 50 mL of dichloromethane, and the solution was washed with 2 × 100 mL of 10% aqueous solution of sodium thiosulfate, and the aqueous washings were back-extracted with 2 × 100 mL of dichloromethane. The combined organic phases were dried (sodium sulfate) and evaporated to dryness, and the residue was purified by silica gel column chromatography eluting with 50% ethyl acetate/cyclohexane. This afforded the title compounds **2**β and **2**α (R = ethyl; R′ = benzyl) in a ratio of 1:1.38 (3.5 g, 85% yield): ^{1}NMR ($CDCl_3$) 0.9 (t, 3H, CH_2CH_3 of α-anomer), 1.03 (t, 3H, CH_2CH_3 of β-anomer), 2.6−2.1 (m, 2H, H-2′a,b), 3.3−3.55 (m, 2H, H-5′a,b of α-anomer), 3.78−3.6 (m, 2H, H-5′a,b of β-anomer), 3.7 (m, 1H, H-4′ of β-anomer), 3.97 (m, 1H, H-4′ of α-anomer), 4.24 (m, 1H, H-3′ of β-anomer), 4.32 (m, 1H, H-3′ of α-anomer), 4.43−4.62 (m, 2H, PhCH_2), 6.36 (dd, 1H, H-1′ of α-anomer), 6.45 (t, 1H, H-1′ of β-anomer), 7.2−7.4 (m, 10H, Ph), 7.7 (s, 1H, H-6 of β-anomer), 7.91 (s, 1H, H-6 of α-anomer), 8.35 (br s, 1H, NH); MS *m*/*z* 452 M^+.

Condensation Reaction with Trimethylsilyl Trifluoromethanesulfonate Catalysis. 1-(2-deoxy-4-thio-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-5-(prop-1-ynyl)-uracil (2β, R = Prop-1-ynyl; R′ = *p*-toluoyl) and 1-(2-Deoxy-4-thio-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl)uracil (2α, R = Prop-1-ynyl; R′ = *p*-Toluoyl). To a suspension of 5-(2-prop-1-ynyl)uracil (0.112 g, 0.75 mmol) in hexamethyldisilazane (3 mL) were added chlorotrimethylsilane (1 mL, 8 mmol) and ammonium sulfate (0.002 g), and the mixture was heated at reflux for 4 h. The resulting clear solution was distilled to remove all volatiles and the remaining clear syrup of the silylated base was taken up in 6 mL of dry acetonitrile and added to **1f** (0.2 g, 0.47 mmol) in 10 mL of acetonitrile. To the resulting solution stirred at 0 °C was added trimethylsilyl trifluoromethanesulfonate (0.096 mL, 0.5 mmol), and stirring was maintained at 0 °C for 15 min. The reaction mixture was then diluted with 20 mL of dichloromethane and washed with a saturated solution of sodium bicarbonate, and the aqueous washings were back-extracted with dichloromethane. The combined organic phases were dried (sodium sulfate) and evaporated to dryness, and the residue was purified by silica gel column chromatography eluting with 60% ethyl acetate/cyclohexane. This afforded the title compounds **2**β and **2**α (R = prop-1-ynyl; R′ = *p*-toluoyl) in a ratio of 1:1.47 (0.21 g, 80% yield): ^{1}H NMR (Me_2SO-d_6) 1.93 (s, 3H, propynyl-CH_3 of α-anomer), 2.0 (s, 3H, propynyl-CH_3 of β-anomer), 2.4 (s, 6H, phenyl-CH_3), 2.3−3.1 (m, 2H, H-2′), 3.9−4.1 (m, 1H, H-4′ of α-anomer), 4.38 (m, 2H, H-5′),

4.45−4.75 (m, 1H, H-4′ of β-anomer), 5.65−5.82 (m, 1H, H-3′), 6.25−6.5 (m, 1H, H-1′), 7.25 (m, 4H, aromatic H's), 7.8−8.0 (m, 4H, aromatic H's), 8.15 (s, 1H, H-6 of β-anomer), 8.3 (s, 1H, H-6 of α-anomer), 11.65 (bs, 1H, NH); MS *m/z* 518 M^+.

Deprotection with Boron Trichloride. 2′-Deoxy-5-ethyl-4′-thiouridine (3i). To a vigorously stirred solution of the anomeric mixture **2**α/**2**β (R = ethyl, R′ = benzyl) (0.23 g, 0.51 mmol) in 10 mL of dry dichloromethane at −78 °C under nitrogen was slowly added a 1 M solution of boron trichloride (15.24 mL, 15.24 mmol) in dichloromethane, keeping the reaction temperature below −75 °C during the addition. After the addition was complete, the mixture was stirred at −78 °C for 8 h and then quenched at that temperature by the cautious addition of 30 mL of a 1:1 mixture of dry dichloromethane/methanol. The mixture was then allowed to warm slowly to ambient temperature and evaporated to dryness. The residue was purified by silica gel column chromatography eluting with 10% methanol/chloroform, and the resulting anomeric nucleoside mixture was further purified by preparative reversed-phase HPLC on a Zorbax-C_8 column eluting with 10% acetonitrile/water to give the separated anomers of the required product, **3i**. α-Anomer (0.016 g, 19% of available α-anomer): ^{1}H NMR (Me_2SO-d_6) 1.05 (t, 3H, CH_2CH_3), 2.05 (dt, 1H, H-2′), 2.25 (q, 2H, CH_2CH_3), 2.55 (m, 1H, H-2′, partially obscured by solvent), 3.45−3.7 (m, 3H, H-4′ and H-5′), 4.34 (m, 1H, H-3′), 5.00 (t, 1H, OH-5′), 5.50 (d, 1H, OH-3′), 6.2 (q, 1H, H-1′), 8.12 (s, 1H, H-6), 11.1 (bs, 1H, NH); MS *m/z* 272 M^+. Anal. ($C_{11}H_{16}N_2O_4S\cdot H_2O$) C, H, N. β-Anomer (0.023 g, 40% yield of available β-anomer): ^{1}H NMR (Me_2SO-d_6) 1.05 (t, 3H, CH_2CH_3), 2.25−2.4 (m, 4H, H-2′ and CH_2CH_3), 3.3 (m, 1H, H-4′ partially obscured by DOH), 3.62 (m, 2H, H-5′), 4.37 (m, 1H, H-3′), 5.16 (t, 1H, OH-5′), 5.24 (d, 1H, OH-3′), 6.3 (t, 1H, H-1′), 7.8 (s, 1H, H-6), 11.28 (bs, 1H, NH); MS *m/z* 272 M^+. Anal. ($C_{11}H_{16}N_2O_4S\cdot 0.3H_2O$) C, H, N.

Deprotection with Sodium Methoxide. 2′-Deoxy-5-(prop-1-ynyl)-4′-thiouridine (3xii). The anomeric mixture **2**α/**2**β (R = prop-1-ynyl, R′ = *p*-toluoyl) (0.206 g, 0.397 mmol) was dissolved in 15 mL of methanol containing sodium methoxide (0.021 g, 0.397 mmol) and kept at ambient temperature overnight. The solution was neutralized with Dowex 50 (H^+) ion-exchange resin and filtered, and the filtrate was evaporated to dryness. The resulting residue was washed with 3 × 4 mL of ether, 10 mL of hot acetone, and finally 2 × 7 mL of methanol. This gave the required compound, **3xii**, as the pure β-anomer, homogeneous by analytical reversed-phase HPLC on a Zorbax C_8 column eluting with 20% acetonitrile/water (0.03 g, 66% yield of available β-anomer): ^{1}H NMR (Me_2SO-d_6) 2.0 (s, 3H, propynyl-CH_3), 2.15 (m, 2H, H-2′), 3.3 (m, 1H, H-4′ partially obscured by DOH), 3.6 (m, 2H, H-5′), 4.3 (m, 1H, H-3′), 5.1−5.3 (m, 2H, OH-3′ and OH-5′), 6.25 (t, 1H, H-1′), 8.7 (s, 1H, H-6), 11.55 (bs, 1H, NH); MS *m/z* 282 M^+. Anal. ($C_{12}H_{14}N_2O_4S\cdot 1.22H_2O$) C; H: calcd, 5.40; found, 4.55; N: calcd, 9.21; found 8.75.

2′-Deoxy-4′-thio-5-vinyluridine (3viii). A mixture of **3xxx** (0.37 g, 1 mmol) and *N*-ethyldiisopropylamine (0.26 g, 2 mmol) in 10 mL of dry pyridine was cooled with stirring to −3 °C, and then *p*-toluoyl chloride (0.8 mL, 6 mmol) was added in small portions. After 5 min, the reaction mixture was stirred at room temperature for 5 h and quenched with 1 mL of water. The mixture was then evaporated *in vacuo* to give a thick oil, which was dissolved in 35 mL of chloroform and washed with 2 × 20 mL of water. The organic layer was dried ($MgSO_4$) and evaporated to dryness, and the residue was purified by silica gel column chromatography eluting with 50% ethyl acetate/hexane to give **4** (R = *p*-toluoyl) (0.627 g, 87% yield). A mixture of this intermediate (0.22 g, 0.305 mmol), tetravinyltin (0.1 mL, 0.7 mmol), and tetrakistriphenylphosphine palladium(0) (0.041 g, 0.035 mmol) in 3.5 mL of hexamethylphosphoramide was stirred under nitrogen at 75 °C for 17 h. After the mixture was cooled to room temperature, 25 mL of water was added and the mixture extracted with 2 × 25 mL of ether. The combined ethereal extracts were dried (magnesium sulfate), evaporated *in vacuo* to give the chromatographically pure protected 5-vinyl intermediate (0.185 g, 97% yield). This was deprotected by treatment at room temperature with 60 mL of a 0.05 mol solution of sodium methoxide in methanol for 2.5 h. The mixture was then neutralized with Dowex 50 (H^+) resin and filtered, the filtrate was evaporated to dryness, and the residue was purified by silica gel column chromatography eluting with 15% methanol/chloroform to give the title compound **3viii** (0.022 g, 27% yield): mp 246 °C; ^{1}H NMR (Me_2SO-d_6) d 2.21 (m, 2H, H-2′), 3.32 (m, 1H, H-4′), 3.63 (m, 2H, H-5′), 4.36 (m, 1H, H-3′), 5.14 (dd, 1H, vinylic), 5.26 (m, 2H, OH-3′ and OH-5′), 6.00 (dd, 1H, vinylic), 6.26 (t, 1H, H-1′), 6.3−6.5 (dd, 1H, vinylic), 8.20 ppm (s, 1H, H-6); MS *m/z* 271 $(M + H)^+$. Anal. ($C_{11}H_{14}N_2O_4S$) C, H, N.

2′-Deoxy-5-isopropenyl-4′-thiouridine (3ix). To a stirred solution of (tetrakistriphenylphosphine)palladium(0) (0.038 g, 0.03 mmol) in 40 mL of HMPA under nitrogen was added **4** (R = H) (0.2 g, 0.33 mmol) followed by isopropenyltrimethyltin (0.15 g, 0.73 mmol) and one crystal of 2,6-di-*tert*-butyl-*p*-cresol (as a radical inhibitor), and the mixture was heated at 100 °C for 20 h. Following a similar workup to that for the synthesis of **3viii**, the *p*-toluoyl-protected intermediate was obtained (0.043 g, 25% yield) following silica gel column chromatography eluting with 15% methanol/dichloromethane. Similar deprotection with sodium methoxide afforded the title compound **3ix** after reversed-phase HPLC purification using a 0−95% linear gradient of acetonitrile/water on a Zorbax C_{18} column (0.01 g, 46% yield): ^{1}H NMR (Me_2SO-d_6) 1.95 (s, 3H, Me), 2.22 (m, 2H, H-2′), 3.3 (m, 1H, H-4′), 3.6 (m, 2H, H-5′), 4.35 (m, 1H, H-3′), 5.05 (m, 1H, vinylic), 5.22 (m, 2H, OH-3′ and OH-5′), 5.8 (m, 1H, vinylic), 6.26 (t, 1H, H-1′), 8.03 (s, 1H, H-6), 11.32 ppm (bs, 1H, NH); MS *m/z* 284 M^+. Anal ($C_{12}H_{16}N_2O_4S$) C, H, N.

5-Chloro-2′-deoxy-4′-thiouridine (3xxviii). A suspension of a 1:1 mixture of **5i** and **5ii** (5.3 g, 19 mmol) and cytidine deaminase from *E. coli* (357 units) in 150 mL of water was gently stirred at 37 °C overnight, and the solvent was evaporated. The residue was dissolved in the minimum volume of methanol, adsorbed onto silica gel, and purified by silica gel column chromatography eluting with 5−20% methanol/dichloromethane gradient. The pooled product fractions were evaporated to dryness, and the residual solid was recrystallized twice from methanol to give the title compound **3xxviii** (0.8 g, 30% yield based on **5i**): mp 221−222 °C; ^{1}H NMR (Me_2SO-d_6) 2.22 (m, 2H, H-2′), 3.3 (m, 1H, H-4′), 3.65 (m, 2H, H-5′), 4.35 (m, 1H, H-3′), 5.23 (m, 2H, OH-3′ and OH-5′), 6.22 (t, 1H, H-1′), 8.43 (s, 1H, H-6), 11.85 ppm (bs, 1H, NH); MS *m/z* 278 M^+. Anal. ($C_9H_{11}ClN_2O_4S$) C, H, N.

(*E*)-5-Propen-1-yluracil. To a solution of uracil (1 g, 9 mmol) in 200 mL of water at 70 °C was added mercuric acetate (2.9 g, 9.1 mmol), and the mixture was stirred for 7 days. After the mixture was cooled to room temperature, sodium chloride (1.5 g, 25.6 mmol) was added, and the mixture stirred for 4 h. The resulting thick suspension was filtered, washed with water, and dried under high vacuum to give 5-chloromercuriuracil (2.27 g). To this intermediate (1 g, 2.9 mmol) in 25 mL of acetonitrile was added lithium tetrachloropalladate(II) (0.76 g, 2.9 mmol) and allyl chloride (2.9 mL, 35.6 mmol), and the mixture was stirred at room temperature for 7 days. The resulting solid was filtered off, and the filtrate was evaporated to dryness. The residue was taken up in 75 mL of methanol, and hydrogen sulfide was bubbled through the solution for a few minutes. The resulting black solid was filtered off, and the colorless filtrate was evaporated to dryness. The residue was purified by silica gel column chromatography eluting with 8% methanol/dichloromethane to give 5-allyluracil (0.085 g). To a suspension of this (0.08 g, 0.5 mmol) in 50% aqueous ethanol was added tris(triphenylphosphine)rhodium(I) chloride (0.09 g, 0.1 mmol), and the mixture was heated under reflux for 72 h. The solvent was evaporated, and the residue was purified by silica gel column chromatography eluting with 5% methanol/dichloromethane to give the title compound (0.056 g, 70%): ^{1}H NMR (Me_2SO-d_6) d 1.75 (m, 3H, CH_3), 6.05 (d, 1H, vinylic, J = 14 Hz), 6.4 (m, 1H, vinylic), 7.42 (s, 1H, H-6), 11 ppm (bs, 2H, NH).

Viral Plaque Reduction Assays. Antiviral assays were performed using an adaptation of the plaque reduction assay described by Crumpacker and co-workers.[42] Twenty-four well plates containing monolayers of MRC 5 cells (human embryo lung fibroblasts, ATCC CCL 171) were used for assays of

human cytomegaiovirus (HCMV strain AD169) and varicella zoster virus (VZV strain G31), and monolayers of Varo cells (African Green monkey kidney, ATCC CCLB1) were used for herpes simplex virus type 1 (HSV 1) strain SC16 and HSV 2 (strain 186). Monolayers were infected with virus at a multiplicity calculated to produce 60−80 plaques per well. Infected cells were overlaid with liquid growth medium containing various known concentrations of the compound under investigation, and, in the case of HCMV, HSV 1, and HSV 2, carboxymethyl cellulose to prevent the formation of secondary plaques. Following a suitable period of incubation, plaques were fixed with formol saline and stained, and their numbers were determined. For IC_{50} determination, a dose-response curve was obtained and from this the 50% inhibitory concentration (IC_{50}) was obtained.

Cytotoxicity Assay. Subconfluent cultures of Vero or MRC-5 cells were grown in 96-well microtiter plates in the presence of different dilutions of drug. Cell numbers present at 96 h (Varb) and 7 days (MRC-5) were estimated, on replicate cultures, using uptake of a tetrazolum dye (MTT). The concentration required for a 50% inhibition of cell growth compared to control cells grown in the absence of compound is termed $CCID_{50}$. Cytotoxicity assays were performed initially using Vero cells, which have a faster replication cycle and, therefore, increased metabolism, compared with MRC-5 cells. However, for compounds of particular interest, the assays are repeated using MRC-5 cells (e.g. **3i**).

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Supporting Information Available: Mass spectral data for compounds **3ii**, **3xii**, **3xv**, **3xxiii**, **3xxiv**, and **3xxvi** and HPLC data for compounds **3vii**, **3x**, **3xi**, **3xiii**, **3xxvii**, **3xxx**, **3xxxii**, **3xxxiii**, **3xv**, and **3xvii** (2 pages). Ordering information is given on any current masthead page.

References

(1) Montgomery, J. A. *Med. Res. Rev.* **1982**, *2*, 271−308.
(2) Miura, G.; Gordon, R.; Montgomery, J. A.; Chiang, P. In *Purine Pyrimidine Metabolism in Man*; Nyhan, E., Thompson, L., Watts, R., Eds.; Plenum Publ. Corp.: New York 1986; Part B, pp 667−672.
(3) Parks, R. E., Jr.; Stoeckler, J. D.; Cambor, C.; Savarese, T. M.; Crabtree, G. W.; Chu, S.-H. In *Molecular Actions and Targets for Cancer Chemotherapeutic Agents*; Sartorelli, A. C., Lazo, J. S., Bertino, J. R., Eds.; Academic Press: New York, 1981; pp 229−252.
(4) Reist, E. J.; Gueffroy, D. E.; Goodman, L. *J. Am. Chem. Soc.* **1964**, *86*, 5658−5663.
(5) Bobek, M.; Whistler, R. L.; Bloch, A. *J. Med. Chem.* **1970**, *13*, 411−413.
(6) Bobek, M.; Whistler, R. L.; Bloch, A. *J. Med. Chem.* **1972**, *15*, 168−171.
(7) Ototani, N.; Whistler, R. L. *J. Med. Chem.* **1974**, *17*, 535−537.
(8) Bobek, M.; Bloch, A.; Parthasarathy, R.; Whistler, R. L. *J. Med. Chem.* **1975**, *18*, 784−787.
(9) Fu, Y.-L.; Bobek, M. In *Nucleic Acid Chemistry*; Townsend, L. B., Tipson, R. S., Eds.; Wiley, New York: 1978; pp 317−323.
(10) Dyson, M. R.; Coe, P. L.; Walker, R. T. *Nucleic Acids Res. Symp. Ser.* **1991**, *24*, 1−4.
(11) Dyson, M. R.; Coe, P. L.; Walker, R. T. *J. Chem. Soc., Chem. Commun.* **1991**, 741−742.
(12) Dyson, M. R.; Coe, P. L.; Walker, R. T. *J. Med. Chem.* **1991**, *34*, 2782−2786.
(13) Secrist, J. A., III; Riggs, R. M.; Tiwari, K. N.; Montgomery, J. A. *J. Med. Chem.* **1992**, *35*, 533−538.
(14) Tber, B.; Fahmi, N.; Ronco, G.; Mackenzie, G.; Villa, P.; Ville, G. *Collect. Czech. Chem. Commun.* **1993**, *58*, 18−21.
(15) Secrist, J. A., III; Tiwari, K. N.; Riordan, J. M.; Montgomery, J. A. *J. Med. Chem.* **1991**, *34*, 2361−2366.
(16) Dyson, M. R.; Coe, P. L.; Walker, R. T. *Carbohydr. Res.* **1991**, *216*, 237−248.
(17) Horton, D.; Markovs, R. A. *Carbohydr. Res.* **1980**, *80*, 356−363.
(18) Sugimura, H.; Osumi, K.; Yamazaki, T.; Yamaya, T. *Tetrahedron Lett.* **1991**, *32*, 1813−1816.
(19) Sugimura, H.; Sugino, K.; Osumi, K. *Tetrahedron Lett.* **1992**, *33*, 2515−2516.
(20) Basnak, I.; Farkas, J. *Collect. Czech. Chem. Commun.* **1979**, *44*, 2426−2437.
(21) Basnak, I.; Balkan, A.; Coe, P. L.; Walker, R. T. *Nucleosides Nucleotides* **1994**, *13*, 177−196.
(22) Su, T. S.; Watanabe, K. A.; Schinazi, R. F.; Fox, J. J. *J. Med. Chem.* **1986**, *29*, 151−154.
(23) Perman, J.; Sharma, R. A.; Bobek, M. *Tetrahedron Lett.* **1976**, *28*, 2427−2430.
(24) Spector, T.; Porter, D. J. T.; Rahim, S. G. World Patent No. 9201452; *Chem. Abstr. 116*, 207803y.
(25) Fissekis, J. D.; Sweet, F. *J. Org. Chem.* **1973**, *38*, 264−269.
(26) Evans, C. H.; Jones, A. S.; Walker, R. T. *Tetrahedron* **1973**, *29*, 1611−1614.
(27) Griengl, H.; Wanek, E.; Schwarz, W.; Streicher, W.; Rosenworth, B.; De Clercq, E. *J. Med. Chem.* **1987**, *30*, 1199−1204.
(28) Griengl, H.; Bodenteich, M.; Hayden, W.; Wanek, E.; Streicher, W.; Stuetz, P.; Bachmayer, H.; Ghazzouli, I.; Rosenwirth, B. *J. Med. Chem.* **1985**, *28*, 1679−1684.
(29) Bobek, M.; Kavai, I.; De Clercq, E. *J. Med. Chem.* **1987**, *30*, 1494−1497.
(30) Barr, P. J.; Jones, A. S.; Verhelst, G.; Walker, R. T. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1665−1670.
(31) Coe, P. L.; Harnden, M. R.; Jones, A. S.; Noble, S. A.; Walker, R. T. *J. Med. Chem.* **1982**, *25*, 1329−1334.
(32) Giner-Sorolla, A.; Medrek, L. *J. Med. Chem.* **1966**, *9*, 97−101.
(33) Chesterfield, J. H.; McOmie, J. F. W.; Tute, M. S. *J. Chem. Soc.* **1960**, 4590−4596.
(34) Frass, E.; Draminski, M.; Fiszer, B. *Rocz. Chem.* **1974**, *48*, 971−980.
(35) Herdewijn, P.; Kerremans, L.; Wigerink, P.; Vandendriessche, F.; Van Aerschot, A. *Tetrahedron Lett.* **1991**, *32*, 4397−4400.
(36) Eaborn, C.; Waters, J. A. *J. Chem. Soc.* **1962**, 1131−1132.
(37) Ryu, E. K.; Kim, J. N. *Nucleosides Nucleotides* **1989**, *8*, 43−8.
(38) De Clercq, E. In *Approaches To Antiviral Agents*; Harnden, M. R., Ed.; Macmillan Press: London, 1985; pp 57−99.
(39) Rahim, S. G.; Trevidi, N.; Selway, J.; Darby, G.; Collins, P.; Powell, K. L.; Purifoy, D. J. M. *Antiviral Chem. Chemother.* **1992**, *3*, 293−297.
(40) De Clercq, E.; Balzarini, J.; Torrence, P. F.; Mertes, M. P.; Schmidt, C. L.; Shugar, D.; Barr, P. J.; Jones, A. S.; Verhelst, G.; Walker, R. T. *Mol. Pharmacol.* **1981**, *19*, 321−330.
(41) Rahim, S. G.; Duggan, M. J. H.; Walker, R. T.; Jones, A. S.; Dyer, R. L.; Balzarini, J.; De Clercq, E. *Nucleic Acids Res.* **1982**, *10*, 5285−5295.
(42) Crumpacker, C. S.; Schnipper, L. E.; Zaia, J. A.; Levine, M. *Antimicrob. Agents Chemother.* **1979**, *15*, 642−645.

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