1280, 1265, 905, 760 sh, 755, 480, 410 cm^{-1}. Anal ($C_{11}H_{17}N_3O_3 \cdot {}^1/_4H_2O$) C, H, N.

(±)-1-[(1α,3α,4α)-3-Azido-4-[(triphenylmethoxy)methyl]cyclopentyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (14). A solution of 2.42 g (4.32 mmol) of mesylate **13**[16] and 0.528 g (10.8 mmol) of lithium azide in 120 mL of dry dimethylformamide was heated at 100 °C for 20 h. The reaction mixture was concentrated in vacuo to dryness and thoroughly dried at high vacuum. The residue was dissolved in 5 mL of 95:5 chloroform–methanol and filtered to remove inorganics, and the filtrate was applied to a column containing 90 g of silica gel. The column was eluted with 95:5 chloroform–methanol, and product-containing fractions (determined by TLC) were combined and concentrated in vacuo to dryness. The residue crystallized when triturated with methanol, and **14** was collected by filtration, washed with cold methanol, and dried in vacuo: yield, 982 mg (45%); mp 210–212 °C (inserted at 110 °C, 3 °C/min); TLC, 1 spot (40 mcg applied, 95:5 chloroform–methanol); MS (direct-probe temperature, 250 °C) *m/e* 507 (M), 479 (M – N_2), 448, 447, 429, 401, 326, 264 (M – CPh_3), 260, 248 (M – $OCPh_3$), 423 (CPh_3), 183, 165, 127 (Thy + 2 H), 126 (Thy + H); IR (strong and medium-strong bands, 2200–800-cm^{-1} region) 2105, 1695, 1680, 1645, 1470, 1445, 1270, 1065 cm^{-1}. Anal. ($C_{30}H_{29}N_5O_3$) C, H, N. The filtrate deposited additional crystalline **14** upon standing: weight, 228 mg (10%); mp 206–210 °C (inserted at 100 °C, 3 °C/min).

Concentration of later fractions from the silica gel column described in this procedure and crystallization of the crude residue in methanol afforded an 8% yield of **9**: mp 250–252 °C (inserted at 110 °C, 3 °C/min); TLC, 1 spot identical with authentic **9**[16] (40 and 80 mcg applied, 95:5 chloroform–methanol); MS (direct-probe temperature 260 °C) *m/e* 464 (M), 387 (M – Ph), 243 (CPh_3), 221 (M – CPh_3).

(±)-1-[(1α,3α,4α)-3-Azido-4-(hydroxymethyl)cyclopentyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (15). Azide **14** (450 mg, 0.89 mmol) was treated with 80% acetic acid (20 mL) and was purified according to the procedure described for the preparation of **11**. The glassy residue obtained by concentrating column fractions that contained product (determined by TLC) crystallized when triturated with ethyl acetate: yield of **15**, 178 mg (76%); mp 150–152 °C (inserted at 100 °C, 3 °C/min); UV λ_{max} 273 nm (ε 10300) at pH 1, 273 (ε 10400) at pH 7, 271 (ε 8000) at pH 13; MS (direct-probe temperature, 20 °C) *m/e* 266 (M + 1), 265 (M), 193, 180, 127 (Thy + 2 H), 126 (Thy + H); IR (strong and medium-strong bands, 2200–700-cm^{-1} region) 2110 s, 1705 s, 1680 sh, 1665 vs, 1340, 1280, 1265, 1025 cm^{-1}. Anal. ($C_{11}H_{15}N_5O_3$) C, H, N.

(±)-1-[(1α,3α,4α)-3-Amino-4-(hydroxymethyl)cyclopentyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (16). Compound **16** was prepared from **15** (125 mg, 0.47 mmol) and purified by the procedure described for the preparation of **8**. The residual colorless glass crystallized upon trituration with ethyl acetate and was filtered away, washed with ethyl acetate, and dried in vacuo at 56 °C for 2 h: yield of white crystals, 90 mg (80%); mp, sinters 162 °C, melts 165–168 °C with mild dec (inserted at 100 °C, 3 °C/min); TLC, 1 spot (40 or 80 mcg applied, 7:3 2-propanol–1 M ammonium acetate as developing solvent); UV λ_{max} 272 nm (ε 10300) at pH 1, 271 (ε 10200) at pH 7, 272 (ε 8100) at pH 13; MS (FABMS) *m/e* 240 (M + 1); IR (strong and medium-strong bands, 1800–400-cm^{-1} region) 1680, 1665 sh, 1640 sh, 1605 sh, 1370, 1290, 1075, 760, 585, 425 cm^{-1}. Anal ($C_{11}H_{17}N_3O_3$) C, H, N.

Antiviral Evaluations in Vitro. The compounds listed in Table I were tested for inhibition of the cytopathogenic effects produced by strain 377 (TK$^+$) or strain HF (TK$^-$) of HSV-1 or strain MS of HSV-2. The data summarized in Table I were acquired by methods and procedures described previously for the evaluation of compounds for antiviral activity in vitro.[22] The general assay method was described by Ehrlich et al.,[21] but some modifications were incorporated.

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Registry No. **5**, 87491-47-2; **6**, 100020-47-1; **7**, 100020-48-2; **8**, 100020-49-3; **9**, 87470-97-1; **10**, 100020-50-6; **11**, 100020-51-7; **12**, 100020-52-8; **13**, 87470-96-0; **14**, 100101-39-1; **15**, 100101-40-4; **16**, 100101-41-5.

Synthesis, Structure, and Antitumor and Antiviral Activities of a Series of 5-Halouridine Cyclic 3′,5′-Monophosphates

József Béres,[†,‡] Wesley G. Bentrude,*[§] Alajos Kálmán,[‡] László Párkányi,[‡] Jan Balzarini,[∥] and Erik De Clercq[∥]

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112, Central Research Institute for Chemistry of the Hungarian Academy of Sciences, H-1525 Budapest, Hungary, and Rega Institute for Medical Research, University of Leuven, B-3000 Leuven, Belgium. *Received May 2, 1985*

A series of potential prodrug 5-halouridine 3′,5′-cyclic monophosphates (5-X-cUMPs, X = F, Cl, Br, I, **1**–**4**) has been prepared and tested for antitumor activity against murine leukemia L1210/0 and human lymphoblast Raji/0 cells and their deoxythymidine kinase deficient (TK$^-$) counterparts, as well as for antiviral activity in primary rabbit kidney cells infected with herpes simplex virus type 1 or 2, vaccinia virus, or vesicular stomatitis virus. The 5-halopyrimidine bases, nucleosides (5-X-U), and 5′-monophosphates (5-X-UMP) were tested for comparison. 5-F-cUMP (**1**) showed reasonably potent inhibition of tumor cell proliferation (ID_{50} = 0.33–1.6 μg/mL), while the remaining diesters displayed ID_{50}'s ranging from 210 to >1000 μg/mL. 5-F-cUMP was 70- to 300-fold less active than 5-F-dU in the same systems. With TK$^-$ L1210 cells, 5-F-cUMP was as potent as with the normal (L1210/0) line but was about fourfold less active with TK$^-$ Raji cells compared to Raji/0 cells. The 5-X-cUMPs showed little potency as antivirals. A single-crystal X-ray analysis of the ammonium salt of 5-I-cUMP confirmed its structure and showed the conformation of the phosphate ring to be the expected chair. The ribose pucker is near $^3_4$T, and the torsion angle about the β-glycosidic N(1)–C(1′) bond is in the syn range (–84.8°).

5-Fluorouracil (5-F-Ura) and 5-fluoro-2′-deoxyuridine (5-F-dU) are clinically useful antitumor agents.[1,2] 5-F-dU also shows highly selective anti-herpes activity (HSV-1) in cell cultures.[3] 5-Fluorouridine (5-FU) is an antitumor

† Postdoctoral fellow at the University of Utah, 1982–1984.
‡ Hungarian Academy of Sciences.
§ University of Utah.
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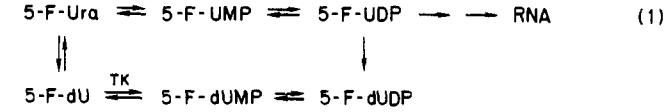
Table I. Synthetic Data for Compounds 1–4

compd	formula	anal.	isolated yields, %	R_f 1[d]	R_f 2[d]
1	$C_9H_{13}FN_3O_8P$	C, H, F, N, P	40[b]	0.40[c] 0.44[e]	0.51[c]
2	$C_9H_{13}ClN_3O_8P$	C, H, Cl, N, P	65[a]	0.45[c] 0.47[e]	0.51[c]
3	$C_9H_{13}BrN_3O_8P$	C, H, Br, N, P	67[a]	0.45[c] 0.48[e]	0.51[c]
4	$C_9H_{13}IN_3O_8P$	C, H, I, N, P	65[a]	0.48[c] 0.51[e]	0.51[c]

[a] Direct halogenations. [b] DCC ring closure. [c] On silica gel TLC plates. [d] Solvent system. See Experimental Section. [e] On cellulose TLC sheets.

agent of high activity but is highly toxic,[4] perhaps because of its great ease of cell penetration.[5] 5-F-Ura and 5-F-dU themselves display undesirable levels of toxicity to normal cells, e.g. those of bone marrow.[6] Resistance to these drugs as antitumor agents is an additional problem. The 5'-monophosphate of 5-F-dU (5-F-dUMP), which functions as a thymidylate synthetase inhibitor,[7] is converted in vivo to 5-F-Ura,[8] reducing the efficacy of 5-F-dU. Cells that become devoid of normal deoxythymidine kinase (TK) activity develop resistance to 5-F-dU.[9] A number of recent reports have addressed these problems through preparation of prodrug forms of 5-F-Ura (e.g. Ftorafur,[10] peptidyl derivatives,[11] 5'-deoxy-5-fluorouridine[12]) and 5-F-dUMP (various neutral phosphate esters and phosphoramidates[13]).

In the present study, a series of 5-halouridine cyclic 3',5'-monophosphates[14] (5-X-cUMPs, 1–4) were prepared and tested along with the corresponding nucleosides for in vitro antitumor and antiviral activity. 5-F-dU and (*E*)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) served as reference compounds. Monocharged 1–4 potentially can enter the cell and become involved in the metabolic cycle shown below which applies to 5-fluoropyrimidine derivatives.[1,2]



(1)

Thus, diester 1 is a potential target for hydrolysis to 5-fluorouridine 5'-monophosphate (5-F-UMP) under catalysis by the recently discovered pyrimidine phosphodiesterases[15] found to be present in a variety of tissues.[15c] Drug resistance to 5-F-Ura or 5-F-dU resulting from loss of thymidine kinase (TK) activity[9] might be circumvented through *indirect* formation of 5-F-dUMP via 5-F-UMP → 5-F-UDP → 5-F-dUDP → 5-F-dUMP. In its role as a 5-F-UMP prodrug, 5-F-cUMP also could obviate the need for uridine kinase to activate 5-FU. A phosphodiesterase active with cytidine cyclic 3',5'-monophosphates has been obtained from leukemia L1210 cells.[15f] Differential activity between cancer, virally infected, and normal cells would provide a basis for drug selectivity.

Results and Discussion

Chemistry. The series of 5-halouridine 3',5'-cyclic monophosphates, 5-X-cUMP's (1–4), was prepared (Table I) in a straightforward manner. 5-F-cUMP, 1, previously obtained by direct fluorination of cUMP,[16] resulted on ring closure of the *N,N'*-dicyclohexyl-4-morpholinecarboxamidine salt of 5-fluorouridine 5'-monophosphate (5-F-UMP) by use of dicyclohexylcarbodiimide (DCC) in pyridine at reflux temperature as described earlier for the synthesis of other ribonucleoside 3',5'-cyclic monophosphates.[17] The required 5-F-UMP precursor to 5-F-cUMP was obtained by a modified Yoshikawa method.[18,19] ^1H and ^{13}C NMR data confirmed the structure of 5-F-UMP and gave no evidence for the formation of the 3'-monophosphate, a potential sideproduct.[19]

5-Cl-cUMP, **2**, resulted on direct halogentation of the sodium salt of cUMP itself by use of *N*-chlorosuccinimide (NCS) in glacial acetic acid at reflux temperature for half an hour. At ambient temperature, no 5-Cl-cUMP could be detected by TLC after 3 h. Similarly, 5-Br-cUMP, **3**, was prepared on reaction of *N*-bromosuccinimide (NBS) with cUMP sodium salt, as described earlier.[20]

N-Iodosuccinimide (NIS) underwent reaction at reflux temperature with cUMP sodium salt in glacial acetic acid for half an hour to yield the 5-iodo derivative **4**. At ambient temperature, the cUMP sodium salt also was completely consumed, but 5-I-cUMP could only be isolated in a low yield (12%). Under this condition, in addition to **4**, an alkaline-labile iodo derivative of cUMP was also formed, which on alkaline treatment (pH ≥7) released I_2 and regenerated cUMP. Only a trace of 5-I-cUMP could

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Table II. Cytostatic Activity of 5-Halouracils, 5-Halouridines, 5-Halo-UMP's, and 5-Halo-cUMP's 1–4

	ID_{50},[a] (μg/mL)			
compd	L1210/0[b]	L1210/BdU[c]	Raji/0[d]	Raji/TK⁻[e]
5-fluorouracil	0.208	0.286	1.35	3.37
5-fluoro-U	0.013	0.019	0.023	0.085
5-fluoro-UMP	0.024	0.030	0.029	0.141
5-fluoro-cUMP (1)	0.340	0.332	0.416	1.64
5-chlorouracil	455	660	>1000	>1000
5-chloro-cUMP (2)	>1000	>1000	278	369
5-bromouracil	>1000	>1000	>1000	>1000
5-bromo-U	210	335	32	950
5-bromo-UMP	385	376	48	>1000
5-bromo-cUMP (3)	315	294	210	241
5-iodouracil	>1000	>1000	>1000	612
5-iodo-U	>1000	>1000	639	738
5-iodo-UMP	703	>1000	>1000	>1000
5-iodo-cUMP (4)	315	344	359	722
5-fluoro-dU[f]	0.001	1.75	0.006	1.03

[a] Inhibitory dose-50 or dose required to inhibit tumor cell proliferation by 50%. [b] Murine leukemia L1210 cells, designated L1210/0. [c] Deoxythymidine (dThd) kinase deficient L1210 cells, designated L1210/BdU, selected for their ability to grow in the presence of 260 μg/mL 5-bromo-dU.[38] [d] Human lymphoblast Raji cells, designated Raji/0. [e] dThd kinase deficient Raji cell line, designated Raji/TK⁻.[38] [f] Reference compound: 5-fluoro-2′-deoxyuridine.[38]

be detected by TLC after 2 h in an attempted direct I_2/HIO_3 iodination[21] of the cUMP sodium salt in an acetic acid/CCl_4/H_2O medium at room temperature. At elevated temperatures glycosidic bond cleavage was favored.[17] NCS,[22] NBS,[23] and NIS[24] were previously used in the halogenations of heterobases, nucleosides, and nucleotides but not for the preparation of halo derivatives of cyclic 3′,5′-monophosphates, except for the 5-bromo compound **3**.[20]

The 5-halo-cUMP's (1–4) were routinely isolated by DEAE-Sephadex A-25 anion exchange column chromatography using a linear aqueous salt gradient. The starting cUMP could be easily separated from **2**–**4** due to the different acidities of the N3 base hydrogens. The structures of 1–4 were confirmed by X-ray (vide infra, compound **4**) and ^1H and ^{13}C (see paragraph below on supplementary material, Table I) NMR spectroscopy, as well as UV and mass spectrometry and quantitative elemental analysis (Table I). In the ^1H spectra the presence in each case of sharp singlet signal at about δ 5.6 confirmed the β nature of the configuration at anomeric C1′.[25] Diagnostic of the presence of the 5-fluoro substituent in **1** was the 7.1-Hz $^3J_{HF}$ value noted for H6.[26] For **2**–**4** a *singlet* for H6 in the range δ 7.84–7.88 was observed, which is indicative of halogen substitution at C5. The ^{13}C chemical shifts and J_{PC} values for 1–4 (Table II) are typical of those found for other nucleoside cyclic 3′,5′-monophosphates and cUMP in particular.[27] The chemical shift assignments to

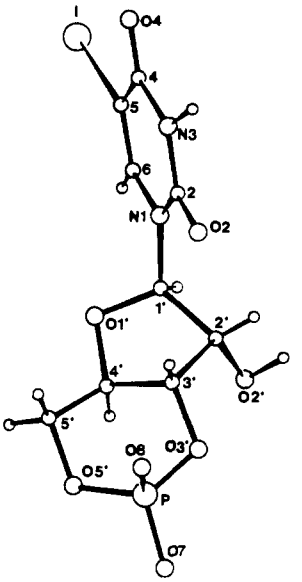

Figure 1. A perspective view of the molecular structure with atomic numbering. Bare numbers are for carbon atoms unless indicated otherwise. The H atoms are shown but not labeled.

C3′ and C4′ follow the revisions recently made for similar diesters on the basis of single frequency decoupling experiments.[28] The 231.8-Hz $^1J_{CF}$ and the 34.9-Hz $^2J_{CF}$ values found for C5 and C6 of **1** are helpful in confirming that structure as well. The effect of the halogen atoms on the carbon-5 shieldings also verified the substitution and its location on the base. Carbon-5 substituted by iodine is more shielded than when substituted with bromine, chlorine, or fluorine.[29] UV spectra of 1–4 were also consistent with the expected structures (Experimental Section). The auxochrome halogen substitutions at the 5-position find expression in the bathochromic shifts of the UV absorption of the uracil base (UV data of cUMP: λ_{max} 259, λ_{min} 228 (pH 2); λ_{max} 259, λ_{min} 228 (pH 7); λ_{max} 259, λ_{min} 228 nm (pH 11). Trimethylsilylation of 1–4 prior to electron-impact mass spectrometry led to tri- and/or disilylation as evidenced by the observation of the corresponding M − 15 peaks (Experimental Section).

X-ray Determination of the Molecular Structure of 4. The structure of **4**, and by inference those of 1–3, was verified by its X-ray crystal structure (Figure 1). The pyrimidine base is nearly planar, and iodine is only 0.046 (1) Å out of its least-squares plane [$-0.9537X + 0.0649Y - 0.2936Z = 4.9157$, maximum deviation 0.026 (6) Å]. As in the 5-iodo-2′-deoxyuridine 3′,5′-cyclic monophosphate *PO*-methyl ester,[30] the iodine of **4**, because of its electron-withdrawing effect, increases the C(4)–C(5)–C(6) bond angle by about 3° compared to that observed in thymidine[31] and in other 5-alkyl derivatives.[32] The torsion angle about the pseudoaxial glycosidic N(1)–C(1′) bond falls in the syn range (χ = −84.8 (8)°). The corresponding χ value for the 5-iodo cyclic methyl phosphate[30] is −98.1°. The

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Table III. Antiviral Activity of Compounds 1–4

virus	MIC_{50},[a] (μg/mL)				
	1	2	3	4	BVDU[b]
HSV-1 (KOS)[c]	>100	>400	>200	200	0.02
HSV-1 (F)	>100	>400	>200	40	0.02
HSV-1 (McIntyre)	>100	>400	200	20	0.02
HSV-2 (G)	>100	>400	>200	>400	1
HSV-2 (196)	>100	>400	>200	>400	100
HSV-2 (Lyons)	>100	>400	150	>400	1
vaccinia virus	20	>400	>200	>400	2
vesicular stomatitis virus	150	>400	>200	>400	>400

[a] Minimum inhibitory concentration required to reduce virus-induced cytopathogenicity in primary rabbit kidney cell cultured by 50%. Cytotoxicity, as revealed by a microscopically detectable alteration of normal cell morphology, was observed for 1 at a concentration of ≥100 μg/mL and for 3 at a concentration of 400 μg/mL. For 2 and 4 no cytotoxicity was noted at the highest concentration tested (400 μg/mL). [b] Reference compound: (*E*)-5-(2-bromovinyl)-2'-deoxyuridine.[42] [c] HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2.

similarity between the furanose rings of these two compounds is also conspicuous, albeit 4 possesses an additional 2'-OH group. Both are slightly distorted half chairs with a C_2 axis passing approximately through atom C(1'). The puckering amplitudes[33] (Q) and the lowest asymmetry factors[34] (fC_2) are for 4, Q = 0.43 (1) Å, fC_2(C1') = 2.0 pm; and for the 5-iodo cyclic methyl phosphate, Q = 0.43(1) Å, fC_2(C1') = 4.7 pm.

A similar half chair sugar ring (fC_2 = 3.0 pm) was found in the crystal structure of ammonium 5-fluoro-2'-deoxyuridine cyclic 3',5'-monophosphate trihydrate.[35] This form is quite near to a $^3_4$T pucker[36] and can be attributed to the trans nature of the fusion of the ribose to the 1,3,2-dioxaphosphorinane ring. The chair conformation of the latter ring (Q = 0.55 (1) Å) can be characterized by the interplane dihedral angles between the least-squares plane O(3'), C(3'), C(5'), O(5') [$0.4137X - 0.7884Y - 0.4552Z = -8.6411$] and the plane C(3'), C(4'), C(5') [$0.0054X + 0.9265Y - 0.3762Z = -5.1928$] (56.2 (4)°) and also with the plane O(3'), P, O(5'), [$0.1062X - 0.9831Y + 0.1489Z = 2.1465$] (41.3 (3)°). The sharpest pucker of the six-membered ring is shown at the C(3')–C(4') trans junction (ϕ' = 65.0 (9)°). Bond lengths and angles of 4 are similar to those found for other pyrimidine cyclic 3',5'-monophosphates. Characteristic are the angles C(3')–O(3')-P, 112.9 (6)°, and C(5')–O(5')–P, 121.4 (7)° showing the distortion of the 1,3,2-dioxaphosphorinane ring. Full tables of bond lengths, bond angles, and dihedral angles are available as supplementary material.

Antiproliferative Activity. Compound 1 was 500- to 3000-fold more inhibitory to the proliferation of L1210/0 and Raji/0 cells than compounds 2–4 but 70- to 300-fold less potent in its cytostatic activity than the reference compound 5-F-dU (Table III). Compounds 1–4 showed similar inhibitory activities against the deoxythymidine (dThd) kinase deficient L1210/BdUrd and Raji/TK$^-$ sublines and their parental L1210/0 and Raji/0 cell lines, except for 1, which was 4-fold less active against Raji/TK$^-$ than Raji/0 cells. The inhibitory effects of the 5-halouracils, 5-halouridines, and 5-halouridine 5'-monophosphates on the proliferation of L1210 and Raji cells was, as a rule, comparable to that of the 5-halouridine cyclic 3',5'-monophosphates. Exceptions include 5-fluorouridine and 5-fluorouridine 5'-monophosphate which inhibited tumor cell proliferation at a 10- to 25-fold lower concentration than compound 1. Also 5-bromouridine and 5-bromouridine 5'-monophosphate were about 5 times more inhibitory to Raji/0 cell proliferation than was compound 3.

Antiviral Activity. Compounds 1–4 did not exhibit a marked antiviral activity, except for 1 against vaccinia virus and 4 against herpes simplex virus type 1 (Table III). Yet, compound 4 was 1000 times less potent as an inhibitor of HSV-1 (McIntyre strain) than the reference compound BVDU. The 5-halouracils, 5-halouridines, and their 5'-monophosphates were generally inactive against herpes simplex virus (type 1 or 2), vaccinia virus, and vesicular stomatitis virus at concentrations up to 400 μg/mL (data not shown). The notable exceptions to this rule were 5-fluorouridine and 5-fluorouridine 5'-monophosphate which inhibited the cytopathic effects of vaccinia and vesicular stomatitis virus at a concentration of 2 μg/mL: however, these compounds were also cytotoxic for the host cells (primary rabbit kidney cells), as revealed by a microscopically detectable alternation of normal cell morphology, at a concentration of ≥10 μg/mL. 5-Bromouridine showed inhibitory effects on HSV-1 (F) at 150 μg/mL and HSV-2 (Lyons) at 70 μg/mL.

Protein Kinase Activity. Preliminary results showed 1–4 to interact with protein kinase type I (rabbit skeletal muscle) with K_a (concentration for half-maximal activation) values ranging 1.8–10 μM (K_a for cAMP = 30 nM). The presence of the pyrimidine base rather than a purine one evidently renders the cyclic nucleotides of the present study less effective activators of the kinase. Details of these experiments will be reported elsewhere.

Conclusions

5-F-Ura, 5-F-U, 5-F-UMP, and 5-F-cUMP all show marked activity as cytostatic agents in the initial in vitro tests reported here. As was demonstrated previously with 5-fluorocytidine,[37] the cyclic diester 1 is less potent (11–26×) than the nucleoside or 5'-monophosphate. Whether increased selectivity may be a property of 1 awaits animal testing. No evident advantage of 1 against TK$^-$ cells is seen; hence it may not be subject to facile conversion to the 5'-monophosphate enzymatically, if indeed 1 readily enters cells. The nonetheless considerable potency of 1 may derive from its ability to serve as a prodrug form of 5-FU, released by slow extracellular, nonenzymatic hydrolysis. The low potency of 2–4 is not surprising since the antitumor activity of the nucleosides and 5'-monophosphates is low (vide supra) and the corresponding 5-X-2'-deoxyuridines (X = Cl, Br, I), the monophosphates of which could be formed via the reaction sequence (1), are not potent inhibitors of L1210 and Raji cell proliferation.[38] The maintenance of potency of the 5-fluoro compounds in general against TK$^-$ cells is noteworthy, but the reason for it is not known. Although phosphorylation of 2'-deoxyribonucleosides (e.g. 5-Br-dU) may not occur, uridine kinase activity may be present.

The 5-halouridine cyclic 3',5'-monophosphates show little potency as antivirals. The selectivity of 4 (inhibitory

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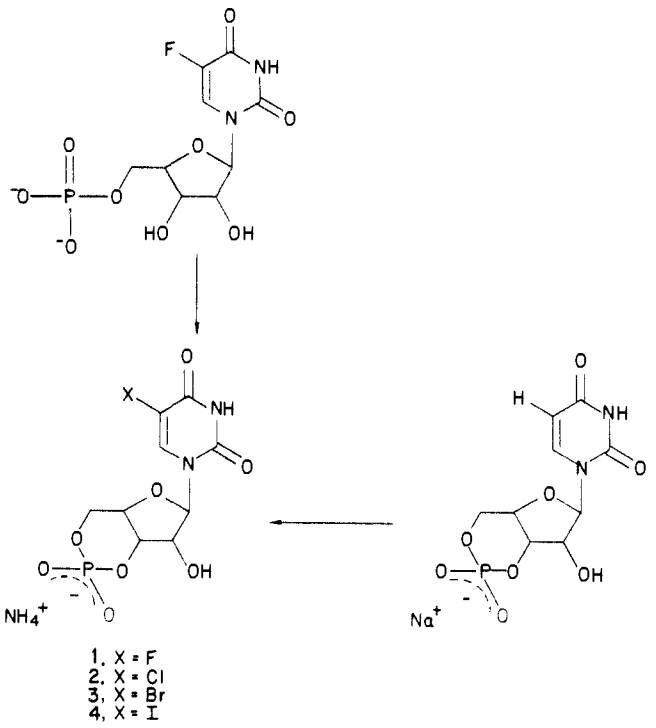
Scheme I



vs. cytotoxic dose) toward HSV-1 (F and McIntyre) is increased somewhat compared to that for the active 5-FU and 5-F-UMP (vaccinia virus). Increased selectivity in the cyclic diester of 5-F-cytidine relative to the nucleoside itself and 5′-monophosphate was noted earlier.[37] The generally poor activity of 1 means that it either is not transported into the cells or is not converted intracellularly to the 5′-monophosphate. In addition, 1 apparently is not a good extracellular prodrug source of 5-FU or 5-F-UMP. Furthermore, the metabolic reaction (reaction sequence 1) which could supply 5-halo-2′-deoxyuridines or their 5′-monophosphates does not operate efficiently as these nucleosides all have ID_{50} values toward HSV-1 of 0.1–0.2 μg/mL.[39]

Experimental Section

Chromatography. Precoated silica gel (Kieselgel 60 F_{254}, 0.2 mm × 20 cm × 20 cm, Merck, Darmstadt, F.R.G.) and cellulose (Cellulose F_{254}, 0.1 mm × 20 cm × 20 cm, Merck) TLC sheets were used to follow the reactions and check product purity. Solvent systems (v/v) for TLC were (1) isobutyric acid–25% ammonium hydroxide–water = 66:1:33 and (2) 2-propanol–25% ammonium hydroxide–water = 7:1:2 with added H_3BO_3. DEAE-Sephadex A-25 (Pharmacia Fine Chemicals, Sweden) was purchased from Sigma Chemical Co.

Spectroscopy. Proton spectra were recorded in Me_2SO-d_6 with a Varian SC-300 FT NMR system operating at 300.3 MHz. Carbon-13 spectra were acquired in D_2O solvent on the same instrument operating at 75.5 MHz. ^1H chemical shifts (δ) are in ppm downfield from Me_4Si while those for ^{13}C are downfield from external $Me_3SiCH_2CH_2CO_2Na$. UV spectra were recorded on a Varian Cary 17D UV spectrophotometer system at three different pH levels [pH 2 (10^{-2} M HCl); pH 7 (0.02 M KH_2PO_4/0.02 M K_2HPO_4); and pH 11 (10^{-3} M NaOH)]. Electron-impact mass spectra were acquired with a Varian MAT 112S mass spectrometer with ionizing energy of 80 eV and an ion source temperature of 270 °C. All samples were introduced by the direct probe method following trimethylsilylation which was carried out by the reaction of 30 μL of *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) and 10 μL of pyridine with ca. 0.2 mg of 1–4 at 100 °C for 1 h in a glass capillary tube.

Chemistry. 5-Fluorouridine was purchased from Fluka Chemical Corp. Uridine 3′,5′-cyclic phosphate sodium salt was a generous gift from Prof. Roland K. Robins. Trimethyl phosphate was vacuum distilled with the exclusion of atmospheric moisture prior to use. Phosphoryl chloride, pyridine, and glacial acetic acid were freshly distilled from phosphorus pentoxide.

5-Fluorouridine 5′-Monophosphate Diammonium Salt. To a stirred solution of 5-fluorouridine (0.131 g, 0.5 mmol) in trimethyl phosphate (1.25 mL) at 0 °C was added phosphoryl chloride in two portions (0.045 mL, 0.5 mmol each) with a 2-h interval between additions. After 10 h at 0 °C the reaction mixture was quenched with ice–water (5 mL) containing NH_4HCO_3 (0.474 g, 6 mmol). This solution was applied to a DEAE-Sephadex A-25 (HCO_3^-) column (2.7 × 25 cm) which was washed with water (ca. 0.5 L) until no more UV absorbance (260 nm) was observed. Elution (18 mL/15 min per fraction) with a linear gradient of water (1.5 L) and 1.0 M ammonium hydrogen carbonate (1.5 L) gave the desired product (0.067 g, 0.18 mmol, 36%), isolated by evaporation of fractions 64–69. Anal. ($C_9H_{18}FN_4O_9P$) C, H, F, N, P. R_f (solvent system 1, silica gel) 0.31, (solvent system 1, cellulose) 0.33, (solvent system 2, silica gel) 0.07; ^1H NMR (Me_2SO-d_6) δ 8.16 (d, J_{HF} = 7.1 Hz, 1 H, H6), 5.77 (d, $J_{H1'H2'}$ = 6.5 Hz, 1 H, H1′), 4.14–4.17 (m, 1 H, H2′), 4.04–4.06 (m, 1 H, H3′), 3.92 (m, 1 H, H4′), 3.75–3.82 (m, 2 H, H5′, H5″); ^{13}C NMR (D_2O) δ 169.2 (d, J_{CF} = 26.5 Hz, C4), 160.0 (C2), 151.1 (d, J_{CF} = 232.4 Hz, C5), 135.1 (d, J_{CF} = 34.2 Hz, C6), 98.1 (C1′), 93.0 (d, J_{CP} = 7.3 Hz, C4′), 83.3 (C3′), 79.1 (C2′), 73.2 (d, J_{CP} = 4.4 Hz, C5′).

5-Fluorouridine 3′,5′-Cyclic Monophosphate Ammonium Salt (1). To a solution of 5-fluorouridine 5′-phosphate diammonium salt (0.200 g, 0.53 mmol) in water (10 mL) was added *N,N′*-dicyclohexyl-4-morpholinecarboxamidine (0.156 g, 0.53 mmol) in pyridine (10 mL). The solution was evaporated to dryness, and the residue was dried (P_2O_5) in vacuum overnight. The residue thus obtained was dissolved in pyridine (50 mL). This solution was added dropwise to a refluxing solution of dicyclohexylcarbodiimide (0.547 g, 2.65 mmol), in pyridine (50 mL) over a period of 1 h. The reflux temperature was maintained for an additional 1 h. Then the solution was evaporated to dryness, and 50 mL each of ether and water were added. The insoluble dicyclohexylurea was filtered off. The aqueous phase was concentrated to a smaller volume (ca. 20 mL) and applied to a DEAE-Sephadex A-25 (HCO_3^-) column (2.7 × 25 cm). The column was washed with water (ca. 0.5 L) until no more UV absorbance (260 nm) was observed and then eluted (18 mL/9 min per fraction) using a linear gradient of water (1.0 L) and 1 M ammonium bicarbonate (1.0 L). Salt 1 (0.073 g, 0.21 mmol, 40%) was isolated by evaporation of fractions 56–60: UV, λ_{max} 267, λ_{min} 232 (pH 2); λ_{max} 267, λ_{min} 232 (pH 7); λ_{max} 268, λ_{min} 248 (pH 11); EI-MS, *m/e* (relative intensity) 453, M^+ + 2 Me_3Si – 15 (4.8); ^1H NMR (Me_2SO-d_6) δ 7.84 (d, 1 H, J_{HF} = 7.1 Hz, H6), 5.57 (s, 1 H, H1′), 4.13–4.20 (m, 2 H, H3′, H2′), 4.04–4.11 (m, 1 H, H5′), 3.84–3.85 (m, 1 H, H5″), 3.80–3.82 (m, 1 H, H4′).

5-Chlorouridine 3′,5′-Cyclic Monophosphate Ammonium Salt (2). To a solution of cUMP sodium salt (0.328 g, 1.0 mmol) in glacial acetic acid (2.5 mL) was added *N*-chlorosuccinimide (0.174 g, 1.3 mmol). The reaction mixture was kept at reflux temperature (ca. 118 °C) for 30 min and then evaporated to dryness. The residue was coevaporated with small portions (3 × 10 mL) of methanol and then dissolved in methanol (10 mL) and precipitated with an excess of ether. The crude product (0.338 g) was dissolved in water (5 mL, pH 3). This solution, after its pH was adjusted to 7 with 1 M sodium hydroxide, was applied to a DEAE-Sephadex A-25 (HCO_3^-) column (2.5 × 25). The column was washed with water (ca. 0.5 L) and then was eluted (18 mL/13 min per fraction) with a linear gradient of water (1.0 L) and 1 M ammonium hydrogencarbonate (1.0 L). Salt 2 (0.201 g, 0.65 mmol, 65%) was isolated by evaporation of fractions 65–69: UV, λ_{max} 275, λ_{min} 238 (pH 2); λ_{max} 275, λ_{min} 240 (pH 7); λ_{max} 273, λ_{min} 248 nm (pH 11); EI-MS, *m/e* (relative intensity) 470, M^+ + 2 Me_3Si – 15 (3.8); 542, M^+ + 3 Me_3Si – 15 (2.3); ^1H NMR (Me_2SO-d_6) δ 7.84 (s, 1 H, H6), 5.57 (s, 1 H, H1′), 4.16–4.24 (m,

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H, H3', H2'), 4.03–4.09 (m, 1 H, H5'), 3.83–3.85 (m, 1 H, H5''), 3.80–3.83 (m, 1 H, H4').

5-Bromouridine 3',5'-Cyclic Monophosphate Ammonium Salt (3). Compound **3** was obtained as described earlier in the literature.[20] Salt **3** was eluted (18 mL/12 min per fraction) from a DEAE-Sephadex A-25 ((HCO_3^-) column (2.7 × 25 cm) using a linear gradient of water (1 L) and 1 M ammonium bicarbonate (1 L). Product **3** (yield 67%) was isolated by evaporation of fractions 52–60: UV, λ_{max} 278, λ_{min} 241 (pH 2); λ_{max} 278, λ_{min} 242 (pH 7); λ_{max} 275, λ_{min} 250 nm (pH 11); EI-MS, *m/e* (relative intensity) 514, $M^+ + 2\ Me_3Si - 15$ (6.4); 587, $M^+ + 3\ Me_3Si - 15$ (9.5); ^1H NMR (Me_2SO-d_6) δ 7.88 (s, 1 H, H6), 5.56 (s, 1 H, H1'), 4.12–4.40 (m, 2 H, H3', H2'), 4.00–4.16 (m, 1 H, H5'), 3.84–3.87 (m, 1 H, H5''), 3.82 (m, 1 H, H4').

5-Iodouridine 3',5'-Cyclic Monophosphate Ammonium Salt (4). A solution of cUMP sodium salt (0.328 g, 1 mmol) and *N*-iodosuccinimide (0.292 g, 1.3 mmol) in glacial acetic acid (2.5 mL) was refluxed (ca. 118 °C) for 30 min. The reaction mixture was evaporated to dryness and coevaporated with small portions of methanol (3 × 10 mL). The residue obtained was dissolved in methanol (5 mL) and the crude product (0.415 g) was precipitated with an excess of ether. This solid material was dissolved in water (10 mL, pH 3) and the pH of the solution was adjusted to 8 by addition of 1 M sodium hydroxide. The solution was applied to a DEAE-Sephadex A-25 (HCO_3^-) column (2.5 × 24 cm). The column was washed with water (ca. 0.5 L) and then eluted (18 mL/10 min per fraction) with a linear gradient of water (1.5 L) and 1 M ammonium bicarbonate (1.5 L). Salt **4** (0.295 g, 0.65 mmol, 65%) was isolated by evaporation of fractions 77–85: UV, λ_{max} 287, λ_{min} 245 (pH 2); λ_{max} 286, λ_{min} 246 (pH 7), λ_{max} 279, λ_{min} 250 nm (pH 11); EI-MS, *m/e* (relative intensity) 561, $M^+ + 2\ Me_3Si - 15$ (7.1); ^1H NMR (Me_2SO-d_6) δ 7.87 (s, 1 H, H6), 5.55 (s, 1 H, H1'), 4.14–4.23 (m, 2 H, H3', H2'), 3.95–4.13 (m, 1 H, H5'), 3.82–3.93 (m, 1 H, H5''), 3.80 (m, 1 H, H4'').

X-ray Analysis of Ammonium 5-Iodouridine 3',5'-Cyclic Monophosphate Dihydrate (4). For $C_9H_9IN_2O_8P^-\cdot NH_4^+\cdot 2H_2O$ (mol wt 485.1), the monoclinic space group *C*2 was uniquely established from the systematic absences: *hkl* when $h + k \neq 2n$, *0k0* when $k \neq 2n$. The size of the crystal selected for X-ray measurements was about 0.02 × 0.12 × 0.40 mm^3. The precise cell dimensions: a = 14.471 (4) Å, b = 7.387 (3) Å, c = 15.353 (3) Å, β = 97.24 (2)°, U = 1628.1 (15) $Å^3$ (Z = 4, D_{calcd} = 1.979 g cm^{-3}, $F(000)$ = 960) were determined by least-squares refinement of diffractometer angles for 25 automatically centered reflections. The reflection intensities were collected on a computer controlled Enraf-Nonius CAD-4 diffractometer at 22 °C, using graphite monochromated Mo Kα radiation (λ = 0.71073 Å) with $\omega/2\theta$ scan in the range $1.5 \leq \theta \leq 30.0°$. The scan rate for each reflection was determined by a rapid prescan at 10° min^{-1} in θ at which point any reflection with $I < \sigma(I)$ was coded as unobserved. Three standard reflections ($\bar{6}$,0,12; 131; 600) were monitored every hour and showed no significant deviation (≈2.8%). A total of 2379 reflections were recorded of which after correction for Lorentz and polarization effects 2112 with $|F|^2 > 2.0\sigma(F^2)$ were taken as observed. Fractional coordinates of the I atom were determined by the Patterson method. The iodine contribution alone gave R = 0.244. Subsequent structure factor and Fourier calculations revealed the positions of all non-hydrogen atoms forming the nucleotide molecule. The structural model was refined isotropically by full-matrix least squares to an R value of 0.097. At this stage a spherical empirical absorption correction (μ = 20.9 cm^{-1}) was calculated by using program DIFABS.[40] The minimum and maximum absorption corrections were 0.838 and 1.347, respectively. This reduced R to 0.071. Coordinates of H atoms bound to C atoms were generated from assumed geometries while those belonging to the NH and OH groups were located in difference electron density calculations. The H positions were only included with an individual isotropic temperature factor in the structure factor calculations. Although positional disorder of the water molecules was observed, the refinement converged at 0.034 (R_w = 0.039, R_{tot} = 0.045) (S = 1.91). The atomic scattering factors were taken from standard tables.[41] Analysis of the disordered hydrogen bond network is in progress. For additional details, see supplementary material available paragraph.

Antitumor Assays. L1210/0, L1210/BdUrd, Raji/0, and Raji/TK^- cell lines were characterized as described.[38] The antitumor assays were performed according to previously established procedures.[43]

Antiviral assays were performed as reported previously.[39c] The origin and preparation of the virus stocks have also been documented in ref 39c.

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Registry No. 1, 99641-46-0: **2**, 99641-50-6; **2** (sodium salt), 99641-51-7; **3**, 99641-47-1; **4**, 99641-48-2; **4** (sodium salt), 99641-49-3; 5-F-UMP (diammonium salt), 99631-71-7; 5-FU, 316-46-1; 5-F-UMP morpholide (ammonium salt), 83858-41-7; cUMP (sodium salt), 56632-58-7; phosphoryl chloride, 10025-87-3.

Supplementary Material Available: Fractional coordinates, anisotropic thermal parameters, bond distances, bond angles, and torsion angles are available. ^{13}C NMR parameters for 1–4 also may be obtained (7 pages). Ordering information is given on any current masthead page. Observed and calculated structure factors can be obtained from A. Kálmán on request.

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