mol) was added dropwise at −50 °C with stirring. The reaction mixture was allowed to warm to ambient temperature, stirred for 16 h, and then adjusted to neutral pH with HOAc (3.5 mL, 0.06 mol). Evaporation of the THF solution at reduced pressure gave the crude ethyl ester of **9** (7.1 g), which was hydrolyzed according to the previously published procedure[2] to give 2.4 g (35%) of **9** as a light tan foam: NMR ($CDCl_3$) δ 6.5 (s, 1, NH), 1.5 (s, 3, C-CH_3). Anal. ($C_{20}H_{21}NO_4$) C, H, N.

1-[5-(Benzoylamino)-5-methyl-1,4-dioxo-6-phenylhexyl]-L-proline (10). When the previously described procedure was used, compound **9** (2.3 g, 0.0068 mol) gave 1.5 g (50%) of **10** as a light tan, glossy foam: mp 90–100 °C; $[\alpha]^{23}_D$ −73.5° (*c* 1.05, $CHCl_3$). Anal. ($C_{25}H_{28}H_2O_5 \cdot 0.5H_2O$) C, H, N.

Methyl [3-(Benzoylamino)-2-oxo-4-phenylbutoxy]acetate (17). Triethylamine (7.5 mL, 0.055 mol) was added dropwise with stirring and cooling in an ice bath to a solution of 2-phenyl-4-(phenylmethyl)-5(4*H*)-oxazolone (12.55 g, 0.05 mol) and methyl 2-(chloroformylmethoxy)acetate[8] (8.35 g, 0.05 mol) in THF (100 mL). After 2 h, the ice bath was removed, and the suspension was allowed to stand overnight. The filtrate was evaporated at reduced pressure at <50 °C to give a quantitative yield of acylated oxazolone [TLC (*i*-Pr_2O) R_f 0.64]. The crude product was dissolved in pyridine (60 mL), warmed to 80 °C, and HOAc (45 mL) was added in one lot. The solution was heated on a steam bath with stirring for 1 h and evaporated at reduced pressure. The crude product was crystallized from *i*-Pr_2O to yield 14 g (79%) of **17**, mp 117–119 °C. Anal. ($C_{20}H_{21}NO_5$) C, H, N.

[3-(Benzoylamino)-2-oxo-4-phenylbutoxy]acetic Acid (18). A solution of **17** (13.8 g, 0.039 mol) in 200 mL of THF and 90 mL of aqueous NaOH (0.5 N) was warmed to 40 °C and then allowed to stand for 20 h at ambient temperature. THF was evaporated at reduced pressure at <40 °C, and the solution was acidified to pH 4 with dilute HCl. The product was collected by filtration, washed with H_2O, and recrystallized from EtOAc to give 8.6 g (65%) of **18**, mp 140–142 °C. Anal. ($C_{19}H_{19}NO_5$) C, H, N.

Ethyl *N*-(Carboxymethyl)-*N*-[(4-methylphenyl)-sulfonyl]glycinate (19). Ethyl *N*-[(4-methylphenyl)sulfonyl]-glycinate[10] (49 g, 0.19 mol) in DMF (190 mL) was converted to the Na salt with NaH (0.19 mol) and alkylated with benzyl chloroacetate (35 g, 0.19 mol). The crude product, showing one spot only on TLC, was catalytically debenzylated in the presence of Pd/C in THF. The crude product was slurried in *i*-Pr_2O (300 mL) to give 43.4 g (72%) of **19**, mp ~100 °C. A sample was recrystallized from *i*-Pr_2O to give a white solid, mp 104–105 °C. Anal. ($C_{13}H_{17}NO_6S$) C, H, N.

1-[[[3-(Benzoylamino)-2-oxo-4-phenylbutyl]amino]-acetyl]-L-proline (14). To a solution of **13** (7.9 g, 0.013 mol) in liquid NH_3 (300 mL) was added finely cut Na (2.9 g, 0.126 mol) until the reaction mixture remained dark blue. After 0.5 h, NH_4Cl (7.5 g, 0.14 mol) was added. Liquid NH_3 was allowed to evaporate. The residue was slurried in H_2O (100 mL). The pH was adjusted to ~5 with HOAc. The product was taken up in CH_2Cl_2 and was washed with H_2O. The crude product (2.8 g) was dissolved in boiling acetone and precipitated on concentration and cooling as a tan powder: yield 1.8 g (32%); mp 150–155 °C. Anal. ($C_{24}H_{27}N_3O_5$) C, H, N.

Biological Methods. The in vitro ACE inhibitory activity was determined by a radioassay procedure reported previously.[2] The oral testing for antihypertensive activity was carried out in renal hypertensive rats (n = 2) at a dose of 30 mg/kg as described previously.[2]

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Synthesis and Biological Activity of 5′-Substituted 5-Fluoropyrimidine Nucleosides

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5′-Deoxy-5-fluorouridine (5′-dFUrd, **1**) possesses a significantly higher chemotherapeutic index than other fluoropyrimidines as a result of its being selectivity cleaved in tumors to 5-fluorouracil (FUra) by uridine phosphorylase. Because **1** is a relatively poor substrate for this enzyme, we synthesized a series of 5′-deoxy-5′-substituted-5-fluorouridine (FUrd) derivatives in an effort to obtain compounds that might have improved substrate interactions compared to **1** and thus possibly be better prodrugs of FUra. Three derivatives, 5′-*O*-tosyl-FUrd (**13**), 5′-*O*-mesyl-FUrd (**14**), and 5′-deoxy-5′-bromo-FUrd (**15**), had cytostatic activity against L1210 and CCRF-CEM leukemic cells in culture superior to that of **1**. In preliminary in vivo antitumor studies against L1210 leukemic cells in mice, 5′-deoxy-5′-chloro-FUrd (**4**), 5′-*O*-mesyl-FUrd (**14**), and 5′-deoxy-5′-fluoro-FUrd (**18**) gave percent increases in life span of 64, 58, and 58, respectively, compared to a value of 20 for compound **1**.

Considerable interest has been generated recently in the newly synthesized fluoropyrimidine 5′-deoxy-5-fluorouridine (5′-dFUrd, **1**)[1,2] by the discovery that this compound (1) possesses superior antitumor activity against experimental tumors in animals and (2) causes considerably less host toxicity compared to the well-known clinically used fluoropyrimidines 5-fluorouracil (FUra), 5-fluorodeoxyuridine (FdUrd), and Ftorafur (Ft).[3,4] Because **1** lacks a 5′-hydroxy group, it cannot be directly phosphorylated by pyrimidine kinases, and so the conversion to nucleotides that is necessary for cytotoxicity must be effected via alternate pathways. There is now good evidence that the activity of **1** against tumor cells in culture depends on its cleavage to FUra by uridine phosphorylase, an enzyme which is not ubiquitously present as is thymidine phosphorylase but is distributed unequally among various tissues and organs.[5] Uridine phosphorylase activity has been found to be considerably higher in Walker carcinoma 256,[5] hepatomas,[6] and solid sarcoma 180[5,7] than in the surrounding normal tissue. These observations are

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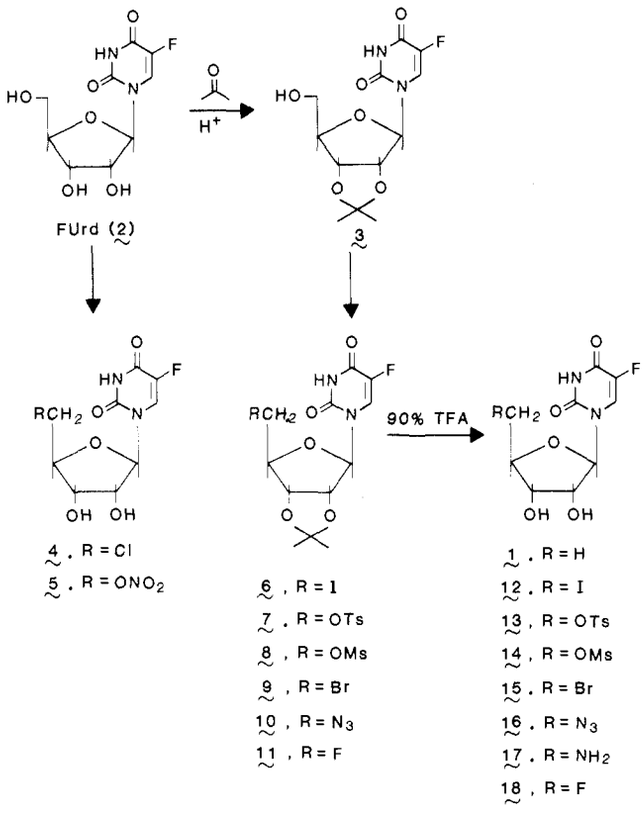
Scheme I



consistent with recent studies showing that administration of **1** to tumor-bearing mice gives rise to significantly greater concentrations of FUra in tumor tissue than in other tissues of the animal; such a selective distribution of FUra was not seen upon dosing with either FUra itself or Ft.[8] The apparent tumor-selective generation of FUra from **1** provides a convincing explanation for the substantially better chemotherapeutic index of **1** compared to the other fluoropyrimidines.

We have synthesized a series of 5′-substituted derivatives of 5-fluorouridine (FUrd, **2**) in order to investigate the effect of structural changes at this position on biological activity, in the hope that the proper substituents could lead to even better prodrugs of FUra. For example, an increased rate of generation of FUra within tumor cells might be achieved with compounds having an enhanced substrate interaction with uridine phosphorylase. Kinetics studies performed with isolated uridine phosphorylase showed that **1** is a relatively poor substrate for this enzyme, with a K_m value about 13-fold higher than that of **2**. This ratio is probably reflected in the high doses of **1** that are necessary to obtain the maximal therapeutic effect.[3-5,9] Structural modifications could also be used to alter the tissue distribution and rate of excretion of the prodrug. In this paper, we describe the synthesis of the 5′-substituted derivatives of **2**, their cytostatic activities against L1210 mouse leukemia and CCRF-CEM human leukemia cells in culture, and a preliminary evaluation of in vivo antitumor activity against L1210 leukemia in mice.

Chemistry. FUrd (**2**), the starting material for all compounds in Scheme I, was synthesized by published procedures.[10,11] The synthesis of 5′-deoxy-5′-chloro-FUrd (**4**) was carried out by the method of Hřebabecký and Beránek.[1] 5′-*O*-Nitro-FUrd (**5**) was prepared by treatment of unprotected FUrd with nitric acid at −70 °C, according to a general procedure developed or the 5′-O-nitration of pyrimidine nucleosides.[12] This method gave a mixture of mono-, di-, and tri-*O*-nitrates of FUrd from which **5** was separated by preparative layer chromatography in 30% yield. The synthesis of **5** had been previously reported in a patent[13] without, however, any description of physical or chemical properties. While this work was in progress, Chwang et al.[14] synthesized **5** by nitration of 2′,3′-*O*-acetyl-FUrd and subsequent deacetylation. The synthesis of the rest of the compounds in this series required using the blocked nucleoside, 2′,3′-*O*-isopropylidene-FUrd (**3**)[15] as an intermediate. After the appropriate reaction(s) was performed on the 5′-position, the isopropylidene group was removed with 90% trifluoroacetic acid to give the desired 5′-substituted derivatives (Scheme I). The procedures of Cook et al.[2] were used to obtain 5′-deoxy-5′-iodo-FUrd (**12**) and compound **1**. Treatment of **3** with *p*-toluenesulfonyl chloride in pyridine, followed by deblocking, gave 5′-*O*-tosyl-FUrd (**13**). Reaction of **3** with methanesulfonyl chloride and removal of the isoproylidene group afforded 5′-*O*-mesyl-FUrd (**14**). When 5′-*O*-mesyl-2′,3′-*O*-isopropylidene-FUrd (**8**) was refluxed in acetone in the presence of LiBr, the protected nucleoside **9** was obtained, which, upon deblocking, was converted into 5′-deoxy-5′-bromo-FUrd (**15**). Treatment of **8** with LiN_3 in DMF and deblocking of the resulting compound **10** gave 5′-deoxy-5′-azido-FUrd (**16**). Triphenylphosphine has been used for the conversion of azides into amines.[16] Treatment of **16** with this reagent in pyridine at room temperature, followed by hydrolysis of the intermediate with concentrated NH_4OH, afforded 5′-deoxy-5′-amino-FUrd (**17**), which gave a positive ninhydrin reaction. 5′-Deoxy-5′-fluoro-FUrd (**18**) was obtained by treatment of **8** with KF in ethylene glycol

Table I. Inhibition by 5′-Substituted FUrd Derivatives on the Growth of L1210 Mouse Leukemia and CCRF-CEM Human Leukemia Cells in Culture

compd	IC_{50},[a] M	
	L1210	CCRF-CEM
FUra	5×10^{-7}	5×10^{-6}
2	5×10^{-9}	5×10^{-8}
1	3.6×10^{-6}	2.2×10^{-5}
4	3.4×10^{-6}	3.3×10^{-6}
5	*b*	*b*
12	5.0×10^{-6}	2.7×10^{-5}
13	4.6×10^{-7}	1.8×10^{-6}
14	3.2×10^{-7}	6.6×10^{-7}
15	8.0×10^{-7}	3.1×10^{-6}
16	1.7×10^{-4}	3.5×10^{-4}
17	8.7×10^{-6}	4.9×10^{-5}
18	2.9×10^{-5}	1.4×10^{-4}

[a] Concentration required for 50% inhibition growth. [b] No growth inhibition was observed at a concentration of 10^{-4} M.

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Table II. Antitumor Activity of 5′-Substituted FUrd Derivatives against L1210 Leukemia in Mice[a]

compd	ip dose, (mg/kg)/day	change of body wt after 7 days, %	mortality (mean ± SD), days	ILS,[b] %
none		+14.4	10.6 ± 0.5	
1	250	0	12.8 ± 1.7	20
	150	+4.8	12.0 ± 1.0	13
	100	+5.7	11.4 ± 0.5	8
4	250	−4.6	17.4 ± 3.3	64
	150	−3.5	16.0 ± 2.5	51
	100	−0.8	15.6 ± 1.9	47
12	200	−7.5	13.2 ± 2.4	25
	100	0	13.2 ± 2.7	25
	50	0	12.2 ± 2.1	16
14	250	−1.7	16.8 ± 2.1	58
	150	+1.3	14.8 ± 0.8	40
	100	0	13.4 ± 1.6	26
15	250	−1.8	14.2 ± 2.5	34
	150	+0.8	15.0 ± 1.8	41
	100	+1.7	14.2 ± 1.6	34
17	250	−0.9	13.6 ± 0.8	28
	150	−5.5	12.8 ± 0.4	19
	100	+1.8	12.4 ± 0.5	17
18	250	+2.3	16.8 ± 3.1	58
	150	+0.9	13.8 ± 1.9	30
	100	−5.6	14.0 ± 0.7	32

[a] Groups of five female DBA/2 mice were implanted ip with 10^5 L1210 cells on day 0. Treatment was begun by inoculation on day 1 and continued through day 5 (q.d. 1–5). Animals were weighed on days 1 and 7, and the weight change was expressed as a percentage of the initial weight. [b] Increase in life span.

and subsequent removal of the blocking group. The procedure of Schütt et al.[17] for the synthesis of 5′-deoxy-5′-fluorouridine involving nucleophilic substitution of the tosyl group by fluoride proved to be less satisfactory because it required a long reaction time and gave a difficultly separable mixture of products. A ^{19}F NMR of **18** showed that the 5′-fluorine was geminally split by the 5′-protons, giving a triplet with a coupling constant of 30 Hz, and vicinally split by the 4′-proton, giving a doublet with a coupling constant of 48 Hz.

Biological Activity. Compounds **1**, **4**, **5**, and **12–18** were tested as inhibitors of the growth of L1210 mouse leukemia and CCRF-CEM human leukemia cells in culture (Table I). 5′-*O*-Nitro-FUrd (**5**) was found to be without effect on the growth of L1210 cells or CCRF-CEM cells even at 10^{-4} M.[18] A number of compounds, viz., **13–15**, had cytotostatic activity significantly superior to that of **1**. The relatively low activity of 5′-deoxy-5′-amino-FUrd (**17**) was somewhat surprising, because we expected that the amino group would effectively simulate the 5′-hydroxy group of uridine and thus allow **17** to be a good substrate for cleavage by uridine phosphorylase. However, the fact that the 5′-amino group is largely protonated at physiological pH and thus bears a positive charge may affect interaction of the nucleoside with the enzyme and/or the cellular uptake. Preliminary in vivo antitumor evaluation was carried out with compounds **1**, **4**, **12**, **14**, **15**, **17**, and **18** against L1210 leukemia in mice (Table II). The results of these experiments indicate that 5′-deoxy-5′-chloro- (**4**), 5′-*O*-mesyl- (**14**), and 5′-deoxy-5′-fluoro-FUrd (**18**) derivatives had substantially better activity than **1**. Work is in progress to determine the kinetic constants involved in the interaction of these compounds with uridine phosphorylase isolated from L1210 cells to determine whether there is any correlation of substrate properties with biological activity.

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(18) Chwang et al.[14] reported that **5** had a "significant antitumor activity". It should be stressed that great care must be taken to purify compounds obtained by derivatizing already potent growth inhibitors. Because **2** has an IC_{50} value on the order of 10^{-8} M, with most cell lines as little as 1% contamination of a derivative with this material would result in significant inhibition of cell growth and thus lead to an erroneous conclusion regarding the activity of the compound. In all of the samples we used for cell culture experiments, contamination with FUrd (**2**) was below the level of detection of the HPLC instrument (i.e., less than 0.1%).

Experimental Section

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was done using 0.2-mm thickness silica gel F plates obtained from E. Merck. The preparative separations were carried out on Analtech 1- or 2-mm (20 × 20 cm) silica gel F glass plates. Du Pont 836 high-pressure liquid chromatography (HPLC) equipped with Hewlett Packard 3380A integrator was used to check the purity of the samples. UV spectra were obtained using a Beckman 25 spectrophotometer, NMR spectra were obtained using a Varian XL-200 spectrophotometer, and mass spectral data were taken with a Hewlett Packard GC/MS 5985A equipped with a dual EI/CI source at 70 eV. The elemental analysis were performed by Spang Micro Analytical Laboratory, Eagle Harbor, MI, and Galbraith Labortory, Inc., Knoxville, TN, and were within ±0.4% of the theoretical values.

5′-Deoxy-5-fluorouridine (1). The method of Cook et al.[2] was followed to synthesize **1** from 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylidene-5-fluorouridine (**6**), mp 184–186 °C (lit.[2] mp 186–188 °C).

5′-Deoxy-5′-chloro-5-fluorouridine (4). This compound was prepared by the method of Hřebabecký and Beránek[1] and crystallized from 2-propanol, mp 177–179 °C (lit.[1] mp 181–182 °C).

5′-*O*-Nitro-5-fluorouridine (5). To precooled (−70 °C) 90% nitric acid (ρ = 1.48, 3.75 mL) was added **2** (0.64 g, 2.45 mmol) with vigorous stirring. The solution became clear in 15–20 min and was stirred for 1 h at −70 °C. At this time more nitric acid (3.75 mL) was added, and the solution was stirred for an additional 30 min. Ice–water (50 mL) and ethyl acetate (50 mL) were added, and the solution neutralized slowly with sodium bicarbonate while stirring. The aqueous phase was extracted with ethyl acetate (6 × 25 mL), which was dried overnight over sodium sulfate and then evaporated to dryness. The syrup was purified by preparative layer chromatography ($CHCl_3$–MeOH, 9:1), and crystallized from acetone–chloroform to yield **5** (0.21 g, 30%): mp 158–160 °C (lit.[14] mp 160 °C); MS, *m/e* 307.2 (M^+); NMR (Me_2SO-d_6) δ 7.72 (d, 1, J = 7.4 Hz, CHCF), 5.62 (dd, 1, J = 5.2 Hz, $C_{1'}$ H), 5.3 (m, 2, OH), 4.55 (m, 2,5′-CH_2ONO_2), 4.04–4.35 (m, 3, $C_{2'}$H, $C_{3'}$H, $C_{4'}$ H). Anal. ($C_{10}H_{10}FN_3O_8 \cdot 0.5H_2O$) C, H, N.

5′-Deoxy-5′-iodo-2′,3′-*O*-isopropylidene-5-fluorouridine (6) and 5′-Deoxy-5′-iodo-5-fluorouridine (12). The syntheses of **6** and **12** were carried out via 2′,3′-*O*-isopropylidene-FUrd (**3**) by the method of Cook et al.[2] **6**: mp 200–202 °C (lit.[2] mp 202–203.5 °C). **12**: mp 172–174 °C (lit.[2] mp 174.5–175.5 °C).

5′-*O*-Tosyl-2′,3′-*O*-isopropylidene-5-fluorouridine (7) and 5′-*O*-Tosyl-5-fluorouridine (13). To a solution of **3** (1.05 g, 3.5 mmol) in dry pyridine (10 mL) at 0 °C was added *p*-toluenesulfonyl chloride (1.33 g, 7.00 mmol). After being stirred for 18 h at 0 °C, the solution was concentrated, and the residue was partitioned between a cold aqueous saturated solution of cadmium chloride (100 mL) and ethyl acetate (100 mL). The biphasic system was stirred at room temperature for 10 min and then filtered through Celite to remove the cadmium chloride–pyridine complex. The aqueous layer was extracted with ethyl acetate 2 × 50 mL), washed twice with water, dried overnight over sodium sulfate, and evaporated to dryness to give **7** in the form of a syrup. The syrup was dissolved in 90% aqueous trifluoroacetic acid (10 mL). After 30 min at room temperature, the solution was evaporated to dryness. Ethanol was added and evaporated several times, and **13** (1.1 g, 70%) was then crystallized from ethanol: mp 175–177 °C; UV (MeOH) λ_{max} 268–269 nm (ϵ 9510); NMR

(Me_2SO-d_6) δ 11.8 (br s, 1, NH), 7.80 (d, 3, J = 7.8 Hz, 2 aromatic H and CHCF), 7.48 (d, 2, J = 8 Hz, 2 aromatic H), 5.70 (dd, 1, J = 1.4 and 5 Hz, $C_{1'}$ H), 5.4 (m, 2, OH), 4.22 (d, 1, J = 4 Hz, $C_{2'}$ H), 4.02 (m, 1, $C_{3'}$ H), 3.91 (m, 1, $C_{4'}$ H), 3.34 (m, 2, 5'-CH_2OTos), 2.40 (s, 3, CH_3 of p-Tos). Anal. ($C_{16}H_{17}FN_2O_8S$) C, H, F, N.

5'-*O*-Mesyl-2',3'-*O*-isopropylidine-5-fluorouridine (8) and 5'-Deoxy-5'-*O*-mesyl-5-fluorouridine (14). A solution of **3** (2.5 g, 8.20 mmol) in dry pyridine (25 mL) was treated at 0 °C with methanesulfonyl chloride (3.5 mL) and stirred for 3 h. The solution was then concentrated and partitioned beween a cold aqueous saturated solution of cadmium chloride (100 mL) and ethyl acetate (150 mL). The biphasic mixture was stirred at room temperature for 10 min and filtered through Celite. The aqueous layer was extracted with ethyl acetate (2 × 50 mL), which was washed twice with water, dried overnight over sodium sulfate, and evaporated to dryness to give **8** (2.45 g, 78%). An analytical sample of **8** was obtained from ethanol: mp 157–159 °C; NMR (Me_2SO-d_6) δ 8.06 (d, 1, J = 7 Hz, CHCF), 5.77 (dd, 1, J = 3.8 and 5.2 Hz, $C_{1'}$ H), 5.08 (dd, 1, J = 3.4 and 7.6 Hz, $C_{2'}$ H), 4.81 (dd, 1, J = 4 and 6.4 Hz, $C_{3'}$ H), 4.40 (m, 1, $C_{4'}$ H), 3.34 (s, 2, 5'-CH_2OMes), 3.18 (s, 3, CH_3SO_2), 1.28 and 1.48 [s, 3, $(CH_3)_2$C]. Anal. ($C_{13}H_{17}FN_2O_8S$) C, H, F, N.

The isopropylidene derivative **8** (1.3 g, 3.4 mmol) was placed in 90% aqueous trifluoroacetic acid (10 mL) for 30 min, which was then evaporated. After repeated addition–evaporation of ethanol, the residue was crystallized from ethanol to give **14** (0.9 g, 78%): mp 166–168 °C; MS, m/e 340.2 (M^+); UV (MeOH) λ_{max} 268–269 (ε 9650); NMR (Me_2SO-d_6) δ 7.97 (d, 1, J = 7 Hz, CHCF), 5.77 (dd, 1, J = 3.8 and 5.2 Hz, $C_{1'}$ H), 5.5 (m, 2, OH), 4.41 (d, 1, J = 5.4 Hz, $C_{2'}$ H), 3.94–4.09 (m, 2, $C_{3'}$ H and $C_{4'}$ H), 3.35 (s, 2,5'-CH_2OMes), 3.20 (s, 3, CH_3SO_2). Anal. ($C_{10}H_{13}FN_2O_8S$) C, H, F, N.

5'-Deoxy-5'-bromo-2',3'-*O*-isopropylidene-5-fluorouridine (9) and 5'-Deoxy-5'-bromo-5-fluorouridine (15). A solution of **8** (1.33 g, 3.5 mmol) and lithium bromide (3.47 g, 40 mmol) in dry acetone (70 mL) was stirred and heated at reflux temperature for 10 h. The reaction mixture was concentrated in vacuo and then partitioned between ethyl acetate (50 mL) and water (30 mL). The aqueous layer was extracted with ethyl acetate (4 × 40 mL), which was washed with water, dried overnight over sodium sulfate, and evaporated to give **9** in the form of a syrup. The syrup was placed in 90% aqueous trifluoroacetic acid (10 mL) for 30 min, which was then evaporated. After several additions–evaporation of ethanol, **15** (0.90 g, 80%) was crystallized from ethyl acetate: mp 168–170 °C; MS, m/e 325 (M^+); UV (MeOH) λ_{max} 268–269 (ε 9420); NMR (Me_2SO-d_6) δ 7.98 (d, 1, J = 6.8 Hz, CHCF), 5.79 (dd, 1, J = 4 and 5.8 Hz, $C_{1'}$ H), 5.55 (m, 2, OH), 4.28 (dd, J = 4 and 8 Hz, $C_{2'}$ H), 3.95–4.15 (m, 2, $C_{3'}$ H and $C_{4'}$ H), 3.88 (m, 2,5'-CH_2Br). Anal. ($C_9H_{10}FBrN_2O_5$·0.5H_2O) C, H, F, Br, N.

5'-Deoxy-5'-azido-2',3'-*O*-isopropylidene-5-fluorouridine (10) and 5'-Deoxy-5'-azido-5-fluorouridine (16). A solution of **8** (2.0 g, 5.26 mmol) in dry DMF (40 mL) and lithium azide (1.0 g, 20.42 mmol) was heated for 2 h at 75–80 °C. The DMF was evaporated to dryness, and the residue was partitioned between cold water (100 mL) and ethyl acetate (75 mL). The aqueous layer was extracted twice with ethyl acetate (50 mL), which was dried overnight over sodium sulfate and evaporated to dryness to give **10** (1.25 g, 72%). An analytical sample of **10** was obtained from ethanol: mp 165–167 °C; MS, m/e 327.1 (M^+); NMR (Me_2SO-d_6) δ 8.12 (d, 1, J = 6.8 Hz, CHCF), 5.76 (d, 1, J = 2.0 Hz, $C_{1'}$ H), 5.07 (dd, 1, J = 2.6 and 6.4 Hz, $C_{2'}$ H), 4.76 (dd, 1, J = 4.2 and 6.4 Hz, $C_{3'}$ H), 4.41 (m, 1, $C_{4'}$ H), 3.57 (m, 2,5'-CH_2N_3), 1.47 and 1.27 [s, 3, $(CH_3)_2$C]. Anal. ($C_{12}H_{14}FN_5O_5$) C, H, F, N.

Compound **10** (1.0 g, 3.05 mmol) was allowed to stand for 30 min in 90% aqueous trifluoroacetic acid (8 mL), which was then evaporated. Repeated addition–evaporation of ethanol gave a white solid, which was recrystallized from ethanol to give **16** (0.65 g, 75%): mp 166–168 °C; MS, m/e 287.1 (M^+); UV (MeOH) λ_{max} 268–269 (ε 8220); NMR (Me_2SO-d_6) δ 8.02 (d, 1, J = 7 Hz, CHCF), 5.75 (dd, 1, J = 1.6 and 5.2 Hz, $C_{1'}$ H), 5.49 (d, 1, J = 6 Hz, OH), 5.30 (d, 1, J = 4.4 Hz, OH), 4.14 (d, 1, J = 5.2 Hz, $C_{2'}$ H), 3.92 (m, 2, $C_{3'}$ H, $C_{4'}$ H), 3.57 (m, 2,5'-CH_2N_3). Anal. ($C_9H_{10}FN_5O_5$) C, H, F, N.

5'-Deoxy-5'-amino-5-fluorouridine (17). A mixture of **16** (0.38 g, 1.33 mmol) and triphenylphosphine (0.56 g, 2.12 mmol) in dry pyridine (15 mL) was stirred at room temperature for 1 h. To the reaction mixture was added concentrated NH_4OH (1.7 mL), and the solution was stirred at room temperature for 3 h. The solvent was evaporated and several repeated additions–evaporations of ethanol yielded a white solid. The solid was triturated with ether (50 mL), and the suspension was filtered and washed with benzene–ether (1:1, 250 mL). The white solid was dissolved in water (50 mL), and the insoluble material was removed by filtration. The aqueous solution was evaporated to dryness in vacuo, and the residue crystallized from ethanol to give **17** (0.21 g, 57%): mp 135 °C dec; UV (MeOH) λ_{max} 268–269 (ε 8950); NMR (Me_2SO-d_6) δ 8.32 (d, 1, J = 7.4 Hz, CHCF), 3.91–4.40 (m, 3, $C_{2'}$ H, $C_{3'}$ H, $C_{4'}$ H), 5.72 (d, 1, J = 7 Hz, $C_{1'}$ H), 3.75 (m, 2, 5'-CH_2NH_2,D_2O exchangeable). Anal. ($C_9H_{12}FN_3O_5$) C, H, F, N.

5'-Deoxy-5'-fluoro-2',3'-*O*-isopropylidene-5-fluorouridine (11) and 5'-Deoxy-5'-fluoro-5-fluorouridine (18). A mixture of dried **8** (1.35 g, 3.55 mmol) and potassium fluoride (1.00, 17.25 mmol) in ethylene glycol (7 mL) was heated at 140–150 °C. After the mixture became clear, it was heated at this temperature for an additional 20 min. Then acetone (200 mL) was added to precipitate the potassium mesylate. The salt was removed by filtration, and the acetone was evaporated. The residue was lyophilized to remove ethylene glycol. Preparative TLC ($CHCl_3$–acetone, 3:1) afforded **11** in the form of a syrup, which was placed in 90% aqueous trifluoroacetic acid (10 mL) for 30 min. The solvent was evaporated, and repeated addition–evaporation of ethanol gave $J_{C_4'H-F}$ solid residue, which was crystallized from ethanol to give **18** (0.29 g, 31%): mp 177–179 °C; MS, m/e 264.1 (M^+); UV (MeOH) λ_{max} 268–269 nm (ε 8250); NMR (Me_2SO-d_6) δ 7.82 (d, 1, J = 7 Hz, CHCF), 5.74 (dd, 1, J = 2 and 6 Hz, $C_{1'}$ H), 5.55 (d, 1, J = 5 Hz, OH), 5.35 (d, 1, J = 5.2 Hz, OH), 4.77 (dd, 1, J = 2.6 and 6.4 Hz, $C_{2'}$ H), 4.51 (d, 1, J = 36 Hz, $C_{3'}$ H), 3.93–4.05 (m, 3, $C_{4'}$ H, 5'-CH_2F); ^{19}F NMR (Me_2SO-d_6) J_{H6-F} = 5.6 Hz, $J_{C_4'H-F}$ = 48 Hz, $J_{C_5'H-F}$ = 30 Hz. Anal. ($C_9H_{10}F_2N_2O_5$) C, H, F, N.

Liquid Chromatography. High-pressure liquid chromatography was performed using a C_{18} reverse-phase column (Zorbax DDS, 4.6 × 150 mm) with a fixed wavelength (254 nm) UV detector at ambient temperature. The column was eluted using 2–10% methanol in water (flow rate, 2 mL/min). This methodology permitted the facile separation of FUrd (**2**) (t_r 3.6 min in 5% methanol) from the other nucleosides described in this paper.

Biological Testing. For biological testing, each compound was repeatedly chromatographed on preparative TLC plates until no FUrd (**2**) could be detected by HPLC (see ref 18). Aliquots of 10^5 mycoplasma-free L1210 or CCRF-CEM cells were inoculated into flasks containing RPMI 1640 medium supplemented with 10% fetal calf serum and the compound to be tested, to give a final volume of 2.0 mL. The cells were allowed to grow for 48 h and then were counted.

Antitumor Testing. Groups of five female DBA/2 mice, weighing between 18 and 22 g, were implanted intraperitoneally (ip) on day 0 with 10^5 L1210 cells (0.1 mL). Test compounds were dissolved in PBS. Intraperitoneal injection of the 0.2 mL of the test compound began the next day after tumor implantation and was continued for 5 days (q.d. 1–5 dose schedule). Control groups of animals received PBS. Results are reported in percent change in weight after the 7th day, mean mortality, and percent increase in life span.

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