

## Synthesis and Antiviral Activity of 5-Thien-2-yl-2'-deoxyuridine Analogues

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A number of 5-heteroaromatic-substituted 2'-deoxyuridines were synthesized from 5-iodo-2'-deoxyuridine using tetraorganotin reagents and palladium complexes as catalyst. The palladium-catalyzed cross-coupling reaction between 5-iodo-2'-deoxyuridine and stannylated heteroaromatics was optimized for the synthesis of the 5-thien-3-yl-2'-deoxyuridine and 5-furan-3-yl-2'-deoxyuridine. 5-(5-Iodothien-2-yl)-2'-deoxyuridine was used as starting material for the synthesis of 5-(5-methylthien-2-yl)-2'-deoxyuridine, 5-(5-vinylthien-2-yl)-2'-deoxyuridine, and 5-(5-ethynylthien-2-yl)-2'-deoxyuridine. 5-(5-Nitrothien-2-yl)-2'-deoxyuridine was synthesized using ceric ammonium nitrate as reagent. 5-(Isoxazol-5-yl)-2'-deoxyuridine was synthesized from 5-(3-oxopropyn-1-yl)-2'-deoxyuridine. Finally, 5-(5-chlorothien-2-yl)- $\beta$ -D-arabinofuranosyluracil and 5-(5-bromothien-2-yl)- $\beta$ -D-arabinofuranosyluracil were obtained by halogenation of 5-thien-2-yl- $\beta$ -D-arabinofuranosyluracil. Introduction of an alkyl substituent in the 5-position of the thienyl group of 5-thien-2-yl-2'-deoxyuridine or substitution of the 2-deoxyribofuranose ring by an arabinofuranose moiety gave decreased activity against HSV-1 and VZV replication when compared with the 5''-halogenated-5-thien-2-yl-2'-deoxyuridines. 5-(5-Bromothien-2-yl)-2'-deoxyuridine caused prompt healing of HSV-1 keratitis when administered as eye drops (0.2%) to rabbits.

### Introduction

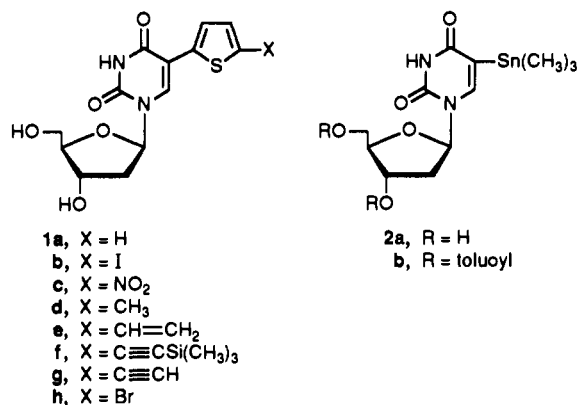
Recent advances in carbon-carbon coupling chemistry using transition metal catalysts and organotin compounds have offered a number of powerful synthetic possibilities to nucleoside chemists. Several publications dealing with the synthesis of uridines with unsaturated substituents in the 5 position have recently appeared. The coupling of 5-iodo-2'-deoxyuridine with alkenylstannanes was reported by Crisp.<sup>1</sup> The same group also described the coupling of 5-[(trifluoromethyl)sulfonyl]uridine tri-*O*-acetate with a number of vinyl and arylstannanes.<sup>2</sup> These aromatic rings were also introduced in the 5-position of both uridine and 2'-deoxyuridine using functionalized and nonfunctionalized arylboronic acids and aryltrimethylstannanes.<sup>3,4</sup> Yamamoto reported the synthesis of arylboron-10 5-substituted uridines, proving that the palladium catalyzed reaction proceeds selectively at the C-Sn bond rather than the C-B bond.<sup>5</sup> Casalnuovo and Calabrese described the coupling of unprotected 5-iodo-2'-deoxyuridine (IdUrd) with alkynes in aqueous medium using a water-soluble Pd(0) complex.<sup>6</sup> Coupling of uridine with a number of vinyl and allylic triflates<sup>7</sup> was reported by Hassan. Farina et al. applied the "Stille reaction" onto 5-iodouracil, 5-iodo-2'-deoxyuridine, and 5-iodouridine.<sup>8</sup>

The coupling of heteroaromatics to the 5-position of 2'-deoxyuridine was attempted by Pichat using the ZnCl<sub>2</sub>-salt method some 10 years ago.<sup>9</sup> In a previous article we described an improved method using the trialkylstannanes of the heteroaromatics.<sup>10</sup> Some of these compounds were also synthesized by Hassan using either the chloromercuri approach<sup>11</sup> or a photochemical method.<sup>12</sup> Here we describe the synthesis and antiviral activity of a number of closely

related analogues of 5-thien-2-yl-2'-deoxyuridine and of the 5''-halogenated derivatives of 5-thien-2-yl-2'-deoxyuridine.

### Chemistry

We previously reported an efficient method for the synthesis of 5-thien-2-yl-2'-deoxyuridine<sup>10</sup> (1a). In extension of these investigations the synthesis of 5-(trimethylstannyl)-2'-deoxyuridine (2a) was attempted. This



compound should allow a number of "inverse" Pd catalyzed couplings, i.e. between the 5-(trimethylstannyl) nucleoside and a number of halogenated heterocycles. Treatment of 3',5'-di-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyuridine with 2.2 equiv of *sec*-butyllithium in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was reported to result in a highly regioselective lithiation at the C-5 position of the uracil base.<sup>13</sup> Addition of an excess of trimethylstannyl chloride, however, resulted in the formation of several products which were not identified. The use of hexamethylditin and a palladium catalyst proved to be a better method. Unprotected 5-iodo-2'-deoxyuridine, hexamethylditin, and a catalytical amount of tetrakis(tri-

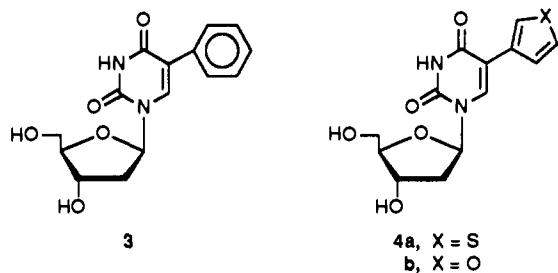
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phenylphosphine)palladium(0) were heated at reflux in dioxane. Two products were formed: the compound with the higher mobility on TLC was isolated in 50% yield and proven to be the trimethylstannyl derivative **2a**. The second compound was identified as 2'-deoxyuridine. The synthesis of **2a** was optimized using 3',5'-di-*O*-toluoyl-5-iodo-2'-deoxyuridine and ethyl acetate as solvent: after 24 h, 75% of the trimethylstannyl derivative **2b** was isolated. The rate of the reaction could be increased by adding potassium fluoride. The fluoride anion is known to weaken the Sn-Sn bond. However, the yield of the reaction decreased to 30%. 5-Phenyl-2'-deoxyuridine (**3**) and 5-(5-iodothiophen-2-yl)-2'-deoxyuridine (**1b**) were obtained in 50% yield, starting from **2b** by reaction with iodobenzene and 2,5-diiodothiophene.



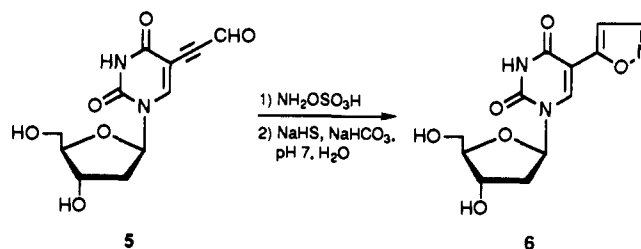
5-Thien-3-yl-2'-deoxyuridine (**4a**) and 5-furan-3-yl-2'-deoxyuridine (**4b**) were prepared using a slightly modified method as described before for **1a**.<sup>10</sup> The synthesis of these compounds could be improved by using *N*-methylpyrrolidinone (NMP) as solvent and a mixture of Pd(OAc)<sub>2</sub>, triphenylphosphine, and triethylamine as catalyst. Following this procedure 3',5'-di-*O*-acetyl-5-iodo-2'-deoxyuridine was converted to **1a** (room temperature) and to **4a** and **4b**.

The synthesis of **1b** was also attempted starting from readily available 5-thien-2-yl-2'-deoxyuridine (**1a**). The reactions were carried out on the acylated compounds. Iodine in carbon tetrachloride was found to be an inappropriate halogenation agent. Addition of a catalytical amount of cerium(IV) allowed a complete transformation at room temperature. The reaction mixture contains two compounds: 5-(5-iodothiophen-2-yl)-2'-deoxyuridine (**1b**) and 5-(5-nitrothien-2-yl)-2'-deoxyuridine (**1c**). When the amount of (NH<sub>4</sub>)<sub>2</sub>Ce(NO<sub>3</sub>)<sub>6</sub> was decreased, the formation of the nitrated compound diminished. Normally, ceric ammonium nitrate (CAN) is used as an oxidizing agent (for oxidation or oxidative cleavage). It can also be used in aromatic substitution reactions. The use of CAN as nitrating agent for polyaromatics has been mentioned in the literature.<sup>15</sup> However, CAN is not a nitrating agent of general applicability and it has not previously been used for the nitration of heteroaromatic rings.

The 5'-alkylated derivatives **1d-g** were obtained starting from acylated 5-(5-iodothiophen-2-yl)-2'-deoxyuridine using the "Stille reaction". A methyl group was introduced using tetramethyltin as alkylating agent. This strategy was described earlier for the conversion of 5-iodo-2'-deoxyuridine to thymidine and requires protection of the uracil base.<sup>16</sup> Vinyl and acetylenic groups were introduced using vinyltributyltin, (trimethylsilyl)acetylene, and palladium catalysts following earlier published methods.<sup>17</sup>

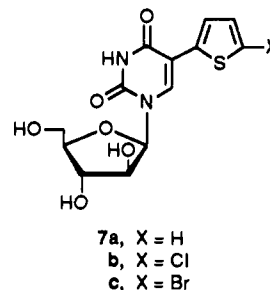
In a further extension to study the structure-activity relationship of 5-heterocyclic-substituted 2'-deoxyuridines<sup>10,18</sup> we were also interested in the isothiazole compound. Recently an Italian group reported an at-

tractive "one-pot" synthesis of isothiazoles starting from  $\alpha$ -keto alkynes, hydroxylamine-*O*-sulfonic acid, and NaHS in aqueous medium.<sup>19</sup> When we applied this method to 5-(3-oxopropyn-1-yl)-2'-deoxyuridine<sup>20</sup> (**5**), an isoxazole



ring instead of an isothiazole ring was formed. The reaction was carried out at different pH's (4, 7, and 10): in all cases compound **6** was the main product. The reaction was faster in basic medium (3 h) than in acidic medium (4 days).

As 5-substituted 2'-deoxyuridines are good substrates for the sugar base cleavage reaction catalyzed by phosphorylases, the arabinofuranosyl analogues **7a** and **7b** were



also synthesized. It is well known that nucleosides with an arabinofuranosyl sugar moiety are more resistant to phosphorolytic cleavage of the N-glycosidic bond than the 2'-deoxy congeners.<sup>21</sup> The arabinofuranosyl analogues were made starting from 5-thien-2-yl- $\beta$ -D-arabinofuranosyluracil<sup>10</sup> (**7a**) using the same methods as described for the 2'-deoxyuridine derivatives.

### Antiviral Activity

Introduction of an iodine atom at the 5'' position of 5-thien-2-yl-2'-deoxyuridine gave a compound (**1b**) that showed almost the same antiviral potency (Table I) as its bromo and chloro counterparts.<sup>10</sup> Also the halogenated arabinofuranosyl derivatives **7b,c** were potent inhibitors of herpes simplex virus type 1 (HSV-1). A 10-fold increase in activity against HSV-1 was noted when the thiophene ring was halogenated in the 5'' position. The thien-3-yl (**4a**) and the furan-3-yl (**4b**) derivatives showed antiviral effects that were comparable to those of the 2-yl derivatives. Introduction of alkyl substituents at the 5'' position **1d-g** gave compounds with moderate activity against HSV-1. 5-(5-Nitrothien-2-yl)-2'-deoxyuridine (**1c**) and 5-(isoxazol-5-yl)-2'-deoxyuridine (**6**) showed only weak activity against HSV-1. Introduction of a methyl (**1d**), vinyl (**1e**), or ethynyl (**1g**) group at the 5'' position led to compounds that were active against HSV-1 in the concentration range of 0.1 to 1  $\mu$ g/mL. Against varicella-zoster virus (VZV) the methyl analogue was more active than the vinyl (**1e**) or ethynyl (**1g**) derivative.

None of the compounds showed an appreciable activity against HSV-2 or thymidine kinase deficient (TK<sup>-</sup>) HSV-1 and VZV strains; nor did they prove inhibitory to cytomegalovirus (CMV). Inhibition of cell growth was

Table I. Antiviral Activity and Cytotoxicity in Vitro

virus	minimum inhibitory concentration ( $\mu\text{g/mL}$ ) <sup>a</sup>												
	BrVdUrd	1a	7b	7c	4a	4b	1b	1c	1d	1e	1f	1g	6
HSV-1 (KOS)	0.01	1.5	0.15	0.08	0.3	0.5	0.04	2	0.2	1.0	0.07	0.4	20
HSV-1 (F)	0.02	0.35	0.05	0.07	0.6	0.5	ND <sup>b</sup>	ND	0.2	ND	ND	0.2	20
HSV-1 (McIntyre)	0.01	0.3	0.015	0.02	0.04	0.07	ND	ND	0.7	ND	ND	0.2	2
HSV-2 (G)	70	50	300	70	70	150	>40	150	50	>200	>40	>200	300
HSV-2 (196)	>400	50	150	70	100	150	ND	ND	150	ND	ND	>200	300
HSV-2 (Lyons)	70	20	150	20	70	30	ND	ND	20	ND	ND	>200	>400
TK- HSV-1 (B2006)	>200	>100	>400	>100	150	100	>40	>200	400	>200	>40	>200	300
TK- HSV-1 (VMW 1837)	10	>100	>400	>100	>100	>200	>40	150	150	>200	>40	>200	>400
CMV (AD-169)	ND	60	30	30	>40	80	>40	>40	>40	>1.0	>10	>10	ND
CMV (Davis)	ND	40	70	35	>40	80	>40	>40	>40	>1.0	>10	>10	ND
VZV (Oka)	0.004	3	0.08	0.05	1.5	50	0.07	7	0.08	7	0.2	0.25	0.48
VSV (YS)	0.004	4	0.18	0.06	4	50	0.07	5	0.3	2	0.60	0.40	0.11
TK- VZV (07-1)	>40	8	60	40	35	>40	10	40	>40	7	21	5	ND
TK- VZV (YS/R)	>40	30	37	40	20	>40	40	>40	>40	10	20	17	10
VSV	>200	>100	>400	>100	>100	>200	>40	>200	>400	>200	>40	>200	>400
VV	0.2	20	>150	20	>40	>40	>40	150	>200	70	>40	>200	>400
morphological alteration	$\geq 400$	100	>400	>40	>100	>40	100	>200	>200	400	100	400	20
cell growth	>50	45	>50	>50	>50	>50	>50	>50	>50	3.5	10	14	>50

<sup>a</sup> Concentration required to reduce virus-induced cytopathicity or cell growth by 50%; for morphologic alteration, it corresponded to the minimum concentration required to cause a microscopically detectable alteration of cell morphology. <sup>b</sup> Not determined.

noted with compounds 10e-g. The 5'-iodinated thiophene derivative 1b was as active against VZV as its bromo and chloro counterparts. Also both halogenated arabinofuranosyl derivatives 7b,c were about 150 times more active against VZV than their nonhalogenated analogue.

While the nonhalogenated furan and thiophene derivatives (4a and 4b) were only weakly active against VZV, the chlorinated and brominated thiophenes were equally effective against both HSV-1 and VZV, irrespective of whether the sugar moiety was the 2-deoxy-<sup>10</sup> or arabinofuranosyl configuration (7b and 7c). The 5'-iodinated thiophene 1b also followed this rule. The antiviral activity of these compounds was dependent on phosphorylation by the virus-encoded thymidine kinase, as none of them was active against TK- HSV-1 or TK- VZV. Also, the activity spectrum of the 5'-chlorinated and 5'-brominated 5-thien-2-yl derivatives was virtually limited to HSV-1 and VZV and thus similar to that of BrVdUrd.

The in vivo activity of this group of compounds was investigated in two experiments. First, the survival of mice after intraperitoneal infection with HSV-1(KOS) and oral administration of compound 7c was determined, according to a previously established procedure.<sup>22</sup> Compound 7c was chosen because (i) the synthesis of the 5-(5-bromothien-2-yl) derivatives gives higher yields and less complex reaction mixtures than the synthesis of their chloro counterparts, and (ii) 5-substituted arabinofuranosyluracil derivatives are more resistant to deoxyuridine (thymidine) phosphorylases than their 2'-deoxy analogues. In vivo, this degradation reaction primarily occurs in the liver and may cause an important first-pass elimination of the drug. Compound 7c was administered at 25, 100, and 250 mg/kg per day as was the reference compound BrVdUrd. Because 7c at the highest concentration (2.5 mg/mL) could not be dissolved in water and did precipitate from a hot 90:10 mixture of water and propylene glycol, it was decided to use a 90:10 mixture of Sirupus Simplex (Ph. Belg. IV) and propylene glycol. Using this mixture, a homogenous suspension was obtained. Also for the placebo and the three BrVdUrd groups the same syrup was used as the drug vehicle. The drugs were administered orally once a day (via gavage) during 5 days starting on the day of infection. The survival of the mice was followed during 20 days. From Table II it can be concluded that

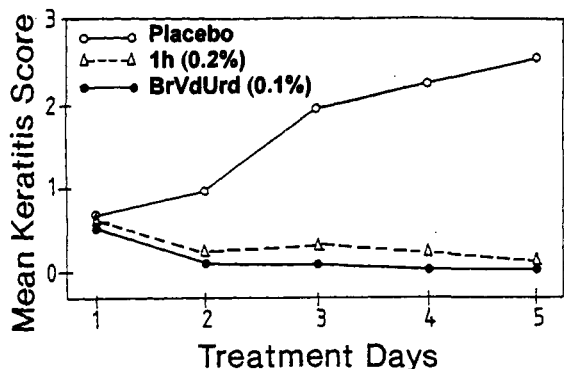
Table II. Antiviral Efficacy of 7c and BrVdUrd in Mice Injected Intraperitoneally with HSV-1 (KOS)

compd <sup>a</sup>	dose (mg/kg per day)	number of mice surviving at day after infection					
		0	3	6	9	12	20
7c	250	10	10	8	5	5	5
	100	10	10	8	1	1	1
	25	10	10	10	2	2	2
BrVdUrd	250	10	10	10	10	10	9
	100	10	9	9	8	8	7
	25	10	10	10	4	3	3
placebo	10	10	4	1	1	1	

<sup>a</sup> Administered orally (via gavage) once daily for 5 days (starting on the day of infection).

compound 7c is less active than BrVdUrd against HSV-1(KOS) infection (at the highest dose 50% protection was achieved). When administered at a lower dose, no protective effect was noted. In contrast, BrVdUrd afforded 90% protection at the highest dose (250 mg/kg per day) and was still protective at lower doses.

Compound 1h was evaluated in an herpetic keratitis model, according to a previously established procedure.<sup>23</sup> In this experiment the eyes of 30 rabbits were infected with HSV-1 (strain McIntyre) and the healing of the keratitis lesions (determined every day in a blind fashion) after topical application of the compounds (compound 1h, BrVdUrd, placebo) was determined. The compounds were formulated as eyedrops. Twenty microliters (1 drop) was instilled into the eyes eight times a day at 1-h intervals. Deoxyuridine (thymidine) phosphorylase activity is expected to be low or absent in the tears and corneal tissue. Therefore, we selected 1h (with a 2'-deoxyribofuranosyl sugar moiety) for this experiment. A concentration of 0.2% was chosen. However, the compound did not dissolve in water at a pH below 10. The compound was then dissolved in a 0.9% solution of sodium chloride in water at pH 10.25. The solutions were sterilized by filtration. A placebo group was included, which received a sterile 0.9% solution of NaCl at pH 10.25. BrVdUrd was included as a positive control, in the same solvent and at the same pH, at a concentration of 0.1%. From Figure 1 it is evident that compound 1h is about as effective as BrVdUrd in the topical treatment of HSV-1 keratitis in rabbits.



**Figure 1.** Effect of 5-(5-bromothien-2-yl)-2'-deoxyuridine 0.2% eyedrops (1h), as compared to BrVdUrd 0.1% eyedrops, on epithelial HSV-1 keratitis in rabbits. Treatment was started 110 h after infection. Eyedrops were administered at a rate of 1 eyedrop every hour, eight times a day for 5 days.

### Experimental Section

Melting points were determined in capillary tubes with a Büchi-Tottoli apparatus and are uncorrected. Ultraviolet spectra were recorded with a Philips PU 8700 UV/Vis spectrophotometer. The  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were determined with a JEOL FX 90Q spectrometer with tetramethylsilane as internal standard for the  $^1\text{H}$  NMR spectra and  $\text{DMSO}-d_6$  (39.6 ppm) for the  $^{13}\text{C}$  NMR spectra (s = singlet, d = doublet, t = triplet, br s = broad signal, m = multiplet). Precoated Merck silica gel F254 plates were used for TLC, and the spots were examined with UV light and sulfuric acid-anisaldehyde spray. Column chromatography was performed on Merck silica gel (0.063–0.200 nm). Anhydrous solvents were obtained as follows: tetrahydrofuran and dioxane were refluxed overnight on lithium aluminum hydride and distilled; dichloromethane was stored for 1 week on anhydrous calcium chloride, filtered, and distilled; water was removed from *N,N*-dimethylformamide by distillation with benzene followed by distillation in vacuo; toluene was refluxed overnight on sodium and distilled. Pyridine was dried by distillation after it had been refluxed for 24 h on potassium hydroxide.

The elemental analysis data are within 0.4% of the calculated values.

**5-(5-Chlorothien-2-yl)- $\beta$ -D-arabinofuranosyluracil (7b).** An amount of 500 mg (1.10 mmol) of 5-thien-2-yl-2',3',5'-tri-*O*-acetylurabinofuranosyluracil was dissolved in 25 mL of pyridine, and 175 mg (1.33 mmol) of *N*-chlorosuccinimide (NCS) was added. This mixture was stirred for 1 h at 70 °C. The mixture was evaporated to dryness and coevaporated twice with toluene. Chromatographic purification ( $\text{CH}_2\text{Cl}_2$ -MeOH, 87:13) yielded 200 mg (37%) of a foam. This foam was taken up in 20 mL of methanol saturated with ammonia. After evaporation and purification, 110 mg of 7b was obtained. The product was crystallized from 2-propanol: mp 232 °C; UV (MeOH)  $\lambda_{\text{max}}$  276 nm ( $\epsilon = 8500$ ),  $\lambda_{\text{max}}$  325 nm ( $\epsilon = 10600$ );  $^1\text{H}$  NMR (polysol)  $\delta$  3.73 (m, 3 H, H-2' and H-5'), 4.02 (m, 2 H, H-3' and H-4'), 5.34–5.55 (br s, 3 H,  $\text{D}_2\text{O}$  exchangeable 2'-OH, 3'-OH and 5'-OH), 6.08 (d, 1 H, H-1'), 6.86–7.13 (2  $\times$  d, 2 H, H-3'' and H-4''), 8.34 (s, 1 H, H-6), 11.85 (s, 1 H, NH) ppm;  $^{13}\text{C}$  NMR  $\delta$  60.2 (C-5'), 74.8 (C-3'), 75.5 (C-2'), 84.5 (C-4'), 85.7 (C-1'), 106.7 (C-5), 121.8 and 126.5 (C-3'' and C-4''), 128.3 (C-5''), 133.4 (C-2''), 137.7 (C-6), 149.8 (C-2), 161.5 (C-4) ppm. Anal. ( $\text{C}_{13}\text{H}_{13}\text{ClN}_2\text{O}_6\text{S}$ ) C, H, N.

**5-(5-Bromothien-2-yl)- $\beta$ -D-arabinofuranosyluracil (7c).** An amount of 200 mg (0.44 mmol) of 5-thien-2-yl-2',3',5'-tri-*O*-acetylurabinofuranosyluracil was dissolved in 25 mL of  $\text{CH}_2\text{Cl}_2$ . At 0 °C a solution of  $\text{Br}_2$  in  $\text{CCl}_4$  (0.033 mol/L, 15 mL) was added dropwise (20 min). The red color of bromine disappeared immediately. TLC evaluation revealed that all of the starting material had been transformed in a more lipophilic product. The solution was extracted with water (2  $\times$  25 mL), dried on  $\text{Na}_2\text{SO}_4$ , and evaporated. Chromatographic purification yielded 194 mg (83%) of an oil. The protective groups were removed with 20 mL of methanol saturated with ammonia. After evaporation the resulting oil was taken up in acetone and precipitated on addition

of heptane: 125 mg of 7b was obtained; mp 220–222 °C; UV (MeOH)  $\lambda_{\text{max}}$  276 nm ( $\epsilon = 14093$ ),  $\lambda_{\text{max}}$  325 nm ( $\epsilon = 19295$ );  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  3.75 (s, 3 H, H-2' and H-5'), 4.12 (m, 2 H, H-3' and H-4'), 5.41–5.61 (br s, 3 H,  $\text{D}_2\text{O}$  exchangeable, 2'-OH, 3'-OH, and 5'-OH), 6.15 (d, 1 H, H-1'), 4.18 (2  $\times$  d, 2 H, H-3'' and H-4''), 8.40 (s, 1 H, H-6), 11.8 (s, 1 H, NH) ppm;  $^{13}\text{C}$  NMR  $\delta$  60.1 (C-5'), 74.7 (C-3'), 75.5 (C-2'), 84.5 (C-4'), 85.3 (C-1'), 106.7 (C-5), 121.07, 122.0 and 129.0 (C-3'', C-4'', C-5''), 135.9 (C-2''), 137.1 (C-4) ppm. Anal. ( $\text{C}_{13}\text{H}_{13}\text{BrN}_2\text{O}_6\text{S}$ ) C, H, N.

**5-(Trimethylstannyl)-2'-deoxyuridine (2a).** A solution of 500 mg (1.41 mmol) of 5-iodo-2'-deoxyuridine in 20 mL of dioxane was added 23 mg of dichlorobis(triphenylphosphine)palladium(II) and 1 g (3.05 mmol) of hexamethylditin. The mixture was heated for 3 h until all of the starting material had disappeared. The solution was cooled and evaporated. Chromatographic purification ( $\text{CHCl}_3$ -MeOH, 94:6) yielded 290 mg (52%) of 5-(trimethylstannyl) derivative. Despite different attempts, the compound could not be crystallized: UV (MeOH)  $\lambda_{\text{max}}$  267 nm;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  0.72 (s, 9 H,  $\text{Me}_3\text{Sn}$ ), 2.62 (m, H-2' + DMSO signal), 4.08 (t, 2 H, H-5'), 4.31 (m, 1 H, H-4'), 4.78 (m, 1 H, H-3'), 5.48 (t, 1 H, 5'-OH), 5.72 (d, 1 H, 3'-OH), 6.70 (t, 1 H, H-1'), 8.15 (s, 1 H, H-6), 11.60 (br, 1 H, NH) ppm;  $^{13}\text{C}$  NMR:  $\delta$  -9.1 ( $\text{Me}_3\text{Sn}$ ), 39.9 (C-2'), 61.2 (C-5'), 70.5 (C-3'), 84.2 (C-1'), 87.4 (C-4'), 111.3 (C-5), 144.3 (C-6), 150.8 (C-2), 166.2 (C-4) ppm.

**B.** A solution of 227 mg (0.4 mmol) of 3',5'-di-*O*-toluoyl-5-iodo-2'-deoxyuridine, 163 mg (0.5 mmol) of hexamethylditin, and 46 mg (0.04 mmol) of palladium tetrakis(triphenylphosphine) in 15 mL of EtOAc was refluxed for 24 h under an inert atmosphere. The solution was cooled and evaporated. Chromatographic purification (silica gel,  $\text{CH}_2\text{Cl}_2$ -MeOH, 98:2) gave 180 mg (72%) of 2b as a foam.

**5-Phenyl-2'-deoxyuridine (3).** An amount of 190 mg (0.3 mmol) of 3',5'-di-*O*-toluoyl-5-(trimethylstannyl)-2'-deoxyuridine was taken up in 50 mL of toluene, 163 mg (0.8 mmol) of iodobenzene, and 46 mg (0.06 mmol) of tetrakis(triphenylphosphine)Pd(O) were added. The mixture was refluxed overnight, cooled, and evaporated. The residual oil was taken up in 20 mL of 0.1 M sodium methoxide in methanol and stirred for 2 h at room temperature. Finally the mixture was purified by preparative thin-layer chromatography; 45.6 mg of 5-phenyl-2'-deoxyuridine was obtained. The compound was identified by UV, MS, and NMR and was identical with the literature data:<sup>14</sup>  $^{13}\text{C}$  NMR  $\delta$  40.1 (C-2'), 61.0 (C-5'), 70.3 (C-3'), 84.6 (C-1'), 87.6 (C-4'), 113.5 (C-5), 127.2, 127.9, 128.1 and 132.2 (aromatic-C), 137.9 (C-6), 149.9 (C-2), 1.62 (C-4) ppm.

**5-Thien-3-yl-2'-deoxyuridine (4a).** To a solution of 353 mg (1 mmol) of 5-iodo-2'-deoxyuridine in 10 mL of pyridine was added 2 mL of acetic anhydride. The mixture was evaporated and treated again with pyridine and acetic acid and evaporated. The oil was evaporated with 10 mL of toluene and with 10 mL of *m*-xylene. Under anhydrous conditions were added 10 mL of *N*-methylpyrrolidinone (NMP), 22 mg of Pd(OAc)<sub>2</sub> (0.1 mmol), 44 mg (0.2 mmol) of triphenylphosphine, and 100 mg (1 mmol) of Et<sub>3</sub>N. After 10 min, 1 g (2.7 mmol) of 3-(tributylstannyl)thiophene was added. The mixture was heated for 1 h at 80 °C (under nitrogen atmosphere), cooled, and poured into 150 mL of Et<sub>2</sub>O. The organic phase was extracted two times with 150 mL of H<sub>2</sub>O, dried, and evaporated. The residual oil was taken up in 50 mL of methanol saturated with ammonia and stirred for 16 h. Chromatographic purification yielded 170 mg (55%) of 5-thien-3-yl-2'-deoxyuridine as a solid which was crystallized from acetonitrile: mp 201–203 °C; UV (MeOH)  $\lambda_{\text{max}}$  = 268 nm ( $\epsilon = 9700$ ),  $\lambda_{\text{max}}$  = 299 nm ( $\epsilon = 9300$ );  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  2.20 (t, 3 H, H-2'), 3.66 (br s, 2 H, H-5'), 3.85 (m, 1 H, H-4'), 4.31 (m, 1 H, H-3'), 5.24 (br s, 2 H, 3'- and 5'-OH), 6.22 (t, 1 H, H-1'), 7.31–7.72 (br s, 2 H,  $J = 4.8$  Hz and  $J = 0.9$  Hz, H-4'' and  $J = 4.8$  Hz,  $J = 1.3$  Hz, H-5''), 7.94 (dd, 1 H,  $J = 1.3$  Hz and  $J = 0.9$  Hz, H-2''), 8.42 (s, 1 H, H-6), 11.41 (br s, 1 H, NH) ppm;  $^{13}\text{C}$  NMR  $\delta$  40.3 (C-2'), 61.0 (C-5'), 70.1 (C-3'), 84.7 (C-1'), 87.6 (C-4'), 109.1 (C-5), 121.6, 125.4, 125.8, 133.1 (C-2'', C-3'', C-4'', C-5''), 136.8 (C-6), 149.5 (C-2), 161.8 (C-4) ppm. Anal. ( $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_5\text{S}$ ) C, H, N.

**5-Furan-3-yl-2'-deoxyuridine (4b).** Compound 4b was synthesized following the same method as for compound 4a using 3-(tributylstannyl)furan; the yield after deprotection was 44% and 4b was crystallized from acetonitrile: mp 215–216 °C; UV

(MeOH)  $\lambda_{\max}$  239 nm ( $\epsilon = 9000$ ),  $\lambda_{\max} = 300$  nm ( $\epsilon = 8400$ );  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  2.20 (t, 2 H, H-2'), 3.67 (br s, 2 H, H-5'), 3.82 (m, 1 H, H-4'), 4.33 (m, 1 H, H-3'), 5.29 (t and d, 2 H, 3'-OH and 5'-OH), 6.21 (t, 1 H, H-1'), 6.76 (dd, 1 H,  $J = 0.6$  and 2 Hz, H-4''), 7.67 (dd, 1 H,  $J = 2$  and 1.6 Hz, H-5''), 8.14 (dd, 1 H,  $J = 0.6$  and 1.6 Hz, H-2''), 8.36 (s, 1 H, H-6), 11.39 (br s, 1 H, NH) ppm;  $^{13}\text{C}$  NMR  $\delta$  (H-2', hidden by DMSO- $d_6$  signal), 61.1 (C-5'), 70.2 (C-3'), 85.0 (C-1'), 87.7 (C-4'), 106.7 (C-5), 107.8, 117.9, 135.8 and 143.2 (C-2'), C-3'', C-4'', C-5''), 140.2 (C-6), 149.6 (C-2), 161.7 (C-4) ppm. Anal. ( $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_6$ ) C, H, N.

**5-(5-Iodothien-2-yl)-2'-deoxyuridine (1b).** An amount of 185 mg (0.60 mmol) of 5-thien-2-yl-2'-deoxyuridine was dissolved in 10 mL of pyridine and 2 mL of acetic anhydride was added. The mixture was evaporated and coevaporated twice with toluene; TLC analysis ( $\text{CHCl}_3$ -MeOH, 95:5) showed that the transformation into the 3',5'-di-*O*-acetyl analogue was complete. The resulting oil was taken up in 15 mL of acetonitrile, and 183 mg (0.72 mmol) of iodine and 92 mg (0.17 mmol) of ceric ammonium nitrate were added. This mixture was stirred for 2 h at room temperature. The solvent was evaporated and the residue was taken up in a mixture of ethyl acetate (25 mL), 5% NaHSO<sub>3</sub> in H<sub>2</sub>O (5 mL), and saturated aqueous NaCl (5 mL). The organic layer was isolated and the aqueous layer was extracted with ethyl acetate (25 mL). The combined organic layer was dried on Na<sub>2</sub>SO<sub>4</sub> and evaporated. After chromatographic purification ( $\text{CH}_2\text{Cl}_2$ -CH<sub>3</sub>CN, 80:20), 159 mg (54%) of 5-(5-iodothien-2-yl)-3',5'-di-*O*-acetyl-2'-deoxyuridine was obtained as a yellow solid. The protective groups were removed by treatment with 20 mL of methanol saturated with ammonia. The product was obtained as a foam: UV (MeOH)  $\lambda_{\max}$  274 nm ( $\epsilon = 10000$ ),  $\lambda_{\max}$  332 nm ( $\epsilon = 12550$ );  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  2.22 (t, 2 H, H-2'), 3.68 (br s, 2 H, H-5'), 3.84 (m, 1 H, H-4'), 4.32 (m, 1 H, H-3'), 5.30 (br s, 2 H, 3' and 5'-OH), 6.19 (t, 1 H, H-1'), 7.09 and 7.24 (2 x, 2 x 1 H, H-3'' and H-4''), 8.61 (s, 1 H, H-6), 11.77 (s, 1 H, NH) ppm;  $^{13}\text{C}$  NMR  $\delta$  40.5 (C-2'), 60.8 (C-5'), 69.9 (C-3'), 76.1 (C-5''), 85.1 (C-1'), 87.6 (C-4'), 108.0 (C-5), 123.5 (C-3''), 135.9 (C-2'' and C-4''), 139.9 (C-6), 149.3 (C-2), 161.4 (C-4) ppm. Anal. ( $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_5\text{SI}$ ) C, H, N. This compound also was prepared in 47% yield following exactly the same method as for 3 but using 2,5-diiodothiophene as halogenated heterocycle.

**5-(5-Nitrothien-2-yl)-2'-deoxyuridine (1c).** To a solution of 220 mg (0.5 mmol) of 3',5'-di-*O*-acetyl-5-thien-2-yl-2'-deoxyuridine in 10 mL of acetonitrile was added 330 mg (0.6 mmol) of ceric ammonium nitrate. A green color appeared immediately and the solution was stirred for 4 h at room temperature until all of the starting material had been transformed to a yellow product. The solvent was evaporated and the inorganic salts were removed by flash chromatography on silica gel. The protective groups were removed with methanol saturated with ammonia (16 h). Chromatographic purification (silica gel,  $\text{CH}_2\text{Cl}_2$ -MeOH, 94:6) gave 70 mg (40%) of 1c contaminated with a more polar compound. Pure 1c (20 mg) was obtained by a second purification on HPLC (Rogel RP, MeOH-H<sub>2</sub>O, 95:5): UV (MeOH)  $\lambda_{\max}$  391 nm ( $\epsilon = 18000$ ); CIMS ( $\text{C}_4\text{H}_{10}$ ) 356 (MH<sup>+</sup>);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  2.32 (m, 2 H, H-2'), 3.63 (br s, 2 H, H-5'), 3.91 (m, 1 H, H-4'), 4.30 (m, 1 H, H-3'), 5.04 (t, 1 H, 5'-OH), 5.29 (d, 1 H, 3'-OH), 6.15 (t, 1 H, H-1'), 7.10 (d, 1 H,  $J = 4.0$  Hz, H-3''), 7.72 (d, 1 H,  $J = 4.0$  Hz, H-4''), 8.63 (s, 1 H, H-6) ppm;  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  (C-2' hidden by DMSO- $d_6$  signal), 61.0 (C-5'), 70.2 (C-3'), 85.8 (C-1'), 88.1 (C-4'), 102.8 (C-5), 110.8 and 115.5 (C-3'' and C-4''), 139.3 (C-6), 149.2, 150.3 and 151.1 (C-2'', C-5'' and C-2), 160.0 (C-4) ppm. Anal. ( $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_7\text{S}$ ) C, H, N.

**5-(5-Methylthien-2-yl)-2'-deoxyuridine (1d).** A mixture of 560 mg (0.7 mmol) of 3-*N*,3'-*O*,5'-*O*-tritoluoyl-5-(5-iodothien-2-yl)-2'-deoxyuridine (prepared according to ref 18) and 90 mg of tetrakis(triphenylphosphine)palladium(0) in 10 mL of NMP was heated under a nitrogen atmosphere for 10 min at 60 °C. Then, 180 mg (1.4 mmol) of tetramethyltin was added. The solution was kept at 60 °C with exclusion of moisture until all of the starting material had been transformed to a more lipophilic product (16 h). The solution was cooled, poured into 100 mL of diethyl ether, and washed twice with 100 mL of water. After drying on sodium sulfate, evaporation, and chromatographic purification, 310 mg (65%) of the 5''-methylated product was obtained as a foam. The protective groups were removed by treatment for 5 days at room temperature with 50 mL of methanol

saturated with ammonia. After evaporation and chromatographic purification, 97 mg (66% yield) of 5-(5-methylthien-2-yl)-2'-deoxyuridine was obtained. The compound was crystallized from acetone: mp 197-199 °C; UV (MeOH)  $\lambda_{\max}$  266 nm ( $\epsilon = 11000$ ),  $\lambda_{\max}$  324 nm ( $\epsilon = 10800$ );  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  2.20 (t, 2 H, H-2'), 2.42 (s, 3 H, 5''-Me), 3.67 (br s, 2 H, H-5'), 3.85 (m, 1 H, H-4'), 4.31 (m, 1 H, H-3'), 5.27 (br s, 2 H, D<sub>2</sub>O exchangeable, 3'-OH and 5'-OH), 6.21 (t, 1 H, H-1'), 6.71 (d, 1 H,  $J = 3.5$  Hz, H-4''), 7.19 (d, 1 H,  $J = 3.5$  Hz, H-3''), 8.44 (s, 1 H, H-6), 11.60 (s, 1 H, NH) ppm;  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  14.8 (5''-Me), (C-2' hidden by DMSO signal), 61.0 (C-5'), 70.2 (C-3'), 84.8 (C-1'), 87.7 (C-4'), 108.7 (C-5), 122.8 and 124.8 (C-3'' and C-4''), 131.7 (C-2''), 135.0 (C-6), 138.8 (C-5''), 149.4 (C-2), 161.3 (C-4) ppm. Anal. ( $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_5$ ) C, H, N.

**5-(5-Vinylthien-2-yl)-2'-deoxyuridine (1e).** A mixture of 700 mg (1.4 mmol) of 3'-*O*,5'-*O*-diacetyl-5-(5-iodothien-2-yl)-2'-deoxyuridine, 33 mg (0.15 mmol) of palladium acetate, and 66 mg (0.3 mmol) of triphenylphosphine in 10 mL of NMP was heated for 10 min at 60 °C under a nitrogen atmosphere; 650 mg (2 mmol) of vinyltributyltin were added and the mixture was kept for 4 h at 60 °C. The solution was cooled and poured into 100 mL of ethyl acetate. The organic phase was washed twice with 100 mL of water, dried, and evaporated. Flash column chromatography gave 360 mg (64%) of the protected intermediate which was treated with 25 mL of MeOH saturated with ammonia for 16 h. Column chromatography (silica gel,  $\text{CH}_2\text{Cl}_2$ -MeOH, 94:6) gave 150 mg of 1e contaminated with a fluorescent product. A second purification (HPLC, Rogel RP, MeOH-H<sub>2</sub>O 95:5) yielded 15 mg of pure 5-(5-vinylthien-2-yl)-2'-deoxyuridine: UV (MeOH)  $\lambda_{\max}$  342 nm ( $\epsilon = 14500$ );  $^1\text{H}$  NMR (DMSO- $d_6$  + D<sub>2</sub>O)  $\delta$  2.22 (t, 2 H, H-2'), 3.67 (br s, 2 H, H-5'), 3.85 (m, 1 H, H-4'), 4.32 (m, 1 H, H-3'), 5.11 (d, 1 H,  $J = 10.9$  Hz, CH=CH<sub>2</sub> cis), 5.50 (d, 1 H,  $J = 17.4$  Hz, CH=CH<sub>2</sub> trans), 6.21 (t, 1 H, H-1'), 6.84 (dd, 1 H,  $J = 10.9$  and 17.4 Hz, CH=CH<sub>2</sub>), 7.01 (d, 1 H,  $J = 4.0$  Hz, H-4''), 7.31 (d, 1 H,  $J = 4.0$  Hz, H-3''), 8.58 (s, 1 H, H-6) ppm;  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  40.6 (C-2'), 61.0 (C-5'), 70.2 (C-3'), 85.3 (C-1'), 87.8 (C-4'), 108. (C-5), 113.1 (CH=CH<sub>2</sub>), 123.5, 126.2 and 130.3 (C-3'', C-4'' and CH=CH<sub>2</sub>), 133.4 and 141.8 (C-2'' and C-5''), 136.1 (C-6), 149.5 (C-2), 161.6 (C-4) ppm. Anal. ( $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_5\text{S}$ ) C, N, H.

**5-[5-(Trimethylsilyl)ethynyl]thien-2-yl]-2'-deoxyuridine (1f).** An amount of 460 mg (0.9 mmol) of 3',5'-di-*O*-acetyl-5-(5-iodothien-2-yl)-2'-deoxyuridine was suspended in 50 mL of deoxygenated triethylamine; 15 mg of CuI and 15 mg of bis-(triphenylphosphine)dichloropalladium(II) and 250  $\mu\text{L}$  of (trimethylsilyl)acetylene were added. The mixture was heated under a nitrogen atmosphere for 6 h at 60 °C. The solution was cooled and evaporated. Chromatographic purification (silica gel,  $\text{CH}_2\text{Cl}_2$ -MeOH, 99:1) gave 286 mg (65%) of the protected intermediate as an oil. This oil was taken up in 25 mL of methanol saturated with ammonia. A first purification (silica gel,  $\text{CH}_2\text{Cl}_2$ -MeOH, 94:6) gave 184 mg (80%) of 1f containing some minor colored impurities. A second purification on HPLC (Rogel RP, MeOH-H<sub>2</sub>O, 95:5) was done, giving 25 mg of pure 10c: UV (MeOH)  $\lambda_{\max}$  342 nm ( $\epsilon = 18000$ );  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  0.22 (s, 9 H, Me<sub>3</sub>Si), 2.23 (t, 2 H, H-2'), 3.68 (br s, 2 H, H-5'), 3.89 (m, 1 H, H-4'), 4.33 (m, 1 H, H-3'), 5.26 (d, 1 H, 3'-OH), 5.36 (t, 1 H, 5'-OH), 6.20 (t, 1 H, H-1'), 7.29 (m, 2 H, H-3'' and H-4''), 8.71 (s, 1 H, H-6), 11.77 (s, 1 H, NH) ppm;  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  -0.1 (Me<sub>3</sub>Si), 40.6 (C-2'), 60.7 (C-5'), 69.8 (C-3'), 85.1 (C-1'), 87.7 (C-4'), 98.4 and 99.3 (C=C-), 107.6 (C-5), 120.8 (C-5''), 121.9 (C-3''), 132.4 (C-4''), 136.2 (C-2''), 136.7 (C-6), 149.2 (C-2), 161.4 (C-4) ppm. Anal. ( $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_5\text{SSi}$ -H<sub>2</sub>O) C, H, N.

**5-(5-Ethynylthien-2-yl)-2'-deoxyuridine (1g).** A mixture of 58 mg (1 mmol) of KF, 210 mg (1 mmol) of tetraethylammonium bromide, and 301 mg (0.6 mmol) of 3',5'-di-*O*-acetyl-5-[5-(trimethylsilyl)ethynyl]thien-2-yl]-2'-deoxyuridine in 25 mL of acetonitrile was refluxed for 2 h. The solution was cooled, evaporated, taken up in 25 mL of methanol saturated with ammonia and stirred for 16 h. After evaporation and a first chromatographic purification (silica gel,  $\text{CH}_2\text{Cl}_2$ -MeOH, 94:6), 80 mg (40%) of 5-(5-ethynylthien-2-yl)-2'-deoxyuridine was obtained. A second purification (HPLC, Rogel RP, MeOH-H<sub>2</sub>O, 95:5) yielded an analytically pure sample: UV (MeOH)  $\lambda_{\max}$  336 nm ( $\epsilon = 16350$ );  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  2.24 (t, 2 H, H-2'), 3.70 (br s, 2 H, H-5'), 3.85 (m, 1 H, H-4'), 4.32 (m, 1 H, H-3'), 4.51 (s, 1

H, C≡CH), 6.21 (t, 1 H, H-1'), 7.31 (s, 2 H, H-3'' and H-4''), 8.73 (s, 1 H, H-1') ppm; <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 40.5 (C-2'), 60.7 (C-5'), 69.8 (C-3'), 77.4 (C≡CH), 85.1 (C≡CH), 85.3 (C-1'), 87.7 (C-4'), 107.6 (C-5), 120.3 (C-5''), 121.8 (C-3''), 132.4 (C-4''), 136.0 (C-2''), 136.7 (C-6), 149.2 (C-2), 161.4 (C-4) ppm. Anal. (C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>5</sub>S) C, H, N.

**5-Isoxazol-5-yl-2'-deoxyuridine (6).** An amount of 180 mg (0.64 mmol) of 5-(3-oxopropyn-1-yl)-2'-deoxyuridine was dissolved in 5 mL of MeOH and 25 mL of H<sub>2</sub>O, and 80 mg (0.7 mmol) of hydroxylamine-*O*-sulfonic acid were added. Then 0.5 mL of a 1.4 M NaHS solution in H<sub>2</sub>O and 60 mg (0.7 mmol) of sodium hydrogen carbonate were added. The mixture was stirred for 16 h and a white precipitate was formed. After evaporation and chromatographic purification, 190 mg (90%) of the isoxazole was obtained. This compound was crystallized from acetone: mp 195–197 °C; UV (MeOH) λ<sub>max</sub> 245 nm (ε = 11 350), λ<sub>max</sub> 300 nm (ε = 15 850); CIMS (NH<sub>3</sub>) 296 (MH<sup>+</sup>); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 2.24 (t, 2 H, H-2'), 3.65 (d, 2 H, H-5'), 3.88 (m, 1 H, H-4'), 4.30 (m, 1 H, H-3'), 5.11 (t, 1 H, 5'-OH), 5.22 (d, 1 H, 3'-OH), 6.20 (t, 1 H, H-1'), 6.81 (d, *J* = 1.8 Hz, 1 H, H-4''), 8.56 (d, *J* = 1.8 Hz, 1 H, H-3''), 8.69 (s, 1 H, H-6), 11.63 (br s, 1 H, NH) ppm; <sup>13</sup>C NMR δ 40.4 (C-2'), 60.5 (C-5'), 70.2 (C-3'), 85.3 (C-1'), 87.8 (C-4'), 100.8 (C-4''), 102.1 (C-5), 139.2 (C-6), 149.3 (C-2), 151.1 (C-3'), 159.7 and 162.0 (C-4 and C-5') ppm. Anal. (C<sub>12</sub>H<sub>13</sub>N<sub>3</sub>O<sub>6</sub>H<sub>2</sub>O) C, H, N.

**Antiviral Assays.** The *in vitro* antiviral assays were performed as described previously.<sup>24,25</sup> The origin of the viruses [herpes simplex virus type 1 (HSV-1, strain KOS, F, and McIntyre), thymidine kinase deficient (TK<sup>-</sup>, strains B2006 and VMW 1837), herpes simplex virus type 2 (HSV-2, strain G, 196, and Lyons), varicella-zoster virus (VZV, strain Oka, and YS), TK<sup>-</sup> VZV (strains 07-1 and YS-R), vaccinia virus (VV), vesicular stomatitis virus (VZV), and cytomegalovirus (CMV, strain AD-169, and Davis) has been described.<sup>24,26</sup> Cytotoxicity measurements were based on either microscopically detectable alteration of normal cell morphology or inhibition of cell growth. The antiviral activity and cytotoxicity assay were performed in human embryonic skin-nude (E<sub>6</sub>SM) or human embryonic lung (HEL) cells seeded in 96-well microtiter plates.

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