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(*E*)-5-(3-OXOPROPEN-1-YL)-2′-DEOXYURIDINE AND (*E*)-5-(3-OXOPROPEN-1-YL)-2′,3′-DIDEOXYURIDINE; NEW ANTIVIRAL AGENTS: SYNTHESES AND BIOLOGICAL ACTIVITY

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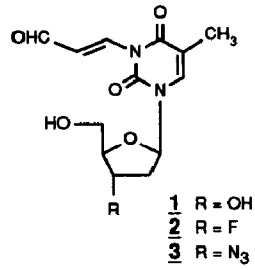
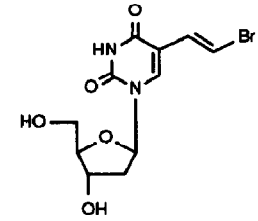
Abstract: The syntheses of the 5-(3-oxopropen-1-yl) derivatives of dU (5) and ddU (6) and their biological activity are reported. Good antiviral activity (EC_{50}, 1.4 μg/mL) and selectivity (SI > 71.4) is shown by 5 against VZV, whereas in the case of 6 the antiviral activity (EC_{50}, 2.6 μg/mL; SI > 38.5) against EBV is greater than that of Acyclovir (EC_{50}, 9.3 μg/mL).

Previously we have shown that 3-(3-oxopropen-1-yl)thymidine (1) has significant cytotoxic activity against a variety of tumor cells, and that it inhibits DNA synthesis selectively in HeLa cells. It also blocks enzymes-thymidine kinase and DNA polymerase-α.[1,2] Based on this finding a variety of 3-(3-oxopropen-1-yl)-2′,3′-dideoxythymidine and uridine derivatives have been synthesized by ourselves[3] and others[4] as potential anticancer agents and evaluated against a number of tumor cells. Among the compounds tested, 3-(3-oxopropen-1-yl) derivatives of 3′-fluoro-2′,3′-dideoxythymidine (2) and 3′-azido-2′,3′-dideoxythymidine (3) were found to be the most active with ED_{50} values of 0.2 and 0.5 μM, respectively, against P388 leukemia cell lines.[4] Moreover, 3 has shown antiviral activity against HIV-1 with an EC_{50} value of



1 R = OH
2 R = F
3 R = N_3



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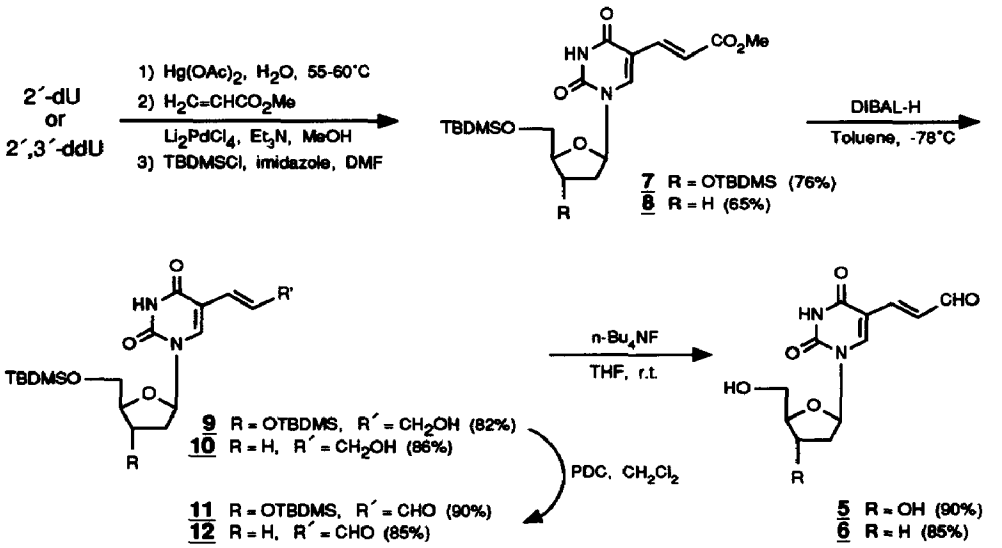
0.01 μM in human PBM (peripheral blood mononuclear) cells.[5] It is more active than CS-87 (EC_{50}, 0.2 μM) but less active than AZT (EC_{50}, 0.002 μM) in PBM cells.[5] A number of these compounds and related derivatives also have been evaluated for their ability to block thymidylate synthesis in L1210 cells.[3]

These findings suggest that the 3-oxopropen-1-yl group contributes significantly to the biological activity of these compounds. In line with this reasoning we explored the possibility of introducing the 3-oxopropen-1-yl group into the 5-position of uridine derivatives. The two compounds that we selected as targets in this series were 5-(3-oxopropen-1-yl)-2′-deoxyuridine (5) and 5-(3-oxopropen-1-yl)-2′,3′-dideoxyuridine (6). These two compounds bear some analogy in structure to (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU, 4) which is a potent inhibitor of herpes simplex virus (HSV).[6] In the present report, we describe the synthesis of 5 and 6 and their biological activity against various viruses.

In approaching the synthesis of the desired nucleoside, a coupling reaction between an organopalladium derivative and acrolein appeared to be the most direct route. Heck has reviewed the addition of arylpalladium complexes to such electron-deficient olefins.[7] However, only in one single case is a nucleoside involved and this is described by Bergstrom and coworkers who were able to couple 5-acetoxymercuri-uridine with methyl acrylate in excellent yield.[8] When we applied the reaction sequence to 2′-deoxyuridine neither acrolein nor acrylonitrile gave any coupled product. However, as in the ribonucleoside series the reaction worked very well with methyl acrylate. Thus we pursued the synthesis of **5** and **6** indirectly proceeding through the ester **7** and **8**. The one-pot synthesis of both of the latter compounds can be achieved in good yield by a slight modification of the Bergstrom procedure (Scheme 1).



Scheme 1. Synthesis of (E)-5-(3-Oxopropen-1-yl)-2′-deoxyuridine (**5**) and (E)-5-(3-Oxopropen-1-yl)- 2′,3′-dideoxyuridine (**6**).

The following is typical of the method: A solution of 2′-deoxyuridine (1.0 g) and mercuric acetate (1.05 eq) in water (10 mL) warmed to 55-60°C for 6 h, resulted in a thick white suspension. After removal of the water on a rotary evaporator, the white solid residue was further dried over P_2O_5 in the vacuum desiccator for 5 h.[9] To this 5-acetoxymercuri-2′-deoxyuridine was added Li_2PdCl_4 (0.1 N, 1.1 eq) in MeOH, followed by methyl acrylate (10 eq) and Et_3N (3 eq) at room temperature. After 12-16 h, H_2S was bubbled through the black reaction mixture for about 1 min, and the reaction mixture was filtered through Celite to remove the precipitated metal sulfides. The yellow filtrate was then concentrated to dryness on a rotary evaporator. The resulting gummy residue was treated with TBDMSCl (2.4 eq) and imidazole (4.8 eq) in DMF at room temperature. After being stirred overnight, the reaction mixture was poured into 100 mL of water and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, $CHCl_3$:hexane = 1:1) to afford the desired product **7** in 76% yield as white crystals (CH_2Cl_2-pentane).[10]

The selective reduction of ester **7** was accomplished with 3.3 eq of DIBAL-H in toluene at -78°C

within 3 h to afford the alcohol **9** (82%) as a yellow foam.[11] Oxidation (PDC, CH_2Cl_2, 25°C) of the latter then afforded the acrolein **11** (mp 117-119°C) in 90% yield.[12] Removal of the silyl group with n-Bu_4NF in THF at room temperature then gave 5-(3-oxopropen-1-yl)-2′-deoxyuridine (**5**).[13] The six-step sequence was accomplished in an overall yield of 50%. Synthesis of (*E*)-5-(3-oxopropen-1-yl)-2′,3′-dideoxyuridine (**6**)[14] was carried out similarly from ddU, and was being obtained as a white foam in 40% overall yield (compound **10**, a yellow foam; compound **12**, mp 127-129°C).

Biological Activity: The activity of both **5** and **6** against HIV-1 and HIV-1 reverse transcriptase was evaluated in MT-2 cell lines. However, neither compound was found to be active at the highest concentration used (100 μM for RT activity and 35 μM for anti-HIV-1 activity and cytotoxicity) in two different assays. In addition, the antiviral activities of these two compounds were evaluated *in vitro* against selected strains of human herpes viruses and respiratory viruses. 5-(3-Oxopropen-1-yl)-2′-deoxyuridine (**5**) showed good antiviral activity (EC_{50}, 1.4 μg/mL) and selectivity (SI, selective index = CC_{50}/EC_{50} > 71.4) against Varicella Zoster virus (VZV). However, its potency is slightly less than that of acyclovir (EC_{50}, 0.7 μg/mL). This compound also showed antiviral activity (EC_{50}, 22 μg/mL; SI > 4.5) against Epstein-Barr virus (EBV) (acyclovir; EC_{50}, 9.3 μg/mL). However, in the case of

Compound		HSV-1	HSV-2	HCMV	VZV	EBV
5	EC_{50}(μg/mL)	> 100	> 100	94.8	1.4	22.1
	CC_{50} (μg/mL)	> 100	> 100	> 100	> 100	>100
	SI (CC_{50}/EC_{50})	1	1	> 1	> 71.4	> 4.5
6	EC_{50}(μg/mL)	> 100	> 100	> 100	-	2.6
	CC_{50} (μg/mL)	> 100	> 100	> 100	-	> 100
	SI (CC_{50}/EC_{50})	1	1	1	-	> 38.5
Acyclovir	EC_{50}(μg/mL)	0.10	0.20	0.04	0.7	9.3

Table 1. Antiviral Activity against Human Herpesviruses.

5-(3-oxopropen-1-yl)-2′,3′-dideoxyuridine (**6**) the antiviral activity (EC_{50}, 2.6 μg/mL; SI > 38.5) against EBV is more potent than that of acyclovir (EC_{50}, 9.3 μg/mL). Nevertheless, these compounds did not show antiviral activity against human herpes simplex virus type 1 or 2 (HSV-1 or HSV-2), or against human cytomegalovirus (HCMV). Moreover, they were found to be inactive *in vitro* against respiratory viruses such as influenza A or B (Flu-A or Flu-B), respiratory syncytial virus (RSV), parainfluenza virus type-3 (PIV-3), adenovirus type-5 (AD-5), and measles virus.

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9. When this 5-acetoxymercuri-2′-deoxyuridine is stored in the vacuum desiccator at room temperature for more than 4-5 days, it loses its ability to react with alkenes such as methyl acrylate and allylic halides.

10. **Compound 7**: mp 142-143°C; homogeneous by TLC analysis [R_f, 0.64 (EtOAc), 0.34 ($CHCl_3$: hexane = 2:1); ^1H NMR (300 MHz, $CDCl_3$) δ 9.14 (bs, 1 H), 7.99 (s, 1 H), 7.29 (d, 1 H, J = 15.7 Hz), 7.04 (d, 1 H, J = 15.7 Hz), 6.30 (dd, 1 H, J = 6.0, 7.2 Hz), 4.41 (m, 1 H), 4.01 (m, 1 H), 3.91 (dd, 1 H, J = 2.5, 11.5 Hz), 3.76-3.81 (m, 4 H), 2.39 (m, 1 H), 2.06 (m, 1 H), 0.94 (s, 9 H), 0.90 (s, 9 H), 0.15 (s, 3 H), 0.14 (s, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.73, 161.02, 148.94, 142.05, 136.34, 119.41, 109.80, 88.50, 85.99, 72.32, 63.02, 51.43, 42.11, 25.92, 25.70, 18.43, 17.97, -4.67, -4.86, -5.39; FAB mass *m/e* 541 (M^+ + H). **compound 8**: mp 144-145°C; homogeneous by TLC analysis [R_f, 0.52 (EtOAc), 0.20 ($CHCl_3$: hexane = 2:1); ^1H NMR (300 MHz, $CDCl_3$) δ 8.73 (bs, 1 H), 8.12 (s, 1 H), 7.28 (d, 1 H, J = 15.7 Hz), 7.05 (d, 1 H, J = 15.7 Hz), 6.03 (dd, 1 H, J = 6.3, 3.9 Hz), 4.22 (m, 1 H), 4.07 (dd, 1 H, J = 11.7, 2.5 Hz), 3.72-3.82 (m, 4 H), 2.45 (m, 1 H), 1.97-2.10 (m, 3 H), 0.94 (s, 9 H), 0.15 (s, 3 H), 0.13 (s, 3 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.78, 161.03, 149.00, 142.55, 136.66, 119.19, 109.13, 87.01, 82.17, 64.25, 51.45, 33.35, 25.88, 24.86, 18.60, -5.29, -5.37; FAB mass *m/e* 411 (M^+ + H).

11. Originally we had tried to reduce the ester group to the aldehyde using 1.0 eq. of DIBAL-H, but by TLC analysis most of starting material still remained. When 2.0 eq. of DIBAL-H was used, three major spots were observed on TLC analysis comprising small amounts of starting material, the desired alcohol, and possibly the corresponding aldehyde. This result is likely due to the consumption of one equivalent of the hydride by the acidic NH of the ring.

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13. **Compound 5**: mp 169-170°C; homogeneous by TLC analysis [R_f, 0.10 (3% MeOH/EtOAc), 0.23 (5% MeOH/EtOAc); ^1H NMR (300 MHz, DMSO-d_6) δ 11.72 (s, 1 H, NH), 9.51 (d, 1H, J = 8.0 Hz, -CHO), 8.53 (s, 1 H, H-6), 7.39 (d, 1 H, J = 15.8 Hz, -C*H*=CH-CHO), 6.96 (dd, 1 H, J = 15.8, 8.0 Hz, -CH=C*H*-CHO), 6.13 (t, 1 H, J = 6.3 Hz, H-1′), 5.29 (d, 1 H, J = 4.3 Hz, 3′-OH), 5.20 (t, 1 H, J = 5.1 Hz, 5′-OH), 4.27 (m, 1 H, H-3′), 3.83 (m, 1 H, H-4′), 3.64 (m, 2 H, H-5′), 2.21 (m, 2 H, H-2′); ^{13}C NMR (75 MHz, DMSO-d_6) δ 194.25 (-CHO), 161.30, 149.17, 146.30, 144.25, 127.00, 108.21, 87.70, 85.13, 69.63, 60.72, 40.19; IR (KBr) ν 3447, 2743, 1734, 1676, 1608 cm^{-1}; UV (MeOH) λ_{max} 312, 276 nm; FAB mass *m/e* 283 (M^+ + H).

14. **Compound 6**: homogeneous by TLC analysis [R_f, 0.20 (3% MeOH/EtOAc), 0.41 (5% MeOH/EtOAc); ^1H NMR (300 MHz, DMSO-d_6) δ 11.68 (s, 1 H, NH), 9.49 (d, 1 H, J = 8.0 Hz, -CHO), 8.37 (s, 1 H, H-6), 7.37 (d, 1 H, J = 15.8 Hz, -C*H*=CH-CHO), 6.93 (dd, 1 H, J = 15.8, 8.0 Hz, -CH=C*H*-CHO), 5.94 (dd, 1 H, J = 6.6, 2.4 Hz, H-1′), 5.32 (t, 1 H, J = 5.2 Hz, 5′-OH), 4.09 (m, 1 H, H-4′), 3.80 (m, 1 H, H-5′), 3.58 (m, 1 H, H-5′), 2.32 (m, 1 H, H-2′), 2.11 (m, 1 H, H-2′), 1.86 (m, 2 H, H-3′); ^{13}C NMR (75 MHz, DMSO-d_6) δ 194.27 (-CHO), 161.48, 149.24, 146.54, 144.43, 126.66, 107.47, 86.26, 82.60, 61.24, 32.49, 23.75; IR (KBr) ν 3393, 2731, 1725, 1676, 1601 cm^{-1}; UV (MeOH) λ_{max} 309, 270 nm; FAB mass *m/e* 267 (M^+ + H).

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