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SYNTHESIS AND ANTI-HERPES ACTIVITY OF 5-TRIFLUOROVINYL-2'-DEOXYURIDINE

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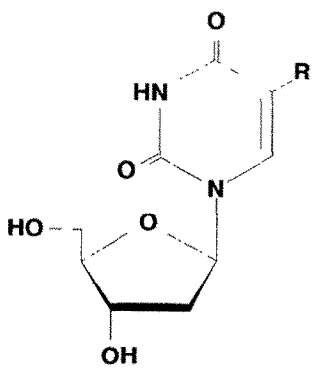
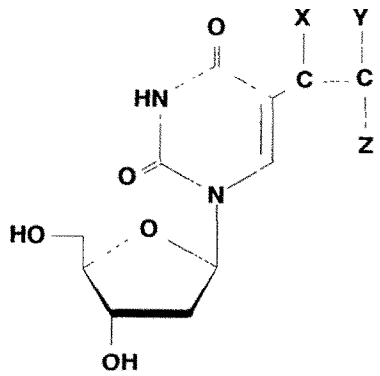
Abstract: *5-Trifluorovinyl-2'-deoxyuridine was synthesized from protected 5-iodo-2'-deoxyuridine and tetrakis(perfluorovinyl)tin. The compound demonstrates significant activity against HSV-1 but low activity against HSV-2.*

The introduction of fluorine containing substituents in the 5-position of 2'-deoxyuridine has led to potent antiviral and/or antitumor nucleoside analogues. 5-Fluoro-2'-deoxyuridine (**1**) and 5-trifluoromethyl-2'-deoxyuridine (**2**) are potent inhibitors of deoxythymidylate synthase after anabolic phosphorylation [1]. These compounds are used as antitumoral (i.e. 5-fluorouracil) or antiviral (**2**) agents, respectively. 5-Trifluoromethyl-2'-deoxyuridine was synthesized by Heidelberger et al. from 5-trifluoromethyluracil by an enzymatic procedure[2]. Later, methods were described for the direct introduction of a trifluoromethyl group (CF_3I, Cu in HMPA) in the 5-position of pyrimidine nucleosides[3]. This method proved also useful for the synthesis of the pentafluoroethyl analogue **3**[4].In contrast to 5-trifluoromethyl-2'-deoxyuridine, however, the pentafluoroethyl analogue **3** is devoid of significant activity against herpes simplex virus type I (HSV-I) and several neoplastic cells [4].

A second group of interesting fluorinated nucleoside analogues are those derived from (*E*)-5-(2-bromovinyl)-2'-deoxyuridine (BrVdUrd) **4**, which is a nucleoside analogue with high activity and selectivity against both HSV-1 and VZV (varicella zoster virus) replication[5,6]. It is less active against HSV-2 infections. Several fluorinated analogues of BrVdUrd were synthesized. 5-(2-Fluorovinyl)-2'-deoxyuridine (**5**) was synthesized by Bärwolff from 5-(2-fluoro-2-ethoxycarbonylethyl)-2'-deoxyuridine[7]. The 2-chloro-1,2-difluorovinyl analogues **6** (E) and **7** (Z) and the 2,2-dichloro-1-fluorovinyl analogue **8** were synthesized by Coe et al. through a sugar-base condensation reaction in low yield[8]. An analogous procedure was used by Bobek et al. for the preparation of 5-(2,2-difluorovinyl)-2'-deoxyuridine (**9**)[9]. In contrast to **6**, **7** and **8**, 5-(2-fluorovinyl)-2'-deoxyuridine **5** and 5-(2,2-difluorovinyl)-2'-deoxyuridine (**9**) demonstrate significant activity against HSV-1 replication (**5**: 1 μg/ml[10]; **9**: 0.2 μg/ml [9]).These results prompted us to synthesize 5-(1,2,2-trifluorovinyl)-2'-deoxyuridine (**10**).

Modifications of the original Heck reaction[11] have allowed the preparation of a wide variety of unsaturated 5-substituted-2'-deoxyuridine derivatives[12]. Recently these reactions are carried out using organoborane or organostannanes as substrates[13,14]. Based on our experience with symmetric organotin derivatives for carrying out cross-coupling reactions[14], we decided to synthesize the title





1 = R = F

2 = R = CF_3

3 = R = CF_2CF_3

	X	Y	Z
4 =	H	Br	H
5 =	H	F	H
6 =	F	Cl	F
7 =	F	F	Cl
8 =	F	Cl	Cl
9 =	H	F	F

compound **10** starting from the appropriately protected 5-iodo-2'-deoxyuridine and tetrakis(perfluorovinyl)tin. Tetrakis(perfluorovinyl)tin was synthesized from tin tetrachloride, magnesium and bromotrifluoroethylene as described by Kaesz et al [15]. The reagent was purified by distillation at 23 mbar (bp 55-58°C). Reaction of 3'-O,5'-O,N^3-tritoluoyl-5-iodo-2'-deoxyuridine[14] with tetrakis(perfluorovinyl)tin in N-methylpyrrolidone in the presence of $Pd(OAc)_2$, triphenylphosphine and triethylamine afforded the tritoluoyl derivative of **10**. The protecting groups were removed with ammonia in methanol.

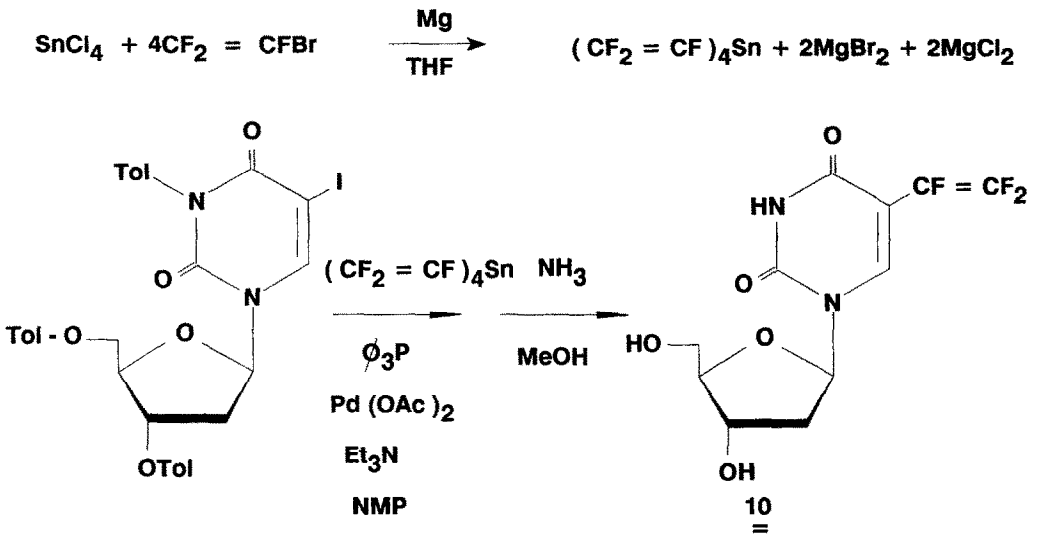


Table 1

Antiviral activity of 5-trifluorovinyl-2'-deoxyuridine in E_6SM cell cultures

Compound	Minimum cytotoxic concentration[a] (μg/mL)	Minimum antiviral concentration[b] (μg/mL)				
		HSV-1 (KOS)	HSV-2 (G)	Vaccinia virus	TK^- HSV-1 (B2006)	TK^- HSV-1 (VMW 1837)
10	100	0.05	13	8	13	1.5
4 (BrVdUrd)	200	0.02	100	0.3	100	40

[a]Required to cause a microscopically detectable alteration of normal cell morphology
[b]Required to reduce virus-induced cytopathogenicity by 50%

Table 2

Antiviral activity of 5-trifluorovinyl-2'-deoxyuridine in HEL cell cultures

Compound	Minimum cytotoxic concentration[a] (μg/mL)	Minimum antiviral concentration[b] (μg/mL) VZV (OKA)	VZV (YS)	TK⁻ VZV (07/1)	TK⁻ VZV (YS/R)
10	10	0.16	0.55	13.6	11.6
4 (BrVdUrd)	200	0.002	0.004	>10	>10

[a]Required to reduce cell growth by 50%
[b]Required to reduce virus-induced focus formation by 50%

The activity found for 5-(1,2,2-trifluorovinyl)-2'-deoxyuridine (**10**) against HSV-1 and HSV-2 (Table 1) is comparable to the activity described for the 2,2-difluorovinyl analogue **9**[9]. 5-(1,2,2-Trifluorovinyl)-2'-deoxyuridine is slightly less active than BrVdUrd against HSV-1 but slightly more active than BrVdUrd against HSV-2. The fact that it is less active against TK^- than wild-type (TK^+) HSV-1 points to the importance of the viral thymidine kinase for its intracellular activation by phosphorylation. Also, compound **10** was about 20 to 100 times more active against TK^+ VZV than TK^- VZV (Table 2), again pointing to the importance of the viral thymidine kinase for its activation. Yet, the activity of **10** against TK^+ VZV is significant lower (100 times) than that of BrVdUrd. While moderate activity against vaccinia virus was observed, 5-(1,2,2-Trifluorovinyl)-2'-deoxyuridine proved to be inactive against vesicular stomatitis virus, poliovirus-1, parainfluenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4 and Semliki forest virus at the highest concentration tested (100 μg/mL).

In conclusion, the introduction of a fluorine substituent in the 1 position of the vinyl group does not abolish the anti-herpes activity of 5-(2,2-difluorovinyl)-2'-deoxyuridine. In contrast, substitution of one of the fluorine atoms in the 2 position of **10** by a chlorine atom significantly diminishes the biological activity of **9**[8].

Experimental

5-(1,2,2-trifluorovinyl)-2'-deoxyuridine (10)

A solution of 1.06 g (1.5 mmol) 3'-O,5'-O,N^3-tritoluoyl-5-iodo-2'-deoxyuridine[14], 780 mg (3 mmol) triphenylphosphine, 330 mg (1.5 mmol) $Pd(OAc)_2$ and 2.1 ml (15 mmol) triethylamine in N-methylpyrrolidone (15 ml) was stirred for 10 min at room temperature under nitrogen, after which 1.32 g (3 mmol) of tetrakis(perfluorovinyl)tin was added. The reaction mixture was stirred for 2 hours at room

temperature, poured into H_2O and extracted with Et_2O (twice). The organic layers were combined, dried and dissolved in methanol saturated with ammonia. The mixture was kept for 48 h at room temperature, evaporated, purified by column chromatography (silica gel CH_2Cl_2-MeOH 95:5) and precipitated from acetone. Yield : 100 mg (0,32 mmol, 21 %).

3'-O,5'-O,N^3-tritoluoyl-5-(1,2,2-trifluorivinyl)-2'-deoxyuridine : MS CI m/e: 680 ($M+NH_4^+$); 328 (BH + NH_4^+). ^1H NMR (CD_2Cl_2) : 2.35-2.45 (m, H-2', 3xCH_3); 2.84 (dd, H-2"); 4.61 (m, H-4'); 4.67 (dd, H-5'); 4.74 (dd, H-5"); 5.63 (2xt, H-3'); 6.37 (dd, H-1'); 7.30 (m, aromatic-H); 7.79 (d, H-6); 7.92 (m, aromatic-H) ppm.

5-(1,2,2-trifluorovinyl)-2'-deoxyuridine : TLC (CH_2Cl_2-MeOH : 90:10) Rf 0.35. UV λ_{max}=273 nm. MS CI m/e : 326 ($M+NH4^+$); 309 ($M+H^+$); 192 ($B+H^+$); 117 (S). ^{13}C NMR (DMSO-d_6): : 42.0 (C-2'); 62.3 (C-5'); 71.7 (C-3'); 87.3 (C-4'); 89.2 (C-1') ppm. ^1H NMR (CD_3OD) : 2.05-2.50 (m, H-2', H-2"); 3.78 (m, H-5', H-5"); 3.93 (m, H-4'); 4.40 (m, H-3'); 6.22 (t, J = 6.2 Hz, H-1'); 8.48 (d, J = 2.2 Hz, H-6) ppm. Elem. Anal. ($C_{11}H_{11}N_2O_5F_3.C_3H_6O$) Calcul. C:45.91%, H:4.68%, N:7.65% found: C:45.61%, H:4.44%, N:7.68%.

The methods used for measuring the inhibitory effects of the compounds on virus-induced cytopathogenicity have been described previously[16].

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