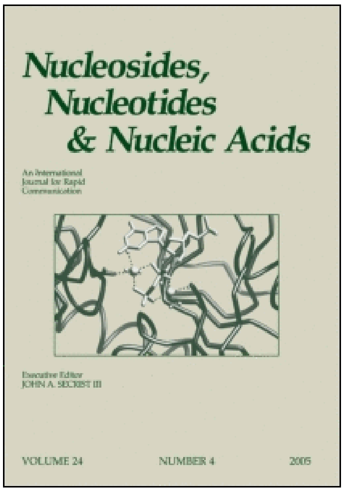

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SYNTHESIS AND ANTIVIRAL ACTIVITIES OF SOME NEW 5-HETEROAROMATIC SUBSTITUTED DERIVATIVES OF 2'-DEOXYURIDINE

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Abstract: Eight new 5-heteroaromatic substituted analogues of 2'-deoxyuridine have been synthesized and evaluated for their inhibitory properties against a panel of different viruses. Several analogues containing a substituted thiophene moiety proved to be highly selective against herpes simplex virus type 1 (HSV-1).

We recently described the synthesis and antiviral activity of 2'-deoxyuridine analogues having a thiophene substituent in the 5-position represented by 5-(thien-2-yl)-2'-deoxyuridine[1] (**1**), 5-(thien-3-yl)-2'-deoxyuridine[2] (**2**), 5-(5-bromothien-2-yl)-2'-deoxyuridine[1] (**3**) and 5-(5-chlorothien-2-yl)-2'-deoxyuridine[1] (**4**). All these molecules show high and selective activity against the replication of herpes simplex virus type 1 (HSV-1)[1] and varicella-zoster virus (VZV)[2], which relies on their selective phosphorylation by the virus-induced thymidine kinases. Since introduction of an halogen in the 5"-position of the thien-2-yl ring (**3**,**4**) leads to a remarkable increase in potency and selectivity against HSV-1 and VZV, we decided to prepare some more thienyl derivatives (**5-9**) for further structure-activity relationship studies. In an effort to try to increase the activity of 5-(isoxazol-5-yl)-2'-deoxyuridine, the isoxazolyl derivatives **10** and **11** likewise were prepared. After studying the physicochemical properties of several of these congeners, the hypothesis was formulated that compound **12** should be a good substrate for HSV-1 TK[3]. Therefore, the synthesis of these new analogues (**5-12**) was undertaken and will be described along with their antiviral activities.

Following acylation of **3**, treatment with a slight excess of bromine in CCl_4 quantitatively afforded the dibrominated analogue. Deacylation gave **5**. Zinc mediated reduction on the other hand (43% yield) followed by deacylation gave the 5-(3-bromothien-2-yl) derivative **6**. The dibrominated analogue **5** can be obtained directly from **1** as well, using more then 2 equivalents of bromine. Analogous bromination of acylated **2** with one equivalent of bromine, followed by deacylation with ammonia, afforded the 5-(2-bromothien-3-yl) congener **7**. The ortho positioning of the substituents in **6** and **7** is reflected by the coupling constants ($J_{4'',5''}$ = 5.7 Hz) in the ^1H NMR spectrum.

Table: Antiviral activity and cytotoxicity of the 5-heteroaromatic substituted 2'-deoxyuridine analogues in human embryonic skin-muscle (E_6SM) fibroblast cells

Compound	Minimum cytotoxic concentration[a] (µg/ml)	Minimal inhibitory concentration[b] (µg/ml)		
		Herpes simplex virus-1 (KOS)	Herpes simplex virus-1 TK$^-$ (B2006)	Vaccinia virus
1	>400	0.45	300	20
2	>100	0.3	150	>40
3	>400	0.03	150	>200
4	>400	0.02	>200	>200
5	400	0.7	20	150
6	>400	0.04	300	>400
7	>400	2	>400	>400
8	>400	0.07	20	70
9	≥10	2	>10	>10
10	400	>40	400	>100
11	≥100	>40	≥100	≥100
12	>100	>100	>100	>100
BVDU	>400	0.004	4	0.04

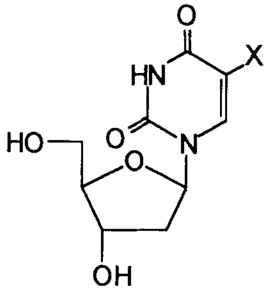
[a] MCC, required to cause a microscopically detectable alteration of normal cell morphology
[b] MIC, required to reduce virus-induced cytopathogenicity by 50%

Acylation of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU, X = CH=CHBr) and palladium catalyzed cross-coupling with 2-tributylstannylthiophene for 3 h at 110°C in NMP ($Pd(OAc)_2$, Ph_3As, Et_3N, 43% yield) afforded after deprotection the derivative **8**.

The 5-(5,2'-bithien-2-yl) congener was prepared starting from **3**. Acylation, followed by analogous cross-coupling with 2-tributylstannylthiophene for 3 h at 60°C afforded 40% of the protected **9**. Deprotection and crystallization from MeOH gave green fluorescent needles in 85% yield.

Isoxazolyl substituted nucleosides **10** and **11** were prepared by 1,3-dipolar cyclo-addition reactions of respectively furane-2-carbonitrile *N*-oxide and thiophene-2-carbo-nitrile *N*-oxide on the well-known protected 5-ethynyl-2'-deoxyuridine[4] in low yield. The *N*-oxides were obtained from the respective 2-carboxaldoximes.

Synthesis of the desired 5-(isothiazol-5-yl)-2'-deoxyuridine (**12**) proved very cumbersome. Preparation of isothiazole itself starting from propynaldehyde was possible only when using liquid



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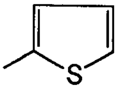

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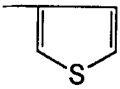

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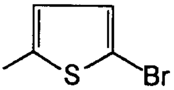

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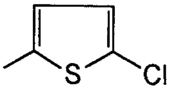

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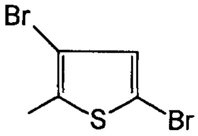

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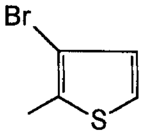

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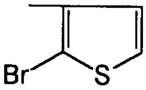

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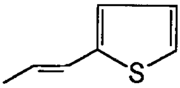

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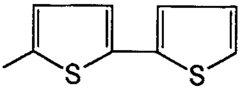

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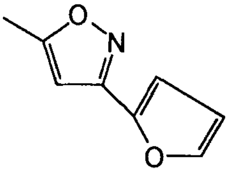

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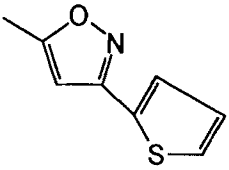

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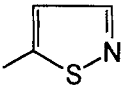

12

ammonia for ring closure of the addition product with thiosulfate[5]. The tributyltin derivative was prepared in 43% yield with butyllithium and tributyltin chloride. Palladium catalyzed cross-coupling with 5-iodo-2'-deoxyuridine, however, failed under a variety of reaction conditions. Therefore the isothiazole moiety had to be built up gradually on 2'-deoxyuridine. Cross-coupling of the 5-iodo congener (X = I) with propynaldehyde diethylacetal (91% yield) was followed by deprotection of the acetal moiety with 80% acetic acid (51% yield) and finally ring closure in liquid ammonia to obtain the desired analogue **12**.

Antiviral activities are shown in the Table. The analogues **10** and **11** with a substituted 5-isoxazole moiety were devoid of any activity. Likewise, the 5-isothiazole analogue **12**, expected to be active against herpes simplex virus type 1 (HSV-1) or to have at least good affinity for the HSV-1 thymidine kinase according to the above mentioned biophysical studies[3], did not display any inhibitory properties against either HSV-1 or vaccinia virus infection. The newly synthesized analogues **5-8** containing a substituted thiophene moiety, all showed moderate to good activity against HSV-1 in the order **6>8>5>7**, with all compounds being very selective, not displaying any activity against other viruses. A bromine substituent at the 5"-position (as in **3**) or at the 3"-position (as in **6**) confers about the same highly selective activity to both analogues [minimal inhibitory concentration (MIC): 0.03 and 0.04 µg/mL, respectively]. Given the assumption that the 5-substituent should not be too bulky[6], the activity of (*E*)-5-(2-thienylvinyl)-2'-deoxyuridine (**8**) is rather remarkable (MIC: 0.07 µg/mL). The compound could be considered as an analogue of BVDU, with a thiophene ring replacing bromine as substituent on the vinyl, but at the expense of a 15- to 20-fold lower activity (MIC for BVDU: 0.004 µg/mL). Only compound **9** with a dithienyl moiety at the 5-position, proved quite cytotoxic [minimal cytotoxic concentration (MCC): >10 µg/mL]. Therefore, the antiviral activity found for this compound (MIC: 2 µg/mL), cannot be considered as specific.

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