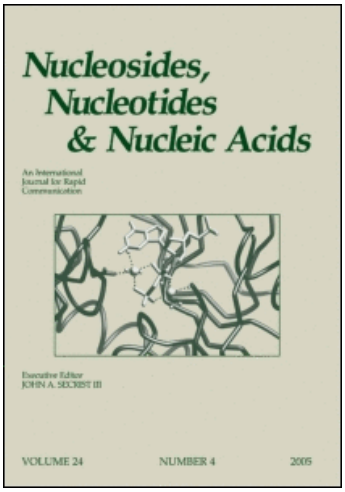

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF VARIOUS 5-SUBSTITUTED 2'-DEOXYURIDINES AND -CYTIDINES

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Abstract: 5-Cyclopropyl-2'-deoxycytidine and some 5-aryl-2'-deoxyuridines and -cytidines have been prepared and their inhibition of HIV have been tested.

A number of nucleoside analogues display potent activities against human immunodeficiency virus (HIV). A common structural feature shared by most of these analogues is the absence of hydroxyl substituents at positions 2' and 3' of the furanose ring and the presence of the naturally occurring purine or pyrimidine bases. Representative examples of such compounds are 3'-azido-2',3'-dideoxythymidine (AZT), 3'-fluoro-2',3'-dideoxythymidine (FLT), 2',3'-dideoxyinosine (ddI), 2',3'-dideoxycytidine (ddC) and 2',3'-dideoxy-2',3'-didehydrothymidine (D4T). The structure-activity correlations of these and other anti-HIV nucleoside analogues have been reviewed.[1]

Apart from ddC, several other cytidine analogues lacking hydroxyl substituents in the 2' or 3' positions of the furanose ring are active against HIV [1] and a cytidine homologue, 2',3'-dideoxy-3'-hydroxymethylcytidine is a potent inhibitor.[2,3] These analogues exert their antiviral activities by being transformed to triphosphates which act as inhibitors of HIV reverse transcriptase.

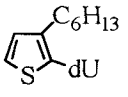
We have previously shown that 5-aryl and 5-heteroaryl substituted 2'-deoxyuridine analogues display anti-HIV activities when tested in H9 cells.[4] The results however, were dependent on the assay conditions and difficult to explain.[5]

Against this background and in view of the broad substrate tolerance of deoxycytidine kinase (dCK) for phosphorylating nucleosides and cytidine analogues to monophosphates[6] we decided to prepare and investigate 5-aryl and 5-heteroaryl substituted 2'-deoxycytidine analogues as potential inhibitors of HIV.

Previously we prepared 5-(3-n-hexyl-2-thienyl)- and 5-(3-methyl-2-thienyl)-2'-deoxy-3',5'-di-O-acetyluridine by Pd-catalyzed coupling of 5-iodo-2'-deoxy-3',5'-di-O-acetyluridine with the corresponding trimethylstannyl heteroaryls in low yields.[7] Some 5-heteroaryl-2'-deoxyuridines have been obtained by Pd-catalyzed coupling of 5-iodo-2'-deoxyuridines with organozinc reagents.[8] 5-Heteroaryl-2'-deoxyuridines[9] and some 5-heteroaryl-2'-deoxyuridine-5'-phosphates[10] were prepared photochemically. 5-Phenyl-2'-deoxyuridines have been prepared by a Pd-catalyzed coupling reaction of 5-(chloromercuri)-2'-deoxyuridine with various iodobenzenes.[11,12] 5-Phenyl- and 5-(2,5-dimethoxyphenyl)-2'-deoxyuridine were prepared photochemically by coupling of the pertrimethylsilylated 5-iodo-2'-deoxyuridine with benzene and 1,4-dimethoxybenzene.[12] Various phenyl-substituted cytidines have been prepared from the corresponding phenyl cytosines.[13] Uridine triflate has been coupled with organostannanes, using palladium as catalyst.[14] The Pd-catalyzed coupling of 5-iodo-2'-deoxy-3',5'-di-O-p-toluoyluridine with alkenyl stannanes gave 5-alkenyl-2'-deoxyuridines.[15] 5-Aryluridines and 5-aryl-2'-deoxyuridines were obtained by the Pd-catalyzed coupling of 5-iodouridine and 5-iodo-2'-deoxyuridine with arylboronic acids and aryl-trimethylstannanes.[16]

In the present communication we describe the preparation and anti HIV activities of 2'-deoxyuridines having n-hexyl- and methylthiophenes and 2'-deoxycytidines having thiophene,

phenylthiophene, thiazole, selenophene, 1-methyl-pyrrole, furan, pyridine, benzene and cyclopropane in the 5-position.



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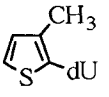

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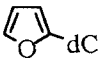

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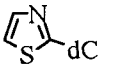

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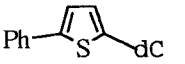

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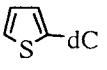

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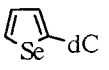

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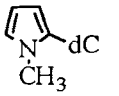
8a



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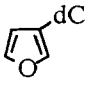

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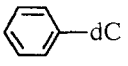

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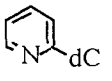

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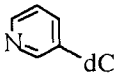

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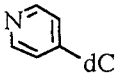
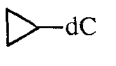


14a



15a

Results

We previously prepared various 5-heteroaryl substituted uracils[17,18] as well as some 5-acyclosubstituted uracils,[18] which could easily be converted to the corresponding 2'-deoxyuridines.[19] The simplest approach to 5-heteroaryl-2'-deoxycytidine would have been to convert the readily available 5-heteroaryl-2'-deoxyuridines to 2'-deoxycytidines via the 4-(1,2,4-triazole)-derivatives.[20,21]

Unfortunately we were not able to prepare 5-(2-thienyl)-, 5-(2-thiazoyl)- and 5-(5-phenyl-2-thienyl)-2'-deoxy-3',5'-di-O-acetylcytidine from the corresponding 5-heteroaryl-2'-deoxy-3',5'-di-O-acetyluridines.[7] Neither were we successful in preparing 5-(2-thienyl)-2'-deoxy-3',5'-di-O-p-toluoylcytidine from 5-(2-thienyl)-2'-deoxy-3',5'-di-O-p-toluoyluridine.[4] The failure of previous attempts, to convert 5-trimethylsilyl-2'-deoxy-3'-5'-di-O-p-toluoyluridine to the corresponding cytidine have been explained by steric hindrance of the voluminous 5-substituent.[22,23] Other methods[24,25] for the conversion of uridines to cytidines were not tried.

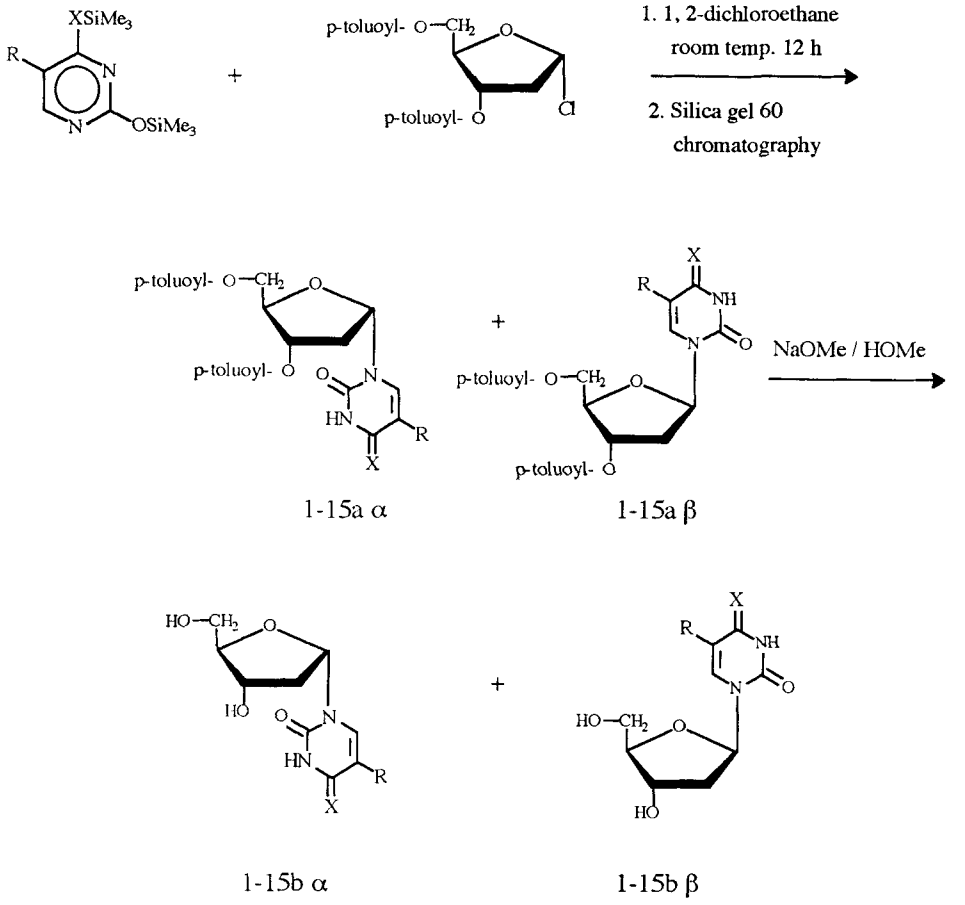
This drawback prompted us to develop a new synthetic route for 5-heteroarylcytosines.[26] A similar approach was used in the synthesis of 5-cyclopropylcytosine.[27] These cytosines could readily be transformed to the corresponding 2'-deoxy-3',5'-di-O-p-toluoylcytidines by a glycosylation reaction[19] with 2-deoxy-3,5-di-O-p-toluoyl-D-erythrofuranosyl chloride[28] in anhydrous 1,2-dichloroethane in the absence of catalyst.

We found variable α/β ratios for the different 5-substituted disilylated pyrimidine bases. This indicates that the 5-substituents influence the rates of the glycosylation reaction, according to the known glycosylation mechanism.[19] The corresponding reaction with an 2'-acyloxy substituent in the sugar is known to yield exclusively the β-anomer.[29]

No significant difference in the yields was found for the different types of 5-substituents, with more or less electron deficient character, and no significant relation between the α/β ratios and the yields was found. This was probably due to the absence of side-reactions. It has been shown that an electron withdrawing substituent, such as the nitro, in the five position of silylated uracils, increases the reactivity in the glycosylation reaction with an 1-O-acetyl sugar in the presence of $SnCl_4$.[29]

The rather high reactivity of all the bis-trimethylsilylpyrimidine bases,[18,26,27] used in this reaction excluded the need for catalysis. This made it easier to perform the reaction under completely anhydrous conditions. The absence of the catalyst also allowed traces of the silylating agent HMDS.[29] Furthermore, running the reactions in the absence of a catalyst led to almost equal ammounts of the α and β anomers for most of the compounds. This was desirable as our intentions were to test the antiviral properties of both the α and the β anomer, since some α anomers are known to exhibit antimetabolic activity.[19,30,31]

One problem was the poor yields of the β anomer for the compounds **1a**, **2a**, **6a** and **15a**, which made the HPLC purification procedure more tedious. The longer retention times of



X= O for compounds 1 and 2, X= NH for compounds 3-15.

SCHEME 1

the β anomers made them more sensitive to contaminations from the α anomers than the reverse. This was due to the tailing appearence of the collected fractions. By running the reactions in the presence of copper(I)iodide,[32] better yields of the β-anomers could be obtained. No 3-N glycosylation could be detected. This was probably due to the 5-substituent of the pyrimidine which is known to sterically promote the 1-N-selectivity.[33]

Completion of the reactions was determined by t.l.c. (silica gel 60, F 254, Merck). The crude reaction mixtures were hydrolyzed (the 4-trimethylsilyl groups were replaced by protons) and purified by column chromatography, using silica gel 60 and a mixture of dichloromethane and methanol as eluent. The hydrolysis of the 4-O-trimethylsilyl group has also been achieved by treatment with sodium bicarbonate in dichloromethane.[34] The resolution obtained by column chromatography (without recycling the product) was insufficient to give complete separation of the α and the β anomers. Instead the α and β anomers for compounds **1a - 15a** were separated by reversed phase HPLC.

In the alkaline solvolysis of the protecting ester groups, it was essential to avoid alkaline deamination of the cytidines (**3a - 15a**) to the corresponding uridines.[35] The protecting groups of the sugar moiety for **1a - 15a** (α and β) were therefore removed by treatment with a dilute solution of sodium methoxide (0.026 M). The resulting solvolyzed mixtures, containing the deprotected nucleosides, p-toluoylate and sodium methoxide in methanol were easily separated by silica gel column chromatography (without pre-concentration of the reaction mixtures) using dichloromethane followed by a mixture of dichloromethane and methanol as eluents, giving the corresponding deprotected nucleosides **1b-α - 15b-α** and **1b-β - 15b-β**. Other workup procedures after the sodium methoxide ester solvolysis consisted in the use of one equi. of Dowex 50 (H^+),[36] (more than one equi. would trap the cytidines) and acidification with acetic acid followed by the use of Dowex 1-X2 (OH^-).[37]

We studied the chromatographic properties of the 2'-deoxy-3',5'-di-O-p-toluoyl- and the 2'-deoxynucleosides on silica t.l.c. plates. We were surprised by the extraordinary low Rf values of the α and β forms of the 5-(3- and 4-pyridyl substituted derivatives (**13a, 14a, 13b** and **14b**).

The isomeric derivative, 5-(2-pyridyl)substituted compound **12a-α** had an Rf value, which approximately was five times higher than the Rf value for **13a-α** and **14a-α**. A similar

TABLE 1. Inhibition of HIV multiplication in H9 cell growth of uninfected H9 cells by 5-substituted 2'-deoxyuridine and cytidine analogues.

Compound	% inhib. in H9 cells		% inhib.of H9 cell growth		Compound	% inhib. in H9 cells		% inhib. of H9 cell growth	
	a	b	a	b		a	b	a	b[1]
1a-α	75-90	65	50	15	9a-α	>90T	<1		
1a-β	65-75	1 -70	40	40	9a-β	1 -30	<1	>90	10
1b-α	5 -30	10-20			9b-α	1 - 5			
1b-β	25-45	5 -30	35	15	9b-β	1 -15			
2a-α	>90	35-85	60	<1	10a-α	>90(T)	40-80	>90	10
2a-β	30->90	1 -10			10a-β	>90	20-75	15	<1
2b-α	1 -15	<1			10b-α	1 -40	1 -45		
2b-β	1 -30				10b-β	1 -40	25-50		
3a-α	67->90(T)[2]	1 - 5	50	<1	11a-α	>90(T)	65-90	>90	15
3a-β	86T->90T[2]	1->90			11a-β	>90(T)	15-90	>90	7
3b-α	20-35	5 -15			11b-α	30	40	5	5
3b-β	15-35				11b-β	25-40	35	5	5
4a-α	50-90(T)				12a-α	80->90(T)	50-75	>90	15
4a-β	>90T	1-50(T)	25	1-20	12a-β	>90T	80	90	30
4b-α	1 -25	1 -10			12b-α	5 -25	1 -15		
4b-β	1 -20	10-25			12b-β	1 -25	1 -20		
5a-α	>90T	1 -70	70-80	22	13a-α	>90(T)	60-90	55	2
5a-β	>99T	1 -20			13a-β	50->90(T)	1 -60	40	2
5b-α	<1-70	1 -10			13b-α	10-40	1 -30		
5b-β	25-40	1 -20			13b-β	15-20			
6a-α	>90T	1 - 6			14a-α	>90(T)	1 -90	70	16
6a-β	>90T	>90	70-94	<1	14a-β	40-75	1 -40	12	9
6b-α	<1	<1			14b-α	30-40	30-40	40	3
6b-β	<1-20	<1-10			14b-β	5 -35		5	
7a-α	>90T	50-55	>90	30	15a-α	99T	10		
7a-β	>90(T)	1-90(T)	>90	2	15a-β	99T	1		
7b-α	1 -10				15b-α	36	20		
7b-β	1 - 5				15b-β	1	1		
8a-α	>90(T)	35-70	80	15	16 -β	5	5		
8a-β	>90(T)	1 -50	40	5	17 -β	10	20		
8b-α	5 -15				18 -β	1	1		
8b-β	<1								

1. a = 10 μg/ml, b = 1 μg/ml

2. T: Toxic and causing cell destruction. (T): Toxic and causing morphological changes of the cell.

TABLE 2. ^{1}H NMR chemical shifts (ppm) for some 5-ary-2'-deoxy-3',5'-di-O-p-toluoylnucleosides in $CDCl_3$.

Com-	5-Arylprotons						Sugar protons						
pound	H6	H2	H3	H4	H5	H6	H1	H2a	H2b	H3	H4	H5a	H5b
1a-α	7.74			6.90	7.25		6.40	3.01	2.57	5.63	4.83	4.56	4.52
2a-α	7.75			6.83	7.21		6.39	3.00	2.59	5.62	4.86	4.56	4.52
3a-α	7.87		6.24	6.40	7.40		6.37	2.96	2.63	5.61	4.92	4.55	4.51
4a-α	8.16			7.68	7.08		6.40	2.99	2.72	5.62	4.97	4.61	4.57
5a-α	7.75		6.86	7.21			6.39	2.98	2.69	5.58	4.90	4.56	4.52
6a-α	7.68		6.87	7.03	7.30		6.32	2.94	2.69	5.57	4.86	4.54	4.50
7a-α	7.67		7.01	7.23	8.01		6.32	2.93	2.72	5.56	4.86	4.55	4.51
8a-α	7.60	7.00		6.91	7.37		6.36	2.95	2.68	5.56	4.86	4.54	4.50
9a-α	7.61		5.86	6.10	6.67		6.31	2.95	2.72	5.54	4.82	4.55	4.51
10a-α	7.57	7.20		6.28	7.45		6.35	2.95	2.68	5.56	4.86	4.55	4.51
11a-α	7.57		7.10 - 7.35				6.38	2.97	2.73	5.56	4.85	4.54	4.50
12a-α	8.16		7.25	7.48	7.12	8.52	6.45	3.00	2.72	5.62	4.96	4.59	4.55
13a-α	7.58	8.40		7.45	7.26	8.58	6.33	2.95	2.71	5.55	4.86	4.54	4.50
14a-α	7.61	8.53	7.05		7.05	8.83	6.33	2.96	2.65	5.54	4.88	4.53	4.49
1a-β	7.63			6.82	7.17		6.47	2.32	2.75	5.60+	4.56	4.72	4.62
2a-β	7.66			6.74	7.14		6.48	2.32	2.78	5.61	4.68	4.69	4.55
3a-β	7.92		6.18	6.33	7.29		6.46	2.22	3.00	5.61	4.60	4.80	4.66
4a-β	8.27			7.63	7.04		6.43	2.28	3.12	5.63	4.67	4.83	4.68
5a-β	7.78		6.84	7.14			6.49	2.26	2.97	5.60	4.58	4.75	4.63
6a-β	7.24		6.85	6.97	7.25		6.46	2.25	2.99	5.59	4.59	4.72	4.63
7a-β	7.70		7.00	7.18	7.96		6.43	2.24	2.94	5,58	4.57	4.71	4.63
8a-β	7.61	7.01		6.90	7.32		6.47	2.22	2.95	5.50	4.56	4.76	4.65
9a-β	7.56		5.95	6.10	6.63		6.44	2.19	2.91	5.56	4.54	4.69	4.62
10a-β	7.56	7.26		6.27	7.39		6.46	2.21	2.93	5.59	4.56	4.76	4.61
11a-β	7.57		7.10 - 7.35				6.49	2.21	2.93	5.59	4.54	4.61	4.71
12a-β	8.24		7.25	7.38	7.09	8.45	6.51	2.23	3.07	5.63	4.63	4.87	4.68
13a-β	7.60	8.43		7.43	7.21	8.55	6.42	2.21	2.95	5.58	4.57	4.74	4.59
14a-β	7.70	8.52	7.04		7.04	8.52	6.46	2.23	3.01	5.62	4.60	4.81	4.58

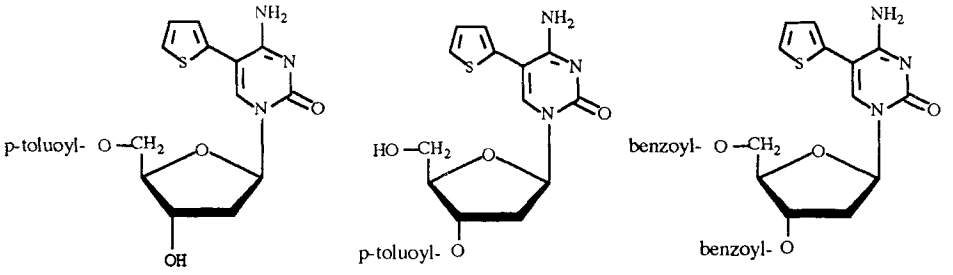
pattern was found when **12a-β**, and the deprotected **12b-α** and **12b-β** were compared with the corresponding isomers **13a-β**, **14a-β**, **13b-α**, **14b-α**, **13b-β** and **14b-β**.

The ^{1}H NMR data for compounds **1a - 14a** are given in TABLES 2 and 3. The pyrimidine proton was found in an interval 7.24 - 8.99 ppm and all 3',5'-O-P-toluoyl protons were found at 2.23 - 2.94 and 6.89 - 7.96 ppm.

TABLE 3. ^{1}H NMR coupling constants (Hz) for some 5-aryl-2'-deoxy-3',5'-di-O-p-toluoylnucleocides in $CDCl_3$.

Compound	Couplings in the 5-aryl unit						Couplings in the sugar unit					
	2-4	2-5	3-4	3-5	4-5	5-6	1-2a	2a-2b	2a-3	4-5a	4-5b	5a-5b
1a-α					5.2		6.6	15.4	6.7	4.1	4.2	12.1
2a-α					5.1		6.8	15.6	6.6	4.1	4.1	12.0
3a-α			3.3	-	1.7		6.3	15.5	6.1	4.1	4.2	11.8
4a-α					3.4		6.3	15.3	6.0	3.4	3.6	10.9
5a-α			3.7				6.4	15.4	6.3	4.0	4.1	11.9
6a-α			3.5	1.0	5.2		6.1	15.5	6.6	3.5	3.6	11.2
7a-α			3.7	1.1	5.7		6.4	15.5	6.2	3.5	3.7	11.0
8a-α	1.3	3.0			4.9		6.6	15.0	6.2	3.9	4.1	11.9
9a-α			3.5	1.7	2.7		6.1	15.5	6.2	4.0	4.0	12.1
10a-α	-	-			-		6.2	15.4	6.0	3.9	4.2	11.9
11a-α	-		-	-	-	-	6.1	15.5	6.2	3.8	4.1	11.7
12a-α			8.0		8.1	5.4	6.0	15.5	6.1	4.1	4.1	12.2
13a-α					-	-	6.1	15.2	6.1	3.6	3.6	11.2
14a-α						-	6.2	15.6	6.2	4.1	4.3	11.8
						1-2a	1-2b	2a-2b	2a-3	4-5a	4-5b	5a-5b
1a-β					5.2	8.6	6.0	15.7	5.6	4.3	3.1	12.2
2a-β					5.1	8.7	5.5	16.0	6.5	3.4	2.8	-
3a-β			3.4	0.7	1.9	8.3	5.3	15.2	6.4	2.8	4.3	12.2
4a-β					3.4	8.2	5.2	15.5	6.4	4.1	3.3	13.6
5a-β			3.7			8.2	5.3	14.9	6.5	2.7	4.1	12.1
6a-β			3.5	1.1	5.2	8.4	5.7	15.5	6.5	3.1	4.0	12.1
7a-β			3.7	1.1	5.7	8.5	5.4	15.3	6.4	3.0	4.0	12.1
8a-β	1.3	3.0			5.0	8.5	5.3	16.2	6.4	2.8	4.3	11.9
9a-β			3.6	1,7	2.7	8.6	5.3	15.8	6.4	3.2	4.3	12.2
10a-β	0.7	1.5			1.7	8.4	5.4	15.4	6.5	2.7	3.3	12.1
11a-β	-	-	-	-	-	8.5	5.5	15.2	6.3	3.0	4.1	12.1
12a-β			7		9	8.2	5.0	15.2	6.6	2.3	4.7	12.1
13a-β					7.7	8.4	5.2	15.6	6.6	2.1	3.4	11.5
14a-β						8.4	5.4	15.4	6.5	4.0	3.0	13.1

We were interested in how the antiviral activity was influenced by the presense of p-toluoyl ester groups in the 3' or 5' positions and by 3',5'-di-O-benzoyl instead of 3',5'-p-toluoyl ester groups. 5-(2-Thienyl)-β-2'-deoxy-5'-O-p-toluoylcytidine (**16**-β) and 5-(2-thienyl)-β-2'-deoxy-3'-O-p-toluoylcytidine (**17**-β) were prepared by partial solvolysis of the



16 β 17 β 18 β

SCHEME 2

previously prepared diester **6a-β**. 5-(2-Thienyl)-β-2'-deoxy-3',5'-di-O-benzoylcytidine (**18-β**) was prepared by esterfication of **6b-β** (SCHEME 2).

Antiviral activity

The synthesised compounds were investigated for their effects on inhibition of HIV multiplication in H9 cells. In case of antiviral activities their effects on growth of uninfected H9 cells were studied, for determining the selective activity. In each case 2 to 3 determinations have been made. The results are given in TABLE 1. It can be seen, that in general the compounds with 3',5'-ditoluoyl protecting group inhibit virus replication (**1a-α, β** to **15a-α, β**) whereas the unprotected nucleoside analogues (**1b-α, β** to **15b-α, β**) are at best only marginally active. Also most of the compounds with an anti-HIV activity are non-selective, inhibiting also the growth of uninfected cells.This is shown in TABLE 1, where the toxicity is indicated as ranging from cell destruction for some compounds to morphological changes of the cells or to inhibition of cell growth of uninfected cells. This probably contributes to the varying inhibition seen for some compounds at one concentration. Only a few compounds seem to have a limited selectivity, with the ratio for inhibition of HIV and

for inhibiting growth of uninfected cells in the range of 4 to >10, at concentrations of 1 μg/ml, i.e. the uridine analogue **2a-α**, and the cytidine analogues **6a-β**, **10a-β** and **13a-β**. The lack of activity for the corresponing unprotected compounds suggests that the mechanism of activity for these compounds differs from that of other known nucleoside analogues.

Experimental

Melting points are uncorrected. The ^{1}H NMR spectra were recorded on a Varian XL-300 spectrometer. The mass spectra were recorded on a Finnigan 4021 and a JEOL JMS - SX 102 spectrometer.

The assays for determining the inhibition of HIV multiplication and growth of uninfected cells were performed as previously described.[38] H9 cells were used in the assays and after incubating HIV infected cells with the compounds for 6 days, reverse transcriptase activity was used as an end point for determining HIV activity relative to a control.

*General procedure for preparation of 5-substituted-2'-deoxy-3',5'-di-O-p-toluoylnucleosides. (**1a-15a** α and β)*

To a stirred solution of 2.59 mmol of 5-aryl-2,4-ditrimethylsilyloxypyrimidine, 5-aryl- or 5-cyclopropyl- (2/5 of the described scale) 2,4-bis-O,N-trimethylsilylcytosine (prepared by moderate reflux of the 5-aryluracil,[18] 5-arylcytosine,[26] or 5-cyclopropylcytosine[27] in 2 ml of hexamethyldisilazane with 5 mg of ammonium sulfate as catalyst) and 40 ml of anhydrous 1,2-dichloroethane, 0.98 g (2.53 mmol) of 2-deoxy-3,5-di-O-p-toluoyl-D-erythro-pentosyl chloride[28] dissolved in 60 ml anhydrous 1,2-dichloroethane was added dropwise under nitrogen at 0 °C. The reaction mixture was allowed to reach room temperature and was stirred under nitrogen for 12 h. The solvent was evaporated and the crude reaction mixture was hydrolyzed and purified by column chromatography by using silica gel 60 and dichloromethane/methanol (19:1) as eluents, except for **1a** and **2a** and for **13a** and **14a** where the proportions were 39:1 and 9:1 respectively. This resulted in a mixture

containing only the α and the β anomers. The two anomers were seperated by HPLC using a dynamax RP C_{18} 150A column. For ^1H NMR data see TABLES 2 and 3.

*General procedure for the copper (I) iodide catalyzed preparation of 5-substituted nucleosides (**1a, 2a, 6a** and **15a** α and β)*

To a stirred solution of 2,07 mmol of 5-aryl-2,4-di-trimethylsilyloxypyrimidine, 5-(2-thienyl)-2,4-bis-O,N-trimethylsilylcytosine, or 5-cyclopropyl-2,4-bis-O,N-trimethylsilylcytosine (1/3 of the described scale) prepared as discribed above, 0.39 g (2.07 mmol) of anhydrous copper iodide and 32 ml of dry 1,2-dichloroethane, 0.78 g (2.00 mmol) of 2-deoxy-3,5-di-O-p-toluoyl-D-erythropentosyl chloride[28] dissolved in 48 ml of anhydrous 1,2-dichloroethane, was added dropwise under nitrogen, at 0 °C. The procedure was otherwise performed as described above.

*5-(3-n-Hexyl-2-thienyl)-2'-deoxy-3',5'-di-O-p-toluoyluridine (**1a**).* Yield 87 %, α/β 51 in the presence of copper-(1)iodide 1.6, eluent HPLC acetonitrile/chloroform/2-propanol/water (61.3:4.7:5.7:28.3).

***1a** α* Retention time 85 min, mp 56-58 °C. Anal. calcd. for $C_{35}H_{38}N_2O_7S$: C 66.6; H 6.07; N4.44; MWt 630.2400. Found: C 66.7; H 6.1; N 4.5; M+H 631.

***1a** β* Retention time 93 min, mp 56-60 °C. Found: M+H 631.2479.

*5-(3-methyl-2-thienyl)-2'-deoxy-3',5'-di-O-p-toluoyluridine (**2a**).* Yield 73 %, α/β 4.4, eluent HPLC acetonitrile/-water (63:37).

2a-α Retention time 86 min, mp 85-87 °C. Anal. calcd. for $C_{30}H_{28}N_2O_7S$: C 64.3; H 5.03; N 5.00; MWt 560.1618. Found: C 63.9; H 5.0; N 4.8; M+H 561.

2a-β Retention time 93 min, mp 77-78 °C. Found M+H 561.1713.

*5-(2-Furyl)-2'-deoxy-3',5'-di-O-p-toluoylcytidine (**3a**).* Yield 75 %, α/β 3.2, eluent HPLC acetonitrile/water (60:40).

3a-α Retention time 60 min, mp 100-102 °C. Anal calcd. for $C_{29}H_{27}N_3O_7$: C 65.8; H 5.14 N 7.93; MWt 529.1850. Found: C 65.6; H 5.1; N 7.9; M+H 530.

3a-β Retention time 71 min, mp 117-119 °C. Found: M+H 530.1941.

5-(2-Tiazoyl)-2'-deoxy-3',5'-di-O-p-toluoylcytidine ***(4a)***. Yield 69 %, α/β 0.76, eluent HPLC acetonitrile/chloroform/2-propanol/water (61.3:4.7:5.7:28.3).

4a-α Retention time 40 min, mp 215-217 °C. Anal. calcd, for $C_{28}H_{26}N_4O_6S$: C 61.5; H4.79; N 10.2: MWt 546.1573. Found: C 61.4; H 4.7; N 10.2; M+H 547.

4a-β Retention time 43 min, mp 147-149 °C. Found: M+H 547.1655.

5-(5-Phenyl-2-thienyl)-2'-deoxy-3',5'-di-O-p-toluoyl-cytidine ***(5a)***. Yield 59 %, α/β 0.87, eluent HPLC acetonitrile/water (63:37).

5a-α Retention time 78 min, mp 111-113 °C. Anal. calcd. for $C_{35}H_{31}N_3O_6S$: MWt 621.1934. Found: 622.1993.

5a-β Retention time 94 min, mp 115-117 °C. Found: M+H 622.2012.

5-(2-Thienyl)-2'-deoxy-3',5'-di-O-p-toluoylcytidine ***(6a)***. Yield 79 %, α/β 0.87 with copper(1)iodide 0.72, eluent HPLC acetonitrile/water (55:45).

6a-α Retention time 78 min, mp 105-106 °C. Anal. calcd. for $C_{29}H_{27}N_3O_6S$: C 63.8; H 4.99; N 7.70; MWt 545.1621. Found: C 63.4; H 4.9; N 7.6; M+H 546.

6a-β Retention time 94 min, mp 110-112 °C. Found M+H 546.1683.

5-(2-selenienyl)-2'-deoxy-3',5'-di-O-p-toluoylcytidine ***(7a)***. Yield 68 %, α/β 1.2, eluent HPLC acetonitrile/water (55:45).

7a-α Retention time 100 min, mp 107-108 °C. Anal. calcd. for $C_{29}H_{27}N_3O_6Se$: Mwt 593.1065. Found M+H 594.1151.

7a-β Retention time 118 min, mp 105-107 °C. Found: 594.1136.

5-(3-Thienyl)-2'-deoxy-3',5'-di-O-p-toluoylcytidine ***(8a)***. Yield 71 %, α/β 0.75, eluent HPLC acetonitrile/water (60:40)

8a-α Retention time 66 min, mp 106-108 °C. Anal. Calcd. for $C_{29}H_{27}N_3O_6S$: MWt 545.1621. Found: 546,1721.

8a-β Retention time 82 min, mp 107-108 °C. Found: M+H 546.1697.

5-(1-Methyl-2-pyrrolyl)-2'-deoxy-3',5'-di-O-p-toluoyl-cytidine ***(9a)***. Yield 82 %, α/β 1.4, eluent HPLC acetonitrile/water (60:40).

9a-α Retention time 64 min, mp 105-107 °C. Anal. calcd. for $C_{30}H_{30}N_4O_6$: C 66.4; H 5.57; N 10.3; MWt 542.2166. Found: C 66.4; H 5.7; N 10.1; M+H 543.

9a-β Retention time 74 min, mp 102-104 °C. Found: M+H 543.2220.

5-(3-Furyl)-2'-deoxy-3',5'-di-O-p-toluoylcytidine ***(10a)***. Yield 76 %, α/β 0.62, eluent HPLC acetonitrile/water (60:40).

10a-α Retention time 44 min, mp 99-101 °C. Anal. calcd. for $C_{29}H_{27}N_3O_7$: MWt 529.1850. Found. M+H 530.1938.

10a-β Retention time 53 min, mp 103-105 °C. Found: M+H 530.1927.

5-Pheny-2'-deoxy-3',5'-di-O-p-toluoylcytidine ***(11a)***. Yield 49 %, α/β 0.92, eluent HPLC acetonitrile/water (60:40).

11a-α Retention time 56 min, mp 107-109 °C. Anal. calcd. for $C_{31}H_{29}N_3O_6$: MWt 539.2057. Found: M+H 540.2129.

11a-β Retention time 67 min, mp 96-98 °C. Found: 540.2113.

5-(2-Pyridyl)-2'-deoxy-3',5'-di-O-p-toluoylcytidine

(12a). Yield 78 %, α/β 0.53, eluent HPLC acetonitrile/water (58:42).

12a-α Retention time 51 min, mp 96-98 °C. Anal. calcd. for $C_{30}H_{28}N_4O_6$: MWt 540.2009.

12a-β Retention time 61 min, mp 98-100 °C. Found M+H 541.2073.

5-(Pyridyl)-2'-deoxy-3',5'-di-O-p-toluoylcytidine ***(13a)***. Yield 58 %, α/β 2.4, eluent HPLC acetonitrile/water (52:48).

13a-α Retention time 60 min, mp 111-113 °C. Anal. calcd. for $C_{30}H_{28}N_4O_6$: C 66.3; H 5.22; N 10.4; MWT 540.2009. Found: C 66.3; H 5.1; N 10.2; M+H 541.

13a-β Retention time 60 min, mp 115-116 °C. Found: M+H 541.2094.

5-(4-Pyridyl)-2'-deoxy-3',5'-di-O-p-toluoylcytidine ***(14a)***. Yield 70 %, α/β 3.4, eluent HPLC acetonitrile/water (50:50).

14a-α Retention time 43 min, mp 146-148 °C. Anal calcd. for $C_{30}H_{28}N_4O_6$: MWT 540.2009. Found: M+H 541.2100.

14a-β Retention time 52 min, mp 118-120 °C. Found: M+H 541.2081.

5-Cyclopropyl-2'-deoxy-3',5'-di-O-p-toluoylcytidine ***(15a)***. Yield 77 %, α/β 3.6 with copper(1)iodide 1.2, eluent HPLC acetonitrile/water (55:45).

15a-α Retention time 81 min, mp 90-94 °C. Anal. calcd. for $C_{28}H_{29}N_3O_6$: MWt 503.2057. Found: 504.2144. ^1H NMR ($CDCl_3$) δ 7.41 (1H), 6.29 (1H), 5.54 (1H), 4.87 (1H), 4.54 (2H), 2.92 (1H), 2.62 (1H), 1.33 (1H), 0.73 (2H), 0.29 (2H).

15a-β Retention time 95 min, mp 100-102 °C. Found: 504.2144. ^1H NMR ($CDCl_3$) δ 7.43 (1H), 6.43 (1H), 5.59 (1H), 4.76 (1H),

4.64 (1H), 4.55 (1H), 2.91 (1H), 2.20 (1H), 1.22 (1H), 0.61 (2H), 0.26 (1H).

*General procedure for the removal of the 3',5'-O-p-toluoyl groups (**1b - 15b** α and β).*

A 25 ml pressure bottle was charged with 0.10 mmol of the α or β 2'-deoxy-3',5'-di-O-p-toluoyl nucleoside (**1a-15a**), which was dissolved in 10 ml of methanol. Sodium methoxide, 1.5 ml, (0.20 M) was added. The mixture was stirred for 24 h. If the reactant still could be detected by t.l.c. analysis, the reaction mixture was allowed to continue for another 24 h. The crude reaction mixture (including the methanol), was placed on a chromatography column with silica gel 60 which was eluated with dichloromethane followed by dichloromethane/methanol (2:1), except for **1b** and **2b** and for **13b** and **14b** where the proportions were (3:1) and (1:1) respectively. **15b** was eluated through a short silica gel column with methanol followed by evaporation prior to the chromatographic separation described above.

*5-(3-n-Hexyl-2-thienyl)-2'-deoxyuridine (**1b**).*

1b-α Yield 51 %, mp 86-88 °C. Anal. calcd. for $C_{19}H_{26}N_2O_5S$: MWt 394.1563. Found: M+H 395.1630.

1b-β Yield 39 %, mp 94-96 °C. Found: M+H 395.1631.

*5-(3-Methyl-2-thienyl)-2'-deoxyuridine (**2b**).*

2b-α Yield 56 %, mp 106-108 °C. Anal. calcd. for $C_{14}H_{16}N_2O_5S$: MWt 324.0780. Found: M+H 325.0860.

2b-β Yield 56 %, mp 108-110 °C. Found: M+H 325.0869.

*5-(2-Fury-)-2'-ddeoxycytidine (**3b**).*

3b-α Yield 58 %, mp 162-164 °C. Anal. calcd. for $C_{13}H_{15}N_3O_5$: MWt 293.1012. Found M+H 294.1093.

3b-β Yield 54 %, mp 224-226 °C. Found: M+H 294.1096.

*5-(Thiazolyl)-2'-deoxycytidine (**4b**).*

4b-α Yield 71 %, mp 228-230 °C. Anal. calcd. for $C_{12}H_{14}N_4O_4S$: MWt 310.0736. Found: M+H 311.0815.

4b-β Yield 39 %, mp 216-218 °C. Found: M+H 311.0822.

*5-(5-Phenyl-2-thienyl)-2'-deoxycytidine (**5b**).*

5b-α Yield 49 %, mp 121-122 °C. Anal. calcd for $C_{19}H_{19}N_3O_4S$: MWt 385.1097. Found: M+H 386.1171.

5b-β Yield 62 %, mp 218-220 °C. Found: M+H 386.1185.

*5-(2-thieny)-2'-deoxycytidine (**6b**).*

6b-α Yield 61 %, mp 180-181 °C. Anal. calcd. for $C_{13}H_{15}N_3O_4S$: 309.0783. Found: M+H 310.0862.

6b-β Yield 77 %, mp 200-201 °C. Found: M+H 310.0859.

*5-(2-Selenienyl)-2'-deoxycytidine (**7b**).*

7b-α Yield 53 %, mp 194-195 °C. Anal. calcd. for $C_{13}H_{15}N_3O_4Se$: MWt 357,0228. Found: M+H 358.0305. ^1H NMR (CD_3OD) δ 8.19 (1H), 7.98 (1H), 7.37 (1H), 7.30 (1H), 6.22 (1H), 4.57 (1H), 4.36 (1H), 4.33 (1H), 3.61 (1H), 2.71 (1H), 2.13 (1H).

7b-β Yield 59 %, mp 205-207 °C. Found: M+H 358.0313. ^1H NMR (CD_3OD) δ 8.23 (1H), 8.19 (1H), 7.36 (1H), 7.30 (1H), 6.28 (1H), 4.39 (1H), 3.96 (1H), 3.81 (1H); 3.72 (1H), 2.42 (1H), 2.22 (1H).

*5-(3-Thienyl)-2'-deoxycytidine (**8b**).*

8b-α Yield 58 %, mp 202-204 °C. Anal calcd. for $C_{13}H_{15}N_3O_4S$: MWt 309.0783. Found: M+H 310.0854.

8b-β Yield 74 %, mp 222-224 °C. Found: M+H 310.0857.

*5-(1-Methyl-2-pyrrolyl)-2'-deoxycytidine (**9b**).*

9b-α Yield 56 %, mp 145-147 °C. Anal. calcd. for $C_{14}H_{18}N_4O_4$: MWt 306.1328. Found: M+H 307.1394.

9b-β Yield 65 %, mp 206-208 °C. Found: M+H 307.1394.

*5-(3-Furyl)-2'-deocycytidine (**10b**).*

10b-α Yield 85 %, mp 215-216 °C. Anal. calcd. for $C_{13}H_{15}N_3O_5$: MWt 293.1012. Found: M+H 294.1093.

10b-β Yield 58 %, mp 203-205 °C. Found: M+H 294.1095.

*5-Pheny-2'-deoxycytidine (**11b**).*

11b-α Yield 76 %, mp 196-198 °C. Anal. calcd. for $C_{15}H_{17}N_3O_4$: MWt 303.1219. Found: M+H 304.1294.

11b-β Yield 89 %, mp 215-216 °C. Found: M+H 304.1297.

*5-(2-Pyridyl)-2'-deoxycytidine (**12b**).*

12b-α Yield 85 %, mp 209-210 °C. Anal. calcd. for $C_{14}H_{16}N_4O_4$: MWt 304.1172. Found: M+H 305.1256. ^{1}H NMR (CD_3OD) δ 8.62 (1H), 8.58 (1H), 7.87 (1H), 7.74 (1H), 7.31 (1H), 6.31 (1H), 4.47 (1H), 4.42 (1H), 3.66 (1H), 3.62 (1H), 2.75 (1H), 2.18 (1H).

12b-β Yield 59 %, mp 200-202 °C. Found: M+H 305.1256. ^{1}H NMR (CD_3OD) δ 8.99 (1H), 8.56 (1H), 7.82 (2H), 7.25 (1H), 6.31 (1H), 4.46 (1H), 4.00 (1H), 3.94 (1H); 3.82 (1H), 2.46 (1H), 2.28 (1H).

*5-(3-Pyridyl)-2'-deoxycytidiene (**13b**).*

13b-α Yield 82 %, mp 195-198 °C. Anal. calcd. for $C_{14}H_{16}N_4O_4$: MWt 304.1172. Found: M+H 305.1261.

13b-β Yield 89 %, mp 223-225 °C. Found: M+H 305.1249.

*5-(4-Pyridyl)-2'-deoxycytidine (**14b**).*

14b-α Yield 82 %, mp 212-214 °C. Anal. calcd. for $C_{14}H_{16}N_4O_4$: MWt 304.1172. Found: M+H 305.1250.

14b-β Yield 79 %, mp 250-252 °C. Found: M+H 305.1255.

*5-Cyclopropyl-2'-deoxycytidine (**15b**).*

15b-α Yield 85 %, mp 188-192 °C. Anal. calcd. for $C_{12}H_{17}N_3O_4$: MWt 267.1219. Found: M+H 268.1297. ^{1}H NMR (CD_3OD) δ 7.73 (1H), 6.18 (1H), 4.33 (1H), 4.29 (1H), 3.58 (2H), 2.65 (1H), 2.00 (1H), 1.48 (1H), 0.87 (2H), 0.51 (2H).

15b-β Yield 89 %, mp 196-200 °C. Found: M+H 268.1291. ^{1}H NMR

(CD_3OD) δ 7.94 (1H), 6.26 (1H), 4.37 (1H), 3.92 (1H), 3.83 (1H), 3.74 (1H), 2.32 (1H), 2.13 (1H), 1.46 (1H), 0.87 (2H), 0.87 (2H).

*5-(2-Thienyl)-β-2'-deoxy-5'-O-p-toluoylcytidine (**16-β**) and 5-(2- thienyl)-β-2'-deoxy-3'-O-p-toluoylcytidine (**17-β**)*

A 25 ml pressure bottle was charged with 100 mg (0.18 mmol) of 5-(2-thienyl)-β-2'-deoxy-3',5'-di-O-p-toluoylcytidine(**6a-β**),which was dissolved in 20 ml of methanol. Sodium methoxide, 3.0 ml (0.20 M) was added. The mixture was stirred for 20 min, the reaction was terminated by eluating the product mixture through a short silica gel column with methanol. The product mixture of compound **16-β**, **17-β**, reactant (**6a-β**) and small amounts of the completely hydrolyzed product (**6b-β**) was separated by a HPLC dynamax RP C18 150A column using acetonitrile/water (55:45) as eluent.

16-β Yield 29 mg (37 %), mp 270-2 °C. Anal. calcd. for $C_{21}H_{21}N_3O_5S$: C 59.0; H 4.95; N 9.83; MWt 427.1202. Found: C 59.2; H 4.8; N 9.8; M+H 428.1279. ^1H NMR ($(CD_3)SO$) δ 7.61 (1H), 7.49 (1H), 7.04 (1H), 6.98 (1H), 6.20 (1H), 5.44 (1H), 4.48 (1H), 4.38 (1H), 2.27 (1H), 2.15 (1H).

17-β Yield 11 mg (14 %), mp 258-60 °C. Found: C 59.0; H 5.0; N 9.6; M+H 428.1292. ^1H NMR ($CDCl_3$) δ 7.94 (1H), 7.39 (1H), 7.13 (1H), 7.10 (1H), 6.32 (1H), 5.59 (1H), 4.28 (1H), 3.98 (1H), 2.73 (1H), 2.63 (1H).

*5-(2-Thienyl)-β-2'-deoxy-3',5'-di-O-benzoylcutidine (**18-β**).*

A pressure bottle was charged with 50 mg (0.16 mmol) of **6b-β** and 1 ml of pyridine, 99 mg (0.65 mmol) of benzoylchloride was added dropwise at 0 °C. The mixture was stirred for 72 h at room temperature. The pyridine was evaporated at room temperature. Ethyl acetate (10 ml) was added which was extracted twice with water (10 ml) and dried with magnesium

sulfate, followed by silica gel chromatography using methanol/dichloromethane (1:19) as eluent. The product was finally chromatographed on a HPLC polygosil RP C18 500x1/2'' column using acetonitrile/water/tetrahydrofuran (55:35:10) as eluent. Yield 60 mg (87%), mp 132-4 °C. Anal. calcd. for $C_{27}H_{23}N_3O_6S$: MWt 217.1308. Found: (M+H) 518.1401. ^1H NMR ($CDCl_3$) δ 8.07 (1H), 7.36 (1H), 7.11 (1H), 6.86 (1H), 6.48 (1H), 5.68 (1H), 4.84 (1H), 4.75 (1H), 4.65 (1H), 2.93 (1H), 2.38 (1H).

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