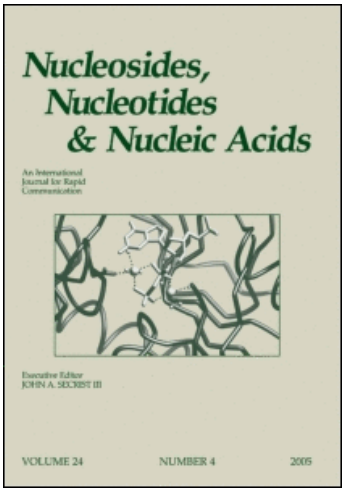

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SYNTHESIS OF SOME NOVEL ACYCLOLUMAZINE N-1 NUCLEOSIDES

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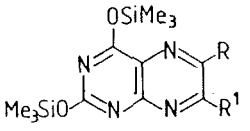
Abstract. Reaction of (2-acetoxyethoxy)methyl bromide with the silylated lumazine bases (1-6) in the presence of n-Bu_4NI leads to the formation of the nucleosides 8, 10, 12, 14, 16 and 18 respectively. Deacetylation with methanolic ammonia afforded the free nucleosides 9, 11, 13, 15, 17 and 19, respectively, in good yields. Structural proofs of the newly synthesized compounds are based on elemental analyses, UV and ^1H-NMR spactra. None of the acyclic nucleosides exhibited antiviral activity against HSV-1 *in vitro*.

The antiviral activity of some acyclic nucleosides had led in recent years to several examples of their preparations[1]. 9-[(2-hydroxyethoxy)methyl]guanine[2,3] (acyclovir) has been shown to be a useful chemotherapeutic agent in the treatment of patients infected by the Herpes simplex virus (HSV)[4]. Various derivatives of benzylacyclouridines[5] were described as potent inhibitors of uridine phosphorylase omitting the selective toxicity of 5-fluoro-2'-deoxyuridine (FdUrd)[6].

Recently, new acyclic as-triazine nucleosides[7] were synthesized and evaluated as inhibitors of orotidylatephosphoribosyltransferase. Moreover, a new type of acyclic 2'-azido-2'-deoxy thymidine together with the cytidine and adenosine analogues[8] have been reported for evaluation of their activity against the human immunodeficiency virus responsible for AIDS[9]. On the other hand, the phosphoramidate derivatives[10] of some acyclic nucleosides have been identified as having an inhibitory affect on the proliferation of tumor cells.

We present here the synthesis of various 6- and/or 7-substituted acyclic lumazine nucleosides (scheme 1) which are promising candidates for biological activity because of their close structural resemblance to the acyclouridine nucleosides.

Treatment of the trimethylsilylated derivatives of the lumazine base, its 6,7-dimethyl, 6,7-diphenyl, 6,7-dipyridyl, 7-phenyl, and 7-p-chlorophenyl derivatives (1-6) with (2-acetoxyethoxy)methyl bromide[11] in the presence of n-Bu_4NI as catalyst in dry acetonitrile as solvent at room temperature gave, after chromatographic purification, the corresponding nucleosides (8, 10, 12, 14, 16 and 18) respectively. Deacetylation to the free acyclic nucleosides 9, 11, 13, 15, 17, and 19, respectively, was performed by treatment with methanolic ammonia at room temperature. The site of attachment of the alkyl substituent to the hetero bases was concluded from their UV spectral (Table 1) comparison with known structurally proven lumazine analogues. Thus, the spectra showed very close similarity to those of the glycosylated lumazines[11,12] (20), its 6,7-dimethyl[12] (21), 6,7-diphenyl[12,14-16] (22), 6,7-dipyridyl[17] (23),



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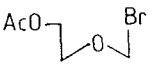

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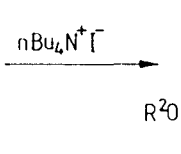
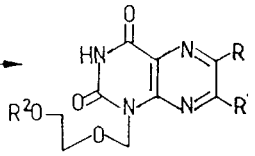
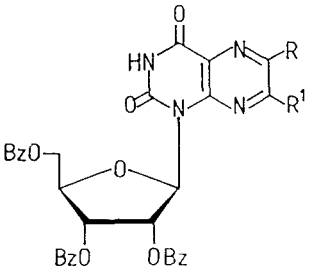




	R	R^1
1	H	H
2	CH_3	CH_3
3	C_6H_5	C_6H_5
4	C_5H_4N	C_5H_4N
5	H	C_6H_5
6	H	p-Cl-C_6H_4

	R	R^1	R^2
8	H	H	Ac
9	H	H	H
10	CH_3	CH_3	Ac
11	CH_3	CH_3	H
12	C_6H_5	C_6H_5	Ac
13	C_6H_5	C_6H_5	H
14	C_5H_4N	C_5H_4N	Ac
15	C_5H_4N	C_5H_4N	H
16	H	C_6H_5	Ac
17	H	C_6H_5	H
18	H	p-Cl-C_6H_4	Ac
19	H	p-Cl-C_6H_4	H



	R	R^1
20	H	H
21	CH_3	CH_3
22	C_6H_5	C_6H_5
23	C_5H_4N	C_5H_4N
24	H	C_6H_5
25	H	p-Cl-C_6H_4

Table 1. Physical Data of some Acyclolumazine Nucleosides.

Compound	UV - Absorption Spectra λ_{max} (nm)			log ε		
8	230	[245]	316	4.08	[3.95]	3.95
9	230	[240]	316	4.12	[3.96]	3.93
10	[227]	249	332	[4.06]	3.94	3.94
11	[228]	250	331	[4.07]	3.96	3.95
12	[223]	273	360	[4.41]	4.22	4.14
13	[220]	274	363	[4.44]	4.21	4.16
14	215	274	349	4.40	4.35	4.07
15	214	274	348	4.52	4.36	4.06
16	225	[273]	347	4.26	[3.89]	4.24
17	224	[272]	347	4.30	[3.86]	4.20
18	225	[276]	353	4.27	[4.38]	4.31
19	[214]	279	354	[4.24]	4.40	4.30

[ ] = Shoulder; all the compounds are measured in MeOH and show the neutral form.

7- phenyl[18] (24) and 7-p-chlorophenyl[18] (25) nucleosides. Therefore, the N-1 substitution clearly depicts the correct molecular structures. The structural features of these compounds were further established and proven by their ^{1}H-NMR spectra analysis (Table 2). The singlets in the region of 5.50-5.95 were attributed to the two *gem*-protons at C-1′, while the two *pseudo*-triplets are representing the other four protons at C-3′ and C-4′. Furthermore, all the newly synthesized products except (8-11) reveal the presence of the aromatic protons of the phenyl and pyridyl substituents at low field.

Table 1. Physical Data of some Acylolumazine Nucleosides (continuation)

com-pound	UV - Absorption spectra λmax (nm)			log ε		
20	231		315	4.72		3.84
21	229		326	4.75		4.01
22	228	272	358	4.84	4.35	4.16
23	228	273	346	4.80	4.29	4.06
24	227	274	352	4.75	4.08	4.34
25	228	274	349	4.79	4.06	4.36

BIOLOGICAL SCREENINIG

The compounds 9, 11, 13, 15, 17 and 19 were tested against HSV-1 and were found to be inactive.

E X P E R I M E N T A L

Melting points are not corrected. UV spectra were recorded on a Perkin Elmer spectrophotometer Lambda 5; ^{1}H-NMR spectra were recorded on a Bruker WM-250 high resolution spectrometer with tetramethylsilane as an internal standard and on a δ-scale in ppm. Thin layer chromatography was performed on silica gel sheets F 1550 LS 250 of Schleicher & Schüll. Column chromatography was performed on silica gel (70-230 mesh; Merck).

Synthesis of 1-[(2-acetoxyethoxy)methyl]lumazines (8, 10, 12, 14, 16 and 18). General procedure. A mixture of the lumazine derivatives (6.0 mmole) and a few crystals of ammonium sulphate were heated in hexamethyldisilazane (HMDS) (20 ml)

Table 2. ^{1}H-NMR Spectra of some Acyclolumazine Nucleosides in $CDCl_3$ and D_6-DMSO*

Compound	NH	H-1',1"	H3',3" (J)	H4',4" (J)	OH	OAc	Other Signals
8	9.19s	5.77s	3.87t (5.0)	4.16t (4.5)	-	1.96s	8.61 (H-7); 8.65 (H-6)
9*	12.01s	5.59s	3.60t (5.0)	4.16t (4.5)	4.60m	-	8.60 (H-7); 8.76 (H-6)
10	9.12s	5.62s	3.72t (5.0)	4.01t (4.5)	-	1.94s	2.56, 2.62 (2 CH_3)
11*	11.89s	5.54s	3.57t (5.0)	3.95t (4.5)	4.59m	-	2.48, 2.59 (2 CH_3)
12	8.82s	5.83s	3.89t (5.0)	4.18t (4.5)	-	1.96s	7.21-7.47m (-C_6H_5)
13*	12.05s	5.68s	3.66t (5.5)	3.46t (5.0)	4.64m	-	7.37-7.49m (-C_6H_5)
14	9.09s	5.84s	(3.87t (5.0)	4.16t (4.5)	-	1.95s	7.22-8.29m (-C_5H_4N)
15*	10.87s	5.69s	3.76t (5.5)	3.47t (5.0)	4.82m	-	7.33-8.29m (-C_5H_4N)
16	9.59s	5.94s	3.98t (5.0)	4.25t (4.5)	-	2.01s	9.09 (H-6); 7.57-8.18m (-C_6H_5)
17*	11.98s	5.71s	3.60t (5.5)	3.47t (5.5)	4.82m	-	9.24 (H-6); 7.58-8.30m; (-C_6H_5)
18	9.62s	5.96s	3.96t (5.5)	4.30t (4.5)	-	2.16s	9.01 (H-6); 7.34-8.01m; (p-ClC_6H_4)
19*	12.02s	5.82s	3.62t (5.0)	3.52t (5.0)	4.94m	-	9.18 (H-6); 7.38-8.42m; (p-ClC_6H_4)

s = singlet; t = triplet; m = multiplet.

unde reflux until a clear solution was obtained. After cooling, the excess of HMDS was removed in *vacuo* to give the silylated products (1-6). These products were dissolved in acetonitrile (20 ml) containing n-Bu_4NI (0.11 g, 0.03 mmole), and then (2-acetoxyethoxy)methyl bromide (0.50 g, 2.53 mmole) was added under a nitrogen atmosphere. After stirring for 4-5 h at room temperature, the reaction mixture was partitioned between $CHCl_3$ and aqueous sodium bicarbonate solution. The organic extract was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was applied to a silica gel column and elution with chloform-methanol (95:5) afforded the desired nucleosides as a amorphous solid, which then were recrystallized from the appropriate solvent.

1-[(2-Acetoxyethoxy)methyl]lumazine (8). Yield 0.89 g (53%), m.p. 115-120°C (recrystallized from ethyl acetate)

Anal. Calc. for $C_{11}H_{12}N_4O_5$ (280.2): C, 47.14; H, 4.31; N, 19.99. Found: C, 47.31; H, 4.25; N, 20.13.

6,7-Dimethyl-1-[(2-acetoxyethoxy)methyl]lumazine (10). Yield 1.14 g (62%), m.p. 135-139°C (recrystallized from ethyl acetate).

Anal. Calc. for $C_{13}H_{16}N_4O_4$ (308.3): C, 50.64; H, 5.23; N, 18.17. Found; C, 50.85; H, 5.15; N, 18.09.

6,7-Diphenyl-1-[(2-acetoxyethoxy)methyl]lumazine (12). Yield 1.55 g (60%), m.p. 159-162°C (recrystallized from $CHCl_3$/MeOH).

Anal. Calc. for $C_{23}H_{20}N_4O_5$ (432.4): C, 63.88; H, 4.66; N, 12.95. Found: C, 63.59; H, 4.65; N, 13.20.

6,7-Bis-(4-pyridyl)-1-[(2-acetoxyethoxy)methyl]lumazine (14). Yield 1.44 g (55%). m.p. 107-109°C (recrystallized from ethyl acetate).

Anal. Calc. for $C_{21}H_{18}N_8O_5$ (434.4):C, 58.06; H, 4.17; N, 19.34. Found: C, 57.76; H, 4.24; N, 19.53.

7-Phenyl-1-[(2-acetoxyethoxy)methyl]lumazine (16). Yield 1.41 g (66%), m.p. 148-152°C (recrystallized from $CHCl_3$/MeOH).

Anal. Calc. for $C_{17}H_{16}N_4O_5$ (356.3): C, 57.30; H, 4.52; N, 15.72. Found: C, 57.00; H, 4.68; N, 15.47.

7-p-Chlorophenyl-1-[(2-acetoxyethoxy)methyl] lumazine (18). Yield 0.98 g (52%), m.p. 151-155°C (recrystallized from CHCl3/ MeOH).

Anal. Calc. for $C_{17}H_{15}ClN_4O_5$ (390.8): C, 57.25; H, 3.87; N, 14.33. Found: C, 52.85; H, 3.95; N, 14.41.

Synthesis of 6,7-substituted-1-[(2-hydroxyethoxy)methyl] lumazines (9, 11, 13, 15, 17 and 19). General procedure. In a solution of 16% methanolic ammonia (20 ml) were stirred compounds (8, 10, 12, 14, 16 and 18) (1.5 mmole) for 3.5 h at room temperature. The solution was neutralized with Dowex-50 (H^+), filtered and then evaporated in *vacuo* to dryness. The residues were stirred with ether for 2 h , the solids filtered off and then recrystallized from MeOH.

1-[(2-Hydroxyethoxy)methyl]lumazine (9). Yield 0.31 g (86%), m.p. 159-161°C.

Anal. Calc. for $C_9H_{10}N_4O_4$ (238.2): C, 45.38; H, 4.23; N, 23.52. Found: C, 45.05; H, 4.27; N,23.43.

6,7-Dimethyl-1-[(2-hydroxyethoxy)methyl]lumazine (11). Yield 0.32 g (81%), m.p. 176-180°C.

Anal. Calc. for $C_{11}H_{14}N_4O_4$ (266.3) : C, 49.62; H, 5.30; N, 21.04. Found: C, 49.73; H, 5.42; N, 21.15.

6,7-Diphenyl-1-[(2-hydroxyethoxy)methyl]lumazine (13). Yield 0.44 g (75%), m.p. 188-190°C.

Anal. Calc. for $C_{21}H_{18}N_4O_4$ (390.40): C, 64.61; H, 4.64; N, 14.35. Found: C, 64.88; H, 4.61; N, 14.08.

6,7-Bis-(-pyridyl)-1-[(2-hydroxyethoxy)methyl]lumazine (15). Yield 0.42 g (71%). m.p. 118-120°C.

Anal. Calc. for $C_{19}H_{16}N_8O_4$ (392.4): C, 58.17; H, 4.11; N, 21.41. Found: C, 7.98; H, 4.05; N, 21.09.

7-Phenyl-1-[(2-hydroxyethoxy)methyl]lumazine (17). Yield 0.38 g (81%), m.p. 196-200°C.

Anal. Calc. for $C_{15}H_{14}N_4O_4$ (314.3): C, 57.32; H, 4.49; N, 17.82. Found: C, 57.13; H, 4.56; N, 18.18.

7-p-Chlorophenyl-1-[(2-hydroxyethoxy)methyl]lumazine (19). Yield 0.46 g (88%), m.p. 192-196°C.

Anal. Calc. for $C_{15}H_{13}ClN_4O_4$ (348.86): C, 51.66; H, 3.76; N, 16.06. Found: C, 51.60; H, 3.71; N, 15.72

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