5–AMINO DERIVATIVES OF 2',3'–DIDEOXYNUCLEOSIDES FOR EVALUATION OF ANTI–HIV ACTIVITY

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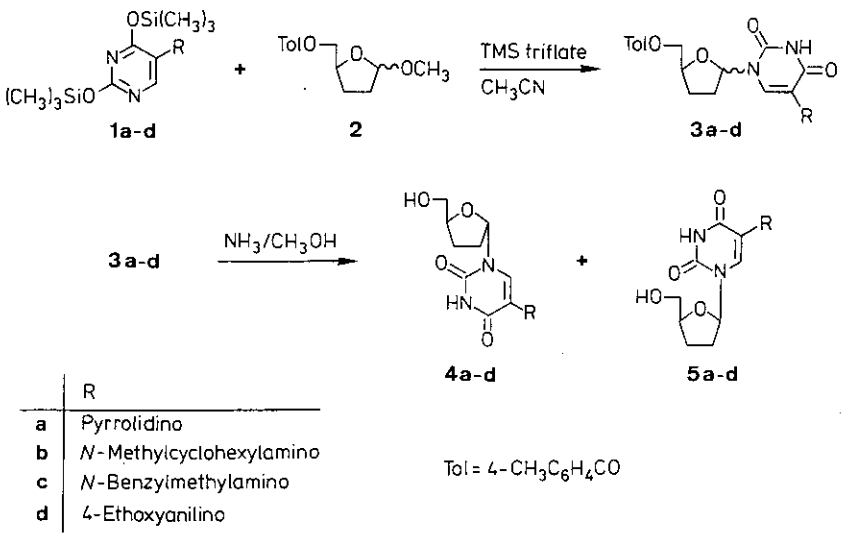
Abstract – Reaction of protected 2,3-dideoxy-D-ribose (**2**) with silylated 5-amino derivatives of uracil using trimethylsilyl trifluoromethanesulfonate as catalyst afforded the 2',3'-dideoxynucleosides (**3a–d**) which were deprotected with methanolic ammonia and separated by chromatography to give α-anomers (**4a–d**) and β-anomers (**5a–d**). Compounds (**3a–c**) were converted to 4-(1,2,4-triazol-1-yl) derivatives (**6a–c**). Ammonia in dioxane converted the 4-(1,2,4-triazole-1-yl)pyrimidin-2(1*H*)-one moiety into cytosin-1-yl. In case of **6b**, 4-methoxypyrimidin-2-one 2,3–dideoxyriboside was accomplished *via* transformation of the 4-triazolyl moiety with methanol on silica. Methanolic ammonia was used for deprotection of the sugar moiety to afford **7–10**.

There is a need for compounds that may be effective in the therapy of acquired immunodeficiency syndrome (AIDS). Among the first compounds identified as having an inhibitory effect against retroviruses, particularly the human immunodeficiency virus (HIV) and hence of potential use in the therapy of AIDS are 3'-azido-3'-deoxythymidine[1] (AZT) and 2',3'-dideoxycytidine[2] (DDC). These compounds are able to enter cells and are converted by cellular enzymes to their triphosphates which are potent competitive inhibitors of reverse transcriptase. Since these analogues do not have the 3'-hydroxy group of the natural substrates, DNA chain elongation is precluded. T.–S. Lin[3] has reported the evaluation of 5-amino AZT derivatives as agents against HIV. Therefore we found it of interest to synthesize a series of 5-amino-2',3'-dideoxynucleosides to offer a chance to find compounds with less prominent side effects than those observed for AZT and DDC. In

the case of AZT, the key toxicity that should be obviated is the suppression of bone marrow; in the case of DDC, the key toxicity is peripheral neuropathy.[4]

RESULTS AND DISCUSSION

5-Pyrrolidino, 5-(*N*-methylcyclohexylamino), 5-(*N*-benzylmethylamino) and 5-(4-ethoxyanilino)uracils[5] were silylated by the method of Wittenburg[6] to give the corresponding silylated derivatives (**1a–d**). Coupling of methyl 2,3-dideoxy-5-*O*-p-toluoyl-D-*glycero*-pentofuranoside (**2**)[7] with the silylated compounds (**1a–d**) using the trimethylsilyl trifluoromethanesulfonate (TMS triflate) method of Vorbrüggen[8] in dry acetonitrile at room temperature for 0.5–3 h gave an anomeric mixture of the corresponding protected 2',3'-dideoxynucleosides (**3a–d**) in 36–88% yield. In all cases the anomeric ratio β/α was close to 2:3. The anomers of compound (**3b**) were separated by use of preparative hplc. Treatment of **3a–d** with 1:1 mixture of methanol and conc. ammonia solution at room temperature for 24–48 h resulted in complete deprotection of the hydroxy group in the sugar moiety. The purification and separation were carried out by column chromatography on silica gel to give the α-anomers (**4a–d**) in 24–70% yield, and β-anomers (**5a–d**) in 20–48% yield.

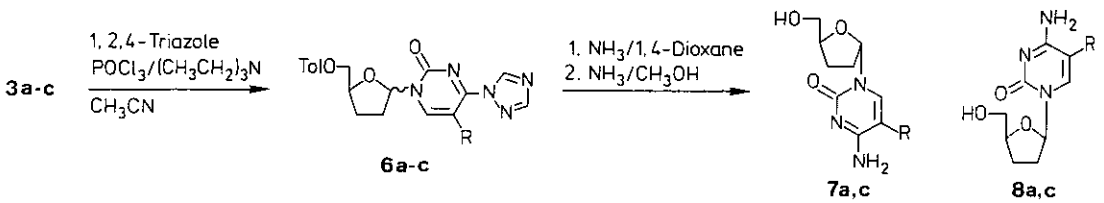


	R
a	Pyrrolidino
b	*N*-Methylcyclohexylamino
c	*N*-Benzylmethylamino
d	4-Ethoxyanilino

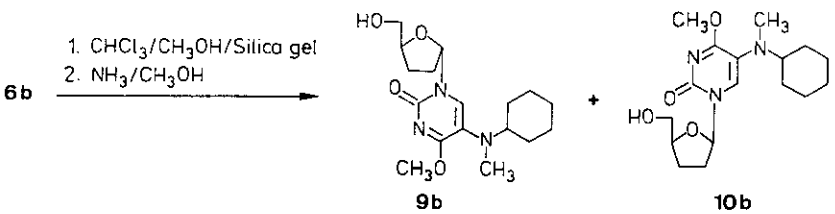
Scheme 1

4-(1,2,4-Triazol-1-yl)pyrimidin-2(1*H*)-ones (α- and β-anomers) were prepared by treating **3a–c** with putative tris(1*H*-1,2,4-triazol-1-yl)phosphine oxide[9] in the presence of 1,2,4-triazole and triethylamine in acetonitrile at room temperature. Since the triazole derivative (**6a**) was hydrolysed by water, a non-aqueous work-up was used for this compound. Reaction of the 4-triazole derivatives (**6a,c**) with aqueous ammonia in dioxane solution at room temperature yielded the cytosine derivatives. Subsequent removal of the toluoyl group by

treatment with methanolic ammonia at room temperature and followed by chromatographic purification afforded the unprotected cytosine nucleosides as α-anomers (**7a,c**) in 23 and 45% yields and as β-anomers (**8a,c**) in 9 and 15% yields.



When the triazole of compound (**6b**) was applied on a silica gel column and eluted with 5% methanol in chloroform, it was completely converted into the 4-methoxypyrimidin-2(1*H*)-one derivatives (**9b**) and (**10b**) after deprotection with ammonia in methanol and separation with hplc.



The β-isomer assignments of compounds (**5a–d**) were made by comparison with the ^{13}C–nmr and ^{1}H–nmr of 5-ethyl-2',3'-dideoxyuridine[10] and 5-alkoxymethyluridines.[7] Almost identical differences of the chemical shifts between α- and β-anomers were observed in the sugar moiety. Also the stereochemistry of nucleosides (**7a,c**) and (**8a,c**) was assigned on the basis of the corresponding ^{1}H–nmr spectra of α- and β-anomers of 2',3'-dideoxycytidine.[11]

The nucleosides (**3a–d**, **4b,c**, **5a–d**, **7a,c**, and **8a,c**) were selected for *in vitro* studies of biological effects. The compounds did not show any significant activity at non-cytotoxic concentrations against Herpes Simplex Virus, type 1 (HSV–1), strain McIntyre, when tested in a continuous cell line from rabbit cornea (SIRC) which was maintained in Eagle's MEM containing 1% fetal calf serum (FCS) and the test compounds. The same compounds were also devoid of activity at non–cytotoxic concentrations against HIV–1 (strain HTLV–IIIB) in MT–4 cells. MT–4 cells were incubated with virus, washed and added in a proportion of 1:10 to uninfected MT–4 cells which had been preincubated in test compound containing culture medium (RPM 1640 containing 10% FCS) for 2 h. The MT–4 cells were maintained with the culture medium like-

wise containing the test compound. Expression of HIV in culture medium was quantitated by HIV antigene detection ELISA.[12] For both HSV–1 and HIV–1 the concentration of the test compound was 100 μM, except for the compound **3c** which was toxic against SIRC and MT–4 cells at 100 μM. Also compound **3b(β)** showed toxicity against SIRC at 100 μM. At 10 μM these compounds showed no activity, neither against HIV–1 nor HSV–1.

EXPERIMENTAL

Silica gel tlc was performed on 60F–254 precoated plates (Merck) and column chromatography was performed on Merck silica gel (0.040–0.063 and 0.025–0.04 mm in the ratio 2:1). Elemental analysis was carried out at NOVO Microanalytical Laboratory, Novo Allé, DK–2880 Bagsvaerd. Mass spectra were obtained on a Varian MAT 311A mass spectrometer. The ^{1}H–nmr and ^{13}C–nmr spectra were determined on a Bruker AC 250FT nmr spectrometer using tetramethylsilane as the internal standard.

5-Amino-1-[2,3-dideoxy-5-O-(4-methylbenzoyl)-D-glycero-pentofuranosyl]uracil derivatives (**3a–d**).
To a stirred solution of compound (**2**) (3.38 g, 13.5 mmol) and the silylated uracil derivatives (**1a–d**) (15.5 mmol) in acetonitrile (70 ml) was added dropwise trimethylsilyl trifluoromethanesulfonate (2.8 ml, 15.5 mmol) in anhydrous acetonitrile (10 ml) at 0°C for 15 min. The mixture was stirred for 0.5–3 h at room temperature. The reaction solution was diluted with CH_2Cl_2 (250 ml) and extracted with ice-cold saturated aqueous $NaHCO_3$. The aqueous solutions were extracted with dichloromethane. The combined organic layers were washed with cold water, dried (Na_2SO_4) and evaporated under reduced pressure to give a syrup which was chromatographed on silica gel with ether/petroleum ether (8:2) to give 36–88% of **3a–d** (compound (**3b**) was eluated with $CHCl_3/CH_3OH$ (99:1) and (**3d**) with $CHCl_3$). Anomers of **3b** (2.25 g) were separated by hplc with 41% ethanol/water on a C4, 15–20 μm, 300 A reversed phase column to give pure α- and β-anomers. Solid compounds were washed with ether.

1-(2,3-Dideoxy-5-O-(4-methylbenzoyl)-α-D-glycero-pentofuranosyl)-5-(N-methylcyclohexylamino)uracil [**3b(α)**].
1.3 g (22%) as an oil. Ms: m/z 441 (M^+). ^{1}H–Nmr ($CDCl_3$): δ 0.95–1.26 (6H, m, cyclohexyl), 1.42–1.78 (4H, m, cyclohexyl), 1.94–2.59 (7H, m, 2'–H, 3'–H and p–CH_3), 2.62 (3H, s, CH_3), 3.25 (1H, m, cyclohexyl), 4.34 (1H, dd, J = 5.3 Hz and 11.8 Hz, 5'–H), 4.43 (1H, dd, J = 3.8 Hz and 11.8 Hz, 5'–H), 4.71 (1H, m, 4'–H), 6.16 (1H, dd, J = 4.5 Hz and 6.2 Hz, 1'–H), 6.86 (1H, s, 6–H), 7.26 (2H, d, J = 8.1 Hz, Ar–H), 7.94 (2H, d, J = 8.1 Hz, Ar–H), 9.43 (1H, s, N3–H). ^{13}C–Nmr ($CDCl_3$): δ 21.5 (p–CH_3), 25.4, 25.5 and 25.8

(cyclohexyl and C–3'), 29.8, (cyclohexyl), 32.1 (C–2'), 35.1 (CH_3), 59.1 (cyclohexyl), 65.9 (C–5'), 78.7 (C–4'), 87.4 (C–1'), 126.8 (C–5), 127.9, 129.0, 129.5 and 143.8 (C_6H_4 and C–6), 149.3 (C–2), 161.3 (C–4), 166.2 (C=O).

Table. Microanalyses of the anomeric compounds (**3**, **4/5**, **7/8**, and **9/10**).

No.	Formula		Analysis C	H	N
3b	$C_{24}H_{31}N_3O_5$	Calcd	65.29	7.08	9.52
		Found	65.14	7.13	9.35
4a/5a	$C_{13}H_{19}N_3O_4$	Calcd	55.51	6.81	14.94
		Found	55.13	6.79	14.72
4b/5b	$C_{16}H_{25}N_3O_4 \cdot \frac{1}{4}H_2O$	Calcd	58.61	7.84	12.81
		Found	58.66	7.81	12.58
4c/5c	$C_{17}H_{21}N_3O_4$	Calcd	61.62	6.39	12.68
		Found	61.28	6.41	12.37
4d/5d	$C_{17}H_{21}N_3O_5 \cdot \frac{1}{4}H_2O$	Calcd	58.02	6.16	11.94
		Found	58.32	6.09	11.82
7a/8a	$C_{13}H_{20}N_4O_3 \cdot \frac{1}{4}H_2O$	Calcd	54.82	7.25	19.67
		Found	55.16	7.14	19.67
7c/8c	$C_{17}H_{22}N_4O_3 \cdot \frac{1}{2}H_2O$	Calcd	60.16	6.83	16.51
		Found	60.47	6.69	16.45
9b/10b	$C_{17}H_{27}N_3O_4 \cdot H_2O$	Calcd	57.45	8.22	11.82
		Found	57.23	8.01	11.22

2',3'-Dideoxy-5'-O-(4-methylbenzoyl)-5-(N-methylcyclohexylamino)uridine [**3b**(*β*)].

0.71 g (12%); mp 117–118°C. Ms: m/z 441 (M^+). ^{1}H–Nmr ($CDCl_3$): δ 0.97–1.25 (6H, m, cyclohexyl), 1.56–1.72 (4H, m, cyclohexyl), 1.92–2.30 (4H, m, 2'–H and 3'–H), 2.42 (3H, s, *p*–CH_3), 2.44 (3H, s, CH_3),

3.20 (1H, m, cyclohexyl), 4.45 (2H, m, 5'–H), 4.57 (1H, m, 4'–H), 6.14 (1H, t, J = 5.7 Hz, 1'–H), 6.93 (1H, s, 6–H), 7.24 (2H, d, J = 8.1 Hz, Ar–H), 7.93 (2H, d, J = 8.1 Hz, Ar–H), 9.07 (1H, s, N3–H). ^{13}C–Nmr ($CDCl_3$): δ 21.5 (p–CH_3), 25.5, 25.8 and 26.5 (cyclohexyl and C–3'), 29.6 (cyclohexyl), 31.6 (C–2'), 34.6 (CH_3), 59.0 (cyclohexyl), 65.9 (C–5'), 77.7 (C–4'), 86.1 (C–1'), 126.8 (C–5), 127.4, 129.1, 129.6 and 144.0 (C_6H_4, C–6), 149.3 (C–2), 161.1 (C–4), 166.3 (C=O).

5-Amino-1-(2,3-dideoxy-D-glycero-pentafuranosyl)uracil derivatives (**4a–d**) *and* (**5a–d**).

A solution of **3a–d** (2.5 mmol) in a 1:1 mixture (72 ml) of methanol and conc. ammonia was stirred at room temperature for 40–48 h. The reaction mixtures were concentrated under reduced pressure and the residue was chromatographed on silica gel (15–40 g) with ether/petroleum ether (99:1) (compound (**3b**) with 2% CH_3OH in $CHCl_3$) to give α- (**4**) and β-anomers (**5**) which in case of solids were washed with ether.

1-(2,3-Dideoxy-α-D-glycero-pentofuranosyl)-5-pyrrolidinouracil (**4a**).

260 mg (37%); mp 138–140°C. Ms: m/z 281 (M^+). ^{1}H–Nmr (DMSO–d_6): δ 1.80 (4H, br s, pyrrolidino), 1.92–2.33 (4H, m, 2'–H and 3'–H), 3.04 (4H, br s, pyrrolidino), 3.37 (2H, m, 5'–H), 4.33 (1H, m, 4'–H); 4.80 (1H, br s, OH), 6.04 (1H, dd, J = 4.7 Hz and 6.4 Hz, 1'–H), 6.51 (1H, s, 6–H), 11.23 (1H, s, N3–H). ^{13}C–Nmr (DMSO–d_6): δ 23.5 (2 x CH_2), 26.2 (C–3'), 30.7 (C–2'), 49.3 (2 x CH_2), 63.5 (C–5'), 81.3 (C–4'), 85.8 (C–1'), 118.2 (C–5), 126.0 (C–6), 148.8 (C–2), 160.4 (C–4).

2',3'-Dideoxy-5-pyrrolidinouridine (**5a**).

113 mg (16%); mp 163–165°C. Ms: m/z 281 (M^+). ^{1}H–Nmr (DMSO–d_6): δ 1.78 (4H, m, pyrrolidino), 1.86–2.35 (4H, m, 2'–H and 3'–H), 3.01 (4H, m, pyrrolidino), 3.52 (1H, m, 5'–H), 3.70 (1H, m, 5'–H), 4.02 (1H, m, 4'–H), 5.07 (1H, t, J = 4.9 Hz, OH), 6.03 (1H, dd, J = 3.2 Hz and 6.9 Hz, 1'–H), 7.13 (1H, s, 6–H), 11.17 (1H, br s, N3–H). ^{13}C–Nmr (DMSO–d_6): δ 23.4 (pyrrolidino), 25.0 (C–3'), 31.6 (C–2'), 49.3 (pyrrolidino), 61.9 (C–5'), 81.1 (C–4'), 84.8 (C–1'), 119.0 (C–5), 125.8 (C–6), 148.8 (C–2) 160.4 (C–4).

1-(2,3-Dideoxy-α-D-glycero-pentofuranosyl)-5-(N-methylcyclohexylamino)uracil (**4b**).

565 mg (70%) as an oil. Ms: m/z 323 (M^+). ^{1}H–Nmr (DMSO–d_6): δ 1.06–1.20 (6H, m, cyclohexyl), 1.53–1.82 (4H, m, cyclohexyl), 1.93–2.34 (4H, m, 2'–H and 3'–H), 2.50 (3H, s, CH_3), 3.16 (1H, m, cyclohexyl), 3.40 (2H, m, 5'–H), 4.34 (1H, br s, 4'–H), 4.80 (1H, br s, OH), 6.00 (1H, br s, 1'–H), 6.84 (1H, s, 6–H), 11.21 (1H, s, N3–H). ^{13}C–Nmr (DMSO–d_6): δ 25.1, 25.5 and 26.0 (cyclohexyl and C–3'), 29.2 (cyclohexyl), 31.0 (C–2'), 34.6 (CH_3), 58.2 (cyclohexyl), 63.4 (C–5'), 81.3 (C–4'), 86.1 (C–1'), 125.8 (C–5), 128.2 (C–6), 149.2 (C–2), 161.2 (C–4).

5-(N-Methylcyclohexylamino)-2',3'-dideoxyuridine (**5b**).

388 mg (48%); mp 153–155° C. Ms: m/z 323 (M^+). ^{1}H–Nmr (DMSO–d_6): δ 1.09–1.27 (6H, m, cyclohexyl), 1.57–1.87 (4H, m, cyclohexyl), 1.89–2.25 (4H, m, 2'–H and 3'–H), 2.46 (3H, s, CH_3), 3.17 (1H, m, cyclohexyl), 3.54 (1H, br s, 5'–H); 3.67 (1H, br s, 5'–H), 4.02 (1H, br s, 4'–H), 5.06 (1H, br s, OH), 6.00 (1H, br s, 1'–H), 7.38 (1H, s, 6–H), 11.16 (1H, s, N3–H). ^{13}C–Nmr (DMSO–d_6): δ 24.9, 25.2 and 25.5 (cyclohexyl and C–3'), 28.9 (cyclohexyl), 31.6 (C–2'), 34.1 (CH_3), 58.0 (cyclohexyl), 61.9 (C–5'), 81.2 (C–4'), 84.9 (C–1'), 125.9 (C–5), 127.6 (C–6), 149.1 (C–2), 161.1 (C–4).

5-(N-Benzylmethylamino)-1-(2,3-dideoxy-α-D-glycero-pentofuranosyl)uracil (**4c**).

290 mg (35%), hygroscopic solid. Ms: m/z 331 (M^+). ^{1}H–Nmr ($CDCl_3$): δ 1.80–2.58 (4H, m, 2'–H and 3'–H), 2.63 (3H, s, CH_3), 3.04 (1H, br s, OH), 3.52 (1H, dd, J = 5.3 Hz and 11.9 Hz, 5'–H), 3.70 (1H, m, 5'–H), 4.10 (1H, d, J = 13.9 Hz, CH_2), 4.20 (1H, d, J = 13.8 Hz, CH_2), 4.31 (1H, br s, 4'–H), 6.12 (1H, d, J = 4.6 Hz, 1'–H), 6.61 (1H, s, 6–H), 7.26 (5H, m, Ar–H), 9.81 (1H, br s, N3–H). ^{13}C–Nmr ($CDCl_3$): δ 25.5 (C–3'), 31.9 (C–2'), 39.5 (CH_3), 57.8 (CH_2), 64.3 (C–5'), 81.6 (C–4'), 86.8 (C–1'), 125.5, 126.8, 127.1, 128.1, 128.7 and 137.3 (C–5, C–6 and phenyl), 149.4 (C–2), 161.1 (C–4).

5-(N-Benzylmethylamino)-2',3'-dideoxyuridine (**5c**).

124 mg (15%) as an oil. Ms: m/z 331 (M^+). ^{1}H–Nmr ($CDCl_3$): δ 1.87–2.28 (4H, m, 2'–H, 3'–H), 2.54 (3H, s, CH_3), 3.36 (1H, br s, OH), 3.61 (1H, m, 5'–H), 3.88 (1H, d, J = 11.2 Hz, 5'–H), 4.11 (3H, m, 4'–H and CH_2), 6.11 (1H, d, J = 4.2 Hz, 1'–H), 7.11 (1H, s, 6–H), 7.27 (5H, br s, Ar–H), 10.10 (1H, br s, N3–H). ^{13}C–Nmr ($CDCl_3$): δ 24.9 (C–3'), 31.9 (C–2'), 39.0 (CH_3), 57.6 (CH_2), 62.9 (C–5'), 81.2 (C–4'), 85.8 (C–1'), 125.9, 126.9, 127.9, 128.7 and 137.2 (C–5, C–6 and phenyl), 149.4 (C–2), 161.1 (C–4).

1-(2,3-Dideoxy-α-D-glycero-pentofuranosyl)-5-(4-ethoxyanilino)uracil (**4d**).

208 mg (24%); mp 180–182° C. Ms: m/z 347 (M^+). ^{1}H–Nmr (DMSO–d_6): δ 1.28 (3H, t, J = 6.7 Hz, CH_3), 1.84–2.34 (4H, m, 2'–H and 3'–H), 3.37 (2H, m, 5'–H), 3.92 (2H, q, J = 6.7 Hz, CH_2), 4.27 (1H, br s, 4'–H), 4.79 (1H, br s, OH), 6.04 (1H, br s, 1'–H), 6.79 (5H, s, Ar–H), 7.23 (1H, s, 6–H), 11.48 (1H, s, N3–H). ^{13}C–Nmr (DMSO–d_6): δ 14.6 (CH_3), 25.8 (C–3'), 31.1 (C–2'), 63.2 (CH_2), 63.4 (C–5'), 81.4 (C–4'), 86.1 (C–1'), 115.0 and 117.3 (phenyl), 118.8 (C–5), 124.0 (C–6), 138.0 (phenyl), 148.8 (C–2), 152.0 (phenyl), 161.0 (C–4).

5-(4-Ethoxyanilino)-2',3'-dideoxyuridine (**5d**).

174 mg (20%); mp 145–147° C. Ms: m/z 347 (M^+). ^{1}H–Nmr (DMSO–d_6): δ 1.29 (3H, t, J = 6.9 Hz, CH_3),

1.76–2.36 (4H, m, 2'–H and 3'–H), 3.48 (1H, d, J = 10.8 Hz, 5'–H), 3.60 (1H, d, J = 11.0 Hz, 5'–H), 3.88–4.00 (3H, m, CH_2 and 4'–H), 4.94 (1H, br s, OH), 6.04 (1H, dd, J = 4.0 Hz and 6.6 Hz, 1'–H), 6.77 (2H, d, J = 7.9 Hz, Ar–H), 6.86 (2H, d, J = 8.9 Hz, Ar–H), 7.57 (1H, s, 6–H), 11.49 (1H, s, N3–H). ^{13}C–Nmr (DMSO–d_6): δ 14.6 (CH_3), 25.4 (C–3'), 31.2 (C–2'), 62.3 (CH_2), 63.1 (C–5'), 80.9 (C–4'), 84.8 (C–1'), 115.0 and 117.2 (phenyl), 118.7 (C–5), 123.3 (C–6), 137.8 (phenyl), 148.8 (C–2), 151.9 (phenyl), 160.9 (C–4).

5-Amino-1-(2,3-dideoxy-5-O-(4-methylbenzoyl)-D-glycero-pentofuranosyl)-4-(1,2,4-triazol-1-yl)pyrimidin-2(1H)-one derivatives (**6**).

Triethylamine (5.4 ml, 39 mmol) was added dropwise to a stirred, cooled (ice water bath) mixture of 1,2,4-triazole (2.8 g, 40 mmol), phosphoryl chloride (0.81 ml, 8.7 mmol) and acetonitrile (25 ml). Compounds (**3a–c**) (4.5 mmol) in acetonitrile (15 ml) were added and the reaction mixture was stirred at room temperature for 13–18 h. Triethylamine (3.7 ml, 27 mmol) and water (0.97 ml, 54 mmol) were then added and the solvents were evaporated under reduced pressure. The residue was partitioned between $CHCl_3$ (250 ml) and saturated aqueous $NaHCO_3$. (Compound (**6a**) without addition of water and the work-up was done after the next step). The organic layer was dried ($MgSO_4$) and evaporated. Yield: (**6a**) 79%; (**6b**) 95%; (**6c**) 91%.

5-Amino-1-(2,3-dideoxy-α,β-D-glycero-pentofuranosyl)cytosine derivatives (**7a,c**) *and* (**8a,c**).

A solution of triazole derivatives (**6a,c**) (2.4 mmol) and 20% aqueous ammonia (13 ml) in 1,4-dioxane (40 ml) was stirred at room temperature. After 1 h the mixture was evaporated under reduced pressure. (The residue from reaction of (**6a**) was partitioned between $CHCl_3$ (250 ml) and saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$) and evaporated). The residue was dissolved in saturated methanolic ammonia (37 ml) and methanol (37 ml). After 24–48 h the mixtures were evaporated to dryness and the residue was chromatographed on a silica gel with ether/methanol (20:1–10:1) to give pure α (**7**) and β (**8**).

1-(2,3-Dideoxy-α-D-glycero-pentofuranosyl)-5-pyrrolidinocytosine (**7a**).

154 mg (23%); mp 204–206° C. Ms: m/z 280 (M^+). ^{1}H–Nmr (DMSO–d_6): δ 1.74–2.28 (8H, m, 2 x CH_2, 2'–H and 3'–H), 2.84 (4H, br s, 2 x CH_2), 3.40 (2H, br s, 5'–H), 4.35 (1H, m, 4'–H), 4.77 (1H, t, J = 5.4 Hz, OH), 5.96 (1H, m, 1'–H), 6.60 (1H, br s, NH_2), 7.14 (1H, s, 6–H), 7.30 (1H, br s, NH_2). ^{13}C–Nmr (DMSO–d_6): δ 23.3 (2 x CH_2), 24.3 (C–3'), 31.6 (C–2'), 51.3 (2 x CH_2), 63.5 (C–5'), 81.1 (C–4'), 86.7 (C–1'), 118.6 (C–5), 127.9 (C–6), 153.8 (C–2), 162.9 (C–4).

2',3'-Dideoxy-5-pyrrolidinocytidine (**8a**).

60 mg (9%); mp 250° C (decomp.). Ms: m/z 280 (M^+). ^{1}H–Nmr (DMSO–d_6): δ 1.81–2.29 (8H, m, 2 x CH_2, 2'–H and 3'–H), 2.81 (4H, br s, 2 x CH_2), 3.54 (1H, m, 5'–H), 3.74 (1H, d, J = 11.8 Hz, 5'–H), 4.03 (1H, m, 4'–H), 5.14 (1H, br s, OH), 5.94 (1H, m, 1'–H), 6.70 (1H, br s, NH_2), 7.41 (1H, br s, NH_2), 7.85 (1H, s, 6–H). ^{13}C–Nmr (DMSO–d_6): δ 23.3 (2 x CH_2), 24.2 (C–3'), 32.6 (C–2'), 51.3 (2 x CH_2), 61.6 (C–5'), 81.5 (C–4'), 85.8 (C–1'), 118.4 (C–5), 129.2 (C–6), 153.5 (C–2), 162.5 (C–4).

1-(2,3-Dideoxy-α-D-glycero-pentofuranosyl)-5-(N-Benzylmethylamino)cytosine (**7c**).

357 mg (45%); mp 149–150° C. Ms: m/z 330 (M^+). ^{1}H–Nmr (DMSO–d_6): δ 1.76–2.23 (4H, m, 2'–H and 3'–H), 2.48 (1H, s, CH_3), 3.39 (2H, br s, 5'–H), 3.97 (2H, s, CH_2), 4.31 (1H, br s, 4'–H), 4.79 (1H, br s, OH), 5.92 (1H, br s, 1'–H), 6.77 (1H, br s, NH_2), 7.27 (1H, s, 6–H), 7.31 (6H, m, NH_2 and Ar–H). ^{13}C–Nmr (DMSO–d_6): δ 25.3 (C–3'), 31.6 (C–2'), 42.1 (CH_3), 58.7 (CH_2), 63.3 (C–5'), 81.1 (C–4'), 86.7 (C–1'), 119.4 (C–5), 126.9, 128.0, 128.5 (phenyl), 131.9 (C–6), 137.5 (phenyl), 153.6 (C–2), 163.2 (C–4).

5-(N-Benzylmethylamino)-2',3'-dideoxycytidine (**8c**).

119 mg (15%); mp 183–185° C. Ms: m/z 330 (M^+). ^{1}H–Nmr (DMSO–d_6): δ 1.72–2.24 (4H, m, 2'–H and 3'–H), 2.44 (3H, s, CH_3), 3.55 (1H, d, J = 11.9 Hz, 5'–H), 3.76 (1H, d, J = 11.6 Hz, 5'–H), 3.90 (2H, s, CH_2), 4.01 (1H, m, 4'–H), 5.24 (1H, br s, OH), 5.90 (1H, m, 1'–H), 6.72 (1H, br s, NH_2), 7.22–7.36 (6H, m, NH_2 and Ar–H), 7.92 (1H, s, 6–H). ^{13}C–Nmr (DMSO–d_6): δ 24.1 (C–3'), 32.6 (C–2'), 42.4 (CH_3), 59.0 (CH_2), 61.5 (C–5'), 81.5 (C–4'), 85.6 (C–1'), 119.3 (C–5), 126.9, 127.9, 128.6 (phenyl), 132.9 (C–6), 137.7 (phenyl), 153.7 (C–2), 163.1 (C–4).

1-(2,3-Dideoxy-D-glycero-pentofuranosyl)-4-methoxypyrimidin-2(1H)-one (**9b**) *and* (**10b**).

Compound (**6b**) was chromatographed on silica gel with methanol/chloroform (1:20) to give the corresponding 4-methoxy derivatives. The residue (1.45 g, 3.1 mmol) was dissolved in methanol (48 ml) and saturated methanolic ammonia (48 ml). After 24 h the product was evaporated to dryness. The isomers were separated by hplc with isocratic 26% ethanol in water on a reversed phase column (RP–4, 15–20 μm, 300 A) to give pure α- (**9b**) and β- (**10b**) anomers.

1-(2,3-Dideoxy-α-D-glycero-pentofuranosyl)-4-methoxy-5-(N-methylcyclohexylamino)pyrimidin-2(1H)-one (**9b**).

0.52 g (50%) as an oil. Ms: m/z 337 (M^+). ^{1}H Nmr ($CDCl_3$): δ 1.00–1.17 (6H, m, cyclohexyl), 1.66 (4H, br s, cyclohexyl), 1.86–2.53 (7H, m, CH_3, 2'–H and 3'–H), 2.76 (1H, m, cyclohexyl), 3.55 (1H, dd, J = 5.2 Hz

and 11.6 Hz, 5'–H), 3.65 (1H, dd, J = 3.7 Hz and 11.6 Hz, 5'–H), 3.91 (3H, s, CH_3), 4.43 (1H, br s, 4'–H), 6.03 (1H, br s, 1'–H), 7.23 (1H, s, 6–H). ^{13}C Nmr ($CDCl_3$): δ 24.8, 24.9 and 25.3 (cyclohexyl and C–3'), 29.0 (cyclohexyl), 32.2 (C–2'), 35.9 (CH_3), 54.0 (cyclohexyl), 60.2 (CH_3), 63.8 (C–5'), 81.7 (C–4'), 88.1 (C–1'), 121.0 (C–5), 134.0 (C–6), 154.1 (C–2), 168.4 (C–4).

1-(2,3-Dideoxy-β-D-glyceropentofuranosyl)-4-methoxy-5-(N-methylcyclohexylamino)pyrimidin-2(1H)-one (**10b**).

0.2 g (19%) as an oil. Ms: m/z 337 (M^+). ^{1}H–Nmr ($CDCl_3$): δ 1.07–1.30 (6H, m, cyclohexyl), 1.75 (4H, m, cyclohexyl), 1.91–2.55 (4H, m, 2'–H and 3'–H), 2.61 (3H, s, CH_3), 2.83 (1H, br s, cyclohexyl), 3.81 (1H, m, 5'–H), 3.99–4.09 (4H, m, CH_3 and 5'–H), 4.21 (1H, m, 4'–H), 6.08 (1H, dd, J = 2.7 Hz and 6.5 Hz, 1'–H), 8.01 (1H, s, 6–H). ^{13}C–Nmr ($CDCl_3$): δ 24.2, 25.3 and 25.6 (cyclohexyl and C–3'), 29.3 (cyclohexyl), 33.0 (C–2'), 35.5 (CH_3), 54.2 (OCH_3), 60.5 (cyclohexyl), 62.5 (C–5'), 82.2 (C–4'), 87.5 (C–1'), 121.3 (C–5), 134.9 (C–6), 154.3 (C–2), 168.1 (C–4).

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