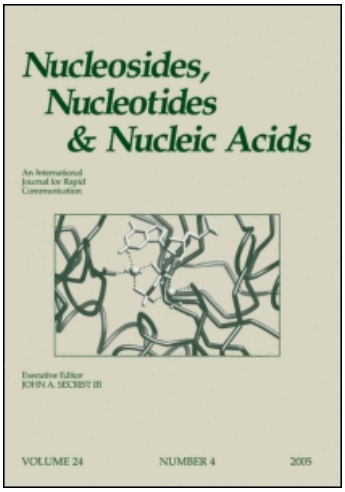

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Uridine-5'-Diphosphate Glucose Analogues. 2[1]. Nucleoside Modified Analogues of Antiviral 5'-O-[[[[(α-D-Glucopyranosyl)Oxy Carbonyl]Amino]Sulfonyl]Uridine Derivatives

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URIDINE-5'-DIPHOSPHATE GLUCOSE ANALOGUES.2[1]. NUCLEOSIDE MODIFIED ANALOGUES OF ANTIVIRAL 5'-O-[[[[(α-D-GLUCOPYRANOSYL)OXY] CARBONYL]AMINO]SULFONYL]URIDINE DERIVATIVES

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SUMMARY. A series of uridine modified analogues of antiviral 5'-O-[[[[(α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]uridine derivatives has been synthesized by reaction of suitably protected glucose and glucosamine derivatives with $ClSO_2$-N=C=O and thymidine, 2'-deoxyuridine, 3-methyluridine, 5,6-dihydrouridine and 1-[(2-hydroxyethoxy)methyl] uracil derivatives. The antiviral activity against HSV-1 has been determined.

Certain compounds that interfere with protein glycosylation, such as the metabolites of 2-deoxyglucose, uridinediphosphate-2-deoxyglucose (UDP-2dGlc) and guanosinediphosphate-2-deoxyglucose (GDP-2dGlc), or the nucleoside antibiotics, derived from uridine and 5,6-dihydrouridine, tunicamycins and streptovirudins, have antiviral activity against enveloped viruses[2,3,4,5]. These compounds show common structural features, since all of them have a glycosyl residue linked to the 5'-position of the nucleoside moiety by a 5-atom bridge. Based on these facts, we designed, synthesized and tested as antivirals a series of analogues of UDP-glucose (UDP-Glc), namely 5'-O-[[[[(α-D-glucopyranosyl)oxy]carbonyl] amino]sulfonyl]uridine derivatives 1, in which the diphosphate bridge was replaced by an isosteric -O-CO-NH-SO_2-O residue[1]. Among these analogues, those in which the glucose hydroxyl protecting groups were benzyl or benzoyl groups, 1[R^1=Bn,Bz; R^2=$C(CH_3)_2$,H; X=O] were effective. It seems to be due to a favorable partition coefficient, since the deprotected and acetyl or palmitoyl protected analogues were inactive. Compound 1[R^1=Bn; R^2=$C(CH_3)_2$; X=O] was also tested as protein glycosylation inhibitor, and in contrast to what happened with 2-deoxyglucose and tunicamycin, it inhibited the glycosylation of viral proteins to a greater extent than that of cellular proteins[1]. Our interest in elucida-

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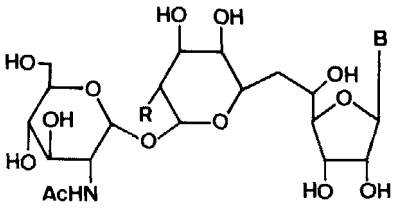
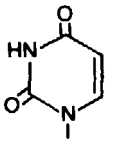


$R = (CH_3)_2CH-(CH_2)_n-CH=CH-CONH$

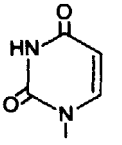
TUNICAMYCIN

n=8-11 ; B =



STREPTOVIRUDIN

n=6-8 ; B=



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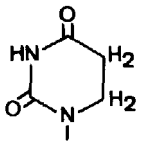
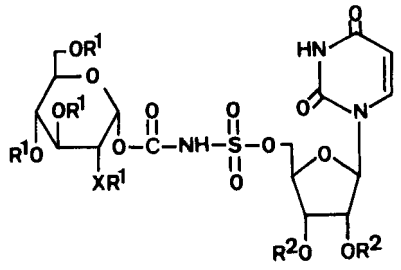


ting the structural requirements of these UDP-Glc analogues that are necessary for antiviral activity, prompted us to achieve modifications in the three parts of the molecule, i.e., uridine, oxicarbonylaminosulfonyl bridge[6] and hexose[7].

The present paper describes the synthesis and antiviral activity against herpes simplex virus type 1 (HSV-1) of several nucleoside modified analogues of 1 in which the uridine moiety has been replaced by thymidine, 2'-deoxyuridine, 3-methyluridine[8], 5,6-dihydrouridine and the acyclic nucleoside 1-[(2-hydroxyethoxy)methyl]uracil[9].

By a similar procedure to that reported for the synthesis of UDP-Glc analogues 1[1] [R^1= Bn, Bz, Ac, Pmt; R^2=$C(CH_3)_2$; X=O,NH], compounds 2-8 were prepared by treatment of the corresponding protected α-glucopyranose having the 1-OH free with chlorosulfonyl isocyanate, followed by *in situ* reaction of the unstable intermediate [[[(chlorosulfonyl)amino]carbonyl] oxy]glucose derivative with 3'-O-acetylthimidine or the uridine modified analogue. Thus, one pot reaction of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose with chlorosulfonyl isocyanate and 3'-O-acetylthymidine, 2',3'-O-isopropylidene-3-methyluridine, 2',3'-O-isopropylidene-5,6-dihydrouridine and 1-[(2-hydroxyethoxy)methyl]uracil, in acetonitrile or methylene chloride and with exclusion of moisture gave 5'-O-[[[[(2",3", 4",6"-tetra-O-benzyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-3'-O-acetylthymide (2),-2',3'-O-isopropylidene-3-methyluridine (5),-2',3'-O-isopropylidene-5,6-dihydrouridine (6) and 1-[2-[[[[(2',3',4',6'-tetra-O-benzyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]oxyethoxymethyl]

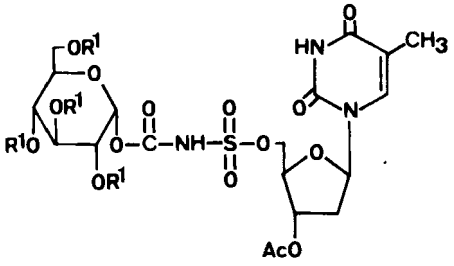


1

R^1=H, Acetyl, benzoyl, benzyl, Palmitoyl

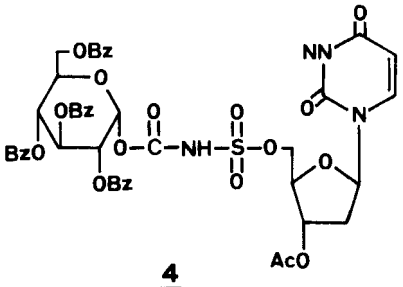
R^2=H, Isopropylidene

X=O, NH



2: R^1= Bn

3: R^1= Bz



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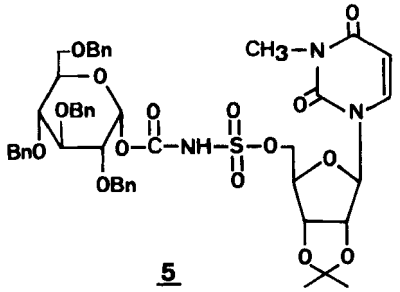

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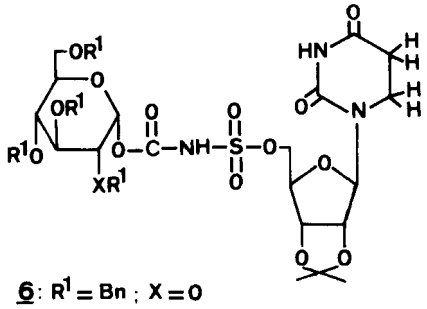
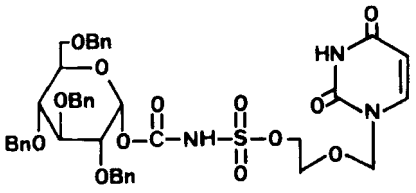


6: R^1 = Bn ; X = O

7: R^1 = Ac ; X = NH

8: R^1 = H ; X = O



9

uracil (9). Similar reactions of 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranose with 3'-O-acetylthymidine or 2'-deoxy-3'-O-acetyluridine afforded 5'-O-[[[[(2",3",4",6"-tetra-O-benzoyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-3'-O-acetylthymidine (3) or 2'-deoxy-3'-O-acetyluridine (4). Following the same procedure, the reaction of 2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-α-D-glucopyranose with 2',3'-O-isopropylidene-5,6-dihydrouridine gave 5'-O-[[[[(2"-acetamido-2"-deoxy-3",4",6"-tri-O-acetyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2',3'-O-isopropylidene-5,6-dihydrouridine (7).

The starting acylated hexopyranoses 2,3,4,6-tetra-O-benzoyl and 2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-α-D-glucopyranose were easily prepared from 1,2,3,4,6-penta-O-benzoyl-β-D-glucopyranose and 2-acetamido-2-deoxy-1,3,4,6-tetra-O-acetyl-α-D-glucopyranose by treatment with a solution of ammonia in acetonitrile following a procedure recently reported for the regio- and stereoselective 1-O-deacylation of peracylated glycopyranoses[10].

The 5'-O-[[[[(α-D-glucosamine)oxy]carbonyl]amino]sulfonyl]-5,6-dihydrouridine derivative 7 was also obtained by hydrogenation of the previously reported uridine analog 1 [R^1=Ac; R^2=$C(CH_3)_2$; X=NH][1] at room temperature and 45 psi over Pd/C. A similar reaction using the analogue of UDP-benzylated glucose 1 [R^1=Bn; R^2=$C(CH_3)_2$; X=O] resulted in the removal of the glucose benzyl protecting groups and the hydrogenation of the uracil moiety to provide 5'-O-[[[[(α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2',3'-O-isopropylidene-5,6-dihydrouridine (8).

Structural assignments of all these compounds were made on the basis of their analytical and ^{1}H NMR spectral data. The attachment of the [[[(α-glucopyranosyl)oxy]carbonyl]amino]sulfonyl residue to the 5'-O-position of the nucleoside or to the 2-position of the ethoxy group of the acyclic uridine analogue, in the case of compound 9, was demonstrated by the ≃ 0.5 ppm downfield chemical shift of the CH_2 protons in these positions as compared to those of the corresponding ribosides, 2'-deoxyribosides or acyclic uridine used as starting materials. Further support for this attachment in compounds 2-4 and 6-9 came from the presence of singlets at δ 10.30-11.40 assigned to the 3-NH uracil or dihydrouracil proton as compared to the same proton of 2',3'-O-isopropylideneuridine which appeared at δ 11.43 ppm. The α-anomeric configuration of the glucose or glucosamine moieties was evident from the $J_{1",2"}$=3-3.5 Hz coupling constant values.

TABLE 1. Comparative *in vitro* antiherpes activity and toxicity of 1[R^1=Bn,Bz; R^2=$C(CH_3)_2$,H] and the uridine modified analogues 3, 4 and 9 in HeLa cells[11]

Compound	CPE_{50} [(a)], μM	Tox_{50} [(b)], μM
3	70	100
4	30	200
9	30	100
1 [R^1=Bn; R^2=$C(CH_3)_2$; X=O]	85	230
1 (R^1=Bn; R_2=H; X=O)	90	360
1 [R^1=Bz; R^2=$C(CH_3)_2$; X=O]	30	220
1 (R^1=Bz; R_2=H; X=O)	75	>220

[(a)] CPE_{50} is the concentration of compound (μM) that protects by 50% the cytopathic effect induced by HSV-1. [(b)] Tox_{50} is the concentration of compound that induces 50% of cell toxicity.

All these nucleoside modified analogues of 5'-O-[[[[(α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]uridine derivatives were tested in HeLa cell cultures against HSV-1[11]. The 3-methyluridine and dihydrouridine derivatives 5-8 as well as the thymidine derivative 2 in which the glucose moiety is protected with benzyl groups, failed to show any appreciable antiviral effect. Table 1 shows the activity and toxicity data of those compounds which were effective including, for comparative purposes, the data from the parent compounds 1[R^1=Bn,Bz; R^2=$C(CH_3)_2$,H; X=O]. As it is shown, the uridine modified derivatives 3, 4 and 9 displayed an activity comparable to that of the reference compounds 1, bearing an uridine moiety. However, its toxicity, specially in the case of the thymidine and acyclic uridine derivatives 3 and 9 was higher than that of the reference analogues. These results indicate that the presence of the uridine moiety is very important for the activity of the 5'-O-[[[[(α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]uridine derivatives previously reported[1], being these analogues of UDP-glucose more tolerant of changing the ribosyl moiety than altering the uracil portion.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded at 90 MHz on a Varian EM-390 spectrometer and at 300 MHz on a Varian XL-300 spectrometer using Me_4Si as internal standard. Analytical thin-layer

chromatography was performed on aluminium sheets coated with a 0.2 mm layer of silica gel 60 F_{254} (Merck). Preparative layer chromatography was performed on 20 x 20 cm glass plates coated with a 2 mm layer of silica gel PF_{254} (Merck). Compounds were detected with a UV light (254 nm) or by spraying the plate with an ethanol-sulfuric acid (3:7) mixture and heating.

5'-O-[[[[(2",3",4",6"-Tetra-O-benzyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-3'-O-acetylthymidine (2). A solution of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose (3.24 g, 6 mmol) in dry methylene chloride (30 mL) cooled at -20 to -15°C was treated in the absence of humidity with chlorosulfonyl isocyanate (0.52 mL, 6 mmol). The mixture was stirred at -20 to -15°C until the glucose derivative disappeared and then a solution of 3'-O-acetylthymidine (1.13 g, 4 mmol) in dry acetonitrile (75 mL) containing dry pyridine (0.48 mL, 6 mmol) was added. The mixture was stirred at room temperature overnight, evaporated under reduced pressure and the residue was chromatographed by preparative TLC using $CHCl_3$-acetone (1:1) to give 2 (1.20 g, 33%) as a foam. ^{1}H NMR (DMSO) δ 1.80(s, 3H, CH_3), 2.00 (s, 3H, OAc), 4.00-4.18(m, 3H, H-4',H-5'), 6.09(d, 1H, H-1", $J_{1",2"}$=3.5 Hz), 6.22(t, 1H, H-1', $J_{1',2'}$=7.0 Hz), 11.30(bs, 1H, NH-3, D_2O exchangeable).

Anal. Calcd. for $C_{47}H_{51}N_3O_{15}S$: C, 60.71; H, 5.48; N, 4.52; S, 3.44. Found: C, 60.92; H, 5.39; N, 4.75; S, 3.03.

5'-O-[[[[(2",3",4",6"-Tetra-O-benzoyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-3'-O-acetylthymidine (3). Following the procedure described for 2, a solution of 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranose (0.596 g, 1 mmol) in dry methylene chloride (10 mL) reacted with chlorosulfonyl isocyanate (0.09 mL, 1 mmol) and 3'-O-acetylthymidine (0.29 g, 1 mmol) in dry acetonitrile (20 mL) containing dry pyridine (0.08 mL, 1 mmol) to afford, after preparative TLC purification using EtOAc-MeOH (8:1) as solvent, compound 3 (0.295 g, 30%), mp 164-165°C (from EtOAc); ^{1}H NMR (DMSO) δ 1.80(s, 3H, CH_3), 2.00(s, 3H, OAc), 4.00-4.18(m, 3, H-4', H-5'), 6.18(t, 1H, H-1', $J_{1',2'}$=7.0 Hz), 6.31(d, 1H, H-1", $J_{1",2"}$=3.0 Hz), 11.40 (bs, 1H, NH-3, D_2O exchangeable).

Anal. Calcd. for $C_{47}H_{43}N_3O_{19}S$: C, 57.25; H, 4.37; N, 4.26; S, 3.25. Found: C, 56.99; H, 4.14; N, 4.30; S, 3.18.

5'-O-[[[[(2",3",4",6"-Tetra-O-benzoyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2'-deoxy-3'-O-acetyluridine (4). 2,3,4,6-Tetra-O-benzoyl-α-D-glucopyranose (0.596 g, 1 mmol) reacted with chlorosulfonyl isocyanate (0.09 mL, 1 mmol) and 2'-deoxy-3'-O-acetyluridine (0.284 g, 1

mmol) as described for the preparation of 3, to give 4 (0.233 g, 24%), mp 150-152°C (from EtOAc); ^{1}H NMR (DMSO) δ 2.00(s, 3, OAc), 4.00-4.18(m, 3, H-4', H-5'), 6.10(t, 1H, H-1', $J_{1',2'}$=7.0 Hz), 6.33(d, 1H, H-1", $J_{1",2"}$= 3.0 Hz), 11.30(bs, 1H, NH-3, D_2O exchangeable).

Anal. Calcd. for $C_{46}H_{41}N_3O_{19}S$: C, 56.85; H, 4.22; N, 4.33; S, 3.29. Found: C, 56.68; H, 4.48; N, 4.41; S, 3.37.

5'-O-[[[[(2",3",4",6"-Tetra-O-benzyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2',3'-O-isopropylidene-3-methyluridine (5). Reaction of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose (3.24 g, 6 mmol) with chlorosulfonyl isocyanate (0.52 mL, 6 mmol) and 2',3'-O-isopropylidene-3-methyluridine (1.19 g, 4 mmol) as described for 2, gave, after preparative TLC with $CHCl_3$-acetone (1:1), compound 5 (1.2 g, 27%) as a foam. ^{1}H NMR (DMSO) δ 1.26 and 1.47 (2s, 6H, isopropylidene), 3.11(s, 3H, N-CH_3), 3.97-4.13 (m, 2H, H-5'), 5.90(d, 1H, H-1', $J_{1',2'}$=2 Hz), 6.08(d, 1H, H-1", $J_{1",2"}$= 3.5 Hz).

Anal. Calcd. for $C_{48}H_{53}N_3O_{15}S$: C, 61.08; H, 5.62; N, 4.45; S, 3.39. Found: C, 61.23; H, 5.34; N, 4.09; S, 3.51.

5'-O-[[[[(2",3",4",6"-Tetra-O-benzyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2',3'-O-isopropylidene-5,6-dihydrouridine (6). 2,3,4, 6-Tetra-O-benzyl-α-D-glucopyranose (3.24 g, 6 mmol) reacted with chlorosulfonyl isocyanate (0.52 mL, 6 mmol) and 2',3'-O-isopropylidene-5,6-dihydrouridine (1.14 g, 4 mmol) as described for 2, to afford, after preparative TLC with $CHCl_3$-acetone (1:1), compound 6 (1.40 g, 37%) as a foam. ^{1}H NMR (DMSO) δ 1.27 and 1.46 (2s, 6H, isopropylidene), 2.43-2.62(m, 2H, H-5), 3.35-3.60(m, 2H, H-6), 3.82-4.00(m, 2H, H-5'), 5.78(d, 1H, H-1', $J_{1',2'}$= 3.1 Hz), 6.08(d, 1H, H-1", $J_{1",2"}$= 3.5 Hz), 10.50(bs, 1H, NH-3, D_2O exchangeable).

Anal. Calcd. for $C_{47}H_{53}N_3O_{15}S$: C, 60.58; H, 5.69; N, 4.51; S, 3.43. Found: C, 60.81; H, 5.46; N, 4.61; S, 3.39.

5'-O-[[[[(2"-Acetamido-2"-deoxy-3",4",6"-tri-O-acetyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2',3'-O-isopropylidene-5,6-dihydrouridine (7). Method a: A solution of 2-acetamido-2-deoxy-3,4,6-tri-O-acetyl -α-D-glucopyranose (1.0 g, 2.8 mmol) in dry acetonitrile (20 mL) reacted with chlorosulfonyl isocyanate (0.24 mL, 2.8 mmol) and 2',3'-O-isopropylidene-5,6-dihydrouridine (0.82 g, 2.8 mmol) as described above for the synthesis of 2. Preparative TLC of the crude reaction product using EtOAc--MeOH (8:1) gave compound 7 (0.51 g, 25%) as a foam. ^{1}H NMR (DSMO) δ 1.26 and 1.45 (2s, 6H, isopropylidene), 1.79(s, 3H, NHAc), 1.90, 1.96 and 2.00 (3s, 9H, OAc), 2.40-2.60(m, 2H, H-5), 3.12-3.38(m, 2H, H-6), 3.83-4.20(m, 6H, H-4', H-5', H-5", H-6"), 5.70(d, 1H, H-1", $J_{1",2"}$= 3.5 Hz), 5.76(d,

1H, H-1', $J_{1',2'}$= 2.5 Hz), 8.00(d, 1H, NHAc, $J_{NH,2''}$= 9 Hz), 10.30(bs, 1H, NH-3, D_2O exchangeable).

Anal. Calcd. for $C_{27}H_{38}N_4O_{18}S$: C, 43.90; H, 5.15; N, 7.59; S, 4.34. Found: C, 43.59; H, 5.05; N, 7.23; S, 4.53.

Method b: A solution of 5'-O-[[[[(2''-acetamido-2''-deoxy-3'',4'',6''-tri-O-acetyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2',3'-O-isopropylideneuridine[1] (0.416 g, 0.565 mmol) in MeOH (15 mL) was hydrogenated over 10% Pd/C (0.2 g) at room temperature and 45 psi for 30 hours. Filtration and evaporation of the filtrate left a residue which was purified by preparative TLC using EtOAc-MeOH (10:1) to provide 7 (0.333 g, 80%) identical in all respects to that described above.

5'-O-[[[[(α-D-Glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2',3',-O-isopropylidene-5,6-dihydrouridine (8). A solution of 5'-O-[[[[(2'',3'',4'',6''-tetra-O-benzyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2',3'-O-isopropylideneuridine[1] (1 g, 1.08 mmol) in MeOH (50 mL) was hydrogenated over Pd/C (0.4 g) at 35-40°C and 45 psi for 24 hours. Filtration and evaporation of the filtrate left a residue which was chromatographed by preparative TLC using $CHCl_3$-MeOH (10:1) to give compound 8 (0.6 g, 97%) as a foam. ^1H NMR (DMSO + D_2O) δ 1.30 and 1.48 (2s, 6H, isopropylidene), 2.42-2.62(m, 2H, H-5), 3.10-3.70(m, 5H, H-5'', H-6'', H-6), 5.78(d, 1H, H-1'', $J_{1'',2''}$=3.5 Hz), 5.85(d, 1H, H-1', $J_{1',2'}$=2.5 Hz).

Anal. Calcd. for $C_{19}H_{29}N_3O_{15}S$: C, 39.92; H, 5.07; N, 7.35; S, 5.60. Found: C, 39.73; H, 5.21; N, 7.02; S, 5.75.

1-[2-[[[[(2',3',4',6'-Tetra-O-benzyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]oxyethoxymethyl]uracil(9). Reaction of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose (0.54 g, 1 mmol) in dry methylene chloride (20 mL) with chlorosulfonyl isocyanate (0.09 mL, 1 mmol) and 1-[(2-hydroxyethoxy)methyl]uracil (0.19 g, 1 mmol) in dry methylene chloride (50 mL) containing dry pyridine (0.08 mL, 1 mmol) and workup as described for the preparation of 2 afforded, after preparative TLC using EtOAc-MeOH (8:1), compound 9 (0.35 g, 42%) as a foam. ^1H NMR (DMSO) δ 5.20(m, 2H, O-CH_2-uracil), 6.13(d, 1H, H-1', $J_{1',2'}$=3.5 Hz), 11.30(bs, 1H, NH-3, D_2O exchangeable).

Anal. Calcd. for $C_{42}H_{45}N_3O_{15}S$: C, 60.65; H, 5.41; N, 5.05; S, 3.85. Found: C, 60.42; H, 5.01; N, 4.83; S, 3.54.

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REFERENCES

1. Paper nº 1 in the series "Uridine 5'-Diphosphate Glucose Analogues": M.J. Camarasa, P. Fernández-Resa, M.T. García-López, F.G. De las Heras, P.P. Méndez-Castrillón, B. Alarcón, L. Carrasco, J. Med. Chem. 28, 40 (1985).
2. H.D. Klenk, R.T. Schwarz, Antiviral Res. 2, 177 (1982).
3. R.T. Schwarz, R. Datema, Adv. Carbohydr. Chem. Biochem. 40, 287 (1982).
4. E. de Clercq, Biochem. J. 205, 1 (1982).
5. D. Shugar in "Medicinal Chemistry Advances", F.G. de las Heras and S. Vega Eds. Pergamon Press, Oxford (1981), p. 225.
6. P. Fernández-Resa, M.T. García-López, F.G. De las Heras, A. San Félix, B. Alarcón and L. Carrasco, Eur. J. Med. Chem., in press.
7. J. Fiandor, M.T. García-López, F.G. De las Heras, P.P. Méndez-Castrillón, A.San Félix, B. Alarcón and L. Carrasco. Unpublished Results.
8. W. Szer, D. Shugar in "Synthetic Procedures in Nucleic Acid Chemistry", W.W. Zorbach and R.S. Tipson Eds., Wiley-Interscience, New York, N.Y. (1968), Vol. 1, p. 433.
9. M.J. Robins, P.W. Hatfield, Can. J. Chem. 60, 547 (1982).
10. J. Fiandor, M.T. García-López, F.G. De las Heras, P.P. Méndez-Castrillón, Synthesis, 1121 (1985).
11. Biological tests were performed by Dr. B. Alarcón and Dr. L. Carrasco at the Centro de Biología Molecular, Universidad Autónoma de Madrid, Canto Blanco, 28034-Madrid.

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