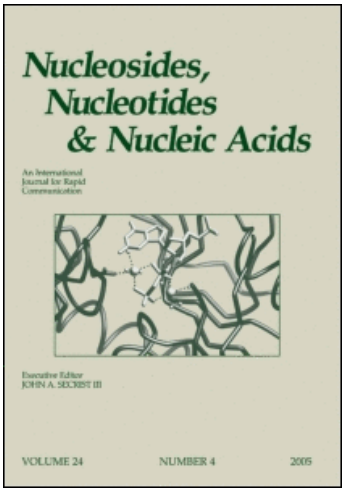

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Analogues of Uridinediphosphatehexoses. A New Type of Protein Glycosylation Inhibitors That Show Antiviral Activity

M. J. Camarasa[a]; P. Fernández-resa[a]; M. T. García-lópez[a]; F. G. de las Heras[ab]; P. P. Méndez-castrillónt[a]; B. Alarcón[b]; L. Carrasco[b]
[a] Instituto de Química Médica, Madrid [b] Centro de Biología Molecular, Universidad Autónoma de Madrid, Madrid, SPAIN

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ANALOGUES OF URIDINEDIPHOSPHATEHEXOSES. A NEW TYPE OF PROTEIN GLYCOSYLATION INHIBITORS THAT SHOW ANTIVIRAL ACTIVITY.

M.J. Camarasa‡ P. Fernández-Resa‡ M.T. García-López‡ F.G. de las Heras+*, P.P. Méndez-Castrillón‡ B. Alarcón#‡ and L. Carrasco#‡

+Instituto de Química Médica, Juan de la Cierva 3, 28006-Madrid. #Centro de Biología Molecular, Universidad Autónoma de Madrid, Canto Blanco, 28034-Madrid. SPAIN.

SUMMARY. A series of analogues of UDP-Glc and UDP-GlcNAc prepared by reaction of protected hexoses with $ClSO_2NCO$ and 2'3'-O-isopropylideneuridine, inhibited glycosylation of proteins in HSV-1 infected HeLa cells and were active against several enveloped viruses.

Glycosylation inhibitors show a variety of biological effects[1,2].For instance, 2-deoxy-D-glucose is an antiviral agent which is transformed to UDP-2dGlc and GDP-2dGlc and as such interferes with N-glycosylation of proteins[1,2]. Nucleoside antibiotics tunicamycin and streptovirudin are protein glycosylation inhibitors[1] structurally related to the active metabolites of 2-deoxy-D-glucose and to the natural nucleosidediphosphate-sugars, which donate glycosyl residues in the biosynthesis of polisaccharides, glycolipids, glycoproteins, etc. All these compounds have a glycosyl residue linked to the 5'-position of a nucleoside by a 5-atom bridge. We assumed that this is an essential structrural requirement for these compounds to act as substrates or inhibitors of glycosyltransferases and, therefore, we designed, synthesized and tested as protein glycosylation inhibitors and as antiviral agents a series of analogues of UDP-Glc and UDP-GlNAc in which the diphosphate bridge has been replaced by an isosteric -O-CO-NH-SO_2-O- residue.

One pot reaction of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose with chlorosulfonyl isocyanate and 2'3'-O-isopropylideneuridine in acetonitrile afforded compound 6 in 40% yield. The formation of the indicated bridge glucose-O-CO-NH-SO_2-O-uridine was demonstrated by the obtention of carbamate 1, when the intermediate 2, obtained in the first step of the above one pot reaction, was left in contact with the ambient. Small amounts of 4 and 5 were also obtained as byproducts. Reaction of 2 with ammonia in acetonitrile gave 3. Similar reactions of other hexoses such as tetra-O-

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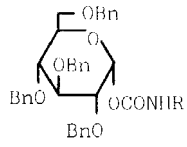
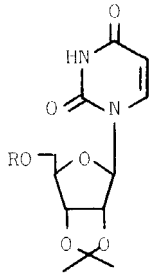
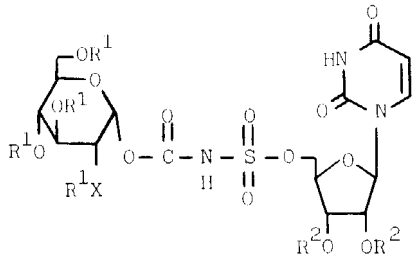


1, R = H
2, R = SO_2Cl
3, R = SO_2NH_2



4, R = $CONH_2$
5, R = SO_2NH_2



6, R^1 = Bn; R^2 = CMe_2; X = O
7, R^1 = Bn; R^2 = H ; X = O
8, R^1 = Bz; R^2 = CMe_2; X = O
9, R^1 = Bz; R^2 = H ; X = O
10, R^1 = Ac; R^2 = CMe_2; X = O
11, R^1 = Pmt; R^2 = CMe_2; X = O
12, R^1 = H ; R^2 = CMe_2; X = O
13, R^1 = Ac; R^2 = CMe_2; X = NH
14, R^1 = Ac; R^2 = H ; X = NH

Pmt = Palmitoyl; Bn = Benzyl;
Bz = Benzoyl; Ac = Acetyl.

benzoyl, tetra-O-acetyl, and tetra-O-palmitoyl-α-D-glucopyranose and 2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-α-D-glucopyranose with $ClSO_2NCO$ and 2'3'-O-isopropylideneuridine afforded analogues of UDP-hexoses 8, 10, 11 and 13 in ≃ 40% yield, respectively. Removal of 2'3'-O-isopropylidine protecting groups from uridine moiety of compounds 6, 8 and 13 was achieved by treatment with TFA acid/water to give 7, 9 and 14 in 55-60% yield. Removal of acetyl protecting groups from 10 by treatment with methanolic ammonia afforded 15 in 54% yield.

Compound 6, at a concentration of 100 μM completely blocked glycosylation of HSV-1 proteins, while produced an inhibition of 73% on the glycosylation of uninfected control cell proteins. At the same concentration of 100 μM it had no effect on the synthesis of proteins after 48 h. Compound 6 and those having a favourable partition coefficient lipid/water, i.e. 7, 8 and 9 have an antiviral effect, as measured by their protection of the cytopathic effect induced by HSV-1 replication. Compounds 1 and 5, which are fragments of 6, are devoid of activity. They also show a moderate selectivity when protection of the infected cell monolayer and toxicity to the culture cells are compared.

The production of new infectious HSV-1 was measured by the plaque assay method. At 50 μM of 6, the reduction of new infectious HSV-1 was 98% and at 100 μM the reduction was 99.6%. The effect of 6 on cell multiplic-

TABLE. In vitro antiherpes activity and toxicity of UDP-glucose analogues

Compound	CPE_{50} (a), μM	TOX_{50} (b), μM
9	85	230
10	90	360
11	30	220
12	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% cell toxicity.

ation was also examined. A concentration of 50 μM of 6 did not reduce at all the rate of HeLa cell growth, while a concentration of 100 μM reduced it by 15% after 48 h incubation. Compound 6 was also active against other enveloped viruses, such as vesicular stomatitis virus and Semliki Forest virus, and had no effect on the growth of naked viruses, such as polio-virus and encephalomyocarditis virus.

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