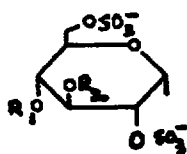
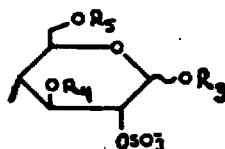


nose, galactose, glucosamine, galactosamine, glucuronic acid, iduronic acid, xylose, arabinose or disaccharides thereof. Preferably, A represents a glucose derivative having the structure II:



(II)

and B represents a glucose derivative having the structure III:



(III)

in which R_1 , R_2 , R_3 , R_4 and R_5 are independently selected from hydrogen, alkyl, aryl, aralkyl, or SO_3^- , whereas alkyl, aryl, and aralkyl has the previously given meanings, or their derivatives in which the charged moieties are compensated by counter-ions. Very suitable derivatives II and III are those in which R_1 , R_2 , and R_3 are methyl, R_4 and R_5 are SO_3^- , and OR_3 adopts preferably the α -configuration. Another suitable group A has structure II in which R_1 is methyl, and R_2 is SO_3^- , and another suitable group B has structure III in which R_4 and R_5 are SO_3^- , and R_3 is an alkyl group with 6-20 carbon atoms.

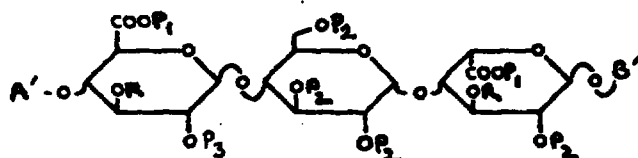
It is generally believed that multipoint key polar interactions are of essential importance throughout molecular biology for ensuring high selectivity in noncovalent molecular associations, and that substitution of only one of the key hydroxy groups of an oligosaccharide by a hydrophobic group (and invariably a number of the hydroxy groups prove outstandingly essential to complex formation) can result in complete loss of the affinity by the protein. Remarkably, however, the preferred compounds of this invention having O-alkyl and O-sulfate groups without having free hydroxy groups, still show the full-blown activity.

The counter-ions which compensate the charged moieties are pharmaceutically acceptable counter-ions, like hydrogen, or more preferably alkali or earth-alkali metal ions, like sodium or calcium.

The carbohydrates according to this invention may be prepared according to well known methods described and used for the synthesis of polysaccharides. In this respect, particular reference is made to the previously mentioned European patent 0,301,618, in which methods for the synthesis of polysaccharides are disclosed.

A stepwise condensation of the monosaccharides and the groups A and B is possible. In general, however, building blocks consisting of D-glucose, L-idose, D-glucuronic acid or L-iduronic acid, suitably functionalized with the required alkyl, aryl, or aralkyl groups or by temporarily protective groups, are condensed together in the desired order. In this way the (protected) trisaccharide unit can be prepared, which can be coupled with A and B, or protected derivatives thereof. It is also possible to condense a part of the trisaccharide unit with B or a protected derivative thereof, after which the compound obtained is coupled with the remaining part of the trisaccharide, which may already be provided with group A or a protected derivative thereof. If A is not yet attached to the remaining part of the trisaccharide, the condensed saccharide obtained can be coupled to A (or a protected derivative thereof) in a manner known *per se*. In a similar manner, a part of the (protected) trisaccharide unit containing A can be coupled to the other part, which may be provided with B (or a protected derivative thereof), after which, if B is not present, the coupling product is condensed with B or a protected derivative thereof. Suitable protective groups are well known in carbohydrate chemistry. Preferred protective groups include benzyl and acetyl for hydroxy groups, and methyl and benzyl for the carboxylate group of uronic acids. Other protective groups like levulinoyl, chloroacetyl, trityl, benzoyl, etc., may be used with equal success. Coupling of the saccharides is performed in a manner known in the art, e.g. deprotection of the 1-position of the glycosyl-donor, activation of this position (e.g. by making a bromide, pentenyl, fluoride or trichloroacetamide derivative) and coupling the activated glycosyl-donor with an optionally protected glycosyl-acceptor.

This process of stepwise or building block synthesis affords a protected carbohydrate derivative comprising a trisaccharide unit of the general formula:



(IV)

in which R is alkyl, aryl, or aralkyl as previously defined, P₁ is an acid protective group (preferably methyl or benzyl), P₂ is a hydroxy protective group (preferably benzyl or acetyl), P₃ is a hydroxy protective group or the required alkyl, aryl, or aralkyl group, and A' and B' are A and B respectively, or protected derivatives thereof. Carbohydrate derivative IV can be deprotected and sulfated in a manner as described in the previously mentioned EP 0,301,618, in order to obtain the carbohydrate derivative according to formula I. Suitable deprotection methods are, for example, basic hydrolysis for acetyl- and methyl-esters, and hydrogenolysis for benzyl ethers. Sulfation can successfully be performed with complexes of sulfur trioxide with bases like trimethylamine, triethylamine or pyridine in a suitable solvent.

For the treatment of venous thrombosis or for the inhibition of smooth muscle cell proliferation the compounds of the invention may be administered enterally or parenterally, and for humans preferably in a daily dosage of 0,001-10 mg per kg body weight. Mixed with pharmaceutically suitable auxiliaries, the compounds may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the compounds can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, e.g. a nasal spray.

The invention is further illustrated by the following examples.

Example 1

methyl 0-3,4-di-O-methyl-2,6-di-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-methyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-3-O-methyl-2-O-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranoside undecakis sodium salt

a. methyl 6-O-acetyl-3,4-di-O-methyl-2-O-phenylmethyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-(methyl 2,3-di-O-methyl- β -D-glucopyranosyluronate)-(1 $\rightarrow$ 4)-O-3,6-di-O-acetyl-2-O-phenylmethyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-(methyl 2-O-acetyl-3-O-methyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-acetyl- α -D-glucopyranoside (0,061 mmol; prepared according to the methods described in EP 84,999) was dissolved in 4,2 ml of chloroform and added to a mixture of 3 ml of chloroform, 18 ml of methanol and 3,7 ml of 4N sodium hydroxide. The mixture was stirred for 20 h at room temperature and after neutralizing with a diluted aqueous hydrochloric acid solution, evaporated to dryness. The residue was treated with methanol and the insoluble salts were filtered off. The filtrate was evaporated to dryness to obtain methyl 0-3,4-di-O-methyl-2-O-phenylmethyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-methyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O-2-O-phenylmethyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-3-O-methyl- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-O- α -D-glucopyranoside disodium salt.

b. Crude methyl 0-3,4-di-O-methyl-2-O-phenylmethyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-methyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O-2-O-phenylmethyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-3-O-methyl- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-O- α -D-glucopyranoside disodium salt was dissolved in a mixture of 3 ml of water and 1 ml of methanol and 50 mg of 10% Pd/C were added. The mixture was stirred under an atmosphere of hydrogen for 24 h at room temperature. After filtration the filtrate was evaporated to dryness, dissolved in water and desalted on Sephadex G-25. The combined fractions containing the pentasaccharide were evaporated to dryness to give methyl 3,4-di-O-methyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-methyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-3-O-methyl- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-O- α -D-glucopyranoside disodium salt.

c. methyl 0-3,4-di-O-methyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-methyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-3-O-methyl- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-O- α -D-glucopyranoside di sodium salt was dissolved in a mixture of 2,5 ml of dry dimethylformamide and 1,4 mmol triethylamine sulfur trioxide complex. The mixture was stirred for 20 h at 50 °C, after which the mixture was cooled to room temperature and a mixture of 500 mg of sodium hydrogen carbonate in 7 ml of water was added. The mixture was stirred for 30 min and then evaporated to dryness. The residue was dissolved in water, desalted on Sephadex G-25, after which the combined fractions were freeze-dried to give amorphous methyl 0-3,4-di-O-methyl-2,6-di-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-methyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-3-O-methyl-2-O-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-O-2,

3,6-tri-O-sulfo- α -D-glucopyranoside undecakis sodium salt. $[\alpha]_D^{20} = +51.3^\circ$ (c 0.4; water). Anomeric protons chemical shifts: 4.68; 5.14; 5.25; 5.28; and 5.40 ppm.

Example 2

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In a similar manner as described in Example 1 can be prepared:

methyl O-2,3,4,6-tetra-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-methyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-3-O-methyl-2-O-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranoside tridecakis sodium salt. $[\alpha]_D^{20} = +44.5^\circ$ (c 1; water). Anomeric protons chemical shifts: 4.52; 4.79; 4.97; 5.36; and 5.48 ppm.

methyl O-2,3,4,6-tetra-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-3-O-methyl-2-O-sulfo- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-3-O-methyl-2-O-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranoside tetradecakis sodium salt. $[\alpha]_D^{20} = +45.1^\circ$ (c 1; water). Anomeric protons chemical shifts: 4.76; 5.14; 5.15; 5.48; and 5.64 ppm.

methyl O-3,4-di-O-tetradecyl-2,6-di-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-methyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-3-O-methyl-2-O-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranoside undecakis sodium salt. $[\alpha]_D^{20} = +39.0^\circ$ (c 1; water). Anomeric protons chemical shifts: 4.66; 5.09; 5.24; 5.47; and 5.57 ppm.

methyl O-3,4-di-O-n-hexyl-2,6-di-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-methyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-3-O-methyl-2-O-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranoside undecakis sodium salt. $[\alpha]_D^{20} = +40.8^\circ$ (c 1; water). Anomeric protons chemical shifts: 4.68; 5.14; 5.16; 5.52; and 5.56 ppm.

methyl O-3,4-di-O-methyl-2,6-di-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-3-O-methyl-2-O-sulfo- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-3-O-methyl-2-O-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranoside dodecakis sodium salt. $[\alpha]_D^{20} = +38.5^\circ$ (c 1; water). Anomeric protons chemical shifts: 5.13; 5.14; 5.31; and 5.56 ppm.

methyl O-[(4-phenylmethoxycarbonylamino)phenyl]-2,3,6-tri-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-methyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-3-O-methyl-2-O-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranoside dodecakis sodium salt. $[\alpha]_D^{20} = +56.0^\circ$ (c 1; water). Anomeric protons chemical shifts: 4.69; 5.16; 5.54; and 5.67 ppm.

methyl O-(4-aminophenyl)-2,3,6-tri-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-methyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-3-O-methyl-2-O-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranoside dodecakis sodium salt. $[\alpha]_D^{20} = +56.0^\circ$ (c 1; water). Anomeric protons chemical shifts: 4.69; 5.14; 5.16; 5.52; and 5.65 ppm.

methyl O-(4-sulfonaminophenyl)-2,3,6-tri-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-methyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-3-O-methyl-2-O-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranoside tridecakis sodium salt. $[\alpha]_D^{20} = +57.0^\circ$ (c 1; water). Anomeric protons chemical shifts: 4.69; 5.13; 5.13; 5.53; and 5.67 ppm.

Example 3

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methyl O-3,4-di-O-methyl-2,6-di-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-methyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-3-O-octyl-2-O-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- α -D-glucopyranoside undecakis sodium salt.

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a. methyl O-6-O-acetyl-3,4-di-O-methyl-2-O-phenylmethyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-(phenylmethyl 2,3-di-O-methyl- β -D-glucopyranuronosyluronate)-(1 $\rightarrow$ 4)-O-3,6-di-O-acetyl-2-O-phenylmethyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-(phenylmethyl 2-O-benzoyl-3-O-octyl- α -L-idopyranuronosyluronate)-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-benzoyl- α -D-glucopyranoside (0.051 mmol) was dissolved in methanol and the catalyst (10% Pd/C) was added. The mixture was stirred under an atmosphere of hydrogen for 2 days at room temperature then, after filtration, the solvent was evaporated to dryness to give methyl O-6-O-acetyl-3,4-di-O-methyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-methyl- β -D-glucopyranuronate-(1 $\rightarrow$ 4)-O-3,6-di-O-acetyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2-O-benzoyl-3-O-octyl- α -L-idopyranuronate-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-benzoyl- α -D-glucopyranoside.

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b. methyl O-6-O-acetyl-3,4-di-O-methyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-methyl- β -D-glucopyranuronate-(1 $\rightarrow$ 4)-O-3,6-di-O-acetyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2-O-benzoyl-3-O-octyl- α -L-idopyranuronate)-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-benzoyl- α -D-glucopyranoside was dissolved in methanol (8 ml) and sodium hydroxide (5N solution) was added (0.9 ml). After 15 minutes at room temperature the solution was neutralized with

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Dowex-50-H⁺ resin, filtered and evaporated to dryness to give methyl 0-3,4-di-0-methyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-2,3-di-0-methyl- β -D-glucopyranuronate-(1 $\rightarrow$ 4)-0- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-3-0-octyl- α -L-idopyranuronate-(1 $\rightarrow$ 4)-0- α -D-glucopyranoside (48 mg).

c. methyl 0-3,4-di-0-methyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-2,3-di-0-methyl- β -D-glucopyranuronate-(1 $\rightarrow$ 4)-0- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-3-0-octyl- α -L-idopyranuronate-(1 $\rightarrow$ 4)-0- α -D-glucopyranoside (48 mg) was dissolved in dimethylformamide (1.4 ml) and sulfur trioxidetriethylamine complex (1.8 mmol) was added. After one night at 55 °C the mixture was cooled to room temperature and a mixture of sodium hydrogen carbonate (500 mg) and water (2 ml) was added. After evaporation the residue was layered on top of a Sephadex G25 column and eluted with water. The appropriate fractions were combined and freeze dried to give methyl 0-3,4-di-0-methyl-2,6-di-0-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-2,3-di-0-methyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-0-2,3,6-tri-0-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-3-0-octyl-2-0-sulfo- α -L-isopyranuronosyl-(1 $\rightarrow$ 4)-0-2,3,6-tri-0-sulfo- α -D-glucopyranoside undecakis sodium salt. $[\alpha]_D^{20} = +40^\circ$ (c 1.2; water). Anomeric protons chemical shifts: 4.68; 5.12; 5.13; 5.52; and 5.53 ppm.

Example 4

In a similar manner, as described in Example 3, were prepared:

methyl 0-3,4-di-0-methyl-2,6-di-0-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-2,3-di-0-methyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-0-2,3,6-tri-0-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-3-0-butyl-2-0-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-0-2,3,6-tri-0-sulfo- α -D-glucopyranoside undecakis sodium salt.

$[\alpha]_D^{20} = +40^\circ$ (c 0.86; water).

methyl 0-3,4-di-0-methyl-2,6-di-0-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-2,3-di-0-butyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-0-2,3,6-tri-0-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-3-0-octyl-2-0-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-0-2,3,6-tri-0-sulfo- α -D-glucopyranoside undecakis sodium salt.

$[\alpha]_D^{20} = +38^\circ$ (c 0.95; water).

methyl 0-3,4-di-0-methyl-2,6-di-0-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-2,3-di-0-butyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-0-2,3,6-tri-0-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-3-0-methyl-2-0-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-0-2,3,6-tri-0-sulfo- α -D-glucopyranoside undecakis sodium salt.

$[\alpha]_D^{20} = +43^\circ$ (c 0.92; water).

Claims

Claims for the following Contracting States : AT, BE, DE, DK, FR, GB, IT, NL, SE

1. A carbohydrate derivative comprising a trisaccharide unit of the general formula I



in which R is alkyl, aryl, or aralkyl;

Q is alkyl, aryl, aralkyl, or SO_3^- ;

A and B are independently selected from hydrogen, alkyl, aryl, aralkyl, or a carbohydrate group; and the charged moieties are compensated by counter-ions.

2. The carbohydrate derivative according to claim 1, characterized in that R represents methyl and Q represents methyl.

3. The carbohydrate derivative according to claim 1, characterized in that R represents methyl and Q represents SO_3^- .

4. The carbohydrate derivative according to claim 2 or 3, characterized in that A represents:

Dowex-50-H⁺ resin, filtered and evaporated to dryness to give methyl 0-3,4-di-0-methyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-2,3-di-0-methyl- β -D-glucopyranuronate-(1 $\rightarrow$ 4)-0- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-3-0-octyl- α -L-idopyranuronate-(1 $\rightarrow$ 4)-0- α -D-glucopyranoside (48 mg).

c. methyl 0-3,4-di-0-methyl- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-2,3-di-0-methyl- β -D-glucopyranuronate-(1 $\rightarrow$ 4)-0- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-3-0-octyl- α -L-idopyranuronate-(1 $\rightarrow$ 4)-0- α -D-glucopyranoside (48 mg) was dissolved in dimethylformamide (1.4 ml) and sulfur trioxidetriethylamine complex (1.8 mmol) was added. After one night at 55 °C the mixture was cooled to room temperature and a mixture of sodium hydrogen carbonate (500 mg) and water (2 ml) was added. After evaporation the residue was layered on top of a Sephadex G25 column and eluted with water. The appropriate fractions were combined and freeze dried to give methyl 0-3,4-di-0-methyl-2,6-di-0-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-2,3-di-0-methyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-0-2,3,6-tri-0-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-3-0-octyl-2-0-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-0-2,3,6-tri-0-sulfo- α -D-glucopyranoside undecakis sodium salt. $[\alpha]_D^{20} = +40^\circ$ (c 1.2; water). Anomeric protons chemical shifts: 4.68; 5.12; 5.13; 5.52; and 5.53 ppm.

Example 4

In a similar manner, as described in Example 3, were prepared:

methyl 0-3,4-di-0-methyl-2,6-di-0-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-2,3-di-0-methyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-0-2,3,6-tri-0-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-3-0-butyl-2-0-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-0-2,3,6-tri-0-sulfo- α -D-glucopyranoside undecakis sodium salt.

$[\alpha]_D^{20} = +40^\circ$ (c 0.86; water).

methyl 0-3,4-di-0-methyl-2,6-di-0-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-2,3-di-0-butyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-0-2,3,6-tri-0-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-3-0-octyl-2-0-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-0-2,3,6-tri-0-sulfo- α -D-glucopyranoside undecakis sodium salt.

$[\alpha]_D^{20} = +38^\circ$ (c 0.95; water).

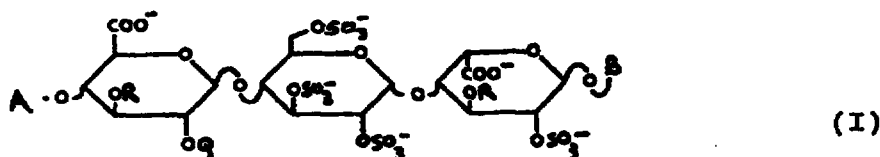
methyl 0-3,4-di-0-methyl-2,6-di-0-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-2,3-di-0-butyl- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-0-2,3,6-tri-0-sulfo- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-0-3-0-methyl-2-0-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-0-2,3,6-tri-0-sulfo- α -D-glucopyranoside undecakis sodium salt.

$[\alpha]_D^{20} = +43^\circ$ (c 0.92; water).

Claims

Claims for the following Contracting States : AT, BE, DE, DK, FR, GB, IT, NL, SE

1. A carbohydrate derivative comprising a trisaccharide unit of the general formula I



in which R is alkyl, aryl, or aralkyl;

Q is alkyl, aryl, aralkyl, or SO₃⁻;

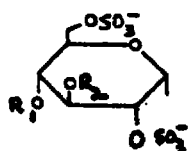
A and B are independently selected from hydrogen, alkyl, aryl, aralkyl, or a carbohydrate group; and the charged moieties are compensated by counter-ions.

2. The carbohydrate derivative according to claim 1, characterized in that R represents methyl and Q represents methyl.

3. The carbohydrate derivative according to claim 1, characterized in that R represents methyl and Q represents SO₃⁻.

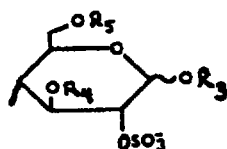
4. The carbohydrate derivative according to claim 2 or 3, characterized in that A represents:





(II)

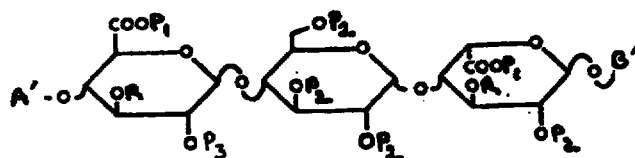
and B represents:



(III)

in which R_1 , R_2 , R_3 , R_4 and R_5 are independently selected from hydrogen, alkyl, aryl, aralkyl, or SO_3^- .

5. The carbohydrate derivative according to claim 4, characterized in that R_1 , R_2 , and R_3 are methyl, R_4 and R_5 are SO_3^- , and OR_3 has the α -configuration.
6. A process for the preparation of the carbohydrate derivative of claim 1, characterized in that a protected carbohydrate derivative comprising a trisaccharide unit of the general formula:



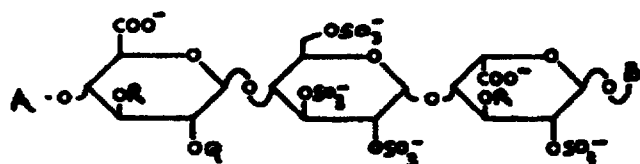
(IV)

in which R is alkyl, aryl, or aralkyl, P_1 is an acid protective group, P_2 is a hydroxy protective group, P_3 is a hydroxy protective group or an alkyl, aryl, or aralkyl group, and A' and B' are A and B respectively, or protected derivatives thereof, is deprotected and sulfated in a manner known in the art.

7. A pharmaceutical composition comprising the carbohydrate derivative of claim 1, admixed with pharmaceutically acceptable auxiliaries.
8. A use of the carbohydrate derivative of claim 1 for the manufacture of a medicament for the treatment of thrombosis and inhibition of muscle cell proliferation.
9. The carbohydrate derivative according to any one of claims 1-5 for use in therapy.

Claims for the following Contracting States : ES, GR

1. A process for the preparation of a carbohydrate derivative comprising a trisaccharide unit having the general formula I



(I)

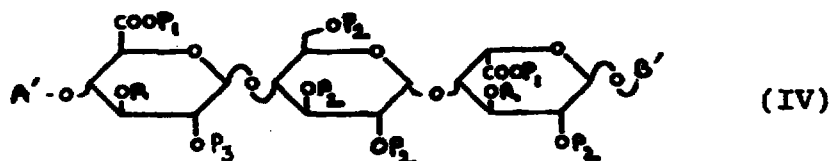
in which R is alkyl, aryl, or aralkyl;

Q is alkyl, aryl, aralkyl, or SO_3^- ;

A and B are independently selected from hydrogen, alkyl, aryl, aralkyl, or a carbohydrate group; and the



charged moieties are compensated by counterions, characterized in that a protected carbohydrate derivative comprising a trisaccharide unit of the general formula IV

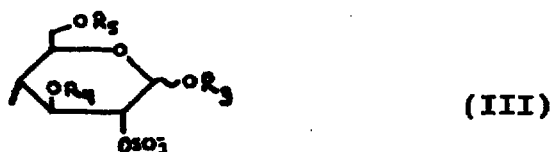


in which R is alkyl, aryl, or aralkyl, P₁ is an acid protective group, P₂ is a hydroxy protective group, P₃ is a hydroxy protective group or an alkyl, aryl, or aralkyl group, and A' and B' are A and B respectively, or protected derivatives thereof, is deprotected and sulfated in a manner known in the art.

2. The process according to claim 1, wherein R represents methyl and Q represents methyl.
3. The process according to claim 1, wherein R represents methyl and Q represents SO₃⁻.
4. The process according to claim 2 or 3, wherein A represents:



and B represents:



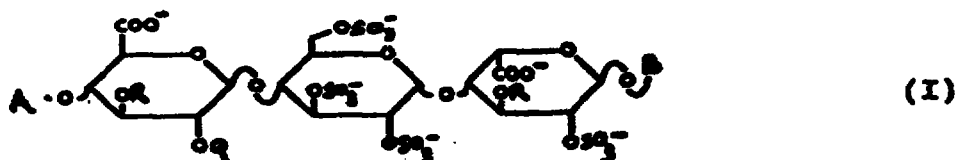
in which R₁, R₂, R₃, R₄ and R₅ are independently selected from hydrogen, alkyl, aryl, aralkyl, or SO₃⁻

5. The process according to claim 4, wherein R₁, R₂, and R₃ are methyl, R₄ and R₅ are SO₃⁻, and OR₃ has the α-configuration.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, DE, DK, FR, GB, IT, NL, SE

1. Ein Kohlehydratderivat, umfassend eine Trisaccharid-Einheit der allgemeinen Formel I

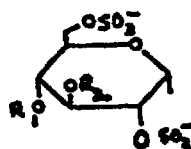


in welcher
R Alkyl, Aryl oder Aralkyl ist;



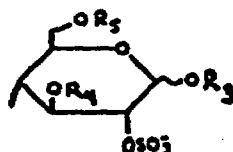
Q Alkyl, Aryl, Aralkyl oder SO_3^- ist;
 A und B unabhängig voneinander ausgewählt sind aus Wasserstoff, Alkyl, Aryl, Aralkyl oder einer Kohlehydratgruppe;
 und die geladenen Gruppierungen durch Gegenionen kompensiert sind.

2. Das Kohlehydratderivat nach Anspruch 1, dadurch gekennzeichnet, dass R Methyl und Q Methyl darstellen.
3. Das Kohlehydratderivat nach Anspruch 1, dadurch gekennzeichnet, dass R Methyl bedeutet und Q SO_3^- darstellt.
4. Das Kohlehydratderivat nach Anspruch 2 oder 3, dadurch gekennzeichnet, dass A



(II)

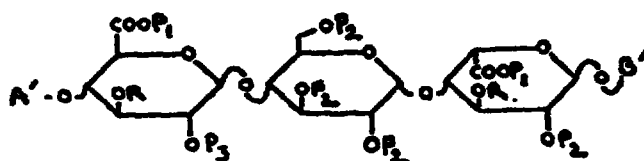
bedeutet und B



(III)

bedeutet, in welchen R_1 , R_2 , R_3 , R_4 und R_5 unabhängig voneinander ausgewählt sind aus Wasserstoff, Alkyl, Aryl, Aralkyl oder SO_3^- .

5. Das Kohlehydratderivat nach Anspruch 4, dadurch gekennzeichnet, dass R_1 , R_2 und R_3 Methyl sind, R_4 und R_5 SO_3^- sind und OR_3 die α -Konfiguration aufweist.
6. Verfahren zur Herstellung des Kohlehydratderivates nach Anspruch 1, dadurch gekennzeichnet, dass ein geschütztes Kohlehydratderivat, welches eine Trisaccharideinheit der allgemeinen Formel IV



(IV)

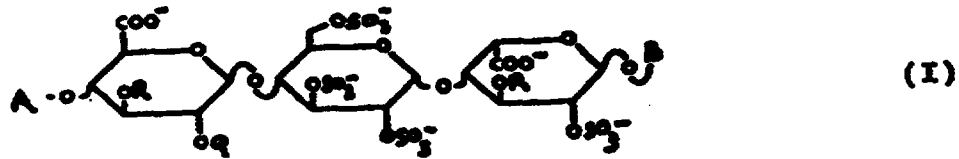
umfasst, in welcher R Alkyl, Aryl oder Aralkyl ist, P_1 eine Säureschutzgruppe ist, P_2 eine Hydroxyschutzgruppe ist, P_3 eine Hydroxyschutzgruppe oder eine Alkyl-, Aryl- oder Aralkylgruppe ist und A' und B' gleich A bzw. B sind oder geschützte Derivate davon, von der Schutzgruppe befreit und in einer in Fachkreisen bekannten Weise sulfatiert wird.

7. Pharmazeutische Zusammensetzung, umfassend das Kohlehydratderivat nach Anspruch 1, vermischt mit pharmazeutisch annehmbaren Hilfsstoffen.
8. Eine Verwendung des Kohlehydratderivates nach Anspruch 1 zur Herstellung eines Medikamentes für die Behandlung von Thrombose und für die Verhinderung von Muskelzellerproliferation.
9. Das Kohlehydratderivat nach einem der Ansprüche 1 bis 5 zur Verwendung in der Therapie.



Patentansprüche für folgende Vertragsstaaten : GR, ES

1. Verfahren zur Herstellung eines Kohlehydratderivates, welches eine Trisaccharideinheit der allgemeinen Formel I



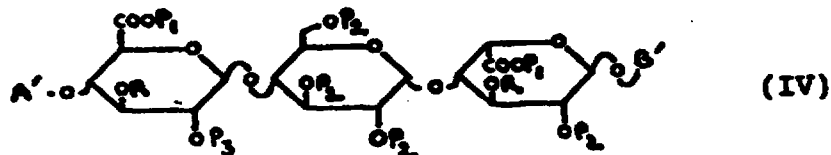
umfasst, in welcher

R Alkyl, Aryl oder Aralkyl ist;

Q Alkyl, Aryl, Aralkyl oder SO_3^- ist;

A und B unabhängig voneinander ausgewählt sind aus Wasserstoff, Alkyl, Aryl, Aralkyl oder einer Kohlehydratgruppe

und die geladenen Gruppierungen durch Gegenionen kompensiert sind, dadurch gekennzeichnet, dass ein geschütztes Kohlehydratderivat, welches eine Trisaccharideinheit der allgemeinen Formel IV



umfasst, in welcher

R Alkyl, Aryl oder Aralkyl ist,

P₁ eine Säureschutzgruppe ist,

P₂ eine Hydroxyschutzgruppe ist,

P₃ eine Hydroxyschutzgruppe oder eine Alkyl-, Aryl- oder Aralkylgruppe ist und

A' und B' gleich A bzw. B sind oder geschützte Derivate davon,

von der Schutzgruppe befreit und auf in Fachkreisen bekannte Weise sulfatiert wird.

2. Das Verfahren nach Anspruch 1, in welchem R Methyl bedeutet und Q Methyl bedeutet.
3. Verfahren nach Anspruch 1, in welchem R Methyl bedeutet und Q SO_3^- darstellt.
4. Das Verfahren nach Anspruch 2 oder 3, in welchem A



darstellt und B



darstellt, in welchen R₁, R₂, R₃, R₄ und R₅ unabhängig voneinander ausgewählt sind aus Wasserstoff,



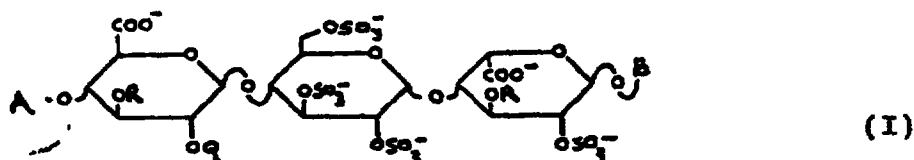
Alkyl, Aryl, Aralkyl oder SO_3^- .

5. Das Verfahren nach Anspruch 4, in welchem R_1 , R_2 und R_3 Methyl sind, R_4 und R_5 SO_3^- sind und OR_6 die α -Konfiguration aufweisen.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, DE, DK, FR, GB, IT, NL, SE

1. Un dérivé d'hydrate de carbone comprenant une unité trisaccharidique de formule générale I:



dans laquelle:

R est un radical alkyle, aryle ou aralkyle;

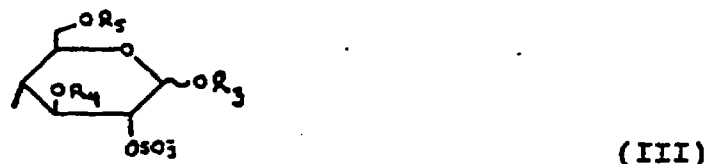
Q est un radical alkyle, aryle, aralkyle, ou SO_3^- ;

A et B sont choisis, indépendamment l'un de l'autre, dans le groupe comprenant l'atome d'hydrogène, les radicaux alkyle, aryle, aralkyle ou un résidu d'hydrate de carbone; les radicaux portant une charge étant compensée par des contre-ions.

2. Le dérivé d'hydrate de carbone selon la revendication 1, caractérisé en ce que R représente un radical méthyle et Q représente un radical méthyle.
3. Le dérivé d'hydrate de carbone selon la revendication 1, caractérisé en ce que R représente un radical méthyle et Q représente SO_3^- .
4. Un dérivé d'hydrate de carbone selon les revendications 2 ou 3, caractérisé en ce que A représente:



et B représente:



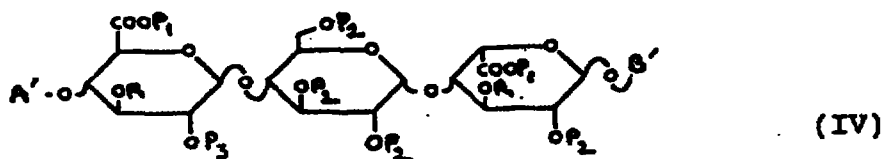
dans lesquelles:

R_1 , R_2 , R_3 , R_4 et R_5 sont choisis, de façon indépendante, parmi l'hydrogène, les radicaux alkyle, aryle, aralkyle, ou SO_3^- .

5. Le dérivé d'hydrate de carbone selon la revendication 4, caractérisé en ce que R_1 , R_2 et R_3 sont des radicaux méthyles, R_4 et R_5 représentent SO_3^- , et OR_6 présente une configuration α .
6. Un procédé pour la préparation d'un dérivé d'hydrate de carbone selon la revendication 1, caractérisé en



ce que le dérivé d'hydrate de carbone protégé comprenant une unité trisaccharide de formule générale:



dans laquelle:

R est un radical alkyle, aryle ou aralkyle,

P₁ est un groupe protecteur acide,

P₂ est un groupe protecteur hydroxy,

P₃ est un groupe protecteur hydroxy ou un groupe alkyle, aryle ou aralkyle et

A' et B' sont respectivement A et B ou leurs dérivés protégés, est déprotégé et sulfaté selon une méthode connue de la technique

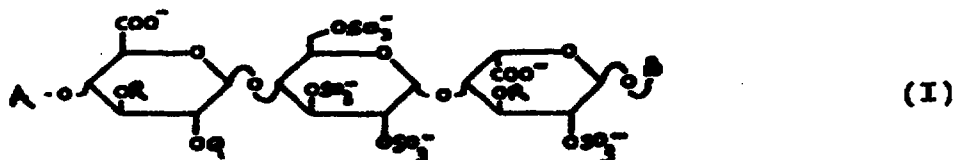
7. Une composition pharmaceutique comprenant des dérivés d'hydrate de carbone selon la revendication 1, mélangés à des auxiliaires pharmaceutiquement acceptables.

8. L'utilisation de dérivé d'hydrate de carbone selon la revendication 1, pour la fabrication d'un médicament pour le traitement de thrombose et l'inhibition de la prolifération des cellules musculaires.

9. Dérivé d'hydrate de carbone selon l'une quelconque des revendications 1 à 5, pour une utilisation en thérapeutique.

Revendications pour les Etats contractants suivants : ES, GR

1. Un procédé pour la préparation d'un dérivé d'hydrate de carbone comprenant une unité trisaccharidique ayant la formule générale:

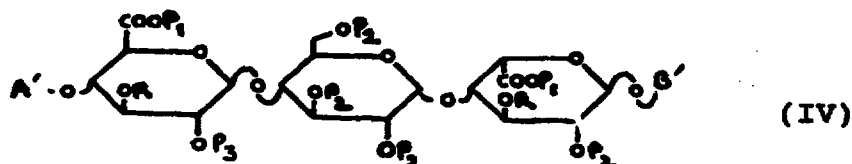


dans laquelle:

R est un radical alkyle, aryle ou aralkyle;

Q est un radical alkyle, aryle, aralkyle, ou SO₃⁻;

A et B sont choisis, indépendamment l'un de l'autre, dans le groupe contenant l'atome d'hydrogène, les radicaux alkyle, aryle, aralkyle ou un résidu d'hydrate de carbone; les radicaux portant une charge étant composée par des contre-ions, caractérisé en ce que le dérivé d'hydrate de carbone protégé comprenant une unité trisaccharidique de formule générale IV



dans laquelle:

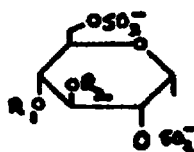
R est un radical alkyle, aryle ou aralkyle,

P₁ est un groupe protecteur acide,



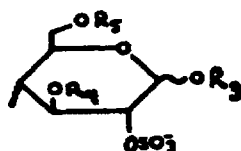
P_2 est un groupe protecteur hydroxy,
 P_3 est un groupe protecteur hydroxy ou un groupe alkyle, aryle ou aralkyle, et
 A' et B' sont respectivement A et B ou leurs dérivés protégés,
 est déprotégé et sulfaté selon une méthode connue de la technique.

2. Un procédé selon la revendication 1, dans lequel:
 R représente un radical méthyle et
 Q représente un radical méthyle.
3. Un procédé selon la revendication 1, dans lequel:
 R représente un radical méthyle et
 Q représente SO_3^- .
4. Un procédé selon la revendication 2 ou 3, dans lequel:
 A représente



(II)

et B représente



(III)

dans lesquels:

R_1 , R_2 , R_3 , R_4 et R_5 sont choisis, indépendamment l'un de l'autre, parmi l'hydrogène, les groupes alkyle, aryle, aralkyle, ou SO_3^- .

5. Un procédé selon la revendication 4 dans lequel R_1 , R_2 et R_3 sont des radicaux méthyles, R_4 et R_5 sont SO_3^- , et OR_3 a une configuration α .

