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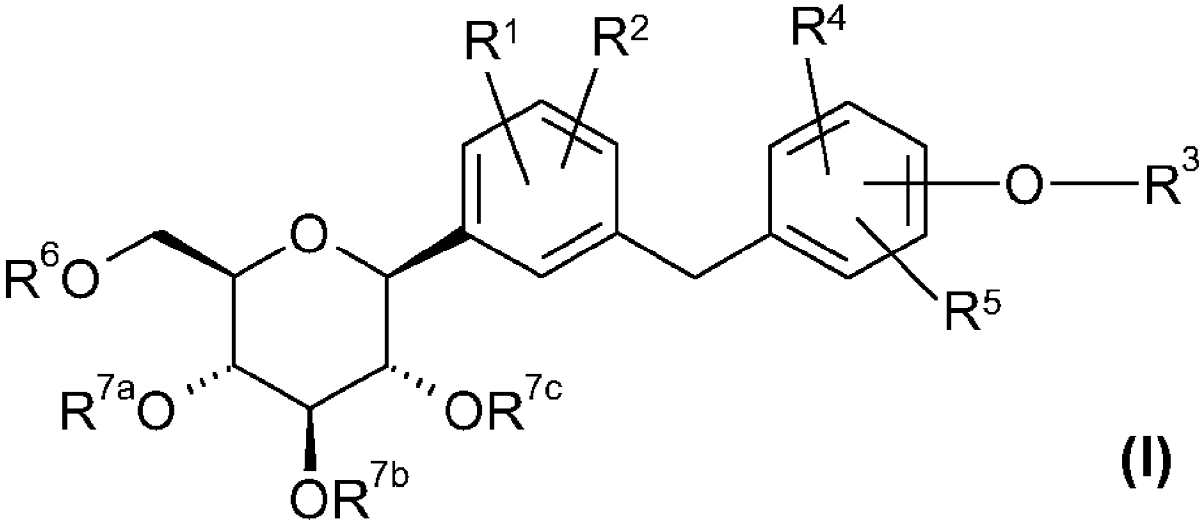
(54) Title: GLUCOPYRANOSYL-SUBSTITUTED BENZYL-BENZENE DERIVATIVES, MEDICAMENTS CONTAINING SUCH COMPOUNDS, THEIR USE AND PROCESS FOR THEIR MANUFACTURE



(I)

(57) Abrégé/Abstract:

Glucopyranosyl-substituted benzyl-benzene derivatives of the general formula (I) where the groups R^1 to R^6 as well as R^{7a}, R^{7b}, R^{7c} are defined according to claim 1, including the tautomers, the stereoisomers thereof, the mixtures thereof and the salts thereof. The Compounds according to the invention are suitable for the treatment of metabolic disorders.

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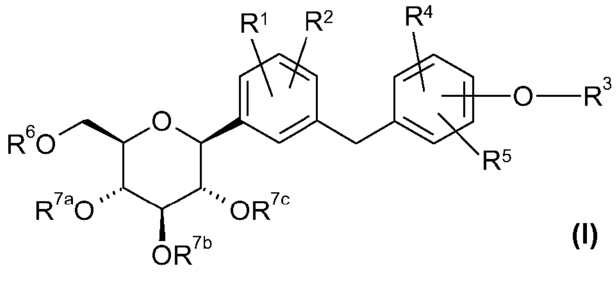
(54) Title: GLUCOPYRANOSYL-SUBSTITUTED BENZYL-BENZENE DERIVATIVES, MEDICAMENTS CONTAINING SUCH COMPOUNDS, THEIR USE AND PROCESS FOR THEIR MANUFACTURE



(I)

(57) Abstract: Glucopyranosyl-substituted benzyl-benzene derivatives of the general formula (I) where the groups R^1 to R^6 as well as R^{7a}, R^{7b}, R^{7c} are defined according to claim 1, including the tautomers, the stereoisomers thereof, the mixtures thereof and the salts thereof. The Compounds according to the invention are suitable for the treatment of metabolic disorders.

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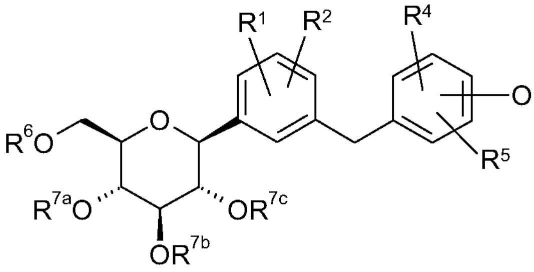
Glucopyranosyl-substituted benzyl-benzene derivatives, medicaments containing such compounds, their use and process for their manufacture

The present invention relates to glucopyranosyl-substituted benzyl-benzene derivatives of the general formula I


I

wherein the groups R^1 to R^6 and R^{7a}, R^{7b}, R^{7c} are as defined hereinafter, including the tautomers, the stereoisomers, the mixtures thereof and the salts thereof. The invention further relates to pharmaceutical compositions containing a compound of formula I according to the invention as well as the use of a compound according to the invention for preparing a pharmaceutical composition for the treatment of metabolic disorders. In addition, the invention relates to processes for preparing a pharmaceutical composition as well as a compound according to the invention.

In the literature, compounds which have an inhibitory effect on the sodium-dependent glucose cotransporter SGLT2 are proposed for the treatment of diseases, particularly diabetes.

Glucopyranosyloxy- and glucopyranosyl-substituted aromatic groups and the preparation thereof and their possible activity as SGLT2 inhibitors are known from published International applications WO 98/31697, WO 01/27128, WO 02/083066, WO 03/099836, WO 2004/063209, WO 2004/080990, WO 2004/013118, WO 2004/052902, WO 2004/052903, WO 2005/092877 and US application US 2003/0114390.

Aim of the invention

The aim of the present invention is to find new pyranosyl-substituted benzene derivatives, particularly those which are active with regard to the sodium-dependent glucose cotransporter SGLT, particularly SGLT2. A further aim of the present invention is to discover pyranosyl-substituted benzene derivatives which have a good to very good inhibitory effect on the sodium-dependent glucose cotransporter SGLT2 *in vitro* and/or *in vivo* and/or have good to very good pharmacological and/or pharmacokinetic and/or physicochemical properties.

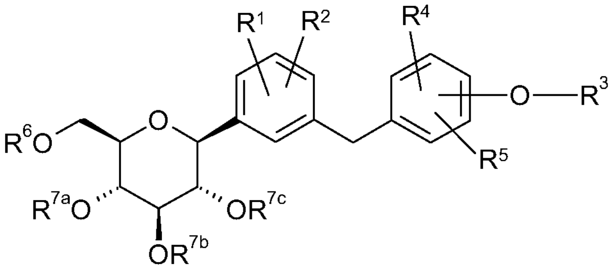
A further aim of the present invention is to provide new pharmaceutical compositions which are suitable for the prevention and/or treatment of metabolic disorders, particularly diabetes.

The invention also sets out to provide a process for preparing the compounds according to the invention.

Other aims of the present invention will become apparent to the skilled man directly from the foregoing and following remarks.

Object of the invention

In a first aspect the present invention relates to glucopyranosyl-substituted benzyl-benzene derivatives of general formula I



I

wherein

R^1 denotes hydrogen, fluorine, chlorine, bromine, iodine, C_{1-4}-alkyl, C_{2-6}-alkynyl, C_{1-4}-alkoxy, C_{2-4}-alkenyl-C_{1-4}-alkoxy, C_{2-4}-alkynyl-C_{1-4}-alkoxy, methyl substituted by 1 to 3 fluorine atoms, ethyl substituted by 1 to 5 fluorine atoms, methoxy substituted by 1 to 3 fluorine atoms, ethoxy substituted by 1 to 5 fluorine atoms, C_{1-4}-alkyl substituted by a hydroxy or C_{1-3}-alkoxy group, C_{2-4}-alkoxy substituted by a hydroxy or C_{1-3}-alkoxy group, C_{2-6}-alkenyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-3}-alkyl, C_{3-7}-cycloalkyloxy, C_{3-7}-cycloalkyl-C_{1-3}-alkoxy, C_{5-7}-cycloalkenyloxy, hydroxy, amino, nitro or cyano, while in the C_{5-6}-cycloalkyl groups a methylene group may be replaced by O;

R^2 denotes hydrogen, fluorine, chlorine, bromine, hydroxy, C_{1-4}-alkyl, C_{1-4}-alkoxy, cyano or nitro, while the alkyl or alkoxy group may be mono- or polysubstituted by fluorine, and

R^3 denotes C_{3-7}-cycloalkyl, tetrahydrofuranyl or tetrahydropyranyl, which are substituted with one to four substituents L2, or R^3 denotes C_{5-7}-cycloalkanonyl which may be substituted with one to four substituents L2; and

R^4, R^5 independently of one another denote hydrogen, fluorine, chlorine, bromine, iodine, cyano, nitro, C_{1-3}-alkyl, C_{1-3}-alkoxy, or a methyl- or methoxy-group substituted by 1 to 3 fluorine atoms,

L1 independently of one another are selected from among fluorine, chlorine, bromine, iodine, hydroxy, cyano, C_{1-3}-alkyl, difluoromethyl, trifluoromethyl, C_{1-3}-alkoxy, difluoromethoxy, trifluoromethoxy, amino, C_{1-3}-alkyl-amino and di(C_{1-3}-alkyl)-amino; and

L2 independently of one another are selected from among fluorine, chlorine, hydroxy, hydroxyl-C_{1-4}-alkyl, C_{1-4}-alkoxy, trifluoromethoxy, C_{1-4}-alkoxy-C_{1-4}-alkyl, cyano, hydroxycarbonyl, (C_{1-4}-alkyl)oxycarbonyl, aminocarbonyl, C_{1-4}-alkyl, trifluoromethyl, amino, C_{1-4}-alkyl-carbonylamino, C_{1-3}-alkyl-amino and di(C_{1-3}-alkyl)-amino; and

R^6 , R^{7a},
R^{7b}, R^{7c} independently of one another have a meaning selected from among hydrogen, (C_{1-18}-alkyl)carbonyl, (C_{1-18}-alkyl)oxycarbonyl, arylcarbonyl and aryl-(C_{1-3}-alkyl)-carbonyl, while the aryl-groups may be mono- or disubstituted independently of one another by identical or different groups L1;

while by the aryl groups mentioned in the definition of the above groups are meant phenyl or naphthyl groups which may be substituted as defined; and

while, unless otherwise stated, the above-mentioned alkyl groups may be straight-chain or branched, the tautomers, the stereoisomers thereof, the mixtures thereof and the salts thereof.

The compounds of general formula I according to the invention and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly an inhibitory effect on the sodium-dependent glucose cotransporter SGLT, particularly SGLT2. Moreover compounds according to the invention may have an inhibitory effect on the sodium-dependent glucose cotransporter SGLT1. Compared with a possible inhibitory effect on SGLT1 the compounds according to the invention preferably inhibit SGLT2 selectively.

The present invention also relates to the physiologically acceptable salts of the compounds according to the invention with inorganic or organic acids.

This invention also relates to pharmaceutical compositions, containing at least one compound according to the invention or a physiologically acceptable salt according to the invention, optionally together with one or more inert carriers and/or diluents.

This invention also relates to the use of at least one compound according to the invention or one of the physiologically acceptable salts thereof for preparing a pharmaceutical composition which is suitable for the treatment or prevention or diseases or conditions which can be influenced by inhibiting the sodium-dependent glucose cotransporter SGLT, particularly SGLT2.

This invention also relates to the use of at least one compound according to the invention or one of the physiologically acceptable salts thereof for preparing a pharmaceutical composition which is suitable for the treatment of metabolic disorders.

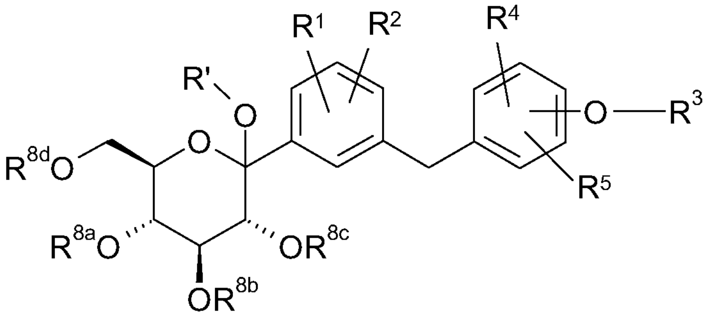
This invention also relates to the use of at least one compound according to the invention or one of the physiologically acceptable salts thereof for preparing a pharmaceutical composition for inhibiting the sodium-dependent glucose cotransporter SGLT, particularly SGLT2.

The invention further relates to a process for preparing a pharmaceutical composition according to the invention, characterised in that a compound according to the invention or one of the physiologically acceptable salts thereof is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

The present invention also relates to a process for preparing the compounds of general formula I according to the invention, characterised in that

a) in order to prepare compounds of general formula I which are defined as hereinbefore and hereinafter,

a compound of general formula II



II

wherein

R'	denotes H, C_{1-4}-alkyl, (C_{1-18}-alkyl)carbonyl, (C_{1-18}-alkyl)oxycarbonyl, arylcarbonyl and aryl-(C_{1-3}-alkyl)-carbonyl, wherein the alkyl or aryl groups may be mono- or polysubstituted by halogen;
R^{8a}, R^{8b}, R^{8c}, R^{8d}	independently of one another have one of the meanings given hereinbefore and hereinafter for the groups R^6, R^{7a}, R^{7b}, R^{7c}, or denote a benzyl group or a $R^aR^bR^cSi$ group or a ketal or acetal group, particularly an alkylidene or arylalkylidene ketal or acetal group, while in each case two adjacent groups R^{8a}, R^{8b}, R^{8c}, R^{8d} may form a cyclic silyl ketal, ketal or acetal group or a 1,2-di(C_{1-3}-alkoxy)-1,2-di(C_{1-3}-alkyl)-ethylene bridge, while the above-mentioned ethylene bridge forms, together with two oxygen atoms and the two associated carbon atoms of the pyranose ring, a substituted dioxane ring, particularly a 2,3-dimethyl-2,3-di(C_{1-3}-alkoxy)-1,4-dioxane ring, and while alkyl, aryl and/or benzyl groups may be mono- or polysubstituted by halogen or C_{1-3}-alkoxy, and while benzyl groups may also be substituted by a di-(C_{1-3}-alkyl)amino group; and
R^a, R^b, R^c	independently of one another denote C_{1-4}-alkyl, aryl or aryl-C_{1-3}-alkyl, wherein the aryl or alkyl groups may be mono- or polysubstituted by halogen;

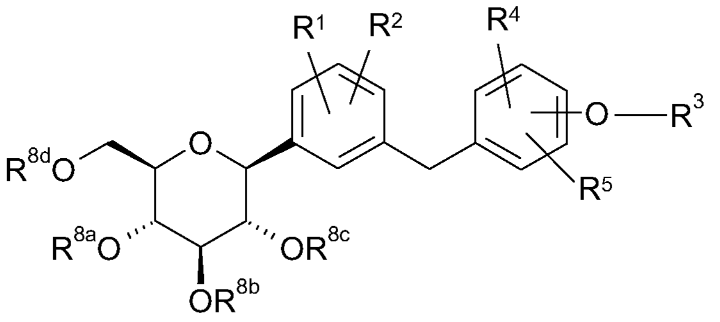
while by the aryl groups mentioned in the definition of the above groups are meant phenyl or naphthyl groups, preferably phenyl groups;

and wherein the groups R^1 to R^5 and R^6, R^{7a}, R^{7b}, R^{7c} are defined as hereinbefore and hereinafter;

is reacted with a reducing agent in the presence of a Lewis or Brønsted acid, while any protective groups present are cleaved simultaneously or subsequently; or

b) in order to prepare compounds of general formula I wherein R^6, R^{7a}, R^{7b} and R^{7c} denote hydrogen,

a compound of general formula III



III

wherein R^{8a}, R^{8b}, R^{8c}, R^{8d} and R^1 to R^5 are defined as hereinbefore and hereinafter, but at least one of the groups R^{8a}, R^{8b}, R^{8c}, R^{8d} does not denote hydrogen, is hydrolysed, and

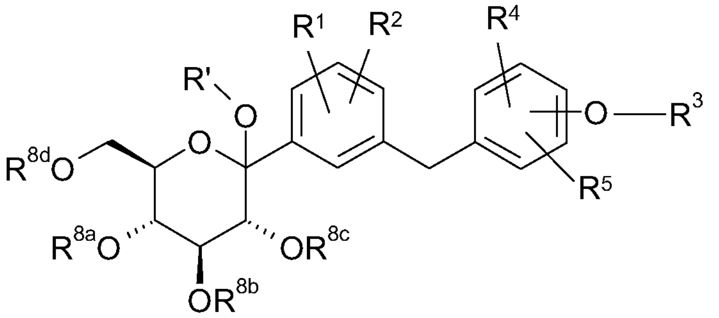
if desired a compound of general formula I thus obtained wherein R^6 denotes a hydrogen atom, is converted by acylation into a corresponding acyl compound of general formula I, and/or

if necessary any protective group used in the reactions described above is cleaved and/or

if desired a compound of general formula I thus obtained is resolved into its stereoisomers and/or

if desired a compound of general formula I thus obtained is converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts thereof.

This invention further relates to a process for preparing compounds of general formula II



II

wherein

R' denotes H, C_{1-4}-alkyl, (C_{1-18}-alkyl)carbonyl, (C_{1-18}-alkyl)oxycarbonyl, arylcarbonyl and aryl-(C_{1-3}-alkyl)-carbonyl, wherein the alkyl or aryl groups may be mono- or polysubstituted by halogen;

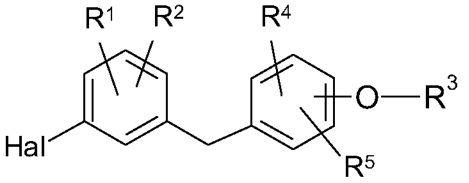
R^{8a}, R^{8b}, R^{8c}, R^{8d} independently of one another has one of the meanings given for the groups R^6, R^{7a}, R^{7b}, R^{7c}, or denote a benzyl group or a $R^aR^bR^cSi$ group or a ketal or acetal group, while in each case two adjacent groups R^{8a}, R^{8b}, R^{8c}, R^{8d} may form a cyclic silyl ketal, ketal or acetal group or may form, with two oxygen atoms of the pyranose ring, a substituted 2,3-oxydioxane ring, particularly a 2,3-dimethyl-2,3-di(C_{1-3}-alkoxy)-1,4-dioxane ring, and while alkyl, aryl and/or benzyl groups may be mono- or polysubstituted by halogen or C_{1-3}-alkoxy, and while benzyl groups may also be substituted by a di-(C_{1-3}-alkyl)amino group; and

R^a, R^b, R^c independently of one another denote C_{1-4}-alkyl, aryl or aryl-C_{1-3}-alkyl, while the alkyl or aryl groups may be mono- or polysubstituted by halogen;

while by the aryl groups mentioned in the definition of the above groups are meant phenyl or naphthyl groups, preferably phenyl groups;

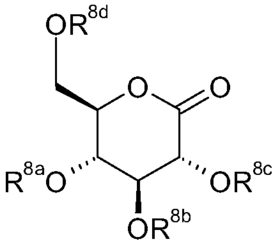
and R^1 to R^5, R^6, R^{7a}, R^{7b}, R^{7c} are defined as hereinbefore and hereinafter,

wherein an organometallic compound (V) which may be obtained by halogen-metal exchange or by inserting a metal in the carbon-halogen bond of a halogen-benzylbenzene compound of general formula IV



IV

wherein Hal denotes Cl, Br and I and R^1 to R^5 are defined as hereinbefore and hereinafter, and optionally subsequent transmetallation, is added to a gluconolactone of general formula VI



VI

wherein R^{8a}, R^{8b}, R^{8c}, R^{8d} are defined as hereinbefore and hereinafter, and

then the resulting adduct, is reacted, preferably *in situ*, with water or an alcohol R'-OH, while R' denotes optionally substituted C_{1-4}-alkyl, in the presence of an acid, such as for example methanesulfonic acid, sulfuric acid, hydrochloric acid, acetic acid or ammonium chloride, and optionally the product obtained in the reaction with water wherein R' denotes H is converted, in a subsequent reaction, with an acylating agent, such as for example the corresponding acid chloride or anhydride, into the product of formula II wherein R' denotes (C_{1-18}-alkyl)-carbonyl, (C_{1-18}-alkyl)oxycarbonyl, arylcarbonyl or aryl-(C_{1-3}-alkyl)-carbonyl, which may be substituted as specified.

The intermediate products listed, particularly those of formula IV, formula II and formula III, are also a subject of this invention.

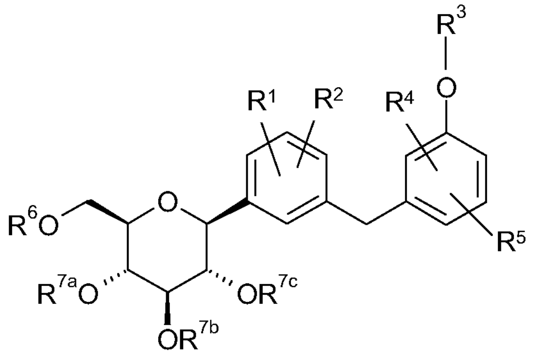
Detailed Description of the invention

Unless otherwise stated, the groups, residues and substituents, particularly R^1 to R^5, L1, L2, R^6 , R^{7a}, R^{7b}, R^{7c}, R^{8a}, R^{8b}, R^{8c}, R^{8d}, are defined as above and hereinafter.

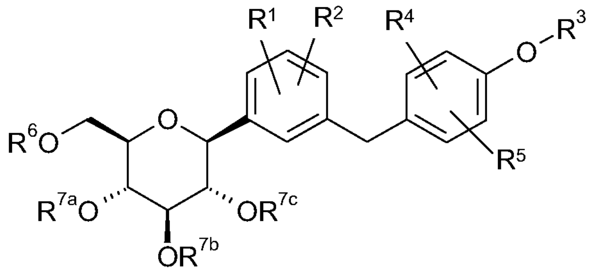
If residues, substituents or groups occur several times in a compound, as for example L1 and L2, they may have the same or different meanings.

Some preferred meanings of individual groups and substituents of the compounds according to the invention will be given hereinafter.

The group -O-R^3 is preferably in the meta or para position of the phenyl-ring relative to the -CH_2-bridge, so that compounds according to the following formulae I.1 and I.2, particularly formula I.2, are preferred:



I.1



I.2

The group R^1 preferably denotes hydrogen, fluorine, chlorine, bromine, C_{1-4}-alkyl, C_{1-4}-alkoxy, methyl substituted by 1 to 3 fluorine atoms, methoxy substituted by 1 to 3 fluorine atoms, C_{3-7}-cycloalkyloxy or C_{3-7}-cycloalkyl-C_{1-3}-alkoxy, while in the C_{5-6}-cycloalkyl groups a methylene group may be replaced by O.

Particularly preferred meanings of R^1 are hydrogen, fluorine, chlorine, methyl, methoxy, ethoxy, cyclopentyloxy, cyclohexyloxy, tetrahydrofuran-3-yloxy and tetrahydropyran-4-yl-oxy; particularly methyl and chlorine.

Preferred meanings of the group R^2 are hydrogen, fluorine, chlorine, methyl, methoxy, ethoxy and methyl substituted by 1 to 3 fluorine atoms.

Particularly preferred meanings of the group R^2 are hydrogen, fluorine, methoxy, ethoxy and methyl, particularly hydrogen.

Preferred meanings of the group R^3 are C_{3-7}-cycloalkyl, tetrahydrofuranyl or tetrahydropyranyl, in particular cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuran-3-yl, tetrahydropyran-3-yl or tetrahydropyran-4-yl, which are substituted with one or two substituents L2; particularly cyclopentyl and cyclohexyl substituted with one substituent L2. In addition preferred meanings of the group R^3 are cyclopentanonyl or cyclohexanonyl which may be substituted with one or two substituents L2.

Examples of particularly preferred meanings of R^3 are 2-hydroxy-cyclopropyl, 2-hydroxy-cyclobutyl, 3-hydroxy-cyclobutyl, 2-hydroxy-cyclopentyl, 3-hydroxy-cyclopentyl, 2-hydroxy-cyclohexyl, 3-hydroxy-cyclohexyl, 4-hydroxy-cyclohexyl, 2-methoxy-cyclopropyl, 2-methoxy-cyclobutyl, 3-methoxy-cyclobutyl, 2-methoxy-cyclopentyl, 3-methoxy-cyclopentyl, 2-methoxy-cyclohexyl, 3-methoxy-cyclohexyl, 4-methoxy-cyclohexyl, 1-hydroxymethyl-cyclopentyl, 1-hydroxymethyl-cyclohexyl, 1-methoxymethyl-cyclopentyl, 1-methoxymethyl-cyclohexyl, 4-hydroxy-tetrahydrofuran-3-yl, 4-methoxy-tetrahydrofuran-3-yl, 3-hydroxy-tetrahydropyran-4-yl and 4-hydroxy-tetrahydropyran-3-yl, which may be substituted with an additional substituent L2. Additional examples of particularly preferred meanings of R^3 are 2-oxo-cyclopentyl and 2-oxo-cyclohexyl, which may be substituted with an additional substituent L2.

In case the group R^3 denotes a tetrahydrofuranyl- or tetrahydropyranyl-ring, bearing a substituent L^2 that equals hydroxy, amino, C_{1-3}-alkyl-amino or di(C_{1-3}-alkyl)-amino, then this substituent L^2 is preferably not attached to the carbon-atom of the tetrahydrofuranyl- or tetrahydropyranyl-ring next to the oxygen atom of the ring.

Preferred meanings of the group L1 independently of one another are selected from among fluorine, chlorine, bromine, cyano, hydroxy, C_{1-3}-alkyl, difluoromethyl, trifluoromethyl, C_{1-3}-alkoxy, difluoromethoxy, trifluoromethoxy and di(C_{1-3}-alkyl)-amino.

Particularly preferred meanings of the group L1 are selected from fluorine, chlorine, hydroxy, trifluoromethyl, ethyl, methoxy, ethoxy and dimethylamino, particularly methyl, ethyl, methoxy, ethoxy and dimethylamino.

Preferred meanings of the group L2 independently of one another are selected from among fluorine, hydroxy, hydroxy-C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkoxy-C_{1-4}-alkyl, C_{1-4}-alkyl, trifluoromethyl, C_{1-4}-alkyl-carbonylamino, hydroxycarbonyl and C_{1-4}-alkoxycarbonyl.

Particularly preferred meanings of the group L2 are selected from fluorine, hydroxy, hydroxy-C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkoxy-C_{1-4}-alkyl, C_{1-4}-alkyl, hydroxycarbonyl and C_{1-4}-alkoxy-carbonyl; particularly hydroxy, hydroxymethyl, methoxymethyl, methoxy, methyl, hydroxycarbonyl, methoxycarbonyl and ethoxycarbonyl.

Preferred meanings of the group R^4 are hydrogen and fluorine, particularly hydrogen.

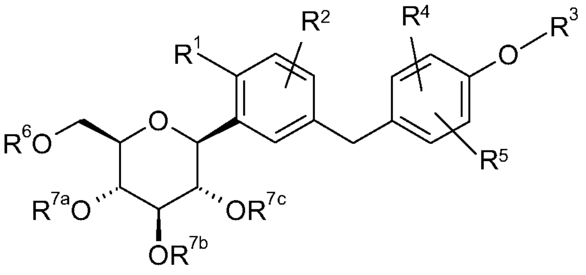
Preferred meanings of the group R^5 are hydrogen and fluorine, particularly hydrogen.

The group R^6 preferably denotes according to the invention hydrogen, (C_{1-8}-alkyl)oxy-carbonyl, C_{1-8}-alkylcarbonyl or benzoyl, particularly hydrogen or (C_{1-6}-alkyl)oxycarbonyl or C_{1-6}-alkylcarbonyl, particularly preferably hydrogen, methylcarbonyl, methoxycarbonyl or ethoxycarbonyl, most particularly preferably hydrogen.

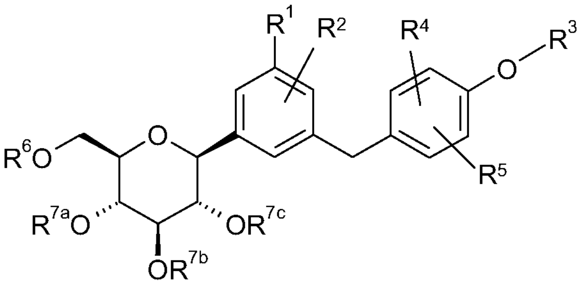
The substituents R^{7a}, R^{7b}, R^{7c} preferably represent independently of one another hydrogen, (C_{1-8}-alkyl)oxycarbonyl, (C_{1-18}-alkyl)carbonyl or benzoyl, particularly hydrogen, (C_{1-6}-alkyl)oxy-carbonyl or (C_{1-8}-alkyl)carbonyl, particularly preferably hydrogen, methoxycarbonyl, ethoxy-carbonyl, methylcarbonyl or ethylcarbonyl. Most particularly preferably R^{7a}, R^{7b} and R^{7c} represent hydrogen.

The compounds of formula I wherein R^6, R^{7a}, R^{7b} and R^{7c} according to the invention have a meaning other than hydrogen, for example C_{1-8}-alkylcarbonyl, are preferably suitable as intermediate products for the synthesis of compounds of formula I wherein R^6, R^{7a}, R^{7b} and R^{7c} denote hydrogen.

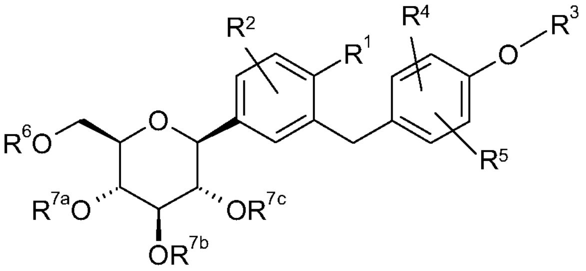
Particularly preferred compounds of general formula I are selected from among formulae I.2a to I.2d, particularly I.2c:



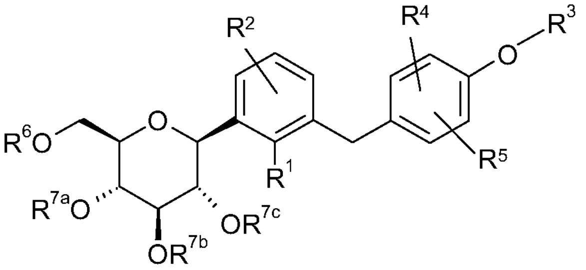
I.2a



I.2b



I.2c



I.2d

while the groups R^1 to R^6 and R^{7a}, R^{7b}, R^{7c} have one of the meanings given previously, particularly have one of the given meanings specified as being preferred; and particularly

R^1 denotes hydrogen, fluorine, chlorine, bromine, C_{1-4}-alkyl, C_{1-4}-alkoxy, methyl substituted by 1 to 3 fluorine atoms, methoxy substituted by 1 to 3 fluorine atoms, C_{3-7}-cycloalkyloxy or C_{3-7}-cycloalkyl-C_{1-3}-alkoxy, while in the C_{5-6}-cycloalkyl groups a methylene group may be replaced by O; R^1 particularly preferably denotes hydrogen, fluorine, chlorine, methyl, methoxy, ethoxy, cyclopentyloxy, cyclohexyloxy, tetrahydrofuran-3-yloxy or tetrahydropyran-4-yl-oxy; and

R^2 denotes hydrogen, fluorine, methoxy, ethoxy or methyl, particularly hydrogen; and

R^3 denotes C_{3-7}-cycloalkyl, tetrahydrofuranyl or tetrahydropyranyl, in particular cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuran-3-yl, tetrahydropyran-3-yl or tetrahydropyran-4-yl, which are substituted with one to four substituents L2; or R^3 denotes cyclopentanonyl or cyclohexanonyl which may be substituted with one or two substituents L2; and

R^4 denotes hydrogen or fluorine, particularly hydrogen; and

R^5 denotes hydrogen or fluorine, particularly hydrogen; and

L1 independently of one another are selected from among fluorine, chlorine, bromine, cyano, hydroxy, C_{1-3}-alkyl, difluoromethyl, trifluoromethyl, C_{1-3}-alkoxy, difluoromethoxy, trifluoromethoxy and di(C_{1-3}-alkyl)-amino; particularly selected from among fluorine, chlorine, hydroxy, methyl, trifluoromethyl, ethyl, methoxy, ethoxy and dimethylamino; most preferably selected from among methyl, ethyl, methoxy, ethoxy and dimethylamino; and

L2 independently of one another are selected from among fluorine, hydroxy, hydroxy-C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkoxy-C_{1-4}-alkyl, C_{1-4}-alkyl, trifluoromethyl, C_{1-4}-alkyl-carbonylamino, hydroxycarbonyl and C_{1-4}-alkyloxycarbonyl; particularly hydroxy, hydroxymethyl, methoxymethyl, methoxy, methyl, hydroxycarbonyl, methoxycarbonyl and ethoxycarbonyl; and

R^6 denotes hydrogen, (C_{1-6}-alkyl)oxycarbonyl, (C_{1-6}-alkyl)carbonyl or benzoyl, particularly hydrogen, methylcarbonyl, methoxycarbonyl or ethoxycarbonyl, most particularly preferably hydrogen; and

R^{7a}, R^{7b}, R^{7c} independently of one another represent hydrogen, (C_{1-6}-alkyl)oxycarbonyl, (C_{1-8}-alkyl)carbonyl or benzoyl, particularly hydrogen, methoxycarbonyl, ethoxycarbonyl, methylcarbonyl or ethylcarbonyl, particularly preferably hydrogen;

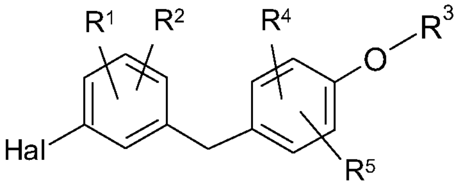
including the tautomers, the stereoisomers, the mixtures thereof and the salts thereof.

According to a variant of the embodiments given hereinbefore, other preferred compounds are those wherein the phenyl group which carries the substituent -O-R^3 has at least one other substituent R^4 and/or R^5 which is different from hydrogen. According to this variant, particularly preferred compounds are those which have a substituent R^4 representing fluorine.

The compounds of general formula I specified in the experimental section that follows, and the derivatives thereof, wherein R^6 has a meaning according to the invention other than hydrogen, particularly wherein R^6 denotes acetyl, ethoxycarbonyl or methoxycarbonyl, including the tautomers, the stereoisomers thereof and the mixtures thereof, are preferred according to another variant of this invention.

In the processes according to the invention the groups R^1, R^2, R^3, R^4 and R^5 preferably have the meanings specified hereinbefore as being preferred. Moreover R' preferably denotes H, C_{1-3}-alkyl or benzyl, particularly H, ethyl or methyl. The groups R^{8a}, R^{8b}, R^{8c} and R^{8d} independently of one another preferably denote H, C_{1-4}-alkylcarbonyl or benzyl, particularly H, methylcarbonyl, ethylcarbonyl or benzyl.

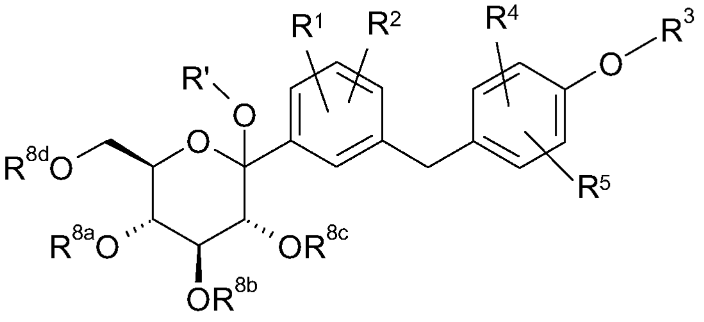
The invention also relates to compounds of general formula IV, particularly of general formula IV'



IV'

wherein Hal denotes chlorine, bromine or iodine and the groups R^1, R^2, R^3, R^4 and R^5 are as hereinbefore defined, as intermediate products or starting materials in the synthesis of the compounds according to the invention. Particularly preferably, the groups R^1, R^2, R^3, R^4 and R^5 have the meanings given following formulae I.2a to I.2d.

The invention also relates to compounds of general formula II, particularly of general formula II'



II'

wherein R', R^{8a}, R^{8b}, R^{8c}, R^{8d}, R^1, R^2, R^3, R^4 and R^5 are defined as hereinbefore and hereinafter; particularly wherein R' denotes H, C_{1-3}-alkyl or benzyl, particularly H, ethyl or methyl; and the groups R^{8a}, R^{8b}, R^{8c} and R^{8d} independently of one another represent H, C_{1-4}-alkylcarbonyl or benzyl, particularly H, methylcarbonyl, ethylcarbonyl or benzyl and the groups R^1, R^2, R^3, R^4 and R^5 are as hereinbefore defined. These compounds may serve as intermediate products or starting materials in the synthesis of the compounds according to the invention. Particularly preferably the groups R^1, R^2, R^3, R^4 and R^5 have the meanings given following formulae I.2a to I.2d.

Some terms used above and hereinafter to describe the compounds according to the invention will now be defined more closely.

The term halogen denotes an atom selected from the group consisting of F, Cl, Br and I, particularly F, Cl and Br.

The term C_{1-n}-alkyl, wherein n may have a value of 1 to 18, denotes a saturated, branched or unbranched hydrocarbon group with 1 to n C atoms. Examples of such groups include methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, tert-pentyl, n-hexyl, iso-hexyl, etc.

The term C_{2-n}-alkynyl, wherein n has a value of 3 to 6, denotes a branched or unbranched hydrocarbon group with 2 to n C atoms and a C≡C triple bond. Examples of such groups include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl etc. Unless otherwise stated alkynyl groups are connected to the remainder of the molecule via the C atom in position 1. Therefore terms such as 1-propynyl, 2-propynyl, 1-butynyl, etc. are equivalent to the terms 1-propyn-1-yl, 2-propyn-1-yl, 1-butyn-1-yl, etc.. This also applies analogously to C_{2-n}-alkenyl groups.

The term C_{1-n}-alkoxy denotes a C_{1-n}-alkyl-O group, wherein C_{1-n}-alkyl is as hereinbefore defined. Examples of such groups include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, n-pentoxy, iso-pentoxy, neo-pentoxy, tert-pentoxy, n-hexoxy, iso-hexoxy etc.

The term C_{1-n}-alkylcarbonyl denotes a C_{1-n}-alkyl-C(=O) group, wherein C_{1-n}-alkyl is as hereinbefore defined. Examples of such groups include methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, iso-propylcarbonyl, n-butylcarbonyl, iso-butylcarbonyl, sec-butylcarbonyl, tert-butylcarbonyl, n-pentylcarbonyl, iso-pentylcarbonyl, neo-pentylcarbonyl, tert-pentylcarbonyl, n-hexylcarbonyl, iso-hexylcarbonyl, etc.

The term C_{3-n}-cycloalkyl denotes a saturated mono-, bi-, tri- or spirocarbocyclic group with 3 to n C atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, decalinyl, bicyclo[3.2.1.]octyl, spiro[4.5]decyl, norpinyl, norbonyl, norcaryl, adamantyl, etc. Preferably the term C_{3-7}-cycloalkyl denotes saturated monocyclic groups.

The term C_{5-n}-cycloalkenyl denotes a C_{5-n}-cycloalkyl group which is as hereinbefore defined and additionally has at least one unsaturated C=C double bond.

The term C_{3-n}-cycloalkylcarbonyl denotes a C_{3-n}-cycloalkyl-C(=O) group wherein C_{3-n}-cycloalkyl is as hereinbefore defined.

The term tri-(C_{1-4}-alkyl)silyl comprises silyl groups which have identical or two or three different alkyl groups.

The term di-(C_{1-3}-alkyl)amino comprises amino groups which have identical or two different alkyl groups.

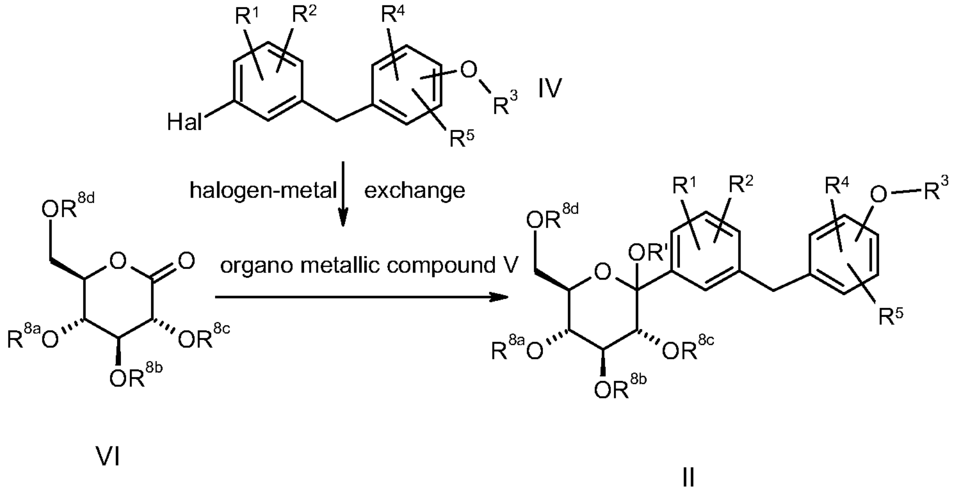
The term aryl preferably denotes naphthyl or phenyl, more preferably phenyl.

The nomenclature in structural formulas used above and hereinafter, in which a bond of a substituent of a cyclic group, as e.g. a phenyl ring, is shown towards the centre of the cyclic group, denotes, unless otherwise stated, that this substituent may be bound to any free position of the cyclic group bearing an H atom.

The compounds according to the invention may be obtained using methods of synthesis known in principle. Preferably the compounds are obtained by the following methods according to the invention which are described in more detail hereinafter.

The glucose derivatives of formula II according to the invention may be synthesised from D-gluconolactone or a derivative thereof by adding the desired benzylbenzene compound in the form of an organometallic compound (Scheme 1).

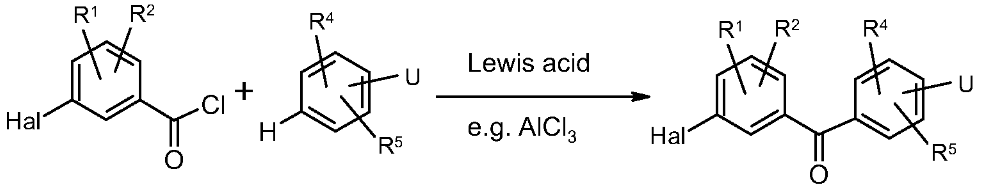
Scheme 1: Addition of an Organometal Compound to a Gluconolactone



The reaction according to Scheme 1 is preferably carried out starting from a halogenated benzylbenzene compound of general formula IV, wherein Hal denotes chlorine, bromine, or iodine. Starting from the haloaromatic compound IV the corresponding organometallic compound (V) may be prepared either by means of a so-called halogen-metal exchange reaction or by inserting the metal into the carbon-halogen bond. The halogen-metal exchange with bromine or iodine-substituted aromatic groups may be carried out for example with an organolithium compound such as e.g. n-, sec- or tert-butyllithium and thereby yields the corresponding lithiated aromatic group. The analogous magnesium compound may also be generated by a halogen-metal exchange with a suitable Grignard reagent such as e.g. isopropylmagnesium bromide or diisopropylmagnesium. The reactions are preferably carried out between 0 and -100°C, particularly preferably between -10 and -80 °C, in an inert solvent or mixtures thereof, such as for example diethyl ether, tetrahydrofuran, toluene, hexane, or methylene chloride. The magnesium or lithium compounds thus obtained may optionally be transmetallated with metal salts such as e.g. cerium trichloride, to form alternative organometal compounds (V) suitable for addition. Alternatively, the organometallic compound (V) may also be prepared by inserting a metal into the carbon-halogen bond of the haloaromatic compound IV. Metals such as e.g. lithium or magnesium are suitable for this. The addition of the organometallic compound V to gluconolactone or derivatives thereof of formula VI is preferably carried out at temperatures between 0 and -100°C, particularly preferably at -30 to -80°C, in an inert solvent or mixtures thereof, to obtain the compound of formula II. The lithiation and/or coupling reaction may also be carried out in microreactors and/or micromixers in order to avoid low temperatures; for example analogously to the processes described in WO 2004/076470. Suitable solvents for the addition of the metallated phenyl group to the appropriately protected gluconolactone are e.g. diethyl ether, toluene, methylene chloride, hexane, tetrahydrofuran or mixtures thereof. The addition reactions may be carried out without any further adjuvants or in the case of sluggishly reacting coupling partners in the presence of Lewis acids such as e.g. BF_3*OEt_2 or Me_3SiCl (see M. Schlosser, Organometallics in Synthesis, John Wiley & Sons, Chichester/New York/Brisbane/Toronto/Singapore, 1994). Preferred definitions of the groups R^{8a}, R^{8b}, R^{8c} and R^{8d} are benzyl, substituted benzyl, trialkylsilyl, particularly preferably trimethylsilyl, triisopropylsilyl, 4-methoxybenzyl and benzyl. If two adjacent groups of the group consisting of R^{8a}, R^{8b}, R^{8c} and R^{8d} are linked together, these two groups are preferably part of a benzylideneacetal, 4-methoxybenzylideneacetal, isopropylketal, diisopropylsilylidene ketal or constitute a 2,3-dimethoxy-butylene group which is linked via the 2 and 3 positions of the butane with the adjacent oxygen atoms of the pyranose ring. The group R' preferably denotes hydrogen or C_{1-4}-alkyl, particularly preferably hydrogen, methyl or ethyl. The group R' is inserted after the addition of the organometallic compound V or a derivative thereof to the gluconolactone VI. For this purpose the reaction solution is treated with an alcohol such as e.g. methanol or ethanol or water in the presence of an acid such as e.g. methanesulfonic acid, toluenesulfonic acid, sulfuric acid, or hydrochloric acid.

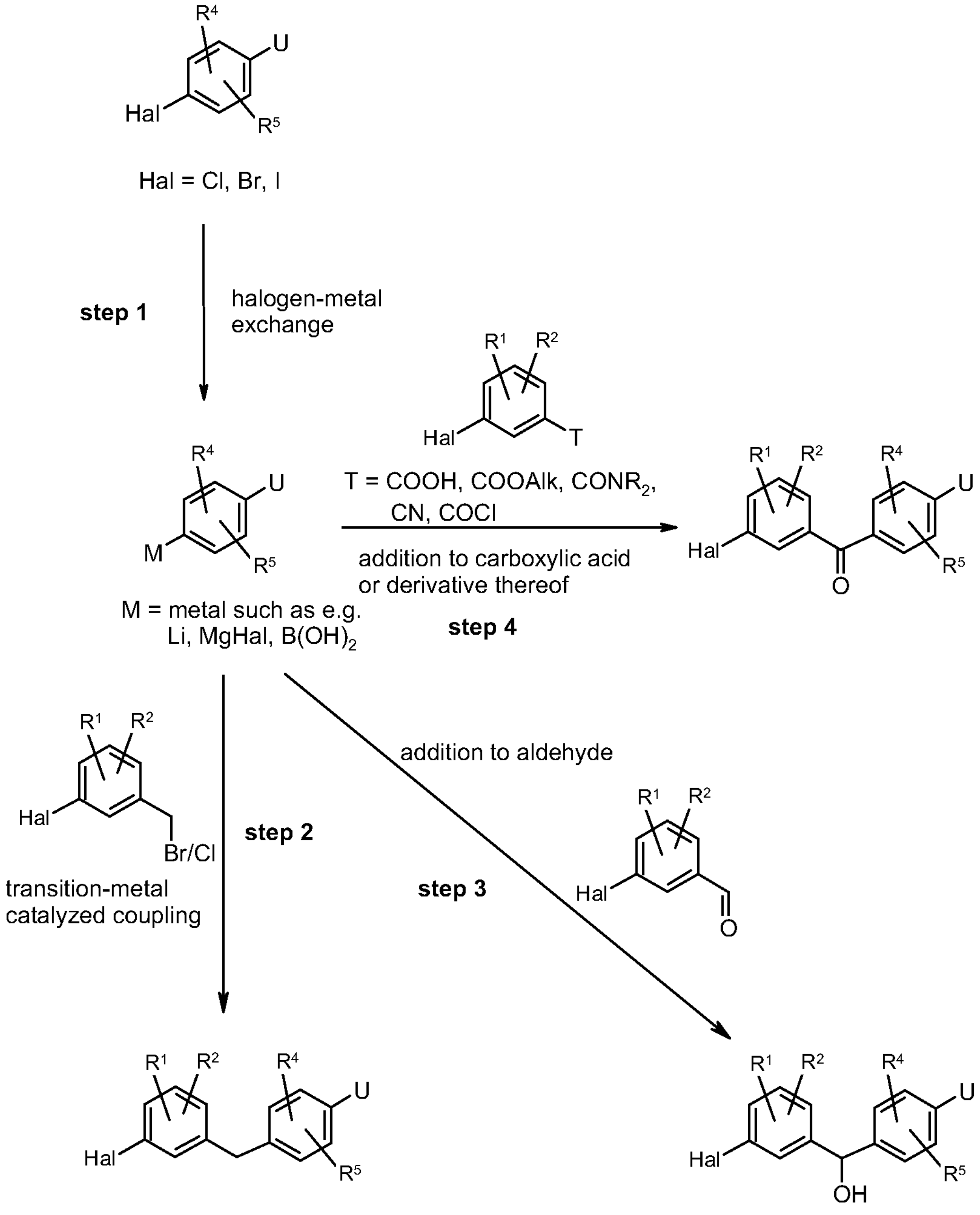
The synthesis of haloaromatic compound of formula IV may be carried out using standard transformations in organic chemistry or at least methods known from the specialist literature in organic synthesis (see inter alia J. March, Advanced Organic Reactions, Reactions, Mechanisms, and Structure, 4th Edition, John Wiley & Sons, Chichester/New York/Brisbane/Toronto/Singapore, 1992 and literature cited therein). More specifically, the use of transition metals and organo metal compounds for the synthesis of aromatic compounds has been detailed in different monographs (see e.g. L. Brandsma, S.F. Vasilevsky, H.D. Verkruijsse, Application of Transition Metal Catalysts in Organic Synthesis, Springer-Verlag, Berlin/Heidelberg, 1998; M. Schlosser, Organometallics in Synthesis, John Wiley & Sons, Chichester/New York/Brisbane/Toronto/Singapore, 1994; P.J. Stang, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, **1997** and references quoted therein). The synthesis strategies described in the following provide a demonstration of this, by way of example.

Scheme 2: Synthesis of Diarylketones



Scheme 2 shows the preparation of a precursor compound that may serve for the synthesis of the haloaromatic compounds of formula IV and IVa, respectively, starting from a benzoylchloride and a second aromatic group applying Friedel-Crafts acylation conditions or variations thereof. The second aromatic compound bears a substituent U selected from halogen such as fluorine, chlorine, bromine and iodine, O-C_{1-4}-alkyl, or O-R^3 wherein incompatible residues may be protected or masked. This classic reaction has a wide substrate scope and is commonly carried out in the presence of a catalyst which is used in catalytic or stoichiometric amounts, such as e.g. $AlCl_3$, $FeCl_3$, iodine, iron, $ZnCl_2$, sulfuric acid, or trifluoromethanesulfonic acid. Instead of the benzoyl chloride the corresponding carboxylic acid, anhydride, ester or benzonitrile may be used as well. The reactions are preferentially carried out in chlorinated hydrocarbons such as e.g. dichloromethane and 1,2-dichloroethane at temperatures ranging from -30 to 120°C, preferably at 30 to 100°C. However, solvent-free reactions or reactions in a microwave oven are also possible.

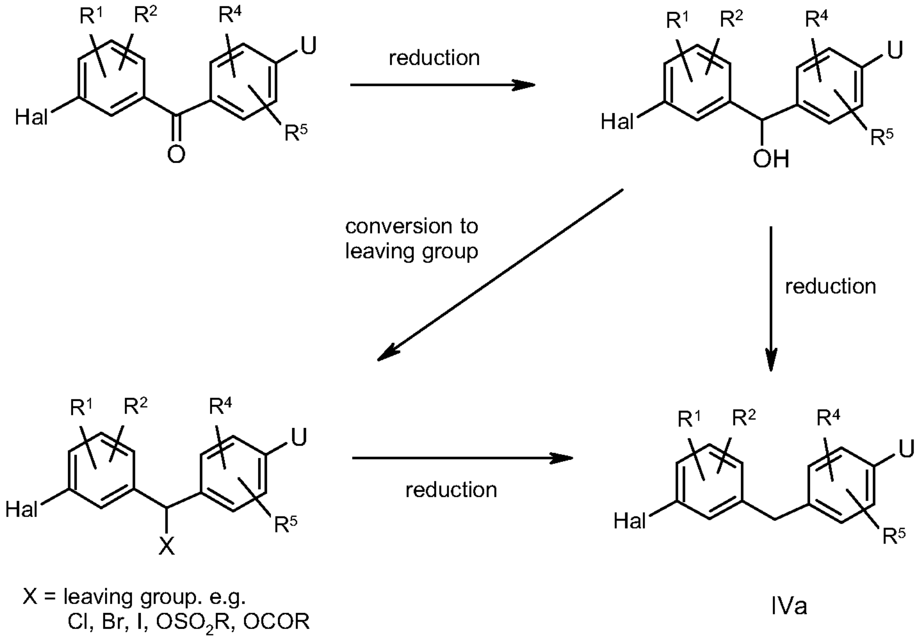
Scheme 3: Synthesis of Diarylmethanes and Possible Precursor Compounds thereof



IVa

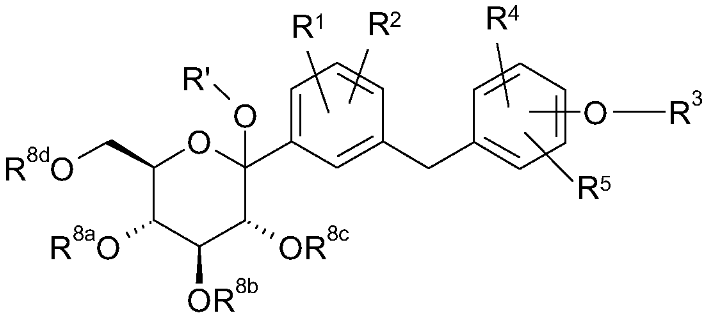
In Scheme 3 the term "Alk" denotes C_{1-3}-alkyl and each substituent R is independently selected from each other from the group consisting of H, C_{1-3}-alkyl and C_{1-3}-alkoxy, while the remaining groups R^1 to R^5 are defined as hereinbefore. The Scheme 3 delineates the synthesis of diarylmethanes and possible precursor compounds thereof starting from a metalated phenyl group that bears a residue U that is selected from a group consisting of an fluorine, chlorine, bromine, iodine, pseudohalogen group such as e.g. trifluoromethanesulfonate, O-C_{1-4}-alkyl, or O-R^3 wherein incompatible groups may be protected or masked. Lithium or magnesium substituted aromatic compounds may be synthesized from chlorinated, brominated, or iodinated aromats by a halogen-metal exchange reaction with e.g. butyllithium, isopropylmagnesiumhalogenide, or diispropylmagnesium or by insertion of the elemental metal into the halogen-carbon bond. The corresponding boron substituted compound such as e.g. boronic acid, boronic acid ester, or dialkylarylborane, is accessible from these metallated phenyl groups by reaction with a boron electrophile such as e.g. boronic acid ester or a derivative thereof. In addition, the borylated aromatic compound may also be prepared from the corresponding halogenated or pseudohalogenated precursor and a diboron or borane compound through a transition metal, e.g. palladium, catalyzed reaction (see e.g. *Tetrahedron Lett.* **2003**, p. 4895-4898 and references quoted therein). The lithium or magnesium substituted phenyl compounds add to benzaldehydes (step 3) and benzoic acids or derivatives thereof (step 4) such as benzoic acid esters, benzamides such as e.g. of the Weinreb type, benzonitriles, or benzoyl chlorides. These reactions may principally be conducted without an additional transition metal catalyst or transmetalation to another metal such as e.g. cerium or zinc; sometimes the use of one of the latter alternatives is advantageous. Aryl boronic acids can be added to benzaldehydes by means of a rhodium catalyst furnishing the respective diarylmethanol (see e.g. *Adv. Synth. Catal.* **2001**, p. 343-350 and references quoted therein). Moreover, arylboronic acids, esters thereof, dialkylarylboranes, or aryltrifluoroborates may be coupled with benzoyl chlorides mediated by a transition metal such as e.g. palladium, a complex or a salt thereof delivering diarylketones. Metallated phenyl groups can be reacted with benzyl electrophiles such as benzyl chlorides, bromides, or iodides affording diarylmethanes. Lithium or magnesium derivatized phenyl compounds are reacted favorably but not always necessarily in the presence of a transition metal as e.g. copper, iron, or palladium (see e.g. *Org. Lett.* **2001**, *3*, 2871-2874 and references quoted therein). Transmetallation from lithium or magnesium to e.g. boron, tin, silicon, or zinc furnishes e.g. the corresponding aromatic boronic acids, stannanes, silanes or zinc compounds, respectively, that may undergo coupling with benzyl electrophiles, e.g. benzyl halogenides, phosphates, sulfonates, or carboxylic esters. The reaction is conducted in the presence of a transition metal, e.g. palladium, nickel, rhodium, copper, or iron (see *Tetrahedron Lett.* **2004**, p. 8225-8228 and references cited therein).

Scheme 4: Reduction of Diarylketones and Diarylmethanols to Diarylmethanes



In Scheme 4 the substituent R denotes C_{1-3}-alkyl or aryl while the remaining substituents R^1 to R^5 are defined as hereinbefore. Starting from the diarylketone or diarylmethanol the diarylmethane is accessible in one or two reaction steps. U is selected from a group comprising fluorine, chlorine, bromine, iodine, pseudohalogen groups such as e.g. trifluoromethanesulfonate, O-C_{1-4}-alkyl, or O-R^3 wherein incompatible groups may be protected or masked. The diarylketone may be reduced to the diarylmethane in two steps via the corresponding diphenylmethanol or in one step. In the two-step variant the ketone is reduced with a reducing agent such as for example a metal hydride such as e.g. $NaBH_4$, $LiAlH_4$ or iBu_2AlH to form the alcohol. The resulting alcohol can be converted in the presence of a Lewis acid such as for example BF_3*OEt_2, trifluoroacetic acid, $InCl_3$ or $AlCl_3$ with a reducing agent such as e.g. Et_3SiH, $NaBH_4$, or Ph_2SiClH to the desired diphenylmethane. The one-step process starting from the ketone to obtain the diphenylmethane may be carried out e.g. with a silane such as e.g. Et_3SiH, a borohydride such as e.g. $NaBH_4$ or an aluminum hydride such as $LiAlH_4$ in the presence of a Lewis acid such as for example BF_3*OEt_2, tris(pentafluorophenyl)borane, trifluoroacetic acid, aluminum chloride or $InCl_3$. The reactions are preferably carried out in solvents such as e.g. halogenated hydrocarbons such as dichloromethane, toluene, or acetonitrile at temperatures of -30 to 150°C, preferably at 20 to 100°C. Reductions with hydrogen in the presence of a transition metal catalyst such as e.g. Pd on charcoal are another possible method of synthesis. Reductions according to Wolff-Kishner or variants thereof are also possible. The ketone is first of all converted with hydrazine or a derivative thereof, such as e.g. 1,2-bis(tert-butyldimethylsilyl)hydrazine, into the hydrazone which breaks down under strongly basic reaction conditions and heating to form the diphenylmethane and nitrogen. The reaction may be carried out in one reaction step or after isolation of the hydrazone or a derivative thereof in two separate reaction steps. Suitable bases include e.g. KOH, NaOH or KOtBu in solvents such as e.g. ethyleneglycol, toluene, DMSO, 2-(2-butoxyethoxy)ethanol or t-butanol; solvent-free reactions are also possible. The reactions may be carried out at temperatures between 20 to 250°C, preferably between 80 to 200°C. An alternative to the basic conditions of the Wolff-Kishner reduction is the Clemmensen reduction which takes place under acidic conditions, which may also be used here. The alcohol function in diarylmethanol may also first be transformed into a leaving group such as e.g. chloride, bromide, iodide, acetate, phosphate, or sulfate; the subsequent reduction step to form the diarylmethane is widely described in the organic chemistry literature. Reduction of the carbonyl group or a benzylic leaving group such as e.g. hydroxyl to form the corresponding diarylmethane may also be conducted with hydrogen as the reducing agent in the presence of a transition metal catalyst such as e.g. palladium, nickel, rhodium or platinum.

In order to prepare compounds of general formula I, in process a) according to the invention, a compound of general formula II



II

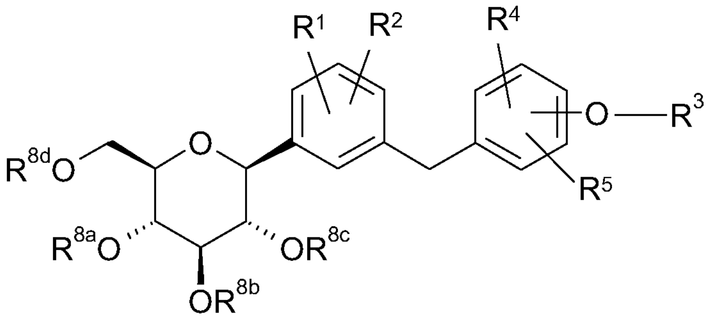
wherein R', R^1 to R^5 are as hereinbefore defined and

R^{8a}, R^{8b}, R^{8c}, R^{8d} are as hereinbefore defined and independently of one another represent for example acetyl, pivaloyl, benzoyl, tert-butoxycarbonyl, benzyloxycarbonyl, trialkylsilyl, benzyl or substituted benzyl or in each case two adjacent groups R^{8a}, R^{8b}, R^{8c}, R^{8d} are combined a benzylideneacetal, diisopropylsilylideneketal or isopropylideneketal or a 2,3-dimethoxy-butylene group which is linked via position 2 and 3 of the butylene group to the oxygen atoms of the pyranose ring and forms with them a substituted dioxane,

which may be obtained as hereinbefore described, is reacted with a reducing agent in the presence of a Lewis or Brønsted acid.

Suitable reducing agents for the reaction include for example silanes, such as triethyl-, tripropyl-, triisopropyl- or diphenylsilane, sodium borohydride, sodium cyanoborohydride, zinc borohydride, boranes, lithium aluminium hydride, diisobutylaluminium hydride or samarium iodide. The reductions are carried out without or in the presence of a suitable Brønsted acid, such as e.g. hydrochloric acid, toluenesulphonic acid, trifluoroacetic acid or acetic acid, or Lewis acid, such as e.g. boron trifluoride etherate, trimethylsilyltriflate, titaniium tetrachloride, tin tetrachloride, scandium triflate or zinc iodide. Depending on the reducing agent and the acid used the reaction may be carried out in a solvent, such as for example methylene chloride, chloroform, acetonitrile, toluene, hexane, diethyl ether, tetrahydrofuran, dioxane, ethanol, water or mixtures thereof at temperatures between -60°C and 120°C. One particularly suitable combination of reagents consists for example of triethylsilane and boron trifluoride etherate, which is conveniently used in acetonitrile or dichloromethane at temperatures of -60°C and 60°C. Moreover, hydrogen may be used in the presence of a transition metal catalyst, such as e.g. palladium on charcoal or Raney nickel, in solvents such as tetrahydrofuran, ethyl acetate, methanol, ethanol, water or acetic acid, for the transformation described.

Alternatively, in order to prepare compounds of general formula I according to process b) according to the invention, in a compound of general formula III



III

wherein R^1 to R^5 are as hereinbefore defined and R^{8a} to R^{8d} denote one of the protective groups defined hereinbefore, such as e.g. an acyl, arylmethyl, acetal, ketal or silyl group, and which may be obtained for example by reduction from the compound of formula II as hereinbefore described, the protective groups are cleaved.

Any acyl protecting group used is cleaved for example hydrolytically in an aqueous solvent, e.g. in water, isopropanol/water, acetic acid/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulfuric acid or in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide or aprotically, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 120°C, preferably at temperatures between 10 and 100°C. A trifluoroacetyl group is preferably cleaved by treating with an acid such as hydrochloric acid, optionally in the presence of a solvent such as acetic acid at temperatures between 50 and 120°C or by treating with sodium hydroxide solution optionally in the presence of a solvent such as tetrahydrofuran or methanol at temperatures between 0 and 50°C.

Any acetal or ketal protecting group used is cleaved for example hydrolytically in an aqueous solvent, e.g. in water, isopropanol/water, acetic acid/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulfuric acid or aprotically, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 120°C, preferably at temperatures between 10 and 100°C.

A trimethylsilyl group is cleaved for example in water, an aqueous solvent mixture or a lower alcohol such as methanol or ethanol in the presence of a base such as lithium hydroxide, sodium hydroxide, potassium carbonate or sodium methoxide.
In aqueous or alcoholic solvents, acids such as e.g. hydrochloric acid, trifluoroacetic acid or acetic acid are also suitable. For cleaving in organic solvents, such as for example diethyl ether, tetrahydrofuran or dichloromethane, it is also suitable to use fluoride reagents, such as e.g. tetrabutylammonium fluoride.

A benzyl, methoxybenzyl or benzyloxycarbonyl group is advantageously cleaved hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 100°C, but preferably at ambient temperatures between 20 and 60°C, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar. A 2,4-dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisole.

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid or by treating with iodotrimethylsilane optionally using a solvent such as methylene chloride, dioxane, methanol or diethylether.

In the reactions described hereinbefore, any reactive groups present such as ethynyl, hydroxy, amino, alkylamino or imino groups may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction.

For example, a protecting group for an ethynyl group may be trialkylsilyl such as e.g. trimethylsilyl and triisopropylsilyl or dialkyl-hydroxymethyl such as e.g. 2-hydroxyisoprop-2-yl.

For example, a protecting group for a hydroxy group may be a trimethylsilyl, acetyl, trityl, benzyl or tetrahydropyranyl group.

Protecting groups for an amino, alkylamino or imino group may be, for example, a formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group.

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as mentioned hereinbefore. Thus, for example, *cis/trans* mixtures may be resolved into their *cis* and *trans* isomers, and compounds with at least one optically active carbon atom may be separated into their enantiomers.

Thus, for example, the *cis/trans* mixtures may be resolved by chromatography into the *cis* and *trans* isomers thereof, the compounds of general formula I obtained which occur as racemates may be separated by methods known *per se* (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known per se, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be for example (+) or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)-or (-)-menthyloxycarbonyl.

Furthermore, the compounds of formula I may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

Moreover, the compounds obtained may be converted into mixtures, for example 1:1 or 1:2 mixtures with amino acids, particularly with alpha-amino acids such as proline or phenylalanine, which may have particularly favourable properties such as a high crystallinity.

The compounds according to the invention are advantageously also obtainable using the methods described in the examples that follow, which may also be combined for this purpose with methods known to the skilled man from the literature, for example the methods described in WO 98/31697, WO 01/27128, WO 02/083066, WO 03/099836 and WO 2004/063209.

As already mentioned, the compounds of general formula I according to the invention and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly an inhibitory effect on the sodium-dependent glucose cotransporter SGLT, preferably SGLT2.

The biological properties of the new compounds may be investigated as follows:

The ability of the substances to inhibit the SGLT-2 activity may be demonstrated in a test set-up in which a CHO-K1 cell line (ATCC No. CCL 61) or alternatively an HEK293 cell line (ATCC No. CRL-1573), which is stably transfected with an expression vector pZeoSV (Invitrogen, EMBL accession number L36849) , which contains the cDNA for the coding sequence of the human sodium glucose cotransporter 2 (Genbank Acc. No.NM_003041) (CHO-hSGLT2 or HEK-hSGLT2). These cell lines transport ^{14}C-labelled alpha-methyl-glucopyranoside (^{14}C-AMG, Amersham) into the interior of the cell in sodium-dependent manner.

The SGLT-2 assay is carried out as follows:

CHO-hSGLT2 cells are cultivated in Ham´s F12 Medium (BioWhittaker) with 10% foetal calf serum and 250 µg/ml zeocin (Invitrogen), and HEK293-hSGLT2 cells are cultivated in DMEM medium with 10% foetal calf serum and 250 µg/ml zeocin (Invitrogen). The cells are detached from the culture flasks by washing twice with PBS and subsequently treating with trypsin/EDTA. After the addition of cell culture medium the cells are centrifuged, resuspended in culture medium and counted in a Casy cell counter. Then 40,000 cells per well are seeded into a white, 96-well plate coated with poly-D-lysine and incubated overnight at 37°C, 5% CO_2. The cells are washed twice with 250 µl of assay buffer (Hanks Balanced Salt Solution, 137 mM NaCl, 5.4 mM KCl, 2.8 mM $CaCl_2$, 1.2 mM $MgSO_4$ and 10 mM HEPES (pH7.4), 50 µg/ml of gentamycin). 250 µl of assay buffer and 5 µl of test compound are then added to each well and the plate is incubated for a further 15 minutes in the incubator. 5 µl of 10% DMSO are used as the negative control. The reaction is started by adding 5 µl of ^{14}C-AMG (0.05 µCi) to each well. After 2 hours' incubation at 37°C, 5% CO_2, the cells are washed again with 250 µl of PBS (20°C) and then lysed by the addition of 25 µl of 0.1 N NaOH (5 min. at 37°C). 200 µl of MicroScint20 (Packard) are added to each well and incubation is continued for a further 20 min at 37°C. After this incubation the radioactivity of the ^{14}C-AMG absorbed is measured in a Topcount (Packard) using a ^{14}C scintillation program.

To determine the selectivity with respect to human SGLT1 an analogous test is set up in which the cDNA for hSGLT1 (Genbank Acc. No. NM000343) instead of hSGLT2 cDNA is expressed in CHO-K1 or HEK293 cells.

The compounds of general formula I according to the invention may for example have EC50 values below 1000 nM, particularly below 200 nM, most preferably below 50 nM.

In view of their ability to inhibit the SGLT activity, the compounds of general formula I according to the invention and the corresponding pharmaceutically acceptable salts thereof are theoretically suitable for the treatment and/or preventative treatment of all those conditions or diseases which may be affected by the inhibition of the SGLT activity, particularly the SGLT-2 activity. Therefore, compounds according to the invention are particularly suitable for the prevention or treatment of diseases, particularly metabolic disorders, or conditions such as type 1 and type 2 diabetes mellitus, complications of diabetes (such as e.g. retinopathy, nephropathy or neuropathies, diabetic foot, ulcers, macroangiopathies), metabolic acidosis or ketosis, reactive hypoglycaemia, hyperinsulinaemia, glucose metabolic disorder, insulin resistance, metabolic syndrome, dyslipidaemias of different origins, atherosclerosis and related diseases, obesity, high blood pressure, chronic heart failure, edema and hyperuricaemia. These substances are also suitable for preventing beta-cell degeneration such as e.g. apoptosis or necrosis of pancreatic beta cells. The substances are also suitable for improving or restoring the functionality of pancreatic cells, and also of increasing the number and size of pancreatic beta cells. The compounds according to the invention may also be used as diuretics or antihypertensives and are suitable for the prevention and treatment of acute renal failure.

In particular, the compounds according to the invention, including the physiologically acceptable salts thereof, are suitable for the prevention or treatment of diabetes, particularly type 1 and type 2 diabetes mellitus, and/or diabetic complications.

The dosage required to achieve the corresponding activity for treatment or prevention usually depends on the compound which is to be administered, the patient, the nature and gravity of the illness or condition and the method and frequency of administration and is for the patient's doctor to decide. Expediently, the dosage may be from 1 to 100 mg, preferably 1 to 30 mg, by intravenous route, and 1 to 1000 mg, preferably 1 to 100 mg, by oral route, in each case administered 1 to 4 times a day. For this purpose, the compounds of formula I prepared according to the invention may be formulated, optionally together with other active substances, together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, to produce conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

The compounds according to the invention may also be used in conjunction with other active substances, particularly for the treatment and/or prevention of the diseases and conditions mentioned above. Other active substances which are suitable for such combinations include for example those which potentiate the therapeutic effect of an SGLT antagonist according to the invention with respect to one of the indications mentioned and/or which allow the dosage of an SGLT antagonist according to the invention to be reduced. Therapeutic agents which are suitable for such a combination include, for example, antidiabetic agents such as metformin, sulphonylureas (e.g. glibenclamide, tolbutamide, glimepiride), nateglinide, repaglinide, thiazolidinediones (e.g. rosiglitazone, pioglitazone), PPAR-gamma-agonists (e.g. GI 262570) and antagonists, PPAR-gamma/alpha modulators (e.g. KRP 297), alpha-glucosidase inhibitors (e.g. acarbose, voglibose), DPPIV inhibitors (e.g. LAF237, MK-431), alpha2-antagonists, insulin and insulin analogues, GLP-1 and GLP-1 analogues (e.g. exendin-4) or amylin. The list also includes inhibitors of protein tyrosinephosphatase 1, substances that affect deregulated glucose production in the liver, such as e.g. inhibitors of glucose-6-phosphatase, or fructose-1,6-bisphosphatase, glycogen phosphorylase, glucagon receptor antagonists and inhibitors of phosphoenol pyruvate carboxykinase, glycogen synthase kinase or pyruvate dehydrokinase, lipid lowering agents such as for example HMG-CoA-reductase inhibitors (e.g. simvastatin, atorvastatin), fibrates (e.g. bezafibrate, fenofibrate), nicotinic acid and the derivatives thereof, PPAR-alpha agonists, PPAR-delta agonists, ACAT inhibitors (e.g. avasimibe) or cholesterol absorption inhibitors such as, for example, ezetimibe, bile acid-binding substances such as, for example, cholestyramine, inhibitors of ileac bile acid transport, HDL-raising compounds such as CETP inhibitors or ABC1 regulators or active substances for treating obesity, such as sibutramine or tetrahydrolipostatin, dexfenfluramine, axokine, antagonists of the cannabinoid1 receptor, MCH-1 receptor antagonists, MC4 receptor agonists, NPY5 or NPY2 antagonists or ß3-agonists such as SB-418790 or AD-9677 and agonists of the 5HT2c receptor.

Moreover, combinations with drugs for influencing high blood pressure, chronic heart failure or atherosclerosis such as e.g. A-II antagonists or ACE inhibitors, ECE inhibitors, diuretics, ß-blockers, Ca-antagonists, centrally acting antihypertensives, antagonists of the alpha-2-adrenergic receptor, inhibitors of neutral endopeptidase, thrombocyte aggregation inhibitors and others or combinations thereof are suitable. Examples of angiotensin II receptor antagonists are candesartan cilexetil, potassium losartan, eprosartan mesylate, valsartan, telmisartan, irbesartan, EXP-3174, L-158809, EXP-3312, olmesartan, medoxomil, tasosartan, KT-3-671, GA-0113, RU-64276, EMD-90423, BR-9701, etc. Angiotensin II receptor antagonists are preferably used for the treatment or prevention of high blood pressure and complications of diabetes, often combined with a diuretic such as hydrochlorothiazide.

A combination with uric acid synthesis inhibitors or uricosurics is suitable for the treatment or prevention of gout.

A combination with GABA-receptor antagonists, Na-channel blockers, topiramat, protein-kinase C inhibitors, advanced glycation end product inhibitors or aldose reductase inhibitors may be used for the treatment or prevention of complications of diabetes.

The dosage for the combination partners mentioned above is usefully 1/5 of the lowest dose normally recommended up to 1/1 of the normally recommended dose.

Therefore, in another aspect, this invention relates to the use of a compound according to the invention or a physiologically acceptable salt of such a compound combined with at least one of the active substances described above as a combination partner, for preparing a pharmaceutical composition which is suitable for the treatment or prevention of diseases or conditions which can be affected by inhibiting the sodium-dependent glucose cotransporter SGLT. These are preferably metabolic diseases, particularly one of the diseases or conditions listed above, most particularly diabetes or diabetic complications.

The use of the compound according to the invention, or a physiologically acceptable salt thereof, in combination with another active substance may take place simultaneously or at staggered times, but particularly within a short space of time. If they are administered simultaneously, the two active substances are given to the patient together; while if they are used at staggered times the two active substances are given to the patient within a period of less than or equal to 12 hours, but particularly less than or equal to 6 hours.

Consequently, in another aspect, this invention relates to a pharmaceutical composition which comprises a compound according to the invention or a physiologically acceptable salt of such a compound and at least one of the active substances described above as combination partners, optionally together with one or more inert carriers and/or diluents.

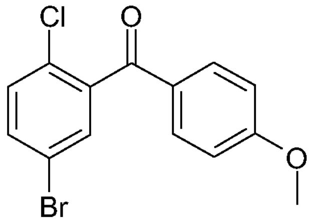
Thus, for example, a pharmaceutical composition according to the invention comprises a combination of a compound of formula I according to the invention or a physiologically acceptable salt of such a compound and at least one angiotensin II receptor antagonist optionally together with one or more inert carriers and/or diluents.

The compound according to the invention, or a physiologically acceptable salt thereof, and the additional active substance to be combined therewith may both be present together in one formulation, for example a tablet or capsule, or separately in two identical or different formulations, for example as a so-called kit-of-parts.

In the foregoing and following text, H atoms of hydroxyl groups are not explicitly shown in every case in structural formulae. The term "ambient temperature" means temperatures in the range from 20 to 25°C. The Examples that follow are intended to illustrate the present invention without restricting it:

Preparation of the starting compounds:

Example I



(5-Bromo-2-chloro-phenyl)-(4-methoxy-phenyl)-methanone

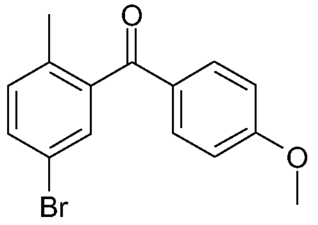
38.3 mL oxalyl chloride and 0.8 mL of dimethylformamide are added to a mixture of 100 g of 5-bromo-2-chloro-benzoic acid in 500 mL dichloromethane. The reaction mixture is stirred for 14 h, then filtered and separated from all volatile constituents in the rotary evaporator. The residue is dissolved in 150 mL dichloromethane, the solution is cooled to -5 °C, and 46.5 g of anisole are added. Then 51.5 g of aluminum trichloride are added batchwise so that the temperature does not exceed 5 °C. The solution is stirred for another 1 h at 1-5 °C and then poured onto ice. The organic phase is separated and the aqueous phase is extracted another three times with dichloromethane. The combined organic phases are washed with aqueous 1 M hydrochloric acid, twice with 1 M sodium hydroxide solution and with brine. Then the organic phase is dried, the solvent is removed and the residue is recrystallised from ethanol.

Yield: 86.3 g (64% of theory)

Mass spectrum (ESI$^+$): m/z = 325/327/329 (Br+Cl) [M+H]$^+$

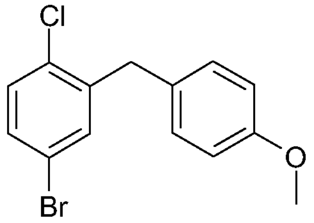
The following compound may be obtained analogously to Example I:

(1) (5-bromo-2-methyl)-(4-methoxy-phenyl)-methanone



Mass spectrum (ESI$^+$): m/z = 305/307 (Br) [M+H]$^+$

Example II

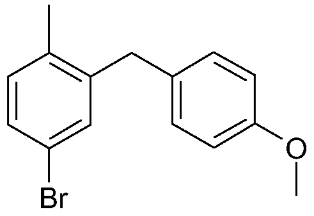


4-Bromo-1-chloro-2-(4-methoxy-benzyl)-benzene

A solution of 86.2 g (5-bromo-2-chloro-phenyl)-(4-methoxy-phenyl)-methanone and 101.5 mL triethylsilane in 75 mL dichloromethane and 150 mL acetonitrile is cooled to 10 °C. Then with stirring 50.8 mL of boron trifluoride etherate are added so that the temperature does not exceed 20 °C. The solution is stirred for 14 h at ambient temperature, before another 9 mL triethylsilane and 4.4 mL boron trifluoride etherate are added. The solution is stirred for a further 3 h at 45-50 °C and then cooled to ambient temperature. A solution of 28 g potassium hydroxide in 70 mL of water is added and the resultant mixture is stirred for 2 h. Then the organic phase is separated and the aqueous phase is extracted another three times with diisopropylether. The combined organic phases are washed twice with 2 M potassium hydroxide solution and once with brine and then dried over sodium sulfate. After the solvent has been eliminated the residue is stirred in ethanol, separated off again and dried at 60 °C.
Yield: 50.0 g (61% of theory)
Mass spectrum (ESI$^+$): m/z = 310/312/314 (Br+Cl) $[M+H]^+$

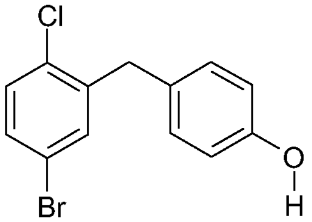
The following compound may be obtained analogously to Example II:

(1) (5-bromo-2-methyl)-(4-methoxy-phenyl)-methane



Mass spectrum (EI): m/z = 290/292 (Br) $[M]^+$

Example III

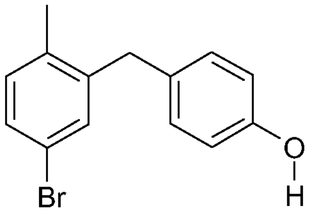


4-(5-Bromo-2-chloro-benzyl)-phenol

A solution of 14.8 g 4-bromo-1-chloro-2-(4-methoxy-benzyl)-benzene in 150 mL dichloromethane is cooled in an ice bath. Then 50 mL of a 1 M solution of boron tribromide in dichloromethane are added, and the solution is stirred for 2 h at ambient temperature. The solution is then cooled in an ice bath again, and saturated potassium carbonate solution is added dropwise. At ambient temperature the mixture is adjusted with aqueous 1 M hydrochloric acid to a pH of 1, the organic phase is separated and the aqueous phase is extracted another three times with ethyl acetate. The combined organic phases are dried over sodium sulfate, and the solvent is removed completely.
Yield: 13.9 g (98% of theory)
Mass spectrum (ESI$^-$): m/z = 295/297/299 (Br+Cl) [M-H]$^-$

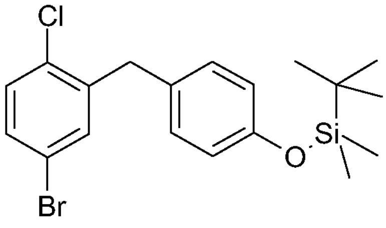
The following compound may be obtained analogously to Example III:

(1) 4-(5-bromo-2-methyl-benzyl)-phenol



Mass spectrum (ESI$^-$): m/z = 275/277 (Br) [M-H]$^-$

Example IV

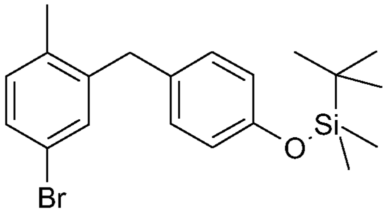


[4-(5-Bromo-2-chloro-benzyl)-phenoxy]-tert-butyl-dimethyl-silane

A solution of 13.9 g 4-(5-bromo-2-chloro-benzyl)-phenol in 140 mL dichloromethane is cooled in an ice bath. Then 7.54 g tert-butyldimethylsilylchlorid in 20 mL dichloromethane are added followed by 9.8 mL triethylamine and 0.5 g 4-dimethylaminopyridine. The solution is stirred for 16 h at ambient temperature and then diluted with 100 mL dichloromethane. The organic phase is washed twice with aqueous 1 M hydrochloric acid and once with aqueous sodium hydrogen carbonate solution and then dried over sodium sulfate. After the solvent has been removed the residue is filtered through silica gel (cyclohexane/ethyl acetate 100:1).
Yield: 16.8 g (87% of theory)
Mass spectrum (EI): m/z = 410/412/414 (Br+Cl) $[M]^+$

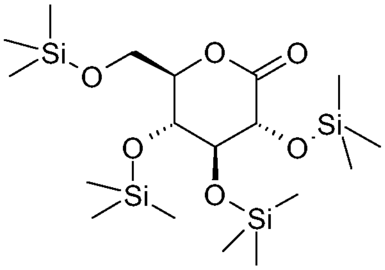
The following compound may be obtained analogously to Example IV:

(1) [4-(5-bromo-2-methyl-benzyl)-phenoxy]-tert-butyl-dimethyl-silane



Mass spectrum (EI): m/z = 390/392 (Br) $[M]^+$

Example V



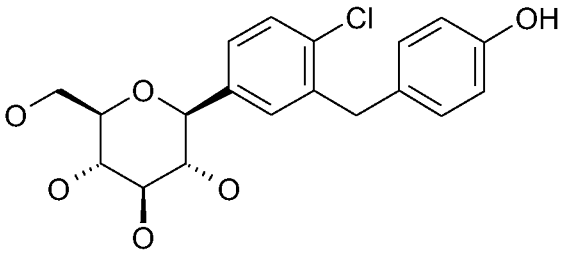
2,3,4,6-Tetrakis-O-(trimethylsilyl)-D-glucopyranone

A solution of 20 g D-glucono-1,5-lactone and 98.5 mL N-methylmorpholine in 200 mL of tetrahydrofuran is cooled to -5 °C. Then 85 mL trimethylsilylchloride are added dropwise so that the temperature does not exceed 5 °C. The solution is then stirred for 1 h at ambient temperature, 5 h at 35 °C and again for 14 h at ambient temperature. After the addition of 300 mL of toluene the solution is cooled in an ice bath, and 500 mL of water are added so that the temperature does not exceed 10 °C. The organic phase is then separated and washed in each case once with aqueous sodium dihydrogen phosphate solution, water and brine. The solvent is removed and the residue is azeotropically dried with toluene.

Yield: 52.5 g (approx. 90% pure)

Mass spectrum (ESI$^+$): m/z = 467 [M+H]$^+$

Example VI



1-Chloro-4-(ß-D-glucopyranos-1-yl)-2-(4-hydroxybenzyl)-benzene

A solution of 4.0 g [4-(5-bromo-2-chloro-benzyl)-phenoxy]-tert-butyl-dimethyl-silane in 42 mL dry diethyl ether is cooled to -80 °C under argon. 11.6 mL of a 1.7 M solution of tert-butyllithium in pentane are slowly added dropwise to the cooled solution, and then the solution is stirred for 30 min at -80 °C. This solution is then added dropwise through a transfer needle, which is cooled with dry ice, to a solution of 4.78 g 2,3,4,6-tetrakis-O-(trimethylsilyl)-D-glucopyranone in 38 mL diethyl ether chilled to -80 °C. The resulting solution is stirred for 3 h at -78 °C. Then a solution of 1.1 mL methanesulfonic acid in 35 mL of methanol is added and the solution is stirred for 16 h at ambient temperature. The solution is then neutralised with solid sodium hydrogen carbonate, ethyl acetate is added and the methanol is removed together with the ether. Aqueous sodium hydrogen carbonate solution is added to the remaining solution and the resultant mixture is extracted four times with ethyl acetate. The organic phases are dried over sodium sulfate and evaporated down. The residue is dissolved in 30 mL acetonitrile and 30 mL dichloromethane and the resulting solution is cooled to -10 °C. After the addition of 4.4 mL triethylsilane 2.6 mL boron trifluoride etherate are added dropwise so that the temperature does not exceed -5 °C. After the addition the solution is stirred for another 5 h at -5 to -10 °C and then quenched by the addition of aqueous sodium hydrogen carbonate solution. The organic phase is separated and the aqueous phase is extracted four times with ethyl acetate. The combined organic phases are dried over sodium sulfate, the solvent is removed and the residue is purified using silica gel. The product then obtained is an approx. 6:1 mixture of β/α which can be converted into the pure β-anomer by global acetylation of the hydroxy groups with acetic anhydride and pyridine in dichloromethane and recrystallisation of the product from ethanol. The crystallized pure acetylated β-anomer is converted into the title compound by global deprotection with 4 M potassium hydroxide solution in methanol.

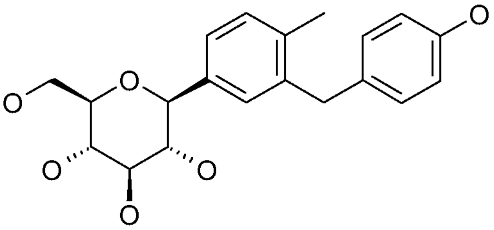
Yield: 1.6 g (46% of theory)

Mass spectrum (ESI$^+$): m/z = 398/400 (Cl) $[M+H]^+$

The following compounds may be obtained analogously to Example VI:

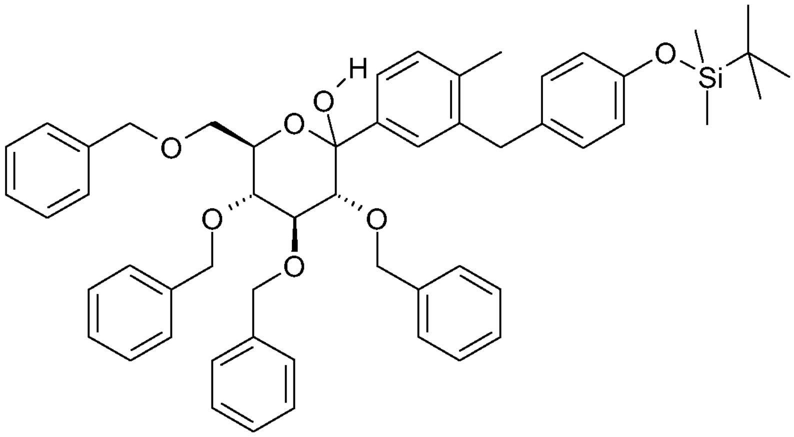
(1) 1-Methyl-4-(ß-D-glucopyranos-1-yl)-2-(4-hydroxybenzyl)-benzene

After the addition of the lithiated aromatic compound to the silylated gluconolactone this reaction is better quenched with 1% acetic acid in water instead of methanesulfonic acid in methanol. The crude product obtained after aqueous work-up is subsequently equilibrated to the more stable anomer (featuring the methoxy group in axial and the aryl residue in equatorial position) with a catalytic amount of methanesulfonic acid in methanol.



Mass spectrum (ESI$^+$): m/z = 660 $[M+NH_4]^+$

Example VII



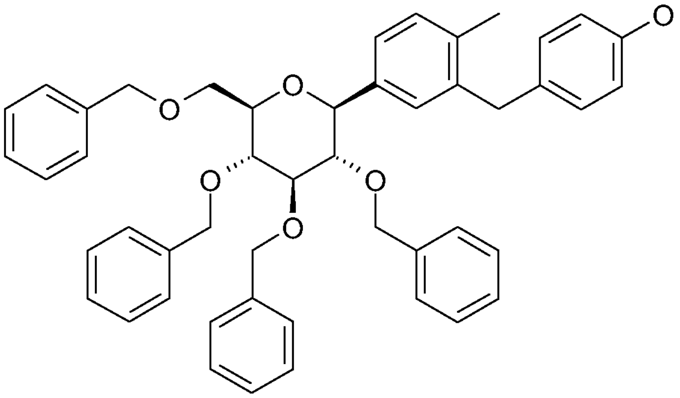
1-(2,3,4,6-Tetra-O-benzyl-1-hydroxy-D-glucopyranos-1-yl)-3-[4-(tert-butyl-dimethyl-silyloxy)-benzyl]-4-methyl-benzene

A solution of 0.34 g [4-(5-bromo-2-methyl-benzyl)-phenoxy]-tert-butyl-dimethyl-silane in 3 mL dry tetrahydrofuran is cooled to -80 °C under argon. 0.54 mL of a 1.6 M solution of n-butyllithium in hexane are added dropwise to the cooled solution, and the resultant solution is stirred for 1.5 h at -78 °C. A solution of 0.43 g 2,3,4,6-tetra-O-benzyl-D-glucopyranone in 2.5 mL of tetrahydrofuran chilled to -80 °C is added dropwise to this solution by means of a transfer needle. The resulting solution is stirred for 5 h at -78 °C. The reaction is quenched with a solution of 0.1 mL acetic acid in 1 mL of tetrahydrofuran and heated to ambient temperature. Then aqueous sodium hydrogen carbonate solution is added and the resulting mixture is extracted four times with ethyl acetate. The combined organic phases are dried over sodium sulfate and the solvent is removed under reduced pressure. The residue is purified by chromatography on silica gel (cyclohexane/ethyl acetate 15:1->4:1).

Yield: 0.48 g (approx. 88% pure)

Mass spectrum (ESI$^+$): m/z = 868 $[M+H]^+$

Example VIII



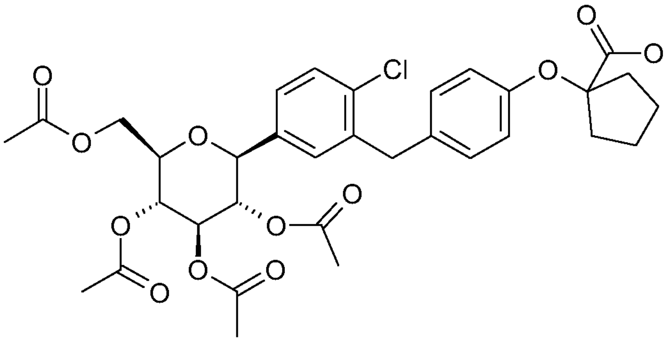
1-(2,3,4,6-tetra-O-benzyl-ß-D-glucopyranos-1-yl)-3-(4-hydroxy-benzyl)-4-methyl-benzene

A solution of 0.48 g (approx. 88% pure) 1-(2,3,4,6-tetra-O-benzyl-1-hydroxy-D-glucopyranosyl)-3-[4-(tert-butyl-dimethyl-silyloxy)-benzyl]-4-methyl-benzene in 3.5 mL dry acetonitrile is cooled to -40 °C under argon. 0.13 mL triisopropylsilane and 0.08 mL boron trifluoride etherate are added dropwise to the cooled solution. The solution is stirred for 3 h at -35 °C, before another 0.02 mL of triisopropylsilane and 0.01 mL of boron trifluoride etherate are added. After a further 2 h at -40 °C aqueous potassium carbonate solution is added and the resultant solution is stirred for 1 h at ambient temperature. Then it is diluted with water and extracted four times with ethyl acetate. The organic phase is dried over sodium sulfate, concentrated in vacuo and chromatographed through silica gel (cyclohexane/ethyl acetate 10:1->4:1).

Yield: 0.24 g (68% of theory).

Mass spectrum (ESI$^+$): m/z = 738 $[M+NH_4]^+$

Example IX



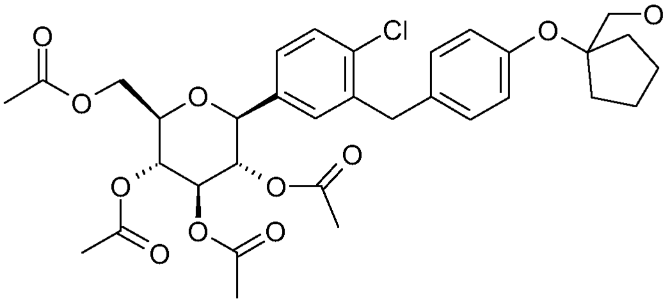
1-Chloro-4-(2,3,4,6-tetra-*O*-acetyl-ß-D-glucopyranos-1-yl)-2-[4-(1-hydroxycarbonyl-cyclopent-1-yloxy)-benzyl]-benzene

To a solution of 1-chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-(1-hydroxycarbonyl-cyclopent-1-yloxy)-benzyl]-benzene (6.50 g; preparation see Example 4) in dichloromethane (50 mL) is added consecutively pyridine (9 mL), acetic acid anhydride (10 mL) and 4-dimethylaminopyridine (0.5 g). The reaction solution is stirred at ambient temperature for 16 h and then diluted with dichloromethane (50 mL). The resulting solution is washed with aqueous hydrochloric acid (1 mol/l) and aqueous $NaHCO_3$ solution and dried (Na_2SO_4). The product is obtained after removal of the solvent.

Yield: 6.46 g (74% of theory)

Mass spectrum (ESI^+): m/z = 678/680 (Cl) $[M+NH_4]^+$

Example X



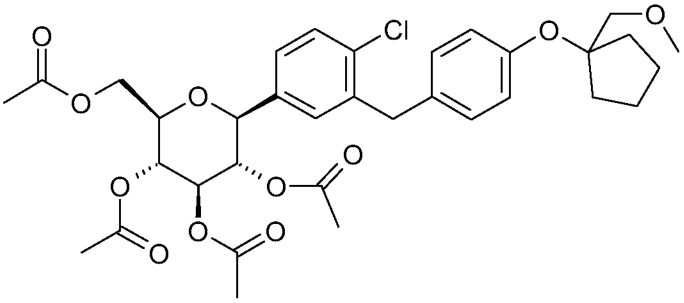
1-Chloro-4-(2,3,4,6-tetra-*O*-acetyl-ß-D-glucopyranos-1-yl)-2-[4-(1-hydroxymethyl-cyclopent-1-yloxy)-benzyl]-benzene

To a solution of 1-chloro-4-(2,3,4,6-tetra-*O*-acetyl-ß-D-glucopyranos-1-yl)-2-[4-(1-hydroxycarbonyl-cyclopent-1-yloxy)-benzyl]-benzene (1.50 g) in dichloromethane (7 mL) cooled in an ice-bath is added oxalyl chloride (1 mL). The solution is stirred at ambient temperature for 4 h and then concentrated under reduced pressure. The residue is dissolved in dry tetrahydrofuran (4 mL), cooled in an ice-bath and treated with sodium borohydride (86 mg). The resultant mixture is stirred at room temperature for 16 h. Water is added and the resulting mixture is extracted with ethyl acetate. The combined extracts are dried (Na_2SO_4), the solvent is removed *in vacuo* and the residue is purified by chromatography on silica gel (cyclohexane/ethyl acetate 1:0->2:1).

Yield: 1.15 g (78% of theory)

Mass spectrum (ESI^+): m/z = 664/666 (Cl) $[M+NH_4]^+$

Example XI



1-Chloro-4-(2,3,4,6-tetra-O-acetyl-ß-D-glucopyranos-1-yl)-2-[4-(1-methoxymethyl-cyclopent-1-yloxy)-benzyl]-benzene

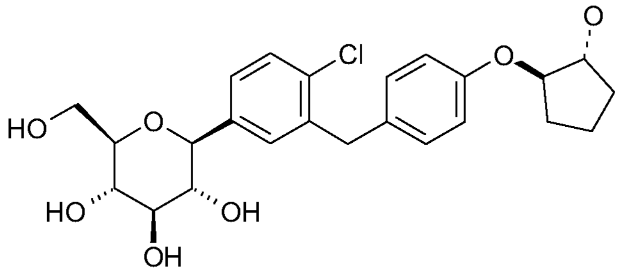
To a solution of 1-chloro-4-(2,3,4,6-tetra-*O*-acetyl-ß-D-glucopyranos-1-yl)-2-[4-(1-hydroxymethyl-cyclopent-1-yloxy)-benzyl]-benzene (0.56 g) in dichloromethane (4 mL) chilled in an ice-bath is added tetrafluoroboric acid (0.12 mL) and trimethylsilyldiazomethane (0.45 mL). The solution is stirred at ambient temperature for 1 h and then quenched with water. The resultant mixture is extracted with dichloromethane, the combined extracts are dried (Na_2SO_4), the solvent is removed and the residue is purified by chromatography on silica gel (cyclohexane/ethyl acetate 1:0->2:1).

Yield: 0.38 g (67% of theory)

Mass spectrum (ESI^+): m/z = 678/680 (Cl) $[M+NH_4]^+$

Preparation of the end compounds:

Example 1



1-Chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-(*trans*-2-hydroxy-cyclopent-1-yloxy)-benzyl]-benzene

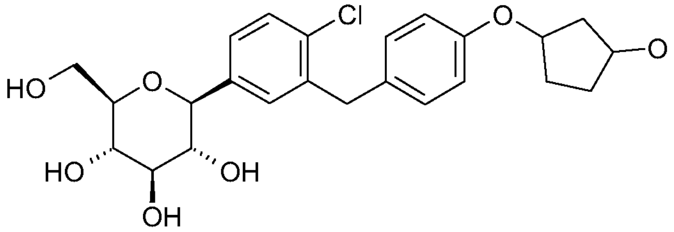
A mixture of 1-chloro-4-(ß-D-glucopyranos-1-yl)-2-(4-hydroxybenzyl)-benzene (0.50 g), cyclopentene oxide (1.50 g) and potassium carbonate (0.45 g) in ethanol (1.5 mL) is stirred for 75 min at 100 °C in a microwave oven. After cooling to ambient temperature, water is added and the resultant mixture is extracted with ethyl acetate. After drying the combined organic phases over sodium sulfate, the solvent is removed and the residue is purified by chromatography on silica gel (dichloromethane/methanol 9:1->1:1).

Yield: 300 mg (49% of theory)

Mass spectrum (ESI$^+$): m/z = 465/467 (Cl) $[M+H]^+$

The two diastereomeric isomers, 1-chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-((1*R*,2*R*)-2-hydroxy-cyclopent-1-yloxy)-benzyl]-benzene and 1-chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-((1*S*,2*S*)-2-hydroxy-cyclopent-1-yloxy)-benzyl]-benzene can be separated by HPLC on chiral phase (DAICEL AD-H, 250 x 4, 6 mmm, 5 µm; hexane+aminocyclohexane/ethanol 70:30, 1 ml/min) to obtain the diastereomerically pure compounds.

Example 2



1-Chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-(3-hydroxy-cyclopent-1-yloxy)-benzyl]-benzene

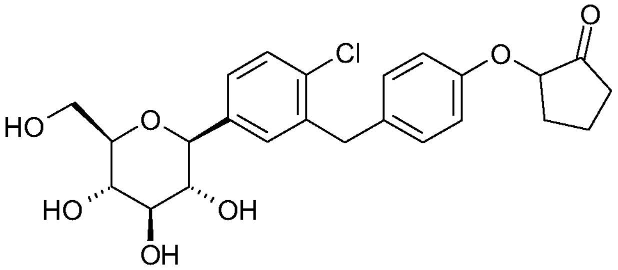
A mixture of 1-chloro-4-(ß-D-glucopyranos-1-yl)-2-(4-hydroxybenzyl)-benzene (0.25 g), 3-hydroxy-cyclopent-1-yl p-tolylsulfonate (0.19 g) and cesium carbonate (0.33 g) in dimethylformamide (1.5 mL) is stirred at 70 °C for 16 h. After cooling to ambient temperature, water is added and the resultant mixture is extracted with ethyl acetate. The combined organic phases are dried (Na_2SO_4), the solvent is removed and the residue is purified by chromatography on silica gel (dichloromethane/methanol 1:0->4:1).

Yield: 90 mg (29% of theory)

Mass spectrum (ESI$^+$): m/z = 482/484 (Cl) $[M+NH_4]^+$

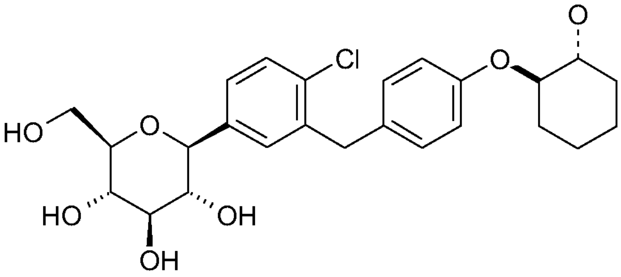
The following compound may be obtained analogously to Example 2:

(3) 1-Chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-(2-oxo-cyclopent-1-yloxy)-benzyl]-benzene



The compound is prepared using 1-chloro-cyclopentene oxide (is prepared from 1-chloro-cyclopentene and m-chloroperoxybenzoic acid in dichloromethane) as the electropile

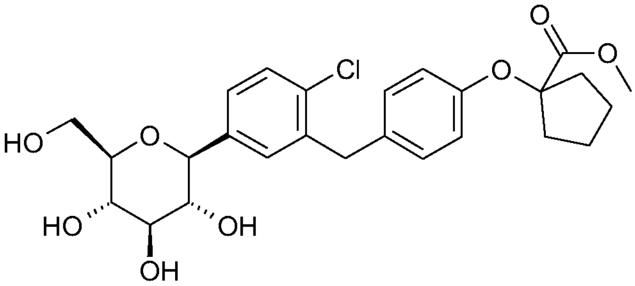
(4) 1-Chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-(*trans*-2-hydroxy-cyclohex-1-yloxy)-benzyl]-benzene



Mass spectrum (ESI): m/z = 496/498 (Cl) $[M]^+$

The reaction is conducted with cyclohexene oxide at 100 °C.

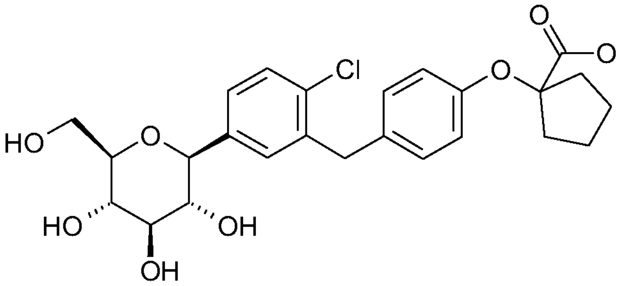
Example 5



1-Chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-(1-methoxycarbonyl-cyclopent-1-yloxy)-benzyl]-benzene

A mixture of 1-chloro-4-(ß-D-glucopyranos-1-yl)-2-(4-hydroxybenzyl)-benzene (0.46 g), 1-bromo-1-methoxycarbonylcyclopentane (0.87 g), potassium iodide (0.1 g) and potassium carbonate (0.5 g) in methanol (5 mL) is stirred at reflux for 16 h. After cooling to ambient temperature, water is added and the resultant mixture is extracted with ethyl acetate. The combined organic phases are dried (Na_2SO_4), the solvent is removed and the residue is purified by chromatography on silica gel (dichloromethane/methanol 1:0->4:1).
Yield: 180 mg (30% of theory)
Mass spectrum (ESI^+): m/z = 524/526 (Cl) $[M+NH_4]^+$

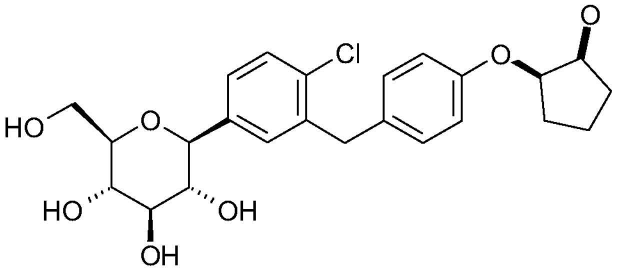
Example 6



1-Chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-(1-hydroxycarbonyl-cyclopent-1-yloxy)-benzyl]-benzene

A solution of 1-chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-(1-methoxycarbonyl-cyclopent-1-yloxy)-benzyl]-benzene (0.20 g) in aqueous potassium hydroxide solution (4 mol/l, 5 mL) and methanol (5 mL) is stirred at ambient temperature for 4 h. After neutralizing with aqueous hydrochloric acid (1 mol/l), the mixture is concentrated under reduced pressure, diluted with aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic phases are dried (Na_2SO_4), the solvent is removed and the residue is purified by chromatography on silica gel (dichloromethane/methanol 1:0->4:1).
Yield: 31 mg (16% of theory)
Mass spectrum (ESI^+): m/z = 510/512 (Cl) $[M+NH_4]^+$

Example 7



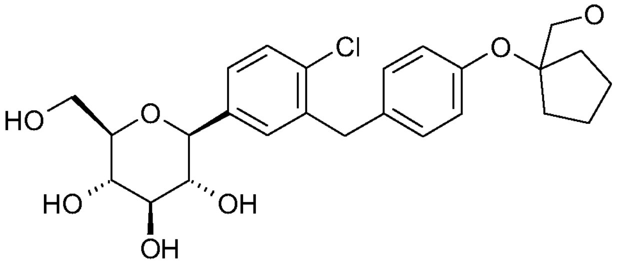
1-Chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-(*cis*-2-hydroxy-cyclopent-1-yloxy)-benzyl]-benzene

To a solution of 1-chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-(2-oxo-cyclopent-1-yloxy)-benzyl]-benzene (0.10 g) in dry tetrahydrofuran (3 mL) chilled to -78 °C is added L-selelctride (1 mol/l in tetrahydrofuran, 0.33 mL). The resulting solution is stirred at -78 °C for 2 h, then diluted with dichloromethane and quenched with aqueous hydrochloric acid (1 mol/l). The organic layer is separated and the aqueous phase is extracted with dichloromethane. The combined organic layers are dried (Na_2SO_4), the solvent is removed *in vacuo* and the residue is purified by chromatography on silica gel (dichloromethane/methanol 1:0->4:1).

Yield: 40 mg (42% of theory)

Mass spectrum (ESI$^+$): m/z = 482/484 (Cl) $[M+NH_4]^+$

Example 8



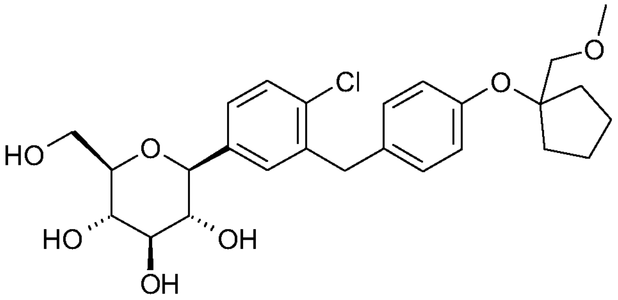
1-Chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-(1-hydroxymethyl-cyclopent-1-yloxy)-benzyl]-benzene

To a solution of 1-chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-(1-methoxycarbonyl-cyclopent-1-yloxy)-benzyl]-benzene (0.15 g) in dry tetrahydrofuran (3 mL) chilled in an ice-bath is added lithium borohydride (8 mg). The reaction mixture is stirred at ambient temperature for 16 h. Aqueous $NaHCO_3$ solution is added and the resulting mixture is extracted with ethyl acetate. The combined organic layers are dried (Na_2SO_4), the solvent is removed and the residue is purified by chromatography on silica gel (dichloromethane/methanol 1:0->4:1).

Yield: 128 mg (90% of theory)

Mass spectrum (ESI$^+$): m/z = 496/498 (Cl) $[M+NH_4]^+$

Example 9



1-Chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-(1-methoxymethyl-cyclopent-1-yloxy)-benzyl]-benzene

To a solution of 1-chloro-4-(2,3,4,6-tetra-*O*-acetyl-ß-D-glucopyranos-1-yl)-2-[4-(1-methoxmethyl-cyclopent-1-yloxy)-benzyl]-benzene (0.39 g) in tetrahydrofuran (3 mL) is added pyrrolidine (0.22 mL). The solution is stirred at ambient temperature for 16 h. After dilution with ethyl acetate, the resulting solution is washed with aqueous hydrochloric acid (1 mol/l), dried (Na_2SO_4) and the solvent is removed under reduced pressure. The residue is purified by HPLC on reversed phase (YMC C18; water/acetonitrile 95:5->2:98).

Yield: 116 mg (40% of theory)

Mass spectrum (ESI^+): m/z = 510/512 (Cl) $[M+NH_4]^+$

The following compounds are also prepared analogously to the above-mentioned Examples and other methods known from the literature:

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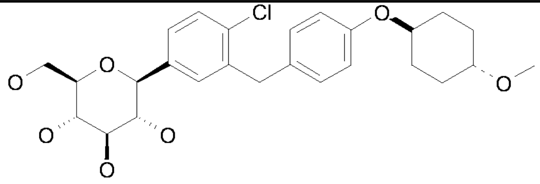
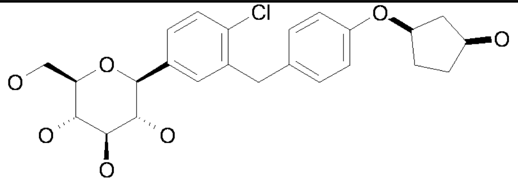
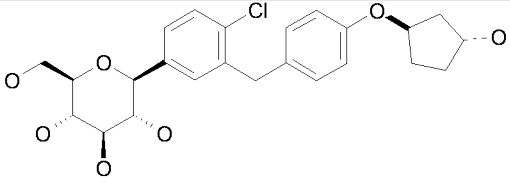
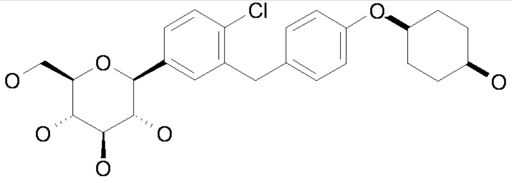
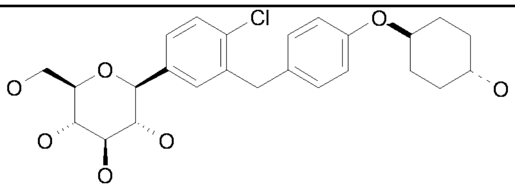
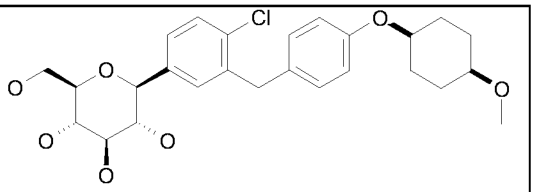
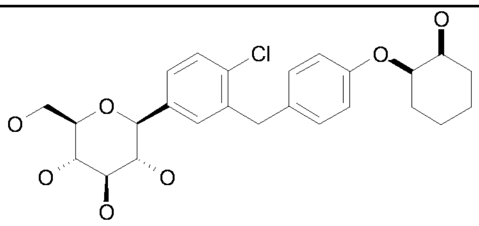
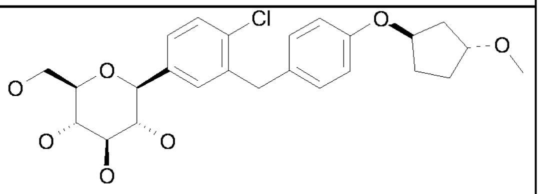
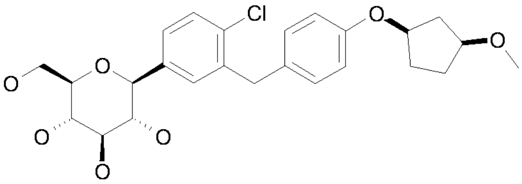
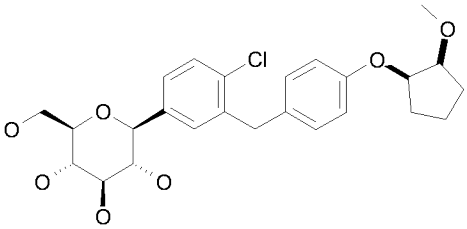
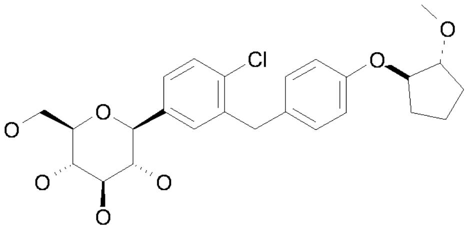
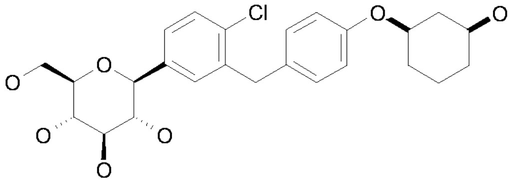
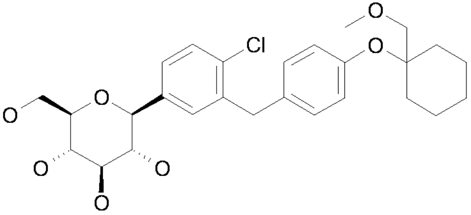
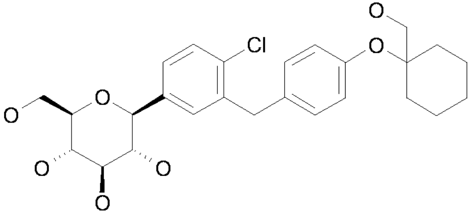
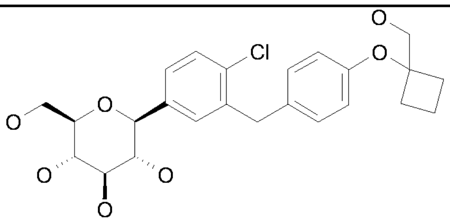
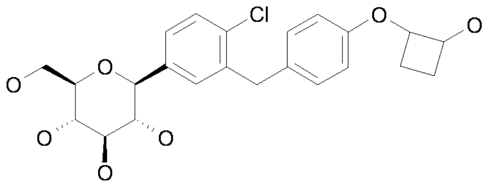
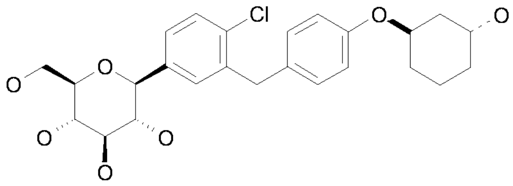
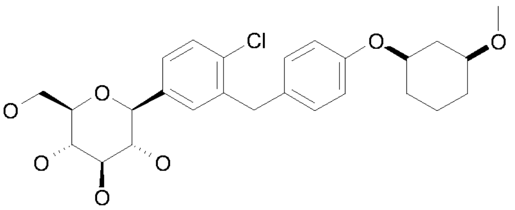
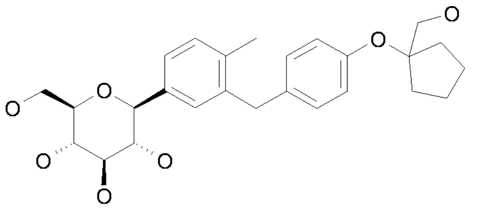
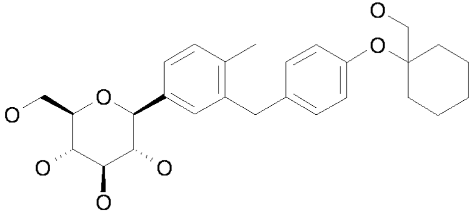
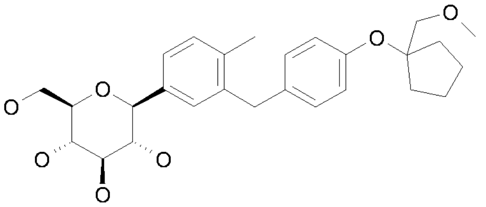
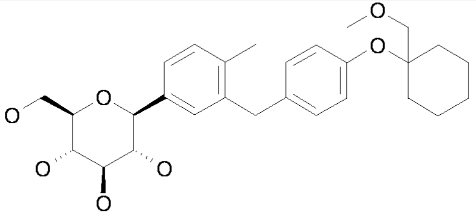
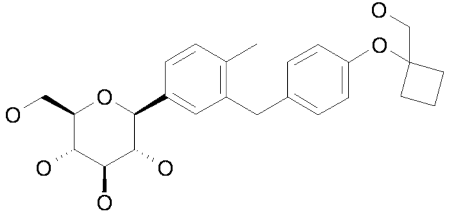
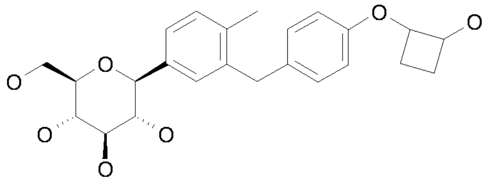
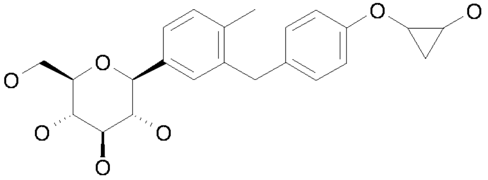
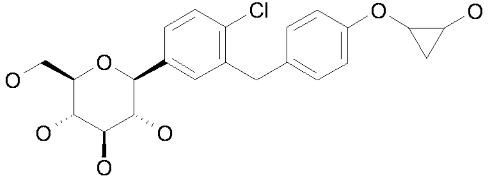
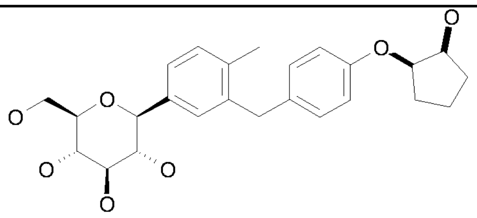
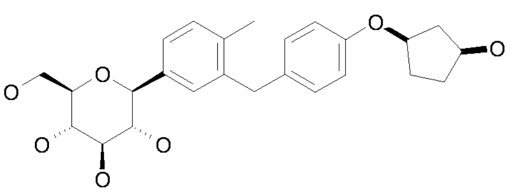
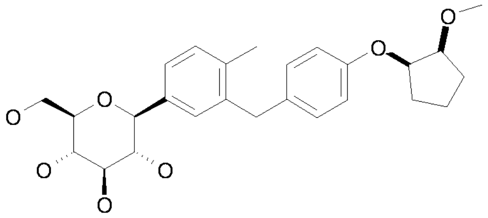
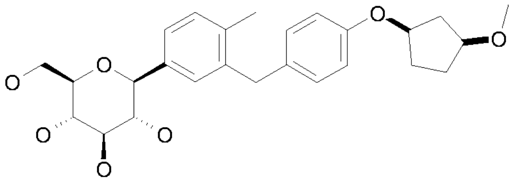
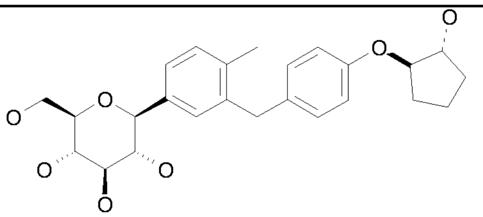
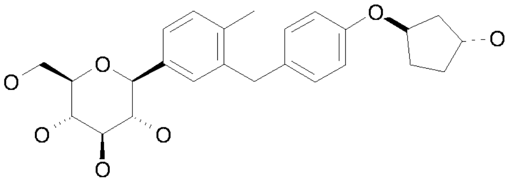
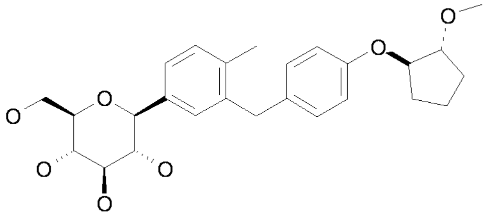
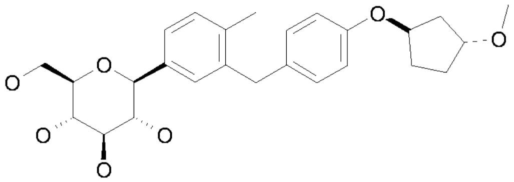
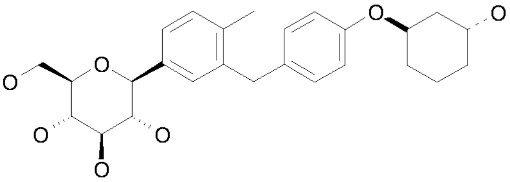
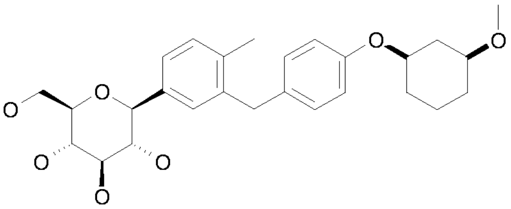
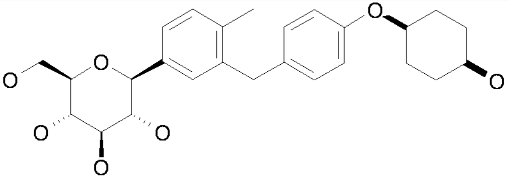
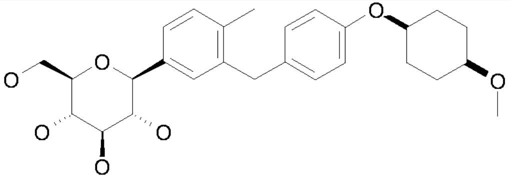
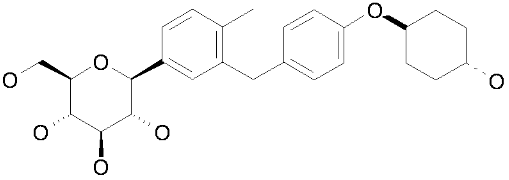
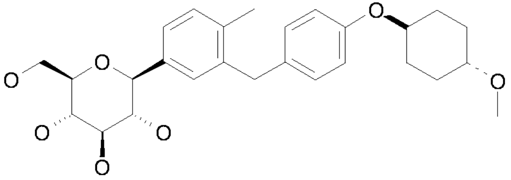
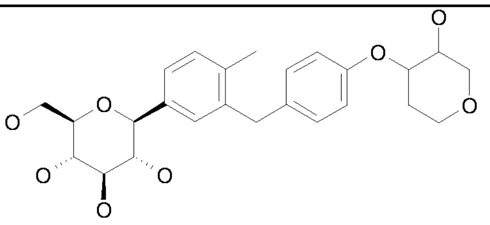
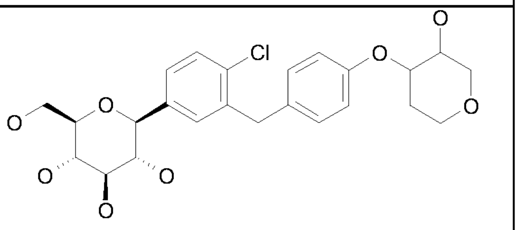
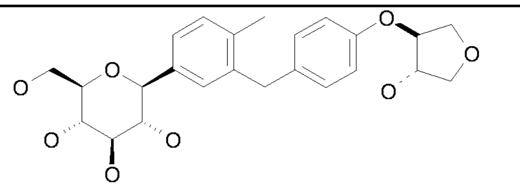
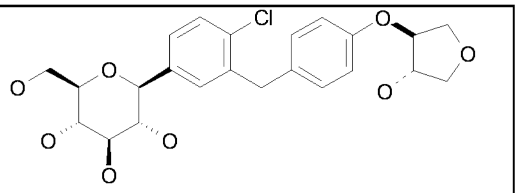
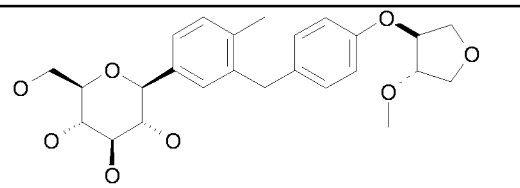
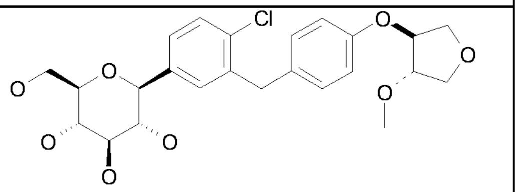
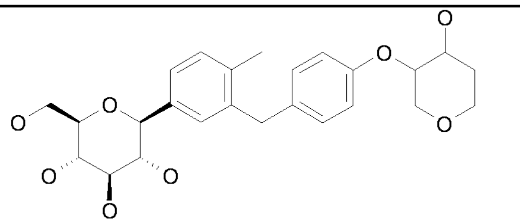
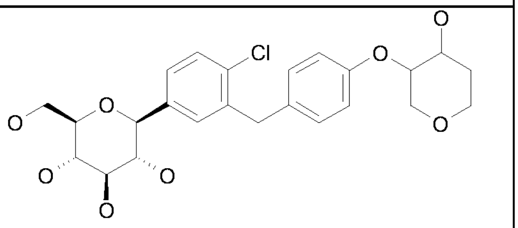
10		11	
12		13	

14		15	
16		17	
18		19	
20		21	
22		23	
24		25	

26		27	
28		29	
30		31	
32		33	
34		35	
36		37	

38		39	
40		41	
42		43	
44		45	
46		47	
48		49	
50		51	

52		53	
54		55	
56		57	

Some examples of formulations will now be described in which the term "active substance" denotes one or more compounds according to the invention, including the salts thereof. In the case of one of the combinations with one or additional active substances as described previously, the term "active substance" also includes the additional active substances.

Example A

Tablets containing 100 mg of active substance

Composition:

1 tablet contains:

active substance	100.0 mg
lactose	80.0 mg
corn starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	2.0 mg
	220.0 mg

Method of Preparation:

The active substance, lactose and starch are mixed together and uniformly moistened with an aqueous solution of the polyvinylpyrrolidone. After the moist composition has been screened (2.0 mm mesh size) and dried in a rack-type drier at 50°C it is screened again (1.5 mm mesh size) and the lubricant is added. The finished mixture is compressed to form tablets.

Weight of tablet: 220 mg
Diameter: 10 mm, biplanar, facetted on both sides and notched on one side.

Example B

Tablets containing 150 mg of active substance

Composition:

1 tablet contains:

active substance	150.0 mg
powdered lactose	89.0 mg
corn starch	40.0 mg
colloidal silica	10.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	1.0 mg
	300.0 mg

Preparation:

The active substance mixed with lactose, corn starch and silica is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm. The granules, dried at 45°C, are passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are pressed from the mixture.

Weight of tablet: 300 mg
die: 10 mm, flat

Example C

Hard gelatine capsules containing 150 mg of active substance

Composition:

1 capsule contains:

active substance		150.0 mg
corn starch (dried)	approx.	180.0 mg
lactose (powdered)	approx.	87.0 mg
magnesium stearate		3.0 mg
	approx.	420.0 mg

Preparation:

The active substance is mixed with the excipients, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatine capsules.

Capsule filling: approx. 320 mg
Capsule shell: size 1 hard gelatine capsule.

Example D

Suppositories containing 150 mg of active substance

Composition:

1 suppository contains:

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitan monostearate	840.0 mg
	2,000.0 mg

Preparation:

After the suppository mass has been melted the active substance is homogeneously distributed therein and the melt is poured into chilled moulds.

Example E

Ampoules containing 10 mg active substance

Composition:

active substance		10.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	2.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 2 ml ampoules.

Example F

Ampoules containing 50 mg of active substance

Composition:

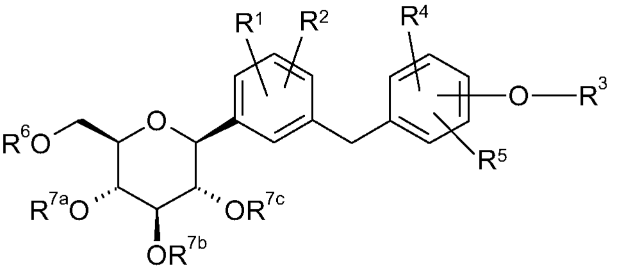
active substance		50.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	10.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 10 ml ampoules.

Claims

1. Glucopyranosyl-substituted benzyl-benzene derivatives of general formula I



I

wherein

R^1 denotes hydrogen, fluorine, chlorine, bromine, iodine, C_{1-4}-alkyl, C_{2-6}-alkynyl, C_{1-4}-alkoxy, C_{2-4}-alkenyl-C_{1-4}-alkoxy, C_{2-4}-alkynyl-C_{1-4}-alkoxy, methyl substituted by 1 to 3 fluorine atoms, ethyl substituted by 1 to 5 fluorine atoms, methoxy substituted by 1 to 3 fluorine atoms, ethoxy substituted by 1 to 5 fluorine atoms, C_{1-4}-alkyl substituted by a hydroxy or C_{1-3}-alkoxy group, C_{2-4}-alkoxy substituted by a hydroxy or C_{1-3}-alkoxy group, C_{2-6}-alkenyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-3}-alkyl, C_{3-7}-cycloalkyloxy, C_{3-7}-cycloalkyl-C_{1-3}-alkoxy, C_{5-7}-cycloalkenyloxy, hydroxy, amino, nitro or cyano, while in the C_{5-6}-cycloalkyl groups a methylene group may be replaced by O;

R^2 denotes hydrogen, fluorine, chlorine, bromine, hydroxy, C_{1-4}-alkyl, C_{1-4}-alkoxy, cyano or nitro, while the alkyl or alkoxy group may be mono- or polysubstituted by fluorine, and

R^3 denotes C_{3-7}-cycloalkyl, tetrahydrofuranyl or tetrahydropyranyl, which are substituted with one to four substituents L2, or R^3 denotes C_{5-7}-cycloalkanonyl which may be substituted with one to four substituents L2; and

R^4, R^5 independently of one another denote hydrogen, fluorine, chlorine, bromine, iodine, cyano, nitro, C_{1-3}-alkyl, C_{1-3}-alkoxy or a methyl- or methoxy-group substituted by 1 to 3 fluorine atoms, L1 independently of one another are selected from among fluorine, chlorine, bromine, iodine, hydroxy, cyano, C_{1-3}-alkyl, difluoromethyl, trifluoromethyl, C_{1-3}-alkoxy, difluoromethoxy, trifluoromethoxy, amino, C_{1-3}-alkyl-amino and di(C_{1-3}-alkyl)-amino; and

L2 independently of one another are selected from among fluorine, chlorine, hydroxy, hydroxyl-C_{1-4}-alkyl, C_{1-4}-alkoxy, trifluoromethoxy, C_{1-4}-alkoxy-C_{1-4}-alkyl, cyano, hydroxycarbonyl, (C_{1-4}-alkyl)oxycarbonyl, aminocarbonyl, C_{1-4}-alkyl, trifluoromethyl, amino, C_{1-4}-alkyl-carbonylamino, C_{1-3}-alkyl-amino and di(C_{1-3}-alkyl)-amino; and

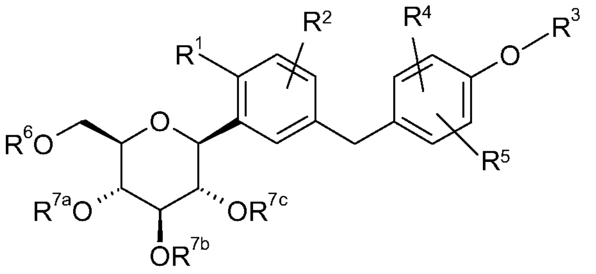
R^6 , R^{7a},
R^{7b}, R^{7c} independently of one another have a meaning selected from among hydrogen, (C_{1-18}-alkyl)carbonyl, (C_{1-18}-alkyl)oxycarbonyl, arylcarbonyl and aryl-(C_{1-3}-alkyl)-carbonyl, while the aryl-groups may be mono- or disubstituted independently of one another by identical or different groups L1;

while by the aryl groups mentioned in the definition of the above groups are meant phenyl or naphthyl groups which may be substituted as defined; and

while, unless otherwise stated, the above-mentioned alkyl groups may be straight-chain or branched,

the tautomers, the stereoisomers thereof, the mixtures thereof and the salts thereof.

2. Glucopyranosyl-substituted benzyl-benzene derivatives of general formula I.2



I.2a

wherein the groups R^1 to R^6 and R^{7a}, R^{7b} and R^{7c} are defined as in claim 1.

3. Glucopyranosyl-substituted benzyl-benzene derivatives according to claim 1 or 2, characterised in that the group R^3 denotes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuran-3-yl, tetrahydropyran-3-yl or tetrahydropyran-4-yl, which are substituted with one or two substituents L2; or R^3 denotes cyclopentanonyl or cyclohexanonyl which may be substituted with one or two substituents L2; wherein L2 is defined as in claim 1.

4. Glucopyranosyl-substituted benzyl-benzene derivatives according to one or more of claims 1 to 3, characterised in that the group R^1 denotes hydrogen, fluorine, chlorine, bromine, C_{1-4}-alkyl, C_{1-4}-alkoxy, methyl substituted by 1 to 3 fluorine atoms, methoxy substituted by 1 to 3 fluorine atoms, C_{3-7}-cycloalkyloxy or C_{3-7}-cycloalkyl-C_{1-3}-alkoxy, while in the C_{5-6}-cycloalkyl groups a methylene group may be replaced by O.

5. Glucopyranosyl-substituted benzyl-benzene derivatives according to one or more of claims 1 to 4, characterised in that the group R^2 denotes hydrogen, fluorine, chlorine, methyl, methoxy, ethoxy and methyl substituted by 1 to 3 fluorine atoms.

6. Glucopyranosyl-substituted benzyl-benzene derivatives according to one or more of claims 1 to 5, characterised in that the groups R^4 and/or R^5 independently of one another represent hydrogen or fluorine.

7. Glucopyranosyl-substituted benzyl-benzene derivatives according to one or more of claims 1 to 6, characterised in that the group R^6 denotes hydrogen, (C_{1-8}-alkyl)oxycarbonyl, C_{1-8}-alkylcarbonyl or benzoyl.

8. Glucopyranosyl-substituted benzyl-benzene derivatives according to one or more of claims 1 to 7, characterised in that the groups R^{7a}, R^{7b}, R^{7c} represent hydrogen.

9. Physiologically acceptable salts of the compounds according to at least one of claims 1 to 8 with inorganic or organic acids.

10. Pharmaceutical composition, containing a compound according to one or more of claims 1 to 8 or a physiologically acceptable salt according to claim 9, optionally together with one or more inert carriers and/or diluents.

11. Use of at least one compound according to one or more of claims 1 to 8 or a physiologically acceptable salt according to claim 9 for preparing a pharmaceutical composition which is suitable for the treatment or prevention of diseases or conditions which can be influenced by inhibiting the sodium-dependent glucose cotransporter SGLT.

12. Use of at least one compound according to one or more of claims 1 to 8 or a physiologically acceptable salt according to claim 9 for preparing a pharmaceutical composition which is suitable for the treatment or prevention of metabolic disorders.

13. Use according to claim 12, characterised in that the metabolic disorder is selected from the group consisting of type 1 and type 2 diabetes mellitus, complications of diabetes, metabolic acidosis or ketosis, reactive hypoglycaemia, hyperinsulinaemia, glucose metabolic disorder, insulin resistance, metabolic syndrome, dyslipidaemias of different origins, atherosclerosis and related diseases, obesity, high blood pressure, chronic heart failure, edema and hyperuricaemia.

14. Use of at least one compound according to at least one of claims 1 to 8 or a physiologically acceptable salt according to claim 9 for preparing a pharmaceutical composition for inhibiting the sodium-dependent glucose cotransporter SGLT2.

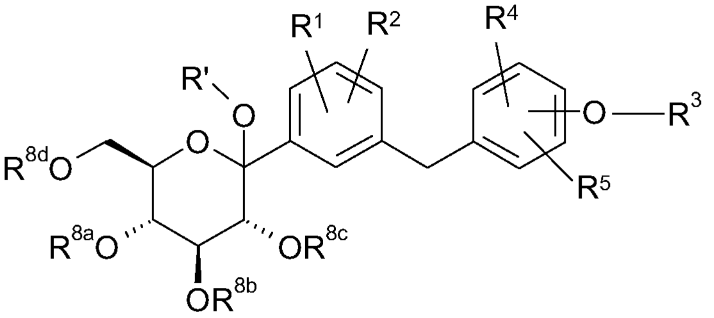
15. Use of at least one compound according to at least one of claims 1 to 8 or a physiologically acceptable salt according to claim 9 for preparing a pharmaceutical composition for preventing the degeneration of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells.

16. Use of at least one compound according to at least one of claims 1 to 8 or a physiologically acceptable salt according to claim 9 for preparing diuretics and/or antihypertensives.

17. Process for preparing a pharmaceutical composition according to claim 10, characterised in that a compound according to at least one of claims 1 to 8 or a

physiologically acceptable salt according to claim 9 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

18. Process for preparing a compound of general formula I according to one or more of the claims 1 to 8, characterised in that a compound of general formula II



II

wherein

R' denotes H, C_{1-4}-alkyl, (C_{1-18}-alkyl)carbonyl, (C_{1-18}-alkyl)oxycarbonyl, arylcarbonyl and aryl-(C_{1-3}-alkyl)-carbonyl, wherein the alkyl or aryl groups may be mono- or polysubstituted by halogen;

R^{8a}, R^{8b}, R^{8c}, R^{8d} independently of one another have one of the meanings given for the groups R^6, R^{7a}, R^{7b}, R^{7c}, or denote a benzyl group or a $R^aR^bR^cSi$ group or a ketal or acetal group, while in each case two adjacent groups R^{8a}, R^{8b}, R^{8c}, R^{8d} may form a cyclic silyl ketal, ketal or acetal group or a 1,2-di(C_{1-3}-alkoxy)-1,2-di(C_{1-3}-alkyl)-ethylene bridge, while the above-mentioned ethylene bridge forms, together with two oxygen atoms and the two associated carbon atoms of the pyranose ring, a substituted dioxane ring, and while alkyl, aryl and/or benzyl groups may be mono- or polysubstituted by halogen or C_{1-3}-alkoxy, and while benzyl groups may also be substituted by a di-(C_{1-3}-alkyl)amino group; and

R^a, R^b, R^c independently of one another denote C_{1-4}-alkyl, aryl or aryl-C_{1-3}-alkyl, wherein the aryl or alkyl groups may be mono- or polysubstituted by halogen;

while by the aryl groups mentioned in the definition of the above groups are meant phenyl or naphthyl groups, preferably phenyl groups;

and R^1 to R^5 and R^6, R^{7a}, R^{7b}, R^{7c} have the meanings given in claims 1 to 8, is reacted with a reducing agent in the presence of a Lewis or Brønsted acid, while any protective groups present are cleaved simultaneously or subsequently;

if desired a compound of general formula I thus obtained wherein R^6 denotes a hydrogen atom, is converted by acylation into a corresponding acyl compound of general formula I, and/or

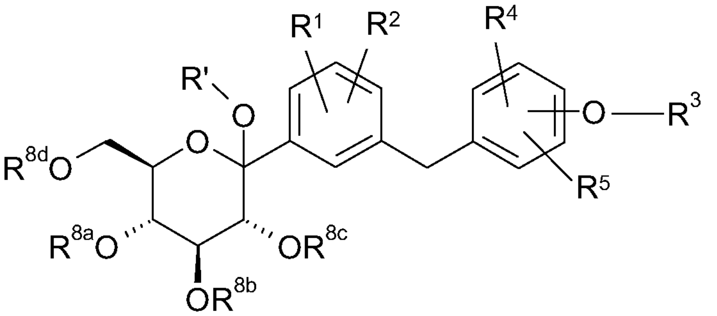
if necessary any protective group used in the reactions described above is cleaved and/or

if desired a compound of general formula I thus obtained is resolved into its stereoisomers and/or

if desired a compound of general formula I thus obtained is converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts thereof.

19. Process according to claim 18, characterised in that the compound of general formula II is obtained by the process described in claim 20 or 21.

20. Process for preparing compounds of general formula II



II

wherein

R' denotes H, C_{1-4}-alkyl, (C_{1-18}-alkyl)carbonyl, (C_{1-18}-alkyl)oxycarbonyl, arylcarbonyl and aryl-(C_{1-3}-alkyl)-carbonyl, wherein the alkyl or aryl groups may be mono- or polysubstituted by halogen;

R^{8a}, R^{8b},

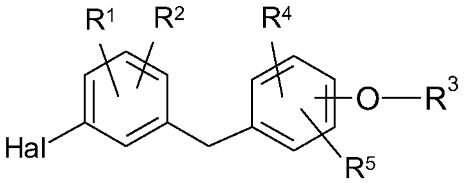
R^{8c}, R^{8d} independently of one another have one of the meanings given for the groups R^6, R^{7a}, R^{7b}, R^{7c}, or denote a benzyl group or a $R^aR^bR^cSi$ group or a ketal or acetal group, while in each case two adjacent groups R^{8a}, R^{8b}, R^{8c}, R^{8d} may form a cyclic silyl ketal, ketal or acetal group or a 1,2-di(C_{1-3}-alkoxy)-1,2-di(C_{1-3}-alkyl)-ethylene bridge, while the above-mentioned ethylene bridge forms, together with two oxygen atoms and the two associated carbon atoms of the pyranose ring, a substituted dioxane ring, and while alkyl, aryl and/or benzyl groups may be mono- or polysubstituted by halogen or C_{1-3}-alkoxy, and while benzyl groups may also be substituted by a di-(C_{1-3}-alkyl)amino group; and

R^a, R^b, R^c independently of one another denote C_{1-4}-alkyl, aryl or aryl-C_{1-3}-alkyl, wherein the aryl or alkyl groups may be mono- or polysubstituted by halogen;

while by the aryl groups mentioned in the definition of the above groups are meant phenyl or naphthyl groups, preferably phenyl groups;

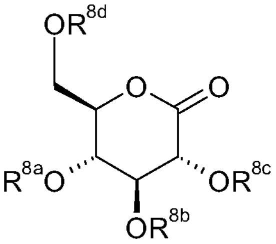
and R^1 to R^5 and R^6, R^{7a}, R^{7b}, R^{7c} have the meanings given in one or more of the claims 1 to 8,

wherein an organometallic compound (V) which may be obtained by halogen-metal exchange or by the insertion of a metal in the carbon-halogen bond of a halogen-benzylbenzene compound of general formula IV



IV

wherein Hal denotes Cl, Br and I and R^1 to R^5 are as hereinbefore defined, and optionally subsequent transmetallation, is added to a gluconolactone of general formula VI

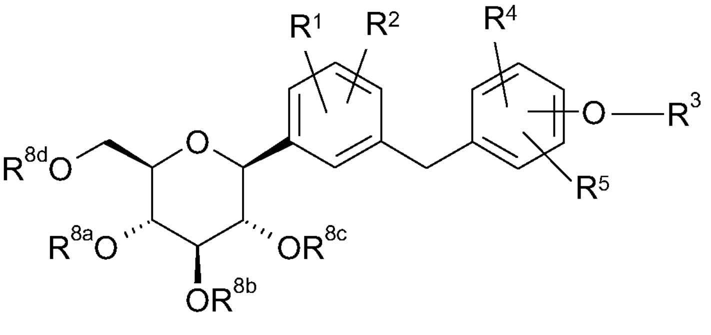

VI

wherein R^{8a}, R^{8b}, R^{8c}, R^{8d} are as hereinbefore defined, and

then the resulting adduct is reacted with water or an alcohol R'-OH, where R' denotes optionally substituted C_{1-4}-alkyl, in the presence of an acid and optionally the product obtained in the reaction with water wherein R' denotes H is converted in a subsequent reaction with an acylating agent into the product of formula II wherein R' denotes (C_{1-18}-alkyl)carbonyl, (C_{1-18}-alkyl)oxycarbonyl, arylcarbonyl or aryl-(C_{1-3}-alkyl)-carbonyl, which may be substituted as specified.

21. Process according to claim 20, characterised in that the organometallic compound (V) is a lithium or magnesium compound.

22. Process for preparing the compounds of general formula I according to one or more of the claims 1 to 8, wherein R^6, R^{7a}, R^{7b} and R^{7c} represent hydrogen, characterised in that a compound of general formula III


III

wherein

R^{8a}, R^{8b}, R^{8c}, R^{8d} independently of one another have one of the meanings given for the groups R^6 , R^{7a}, R^{7b}, R^{7c}, but at least one of the groups R^{8a}, R^{8b}, R^{8c}, R^{8d}

does not denote hydrogen, or denotes a benzyl group or a $R^aR^bR^cSi$ group or a ketal or acetal group, while in each case two adjacent groups R^{8a}, R^{8b}, R^{8c}, R^{8d} may form a cyclic silyl ketal, ketal or acetal group or a 1,2-di(C_{1-3}-alkoxy)-1,2-di(C_{1-3}-alkyl)-ethylene bridge, while the above-mentioned ethylene bridge forms a substituted dioxane ring together with two oxygen atoms and the associated two carbon atoms of the pyranose ring, and while alkyl, aryl and/or benzyl groups may be mono- or polysubstituted by halogen or C_{1-3}-alkoxy, and while benzyl groups may also be substituted by a di-(C_{1-3}-alkyl)amino group; and

R^a, R^b, R^c independently of one another represent C_{1-4}-alkyl, aryl or aryl-C_{1-3}-alkyl, while the alkyl or aryl groups may be mono- or polysubstituted by halogen;

while by the aryl groups mentioned in the definition of the above groups are meant phenyl or naphthyl groups, preferably phenyl groups;

and R^1 to R^5, R^6, R^{7a}, R^{7b}, R^{7c} have the meanings given in one or more of the claims 1 to 8,

is hydrolysed, and

if desired a compound of general formula I thus obtained wherein R^6 denotes a hydrogen atom is converted by acylation into a corresponding acyl compound of general formula I, and/or

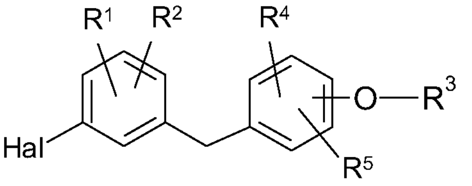
if necessary any protective group used in the reactions described above is cleaved and/or

if desired a compound of general formula I thus obtained is resolved into its stereoisomers and/or

if desired a compound of general formula I thus obtained is converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts thereof.

23. Process according to claim 22, characterised in that the compound of formula III is obtained by a process according to claim 18 or 19.

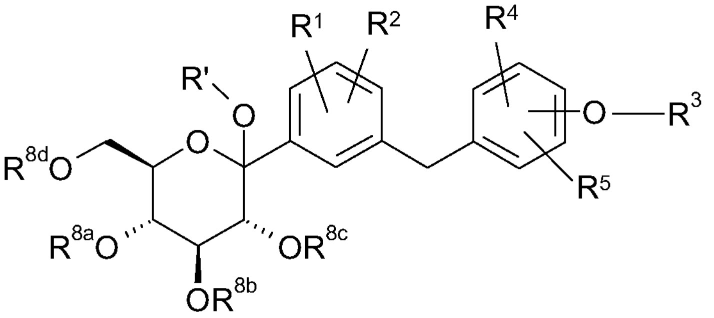
24. Compound of general formula IV



IV

wherein Hal denotes chlorine, bromine or iodine and the groups R^1, R^2, R^3, R^4 and R^5 are defined as in one or more of Claims 1 to 6.

25. Compound of general formula II



II

wherein

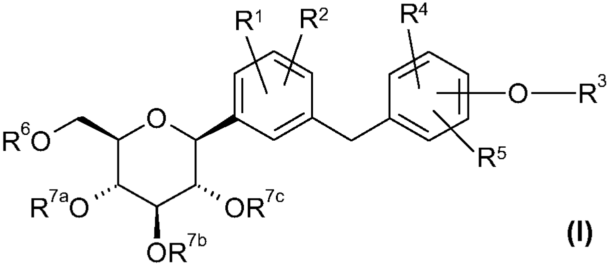
R' denotes H, C_{1-4}-alkyl, (C_{1-18}-alkyl)carbonyl, (C_{1-18}-alkyl)oxycarbonyl, arylcarbonyl and aryl-(C_{1-3}-alkyl)-carbonyl, wherein the alkyl or aryl groups may be mono- or polysubstituted by halogen;

R^{8a}, R^{8b}, R^{8c}, R^{8d} independently of one another have one of the meanings given for the groups R^6 , R^{7a}, R^{7b}, R^{7c}, or denote a benzyl group or a $R^aR^bR^cSi$ group or a ketal or acetal group, while in each case two adjacent groups R^{8a}, R^{8b}, R^{8c}, R^{8d} may form a cyclic silyl ketal, ketal or acetal group or a 1,2-di(C_{1-3}-alkoxy)-1,2-di(C_{1-3}-alkyl)-ethylene bridge, while the above-mentioned ethylene bridge forms, together with two oxygen atoms and the two associated carbon atoms of the pyranose ring, a substituted dioxane ring, and while alkyl, aryl and/or benzyl groups may be mono- or polysubstituted by halogen or C_{1-3}-alkoxy, and while benzyl groups may also be substituted by a di-(C_{1-3}-alkyl)amino group; and

R^a, R^b, R^c independently of one another denote C_{1-4}-alkyl, aryl or aryl-C_{1-3}-alkyl, while the alkyl or aryl groups may be mono- or polysubstituted by halogen;

while by the aryl groups mentioned in the definition of the above groups are meant phenyl or naphthyl groups, preferably phenyl groups;

and R^1 to R^5 are defined as in one or more of Claims 1 to 6.



(I)