

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

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Apoderado: Emilio Ferrero

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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	Evento	001
	Actuación	430
	Oficio	
	Folios	313175

Patente de Invención ☒

Vía PCT fase nacional ☒ Cap. I ☒ Cap. II ☐

No. Sol. Internacional PCT/JP2005/013634

Fecha de Presentación Interna de WO 2006/011469

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

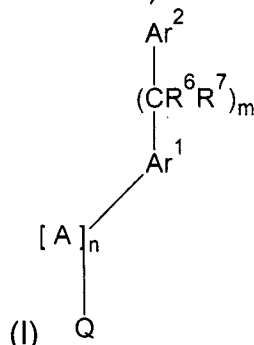
1. Documentos estudiados

- 1.1. Descripción: Folios: 274 a 511 Como se radicó inicialmente.
- 1.2. Reivindicaciones: Folios: 512 a 513 Como se radicó inicialmente.
- 1.3. Prioridad: Folio 1: JP 2004-217065; 26/jul/2004
 JP 2004-340104; 25/nov/2004

2. Objeto de la invención

Título de la solicitud: DERIVAO NOVEDOSO DE CICLOHEXANO, PRODROGA DE ÉSTE, Y AGENTE TERAPÉUTICO QUE CONTIENE EL MISMO PARA DIABETES.

Definir el objeto de la invención tal como aparece reivindicado son los derivados de (arilal-quilC₁₋₃-ariloxi)-6-(hidroximetil)ciclohexano-1,2,3-triol de fórmula Markush:



- Reivindicaciones 1-13: Un compuesto de la fórmula (I).
- Reivindicación 14-16: Composiciones que los contienen
- Reivindicación 17: Procedimiento de tratamiento que consiste en administrar un compuesto a un paciente.

Se catalogó la invención, según la Clasificación Internacional de Patentes (IPC.): C07C43/23, C07D 209/12, A61K31/085, A61P3/04.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486 de la C.A.N.)

-Las reivindicaciones 1-7 son muy amplias y especulativas, toda vez que la fórmula Markush (I) no tiene ninguna porción fija, todas sus partes con mutantes y sumado a sus posibles combinaciones no encuentran sustento técnico real en la descripción, además los significados de los sustituyentes Ar^1 y Ar^2 está en términos denominaciones genéricas, que encierran un incalculable número de estructuras que tampoco encuentran sustento en la descripción, además que no tiene perfectamente delimitado el alcance de la invención, todo eso es inaceptable en la reivindicaciones. Es especulativo porque **no son extrapolaciones estrechamente relacionadas** con lo que se describió, las reivindicaciones deberían presentar una generalización razonable de los ejemplos dados en la parte descriptiva.

-También se reclama "prodrogas" el término técnico correcto es "**profarmaco**" y es para cuando realmente existen estructuras que al metabolizarse proporcionan un principio activo deseado libre. Para el presente caso es puramente imaginativo, ya aque conduce a un alcance indefinido sin claridad, porque el termino profarmaco incluye compuestos obtenidos a partir de otro compuesto mediante reacciones químicas para obtener estructuras que están estructuralmente alejadas del material de partida. Además, es un intento de definir la materia en términos del resultado a conseguir. Por lo tanto, no es permisible este tipo reivindicaciones.

Las reivindicaciones 14, 15 y 16 no es claras, ya que el encabezado no es congruente con el resto del texto de la reivindicación, se encabeza como una composición farmacéutica y el texto que debe ser expresado como características técnicas o elementos técnicos constitutivos, es una mezcla de uso y método de tratamiento, lo cual no define técnicamente la composición farmacéutica.

Las reivindicaciones no cumplen con el requisito de definición, claridad, concisión o sustento por la descripción de acuerdo al art. 30 de la Decisión 486.y/o art.22 Tratado PCT.

4. Excepción a la patentabilidad (artículo 20 D486 literal d))

-La reivindicación 17 reclama un método de tratamiento para el cuerpo humano o animal, por lo tanto se encuentra comprendido en lo dispuesto por el artículo 20 D486 literal d).

5. Determinación del Estado de la Técnica

Considerando la fecha de prioridad reclamada de la presente solicitud de patente 26/jul/2004, se realizó la búsqueda del estado de la técnica, en bases de datos donde ésta oficina tiene acceso libre, para búsquedas de documentos relacionados con la materia que se reclama como nueva e inventiva en la presente solicitud.

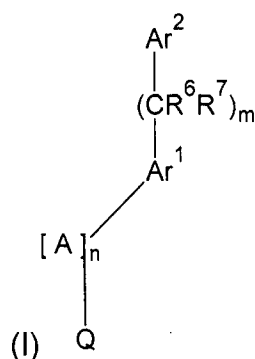
Algunos de los documentos más relevantes se presentan en la siguiente tabla:

Nº	Documento	Título	Fecha de publicación*
D1	WO01/068660	Glucopyranoisyoxy benzylbenzene derivatives, medicinal compositions containing de same and intermediates for the preparation of the derivatives.	20/sep/2001
D2	WO0174834	o-glucoside SGLT2 inhibitors and method	11/oct/2001
D3	US20020137903	C-aryl glucoside SGLT2 inhibitors and method	26/sep/2002
D4	WO02064606	Glucopyranoisyoxybenzylbenzene derivatives and medicinal use thereof	22/ago/2002
D5	WO0236602	Novel Pyrazole derivatives and diabetes remedies containing the same	10/may/2002
D6	US20030114390	C-aryl glucoside SGLT2 inhibitors and method	19/jun/2003
D7	WO2004058790	Nitrogen-containing heterocyclic derivatives medicinal compositions containing de same and medicinal use thereof	15/jul/2004
D8	WO2004007517	Novel thiophenylglycoside derivatives and method for production thereof medicaments, comprising said compounds and use thereof	22/ene/2004

12. Análisis de patentabilidad (artículo 14 D.486 de la C.A.N.)

12.1 Novedad (artículo 16 D486 de la C.A.N.)

La solicitud en estudio reclama como nuevo e inventivo:
los derivados de (arilal-quilC₁₋₃-ariloxi)-6-(hidroximetil)ciclohexano-1,2,3-triol de fórmula Markush:



- Al comparar la materia reclamada en la presente solicitud, con el estado de la técnica, esta oficina encuentra:

Que D1 [WO01068660=EP1270584], especialmente en la pags.1,2,4,5,11,12-17; D2[WO0174834] especialmente pags.7-14,29-32,48-50, ejemplos 6-101; D3[US20020137903] especialmente pags. 1-7,12-14; D4[WO02064606=EP1338603] especialmente pags. 1-12, 21-24, ejemplos 2-40; D5[WO0236602] especialmente pags.1-8, 10, 13, 26-28; D6[US20030114390] especialmente pags. 1,3-10 y reivindicaciones; D7 [WO2004058790=EP1577317] todo, especialmente pags.1, 3-10,24,25, 26, tabla 1 y reivindicaciones; D8 [WO2004007517] especialmente pags. 1-4, 12,14,16, tabla 1; tal como puede verse en las anterioridades ya divulgan compuestos reclamados bajo la fórmula Markush I de la solicitud. En consecuencia, los compuestos reclamados ya habían sido divulgados, así como las composiciones farmacéuticas que los contienen por lo tanto la presente solicitud no cumple con el requisito exigido en el artículo 16 D486 de la C.A.N

13. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

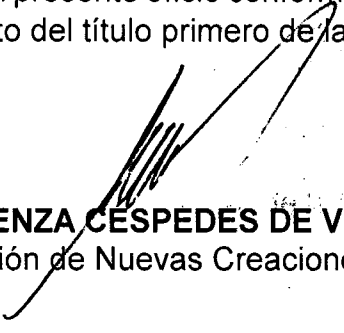
*Cuando un solicitud no cumple con el requisito de novedad obviamente no posee nivel inventivo.

Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	1-17	Novedad
D2	1-17	Novedad
D3	1-17	Novedad
D4	1-17	Novedad
D5	1-17	Novedad
D6	1-17	Novedad
D7	1-17	Novedad
D8	1-17	Novedad

14 Respuesta a los argumentos del solicitante:

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha

_____ 8 OCT. 2012

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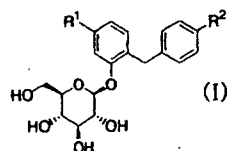
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(54) **GLUCOPYRANOSYLOXY BENZYL BENZENE DERIVATIVES, MEDICINAL COMPOSITIONS CONTAINING THE SAME AND INTERMEDIATES FOR THE PREPARATION OF THE DERIVATIVES**

(57) The present invention relates to glucopyranosyloxybenzylbenzene derivatives represented by the general formula:



wherein R¹ represents a hydrogen atom or a hydroxy (lower alkyl) group; and R² represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a hydroxy(lower alkyl) group, a hydroxy(lower alkoxy) group, a hydroxy(lower alkylthio) group etc., and salts thereof, which have an excellent inhibitory activity in human SGLT2 and are useful as agents for the prevention or treatment of diabetes, obesity etc., and intermediates thereof.

EP 1 270 584 A1

Description

Technical Field

[0001] The present invention relates to glucopyranosyloxybenzylbenzene derivatives and pharmaceutically acceptable salts thereof which are useful as medicaments, pharmaceutical compositions comprising the same and intermediates thereof.

Background Art

[0002] Diabetes is one of lifestyle-related diseases with the background of change of eating habit and lack of exercise. Hence, diet and exercise therapies are performed in patients with diabetes. Furthermore, when its sufficient control and continuous performance are difficult, drug treatment is simultaneously performed. Now, biguanides, sulfonylureas and agents for reducing insulin resistance have been employed as antidiabetic agents. However, biguanides and sulfonylureas show occasionally adverse effects such as lactic acidosis and hypoglycemia, respectively. In a case of using agents for reducing insulin resistance, adverse effects such as edema occasionally are observed, and it is also concerned for advancing obesity. Therefore, in order to solve these problems, it has been desired to develop antidiabetic agents having a new mechanism.

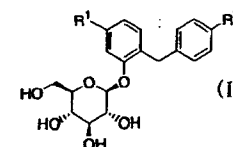
[0003] In recent years, development of new type antidiabetic agents has been progressing, which promote urinary glucose excretion and lower blood glucose level by preventing excess glucose reabsorption at the kidney (J. Clin. Invest., Vol.79, pp.1510-1515 (1987)). In addition, it is reported that SGLT2 (Na⁺/glucose cotransporter 2) is present in the S1 segment of the kidney's proximal tubule and participates mainly in reabsorption of glucose filtrated through glomerular (J. Clin. Invest., Vol.93, pp.397-404 (1994)). Accordingly, inhibiting a human SGLT2 activity prevents reabsorption of excess glucose at the kidney, subsequently promotes excreting excess glucose through the urine, and normalizes blood glucose level. Therefore, fast development of antidiabetic agents, which have a potent inhibitory activity in human SGLT2 and have a new mechanism, has been desired. Furthermore, since such agents promote the excretion of excess glucose through the urine and consequently the glucose accumulation in the body is decreased, they are also expected to have a preventing effect on obesity.

Disclosure of the Invention

[0004] The present inventors have studied earnestly to find compounds having an inhibitory activity in human SGLT2. As a result, it was found that glucopyranosyloxybenzylbenzene derivatives represented by the following general formula (I) show an excellent inhibitory activity in human SGLT2 as mentioned below, thereby forming the basis of the present invention.

[0005] The present invention is to provide the following glucopyranosyloxybenzylbenzene derivatives and pharmaceutically acceptable salts thereof, which show an inhibitory activity in human SGLT2 *in vivo* and exert a hypoglycemic effect by excreting excess glucose in the urine through preventing the reabsorption of such glucose at the kidney, pharmaceutical compositions comprising the same and intermediates thereof.

[0006] This is, the present invention relates to a glucopyranosyloxybenzylbenzene derivative represented by the general formula:



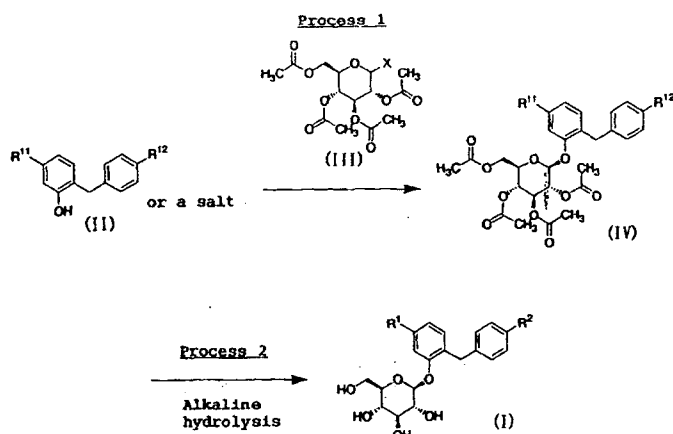
wherein R¹ represents a hydrogen atom or a hydroxy(lower alkyl) group; and R² represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a hydroxy(lower alkyl) group, a hydroxy(lower alkoxy) group, a hydroxy(lower alkylthio) group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group or a lower alkoxy-substituted (lower alkylthio) group, or a pharmaceutically acceptable salt thereof.

[0007] The present invention relates to a pharmaceutical composition comprising as the active ingredient a glucopyranosyloxybenzylbenzene derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof.

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[0014] For example, the compounds represented by the above general formula (I) of the present invention can be prepared using a benzylphenol derivative represented by the general formula (II) of the present invention according to the following procedure:



wherein R^{11} represents a hydrogen atom or a protected hydroxy (lower alkyl) group; R^{12} represented a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a protected hydroxy (lower alkyl) group, a protected hydroxy (lower alkylthio) group, an lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkylthio) group; X represents a leaving group such as a trichloroacetimidoyloxy group, an acetoxy group, a bromine atom or a fluorine atom; and R^1 and R^2 have the same meanings as defined above.

Process 1

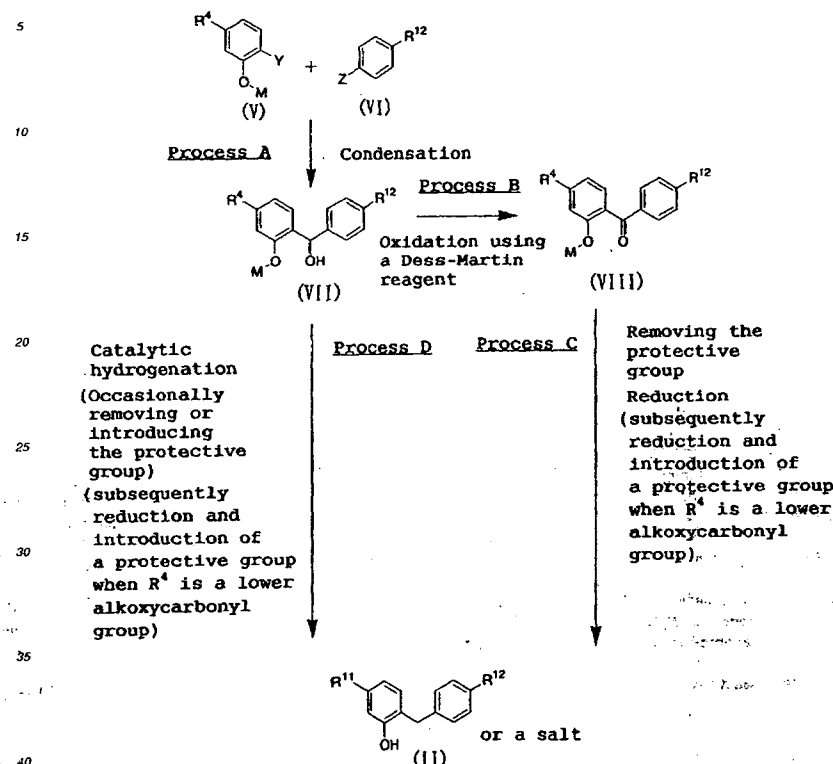
[0015] A glucoside represented by the above general formula (IV) can be prepared by subjecting a benzylphenol derivative represented by the above general formula (II) or a salt thereof to glucosidation using a glycosyl-donor represented by the above general formula (III) such as 2,3,4,6-tetra-O-acetyl-1-O-trichloroacetimidoyl- α -D-glucopyranose, 1,2,3,4,6-penta-O-acetyl- β -D-glucopyranose, 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide and 2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl fluoride in the presence of an activating reagent such as boron trifluoride diethyl ether complex, silver trifluoromethanesulfonate, tin(IV) chloride or trimethylsilyl trifluoromethanesulfonate in an inert solvent. As the solvent used, dichloromethane, toluene, acetonitrile, nitromethane, ethyl acetate, diethyl ether, chloroform, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from -30°C to reflux temperature, and the reaction time is usually from 10 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature.

Process 2

[0016] A compound (I) of the present invention can be prepared by subjecting a glucoside represented by the above general formula (IV) to alkaline hydrolysis to remove the hydroxy-protective groups. As the solvent used, water, methanol, ethanol, tetrahydrofuran, a mixed solvent thereof and the like can be illustrated, and as alkaline materials, sodium hydroxide, sodium methoxide, sodium ethoxide or the like can be used. The treatment temperature is usually from 0°C to reflux temperature, and the treatment time is usually from 30 minutes to 6 hours, varying based on a used starting material, solvent and treatment temperature. Such treatment can be carried out by suitably changing or adding an other procedure in the usual way depending on a used hydroxy-protective group.

[0017] For example, the compounds represented by the above general formula (II) of the present invention and salts thereof which are used as starting materials in the aforementioned production process can be prepared according to

the following procedure:



wherein M represents a hydrogen atom or a hydroxy-protective group; R^4 represents a hydrogen atom, a protected hydroxy (lower alkyl) group or a lower alkoxycarbonyl group; one of Y and Z is MgBr, MgCl, MgI or a lithium atom, while the other is a formyl group; and R^{11} and R^{12} have the same meanings as defined above. Process A

[0018] A compound represented by the above general formula (VII) can be prepared by condensing a benzaldehyde derivative represented by the above general formula (V) with a Grignard reagent or a lithium reagent represented by the above general formula (VI), or by condensing a Grignard reagent or a lithium reagent represented by the above general formula (V) with a benzaldehyde derivative represented by the above general formula (VI) in an inert solvent. As the solvent used, tetrahydrofuran, diethyl ether, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from -78°C to reflux temperature, and the reaction time is usually from 10 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature.

Process B

[0019] A compound represented by the above general formula (VIII) can be prepared by subjecting a compound represented by the above general formula (VII) to oxidation using a Dess-Martin reagent in an inert solvent. As the solvent used, dichloromethane, chloroform, acetonitrile, a mixed solvent thereof and the like can be illustrated. The

residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 4/1) to give a diphenylmethanol compound (0.91g). The obtained diphenylmethanol compound (0.90g) was dissolved in dichloromethane (15mL). To the solution was added a Dess-Martin reagent (1,1,1-tri(acetoxy)-1,1-dihydro-1,2-benzodioxol-3(1H)-one) (1.5g), and the mixture was stirred at 25°C for 26 hours. To the reaction mixture were added diethyl ether (75mL) and 1mol/L aqueous sodium hydroxide solution (30mL), the mixture was stirred vigorously, and the organic layer was separated. The organic layer was washed with 1mol/L aqueous sodium hydroxide solution (30mL), water (30mL, 3 times) and brine (30mL), dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate - 15/1-9/1) to afford a ketone compound (0.82g). A mixture of the obtained ketone compound (0.81g), p-toluenesulfonic acid monohydrate (0.10g) and methanol (14mL) was stirred at 60°C for 4 hours. After cooling to ambient temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate - 15/1) to give a deprotected compound (0.69g). The obtained deprotected compound (0.68g) was dissolved in tetrahydrofuran (11mL), triethylamine (0.41mL) and methyl chloroformate (0.22mL) were added to the solution, and the mixture was stirred at 25°C for 1 hour. Furthermore, triethylamine (0.11mL) and methyl chloroformate (0.061mL) were added to the reaction mixture, and the mixture was stirred for 30 minutes. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (14mL) and water (7mL), sodium borohydride (0.40g) was added to the solution, and the mixture was stirred at 25°C for 7 hours. To the reaction mixture was added dropwise 1mol/L hydrochloric acid (15mL), and the mixture was extracted with ethyl acetate (75mL). The extract was washed with water (20mL), a saturated aqueous sodium hydrogen carbonate solution (20mL) and brine (20mL), dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate - 8/1) to give 2-(4-ethylthiobenzyl)phenol (0.62g).

¹H-NMR (CDCl₃) δ ppm:
1.29 (3H, t, J=7.3Hz), 2.90 (2H, q, J=7.3Hz), 3.96 (2H, s), 4.62 (1H, s), 6.75-6.80 (1H, m), 6.85-6.95 (1H, m), 7.05-7.20 (4H, m), 7.20-7.30 (2H, m)

Reference Example 14

2-(4-Methoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

[0043] To a solution of 2-(4-methoxybenzyl)phenol (46mg) and 2,3,4,6-tetra-O-acetyl-1-O-trichloroacetimidoyl-α-D-glucopyranose (0.13g) in dichloromethane (2mL) was added boron trifluoride diethyl ether complex (0.033mL), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was purified by column chromatography on aminopropyl silica gel (eluent: dichloromethane) to give 2-(4-methoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (0.11g).

¹H-NMR (CDCl₃) δ ppm:
1.91 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.08 (3H, s), 3.77 (3H, s), 3.80-3.95 (3H, m), 4.17 (1H, dd, J=2.5, 12.2Hz), 4.29 (1H, dd, J=5.5, 12.2Hz), 5.11 (1H, d, J=7.5Hz), 5.10-5.25 (1H, m), 5.25-5.40 (2H, m), 6.75-6.85 (2H, m), 6.95-7.10 (5H, m), 7.10-7.25 (1H, m)

Reference Example 15

2-(4-Methylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

[0044] The title compound was prepared in a similar manner to that described in Reference Example 14 using 2-(4-methylbenzyl)phenol instead of 2-(4-methoxybenzyl)phenol.

¹H-NMR (CDCl₃) δ ppm:
1.89 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 2.30 (3H, s), 3.80-3.95 (3H, m), 4.17 (1H, dd, J=2.5, 12.3Hz), 4.28 (1H, dd, J=5.5, 12.3Hz), 5.11 (1H, d, J=7.5Hz), 5.10-5.25 (1H, m), 5.25-5.40 (2H, m), 6.90-7.20 (8H, m)

Reference Example 16

2-(4-Ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

[0045] The title compound was prepared in a similar manner to that described in Reference Example 14 using 2-(4-ethylbenzyl)phenol instead of 2-(4-methoxybenzyl)phenol.

¹H-NMR (CDCl₃) δ ppm:
1.20 (3H, t, J=7.6Hz), 1.87 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.08 (3H, s), 2.60 (2H, q, J=7.6Hz), 3.80-4.00 (3H, m),

4.18 (1H, dd, J=2.3, 12.2Hz), 4.28 (1H, dd, J=5.4, 12.2Hz), 5.11 (1H, d, J=7.5Hz), 5.10-5.25 (1H, m), 5.25-5.40 (2H, m), 6.90-7.25 (8H, m)

Reference Example 17

2-(4-Isobutylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

[0046] The title compound was prepared in a similar manner to that described in Reference Example 14 using 2-(4-isobutylbenzyl)phenol instead of 2-(4-methoxybenzyl)phenol.

¹H-NMR (CDCl₃) δ ppm:
0.88 (6H, d, J=6.6Hz), 1.75-1.90 (1H, m), 1.87 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.08 (3H, s), 2.42 (2H, d, J=7.2Hz), 3.80-3.95 (3H, m), 4.18 (1H, dd, J=2.4, 12.3Hz), 4.29 (1H, dd, J=5.5, 12.3Hz), 5.11 (1H, d, J=7.6Hz), 5.10-5.25 (1H, m), 5.25-5.40 (2H, m), 6.90-7.25 (8H, m)

Reference Example 18

2-(4-Ethoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

[0047] The title compound was prepared in a similar manner to that described in Reference Example 14 using 2-(4-ethoxybenzyl)phenol instead of 2-(4-methoxybenzyl)phenol.

¹H-NMR (CDCl₃) δ ppm:
1.39 (3H, t, J=7.0Hz), 1.91 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 3.80-3.95 (3H, m), 3.99 (2H, q, J=7.0Hz), 4.18 (1H, dd, J=2.5, 12.3Hz), 4.28 (1H, dd, J=5.6, 12.3Hz), 5.10 (1H, d, J=7.7Hz), 5.15-5.25 (1H, m), 5.25-5.40 (2H, m), 6.75-6.85 (2H, m), 6.95-7.10 (5H, m), 7.10-7.20 (1H, m)

Reference Example 19

2-(4-Isopropoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

[0048] The title compound was prepared in a similar manner to that described in Reference Example 14 using 2-(4-isopropoxybenzyl)phenol instead of 2-(4-methoxybenzyl)phenol.

¹H-NMR (CDCl₃) δ ppm:
1.30 (6H, d, J=6.0Hz), 1.90 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.08 (3H, s), 3.80-3.90 (3H, m), 4.18 (1H, dd, J=2.3, 12.3Hz), 4.28 (1H, dd, J=5.5, 12.3Hz), 4.48 (1H, heptet, J=6.0Hz), 5.10 (1H, d, J=7.7Hz), 5.10-5.25 (1H, m), 5.25-5.40 (2H, m), 6.70-6.85 (2H, m), 6.90-7.10 (5H, m), 7.10-7.20 (1H, m)

Reference Example 20

5-Acetoxyethyl-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

[0049] The title compound was prepared in a similar manner to that described in Reference Example 14 using 5-acetoxy-methyl-2-(4-ethylbenzyl)phenol instead of 2-(4-methoxybenzyl)phenol.

¹H-NMR (CDCl₃) δ ppm:
1.20 (3H, t, J=7.6Hz), 1.88 (3H, s), 2.02 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 2.09 (3H, s), 2.60 (2H, q, J=7.6Hz), 3.80-3.95 (3H, m), 4.20 (1H, dd, J=2.4, 12.3Hz), 4.27 (1H, dd, J=5.3, 12.3Hz), 5.00-5.10 (2H, m), 5.13 (1H, d, J=7.4Hz), 5.15-5.40 (3H, m), 6.95-7.15 (7H, m)

Reference Example 21

Acetoxyethyl-2-(4-propoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

[0050] The title compound was prepared in a similar manner to that described in Reference Example 14 using 5-acetoxy-methyl-2-(4-propoxybenzyl)phenol instead of 2-(4-methoxybenzyl)phenol.

¹H-NMR (CDCl₃) δ ppm:
1.01 (3H, t, J=7.4Hz), 1.70-1.85 (2H, m), 1.92 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 2.09 (3H, s), 3.80-3.95 (5H, m), 4.20 (1H, dd, J=2.4, 12.3Hz), 4.27 (1H, dd, J=5.3, 12.3Hz), 5.00-5.10 (2H, m), 5.12 (1H, d, J=7.4Hz), 5.15-5.40 (3H, m), 6.75-6.85 (2H, m), 6.95-7.10 (5H, m)

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Reference Example 22

2-[4-(2-Acetoxyethyl)benzyl]-5-acetoxymethylphenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

[0051] The title compound was prepared in a similar manner to that described in Reference Example 14 using 2-[4-(2-acetoxyethyl)benzyl]-5-acetoxymethylphenol instead of 2-(4-methoxybenzyl)phenol.

¹H-NMR (CDCl₃) δ ppm:

1.89 (3H, s), 2.03 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 2.09 (3H, s), 2.88 (2H, t, J=7.1Hz), 3.85-3.95 (3H, m), 4.15-4.35 (4H, m), 5.00-5.10 (2H, m), 5.13 (1H, d, J=7.5Hz), 5.15-5.40 (3H, m), 6.95-7.15 (7H, m)

Example 1

2-(4-Methoxybenzyl)phenyl β-D-glucopyranoside

[0052] Sodium methoxide (28% methanol solution; 0.12mL) was added to a solution of 2-(4-methoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (0.11g) in methanol (4mL), and the mixture was stirred at room temperature for 30 minutes. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to give 2-(4-methoxybenzyl)phenyl β-D-glucopyranoside (65mg).

¹H-NMR (CD₃OD) δ ppm:

3.35-3.55 (4H, m), 3.69 (1H, dd, J=5.1, 12.1Hz), 3.73 (3H, s), 3.80-4.00 (2H, m), 4.03 (1H, d, J=15.1Hz), 4.91 (1H, d, J=7.4Hz), 6.75-6.85 (2H, m), 6.85-6.95 (1H, m), 6.95-7.10 (1H, m), 7.10-7.20 (4H, m)

Example 2

2-(4-Methylbenzyl)phenyl β-D-glucopyranoside

[0053] The title compound was prepared in a similar manner to that described in Example 1 using 2-(4-methylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside instead of 2-(4-methoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside.

¹H-NMR (CD₃OD) δ ppm:

2.27 (3H, s), 3.35-3.55 (4H, m), 3.69 (1H, dd, J=5.2, 12.0Hz), 3.80-3.90 (1H, m), 3.94 (1H, d, J=15.0Hz), 4.05 (1H, d, J=15.0Hz), 4.85-4.95 (1H, m), 6.85-6.95 (1H, m), 6.95-7.20 (7H, m)

Example 3

2-(4-Ethylbenzyl)phenyl β-D-glucopyranoside

[0054] The title compound was prepared in a similar manner to that described in Example 1 using 2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside instead of 2-(4-methoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside.

¹H-NMR (CD₃OD) δ ppm:

1.15-1.25 (3H, m), 2.50-2.65 (2H, m), 3.35-3.55 (4H, m), 3.65-3.75 (1H, m), 3.80-4.00 (2H, m), 4.06 (1H, d, J=14.9Hz), 4.85-5.00 (1H, m), 6.85-7.00 (1H, m), 7.00-7.20 (7H, m)

Example 4

2-(4-Isobutylbenzyl)phenyl β-D-glucopyranoside

[0055] The title compound was prepared in a similar manner to that described in Example 1 using 2-(4-isobutylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside instead of 2-(4-methoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside.

¹H-NMR (CD₃OD) δ ppm:

0.80-0.95 (6H, m), 1.70-1.90 (1H, m), 2.41 (2H, d, J=7.1Hz), 3.30-3.55 (4H, m), 3.60-3.75 (1H, m), 3.80-3.95 (1H, m), 3.95 (1H, d, J=15.0Hz), 4.06 (1H, d, J=15.0Hz), 4.85-4.95 (1H, m), 6.80-7.20 (8H, m)

Example 5

2-(4-Ethoxybenzyl)phenyl β-D-glucopyranoside

[0056] The title compound was prepared in a similar manner to that described in Example 1 using 2-(4-ethoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside instead of 2-(4-methoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside.

¹H-NMR (CD₃OD) δ ppm:

1.35 (3H, t, J=6.8Hz), 3.35-3.55 (4H, m), 3.60-3.75 (1H, m), 3.80-4.10 (5H, m), 4.90 (1H, d, J=7.1Hz), 6.70-6.85 (2H, m), 6.85-6.95 (1H, m), 7.00-7.20 (5H, m)

Example 6

2-(4-Isopropoxybenzyl)phenyl β-D-Glucopyranoside

[0057] The title compound was prepared in a similar manner to that described in Example 1 using 2-(4-isopropoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside instead of 2-(4-methoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside.

¹H-NMR (CD₃OD) δ ppm:

1.27 (6H, d, J=6.0Hz), 3.35-3.55 (4H, m), 3.69 (1H, dd, J=5.4, 12.1Hz), 3.88 (1H, dd, J=2.0, 12.1Hz), 3.91 (1H, d, J=15.0Hz), 4.02 (1H, d, J=15.0Hz), 4.51 (1H, heptet, J=6.0Hz), 4.91 (1H, d, J=7.7Hz), 6.70-6.85 (2H, m), 6.85-6.95 (1H, m), 7.00-7.10 (1H, m), 7.10-7.20 (4H, m)

Example 7

5-Hydroxymethyl-2-(4-propoxybenzyl)phenyl β-D-glucopyranoside

[0058] The title compound was prepared in a similar manner to that described in Example 1 using 5-acetoxymethyl-2-(4-propoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside instead of 2-(4-methoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside.

¹H-NMR (CD₃OD) δ ppm:

1.02 (3H, t, J=7.4Hz), 1.70-1.85 (2H, m), 3.30-3.55 (4H, m), 3.65-3.75 (1H, m), 3.80-3.95 (4H, m), 4.00 (1H, d, J=15.0Hz), 4.54 (2H, s), 4.93 (1H, d, J=7.4Hz), 6.70-6.85 (2H, m), 6.85-6.95 (1H, m), 7.02 (1H, d, J=7.7Hz), 7.05-7.20 (3H, m)

Example 8

2-(4-Ethylbenzyl)-5-hydroxymethylphenyl β-D-glucopyranoside

[0059] The title compound was prepared in a similar manner to that described in Example 1 using 5-acetoxymethyl-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside instead of 2-(4-methoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside.

¹H-NMR (CD₃OD) δ ppm:

1.19 (3H, t, J=7.6Hz), 2.57 (2H, q, J=7.6Hz), 3.30-3.55 (4H, m), 3.65-3.75 (1H, m), 3.85-4.00 (2H, m), 4.04 (1H, d, J=15.0Hz), 4.54 (2H, s), 4.93 (1H, d, J=7.4Hz), 6.85-6.95 (1H, m), 7.02 (1H, d, J=7.7Hz), 7.06 (2H, d, J=8.1Hz), 7.10-7.20 (3H, m)

Example 9

2-[4-(2-Hydroxyethyl)benzyl]-5-hydroxymethylphenyl β-D-glucopyranoside

[0060] The title compound was prepared in a similar manner to that described in Example 1 using 2-[4-(2-acetoxyethyl)benzyl]-5-acetoxymethylphenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside instead of 2-(4-methoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside.

¹H-NMR (CD₃OD) δ ppm:

2.76 (2H, t, J=7.1Hz), 3.30-3.55 (4H, m), 3.60-3.75 (3H, m), 3.85-4.00 (2H, m), 4.05 (1H, d, J=14.6Hz), 4.54 (2H, s), 4.92 (1H, d, J=7.2Hz), 6.85-6.95 (1H, m), 7.03 (1H, d, J=7.9Hz), 7.09 (2H, d, J=7.8Hz), 7.10-7.20 (3H, m)

Example 10

2-[4-(2-Hydroxyethyl)benzyl]phenyl β-D-glucopyranoside

[0061] To a solution of 2-[4-(2-benzoyloxyethyl)benzyl]phenol (0.49g) and 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (1.7g) in toluene (5.2mL) and dichloromethane (2.2mL) was added boron trifluoride diethyl ether complex (0.56mL), and the mixture was stirred at 25°C for 8 hours. To the reaction mixture were added ethyl acetate (70mL) and a saturated aqueous sodium hydrogen carbonate solution (25mL), and the organic layer was separated. The organic layer was washed with brine (25mL) and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in methanol (5mL) and tetrahydrofuran (2.5mL), sodium methoxide (28% methanol solution, 0.14mL) was added to the solution, and the resulting mixture was stirred at 25°C for 12.5 hours. To the reaction mixture were added ethyl acetate (75mL) and water (20mL) and the organic layer was separated. The organic layer was washed with brine (20mL) and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in methanol (7.5mL), sodium methoxide (28% methanol solution, 0.085mL) was added to the solution, and the resulting mixture was stirred at 25°C for 5 hours. The reaction mixture was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 4/1). The solvent was removed under reduced pressure, diethyl ether was added to the residue, and the resulting precipitates were collected by filtration. The obtained solid was washed with diethyl ether and dried under reduced pressure to give 2-[4-(2-hydroxyethyl)benzyl]phenyl β-D-glucopyranoside (0.47g).

¹H-NMR (CD₃OD) δ ppm:

2.76 (2H, t, J=7.1Hz), 3.35-3.55 (4H, m), 3.65-3.75 (3H, m), 3.88 (1H, dd, J=1.8, 11.8Hz), 3.95 (1H, d, J=15.2Hz), 4.07 (1H, d, J=15.2Hz), 4.90 (1H, d, J=7.4Hz), 6.85-6.95 (1H, m), 7.00-7.20 (7H, m)

Example 11

2-[4-(3-Hydroxypropyl)benzyl]phenyl β-D-glucopyranoside

[0062] The title compound was prepared in a similar manner to that described in Example 10 using 2-[4-(3-benzoyloxy-propyl)benzyl]phenol instead of 2-[4-(2-benzoyloxyethyl)-benzyl]phenol.

¹H-NMR (CD₃OD) δ ppm:

1.70-1.85 (2H, m), 2.55-2.65 (2H, m), 3.30-3.60 (6H, m), 3.69 (1H, dd, J=5.2, 11.9Hz), 3.88 (1H, dd, J=2.0, 11.9Hz), 3.95 (1H, d, J=15.1Hz), 4.06 (1H, d, J=15.1Hz), 4.90 (1H, d, J=7.3Hz), 6.85-6.95 (1H, m), 7.00-7.20 (7H, m)

Example 12

2-[4-Ethylthiobenzyl]phenyl β-D-glucopyranoside

[0063] To a solution of 2-[4-ethylthiobenzyl]phenol (0.51g) and 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (2.4g) in toluene (6.3mL) and dichloromethane (2.7mL) was added boron trifluoride diethyl ether complex (0.78mL), and the mixture was stirred at room temperature for 9 hours. To the reaction mixture were added ethyl acetate (70mL) and a saturated aqueous sodium hydrogen carbonate solution (25mL), and the organic layer was separated. The organic layer was washed with brine (25mL), dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in methanol (10.5mL), sodium methoxide (28% methanol solution, 0.08mL) was added to the solution, and the mixture was stirred at 25°C for 18 hours. To the reaction mixture were added ethyl acetate (75mL) and water (20mL), and the organic layer was separated. The organic layer was washed with brine (20mL), dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1). The solvent was removed under reduced pressure, diethyl ether was added to the residue, and the resulting precipitates were collected by filtration. The obtained colorless solid was washed with diethyl ether and dried under reduced pressure to give 2-[4-ethylthiobenzyl]phenyl β-D-glucopyranoside (0.51g).

¹H-NMR (CD₃OD) δ ppm:

1.24 (3H, t, J=7.3Hz), 2.88 (2H, q, J=7.3Hz), 3.35-3.55 (4H, m), 3.69 (1H, dd, J=5.0, 12.2Hz), 3.88 (1H, dd, J=2.0, 12.2Hz), 3.95 (1H, d, J=15.1Hz), 4.08 (1H, d, J=15.1Hz), 4.91 (1H, d, J=7.3Hz), 6.85-7.00 (1H, m), 7.00-7.10 (1H, m), 7.10-7.30 (6H, m)

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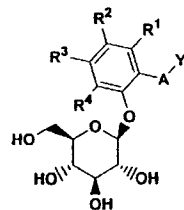
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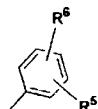
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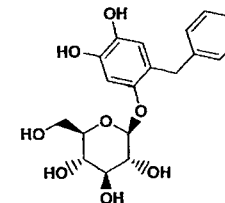
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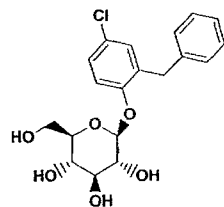


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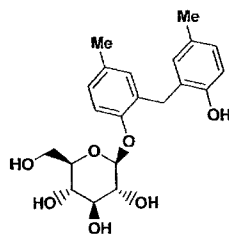
(57) Abstract: Formula (1) wherein Y is
formula (a) or heteroaryl; A is -(CH₂)_m, S,
-NH(CH₂)_n, or (CH₂)_n where n is 0-3 and m
is 0-2; and R¹ to R⁶ are as defined herein. A
method is also provided for treating diabetes
and related diseases employing an SGLT2
inhibiting amount of the above compound alone
or in combination with one, two or more other
antidiabetic agents, and/or one, two or more
hypolipidemic agents.JP 08027006-A discloses derivatives of structure **A**
where various combinations of the glucose hydroxyl are
acylated and appears to be similar to EP 598359A1EP 684254-A1 appears to encompass derivatives of
structure **B** disclosed in JP 09188625A.Other disclosures and publications which disclose
SGLT2 inhibitors are as following:K. Tsujihara, et. al., Chem. Pharm. Bull. **44**,
1174-1180 (1996)M. Hongu et. al., Chem. Pharm. Bull. **46**, 22-33
(1998)M. Hongu et. al., Chem. Pharm. Bull. **46**, 1545-1555
(1998)A. Oku et. al., Diabetes, **48**, 1794-1800 (1999)JP 10245391 (Dainippon) discloses 500 structures
as hypoglycemic agents for treatment of diabetes. These
are O-glucosides of hydroxylated coumarins.Other references disclosing structures of O-
arylglucosides, shown below, which are closely related to
the genus disclosed herein are:1) G. K. Jain et. al., Indian J. Chem., **26B**, 163-166
(1989)2) A. Levai et. al., Acta Chim. Acad. Sci. Hung.,
84, 99-107 (1975)

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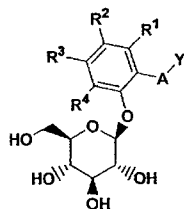


3) H. Kaemmerer et al., *Makromol. Chem.*, **182**, 1351-1361 (1981)

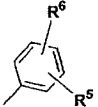


Description of the Invention

In accordance with the present invention, O-aryl glucoside compounds are provided which have the structure I.



wherein

when Y is  or heteroaryl;

R¹, R², R³, and R⁴ are the same or different and are independently selected from hydrogen, OH, OR⁷, lower alkyl, or halogen, or two of R¹, R², R³, and R⁴ together with the carbons to which they are attached can form an annelated five, six or seven membered carbocycle or

heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO₂;

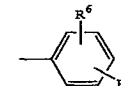
R⁵ and R⁶ are the same or different and are independently selected from hydrogen, OH, OR^{7a}, -OAr^{yl}, -OCH₂Ar^{yl}, lower alkyl, cycloalkyl, Ar^{yl}, arylalkyl, CF₃, arylalkenyl, -OCHF₂, -OCF₃, halogen, -CN, -CO₂R^{7b}, -CO₂H, COR^{8f}, CHOHR^{8g}, CH(OR^{7b})R^{8h}, -CONR^{8a}, -NHCOR^{7c}, -NHSO₂R^{7d}, -NHSO₂Ar^{yl}, -SR^{7e}, -SOR^{7f}, -SO₂R^{7g}, -SO₂Ar^{yl}, -OCH₂CO₂R⁷ⁱ, -OCH₂CO₂H, -OCH₂CONR^{8b}R^{8c}, -OCH₂CH₂NR^{8d}R^{8e}, or a five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO₂, or R⁵ and R⁶ together with the carbons to which they are attached form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO₂;

R⁷, R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, R^{7g}, R^{7h}, and R⁷ⁱ are independently lower alkyl;

R⁸, R^{8a}, R^{8b}, R^{8c}, R^{8d}, R^{8e}, R^{8f}, R^{8g}, and R^{8h} are the same or different and are independently selected from hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or together with the nitrogen to which they are attached form an annelated five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO₂;

A is O(CH₂)_m, S, NH(CH₂)_m, or (CH₂)_n where n is 0-3 and m is 0-2, and a pharmaceutically acceptable salt thereof, all stereoisomers thereof, and all prodrug esters thereof.

The compounds of formula I of the invention as defined above also include the following provisos that



where A is CH₂ and Y is and when

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- 1) R^1 is OH and R^3 is alkyl, at least one of R^1 , R^4 , R^5 and R^6 is not hydrogen, and preferably 4- R^6 is other than hydrogen;
- 2) R^2 and R^3 are OH, at least one of R^1 , R^4 , R^5 and R^6 is not hydrogen, and preferably 4- R^6 is other than hydrogen;
- 3) R^2 is methyl, R^5 is OH, and R^6 is alkyl, at least one of R^1 , R^3 , and R^4 is not hydrogen; and
- 4) R^2 is chlorine, at least one of R^1 , R^3 , R^4 , R^5 and R^6 is not hydrogen, and preferably 4- R^6 is other than hydrogen.

In the compounds of formula I, where A is $O(CH_2)_m$ or $NH(CH_2)_m$, the heteroatom O or N will be linked to the aryl ring directly joined to the glucoside moiety.

The compounds of formula I of the invention possess activity as inhibitors of the sodium dependent glucose transporters found in the intestine and kidney of mammals and are useful in the treatment of diabetes and the micro- and macro-vascular complications of diabetes such as retinopathy, neuropathy, nephropathy, and wound healing.

The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds and for methods of using such compounds.

In addition, in accordance with the present invention, a method is provided for treating diabetes, especially type II diabetes and related diseases including complications of diabetes, including retinopathy, neuropathy, nephropathy and wound healing, and related diseases such as insulin resistance, hyperglycemia, hyperinsulinemia, Syndrome X, elevated blood levels of fatty acids or glycerol, obesity, hypertriglyceridemia, atherosclerosis and hypertension, and for increasing high density lipoprotein levels, wherein a therapeutically effective amount of a compound

of structure I of the invention is administered to a human patient in need of treatment.

In addition, in accordance with the present invention, a method is provided for treating diabetes and related diseases as defined above and hereinafter, wherein a therapeutically effective amount of a combination of a compound of structure I of the invention and one, two or more of other types antidiabetic agents and/or one, two or more other types of therapeutic agents is administered to a human patient in need of treatment.

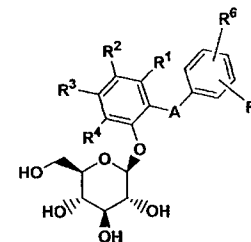
The conditions, diseases, and maladies collectively referred to as "Syndrome X" (also known as Metabolic Syndrome) are detailed in Johannsson *J. Clin. Endocrinol. Metab.*, 82, 727-34 (1997).

The term "other type of therapeutic agents" as employed herein refers to one or more antidiabetic agents (other than SGLT2 inhibitors of formula I), one or more anti-obesity agents, and/or one or more lipid-lowering agents (including anti-atherosclerosis agents).

In the above method of the invention, the compound of structure I will be employed in a weight ratio to the antidiabetic agent(s) and/or hypolipidemic agent(s) (depending upon its mode of operation) within the range from about 0.01:1 to about 300:1, preferably from about 0.1:1 to about 100:1, and more preferably from about 0.1:1 to about 10:1.

Preferred are compounds of formula IA

IA



wherein A is CH_2 or O or S.

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More preferred are compounds of formula IA where A is CH₂;

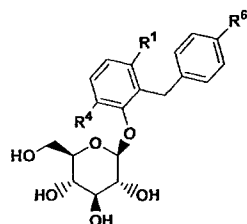
R¹ is H, halogen or alkyl;

R² and R³ are each H;

R⁵ is H.

Most preferred are compounds of formula I of the structure IB

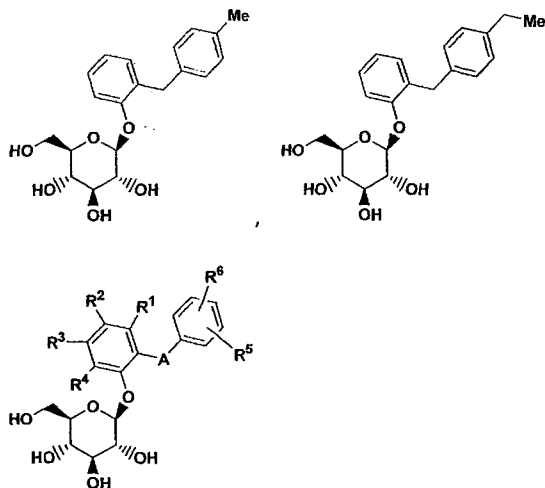
IB



where R¹ is hydrogen, halogen or alkyl or R¹ and R⁴ are independently H or alkyl;

R⁶ is hydrogen, alkyl, R^{7a}O, CHF₂O, CF₃O or R^{7e}S.

Examples of preferred compounds of formula I of the invention include compounds having the structure



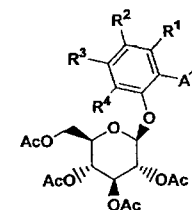
*R⁶ = H unless otherwise indicated

A	R ¹	R ²	R ³	R ⁴	R ⁵
CH ₂	H	H	H	H	4-MeO
CH ₂	H	H	H	H	4-tBu
CH ₂	H	H	H	H	4-MeS
CH ₂	H	H	H	H	4-iPr
CH ₂	H	H	H	H	4-Cl
CH ₂	H	H	H	H	4-CF ₃
CH ₂	H	H	H	H	4-CF ₃ O
CH ₂	Me	H	H	H	H
CH ₂	H	H	H	Me	4-MeS
CH ₂	H	H	H	Me	4-Me
CH ₂	Cl	H	H	H	H

The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds and for methods of using such compounds.

The compounds of formula I of the invention may be prepared as shown in the following reaction schemes and description thereof wherein temperatures are expressed in degrees Centigrade.

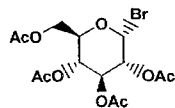
Compounds of formula I of the invention can be prepared from compounds of formula II



by treatment of II with a base such as LiOH or NaOH in a solvent such as 3:1 MeOH/H₂O or 3:2:1 MeOH/THF/H₂O.

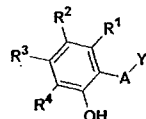
Compounds of formula II can be prepared by reacting commercially available 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide III

III



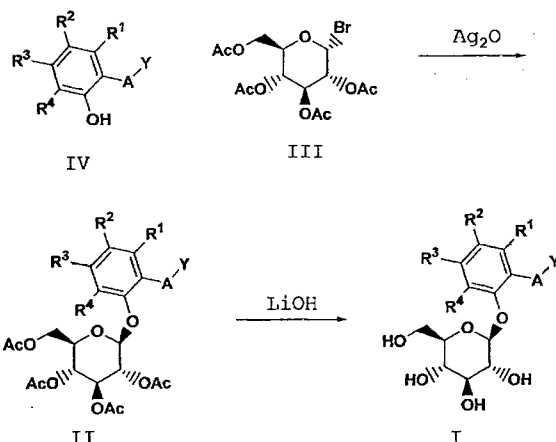
with compounds of formula IV

IV



in the presence of Ag_2O in a solvent such as lutidine or quinoline or in the presence of silver triflate in a solvent such as CH_2Cl_2 containing a base such as 2,6-di-*t*-butyl-4-methylpyridine.

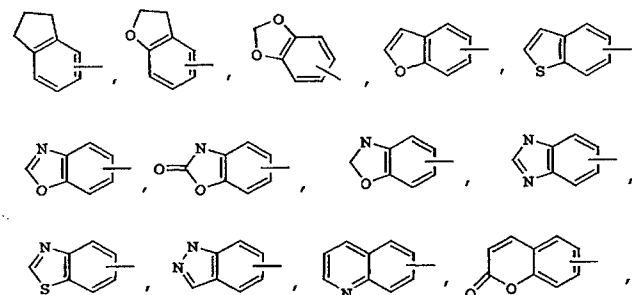
Scheme 1



Compounds of formula IV where A is $(\text{CH}_2)_n$ with $n = 1-3$ can be prepared from compounds of formula V

The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

- Unless otherwise indicated, the term "aryl" or "Aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may optionally include one to three additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings for example



and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, alkoxycarbonyl, arylcarbonyl, arylalkenyl, aminocarbonylaryl, arylthio, arylsulfinyl, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the

definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonaminocarbonyl and/or any of the alkyl substituents set out herein.

Unless otherwise indicated, the term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

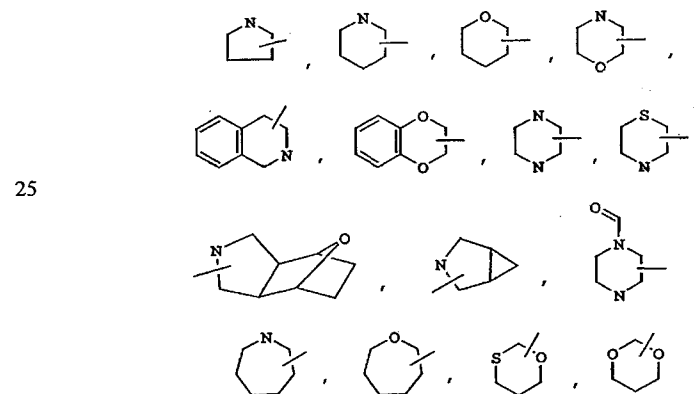
Unless otherwise indicated, the term "substituted amino" as employed herein alone or as part of another group refers to amino substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl or thioalkyl. These substituents may be further substituted with a carboxylic acid and/or any of the alkyl substituents as set out above. In addition, the amino substituents may be taken together with the nitrogen atom to which they are attached to form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiomorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-azepinyl, optionally substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy.

Unless otherwise indicated, the term "lower alkylthio", "alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

Unless otherwise indicated, the term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

Unless otherwise indicated, the term "acyl" as employed herein by itself or part of another group, as defined herein, refers to an organic radical linked to a carbonyl $\left(\begin{smallmatrix} \text{O} \\ \parallel \\ \text{C} \end{smallmatrix} \right)$ group; examples of acyl groups include any of the alkyl substituents attached to a carbonyl, such as alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl, cycloheteroalkanoyl and the like.

Unless otherwise indicated, the term "cycloheteroalkyl" as used herein alone or as part of another group refers to a 5-, 6- or 7-membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(\text{CH}_2)_p$ (where p is 1, 2 or 3), such as

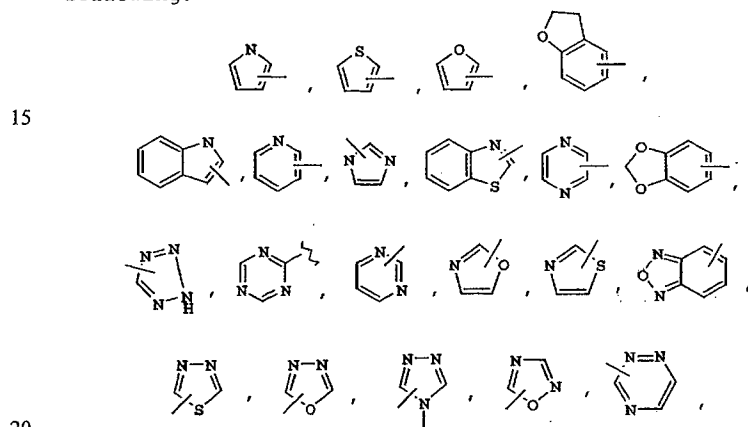


30 and the like. The above groups may include 1 to 4 substituents such as alkyl, halo, oxo and/or any of of the alkyl substituents set out herein. In addition, any

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of the cycloheteroalkyl rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

Unless otherwise indicated, the term "heteroaryl" as used herein alone or as part of another group refers to a 5- or 6- membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur, and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), and includes possible N-oxides. The heteroaryl group may optionally include 1 to 4 substituents such as any of the alkyl substituents set out above. Examples of heteroaryl groups include the following:



and the like.

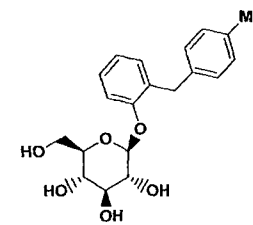
The term "cycloheteroalkylalkyl" as used herein alone or as part of another group refers to cycloheteroalkyl groups as defined above linked through a C atom or heteroatom to a $(CH_2)_p$ chain.

The term "heteroarylalkyl" or "heteroarylalkenyl" as used herein alone or as part of another group refers to a heteroaryl group as defined above linked through a C atom or heteroatom to a $-(CH_2)_p-$ chain, alkylene or alkenylene as defined above.

Ryan MJ, Johnson G, Kirk J, Fuerstenberg SM, Zager RA and Torok-Storb B. 1994. HK-2: an immortalized proximal tubule epithelial cell line from normal adult human kidney. *Kidney International* 45: 48-57.

The following Working Examples represent preferred embodiments of the present invention. All temperatures are expressed in degrees Centigrade unless otherwise indicated.

Example 1



A. 4-Methyl-2'-hydroxybenzhydrol

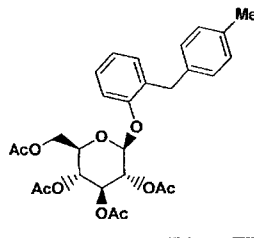
15 To a 500ml round bottom flask containing 100 mL of THF under Ar was added commercial 1 M p-methylphenyl magnesium bromide/Et₂O (100 mL, 100 mmol). Subsequently, salicylaldehyde (4.9 g, 40.3 mmol) was added dropwise in four equal portions spaced over 2 hr. After 20 min, once HPLC analysis revealed the aldehyde to be consumed, the reaction was quenched by dropwise addition of 26 ml of sat'd NH₄Cl/H₂O to produce a white paste. To this suspension was added 200 mL of PhMe and sufficient H₂O to permit stirring. The organic layer was decanted whereupon the white paste was triterated a second time with 1:1 THF/PhMe. After decanting, the combined organic layers were concentrated using a rotary evaporator to obtain 9.7 g of crude 4-methyl-2'-hydroxybenzhydrol.

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B. 2-(4'-Methylbenzyl)phenol

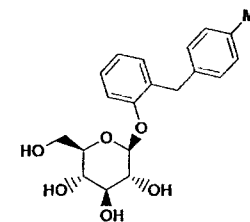
To a solution of crude Part A 4-methyl-2'-hydroxybenzhydrol (9.7 g containing no more than 40 mmol) in 175 mL of MeOH was added 0.59 g of 10% Pd/C and 1.75 mL of TFA. The suspension was stirred for 40 hr under 1
 5 atmos. H₂, filtered through celite and concentrated to yield 8.6 of crude 2-(4'-methylbenzyl)phenol as an oil.

C.



A mixture of Part B 2-(p-methylbenzyl)phenol (8.6 g, containing no more than 37 mmol), 2,6-di-*t*-butyl-4-methylpyridine (10.6 g, 52 mmol), 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide (17.5 g, 43 mmol) in 270 mL CH₂Cl₂ was stirred until homogeneous prior to cooling to 0°. After addition of AgOTf (12.2 g, 47 mmol) to the cold solution, the reaction was stirred 1 hr prior to addition of additional 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide (7.6 g, 18 mmol) and AgOTf (6.5 g, 25 mmol). An additional 100 mL of CH₂Cl₂ was required to dilute the suspension to maintain stirring. After 30 min, the suspension was directly loaded on a silica gel column which was eluted initially with 25% EtOAc/hexane.
 25 The undesired minor α anomeric product eluted first followed by desired title β -O-glucoside tetraacetate as the eluant increased from 25-35% EtOAc/hexane. After concentration, the crude product, dissolved in the minimum EtOAc, was induced to crystallize by addition of
 30 hexane. A total of 8.25 g of pure desired title beta isomer plus ~3 g of impure material was obtained.

D.



To a solution of Part C compound (8.25 g, 15 mmol) in 35 mL of CH₂Cl₂ was added MeOH (200 mL) followed by 0.7 mL of 1 N NaOH in H₂O. After 2 hr, when the reaction was complete as determined by HPLC, the volatiles were removed using a rotary evaporator. The residue, dissolved in a 1:10:10 mixture of H₂O/CH₂Cl₂/MeOH (42 mL), was
 5 diluted with CH₂Cl₂ (400 mL) and subsequently loaded onto a silica gel column. The desired product (5.68 g), after elution with 5-7% of MeOH/CH₂Cl₂ and removal of the volatiles, was isolated as a white solid.

15 ¹H NMR (400 MHz, CD₃OD) δ 7.15-7.08 (m, 4H), 7.05 (m, 3H), 6.91 (m, 1H), 4.93 (d, 1H, obscured), 4.04 (d, 1H, J=14 Hz), 3.95 (d, 1H, J=14 Hz), 3.88 (d, 1H, J=12 Hz), 3.68 (dd, 1H, J=12, 3 Hz), 3.52-3.36 (m, 4H), 2.27 (s, 3H).

20 HPLC retention time: 6.88 min, Zorbax C-18 4.6x75mm, 2.5 mL/min, detection at 220 nm, 8 min gradient 0-100% B hold 3 min at 100% B. Solvent A: 10% MeOH/H₂O + 0.2 % H₃PO₄. Solvent B: 90% MeOH/H₂O + 0.2 % H₃PO₄.

25 Anal Calcd for C₂₀H₂₄O₆ LC-MS (M+Na) 383

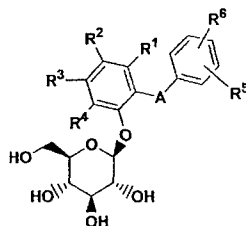
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Anal Calcd for $C_{19}H_{22}O_6S$ LC-MS: [M+H] 379, [M+Na] 401, [2M+Na] 779.

5

Examples 6 to 99

In a manner analogous to that of Examples 1 to 5, the compounds of the invention in the following table were prepared.



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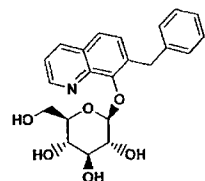
*(R⁶ = H unless otherwise indicated)

Ex. #	A	R ¹	R ²	R ³	R ⁴	R ⁵ *	MS or LC/MS (M + H) *
6	CH ₂	H	H	H	H	H	347
7	CH ₂	H	H	H	H	2-HO	363
8	CH ₂	H	H	H	H	4-MeO	377
9	CH ₂	H	H	H	H	4-tBu	403
10	CH ₂	H	H	H	H	4-MeS	393
11	CH ₂	H	H	H	H	4-Ph	423
12	CH ₂	H	H	H	H	4-BnO	453
13	CH ₂	H	H	H	H	4-iPr	389
14	CH ₂	H	H	H	H	4-Cl	381
15	CH ₂	H	H	H	H	4-MeSO ₂	425
16	CH ₂	H	H	H	H	4-CF ₃	415
17	CH ₂	H	H	H	H	4-CF ₃ O	431
18	CH ₂	H	H	H	H	4-OCH ₂ CO ₂ H	426
19	CH ₂	H	H	H	H	4-OCH ₂ CO ₂ Me	435
20	CH ₂	H	H	H	H	4-OCH ₂ CONET ₂	476
21	CH ₂	H	H	H	H	4-OCH ₂ CH ₂ NMe ₂	434

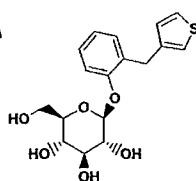
22	CH ₂	H	H	H	H	4-styrenyl	449
23	CH ₂	H	H	H	H	3-Me	361
24	CH ₂	H	H	H	H	3-MeO	377
25	CH ₂	H	H	H	H	2-MeO	377
26	CH ₂	H	H	H	H	2-Et	375
27	CH ₂	H	H	H	H	2,4-Me ₂	375
28	CH ₂	H	H	H	H	3-Cl, 4-Me	394
29	CH ₂	H	H	H	H	3,4-OCH ₂ O	391
30	CH ₂	Cl	H	H	H	H	381
31	CH ₂	Me	H	H	H	H	361
32	CH ₂	H	Me	H	H	H	361
33	CH ₂	H	F	H	H	H	365
34	CH ₂	H	Cl	H	H	H	381
35	CH ₂	H	(p-MeBn)	H	H	H	465
36	CH ₂	H	Cl	H	H	2-HO, 5-Cl	431
37	CH ₂	H	Cl	H	Br	H	459
38	CH ₂	H	Br	H	Br	H	503
39	CH ₂	H	(1,1,3,3-Me ₄ -Bu)	H	H	2,4-Cl ₂	527
40	CH ₂	H	H	MeO	H	H	377
41	CH ₂	H	H	MeO	H	4-Me	391
42	CH ₂	H	H	PrO	H	H	405
43	CH ₂	H	H	Me	H	H	361
44	CH ₂	H	H	Cl	H	H	381
45	CH ₂	H	H	H	Cl	H	381
46	CH ₂	H	H	H	Me	4-MeS	407
47	CH ₂	H	H	H	Me	4-HO	377
48	CH ₂	H	H	H	Me	4-Me	375
49	CH ₂	H	H	H	Me	4-MeSO ₂	439
50	Bond	H	H	H	H	H	333
51	(CH ₂) ₂	H	H	H	H	H	361
52	(CH ₂) ₃	H	H	H	H	H	375
53	OCH ₂	H	H	H	H	H	363
54	OCH ₂ CH ₂	H	H	H	H	4-MeO	407

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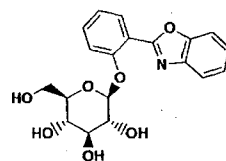
55	NH	H	H	H	H	4-Me	361
56	NHCH ₂	H	H	H	H	H	362
57	NHCH ₂	H	H	H	H	4-Me	376
58	NHCH ₂	H	H	H	H	2,3-Benzo	412
59	NHCH ₂	H	H	H	H	4-MeO	392
60	NHCH ₂	H	H	H	F	4-CF ₃	430
61	NHCH ₂	H	H	H	H	3-Me	376
62	NHCH ₂	H	H	H	H	4-Me ₂ N	405
63	NHCH ₂	H	H	H	H	4-MeS	408
64	NHCH ₂	H	H	H	H	2-Me	376
65	NHCH ₂	H	H	H	H	2,3-OCH ₂ O	406
66	NHCH ₂ CH ₂	H	H	H	H	H	376



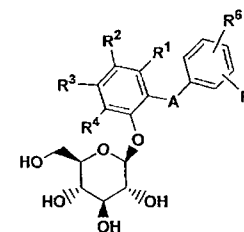
Example 67
M+H 398



Example 68
M+H 353



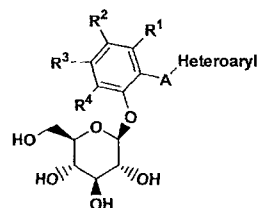
Example 69
M+H 374



*(R⁶ = H unless otherwise indicated)

Ex. #	A	R ¹	R ²	R ³	R ⁴	R ⁵	MS or LC/MS (M+H) ⁺
70	CH ₂	Me	H	H	H	4-Me	392 (M+NH ₄)
71	CH ₂	Me	H	H	H	4-Et	387 (M-H)
72	CH ₂	Me	H	H	H	4-Cl	
73	CH ₂	Me	H	H	H	4-MeS	
74	CH ₂	Me	H	H	H	4-MeO	
75	CH ₂	Me	H	H	H	4-HO	
76	CH ₂	Me	H	H	H	4-MeSO ₂	
77	CH ₂	Me	H	H	H	4-CF ₃ O	502 (M-H+MeCO ₂ ⁻)
78	CH ₂	Me	H	H	H	4-CF ₃	
79	CH ₂	Me	H	H	H	4-Ac	
80	CH ₂	Me	H	H	H	4-HOCH ₂	
81	CH ₂	Me	H	H	H	4-CHF ₂ O	
82	CH ₂	H	H	H	Me	4-Et	
83	CH ₂	H	H	H	Me	4-CHF ₂ O	
84	CH ₂	H	H	H	Me	H	378 (M+NH ₄)
85	CH ₂	H	H	H	Me	4-Cl	
86	CH ₂	H	H	H	Me	4-AC	
87	CH ₂	H	H	H	Me	4-HOCH ₂	
88	CH ₂	H	H	H	Me	4-CF ₃ O	
89	CH ₂	H	H	H	Me	4-CH ₃ O	408 (M+NH ₄)
90	CH ₂	H	H	H	H	4-Ac	
91	CH ₂	H	H	H	H	4-HOCH ₂	
92	CH ₂	H	H	H	H	4-CHF ₂ O	

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Ex #	A	R ¹	R ²	R ³	R ⁴	Heteroaryl
93	CH ₂	H	H	H	H	2-Pyridine
94	CH ₂	H	H	H	H	3-Pyridine
95	CH ₂	H	H	H	H	2-Oxazole
96	CH ₂	H	H	H	H	2-Thiazole
97	CH ₂	H	H	H	H	2-Benzthiazole
98	CH ₂	H	H	H	H	3-Quinoline
99	CH ₂	Me	H	H	H	2-Oxazole
100	CH ₂	H	H	H	Me	2-Thiazol
101	CH ₂	H	H	H	Me	2-Oxazole



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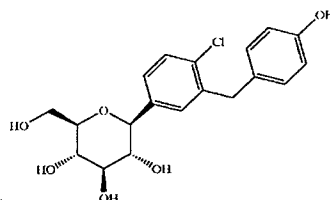
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-
- filed on Oct. 4, 2000, now Pat. No. 6,414,126.
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(52) U.S. Cl. 536/1.11; 514/23

(57) ABSTRACT

An SGLT2 inhibiting compound is provided having the
formulaA method is also provided for treating diabetes and related
diseases employing an SGLT2 inhibiting amount of the
above compound alone or in combination with another
antidiabetic agent or other therapeutic agent.

US 2002/0137903 A1

Sep. 26, 2002

C-ARYL GLUCOSIDE SGLT2 INHIBITORS AND
METHOD[0001] This application is a continuation-in-part of U.S.
application Ser. No. 09/679,027 filed Oct. 4, 2000 which
takes priority from U.S. provisional application No. 60/194,
615 filed Apr. 5, 2000 and U.S. provisional application No.
60/158,773 filed Oct. 12, 1999.

FIELD OF THE INVENTION

[0002] The present invention relates to C-aryl glucosides
which are inhibitors of sodium dependent glucose transport-
ers found in the intestine and kidney (SGLT2) and to a
method for treating diabetes, especially type II diabetes, as
well as hyperglycemia, hyperinsulinemia, obesity, hypertri-
glyceridemia, Syndrome X, diabetic complications, athero-
sclerosis and related diseases, employing such C-aryl glu-
cosides alone or in combination with one, two or more other
type antidiabetic agent and/or one, two or more other type
therapeutic agents such as hypolipidemic agents.

BACKGROUND OF THE INVENTION

[0003] Approximately 100 million people worldwide suf-
fer from type II diabetes (NIDDM), which is characterized
by hyperglycemia due to excessive hepatic glucose produc-
tion and peripheral insulin resistance, the root causes for
which are as yet unknown. Hyperglycemia is considered to
be the major risk factor for the development of diabetic
complications, and is likely to contribute directly to the
impairment of insulin secretion seen in advanced NIDDM.
Normalization of plasma glucose in NIDDM patients would
be predicted to improve insulin action, and to offset the
development of diabetic complications. An inhibitor of the
sodium-dependent glucose transporter SGLT2 in the kidney
would be expected to aid in the normalization of plasma
glucose levels, and perhaps body weight, by enhancing
glucose excretion.[0004] The development of novel, safe, and orally active
antidiabetic agents is also desired in order to complement
existing therapies, including the sulfonylureas, thiazo-
lidinediones, metformin, and insulin, and to avoid the poten-
tial side effects associated with the use of these other agents.[0005] Hyperglycemia is a hallmark of type II diabetes
(NIDDM); consistent control of plasma glucose levels in
diabetes can offset the development of diabetic complica-
tions and beta cell failure seen in advanced disease. Plasma
glucose is normally filtered in the kidney in the glomerulus
and actively reabsorbed in the proximal tubule. SGLT2
appears to be the major transporter responsible for the
reuptake of glucose at this site. The SGLT specific inhibitor
phlorizin or closely related analogs inhibit this reuptake
process in diabetic rodents and dogs resulting in normaliza-
tion of plasma glucose levels by promoting glucose excre-
tion without hypoglycemic side effects. Long term (6 month)
treatment of Zucker diabetic rats with an SGLT2 inhibitor
has been reported to improve insulin response to glycemia,
improve insulin sensitivity, and delay the onset of nephro-
pathy and neuropathy in these animals, with no detectablepathology in the kidney and no electrolyte imbalance in
plasma. Selective inhibition of SGLT2 in diabetic patients
would be expected to normalize plasma glucose by enhanc-
ing the excretion of glucose in the urine, thereby improving
insulin sensitivity, and delaying the development of diabetic
complications.[0006] Ninety percent of glucose reuptake in the kidney
occurs in the epithelial cells of the early S1 segment of the
renal cortical proximal tubule, and SGLT2 is likely to be the
major transporter responsible for this reuptake. SGLT2 is a
672 amino acid protein containing 14 membrane-spanning
segments that is predominantly expressed in the early S1
segment of the renal proximal tubules. The substrate speci-
ficity, sodium dependence, and localization of SGLT2 are
consistent with the properties of the high capacity, low
affinity, sodium-dependent glucose transporter previously
characterized in human cortical kidney proximal tubules. In
addition, hybrid depletion studies implicate SGLT2 as the
predominant Na⁺/glucose cotransporter in the S1 segment of
the proximal tubule, since virtually all Na-dependent glu-
cose transport activity encoded in mRNA from rat kidney
cortex is inhibited by an antisense oligonucleotide specific to
rat SGLT2. SGLT2 is a candidate gene for some forms of
familial glucosuria, a genetic abnormality in which renal
glucose reabsorption is impaired to varying degrees. None
of these syndromes investigated to date map to the SGLT2
locus on chromosome 16. However, the studies of highly
homologous rodent SGLTs strongly implicate SGLT2 as the
major renal sodium-dependent transporter of glucose and
suggest that the glucosuria locus that has been mapped
encodes an SGLT2 regulator. Inhibition of SGLT2 would be
predicted to reduce plasma glucose levels via enhanced
glucose excretion in diabetic patients.[0007] SGLT1, another Na-dependent glucose cotrans-
porter that is 60% identical to SGLT2 at the amino acid
level, is expressed in the small intestine and in the more
distal S3 segment of the renal proximal tubule. Despite their
sequence similarities, human SGLT1 and SGLT2 are bio-
chemically distinguishable. For SGLT1, the molar ratio of
Na⁺ to glucose transported is 2:1, whereas for SGLT2, the
ratio is 1:1. The K_m for Na⁺ is 32 and 250-300, for SGLT1
and SGLT2, respectively. K_m values for uptake of glucose
and the nonmetabolizable glucose analog α-methyl-D-glu-
copyranoside (AMG) are similar for SGLT1 and SGLT2, i.e.
0.8 and 1.6 mM (glucose) and 0.4 and 1.6 mM (AMG) for
SGLT1 and SGLT2 transporters, respectively. However, the
two transporters do vary in their substrate specificities for
sugars such as galactose, which is a substrate for SGLT1
only.[0008] Administration of phlorizin, a specific inhibitor of
SGLT activity, provided proof of concept in vivo by pro-
moting glucose excretion, lowering fasting and fed plasma
glucose, and promoting glucose utilization without hypogly-
cemic side effects in several diabetic rodent models and in
one canine diabetes model. No adverse effects on plasma ion
balance, renal function or renal morphology have been
observed as a consequence of phlorizin treatment for as long

D3

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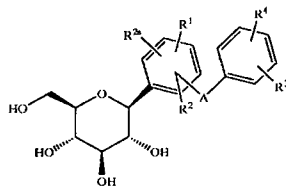
as two weeks. In addition, no hypoglycemic or other adverse effects have been observed when phlorizin is administered to normal animals, despite the presence of glycosuria. Administration of an inhibitor of renal SGLTs for a 6-month period (Tanabe Seiyaku) was reported to improve fasting and fed plasma glucose, improve insulin secretion and utilization in obese NIDDM rat models, and offset the development of nephropathy and neuropathy in the absence of hypoglycemic or renal side effects.

[0009] Phlorizin itself is unattractive as an oral drug since it is a nonspecific SGLT1/SGLT2 inhibitor that is hydrolyzed in the gut to its aglycone phloretin, which is a potent inhibitor of facilitated glucose transport. Concurrent inhibition of facilitative glucose transporters (GLUTs) is undesirable since such inhibitors would be predicted to exacerbate peripheral insulin resistance as well as promote hypoglycemia in the CNS. Inhibition of SGLT1 could also have serious adverse consequences as is illustrated by the hereditary syndrome glucose/galactose malabsorption (GGM), in which mutations in the SGLT1 cotransporter result in impaired glucose uptake in the intestine, and life-threatening diarrhea and dehydration. The biochemical differences between SGLT2 and SGLT1, as well as the degree of sequence divergence between them, allow for identification of selective SGLT2 inhibitors.

[0010] The familial glycosuria syndromes are conditions in which intestinal glucose transport, and renal transport of other ions and amino acids, are normal. Familial glycosuria patients appear to develop normally, have normal plasma glucose levels, and appear to suffer no major health deficits as a consequence of their disorder, despite sometimes quite high (110-114 g/daily) levels of glucose excreted. The major symptoms evident in these patients include polyphagia, polyuria and polydipsia, and the kidneys appear to be normal in structure and function. Thus, from the evidence available thus far, defects in renal reuptake of glucose appear to have minimal long term negative consequences in otherwise normal individuals.

[0011] The following references disclose C-aryl glucoside SGLT2 inhibitors for treating diabetes.

[0012] WO 01/27128 discloses compounds of the structure



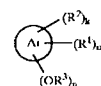
[0013] where

[0014] A is O, S, NH, or $(CH_2)_n$ where n is 0-3;

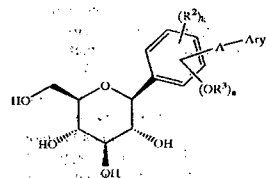
[0015] R^1 , R^2 and R^{2a} are independently hydrogen, OH, OR^a, alkyl, Cl₃, OCHF₂, OCF₃, SR²⁰ or halogen, etc;

[0016] R^1 and R^2 are independently hydrogen, OH, OR^a, OAr¹, OCH₂Ar¹, alkyl, cycloalkyl, Cl¹, OCHF₂, —OCF₃, halogen, etc. These compounds are reported to be inhibitors of the SGLT2 transporter and consequently represent a mode for treatment of diabetes and complications thereof.

[0017] WO 98/31697 discloses compounds of the structure



[0018] Where Ar includes, among others, phenyl, biphenyl, diphenylmethane, diphenylethane, and diphenylether, and R^1 is a glycoside, R^2 is H, OH, amino, halogen, carboxy, alkyl, cycloalkyl, or carboxamido, and R^3 is hydrogen, alkyl, or acyl, and k, m, and n are independently 1-4. A subset of compounds disclosed in WO 98/31697 contains compounds of the following structures

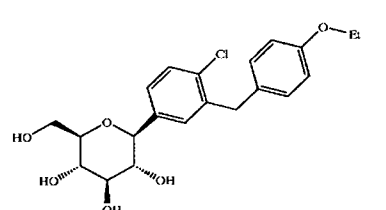


A is O or $(CH_2)_k$ where k is 0-3
 R^1 is hydrogen, alkyl, or acyl group where r is 1-4
 R^2 is hydrogen, alkyl, OH, NH₂, halogen, CO₂H or carboxinide where k is 1-4

[0019] which are disclosed for use in the treatment or prevention of inflammatory diseases, autoimmune diseases, infections, cancer, and cancer metastasis, reperfusion disorders, thrombosis, ulcer, wounds, osteoporosis, diabetes mellitus and atherosclerosis, among others.

DESCRIPTION OF THE INVENTION

[0020] In accordance with the present invention, a C-aryl glucoside compound is provided which has the structure



[0021] including pharmaceutically acceptable salts thereof, all stereoisomers thereof, and all prodrug esters thereof.

[0022] The compound of formula I possesses activity as inhibitors of the sodium dependent glucose transporters found in the intestine and kidney of mammals and is useful in the treatment of diabetes and the micro- and macrovascular complications of diabetes such as retinopathy, neuropathy, nephropathy, and wound healing.

[0023] The present invention provides for compound of formula I, pharmaceutical compositions employing such a compound and for methods of using such a compound.

[0024] In addition, in accordance with the present invention, a method is provided for treating or delaying the progression or onset of diabetes, especially type I and type II diabetes, including complications of diabetes, including retinopathy, neuropathy, nephropathy and delayed wound healing, and related diseases such as insulin resistance (impaired glucose homeostasis), hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, obesity, hyperlipidemia including hypertriglyceridemia, Syndrome X, atherosclerosis and hypertension, and for increasing high density lipoprotein levels, wherein a therapeutically effective amount of a compound of structure I is administered to a human patient in need of treatment.

[0025] In addition, in accordance with the present invention, a method is provided for treating diabetes and related diseases as defined above and hereinafter, wherein a therapeutically effective amount of a combination of a compound of structure I and another type of antidiabetic agent and/or another type of therapeutic agent such as a hypolipemic agent is administered to a human patient in need of treatment.

[0026] The conditions, diseases, and maladies collectively referred to as "Syndrome X" (also known as Metabolic Syndrome) are detailed in Johansson *J. Clin. Endocrinol. Metab.*, 82, 727-34 (1997).

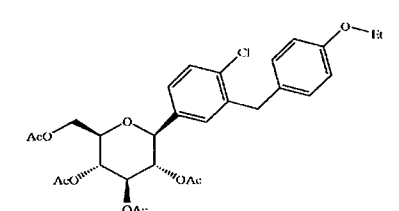
[0027] The term "other type of therapeutic agents" as employed herein refers to one or more antidiabetic agents (other than SGLT2 inhibitors of formula I), one or more anti-obesity agents, anti-hypertensive agents, anti-platelet agents, anti-atherosclerotic agents and/or one or more lipid-lowering agents (including anti-atherosclerosis agents).

[0028] In the above method of the invention, the compound of structure I of the invention will be employed in a weight ratio to the one, two or more antidiabetic agent and/or one, two or more other type therapeutic agent (depending upon its mode of operation) within the range from about 0.01:1 to about 300:1, preferably from about 0.1:1 to about 10:1.

DETAILED DESCRIPTION OF THE INVENTION

[0029] The compound of formula I of the invention can be prepared as shown in the following reaction scheme and description thereof wherein temperatures are expressed in degrees Centigrade.

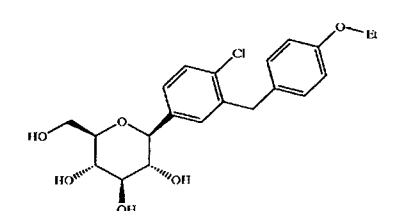
[0030] Compound of formula I can be prepared as shown in Scheme 1 by treatment of compound of formula II



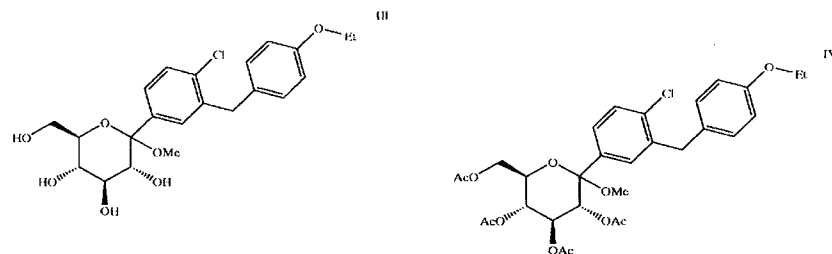
[0031] with a base such as LiOH or NaOH in a solvent such as a 1:2:3 mixture of H₂O/THF/MeOH or aq. MeOH or aq. EtOH.

[0032] The compound of formula II (which is a novel intermediate that readily crystallizes) provides a convenient means to purify crude compound of formula Ia which was obtained as a mixture of α and β anomers.

[0033] The compound of formula II can be prepared by treatment of compound of formula Ia with Ac₂O in a solvent such as CH₂Cl₂ containing pyridine and a catalyst such as dimethylaminopyridine (DMAP).

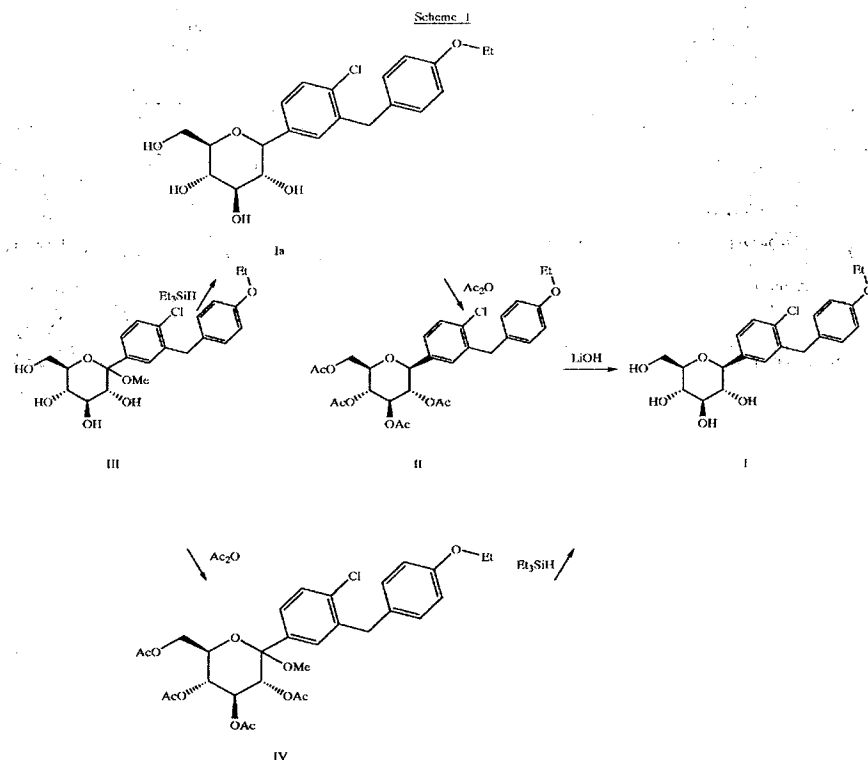


[0034] Compounds of formula Ia can be prepared by reduction of a compound of formula III with a reducing agent such as Et₃SiH in a solvent such as 1:1 CH₂Cl₂/MeCN at -10° in the presence of a Lewis acid catalyst such as BF₃·Et₂O.

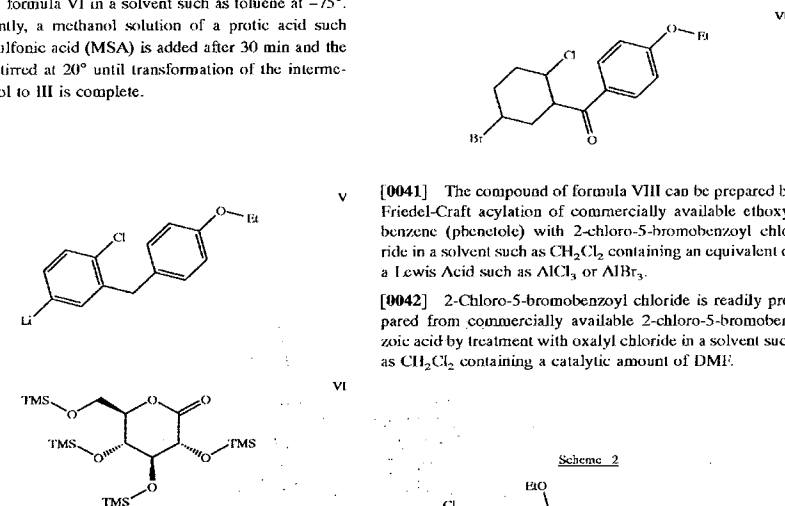


[0035] The compound of formula II can alternatively be prepared from compound of formula III by first acetylating compound of formula III with Ac_2O in a solvent such as toluene or CH_2Cl_2 containing a base such as Hunig's base or Et_3N and a catalyst such as DMAP to generate compound of formula IV.

[0036] Subsequent conversion of compound of formula IV to compound of formula II can be achieved by treatment at 20° with a reducing agent such as Et_3SiH in a solvent such as MeCN containing 1 equiv of H_2O and a Lewis acid catalyst such as $\text{BF}_3 \cdot \text{Et}_2\text{O}$.



[0037] The compound of formula III can be prepared, as outlined in Scheme 2, by 1) addition of a cold THF solution of an aryl lithium of formula V to a persilylated gluconolactone of formula VI in a solvent such as toluene at -75° . Subsequently, a methanol solution of a protic acid such as methanesulfonic acid (MSA) is added after 30 min and the solution stirred at 20° until transformation of the intermediate lactol to III is complete.



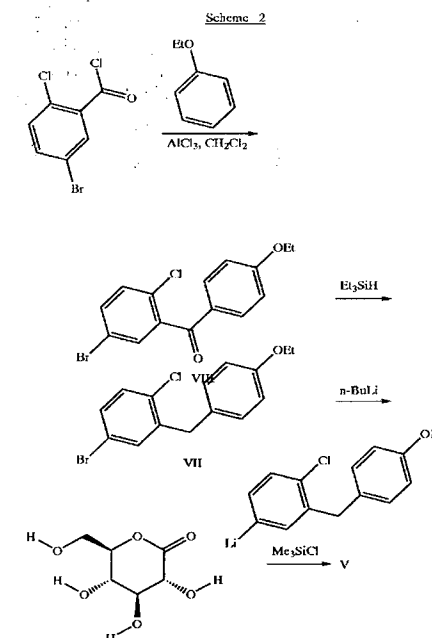
[0041] The compound of formula VIII can be prepared by Friedel-Craft acylation of commercially available ethoxybenzene (phenetole) with 2-chloro-5-bromobenzoyl chloride in a solvent such as CH_2Cl_2 containing an equivalent of a Lewis Acid such as AlCl_3 or AlBr_3 .

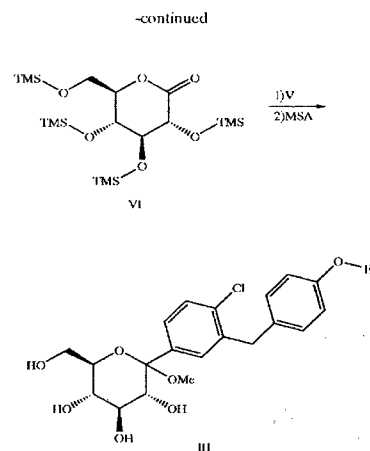
[0042] 2-Chloro-5-bromobenzoyl chloride is readily prepared from commercially available 2-chloro-5-bromobenzoic acid by treatment with oxalyl chloride in a solvent such as CH_2Cl_2 containing a catalytic amount of DME.

[0038] The compound of formula VI can be prepared by treatment of commercially available D-gluconolactone with a silylating agent such as trimethylsilyl chloride in a solvent such as THF containing a base such as N-methylmorpholine.

[0039] The compound of formula V can be prepared by treatment of compound of formula VII with an alkyl lithium such as $n\text{-BuLi}$ or $t\text{-BuLi}$ in a solvent such as THF at -75° .

[0040] The compound of formula VII can be readily prepared by treatment of compound of formula VIII with a reducing agent such as Et_3SiH in a solvent such as 1:1 $\text{CH}_2\text{Cl}_2/\text{MeCN}$ at 0° - 20° in the presence of a Lewis acid catalyst such as $\text{BF}_3 \cdot \text{Et}_2\text{O}$.





[0043] Listed below are definitions of various terms used in the description of the instant invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or as part of a larger group.

[0044] The following abbreviations are employed herein:

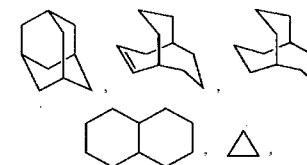
- [0045] Ph=phenyl
- [0046] Bn=benzyl
- [0047] t-Bu=tertiary butyl
- [0048] Me=methyl
- [0049] Et=ethyl
- [0050] TMS=trimethylsilyl
- [0051] TBS=tert-butyl dimethylsilyl
- [0052] THF=tetrahydrofuran
- [0053] Et₂O=diethyl ether
- [0054] EtOAc=ethyl acetate
- [0055] DMF=dimethyl formamide
- [0056] MeOH=methanol
- [0057] EtOH=ethanol
- [0058] i-PrOH=isopropanol
- [0059] HOAc or AcOH=acetic acid
- [0060] TFA=trifluoroacetic acid
- [0061] i-Pr₂NEt=diisopropylethylamine
- [0062] Et₃N=triethylamine

- [0063] DMAP=4-dimethylaminopyridine
- [0064] NaBH₄=sodium borohydride
- [0065] n-BuLi=n-butyllithium
- [0066] Pd/C=palladium on carbon
- [0067] KOH=potassium hydroxide
- [0068] NaOH=sodium hydroxide
- [0069] LiOH=lithium hydroxide
- [0070] K₂CO₃=potassium carbonate
- [0071] NaHCO₃=sodium bicarbonate
- [0072] Ar=argon
- [0073] N₂=nitrogen
- [0074] min=minute(s)
- [0075] h or hr=hour(s)
- [0076] l=liter
- [0077] mL=milliliter
- [0078] μ L=microliter
- [0079] g=gram(s)
- [0080] mg=milligram(s)
- [0081] mol=moles
- [0082] mmol=millimole(s)
- [0083] meq=milliequivalent
- [0084] RT=room temperature
- [0085] sat or sat'd=saturated
- [0086] aq.=aqueous
- [0087] TLC=thin layer chromatography
- [0088] HPLC=high performance liquid chromatography
- [0089] LC/MS=high performance liquid chromatography/mass spectrometry
- [0090] MS or Mass Spec=mass spectrometry
- [0091] NMR=nuclear magnetic resonance
- [0092] mp=melting point

[0093] Unless otherwise indicated, the term "lower alkyl" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons containing 1 to 8 carbons, and the terms "alkyl" and "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons containing 1 to 20 carbons, preferably 1 to 10 carbons, more preferably 1 to 8 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl,

2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 1 to 4 substituents such as halo, for example F, Br, Cl or I or CF₃, alkyl, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkyloxy, optionally substituted amino, hydroxy, hydroxyalkyl, acyl, alkanoyl, heteroaryl, heteroaryloxy, cycloheteroalkyl, arylheteroaryl, arylalkoxycarbonyl, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or alkylthio.

[0094] Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 3 to 10 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,



[0095] any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol and/or alkylthio and/or any of the alkyl substituents.

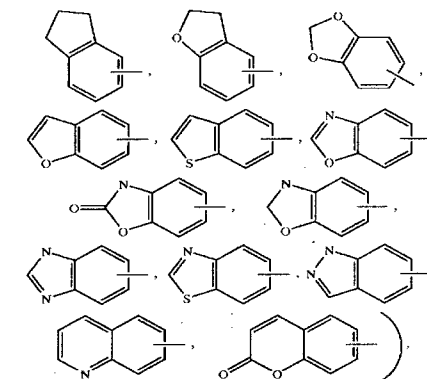
[0096] The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

[0097] The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine, with chlorine or fluorine being preferred.

[0098] The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

[0099] Unless otherwise indicated, the term "aryl" or "Aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or

naphthyl including 1-naphthyl and 2-naphthyl) and may optionally include one to three additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings for example



[0100] and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, alkoxy, carbonyl, arylcarbonyl, arylalkenyl, aminocarbonyl, arylthio, arylsulfenyl, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylamino, carbonyl, arylamino, carbonyl, alkoxy, carbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfenyl, arylsulfonamido, arylsulfonamido and arylsulfonamido carbonyl and/or any of the alkyl substituents set out herein.

[0101] Unless otherwise indicated, the term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

[0102] Unless otherwise indicated, the term "lower alkylthio", "alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

[0103] The term "polyhaloalkyl" as used herein refers to an "alkyl" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF₃CH₂, CF₃ or CF₃CF₂CH₂.

[0104] The term "polyhaloalkyloxy" as used herein refers to an "alkoxy" or "alkyloxy" group as defined above which

humans, monkeys, dogs, etc. by an oral route, for example, in the form of tablets, capsules, granules or powders, or they can be administered by a parenteral route in the form of injectable preparations, or they can be administered intranasally or in transdermal patches. The dose for adults is preferably between 10 and 2,000 mg per day, which can be administered in a single dose or in the form of individual doses from 1-4 times per day.

[0172] A typical injectable preparation is produced by aseptically placing 250 mg of compounds of structure 1 into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectable preparation.

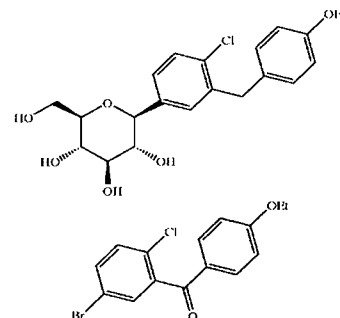
[0173] SGLT2 inhibitor activity of the compounds of the invention may be determined by use of an assay system as set out below.

[0174] Assay for SGLT2 Activity

[0175] The mRNA sequence for human SGLT2 (GenBank #M95549) was cloned by reverse-transcription and amplification from human kidney mRNA, using standard molecular biology techniques. The cDNA sequence was stably transfected into CHO cells, and clones were assayed for SGLT2 activity essentially as described in Ryan et al. (1994). Evaluation of inhibition of SGLT2 activity in a clonally selected cell line was performed essentially as described in Ryan et al., with the following modifications. Cells were grown in 96-well plates for 2-4 days to 75,000 or 30,000 cells per well in F-12 nutrient mixture (Ham's F-12), 10% fetal bovine serum, 300 µg/ml Geneticin and penicillin-streptomycin. At confluence, cells were washed twice with 10 mM Hepes/Tris, pH 7.4, 137 mM N-methyl-D-glucamine, 5.4 mM KCl, 2.8 mM CaCl₂, 1.2 mM MgSO₄. Cells then were incubated with 10 µM [¹⁴C]AMG, and 10 µM inhibitor (final DMSO=0.5%) in 10 mM Hepes/Tris, pH 7.4, 137 mM NaCl, 5.4 mM KCl, 2.8 mM CaCl₂, 1.2 mM MgSO₄ at 37° C. for 1.5 hr. Uptake assays were quenched with ice cold 1xPBS containing 0.5 mM phlorizin, and cells were then lysed with 0.1% NaOH. After addition of MicroScint scintillation fluid, the cells were allowed to shake for 1 hour, and then [¹⁴C]AMG was quantitated on a TopCount scintillation counter. Controls were performed with and without NaCl. For determination of EC₅₀ values, 10 inhibitor concentrations were used over 2 log intervals in the appropriate response range, and triplicate plates were averaged across plates.

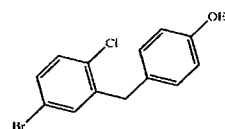
[0176] Ryan M J, Johnson G, Kirk J, Fuerstenberg S M, Zager R A and Torok-Storb B. 1994. HK-2: an immortalized proximal tubule epithelial cell line from normal adult human kidney. *Kidney International* 45: 48-57.

[0177] The following Working Examples represent preferred embodiments of the present invention. All temperatures are expressed in degrees Centigrade unless otherwise indicated.



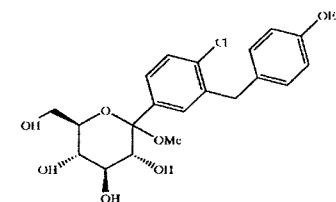
[0178] A. 5-Bromo-2-chloro-4'-ethoxybenzophenone

[0179] To a stirred suspension of commercial 5-bromo-2-chlorobenzoic acid (250 g, 1.06 mol) in 450 mL of CH₂Cl₂ containing oxalyl chloride (1.1 mol) was added 1.5 mL of DMF. Once the vigorous evolution of gas ceased, the reaction was stirred overnight prior to removal of the volatiles under vacuum using a rotary evaporator. After dissolving the crude 5-bromo-2-chlorobenzoyl chloride in 200 mL of CH₂Cl₂, the yellow solution was transferred to a 2 L 3-neck flask equipped with an overhead stirrer and an internal thermometer. The stirred mixture was cooled to -3° prior to adding phenetole (130 g, 1.08 mol). AlCl₃ (140 g, 1.07 mol) was added via a solid addition funnel over 30 min to insure that the temperature did not exceed 4°. The copious amounts of HCl gas which began to evolve after 60% of the AlCl₃ had been added were trapped by passing the gas over a stirred cone. NaOH solution. HPLC revealed the reaction to be 95% complete 10 minutes after the addition was finished. After the mixture was stirred at 4° for 1 hr, the reaction was quenched by pouring over ice. Subsequently, the suspension was diluted with H₂O (1 L) and extracted 3x with CH₂Cl₂. The combined organic extracts were washed 2x with 1N HCl, 1x with H₂O, 2x with 1M NaOH, and 2x with brine prior to drying over Na₂SO₄. After removal of the volatiles, HPLC revealed the residue to be a 1:7 mixture of ortho/para isomers. Recrystallization 2x from 400 mL of absolute EtOH yielded 230 g (64%) of 5-bromo-2-chloro-4'-ethoxybenzophenone.

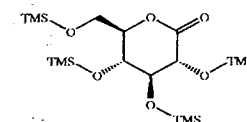


[0180] B. 5-Bromo-2-chloro-4'-ethoxydiphenylmethane

[0181] To a stirred solution of Et₃SiH (400 mL, 2.51 mol) and 5-bromo-2-chloro-4'-ethoxybenzophenone (390 g, 1.15 mol) in 900 mL of a 1:2 mixture 1,2-dichloroethane/MeCN at 10° C. was added BF₃·Et₂O (150 mL, 1.58 mol) at such a rate that the temperature did not exceed 20°. Caution a moderate exotherm insures during the addition. After stirring overnight at 20° C., HPLC revealed the reaction to be 90% complete. After adding an additional 40 mL Et₃SiH and 15 mL of BF₃·Et₂O, the reaction was heated to 50° for 3 hr. (Note elevated temperatures increase formation of the Ritter reaction product N-acetyl 5-bromo-2-chloro-4'-ethoxydiphenylmethanamine). Upon cooling, the reaction was quenched with 120 g of KOH in 300 mL of H₂O. After stirring 2 hr, the layers were separated. The aqueous layer was extracted 2x with CH₂Cl₂; the combined organic layers were washed 1x with 300 mL portions of 2M KOH, 2x with H₂O containing 10% brine to aid phase separation and with brine 2x prior to drying over Na₂SO₄. After removal of the volatiles, the residue was recrystallized from absolute EtOH to yield 230 g of 5-bromo-2-chloro-4'-ethoxydiphenylmethane as a white solid.

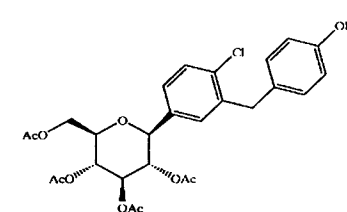


[0184] To a stirred -78° solution of Part B 5-bromo-2-chloro-4'-ethoxydiphenylmethane (150 g, 0.46 mol) in 1.15 L of 1:2 dry THF/toluene under Ar was added 184 mL of 2.5 M n-BuLi in hexane dropwise to insure the temperature remained below -70°. After stirring for 30 minutes following the addition, this solution was transferred by cannula to a stirred -78° solution of Part C 2,3,4,6-tetra-O-trimethylsilyl-β-D-glucolactone (236 g, 0.51 mol) in 1.1 L of toluene at a rate that maintained the reaction below -70°. The solution was stirred for 30 min at -78° prior to quenching by addition of 1 L of MeOH containing methanesulfonic acid (41.8 mL, 0.64 mol). The reaction stirred overnight as the temperature rose to 20° C. HPLC analysis reveals two new peaks corresponding to the mass of the expected O-methylglucoside; the ratio typically varies from 95:5 to 80:20. The desired product corresponds to the major one with shorter retention time. Note longer reaction times or addition of 50% more methanesulfonic acid will convert all of the isomeric product to the desired O-methylglucoside. The reaction, once complete, was quenched by the addition of NaHCO₃ (37 g, 0.37 mol) in 200 mL of H₂O. If the pH was not weakly basic, more NaHCO₃ was added prior to dilution 2 fold with H₂O and 3 extractions with EtOAc. The combined EtOAc fractions were washed with brine and dried over Na₂SO₄. After concentration using a rotary evaporator, the residue was dissolved in hot toluene (150 mL). The resulting solution was poured into a liter of stirred hexane. The precipitate was collected by vacuum filtration; the resulting filter cake was washed 2x with 500 mL of hexane and then air dried to yield 171 g of title compound in the form of a white solid.

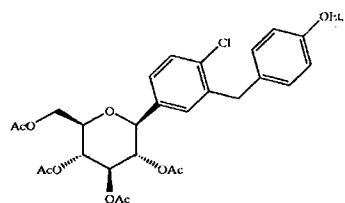


[0182] C. 2,3,4,6-tetra-O-Trimethylsilyl-β-D-glucolactone

[0183] To a stirred -5° C. solution of gluconolactone (239 g, 1.34 mol) and N-methylmorpholine (1180 mL, 10.73 mol) in 2.4 L of THF under Ar was added trimethylsilyl chloride (1022 mL, 8.05 mol) via dropping funnel at a rate such that the temperature did not exceed 5° C. After 1 hr the stirred reaction was heated to 35° C. for 5 hr whereupon it was allowed to cool to 20° C. as the reaction stirred overnight. After dilution with 3.6 L of toluene, the mixture was cooled to 0-5° C. prior to cautiously adding 7 L of H₂O at a rate such that the temperature did not exceed 10° C. Note, a severe exotherm results upon addition of the first portion of H₂O. After mixing, the phases were allowed to separate and then split. The organic phase was washed with aq. NaI₂PO₄ (2 L), H₂O (1 L), and brine (1 L). The organic layer was then concentrated under vacuum using a rotary evaporator; the resultant light yellow oil was twice taken up 250 mL of toluene and reconcentrated to yield 616 g of title compound.



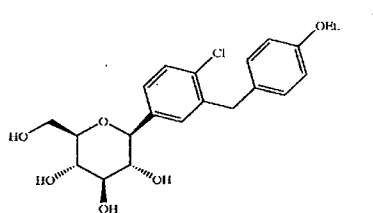
[0185] To a stirred -10° solution of Part D O-methylglucoside (123 g, 0.28 mol) in 1.2 L of 1:1 $\text{CH}_2\text{Cl}_2/\text{MeCN}$ was added Et_3SiH (65.27 g, 0.56 mol) followed by addition of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (59.75 g, 0.42 mol) at a rate such that the temperature was maintained between -5 – 10° . The stirred solution was allowed to warm to 0° over 5 hr. When HPLC analysis revealed that the reaction was complete, the reaction was quenched by addition of satd. aq. NaHCO_3 (310 mL). The organic volatiles were removed under vacuum using a rotary evaporator. The residue was partitioned between 2 L each of EtOAc and H_2O . After separating phases, the H_2O layer was extracted 2x with 2 L portions of EtOAc . The combined organic phases were washed with H_2O (2 L) and with brine (2 L) prior to drying over MgSO_4 and then concentrated using a rotary evaporator to yield 104.6 g of yellow solidified foam. After dissolution of this residue in CH_2Cl_2 (750 mL), pyridine (200 g, 2.53 mol) was added followed by Ac_2O (261.1 g, 2.56 mol) in one portion. After the resulting exotherm raising the temperature from 28° to 47° had subsided, DMAP (1.56 g, 13 mmol) was added. The reaction was quenched after 1.5 hr by addition of H_2O (1.8 L) once HPLC analysis indicated the reaction to be complete. The mixture was extracted 2x with CH_2Cl_2 (total volume 2.7 L); the combined organic layers were washed 2x with 1N HCl (1.8 L), 2x with brine (1.8 L) prior to drying over MgSO_4 . The residue, after concentration using a rotary evaporator, was recrystallized from absolute EtOH (750 mL) to yield 89.5 g of the desired tetraacetylated β -C-glucoside as a white solid. The mother liquors contained the corresponding α -C-glucoside as well as a more polar furanose isomer.



[0186] Alternatively the O-methylglucoside of Part D can first be acetylated and then reduced to yield the desired tetraacetylated C-arylglucoside utilizing the following procedure.

[0187] A solution of Part D O-methylglucoside (3.0 g, 6.8 mmol) in toluene (45 mL) containing diisopropylethylamine (6.9 mL, 40 mmol) was cooled to 0° prior to addition of acetic anhydride (3.35 mL, 35.5 mmol) and DMAP (84 mg, 0.68 mmol). The solution was allowed to gradually warm to 20° ; after six hours, the analysis revealed complete conversion to tetraacetate. The reaction was quenched by addition of 50 mL of 20% H_3PO_4 . After separation of the layers, the aq. phase was extracted 2x with toluene. The combined organic phases were washed 1x with 50 mL of H_2O prior to concentration under vacuum. The resultant oil was dissolved in 20 mL of toluene and reconcentrated to yield a thick oil (4.15 g) that was used without further purification.

[0188] A solution of the above crude oil (4.15 g, 6.8 mmol) in MeCN (60 mL) containing one equivalent of H_2O (123 mg, 6.8 mmol) was cooled to 0° prior to addition of Et_3SiH (3.27 mL, 20.5 mmol) followed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.73 mL, 13.7 mmol). After stirring for 1 hr, the solution was allowed to warm to 20° . After 4 hr, once periodic HPLC analysis revealed that the reaction was no longer progressing beyond 60%, an additional 2 mL of Et_3SiH and 1 mL of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ was added. Two hours later, no starting material remained by HPLC analysis. After adding aq. NaHCO_3 to quench the reaction, the mixture was stirred 30 min prior to being extracted 3x with EtOAc . The combined organic layers were washed 1x with aq. NaHCO_3 and brine prior to drying over Na_2SO_4 . The oil obtained after concentration under vacuum was dissolved in 70 mL of hot 25% $\text{EtOAc}/\text{hexane}$. Upon cooling, 2.45 g of desired tetraacetylated β -C-arylglucoside crystallized which was subsequently isolated by filtration.



[0189] To a stirred 20° solution of tetraacetylated β -C-glucoside (27.2 g, 49 mmol) (prepared as described in Part E), in 480 mL of 2:3:1 $\text{THF}/\text{MeOH}/\text{H}_2\text{O}$ was added $\text{LiOH} \cdot \text{H}_2\text{O}$ (2.3 g, 57 mmol). After stirring overnight, the volatiles were removed using a rotary evaporator. The residue, after being dissolved in EtOAc (300 mL), was washed 1x with brine (150 mL), 1x with brine (50 mL) containing 10 mL of 5% aq. KHSO_4 and finally with brine (50 mL) prior to drying over Na_2SO_4 . The volatiles were removed using a rotary evaporator and the resultant oil in the minimum amount of CH_2Cl_2 foamed under vacuum to yield 20.4 g of desired title C-arylglucoside as a glassy off white solid containing 0.11 mol % of EtOAc .

[0190] HPLC retention time: 7.08 min, 94% pure, YMC S5 C-18 4.6x50 mm column, 2.5 mL/min, detection at 220 nm; 8 min gradient 0-100% B hold 5 min at 100% B. Solvent A: 10% $\text{MeOH}/\text{H}_2\text{O}$ +0.2% H_3PO_4 . Solvent B: 90% $\text{MeOH}/\text{H}_2\text{O}$ +0.2% H_3PO_4 .

[0191] ^1H NMR (500 MHz, CD_3OD) δ 7.33 (d, 1H, J=6 Hz), 7.31 (d, 1H, J=2.2 Hz), 7.31 (dd, 1H, J=6 Hz, J=2.2 Hz), 7.07 (d, 2H, J=8.8 Hz), 6.78 (d, 2H, J=8.8 Hz), 4.07-3.90 (m, 7H), 3.85 (d, 1H, J=10.6 Hz), 3.69 (dd, 1H, J=5.3, 10.6 Hz), 3.42-3.25 (m, 4H) Hz), 1.34 (t, 3H, J=7 Hz).

[0192] ^{13}C NMR (125 MHz, CD_3OD) δ 158.8, 140.0, 139.9, 134.4, 132.9, 131.9, 130.8, 130.1, 128.2, 115.5, 82.9, 82.2, 79.7, 76.4, 71.9, 64.5, 63.1, 39.2, 15.2.

[0193] Anal Calcd for $\text{C}_{21}\text{H}_{25}\text{ClO}_6$ LC-MS $[\text{M}+\text{Na}^+]$ 431; found 431.

D4

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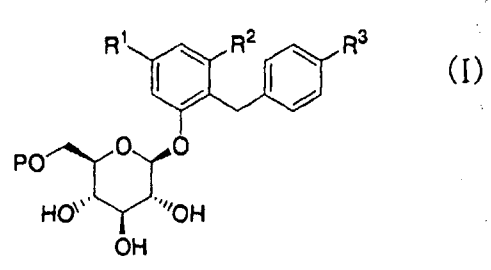
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(54) Title: GLUCOPYRANOSYLOXYBENZYL BENZENE DERIVATIVES AND MEDICINAL USE THEREOF

(54) 発明の名称: グルコピラノシルオキシベンジルベンゼン誘導体及びその医薬用途



(57) Abstract: Glucopyranosyloxybenzyl benzene derivatives represented by the following general formula (I) and pharmacologically acceptable salts thereof which are useful as preventives or remedies for diseases caused by hyperglycemia such as diabetes, complications of diabetes and obesity because of having an improved oral absorability and exerting an excellent human SGLT2 activity inhibitory effect (*in vivo*): (I) wherein P represents hydrogen or a group constituting a prodrug; R¹ represents hydrogen, optionally substituted amino, carbamoyl, optionally substituted lower alkyl, optionally substituted lower alkoxy, etc.; R² represents hydrogen or lower alkyl; and R³ represents optionally substituted lower alkyl, optionally substituted lower

alkoxy, optionally substituted lower alkylthio etc.

[続葉有]

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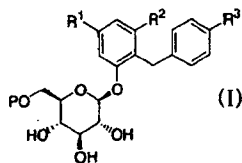
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(54) GLUCOPYRANOSYLOXYBENZYL BENZENE DERIVATIVES AND MEDICINAL USE THEREOF

(57) The present invention provides glucopyranosyloxybenzylbenzene derivatives represented by the general formula:



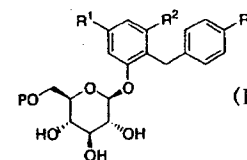
wherein P represents a hydrogen atom or a group forming a prodrug; R¹ represents a hydrogen atom, an optionally substituted amino group, a carbamoyl group, an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group, etc.; R² represents a hydrogen atom or a lower alkyl group; and R³ represents an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group, an optionally substituted lower alkythio group, etc., which have an improved oral absorption, and exert an inhibitory activity in human SGLT2, and therefore are useful as drugs for the prevention or treatment of a disease associated with hyperglycemia such as diabetes, diabetic complications or obesity, or pharmaceutically acceptable salts thereof, and pharmaceutical uses thereof.

Description

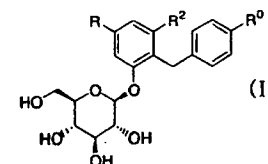
Technical Field

5 [0001] The present invention relates to glucopyranosyloxybenzylbenzene derivatives and pharmaceutically acceptable salts thereof which are useful as medicaments and pharmaceutical uses thereof.

[0002] More particularly, the present invention relates to glucopyranosyloxybenzylbenzene derivatives represented by the general formula:



wherein P represents a hydrogen atom or a group forming a prodrug; R¹ represents a hydrogen atom, an amino group, a mono or di (lower alkyl)-substituted amino group, a cyano group, a carbamoyl group, a lower alkyl group, a lower alkoxy group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a carbamoyl (lower alkyl) group, a lower alkoxy carbonyl-substituted (lower alkyl) group, a lower alkoxy carbonyl-substituted (lower alkoxy) group, a carboxy (lower alkyl) group, a carboxy (lower alkoxy) group, or a group represented by the general formula: P¹-O-A¹- wherein P¹ represents a hydrogen atom or a group forming a prodrug; and A¹ represents a single bond, a lower alkylene group, or a lower alkyleneoxy group; R² represents a hydrogen atom or a lower alkyl group; R³ represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a lower alkenyloxy group, an aralkyloxy group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a lower alkoxy-substituted (lower alkylthio) group, a carboxy group, a lower alkoxy carbonyl group, a cyano group, an aralkyloxy (lower alkyl) group, a cyano (lower alkyl) group, a carbamoyl group, a carbamoyl (lower alkyl) group, an amino group, a mono or di (lower alkyl)-substituted amino group, a lower alkoxy carbonyl-substituted (lower alkyl) group, a lower alkoxy carbonyl-substituted (lower alkoxy) group, a carboxy (lower alkyl) group, a carboxy (lower alkoxy) group, or a group represented by the general formula: P²-O-A²- wherein P² represents a hydrogen atom or a group forming a prodrug; and A² represents a lower alkylene group, a lower alkyleneoxy group, a lower alkylene thio group, or a lower alkenylene group; and with the proviso that both of R¹ and R² do not represent hydrogen atoms when at least one of P, P¹ and P² represents a group forming a prodrug and R³ represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, or lower alkoxy-substituted (lower alkylthio) group, or pharmaceutically acceptable salts thereof, which are useful as agents for the prevention or treatment of a disease such as diabetes, diabetic complications or obesity, of which glucopyranosylphenylbenzene derivatives, which have an inhibitory activity in human SGLT2, represented by the general formula:



wherein R represents a hydrogen atom, an amino group, a mono or di(lower alkyl)-substituted amino group, a cyano

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group, a carbamoyl group, a lower alkyl group, a lower alkoxy group, a lower alkoxy-substituted (lower alkyl), a lower alkoxy-substituted (lower alkoxy) group, a carbamoyl(lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkoxy) group, a carboxy(lower alkyl) group, a carboxy(lower alkoxy) group, or a group represented by the general formula: HO-A¹, wherein A¹ represents a single bond, a lower alkylene group, or a lower alkyleneoxy group; R² represents a hydrogen atom or a lower alkyl group; R³ represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a lower alkenyloxy group, an aralkyloxy group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a lower alkoxy-substituted (lower alkylthio) group, a carboxy group, a lower alkoxy-carbonyl group, a cyano group, an aralkyloxy (lower alkyl) group, a cyano(lower alkyl) group, a carbamoyl group, a carbamoyl (lower alkyl) group, an amino group, a mono or di (lower alkyl)-substituted amino group, a lower alkoxy-carbonyl-substituted (lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkoxy) group, a carboxy(lower alkyl) group, a carboxy(lower alkoxy) group, or a group represented by the general formula: HO-A², wherein A² represents a lower alkylene group, a lower alkyleneoxy group, a lower alkylene-thio group, or a lower alkenylene group; and with the proviso that both of R and R² do not represent hydrogen atoms when R⁰ represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, or lower alkoxy-substituted (lower alkylthio) group, are active forms, and to pharmaceutical uses thereof.

Background Art

[0003] Diabetes is one of lifestyle-related diseases with the background of change of eating habit and lack of exercise. Hence, diet and exercise therapies are performed in patients with diabetes. Furthermore, when its sufficient control and continuous performance are difficult, drug treatment is simultaneously performed. Now, biguanides, sulfonylureas and insulin sensitivity enhancers have been employed as antidiabetic agents. However, biguanides and sulfonylureas show occasionally adverse effects such as lactic acidosis and hypoglycemia, respectively. In a case of using agents for reducing insulin resistance, adverse effects such as edema are occasionally observed, and it is also concerned for advancing obesity. Therefore, in order to solve these problems, it has been desired to develop antidiabetic agents having a new mechanism.

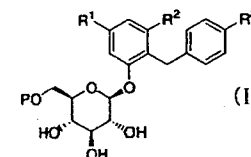
[0004] In recent years, development of new type antidiabetic agents has been progressing, which promote urinary glucose excretion and lower blood glucose level by preventing excess glucose reabsorption at the kidney (J. Clin. Invest., Vol.79, pp.1510-1515 (1987)). In addition, it is reported that SGLT2 (Na⁺/glucose cotransporter 2) is present in the S1 segment of the kidney's proximal tubule and participates mainly in reabsorption of glucose filtrated through glomerular (J. Clin. Invest., Vol.93, pp.397-404 (1994)). Accordingly, inhibiting a human SGLT2 activity prevents reabsorption of excess glucose at the kidney, subsequently promotes excreting excess glucose through the urine, and normalizes blood glucose level. Therefore, fast development of antidiabetic agents which have a potent inhibitory activity in human SGLT2 and have a new mechanism has been desired. In addition, since such agents promote the excretion of excess glucose through the urine and consequently the glucose accumulation in the body is decreased, they are also expected to have a preventing or alleviating effect on obesity and a urinating effect. Furthermore, the agents are considered to be useful for various related diseases which occur accompanying the progress of diabetes or obesity due to hyperglycemia.

Disclosure of the Invention

[0005] The present inventors have studied earnestly to find compounds having an inhibitory activity in human SGLT2. As a result, it was found that compounds represented by the above general formula (I) are converted into glucopyranosyloxybenzylbenzene derivatives represented by the above general formula (II) as their active forms *in vivo*, and show an excellent inhibitory activity in human SGLT2 as mentioned below, thereby forming the basis of the present invention.

[0006] The present invention is to provide the following glucopyranosyloxybenzylbenzene derivatives and pharmaceutically acceptable salts thereof, which exert an inhibitory activity in human SGLT2 *in vivo* and show an excellent hypoglycemic effect by excreting excess glucose in the urine through preventing the reabsorption of such glucose at the kidney, and pharmaceutical uses thereof.

[0007] This is, the present invention relates to a glucopyranosyloxybenzylbenzene derivative represented by the general formula:



wherein P represents a hydrogen atom or a group forming a prodrug; R¹ represents a hydrogen atom, an amino group, a mono or di(lower alkyl)-substituted amino group, a cyano group, a carbamoyl group, a lower alkyl group, a lower alkoxy group, a lower alkoxy-substituted (lower alkyl), a lower alkoxy-substituted (lower alkoxy) group, a carbamoyl (lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkoxy) group, a carboxy(lower alkyl) group, a carboxy(lower alkoxy) group, or a group represented by the general formula: P¹-O-A¹, wherein P¹ represents a hydrogen atom or a group forming a prodrug; and A¹ represents a single bond, a lower alkylene group, or a lower alkyleneoxy group; R² represents a hydrogen atom or a lower alkyl group; R³ represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a lower alkenyloxy group, an aralkyloxy group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a lower alkoxy-substituted (lower alkylthio) group, a carboxy group, a lower alkoxy-carbonyl group, a cyano group, an aralkyloxy (lower alkyl) group, a cyano(lower alkyl) group, a carbamoyl group, a carbamoyl (lower alkyl) group, an amino group, a mono or di (lower alkyl)-substituted amino group, a lower alkoxy-carbonyl-substituted (lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkoxy) group, a carboxy(lower alkyl) group, a carboxy(lower alkoxy) group, or a group represented by the general formula: P²-O-A², wherein P² represents a hydrogen atom or a group forming a prodrug; and A² represents a lower alkylene group, a lower alkyleneoxy group, a lower alkylene-thio group, or a lower alkenylene group; and with the proviso that both of R¹ and R² do not represent hydrogen atoms when at least one of P, P¹ and P² represents a group forming a prodrug and R³ represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, or lower alkoxy-substituted (lower alkylthio) group, or a pharmaceutically acceptable salt thereof.

[0008] The present invention relates to a pharmaceutical composition, a human SGLT2 inhibitor and an agent for the prevention or treatment of a disease associated with hyperglycemia, which comprises as the active ingredient a glucopyranosyloxybenzylbenzene derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof.

[0009] The present invention relates to a method for the prevention or treatment of a disease associated with hyperglycemia, which comprises administering an effective amount of a glucopyranosyloxybenzylbenzene derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof.

[0010] The present invention relates to a use of a glucopyranosyloxybenzylbenzene derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for the prevention or treatment of a disease associated with hyperglycemia.

[0011] Furthermore, the present invention relates to a pharmaceutical combination which comprises (A) a glucopyranosyloxybenzylbenzene derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof, and (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ -aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF- κ B inhibitor, a lipid peroxidase inhibitor, an N-acetylated- α -linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylidantoin, EGB-761, bimecromol, sulodexide, Y-128, a hydroxymethyl-glutaryl coenzyme A reductase inhibitor, afibric acid derivative, a β_2 -adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, proboc, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxigenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester

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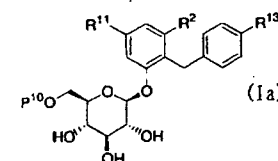
transfer protein-inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an α_2 -adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalizer. The present invention relates to a method for the prevention or treatment of a disease associated with hyperglycemia, which comprises administering an effective amount of (A) a glucopyranosyloxybenzylbenzene derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof, in combination with (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ -aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF- κ B inhibitor, a lipid peroxidase inhibitor, an N-acetylated- α -linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylthiandantoin, EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-glutaryl coenzyme A reductase inhibitor, a fibrin acid derivative, a β_2 -adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, proboc, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxigenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an α_2 -adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalizer.

[0012] The present invention relates to a use of (A) a glucopyranosyloxybenzylbenzene derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof, and (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ -aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF- κ B inhibitor, a lipid peroxidase inhibitor, an N-acetylated- α -linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylthiandantoin, EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-glutaryl coenzyme A reductase inhibitor, a fibrin acid derivative, a β_2 -adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, proboc, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxigenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an α_2 -adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalizer, for the manufacture of a pharmaceutical composition for the prevention or treatment of a disease associated with hyperglycemia.

[0013] In the present invention, the term "prodrug" means a compound which is converted into a glucopyranosyloxybenzylbenzene derivative represented by the above general formula (II) as an active form thereof *in vivo*. As examples of groups forming prodrugs, a hydroxy-protective group used generally as a prodrug, such as a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxy-carbonyl-substituted (lower acyl) group, a lower alkoxy-carbonyl group and a lower alkoxy-substituted (lower alkoxy-carbonyl) group, are illustrated.

[0014] As the glucopyranosyloxybenzylbenzene derivatives represented by the above general formula (I), for exam-

ple, compounds represented by the general formula:



wherein P¹⁰ represents a hydrogen atom, a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxy-carbonyl-substituted (lower acyl) group, a lower alkoxy-carbonyl group or a lower alkoxy-substituted (lower alkoxy-carbonyl) group; R¹¹ represents a hydrogen atom, an amino group, a mono or di (lower alkyl)-substituted amino group, a cyano group, a carbamoyl group, a lower alkyl group, a lower alkoxy group, a lower alkoxy-substituted (lower alkyl), a lower alkoxy-substituted (lower alkoxy) group, a carbamoyl(lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkoxy) group, a carboxy(lower alkyl) group, a carboxy (lower alkoxy) group or a group represented by the general formula: P¹¹-O-A¹, wherein P¹¹ represents a hydrogen atom or a lower alkyl group, a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxy-carbonyl-substituted (lower acyl) group, a lower alkoxy-carbonyl group and a lower alkoxy-substituted (lower alkoxy-carbonyl) group; and A¹ represents a single bond, a lower alkylene group or a lower alkenyleneoxy group; R² represents a hydrogen atom or a lower alkyl group; R¹³ represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a lower alkenyleneoxy group, an aralkyloxy group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a lower alkoxy-substituted (lower alkylthio) group, a carboxy group, a lower alkoxy-carbonyl group, a cyano group, an aralkyloxy (lower alkyl) group, a cyano(lower alkyl) group, a carbamoyl group, a carbamoyl (lower alkyl) group, an amino group, a mono or di (lower alkyl)-substituted amino group, a lower alkoxy-carbonyl-substituted (lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkoxy) group, a carboxy (lower alkyl) group, a carboxy(lower alkoxy) group or a group represented by the general formula: P¹²-O-A², wherein P¹² represents a hydrogen atom, a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxy-carbonyl-substituted (lower acyl) group, a lower alkoxy-carbonyl group or a lower alkoxy-substituted (lower alkoxy-carbonyl) group; and A² represents a lower alkylene group, a lower alkenyleneoxy group, a lower alkenylene group or a lower alkenylene group; and with the proviso that both of R¹¹ and R¹² do not represent hydrogen atoms when at least one of P¹⁰, P¹¹ and P¹² represents a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxy-carbonyl-substituted (lower acyl) group, a lower alkoxy-carbonyl group or a lower alkoxy-substituted (lower alkoxy-carbonyl) group and R¹³ represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group or lower alkoxy-substituted (lower alkylthio) group, or pharmaceutically acceptable salts thereof are illustrated.

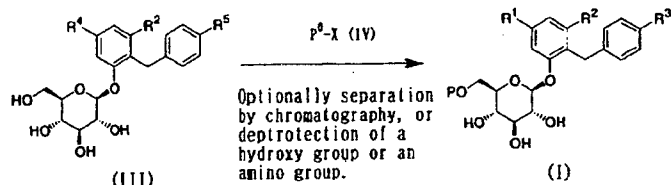
[0015] In the present invention, the term "lower alkyl group" means a straight-chained or branched alkyl group having 1 to 6 carbon atoms such as a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a pentyl group, an isopentyl group, a neopentyl group, a tert-pentyl group, a hexyl group or the like; the term "lower alkoxy group" means a straight-chained or branched alkoxy group having 1 to 6 carbon atoms such as a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, an isobutoxy group, a sec-butoxy group, a tert-butoxy group, a pentyloxy group, an isopentyloxy group, a neopentyloxy group, a tert-pentyloxy group, a hexyloxy group or the like; and the term "lower alkylthio group" means a straight-chained or branched alkylthio group having 1 to 6 carbon atoms such as a methylthio group, an ethylthio group, a propylthio group, an isopropylthio group, a butylthio group, an isobutylthio group, a sec-butylthio group, a tert-butylthio group, a pentythio group, an isopentythio group, a neopentythio group, a tert-pentythio group, a hexylthio group or the like. The term "lower alkoxy-substituted (lower alkyl) group" means the above lower alkyl group substituted by the above lower alkoxy group; the term "lower alkoxy-substituted (lower alkoxy) group" means the above lower alkoxy group substituted by the above lower alkoxy group; and the term "lower alkoxy-substituted (lower alkylthio) group" means the above lower alkylthio group substituted by the above lower alkoxy group. The term "lower alkenylene group" means a straight-chained or branched alkenylene group having 1 to 6 carbon atoms such as a methylene group, an ethylene group, a trimethylene group, a propylene group or the like; the term "lower alkenyleneoxy group" means a straight-chained or branched alkenyleneoxy group having 1 to 6 carbon atoms; the term "lower alkenethio group" means a straight-chained or branched alkenethio group having 1 to 6 carbon atoms, and the term "lower alkenylene group" means a straight-chained or branched alkenylene group having 3 to 6 carbon atoms such as a 1-propenylene group or the like.

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The term "lower alkenyloxy group" means a straight-chained or branched alkenyloxy group having 2 to 6 carbon atoms such as an allyloxy group or the like; the term "araalkyloxy group" means the above lower alkoxy group substituted by an aryl group such as a phenyl group, a naphthyl group, such as a benzyloxy group or the like; the term "araalkyloxy (lower alkyl) group" means the above lower alkyl group substituted by the above araalkyloxy group; the term "cyano (lower alkyl) group" means the above lower alkyl group substituted by a cyano group; the term "carbamoyl (lower alkyl) group" means the above lower alkyl group substituted by a carbamoyl group; and the term "mono or di(lower alkyl) substituted amino group" means an amino group mono- or di-substituted by the above lower alkyl group. The term "lower alkoxy-carbonyl group" means a straight-chained, branched or cyclic alkoxy-carbonyl group having 2 to 7 carbon atoms such as a methoxycarbonyl group, an ethoxycarbonyl group, a propyloxycarbonyl group, an isopropylloxycarbonyl group, a butyloxycarbonyl group, an isobutyloxycarbonyl group, a sec-butyloxycarbonyl group, a tert-butyloxycarbonyl group, a pentyloxycarbonyl group, an isopentyloxycarbonyl group, a neopentyloxycarbonyl group, a tert-pentyloxycarbonyl group, a hexyloxycarbonyl group, and a cyclohexyloxycarbonyl group or the like; the term "lower alkoxy-carbonyl-substituted (lower alkyl) group" means the above lower alkyl group substituted by the above lower alkoxy-carbonyl group; the term "lower alkoxy-carbonyl-substituted (lower alkoxy) group" means the above lower alkoxy group substituted by the above lower alkoxy-carbonyl group; and the term "lower alkoxy-substituted (lower alkoxy-carbonyl) group" means the above lower alkoxy group substituted by the above alkoxy group such as a 2-methoxyethoxycarbonyl group. The term "carboxy(lower alkyl) group" means the above lower alkyl group substituted by a carboxy group; and the term "carboxy (lower alkoxy) group" means the above lower alkoxy group substituted by a carboxy group. The term "lower acyl group" means a straight-chained, branched or cyclic acyl group having 2 to 7 carbon atoms such as an acetyl group, a propionyl group, a butyryl group, an isobutyryl group, a pivaloyl group, a hexanoyl group and a cyclohexyloxycarbonyl group; and the term "lower alkoxy-substituted (lower acyl) group" means the above lower alkoxy group substituted by the above lower alkoxy-carbonyl group such as a 3-(ethoxycarbonyl)propionyl group.

[0016] As a group forming a prodrug in the present invention, a lower acyl group or a lower alkoxy-carbonyl group is preferable. As compounds of the present invention, prodrugs of 2-(4-ethylbenzyl)-5-hydroxymethylphenyl β -D-glucopyranoside or 2-[4-(2-hydroxyethyl)benzyl]phenyl β -D-glucopyranoside, such as 2-(4-ethylbenzyl)-5-hydroxymethylphenyl 6-O-ethoxycarbonyl- β -D-glucopyranoside, 2-(4-ethylbenzyl)-5-pivaloyloxymethylphenyl β -D-glucopyranoside, 2-(4-ethylbenzyl)-5-hydroxymethylphenyl 6-O-butyl- β -D-glucopyranoside, 5-acetoxymethyl-2-(4-ethylbenzyl)phenyl 6-O-acetyl- β -D-glucopyranoside, 2-(4-ethylbenzyl)-5-(ethoxycarbonyloxymethyl)phenyl β -D-glucopyranoside, 2-(4-ethylbenzyl)-5-hydroxymethylphenyl 6-O-hexanoyl- β -D-glucopyranoside, 2-(4-ethylbenzyl)-5-hydroxymethylphenyl 6-O-pivaloyl- β -D-glucopyranoside, 2-(4-ethylbenzyl)-5-hydroxymethylphenyl 6-O-isobutyl-oxycarbonyl- β -D-glucopyranoside, 2-(4-ethylbenzyl)-5-hydroxymethylphenyl 6-O-isopropylloxycarbonyl- β -D-glucopyranoside, 2-[4-(2-hydroxyethyl)benzyl]phenyl 6-O-ethoxycarbonyl- β -D-glucopyranoside, 2-[4-(2-hydroxyethyl)benzyl]phenyl 6-O-acetyl- β -D-glucopyranoside, 2-[4-(2-acetoxyethyl)benzyl]phenyl 6-O-acetyl- β -D-glucopyranoside or the like, are preferable.

[0017] The compounds represented by the above general formula (I) of the present invention can be prepared, for example, by introducing a hydroxy-protective group usable in a prodrug into a hydroxy group of a glucopyranosyloxybenzylbenzene derivative represented by the following general formula (III) according to the following procedure or analogous procedures thereof:

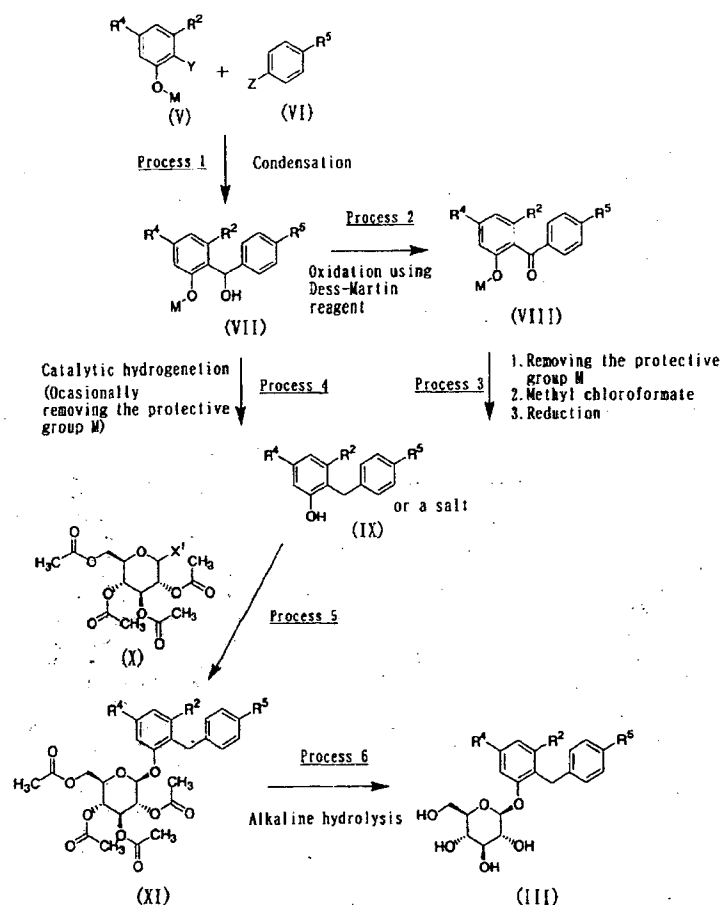


wherein P^0 represents a group forming a prodrug; R^4 represents a hydrogen atom, an optionally protected amino group, an optionally protected mono (lower alkyl) -substituted amino group, a di(lower alkyl)-substituted amino group, a cyano group, a carbamoyl group, a lower alkyl group, a lower alkoxy group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a carbamoyl(lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkoxy) group, a carboxy(lower alkyl) group, a carboxy(lower alkoxy) group or a group represented by the general formula: $P^{31}-O-A^1$, wherein P^{31} represents a hydrogen atom or a

hydroxy-protective group; and A^1 represents a single bond, a lower alkylene group or a lower alkenyloxy group; R^5 represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a lower alkenyloxy group, an araalkyloxy group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a lower alkoxy-substituted (lower alkylthio) group, a carboxy group, a lower alkoxy-carbonyl group, a cyano group, an araalkyloxy(lower alkyl) group, a cyano(lower alkyl) group, a carbamoyl group, a carbamoyl(lower alkyl) group, an optionally protected amino group, an optionally protected mono(lower alkyl)-substituted amino group, a di(lower alkyl)-substituted amino group, a lower alkoxy-carbonyl-substituted (lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkoxy) group, a carboxy(lower alkyl) group, a carboxy(lower alkoxy) group or a group represented by the general formula: $P^{32}-O-A^2$, wherein P^{32} represents a hydrogen atom or a hydroxy-protective group; and A^2 represents a lower alkylene group, a lower alkenyloxy group, a lower alkenylthio group or a lower alkenylene group; X represents a leaving group such as a bromine atom or a chlorine atom; and P, R^1 , R^2 and R^3 have the same meanings as defined above.

[0018] A prodrug represented by the above general formula (I) can be prepared by protecting a hydroxy group of a glucopyranosyloxybenzylbenzene derivative represented by the above general formula (III) with a reagent for protecting represented by the above general formula (IV) in the presence of a base such as pyridine, triethylamine, *N,N*-diisopropylethylamine, picoline, lutidine, collidine, quinuclidine, 1,2,2,6,6-pentamethylpiperidine or 1,4-diazabicyclo[2.2.2]octane in an inert solvent or without any solvent, occasionally followed by isolating the desired compound using column chromatography etc. or removing the hydroxy- and/or amino-protective group in conventional means. As the inert solvent used in the reaction to prepare a prodrug, dichloromethane, acetonitrile, ethyl acetate, diisopropyl ether, chloroform, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, acetone, *tert*-butanol, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from -40°C to reflux temperature, and the reaction time is usually from 30 minutes to 2 days, varying based on a used starting material, solvent and reaction temperature.

[0019] For example, the compounds represented by the above general formula (II) which are used as starting materials in the aforementioned production process can be prepared according to the following procedure:



wherein M represents a hydroxy-protective group; X^1 represents a leaving group such as a trichloroacetoimidoyloxy group, an acetoxy group, a bromine atom or a fluorine atom; one of Y and Z is MgBr, MgCl, MgI or a lithium atom, while the other is a formyl group; and R^2 , R^4 and R^5 have the same meanings as defined above.

Process 1

[0020] A compound represented by the above general formula (VII) can be prepared by condensing a benzaldehyde derivative represented by the above general formula (V) with a Grignard reagent or a lithium reagent represented by the above general formula (VI), or by condensing a Grignard reagent or a lithium reagent represented by the above general formula (V) with a benzaldehyde derivative represented by the above general formula (VI) in an inert solvent.

As the solvent used, tetrahydrofuran, diethyl ether, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from -78°C to reflux temperature, and the reaction time is usually from 10 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature.

Process 2

[0021] A compound represented by the above general formula (VIII) can be prepared by subjecting a compound represented by the above general formula (VII) to oxidation using a Dess-Martin reagent in an inert solvent. As the solvent used, dichloromethane, chloroform, acetonitrile, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on a used starting material, solvent and reaction temperature.

Process 3

[0022] A compound represented by the above general formula (IX) can be prepared by removing the protective group M of a compound represented by the above general formula (VIII) in conventional means, condensing the resulting compound with methyl chloroformate in the presence of a base such as triethylamine, diisopropylethylamine or *N,N*-dimethylaminopyridine in an inert solvent, and subjecting the resulting carbonate derivative to reduction using a reducing agent such as sodium borohydride. As the solvent used in the condensation reaction, tetrahydrofuran, dichloromethane, acetonitrile, ethyl acetate, diethyl ether, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 30 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature. As the solvent used in the reduction reaction, a mixed solvent with tetrahydrofuran and water, and the like can be illustrated. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on a used starting material, solvent and reaction temperature. The compound represented by the above general formula (IX) can be converted into a salt thereof such as a sodium salt or a potassium salt in the usual way.

Process 4

[0023] A compound represented by the above general formula (IX) can be prepared by subjecting a compound represented by the above general formula (VII) to catalytic hydrogenation using a palladium catalyst such as palladium-carbon powder in the presence or absence of an acid such as hydrochloric acid in an inert solvent, and removing a protective group M in the usual way as occasion demands. As the solvent used in the catalytic hydrogenation, methanol, ethanol, tetrahydrofuran, ethyl acetate, acetic acid, isopropanol, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 30 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature. The compound represented by the above general formula (IX) can be converted into a salt thereof such as a sodium salt or a potassium salt in the usual way.

[0024] In the above general formulae (V), (VI), (VII), (VIII) and (IX) in the above processes 1 to 4, a compound wherein R^4 represents an optionally protected amino group, an optionally protected mono(lower alkyl)-substituted amino group, a di(lower alkyl)-substituted amino group, a cyano group, a carbamoyl group, a carbamoyl(lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkyl) group, a carboxy(lower alkyl) group or a group represented by the general formula: $P^{31}-O-A^{11}$, wherein P^{31} represents a hydrogen atom or a hydroxy-protective group; and A^{11} represents a lower alkylene group; and/or R^5 represents a cyano group, a cyano(lower alkyl) group, a carbamoyl group, a carbamoyl(lower alkyl) group, an optionally protected amino group, an optionally protected mono(lower alkyl)-substituted amino group, a di(lower alkyl)-substituted amino group, a lower alkoxy-carbonyl-substituted (lower alkyl) group, a carboxy(lower alkyl) group or a group represented by the general formula: $P^{32}-O-A^{12}$, wherein P^{32} represents a hydrogen atom or a hydroxy-protective group; and A^{12} represents a lower alkylene group or a lower alkenylene group can be converted into a corresponding compound with a lower alkoxy-carbonyl group as a substituent group in an usual way and then can be subjected to the next processes 1 to 6.

Process 5

[0025] A glucoside represented by the above general formula (XI) can be prepared by subjecting a benzylphenol derivative represented by the above general formula (IX) or a salt thereof to glucosidation using a glycosyl-donor represented by the above general formula (X) such as 2,3,4,6-tetra-O-acetyl-1-O-trichloroacetoimidoyl- α -D-glucopyranose, 2,3,4,6-tetra-O-acetyl-1-O-trichloroacetoimidoyl- β -D-glucopyranose, 1,2,3,4,6-penta-O-acetyl- β -D-glucopyranose, 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide or 2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl fluoride in

the presence of an activating reagent such as boron trifluoride diethyl ether complex, silver trifluoromethanesulfonate, tin(IV) chloride or trimethylsilyl trifluoromethanesulfonate in an inert solvent. As the solvent used, dichloromethane, toluene, acetonitrile, nitromethane, ethyl acetate, diethyl ether, chloroform, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from -30°C to reflux temperature, and the reaction time is usually from 10 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature.

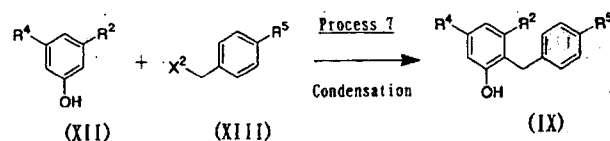
[0026] Among compounds represented by the above general formula (XI), a compound wherein R⁴ is a protected mono(lower alkyl)-substituted amino group can also be prepared by subjecting the corresponding compound wherein R⁴ is a protected amino group obtained by the above process 5 to reaction with a proper agent introducing a lower alkyl group such as a lower alkyl halide, mesylic acid ester, tosylic acid ester and the like in the presence of an alkaline material such as sodium hydride, potassium carbonate or the like in a solvent such as tetrahydrofuran, *N,N*-dimethylformamide, dimethyl sulfoxide, a mixed solvent thereof or the like.

Process 6

[0027] A compound represented by the above general formula (III) can be prepared by subjecting a glucoside represented by the above general formula (XI) to alkaline hydrolysis to remove the acetyl groups. As the solvent used, water, methanol, ethanol, tetrahydrofuran, a mixed solvent thereof and the like can be illustrated, and as alkaline materials, sodium hydroxide, sodium methoxide, sodium ethoxide or the like can be used. The treatment temperature is usually from 0°C to reflux temperature, and the treatment time is usually from 30 minutes to 6 hours, varying based on a used starting material, solvent and treatment temperature. In the case that R⁴ or/and R⁵ has a hydroxy- or amino-protective group, such treatment of the above process can be carried out by suitably changing in conventional means depending on a used protective group as occasion demands, or can be followed by another procedure to remove the protective group in conventional means to prepare a desired compound represented by the above general formula (III).

[0028] In the aforementioned production process, the term "hydroxy-protective group" means a hydroxy-protective group used in general organic reactions such as a benzyl group, a methoxymethyl group, an acetyl group, *tert*-butylmethylsilyl group, *tert*-butyldiphenylsilyl group and the like, and the term "amino-protective group" means an amino-protective group used in general organic reactions such as a benzyloxycarbonyl group, a *tert*-butoxycarbonyl group, a phthaloyl group, a benzyl group, an acetyl group and the like.

[0029] A compound represented by the above general formula (IX) which was used in the aforementioned production process can be prepared according to the following procedure:

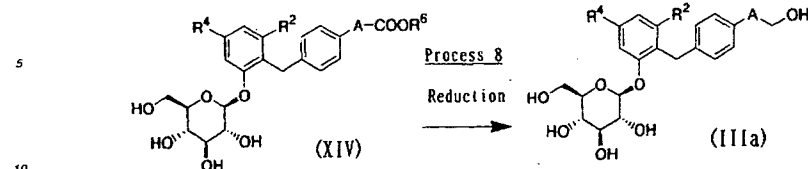


wherein X² represents a leaving group such as a chlorine atom or the like; and R², R⁴ and R⁵ have the same meanings as defined above.

Process 7

[0030] A compound represented by the above general formula (IX) can be prepared by subjecting a phenol derivative represented by the above general formula (XII) to benzylation using a benzyl derivative represented by the above formula (XIII) in the presence of an alkaline material such as lithium hydroxide or the like without any solvent. The reaction temperature is usually from 50°C to 200°C, and the reaction time is usually from 30 minutes to 1 day, varying based on used starting material, solvent and reaction temperature.

[0031] Of compounds represented by the above general formula (III), a compound represented by the following general formula (IIa), for example, can be prepared using a carboxylic acid derivative represented by the following general formula (XIV) according to the following procedure;

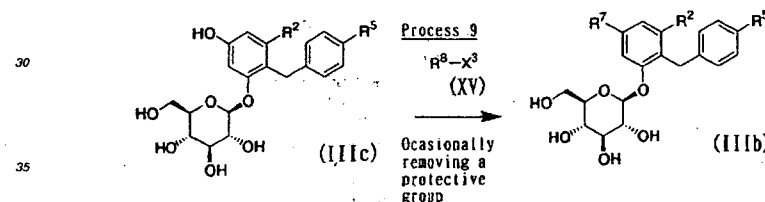


wherein A represents a straight-chained or branched alkyl group having 1 to 5 carbon atoms or a straight-chained or branched alkenyl group having 2 to 5 carbon atoms; R⁶ represents a hydrogen atom or a lower alkyl group; and R² and R⁴ have the same meanings as defined above.

Process 8

[0032] A compound represented by the above general formula (IIa) can be prepared by subjecting a carboxylic acid derivative represented by the above general formula (XIV) to reduction using a reducing agent such as lithium aluminum hydride, borane, lithium borohydride or the like in a solvent such as tetrahydrofuran, diethyl ether, methanol, ethanol, a mixed solvent thereof or the like. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 30 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature.

[0033] Of compounds represented by the above general formula (III), a compound represented by the following general formula (IIb), for example, can be prepared using a phenol derivative represented by the following general formula (IIc) according to the following procedure;



wherein R⁷ represents a lower alkoxy group, a lower alkoxy-substituted (lower alkoxy) group, a lower alkoxy-carbonyl-substituted (lower alkoxy) group, a carboxy (lower alkoxy) group or a group represented by the general formula: P³¹-O-A²¹, wherein P³¹ represents a hydrogen atom or a hydroxy-protective group; and A²¹ represents a lower alkyleneoxy group; R⁸ represents a lower alkyl group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkyl) group, or a group represented by the general formula: P³¹-O-A³¹, wherein P³¹ represents a hydrogen atom or a hydroxy-protective group; and A³¹ represents a lower alkylene group; X³ represents a leaving group such as a chlorine atom, a bromine atom, an iodine atom, a mesyloxy group, a tosyloxy group or the like; and R² and R⁵ have the same meanings as defined above.

Process 9

[0034] A compound represented by the above general formula (IIb) can be prepared by subjecting a phenol derivative represented by the above general formula (IIc) to O-alkylation using an alkylating agent represented by the above general formula (XV) in the presence of an alkaline material such as sodium hydride, potassium carbonate, cesium carbonate, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium hydrogen carbonate or the like in a solvent such as tetrahydrofuran, *N,N*-dimethylformamide, dimethyl sulfoxide, acetonitrile, a mixed solvent thereof or the like, and followed by deprotection in an usual way as occasional demands. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 30 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature.

(1H, d, ν 5 Hz), 6.87 (1H, dd, J 1.5, 7.7 Hz), 7.05-7.20 (5H, m)

Reference Example 10

5-Acetoxyethyl-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside

[0083] To a solution of 5-acetoxyethyl-2-(4-ethylbenzyl)phenol (0.59 g) and 2,3,4,6-tetra-O-acetyl-1-O-trichloroacetoimidoyl- α -D-glucopyranose (1.1 g) in dichloromethane (15 mL) was added boron trifluoride diethyl ether complex (0.31 mL), and the mixture was stirred at 0 °C for 30 minutes. The reaction mixture was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 2/1-3/2) to give 5-acetoxyethyl-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside (1.0 g).

¹H-NMR (CDCl₃) δ ppm:

1.20 (3H, t, J=7.6 Hz), 1.88 (3H, s), 2.02 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 2.09 (3H, s), 2.60 (2H, q, J=7.6 Hz), 3.80-3.95 (3H, m), 4.20 (1H, dd, J=2.4, 12.3 Hz), 4.27 (1H, dd, J=5.3, 12.3 Hz), 5.00-5.10 (2H, m), 5.13 (1H, d, J=7.4 Hz), 5.15-5.40 (3H, m), 6.95-7.15 (7H, m)

Reference Example 11

5-Acetoxyethyl-2-(4-propoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside

[0084] The title compound was prepared in a similar manner to that described in Reference Example 10 using 5-acetoxyethyl-2-(4-propoxybenzyl)phenol instead of 5-acetoxyethyl-2-(4-ethylbenzyl)phenol.

¹H-NMR (CDCl₃) δ ppm:

1.01 (3H, t, J=7.4 Hz), 1.70-1.85 (2H, m), 1.92 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 2.09 (3H, s), 3.80-3.95 (5H, m), 4.20 (1H, dd, J=2.4, 12.3 Hz), 4.27 (1H, dd, J=5.3, 12.3 Hz), 5.00-5.10 (2H, m), 5.12 (1H, d, J=7.4 Hz), 5.15-5.40 (3H, m), 6.75-6.85 (2H, m), 6.95-7.10 (5H, m)

Reference Example 12

2-[4-(2-Acetoxyethyl)benzyl]-5-acetoxyethylphenyl β -D-glucopyranoside

[0085] The title compound was prepared in a similar manner to that described in Reference Example 10 using 2-[4-(2-acetoxyethyl)benzyl]-5-acetoxyethylphenol instead of 5-acetoxyethyl-2-(4-ethylbenzyl)phenol.

¹H-NMR (CDCl₃) δ ppm:

1.89 (3H, s), 2.03 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 2.09 (3H, s), 2.88 (2H, t, J=7.1 Hz), 3.85-3.95 (3H, m), 4.15-4.35 (4H, m), 5.00-5.10 (2H, m), 5.13 (1H, d, J=7.5 Hz), 5.15-5.40 (3H, m), 6.95-7.15 (7H, m)

Reference Example 13

2-(4-Ethylbenzyl)-5-hydroxymethylphenyl β -D-glucopyranoside

[0086] Sodium methoxide (28% methanol solution; 0.3 mL) was added to a solution of 5-acetoxyethyl-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside (1.0 g) in methanol (12 mL), and the mixture was stirred at room temperature for 40 minutes. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 7/1) to give 2-(4-ethylbenzyl)-5-hydroxymethylphenyl β -D-glucopyranoside (0.68 g).

¹H-NMR (CD₃OD) δ ppm:

1.19 (3H, t, J=7.6 Hz), 2.57 (2H, q, J=7.6 Hz), 3.30-3.55 (4H, m), 3.65-3.75 (1H, m), 3.85-4.00 (2H, m), 4.04 (1H, d, J=15.0 Hz), 4.54 (2H, s), 4.93 (1H, d, J=7.4 Hz), 6.85-6.95 (1H, m), 7.02 (1H, d, J=7.7 Hz), 7.06 (2H, d, J=8.1 Hz), 7.10-7.20 (3H, m)

Reference Example 14

5-Hydroxymethyl-2-(4-propoxybenzyl)phenyl β -D-glucopyranoside

[0087] The title compound was prepared in a similar manner to that described in Reference Example 13 using 5-acetoxyethyl-2-(4-propoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside instead of 5-acetoxyethyl-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside.

¹H-NMR (CD₃OD) δ ppm:

1.02 (3H, t, J=7.4 Hz), 1.70-1.85 (2H, m), 3.30-3.55 (4H, m), 3.65-3.75 (1H, m), 3.80-3.95 (4H, m), 4.00 (1H, d, J=15.0 Hz), 4.54 (2H, s), 4.93 (1H, d, J=7.4 Hz), 6.70-6.85 (2H, m), 6.85-6.95 (1H, m), 7.02 (1H, d, J=7.7 Hz), 7.05-7.20 (3H, m)

Reference Example 15

2-[4-(2-Hydroxyethyl)benzyl]-5-hydroxymethylphenyl β -D-glucopyranoside

[0088] The title compound was prepared in a similar manner to that described in Reference Example 13 using 2-[4-(2-acetoxyethyl)benzyl]-5-acetoxyethylphenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside instead of 5-acetoxyethyl-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside.

¹H-NMR (CD₃OD) δ ppm:

2.76 (2H, t, J=7.1 Hz), 3.30-3.55 (4H, m), 3.60-3.75 (3H, m), 3.85-4.00 (2H, m), 4.05 (1H, d, J=14.6 Hz), 4.54 (2H, s), 4.92 (1H, d, J=7.2 Hz), 6.85-6.95 (1H, m), 7.03 (1H, d, J=7.9 Hz), 7.09 (2H, d, J=7.8 Hz), 7.10-7.20 (3H, m)

Reference Example 16

2-[4-(2-Hydroxyethyl)benzyl]phenyl β -D-glucopyranoside

[0089] To a solution of 2-[4-(2-benzoyloxyethyl)benzyl]phenol (0.49 g) and 1,2,3,4,6-penta-O-acetyl- β -D-glucopyranose (1.7 g) in toluene (5.2 mL) and dichloromethane (2.2 mL) was added boron trifluoride diethyl ether complex (0.56 mL), and the mixture was stirred at 25 °C for 8 hours. To the reaction mixture were added ethyl acetate (70 mL) and a saturated aqueous sodium hydrogen carbonate solution (25 mL), and the organic layer was separated. The organic layer was washed with brine (25 mL) and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in methanol (5 mL) and tetrahydrofuran (2.5 mL), sodium methoxide (28% methanol solution, 0.14 mL) was added to the solution, and the resulting mixture was stirred at 25 °C for 12.5 hours. To the reaction mixture were added ethyl acetate (75 mL) and water (20 mL), and the organic layer was separated. The organic layer was washed with brine (20 mL) and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in methanol (7.5 mL), sodium methoxide (28% methanol solution, 0.085 mL) was added to the solution, and the resulting mixture was stirred at 25 °C for 5 hours. The reaction mixture was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 4/1). The solvent was removed under reduced pressure, diethyl ether was added to the residue, and the resulting precipitates were collected by filtration. The obtained solid was washed with diethyl ether and dried under reduced pressure to give 2-[4-(2-hydroxyethyl)benzyl]phenyl β -D-glucopyranoside (0.47 g).

¹H-NMR (CD₃OD) δ ppm:

2.76 (2H, t, J=7.1 Hz), 3.35-3.55 (4H, m), 3.65-3.75 (3H, m), 3.88 (1H, dd, J=1.8, 11.8 Hz), 3.95 (1H, d, J=15.2 Hz), 4.07 (1H, d, J=15.2 Hz), 4.90 (1H, d, J=7.4 Hz), 6.85-6.95 (1H, m), 7.00-7.20 (7H, m)

Reference Example 17

2-[4-(3-Hydroxypropyl)benzyl]phenyl β -D-glucopyranoside

[0090] The title compound was prepared in a similar manner to that described in Reference Example 16 using 2-[4-(3-benzoyloxypropyl)benzyl]phenol instead of 2-[4-(2-benzoyloxyethyl)benzyl]phenol.

¹H-NMR (CD₃OD) δ ppm:

1.70-1.85 (2H, m), 2.55-2.65 (2H, m), 3.30-3.60 (6H, m), 3.69 (1H, dd, J=5.2, 11.9 Hz), 3.88 (1H, dd, J=2.0, 11.9 Hz), 3.95 (1H, d, J=15.1 Hz), 4.06 (1H, d, J=15.1 Hz), 4.90 (1H, d, J=7.3 Hz), 6.85-6.95 (1H, m), 7.00-7.20 (7H, m)

Reference Example 18

Methyl 4-[(2-benzoyloxyphenyl)hydroxymethyl]benzoate

[0091] A Grignard reagent was prepared from 2-benzoyloxybromobenzene (5.3 g), magnesium (0.49 g) and tetrahydrofuran (160 mL). The obtained Grignard reagent was added to a solution of methyl terephthalaldehyde (3.3 g) in tetrahydrofuran (60 mL), and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added water and dilute hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue

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Reference Example 23

Ethyl (E)-3-[4-(2-hydroxybenzyl)phenyl]acrylate

[0096] To a solution of triethyl phosphonoacetate (0.89 mL) in tetrahydrofuran (30 mL) was added potassium tert-butoxide (0.50 g), and the mixture was stirred at room temperature for 15 minutes. A solution of 4-(2-benzoyloxybenzyl)benzaldehyde (1.0 g) in tetrahydrofuran (10 mL) was added to the reaction mixture, and the mixture was stirred at room temperature for 6 hours. To the resulting mixture was added dilute hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 10/1) to give ethyl (E)-3-[4-(2-benzoyloxybenzyl)phenyl]acrylate (0.86 g). To the obtained ethyl (E)-3-[4-(2-benzoyloxybenzyl)phenyl]acrylate (0.86 g) were added trifluoroacetic acid (9.5 mL), water (0.5 mL) and dimethyl sulfide (1.0 mL), and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 3/1) to give ethyl (E)-3-[4-(2-hydroxybenzyl)phenyl]acrylate (0.51 g).

¹H-NMR (CDCl₃) δ ppm:

1.33 (3H, t, J=7.2Hz), 4.01 (2H, s), 4.26 (2H, q, J=7.2Hz), 4.96 (1H, s), 6.38 (1H, d, J=16.1Hz), 6.75-6.80 (1H, m), 6.85-6.95 (1H, m), 7.05-7.20 (2H, m), 7.20-7.30 (2H, m), 7.40-7.50 (2H, m), 7.65 (1H, d, J=16.1Hz)

Reference Example 24

(E)-2-[4-(2-Ethoxycarbonylviny)benzyl]phenyl β-D-glucopyranoside

[0097] To a suspension of ethyl (E)-3-[4-(2-hydroxybenzyl)phenyl]acrylate (0.34 g) and 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose (1.4 g) in dichloromethane (3 mL) and toluene (9 mL) was added boron trifluoride diethyl ether complex (0.45 mL), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 4/1) to give (E)-2-[4-(2-ethoxycarbonylviny)benzyl]phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (0.47 g). To the solution of the obtained (E)-2-[4-(2-ethoxycarbonylviny)benzyl]phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (0.46 g) in methanol (5 mL) was added sodium methoxide (0.010 g), and the resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: ethyl acetate) to give (E)-2-[4-(2-ethoxycarbonylviny)benzyl]phenyl β-D-glucopyranoside (0.31 g).

¹H-NMR (CD₃OD) δ ppm:

1.31 (3H, t, J=7.2Hz), 3.30-3.55 (4H, m), 3.68 (1H, dd, J=5.3, 12.0Hz), 3.88 (1H, dd, J=1.9, 12.0Hz), 4.00 (1H, d, J=14.9Hz), 4.15 (1H, dd, J=14.9Hz), 4.22 (2H, q, J=7.2Hz), 4.92 (1H, d, J=7.1Hz), 6.45 (1H, d, J=16.1Hz), 6.90-7.00 (1H, m), 7.05-7.20 (3H, m), 7.25-7.35 (2H, m), 7.45-7.55 (2H, m), 7.64 (1H, d, J=16.1Hz)

Reference Example 25

2-[4-Methoxycarbonylbenzyl]phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

[0098] To a suspension of methyl 4-(2-hydroxybenzyl)benzoate (0.053g) and 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose (0.26 g) in dichloromethane (1 mL) and toluene (3 mL) was added boron trifluoride diethyl ether complex (0.083 mL), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 4/1) to give 2-[4-methoxycarbonylbenzyl]phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (0.067 g).

¹H-NMR (CDCl₃) δ ppm:

1.87 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 3.80-4.05 (6H, m), 4.16 (1H, dd, J=2.7, 12.4Hz), 4.28 (1H, dd, J=5.8, 12.4Hz), 5.10-5.20 (2H, m), 5.25-5.35 (2H, m), 6.95-7.10 (3H, m), 7.15-7.25 (3H, m), 7.90-7.95 (2H, m)

Reference Example 26

4-Allyloxy-2'-(methoxymethoxy)diphenylmethanol

[0099] A Grignard reagent was prepared from 4-allyloxybromobenzene (1.7 g), magnesium (0.19 g), a catalytic amount of iodine and tetrahydrofuran (3 mL). To the obtained Grignard reagent was added a solution of 2-(methoxymethoxy)benzaldehyde (0.88 g) in tetrahydrofuran (19 mL), and the mixture was stirred at room temperature for 30 minutes.

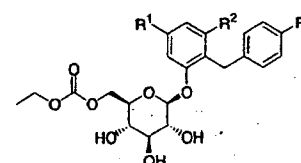
ridine (2 mL) was added ethyl chloroformate (0.037 mL, 2 mol equivalent), and the mixture was stirred at room temperature for 17 hours. To the reaction mixture was added 1 mol/L hydrochloric acid, and the mixture was extracted with ethyl acetate. The extract was washed with 1 mol/L hydrochloric acid and water, and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel (eluent: dichloromethane/methanol 10/1) and recrystallized (recrystallization solvent: acetone/hexane 1/1) to give 2-(4-ethylbenzyl)-5-hydroxymethylphenyl 6-O-ethoxycarbonyl-β-D-glucopyranoside (0.020 g).

¹H-NMR (CD₃OD) δ ppm:

1.19 (3H, t, J=7.5Hz), 1.20-1.30 (3H, m), 2.57 (2H, q, J=7.5Hz), 3.30-3.55 (3H, m), 3.55-3.65 (1H, m), 3.94 (1H, d, J=15.0Hz), 4.02 (1H, d, J=15.0Hz), 4.05-4.20 (2H, m), 4.26 (1H, dd, J=6.6, 11.7Hz), 4.47 (1H, dd, J=2.3, 11.7Hz), 4.50-4.60 (2H, m), 4.90 (1H, d, J=7.4Hz), 6.90-7.15 (7H, m)

Example 2-27

[0191] The compounds listed in Table 1 were prepared in a similar manner to that described in Example 1 using their corresponding starting materials.



[Table 1]

Example No.	R ¹	R ²	R ³
2	Hydroxymethyl group	Hydrogen atom	Propoxy group
3	Hydrogen atom	Hydrogen atom	3-Hydroxypropyl group
4	Methyl group	Methyl group	Methoxy group
5	Hydroxymethyl group	Hydrogen atom	2-Hydroxyethyl group
6	Methoxy group	Hydrogen atom	Methoxy group
7	Methoxymethyl group	Hydrogen atom	Methoxy group
8	Methyl group	Methyl group	3-Hydroxypropyl group
9	Methyl group	Methyl group	2-Hydroxyethyl group
10	Amino group	Hydrogen atom	Ethyl group
11	N-Methylamino group	Hydrogen atom	Ethyl group
12	Carbamoyl group	Hydrogen atom	Ethyl group
13	Carbamoylmethyl group	Hydrogen atom	Ethyl group
14	Cyano group	Hydrogen atom	Methoxy group
15	Methoxymethoxy group	Hydrogen atom	Ethyl group
16	Hydroxy group	Hydrogen atom	Ethyl group
17	2-Hydroxyethoxy group	Hydrogen atom	Ethyl group
18	3-(Ethoxycarbonyl)propyloxy group	Hydrogen atom	Ethyl group
19	Methoxy group	Hydrogen atom	2-Hydroxyethyl group

Table 1 (continued)

Example No.	R ¹	R ²	R ³
20	Hydrogen atom	Hydrogen atom	Benzoyloxy group
21	Hydrogen atom	Hydrogen atom	Carboxy group
22	Hydrogen atom	Hydrogen atom	Allyloxy group
23	Hydrogen atom	Hydrogen atom	<i>N,N</i> -Dimethylamino group
24	Hydrogen atom	Hydrogen atom	Methoxycarbonyl group
25	Hydrogen atom	Hydrogen atom	Cyanomethyl group
26	Hydrogen atom	Hydrogen atom	Carbamoyl group
27	Hydrogen atom	Hydrogen atom	(E)-3-Hydroxy-1-propenyl group

Example 28

2-(4-Ethylbenzyl)-5-pivaloyloxymethylphenyl β-D-glucopyranoside

[0192] The title compound was prepared in a similar manner to that described in Example 1 using pivaloyl chloride (1.5 mol equivalent) instead of ethyl chloroformate.

¹H-NMR (CD₃OD) δ ppm:

1.15-1.25 (12H, m), 2.58 (2H, q, J=7.6Hz), 3.35-3.55 (4H, m), 3.65-3.75 (1H, m), 3.85-3.95 (1H, m), 3.94 (1H, d, J=15.1Hz), 4.05 (1H, d, J=15.1Hz), 4.92 (1H, d, J=7.5Hz), 5.05 (2H, s), 6.91 (1H, dd, J=1.1, 7.8Hz), 7.03 (1H, d, J=7.8Hz), 7.07 (2H, d, J=8.0Hz), 7.13 (2H, d, J=8.0Hz), 7.16 (1H, d, J=1.1Hz)

Example 29

2-(4-Ethylbenzyl)-5-hydroxymethylphenyl 6-O-butyryl-β-D-glucopyranoside

[0193] The title compound was prepared in a similar manner to that described in Example 1 using butyryl chloride (2.5 mol equivalent) instead of ethyl chloroformate.

¹H-NMR (CD₃OD) δ ppm:

0.90 (3H, t, J=7.4Hz), 1.19 (3H, t, J=7.6Hz), 1.50-1.65 (2H, m), 2.25-2.35 (2H, m), 2.58 (2H, q, J=7.6Hz), 3.30-3.55 (3H, m), 3.55-3.65 (1H, m), 3.95 (1H, d, J=15.1Hz), 4.02 (1H, d, J=15.1Hz), 4.21 (1H, dd, J=6.4, 11.8Hz), 4.35-4.50 (1H, m), 4.55 (2H, s), 4.91 (1H, d, J=7.1Hz), 6.90-7.15 (7H, m)

Example 30

5-Acetoxymethyl-2-(4-ethylbenzyl)phenyl 6-O-acetyl-β-D-glucopyranoside

[0194] The title compound was prepared in a similar manner to that described in Example 1 using acetyl chloride (2.5 mol equivalent) instead of ethyl chloroformate.

¹H-NMR (CD₃OD) δ ppm:

1.19 (3H, t, J=7.6Hz), 2.03 (3H, s), 2.06 (3H, s), 2.58 (2H, q, J=7.6Hz), 3.30-3.55 (3H, m), 3.55-3.70 (1H, m), 3.95 (1H, d, J=15.1Hz), 4.03 (1H, d, J=15.1Hz), 4.21 (1H, dd, J=6.4, 11.9Hz), 4.42 (1H, dd, J=2.0, 11.9Hz), 4.89 (1H, d, J=7.2Hz), 5.00-5.10 (2H, m), 6.90-7.15 (7H, m)

Example 31

2-(4-Ethylbenzyl)-5-(ethoxycarbonyloxymethyl)phenyl β-D-glucopyranoside

[0195] The title compound was prepared in a similar manner to that described in Example 1.

¹H-NMR (CD₃OD) δ ppm:

1.19 (3H, t, J=7.6Hz), 1.26 (3H, t, J=7.1Hz), 2.58 (2H, q, J=7.6Hz), 3.35-3.55 (4H, m), 3.71 (1H, dd, J=5.0, 12.0Hz), 3.89 (1H, dd, J=1.9, 12.0Hz), 3.95 (1H, d, J=15.0Hz), 4.05 (1H, d, J=15.0Hz), 4.16 (2H, q, J=7.1Hz), 4.92 (1H, d, J=7.4Hz), 5.00-5.15 (2H, m), 6.94 (1H, dd, J=1.4, 7.7Hz), 7.04 (1H, d, J=7.7Hz), 7.07 (2H, d, J=8.0Hz), 7.13 (2H, d,

J=8.0Hz), 7.19 (1H, d, J=1.4Hz)

Example 32

2-(4-Ethylbenzyl)-5-hydroxymethylphenyl 6-O-hexanoyl-β-D-glucopyranoside

[0196] The title compound was prepared in a similar manner to that described in Example 1 using hexanoyl chloride (2.5 mol equivalent) instead of ethyl chloroformate.

¹H-NMR (CD₃OD) δ ppm:

0.86 (3H, t, J=7.1Hz), 1.19 (3H, t, J=7.6Hz), 1.20-1.35 (4H, m), 1.50-1.65 (2H, m), 2.25-2.40 (2H, m), 2.50-2.65 (2H, m), 3.30-3.55 (3H, m), 3.55-3.65 (1H, m), 3.95 (1H, d, J=14.9Hz), 4.02 (1H, d, J=14.9Hz), 4.21 (1H, dd, J=6.3, 11.9Hz), 4.35-4.50 (1H, m), 4.55 (2H, s), 4.91 (1H, d, J=7.2Hz), 6.85-7.20 (7H, m)

Example 33

2-(4-Ethylbenzyl)-5-hydroxymethylphenyl 6-O-pivaloyl-β-D-glucopyranoside

[0197] The title compound was prepared in a similar manner to that described in Example 1 using pivaloyl chloride (1.5 mol equivalent) instead of ethyl chloroformate.

¹H-NMR (CD₃OD) δ ppm:

1.14 (9H, s), 1.19 (3H, t, J=7.6Hz), 2.57 (2H, q, J=7.6Hz), 3.30-3.50 (3H, m), 3.50-3.65 (1H, m), 3.95 (1H, d, J=14.8Hz), 4.01 (1H, d, J=14.8Hz), 4.17 (1H, dd, J=6.3, 11.8Hz), 4.42 (1H, dd, J=2.2, 11.8Hz), 4.54 (2H, s), 4.90-5.00 (1H, m), 6.90-7.15 (7H, m)

Example 34

2-(4-Ethylbenzyl)-5-hydroxymethylphenyl 6-O-isobutyloxycarbonyl-β-D-glucopyranoside

[0198] The title compound was prepared in a similar manner to that described in Example 1 using isobutyl chloroformate (2.0 mol equivalent) instead of ethyl chloroformate.

¹H-NMR (CD₃OD) δ ppm:

0.89 (6H, d, J=6.6Hz), 1.17 (3H, t, J=7.6Hz), 1.80-1.95 (1H, m), 2.56 (2H, q, J=7.6Hz), 3.40-3.60 (3H, m), 3.60-3.70 (1H, m), 3.80-3.90 (2H, m), 3.94 (1H, d, J=15.0Hz), 4.02 (1H, d, J=15.0Hz), 4.29 (1H, dd, J=5.9, 11.7Hz), 4.49 (1H, dd, J=2.0, 11.7Hz), 4.56 (2H, s), 4.80-5.00 (1H, m), 6.90-7.20 (7H, m)

Example 35

2-(4-Ethylbenzyl)-5-hydroxymethylphenyl 6-O-isopropoxyloxycarbonyl-β-D-glucopyranoside

[0199] The title compound was prepared in a similar manner to that described in Example 1 using isopropyl chloroformate (2.0 mol equivalent) instead of ethyl chloroformate.

¹H-NMR (CD₃OD) δ ppm:

1.19 (3H, t, J=7.5Hz), 1.22 (3H, d, J=6.1Hz), 1.24 (3H, d, J=6.1Hz), 2.57 (2H, q, J=7.5Hz), 3.30-3.55 (3H, m), 3.55-3.70 (1H, m), 3.95 (1H, d, J=15.0Hz), 4.02 (1H, d, J=15.0Hz), 4.25 (1H, dd, J=6.3, 11.7Hz), 4.46 (1H, dd, J=2.3, 11.7Hz), 4.50-4.60 (2H, m), 4.70-4.85 (1H, m), 4.85-4.95 (1H, m), 6.90-7.20 (7H, m)

Example 36

2-[4-(2-Benzoyloxyethyl)benzyl]phenyl 6-O-ethoxycarbonyl-β-D-glucopyranoside

[0200] The title compound was prepared in a similar manner to that described in Example 1 using 2-[4-(2-benzoyloxyethyl)benzyl]phenyl β-D-glucopyranoside instead of 2-(4-ethylbenzyl)-5-hydroxymethylphenyl β-D-glucopyranoside.

¹H-NMR (CD₃OD) δ ppm:

1.22 (3H, t, J=7.1Hz), 2.84 (2H, t, J=7.0Hz), 3.35-3.40 (1H, m), 3.40-3.55 (2H, m), 3.55-3.65 (1H, m), 3.66 (2H, t, J=7.0Hz), 3.97 (1H, d, J=15.3Hz), 4.06 (1H, d, J=15.3Hz), 4.05-4.20 (2H, m), 4.28 (1H, dd, J=6.1, 11.7Hz), 4.44 (1H, dd, J=2.1, 11.7Hz), 4.48 (2H, s), 4.89 (1H, d, J=7.8Hz), 6.85-6.95 (1H, m), 7.00-7.05 (1H, m), 7.05-7.20 (6H, m), 7.20-7.35 (5H, m)

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Example 37

2-[4-(2-Hydroxyethyl)benzyl]phenyl 6-O-ethoxycarbonyl- β -D-glucopyranoside

[0201] To a solution of 2-[4-(2-benzyloxyethyl)benzyl]phenyl 6-O-ethoxycarbonyl- β -D-glucopyranoside (0.18 g) in ethyl acetate (4 mL) and ethanol (1 mL) was added 10% palladium-carbon powder (0.072 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 18 hours. Insoluble materials were removed by filtration, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 20/1-10/1) to give 2-[4-(2-hydroxyethyl)benzyl]phenyl 6-O-ethoxycarbonyl- β -D-glucopyranoside (0.11 g).

¹H-NMR (CD₃OD) δ ppm:

1.23 (3H, t, J=7.0Hz), 2.76 (2H, t, J=7.1Hz), 3.30-3.55 (3H, m), 3.55-3.65 (1H, m), 3.71 (2H, t, J=7.1Hz), 3.96 (1H, d, J=15.1Hz), 4.05 (1H, d, J=15.1Hz), 4.05-4.20 (2H, m), 4.29 (1H, dd, J=6.5, 11.7Hz), 4.44 (1H, dd, J=2.2, 11.7Hz), 4.88 (1H, d, J=7.5Hz), 6.85-6.95 (1H, m), 7.00-7.05 (1H, m), 7.05-7.20 (6H, m)

Example 38

2-[4-(2-Benzyloxyethyl)benzyl]phenyl 6-O-acetyl- β -D-glucopyranoside

[0202] The title compound was prepared in a similar manner to that described in Example 36 using acetyl chloride instead of ethyl chloroformate.

¹H-NMR (CD₃OD) δ ppm:

2.01 (3H, s), 2.84 (2H, t, J=6.9Hz), 3.30-3.55 (3H, m), 3.55-3.65 (1H, m), 3.66 (2H, t, J=6.9Hz), 3.97 (1H, d, J=14.9Hz), 4.06 (1H, d, J=14.9Hz), 4.23 (1H, dd, J=6.4, 11.9Hz), 4.38 (1H, dd, J=2.2, 11.9Hz), 4.48 (2H, s), 4.89 (1H, d, J=7.4Hz), 6.85-6.95 (1H, m), 7.00-7.05 (1H, m), 7.05-7.20 (6H, m), 7.20-7.35 (5H, m)

Example 39

2-[4-(2-Hydroxyethyl)benzyl]phenyl 6-O-acetyl- β -D-glucopyranoside

[0203] The title compound was prepared in a similar manner to that described in Example 37 using 2-[4-(2-benzyloxyethyl)benzyl]phenyl 6-O-acetyl- β -D-glucopyranoside instead of 2-[4-(2-benzyloxyethyl)benzyl]phenyl 6-O-ethoxycarbonyl- β -D-glucopyranoside.

¹H-NMR (CD₃OD) δ ppm:

2.02 (3H, s), 2.76 (2H, t, J=7.1Hz), 3.30-3.55 (3H, m), 3.55-3.65 (1H, m), 3.71 (2H, t, J=7.1Hz), 3.96 (1H, d, J=15.0Hz), 4.05 (1H, d, J=15.0Hz), 4.23 (1H, dd, J=6.4, 11.8Hz), 4.38 (1H, dd, J=2.2, 11.8Hz), 4.88 (1H, d, J=7.8Hz), 6.90-6.95 (1H, m), 7.00-7.20 (7H, m)

Example 40

2-[4-(2-Acetoxyethyl)benzyl]phenyl 6-O-acetyl- β -D-glucopyranoside

[0204] The title compound was prepared in a similar manner to that described in Example 38 using 2-[4-(2-hydroxyethyl)benzyl]phenyl 6-O-acetyl- β -D-glucopyranoside instead of 2-[4-(2-benzyloxyethyl)benzyl]phenyl 6-O-acetyl- β -D-glucopyranoside.

¹H-NMR (CD₃OD) δ ppm:

1.98 (3H, s), 2.02 (3H, s), 2.86 (2H, t, J=6.9Hz), 3.30-3.55 (3H, m), 3.55-3.65 (1H, m), 3.97 (1H, d, J=15.1Hz), 4.06 (1H, d, J=15.1Hz), 4.15-4.30 (3H, m), 4.38 (1H, dd, J=2.2, 12.2Hz), 4.89 (1H, d, J=7.6Hz), 6.90-7.00 (1H, m), 7.00-7.20 (7H, m)

Test Example 1

Assay for inhibitory effect on human SGLT2 activity 1) Construction of the plasmid vector expressing human SGLT2

[0205] Preparation of the cDNA library for PCR amplification was performed by reverse transcription of a total RNA deprived from human kidney (Ori gene) with oligo dT as the primer, using SUPERScript Preamplification System (Gibco-BRL: LIFE TECHNOLOGIES). The DNA fragment coding for human SGLT2 was amplified by the PCR reaction, in which the human kidney cDNA library described above was used as the template and the following oligo nucleotides

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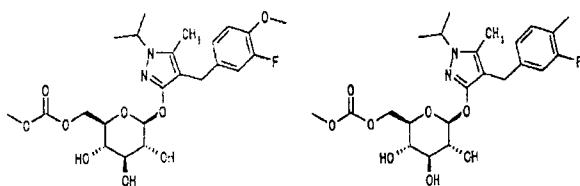
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[続葉有]

(54) Title: NOVEL PYRAZOLE DERIVATIVES AND DIABETES REMEDIES CONTAINING THE SAME

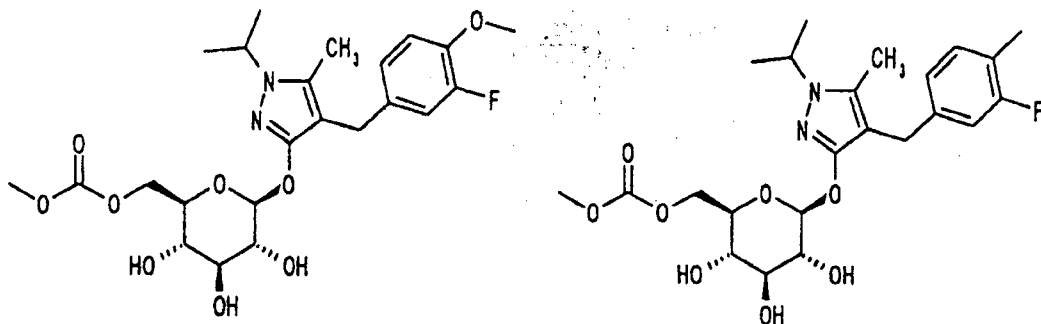
(54) 発明の名称: 新規ピラゾール誘導体及びそれらを含有する糖尿病治療薬



(57) Abstract: Pyrazole-O-glycoside derivatives represented by the formulae (i) and (ii), which are useful as diabetes remedies.

(57) 要約:

本発明は、糖尿病治療薬として用いる下記式で表されるピラゾール-O-グリコシド誘導体を提供する。



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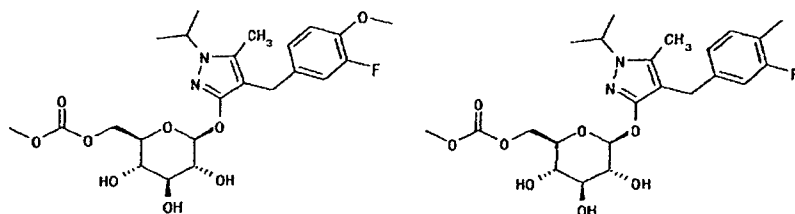
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(54) **NOVEL PYRAZOLE DERIVATIVES AND DIABETES REMEDIES CONTAINING THE SAME**

(57) The present invention provides pyrazole-O-glycoside derivatives represented by the following formulae, used as a diabetic medicine.



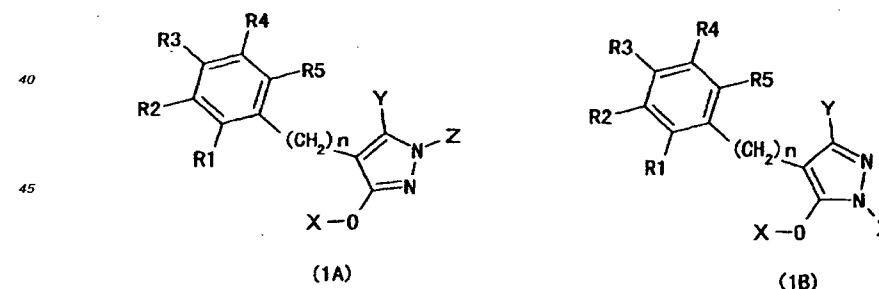
Description

Background of the Invention

- 5 [0001] The present invention relates to new pyrazole derivatives and diabetic medicine which have those compounds as an active ingredient.
- [0002] Na⁺-dependent glucose transporter (SGLT) is a membrane protein which transports glucose, and SGLT-1 and SGLT-2 are known. SGLT-2 mainly expresses in renal uriniferous tubules. Glucose that is filtered in glomeruli is reabsorbed at the renal uriniferous tubules via SGLT, and the glucose taken is reused in the body through the bloodstream.
- 10 When SGLT is inhibited, the amount of the glucose reabsorbed at renal uriniferous tubules lowers, and the glucose is discharged through urine. As a result, it is considered that the level of blood sugar decreases. At the present time, no medicine is clinically used such as that inhibiting reabsorption of glucose in the kidney.

Disclosure of the Invention

- 15 [0003] The object of the present invention is to provide new pyrazole derivatives.
- [0004] The object of the present invention is also to provide a pharmaceutical composition containing the new compounds.
- [0005] The object of the present invention is also to provide a pharmaceutical composition for the treatment of diabetes which comprises the new compound.
- 20 [0006] The object of the present invention is to find and provide diabetic-medicine which is easy to synthesize, less toxic and has higher curative effect.
- [0007] The present invention also intends to provide urinary sugar excretion inducers which have the new compounds.
- 25 [0008] Further, the present invention intends to provide the use of the new compounds for producing a pharmaceutical composition which reduces renal glucose reabsorption at renal uriniferous tubules.
- [0009] The inventors have synthesized various derivatives (1A) or (1B) wherein glucose (namely, β -D-glucopyranose) or glucuronic acid (namely, β -D-glucopyranoside uronic acid) is bonded to pyrazole, and vigorously investigated the action of those derivatives on urinary sugar excretion. As the result of animal tests, they have found that the compounds of general formula (1A) or (1B) have the outstanding action on urinary sugar excretion and completed the present invention. These compounds have not ever been synthesized and, therefore, are completely new pyrazole-O-glycoside derivatives and pyrazole-O-glucuronide derivatives.
- 30 [0010] Namely, the present invention provides pyrazole derivatives of the following general formula (1A) or (1B) or pharmaceutically acceptable salts thereof:



wherein X represents a β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated or β -D-glucuronyl group, of which one or more hydroxyl groups may be acylated and carboxyl group may be esterified; Y represents a lower alkyl group or perfluoro lower alkyl group; Z represents a hydrogen atom, lower alkyl group, perfluoro lower alkyl group, aralkyl group or phenyl group; R1 to R5 may be the same or different and represent a hydrogen atom, lower alkyl group, perfluoro lower alkyl group, lower alkoxy group, perfluoro lower alkoxy group, lower alkylthio group, perfluoro lower alkylthio group, lower alkyl amino group, halogeno group, lower alkanoyl group, lower alkenyl group or lower alkynyl group, and n represents an integer from 0 to 3.

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[0011] The present invention provides a pharmaceutical composition which comprises the above-mentioned pyrazole derivatives or pharmaceutically acceptable salts thereof as an active ingredient.

[0012] The present invention also provides a pharmaceutical composition for the treatment of diabetes which comprises the above-mentioned pyrazole derivatives or pharmaceutically acceptable salts thereof as an active ingredient.

[0013] The present invention also provides urinary sugar excretion inducers which comprise the above-mentioned pyrazole derivatives or pharmaceutically acceptable salts thereof as an active ingredient.

[0014] Further, the present invention provides the use of the above-mentioned pyrazole derivatives or pharmaceutically acceptable salts thereof for producing a pharmaceutical composition which reduces renal glucose reabsorption at renal uriniferous tubules.

Best Mode for Carrying out the Invention

[0015] The term "lower" in the present specification indicates 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms. The terms "alkyl", "alkenyl" and "alkynyl" in alkyl group, perfluoro lower alkyl group, lower alkoxy group, perfluoro lower alkoxy group, lower alkylthio group, perfluoro lower alkylthio group, lower alkyl amino group, lower alkanoyl group, lower alkenyl group or lower alkynyl group may be linear or branched.

[0016] An alkyl part in "alkyl group" in the present specification is a lower alkyl group. An aryl part in "aralkyl group" is a monocyclic or bicyclic aromatic substituent having 5 to 12 carbon atoms.

[0017] Examples of the alkyl group include methyl group, ethyl group, propyl group, butyl group, pentyl group, isopropyl group, isobutyl group and isopentyl group. The perfluoro lower alkyl group is, for example, a trifluoromethyl group. Examples of the lower alkoxy group are methoxy group, ethoxy group, propyloxy group and isopropoxy group. The perfluoro lower alkoxy group is, for example, a trifluoromethoxy group. The lower alkylthio group includes such as methylthio group, ethylthio group and propylthio group. The perfluoro lower alkylthio group is, for example, trifluoromethylthio group. The lower alkyl amino group includes such as methyl amino group, ethyl amino group, propyl amino group, dimethyl amino group and diethyl amino group. The lower alkanoyl group is, for example, acetyl group and propionyl group. The lower alkenyl group includes such as vinyl group, propenyl group and 2-methyl-1-propenyl group. The lower alkynyl group is, for example, ethynyl group and propynyl group. The aralkyl group includes such as benzyl group, benzyl group of which a benzene ring may have one or more substituents, phenethyl group and phenethyl group of which a benzene ring may have one or more substituents. The substituents of benzyl group and phenethyl group herein include lower alkoxy group, lower alkyl group, halogeno group and halogeno lower alkyl group. Examples of the halogeno group are fluorine atom, bromine atom, chlorine atom and iodine atom.

[0018] The groups for acylating hydroxyl group include acyl group and carbamate group; acyl group includes such as acetyl group, propionyl group, benzoyl group and pivaloyl group; carbamate group includes such as methyl carbonate group, ethyl carbonate group, propyl carbonate group, isopropyl carbonate group and phenyl carbonate group. The groups for esterifying carboxyl group include lower alkyl group such as methyl group, ethyl group, propyl group and isopropyl group.

[0019] In the above-mentioned general formula (1A) or (1B), one or more hydroxyl groups of β -D-glucopyranosyl group which is a group represented by X may be acylated. Especially, one or more hydroxyl groups of the said group may be acylated with the groups selected from alkanoyl groups having 2 to 20 carbon atoms, lower alkoxycarbonyl groups and benzoyl group. Examples of such groups are 6-O-acetyl- β -D-glucopyranosyl group and 6-O-methoxycarbonyl- β -D-glucopyranosyl group.

[0020] Further, one or more hydroxyl groups of β -D-glucuronyl group which is a group represented by X may be acylated and its carboxyl group may be esterified. Especially, one or more hydroxyl groups of the said group may be acylated with the groups selected from alkanoyl groups having 2 to 20 carbon atoms, lower alkoxycarbonyl groups and benzoyl group and its carboxylic acid may be esterified with lower alkyl group. An example of such groups is 6-O-methyl- β -D-glucuronyl group.

[0021] The groups represented by X are preferably β -D-glucopyranosyl group, 6-O-acetyl- β -D-glucopyranosyl group, 6-O-methoxycarbonyl- β -D-glucopyranosyl group, β -D-glucuronyl group and 6-O-methyl- β -D-glucuronyl group. Among them, β -D-glucopyranosyl group and β -D-glucuronyl group are more preferable. Particularly, the group represented by X is preferably β -D-glucopyranosyl group of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl groups having 2 to 20 carbon atoms, lower alkoxycarbonyl groups and benzoyl group. It is more preferable that the group is acylated with alkanoyl group having 2 to 6 carbon atoms or lower alkoxycarbonyl group. Among them, one hydroxyl group is preferably acylated. Most preferably, the hydroxyl group connected to a carbon atom at the 6th position is acylated. Examples of such groups represented by X are 6-O-acetyl- β -D-glucopyranosyl group and 6-O-methoxycarbonyl- β -D-glucopyranosyl group.

[0022] The groups represented by Y are preferably lower alkyl group having 1 to 3 carbon atoms or perfluoro lower alkyl group having 1 to 6 carbon atoms. A methyl group and trifluoromethyl group are particularly preferable.

[0023] The groups represented by Z are preferably hydrogen atom and lower alkyl group having 1 to 6 carbon atoms.

A hydrogen atom, lower alkyl group having 1 to 3 carbon atoms, unsubstituted aralkyl group or aralkyl group of which an aryl part at the 4th position is substituted and unsubstituted phenyl group are also preferable. Further, hydrogen atom, methyl group, ethyl group, propyl group, isopropyl group, unsubstituted benzyl group or benzyl group of which an aryl part at the 4th position is substituted and unsubstituted phenyl group are more preferable. Among them, hydrogen atom, methyl group, ethyl group, propyl group and isopropyl group are more preferable, and isopropyl group is particularly preferable.

[0024] The groups represented by R1 to R5 are preferably lower alkyl group having 1 to 6 carbon atoms, lower alkylthio group having 1 to 6 carbon atoms, halogeno atom, lower alkoxy group, lower alkenyl group and lower alkynyl group. A methyl group, ethyl group, methylthio group, ethylthio group, fluorine atom, methoxy group, vinyl group, propenyl group, ethynyl group and propynyl group are more preferable. It is particularly preferable that one or two groups represented by R1 to R5 are one of the above-mentioned preferable groups and the rest of the groups are hydrogen atom. In this case, at least R3 is preferably one of the above-mentioned preferable groups. When two groups in R1 to R5 are one of the above-mentioned preferable groups, they may be the same or different from each other, but they are preferably different from each other. Further, when R3 is either lower alkyl group, lower alkoxy group, lower alkenyl group or lower alkynyl group, R4 or R5 is preferably a fluorine atom. It is preferable that one of R1, R2, R4 and R5 is halogeno group, or R1, R2, R4 and R5 are all hydrogen atom and R3 is lower alkyl group, lower alkoxy group, lower alkenyl group or lower alkynyl group. It is also preferable that one of R1, R2, R4 and R5 is a fluorine atom and R3 is methyl group, ethyl group, methoxy group, vinyl group or ethynyl group.

[0025] It is preferable that n represents an integer 1.

[0026] Y in general formula (1A) or (1B) is preferably trifluoromethyl group.

[0027] Further, it is preferable that in general formula (1A) or (1B), Y is trifluoromethyl group and n is 1.

[0028] It is also preferable that in general formula (1A) or (1B), Y is trifluoromethyl group, n is 1 and X is β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group.

[0029] It is also preferable that in general formula (1A) or (1B), Y is trifluoromethyl group, n is 1 and X is β -D-glucuronyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group and its carboxylic acid may be esterified with alkyl group.

[0030] It is also preferable that in general formula (1A) or (1B), Y is trifluoromethyl group, n is 1 and X is β -D-glucopyranosyl group.

[0031] It is also preferable that in general formula (1A) or (1B), Y is trifluoromethyl group, n is 1 and X is 6-acetyl- β -D-glucopyranosyl group.

[0032] It is also preferable that in general formula (1A) or (1B), Y is trifluoromethyl group, n is 1 and X is 6-carbomethoxy- β -D-glucopyranosyl group.

[0033] It is also preferable that in general formula (1A) or (1B), Y is trifluoromethyl group, n is 1 and X is β -D-glucuronyl group.

[0034] It is also preferable that in general formula (1A) or (1B), Y is trifluoromethyl group, n is 1 and X is 6-methyl- β -D-glucuronyl group.

[0035] It is also preferable that in general formula (1A) or (1B), X is β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group.

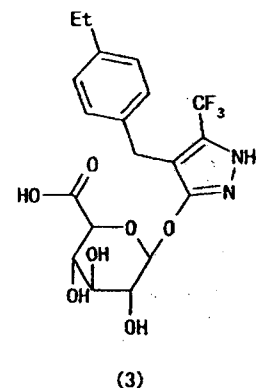
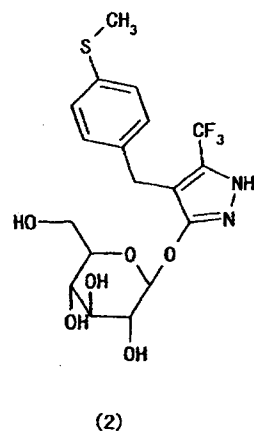
[0036] It is also preferable that in general formula (1A) or (1B), X is β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with lower alkoxycarbonyl group.

[0037] It is also preferable that in general formula (1A) or (1B), Y is lower alkyl group having 1 to 3 carbon atoms or perfluoro lower alkyl group having 1 to 6 carbon atoms; n is 1; X is β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z is a hydrogen atom, lower alkyl group having 1 to 3 carbon atoms, unsubstituted aralkyl group or aralkyl group of which an aryl part at the 4th position is substituted or unsubstituted phenyl group; one of R1, R2, R4 and R5 is a halogeno group, or R1, R2, R4 and R5 are all hydrogen atom and R3 is a lower alkyl group, lower alkoxy group, halogeno group, lower alkenyl group or lower alkynyl group.

[0038] It is also preferable that in general formula (1A) or (1B), Y is a methyl group; n is 1; X is β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z is an isopropyl group; R3 is a lower alkyl group and R4 or R5 is a fluorine atom.

[0039] It is also preferable that in general formula (1A) or (1B), Y is a methyl group; n is 1; X is β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z is an isopropyl group; R3 is a lower alkoxy group and R4 or R5 is a fluorine atom.

- 4-[(4-ethylphenyl) methyl]-1-[(4-methoxyphenyl) methyl]-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside;
 4'-[(4-ethylphenyl) methyl]-1'[(4'-methoxyphenyl) methyl]-5'-trifluoromethyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
 4-[(4-ethylphenyl) methyl]-1-phenyl-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside;
 4'-[(4'-ethylphenyl) methyl]-1'-phenyl-5'-trifluoromethyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
 4-[(3-fluoro-4-methoxyphenyl) methyl]-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside;
 4'-[(3'-fluoro-4'-methoxyphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
 4-[(2-fluoro-4-methoxyphenyl) methyl]-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside;
 4'-[(2'-fluoro-4'-methoxyphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
 4-[(3-fluoro-4-methylphenyl) methyl]-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside; and
 4'-[(3'-fluoro-4'-methylphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside.
 [0047] Among the above-mentioned examples, the following compounds or pharmaceutically acceptable salts thereof are particularly preferable:



- [0048] The following compounds or pharmaceutically acceptable salts thereof are also preferable:
 4'-[(4-ethylphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside; and
 4-[(4-ethylphenyl) methyl]-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside.
 [0049] As methods for producing pyrazole derivatives (1A) or (1B) in the present invention, for example, the compounds are produced in accordance with methods described below when X is β -D-glucopyranosyl group or β -D-glucuronyl group.

Description

Background of the Invention

[0001] The present invention relates to new pyrazole derivatives and diabetic medicine which have those compounds as an active ingredient.

[0002] Na⁺-dependent glucose transporter (SGLT) is a membrane protein which transports glucose, and SGLT-1 and SGLT-2 are known. SGLT-2 mainly expresses in renal uriniferous tubules. Glucose that is filtered in glomeruli is reabsorbed at the renal uriniferous tubules via SGLT, and the glucose taken is reused in the body through the bloodstream. When SGLT is inhibited, the amount of the glucose reabsorbed at renal uriniferous tubules lowers, and the glucose is discharged through urine. As a result, it is considered that the level of blood sugar decreases. At the present time, no medicine is clinically used such as that inhibiting reabsorption of glucose in the kidney.

Disclosure of the Invention

[0003] The object of the present invention is to provide new pyrazole derivatives.

[0004] The object of the present invention is also to provide a pharmaceutical composition containing the new compounds.

[0005] The object of the present invention is also to provide a pharmaceutical composition for the treatment of diabetes which comprises the new compound.

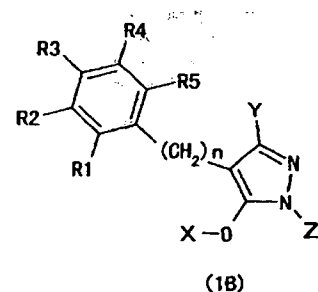
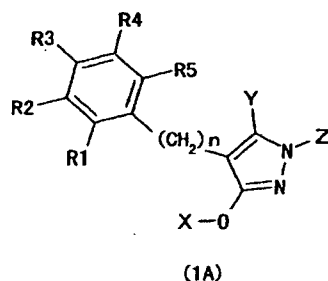
[0006] The object of the present invention is to find and provide diabetic-medicine which is easy to synthesize, less toxic and has higher curative effect.

[0007] The present invention also intends to provide urinary sugar excretion inducers which have the new compounds.

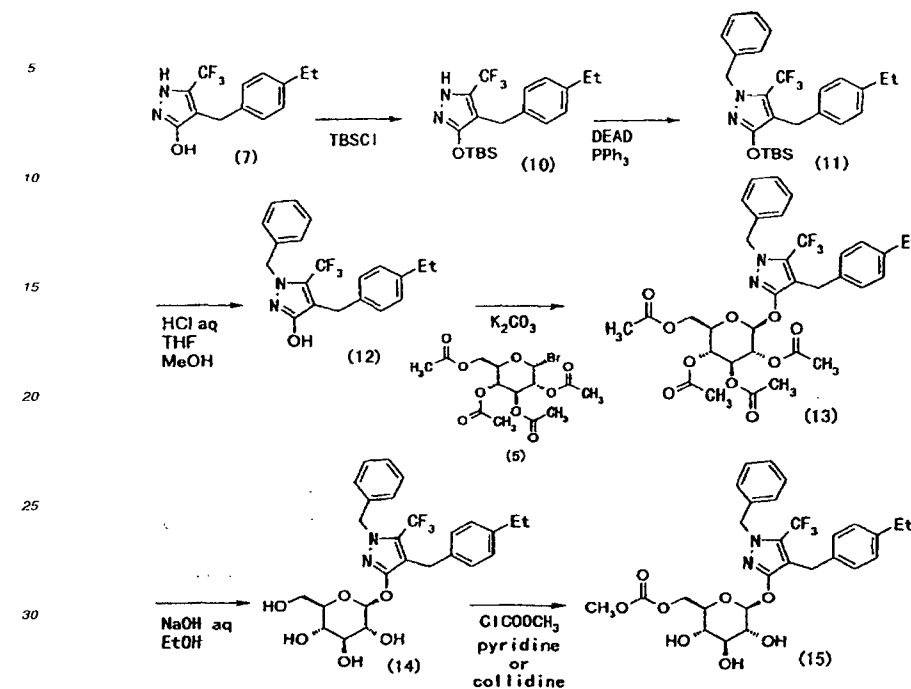
[0008] Further, the present invention intends to provide the use of the new compounds for producing a pharmaceutical composition which reduces renal glucose reabsorption at renal uriniferous tubules.

[0009] The inventors have synthesized various derivatives (1A) or (1B) wherein glucose (namely, β-D-glucopyranose) or glucuronic acid (namely, β-D-glucopyranoside uronic acid) is bonded to pyrazole, and vigorously investigated the action of those derivatives on urinary sugar excretion. As the result of animal tests, they have found that the compounds of general formula (1A) or (1B) have the outstanding action on urinary sugar excretion and completed the present invention. These compounds have not ever been synthesized and, therefore, are completely new pyrazole-O-glycoside derivatives and pyrazole-O-glucuronide derivatives.

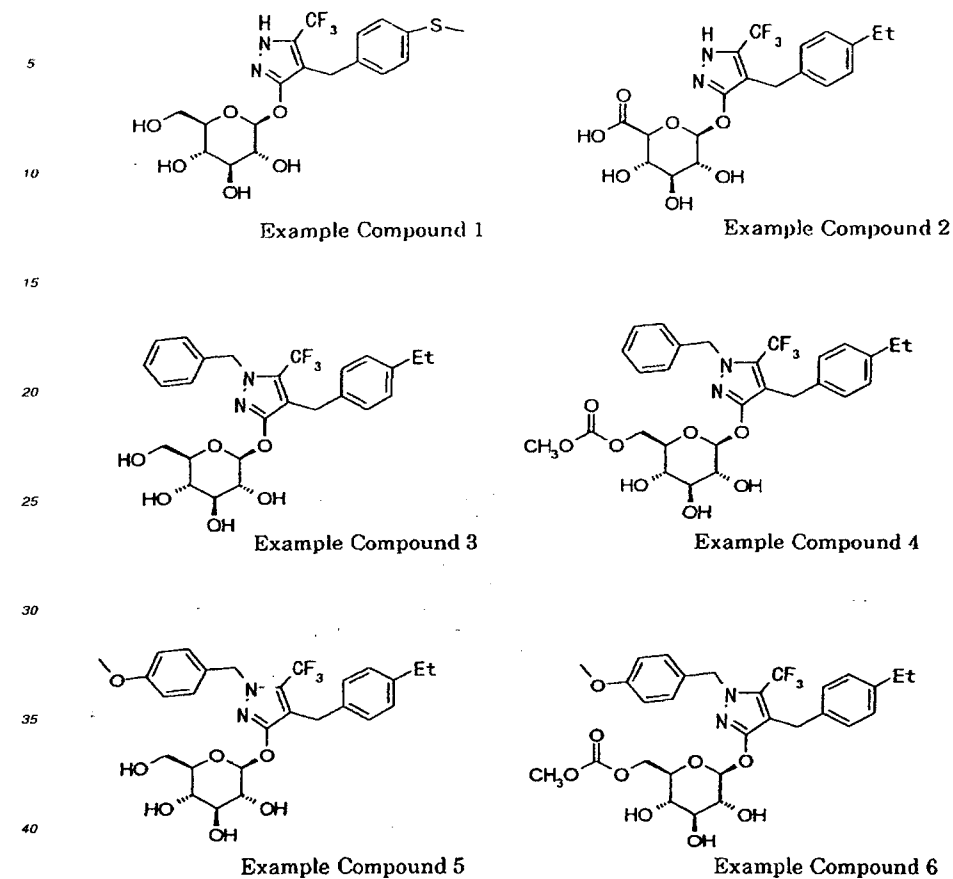
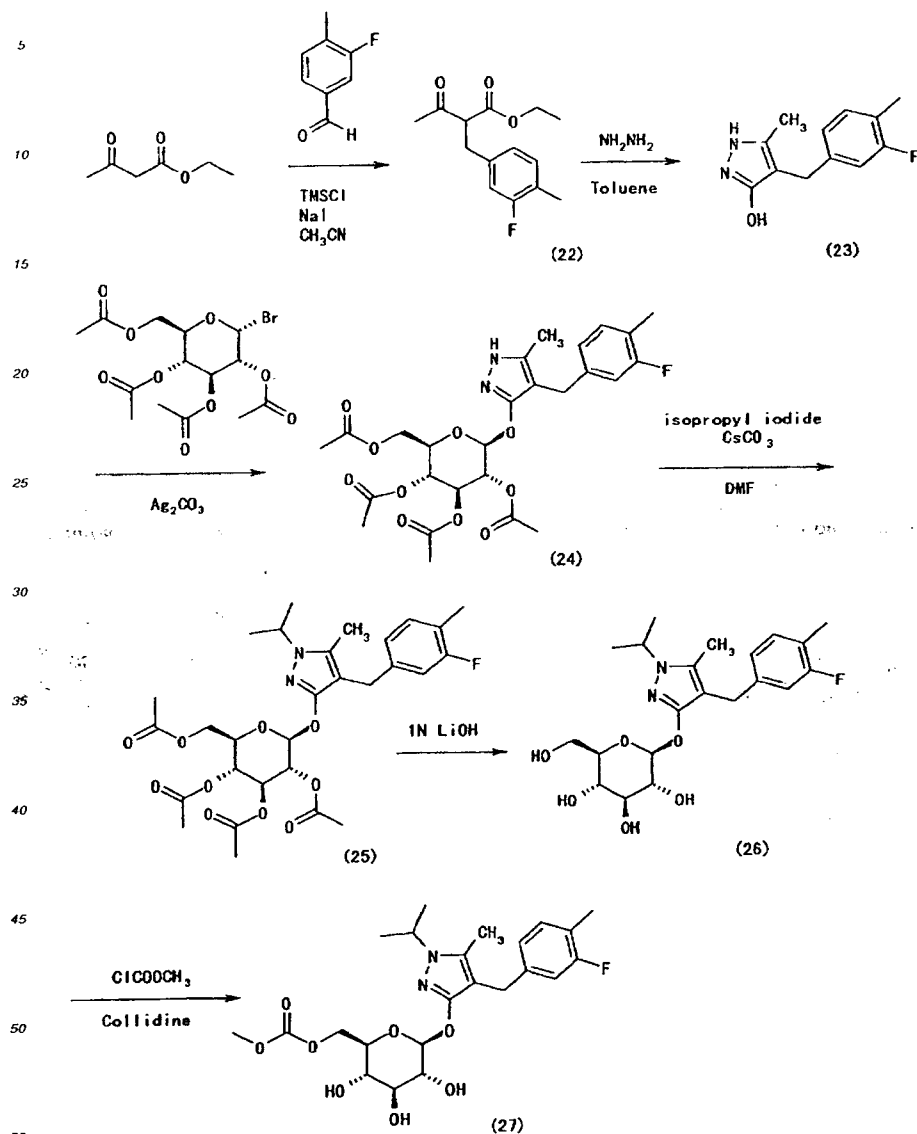
[0010] Namely, the present invention provides pyrazole derivatives of the following general formula (1A) or (1B) or pharmaceutically acceptable salts thereof:



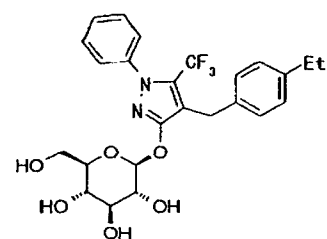
wherein X represents a β-D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated or β-D-glucuronyl group, of which one or more hydroxyl groups may be acylated and carboxyl group may be esterified; Y represents a lower alkyl group or perfluoro lower alkyl group; Z represents a hydrogen atom, lower alkyl group, perfluoro lower alkyl group, aralkyl group or phenyl group; R1 to R5 may be the same or different and represent a hydrogen atom, lower alkyl group, perfluoro lower alkyl group, lower alkoxy group, perfluoro lower alkoxy group, lower alkylthio group, perfluoro lower alkylthio group, lower alkyl amino group, halogeno group, lower alkanoyl group, lower alkenyl group or lower alkynyl group, and n represents an integer from 0 to 3.



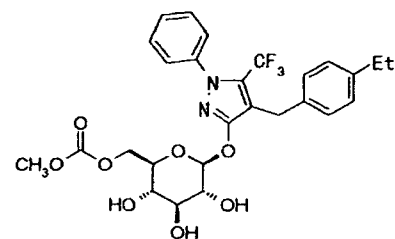
[0053] For example, the compound shown as the compound (21) of the present invention can be obtained by methods described as follows. Ethyl acetoacetate and 3-fluoro-4-methoxybenzaldehyde are reacted with trimethylsilylchloride and sodium iodide in acetonitrile to obtain an intermediate (16) and by forming a ring structure with hydrazine, 1,2-dihydro-4-((3-fluoro-4-methoxyphenyl) methyl)-5-methyl-3H-pyrazole-3-one (17) can be obtained. Then, 2,3,4,6-tetrabenzylglucopyranose is reacted with a hydroxyl group on pyrazole thereof in accordance with Mitsunobu reaction to obtain (18) and a nitrogen atom in the 1st position of pyrazole thereof is isopropylated by cesium carbonate and isopropyl iodide to obtain compound (19). A benzyl-protecting group of (19) is deprotected under hydrogen atmosphere by 20%Pd(OH)₂ to obtain compound (20), and a hydroxyl group at the 6th position of (20) is reacted with methyl chlorocarbonate in collidine to obtain the intended compound (21).



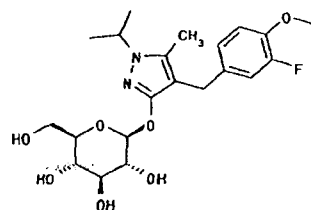
[0055] Pyrazole-O-glycoside derivatives and pyrazole-O-glucuronide derivatives of the present invention produced by the above-mentioned methods can be easily isolated and purified from the reaction mixture by ordinary methods



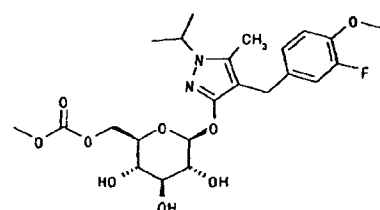
Example Compound 7



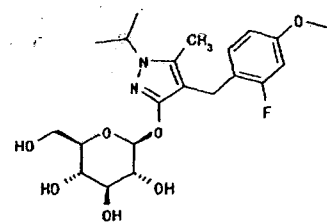
Example Compound 8



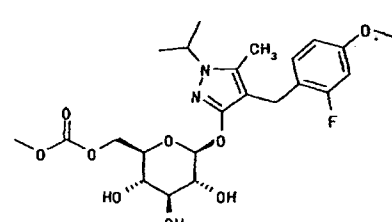
Example Compound 9



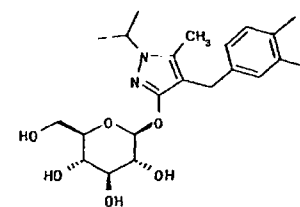
Example Compound 10



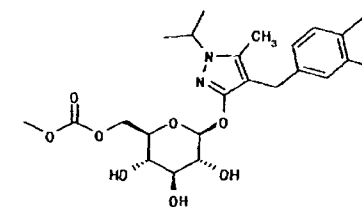
Example Compound 11



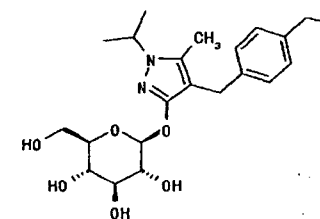
Example Compound 12



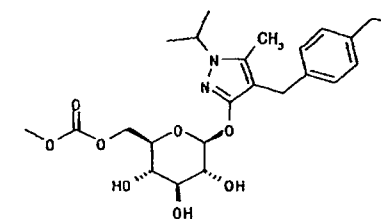
Example Compound 13



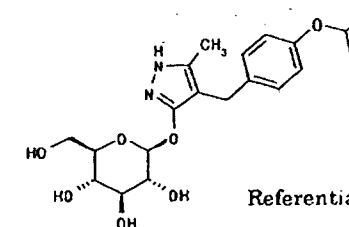
Example Compound 14



Example Compound 15



Example Compound 16



Referential Example Compound 1

Example 17

Evaluation of inhibiting activity on renal brush border membrane glucose uptake

[0111] The test compound was dissolved in 100mM Mannitol-10mM HEPES/Tris (pH7.4) and solutions having various concentrations were prepared.

Renal brush border membrane was prepared from a rat kidney and the solutions of the test compounds were added thereto and the product was incubated at 37°C for 30 minutes. Then ¹⁴C-D-glucose was added and the mixture was incubated for 1 minute. After the reaction of glucose uptake was stopped by a solution containing 1mM of phloridzin, the activity of ¹⁴C-D-glucose on ¹⁴C was measured by a liquid scintillation counter. The intensity of inhibition was calculated by subtracting the amount of taken glucose that is independent on sodium from the amount of taken glucose of the object samples. The results of the evaluation are shown in Table 1.

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—SOR^{5c}, —SO₂R^{5a}, —SO₂Aryl, or a five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO₂, or R⁵ and R⁶ together with the carbons to which they are attached form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO₂;

[0035] R⁵, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R^{5g}, R^{5h} and R⁵ⁱ are independently alkyl;

[0036] R⁶, R^{6a}, R^{6b}, R^{6c} and R^{6d} are independently hydrogen, alkyl, aryl, alkylaryl or cycloalkyl, or R⁶ and R^{6a} together with the nitrogen to which they are attached form an annelated five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO₂;

[0037] A is O, S, NH, or (CH₂)_n, where n is 0-3, and a pharmaceutically acceptable salt thereof, all stereoisomers thereof, and all prodrug esters thereof.

[0038] The compounds of formula I possess activity as inhibitors of the sodium dependent glucose transporters found in the intestine and kidney of mammals and are useful in the treatment of diabetes and the micro- and macrovascular complications of diabetes such as retinopathy, neuropathy, nephropathy, and wound healing.

[0039] The present invention provides, in particular, for methods of using such compounds.

[0040] Specifically, in accordance with the present invention, a method is provided for treating or delaying the progression or onset of diabetes, especially type I and type II diabetes, including complications of diabetes, including retinopathy, neuropathy, nephropathy and delayed wound healing, and related diseases such as insulin resistance (impaired glucose homeostasis), hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, obesity, hyperlipidemia including hypertriglyceridemia, Syndrome X, atherosclerosis and hypertension, and for increasing high density lipoprotein levels, wherein a therapeutically effective amount of a compound of structure I is administered to a human patient in need of treatment.

[0041] In addition, in accordance with the present invention, a method is provided for treating diabetes and related diseases as defined above and hereinafter, wherein a therapeutically effective amount of a combination of a compound of structure I and another type of antidiabetic agent and/or another type of therapeutic agent such as a hypolipidemic agent is administered to a human patient in need of treatment.

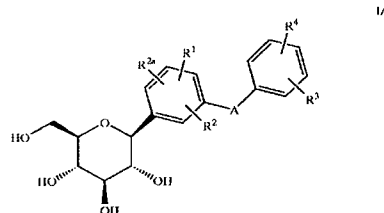
[0042] The conditions, diseases, and maladies collectively referred to as "Syndrome X" (also known as Metabolic Syndrome) are detailed in Johansson *J. Clin. Endocrinol. Metab.*, 82, 727-34 (1997).

[0043] The term "other type of therapeutic agents" as employed herein refers to one or more antidiabetic agents (other than SGLT2 inhibitors of formula I), one or more anti-obesity agents, anti-hypertensive agents, anti-platelet agents, anti-atherosclerotic agents and/or one or more lipid-lowering agents (including anti-atherosclerosis agents).

[0044] In the above method of the invention, the compound of structure I of the invention will be employed in a

weight ratio to the one, two or more antidiabetic agent and/or one, two or more other type therapeutic agent (depending upon its mode of operation) within the range from about 0.01:1 to about 300:1, preferably from about 0.1:1 to about 10:1.

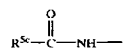
[0045] Preferred is the use of compounds of formula IA



[0046] wherein A is CH₂ or O or S and is linked meta to the glucoside;

[0047] R¹, R² and R^{2a} are independently selected from H, lower alkyl, halogen, OR⁵, or OCHF₂ or two of R¹, R² and R^{2a} are H and the other is lower alkyl, halogen, OR⁵ or OCHF₂;

[0048] R³ and R⁴ are independently selected from lower alkyl, OR^{5a}, —OCHF₂, —SR^{5c}, OH, —(CO₂R^{5b}), —3,4-(OCH₂O)—, —(OR^{6b}), CH(OH)R^{6c}, —CH(OR^{5b})R^{6d}, CF₃,



[0049] —SOR^{5f}, —SO₂R^{5a}, aryl, —NHSO₂Aryl, —NHSO₂R^{5d}, COOH, thiadiazole, tetrazole, —OCH₂Aryl, —OCF₃, OAr, or H.

[0050] More preferred is the use of compounds of formula I where A is CH₂;

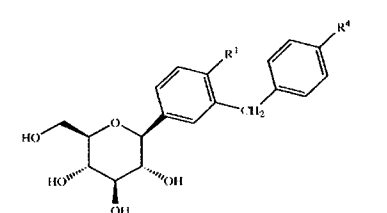
[0051] R¹ is hydrogen, halogen or lower alkyl;

[0052] R² and R^{2a} are each H;

[0053] R³ is H;

[0054] R⁴ is lower alkyl, —COR^{6b}, —CH(OH)R^{6c}, —CH(OR^{5b})R^{6d}, R^{6d}, R^{6d}, R^{5e}O, —OCHF₂, OCF₃ or —SR^{5c}.

[0055] Most preferred is the use of compound of formula I of the structure IB

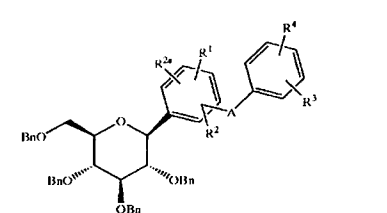


[0056] where R¹ is hydrogen, halogen or lower alkyl or R⁴ is lower alkyl, R^{5a}O, —OCHF₂, or —SR^{5c}. It read that that R¹ be linked para to the glucoside bond the substituent be linked at the para position.

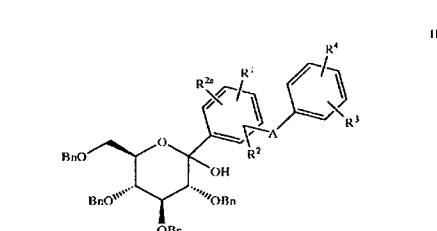
DETAILED DESCRIPTION OF THE II

[0057] The compounds of formula I can be prepared as shown in the following reaction schemes and depicted here hereof wherein temperatures are expressed in degrees Celsius.

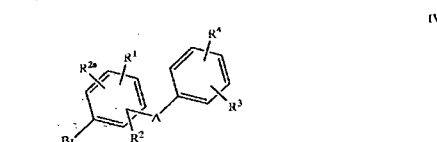
[0058] Compounds of formula I can be prepared in accordance with Scheme 1 by treatment of compounds of formula



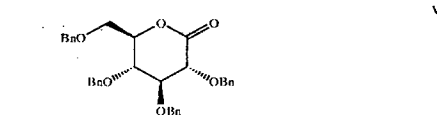
Et₃SiH or preferably (iPr)₃SiH in a solvent such as MeCN or mixtures of MeCN/CH₂Cl₂ containing a Lewis acid such as BF₃·Et₂O at -30°.



[0061] Compounds of formula III can be prepared by coupling of a compound of formula IV

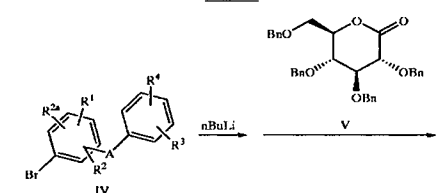


[0062] with compound V.



[0063] Compounds of formula IV are activated for coupling by treatment with n-BuLi or t-BuLi at -78° in a solvent such as THF prior to addition of lactone V. Preparation of lactone V is described in R. Benhaddou, S. Czerniecki, et al., *Carbohydr. Res.*, 260 (1994), 243-250.

Scheme 1

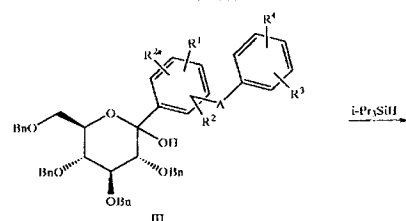


[0059] (where Bn=benzyl; with II₂ in the presence of a catalyst such as Pd/C or PdCl₂ using a solvent such as MeOH or EtOH) preferably Pd(OH)₂ using a solvent such as EtOAc. Alternatively, compounds of formula I can be prepared by treatment of compounds of formula II with a Lewis acid such as BF₃·Et₂O, BCl₃, or BCl₃·Me₂S in a solvent such as CH₂Cl₂. Compounds of formula I can also be prepared by treatment of compounds of formula II in a solvent such as EtSH containing BF₃·Et₂O, at 20°.

[0060] Compounds of formula II can be prepared by treatment of compounds of formula III with silanes such as

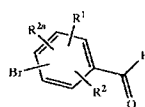
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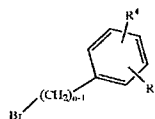
[0065] with silanes such as Et_3SiH in a solvent such as MeCN or CH_2Cl_2 containing a Lewis acid such as $\text{BF}_3 \cdot \text{Et}_2\text{O}$ or TFA at $+30^\circ$ to $+60^\circ$.

[0066] Compounds of formula VI can be prepared by coupling commercially available bromobenzaldehydes of formula VII



VII

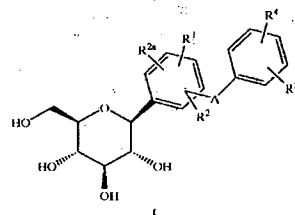
[0067] with either the lithium or magnesium organometallic derivative of compounds of formula VIII



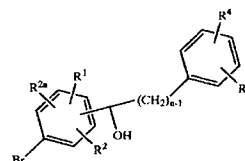
VIII

[0068] in a solvent such as Et_2O or THF using conditions familiar to those skilled in the art.

[0069] Compounds of formula VIII are either commercially available or readily prepared by standard methods known to those skilled in the art.

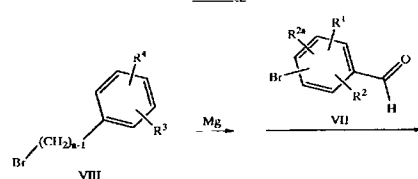


[0064] Compounds of formula IV where A is $(\text{CH}_2)_n$ where $n=1-3$ can be prepared as shown in Scheme 2 by treatment of compounds of formula VI

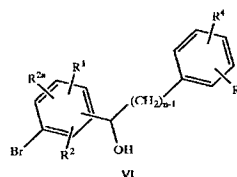


VI

Scheme 2

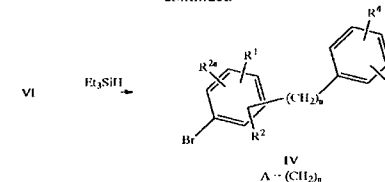


VII



IX

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IV

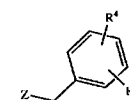
A = $(\text{CH}_2)_n$

[0070] Compounds of formula I where R^4 is $\text{CH}(\text{OR}^6)\text{R}^{6d}$ can be prepared by treatment of compounds of formula I where R^4 is COR^{6b} sequentially with 1) an acylating agent such as Ac_2O in a solvent such as pyridine alone or CH_2Cl_2 containing 1.5 equivalents of a base such as Et_3N , 2) a reducing agent such as NaBH_4 in a solvent such as EtOH , 3) an alkylating agent such as R^{6d}Br or R^{6d}I in the presence of a base such as NAH in a solvent such as DMF , and 4) alkaline ester hydrolysis conditions such as LiOH in a 2:3:1 mixture of $\text{THF}/\text{MeOH}/\text{H}_2\text{O}$.

[0071] Compounds of formula I where R^4 is $\text{CH}(\text{OH})\text{R}^{6c}$ can be prepared by treatment of compounds of formula I where R^4 is COR^{6b} with a reducing agent such as NaBH_4 in a solvent such as EtOH .

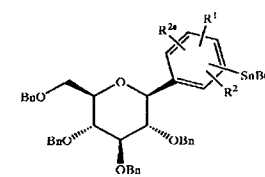
[0072] Compounds of formula I where R^4 is COR^{6b} can be prepared by treatment of compounds of formula II where R^4 is COR^{6b} with a Lewis acid such as BCl_3 or BBr_3 at -78° in a solvent such as CH_2Cl_2 .

[0073] Compounds of formula II where A is CH_2 and R^4 is $-\text{COR}^{6b}$ can be prepared as shown in Scheme 3 by coupling commercially available or readily accessible compounds of formula IX



IX

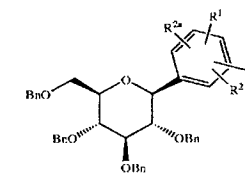
[0074] where Z is Br or Cl with compounds of formula X



X

[0075] by heating the two components in a solvent such as PhMe in the presence of a catalyst such as $\text{Pd}(\text{PPh}_3)_4$.

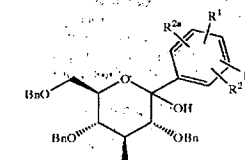
[0076] Compounds of formula X can be prepared from compounds of formula XI



XI

[0077] by treatment with $(\text{Bu}_3\text{Sn})_2$ and a catalyst such as $\text{Pd}(\text{Ph}_3\text{P})_4$ in a solvent such as toluene.

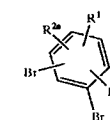
[0078] Compounds of formula XI can be prepared from compounds of formula XII



XII

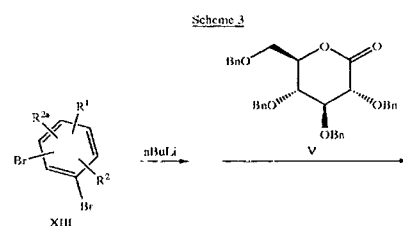
[0079] by treatment with silanes such as $i\text{Pr}_3\text{SiH}$ or Et_3SiH in a solvent such as MeCN containing a Lewis acid such as $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at -30° .

[0080] Compounds of formula XII can be prepared by coupling compound V with the organolithium obtained upon treatment of compounds of formula XIII

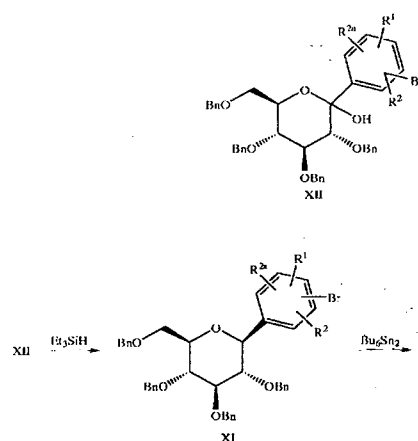
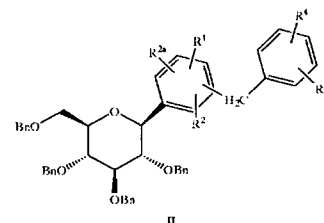


XIII

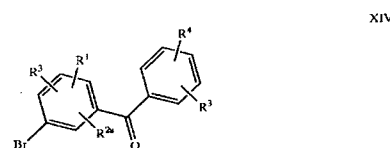
[0081] with $n\text{-BuLi}$ or $t\text{-BuLi}$ at -78° in THF.



-continued



[0082] An alternative synthesis (Scheme 4) of compounds of formula IV where A is CH_2 entails reduction of compounds of formula XIV

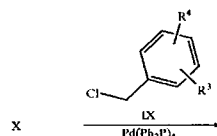
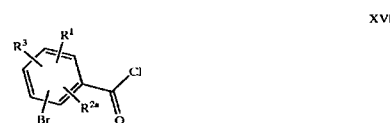


[0083] with a reducing agent such as Et_3SiH in a solvent such as MeCN or CH_2Cl_2 or mixtures thereof containing a catalyst such as $\text{BF}_3 \cdot \text{Et}_2\text{O}$.

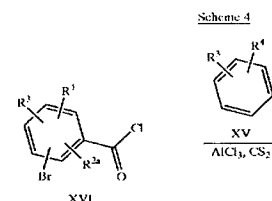
[0084] Compounds of formula XIV can be readily prepared by Friedel-Craft acylation of commercially available hydrocarbons of formula XV



[0085] with readily available acid chlorides of formula XVI



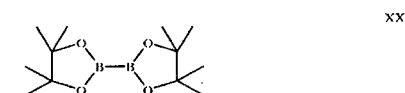
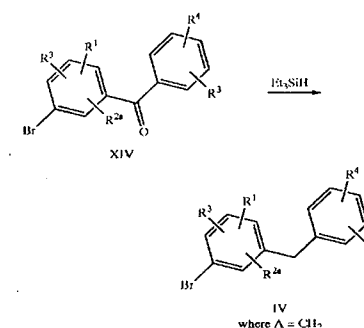
[0086] in a solvent such as CS_2 containing two equivalents of a Lewis Acid such as AlCl_3 or AlBr_3 .



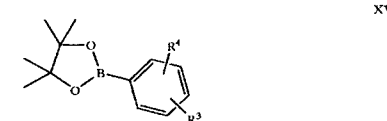
[0089] Coupling entails heating in the presence of a catalyst such as $\text{Pd}(\text{PPh}_3)_4$ employing a solvent such as 3:1 PhMe/EtOH containing Na_2CO_3 . Compounds of formula XVIII are either commercially available or can be prepared upon treatment of compounds of formula XVII with BCl_3 in a solvent such as CH_2Cl_2 . Compounds of formula XVII can be prepared by heating compounds of formula XIX



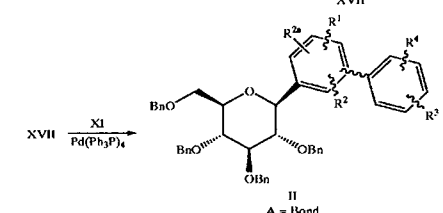
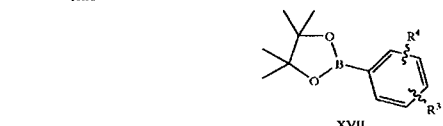
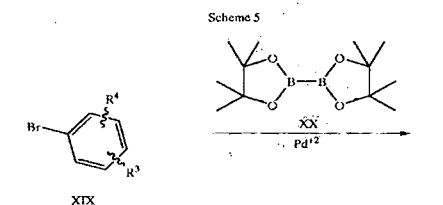
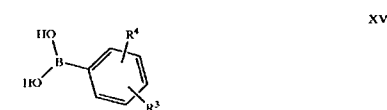
[0090] in a solvent such as DMSO containing a catalyst such as $\text{PdCl}_2 \cdot \text{dppf}$ and a base such as KOAc with compound XX.



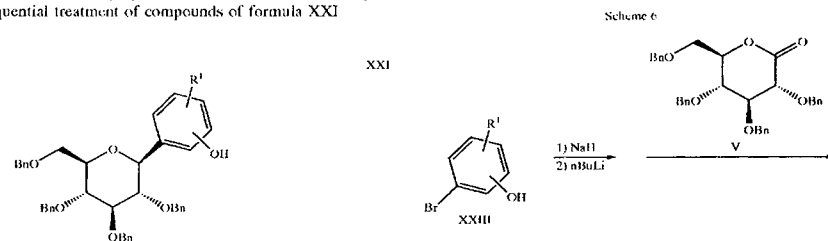
[0087] Compounds of formula II where A is a bond can be prepared as shown in Scheme 5 by coupling compounds of formula XI with compounds of formula XVII



[0088] or the corresponding boronic acid XVIII.

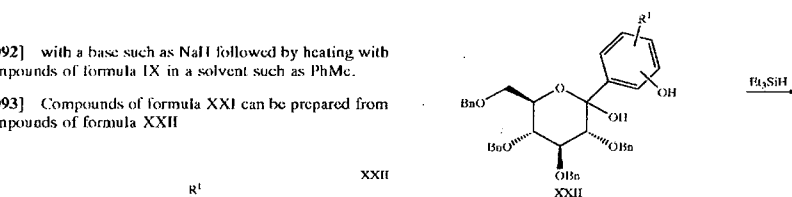


[0091] Compounds of formula II, where A=CH₂, and R²=OH, can be prepared as shown in Scheme 6 upon sequential treatment of compounds of formula XXI



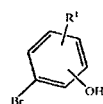
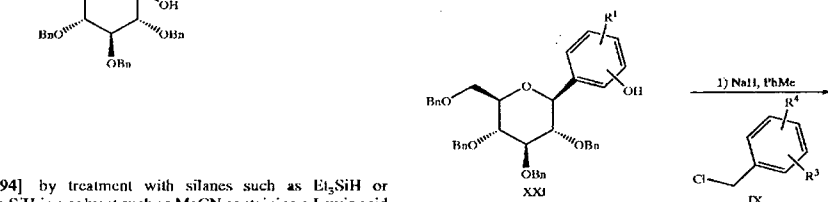
[0092] with a base such as NaH followed by heating with compounds of formula IX in a solvent such as PhMe.

[0093] Compounds of formula XXI can be prepared from compounds of formula XXII

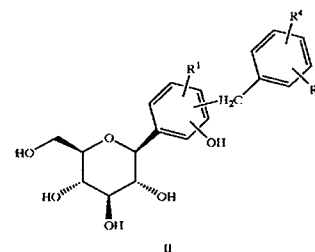


[0094] by treatment with silanes such as Et₃SiH or i-Pr₃SiH in a solvent such as MeCN containing a Lewis acid such as BF₃·Et₂O at -30°.

[0095] Compounds of formula XXII can be prepared by coupling the compound of formula V with activated metalated derivatives of compounds of formula XXIII



[0096] which are prepared by sequential treatment of XXIII with a base such as NaH, KH, or KOtBu followed by an alkyl lithium such as nBuLi or tBuLi in a solvent such as dry THF.



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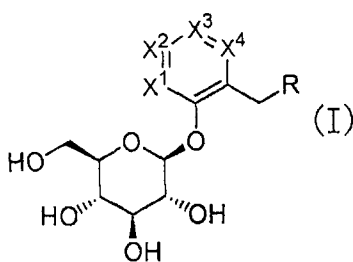
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(54) Title: NITROGEN-CONTAINING HETEROCYCLIC DERIVATIVES, MEDICINAL COMPOSITIONS CONTAINING THE SAME AND MEDICINAL USE THEREOF

(54) 発明の名称: 含窒素複素環誘導体、それを含有する医薬組成物およびその医薬用途



(57) Abstract: It is intended to provide a nitrogen-containing heterocyclic derivative which has an excellent effect of inhibiting human SGLT2 activity and is useful as a preventive or a remedy for diseases caused by hyperglycemia such as diabetes, diabetic complications and obesity, its pharmaceutically acceptable salt, prodrugs thereof, medicinal compositions containing the same and medicinal use thereof: (I) wherein X¹ represents N or CR¹; X² represents N or CR²; X³ represents N or CR³; X⁴ represents N or CR⁴, provided that 1 or 2 of X¹ to X⁴ are N; R represents optionally substituted C₃₋₈ cycloalkyl, optionally substituted C₆₋₁₀ aryl, etc.; and R¹ to R⁴ represent each H, a halogen, etc.

(R14)

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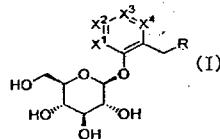
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(54) **NITROGEN-CONTAINING HETEROCYCLIC DERIVATIVES, MEDICINAL COMPOSITIONS CONTAINING THE SAME AND MEDICINAL USE THEREOF.**

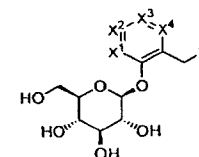
(57) The present invention provides nitrogen-containing heterocyclic derivatives represented by the general formula:



wherein X^1 represents N or CR²; X^2 represents N or CR²; X^3 represents N or CR³; X^4 represents N or CR⁴; and with the proviso that one or two of X^1 to X^4 represent N; R represents optionally substituted C_{1-10} cycloalkyl, optionally substituted C_{6-10} aryl, etc.; R² to R⁴ represent H, a halogen atom, etc.; or pharmaceutically acceptable salts thereof, or prodrugs thereof, which exert an excellent inhibitory activity in human SGLT2 and are useful as agents for the prevention or treatment of a disease associated with hyperglycemia such as diabetes, diabetic complications, obesity or the like, pharmaceutical compositions comprising the same, and medicinal uses thereof.

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(I)

[wherein X^1 represents N or CR²;

X^2 represents N or CR²;

X^3 represents N or CR³;

X^4 represents N or CR⁴;

and with the proviso that one or two of X^1 , X^2 , X^3 and X^4 represent N;

R represents a C_{3-8} cycloalkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (A), a C_{6-10} aryl group which may have the same or different 1 to 3 groups selected from the following substituent group (B), a C_{2-9} heterocycloalkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (B); R¹ to R⁴ are the same or different, independently represents a hydrogen atom or a group selected from the following substituent group (D);

substituent group (A) consists of a halogen atom, a nitro group, a cyano group, an oxo group, -G¹, -OG², -SG², -N(G²)₂, -C(=O)G², -C(=O)OG², -C(=O)N(G²)₂, -S(=O)₂G¹, -S(=O)₂OG², -S(=O)₂N(G²)₂, -S(=O)₂G¹, -OC(=O)G¹, -OC(=O)N(G²)₂, -NHC(=O)G², -OS(=O)₂G¹, -NHS(=O)₂G¹ and -C(=O)NHS(=O)₂G¹;

substituent group (B) consists of a halogen atom, a nitro group, a cyano group, -G¹, -OG², -SG², -N(G²)₂, -G³OG⁴, -G³N(G⁴)₂, -C(=O)G², -C(=O)OG², -C(=O)N(G²)₂, -S(=O)₂G¹, -S(=O)₂OG², -S(=O)₂N(G²)₂, -S(=O)₂G¹, -OC(=O)G¹, -OC(=O)N(G²)₂, -NHC(=O)G², -OS(=O)₂G¹, -NHS(=O)₂G¹ and -C(=O)NHS(=O)₂G¹;

(in the substituent group (A) and/or (B), G¹ represents a C_{1-6} alkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (C), a C_{2-6} alkenyl group which may have the same or different 1 to 3 groups selected from the following substituent group (C), a C_{3-8} cycloalkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (C), a C_{6-10} aryl group which may have the same or different 1 to 3 groups selected from the following substituent group (D), a C_{2-9} heterocycloalkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (D);

G² represents a hydrogen atom, a C_{1-6} alkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (C), a C_{2-6} alkenyl group which may have the same or different 1 to 3 groups selected from the following substituent group (C), a C_{2-6} alkenyl group which may have the same or different 1 to 3 groups selected from the following substituent group (C), a C_{3-8} cycloalkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (D), a C_{6-10} aryl group which may have the same or different 1 to 3 groups selected from the following substituent group (D), and with the proviso that G² are the same or different when there are more than one G² in the substituents;

G³ represents a C_{1-6} alkyl group;

G⁴ represents a C_{1-6} alkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (C), and with the proviso that G⁴ are the same or different when there are more than one G⁴ in the substituents;

substituent group (C) consists of a halogen atom, a nitro group, a cyano group, an oxo group, -G⁵, -OG⁵, -SG⁵, -N(G⁵)₂, -C(=O)G⁵, -C(=O)OG⁵, -C(=O)N(G⁵)₂, -S(=O)₂G⁵, -S(=O)₂OG⁵, -S(=O)₂N(G⁵)₂, -S(=O)₂G⁵, -OC(=O)G⁵, -OC(=O)N(G⁵)₂, -NHC(=O)G⁵, -OS(=O)₂G⁵, -NHS(=O)₂G⁵ and -C(=O)NHS(=O)₂G⁵; and substituent group (D) consists of a halogen atom, a nitro group, a cyano group, -G⁵, -OG⁵, -SG⁵, -N(G⁵)₂, -C(=O)G⁵, -C(=O)OG⁵, -C(=O)N(G⁵)₂, -S(=O)₂G⁵, -S(=O)₂OG⁵, -S(=O)₂N(G⁵)₂, -S(=O)₂G⁵, -OC(=O)G⁵, -OC(=O)N(G⁵)₂, -NHC(=O)G⁵, -OS(=O)₂G⁵, -NHS(=O)₂G⁵ and -C(=O)NHS(=O)₂G⁵;

(in the substituent group (C) and/or (D), G⁵ represents a C_{1-6} alkyl group, a HO-C₁₋₆ alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkenyl group, a C_{3-8} cycloalkyl group, a C_{6-10} aryl group, a C_{2-9} heterocycloalkyl group or a C_{1-9}

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heteroaryl group.

G⁶ represents a hydrogen atom, a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₃₋₈ cycloalkyl group, a C₆₋₁₀ aryl group, a C₂₋₉ heterocycloalkyl group or a C₁₋₉ heteroaryl group, and with the proviso that G⁶ are the same or different when there are more than one G⁶ in the substituents))

and with the proviso that when X¹ and X³ independently represent N or CH;

X² represents N or CH² (with the proviso that R² represents a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group, a C₃₋₈ cycloalkyl group, -O-C₁₋₆ alkyl, an amino group, -NH-C₂₋₇ acyl, -NH-C₁₋₆ alkyl or -N(C₁₋₆ alkyl)₂), and X⁴ represents N or CH⁴ (with the proviso that R⁴ represents a hydrogen atom or a C₁₋₆ alkyl group), R represents the above defined group except for the following substituent:



(wherein Z represents a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group which may have a substituent selected from the following substituent group (α), -O-C₁₋₆ alkyl which may have a substituent selected from the following substituent group (β), -S-C₁₋₆ alkyl which may have a substituent selected from the following substituent group (β) or a C₃₋₈ cycloalkyl group; substituent group (α) consists of a halogen atom, a hydroxy group and -O-C₁₋₆ alkyl; and substituent group (β) consists of a hydroxy group and -O-C₁₋₆ alkyl) or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

[2] a nitrogen-containing heterocyclic derivative as described in the above [1] wherein R represents a phenyl group which may have the same or different 1 to 3 groups selected from the following substituent group (B), or a pharmaceutically acceptable salt thereof, or a prodrug thereof

[wherein substituent group (B) consists of a halogen atom, a nitro group, a cyano group, -G¹, -OG², -SG², -N(G²)₂, -G³OG⁴, -G³N(G⁴)₂, -C(=O)G², -C(=O)N(G²)₂, -S(=O)₂G², -S(=O)₂OG², -S(=O)₂N(G²)₂, -S(=O)G¹, -OC(=O)G¹, -OC(=O)N(G²)₂, -NHC(=O)G², -OS(=O)G¹, -NHS(=O)₂G¹ and -C(=O)NHS(=O)₂G¹

(in the substituent group (B), G¹ represents a C₁₋₆ alkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (C), a C₂₋₆ alkenyl group which may have the same or different 1 to 3 groups selected from the following substituent group (C), a C₂₋₆ alkynyl group which may have the same or different 1 to 3 groups selected from the following substituent group (C), a C₃₋₈ cycloalkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (C), a C₆₋₁₀ aryl group which may have the same or different 1 to 3 groups selected from the following substituent group (D), a C₂₋₉ heterocycloalkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (C), a C₁₋₉ heteroaryl group which may have the same or different 1 to 3 groups selected from the following substituent group (D);

G² represents a hydrogen atom, a C₁₋₆ alkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (C), a C₂₋₆ alkenyl group which may have the same or different 1 to 3 groups selected from the following substituent group (C), a C₂₋₆ alkynyl group which may have the same or different 1 to 3 groups selected from the following substituent group (C), a C₃₋₈ cycloalkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (C), a C₆₋₁₀ aryl group which may have the same or different 1 to 3 groups selected from the following substituent group (D), a C₂₋₉ heterocycloalkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (D), a C₁₋₉ heteroaryl group which may have the same or different 1 to 3 groups selected from the following substituent group (D), and with the proviso that G² are the same or different when there are more than one G² in the substituents; G³ represents a C₁₋₆ alkyl group;

G⁴ represents a C₁₋₆ alkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (C), and with the proviso that G⁴ are the same or different when there are more than one G⁴ in the substituents;

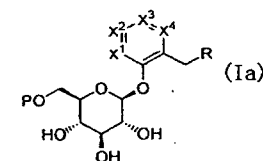
substituent group (C) consists of a halogen atom, a nitro group, a cyano group, an oxo group, -G⁵, -OG⁶, -SG⁶, -N(G⁶)₂, -C(=O)G⁶, -C(=O)OG⁶, -C(=O)N(G⁶)₂, -S(=O)₂G⁶, -S(=O)₂OG⁶, -S(=O)₂N(G⁶)₂, -S(=O)G⁵, -OC(=O)G⁵, -OC(=O)N(G⁶)₂, -NHC(=O)G⁶, -OS(=O)G⁵, -NHS(=O)₂G⁵ and -C(=O)NHS(=O)₂G⁵; and

substituent group (D) consists of a halogen atom, a nitro group, a cyano group, -G⁵, -OG⁶, -SG⁶, -N(G⁶)₂, -C(=O)G⁶, -C(=O)OG⁶, -C(=O)N(G⁶)₂, -S(=O)₂G⁶, -S(=O)₂OG⁶, -S(=O)₂N(G⁶)₂, -S(=O)G⁵, -OC(=O)G⁵, -OC(=O)N(G⁶)₂, -NHC(=O)G⁶, -OS(=O)G⁵, -NHS(=O)₂G⁵ and -C(=O)NHS(=O)₂G⁵

(in the substituent group (C) and/or (D), G⁵ represents a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₃₋₈ cycloalkyl group, a C₆₋₁₀ aryl group, a C₂₋₉ heterocycloalkyl group or a C₁₋₉ heteroaryl group; and

naphthyl group. The term "C₂₋₉ heterocycloalkyl group" means a group derived from a 3 to 8-membered heterocycloalkyl group containing the same or different 1 or 2 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring such as morpholine, thiomorpholine, tetrahydrofuran, tetrahydropyran, aziridine, azetidine, pyrrolidine, imidazolidine, oxazoline, piperidine, piperazine, pyrazolidine or the like, or a group derived from a 5 or 6-membered heterocycloalkyl group as defined above fused with an aliphatic or aromatic carbocycle or a heterocycle such as a cyclohexane ring, a benzene ring, a pyridine ring or the like. The term "C₁₋₉ heteroaryl group" means a group derived from a 5 or 6-membered heteroaryl group containing the same or different 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring such as thiazole, oxazole, isothiazole, isoxazole, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, thiophene, imidazole, pyrazole, oxadiazole, thiadiazole, tetrazole, furazan or the like, or a group derived from the above heteroaryl group fused with a 5 or 6-membered aromatic carbocycle or heterocycle such as a benzene ring, a pyrazole ring, a pyridine ring or the like. The term "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

[0009] In the present invention, the term "prodrug" means a compound which is converted into a nitrogen-containing heterocyclic derivative represented by the above general formula (I) as an active form thereof *in vivo*. As prodrugs of a nitrogen-containing heterocyclic derivative represented by the above general formula (I) or pharmaceutically acceptable salts, for example, a compound represented by the general formula:



wherein P represents a group forming a prodrug; and X¹, X², X³, X⁴ and R have the same meanings as defined above, or a pharmaceutically acceptable salt thereof are illustrated.

[0010] As examples of groups forming prodrugs, a hydroxy-protective group which can be used generally in a prodrug such as a C₂₋₂₀ acyl group, a C₁₋₆ alkyl-O-C₂₋₇ acyl group, a C₁₋₆ alkyl-OC(=O)-C₂₋₇ acyl group, a C₁₋₆ alkyl-OC(=O)-C₁₋₆ alkyl-O-C₁₋₆alkyl-OC(=O)-, a benzoyl group, a C₂₋₇ acyl-O-methyl group, a 1-(C₂₋₇acyl-O)-ethyl group, a C₁₋₆alkyl-OC(=O)-O-methyl group, a 1-(C₁₋₆alkyl-OC(=O)-O)-ethyl group, a C₃₋₈ cycloalkyl-OC(=O)-O-methyl group, a 1-(C₃₋₈ cycloalkyl-OC(=O)-O)-ethyl group, an ester group condensed with an amino acid, a phosphoric acid derivative or a cinnamic acid derivative and the like can be illustrated, and an amino-protective group which can be used generally in a prodrug such as a C₂₋₇ acyl group, a C₁₋₆ alkyl-O-C₂₋₇ acyl group, a C₁₋₆ alkyl-OC(=O)-C₂₋₇ acyl group, a C₁₋₆ alkyl-OC(=O)-C₁₋₆ alkyl-O-C₁₋₆alkyl-OC(=O)-, a benzoyl group, a C₂₋₇ acyl-O-methyl group, a 1-(C₂₋₇acyl-O)-ethyl group, a C₁₋₆alkyl-OC(=O)-O-methyl group, a 1-(C₁₋₆alkyl-OC(=O)-O)-ethyl group, a C₃₋₈ cycloalkyl-OC(=O)-O-methyl group, a 1-(C₃₋₈ cycloalkyl-OC(=O)-O)-ethyl group, an amide group condensed with an amino acid and the like can be illustrated. Moreover, a sulfonamide-protective group which can be used generally in a prodrug such as a C₂₋₇ acyl-O-methyl group, a 1-(C₂₋₇acyl-O)-ethyl group, a C₁₋₆alkyl-OC(=O)-O-methyl group, a 1-(C₁₋₆alkyl-OC(=O)-O)-ethyl group, a C₃₋₈ cycloalkyl-OC(=O)-O-methyl group, a 1-(C₃₋₈ cycloalkyl-OC(=O)-O)-ethyl group, a C₁₋₆alkyl-OC(=O)-O-methyl group, a 1-(C₁₋₆alkyl-OC(=O)-O)-ethyl group and the like can be illustrated. Furthermore, as examples of groups forming prodrugs, a sugar residue such as a glucopyranosyl group, a galactopyranosyl group and the like can be illustrated, for example, such a group can be introduced into the hydroxy group at the 4 or 6-position of the glucopyranosyl group. Of the compounds of the present invention, in a prodrug, a group forming a prodrug may be at any hydroxy group, amino group, sulfonamide group or the like, and two or more such groups are acceptable. The term "C₂₋₂₀ acyl group" means a straight-chained or branched acyl group having 2 to 20 carbon atoms such as an acetyl group, a propionyl group, a butyryl group, an isobutyryl group, a valeryl group, a pivaloyl group, a hexanoyl group, a lauroyl group, a myristoyl group, a palmitoyl group, a stearoyl group or the like.

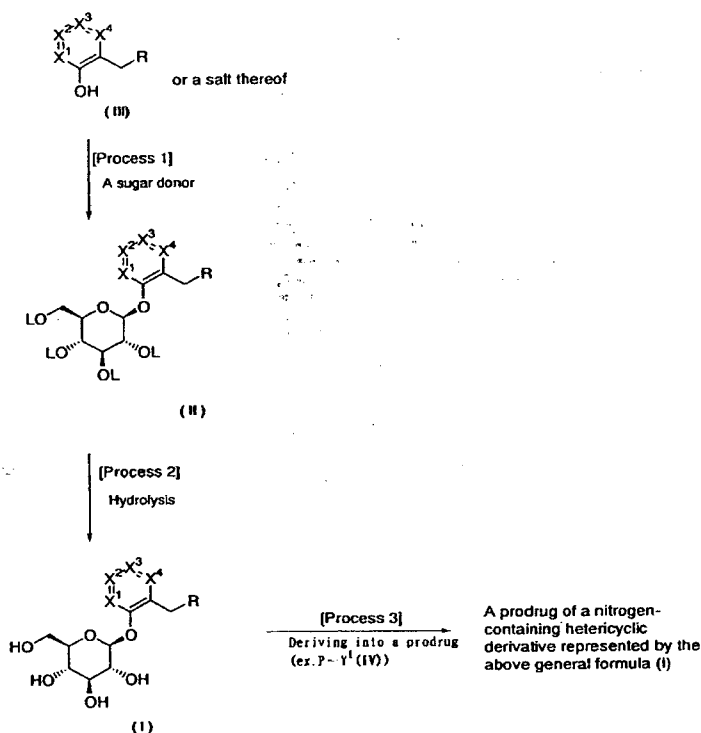
[0011] The term "hydroxy-protective group" means a hydroxy-protective group used in general organic syntheses such as a benzyl group, ap-methoxybenzyl group, ap-nitrobenzyl group, a methoxymethyl group, a methyl group, an acetyl group, a *tert*-butyldimethylsilyl group, an allyl group, a benzoyl group, a pivaloyl group, a benzyloxycarbonyl group, a 2-trimethylsilylethoxymethyl group or the like; the term "thiol-protective group" means a thiol-protective group used in general organic syntheses such as a benzyl group, a p-methoxybenzyl group, a p-nitrobenzyl group, an acetyl group, a benzoyl group, a pivaloyl group, a benzyloxycarbonyl group or the like; the term "amino-protective group"

means an amino-protective group used in general organic syntheses such as a benzyloxycarbonyl group, a *tert*-butoxycarbonyl group, a benzyl group, a *p*-methoxybenzyl group, a trifluoroacetyl group, an acetyl group or the like; and the term "carboxy-protective group" means a carboxy-protective group used in general organic syntheses such as a benzyl group, a *tert*-butyldimethylsilyl group, an allyl group or the like.

[0012] As examples of nitrogen-containing heterocyclic derivatives represented by the above general formula (I) of the present invention, various pyridine derivatives, various pyridazine derivatives, various pyrimidine derivatives, various pyrazine derivatives, various triazine derivatives and various tetrazine derivatives can be illustrated. In addition, in cases that there are tautomers in the present compounds, the present invention includes all tautomers.

[0013] The nitrogen-containing heterocyclic derivatives represented by the above general formula (I) of the present invention and prodrugs thereof can be prepared, for example, according to the reactions described by the following Scheme 1.

Scheme 1



wherein L represents a hydroxy-protective group; P represents a group forming a prodrug; Y^1 represents a leaving group such as a chlorine atom, a bromine atom or the like; and X^1 , X^2 , X^3 , X^4 and R have the same meanings as defined above.

Process 1

[0014] A corresponding compound represented by the above general formula (II) can be prepared by subjecting an alcohol compound represented by the above formula (III) or a salt thereof to glycosidation using a sugar donor such as acetobromo- α -D-glucose in the presence of a silver salt such as silver carbonate, silver oxide or the like or a base such as potassium carbonate, sodium hydride or the like in an inert solvent. As the solvent used in the glycosidation reaction, for example, acetonitrile, tetrahydrofuran, dichloromethane, toluene, *N,N*-dimethylformamide, a mixed solvent and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 2 hours to 2 days, varying based on a used starting material, solvent and reaction temperature.

Process 2

[0015] A nitrogen-containing heterocyclic derivative represented by the above general formula (I) of the present invention can be prepared by subjecting a compound represented by the above general formula (II) to alkaline hydrolysis. As the solvent used in the alkaline hydrolysis, methanol, ethanol, tetrahydrofuran, water, a mixed solvent thereof and the like can be illustrated, and as the base used, sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide and the like can be illustrated. The reaction temperature is usually from 0°C to room temperature, and the reaction time is usually from 30 minutes to 6 hours, varying based on a used starting material, solvent and reaction temperature.

Process 3

[0016] A prodrug of a nitrogen-containing heterocyclic derivative represented by the above general formula (I) (for example, a prodrug represented by the above general formula (Ia)) can be prepared by introducing hydroxy-protective groups generally capable for use in a prodrug into hydroxy groups of a nitrogen-containing heterocyclic derivative represented by the above general formula (I) using, for example, an agent for introducing a hydroxy-protective group represented by the above general formula (IV) in the usual way.

[0017] For example, a compound represented by the above general formula (III) used as a starting material in the above production method (Scheme 1) can be prepared according to the reactions as described in the following Scheme 2.

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agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproduct formation inhibitor, a protein kinase C inhibitor, a γ -aminobutyric acid antagonist, a sodium channel antagonist, a transcript factor NF- κ B inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated- α linked-acid-dipeptidase inhibitor, insulin-like growth factor I, platelet-derived growth factor, a platelet derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhydantoin, EGB-761, bimocromol, sulodexide, Y-128, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist and a diuretic agent is preferable; and the combination with at least one member of the group consisting of an aldose reductase inhibitor, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor and an angiotensin II receptor antagonist is more preferable. Furthermore, for obesity, the combination with at least one member of the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, insulin or an insulin analogue, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinositol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, a β_2 -adrenoceptor agonist and an appetite suppressant is preferable; and the combination with at least one member of the group consisting of a β_2 -adrenoceptor agonist and an appetite suppressant is more preferable.

[0081] When the pharmaceutical compositions of the present invention are employed in the practical treatment, various dosage forms are used depending on their uses. As examples of the dosage forms, powders, granules, fine granules, dry syrups, tablets, capsules, injections, solutions, ointments, suppositories, poultices and the like are illustrated, which are orally or parenterally administered.

[0082] These pharmaceutical compositions can be prepared by admixing with or by diluting with and dissolving in an appropriate pharmaceutical additive such as excipients, disintegrators, binders, lubricants, diluents, buffers, isotonicities, antiseptics, moistening agents, emulsifiers, dispersing agents, stabilizing agents, dissolving aids and the like, and formulating the mixture in accordance with pharmaceutically conventional methods depending on their dosage forms. In case of the use of the compound of the present invention in combination with the drugs other than SGLT2 inhibitors, they can be prepared by formulating each active ingredient together or individually.

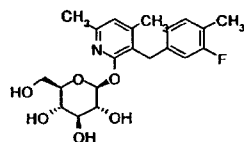
[0083] When the pharmaceutical compositions of the present invention are employed in the practical treatment, the dosage of a nitrogen-containing heterocyclic derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof, or a prodrug thereof as the active ingredient is appropriately decided depending on the age, sex, body weight and degree of symptoms and treatment of each patient, which is approximately within the range of from 0.1 to 1,000 mg per day per adult human in the case of oral administration and approximately within the range of from 0.01 to 300 mg per day per adult human in the case of parenteral administration, and the daily dose can be divided into one to several doses per day and administered suitably. Also, in case of the use of the compound of the present invention in combination with the drugs other than SGLT2 inhibitors, the dosage of the compound of the present invention can be decreased depending on the dosage of the drugs other than SGLT2 inhibitors.

Examples

[0084] The present invention is further illustrated in more detail by way of the following Examples and Test Examples. However, the present invention is not limited thereto.

Example 1

[0085]



Process 1

2-Benzoyloxy-4,6-dimethylpyridin-3-yl 3-fluoro-4-methylphenyl methanol

[0086] A Grignard reagent was prepared in the usual way using 1-bromo-3-fluoro-4-methylbenzene (0.53g), Magnesium (0.069g), a catalytic amount of iodine and tetrahydrofuran (5mL). To a tetrahydrofuran solution of the Grignard reagent was added a solution of 2-benzoyloxy-3-formyl-4,6-dimethylpyridine (0.34g) in tetrahydrofuran (5mL) at 0°C. After the reaction mixture was stirred at room temperature for 1 hour, a saturated aqueous ammonium solution and water were added, and the mixture was extracted with diethyl ether. The organic layer was washed with brine and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 6/1) to give the title compound (0.39g).

Process 2

3-(3-fluoro-4-methylbenzyl)-4,6-dimethyl-1H-pyridin-2-one

[0087] To a solution of 2-benzoyloxy-4,6-dimethylpyridin-3-yl 3-fluoro-4-methylphenyl methanol (0.39g) in ethanol (10mL) was added a catalytic amount of palladium carbon powder, and the mixture was stirred at room temperature under a nitrogen atmosphere overnight. After the insoluble material was removed by filtration, the solvent of the filtrate was removed to give the title compound (0.22g).

¹H-NMR (CDCl₃) δ ppm:

2.14 (3H, s), 2.20 (3H, d, J=1.1Hz), 2.22 (3H, s), 3.88 (2H, s), 5.86 (1H, s), 6.85-6.95 (2H, m), 6.95-7.10 (1H, m)

Process 3

2-(2,3,4,6-Tetra-O-acetyl-beta-D-glucopyranosyloxy)-3-(3-fluoro-4-methylbenzyl)-4,6-dimethylpyridine

[0088] To a solution of 3-(3-fluoro-4-methylbenzyl)-4,6-dimethyl-1H-pyridin-2-one (0.08g) and acetobromo- α -D-glucose (0.15g) in dichloromethane (2mL) was added silver carbonate (0.090g), and the mixture was stirred at room temperature overnight in the shade. The insoluble material was removed by filtration, and the filtrate was purified by column chromatography on aminopropylated silica gel (dichloromethane) to give the title compound (0.17g).

¹H-NMR (CDCl₃) δ ppm:

1.78 (3H, s), 2.00 (3H, s), 2.04 (3H, s), 2.16 (3H, s), 2.17-2.20 (3H, m), 2.38 (3H, s), 3.79 (1H, d, J=15.7Hz), 3.93 (1H, ddd, J=2.5, 4.7, 10.1Hz), 3.97 (1H, d, J=15.7Hz), 4.13 (1H, dd, J=2.5, 12.3Hz), 4.25 (1H, dd, J=4.7, 12.3Hz), 5.10-5.20 (1H, m), 5.25-5.40 (2H, m), 6.15-6.25 (1H, m), 6.60-6.70 (2H, m), 6.75-6.80 (1H, m), 6.95-7.05 (1H, m)

Process 4

2-(beta-D-Glucopyranosyloxy)-3-(3-fluoro-4-methylbenzyl)-4,6-dimethylpyridine

[0089] To a solution of 2-(2,3,4,6-tetra-O-acetyl-beta-D-glucopyranosyloxy)-3-(3-fluoro-4-methylbenzyl)-4,6-dimethylpyridine (0.17g) in methanol (5mL) was added sodium methoxide (28% methanol solution, 0.028mL), and the mixture was stirred at room temperature for 1 hour. The solvent of the reaction mixture was removed, and the residue was purified by column chromatography on silica gel (dichloromethane/methanol = 10/1) to give the title compound (0.081g).

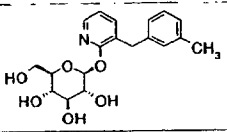
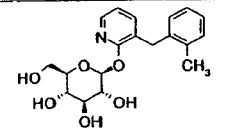
¹H-NMR (CD₃OD) δ ppm:

2.17 (6H, s), 2.36 (3H, s), 3.30-3.55 (4H, m), 3.67 (1H, dd, J=5.3, 11.9Hz), 3.84 (1H, dd, J=2.4, 11.9Hz), 3.94 (1H, d, J=15.6Hz), 4.06 (1H, d, J=15.6Hz), 5.85-6.00 (1H, m), 6.70-6.80 (1H, m), 6.80-6.95 (2H, m), 7.00-7.10 (1H, m)

Examples 2-3

[0090] The compounds described in Table 1 were prepared in a similar manner to that described in Example 1 using corresponding starting materials.

[Table 1]

Example number	Chemical structure	¹ H-NMR (CD ₃ OD) δ ppm:
Example 2		2.29 (3H, s), 3.35-3.60 (4H, m), 3.68 (1H, dd, J=5.0, 12.0Hz), 3.84 (1H, d, J=12.0Hz), 3.92 (1H, d, J=15.4Hz), 3.96 (1H, d, J=15.4Hz), 5.80-5.95 (1H, m), 6.85-7.20 (5H, m), 7.30-7.45 (1H, m), 7.90-8.05 (1H, m)
Example 3		2.20 (3H, s), 3.35-3.60 (4H, m), 3.70 (1H, dd, 5.0, 12.0Hz), 3.85 (1H, dd, J=2.1, 12.0Hz), 3.97 (1H, d, J=16.7Hz), 4.02 (1H, d, J=16.7Hz), 5.85-5.95 (1H, m), 6.80-6.95 (1H, m), 7.00-7.25 (5H, m), 7.90-8.05 (1H, m)

Test Example 1

Assay for inhibitory effects on human SGLT2 activity

1) Cloning and construction of the vector expressing human SGLT2

[0091] The cDNA library was prepared for PCR amplification by reverse transcription from total RNA deprived from human kidney (Origene) using oligo-dT as a primer. Using this cDNA library as a template, the base sequence coding 2 to 2039 bp of human SGLT2 (ACCESSION: M95549, M95299), which was reported by R. G. Wells et al., was amplified by PCR method and inserted into the multi-cloning site of pcDNA3.1(-) (Invitrogen). The DNA sequence inserted was perfectly matched to the previously reported sequence.

2) Establishment of cell line stably expressing human SGLT2

[0092] The expression vector of human SGLT2 was digested by Sca I into a linear DNA. The linear DNA was transfected into CHO-K1 cells by means of lipofection (Effectene Transfection Reagent: QIAGEN). Neomycin resistant cell lines were obtained by culture in the medium containing 1 mg/mL of G418 (LIFE TECHNOLOGIES), and then the activity against the uptake of methyl-α-D-glucopyranoside was measured by the method described below. The cell line, which showed the greatest uptake activity, was selected and designated as CS2-5E. Afterward, CS2-5E cells were cultured in the presence of G418 at 200 µg/mL.

3) Measurement of the inhibitory activity against the uptake of methyl-α-D-glucopyranoside (α-MG)

[0093] CS2-5E cells were seeded into a 96-well culture plate at a density of 3×10^4 cells/well and cultured for 2 days, and were used in the uptake assay. A mixture of non-radiolabeled (Sigma) and ¹⁴C- labeled α-MG (Amersham Pharmacia Biotech) was added to the uptake buffer (pH 7.4; containing 140 mM sodium chloride, 2 mM potassium chloride, 1 mM calcium chloride, 1 mM magnesium chloride, 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethane sulfonic acid, and 5 mM tris(hydroxymethyl)aminomethane) at the final concentration of 1 mM. A test compound was dissolved in dimethyl sulfoxide, and then appropriately diluted with distilled water. The test compound solution was added to the uptake buffer containing 1 mM α-MG, and designated as a measurement buffer. For the control group, the measurement buffer without any test compound was prepared. For measuring the basal uptake, a basal uptake measurement buffer which contains 140 mM choline chloride instead of sodium chloride was prepared. After removing the culture medium of cells, 180 µL of the pre-treatment buffer (the basal uptake buffer without α-MG) was added to each well and incubated at 37° C for 10 minutes. After repeating once the same treatment, the pre-treatment buffer was removed. To each well was added 75 µL of the measurement buffer or the basal uptake buffer was added and incubated at 37° C. After 1 hour, the measurement buffer was removed, and cells were washed twice with 180 µL per well of the washing buffer (the basal uptake buffer containing 10 mM non-labeled α-MG). The cells were solubilized by 75 µL per well of 0.2 mol/L

C₆)-Alkyl, (C₂-C₆)-Alkenyl, (C₂-C₆)-Alkyl, (C₁-C₆)-Alkoxy, HO-(C₁-C₆)-Alkyl, (C₁-C₆)-Alkoxy-(C₁-C₆)-alkyl, Phenyl, Benzyl, (C₁-C₄)-Alkylcarbonyl, wobei in den Alkyl- und Alkoxyresten ein, mehrere, oder alle Wasserstoff(e) durch Fluor ersetzt sein können;

SO₂-NH₂, SO₂NH(C₁-C₆)-Alkyl, SO₂N[(C₁-C₆)-Alkyl]₂, S-(C₁-C₆)-Alkyl, S-(CH₂)_o-Phenyl, SO-(C₁-C₆)-Alkyl, SO-(CH₂)_o-Phenyl, SO₂-(C₁-C₆)-Alkyl, SO₂-(CH₂)_o-Phenyl, wobei o = 0 – 6 sein kann und der Phenylrest bis zu zweifach mit F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, (C₁-C₆)-Alkoxy, (C₁-C₆)-Alkyl, NH₂ substituiert sein kann;

NH₂, NH-(C₁-C₆)-Alkyl, N[(C₁-C₆)-Alkyl]₂, NH(C₁-C₇)-Acyl, Phenyl, O-(CH₂)_o-Phenyl, wobei o = 0 – 6 sein kann, wobei der Phenylring ein bis 3-fach substituiert sein kann mit F, Cl, Br, J, OH, CF₃, NO₂, CN, OCF₃, (C₁-C₆)-Alkoxy, (C₁-C₆)-Alkyl, NH₂, NH(C₁-C₆)-Alkyl, N[(C₁-C₆)-Alkyl]₂, SO₂-CH₃, COOH, COO-(C₁-C₆)-Alkyl, CONH₂;

(C₀-C₁₅)-Alkandiyl, wobei ein oder mehrere C-Atome des Alkandiylrests unabhängig voneinander durch -O-, -(C=O)-, -CH=CH-, -C≡C-, -S-, -CH(OH)-, -CHF-, -CF₂-, -(S=O)-, -(SO₂)-, -N[(C₁-C₆)-Alkyl]-, -N[(C₁-C₆)-Alkyl-Phenyl]- oder -NH- ersetzt sein können;

n eine Zahl von 0 bis 4;

Cyc1 ein 3 bis 7 gliedriger gesättigter, teilweise gesättigter oder ungesättigter Ring, wobei 1 C-Atom durch O oder S ersetzt sein kann;

R3, R4, R5 Wasserstoff, F, Cl, Br, J, OH, NO₂, CN, COOH, COO(C₁-C₆)-Alkyl, CO(C₁-C₄)-Alkyl, CONH₂, CONH(C₁-C₆)-Alkyl, CON[(C₁-C₆)-Alkyl]₂, (C₁-C₆)-Alkyl, (C₂-C₆)-Alkenyl, (C₂-C₆)-Alkyl, (C₁-C₁₂)-Alkoxy, HO-(C₁-C₆)-Alkyl, (C₁-C₆)-Alkoxy-(C₁-C₆)-alkyl, wobei in den Alkyl- und Alkoxyresten ein, mehrere, oder alle Wasserstoff(e) durch Fluor ersetzt sein können; SO₂-NH₂, SO₂NH(C₁-C₆)-Alkyl, SO₂N[(C₁-C₆)-Alkyl]₂, S-(C₁-C₆)-Alkyl, S-(CH₂)_o-Phenyl, SO-(C₁-C₆)-Alkyl, SO-(CH₂)_o-Phenyl, SO₂-(C₁-C₆)-Alkyl,

SO₂-(CH₂)_o-Phenyl, wobei o = 0 – 6 sein kann und der Phenylrest bis zu zweifach mit F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, (C₁-C₆)-Alkoxy, (C₁-C₆)-Alkyl, NH₂ substituiert sein kann;

NH₂, NH-(C₁-C₆)-Alkyl, N[(C₁-C₆)-Alkyl]₂, NH(C₁-C₇)-Acyl, Phenyl, (CH₂)_o-Phenyl, O-(CH₂)_o-Phenyl, wobei o = 0 – 6 sein kann, wobei der Phenylring ein bis 3-fach substituiert sein kann mit F, Cl, Br, J, OH, CF₃, NO₂, CN, OCF₃, (C₁-C₆)-Alkoxy, (C₁-C₆)-Alkyl, NH₂, NH(C₁-C₆)-Alkyl, N[(C₁-C₆)-Alkyl]₂, SO₂-CH₃, COOH, COO-(C₁-C₆)-Alkyl, CONH₂; oder

gemeinsam mit den sie tragenden C-Atomen einen 5 bis 7 gliedrigen, gesättigten, teilweise oder vollständig ungesättigten Ring Cyc2, wobei 1 oder 2 C-Atom(e) des Ringes auch durch N, O oder S ersetzt sein können und Cyc2 gegebenenfalls durch (C₁-C₆)-Alkyl, (C₂-C₆)-Alkenyl, (C₂-C₆)-Alkyl, wobei jeweils eine CH₂-Gruppe durch O ersetzt sein kann, oder durch H, F, Cl, OH, CF₃, NO₂, CN, COO(C₁-C₄)-Alkyl, CONH₂, CONH(C₁-C₄)-Alkyl, OCF₃ substituiert sein kann und

Wasserstoff;

sowie deren pharmazeutisch verträglichen Salze.

Bevorzugt sind Verbindungen der Formel I, worin A mit dem Thienylring in 2 Position verknüpft ist.

Bevorzugt sind ferner Verbindungen der Formel I, worin bedeuten

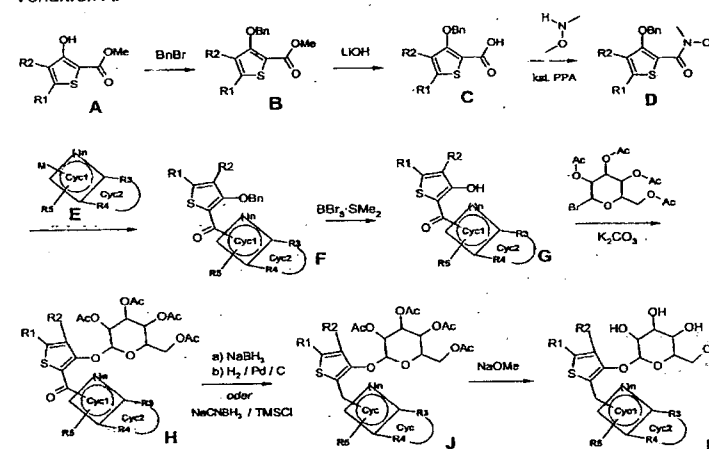
R1, R2 Wasserstoff, F, Cl, Br, J, OH, NO₂, CN, COOH, CO(C₁-C₆)-Alkyl, COO(C₁-C₆)-Alkyl, CONH₂, CONH(C₁-C₆)-Alkyl, CON[(C₁-C₆)-Alkyl]₂, (C₁-C₆)-Alkyl, (C₂-C₆)-Alkenyl, (C₂-C₆)-Alkyl, (C₁-C₆)-Alkoxy, HO-(C₁-C₆)-Alkyl, (C₁-C₆)-Alkoxy-(C₁-C₆)-alkyl, Phenyl, Benzyl, (C₁-C₄)-Alkylcarbonyl, SO-(C₁-C₆)-Alkyl, wobei in den Alkyl- und Alkoxyresten ein, mehrere, oder alle Wasserstoff(e) durch Fluor ersetzt sein können;

- A (C₀-C₁₅)-Alkandyl, wobei ein oder mehrere C-Atom(e) des Alkandylrests unabhängig voneinander durch -O-, -(C=O)-, -CH=CH-, -C≡C-, -S-, -CH(OH)-, -CHF-, -CF₂-, -(S=O)-, -(SO₂)-, -N((C₁-C₆)-Alkyl)-, -N((C₁-C₆)-Alkyl-Phenyl)- oder -NH- ersetzt sein können;
- n eine Zahl 2 oder 3;
- Cyc1 ein 5 bis 6 gliedriger gesättigter, teilweise gesättigter oder ungesättigter Ring, wobei 1 C-Atom durch O oder S ersetzt sein kann;
- R3, R4, R5 Wasserstoff, F, Cl, Br, J, OH, NO₂, CN, COOH, COO(C₁-C₆)-Alkyl, CO(C₁-C₄)-Alkyl, CONH₂, CONH(C₁-C₆)-Alkyl, CON[(C₁-C₆)-Alkyl]₂, (C₁-C₆)-Alkyl, (C₂-C₆)-Alkenyl, (C₂-C₆)-Alkyl, (C₁-C₁₂)-Alkoxy, HO-(C₁-C₆)-Alkyl, (C₁-C₆)-Alkoxy-(C₁-C₆)-alkyl, (C₁-C₄)-Alkyl-Phenyl, (C₁-C₄)-Alkoxy-Phenyl, S-(C₁-C₆)-Alkyl, SO-(C₁-C₆)-Alkyl, wobei in den Alkyl- und Alkoxyresten ein, mehrere, oder alle Wasserstoff(e) durch Fluor ersetzt sein können; oder
- R3 und R4 gemeinsam mit den sie tragenden C-Atomen einen 5 bis 7 gliedrigen, gesättigten, teilweise oder vollständig ungesättigten Ring Cyc2, wobei 1 oder 2 C-Atom(e) des Ringes auch durch N, O oder S ersetzt sein können und Cyc2 gegebenenfalls durch (C₁-C₆)-Alkyl, (C₂-C₅)-Alkenyl, (C₂-C₅)-Alkyl, wobei jeweils eine CH₂-Gruppe durch O ersetzt sein kann, oder durch H, F, Cl, OH, CF₃, NO₂, CN, COO(C₁-C₄)-Alkyl, CONH₂, CONH(C₁-C₄)-Alkyl, OCF₃ substituiert sein kann, und
- R5 Wasserstoff.

Besonders bevorzugt sind Verbindungen der Formel I, worin

- R1, R2 Wasserstoff, (C₁-C₆)-Alkyl, (C₁-C₄)-Alkoxy, HO-(C₁-C₄)-Alkyl, (C₁-C₄)-Alkoxy-(C₁-C₄)-alkyl, F, Cl, CF₃, OCF₃, OCH₂CF₃, (C₁-C₄)-Alkyl-CF₂,

Verfahren A:

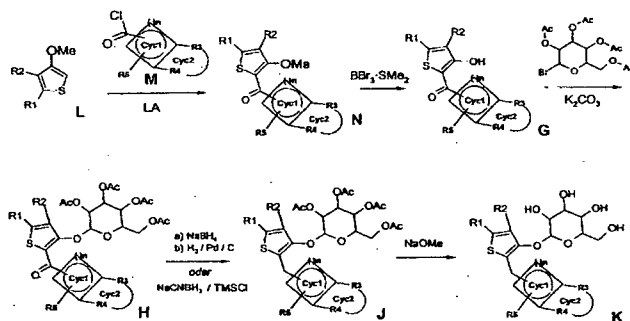


- 5 Es wird die Verbindung der allgemeinen Formel A, wobei R1 und R2 die oben beschriebenen Bedeutungen haben, in DMF mit CsCO₃ oder einer anderen geeigneten Base deprotoniert und anschließend mit Benzylbromid umgesetzt, wobei eine Verbindung der allgemeinen Formel B erhalten wird.
- 10 Die Verbindung B wird in einer Mischung aus Methanol, Tetrahydrofuran und Wasser gelöst und durch Umsetzung mit Lithiumhydroxid in die Verbindung der allgemeinen Formel C überführt.

Die Verbindung C wird mit N,O-Dimethylhydroxylamin unter Verwendung von

- 15 Propanphosphonsäureanhydrid oder einem anderen geeigneten Aktivierungsreagenz zur Knüpfung von Amidbindungen in die Verbindung der allgemeinen Formel D überführt.

14



Die Verbindung der allgemeinen Formel L, wobei R1 und R2 die oben beschriebenen 5 Bedeutungen haben, wird in Methylenchlorid gelöst und unter Eiskühlung mit einer Verbindung der allgemeinen Formel M, wobei Cyc1, Cyc2, n, R3, R4, R5 die oben beschriebenen Bedeutungen haben, zur Verbindung der allgemeinen Formel N umgesetzt.

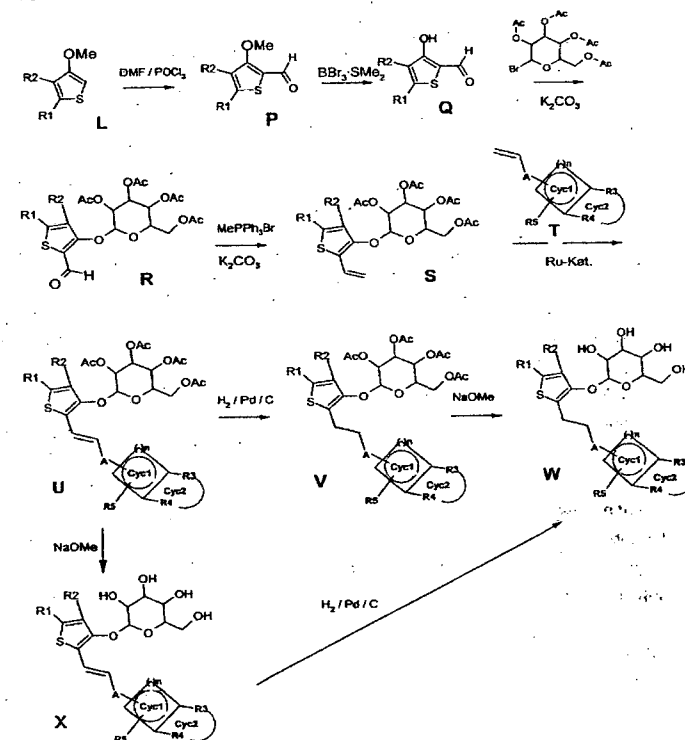
10 Die Verbindung N wird in Methylenchlorid gelöst und mit BBr_3 -Dimethylsulfidkomplex umgesetzt, und man erhält so die Verbindung der allgemeinen Formel G.

Die Verbindung G wird mit Essigsäure-4,5-diacetoxy-6-acetoxymethyl-2-bromotetrahydro-pyran-3-yl-ester und Kaliumcarbonat in einer Mischung aus Methylenchlorid 15 und Wasser in die Verbindung der allgemeinen Formel H umgesetzt.

Die Verbindung H wird entweder zunächst mit Natriumborhydrid in einer Mischung aus Methanol und Tetrahydrofuran umgesetzt und anschließend in Ethanol unter Wasserstoffatmosphäre in Gegenwart von Palladium auf Kohle in die Verbindung der 20 allgemeinen Formel J überführt, oder die Verbindung H wird in Acetonitril gelöst und in einer Mischung aus Natriumcyanoborhydrid und Chlortrimethylsilan direkt zur Verbindung der allgemeinen Formel J umgesetzt.

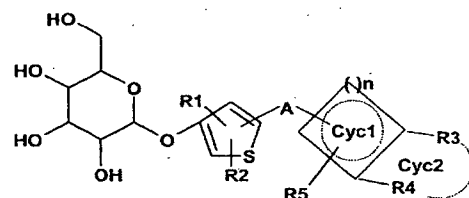
16

Verfahren C:



Es wird die Verbindung der allgemeinen Formel L, wobei R1 und R2 die oben 5 beschriebenen Bedeutungen haben, in DMF gelöst und mit Phosphorylchlorid versetzt, wobei eine Verbindung der allgemeinen Formel P erhalten wird.

Tabelle 1: Verbindungen der Formel I



5

Bsp.	R1, R2	A (Verknüpfung in 2-Position Thienyl)	Cyc1	R3, R4, R5	MS*
1	H, H	-CO-CH ₂ -CH ₂ -	Ph	4-O-CH ₃ , H, H	ok
2	H, H	-CO-CH ₂ -CH ₂ -	Ph	3-O-(CH ₂) ₂ -O-4, H	ok
3	H, H	-CO-CH ₂ -CH ₂ -	Ph	3-O-CH ₂ -O-4, H	ok
4	H, H	-CO-CH ₂ -CH ₂ -	Ph	3-CH=CH-O-4, H	ok
5	H, H	-CO-CH ₂ -CH ₂ -	3-Thiophen	H, H, H	ok
6	H, H	-CO-CH ₂ -CH ₂ -	2-Thiophen	H, H, H	ok
7	H, H	-CH ₂ -	Ph	4-O-CH ₃ , H, H	ok
8	H, H	-CO-	Ph	4-O-CH ₃ , H, H	ok
9	H, H	-CH ₂ -	Ph	H, H, H	ok
10	H, H	-CH(OH)-	Ph	H, H, H	ok
11	H, H	-CH ₂ -	Ph	4-O-C ₂ H ₅ , H, H	ok
12	H, H	-CH ₂ -	Ph	3-O-CH ₃ , 4-O-CH ₃ , H	ok
13	H, H	-CH ₂ -	Ph	4-O-C ₇ H ₁₀ , H, H	ok
14	H, H	-CH ₂ -	Ph	4-F, H, H	ok
15	H, H	-CH ₂ -	Ph	4-I, H, H	ok
16	H, H	-CH ₂ -	Ph	4-NO ₂ , H, H	ok
17	H, H	-CH ₂ -	Ph	4-CH ₃ , H, H	ok

18	H, H	-CH ₂ -	Ph	3-CH ₃ , H, H	ok
19	H, H	-CH ₂ -	Ph	2-CH ₃ , H, H	ok
20	H, H	-CH ₂ -	Ph	4-C ₂ H ₅ , H, H	ok
21	H, H	-CH ₂ -	Ph	3-CH ₃ , 4-O-CH ₃ , 5-CH ₃	ok
22	H, H	-CH ₂ -	Ph	3-O-CF ₂ -O-4, H	ok
23	H, H	-CH ₂ -	Ph	4-C ₃ H ₇ , H, H	ok
24	H, H	-CH ₂ -	Ph	4-C(CH ₃) ₃ , H, H	ok
25	H, H	-CH ₂ -	Ph	4-OH, H, H	ok
26	H, H	-CH ₂ -	Ph	4-O-CH ₂ -Ph, H, H	ok
27	H, H	-CH ₂ -	3-Thiophen	H, H, H	ok
28	H, H	-CH ₂ -	2-Thiophen	4-CH=CH-CH=5, H	ok
29	H, H	-CH ₂ -	Ph	3-O-CH ₃ , H, H	ok
30	H, H	-CH ₂ -	Ph	4-CN, H, H	ok
31	H, H	-CH ₂ -	Ph	3-O-CH ₂ -O-4, H, H	ok
32	H, H	-CH ₂ -	Ph	4-S-CH ₃ , H, H	ok
33	H, H	-CH ₂ -	Ph	4-O-C ₄ H ₉ , H, H	ok
34	H, H	-CH ₂ -	Ph	4-OCF ₃ , H, H	ok
35	H, H	-CH ₂ -	Ph	4-COOH, H, H	ok
36	H, H	-CH ₂ -CH ₂ -	Ph	4-O-CH ₃ , H, H	ok
37	H, H	-CH=CH-	Ph	4-O-CH ₃ , H, H	ok
38	H, H	-CH=CH-	Ph	4-F, H, H	ok
39	H, H	-CH=CH-	Ph	4-Cl, H, H	ok
40	H, H	-CH=CH-	Ph	4-O-C ₂ H ₅ , H, H	ok
41	H, H	-CH=CH-	Ph	4-CH ₃ , H, H	ok
42	H, H	-CH=CH-	Ph	4-OH, H, H	ok
43	H, H	-CH ₂ -CH ₂ -	Ph	4-F, H, H	ok
44	H, H	-CH ₂ -CH ₂ -	Ph	4-Cl, H, H	ok
45	H, H	-CH ₂ -CH ₂ -	Ph	4-O-C ₂ H ₅ , H, H	ok
46	H, H	-CH ₂ -CH ₂ -	Ph	4-CH ₃ , H, H	ok
47	H, H	-CH ₂ -CH ₂ -	Ph	4-OH, H, H	ok
48	H, H	-CH=CH-CH ₂ -	Ph	4-O-CH ₃ , H, H	ok

49	H, H	-CH ₂ -CH ₂ -CH ₂ -	Ph	4-O-CH ₃ , H, H	ok
50	H, H	-CH=CH-CH ₂ -	Ph	3-O-CH ₂ -O-4, H	ok
51	5-CH(CH ₃) ₂ , H	-CH ₂ -	Ph	4-O-CH ₃ , H, H	ok
52	5-Ph, H	-CH ₂ -	Ph	4-O-CH ₃ , H, H	ok
53	5-CH ₃ , H	-CH ₂ -	Ph	4-O-CH ₃ , H, H	ok
54	5-CF ₃ , H	-CH ₂ -	Ph	4-O-CH ₃ , H, H	ok
55	H, H	-CO-NH-CH ₂ -	Ph	H, H, H	ok
56	H, H	-CO-NH-CH ₂ -	Ph	4-O-CH ₃ , H, H	ok
57	H, H	-CO-NH-CH ₂ -	Ph	3-O-CH ₂ -O-4, H	ok
58	H, H	-CO-NH-CH ₂ -	Ph	4-O-CF ₃ , H, H	ok

* Unter der Angabe "MS ist ok" wird verstanden, dass ein Massenspektrum oder
 5 HPLC/MS gemessen wurde und in diesem der Molpeak M+1 (MH⁺) und/oder M+18
 (MNH₄⁺) und/oder M+23 (MNa⁺) nachgewiesen wurde