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(54) Title: COMBINATION THERAPY COMPRISING SGLT INHIBITORS AND DPP4 INHIBITORS

(57) Abstract: The present invention relates to combination therapy comprising a DPP4 inhibitor and an SGLT inhibitor. The combination of the present invention leads to increase plasma GLP-1 level and the combination is useful for prevention or treatment of conditions such as diabetes and diseases related to diabetes.

DESCRIPTION

COMBINATION THERAPY COMPRISING
SGLT INHIBITORS AND DPP4 INHIBITORS

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TECHNICAL FIELD

The present invention relates to compositions and methods for increasing plasma active GLP-1 level in a mammal. The present invention further relates to compositions and methods for ameliorating conditions by increasing plasma active GLP-1 level.

BACKGROUND ART

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Glucagon-like peptide-1 (GLP-1) is an incretin hormone that is released from L-cells in lower small intestine after food intake. GLP-1 has been shown to stimulate glucose-dependent insulin secretion from pancreatic β -cells and increase pancreatic β -cell mass. GLP-1 has also been shown to reduce the rate of gastric emptying and promote satiety. However, GLP-1 is rapidly cleaved by dipeptidyl peptidase 4 (DPP4) leading to inactivation of its biological activity. Therefore, DPP4 inhibitors are considered to be useful as anti-diabetics or anti-obesity agents.

Sodium-glucose co-transporters (SGLTs), primarily found in the intestine and the kidney, are a family of proteins involved in glucose absorption. Plasma glucose is filtered in the glomerulus and is reabsorbed by SGLTs in the proximal tubules. Therefore, inhibition of SGLTs cause excretion of blood glucose into urine and leads to reduction of plasma glucose level. In fact, it is confirmed that by continuous subcutaneous administration of an SGLT inhibitor, phlorizin, to diabetic animal models, the blood

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glucose level thereof can be normalized, and that by keeping the blood glucose level normal for a long time, the insulin secretion and insulin resistance can be improved [cf., Journal of Clinical Investigation, vol. 79, p. 1510 (1987); *ibid.*, vol. 80, p. 1037 (1987); *ibid.*, vol. 87, p. 561 (1991)].

In addition, by treating diabetic animal models with an SGLT inhibitor for a long time, insulin secretion response and insulin sensitivity of the animal models are improved without incurring any adverse affects on the kidney or imbalance in blood levels of electrolytes, and as a result, the onset and progress of diabetic nephropathy and diabetic neuropathy are prevented [cf., Journal of Medicinal Chemistry, vol. 42, p. 5311 (1999); British Journal of Pharmacology, vol. 132, p. 578 (2001)].

In view of the above, SGLT inhibitors are expected to improve insulin secretion and insulin resistance by decreasing the blood glucose level in diabetic patients and to prevent the onset and progress of diabetes mellitus and diabetic complications.

DISCLOSURE OF INVENTION

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The inventors of the present invention have found that administration of an SGLT inhibitor in combination with a DPP4 inhibitor can provide an unexpected synergistic effect in increasing plasma active GLP-1 level in a patient over that provided by administration of the SGLT inhibitor or the DPP4 inhibitor alone.

Accordingly, in one aspect, the present invention relates to combination of an SGLT inhibitor and a DPP4 inhibitor such that the combination provides an effect in increasing plasma active GLP-1 level in a patient over that

provided by the SGLT inhibitor or the DPP4 inhibitor alone.

In another aspect, the present invention relates to use of combination of an SGLT inhibitor and DPP4 inhibitor
5 for preventing or treating some sort of disease which is associated with plasma active GLP-1 level.

In another aspect, the present invention relates to a pharmaceutical composition comprising an SGLT inhibitor and
10 a DPP4 inhibitor for use in prevention or treatment of some sort of disease which is associated with plasma active GLP-1 level.

In another aspect, the present invention relates to a
15 method of preventing or treating some sort of disease which is associated with plasma active GLP-1 level comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprising an SGLT inhibitor and a DPP4 inhibitor.

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In another aspect, the present invention relates to use of an SGLT inhibitor and a DPP4 inhibitor for the manufacture of a medicament for the prevention or treatment of some sort of disease which is associated with plasma
25 active GLP-1 level.

In another aspect, the present invention relates to a product containing an SGLT inhibitor and a DPP4 inhibitor as a combined preparation for simultaneous, separate or
30 sequential administration for preventing or treating a disease associated with plasma active GLP-1 level.

DETAILED DESCRIPTION OF THE INVENTION

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As used herein, the term "diabetes" encompasses both insulin-dependent diabetes mellitus (also known as Type 1

diabetes) and non-insulin-dependent diabetes mellitus (also known as Type 2 diabetes).

The term "disease which is associated with plasma
5 active GLP-1 level" includes diabetes, a condition related to diabetes, obesity, myocardial infarction, stroke, learning impairment, memory impairment, and a neurodegenerative disorder.

10 The term "condition related to diabetes" includes hyperglycemia, impaired glucose tolerance, impaired fasting glucose, insulin resistance, pancreatic beta-cell insufficiency, enteroendocrine cell insufficiency, glucosuria, metabolic acidosis, cataracts, diabetic nephropathy,
15 diabetic neuropathy, diabetic retinopathy, diabetic coronary artery disease, diabetic cerebrovascular disease, diabetic peripheral vascular disease, metabolic syndrome, hyperlipidemia, atherosclerosis, stroke, hypertension, and obesity.

20

The term "halogen" or "halo" refers to chlorine, bromine, fluorine and iodine, and chlorine and fluorine are preferable.

25

The term "alkyl" means a straight or branched saturated monovalent hydrocarbon chain having 1 to 12 carbon atoms, unless otherwise noted. The straight chain or branched chain alkyl group having 1 to 6 carbon atoms is preferable, and the straight chain or branched chain alkyl
30 group having 1 to 4 carbon atoms is more preferable.

30

Examples of alkyl include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, and various branched chain isomers thereof. Further,
35 the alkyl group may optionally and independently be substituted by 1 to 4 substituents as listed below, if

necessary.

The term "alkylene" means a straight or branched divalent saturated hydrocarbon chain having 1 to 12 carbon atoms, unless otherwise noted. The straight chain or branched chain alkylene group having 1 to 6 carbon atoms is preferable, and the straight chain or branched chain alkylene group having 1 to 4 carbon atoms is more preferable. Examples of alkylene include methylene, ethylene, propylene, and trimethylene. If necessary, the alkylene group may optionally be substituted similarly to "alkyl" as mentioned above.

When alkylene attaches at two different carbon atoms of the benzene ring, they form an annelated five, six or seven membered carbocycle together with the carbon atoms to which they are attached, and may optionally be substituted by one or more substituents defined below.

The term "alkenyl" means a straight or branched monovalent hydrocarbon chain having 2 to 12 carbon atoms and having at least one double bond, unless otherwise noted. Preferable "alkenyl" is a straight chain or branched chain alkenyl group having 2 to 6 carbon atoms, and the straight chain or branched chain alkenyl group having 2 to 4 carbon atoms is more preferable. Examples of alkenyl include vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, and 4,8,12-tetradecatrienyl. The alkenyl group may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary.

The term "alkenylene" means a straight or branched divalent hydrocarbon chain having 2 to 12 carbon atoms and having at least one double bond, unless otherwise noted.

The straight chain or branched chain alkenylene group having 2 to 6 carbon atoms is preferable, and the straight chain or branched chain alkenylene group having 2 to 4 carbon atoms is more preferable. Examples of alkenylene include vinylene, propenylene, butadienylene. If necessary, the alkenylene group may optionally be substituted by 1 to 4 substituents as mentioned below, if necessary.

When an alkenylene group attaches at two different carbon atoms of a benzene ring, they form an annelated five, six or seven membered carbocycle (e.g., a fused benzene ring) together with the carbon atoms to which they are attached, and may optionally be substituted by one or more substituents defined below.

15

The term "alkynyl" means a straight or branched monovalent hydrocarbon chain having at least one triple bond, unless otherwise noted. The preferable alkynyl group is a straight chain or branched chain alkynyl group having 2 to 6 carbon atoms, and the straight chain or branched chain alkynyl group having 2 to 4 carbon atoms is more preferable. Examples of "alkynyl" include 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl, 3-undecynyl, and 4-dodecynyl. The alkynyl group may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary.

30

The term "cycloalkyl" means a monocyclic or bicyclic monovalent saturated hydrocarbon ring having 3 to 12 carbon atoms, unless otherwise noted, and the monocyclic saturated hydrocarbon group having 3 to 7 carbon atoms is more preferable. Examples of cycloalkyl include monocyclic and bicyclic alkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and cyclodecyl. These

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groups may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary. The cycloalkyl group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO₂ within the ring, if necessary), and the condensed saturated hydrocarbon ring and the condensed unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "cycloalkylidene" means a monocyclic or bicyclic divalent saturated hydrocarbon ring having 3 to 12 carbon atoms, unless otherwise noted, and the monocyclic saturated hydrocarbon group having 3 to 6 carbon atoms is preferable. Examples of "cycloalkylidene" include monocyclic and bicyclic alkylidene such as cyclopropylidene, cyclobutylidene, cyclopentylidene, and cyclohexylidene. These groups may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary. Besides, the cycloalkylidene group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO₂ within the ring, if necessary), and the condensed saturated hydrocarbon ring and the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "cycloalkenyl" means a monocyclic or bicyclic monovalent unsaturated hydrocarbon ring having 4 to 12 carbon atoms and having at least one double bond, unless otherwise noted. The preferable cycloalkenyl group is a monocyclic unsaturated hydrocarbon group having 4 to 7

carbon atoms. Examples of "cycloalkenyl" include monocyclic alkenyl such as cyclopentenyl, cyclopentadienyl, and cyclohexenyl. These groups may optionally and independently be substituted by 1 to 4 substituents as
5 mentioned below, if necessary. Besides, the cycloalkenyl group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a
10 sulfur atom, SO or SO₂ within the ring, if necessary), and the condensed saturated hydrocarbon ring and the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

15

The term "cycloalkynyl" means a monocyclic or bicyclic unsaturated hydrocarbon ring having 6 to 12 carbon atoms, and having at least one triple bond, unless otherwise noted. The preferable cycloalkynyl group is a
20 monocyclic unsaturated hydrocarbon group having 6 to 8 carbon atoms. Examples of "cycloalkynyl" include monocyclic alkynyl such as cyclooctynyl, and cyclodecynyl. These groups may optionally be substituted by 1 to 4 substituents as mentioned below, if necessary. Besides,
25 the cycloalkynyl group may optionally and independently be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO
30 or SO₂ within the ring, if necessary), and the condensed saturated hydrocarbon ring or the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

35

The term "aryl" or "Aryl" means a monocyclic or bicyclic monovalent aromatic hydrocarbon group having 6 to

10 carbon atoms, unless otherwise noted. Examples of aryl include phenyl and naphthyl (including 1-naphthyl group and 2-naphthyl group). These groups may optionally and independently be substituted by 1 to 4 substituents as
5 mentioned below, if necessary. Besides, the aryl group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a
10 sulfur atom, SO or SO₂ within the ring, if necessary), and the condensed saturated hydrocarbon ring or the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

15 The term "unsaturated monocyclic heterocyclic ring" means an unsaturated hydrocarbon ring containing 1-4 heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom, and the preferable one is a 4- to 7-membered saturated or unsaturated hydrocarbon ring
20 containing 1-4 heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom, unless otherwise noted. Examples of the unsaturated monocyclic heterocyclic ring are pyridine, pyrimidine, pyrazine, furan, thiophene, pyrrole, imidazole, pyrazole, oxazole, isoxazole,
25 4,5-dihydrooxazolyl, thiazole, isothiazole, thiadiazole, triazole, and tetrazole. Among them, pyridine, pyrimidine, pyrazine, furan, thiophene, pyrrole, imidazole, oxazole, and thiazole can be preferably used. The unsaturated monocyclic heterocyclic ring may optionally and independ-
30 ently be substituted by 1-4 substituents as mentioned below, if necessary.

The term "unsaturated fused heterobicyclic ring" means a hydrocarbon ring comprised of a saturated or a
35 unsaturated hydrocarbon ring condensed with the above mentioned unsaturated monocyclic heterocyclic ring where

said saturated hydrocarbon ring and said unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO, or SO₂ within the ring, if necessary. Examples of the unsaturated fused heterobicyclic ring include benzothiophene, indole, tetrahydrobenzothiophene, benzofuran, isoquinoline, thienothiophene, thienopyridine, quinoline, indoline, isoindoline, benzothiazole, benzoxazole, indazole, and dihydroisoquinoline. Further, the "heterocyclic ring" also includes possible N- or S-oxides thereof.

The term "heterocyclyl" means a monovalent group of the above-mentioned unsaturated monocyclic heterocyclic ring or unsaturated fused heterobicyclic ring and a monovalent group of the saturated version of the above-mentioned unsaturated monocyclic heterocyclic or unsaturated fused heterobicyclic ring. If necessary, the heterocyclyl may optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "alkanoyl" includes formyl and alkyl linked to carbonyl, unless otherwise noted.

The term "alkoxy" includes alkyl linked to oxygen, unless otherwise noted.

Examples of the substituent for the above each group includes halogen (e.g., fluorine, chlorine, bromine, and iodine), nitro, cyano, oxo, hydroxy, mercapto, carboxyl, sulfo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyldenemethyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclyl, alkoxy, alkenyloxy, alkynyloxy, cycloalkyloxy, cycloalkenyloxy, cycloalkynyloxy, aryloxy, heterocyclyloxy, alkanoyl, alkenylcarbonyl, alkynylcarbonyl, cycloalkylcarbonyl, cycloalkenylcarbonyl, cycloalkynylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, alkoxycarbonyl,

alkenyloxycarbonyl, alkynyloxycarbonyl, cycloalkyloxy-
carbonyl, cycloalkenyloxycarbonyl, cycloalkynyloxycarbonyl,
aryloxycarbonyl, heterocyclyloxycarbonyl, alkanoyloxy,
alkenylcarbonyloxy, alkynylcarbonyloxy, cycloalkylcarbonyl-
5 oxy, cycloalkenylcarbonyloxy, cycloalkynylcarbonyloxy,
arylcarbonyloxy, heterocyclylcarbonyloxy, alkylthio,
alkenylthio, alkynylthio, cycloalkylthio, cycloalkenylthio,
cycloalkynylthio, arylthio, heterocyclylthio, amino, mono-
or di-alkylamino, mono- or di-alkanoylamino, mono- or di-
10 alkoxy-carbonylamino, mono- or di-arylcarbonylamino, alkyl-
sulfinylamino, alkylsulfonylamino, arylsulfinylamino,
arylsulfonylamino, carbamoyl, mono- or di-alkylcarbamoyl,
mono- or di-arylcarbamoyl, alkylsulfinyl, alkenylsulfinyl,
alkynylsulfinyl, cycloalkylsulfinyl, cycloalkenylsulfinyl,
15 cycloalkynylsulfinyl, arylsulfinyl, heterocyclylsulfinyl,
alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, cyclo-
alkylsulfonyl, cycloalkenylsulfonyl, cycloalkynylsulfonyl,
arylsulfonyl, and heterocyclylsulfonyl. Each group
mentioned above may optionally be substituted by these
20 substituents.

Further, the terms such as haloalkyl, halo-lower
alkyl, haloalkoxy, halo-lower alkoxy, halophenyl, and
haloheterocyclyl mean alkyl, lower alkyl, alkoxy, lower
25 alkoxy, phenyl group or heterocyclyl (hereinafter, referred
to as "alkyl, etc.") being substituted by one or more
halogen, respectively. Preferable examples include alkyl,
etc., being substituted by 1 to 7 halogen, and more
preferable examples include alkyl, etc., being substituted
30 by 1 to 5 halogen. Similarly, the terms such as hydroxy-
alkyl, hydroxy-lower alkyl, hydroxyalkoxy, hydroxy-lower
alkoxy and hydroxyphenyl mean alkyl, etc., being substi-
tuted by one or more hydroxy groups. Preferable examples
include alkyl, etc., being substituted by 1 to 4 hydroxy
35 groups, and more preferable examples include alkyl, etc.,
being substituted by 1 to 2 hydroxy groups. Further, the

terms such as alkoxyalkyl, lower alkoxyalkyl, alkoxy-lower alkyl, lower alkoxy-lower alkyl, alkoxyalkoxy, lower alkoxyalkoxy, alkoxy-lower alkoxy, lower alkoxy-lower alkoxy, alkoxyphenyl, and lower alkoxyphenyl means alkyl, etc., being substituted by one or more alkoxy groups. Preferable examples include alkyl, etc., being substituted by 1 to 4 alkoxy groups, and more preferable examples include alkyl, etc., being substituted by 1 to 2 alkoxy groups.

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The terms "arylakyl" and "arylalkoxy" as used alone or as part of another group refer to alkyl and alkoxy groups as described above having an aryl substituent.

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The term "lower" used in the definitions for the formulae in the present specification means a straight or branched carbon chain having 1 to 6 carbon atoms, unless defined otherwise. More preferably, it means a straight or branched carbon chain having 1 to 4 carbon atoms.

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The term "prodrug" means an ester or carbonate, which can be formed by reacting one or more hydroxy groups of the compound used in the combination therapy of the present invention with an acylating agent by a conventional method. Examples of the ester include acetate, pivalate, methylcarbonate, and benzoate. Further, the term "prodrug" also means an ester or amide, which can be similarly formed by reacting one or more hydroxy groups of the compound used in the combination therapy of the present invention with an α -amino acid or a β -amino acid using a condensing agent by a conventional method.

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Examples of a pharmaceutically acceptable salt of SGLT inhibitors or DPP4 inhibitors include a salt with an alkali metal (e.g., lithium, sodium, and potassium); a salt with an alkaline earth metal (e.g., calcium, and

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magnesium); a salt with zinc or aluminum; a salt with an organic base (e.g., ammonia, choline, diethanolamine, lysine, ethylenediamine, t-butylamine, t-octylamine, tris(hydroxymethyl)aminomethane, N-methyl-glucosamine, 5 triethanolamine and dehydroabietylamine); a salt with an inorganic acid (e.g., hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid); a salt with an organic acid (e.g., formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, 10 succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, and benzenesulfonic acid); and a salt with an acidic amino acid (e.g., aspartic acid, and glutamic acid).

15

Additionally, the term "pharmaceutically acceptable salt" used herein encompass solvates, and hydrates thereof.

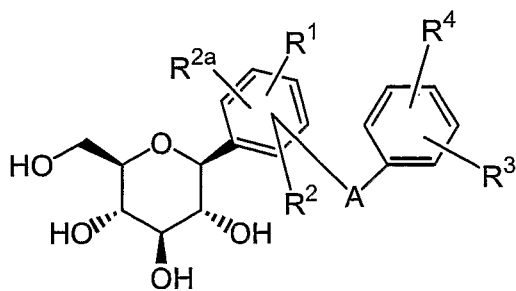
It is evident that some compounds used in the 20 compositions or combination of the present invention may have one or more asymmetric carbon atoms in their structure. It is intended that the present invention includes within its scope the stereochemically pure isomeric forms of the compounds as well as their racemates. Stereochemically pure 25 isomeric forms may be obtained by the methods well known to those skilled in the art. Diastereoisomers may be separated by physical separation methods such as fractional crystallization and chromatographic techniques, and enantiomers may be separated from each other by the 30 selective crystallization of the diastereomeric salts with optically active acids or bases or by chiral chromatography. Pure stereoisomers may also be prepared synthetically from appropriate stereochemically pure starting materials, or by using stereospecific reactions.

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SGLT inhibitors are well known to those skilled in

the art, and examples of the SGLT inhibitors are described in many publications or patent literatures.

In an embodiment of the present invention, SGLT inhibitors are the C-aryl glucosides disclosed in WO 01/27128 pamphlet, which are represented by Formula (1):



wherein:

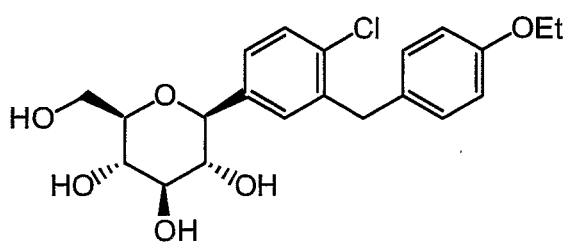
- R^1 , R^2 and R^{2a} are independently hydrogen, OH, OR^5 , alkyl, CF_3 , $OCHF_2$, OCF_3 , SR^{5i} or halogen, or two of R^1 , R^2 and R^{2a} together with the carbons to which they are attached can form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2 ;
- R^3 and R^4 are independently hydrogen, OH, OR^{5a} , OAr , OCH_2Ar , alkyl, cycloalkyl, CF_3 , $-OCHF_2$, $-OCF_3$, halogen, $-CN$, $-CO_2R^{5b}$, $-CO_2H$, $-COR^{6b}$, $-CH(OH)R^{6c}$, $-CH(OR^{5h})R^{6d}$, $-CONR^6R^{6a}$, $-NHCOR^{5c}$, $-NHSO_2R^{5d}$, $-NHSO_2Ar$, Ar , $-SR^{5e}$, $-SOR^{5f}$, $-SO_2R^{5g}$, $-SO_2Ar$, 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 SO_2 , or R^3 and R^4 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 SO_2 ;
- R^5 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^{5g} , R^{5h} and R^{5i} are independently alkyl;
- R^6 , R^{6a} , R^{6b} , R^{6c} and R^{6d} are independently hydrogen, alkyl, aryl, alkylaryl or cycloalkyl, or R^6 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;

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.

In a preferable embodiment of the present invention, the SGLT inhibitor is Dapagliflozin represented by Formula

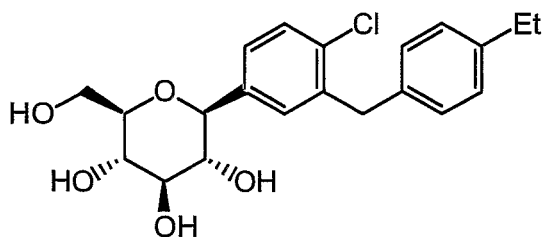
10 (2):



(2)

a pharmaceutically acceptable salt thereof, a stereoisomer thereof, or a prodrug ester thereof.

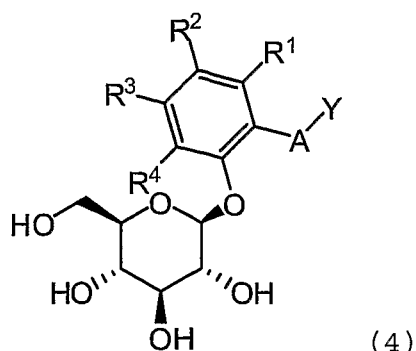
15 In another preferable embodiment of the present invention, the SGLT inhibitor is the C-aryl glucoside compound disclosed in WO 2006/034489 pamphlet, which is represented by Formula (3):



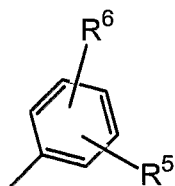
(3)

20 a pharmaceutically acceptable salt thereof, a stereoisomer thereof, or a prodrug ester thereof.

In an embodiment of the present invention, the SGLT inhibitors are O-aryl glucoside compounds disclosed in WO 25 01/74834 pamphlet, which are represented by Formula (4):



wherein Y is



or heteroaryl;

5 R^1 , R^2 , R^3 , and R^4 are the same or different and are independently selected from hydrogen, OH, OR^7 , lower alkyl, or halogen, or two of R^1 , R^2 , R^3 , and R^4 together with the carbons to which they are attached can form an annelated five, six or seven membered carbocycle or heterocycle which
10 may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2 ;

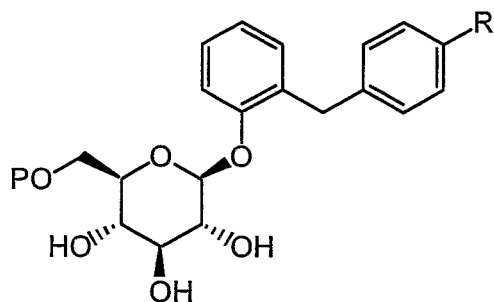
R^5 and R^6 are the same or different and are independently selected from hydrogen, OH, OR^{7a} , -OAryl, - OCH_2 Aryl, lower alkyl, cycloalkyl, Aryl, arylalkyl, CF_3 , arylalkenyl,
15 - $OCHF_2$, - OCF_3 , halogen, -CN, - CO_2R^{7b} , - CO_2H , COR^{8f} , $CHOHR^{8g}$, $CH(OR^{7h})R^{8h}$, - $CONR^{8a}R^{8a}$, - $NHCOR^{7c}$, - $NHSO_2R^{7d}$, - $NHSO_2$ Aryl, - SR^{7e} , - SOR^{7e} , - SO_2R^{7g} , - SO_2 Aryl, - $OCH_2CO_2R^{7i}$, - OCH_2CO_2H , - $OCH_2CONR^{8b}R^{8c}$, - $OCH_2CH_2NR^{8d}R^{8e}$, or a five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms
20 in the ring which are N, O, S, SO, and/or SO_2 , or R^5 and R^6 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 SO_2 ;

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

R^b , 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.

10

In an embodiment of the present invention, the SGLT inhibitors are the glucopyranosyloxybenzylbenzene derivatives disclosed in WO 02/028872 pamphlet, which are represented by Formula (5):



15

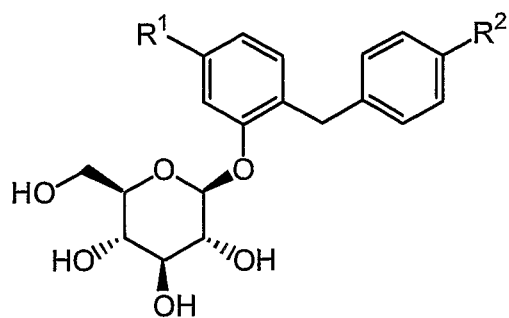
(5)

wherein P represents a group forming a prodrug; and R represents lower alkyl, lower alkoxy, lower alkylthio, lower alkoxy-substituted lower alkyl, lower alkoxy-substituted lower alkoxy or lower alkoxy-substituted lower alkylthio.

20

In an embodiment of the present invention, the SGLT inhibitors are the glucopyranosyloxybenzyl-benzene derivatives disclosed in WO 01/68660 pamphlet, which are represented by Formula (6):

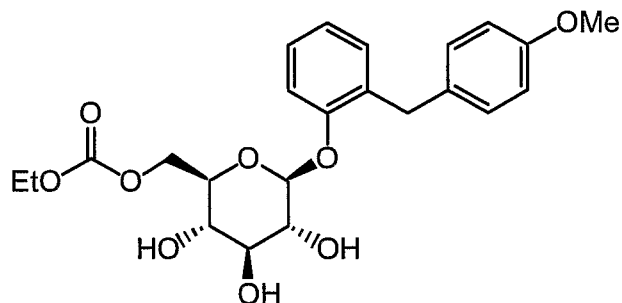
25



(6)

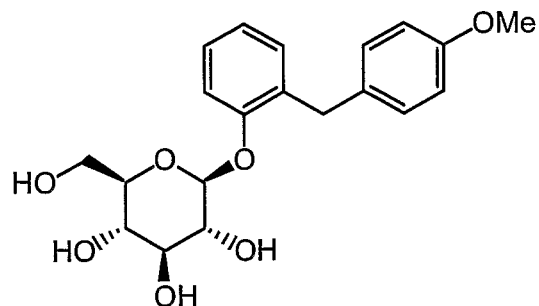
wherein R¹ represents hydrogen or hydroxy(lower alkyl); and R² represents lower alkyl, lower alkoxy, lower alkylthio, hydroxy(lower alkyl), hydroxy(lower alkoxy), hydroxy(lower alkylthio), lower alkoxy-substituted (lower alkyl), lower alkoxy-substituted (lower alkoxy) or lower alkoxy-substituted (lower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

10 In a preferable embodiment of the present invention, the SGLT inhibitor is Sertgliflozin represented by Formula (7):



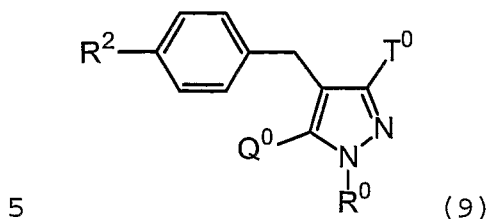
(7).

15 In another preferable embodiment of the present invention, the SGLT inhibitor is Sertgliflozin-A represented by Formula (8):

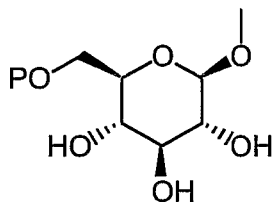


(8).

In an embodiment of the present invention, the SGLT inhibitors are the glucopyranosyloxypyrazole derivatives disclosed in WO 02/053573 pamphlet, which are represented by Formula (9):



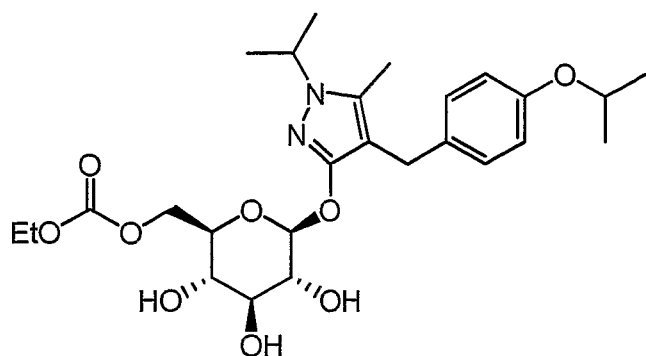
wherein R represents hydrogen, lower alkyl or a group forming a prodrug; one of Q and T represents a group represented by the formula:



- 10 (wherein P represents hydrogen or a group forming a prodrug), while the other represents lower alkyl or halo(lower alkyl);
- R^2 represents hydrogen, lower alkyl, lower alkoxy, lower alkylthio, halo(lower alkyl) or halogen;
- 15 with the proviso that P does not represent hydrogen when R represents hydrogen or lower alkyl, or a pharmaceutically acceptable salt thereof.

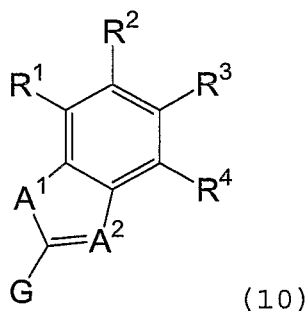
In a preferable embodiment of the present invention, the SGLT inhibitor is Remogliflozin represented by Formula (9a):

20



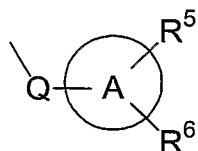
(9a).

In an embodiment of the present invention, the SGLT inhibitors are the compounds disclosed in WO 2005/085265 pamphlet, which are represented by Formula (10):



(10)

wherein one of R^1 and R^4 represents a group of the formula:



in which R^5 and R^6 independently represent hydrogen,
 10 hydroxy, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6}
 alkoxy, C_{2-6} alkenyloxy, C_{1-6} alkylthio, C_{2-6} alkenylthio,
 halo(C_{1-6} alkyl), halo(C_{1-6} alkoxy), halo(C_{1-6} alkylthio),
 hydroxy(C_{1-6} alkyl), hydroxy(C_{2-6} alkenyl), hydroxy(C_{1-6}
 alkoxy), hydroxy(C_{1-6} alkylthio), carboxy, carboxy(C_{1-6}
 15 alkyl), carboxy(C_{2-6} alkenyl), carboxy(C_{1-6} alkoxy),
 carboxy(C_{1-6} alkylthio), C_{2-7} alkoxy-carbonyl, C_{2-7} alkoxy-
 carbonyl(C_{1-6} alkyl), C_{2-7} alkoxy-carbonyl(C_{2-6} alkenyl), C_{2-7}
 alkoxy-carbonyl(C_{1-6} alkoxy), C_{2-7} alkoxy-carbonyl(C_{1-6} alkyl-
 thio), C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, -U-V-W-N(R^7)-Z,
 20 or any of the following substituents (i) to (xxviii) which

may have 1 to 3 substituents selected from the following substituent group α on the ring;

(i) C₆₋₁₀ aryl, (ii) C₆₋₁₀ aryl-O-, (iii) C₆₋₁₀ aryl-S-, (iv) C₆₋₁₀ aryl(C₁₋₆ alkyl), (v) C₆₋₁₀ aryl(C₁₋₆ alkoxy), (vi) C₆₋₁₀ aryl(C₁₋₆ alkylthio), (vii) heteroaryl, (viii) heteroaryl-O-, (ix) heteroaryl-S-, (x) heteroaryl(C₁₋₆ alkyl), (xi) heteroaryl(C₁₋₆ alkoxy), (xii) heteroaryl(C₁₋₆ alkylthio), (xiii) C₃₋₇ cycloalkyl, (xiv) C₃₋₇ cycloalkyl-O-, (xv) C₃₋₇ cycloalkyl-S-, (xvi) C₃₋₇ cycloalkyl(C₁₋₆ alkyl), (xvii) C₃₋₇ cycloalkyl(C₁₋₆ alkoxy), (xviii) C₃₋₇ cycloalkyl(C₁₋₆ alkylthio), (xix) heterocycloalkyl, (xx) heterocycloalkyl-O-, (xxi) heterocycloalkyl-S-, (xxii) heterocycloalkyl(C₁₋₆ alkyl), (xxiii) heterocycloalkyl(C₁₋₆ alkoxy), (xxiv) heterocycloalkyl(C₁₋₆ alkylthio), (xxv) aromatic cyclic amino, (xxvi) aromatic cyclic amino(C₁₋₆ alkyl), (xxvii) aromatic cyclic amino(C₁₋₆ alkoxy), or (xxviii) aromatic cyclic amino(C₁₋₆ alkylthio),

J represents C₁₋₆ alkenylene which may have hydroxy, or C₂₋₆ alkenylene;

U represents -O-, -S- or a single bond and with the proviso that at least one of V and W is not a single bond when U is -O- or -S-;

V represents C₁₋₆ alkenylene which may have hydroxy, C₂₋₆ alkenylene or a single bond;

W represents -CO-, -SO₂-, -C(=NH)- or a single bond;

Z independently represents hydrogen, C₂₋₇ alkoxy-carbonyl, C₆₋₁₀ aryl(C₂₋₇ alkoxy-carbonyl), formyl, -R^A, -COR^B, -SO₂R^B, -CON(R^C)R^D, -CSN(R^C)R^D, -SO₂NHR^A or -C(=NR^E)N(R^F)R^G;

R⁷, R^A, R^C and R^D independently represent hydrogen, C₁₋₆

alkyl which may have 1 to 5 substituents selected from the following substituent group β , or any of the following substituents (xxix) to (xxxii) which may have 1 to 3 substituents selected from the following substituent group α ;

(xxix) C₆₋₁₀ aryl, (xxx) heteroaryl, (xxxii) C₃₋₇ cycloalkyl or (xxxii) heterocycloalkyl or Z and R⁷ bind together with

the neighboring nitrogen to form aliphatic cyclic amino which may have 1 to 3 substituents selected from the following substituent group α ;
or R^C and R^D bind together with the neighboring nitrogen to
5 form aliphatic cyclic amino which may have 1 to 3 substituents selected from the following substituent group α ;
R^B represents C₂₋₇ alkoxy carbonyl, C₁₋₆ alkylsulfonylamino, C₆₋₁₀ arylsulfonylamino, C₁₋₆ alkyl which may have 1 to 5 substituents selected from the following substituent group
10 β or any of the following substituents (xxxiii) to (xxxvi) which may have 1 to 3 substituents selected from the following substituent group α ;
(xxxiii) C₆₋₁₀ aryl, (xxxiv) heteroaryl, (xxxv) C₃₋₇ cycloalkyl or (xxxvi) heterocycloalkyl,
15 R^E, R^F and R^G independently represent hydrogen, cyano, carbamoyl, C₂₋₇ acyl, C₂₋₇ alkoxy carbonyl, C₆₋₁₀ aryl(C₂₋₇ alkoxy carbonyl), nitro, C₁₋₆ alkylsulfonyl, sulfamide, carbamimidoyl or C₁₋₆ alkyl which may have 1 to 5 substituents selected from the following substituent group
20 β ;
or R^E and R^F bind together to form ethylene;
or R^F and R^G bind together with the neighboring nitrogen to form aliphatic cyclic amino which may have any substituent selected from the following substituent group α ;
25 Q represents -C₁₋₆ alkylene-, -C₂₋₆ alkenylene-, -C₂₋₆ alkynylene-, -C₁₋₆ alkylene-O-, -C₁₋₆ alkylene-S-, -O-C₁₋₆ alkylene-, -S-C₁₋₆ alkylene-, -C₁₋₆ alkylene-O-C₁₋₆ alkylene-, -C₁₋₆ alkylene-S-C₁₋₆ alkylene-, -CON(R⁸)-, -N(R⁸) CO-, -C₁₋₆ alkylene-CON(R⁸)- or -CON(R⁸)-C₁₋₆ alkylene-;
30 R⁸ represents hydrogen or C₁₋₆ alkyl;
ring A represents C₆₋₁₀ aryl or heteroaryl, and the other one of R¹ and R⁴ represents hydrogen, hydroxy, amino, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, cyano, carboxy, C₂₋₇ alkoxy carbonyl, carbamoyl, mono or di(C₁₋₆ alkyl)amino,
35 halo(C₁₋₆ alkyl), hydroxy(C₁₋₆ alkyl), cyano(C₁₋₆ alkyl), carboxy(C₁₋₆ alkyl), C₂₋₇ alkoxy carbonyl(C₁₋₆ alkyl),

carbamoyl(C₁₋₆ alkyl) group, an amino(C₁₋₆ alkyl), mono or di(C₁₋₆ alkyl) amino(C₁₋₆ alkyl), halo(C₁₋₆ alkoxy), hydroxy-(C₁₋₆ alkoxy), carboxy(C₁₋₆ alkoxy), C₂₋₇ alkoxy-carbonyl(C₁₋₆ alkoxy), carbamoyl(C₁₋₆ alkoxy), amino(C₁₋₆ alkoxy), mono or di(C₁₋₆ alkyl)amino(C₁₋₆ alkoxy), C₃₋₇ cycloalkyl, C₃₋₇ cyclo-alkyloxy, C₃₋₇ cycloalkyl(C₁₋₆ alkyl), or C₃₋₇ cycloalkyl(C₁₋₆ alkoxy);

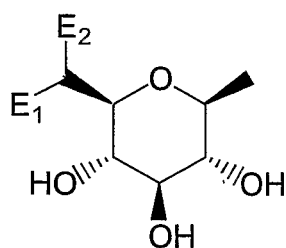
R² and R³ independently represent hydrogen, hydroxy, amino, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, cyano, carboxy, C₂₋₇ alkoxy-carbonyl, carbamoyl, mono or di(C₁₋₆ alkyl)amino, halo(C₁₋₆ alkyl), hydroxy(C₁₋₆ alkyl), cyano(C₁₋₆ alkyl), carboxy(C₁₋₆ alkyl), C₂₋₇ alkoxy-carbonyl(C₁₋₆ alkyl), carbamoyl(C₁₋₆ alkyl), amino(C₁₋₆ alkyl), mono or di(C₁₋₆ alkyl)amino(C₁₋₆ alkyl), halo(C₁₋₆ alkoxy), hydroxy(C₁₋₆ alkoxy), carboxy(C₁₋₆ alkoxy), C₂₋₇ alkoxy-carbonyl (C₁₋₆ alkoxy), carbamoyl(C₁₋₆ alkoxy), amino(C₁₋₆ alkoxy), mono or di(C₁₋₆ alkyl) amino(C₁₋₆ alkoxy), C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyloxy, C₃₋₇ cycloalkyl(C₁₋₆ alkyl), or C₃₋₇ cycloalkyl(C₁₋₆ alkoxy);

A¹ represents O, S or NR⁹;

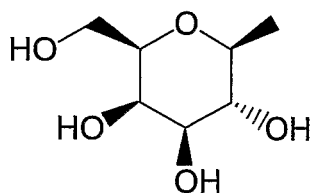
A² represents CH or N;

R⁹ represents hydrogen or C₁₋₆ alkyl;

G represents a group represented by a formula:



or a formula:



E¹ represents hydrogen, fluorine or hydroxy;

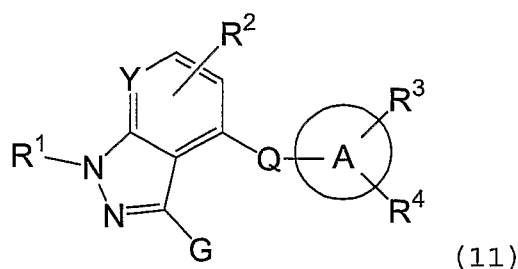
E² represents hydrogen, fluorine, methyl or hydroxymethyl;

[substituent group α]

halogen, hydroxy, amino, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo(C₁₋₆ alkyl), halo(C₁₋₆ alkoxy), hydroxy(C₁₋₆ alkyl), C₂₋₇ alkoxy-carbonyl(C₁₋₆ alkyl), hydroxy(C₁₋₆ alkoxy), amino(C₁₋₆ alkyl), amino(C₁₋₆ alkoxy), mono or di(C₁₋₆ alkyl)amino, mono or
5 di[hydroxy(C₁₋₆ alkyl)]amino, C₁₋₆ alkylsulfonyl, C₁₋₆ alkyl-sulfonylamino, C₁₋₆ alkylsulfonylamino(C₁₋₆ alkyl), carboxy, C₂₋₇ alkoxy-carbonyl, sulfamoyl and -CON(R^H)R^I
[substituent group β]
halogen atom, hydroxy, amino, C₁₋₆ alkoxy, C₁₋₆ alkylthio,
10 halo(C₁₋₆ alkoxy), halo(C₁₋₆ alkylthio), hydroxy(C₁₋₆ alkoxy), hydroxy(C₁₋₆ alkylthio), amino(C₁₋₆ alkoxy), amino(C₁₋₆ alkylthio), mono or di(C₁₋₆ alkyl) amino, mono or di-[hydroxy(C₁₋₆ alkyl)]amino, ureido, sulfamide, mono or di-(C₁₋₆ alkyl) ureido, mono or di[hydroxy(C₁₋₆ alkyl)]ureido,
15 mono or di(C₁₋₆ alkyl)sulfamide, mono or di[hydroxy(C₁₋₆ alkyl)]sulfamide, C₂₋₇ acylamino, amino(C₂₋₇ acylamino), C₁₋₆ alkylsulfonyl, C₁₋₆ alkylsulfonylamino, carbamoyl(C₁₋₆ alkyl-sulfonylamino), carboxy, C₂₋₇ alkoxy-carbonyl group, -CON(R^H) R^I, and any of the following substituents (xxxvii) to (xxxxviii) which may have 1 to 3 substituents selected
20 from the above substituent group α;
(xxxvii) C₆₋₁₀ aryl, (xxxviii) C₆₋₁₀ aryl-O-, (xxxix) C₆₋₁₀ aryl(C₁₋₆ alkoxy), (xxxx) C₆₋₁₀ aryl(C₁₋₆ alkylthio), (xxxxi) heteroaryl, (xxxxii) heteroaryl-O-, (xxxxiii) C₃₋₇
25 cycloalkyl, (xxxxiv) C₃₋₇ cycloalkyl-O-, (xxxxv) hetero-cycloalkyl, (xxxxvi) heterocycloalkyl-O-, (xxxxvii) aliphatic cyclic amino or (xxxxviii) aromatic cyclic amino
R^H and R^I independently represent hydrogen or C₁₋₆ alkyl which may have 1 to 3 substituents selected from the
30 following substituent group γ;
or both of R^H and R^I bind together with the neighboring nitrogen to form aliphatic cyclic amino which may have 1 to 3 substituents selected from the following substituent group δ;
35 [substituent group γ]
halogen, hydroxy, amino, C₁₋₆ alkoxy, halo(C₁₋₆ alkoxy),

hydroxy(C₁₋₆ alkoxy), amino(C₁₋₆ alkoxy), mono or di(C₁₋₆ alkyl)amino, mono or di[hydroxy(C₁₋₆ alkyl)]amino, ureido, sulfamide, mono or di(C₁₋₆ alkyl) ureido, mono or di-[hydroxy(C₁₋₆ alkyl)]ureido, mono or di(C₁₋₆ alkyl)sulfamide,
5 mono or di[hydroxy(C₁₋₆ alkyl)]sulfamide, C₂₋₇ acylamino, amino(C₂₋₇ acylamino), C₁₋₆ alkylsulfonyl, C₁₋₆ alkylsulfonylamino, carbamoyl(C₁₋₆ alkylsulfonylamino), carboxy, C₂₋₇ alkoxy-carbonyl, sulfamoyl and -CON(R^J)R^K
[substituent group δ]
10 halogen, hydroxy, amino, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo(C₁₋₆ alkyl), halo(C₁₋₆ alkoxy), hydroxy(C₁₋₆ alkyl), C₂₋₇ alkoxy-carbonyl(C₁₋₆ alkyl), hydroxy(C₁₋₆ alkoxy), amino(C₁₋₆ alkyl), amino(C₁₋₆ alkoxy), mono or di(C₁₋₆ alkyl)amino, mono or di[hydroxy(C₁₋₆ alkyl)]amino, C₁₋₆ alkylsulfonyl, C₁₋₆
15 alkylsulfonylamino, C₁₋₆ alkylsulfonylamino(C₁₋₆ alkyl), carboxy, C₂₋₇ alkoxy-carbonyl, sulfamoyl and -CON(R^J)R^K
R^J and R^K independently represent hydrogen or C₁₋₆ alkyl which may have any 1 to 3 substituents selected from hydroxy, amino, mono or di(C₁₋₆ alkyl)amino, C₂₋₇ alkoxy-carbonyl and carbamoyl;
20 or both of R^J and R^K bind together with the neighboring nitrogen to form aliphatic cyclic amino which may have any 1 to 3 substituents selected from hydroxy, amino, mono or di(C₁₋₆ alkyl) amino, C₁₋₆ alkyl, hydroxy(C₁₋₆ alkyl), C₂₋₇
25 alkoxy-carbonyl, C₂₋₇ alkoxy-carbonyl(C₁₋₆ alkyl) and carbamoyl, or a pharmaceutically acceptable salt thereof, or a prodrug thereof.

In an embodiment of the present invention, the SGLT
30 inhibitors are the compounds disclosed in WO 2005/085267 pamphlet, which are represented by Formula (11):



wherein

R¹ represents hydrogen, C₁₋₆ alkyl, halo(C₁₋₆ alkyl),

hydroxy(C₁₋₆ alkyl), dihydroxy(C₁₋₆ alkyl), C₁₋₆ alkoxy(C₁₋₆ alkyl), C₂₋₇ alkoxy-carbonyl (C₁₋₆ alkyl), carboxy(C₁₋₆ alkyl), C₂₋₆ alkenyl, -J-N(R⁵)-Z¹, -J-CON(R⁵)-Z¹, or any of the following substituents (a) to (d) which may have any 1 to 3 substituents selected from the following substituent group α on the ring;

10 (a) C₃₋₇ cycloalkyl, (b) C₃₋₇ cycloalkyl(C₁₋₆ alkyl), (c) C₆₋₁₀ aryl or (d) C₁₋₆ aryl(C₆₋₁₀ alkyl),

R² represents hydrogen, halogen or C₁₋₆ alkyl;

R³ and R⁴ independently represent hydrogen, hydroxy, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₂₋₆ alkenyloxy, C₁₋₆ alkylthio, C₂₋₆ alkenylthio, halo(C₁₋₆ alkyl), halo(C₁₋₆ alkoxy), halo(C₁₋₆ alkylthio), hydroxy(C₁₋₆ alkyl), hydroxy(C₂₋₆ alkenyl), hydroxy(C₁₋₆ alkoxy), hydroxy-(C₁₋₆ alkylthio), carboxy, carboxy(C₁₋₆ alkyl), carboxy(C₂₋₆ alkenyl), carboxy(C₁₋₆ alkoxy), carboxy(C₁₋₆ alkylthio), C₂₋₇ alkoxy-carbonyl, C₂₋₇ alkoxy-carbonyl(C₁₋₆ alkyl), C₂₋₇ alkoxy-carbonyl(C₂₋₆ alkenyl), C₂₋₇ alkoxy-carbonyl (C₁₋₆ alkoxy), C₂₋₇ alkoxy-carbonyl(C₁₋₆ alkylthio), C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl group, -U-V-W-N(R⁶)-Z², or any of the following substituents (i) to (xxviii) which may have any 1 to 3 substituents selected from the following substituent group α on the ring;

(i) C₆₋₁₀ aryl, (ii) C₆₋₁₀ aryl-O-, (iii) C₆₋₁₀ aryl-S-, (iv) C₆₋₁₀ aryl(C₁₋₆ alkyl), (v) C₆₋₁₀ aryl(C₁₋₆ alkoxy), (vi) C₆₋₁₀ aryl(C₁₋₆ alkylthio), (vii) heteroaryl, (viii) heteroaryl-O-, (ix) heteroaryl-S-, (x) heteroaryl(C₁₋₆ alkyl), (xi) heteroaryl(C₁₋₆ alkoxy), (xii) heteroaryl(C₁₋₆ alkylthio), (xiii)

C₃₋₇ cycloalkyl, (xiv) C₃₋₇ cycloalkyl-O-, (xv) C₃₋₇ cycloalkyl-S-, (xvi) C₃₋₇ cycloalkyl (C₁₋₆ alkyl), (xvii) C₃₋₇ cycloalkyl(C₁₋₆ alkoxy), (xviii) C₃₋₇ cycloalkyl(C₁₋₆ alkylthio), (xix) heterocycloalkyl, (xx) heterocycloalkyl-O-,
5 (xxi) heterocycloalkyl-S-, (xxii) heterocycloalkyl(C₁₋₆ alkyl), (xxiii) heterocycloalkyl(C₁₋₆ alkoxy), (xxiv) heterocycloalkyl(C₁₋₆ alkylthio), (xxv) aromatic cyclic amino, (xxvi) aromatic cyclic amino(C₁₋₆ alkyl), (xxvii) aromatic cyclic amino(C₁₋₆ alkoxy), or (xxviii) aromatic
10 cyclic amino(C₁₋₆ alkylthio),
J represents C₁₋₆ alkylene which may have hydroxy, or C₂₋₆ alkenylene;
U represents -O-, -S- or a single bond and with the proviso that at least one of V and W is not a single bond when U is
15 -O-or -S-);
V represents C₁₋₆ alkylene which may have hydroxy, C₂₋₆ alkenylene or a single bond;
W represents -CO-, -SO₂-, -C(=NH)- or a single bond;
Z¹ and Z² independently represent hydrogen, C₂₋₇ alkoxy-
20 carbonyl, C₆₋₁₀ aryl(C₂₋₇ alkoxy-carbonyl), formyl, -R^A, -COR^B, -SO₂R^B, -CON(R^C)R^D, -CSN(R^C)R^D, -SO₂NHR^A or -C(=NR^E)N(R^F)R^G; R⁵, R⁶, R^A, R^C and R^D independently represent hydrogen, C₁₋₆ alkyl which may have any 1 to 5 substituents selected from the following substituent group β or any of the following
25 substituents (xxix) to (xxxii) which may have any 1 to 3 substituents selected from the following substituent group α;
α;
(xxix) C₆₋₁₀ aryl, (xxx) heteroaryl, (xxxii) C₃₋₇ cycloalkyl or (xxxii) heterocycloalkyl,
30 or both of Z¹ and R⁵ or both of Z² and R⁶ bind together with the neighboring nitrogen to form aliphatic cyclic amino which may have any 1 to 3 substituents selected from the following substituent group α;
or R^C and R^D bind together with the neighboring nitrogen to
35 form aliphatic cyclic amino which may have any 1 to 3 substituents selected from the following substituent group

α ;

R^B represents C_{2-7} alkoxy carbonyl, C_{1-6} alkylsulfonylamino, C_{6-10} arylsulfonylamino, C_{1-6} alkyl which may have any 1 to 5 substituents selected from the following substituent group

5 β or any of the following substituents (xxxiii) to (xxxvi) which may have any 1 to 3 substituents selected from the following substituent group α ;

(xxxiii) C_{6-10} aryl, (xxxiv) heteroaryl, (xxxv) C_{3-7} cycloalkyl or (xxxvi) heterocycloalkyl,

10 R^E , R^F and R^G independently represent hydrogen, cyano, carbamoyl, C_{2-7} acyl group, C_{2-7} alkoxy carbonyl, C_{6-10} aryl(C_{2-7} alkoxy carbonyl), nitro, C_{1-6} alkylsulfonyl, sulfamoyl, carbamimidoyl or C_{1-6} alkyl which may have any 1 to 5 substituents selected from the following substituent group

15 β ;

or R^E and R^F bind together to form ethylene;

or R^F and R^G bind together with the neighboring nitrogen to form aliphatic cyclic amino which may have a substituent selected from the following substituent group α ;

20 Y represents CH or N;

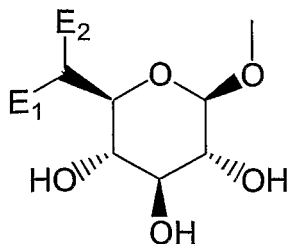
Q represents $-C_{1-6}$ alkylene-, $-C_{2-6}$ alkenylene-, $-C_{2-6}$ alkynylene-, $-C_{1-6}$ alkylene-O-, $-C_{1-6}$ alkylene-S-, $-O-C_{1-6}$ alkylene-, $-S-C_{1-6}$ alkylene-, $-C_{1-6}$ alkylene-O- C_{1-6} alkylene-, $-C_{1-6}$ alkylene-S- C_{1-6} alkylene-, $-CON(R^7)-$, $-N(R^7)CO-$, $-C_{1-6}$ alkylene- $CON(R^7)-$ or $-CON(R^7)-C_{1-6}$ alkylene-;

25

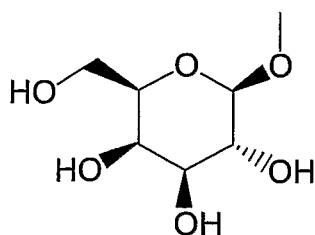
R^7 represents hydrogen or C_{1-6} alkyl;

ring A represents C_{6-10} aryl or heteroaryl;

G represents a group represented by a formula:



30 or a formula:



E^1 represents hydrogen, fluorine or hydroxy;

E^2 represents hydrogen, fluorine, methyl or hydroxymethyl;
[substituent group α]

5 halogen, hydroxy, amino, C_{1-6} alkyl, C_{1-6} alkoxy, halo(C_{1-6} alkyl), a halo(C_{1-6} alkoxy), hydroxy(C_{1-6} alkyl), C_{2-7} alkoxy-carbonyl(C_{1-6} alkyl), hydroxy(C_{1-6} alkoxy), amino(C_{1-6} alkyl), amino(C_{1-6} alkoxy), mono or di(C_{1-6} alkyl)amino, mono or di[hydroxy(C_{1-6} alkyl)]amino, C_{1-6} alkylsulfonyl, C_{1-6} alkyl-sulfonylamino, C_{1-6} alkylsulfonylamino(C_{1-6} alkyl), carboxy, C_{2-7} alkoxy-carbonyl, sulfamoyl and $-\text{CON}(\text{R}^H)\text{R}^I$

[substituent group β]

halogen, hydroxy, amino, C_{1-6} alkoxy, C_{1-6} alkylthio, halo(C_{1-6} alkoxy), halo(C_{1-6} alkylthio), hydroxy(C_{1-6} alkoxy), hydroxy(C_{1-6} alkylthio), amino(C_{1-6} alkoxy), amino(C_{1-6} alkylthio), mono or di(C_{1-6} alkyl) amino, mono or di[hydroxy(C_{1-6} alkyl)]amino, ureido, sulfamide, mono or di(C_{1-6} alkyl) ureido, mono or di[hydroxy(C_{1-6} alkyl)]ureido, mono or di(C_{1-6} alkyl)sulfamide, mono or di[hydroxy(C_{1-6} alkyl)]-sulfamide, C_{2-7} acylamino, amino(C_{2-7} acylamino), C_{1-6} alkyl-sulfonyl, C_{1-6} alkylsulfonylamino, carbamoyl(C_{1-6} alkyl-sulfonylamino), carboxy, C_{2-7} alkoxy-carbonyl, $-\text{CON}(\text{R}^H)\text{R}^I$, and any of the following substituents (xxxvii) to (xxxxviii) which may have any 1 to 3 substituents selected

25 from the above substituent group α on the ring;
(xxxvii) C_{6-10} aryl, (xxxviii) C_{6-10} aryl-O-, (xxxix) C_{6-10} aryl(C_{1-6} alkoxy), (xxxx) C_{6-10} aryl(C_{1-6} alkylthio), (xxxxi) heteroaryl, (xxxxii) heteroaryl-O-, (xxxxiii) C_{3-7} cycloalkyl, (xxxxiv) C_{3-7} cycloalkyl-O-, (xxxxv) heterocycloalkyl, (xxxxvi) heterocycloalkyl-O-, (xxxxvii) aliphatic cyclic amino or (xxxxviii) aromatic cyclic amino

R^H and R^I independently represent hydrogen or C_{1-6} alkyl

which may have any 1 to 3 substituents selected from the following substituent group γ ;

or both of R^H and R^I bind together with the neighboring nitrogen to form aliphatic cyclic amino which may have any

5 1 to 3 substituents selected from the following substituent group δ ;

[substituent group γ]

halogen, hydroxy, amino, C_{1-6} alkoxy, halo(C_{1-6} alkoxy),

hydroxy(C_{1-6}

10 alkoxy), amino(C_{1-6} alkoxy), mono or di(C_{1-6} alkyl)amino,

mono or di[hydroxy(C_{1-6} alkyl)]amino, ureido, sulfamide,

mono or di(C_{1-6} alkyl)ureido, mono or di[hydroxy(C_{1-6}

alkyl)]ureido, mono or di(C_{1-6} alkyl)sulfamide, mono or

di[hydroxy(C_{1-6} alkyl)]sulfamide, C_{2-7} acylamino, amino(C_{2-7}

15 acylamino), C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfonylamino,

carbamoyl(C_{1-6} alkylsulfonylamino), carboxy, C_{2-7} alkoxy-

carbonyl and $-\text{CON}(R^J)R^K$

[substituent group δ]

halogen, hydroxy, amino, C_{1-6} alkyl, C_{1-6} alkoxy, halo(C_{1-6}

20 alkyl), halo(C_{1-6} alkoxy), hydroxy(C_{1-6} alkyl), C_{2-7} alkoxy-

carbonyl(C_{1-6} alkyl), hydroxy(C_{1-6} alkoxy), amino(C_{1-6} alkyl),

amino(C_{1-6} alkoxy), mono or di(C_{1-6} alkyl)amino, mono or

di[hydroxy(C_{1-6} alkyl)]amino, C_{1-6} alkylsulfonyl, C_{1-6} alkyl-

sulfonylamino, C_{1-6} alkylsulfonylamino(C_{1-6} alkyl), carboxy,

25 C_{2-7} alkoxy carbonyl, sulfamoyl and $-\text{CON}(R^J)R^K$

R^J and R^K independently represent hydrogen or C_{1-6} alkyl

which may have any 1 to 3 substituents selected from

hydroxy, amino, mono or di(C_{1-6} alkyl) amino, C_{2-7} alkoxy-

30 carbonyl and carbamoyl;

or both of R^J and R^K bind together with the neighboring nitrogen to form aliphatic cyclic amino which may have any

1 to 3 substituents selected from hydroxy, amino, mono or

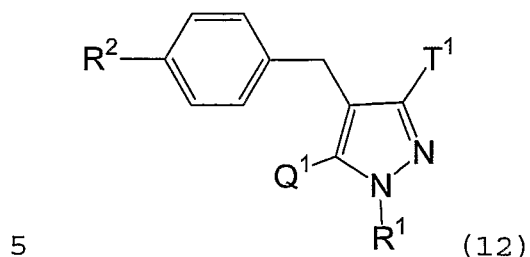
di(C_{1-6} alkyl) amino, C_{1-6} alkyl, hydroxy(C_{1-6} alkyl), C_{2-7}

alkoxy carbonyl, C_{2-7} alkoxy carbonyl (C_{1-6} alkyl) and

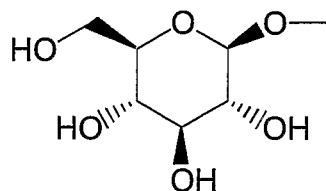
35 carbamoyl, or a pharmaceutically acceptable salt thereof,

or a prodrug thereof.

In an embodiment of the present invention, the SGLT inhibitors are the glucopyranosyloxypyrazole derivatives disclosed in WO 01/16147 pamphlet, which are represented by Formula (12):

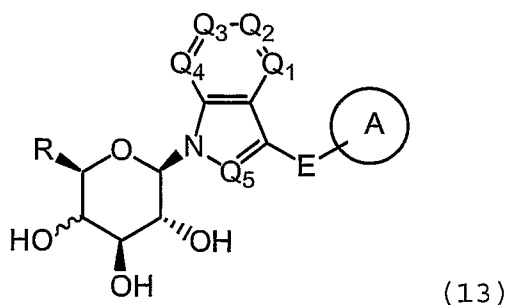


wherein R¹ represents hydrogen or lower alkyl; one of Q¹ and T¹ represents a group represented by the formula:



10 while the other represents lower alkyl or halo(lower alkyl); and R² represents hydrogen, lower alkyl, lower alkoxy, lower alkylthio, halo(lower alkyl) or halogen, or a pharmaceutically acceptable salt thereof.

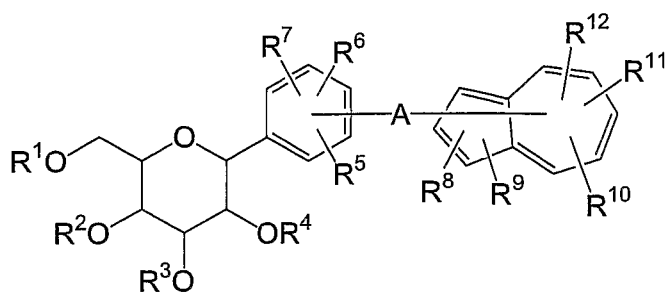
15 In an embodiment of the present invention, the SGLT inhibitors are the compounds disclosed in WO 2006/035796 pamphlet, which are represented by Formula (13):



20 wherein Ring A represents aryl or heteroaryl, each of which may have a substituent(s), Q¹ to Q⁵ are each independently carbon to which hydrogen or a substituent is connected, or nitrogen, E represents a single bond, alkylene, -O-, -S- or -NH-, and R represents methyl, ethyl, fluoromethyl or

hydroxymethyl,
 or a prodrug thereof or a pharmaceutically acceptable salt
 thereof, or a hydrate or solvate thereof.

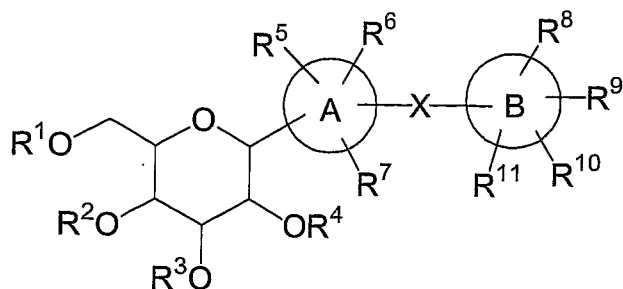
5 In an embodiment of the present invention, the SGLT
 inhibitors are the azulene derivatives disclosed in WO
 2004/013118 pamphlet, which are represented by Formula
 (14) :



10 wherein R¹ to R⁴ individually represent hydrogen, optional-
 ly substituted lower alkyl, -C(=O)-optionally substituted
 lower alkyl, or -optionally substituted lower alkylene-
 optionally substituted aryl,
 R⁵ to R¹² individually represent hydrogen, optionally
 15 substituted lower alkyl, halogen, -OH, -O-optionally
 substituted lower alkyl, -optionally substituted lower
 alkylene-OH, -optionally substituted lower alkylene-O-
 optionally substituted lower alkyl, -O-optionally substi-
 20 -O-optionally substituted lower alkylene-O-optionally substituted lower alkyl,
 -O-optionally substituted lower alkylene-optionally
 substituted aryl, -optionally substituted lower alkylene-O-
 C(=O)-optionally substituted lower alkyl, -COOH, nitro,
 cyano, amino, substituted amino, or -C(=O)-O-optionally
 25 substituted lower alkyl, and
 A represents bond or optionally substituted lower alkylene,
 wherein -A- may be bonded to any one of the positions 1-8
 of the azulene ring, and any two of R⁵, R⁶, and R⁷ may form
 a benzene ring together with the adjacent carbon atoms.

30 In still another embodiment of the present invention,
 the SGLT inhibitors are the compounds disclosed in WO

2004/080990 pamphlet, which are represented by Formula (15):



(15)

wherein A ring represents (1) benzene, (2) five or six-membered monocyclic heteroaryl having 1 to 4 hetero atom(s) selected from N, S, and O, or (3) saturated or unsaturated eight to ten-membered heterobicyclic having 1 to 4 hetero atom(s) selected from N, S, and O;

B ring represents (1) saturated or unsaturated eight to ten-membered heterobicyclic having 1 to 4 hetero atom(s) selected from N, S, and O, (2) saturated or unsaturated five or six-membered heteromonocyclic having 1 to 4 hetero atom(s) selected from N, S, and O, (3) a saturated or an unsaturated eight to ten-membered bicyclic hydrocarbon, or (4) benzene;

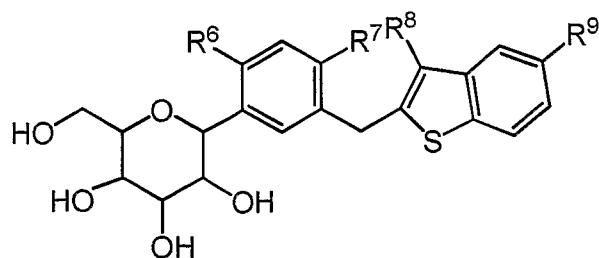
X represents bond or lower alkylene;

wherein Ring A, Ring B, and X have a correlation that (1) when Ring A is benzene, Ring B is a ring other than benzene or that (2) when Ring A is benzene, and Ring B is saturated or unsaturated eight to ten-membered heterobicyclic having 1 to 4 hetero atom(s) selected from N, S, and O including benzene, or saturated or unsaturated eight to ten-membered bicyclic hydrocarbon including benzene, X is bonded to Ring B in a part other than the benzene ring included in Ring B: incidentally, this correlation specifically means that Ring A and Ring B cannot be benzene simultaneously and that when Ring A is benzene and Ring B is benzofuran or indane, X is not benzene constituting a part of Ring B but bonds with furan or cyclopentane;

R¹ to R⁴ individually represent hydrogen, lower alkyl,

-C(=O)-lower alkyl, or -lower alkylene-aryl; and
 R⁵ to R¹¹ individually represent hydrogen, lower alkyl,
 cycloalkyl, halogen, halogen-substituted lower alkyl, -OH,
 =O, -NH₂, lower alkylsulfonyl-, halogen-substituted lower
 5 alkylsulfonyl-, aryl sulfonyl-, aryl, saturated or
 unsaturated five or six-membered heteromonocyclic having 1
 to 4 hetero atom(s) selected from N, S, and O, -lower
 alkylene-OH, -lower alkylene-O-lower alkyl, -lower
 alkylene-O-C(=O)-lower alkyl, -lower alkylene-O-lower
 10 alkylene-COOH, -lower alkylene-O-lower alkylene-C(=O)-O-
 lower alkyl, -lower alkylene-NH₂, -lower alkylene-NH-lower
 alkyl; -lower alkylene-N(lower alkyl)₂, -lower alkylene-NH-
 C(=O)-lower alkyl, -COOH, -CN, -C(=O)-O-lower alkyl,
 -C(=O)-NH₂, -C(=O)-NH-lower alkyl, -C(=O)-N(lower alkyl)₂,
 15 -O-lower alkyl, -O-cycloalkyl, -O-lower alkylene-OH, -O-
 lower alkylene-O-lower alkyl, -O-lower alkylene-COOH, -O-
 lower alkylene-C(=O)-O-lower alkyl, -O-lower alkylene-
 C(=O)-NH₂, -O-lower alkylene-C(=O)-NH-lower alkyl, -O-lower
 alkylene-C(=O)-N(lower alkyl)₂, -O-lower alkylene-CH(OH)-
 20 CH₂(OH), -O-lower alkylene-NH₂, -O-lower alkylene-NH-lower
 alkyl, -O-lower alkylene-N(lower alkyl)₂, -O-lower
 alkylene-NH-C(=O)-lower alkyl, -NH-lower alkyl, -N(lower
 alkyl)₂, -NH-SO₂-lower alkyl, -NH-SO₂-halogen-substituted
 lower alkyl, -NH-lower alkylene-OH, -NH-C(=O)-lower alkyl,
 25 -NH-C(=O)-NH₂, -NH-C(=O)-NH-lower alkyl, -NH-C(=O)-N(lower
 alkyl)₂, or -NH-C(=O)-O-lower alkyl.

In a preferable embodiment of the present invention,
 the SGLT inhibitors are represented by Formula (15a):



30

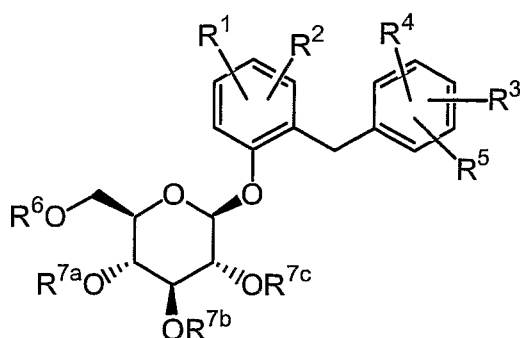
(15a)

wherein: R⁶ represents a hydrogen atom, halogen atom, -OH,

-OMe, -CH₂-OH, -O-(CH₂)₂-OH, -O-(CH₂)₂-NH₂, -COOH, -COOEt, -O-CH₂-COOH, or -O-CH₂-COOEt, R⁷ represents a hydrogen atom or halogen atom, R⁸ represents a hydrogen atom, or -Me, and R⁹ represents a hydrogen atom, -Me, halogen atom, or -OMe.

5

In an embodiment of the present invention, the SGLT inhibitors are the glucopyranosyl-substituted benzene derivatives disclosed in WO 2005/092877 pamphlet, which are represented by Formula (16):



10

(16)

wherein R¹ is selected from the definitions of the group A, and if R³ is selected from the definitions of the group B, R¹ may additionally be selected from hydrogen, fluorine, chlorine, bromine, iodine, C₁₋₄ alkyl, C₂₋₄ alkenyl-C₁₋₄ alkyl, C₂₋₄ alkynyl-C₁₋₄ alkyl, C₂₋₄ alkenyl-C₁₋₄ alkoxy, C₂₋₄ alkynyl-C₁₋₄ alkoxy, C₃₋₇ cycloalkyl-C₁₋₄ alkyl, C₅₋₇ cycloalkenyl-C₁₋₄ alkyl, methyl substituted by 1 to 3 fluorine, ethyl substituted by 1 to 5 fluorine, C₁₋₄ alkoxy, methoxy substituted by 1 to 3 fluorine, ethoxy substituted by 1 to 5 fluorine, C₁₋₄ alkyl substituted by hydroxy or C₁₋₃ alkoxy, C₂₋₄ alkoxy substituted by hydroxy or C₁₋₃ alkoxy, C₃₋₆ cycloalkyl-C₁₋₃ alkoxy or hydroxy, while in the above-mentioned cycloalkyl and cycloalkenyl rings one or two methylene groups may be replaced independently of one another by O or CO;

25

R² denotes hydrogen, fluorine, chlorine, bromine, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano or nitro, while the alkyl or alkoxy group may be mono- or polysubstituted by fluorine; R³ is selected from the definitions of the group B, and if

R¹ is selected from the definitions of the group A, R³ may additionally be selected from the meanings hydrogen, fluorine, chlorine, bromine, iodine, C₁₋₆ alkyl, C₂₋₄ alkenyl-C₁₋₄ alkyl, C₂₋₄ alkynyl-C₁₋₄ alkyl, C₂₋₄ alkenyl-C₁₋₄ alkoxy, C₂₋₄ alkynyl-C₁₋₄ alkoxy, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, C₃₋₇ cycloalkyl-C₁₋₄ alkyl, C₅₋₇ cycloalkenyl-C₁₋₄ alkyl, C₃₋₆ cycloalkylidenemethyl, hydroxy, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl-C₁₋₃ alkoxy, aryl, aryl-C₁₋₃ alkyl, heteroaryl, heteroaryl-C₁₋₃ alkyl, aryloxy, aryl-C₁₋₃ alkyl-oxy, methyl or methoxy substituted by 1 to 3 fluorine, C₂₋₄ alkyl or C₂₋₄ alkoxy substituted by 1 to 5 fluorine, C₁₋₄ alkyl substituted by cyano, C₁₋₄ alkyl substituted by hydroxy or C₁₋₃ alkyloxy, cyano, carboxy, C₁₋₃ alkoxy-carbonyl, aminocarbonyl, (C₁₋₃ alkylamino)carbonyl, di-(C₁₋₃ alkyl)aminocarbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, piperazin-1-ylcarbonyl, 4-(C₁₋₃ alkyl)-piperazin-1-ylcarbonyl, (C₁₋₄ alkyl)carbonylamino, C₁₋₄ alkyl-sulfonylamino, C₁₋₄ alkylsulfanyl, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, arylsulfonylamino, aryl-C₁₋₃ alkylsulfonylamino or arylsulfonyl;

R⁴ and R⁵ independently of one another denote hydrogen, fluorine, chlorine, bromine, iodine, cyano, nitro, C₁₋₃ alkyl, C₁₋₃ alkoxy, or methyl or methoxy substituted by 1 to 3 fluorine,

A denotes C₂₋₆ alkyn-1-yl, C₂₋₆ alken-1-yl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, heteroaryl, C₁₋₄ alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, aminocarbonyl, C₁₋₄ alkylaminocarbonyl, di-(C₁₋₃ alkyl)aminocarbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, piperazin-1-ylcarbonyl, 4-(C₁₋₄ alkyl)piperazin-1-ylcarbonyl, arylamino-carbonyl, heteroarylaminocarbonyl, C₁₋₄ alkoxy-carbonyl, aryl-C₁₋₃ alkoxy-carbonyl, heteroaryl-C₁₋₃ alkoxy-carbonyl, amino, C₁₋₄ alkylamino, di-(C₁₋₃ alkyl)amino, pyrrolidin-1-yl, pyrrolidin-2-on-1-yl, piperidin-1-yl, piperidin-2-on-1-yl, morpholin-4-yl, morpholin-3-on-4-yl, piperazin-1-yl, 4-(C₁₋₃ alkyl)piperazin-1-yl, C₁₋₄ alkyl-

carbonylamino, arylcarbonylamino, heteroarylcarbonylamino, C₃₋₇ cycloalkyloxy, C₅₋₇ cycloalkenyloxy, aryloxy, heteroaryloxy, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₃₋₇ cycloalkylsulfonyl, C₃₋₇ cycloalkylsulfinyl, C₃₋₇ cycloalkylsulfonyl, C₅₋₇ cycloalkenylsulfonyl, C₅₋₇ cycloalkenylsulfinyl, C₅₋₇ cycloalkenylsulfonyl, arylsulfonyl, arylsulfinyl, arylsulfonyl, heteroarylsulfonyl, heteroarylsulfinyl, heteroarylsulfonyl, cyano or nitro, while the above-mentioned alkynyl and alkenyl groups may be mono- or polysubstituted by fluorine or chlorine, and the above-mentioned alkynyl and alkenyl groups may be mono- or di-substituted by identical or different groups L¹, and the above-mentioned cycloalkyl and cycloalkenyl rings independently of one another may be mono- or di-substituted by substituents selected from fluorine and C₁₋₃ alkyl, and in the above-mentioned cycloalkyl and cycloalkenyl rings one or two methylene groups may be replaced independently of one another by O, S, CO, SO, SO₂ or NR^N;

B denotes tri-(C₁₋₄ alkyl)silyl-C₁₋₆ alkyl, C₂₋₆ alkyn-1-yl, C₂₋₆ alken-1-yl, amino, C₁₋₃ alkylamino, di-(C₁₋₃ alkyl)amino, pyrrolidin-1-yl, pyrrolidin-2-on-1-yl, piperidin-1-yl, piperidin-2-on-1-yl, morpholin-4-yl, morpholin-3-on-4-yl, piperazin-1-yl, 4-(C₁₋₃ alkyl)piperazin-1-yl, arylcarbonylamino, heteroarylcarbonylamino, nitro, C₃₋₁₀ cycloalkyloxy, C₅₋₁₀ cycloalkenyloxy, C₃₋₁₀ cycloalkylsulfonyl, C₃₋₁₀ cycloalkylsulfinyl, C₃₋₁₀ cycloalkylsulfonyl, C₅₋₁₀ cycloalkenylsulfonyl, C₅₋₁₀ cycloalkenylsulfinyl, C₅₋₁₀ cycloalkenylsulfonyl, arylsulfonyl, arylsulfinyl, heteroarylsulfonyl or heteroarylsulfinyl, while the above-mentioned alkynyl and alkenyl groups may be mono- or polysubstituted by fluorine or chlorine, and the above-mentioned alkynyl and alkenyl groups may be mono- or di-substituted by identical or different groups L¹; while the above-mentioned cycloalkyl and cycloalkenyl rings may be mono- or di-substituted independently of one another by substituents selected from fluorine and C₁₋₃ alkyl, and in the above-mentioned

cycloalkyl and cycloalkenyl rings one or two methylene groups may be replaced independently of one another by O, S, CO, SO, SO₂ or NR^N;

R^N denotes H, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl or C₁₋₄ alkyl-sulfonyl,

L¹ independently of one another is selected from hydroxy, cyano, nitro, C₃₋₇ cycloalkyl, aryl, heteroaryl, C₁₋₄ alkyl-carbonyl, arylcarbonyl, heteroarylcarbonyl, aminocarbonyl, C₁₋₄ alkylaminocarbonyl, di-(C₁₋₃ alkyl)-aminocarbonyl,

pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, C₁₋₄ alkoxy carbonyl, aryl-C₁₋₃ alkoxy carbonyl, heteroaryl-C₁₋₃ alkoxy carbonyl, C₁₋₄ alkyloxy, aryloxy, heteroaryloxy, C₁₋₄ alkylsulfanyl, arylsulfanyl, heteroarylsulfanyl, C₁₋₄ alkyl-sulfinyl, arylsulfinyl, heteroarylsulfinyl, C₁₋₄ alkyl-sulfonyl, arylsulfonyl and heteroarylsulfonyl;

L² independently of one another is selected from fluorine, chlorine, bromine, iodine, C₁₋₃ alkyl, difluoromethyl, trifluoromethyl, C₁₋₃ alkoxy, difluoromethoxy, trifluoromethoxy and cyano;

R⁶, R^{7a}, R^{7b}, and R^{7c} independently of one another have a meaning selected from hydrogen, (C₁₋₁₈-alkyl)carbonyl, (C₁₋₁₈-alkyl)oxycarbonyl, arylcarbonyl and aryl-(C₁₋₃ alkyl)-carbonyl, while the aryl group mentioned in the definition

of the above groups are meant phenyl or naphthyl group which may be mono- or di-substituted independently of one another by identical or different groups L²; and

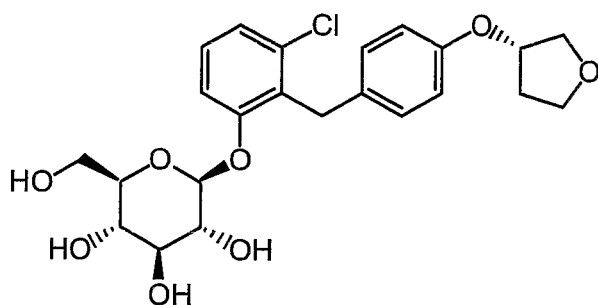
the heteroaryl group mentioned in the definition of the above groups are meant a pyrrolyl, furanyl, thienyl,

pyridyl, indolyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl or tetrazolyl group, or is meant pyrrolyl, furanyl, thienyl or pyridyl, wherein one or two methyne groups are replaced by nitrogen, or is meant indolyl, benzofuranyl, benzothiophenyl, quinolinyl or isoquinolinyl,

wherein one to three methyne groups are replaced by nitrogen, while the above-mentioned heteroaryl groups

independently of one another may be mono- or di-substituted by identical or different groups L^2 ; while, unless otherwise stated, the above-mentioned alkyl group may be straight-chain or branched, the tautomers, the stereo-
5 isomers thereof, the mixtures thereof and the salts thereof.

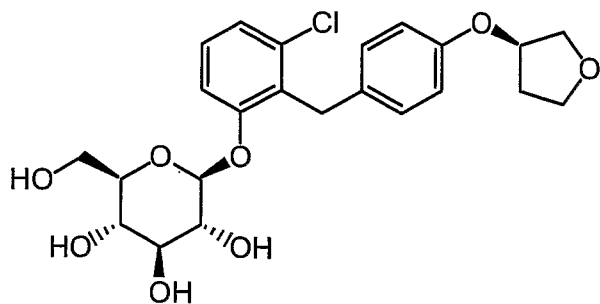
In a preferable embodiment of the present invention, the SGLT inhibitor is the compound disclosed in WO 2006/117359 pamphlet, which is represented by Formula (17):



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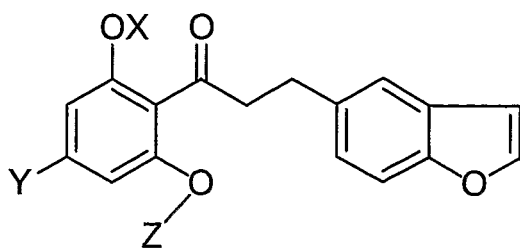
(17).

In another preferable embodiment of the present invention, the SGLT inhibitor is the compound disclosed in WO 2006/117360 pamphlet, which is represented by Formula
15 (18):



(18)

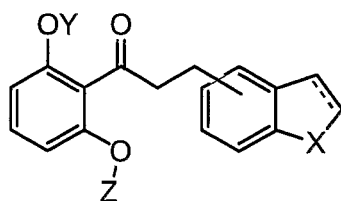
In an embodiment of the present invention, the SGLT inhibitors are the propiophenone derivatives disclosed in
20 U.S. Pat. No. 6,048,842, or a pharmaceutically acceptable salt thereof, which are represented by Formula (19):



(19)

wherein OX is a hydroxy group which may optionally be protected, Y is a lower alkyl group, and Z is a β -D-glucopyranosyl group wherein one or more hydroxy groups may
 5 optionally be protected.

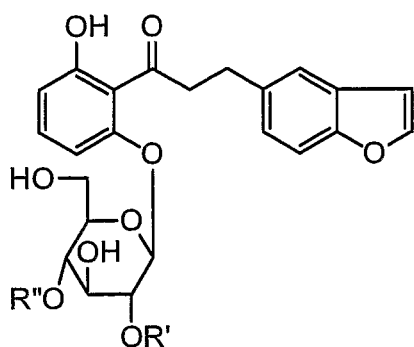
In an embodiment of the present invention, the SGLT inhibitors are the propiophenone derivatives disclosed in U.S. Pat. No. 5,830,873, or a pharmaceutically acceptable
 10 salt thereof, which are represented by Formula (20):



(20)

wherein X is an oxygen atom, a sulfur atom or a methylene group, OY is a protected or unprotected hydroxy group, Z is a β -D-glucopyranosyl group or 4-O-(α -D-glucopyranosyl)- β -D-glucopyranosyl group wherein one or more hydroxy groups of
 15 these groups may optionally be acylated, and the dotted line means the presence or absence of a double bond.

In an embodiment of the present invention, the SGLT inhibitors are the propiophenone derivatives or a pharmaceutically acceptable salt thereof, disclosed in U.S. Pat. No. 5,767,094, which are represented by Formula (21):
 20



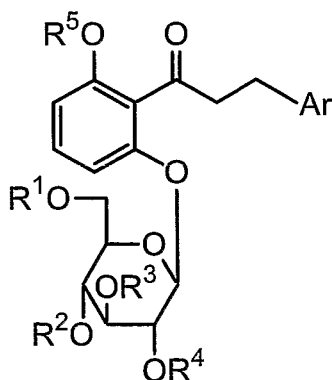
(21)

wherein R' is a lower alkanoyl group, and R'' is a hydrogen atom, or R' is a hydrogen atom, and R'' is a lower alkoxy-carbonyl group.

5

In an embodiment of the present invention, the SGLT inhibitor is the propiophenone derivatives or a pharmaceutically acceptable salt thereof disclosed in U.S. Pat. Nos. 5,424,406 and 5,731,292, which are represented by Formula

10 (22):



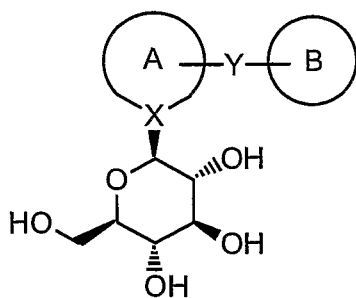
(22)

wherein Ar is an aryl group, R¹ is hydrogen atom or an acyl group, R² is hydrogen atom, an acyl group or α -D-glucopyranosyl group, or R¹ and R² may combine together to form a substituted methylene group, R³ and R⁴ are each hydrogen atom or an acyl group, and OR⁵ is a protected or unprotected hydroxy group or a lower alkoxy group.

15

In an embodiment of the present invention, the SGLT inhibitors are the compounds disclosed in United States Patent Application Publication No. 2005/0233988, which are represented by Formula (23):

20



(23)

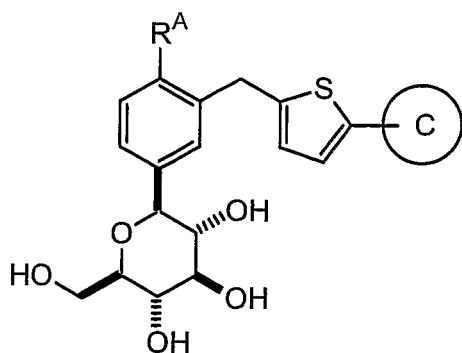
wherein Ring A and Ring B are one of the followings: (1) Ring A is optionally substituted unsaturated heteromonocyclic, and Ring B is optionally substituted unsaturated heteromonocyclic, optionally substituted unsaturated fused heterobicyclic, or optionally substituted benzene, (2) Ring A is optionally substituted benzene, and Ring B is optionally substituted unsaturated heteromonocyclic, or optionally substituted unsaturated fused heterobicyclic wherein Y is linked to the heterocyclic ring of said fused heterobicyclic, or (3) Ring A is optionally substituted unsaturated fused heterobicyclic, wherein the sugar moiety X-(sugar) and the moiety -Y-(Ring B) are both on the same heterocyclic ring of said fused heterobicyclic, and Ring B is optionally substituted unsaturated heteromonocyclic, optionally substituted unsaturated fused heterobicyclic, or optionally substituted benzene;

X is carbon or nitrogen; and

Y is $-(\text{CH}_2)_n-$ (wherein n is 1 or 2);

a pharmaceutically acceptable salt thereof, or a prodrug thereof.

In a preferable embodiment, the SGLT inhibitors are the compounds of Formula (24):



wherein R^A is a halogen atom, or a lower alkyl group;
 Ring C is a phenyl group substituted by 1-3 substituents
 selected from the group consisting of a halogen atom, a
 5 cyano group, a lower alkyl group, a halo-lower alkyl group,
 a lower alkoxy group, a halo-lower alkoxy group, a
 methylenedioxy group, an ethyleneoxy group, a mono- or di-
 lower alkylamino group, a carbamoyl group, and a mono- or
 di-lower alkylcarbamoyl group; or a heterocyclyl group
 10 substituted by 1-3 substituents selected from the group
 consisting of a halogen atom, a cyano group, a lower alkyl
 group, a halo-lower alkyl group, a lower alkoxy group, a
 halo-lower alkoxy group, a mono- or di-lower alkylamino
 group, a carbamoyl group, and a mono- or di-lower alkyl-
 15 carbamoyl group;
 or a pharmaceutically acceptable salt thereof, or a prodrug
 thereof.

Examples of the preferable compounds include:

- 1- (β -D-glucopyranosyl)-4-chloro-3-[5-(5-thiazolyl)-2-
 20 thienylmethyl]benzene;
 1- (β -D-glucopyranosyl)-4-chloro-3-(5-phenyl-2-thienyl-
 methyl)benzene;
 1- (β -D-glucopyranosyl)-4-chloro-3-[5-(2-pyrimidinyl)-2-
 thienylmethyl]benzene;
 25 1- (β -D-glucopyranosyl)-4-methyl-3-[5-(2-pyrimidinyl)-2-
 thienylmethyl]benzene;
 1- (β -D-glucopyranosyl)-4-chloro-3-[5-(3-cyanophenyl)-2-
 thienylmethyl]benzene;
 1- (β -D-glucopyranosyl)-4-chloro-3-[5-(4-cyanophenyl)-2-

thienylmethyl]benzene;

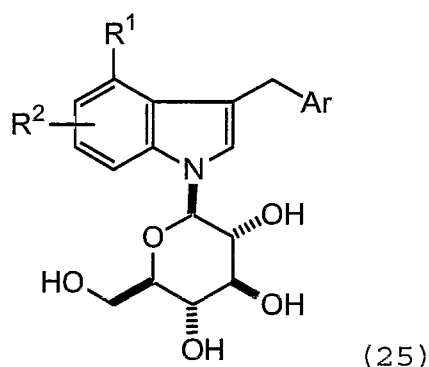
1-(β -D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene;

1-(β -D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-3-pyridyl)-2-thienylmethyl]benzene;

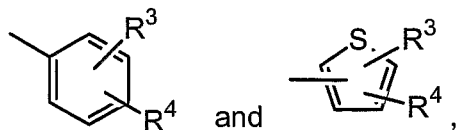
1-(β -D-glucopyranosyl)-4-methyl-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene; and

1-(β -D-glucopyranosyl)-4-methyl-3-[5-(3-difluoromethylphenyl)-2-thienylmethyl]benzene.

10 In an embodiment of the present invention, the SGLT inhibitors are the indole derivatives disclosed in WO 2006/080577 pamphlet, which are represented by Formula (25):



15 wherein R^1 is halogen, or alkyl,
 R^2 is hydrogen, or halogen, and
 Ar is one of the following groups:



in which R^3 and R^4 are independently hydrogen, halogen,
 20 alkyl, cycloalkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio,
 hydroxy, phenyl, halophenyl, cyanophenyl, pyridyl, halo-
 pyridyl, thienyl, or halothienyl, or R^3 and R^4 together
 with carbon atoms to which they are attached form a fused
 benzene, furan or dihydrofuran ring;
 25 or a pharmaceutically acceptable salt thereof.

Examples of the preferable compounds include:

4-chloro-3-(4-ethylphenylmethyl)-1-(β -D-glucopyranosyl)-

indole;

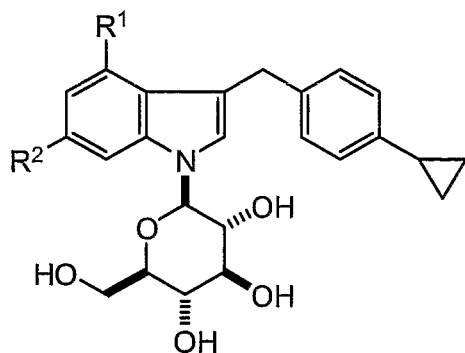
4-chloro-3-(4-ethoxyphenylmethyl)-1-(β -D-glucopyranosyl)-indole;

3-(5-bromothiophen-2-ylmethyl)-4-chloro-1-(β -D-glucopyranosyl)indole;

3-(4-ethylphenylmethyl)-4-fluoro-1-(β -D-glucopyranosyl)-indole; and

4-methyl-3-(4-cyclopropylphenylmethyl)-1-(β -D-glucopyranosyl)indole.

10 In an embodiment of the present invention, the SGLT inhibitors are the indole derivatives disclosed in PCT/JP2007/065213, which are represented by Formula (26):



(26)

15 wherein R^1 is fluorine, or chlorine, and R^2 is hydrogen, or fluorine, or a pharmaceutically acceptable salt thereof.

Examples of the preferable compounds include:

4-chloro-3-(4-cyclopropylphenylmethyl)-1-(β -D-glucopyranosyl)indole,

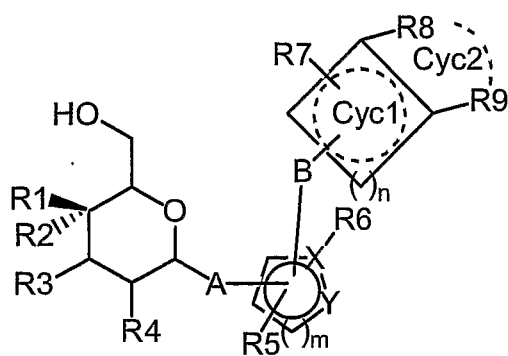
3-(4-cyclopropylphenylmethyl)-4-fluoro-1-(β -D-glucopyranosyl)indole,

4-chloro-3-(4-cyclopropylphenylmethyl)-6-fluoro-1-(β -D-glucopyranosyl)indole, and

3-(4-cyclopropylphenylmethyl)-4,6-difluoro-1-(β -D-glucopyranosyl)indole; and

25 a pharmaceutically acceptable salt thereof.

In an embodiment of the present invention, the SGLT inhibitors are the compounds disclosed in United States Patent Application Publication No. 2004/0259819, which are represented by Formula (27):



(27)

wherein

R1 and R2 are each independently F or H or one of said radicals R1 and R2 may be OH;

5 R3 is OH or F, with the proviso that at least one of the radicals R1, R2 and R3 must be F;

R4 is OH;

A is O, NH, CH₂, S or a bond;

10 X is C, O, S or N, with the proviso that X is C when Y is O or S;

Y is N, O or S;

m is 1 or 2;

15 R5 is hydrogen, F, Cl, Br, I, OH, CF₃, NO₂, CN, COOH, CO(C₁₋₆ alkyl), COO(C₁₋₆ alkyl), CONH₂, CONH(C₁₋₆ alkyl), CON(C₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, HO-(C₁₋₆ alkyl), (C₁₋₆ alkyl)-O-(C₁₋₆ alkyl), phenyl, benzyl, C₁₋₆ alkoxy carbonyl,

20 wherein said CO(C₁₋₆ alkyl), COO(C₁₋₆ alkyl), CONH(C₁₋₆ alkyl), CON(C₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, HO-(C₁₋₆ alkyl), (C₁₋₆ alkyl)-O-(C₁₋₆ alkyl) and C₁₋₆ alkoxy carbonyl radicals are optionally substituted with one or more fluorine atoms,

25 SO₂-NH₂, SO₂NH(C₁₋₆ alkyl), SO₂N(C₁₋₆ alkyl)₂, S-(C₁₋₆ alkyl), S-(CH₂)_o-phenyl, SO-(C₁₋₆ alkyl), SO-(CH₂)_o-phenyl, SO₂-(C₁₋₆ alkyl), SO₂-(CH₂)_o-phenyl,

wherein said SO₂NH(C₁₋₆ alkyl), SO₂N(C₁₋₆ alkyl)₂, S-(C₁₋₆ alkyl), SO-(C₁₋₆ alkyl) and SO₂-(C₁₋₆ alkyl) radicals are optionally substituted with one or more fluorine atoms, and wherein the phenyl ring of said S-(CH₂)_o-phenyl, SO-

(CH₂)_o-phenyl and SO₂-(CH₂)_o-phenyl radicals is optionally mono- or di-substituted with F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, O-(C₁₋₆ alkyl), C₁₋₆ alkyl or NH₂, and wherein o is 0, 1, 2, 3, 4, 5, or 6,

5 NH₂, NH-(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NH(C₁₋₇ acyl), phenyl or O-(CH₂)_o-phenyl,

wherein the phenyl ring of said phenyl and O-(CH₂)_o-phenyl radicals is optionally mono-, di-, or tri-substituted with F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁₋₆ alkyl), C₁₋₆ alkyl, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, SO₂-CH₃, COOH, COO-(C₁₋₆ alkyl) or CONH₂, and wherein o is as hereinabove defined;

or, when Y is S, R5 and R6 taken together with the carbon atoms to which they are attached may form a phenyl ring; R6 is H, C₁₋₆ alkyl, C₁₋₆ alkenyl, C₃₋₆ cycloalkyl, or phenyl wherein said phenyl radical is optionally substituted with halogen or C₁₋₄ alkyl;

B is C₀₋₁₅ alkanediyl, wherein one or more of the carbon atoms in said alkanediyl radical may be replaced, independently of one another, with -O-, -(C=O)-, -CH=CH-, -C≡C-, -S-, -CH(OH)-, -CHF-, -CF₂-, -(S=O)-, -(SO₂)-, -N(C₁₋₆ alkyl)-, -N(C₁₋₆ alkyl-phenyl)- or -NH-;

n is 0, 1, 2, 3 or 4;

Cycl is a 3-, 4-, 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring, wherein one carbon atom of said ring may be replaced by O, N or S;

R7, R8, and R9 are each independently hydrogen, F, Cl, Br, I, OH, CF₃, NO₂, CN, COOH, COO(C₁₋₆ alkyl), CO(C₁₋₄ alkyl), CONH₂, CONH(C₁₋₆ alkyl), CON(C₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₈ alkoxy, HO-(C₁₋₆ alkyl), (C₁₋₆ alkyl)-O-(C₁₋₆ alkyl),

wherein said COO(C₁₋₆ alkyl), CO(C₁₋₄ alkyl), CONH(C₁₋₆ alkyl), CON(C₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₈ alkoxy, HO-(C₁₋₆ alkyl) and (C₁₋₆ alkyl)-O-(C₁₋₆ alkyl) radicals are optionally substituted with one or more fluorine atoms,

SO₂-NH₂, SO₂NH(C₁₋₆ alkyl), SO₂N(C₁₋₆ alkyl)₂, S-(C₁₋₆ alkyl), S-(CH₂)_o-phenyl, SCF₃, SO-(C₁₋₆ alkyl), SO-(CH₂)_o-phenyl, SO₂-(C₁₋₆ alkyl), SO₂-(CH₂)_o-phenyl,

5 wherein said SO₂NH(C₁₋₆ alkyl), SO₂N(C₁₋₆ alkyl)₂, S-(C₁₋₆ alkyl), SO-(C₁₋₆ alkyl) and SO₂-(C₁₋₆ alkyl) radicals are optionally substituted with one or more fluorine atoms, and wherein the phenyl ring of said S-(CH₂)_o-phenyl, SO-(CH₂)_o-phenyl and SO₂-(CH₂)_o-phenyl radicals is optionally mono- or di-substituted with F, Cl, Br, OH, CF₃, NO₂, CN,
10 OCF₃, O-(C₁₋₆ alkyl), C₁₋₆ alkyl or NH₂, and wherein o is as hereinabove defined,

NH₂, NH-(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NH(C₁₋₇ acyl), phenyl or O-(CH₂)_o-phenyl,

15 wherein the phenyl ring of said phenyl and O-(CH₂)_o-phenyl radicals is optionally mono-, di-, or tri-substituted with F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, C₁₋₈ alkoxy, C₁₋₆ alkyl, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, SO₂-CH₃, COOH, COO-(C₁₋₆ alkyl) or CONH₂, and wherein o is as hereinabove defined;

20 or R8 and R9 taken together with the carbon atoms to which they are attached form a 5-, 6- or 7-membered, saturated, partially saturated or completely unsaturated ring herein referred to as Cyc2,

25 wherein one or two carbon atom(s) in said Cyc2 ring are optionally replaced by N, O or S, and wherein said Cyc2 ring is optionally substituted with C₁₋₆ alkyl, C₂₋₅ alkenyl or C₂₋₅ alkynyl,

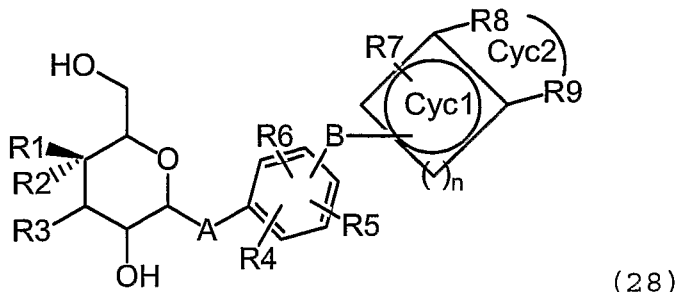
30 wherein said C₁₋₆ alkyl, C₂₋₅ alkenyl and C₂₋₅ alkynyl radicals are optionally substituted with F, Cl, OH, CF₃, NO₂, CN, COO(C₁₋₄ alkyl), CONH₂, CONH(C₁₋₄ alkyl) or OCF₃, and wherein a -CH₂- group contained in said C₁₋₆ alkyl, C₂₋₅ alkenyl and C₂₋₅ alkynyl radicals is optionally replaced by -O-;

and pharmaceutically acceptable salts thereof.

35

In an embodiment of the present invention, the SGLT

inhibitors are the compounds in United States Patent Application Publication No. 2005/0014704, which are represented by Formula (28):



- 5 wherein: R1, R2 are each independently OH, F or H with the proviso that
- when R1 is F, R2 cannot be OH;
 - when R1 is OH, R2 cannot be F; and
 - when R1 is OH, R2 cannot be OH;
- 10 R3 is OH or F,
- with the proviso that at least one of said R1, R2, R3 radicals must be F;
- A is O, NH, CH₂, S or a bond;
- R4, R5, and R6 are each independently hydrogen, F, Cl, Br,
- 15 I, OH, NO₂, CN, COOH, CO(C₁₋₆ alkyl), COO(C₁₋₆ alkyl), CONH₂, CONH(C₁₋₆ alkyl), CON(C₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, HO(C₁₋₆ alkyl), (C₁₋₆ alkyl)-O-(C₁₋₆ alkyl), phenyl or benzyl,
- wherein said CO(C₁₋₆ alkyl), COO(C₁₋₆ alkyl), CONH(C₁₋₆
- 20 alkyl), CON(C₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, HO(C₁₋₆ alkyl), (C₁₋₆ alkyl)-O-(C₁₋₆ alkyl) radicals are optionally substituted with one or more fluorine atoms,
- SO₂-NH₂, SO₂NH(C₁₋₆ alkyl), SO₂N(C₁₋₆ alkyl)₂, S-(C₁₋₆ alkyl),
- 25 S-(CH₂)_o-phenyl, SO-(C₁₋₆ alkyl), SO-(CH₂)_o-phenyl, SO₂-(C₁₋₆ alkyl), SO₂-(CH₂)_o-phenyl,
- wherein the phenyl ring of said S-(CH₂)_o-phenyl, SO-(CH₂)_o-phenyl and SO₂-(CH₂)_o-phenyl radicals may be mono- or disubstituted with F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃,
- 30 O-(C₁₋₆ alkyl), C₁₋₆ alkyl or NH₂ and wherein o is 0, 1, 2, 3, 4, 5 or 6,

NH₂, NH-(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NH(C₁₋₇ acyl), phenyl,
O-(CH₂)_o-phenyl,

wherein the phenyl ring of said phenyl and O-(CH₂)_o-phenyl
radicals may be mono-, di-, or trisubstituted with F, Cl,
5 Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁₋₆ alkyl), C₁₋₆ alkyl,
NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, SO₂-CH₃, COOH, COO-(C₁₋₆
alkyl) or CONH₂ and wherein o is as hereinabove defined;

B is C₀₋₁₅ alkanediyl,

wherein one or more carbon atoms in said C₀₋₁₅ alkanediyl
10 radical are, independently of one another, optionally
replaced by -O-, -(C=O)-, -CH=CH-, -C≡C-, -S-, -CH(OH)-,
-CHF-, -CF₂-, -(S=O)-, -(SO₂)-, -N(C₁₋₆ alkyl)-, -N(C₁₋₆
alkyl-phenyl)- or -NH-;

n is 0, 1, 2, 3 or 4;

15 Cyc1 is a 3-, 4-, 5-, 6-, or 7-membered saturated,
partially saturated or unsaturated ring, wherein one carbon
atom of said ring may be replaced by O, N or S;

R7, R8, R9 R7, R8, and R9 are each independently hydrogen,
F, Cl, Br, I, OH, CF₃, NO₂, CN, COOH, COO(C₁₋₆ alkyl), CO(C<sub>1-
20 4</sub> alkyl), CONH₂, CONH(C₁₋₆ alkyl), CON(C₁₋₆ alkyl)₂, C₁₋₆ alkyl,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₈ alkoxy, HO-(C₁₋₆ alkyl), (C₁₋₆
alkyl)-O-(C₁₋₆ alkyl),

wherein said COO(C₁₋₆ alkyl), CO(C₁₋₄ alkyl), CONH(C₁₋₆
alkyl), CON(C₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆
25 alkynyl, C₁₋₈ alkoxy, HO-(C₁₋₆ alkyl) and (C₁₋₆ alkyl)-O-(C<sub>1-
6</sub> alkyl) radicals are optionally substituted with one or
more fluorine atoms,

SO₂-NH₂, SO₂NH(C₁₋₆ alkyl), SO₂N(C₁₋₆ alkyl)₂, S-(C₁₋₆ alkyl),
S-(CH₂)_o-phenyl, SO-(C₁₋₆ alkyl), SO-(CH₂)_o-phenyl, SO₂-(C₁₋₆
30 alkyl), SO₂-(CH₂)_o-phenyl,

wherein said SO₂NH(C₁₋₆ alkyl), SO₂N(C₁₋₆ alkyl)₂, S-(C₁₋₆
alkyl), SO-(C₁₋₆ alkyl) and SO₂-(C₁₋₆ alkyl) radicals are
optionally substituted with one or more fluorine atoms,
and wherein the phenyl ring of said S-(CH₂)_o-phenyl, SO-
35 (CH₂)_o-phenyl and SO₂-(CH₂)_o-phenyl radicals is optionally
mono- or disubstituted with F, Cl, Br, OH, CF₃, NO₂, CN,

OCF₃, O-(C₁₋₆ alkyl), C₁₋₆ alkyl or NH₂, and wherein o is as hereinabove defined,

NH₂, NH-(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NH(C₁₋₇ acyl), phenyl or O-(CH₂)_o-phenyl,

5 wherein the phenyl ring of said phenyl and O-(CH₂)_o-phenyl radicals is optionally mono-, di-, or trisubstituted with F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, C₁₋₈ alkoxy, C₁₋₆ alkyl, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, SO₂-CH₃, COOH, COO-(C₁₋₆ alkyl) or CONH₂, and wherein o is as hereinabove
10 defined;

or R8 and R9 taken together with the carbon atoms to which they are attached form a 5-, 6- or 7-membered, saturated, partially saturated or unsaturated ring herein referred to as Cyc2,

15 wherein one or two carbon atom(s) in said Cyc2 ring are optionally replaced by N, O or S, and wherein said Cyc2 ring is optionally substituted with C₁₋₆ alkyl, C₂₋₅ alkenyl or C₂₋₅ alkynyl,

wherein said C₁₋₆ alkyl, C₂₋₅ alkenyl and C₂₋₅ alkynyl
20 radicals are optionally substituted with F, Cl, OH, CF₃, NO₂, CN, COO(C₁₋₄ alkyl), CONH₂, CONH(C₁₋₄ alkyl) or OCF₃, and wherein a -CH₂- group contained in said C₁₋₆ alkyl, C₂₋₅ alkenyl and C₂₋₅ alkynyl radicals is optionally replaced by -O-;

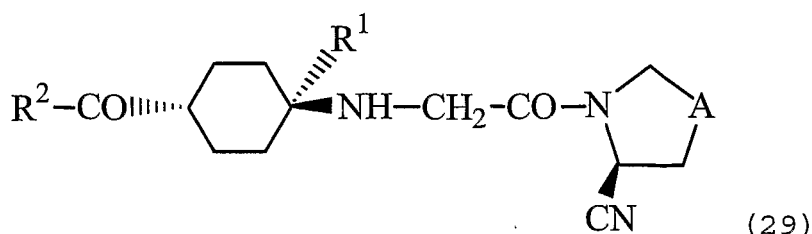
25 and pharmaceutically acceptable salts thereof.

DPP4 inhibitors are well known to those skilled in the art, and examples of DPP4 inhibitors can be found in the following publications:

- 30 (1) TANABE SEIYAKU Co., Ltd.: WO 02/30891 or the corresponding U.S. patent (No. 6,849,622); and WO 02/30890 or the corresponding U.S. patent (No. 7,138,397);
(2) Ferring BV: WO 95/15309, WO 01/40180, WO 01/81304, WO 01/81337, WO 03/000250, and WO 03/035057;
35 (3) Probiodrug: WO 97/40832, EP1082314, WO 99/61431, WO 03/015775;

- (4) Novartis AG: WO 98/19998, WO 00/34241, WO 01/96295, US 6,107,317, US 6,110,949, and US 6,172,081;
- (5) GlaxoSmithKline: WO 03/002531, WO 03/002530, and WO 03/002553;
- 5 (6) Bristol Myers Squibb: WO 01/68603, WO 02/83128, and WO 2005/012249;
- (7) Merck & Co.: WO 02/76450, and WO 03/004498;
- (8) Srryx Inc.: WO 2005/026148, WO 2005/030751, WO 2005/095381, WO 2004/087053, and WO 2004/103993;
- 10 (9) Mitsubishi Pharma Corp.: WO 02/14271, US 7,060,722, US 7,074,794, WO 2003/24942, Japan Patent Publication No. 2002-265439, Japan Patent Publication No. 2005-170792, and WO 2006/088129;
- (10) Taisho Pharma Co., Ltd.: WO 2004/020407;
- 15 (12) Yamanouchi Pharmaceutical Co., Ltd.: WO 2004/009544;
- (13) Kyowa Hakko Kogyo: WO 02/051836;
- (14) Kyorin Seiyaku: WO 2005/075421, WO 2005/077900, and WO 2005/082847;
- (15) Alantos Pharmaceuticals: WO 2006/116157;
- 20 (16) Glenmark Pharmaceuticals: WO 2006/090244, and WO 2005/075426;
- (17) Sanwa Kagaku Kenkyusho: WO 2004/067509; and
- (18) LG lifescience: WO 2005/037828, and WO 2006/104356.

25 In a preferable embodiment of the present invention, DPP4 inhibitors are the aliphatic nitrogen-containing 5-membered ring compounds disclosed in US 6,849,622, which are represented by Formula (29):



30 wherein A represents -CH₂- or -S-, R¹ represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group, and R² represents (1) a

cyclic group which may be substituted, where the cyclic group portion is (i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or (ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or (2) an amino group which may be substituted, or a pharmaceutically acceptable salt thereof.

Examples of the preferable compounds include:

(2S)-2-cyano-1-[trans-4-(dimethylaminocarbonyl)cyclohexylamino]acetylpyrrolidine;

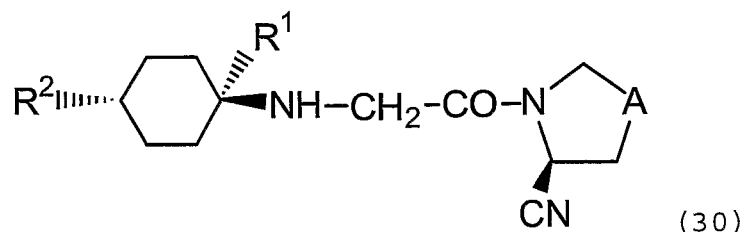
10 (2S)-2-cyano-1-[trans-4-(morpholinocarbonyl)cyclohexylamino]acetylpyrrolidine; and

(2S)-2-cyano-1-[trans-4-(4-acetylpiperazin-1-ylcarbonyl)-cyclohexylamino]acetylpyrrolidine;

and a pharmaceutically acceptable salt (e.g., besylate) of
15 the above compounds.

In another preferable embodiment, DPP4 inhibitors are the aliphatic nitrogen-containing 5-membered ring compounds disclosed in US 7,138,397, which are represented by Formula

20 (30):



wherein A is -CH₂-, R¹ is H, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group, and R² is a piperazinyl group which may be substituted, or a
25 pharmaceutically acceptable salt thereof.

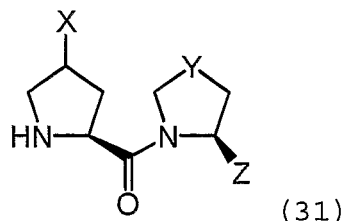
Examples of the preferable compounds include:

(S)-2-cyano-1-[t-4-(4-acetyl-1-piperazinyl)-1-methyl-r-1-cyclohexylamino]acetylpyrrolidine; and

(S)-2-cyano-1-[t-4-(4-propionyl-1-piperazinyl)-1-methyl-r-1-cyclohexylamino]acetylpyrrolidine;

or a pharmaceutically acceptable salt thereof.

In another preferable embodiment, DPP4 inhibitors are the compounds disclosed in US 7,074,794, which are represented by Formula (31):



5 wherein:

- X is $-NR^1R^2$ wherein R^1 and R^2 may be the same or different and each is independently cycloalkylalkyl, arylalkyl, heteroaryl or heteroarylalkyl, or may be bonded to each other to form a heterocycle optionally containing 1 or 2
 10 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having substituents, and the heterocycle optionally being a spiro ring,
- $-NR^3COR^4$ wherein R^3 and R^4 are the same or different and
 15 each is independently a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, arylalkenyl, heteroaryl or heteroarylalkyl,
- $-NR^5CONR^6R^7$ or $-NR^5CH_2CH_2NR^6R^7$ wherein R^5 , R^6 and R^7 are the
 20 same or different and each is independently hydrogen atom, alkyl, acyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, or R^6 and R^7 may be bonded to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle
 25 optionally being condensed with an aromatic ring optionally having substituents,
- $-NR^8SO_2R^9$ wherein R^8 and R^9 are the same or different and each is independently a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or hetero-
 arylalkyl, or
- 30 $-OR^{10}$ or $-OCOR^{11}$ wherein R^{10} and R^{11} are each a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl,

Y is CH₂, CH-OH, S, S=O or SO₂,
Z is a hydrogen atom or cyano, and
of the above-mentioned groups, alkyl, aryl, arylalkyl,
arylalkenyl, heteroaryl, heteroarylalkyl, cycloalkyl,
5 cycloalkylalkyl and heterocycle each optionally have
substituents,
or a pharmaceutically acceptable salt thereof.

In this embodiment, a more preferable compound is 3-
10 [(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-
1-yl]pyrrolidin-2-yl]thiazolidine or a pharmaceutically
acceptable salt thereof (e.g., hydrobromide).

In another preferable embodiment of the present
15 invention, the DPP4 inhibitor is Sitagliptin [developing
code: MK-0431; proprietary name: Januvia; chemical name:
(3R)-3-amino-1-[9-(trifluoromethyl)-1,4,7,8-tetraza-
bicyclo[4.3.0]nona-6,8-dien-4-yl]-4-(2,4,5-trifluoro-
phenyl)butan-1-one], or an equivalent thereof such as a
20 pharmaceutically acceptable salt thereof (e.g., phosphate).

In another preferable embodiment of the present
invention, the DPP4 inhibitor is Vildagliptin [developing
code: LAF237; proprietary name: Galvus; chemical name:
25 (2S)-1-[2-[(3-hydroxy-1-adamantyl)amino]acetyl]pyrrolidine-
2-carbonitrile], or an equivalent thereof such as a
pharmaceutically acceptable salt thereof.

In still another preferable embodiment of the present
30 invention, the DPP4 inhibitor is Saxagliptin (developing
code: BMS-477118; chemical name: (1S,3S,5S)-2-[(2S)-2-
amino-2-(3-hydroxy-1-adamantyl)acetyl]-2-azabicyclo[3.1.0]-
hexane-3-carbonitrile), or an equivalent thereof such as a
pharmaceutically acceptable salt thereof.

35

In still another preferable embodiment of the present

invention, the DPP4 inhibitor is Alogliptin (developing
code: SYR-322; chemical name: 6-[(3R)-3-aminopiperidin-1-
yl]-1-(2-cyanobenzyl)-3-methylpyrimidin-2,4(1H,3H)-dione),
or an equivalent thereof such as a pharmaceutically
5 acceptable salt thereof (e.g., benzoate).

In an embodiment of the present invention, the DPP4
inhibitor is L-threo-isoleucyl pyrrolidide, L-allo-iso-
leucyl thiazolidide, or L-allo-isoleucyl pyrrolidide, or a
10 pharmaceutically acceptable salt thereof.

As mentioned above, the present invention relates to
a method for treating or preventing a disease which is
associated with plasma active GLP-1 level comprising
15 administering to a patient in need thereof a therapeutical-
ly effective amount of an SGLT inhibitor and a DPP4
inhibitor in combination.

In an embodiment of the present invention, the SGLT
20 inhibitor and the DPP4 inhibitor are administered in
amounts sufficient to lower a blood glucose level in the
patient.

In another aspect, the present invention relates to a
25 method for increasing plasma active GLP-1 level comprising
administering to a patient a therapeutically effective
amount of an SGLT inhibitor and a DPP4 inhibitor in
combination.

30 In an embodiment of the present invention, the SGLT
inhibitor and the DPP4 inhibitor are administered in
amounts sufficient to increase plasma active GLP-1 level in
the patient.

35 A combination therapy of the present invention is
useful in treating or preventing a disease which is

associated with plasma active GLP-1 level in a mammal such as a human.

In another aspect, the present invention relates to a
5 pharmaceutical composition comprising an SGLT inhibitor, a
DPP4 inhibitor and a pharmaceutically acceptable carrier or
diluent.

In an embodiment of the present invention, the
10 pharmaceutical composition of the present invention can be
used as an agent to lower a blood glucose level in a
patient.

In an embodiment of the present invention, the
15 pharmaceutical composition of the present invention can be
used as an agent to increase plasma active GLP-1 level in a
patient.

In an embodiment of the present invention, the
20 pharmaceutical composition of the present invention can be
used as an agent for treatment or prevention of a disease
which is associated with plasma active GLP-1 level.

Examples of a disease which is associated with plasma
25 active GLP-1 level include diabetes, a condition related to
diabetes, obesity, myocardial infarction, stroke, learning
or memory impairment, and a neurodegenerative disorder.
Examples of a condition related to diabetes include hyper-
glycemia, impaired glucose tolerance, impaired fasting
30 glucose, insulin resistance, pancreatic β -cell insuffici-
ency, enteroendocrine cell insufficiency, glucosuria,
metabolic acidosis, cataracts, diabetic nephropathy,
diabetic neuropathy, diabetic retinopathy, diabetic
coronary artery disease, diabetic cerebrovascular disease,
35 diabetic peripheral vascular disease, metabolic syndrome,
hyperlipidemia, atherosclerosis, hypertension, and obesity.

Examples of a neurodegenerative disorder include excitotoxic brain damage caused by severe epileptic seizures, Alzheimer's disease, Parkinson's disease, Huntington's disease, prion-associated disease, motor-neuron disease, 5 traumatic brain injury, spinal cord injury, and peripheral neuropathy. Diabetes includes Type 1 or Type 2 diabetes.

The SGLT inhibitors and the DPP4 inhibitors may be administered to a patient by any conventional route of 10 administration, including intravenous, oral, subcutaneous, intramuscular, intradermal and parenteral administration. The SGLT inhibitors and the DPP4 inhibitors can be administered simultaneously, sequentially, or at separate 15 intervals. When simultaneously administered, the SGLT inhibitor and the DPP4 inhibitor can be incorporated into a single pharmaceutical composition or into separate compositions. When separately administered, therapeutically effective amounts of the SGLT inhibitor and the DPP4 20 inhibitor can be administered on a different schedule. Each composition may be formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated elixirs or solutions; and as sustained relief dosage forms and the like. The SGLT inhibitor and the DPP4 inhibitor may be administered via different routes.

25

The SGLT inhibitor and the DPP4 inhibitor are provided in amounts to give a synergistic effect in increasing plasma active GLP-1 level in a patient. Optimal dose of the SGLT inhibitor and the DPP4 inhibitor will vary with 30 patient's age, weight, sex, the particular compound used, the route of administration, and severity of the condition.

In another aspect, the present invention relates to a pharmaceutical composition comprising an SGLT inhibitor and 35 DPP4 inhibitor, together with at least one pharmaceutically acceptable carrier or excipient.

In another aspect, the present invention relates to the use of an SGLT inhibitor and a DPP4 inhibitor for the manufacture of a medicament for the treatment or prevention of a disease associated with plasma active GLP-1 level.

5

In another aspect, the present invention relates to the use of an SGLT inhibitor and a DPP4 inhibitor for the manufacture of a medicament for the treatment or prevention of diabetes.

10

In another aspect, the present invention relates to a product comprising an SGLT inhibitor and DPP4 inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of a disease associated with plasma active GLP-1 level.

15

In another aspect, the present invention relates to a product comprising a SGLT inhibitor and a DPP4 inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of diabetes.

20

The pharmaceutical composition of the present invention is preferably in unit dosage forms such as tablets, capsules, powders, granules, solutions, suspen-
sions, syrups, aerosol, and suppositories.

25

The pharmaceutical composition can be formulated with suitable pharmaceutically acceptable carriers and diluents. Suitable pharmaceutically acceptable carriers and diluents are available to those skilled in the art [see, e.g., Remington: The Science and Practice of Pharmacy, (Gennaro et al., eds.), 20th Edition, 2000]. Examples of the suitable carriers and diluents can include stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, magnesium carbonate, talc, gelatin, tragacanth, dextran sulfate sodium, sodium

30

35

carboxymethylcellulose, methylcellulose, sodium alginate, pectin, dextrin, mannitol, sorbitol, lactose, sucrose, starch, cocoa butter, polyvinyl-pyrrolidone, polyvinyl alcohol, polyethylene glycols, propylene glycol, ethanol, 5 corn oil, cottonseed oil, coconut oil, peanut oil, sesame oil, benzyl alcohol, and other pharmaceutically acceptable materials.

Pharmaceutical compositions may be prepared by 10 methods well known to those skilled in the art, e.g., by means of conventional mixing, dissolving, granulation, levigation, emulsifying, encapsulation, entrapping, lyophilization or spray drying.

15 In a preferable embodiment of the present invention, the SGLT inhibitor is a compound of Formula (23) or a pharmaceutically acceptable salt thereof, described above.

In another preferable embodiment of the present invention, the SGLT inhibitor is a compound of Formula (24) 20 or a pharmaceutically acceptable salt thereof, described above.

In another preferable embodiment of the present invention, the SGLT inhibitor is a compound of Formula (25) or a pharmaceutically acceptable salt thereof, described 25 above.

In another preferable embodiment of the present invention, the SGLT inhibitor is a compound of Formula (26) or a pharmaceutically acceptable salt thereof, described above.

30 In a more preferable embodiment of the present invention, the SGLT inhibitor is Sergliflozin, Remogliflozin or Dapagliflozin, or a pharmaceutically acceptable salt thereof.

35 In a preferable embodiment of the present invention, the DPP4 inhibitor is a compound of Formula (29) or a

pharmaceutically acceptable salt thereof, described above.

In another preferable embodiment of the present invention, the DPP4 inhibitor is a compound of Formula (30) or a pharmaceutically acceptable salt thereof, described above.

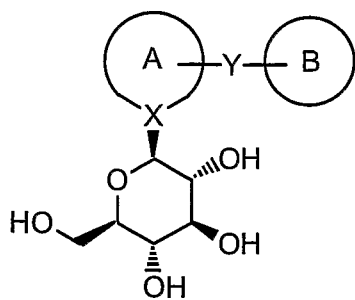
In another preferable embodiment of the present invention, the DPP4 inhibitor is a compound of Formula (31) or a pharmaceutically acceptable salt thereof, described above.

In another preferable embodiment of the present invention, the DPP4 inhibitor is Sitagliptin, Vildagliptin, Saxagliptin or Alogliptin, or a pharmaceutically acceptable salt thereof.

In a more preferable embodiment of the invention, the SGLT inhibitor is Sergliflozin, Remogliflozin or Dapagliflozin, or a pharmaceutically acceptable salt thereof, and the DPP4 inhibitor is Sitagliptin, Vildagliptin, Saxagliptin or Alogliptin, or a pharmaceutically acceptable salt thereof.

Preferable examples of combination of the SGLT inhibitor and DPP4 inhibitor of the present invention include the following:

(a) The SGLT inhibitor is a compound of Formula (23):

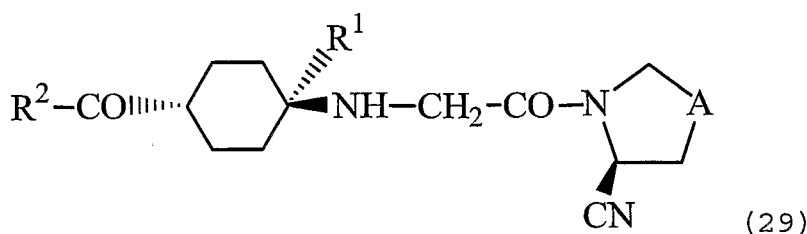


(23)

wherein Ring A and Ring B are one of the followings: (1)

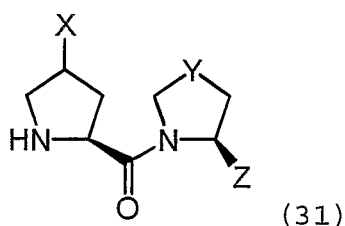
Ring A is optionally substituted unsaturated heteromonocyclic, and Ring B is optionally substituted unsaturated heteromonocyclic, optionally substituted unsaturated fused heterobicyclic, or optionally substituted benzene, (2) Ring
 5 A is optionally substituted benzene, and Ring B is optionally substituted unsaturated heteromonocyclic, or optionally substituted unsaturated fused heterobicyclic wherein Y is linked to the heterocyclic ring of said fused heterobicyclic, or (3) Ring A is optionally substituted
 10 unsaturated fused heterobicyclic, wherein the sugar moiety X-(sugar) and the moiety -Y-(Ring B) are both on the same heterocyclic ring of said fused heterobicyclic, and Ring B is optionally substituted unsaturated heteromonocyclic, optionally substituted unsaturated fused heterobicyclic, or
 15 optionally substituted benzene;
 X is carbon or nitrogen; and
 Y is $-(CH_2)_n-$ (wherein n is 1 or 2); or a pharmaceutically acceptable salt thereof, and

the DPP4 inhibitor is a compound of formula (29):



20
 wherein A represents $-CH_2-$ or $-S-$, R^1 represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group, and R^2 represents (1) a cyclic group which may be substituted, where the cyclic group portion is (i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or (ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or (2) an amino group which may be substituted, or pharmaceutically acceptable salt thereof; or

30 the DPP4 inhibitor is a compound of Formula (31):



wherein:

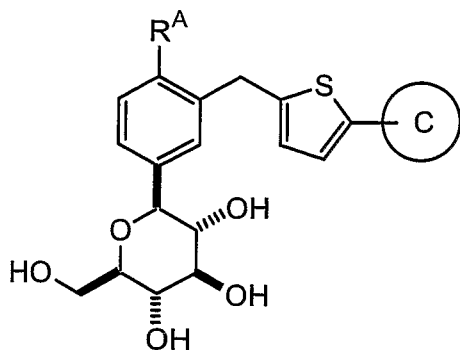
- X is $-NR^1R^2$ wherein R^1 and R^2 may be the same or different and each is independently cycloalkylalkyl, arylalkyl, heteroaryl or heteroarylalkyl, or may be bonded to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having substituents, and the heterocycle optionally being a spiro ring,
- $-NR^3COR^4$ wherein R^3 and R^4 are the same or different and each is independently a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, arylalkenyl, heteroaryl or heteroarylalkyl,
- $-NR^5CONR^6R^7$ or $-NR^5CH_2CH_2NR^6R^7$ wherein R^5 , R^6 and R^7 are the same or different and each is independently hydrogen atom, alkyl, acyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, or R^6 and R^7 may be bonded to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having substituents,
- $-NR^8SO_2R^9$ wherein R^8 and R^9 are the same or different and each is independently a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, or
- $-OR^{10}$ or $-OCOR^{11}$ wherein R^{10} and R^{11} are each a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl,
- Y is CH_2 , $CH-OH$, S, $S=O$ or SO_2 ,
- Z is a hydrogen atom or cyano, and
- of the above-mentioned groups, alkyl, aryl, arylalkyl,

arylalkenyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl and heterocycle each optionally have substituents,

or a pharmaceutically acceptable salt thereof; or

5 the DPP4 inhibitor is Sitagliptin or a pharmaceutically acceptable salt thereof;

(b) The SGLT inhibitor is a compound of Formula (24):



(24)

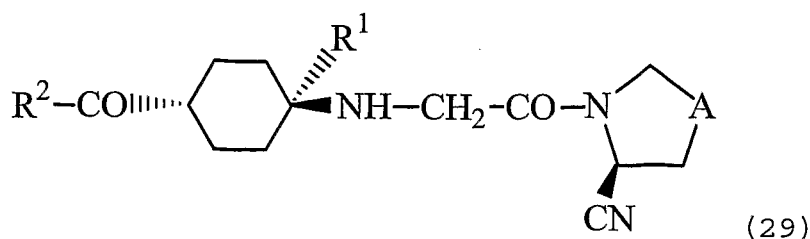
wherein R^A is a halogen atom, or a lower alkyl group;

10 Ring C is a phenyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower
 15 alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-

20 lower alkoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group;

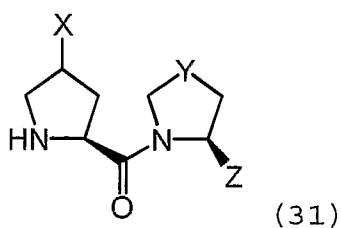
or a pharmaceutically acceptable salt thereof, or a prodrug thereof, and

25 the DPP4 inhibitor is a compound of formula (29):



wherein A represents $-\text{CH}_2-$ or $-\text{S}-$, R^1 represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group, and R^2 represents (1) a
 5 cyclic group which may be substituted, where the cyclic group portion is (i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or (ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or (2) an amino group which may be substituted, or a pharmaceutically acceptable salt thereof; or
 10 thereof; or

the DPP4 inhibitor is a compound of Formula (31):



wherein:

X is $-\text{NR}^1\text{R}^2$ wherein R^1 and R^2 may be the same or different
 15 and each is independently cycloalkylalkyl, arylalkyl, heteroaryl or heteroarylalkyl, or may be bonded to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having
 20 substituents, and the heterocycle optionally being a spiro ring,
 $-\text{NR}^3\text{COR}^4$ wherein R^3 and R^4 are the same or different and each is independently a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, arylalkenyl, heteroaryl
 25 or heteroarylalkyl,
 $-\text{NR}^5\text{CONR}^6\text{R}^7$ or $-\text{NR}^5\text{CH}_2\text{CH}_2\text{NR}^6\text{R}^7$ wherein R^5 , R^6 and R^7 are the same or different and each is independently hydrogen atom, alkyl, acyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl,

heteroaryl or heteroarylalkyl, or R⁶ and R⁷ may be bonded to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having substituents,

-NR⁸SO₂R⁹ wherein R⁸ and R⁹ are the same or different and each is independently a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, or

-OR¹⁰ or -OCOR¹¹ wherein R¹⁰ and R¹¹ are each a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl,

Y is CH₂, CH-OH, S, S=O or SO₂,

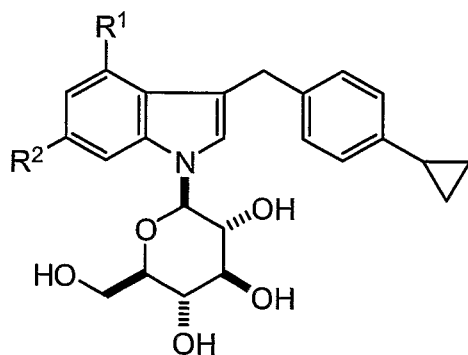
Z is a hydrogen atom or cyano, and

of the above-mentioned groups, alkyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl and heterocycle each optionally have substituents,

or a pharmaceutically acceptable salt thereof; or

the DPP4 inhibitor is Sitagliptin or a pharmaceutically acceptable salt thereof;

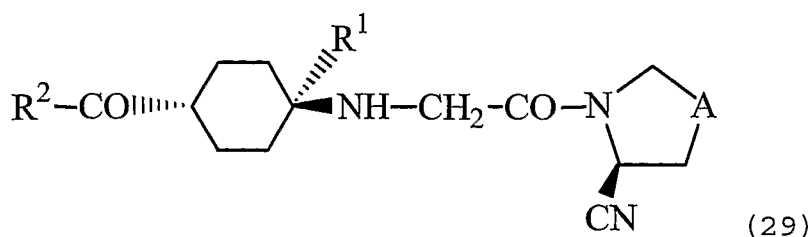
(c) the SGLT inhibitor is a compound of Formula (26):



(26)

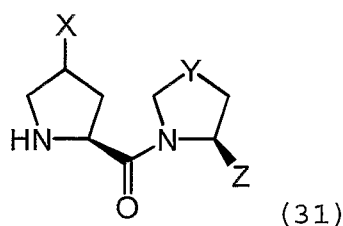
wherein R¹ is fluorine, or chlorine, and R² is hydrogen, or fluorine, or a pharmaceutically acceptable salt thereof; and

the DPP4 inhibitor is a compound of formula (29):



wherein A represents -CH₂- or -S-, R¹ represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group, and R² represents (1) a
 5 cyclic group which may be substituted, where the cyclic group portion is (i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or (ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or (2) an amino group which may be substituted, or a pharmaceutically acceptable salt thereof; or

the DPP4 inhibitor is a compound of Formula (31):



wherein:

X is -NR¹R² wherein R¹ and R² may be the same or different
 15 and each is independently cycloalkylalkyl, arylalkyl, heteroaryl or heteroarylalkyl, or may be bonded to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having
 20 substituents, and the heterocycle optionally being a spiro ring,

-NR³COR⁴ wherein R³ and R⁴ are the same or different and each is independently a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, arylalkenyl, heteroaryl
 25 or heteroarylalkyl,

-NR⁵CONR⁶R⁷ or -NR⁵CH₂CH₂NR⁶R⁷ wherein R⁵, R⁶ and R⁷ are the same or different and each is independently hydrogen atom, alkyl, acyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl,

heteroaryl or heteroarylalkyl, or R⁶ and R⁷ may be bonded to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having substituents,

-NR⁸SO₂R⁹ wherein R⁸ and R⁹ are the same or different and each is independently a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, or

-OR¹⁰ or -OCOR¹¹ wherein R¹⁰ and R¹¹ are each a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl,

Y is CH₂, CH-OH, S, S=O or SO₂,

Z is a hydrogen atom or cyano, and

of the above-mentioned groups, alkyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl and heterocycle each optionally have substituents,

or a pharmaceutically acceptable salt thereof; or

the DPP4 inhibitor is Sitagliptin or a pharmaceutically acceptable salt thereof; and

(d) the SGLT inhibitor is selected from:

(i) 1-(β-D-Glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene or a pharmaceutically acceptable salt thereof;

(ii) 3-(5-(4-Fluorophenyl)-2-thienylmethyl)-1-(β-D-glucopyranosyl)-4-methylbenzene or a pharmaceutically acceptable salt thereof;

(iii) 1-(β-D-Glucopyranosyl)-4-chloro-3-[5-(6-fluoro-3-pyridyl)-2-thienylmethyl]benzene or a pharmaceutically acceptable salt thereof;

(iv) 3-(4-Cyclopropylphenylmethyl)-4-fluoro-1-(β-D-glucopyranosyl)indole or a pharmaceutically acceptable salt thereof; and

(v) 3-(4-Cyclopropylphenylmethyl)-4,6-difluoro-1-(β-D-glucopyranosyl)indole or a pharmaceutically acceptable salt

thereof; and

the DPP4 inhibitor is selected from:

(i) 3-[(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)-piperazin-1-yl]pyrrolidin-2-ylcarbonyl]thiazolidine or a
5 pharmaceutically acceptable salt thereof (e.g., hydro-
bromide);

(ii) Sitagliptin (i.e., (3R)-3-amino-1-[3-(trifluoro-
methyl)-5,6,7,8-tetrahydro-5H-[1,2,4]triazolo[4,3-a]pyra-
zin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one) or a
10 pharmaceutically acceptable salt thereof (e.g., phosphate);
and

(iii) (2S)-2-cyano-1-[trans-4-(dimethylaminocarbonyl)-
cyclohexylamino]acetylpyrrolidine or a pharmaceutically
acceptable salt thereof (e.g., besylate).

15

When the SGLT inhibitor is to be administered orally
or parenterally, the dose can typically be selected from a
range of about 0.01 to 100 mg/kg/day, preferably about 0.01
to 30 mg/kg/day. When the SGLT inhibitor is to be
20 administered orally, the dose can typically be selected
from a range of about 0.03 to 100 mg/kg/day, preferably
about 0.03 to 30 mg/kg/day, more preferably about 0.03 to
10 mg/kg/day. When the SGLT inhibitor is to be admini-
stered parenterally, the dose can typically be selected
25 from a range of about 0.01 to 30 mg/kg/day, preferably
about 0.01 to 10 mg/kg/day, more preferably about 0.01 to 3
mg/kg/day.

When the DPP4 inhibitor is to be administered orally
30 or parenterally, the dose can typically be selected from a
range of about 0.01 to 30 mg/kg/day, preferably about 0.01
to 10 mg/kg/day. When the DPP4 inhibitor is to be admini-
stered orally, the dose can typically be selected from a
range of about 0.03 to 30 mg/kg/day, preferably about 0.03
35 to 10 mg/kg/day, more preferably about 0.03 to 3 mg/kg/day.
When the DPP4 inhibitor is to be administered parenterally,

the dose can typically be selected from a range of about 0.01 to 10 mg/kg/day, preferably about 0.01 to 3 mg/kg/day, more preferably about 0.01 to 1 mg/kg/day.

5 The dose ratio between the respective inhibitors can be selected appropriately, based on patient's age, weight, sex, severity of conditions, and route of administration. For example, the weight:weight dose ratio between the DPP4 inhibitor and the SGLT inhibitor (DPP4 inhibitor : SGLT
10 inhibitor) may typically fall within a range of 1:0.01 to 1:600, preferably 1:0.1 to 1:300, more preferably 1:0.5 to 1:30.

 According to the present invention, both the SGLT
15 inhibitor and the DPP4 inhibitor can be administered once or several times at the daily dose described above.

EXAMPLES

20 Example 1:

Effects of the SGLT inhibitor on plasma active GLP-1 level in glucose-loaded DPP4-deficient rats

(a) Animals:

25 DPP4-deficient male Fisher rats (purchased from Charles River Japan, Inc.)

(b) Methods:

(b-1) Preparation and Administration of Test Compound

30 The test compound was suspended in a solution of 0.5% carboxymethyl cellulose containing 0.2% Tween 80 at the doses indicated in Table 1, and administered to the test group orally at a volume of 5 mL/kg. The vehicle control group was orally administered a solution of 0.5% carboxy-
35 methyl cellulose containing 0.2% Tween 80 at a volume of 5 mL/kg. Just after the administration of the compound or

vehicle, a glucose solution (2 g/kg/5 ml) was given orally.

(b-2) Procedure of Blood Collection and Determination of Plasma Active GLP-1 Level

5 Blood was collected from the caudal vein of an unanesthetized rat just before and 0.5, 1, and 3 hours after glucose loading. Plasma active GLP-1 level was determined by using RAT ENDOCRINE LINCOplex KIT (LINCO Research).

10

(b-3) Test Compound

The following compound was used:

Compound A:

15 1-(β -D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene (see: United States Patent Application Publication No. 2005/0233988).

(c) Results:

The results are shown in Table 1:

20

Table 1

Test Compound	Dose (mg/kg)	GLP-1 concentration at each time point (hr) after oral administration (pM)			
		0	0.5	1	3
control		5.8 \pm 1.1	10.9 \pm 1.6	5.3 \pm 1.8	7.6 \pm 1.9
Compound A	10	6.2 \pm 1.3	24.5 \pm 4.7*	31.3 \pm 7.0**	21.9 \pm 2.4**
Compound A	30	5.3 \pm 0.7	24.9 \pm 3.8**	34.1 \pm 5.7**	27.1 \pm 2.1**

The results are expressed as means \pm SEM (n=6).

25

Statistical differences between groups were assessed by Dunnett's method. *; $P < 0.05$, **; $P < 0.01$ vs. control group.

As shown in the above table 1, Compound A markedly

increased plasma active GLP-1 level in DPP4-deficient rats. This result suggests that the augmentation of plasma active GLP-1 by compound A is DPP4-independent. The most likely explanation for the finding is that Compound A increases
5 the secretion of GLP-1.

Example 2:

Synergistic effect of the SGLT inhibitor and the DPP4 inhibitor on plasma active GLP-1 level in glucose-loaded
10 normal rats

(a) Animals:

DPP4-positive male Fisher rats (purchased from Japan SLC, Inc.)
15

(b) Methods:

(b-1) Preparation and Administration of Test Compounds

Each test compound was suspended in a solution of 0.5% carboxymethyl cellulose containing 0.2% Tween 80 at the doses indicated in Table 2, and administered to the test group orally at a volume of 5 mL/kg. The vehicle control group was orally administered a solution of 0.5% carboxymethyl cellulose containing 0.2% Tween 80 at a volume of 5 mL/kg. Just after the administration of the
25 compound or vehicle, a glucose solution (2 g/kg/5 mL) was given orally.

(b-2) Procedure of Blood Collection and Determination of Plasma Active GLP-1 Level

Blood was collected from the caudal vein of an unanesthetized rat just before and 0.2, 0.5, 1, and 2 hours after glucose loading. Plasma active GLP-1 level was determined by using RAT ENDOCRINE LINCoplex KIT (LINCO Research).
30

35

(b-3) Test Compounds

The following compounds were used:

Compound A:

1- (β -D-Glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene; and

5 Compound B:

(2S)-2-Cyano-1-[trans-4-(morpholinocarbonyl)cyclohexylamino]acetylpyrrolidine (see: United States Patent No. 6,849,622).

10 (c) Results:

The results are shown in Table 2:

Table 2

Test Compound	Dose (mg/kg)	GLP-1 concentration at each time point (hr) after oral administration (pM)				
		0	0.2	0.5	1	2
Control		6.7 \pm 0.3	5.9 \pm 0.6	7.3 \pm 0.3	6.8 \pm 0.5	6.6 \pm 0.4
Compound A	10	7.7 \pm 0.4	7.9 \pm 0.2	10.2 \pm 1.0	9.5 \pm 0.6	9.6 \pm 0.8
Compound A	30	5.9 \pm 0.3	7.1 \pm 0.3	6.7 \pm 0.4	7.5 \pm 0.9	9.0 \pm 0.9
Compound B	3	7.2 \pm 0.6	9.8 \pm 0.7*	9.4 \pm 0.4	8.3 \pm 0.3	7.9 \pm 0.5
Compound A + Compound B	10 + 3	7.4 \pm 0.3	10.1 \pm 1.2**	13.6 \pm 1.0**	12.6 \pm 1.1**	16.8 \pm 3.5**
Compound A + Compound B	30 + 3	6.4 \pm 0.3	10.4 \pm 1.3**	14.0 \pm 1.6**	14.4 \pm 1.4**	21.8 \pm 3.1**

15

The results are expressed as means \pm SEM (n=6).

Statistical differences between groups were assessed by Dunnett's method. *; P<0.05, **; P<0.01 vs. control group.

20

As shown in Table 2, when the SGLT inhibitor was given separately, there was no increase in the active GLP-1 levels. The DPP4 inhibitor treatment alone increased in

plasma active GLP-1 only at 0.2 hr. On the other hand, the combination treatment of Compound A and Compound B produced marked and prolonged increase of plasma active GLP-1 level in DPP4-positive rats.

5

Example 3:

Effects of the SGLT inhibitor and the DPP4 inhibitor on plasma active GLP-1 level in glucose-loaded diabetic mice.

10 (a) Animals:

Male BKS.Cg-+ Lepr^{db}/+Lepr^{db}/Jcl mice; an Animal Model of Type 2 Diabetes (Purchased from CLEA Japan, Inc.)

(b) Methods:

15 (b-1) Preparation and Administration of Test Compounds

Each test compound was suspended in a solution of 0.5% carboxymethyl cellulose containing 0.2% Tween 80 at the doses indicated in Table 3, and administered to the test group orally at a volume of 5 mL/kg. The vehicle control group was orally administered a solution of 0.5% carboxymethyl cellulose containing 0.2% Tween 80 at a volume of 5 mL/kg. Just after the administration of the compound or vehicle, a glucose solution (2 g/kg/5 mL) was given orally.

25

(b-2) Procedure of Blood Collection and Determination of Plasma Active GLP-1 Level

Blood was collected from the caudal vein of an unanesthetized mice just before and 0.5, 1, and 2 hours after glucose loading. Plasma active GLP-1 level was determined by using RAT ENDOCRINE LINCOplex KIT (LINCO Research).

30

(b-3) Test Compounds

35 The following compounds were used:

Compound A:

1- (β -D-Glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene; and

Compound B:

(2S)-2-Cyano-1-[trans-4-(morpholinocarbonyl)cyclohexylamino]acetylpyrrolidine.

(c) Results:

The results are shown in Table 3.

10 Table 3

Test Compound	Dose (mg/kg)	GLP-1 concentration at each time point (hr) after oral administration (pM)			
		0	0.5	1	2
Control		37.2 \pm 11.6	37.0 \pm 11.7	33.9 \pm 11.1	40.8 \pm 13.5
Compound A	10	20.3 \pm 9.6	42.6 \pm 13.4	49.4 \pm 12.0	30.9 \pm 8.2
Compound B	3	18.4 \pm 5.1	30.0 \pm 5.5	46.5 \pm 10.1	25.0 \pm 4.1
Compound A + Compound B	10 + 3	22.8 \pm 3.5	109.2 \pm 20.4**	82.4 \pm 11.6*	55.2 \pm 4.6

The results are expressed as means \pm SEM (n=8).

15 Statistical differences between groups were assessed by Dunnett's method. *; P<0.05, **; P<0.01 vs. control group.

20 As shown in table 3, not only in normal animal but also in animal model of Type 2 diabetes, the combination of Compound A and Compound B significantly increased plasma active GLP-1 level.

Example 4:

25 Synergistic effect of the SGLT inhibitor and the DPP4 inhibitor on plasma active GLP-1 level in glucose-loaded normal rats

(a) Animals:

DPP4-positive male Fisher rats (purchased from Japan SLC, Inc.)

5 (b) Methods:

(b-1) Preparation and Administration of Test Compounds

Each test compound was suspended in a solution of 0.5% carboxymethyl cellulose containing 0.2% Tween 80 at the doses indicated in Table 4, 5 or 6, and administered to
10 the test group orally at a volume of 5 mL/kg. The vehicle control group was orally administered a solution of 0.5% carboxymethyl cellulose containing 0.2% Tween 80 at a volume of 5 mL/kg. Just after the administration of the compound or vehicle, a glucose solution (2 g/kg/5 mL) was
15 given orally.

(b-2) Procedure of Blood Collection and Determination of Plasma Active GLP-1 Level

Blood was collected from the caudal vein of an
20 unanesthetized rat at appropriate time described in the table. Plasma active GLP-1 level was determined by using RAT ENDOCRINE LINCoplex KIT (LINCO Research).

(b-3) Test Compounds

25 The following compounds were used for the tests:

Compound C:

3- (5- (4-Fluorophenyl) -2-thienylmethyl) -1- (β -D-glucopyranosyl) -4-methylbenzene (see: United States Patent Application Publication No. 2005/0233988);

30 Compound D:

1- (β -D-Glucopyranosyl) -4-chloro-3- [5- (6-fluoro-3-pyridyl) -2-thienylmethyl]benzene (see: United States Patent Application Publication No. 2005/0233988);

Compound E:

35 3- (4-Cyclopropylphenylmethyl) -4-fluoro-1- (β -D-glucopyranosyl)indole (see: WO 2008/013322 pamphlet);

Compound F:

3-(4-Cyclopropylphenylmethyl)-4,6-difluoro-1-(β-D-glucopyranosyl)indole (see: WO 2008/013322 pamphlet);

Compound G:

5 3-[(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl]thiazolidine hydrobromide (see United States Patent No. 7,074,794);

Compound H:

Sitagliptin phosphate; and

10 Compound I:

(2S)-2-cyano-1-[trans-4-(dimethylaminocarbonyl)cyclohexylamino]acetylpyrrolidine besylate (see: United States Patent No. 6,849,622).

15 (c) Results:

The results are shown in Tables 4-6:

Table 4

Test Compound	Dose (mg/kg)	GLP-1 concentration at each time point (hr) after oral administration (pM)				
		0	0.2	0.5	1	2
Control		4.4 ± 1.3	10.1 ± 2.3	6.8 ± 1.9	6.0 ± 0.9	5.4 ± 1.3
Compound G	5	5.4 ± 1.8	23.1 ± 3.8 *	9.3 ± 2.0	6.2 ± 1.5	7.0 ± 1.7
Compound C + Compound G	30 + 5	5.4 ± 1.1	25.8 ± 5.1 **	24.0 ± 3.2 **	22.6 ± 7.2 *	24.3 ± 6.2 **
Compound E + Compound G	30 + 5	9.0 ± 1.4	26.0 ± 4.5 **	28.0 ± 3.6 **	28.6 ± 2.4 **	37.7 ± 4.3 **
Compound D + Compound G	30 + 5	5.2 ± 0.9	22.6 ± 2.6 *	25.7 ± 3.2 **	32.6 ± 3.0 **	31.7 ± 1.4 **

20

The results are expressed as means ± SEM (n = 5 or 6). Statistical differences between groups were assessed by

Dunnett's method. * $p < 0.05$, ** $p < 0.01$ vs. control group.

Table 5

Test Compound	Dose (mg/kg)	GLP-1 concentration at 2 hr after oral administration (pM)
Control		3.8 ± 0.4
Compound H	10	4.1 ± 0.5
Compound C + Compound H	30 + 10	15.9 ± 1.0 **
Compound E + Compound H	30 + 10	19.1 ± 2.0 **
Compound F + Compound H	30 + 10	16.7 ± 1.5 **

5

The results are expressed as means \pm SEM ($n = 6$). Statistical differences between groups were assessed by Dunnett's method. * $p < 0.05$, ** $p < 0.01$ vs. control group.

10

Table 6:

Test Compound	Dose (mg/kg)	GLP-1 concentration at 2 hr after oral administration (pM)
Control		5.5 ± 2.5
Compound I	10	4.0 ± 0.6
Compound C + Compound I	30 + 10	21.4 ± 2.3 **
Compound E + Compound I	30 + 10	26.1 ± 3.1 **

The results are expressed as means \pm SEM ($n = 5$ or 6).

15 Statistical differences between groups were assessed by

Dunnett's method.

* $p < 0.05$, ** $p < 0.01$ vs. control group.

As shown in Tables 4-6, the combination treatment of
5 an SGLT inhibitor and a DPP4 inhibitor produced marked and
prolonged increase of plasma active GLP-1 level in DPP4-
positive rats.

These results suggest that the combination of an SGLT
10 inhibitor and a DPP4 inhibitor provided substantial
elevation of plasma active GLP-1 level.

According to the present invention, a combination of
an SGLT inhibitor and a DPP4 inhibitor can be used to
15 prevent or treat some sort of disease which is associated
with plasma active GLP-1 level with a dose of a DPP4
inhibitor substantially lower than that currently contem-
plated for use in monotherapy for said condition, thereby
reducing the likelihood of unwanted side-effects associated
20 with inhibition of DPP4 activity.

Claims

1. A method for treating or preventing diabetes or a condition related to diabetes comprising administering to a patient in need thereof a therapeutically effective amount of an SGLT inhibitor and a DPP4 inhibitor.
2. A method according to claim 1, wherein the SGLT inhibitor and the DPP4 inhibitor are administered in amounts sufficient to lower a blood glucose level in the patient.
3. A method for preventing or treating a disease which is associated with plasma active GLP-1 level comprising administering to a patient in need thereof a therapeutically effective amount of an SGLT inhibitor and a DPP4 inhibitor.
4. A method according to claim 3, wherein the SGLT inhibitor and the DPP4 inhibitor are administered in amounts sufficient to increase plasma active GLP-1 level in the patient.
5. A method for increasing plasma active GLP-1 level comprising administering to a patient a therapeutically effective amount of an SGLT inhibitor and a DPP4 inhibitor.
6. A method according to claim 1, wherein diabetes is Type 2 diabetes.
7. A method according to claim 3, wherein the disease which is associated with plasma active GLP-1 level is selected from diabetes, a condition related to diabetes, myocardial infarction, learning impairment, memory impairment, stroke and a neurodegenerative disorder.

8. A method according to claim 1 or 7, wherein the condition related to diabetes is selected from hyperglycemia, impaired glucose tolerance, impaired fasting glucose, insulin resistance, pancreatic beta-cell insufficiency, enteroendocrine cell insufficiency, glucosuria, metabolic acidosis, cataracts, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, diabetic coronary artery disease, diabetic cerebrovascular disease, diabetic peripheral vascular disease, metabolic syndrome, hyperlipidemia, atherosclerosis, hypertension, and obesity.

9. A method according to claim 7, wherein the neurodegenerative disorder is selected from excitotoxic brain damage caused by severe epileptic seizures, Alzheimer's disease, Parkinson's disease, Huntington's disease, prion-associated disease, motor-neuron disease, traumatic brain injury, spinal cord injury, and peripheral neuropathy.

10. A pharmaceutical composition comprising an SGLT inhibitor, a DPP4 inhibitor and a pharmaceutically acceptable carrier or diluent, wherein the SGLT inhibitor and the DPP4 inhibitor are in amounts sufficient to increase plasma active GLP-1 level in a patient.

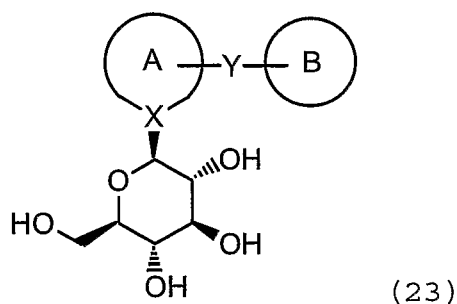
11. A method of preventing or treating diabetes or a condition related thereto comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition as set forth in claim 10.

12. A method of preventing or treating a disease which is associated with plasma active GLP-1 level comprising administering to a patient in need thereof a therapeutically effective amount of the pharmaceutical composition as set forth in claim 10.

13. A method of increasing plasma active GLP-1 level comprising administering to a patient a therapeutically effective amount of the pharmaceutical composition as set forth in claim 10.

5

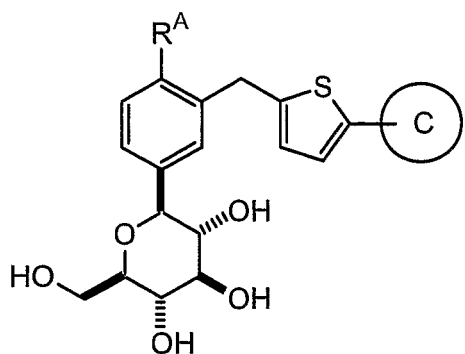
14. The method according to claim 1, wherein the SGLT inhibitor is a compound of Formula (23):



wherein Ring A and Ring B are one of the followings: (1)

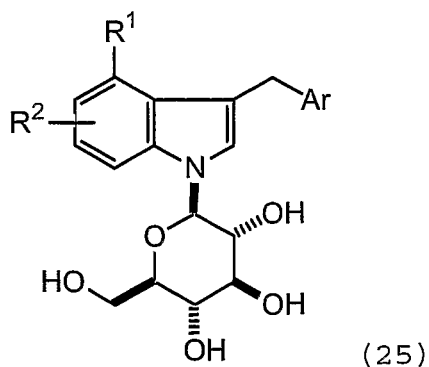
- 10 Ring A is optionally substituted unsaturated heteromonocyclic, and Ring B is optionally substituted unsaturated heteromonocyclic, optionally substituted unsaturated fused heterobicyclic, or optionally substituted benzene, (2) Ring A is optionally substituted benzene, and Ring B is
- 15 optionally substituted unsaturated heteromonocyclic, or optionally substituted unsaturated fused heterobicyclic wherein Y is linked to the heterocyclic ring of said fused heterobicyclic, or (3) Ring A is optionally substituted
- 20 X-(sugar) and the moiety -Y-(Ring B) are both on the same heterocyclic ring of said fused heterobicyclic, and Ring B is optionally substituted unsaturated heteromonocyclic, optionally substituted unsaturated fused heterobicyclic, or optionally substituted benzene;
- 25 X is carbon or nitrogen; and Y is $-(CH_2)_n-$ (wherein n is 1 or 2); or a pharmaceutically acceptable salt thereof.

15. The method according to claim 1, wherein the SGLT
30 inhibitor is a compound of Formula (24):



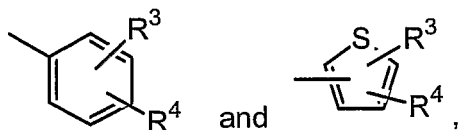
wherein R^A is a halogen atom, or a lower alkyl group;
 Ring C is a phenyl group substituted by 1-3 substituents
 selected from the group consisting of a halogen atom, a
 5 cyano group, a lower alkyl group, a halo-lower alkyl group,
 a lower alkoxy group, a halo-lower alkoxy group, a
 methylenedioxy group, an ethyleneoxy group, a mono- or di-
 lower alkylamino group, a carbamoyl group, and a mono- or
 di-lower alkylcarbamoyl group; or a heterocyclyl group
 10 substituted by 1-3 substituents selected from the group
 consisting of a halogen atom, a cyano group, a lower alkyl
 group, a halo-lower alkyl group, a lower alkoxy group, a
 halo-lower alkoxy group, a mono- or di-lower alkylamino
 group, a carbamoyl group, and a mono- or di-lower
 15 alkylcarbamoyl group;
 or a pharmaceutically acceptable salt thereof.

16. The method according to claim 1, wherein the SGLT
 inhibitor is a compound of Formula (25):



20 wherein R^1 is halogen, or alkyl,
 R^2 is hydrogen, or halogen, and

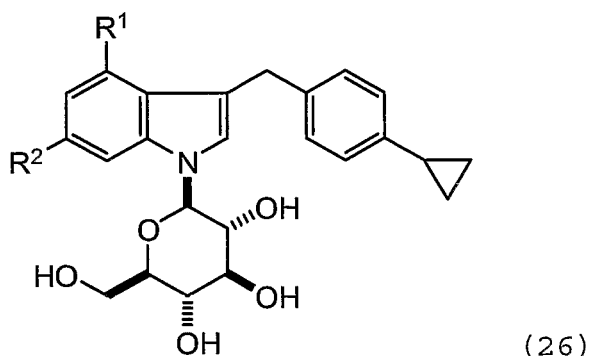
Ar is one of the following groups:



in which R^3 and R^4 are independently hydrogen, halogen, alkyl, cycloalkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, hydroxy, phenyl, halophenyl, cyanophenyl, pyridyl, halopyridyl, thienyl, or halothienyl, or R^3 and R^4 together with carbon atoms to which they are attached form a fused benzene, furan or dihydrofuran ring; or a pharmaceutically acceptable salt thereof.

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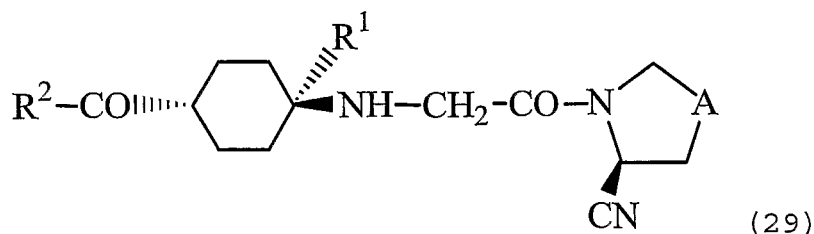
17. The method according to claim 1, wherein the SGLT inhibitor is a compound of Formula (26):



wherein R^1 is fluorine, or chlorine, and R^2 is hydrogen, or fluorine, or a pharmaceutically acceptable salt thereof.

15

18. The method according to claim 1, wherein the DPP4 inhibitor is a compound of Formula (29):

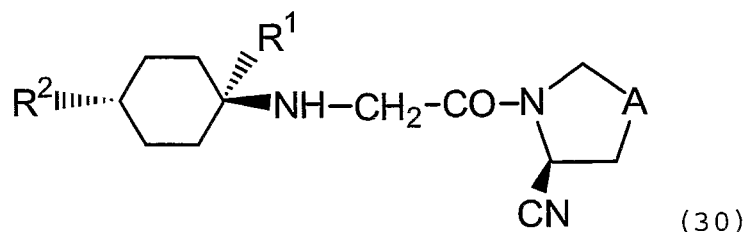


wherein A represents $-CH_2-$ or $-S-$, R^1 represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group, and R^2 represents (1) a cyclic group which may be substituted, where the cyclic

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group portion is (i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or (ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or (2) an amino group which may be substituted, or a pharmaceutically acceptable salt thereof.

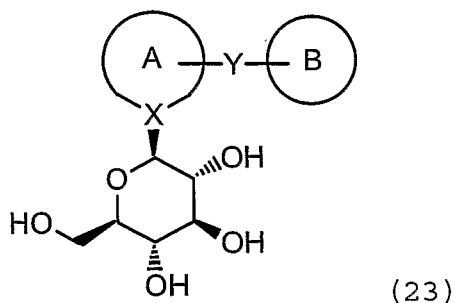
19. The method according to claim 1, wherein the DPP4 inhibitor is a compound of Formula (30):



10 wherein A is $-\text{CH}_2-$, R^1 is H, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group, and R^2 is a piperazinyl group which may be substituted, or a pharmaceutically acceptable salt thereof.

15 20. The method according to claim 1, wherein the SGLT inhibitor is Sergliflozin, Remogliflozin or Dapagliflozin, and the DPP4 inhibitor is Sitagliptin, Vildagliptin, Saxagliptin or Alogliptin.

20 21. The method according to claim 1, wherein the SGLT inhibitor is a compound of Formula (23):



wherein Ring A and Ring B are one of the followings: (1) Ring A is optionally substituted unsaturated hetero-
 25 monocyclic, and Ring B is optionally substituted unsaturated heteromonocyclic, optionally substituted

unsaturated fused heterobicyclic, or optionally substituted benzene, (2) Ring A is optionally substituted benzene, and Ring B is optionally substituted unsaturated heteromono-

5 bicyclic, or optionally substituted unsaturated fused hetero-

said fused heterobicyclic, or (3) Ring A is optionally substituted unsaturated fused heterobicyclic, wherein the sugar moiety X-(sugar) and the moiety -Y-(Ring B) are both on the same heterocyclic ring of said fused heterobicyclic,

10 and Ring B is optionally substituted unsaturated hetero-

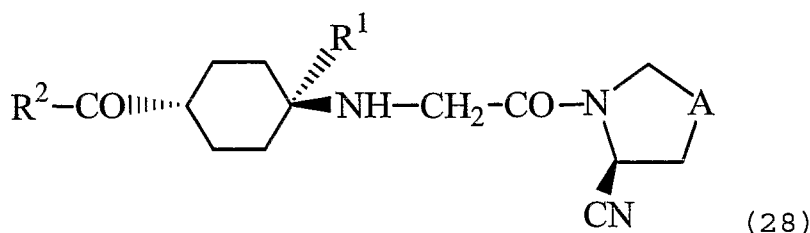
monocyclic, optionally substituted unsaturated fused heterobicyclic, or optionally substituted benzene;

X is carbon or nitrogen; and

Y is $-(\text{CH}_2)_n-$ (wherein n is 1 or 2); or a pharmaceutically

15 acceptable salt thereof; and

the DPP4 inhibitor is a compound of formula (28):



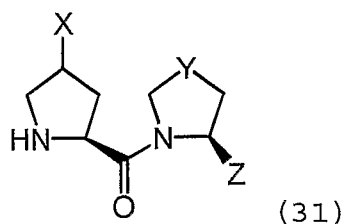
wherein A represents $-\text{CH}_2-$ or $-\text{S}-$, R^1 represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a

20 lower alkoxy lower alkyl group, and R^2 represents (1) a cyclic group which may be substituted, where the cyclic group portion is (i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or (ii) a monocyclic, bicyclic or

tricyclic heterocyclic group, or (2) an amino group which

25 may be substituted, or pharmaceutically acceptable salt thereof; or

a compound of Formula (31):



wherein:

X is $-NR^1R^2$ wherein R^1 and R^2 may be the same or different and each is independently cycloalkylalkyl, arylalkyl, heteroaryl or heteroarylalkyl, or may be bonded to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having substituents, and the heterocycle optionally being a spiro ring,

10 $-NR^3COR^4$ wherein R^3 and R^4 are the same or different and each is independently a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, arylalkenyl, heteroaryl or heteroarylalkyl,

$-NR^5CONR^6R^7$ or $-NR^5CH_2CH_2NR^6R^7$ wherein R^5 , R^6 and R^7 are the same or different and each is independently hydrogen atom, alkyl, acyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, or R^6 and R^7 may be bonded to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having substituents,

20 $-NR^8SO_2R^9$ wherein R^8 and R^9 are the same or different and each is independently a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, or

25 $-OR^{10}$ or $-OCOR^{11}$ wherein R^{10} and R^{11} are each a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl,

Y is CH_2 , $CH-OH$, S, $S=O$ or SO_2 ,

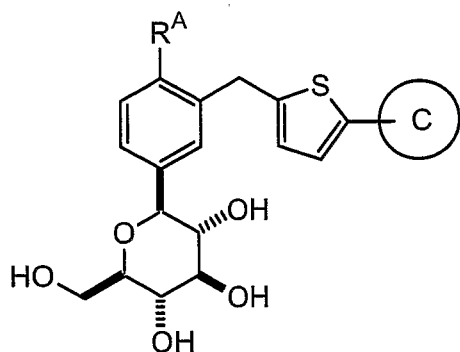
30 Z is a hydrogen atom or cyano, and
of the above-mentioned groups, alkyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl and heterocycle each optionally have substituents,

35 or a pharmaceutically acceptable salt thereof; or

Sitagliptin or a pharmaceutically acceptable salt

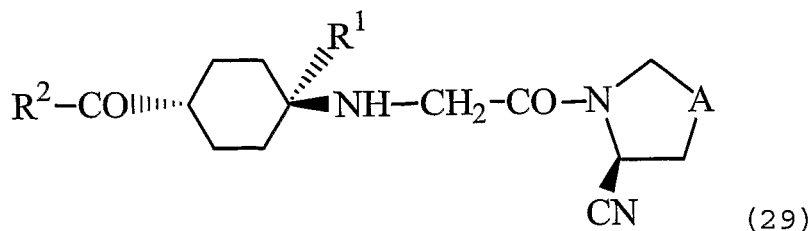
thereof.

22. The method according to claim 1, wherein the SGLT inhibitor is a compound of Formula (24):



wherein R^A is a halogen atom, or a lower alkyl group;
 Ring C is a phenyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group;
 or a pharmaceutically acceptable salt thereof, or a prodrug thereof; and

the DPP4 inhibitor is a compound of formula (29):

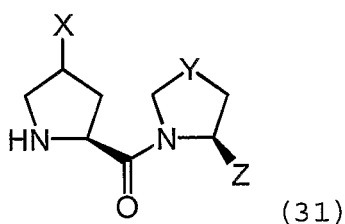


wherein A represents $-CH_2-$ or $-S-$, R^1 represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a

25

lower alkoxy lower alkyl group, and R^2 represents (1) a cyclic group which may be substituted, where the cyclic group portion is (i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or (ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or (2) an amino group which may be substituted, or pharmaceutically acceptable salt thereof; or

a compound of Formula (31):



wherein:

X is $-NR^1R^2$ wherein R^1 and R^2 may be the same or different and each is independently cycloalkylalkyl, arylalkyl, heteroaryl or heteroarylalkyl, or may be bonded to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having substituents, and the heterocycle optionally being a spiro ring,

$-NR^3COR^4$ wherein R^3 and R^4 are the same or different and each is independently a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, arylalkenyl, heteroaryl or heteroarylalkyl,

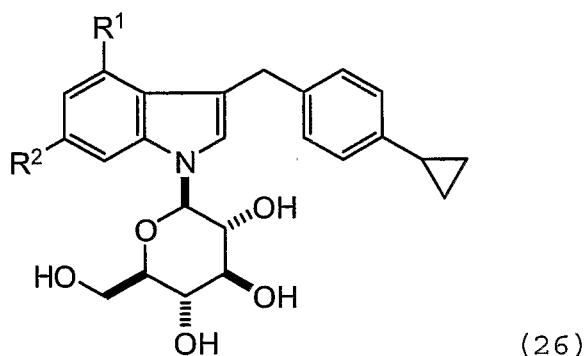
$-NR^5CONR^6R^7$ or $-NR^5CH_2CH_2NR^6R^7$ wherein R^5 , R^6 and R^7 are the same or different and each is independently hydrogen atom, alkyl, acyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, or R^6 and R^7 may be bonded to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having substituents,

$-NR^8SO_2R^9$ wherein R^8 and R^9 are the same or different and each is independently a hydrogen atom, alkyl, cycloalkyl,

cycloalkylalkyl, aryl, arylalkyl, heteroaryl or hetero-
 arylalkyl, or
 -OR¹⁰ or -OCOR¹¹ wherein R¹⁰ and R¹¹ are each a hydrogen atom,
 alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl,
 5 heteroaryl or heteroarylalkyl,
 Y is CH₂, CH-OH, S, S=O or SO₂,
 Z is a hydrogen atom or cyano, and
 of the above-mentioned groups, alkyl, aryl, arylalkyl,
 arylalkenyl, heteroaryl, heteroarylalkyl, cycloalkyl,
 10 cycloalkylalkyl and heterocycle each optionally have
 substituents,
 or a pharmaceutically acceptable salt thereof; or
 Sitagliptin or a pharmaceutically acceptable salt
 thereof.

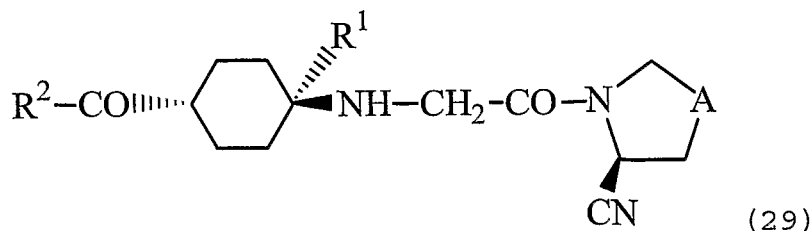
15

23. The method according to claim 1, wherein the SGLT
 inhibitor is a compound of Formula (26):



wherein R¹ is fluorine, or chlorine, and R² is hydrogen, or
 20 fluorine, or a pharmaceutically acceptable salt thereof;
 and

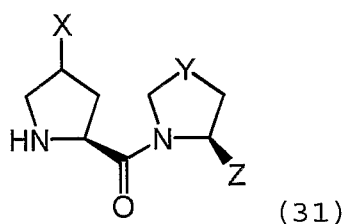
the DPP4 inhibitor is a compound of formula (29):



wherein A represents -CH₂- or -S-, R¹ represents hydrogen
 25 atom, a lower alkyl group, a hydroxy lower alkyl group or a

lower alkoxy lower alkyl group, and R^2 represents (1) a cyclic group which may be substituted, where the cyclic group portion is (i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or (ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or (2) an amino group which may be substituted, or pharmaceutically acceptable salt thereof; or

a compound of Formula (31):



10 wherein:

X is $-NR^1R^2$ wherein R^1 and R^2 may be the same or different and each is independently cycloalkylalkyl, arylalkyl, heteroaryl or heteroarylalkyl, or may be bonded to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having substituents, and the heterocycle optionally being a spiro ring,

20 $-NR^3COR^4$ wherein R^3 and R^4 are the same or different and each is independently a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, arylalkenyl, heteroaryl or heteroarylalkyl,

25 $-NR^5CONR^6R^7$ or $-NR^5CH_2CH_2NR^6R^7$ wherein R^5 , R^6 and R^7 are the same or different and each is independently hydrogen atom, alkyl, acyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, or R^6 and R^7 may be bonded to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having substituents,

30 $-NR^8SO_2R^9$ wherein R^8 and R^9 are the same or different and each is independently a hydrogen atom, alkyl, cycloalkyl,

cycloalkylalkyl, aryl, arylalkyl, heteroaryl or hetero-
arylalkyl, or

-OR¹⁰ or -OCOR¹¹ wherein R¹⁰ and R¹¹ are each a hydrogen atom,
alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl,

5 heteroaryl or heteroarylalkyl,

Y is CH₂, CH-OH, S, S=O or SO₂,

Z is a hydrogen atom or cyano, and

of the above-mentioned groups, alkyl, aryl, arylalkyl,

arylalkenyl, heteroaryl, heteroarylalkyl, cycloalkyl,

10 cycloalkylalkyl and heterocycle each optionally have
substituents,

or a pharmaceutically acceptable salt thereof; or

Sitagliptin or a pharmaceutically acceptable salt
thereof.

15

24. The method according to claim 1, wherein the SGLT
inhibitor is selected from:

1-(β-D-Glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-
2-thienylmethyl]benzene or a pharmaceutically acceptable
20 salt thereof;

3-(5-(4-Fluorophenyl)-2-thienylmethyl)-1-(β-D-glucopyrano-
syl)-4-methylbenzene or a pharmaceutically acceptable salt
thereof;

25 1-(β-D-Glucopyranosyl)-4-chloro-3-[5-(6-fluoro-3-pyridyl)-
2-thienylmethyl]benzene or a pharmaceutically acceptable
salt thereof;

3-(4-Cyclopropylphenylmethyl)-4-fluoro-1-(β-D-glucopyrano-
syl)indole or a pharmaceutically acceptable salt thereof;
and

30 3-(4-Cyclopropylphenylmethyl)-4,6-difluoro-1-(β-D-gluco-
pyranosyl)indole or a pharmaceutically acceptable salt
thereof; and

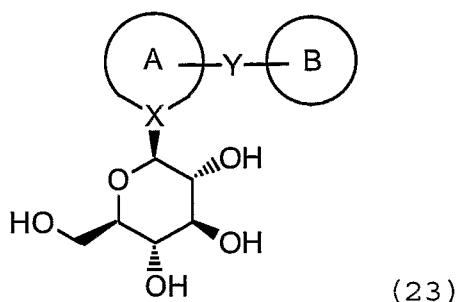
the DPP4 inhibitor is selected from:

35 3-[(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piper-
azin-1-yl]pyrrolidin-2-ylcarbonyl]thiazolidine or a pharma-
ceutically acceptable salt thereof;

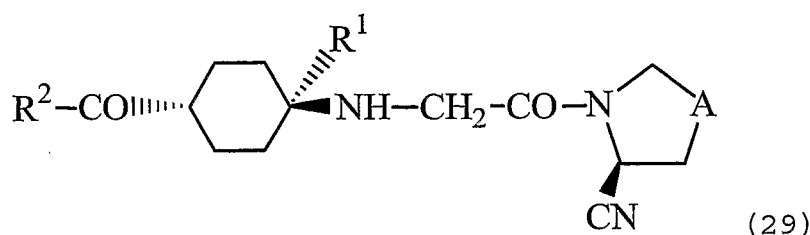
Sitagliptin or a pharmaceutically acceptable salt thereof;
and

(2S)-2-cyano-1-[trans-4-(dimethylaminocarbonyl)cyclohexyl-
amino]acetylpyrrolidine or a pharmaceutically acceptable
5 salt thereof.

25. The pharmaceutical composition according to claim 10,
wherein the SGLT inhibitor is a compound of Formula (23):

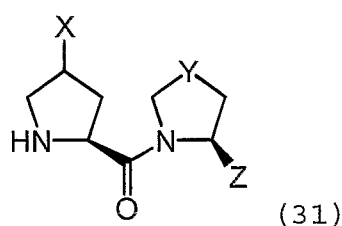


10 wherein Ring A and Ring B are one of the followings: (1)
Ring A is optionally substituted unsaturated heteromono-
cyclic, and Ring B is optionally substituted unsaturated
heteromonocyclic, optionally substituted unsaturated fused
heterobicyclic, or optionally substituted benzene, (2) Ring
15 A is optionally substituted benzene, and Ring B is option-
ally substituted unsaturated heteromonocyclic, or option-
ally substituted unsaturated fused heterobicyclic wherein Y
is linked to the heterocyclic ring of said fused hetero-
bicyclic, or (3) Ring A is optionally substituted
20 unsaturated fused heterobicyclic, wherein the sugar moiety
X-(sugar) and the moiety -Y-(Ring B) are both on the same
heterocyclic ring of said fused heterobicyclic, and Ring B
is optionally substituted unsaturated heteromonocyclic,
optionally substituted unsaturated fused heterobicyclic, or
25 optionally substituted benzene;
X is carbon or nitrogen; and
Y is $-(CH_2)_n-$ (wherein n is 1 or 2); or a pharmaceutically
acceptable salt thereof; and
the DPP4 inhibitor is a compound of formula (29):



wherein A represents $-\text{CH}_2-$ or $-\text{S}-$, R^1 represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group, and R^2 represents (1) a
 5 cyclic group which may be substituted, where the cyclic group portion is (i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or (ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or (2) an amino group which may be substituted, or pharmaceutically acceptable salt
 10 thereof; or

the DPP4 inhibitor is a compound of Formula (31):



wherein:

X is $-\text{NR}^1\text{R}^2$ wherein R^1 and R^2 may be the same or different
 15 and each is independently cycloalkylalkyl, arylalkyl, heteroaryl or heteroarylalkyl, or may be bonded to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having
 20 substituents, and the heterocycle optionally being a spiro ring,
 $-\text{NR}^3\text{COR}^4$ wherein R^3 and R^4 are the same or different and each is independently a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, arylalkenyl, heteroaryl
 25 or heteroarylalkyl,
 $-\text{NR}^5\text{CONR}^6\text{R}^7$ or $-\text{NR}^5\text{CH}_2\text{CH}_2\text{NR}^6\text{R}^7$ wherein R^5 , R^6 and R^7 are the same or different and each is independently hydrogen atom, alkyl, acyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl,

heteroaryl or heteroarylalkyl, or R⁶ and R⁷ may be bonded to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having substituents,

-NR⁸SO₂R⁹ wherein R⁸ and R⁹ are the same or different and each is independently a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroaryl-alkyl, or

10 -OR¹⁰ or -OCOR¹¹ wherein R¹⁰ and R¹¹ are each a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl,

Y is CH₂, CH-OH, S, S=O or SO₂,

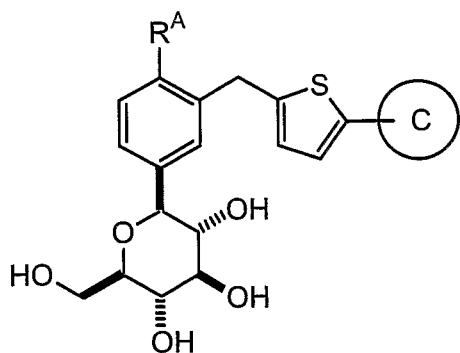
Z is a hydrogen atom or cyano, and

15 of the above-mentioned groups, alkyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl and heterocycle each optionally have substituents,

or a pharmaceutically acceptable salt thereof; or

20 the DPP4 inhibitor is Sitagliptin or a pharmaceutically acceptable salt thereof.

26. The pharmaceutical composition according to claim 10, wherein the SGLT inhibitor is a compound of Formula (24):



25

(24)

wherein R^A is a halogen atom, or a lower alkyl group;
 Ring C is a phenyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group,

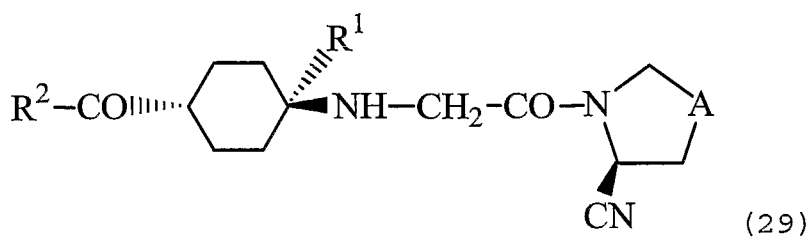
a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group

5 substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkyl-

10 carbamoyl group;

or a pharmaceutically acceptable salt thereof, or a prodrug thereof, and

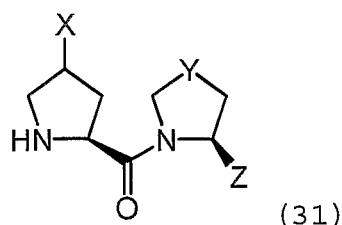
the DPP4 inhibitor is a compound of formula (29):



15 wherein A represents -CH₂- or -S-, R¹ represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group, and R² represents (1) a cyclic group which may be substituted, where the cyclic group portion is (i) a monocyclic, bicyclic or tricyclic

20 hydrocarbon group, or (ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or (2) an amino group which may be substituted, or pharmaceutically acceptable salt thereof; or

the DPP4 inhibitor is a compound of Formula (31):



25

wherein:

X is -NR¹R² wherein R¹ and R² may be the same or different and each is independently cycloalkylalkyl, arylalkyl,

heteroaryl or heteroarylalkyl, or may be bonded to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having
5 substituents, and the heterocycle optionally being a spiro ring,

-NR³COR⁴ wherein R³ and R⁴ are the same or different and each is independently a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, arylalkenyl, heteroaryl
10 or heteroarylalkyl,

-NR⁵CONR⁶R⁷ or -NR⁵CH₂CH₂NR⁶R⁷ wherein R⁵, R⁶ and R⁷ are the same or different and each is independently hydrogen atom, alkyl, acyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, or R⁶ and R⁷ may be bonded
15 to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having substituents,

-NR⁸SO₂R⁹ wherein R⁸ and R⁹ are the same or different and
20 each is independently a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, or

-OR¹⁰ or -OCOR¹¹ wherein R¹⁰ and R¹¹ are each a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl,
25 heteroaryl or heteroarylalkyl,

Y is CH₂, CH-OH, S, S=O or SO₂,

Z is a hydrogen atom or cyano, and

of the above-mentioned groups, alkyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl and heterocycle each optionally have
30 substituents,

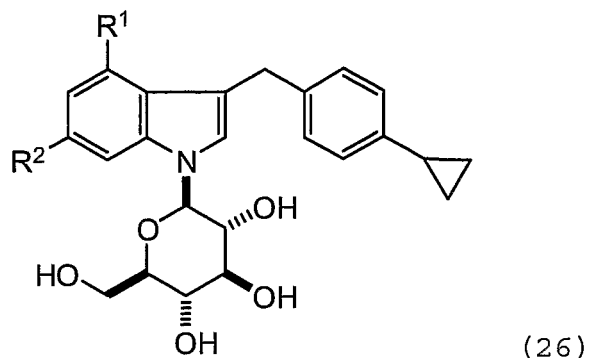
or a pharmaceutically acceptable salt thereof; or

the DPP4 inhibitor is Sitagliptin or a pharmaceutically acceptable salt thereof.

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27. The pharmaceutical composition according to claim 10,

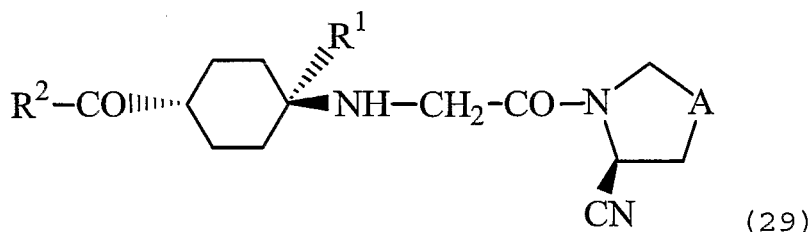
wherein the SGLT inhibitor is a compound of Formula (26):



wherein R¹ is fluorine, or chlorine, and R² is hydrogen, or fluorine, or a pharmaceutically acceptable salt thereof;

5 and

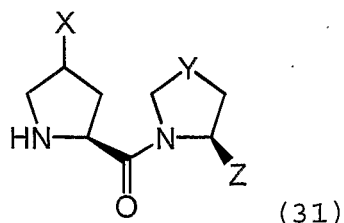
the DPP4 inhibitor is a compound of formula (29):



wherein A represents -CH₂- or -S-, R¹ represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group, and R² represents (1) a cyclic group which may be substituted, where the cyclic group portion is (i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or (ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or (2) an amino group which may be substituted, or a pharmaceutically acceptable salt thereof; or

10
15

the DPP4 inhibitor is a compound of Formula (31):



wherein:

20 X is -NR¹R² wherein R¹ and R² may be the same or different and each is independently cycloalkylalkyl, arylalkyl,

heteroaryl or heteroarylalkyl, or may be bonded to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having
5 substituents, and the heterocycle optionally being a spiro ring,

-NR³COR⁴ wherein R³ and R⁴ are the same or different and each is independently a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, arylalkenyl, heteroaryl
10 or heteroarylalkyl,

-NR⁵CONR⁶R⁷ or -NR⁵CH₂CH₂NR⁶R⁷ wherein R⁵, R⁶ and R⁷ are the same or different and each is independently hydrogen atom, alkyl, acyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, or R⁶ and R⁷ may be bonded
15 to each other to form a heterocycle optionally containing 1 or 2 nitrogen atoms or oxygen atoms, the heterocycle optionally being condensed with an aromatic ring optionally having substituents,

-NR⁸SO₂R⁹ wherein R⁸ and R⁹ are the same or different and each is independently a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or hetero-
20 arylalkyl, or

-OR¹⁰ or -OCOR¹¹ wherein R¹⁰ and R¹¹ are each a hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl,
25 heteroaryl or heteroarylalkyl,

Y is CH₂, CH-OH, S, S=O or SO₂,

Z is a hydrogen atom or cyano, and

of the above-mentioned groups, alkyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, cycloalkyl,
30 cycloalkylalkyl and heterocycle each optionally have substituents,

or a pharmaceutically acceptable salt thereof; or

the DPP4 inhibitor is Sitagliptin or a pharmaceutically acceptable salt thereof.

35

28. The pharmaceutical composition according to claim 10,

wherein the SGLT inhibitor is selected from:

1- (β -D-Glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene or a pharmaceutically acceptable salt thereof;

5 3-(5-(4-Fluorophenyl)-2-thienylmethyl)-1-(β -D-glucopyranosyl)-4-methylbenzene or a pharmaceutically acceptable salt thereof;

1- (β -D-Glucopyranosyl)-4-chloro-3-[5-(6-fluoro-3-pyridyl)-2-thienylmethyl]benzene or a pharmaceutically acceptable
10 salt thereof;

3-(4-Cyclopropylphenylmethyl)-4-fluoro-1-(β -D-glucopyranosyl)indole or a pharmaceutically acceptable salt thereof;
and

3-(4-Cyclopropylphenylmethyl)-4,6-difluoro-1-(β -D-glucopyranosyl)indole or a pharmaceutically acceptable salt
15 thereof; and

the DPP4 inhibitor is selected from:

3-[(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl]thiazolidine or a pharmaceutically acceptable salt thereof;
20

Sitagliptin or a pharmaceutically acceptable salt thereof;
and

(2S)-2-cyano-1-[trans-4-(dimethylaminocarbonyl)cyclohexylamino]acetylpyrrolidine or a pharmaceutically acceptable
25 salt thereof.

29. Use of an SGLT inhibitor in combination with a DPP4 inhibitor as active ingredients for manufacture of a pharmaceutical preparation for treating or preventing a
30 disease associated with plasma active GLP-1 level.

30. A product containing an SGLT inhibitor and a DPP4 inhibitor as a combined preparation for simultaneous, separate or sequential administration for preventing or
35 treating a disease associated with plasma active GLP-1 level.

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2009/051023

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/401 A61K31/7004 A61K31/7008 A61K45/06 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/140191 A (THERACOS INC [US]; CHEN YUANWEI [US]; FENG YAN [CN]; XU BAIHUA [CN]; L) 6 December 2007 (2007-12-06) abstract page 33, paragraph 160 claims 12-15	1-13, 29, 30
X	WO 2005/012326 A (TANABE SEIYAKU CO [JP]; NOMURA SUMIHIRO; KAWANISHI EIJI; UETA KIICHIRO) 10 February 2005 (2005-02-10) abstract page 45, line 20 - line 28 page 46, line 15 - line 30 claim 21	1-16, 29, 30
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

2 April 2009

Date of mailing of the international search report

14/04/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Damiani, Federica

INTERNATIONAL SEARCH REPORT

International application No

PCT/JP2009/051023

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 2006/080577 A (TANABE SEIYAKU CO [JP]; NOMURA SUMIHIRO [JP]; YAMAMOTO YASUO [JP]) 3 August 2006 (2006-08-03) abstract page 74; example 47 page 8, line 30 - page 9, line 10 page 10, line 13 - line 26 claim 19</p> <p style="text-align: center;">-----</p>	1-17, 29, 30
X	<p>EP 1 803 729 A (KISSEI PHARMACEUTICAL [JP]) 4 July 2007 (2007-07-04) abstract page 1 - page 7 page 7, paragraph 25 page 10, paragraphs 60, 62, 64 page 11, paragraph 73 page 26 - page 27</p> <p style="text-align: center;">-----</p>	1-14, 21, 25, 29, 30
X	<p>EP 1 803 721 A (CHUGAI PHARMACEUTICAL CO LTD [JP]) 4 July 2007 (2007-07-04) abstract page 25 - page 84 claim 11</p> <p style="text-align: center;">-----</p>	1-5, 7-14, 16, 29, 30
P, X	<p>WO 2008/131149 A (SQUIBB BRISTOL MYERS CO [US]; GOUGOUTAS JACK Z [US]; MALLEY MARY F [US]) 30 October 2008 (2008-10-30) abstract page 16, paragraph 40 claim 20 page 73, paragraph 198 page 72, paragraph 193</p> <p style="text-align: center;">-----</p>	1-14, 20, 29, 30
X, E	<p>WO 2009/022009 A (BOEHRINGER INGELHEIM INT [DE]; DUGI KLAUS [DE]; MARK MICHAEL [DE]; HIM) 19 February 2009 (2009-02-19) abstract page 24 - page 25; table 1 claims 1-17, 22, 23 page 26, line 34 - line 37</p> <p style="text-align: center;">-----</p>	1-13, 20, 29, 30
P, X	<p>WO 2008/013321 A (MITSUBISHI TANABE PHARMA CORP [JP]; NOMURA SUMIHIRO; HONGU MITSUYA) 31 January 2008 (2008-01-31) abstract page 34, line 8 - line 28 page 72 - page 81 page 82 - page 87 claims 22-27</p> <p style="text-align: center;">-----</p>	1-17, 29, 30
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INTERNATIONAL SEARCH REPORT

International application No

PCT/JP2009/051023

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2008/013322 A (MITSUBISHI TANABE PHARMA CORP [JP]; NOMURA SUMIHIRO; SAKAMAKI SHIGEKI) 31 January 2008 (2008-01-31) abstract page 6, line 15 - line 28 claims 6-10	1-14,16,17,29,30
Y	WO 01/96295 A (NOVARTIS AG [CH]; NOVARTIS ERFIND VERWALT GMBH [AT]; VILLHAUER EDWIN B) 20 December 2001 (2001-12-20) page 31, paragraph 3	1-30
Y	WO 2006/116157 A (ALANTOS PHARMACEUTICALS INC [US]; KROTH HEIKO [DE]; FEUERSTEIN TIM [DE]) 2 November 2006 (2006-11-02) abstract claims 61,66,67	1-30
A	WO 2006/073167 A (ONO PHARMACEUTICAL CO [JP]; NAKAI HISAO [JP]; KONDO TAKASHI [JP]; OTA) 13 July 2006 (2006-07-13) abstract	1-30
A	EP 1 323 710 A (TANABE SEIYAKU CO [JP] MITSUBISHI TANABE PHARMA CORP [JP]) 2 July 2003 (2003-07-02) abstract page 41 - page 74 claims 1,2,22,25,26	1-30

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/JP2009/051023

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WO 2005012326 A	10-02-2005	AU 2004260761 A1 BR PI0413232 A CA 2534024 A1 CN 1829729 A EP 1651658 A1 JP 4130466 B2 JP 2007518683 T JP 2008266328 A KR 20060057589 A KR 20070065454 A MX PA06001274 A SG 145694 A1	10-02-2005 03-10-2006 10-02-2005 06-09-2006 03-05-2006 06-08-2008 12-07-2007 06-11-2008 26-05-2006 22-06-2007 11-04-2006 29-09-2008
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