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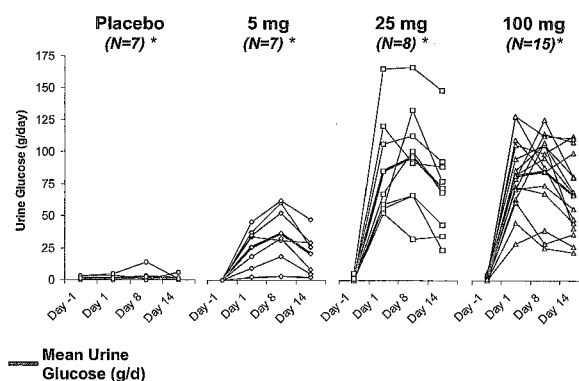
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(54) Title: METHOD FOR TREATING CANCERS HAVING HIGH GLUCOSE REQUIREMENTS EMPLOYING AN SGLT2 INHIBITOR AND COMPOSITIONS THEREOF

FIG. 2

Urine glucose excretion in diabetic subjects treated with Dapagliflozin PGS



(57) Abstract: Methods are provided for treating cancers that have high glucose requirements and that express SGLT2 at levels higher than normal cells, such as metastatic cancers, for example, metastatic lung cancers, employing an SGLT2 inhibitor alone or in combination with a cytotoxic agent and to a composition containing a combination of an SGLT2 inhibitor and a cytotoxic agent.

**METHOD FOR TREATING CANCERS HAVING HIGH GLUCOSE
REQUIREMENTS EMPLOYING AN SGLT2 INHIBITOR AND
COMPOSITIONS THEREOF**

5 This application claims priority to U.S. Provisional Serial No. 61/037,509, filed on March 18, 2008, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

 The invention relates to a method for treating cancers that have high glucose requirements and that express SGLT2 at levels higher than normal cells, comprising
10 administering an SGLT2 inhibitor alone or in combination with a cytotoxic agent, and to compositions thereof.

BACKGROUND OF THE INVENTION

 It is known that cancer cells need increased glucose uptake and utilization as
15 compared to normal cells. Uptake of glucose in cells, including cancer cells, is facilitated by glucose transporters including Na⁺/glucose cotransporter-2 (SGLT2), that utilize the electrochemical sodium gradient to transport glucose against the cells internal concentration gradient.

 Researchers have reported that SGLT2 expression was significantly higher in
20 the metastatic lesions in the liver and lymph node than in the primary lung cancers. SGLT1 expression in the primary lung cancers and their metastatic lesions did not significantly differ. These results indicate that SGLT2 plays a role in glucose uptake in the metastatic lesions of lung cancer.

 The inhibition of SGLT2 as a means to reduce glucose uptake in cancer cells
25 represents a viable therapeutic method for treating cancers. Therefore, compounds or agents that inhibit SGLT2 are attractive targets for treating cancers that have increased expression of SGLT2, such as metastatic lesions associated with lung cancer.

SUMMARY OF THE INVENTION

30 In one aspect, the invention provides a method for treating cancers that express SGLT2 at a level higher than normal cells in a mammal comprising

administering to the mammal in need of such treatment a therapeutically effective amount of an SGLT2 inhibitor.

In another aspect, the invention provides a method for treating cancers that express SGLT2 at higher levels than normal cells in a mammal comprising
5 administering to the mammal in need of such treatment a therapeutically effective amount of a pharmaceutical composition comprising an SGLT2 inhibitor and at least one pharmaceutically acceptable carrier, excipient, or diluent.

In another aspect, the invention provides a method for treating cancers that express SGLT2 at higher levels than normal cells in a mammal comprising
10 administering to the mammal in need of such treatment a therapeutically effective amount of an SGLT2 inhibitor and a cytotoxic agent where the cytotoxic agent is administered prior to, after, or concurrently with the SGLT2 inhibitor.

In another aspect, the invention provides a method for treating cancers that express SGLT2 at higher levels than normal cells in a mammal comprising
15 administering to the mammal in need of such treatment a therapeutically effective amount of a pharmaceutical composition comprising an SGLT2 inhibitor, a cytotoxic agent and at least one pharmaceutically acceptable carrier, excipient, or diluent.

BRIEF DESCRIPTION OF THE FIGURES

20 Figure 1 depicts bar graphs showing an indirect comparison of the amount of glucose excretion in urine/day caused by each of the SGLT2 inhibitors GSK 869,682 and Compound Ia; and

Figure 2 depicts a series of graphs showing urine glucose excretion in diabetic subjects treated with Compound Ia and placebo.

25

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the invention provides a method for treating lung cancer metastatic lesions in a mammal comprising administering to the mammal in need of such treatment a therapeutically effective amount of an SGLT2 inhibitor.

30 In another aspect, the invention provides a method for treating lung cancer metastatic lesions in a mammal comprising administering to the mammal in need of such treatment a therapeutically effective amount of a pharmaceutical composition

comprising an SGLT2 inhibitor and at least one pharmaceutically acceptable carrier, excipient, or diluent.

In another aspect, the invention provides a method for treating lung cancer metastatic lesions in a mammal comprising administering to the mammal in need of
5 such treatment a therapeutically effective amount of an SGLT2 inhibitor and a cytotoxic agent where the cytotoxic agent is administered prior to, after, or concurrently with the SGLT2 inhibitor.

In another aspect, the invention provides a method for treating lung cancer metastatic lesions in a mammal comprising administering to the mammal in need of
10 such treatment a therapeutically effective amount of a pharmaceutical composition comprising an SGLT2 inhibitor, a cytotoxic agent and at least one pharmaceutically acceptable carrier, excipient, or diluent.

In one aspect, the invention provides a method for treating lung cancer metastatic lesions in a human comprising administering to the human in need of such
15 treatment a therapeutically effective amount of an SGLT2 inhibitor.

In another aspect, the invention provides a method for treating lung cancer metastatic lesions in a human comprising administering to the human in need of such treatment a therapeutically effective amount of a pharmaceutical composition
20 comprising an SGLT2 inhibitor and at least one pharmaceutically acceptable carrier, excipient, or diluent.

In another aspect, the invention provides a method for treating lung cancer metastatic lesions in a human comprising administering to the human in need of such treatment a therapeutically effective amount of an SGLT2 inhibitor and a cytotoxic
25 agent where the cytotoxic agent is administered prior to, after, or concurrently with the SGLT2 inhibitor.

In another aspect, the invention provides a method for treating lung cancer metastatic lesions in a human comprising administering to the human in need of such treatment a therapeutically effective amount of a pharmaceutical composition
30 comprising an SGLT2 inhibitor, a cytotoxic agent and at least one pharmaceutically acceptable carrier, excipient, or diluent.

In one aspect, the invention provides a method for treating lung cancer metastatic lesions in the liver of a human comprising administering to the human in need of such treatment a therapeutically effective amount of an SGLT2 inhibitor.

5 In another aspect, the invention provides a method for treating lung cancer metastatic lesions in the liver of a human comprising administering to the human in need of such treatment a therapeutically effective amount of a pharmaceutical composition comprising an SGLT2 inhibitor and at least one pharmaceutically acceptable carrier, excipient, or diluent.

10 In another aspect, the invention provides a method for treating lung cancer metastatic lesions in the liver of a human comprising administering to the human in need of such treatment a therapeutically effective amount of an SGLT2 inhibitor and a cytotoxic agent where the cytotoxic agent is administered prior to, after, or concurrently with the SGLT2 inhibitor.

15 In another aspect, the invention provides a method for treating lung cancer metastatic lesions in the liver of a human comprising administering to the human in need of such treatment a therapeutically effective amount of a pharmaceutical composition comprising an SGLT2 inhibitor, a cytotoxic agent and at least one pharmaceutically acceptable carrier, excipient, or diluent.

20 In one aspect, the invention provides a method for treating lung cancer metastatic lesions in the lymph nodes of a human comprising administering to the human in need of such treatment a therapeutically effective amount of an SGLT2 inhibitor.

25 In another aspect, the invention provides a method for treating lung cancer metastatic lesions in the lymph nodes of a human comprising administering to the human in need of such treatment a therapeutically effective amount of a pharmaceutical composition comprising an SGLT2 inhibitor and at least one pharmaceutically acceptable carrier, excipient, or diluent.

30 In another aspect, the invention provides a method for treating lung cancer metastatic lesions in the lymph nodes of a human comprising administering to the human in need of such treatment a therapeutically effective amount of an SGLT2 inhibitor and a cytotoxic agent where the cytotoxic agent is administered prior to, after, or concurrently with the SGLT2 inhibitor.

In another aspect, the invention provides a method for treating lung cancer metastatic lesions in the lymph nodes of a human comprising administering to the human in need of such treatment a therapeutically effective amount of a pharmaceutical composition comprising an SGLT2 inhibitor, a cytotoxic agent and at least one pharmaceutically acceptable carrier, excipient, or diluent.

In another aspect, the invention provides a use of an SGLT2 inhibitor in the manufacture of a medicament for treating lung cancer metastatic lesions.

In another aspect, the invention provides a combination of a SGLT2 inhibitor and a cytotoxic agent as a medicament for treating lung cancer metastatic lesions, where the cytotoxic agent is administered prior to, after, or concurrently with the SGLT2 inhibitor.

In another aspect, the invention provides a use of an SGLT2 inhibitor in the manufacture of a medicament for treating lung cancer metastatic lesions in the liver.

In another aspect, the invention provides a combination of a SGLT2 inhibitor and a cytotoxic agent as a medicament for treating lung cancer metastatic lesions in the liver, where the cytotoxic agent is administered prior to, after, or concurrently with the SGLT2 inhibitor.

In another aspect, the invention provides a use of an SGLT2 inhibitor in the manufacture of a medicament for treating lung cancer metastatic lesions in the lymph nodes.

In another aspect, the invention provides a combination of a SGLT2 inhibitor and a cytotoxic agent as a medicament for treating lung cancer metastatic lesions in the lymph nodes, where the cytotoxic agent is administered prior to, after, or concurrently with the SGLT2 inhibitor.

The SGLT2 inhibitor is employed in a weight ratio to the optional cytotoxic agent in an amount within the range from about 200:1 to about 0.1:1, preferably from about 100:1 to about 0.2:1.

The dosage for the cytotoxic agent (used in combination with the SGLT2 inhibitor) will be the recommended doses for such cytotoxic agents as disclosed in the latest PHYSICIANS' DESK REFERENCE (PDR) or REMINGTON'S PHARMACEUTICAL SCIENCES (Mack Publishing Co., Easton, PA).

The SGLT2 inhibitor employed in the above-defined methods of the invention will not cause hypoglycemia in non-diabetic humans that is a human who does not suffer from hyperglycemia, and will not cause hypoglycemia in diabetic humans as well.

5 In preferred embodiments of all aspects of the invention, the SGLT2 inhibitor will be administered in amounts below the therapeutic amount (sub-therapeutic amount) as prescribed in generally accepted medical practice for treating diabetes.

The SGLT2 inhibitor employed in the invention is selective for SGLT2 relative to SGLT-1. Higher SGLT2 : SGLT-1 selectivity ratios result in greater
10 effectiveness at eradicating cancer cells.

In carrying out the methods of the invention for treating cancers which express SGLT2 at levels higher than normal cells, the SGLT2 inhibitor may be administered to a patient in need of treatment in a cancer treating amount which can be as high as that which may be used to treat cancers but less than an amount which could cause
15 hypoglycemia. The daily dose may be lowered as successful treatment of cancer cells is achieved. For example, depending upon the patient, and the specific SGLT2 inhibitor employed, the SGLT2 inhibitor may be orally administered in a cancer treating amount from about 1 to about 1000 mg per day, preferably from about 2 to about 400 mg/day, preferably 2.5 to about 75 mg/day, and more preferably 20 to
20 about 50 mg/day, which can be administered in a single dose or in the form of individual doses from 1 to 4 times per day.

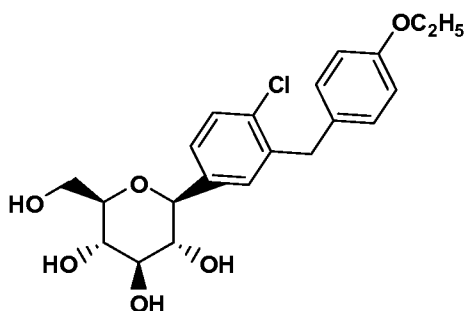
The SGLT2 inhibitor may be administered by injection to a patient in a cancer treating amount from about 1 to about 100 mg/day, preferably from about 1 to about 30 mg/day.

25 The SGLT2 inhibitor suitable for use in accordance with the invention will be a C-arylglucoside or an O-arylglucoside.

Examples of C-arylglucoside (also referred to as C-glucosides) SGLT2 inhibitors which may be employed in the method of the invention, include, but are not limited to the following:

30

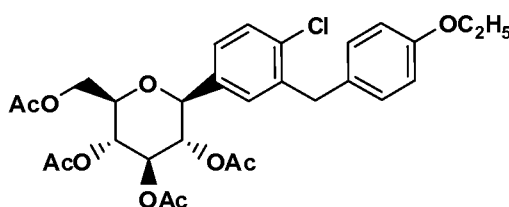
1) Compound I or dapagliflozin



compound I

preferred for use in the invention and its corresponding tetraacetate shown below as

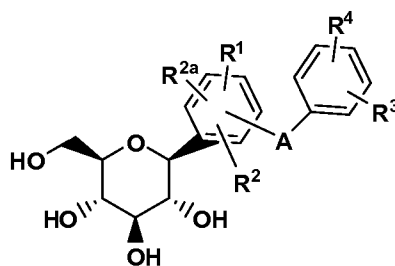
5 compound II



compound II

as disclosed in U.S. Patent No. 6,515,117, (PCT/US03/15591) the disclosure of which is incorporated herein by reference in its entirety for any purpose.

10 2) Compounds of formula III:



III

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} , $OAryl$, OCH_2Aryl , 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}, -CONR⁶R^{6a}, -NHCOR^{5c}, -NHSO₂R^{5d}, -NHSO₂Aryl, aryl, -SR^{5e}, -SOR^{5f}, -SO₂R^{5g}, -SO₂Aryl, or a five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO₂, or R³ and R⁴ together with the carbons to which they are attached form an annelated
 5 five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO₂;

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

R⁶, R^{6a}, R^{6b}, R^{6c} and R^{6d} are independently hydrogen, alkyl, aryl, alkylaryl or cycloalkyl, or R⁶ and R^{6a} together with the nitrogen to which they are attached form
 10 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;

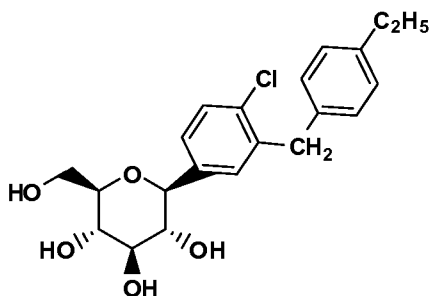
A is O, S, NH, or (CH₂)_n where n is 0-3,

and pharmaceutically-acceptable salts thereof, all stereoisomers thereof, and all prodrug esters thereof.

15 The compounds of formula III as defined above also include compounds wherein where A is (CH₂)_n where n is 0, 1, 2, or 3 or A is O, and at least one of R¹, R², and R^{2a} is OH or OR⁵, then at least one of R¹, R², and R^{2a} is CF₃, OCF₃, or OCHF₂ and/or at least one of R³ and R⁴ is CF₃, -OCHF₂, -OCF₃, CH(OR^{5h})R^{6d}, CH(OH)R^{6c}, COR^{6b}, -CN, -CO₂R^{5b}, -NHCOR^{5c}, -NHSO₂R^{5d}, -NHSO₂Aryl, aryl, -SR^{5e}, -SOR^{5f},
 20 -SO₂R^{5g} or -SO₂Aryl.

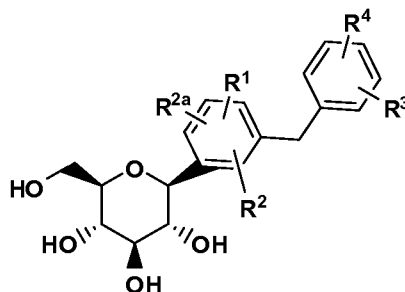
Preferred compounds of formula III as defined above compounds wherein where A is (CH₂)_n where n is 0, 1, 2, or 3 or A is O, and at least one of R¹, R², R^{2a}, R³ and R⁴ is OH or OR⁵, then at least one of R¹, R², and R^{2a} is CF₃, OCF₃, or OCHF₂ and/or at least one of R³ and R⁴ is CF₃, -OCHF₂, -OCF₃, -CN, -CO₂R^{5b}, CH(OR^{5h})R^{6d},
 25 -NHCOR^{5c}, -NHSO₂R^{5d}, -NHSO₂Aryl, aryl, -SR^{5e}, -SOR^{5f}, -SO₂R^{5g}, -SO₂Aryl or halogen.

Preferred for use herein is compound IIIA, shown below, disclosed in U.S. Patent No. 6,414,126 (PCT/US00/27187).



compound IIIA.

- 3) C-aryl glucosides that are crystalline complexes of amino acids, such as L-proline and D-phenylalanine complexes, as disclosed in U.S. Patent No. 6,774,112 (PCT/US02/11066) (the disclosure of which is incorporated herein by reference in its entirety) as follows:



IV

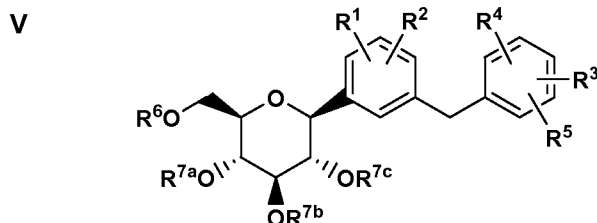
wherein

- 10 R^1 , R^2 and R^{2a} are independently hydrogen, OH, OR^5 , alkyl, $-OCHF_2$, $-OCF_3$, $-SR^{5a}$ or halogen;
- R^3 and R^4 are independently hydrogen, OH, OR^{5b} , alkyl, cycloalkyl, CF_3 , $-OCHF_2$, $-OCF_3$, halogen, $-CONR^{6a}$, $-CO_2R^{5c}$, $-CO_2H$, $-COR^{6b}$, $-CH(OH)R^{6c}$, $-CH(OR^{5d})R^{6d}$, $-CN$, $-NHCOR^{5e}$, $-NHSO_2R^{5f}$, $-NHSO_2Aryl$, $-SR^{5g}$, $-SOR^{5h}$, $-SO_2R^{5f}$,
 15 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, SO_2 ;
- 20 R^5 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^{5g} , R^{5h} and R^{5i} are independently alkyl; and
 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.

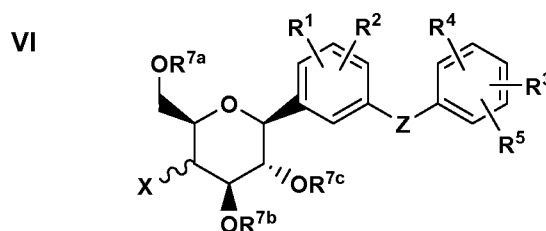
Preferred compounds of formula IV include the L-proline and D-phenylalanine complexes wherein R¹ is p-Cl, and R³ is p-C₂H₅ or p-OC₂H₅;

- 5 4) Glucopyranosyl-substituted benzene derivatives or salts thereof as disclosed in US 2005/0209166 (the disclosure of which is incorporated by reference in its entirety) as follows:



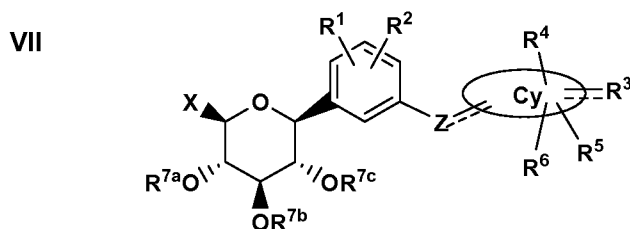
wherein R¹, R², R³, R⁴, R⁵, R⁶, R^{7a}, R^{7b} and R^{7c} are as defined in US 2005/0209166.

- 10 5) D-pyranosyl-substituted phenyls as disclosed in US 2006/0074031 (the disclosure of which is incorporated herein by reference in its entirety) as follows:



wherein R¹, R², R³, R⁴, R⁵, R⁶, R^{7a}, R^{7b}, R^{7c}, X and Z are as defined in US 2006/0074031.

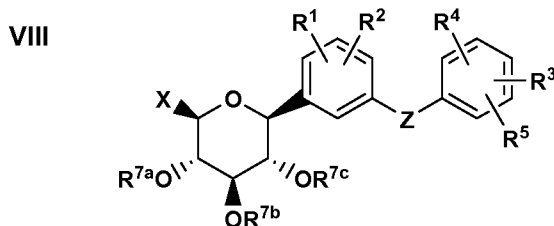
- 15 6) D-xylopyranosyl-substituted cycles or salts thereof as disclosed in US 2006/0035841 (the disclosure of which is incorporated herein by reference in its entirety) as follows:



wherein

- 20 === denotes a single or double bond, and
 Cy, R¹, R², R³, R⁴, R⁵, R⁶, R^{7a}, R^{7b}, R^{7c}, X and Z are as defined in US 2006/0035841.

7) D-xylopyranosyl-substituted phenyls or salts thereof as disclosed in US 2006/0009400 (the disclosure of which is incorporated herein by reference in its entirety) as follows

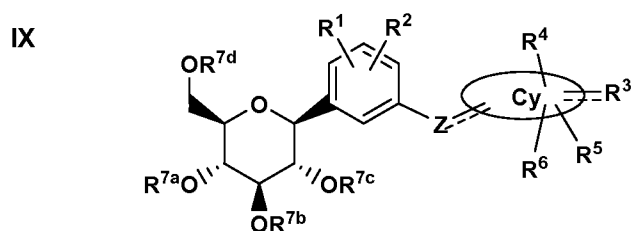


5

wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^{7a} , R^{7b} , R^{7c} , X and Z are as disclosed in US 2006/0009400.

8) D-glucopyranosyl-phenyl-substituted cycles and salts thereof as disclosed in US 2006/0025349 (the disclosure of which is incorporated herein by reference in its entirety) as follows:

10



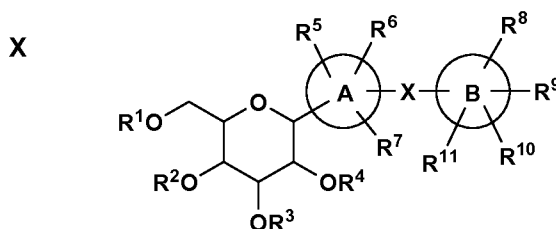
wherein

== denotes a single or double bond, and

Cy, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^{7a} , R^{7b} , R^{7c} , R^{7d} and Z are as defined in US

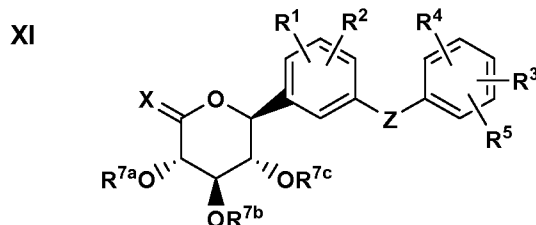
15 2006/0025349.

9) C-glycoside derivatives and salts thereof as disclosed in US 2006/0122126 (the disclosure of which is incorporated herein by reference in its entirety) as follows:



20 wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , X, A and B are as defined in US 2006/0122126.

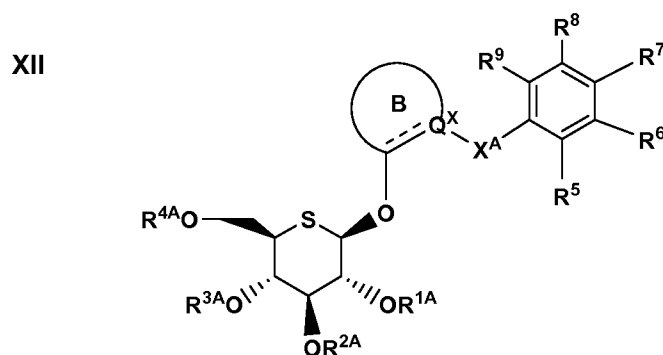
10) D-xylopyranosyl-substituted phenyls as disclosed in US 2006/0019948 (the disclosure of which is incorporated herein by reference in its entirety) as follows:



wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^{7a} , R^{7b} , R^{7c} , X and Z are as defined in US 2006/0019948.

5 Examples of O-glucoside SGLT2 inhibitors which may be employed in the method of the invention include, but are not limited to the following:

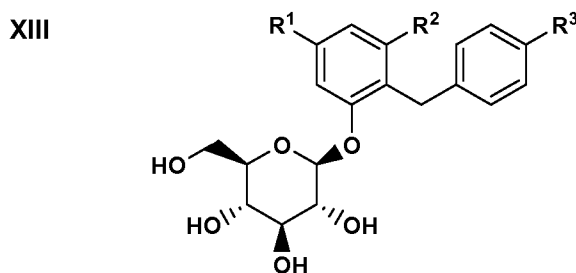
1) 5-Thio- β -D-glucopyranosides or salts or hydrates thereof as disclosed in US 2006/0194809 (the disclosure of which is incorporated by reference in its entirety) as follows:



10

wherein R^{1A} , R^{2A} , R^{3A} , R^{4A} , R^5 , R^6 , R^7 , R^8 , R^9 , Q^x , X^A and B are as defined in US 2006/0194809.

2) Glucopyranoxybenzene derivatives as disclosed in WO 03/01180 (the disclosure of which is incorporated by reference in its entirety) as follows:



15

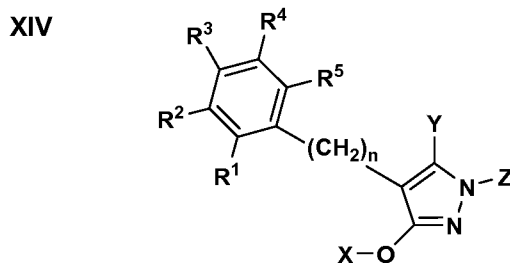
wherein

R^1 represents hydrogen, hydroxyl, optionally substituted amino, cyano, carbamoyl, optionally substituted lower alkyl, optionally substituted lower alkoxy, or optionally substituted cyclic amino;

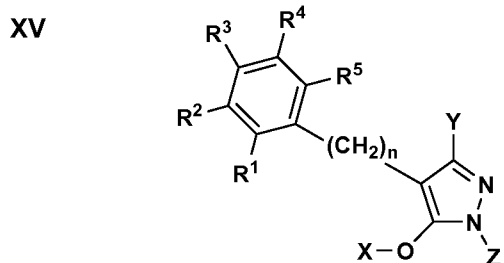
R^2 represents hydrogen or lower alkyl; and

- 5 R^3 represents optionally substituted aryl, optionally substituted cycloalkyl, an optionally substituted aliphatic heterocyclic group, or an optionally substituted aromatic heterocyclic group, a pharmacologically acceptable salt of the derivative, or a prodrug of either.

- 3) Pyrazole derivatives or salts thereof as disclosed in U.S. Patent No. 6,908,905 (the disclosure of which is incorporated herein by reference in its entirety) as follows:

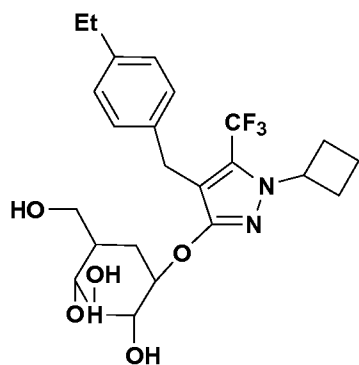


or

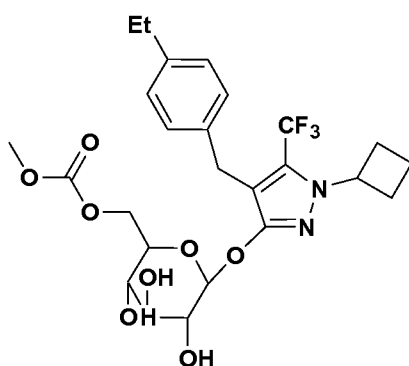


- 15 wherein X represents β -D-glucopyranosyl group, wherein one or more hydroxyl groups may be acylated; Y represents a lower alkyl group or a perfluoro lower alkyl group; Z represents a cyclic alkyl group which may have a substituent(s), a cyclic unsaturated alkyl group which may have a substituent(s), a lower alkyl group having a cyclic alkyl group which may have a substituent(s), or a lower alkyl group having a
- 20 cyclic unsaturated alkyl group which may have a substituent(s); R^1 to R^5 may be the same or different and each represent a hydrogen atom, a lower alkyl group, a perfluoro lower alkyl group, a lower alkyloxy group, a perfluoro lower alkoxy group, a lower alkylthio group, a perfluoro lower alkylthio group, a lower alkylamino group, a halogen group, a lower alkanoyl group, an alkenyl group, a cyclic alkenyl group, an

alkynyl group, a phenyl group which may have a substituent(s), or a lower alkoxycarbonyl group; and n is an integer of 0 to 3 including:

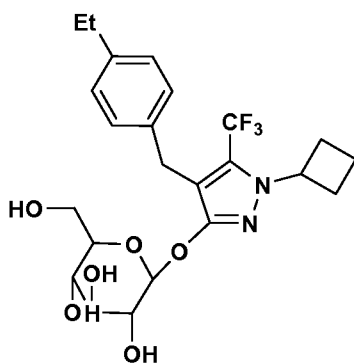


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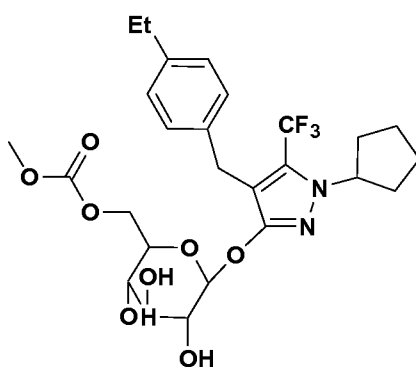


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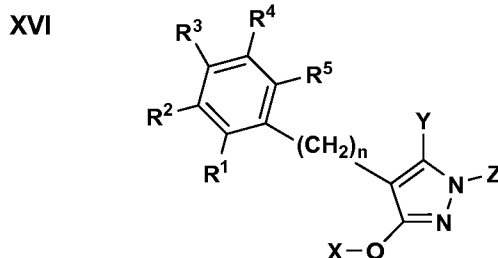


, or



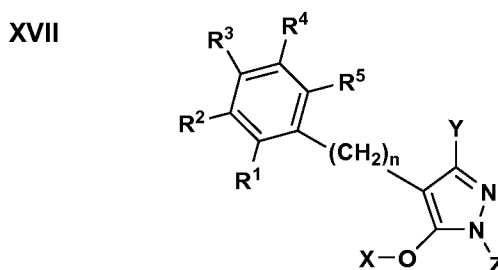
.

4) Pyrazole compounds or salts thereof as disclosed in U.S. Patent No. 6,815,428 (the disclosure of which is incorporated herein by reference in its entirety) as follows:



5

or

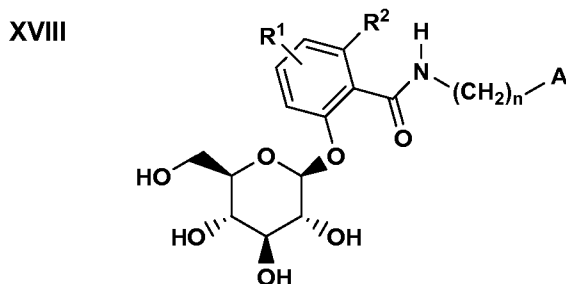


wherein X represents a β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated or a β -D-glucuronyl group, of which one or more hydroxyl groups may be acylated and a carboxyl group may be esterified; Y represents a lower alkyl group or a perfluoro lower alkyl group; Z represents a hydrogen atom, a lower alkyl group, a perfluoro lower alkyl group, an aralkyl group or a phenyl group; R^1 , R^2 , R^4 and R^5 may be the same or different and each represents a hydrogen atom, a lower alkyl group, a perfluoro group, a lower alkoxy group, a fluoro lower alkoxy group, a lower alkylthio group, a perfluoro lower alkylthio group, a lower alkyl amino group, a halogen group, a lower alkanoyl group, a lower alkenyl group or a lower alkynyl group; and n represents an integer from 0 to 3,

wherein at least one of R^1 , R^2 , R^4 and R^5 represents a lower alkyl group having 1 to 6 carbon atoms, lower alkylthio group having 1 to 6 carbon atoms, halogen atom, lower alkoxy group lower alkenyl group or lower alkynyl group; and

R^3 represents a lower alkyl group having a 1 to 6 carbon atoms, a lower alkylthio group having 1 to 6 carbon atoms, a halogen atom, a lower alkoxy group, a lower alkenyl group, or a lower alkynyl group.

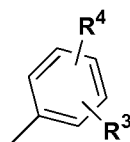
5) O-glucosylated benzamides or salts thereof as disclosed in U.S. Patent No. 6,555,519 (the disclosure of which is incorporated herein by reference in its entirety) as follows:



5 wherein

n is 0, 1 or 2;

A is



10 or heteroaryl which may contain 1 to 4 heteroatoms in the ring which may be selected from N, O, S, SO, and/or SO₂ bearing substituents R³ and R⁴;

R¹ is selected from hydrogen, OR⁵, lower alkyl, aryl, arylalkyl, NHCOR⁵, NR⁶R^{6a}, or halogen;

R² is selected from hydrogen, OH, OR^{5a}, or lower alkyl;

15 R³ and R⁴ are the same or different and are independently selected from hydrogen, OH, OR^{5b}, OAryl, OCH₂Aryl, lower alkyl, cycloalkyl, aryl, arylalkyl, CF₃, -SCF₃, -OCHF₂, -OCF₃, halogen, -CN, -CO₂R^{5c}, -CO₂H, -CONR^{6b}, R^{6c}, -NR^{6d}R^{6e}, -SO₂NH₂, -NHCOR^{5d}, -NHSO₂R^{5e}, -NHSO₂Aryl, -SR^{5f}, -SOR^{5g}, -SO₂R^{5h}, -SO₂Aryl, -OCH₂CO₂R⁵ⁱ, -OCH₂CO₂H, -OCH₂CONR^{6f}R^{6g}, -OCH₂CH₂NR^{6h}R⁶ⁱ, or a five-, six- or seven-membered heterocycle which may contain 1 to 4 heteroatoms in the ring
20 which are N, O, S, SO, and/or SO₂, or R³ and R⁴ 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 heteroatom in the ring which are N, O, S, SO, and/or SO₂;

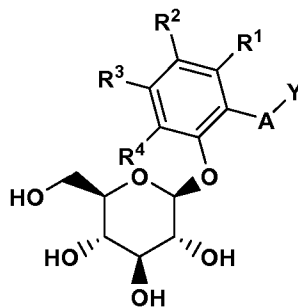
R⁵, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R^{5g}, R^{5h}, and R⁵ⁱ are independently lower alkyl;

25 and

R^6 , R^{6a} , R^{6b} , R^{6c} , R^{6d} , R^{6e} , R^{6f} , R^{6g} , R^{6h} , and R^{6i} are the same or different and are independently selected from hydrogen, alkyl, aryl, arylalkyl or cycloalkyl.

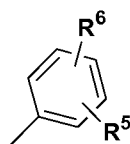
- 6) O-aryl glucosides or salts thereof as disclosed in U.S. Patent No. 6,683,056 (the disclosure of which is incorporated herein by reference in its entirety)
- 5 as follows:

XIX



wherein

when Y is



- 10 or heteroaryl;

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 may contain 1 to 4 heteroatoms

15 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, -OCH₂Aryl, lower alkyl, cycloalkyl, aryl, arylalkyl, CF₃, arylalkenyl, -OCHF₂, -OCF₃, halogen, -CN, -CO₂R^{7b}, -CO₂H, COR^{8f}, CHOHR^{8g}, CH(OR^{7h})R^{8h}, -CONR⁸R^{8a}, -NHCOR^{7c}, -NHSO₂R^{7d}, -NHSO₂Aryl, -SR^{7e}, -SOR^{7f}, -
- 20 SO₂R^{7g}, -SO₂Aryl, -OCH₂CO₂R⁷ⁱ, -OCH₂CO₂H, -OCH₂CONR^{8b}R^{8c}, -OCH₂CH₂NR^{8d}R^{8e}, or a five-, six- or seven-membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or 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
- 25 in the ring which are N, O, S, SO, and/or SO_2 ;

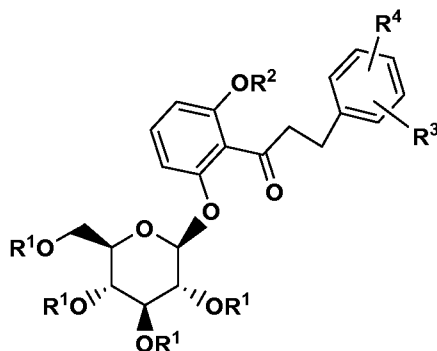
$R^7, R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, R^{7g}, R^{7h}$, and R^{7i} are independently lower alkyl;
 $R^8, R^{8a}, R^{8b}, R^{8c}, R^{8d}, R^{8e}, R^{8f}, R^{8g}$, and R^{8h} are the same or different and are
 independently selected from hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or together
 with the nitrogen to which they are attached form an annelated five-, six- or seven-
 5 membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N,
 O, S, SO, and/or SO₂; and

A is O(CH₂)_m, S, NH(CH₂)_m, or (CH₂)_n where n is 0-3 and m is 0-2.

Other O-aryl glucosides SGLT2 inhibitors which may be used in the invention
 are disclosed in the following references all of which are incorporated herein by
 10 reference.

1) EP 598359A1 (also JP 035988) (and any U.S. counterpart applications)
 (Tanabe Seiyaku) discloses compounds of the following structure

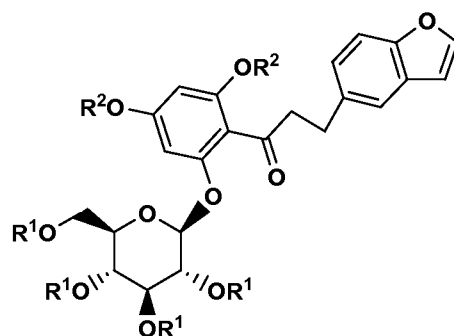
XX



$R^1 = \text{H, acyl,}$
 $R^2 = \text{H, Me}$
 $R^3, R^4 \text{ can be a variety of substituents}$

15 2) EP 0850948A1 (and any U.S. counterpart applications) discloses the
 following structures of genus

XXI

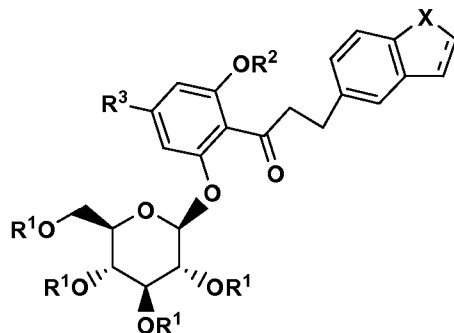


$R^1 = \text{H, acyl, CO(OAlkyl)}$
 $R^2 = \text{H, allyl}$
 $R^3 = \text{H or Me}$

3) JP 09188625A (and any U.S. counterpart applications) expands upon
 20 structure XXI (of EP 0850948A1) to include examples of XXI where R³ is H and
 where the five-membered ring is saturated as well as the counterparts of

benzothiophenes ($O = S$) and indenenes ($O = CH_2$). EP 684254-A1 appears to encompass derivatives of structure XXI disclosed in JP 09188625A.

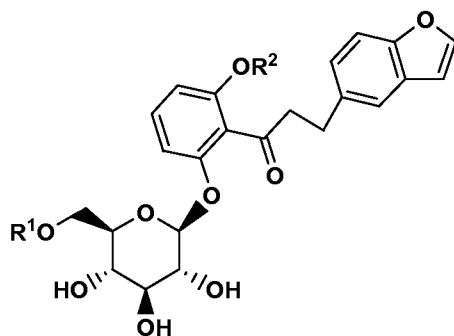
XXII



$R^1 = H, \text{ acyl, CO(OAlkyl)}$
 $R^2 = H, \text{ allyl}$
 $R^3 = H$

- 5 4) JP 09124685A (and any U.S. counterpart applications) expands upon structure XXI for $R^3 = H$ to include derivatives of mono acylated C6 hydroxyl where the acyl group is a substituted benzoic or pyridyl carboxylic acid or a urethane generated from the corresponding phenol.

XXIII

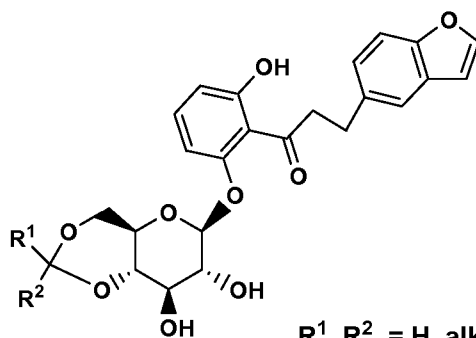


$R^1 = H, \text{ CO-aryl, CO(OAryl)}$
 $R^2 = H$

10

- 5) JP 09124684 (and any U.S. counterpart applications) discloses derivatives of structure XXI

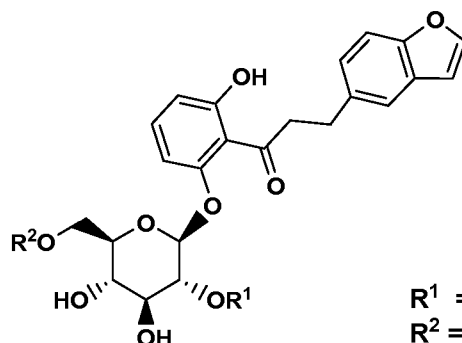
XXIV



$R^1, R^2 = H, \text{ alkyl, alkoxy, aryl or together oxo}$

- 15 6) EP 773226-A1 (and any U.S. counterpart applications) discloses derivatives of structure XXI

XXV



R^1 = alkanoyl if R^2 = H
 R^2 = alkoxycarbonyl if R^1 = H

7) JP 08027006-A (and any U.S. counterpart applications) discloses derivatives of structure XX where various combinations of the glucose hydroxyl are
 5 acylated and appears to be similar to EP 598359A1.

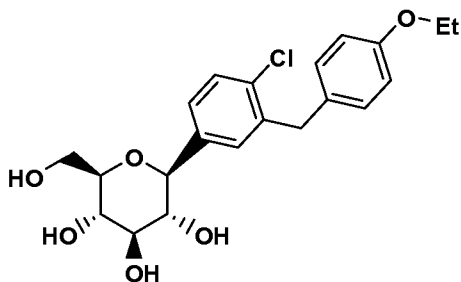
8) EP 684254-A1 (and any U.S. counterpart applications) appears to encompass derivatives of structure XXI disclosed in JP 09188625A.

Other disclosures and publications which disclose SGLT2 inhibitors that can be employed according to the methods of the invention are as follows:

- 10 9) K. Tsujihara et al., *Chem. Pharm. Bull.*, 44:1174-1180 (1996);
 10) M. Hongu et al., *Chem. Pharm. Bull.*, 46:22-33 (1998);
 11) M. Hongu et al., *Chem. Pharm. Bull.*, 46:1545-1555 (1998); and
 12) A. Oku et al., *Diabetes*, 48:1794-1800 (1999).
 13) JP 10245391 (Dainippon) discloses 500 structures as hypoglycemic
 15 agents for treatment of diabetes. These are O-glucosides of hydroxylated coumarins.

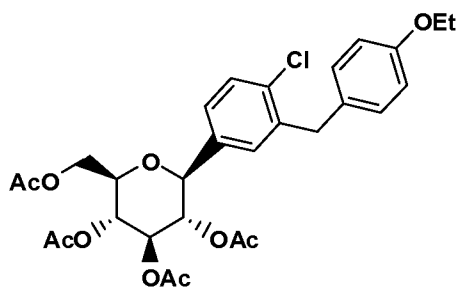
In addition to the above SGLT2 inhibitors, other SGLT2 inhibitors that can be employed using the methods disclosed herein include those disclosed in US 2005/0233982 (Boehringer Ingelheim Corp.), US 2005/0119192 (Kissei Pharmaceutical Co.), WO 2006/035796 (Kissei Pharmaceutical Co.), JP 2006/117651
 20 (Taisho Pharmaceutical Co.), JP 2004/4359630 (Yamanouchi Pharmaceutical Co.), WO 2006/080421 (Chugai Seiyaku Kabushiki Kaishi), US 2005/0233988 (Tanabe Seiyaku Co.), WO 2005/012321 (Tanabe Seiyaku Co.), U.S. Patent No. 7,015,201 (Ajinomoto Co.), WO 2006/058597 (Merck Patent GmbH), WO 2006/011469 (Chugai Seiyaku Kabushiki Kaisha), US 2003/0195235 (Johnson & Johnson), and
 25 WO 2006/037537 (Boehringer Ingelheim).

Preferred SGLT2 inhibitors for use in the methods and compositions of the invention include compound I, compound II, and compound IIIA:



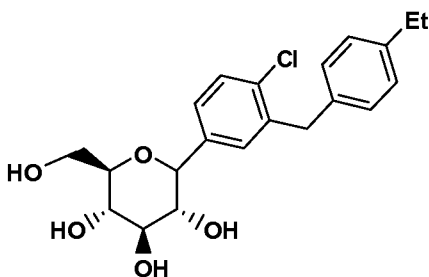
compound I;

- 5 or pharmaceutically acceptable salts thereof, all stereoisomers thereof, or a prodrug ester thereof;



compound II;

- or pharmaceutically-acceptable salts thereof, all stereoisomers thereof, or prodrug
10 esters thereof;

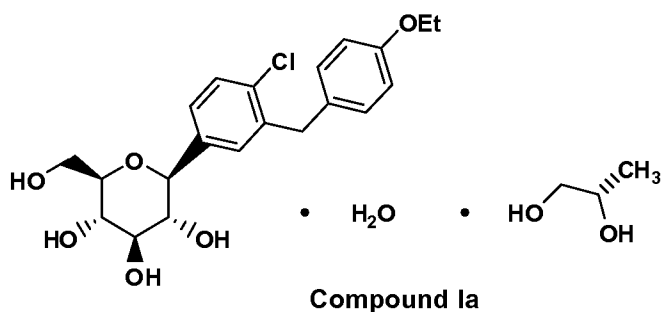


compound IIIA;

- or a pharmaceutically acceptable salts thereof, all stereoisomers thereof, or a prodrug
15 ester thereof.

Also preferred are crystalline forms of compound I above including the crystalline forms disclosed in US published patent application US/2008/0004335, the disclosures of which are incorporated herein by reference in their entirety for any purpose. A most preferred crystalline form of compound I is the (S) propylene glycol

solvate or hydrate, compound Ia or dapagliflozin-PGS, shown below. It is to be understood the (R) propylene glycol solvate or hydrate is also a preferred compound for use in the methods and compositions of the invention.



5 The crystalline structure of compound Ia is characterized by one or more of the following:

a) unit cell parameters substantially equal to the following:

Cell dimensions:

$$a = 11.2688(8) \text{ \AA}$$

10 $b = 4.8093(3) \text{ \AA}$

$$c = 46.723(3) \text{ \AA}$$

$$\alpha = 90 \text{ degrees}$$

$$\beta = 90 \text{ degrees}$$

$$\gamma = 90 \text{ degrees}$$

15 Space group = $P2_12_12_1$

$$\text{Molecules/asymmetric unit} = 1$$

wherein measurement of said crystalline structure is at room temperature and which is characterized by fractional atomic coordinates substantially as listed in Table 4 of U.S. Provisional Application No. 60/817,118;

20 b) a powder x-ray diffraction pattern comprising 2θ values ($\text{CuK}\alpha \lambda = 1.5418 \text{ \AA}$) selected from the group consisting of 3.8 ± 0.1 , 7.6 ± 0.1 , 8.1 ± 0.1 , 8.7 ± 0.1 , 15.2 ± 0.1 , 15.74 ± 0.1 , 17.1 ± 0.1 , 18.9 ± 0.1 and 20.1 ± 0.1 , at room temperature;

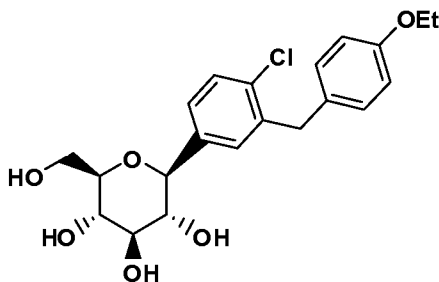
c) a solid state ^{13}C NMR spectrum having substantially similar peak positions at 16.2, 17.6, 39.3, 60.9, 63.3, 69.8, 76.9, 78.7, 79.4, 113.8, 123.6, 129.3, 25 130.5, 132.0, 135.7, 139.1 and 158.0 ppm, as determined on a 400MHz spectrometer relative to TMS at zero;

d) a differential scanning calorimetry thermogram having an endotherm in the range of about 50°C to 78°C or as shown in Figure 7 of U.S. Provisional Application No. 60/817,118;

e) thermal gravimetric analysis curve with about 18.7% weight loss from about room temperature up to about 240°C or as shown in Figure 5 of U.S. Provisional Application No. 60/817,118; or

f) having a proton NMR having substantially similar peak positions as listed in Table 1A of U.S. Provisional Application No. 60/817,118.

A process for the preparation of compound Ia is provided in US/2008/0004335. Generally, compound II (prepared as described in PCT/US03/041373, Examples 17-19) is treated with aqueous base, such as aqueous sodium hydroxide, in an alcohol solvent, such as methanol, preferably under an inert atmosphere, such as nitrogen, at an elevated temperature (between about 50 C and 85 C) to form compound I



Compound I

The reaction mixture containing compound I is treated with an organic solvent such as methyl tert-butyl ether or an alkyl acetate such as ethyl acetate, methyl acetate, isopropyl acetate, or butyl acetate, and (S)-propylene glycol, optionally adding seeds of compound Ia to the mixture, to provide compound Ia.

The SGLT2 inhibitor employed in accordance with the invention can be administered to various mammalian species, such as dogs, cats, humans, etc., in need of treatment. These agents can be administered systemically, such as orally or parenterally.

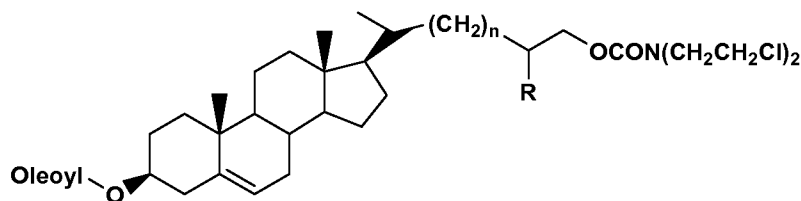
The SGLT-2 inhibitor can be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable formulation. The above dosage forms will also include the necessary physiologically acceptable carrier material,

excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), antioxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

5 The dose administered must be carefully adjusted according to the age, weight, and condition of the patient, as well as the route of administration, dosage form and regimen, and the desired result. In general, the dosage forms described above may be administered containing amounts of SGLT-2 inhibitor of from about 1 to about 1000 mg per day preferably from about 2 to about 400 mg per day, in single or divided doses of one to four times daily.

10 Cytotoxic agents which may be employed in conjunction with the SGLT-2 inhibitors, in accordance with the invention, may be administered in the same or different dosage forms with the SGLT2 inhibitor.

Cytotoxic agents approved by the FDA such as those listed in the Physicians' Desk Reference, 61st Ed. (2007), which may be employed include doxorubicin, doxorubicin valerate, idarubicin HCl, mitomycin, paclitaxel, taxotere, teniposide, etoposide, carboplatin, busulfan, megestrol acetate, mitotane, altretamine, lomustine, carmustine, estramustine phosphate sodium, procarbazine hydrochloride, cytarabine, dasatinib, gemcitabine, as well as an apoptosis agonist, DNA topoisomerase inhibitors, microtubule stimulants, beta tubulin antagonists, tubulin antagonist and
20 microtubule inhibitors, thymidylate synthase inhibitors, DNA antagonists, ErbB inhibitors, angiogenesis inhibitors, DNA topoisomerase ATP hydrolyzing inhibitors, DNA antagonists, endothelial growth factor receptor kinase inhibitors, p21 stimulants, endothelial growth factor receptor kinase inhibitors, p21 stimulants, microtubule inhibitors, dihydrofolate reductase inhibitors, such as ATP-binding cassette, subfamily B (MDR/TAP), member 1, Caspase 3, colony stimulating factor 2,
25 thymidylate synthetase, topoisomerase (DNA) I, tubuline beta polypeptide, Cyclin G1, Cyclin-dependent kinase inhibitor 1A, kinase insert domain receptor (a type III receptor tyrosine kinase), mucin 1 transmembrane, DNA (cytosine-5-)-methyltransferase 1, epidermal growth factor receptor, and eukaryotic translation
30 elongation factor 1 alpha 1, as well as 9-methoxyellipticine, and N-methylellipticinium,



"Cpd 25": n = 1 R = H

1 : n = 1, R = CH₂OC(=O)N(CH₂CH₂Cl)₂

2 : n = 3, R = CH₂OC(=O)N(CH₂CH₂Cl)₂

prednimustine, WB4291 (1-[bis(2-chloroethyl)amino]-3-methylnaphthalene),
daunomycin and vincristine.

5 Preferred cytotoxic agents to be employed herein will depend upon the
particularly neoplastic disease to be treated.

The various cytotoxic agents described above may be employed in dosages
and regimens as generally known in the art or in the PHYSICIANS' DESK REFERENCE
(PDR) or REMINGTON'S PHARMACEUTICAL SCIENCES (Mack Publishing Co., Easton,
PA).

10 Unless otherwise indicated, the dosages and formulations for the SGLT2
inhibitor will be disclosed in the various patents and applications discussed above.

The various formulations of the invention may optionally include one or more
fillers or excipients in an amount within the range of from about 0 to about 90% by
weight and preferably from about 1 to about 80% by weight such as lactose, sugar,
15 corn starch, modified corn starch, mannitol, sorbitol, inorganic salts such as calcium
carbonate and/or cellulose derivatives such as wood cellulose and microcrystalline
cellulose.

One or more binders may be present in addition to or in lieu of the fillers in an
amount within the range of from about 0 to about 35% and preferably from about 0.5
20 to about 30% by weight of the composition. Examples of such binders which are
suitable for use herein include polyvinylpyrrolidone (molecular weight ranging from
about 5000 to about 80,000 and preferably about 40,000), lactose, starches such as
corn starch, modified corn starch, sugars, gum acacia and the like as well as a wax
binder in finely powdered form (less than 500 microns) such as carnauba wax,
25 paraffin, spermaceti, polyethylenes or microcrystalline wax.

Where the composition is to be in the form of a tablet, it will include one or more tableting lubricants in an amount within the range of from about 0.2 to about 8% and preferably from about 0.5 to about 2% by weight of the composition, such as magnesium stearate, stearic acid, palmitic acid, calcium stearate, talc, carnauba wax and the like. Other conventional ingredients which may optionally be present include
5 preservatives, stabilizers, anti-adherents or silica flow conditioners or glidants, such as Syloid brand silicon dioxide as well as FD&C colors.

Tablets of the invention may also include a coating layer which may comprise from 0 to about 15% by weight of the tablet composition. The coating layer may
10 comprise any conventional coating formulations and will include one or more film-formers or binders, such as a hydrophilic polymer like hydroxypropylmethylcellulose, and/or a hydrophobic polymer like methacrylic acid esters neutral polymer, ethyl cellulose, cellulose acetate, polyvinyl alcohol-maleic anhydride copolymers, β -pinene polymers, glyceryl esters of wood resins and the like and one or more plasticizers,
15 such as triethyl citrate, diethyl phthalate, propylene glycol, glycerin, butyl phthalate, castor oil and the like. Both core tablets as well as coating formulations may contain aluminum lakes to provide color.

The film formers are applied from a solvent system containing one or more solvents including water, alcohols like methyl alcohol, ethyl alcohol or isopropyl
20 alcohol, ketones like acetone, or ethylmethyl ketone, chlorinated hydrocarbons like methylene chloride, dichloroethane, and 1,1,1-trichloroethane.

Where a color is employed, the color will be applied together with the film former, plasticizer and solvent compositions.

It will be recognized by one of skill in the art that the amount of drug required
25 for therapeutic effect on administration will, of course, vary with the agent chosen, the nature and severity of the condition and the mammal undergoing treatment, and is ultimately at the discretion of the physician. Furthermore, the optimal quantity and spacing of individual dosages of a drug will be determined by the nature and extent of the weight loss desired, the form, route and site of administration, the particular
30 patient being treated and that such optima can be determined by conventional techniques. It will also be appreciated that the optimal course of treatment, this is, the

number of doses given, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

- An example of a preferred formulation containing an SGLT2 inhibitor for use herein and a process for preparing such formulation are set out in U.S. Provisional Application Serial No. 60/896,286 filed March 22, 2007, the disclosure of which is incorporated herein by reference in its entirety for any purpose.

Preferred tablet formulations in accordance with the invention are set out below.

Material Tablet Dapagliflozin	Range % / mg by weight of 200 mg tablet 0.1 to 70% / 0.2 to 140 mg	Preferred Range % / mg by weight of 200 mg tablet 1 to 50% / 2 to 100 mg
Bulking Agent	2 to 95% / 4 to 190 mg	10 to 85% / 20 to 170 mg
Lactose	0 to 95% / 0 to 190 mg	20 to 75% / 10 to 100 mg
Microcrystalline cellulose	0 to 95% / 0 to 190 mg	20 to 75% / 40 to 150 mg
Disintegrant	0 to 20% / 0 to 40 mg	0.25 to 10% / 0.5 to 20 mg
Croscarmellose sodium	0 to 20% / 0 to 40 mg	2 to 10% / 4 to 20 mg
Crospovidone	4 to 12% / 4 to 20 mg	6 to 10% / 12 to 20 mg
Lubricant	0.1 to 5% / 0.2 to 10 mg	0.2 to 2% / 0.4 to 4 mg
Magnesium Stearate	0.1 to 5% / 0.2 to 10 mg	0.2 to 2% / 0.4 to 4 mg
Anti adherent/glidant Talc, silicon dioxide	0 to 20% / 0 to 40 mg	1 to 4% / 2 to 8 mg

Outer Protective Coating Layer	% / mg by weight of 200 mg tablet	% / mg by weight of 200 mg tablet
Coating polymer, and optional plasticizer, glidants and color	0.5 to 50% / 1 to 100 mg	1 to 5% / 2 to 10 mg

10

Preferred stock granulation formulations (for use in capsules) in accordance with the invention are set out below.

Material Tablet Dapagliflozin	Range % / mg by weight of 200 mg tablet 0.1 to 70% / 0.2 to 140 mg	Preferred Range % / mg by weight of 200 mg tablet 1 to 50% / 2 to 100 mg
Bulking Agent/Binder	2 to 95% / 4 to 190 mg	10 to 85% / 20 to 170 mg
Microcrystalline cellulose	1 to 95% / 1 to 190 mg	20 to 75% / 10 to 100 mg
Pregelatinized starch	0 to 95% / 0 to 190 mg	20 to 75% / 40 to 150 mg
Disintegrant	0 to 20% / 0 to 40 mg	0.25 to 10% / 0.5 to 20 mg
Sodium Starch glycolate	0 to 20% / 0 to 40 mg	2 to 10% / 4 to 20 mg
Lubricant	0.1 to 5% / 0.2 to 10 mg	0.2 to 2% / 0.4 to 4 mg
Magnesium Stearate	0.1 to 5% / 0.2 to 10 mg	0.2 to 2% / 0.4 to 4 mg
Anti adherent/glidant Talc silicon dioxide	0 to 20% / 0 to 40 mg	1 to 4% / 2 to 8 mg

The pharmaceutical formulation for use in the method of the invention in the form of a tablet or capsule may be obtained by a process which includes the steps of:

- a) formulating granules by wet granulation of the SGLT2 inhibitor,
- 5 b) blending the granules with a tableting aid and diluent,
- c) tableting the blend thus obtained into tablets, or
- d) loading the granules into capsules.

The mixture used for forming the granules includes a granulating binder. The
10 granulating binder is preferably a polyvinylpyrrolidone such as, for example, a polyvinylpyrrolidone having a molecular weight of 45,000. The polyvinylpyrrolidone may be used in a proportion of 2 to 4% by weight with respect to the final tablet.

After the granulating step, the granules may be sieved and dried.

The granules are then blended with a diluent and tableting aid. The diluent
15 may be a conventional filler usually used for making tablets, such as microcrystalline cellulose. The tableting aid may be a conventional material, such as magnesium stearate.

A typical injectable preparation is produced by aseptically placing 50 mg of compounds of structure I into a vial, aseptically freeze-drying and sealing. For use,
20 the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectable preparation.

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

25 **ASSAY FOR SGLT2 ACTIVITY**

The mRNA sequence for human SGLT2 (GenBank No. M95549) was cloned by reverse-transcription and amplification from human kidney mRNA, using standard molecular biology techniques. The cDNA sequence was stably transfected into CHO cells, and clones were assayed for SGLT2 activity essentially as described in Ryan et
30 al. (1994) (cited below). Evaluation of inhibition of SGLT2 activity in a clonally selected cell line was performed essentially as described in Ryan et al., with the following modifications. Cells were grown in 96-well plates for 2-4 days to 75,000 or

30,000 cells per well in F-12 nutrient mixture (Ham's F-12), 10% fetal bovine serum, 300 ug/ml Geneticin and penicillin-streptomycin. At confluence, cells were washed twice with 10 mM Hepes/Tris, pH 7.4, 137 mM N-methyl-D-glucamine, 5.4 mM KCl, 2.8 mM CaCl₂, 1.2 mM MgSO₄. Cells then were incubated with 10 μM [¹⁴C]AMG, and 10 μM inhibitor (final DMSO =0.5%) in 10 mM Hepes/Tris, pH 7.4, 137 mM NaCl, 5.4 mM KCl, 2.8 mM CaCl₂, 1.2 mM MgSO₄ at 37°C for 1.5 hr. Uptake assays were quenched with ice cold 1X PBS containing 0.5 mM phlorizin, and cells were then lysed with 0.1% NaOH. After addition of MicroScint scintillation fluid, the cells were allowed to shake for 1 hour, and then [¹⁴C]AMG was quantitated on a TopCount scintillation counter. Controls were performed with and without NaCl. For determination of EC₅₀ values, 10 inhibitor concentrations were used over 2 log intervals in the appropriate response range, and triplicate plates were averaged across plates. Ryan, M.J., Johnson, G., Kirk, J., Fuerstenberg, S.M., Zager, R.A. and Torok-Storb, B., "HK-2: an immortalized proximal tubule epithelial cell line from normal adult human kidney", *Kidney International*, 45:48-57 (1994).

EXAMPLES

The following working Examples are illustrative of the invention. All temperatures are expressed in degrees Centigrade unless otherwise indicated.

EXAMPLES 1 TO 3

Capsules containing compound I were prepared in strengths of 2.5 mg (Example 1), 10 mg (Example 2) and 100 mg (Example 3) as two-piece, gray opaque size #0 (2.5 mg and 10 mg) and size #00 (for 0 mg) hard gelatin capsules.

EXAMPLES 1 AND 2

Composition: 25.0 mg of Granulation containing compound I for Capsules (10.0% w/w as the non-solvated form), filled in Gray, Opaque, Size #0 Capsule Shell.

A. Stock Granulation Composition

Ingredient	Amount (% w/w)
------------	----------------

C. Example 1 Product: Compound I Capsule, 2.5 mg (As the Non-solvated Form)

1. Fill empty capsule shells with sufficient Example 1 Part A stock granulation for capsules (10.0%) w/w (as the non-solvated form), to provide 2.5 mg capsules.
2. De-dust the capsules.

EXAMPLE 2

Product: Compound I Capsule, 10 mg (As the Non-solvated Form)

1. Fill empty capsule shells with Example 1 Part A stock granulation for capsules (10.0 % w/w as the non-solvated form), to provide 10 mg capsules.
2. De-dust the capsules.
3. Weight sort the capsules.

The Example 1 (2.5 mg) and Example 2 (10 mg) capsules are used in treating obesity.

EXAMPLE 3

Compound I Capsule, 100 mg

Composition: 438.6 mg of compound I (Example 3 Part A) Stock Granulation for Capsules (22.8% w/w as the non-solvated form), filled in Gray, Opaque, Size #0 Capsule Shell.

A. Stock Granulation Composition

Ingredient	Amount (% w/w)
Compound I ¹	22.8
Pregelatinized Starch, NF	15.0
Microcrystalline Cellulose, NF ²	55.95
Sodium Starch Glycolate, NF	3.0
Silicon Dioxide, NF	2.0
Magnesium Stearate, NF ³	1.25

- ¹ This amount is expressed in terms of the amount of compound I at 100% purity. The exact amount will vary depending on the purity of compound I.

² The amount of microcrystalline cellulose used will vary depending on the purity of compound I.

³ The preferred amount is 1.25% (w/w). The range is 1.25-1.50% (w/w).

- 5 The stock granulation of Part A and the Example 3 capsules were prepared according to the following procedures.

B. Stock Granulation Procedure

1. Screen silicon dioxide.
- 10 2. Mix silicon dioxide with compound I in a suitable blender.
3. Screen the blend from Step 2, and mix again.
4. Screen pregelatinized starch and microcrystalline cellulose, if necessary.
5. Add ingredients from Step 4 to the blend from Step 3, and mix.
- 15 6. Screen sodium starch glycolate.
7. Add ingredient from Step 6 to the blend from Step 5, and mix.
8. Screen a portion of magnesium stearate.
9. Add ingredient from Step 8 to the blend from Step 7, and mix.
10. Densify the blend from Step 9.
- 20 11. Reduce the densified blend from Step 10.
12. Screen the remaining portion of magnesium stearate.
13. Add ingredient from Step 12 to the granulation from Step 11, and mix.

C. Example 3 Product: Compound I Capsule, 100 mg (As the Non-solvated Form)

- 25 1. Fill empty capsule shells with Example 3 stock granulation for capsules (22.8 % w/w as the non-solvated form).
2. De-dust the capsules.
3. Weight sort the capsules.

30

The so-formed capsules of Example 1 (2.5 mg), Example 2 (10 mg) and Example 3 (100 mg) are used to inhibit or prevent rejection of renal transplant rejection.

5

EXAMPLES 4 TO 6

Tablets containing the SGLT2 inhibitor compound Ia (the (S) propylene glycol solvate or (S) propylene glycol hydrate of compound I) were prepared in strengths of 2.5 mg (Example 4), 10 mg (Example 5) and 50 mg (Example 6) as described below.

10

EXAMPLE 4

Product: Compound Ia Tablet, 2.5 mg

A. Tablet Composition

Ingredient	Amount
Compound Ia ¹	3.075 mg
Microcrystalline Cellulose, NF ²	67.113 mg
Lactose Anhydrous, NF	25.000 mg
Crospovidone, NF	8.750 mg
Croscarmellose Sodium, NF	3.750 mg
Talc, USP	12.500 mg
Silicon Dioxide, NF	2.875 mg
Magnesium Stearate, NF ³	1.938 mg

¹ Compound Ia is a propylene glycol solvate. The amount of non-solvated compound I is theoretically equivalent to 81.29% of compound Ia. The actual amount of compound Ia will depend on the "As Is" purity of the drug.

² This is the compensating excipient. The amount used may vary depending on the "As Is" purity of the drug and/or the actual amount of magnesium stearate used.

³ The target amount is 1.94 mg. Acceptable range is 1.55-2.33 mg.

20

The stock granulation of Part A and the Example 4 tablets were prepared according to the following procedures.

B. Stock Granulation Procedure

1. Deaggregate compound Ia and magnesium stearate separately using a suitable screen.

2. Mix compound Ia with a portion of microcrystalline cellulose in a suitable mixer and transfer it into a suitable blender.
3. "Dry Rinse" the mixer used for mixing Step 2 with a portion of microcrystalline cellulose.
- 5 4. Add the blend from Step 3 to the blend from Step 2.
5. Mix the mixture from Step 4 with remaining microcrystalline cellulose, portion of crospovidone, portion of croscarmellose sodium, portion of silicon dioxide and lactose anhydrous.
6. Add talc and intragranular magnesium stearate to the mixture from
- 10 Step 5 and mix.
7. Compact the powder blend from Step 6.
8. Reduce compact from Step 7 to form granules.
9. Mix the granules from Step 8 with remaining amounts of crospovidone, croscarmellose sodium and silicon dioxide.
- 15 10. Mix the granules from Step 9 with remaining amount of magnesium stearate.

C. Example 4 Product: Compound Ia Tablet, 2.5 mg

1. Setup the tableting equipment.
- 20 2. Compress the Example 4 stock granulation into tablets (2.46% w/w), (2.5 mg).

EXAMPLE 5

Product: Compound Ia Tablet, 10 mg

25 **A. Tablet Composition**

Ingredient	Amount
Compound Ia ¹	12.300 mg
Microcrystalline Cellulose, NF ²	57.888 mg
Lactose Anhydrous, NF	25.000 mg
Crospovidone, NF	8.750 mg
Croscarmellose Sodium, NF	3.750 mg
Talc, USP	12.500 mg
Silicon Dioxide, NF	2.875 mg
Magnesium Stearate, NF ³	1.938 mg

¹ Compound Ia is a propylene glycol solvate. The amount of non-solvated compound Ia is theoretically equivalent to 81.29% of compound Ia. The actual amount of compound Ia will depend on the "As Is" purity of the drug.

5 ² This is the compensating excipient. The amount used may vary depending on the "As Is" purity of the drug and/or the actual amount of magnesium stearate used.

³ The target amount is 1.94 mg. Acceptable range is 1.55-2.33 mg.

The stock granulation of Part A and the Example 5 tablets were prepared according to the following procedures.

10

B. Stock Granulation Procedure

1. Deaggregate compound Ia and magnesium stearate separately using a suitable screen.

15 2. Mix microcrystalline cellulose, compound Ia portion of crospovidone, portion of croscarmellose sodium, portion of silicon dioxide and lactose anhydrous in a suitable blender.

3. Add talc and intragranular magnesium stearate to the mixture from Step 2 and mix in a suitable blender.

4. Compact the powder blend from Step 3.

20 5. Reduce compact from Step 4 to form granules.

6. Mix the granules from Step 5 with remaining amounts of crospovidone, croscarmellose sodium and silicon dioxide.

7. Mix the granules from Step 6 with remaining amount of magnesium stearate.

25

C. Example 5 Product: Compound Ia Tablet, 10 mg

1. Setup the tableting equipment.

2. Compress the Example 5 stock granulation into tablets (9.84% w/w).

EXAMPLE 6**Product: Compound Ia Tablet, 50 mg****A. Tablet Composition**

Ingredient	Amount
Compound Ia ¹	61.660 mg
Microcrystalline Cellulose, NF ²	114.090 mg
Lactose Anhydrous, NF	62.600 mg
Crospovidone, NF	21.910 mg
Croscarmellose Sodium, NF	9.390 mg
Talc, USP	31.300 mg
Silicon Dioxide, NF	7.200 mg
Magnesium Stearate, NF ³	4.850 mg

¹ The amount shown is based on the amount of compound Ia at 100% purity. The exact amount may vary depending on the “As Is” purity of compound Ia.

² This is the compensating excipient. The amount used may vary depending on the “As Is” purity of the drug and/or the actual amount of magnesium stearate used.

³ The target amount is 4.85 mg. Acceptable range is 3.76 – 5.95 mg.

10 The stock granulation of Part A and the Example 6 tablets were prepared according to the following procedures.

B. Stock Granulation Procedure

1. Mix compound Ia microcrystalline cellulose, lactose anhydrous, crospovidone, croscarmellose sodium, talc and silicon dioxide in a suitable blender.
2. Pass the mixture from Step 1 through a suitable mill.
3. Determine the yield from Step 1 and calculate the amount of magnesium stearate required.
4. Mix the mixture from Step 2 in a suitable blender.
5. Mix the mixture from Step 4 with magnesium stearate.
6. Dry granulate the powder blend from Step 5.
7. Size the granulation from Step 6.
8. Determine the yield based on Step 7.
9. Mix the granules from Step 8 with remaining amount of crospovidone, croscarmellose sodium and silicon dioxide.

10. Mix the granules from Step 9 with remaining amount of magnesium stearate.

C. Example 6 Product: Compound Ia PGS Tablet, 50 mg

- 5 1. Setup the tableting equipment.
2. Compress the Example 6 stock granulation (19.7% w/w), into tablets (50 mg).

The so-formed tablets of Example 4 (2.5 mg), Example 5 (10 mg) and
10 Example 6 (50 mg) are used to inhibit or prevent rejection of renal transplant rejection.

EXAMPLE 7

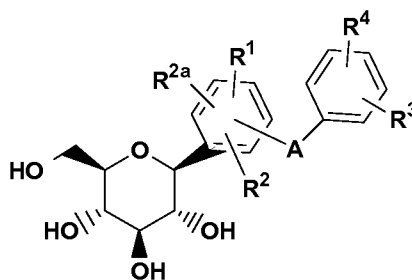
An oral solution (0.5 mg/mL) was prepared by dissolving compound I in a
15 mixture of polyethylene glycol 400, NF and water for injection, USP or purified water (30:70% v/v). The oral solution was clear and colorless. It is used to inhibit or prevent renal transplant rejection.

EXAMPLE 8

20 The glucosuric effects of compound Ia results in significant loss of calories in the urine versus a known SGLT2 inhibitor (GSK 869,682). Thus, as seen in Figure 1, the results of an indirect comparison of two single ascending dose studies of SGLT2 inhibitors is shown. The panel at the top of Figure 1 is from a presentation by GSK in an analyst meeting, showing the amount of glucose excretion/day in healthy subjects
25 taking 50, 100, 200 or 500 mg of GSK 869,682. The panel at the bottom is from study MB-102001, showing the amount of glucose excretion/day in healthy subjects taking 5, 20, 50 or 100 mg of compound Ia. This is further confirmed in a 14-day multiple ascending dose phase 2a study in subjects with type 2 diabetes. Results from the 24-hour glucose excretion are shown in Figure 2 for all subjects in the MB-
30 102003 study. The mean urine glucose is in the darker lines. Compared to subjects on placebo, who had low urine glucose excretion, subjects randomized to compound Ia had higher urine glucose excretion.

WHAT IS CLAIMED IS:

1. A method for treating cancers that express SGLT2 levels higher than normal cells in a mammal comprising administering to the mammal in need of such treatment a therapeutically effective amount of an SGLT2 inhibitor.
2. The method according to Claim 1 wherein the mammal is a human.
3. The method according to Claim 2 wherein the cancer is lung cancer metastatic lesions.
4. The method according to Claim 2 wherein the cancer is lung cancer metastatic lesions of the liver.
5. The method according to Claim 2 wherein the cancer is lung cancer metastatic lesions of the lymph nodes.
6. The method according to Claim 1 wherein the SGLT2 inhibitor is a C-glucoside or an O-glucoside.
7. The method according to Claim 1 wherein the amount of SGLT2 inhibitor has the structure



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 SO₂;

R³ and R⁴ are independently hydrogen, OH, OR^{5a}, OAryl, OCH₂Aryl, alkyl, cycloalkyl, CF₃, -OCHF₂, -OCF₃, halogen, -CN, -CO₂R^{5b}, -CO₂H, COR^{6b}, -CH(OH)R^{6c}, -CH(OR^{5h})R^{6d}, -CONR⁶R^{6a}, -NHCOR^{5c}, -NHSO₂R^{5d}, -NHSO₂Aryl, Aryl, -SR^{5e}, -SOR^{5f}, -SO₂R^{5g}, -SO₂Aryl, or a five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO₂, or R³ and R⁴ together with the carbons to which they are attached form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO₂;

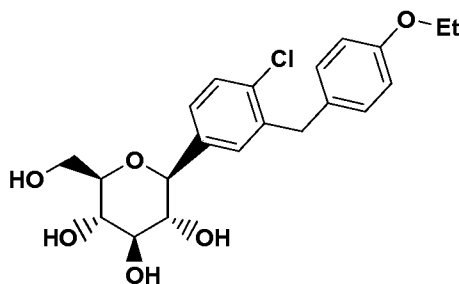
R⁵, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R^{5g}, R^{5h} and R⁵ⁱ are independently alkyl;

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

A is O, S, NH, or (CH₂)_n where n is 0-3, or a pharmaceutically acceptable salt, stereoisomer, or prodrug ester thereof;

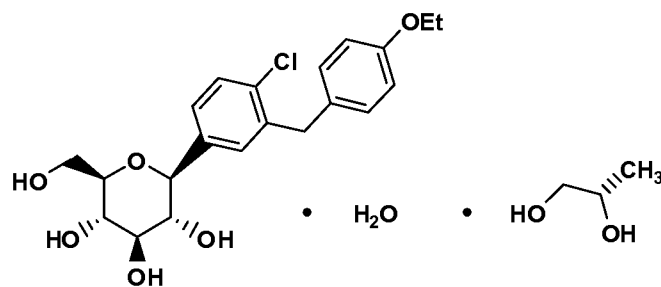
with the proviso that where A is (CH₂)_n where n is 0, 1, 2, or 3 or A is O, and at least one of R¹, R², and R^{2a} is OH or OR⁵, then at least one of R¹, R², and R^{2a} is CF₃, OCF₃, or OCHF₂ and/or at least one of R³ and R⁴ is CF₃, -OCHF₂, -OCF₃, -CN, -CO₂R^{5b}, CH(OR^{5h})R^{6d}, CH(OH)R^{6c}, COR^{6b}, -NHCOR^{5c}, -NHSO₂R^{5d}, -NHSO₂Aryl, Aryl, -SR^{5e}, -SOR^{5f}, -SO₂R^{5g} or -SO₂Aryl.

8. The method according to Claim 1 wherein the SGLT2 inhibitor has the structure



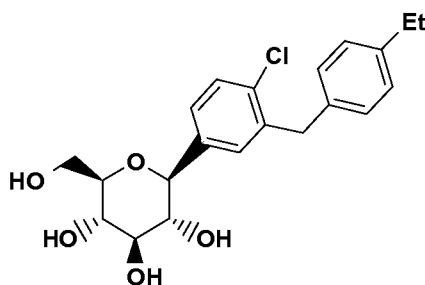
or a pharmaceutically acceptable salt, a stereoisomer thereof, or a prodrug ester thereof.

9. The method according to Claim 1 wherein the SGLT2 inhibitor has the structure



Compound 1a

10. The method as defined in Claim 1 wherein the SGLT2 inhibitor has the structure



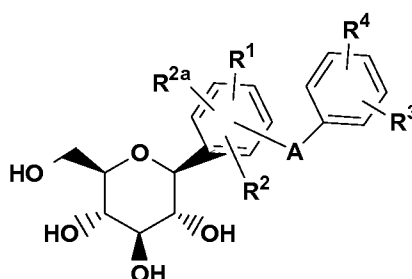
or a pharmaceutically acceptable salt thereof, a stereoisomer thereof, or a prodrug ester thereof.

11. A method for treating cancers that express SGLT2 levels higher than normal cells in a mammal comprising administering to the mammal in need of such treatment a therapeutically effective amount of a pharmaceutical composition comprising an SGLT2 inhibitor and at least one pharmaceutically acceptable carrier, excipient, or diluent.

12. The method according to Claim 11 wherein the mammal is a human.

13. The method according to Claim 12 wherein the cancer is lung cancer metastatic lesions.

14. The method according to Claim 12 wherein the cancer is lung cancer metastatic lesions of the liver.
15. The method according to Claim 12 wherein the cancer is lung cancer metastatic lesions of the lymph nodes.
16. The method according to Claim 11 wherein the SGLT2 inhibitor is a C-glucoside or an O-glucoside.
17. The method according to Claim 11 wherein the amount of SGLT2 inhibitor has the structure



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} , $OAryl$, OCH_2Aryl , alkyl, cycloalkyl, CF_3 , $-OCHF_2$, $-OCF_3$, halogen, $-CN$, $-CO_2R^{5b}$, $-CO_2H$, COR^{6b} , $-CH(OH)R^{6c}$, $-CH(OR^{5h})R^{6d}$, $-CONR^{6e}R^{6a}$, $-NHCOR^{5c}$, $-NHSO_2R^{5d}$, $-NHSO_2Aryl$, $Aryl$, $-SR^{5e}$, $-SOR^{5f}$, $-SO_2R^{5g}$, $-SO_2Aryl$, 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 ;

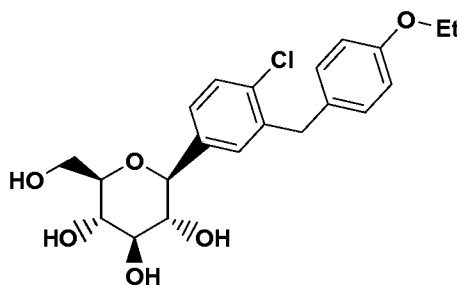
R^5 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^{5g} , R^{5h} and R^{5i} are independently alkyl;

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 SO_2 ;

A is O, S, NH, or $(CH_2)_n$ where n is 0-3, or a pharmaceutically acceptable salt, stereoisomer, or prodrug ester thereof;

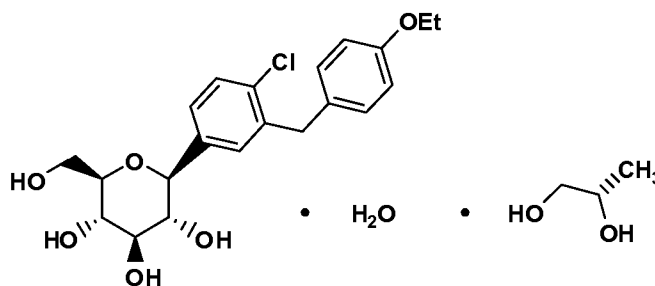
with the proviso that where A is $(CH_2)_n$ where n is 0, 1, 2, or 3 or A is O, and at least one of R^1 , R^2 , and R^{2a} is OH or OR^5 , then at least one of R^1 , R^2 , and R^{2a} is CF_3 , OCF_3 , or $OCHF_2$ and/or at least one of R^3 and R^4 is CF_3 , $-OCHF_2$, $-OCF_3$, $-CN$, $-CO_2R^{5b}$, $CH(OR^{5h})R^{6d}$, $CH(OH)R^{6c}$, COR^{6b} , $-NHCOR^{5c}$, $-NHCO_2R^{5d}$, $-NHCO_2Aryl$, $Aryl$, $-SR^{5e}$, $-SOR^{5f}$, $-SO_2R^{5g}$ or $-SO_2Aryl$.

18. The method according to Claim 11 wherein the SGLT2 inhibitor has the structure



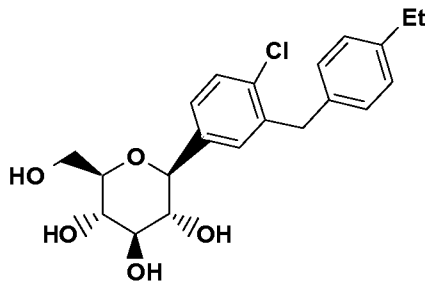
or a pharmaceutically acceptable salt, a stereoisomer thereof, or a prodrug ester thereof.

19. The method according to Claim 11 wherein the SGLT2 inhibitor has the structure



Compound 1a

20. The method as defined in Claim 11 wherein the SGLT2 inhibitor has the structure



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

21. A method for treating cancers that express SGLT2 levels higher than normal cells in a mammal comprising administering to the mammal in need of such treatment a therapeutically effective amount of an SGLT2 inhibitor and a cytotoxic agent where the cytotoxic agent is administered prior to, after, or concurrently with the SGLT2 inhibitor.

22. The method according to Claim 21 wherein the mammal is a human.

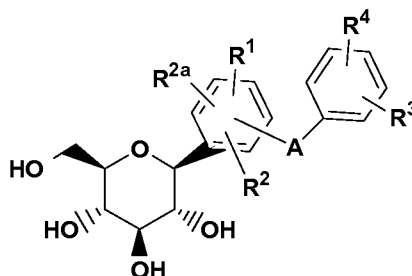
23. The method according to Claim 22 wherein the cancer is lung cancer metastatic lesions.

24. The method according to Claim 22 wherein the cancer is lung cancer metastatic lesions of the liver.

25. The method according to Claim 22 wherein the cancer is lung cancer metastatic lesions of the lymph nodes.

26. The method according to Claim 21 wherein the SGLT2 inhibitor is a C-glucoside or an O-glucoside.

27. The method according to Claim 21 wherein the amount of SGLT2 inhibitor has the structure



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} , $OAryl$, OCH_2Aryl , alkyl, cycloalkyl, CF_3 , $-OCHF_2$, $-OCF_3$, halogen, $-CN$, $-CO_2R^{5b}$, $-CO_2H$, COR^{6b} , $-CH(OH)R^{6c}$, $-CH(OR^{5h})R^{6d}$, $-CONR^{6a}$, $-NHCOR^{5c}$, $-NHSO_2R^{5d}$, $-NHSO_2Aryl$, $Aryl$, $-SR^{5e}$, $-SOR^{5f}$, $-SO_2R^{5g}$, $-SO_2Aryl$, 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 ;

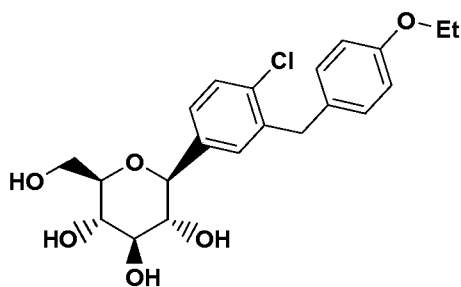
R^5 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^{5g} , R^{5h} and R^{5i} are independently alkyl;

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 SO_2 ;

A is O, S, NH, or $(CH_2)_n$ where n is 0-3, or a pharmaceutically acceptable salt, stereoisomer, or prodrug ester thereof;

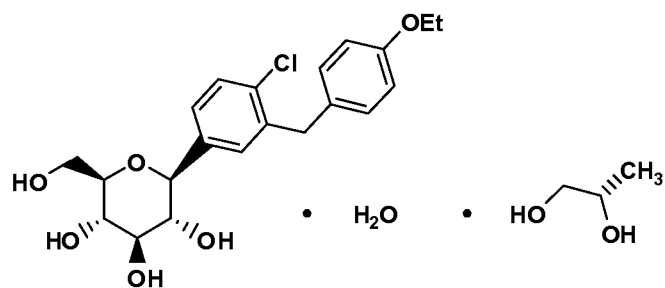
with the proviso that where A is $(CH_2)_n$ where n is 0, 1, 2, or 3 or A is O, and at least one of R^1 , R^2 , and R^{2a} is OH or OR^5 , then at least one of R^1 , R^2 , and R^{2a} is CF_3 , OCF_3 , or $OCHF_2$ and/or at least one of R^3 and R^4 is CF_3 , $-OCHF_2$, $-OCF_3$, $-CN$, $-CO_2R^{5b}$, $CH(OR^{5h})R^{6d}$, $CH(OH)R^{6c}$, COR^{6b} , $-NHCOR^{5c}$, $-NHSO_2R^{5d}$, $-NHSO_2Aryl$, $Aryl$, $-SR^{5e}$, $-SOR^{5f}$, $-SO_2R^{5g}$ or $-SO_2Aryl$.

28. The method according to Claim 21 wherein the SGLT2 inhibitor has the structure



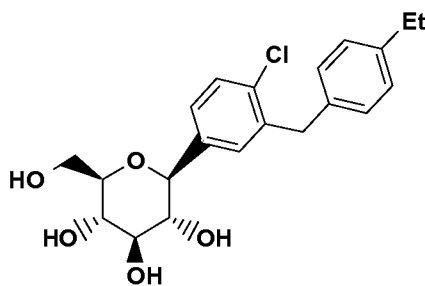
or a pharmaceutically acceptable salt, a stereoisomer thereof, or a prodrug ester thereof.

29. The method according to Claim 21 wherein the SGLT2 inhibitor has the structure



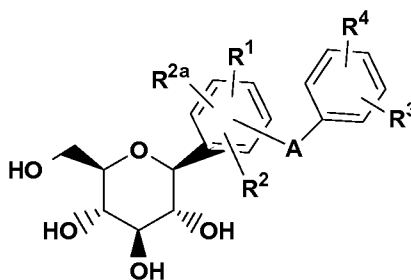
Compound 1a

30. The method as defined in Claim 21 wherein the SGLT2 inhibitor has the structure



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

31. A method for treating cancers that express SGLT2 levels higher than normal cells in a mammal comprising administering to the mammal in need of such treatment a therapeutically effective amount of a pharmaceutical composition comprising an SGLT2 inhibitor, a cytotoxic agent and at least one pharmaceutically acceptable carrier, excipient, or diluent.
32. The method according to Claim 31 wherein the mammal is a human.
33. The method according to Claim 32 wherein the cancer is lung cancer metastatic lesions.
34. The method according to Claim 32 wherein the cancer is lung cancer metastatic lesions of the liver.
35. The method according to Claim 32 wherein the cancer is lung cancer metastatic lesions of the lymph nodes.
36. The method according to Claim 31 wherein the SGLT2 inhibitor is a C-glucoside or an O-glucoside.
37. The method according to Claim 31 wherein the amount of SGLT2 inhibitor has the structure



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 SO₂;

R³ and R⁴ are independently hydrogen, OH, OR^{5a}, OAryl, OCH₂Aryl, alkyl, cycloalkyl, CF₃, -OCHF₂, -OCF₃, halogen, -CN, -CO₂R^{5b}, -CO₂H, COR^{6b}, -CH(OH)R^{6c}, -CH(OR^{5h})R^{6d}, -CONR⁶R^{6a}, -NHCOR^{5c}, -NHSO₂R^{5d}, -NHSO₂Aryl, Aryl, -SR^{5e}, -SOR^{5f}, -SO₂R^{5g}, -SO₂Aryl, or a five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO₂, or R³ and R⁴ together with the carbons to which they are attached form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO₂;

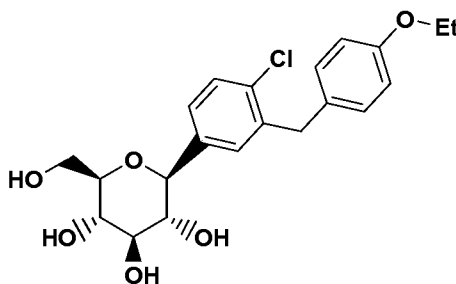
R⁵, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R^{5g}, R^{5h} and R⁵ⁱ are independently alkyl;

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

A is O, S, NH, or (CH₂)_n where n is 0-3, or a pharmaceutically acceptable salt, stereoisomer, or prodrug ester thereof;

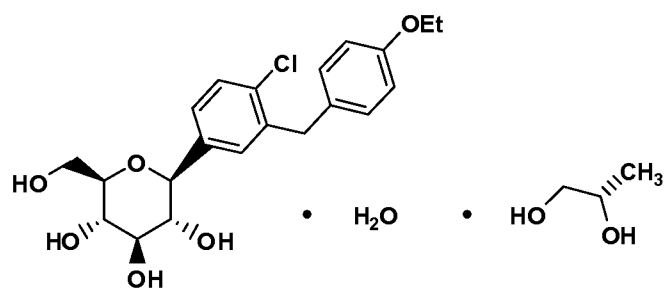
with the proviso that where A is (CH₂)_n where n is 0, 1, 2, or 3 or A is O, and at least one of R¹, R², and R^{2a} is OH or OR⁵, then at least one of R¹, R², and R^{2a} is CF₃, OCF₃, or OCHF₂ and/or at least one of R³ and R⁴ is CF₃, -OCHF₂, -OCF₃, -CN, -CO₂R^{5b}, CH(OR^{5h})R^{6d}, CH(OH)R^{6c}, COR^{6b}, -NHCOR^{5c}, -NHSO₂R^{5d}, -NHSO₂Aryl, Aryl, -SR^{5e}, -SOR^{5f}, -SO₂R^{5g} or -SO₂Aryl.

38. The method according to Claim 31 wherein the SGLT2 inhibitor has the structure



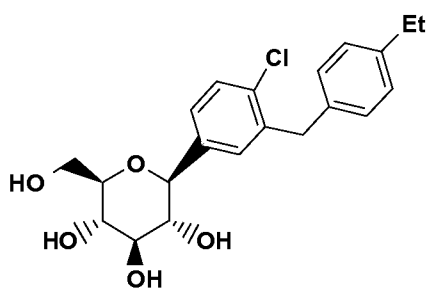
or a pharmaceutically acceptable salt, a stereoisomer thereof, or a prodrug ester thereof.

39. The method according to Claim 31 wherein the SGLT2 inhibitor has the structure



Compound 1a

40. The method as defined in Claim 31 wherein the SGLT2 inhibitor has the structure

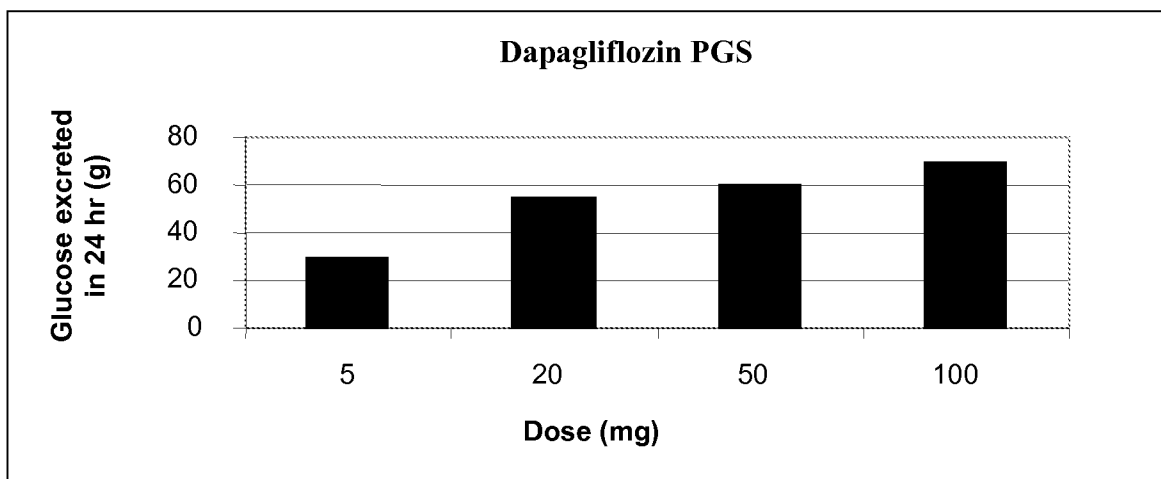
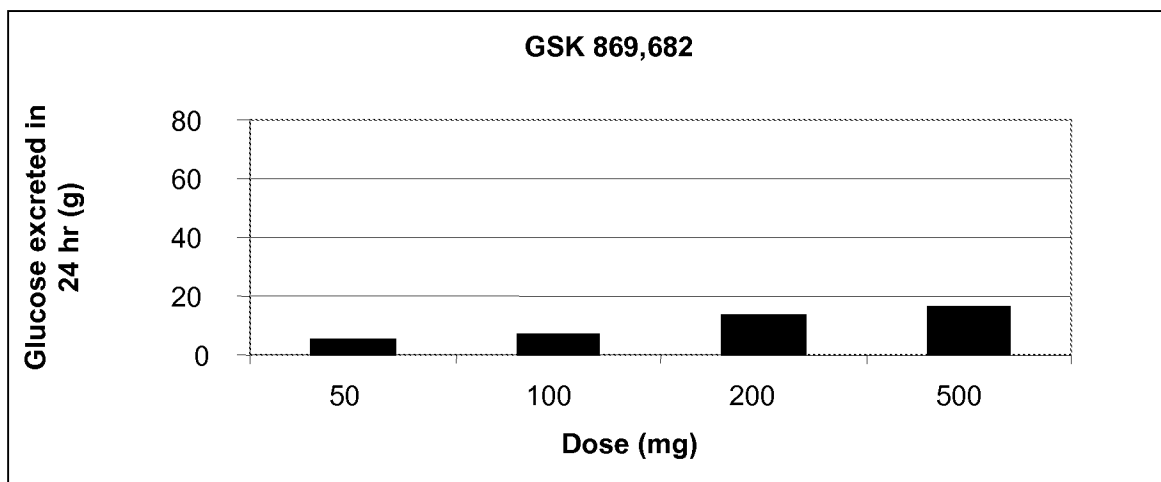


or a pharmaceutically acceptable salt thereof, a stereoisomer thereof, or a prodrug ester thereof.

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FIG. 1

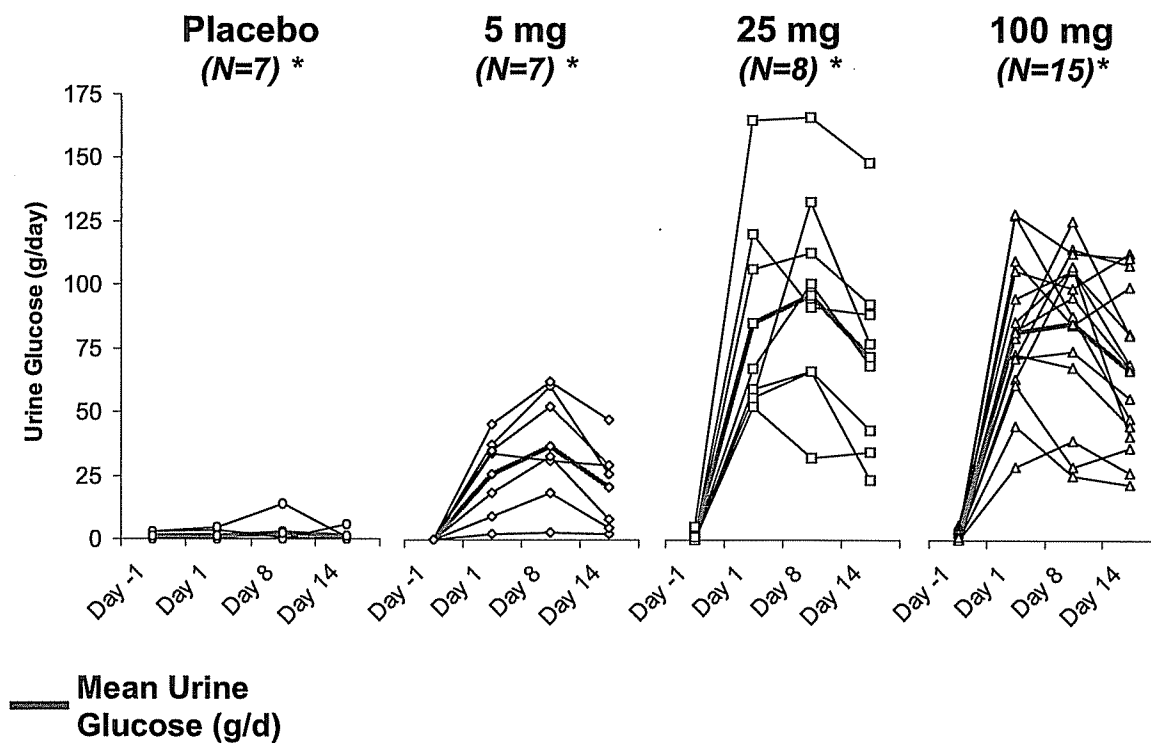
Indirect comparison of GSK 869,682 and Dapagliflozin PGS



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FIG. 2

Urine glucose excretion in diabetic subjects treated with Dapagliflozin PGS



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/037301

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/70 A61P35/04

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 A61P

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, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ISHIKAWA N ET AL: "SGLT GENE EXPRESSION IN PRIMARY LUNG CANCERS AND THEIR METASTATIC LESIONS" JAPANESE JOURNAL OF CANCER RESEARCH; JAPANESE CANCER ASSOCIATION, TOKYO, JP, vol. 92, no. 8, 1 August 2001 (2001-08-01), pages 874-879, XP009054592 ISSN: 0910-5050 page 876, column 2 page 878 ----- -/--	1-40

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *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.
- *Z* document member of the same patent family

Date of the actual completion of the international search

24 April 2009

Date of mailing of the international search report

12/05/2009

Name and mailing address of the ISA/

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Authorized officer

Büttner, Ulf

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/037301

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KOMOROSKI B ET AL: "Dapagliflozin (BMS-512148), a selective SGLT2 inhibitor, inhibits glucose resorption and reduces fasting glucose in patients with type 2 diabetes mellitus" DIABETOLOGIA, vol. 50, no. Suppl. 1, September 2007 (2007-09), page S315, XP009115723 & 43RD ANNUAL MEETING OF THE EUROPEAN-ASSOCIATION-FOR-THE-STUDY-OF-DIAB ETES; AMSTERDAM, NETHERLANDS; SEPTEMBER 18 -21, 2007 ISSN: 0012-186X the whole document	1-40
Y	KLER L ET AL: "Clinical studies to assess safety, pharmacokinetics and pharmacodynamics of sergliflozin, a novel inhibitor of glucose reabsorption" DIABETOLOGIA, vol. 50, no. Suppl. 1, September 2007 (2007-09), pages S376-S377, XP002525147 & 43RD ANNUAL MEETING OF THE EUROPEAN-ASSOCIATION-FOR-THE-STUDY-OF-DIAB ETES; AMSTERDAM, NETHERLANDS; SEPTEMBER 18 -21, 2007 ISSN: 0012-186X the whole document	1-40
Y	US 6 414 126 B1 (ELLSWORTH BRUCE [US] ET AL) 2 July 2002 (2002-07-02) cited in the application claim 2	1-40

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/037301

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2009/037301

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6414126	B1	02-07-2002	NONE