

## TITLE OF THE INVENTION

### **PHARMACEUTICAL FORMULATIONS COMPRISING 1 - (BETA-D-GLUCOPYRANOSYL) - 2 - THIENYLMETHYLBENZENE DERIVATIVES AS INHIBITORS OF SGLT**

## 5                   CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U. S. Provisional Application 61/333,495 filed on May 11, 2010, which is incorporated by reference herein in its entirety.

## 10                   STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

The research and development of the invention described below was not federally sponsored.

## 15                   FIELD OF THE INVENTION

This invention relates to novel pharmaceutical compositions comprising a compound of Formula (I), a prodrug thereof, or a pharmaceutically acceptable salt thereof, disclosed herein, that can be used in the treatment of diabetes mellitus, obesity, diabetic complications, and related diseases.

## BACKGROUND

25           WO 2005/012326, the disclosure of which is hereby incorporated by reference in its entirety, discloses a class of compounds that are inhibitors of sodium-dependent glucose transporter (SGLT) and therapeutic uses for such compounds such as the treatment of diabetes, obesity, diabetic complications, and the like. WO 2005/012326 discloses the compound 1-( $\beta$ -D-glucopyranosyl)-4-  
30 methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene). 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene) hemihydrate and certain

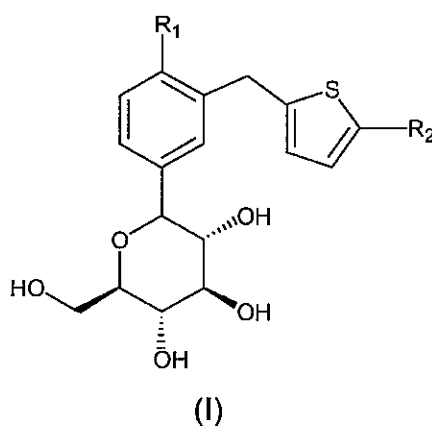
crystal form thereof are disclosed in WO 2008/069327, the disclosure of which is also hereby incorporated by reference in its entirety.

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## SUMMARY OF THE INVENTION

In its many embodiments, the present invention provides a novel pharmaceutical composition of compounds of Formula (I), a prodrug thereof, or a pharmaceutically acceptable salt thereof, and methods of treatment, prevention,  
10 inhibition or amelioration of one or more diseases associated with sodium-dependent glucose transporter using such pharmaceutical compositions.

One aspect of the present invention features an orally administrable pharmaceutical formulation comprising  
15 (a) compound of Formula (I)



wherein

20 R<sub>1</sub> is halo, cyano, optionally substituted lower alkyl, or optionally substituted lower alkoxy; and

R<sub>2</sub> is optionally substituted aryl, or optionally substituted heterocyclyl;  
or a prodrug, or pharmaceutically acceptable salt thereof;

(b) at least one diluent or filler;

25 (c) optionally at least one disintegrant;

(d) optionally at least one binder; and

(e) optionally at least one lubricant;

wherein

the compound of formula (I) is present in an amount within the range of from about

5 1% to about 80% by weight;

the diluent or filler is present in an amount within the range of from about 10% to about 95% by weight;

the disintegrant, if present, is present in an amount within the range of from about 0.1% to about 20% by weight;

10 the binder, if present, is present in an amount within the range of from about 0.1% to about 20% by weight; and

the lubricant, if present, is present in an amount within the range of from about 0.1% to about 5% by weight, all of the above % by weight being based on the weight of the formulation.

15

In certain embodiments, the compound of Formula (I) is a compound of Formula (I-S) as described herein.

In certain embodiments, the present invention is directed to an orally  
20 administrable pharmaceutical formulation comprising a compound of Formula (I) as described herein in combination with a bioavailability-promoting agent.

In certain embodiments, the bioavailability-promoting agent increases the bioavailability of the compound and includes excipients known in the formulation of  
25 pharmaceuticals. Preferably formulating a compound of Formula (I) with the bioavailability-promoting agent results in improved measurable bioavailability of the compound upon administration of the formulation.

Preferably, the present invention is further directed to a bioavailability-  
30 promoting agent that includes a composition of excipients, such as binders, fillers, disintegrants, lubricants or combinations thereof.

In certain embodiments, the formulation of the present invention is a solid oral dosage form that provides for an increased bioavailability of the compound included therein as compared to an oral suspension including the compound in the same amount as the solid oral dosage form.

Additional embodiments and advantages of the invention will become apparent from the detailed discussion, schemes, examples, and claims below.

## BRIEF DESCRIPTION OF THE FIGURES

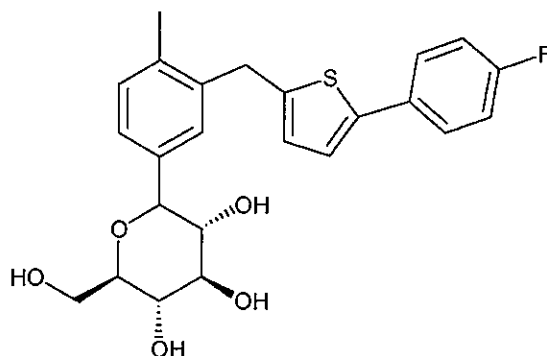
Figure 1A and B provides linear and logarithmic plasma concentration profiles of compound of Formula (I-S) following oral administration of various formulations of compound of Formula (I-S) in dogs.

Figure 2 provides plasma concentration profiles of compound (I-S) following oral administration of various formulations of compound of Formula (I-S) in human subjects.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed in part to an orally administrable pharmaceutical formulation comprising

- 5 (a) a compound of Formula (I-S):



(I-S)

or a prodrug or pharmaceutically acceptable salt thereof;

10

- (b) at least one diluent or filler;  
(c) optionally at least one disintegrant;  
(d) optionally at least one binder; and  
(e) optionally at least one lubricant;

15

wherein

the compound of formula (I-S) is present in an amount within the range of from about 1% to about 80% by weight;

the diluent or filler is present in an amount within the range of from about 10% to about 95% by weight;

20

the disintegrant, if present, is present in an amount within the range of from about 0.1% to about 20% by weight;

the binder, if present, is present in an amount within the range of from about 0.1% to about 20% by weight; and

the lubricant, if present, is present in an amount within the range of from

about 0.1% to about 5% by weight, all of the above % by weight being based on the weight of the formulation.

In certain embodiments, the present invention is directed to an orally  
5 administrable pharmaceutical formulation comprising

(a) a compound of Formula (I-S), or a prodrug or pharmaceutically acceptable salt thereof present in an amount within the range of from about 40% to about 60% by weight;

(b) at least one diluent or filler present in an amount within the range of from  
10 about 30% to about 50% by weight ;

(c) at least one disintegrant in an amount within the range of from about 3% to about 10% by weight;

(d) at least one binder present in an amount within the range of from about 0.5% to about 5% by weight; and

(e) at least one lubricant present in an amount within the range of from  
15 about 0.5% to about 2% by weight;

wherein the % by weight is based on the weight of the formulation.

The compound of Formula (I-S) may also be referred to as 1-( $\beta$ -D-  
20 glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene).

In certain preferred embodiments, the compound of formula (I-S) is the hemihydrate of the compound of Formula (I-S), also referred to as 1-( $\beta$ -D-  
25 glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene) hemihydrate.

In certain embodiments, the invention is directed to a pharmaceutical composition as described herein for use in the manufacture of a pharmaceutical dosage form for oral administration to a mammal in need of treatment,  
30 characterized in that said dosage form can be administered at any time of the day independently of the food taken in by said mammal.

In certain embodiments, the invention is directed to a method of therapy of the human or non-human animal body that comprises administering to said body a therapeutically effective dose of a pharmaceutical composition described herein.

5

In certain embodiments, the invention is directed to a pharmaceutical package suitable for commercial sale comprising a container, an oral dosage form as described herein, and associated with said package written matter non-limited as to whether the dosage form can be administered with or without food.

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#### **A) Terms**

Some terms are defined below and by their usage throughout this disclosure.

15

**“Administering”** or **“administration”** means providing a drug to a patient in a manner that is pharmacologically useful.

**“Patient”** or **“subject”** means an animal, preferably a mammal, more preferably a human, in need of therapeutic intervention.

20

**“Dosage form”** means one or more compounds in a medium, carrier, vehicle, or device suitable for administration to a patient. **“Oral dosage form”** means a dosage form suitable for oral administration.

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**“Dose”** means a unit of drug. Conventionally, a dose is provided as a dosage form. Doses may be administered to patients according to a variety of dosing regimens. Common dosing regimens include once daily orally (qd), twice daily orally (bid), and thrice daily orally (tid).

**“Terminal half-life”** ( $t_{1/2}$ ) is calculated as  $0.693/k$ , wherein “k” means the apparent elimination rate constant, estimated by linear regression of the log-transformed plasma concentration during the terminal log-linear elimination phase.

30

The plasma half-life of a drug ( $t_{1/2}$ ) is the time necessary to halve the plasma concentration, for example to decrease from 100 to 50 mg/L. The knowledge of

the half-life is useful for the determination of the frequency of administration of a drug (the number of intakes per day) for obtaining the desired plasma concentration. Generally, the half-life of a particular drug is independent of the dose administered. In certain exceptional cases, it varies with the dose: it can  
5 increase or decrease according to, for example, the saturation of a mechanism (elimination, catabolism, binding to plasma proteins etc).

“**Area under the curve**” or “**AUC**” is the area as measured under a plasma drug concentration curve, also termed plasma concentration profile. Often, the AUC is specified in terms of the time interval across which the plasma drug  
10 concentration curve is being integrated, for instance  $AUC_{\text{start-finish}}$ . Thus,  $AUC_{0-48h}$  refers to the AUC obtained from integrating the plasma concentration curve over a period of zero to 48 hours, where zero is conventionally the time of administration of the drug or dosage form comprising the drug to a patient.  $AUC_t$  refers to area under the plasma concentration curve from hour 0 to the last detectable  
15 concentration at time  $t$ , calculated by the trapezoidal rule.  $AUC_{\text{inf}}$  refers to the AUC value extrapolated to infinity, calculated as the sum of  $AUC_t$  and the area extrapolated to infinity, calculated by the concentration at time  $t$  ( $C_t$ ) divided by  $k$ . (If the  $t_{1/2}$  value was not estimable for a subject, the mean  $t_{1/2}$  value of that treatment was used to calculate  $AUC_{\text{inf}}$ ).

20 “**Mean area under a plasma concentration profile**” means the mean  $AUC_{\text{inf}}$  obtained over several patients or multiple administrations to the same patient on different occasions with sufficient washout in between dosings to allow drug levels to subside to pre-dose levels, etc., following a single administration of a dosage form to each patient.

25 “**C**” means the concentration of drug in blood plasma, or serum, of a subject, generally expressed as mass per unit volume, typically nanograms per milliliter. For convenience, this concentration may be referred to herein as “drug plasma concentration”, “plasma drug concentration” or “plasma concentration”. The plasma drug concentration at any time following drug administration is  
30 referenced as  $C_{\text{time}}$ , as in  $C_{9h}$  or  $C_{24h}$ , etc. A maximum plasma concentration obtained following administration of a dosage form obtained directly from the

experimental data without interpolation is referred to as  $C_{max}$ . The average or mean plasma concentration obtained during a period of interest is referred to as  $C_{avg}$  or  $C_{mean}$ . “Mean, single dose, maximum plasma concentration  $C_{max}$ ” means the mean  $C_{max}$  obtained over several patients or multiple administrations to the same patient with sufficient washout in between dosing to allow drug levels to subside to pre-dose levels, etc., etc., following a single administration of a dosage form to each patient.

“**Plasma concentration profile**” refers to the curve obtained by plotting plasma concentration of the drug compound versus time. Usually, the convention is that the zero point on the time scale (conventionally on the x axis) is the time of administration of the drug compound or dosage form comprising the drug compound to a patient.

“**Mean time to maximum plasma concentration**” is the mean time elapsed from administration to a patient of a dosage form comprising a drug to the time at which the  $C_{max}$  for that drug is obtained over several patients or multiple administrations to the same patient with sufficient washout in between dosing to allow drug levels to subside to pre-dose levels, etc., following a single administration of the dosage form to each patient, and obtained directly from the experimental data without interpolation.

The **bioavailability** indicates the percentage of the administered drug, which arrives in the central compartment. It is generally measured by comparing the AUC obtained after intravenous administration and after oral administration, for example. After intravenous administration, the AUC obtained corresponds to a bioavailability, which, by definition, is 100%; after oral administration, the AUC corresponds at best to an identical bioavailability. It is generally lower, sometimes null. In contrast, in this application bioavailability is indicated by the maximum plasma concentration  $C_{max}$  reached after administration of the drug. A higher  $C_{max}$  of a drug dosage form is indicative of better drug bioavailability via administering this dosage form.

The **compartment** indicates the fictitious volume in which a drug would be distributed. It can correspond or not to a real volume, for example the volume of

blood called first or central compartment, or the whole body except blood, called second compartment. The central compartment typically includes the plasma and in addition those tissues or parts in tissues in which drug concentrations rapidly come to equilibrium with the plasma. The real anatomical sectors in which the drug is distributed at different concentrations are represented by one, two, rarely three virtual compartments where the concentration of the drug is regarded as homogeneous. The concept of compartment thus makes it possible to model the fate of a drug.

10           The term "**halo**" means chlorine, bromine, iodine, and fluorine, and chlorine and fluorine are preferable.

          The term "**alkyl**" or "**alkyl group**" means a straight or branched saturated monovalent hydrocarbon chain having 1 to 12 carbon atoms. The straight chain or branched chain alkyl group having 1 to 6 carbon atoms is preferable, and the straight chain or branched chain alkyl group having 1 to 4 carbon atoms is more preferable. Examples thereof are methyl group, ethyl group, propyl group, isopropyl group, butyl group, t-butyl group, isobutyl group, pentyl group, hexyl group, isohexyl group, heptyl group, 4,4-dimethylpentyl group, octyl group, 2,2,4-trimethylpentyl group, nonyl group, decyl group, and various branched chain isomers thereof. Further, the alkyl group may optionally and independently be substituted by one to five substituents as listed below, if necessary.

20           "**Alkoxy**" radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups. In some embodiments, the alkoxy may be optionally and independently be substituted with one to five, preferably one to three substituents defined below.

          The term "**alkylene group**" or "**alkylene group**" means a straight or branched divalent saturated hydrocarbon chain having 1 to 12 carbon atoms. 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 thereof are methylene group, ethylene group, propylene group, trimethylene group, etc. If necessary, the

alkylene group may optionally be substituted in the same manner as the above-mentioned "alkyl group". Where alkylene groups as defined above attach 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 group**" means a straight or branched monovalent hydrocarbon chain having 2 to 12 carbon atoms and having at least one double bond. Preferable alkenyl group 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 thereof are vinyl group, 2-propenyl group, 3-butenyl group, 2-butenyl group, 4-pentenyl group, 3-pentenyl group, 2-hexenyl group, 3-hexenyl group, 2-heptenyl group, 3-heptenyl group, 4-heptenyl group, 3-octenyl group, 3-nonenyl group, 4-decenyl group, 3-undecenyl group, 4-dodecenyl group, 4,8,12-tetradecatrienyl group, etc. The alkenyl group may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary.

The term "**alkenylene group**" means a straight or branched divalent hydrocarbon chain having 2 to 12 carbon atoms and having at least one double bond. 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 thereof are vinylene group, propenylene group, butadienylene group, etc. If necessary, the alkylene group may optionally be substituted by 1 to 4 substituents as mentioned below, if necessary. Where alkenylene groups as defined above attach at two different carbon atoms of the 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.

The term "**alkynyl group**" means a straight or branched monovalent hydrocarbon chain having at least one triple bond. 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 thereof are 2-propynyl group, 3-butynyl group, 2-butynyl group, 4-pentynyl group, 3-pentynyl group, 2-hexynyl group, 3-hexynyl group, 2-heptynyl group, 3-heptynyl group, 4-heptynyl group, 3-octynyl group, 3-nonyl group, 4-decynyl group, 3-undecynyl group, 4-dodecynyl group, etc. The alkynyl group may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary.

The term "**cycloalkyl group**" means a monocyclic or bicyclic monovalent saturated hydrocarbon ring having 3 to 12 carbon atoms, and the monocyclic saturated hydrocarbon group having 3 to 7 carbon atoms is more preferable. Examples thereof are a monocyclic alkyl group and a bicyclic alkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group, cyclodecyl group, etc. These 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 SO<sub>2</sub> 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 group**" means a monocyclic or bicyclic divalent saturated hydrocarbon ring having 3 to 12 carbon atoms, and the monocyclic saturated hydrocarbon group having 3 to 6 carbon atoms is preferable. Examples thereof are a monocyclic alkylidene group and a bicyclic alkylidene group such as cyclopropylidene group, cyclobutylidene group, cyclopentylidene group, cyclohexylidene group, etc. 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 SO<sub>2</sub> 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  
5 below.

The term "**cycloalkenyl group**" means a monocyclic or bicyclic monovalent unsaturated hydrocarbon ring having 4 to 12 carbon atoms and having at least one double bond. The preferable cycloalkenyl group is a monocyclic unsaturated hydrocarbon group having 4 to 7 carbon atoms. Examples thereof are monocyclic  
10 alkenyl groups such as cyclopentenyl group, cyclopentadienyl group, cyclohexenyl group, etc. These groups may optionally and independently be substituted by 1 to 4 substituents as 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  
15 ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO<sub>2</sub> 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 "**cycloalkynyl group**" means a monocyclic or bicyclic unsaturated  
20 hydrocarbon ring having 6 to 12 carbon atoms, and having at least one triple bond. The preferable cycloalkynyl group is a monocyclic unsaturated hydrocarbon group having 6 to 8 carbon atoms. Examples thereof are monocyclic alkynyl groups such as cyclooctynyl group, cyclodecynyl group. These groups may optionally be substituted by 1 to 4 substituents as mentioned below, if necessary. Besides, the  
25 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 or SO<sub>2</sub> within the ring, if necessary), and the condensed saturated hydrocarbon ring or the unsaturated  
30 hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "**aryl group**" means a monocyclic or bicyclic monovalent aromatic hydrocarbon group having 6 to 10 carbon atoms. Examples thereof are phenyl group, naphthyl group (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 sulfur atom, SO or SO<sub>2</sub> within the ring, if necessary), and the condensed saturated hydrocarbon ring or the unsaturated  
10 hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

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  
15 a 4- to 7-membered saturated or unsaturated hydrocarbon ring containing 1-4 heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom. Examples thereof are pyridine, pyrimidine, pyrazine, furan, thiophene, pyrrole, imidazole, pyrazole, oxazole, isoxazole, 4,5-dihydrooxazole, thiazole, isothiazole, thiadiazole, triazole, tetrazole, etc. Among them, pyridine, pyrimidine,  
20 pyrazine, furan, thiophene, pyrrole, imidazole, oxazole, and thiazole can be preferably used. The "unsaturated monocyclic heterocyclic ring" may optionally and independently be substituted by 1-4 substituents as mentioned below, if necessary.

The term "**unsaturated fused heterobicyclic ring**" means hydrocarbon  
25 ring comprised of a saturated or a 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 SO<sub>2</sub> within the ring, if necessary. The "unsaturated fused heterobicyclic ring" includes, for  
30 example, benzothiophene, indole, tetrahydrobenzothiophene, benzofuran, isoquinoline, thienothiophene, thienopyridine, quinoline, indoline, isoindoline,

benzothiazole, benzoxazole, indazole, dihydroisoquinoline, etc. 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  
5 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 group**" means a formyl group and ones formed by  
10 binding an "alkyl group" to a carbonyl group.

The term "**substituted**" refers to a radical in which one or more hydrogen atoms are each independently replaced with the same or different substituent(s).

With reference to substituents, the term "**independently**" means that when more than one of such substituent is possible, such substituents may be the same  
15 or different from each other.

It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide  
20 compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

The **substituent** for the above each group includes, for example, a halogen atom (fluorine, chlorine, bromine), a nitro group, a cyano group, an oxo group, a hydroxy group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group,  
25 an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group, a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an  
30 alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenylcarbonyl group, a cycloalkynyloxy group, an arylcarbonyl group, a hetero-cyclylcarbonyl group,

an alkoxy-carbonyl group, an alkenyloxy-carbonyl group, an alkynyloxy-carbonyl group, a cycloalkyloxy-carbonyl group, a cycloalkenyl-oxy-carbonyl group, a cycloalkynyl-oxycarbonyl group, an aryloxycarbonyl group, a hetero-cyclyloxycarbonyl group, an alkanoyloxy group, an alkenyl-carbonyloxy group, an alkynyl-  
 5 carbonyloxy group, a cycloalkyl-carbonyloxy group, a cycloalkenyl-carbonyloxy group, a cycloalkynyl-carbonyloxy group, an arylcarbonyloxy group, a hetero-cyclylcarbonyloxy group, an alkylthio group, an alkenyl-thio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenyl-thio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkyl-  
 10 amino group, a mono- or di-alkanoylamino group, a mono- or di-alkoxy-carbonyl-amino group, a mono- or di-arylcarbonyl-amino group, an alkylsulfinylamino group, an alkyl-sulfonyl-amino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkyl-carbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenyl-sulfinyl group, an  
 15 alkynylsulfinyl group, a cycloalkyl-sulfinyl group, a cycloalkenylsulfinyl group, a cycloalkynyl-sulfinyl group, an arylsulfinyl group, a heterocyclyl-sulfinyl group, an alkyl-sulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cycloalkenyl-sulfonyl group, a cycloalkynylsulfonyl group, an aryl-sulfonyl group, and a heterocyclylsulfonyl group. Each group as  
 20 mentioned above may optionally be substituted by these substituents.

Further, the terms such as a haloalkyl group, a halo-lower alkyl group, a haloalkoxy group, a halo-lower alkoxy group, a halophenyl group, or a haloheterocyclyl group mean an alkyl group, a lower alkyl group, an alkoxy group, a lower alkoxy group, a phenyl group or a heterocyclyl group (hereinafter, referred  
 25 to as an alkyl group, etc.) being substituted by one or more halogen atoms, respectively. Preferable ones are an alkyl group, etc. being substituted by 1 to 7 halogen atoms, and more preferable ones are an alkyl group, etc. being substituted by 1 to 5 halogen atoms. Similarly, the terms such as a hydroxyalkyl group, a hydroxy-lower alkyl group, a hydroxyalkoxy group, a hydroxy-lower alkoxy  
 30 group and a hydroxyphenyl group mean an alkyl group, etc., being substituted by one or more hydroxy groups. Preferable ones are an alkyl group, etc., being

substituted by 1 to 4 hydroxy groups, and more preferable ones are an alkyl group, etc., being substituted by 1 to 2 hydroxy groups. Further, the terms such as an alkoxyalkyl group, a lower alkoxyalkyl group, an alkoxy-lower alkyl group, a lower alkoxy-lower alkyl group, an alkoxyalkoxy group, a lower alkoxyalkoxy group, an alkoxy-lower alkoxy group, a lower alkoxy-lower alkoxy group, an alkoxyphenyl group, and a lower alkoxyphenyl group means an alkyl group, etc., being substituted by one or more alkoxy groups. Preferable ones are an alkyl group, etc., being substituted by 1 to 4 alkoxy groups, and more preferable ones are an alkyl group, etc., being substituted by 1 to 2 alkoxy groups.

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

      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.

      The term "**composition**" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

      The term "**prodrug**" means an ester or carbonate, which is formed by reacting one or more hydroxy groups of the compound of the Formula (I) with an acylating agent substituted by an alkyl, an alkoxy or an aryl by a conventional method to produce acetate, pivalate, methylcarbonate, benzoate, etc. Further, the prodrug includes also an ester or amide, which is similarly formed by reacting one or more hydroxy groups of the compound of the Formula (I) with an  $\alpha$ -amino acid or a  $\beta$ -amino acid, etc. using a condensing agent by a conventional method. In addition, the prodrug includes also ether, which is similarly formed by reacting one or more hydroxy groups of the compound of the Formula (I) with a condensing agent via a conventional method.

**"Pharmaceutically acceptable"** means molecular entities and compositions that are of sufficient purity and quality for use in the formulation of a composition or medicament of the present invention. Since both human use (clinical and over-the-counter) and veterinary use are equally included within the scope of the present invention, a formulation would include a composition or medicament for either human or veterinary use.

The term **"pharmaceutically acceptable salt"** refers includes, for example, a salt with an alkali metal such as lithium, sodium, potassium, etc.; a salt with an alkaline earth metal such as calcium, magnesium, etc.; a salt with zinc or aluminum; a salt with an organic base such as ammonium, choline, diethanolamine, lysine, ethylenediamine, t-butylamine, t-octylamine, tris(hydroxymethyl)aminomethane, N-methyl glucosamine, triethanolamine and dehydroabietylamine; a salt with an inorganic acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, etc.; or a salt with an organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, etc.; or a salt with an acidic amino acid such as aspartic acid, glutamic acid, etc.

The compound of Formula (I) of the present invention also includes a mixture of stereoisomers, or each pure or substantially pure isomer. For example, the present compound may optionally have one or more asymmetric centers at a carbon atom containing any one of substituents. Therefore, the compound of the Formula (I) may exist in the form of enantiomer or diastereomer, or a mixture thereof. When the present compound of Formula (I) contains a double bond, the present compound may exist in the form of geometric isomerism (cis-compound, trans-compound), and when the present compound of Formula (I) contains an unsaturated bond such as carbonyl, then the present compound may exist in the form of a tautomer, and the present compound also includes these isomers or a mixture thereof. The starting compound in the form of a racemic mixture, enantiomer or diastereomer may be used in the processes for preparing the

present compound. When the present compound is obtained in the form of a diastereomer or enantiomer, they can be separated by a conventional method such as chromatography or fractional crystallization.

5 In addition, the present compound of Formula (I) includes an intramolecular salt, hydrate, solvate or polymorphism thereof.

To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term "about". It is understood that whether the term "about" is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the  
10 approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including approximations due to the experimental and/or measurement conditions for such given value.

To provide a more concise description, some of the quantitative expressions herein are recited as a range from about amount X to about amount  
15 Y. It is understood that wherein a range is recited, the range is not limited to the recited upper and lower bounds, but rather includes the full range from about amount X through about amount Y, or any amount or range therein.

## **B) Compounds**

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Compounds of Formula (I) exhibit an excellent inhibitory activity against sodium-dependent glucose transporter, and an excellent glucose lowering effect. Therefore, the formulation of the present invention is useful for treating or delaying the progression or onset of a sodium-dependent glucose transporter mediated  
25 disorder. In particular, the formulation of the present invention is useful for treating or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia,  
30 Syndrome X, diabetic complications, atherosclerosis, or hypertension. In particular, the formulation of the present invention is useful in the treatment or the

prophylaxis of diabetes mellitus (type 1 and type 2 diabetes mellitus, etc.), diabetic complications (such as diabetic retinopathy, diabetic neuropathy, diabetic nephropathy) or obesity, or is useful in the treatment of postprandial hyperglycemia.

5

In certain preferred embodiments,  $R_1$  as shown in Formula (I) is a halogen atom, or a lower alkyl group; and  $R_2$  as shown in Formula (I) phenyl is optionally substituted by 1 to 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.

Preferably drug compounds of Formula (I) used in the disclosed formulation typically possess slight to poor water solubility in their crystalline or amorphous form and hence poor bioavailability, but the present invention is not necessarily limited to compounds with little to no water solubility.

Preferred representative compounds for use in the formulations of the present invention include 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene), or a prodrug or a pharmaceutically acceptable salt thereof. In certain further preferred embodiments, the compound for use in the formulations of the present invention is 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene) hemihydrate.

25

Preferably the 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene), or a prodrug or a pharmaceutically acceptable salt thereof is included in the formulation of the present invention in an amount of from about 25 mg to about 600 mg, preferably from about 50 mg to about 400 mg.

30

In certain further preferred embodiments, the 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene), or a prodrug or a pharmaceutically acceptable salt thereof is included in the formulation of the present invention in an amount of about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, or about 400 mg. In certain further preferred embodiments, the 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene), or a prodrug or a pharmaceutically acceptable salt thereof is included in the formulation of the present invention in an amount of about 100 mg or about 300 mg. In certain embodiments, wherein the 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene) is in the hemihydrate form the 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene) hemihydrate is preferably included in the formulation in an amount of about 25.5 mg, about 51 mg, about 102 mg, about 204 mg, or about 306 mg, preferably in an amount of about 102 mg or about 306 mg.

### C) Formulation

In embodiments of the present invention, the compound is formulated into oral dosage forms suitable for administration to patients in need thereof.

The oral dosage form may be provided in any pharmaceutically acceptable solid dosage form. Preferably, the solid dosage form includes, for example, solid preparation such as tablets, pills, granules, capsules, powders and others. More preferably, the solid dosage form is an oral tablet or capsule formulation. Most preferably the solid dosage form is an oral tablet.

In certain embodiments of the present invention the formulation includes a filler or diluent in the amount of about 10% to about 95% by weight of the formulation, preferably from about 25% to about 90% by weight of the formulation,

more preferably from about 30% to about 50% by weight of the formulation or from about 35% to about 45% by weight of the formulation.

5 In certain embodiments of the present invention the formulation includes a disintegrant in the amount of about 0.1% to about 20% by weight of the formulation, preferably from about 0.25% to about 10% by weight of the formulation, more preferably from about 3% to about 10% by weight of the formulation or from about 5% to about 7% by weight of the formulation.

10 In certain embodiments of the present invention the formulation includes a binder in the amount of about 0.1% to about 20% by weight of the formulation, preferably from about 0.1% to about 10% by weight of the formulation, more preferably from about 0.5% to about 5% by weight of the formulation or from about 1% to about 4% by weight of the formulation.

15 In certain embodiments of the present invention the formulation includes a lubricant in the amount of about 0.1% to about 5% by weight of the formulation, preferably from about 0.1% to about 2% by weight of the formulation, more preferably from about 0.5% to 2% by weight of the formulation or 0.5% to 1.5% by weight of the formulation.

20 In certain embodiments of the present invention the formulation optionally includes a surfactant in the amount of about 0% to about 10% by weight of the formulation, preferably from about 0% to about 5% by weight of the formulation.

25 The solid dosage forms may comprise the compound in combination with various pharmaceutically acceptable excipients, and preferably the dosage form is adapted to provide increased bioavailability of the compound in a manner to obtain the desired clinical effect through oral administration to the patient.

30

The bioavailability promoting agent of the present invention includes any combination of the excipients described herein such that the formulation provides for the increase bioavailability of the compound included the formulation. In certain preferred embodiments, the bioavailability promoting agent includes two or  
5 more excipients described herein.

Pharmaceutically acceptable excipients are known in the art and can be provided according to considerations of desired functionality and process ability. Roles for the excipients in the oral dosage form include but are not limited to fillers,  
10 binders, disintegrants, release controlling agents, glidants, lubricants, coatings and the like.

For example, in one embodiment of the invention, it is desired to have an immediate release profile for the dosage form. To help achieve this profile in a  
15 solid dosage form, the dosage form preferably comprises a disintegrant in an amount as noted herein. In another embodiment of the invention, wherein a controlled or sustained release formulation of the compound is desired. Such a formulation can be achieved by varying the amounts, concentrations and ratios of certain release controlling polymers.

20

In one embodiment, the formulation of the present invention includes the compound in an amount of about 1% to about 80%, preferably from about 5% to about 60% by weight of the formulation, more preferably from about 40% to about 60% by weight of the formulation or about 45% to about 55% by weight of the  
25 formulation. Depending on the desired dose of the compound, one or more of the dosage forms can be administered.

For example, in one preferred embodiment of the invention, an oral release formulation is provided in tablet form comprising about 100 mg of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene),  
30

microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, lactose anhydrous, and magnesium stearate.

5 In another preferred embodiment of the invention, an oral release formulation is provided in tablet form comprising about 300 mg of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene), microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, lactose anhydrous, and magnesium stearate.

10 In another preferred embodiment of the invention, an oral release formulation is provided in tablet form comprising about 102 mg of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene) hemihydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, lactose anhydrous, and magnesium stearate.

15 In another preferred embodiment of the invention, an oral release formulation is provided in tablet form comprising about 306 mg of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene) hemihydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, lactose anhydrous, and magnesium stearate.

20 Fillers or diluents for use in the formulations of the present invention include fillers or diluents typically used in the formulation of pharmaceuticals. Examples of fillers or diluents for use in accordance with the present invention include but are not limited to sugars such as lactose, dextrose, glucose, sucrose, cellulose, 25 starches and carbohydrate derivatives, polysaccharides (including dextrans and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), cyclodextrins, calcium carbonates, magnesium carbonates, microcrystalline cellulose, combinations thereof, and the like. In certain preferred embodiments the filler or 30 diluent is lactose, microcrystalline cellulose, or combination thereof. Several types of microcrystalline cellulose are suitable for use in the formulations described

herein, for example, microcrystalline cellulose selected from the group consisting of Avicel® types: PH101, PH102, PH103, PH105, PH 112, PH113, PH200, PH301, and other types of microcrystalline cellulose, such as silicified microcrystalline cellulose. Several types of lactose are suitable for use in the formulations described herein, for example, lactose selected from the group consisting of anhydrous lactose, lactose monohydrate, lactose fast flo, directly compressible anhydrous lactose, and modified lactose monohydrate. In one embodiment of the invention, the filler or diluent is a combination of microcrystalline cellulose and lactose.

10

Binders for use in the formulations of the present invention include binders commonly used in the formulation of pharmaceuticals. Examples of binders for use in accordance with the present invention include but are not limited to cellulose derivatives (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, and sodium carboxymethyl cellulose), glycol, sucrose, dextrose, corn syrup, polysaccharides (including acacia, targacanth, guar, alginates and starch), corn starch, pregelatinized starch, modified corn starch, gelatin, polyvinylpyrrolidone, polyethylene, polyethylene glycol, combinations thereof and the like. Preferably, the binding agent, if present, is hydroxypropyl cellulose.

20

Disintegrants for use in the formulations of the present invention include disintegrants commonly used in the formulation of pharmaceuticals. Examples of disintegrants for use in accordance with the present invention include but are not limited to starches, clays, celluloses, alginates and gums and crosslinked starches, celluloses and polymers, combinations thereof and the like. Representative disintegrants include microcrystalline cellulose, croscarmellose sodium, alginic acid, sodium alginate, crospovidone, cellulose, agar and related gums, sodium starch glycolate, corn starch, potato starch, sodiumstarch glycolate, Veegum HV, methylcellulose, agar, bentonite, carboxymethylcellulose, alginic acid, guar gum combinations thereof, and the like. Preferably, the disintegrant, if

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present, is a cross-linked cellulose, more preferably cross-linked sodium carboxymethylcellulose or croscarmellose sodium.

Lubricants for use in the formulations of the present invention include  
5 lubricants commonly used in the formulation of pharmaceuticals. Examples of lubricants for use in accordance with the present invention include but are not limited to magnesium carbonate, magnesium laurylsulphate, calcium silicate, talc, fumed silicon dioxide, combinations thereof, and the like. Other useful lubricants include but are not limited to magnesium stearate, calcium stearate, stearic acid,  
10 sodium stearyl fumarate, polyethylene glycol, sodium lauryl sulphate, magnesium lauryl sulphate, sodium benzoate, colloidal silicon dioxide, magnesium oxide, microcrystalline cellulose, starches, mineral oil, waxes, glyceryl behenate, polyethylene glycol, sodium acetate, sodium chloride, combinations thereof, and the like. Preferably, the lubricant, if present, is magnesium stearate or stearic acid,  
15 more preferably magnesium stearate.

Surfactants for use in the formulations of the present invention include surfactants commonly used in the formulation of pharmaceuticals. Examples of surfactants for use in accordance with the present invention include but are not  
20 limited to ionic-and nonionic surfactants or wetting agents commonly used in the formulation of pharmaceuticals, such as ethoxylated castor oil, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives, monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene  
25 derivatives thereof, sodium docusate, sodium laurylsulfate, cholic acid or derivatives thereof, lecithins, phospholipids, combinations thereof, and the like.

Other polymers commonly used as excipients include but are not limited to methylcellulose (MC), ethylcellulose (EC), hydroxyethylcellulose (HEC), methyl  
30 hydroxyethylcellulose (MHEC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose (NaCMC), and the like.

These polymers, either alone or in various combinations, may serve multiple purposes including but not limited to controlling release of the compound of the formulations of the present invention.

- 5           In any case, the appropriate excipients should be selected such that they are compatible with other excipients and do not bind with the drug compound or cause drug degradation.

10           The pharmaceutical formulations disclosed herein can further comprise antioxidants and chelating agents. For example, the pharmaceutical formulations can comprise butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate (PG), sodium metabisulfite, ascorbyl palmitate, potassium metabisulfite, disodium EDTA (ethylenediamine tetraacetic acid; also known as disodium edentate), EDTA, tartaric acid, citric acid, citric acid monohydrate, and  
15   sodium sulfite.

          In another embodiment, the tablet or capsule of the invention has a protective outer layer. The protective outer layer of the tablet or capsule, where present, can include from about 10% to about 95% of polymer based on the  
20   weight of the coating layer, and can be prepared employing conventional procedures. In one embodiment, the outer layer of the tablet or capsule includes from about 20% to about 90% of polymer based on the weight of the coating layer. The formulation can contain at least one coating layer polymer and a coating solvent, for example, water, which is used for processing and removed by drying.  
25   Suitable examples of polymer for the coating layer include, but are not limited to, hydroxypropyl methylcellulose, polyvinyl alcohol (PVA), ethyl cellulose, methacrylic polymers, hydroxypropyl cellulose, and starch. In one embodiment, the coating layer polymer is PVA. In another embodiment, the coating layer polymer is hydroxypropyl cellulose.

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The coating can also optionally include a plasticizer of from about 0% to about 30% by weight, based on the weight of the coating layer. In one embodiment, the plasticizer is from about 15% to about 25% by weight of the coating layer. Suitable plasticizers include, but are not limited to, triacetin, diethyl phthalate, tributyl sebacate, polyethylene glycol (PEG), glycerin, triacetin, and triaethyl citrate, for example.

In another embodiment, the coating can also optionally include an anti-adherent or glidant such as talc, fumed silica, or magnesium stearate, for example.

In another embodiment, the coating can also optionally include an opacifying agent, such as titanium dioxide, for example.

In yet another embodiment, wherein the formulation is a tablet, the tablet may be further coated with a coating layer that provides cosmetic benefits to the dosage form. In certain embodiments, such a coating helps to protect the tablets. In certain embodiments such coating comprises hydroxypropyl methylcellulose, polyethylene glycol, polydextrose, titanium dioxide, and triacetin. In certain other embodiments such coating comprises hydroxypropyl methylcellulose 2910, polyethylene glycol 400, polydextrose, titanium dioxide, carnuba wax, and iron oxide yellow. In at least one embodiment such a coating layer comprises Opadry® II (white) in an amount of from about 0% to about 10% by weight of the tablet; in certain other embodiments in an amount of from about 0% to about 6% by weight of the tablet; and in still other embodiments in an amount of from about, 0% to about 3% by weight of the tablet; and in other embodiments from about 2 to about 4% by weight of the tablet.

#### **D) Additional therapeutic agents**

In another embodiment the formulations of the present invention further include one or more additional therapeutic agents to provide the desired therapeutic effect.

Other therapeutic agent(s) suitable for combination with the formulations of the present invention include, but are not limited to, known therapeutic agents useful in the treatment of the aforementioned disorders associated with SGLT2 activity including: anti-diabetic agents; anti-hyperglycemic agents; hypolipidemic or lipid lowering agents; anti-obesity agents; anti-hypertensive agents and appetite suppressants.

The invention further provides a method for treating or delaying the progression or onset of diseases or disorders associated with SGLT2 activity comprising administering to a mammalian species in need of such treatment a therapeutically effective amount of the pharmaceutical formulation of the invention and one or more of the following: anti-diabetic agent(s), anti-hyperglycemic agent(s); hypolipidemic or lipid lowering agent(s); anti-obesity agent(s); anti-hypertensive agent(s) and appetite suppressant(s).

In one embodiment, the invention provides a method for treating type II diabetes comprising administering to a mammalian species in need of such treatment a therapeutically effective amount of the pharmaceutical formulation of the invention and one or more anti-diabetic agent(s). In another embodiment, the invention provides a method for delaying the progression or onset of type II diabetes comprising administering to a mammalian species in need of such treatment a therapeutically effective amount of the pharmaceutical formulation of the invention and one or more anti-diabetic agent(s).

In another embodiment, the invention provides a method for treating or delaying the progression or onset of type II diabetes comprising administering to a mammalian species in need of such treatment a therapeutically effective amount of the pharmaceutical formulation of the invention and one or more of the following: anti-hyperglycemic agent(s); hypolipidemic or lipid lowering agent(s); anti-obesity agent(s); anti-hypertensive agent(s) and appetite suppressant(s). For

example, the invention provides a method for treating or delaying the progression or onset of type II diabetes comprising administering to a mammalian species in need of such treatment a therapeutically effective amount of a pharmaceutical formulation of the invention and an anti-hyperglycemic agent(s). In another  
5 embodiment, the invention provides a method for treating or delaying the progression or onset of type II diabetes comprising administering to a mammalian species in need of such treatment a therapeutically effective amount of a pharmaceutical formulation of the invention and a hypolipidemic agent(s). In  
10 another embodiment, the invention provides a method for treating or delaying the progression or onset of type II diabetes comprising administering to a mammalian species in need of such treatment a therapeutically effective amount of a pharmaceutical formulation of the invention and an anti-obesity agent(s). In  
15 another embodiment, the invention provides a method for treating or delaying the progression or onset of type II diabetes comprising administering to a mammalian species in need of such treatment a therapeutically effective amount of a pharmaceutical formulation of the invention and an anti-hypertensive agent(s). In  
20 another embodiment, the invention provides a method for treating or delaying the progression or onset of type II diabetes comprising administering to a mammalian species in need of such treatment a therapeutically effective amount of a pharmaceutical formulation of the invention and an appetite suppressant(s).

Examples of suitable anti-diabetic agents for use in combination with the formulations of the present invention include, but are not limited to, biguanides (e.g., metformin or phenformin), glucosidase inhibitors (e.g., acarbose or miglitol),  
25 insulins (including insulin secretagogues or insulin sensitizers), meglitinides (e.g., repaglinide), sulfonylureas (e.g., glimepiride, glyburide, gliclazide, chlorpropamide and glipizide), biguanide/glyburide combinations (e.g., Glucovance®), thiazolidinediones (e.g., troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, glycogen  
30 phosphorylase inhibitors, inhibitors of fatty acid binding protein (aP2), glucagon-like peptide-1 (GLP-1) and other agonists of the GLP-1 receptor, and dipeptidyl

peptidase IV (DPP4) inhibitors.

Other suitable thiazolidinediones include, but are not limited to, MCC-555, faraglitazar, englitazone or darglitazone; isaglitazone, reglitazar, rivoglitazone, 5 liraglutide, and (Z)-1,4-bis-4-[(3,5-dioxo-1,2,4-oxadiazolidin-2-yl-methyl)]phenoxybut-2-ene.

Examples of PPAR-alpha agonists, PPAR-gamma agonists and PPAR alpha/gamma dual agonists include, but are not limited to, muraglitazar, 10 peliglitazar, tesaglitazar AR-HO39242, GW-501516, and IRP297.

Suitable DPP4 inhibitors include, but are not limited to, sitigliptin and saxagliptin.

Examples of suitable anti-hyperglycemic agents for use in combination with the 15 formulations of the present invention include, but are not limited to, glucagon-like peptide-1 (GLP-1) such as GLP-1 (1-36) amide, GLP-1 (7-36) amide, GLP-1 (7-37), exenatide, LY-315902, MK-0431, liraglutide, ZP-10, and CJC-1131.

Examples of suitable hypolipidemic/lipid lowering agents for use in combination 20 with the formulations of the present invention include one or more MTP inhibitors, HMG CoA reductase inhibitors (such as e.g., mevastatin, lovastatin, pravastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, atavastatin, rosuvastatin), squalene synthetase inhibitors, fibric acid derivatives (such as e.g., fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate and the like, probucol, 25 bile acid sequestrants, such as cholestyramine, colestipol and DEAE-Sephadex, as well as lipostabil), ACAT inhibitors, lipoxygenase inhibitors, cholesterol absorption inhibitors, ileal Na<sup>+</sup>/bile acid co-transporter inhibitors, up-regulators of LDL receptor activity, bile acid sequestrants, cholesterol ester transfer protein (e.g., CETP inhibitors, such as torcetrapib and JTT-705, PPAR agonists (as 30 described above) and/or nicotinic acid and derivatives thereof. Preferred hypolipidemic agents include pravastatin, lovastatin, simvastatin, atorvastatin,

fluvastatin, cerivastatin, atavastatin and rosuvastatin, for example.

Examples of suitable anti-hypertensive agents for use in combination with the formulations of the present invention include, but are not limited to, beta  
5 adrenergic blockers, calcium channel blockers (L-type and T-type; e.g. diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafene, chlorthalidone, furosemide, musolimine, bumetanide,  
10 triamterene, amiloride, spironolactone), renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazapril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan), and ET receptor antagonists (e.g., sitaxsentan, and atrisentan).

Examples of suitable anti-obesity agents for use in combination with the  
15 formulations of the present invention include, but are not limited to, beta 3 adrenergic agonists, lipase inhibitors, serotonin (and dopamine) reuptake inhibitors, thyroid receptor beta drugs, 5HT<sub>2C</sub> agonists; MCHR1 antagonists, such as Synaptic SNAP-7941 and Takeda T-226926, melanocortin receptor (MC4R) agonists, melanin-concentrating hormone receptor (MCHR) antagonists, galanin  
20 receptor modulators, orexin antagonists, CCK agonists, NPY1 or NPY5 antagonist, NPY2 and NPY4 modulators, corticotropin releasing factor agonists, histamine receptor-3 (H<sub>3</sub>) modulators, 11-beta-HSD-1 inhibitors, adipopectin receptor modulators, monoamine reuptake inhibitors or releasing agents, ciliary neurotrophic factors, BDNF (brain-derived neurotrophic factor), leptin and leptin  
25 receptor modulators, cannabinoid-1 receptor antagonists, and anorectic agents.

Examples of lipase inhibitors that can be employed in combination with formulations of the present invention include, but are not limited to, orlistat and  
30 ATL-962 (Alizyme).

Serotonin (and dopamine) reuptake inhibitors (or serotonin receptor agonists) that

can be employed in combination with the formulations of the present invention include, but are not limited to, BVT-933, sibutramine, topiramate and axokine.

5 Examples of monoamine reuptake inhibitors that can be employed in combination with the formulations of the present invention include, but are not limited to, fenfluramine, dexfenfluramine, fluvoxamine, fluoxetine, paroxetine, sertraline, chlorphentermine, cloforex, clortermine, picilorex, sibutramine, dexamphetamine, phentermine, phenylpropanolamine and mazindol.

10 Anorectic agents that can be employed in combination with the formulations of the present invention include, but are not limited to, topiramate, dexamphetamine, phentermine, phenylpropanolamine and mazindol.

15 Where any of the formulations of the invention are used in combination with other therapeutic agent(s), the other therapeutic agent(s) can be used, for example, in the amounts indicated in the Physician's Desk Reference, or as otherwise known and used by one of ordinary skill in the art.

20 Where any of the formulations of the invention are used in combination with other therapeutic agent(s), each of the compounds of the combination can be administered simultaneously or sequentially and in any order, and the components can be administered separately or as a fixed combination, in jointly therapeutically effective amounts, for example, in daily dosages as described herein. In one embodiment of the invention, a fixed combination of the invention can be prepared  
25 by mixing a dry granulation of the compound of Formula (I) or (I-S) or formulation of the invention and a dry granulation of the other therapeutic agent(s) and filling the mixture into capsules of desired size, shape, color, or other characteristics, or compressing to form tablets.

## 30 **E) Manufacturing of Formulation**

In certain embodiments, the formulations of the invention are prepared by making an admixture of the drug compound, and a bioavailability-promoting agent. Dissolving these components in a liquid solvent therefore and subsequently removing the solvent may affect this most straightforwardly. Thus viewed from a  
5 further aspect the invention provides a process for the preparation of a pharmaceutical composition, said process comprising: dissolving a drug compound, and the pharmaceutically acceptable excipients in a solvent; removing solvent from the resultant solution; optionally forming the resultant product into desired shapes; and optionally coating the resulting product with a physiologically  
10 tolerable coating material.

Preferably, dosage forms in accordance with the embodiments depicted herein are manufactured by standard techniques. For example, the dosage form may be manufactured by the wet granulation technique. In the wet granulation  
15 technique, the drug and carrier are blended using an aqueous or organic solvent, such as denatured anhydrous ethanol, as the granulation fluid. The remaining ingredients can be dissolved in a portion of the granulation fluid, such as the solvent described above, and this latter prepared wet blend is slowly added to the drug blend with continual mixing in the blender. The granulating fluid is added until  
20 a wet blend is produced, which wet mass blend is then forced through a predetermined screen and dried in a fluid bed dryer. The dried granules are then sized. Next, magnesium stearate, or another suitable lubricant and other excipient materials are added to the drug granulation, and the granulation is put into milling jar sand mixed on a jar mill for 10 minutes. The composition is pressed into a  
25 layer, for example, in a Manesty® press or a Korsch LCT press. For a trilayered core, granules or powders of the drug layer compositions and push layer composition are sequentially placed in an appropriately-sized die with intermediate compression steps being applied to each of the first two layers, followed by a final compression step after the last layer is added to the die to form the trilayered core.  
30 The intermediate compression typically takes place under a force of about 50-100 Newtons. Final stage compression typically takes place at a force of 3500

Newtons or greater, often 3500-5000 Newtons. The compressed cores are fed to a dry coater press, e.g., Kilian® Dry Coaterpress, and subsequently coated with the wall materials as described herein.

5 Pan coating may be conveniently used to provide the completed dosage form. In the pan coating system, the wall-forming composition for the inner wall or the outer wall, as the case may be, is deposited by successive spraying of the appropriate wall composition onto the compressed core accompanied by tumbling in a rotating pan. A pan coater is used because of its availability at commercial  
10 scale. Other techniques can be used for coating the compressed core. Once coated, the wall is dried in a forced-air oven or in a temperature and humidity controlled oven to free the dosage form of solvent(s) used in the manufacturing. Drying conditions will be conventionally chosen on the basis of available equipment, ambient conditions, solvents, coatings, coating thickness, and the like.

15 Other coating techniques can also be employed. For example, one alternative technique uses an air-suspension procedure. This procedure consists of suspending and tumbling the compressed core in a current of air, until a coating is applied to the core. The air-suspension procedure is described in U.S. Patent  
20 No. 2,799,241; in J. Am. Pharm. Assoc., Vol. 48, pp. 451-459 (1959); and, *ibid.*, Vol. 49, pp. 82-84 (1960). The dosage form also can be coated with a Wurster® air-suspension coater using, for example, methylene dichloride-methanol as a cosolvent for the wall forming material. An Aeromatic® air-suspension coater can be used employing a cosolvent.

25 In another embodiment, the drug and other ingredients comprising the drug layer are blended and pressed into a solid layer. The layer possesses dimensions that correspond to the internal dimensions of the area the layer is to occupy in the dosage form, and it also possesses dimensions corresponding to the push layer, if  
30 included, for forming a contacting arrangement therewith. The drug and other ingredients can also be blended with a solvent and mixed into a solid or semisolid

form by conventional methods, such as ballmilling, calendering, stirring or rollmilling, and then pressed into a preselected shape. The compressed cores then may be coated with the inner wall material and the semipermeable wall material as described herein.

5

Another manufacturing process that can be used comprises blending the powdered ingredients in a fluid bed granulator. After the powdered ingredients are dry blended in the granulator, a granulating fluid, for example, polyvinylpyrrolidone in water, is sprayed onto the powders. The coated powders are then dried in the  
10 granulator. This process granulates all the ingredients present therein while adding the granulating fluid. After the granules are dried, a lubricant, such as stearic acid or magnesium stearate, is mixed into the granulation using a blender e.g., V-blender or tote blender. The granules are then pressed and coated in the manner described above.

15

Exemplary solvents suitable for manufacturing the dosage form components comprise aqueous or inert organic solvents that do not adversely harm the materials used in the system. The solvents broadly include members selected from the group consisting of aqueous solvents, alcohols, ketones, esters,  
20 ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatics, heterocyclic solvents and mixtures thereof. Typical solvents include acetone, diacetone alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethylacetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, nhexane, n-heptane, ethylene glycol monoethyl ether,  
25 ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, carbon tetrachloride, nitroethane, nitropropane, tetrachloroethane, ethyl ether, isopropyl ether, cyclohexane, cyclooctane, benzene, toluene, naphtha, 1,4-dioxane, tetrahydrofuran, diglyme, water, aqueous solvents containing inorganic salts such as sodium chloride, calcium chloride, and  
30 the like, and mixtures thereof such as acetone and water, acetone and methanol,

acetone and ethyl alcohol, methylene dichloride and methanol, and ethylene dichloride and methanol.

Exemplary liquid carriers for the present invention include lipophilic solvents  
5 (e.g., oils and lipids), surfactants, and hydrophilic solvents. Exemplary lipophilic solvents, for example, include, but are not limited to, Capmul PG-8, Caprol MPGO, Capryol 90, Plurol Oleique CC497, Capmul MCM, Labrafac PG, N-Decyl Alcohol, Caprol 10G100, Oleic Acid, Vitamin E, Maisine 35-1, Gelucire 33/01, Gelucire 44/14, Lauryl Alcohol, Captex 355EP, Captex 500, Caprylic/Caplic Triglyceride,  
10 Peceol, Caprol ET, Labrafil M2125 CS, Labrafac CC, Labrafil M20 1944 CS, Captex 8277, Myvacet 9-45, Isopropyl Myristate, Caprol PGE 860, Olive Oil, Plurol Oleique, Peanut Oil, Captex 300 Low C6, and Capric Acid.

Exemplary surfactants for example, include, but are not limited to, Vitamin E  
15 TPGS, Cremophor (grades EL, EL-P, and RH40), Labrasol, Tween (grades 20, 60, 80), Pluronic (grades L-31, L-35, L-42, L-64, and L-121), Acconon S-35, Solutol HS-15, and Span (grades 20, and 80).

Exemplary hydrophilic solvents for example, include, but are not limited to,  
20 Isosorbide Dimethyl Ether, Polyethylene Glycol (PEG grades 300, 400, 600, 3000, 4000, 6000, and 8000) and Propylene Glycol (PG).

In general, essentially complete solvent removal will be preferred as the resultant product can then readily be shaped. Shaping may be effected by spray-  
25 drying the solution (to provide the product in particulate form), by evaporation of solvent from solution disposed in molds, by molding (e. g. injection molding), by extrusion and the like. In general the product can be formed when hot and allowed to solidify on cooling. The shaped product may likewise be produced in film or sheet form by evaporation or by pouring a heated mass onto a plate and  
30 evaporating off the solvent.

## F) Formulation Examples

The following formulation examples are illustrative only and are not intended to limit the scope of the inventions in any way. Tablets were prepared  
5 using the ingredients listed in Tables 1.1-1.6 and the following procedure.

In the following examples in Table 1.1-1.6, the exemplified compound, lactose anhydrous, microcrystalline cellulose, and croscarmellose sodium were screened and placed into a fluid bed.

10 Hydroxypropyl cellulose and purified water were mixed to prepare the granulating solution.

The granulating solution was sprayed into the fluid bed to granulate the dry ingredients.

15 When the granulating solution was exhausted, the granulation was dried within the fluid bed.

The dried granules were passed through a suitable mill fitted with an appropriate screen.

The milled granulation was placed in an appropriate blender and combined with screened magnesium stearate.

20 The mixture was blended for an appropriate period of time.

A suitable rotary tablet press was employed to compress the final blend into tablets.

Where a filmcoating was utilized (e.g., Opadry II), the filmcoating powder was mixed with purified water to obtain the film-coating suspension.

25 The tablets were filmcoated in a suitable coating pan and dried.

**Table 1.1: 100mg Tablet Formulation**

| <b>Ingredient</b>                        | <b>Weight (mg/tablet)</b> | <b>% Weight/tablet</b> |
|------------------------------------------|---------------------------|------------------------|
| 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4- |                           |                        |

|                                                                 |               |             |
|-----------------------------------------------------------------|---------------|-------------|
| fluorophenyl)-2-thienylmethyl]benzene) hemihydrate <sup>1</sup> | 102.00        | 51.00%      |
| Silicified Microcrystalline Cellulose                           | 39.26         | 19.63%      |
| Lactose Anhydrous                                               | 39.26         | 19.63%      |
| Hydroxypropyl Cellulose                                         | 6.00          | 3.00%       |
| Croscarmellose Sodium                                           | 12.00         | 6.00%       |
| Magnesium Stearate                                              | 1.48          | 0.74%       |
| <b>Total</b>                                                    | <b>200.00</b> | <b>100%</b> |

<sup>1</sup> amount of hemihydrate equivalent to 100 mg of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene)

**Table 1.2: 25mg Tablet Formulation**

| <b>Ingredient</b>                                                                                       | <b>Weight (mg/tablet)</b> | <b>% Weight/tablet</b> |
|---------------------------------------------------------------------------------------------------------|---------------------------|------------------------|
| 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene) hemihydrate <sup>1</sup> | 25.50                     | 12.75%                 |
| Silicified Microcrystalline Cellulose                                                                   | 81.76                     | 40.88%                 |
| Lactose Anhydrous                                                                                       | 81.76                     | 40.88%                 |
| Hydroxypropyl Cellulose                                                                                 | 1.50                      | 0.75%                  |
| Croscarmellose Sodium                                                                                   | 8.00                      | 4.00%                  |
| Magnesium Stearate                                                                                      | 1.48                      | 0.74%                  |
| <b>Total</b>                                                                                            | <b>200.00</b>             | <b>100%</b>            |

5

<sup>1</sup> amount of hemihydrate equivalent to 25 mg of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene)

**Table 1.3: 200mg Tablet Formulation**

| <b>Ingredient</b>                                                                                       | <b>Weight (mg/tablet)</b> | <b>% Weight/tablet</b> |
|---------------------------------------------------------------------------------------------------------|---------------------------|------------------------|
| 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene) hemihydrate <sup>1</sup> | 204.00                    | 51.00%                 |
| Silicified Microcrystalline Cellulose                                                                   | 78.52                     | 19.63%                 |
| Lactose Anhydrous                                                                                       | 78.52                     | 19.63%                 |
| Hydroxypropyl Cellulose                                                                                 | 12.00                     | 3.00%                  |
| Croscarmellose Sodium                                                                                   | 24.00                     | 6.00%                  |
| Magnesium Stearate                                                                                      | 2.96                      | 0.74%                  |
| <b>Total</b>                                                                                            | <b>400.00</b>             | <b>100%</b>            |

<sup>1</sup> amount of hemihydrate equivalent to 200 mg of 1-(β-D-glucopyranosyl)-4-methyl-

3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene)

**Table 1.4: 50mg Tablet Formulation**

| Ingredient                                                                                              | Weight (mg/tablet) | % Weight/tablet |
|---------------------------------------------------------------------------------------------------------|--------------------|-----------------|
| 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene) hemihydrate <sup>1</sup> | 51.00              | 51.00%          |
| Silicified Microcrystalline Cellulose                                                                   | 19.63              | 19.63%          |
| Lactose Anhydrous                                                                                       | 19.63              | 19.63%          |
| Hydroxypropyl Cellulose                                                                                 | 3.00               | 3.00%           |
| Croscarmellose Sodium                                                                                   | 6.00               | 6.00%           |
| Magnesium Stearate                                                                                      | 0.74               | 0.74%           |
| Total                                                                                                   | 100.00             | 100%            |

5

<sup>1</sup> amount of hemihydrate equivalent to 50 mg of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene)

**Table 1.5: 300mg coated Tablet Formulation**

| Ingredient                                                                                              | Weight (mg/tablet) | % Weight/tablet |
|---------------------------------------------------------------------------------------------------------|--------------------|-----------------|
| 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene) hemihydrate <sup>1</sup> | 306.00             | 51.50%          |
| Microcrystalline Cellulose                                                                              | 117.78             | 19.63%          |
| Lactose Anhydrous                                                                                       | 117.78             | 19.63%          |
| Hydroxypropyl Cellulose                                                                                 | 18.00              | 3.00%           |
| Croscarmellose Sodium                                                                                   | 36.00              | 6.00%           |
| Magnesium Stearate                                                                                      | 4.44               | 0.74%           |
| Total                                                                                                   | 600.00             | 100%            |
| Opadry II <sup>2</sup>                                                                                  | 18.00              | 3.00%           |

10

<sup>1</sup> amount of hemihydrate equivalent to 300 mg of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene)

<sup>2</sup>Tablets are coated to a 3% weight gain with Opadry II

**Table 1.6: 100 mg coated Tablet Formulation**

| Ingredient                                               | Weight (mg/tablet) | % Weight/tablet |
|----------------------------------------------------------|--------------------|-----------------|
| 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2- |                    |                 |

|                                                    |        |        |
|----------------------------------------------------|--------|--------|
| thienylmethyl]benzene)<br>hemihydrate <sup>1</sup> | 102.00 | 51.00% |
| Microcystalline Cellulose                          | 39.26  | 19.63% |
| Lactose Anhydrous                                  | 39.26  | 19.63% |
| Hydroxypropyl Cellulose                            | 6.00   | 3.00%  |
| Croscarmellose Sodium                              | 12.00  | 6.00%  |
| Magnesium Stearate                                 | 1.48   | 0.74%  |
| Total                                              | 200.00 | 100%   |

|                        |      |       |
|------------------------|------|-------|
| Opadry II <sup>2</sup> | 8.00 | 4.00% |
|------------------------|------|-------|

<sup>1</sup> amount of hemihydrate equivalent to 100 mg of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene)

<sup>2</sup>Tablets are coated to a 4% weight gain with Opadry II

5

## G) Biological Examples

### In vivo pharmacokinetic data from dog studies

10 Exposure of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene) in dogs was compared using various orally administrable formulations. Eleven male beagle dogs weighing from 8.0 to 10.0 kg at dose administration and exhibiting good general health were chosen for this study. The dogs were placed into 3 groups according to their weight. Following an overnight  
15 fast each dog received either a single oral suspension dosage or tablet dosage form. In total, three dosage forms of drug compound 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene) were administered: a 5mg/mL nanosuspension, the 100mg Tablet Formulation and 25mg Tablet Formulation. Three fasted dogs in Group 1 received 20mL of a 5mg/mL  
20 nanosuspension; 4 fasted dogs assigned to Group 2 received the 100mg Tablet Formulation (1 tablet per dog; ingredients listed in Table 1.1); and the 4 fasted dogs assigned to Group 3 received the 25mg Tablet Formulation (4 tablets per dog; ingredients listed in Table 1.2).

Following each dose, the dogs received 10 mL of tap water to ensure delivery of the entire dose. Blood samples of about 3 mL were collected via jugular venipuncture, or other suitable site, into K<sub>2</sub> EDTA tubes and placed on wet ice, at times of 0, 0.5, 1, 2, 4, 8, 24, and 48 hours post initial dosing. Plasma was  
5 harvested by centrifugation, and frozen at -20 °C. All samples were placed in amber vials for protection from white light and were processed within two hours of collection.

Plasma samples were analyzed for plasma concentrations of drug  
10 compound 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene) by using a liquid chromatographic-triple quadruple mass spectrometric (LC-MS/MS) assay procedure with a lower limit of quantification of 50 ng/mL. Plasma concentration data were electronically transferred to a Watson™ LIMS computer system. The Watson™ system assigns a value of 0.00  
15 to those concentrations below the lower limit of quantification.

## Table 2

| Dosage/Formulation            | Subject ID | Body Weight (kg) | C <sub>max</sub> (ng/mL) | t <sub>max</sub> (h) | AUC <sub>0-48h</sub> (ng•h/mL) | AUC <sub>inf</sub> (ng•h/mL) | t <sub>1/2</sub> (h) | CL/F (mL/h) |
|-------------------------------|------------|------------------|--------------------------|----------------------|--------------------------------|------------------------------|----------------------|-------------|
| 20mL of 5mg/mL nanosuspension | 1          | 9.10             | 6480                     | 2.00                 | 114000                         | 119000                       | 10.4                 | 763         |
|                               | 2          | 8.10             | 7760                     | 0.500                | 105000                         | 107000                       | 8.01                 | 759         |
|                               | 3          | 9.90             | 4210                     | 1.00                 | 64300                          | 66000                        | 9.24                 | 1500        |
|                               | Mean       | 9.03             | 6150                     | 1.17                 | 94600                          | 97300                        | 9.23                 | 1008        |
|                               | SD         | 0.902            | 1800                     | 0.764                | 26700                          | 27900                        | 1.22                 | 427         |
| 1x100mg tablet                | 4          | 10.0             | 9670                     | 2.00                 | 147000                         | 153000                       | 10.5                 | 656         |
|                               | 5          | 8.00             | 6440                     | 2.00                 | 95800                          | 97300                        | 7.95                 | 1030        |
|                               | 6          | 8.30             | 7910                     | 1.00                 | 116000                         | 118000                       | 8.49                 | 847         |
|                               | 7          | 9.80             | 7230                     | 4.00                 | 137000                         | 142000                       | 9.63                 | 705         |
|                               | Mean       | 9.03             | 7810                     | 2.25                 | 124000                         | 127000                       | 9.13                 | 809         |
|                               | SD         | 1.02             | 1380                     | 1.26                 | 22700                          | 24700                        | 1.13                 | 167         |
| 4x25mg tablets                | 8          | 8.60             | 11100                    | 4.00                 | 180000                         | 188000                       | 10.8                 | 532         |
|                               | 9          | 9.30             | 9640                     | 4.00                 | 155000                         | 161000                       | 9.83                 | 621         |
|                               | 10         | 8.30             | 7460                     | 4.00                 | 157000                         | 163000                       | 10.4                 | 612         |
|                               | 11         | 8.80             | 9360                     | 2.00                 | 109000                         | 112000                       | 8.86                 | 895         |
|                               | Mean       | 8.75             | 9390                     | 3.50                 | 150000                         | 156000                       | 9.97                 | 665         |
|                               | SD         | 0.420            | 1500                     | 1.00                 | 29600                          | 32000                        | 0.845                | 159         |

The nanosuspension used as a control in the study included a 0.5% Methocel<sup>®</sup> suspension measured in weight percentage. Methocel<sup>®</sup> is a hydroxypropyl methylcellulose (HPMC) polymer exhibiting high viscosity and used as a thickener of the suspension. The drug concentration was 5mg of drug per 1mL of suspension volume. A total of 20mL suspension was administered to each dog in the nanosuspension group.

Pharmacokinetic analysis of the plasma concentrations of drug compound 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene was performed to determine the maximum plasma concentration (C<sub>max</sub>), the time to maximum plasma concentration (t<sub>max</sub>), the area under the plasma concentration versus time curve extrapolated to infinity (AUC<sub>inf</sub> and AUC<sub>0-48h</sub>), the terminal half-life (t<sub>1/2</sub>), and the plasma clearance (CL/F) using the WinNonlin Version 4.0.1 (Pharsight) validated computer program.

**Table 3**

| Formulation                   |      | Body Weight (kg) | C <sub>max</sub> (ng/mL) | t <sub>max</sub> (h) | t <sub>1/2</sub> (h) | AUC <sub>0-48h</sub> (ng•h/mL) | AUC <sub>inf</sub> (ng•h/mL) | Bio-availability | CL/F (mL/h) |
|-------------------------------|------|------------------|--------------------------|----------------------|----------------------|--------------------------------|------------------------------|------------------|-------------|
| 20mL of 5mg/mL nanosuspension | Mean | 9.03             | 6150                     | 1.17                 | 9.23                 | 94600                          | 97300                        | Reference        | 1008        |
|                               | SD   | (0.902)          | (1800)                   | (0.764)              | (1.22)               | (26700)                        | (27900)                      |                  | (427)       |
| 1 x 100mg Tablet              | Mean | 9.03             | 7810                     | 2.25                 | 9.13                 | 124000                         | 127000                       | 127              | 809         |
|                               | SD   | (1.020)          | (1380)                   | (1.26)               | (1.13)               | (22700)                        | (24700)                      |                  | (167)       |
| 4 x 25mg Tablet               | Mean | 8.75             | 9390                     | 3.50                 | 9.97                 | 150000                         | 156000                       | 153              | 665         |
|                               | SD   | (0.420)          | (1500)                   | (1.00)               | (0.845)              | (29600)                        | (32000)                      |                  | (159)       |

Following a single 20 mL oral dose of a 5mg/mL nanosuspension of the compound to male beagle dogs, absorption of the compound was rapid based on a mean  $t_{\max}$  value of 1.17 hours and its elimination was slow based on a mean  $t_{1/2}$  value of 9.23 hours. Administration of the single oral dose of 100mg Tablet Formulation or four doses of the 25mg Tablet Formulation of the compound showed delayed absorption of the compound as indicated by mean  $t_{\max}$  values of 2.25 and 3.50 hours, respectively.

Yet, the elimination of the compound after administration of both Tablet Formulations remained slow with mean  $t_{1/2}$  values 9.13 and 9.97 hours, respectively. Based on mean plasma pharmacokinetic parameters that were normalized to 1 mg/kg, the maximum plasma concentration ( $C_{\max}$ ) of the compound following oral administration of one dose of the 100mg Tablet Formulation and four doses of the 25mg Tablet Formulation was higher as compared to the 5mg/mL nanosuspension (FIG. 1A & B).

Furthermore, bioavailability, as indicated by  $AUC_{\text{inf}}$ , following administration of the compound of the 100mg Tablet Formulation or the 25mg Tablet Formulation was higher than after the administration of the 5mg/mL nanosuspension.

#### In vivo pharmacokinetic data from human studies

Healthy human subjects received single oral doses of a liquid nanosuspension or tablet formulation under fed and/or fasted conditions at three different dose levels of the drug compound 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene). The three dose levels included 25 mg (representative formulation listed in Table 1.2), 200 mg (representative formulation listed in Table 1.3) and 400 mg of the drug compound. In particular, the 400 mg tablet dose was achieved by administering two doses of the 200mg Tablet Formulation.

The mean plasma concentration profiles of the compound following oral administration of the 200mg Tablet Formulation under fasted and fed condition and 40 mL of the 5mg/mL liquid nanosuspension (fed condition) are shown in FIG. 2. Similar profiles for the Tablet Formulation versus the nanosuspension were  
5 obtained at doses of 25 mg and 400 mg.

Following 25 and 200 mg doses under fed conditions as shown in Table 4, the median time to maximum plasma concentration ( $t_{max}$ ) of the compound was approximately 1 to 1.5 hours for Tablet Formulations versus 4 hours in case of the  
10 nanosuspension. At the 400 mg dose level, median  $t_{max}$  was approximately 1.75 hours for 2 doses of the 200mg Tablet Formulation versus 2.25 hours in case of the nanosuspension.

For all doses (25 mg, 200 mg, 400 mg), under fed conditions, the mean  $C_{max}$  was lower for the nanosuspension formulation compared to the Tablet  
15 Formulations.

Following administration of 25 and 200 mg doses of the Tablet Formulation, the mean  $C_{max}$  was higher under fasted conditions than under fed conditions. For all doses (25 mg, 200 mg and 400 mg), under fed or fasting (25mg and 200mg  
20 Tablet Formulation only) conditions, mean  $AUC_{inf}$  values of the compound were comparable.

**Table 4**

|                                               | Nanosuspension  | Tablet                     | Tablet          |
|-----------------------------------------------|-----------------|----------------------------|-----------------|
| <b>25 mg Dose</b>                             |                 |                            |                 |
| Food Intake                                   | Fed             | Fasted                     | Fed             |
| Number of subjects                            | 17              | 17                         | 18              |
| C <sub>max</sub> (ng/mL)                      | 130.6 (38.6)    | 217.1 (52.0)               | 183.9 (46.1)    |
| t <sub>max</sub> <sup>a</sup> (hr)            | 4.0 (1-6)       | 1.5 (1-4)                  | 1.0 (1-3)       |
| t <sub>1/2</sub> (hr)                         | 7.9 (1.6)       | 8.1 (1.9)                  | 7.6 (1.2)       |
| AUC <sub>inf</sub> (ng×h/mL)                  | 1,476 (368)     | 1,441 (347)                | 1,462 (421)     |
| Bioavailability                               | Reference       | 166.2                      | 140.8           |
| <b>200 mg Dose</b>                            |                 |                            |                 |
| Food Intake                                   | Fed             | Fasted                     | Fed             |
| Number of subjects                            | 15              | 17                         | 16              |
| C <sub>max</sub> (ng/mL)                      | 985.9 (273.4)   | 1,411.7 (319.8)            | 1,284.3 (320.5) |
| t <sub>max</sub> <sup>a</sup> (hr)            | 4.0 (3-6)       | 1.5 (1-3)                  | 1.5 (1-4)       |
| t <sub>1/2</sub> (hr)                         | 12.4 (4.2)      | 12.1 (2.4)                 | 11.9 (2.6)      |
| AUC <sub>inf</sub> (ng×h/mL)                  | 13,007 (2881)   | 12,291 (2579)              | 12,846 (2489)   |
| Bioavailability                               | Reference       | 143.2                      | 130.3           |
| <b>400 mg Dose</b>                            |                 |                            |                 |
| Food Intake                                   | Fed             | 30 Min. Prior to Breakfast | With Breakfast  |
| Number of subjects                            | 12              | 12                         | 12              |
| C <sub>max</sub> (ng/mL)                      | 1,683.3 (310.1) | 2,412.5 (727.6)            | 2,315.0 (474.9) |
| t <sub>max</sub> <sup>a</sup> (hr)            | 2.25 (0.5-6)    | 1.5 (1-4)                  | 1.75 (1-2.5)    |
| t <sub>1/2</sub> (hr)                         | 11.8 (3.7)      | 11.0 (3.9)                 | 10.1 (4.0)      |
| AUC <sub>inf</sub> (ng×h/mL)                  | 24,520 (4599)   | 26,158 (11263)             | 23,667 (2259)   |
| Bioavailability                               | Reference       | 143.3                      | 137.5           |
| <sup>a</sup> Data represents mean (SD) values |                 |                            |                 |

These data suggest that food had no significant effect on the extent of  
5 bioavailability to the drug compound, but it decreased the rate of absorption as  
evidenced by a decrease in C<sub>max</sub> and delay in t<sub>max</sub>.

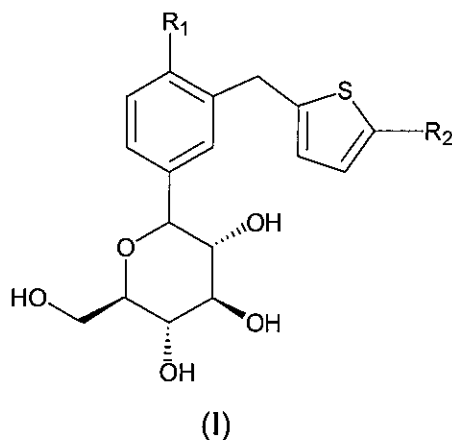
Following tablet administration at the 400 mg dose (2 x 200mg tablets), altering meal-timing (dosing 30 minutes prior to breakfast versus dosing 10 minutes prior to breakfast) did not appear to influence  $t_{\max}$ ,  $t_{1/2}$ ,  $C_{\max}$ , or  $AUC_{\infty}$ .

For all treatment regimens regardless of formulation and food intake, the  
5 mean  $t_{1/2}$  of the drug compound ranged from about 8 to about 12 h.

## **CLAIMS:**

We claim:

1. An orally administrable pharmaceutical formulation comprising  
(a) compound of Formula (I)



wherein

R<sub>1</sub> is halo, cyano, optionally substituted lower alkyl, or optionally substituted lower alkoxy; and

R<sub>2</sub> is optionally substituted aryl, or optionally substituted heterocyclyl;  
or a prodrug, or pharmaceutically acceptable salt thereof;

- (b) at least one diluent or filler;
- (c) optionally at least one disintegrant;
- (d) optionally at least one binder; and
- (e) optionally at least one lubricant;

wherein

the compound of formula (I) is present in an amount within the range of from about 1% to about 80% by weight;

the diluent or filler is present in an amount within the range of from about 10% to about 95% by weight;

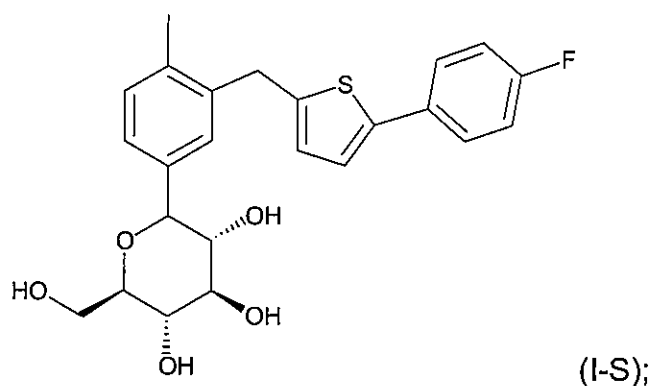
the disintegrant, if present, is present in an amount within the range of from about 0.1% to about 20% by weight;

the binder, if present, is present in an amount within the range of from about 0.1% to about 20% by weight; and

the lubricant, if present, is present in an amount within the range of from about

0.1% to about 5% by weight, all of the above % by weight being based on the weight of the formulation.

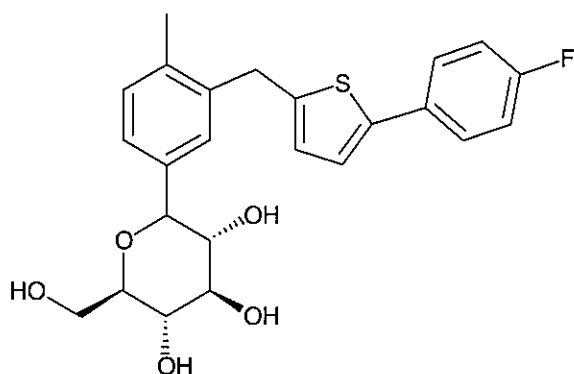
2. The pharmaceutical composition of claim 1 wherein  
R<sub>1</sub> is a halogen atom, or a lower alkyl group; and  
R<sub>2</sub> is phenyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, 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.
3. The pharmaceutical composition of claim 1 wherein the compound of Formula (I) is the compound of formula (I-S):



or a prodrug, or pharmaceutically acceptable salt thereof.

4. The pharmaceutical composition of claim 3, wherein the compound is present in an amount of about 25 mg to about 600 mg.
5. The pharmaceutical composition of claim 3, wherein the compound is present in an amount of about 50 mg to about 300 mg.
6. The pharmaceutical composition of claim 3, wherein the compound is present in an amount of about 100 mg.
7. The pharmaceutical composition of claim 3, wherein the compound is present in an amount of about 300 mg.

8. The pharmaceutical composition of claim 1, wherein the compound is 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene) hemihydrate.
9. The pharmaceutical composition of claim 1, wherein the formulation is a tablet.
10. A method for treating a sodium-dependent glucose transporter mediated disorder, said method comprising administering to a patient in need thereof, the pharmaceutical composition of claim 3 a at a dose of from about 50 mg to about 300 mg once daily.
11. A method for treating a sodium-dependent glucose transporter mediated disorder, said method comprising administering to a patient in need thereof, the pharmaceutical composition of claim 3 at a dose of about 100 mg per day.
12. A method for treating a sodium-dependent glucose transporter mediated disorder, said method comprising administering to a patient in need thereof, the pharmaceutical composition of claim 3 at a dose of about 300 mg per day.
13. An orally administrable pharmaceutical formulation comprising
  - (a) a compound of Formula (I-S)



(I-S),

or a prodrug or pharmaceutically acceptable salt thereof present in an amount within the range of from about 40% to about 60% by weight;

(b) at least one diluent or filler present in an amount within the range of from about 30% to about 50% by weight ;

(c) at least one disintegrant in an amount within the range of from about 3% to about 10% by weight;  
(d) at least one binder present in an amount within the range of from about 0.5% to about 5% by weight; and  
(e) at least one lubricant present in an amount within the range of from about 0.5% to about 2% by weight;  
wherein the % by weight is based on the weight of the formulation.

14. The pharmaceutical composition of claim 13, wherein the compound is 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene) hemihydrate.
15. The pharmaceutical composition of claim 13, wherein the formulation is a tablet.
16. The pharmaceutical composition of claim 14, wherein the formulation is a tablet.