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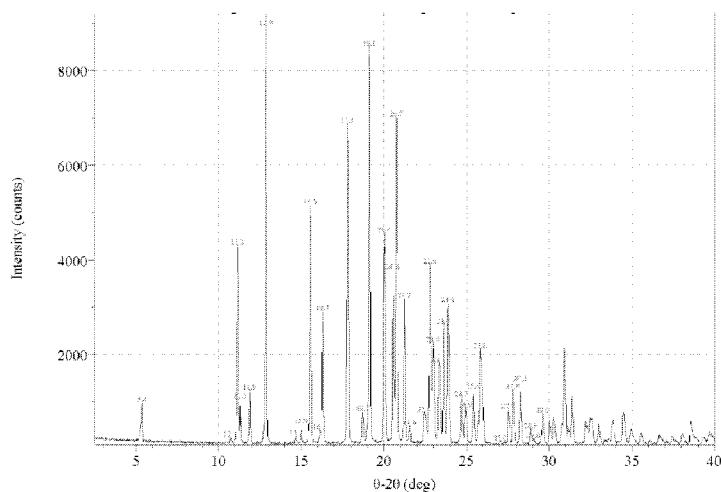
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[Continued on next page]

(54) Title: CRYSTALLINE FORM OF BENZYLBENZENE SGLT2 INHIBITOR

Figure 1.



(57) Abstract: Crystalline forms of a compound having an inhibitory effect on sodium-dependent glucose cotransporter SGLT2 are disclosed. Pharmaceutical compositions, methods of preparing the crystalline compound, and methods of using the crystalline compound, independently or in combination with other therapeutic agents for treating diseases and conditions which are affected by SGLT or SGLT2 inhibition are also disclosed.

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CRYSTALLINE FORM OF BENZYLBENZENE SGLT2 INHIBITOR

CROSS-REFERENCE TO RELATED APPLICATION

[0001] NOT APPLICABLE.

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STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] NOT APPLICABLE

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BACKGROUND OF THE INVENTION

[0003] The sodium-dependent (“active”) glucose cotransporters (SGLTs), including SGLT1 (found predominantly in the intestinal brush border) and SGLT2 (localized in the renal proximal tubule), have been significantly evaluated. In particular, SGLT2 has been found to be responsible for the majority of glucose reuptake by the kidneys. Inhibition of renal SGLT is now considered a useful approach to treating hyperglycemia by increasing the amount of glucose excreted in the urine (Arakawa K, et al., *Br J Pharmacol* 132:578-86, 2001; Oku A, et al., *Diabetes* 48:1794-1800, 1999). The potential of this therapeutic approach is further supported by recent findings that mutations in the SGLT2 gene occur in cases of familial renal glucosuria, an apparently benign syndrome characterized by urinary glucose excretion in the presence of normal serum glucose levels and the absence of general renal dysfunction or other disease (Santer R, et al., *J Am Soc Nephrol* 14:2873-82, 2003). Therefore, compounds which inhibit SGLT, particularly SGLT2, are promising candidates for use as antidiabetic drugs (reviewed in Washburn WN, *Expert Opin Ther Patents* 19:1485-99, 2009). In addition, since cancer cells show increased glucose uptake in comparison to their normal counterparts, SGLT inhibition has been proposed as a method for treating cancer by starving cancer cells. For example, studies suggest that SGLT2 plays a role in glucose uptake in metastatic lesions of lung cancer (Ishikawa N, et al., *Jpn J Cancer Res* 92:874-9, 2001). Thus, SGLT2 inhibitors may also be useful as anticancer agents.

[0004] In addition to pharmaceutical activity, a further consideration for the successful development of a medicament is the parameters which are connected with the physical nature of the active substance itself. Some of these parameters are stability of the active substance under various environmental conditions, stability of the active substance during production of

the pharmaceutical formulation and the stability of the active substance in the final medicament compositions. In order to provide the necessary stability, the pharmaceutically active substance used in the medicament should be as pure as possible, leading to its stability in long-term storage under various environmental conditions.

5 [0005] Another factor to be considered is the uniform distribution of the active substance in the formulation, particularly when the active substance is to be given in low doses. To ensure uniform distribution, the particle size of the active substance can be reduced to a suitable level, e.g. by grinding. However, breakdown of the pharmaceutically active substance as a side effect of the grinding (or micronising) must be avoided. As a result, in view of the hard
10 conditions required during the process, the active substance must be stable throughout the grinding process. Still further, if the active substance is not stable during the grinding process, a homogeneous pharmaceutical formulation with the specified amount of active substance is unlikely to be achieved in a reproducible manner.

15 [0006] Still another consideration associated with the grinding process for preparing the desired pharmaceutical formulation is the input of energy caused by this process and the stress on the surface of the crystals. This may in certain circumstances lead to polymorphous changes, to amorphization or to a change in the crystal lattice. Since the pharmaceutical quality of a pharmaceutical formulation requires that the active substance should always have the same crystalline morphology, the stability and properties of the crystalline active
20 substance are subject to stringent requirements from this point of view as well.

25 [0007] Another consideration for the pharmaceutically active substance is stability in a formulation, which in turn gives rise to a longer shelf life of the particular medicament. In this instance, the shelf life is the length of time during which the medicament can be administered without any risk that the active substance has degraded. High stability of a medicament in the abovementioned pharmaceutical compositions under various storage conditions is therefore an additional advantage for both the patient and the manufacturer.

[0008] Furthermore, the availability of a well-defined crystalline form allows the purification of the drug substance by recrystallization.

30 [0009] Apart from the requirements indicated above, it should be generally borne in mind that any change to the solid state of a pharmaceutical composition which is capable of improving its physical and chemical stability gives a significant advantage over less stable forms of the same medicament.

[0010] The compound of the present invention has been prepared according to the methods of U.S. Publication No. 2009/0118201, filed August 22, 2008, U.S. Application No. 12/545,400, and PCT/US2009/054585, now WO2010/022313, both filed August 21, 2009. The aim of the present invention is to provide a stable crystalline form of the compound 5 which meets important requirements imposed on pharmaceutically active substances as mentioned above.

BRIEF SUMMARY OF THE INVENTION

10 **[0011]** The present invention provides crystalline forms of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol having an inhibitory effect on sodium-dependent glucose cotransporter 2 (SGLT2). The invention also provides pharmaceutical compositions, methods of preparing the crystalline form of the compound, and methods of using the compound, independently or in combination 15 with other therapeutic agents, for treating diseases and conditions which are affected by SGLT2 inhibition.

BRIEF DESCRIPTION OF THE DRAWINGS

20 **[0012]** **Figure 1** provides the X-ray powder diffraction (XRPD) spectra of crystalline (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

[0013] **Figure 2** provides a Table of XRPD data for the XRPD spectra in **Figure 1**.

25 **[0014]** **Figure 3** provides the Raman spectra of crystalline (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

[0015] **Figure 4** provides a Raman peak list for the Raman spectra in **Figure 3**.

30 **[0016]** **Figure 5** provides the thermal gravimetric analysis (TGA) of crystalline (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

[0017] **Figure 6** provides the differential scanning calorimetry (DSC) spectra of crystalline (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol.

[0018] **Figure 7** provides a table of unit cell data for crystalline (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol.

[0019] **Figure 8** provides a scheme for the preparation of crystalline (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol.

10 DETAILED DESCRIPTION OF THE INVENTION

Definitions

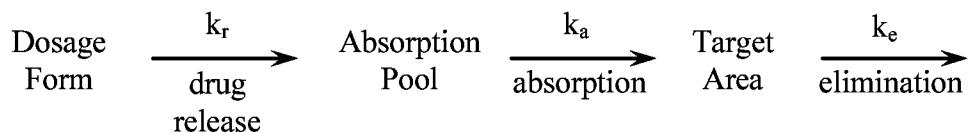
[0020] As used herein, the terms “treating” and “treatment” refer to delaying the onset of, retarding or reversing the progress of, or alleviating or preventing either the disease or condition to which the term applies, or one or more symptoms of such disease or condition.

[0021] As used herein, the term “administering” means oral administration, administration as a suppository, topical contact, intravenous, intraperitoneal, intramuscular, intralesional, intranasal or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route including parenteral, and transmucosal (e.g., oral, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, and the like.

[0022] As used herein, the term “prodrug” refers to a precursor compound that, following administration, releases the biologically active compound *in vivo* via some chemical or physiological process (e.g., a prodrug on reaching physiological pH or through enzyme action is converted to the biologically active compound). A prodrug itself may either lack or possess the desired biological activity.

[0023] As used herein, the term “compound” refers to a molecule produced by any means including, without limitation, synthesis *in vitro* or generation *in situ* or *in vivo*.

[0024] The terms “controlled release,” “sustained release,” “extended release,” and “timed release” are intended to refer interchangeably to any drug-containing formulation in which release of the drug is not immediate, i.e., with a “controlled release” formulation, oral administration does not result in immediate release of the drug into an absorption pool. The 5 terms are used interchangeably with “nonimmediate release” as defined in *Remington: The Science and Practice of Pharmacy*, 21st Ed., Gennaro, Ed., Lippencott Williams & Wilkins (2003). As discussed therein, immediate and nonimmediate release can be defined kinetically by reference to the following equation:



10 **[0025]** The “absorption pool” represents a solution of the drug administered at a particular absorption site, and k_r , k_a and k_e are first-order rate constants for (1) release of the drug from the formulation, (2) absorption, and (3) elimination, respectively. For immediate release dosage forms, the rate constant for drug release k_r is far greater than the absorption rate constant k_a . For controlled release formulations, the opposite is true, i.e., $k_r \ll k_a$, such that 15 the rate of release of drug from the dosage form is the rate-limiting step in the delivery of the drug to the target area.

20 **[0026]** The terms “sustained release” and “extended release” are used in their conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, for example, 12 hours or more, and that preferably, although not necessarily, results in substantially constant blood levels of a drug over an extended time period.

[0027] As used herein, the term “delayed release” refers to a pharmaceutical preparation that passes through the stomach intact and dissolves in the small intestine.

25 **[0028]** As used herein, the term “pharmaceutically acceptable excipient” refers to a substance that aids the administration of an active agent to and absorption by a subject. Pharmaceutical excipients useful in the present invention include, but are not limited to, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors and colors. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0029] As used herein, the term “subject” refers to animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In certain embodiments, the subject is a human.

[0030] As used herein, the terms “therapeutically effective amount or dose” or “therapeutically sufficient amount or dose” or “effective or sufficient amount or dose” refer to a dose that produces therapeutic effects for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); 10 Pickar, *Dosage Calculations* (1999); and Remington: *The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

Crystalline Forms

[0031] The present invention provides a crystalline form of a compound having an inhibitory effect on sodium-dependent glucose cotransporter SGLT, preferably SGLT2. 15 Therefore, the crystalline compound of the present invention is suitable for the prevention and treatment of diseases and conditions, particularly metabolic disorders, including but not limited to type 1 and type 2 diabetes mellitus, hyperglycemia, diabetic complications (such as retinopathy, nephropathy, e.g., progressive renal disease, neuropathy, ulcers, micro- and macroangiopathies, and diabetic foot disease), insulin resistance, metabolic syndrome 20 (Syndrome X), hyperinsulinemia, hypertension, hyperuricemia, obesity, edema, dyslipidemia, chronic heart failure, atherosclerosis and related diseases.

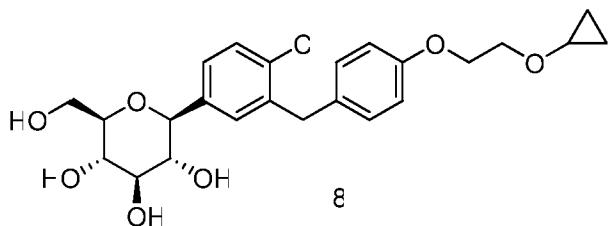
[0032] The present invention also provides pharmaceutical compositions and prodrugs of the crystalline form according to the present invention.

[0033] The present invention further provides synthetic processes for preparing the 25 crystalline compound of the present invention.

[0034] The present invention also provides methods of using the crystalline form of the compound according to the present invention, independently or in combination with other therapeutic agents, for treating diseases and conditions which may be affected by SGLT inhibition.

[0035] The present invention also provides methods of using the compounds according to the present invention for the preparation of a medicament for treating diseases and conditions which may be affected by SGLT inhibition.

[0036] In one aspect, the present invention provides a crystalline form of
5 (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol. The chemical structure is shown below:



[0037] The crystalline compound of the present invention can be characterized by the X-ray powder diffraction (XRPD), the Raman spectra, the differential scanning calorimetry
10 (DSC) endotherm, the thermal gravimetric analysis (TGA) showing decomposition temperature, and the unit cell of the crystal structure.

[0038] In some embodiments, the present invention provides the crystalline form of the compound characterized by the XRPD substantially in accordance with that of **Figure 1** and the peaks substantially in accordance with **Figure 2**. The crystalline compound of the present
15 invention can have any combination of peaks substantially in accordance with **Figure 2**. Moreover, each peak listed in **Figure 2** can have an error range of ± 0.2 degrees 2θ , preferably ± 0.1 degrees 2θ .

[0039] In other embodiments, the crystalline form of the compound is characterized by an X-ray powder diffraction pattern that includes one or more peaks at 5.4, 11.2, 11.3, 11.9, 12.9,
20 15.5, 16.3, 17.8, 19.1, 20.0, 20.6, 20.7, 21.2, 22.8, 23.0, 23.4, 23.6, 23.9, 24.7, 25.4, 25.8, 27.8 and 28.2 degrees 2θ (± 0.1 degrees 2θ), wherein said XRPD is made using $\text{CuK}_{\alpha 1}$ radiation. In another embodiment, the crystalline form of the compound is characterized by an XRPD that includes two or more, three or more, four or more, or five or more peaks at 5.4, 11.2, 11.3, 11.9, 12.9, 15.5, 16.3, 17.8, 19.1, 20.0, 20.6, 20.7, 21.2, 22.8, 23.0, 23.4, 23.6, 23.9, 24.7, 25.4, 25.8 and 28.2 degrees 2θ (± 0.1 degrees 2θ). In some other
25 embodiments, the crystalline form of the compound is characterized by an XRPD that includes peaks at 12.9, 19.1 and 20.7 degrees 2θ (± 0.1 degrees 2θ). In still other embodiments, the crystalline form of the compound is characterized by an XRPD that

includes peaks at 11.2, 12.9, 15.5, 17.8, 19.1, 20.0 and 20.7 degrees 2θ (± 0.1 degrees 2θ). In yet other embodiments, the crystalline form of the compound is characterized by an XRPD that includes peaks at 5.4, 11.2, 11.9, 12.9, 15.5, 16.3, 17.8, and 19.1 degrees 2θ (± 0.1 degrees 2θ). In still yet other embodiments, the crystalline form of the compound is 5 characterized by an XRPD that includes peaks at 5.4, 11.2, 11.9, and 12.9 degrees 2θ (± 0.1 degrees 2θ). In another embodiment, the crystalline form of the compound is characterized by an XRPD including peaks at 11.2 and 12.9 degrees 2θ (± 0.1 degrees 2θ). In other embodiments, the crystalline form of the compound is characterized by the XRPD peaks substantially in accordance with **Figure 2**.

10 [0040] The crystalline compound of the present invention is also characterized by the Raman spectra substantially in accordance with **Figure 3** and the peaks substantially in accordance with **Figure 4**. In some embodiments, the crystalline form of the compound is characterized by a Raman spectra that includes one or more peaks at about 353, 688, 825, 1178, 1205, 1212, 1608, 2945, 3010 and 3063 cm^{-1} . In another embodiment, the crystalline 15 form of the compound is characterized by a Raman spectra that includes two or more, three or more, four or more, or five or more peaks. In other embodiments, the crystalline form of the compound is characterized by the Raman spectra including peaks at about 353, 688 and 825 cm^{-1} . In some other embodiments, the crystalline form of the compound is characterized by the Raman peaks substantially in accordance with **Figure 4**.

20 [0041] The crystalline compound of the present invention is also characterized by the differential scanning calorimetry (DSC) endotherm. In some embodiments, the crystalline form of the compound is characterized by a DSC endotherm at about 136° C.

[0042] The crystalline compound of the present invention is also characterized by the unit cell data substantially in accordance with **Figure 7**. Thermal gravimetric analysis (TGA) can 25 also be used to characterize the crystalline compound of the present invention. For example, a representative TGA is substantially in accordance with that shown in **Figure 5**, demonstrating thermal stability of the crystalline compound above 200° C.

[0043] In some embodiments, the crystalline compound is characterized by at least one of the following: at least one XRPD peak as described above, at least one Raman peak as 30 described above, a DSC endotherm as described above, TGA data regarding thermal stability as described above, and unit cell data as described above and in **Figure 7**. In other embodiments, the crystalline compound is characterized by at least two of the following: at

least one XRPD peak as described above, at least one Raman peak as described above, a DSC endotherm as described above, TGA data regarding thermal stability as described above, and unit cell data as described above and in **Figure 7**. For example, the crystalline compound can be characterized by at least one XRPD peak and at least one Raman peak, or at least one 5 XRPD peak and the DSC endotherm, or at least one Raman peak and the DSC endotherm, or at least one XRPD peak and the unit cell data, or at least one Raman peak and the unit cell data, etc.

[0044] In some embodiments, the crystalline compound of the present invention is characterized by an X-ray powder diffraction (XRPD) pattern that includes one or more 10 peaks at 5.4, 11.2, 11.3, 11.9, 12.9, 15.5, 16.3, 17.8, 19.1, 20.0, 20.6, 20.7, 21.2, 22.8, 23.0, 23.4, 23.6, 23.9, 24.7, 25.4, 25.8, 27.8 and 28.2 degrees 2θ (± 0.1 degrees 2θ), wherein said XRPD is made using $\text{CuK}_{\alpha 1}$ radiation, and a Raman spectra that includes one or more peaks at about 353, 688, 825, 1178, 1205, 1212, 1608, 2945, 3010 and 3063 cm^{-1} . In other 15 embodiments, the crystalline compound of the present invention is characterized by an X-ray powder diffraction (XRPD) pattern that includes one or more peaks at 11.2, 12.9, 15.5, 17.8, 19.1, 20.0, 20.6, 20.7, 21.2 and 22.8 and 28.2 degrees 2θ (± 0.1 degrees 2θ), wherein said XRPD is made using $\text{CuK}_{\alpha 1}$ radiation, and a Raman spectra that includes one or more peaks at about 353, 688, and 825 cm^{-1} . In some other embodiments, the crystalline compound of 20 the present invention is characterized by an X-ray powder diffraction (XRPD) pattern that includes one or more peaks at 11.2 and 12.9 degrees 2θ (± 0.1 degrees 2θ), wherein said XRPD is made using $\text{CuK}_{\alpha 1}$ radiation, and a Raman spectra that includes one or more peaks at about 353, 688, and 825 cm^{-1} .

[0045] In other embodiments, the present invention provides a compound (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-25 (hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol in crystalline form.

[0046] The present invention also includes isotopically-labeled forms of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol, wherein one or more atoms are replaced by one or more atoms having specific atomic mass or mass numbers. Examples of isotopes that can be incorporated into 30 compounds of the invention include, but are not limited to, isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine, sulfur, and chlorine (such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{18}F , ^{35}S and ^{36}Cl). Isotopically-labeled compounds and prodrugs thereof, as well as isotopically-

labeled, pharmaceutically acceptable salts and prodrugs thereof, are within the scope of the present invention. Isotopically-labeled compounds of the present invention are useful in assays of the tissue distribution of the compounds and their prodrugs and metabolites; preferred isotopes for such assays include ^3H and ^{14}C . In addition, in certain circumstances 5 substitution with heavier isotopes, such as deuterium (^2H), can provide increased metabolic stability, which offers therapeutic advantages such as increased *in vivo* half-life or reduced dosage requirements. Isotopically-labeled compounds of this invention and prodrugs thereof can generally be prepared according to the methods described herein by substituting an isotopically-labeled reagent for a non-isotopically labeled reagent.

10 Methods of Making Crystalline Form

[0047] The crystalline form of the present invention can be obtained by a variety of methods, as outlined in **Figure 8**. For example, the crystalline compound **8** can be prepared directly from L-proline complex **7**. Alternatively, the L-proline of L-proline complex **7** can be removed to afford amorphous **8**, which is then crystallized to crystalline **8**. Crystalline **8** 15 can also be prepared directly from crude compound **6**, by first isolating and then crystallizing amorphous **8** to form crystalline **8**.

[0048] Other methods of preparing crystalline **8** are known to one of skill in the art. Moreover, each crystallization process can be repeated to remove additional impurities. In some embodiments, more than one of the various crystallization processes can be used to 20 prepare the crystalline compound of the present invention.

[0049] In some embodiments, crystalline **8** can be prepared from the bis L-proline co-crystal of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol as described in the Examples. Briefly, the co-crystal starting materials is taken up in a suitable solvent (e.g., methanol or ethanol) to 25 obtain a solution, and a precipitating solvent (e.g., water) is added to achieve crystallization of the desired compound.

[0050] Accordingly, the present invention further provides a method for making a crystalline form of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, the 30 method including (a) combining (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol

bis(L-proline) complex and a suitable solvent with mixing to form a solution; (b) adding a precipitating solvent to the solution to provide a mixture; and (c) isolating the crystalline form from the mixture of step (b).

[0051] In other embodiments, the present invention provides a method for making a crystalline form of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol, the method including (a) combining amorphous (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol and a suitable solvent with mixing to form a solution; (b) adding a precipitating solvent to the solution to provide a mixture; and (c) isolating the crystalline form from the mixture of step (b).

[0052] In step (a) of the above methods, the solvent can be any solvent suitable to form a solution, and which is miscible with the precipitating solvent used in step (b). Typically the solvent in step (a) is a polar solvent, which in some embodiments is a protic solvent. Suitable solvents include, C₁-C₄ alcohols, ethylene glycol and polyethylene glycol such as PEG400, alkanoates such as ethyl acetate, isopropyl acetate, propyl acetate, and butyl acetate, acetonitrile, alkanones such as acetone, butanone, methyl ethyl ketone and methyl propyl ketone, and mixtures of two or more of these solvents. More preferred solvents are selected from the group consisting of methanol, ethanol, isopropanol, ethyl acetate, acetone, and mixture of two or more of these solvents. Still further preferred are methanol and ethanol. In one selected embodiment, the solvent used in step (a) is methanol.

[0053] Step (a) of the above methods can be carried out at temperatures generally from about 0° C to the reflux temperature of the solvent (e.g., 65° C for methanol). A preferred temperature range is between about 35° C and 100° C, even more preferably from about 45° C to 80° C. Once a solution is obtained, a precipitating solvent is added. A precipitating solvent is one in which the product is much less soluble than the initial solution solvent. Suitable precipitating solvents include water, ethers, cyclic ethers, alkanes, cycloalkanes, phenyls and mixtures thereof, in particular C₄-C₆-aliphatic ethers, C₆-C₈-alkanes, C₆-C₈-cycloalkanes, phenyls such as benzene, toluene and xylene, and mixtures thereof. Examples of precipitating solvents are diisopropylether, tert-butylmethylether (TBME), cyclohexane, methylcyclohexane, hexane, heptane, octane and mixtures thereof. In one selected embodiment, the precipitating solvent is water.

[0054] The precise ratios of solvents and starting material are less critical to the invention, but optimized ratios can produce greater yields and more uniform crystallized product. The ratio of solvents in the above methods can be any suitable ratio from about 1:1 to about 1:9, including about 1:2, 1:3, 1:4, 1:5, 1:6, 1:7 and about 1:8. The range of solvent ratios is

5 preferably from about 1:1 to about 1:9, more preferably from about 1:2 to about 1:7, even more preferably from about 1:2 to about 1:5. In one group of embodiments, when methanol is used as solvent and water is the precipitating solvent, the ratio of methanol to water in the mixture of step (b) is from about 1:1 to about 1:9 by volume, more preferably about 1:5 by volume.

10 **[0055]** The ratio of complex to solvent, such as a methanol and water mixture, can be any suitable ratio to promote crystallization. For example, the complex to solvent ratio can be from about 1:5 (weight/volume, or w/v) to about 1:50 (w/v), including about 1:6, 1:7, 1:8, 1:9, 1:10, 1:11, 1:12, 1:13, 1:14, 1:15, 1:20, 1:25, 1:30, 1:35, 1:40 and about 1:45 (w/v). The complex to solvent ratio is preferably from about 1:10 to about 1:25 (w/v), more preferably from about 1:10 to about 1:15 (w/v). In another group of embodiments, the ratio of complex to solvent and precipitating solvent in the mixture of step (b) is from about 1:10 to about 1:25 (w/v). In other embodiments, the ratio of complex to methanol and water in the mixture of step (b) is from about 1:10 to about 1:25 (w/v). In some other embodiments, the ratio of complex to methanol and water in the mixture of step (b) is from about 1:2:7 (w/v/v) to about 20 1:3:10 (w/v/v), preferably about 1:2:10 (w/v/v).

25 **[0056]** The mixture for crystallizing crystalline **8** can also contain a variety of other components, such as acids, bases and salts. Acids useful in the present invention include, but are not limited to, acetic acid, formic acid, hydrochloric acid, sulfuric acid, and other weak acids and strong acids. Bases useful in the present invention include, but are not limited to, ammonia, sodium hydroxide, and others. Salts useful in the present invention include, but are not limited to, sodium chloride, potassium chloride, potassium carbonate and others. In some embodiments, the mixture of step (b) in the above methods includes sodium hydroxide. In other embodiments, the mixture of step (b) in the above methods includes sodium chloride.

30 **[0057]** After addition of the precipitating solvent, the mixture is generally kept at room temperature, or cooled, for a sufficient period of time to allow complete crystal formation of the product to occur. The temperature of the mixture in step (b) is preferably about the same as or lower than in step (a). During storage the temperature of the solution containing the

product is preferably lowered to a temperature in the range from -10°C to 25°C or even lower, even more preferably in the range from -5°C to 15°C. Step (b) can be carried out with or without stirring. As noted above, the conditions for step (b) can affect the size, shape and quality of the obtained crystals.

5 [0058] Crystallization of the mixture of step (b) in the methods above, can be induced by methods known in the art, for example by mechanical means such as scratching or rubbing the contact surface of the reaction vessel with e.g. a glass rod. Optionally the saturated or supersaturated solution may be inoculated with seed crystals. The mixture for crystallizing crystalline **8** can also contain a seed crystal of crystalline compound **8**. In some embodiments, 10 the mixture of step (b) in the above methods includes a seed crystal of the crystalline compound of the present invention.

15 [0059] Isolation of the desired crystalline form (in step (c) of the methods above) can be accomplished by removing the solvent and precipitating solvent from the crystals. Generally this is carried out by known methods as for example filtration, suction filtration, decantation or centrifugation. Further isolation can be achieved by removing any excess of the solvent(s) 20 from the crystalline form by methods known to the one skilled in the art as for example application of a vacuum, and/or by heating above 20° C, preferably in a temperature range below 80° C, even more preferably below 50° C.

25 [0060] The amorphous (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol, amorphous compound **8**, can be prepared by a variety of methods known in the art. For example, the amorphous compound **8** can be isolated from crude mixture **6** using known methods of isolating. Alternatively, amorphous compound **8** can be prepared from complex **7** by removing the L-proline using methods known in the art. In some embodiments, the amorphous (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol is prepared from (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol bis(L-proline) by combining (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol bis(L-proline) complex and a suitable solvent mixture with mixing to form a solution, and isolating amorphous (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-

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cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol from the solution. Suitable solvents and solvent mixtures are described above.

Pharmaceutical Compositions

[0061] The present invention further provides a pharmaceutical composition comprising an effective amount of a crystalline form of (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, in a pharmaceutically acceptable excipient.

[0062] The crystalline form provided in this invention can be incorporated into a variety of formulations for therapeutic administration. More particularly, the crystalline form of the present invention can be formulated into pharmaceutical compositions, by formulation with appropriate pharmaceutically acceptable excipients or diluents, and can be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, pills, powders, granules, dragees, gels, slurries, ointments, solutions, suppositories, injections, inhalants and aerosols. As such, administration of the crystalline form of the present invention can be achieved in various ways, including oral, buccal, parenteral, intravenous, intradermal (e.g., subcutaneous, intramuscular), transdermal, etc., administration. Moreover, the crystalline form can be administered in a local rather than systemic manner, for example, in a depot or sustained release formulation.

[0063] Suitable formulations for use in the present invention are found in *Remington: The Science and Practice of Pharmacy*, 21st Ed., Gennaro, Ed., Lippencott Williams & Wilkins (2003), which is hereby incorporated herein by reference. The pharmaceutical compositions described herein can be manufactured in a manner that is known to those of skill in the art, i.e., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. The following methods and excipients are merely exemplary and are in no way limiting.

[0064] In one preferred embodiment, the crystalline form of the present invention is prepared for delivery in a sustained-release, controlled release, extended-release, timed-release or delayed-release formulation, for example, in semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various types of sustained-release materials have been established and are well known by those skilled in the art. Current extended-release formulations include film-coated tablets, multiparticulate or pellet systems,

matrix technologies using hydrophilic or lipophilic materials and wax-based tablets with pore-forming excipients (see, for example, Huang, *et al.* *Drug Dev. Ind. Pharm.* 29:79 (2003); Pearnchob, *et al.* *Drug Dev. Ind. Pharm.* 29:925 (2003); Maggi, *et al.* *Eur. J. Pharm. Biopharm.* 55:99 (2003); Khanvilkar, *et al.*, *Drug Dev. Ind. Pharm.* 228:601 (2002); and

5 Schmidt, *et al.*, *Int. J. Pharm.* 216:9 (2001)). Sustained-release delivery systems can, depending on their design, release the compounds over the course of hours or days, for instance, over 4, 6, 8, 10, 12, 16, 20, 24 hours or more. Usually, sustained release formulations can be prepared using naturally-occurring or synthetic polymers, for instance, polymeric vinyl pyrrolidones, such as polyvinyl pyrrolidone (PVP); carboxyvinyl hydrophilic 10 polymers; hydrophobic and/or hydrophilic hydrocolloids, such as methylcellulose, ethylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose; and carboxypolymethylene.

[0065] The sustained or extended-release formulations can also be prepared using natural ingredients, such as minerals, including titanium dioxide, silicon dioxide, zinc oxide, and clay 15 (see, U.S. Patent 6,638,521, herein incorporated by reference). Exemplified extended release formulations that can be used in delivering a compound of the present invention include those described in U.S. Patent Nos. 6,635,680; 6,624,200; 6,613,361; 6,613,358, 6,596,308; 6,589,563; 6,562,375; 6,548,084; 6,541,020; 6,537,579; 6,528,080 and 6,524,621, each of which is hereby incorporated herein by reference. Controlled release formulations of 20 particular interest include those described in U.S. Patent Nos. 6,607,751; 6,599,529; 6,569,463; 6,565,883; 6,482,440; 6,403,597; 6,319,919; 6,150,354; 6,080,736; 5,672,356; 5,472,704; 5,445,829; 5,312,817 and 5,296,483, each of which is hereby incorporated herein by reference. Those skilled in the art will readily recognize other applicable sustained release formulations.

25 [0066] For oral administration, the crystalline form of the present invention can be formulated readily by combining with pharmaceutically acceptable excipients that are well known in the art. Such excipients enable the compounds to be formulated as tablets, pills, dragees, capsules, emulsions, lipophilic and hydrophilic suspensions, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical 30 preparations for oral use can be obtained by mixing the compounds with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose

preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents can be added, such as a cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

5 [0067] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or 10 magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers can be added. All formulations for oral administration should be in dosages suitable for such administration.

15 [0068] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions can be used, which can optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments can be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

20 [0069] The crystalline forms described herein can also be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. For injection, the compound can be formulated into preparations by dissolving, suspending or emulsifying them in an aqueous or nonaqueous solvent, such as vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, 25 with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives. In some embodiments, the crystalline forms of the invention can be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. Formulations for injection can be presented in unit dosage form, e.g., in ampoules or in multi- 30 dose containers, with an added preservative. The compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[0070] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as 5 ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension can also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient can be in powder form for 10 constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0071] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. For topical administration, the agents are formulated into ointments, creams, salves, powders and gels. In one embodiment, the transdermal 15 delivery agent can be DMSO. Transdermal delivery systems can include, e.g., patches. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. Exemplified transdermal delivery formulations that can find use in the present invention include those described in U.S. Patent Nos. 6,589,549; 6,544,548; 6,517,864; 6,512,010; 6,465,006; 6,379,696; 6,312,717 20 and 6,310,177, each of which are hereby incorporated herein by reference.

[0072] For buccal administration, the compositions can take the form of tablets or lozenges formulated in conventional manner.

[0073] In addition to the formulations described previously, a crystalline form of the present invention can also be formulated as a depot preparation. Such long acting 25 formulations can be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0074] The pharmaceutical compositions also can comprise suitable solid or gel phase 30 carriers or excipients. Examples of such carriers or excipients include but are not limited to

calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[0075] Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in a therapeutically effective amount. The present invention also contemplates pharmaceutical compositions comprising the crystalline forms of the invention in admixture with an effective amount of other therapeutic agents as combination partners, particularly those used for treating diseases and conditions which can be affected by SGLT inhibition, such as antidiabetic agents, lipid-lowering/lipid-modulating agents, agents for treating diabetic complications, anti-obesity agents, antihypertensive agents, antihyperuricemic agents, and agents for treating chronic heart failure, atherosclerosis or related disorders. An effective amount of the compound and/or combination partner will, of course, be dependent on the subject being treated, the severity of the affliction and the manner of administration. Determination of an effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. Generally, an efficacious or effective amount of a compound is determined by first administering a low dose or small amount, and then incrementally increasing the administered dose or dosages until a desired therapeutic effect is observed in the treated subject, with minimal or no toxic side effects. Applicable methods for determining an appropriate dose and dosing schedule for administration of the present invention are described, for example, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 11th Ed., Brunton, Lazo and Parker, Eds., McGraw-Hill (2006), and in *Remington: The Science and Practice of Pharmacy*, 21st Ed., Gennaro, Ed., Lippencott Williams & Wilkins (2003), both of which are hereby incorporated herein by reference.

Methods of Use

[0076] The present invention further provides methods of using the crystalline forms of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol for the prevention and treatment of disease. In one embodiment, the present invention provides a method of treating a disease or condition affected by inhibiting SGLT2, the method including administering to a subject in need thereof a therapeutically effective amount of a composition comprising a crystalline form of the compound of the present invention. Diseases affected by inhibiting SGLT2 include, but are not limited to, type 1 and type 2 diabetes mellitus, hyperglycemia, diabetic

complications (such as retinopathy, nephropathy, neuropathy, ulcers, micro- and macroangiopathies, gout and diabetic foot disease), insulin resistance, metabolic syndrome (Syndrome X), hyperinsulinemia, hypertension, hyperuricemia, obesity, edema, dyslipidemia, chronic heart failure, atherosclerosis, cancer and related diseases, which comprises

5 administering an effective amount of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol, to a subject in need thereof. In another embodiment the invention provides a method of using the crystalline compound, for the preparation of a medicament for treating type 1 and type 2 diabetes mellitus, hyperglycemia, diabetic complications, insulin resistance, metabolic

10 syndrome, hyperinsulinemia, hypertension, hyperuricemia, obesity, edema, dyslipidemia, chronic heart failure, atherosclerosis, cancer and related diseases. In other embodiments, the invention provides a method of treating type 1 diabetes mellitus, type 2 diabetes mellitus, hyperglycemia, diabetic complications, insulin resistance, metabolic syndrome, hyperinsulinemia, hypertension, hyperuricemia, obesity, edema, dyslipidemia, chronic heart

15 failure, atherosclerosis, and cancer.

[0077] In other embodiments, the present invention provides a method of treating diabetes, the method including administering to a subject in need thereof a therapeutically effective amount of a composition comprising a crystalline form of the compound of the present invention. The diabetes can be any suitable form of diabetes, including, but not limited to,

20 type 1 diabetes mellitus, type 2 diabetes mellitus, and diabetic complications. In some embodiments, the diabetes is type 1 diabetes mellitus. In some other embodiments, the diabetes is type 2 diabetes mellitus.

[0078] The present invention also contemplates the use of the crystalline forms of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-

25 (hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol, in combination with other therapeutic agents, particularly those used for treating the above-mentioned diseases and conditions, such as antidiabetic agents, lipid-lowering/lipid-modulating agents, agents for treating diabetic complications, anti-obesity agents, antihypertensive agents, antihyperuricemic agents, and agents for treating chronic heart failure, atherosclerosis or related disorders. Those skilled in

30 the art will appreciate that other therapeutic agents discussed below can have multiple therapeutic uses and the listing of an agent in one particular category should not be construed to limit in any way its usefulness in combination therapy with compounds of the present invention.

[0079] Examples of antidiabetic agents suitable for use in combination with crystalline forms of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol of the present invention include insulin and insulin mimetics, sulfonylureas (such as acetohexamide, carbutamide, chlorpropamide, 5 glibenclamide, glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glisoxepide, glyburide, glyclopamide, tolazamide, tolcyclamide, tolbutamide and the like), insulin secretion enhancers (such as JTT -608, glybzole and the like), biguanides (such as metformin, buformin, phenformin and the like), sulfonylurea/biguanide combinations (such as glyburide/metformin and the like), meglitinides (such as repaglinide, nateglinide, 10 metformin and the like), thiazolidinediones (such as rosiglitazone, pioglitazone, isaglitazone, netoglitazone, rivoglitazone, balaglitazone, darglitazone, CLX-0921 and the like), thiazolidinedione/biguanide combinations (such as pioglitazone/metformin and the like), oxadiazolidinediones (such as YM440 and the like), peroxisome proliferator-activated 15 receptor (PPAR)-gamma agonists (such as farglitazar, metaglidases, MBX-2044, GI 262570, GW1929, GW7845 and the like), PPAR-alpha/gamma dual agonists (such as muraglitazar, naveglitazar, tesaglitazar, peliglitazar, JTT-501, GW-409544, GW-501516 and the like), PPAR-alpha/gamma/delta pan agonists (such as PLX204, GlaxoSmithKline 625019, GlaxoSmithKline 677954 and the like), retinoid-x receptor (RXR) agonists (such as ALRT-268, AGN-4204, MX-6054, AGN-194204, LG-100754, bexarotene and the like), alpha- 20 glucosidase inhibitors (such as acarbose, miglitol and the like), stimulants of insulin receptor tyrosine kinase (such as TER-17411, L-783281, KRX-613 and the like), tripeptidyl peptidase II inhibitors (such as UCL-1397 and the like), dipeptidyl peptidase IV inhibitors (such as sitagliptin, vildagliptin, denagliptin, saxagliptin, NVP-DPP728, P93/01, P32/98, FE 99901, TS-021, TSL-225, GRC8200, compounds described in U.S. Patent Nos. 6,869,947; 6,727,261; 25 6,710,040; 6,432,969; 6,172,081; 6,011,155 and the like), protein tyrosine phosphatase-1B inhibitors (such as KR61639, IDD-3, PTP-3848, PTP-112, OC-86839, PNU-177496, compounds described in Vats, R.K., et al., *Current Science*, Vol. 88, No. 2, 25 January 2005, pp. 241-249, and the like), glycogen phosphorylase inhibitors (such as NN-4201, CP-368296 and the like), glucose-6-phosphatase inhibitors, fructose 1,6-bisphosphatase inhibitors (such 30 as CS-917, MB05032 and the like), pyruvate dehydrogenase inhibitors (such as AZD-7545 and the like), imidazoline derivatives (such as BL11282 and the like), hepatic gluconeogenesis inhibitors (such as FR-225659 and the like), D-chiroinositol, glycogen synthase kinase-3 inhibitors (such as compounds described in Vats, R.K., et al., *Current Science*, Vol. 88, No. 2, 25 January 2005, pp. 241-249, and the like), 11 beta-hydroxysteroid

dehydrogenase type 1 inhibitors (such as carbenoxolone, INCB13739 and the like), glucagon receptor antagonists (such as BAY-27-9955, NN-2501, NNC-92-1687 and the like), glucagon-like peptide-1 (GLP-1), GLP-1 receptor agonists (such as exenatide, liraglutide, CJC-1131, AVE-0100, AZM-134, LY-315902, GlaxoSmithKline 716155 and the like),
5 amylin, amylin analogs and agonists (such as pramlintide and the like), fatty acid binding protein (aP2) inhibitors (such as compounds described in U.S. Patent Nos. 6,984,645; 6,919,323; 6,670,380; 6,649,622; 6,548,529 and the like), beta-3 adrenergic receptor agonists (such as solabegron, CL-316243, L-771047, FR-149175 and the like), and other insulin sensitivity enhancers (such as reglixane, ONO-5816, MBX-102, CRE-1625, FK-614, CLX-
10 0901, CRE-1633, NN-2344, BM-13125, BM-501050, HQL-975, CLX-0900, MBX-668, MBX-675, S-15261, GW-544, AZ-242, LY-510929, AR-H049020, GW-501516 and the like).

[0080] Examples of agents for treating diabetic complications suitable for use in combination with the crystalline compound of the present invention include aldose reductase inhibitors (such as epalrestat, imirestat, tolrestat, minalrestat, ponalrestat, zopolrestat, 15 fidarestat, ascorbyl gamolenate, ADN-138, BAL-ARI8, ZD-5522, ADN-311, GP-1447, IDD-598, risarestat, zenarestat, methosorbinil, AL-1567, M-16209, TAT, AD-5467, AS-3201, NZ-314, SG-210, JTT-811, lindolrestat, sorbinil and the like), inhibitors of advanced glycation end-products (AGE) formation (such as pyridoxamine, OPB-9195, ALT-946, ALT-711, pimagedine and the like), AGE breakers (such as ALT-711 and the like), sulodexide, 5-20 hydroxy-1-methylhydantoin, insulin-like growth factor-I, platelet-derived growth factor, platelet-derived growth factor analogs, epidermal growth factor, nerve growth factor, uridine, protein kinase C inhibitors (such as ruboxistaurin, midostaurin and the like), sodium channel antagonists (such as mexiletine, oxcarbazepine and the like), nuclear factor-kappaB (NF-kappaB) inhibitors (such as dextroamphetamine and the like), lipid peroxidase inhibitors (such as 25 tirilazad mesylate and the like), N-acetylated-alpha-linked-acid-dipeptidase inhibitors (such as GPI-5232, GPI-5693 and the like), and carnitine derivatives (such as carnitine, levacecarnitine, levocarnitine, ST-261 and the like).

[0081] Examples of antihyperuricemic agents suitable for use in combination with the crystalline compound of the present invention include uric acid synthesis inhibitors (such as 30 allopurinol, oxypurinol and the like), uricosuric agents (such as probenecid, sulfapyrazone, benzboromarone and the like) and urinary alkalinizers (such as sodium hydrogen carbonate, potassium citrate, sodium citrate and the like).

[0082] Examples of lipid-lowering/lipid-modulating agents suitable for use in combination with the crystalline compound of the present invention include hydroxymethylglutaryl coenzyme A reductase inhibitors (such as acitemate, atorvastatin, bervastatin, carvastatin, cerivastatin, colestolone, crilvastatin, dalvastatin, fluvastatin, glenvastatin, lovastatin, 5 mevastatin, nisvastatin, pitavastatin, pravastatin, ritonavir, rosuvastatin, saquinavir, simvastatin, visastatin, SC-45355, SQ-33600, CP-83101, BB-476, L-669262, S-2468, DMP-565, U-20685, BMS-180431, BMY-21950, compounds described in U.S. Patent Nos. 5,753,675; 5,691,322; 5,506,219; 4,686,237; 4,647,576; 4,613,610; 4,499,289 and the like), fibrin acid derivatives (such as gemfibrozil, fenofibrate, bezafibrate, beclobrate, binifibrate, 10 ciprofibrate, clinofibrate, clofibrate, etofibrate, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, AHL-157 and the like), PPAR-alpha agonists (such as GlaxoSmithKline 590735 and the like), PPAR-delta agonists (such as GlaxoSmithKline 501516 and the like), acyl-coenzyme A:cholesterol acyltransferase inhibitors (such as avasimibe, eflucimibe, eldacimibe, lecimibe, NTE-122, MCC-147, PD-132301-2, C1-1011, DUP-129, U-73482, U-76807, TS-15 962, RP-70676, P-06139, CP-113818, RP-73163, FR-129169, FY-038, EAB-309, KY-455, LS-3115, FR-145237, T-2591, J-104127, R-755, FCE-27677, FCE-28654, YIC-C8-434, CI-976, RP-64477, F-1394, CS-505, CL-283546, YM-17E, 447C88, YM-750, E-5324, KW-3033, HL-004 and the like), probucol, thyroid hormone receptor agonists (such as 20 liothyronine, levothyroxine, KB-2611, GC-1 and the like), cholesterol absorption inhibitors (such as ezetimibe, SCH48461 and the like), lipoprotein-associated phospholipase A2 inhibitors (such as rilapladib, darapladib and the like), microsomal triglyceride transfer protein inhibitors (such as CP-346086, BMS-201038, compounds described in U.S. Patent Nos. 5,595,872; 5,739,135; 5,712,279; 5,760,246; 5,827,875; 5,885,983; 5,962,440; 6,197,798; 6,617,325; 6,821,967; 6,878,707 and the like), low density lipoprotein receptor 25 activators (such as LY295427, MD-700 and the like), lipoxygenase inhibitors (such as compounds described in WO 97/12615, WO 97/12613, WO 96/38144 and the like), carnitine palmitoyl-transferase inhibitors (such as etomoxir and the like), squalene synthase inhibitors (such as YM-53601, TAK-475, SDZ-268-198, BMS-188494, A-87049, RPR-101821, ZD-9720, RPR-107393, ER-27856, compounds described in U.S. Patent Nos. 5,712,396; 30 4,924,024; 4,871,721 and the like), nicotinic acid derivatives (such as acipimox, nicotinic acid, ricotinamide, nicomol, nericitrol, nicorandil and the like), bile acid sequestrants (such as colestipol, cholestyramine, colestilan, colesevelam, GT-102-279 and the like), sodium/bile acid cotransporter inhibitors (such as 264W94, S-8921, SD-5613 and the like), and

cholesterol ester transfer protein inhibitors (such as torcetrapib, JTT-705, PNU-107368E, SC-795, CP-529414 and the like).

[0083] Examples of anti-obesity agents suitable for use in combination with the crystalline compound of the present invention include serotonin-norepinephrine reuptake inhibitors

5 (such as sibutramine, milnacipran, mirtazapine, venlafaxine, duloxetine, desvenlafaxine and the like), norepinephrine-dopamine reuptake inhibitors (such as radafaxine, bupropion, amineptine and the like), serotonin-norepinephrine-dopamine reuptake inhibitors (such as tesofensine and the like), selective serotonin reuptake inhibitors (such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and the like), selective
10 norepinephrine reuptake inhibitors (such as reboxetine, atomoxetine and the like), norepinephrine releasing stimulants (such as rolipram, YM-992 and the like), anorexiants (such as amphetamine, methamphetamine, dextroamphetamine, phentermine, benzphetamine, phendimetrazine, phenmetrazine, diethylpropion, mazindol, fenfluramine, dexfenfluramine, phenylpropanolamine and the like), dopamine agonists (such as ER-230, doprexin,
15 bromocriptine mesylate and the like), H₃-histamine antagonists (such as impentamine, thioperamide, ciproxifan, clobenpropit, GT-2331, GT-2394, A-331440, and the like), 5-HT_{2c} receptor agonists (such as, 1-(m-chlorophenyl)piperazine (m-CPP), mirtazapine, APD-356 (lorcaserin), SCA-136 (vabicaserin), ORG-12962, ORG-37684, ORG-36262, ORG-8484, Ro-60-175, Ro-60-0332, VER-3323, VER-5593, VER-5384, VER-8775, LY-448100, WAY-
20 161503, WAY-470, WAY-163909, MK-212, BVT.933, YM-348, IL-639, IK-264, ATH-88651, ATHX-105 and the like (see, e.g., Nilsson BM, *J. Med. Chem.* 2006, 49:4023-4034)), beta-3 adrenergic receptor agonists (such as L-796568, CGP 12177, BRL-28410, SR-58611A, ICI-198157, ZD-2079, BMS-194449, BRL-37344, CP-331679, CP-331648, CP-114271, L-750355, BMS-187413, SR-59062A, BMS-210285, LY-377604, SWR-0342SA, AZ-40140,
25 SB-226552, D-7114, BRL-35135, FR-149175, BRL-26830A, CL-316243, AJ-9677, GW-427353, N-5984, GW-2696 and the like), cholecystokinin agonists (such as SR-146131, SSR-125180, BP-3.200, A-71623, A-71378, FPL-15849, GI-248573, GW-7178, GI-181771, GW-7854, GW-5823, and the like), antidepressant/acetylcholinesterase inhibitor combinations (such as venlafaxine/rivastigmine, sertraline/galanthamine and the like), lipase inhibitors
30 (such as orlistat, ATL-962 and the like), anti-epileptic agents (such as topiramate, zonisamide and the like), leptin, leptin analogs and leptin receptor agonists (such as LY-355101 and the like), neuropeptide Y (NPY) receptor antagonists and modulators (such as SR-120819-A, PD-160170, NGD-95-1, BIBP-3226, 1229-U-91, CGP-71683, BIBO-3304, CP-671906-01, J-

115814 and the like), ciliary neurotrophic factor (such as Axokine and the like), thyroid hormone receptor-beta agonists (such as KB-141, GC-1, GC-24, GB98/284425 and the like), cannabinoid CB1 receptor antagonists (such as rimonabant, SR147778, SLV 319 and the like (see, e.g., Antel J et al., *J. Med. Chem.* 2006, 49:4008-4016)), melanin-concentrating

5 hormone receptor antagonists (such as GlaxoSmithKline 803430X, GlaxoSmithKline 856464, SNAP-7941, T-226296 and the like (see, e.g., Handlon AL and Zhou H, *J. Med. Chem.* 2006, 49:4017-4022)), melanocortin-4 receptor agonists (including PT-15, Ro27-3225, THIQ, NBI 55886, NBI 56297, NBI 56453, NBI 58702, NBI 58704, MB243 and the like (see, e.g., Nargund RP et al., *J. Med. Chem.* 2006, 49:4035-4043)), selective muscarinic receptor M₁

10 antagonists (such as telenzepine, pirenzepine and the like), opioid receptor antagonists (such as naltrexone, methylnaltrexone, nalmefene, naloxone, alvimopan, norbinaltorphimine, nalorphine and the like), and combinations thereof.

[0084] Examples of antihypertensive agents and agents for treating chronic heart failure, atherosclerosis or related diseases suitable for use in combination with the crystalline

15 compound of the present invention include bimoclomol, angiotensin-converting enzyme inhibitors (such as captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril and the like), neutral endopeptidase inhibitors (such as thiorphan, omapatrilat, MDL-100240, fasidotril, sampatrilat, GW-660511, mixanpril, SA-7060, E-4030, SLV-306, ecadotril and the like), angiotensin II receptor antagonists (such as candesartan cilexetil, eprosartan, irbesartan, losartan, olmesartan medoxomil, telmisartan, valsartan, tasosartan, enoltasosartan and the like), endothelin-converting enzyme inhibitors (such as CGS 35066, CGS 26303, CGS-31447, SM-19712 and the like), endothelin receptor antagonists (such as tracleer, sitaxsentan, ambrisentan, L-749805, TBC-3214, BMS-182874, BQ-610, TA-0201, SB-215355, PD-180988, BMS-193884, darusentan, TBC-3711, bosentan, tezosentan, J-104132, YM-598, S-0139, SB-234551, RPR-118031A, ATZ-1993, RO-61-1790, ABT-546, enlasentan, BMS-207940 and the like), diuretic agents (such as hydrochlorothiazide, bendroflumethiazide, trichlormethiazide, indapamide, metolazone, furosemide, bumetanide, torsemide, chlorthalidone, metolazone, cyclopenthiazide, hydroflumethiazide, tripamide, mefruside, benzylhydrochlorothiazide, penflutizide, methyclothiazide, azosemide, etacrynic acid, torasemide, piretanide, meticrane, potassium canrenoate, spironolactone, triamterene, aminophylline, cicletanine, LLU-alpha, PNU-80873A, isosorbide, D-mannitol, D-sorbitol, fructose, glycerin, acetazolamide, methazolamide, FR-179544, OPC-31260, lixivaptan, conivaptan and the like), calcium channel antagonists (such as amlodipine, bepridil, diltiazem,

felodipine, isradipine, nicardipen, nimodipine, verapamil, S-verapamil, aranidipine, efondipine, barnidipine, benidipine, manidipine, cilnidipine, nisoldipine, nitrendipine, nifedipine, nilvadipine, felodipine, pranidipine, lercanidipine, isradipine, elgodipine, azelnidipine, lacidipine, vatanidipine, lemildipine, diltiazem, clentiazem, fasudil, bepridil, 5 gallopamil and the like), vasodilating antihypertensive agents (such as indapamide, todralazine, hydralazine, cadralazine, budralazine and the like), beta blockers (such as acebutolol, bisoprolol, esmolol, propanolol, atenolol, labetalol, carvedilol, metoprolol and the like), sympathetic blocking agents (such as amosulalol, terazosin, bunazosin, prazosin, doxazosin, propranolol, atenolol, metoprolol, carvedilol, nifradilol, celiprolol, nebivolol, 10 betaxolol, pindolol, tertatolol, bevantolol, timolol, carteolol, bisoprolol, bopindolol, nifradilol, penbutolol, acebutolol, tilisolol, nadolol, urapidil, indoramin and the like), alpha-2-adrenoceptor agonists (such as clonidine, methyldopa, CHF-1035, guanabenz acetate, guanfacine, moxonidine, lofexidine, talipexole and the like), centrally acting antihypertensive agents (such as reserpine and the like), thrombocyte aggregation inhibitors (such as warfarin, 15 dicumarol, phenprocoumon, acenocoumarol, anisindione, phenindione, ximelagatran and the like), and antiplatelets agents (such as aspirin, clopidogrel, ticlopidine, dipyridamole, cilostazol, ethyl icosapentate, sarpogrelate, dilazep, trapidil, beraprost and the like).

[0085] Furthermore, in another aspect, the invention provides for a pharmaceutical composition comprising effective amounts of a crystalline form of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol, and at least one member selected from the group of therapeutic agents listed above as combination partners, in a pharmaceutically acceptable excipient.

[0086] The crystalline compound of the present invention is also useful for treatment of glucose disorders. In some embodiments, the present invention provides a method of 25 decreasing blood glucose in a subject in need thereof, the method including administering to the subject an effective amount of a composition comprising a crystalline form of the compound of the present invention. In other embodiments, the present invention provides a method of lowering plasma levels of glycated hemoglobin (HbA1c) in a subject in need thereof, the method including administering to the subject an effective amount of a 30 composition comprising a crystalline form of the compound of the present invention. In still other embodiments, the present invention provides a method of increasing the excretion of glucose in the urine of a subject in need thereof, said method comprising administering to the

subject an effective amount of a composition comprising a crystalline form of the compound of the present invention.

[0087] The treatment of the present invention can be administered prophylactically to prevent or delay the onset or progression of a disease or condition (such as hyperglycemia), 5 or therapeutically to achieve a desired effect (such as a desired level of serum glucose) for a sustained period of time.

[0088] The crystalline form of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol can be administered to a subject, e.g., a human patient, a domestic animal such as a cat or a dog, 10 independently or together with a combination partner, in the form of their pharmaceutically acceptable salts or prodrugs, or in the form of a pharmaceutical composition where the compounds and/or combination partners are mixed with suitable carriers or excipient(s) in a therapeutically effective amount. Consequently, the crystalline form of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, and an additional active agent to be combined therewith, can be present in a 15 single formulation, for example a capsule or tablet, or in two separate formulations, which can be the same or different, for example, in the form of a kit comprising selected numbers of doses of each agent.

[0089] The appropriate dosage of compound will vary according to the chosen route of 20 administration and formulation of the composition, among other factors, such as patient response. The dosage can be increased or decreased over time, as required by an individual patient. A patient initially may be given a low dose, which is then increased to an efficacious dosage tolerable to the patient. Typically, a useful dosage for adults may be from 1 to 2000 mg, preferably 1 to 200 mg, when administered by oral route, and from 0.1 to 100 mg, 25 preferably 1 to 30 mg, when administered by intravenous route, in each case administered from 1 to 4 times per day. When a compound of the invention is administered in combination with another therapeutic agent, a useful dosage of the combination partner may be from 20% to 100% of the normally recommended dose.

[0090] Dosage amount and interval can be adjusted individually to provide plasma levels of 30 the active compounds which are sufficient to maintain therapeutic effect. Preferably, therapeutically effective serum levels will be achieved by administering single daily doses, but efficacious multiple daily dose schedules are included in the invention. In cases of local

administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration. One having skill in the art will be able to optimize therapeutically effective local dosages without undue experimentation.

[0091] All publications and patent applications cited in this specification are herein 5 incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Any conflict between any reference cited herein and the teaching of this specification is to be resolved in favor of the latter. Similarly, any conflict between an art-recognized definition of a word or phrase and a definition of the word or phrase as provided in this specification is to be resolved in 10 favor of the latter. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications can be made thereto without departing from the spirit or scope of the appended claims. The invention will be described in greater detail by way of 15 specific examples.

Examples

[0092] The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of noncritical parameters which can be changed or modified to yield essentially the same results.

20 **[0093]** The names of compounds shown in the following examples were derived from the structures shown using the CambridgeSoft Struct=Name algorithm as implemented in ChemDraw Ultra version 10.0. Unless otherwise indicated, the structures of compounds synthesized in the examples below were confirmed using the following procedures:

25 **[0094]** (1) Gas chromatography-mass spectra with electrospray ionization (MS ESI) were obtained with an Agilent 5973N mass spectrometer equipped with an Agilent 6890 gas chromatograph with an HP-5 MS column (0.25 μ m coating; 30 mx0.25 mm). The ion source was maintained at 230 °C and spectra were scanned from 25-500 amu at 3.09 sec per scan.

30 **[0095]** (2) High pressure liquid chromatography mass spectra (LC-MS) were obtained using Finnigan Surveyor HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, an XB-C18 column (4.6x50mm, 5 μ m), and a Finnigan LCQ ion trap

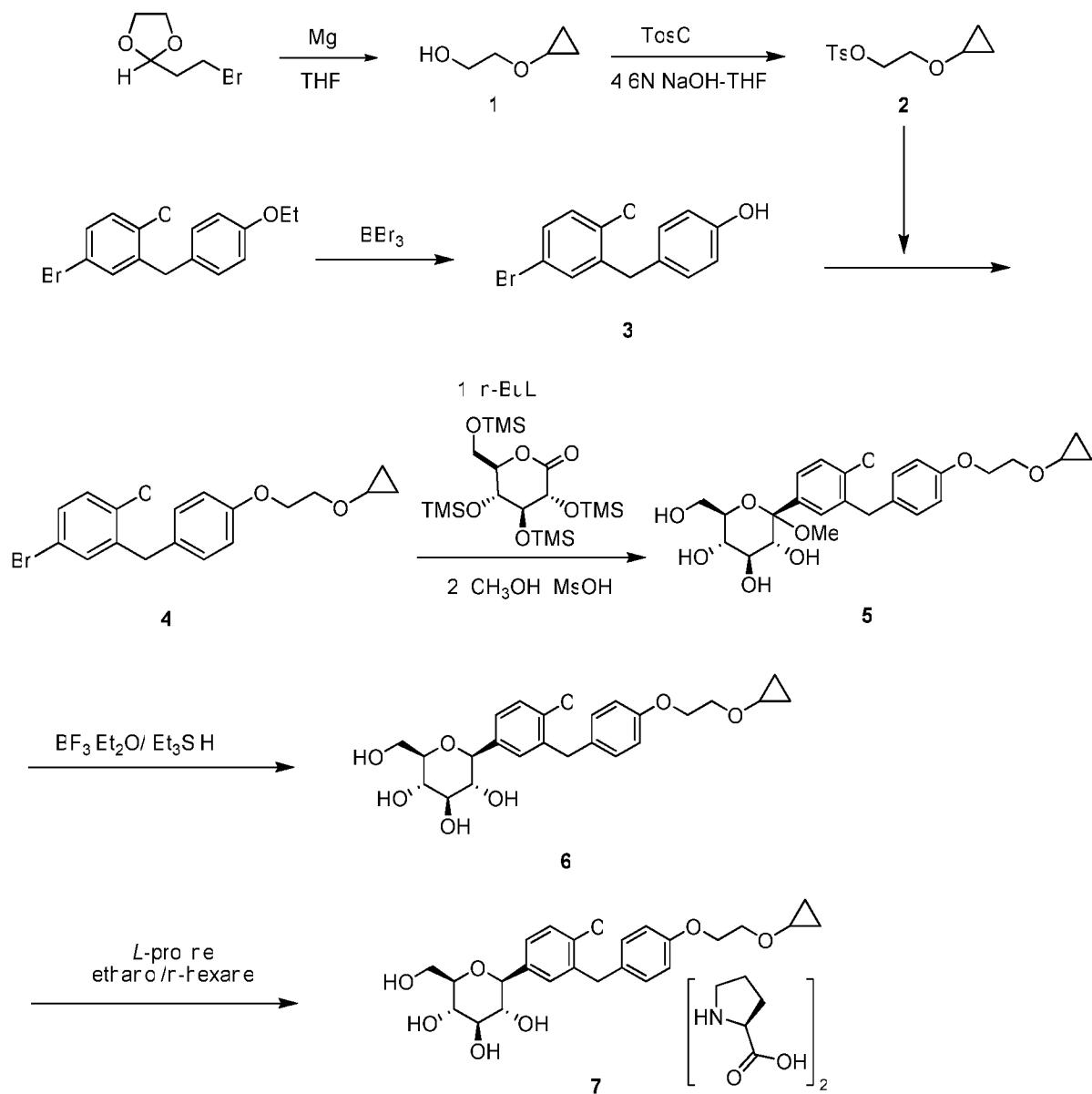
mass spectrometer with electrospray ionization. Spectra were scanned from 80-2000 amu using a variable ion time according to the number of ions in the source. The eluents were B: acetonitrile and D: water. Gradient elution from 10% to 90% B in 8 min at a flow rate of 1.0 mL/min is used with a final hold at 90% B of 7 min. Total run time is 15 min.

5 [0096] (3) Routine one-dimensional NMR spectroscopy was performed on 400 MHz or 300 MHz Varian Mercury-Plus spectrometers. The samples were dissolved in deuterated solvents obtained from Qingdao Tenglong Weibo Technology Co., Ltd., and transferred to 5 mm ID NMR tubes. The spectra were acquired at 293 K. The chemical shifts were recorded on the ppm scale and were referenced to the appropriate solvent signals, such as 2.49 ppm for 10 DMSO-d₆, 1.93 ppm for CD₃CN, 3.30 ppm for CD₃OD, 5.32 ppm for CD₂Cl₂ and 7.26 ppm for CDCl₃ for ¹H spectra.

[0097] When the following abbreviations and acronyms are used throughout the disclosure, they have the following meanings: Ac₂O, acetic anhydride; AcOEt, ethyl acetate; AcOH, acetic acid; AlBr₃, aluminum bromide; AlCl₃, aluminum chloride; BBr₃, boron tribromide; 15 BF₃·Et₂O, boron trifluoride etherate; n-BuLi, *n*-butyllithium; s-BuLi, *s*-butyllithium; t-BuLi, *t*-butyllithium; t-BuOK, potassium tert-butoxide; CaCl₂, calcium chloride; calc., calculated; CD₃OD, methanol-*d*₄; CDCl₃, chloroform-*d*; CF₃SO₃H, trifluoromethanesulfonic acid; CH₂Cl₂, methylene chloride; CH₂I₂, methylene iodide; CH₃CN, acetonitrile; (COCl)₂, oxalyl chloride; DAST, (diethylamino)sulfur trifluoride; DCM, dichloromethane; DIAD, diisopropyl 20 azodicarboxylate; DMAP, 4-dimethylaminopyridine; DMEM, Dulbecco's Modified Eagle Medium; DMF, *N,N*-dimethylformamide; DMP, Dess-Martin periodinane; DMSO, dimethylsulfoxide; EA, ethyl acetate; eq, equivalents; ESI, electrospray ionization; Et, ethyl; Et₃SiH, triethylsilane; EtOAc, ethyl acetate; EtOH, ethanol; FBS, fetal bovine serum; h, hour; H₂, hydrogen gas; H₂SO₄, sulfuric acid; Hepes, 4-(2-hydroxyethyl)-1- 25 piperazineethanesulfonic acid;; ¹H NMR, proton nuclear magnetic resonance; HPLC, high performance liquid chromatography; IPC, In-Process Control; K₂CO₃, potassium carbonate; K₂CrO₇, potassium dichromate; KOH, potassium hydroxide; LC-ESI-MS, liquid chromatography electrospray ionization mass spectrometry; LC-MS, liquid chromatography - mass spectroscopy; Me, methyl; MeOH, methanol; MeSO₃H, methanesulfonic acid; Mg, 30 magnesium; MgCl₂, magnesium chloride; min, minute; MS, mass spectroscopy; MsOH, methanesulfonic acid; NaH, sodium hydride; NaHCO₃, sodium bicarbonate; NaOAc, sodium acetate; NaOH, sodium hydroxide; Na₂SO₄, sodium sulfate; NH₄Cl, ammonium chloride; Pd/C, palladium on carbon; PE, petroleum ether; Ph, phenyl; POCl₃, phosphorus oxychloride;

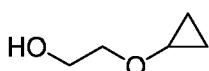
PPh₃, triphenylphosphine; R_f, retention factor; rt, room temperature; SOCl₂, thionyl chloride; TBAI, tetrabutylammonium iodide; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TLC, thin layer chromatography; TMS, trimethylsilyl; Tris, trishydroxymethylaminomethane (or 2-amino-2-(hydroxymethyl)propane-1,3-diol).

5 **Example 1. Preparation of (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-chloro-3-(4-(2-cyclopropoxymethoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, bis(*L*-proline) complex**



10

Example 1A
Preparation of 2-cyclopropoxymethanol (1)

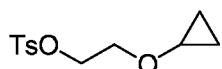


[0098] To a suspension of Mg powder (86.7 g, 3.6 mol) and iodine (cat) in anhydrous THF (0.7 L) was added slowly 1,2-dibromoethane (460 g, 2.4 mol) in anhydrous THF (2 L) slowly at a rate as to keep the internal temperature between 40-55 °C. After the addition, a solution of 2-(2-bromoethyl)-1,3-dioxolane (100g, 0.56 mol) in anhydrous THF (750 mL) was added 5 dropwise. The reaction mixture was kept at 40-55 °C for 16h and was quenched by addition of aqueous solution of ammonium chloride. The mixture was extracted with methylene chloride. The organic layer was dried over sodium sulfate, and concentrated to give the title product (27 g) as yellow oil, which was directly used without further purification.

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Example 1B

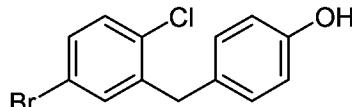
Preparation of 2-cyclopropoxyethyl 4-methylbenzenesulfonate (2)



[0099] To a stirred solution of sodium hydroxide (32 g, 0.8 mol) in water (180 mL) and THF (180 mL) was added Example 1A (27 g, 0.26 mol) at -5 to 0 °C. Afterwards, a solution 15 of *p*-toluenesulfonyl chloride (52 g, 0.27 mol) in THF (360 mL) was added dropwise. The reaction mixture was kept at -5 to 0 °C for 16 h. The reaction mixture was then kept at room temperature for 30 min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2x1.0 L). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to get the crude product as yellow oil (53.3 g). It was used 20 directly without further purification.

Example 1C

Preparation of 4-(5-bromo-2-chlorobenzyl)phenol (3)

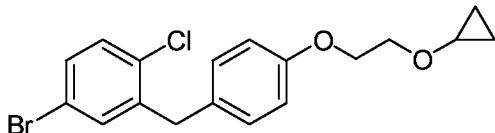


25 [0100] To a stirred solution of 4-bromo-1-chloro-2-(4-ethoxybenzyl)benzene (747 g, 2.31 mol) in dichloromethane was added boron tribromide (1.15 kg, 4.62 mol) slowly at -78 °C. The reaction mixture was allowed to rise to room temperature. When the reaction was complete as measure by TLC, the reaction was quenched with water. The mixture was extracted with dichloromethane. The organic layer was washed with aqueous solution of 30 saturated sodium bicarbonate, water, brine, dried over Na₂SO₄, and concentrated. The residue was recrystallized in petroleum ether to give the title compound as a white solid (460

g, yield 68%). $^1\text{H NMR}$ (CDCl_3 , 400MHz): δ 7.23~7.29 (m, 3H), 7.08 (d, $J=8.8$ Hz, 2H), 6.79 (d, $J=8.8$ Hz, 2H), 5.01 (s, 1H), 4.00 (s, 2H).

Example 1D

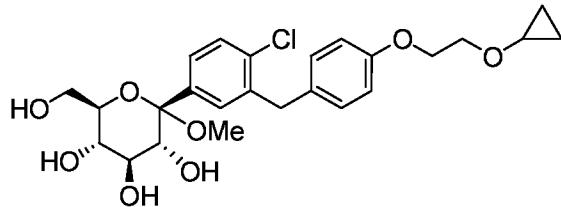
5 Preparation of 4-bromo-1-chloro-2-(4-(2-cyclopropoxyethoxy)benzyl)benzene (4)



[0101] A mixture of Example 1C (56.7 g, 210 mmol) and Cs_2CO_3 (135 g, 420 mmol) in DMF (350 mL) was stirred at room temperature for 0.5 h. Example 1B (53.3 g, 210 mmol) was added. The reaction mixture was stirred at room temperature overnight. It was diluted 10 with water (3 L) and extracted with EtOAc . The organic layer was washed with water, brine, dried over Na_2SO_4 , and concentrated. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether:ethyl acetate (10:1) to give the title compound as liquid (51 g, yield 64%). $^1\text{H NMR}$ (CDCl_3 , 400MHz): δ 7.22~7.29 (m, 3H), 7.08 (d, $J=8.8$ Hz, 2H), 6.88 (d, $J=8.8$ Hz, 2H), 4.10 (t, $J=4.8$ Hz, 2H), 3.86 (t, $J=4.8$ Hz, 2H), 15 3.38-3.32 (m, 1H), 0.62-0.66 (m, 2H), 0.49-0.52(m, 2H).

Example 1E

Preparation of (2S,3R,4S,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)-2-methoxytetrahydro-2*H*-pyran-3,4,5-triol (5)



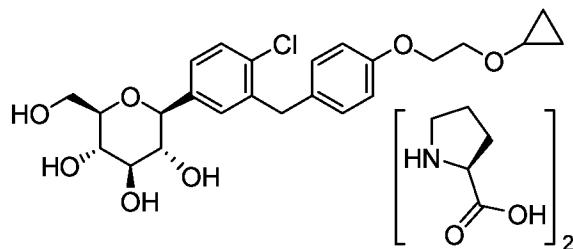
[0102] To a stirred solution of Example 1D (213 g) in anhydrous THF/toluene (1:2 (v/v), 1.7 L) under argon was added n-BuLi (2.5 M hexane, 245.9 mL) drop wise at -60 ± 5 °C. The mixture was stirred for 30 min. before transferred to a stirred solution of 2,3,4,6-tetra-O-trimethylsilyl- β -D-glucolactone (310.5 g) in toluene (1.6 L) at -60 ± 5 °C. The reaction 20 mixture was continuously stirred at -60 ± 5 °C for 1 h before quenching with aqueous solution of saturated ammonium chloride (1.5 L). Then mixture was allowed to warm to room temperature and stirred for 1 h. The organic layer was separated and the water layer 25

was extracted with ethyl acetate (3x500 mL). The combined organic layers were washed with brine (1 L), dried over Na_2SO_4 , and concentrated. The residue was dissolved in methanol (450 mL) and methanesulfonic acid (9.2 mL) was added at 0 °C. The solution was allowed to warm to room temperature and stirred for 20 h. It was quenched with aqueous 5 solution of sodium bicarbonate (50 g) in water (500 mL) and additional water (900 mL) was added. The mixture was extracted with ethyl acetate (3x1.0 L). The combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated and used directly in the next step without further purification.

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Example 1F

Preparation of (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-chloro-3-(4-(2-cyclopropoxymethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, bis(*L*-proline) complex (7)

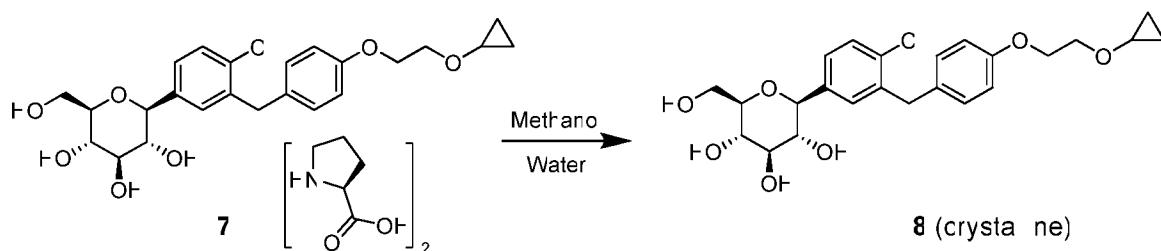


15 [0103] To stirred solution of Example 1E in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ (650 mL:650 mL) at -5 °C was added triethylsilane (28.2 mL, 563 mmol), and followed by $\text{BF}_3\cdot\text{Et}_2\text{O}$ (52.3 mL, 418.9 mmol). The reaction was stirred for 16 h while the temperature was allowed to warm to room temperature gradually. The reaction was quenched with aqueous solution of saturated sodium bicarbonate to pH 8.0. The organic volatiles were removed under vacuum. The 20 residue was partitioned between ethyl acetate (2.25 L) and water (2.25 L). The organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated to give the crude product **6** (230 g, purity 82.3%). This product and L-proline (113.7 g) in $\text{EtOH}/\text{H}_2\text{O}$ (15:1 v/v, 2.09 L) was stirred at 80 °C for 1 h when it became a clear solution. Hexane (3.0 L) was added dropwise into the above hot solution over 50 min, with the temperature being kept at 25 about 60 °C. The reaction mixture was stirred overnight at room temperature. The solid was filtered and washed with $\text{EtOH}/\text{H}_2\text{O}$ (15:1 (v/v), 2x300 mL), hexane (2x900 mL), and dried at 45 °C under vacuum for 10 h to give the pure title compound **7** as a white solid (209 g). Purity (HPLC) 99.2% (UV). **1H NMR** (CD_3OD , 400 MHz): δ 7.25~7.34 (m, 3H), 7.11 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.03-4.11 (m, 5H), 3.96-4.00 (m, 2H), 3.83-3.90 (m,

3H), 3.68-3.72 (m, 1H), 3.36-3.46 (m, 6H), 3.21-3.30 (m, 3H), 2.26-2.34 (m, 2H), 2.08-2.17 (m, 2H), 1.94-2.02 (m, 4H), 0.56-0.57 (m, 2H), 0.52-0.53 (m, 2H).

Example 2. Direct Preparation of Crystalline Compound 8 from Complex 7

[0104] This example illustrates the preparation of a crystalline form of (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy) benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol.



[0105] To a 5.0 L 4-necked flask equipped with a mechanical stirrer was added the starting co-crystal (150.0 g) and methanol (300 mL). The mixture was stirred at room temperature with mechanical stirring (anchor agitator, 2-blades 9 cm) until a cloudy solution/suspension formed, to which distilled water (1500 mL) was added dropwise at a rate of ~12.5 mL/min. As the mixture warmed from the exotherm of adding water to methanol, the mixture became clear after adding about 1/5 to 1/3 of the water. After the addition was completed the reaction was stirred continuously at 80 rpm for another 5 h. The reaction mixture was filtered over medium-speed filter paper and the filter cake was washed with distilled water (450 mL and then 300 mL) and dried under vacuum using an oil pump (~6 mmHg) at 45 °C for 48 hours to give the target product as a white crystalline solid (94.2 g, 93.9% yield, purity (HPLC): 99.3%).

Example 3. Direct Preparation of Crystalline Compound 8 from Complex 7

[0106] This example illustrates alternative conditions for preparing crystalline (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy) benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol

Procedure A:

[0107] A 250 mL of 4-neck flask was charged with the starting complex (10.0 g) and methanol (33.5 mL). After refluxing for 20 min with mechanical stirring a clear solution formed. Water (67.0 mL) was added slowly dropwise to it over 20 min. The reaction mixture was cooled slowly to room temperature (25°C) in oil bath and stirred for another 3 h

at room temperature. The reaction mixture was filtered by filter paper and the filter cake was washed with water (2x20 mL), dried under vacuum at 65 °C for 8 h to give a white crystalline solid. Yield: 6.0 g (89.6%)

Procedure B:

5

[0108] A 250 mL of 4-neck flask was charged with the starting complex (10.0 g) and methanol (33.5 mL). After stirring for 20 min with mechanical stirring, the solids did not completely dissolve. Water (67.0 mL) was added slowly dropwise to it over 20 min. At first all the remaining solids dissolved and later new crystals started to form. The reaction mixture 10 was stirred for another 3 h at room temperature. The reaction mixture was filtered over filter paper and the filter cake was washed with water (2x20 mL), dried under vacuum at 65 °C for 8 h to give a white crystalline solid. Yield: 6.0 g (89.6%).

[0109] Procedures A and B are summarized in the table below with other conditions for preparing crystalline **8** directly from complex **7**.

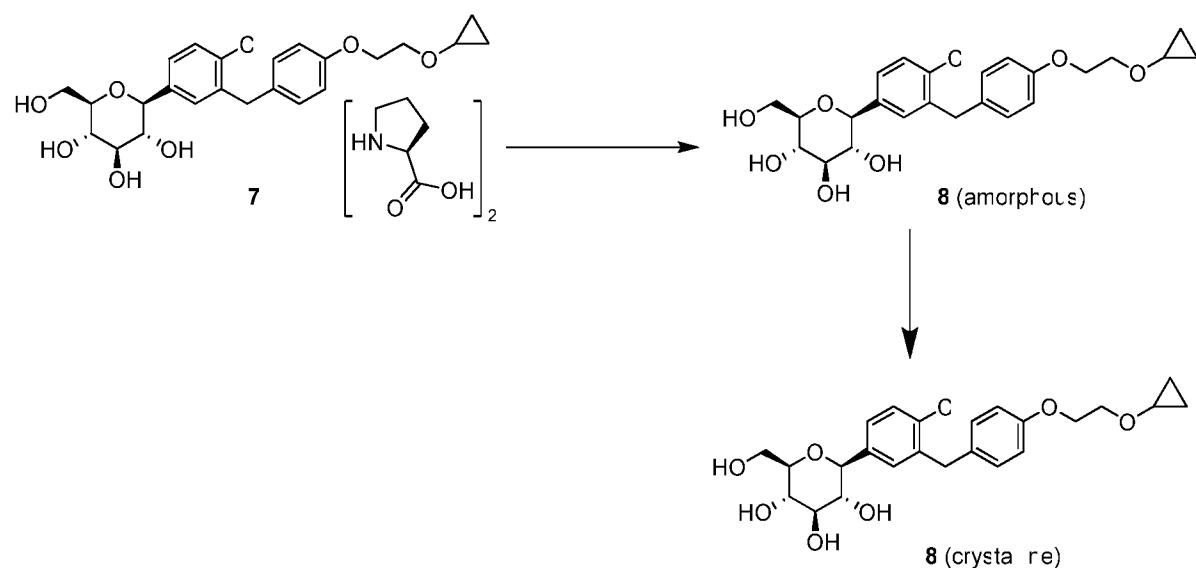
15 **Summary Table of Crystallization Conditions**

Complex (g)	Methanol(mL)	Water(mL)	Temp.(°C)	Yield(%)
4.0	20.0	80.0	70	87.4
10.0	33.5	67.0	25	89.6
10.0	33.5	100.0	25	91.1
10.0	33.5	67.0	70	89.6

Example 4. Direct Preparation of Crystalline Compound 8 from Complex 7

[0110] This example illustrates the preparation of a crystalline form of (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy) benzyl)phenyl)-6- (hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol.

[0111] Compound **7** (14.0 kg) was dissolved in methanol (36.2 kg) and DI water (11.2 kg) and then filtered. Additional DI water (41.3 kg) was added and then seed crystals are added at 35 ± 5 °C to crystallize compound **8** from solution. Additional DI water (41.3 kg) was added 25 to complete precipitation. The resulting slurry was filtered, and the product solids rinsed on the filter with DI water, transferred to trays, and dried under vacuum at ~ 65 °C to afford 8.75 kg of compound **8**.

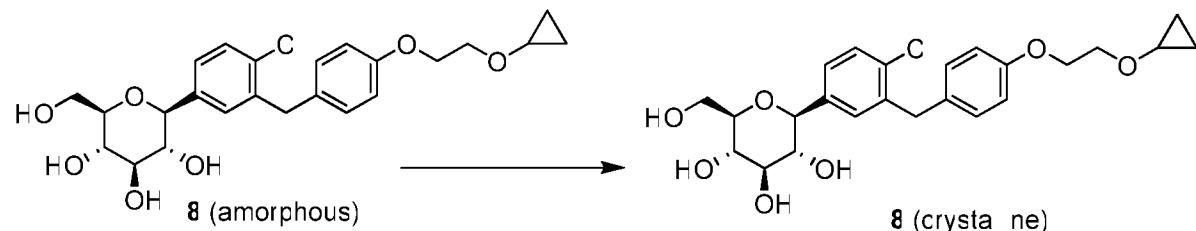
Example 5. Indirect Preparation of Crystalline Compound 8 from Complex 7

[0112] To a 200 L glass lined reactor equipped with a double-tier paddle agitator and a glass condenser was added sequentially complex 7 (7.33 kg), ethyl acetate (67.5 kg) and pure water (74.0 kg). The mixture was heated to reflux and stirred at reflux for 30 min. The reaction mixture was cooled to approximately 50°C and the organic layer was separated and the aqueous layer was extracted with ethyl acetate (34.0 kg). The combined organic layers were washed with pure water (3x74.0 kg) (IPC test showed that the IPC criteria for L-proline residue was met after three water washes). The mixture was concentrated at 40°C under 5 vacuum (~15 mmHg) for 3 h until the liquid level dropped below the lower-tier agitator paddle. The mixture (18 kg) was discharged and transferred to a 20L rotary evaporator. The mixture was concentrated under vacuum (40° C, ~5 mmHg) to a minimum volume. The remaining trace amount of ethyl acetate was removed azeotropically at 40° C under vacuum with methanol (10 kg). The residue was dried under vacuum of an oil pump (~6 mmHg) at 10 40° C for 10 h to give 8 as a white amorphous solid (4.67 kg, purity (HPLC): 99.2%) which was used in the next step without further purification.

[0113] The recrystallization was accomplished by the following steps. To a 100 L glass line reactor equipped with a double-tier paddle agitator and a glass condenser was added the above amorphous 8 (4.67 kg) and methanol (18.0 kg). The mixture was refluxed at 70 °C for 20 30 min until a clear solution formed, to which pure water (45.0 kg) was added over 2 hours. After the addition was completed (the reaction temperature was 41° C), the reaction mixture was cooled to room temperature and stirred at room temperature for 15 hours. The reaction mixture was filtered and the wet cake was washed with pure water (2x15 kg) and dried under

vacuum at 55~60° C for 12 hours to give the target product as an off-white crystalline solid (3.93 kg, yield: 84% in two steps; purity (HPLC): 99.7%).

Example 6. Direct Preparation of Crystalline Compound 8 from Amorphous 8



5

[0114] A 5 L 4-neck flask was charged with **8** (amorphous), 116 g, and methanol (580 mL). The reaction mixture was heated to 60 °C with mechanical stirring and the solution became clear. Water (2320 mL) was added dropwise to the reaction solution at 40 mL/min at 50 °C. The reaction mixture was stirred overnight at room temperature. The reaction mixture was 10 filtered and the filter cake was washed with water (2x200 mL), dried under vacuum at 55 °C for 12 hours, to afford white crystalline **8**. Yield is 112.8 g (97.2%).

Example 7. Low Hygroscopicity of Crystalline Compound 8

[0115] The tendency toward hygroscopicity of crystalline compound **8** in powder form was tested at 75% and 92.5% relative humidity at 25°C for up to 10 days. Reagents included: (1) 15 water: in house, MilliQ, 18.2MΩ; (2) NaCl: AR grade; (3) KNO₃: AR grade; (4) saturated NaCl solution with extra NaCl solid for 25°C/75%RH control; and (5) saturated KNO₃ solution with extra KNO₃ solid for 25°C/92.5%RH control. Equipment used included (1) desiccators, 240 mm ID; and (2) weighing bottles with lids: 50 mm ID x 30 mm height.

[0116] The saturated salt solutions and solids were transferred into individual desiccators, 20 and equilibrated at 25°C at least overnight to reach the desired relative humidity readings. Four weighing bottles were placed into each desiccator, and equilibrated overnight. The empty weighing bottles were weighed and the tare weights recorded (W₁). 0.5 g of crystalline compound **8** was added into three weighing bottles in each desiccator to form a thin layer with thickness of 1-2 mm. The sample weight in each bottle (W₂) was recorded. 25 One empty weighing bottle was used for blank calibration. The bottles were left in each desiccator with lids open. The lids were closed and each bottle accurately weighed on days 1, 5 and 10 (W₃). The bottles were returned to each desiccator with lids open immediately after weighing.

[0117] The following formula was used to calculate the weight increase:

$$\text{Weight Increase \%} = \frac{W_3 - W_1 - W_2 - W_B}{W_2} \times 100\%$$

W_B = the weight increase of empty weighing bottle.

Table 1. Test results of crystal compound 8 at 25°C/75%RH.

Wt	Empty bottle	Sample Weight	Appearance	Bottle + Sample	Sample Weight	Weight Increase	Appearance
Initial							
1	30.36142	0.50434	White powder	30.86727	0.50585	0.32914%	White powder
2	32.96588	0.50631	White powder	33.47323	0.50735	0.23503%	White powder
3	31.27798	0.50066	White powder	31.77934	0.50136	0.16978%	White powder
Blank	31.92783			31.92768	-0.00015		
Average						0.24465%	
1 day							
1							
2							
3							
Blank							
Average						0.15412%	
5 days							
1							
2							
3							
Blank							
Average						0.15412%	
10 days							
1							
2							
3							
Blank							
Average						0.25926%	

Table 2. Test results of crystal compound 8 at 25°C/92.5%RH.

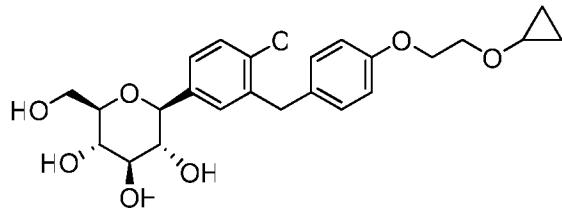
	Empty bottle	Sample Weight	Appearance	Bottle + Sample	Sample Weight	Weight Increase	Appearance
Initial							
1	34.11948	0.50356	White powder	34.62330	0.50382	0.05362%	White powder
2	30.13094	0.50215	White powder	30.63360	0.50266	0.10355%	White powder
3	33.01277	0.50546	White powder	33.51923	0.50646	0.19982%	White powder
Blank	40.35822			40.35821	-0.00001		
Average						0.11900%	
5 days							
1				34.62358	0.50410	0.04170%	White powder
2				30.63446	0.50352	0.20711%	White powder
3				33.51977	0.50700	0.23939%	White powder
Blank				40.35855	0.00033		
Average						0.16273%	
10 days							
1				34.62472	0.50524	0.26015%	White powder
2				30.63428	0.50334	0.16330%	White powder
3				33.51994	0.50717	0.26511%	White powder
Blank				40.35859	0.00037		
Average						0.22952%	

[0118] The weight increases of crystalline compound 8 in powder samples at 75% and 92.5% relative humidity at 25°C for 10 days were below 0.26%. Thus, crystalline compound 5 8 in powder form exhibited low hygroscopicity at the study conditions.

[0119] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in 10 its entirety to the same extent as if each reference was individually incorporated by reference. Where a conflict exists between the instant application and a reference provided herein, the instant application shall dominate.

WHAT IS CLAIMED IS:

1. A crystalline form of the compound of the formula:



2. The crystalline form in accordance with claim 1, characterized by an X-ray powder diffraction (XRPD) pattern that comprises one or more peaks at 5.4, 11.2, 11.3, 11.9, 12.9, 15.5, 16.3, 17.8, 19.1, 20.0, 20.6, 20.7, 21.2, 22.8, 23.0, 23.4, 23.6, 23.9, 24.7, 25.4, 25.8, 27.8 and 28.2 degrees 2θ (± 0.1 degrees 2θ), wherein said XRPD is made using CuK_{α1} radiation.

3. The crystalline form in accordance with claim 2, characterized by an XRPD that comprises peaks at 12.9, 19.1 and 20.7 degrees 2θ (± 0.1 degrees 2θ), wherein said XRPD is made using CuK_{α1} radiation.

4. The crystalline form in accordance with claim 2, characterized by an XRPD that comprises peaks at 11.2, 12.9, 15.5, 17.8, 19.1, 20.0 and 20.7 degrees 2θ (± 0.1 degrees 2θ), wherein said XRPD is made using CuK_{α1} radiation.

5. The crystalline form in accordance with claim 2, characterized by an XRPD that comprises peaks at 11.2, 12.9, 15.5, 17.8, 19.1, 20.0, 20.6, 20.7, 21.2 and 22.8 degrees 2θ (± 0.1 degrees 2θ), wherein said XRPD is made using CuK_{α1} radiation.

6. The crystalline form in accordance with claim 2, characterized by an XRPD that comprises peaks at 5.4, 11.2, 11.9, 12.9, 15.5, 16.3, 17.8, and 19.1 degrees 2θ (± 0.1 degrees 2θ), wherein said XRPD is made using CuK_{α1} radiation.

7. The crystalline form in accordance with claim 2, characterized by an X-ray powder diffraction (XRPD) pattern that comprises peaks at 11.2 and 12.9 degrees 2θ (± 0.1 degrees 2θ), wherein said XRPD is made using CuK_{α1} radiation.

8. The crystalline form in accordance with claim 1, characterized by the XRPD peaks substantially in accordance with those of **Figure 2**.

9. The crystalline form in accordance with claim 1, characterized by a Raman spectra that comprises one or more peaks at about 353, 688, 825, 1178, 1205, 1212, 1608, 2945, 3010 and 3063 cm⁻¹.

10. The crystalline form in accordance with claim 1, characterized by a Raman spectra
5 that comprises peaks at about 353, 688, and 825 cm⁻¹.

11. The crystalline form in accordance with claim 1, characterized by the Raman peaks substantially in accordance with those of **Figure 4**.

12. The crystalline form in accordance with claim 1, characterized by
an X-ray powder diffraction (XRPD) pattern that comprises one or more peaks at 5.4, 11.2,
10 11.3, 11.9, 12.9, 15.5, 16.3, 17.8, 19.1, 20.0, 20.6, 20.7, 21.2, 22.8, 23.0, 23.4, 23.6, 23.9,
24.7, 25.4, 25.8, 27.8 and 28.2 degrees 2θ (± 0.1 degrees 2θ), wherein said XRPD is made
using CuK_{α1} radiation; and
a Raman spectra that comprises one or more peaks at about 353, 688, 825, 1178, 1205, 1212,
1608, 2945, 3010 and 3063 cm⁻¹.

15 13. The crystalline form in accordance with claim 12, characterized by
an X-ray powder diffraction (XRPD) pattern that comprises one or more peaks at 11.2, 12.9,
15.5, 17.8, 19.1, 20.0, 20.6, 20.7, 21.2 and 22.8 and 28.2 degrees 2θ (± 0.1 degrees 2θ),
wherein said XRPD is made using CuK_{α1} radiation; and
a Raman spectra that comprises one or more peaks at about 353, 688, and 825 cm⁻¹.

20 14. The crystalline form in accordance with claim 1, characterized by a DSC endotherm
at about 136° C.

15. The crystalline form in accordance with claim 1, characterized by the unit cell data substantially in accordance with **Figure 7**.

16. A pharmaceutical composition comprising a pharmaceutically acceptable excipient
25 and a crystalline form of the compound (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-
cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

17. A crystalline form of a compound of claim 1 which is isotopically labeled.

18. A method for making a crystalline form of the compound of claim 1, said method comprising the steps:

(a) combining (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol bis(L-proline) complex and a suitable

5 solvent with mixing to form a solution;

(b) adding a precipitating solvent to said solution to provide a mixture; and

(c) isolating said crystalline form from said mixture.

19. The method of claim 18, wherein the solvent of step (a) is selected from the group consisting of methanol and ethanol.

10 **20.** The method of claim 18, wherein the solvent of step (a) is methanol.

21. The method of claim 18, wherein the precipitating solvent is water.

22. The method of claim 18, wherein the solvent of step (a) is methanol and the precipitating solvent is water.

15 **23.** The method of claim 22, wherein the ratio of methanol to water in the mixture of step (b) is from about 1:1 to about 1:9 by volume.

24. The method of claim 22, wherein the ratio of methanol to water in the mixture of step (b) is about 1:5 by volume.

25. The method of claim 18, wherein the ratio of complex to solvent and precipitating solvent in the mixture of step (b) is from about 1:10 to about 1:25 (w/v).

20 **26.** The method of claim 18, wherein the mixture of step (b) further comprises a base.

27. The method of claim 18, wherein the mixture of step (b) further comprises a salt.

28. The method of claim 18, wherein the mixture of step (b) further comprises a seed crystal of the compound of claim 1.

25 **29.** A method for making a crystalline form of the compound of claim 1, said method comprising the steps:

(a) combining amorphous (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol and a suitable solvent with mixing to form a solution;

(b) adding a precipitating solvent to said solution to provide a mixture; and

5 (c) isolating said crystalline form from said mixture.

30. The method of claim 29, wherein the solvent of step (a) is selected from the group consisting of methanol and ethanol.

31. The method of claim 29, wherein the solvent of step (a) is methanol.

32. The method of claim 29, wherein the precipitating solvent is water.

10 33. The method of claim 29, wherein the solvent of step (a) is methanol and the precipitating solvent is water.

34. The method of claim 33, wherein the ratio of methanol to water in the mixture of step (b) is from about 1:1 to about 1:9 by volume.

15 35. The method of claim 33, wherein the ratio of methanol to water in the mixture of step (b) is about 1:5 by volume.

36. The method of claim 29, wherein the ratio of complex to solvent and precipitating solvent in the mixture of step (b) is from about 1:1 to about 1:9 by volume.

37. The method of claim 29, wherein the mixture of step (b) further comprises a seed crystal of the compound of claim 1.

20 38. The method of claim 29, wherein the amorphous (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol is prepared from (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol bis(L-proline) by

(a2) combining (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-

25 6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol bis(L-proline) complex and a suitable solvent mixture with mixing to form a solution; and

(a3) isolating amorphous (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol from said solution of step (a2).

39. The method of claim 38, wherein said solvent mixture of step (a2) comprises an
5 organic solvent and an aqueous solvent.

40. The method of claim 38, wherein said solvent mixture of step (a2) comprises ethyl acetate and water.

41. A method of treating a disease or condition affected by inhibiting SGLT2, said method comprising administering to a subject in need thereof a therapeutically effective
10 amount of a composition comprising a crystalline form of the compound of claim 1, wherein said disease or condition is selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, hyperglycemia, diabetic complications, insulin resistance, metabolic syndrome, hyperinsulinemia, hypertension, hyperuricemia, obesity, edema, dyslipidemia, chronic heart failure, atherosclerosis, and cancer.

15 42. A method of treating a disease or condition affected by inhibiting SGLT2, said method comprising administering to a subject in need thereof a therapeutically effective amount of a composition comprising a crystalline form of the compound of claim 1.

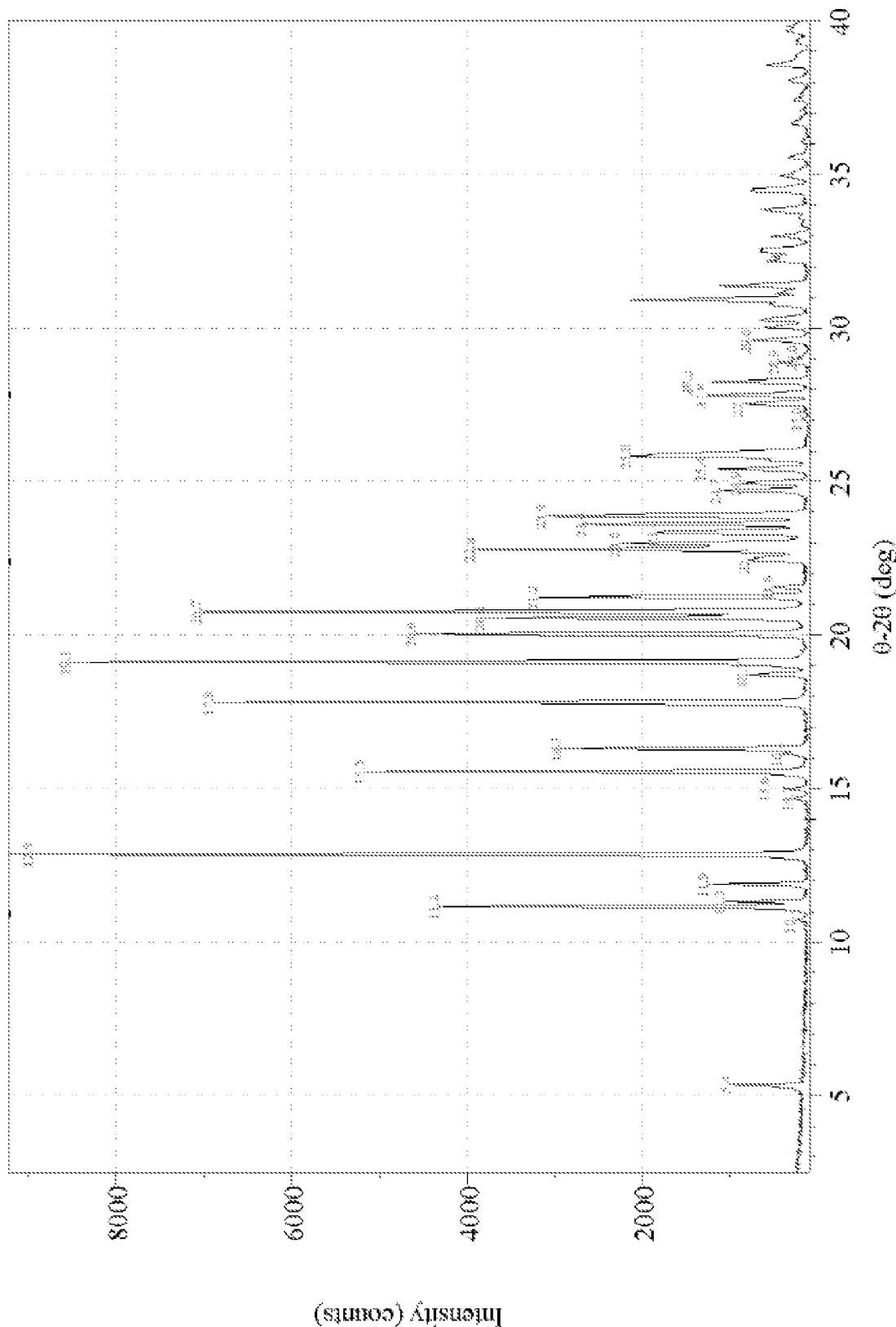
Figure 1.

Figure 2.

2θ	d space (Å)	Intensity (%)
5.4 ± 0.1	16.509 ± 0.314	11
10.7 ± 0.1	8.255 ± 0.078	3
11.2 ± 0.1	7.922 ± 0.071	47
11.3 ± 0.1	7.817 ± 0.069	12
11.9 ± 0.1	7.445 ± 0.063	14
12.9 ± 0.1	6.886 ± 0.054	100
14.7 ± 0.1	6.035 ± 0.041	3
15.0 ± 0.1	5.908 ± 0.039	4
15.5 ± 0.1	5.700 ± 0.037	56
16.1 ± 0.1	5.494 ± 0.034	5
16.3 ± 0.1	5.436 ± 0.033	32
17.8 ± 0.1	4.982 ± 0.028	75
18.7 ± 0.1	4.744 ± 0.025	9
19.1 ± 0.1	4.641 ± 0.024	92
20.0 ± 0.1	4.430 ± 0.022	50
20.6 ± 0.1	4.320 ± 0.021	41
20.7 ± 0.1	4.282 ± 0.021	76
21.2 ± 0.1	4.182 ± 0.020	35
21.6 ± 0.1	4.131 ± 0.019	6
22.4 ± 0.1	3.963 ± 0.018	8
22.8 ± 0.1	3.903 ± 0.017	42
23.0 ± 0.1	3.870 ± 0.017	24
23.4 ± 0.1	3.810 ± 0.016	20
23.6 ± 0.1	3.770 ± 0.016	29
23.9 ± 0.1	3.725 ± 0.015	34
24.7 ± 0.1	3.604 ± 0.014	12
24.9 ± 0.1	3.570 ± 0.014	9
25.4 ± 0.1	3.506 ± 0.014	12
25.8 ± 0.1	3.450 ± 0.013	23
27.0 ± 0.1	3.299 ± 0.012	2
27.5 ± 0.1	3.240 ± 0.012	9
27.8 ± 0.1	3.208 ± 0.011	14
28.2 ± 0.1	3.159 ± 0.011	13
28.9 ± 0.1	3.090 ± 0.010	5
29.0 ± 0.1	3.074 ± 0.010	3
29.6 ± 0.1	3.020 ± 0.010	8

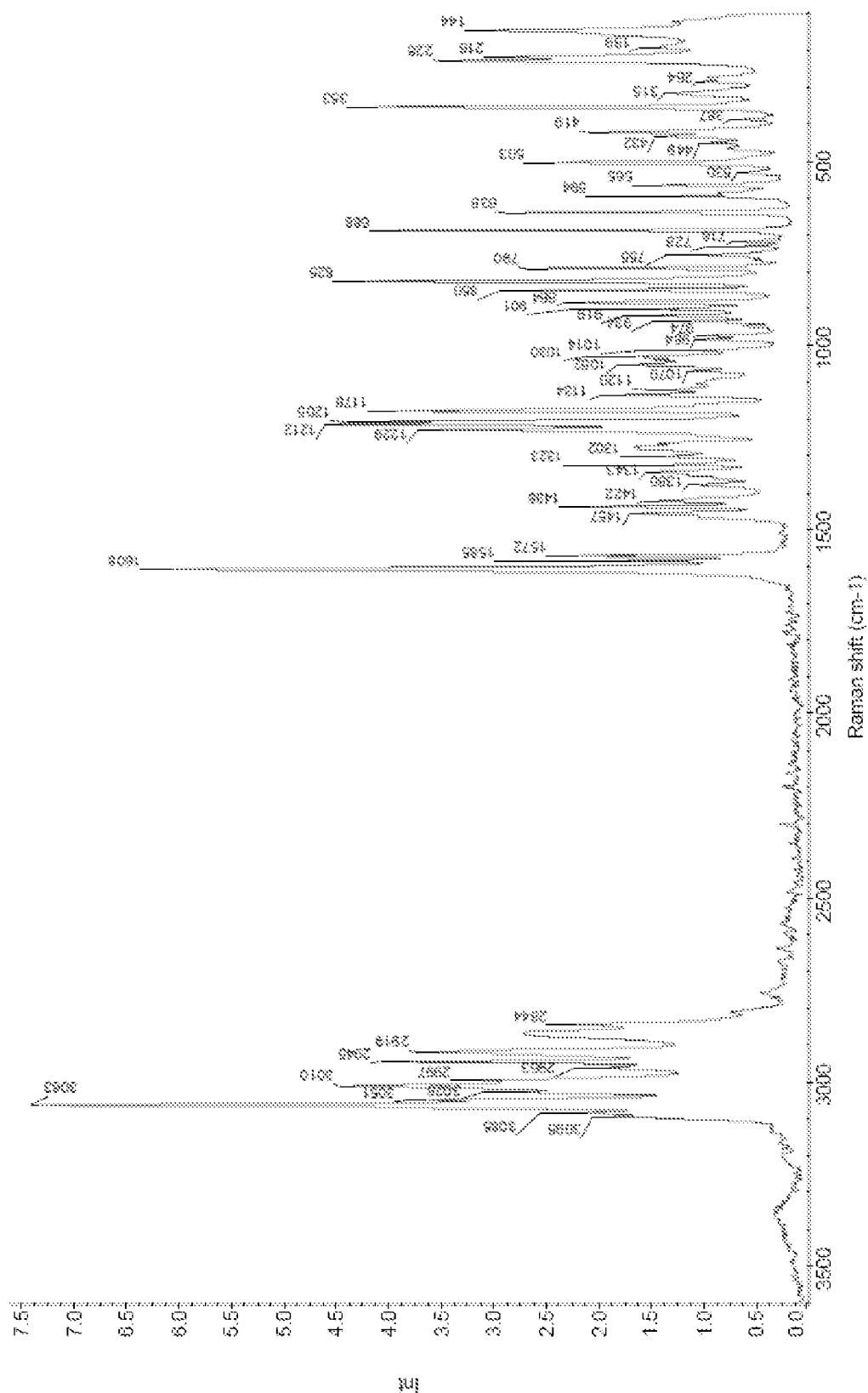
Figure 3.

Figure 4.

Raman peak list for crystalline (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (cm⁻¹)

144	1457
189	1572
216	1585
226	1608
284	2844
315	2919
353	2945
387	2963
419	2997
432	3010
449	3028
503	3051
530	3063
565	3085
594	3095
638	
688	
716	
728	
755	
790	
825	
850	
884	
901	
919	
934	
974	
984	
1014	
1030	
1052	
1070	
1120	
1134	
1178	
1205	
1212	
1229	
1302	
1323	
1343	
1380	
1422	
1438	

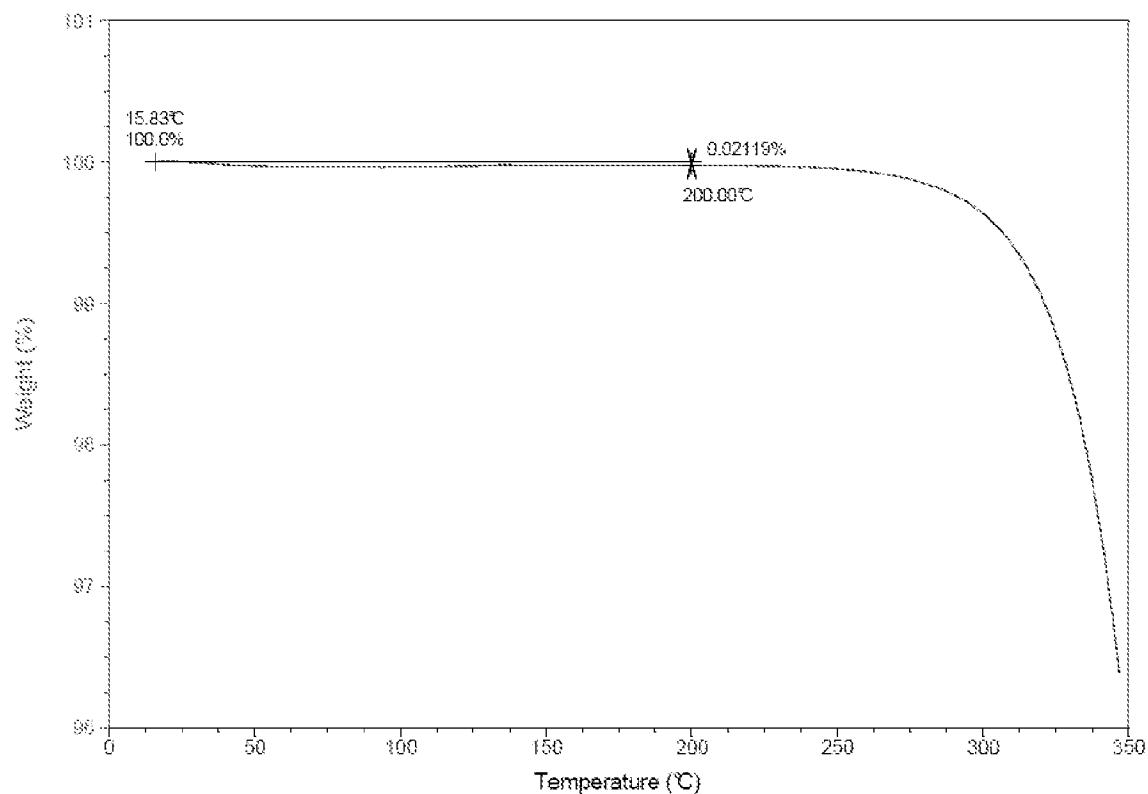
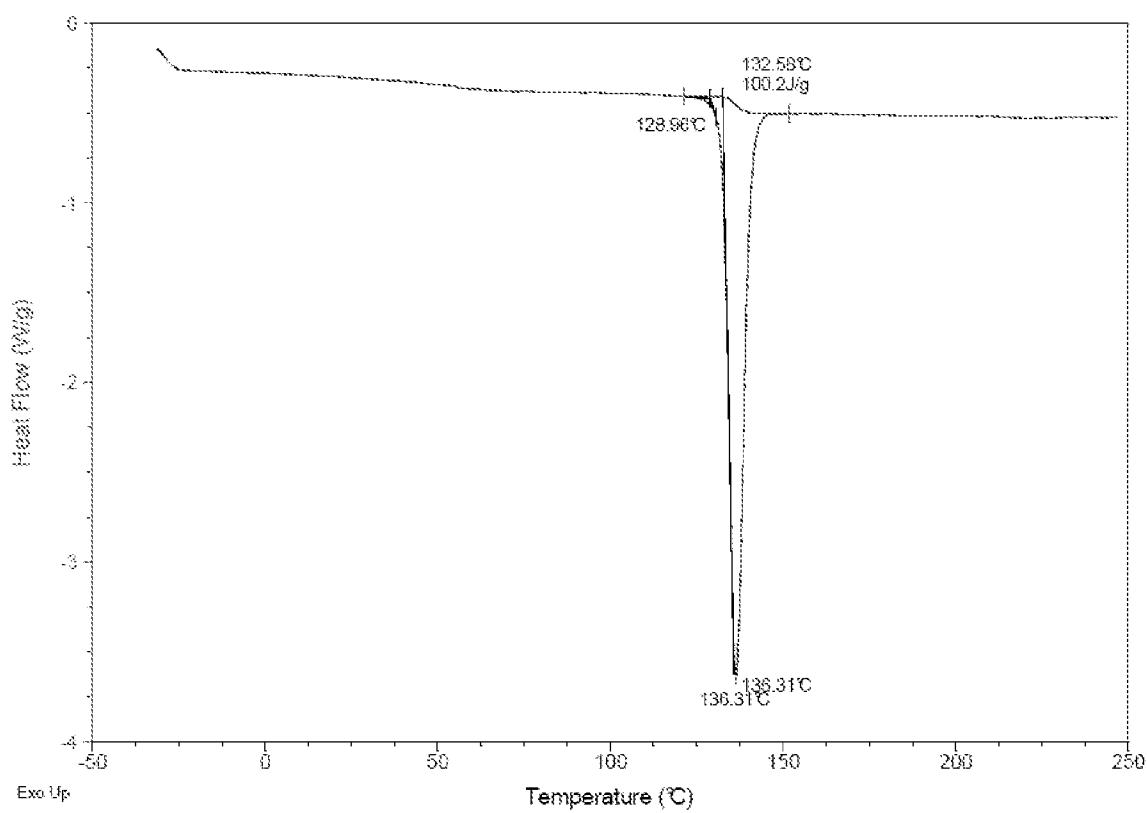
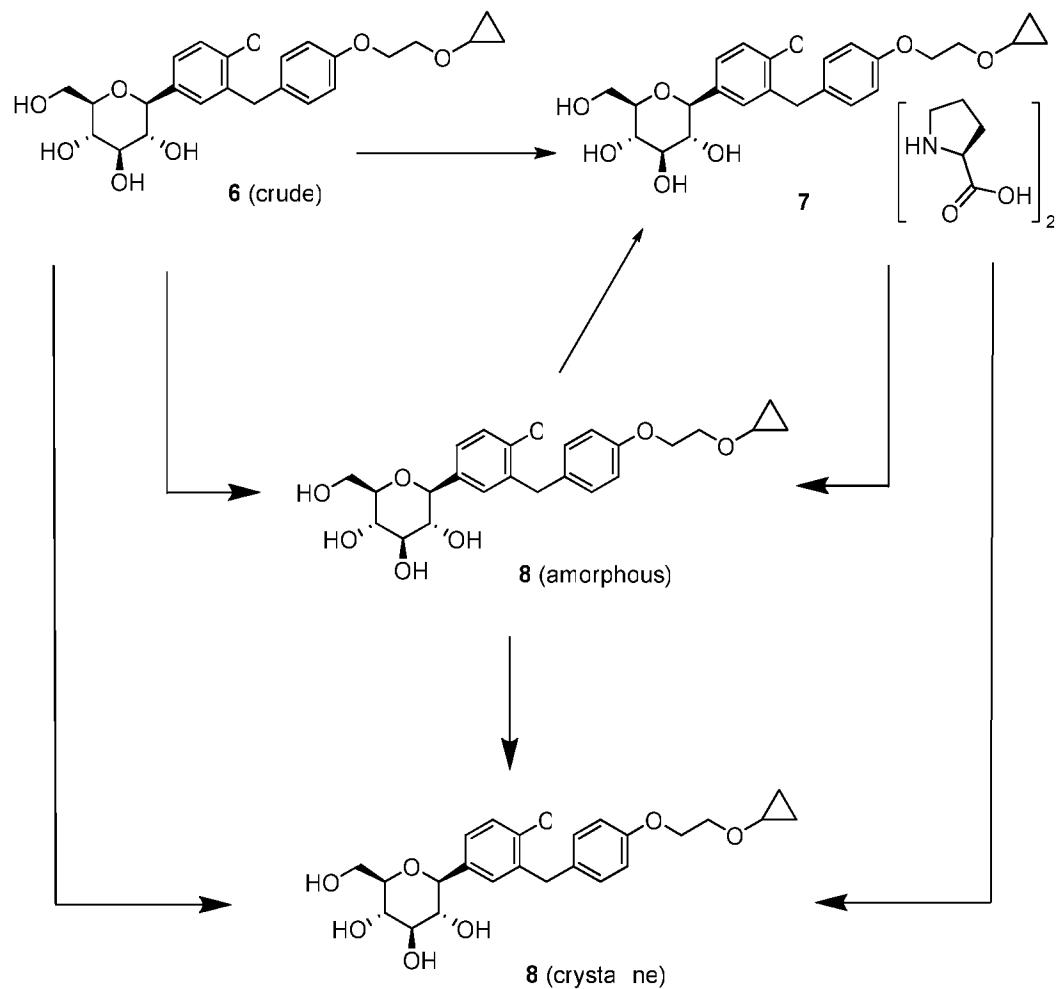
Figure 5.**Figure 6.**

Figure 7.

<i>Family and Space Group</i>	Monoclinic P2 ₁ (#4)
<i>Z' / Z</i>	1 / 2
<i>a</i> (Å)	7.960
<i>b</i> (Å)	8.860
<i>c</i> (Å)	16.560
α (deg)	90
β (deg)	95.71
γ (deg)	90
Volume (Å³/cell)	1162.1
V/Z (Å³/asym. unit)	581.1
Assumed Composition^a	C ₂₄ H ₂₉ O ₇ Cl
Density (g/cm³)^a	1.329
Weight Fraction Solvent (%)^a	N/A

^aDensity and weight fraction solvent are based on the assumed composition.

Figure 8.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2010/073865

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D, A61K, A61P

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

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

CPRS; CNKI; WPI; EPODOC; STN: cotransporter+, SGLT?, crystal+, polycrystal+,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN101754972A (BRISTOL-MYERS SQUIBB COMPANY), 23 Jun. 2010 (23.06.2010), See the whole document.	1-42
A	CN1407990A (BRISTOL-MYERS SQUIBB COMPANY), 02 Apr. 2003 (02.04.2003), See the whole document.	1-42

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
“A” document defining the general state of the art which is not considered to be of particular relevance	“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
“E” earlier application or patent but published on or after the international filing date	“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
“L” document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)	“&” document member of the same patent family
“O” document referring to an oral disclosure, use, exhibition or other means	
“P” document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
01 Mar. 2011 (01.03.2011)

Date of mailing of the international search report
24 Mar. 2011 (24.03.2011)

Name and mailing address of the ISA/CN
The State Intellectual Property Office, the P.R.China
6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China
100088
Facsimile No. 86-10-62019451

Authorized officer
HE, Xiangqiong
Telephone No. (86-10)62084366

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2010/073865

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

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

1. Claims Nos.:

because they relate to subject matter not required to be searched by this Authority, namely:

Claims 41-42 relate to the methods for treatment by therapy/diagnostic method of the human or animal body, which belongs to the requirements of Rule 39.1(iv) of no international searching authority. Nevertheless, a search has been executed for the claims. The search has been carried out for these claims based on the use of the composition in the preparation of pharmaceuticals.

2. Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

Remark on protest

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/CN2010/073865

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
CN101754972A	23.06.2010	US2008287529A1	2008.11.20
		WO2008144346A2	2008.11.27
		WO2008144346A3	2009.01.22
		EP2147008A2	2010.01.27
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CN1407990A	02.04.2003	WO0127128A1	2001.04.19
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		TW254714B1	2006.05.11
		CN1896088A	2007.01.17
		NO323698B1	2007.06.25
		INMUMNP200700019E	2007.08.03
		PH1200002657B1	2006.02.21
		KR100728085B1	2007.06.14
		JP4365554B2	2009.11.18
		IL148806A	2010.06.16
		TH58000A	2010.03.09

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2010/073865

CLASSIFICATION OF SUBJECT MATTER

C07H 7/04 (2006.01) i

A61K 31/70 (2006.01) i

A61P 3/00 (2006.01) i