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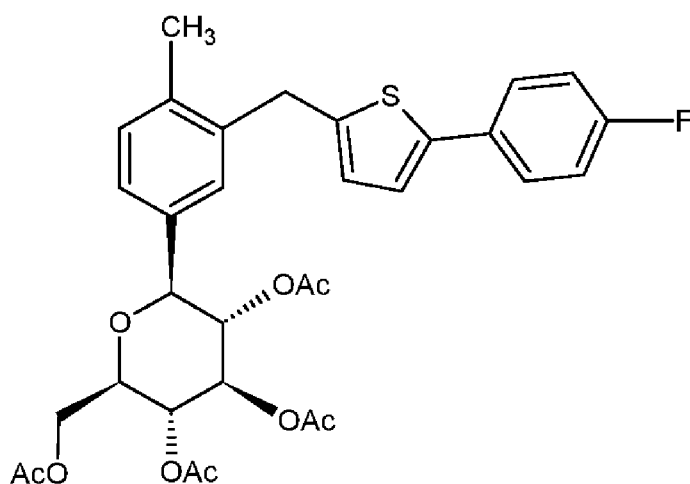
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(54) Title: PROCESS FOR THE PURIFICATION OF CANAGLIFLOZIN



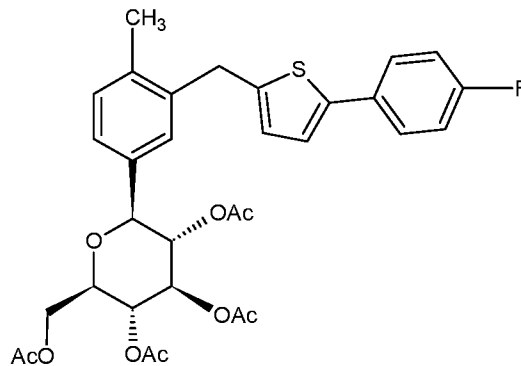
Formula III

(57) Abstract: The present invention provides a process for the preparation of (1S)-2,3,4,6-tetra-O-acetyl-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol of Formula III. The invention also provides a process for the purification of canagliflozin using (1S)-2,3,4,6-tetra-O-acetyl-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol of Formula III.

## PROCESS FOR THE PURIFICATION OF CANAGLIFLOZIN

### Field of the Invention

The present invention provides a process for the preparation of (1*S*)-2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-*D*-glucitol of Formula III. The invention also provides a process for the purification of canagliflozin using (1*S*)-2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-*D*-glucitol of Formula III.

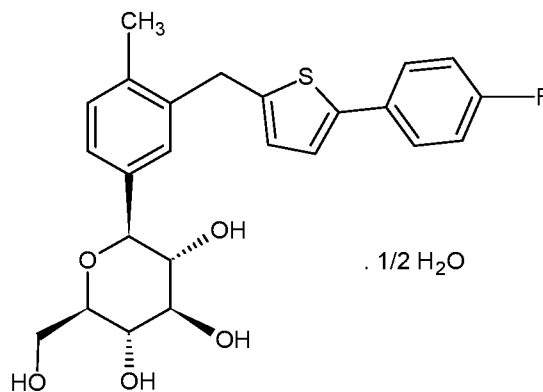


**Formula III**

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### Background of the Invention

Canagliflozin hemihydrate is chemically designated as (1*S*)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-*D*-glucitol hemihydrate and is marketed for the treatment of type 2 diabetes mellitus. Its chemical structure is represented by Formula I.



15

**Formula I**

U.S. Publication No. 2009/0233874 discloses a process for the purification of canagliflozin comprising the step of acetylating crude canagliflozin to (1*S*)-2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-

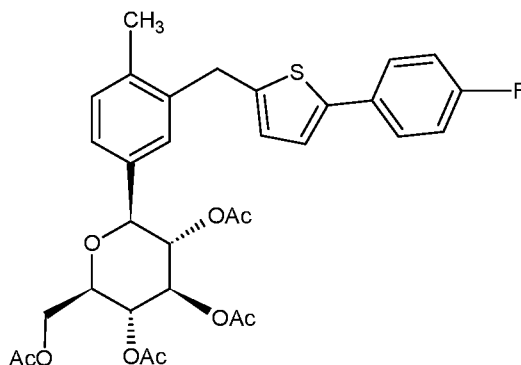
5 canagliflozin. The organic base used in the process is selected from *N*-methylmorpholine, triethylamine, and pyridine, wherein the base is present in an amount ranging from about 3 to about 6 molar equivalents.

There is a need in the art to develop a process for the purification of canagliflozin which circumvents the use of large amounts of organic bases, thereby reducing the  
10 operation cost. The present invention provides an improved process for the preparation of the compound of Formula III.

#### Summary of the Invention

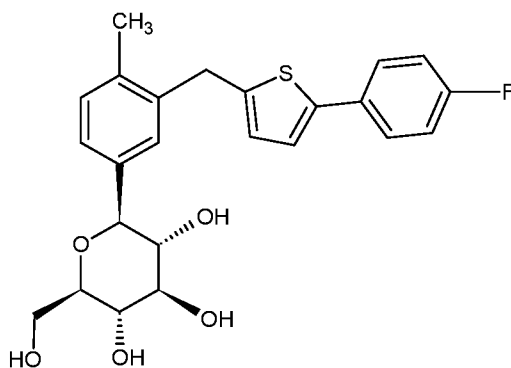
A first aspect of the present invention provides a process for the preparation of a compound of Formula III

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**Formula III**

comprising the step of acetylating canagliflozin of Formula II

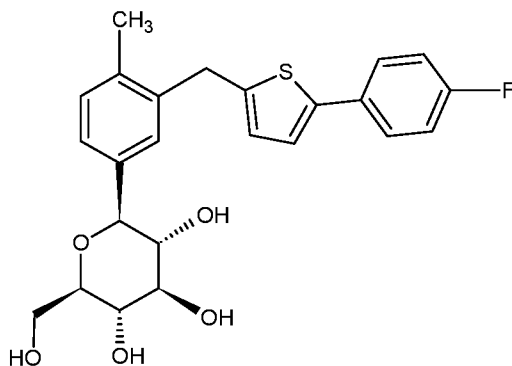


**Formula II**

in a solvent in the presence of a catalytic amount of a base.

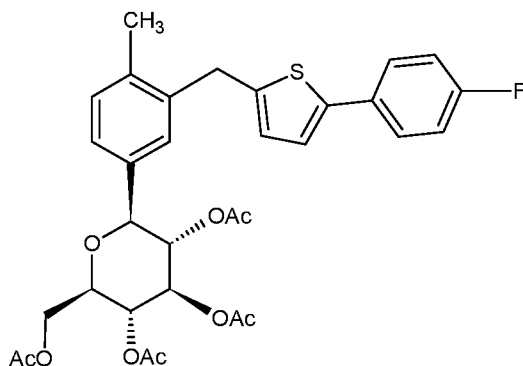
A second aspect of the present invention provides a process for the purification of canagliflozin of Formula II, or solvates thereof, wherein the process comprises the steps of:

- 5 a) acetylating canagliflozin of Formula II



**Formula II**

in a solvent in the presence of a catalytic amount of a base to obtain a compound of Formula III; and



10

**Formula III**

- b) deacetylating the compound of Formula III.

Brief Description of the Figures

Figure 1 depicts an X-Ray Powder Diffraction (XRPD) pattern of an amorphous form of canagliflozin.

15

Figure 2 depicts a Differential Scanning Calorimetry (DSC) thermogram of an amorphous form of canagliflozin.

### Detailed Description of the Invention

The term "about," as used herein, refers to any value which lies within the range defined by a number up to  $\pm 10\%$  of the value.

In the context of the present invention, "solvates" refers to complexes of  
5 canagliflozin with water, methanol, ethanol, *n*-propanol, propanediol, or butynediol.

The term "acetylation," as used herein, refers to the addition of acetyl group(s) to a given compound. The acetylation can be performed by the reaction of a compound with acetylating agents selected from a group comprising acetic anhydride, acetyl chloride, and the like.

10 The term "deacetylation," as used herein, refers to the removal of acetyl group(s) from a given compound.

The phrase "catalytic amount," as used herein, refers to the catalyst present in an amount ranging from 5 molar percent to 15 molar percent relative to the amount of reactant.

15 The phrase "essentially amorphous," as used herein, refers to the compound having a degree of crystallinity of less than 80%, preferably less than 90%, and most preferably less than 95%.

The acetylation of canagliflozin is performed in a solvent selected from a group comprising ketones, chlorinated solvents, and mixtures thereof. Examples of ketone  
20 solvents include acetone, methyl ethyl ketone, methyl isobutyl ketone, diisopropyl ketone, methyl isopropyl ketone, and methyl phenyl ketone. Examples of chlorinated solvents include dichloromethane, chloroform, dichloroethane, and carbon tetrachloride.

In another embodiment of the present invention, the acetylation of canagliflozin of Formula II is performed in the presence of a catalytic amount of a base. Examples of  
25 bases include *N,N'*-dimethylaminopyridine, 4-pyrrolidinopyridine, and *N*-methylpiperazine.

In another embodiment of the present invention, the acetylation of canagliflozin of Formula II is performed using *N,N'*-dimethylaminopyridine, wherein *N,N'*-  
30 dimethylaminopyridine is present in the range of from 5 molar percent to 15 molar percent of canagliflozin.

In another embodiment of the present invention, the acetylation of canagliflozin of Formula II is carried out in the absence of *N*-methylmorpholine, triethylamine, or pyridine.

In another embodiment of the present invention, the acetylation of canagliflozin of Formula II is performed in the presence of a catalytic amount of copper triflate  
5 [Cu(OTf)<sub>2</sub>], copper(II) tetrafluoroborate, or phosphomolybdic acid (PMA).

In another embodiment of the present invention, the deacetylation is performed in the presence of a base. Examples of bases include lithium hydroxide, sodium hydroxide, and the like.

In another embodiment of the present invention, the pure canagliflozin obtained by  
10 the process of the present invention is essentially amorphous.

In general, acetylation of canagliflozin is performed using acetic anhydride in the presence of a catalytic amount of *N,N'*-dimethylaminopyridine in dichloromethane to obtain the compound of Formula III, which upon deacetylation with a base gives pure canagliflozin.

15 The purity of the canagliflozin prepared by the process of the present invention is greater than 99%, as determined by HPLC.

The canagliflozin prepared by the process of the present invention is amorphous in nature as depicted by the XRPD in Figure 1.

The preparation of canagliflozin, which is used as a starting material to prepare the  
20 compound of Formula III, can be prepared by following the processes described in U.S. Patent Nos. 7,943,582 and 7,943,788 and U.S. Patent Publication Nos. 2009/0233874 and 2010/0099883, which are incorporated herein by reference.

## Methods

### HPLC Details

25 For the compound of Formula III, HPLC purity was determined using an ACE<sup>®</sup> C18-PFP (250 x 4.6 mm) 5 μm column with a flow rate of 1.0 mL/minute; column oven temperature 35°C; detector UV at 290 nm; injection volume 10 μL; run time: 60 minutes.

For canagliflozin, HPLC purity was determined using a Kromasil<sup>®</sup> C-18 (150 x 4.6 mm) 3.5 μm column with a flow rate of 1.0 mL/minute; column oven temperature 35°C;  
30 detector UV at 290 nm; injection volume 10 μL; run time: 60 minutes.

## EXAMPLES

### Example 1: Preparation of 2-(4-fluorophenyl)thiophene

Sodium carbonate (130 g) was added to a solution of 2-bromothiophene (100 g) and 4-fluorophenylboronic acid (85.8 g) in dimethoxyethane (400 mL) and de-ionized water (400 mL) at 25°C to 30°C. The reaction mixture was heated at 70°C to 75°C for 30 minutes. Tetrakis(triphenylphosphine)palladium (1 g) was added to the reaction mixture at 70°C to 75°C under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 1 to 2 hours. After completion of the reaction, the reaction mixture was allowed to cool to 25°C to 30°C. Hexane (1000 mL) was added to the reaction mixture at 25°C to 30°C, and then the reaction mixture was stirred for 30 minutes. The reaction mixture was filtered through a Hyflo<sup>®</sup> bed and silica gel (60-120 mesh). De-ionized water (100 mL) was added to the filtrate and the mixture was stirred for 10 to 15 minutes. The reaction mixture was allowed to settle for 15 minutes, and then the layers were separated. The organic layer was washed with de-ionized water (100 mL). The organic layer was concentrated under reduced pressure at 45°C to obtain a residue. Hexanes (100 mL) were added to the residue and the mixture was stirred for 1 to 2 hours at 0°C to 5°C to obtain a solid. The solid was filtered, then washed with pre-cooled hexane, and then dried under reduced pressure to obtain 2-(4-fluorophenyl)thiophene.

Yield: 82.5%

### Example 2: Preparation of (5-bromo-2-methylphenyl)[5-(4-fluorophenyl)thiophen-2-yl]methanone

Oxalyl chloride (64.97 g) was slowly added to a solution of 5-bromo-2-methylbenzoic acid (100 g) in dichloromethane (1000 mL) and dimethylformamide (10 mL) at 25°C to 30°C under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for about one hour. After completion of the reaction, the reaction mixture was concentrated under reduced pressure at a temperature of about 45°C under nitrogen atmosphere. The reaction mass obtained was dissolved in dichloromethane (1000 mL), and then cooled to 0°C under nitrogen atmosphere. 2-(4-Fluorophenyl)thiophene (82.86 g; Example 1) and aluminum chloride (68 g) were added to the reaction mixture at 0°C to 5°C under nitrogen atmosphere. The reaction mixture was stirred for 60 minutes to 90 minutes at 10°C to 15°C under nitrogen atmosphere. After completion of the reaction, the reaction mixture was slowly added to water (1000 mL) at 0°C to 10°C. The reaction

mixture was stirred at 25°C to 30°C for 10 to 15 minutes. The reaction mixture was allowed to settle for 15, minutes and then the layers were separated. Dichloromethane (200 mL) was added to the aqueous layer and the mixture was stirred for 10 minutes to 15 minutes. The mixture was allowed to settle for 15 minutes and then the layers were  
5 separated. The organic layers were combined, and then washed with an aqueous solution of sodium bicarbonate (50 g in 500 mL of de-ionized water). The organic layer was washed with an aqueous solution of sodium chloride (10 g in 200 mL of de-ionized water). The organic layer was concentrated under reduced pressure at a temperature of about 45°C to obtain a residue. Hexanes (500 mL) were added to the residue, and then the reaction  
10 mixture was stirred for 15 minutes to 20 minutes at 25°C to 30°C. The reaction mixture was cooled to 0°C to 5°C, and then stirred for 60 minutes to 120 minutes at the same temperature to obtain a solid. The solid was filtered under reduced pressure, then washed with hexanes (100 mL; pre-cooled), and then dried under reduced pressure at 40°C to 45°C to obtain (5-bromo-2-methylphenyl)[5-(4-fluorophenyl)thiophen-2-yl]methanone.  
15 Yield: 80.4%

Example 3: Preparation of 2-(5-bromo-2-methylbenzyl)-5-(4-fluorophenyl)thiophene

Aluminum chloride (46.12 g) was added to 1,2-dimethoxyethane (260 mL) at 0°C to 5°C. The reaction mixture was stirred for 30 minutes to 40 minutes at 5°C to 10°C. Sodium borohydride (26.19 g) was slowly added to the reaction mixture at 5°C to 10°C.  
20 The reaction mixture was stirred for 25 minutes to 30 minutes at the same temperature. A solution of (5-bromo-2-methylphenyl)[5-(4-fluorophenyl)thiophen-2-yl]methanone (130 g; Example 2) in 1,2-dimethoxyethane (260 mL) was added slowly to the reaction mixture, and then the mixture was stirred for 60 minutes at 15°C to 20°C. The reaction mixture was heated to a temperature of 65°C to 70°C, and then stirred for 5 hours to 6 hours at the  
25 same temperature. After completion of the reaction, the reaction mixture was cooled to a temperature of 0°C to 5°C, and then added to pre-cooled de-ionized water (1300 mL) at 0°C to 10°C. The reaction mixture was stirred for 10 minutes to 15 minutes at the same temperature. Ethyl acetate (1300 mL) was added to the reaction mixture, and then the mixture was stirred for 10 to 15 minutes at 25°C to 30°C. The reaction mixture was  
30 allowed to settle for 15 minutes and then the layers were separated. The aqueous layer was washed with ethyl acetate (260 mL) and the organic layer was separated. The organic layers were combined, and then washed with an aqueous solution of sodium bicarbonate (32.5 g of sodium bicarbonate in 650 mL of de-ionized water). The organic layer was then



washed with de-ionized water (260 mL). The organic layer was concentrated under reduced pressure at a temperature of about 45°C to obtain a solid residue. Methanol (390 mL) was added to the solid residue, and then the mixture was stirred for 60 minutes to 120 minutes at 0°C to 5°C to obtain a solid. The solid was washed with methanol (130 mL),  
5 and then dried under reduced pressure at 40°C to 45°C to obtain 2-(5-bromo-2-methylbenzyl)-5-(4-fluorophenyl)thiophene.

Yield: 93%

Example 4: Preparation of 1-(1-methoxyglucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene

10 A solution of 2-(5-bromo-2-methylbenzyl)-5-(4-fluorophenyl)thiophene (100 g; Example 3) in tetrahydrofuran (200 mL) and toluene (300 mL) was added to a solution of *n*-butyl lithium in hexane (3.2M; 76.8 g) and tetrahydrofuran (200 mL) at -75°C to -65°C under nitrogen atmosphere. The reaction mixture was stirred for 20 minutes to 40 minutes at the same temperature. A solution of 2,3,4,6-tetrakis-*O*-trimethylsilyl-D-glucono-1,5-  
15 lactone (194 g) in toluene (500 mL) was added to the reaction mixture at -70°C to -75°C, and then the mixture was stirred for 60 minutes to 90 minutes at the same temperature. A solution of methanesulphonic acid (66 g) in methanol (700 mL) was slowly added to the reaction mixture at -70°C to -75°C. The reaction mixture was allowed to reach a temperature of 25°C to 30°C, and was then stirred at the same temperature for 12 hours.  
20 After completion of the reaction, the reaction mixture was washed with an aqueous solution of sodium bicarbonate (25 g of sodium bicarbonate in 500 mL of de-ionized water) at 25°C to 30°C. Ethyl acetate (500 mL) was added to the organic layer, and then the mixture was stirred for 10 minutes to 15 minutes. The reaction mixture was allowed to settle for 15 minutes, and then the layers were separated. The aqueous layer was washed  
25 twice with ethyl acetate (500 mL) and the layers were separated. The organic layers were combined, and then washed with an aqueous solution of sodium chloride (10 g of sodium chloride in 200 mL of de-ionized water). The organic layer was concentrated under reduced pressure at 45°C to obtain an oily residue. The oily residue was dissolved in toluene (300 mL) at 40°C to 45°C to obtain a solution. Hexane (1000 mL) was slowly  
30 added to the solution at 25°C to 30°C under a nitrogen atmosphere. The mixture was stirred at the same temperature for 15 minutes to 20 minutes to obtain a solid. The solid was filtered under reduced pressure under nitrogen atmosphere, and then dried for 20

minutes to 30 minutes under nitrogen atmosphere to obtain 1-(1-methoxyglucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene.

Example 5: Preparation of canagliflozin

Triethylsilane (64.43 g) and borontrifluoride-diethyletherate (78.61 g) were added  
5 (one after another) to a solution of 1-(1-methoxyglucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene (the whole quantity obtained from Example 4) in dichloromethane (500 mL) at 0°C to 5°C. The reaction mixture was stirred for 2 hours to 3 hours. After completion of the reaction, an aqueous solution of sodium bicarbonate (25 g of sodium bicarbonate in 500 mL of de-ionized water) was added, and then the reaction  
10 mixture was stirred for 30 minutes at 20°C to 25°C. The reaction mixture was concentrated under reduced pressure to completely recover the organic layer at 45°C. Ethyl acetate (1000 mL) was added to the reaction mixture, and then the mixture was stirred for 10 minutes to 15 minutes. The reaction mixture was allowed to settle, and then the organic layer was separated. The aqueous layer was washed with ethyl acetate, and the  
15 organic layer was separated. The organic layers were combined, and then washed with an aqueous solution of sodium chloride (10 g of sodium chloride in 200 mL of de-ionized water). The organic layer was completely concentrated under reduced pressure at a temperature of about 45°C to obtain canagliflozin.

HPLC Purity: 80%

20 Example 6: Preparation of (1S)-2,3,4,6-tetra-O-acetyl-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol (without pyridine)

Acetic anhydride (19 ml) was added to a solution of canagliflozin (10 g; Example 5) in acetone (100 mL) at a temperature of about 25°C. *N,N'*-dimethylaminopyridine (275 mg) was added to this mixture at about 25°C. The reaction mixture was heated to about  
25 50°C for 5 hours. After completion of the reaction, the reaction mixture was concentrated up to the maximum extent at 40°C to 45°C. Dichloromethane (100 mL) was added to the reaction mass and then the mixture was stirred for 10 minutes at 25°C to 30°C. De-ionized water (100 mL) was added to the reaction mixture, the mixture was stirred for 10 minutes at 25°C to 30°C, and then the layers were separated. The organic layer was  
30 concentrated under reduced pressure at 45°C to obtain a residue. Methanol (20 mL) was added to the residue, the reaction mixture was stirred for 10 minutes to 30 minutes at 50°C to 55°C, and then concentrated under vacuum up to the maximum extent. Methanol (100

mL) was added to the residue and the mixture was heated to 55°C. The reaction mixture was stirred for 15 minutes at 50°C to 55°C, then allowed to cool to about 25°C, and then stirred for 30 minutes at the same temperature. The solid was filtered under reduced pressure, then washed twice with methanol (10 mL), and then dried under reduced pressure for 20 minutes to 30 minutes. Ethyl acetate (40 mL) was added to the wet solid and the mixture was heated to 60°C to 65°C until a clear solution was obtained. The solution was stirred for 10 minutes to 15 minutes at the same temperature, and then methanol (100 mL) was added to the clear solution. The solution was stirred for 10 minutes to 15 minutes at 60°C to 65°C, then cooled slowly to 0°C to 5°C, and then stirred for 40 minutes to 60 minutes to obtain a solid. The solid was filtered under reduced pressure and then washed with ethyl acetate:methanol (1:2; 10 mL). The solid obtained was dried under reduced pressure at 40°C to 45°C to obtain the title compound.

Yield: 7.2 g (0.72 w/w)

HPLC purity: 97.53%

15 Comparative example using pyridine

Preparation of (1S)-2,3,4,6-tetra-O-acetyl-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol

Acetic anhydride (19 mL) was added to a solution of canagliflozin (10 g; Example 5) in dichloromethane (100 mL) and pyridine (16 mL) at a temperature of about 25°C. *N,N'*-dimethylaminopyridine (165 mg) was added at about 25°C. The reaction mixture was stirred for 3 hours to 4 hours at 25°C to 30°C. After completion of the reaction, de-ionized water (100 mL) was added to the reaction mixture, and then the reaction mixture was stirred for 15 minutes to 30 minutes. The reaction mixture was allowed to settle for 15 minutes, and then the layers were separated. Dichloromethane (20 mL) was added to the aqueous layer, and the mixture was stirred for 10 minutes to 15 minutes. The mixture was allowed to settle for 15 minutes, and then the layers were separated. The organic layers were combined, and then washed with ~10% hydrochloric acid (50 mL) and de-ionized water (50 mL). The filtrate was concentrated under reduced pressure at 45°C to obtain a residue. Methanol (100 mL) was added to the residue, and then the reaction mixture was stirred for 10 minutes to 30 minutes at 50°C to 55°C. The reaction mixture was allowed to cool to about 25°C and was then stirred at the same temperature. The solid was filtered under reduced pressure, then washed twice with methanol (10 mL), and then

dried under reduced pressure for 20 minutes to 30 minutes. Ethyl acetate (40 mL) was added to the wet solid and the mixture was heated to 60°C to 65°C until a clear solution was obtained. The solution was stirred for 10 minutes to 15 minutes at the same temperature, and then methanol (100 mL) was added. The solution was stirred for 10  
5 minutes to 15 minutes at 60°C to 65°C, then cooled slowly to 0°C to 5°C, and then stirred for 40 minutes to 60 minutes to obtain a solid. The solid was filtered under reduced pressure and then washed with ethyl acetate:methanol (1:2; 10 mL). The solid obtained was dried under reduced pressure at 40°C to 45°C to obtain the title compound.

Yield: 7.3 g (0.73 w/w)

10 HPLC purity: 96.49%

Example 7: Purification of canagliflozin (Formula II)

An aqueous solution of sodium hydroxide (9 g of sodium hydroxide in 75 mL of de-ionized water) was added to a solution of (1*S*)-2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-1-[3-  
[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol (Formula III; 30 g;  
15 prepared as per Example 6) in methanol (45 mL), and the mixture was stirred for 3 hours to 4 hours at 65°C to 70°C. After completion of the reaction, the reaction mixture was allowed to cool to 15°C to 20°C. The pH of the reaction mixture was adjusted to 6.5 to 7 by the slow addition of an aqueous solution of hydrochloric acid (10%). Methyl *tertiary*-  
butyl ether (300 mL) was added to the reaction mixture, and then the mixture was stirred  
20 for 10 minutes to 15 minutes at 25°C to 30°C. The reaction mixture was allowed to settle for 15 minutes, and then the layers were separated. The organic layer was washed with de-ionized water (150 mL). The organic layer was completely concentrated under reduced pressure at 45°C to obtain a residue. The residue was dissolved in methyl *tertiary*-butyl  
ether (90 mL) at 40°C to 45°C to obtain a clear solution. Hexane (600 mL) was slowly  
25 added to the solution at 25°C to 30°C, and then the mixture was stirred at the same temperature for 10 minutes to 15 minutes to obtain a solid. The solid was filtered under reduced pressure, then washed with hexane (60 mL), and then dried under vacuum to obtain canagliflozin.

Yield: 91.6%

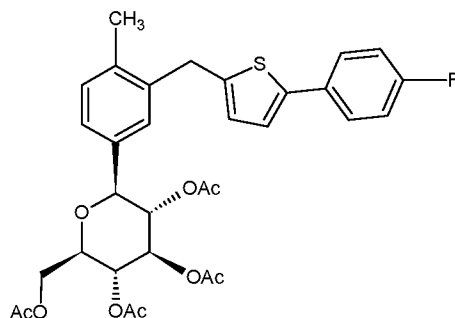
30 HPLC purity: 99.21%

XRPD as depicted in Figure 1

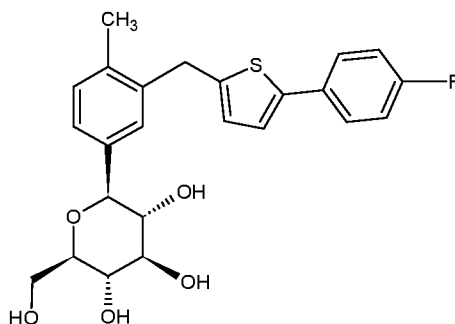
DSC as depicted in Figure 2

**We claim:**

- 1 1. A process for the preparation of a compound of Formula III

**Formula III**

- 4 comprising the step of acetylating canagliflozin of Formula II

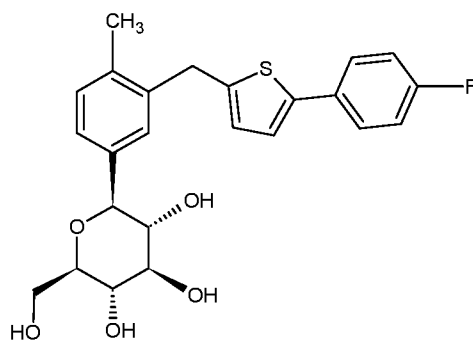
**Formula II**

- 7 in a solvent in the presence of a catalytic amount of a base.

- 1 2. A process of claim 1, wherein the quantity of the base used does not exceed 15  
2 mole% with respect to canagliflozin.

- 1 3. A process for the purification of canagliflozin of Formula II, or solvates thereof,  
2 wherein the process comprises the steps of:

- 3 a) acetylating canagliflozin of Formula II



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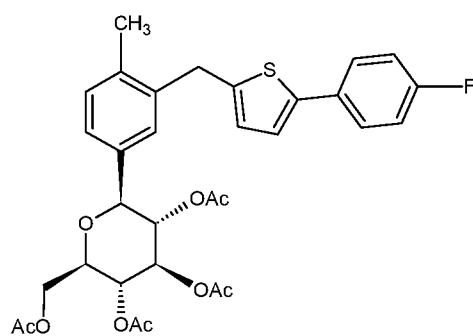
**Formula II**

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in a solvent in the presence of a catalytic amount of a base to obtain a compound of

7

Formula III; and



8

9

**Formula III**

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b) deacetylating the compound of Formula III.

1

4. The process according to claims 1 or 3, wherein the organic base is selected from the group consisting of *N,N'*-dimethylaminopyridine, 4-pyrrolidinopyridine, and *N*-methylpiperazine.

2

3

1

5. The process according to claim 4, wherein the organic base is *N,N'*-dimethylaminopyridine.

2

1

6. The process according to claims 1 or 3, wherein the solvent is selected from the group consisting of ketones and chlorinated hydrocarbons.

2

1

7. The process according to claim 6, wherein the chlorinated hydrocarbon is selected from the group consisting of dichloromethane, chloroform, dichloroethane, carbon tetrachloride, and mixtures thereof.

2

3

1

8. The canagliflozin of Formula II according to claim 1 having a purity of more than 99% as determined by HPLC.

2

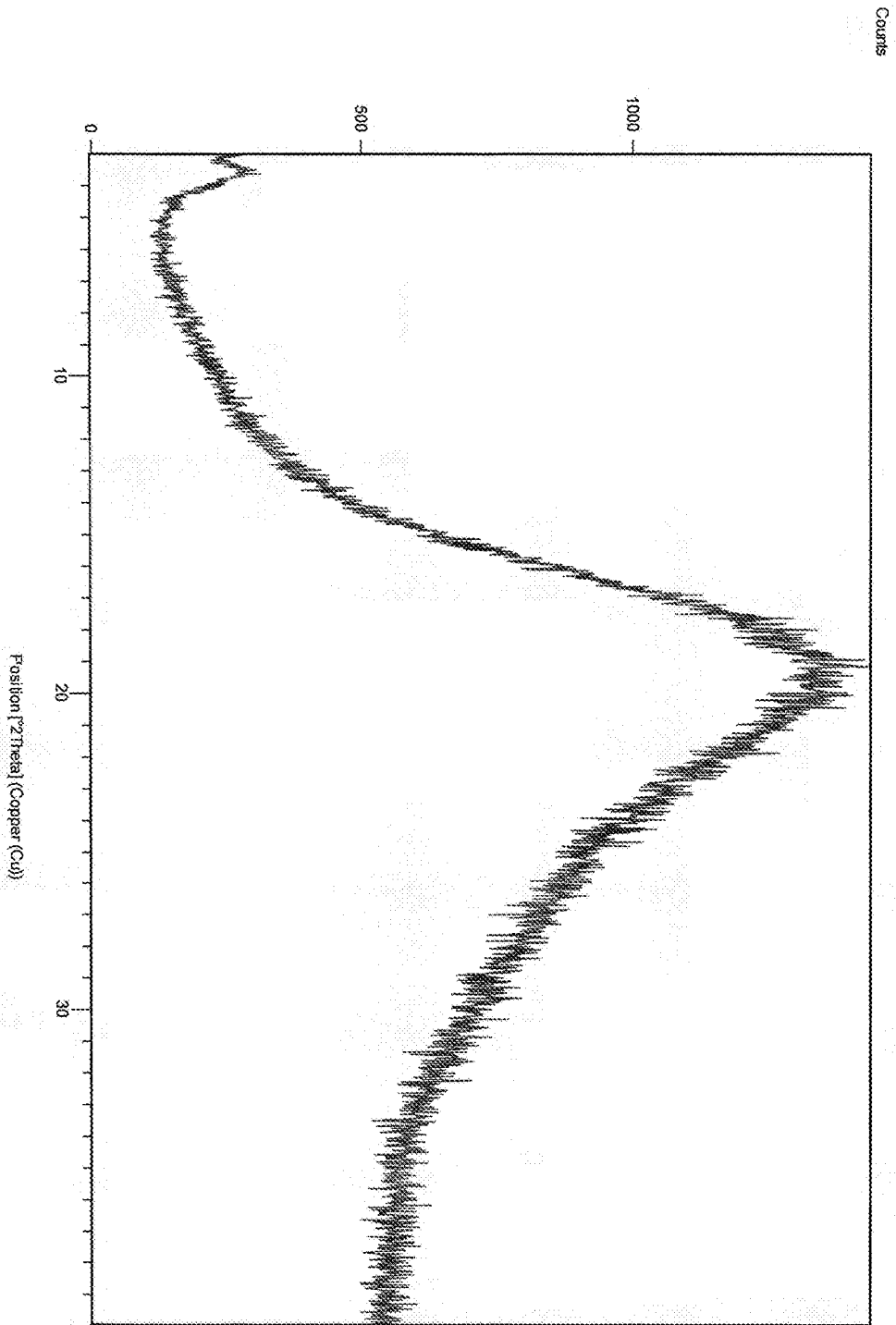


Figure 1

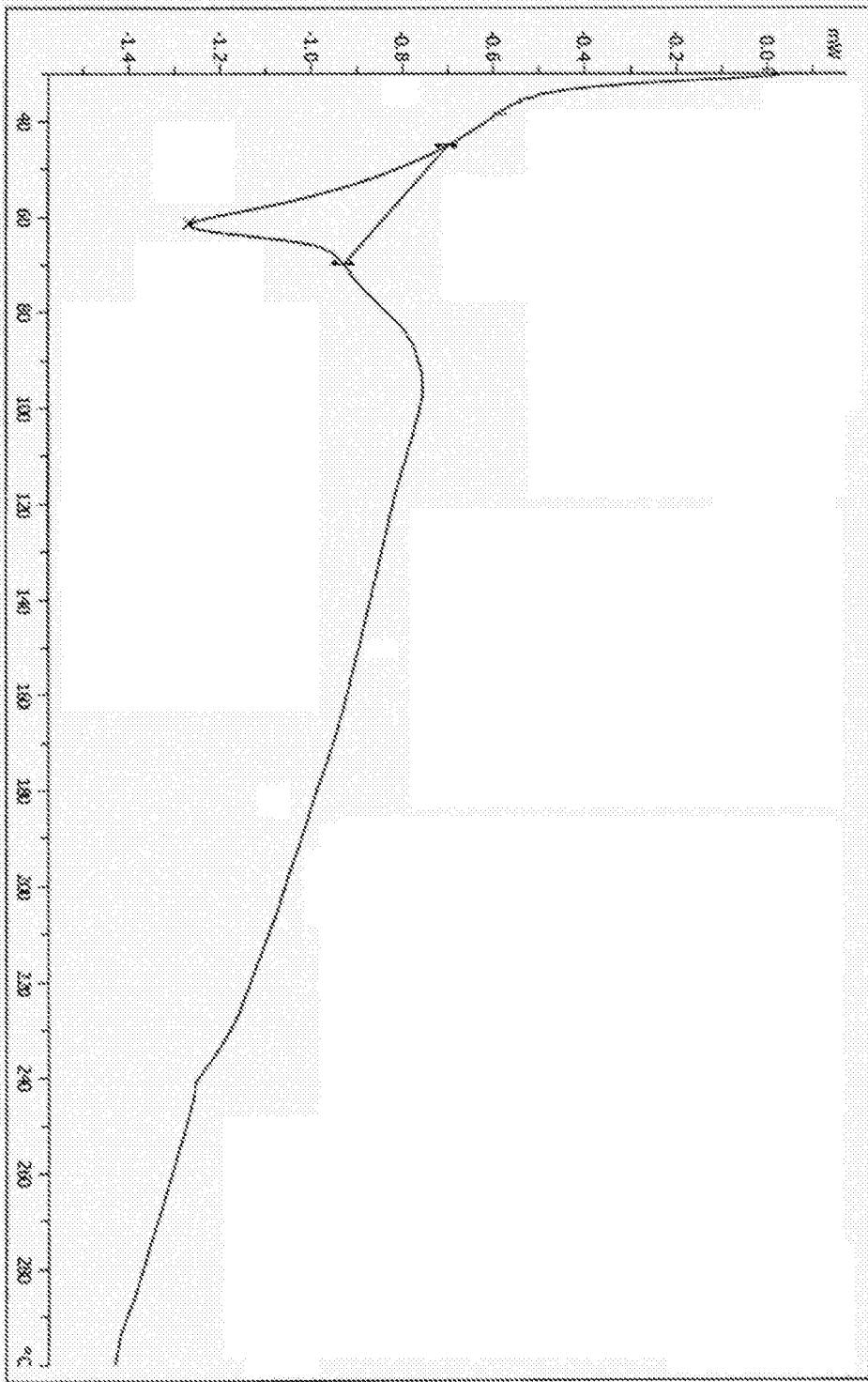


Figure 2



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2015/055793

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(8) - C07H 1/06 (2015.01) CPC - C07H 1/06 (2015.11) According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC(8) - C07H 1/06, 13/04 (2015.01) CPC - C07H 1/06, 13/04, 15/26 (2015.11)		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC - 536/119, 127; IPC(8) - C07H 1/06, 13/04; CPC - C07H 1/06, 13/04, 15/26 (keyword delimited)		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Orbit, PubChem, Google Scholar. Search terms used: glucoside, glucopyranosyl, glucitol, thienyl, fluorophenyl, acetate		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---	US 2009/0233874 A1 (ABDEL-MAGID et al) 17 September 2009 (17.09.2009) entire document	1-5 ---
Y		6-8
Y	US 8,198,464 B2 (KOMENOI et al) 12 June 2012 (12.06.2012) entire document	6-8
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 08 November 2015		Date of mailing of the international search report <b>28 DEC 2015</b>
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300		Authorized officer Blaine Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774