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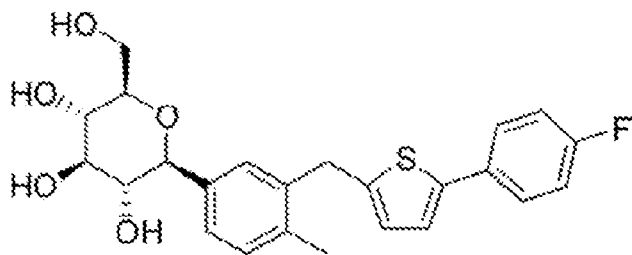
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(54) Title: PROCESS FOR THE PREPARATION OF CANAGLIFLOZIN



(57) Abstract: The present invention relates to a novel process for the preparation of canagliflozin of formula I, (I) and to novel intermediates which are produced during the course of carrying out the novel process.

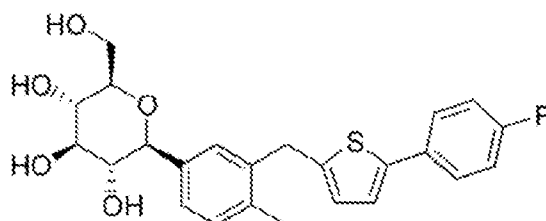
PROCESS FOR THE PREPARATION OF CANAGLIFLOZIN

FIELD OF THE INVENTION:

- 5 The present invention relates to a novel process for the preparation of canagliflozin (a compound of formula I), and to novel intermediates which are produced during the course of carrying out the novel process.

BACKGROUND OF THE INVENTION:

- 10 Diabetes mellitus is a serious and chronic metabolic disease that is characterized by high blood glucose (hyperglycemia) and affects millions of people world-wide.
A significant number of SGLT2 inhibitors are currently in clinical development and a significant portion of these are β -C-arylglucosides.
Among β -C-arylglucosides that possess known SGLT2 inhibition that are currently in clinical
15 development are canagliflozin, empagliflozin, and ipragliflozin.
Canagliflozin of formula I:



Formula I

- 20 or (1S)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]-methyl]-4-methylphenyl]-D-glucitol is an inhibitor of subtype 2 sodium-glucose transport protein (SGLT2), which exhibits an inhibitor activity, against sodium-dependent glucose transporter being present in the intestine and kidney of mammalian species.
25 Several approaches are described in the literature to synthesize canagliflozin.

EP2200606A1 discloses a process for the preparation of compounds having inhibitory activity against sodium-dependent glucose transporter (SGLT2) being present in the intestine or kidney, including canagliflozin and salts thereof.

30

S. Nomura et al., *Journal of Medicinal Chemistry*, 2010, Volume 53, Issue 17, Pages 6355-6360 discloses stereoselective C-Glycosylation reactions with aryl zinc reagents applied to the stereoselective synthesis of canagliflozin.

5 In spite of the prior art disclosures of processes for the synthesis of canagliflozin, there yet remains a continuing need to develop an easy, efficient, economical and commercially viable process.

OBJECTS OF THE INVENTION:

The object of the present invention is to provide a novel process for the preparation canagliflozin of formula I.

10 Yet another object of the present invention is to provide a novel process for the preparation of canagliflozin of formula I which proceeds via novel chemical intermediates.

Yet another object of the present invention is to provide a novel process for the preparation of novel chemical intermediates.

15 Yet another object of the present invention is to provide a process for the preparation of canagliflozin of formula I which is simple, economical and suitable for industrial scale-up.

SUMMARY OF THE INVENTION:

According to the first aspect of the present invention, there is provided a novel process for the preparation of canagliflozin of formula I.

20 According to another aspect of the present invention, there is provided novel intermediates for the preparation of canagliflozin of formula I.

25 According to the first aspect of the present invention, there is provided a novel process for the preparation of novel intermediates.

According to yet another aspect of the present invention, there is provided a novel process for the preparation of canagliflozin of formula I which proceeds via novel intermediates.

30 DETAILED DESCRIPTION OF THE INVENTION:

The present invention provides a novel process for the preparation of canagliflozin through novel intermediates which are more effective and easy to scale up in commercial batches in a convenient and cost effective manner, in high purity.

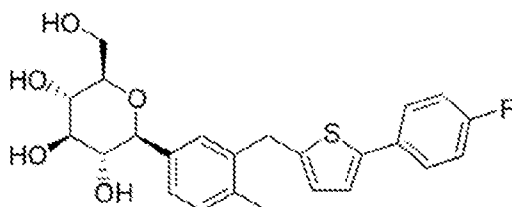
In accordance with the present invention, a novel process through novel intermediates is provided for the preparation of canagliflozin as described hereinafter.

Protecting groups and associated deprotection methods are widely used in organic synthesis. Protecting groups are often used to prevent a particular functional group or part of a molecule (e.g., an amine, a carboxylic acid, a hydroxyl, a heterocycle, etc.) from reacting under certain reaction conditions. Hydroxyl-protecting groups are among the most commonly used protecting groups and are of great importance in organic synthesis.

The term "hydroxyl protecting groups" include, but are not limited to, the protecting groups designated as such and disclosed in Wuts and Greene, *Protective Groups in Organic Synthesis*, 4th ed., John Wiley & Sons: New Jersey, (2007), which is incorporated herein by reference in its entirety.

The term "halogen" includes chloro, bromo, fluoro and iodo.

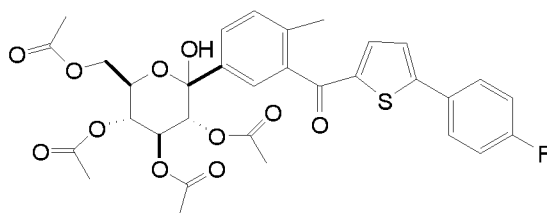
In one aspect of the present invention there is provided a novel process for the preparation of canagliflozin of formula I,



Formula I

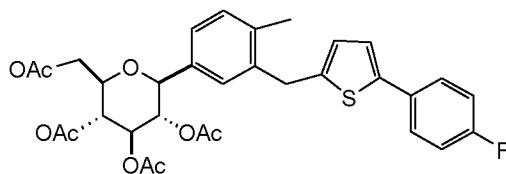
which process comprises the steps of:

reducing a compound of formula IIIc,



formula IIIc

with a suitable reducing agent, optionally in presence of a Lewis Acid and/or a suitable organic solvent, to obtain compound of formula II,



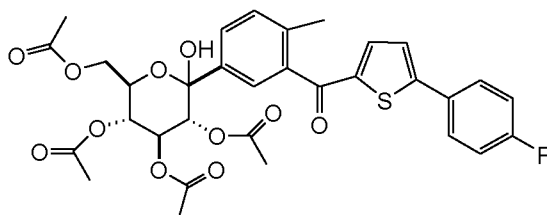
formula II

; and

deprotecting the compound of formula II so formed to obtain a compound of formula I.

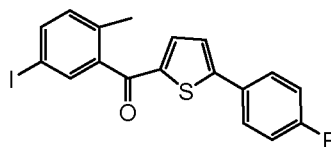
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Yet another aspect of the present invention provides a process for the preparation of a compound of formula IIIc,



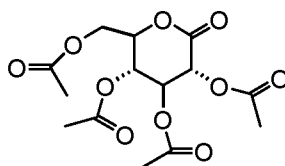
formula IIIc

10 which process comprises condensing a compound of formula IVc,



formula IVc

with a compound of formula Vc,



formula Vc

in presence of a Grignard reagent of formula RMX and a suitable metal ion complex, in one or more suitable organic solvents;

15

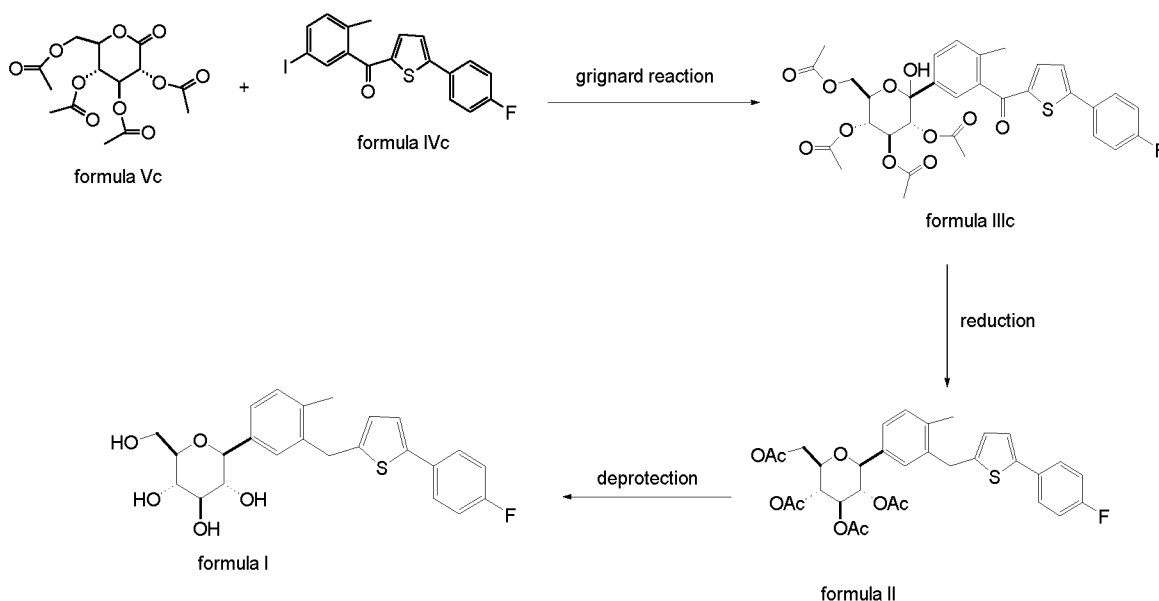
wherein, R is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, alkoxy, aryloxy, thioalkoxy, thioaryloxy, carboxy, thiocarboxy, carbamate, thiocarbamate, amide, thioamide, carbonyl, thiocarbonyl, urea, and thiourea; M is any metal suitable for forming a Grignard reagent; and X is halide.

5

The compound of formula IIIc depicted in Scheme 1 hitherto is a novel intermediate useful in the process for the preparation of canagliflozin as described herein. In one aspect of the present invention, there is provided a compound of formula IIIc, optionally for use as an intermediate in the preparation of canagliflozin.

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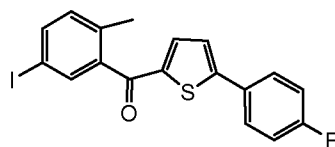
Accordingly, in another aspect of the present invention there is provided a process for the preparation of canagliflozin of formula I is as shown in Scheme 1.



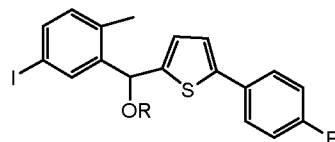
Scheme 1

15

In an alternative embodiment of the present invention, there is provided a process for the preparation of canagliflozin of formula I which comprises the step(s) of reducing and optionally esterifying a compound of formula VIc,

**formula VIId**

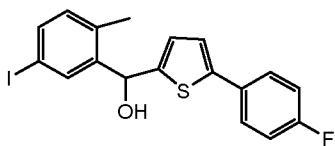
to obtain compound of formula IVd,

**formula IVd**

wherein R is H or lower alkyl, such as C₁₋₆ alkyl.

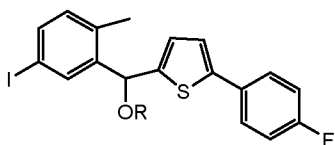
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In one aspect, where R is H, the compound of formula VIId is reduced to obtain a compound of formula IVd-1,

**formula IVd-1**

In another aspect, where R is lower alkyl, the compound of formula IVd-1 is esterified to obtain a compound of formula IVd-2,

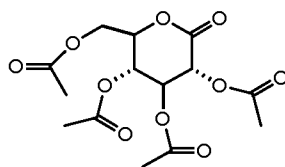
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**formula IVd-2**

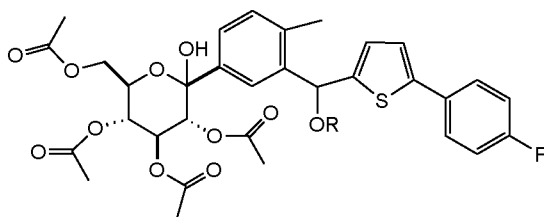
According to another aspect of the present invention, there is provided a process for the preparation of canagliflozin of formula I, which comprises the step(s) of:

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condensing compound IVd with compound of formula Vd,

**formula Vd**

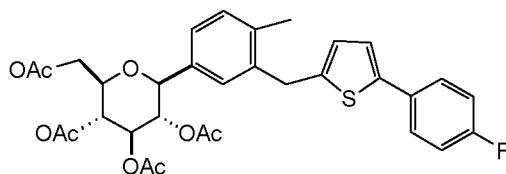
in presence of Grignard reagent of formula RMX and metal ion complex wherein R, M and X are as hereinbefore defined, to form compound of formula IIIId,



formula IIIId

;

- 5 reducing the compound of formula IIIId so formed with a suitable reducing agent, optionally in the presence of a Lewis acid and/or a suitable solvent, to obtain compound of formula II;

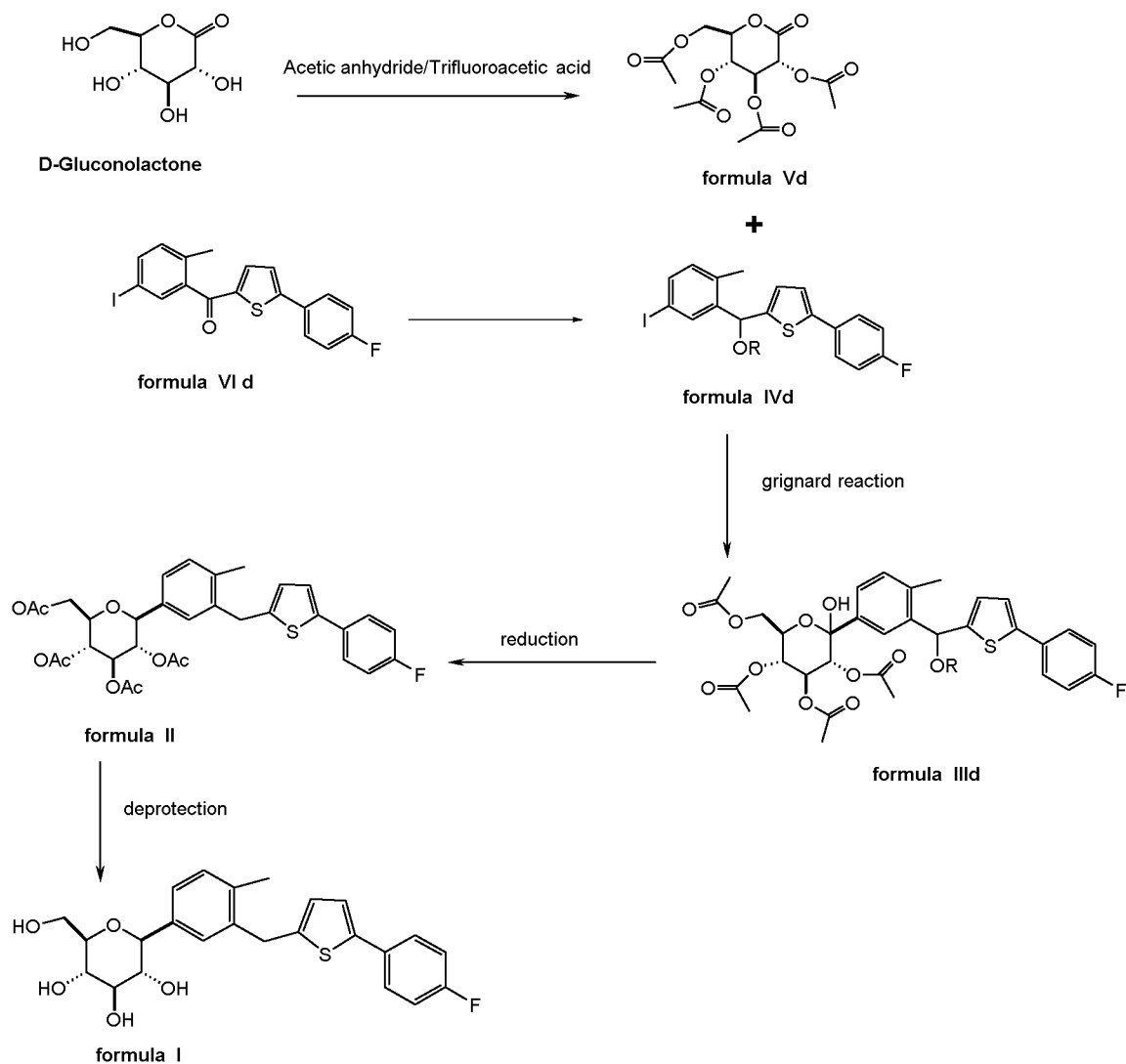


formula II

; and

deprotecting the compound of formula II so formed to obtain a compound of formula I.

- 10 The compounds of formulae IIIId, IVd-1 and IVd-2 depicted in Scheme 2 are hitherto novel intermediates useful in the process for the preparation of canagliflozin as described herein. Accordingly, in one aspect of the present invention, there is provided a compound of formula IIIId, IVd-1 or IVd-2, optionally for use as an intermediate in the preparation of canagliflozin.
- 15 Accordingly, in another aspect of the present invention there is provided a process for the preparation of canagliflozin of formula I as shown in Scheme 2.



Scheme 2

Suitable Grignard reagents which may be employed in the Grignard reaction step of the present invention are commercially available and/or may be prepared according to conventional methods in the art. Non-limiting examples include tert-butyl magnesium chloride, tert-butyl magnesium bromide, tert-amyl magnesium chloride, tert-amyl magnesium bromide, 1,1-diethylpropyl magnesium chloride, 1-methylcyclopentyl magnesium chloride and 1-methylcyclohexylmagnesium chloride, Sec-butyl magnesium chloride, ethyl magnesium bromide, methyl magnesium bromide, vinyl magnesium bromide, allyl magnesium bromide, ethynyl magnesium bromide, and the like.

Suitable metal ion complexes which may be employed in the Grignard reaction step of the present invention include, but are not limited to, n-butyl lithium, sec butyl lithium, hexyl lithium, and the like.

Suitable organic solvents which may be employed in the Grignard reaction step of the present invention include, but are not limited to, one or more of toluene, tetrahydrofuran (THF), diethyl ether, diglyme, methyl t-butyl ether, and the like.

The Grignard reaction step of the present invention is typically carried out at a temperature in the range of from about -60°C to about 60°C.

Non-limiting examples of suitable reducing reagents which may be employed in the processes of the present invention include, but are not limited to, silane reagents such as triethyl silane and triisopropylsilane; borohydrides, such as sodium borohydride (NaBH_4), potassium borohydride (KBH_4), zinc borohydride ($\text{Zn}(\text{BH}_4)_2$), sodium cyanoborohydride (NaBH_3CN) and sodium triacetoxymethylborohydride; and aluminum hydrides such as lithium aluminum hydride.

Suitable Lewis acids which may be employed in the processes of the present invention include boron trifluoride etherate, trimethylsilyl triflate, titanium tetrachloride, tin tetrachloride, hydrochloric acid, toluenesulfonic acid, trifluoroacetic acid, acetic acid, and the like.

Suitable organic solvents which may be employed in the reduction step of the present invention to obtain the compound of formula II include, but are not limited to, one or more of ethers, nitriles, halogenated solvents, dimethylformamide, dimethyl sulfoxide, or any mixture thereof.

The reduction reaction to obtain the compound of formula II is typically carried out at a temperature in the range of from about -40°C to about 60°C.

The deprotection step to obtain canagliflozin of formula I may be undertaken using conventional methods. For example, the compound of formula II may be treated with a suitable deprotection reagent such as a base or an acid in a suitable solvent. The base may be an anhydrous base such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide or the like.

Suitable solvents include alcoholic solvents, preferably methanol, and the like.

Non-limiting examples of reagents which may be employed for the (keto) reduction of the compound of formula VI to obtain the compound of formula IV in accordance with the present invention include borohydrides, such as sodium borohydride (NaBH_4); potassium borohydride (KBH_4); zinc borohydride ($\text{Zn}(\text{BH}_4)_2$); sodium cyanoborohydride (NaBH_3CN); sodium triacetoxymethylborohydride; and aluminum hydrides, such as lithium aluminum hydride and the like.

Suitable solvents which may be employed in the (keto) reduction step to obtain the compound of formula IV include, but are not limited to, one or more of alcohols, esters, ethers, nitriles,

tetrahydrofuran (THF), water, halogenated solvents, dimethylformamide, dimethyl sulfoxide, sulfolane, or any mixture thereof.

The (keto) reduction step is typically carried out at a temperature in the range of from about 0°C to about 100°C.

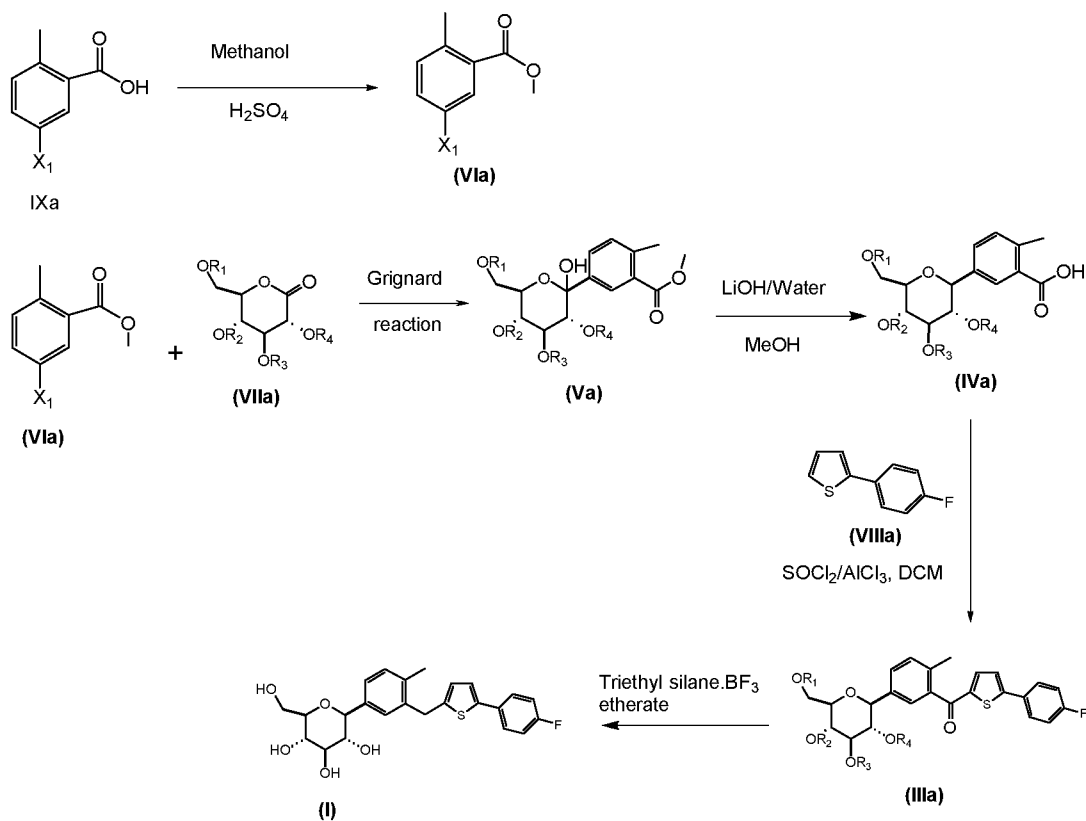
- 5 Suitable acids which may be employed for the esterification step to obtain the compound of formula IVd-2 include, but are not limited to, sulfuric acid, p-toluene sulfonic acid, methane sulfonic acid, methane disulfonic acid, benzenesulfonic acid, methanesulfonic acid, and the like.

- Suitable solvents which may be employed in the esterification step to obtain the compound of formula IVd-2 include, but are not limited to, one or more of alcohols, esters, ethers, nitriles, 10 tetrahydrofuran (THF), water, halogenated solvents, dimethylformamide, dimethyl sulfoxide, sulfolane, or any mixture thereof.

The esterification step is typically carried out at a temperature in the range of from about 0°C to about 100°C.

- 15 In another embodiment of the present invention, there is provided a process for the synthesis of canagliflozin of formula I, as shown in Scheme 3.

- According to the process shown in Scheme 3, a compound of formula VIIa is coupled with a compound of formula VIa to obtain a compound of formula Va, which is then subjected to reduction to obtain a compound of formula IVa. The compound of formula IVa is condensed with a 20 compound of formula VIIIa to obtain a compound of formula IIIa. The compound of formula IIIa is subsequently reduced and deprotected to obtain canagliflozin of formula I. Compound of formula VIa is obtained by esterification of compound of formula IXa.



Scheme 3

In the depicted Scheme 3, R₁, R₂, R₃ and R₄ are hydroxyl protecting groups and X₁ is halogen.

5

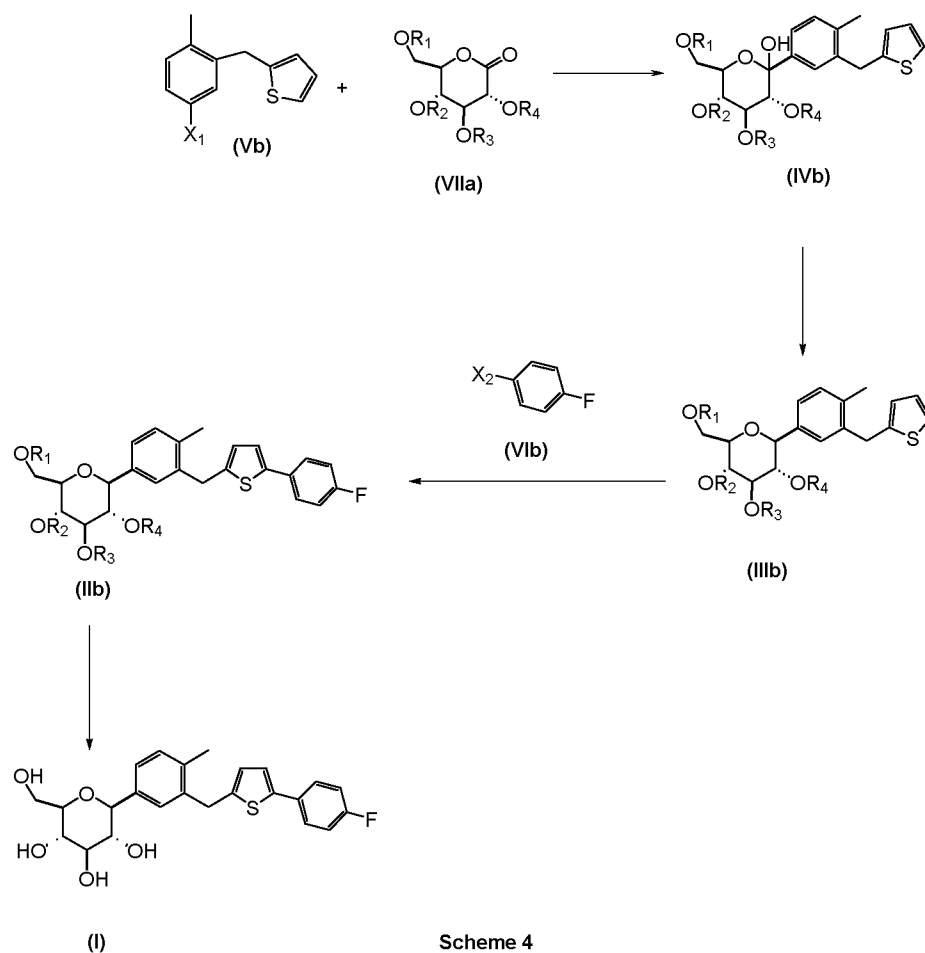
The compounds of formulae IVa and Va are hitherto novel intermediates useful in the process for the preparation of canagliflozin as described herein. In one aspect of the present invention, there is provided a compound of formula IVa or of formula Va, optionally for use as an intermediate in the preparation of canagliflozin.

10

In still another embodiment of the present invention, there is provided a process for the synthesis of canagliflozin of formula I, as shown in Scheme 4.

According to the process shown in Scheme 4, a compound of formula VIIa is coupled with a compound of formula Vb to obtain a compound of formula IVb, which is then subjected to reduction to obtain a compound of formula IIIb. The compound of formula IIIb is subsequently condensed with compound of formula VIb to obtain a compound of formula IIb, which is finally deprotected to obtain canagliflozin of formula I.

15



Scheme 4

In the depicted Scheme 4, R_1 , R_2 , R_3 and R_4 are hydroxyl protecting groups, and X_1 , and X_2 are halogen.

The compounds of formula IIIb and IVb are hitherto novel intermediates useful in the process for the preparation of canagliflozin as described herein.

The present invention will now be further illustrated with reference to the following examples, which do not limit the scope of the invention in any way.

Examples

Example 1 - Preparation of Compound of Formula-IIIc

- 5 Part-A: To a reaction mixture of 100 gm (0.2540 moles) compound of Formula-IV-c in 60 ml toluene, 399 ml (0.3553 moles) of sec-butyl magnesium chloride in lithium chloride complex (15% solution in THF) was charged at 0°C to -5°C and stirred for 2 hours.
- Part-B: The reaction mixture of 110.24 gm (0.3186 moles) of formula Vc (obtained by the protection of D-Gluconolactone using acetic anhydride/trifluoroacetic acid) in 300 ml toluene and
- 10 60.0 ml tetrahydrofuran was cooled to -35°C to -45°C and charged part-A solution slowly into the prepared reaction mixture and stirred for 30-45 minutes at -35°C to -45°C. Charged 20.0 ml Acetic acid and 80ml water until neutral pH of the reaction mixture. The temperature of the reaction mixture was raised to 30°C. Organic layer was separated. Extracted aqueous layer twice with 200 ml toluene. Organic layer was washed with saturated sodium bicarbonate solution and dried over
- 15 sodium sulphate. Solvent was distilled completely under vacuum below 50°C to obtain oily residue. The oily residue was stirred in 400ml acetonitrile and washed with 2 x 250ml methyl cyclohexane. The acetonitrile layer was employed in Example 2.

Example 2 - Preparation Compound of Formula-II

- 20 To acetonitrile layer (obtained in Example 1) and 88.10 gm (0.7709 moles) of triethylsilyl hydride at 30°C, 70.38 gm (0.4958 moles) of boron trifluoride etherate was charged. Reaction mixture was heated to 40°C to 42°C for 1.0 hours. Partially distilled acetonitrile under vacuum below 40°C. 680 ml methanol was charged to the residue and cooled to 10-15°C. pH was adjusted with 18.0 ml ammonium hydroxide to 7.2 to 8.0. Reaction mixture was stirred for 2-3hrs at 10-15°C. The solid
- 25 formed was filtered and recrystallized from isopropanol and acetone to obtain 73 gm of compound of Formula-II.

Example 3 - Preparation of Canagliflozin of Formula I

- 84 gm (0.1372 moles) of compound of Formula-II of Example 2 in 336 ml methanol and 8.89 gm
- 30 (0.1647 moles) of sodium methoxide was refluxed for 1hour. The refluxed mixture was cooled to 30°C and then further cooled to 10°C to 15°C. Dilute acetic acid (8.23 gm in 84 ml water) and 2100 ml of water was charged to the reaction mixture and stirred overnight. The product was filtered and washed with water under nitrogen to obtain 60.94 gm of canagliflozin of formula (I).

Example 4 - Preparation of Canagliflozin of Formula I

Step I - Preparation of Iodophenyl thiophene ketone

To a reaction mixture of 150 gm of iodobenzoic acid in 750ml of dichloromethane and 3.0 ml DMF at 30°C, 69.75 gm thionyl chloride was slowly charged. The reaction mixture was heated to reflux temperature of the solvent and stirred for 1 hour. The reaction mixture was cooled to 0°C to 5°C and was charged with 91 gm anhydrous AlCl₃, and 102 gm fluoro phenyl thiophene diluted in 300 ml dichloromethane. Stirred the reaction mixture at 30°C for 1 hour. The reaction mixture was quenched in crushed ice water mixture at 0-5°C. Organic layer was separated and washed with 750 ml saturated sodium bicarbonate solution. Dichloromethane was distilled under vacuum to obtain crude iodophenyl thiophene ketone. Crude iodophenyl thiophene ketone was recrystallized from 600 ml isopropanol to obtain 222 gm of Iodophenyl thiophene ketone.

Step II - Preparation of Compound of Formula-IVd-1 (R=OH)

To a reaction mixture containing 5.0 gm of Iodophenyl thiophene ketone (obtained in step I) in 25 ml tetrahydrofuran and 0.5 ml water at 30°C, 0.56 gm sodium borohydride was charged and stirred for 4 hour. 25ml of water was charged and the organic layer was separated. Tetrahydrofuran was and distilled off completely under vacuum to obtain 4.6 gm of compound of Formula-IVd-1 (R=OH).

Step III - Preparation of Compound of Formula-IVd-2 (R=OMe)

To a reaction mixture of 6.5 gm of Compound of Formula-IVd-1(R=OH) (obtained in step II) in 65ml methanol, 2.21 gm of methane sulfonic acid was charged at 30°C. The reaction mixture was stirred for 3 hour at 30°C. Organic solvent was distilled under vacuum. The residue obtained was extracted in ethyl acetate and the organic layer was washed with saturated sodium bicarbonate solution. Organic layer was distilled under vacuum to obtain 8.5 gm of compound of Formula-IVd-2 (R=OMe).

Step IV- Preparation of Compound of Formula-IIIId

Part-A: To a reaction mixture of 100 gm (0.2540 moles) compound of Formula-IVd-2 (R=OMe) (obtained in step III) in 60 ml toluene, 4.57 gm of sec-butyl magnesium chloride in lithium chloride (complex (15% solution in THF) was charged at 0°C to -5°C and stirred for 2.0 hours.

Part-B: The reaction mixture of 110.24 gm (0.3186 moles) of formula Vd (obtained by the protection of D-Gluconolactone using acetic anhydride/trifluoroacetic acid) in 300 ml toluene and 60.0 ml tetrahydrofuran was cooled to -35°C to -45°C and charged part-A solution slowly into the prepared reaction mixture and stirred for 30-45 minutes at -35°C to -45°C. Charged 20.0 ml acetic acid & 80ml water till neutral pH of the reaction mixture. The temperature of the reaction mixture was raised to 30°C. Organic layer was separated. Extracted aqueous layer twice with 200 ml toluene. Organic layer was washed with saturated sodium bicarbonate solution and dried over sodium sulphate. Solvent was distilled completely under vacuum below 50°C to obtain oily residue.

The oily residue was stirred in 400ml acetonitrile and washed with 2 x 250ml methyl cyclohexane. The acetonitrile layer was employed in step V.

Step V - Preparation Compound of Formula-IId

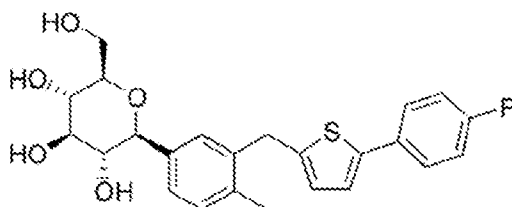
To acetonitrile layer (obtained in step IV) and 88.10 gm (0.7709 moles) of triethylsilyl hydride at 30°C, 70.38 gm (0.4958 moles) of boron trifluoride etherate was charged. Reaction mixture was heated to 40°C to 42°C for 1.0 hours. Partially distilled acetonitrile under vacuum below 40°C. 680 ml methanol was charged to the residue and cooled to 10-15°C. pH was adjusted with 18.0 ml ammonium hydroxide to 7.2 to 8.0. Reaction mixture was stirred for 2-3hrs at 10-15°C. The solid formed was filtered and recrystallized from isopropanol and acetone to obtain 73 gm of compound of Formula-IId.

Step VI - Preparation of Canagliflozin of Formula I

84 gm 0.1372 (moles) of compound of Formula-II d (obtained in step V) in 336 ml methanol and 8.89 gm (0.1647 moles) of sodium methoxide was refluxed for 1hour. The refluxed mixture was cooled to 30°C and then further cooled to 10°C to 15°C. Dilute acetic acid (8.23 gm in 84 ml water) and 2100 ml of water was charged to the reaction mixture and stirred overnight. The product was filtered and washed with water under nitrogen to obtain 60.94 gm of canagliflozin of formula (I).

Claims

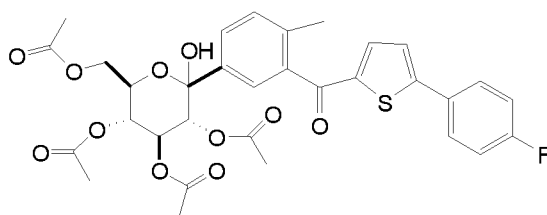
1. A process for preparing canagliflozin of formula I,



Formula I

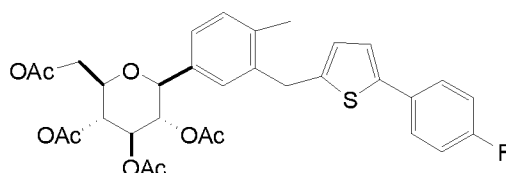
which process comprises the steps of:

reducing a compound of formula IIIc,



formula IIIc

with a suitable reducing agent, optionally in presence of a Lewis acid and/or a suitable organic solvent, to obtain compound of formula II,



formula II

; and

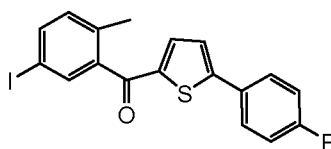
deprotecting the compound of formula II so formed to obtain a compound of formula (I).

2. A process according to claim 1 wherein the reducing agent is selected from the group consisting of silane reducing agents, borohydride reducing agents and aluminum hydride reducing agents.

3. A process according to claim 1 or claim 2 wherein the reducing agent is selected from the group consisting of triethyl silane, triisopropylsilane, sodium borohydride, potassium borohydride, zinc borohydride, sodium cyanoborohydride, sodium triacetoxymborohydride and lithium aluminum hydride.
4. A process according to claim 3 wherein the reducing agent is triethyl silane.
5. A process according to any preceding claim wherein the reduction step is carried out in the presence of a Lewis acid.
6. A process according to claim 5 wherein the Lewis acid is selected the group consisting of boron trifluoride etherate, trimethylsilyl triflate, titanium tetrachloride, tin tetrachloride, hydrochloric acid, toluenesulfonic acid, trifluoroacetic acid and acetic acid.
7. A process according to any preceding claim wherein the organic solvent employed in the reduction step is selected from the group consisting of ethers, nitriles, halogenated solvents, dimethylformamide, dimethyl sulfoxide, or any mixture thereof.
8. A process according to claim 7 wherein the organic solvent is acetonitrile.
9. A process according to any preceding claim wherein the reduction step is carried out at a temperature in the range from about -40°C to about 60°C.
10. A process according to any preceding claim wherein the compound of formula II is deprotected to obtain a compound of formula (I) with an acid or a base, optionally in the presence of a suitable solvent.
11. A process according to claim 10 wherein the base is selected from the group consisting of sodium methoxide, sodium ethoxide, sodium tert-butoxide and potassium tert-butoxide.
12. A process according to claim 10 or 11 wherein the acid or base is anhydrous.
13. A process according to claim 10, 11 or 12 wherein the solvent is an alcohol.

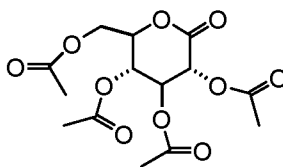
14. A process according to claim 13 wherein the solvent is methanol.

15. A process according to any preceding claim further comprising preparing the compound of formula IIIc by condensing a compound of formula IVc,



formula IVc

with a compound of formula Vc,



formula Vc

in presence of a Grignard reagent of formula RMX and a suitable metal ion complex, in one or more suitable organic solvents;

wherein R is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, alkoxy, aryloxy, thioalkoxy, thioaryloxy, carboxy, thiocarboxy, carbamate, thiocarbamate, amide, thioamide, carbonyl, thiocarbonyl, urea, and thiourea; M is any metal suitable for forming a Grignard reagent; and X is halide.

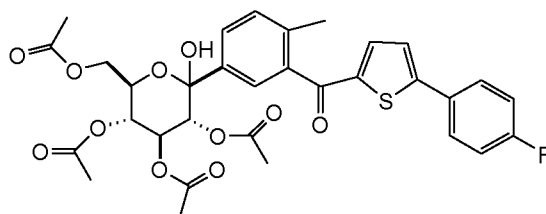
16. A process according to claim 15 wherein the Grignard reagent is selected from the group consisting of tert-butyl magnesium chloride, tert-butyl magnesium bromide, tert-amyl magnesium chloride, tert-amyl magnesium bromide, 1,1-diethylpropylmagnesium chloride, 1-methylcyclopentyl magnesium chloride and 1-methylcyclohexyl magnesium chloride, Sec-butyl magnesium chloride, ethyl magnesium bromide, methyl magnesium bromide, vinyl magnesium bromide, allyl magnesium bromide and ethynylmagnesium bromide.

17. A process according to claim 15 or 16 wherein the metal ion complex is selected from n-butyl lithium, sec butyl lithium and hexyl lithium.

18. A process according to any one of claims 15 to 17 wherein the organic solvent is selected from toluene, tetrahydrofuran (THF), diethyl ether, diglyme and methyl t-butyl ether.

19. A process according to any one of claims 15 to 18 wherein the Grignard reaction is carried out at a temperature in the range of from about -60°C to about 60°C.

20. A compound of formula IIIc,



formula IIIc

21. A compound of formula IIIc according to claim 20 for use as an intermediate in the preparation of canagliflozin of formula I

22. A pharmaceutical composition comprising canagliflozin of formula I prepared according to a process according to any one of claims 1 to 19, and a pharmaceutically acceptable excipient or carrier.

23. Canagliflozin of formula I prepared substantially as described herein with reference to the Examples.

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2015/053567

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D409/10
 ADD.

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)
 C07D

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)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X,P	CN 104 557 895 A (JIANGSU JIAYI PHARMACEUTICAL CO LTD) 29 April 2015 (2015-04-29) paragraph [[0008]] -----	1-23



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"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

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Date of the actual completion of the international search

15 January 2016

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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