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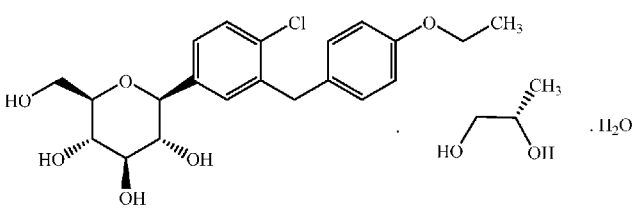
(54) Title: PROCESS FOR THE PREPARATION OF DAPAGLIFLOZIN



Formula II

(57) Abstract: The present invention discloses a novel process for the preparation of Dapagliflozin (S)-propylene glycol hydrate of Formula II. (Formula II)

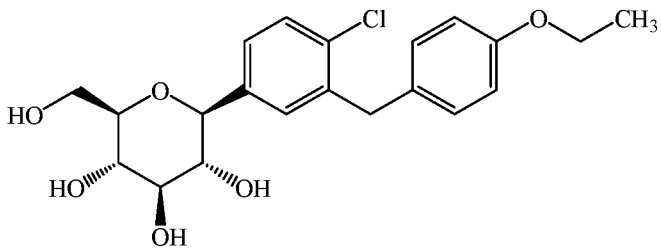
"PROCESS FOR THE PREPARATION OF DAPAGLIFLOZIN"

FIELD OF THE INVENTION:

The present invention relates to a novel process for the preparation of Dapagliflozin or its (S)-propylene glycol hydrate.

BACKGROUND OF THE INVENTION:

The compound (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol commonly known as dapagliflozin represented below as compound of Formula I, belongs to sodium-glucose co-transporter inhibitors (SGLTs).

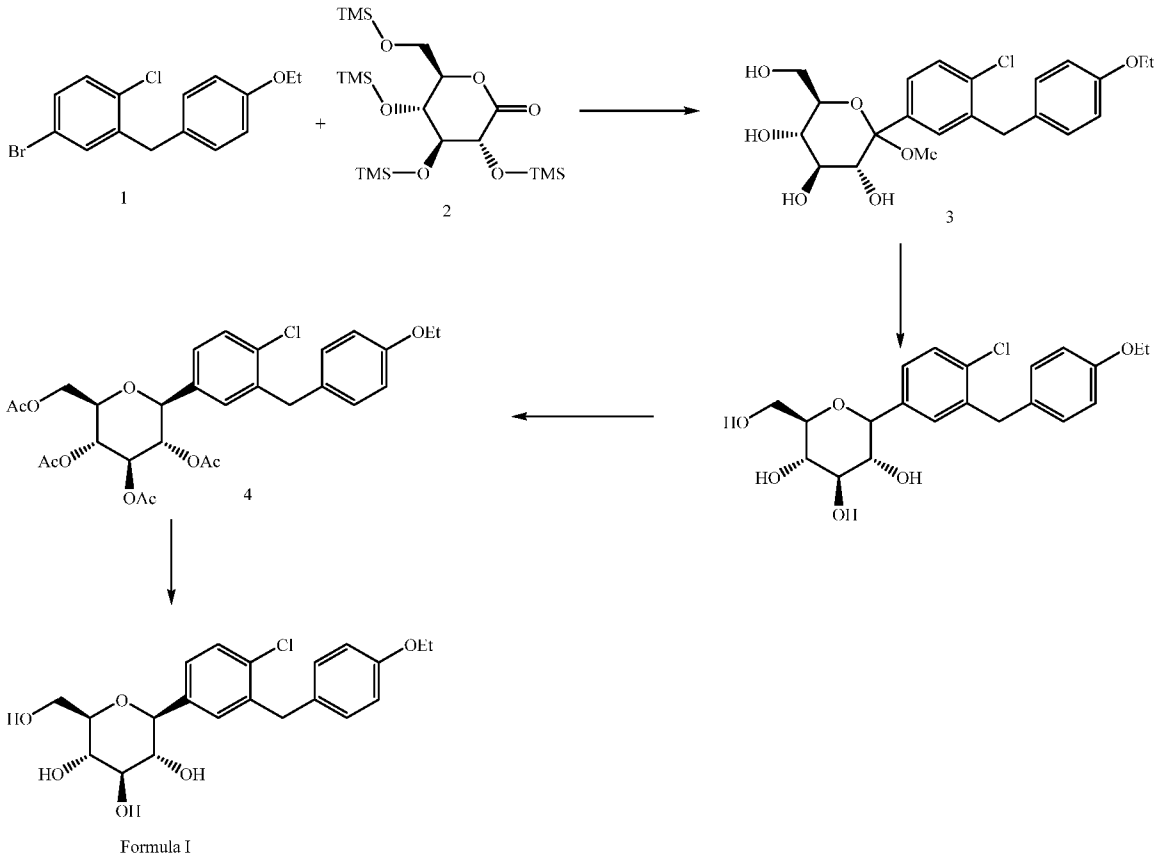


Formula I

SGLTs such as SGLT1 and SGLT2 inhibitors provide new therapeutic targets to reduce hyperglycemia in patients with diabetes. SGLT2 is responsible for reabsorption of most of the glucose filtered by the kidney. Inhibitors with varying specificities for these transporters can slow the rate of intestinal glucose absorption and increase the renal elimination of glucose into the urine.

Currently various SGLT2 inhibitor drugs have been approved or in clinical phase for treatment of type 2 diabetes. A significant numbers of SGLT2 are β-C-arylglucosides derived drug candidates, most of which comprises a central 1-deoxyglucose ring moiety that is arylated at C1. Dapagliflozin is one of the approved SGLT2 inhibitor which is marketed under the trade name Farxiga in U.S. and Forxiga in Europe.

Dapagliflozin and its pharmaceutically acceptable salts and process for their preparation are described in US 6,515,117 ("US'117 Patent). Process described in US'117 patent involves reacting 4-bromo-1-chloro-2-(4-ethoxybenyl)benzene compound 1 with 2,3,4,6-tetra-O-trimethylsilyl-D-gluconolactone compound 2, the intermediate formed on reaction with methanol and methanesulfonic acid results in desilylated O-methylglucoside compound 3. The compound 3 on demethoxylation yields diastereomeric mixture of Dapagliflozin. The diastereomeric mixture of Dapagliflozin is further acetylated with acetic anhydride in presence of pyridine and dimethylaminopyridine yields the acetylated compound 4. Compound 4 was recrystallized from absolute ethanol yielded the desired tetra-acetylated β-C-glucoside as a white solid. Compound tetra-acetylated β-C-glucoside is treated with lithium hydroxide hydrate, undergoes deprotection to yield the compound dapagliflozin of Formula I. The reaction is represented as in scheme 1 below;



Scheme 1

Process discloses, the reaction where after C-C bond formation resultant hemiketal formed is methylated using methanesulfonic acid. During the process trimethylsilyl groups get hydrolyzed. After demethoxylation compound, crude Dapagliflozin is protected again doing acetylation and the resultant compound is purified. After deacetylation the compound pure dapagliflozin of Formula I is isolated. The repeated protection and deprotection to isolate the required compound increases the number of process steps, thereby results in increasing the cost of production and thus affects economy of the process.

There are various patents, patent applications and journals viz., WO 2004063209, WO2007093610, US8952139, US7745414, US9193751, IN3942/CHE/2010, WO2010022313, Journal of Medicinal Chemistry, 51(5), 1145-1149 (2008), Journal of Medicinal Chemistry, 57(4), 1236-1251 (2014), Chinese Journal of Synthetic Chemistry, 18(3), 389-392 (2010), Organic Letters, 14(6), 1480-1483 (2012), which discloses the process for the preparation of dapagliflozin. Most of these processes involve glucose or gluconolactone moiety for the preparation of the required compound.

One of the processes discloses the protection of hydroxyl group of the gluconolactone moiety with acetyl group using controlled substance acetic anhydride. The protected gluconolactone is not available commercially and has to be prepared before the reaction.

Yet another process disclosed in the prior art, where the protection of hydroxyl group of the glucose moiety is carried out with pivaloyl chloride to get the compound pivaloyl-D-glucopyranose. Before the C-C bond formation, the pivaloyl-D-glucopyranose is reacted with bromine reagent to yield pivaloyl glucopyranosyl bromide compound which increases the number of steps and handling of bromine reagent.

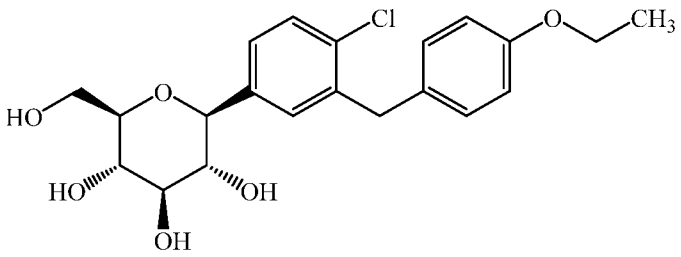
The drawbacks of the above prior arts are:

1. compounds glucose or gluconolactone when protected with pivaloyl, acetyl or trimethylsilyl groups need to be freshly prepared as the resultant compounds are unstable and not available on commercial scale;
2. lack of stereoselectivity during formation of β-C-aryl glucoside reduces the yield of the product;
3. process requires couple of protection and deprotection of the glucose moiety, or formation of complex for obtaining pure compound, which increases the number of steps and loss in yield of the final compound making the process uneconomical and cumbersome; and
4. glucose compound when protected with pivaloyl group requires the pivaloyl-D-glucopyranose compound to react with bromine reagent which increases the process cost and the number of steps and also involves the problem of handling of bromine reagent.

In view of the above, there remains a need for stereoselective, more efficient and economic process for the preparation of dapagliflozin the compound of Formula I. The present inventors ameliorates the prior art drawbacks by using the commercially available and stable Benzyl-D-glucopyranose moiety for the C-C bond formation yielding intermediate compound which does not undergo deprotection during condensation reaction in presence of base.

OBJECTIVE OF THE INVENTION:

The objective of present invention is to develop cost effective process employing industrially safe and readily available starting materials for the preparation of dapagliflozin compound of Formula I,

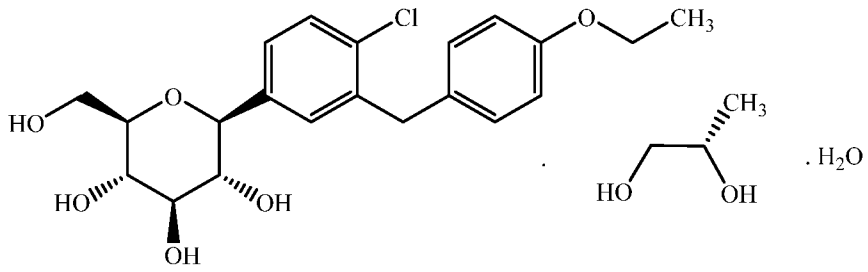


Formula I

Yet another objective of the present invention is to prepare dapagliflozin with stereoselective orientation to obtain more of β-anomer.

Yet another objective of the present invention is to carry out debenzylation using easily available cost effective reagent.

Yet another objective of the present invention is to prepare the compound Dapagliflozin (S)-propylene glycol hydrate of Formula II

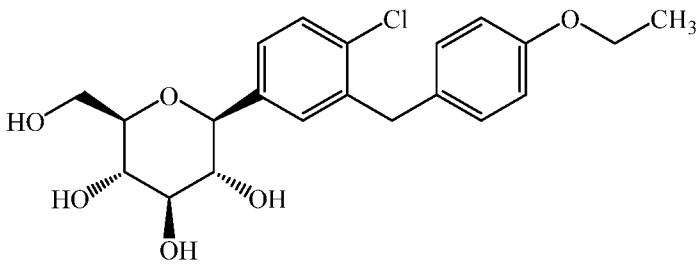


Formula II

SUMMARY OF THE INVENTION:

Accordingly, the present invention provides a process for preparing dapagliflozin, the compound of Formula I using readily available, cost effective, and industrially safe starting materials.

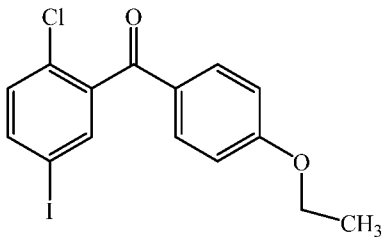
Accordingly the present invention provides a process for the preparation of dapagliflozin the compound of Formula I or its (S)-propylene glycol hydrate,



Formula I

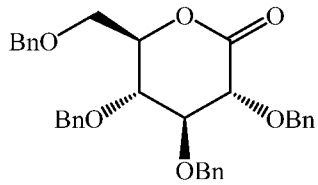
which process comprises;

a) reacting the compound (2-chloro-5-iodophenyl)(4-ethoxyphenyl)methanone of Formula III



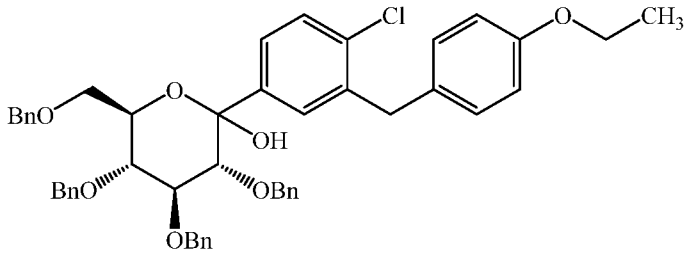
Formula III

with the compound (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl) tetrahydro-2H-pyran-2-one of Formula IV



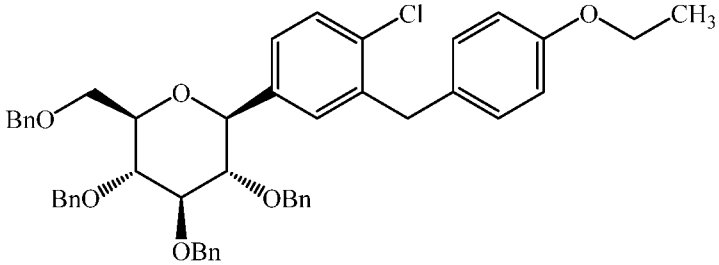
Formula IV

to obtain the compound (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2H-pyran-2-ol of Formula V;



Formula V

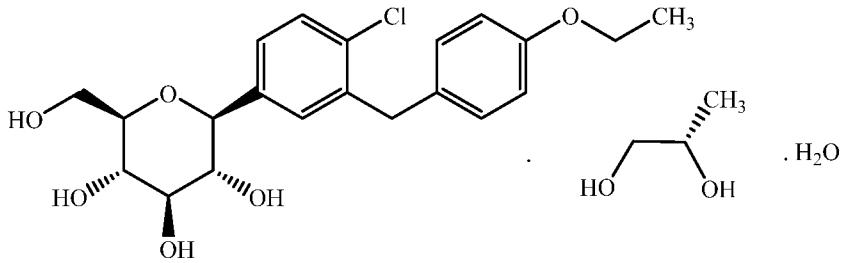
b) reacting the compound of Formula V with a reducing reagent and boron trifluoride-diethyl etherate in presence of solvent to obtain the compound (2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl) tetrahydro-2H-pyran of Formula VI;



Formula VI

c) deprotecting the compound of Formula VI using deprotecting reagent in presence of solvent to optionally isolate the compound (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol of Formula I (Dapagliflozin);

d) crystallising the compound of Formula I, with (S)-propylene glycol in presence of solvent to isolate corresponding solvate, dapagliflozin (S)-propylene glycol hydrate compound of formula II; and



Formula II

e) purifying the compound of Formula II in suitable solvent to isolate pure compound of Formula II.

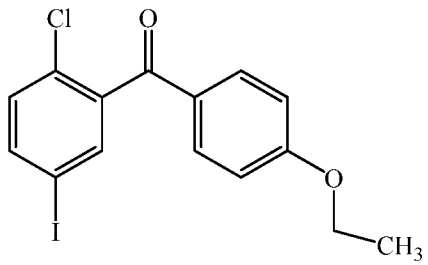
These and the other objects of the present invention will be apparent from the following detailed description.

DETAILED DESCRITION OF THE INVENTION:

Unless specified otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art, to which this invention belongs. To describe the invention, certain terms are defined herein specifically as follows.

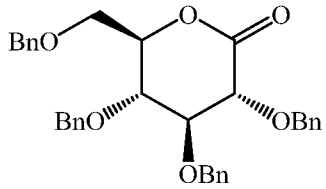
In an aspect, the present invention relates to a process for the preparation of dapagliflozin, the compound of Formula I or its (S)-propylene glycol hydrate of formula II, which process comprises the steps of:

a) reacting the compound (2-chloro-5-iodophenyl)(4-ethoxyphenyl)methanone of Formula III



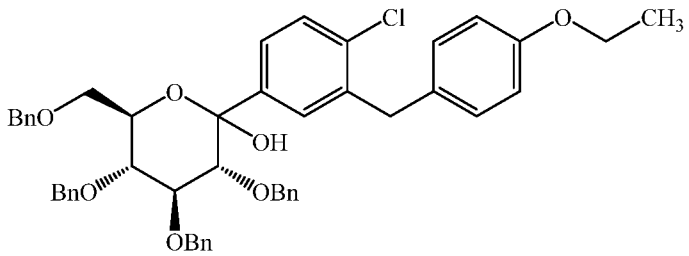
Formula III

with the compound (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-one of Formula IV



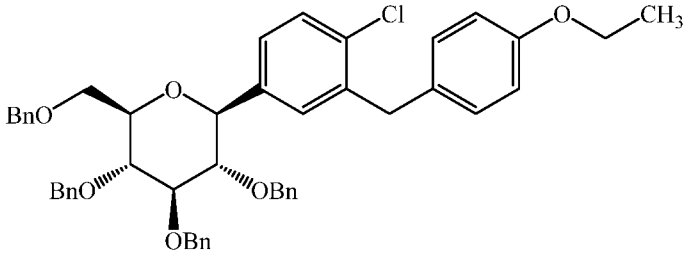
Formula IV

to obtain the compound (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2H-pyran-2-ol of Formula V;



Formula V

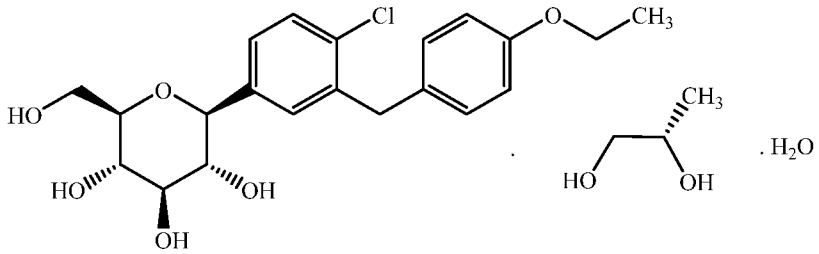
b) reacting the intermediate compound of Formula V with a reducing reagent and boron trifluoride-diethyl etherate in presence of solvent to obtain the compound (2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2H-pyran of Formula VI;



Formula VI

c) deprotecting the compound of Formula VI using deprotecting reagent in presence of solvent to optionally isolate the compound (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol of Formula I (Dapagliflozin);

d) crystallising the compound of Formula I, with (S)-propylene glycol in presence of solvent to isolate the corresponding solvate, dapagliflozin (S)-propylene glycol hydrate compound of formula II; and



Formula II

e) purifying the compound of Formula II in suitable solvent to isolate pure compound of Formula II.

In an embodiment of the present invention in step (a) the compound (2-chloro-5-iodophenyl)(4-ethoxyphenyl)methanone of Formula III is reacted with the compound (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-one of Formula IV in presence of a reagent selected from the group consisting of phenylsilane, tri-n-propylsilane, dimethylphenylsilane, polymethylhydroxysilane, triethylsilane, tris(trimethylsilyl)silane, triisobutylsilane, triphenylsilane, tert-butyldimethylsilane, triisopropylsilane, diisobutylaluminium hydride, lithium aluminum hydride, sodium borohydride, boron trifluoride-diethyl etherate and titanium tetrachloride. The preferred reagent used are selected from triethylsilane, phenylsilane, tris(trimethylsilyl)silane, boron trifluoride-diethyl etherate and titanium tetrachloride. The reaction is carried out in presence of a solvent selected from the group consisting of dichloromethane, dichloroethane, acetonitrile, toluene, tetrahydrofuran, diethyl ether or a mixture thereof. The reaction is carried out at the temperature in the range of -80°C to 30°C. The preferred temperature

of the reaction is in the range of 10°C to 30°C. After completion of the reaction, the reaction mass is quenched with water and diluted with toluene. Stirred and separated the organic layer, charged the compound (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl) tetrahydro-2H-pyran-2-one of Formula IV and tetrahydrofuran. Charged a base selected from the group consisting of n-butyllithium, Mg-diisobutylaluminium hydride (Mg-DIBAL-H), isopropyl magnesium chloride-LiCl and 2,2,6,6-tetramethylpiperidide-MgCl-LiCl (TMPMgCl-LiCl). The preferred temperature range for the reaction is -80°C to -30°C, wherein the most preferred temperature range for the reaction is -80°C to -60°C. After completion of the reaction, the reaction mass is quenched with dilute solution of mild base selected from the group consisting of sodium bicarbonate, sodium carbonate, potassium carbonate and potassium bicarbonate. The organic layer is separated and extracted the aqueous layer with toluene. Combined toluene layer was washed with brine solution and concentrated under reduced pressure to get the residual mass of the compound (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2H-pyran-2-ol of Formula V. The compound of Formula V is further purified using solvent selected from the group consisting of methanol, ethanol, isopropyl alcohol and butanol to isolate the pure compound (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl) tetrahydro-2H-pyran-2-ol of Formula V.

The compound (2-chloro-5-iodophenyl)(4-ethoxyphenyl)methanone of Formula III used in the present invention can be procured commercially or can be prepared as per the process disclosed in the prior art.

The compound (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-one of Formula IV used in the reaction of the present invention is prepared form commercially available compound 2,3,4,6-tetra-O-benzyl-D-glucopyranose, the compound 5. The compound 5 is subjected to oxidation using sodium hypochlorite solution in

presence of buffer, catalyst and solvent medium to prepare solution of 2,3,4,6-tetra-O-benzyl-D-gluconolactone by maintaining the temperature of the reaction at -5°C to 30°C and pH of the reaction at 7.0 to 8.0. The solvent used in the reaction is selected from group consisting of dichloromethane, dichloroethane, chloroform, toluene, xylene, tetrahydrofuran, ether, water either alone or in combinations thereof. The preferred buffer used for the reaction is sodium bicarbonate and acetic acid. The catalyst used for the reaction is 2,2,6,6-teteamethylpiperidine-1-oxyl either alone or in combination with potassium bromide. The reaction completion is monitored on HPLC. The reaction mass is quenched by adding aqueous sodium thiosulphate solution. The reaction is worked up by separating the organic layer and concentrated to obtain residual mass of the compound 2,3,4,6-tetra-O-benzyl-D-gluconolactone of Formula IV.

In yet another embodiment of the present invention, the reaction of step (b), the compound of (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-chloro-3-(4-ethoxybenzyl)- phenyl)tetrahydro-2H-pyran-2-ol of Formula V, as obtained in the above step (a) is subjected to reduction of hemiketal using a reducing reagent and boron trifluoride-diethyl etherate in presence of a solvent to obtain the intermediate compound (2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl) tetrahydro-2H-pyran of Formula VI.

In an embodiment of the present invention, the reducing reagent used for reduction of hemiketal is selected from group of reagents, such as phenylsilane, tri-n-propylsilane, dimethylphenylsilane, triethylsilane, tris(trimethylsilyl)silane, triisobutylsilane, triphenylsilane, tert-butyldimethylsilane, triisopropylsilane and diisobutylaluminium hydride. The preferred reagent that can be used for the reduction are triethylsilane, phenylsilane, and tris(trimethylsilyl)silane, whereas the most preferred reagents for the reduction used is triethylsilane. The solvent used for the reduction reaction is selected from the group of solvents consisting of dichloromethane, dichloroethane, toluene, xylene tetrahydrofuran, ether, ethyl

acetate and acetonitrile either alone or mixture thereof. The reaction is carried out at temperature in the range of 20°C to 30°C. The completion of reaction is monitored on TLC/HPLC. After completion the reaction is quenched with water and neutralised the quenched mass with ammonia solution. Separated the organic layer, washed and concentrated the solvent under vacuum at 40°C to 45°C to get the residual mass.

In an embodiment of the present invention the residual mass is treated with a solvent selected from the group consisting of methanol, ethanol, isopropyl alcohol, butanol, acetone and ethyl acetate either alone or in combinations thereof to isolate the compound (2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetra- hydro-2H-pyran of Formula VI.

In yet another embodiment of the present invention, the reaction of step (c), the compound (2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-chloro-3-(4-ethoxy-benzyl)phenyl)tetrahydro-2H-pyran of Formula VI, as obtained in the above step (b) is subjected to deprotection / debenzylation using deprotection reagents selected from sodium iodide/boron trifluoride-diethyl etherate or Palladium/carbon or iodotrimethylsilane or palladium hydroxide/carbon reagent in presence of a solvent selected from the group consisting of acetonitrile, methanol, ethanol, isopropanol, tetrahydrofuran, diethyl ether, toluene, dichloromethane, dichloroethane and water or in combinations thereof to yield the compound of Formula I.

In an embodiment of the present invention the preferred deprotection reagent is sodium iodide/boron trifluoride-diethyl etherate. The temperature of the reaction is maintained in the range of 0°C to 40°C for 3 to 5 hours. The reaction is monitored on HPLC for the completion. After completion of the reaction the reaction mixture is quenched with triethyl amine at 25°C to 30°C and stirred for four hours, the precipitated solid mass is filtered. Charged the wet solid mass in water and made the pH acidic by using concentrated hydrochloric acid. The

product is extracted using the solvent selected from the group consisting of methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate and isopropyl acetate, wherein the preferred solvent used is methyl isobutyl ketone. The organic layer is washed with water. The solvent is concentrated under reduced pressure till half of the volume.

In an embodiment of the present invention, to the concentrated solution, (S)-propylene glycol is charged and stirred. An anti-solvent selected from the group consisting of n-hexane, n-heptane and cyclohexane is added to isolate the crude compound dapagliflozin (S)-propylene glycol hydrate of formula II.

In an embodiment of the present invention, the crude compound dapagliflozin (S)-propylene glycol hydrate of formula II is purified using the solvents selected from the group consisting of ethyl acetate, methanol, methyl ethyl ketone, methyl isobutyl ketone, isopropyl acetate and water either alone or in combinations thereof. To the clear solution of dapagliflozin (S)-propylene glycol hydrate of formula II charged (S)-propylene glycol solvent, water and an anti-solvent selected from the group of solvents such as n- hexane, n-heptane and cyclohexane to precipitate the pure product. The precipitated product is filtered to isolate the pure compound dapagliflozin (S)-propylene glycol hydrate of Formula II.

The present invention is further illustrated in detail with reference to the following examples. It is desired that the examples be considered in all respects as illustrative only and non restrictive to the invention.

EXAMPLES:

Example 1: Synthesis of (2-chloro-5-iodophenyl)(4-ethoxyphenyl)methanone of Formula III:

Charged 2-chloro-5-iodobenzoic acid (200 gm, 0.7080 moles), dichloromethane (1000 ml) and N,N-dimethylformamide (5 ml) at 25°C to 30°C. Under stirring

slowly charged oxalyl chloride (107.9 gm, 0.8496 moles) and maintained stirring for one hour. Applied cooling and cooled the reaction mass to -15°C to -10°C. Charged aluminum chloride (113.29gm, 0.8496 moles) maintaining the reaction mass temperature at -10°C to -5°C and stirred for 30 minutes. Charged phenatole (86.49gm, 0.7080 moles) to the reaction mixture and maintained under stirring for 2 hours at -10°C to -5°C. The progress of the reaction was monitored by HPLC. After completion of the reaction the reaction mixture was quenched by adding water and dilute hydrochloric acid. Raised the temperature of the reaction mixture to 25°C to 30°C and maintained for 30 minutes. Separated the organic layer, extracted the aqueous layer again with dichloromethane (400 ml). The combined organic layer was washed with 10% of sodium bicarbonate solution (600 ml) followed with 5% brine solution (600 ml). Concentrated the organic layer under reduced pressure maintaining temperature below 45°C to get the residual mass. Charged methanol (1000 ml), heated to reflux and maintained for 3 hours. Cooled the reaction mass to 25°C - 30°C, filtered the solid and dried till constant weight to get (2-chloro-5-iodophenyl)(4-ethoxyphenyl)methanone.

Yield = 201 gm (73.47%).

Example 2 : Synthesis of (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)- tetrahydro-2H-pyran-2-one of Formula IV:

To water (400 ml) charged sodium bicarbonate (53.44 gm) and stirred. To the solution charged acetic acid (26.63 gm) and potassium bromide (1.6 gm), stirred for 15 minutes. Charged solution of 2,3,4,6-tetra-O-benzyl-D-glucopyranose (200gm, 0.37 moles) in dichloromethane (1000 ml) to the reaction mass and cooled to maintain the temperature at 20°C - 25°C. Charged 2,2,6,6-tetramethylpiperidine-1-oxyl (0.8 gm.) to the reaction mass. Maintaining the temperature slowly charged 10% sodium hypochlorite solution (325 gm, 0.436 moles) and maintained the temperature between 20°C to 35°C. The progress of the reaction was monitored by HPLC. After completion of the reaction the reaction mixture was quenched by adding aqueous solution of sodium thiosulphate (50 gm in 200 ml water). Reaction mixture was stirred for 30

minutes. Separated the organic layer and again aqueous layer was extracted with dichloromethane (400 ml). The combined organic layer was washed with 10% brine solution (2 x 600 ml) and concentrated the organic layer under reduced pressure to get the compound (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl) tetrahydro-2H-pyran-2-one of Formula IV.

Yield = 306 gms (95.98%).

Example 3: Synthesis of (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2H-pyran-2-ol of Formula V:

Charged under nitrogen atmosphere (2-chloro-5-iodophenyl)(4-ethoxyphenyl)methanone (200 gm, 0.5173 moles) and acetonitrile (800 ml).The reaction mass cooled to 10°C-15°C and under stirring charged triethylsilane (210.54 gm, 1.810 moles) and followed by a slow addition of boron trifluoride-diethyl etherate (146.85, 1.037 moles). After addition was complete raised the temperature to 25°C to 30°C and maintained the reaction mixture for 2.0 hours. The reaction progress was monitored on TLC. After complete reaction, the reaction mass was quenched with water (600 ml) and distilled out solvent under reduced pressure maintaining temperature below 55°C. Charged water (400 ml) and toluene (600 ml) and stirred reaction mass for 30 minutes. Separated the organic layer and extracted the aqueous layer again with toluene (400 ml). The combined organic layers washed with diluted ammonia solution (600 ml) and further washed with 10% brine solution (600 ml), the organic layer was concentrated under vacuum at 40°C - 45°C till volume of the reaction mass reduces to half; charged the compound (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-one (306 gms, 0.5681 moles) and tetrahydrofuran (400 ml), under nitrogen atmosphere. Applied cooling to the resulting mixture to about -70°C and charged n-butyllithium in hexane 1.6M (420.53 ml, 0.6724 moles) maintaining the temperature at -70°C to -60°C.The reaction progress was monitored by HPLC. After the reaction completion, quenched the reaction with 10% sodium bicarbonate solution (600 ml) and raised

the temperature slowly to attain 25°C to 30°C. The organic layer separated and extracted the aqueous layer with toluene (400 ml). The combined organic layer washed with (10%) brine solution (600 ml) and concentrated under reduced pressure to get the residual mass. Charged methanol (2000 ml) to the residual mass raised the temperature to reflux and maintained. Cooled the reaction mass to 25°C to 30°C and filtered the solid to isolate (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2H-pyran-2-ol of Formula V.

Yield = 246gm (60.09%).

Example 4: Synthesis of (2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2H-pyran of Formula VI.

Charged under nitrogen atmosphere (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2H-pyran-2-ol (200 gm, 0.02546 moles) to the mixture of solvents ethyl acetate (1000 ml) and acetonitrile (200 ml). Cooled the reaction mass to 20°C to 25°C and maintained. Charged triethylsilane (44.4 gm, 0.3819 moles) and followed by a slow addition of boron trifluoride-diethyl etherate (54.21 gm, 0.3819 moles). Maintained the reaction mixture under stirring for 2.0 hours at 25°C to 30°C. The reaction progress was monitored on TLC. After complete reaction the reaction mass was quenched with water (600ml) and adjusts pH~7-10 of reaction mixture using 25% ammonia solution. Separated the organic layer and extracted the aqueous layer with ethyl acetate (400 ml). The combined organic layers washed with 10% brine solution (400 ml). Concentrated the organic layer under reduced pressure maintaining the temperature below 45°C to get the residual mass. Charged methanol (800 ml) and acetone (320 ml) to the residual mass and stirred. Raised the temperature of the reaction mass to reflux and maintained. Charged additional methanol (1200 ml) to the reaction mass and cooled to 40°C to 45°C. Maintained at 40°C to 45°C under stirring for 3 hours. Cooled the reaction mass to 25°C to 30°C and filtered the separated solid, washed the solid mass and dried

till constant weight to get (2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2H-pyran of Formula VI.

Yield = 130 gm (66.35 %).

Example 5: Preparation of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (S)-propylene glycol solvate hydrate:

Charged (2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2H-pyran (100 gm, 0.1299 moles) to acetonitrile (700 ml) and stirred. Charged sodium iodide (200 gm, 1.335 moles), water (25 ml) and boron trifluoride-diethyl etherate (226 gm, 1.592 moles) at 25°C to 30°C. The reaction mixture was stirred maintaining temperature at 30°C to 35°C for 3 hours. The completion of reaction was monitored on TLC. After reaction completion, the reaction mixture was quenched by adding triethylamine (250 ml) maintaining temperature at 25°C to 30°C and stirred for 4 hours. Filtered the solid mass, charged the wet cake in water (500 ml) and adjusted the pH~2-3 using conc. hydrochloric acid. The solution was extracted with methyl isobutyl ketone (500 ml) and separated the organic layer. The aqueous layer was further extracted with methyl isobutyl ketone (500 ml). Combined the organic layer, washed with water (3 x 300 ml) and concentrated the solvent under reduced pressure up to half the volume. To the solution charged (S)-propylene glycol (10.38, 0.1364 moles), water (3 ml) and stirred. Charged cyclohexane (500 ml) to precipitate the solid mass. Filtered the solid washed and dried the product till constant weight to isolate crude (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (S)-propylene glycol solvate hydrate **(Dapagliflozin (S)-propylene glycol hydrate).**

Yield: 49.0gm (75.07%);

Purity by HPLC: 99.23%.

Purification of Dapagliflozin (S)-propylene glycol hydrate:

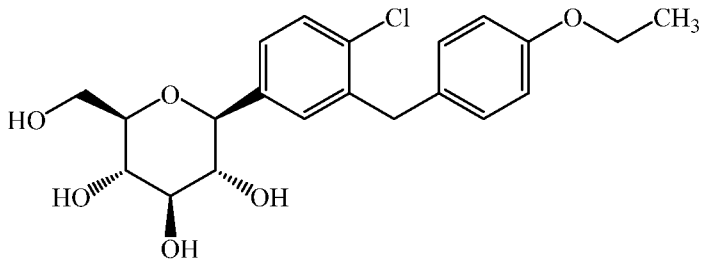
Charged crude dapagliflozin (S)-propylene glycol hydrate (40 gm) in methyl isobutyl ketone (400 ml). Raised the temperature under stirring to 50°C to 55°C. To the solution charged activated charcoal (2.0 gm) and stirred for 30 minutes. Filtered charcoal through hyflo bed. To the filtrate charged (S)-propylene glycol (3.04 gm, 0.0399 moles) and water (0.8 ml), stirred the reaction solution. Charged cyclohexane (80 ml) at 25°C to 30°C and stirred. Filtered the solid mass, washed and dried to get the pure compound Dapagliflozin (S)-propylene glycol hydrate.

Yield = 35.20 gm (88.0%);

Purity by HPLC: 99.80%.

We Claims,

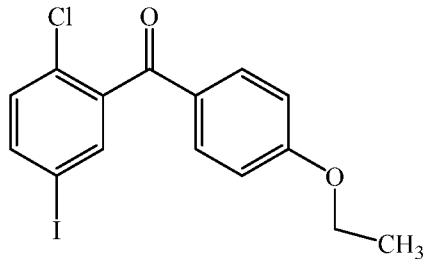
1. A process for the preparation of dapagliflozin, the compound of Formula I or its (S)-propylene glycol hydrate,



Formula I

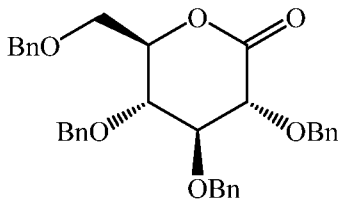
which comprises the steps of:

a) reacting the compound (2-chloro-5-iodophenyl)(4-ethoxyphenyl)methanone of Formula III



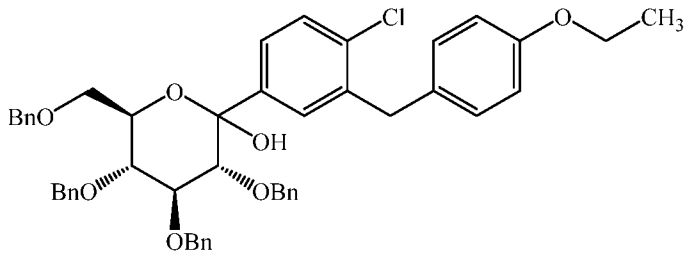
Formula III

with the compound (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl) tetrahydro-2H-pyran-2-one of Formula IV



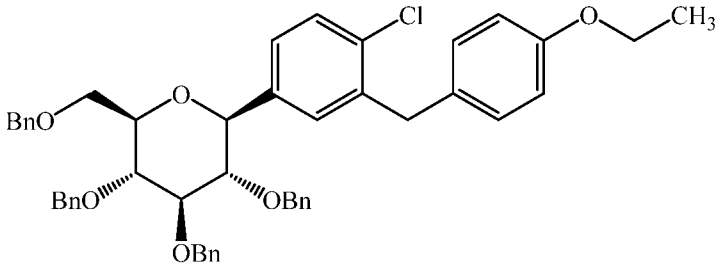
Formula IV

to obtain the compound (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2H-pyran-2-ol of Formula V;



Formula V

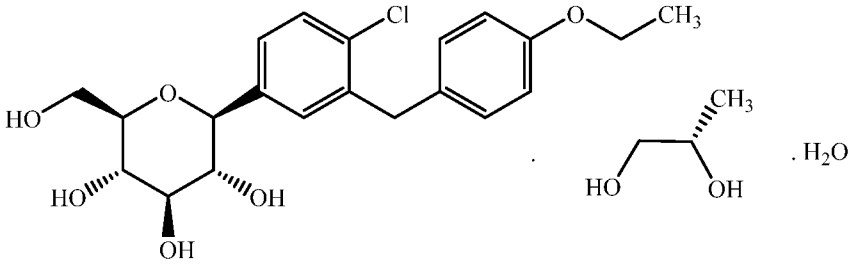
b) reacting the compound of Formula V with a reducing reagent and boron trifluoride-diethyl etherate in presence of solvent to obtain the compound (2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2H-pyran of Formula VI;



Formula VI

c) deprotecting the compound of Formula VI using a deprotecting reagent in presence of solvent to optionally isolate the compound (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (Dapagliflozin) of Formula I;

d) crystallising the compound of Formula I with (S)-propylene glycol in presence of solvent to isolate the corresponding solvate dapagliflozin (S)-propylene glycol hydrate compound of formula II; and



Formula II

e) purifying the compound of Formula II in suitable solvent to isolate pure compound of Formula II.

2. The process according to claim 1, wherein the reaction in step (a) is carried out in the presence of solvent selected from the group consisting of dichloromethane, dichloroethane, acetonitrile, toluene, tetrahydrofuran, diethyl ether, or a mixture thereof.
3. The process according to claim 1, wherein the reaction in step (a) is carried out in presence of reagents selected from the group consisting of phenylsilane, polymethylhydroxysilane, tri-n-propylsilane, dimethylphenylsilane, triethylsilane, tris(trimethylsilyl)silane, triisobutylsilane, triphenylsilane, tert-butyldimethylsilane, triisopropylsilane, diisobutylaluminium hydride, lithium aluminum hydride, sodium borohydride, boron trifluoride-diethyl etherate and titanium tetrachloride or mixture thereof.
4. The process according to claim 1, wherein, the reaction of step (a) is carried out in presence of a base selected from the group consisting of n-butyllithium, Mg-DIBAL-H, TMPMgCl-LiCl and isopropyl magnesium chloride-LiCl.
5. The process according to claim 1, wherein, the reaction of step (a) is carried out at a suitable temperature, ranging from -80°C to 30°C.
6. The process according to claim 1, wherein, the reaction of step (a) is carried out at a suitable temperature, preferably at a temperature ranging from -80°C to -30°C.
7. The process according to claim 1, wherein the reducing reagent used in step (b) is selected from the group consisting of phenylsilane, tri-n-propylsilane, dimethylphenylsilane, triethylsilane, tris(trimethylsilyl)silane, triisobutylsilane, triphenylsilane, tert-butyldimethylsilane, triisopropylsilane and diisobutylaluminium hydride.
8. The process according to claim 1, wherein the solvent used in step (b) is selected from the group consisting of dichloromethane, dichloroethane,

toluene, xylene tetrahydrofuran, ether, ethyl acetate and acetonitrile either alone or mixture thereof.

9. The process according to claim 1, wherein the deprotection agent of step (c) is selected from the group consisting of sodium iodide/boron trifluoride-diethyl etherate or Palladium/carbon or iodotrimethylsilane or palladium hydroxide/carbon.
10. The process according to claim 1, wherein the deprotection reaction in step (c) is carried out in presence of solvent selected from the group consisting of acetonitrile, methanol, ethanol, isopropanol, tetrahydrofuran, diethyl ether, toluene, dichloromethane, dichloroethane and water or in combinations thereof.
11. The process according to claim 1, wherein the crystallisation in step (d) is carried out in presence of solvent selected from the group consisting of ethyl acetate, methanol, methyl ethyl ketone, methyl isobutyl ketone, isopropyl acetate and water either alone or in combinations thereof.
12. The process according to claim 1, wherein the crystallisation in step (d) involves use of anti-solvent selected from the group consisting of n-hexane, n-heptane and cyclohexane.
13. The process according to claim 1, wherein purification of the compound of Formula II in step e) is carried out using a solvent selected from the group consisting of ethyl acetate, methanol, methyl ethyl ketone, methyl isobutyl ketone, isopropyl acetate, water, (S)-propylene glycol and an anti-solvent is selected from the group consisting of n-hexane, n-heptane, cyclohexane either alone or in combinations thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2018/050048

A. CLASSIFICATION OF SUBJECT MATTER
C07D309/10 Version=2018.01

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)

TotalPatent One, Google Patents

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US9193751 B2 (THERACOS INC) 24 NOVEMBER 2015 (24-11-2015); cited in the application; the whole document; particularly, example 22	1-13
Y	WO2015132803 A2 (MSN LAB PRIVATE LTD) 11 SEPTEMBER 2015 (11-09-2015); scheme, page 8; examples	1-13
Y	US6515117 B2 (SQUIBB BRISTOL MYERS CO) 04 FEBRUARY 2003 (04-02-2003); cited in the application; scheme 2, page 9-10; example	1-13
Y	WO2004063209 A2 (SQUIBB BRISTOL MYERS CO) 29 JULY 2004 (29-07-2004); cited in the application; examples 16-20	1-13

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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"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	Date of mailing of the international search report
27-04-2018	27-04-2018
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Manganna Dora Sambha Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2018/050048

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