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(54) Title: PROCESS FOR PREPARATION OF NEBIVOLOL AND IT'S SALTS

(57) Abstract: The present invention discloses a new process for preparation of Nebivolol or it's pharmaceutically acceptable salt. More particularly, the invention discloses an improved economical process for the preparation of intermediate, 6-fluoro-3,4- dihydro-2H-1-benzopyran-2-carboxaldehyde of Formula – II, converting the 6- fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde of Formula – II into mixture of [R*(S*)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran and [R*(R*)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran of Formula-V and separation of diastereomers of (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)- 2H-benzopran by forming azeotrope.

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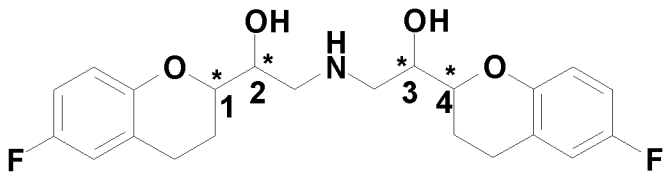
"PROCESS FOR PREPARATION OF NEBIVOLOL AND IT'S SALTS"

Field of the invention:

The present invention relates to a new process for preparation of Nebivolol or it's pharmaceutically acceptable salt. More particularly, the invention relates to an improved economical process for the preparation of intermediate, 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde of Formula – II, converting the 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde of Formula – II into mixture of [R*(S*)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran and [R*(R*)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran of Formula-V and separation of diastereomers of (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopran by forming azeotrope.

Background of Invention:

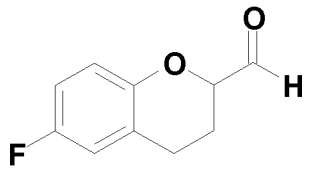
Nebivolol is chemically known as (±)(αR*,α'R*,2R*,2'S*)-α,α'-[iminobis(methylene)]bis[6-fluoro-3,4-dihydro-2H-l-benzopyran-2-methanol] having Formula.



The Nebivolol structure has four stereogenic centers, which are indicated as 1, 2, 3 and 4. Nebivolol is a mixture of equal amounts of two enantiomers having (S,R,R,R) and (R,S,S,S) configuration.

Nebivolol is useful in the treatment and prevention of coronary vascular disorders.

Nebivolol is first disclosed in U.S Patent no. 4,654,362. This patent discloses a process for preparing Nebivolol using a key intermediate, 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde of Formula – II.



Formula-II

In the '362 patent, 6-Fluoro-4-oxo-4H-chromene-2-carboxylic acid is reduced with hydrogen in presence of 10% Pd/C catalyst to obtain 6-fluoro-3,4-dihydro-2H-chromene-2-carboxylic acid. The 6- fluoro-3,4-dihydro-2H-chromene-2-carboxylic acid is esterified with ethanolicHCl to obtain corresponding ethyl ester of 6-fluoro-3,4-dihydro-2H-chromene-2-carboxylic acid which is reduced with sodium dihydro-bis(2-methoxyethoxy)aluminate (also known as vitride) in benzene at reflux conditions to obtain (6-fluoro-3,4-dihydro-2H-chromen-2-yl)methanol, which is further reacted with oxalyl chloride in a mixture of dichloromethane and dimethyl sulfoxide at -60°C to obtain6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde.This carboxaldehyde is further reacted with trimethylsulfoxonium iodide to obtain mixture of RS/SR & RR/SS of 6-Fluoro-3,4-dihydro-2-oxiran-2-yl-2H-benzopran. The stereoisomers are separated by chromatorgraphy into two racemic mixtures (R,S)-, (S,R)-epoxides (Mixture A) and (S,S)-, (R,R)-epoxides (Mixture B). The separated isomers are further converted into Nebivolol.

However this process involves corrosive chemicals such as oxalylchlorideand chromatography method is involved to separate the isomers. The chromatography method is not industrially feasible and economically unviable.

Later publication, WO 2006/025070 describes an improved process for Nebivolol synthesis wherein the diasteomeric mixture of RS/SR & RR/SS of 6-Fluoro-3,4-dihydro-2-oxiran-2-yl-2H-benzopran are separated into the known mixture Aand mixture B by using column chromatography.

The problem of chromatography method is solved to some extent by another patent application, US20120108826 (ZACH systems). This patent application discloses separation of the diasteomeric mixture of RS/SR & RR/SS of 6-Fluoro-3,4-dihydro-2-oxiran-2-yl-2H-benzopran by fractional distillation using specific column of about 1.2 meter height filled with a packing material that ensures an efficiency corresponding to 10-25 theoretical plates. However this fractional distillation is also having problems of low recovery of separated isomers due to exposing the material to higher temperature for prolonged period of time. Also constructing the specific column on commercial scale poses difficulties.

An Indian patent, IN221733, discloses reaction of (6-fluoro-3.4-dihydro-2H-chromene-2-carboxylic acid with an acid activating agent, and an amine RR'NH, wherein R and R' are independently H, alkyl or aryl, optionally joined together with or without a heteroatom selected from O, N and S, to give (6-fluoro-3,4-dihydro-2H-chromen-2yl)methanone which is reduced using alkoxy metal hydride to obtain 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde. This process also involves multiple and lengthy processes leading to increased time cycle and production cost.

The problem of lengthy steps is solved in US6545040 patent by obtaining (+)-(S)-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde in a single step. The US‘040 patent discloses reaction of (+)-(S)-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid with [bis(2-methylpropyl)]aluminum hydride (DIBAL) in presence of 1,1′-carbonylbis[1H-imidazole] at -70°C in tetrahydrofuran solvent to obtain (+)-(S)-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde in 59% yield. However, this process suffers lower yield and

involves operating at -70°C temperature which is not industrially viable and scalable.

An Indian patent application, 2703/CHE/2008, disclosesan improved process for the preparation of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde by reducing an ester of (6-fluoro-3.4-dihydro-2H-chromene-2-carboxylic acid using Vitride at -70°C in solvents such as toluene and xylene. The same reaction is also reported in WO2014111903, which discloses reduction of methyl ester of 6-fluoro-3.4-dihydro-2H-chromene-2-carboxylic acid using Vitride at -73°C to -78°C to obtain 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehydewith 18.5% of (6-fluoro-3,4-dihydro-2H-chromen-2-yl)methanol as impurity due to uncontrolled reduction.

From the '2703 and '903 publications, it is evident that the alcohol impurity, 6-fluoro-3,4-dihydro-2H-chromen-2-yl)methanol, is formed due to un controlled over reduction. This impurity is formed even when the reduction is performed at substantially lower temperatures between -70°C to -78°C. Thus the single step process poses dual problems of 1) conducting reaction at substantially lower temperatures between -70°C to -78°C which is not industrially feasible and the process is not scalable, and 2) formation of the alcohol impurity, 6-fluoro-3,4-dihydro-2H-chromen-2-yl)methanol, is not controlled even after conducting the reaction at -70°C to -78°C leading to yield loss, and incorporation of additional purification steps to remove the impurity, increases the production cost.

The U.S Patent 4,654,362 further discloses reaction of the 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde with trimethylsulfoxonium iodide to obtain mixture of RS/SR & RR/SS of 6-Fluoro-3,4-dihydro-2-oxiran-2-yl-2H-benzopran. The stereoisomers are separated by chromatography into two racemic mixtures (R,S)-, (S,R)-epoxides (Mixture A) and (S,S)-, (R,R)-epoxides (Mixture B).

Therefore, the objective of the present invention is to separate diastereomers of (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopran and to prepare the intermediate, 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde, from esters of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid to overcome the problems stated above by minimizing the formation of alcohol impurity while performing the reduction reaction at optimum temperatures, thereby making the process industrially feasible and economically viable.

Summary of Invention:

The present inventors have, surprisingly, found a novel process for preparation of Nebivolol or its pharmaceutically acceptable saltwhich comprises preparation of intermediate, 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde of Formula – II, converting the 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde of Formula – II into mixture of [R*(S*)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran and [R*(R*)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran of Formula-V and separation of diastereomers of (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopran by forming azeotrope.

Accordingly in one aspect, the invention provides a process of preparation of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde of Formula–II, which comprises;
reducing the esters of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid of Formula – I, wherein R1 denotes linear or branched (C1-C8)-alkyl, cycloalkyl, aryl; ,in presence a secondary amine, with a reducing agent to obtain of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde of Formula–II. The invention is depicted in Scheme-1.

The novel process of isolation of one of diastereomer (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopran having RS/SR configuration from the mixture of (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopranhaving

RS/SRand (R*)-6-Fluoro-3,4-dihydro-2-((R*)-oxiran-2-yl)-2H-benzopran having RR/SS configuration comprises addition of an agent to the mixture to form azeotrope. Surprisingly it is found that the agent is forming azeotrope with one of the diastereomers, (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopran and the azeotrope is getting distilled at much lower temperature enabling the isolation of the diasteromer from its mixture.

Accordingly, another aspect of the present invention provides a novel process for preparation of Nebivolol or its pharmaceutically acceptable salt of Formula – IV, which comprises;

a) adding an agent to mixture of (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopran and (R*)-6-Fluoro-3,4-dihydro-2-((R*)-oxiran-2-yl)-2H-benzopran of Formula–V to form azeotrope;
b) isolatingdiastereomer (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopranof Formula–V-A from the azeotrope and obtaining R*)-6-Fluoro-3,4-dihydro-2-((R*)-oxiran-2-yl)-2H-benzopran of Formula – V-B; and
c) converting the (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopranof Formula–V-A and R*)-6-Fluoro-3,4-dihydro-2-((R*)-oxiran-2-yl)-2H-benzopran of Formula–V-B into Nebivolol or its pharmaceutically acceptable salt of Formula – IV.

In a preferred embodiment, the agents are suitable solvents which are immiscible with OXI and having higher boiling points may be used to form azeotrope with diastereomer (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopranof Formula–V-A.

Brief description of the drawings:

Figure 1 shows schematic drawing of the system displaying separation of OXI-A and OXI-B by azeotropic distillation.

Description of Invention:

The invention will now be described in detail in connection with certain preferred andoptional embodiments, so that various aspects thereof may be more fully understood andappreciated.

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

Unless stated to the contrary, any of the words, "including", "includes", "comprising", and "comprises" mean "including without limitation" and shall not be construed to limit any general statement that it follows to the specific or similar items.

Abbreviations:

OXI : 6-Fluoro-3,4-dihydro-2-oxiran-2-yl-2H-benzopran (Mixture of RS/SR & RR/SS)

OXI-A :(R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopran, OR [R*(S*)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran of and (Mixture of RS &SR)

OXI-B :(R*)-6-Fluoro-3,4-dihydro-2-((R*)-oxiran-2-yl)-2H-benzopran OR [R*(R*)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran(Mixture of RR &SS)

Azeotrope:

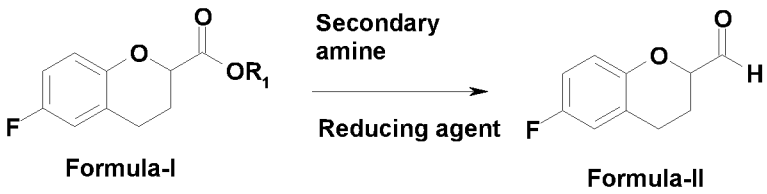
An *azeotrope* or a constant boiling mixture is a mixture of two or more liquids whose proportions cannot be altered by simple distillation. This happens because, when an *azeotrope* is boiled, the vapour has the same proportions of constituents as the unboiled mixture.

The present invention provides an improved economical process to prepare Nebivolol or it's pharmaceutically acceptable salts.

Accordingly in one aspect, the invention provides a process of preparation of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde of Formula–II, which comprises;

reducing the esters of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid of Formula – I, wherein R_1 denotes linear or branched (C1-C8)-alkyl, cycloalkyl, aryl; ,in presence a secondary amine, with a reducing agent to obtain of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde of Formula–II. The invention is depicted in Scheme-1.

Scheme-1



Formula-I Formula-II

The secondary amines may be open chain (R_2R_3NH) or a cyclic amine which may be pyrrolidine (five membered) or six membered ring of Formula-III;

Pyrrolidine Formula-III

wherein, $R_2$and R_3denote independently linear or branched (C1-C8)-alkyl, cycloalkyl, phenyl and benzyl; X denotes O or N-R_4 ; and R_4 denotes H, linear or branched (C1-C8)-alkyl, cycloalkyl,phenyl or benzyl. However, dipropyl amine and n-methyl aniline are preferred from open chain secondary amines. Morpholine and N-methyl piperazine are preferred from cyclic six membered ring of formula-III.

The reducing agents include, but not limited, to metal hydrides such as lithium aluminium hydride and sodium borohydride; alkyl aluminium hydrides such as

diisobutyl aluminum hydride (DIBAL), or alkoxy aluminium hydrides such as sodium bis(2-methoxyethoxy)aluminium hydride (it is also called Vitride), lithium diethoxyaluminiumdihydride and lithium tri-tert-butoxyaluminium hydride. However Vitride is preferred reagent from alkoxy aluminium hydrides.

In a preferred embodiment, the esters of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid of Formula – I, wherein R_1 denotes methyl or ethyl are reduced with Vitride in presence of a morpholine or N-methyl piperazine.

According to the present invention, the reducing agent and the secondary amine are separately mixed in a suitable solvent to form a mixture or complex. Then the mixture/complex is reacted with the esters of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid of Formula–I to obtain the 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde of Formula–II. Typically the reducing agent is taken in a solvent, cooled the mixture to about 10°C under nitrogen followed by addition of secondary amine at the same temperature. After addition of the amine, the mixture is equilibrated for another 15 to 30 minutes. Then the mixture of reducing agent-secondary amine is added into ester of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid of Formula–I for completing reduction reaction.

The reduction reaction may be performed in suitable solvents. Suitable solvents for conducting reduction reaction include, but not limited to, aliphatic or aromatic hydrocarbons, chlorinated hydrocarbons, nitriles, ethers etc. Chlorinated hydrocarbons preferably include methylenedichloride, ethylenedichloride, chloroform, carbon tetrachloride. Nitrile solvents include acetonitrile and propionitrile. Aromatic hydrocarbons preferably selected from benzene, toluene, xylene, and aliphatic hydrocarbons include hexane, cyclohexane, heptane etc. Ethers include tetrahydrofuran, diisopropyl ether or diethyl ether. However, most preferred solvents are toluene, xylene or tetrahydrofuran.

In another preferred embodiment, the reduction reaction is conducted typically from -25°C to 10°C temperature. However, the preferred temperature range varies

between -15°C to 0°C temperature. Molar ratio of secondary amine may be used in the range of 1 mole to 4 moles relative to esters of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid of Formula – I. However, the preferred range is 1.5 to 1.7 moles. Alkoxy aluminium hydrides may be used in the range of 1 to 2 moles relative to esters of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid of Formula – I.However, the preferred range of alkoxy aluminium hydrides is 1.3 to 1.5 moles.

Typically the reduction reaction completes in 2-3 hours to form 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde. After completion of reaction, the mass is quenched with methanol followed by dilute hydrochloric acid. Then the reaction mass is extracted with suitable solvents followed by concentration to isolate the 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde.

According to another aspect, there is provided a process for preparation of Nebivolol or its pharmaceutically acceptable salts such as hydrochloride or hydrobromide salts. Accordingly the 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde prepared as per the present invention mentioned above is converted into Nebivolol or its pharmaceutically acceptable salt.

Accordingly, the 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde is reacted with trimethylsulfoxonium iodide in presence of base, sodium methoxide, in dimethyl sulfoxide solvent to obtain mixture of [R*(S*)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran of formula-Vaand [R*(R*)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran of formula-Vb.

According to another aspect, there is provided a process for preparation of Nebivolol or its pharmaceutically acceptable salt, which comprises isolation of one ofdiastereomer (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopran having RS/SR configuration from the mixture of (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopranhaving RS/SR and (R*)-6-Fluoro-3,4-dihydro-2-

((R*)-oxiran-2-yl)-2H-benzopran having RR/SS configuration by adding an agent to form azeotrope.

In one embodiment, the agents are suitable solvents which are immiscible with OXI and having higher boiling points may be used to form azeotrope with diastereomer (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopranof Formula–V-A.

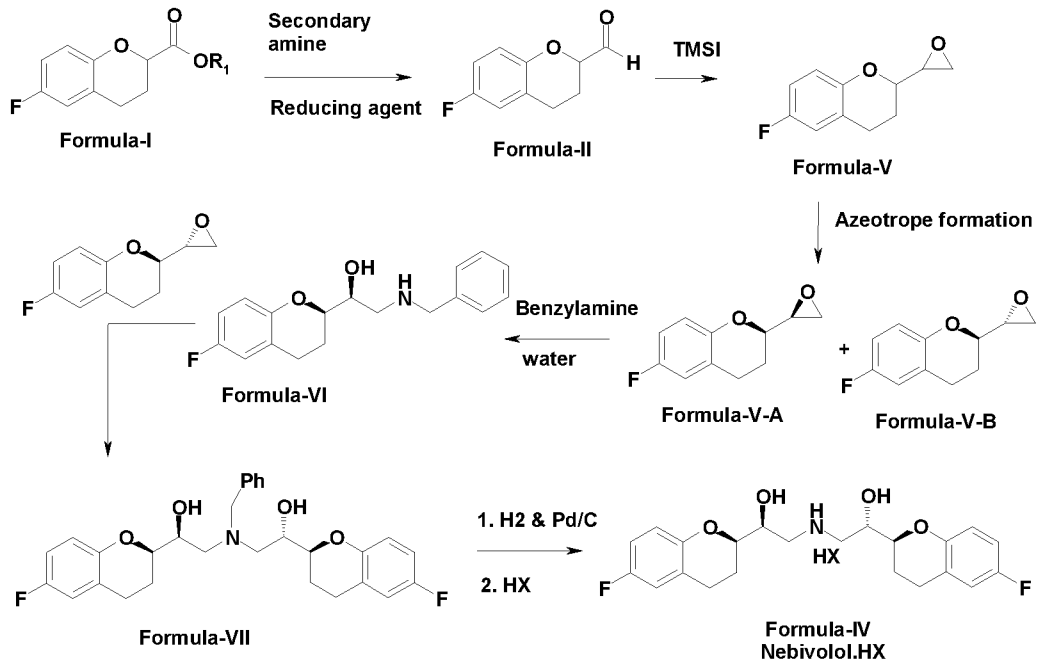
The suitable solvents for forming azeotrope may include but not limited to glycols, sulfolenes, glymes, glycerol ethers, hydrocarbons, crown ethers such as 12-crown-4, nitrobenzene, biphenyl, diphenylether, acetophenone. Glycols include glycerol, monoethyleneglycol, diethyleneglycol, triethyleneglycol, 1,3-Proapnediol, 1,4-Butanediol, 1,2-Butanediol and 1,3-Butanediol. Sulfolenes include 2-sulfolene, 3-sulfolene, 3-methyl-2-sulfolene, 3-methyl-3-sulfolene, and 3-ethyl-3-sulfolene. Glymes include diglyme, triglyme, tetraglyme. Glycerol ethers include 1,2,3-trimethoxy propane, 1,2,3-triethoxy propane. Hydrocarbons include open chain hydrocarbons like 2-methyldecane, 3-methyldecane, 9-butyldocosane and cyclic hydrocarbons like 1-methyl-2-pentyl cyclohexane. However, preferred solvent is monoethyleneglycol ordiethyleneglycol.

Usually the process involves addition of agent to the OXI and heated under vacuum at about 2 torr to form azeotrope. It is surprisingly found that OXI-A isomer forms azeotrope with the agent at much lower vapor temperature of 69-70°C (when monoethyleneglycol used as agent) which is collected as distillate. The azeotrope containing two layers- top layer (agent) and bottom layer-(OXI-A rich layer) are separated, the top layer is refluxed back to the distillation flask. The azeotropic distillation is carried out till maximum OXI-A isomer is separated from OXI-B. Finally enriched OXI-B isomer retained in the distillation flask along with the agent is separated to obtain enriched OXI-B.

The [R*(S*)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran of formula-Va(OXI-A) is reacted with benzylamine in water to obtain [R*(S*)]-6-fluoro-3,4-dihydro-[α]-[[(phenylmethyl)-amino] methyl]-2H-1-benzopyan-2-methanol of formula-VI, which is further reacted with [R*(R*)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran of formula-Vb(OXI-B) in methanol at reflux temperature to obtain [2S*[1R*,5R*(R*)]α,α'-[[(phenylmethyl)imino]bismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol]. The [2S*[1R*,5R*(R*)]α,α'-[[(phenylmethyl)imino]bismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] is debenzylated using hydrogen in presence of Pd/C catalyst in acetic acid solvent. After completion of reaction, catalyst is separated by filtration. The filtrate containing Nebivolol base is treated with acid (HX) such as hydrogen chloride gas to obtain Nebivolol hydrochloride salt in one pot.

The invention is depicted in scheme-2:

Scheme-2:



The following examples, which include preferred embodiments, is intended to illustrate the practice of this invention, it being understood that the particulars

shown are by way of example and for purpose of illustrative discussion of preferred embodiments of the invention.

The following examples are presented to further explain the invention with experimental conditions, which are purely illustrative and are not intended to limit the scope of the claimed invention.

Stage-1: Preparation of Methyl 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylate.

100 gm of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid was charged in 500 ml of methanol under stirring and then added 2 gms of concentrated sulfuric acid at around 30°C. Then, reaction mixture was slowly heated to reflux temperature. Reaction was maintained at the reflux temperature. After reaction, methanol was distilled and product was extracted with toluene. Toluene solution was washed with 5% sodium bicarbonate solution. Toluene layer was concentrated to get 104 gm of Methyl 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylate.
Yield= 97%. Purity (GC area%)= 99.5%

Stage-2: Preparation of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde (Formula-II).

Example-1
206 gm of vitride (70% toluene solution) was taken in 500 ml toluene at 10°C, under nitrogen atmosphere. 69.7 gm of morpholine was added into it at the same temperature. The mixture was stirred for 15 minutes. In another flask, 100 gm of methyl 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylate was taken in 500 ml of toluene and was cooled to -10°C. Then, the above vitride+ morpholine solution was slowly added into methyl 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylate solution at about -10°C and was stirred at same temperature for 2 hrs.

Reaction mass was then quenched with methanol followed by dilute hydrochloric acid, extracted with toluene and concentrated to get 84 gm of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde.
Yield= 98%, Purity= 95.8% (GC area%), Alcohol impurity = 2.8%

Example-2

178 gm of vitride (70% toluene solution) was taken in 500 ml toluene at around 10°C, under nitrogen atmosphere. 69.4 gm of N-methyl piperazine was slowly added into it at the same temperature. The reaction mixture was stirred for 15 minutes. In another flask, 100 gm of Methyl 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylate was taken in 500 ml of toluene and cooled to -10°C. Then the above vitride + N-methyl piperazine solution was slowly added into the Methyl 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylate solution at about -10°C and was stirred at the same temperature for 2 hrs. Reaction mass was then quenched with methanol followed by dilute hydrochloric acid, extracted with toluene and concentrated to get 79.4gm of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde.
Yield= 92.7%, Purity= 91% (GC area%), Alcohol impurity = 1.68%

Stage-3:6-Fluoro-3,4-dihydro-2-oxiran-2-yl-2H-benzopran (Mixture of RS/SR & RR/SS) (OXI).

124.7 gm of trimethylsulfoxonium iodide was taken into 425 ml of dimethyl sulfoxide. It was cooled below 15°C and to this charged 25.5 gm of sodium methoxide and the mass was stirred at 15°C for 2 hrs. In another flask, prepared solution of 85 gm of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde in 425 ml MDC. This MDC solution was slowly added into above trimethylsulfoxonium iodide + sodium Methoxide dimethyl sulfoxide solution, while maintaining the temperature at 10 to 15°C and continued stirring for 2 hrs. The reaction mixture was then quenched into ice-cold water, aqueous layer extracted with MDC. MDC layer was washed with water and concentrated.

Concentrated mass then distilled under vacuum to give 69 gm of 6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran as a mixture of A and B.
(Yield= 75%, HPLC assay: Formula-VA=60%, Formula-VB =29.6%)

Separation of OXI-A (Formula-VA) & OXI-B (Formula-VB) by forming azeotrope:

Arranged azeotropic distillation using 1 liter capacity Round bottom flask (RBF), equipped with temperature pocket, 1 meter pack column (SS wire mesh rolls), column head attached to a condenser followed by Dean & Stark apparatus to get layer separation of compound of Formula-VA and monoethylene glycol in distillate.
Packed column is used to provide rectification stages for enrichment of azeotropic composition in the distillate (OXI-A + mono ethylene glycol). Provision of sufficient rectification stages ensures more pure heterogeneous azeotrope obtaining at the top.
Vacuum was applied from the top of the condenser using high vacuum pump with vacuum gauge.
The compound OXI 150 gm and Ethylene glycol 150 gm were charged in RBF. Then vacuum (~2 torr) was applied and started heating to get reflux through Dean & Stark apparatus. Layer separation was observed in Dean & Stark side arm. Top layer (Ethylene glycol layer) was refluxed back to the column and bottom layer (OXI-A rich layer) was collected at vapor temperature = 69-70°C, vacuum= 1.8-2.1 torr and Bottom (Re-boiler) temperature= 80-95°C.
Distillate (OXI-A rich) = 50 gm
(Purity by GC area%: OXI-A = 96.2%)
Bottom Residual mass : 138 gm (having two layers).

- Top layer: 21 gm; was of monoethylene glycol.
- Bottom layer: 117 gm ; OXI-B rich

(Purity of OXI-B rich layer by GC area% : OXI-B = 51.8%)

Above OXI-B rich bottom layer was further subjected to direct distillation under vacuum. OXI-B pure collected at pot temperature 76-82°C, vapor temperature 78-91°C and vacuum 1-1.5 torr. Distillate collected = 16.7 gm
(Purity by GC area%: OXI-B = 91.2%)

Stage-4: Preparation of [R*(S*)]-6-fluoro-3,4-dihydro-[α]-[[(phenylmethyl)-amino]
methyl]-2H-1-benzopyan-2-methanol (Formula-VI):

276.0 gm of benzylamine was taken in 400 ml of water at around 25 to 30°C and 100 gm of [R*(S*)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran was added at around 10°C. Then reaction mass was stirred at 10-15°C for 1 hr. Further temperature was raised to 30°C and stirred for 5 hrs. Then the mass was cooled to 0-5°C, filtered, washed with chilled water and dried to get 136 gm of [R*(S*)]-6-fluoro-3,4-dihydro-[α]-[[(phenylmethyl)-amino]methyl]-2H-1-benzopyan-2-methanol (Formula-VI) Yield = 87.8%, Purity= 98.2% (HPLC area%).

Stage-5: Preparation of [2S*[1R*,5R*(R*)] α,α'-[[(phenylmethyl)imino]bismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] (Formula-VII)

125 gm of [R*(S*)]-6-fluoro-3,4-dihydro-[α]-[[(phenylmethyl)amino]methyl]-2H-1-benzopyan-2-methanol (Formula-VI) was taken in 500 ml of methanol at 30°C. To this added 80.6 gm of [R*(R*)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran at around 30°C. The reaction mass was heated to reflux and stirred at reflux for 15 hr. Then slowly added water and stirred for 1 hr. The mass was then cooled to -5 to 0°C, stirred for 24 hrs and filtered, washed with chilled methanol and dried to get 109.5 gm of crude 2S*[1R*,5R*(R*)] α,α'-[[(phenylmethyl)imino] bis -methylene] bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol]. It was then purified in methanol to get 87.7gm of

2S*[1R*,5R*(R*)] α,α'-[[(phenylmethyl)imino] bis -methylene] bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol].

Yield = 42.9% Purity=99% (HPLC area%). Undesired isomer: 0.32%

Stage-6: Preparation of Nebivolol.HCl (one pot method)

50 gm of [2S*[1R*,5R*(R*)] α, α'-[[(phenylmethyl)imino]bismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol and 2.5 gm of Pd/C was taken in 200 ml of acetic acid at 30°C, was hydrogenated under 5 kg/cm2 of hydrogen pressure at 30-35°C. Then filtered off catalyst and purged dry hydrogen chloride gas in the filtrate. Precipitated product was filtered, washed with acetic acid followed by methanol, filtered and dried to give 36.6 gm of Nebivolol.HCl.

Yield=83.8%. Purity= 99.8%.

We claim;

1) A process for preparation of Nebivolol or its pharmaceutically acceptable salt of Formula – IV, which comprises;
   a) adding an agent to mixture of (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopran and (R*)-6-Fluoro-3,4-dihydro-2-((R*)-oxiran-2-yl)-2H-benzopran of Formula–V to form azeotrope;
   b) isolating diastereomer (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopran of Formula–V-A from the azeotrope and obtaining R*)-6-Fluoro-3,4-dihydro-2-((R*)-oxiran-2-yl)-2H-benzopran of Formula – V-B; and
   c) converting the (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopran of Formula–V-A and R*)-6-Fluoro-3,4-dihydro-2-((R*)-oxiran-2-yl)-2H-benzopran of Formula–V-B into Nebivolol or its pharmaceutically acceptable salt of Formula – IV.
2) The process as claimed in claim 1, where in the agent is selected from a group consisting of glycols, sulfolenes, nitrobenzene, biphenyl, diphenylether and acetophenone.
3) The process as claimed in claim 2, where in the glycol is selected from a group consisting of monoethyleneglycol, diethyleneglycol, triethyleneglycol, 1,3-Proapnediol, 1,4-Butanediol, 1,2-Butanediol and 1,3-Butanediol.
4) The process as claimed in claim 3, where in the glycol is monoethyleneglycol or diethyleneglycol.
5) The process as claimed in claim 3, where in the azeotrope formation is carried out under vacuum.
6) The process as claimed in claim 1, wherein the step c further comprises;
   a) reacting the (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopran Formula–V-A with benzyl amine to obtain [R*(S*)]-6-

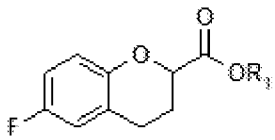
fluoro-3,4-dihydro-[α]-[[(phenylmethyl)-amino]methyl]-2H-1-benzopyan-2-methanol of Formula–VI;

b) reacting the [R*(S*)]-6-fluoro-3,4-dihydro-[α]-[[(phenylmethyl)-amino] methyl]-2H-1-benzopyan-2-methanol of Formula – VI with (R*)-6-Fluoro-3,4-dihydro-2-((R*)-oxiran-2-yl)-2H-benzopran of Formula–V-B to obtain [2S*[1R*,5R*(R*)] α,α'-[[(phenylmethyl)imino]bismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] of Formula–VII; and

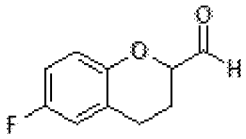
c) convertingthe [2S*[1R*,5R*(R*)] α,α'-[[(phenylmethyl)imino]bismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] of Formula–VII intoNebivolol or pharmaceutically acceptable salt of Formula-IV.

7) The process as claimed in claim 1, wherein themixture of (R*)-6-Fluoro-3,4-dihydro-2-((S*)-oxiran-2-yl)-2H-benzopran and (R*)-6-Fluoro-3,4-dihydro-2-((R*)-oxiran-2-yl)-2H-benzopran of Formula–V is prepared by a process comprising steps of

a) reducing the esters of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid of Formula – I, in presence of a secondary amine with a reducing agent to obtain of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde of Formula – II; and



Formula-I



Formula-II

wherein R_1 denotes linear or branched (C1-C8)-alkyl, cycloalkyl, aryl;

b) reacting the 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde of Formula – II with trimethylsulfoxonium iodide in presence of a base to obtain mixture of [R*(S*)]-6-fluoro-3,4-

dihydro-2-oxiranyl-2H-1-benzopyran and [R*(R*)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran of Formula-V.

8) The process as claimed in claim 7, wherein R1 is selected from methyl or ethyl.
9) The process according to claim 7, wherein reducing agent is selected from the group consisting of metal hydrides, alkyl aluminium hydrides or alkoxyaluminium hydrides.
10) The process according to claim 9, wherein the alkoxyaluminium hydride is Vitride.
11) The process according to claim 7, the secondary amine is selected from the group consisting of R2R3NH, pyrrolidine, six membered cyclic secondary amine of formula-III;

Formula-III

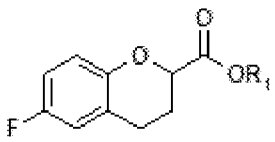
wherein, R2 and R3 denote independently linear or branched (C1-C8)-alkyl, cycloalkyl, phenyl and benzyl; X denotes O or N-R4; and R4 denotes H, linear or branched (C1-C8)-alkyl, cycloalkyl; phenyl or benzyl.

12) The process according to claim 11, wherein secondary amine is selected from the group consisting of morpholine, N-methyl piperazine, dipropyl amine or n-methyl aniline.
13) The process according to claim 7, wherein the reduction reaction of step-a is performed at a temperature range of -25°C to 10°C.
14) The process according to claim 7, wherein the secondary amine of Formula-III is used in the range of 1 mole to 4 moles relative to esters of 6-fluoro-3,4-dihydro-2H-1- benzopyran-2-carboxylic acid of Formula – I.
15) The process according to claim 7, wherein the alkoxyaluminium hydride is used in the range of 1 to 2 moles relative to esters of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid of Formula – I.

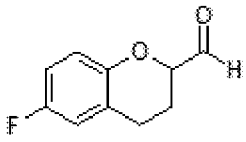
16) The process according to claim 7, wherein the reduction reaction of step a is performed in solvent selected from aliphatic or aromatic hydrocarbons, chlorinated
hydrocarbons, nitriles and ethers.

17) The process according to claim 7, wherein the aromatic hydrocarbon solvent is toluene or xylene and ether solvent is tetrahydrofuran.

18) A process for preparation of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde of Formula – II comprising;
reducing the esters of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid of Formula – I, in presence a secondary amine, with alkyl aluminium hydrides or alkoxyaluminium hydrides to obtain of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde of Formula – II.



Formula-I



Formula-II

wherein R_1 denotes linear or branched (C1-C8)-alkyl, cycloalkyl or aryl

I/I

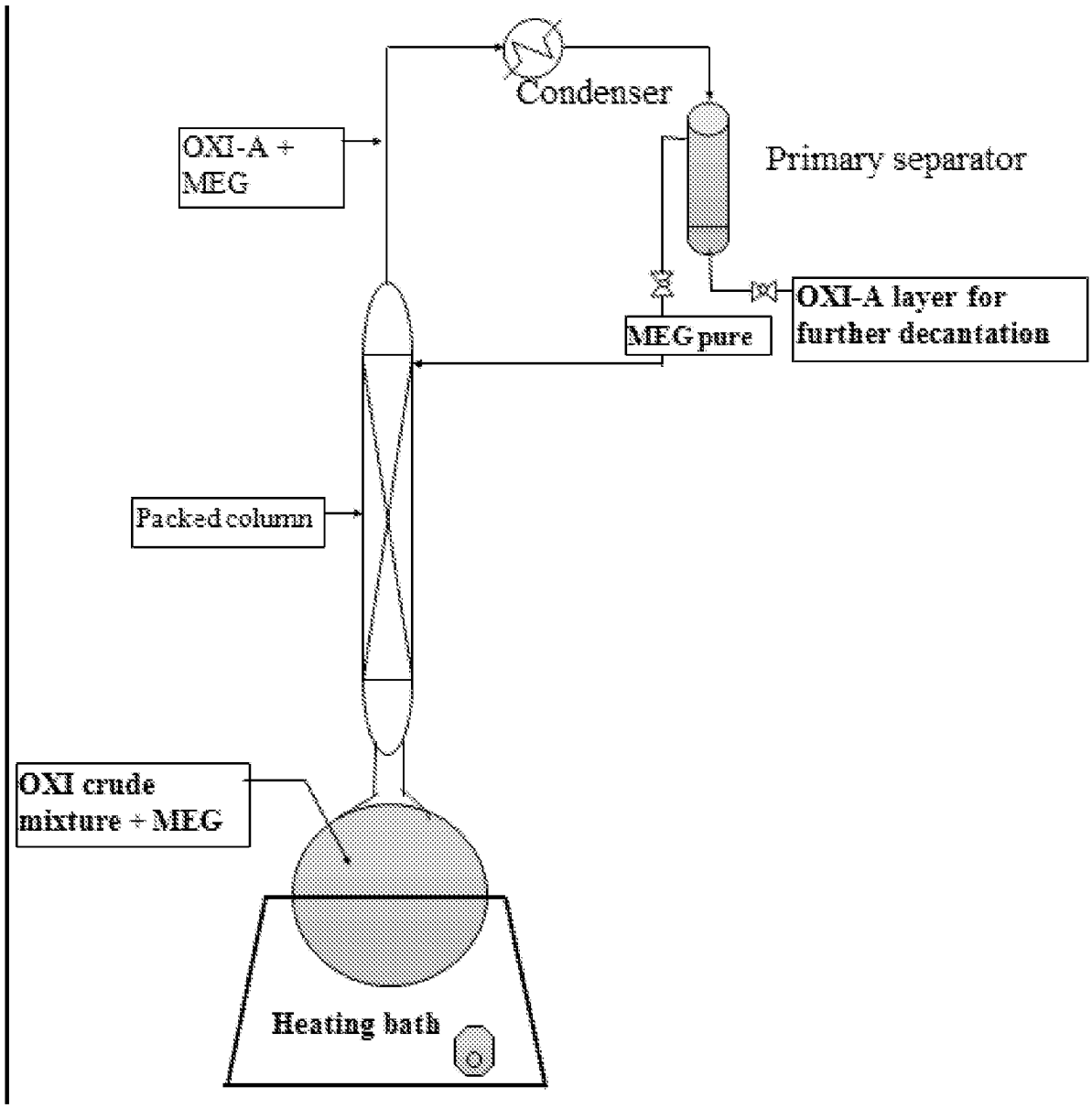

Condenser
OXI-A + MEG
Primary separator
OXI-A layer for further decantation
MEG pure
Packed column
OXI crude mixture + MEG
Heating bath

Figure I

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2016/050144

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/00 Version=2016.01

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)

A61K

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)

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Wo2006025070 A2 (TORRENT PHARMACEUTICALS LTD[IN]) 09 march 2006(2006-03-09). Reactions 4-8;Examples 3-5;Claims 1,2	1-6
Y	WO 2010089764 A2 (MSN LAB LTD[IN]) 12 august 2010 (2010-08-12) Example 3;claim 1	1-6
Y	US20120108826 A1 (COTARCA LIVIUSet al [IT]) 03 may 2012 (2012-05-03) Claim 1;Example 1	1-6

☐ Further documents are listed in the continuation of Box C. ☒ 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	Date of mailing of the international search report
14-10-2016	14-10-2016

Name and mailing address of the ISA/	Authorized officer
Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075	K Janardana
Facsimile No.	Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2016/050144

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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

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

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

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

1.claims 1-6

a process for the preparation of Nebivolol or its pharmaceutically acceptable salt of Formula-IV, which can be obtained by adding an agent to compound of formula V.

2.claims 7-17

a process for the preparation of compound of formula-V from formula-I and Formula-II which is used as intermediate in the synthesis of nebivolol;

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-6

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Continuation of Observations where unity of invention is lacking(Box III)

3.claim 18

process for the preparation of compound of formula-I from formula-I which is used as intermediate in the synthesis of nebivolol;
The technical problem addressed by the second group of claims 7-17 appears to be the provision of further process for the preparation of the formula-v, which is already used as intermediate in the synthesis of nebivolol in WO20060250070 example 4.
The technical problem addressed by the third group claim 18 appears to be the provision of a further process for the preparation of the formula-II, which is already used as intermediate in the synthesis of nebivolol in document WO2006025070(example 2) and WO2014111903(claim 1 and examples 3,4).
There is no common element linking the three groups of invention since these two intermediates do not share any structural features.The special technical feature of the first group of claims which makes the contribution.As the special technical features of the three groups of invention are not the same or corresponding, the claimed inventions are not
linked as to form a single general inventive concept and the requirements of unity are not fulfilled.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2016/050144

Citation	Pub.Date	Family	Pub.Date
WO 2006025070 A2	09-03-2006	EP 1741712 A2	10-01-2007
		US 2013296583 A1	07-11-2013
		JP 2015057407 A	26-03-2015
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		JP 2012533588 A	27-12-2012
		EP 2456768 A1	30-05-2012
		CN 102471325 A	23-05-2012
		AU 2010275690 B2	21-07-2016