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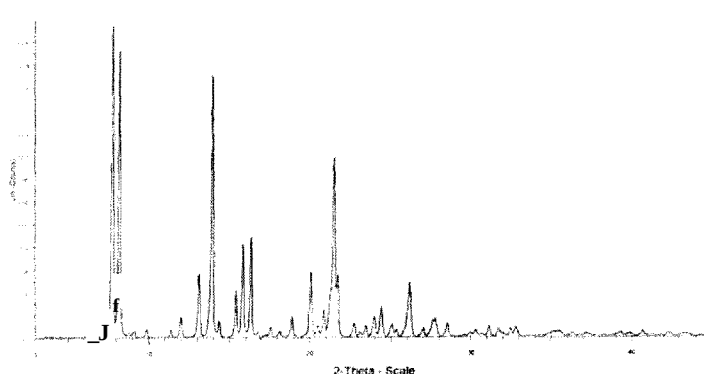
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(54) Title: PROCESS FOR PREPARATION OF N-[2-BUTYL-3-[4-[3-(DIBUTYLAMINO)PROPOXY]BENZOYL]-5-BENZO-
FURANYLMETHANESULFONAMIDE, ACID ADDITION SALTS AND PRODUCT THEREOF

FIG. 1



(57) Abstract: The present invention relates to a process for the preparation of highly pure N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranylmethanesulfonamide and pharmaceutically acceptable salts thereof having HPLC purity greater than 99.5%.

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PROCESS FOR PREPARATION OF N-[2-BUTYL-3-[4-[3-(DIBUTYLAMINO)PROPOXY]BENZOYL]-5-BENZOFURANYL]METHANESULFONAMIDE, ACID ADDITION SALTS AND PRODUCT THEREOF

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Related Application

The invention disclosed in Indian Patent Application No. 2716/MUM/2010, filed on September 27, 2010, is cognate with the invention disclosed in Indian Patent Application no. 1979/MUM/2010 filed on July 9, 2010, in a way that they constitute a single invention.

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Field of Invention

The present invention relates to a novel process for the preparing *N*-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide and pharmaceutically acceptable salts thereof and its intermediates.

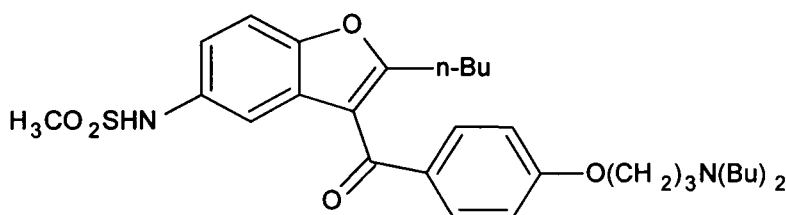
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Background of the Invention

Dronedarone, SR 33589, is marketed under the brand name Multaq® (US) for the treatment of arrhythmia which is available as tablet in strength of 400 mg. Dronedarone, which is chemically known as *N*-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide, having a formula (I) was first disclosed in US 5,223,510 (US'510).

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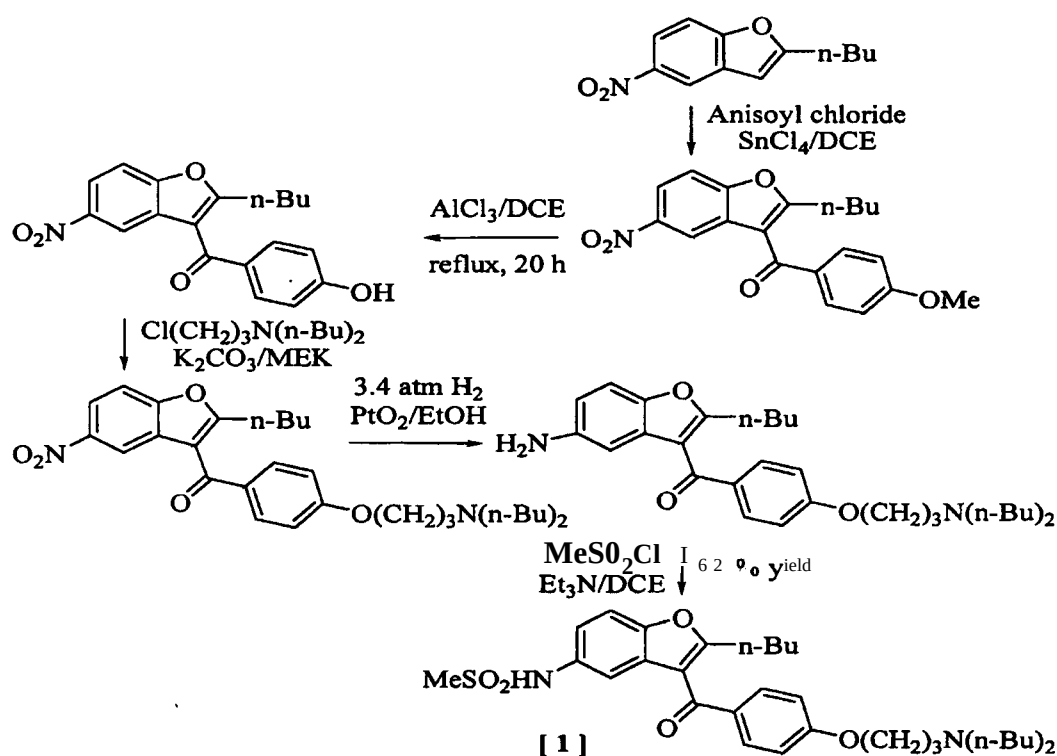


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In addition, US' 510 disclose several processes for preparation of the dronedarone along with its therapeutic use. One of the processes for preparing

dronedarone (I) disclosed in US' 510, starts from 2-butyl-5-nitrobenzofuran is depicted according to the following scheme 1:

5



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More specifically, this method when applied to the preparation of dronedarone hydrochloride comprise steps of,

- a) Hydrogenation of 2-butyl-3-(4-[3-(dibutylamino)propoxy]-5-nitrobenzofuran in the presence of platinum oxide, which gives 5-amino-2-butyl-3-[4-(3-dibutylamino propoxy)]benzoyl benzofuran.
- b) Reaction of 5-aminobenzofuran derivative obtained above with methanesulfonyl chloride in solvent dichloromethane in presence of a base,

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triethylamine, gives 2-n-butyl 3-[4-(3-di-n-butylaminopropoxy)benzoyl]-5-methylsulfoamido benzofuran as an oily mass,

- c) The above product was purified by column chromatography using silica column to give dronedarone as base.
- 5 d) The hydrochloride salt of Dronedarone was prepared by addition of hydrochloride in ether in solution of Dronedarone base in ethyl acetate.

Further, US'510 describes the use of catalyst such as platinum or palladium oxide, zinc in a hydrochloric acid medium or tin in a hydrochloric acid medium
10 for hydrogenating of nitro group of the derivative into amino group. The same reaction is depicted in the form of example 1(f) in US'510 which discloses process for preparing 5-Amino-2-butyl-3-[4-(3-dibutylamino-propoxy)benzoyl]-2-(n-butyl)-benzofuran from 2-(n-butyl)-3-[4--(3-dibutylamino-propoxy)benzoyl]-5-nitrobenzofuran by means of platinum oxide under pressure
15 of 3.4 atmosphere.

Example 3 of US' 510 discloses a process for preparing sulfonamide salt of 5-amino-2-butyl-3-[4-aminoalkoxy] benzoylbenzofuran by condensation of solution of methanesulfonyl chloride in dichloromethane with 5-amino-3-[4-(3-
20 di-(n-butyl)amino-propoxy)benzoyl]-2-(n-butyl)benzofuran in presence of triethylamine to get dronedarone base which is further purified by means of chromatography on a column of silica. The pure dronedarone base obtained in preceding step is crystallized by hexane followed by addition of hydrogen chloride in ether to solution of pure dronedarone in ethyl acetate to get
25 dronedarone hydrochloride which is recrystallized in acetone with purity of about 98.0%.

The processes disclosed in above said examples of US'510 patent are time-consuming and costly by reason of using silica column for purification of crude
30 dronedarone as well as isolating dronedarone base instead of dronedarone

- hydrochloride directly from the condensation stage where more reaction time (around 24 Hr) leads to the formation of disulfonamide impurity and the same remains in to final product which is difficult to remove. In addition to this disadvantages, hydrogenation of 2-butyl-3-(4-[3-(dibutylamino)propoxy]-5-nitrobenzofuran by means of high oxidizing agents keto group of intermediate gets reduced to form impurity which carries forward to final product. Henceforth the product obtained from column chromatography is having purity of only- 96% by HPLC.
- 10 Noel Fino *et. al.* in US 6,828,448 discloses process for preparing dronedarone hydrochloride comprising catalytic hydrogenation of 2-butyl-5-nitrobenzofuran by means of platinum derivative such as platinum oxide or an ammonium formate/palladized charcoal system to get 5-amino-2-butylbenzofuran which is further treated with methanesulfonyl chloride or methanesulfonic anhydride in
- 15 presence of acid acceptor. Then after methanesulfonamido derivative obtained from the preceding step is reacted with 4-[3-(dibutylamino)propoxy]benzoyl hydrochloride in presence of Lewis acid (aluminum chloride) as catalyst followed by hydrolysis to get dronedarone hydrochloride.
- 20 However, this method uses aluminum chloride which when employed on industrial scale causes high discharge of aluminum hydroxide whose treatment, in order to avoid problems of pollution is expensive. Moreover, the amounts of impurity generated at every stage increases in its subsequent impurity and remains with high amount in final product. In consequence of impurity,
- 25 purification method first converts dronedarone hydrochloride into dronedarone base which revert back to dronedarone hydrochloride which leads to prolonged and costly process.
- Michael Biard *et. al.* in US 6,846,936 discloses 2-butyl-3-(4-[3-(dibutylamino)propoxy]benzoyl)-5-nitrobenzofuran hydrochloride as a product, process of
- 30

preparation and use of the same as synthetic intermediate for preparation of dronedarone. Example 6 of US'936 discloses the use of ethyl acetate and ether to make a solution of dronedarone and hydrochloric acid respectively to obtain dronedarone hydrochloride which is further recrystallized by means of acetone.

5

However, each of the methods has drawbacks in that the desired compound can not be obtained easily in high purity and the processes disclosed are time consuming when employed for industrial application.

- 10 In light of the existing processes, there still exists a need to develop an improved chemical process for preparing dronedarone hydrochloride in high purity with optimum yield.

Object and Summary of the invention

- 15 It is an object of the present invention to provide simple, cost effective and eco-friendly process for the preparation of highly pure *N*-[2-butyl-3-[4-[3-(dibutylamino) propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide and its pharmaceutical acceptable salts.
- 20 It is another object of the present invention to provide *N*-[2-butyl-3-[4-[3-(dibutylamino) propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide (dronedarone) and its pharmaceutically acceptable salts having HPLC purity of 99.5% with disulfonamide and DRN-amino impurity less than 0.15%. .
- 25 It is still another object of the present invention to provide dronedarone hydrohalide in amorphous form and process for preparing the same.

It is yet another object of the invention is to obtain stable, pure acid addition salts of dronedarone having high purity.

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It is yet another object of the invention to obtain stable acid addition salts of 2-butyl-5-amino-3-[4-(3-(dibutylamino)propoxy)benzoyl]]benzofuran in crystalline and amorphous forms.

5 The above and other objects of the present invention are attained according to following preferred embodiments of the present invention. However the scope of the invention is not restricted to the particular embodiments discussed herein after.

10 In accordance with one embodiment of the present invention, there are provided highly pure N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methane sulfonamide hydrohalide having purity greater than 99.5% with disulfonamide and DRN-amino impurity less than 0.15%, wherein the hydrohalide is hydrochloride and hydrobromide.

15

In accordance with another embodiment of the present invention, there is provided a process for preparing highly pure N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide

hydrohalide having purity greater than 99.5% comprising hydrogenating 2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-nitrobenzofuran by means of a catalyst in presence of a hydrogen transfer reagent to obtain 5-amino-2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]benzofuran optionally converted into its acid addition salts followed by condensing the 5-amino-2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]benzofuran or its acid addition salts with
20 methane sulphonyl halide in presence of water and/or organic solvent to obtain N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrohalide, and isolating the N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrohalide thereof.

30

In accordance with still another embodiment of the present invention the hydrohalide is hydrochloride and hydrobromide.

5 In accordance with yet another embodiment of the present invention the process for preparing highly pure N-[2-butyl-3-[4-(3-(di-n-butylamino)propoxy)benzoyl]-5-benzofuranyl]methanesulfonamide hydrohalide optionally employing a base during condensation.

10 In accordance with yet another embodiment of the present invention, there is provided an improved process for preparing 5-amino-2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]benzofuran by hydrogenating 2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-nitrobenzofuran in presence of catalyst and hydrogen transfer reagent where 2-butyl-5-amino-3-[4-[3-(dibutylamino)propoxy]benzoyl]-benzofuran is optionally converted into its acid
15 addition salts. .

In accordance with yet another embodiment of the present invention, there is provided an improved process for preparing N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide or its acid
20 addition salts comprising condensing 2-butyl-5-amino-3-[4-(3-(dibutylamino)propoxy]benzoyl]]benzofuran or its acid addition salts with methane sulphonyl halide in presence of water and/or organic solvent and optionally a base.

25 In accordance with still another embodiment of the present invention, there is provided a process for purifying N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide and its acid addition salts, wherein the process comprising dissolving acid addition salts of N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-

benzofuranyl]methanesulfonamide in a mixture of acetone and water followed by isolation. .

5 In accordance with yet another embodiment of the present invention , there is provided a crystalline N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methane sulfonamide free base characterized by PXRD having peaks at 5.52, 8.21, 10.91, 13.62, 15.52, 16.33, 16.60, 17.74, 19.04, 19.91, 21.78, 23.79, 24.52, 25.04 and 30.05 ± 0.2 2 θ values as depicted in figure 7.

10 In accordance with still another embodiment of the present invention, there is provided a process for isolating N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide free base, having HPLC purity of >99.5%, by reacting an acid addition salts of N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide
15 with suitable base in presence of solvent.

In accordance with still another embodiment of the present invention, there is provided a crystalline N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methane sulfonamide hydrobromide salt.

20

In accordance with yet another embodiment of the present invention, there is provided an amorphous N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methane sulfonamide hydrobromide salt.

25 In accordance with yet another embodiment of the present invention, there is provided an amorphous N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methane sulfonamide hydrochloride salt.

In accordance with still another embodiment of the present invention, there is
30 provided a process for preparing amorphous N-[2-butyl-3-[4-[3-

(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrohalide, wherein the process comprising dissolving crystalline N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide. hydrochloride/ hydrobromide in a solvent followed by isolating an amorphous solid.

In accordance with still another embodiment of the present invention, there is provided an amorphous hydrochloride salt of 2-butyl-5-amino-3-[4-(3-(dibutylamino)propoxy] benzoyl]]benzofuran characterized by PXRD as depicted in figure 5.

In accordance with still another embodiment of the present invention, there is provided a crystalline oxalate salt of 2-butyl-5-amino-3-[4-(3-(dibutylamino)propoxy]benzoyl]] benzofuran, characterized by PXRD having peaks at 7.45, 8.15, 10.00, 10.66, 13.06, 15.27, 17.55, 20.07, 21.43, 22.45, 23.42, 23.76, 25.09, 26.18 and 30.06 ± 0.2 2θ values as shown in figure 6

Brief Description of the Drawings

Further objects of the present invention together with additional features contributing thereto and advantages accruing there from will be apparent from the following description of preferred embodiments of the invention which are shown in the accompanying drawing figures wherein :

FIG. 1 is a characteristic powder x-ray diffraction pattern of crystalline N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrochloride of the present invention.

FIG. 2 is a characteristic powder x-ray diffraction pattern of amorphous N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrochloride of the present invention.

FIG. 3 is a characteristic powder x-ray diffraction pattern of amorphous N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrobromide of the present invention.

5

FIG. 4 is a characteristic powder x-ray diffraction pattern of crystalline N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrobromide of the present invention.

10 FIG. 5 is a characteristic powder x-ray diffraction pattern of amorphous form of hydrochloride salt of compound of 2-butyl-5-amino-3-[4-(3-(dibutylamino)propoxy]benzoyl]]benzofuran of the present invention.

15 FIG. 6 is a characteristic powder x-ray diffraction pattern of crystalline form of oxalate salt of compound of 2-butyl-5-amino-3-[4-(3-(dibutylamino)propoxy]benzoyl]] benzofuran of the present invention.

FIG. 7 is a characteristic powder x-ray diffraction pattern of crystalline form of N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide free base of the present invention.

20

Detailed Description of the Invention

While this specification concludes with claims particularly pointing out and distinctly claiming that, which is regarded as the invention, it is anticipated that

25 the invention can be more readily understood through reading the following detailed description of the invention and study of the included examples.

The present invention discloses highly pure N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide

30 (dronaderone) hydrohalide having purity greater than 99.5% with disulfonamide

and DRN-amino impurity less than 0.15% and process for preparing the same thereof. In addition the present invention discloses acid addition salts of the same and polymorphic form thereof.

In accordance with the present invention, the hydrohalide is preferably
5 hydrochloride and hydrobromide.

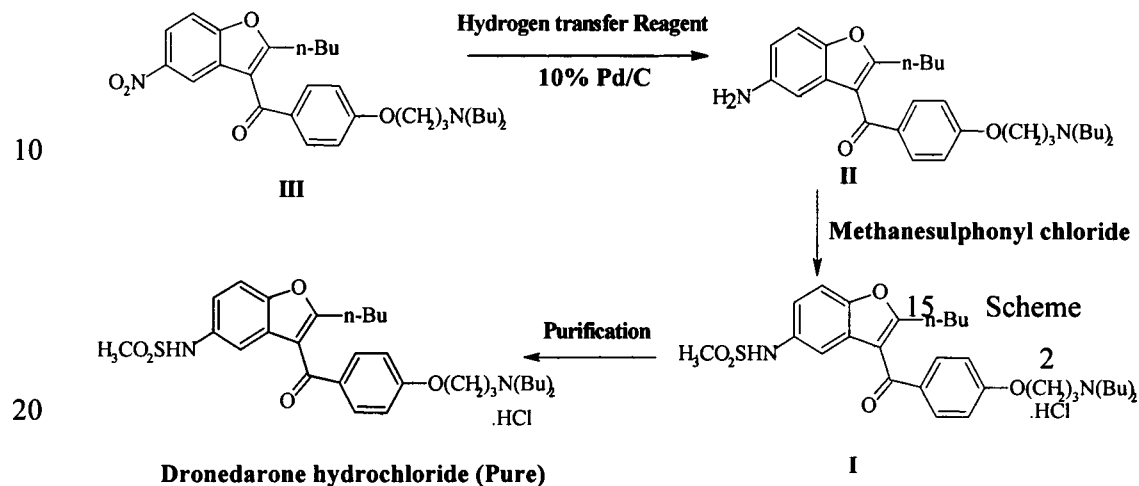
According to the invention, the process for preparing highly pure N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrohalide having purity greater than 99.5% comprises the following steps:

- 10 a) hydrogenating 2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-nitrobenzofuran (formula III) by means of a catalyst in presence of a hydrogen transfer reagent to obtain 5-amino-2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]benzofuran (formula II) optionally converted into its acid addition salts,
- 15 b) condensing the 5-amino-2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]benzofuran or its acid addition salts with methane sulphonyl halide in presence of water and/or organic solvent to obtain N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrohalide, and
- 20 c) isolating the N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrohalide (formula I) thereof.

In accordance with the present invention the salts of dronedarone are obtained directly from condensation stage, exclusive of isolation of dronedarone base
25 which reduces the reaction time and provides the product in optimum yield with HPLC purity of >99.0%.

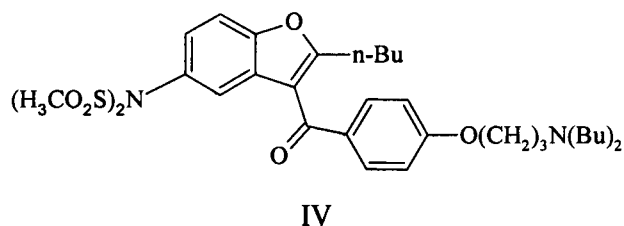
The process according to an embodiment of the present invention can be presented as shown in scheme 2.

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The disclosed embodiment of the present invention as shown above deals with the highly pure dronedarone hydrochloride with the purity of >99% in optimum yield where the impurities are restricted to less than 0.15%. The impurities mentioned herein are given below as sulfonamide (formula IV) impurity and DRN-amino impurity II.



35 As per the present invention the first embodiment is the hydrogenation of the compound of formula III in presence of catalyst and suitable hydrogen transfer catalyst. A suitable catalyst employed are selected from group comprising platinum or palladium charcoal system, palladium, or Raney Ni, zinc dust, mixture of zinc and hydrochloride acid, stannous chloride, mixture of tin and

hydrochloric acid, rhodium and platinum. According to the present invention, the hydrogen transfer reagents are selected from the group consisting of but not limited to hydrogen gas, aliphatic alcohol, alkali metal and amine esters of fatty acids exemplified by sodium acetate, ammonium formate, sodium formate and potassium formate preferably ammonium formate and sodium formate or mixtures thereof. In accordance with a preferred embodiment of the present invention, the molar ratio of compound of 2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-nitrobenzofuran (formula III) to the hydrogen transfer reagents can be 1:1 to 1: 5, preferably 1: 2 to 1:4, more preferably 1: 2.5.

10

The reaction is usually carried out in an solvent and solvents used during the hydrogenation reaction are selected from the group consisting of but not limited to ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, 2-methyl tetrahydrofuran; organic acid such as formic acid, acetic acid; alcohol such as methanol, ethanol, isopropyl alcohol, butanol, propanol; or mixture thereof.

15

The reaction temperature is usually within range between 20°C to reflux temperature of the solvent used in the reaction. The above hydrogenation reaction is carried out at atmospheric pressure as well as at high pressure depending on the hydrogen transfer reagents used along with catalyst for the reaction. Alternatively, the reaction can also be carried out in inert atmosphere.

20

The compound of formula II obtained from hydrogenation step can optionally be isolated as such *i.e.* free DRN-amino base or as its acid addition salts wherein acid addition salts include oxalate, tartarate, fumarate, hydrochloride, hydrobromide and the like. These salts are prepared by reacting compound of formula II with an acid in a solvent followed by the addition of anti solvents. The solvent used herein is selected from the group comprising of alcohol such as methanol, ethanol, propanol, iso-propanol, butanol, iso-butanol and the like. The

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anti-solvent used herein is selected from the group consisting of but not limited to ether such as diethyl ether, diisopropyl ether and the like. The obtained acid addition salts are having the purity of >98.5% by HPLC and further characterized as crystalline as well as amorphous form.

5

In accordance with a second embodiment of the invention, there is disclosed the sulfonylation reaction of compound of formula II or its acid addition salt to obtain dronedarone or its acid addition salt. The solvent used for sulfonylation step herein is selected from the group consisting of water or organic solvents. The

10 organic solvent used herein is selected from the group consisting of but not limited to alcohol such as methanol, ethanol; ketone such as acetone, methyl isobutyl ketone, methyl ethyl ketone; nitrile such as acetonitrile, propionitrile; dimethylformamide, dimethylsulfoxide, ether such as tetrahydrofuran, dioxane; ester such as ethyl acetate, n-butyl acetate, isopropyl acetate; aromatic
15 hydrocarbon such as toluene, xylene; chlorinated hydrocarbon such as chloroform, carbon tetrachloride, methylene dichloride or mixtures thereof.

The reaction temperature is usually about -10°C - 60°C, preferably about 20-40°C, more preferably about 35-45°C. The molar ratio of methane sulphonyl
20 halide to the compound of formula II is in the ratio of 0.7-2.0. In addition to the above, base is optionally added during condensation reaction in the molar ratio of 0.5 to 1.5 with respect to compound II where the base is selected from the group consisting of but not limited to organic or inorganic base. Organic base used herein is selected from the group consisting of but not limited to triethyl amine,
25 diisopropyl amine, diisopropyl ethyl amine, N-methylpyrrolidone, pyridine, morphine and the like. Inorganic base used herein is selected from the group consisting of but not limited to alkali metal, alkaline earth metal hydroxide, carbonate, hydroxy carbonate such as sodium hydroxide, sodium carbonate, sodium hydroxycarbonate, potassium hydroxide, potassium carbonate, potassium

hydroxycarbonate and the like. The methane sulfonyl halide used herein is selected from the group consisting of methane sulfonyl chloride or bromide.

5 The product obtained from the above sulfonylation reaction is in the form of either hydrochloride or hydrobromide salt. The dronedarone hydrochloride salt or hydrobromide salt thus obtained is in crystalline form which is optionally purified further to get HPLC purity of $\geq 99.5\%$ with disulfonamide impurity as $< 0.15\%$ and DRN-amino impurity as $< 0.15\%$.

10 In accordance with another embodiment of the invention is the purification process of dronedarone acid addition salt wherein acid addition salts of dronedarone is dissolved in mixture of acetone and water in the molar ratio of 1:0.03 followed by cooling to isolate crystalline acid addition salts of dronedarone with desired purity.

15 In accordance with a still further embodiment of the present invention a dronedarone free base with HPLC purity of $\geq 99.5\%$ is isolated. The pure dronedarone free base as solid can be prepared by reacting acid addition salts of dronedarone with suitable base in presence of solvent. The base used herein is
20 selected from the group consisting of organic base such as triethyl amine, diisopropyl amine, diisopropyl ethyl amine and the like or inorganic base such as ammonia, alkali metal, alkaline earth metal hydroxide such as sodium hydroxide, potassium hydroxide; carbonate such as sodium carbonate, potassium carbonate; hydroxy carbonate such as sodium hydroxycarbonate, potassium hydroxy
25 carbonate and the like. The solvent used herein is water immiscible solvent selected from the group consisting of but not limited to ester such as ethyl acetate, butyl acetate, propyl acetate; halogenated solvents such as methylene dichloride, trichloromethane; hydrocarbon solvent such as toluene, xylene; hydrocarbons such as hexane, heptane, cyclohexane, pentane; alcohol such as n-
30 butanol, isopropanol and the like or mixture thereof. The dronedarone free base

can be further converted to its acid addition salts by reaction it with acid in presence of solvent. The acid used herein is selected from the group consisting of but not limited to oxalic acid, malic acid, tartaric acid, fumaric acid, succinic acid, acetic acid, salicylic acid, phthalic acid, hydrochloric acid, hydrobromic and sulfuric acid preferably hydrochloride salt or hydrobromide salt. The solvent used herein is selected from the group consisting of but not limited to ester such as ethyl acetate, propyl acetate, butyl acetate.

According to an embodiment of the invention, there is provided a crystalline N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide free base characterized by PXRD having peaks at 5.52, 8.21, 10.91, 13.62, 15.52, 16.33, 16.60, 17.74, 19.04, 19.91, 21.78, 23.79, 24.52, 25.04 and 30.05 ± 0.2 2θ values as depicted in figure 7.

According to another embodiment of the invention, there is provided a crystalline N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrobromide salt characterized by PXRD having peaks at 7.65, 7.75, 8.08, 11.87, 13.11, 13.70, 15.54, 15.64, 16.20, 20.19, 20.73, 21.02, 21.23, 21.62, 24.08, 25.95, 27.39 and 28.20 ± 0.2 2θ values as shown in figure 4.

According to still another embodiment of the invention, there is provided an amorphous N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methane sulfonamide hydrobromide salt characterized by PXRD as shown in figure 3.

According to yet another embodiment of the invention, there is provided an amorphous N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrochloride salt is characterized by PXRD as shown in figure 2.

According to yet another embodiment of the invention, there is provided a process for preparing the amorphous N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide

5 hydrohalide, wherein the process comprising dissolving crystalline N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrochloride/ hydrobromide in a solvent followed by isolating an amorphous solid. The isolation is performed by filtration or by addition of anti-solvent selected from the group comprising ether such as diethyl ether, diisopropyl ether

10 and the like. The solvent employed is selected from the group comprising of chlorinated solvents such as methylene dichloride, trichloromethane or mixtures thereof in the temperature range of 0 to 70°C, preferably 15-60°C, more preferably 25-50°C. The obtained solution is further evaporated to get the residue which can further isolated as solid either by means of filtration or by addition of

15 solvent selected from the group comprising of ether such as , diethyl ether, diisopropyl ether and the like. The purity of the compound obtained herewith is $\geq 99.5\%$ by HPLC.

In accordance with the invention, there is provided an amorphous hydrochloride

20 salt of 2-butyl-5-amino-3-[4-[3-(dibutylamino)propoxy]benzoyl]benzofuran characterized by PXRD as depicted in figure 5.

In accordance with the invention, there is provided a crystalline oxalate salt of 2-butyl-5-amino-3-[4-[3-(dibutylamino)propoxy]benzoyl]benzofuran, characterized

25 by PXRD having peaks at 7.45, 8.15, 10.00, 10.66, 13.06, 15.27, 17.55, 20.07, 21.43, 22.45, 23.42, 23.76, 25.09, 26.18 and 30.06 ± 0.2 2θ values as shown in figure 6.

In the following section preferred embodiments are described by way of examples to illustrate the process of the invention. However, these are not intended in any way to limit the scope of the present invention.

5 **Exapmle-1**

Preparation _____ of _____ 5-amino-[2-butyl-3-r4-(3-dibutylamino)propoxy]benzoyl1benzofuran

To a mixture of 2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-nitrobenzofuran (10gm) and Pd on carbon (10%) (1gm) in methanol (80 ml),
 10 ammonium formate (6.20gm) was added followed by stirring for few hours. On completion of a reaction catalyst was filtered and methanol was distilled out under vacuum to give oily mass. To this oily mass dichloromethane (50ml) was added followed by washing it with water (50ml). Layers were separated and organic layer was distilled out to give title compound as oily mass (9.0 gm).
 15 HPLC Purity >98%.

Example-2

Preparation _____ of _____ N-i2-butyl-3-r4-(3-(di-n-butylamino)propoxy)benzoyl1-5-benzofuranyll methanesulfonamide hydrochloride

20 To a solution of 5-amino-2-butyl-3-[4-[3-(dibutylamino)propoxy]]benzoyl]benzofuran (10 gm) in water (250ml), methanesulfonyl chloride (2.39gm) was added. Reaction mass was stirred for 2 hrs and filtered followed by washing with water. The solid obtained was dried at 55°C with HPLC purity >99% and disulphonamide impurity <0.15%. The
 25 obtained product is crystalline in nature as shown in Fig 1.

Example-3

Preparation _____ of _____ amorphous _____ N-r2-butyl-3-r4-(3-(di-n-butylamino)propoxy)benzoyl1-5-benzofuranyllmethanesulfonamide
 30 hydrochloride

N-[2-Butyl-3-[4-(3-(di-n-butylamino)propoxy)benzoyl]-5-benzofuranyl]methanesulfon amide hydrochloride (5 gm) was dissolved in dichloromethane (25 ml) followed by distillation under vacuum to get residue and to this residue diisopropyl ether was added. The reaction mixture was stirred and
 5 the solid obtained was filtered and dried in vacuum at 45°C. The product (4.0 gm) obtained was amorphous in nature as shown in Fig 2.

Example-4

Preparation of amorphous N-[2-butyl-3-r4-(3-(di-n-butylamino)propoxy)benzoyl]-5-benzofuranyl methanesulfonamide hydrochloride
 10 butylamino)propoxy)benzoyl]-5-benzofuranyl methanesulfonamide
hydrochloride

N-[2-Butyl-3-[4-(3-(di-n-butylamino)propoxy)benzoyl]-5-benzofuranyl] methanesulfon amide hydrochloride (5 gm) was dissolved in dichloromethane (25 ml). The solvent is removed by distillation under vacuum and the solid thus
 15 obtained is further dried at 45°C to get a product in amorphous form.

Example-5

Preparation of N-2-butyl-3-[4-(3-(di-n-butylamino)propoxy)benzoyl]-5-benzofuranyl methanesulfonamide hydrobromide (Dronedarone Hydrobromide)
 20 Hydrogen bromide in ether was added to the solution of N-[2-butyl-3[4-(3-dibutylamino)propoxy)benzoyl]-5-benzofuran] methanesulfonamide (10 gm) in anhydrous ethyl acetate (100 ml). The mixture was stirred continuously till the precipitation of the product. The product thus obtained was filtered; wet cake was washed with ethyl acetate and dried to get N-[2-butyl-3-[4-(3-(di-n-
 25 butylamino)propoxy)benzoyl]-5-benzofuranyl] methanesulfonamide hydrobromide having purity of > 99.5 % measured by HPLC.

Example-6

Preparation _____ of _____ amorphous _____ N-[2-butyl-3-[4-(3-(di-n-butylamino)propoxy)benzoyl]-5-benzofuranyl]methanesulfonamide hydrobromide

- 5 N-[2-Butyl-3-[4-(3-(di-n-butylamino)propoxy)benzoyl]-5-benzofuranyl]methanesulfonamide hydrobromide (5gm) was dissolved in dichloromethane (25ml). The solvent is removed by distillation under vacuum and the solid thus obtained is further dried at 45°C to get a product in amorphous form.

10 **Example-7**

Preparation _____ of _____ amorphous _____ N-[2-butyl-3-[4-(3-(di-n-butylamino)propoxy)benzoyl]-5-benzofuranyl]methanesulfonamide hydrobromide

- 15 N-[2-butyl-3-[4-(3-(di-n-butylamino)propoxy)benzoyl]-5-benzofuranyl]methanesulfonamide hydrobromide (5gm) was dissolved in dichloromethane (25 ml) followed by distillation under vacuum to get residue and to this residue diisopropyl ether was added. The reaction mixture was stirred and the solid obtained was filtered and dried in vacuum at 45°C. The product (4.0gm) obtained was amorphous in nature.

20

Example-8

Preparation _____ of _____ N-[2-butyl-3-[4-(3-(di-n-butylamino)propoxy)benzoyl]-5-benzofuranyl]methanesulfonamide (Dronedarone Base)

- 25 N-[2-Butyl-3-[4-(3-(di-n-butylamino)propoxy)benzoyl]-5-benzofuranyl]methanesulfonamide hydrochloride (10 gm) was dissolved in dichloromethane (100 ml). The solution was neutralized by ammonia solution and the product was extracted in dichloromethane where the dichloromethane was removed under reduced pressure to get oily mass. The product was
- 30 precipitated out from oily mass by adding hexane (100 ml) with continuous

stirring. The product was filtered; wet cake was washed with hexane and dried to get N-[2-butyl-3-[4-(3-(di-n-butylamino)propoxy)benzoyl]-5-benzofuranyl]methanesulfonamide with purity of $\geq 99.5\%$ measured by HPLC.

5

Example-9

Preparation _____ of _____ 5-amino-2-n-butyl-3-[4-(3-di-n-butylaminopropoxy)benzoyl]benzofuran hydrochloride

5-Amino-2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]benzofuran (10gm) was dissolved in dichloromethane (100 ml) was reacted with hydrochloride gas to
 10 adjust the pH of the reaction mixture at 0.5-1.5. Dichloromethane was removed and acetone was added to the oily mass to get clear solution. The acetone was removed completely under vacuum to get the solid product with HPLC purity $\geq 98.5\%$.

15 While this invention has been described in detail with reference to certain preferred embodiments, it should be appreciated that the present invention is not limited to those precise embodiments. Rather, in view of the present disclosure, which describes the current best mode for practicing the invention, many modifications and variations would present themselves to those skilled in the art
 20 without departing from the scope and spirit of this invention.

What is claimed is:

1. Highly pure N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrohalide having purity greater than
5 99.5% with disulfonamide and DRN-amino impurity less than 0.15%.

2. The N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl] methanesulfonamide as claimed in claim 1, wherein the hydrohalide is hydrochloride and hydrobromide.
10

3. A process for preparing highly pure N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrohalide having purity greater than 99.5% wherein the process comprising:

a) hydrogenating 2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-nitrobenzofuran by means of a
15 catalyst in presence of a hydrogen transfer reagent to obtain 5-amino-2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]benzofuran optionally converted into its acid addition salts;

b) condensing the 5-amino-2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]benzofuran or its acid addition salts with methane sulphonyl halide in presence of water and/or organic solvent to obtain N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrohalide; and
20

c) isolating the N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrohalide thereof.
25

4. The process as claimed in claim 3, wherein the hydrohalide is hydrochloride and hydrobromide.
30

5. The process as claimed in claim 3, wherein the catalyst employed is selected from the group comprising platinum or palladium charcoal system, palladium, or Raney Ni, zinc dust, mixture of zinc and hydrochloride acid, stannous chloride, mixture of tin and hydrochloric acid, rhodium and platinum.

5

6. The process as claimed in claim 3, wherein the hydrogen transfer reagent is selected from the group consisting of hydrogen gas, aliphatic alcohol, alkali metal and amine esters of fatty acids.

10

7. The process as claimed in claim 6, wherein the ester of fatty acids employed is selected from sodium acetate, ammonium formate, sodium formate and potassium formate preferably ammonium formate and/or sodium formate or mixtures thereof.

15

8. The process as claimed in claim 3, wherein the hydrogenation reaction is carried out in presence of a solvent selected from the group consisting of ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, 2-methyl tetrahydrofuran; organic acid such as formic acid, acetic acid; alcohol such as methanol, ethanol, isopropyl alcohol, butanol, propanol; or mixture thereof.

20

9. The process as claimed in claim 3, wherein the molar ratio of the 2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-nitrobenzofuran to the hydrogen transfer reagent is in the range of 1:1 to 1:5.

25

10. The process as claimed in claim 3, wherein the organic solvent employed is selected from the group comprising alcohol such as methanol, ethanol; ketone such as acetone, methyl isobutyl ketone, methyl ethyl ketone; nitrile such as acetonitrile, propionitrile; dimethylformamide, dimethylsulfoxide, ether such as tetrahydrofuran, dioxane; ester such as ethyl acetate, n-butyl acetate,

30

isopropyl acetate; aromatic hydrocarbon such as toluene, xylene; chlorinated hydrocarbon such as chloroform, carbon tetrachloride, methylene dichloride or mixtures thereof.

5 11. The process as claimed in claim 3, wherein the methane sulfonyl halide used is methane sulfonyl chloride and methane sulfonyl bromide.

12. A process as claimed in claim 3, wherein the process optionally employing a base in step (b).

10

13. The process as claimed in claim 12, wherein the base employed is selected from organic or inorganic base where the organic base is selected from the group consisting of triethyl amine, diisopropyl amine, diisopropyl ethyl amine, N-methylpyrrolidone, pyridine, morphine whereas inorganic base is
15 selected from the group consisting of alkali metal, alkaline earth metal hydroxide, carbonate, hydroxycarbonate such as sodium hydroxide, sodium carbonate, sodium hydroxycarbonate, potassium hydroxide, potassium carbonate, potassium hydroxycarbonate.

20 14. An improved process for preparing 5-amino-2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]benzofuran by hydrogenating 2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-nitrobenzofuran in presence of catalyst and hydrogen transfer reagent where 2-butyl-5-amino-3-[4-[3-(dibutylamino)propoxy]benzoyl]-benzofuran is optionally converted into its acid
25 addition salts.

15. The process as claimed in claim 14, wherein the catalyst employed is selected from the group comprising platinum or palladium charcoal system, palladium, or Raney Ni, zinc dust, mixture of zinc and hydrochloride acid,
30 stannous chloride, mixture of tin and hydrochloric acid, rhodium and platinum.

16. The process as claimed in claim 14, wherein the hydrogen transfer reagent is selected from the group consisting of hydrogen gas, aliphatic alcohol, alkali metal and amine esters of fatty acids including sodium acetate,
5 ammonium formate, sodium formate and potassium formate preferably ammonium formate and sodium formate or mixtures thereof.

17. The process as claimed in claim 14, wherein the reaction is carried out in a solvent selected from the group consisting of ether such as diethyl ether,
10 diisopropyl ether, tetrahydrofuran, dioxane, 2-methyl tetrahydrofuran; organic acid such as formic acid, acetic acid; alcohol such as methanol, ethanol, isopropyl alcohol, butanol, propanol; or mixture thereof.

18. The process as claimed in claim 14, wherein the molar ratio of the
15 2-butyl-3-[4-(3-(dibutylamino)propoxy)benzoyl]]-5-nitrobenzofuran to the hydrogen transfer reagents is in the range of 1:1 to 1: 5.

19. The process as claimed in claim 14, wherein acid employed to obtain acid addition salts is selected from the group comprising oxalic acid,
20 tartaric acid, fumaric acid, hydrochloride and hydrobromide.

20. An improved process for preparing N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide or its acid addition salts comprising condensing 2-butyl-5-amino-3-[4-[3-(dibutylamino)propoxy]benzoyl]benzofuran or its acid addition salts with
25 methane sulphonyl halide in presence of water and/or organic solvent and optionally a base.

21. The process as claimed in claim 20, wherein the acid addition salt
30 is hydrochloride and hydrobromide.

22. The process as claimed in claim 20, wherein the organic solvent employed is selected from the group comprising alcohol such as methanol, ethanol; ketone such as acetone, methyl isobutyl ketone, methyl ethyl ketone; 5 nitrile such as acetonitrile, propionitrile; dimethylformamide, dimethylsulfoxide, ether such as tetrahydrofuran, dioxane; ester such as ethyl acetate, n-butyl acetate, isopropyl acetate; aromatic hydrocarbon such as toluene, xylene; chlorinated hydrocarbon such as chloroform, carbon tetrachloride, methylene dichloride or mixtures thereof.

10

23. The process as claimed in claim 20, wherein the base employed is selected from organic or inorganic base where the organic base is selected from the group consisting of triethyl amine, diisopropyl amine, diisopropyl ethyl amine, N-methylpyrrolidone, pyridine, morphine and inorganic base is selected 15 from the group consisting of alkali metal, alkaline earth metal hydroxide, carbonate, hydroxycarbonate.

24. The process as claimed in claim 20, wherein the reaction is carried out at temperature about -10°C to 60°C.

20

25. The process as claimed in claim 20, wherein the methane sulfonyl halide employed is in molar ratio of 0.7-2.0 with respect to compound of 5-amino-2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]benzofuran.

26. The process as claimed in claim 20, wherein the methane sulfonyl halide employed is methane sulfonyl chloride or methane sulfonyl bromide.

27. A process for purifying N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide and its 30 acid addition salts, wherein the process comprising dissolving acid addition salts

of N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide in a mixture of acetone and water followed by isolation.

5 28. A crystalline N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide free base characterized by PXRD having peaks at 5.52, 8.21, 10.91, 13.62, 15.52, 16.33, 16.60, 17.74, 19.04, 19.91, 21.78, 23.79, 24.52, 25.04 and 30.05 ± 0.2 2 θ values as depicted in figure 7.

10 29. A process for isolating N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide free base, having HPLC purity of >99.5%, by reacting an acid addition salts of N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide with suitable base in presence of solvent.

15 30. The process as claimed in claim 29, wherein base is selected from the group consisting of organic base such as triethyl amine, diisopropyl amine, diisopropyl ethyl amine and the like or inorganic base such as ammonia, alkali metal, alkaline earth metal hydroxide such as sodium hydroxide, potassium
20 hydroxide; carbonate such as sodium carbonate, potassium carbonate; hydroxycarbonate such as sodium hydroxycarbonate, potassium hydroxycarbonate and the like.

25 31. The process as claimed in claim 29, wherein the solvent employed is water immiscible selected from the group consisting of ester such as ethyl acetate, butyl acetate, propyl acetate; halogenated solvents such as methylene dichloride, trichloromethane; hydrocarbon solvent such as toluene, xylene; hydrocarbons such as hexane, heptane, cyclohexane, pentane; alcohol such as butanol, iso-propanol and the like or mixture thereof.

30

32. A crystalline N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrobromide salt.

33. The crystalline N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrobromide salt as claimed in claim 32 is characterized by PXRD having peaks at 7.65, 7.75, 8.08, 11.87, 13.11, 13.70, 15.54, 15.64, 16.20, 20.19, 20.73, 21.02, 21.23, 21.62, 24.08, 25.95, 27.39 and 28.20 ± 0.2 2θ values as shown in figure 4.

34. An amorphous N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrobromide salt.

35. The amorphous N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrobromide salt as claimed in claim 34 is characterized by PXRD as shown in figure 3.

36. An amorphous N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrochloride salt.

37. The amorphous N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrochloride salt as claimed in claim 36, is characterized by PXRD having peaks as shown in figure 2.

38. A process for preparing amorphous N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrohalide, wherein the process comprising dissolving crystalline N-[2-butyl-3-

[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide hydrochloride/ hydrobromide in a solvent followed by isolating an amorphous solid.

5 39. The process as claimed in claim 38, wherein the isolation is performed by filtration.

 40. The process as claimed in claim 38, wherein the isolation is performed by addition of anti-solvent selected from the group comprising ether
10 such as diethyl ether, diisopropyl ether and the like.

 41. The process as claimed in claim 38, wherein the solvent employed is selected from the group comprising of chlorinated solvents such as methylene dichloride, trichloromethane or mixtures thereof.

15

 42. Amorphous hydrochloride salt of 2-butyl-5-amino-3-[4-[3-(dibutylamino) propoxy]benzoyl]benzofuran characterized by PXRD as depicted in figure 5.

20

 43. Crystalline oxalate salt of 2-butyl-5-amino-3-[4-[3-(dibutylamino)propoxy]benzoyl]benzofuran, characterized by PXRD having peaks at 7.45, 8.15, 10.00, 10.66, 13.06, 15.27, 17.55, 20.07, 21.43, 22.45, 23.42, 23.76, 25.09, 26.18 and 30.06 ± 0.2 2 Θ values as shown in figure 6.

25

FIG. 1

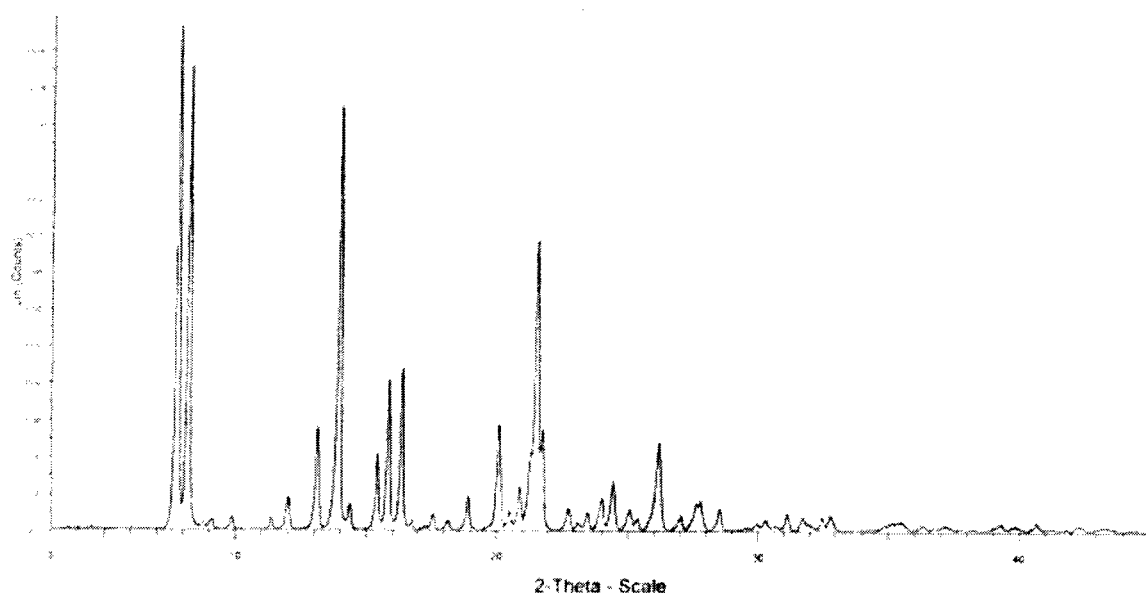


FIG. 2

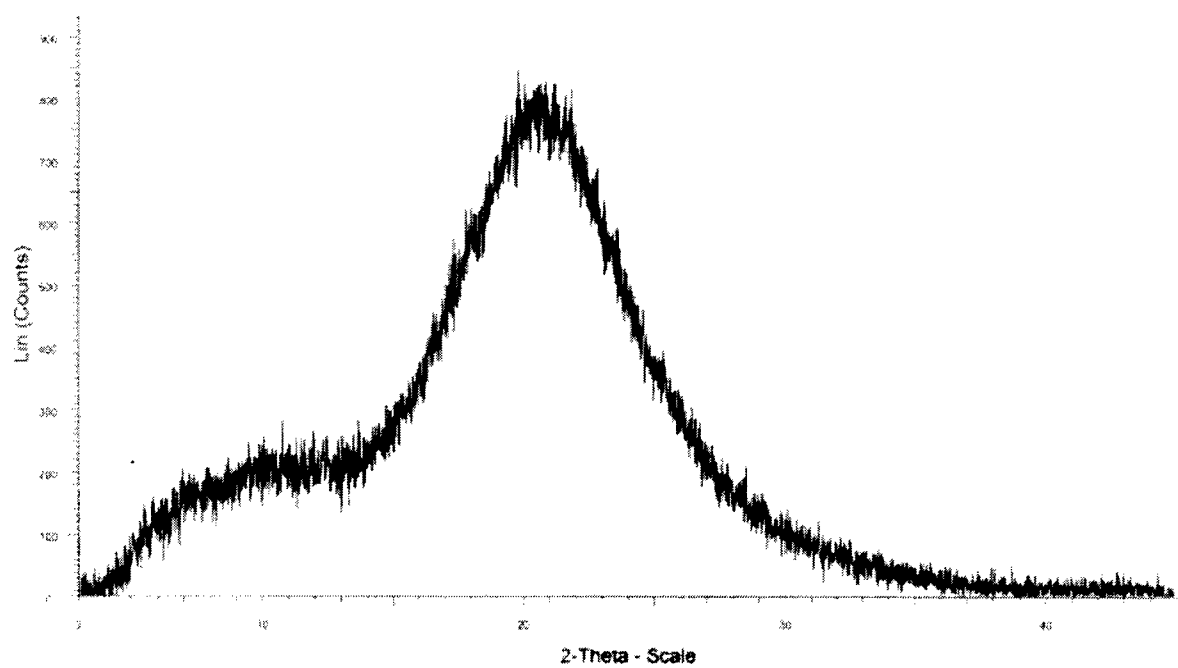


FIG. 3

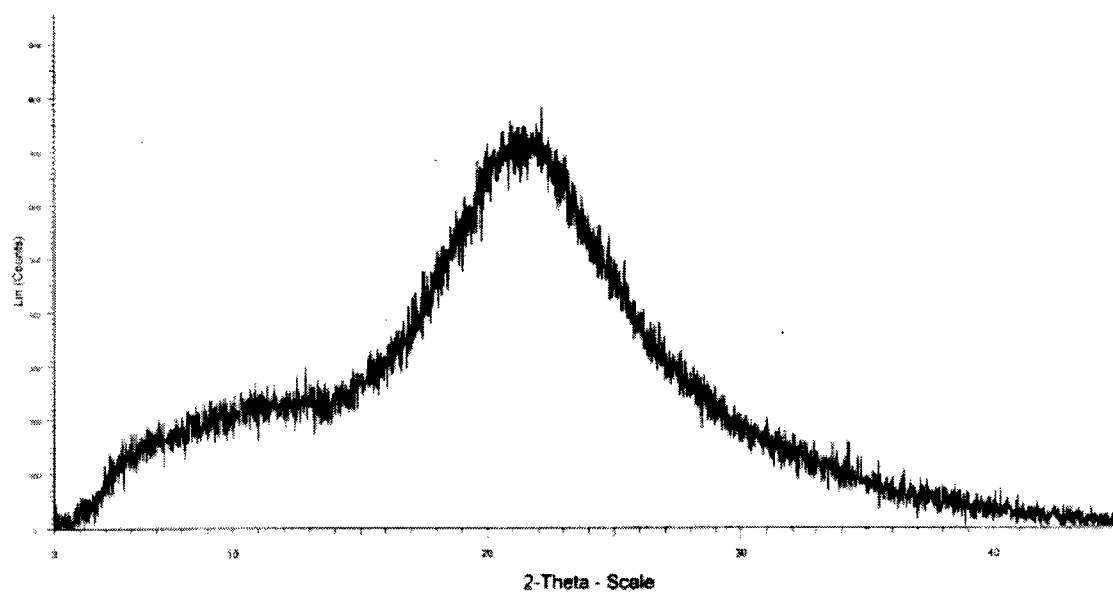


FIG. 4

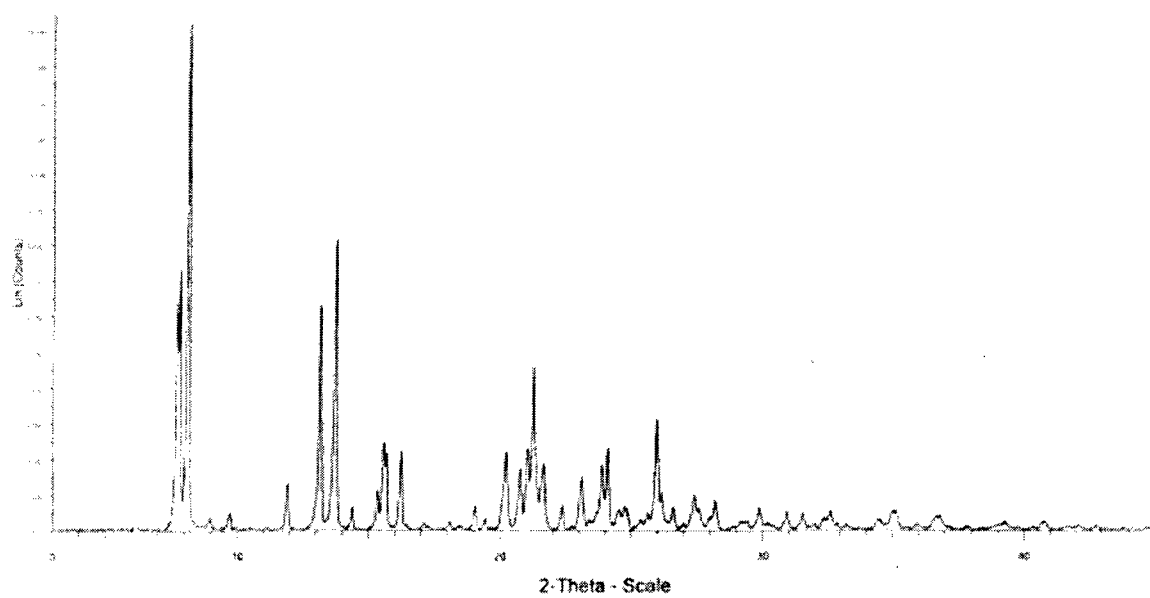


FIG. 5

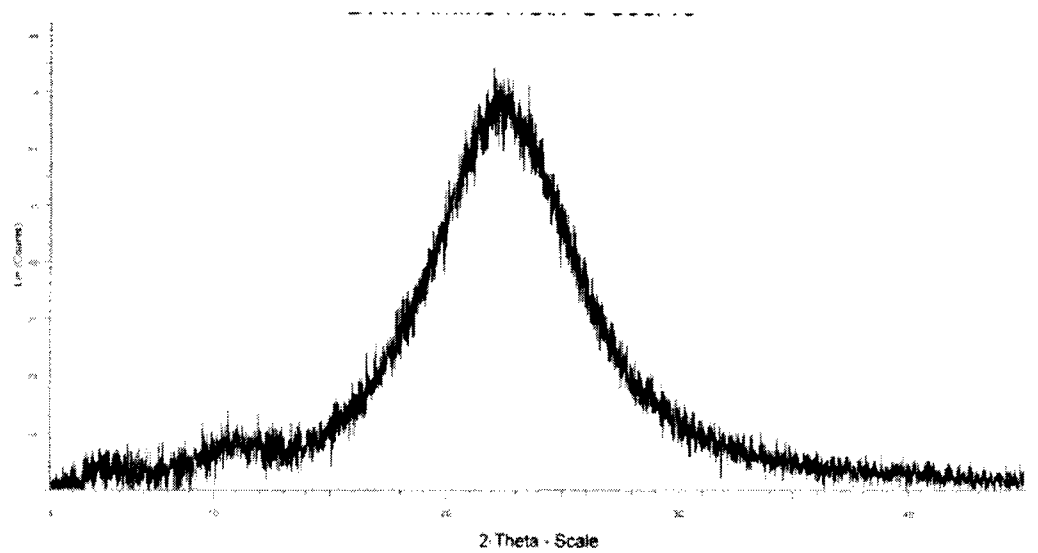


FIG. 6

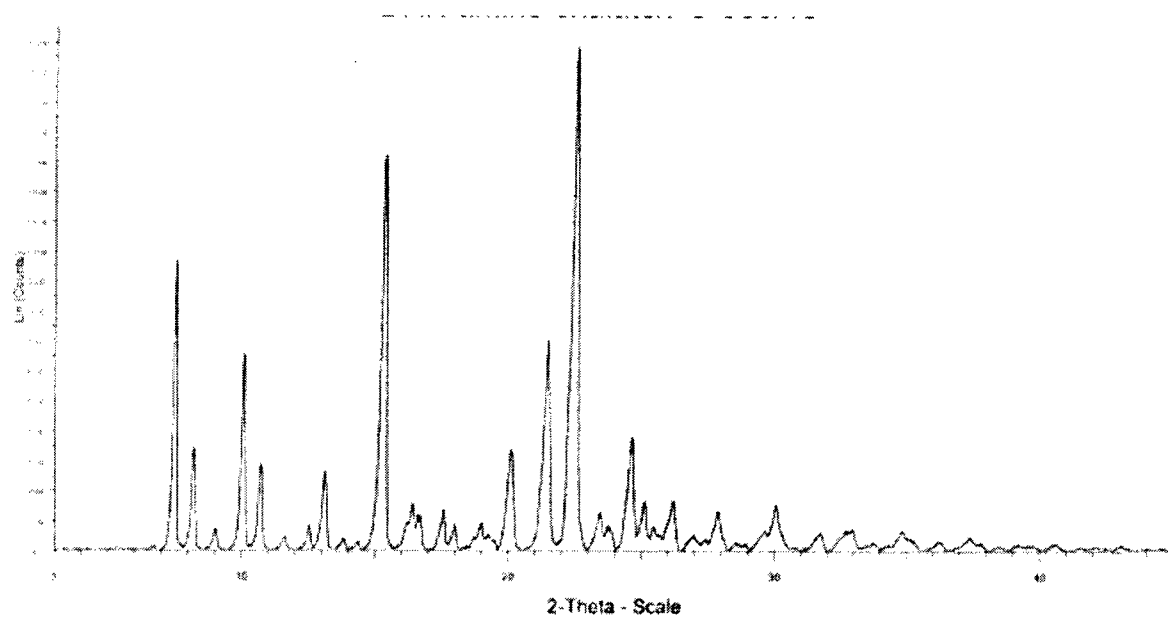


FIG. 7

