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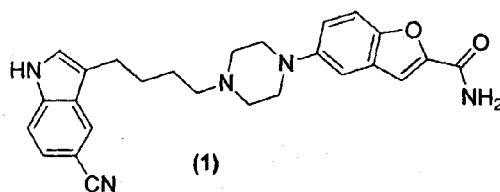
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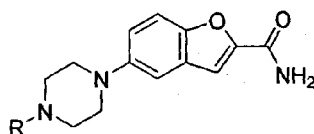
(54) **Title:** POLYMORPHIC FORM OF 5-(4-[4-(5-CYANO-1H-INDOL-3- YL)BUTYL]PIPERAZIN-1-YL) BENZOFURAN-2-CARBOXAMIDE

(1)



(1)

(X)



(57) **Abstract:** The present invention relates to a process for the preparation of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl)benzofuran-2-carboxamide of Formula (1) or its pharmaceutically acceptable salt, solvates or hydrates thereof. In particular, the present invention provides a novel intermediate compound, 5-(4-substitutedpiperazin-1-yl)benzofuran-2-carboxamide of Formula (X). The present invention further provides solid state form of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl)benzofuran-2-carboxamide of Formula (1) and process for its preparation.

POLYMORPHIC FORM OF 5-(4-[4-(5-CYANO-1H-INDOL-3-YL)BUTYL]PIPERAZIN-1-YL) BENZOFURAN-2-CARBOXAMIDE

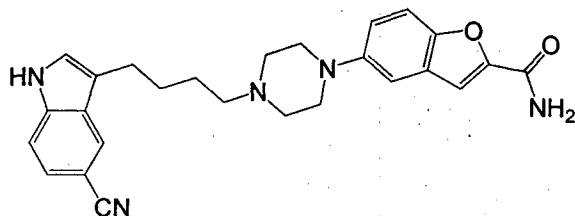
FIELD OF THE INVENTION

5 The present invention relates to a process for the preparation of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl)benzofuran-2-carboxamide of Formula (1) or its pharmaceutically acceptable salt, solvates or hydrates thereof. In particular, the present invention provides a novel intermediate compound, 5-(4-substitutedpiperazin-1-yl)benzofuran-2-carboxamide of Formula (X).

10 The present invention further provides solid state form of 5-(4-[4-(5-cyano-1H-indol-3-yl) butyl]piperazin-1-yl)benzofuran-2-carboxamide of Formula (1) and process for its preparation.

BACKGROUND OF THE INVENTION

U.S. Patent No. 5,532,241 discloses 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl) benzofuran-2-carboxamide i.e. vilazodone of Formula (1)



(1)

or its pharmaceutically acceptable salt. The '241 patent discloses process for preparing vilazodone or its pharmaceutically acceptable salt thereof.

20 U.S. Patent No. 5,977,112 relates to process for preparing intermediate involved in the preparation of vilazodone or its pharmaceutically acceptable salt thereof.

U.S. Patent No. 6,509,475 B1 relates to process for preparing intermediate involved in the preparation of vilazodone or its pharmaceutically acceptable salt

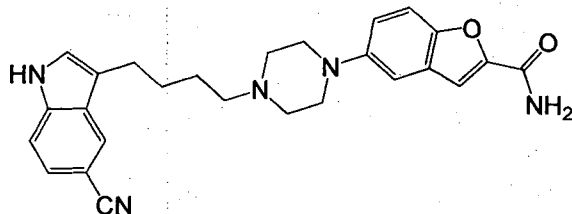
25 thereof.

U.S. Patent No. 7,834,020 B2 (the US '020 B2) claims vilazodone hydrochloride anhydrate in crystalline modification IV (Form IV) characterized by XRD. The US '020 B2 discloses total 15 crystalline forms of Vilazodone HCl designated as crystalline Form-I to Form-XI and Form-XIII to Form-XVI.

U.S. Patent No. 7,981,894 B2 claims vilazodone hydrochloride monohydrate in crystalline modification V (Form-V) having characteristic peaks in XRD.

SUMMARY OF THE INVENTION

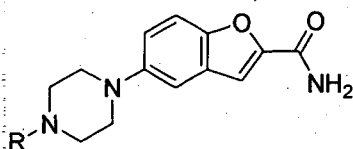
In general aspect, the invention provides a new process for the preparation of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl)benzofuran-2-carboxamide of Formula (1) or its pharmaceutically acceptable salts, solvates or hydrates thereof. The compound of Formula (1) is known as vilazodone.



(1)

In another aspect, the present invention provides vilazodone of Formula (1) or its pharmaceutically acceptable salts, solvates or hydrates thereof having a total purity of greater than about 99%, specifically greater than about 99.5%, most specifically greater than about 99.9%, as measured by HPLC.

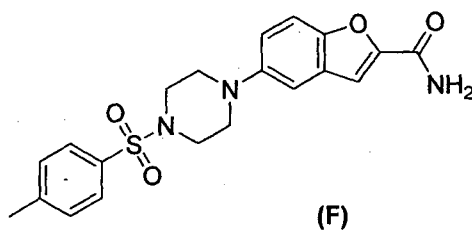
Another aspect of the present invention provides a novel intermediate compounds, 5-(4-substituted piperazin-1-yl)benzofuran-2-carboxamide of Formula (X),



(X)

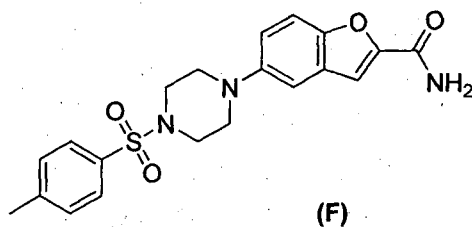
wherein R is a suitable amino protecting group selected from, methanesulfonamide, p-methoxybenzyl carbonyl, p-toluenesulfonamide, tert-butyloxycarbonyl (BOC), 9-fluorenylmethyloxycarbonyl (Fmoc), benzyl carbamate, acetamide, phthalimide, carbobenzyloxy (Cbz), acetyl, benzoyl, benzyl, carbamates, p-methoxybenzyl, p-methoxyphenyl and the like.

In another general aspect, the present invention provides a novel intermediate compound, 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F).

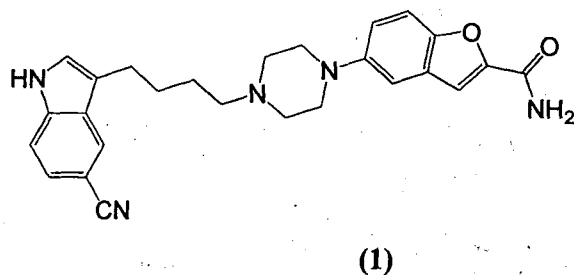


In another general aspect, the present invention provides the use of the novel intermediate 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F) for the preparation of vilazodone.

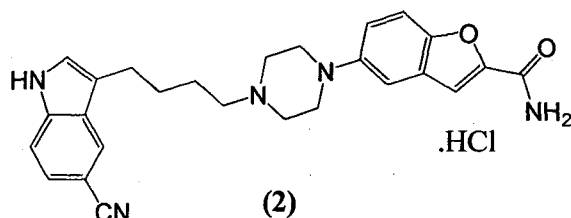
Another aspect of present invention provides a process for the preparation of the novel intermediate 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F)



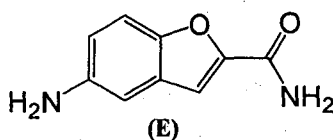
In another general aspect, the present invention provides the use of solid state form of novel intermediate 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F) in the preparation of vilazodone of Formula (1)



or its pharmaceutically acceptable salts thereof, particularly vilazodone hydrochloride salt of Formula (2)



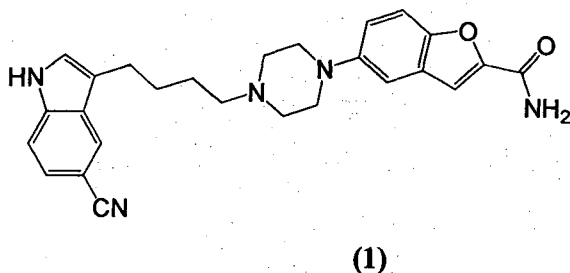
In another general aspect, the present invention provides an improved process for preparing 5-aminobenzofuran-2-carboxamide of Formula (E),



comprising of:

- i) reacting salicylaldehyde with chloroacetic acid in an organic solvent and a base to obtain 2-(2-formylphenoxy) acetic acid of Formula (A);
- ii) nitrating 2-(2-formylphenoxy)acetic acid of Formula (A) to obtain 2-(2-formyl-4-nitrophenoxy)acetic acid of Formula (B);
- iii) cyclizing 2-(2-formyl-4-nitrophenoxy) acetic acid of Formula (B) to obtain 5-nitrobenzofuran-2-carboxylic acid of Formula (C);
- iv) converting 5-nitrobenzofuran-2-carboxylic acid of Formula (C) to 5-nitrobenzofuran-2-carboxamide of Formula (D);
- vi) reducing 5-nitrobenzofuran-2-carboxamide of Formula (D) to obtain 5-aminobenzofuran-2-carboxamide of Formula (E).

In another general aspect, the present invention provides a solid state form of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl) benzofuran-2-carboxamide i.e. vilazodone of Formula (1)



The solid state form of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl)benzofuran-2-carboxamide i.e. vilazodone of Formula (1) has been designated as Form-A.

In another aspect, the present invention provides a solid state Form-A of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl)benzofuran-2-carboxamide i.e. vilazodone of Formula (1) is characterized by XRD, DSC and TGA.

In another aspect, the present invention provides the use of solid state Form-A of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl)benzofuran-2-carboxamide i.e. vilazodone of Formula (1) in the preparation of vilazodone hydrochloride.

In another aspect, the present invention provides solid state form of hydrate or solvate of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl) benzofuran-2-carboxamide i.e. vilazodone of Formula (1).

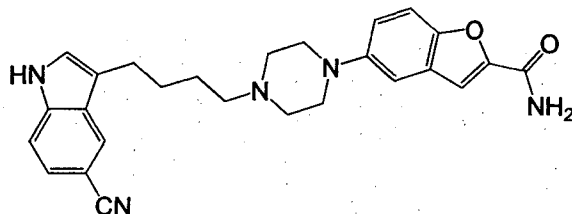
In another aspect, the present invention provides solid state form of solvate of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl)benzofuran-2-carboxamide i.e. vilazodone of Formula (1).

In another aspect, the present invention provides solid state form of methanol solvate of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl) benzofuran-2-carboxamide i.e. vilazodone of Formula (1) is characterized by XRD, DSC and TGA.

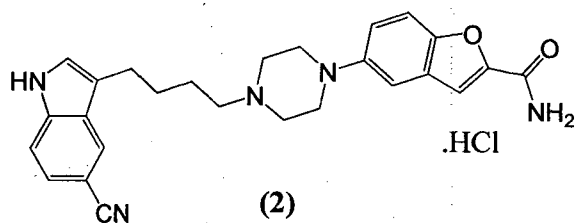
In another aspect, the present invention provides a solid state Form-A of vilazodone of Formula (1) having a total purity of greater than about 99%, specifically greater than about 99.5%, more specifically greater than about 99.9%, and most specifically greater than about 99.98% as measured by HPLC.

In another aspect, the present invention provides a process for preparing solid state Form-A of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl)benzofuran-2-carboxamide i.e. vilazodone of Formula (1).

In another aspect, the present invention provides the use of solid state Form-A of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl) benzofuran-2-carboxamide i.e. vilazodone of Formula (1)



in the preparation of Vilazodone Hydrochloride of Formula (2).



BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS

FIG. 1: Shows X-ray diffractogram (XRD) of solid state Form-A of vilazodone of Formula (1).

FIG. 2: Shows differential scanning calorimetry (DSC) of solid state Form-A of vilazodone of Formula (1).

FIG. 3: Shows thermal gravimetric analysis (TGA) of solid state Form-A of vilazodone of Formula (1).

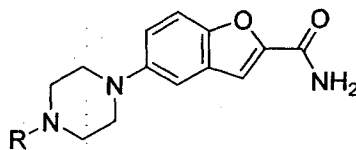
FIG. 4: Shows X-ray diffractogram (XRD) of methanol solvate of vilazodone of Formula (1).

FIG. 5: Shows differential scanning calorimetry (DSC) of methanol solvate of vilazodone of Formula (1).

FIG. 6: Shows thermal gravimetric analysis (TGA) of methanol solvate of vilazodone of Formula (1).

DETAILED DESCRIPTION OF THE INVENTION

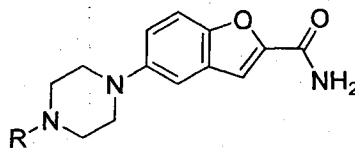
In general aspect, the present invention provides a novel intermediate compounds, 5-(4-substitutedpiperazin-1-yl)benzofuran-2-carboxamide of Formula (X)



(X)

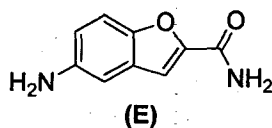
wherein R is a suitable amino protecting group selected from, methansulfonamide, p-methoxybenzyl carbonyl, p-toluenesulfonamide, tert-butyloxycarbonyl (BOC), 9-fluorenylmethyloxycarbonyl (Fmoc), benzyl carbamate, acetamide, phthalimide, carbobenzyloxy (Cbz), acetyl, benzoyl, benzyl, carbamates, p-methoxybenzyl, p-methoxyphenyl and the like. More particularly, the suitable protecting group is p-toluenesulfonamide (tosyl).

Another aspect of the invention provides a process for the preparation of the novel compounds of Formula (X)

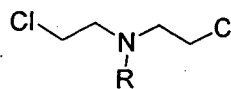


(X)

wherein R is a suitable amino protecting group selected from, methansulfonamide, p-methoxybenzyl carbonyl, p-toluenesulfonamide, tert-butyloxycarbonyl (BOC), 9-fluorenylmethyloxycarbonyl (Fmoc), benzyl carbamate, acetamide, phthalimide, carbobenzyloxy (Cbz), acetyl, benzoyl, benzyl, carbamates, p-methoxybenzyl or p-methoxyphenyl; comprising reacting 5-aminobenzofuran-2-carboxamide of Formula (E) or its salt with compound of Formula (P),



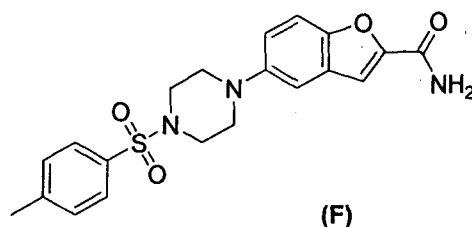
(E)



(P)

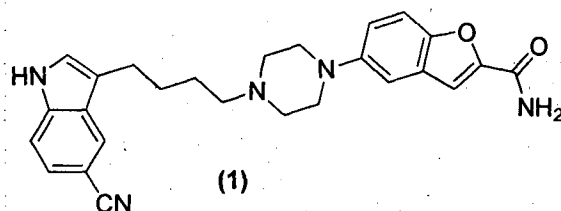
in the presence of a base in a suitable solvent to obtain 5-(4-substitutedpiperazin-1-yl)benzofuran-2-carboxamide of Formula (X).

In another general aspect, the present invention provides the novel intermediate, 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F).



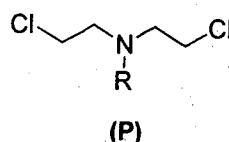
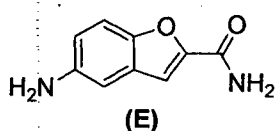
Another aspect of the present invention provides, the novel intermediate, 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F) having purity higher than around about 95%, more particularly higher than around about 98%, more particularly higher than around about 99% and even more particularly higher than around about 99.5%.

Another aspect of the present invention provides the process for the preparation of vilazodone of Formula (I) or its pharmaceutically acceptable salts, solvates, hydrates thereof

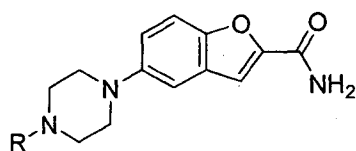


comprising;

- (i) reacting 5-aminobenzofuran-2-carboxamide of Formula (E) or its salt with compound of Formula (P),

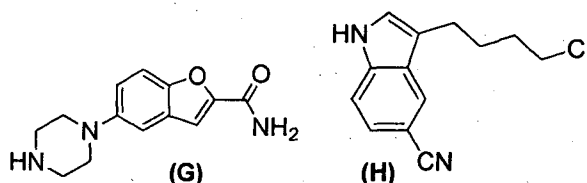


wherein R is a suitable amino protecting group selected from, methansulfonamide, p-methoxybenzyl carbonyl, p-toluenesulfonamide, tert-butyloxycarbonyl (BOC), 9-fluorenylmethyloxycarbonyl (Fmoc), benzyl carbamate, acetamide, phthalimide, carbobenzyloxy (Cbz), acetyl, benzoyl, benzyl, carbamates, p-methoxybenzyl, p-methoxyphenyl, in the presence of a base in a suitable solvent to obtain 5-(4-substitutedpiperazin-1-yl)benzofuran-2-carboxamide of Formula (X);



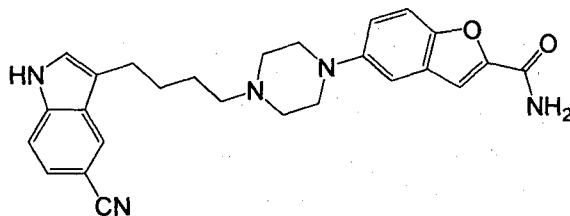
(X)

- (ii) deprotecting the 5-(4-substitutedpiperazin-1-yl)benzofuran-2-carboxamide of Formula (X) to obtain 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G);



- (iii) reacting 5-(1-piperazinyl)benzofuran-2-carboxamide of Formula (G) with 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula (H) in an organic solvent in the presence of a base to obtain vilazodone of Formula (1) or its pharmaceutically acceptable salts, solvates, hydrates thereof.

Preferably, the invention provides the process for the preparation of vilazodone of Formula (1) or its pharmaceutically acceptable salts, solvates or hydrates thereof,

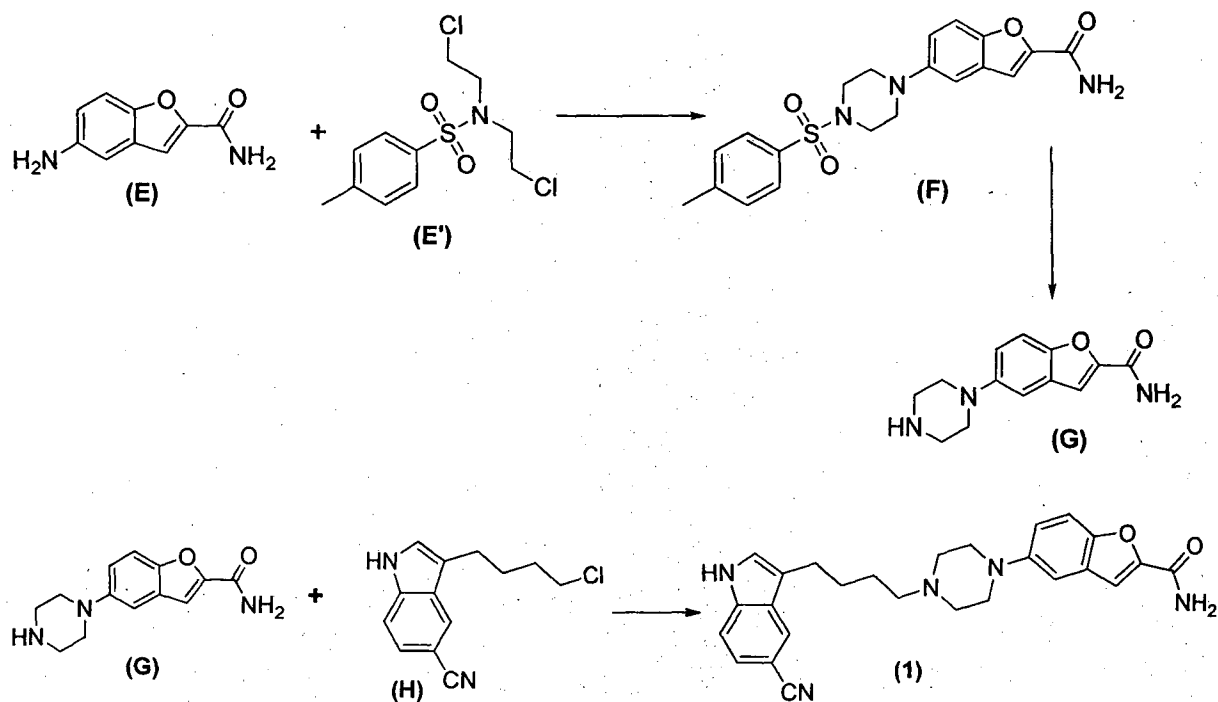


(1)

comprising;

- (i) reacting 5-aminobenzofuran-2-carboxamide of Formula (E) with N,N-bis(2-chloroethyl)-4-methylbenzenesulfonamide of Formula (E') in the presence of a base in a suitable solvent to provide 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F);
- (ii) deprotecting 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F) in the presence of an acid to obtain 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G) or its salts;
- (iii) reacting 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G) or its salts with 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula (H) in the presence of a

base in a suitable solvent, optionally in the presence of phase transfer catalyst to obtain vilazodone of Formula (1) or its pharmaceutically acceptable salts, solvate, hydrates thereof.



Scheme-1

In the preferred embodiments, 5-aminobenzofuran-2-carboxamide of Formula (E) is reacted with N,N-bis(2-chloroethyl)-4-methylbenzenesulfonamide of Formula (E') in the presence of a base in a suitable solvent to provide novel compound, 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F).

The suitable solvent for step (i) comprises one or more of hydrocarbons, nitriles, amides, alcohol, ketones, ester and the like. In particular, the suitable solvent comprises toluene, xylene, ethylbenzene dimethyl formamide, dimethyl acetamide, acetonitrile, C₁-C₄ straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate and the likes. Particularly, the solvent may be methanol.

The suitable base for step (i) comprises of an alkali and alkaline metal hydroxide and carbonate or organic base, in particular the suitable alkali metal hydroxide comprises of sodium hydroxide, potassium hydroxide, lithium hydroxide, and the like,

carbonate comprises of sodium carbonate, potassium carbonate, cesium carbonate and the like, organic base comprises of triethylamine, diisopropylethylamine, isopropyl amine. Particularly, the base may be Diisopropylethylamine or triethyl amine.

The novel compound, 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F) is further underwent deprotection. The deprotection may be carried out by using acid.

The suitable acid in step (ii) may be selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, acetic acid, benzoic acid, p-hydroxy benzoic acid and like or a mixture thereof. More particularly the acid used is a mixture of Hydrobromic acid, acetic acid as well as p-Hydroxy benzoic acid or sulfuric acid.

The suitable solvent used in step (ii) for removal of amino group protection from 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F) is selected from one or more of water, hydrocarbons, nitriles, amides, alcohol, ketones, ester and the like. In particular, the suitable solvent comprises water, toluene, xylene, ethylbenzene dimethyl formamide, dimethyl acetamide, acetonitrile, C₁-C₄ straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate and the likes. Particularly, the solvent may be water and ethyl acetate.

The 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G) is isolated in the solid state form by reacting with a base in a suitable solvent. The suitable base comprises of an alkali and alkaline metal hydroxide and carbonate, in particular the suitable alkali metal hydroxide comprises of sodium hydroxide, potassium hydroxide, lithium hydroxide, and the like, carbonate comprises of sodium carbonate, potassium carbonate, cesium carbonate and the like. Particularly, the base may be sodium hydroxide.

The suitable solvent for the isolation of 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G) in solid state form comprises one or more of hydrocarbons, water, nitriles, amides, alcohol, ketones, ester and the like. In particular, the suitable solvent comprises toluene, xylene, ethylbenzene dimethyl formamide, dimethyl acetamide, acetonitrile, C₁-C₄ straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate and the likes. Particularly, the solvent may be ethyl acetate.

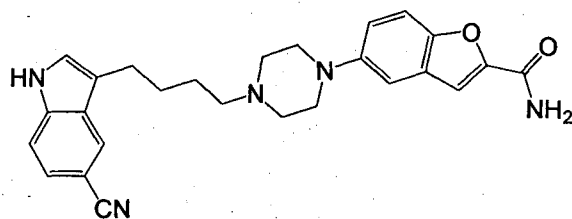
The 5-(1-piperazinyl) benzofuran-2- carboxamide of Formula (G) or its salts is reacted with 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula (H) in the presence of a base in a suitable solvent, optionally in the presence of phase transfer catalyst to obtain vilazodone of Formula (1).

5 The suitable solvent comprises one or more of water, water miscible solvent, polar solvent, hydrocarbons, amide, sulfoxide, ester. Preferably, the solvent comprises of toluene, xylene, ethylbenzene, dimethyl formamide, dimethyl acetamide, dimethyl sulfoxide, acetonitrile, C₁-C₄ straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate, N-
10 methyl pyrrolidone.

The suitable base for step (iv) is selected from an organic or inorganic base; an organic base may be a tertiary amine base such as trimethylamine, triethylamine, N-methylpiperidine, an inorganic base may be an alkali and alkaline metal hydroxide and carbonate, preferably triethylamine.

15 The reaction of step (iv) optionally carried out in the presence of phase transfer catalyst. The suitable phase transfer catalyst comprises of crown ethers, hexadecyltributylphosphonium bromide, tetra-n-butylammonium bromide, methyltrioctyl- ammonium chloride or other known phase transfer catalyst which facilitates the reaction, preferably the phase transfer catalyst may be crown ethers.

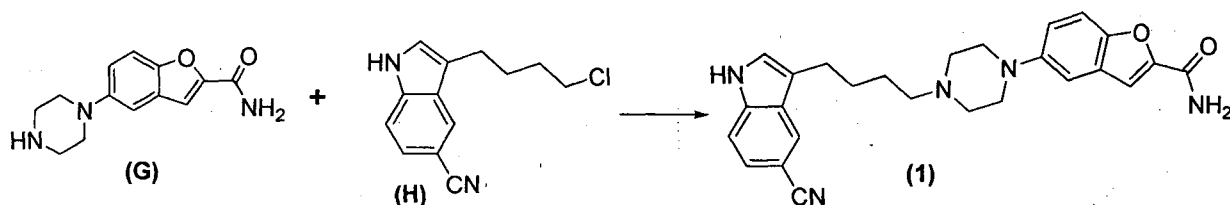
20 Another aspect of the present invention provides, a process for the preparation of a solid state form of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl) benzofuran-2-carboxamide i.e. vilazodone of Formula (1),



(1)

25 comprising the steps of:

- (i) reacting 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G) or its salt with 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula (H) in the presence of a phase transfer catalyst and a base in a suitable solvent; and



(ii) isolating the solid state form of vilazodone of Formula (1).

The suitable solvent for step (i) is one or more of solvent comprises of hydrocarbons, nitriles, amides, alcohol, ketones, ester and the like. In particular, the
 5 suitable solvent comprises toluene, xylene, ethylbenzene dimethyl formamide, dimethyl acetamide, acetonitrile, C₁-C₄ straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate & butyl acetate and the like.

The base for step (i) comprises of an organic or inorganic base; an organic base
 10 may be selected from diisopropylethylamine, diisopropylamine, trimethylamine, diethylamine, piperidine, morpholine, pyridine, DBU, DABCO and the like; the inorganic base comprises of an alkali and alkaline metal hydroxide and carbonate, in particular the suitable alkali metal hydroxide comprises of sodium hydroxide, potassium hydroxide, lithium hydroxide, and the like, carbonate comprises of sodium
 15 carbonate, potassium carbonate, cesium carbonate and the like. Particularly, the base selected may be diisopropylethylamine.

The phase transfer catalyst comprises of crown ethers, hexadecyltributylphosphonium bromide, tetra-n-butylammonium bromide, methyltrioctyl- ammonium chloride or other known phase transfer catalyst which
 20 facilitates the reaction, particularly the phase transfer catalyst may be crown ethers.

The solid state form of vilazodone of Formula (1) is isolated by treating with suitable solvent comprises of hydrocarbons, nitriles, amides, alcohol, ketones, ester and the like. In particular, the suitable solvent comprises toluene, xylene, ethylbenzene dimethyl formamide, dimethyl acetamide, acetonitrile, C₁-C₄ straight chain or branched
 25 alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate and butyl acetate and the like. Particularly, the solvent may be methanol.

In general aspect, the present invention provides a solid state form of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl) benzofuran-2-carboxamide i.e. vilazodone of Formula (1), which is designated as Form-A.

A solid state Form-A of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl) benzofuran-2-carboxamide i.e. vilazodone of Formula (1) is characterized by X-ray powder diffraction having characteristic peaks at about 8.9, 11.4, 12.6, 14.3, 16.6, 18.7, 20.2, 21.5, 24.4, 27.1 and 28.0 ± 0.2 degree 2θ .

5 A solid state Form-A of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl) benzofuran-2-carboxamide i.e. vilazodone of Formula (1) is further characterized by X-ray powder diffraction having characteristic peaks at about 13.7, 15.0, 16.0, 17.8, 20.8, 22.7, 23.5, 29.4, 30.0, 31.3 and 32.6 ± 0.2 degree 2θ .

A solid state Form-A of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-
10 yl)benzofuran-2-carboxamide i.e. vilazodone of Formula (1) is characterized by X-ray powder diffraction as depicted in FIG.1.

A solid state Form-A of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl)benzofuran-2-carboxamide i.e. vilazodone of Formula (1) is characterized by Differential Scanning Calorimetry (DSC) having peak at about 292°C respectively.

15 A solid state Form-A of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl)benzofuran-2-carboxamide i.e. vilazodone of Formula (1) is characterized by Differential Scanning Calorimetry as depicted in FIG.2.

A solid state Form-A of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl)benzofuran-2-carboxamide i.e. vilazodone of Formula (1) is characterized by
20 Thermal gravimetric analysis (TGA) having water loss of less than 1%.

A solid state Form-A of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl) benzofuran-2-carboxamide i.e. vilazodone of Formula (1) is characterized by Thermal gravimetric analysis (TGA) as depicted in FIG.3.

A solid state Form-A of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-
25 yl)benzofuran-2-carboxamide i.e. vilazodone of Formula (1) is an anhydrous form.

In another aspect, the present invention provides the usage of solid state Form-A of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl) benzofuran-2-carboxamide i.e. vilazodone of Formula (1) in the preparation of Vilazodone hydrochloride of Formula (2).

30 In another aspect, the present invention provides solid state form of hydrate or solvate of vilazodone of Formula (1).

In another aspect, the present invention provides solid state form of methanol solvate of vilazodone of Formula (1).

In another aspect the present invention provides solid state form of methanol solvate of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl) benzofuran-2-carboxamide i.e. vilazodone of Formula (1) is characterized by X-ray powder diffraction having characteristic peaks at about 8.3, 12.3, 12.8, 16.0, 18.4, 19.0, 19.6, 21.0, 24.4, 25.2, 25.6, 26.2, 27.7 and 29.8 ± 0.2 degree 2θ .

A solid state form of methanol solvate of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl) benzofuran-2-carboxamide i.e. vilazodone of Formula (1) is further characterized by X-ray powder diffraction having characteristic peaks at about 8.9, 10.7, 11.4, 13.3, 14.4, 15.0, 16.8, 17.6, 20.1, 22.1, 22.4, 23.3, 27.2, 28.6, 29.4, 32.2 and 32.5 ± 0.2 degree 2θ .

A solid state form of methanol solvate of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl)benzofuran-2-carboxamide i.e. vilazodone of Formula (1) is characterized by X-ray powder diffraction as depicted in FIG. 4.

A solid state form of methanol solvate of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl)benzofuran-2-carboxamide i.e. vilazodone of Formula (1) is characterized by Differential Scanning Calorimetry (DSC) having two peaks at about 113°C and 288°C respectively.

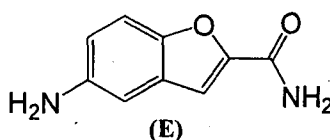
A solid state form of methanol solvate of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl)benzofuran-2-carboxamide i.e. vilazodone of Formula (1) is characterized by Differential Scanning Calorimetry (DSC) as depicted in FIG. 5.

A solid state form of methanol solvate of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl)benzofuran-2-carboxamide i.e. vilazodone of Formula (1) is characterized by Thermal gravimetric analysis (TGA) having weight loss of more than 6.0%.

A solid state form of methanol solvate of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl) benzofuran-2-carboxamide i.e. vilazodone of Formula (1) is characterized by Thermal gravimetric analysis (TGA) as depicted in FIG. 6.

A solid state form of methanol solvate of Form-A of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl)benzofuran-2-carboxamide i.e. vilazodone of Formula (1) is a methanol solvate form.

According to another aspect, the invention provides an improved process for the preparation of 5-aminobenzofuran-2-carboxamide of Formula (E),



comprising the steps of:

- (i) reacting salicylaldehyde with chloroacetic acid in an organic solvent and a base to obtain 2-(2-formylphenoxy) acetic acid of Formula (A);
- 5 (ii) nitrating 2-(2-formylphenoxy) acetic acid of Formula (A) to obtain 2-(2-formyl-4-nitrophenoxy) acetic acid of Formula (B);
- (iii) cyclizing 2-(2-formyl-4-nitrophenoxy) acetic acid of Formula (B) to obtain 5-nitrobenzofuran-2-carboxylic acid of Formula (C);
- (iv) converting 5-nitrobenzofuran-2-carboxylic acid of Formula (C) to 5-nitrobenzofuran-2-carboxamide of Formula (D);
- 10 (v) reducing 5-nitrobenzofuran-2-carboxamide of Formula (D) to obtain 5-aminobenzofuran-2-carboxamide of Formula (E).

The organic solvent for step (i) is selected from group comprising of water, aromatic hydrocarbons, C₃₋₈ ketones, C₃₋₄ esters, C₂₋₈ alcohols, ethers, or a mixture thereof, preferably water.

The base for step (i) is selected from group comprising of alkali and alkaline metal hydroxides, carbonates, bicarbonates, preferably sodium hydroxide.

The acid for step (ii) is selected from group comprising of sulfuric acid, nitric acid or both, preferably both sulfuric acid and nitric acid.

20 The cyclization of 2-(2-formyl-4-nitrophenoxy) acetic acid of Formula (B) is carried out using reagents like acetic anhydride and suitable base such as sodium acetate.

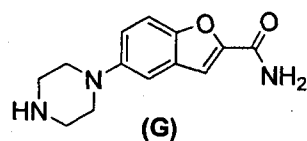
In preferred aspect, 5-nitrobenzofuran-2-carboxylic acid is converted to 5-nitrobenzofuran-2-carboxamide of Formula (D) by reacting with thionyl chloride in solvent comprises of aromatic hydrocarbons, dimethyl formamide (DMF), C₃₋₈ ketones, C₃₋₄ esters, C₂₋₈ alcohols, ethers, or a mixture thereof, preferably toluene and DMF formation of 5-nitrobenzofuran-2-carbonyl chloride, which was reacted with ammonia to obtain 5-nitrobenzofuran-2-carboxamide of Formula (D).

30 The suitable metal catalyst for reduction of 5-nitrobenzofuran-2-carboxamide of Formula (D) to 5-aminobenzofuran-2-carboxamide of Formula (E) in step (vi) is selected from the group comprising of Raney-Ni, zinc chloride, Fe/HCl, Pd/C, sodium dithionite, sodium formaldehyde sulfoxylate (Safolite) etc, preferably Raney-Ni.

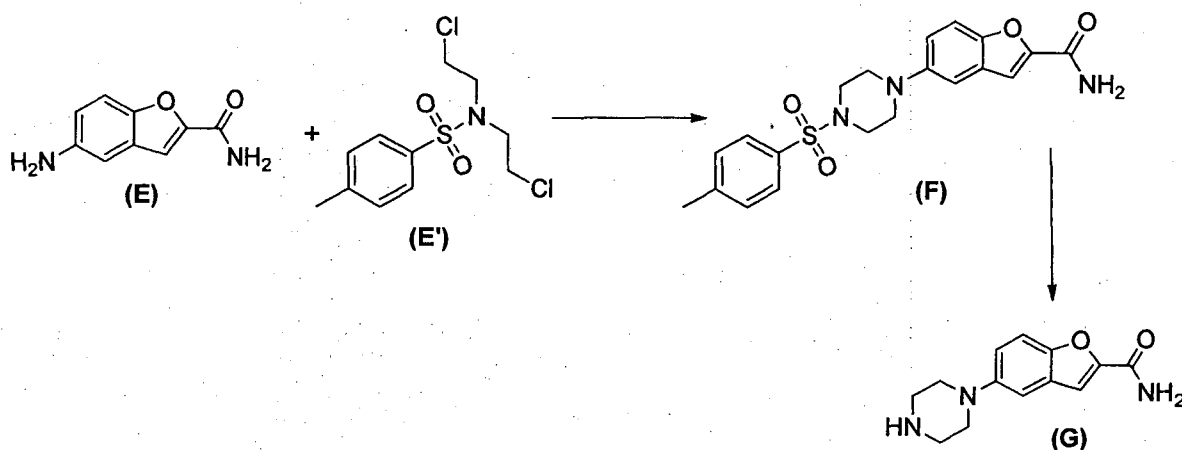
The suitable organic solvent for reduction step (vi) is selected from C₁-C₅ alcohols, water or a mixture thereof, preferably methanol.

Another aspect of the present invention provides, a new process for the preparation of solid state form of 5-(1-piperaziny) benzofuran-2-carboxamide of

5 Formula (G)



comprising the steps of:



- 10 (i) reacting 5-aminobenzofuran-2-carboxamide of Formula (E) with N,N-bis(2-chloroethyl)-4-methylbenzenesulfonamide of Formula (E') in presence of a base in a suitable solvent to obtain 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F);
- (ii) deprotecting 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F) in
- 15 the presence of an acid to obtain 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G) or its salts; and
- (iii) isolating the solid state form of 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G) in presence of a base.

20 The suitable solvent for step (i) comprises one or more of hydrocarbons, nitriles, amides, alcohol, ketones, ester and the like. In particular, the suitable solvent comprises toluene, xylene, ethylbenzene dimethyl formamide, dimethyl acetamide, acetonitrile, C₁-C₄ straight chain or branched alcohols, acetone, methyl isobutyl ketone,

methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate and the likes. Particularly, the solvent may be methanol.

The suitable base for step (i) comprises of an alkali and alkaline metal hydroxide and carbonate or organic base, in particular the suitable alkali metal hydroxide comprises of sodium hydroxide, potassium hydroxide, lithium hydroxide, and the like, carbonate comprises of sodium carbonate, potassium carbonate, cesium carbonate and the like or organic base comprise of triethylamine, diisopropylethylamine, isopropylamine. Particularly, the base may be diisopropylethylamine.

The suitable solvent used in step (ii) for removal of amino group protection from 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F) is selected from one or more of hydrocarbons, nitriles, amides, alcohol, ketones, ester and the like. In particular, the suitable solvent comprises toluene, xylene, ethylbenzene dimethyl formamide, dimethyl acetamide, acetonitrile, C₁-C₄ straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate and the likes. Particularly, the solvent may be water and ethyl acetate.

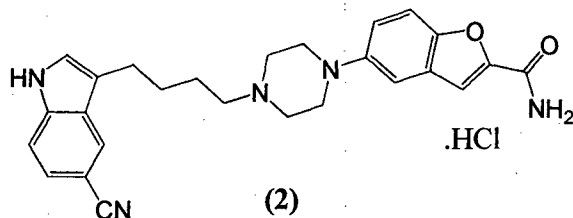
The suitable acid in step (ii) may be selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, acetic acid, benzoic acid, p-hydroxy benzoic acid and like or a mixture thereof. More particularly the acid used is sulfuric acid.

The suitable solvent for step (iii) for isolating a solid state form of 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G) comprises one or more of hydrocarbons, water, nitriles, amides, alcohol, ketones, ester and the like. In particular, the suitable solvent comprises toluene, xylene, ethylbenzene dimethyl formamide, dimethyl acetamide, acetonitrile, C₁-C₄ straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate and the likes. Particularly, the solvent may be ethyl acetate.

The suitable base employed in step (iii) comprises of an alkali and alkaline metal hydroxide and carbonate, in particular the suitable alkali metal hydroxide comprises of sodium hydroxide, potassium hydroxide, lithium hydroxide, and the like, carbonate comprises of sodium carbonate, potassium carbonate, cesium carbonate and the like. Particularly, the base may be sodium hydroxide.

According to another aspect of the present invention is to provide a process for preparing

vilazodone hydrochloride of Formula (2)



the process comprising treating a solid state form of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]- piperazin-1-yl) benzofuran-2-carboxamide of Formula (1) with hydrochloric acid in a suitable solvent and isolating vilazodone hydrochloride of Formula (2).

The solid state form of vilazodone of Formula (1) may be crystalline Form A or methanol solvate.

The suitable organic solvent for step (i) is selected from the group comprising of C₁-C₅ alcohols, hydrocarbons, acetonitrile, dimethyl formamide (DMF), preferably methanol.

According to another aspect, the present invention provides vilazodone hydrochloride having particle size in terms of d₉₅ is less than about 100 microns.

According to another aspect, the present invention provides vilazodone hydrochloride having particle size in terms of d₉₅ is less than about 50 microns.

According to another aspect, the present invention provides vilazodone hydrochloride having particle size in terms of d₉₅ is less than about 10 microns.

According to another aspect, the present invention provides a process for controlling the particle size of vilazodone hydrochloride having particle size in terms of d₉₅ is less than about 100 microns.

A process for preparing Vilazodone Hydrochloride having particle size in terms of d₉₅ is less than about 50 microns, more particularly, less than about 10 microns comprising the steps of:

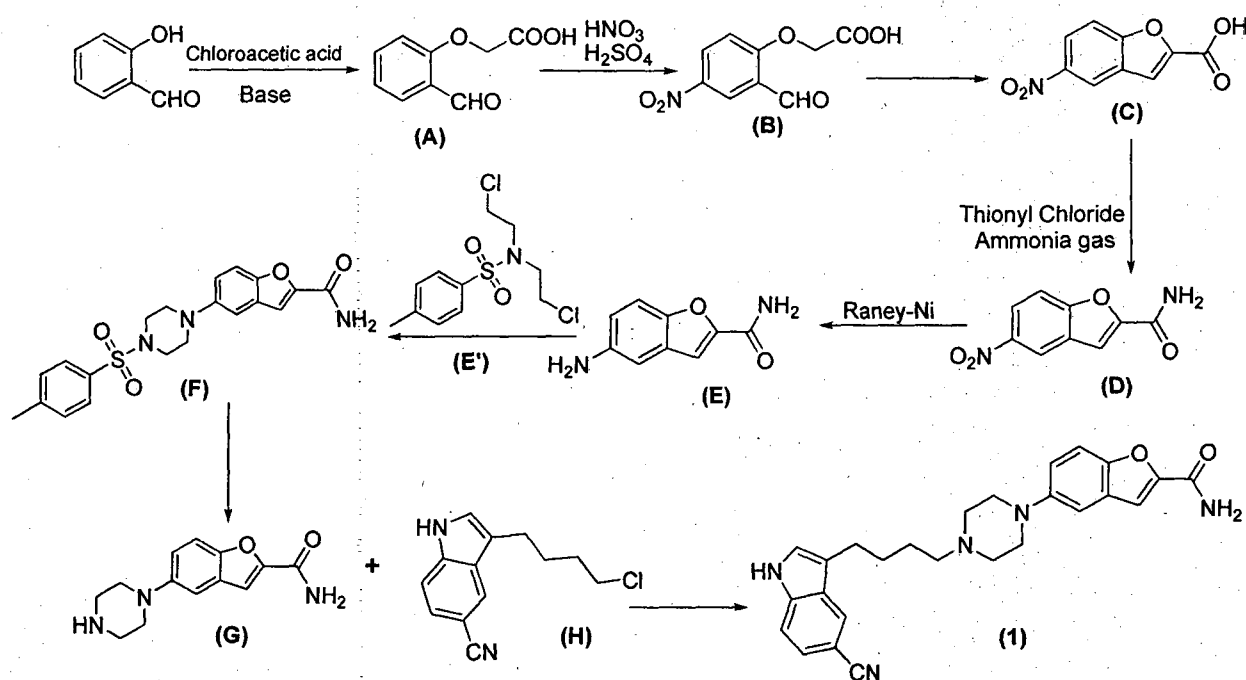
- (i) milling vilazodone hydrochloride having particle size in terms of d₉₅ is greater than about 100 microns;
- (ii) slurring micronized vilazodone hydrochloride in one or more solvents;
- (iii) isolating vilazodone hydrochloride having particle size in terms of d₉₅ is less than about 10 microns.

According to another aspect of the present invention is to provide vilazodone of Formula (1) or its pharmaceutically acceptable salts, solvates, hydrates thereof having

a total purity of greater than about 99%, specifically greater than about 99.5%, more specifically greater than about 99.9%, and most specifically greater than about 99.97% as measured by HPLC.

According to another aspect of the present invention is to provide a pharmaceutical composition comprising of vilazodone of Formula (1) or its pharmaceutically acceptable salt and which includes one or more pharmaceutically acceptable excipients/diluents. The pharmaceutical composition of the present invention may be in the form of a solid or liquid dosage forms for oral, parenteral or topical use and may have immediate or sustained release characteristics. The dosage forms possible include tablets, capsules, powders, granules, creams, lotions, ointments, injectables, ophthalmic or optic solutions, suspensions, elixirs and the like.

According to the present invention, the process for the preparation of Vilazodone of Formula (1) can be illustrated by below mentioned **Scheme-2**, which should not be considered as limiting the scope of the invention.



Scheme-2

Examples

While the present invention is described with respect to particular examples and preferred aspects, it is understood that the present invention is not limited to these examples and aspects. The present invention, therefore, includes variations from the particular examples aspects described herein, as will be apparent to one of skill in the art.

Example 1:

Preparation of 2-(2-formylphenoxy) acetic acid of Formula (A)

Water (700 ml), salicylaldehyde (100 g), chloroacetic acid (77 g) and sodium hydroxide solution (165 ml) were added to a four-neck two litre round bottom flask at 30°C. The reaction mass was heated to 100°C and maintained for 3 hours. Conc.HCl (100 ml) was added to adjust pH 1 to 2. The reaction mass was cooled to 30°C and further cooled to 15°C and stirred for 1 hour. The product was filtered and washed with chilled water (2 x 25 ml) to afford 2-(2-formylphenoxy) acetic acid of Formula (A).

Example 2:

Preparation of 2-(2-formyl-4-nitrophenoxy) acetic acid of Formula (B)

Sulfuric acid (550 ml) added to a four-neck two litre round bottom flask at 35°C and cooled to 5°C and added lot wise 2-(2-formylphenoxy)acetic acid of Formula (A) (100 g). The reaction mass was stirred for 15 minutes. In another two litre round bottom flask nitric acid (45 ml) was added at 35°C. The reaction mass was cooled to 15°C followed by addition of sulfuric acid (50 ml) and stirred for 15 minutes. The reaction mass of second round bottom flask was added into first round bottom flask at 5°C and stirred for 1 hour below 15°C. In another round bottom flask water (1500 ml) was added at 35°C and cooled to 10°C. The reaction mass of first round bottom flask was dumped into third round bottom flask having water and stirred for 1 hour. Finally the product was washed chilled water (2 x 100 ml) at 35°C to afford 2-(2-formyl-4-nitrophenoxy) acetic acid of Formula (B).

Example 3:

Preparation of 5-nitrobenzofuran-2-carboxylic acid of Formula (C)

Acetic anhydride (500 ml) and 2-(2-formyl-4-nitrophenoxy) acetic acid of Formula (B) (100 g) were added to a four-neck two liter round bottom flask at 35°C and stirred for 15 minutes. Anhydrous sodium acetate (150 g) was added to the reaction mass and heated to 125°C and maintained for 8 hours. The reaction mass was cooled to 100°C and further cooled to 80°C and toluene (200 ml) was added. The reaction mass was stirred for 30 minutes and under vacuum up to 85°C and cooled to 35 35°C. Water

(500 ml) was added and conc. HCl (200 ml) was added to adjust pH 1-2. The reaction mass was stirred for 60 minutes. The product was washed with water (500 ml) and stirred for 30 minutes at 35°C. The product was dried for 16 hours at 65°C. Toluene (200 ml) was added to the product at 35°C and heated to 90°C and maintained for 30 minutes and cooled to 35°C, further cooled to 5°C and maintained for 30 minutes. The product was washed with chilled toluene (2 x 25 ml) to afford 5-nitrobenzofuran-2-carboxylic acid of Formula (C).

Example 4:

10 Preparation of 5-nitrobenzofuran-2-carboxamide of Formula (D)

Toluene (1200 ml) and 5-nitrobenzofuran-2-carboxylic acid of Formula (C) were added to a four-neck two litre round bottom flask at 35°C and stirred for 15 minutes. DMF (10 ml) was added and heated to 70°C followed by addition of thionyl chloride (86.4 g) and heated to 115°C and maintained for 30 minutes. Toluene was distilled out and reaction mass was cooled to 35°C and further cooled to 10°C. Ammonia gas was passed till pH was 8 to 9. The product was washed with Toluene (2 X 100 ml) and dried for 60 minutes and dried in hot air oven at for 12.0 hrs at 65°C. To the obtained product DMF (250 ml) was added at 35°C and heated to 130°C. The reaction mass was stirred for 30 minutes and cooled to 95°C followed by addition of water (2300 ml) and stirred for 30 minutes. The reaction mass was cooled to 50°C. The product was filtered and washed with water (2 x 100 ml) to afford 5-nitrobenzofuran-2-carboxamide of Formula (D).

Example 5:

25 Preparation of 5-aminobenzofuran-2-carboxamide of Formula (E)

In a 5.0 lit Autoclave methanol (2000 ml) and 5-nitrobenzofuran-2-carboxamide of Formula (D) (100 g) and Raney Nickel (40.0 g) were added at 35°C. The reaction mass was flushed with two times Nitrogen pressure (0.5-1.0 Kg) and released. Hydrogen pressure up to 5.0 Kg/cm² was applied at 35°C. The reaction mass was heated to 60°C and maintained at 6.0 Kg/cm² pressure for 14 hours at 60°C. The reaction mass was cooled to 35°C and Hydrogen pressure was released. Organic layer was distilled out under vacuum at 60°C. Hexane (50 ml) was added and stirred for 30 minutes and reaction was cooled to 35°C. The product was washed with hexane (2 x 25 ml) to afford 5-aminobenzofuran-2-carboxamide of Formula (E).

Example 6:

Preparation of N,N-bis(2-chloroethyl)-4-methylbenzenesulfonamide (E')

To a reaction flask, 100 g. of bis(2-chloroethyl)amine hydrochloride and 500 ml. of MDC were added and stirred. To the reaction mass was added Triethyl amine as a base and again stirred for 15 minutes at room temperature. p-toluene sulfonylchloride solution (in MDC) was added to the reaction mass and heated to 40⁰ C and maintained for 6 hours. TLC was checked for completion of reaction and treated with 250 ml of water and organic layer was separated. To this reaction mass, was added 250 ml of 10% HCl solution and stirred. The organic layer was separated, treated with sodium sulfate and washed thrice with MDC as the solvent was removed under vacuum. To this mass hexane was added and again removed under vacuum twice. Once again Hexane was added and reaction mass stirred for two hours and cooled which afforded the product N,N-bis(2-chloroethyl)-4-methylbenzene sulfonamide which was filtered, washed with hexane and dried.

Example 7:**Preparation of 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F)**

1200 ml DIPEA as a base and 5-aminobenzofuran-2-carboxamide (E) were added to a reaction flask and stirred for 15 minutes to which 252 g of N,N-bis(2-chloroethyl)-4-methylbenzenesulfonamide was added, stirred, heated at 120⁰ C and maintained for 10 hours. The completion of reaction was checked by TLC and cooled after which DIPEA was decanted and 1000 ml of Methanol was added to it. The mass was again heated to about 55⁰ C and stirred for 1 hour after which it was cooled to afford with 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide (F) which was filtered under vacuum, and washed with methanol and dried.

Example 8:**Preparation of 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G)**

To a mixture of 500 ml of Hydrobromic Acid in Acetic Acid was added portion wise 169 g of p-Hydroxy Benzoic Acid and stirred. To this mixture was added portion wise 100 g of 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide (F) and stirred for some time after which the temperature was raised to around 50 °C and the mass was stirred for 3 hours. After the completion of reaction was checked by TLC, it was slowly cooled at around 10 °C and 1.5 liters of cold water was added to it. The solid obtained was filtered and washed with Ethyl Acetate four times and the aqueous layer was then collected and the pH was adjusted to 10 by using sodium hydroxide solution. The mass

was stirred for half an hour and the solid thus obtained was filtered, washed with water and dried to afford 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G)

Example 9:

Preparation of vilazodone of Formula (1)

5 Acetonitrile (500 ml), 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G) (100 g), 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula (H) and Triethyl amine (200 g) were added to a four-neck two litre round bottom flask at 35°C and reaction mass was heated to 80°C and maintained for 48 hours. The reaction mass was cooled to 55°C to afford vilazodone of Formula (1).

10 **Example 10:**

Preparation of solid state Form-A of vilazodone of Formula (1)

DMSO (1000 ml), 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G) (100 g), 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula (H), 18-crown-6-ether (40 g) and diisopropylethyl amine (DIPEA) (225 ml) were added to a four-neck two
15 litre round bottom flask at 35°C and reaction mass was heated to 80°C and maintained for 30 hours. The reaction mass was cooled to 55°C. The reaction mass was treated with EDTA (0.3 g) and charcoal (10 g). The residue was filtered and treated with DMSO (800 ml) at 80-85°C and stirred for 15 minutes. The reaction mass was treated with acetone at 20-25°C and stirred for 1 hour. The reaction mass was washed with
20 acetone (2 x 100 ml) afforded vilazodone free base.

Vilazodone free base (100 g), acetic acid (720 ml) and methanol (500 ml) were added at 25-30°C and stirred for 10 minutes. The reaction mass is heated to 80-81°C and treated with activated charcoal (10 g) and stirred for 15-20 min. The reaction mass was cooled to 15-20°C, filtered and washed with methanol (2 X 100 ml). The product
25 was dried in hot air oven at 60-65°C for 12-14 hours. The product was further dried in oven at 105°C for 4 hours afforded solid state Form-A of vilazodone of Formula (1).

Example 11:

Preparation of solid state form of methanol solvate of Vilazodone of Formula (1)

DMSO (1000 ml), 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G)
30 (100 g), 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula (H), 18-crown-6-ether (40 g) and diisopropylethyl amine (DIPEA) (225 ml) were added to a four-neck two litre round bottom flask at 35°C and reaction mass was heated to 80°C and maintained for 30 hours. The reaction mass was cooled to 55°C. The reaction mass was treated with EDTA (0.3 g) and charcoal (10 g). The residue was filtered and treated with

DMSO (800 ml) at 80-85°C and stirred for 15 minutes. The reaction mass was treated with acetone at 20-25°C and stirred for 1 hour. The reaction mass was washed with acetone (2 x 100 ml) afforded vilazodone free base.

Vilazodone free base (100 g), acetic acid (720 ml) and methanol (500 ml) were added at 25-30°C and stirred for 10 minutes. The reaction mass is heated to 80-81°C and treated with activated charcoal (10 g) and stirred for 15-20 min. The reaction mass was cooled to 15-20°C, filtered and washed with methanol (2 X 100 ml). The product was dried in hot air oven at 60-65°C for 12-14 hours afforded solid state form of methanol solvate of vilazodone of Formula (1).

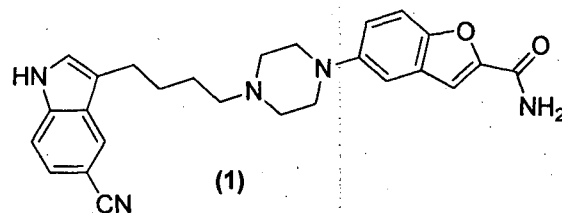
Example 12:

Preparation of Vilazodone hydrochloride

IPA (200 ml) was added to vilazodone free base of Formula (1) (100 g) in a four-neck two litre round bottom flask at 35°C followed by addition of IPA HCl (198.4 g) and stirred for 30 minutes. The reaction mass was heated to 80°C and stirred 30 minutes. The reaction mass was cooled to 35°C and further cooled to 5°C. The product was filtered and washed with IPA (2 x 25 ml) to afford vilazodone Hydrochloride.

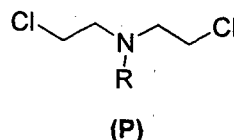
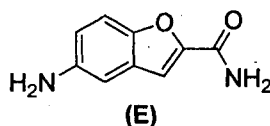
We claim:

1. A process for the preparation of vilazodone of Formula (I) or its pharmaceutically acceptable salts, solvates, hydrates thereof

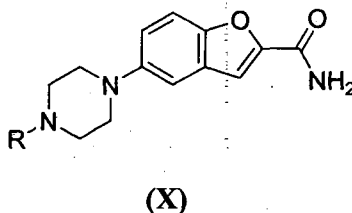


which comprises;

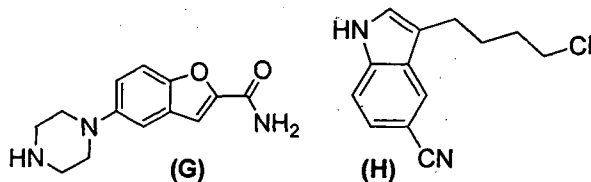
- (i) reacting 5-aminobenzofuran-2-carboxamide of Formula (E) or its salt with compound of Formula (P),



wherein R is a suitable amino protecting group selected from, methansulfonamide, p-methoxybenzyl carbonyl, p-toluenesulfonamide, tert-butyloxycarbonyl (BOC), 9-fluorenylmethyloxycarbonyl (Fmoc), benzyl carbamate, acetamide, phthalimide, carbobenzyloxy (Cbz), acetyl, benzoyl, benzyl, carbamates, p-methoxybenzyl, p-methoxyphenyl, in presence of a base in suitable solvent to obtain 5-(4-substitutedpiperazin-1-yl)benzofuran-2-carboxamide of Formula (X);



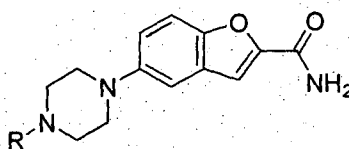
- (ii) deprotecting the 5-(4-substitutedpiperazin-1-yl)benzofuran-2-carboxamide of Formula (X) to obtain 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G);



- (iii) reacting 5-(1-piperazinyl)benzofuran-2-carboxamide of Formula (G) with 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula (H) in an organic solvent in the

presence of a base to obtain vilazodone of Formula (1) or its pharmaceutically acceptable salts, solvates, hydrates thereof.

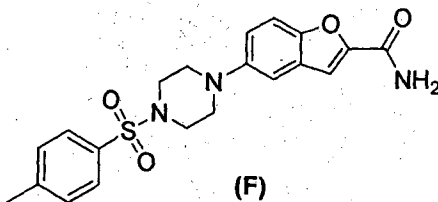
2. The process as claimed in claim 1, wherein R is p-toluenesulfonamide.
3. The process as claimed in claim 1, wherein the base is selected from an alkali and alkaline metal hydroxide and carbonate or organic base comprises of sodium hydroxide, potassium hydroxide, lithium hydroxide sodium carbonate, potassium carbonate, cesium carbonate organic base comprises of triethylamine, diisopropylethylamine, isopropyl amine.
4. The process as claimed in claim 1, wherein the suitable solvent is selected from one or more of hydrocarbons, nitriles, amides, alcohol, ketones, ester comprises of toluene, xylene, ethylbenzene dimethyl formamide, dimethyl acetamide, acetonitrile, C₁-C₄ straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate.
5. A novel compound of Formula (X);



(X)

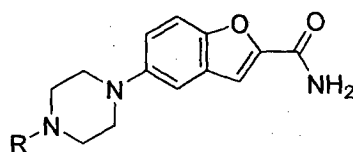
wherein R is a suitable amino protecting group selected from, methansulfonamide, p-methoxybenzyl carbonyl, p-toluenesulfonamide, tert-butyloxycarbonyl (BOC), 9-fluorenylmethyloxycarbonyl (Fmoc), benzyl carbamate, acetamide, phthalimide, carbobenzyloxy (Cbz), acetyl, benzoyl, benzyl, carbamates, p-methoxybenzyl or p-methoxyphenyl.

6. A novel compound of Formula (F)



(F)

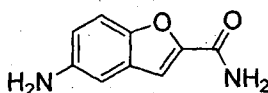
7. A process for the preparation of vilazodone of Formula (1) or its pharmaceutically acceptable salts thereof by using the novel compounds of Formula (X) or Formula (F).
8. A process for the preparation of a novel compound of Formula (X)



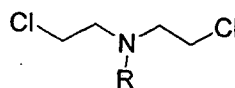
(X)

wherein R is a suitable amino protecting group selected from, methansulfonamide, p-methoxybenzyl carbonyl, p-toluenesulfonamide, tert-butyloxycarbonyl (BOC), 9-fluorenylmethyloxycarbonyl (Fmoc), benzyl carbamate, acetamide, phthalimide, carbobenzyloxy (Cbz), acetyl, benzoyl, benzyl, carbamates, p-methoxybenzyl or p-methoxyphenyl;

which comprises reacting 5-aminobenzofuran-2-carboxamide of Formula (E) or its salt with compound of Formula (P),



(E)



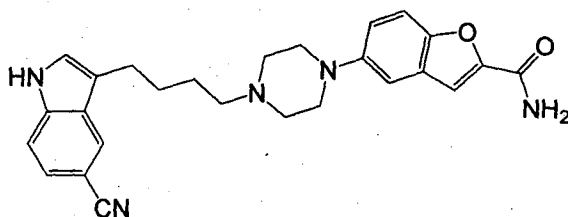
(P)

in the presence of a base in a suitable solvent to obtain 5-(4-substitutedpiperazin-1-yl)benzofuran-2-carboxamide of Formula (X).

9. The process as claimed in claim 8, wherein the base is selected from an alkali and alkaline metal hydroxide and carbonate or organic base comprises of sodium hydroxide, potassium hydroxide, lithium hydroxide sodium carbonate, potassium carbonate, cesium carbonate organic base comprises of triethylamine, diisopropylethylamine, isopropyl amine.

10. The process as claimed in claim 8, wherein the suitable solvent is selected from one or more of hydrocarbons, nitriles, amides, alcohol, ketones, ester comprises of toluene, xylene, ethylbenzene dimethyl formamide, dimethyl acetamide, acetonitrile, C₁-C₄ straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate.

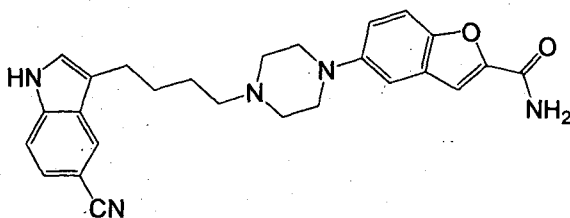
11. A process for the preparation of vilazodone of Formula (1) or its pharmaceutically acceptable salts, solvates or hydrates thereof,



(1)

comprising:

- (i) reacting 5-aminobenzofuran-2-carboxamide of Formula (E) with N,N-bis(2-chloroethyl)-4-methylbenzenesulfonamide of Formula (E') in the presence of a base in a suitable solvent to provide 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F);
 - (ii) deprotecting 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F) in the presence of an acid to obtain 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G) or its salts; and
 - (iii) reacting 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G) or its salts with 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula (H) in the presence of a base in a suitable solvent, optionally in the presence of phase transfer catalyst to obtain vilazodone of Formula (1) or its pharmaceutically acceptable salts, solvate, hydrates thereof.
12. The process as claimed in claim 11, wherein the acid selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, acetic acid, benzoic acid, p-hydroxy benzoic acid and like or mixtures thereof.
 13. The process as claimed in claim 11, wherein the phase transfer catalyst is comprises of crown ethers, hexadecyltributylphosphonium bromide, tetra-n-butylammonium bromide, methyltrioctyl-ammonium chloride.
 14. A process for the preparation of a solid state form of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl) benzofuran-2-carboxamide i.e. vilazodone of Formula (1),



(1)

the process comprising:

- (i) reacting 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G) or its salt with 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula (H) in the presence of a phase transfer catalyst and a base in a suitable solvent; and
- (ii) isolating the solid state form of vilazodone of Formula (1).

15. A solid state form of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl) benzofuran-2-carboxamide of Formula (1).
16. A solid state Form A of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl) benzofuran-2-carboxamide of Formula (1), which is characterized by any of the
5 followings:
- (a) X-ray powder diffraction having characteristic peaks at about 8.9, 11.4, 12.6, 14.3, 16.6, 18.7, 20.2, 21.5, 24.4, 27.1 and 28.0 ± 0.2 degree 2θ .
 - (b) Differential Scanning Calorimetry (DSC) having peak at about 292°C respectively.
 - (c) Thermal gravimetric analysis (TGA) having water loss of less than 1%.
- 10 17. A solid state form of methanol solvate of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl) benzofuran-2-carboxamide i.e. Vilazodone of Formula (1) is characterized by any of the followings:
- (a) X-ray powder diffraction having characteristic peaks at about 8.3, 12.3, 12.8, 16.0, 18.4, 19.0, 19.6, 21.0, 24.4, 25.2, 25.6, 26.2, 27.7 and 29.8 ± 0.2 degree 2θ .
 - 15 (b) Differential Scanning Calorimetry (DSC) having two peaks at about 113°C and 288°C respectively.
 - (c) Thermal gravimetric analysis (TGA) having weight loss of more than 6.0%.
18. A process for preparing vilazodone hydrochloride of Formula (2), the process comprising reacting solid state form of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl]-
20 piperazin-1-yl) benzofuran-2-carboxamide of Formula (1) with hydrochloric acid in a suitable solvent and isolating vilazodone hydrochloride of Formula (2).
19. The process as claimed claim 18, wherein the suitable solvent is selected from the group comprising of $\text{C}_1\text{-C}_5$ alcohols, hydrocarbons, acetonitrile, dimethyl formamide (DMF).
- 25 20. A vilazodone hydrochloride having particle size in terms of d_{95} is less than about 100 microns.
21. A vilazodone hydrochloride having particle size in terms of d_{95} is less than about 50 microns.
22. A vilazodone hydrochloride having particle size in terms of d_{95} is less than about
30 10 microns.
23. A process for preparing vilazodone hydrochloride having particle size in terms of d_{95} is less than about 50 microns, more particularly, less than about 10 microns comprising the steps of:

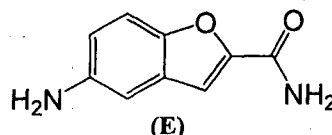
(i) milling vilazodone hydrochloride having particle size in terms of d95 is greater than about 100 microns;

(ii) slurring micronized vilazodone hydrochloride in one or more solvents;

(iii) isolating vilazodone hydrochloride having particle size in terms of d95 is less than about 10 microns.

24. A vilazodone of Formula (1) or its pharmaceutically acceptable salts, solvates, hydrates thereof having a total purity of greater than about 99%, specifically greater than about 99.5%, more specifically greater than about 99.9%, and most specifically greater than about 99.97% as measured by HPLC.

25. An improved process for preparing 5-aminobenzofuran-2-carboxamide of Formula (E),



comprising the steps of:

i) reacting salicylaldehyde with chloroacetic acid in an organic solvent and a base to obtain 2-(2-formylphenoxy) acetic acid of Formula (A);

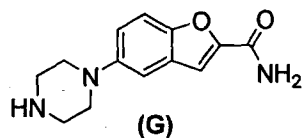
ii) nitrating 2-(2-formylphenoxy)acetic acid of Formula (A) to obtain 2-(2-formyl-4-nitrophenoxy)acetic acid of Formula (B);

iii) cyclizing 2-(2-formyl-4-nitrophenoxy) acetic acid of Formula (B) to obtain 5-nitrobenzofuran-2-carboxylic acid of Formula (C);

iv) converting 5-nitrobenzofuran-2-carboxylic acid of Formula (C) to 5-nitrobenzofuran-2-carboxamide of Formula (D);

vi) reducing 5-nitrobenzofuran-2-carboxamide of Formula (D) to obtain 5-aminobenzofuran-2-carboxamide of Formula (E).

26. A process for the preparation of solid state form of 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G)



comprising the steps of:

- (i) reacting 5-aminobenzofuran-2-carboxamide of Formula (E) with N,N-bis(2-chloroethyl)-4-methylbenzenesulfonamide of Formula (E') in presence of a base in a suitable solvent to obtain 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F);
- 5 (ii) deprotecting 5-(4-tosylpiperazin-1-yl)benzofuran-2-carboxamide of Formula (F) in the presence of an acid to obtain 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G) or its salts; and
- (iii) isolating the solid state form of 5-(1-piperazinyl) benzofuran-2-carboxamide of Formula (G) in presence of a base.

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FIG. 1

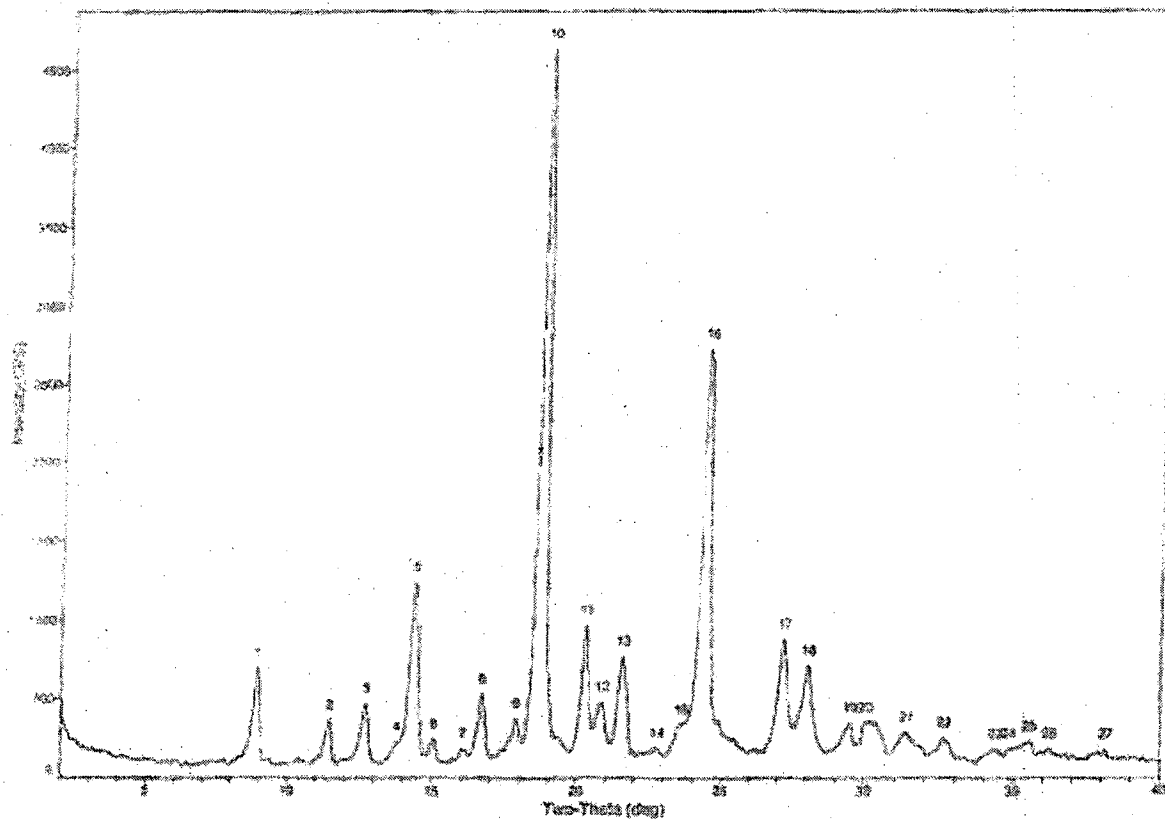


FIG. 2

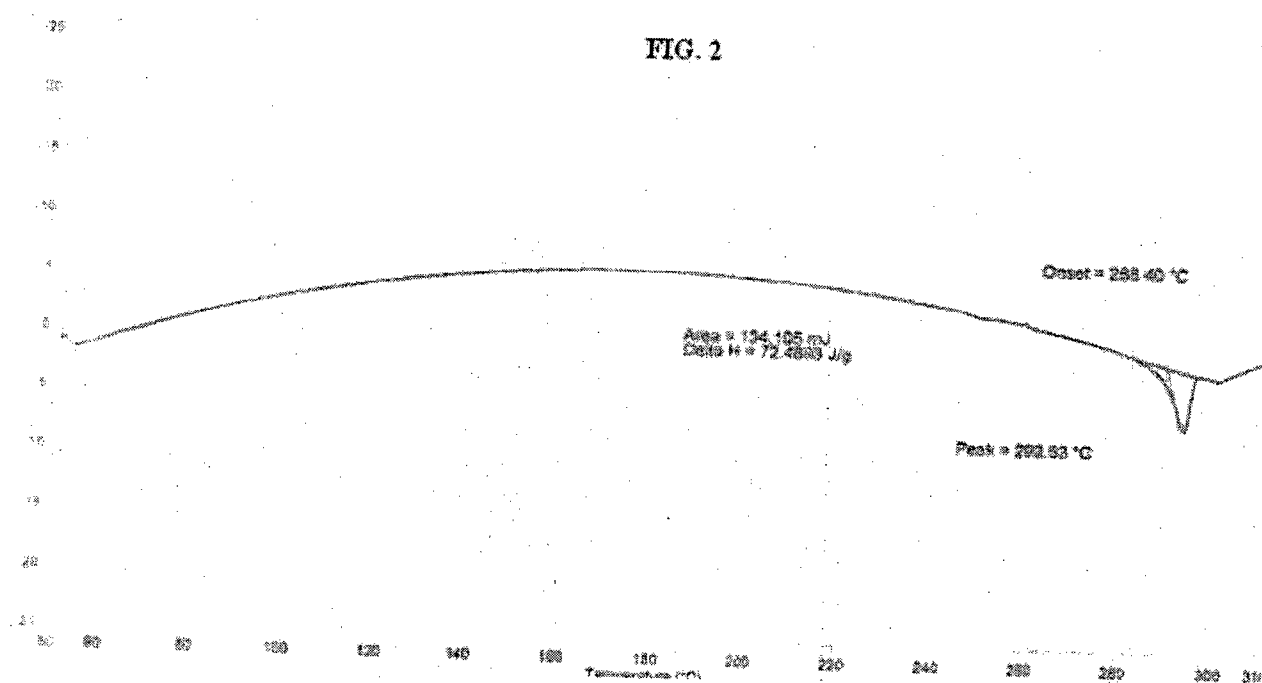


FIG. 3

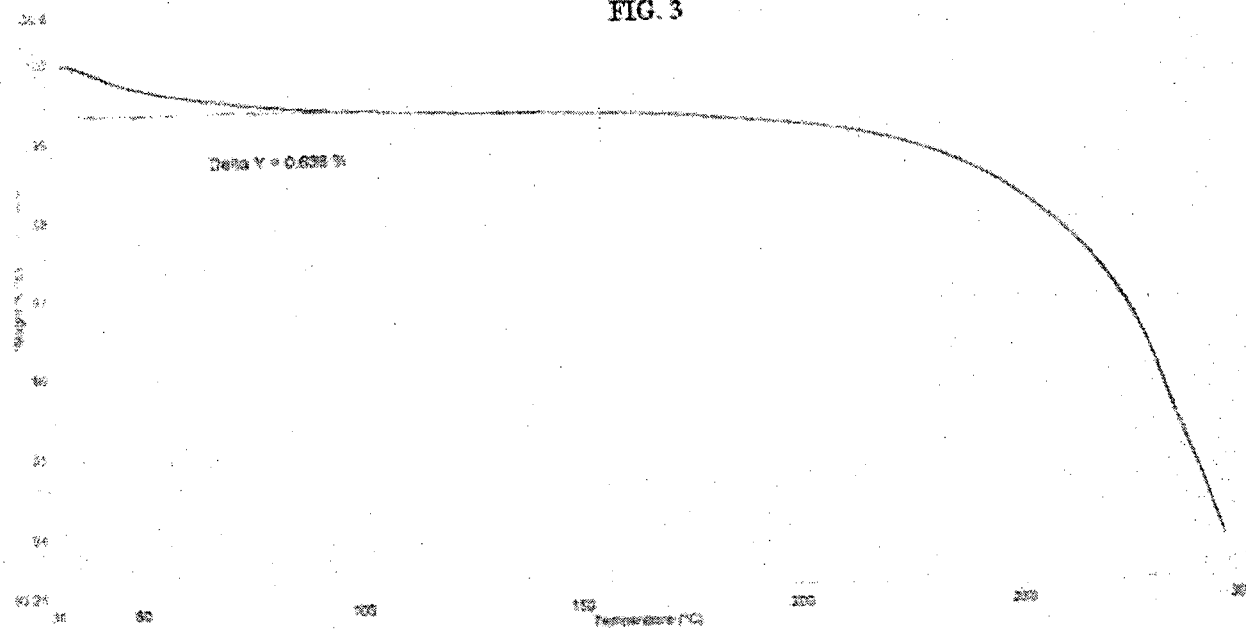


FIG. 4

