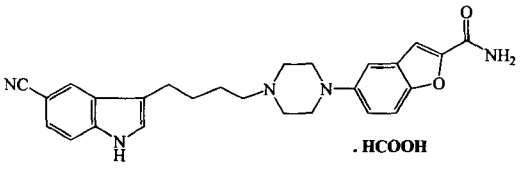
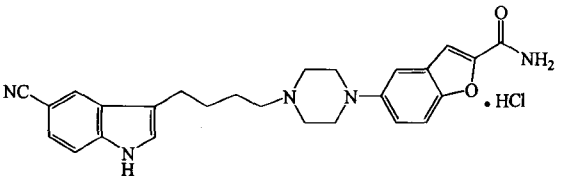
# Abstract

The present invention relates to formic acid salt as well as its crystalline form of antidepressant drug i.e., 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofurancarboxamide compound of formula-1, which is useful in the preparation of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide hydrochloride compound of formula-1a and process for its preparation.



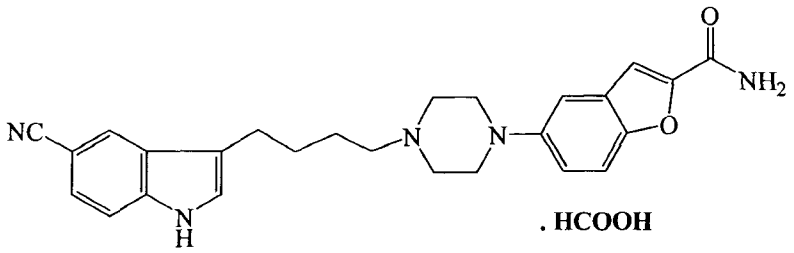

Formula-1




Formula-1a

**Claims:**

1. The formic acid salt of 5-[4-[4-(5-cyano-1Hindol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide:




2. Crystalline formic acid salt of 5-[4-[4-(5-cyano-1Hindol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide.

3. The crystalline form (Form-M) according to claim-2, is characterized by:
   i. its X-ray powder diffractogram having peaks at 7.7, 8.5, 10.4, 11.9, 14.4, 15.5, 18.0, 19.1, 20.0, 21.0, 21.9, 24.0, 26.4, 27.0 and 29.3 degrees of two-theta as illustrated in figure-1;
   ii. its DSC thermogram showing endotherm as illustrated in figure-2;
   iii. its IR spectrum as illustrated in figure-3.

4. Crystalline form-M of formic acid salt of 5-[4-[4-(5-cyano-1Hindol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide of claim-3 is further characterized by its X-ray powder diffractogram having peaks at 7.2, 7.4, 8.5, 10.4, 11.9, 12.2, 14.4, 14.7, 15.5, 16.6, 17.2, 18.0, 19.1, 20.0, 20.5, 21.0, 21.4, 21.9, 23.2, 24.0, 24.6, 26.4, 27.0, 29.3 and 29.9 degrees of two-theta as illustrated in figure-1.

5. A process for the preparation of formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide compound of formula-1, comprising of the following steps:
   a) Dissolving the 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide in formic acid,
   b) adding a suitable solvent to the reaction mixture,
   c) stirring the reaction mixture,

d) filtering the precipitated solid and drying to provide formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide compound of formula-1.

6. A process according to claim-5, wherein,
in step-b) the suitable solvent is selected from ester solvents, ketone solvents, chloro solvents, alcohol solvents, ether solvents, hydrocarbon solvents, polar aprotic solvents, polar solvents like water and mixture thereof; preferably the suitable solvent is selected from polar solvents such as water.

7. A process for the preparation of crystalline form-M of formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofurancarboxamide compound of formula-1, comprising of the following steps;
   a) Dissolving the 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide in formic acid,
   b) adding isopropanol to the reaction mixture,
   c) stirring the reaction mixture,
   d) filtering the precipitated solid and drying to provide crystalline form-M of formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide compound of formula-1.

8. A process for the preparation of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide hydrochloride form-XVI compound of formula-1a, comprising of the following steps;
   a) Dissolving the formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide in formic acid,
   b) adding aqueous hydrochloric acid to the reaction mixture,
   c) filtering the reaction mixture,
   d) adding water to the filtrate obtained in step-c),
   e) stirring the reaction mixture,
   f) filtering the precipitated solid,
   g) adding aqueous hydrochloric acid to the solid obtained in step-f),

h) stirring the reaction mixture,

i) filtering the solid and drying to provide form-XVI of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide hydrochloride compound of formula-1a.

9. A process for the preparation of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide hydrochloride form-XVI compound of formula-1a, comprising of the following steps;

a) Dissolving the crystalline form-M of formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide in formic acid,

b) adding aqueous hydrochloric acid to the reaction mixture,

c) filtering the reaction mixture,

d) adding water to the filtrate obtained in step-c),

e) stirring the reaction mixture,

f) filtering the precipitated solid,

g) adding aqueous hydrochloric acid to the solid obtained in step-f),

h) stirring the reaction mixture,

i) filtering the solid and drying to provide form-XVI of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide hydrochloride compound of formula-1a.

10. Use of formic acid salt as well as its crystalline form-M of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofurancarboxamide obtained according to any of the preceding claims in the preparation of pure Vilazodone free base as well as Vilazodone hydrochloride form-XVI.

Dated this day 15th of February 2014.

**Authorized Signatory**

**(Srinivasan Thirumalai Rajan)**

**MSN Laboratories Private Limited**

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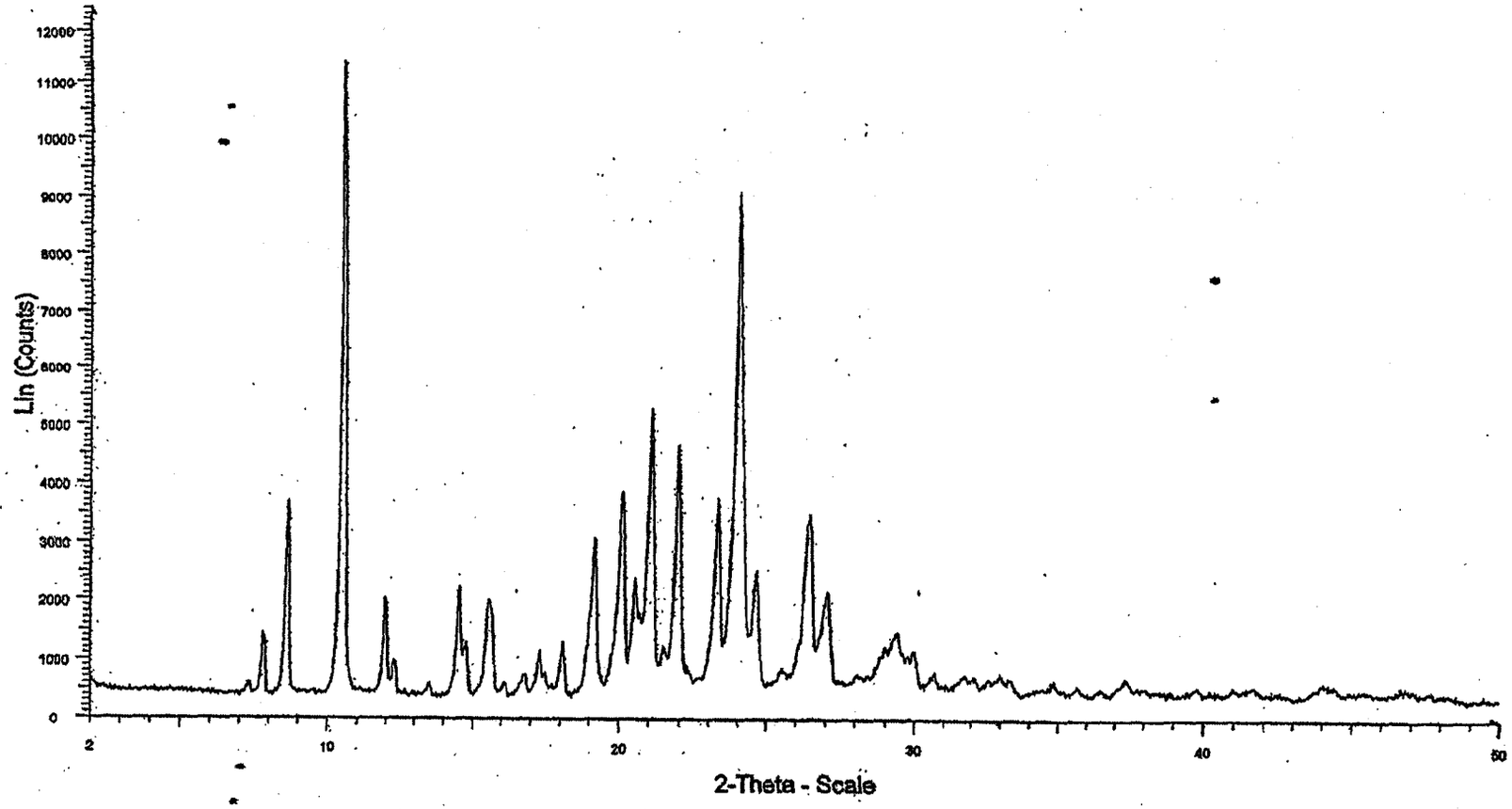


**Figure-1**

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**Signature & Date**

DSC

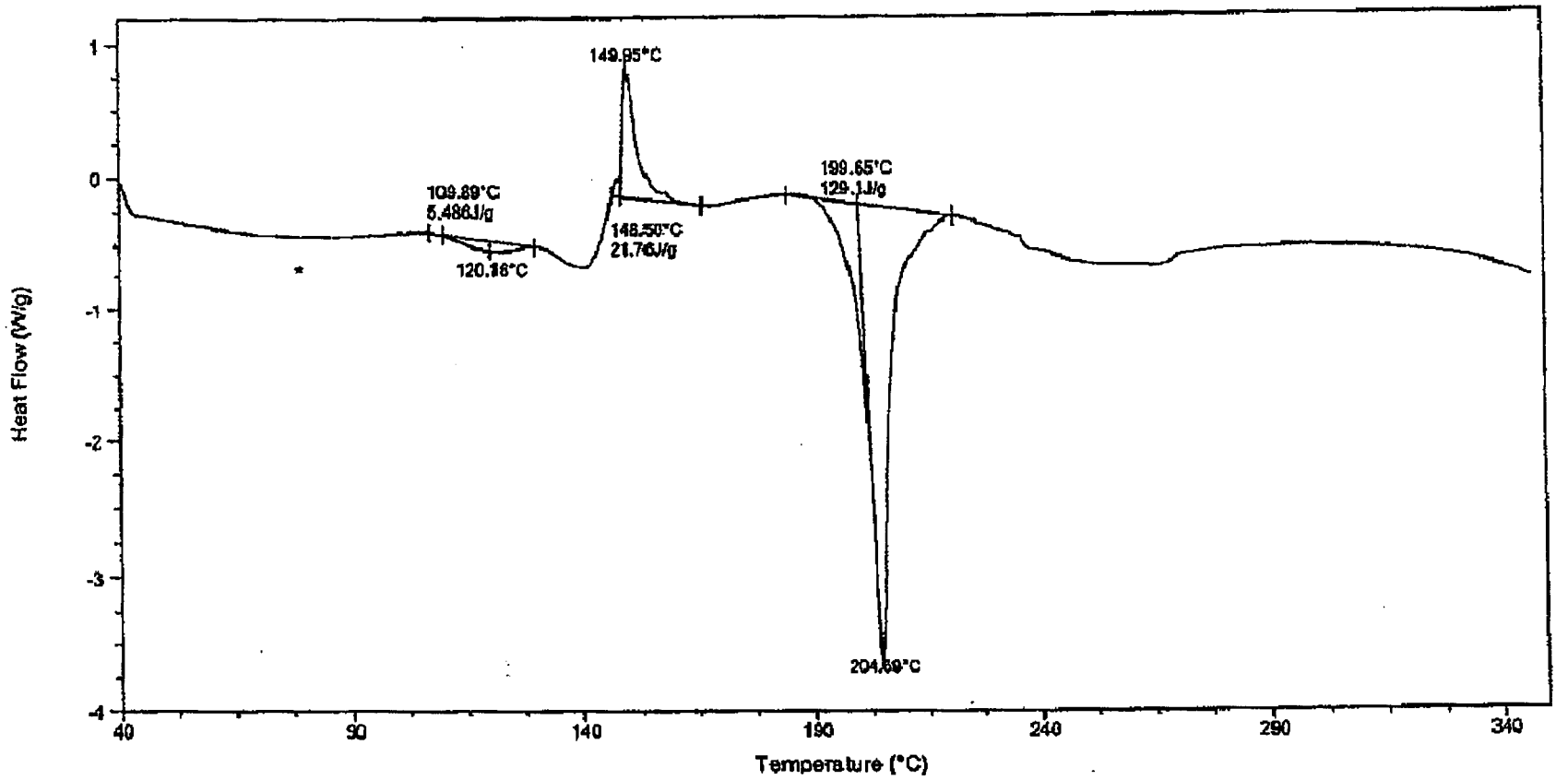


Figure-2

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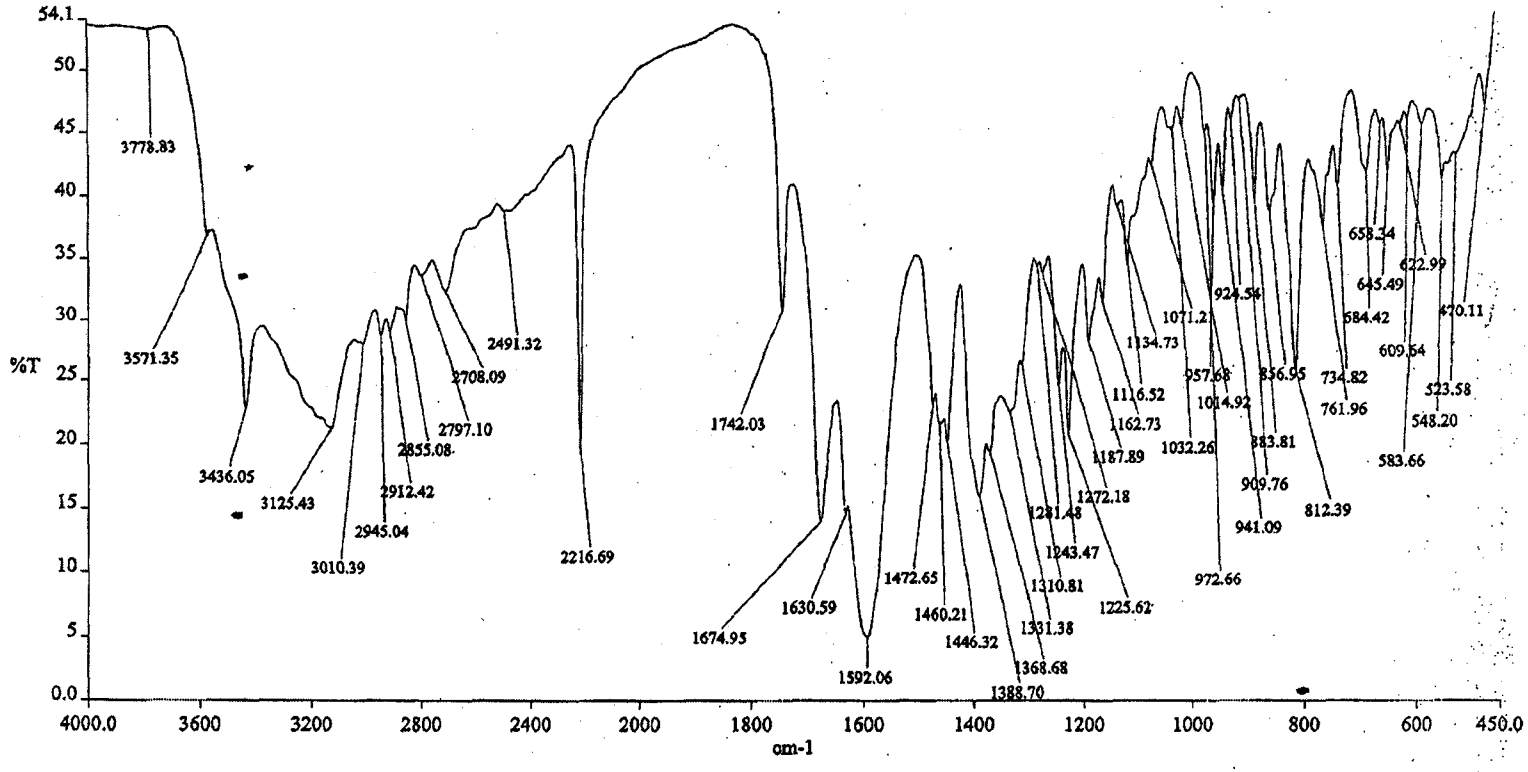


**Figure-3**

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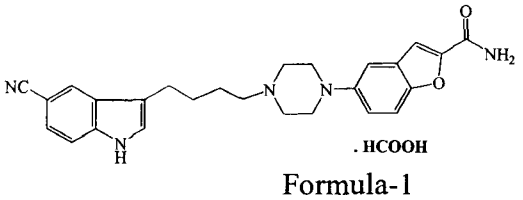
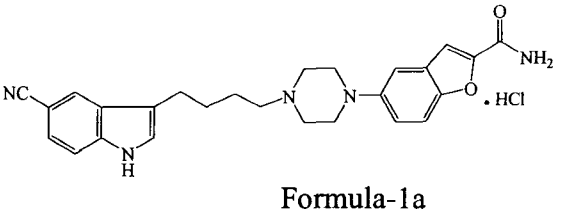
**Field of Invention:**

The present invention provides a formic acid salt as well as its crystalline form of antidepressant drug i.e., 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofurancarboxamide compound of formula-1, which is useful in the preparation of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide hydrochloride compound of formula-1a and process for its preparation.




Formula-1




Formula-1a

**Back ground of the Invention:**

US 5,532,241 (hereafter referred to as "241") first disclosed 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide and its hydrochloride salt compound of formula-1a which is commonly known as vilazodone hydrochloride, an antidepressant agent, which acts as a serotonin reuptake inhibitor.

"241" first disclosed the process for the preparation of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide and its hydrochloride salt compound of formula-1a by reacting 5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxylic acid with 2-chloro-1-methylpyridinium methanesulfonate in the presence of N-methyl pyrrolidine and ammonia gas to provide vilazodone as free base. Further, vilazodone free base is dissolved in propanolic hydrochloric acid solution to precipitate hydrochloride salt of compound of formula-1a.

US7834020 (hereafter referred to as "020") describes several crystalline forms of vilazodone hydrochloride, such as Form-I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XIII, XIV, XV and XVI and process for their preparation.

Crystalline Form-N of methanesulfonate of Vilazodone was protected through IN patent application number: 4014/CHE/2012.

Different salts of Vilazodone such as HBr, phosphoric acid, benzene sulfonic acid, nitric acid and paratoulene sulfonic acid were protected through IN patent application number: 4629/CHE/2012.

**Brief description of the Invention:**

The first aspect of the present invention is to provide formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide compound of formula-1 and its crystalline form herein after designated as Form-M.

The second aspect of the present invention is to provide a process for the preparation of formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide compound of formula-1, comprising of the following steps:

a) Dissolving the 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide in formic acid,
b) adding a suitable solvent to the reaction mixture,
c) stirring the reaction mixture,
d) filtering the precipitated solid and drying to provide formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofurancarboxamide compound of formula-1.

The third aspect of the present invention is to provide a process for the preparation of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide hydrochloride form-XVI compound of formula-1a, comprising of the following steps:

a) Dissolving the formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide in a suitable acid,
b) adding a suitable hydrochloric acid source to the reaction mixture,
c) filtering the reaction mixture,
d) adding a suitable solvent to the filtrate obtained in step-c),
e) stirring the reaction mixture,
f) filtering the precipitated solid,
g) adding a suitable hydrochloric acid source to the solid obtained in step-f),

h) stirring the reaction mixture,

i) filtering the solid and drying to provide form-XVI of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide hydrochloride compound of formula-1a.

**Brief description of the Drawings:**

**Figure 1:** Illustrates the PXRD pattern of crystalline Form-M of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide.

**Figure 2:** Illustrates the DSC thermogram of crystalline Form-M of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide.

**Figure 3:** Illustrates the IR spectrum of crystalline Form-M of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide.

**Detailed description of the Invention:**

As used herein the term "suitable solvent" is selected from "alcoholic solvents" such as methanol, ethanol, isopropanol, n-propanol, n-butanol, iso-butanol, ethylene glycol and the like; "ester solvents" such as ethyl acetate, methyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, isopropyl acetate and the like, "ether solvents" such as tetrahydrofuran, diethylether, methyl tert-butylether, 1,4-dioxane and the like; "hydrocarbon solvents" such as toluene, xylene, cyclohexane, hexane, heptane, n-pentane and the like; "chloro solvents" such as methylene chloride, ethylene dichloride, carbon tetrachloride, chloroform and the like; "polar aprotic solvents" such as dimethyl formamide, dimethylacetamide, dimethylsulfoxide and the like; "nitrile solvents" such as acetonitrile, propionitrile, isobutyronitrile and the like; "ketone solvents" such as acetone, methyl isobutyl ketone, methyl ethyl ketone; polar solvent such as water and the like.

The suitable hydrochloric acid source is selected from HCl gas, aqueous HCl, dry HCl, ethyl acetate-HCl, IPA-HCl, ethanol-HCl, methanol-HCl.

As used herein the term "suitable acid" is selected from formic acid, acetic acid, propionic acid, butanoic acid, pentanoic acid, hexanoic acid and the like.

The first aspect of the present invention provides a formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide and its crystalline form herein after designated as Form-M. The said crystalline form-M is characterized by:

a) Its powder X-ray diffractogram having peaks at 7.2, 7.4, 7.7, 8.5, 10.4, 11.9, 12.2, 14.4, 14.7, 15.5, 16.6, 17.2, 18.0, 19.1, 20.0, 21.0, 20.5, 21.0, 21.4, 21.9, 23.2, 24.0, 24.6, 26.4, 27.0 and 29.3 and 29.9 degrees of two-theta as illustrated in figure-1.
b) its DSC thermogram showing endotherm at 204.69°C as illustrated in figure-2;
c) its IR spectrum as illustrated in figure-3.

The second aspect of the present invention provides a process for the preparation of formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide compound of formula-1, comprising of the following steps:

a) Dissolving the 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide in formic acid,
b) adding a suitable solvent to the reaction mixture,
c) stirring the reaction mixture,
d) filtering the precipitated solid and drying to provide formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide.

Wherein,

in step-b) the suitable solvent is selected from ester solvents, ketone solvents, chloro solvents, alcohol solvents, ether solvents, hydrocarbon solvents, polar aprotic solvents, polar solvents like water and mixture thereof; preferably the suitable solvent is selected from polar solvents such as water.

The preferred embodiment of the present invention provides a process for the preparation of formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide, comprising of the following steps:

a) Dissolving the 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide in formic acid,
b) adding isopropanol to the reaction mixture,
c) stirring the reaction mixture,

d) filtering the precipitated solid and drying to provide formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofurancarboxamide compound of formula-1.

The preferred embodiment of the present invention provides a process for the preparation of crystalline Form-M of formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide, comprising of the following steps:

a) Dissolving the 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide in formic acid,
b) adding isopropanol to the reaction mixture,
c) stirring the reaction mixture,
d) filtering the precipitated solid and drying to provide crystalline form-M of formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide compound of formula-1.

The starting material i.e., 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide utilized in the present invention can be prepared by any of the known prior art process.

The third aspect of the present invention provides a process for the preparation of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofurancarboxamide hydrochloride form-XVI compound of formula-1a, comprising of the following steps:

a) Dissolving the formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide in a suitable acid,
b) adding a suitable hydrochloric acid source to the reaction mixture,
c) filtering the reaction mixture,
d) adding a suitable solvent to the filtrate obtained in step-c),
e) stirring the reaction mixture,
f) filtering the precipitated solid,
g) adding a suitable hydrochloric acid source to the solid obtained in step-f),
h) stirring the reaction mixture,
i) filtering the solid and drying to provide form-XVI of 5-[4-[4-(5-cyano-1H-indol-

3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide hydrochloride compound of formula-1a.

Wherein,

in step-a) the suitable acid is selected from formic acid, acetic acid, propionic acid, butanoic acid, pentanoic acid, hexanoic acid and the like;

in step-b) & g) the suitable hydrochloric acid source is selected from HCl gas, aqueous HCl, dry HCl, ethyl acetate-HCl, IPA-HCl, ethanol-HCl, methanol-HCl;

in step-d) the suitable solvent is same as defined in step-b) of the second aspect of the present invention.

The preferred embodiment of the present invention provides a process for the preparation of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide hydrochloride form-XVI compound of formula-1a, comprising of the following steps;

a) Dissolving the formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide in formic acid,
b) adding aqueous hydrochloric acid to the reaction mixture,
c) filtering the reaction mixture,
d) adding water to the filtrate obtained in step-c),
e) stirring the reaction mixture,
f) filtering the precipitated solid,
g) adding aqueous hydrochloric acid to the solid obtained in step-f),
h) stirring the reaction mixture,
i) filtering the solid and drying to provide form-XVI of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide hydrochloride compound of formula-1a.

The preferred embodiment of the present invention provides a process for the preparation of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide hydrochloride form-XVI compound of formula-1a, comprising of the following steps;

a) Dissolving the crystalline form-M of formic acid salt of 5-[4-[4-(5-cyano-1H-

indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide in formic acid,

b) adding aqueous hydrochloric acid to the reaction mixture,
c) filtering the reaction mixture,
d) adding water to the filtrate obtained in step-c),
e) stirring the reaction mixture,
f) filtering the precipitated solid,
g) adding aqueous hydrochloric acid to the solid obtained in step-f),
h) stirring the reaction mixture,
i) filtering the solid and drying to provide form-XVI of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide hydrochloride compound of formula-1a.

The formic acid salt as well as its crystalline form-M of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofurancarboxamide of the present invention is useful in the preparation of pure freebase of Vilazodone as well as form-XVI of Vilazodone hydrochloride.

The formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofurancarboxamide of the present invention can be converted in to its freebase by treating with a suitable base or by using any known methods.

PXRD analysis of compound produced by the present invention were carried out using BRUKER/AXS X-Ray diffractometer using Cu Kα radiation of wavelength 1.5406 A° and continuous scan speed of 0.03°/min.

Differential scanning calorimetric (DSC) analysis was performed with Q10 V9.6 Build 290 calorimeter. Samples of about 2 to 3 milligrams held in a closed pan were analyzed at a heating rate of 10° per minute.

**HPLC Method of Analysis of formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide.**

Apparatus: A liquid chromatographic system is to be equipped with variable wavelength UV-detector; Column: Symmetry C18, 150 x 4.6mm, 3.5 µm (or) equivalent; Flow rate: 1.0 ml/min; Wavelength: 242 nm; Column Temperature: 40°C; Injection volume: 5 µL; Run time: 35 min; Diluent: Water : Isopropyl alcohol (1:1) v/v; Needle wash: Water : Isopropyl alcohol (1:1) v/v; Elution: Gradient; Mobile phase-A: Buffer (100%); Mobile phase-B: Acetonitrile: Buffer (70:30) v/v; Buffer: 2.72 grams of potassium dihydrogen phosphate and 3.0 grams of 1-Octane sulphonic acid in 1000 ml of water. Adjust pH to 2.0 with diluted orthophosphoric acid and filtered through 0.22µm Nylon membrane filter paper and sonicate to degas it.

The compound produced by the present invention can be further micronized or milled to get the desired particle size to achieve desired solubility profile based on different forms of pharmaceutical composition requirements. Techniques that may be used for particle size reduction include, but not limited to ball, roller and hammer mills, and jet mills. Milling or micronization may be performed before drying, or after the completion of drying of the product.

The process described in the present invention was demonstrated in examples illustrated below. These examples are provided as illustration only and therefore should not be construed as limitation of the scope of the invention.

**Examples:**

**Example-1:**

**Preparation of formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide**

Formic acid (300 ml) was added to 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide (100 gms) at 25-30°C and stirred for 15 minutes. Isopropanol (1500 ml) was added to the reaction mixture at 25-30°C and stirred for 2-3 hours at the same temperature. Filtered the precipitated solid, washed with isopropanol

and dried to get the title compound.

Yield: 95.5 gms. Melting point: 199-204°C.

Purity by HPLC 99.65 %; Diamide Impurity: Not detected; Acid Impurity: 0.04 %; Ester Impurity: Not detected; Unknown Impurity: 0.05 %.

The PXRD of the obtained compound is shown in figure-1.

**Example-2:**

**Preparation of Form-XVI of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide hydrochloride [Formula-1a]**

Formic acid (250 ml) was added to formic acid salt of 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-2-benzofuran carboxamide (100 gms) obtained in example-1 at 25-30°C and stirred for 15 minutes at the same temperature. Slowly aqueous hydrochloric acid (34.5 ml) was added to the reaction mixture at 25-30°C. Filtered the reaction mixture through hy-flow bed and washed with formic acid (50 ml). To the obtained filtrate, slowly water (1000 ml) was added at 25-30°C and stirred for 2 hours at the same temperature. Filtered the precipitated solid and washed with water. To the obtained wet solid, aqueous hydrochloric acid was added at 25-30°C and stirred the reaction mixture for 2 hours at the same temperature. Filtered the solid, washed with water and dried to get the title compound.

Yield: 96.2 gms.

Melting point 284-288°C.

Formic acid content: 1100 ppm.