Abstract:
The present invention provides a novel intermediate of vilazodone and its process of preparation. The present invention further provides a process for preparing vilazodone or a pharmaceutically acceptable salt thereof using the novel intermediate.
PROCESS FOR THE PREPARATION OF VILAZODONE OR
PHARMACEUTICALLY ACCEPTABLE SALT THEREOF

Field of the Invention

The present invention provides a novel intermediate of vilazodone and its process of preparation. The present invention further provides a process for preparing vilazodone or a pharmaceutically acceptable salt thereof using the novel intermediate.

Background of the Invention

Vilazodone free base is chemically described as $5\{-4\{-4\{(5\text{-cyano-1H-indol-3-yl})\text{-butyl}\}\text{piperazin-1-yl}\}\text{-1-benzofuran-2-carboxamide}\}$ of Formula I.

![Formula I](image)

Vilazodone hydrochloride is chemically described as $5\{-4\{-4\{(5\text{-cyano-1H-indol-3-yl})\text{-butyl}\}\text{piperazin-1-yl}\}\text{-1-benzofuran-2-carboxamide\text{hydrochloride}}$ of Formula II.

![Formula II](image)

Vilazodone hydrochloride is indicated for the treatment of major depressive disorder (MDD).

Summary of the Invention

The present invention provides a novel intermediate of vilazodone and its process of preparation. The present invention further provides a process for preparing vilazodone or a pharmaceutically acceptable salt thereof using the novel intermediate.

In one general aspect, the invention relates to a novel intermediate compound of Formula III.

\[
\text{FORMULA III}
\]

In another general aspect, the invention relates to a process for the preparation of 5-(4-formylpiperazin-1-yl)-1-benzofuran-2-carboxamide of Formula III,

\[
\text{FORMULA III}
\]

The process includes the steps of:

a) formylating ethyl 5-((piperazin-1-yl)-l-benzofuran-2-carboxylate compound of Formula IV or its salt; and
b) isolating 5-(4-formylpiperazin-1-yl)-1-benzofuran-2-carboxamide of Formula III from the reaction mixture thereof.

Embodiments of the process may include one or more of the following features. For example, the formylation of the compound of Formula IV or its salt may be carried out in the presence of a formylating agent.

The formylating agent may be selected from the group consisting of formamide, chloral, formic acid-dicyclohexylcarbodiimide, formic acid-1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC1), formic acid-zinc chloride, formic acid-polyethylene glycol 400, activated formic acid esters, acetic formic anhydride, ammonium formate, 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), or mixtures thereof. In particular, the formylating agent is formamide.

In the process, the formylation of the compound of Formula IV or its salt may be carried out in the presence of a base and a solvent. The base may be sodium methoxide. The solvent may be selected from the group consisting of halogenated hydrocarbons, alcohols, ketones, N-methyl pyrrolidone, formamides, ethers, nitriles, aromatic and aliphatic hydrocarbons, or mixtures thereof. In particular, the solvents may be selected from formamide, dichloromethane, methanol, or mixtures thereof.

In another general aspect, the invention relates to a process for the preparation of vilazodone free base of Formula I
FORMULA I

or pharmaceutically acceptable salts thereof. The process includes the steps of

a) formylating ethyl 5-(piperazin-1-yl)-1-benzofuran-2-carboxylate compound of Formula IV or its salt

FORMULA IV

to give 5-(4-formylpiperazin-1-yl)-1-benzofuran-2-carboxamide of Formula III:

FORMULA III

b) converting 5-(4-formylpiperazin-1-yl)-1-benzofuran-2-carboxamide of Formula III to 5-(piperazin-1-yl)-1-benzofuran-2-carboxamide of Formula V:

FORMULA V
c) reacting 5-(piperazin-1-yl)-1-benzofuran-2-carboxamide of Formula V with 3-(4-chlorobuty1)-1H-indole-5-carbonitrile of Formula VI;

\[
\text{FORMULA VI}
\]

5 d) isolating vilazodone free base of Formula I from the reaction mixture thereof; and

e) optionally converting the compound of Formula I to its pharmaceutically acceptable salts.

Embodiments of the process may include one or more of the following features.

For example, the formylation of the compound of Formula IV or its salt may be carried out in the presence of a formylating agent.

The formylating agent may be selected from the group consisting of formamide, chloral, formic acid-dicyclohexylcarbodiimide, formic acid-1-ethyl-3(3-dimethylaminopropyl)carbodiimide (EDC1), formic acid-zinc chloride, formic acid-polyethylene glycol 400, activated formic acid esters, acetic formic anhydride, ammonium formate, 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), or mixtures thereof. In particular, the formylating agent is formamide.

In the process, the formylation of the compound of Formula IV or its salt may be carried out in the presence of a base and a solvent. The base may be sodium methoxide.

The solvent may be selected from the group consisting of halogenated hydrocarbons, alcohols, ketones, N-methyl pyrrolidone, formamides, ethers, nitriles, aromatic and aliphatic hydrocarbons, or mixtures thereof. In particular, the solvents may be selected from formamide, dichloromethane, methanol, or mixtures thereof.

In the process, the compound of Formula III may be converted to the compound of Formula V in step b) in the presence of an acid and a solvent. The acid may be selected from the group consisting of inorganic or organic acids. The solvent may be selected from
the group consisting of water, alcohol, esters, nitriles, amides, ketones, ethers, aromatic or aliphatic hydrocarbons, dimethyl sulfoxide, or mixtures thereof. In particular, the solvent may be water.

The reaction of the compound of Formula V and the compound of Formula VI in step c) may be carried out in the presence of a base and a solvent. The solvent may be selected from the group consisting of water, organic solvent, or mixtures thereof. The solvent may be water alone or in combination with 2-propanol, 1-propanol, dimethyl formamide, or toluene. The base may be selected from the group consisting of organic or inorganic bases.

In the process, the reaction mixture of the compound of the Formula V and the compound of Formula VI may be treated with hydrobromic acid before converting to vilazodone free base.

In the process, the pharmaceutically acceptable salt in step e) may be the hydrochloric acid salt.

**Detailed Description of the Invention**

The term "treating", as used herein, includes adding, dissolving, slurrying, stirring, or combinations thereof.

The term "about", as used herein, refers to any value which lies within the range defined by a variation of up to ±10% of the value.

The term "isolating", as used herein, refers to an isolation process by means of filtration, decantation, extraction, distillation, evaporation, chromatography, precipitation, centrifugation, recrystallization, or combinations thereof.

A first aspect of the present invention provides a novel intermediate compound of Formula III.

![Formula III](image)
The novel intermediate compound of Formula III is chemically described as 5-(4-formylpiperazin-1-yl)-1-benzofuran-2-carboxamide.

A second aspect of the present invention provides a process for the preparation of 5-(4-formylpiperazin-1-yl)-1-benzofuran-2-carboxamide of Formula III

\[ \text{FORMULA III} \]

wherein the process comprises:

a) formylating ethyl 5-(piperazin-1-yl)-1-benzofuran-2-carboxylate compound of Formula IV or its salt; and

\[ \text{FORMULA IV} \]

b) isolating 5-(4-formylpiperazin-1-yl)-1-benzofuran-2-carboxamide of Formula III from the reaction mixture thereof.

The compound of Formula IV or its salt may be prepared by methods known in the literature, for example, in U.S. Patent Nos. 5,532,241, and 5,723,614. The preferred salt of the compound of Formula IV is hydrochloride salt. The formylation of the compound of Formula IV or its salt may be carried out in the presence of a formylating agent. The formylating agent is selected from the group consisting of formamide, chloral, formic acid- dicyclohexylcarbodiimide, formic acid- 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC1), formic acid - zinc chloride, formic acid - polyethylene glycol 400, activated formic acid esters, acetic formic anhydride, ammonium formate, 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), or mixtures thereof. The preferred formylating agent is formamide.
The formylation of the compound of Formula IV or its salt is carried out in the presence of a solvent and a base. The solvent is selected from the group consisting of halogenated hydrocarbons, alcohols, ketones, N-methyl pyrrolidone, formamides, ethers, nitriles, aromatic and aliphatic hydrocarbons, or mixtures thereof. Suitable alcoholic solvents are methanol, 2-propanol, or 1-propanol. A suitable nitrile solvent is acetonitrile. Suitable ether solvents are diisopropyl ether, methyl t-butyl, or ether. Suitable aromatic and aliphatic hydrocarbons solvents are hexane, heptane, or toluene. A suitable halogenated hydrocarbon solvent is dichloromethane. The preferred solvents are formamide, dichloromethane, methanol, or mixtures thereof.

The base is selected from the group consisting of alkali metal alkoxide or organic bases. The organic base is selected from the group consisting of ammonia, triethyl amine, or diisopropyl ethyl amine. The preferred alkali metal alkoxide is sodium methoxide. The formylation of the compound of Formula IV or its salt is carried out at a temperature of about 10°C to about 40°C, preferably at about 20°C to about 30°C. The formylation of the compound of Formula IV or its salt is carried out for about 2 hours to about 8 hours, preferably for about 4 hours to about 6 hours.

The compound of Formula III may optionally be isolated by filtration, concentration, precipitation, cooling, centrifugation, decantation, or combinations thereof.

A third aspect of the present invention provides a process for the preparation of vilazodone free base of Formula I

\[
\text{FORMULA I}
\]

or its pharmaceutically acceptable salts which comprises:

a) formylating ethyl 5-(piperazin-1-yl)-1-benzofuran-2-carboxylate compound of Formula IV or its salt
to give 5-(4-formylpiperazin-1-yl)-1-benzofuran-2-carboxamide of Formula III:

FORMULA III

b) converting 5-(4-formylpiperazin-1-yl)-1-benzofuran-2-carboxamide of Formula III to 5-(piperazin-1-yl)-1-benzofuran-2-carboxamide of Formula V:

FORMULA V

c) reacting 5-(piperazin-1-yl)-1-benzofuran-2-carboxamide of Formula V with 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula VI:
d) isolating vilazodone free base of Formula I from the reaction mixture thereof; and

e) optionally converting the compound of Formula I to its pharmaceutically acceptable salts.

The compound of Formula IV or its salt may be prepared by methods known in the literature, for example, in U.S. Patent Nos. 5,532,241, and 5,723,614. The preferred salt of the compound of Formula IV is hydrochloride salt. The formylation of the compound of Formula IV or its salt is carried out as described in the second aspect.

The compound of Formula III may optionally be isolated by filtration, concentration, precipitation, cooling, centrifugation, decantation, or combinations thereof.

The compound of Formula III is converted to the compound of Formula V in the presence of an acid and a solvent. The acid is selected from the group consisting of inorganic or organic acid. The preferred inorganic acid is hydrochloric acid. The solvent is selected from the group consisting of water, alcohols, esters, nitriles, amides, ketones, ethers, aromatic or aliphatic hydrocarbons, dimethyl sulfoxide, or mixtures thereof. Suitable alcoholic solvents are methanol, 2-propanol, or 1-propanol. A suitable nitrile solvent is acetonitrile. Suitable ester solvents are ethyl acetate or propyl acetate. Suitable ether solvents are diisopropyl ether or methyl t-butyl ether. Suitable aromatic and aliphatic hydrocarbon solvents are hexane, heptane, or toluene. A suitable amide solvent is formamide. The preferred solvent is water.

The compound of Formula III is converted to the compound of Formula V at about 10°C to about 70°C, preferably at about 30°C to about 60°C. The conversion of the compound of Formula III to the compound of Formula V is carried out for about 1 hour to about 6 hours, preferably for about 2 hours to about 4 hours.

The reaction of the compound of Formula V and the compound of Formula VI is carried out in the presence of a base and a solvent. The solvent is selected from the group consisting of water, organic solvent, or mixtures thereof. The organic solvent is selected from the group consisting of alcohols, ketones, nitriles, amides, aromatic or aliphatic hydrocarbons, dimethyl sulfoxide, or mixtures thereof. Suitable alcoholic solvents are methanol, 2-propanol, or 1-propanol. A suitable nitrile solvent is acetonitrile. Suitable amide solvents are N-methylpyrrolidone or dimethyl formamide. Suitable ketonic
solvents are acetone or methyl isobutyl ketone. A suitable aromatic hydrocarbon solvent is toluene. The preferred solvent is water, either alone or in combination with 2-propanol, 1-propanol, dimethyl formamide, or toluene. Preferably, the treatment of compound of Formula V and compound of Formula VI is carried out in the presence of only water without using any other solvent.

The base is selected from the group consisting of organic bases or inorganic bases. Suitable organic bases are triethyl amine, diisopropyl amine, diisopropyl ethylamine, 4-dimethylaminopyridine, pyrollidine, or N-methyl morpholine. The preferred organic base is triethylamine. Suitable inorganic bases are hydroxides, or carbonates and bicarbonates of alkali or alkaline metal. Suitable carbonates or bicarbonates of alkali or alkaline metal are sodium carbonate, potassium carbonate, magnesium carbonate, sodium bicarbonate, or potassium bicarbonate. The preferable inorganic base is potassium carbonate. The treatment of the compound of Formula V and the compound of Formula VI is carried out in the presence of alkali metal halides, for example, sodium iodide.

The treatment of the compound of Formula V and the compound of Formula VI is carried out at a temperature of about 20°C to about 140°C, preferably at about 50°C to about 120°C. The treatment of the compound of Formula V and the compound of Formula VI is carried for about 2 hours to about 35 hours, preferably for about 5 hours to about 30 hours.

The reaction mixture of the compound of Formula V and the compound of Formula VI is treated with hydrobromic acid before converting to vilazodone free base. The hydrobromic acid may be diluted or concentrated. The hydrobromic acid may be used in a solution form or a gaseous form. The solution of hydrobromic acid may be aqueous or in an organic solvent. The preferred organic solvents are methanol, ethanol, or 2-propanol.

The treatment of the reaction mixture of the compound of Formula V and the compound of Formula VI with hydrobromic acid is carried out in the presence of an organic solvent. The organic solvent is selected from the group consisting of alcohols, ketones, esters, formamides, water, halogenated hydrocarbons, N-methyl pyrollidone, or combinations thereof. Suitable alcoholic solvents are methanol, ethanol, 2-propanol, 1-propanol, butanol, or methylated ethanol. Suitable ketonic solvents are acetone or methyl
isobutyl ketone. Suitable ester solvents are ethyl acetate or isopropyl acetate. A suitable halogenated hydrocarbon is dichloromethane. The preferred solvents include N-methyl pyrrolidone in combination with 2-propanol, methanol, or methylated ethanol.

The dissolution of the reaction mixture of the compound of Formula V and the compound of Formula VI with hydrobromic acid is carried out at a temperature of about 10°C to about 40°C, preferably at about 20°C to about 30°C. The dissolution of the reaction mixture of the compound of Formula V and the compound of Formula VI with hydrobromic acid is carried out for about 5 minutes to about 25 hours, preferably for about 7 hours to about 18 hours. The vilazodone hydrobromide salt may optionally be isolated by filtration, decantation, drying, vacuum drying, or combinations thereof.

The vilazodone hydrobromide may be converted to vilazodone free base. The conversion of vilazodone hydrobromide to vilazodone free base is carried out in the presence of a base and a solvent. The base is selected from the group consisting of organic or inorganic bases. The inorganic bases are selected from the group consisting of carbonates, bicarbonates, or hydroxides. The preferred base for the conversion of vilazodone hydrobromide to vilazodone free base is sodium bicarbonate. The base for the conversion of vilazodone hydrobromide to vilazodone free base is used as a solid or an aqueous solution.

The solvent for the conversion of vilazodone hydrobromide to vilazodone free base is selected from the group consisting of water, an organic solvent, or combinations thereof. The organic solvent is selected from the group consisting of alcohols, esters, halogenated hydrocarbons, ketones, amides, nitriles, or combinations thereof. Suitable alcoholic solvents are methanol, ethanol, methylated ethanol, 2-propanol, 1-propanol, or butanol. Suitable ester solvents are ethyl acetate, methyl acetate, or isopropyl acetate. A suitable halogenated hydrocarbon is dichloromethane. Suitable ketonic solvents are acetone or methyl isobutyl ketone. Suitable amide solvents are N-methylpyrrolidone, dimethyl acetamide, or dimethyl formamide. A suitable nitrile solvent is acetonitrile. The preferred solvent is water in combination with methanol, ethanol, or 2-propanol.

The conversion of vilazodone hydrobromide to vilazodone free base is carried out at a temperature of about 10°C to about 100°C, preferably at about 20°C to about 85°C.
The dissolution of vilazodone free base with water and an alcoholic solvent is carried out for about 30 minutes to about 6 hours, preferably for about 1 hour to about 4 hours.

The vilazodone free base of Formula I may be isolated by filtration, concentration, precipitation, cooling, centrifugation, decantation, or combinations thereof.

The vilazodone free base obtained by the present invention may be converted to its pharmaceutically acceptable salt, for example, hydrochloric acid salt.

The vilazodone free base is treated with hydrochloric acid in the presence of water, alcohols, amides, halogenated hydrocarbons, esters, or mixtures thereof. Suitable alcoholic solvents are methanol, ethanol, 2-propanol, 1-propanol, or butanol. Suitable amide solvents are N-methylpyrrolidone, dimethyl acetamide, or dimethyl formamide. Suitable halogenated hydrocarbon solvents are dichloromethane or chloroform. Suitable ester solvents are ethyl acetate, methyl acetate, or isopropyl acetate. The preferred solvents are 2-propanol, either alone or in combination with N-methylpyrrolidone, or water.

The treatment of vilazodone free base with hydrochloric acid is carried out at a temperature of about 50°C to about 100°C, preferably at about 70°C to about 85°C. The treatment of the reaction mixture obtained in step c) with hydrochloric acid is carried out for about 30 minutes to about 2 hours, preferably for about 60 minutes to about 2 hours. The hydrochloric acid may be dilute or concentrated. The hydrochloric acid is used in solution or gaseous form. The solution of hydrochloric acid is aqueous or in an alcoholic solvent. The preferred alcoholic solvent for the preparation of hydrochloric acid solution is 2-propanol.

The vilazodone hydrochloride salt may be isolated by filtration, distillation, evaporation, centrifugation, decantation, drying, vacuum drying, or combinations thereof.

The vilazodone hydrochloride prepared by the present invention may be characterized using X-ray powder diffraction (XRPD) patterns.

In the following section, embodiments are described by way of examples to illustrate the process of the invention. Several variants of these examples would be evident to persons ordinarily skilled in the art.
EXAMPLES

Example 1: Preparation of 5-(piperazin-1-yl)-l-benzofuran-2-carboxamide

Step A: Preparation of ethyl-5-amino-l-benzofuran-2-carboxylate

Ethyl-5-nitro-l-benzofuran-2-carboxylate (100 g) was added to methanol (500 mL). 2.5% (w/w) Palladium/carbon (10 g in 10 mL water) was added to the hydrogenator. The hydrogen gas was passed at a pressure of 1 to 4 kg/cm² for 2 hours to 4 hours at 25°C to 50°C. The reaction mixture was filtered through a Celite® filter. The solvent was recovered under vacuum. A mixture of de-ionized water (500 mL) and dichloromethane (300 mL) was added to the reaction mixture and the layers obtained were separated. The organic layer was recovered under vacuum to obtain the title compound.

Yield (Wet): 82 g

Step B: Preparation of ethyl-5-(piperazine-1-yl)-l-benzofuran-2-carboxylate hydrochloride

Ethyl-5-amino-l-benzofuran-2-carboxylate prepared in step A (82 g) was added to N, N-Bis-2-chloroethylamine hydrochloride (91.14 g) and 1, 2-dichlorobenzene (500 mL) at 20°C to 30°C. The temperature of the reaction mixture was increased to 180°C and the reaction mixture was further heated for 2 hours to 4 hours. The reaction mixture was cooled to 20°C to 30°C and filtered. The solid obtained was washed with dichloromethane (400 mL) at 20°C to 30°C to obtain the title compound.

Yield (Wet): 210 g

Step C: Preparation of 5-(4-formylpiperazin-1-yl)-l-benzofuran-2-carboxamide

Ethyl-5-(piperazine-1-yl)-l-benzofuran-2-carboxylate hydrochloride (210 g) prepared in step B was added to dichloromethane (800 mL) and the pH was adjusted to 7 to 8 with 5% sodium bicarbonate solution. The organic layer was separated and dichloromethane was recovered completely under vacuum. Formamide (500 mL) was added to the reaction mixture along with 30% methanolic solution of sodium methoxide (76.6 g). The reaction mixture was stirred for 2 hours at 20°C to 30°C. Deionized water (1000 mL) was added to the reaction mixture and the reaction mixture was stirred at 10°C for 1 hour. The solid obtained was filtered and washed with deionized water (200 mL) to obtain the title compound.
Yield (Wet): 79 g

Mass data (m/e): 274.3 (M+l)

NMR data (DMSO-d<sub>6</sub>): 3.06-3.08 (m, 2H), 3.12-3.14 (m, 2H), 3.52-3.57 (m, 4H), 7.22 (s, 2H), 7.43 (s, 1H), 7.49-7.52 (D, 1H), 7.63 (br s, 1H), 8.06 (br s, 1H), and 8.09 (s, 1H).

Step D: 5-(Piperazin-l-yl)-l-benzofuran-2-carboxamide

5-(4-Formylpiperazin-l-yl)-l-benzofuran-2-carboxamide (79 g) prepared in step C was added to concentrated hydrochloric acid (100 mL) and stirred at 45°C to 50°C for 60 minutes. Deionized water (300 mL) was added to the reaction mixture and the pH was adjusted to 10.5 with 20% sodium hydroxide solution (275 mL) at 10°C to 25°C. The reaction mixture was filtered and the solid obtained was washed with deionized water (200 mL). The solid obtained was dried in an air oven for 16 hours at 50°C to 55°C to obtain the title compound.

Yield: 24 g

Example 2: Preparation of vilazodone free base

5-Piperazin-l-yl-benzofuran-2-caboxamide (2.0 g) was added to 3-(4-chlorobutyl)-1H-indole-5-carbonitrile (1.9 g) in dimethyl formamide (20 mL). Potassium carbonate (1.2 g) was added to the reaction mixture and heated to 80°C to 85°C and maintained for 5 hours. The reaction mixture was cooled to 35°C and water (50 mL) was added to the reaction mixture. The reaction mixture was stirred for 2 hours and filtered. The solid obtained was dried under vacuum at 45°C to 50°C to obtain the title compound.

Yield: 1.0 g

Example 3: Preparation of vilazodone free base

Potassium carbonate (2.8 g) was added to water (25 mL) and stirred for 10 minutes. 5-Piperazin-l-ylbenzofuran-2-caboxamide (5.0 g), 3-(4-chlorobutyl)-1H-indole-5-carbonitrile (5.7 g), and toluene (25 mL) were added to the reaction mixture and the reaction mixture was heated to 90°C to 95°C for 29 hours. The reaction mixture was cooled to 30°C, filtered, and washed with water (25 mL). The solid obtained was dried at 45°C to 50°C to obtain the title compound.

Yield: 7.0 g
Example 4: Preparation of vilazodone hydrochloride

Vilazodone free base (10.0 g) was added to 2-propanol (430 mL). The reaction mixture was heated to 80°C to 83°C. The reaction mixture was filtered. The reaction mixture was heated to 70°C to 80°C and a solution of 0.1N 2-propanolic hydrochloride (230 mL) was added to the reaction mixture at 70°C to 80°C over 20 minutes. The reaction mixture was cooled to 25°C to 30°C, and stirred for 2.5 hours. The solid obtained was filtered, washed with diethyl ether (30 mL), and dried under vacuum at 20°C to 30°C for 12 hours to obtain the title compound.

Yield (Wet): 104 g

Example 5: Preparation of vilazodone hydrobromide

5-(Piperazin-1-yl)-1-benzofuran-2-carboxamide (50 g) and 3-(4-chlorobutyl)-1H-indole-5-carbonitrile (52.3 g) were added to N-methyl pyrrolidone (250 mL) at 30°C. The temperature of the reaction mixture was increased to 120°C and maintained at 115°C to 120°C for 2 hours. Tributylamine (38 g) was added to the reaction mixture at 115°C to 117°C and maintained at 115°C to 120°C for 6 hours. The reaction mixture was cooled to 30°C. A solution of 2-propanol (500 mL) and concentrated (40% to 48%) hydrobromic acid (37 g) was added to the reaction mixture at 25°C to 30°C and seeded with vilazodone hydrobromide (0.25 g) at 25°C to 30°C. The reaction mixture was stirred at 25°C to 30°C for 6 hours. The reaction mixture was filtered and washed with 2-propanol (50 mL x 4) at 20°C to 30°C to obtain the title compound.

Yield (Wet): 89 g

Example 6: Preparation of vilazodone hydrobromide

Vilazodone hydrobromide (88 g) prepared according to Example 5 was added to N-methyl pyrrolidone (250 mL) and concentrated hydrobromic acid (5 mL). The reaction mixture was heated to 55°C. 2-Propanol (250 mL) was added to the reaction mixture at 50°C to 55°C, and cooled to 30°C. The reaction mixture was stirred for 1 hour at 25°C to 30°C. The reaction mixture was filtered and washed with 2-propanol (50 mL x 2) at 20°C to 30°C to obtain the title compound.

Yield (Wet): 104 g
Example 7: Preparation of vilazodone free base.

Vilazodone hydrobromide (102 g) prepared according to Example 6 was added to a mixture of 2-propanol (1000 mL) and deionized water (500 mL). The reaction mixture was heated to 70°C. Activated carbon (10 g) was added to the reaction mixture at 70°C. The reaction mixture was filtered and washed with a mixture of 2-propanol (100 mL) and deionized water (50 mL). The pH of the reaction mixture was adjusted to 7 with sodium bicarbonate solution (150 mL) at 65°C to 70°C. The reaction mixture was cooled to 30°C and stirred for 30 minutes. The reaction mixture was filtered and washed with 2-propanol (50 mL x 2) at 20°C to 30°C. The solid obtained was dried under an air oven at 50°C to 55°C for 16 hours to obtain the title compound.

Yield: 42.5 g

Example 8: Preparation of vilazodone hydrochloride.

Vilazodone free base (40 g) prepared according to Example 7 was added to 2-propanol (1720 mL) at 20°C to 30°C. The temperature of the reaction mixture was increased to 82°C. Deionized water (80 mL) was added to the reaction mixture at 78°C to 80°C. Activated carbon (2 g) was added at 80°C and maintained for 30 minutes. The reaction mixture was filtered and washed with 2-propanol (200 mL) at 80°C. A solution of 0.1 N 2-propanolic hydrochloride (9.4 g concentrated hydrochloric acid in 904 mL 2-propanol) was added to the reaction mixture over 60 minutes at 78°C to 80°C. The reaction mixture was cooled to 55°C. The reaction mixture was filtered and washed with 2-propanol (80 mL) at 55°C. The reaction mixture was dried under vacuum at 50°C to 55°C for 16 hours to obtain the title compound.

Yield: 39.5 g
We claim:

1. A novel intermediate compound of Formula III.

![Formula III](image)

2. A process for the preparation of 5-(4-formylpiperazin-1-yl)-1-benzofuran-2-carboxamide of Formula III, wherein the process comprises:

a) formylating ethyl 5-(piperazin-1-yl)-1-benzofuran-2-carboxylate compound of Formula IV or its salt; and

![Formula IV](image)

b) isolating 5-(4-formylpiperazin-1-yl)-1-benzofuran-2-carboxamide of Formula III from the reaction mixture thereof.
3. A process for the preparation of vilazodone free base of Formula I

\[
\text{FORMULA I}
\]

or pharmaceutically acceptable salts thereof, wherein the process comprises:

a) formylating ethyl 5-(piperazin-1-yl)-1-benzofuran-2-carboxylate compound of Formula IV or its salt

\[
\text{FORMULA IV}
\]

to give 5-(4-formylpiperazin-1-yl)-1-benzofuran-2-carboxamide of Formula III:

\[
\text{FORMULA III}
\]

b) converting 5-(4-formylpiperazin-1-yl)-1-benzofuran-2-carboxamide of Formula III to 5-(piperazin-1-yl)-1-benzofuran-2-carboxamide of Formula V;
c) reacting 5-(piperazin-1-yl)-1-benzofuran-2-carboxamide of Formula V with 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula VI;

d) isolating vilazodone free base of Formula I from the reaction mixture thereof;

e) optionally converting the compound of Formula I to its pharmaceutically acceptable salts.

4. The process according to claims 2 or 3, wherein the formylation of the compound of Formula IV or its salt is carried out in the presence of formylating agent.

5. The process according to claim 4, wherein the formylating agent is selected from the group consisting of formamide, chloral, formic acid- dicyclohexylcarbodiimide, formic acid- 1-ethyl-3(3-dimethylaminopropyl)carbodiimide (EDC1), formic acid - zinc chloride, formic acid - polyethylene glycol 400, activated formic acid esters, acetic formic anhydride, ammonium formate, 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), or mixtures thereof.

6. The process according to claim 4, wherein the formylating agent is formamide.

7. The process according to claims 2 or 3, wherein the formylation of the compound of Formula IV or its salt is carried out in the presence of a base and a solvent.

8. The process according to claim 7, wherein the base is sodium methoxide.
9. The process according to claim 7, wherein the solvent is selected from the group consisting of halogenated hydrocarbons, alcohols, ketones, N-methyl pyrrolidone, formamides, ethers, nitriles, aromatic and aliphatic hydrocarbons, or mixtures thereof.

10. The process according to claim 9, wherein the solvents are formamide, dichloromethane, methanol, or mixtures thereof.

11. The process according to claim 3, wherein the compound of Formula III is converted to the compound of Formula V in step b) in the presence of an acid and a solvent.

12. The process according to claim 11, wherein the acid is selected from the group consisting of inorganic or organic acids.

13. The process according to claim 11, wherein the solvent is selected from the group consisting of water, alcohol, esters, nitriles, amides, ketones, ethers, aromatic or aliphatic hydrocarbons, dimethyl sulfoxide, or mixtures thereof.

14. The process according to claim 13, wherein the solvent is water.

15. The process according to claim 3, wherein the reaction of the compound of Formula V and the compound of Formula VI in step c) is carried out in the presence of a base and a solvent.

16. The process according to claim 15, wherein the solvent is selected from the group consisting of water, organic solvent, or mixtures thereof.

17. The process according to claim 16, wherein the solvent is water alone or in combination with 2-propanol, 1-propanol, dimethyl formamide, or toluene.

18. The process according to claim 15, wherein the base is selected from the group consisting of organic or inorganic bases.

19. The process according to claim 3, wherein the reaction mixture of the compound of the Formula V and the compound of Formula VI is treated with hydrobromic acid before converting to vilazodone free base.

20. The process according to claim 3, wherein the pharmaceutically acceptable salt in step e) is hydrochloric acid salt.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D405/12 C07D307/85

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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

**Date of the actual completion of the international search** 4 February 2014

**Date of mailing of the international search report** 13/02/2014

**Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016**

**Authorized officer** Koch, Kri sti an
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