POLYMORPHIC FORMS OF 1-'4-(5-CYANOINDOL-3-YL)BUTYL!-4-(2-CARBAMOYLBENZOFURAN-5-YL)PIPERAZINE HYDROCHLORIDE

FIELD OF THE INVENTION

The present invention relates to novel compounds, to processes for preparing them and to their use in treating medical disorders.

BACKGROUND OF THE INVENTION

1-[4-(5-Cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine, its physiologically acceptable salts thereof (US 5,532,241, column 7, lines 30 to 58), a process (US 5,532,241, Example 4) by which it/they can be prepared and their use in treating certain medical disorders are known from U.S. Patent US 5,532,241 and WO 00/72832.

Example 4 of US 5,532,241 describes the preparation of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride by reacting 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine at first with 2-chloro-1-methylpyridinium methanesulfonate in N-methylpyrrolidine and then with dried NH_3. Customary working up gives the free base 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine. 700 mg of the base are dissolved in 30 ml 2-propanol under heating and then treated with 0.1n 2-propanolic HCL-solution (Merck-Art. No. 1.00326) until precipitation of hydrochloride is complete. The precipitate was filtered off and washed with diethylether and dried at room temperature to yield 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride having a melting point of 269-272°C. There is no clear teaching elsewhere in the document of any alternative route or modification to the process which would generate new crystal modifications of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride or new solvates or hydrates of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride in different crystal modifications.

Former 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride having a melting point of 269-272°C was a mixture of amorphous 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride, crystallized 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-

carbamoyl-benzofuran-5-yl)-piperazine hydrochloride and the free base 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine.

Certain crystalline, i.e. morphological forms of pharmaceutical compounds may be of interest to those involved in the development of a suitable dosage form because if the morphological form is not held constant during clinical and stability studies, the exact dosage used or measured may not be comparable from one lot to the next. Once a pharmaceutical compound is produced for use, it is important to recognize the morphological form delivered in each dosage form to assure that the production process use the same form and that the same amount of drug is included in each dosage. Therefore, it is imperative to assure that either a single morphological form or some known combination of morphological forms is present. In addition, certain morphological forms may exhibit enhanced thermodynamic stability and may be more suitable than other morphological forms for inclusion in pharmaceutical formulations.

SUMMARY OF THE INVENTION

Methods for preparing pure crystals of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride have now been found. Furthermore, surprinsingly, 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine dihydrochloride, six (five + dihydrochloride XIII) new forms of 1-[4-(5-Cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride, three new forms of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride hydrate, six new forms of solvates of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride and pure amorphous 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride have been found as have processes for their preparation. These forms are hereinafter referred to as I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XIII, XIV, XV and XVI respectively. Throughout the specification, the term "Form" is generally used as a synonym for the term "modification" or "crystalline modification".

Accordingly, the present invention provides solvates of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride in crystalline modifications and their use for the treatment and prevention of depressive disorders, anxiety disorders, bipolar disorders, mania, dementia, substance-related disorders, sexual dysfunctions, eating disorders, obesity, fibromyalgia, sleeping disorders, psychiatric disorders, cerebral infarct, tension, for the therapy of side-effects in the treatment of hypertension, cerebral disorders, chronic pain, acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome and undesired puerperal lactation.

The present invention furthermore provides 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride hydrates in crystalline modifications and their use for the treatment and prevention of depressive disorders, anxiety disorders, bipolar disorders, mania, dementia, substance-related disorders, sexual dysfunctions, eating disorders, obesity, fibromyalgia, sleeping disorders, psychiatric disorders, cerebral infarct, tension, for the therapy of side-effects in the treatment of hypertension, cerebral disorders, chronic pain, acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome and undesired puerperal lactation.

The present invention also provides 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride anhydrates in crystalline modifications and their use for the treatment and prevention of depressive disorders, anxiety disorders, bipolar disorders, mania, dementia, substance-related disorders, sexual dysfunctions, eating disorders, obesity, fibromyalgia, sleeping disorders, psychiatric disorders, cerebral infarct, tension, for the therapy of side-effects in the treatment of hypertension, cerebral disorders, chronic pain, acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome and undesired puerperal lactation.

The present invention relates additionally to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine dihydrochloride in its crystalline modification and its use for the treatment and prevention of depressive disorders, anxiety disorders, bipolar disorders, mania, dementia, substance-related disorders, sexual dysfunctions, eating disorders, obesity, fibromyalgia, sleeping disorders, psychiatric disorders, cerebral infarct,

tension, for the therapy of side-effects in the treatment of hypertension, cerebral disorders, chronic pain, acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome and undesired puerperal lactation.

The present invention relates additionally to pure amorphous 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride and its use for the treatment and prevention of depressive disorders, anxiety disorders, bipolar disorders, mania, dementia, substance-related disorders, sexual dysfunctions, eating disorders, obesity, fibromyalgia, sleeping disorders, psychiatric disorders, cerebral infarct, tension, for the therapy of side-effects in the treatment of hypertension, cerebral disorders, chronic pain, acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome and undesired puerperal lactation.

BRIEF DESCRIPTION OF THE FIGURES

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Fig. 2 is an IR absorption spectra of Form II
Fig. 3 is an IR absorption spectra of Form XV
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DETAILED DESCRIPTION OF THE INVENTION

It has been found that 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride is able to form solvates in crystalline modifications. Examples of such solvates include solvates from water, solvates from alcohols such as methanol, ethanol, propan-1-ol or propan-2-ol; solvates from organic esters such as ethyl acetate; solvates from nitriles such as acetonitrile; solvates from ketones such as acetone and butanone; solvates from ethers such as tetrahydrofuran and solvates

from chlorinated hydrocarbons such as chloroform and solvates of hydrocarbons such as n-heptane or toluene. Preferred solvates are formed with polar solvents, preferably water, alcohols, organic esters, nitriles, ketones and ethers.

Preferably, 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride forms solvates with acetone, tetrahydrofuran, methanol, ethyl acetate or n-heptane in crystalline modifications that means the bound solvent together with 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride build the crystal structure. The molar ratio of the solvent to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride could vary as known to skilled persons in the art. Preferably, the molar ratio is between 0,25:1 to 2,5:1, more preferably between 0,5:1 to 1:1, most preferably 1:1. (n-heptan solvate 1/15 : 1)

It should be understood that the present solvates of the invention may contain unbound water that is to say water which is other than water of crystallization.

Preferred forms of solvates of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride include:

a) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride solvate with acetone in Form I; (as hereinafter defined)

b) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride solvate with tetrahydrofuran in Form II; (as hereinafter defined)

c) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride solvate with tetrahydrofuran in Form XV; (as hereinafter defined)

d) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride solvate with tetrahydrofuran in Form X; (as hereinafter defined)

e) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride solvate with methanol in Form XI; (as hereinafter defined)

f) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride solvate with n-heptane in Form XIV; (as hereinafter defined).

Generally, the specific crystalline forms of the present invention have certain advantages over the product obtained according to US 5,532,241. Among others, the most important advantages are:
reduced hygroscopicity,
better compressibility during the tablating process,
prolonged shelf life,
better thermodynamic stability, i.e. stabilty against heat and humidity,
better resitstance to sunlight, i.e. UV-light,
increased bulk density,
improved solubility,
bioavailability characteristics which are constant from one batch to the other,
better flow and handling properties in the tableting process,
improved color stabiltiy,
better filtration properties in the production process.

Therefore, by use of the crystalline forms of the present invention, it is possible to obtain galenic formulations having imporved homogenicity, stability, purity and uniformity from one batch to the other.

Form I according to the invention has the characteristic IR absorption spectra as shown in Fig. 1 and the characteristic X-ray diffraction pattern as shown in Fig. 12. XRD pattern were recorded using a x-ray powder diffractometer (Bruker AXS D5000) in transmission mode (Cu K alpha 1, PSD).
IR absorption spectra were measured in the spectral range 4000 - 400 cm^{-1} on a Bruker IFS48. Spectral resolution was 2 cm^{-1}. Sample preparation was performed generally as KBr disk. The spectra contains additionally a specific acetone absoption band at 1709cm^{-1}.

Form I can be further characterized with the aid of thermal analysis measured in the range of 30° to 350 °C. Fig. 28 shows the DSC (TA Instruments DSC 2920) and TGA (TA Instruments TGA 2950)

measurements. Form I shows a desolvation process between 50°C and 180°C. Analysis by thermogravimetry showed the presence of 10 weight-% to 11 weight-% of acetone (theory of 1 : 1 solvate 10.82 weight-%). The DSC measurement gives a phase transition to form VII between 200°C and 260°C. The thermoanalytically resulting form VII melts between 280°C and 290°C.

The molar ratio of acetone to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride in said crystal modification is 1:1, that means the compound of the invention in crystal modification of Form I is 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride monoacetonate.

The invention also provides a process for preparing the above Form I according to the invention, which comprises:

(1) dispersing 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine in acetone
(2) converting the 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine base, by addition of 1N hydrochloric acid into the hydrochloride salt at temperatures between 30°C and the boiling point of acetone, preferably between 40° C and 50°C
(3) precipitation of Form I at room temperature
(4) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride acetonate by filtration, and drying in vacuo at room temperature.

Alternatively, Form I can be prepared according to a process which comprises:

(1) suspending Form III of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride, which will be described later in detail, in acetone
(2) stirring at room temperature between a few hours or days, preferably 10 to 20 days,
(3) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride solvate with tetrahydrofuran by filtration, and drying in vacuo at room temperature.

Form II according to the invention has the characteristic IR absorption spectra as shown in Fig. 2 and the characteristic X-ray diffraction pattern as shown in Fig. 13. XRD pattern were recorded using a x-ray powder diffractometer (Bruker AXS D5000) in transmission mode (Cu K alpha 1, PSD).

IR absorption spectra were measured in the spectral range 4000 - 400 cm^{-1} on a Bruker IFS48. Spectral resolution was 2 cm^{-1}. The spectra as shown in the figures were converted to transmission.

Form II can be further characterized with the aid of thermal analysis measured in the range of 30° to 350°C. Fig. 29 shows the DSC (TA Instruments DSC 2920) and TGA (TA Instruments TGA 2950) measurements. Form II shows a desolvation process between 120°C and 180°C. Analysis by thermogravimetry showed the presence of 13 weight-% to 14 weight-% of THF (theory of 1 : 1 solvate 13.11 weight-%). The DSC measurement gives a phase transition to form VII between 200°C and 260°C. The thermoanalytically resulting form VII melts between 280°C and 290°C.

The molar ratio of tetrahydrofuran to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride in said crystal modification is 1:1, that means the compound of the invention in crystal modification of Form II is a monosolvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with tetrahydrofuran.

The invention also provides a process for preparing the above Form II according to the invention, which comprises:

(1) dispersing 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine in tetrahydrofuran
(2) converting the 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine base, by addition of 1N hydrochloric acid into the hydrochloride salt at temperatures between 10°C and 60°C, preferably between 20° C and 30°C
(3) precipitation of Form II between -10°C and 10°C
(4) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride solvate with tetrahydrofuran by filtration, and drying in vacuo at room temperature.

Alternatively, Form II can be prepared according to a process which comprises:

(1) suspending Form III of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride, which will be described later in detail, in tetrahydrofuran
(2) stirring at room temperature between a few hours or days, preferably 15 to 30 days,
(3) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride acetonate by filtration, and drying in vacuo at room temperature.

Form XV according to the invention has the characteristic IR absorption spectra as shown in Fig. 3 and the characteristic X-ray diffraction pattern as shown in Fig. 14. XRD pattern were recorded using a x-ray powder diffractometer (Bruker AXS D5000) in transmission mode (Cu K alpha 1, PSD).

IR absorption spectra were measured in the spectral range 4000 - 400 cm^{-1} on a Bruker IFS48. Spectral resolution was 2 cm^{-1}. The spectra as shown in the figures were converted to transmission.

Form XV can be further characterized with the aid of thermal analysis measured in the range of 30° to 350 °C. Fig. 39 shows the DSC (TA Instruments DSC 2920) and TGA (TA Instruments TGA 2950) measurements. Form XV shows a desolvation process between 75°C and 180°C. Analysis by thermogravimetry showed the presence of 13 weight-% to 14 weight-% of THF (theory of 1 : 1 solvate 13.11 weight-%). The DSC measurement gives a phase transition to form VII between 200°C and 260°C. The thermoanalytically resulting form VII melts between 280°C and 290°C. The molar ratio of tetrahydrofuran to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride in said crystal modification is 1:1, that means the compound of the invention in crystal modification of Form XV is a monosolvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with tetrahydrofuran.

The invention also provides a process for preparing the above Form XV according to the invention, which comprises:

(1) dispersing 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine in tetrahydrofuran

(2) converting the 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine base, by addition of 1N hydrochloric acid into the hydrochloride salt at temperatures between -10°C and 10°C, preferably between -5° C and +5°C

(3) precipitation of Form XV at room temperature

(4) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride solvate with tetrahydrofuran by filtration, and drying in vacuo at room temperature.

Form X according to the invention has the characteristic X-ray diffraction pattern as shown in Fig. 15. XRD pattern were recorded using a x-ray powder diffractometer (Bruker AXS D5000) in transmission mode (Cu K alpha 1, PSD).

The molar ratio of tetrahydrofuran to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride in said crystal modification is 0,5:1, that means the compound of the invention in crystal modification of Form X is a hemisolvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with tetrahydrofuran.

The invention also provides a process for preparing the above Form X according to the invention, which comprises:

(1) dispersing 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine in tetrahydrofuran

(2) converting the 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine base, by addition of 1N hydrochloric acid into the hydrochloride salt at temperatures between 10°C and 40°C, preferably between 20° C and 30°C

(3) precipitation of Form X at room temperature

(4) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride solvate with

tetrahydrofuran by filtration, and drying at temperatures up to 80°C maximum.

Form XI according to the invention has the characteristic IR absorption spectra as shown in Fig. 4 and the characteristic X-ray diffraction pattern as shown in Fig. 16. XRD pattern were recorded using a x-ray powder diffractometer (Bruker AXS D5000) in transmission mode (Cu K alpha 1, PSD).
IR absorption spectra were measured in the spectral range 4000 - 400 cm^{-1} on a Bruker IFS48. Spectral resolution was 2 cm^{-1}. The spectra as shown in the figures were converted to transmission.
Form XI can be further characterized with the aid of a thermal analysis measured in the range of 30° to 350 °C. Fig. 37 shows the DSC (TA Instruments DSC 2920) and TGA (TA Instruments TGA 2950) measurements. Form XI shows a desolvation process between 75°C and 150°C. Analysis by thermogravimetry showed the presence of 6 weight-weight-% to 7 weight-weight-% of methanol (theory of 1 : 1 solvate 6.28 weight-%). The DSC measurement gives a phase transition to form VII between 200°C and 260°C. The thermoanalytically resulting form VII melts between 280°C and 290°C
The molar ratio of methanol to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride in said crystal modification is 1:1, that means the compound of the invention in the crystalline modification of Form XI is a monosolvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with methanol.

The invention also provides a process for preparing the above Form XI according to the invention, which comprises:

(1) suspending Form VI of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride, which will be described later in detail, in methanol at temperatures between 55°C and the boiling point of methanol
(2) cooling down the reaction mixture to temperatures between -40° and -10°C, preferably to -30°C

(3) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride methanolate by filtration at room temperature, and drying in vacuo at room temperature.

Form XIV according to the invention has the characteristic IR absorption spectra as shown in Fig. 5 and the characteristic X-ray diffraction pattern as shown in Fig. 17. XRD pattern were recorded using a x-ray powder diffractometer (Bruker AXS D5000) in transmission mode (Cu K alpha 1, PSD).

IR absorption spectra were measured in the spectral range 4000 - 400 cm^{-1} on a Bruker IFS48. Spectral resolution was 2 cm^{-1}. The spectra as shown in the figures were converted to transmission.

Form XIV can be further characterized with the aid of a thermal analysis measured in the range of 30°C and 350°C. Fig. 38 shows the DSC (TA Instruments DSC 2920) and TGA (TA Instruments TGA 2950) measurements. Analysis by thermogravimetry showed the presence of 1 weight-% to 3 weight-% of n-heptane (theory of 15 : 1 solvate 1.37 weight-%, theory of 10 : 1 solvate 2.05 weight-%).

The molar ratio of n-heptane to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride in said crystal modification is between 1:10 and 1:15, that means the compound of the invention in crystal modification of Form XIV is a solvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with n-heptane. The DSC measurement gives phase transitions between 80°C and 120°C and between 200°C and 260°C. The thermoanalytically resulting form VII melts between 280°C and 290°C

The invention also provides a process for preparing the above Form XIV according to the invention, which comprises:

(1) suspending Form III of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride, which will be described later in detail, in n-heptane

(2) stirring at room temperature between a few hours or days, preferably 15 to 30 days,

(3) recovering the precipitated solvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with n-heptane by filtration, and drying in vacuo at room temperature.

Additionally, it has been found that 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride is able to form hydrates in crystalline modifications. Preferably, the molar ratio of water to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride is between 0,25:1 to 2,5:1, more preferably between 0,5:1 to 1:1, most preferably 1:1.

It should be understood that the present hydrates of the invention may contain unbound water that is to say water which is other than water of crystallization.

Preferred forms of hydrates of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride include:
a) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride monohydrate in Form V; (as hereinafter defined)
b) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride in Form VI; (as hereinafter defined)
c) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride hemihydrate in Form VIII; (as hereinafter defined)

Form V according to the invention has the characteristic IR absorption spectra as shown in Fig. 6 and the characteristic X-ray diffraction pattern as shown in Fig. 18. XRD pattern were recorded using a x-ray powder diffractometer (Bruker AXS D5000) in transmission mode (Cu K alpha 1, PSD).
IR absorption spectra were measured in the spectral range 4000 - 400 cm^{-1} on a Bruker IFS48. Spectral resolution was 2 cm^{-1}. Sample preparation was performed generally as KBr disk.

Form V can be further characterized with the aid of a thermal analysis measured in the range of 30° to 350 °C. Fig. 32 shows the DSC (TA Instruments DSC 2920) and TGA (TA Instruments TGA 2950)

measurements. Form V shows a dehydration process between 25°C and 100°C. Analysis by thermogravimetry showed the presence of 3 weight-% to 4 weight-% of water (theory of 1 : 1 solvate 3.63 weight-%). The DSC measurement gives a phase transition to form VII between 200°C and 260°C. The thermoanalytically resulting form VII melts between 280°C and 290°C.

Form V of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride monohydrate according to the invention has surprising advantages with regard to its stability under conditions of high humidity. Form V according to the invention is obtained as colorless solid substance in form of well defined crystals.

The invention also provides a process for preparing the above Form V according to the invention, which comprises:

(1) dispersing 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine in tetrahydrofuran
(2) converting the 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine base, by addition of aqueous hydrochloric acid into the hydrochloride salt
(3) precipitation of Form V at room temperature
(4) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride monohydrate by filtration, and drying in vacuo at room temperature.

Alternatively, Form V can be prepared according to a process which comprises:

(1) stirring of Form IV of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride, which will be described later in detail, in water with an amount of 5 to 10 times more relating to Form IV
(3) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride monohydrate by filtration, and drying in vacuo at room temperature untill the forming of the monohydrate of Form V without excess of water.

Alternatively, Form V can be prepared according to a process which comprises:

(1) stirring of Form XIII of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine dihydrochloride, which will be described later in detail, in water

(3) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride monohydrate by filtration, and drying in vacuo at room temperature.

Form VI according to the invention has the characteristic IR absorption spectra as shown in Fig. 7 and the characteristic X-ray diffraction pattern as shown in Fig. 19. XRD pattern were recorded using a x-ray powder diffractometer (Bruker AXS D5000) in transmission mode (Cu K alpha 1, PSD).

IR absorption spectra were measured in the spectral range 4000 - 400 cm^{-1} on a Bruker IFS48. Spectral resolution was 2 cm^{-1}. Sample preparation was performed generally as KBr disk.

Form VI can be further characterized with the aid of a thermal analysis measured in the range of 30° to 350 °C. Fig. 33 shows the DSC (TA Instruments DSC 2920) and TGA (TA Instruments TGA 2950) measurements. Form VI shows a dehydration process between 25°C and 100°C. Analysis by thermogravimetry showed the presence of 6 weight-% to 7 weight-% of water (theory of 1 : 1.75 solvate 6.19 weight-%). The DSC measurement gives a phase transition to form VII between 200°C and 260°C. The thermoanalytically resulting form VII melts between 280°C and 290°C.

The invention also provides a process for preparing the above Form VI according to the invention, which comprises:

(1) stirring of Form IV of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride, which will be described later in detail, in water in which the relative proportions of salt to water are between 1:5 and 1:10

(3) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride sesquihydrate by filtration, and drying in vacuo at room temperature

Alternatively, Form VI can be prepared according to a process which comprises:

(1) stirring of Form II of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride, as described above, in water for one hour

(3) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride sesquihydrate by filtration, and drying in vacuo at room temperature.

Form VIII according to the invention has the characteristic IR absorption spectra as shown in Fig. 8 and the characteristic X-ray diffraction pattern as shown in Fig. 20. XRD pattern were recorded using a x-ray powder diffractometer (Bruker AXS D5000) in transmission mode (Cu K alpha 1, PSD).
IR absorption spectra were measured in the spectral range 4000 - 400 cm^{-1} on a Bruker IFS48. Spectral resolution was 2 cm^{-1}. Sample preparation was performed generally as KBr disk.

Form VIII can be further characterized with the aid of a thermal analysis measured in the range of 30°C to 350°C. Fig. 35 shows the DSC (TA Instruments DSC 2920) and TGA (TA Instruments TGA 2950) measurements. Form VIII shows a dehydration process between 25°C and 125°C. Analysis by thermogravimetry showed the presence of 1 weight-% to 2 weight-% of water (theory of 1 : 0.5 solvate 1.85 weight-%). The DSC measurement gives a melting of resulted form IX around 268°C. The thermoanalytically resulting form VII melts between 280°C and 290°C.

The invention also provides a process for preparing the above Form VIII according to the invention, which comprises:

(1) stirring of Form VI of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride, as described above, in water for more than 12 hours

(2) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride hemihydrate by filtration, and drying in vacuo at room temperature.

Alternatively, Form VIII can be prepared according to a process which comprises:

(1) stirring of Form II of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride, as described above, in water for 12 hours

(2) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride hemihydrate by filtration, and drying in vacuo at room temperature.

Additionally, it has been found that 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride form crystalline modifications as anhydrates.

It should be understood that the present anhydrates of the invention may contain unbound water that is to say water which is other than water of crystallization.

Preferred forms of anhydrates of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride include:

a) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride in Form IV; (as hereinafter defined)

b) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride in Form III; (as hereinafter defined)

c) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride in Form VII; (as hereinafter defined)

d) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride in Form IX; (as hereinafter defined)

Form IV according to the invention has the characteristic IR absorption spectra as shown in Fig. 9 and the characteristic X-ray diffraction pattern as shown in Fig. 21. XRD pattern were recorded using a x-ray powder diffractometer (Bruker AXS D5000) in transmission mode (Cu K alpha 1, PSD).

IR absorption spectra were measured in the spectral range 4000 - 400 cm^{-1} on a Bruker IFS48. Spectral resolution was 2 cm^{-1}. Sample preparation was performed generally as KBr disk.

Form IV can be further characterized with the aid of a thermal analysis measured in the range of 30° to 350 °C. Fig. 31 shows the DSC (TA Instruments DSC 2920) and TGA (TA Instruments TGA 2950) measurements. The DSC measurement gives a phase transition to form VII between 200°C and 260°C. The thermoanalytically resulting form VII melts between 280°C and 290°C.

Owing to its crystalline properties, Form IV of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride according to the invention has surprising advantages with regard to its solubility and for its pharmaceutical processing into solid dosage forms. The solubility of Form IV in water is 0,328 μg/ml. Form IV according to the invention is obtained as colorless solid substance in form of well defined crystals.
As shown in Figure 27, Form IV is the most stable form at higher temperatures, e.g. > 100°C.

The invention also provides a process for preparing the above Form IV according to the invention, which comprises:

(1) dispersing 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine in tetrahydrofuran
(2) converting the 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine base, by addition of aqueous hydrochloric acid into the hydrochloride salt at temperatures between 20° and 30°C
(3) precipitation of Form V at room temperature
(4) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride monohydrate Form V by filtration
(5) drying of Form V in vacuo at temperatures of 85° to 90°C to give Form IV.

Alternatively, Form IV can be prepared according to a process which comprises:

(1) drying of Form XI of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride monomethanolate, as described above, at temperatures between 55° and 65°C to give Form IV.

This particular polymorphic form (herein designated "Form IV") has superior properties over other crystalline forms and is more suitable for inclusion in pharmaceutical formulations.

Form III according to the invention has the characteristic IR absorption spectra as shown in Fig. 10 and the characteristic X-ray diffraction pattern as shown in Fig. 22. XRD pattern were recorded using a x-ray powder diffractometer (Bruker AXS D5000) in transmission mode (Cu K alpha 1, PSD).
IR absorption spectra were measured in the spectral range 4000 - 400 cm^{-1} on a Bruker IFS48. Spectral resolution was 2 cm^{-1}. Sample preparation was performed generally as KBr disk.

Form III can be further characterized with the aid of a thermal analysis measured in the range of 30° to 350 °C. Fig. 30 shows the DSC (TA Instruments DSC 2920) and TGA (TA Instruments TGA 2950) measurements. The DSC measurement gives a phase transition to form VII between 200°C and 260°C. The thermoanalytically resulting form VII melts between 280°C and 290°.

Owing to its crystalline properties, Form III of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride according to the invention is the most stable form at room temperature, that means the thermodynamically stable form at room temperature (Fig. 27). Form III according to the invention is obtained as colorless solid substance in form of well defined crystals.

The invention also provides a process for preparing the above Form III according to the invention, which comprises:

(1) dispersing 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine in tetrahydrofuran

(2) converting the 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine base, by addition of 1N hydrochloric acid into the hydrochloride salt at temperatures between 10°C and 40°C, preferably between 20° C and 30°C

(3) precipitation of Form II at room temperature

(4) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride solvate with tetrahydrofuran by filtration

(5) drying of Form II in vacuo at temperatures of at least 100°C to give Form III.

Form VII according to the invention has the characteristic IR absorption spectra as shown in Fig. 11 and the characteristic X-ray diffraction pattern as shown in Fig. 23. XRD pattern were recorded using a x-ray powder diffractometer (Bruker AXS D5000) in transmission mode (Cu K alpha 1, PSD).

IR absorption spectra were measured in the spectral range 4000 - 400 cm^{-1} on a Bruker IFS48. Spectral resolution was 2 cm^{-1}. Sample preparation was performed generally as KBr disk.

Form VII can be further characterized with the aid of a thermal analysis measured in the range of 30° to 350 °C. Fig. 34 shows the DSC (TA Instruments DSC 2920) and TGA (TA Instruments TGA 2950) measurements. The DSC measurement indicates the melting point of the pure Form VII at 288°C.

Form VII is the high temperature form of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride according to the invention. Form VII according to the invention is obtained as colorless solid substance in form of well defined crystals.

The invention also provides a process for preparing the above Form VII according to the invention, which comprises:

(1) tempering Form IV of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride, as described above, at temperatures of at least 200°C, preferably at 250°C, for 30 minutes.

Form IX according to the invention has the characteristic X-ray diffraction pattern as shown in Fig. 24. XRD pattern were recorded using a x-ray powder diffractometer (Bruker AXS D5000) in transmission mode (Cu K alpha 1, PSD).

Form IX can be further characterized with the aid of a thermal analysis measured in the range of 30° to 350 °C Fig. 36 shows the DSC (TA Instruments DSC 2920) and TGA (TA Instruments TGA 2950) measurements. The DSC measurement gives of the melting of form IX at 267°C followed by a recrystallisation to form VII. The thermoanalytically resulting form VII melts between 280°C and 290°C.

Form IX according to the invention is obtained as colorless solid substance in form of well defined crystals.

The invention also provides a process for preparing the above Form IX according to the invention, which comprises:

(1) drying of Form VIII of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride, as described above, at temperatures between 90°C and 110°C to give Form IX.

Additionally, it has been found that 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine dihydrochloride form crystalline modifications.
It should be understood that the present dihydrochlorides of the invention may contain unbound water that is to say water which is other than water of crystallization.

A preferred form of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine dihydrochloride is 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine dihydrochloride in Form XIII; (as hereinafter defined).

Form XIII (dihydrochloride) according to the invention has the characteristic X-ray diffraction pattern as shown in Fig. 25. XRD pattern were recorded

using a x-ray powder diffractometer (Bruker AXS D5000) in transmission mode (Cu K alpha 1, PSD).

Form XIII according to the invention is obtained as colorless solid substance in form of well defined crystals.

The invention also provides a process for preparing the above Form XIII according to the invention, which comprises:

(1) dispersing 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine in an organic solvent chosen from the group consisting of tetrahydrofuran, ethanol, isopropanol or mixtures thereof with water
(2) converting the 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine base, by addition of 2N or concentrated hydrochloric acid into the hydrochloride salt at temperatures between 20° and 30°C
(3) precipitation of Form XIII at room temperature
(4) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine dihydrochloride Form XIII by filtration
(5) drying of Form XIII in vacuo at room temperature.

Preferably, the solvates of the present invention are in a form having a dense crystalline structure which enables the raw active ingredient to be easily formulated into final dosage form.

Additionally, Form XVI of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride has been found.

Form XVI according to the invention has the characteristic X-ray diffraction pattern as shown in Fig. 26. XRD pattern were recorded using a x-ray powder diffractometer (Bruker AXS D5000) in transmission mode (Cu K alpha 1, PSD).

The invention also provides a process for preparing the above Form XVI according to the invention, which comprises:

(1) dissolving 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride in acetonitrile and water in the molar ratio 1:1
(2) freeze-drying or spray-driying overnight to give Form XVI of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride.

Similarly, the freeze-dry process can be performed in other mixtures of water miscible organic solvent (tetrahydrofuran, alcohols, N-methylpyrrolidon) with water.

Additionally, a pure amorphous Form of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride has been found.

It has been found that due to the solubility and bioavailability properties, Form II and Form VIII are useful as an ingredient of extended release formulations. Form II is especially useful as an ingredient of extended release formulations.

These Forms of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride or dihydrochloride, as referred to as Forms I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XIII, XIV, XV and XVI respectively and all of which are hereinafter referred to as the "products of the invention" can be used to treat and prevent the disorders:
depressive disorders, including the sub-type disorders major depressive disorder and dysthymic disorder, adolescent depression, anxiety disorders, including the sub-type anxiety disorders chosen from the sub-types panic disorder with and/or without agoraphobia, agoraphobia, obsessive-compulsive spectrum disorders, social phobia, specific phobia including neophobia, posttraumatic stress disorder, acute stress indication or generalized-anxiety disorder, bipolar disorders, mania, dementia, including Alzheimer's disease and multi-infarct, substance-related disorders, sexual dysfunctions including premature ejaculation, eating disorders including *anorexia nervosa and bulimia nervosa and/or obesity, fibromyalgia, chronic* pain, sleeping disorders including dyssomnias and narcolepsy, psychiatric disorders like psychoses, schizophrenia or schizoaffective disorder,

cerebral infarct like stroke and cerebral ischemia, CNS disorders such as tension.
They are also useful for the therapy of side-effects in the treatment of hypertension (e.g. with α-methyldopa) and for the prophylaxis and therapy of cerebral disorders, in endocrinology and gynecology, e.g. for the treatment of acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome or undesired puerperal lactation.

These disorders are herein after referred to as "the Disorders".

The present invention further provides pharmaceutical compositions or medicaments comprising a Product of the Invention. The pharmaceutical composition may comprise additionally one or more conventional auxiliary substances and/or carriers.

Thus, the Products of the Invention can be formulated into the conventional forms of administration, including peroral and parenteral forms of administration. Tablets or capsules are preferred formulations. They can be produced by conventional mixing processes and with the use of conventional auxiliary substances and carriers, as well as binders, disintegrants, flavorings and the like. The dose corresponds to that mentioned in US 5,532,241.

Additionally, the invention relates to the use of a pharmaceutical composition containing at least one product of the invention for the treatment of the Disorders.

The following compositions are prefered:
A Composition comprising Form IV and Form V.
A Composition comprising Form IV and Form V in a molar ratio of about 100 to 1 to 10 to 1.
A Pharmaceutical preparation comprising an active ingredient consisting essentially of a mixture of Form IV and Form V.
A Pharmaceutical preparation comprising an active ingredient consisting essentially of a mixture of Form IV and Form V in a molar ratio of about 100 to 1 to 10 to 1.

An extended release formulation comprising Form I and/or Form III and/or form VIII is also preferred.

Furthermore, the present invention relates to the use of Products of the Invention for the manufacture of a medicament for the treatment of and prevention of the Disorders, such as depressive disorders, adolescent depression, anxiety disorders, bipolar disorders, mania, dementia, substance-related disorders, sexual dysfunctions, eating disorders, obesity, fibromyalgia, chronic pain, sleeping disorders, psychiatric disorders, cerebral infarct, tension, for the therapy of side-effects in the treatment of hypertension, cerebral disorders, chronic pain, acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome and undesired puerperal lactation.

The present invention further provides a method for treating and/or preventing any one or more of the Disorders by administering an effective and/or prophylactic amount of the Products of the Invention to a patient in need thereof.

Preferably, the Disorders which are treated are depression, anxiety disorders, more preferably social anxiety disorder, panic disorder generalised anxiety disorder, posttraumatic stress disorder and/or obsessive compulsive disorder.

Accordingly, the present invention is further concerned with pharmaceutical formulations comprising this polymorphic form as an active ingredient, and the use of this polymorphic form and its formulations in the treatment of certain disorders.

For the treatment of certain conditions it may be desirable to employ the specific crystalline forms of the present invention in conjunction with another pharmacologically active agent. It will be appreciated that the compound of the present invention may be presented together with another therapeutic agent as a combined preparation for simultaneous, separate or

sequential use for the relief of emesis. Such combined preparations may be, for example, in the form of a twin pack.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The preferred specific embodiments and examples are, therefore, to be construed as merely illustrative, and not limitative to the remainder of the disclosure in any way whatsoever.
The entire disclosures of all applications, patents, and publications cited above and below, are hereby incorporated by reference.

Examples

Example 1:

Production of Form I of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride:

Method 1:

1 g of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine is dissolved in 80 ml of acetone. The temperature of the solution is allowed to come to 50°C and 0,5 ml of 1N hydrochloric acid is added to the reaction mixture. After stirring for 2 to 3 minutes the reaction mixture is cooled to room temperature and precipitation occurs. Suction filtration of the precipitated crystals is effected. Drying in vacuo at room temperature to constant weight leads to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride acetonate Form I.

Method 2:

2,25 g of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride Form III are dispersed in 200 ml of acetone. After stirring for 14 days the precipitated crystals are recovered by filtration, and drying in vacuo at room temperature to constant weight leads to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride acetonate Form I which present the IR absorption spectra of Fig. 1 and the x-ray diffraction spectrum of Fig. 12.

Example 2:

Production of Form II of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride:

Method 1:

1 g of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine is dissolved in 46,6 g tetrahydrofuran and 2,2 g 1N hydrochloric acid is added to the reaction mixture. After precipitation and stiring for 30 minutes suction filtration of the precipitated crystals is effected. Drying in vacuo at room temperature to constant weight leads to the monosolvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with tetrahydrofuran of Form II which present the IR absorption spectra of Fig. 2 and the x-ray diffraction spectrum of Fig. 13.

Method 2:

3 g of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride Form III are dispersed in 400 ml of tetrahydrofuran. After stirring for 20 days the precipitated crystals are recovered by filtration. Drying in vacuo at room temperature to constant weight leads to the solvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with tetrahydrofuran of Form II.

Example 3:

Production of Form XV of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride:

10 ml of 1N hydrochlorid acid are added to a solution of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride in tetrahydrofuran [200 ml] (molar ratio base to tetrahydrofuran = 1:48) at 0°C. After stirring for 30 min the precipitated crystals are recovered by filtration. Drying in vacuo at room temperature to constant weight leads to the solvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with tetrahydrofuran of Form XV which present the IR absorption spectra of Fig. 3 and the x-ray diffraction spectrum of Fig. 14.

Example 4:

Production of Form X of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride:

8,6 g of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine is dissolved in tetrahydrofuran and 19,4 ml 1N hydrochloric acid and 7,4 ml water are added within 30 minutes to this solution at 35-37°C. After stirring of five hours, precipitation occurs and suction filtration is effected. Drying in vacuo at room temperature to constant weight leads to the solvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with tetrahydrofuran of Form X which present the x-ray diffraction spectrum of Fig. 15.

Example 5:

Production of Form XI of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride:

3 g of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride Form IV are dispersed in 500 ml of methanol at 60°C. The reaction mixture is cooled to -30°C and precipitation occurs. Suction filtration of the prepcipitated crystals is effected at room temperature. Drying in vacuo to constant weight leads to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride methanolate of Form XI which present the IR absorption spectra of Fig. 4 and the x-ray diffraction spectrum of Fig. 16.

Example 6:

Production of Form XIV of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride:

3,6 g of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride Form III are dispersed in 75 ml of n-heptane. After stirring for three weeks suction filtration of the prepcipitated crystals is effected at room temperature. Drying in vacuo to constant weight at room temperature leads to the solvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with n-heptane of

Form XIV which present the IR absorption spectra of Fig. 5 and the x-ray diffraction spectrum of Fig. 17.

Example 7:

Production of Form V of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride:

Method 1:

To a solution of 1 g of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine in 32,6 g tetrahydrofuran 2,1 g hydrochloric acid (37weight-%) are added. After stirring suction filtration of the precipitated crystals is effected. Drying in vacuo to constant weight at room temperature leads to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride hydrate of Form V which present the IR absorption spectra of Fig. 6 and the x-ray diffraction spectrum of Fig. 18.

Method 2:

2,25 g of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride Form IV are dispersed in 10 bis 20 g water. After stirring for 24 to 48 hours the crystals are recovered by filtration, and drying in vacuo to constant weight at room temperature leads to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride hydrate of Form V.

Method 3:

10 g of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine dihydrochloride Form XIII are dispersed in 1 l water. After stirring for 48 hours the crystals are recovered by filtration, and drying in vacuo to constant weight at room temperature leads to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride hydrate of Form V.

Example 8:

Production of Form VI of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride:

Method 2:
10 g of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride Form II are dispersed in 100 ml water. After stirring for 1 hour the crystals are recovered by filtration, and drying in vacuo to constant weight at room temperature leads to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride hydrate of Form VI.

Example 9:
Production of Form VIII of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride:

Method 1:
1 g of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride Form VI are dispersed in 10 ml water. After stirring for 12 hours the crystals are recovered by filtration, and drying in vacuo to constant weight at room temperature leads to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride hydrate of Form VIII which present the IR absorption spectra of Fig. 8 and the x-ray diffraction spectrum of Fig. 20.

Method 2:
10 g of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride Form II are dispersed in 10 to 20 g water. After stirring for more than 1 hour the crystals are recovered by filtration, and drying in vacuo to constant weight at room temperature leads to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride hydrate of Form VIII. (After stirring for about 1 hour Form VI ocurrs as an intermediate which is subsequently converted into Form VIII)

Example 10:
Production of Form IV of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride:

Method 1:

Drying of Form V prepared according to example 7 in vacuo to constant weight at 85° to 90°C leads to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride of Form IV which present the IR absorption spectra of Fig. 9 and the x-ray diffraction spectrum of Fig. 21.

Method 2:
Drying of Form XI prepared according to example 5 in vacuo to constant weight at 60°C leads to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride of Form IV.

Example 11:
Production of Form III of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride:

Drying of Form II prepared according to example 2 in vacuo to constant weight at 100° to 110°C leads to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride of Form III which present the IR absorption spectra of Fig. 10 and the x-ray diffraction spectrum of Fig. 22.

Example 12:
Production of Form VII of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride:

Tempering of Form IV prepared according to example 10 for 10 minutes at 250°C leads to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride of Form VII which present the IR absorption spectra of Fig. 11 and the x-ray diffraction spectrum of Fig. 23.

Example 13:
Production of Form IX of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride:

Drying of Form VIII prepared according to example 9 in vacuo to constant weight at 100° to 110°C leads to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-

carbamoyl-benzofuran-5-yl)-piperazine hydrochloride of Form IX which present the x-ray diffraction spectrum of Fig. 24.

Example 14:

Production of Form XIII of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine dihydrochloride:

3 g of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine is dissolved in 100 ml of tetrahydrofuran and 10 ml of 2N or concentrated hydrochloric acid. After stirring for 2 to 3 minutes suction filtration of the precipitated crystals is effected. Drying in vacuo at room temperature to constant weight leads to 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine dihydrochloride of Form XIII which present the characteristic x-ray diffraction spectrum of Fig. 25.

Example 15:

Production of Form XVI of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride:

Method 1: Freeze-dry

500 mg of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride of Form IV, III, VII or IX are dissolved in a mixture of 100 ml acetonitril and 100 ml water. The solution is freeze-dried over night to yield 500 mg of a white powder which present the characteristic x-ray diffraction spectrum of Fig. 26.

Advantage: 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride is better soluble in the solvent mixture than in each solvent alone. Similarly the freeze-dry process can be performed in other mixtures of water miscible organic solvent (tetrahydrofuran, alcohols, N-methylpyrrolidon) with water.

Method 2:

b) Spray-dry

500 mg 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride of Form IV, III, VII or IX are dissolved in a mixture

of 100 ml acetonitril and 100 ml water. The solution is spray-dried to yield Form XVI.

Example 16:

Solubility data of Forms II, III, IV, V, VI and VIII are measured according to Alex Avdeef et al, Pharm. Pharmacol. Commun. 1998, 4, 165-178 and Alex Avdeef et al, Pharmaceutical Research 2000, 17, 85-89 via potentiometric titration.

The pSOLTM solubility profiler, automatically collects potentiometric data, calculates the pH-solubility profiles, and prints the values at 0.1 pH unit intervals. Intrinsic solubilities in the milli-, micro- and nanogram levels can be determined. Also presented are two new concepts, the Flux Factor Profile and Dose Limit Profile. Both concepts follow the guidelines consistent with the BioPharmaceutics Classification Scheme.

Table II:

Solubility data in µg/ml

Form I	Form II	Form III	Form IV	Form V	Form VI	Form VIII
0.08	0,03	0,12	0,33	0,18	0,23	0,10

Below are given the most relevant peaks of the IR-spectra of the individual Forms:

Form I

3459 (m), 3335 (w), 3271 (m), 3252 (w), 3202 (m), 3180 (m), 3148 (m), 3039 (w), 3009 (w), 2941 (m), 2868 (m), 2847 (m), 2660 (m), 2579 (m), 2487 (w), 2451 (m), 2212 (m), 1761 (w), 1711 (s), 1673 (s), 1617 (m), 1597 (s), 1577 (m), 1473 (m), 1468 (m), 1444 (m), 1423 (w), 1400 (m), 1364 (s), 1319 (w), 1302 (w), 1279 (w), 1265 (m), 1244 (w), 1225 (s), 1197 (w), 1184 (m), 1171 (m), 1136 (w), 1115 (m), 1100 (m), 1093 (sh), 1034 (w), 1013 (w), 973 (w), 956 (m), 939 (m), 925 (w), 881 (m), 864 (m), 841 (w), 832 (w), 821 (m), 801 (m), 762 (m), 738 (m), 730 (w), 689 (sh), 673 (m), 644 (m), 622 (w), 607 (w), 580 (w), 543 (w), 534 (w), 508 (m), 500 (m), 491 (m), 471 (w), 454 (w).

Form II

3458 (m), 3424 (sh), 3348 (w), 3277 (w), 3204 (m), 3184 (m), 3036 (w), 3008 (w), 2972 (sh), 2938 (m), 2863 (m), 2659 (m), 2597 (m), 2579 (m), 2556 (m), 2459 (m), 2210 (m), 1736 (w), 1677 (s), 1618 (m), 1601 (s), 1578 (m), 1552 (sh), 1474 (m), 1446 (m), 1402 (m), 1376 (m), 1368 (m), 1320 (m), 1302 (w), 1275 (w), 1262 (m), 1250 (m), 1221 (m), 1198 (w), 1186 (m), 1169 (m), 1156 (w), 1131 (w), 1116 (w), 1101 (w), 1065 (m), 1034 (w), 1011 (w), 974 (w), 955 (m), 941 (m), 925 (w), 913 (w), 881 (m), 859 (w), 833 (w), 817 (w), 809 (w), 800 (m), 762 (w), 739 (w), 694 (w), 676 (w), 640 (m), 607 (w), 583 (w), 542 (w), 506 (w), 495 (w), 455 (w).

Form III

3460 (m), 3337 (w), 3269 (m), 3257 (m), 3177 (m), 3145 (m), 3061 (m), 3033 (m), 3001 (w), 2936 (m), 2922 (sh), 2865 (m), 2837 (w), 2787 (w), 2655 (m), 2591 (m), 2457 (m), 2218 (m), 1674 (s), 1618 (m), 1598 (s), 1577 (m), 1473 (m), 1463 (m), 1453 (sh), 1445 (m), 1402 (m), 1380 (m), 1368 (m), 1356 (m), 1329 (m), 1320 (m), 1304 (w), 1284 (w), 1265 (m), 1256 (m), 1240 (m), 1226 (m), 1215 (m), 1186 (m), 1172 (m), 1124 (m), 1097 (m), 1088 (sh), 1059 (w), 1035 (w), 987 (w), 955 (m), 941 (m), 924 (w), 918 (sh), 879 (m), 853 (w), 835 (w), 809 (m), 800 (m), 784 (w), 762 (m), 736 (w), 677 (w), 659 (w), 629 (m), 608 (w), 581 (w), 544 (w), 495 (w), 478 (m), 454 (w).

Form IV

3437 (m), 3328 (w), 3273 (w), 3030 (m), 3006 (m), 2987 (m), 2938 (m), 2915 (m), 2875 (m), 2845 (m), 2660 (m), 2459 (m), 2222 (s), 1899 (w), 1670 (s), 1602 (s), 1577 (s), 1475 (m), 1444 (s), 1370 (s), 1320 (m), 1304 (m), 1281 (m), 1275 (m), 1249 (m), 1227 (s), 1186 (m), 1162 (m), 1141 (w), 1131 (w), 1112 (m), 1099 (w), 1082 (w), 1032 (w), 971 (w), 951 (m), 942 (m), 909 (w), 881 (m), 854 (w), 822 (m), 768 (w), 733 (w), 691 (w), 660 (w), 642 (w), 628 (w), 607 (w), 581 (w), 526 (m), 502 (w), 493 (w), 471 (w), 461 (w).

Form V

3483 (s), 3460 (s), 3222 (s), 3192 (m), 3007 (w), 2947 (m), 2864 (w), 2838 (w), 2784 (w), 2682 (m), 2606 (m), 2478 (w), 2461 (w), 2219 (m), 1669 (s), 1604 (s), 1575 (m), 1474 (m), 1461 (m), 1444 (m), 1402 (m), 1382 (m),

1371 (sh), 1362 (m), 1321 (w), 1304 (w), 1271 (m), 1263 (sh), 1247 (m), 1226 (m), 1185 (m), 1160 (m), 1137 (w), 1113 (m), 1101 (w), 1091 (w), 1082 (w), 1058 (w), 1048 (w), 1030 (w), 1008 (w), 972 (w), 954 (m), 942 (m), 917 (w), 883 (w), 857 (w), 822 (m), 815 (m), 767 (w), 739 (w), 682 (w), 661 (w), 641 (w), 624 (w), 591 (w), 583 (w), 529 (m), 499 (w).

Form VI

3410 (s), 3334 (sh), 3271 (s), 3217 (s), 3188 (s), 3172 (s), 3032 (sh), 2938 (m), 2915 (m), 2846 (m), 2675 (m), 2581 (m), 2539 (sh), 2449 (m), 2216 (s), 1670 (s), 1603 (s), 1593 (s), 1577 (s), 1470 (m), 1444 (s), 1397 (m), 1381 (s), 1369 (sh), 1350 (m), 1323 (m), 1304 (m), 1272 (m), 1247 (m), 1219 (s), 1187 (m), 1164 (m), 1132 (m), 1120 (m), 1099 (m), 1030 (w), 1008 (w), 983 (w), 960 (m), 942 (m), 920 (w), 887 (m), 854 (w), 838 (w), 815 (m), 776 (sh), 767 (w), 739 (w), 727 (sh), 677 (w), 655 (w), 635 (m), 607 (w), 542 (w), 530 (w), 499 (w), 472 (w), 426 (w).

Form VII

3480 (sh), 3459 (s), 3166 (m), 3146 (m), 3031 (m), 3007 (m), 2926 (m), 2870 (sh), 2853 (m), 2664 (m), 2570 (m), 2540 (sh), 2460 (m), 2221 (m), 1673 (s), 1613 (sh), 1592 (s), 1578 (sh), 1552 (m), 1475 (m), 1445 (m), 1398 (m), 1366 (m), 1319 (m), 1303 (m), 1275 (m), 1248 (m), 1226 (m), 1187 (m), 1177 (m), 1161 (m), 1133 (w), 1114 (w), 1101 (w), 1033 (w), 1009 (w), 973 (w), 952 (m), 942 (m), 925 (w), 919 (w), 882 (m), 855 (w), 823 (m), 815 (m), 769 (w), 735 (w), 690 (w), 642 (m), 627 (w), 608 (w), 581 (w), 571 (w), 559 (w), 547 (w), 501 (w).

Form VIII

3379 (m), 3342 (m), 3298 (m), 3234 (m), 3188 (s), 3141 (s), 3027 (w), 2938 (m), 2866 (w), 2844 (m), 2787 (w), 2729 (w), 2679 (m), 2598 (m), 2210 (s), 1658 (s), 1611 (s), 1576 (w), 1556 (m), 1472 (m), 1464 (m), 1443 (s), 1404 (s), 1385 (sh), 1369 (m), 1331 (sh), 1321 (m), 1302 (w), 1286 (w), 1264 (w), 1249 (m), 1230 (s), 1177 (m), 1162 (m), 1128 (w), 1117 (w), 1099 (w), 1084 (w), 1033 (w), 1008 (w), 971 (w), 958 (m), 941 (m), 926 (w), 917 (w), 898 (w), 882 (w), 870 (w), 857 (w), 836 (w), 826 (w), 803 (s), 767 (w), 733 (w), 687 (m), 655 (w), 641 (m), 618 (w), 599 (w), 554 (w), 535 (w), 503 (w), 493 (w), 470 (w), 439 (w).

Form XI

3415 (s), 3290 (m), 3282 (m), 3234 (s), 3196 (s), 3176 (s), 3005 (m), 2993 (m), 2938 (m), 2849 (m), 2678 (m), 2629 (m), 2592 (m), 2473 (m), 2457 (m), 2217 (s), 1680 (s), 1673 (s), 1608 (s), 1594 (sh), 1576 (s), 1474 (m), 1457 (sh), 1440 (s), 1427 (sh), 1401 (m), 1372 (m), 1365 (m), 1354 (m), 1321 (m), 1304 (sh), 1281 (m), 1263 (w), 1247 (m), 1236 (m), 1222 (s), 1185 (m), 1175 (m), 1169 (m), 1160 (sh), 1128 (m), 1121 (m), 1100 (m), 1086 (m), 1032 (w), 1019 (w), 978 (w), 958 (m), 942 (m), 921 (w), 893 (w), 884 (m), 856 (m), 813 (m), 775 (w), 764 (w), 739 (w), 731 (w), 699 (w), 673 (m), 658 (w), 634 (m), 608 (m), 567 (m), 544 (m), 535 (w), 502 (w), 492 (w), 476 (w), 466 (w), 455 (w).

Form XIV

3458 (s), 2923 (m), 2853 (m), 2696 (w), 2595 (w), 2456 (w), 2218 (m), 1674 (s), 1617 (m), 1598 (s), 1580 (sh), 1559 (sh), 1472 (m), 1445 (m), 1401 (m), 1383 (m), 1369 (m), 1321 (m), 1304 (w), 1263 (sh), 1240 (m), 1226 (m), 1216 (m), 1186 (m), 1169 (m), 1159 (m), 1123 (m), 1096 (m), 1057 (w), 1034 (w), 986 (w), 956 (m), 941 (m), 924 (w), 883 (w), 864 (w), 853 (m), 810 (m), 801 (m), 762 (m), 735 (m), 641 (w), 629 (m), 501 (m).

Form XV

3458 (s), 3281 (m), 3227 (m), 3187 (sh), 2935 (m), 2925 (sh), 2866 (w), 2701 (w), 2594 (w), 2455 (w), 2217 (m), 1675 (s), 1617 (m), 1598 (m), 1578 (m), 1472 (m), 1444 (m), 1401 (m), 1380 (m), 1369 (m), 1357 (sh), 1320 (w), 1303 (w), 1265 (m), 1241 (m), 1227 (m), 1215 (m), 1203 (w), 1186 (w), 1172 (m), 1123 (w), 1097 (w), 1087 (w), 1032 (w), 986 (w), 956 (w), 941 (m), 924 (w), 882 (w), 853 (w), 835 (w), 812 (w), 802 (w), 762 (w), 736 (w), 676 (w), 641 (w), 630 (w).

Below are given the most relevant peaks of the Raman-spectra of the individual Forms with an estimated accuracy of +/- 5 cm^{-1}:

Form I:

3128 (m), 3071 (m), 3044 (w), 3011 (w), 2993 (m), 2975 (m), 2956 (m), 2912 (m), 2868 (m), 2849 (m), 2214 (s), 1674 (m), 1618 (m), 1594 (s), 1578 (s), 1553 (m), 1475 (w), 1446 (m), 1400 (w), 1367 (m), 1347 (m), 1337 (m),

1322 (m), 1303 (m), 1282 (m), 1267 (m), 1244 (s), 1229 (m), 1184 (m), 1174 (m), 1138 (m), 1097 (m), 1052 (m), 1033 (m), 1014 (m), 974 (w), 957 (w), 940 (m), 925 (w), 914 (w), 881 (m), 836 (w), 818 (m), 794 (w), 783 (w), 767 (w), 753 (w), 729 (w), 693 (w), 674 (w), 658 (w), 644 (w), 625 (w), 608 (w), 587 (w), 581 (w), 540 (w), 503 (w), 492 (w), 477 (w), 443 (w), 438 (w), 407 (w), 380 (w), 328 (w), 298 (w), 268 (w), 252 (w), 230 (w), 211 (w).

Form II:
3128 (w), 3113 (w), 3068 (m), 3040 (w), 3031 (w), 2992 (m), 2974 (m), 2957 (m), 2905 (m), 2865 (m), 2850 (m), 2222 (m), 2210 (s), 1679 (m), 1617 (m), 1603 (s), 1579 (s), 1552 (m), 1476 (w), 1447 (m), 1404 (w), 1369 (m), 1358 (m), 1347 (m), 1323 (m), 1304 (m), 1277 (m), 1266 (m), 1245 (m), 1233 (w), 1220 (w), 1186 (m), 1176 (m), 1134 (w), 1102 (w), 1051 (m), 1033 (m), 1010 (w), 974 (w), 957 (w), 942 (m), 927 (w), 917 (w), 882 (m), 862 (w), 846 (w), 830 (m), 819 (m), 786 (w), 767 (w), 755 (w), 735 (w), 695 (w), 679 (w), 661 (w), 641 (w), 632 (w), 608 (w), 586 (w), 541 (w), 506 (w), 495 (w), 477 (w), 447 (w), 438 (w), 405 (w), 379 (w), 330 (w), 298 (w), 270 (w), 255 (w), 228 (w), 212 (m).

Form III:
3128 (w), 3087 (sh), 3061 (m), 2995 (m), 2984 (m), 2966 (m), 2957 (m), 2939 (m), 2916 (m), 2867 (m), 2790 (w), 2220 (s), 1675 (m), 1619 (s), 1595 (s), 1579 (s), 1554 (m), 1476 (w), 1446 (m), 1404 (w), 1376 (w), 1352 (m), 1328 (m), 1303 (m), 1285 (m), 1272 (m), 1266 (m), 1247 (s), 1228 (w), 1215 (w), 1170 (m), 1137 (w), 1098 (m), 1058 (w), 1034 (w), 989 (w), 957 (m), 942 (m), 924 (m), 884 (m), 858 (w), 839 (m), 826 (m), 783 (w), 752 (w), 731 (w), 702 (w), 678 (w), 659 (w), 628 (w), 609 (w), 581 (w), 563 (w), 546 (w), 496 (w), 482 (w), 469 (w), 444 (w), 409 (m), 367 (w), 352 (w), 328 (w), 285 (w), 264 (w), 249 (w), 212 (m).

Form IV:
3160 (w), 3145 (w), 3109 (m), 3073 (m), 3008(w), 2987 (m), 2973 (m), 2959 (w), 2936 (w), 2910 (m), 2870 (w), 2849 (m), 2797 (w), 2226 (s), 1665 (w), 1622 (m), 1588 (s), 1549 (m), 1478 (m), 1445 (m), 1410 (w), 1355 (m), 1346 (m), 1322 (m), 1277 (m), 1252 (m), 1189 (m), 1144 (w), 1116 (m), 1049 (w), 1034 (w), 1005 (w), 973 (w), 943 (m), 927 (w), 916 (w), 883 (m),

831 (m), 817 (w), 770 (w), 757 (w), 736 (w), 695 (w), 685 (w), 661 (w), 642 (w), 628 (w), 610 (w), 587 (w), 536 (w), 504 (w), 493 (w), 475 (w), 460 (w), 439 (w), 409 (w), 390 (w), 344 (w), 317 (w), 277 (w), 248 (w), 223 (w).

Form V::
3112 (w), 3091 (m), 3074 (m), 3028 (w), 3004 (w), 2081 (m), 2933 (w), 2919 (m), 2866 (w), 2841 (w), 2787 (w), 2222 (s), 1663 (w), 1618 (m), 1607 (m), 1577 (s), 1552 (m), 1478 (m), 1440 (m), 1406 (w), 1381 (m), 1358 (m), 1342 (m), 1321 (m), 1307 (m), 1276 (m), 1252 (m), 1235 (m), 1189 (m), 1143 (w), 1105 (w), 1092 (w), 1052 (w), 1012 (w), 974 (w), 944 (m), 927 (w), 918 (w), 885 (m), 860 (w), 847 (w), 830 (m), 771 (m), 757 (w), 736 (w), 696 (w), 684 (w), 660 (w), 642 (w), 626 (w), 610 (w), 583 (w), 541 (m), 501 (w), 478 (w), 441 (w), 410 (w), 381 (w), 323 (w), 302 (w), 282 (w), 239 (w), 226 (w).

Form XI:
3133 (m), 3094 (w), 3078 (m), 3060 (m), 3004 (w), 2989 (m), 2968 (m), 2943 (m), 2923 (w), 2897 (m), 2871 (w), 2852 (w), 2835 (w), 2221 (s), 1676 (m), 1613 (s), 1578 (s), 1544 (m), 1473 (m), 1447 (m), 1424 (m), 1401 (w), 1375 (m), 1353 (m), 1342 (m), 1325 (m), 1302 (m), 1279 (m), 1264 (m), 1246 (m), 1233 (m), 1222 (w), 1197 (w), 1186 (w), 1171 (m), 1130 (w), 1102 (w), 1078 (m), 1049 (w), 1018 (w), 983 (w), 959 (w), 942 (m), 923 (m), 886 (m), 857 (w), 838 (m), 817 (m), 765 (w), 749 (w), 733 (w), 698 (w), 673 (w), 658 (w), 634 (w), 627 (w), 609 (w), 566 (w), 546 (w), 535 (w), 503 (w), 492 (w), 481 (w), 467 (w), 440 (w), 432 (w), 406 (m), 366 (w), 354 (w), 327 (w), 285 (w), 241 (w).

Form XIV:
3128 (w), 3061 (m), 3002 (m), 2995 (m), 2983 (w), 2966 (m), 2957 (m), 2938 (m), 2914 (m), 2867 (m), 2219 (s), 1675 (m), 1619 (s), 1596 (s), 1579 (s), 1554 (m), 1475 (w), 1446 (m), 1404 (w), 1374 (w), 1352 (m), 1329 (w), 1322 (w), 1303 (m), 1285 (m), 1273 (m), 1265 (m), 1247 (m), 1228 (w), 1216 (w), 1204 (w), 1187 (w), 1170 (m), 1137 (w), 1098 (m), 1058 (w), 1034 (w), 989 (w), 958 (w), 942 (m), 924 (m), 884 (m), 858 (w), 840 (m), 825 (w), 782 (w), 752 (w), 732 (w), 701 (w), 678 (w), 657 (w), 629 (w), 609 (w), 581 (w), 563 (w), 546 (w), 536 (w), 496 (w), 482 (w), 469 (w), 443 (w),

409 (m), 397 (w), 367 (w), 328 (w), 319 (w), 286 (w), 265 (w), 248 (w), 212 (w).

Table III:
Data of powder-XRD-pattern of polymorphic Forms.
(10 characteristic peaks of each polymorph have been taken for evaluation. The XRD instrument is controlled for 2Theta ±0.1 °).

Form I:

No.	d (Å)	2θ	I/I_0
1	8,501	10,40	21
2	7,898	11,19	17
3	6,606	13,39	31
4	6,532	13,54	25
5	6,416	13,79	26
6	5,590	15,84	28
7	4,210	21,09	63
8	3,761	23,64	18
9	3,632	24,49	100
10	3,452	25,79	26

Form II:

No.	d (Å)	2θ	I/I_0
1	8,426	10,49	29
2	7,541	11,73	25
3	6,742	13,12	41
4	6,119	14,46	33
5	5,455	16,24	39
6	4,592	19,32	30
7	4,425	20,05	26
8	4,083	21,75	54

9	3,782	23,50	100
10	3,380	26,35	37

Form III:

No.	d (Å)	2θ	I/I_0
1	15,165	5,82	32
2	8,034	11,00	27
3	5,944	14,89	27
4	5,224	16,96	23
5	5,089	17,41	15
6	4,932	17,97	18
7	4,195	21,16	23
8	4,029	22,05	35
9	3,520	25,28	100
10	3,181	28,03	16

Form IV:

No.	d (Å)	2θ	I/I_0
1	9,732	9,08	22
2	6,885	12,85	10
3	6,102	14,50	22
4	5,246	16,89	9
5	4,695	18,89	100
6	4,344	20,43	20
7	4,088	21,72	12
8	3,615	24,61	67
9	3,258	27,35	17
10	3,164	28,18	12

Form V:

No.	d (Å)	2θ	I/I_0
1	9,466	9,34	14
2	8,166	10,83	15
3	6,807	13,00	20
4	6,569	13,47	12
5	4,742	18,70	16
6	4,563	19,44	100
7	4,416	20,09	32
8	4,231	20,98	12
9	3,503	25,41	64
10	3,408	26,13	14

Form VI:

No.	d (Å)	2θ	I/I_0
1	9,762	9,05	29
2	8,841	10,00	17
3	6,780	13,05	52
4	4,250	20,89	42
5	4,177	21,26	100
6	3,888	22,85	37
7	3,846	23,11	20
8	3,766	23,61	41
9	3,724	23,87	17
10	3,594	24,76	20

Form VII:

No.	d (Å)	2θ	I/I_0
1	8,472	10,43	18
2	6,336	13,97	10
3	5,476	16,17	10

4	4,893	18,12	9
5	4,664	19,01	100
6	4,236	20,96	30
7	3,676	24,19	10
8	3,609	24,65	71
9	3,561	24,99	8
10	3,071	29,05	16

Form VIII:

No.	d (Å)	2θ	I/I_0
1	7,656	11,55	18
2	6,672	13,26	34
3	6,538	13,53	20
4	5,721	15,48	20
5	5,244	16,89	54
6	4,700	18,87	25
7	4,475	19,82	45
8	4,330	20,49	34
9	3,745	23,74	100
10	3,240	27,50	20

Form IX:

No.	d (Å)	2θ	I/I_0
1	7,044	12,56	31
2	6,712	13,18	22
3	5,487	16,14	40
4	5,218	16,98	30
5	4,897	18,10	46
6	4,714	18,81	42
7	4,445	19,96	67
8	3,554	25,04	100

9	3,333	26,72	32
10	3,173	28,10	31

Form X:

No.	d (Å)	2θ	I/I_0
1	15,817	5,58	31
2	9,123	9,69	23
3	8,280	10,68	27
4	7,953	11,12	28
5	6,561	13,48	42
6	6,440	13,74	36
7	5,507	16,08	35
8	4,167	21,30	98
9	4,132	21,49	49
10	3,576	24,88	100

Form XI:

No.	d (Å)	2θ	I/I_0
1	10,348	8,54	39
2	7,077	12,50	25
3	6,717	13,17	28
4	4,778	18,56	23
5	4,599	19,28	34
6	4,490	19,76	100
7	4,239	20,94	51
8	4,186	21,21	18
9	3,504	25,40	66
10	3,391	26,26	69

Form XIII:

No.	d (Å)	2θ	I/I_0
1	6,579	13,45	85
2	6,121	14,46	63
3	5,424	16,33	28
4	5,047	17,56	47
5	4,884	18,15	21
6	4,344	20,43	64
7	4,301	20,63	25
8	4,181	21,24	100
9	3,414	26,08	45
10	3,145	28,36	23

Form XIV:

No.	d (Å)	2θ	I/I_0
1	15,012	5,88	29
2	7,980	11,08	20
3	5,182	17,10	24
4	4,886	18,14	100
5	4,189	21,19	20
6	3,999	22,21	24
7	3,494	25,47	64
8*			
9*			
10*			

* Further peaks exhibit intensities < 3*noise.

Form XV:

No.	d (Å)	2θ	I/I_0
1	16,422	5,38	27
2	9,225	9,58	55

3	8,281	10,68	38
4	6,430	13,76	66
5	5,541	15,98	44
6	3,985	22,29	65
7	3,782	23,50	43
8	3,592	24,77	60
9	3,389	26,28	100
10	3,358	26,52	30

Form XVI:

No.	d (Å)	2θ	I/I_0
1	11,249	7,85	36
2	10,139	8,71	46
3	8,348	10,59	100
4	4,555	19,47	31
5	4,201	21,13	51
6	3,955	22,46	50
7	3,749	23,72	40
8	3,629	24,51	87
9	3,325	26,79	44
10	2,817	31,74	44

Claims

1. A compound which is 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride solvate in its crystalline modification.

2. A solvate according to claim 1 as 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride monoacetonate in crystalline modification I.

3. A solvate according to claim 1 as 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride as monosolvate with tetrahydrofuran in crystalline modification II.

4. A solvate according to claim 1 as 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride monosolvate with tetrahydrofuran in crystalline modification XV.

5. A solvate according to claim 1 as 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride hemisolvate with tetrahydrofuran in crystalline modification X.

6. A solvate according to claim 1 as 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride monomethanolate in crystalline modification XI.

7. A solvate according to claim 1 as 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride monosolvate with n-heptane in crystalline modification XIV.

8. A pharmaceutical composition comprising a compound according to any one of claims 1 to 7.

9. Use of compounds according to any one of claims 1 to 7 for the manufacture of a medicament for the treatment of and prevention of depressive disorders, anxiety disorders, bipolar disorders, mania,

dementia, substance-related disorders, sexual dysfunctions, eating disorders, obesity, fibromyalgia, sleeping disorders, psychiatric disorders, cerebral infarct, tension, for the therapy of side-effects in the treatment of hypertension, cerebral disorders, chronic pain, acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome and undesired puerperal lactation.

10. A compound which is 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride hydrate in its crystalline modification.

11. A hydrate according to claim 10 as 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride monohydrate in crystalline modification V.

12. A hydrate according to claim 10 as 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride sesquihydrate in crystalline modification VI.

13. A hydrate according to claim 10 as 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride hemihydrate in crystalline modification VIII.

14. A pharmaceutical composition comprising a compound according to any one of claims 10 to 13.

15. Use of compounds according to any one of claims 10 to 13 for the manufacture of a medicament for the treatment of and prevention of depressive disorders, anxiety disorders, bipolar disorders, mania, dementia, substance-related disorders, sexual dysfunctions, eating disorders, obesity, fibromyalgia, sleeping disorders, psychiatric disorders, cerebral infarct, tension, for the therapy of side-effects in the treatment of hypertension, cerebral disorders, chronic pain, acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome and undesired puerperal lactation.

16. A compound which is 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride anhydrate in its crystalline modification.

17. A compound according to claim 16 in crystalline modification IV.

18. A compound according to claim 16 in crystalline modification III.

19. A compound according to claim 16 in crystalline modification VII.

20. A compound according to claim 16 in crystalline modification IX.

21. A pharmaceutical composition comprising a compound according to any one of claims 16 to 20.

22. Use of compounds according to any one of claims 16 to 20 for the manufacture of a medicament for the treatment of and prevention of depressive disorders, anxiety disorders, bipolar disorders, mania, dementia, substance-related disorders, sexual dysfunctions, eating disorders, obesity, fibromyalgia, sleeping disorders, psychiatric disorders, cerebral infarct, tension, for the therapy of side-effects in the treatment of hypertension, cerebral disorders, chronic pain, acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome and undesired puerperal lactation.

23. A compound which is 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine dihydrochloride in its crystalline modification.

24. A dihydrochloride according to claim 23 as 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine dihydrochloride in crystalline modification XIII.

25. A pharmaceutical composition comprising a compound according to claim 23 or 24.

26. Use of compounds according to claims 23 or 24 for the manufacture of a medicament for the treatment of and prevention of depressive disorders, anxiety disorders, bipolar disorders, mania, dementia, substance-related disorders, sexual dysfunctions, eating disorders, obesity, fibromyalgia, sleeping disorders, psychiatric disorders, cerebral infarct, tension, for the therapy of side-effects in the treatment of hypertension, cerebral disorders, chronic pain, acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome and undesired puerperal lactation.

27. A compound which is amorphous 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride.

28. A pharmaceutical composition comprising a compound according to claim 27.

29. Use of compounds according to claim 27 for the manufacture of a medicament for the treatment of and prevention of depressive disorders, anxiety disorders, bipolar disorders, mania, dementia, substance-related disorders, sexual dysfunctions, eating disorders, obesity, fibromyalgia, sleeping disorders, psychiatric disorders, cerebral infarct, tension, for the therapy of side-effects in the treatment of hypertension, cerebral disorders, chronic pain, acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome and undesired puerperal lactation.

30. Process for preparing Form I according to claim 2, which comprises:

(1) dispersing 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine in acetone

(2) converting the 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine base, by addition of 1N hydrochloric acid into the hydrochloride salt at temperatures between 30°C and the boiling point of acetone, preferably between 40° C and 50°C

(3) precipitation of Form I at room temperature

(4) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride acetonate by filtration, and drying in vacuo at room temperature.

31. Process for preparing Form I according to claim 2 which comprises:
(1) suspending Form III of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride according to claim 18 in acetone
(2) stirring at room temperature between a few hours or days, preferably 10 to 20 days,
(3) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride acetonate by filtration, and drying in vacuo at room temperature.

32. Process for preparing Form II according to claim 3, which comprises:
(1) dispersing 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine in tetrahydrofuran
(2) converting the 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine base, by addition of 1N hydrochloric acid into the hydrochloride salt at temperatures between 10°C and 60°C
(3) precipitation of Form II at room temperature
(4) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride solvate with tetrahydrofuran by filtration, and drying in vacuo at room temperature.

33. Process for preparing Form II according to claim 3 which comprises:
(1) suspending Form III of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride according to claim 18 in tetrahydrofuran
(2) stirring at room temperature between a few hours or days, preferably 15 to 30 days,
(3) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride acetonate by filtration, and drying in vacuo at room temperature.

34. Process for preparing Form XV according to claim 4, which comprises:
(1) dispersing 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine in tetrahydrofuran

(2) converting the 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine base, by addition of 1N hydrochloric acid into the hydrochloride salt at temperatures between -10°C and 10°C
(3) precipitation of Form XV at room temperature
(4) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride solvate with tetrahydrofuran by filtration, and drying in vacuo at room temperature.

35. Process for preparing Form X according to claim 5, which comprises:
(1) dispersing 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine in tetrahydrofuran
(2) converting the 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine base, by addition of 1N hydrochloric acid into the hydrochloride salt at temperatures between 10°C and 40°C
(3) precipitation of Form II at room temperature
(4) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride solvate with tetrahydrofuran by filtration, and drying at temperatures up to 80°C maximum.

36. Process for preparing Form XI according to claim 6, which comprises:
(1) suspending Form VI of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride according to claim 12 in methanol methanol at temperatures between 55°C and the boiling point of methanol
(2) cooling down the reaction mixture to temperatures between -40° and -10°C
(3) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride methanolate by filtration at room temperature, and drying in vacuo at room temperature.

37. Process for preparing Form V according to claim 11, which comprises:
(1) dispersing 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine in tetrahydrofuran

(2) converting the 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine base, by addition of aqueous hydrochloric acid into the hydrochloride salt
(3) precipitation of Form V at room temperature
(4) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride monohydrate by filtration, and drying in vacuo at room temperature.

38. Process for preparing Form V according to claim 11, which comprises:
(1) stirring of Form IV of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride according to claim 17 in water with an amount of 5 to 10 times more relating to Form IV
(3) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride monohydrate by filtration, and drying in vacuo at room temperature untill the forming of the monohydrate of Form V without excess of water.

39. Process for preparing Form V according to claim11, which comprises:
(1) stirring of Form XIII of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine dihydrochloride according to claim 24 in water
(3) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride monohydrate by filtration, and drying in vacuo at room temperature.

40. Process for preparing VI according to claim 12, which comprises:
(1) stirring of Form IV of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride according to claim 17 in water in which the relative proportions of salt to water are between 1:5 and 1:10
(3) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride sesquihydrate by filtration, and drying in vacuo at room temperature.

41. Process for preparing Form VI according to claim 12, which comprises:

(1) stirring of Form II of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride according to claim 2 in water for at least one hour
(3) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride sesquihydrate by filtration, and drying in vacuo at room temperature.

42. Process for preparing Form VIII according to claim 13, which comprises:
(1) stirring of Form VI of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride sesquihydrate according to claim 12 in water for more than 12 hours
(3) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride hemihydrate by filtration, and drying in vacuo at room temperature.

43. Process for preparing Form VIII according to claim 13, which comprises:
(1) stirring of Form II of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride according to claim 2 in water for 12 hours
(3) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride hemihydrate by filtration, and drying in vacuo at room temperature.

44. Process for preparing Form IV according to claim 17, which comprises:
(1) drying of Form V according to claim 11 in vacuo at temperatures of 85° to 90°C.

45. Process for preparing Form IV according to claim 17, which comprises:
(1) drying of Form XI of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride monomethanolate according to claim 6 at temperatures between 55° and 65°C.

45. Process for preparing Form III according to claim 18, which comprises:

(1) drying of Form II according to claim 3 in vacuo at temperatures of at least 100°C.

46. Process for preparing Form VII according to claim 19, which comprises:
(1) tempering Form IV of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride according to claim 17 at temperatures of at least 200°C.

47. Process for preparing Form IX according to claim 20, which comprises:
(1) drying of Form VIII of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride according to claim 13 at temperatures between 90°C and 110°C.

48. Process for preparing Form XIII according to claim 24, which comprises:
(1) dispersing 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine in an organic solvent chosen from the group consisting of tetrahydrofuran, ethanol, isopropanol or mixtures thereof with water
(2) converting the 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine base, by addition of 2N or concentrated hydrochloric acid into the hydrochloride salt at temperatures between 20° and 30°C
(3) precipitation of Form XIII at room temperature
(4) recovering the precipitated 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine dihydrochloride Form XIII by filtration
(5) drying of Form XIII in vacuo at room temperature.

49. Process for preparing Form XVI according to claim 27, which comprises:
(1) dissolving 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride of Form IV, II, VII or IX in acetonitrile and water in the molar ratio 1:1
(2) freeze-drying or spray-driying overnight to give Form XVI of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride.

50. Composition comprising Form IV according to claim 17 and Form V according to claim 11.

51. Composition comprising Form IV according to claim 17 and Form V according to claim 11 in a molar ratio of about 100 to 1 to 10 to 1.

52. Pharmaceutical preparation comprising an active ingredient consisting essentially of a mixture of Form IV according to claim 17 and Form V according to claim 11.

53. Pharmaceutical preparation comprising an active ingredient consisting essentially of a mixture of Form IV according to claim 17 and Form V according to claim 11 in a molar ratio of about 100 to 1 to 10 to 1.

54. Use of a composition according to claims 50 and/or 51 for the manufacture of a medicament.

55. Extended release formulation comprising Form I according to claim 2 and/or Form III according to claim 18 and/or form VIII according to claim 13.