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(19) **United States**(12) **Patent Application Publication****Kovanyine Lax et al.**(10) **Pub. No.: US 2009/0137563 A1**(43) **Pub. Date: May 28, 2009**(54) **PROCESS FOR THE PREPARATION OF OLANZAPINE**

(76) Inventors: **Gyorgyi Kovanyine Lax**, Budapest (HU); **Gabor Nemeth**, Budapest (HU); **Gyorgy Krasznay**, Budapest (HU); **Norbert Mesterhazy**, Szombathely (HU); **Kalman Nagy**, Budapest (HU); **Gyorgyi Vereczkeyne Donath**, Budapest (HU); **Zsuzsanna Szent-Kirallyi**, Budapest (HU)

Correspondence Address:

K.F. ROSS P.C.**5683 RIVERDALE AVENUE, SUITE 203 BOX 900
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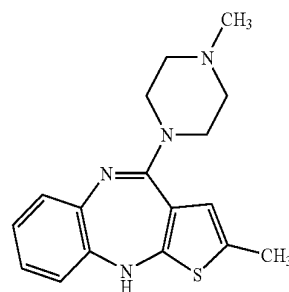
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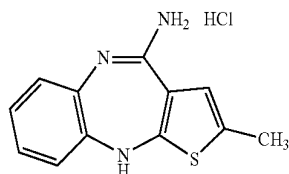
Publication Classification(51) **Int. Cl.****A61K 31/551** (2006.01)**C07D 495/04** (2006.01)**A61P 25/18** (2006.01)(52) **U.S. Cl. 514/220; 540/578**(57) **ABSTRACT**

The invention relates to a process for the preparation of 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno-[2,3-b][1,5]benzodiazepine (olanzapine) of the formula (I) by reacting 4-amino-2-methyl-10H-thieno [2,3-b][1,5]benzodiazepine hydrochloride of the formula (II) with N-methylpiperazine in an organic solvent, which comprises carrying out the reaction in the mixture of toluene and 1,3-dimethyl-2-imidazolidinone. The invention also encompasses new 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno [2,3-b][1,5]benzodiazepine dihydrochloride trihydrate of the formula (IB), the preparation thereof and pharmaceutical compositions comprising said new compound.



IA

(I)



II

(II)

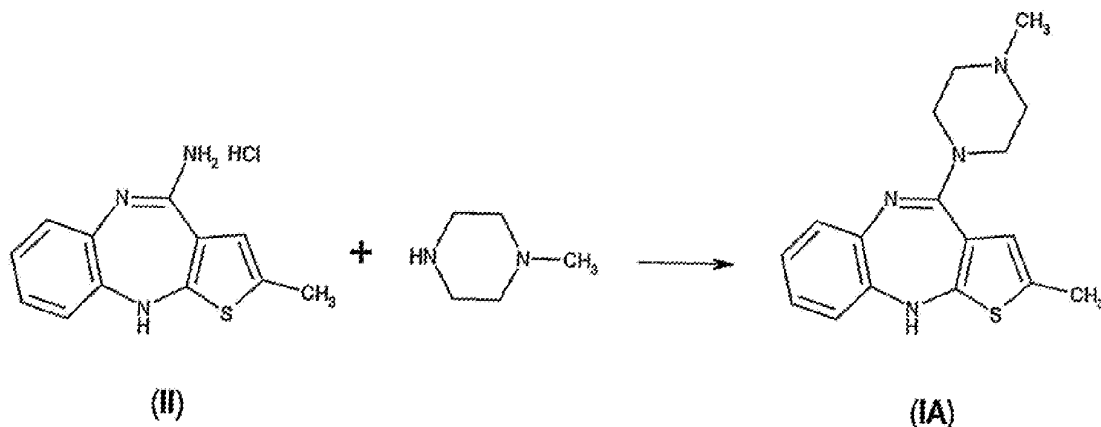
Reaction scheme 1

Fig. 1 Reaction scheme 1

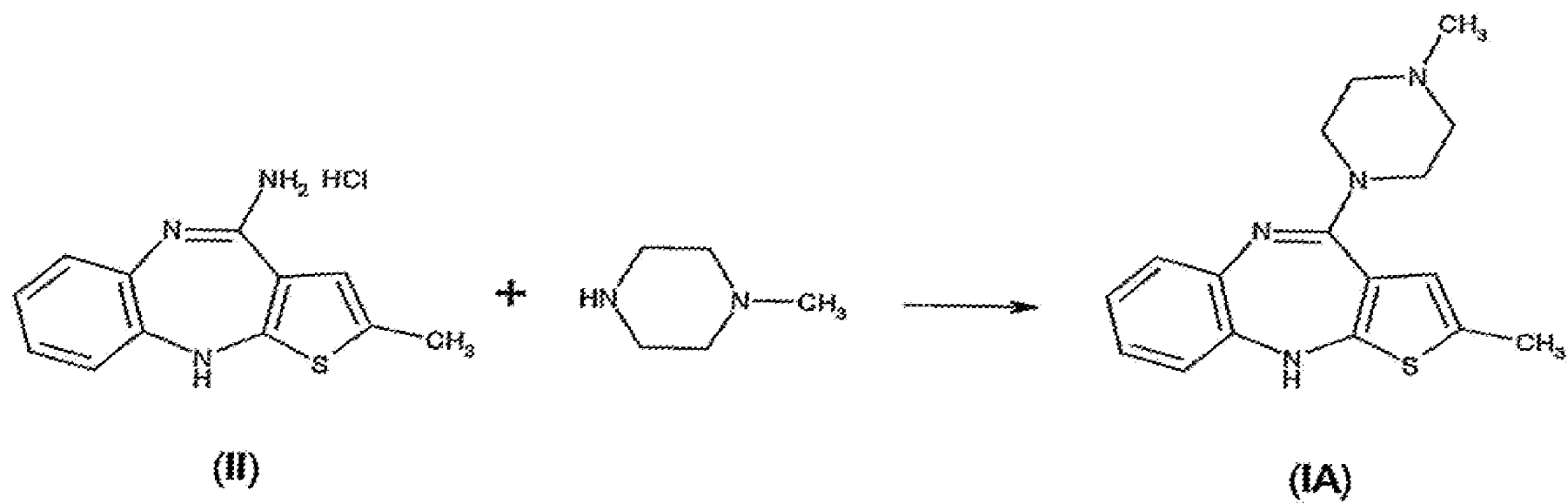
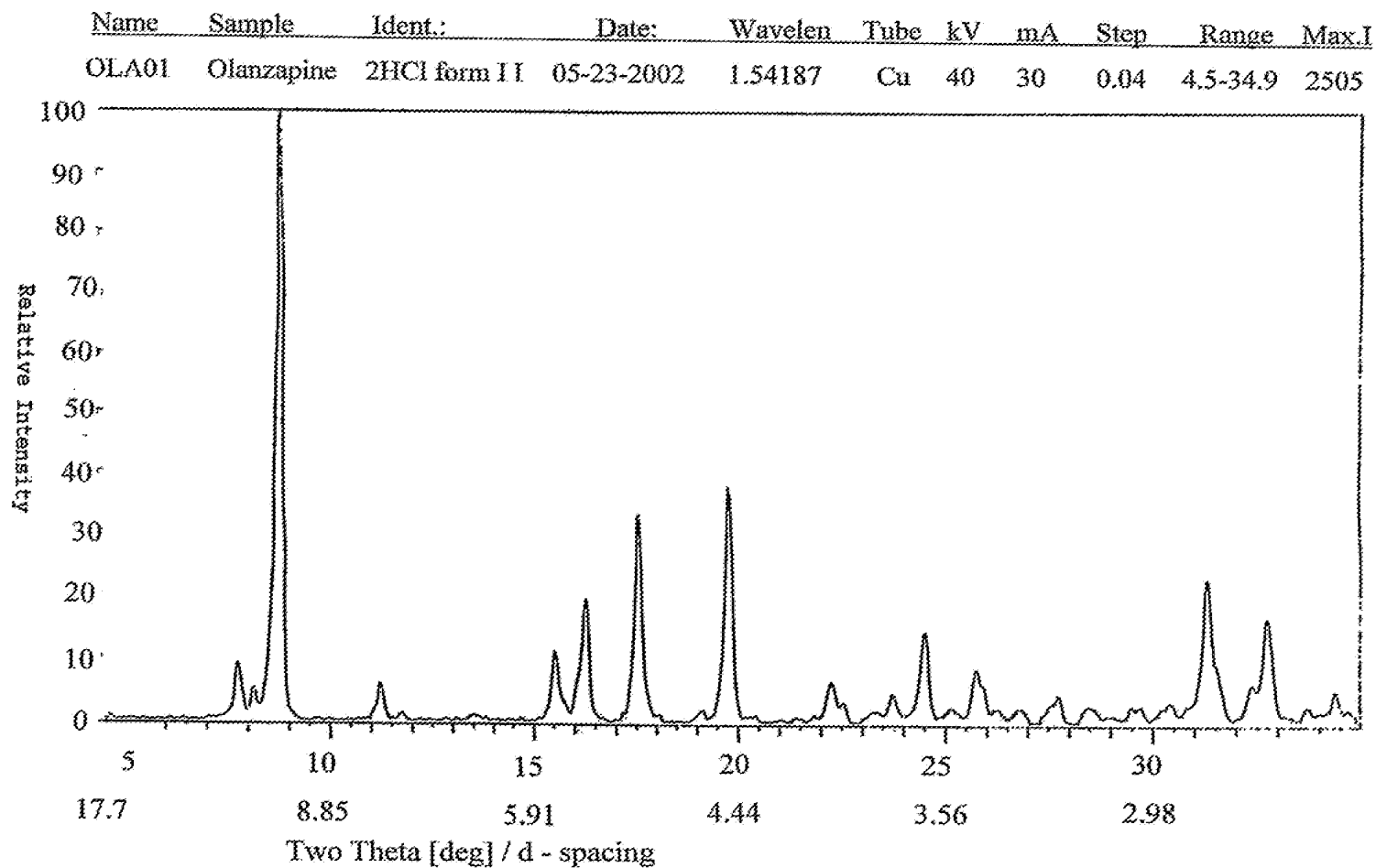


Fig. 2 Olanzapine dihydrochloride trihydrate

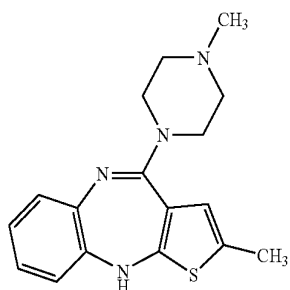


PROCESS FOR THE PREPARATION OF OLANZAPINE

TECHNICAL FIELD OF THE INVENTION

[0001] The present invention relates to an improved process for the preparation of olanzapine, to a new olanzapine salt hydrate and the preparation thereof. The invention also relates to pharmaceutical compositions containing said new olanzapine salt hydrate and the use thereof for the treatment of psychotic conditions.

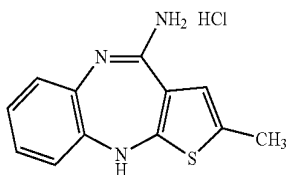
[0002] It is known that 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno[2,3-b][1,5]benzodiazepine of the formula (IA)



IA

(hereinafter referred to as “olanzapine”) is a valuable antipsychotic drug.

[0003] Olanzapine was described the first time in EP 454, 436. According to the final step of the synthesis provided in said patent specification 4-amino-2-methyl-10H-thieno[2,3-b]-[1,5]benzodiazepine hydrochloride of the formula (II)



II

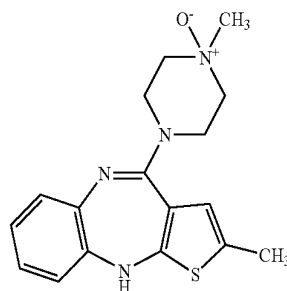
is reacted with an excess amount of N-methylpiperazine for 20 hours under nitrogen atmosphere, in a 1:1 mixture of toluene and dimethyl sulfoxide, at the boiling point of the mixture, and the reaction mixture is cooled to 50° C. Olanzapine is crystallized by adding some water to the mixture, and the thus-obtained crude product is recrystallized from acetonitrile. The desired olanzapine is obtained in a yield of 48%. The reaction is depicted in reaction scheme 1.

[0004] International patent application WO 2004/094433 A1 provides two new polymorphic forms of olanzapine dihydrochloride, furthermore a new polymorphic olanzapine monohydrochloride.

[0005] European patent specification No. 733,635 discloses the preparation of olanzapine of so-called “technical quality”. This process is also carried out according to reaction scheme 1, with the difference that six times amount of dimethyl sulfoxide is used at a temperature of 120° C. The reaction is detected by HPLC. The reaction is performed until 5% of residual starting substance of the formula (II) has remained in the mixture. Then it is cooled to 20° C. and olanzapine is

crystallized at 5° C. by subsequently adding a tenfold amount of methanol and a threefold amount of water to the mixture. The yield of the thus-obtained crude olanzapine base amounts to 76.7%.

[0006] The inventors of the present invention have repeated the above reaction carried out in dimethyl sulfoxide or in a 1:1 mixture of toluene and dimethyl sulfoxide as specified in the prior art. During the reproduction it has been found that an undesirable amount of olanzapine N-oxide of the formula (III)



III

is formed even if the reaction is carried out under inert gas atmosphere (e.g. nitrogen or argon). This is even more surprising because—according to the experiments of the inventors of the present invention—dimethyl sulfoxide does not oxidize olanzapine, in spite of that according to many publications available in the literature dimethyl sulfoxide acts as an oxidizing agent. In spite of this fact, if dimethyl sulfoxide is applied as solvent for the reaction depicted in reaction scheme 1, a higher amount of the undesired the N-oxide of the formula (III) is formed. The stricter and stricter analytical requirements raised towards the pharmaceutical substances call for the strongest possible decrease in the amount of impurities, such as the N-oxide of the formula (III). According to the experiences of the inventors of the present invention the amount of the impurity of the formula (III) being present in the pharmaceutical composition containing olanzapine as active ingredient increases during storage. Due to the structural similarity between olanzapine and its N-oxide of the formula (III) the separation of the two compounds—that is the removal of the impurity of the formula (III)—is cumbersome on the one part and inevitably leads to losses on the other.

SUMMARY OF THE INVENTION

[0007] It is the object of the present invention to elaborate an industrially applicable process for the preparation of olanzapine, which enables the minimalization of the formation of N-oxide of the formula (III).

[0008] The above object is solved by the present invention.

[0009] The present invention is based on the recognition that if instead of dimethyl sulfoxide the reaction is carried out in the mixture of another dipolar aprotic solvent—that is in 1,3-dimethyl-2-imidazolidinone—and toluene, olanzapine N-oxide of the formula (III) is formed in a considerably smaller amount, which is not problematical in respect of the stability of the composition, because even during long-term storage it does not increase beyond the limit permitted in pharmaceutical compositions.

DETAILS OF THE INVENTION

[0010] According to an aspect of the present invention there is provided a process for the preparation of 2-methyl-4-(4-

methylpiperazin-1-yl)-10H-thieno-[2,3-b][1,5]benzodiazepine (olanzapine) of the formula (IA) by reacting 4-amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine hydrochloride of the formula (II) with N-methylpiperazine in an organic solvent, which comprises carrying out the reaction in the mixture of toluene and 1,3-dimethyl-2-imidazolidinone.

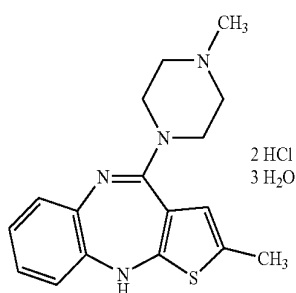
[0011] 1,3-Dimethyl-2-imidazolidinone possesses favourable pharmaceutical properties. It is a strongly polar aprotic solvent, which is stable in the presence of acids and alkalis even at high temperatures, and it is not corrosive. The boiling and ignition points of 1,3-dimethyl-2-imidazolidinone are high (225° C. and 120° C., respectively), LD₅₀=2840 mg/kg. Due to its high permittivity and solvation effects 1,3-dimethyl-2-imidazolidinone activates the reagents. A further advantage of the application of 1,3-dimethyl-2-imidazolidinone resides in the fact that it eliminates the oxidative, unpleasant environmental and labour safety properties of dimethyl sulfoxide.

[0012] During the reaction N-methyl piperazine is preferably applied in an excess quantity.

[0013] The reaction is preferably carried out in a 3:1 mixture, particularly preferably in a 1:1 mixture, more preferably in a 2:1 mixture of toluene and 1,3-dimethyl-2-imidazolidinone. The reaction is carried out at a temperature between 100° C. and 130° C. The reaction is performed under an inert gas atmosphere (preferably nitrogen or argon).

[0014] A further advantage of the process according to the invention resides in the fact that the reaction can be performed in a considerably shorter period of time (within 8 to 11 hours, preferably within 9 hours) than the one provided in the prior art, which is carried out in dimethyl sulfoxide medium and takes 20 hours. The olanzapine base obtained after evaporating the reaction mixture is of high purity. If desired, the product can be recrystallized from acetonitrile.

[0015] According to another aspect of the present invention there is provided a process for the preparation of 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno-[2,3-b][1,5]benzodiazepine dihydrochloride trihydrate of the formula (IB),



which comprises reacting 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno-[2,3-b][1,5]benzodiazepine of the formula (IA) in an aqueous ethanol medium with hydrogen chloride.

[0016] The reaction can preferably be carried out in an 8:2 mixture, particularly preferably in a 9:1 mixture of ethanol and water.

[0017] One can also proceed by adding an aqueous hydrogen chloride solution to the suspension of 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno[2,3-b][1,5]benzodiazepine of the formula (IA) in ethanol. Preferably 37% aqueous hydrogen chloride solution is applied.

[0018] The above process enables the preparation of 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno[2,3-b][1,5]benzodiazepine dihydrochloride trihydrate of the formula (IB) in a purity as high as 99.9% by HPLC in a yield as excellent as 83.5%.

[0019] According to a further aspect of the present invention there is provided the new 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno[2,3-b][1,5]benzodiazepine dihydrochloride trihydrate of the formula (IB).

[0020] The X-ray powder diffraction pattern of 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno[2,3-b][1,5]benzodiazepine dihydrochloride trihydrate of the formula (II) measured by using CuK α radiation corresponds to diagram 1 and can be characterized by the X-ray powder diffraction pattern expressed below:

[0021] Position of diffraction lines and relative intensities (>5%)

Peak No.	2 θ th [deg]	D(hkl) [Å]	I(abs) [cps]	I(rel) [%]
1	7.78	11.3638	219	8.74
2	8.17	10.8222	124	4.95
3	8.79	10.0557	2505	100.00
4	11.26	7.8611	143	5.71
5	15.54	5.7012	265	10.58
6	16.28	5.4444	478	19.08
7	17.55	5.0524	817	32.61
8	19.78	4.4885	933	37.25
9	22.26	3.9945	153	6.11
10	24.51	3.6315	348	13.89
11	25.75	3.4605	202	8.06
12	25.93	3.4362	131	5.23
13	31.30	2.8580	558	22.28
14	31.53	2.8375	202	8.06
15	32.38	2.7651	145	5.79
16	32.74	2.7355	404	16.13

[0022] The above data were determined under the following conditions:

[0023] Equipment:

[0024] PHILIPS-XPRT PW 3710 powder diffractometer

[0025] Radiation: Cu K α (λ : 1.54190 Å)

[0026] Monochromator: graphite

[0027] Excitation voltage: 40 kV

[0028] Anode current: 30 mA

[0029] Method:

[0030] Standard reference substance: SRM 675

[0031] Mica Powder (synthetic fluorophlogopite), serial number: 981307.

[0032] The measurement was continuous: $\Theta/2\Theta$ scan: 4.5°-35.00° 2 Θ

[0033] Step size: 0.02-0.04°

[0034] Sample: surface plain, width 0.5 mm, in quartz kvarz sample holder, measured and stored at room temperature.

[0035] 2-Methyl-4-(4-methylpiperazin-1-yl)-10H-thieno[2,3-b][1,5]benzodiazepine dihydrochloride trihydrate (olanzapine dihydrochloride trihydrate) of the formula (IB) is a highly advantageous crystalline form. The product is a morphologically uniform, stable substance having excellent filtration, drying and storing characteristics, and its storage does not require special circumstances.

[0036] According to a further aspect of the present invention there is provided a pharmaceutical composition comprising as active ingredient 2-methyl-4-(4-methylpiperazin-1-

yl)-10H-thieno[2,3-b][1,5]benzodiazepine dihydrochloride trihydrate of the formula (IB) in admixture with inert solid or liquid pharmaceutical carriers and/or auxiliary agents.

[0037] According to a still further aspect of the present invention there is provided a process for the preparation of a pharmaceutical composition, which comprises admixing 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno-[2,3-b][1,5]benzodiazepine dihydrochloride trihydrate of the formula (IB) with a pharmaceutically acceptable solid or liquid carrier and/or auxiliary agent and bringing the mixture to galenic form.

[0038] The pharmaceutical compositions according to the invention can be prepared by methods conventionally applied in pharmaceutical industry. The pharmaceutical compositions according to the invention can be administered orally (e.g. tablets, coated tablets, capsules, pilules, solutions, suspensions or emulsions), rectally (e.g. suppositories), parenterally (e.g. intravenously, intraperitoneally, etc.) or transdermally.

[0039] The pharmaceutical compositions according to the invention may contain usual pharmaceutical carriers and/or auxiliary agents. As carrier magnesium carbonate, magnesium stearate, talc, sucrose, lactose, pectin, dextrin, starch, gelatine, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting wax, cocoa butter etc. can be used. In case of capsules the carrier is generally the wall of the capsule so that no additional carrier is needed. As oral administration form the lozenge and sachet can also be mentioned. Tablets, powders, capsules, pilules, sachets and lozenges are solid forms particularly suitable for oral administration.

[0040] Suppositories may contain low melting waxes (e.g. mixtures of fatty acid triglycerides or cocoa butter) as carrier. Suppositories can be prepared by melting the wax, homogeneously distributing the active ingredient in the melt, pouring the melt homogenous mixture into mould forms of suitable size and form, and allowing the mixture to solidify under cooling.

[0041] Tablets can be prepared by admixing the active ingredient with suitable carriers in the appropriate ratio and pressing the mixture into tablets of suitable size and form.

[0042] Powders are prepared by admixing the finely powdered active ingredient with finely powdered carriers.

[0043] As liquid pharmaceutical compositions optionally sustained release solutions, suspensions and emulsions can be mentioned. Aqueous solutions and aqueous propylene glycol solutions are advantageous. Liquid pharmaceutical compositions suitable for parenteral administration can be preferably prepared in the form of aqueous polyethylene glycol solutions.

[0044] Aqueous solutions suitable for oral administration can be produced by dissolving the active ingredient in water and adding suitable colouring, aromatizing, stabilizing agents and thickeners.

[0045] Aqueous suspensions suitable for oral administration can be prepared by suspending the active ingredient in water in presence of a viscous substance (e.g. natural or artificial gums, resins, methyl cellulose, sodium carboxymethyl cellulose or other known suspending agents).

[0046] Another type of solid pharmaceutical compositions can be converted into liquid compositions immediately before use and administered orally into the organism in liquid form. Solutions, suspensions or emulsions can be mentioned as such liquid forms of administration which contain, in addition to the active ingredient, colouring agents, aromatizing

agents, preservatives, buffers, artificial or natural sweeteners, dispersing agents, thickeners, etc.

[0047] The pharmaceutical compositions of the present invention are preferably prepared in dosage unit form. Such dosage units contain the desired amount of the active ingredient. The dosage units can be put on the market in packages containing discrete amounts of the compositions (e.g. packed tablets, capsules or powders in vials or ampoules). The term "dosage unit" relates to the capsules, tablets, lozenges, sachets per se and also to the packaging which contains the suitable number of dosage units.

[0048] The active ingredient may be released from the pharmaceutical compositions according to the present invention immediately or in a delayed manner.

[0049] The pharmaceutical compositions according to the present invention usually contain about 0.1-100 mg, preferably about 0.5-50 mg of active ingredient.

[0050] According to a still further aspect of the present invention there is provided the use of 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno[2,3-b]-[1,5]benzodiazepine dihydrochloride trihydrate of the formula (IB) as a pharmaceutically active ingredient.

[0051] According to a particular aspect of the present invention there is provided the use of 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno[2,3-b]-[1,5]benzodiazepine dihydrochloride trihydrate of the formula (IB) for the preparation of pharmaceutical compositions having antipsychotic activity.

[0052] According to a still further aspect of the present invention there is provided a method for the treatment of psychotic conditions, which comprises administering to a patient in need of such treatment a pharmaceutically active amount of 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno[2,3-b][1,5]benzodiazepine dihydrochloride trihydrate of the formula (IB).

[0053] The invention involves the following advantages:

[0054] During the preparation of olanzapine base a lower amount of the undesired N-oxide contamination of the formula (III) is formed;

[0055] The process provides the preparation of high-purity olanzapine in an excellent yield;

[0056] During the preparation of olanzapine a solvent having good physical properties and suitable in respect of environmental and labour safety considerations is applied;

[0057] olanzapine can be prepared in a considerably shorter period of time;

[0058] the new olanzapine dihydrochloride trihydrate according to the invention is a morphologically uniform crystalline form having excellent filtration, drying and storing characteristics, which can be used to advantage in the pharmaceutical industry.

[0059] Further details of the present invention are provided in the following examples without limiting the scope of protection to said examples.

EXAMPLE 1

Olanzapine Base: (IA)

[0060] To a mixture of 53.77 g (0.2 mole) of 4-amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine hydrochloride, 538 cm³ of toluene and 269 cm³ of DMI (1,3-dimethyl-2-imidazolidinone) 186 cm³ (167.4 g, 1.67 mole) of N-methylpiperazine are added under stirring, an argon stream

is generated, and the reaction mixture is heated to the boiling point (126° C.) with the aid of an oil bath.

[0061] The mixture is allowed to boil for 9 hours until 1% amount of starting substance can be detected by HPLC. It is then evaporated at a temperature of 50-55° C. under 5-10 mbar. The thus-obtained residue is cooled with ice-water to a temperature of about 3-5° C., 320 cm³ of water are dropwise added to it, while the product continuously separates from the reaction mixture. It is stirred further at a temperature of 5° C. for 1 hour, filtered, washed with 120 cm³ of water and dried with the aid of an infrared lamp. Thus 56 g (89.6%) of base are obtained. (M.p.: 189-193° C., HPLC: 98%), which is recrystallized from a 14-times amount of acetonitrile to yield 42.6 g (76%) of the desired compound. M.p.: 194-196° C., HPLC: 99.87%.

[0062] ¹HNMR (DMSO, i500): δ: 7.59 (s, 1H), 6.84 (m, 1H), 6.81 (m, 1H), 6.79 (dd, 1H), 6.69 (dd, 1H), 6.33 (d, 1H, J=1.1 Hz), 3.33 (m, 4H), 2.37 (t, 4H), 2.27 (d, 3H, J=1.1 Hz), 2.20 (s, 3H).

EXAMPLE 2

Olanzapine Base: (IA)

[0063] To a mixture of 5 g (0.019 mole) of 4-amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine hydrochloride, 50 cm³ of toluene and 50 cm³ of DMI 17.5 cm³ of N-methylpiperazine are added under stirring, an argon stream is generated, and the reaction mixture is kept boiling for 11 hours at a temperature of 130° C. with the aid of an oil bath. Then it is evaporated at a temperature between 50° C. and 55° C. under 5-10 mbar.

[0064] The thus-obtained brown residue is cooled to a temperature of about 3-5° C. with the aid of ice water, under stirring. Then 30 cm³ of water are dropped to it at the same temperature. It is stirred further for 1 hour, washed with water and dried. Thus 4.5 g (77.1%) of the desired compound are obtained. M.p.: 193-196° C., HPLC: 98.8%.

EXAMPLE 3

Olanzapine Base: (IA)

[0065] To a mixture of 26.58 g (0.1 mole) of 4-amino-2-methyl-10H-thieno [2,3-b][1,5]benzodiazepine hydrochloride, 266 cm³ of toluene and 83 cm³ of DMI 93 cm³ of N-methylpiperazine are added under stirring, an argon stream is generated, and the mixture is boiled in an oil bath at a temperature of 120° C. for 9 hours. The reaction mixture is then evaporated at a temperature of 50-55° C. under 5-10 mbar.

[0066] The thus-obtained brown residue is cooled to a temperature of about 3-5° C. with ice water, under stirring, and 160 cm³ of water are dropped to it at the same temperature. The mixture is stirred further for 1 hour at a temperature of about 5° C., filtered, washed with 60 cm³ of water and dried. Thus 23.7 g (76%) of the desired compound are obtained. M.p.: 194-196° C, HPLC: 99.18%.

EXAMPLE 4

Olanzapine Dihydrochloride Trihydrate: (IB)

[0067] 42.6 g (0.14 mole) of olanzapine base are suspended in a mixture of 680 cm³ of ethanol and 68 cm³ of water, and 29.2 cm³ of 37% hydrogen chloride are dropped to the suspension under stirring. During the addition of hydrogen chlo-

ride the suspension turns into solution, then the yellow crystalline product separates continuously. The mixture is stirred further for 2 hours. The suspension is then filtered, washed with twice with 15 cm³ each of cooled ethanol and dried under an infrared lamp. Thus 51.4 g (83.5%) of the desired product are obtained. M.p. (Koffler): 201-240° C. (continuous decomposition).

[0068] HPLC: 99.9%.

EXAMPLE 5

Olanzapine Dihydrochloride trihydrate: (IB)

[0069] To a suspension of 5 g (0.016 mole) of olanzapine base in 80 ml of ethanol 3.3 ml of 37% hydrogen chloride solution are dropped at a temperature of 25° C., under vigorous stirring (1.46 g, 0.04 mole) under 2 hours. The mixture is then stirred further for 2 hours at a temperature of 25° C., to the thus-obtained suspension 16 ml of water are dropped, and the suspension is stirred at a temperature of 25° C. for 24 hours. The thus-obtained yellow crystalline substance is filtered off and dried. Thus 5.8 g (82%) of the desired compound are obtained.

EXAMPLE 6

Olanzapine Dihydrochloride Trihydrate: (IB)

[0070] To a suspension of 5 g (0.016 mole) of olanzapine base in 80 ml of ethanol 3.3 ml of 37% hydrogen chloride solution (1.46 g, 0.04 mole) are dropped within 2 hours at 25° C., under vigorous stirring. Then 16 ml of water are added to the mixture. During the addition of water a solution is formed, and in half an hour crystals begin to separate. The suspension is stirred for 24 hours, filtered and dried. Thus 4.2 g (60%) of the desired compound are obtained.

EXAMPLE 7

4-{2-Methyl-10H-thieno[2,3-b][1,5]benzodiazepin-4-yl}-1-methylpiperazine 1-oxide (III) [olanzapine N-oxide]

[0071] 5.0 g (0.016 mole) of olanzapine base are suspended in 50 cm³ of dichloromethane, the suspension is cooled to 0-5° C., and 4.05 g of 75% (3.03 g, 0.016 mole) of m-chloroperoxybenzoic acid are added to it. The mixture is stirred further first for 2 hours at a temperature of 0-5° C., then for 10 hours at 10-12° C. and processed as follows: it is poured onto 100 cm³ of water under stirring and extracted 3 times with 150 cm³ each of dichloromethane. The organic phase is washed subsequently with sodium chloride solution and water. Following the extraction "N-oxide" separate from the aqueous phase in form of white precipitates. The mixture is then filtered. Thus 4.1 g (79.1%) of the desired substance are obtained.

[0072] M.p.: 204-206° C., HPLC: 99.6%.

[0073] 2.78 g of substance are obtained by the evaporation of the organic phase, which contains olanzapine base as well. Subjecting it to column chromatography in a 6:4 mixture of toluene and methanol a further amount of 1.6 g of substance is obtained, which is suspended in ether and recrystallized from ethanol. Thus a further amount of 0.8 g of product is obtained, HPLC: 99.7%.

[0074] Elementary analysis for the formula C₁₇H₂₀N₄OS×1.5 H₂O=355.44

	C %	H %	N %
Calculated:	57.39	6.47	15.76
Found:	57.25	6.5	15.8

[0075] IR(KBr): 3213, 3051, 2945, 2915, 1588, 1563, 1466, 1416, 1283, 1220, 1136

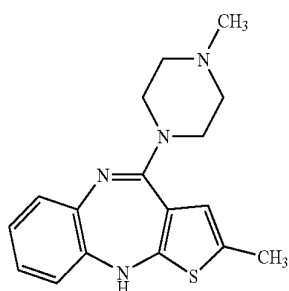
[0076] ¹HNMR (DMSO, i500): δ: 7.97 (s, 1H), 6.85 (t, 1H), 6.83 (t, 1H), 6.81 (dd, 1H),

[0077] 6.73 (dd, 1H), 6.39 (s, 1H), 3.78 (d, 2H), 3.6 (t, 2H), 3.42 (t, 2H), 3.11 (s, 3H), 2.96 (d, 2H), 2.27 (s, 3H)

[0078] ¹³CNMR (DMSO, i500): δ: 157.04, 154.2, 144.27, 140.6, 128.33, 127.72, 123.86, 123.66, 122.66, 119.20, 117.78, 64.75, 60.37, 41.47, 15.27

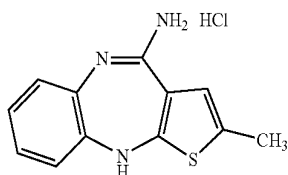
[0079] According to mass spectrometry M+H is at 329, fragment ions can be found at the m/z values of 311, 285, 229.

1. A process for the preparation of 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno-[2,3-b][1,5]benzodiazepine (olanzapine) of the formula (IA)



(IA)

by reacting 4-amino-2-methyl-10H-thieno [2,3-b][1,5]benzodiazepine hydrochloride of the formula (II)



(II)

with N-methylpiperazine in an organic solvent, which comprises carrying out the reaction in the mixture of toluene and 1,3-dimethyl-2-imidazolidinone.

2. A process as claimed in claim 1, which comprises using a 3:1 mixture by volume of toluene and 1,3-dimethyl-2-imidazolidinone.

3. A process as claimed in claim 1, which comprises using a 1:1 mixture by volume of toluene and 1,3-dimethyl-2-imidazolidinone.

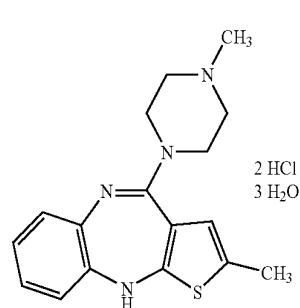
4. A process as claimed in claim 1, which comprises using a 2:1 mixture by volume of toluene and 1,3-dimethyl-2-imidazolidinone.

5. A process as claimed in claim 1, which comprises carrying out the reaction at a temperature between 100° C. and 130° C.

6. A process as claimed in claim 1, which comprises carrying out the reaction within 8 to 11 hours.

7. A process as claimed in claim 6, which comprises carrying out the reaction within 9 hours.

8. A process for the preparation of 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno-[2,3-b][1,5]benzodiazepine dihydrochloride trihydrate of the formula (IB),



(IB)

which comprises reacting 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno [2,3-b][1,5]benzodiazepine of the formula (IA) with hydrogen chloride in an aqueous ethanol medium.

9. A process as claimed in claim 8, which comprises carrying out the reaction in a 8:2 mixture by volume of ethanol and water.

10. A process as claimed in claim 8, which comprises carrying out the reaction in a 9:1 mixture by volume of ethanol and water.

11. A process as claimed in claim 8, which comprises adding an aqueous hydrogen chloride solution to a suspension of 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno [2,3-b][1,5]benzodiazepine of the formula (IA) in ethanol.

12. A process as claimed in claim 11, which comprises using 37% aqueous hydrogen chloride solution.

13. A process as claimed in 8, which comprises carrying out the reaction at a temperature between 20° C. and 50° C., preferably at a temperature of 25° C.

14. 2-Methyl-4-(4-methylpiperazin-1-yl)-10H-thieno [2,3-b]-[1,5]benzodiazepine dihydrochloride trihydrate of the formula (IB).

15. 2-Methyl-4-(4-methylpiperazin-1-yl)-10H-thieno [2,3-b][1,5]benzodiazepine dihydrochloride trihydrate of the formula (IB) as claimed in claim 14, characterized by the X-ray powder diffraction pattern measured using CuK α radiation corresponding to diagram 1 and expressed in the following Table:

Position of diffraction lines and relative intensities (>5%)				
Peak No.	2 th [deg]	D(hkl) [Å]	I(abs) [cps]	I(rel) [%]
1	7.78	11.3638	219	8.74
2	8.17	10.8222	124	4.95
3	8.79	10.0557	2505	100.00
4	11.26	7.8611	143	5.71
5	15.54	5.7012	265	10.58
6	16.28	5.4444	478	19.08
7	17.55	5.0524	817	32.61
8	19.78	4.4885	933	37.25
9	22.26	3.9945	153	6.11
10	24.51	3.6315	348	13.89

-continued

Position of diffraction lines and relative intensities (>5%)				
Peak No.	2*th [deg]	D(hkl) [Å]	I(abs) [cps]	I(rel) [%]
11	25.75	3.4605	202	8.06
12	25.93	3.4362	131	5.23
13	31.30	2.8580	558	22.28
14	31.53	2.8375	202	8.06
15	32.38	2.7651	145	5.79
16	32.74	2.7355	404	16.13

16. Pharmaceutical compositions comprising as active ingredient 2-methyl-4-(4-methyl-piperazin-1-yl) -10H-thieno [2,3-b][1,5]benzodiazepine dihydrochloride trihydrate of the formula (IB) in admixture with inert solid or liquid pharmaceutical carriers and/or auxiliary agents.

17. A process for the preparation of a pharmaceutical composition as claimed in claim 16, which comprises admixing

2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno-[2,3-b][1,5]benzodiazepine dihydrochloride trihydrate of the formula (IB) with a pharmaceutically acceptable solid or liquid carrier and/or auxiliary agent and bringing the mixture to galenic form.

18. Use of 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno [2,3-b][1,5]-benzodiazepine dihydrochloride trihydrate of the formula (IB) for the preparation of pharmaceutical compositions.

19. Use of 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno [2,3-b][1,5]-benzodiazepine dihydrochloride trihydrate of the formula (IB) for the preparation of pharmaceutical compositions having antipsychotic activity.

20. A method for antipsychotic treatment/which comprises administering to the patient in need of such treatment a pharmaceutically efficient amount of 2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno [2,3-b][1,5]benzodiazepine dihydrochloride trihydrate of the formula (IB).

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