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(54) Title: A PROCESS FOR THE PREPARATION OF OLANZAPINE AND AN INTERMEDIATE THEREFOR

(57) Abstract: The invention relates to a process for the preparation of olanzapine which process consists in N-methylation of 2-methyl-4-piperazin-1-yl-10H-thieno[2,3-b][1,5]benzodiazepine. The invention relates also to a new intermediate compound, 2-methyl-4-(4-formyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]-benzodiazepine of formula III and a process for the preparation thereof.



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A process for the preparation of olanzapine and an intermediate therefor

Technical field

5 The invention relates to a process for olanzapine preparation, in particular to the process for olanzapine preparation using *N*-demethylolanzapine as a starting material, to a new *N*-demethylolanzapine derivative being an intermediate for olanzapine preparation and to a process for the preparation of this new
10 *N*-demethylolanzapine derivative using *N*-demethylolanzapine as a starting material.

Background of the invention

Olanzapine, or 2-methyl-4-[4-methyl-1-piperazinyl]-10H-thieno[2,3-*b*][1,5]-benzodiazepine, is a recognised drug acting on
15 the central nervous system and is known, among others, from EP 0454436.

In EP 0454436 there are disclosed processes for olanzapine preparation. One of the known procedures consists in reduction and cyclization reaction of 2-(2-nitroanilino)-5-methylthiophen-3-
20 carbonitrile with stannous chloride SnCl₂ in an aqueous-alcoholic solution of hydrogen chloride, followed by a reaction of thus formed 4-amino-2-methyl-10H-thieno[2,3-*b*][1,5]-benzodiazepine with *N*-methylpiperazine in an organic solvent such as anisole, toluene, dimethylformamide or dimethylsulphoxide (DMSO), preferably at a
25 temperature from 100 to 150°C, to produce olanzapine. Another of the known procedures consists in cyclization of 1-[[2-(2-aminoaniline)-5-methylthiophen-3-yl]carbonyl]-4-methylpiperazine, which is in turn obtained from methyl cyanoacetate in a series of laborious steps requiring specific complex reaction conditions, re-
30 actants and reducing agents as well as high-boiling and hard to remove solvents, like toluene, DMF, DMSO, etc.. The reaction yields of the prior-art processes are not high. Further disadvantage

of the prior-art processes is generation of impurities which have to be removed by repeated crystallizations, what has adverse effect on the process efficiency.

The aim of this invention was to develop a new process for olanzapine preparation, which would not require the use of hard-to-remove organic solvents.

Further aim was to develop a new process for olanzapine preparation, which would involve more simple chemical procedures, while allowing to obtain high yields of the final product having satisfactory purity.

To remove the aforementioned deficiencies of the prior art the applicants have developed new processes for olanzapine preparation, wherein *N*-demethylolanzapine, that is, 2-methyl-4-piperazin-1-yl-10H-thieno[2,3-*b*][1,5]benzodiazepine is used as the starting material, which is subjected to *N*-methylation to form olanzapine.

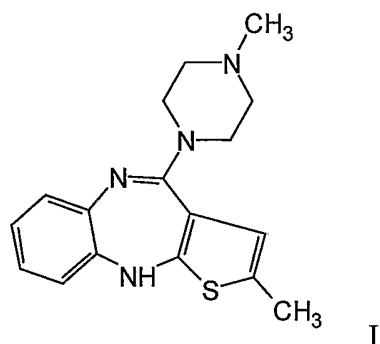
According to the processes of the invention crude olanzapine is produced which is as pure as the one obtained by prior art processes, in mild conditions with relatively short reaction times and low reaction temperatures. The use of low-volatile solvents and generation of great amounts of impurities is avoided.

N-Demethylolanzapine is a compound known as an olanzapine metabolite and is described by Calligaro *et al.*, *Biorg. & Med. Chem. Letters*, 1, 25-39, (1997), and in the publication of the international patent application WO00/30650. This compound can readily be made by a reaction of the known compound 4-amino-2-methyl-10H-thieno[2,3-*b*][1,5]benzodiazepine with piperazine as described by Calligaro *et al.*, *Biorg. & Med. Chem. Letters*, 1, 25-39, (1997).

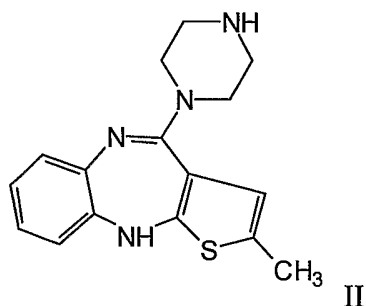
Detailed description of the invention

According to the first aspect of the invention, there is provided a process for the preparation of olanzapine of formula I

3



which comprises *N*-methylation of 2-methyl-4-piperazin-1-yl-10H-thieno[2,3-*b*][1,5]benzodiazepine (*N*-demethylolanzapine) of formula II



5

In the first variant of this first aspect of the invention said *N*-methylation is carried out by reductive *N*-methylation of *N*-demethylolanzapine with formaldehyde in the presence of a reducing agent.

10 In the first embodiment of this first variant a borohydride of a Group I or II metal can be used as said reducing agent and the reaction can be performed in an aqueous medium at a temperature in the range from -10°C to $+20^{\circ}\text{C}$.

An alkali-metal borohydride may be used, in particular sodium borohydride. The preferred reaction temperature range is
15 zero to 5°C .

The reductive *N*-methylation using formaldehyde in the presence of a borohydride is carried out in a simple manner which is as such known in the art. Typically, the reaction is performed in an
20 aqueous solution in the presence of acetic acid and sodium acetate as a buffer. Into the reaction mixture containing *N*-demethyl-

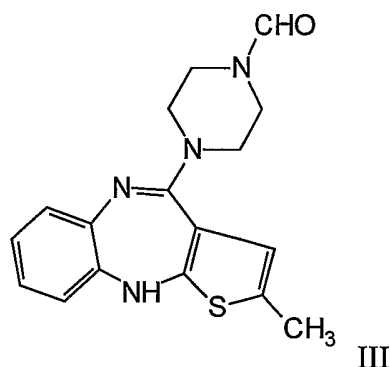
olanzapine and formaldehyde upon its cooling the borohydride is added portionwise. After completion of the reaction the mixture is made alkaline, thereby the crude olanzapine precipitates and the precipitate is subsequently isolated.

5 Alternatively, in the second embodiment of this first variant of the process, said reductive *N*-methylation with formaldehyde can also be carried out using formic acid as said reducing agent.

10 The *N*-methylation with formaldehyde in formic acid is generally known as the Eschweiler-Clarke reaction. The procedure is simple and is known in the art as such. In general, for one mole of olanzapine about 1.25 mole of formaldehyde is taken (in a little excess because of formaldehyde volatility) and 2-4 moles of formic acid which serves here also as a solvent in the reaction. Formaldehyde can also be used in the form of a 35-% formalin. The reaction
15 is carried out in an aqueous solution at the reflux temperature of the reaction mixture. After completion of the reaction, the reaction mixture is allowed to cool thereby crude olanzapine precipitates.

20 In the third embodiment of this variant first of the process, the said reductive *N*-methylation with formaldehyde can alternatively be carried out by low- or medium-pressure catalytic hydrogenation with hydrogen in the presence of a metal catalyst. As a metal catalyst can be used, for instance, platinum, palladium and nickel catalysts, e.g. Pd/C, Pt/C or Raney's nickel. The catalytic hydrogenation reaction in the presence of metallic catalysts is as
25 such well known in the art and is described in handbooks.

30 In a second variant of the first aspect of the invention, the said *N*-methylation is carried out in such a manner that *N*-demethylolanzapine of formula II is reacted with ethyl formate, optionally in the presence of a solvent, and subsequently thus produced 2-methyl-4-(4-formyl-1-piperazinyl)-10H-thieno[2,3-*b*]-[1,5]benzodiazepine (*N*-demethyl-*N*-formylolanzapine) of formula III



is subjected to a reduction.

The said reduction of (N-demethyl-N-formylolanzapine) can be carried out with a Group I or II metal borohydride in an aqueous medium at a temperature in the range from -10°C to $+20^{\circ}\text{C}$.

Preferably, an alkali-metal borohydride, in particular sodium borohydride, is used.

A preferred reaction temperature is a temperature in the range from zero to 5°C .

The borohydride reduction can be run similarly as described above for the first variant of the process.

The manner of carrying out the reaction with ethyl formate is simple and known in the art as such. Typically ethyl formate, which also serves as a reaction solvent, is used in considerable excess (about 70 moles of ethyl formate per 1 mole of *N*-demethylolanzapine). The amount of the ethyl formate used can be decreased by half, if an inert organic solvent, like tetrahydrofuran, is introduced as a co-solvent. The reaction is carried out at the reflux temperature of the reaction medium. On cooling *N*-demethyl-*N*-formylolanzapine precipitates from the reaction mixture.

In a third variant of the first aspect of the invention, the said *N*-methylation is carried out by direct methylation of *N*-demethylolanzapine with a methylating agent.

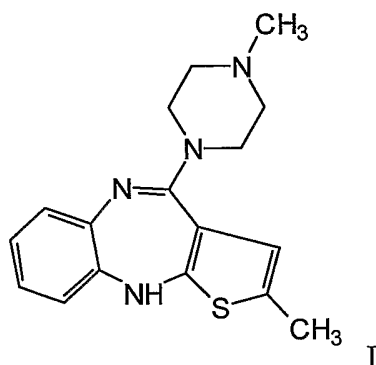
Methylating agents typically employed in the art for direct methylation of amines are suitable here. Non-limiting examples are methyl halogenides, dimethyl sulphate, methyl arylsulphonates

and methyl alkylsulphonates. Preferably methyl iodide is used. The procedure of the methylation reaction with methylating agents is generally known in the art as such. The methylation is typically carried out in inert polar solvents like alcohols, e.g. methanol, ethanol, isopropanol, butanol, etc.; ethers, e.g. THF, dioxan; chloroform; aprotic bipolar solvents, e.g. dimethylformamide, dimethylsulphoxide, in the presence of an organic base (a tertiary amine) or an inorganic base (like potassium carbonate), at ambient temperature. One mole of the methylating agent is used per one mole of N-demethylolanzapine.

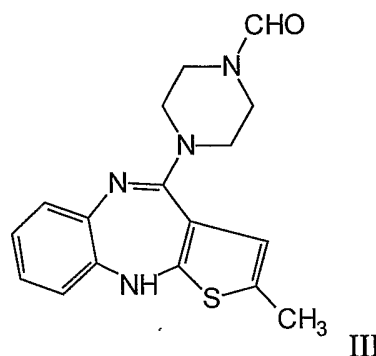
Preferably methyl iodide is used as the methylating agent.

In a second aspect the invention provides a process for the preparation of olanzapine (2-methyl-4-[4-methyl-1-piperazinyl]-10H-thieno-[2,3-*b*][1,5]-benzodiazepine), of the structural formula

15 I,



which process comprises reduction of 2-methyl-4-(4-formyl-1-piperazinyl)-10H-thieno[2,3-*b*][1,5]-benzodiazepine (*N*-demethyl-*N*-formylolanzapine) of formula III



Preferably the *N*-demethyl-*N*-formylolanzapine is produced in a reaction of *N*-demethylolanzapine with ethyl formate, optionally in the presence of a solvent.

Preferably, the said reduction reaction is carried out with a Group I or II metal borohydride as said reducing agent in an aqueous medium at a temperature in the range from -10°C to $+20^{\circ}\text{C}$.

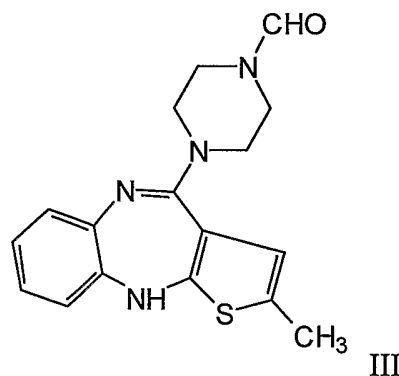
Preferably, an alkali-metal borohydride, in particular sodium borohydride, is used.

The preferred reaction temperature is a temperature in the range from 0°C to 5°C .

The reduction with borohydride is conducted using the procedure which as such is known in the art. Typically, the reaction is carried out in an aqueous medium, in the presence of acetic acid and sodium acetate as a buffer. The borohydride is added portionwise to the cooled reaction mixture containing *N*-demethyl-*N*-formylolanzapine. After reaction is complete, the reaction mixture is made alkaline, thereby crude olanzapine precipitates and the precipitate is subsequently isolated.

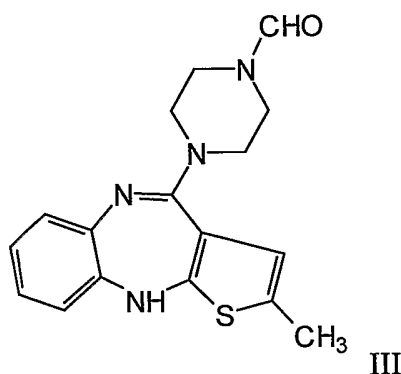
N-Demethyl-*N*-formylolanzapine is a new compound, not disclosed in the prior-art.

Accordingly, in its third aspect the invention provides also a new compound, *N*-demethylolanzapine derivative, that is 2-methyl-4-(4-formyl-1-piperazinyl)-10H-thieno[2,3-*b*][1,5]-benzodiazepine (*N*-demethyl-*N*-formylolanzapine) of formula III:

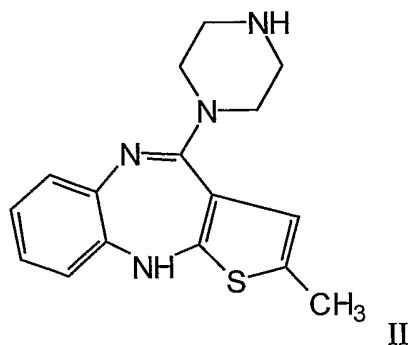


As stated above, *N*-demethyl-*N*-formylolanzapine is useful as an intermediate in the olanzapine preparation. Olanzapine is prepared by reduction of *N*-demethyl-*N*-formylolanzapine.

In the fourth aspect the invention provides a process for the
5 preparation of 2-methyl-4-(4-formyl-1-piperazinyl)-10H-thieno[2,3-*b*][1,5]-benzodiazepine (*N*-demethyl-*N*-formylolanzapine) of formula III,



which process comprises reaction of 2-methyl-4-piperazin-1-yl-
10 10H-thiene-[2,3-*b*][1,5]-benzodiazepine (*N*-demethylolanzapine) of formula II



with ethyl formate.

The reaction with ethyl formate is carried out as described
15 above for the second variant of the first aspect of the invention, that is for the preparation of olanzapine by reaction of *N*-demethylolanzapine of formula II with ethyl formate and then reduction.

The invention will be described in more detail with reference to the following, non-limiting examples, which should not be construed as the limitation of its scope.

Example 1.

5 *N*-Demethylolanzapine Preparation

A mixture of 4-amino-2-methyl-10H-thieno[2,3-*b*][1,5]benzodiazepine hydrochloride (3 g, 11.3 mmol), piperazine (7 g, 81.4 mmol) in 15 ml of DMSO and 15 ml of toluene was heated to reflux under an inert gas atmosphere, with no access of moisture of the
10 air. The reaction mixture was refluxed for 2 h.

After completion of the reaction the reaction mixture was cooled in an ice-bath and 30 ml of distilled water was added. The mixture was stirred at 5°C for 1 h until completion of the formation of a precipitate. The light-yellow precipitate was filtered off, washed
15 with water and dried in a vacuum desiccator over silica gel. 2.89 g (yield 85,7%) of *N*-Demethylolanzapine was obtained; m.p. 144.5°C.

Example 2

Olanzapine Preparation by Reductive Alkylation of *N*-Demethylolanzapine with Formaldehyde in the Presence of
20 Sodium Borohydride

A mixture of *N*-demethylolanzapine (10 g, 33.5 mmol), anhydrous sodium acetate (6.6 g, 80 mmol) (or an equivalent amount of the acetate hydrate), 34 ml glacial acetic acid, 20 ml of 37-% aqueous formalin and 100 ml of distilled water was cooled to 0°C.
25 Subsequently, sodium borohydride (8.5 g, 0.22 mmol) was added in small portions while maintaining temperature at 0°C and with vigorous stirring. Upon addition of the total amount of the borohydride the foaming solution was stirred at a low temperature for 1 h, then it was made alkaline to a pH = ca. 9 with 2N NaOH aq. The
30 light-yellow precipitate produced was filtered off and washed with water. The crude product was dried in a circulating-air oven at ca. 25°C. 10.2 g of olanzapine was obtained with a purity 97% as de-

terminated by HPLC (yield: 97,3%).

Example 3

Olanzapine Preparation by Methylation of N-Demethyl-
olanzapine with Methyl Iodide

5 *N*-Demethylolanzapine (2.8 g, 9.4 mmol), methyl iodide (1.33 g, 9.4 mmol), and potassium carbonate (3.89 g, 28.2 mmol) in 20 ml of methanol were stirred for 8 h at a room temperature. Subsequently, 20 ml of distilled water were added into the mixture and the whole was cooled in an ice-bath until a light-yellow precipitate
10 was formed. The precipitate was filtered off, washed with water to obtain 1.5 g of olanzapine of a 90% purity as determined by HLPC (yield: 51%).

Example 4

Olanzapine Preparation by Reductive *N*-Methylation with For-
15 maldehyde in Formic Acid (the Eschweiler-Clarke Reaction)

A mixture of 20 ml of 85-% formic acid and 14 ml of an 37-% aqueous formaldehyde was cooled in an ice-bath to 0°C. While cooling *N*-demethylolanzapine (50 g, 0.168 mol) was added under vigorous stirring. After addition of the amine the mixture was
20 heater to reflux in an oil bath and maintained under reflux for 8 h. Then the mixture was cooled in an ice-bath and gently made alkaline to a pH = ca. 8 with 2N NaOH aq. The yellow precipitate formed was filtered off, washed with water and dried. Crude olanzapine was obtained (40 g) of a purity of 95% by HPLC (yield:
25 76,2%).

Example 5

Preparation of *N*-demethyl-*N*-formylolanzapine (i.e. 2-methyl-4-(4-formyl-1-piperaziny)-10H-thieno[2,3-b][1,5]-benzodiazepine)

A solution of 5 g (16.8 mmol) of *N*-demethylolanzapine in 100
30 ml of ethyl formate and 100 ml of tetrahydrofuran was kept under reflux for 20 h. Subsequently, the mixture was cooled in an ice-bath. The pale beige precipitate formed was filtered off and dried in

the air. The product, 2-methyl-4-(4-formyl-1-piperaziny)-10H-thieno[2,3-*b*][1,5]-benzodiazepine was obtained in a 4 g quantity (yield: 72,9%). The structure of the compound produced was confirmed by the NMR and MS analyses.

- 5 NMR (CDCl₃) δ ppm: 2.32 (d, J = 1.2 Hz, 3H); 3.38-3.69 (m, 8H); 4.88 (s, 1H); 6.29 (d, J = 1.2 Hz, 1H); 6.57-7.07 (m, 4H); 8.11 (s, 1H), MS: 255 (100%), M-1 = 325 (58%), M = 326 (12%).

Example 6

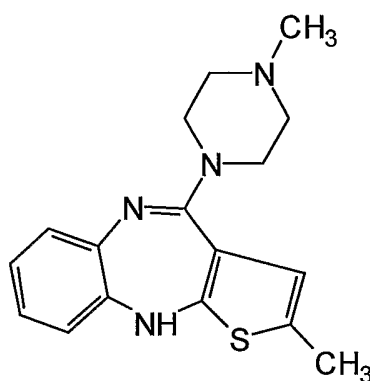
Preparation of olanzapine by reduction of *N*-demethyl-*N*-formylolanzapine

10

- A mixture of 2-methyl-4-(4-formyl-1-piperaziny)-10H-thieno[2,3-*b*][1,5]-benzodiazepine (3 g, 9.2 mmol), sodium acetate (1 g, 12.2 mmol), 15 ml of glacial acetic acid and 15 ml of distilled water was cooled in an ice-bath to 0°C. Under vigorous stirring sodium
- 15 borohydride (4 g, 9.4 mmol) was added portionwise. The stirring and cooling were continued for about 0.5 h after completion of the borohydride addition. Subsequently, the mixture was made alkaline to a pH = ca. 9 with 2N NaOH aq. The light-yellow precipitate formed was filtered off, washed with water and dried in an air-
- 20 circulation oven at a temperature of ca. 25°C. Olanzapine was obtained (2.5 g) of an 88% purity as determined by HPLC (yield: 86,9%).

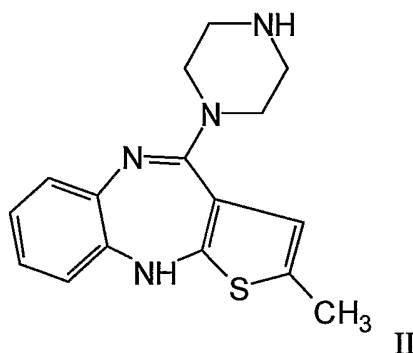
Patent Claims

1. A process for the preparation of olanzapine of formula I



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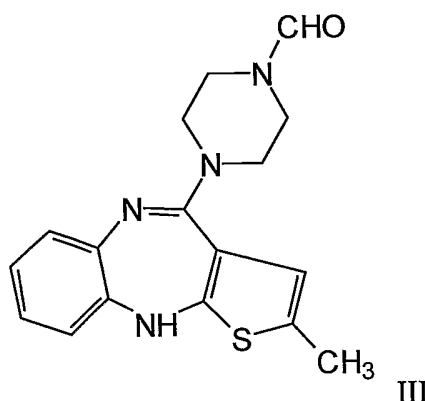
which process comprises N-methylation of 2-methyl-4-piperazin-1-yl-10H-thieno[2,3-*b*][1,5]benzodiazepine (*N*-demethylolanzapine) of formula II



II

2. The process according to Claim 1, wherein said N-methylation of *N*-demethylolanzapine is performed by reductive N-methylation with formaldehyde in the presence of a reducing agent.
3. The process according to Claim 2, wherein said reductive N-methylation is performed with a Group I or II metal borohydride as a reducing agent in an aqueous environment at a temperature in the range from -10°C to +20°C and.

4. The process according to Claim 3, wherein the borohydride is an alkaline-metal borohydride, in particular sodium borohydride.
5. The process according to Claim 3 or 4, wherein the said reductive N-methylation is performed at a temperature in the range from 0°C to 5°C.
6. The process according to Claim 2, wherein said reductive N-methylation is performed in an aqueous medium with formic acid as the reducing agent.
- 10 7. The process according to Claim 2, wherein said reductive N-methylation is performed by catalytic hydrogenation in the presence of a metal catalyst.
8. The process according to Claim 1, wherein said N-methylation of N-demethylolanzapine is performed by reacting N-demethylolanzapine with ethyl formate, optionally in the presence of a solvent, to form 2-methyl-4-(4-formyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (N-demethyl-N-formylolanzapine) of formula III
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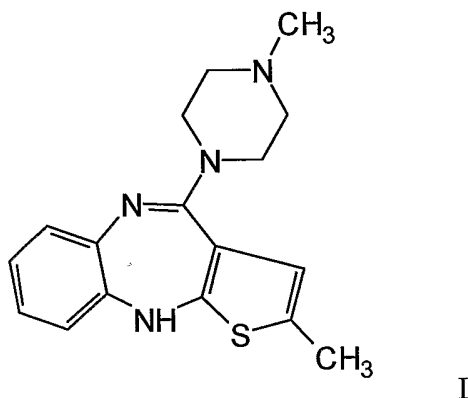


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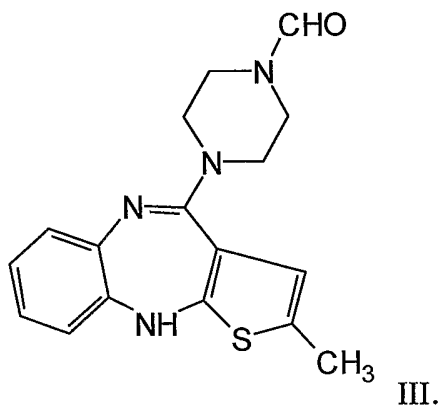
and then reducing N-demethyl-N-formylolanzapine of formula III thus formed.

9. The process according to Claim 8, wherein said reduction is carried out with a Group I or II metal borohydride in an aqueous medium at a temperature in the range from -10 to +20°C.
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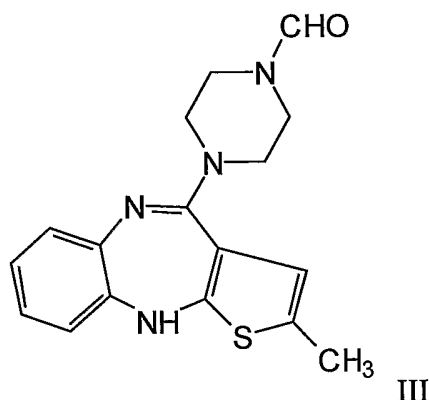
10. The process according to Claim 9, wherein said borohydride is an alkali-metal borohydride, in particular sodium borohydride.
11. The process according to Claim 1, wherein said N-methylation of *N*-demethylolanzapine is performed with a methylating agent.
12. The process according to Claim 11, wherein said methylating agent is selected from the group consisting of methyl halogenides, dimethyl sulphate, methyl arylsulphonates and methyl alkylsulphonates.
13. The process according to Claim 12, wherein said methylating agent is methyl iodide.
14. A process for the preparation of olanzapine of formula I



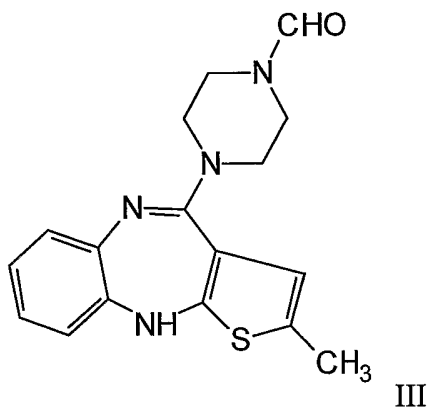
- 15 which process comprises reduction of 2-methyl-4-(4-formyl-1-piperazinyl)-10H-thieno[2,3-*b*][1,5]benzodiazepine (*N*-demethyl-*N*-formylolanzapine) of formula III



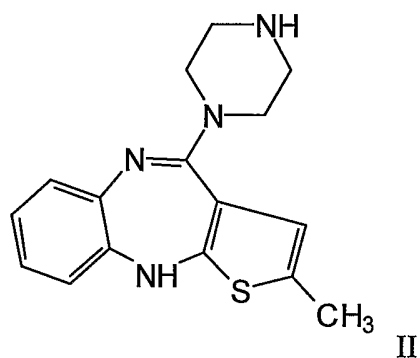
15. The process according to Claim 14, wherein said reduction is carried out with a Group I or II metal borohydride in an aqueous medium at a temperature in the range of -10 to +20°C.
16. The process according to Claim 15, wherein said borohydride is an alkali-metal borohydride, in particular sodium borohydride.
17. The process according to any of the claims 14 to 16, wherein said *N*-demethyl-*N*-formylolanzapine is produced in a reaction of *N*-demethylolanzapine with ethyl formate, optionally in the presence of a solvent.
18. 2-Methyl-4-(4-formyl-1-piperaziny)-10H-thieno[2,3-*b*][1,5]-benzodiazepine (*N*-demethyl-*N*-formylolanzapine) of formula III



19. A process for the preparation of 2-methyl-4-(4-formyl-1-piperaziny)-10H-thieno[2,3-*b*][1,5]-benzodiazepine (*N*-demethyl-*N*-formylolanzapine) of formula III,



which process comprises reaction of 2-methyl-4-piperazin-1-yl-10H-thiene[2,3-*b*][1,5]benzodiazepine (*N*-demethylolanzapine) of formula II



with ethyl formate, optionally in the presence of a solvent.

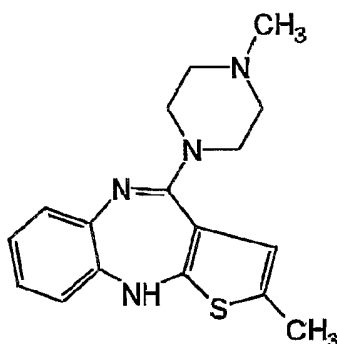
AMENDED CLAIMS

[received by the International Bureau on 26 November 2003 (26.11.03);
original claims 1-19 replaced by new claims 1-15 (5 pages)]

+ STATEMENT

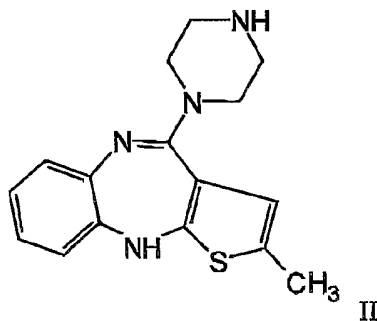
Patent Claims

1. A process for the preparation of olanzapine of formula I



I

which process comprises reductive N-methylation of 2-methyl-4-piperazin-1-yl-10H-thieno[2,3-b][1,5]benzodiazepine (*N*-demethyl-olanzapine) of formula II



II

- with formaldehyde in the presence of a reducing agent.

2. The process according to Claim 1, wherein said reductive N-methylation is performed with a Group I or II metal borohydride as the reducing agent in an aqueous environment at a temperature in the range from -10°C to $+20^{\circ}\text{C}$.

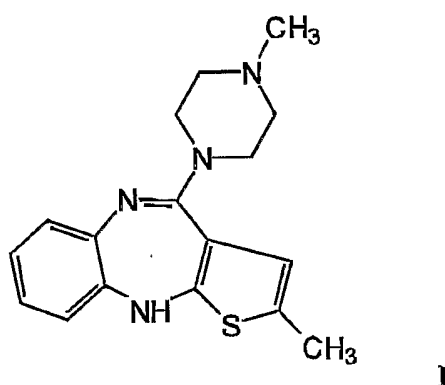
3. The process according to Claim 2, wherein the borohydride is an alkaline-metal borohydride, in particular sodium borohydride.

4. The process according to Claim 2 or 3, wherein the said reductive N-methylation is performed at a temperature in the range from 0°C to 5°C.

5. The process according to Claim 1, wherein said reductive N-methylation is performed in an aqueous medium with formic acid as the reducing agent.

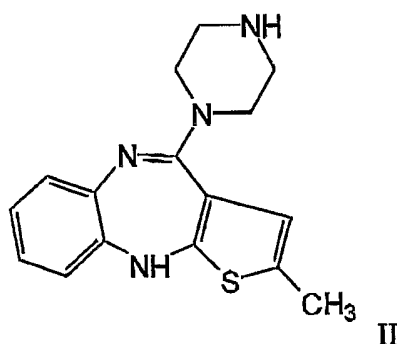
6. The process according to Claim 1, wherein said reductive N-methylation is performed by catalytic hydrogenation in the presence of a metal catalyst.

10 7. A process for the preparation of olanzapine of formula I

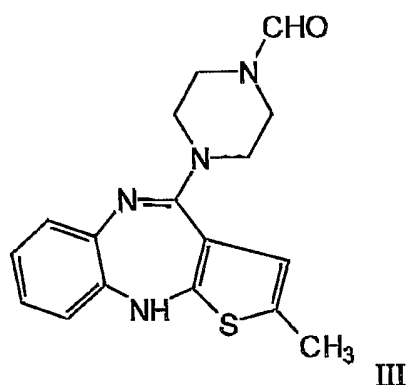


which process comprises reacting 2-methyl-4-piperazin-1-yl-10H-thieno[2,3-b][1,5]benzodiazepine (*N*-demethylolanzapine) of formula

15 II



with ethyl formate, optionally in the presence of a solvent, to form 2-methyl-4-(4-formyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (*N*-demethyl-*N*-formylolanzapine) of formula III

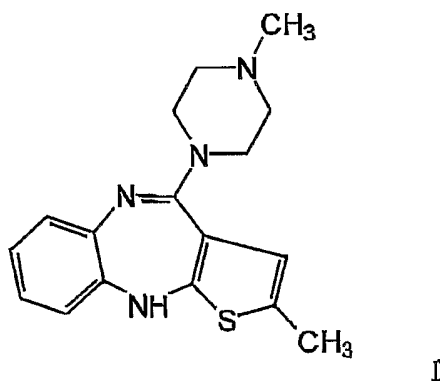


and then reducing *N*-demethyl-*N*-formylolanzapine of formula III thus formed.

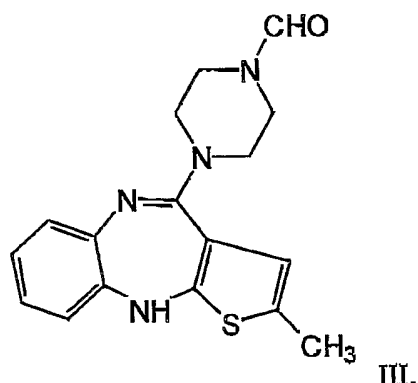
5 8. The process according to Claim 7, wherein said reduction is carried out with a Group I or II metal borohydride in an aqueous medium at a temperature in the range from -10 to +20°C.

9. The process according to Claim 8, wherein said borohydride is an alkali-metal borohydride, in particular sodium
10 borohydride.

10. A process for the preparation of olanzapine of formula I



which process comprises reduction of 2-methyl-4-(4-formyl-1-piperazinyl)-10H-thieno[2,3-*b*][1,5]benzodiazepine (*N*-demethyl-*N*-formylolanzapine) of formula III
15 formylolanzapine) of formula III

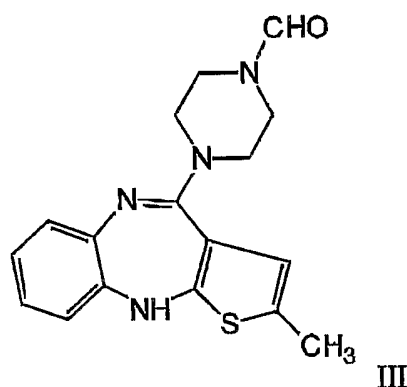


11. The process according to Claim 10, wherein said reduction is carried out with a Group I or II metal borohydride in an aqueous medium at a temperature in the range of -10 to +20°C.

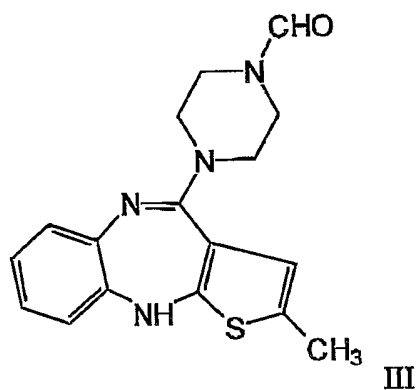
5 12. The process according to Claim 11, wherein said borohydride is an alkali-metal borohydride, in particular sodium borohydride.

13. The process according to any of the claims 10 to 12, wherein said *N*-demethyl-*N*-formylolanzapine is produced in a reaction of *N*-demethylolanzapine with ethyl formate, optionally in
10 the presence of a solvent.

14. 2-Methyl-4-(4-formyl-1-piperazinyl)-10H-thieno[2,3-*b*]-[1,5]benzodiazepine (*N*-demethyl-*N*-formylolanzapine) of formula III

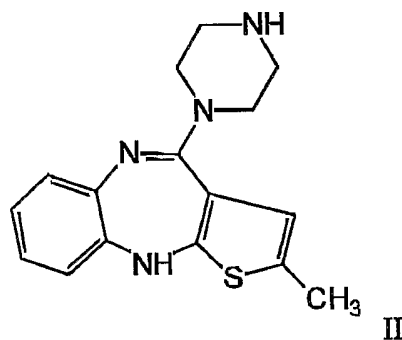


15 15. A process for the preparation of 2-methyl-4-(4-formyl-1-piperazinyl)-10H-thieno[2,3-*b*][1,5]-benzodiazepine (*N*-demethyl-*N*-formylolanzapine) of formula III,



which process comprises reaction of 2-methyl-4-piperazin-1-yl-10H-thieno[2,3-*b*][1,5]benzodiazepine (*N*-demethylolanzapine) of formula II

5



with ethyl formate, optionally in the presence of a solvent.

Statement under article 19(1)

Original claim 1 has been amended by incorporating the contents of original claim 2 therein.

Original claim 7 has been amended by making it independent and incorporating the preamble of original claim 1 therein.

Original claim 3 has been amended by canceling the word "and" in line 17.

Original claims 2, 11, 12 and 13 have been cancelled.

Original claims 3 to 7 and 9, 10, 14 to 19 have been renumbered to bear the numbers 4 to 6, 8, 9, 10 to 15, respectively.

Additionally, dependence of original claims 3 to 7, 9, 10, 14 to 19 has been amended in accordance with new numbering.

The amendments made imply the necessity of amending respective passages on sheets 3 to 5 of the description as well as cancellation of the passage from page 5. line 21 to page 6, line 11.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 03/02181

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D495/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CALLIGARO D O ET AL: "The synthesis and biological activity of some known and putative metabolites of the atypical antipsychotic agent olanzapine (LY170053)" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 7, no. 1, 7 January 1997 (1997-01-07), pages 25-30, XP004135960 ISSN: 0960-894X page 27; figure 1	1-10
X	GB 1 533 235 A (LILLY INDUSTRIES LTD) 22 November 1978 (1978-11-22) claims 1,9	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

17 September 2003

Date of mailing of the international search report

26/09/2003

Name and mailing address of the ISA

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Authorized officer

Grassi, D

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 03/02181

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1 (part), 2-7

A process in which the N-methylation is performed by reductive N-methylation.

2. Claims: 1 (part), 8-10,14-19

A process in which the N-methylation is performed by reacting N-demethylolanzapine with ethyl formate.

3. Claims: 1 (part),11-13

A process in which the N-methylation is performed by reacting N-demethylolanzapine with a methylating agent.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 03/02181

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