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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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(54) Title: IMPROVED PROCESSES FOR THE SYNTHESIS OF OLANZAPINE

(57) Abstract: There is provided a process for the preparation of olanzapine comprising: i) reacting 4-amino-2-methyl-10*H*-thieno-[2, 3-*b*][1,5]benzodiazepine and N-methylpiperazine in a C1 to C4 alcoholic solvent or mixture thereof at suitable temperature and for a suitable time, ii) cooling the reaction mixture, and iii) isolating the precipitated olanzapine.

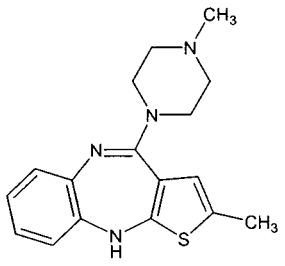
WO 2009/000067 A1

TITLE

IMPROVED PROCESSES FOR THE SYNTHESIS OF OLANZAPINE

BACKGROUND OF THE INVENTION

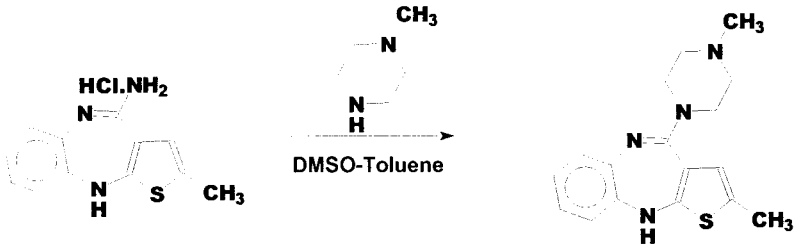
Olanzapine (**1**, 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5] benzodiazepine) is a second generation anti-psychotic drug marketed as Zyprexa® by Eli Lilly and Company. It is useful for the treatment of disorders such as schizophrenia, bipolar disorder, psychotic depression and Tourette syndrome. This pharmaceutical acts as an antagonist on 5-HT_2 serotonin receptors as well as the D_1/D_2 dopamine receptors and also exhibits anticholinergic and antimuscarine properties.



1, Olanzapine (*Zyprexa*®)

Structurally olanzapine belongs to the benzodiazepine family. The synthesis of olanzapine was disclosed, for example, in U.S. 5,229,382, involving the condensation of 4-amino-2-methyl-10*H*-thieno-[2,3-*b*][1,5]benzodiazepine and N-methylpiperazine in a mixture of the high boiling and aprotic solvents, dimethylsulfoxide and toluene (Scheme 1). However, this process suffers from the use of high volumes of solvents and the necessity of having a large excess of N-methylpiperazine. Of equal importance is the low yield (less than 35%) and poor recoverability of the dimethylsulfoxide solvent.

Scheme 1



EP 454436 B1 discloses the synthesis of olanzapine *via* the titanium tetrachloride ($TiCl_4$)-mediated reaction of N-methylpiperazine and methyl-2-(2-aminoanilino)-5-methylthiophene-3-carboxylate. The use of the toxic and environmentally hazardous reagent $TiCl_4$ makes the process unattractive on an industrial scale.

US 2004/0048854 A1 teaches a modified process for the preparation of olanzapine using only dimethylsulfoxide as the solvent, but this process requires tedious work-up steps employing acid and base treatments, and halogenated solvents. Also, like the route described in U.S. 5,229,382, the dimethylsulfoxide solvent is very difficult to recover.

US 2005/0159408 discloses a method of synthesizing olanzapine without using solvent, where N-methylpiperazine is used in large excess and the reaction occurred under harsh conditions (high temperature over 125°C). Again the work-up is tedious and some solvents, like dimethylsulfoxide used in the work-up, have poor recoverability. In the same patent application, processes for preparing olanzapine are disclosed where low boiling organic solvents such as acetone, acetonitrile, hexane, heptane and dimethylformamide are used and the yield, ranged from 51% to 91%. However, the product is isolated in granular form and the purity is not reported.

Therefore, it is an object of the present invention to develop a robust and high-yielding process for producing olanzapine which is suitable for

commercial scale production and overcomes the deficiencies in the prior art processes.

Further and other objects of the invention will become apparent to those skilled in the art when considering the following summary of the invention and the more detailed description of the embodiments of the invention described herein.

SUMMARY OF THE INVENTION

According to one aspect of the invention, there is provided a process for the preparation of olanzapine comprising:

i) reacting 4-amino-2-methyl-10*H*-thieno-[2,3-*b*][1,5]benzodiazepine and N-methylpiperazine in a C1 to C4 alcoholic solvent or mixture thereof at suitable temperature and for a suitable time,

ii) cooling the reaction mixture, and

iii) isolating the precipitated olanzapine.

Optionally, water is added to the reaction mixture and the precipitated olanzapine is isolated.

Surprisingly, we have found that low boiling alcohols represent highly desirable solvents for the condensation reaction of 4-amino-2-methyl-10*H*-thieno-[2,3-*b*][1,5]benzodiazepine and N-methylpiperazine. The advantages of these solvents relative to the processes of the prior art include: 1) environmentally friendly solvents are employed; 2) toxic reagents, like $TiCl_4$, are not required; 3) solvents can be easily recovered and re-used; and 4) the olanzapine produced is isolated in high yield and purity.

According to another aspect of the invention, the use of a C1 to C4 alcohol as the reaction medium in the process results in a surprisingly rapid reaction completion, permitting the use of relatively low temperatures and allowing

reduced process cycle times. Moreover, the use of a C1 to C4 alcohol as a reaction medium for the processes of the instant invention furnishes olanzapine which meets the high purity (>99.5%) specifications for use as a pharmaceutical active.

According to yet another aspect of the invention, since C1 to C4 alcohols are largely water miscible, the work-up procedure is streamlined because water can be employed as an effective anti-solvent to precipitate the olanzapine product.

In a preferred embodiment, olanzapine can be produced by reacting 4-amino-2-methyl-10*H*-thieno-[2,3-*b*][1,5]benzodiazepine with N-methylpiperazine in a C1 to C4 alcoholic solvent or solvent mixture at suitable temperature and for a suitable time. The C1 to C4 alcoholic solvent can be selected from methanol, ethanol, n-propanol, 2-propanol and 2-butanol, n-butanol, isobutanol, and *tert*-butanol, and combinations thereof. The most preferred alcoholic solvents are 2-propanol and 2-butanol. The volume of the solvent used can be 1 to 8 volumes, preferably 2 to 6 volumes, and most preferably 2 to 4 volumes. The volume of N-methylpiperzine used can be 1 to 5 volumes, more preferably 2 to 3 volumes, and most preferably 2 to 2.5 volumes. The term volumes refers to litres of solvent per kilograms of 4-amino-2-methyl-10*H*-thieno-[2,3-*b*][1,5]benzodiazepine.

The reaction temperature can be between about 50°C to about 150°C, preferably about 80°C to about 120°C, and most preferably about 90°C to about 120°C.

The reaction time can range from 5 to 30 hours, preferably 10 to 25 hours and most preferably 10 to 20 hours.

In another embodiment of the invention, after reaction completion, the reaction mixture can be cooled to 0°C to 75°C, more preferably 10°C to 65°C,

and most preferably 20°C to 60°C, wherein the product can be isolated by direct filtration; or optionally water can be added as an anti-solvent to facilitate precipitation and isolation by filtration. For the processes where water is used to effect precipitation, the amount of water required can be 0.1 to 8 volumes, preferably 0.5 to 6 volumes, and most preferably 1 to 4 volumes, wherein volumes has the same meaning as set out above. The use of water as an anti-solvent has the additional unexpected advantage of removing the synthetic by-products and the reaction solvent. Filtration of the product and washing with water also avoids a tedious liquid-liquid extractive work-up which represents a deficiency in prior art processes.

The following non-limiting examples further illustrate the manner of carrying out the inventive processes described herein.

Example 1:

4-Amino-2-methyl-10*H*-thieno-[2,3-*b*][1,5]benzodiazepine (50 g, 0.19 mol), N-methylpiperazine (125 mL, 2.5 vol) and 2-propanol (150 mL, 3 vol) were charged into a three-necked round bottom flask, equipped with reflux condenser, overhead stirrer, and thermometer. The reaction mixture was heated to reflux (about 100°C) slowly under a nitrogen atmosphere and then refluxed overnight. The reaction mixture was allowed to cool slowly to below 40°C (about 1h), whereupon solid precipitates out. This precipitate was then isolated by filtration and the resulting light yellow solid was twice washed with 2-propanol (100 mL). The light yellow solid was stirred with water (4 volumes) for 2.5 hours, filtered, and the resulting solid, was washed twice with water (2 volumes) and dried to furnish olanzapine (47 g, 80%).

Example 2:

4-Amino-2-methyl-10*H*-thieno-[2,3-*b*][1,5]benzodiazepine (100 g, 0.38 mol), N-methylpiperazine (250 mL, 2.5 vol) and 2-butanol (200 mL, 2 vol) were charged into a three-necked round bottom flask equipped with a reflux condenser, overhead stirrer, and thermometer. The reaction mixture was heated to reflux at 118°C under a nitrogen atmosphere and refluxed

overnight. The reaction mixture was allowed to cool to below 55°C whereupon water (300 mL, 3 volumes) was added to precipitate out the solid. It was isolated by Buchner filtration and the light yellow solid was washed twice with 25% aqueous 2-butanol (100 mL) and then once with 2-butanol (100 mL) and dried to provide olanzapine in 84% yield (98.7 g).

Example 3:

4-Amino-2-methyl-10*H*-thieno-[2,3-*b*][1,5]benzodiazepine (100 g, 0.38 mol), N-methylpiperazine (250 mL, 2.5 vol) and 2-propanol (200 mL, 2 vol) were charged into a three-necked round bottom flask equipped with reflux condenser, overhead stirrer, and thermometer. The reaction mixture was heated to reflux at 102°C under a nitrogen atmosphere overnight. The reaction mixture was allowed to cool to below 55°C whereupon water (250 mL, 2.5 volumes) was added to precipitate out the solid. The light yellow solid was isolated by Buchner filtration and twice washed with 25% aqueous 2-propanol (100 mL) and then once with 2-propanol (100 mL). It was dried *in vacuo* to provide olanzapine in 86.5% yield (101.7 g).

Example 4:

4-Amino-2-methyl-10*H*-thieno-[2,3-*b*][1,5]benzodiazepine (5 g, 0.02 mol), N-methylpiperazine (12.5 mL, 2.5 vol) and 1-propanol (15 mL, 3 vol) were charged into a three-necked round bottom flask equipped with a reflux condenser, overhead stirrer, and thermometer. The reaction mixture was heated slowly to 110°C under a nitrogen atmosphere and then refluxed overnight. The reaction mixture was cooled to below 50°C whereupon water (15 mL, 3 volumes) was added to precipitate out the solid, which was isolated by Buchner filtration. The resulting light yellow solid was washed twice with water (5 mL) and dried to afford olanzapine in 89% yield (5.22 g).

Example 5:

4-Amino-2-methyl-10*H*-thieno-[2,3-*b*][1,5]benzodiazepine (5 g, 0.02 mol), N-methylpiperazine (12.5 mL, 2.5 vol) and ethanol (15 mL, 3 vol) were charged into a three-necked round bottom flask equipped with a reflux condenser,

overhead stirrer, and thermometer. The reaction mixture was slowly heated to reflux (94°C) under a nitrogen atmosphere and kept at this temperature overnight. The reaction mixture was cooled to below 50°C and water (10 mL, 2 vol) was added to precipitate out the solid, which was isolated by filtration. The light yellow solid was washed twice with water (5 mL) and dried to furnish pure olanzapine in 72% yield (4.2 g).

Example 6:

4-Amino-2-methyl-10H-thieno-[2,3-b][1,5]benzodiazepine (5 g, 0.02 mol), N-methylpiperazine (12.5 mL, 2.5 vol) and methanol (15 mL, 3 vol) were charged into a three-necked round bottom flask equipped with a reflux condenser, overhead stirrer, and thermometer. The reaction mixture was slowly heated under nitrogen to reflux (75°C) and kept at this temperature overnight. The reaction mixture was allowed to cool to below 50°C and water (15 mL, 3 vol) was added. The precipitated light yellow solid was isolated by filtration, then was washed twice with water (5 mL) and dried to provide olanzapine in 74% yield (4.35 g).

As many changes can be made to the invention without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

CLAIMS

1. A process for the preparation of olanzapine comprising:
   i) reacting 4-amino-2-methyl-10*H*-thieno-[2,3-*b*][1,5]benzodiazepine and N-methylpiperazine in a C1 to C4 alcoholic solvent or mixture at suitable reaction temperature and for a suitable reaction time,
   ii) cooling the reaction mixture, and
   iii) isolating the precipitated olanzapine.

2. The process of claim 1 wherein water is added after the cooling of the reaction mixture.

3. The process of claim 1 or 2 wherein the alcoholic solvent is selected from the group consisting of methanol, ethanol, n-propanol, 2-propanol, 2-butanol and combinations thereof.

4. The process of claim 1 or 2 wherein the alcoholic solvent is methanol.

5. The process of claim 1 or 2 wherein the alcoholic solvent is ethanol.

6. The process of claim 1 or 2 wherein the alcoholic solvent is n-propanol.

7. The process of claim 1 or 2 wherein the alcoholic solvent is 2-propanol.

8. The process of claim 1 or 2 wherein the alcoholic solvent is 2-butanol.

9. The process of claim 1 to 8 wherein the reaction temperature is about 50°C to about 150°C.

10. The process of claim 1 to 8 wherein the reaction temperature is about 80°C to about 120°C.

11. The process of claim 1 to 8 wherein the reaction time is 5 to 30 h.

12. The process of claim 1 to 8 wherein the olanzapine is isolated directly as a solid.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2008/001123

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***C07D 495/04*** (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D 495/04

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
STN (chemical names), Delphion (Olanzapine), Canadian Patent Database, Espacenet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO96/30374 Bunnell et al. 3 October 1996 (3-10-1999) Pages 1-2 of description, exemple 1 and claim 10	1-7, 9-12
Y	WO05/063771 Dolitzky et al. 14 July 2005 (14/07/2005) Pages 2-4 of description and Claims	1-7, 9-12

[ ] Further documents are listed in the continuation of Box C.

[X] See patent family 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 application or patent but published on or after the international filing date

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"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 July 2008 (22-07-2008)	08 September 2008 (08-09-2008)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Eliane Rutinduka 819- 956-0527

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2008/001123

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