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सत्यमेव जयते

क्रमांक : 033119120
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GOVERNMENT OF INDIA
पेटेंट कार्यालय
THE PATENT OFFICE

पेटेंट प्रमाणपत्र
PATENT CERTIFICATE

(Rule 74 Of The Patents Rules)

पेटेंट सं. / Patent No.	:	389779
आवेदन सं. / Application No.	:	201731028156
फाइल करने की तारीख / Date of Filing	:	08/08/2017
पेटेंटी / Patentee	:	WEST BENGAL CHEMICAL INDUSTRIES LIMITED

प्रमाणित किया जाता है कि पेटेंटी को उपरोक्त आवेदन में यथाप्रकटित A COST EFFECTIVE PROCESS FOR PREPARATION OF ENCLOMIPHENE CITRATE नामक आविष्कार के लिए, पेटेंट अधिनियम, १९७० के उपबंधों के अनुसार आज तारीख 8th day of August 2017 से बीस वर्ष की अवधि के लिए पेटेंट अनुदत्त किया गया है।

It is hereby certified that a patent has been granted to the patentee for an invention entitled A COST EFFECTIVE PROCESS FOR PREPARATION OF ENCLOMIPHENE CITRATE as disclosed in the above mentioned application for the term of 20 years from the 8th day of August 2017 in accordance with the provisions of the Patents Act,1970.

एकस्य कार्यालय THE PATENT OFFICE GOVT.OF INDIA भारत सरकार

अनुदान की तारीख :
Date of Grant : 19/02/2022

पेटेंट नियंत्रक
Controller of Patent

टिप्पणी - इस पेटेंट के नवीकरण के लिए फीस, यदि इसे बनाए रखा जाना है, **8th day of August 2019** को और उसके पश्चात प्रत्येक वर्ष मे उसी दिन देय होगी।

Note. - The fees for renewal of this patent, if it is to be maintained will fall / has fallen due on 8th day of August 2019 and on the same day in every year thereafter.

389779

Indian Patent

Patent Number: 389779
Date of Patent: 19 Feb, 2022

A cost-effective process of preparation of Enclomiphene Citrate

Inventor: **NIladri Samanta**

Assignee: **West Bengal Chemical Industries Limited**

Application: **201731028156**

Filed: **08 Aug, 2017**

ABSTRACT:

The invention disclosed herein is an improved cost-effective process for preparation of Enclomiphene citrate in high yield and improved quality.

2 Claims, No Drawings

Claims

1. A cost effective, improved process for preparation of Enclomiphene citrate in high yield and purity comprises;
   (i) Reacting methanolic solution of clomiphene citrate with racemic BNPA to obtain BNPA-Enclomiphene salt followed by washing with chilled methanol until the Z-isomer content is below 5 %.
   (ii) Extracting Enclomiphene from BNPA-Enclomiphene salt of step
   (iii) Using aqueous ammonia and organic solvent followed by addition of citric acid in ethanol to the organic layer to yield Enclomipheme citrate.
2. The process as claimed in claim 1; wherein methanol/ethanol is the organic solvent used of step (ii).

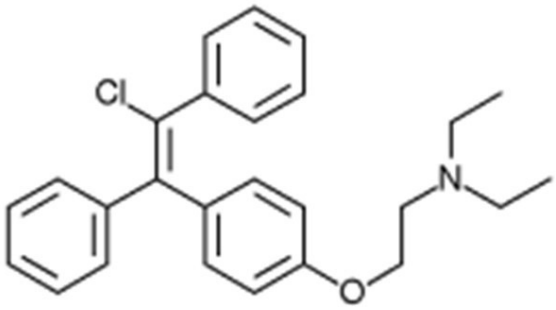
1. TITLE OF THE INVENTION: "A COST EFFECTIVE PROCESS FOR PREPARATION OF ENCLOMIPHENE CITRATE"
APPLICANT: NAME: WEST BENGAL CHEMICAL INDUSTRIES LIMITED NATIONALITY: An Indian Company incorporated under the Companies Act, 1956 ADDRESS: 145/1, Jessore Road, Kolkata 700 089, India.
3. PREAMBLE TO THE DESCRIPTION:
The following specification particularly describes the invention and the manner in which it is to be performed.

Technical field of the Invention:

The present invention relates to a cost effective and improved process for preparation of Enclomiphene citrate.

Background of the Invention:

Enclomiphene, chemically is 2-[4-[(E)-2-Chloro-1,2-diphenylethenyl]phenoxy]-N,N-Diethylethanamineof formula (I). Enclomiphene is a non-steroidal selective estrogen receptor modulator (SERM) of the Triphenylethylene group.



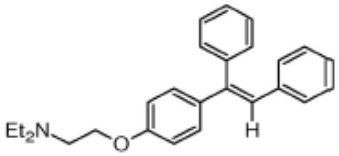
(I)

Enclomifene acts by antagonizing the estrogen receptor in the pituitary gland, which reduces adverse response by estrogen on the hypothalamic-pituitary-gonadal axis, thereby increasing gonadotropin secretion and hence gonadal production of testosterone.

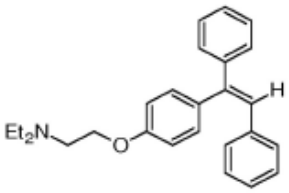
Enclomifene is one of the two stereoisomers of clomifene, which itself is a non-racemic mixture of 38% zuclomifene and 62% enclomifene. Enclomifene is the (E)-enantiomer of clomifene, while zuclomifene is the (Z)-enantiomer. Whereas, zuclomifene is more estrogenic, enclomifene is more antiestrogenic. Enantiopure enclomifene is more favorable than clomifene as a progonadotropin for the treatment of male hypogonadism.

US2914563 in Example 3 discloses a process for the preparation of trans-Clomiphene citrate (i.e. Enclomiphene citrate) containing 30% to 50% of cis-Clomiphene, as citrate, by reaction of 1-p-(β-diethylaminoethoxy)phenyl]-1,2-diphenylethylene hydrochloride with N-chlorosuccinimide in dry chloroform under reflux.

WO2016066584 discloses Enclomiphene citrate of formula (III) having a melting point 150oC and its preparation comprising adding citric acid to a solution of trans-clomiphene (Enclomiphene) in ethanol. Trans-clomiphene, which is Enclomiphene, is prepared by reacting mixture of geometric isomers of formula (V-E) and (V-Z) or salts with a chlorinating agent in an organic solvent such as methylene chloride in presence of acetic acid or trifluoro acetic acid in higher ratio compared to the cis-isomer (in a ratio from 75:25 to 99:1).



(V-E)



(V-Z)

US3848030 in Examples 31 discloses a process for the preparation of cis–clomiphene by reacting methanolic solution of clomiphene dihydrogen citrate with racemic binaphthyl-phosphoric acid (BPA) to obtain clomiphene-BPA salt which is further extracted with ethyl ether and 2N ammonia solution and further treated with citric acid in ethanol to obtain cis-clomiphene. Example 32 of US'030 discloses separation of trans-clomiphene (Enclomiphene) as citrate from the stored methanolic solution of cis-clomiphene obtained in Example 31. Accordingly, the stored methanolic solution of cis-clomiphene obtained in Example 31 was made alkaline with concentrated ammonia and the mixture was extracted in ether, washed, dried. To the dry mixture was added citric acid in ethanol to obtain trans-Enclomiphene. The process disclosed in Example 31 and Example 32 of US'030 is a two-step process to obtain trans-clomiphene i.e. Enclomiphene. Accordingly, the process comprises extraction of the cis-isomer from clomiphene-BPA complex and further extraction of trans-isomer from the methanolic cis-isomer of Example 31. The process for preparation of Enclomiphene disclosed in US'030 is multistep cumbersome process, requires large amount of solvents and is not industrially feasible. Moreover, the process in US'030 is silent on the purity of Enclomiphene obtained in Example 32.

Further, Binaphthylphosphoric Acid (BPA) was prepared at 0°C as shown in Example 1 of US'030.

The present inventors therefore felt that there is a scope to provide an improved cost effective process for the preparation of Enclomiphene and salts thereof which can give high yield and improved quality of the product.

Summary of the Invention:

In accordance with the above, the present invention provides improved cost effective process for preparation of Enclomiphene citrate in high yield and improved quality comprising;

(i) reacting methanolic solution of clomiphene citrate with racemic BNPA to obtain BNPA-Enclomiphene salt followed by washing with chilled methanol until the Z-isomer content is below 5%; and
(ii) extracting Enclomiphene from BNPA-Enclomiphene salt of step (i) using aqueous ammonia and organic solvent followed by addition of citric acid in ethanol to the organic layer to yield Enclomiphene citrate.

Detailed description of the Invention:

The invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be more fully understood and appreciated.

Abbreviations:

BINOL: 1, 1'-Bi-2-naphthol
BNPA: Binaphthyl Phosphoric Acid

To meet the objectives, the present invention provides cost effective process for preparation of Enclomiphene citrate having Z-isomer less than 5% which the prior art processes has failed to achieve. The present inventors have come up with process wherein the undesired Z-isomer is reduced at the early stage of the resolution process, thus making the process simple, cost effective and industrially feasible.

In an embodiment, the improved, cost effective process for preparation of Enclomiphene citrate in high yield and improved quality comprises;

(i) reacting methanolic solution of clomiphene citrate with racemic BNPA to obtain BNPA-Enclomiphene salt followed by washing with chilled methanol until the Z-isomer content is below 5%; and
(ii) extracting Enclomiphene from BNPA-Enclomiphene salt of step (i) using aqueous ammonia and organic solvent followed by addition of citric acid in ethanol to the organic layer to yield Enclomiphene citrate.

The organic solvents used in the reaction step (ii) are selected from polar protic and aprotic solvent such as C1-C5 alcohols, aliphatic hydrocarbons, THF, DMSO, ethyl acetate, acetone, DMF and the like alone or in combinations thereof; preferably ethyl acetate.

Accordingly, racemic BNPA was added to methanolic solution of clomiphene citrate at room temperature to obtain BNPA-Enclomiphene salt. The salt was filtered and washed severally with chilled methanol (12±2o C) until the Z-isomer content was less than 5% and dried. To the BNPA-Enclomiphene salt was added DM water (50 L) followed by adding portion wise aqueous ammonia solution (8L) at 25-28oC. Ethyl acetate (45 L) was then added to the mixture with continuous stirring for about 60 minutes. The solution was allowed to settle and the organic layer was separated and stored. The aqueous layers were repeatedly washed with ethyl acetate (2 x 22.5 L) and the organic layer was separated and stored. The washings were continued till the pH of the aqueous layer was about 7.

To the stored organic layer was added citric acid in ethanol and the mixture was stirred for about 7-8 hours. The mixture was filtered and the filtrate was further washed with chilled ethyl acetate (2L; 10±2oC) to ensure complete extraction of the product. The filtrate was discarded and the residue was dried to obtain Enclomiphene citrate with water content less than 4%.

In an embodiment, the variable solubility of the E and Z-isomer of clomiphene in methanol is effectively used in the present process. The Enclomiphene is methanol insoluble whereas the Z-clomiphene is methanol soluble. Hence, washings with methanol in the first step of the present process efficiently removes most of the Z-isomer and the E-isomer remains as a solid (min of 95%) with Z-isomer content less than 5%.

In another embodiment, the resolving agent BNPA used in the present process was obtained by stirring a mixture of pyridine, BINOL and Phosphorous oxychloride at a temperature ranging from 95°C to 140°C. This was followed by addition of 6(N) HCl under stirring and the solution was cooled to 10 to 30°C. The mixture was filtered, and to the residual mass was added 6(N) HCl under stirring for about 7 hrs. allowing the temperature to raise upto about 35-37°C. Then the aqueous residual mass obtained after filtration was heated upto 50-52°C and dried to yield BNPA till LOD was below 1%.

In a further embodiment of the process, BINOL was obtained by mixing beta-naphthol and ferric chloride in DM water at a temperature ranging from 90 to 110oC

under stirring. The solution was filtered and the residue was washed with warm water (about 68-73oC), adjusting the pH of the filtrate at 7, followed by drying to obtain BINOL till LOD was below 1%.

The Enclomiphene citrate obtained by the process of the present invention is characterized by HPLC having E-isomer in the range of 95-97% and the Z-isomer in the range of 3-5%. In an embodiment, the present invention provides a pharmaceutical composition comprising an effective amount of Enclomiphene citrate obtained by the present process along with other pharmaceutically acceptable excipients for the treatment of male hypogonadism.

The invention further provides a method of treating male hypogonadism by administering to a subject in need thereof an effective amount of pharmaceutical composition comprising Enclomiphene citrate obtained by the present process along with other pharmaceutically acceptable excipients.

In an embodiment, the present invention describes a process which avoids the additional step of separation of the cis-isomer (Z-isomer) of clomiphene as employed in the prior art process. The yields and purity of Enclomiphene is improved by the work up procedures in each stage of the process. There is less use of organic solvents, no additional purification procedures which make the process cost effective over the art.

The following examples, which include preferred embodiments, will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purpose of illustrative discussion of preferred embodiments of the invention.

Examples:

Example 1: Process for preparation of BINOL

DM water (375 L) was added into the 1000 L reactor and heated to 90°C followed by addition of Beta-naphthol (9 Kg). The solution was left under stirring at 100±2°C for another 1 hr. The previously prepared Ferric Chloride solution [15.5 L of FeCL3 (41%) in 42 L DM water] was added gradually to avoid lump formation. The suspension was stirred for another 10 min and then TLC was checked for completion of the reaction. The reaction mass was filtered in centrifuge machine. The residue was washed with warm water (70±2°C) till pH of the filtrate was 7. Then the mass was transferred to FBD (Fluid Bed Dryer) and dried at 50±2°C. Drying was continued till LOD was below 1%.

Yield: 6.6Kg; Purity: 97%

Example 2: Process for preparation of BNPA

Pyridine (9.9 L) was charged to the 50 L glass reactor at 120 rpm. BINOL (2.2 Kg) from example 1 was added slowly under same stirring conditions. Phosphorous oxychloride (3.3 Kg) was then added gradually such that the temperature increased to 97°C at 120 rpm. TLC was checked 30 min after the addition was completed. DM water (1.1 L) was added very slowly at such a rate that the temperature at 120°C at 120 rpm. The reaction mixture was transferred to 100 L glass reactor at temperature 10-30oC. 6(N) HCl (12.1L) and DM water (12.1L) was charged to the said 100L glass reactor and the solution was cooled to 10±2°C.Stirring was continued for another 2 hours. The reaction mass was filtered using Nutsche filter (100L). The filtrate was discarded and the residual mass was fed in to the glass reactor (50L). 6N HCl (7.15L) and 7.15L DM water and the residual mass at 200rpm were charged in the glass reactor (50L) and the mixture was stirred for 8 hours. Suspension obtained was filtered using 100L Nutsche filter and the filtrate was discarded. The residual cake (at 200rpm) and DM water (20L) were charged to the 100L glass reactor and the solution was heated upto48°C. Stirring was continued maintaining temperature 50±2oC. The suspension was filtered using 100L Nutsche filter and filtrate was discarded. The residual mass was washed with DM water (2.2L). Then the mass was dried in tray dryer at 50±2°C. Drying was continued till LOD was below 1% to obtain BNPA. Yield: 2.5 Kg; Purity: 95%

Example 3: Process for preparation of BNPA-Enclomiphene salt

Methanol (54.2 L) was charged in the 100L glass reactor. Clomiphene citrate (7.4 Kg) was added slowly at room temperature and stirred at 180 rpm. BNPA (5 Kg) was added at same temperature with continuous stirring. The solution was filtered through 100L Nutsche filter to obtain residue. The residue was washed with chilled methanol (12±2°C) for about 5-6 times (4.5 L each time) till Z isomer content is below 5%. The mass was transferred to trays and dried in vacuum tray dryer at 50±2°C till LOD was below 5% to obtain BNPA-Enclomiphene salt. Yield: 3.5Kg; Purity: E isomer 97%; Z isomer 3%.

Example 4: Process for preparation of Enclomiphene citrate

BNPA-Enclomiphene salt (5.3Kg) from Example 1 was added portion wise at 150 rpm to aqueous ammonia solution (7.71L) at 25-28oC. Ethyl acetate (44.42L) was added to the mixture with continuous stirring at 150rpm for 60 minutes. The solution was allowed to

settle for 30 mins and the organic layer was separated and stored. The aqueous layer was repeatedly washed with ethyl acetate (22.21L x 2) under stirring for 50 mins, settled for 30 mins and the organic layer was separated and stored. To the pre-stored organic layer was added DM water (22.21L) with stirring for 30 mins. The solution was allowed to settle for 15mins. The washings were continued till the pH of the aqueous layer was about 7 and was then discarded. To the stored organic layer was added citric acid in ethanol (1.61Kg Citric acid in 3.96L Ethanol) and the mixture was stirred for 8 hours. The mixture was filtered using Nutsche filter and the filtrate was further washed with chilled ethyl acetate (12±2°C) to ensure complete extraction of the product. The filtrate was discarded and the residue was dried using vacuum tray dryer at 52oC to obtain Enclomiphene citrate with water content less than 4%.

Yield: 5.3Kg; Purity: E isomer 97%; Z isomer 3%

Claims

1. A cost effective, improved process for preparation of Enclomiphene citrate in high yield and purity comprises;
   (i) Reacting methanolic solution of clomiphene citrate with racemic BNPA to obtain BNPA-Enclomiphene salt followed by washing with chilled methanol until the Z-isomer content is below 5 %.
   (ii) Extracting Enclomiphene from BNPA-Enclomiphene salt of step
   (iii) Using aqueous ammonia and organic solvent followed by addition of citric acid in ethanol to the organic layer to yield Enclomipheme citrate.

2. The process as claimed in claim 1; wherein methanol/ethanol is the organic solvent used of step (ii).

A cost-effective process of preparation of Enclomiphene Citrate

ABSTRACT

The invention disclosed herein is an improved cost-effective process for preparation of Enclomiphene citrate in high yield and improved quality.