(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 June 2007 (21.06.2007)

(21) International Application Number:
PCT/IN2006/000357

(22) International Filing Date:

(51) International Patent Classification:
C07D 253/06 (2006.01)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1532/MUM/2005

(51) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: A NOVEL PROCESS FOR THE SYNTHESIS OF LAMOTRIGINE AND ITS INTERMEDIATE

(57) Abstract: This invention discloses a process for the preparation of 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine of a formula (I), commonly known as Lamotrigine which comprises the step of reacting aminoguanidine bicarbonate and 2,3-dichlorobenzoyl chloride with a reagent prepared by dissolving phosphorus pentoxide and methanol sulfonic acid, to produce a novel intermediate 2-(2,3-dichlorophenyl)-2-(aminoguanidine)-acetonitrile monomesylate which is further cyclized to lamotrigine without basification.
TITLE - A NOVEL PROCESS FOR THE SYNTHESIS OF LAMOTRIGINE AND ITS INTERMEDIATE

FIELD OF INVENTION

This invention relates to a new method for preparing a pharmaceutically active compound with antiepileptic properties.

BACKGROUND OF INVENTION

3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine of a formula (I), commonly known as Lamotrigine, is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder. For epilepsy it is used to treat partial seizures, primary and secondary tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome. It also acts as a mood stabilizer. It is the only anticonvulsant mood stabilizer that treats the depressive as well as the manic phases of bipolar disorders.

Its analogues were first disclosed in British patent 759,014 (1956). According to the process described in the European patent 21121, 2,3-dichlorobenzoyl cyanide is reacted with hydrogencarbonate salt of aminoguanidine in dimethylsulfoxide as a solvent, in the presence of 8N Nitric acid for 7 days. The obtained adduct is cyclized with methanolic potassium hydroxide solution to give the final product in 15% yield-calculated on starting material 2,3-dichlorobenzoylcyanide. The disadvantages of the
above processes are extremely aggressive reaction medium, the long reaction time as well as very low yield.

The European patent 247892 describes a process in which 8 M solution of Sulphuric acid is used instead of 8 N Nitric acid in the condensation reaction and the reaction time is 41 hrs. The cyclisation is carried out in n-propanol at reflux temperature to yield 41% of the product. A similar process is disclosed in WO 2000/35888, in which condensation is carried out in a mixture of dilute Sulphuric acid and acetonitrile for 60 hrs. and then cyclisation is carried out with 1% aqueous potassium hydroxide. The crude product is purified by recrystallisation in methanol with the help of clarifier to yield 44% of product. These processes have similar disadvantages like low yield, aggressive medium and long reaction time.

US633198 also describes a process, which is modification of the above process, where cyclisation is carried out in n-propanol to get 60% yield of product with reaction time of 4.4 to 48 hrs. This has also a disadvantage of long reaction time and aggressive reaction medium.

US6329521 describes the preparation of intermediate Schiff base. It also includes the condensation of 2,3-dichlorobenzoylcyanide with aminoguanidine in acetonitrile in presence of polyphosphoric acid and in absence of water, at 50° C. for 22 hrs. The process provides an improved yield of Schiff base. However, the process uses large quantities of polyphosphoric acid and acetonitrile, which add to the cost of product, and also the process produces a large quantity of acidic effluent making the process commercially unattractive.

US6639072 also describes the similar process for preparing Schiff base using 2,3-dichlorobenzoyl cyanide, aminoguanidine bicarbonate, and concentrated Sulphuric acid. Using p-toluene sulphoninic acid as a catalyst and toluene as a solvent at 110° C.
Although under such condition a reduced reaction time is achieved but the overall yield (50%) and quality suffer.

Another route of synthesis of lamotrigine is disclosed in WO96/20934, which involves photochemical reaction of the intermediate in a photochemical reactor using ultraviolet radiation and expensive and hazardous reagent. Therefore this process is not suitable for industrial scale production of lamotrigine.

PCT publication WO96/20935 describes a six-steps process, which is difficult to carry out, and hardly realizable on industrial scale, as well as the yield of the final product is very low. The disadvantages of this process are complicated synthesis and applied hazardous reagents.

Another process disclosed in British patent 2395483 describes the preparation of Schiff base using Sulphuric acid, 2,3-dichlorobenzoyl cyanide and Aminoguanidine bicarbonate at temperature 50°C. Schiff base is isolated by sodium hydroxide solution. It involves an unnecessary additional step as well as the overall yield is also moderate only.

PCT application WO03/078407 describes a process in which aminoguanidine is condensed with 2,3-dichlorobenzoyl cyanide in presence of methane sulphonic acid in a polar solvent e.g. DMSO, DMF or NMP, subsequently the dehydrating agents are used such as thionyl chloride, phosphorous oxychloride, phosphorous trichloride or phosgene, then the formed product is basified with KOH solution and isolated. The isolated product is cyclized in presence of potassium hydroxide and IPA and isolated as a monohydrate, by addition of water. The use of hazardous dehydrating agent, polar solvent and organic acids makes it uneconomical as well as hazardous for environment.
PCT publication) WO2004/026845 describes a process in which aminoguanidine bicarbonate is treated with methane sulfonic acid to form dimesylate salt, which is isolated and further condensed with 2,3-dichlorobenzoyl cyanide in presence of methane sulfonic acid and acetonitrile. Followed by in situ cyclisation using magnesium oxide, the crude lamotrigine is obtained which is crystallised in acetone. This process is also not industrially attractive due to low yield and use of class II solvent. The patent is salient about the quality of the product.

Although a process described in PCT publication WO2004/039767 has avoided the use of hazardous solvents to prepare intermediate, 2-(2,3-dichlorophenyl)-2- (aminoguanidine) acetonitrile salt, but it still involves isolation of Schiff base by sodium hydroxide solution. Which involves unnecessary additional step as well as results low yield (65%).

Thus from the above mentioned facts, it is evident that despite the several routes known for synthesis of lamotrigine, there is still need for a route which is safe, convenient, efficient, economical and less time consuming.

Surprisingly, we found a novel process for preparation of lamotrigine without basification of the intermediate, 2-(2,3-dichlorophenyl)-2-(aminoguanidine) acetonitrile monofnesylate. This process is economical, involves short reaction time, less number of reaction steps and provides high yield and desired quality with controlled impurity profile.

SUMMARY OF THE INVENTION

Accordingly, an object of the invention is to provide a process for the preparation of 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine of a formula (I), commonly known as Lamotrigine, in high yield and having high grade purity, with highly satisfactory impurity profile, and other quality parameter like colour, residual solvent content,
moisture content, flowability and which can be easily converted into pharmaceutical composition.

Another object of the invention is to provide a process for the preparation of 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine of a formula (I), commonly known as Lamotrigine, which is safe and convenient.

Another object of the invention is to provide a process for the preparation of 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine of a formula (I), commonly known as Lamotrigine, which is less time consuming as well as involves less number of reaction steps.

Another object of the invention is to provide a process for the preparation of 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine of a formula (I), commonly known as Lamotrigine, which is efficient and economical.

Another object of the invention is to provide a process for the preparation of 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine of a formula (I), commonly known as Lamotrigine, which is suitable for industrial scale manufacture.

According to the invention, there is provided a novel process for the preparation of Lamotrigine of formula (I) and its intermediate having formula (I) which comprises:

a) Preparation of reagent by dissolving phosphorous pentoxide in methane sulfonic acid. Subsequent addition of Aminoguanidine bicarbonate and 2,3-dichlorobenzoylcyanide under anhydrous condition. Followed by stirring at temperature range of 15-60°C, which leads to an intermediate salt of formula (II). Isolating intermediate salt by quenching the reaction mass in water at temperature range 20-40°C.

b) Cyclisation of intermediate salt into Lamotrigine using potassium carbonate and alcohol.
c) Crystalisation in isopropyl alcohol.

DETAILED DESCRIPTION OF INVENTION

1. The present invention provides a novel process for the preparation of lamotrigine and its intermediate having formula (II), which comprises:

a) preparation of reagent by dissolving phosphorous penta oxide in methane sulfonic acid.

b) treatment of aminoguanidine bicarbonate and 2,3-dichlorobenzoyl cyanide with the reagent formed in (a) under anhydrous condition to form an intermediate of formula (II)

c) Isolation of intermediate of formula (II)

d) Cyclisation of the intermediate of formula (II) to form crude Lamotrigine using potassium carbonate and alcohol.

e) Crystalisation of the obtained crude material by isopropyl alcohol.

Scheme

[Diagram showing the chemical reactions and formulas (I) and (II)]
The reagent is prepared by dissolving phosphorus pentaoxide in methane sulfonic acid and stirring for two hours at room temperature. Methane sulfonic acid and phosphorus pentaoxide may be taken in molar ratio of 9:1. Aminoguanidine bicarbonate is added to the prepared reagent. Subsequently, 2,3-dichlorobenzoyleyanide is added. The reaction mass is stirred for 15-30 hrs. preferably for 20-24 hrs. 2-(2,3-Dichlorophenyl)-2-(aminoguanidine)-acetonitrile monomesylate having formula (II) is isolated by addition of reaction mass into water while maintaining the temperature in the range of 20-40°C. preferably in the range of 20-25X.

The isolated intermediate salt i.e. 2-(2,3-dichlorophenyl)-2-(aminoguanidine)-acetonitrile monomesylate of formula (II) is directly taken for cyclisation without any basification. Intermediate salt, 2-(2,3-dichlorophenyl)-2-(aminoguanidine)-acetonitrile monomesylate of formula (II) is cyclized by refluxing it in potassium carbonate & lower alkyl alcohol to obtain crude lamotrigine. The lower alkyl alcohol may be straight chain C1-C3 aliphatic alcohol such as methanol, Isopropanol, or ethanol and preferably methanol. Similarly in addition to monomesylate salt intermediate having formula (II), many other acid addition salt e.g. hydrochloric acid salt, Sulphuric acid salt, etc., can be converted to the crude lamotrigine without basification.

The isolated crude Lamotrigine can be recrystallized by dissolving it in a solution of Isopropanol - water in a ratio 9:1 at reflux temperature and by treating with activated carbon. The hot solution is filtered through hyflow and water is removed by azeotropic distillation of isopropanol till water content reaches to less than 1%. The
obtained solid is filtered and dried under vacuum at 65°C for 15-20 hrs, to get anhydrous lamotrigine.

In the present invention, phosphorus pentaoxide used to prepare a reagent is solid in nature and the quantity required for the reaction is low i.e. in the ratio 1:1.5 molar ratio. It is relatively less hazardous as compared to the drying agents used in all state of the art process. No toxic solvent has been used hence the process is green. The reaction for the preparation of intermediate is carried out at room temperature. It makes the process, economical and the product purer since the formation of undesired impurity suppressed at this temperature.

The present process avoids the basification of the intermediate \(2-(2,3\text{-dichlorophenyl})-2\text{-}(\text{aminoguanidine})\text{-acetonitrile monomesylate of formula (II)}\) to Schiff base. It significantly reduces the production cost at industrial scale. For cyclisation of the \(2-(2,3\text{-dichlorophenyl})-2\text{-}(\text{aminoguanidine})\text{-acetonitrile monomesylate mild base is used which further improves the quality.}

The invention is explained in detail in the following examples, which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention in any way.

**Example**

\[2-(2,3\text{-dichlorophenyl})-2\text{-}(\text{aminoguanidine})\text{-acetonitrile monomesylate}\]

1750 ml of Methane sulfonic acid was added to a round-bottom flask. 350gm (2.46 mol) Phosphorous pentoxide was added to it and stirred the solution for 2.0 hrs. Aminoguanidine bicarbonate (357 g, 2.62 mol) was added slowly at temperature 25-30°C, and stirred for 1.0 hr. 350.0 g (1.75 mol) 2,3-Dichlorobenzoyl cyanide was
added to this solution. The reaction mixture was stirred for 24 hrs. at ambient temperature. The progress of the reaction was monitored by HPLC. The reaction mass was quenched in 8.7 litre of water maintaining the reaction temperature below 15-20° C. The solid was filtered and washed with water. After drying, 638 g of crude 2-(2,3-dichlorophenyl)-2-(aminoguanidine)-acetonitrile monomesylate was obtained.

H-NMR
(400 MHz, DMSO-D6): 8.3(S J 7.6 Hz, 3H), 7.8 (dd, J=I 8; 66,7.93 Hz, 2H), 7.5(t, J=7.93; 1H) 2.4(br s, NH2).

Example 2

3,5-diamino-6- (2, 3-dichlorophenyl)-l, 2, 4-triazine

A round bottom flask was charged with 621 g of crude 2-(2,3-dichlorophenyl)-2-(aminoguanidine) acetonitrile monomesylate obtained in example I and to it 4200 ml of methanol and 218 g (1.58 mol.) of potassium carbonate was added. The reaction mixture was refluxed for 7 hrs. The reaction was monitored by HPLC. After completion of the reaction, 4.0 litres of water was added to the reaction mass. The reaction mass was cooled to 25-30° C. The solid was filtered and washed with water. 404 g of the title product was obtained as a wet cake.

Example 3

Crystallization of 3,5-diamino-6- (2, 3-dichlorophenyl)-l, 2, 4-triazine

The crude lamotrigine (404 g) obtained in example 2 was taken into a mixture of 3600 ml isopropyl alcohol and 600 ml of water. The reaction mass was refluxed till the solution became clear. 4.0 g Activated carbon was added to the solution and refluxed for 1 hr. The hot solution was filtered through celite. Clear filtrate was distilled and
striped with isopropyl alcohol till water content of distillate reached to less than 1.0%. Concentrated the reaction mass up to 3.5 volumes. Cooled the mass to 25-30°C and filtered the solid. Dried under vacuum at 65°C for 12 hrs to yield 325.2 g (72%) of the crystalline lamotrigine.

M.P.: 216 - 217°C.

MS (m/z): 256.3 [M+]

H-NMR (400 MHz, DMSO-D6): 7.7 (d, J=7.3 Hz, IH), 7.40 (t, J=7.8 Hz IH), 7.4 (d, J=6.83 Hz, IH), 6.70 (br s, -NH2), 6.5 (br s, -NH2).

13-C-NMR (75 MHz, DMSO-D6): 162.1, 154.1, 138.3, 136.8, 132.0, 131.6, 130.6, 128.5.

Elemental analysis: C  H  N

Calculated: 42.21  2.76  27.35

Found: 41.12  2.44  26.49
We Claim:

1. A process for the synthesis of 3, 5-diamino-6-(2, 3-dichlorophenyl)-1, 2, 4-triazine comprising:
   
   a) preparation of reagent by dissolving phosphorous pentaoxide in methane sulfonic acid;
   
   b) treatment of aminoguanidine bicarbonate and 2,3-dichlorobenzoylcyanide with the reagent formed in (a) to form an intermediate of formula (II);

   
   ![](image)

   Formula (II)

   c) isolation of intermediate of formula (II);

   d) cyclisation of the intermediate of formula (II) to form crude Lamotrigine using potassium carbonate and lower alkyl alcohol.

   e) crystalisation of the obtained crude material by isopropyl alcohol.

2. The process according to claim 1, where the treatment in (b) is carried out at a temperature range of 20-60°C preferably 25-35°C.

3. The process according to claim 1, where isolation of intermediate is carried out by quenching the reaction mass in water at temperature range of 20-30°C.

4. The process according to claim 1, wherein the lower alkyl alcohol used in step (d) is methanol.

5. 2-(2,3-dichlorophenyl)-2-(aminoguanidine)-acetonitrile monomesylate of formula (II)
6. A process of conversion of acid addition salt of Schiff base to lamotrigine without basification.

7. A process as claimed in claim 6, wherein the acid addition salt of Schiff base is any of the HCl, H₂SO₄, NO₂ salt of Schiff base.
**INTERNATIONAL SEARCH REPORT**

**INTERNATIONAL APPLICATION**

**International application No.**
PCT/IN 2006/000357

**A. CLASSIFICATION OF SUBJECT MATTER**

**IPC®: C07D 253/06** (2006.01)

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

**IPC®: 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 practicable, search terms used)

CAS-databases

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>WO 2004/039767 A1 (LABORATORIOS VITA, S.A.) 13 May 2004 (13.05.2004) examples 3-6</td>
<td>6, 7</td>
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<td>A</td>
<td>WO 2000/035888 A1 (VYAS SHARAD KUMAR) 22 June 2000 (22.06.2000) claims</td>
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**D. Further documents are listed in the continuation of Box C.**

**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

"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)

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**Name and mailing address of the ISA/ AT**

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