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(54) Title: A PROCESS FOR THE PREPARATION OF ALMOTRIPTAN

(57) Abstract: The present invention encompasses a method for the preparation of Almotriptan and its pharmaceutically acceptable salts comprises, i) Methylation of 3-[5-(l- Pyrrolidinyl sulfonyl methyl) lH-indol-yl] ethane amine ii) Treating crude Almotriptan with a hydroxy benzoic acid yields hydroxy benzoic acid addition salt of Almotriptan iii) Converting Almotriptan hydroxy benzoic acid addition salt to Almotriptan and iv) Salification of Almotriptan to its pharmaceutically acceptable salts

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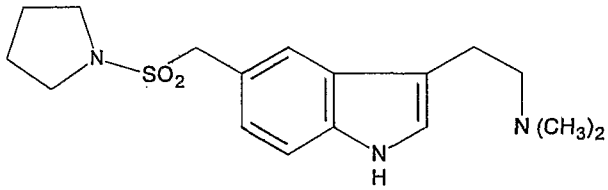
"A process for the preparation of Almotriptan"

The present invention relates to 1-[[[3-[2-(Dimethyl amino) ethyl]-1H-indol-5-yl]-methyl] sulfonyl] pyrrolidinone (Almotriptan) and its pharmaceutically acceptable salts, process for preparation thereof using the novel 1-[[[3-[2-(Dimethyl amino) ethyl]-1H-indol-5-yl]-methyl] sulfonyl] pyrrolidinone salicylate salt.

Background of the Invention:

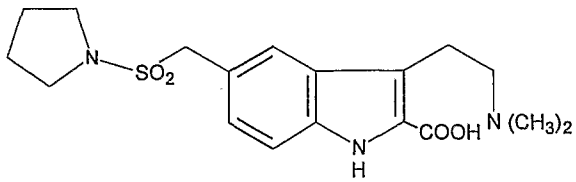
1-[[[3 - [2-(Dimethylamino) ethyl] - 1H-indol – 5 - yl] - methyl] sulfonyl] pyrrolidinone (Almotriptan) has the formula as given below



Almotriptan

Almotriptan is a selective 5-$HT_{1B/1D}$ agonist used as a therapy for migraine headache, shows high and specific affinity for 5-$HT_{1B/1D}$ receptors in cranial vessels, but poor affinity for 5-HT_{1A} and 5-HT_7 receptors in peripheral arteries and therefore cause less side effects of hypertension by a central nervous system action and other side effects.

U.S. Pat. No. 5,565,447 discloses Almotriptan, its acid addition salts and the process for preparation. The disclosed process involves the decarboxylation of a carboxylic acid (Formula –I), in an inert organic solvent, in the presence of copper derivatives as a catalyst.



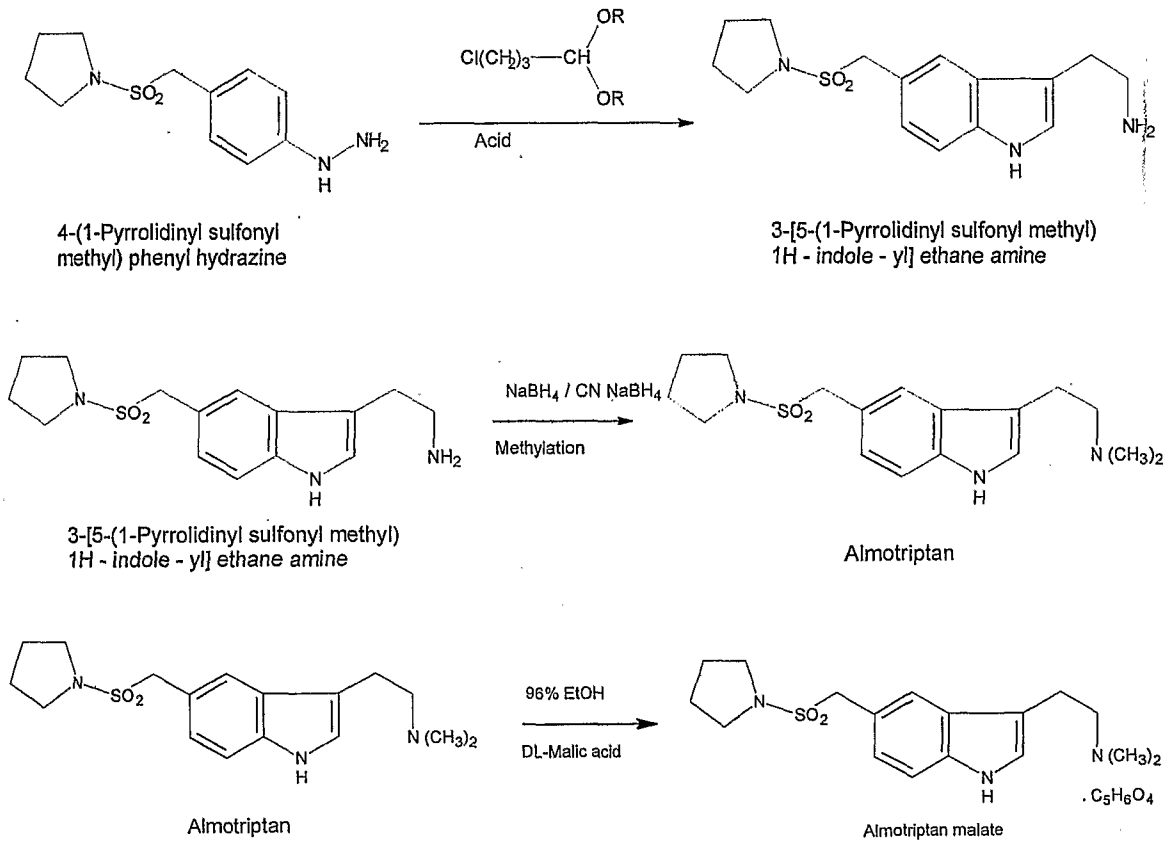
Formula-I

The disclosed process involves the column chromatographic purification with silica gel with methylene chloride: ethanol: ammonium hydroxide (60:8:1) as eluent. The

U.S. Patent further discloses that the Almotriptan can be converted to acid addition salts with acids in appropriate solvents. Suitable acid addition salts disclosed are those derived from inorganic acids; for example hydrochloric acid and sulphuric acid.

Spanish Pat. No. 2,084,560 discloses the conversion of Almotriptan to its acid addition salts derived from organic, inorganic acids like malate, tartrate, succinate or hydrochloride. The procedure involved for preparation of DL-malate salt is by saltification with DL-malic acid in 96% ethanol.

Research Disclosure (1998) 412 discloses the synthetic pathway for preparation of Almotriptan by a sequence of reactions starting from the 4-substituted anilines (Scheme-1). The process for preparation of Almotriptan was also disclosed in Tetrahedron, 57 (2001) 1041 - 1048. The disclosed processes results the Almotriptan whose purity is not mentioned.



Scheme-1

In the above-mentioned prior art processes Almotriptan malate with pharmaceutically acceptable purity is achieved by the saltification of pure Almotriptan with malic acid.

It is observed that Almotriptan pharmaceutically acceptable salts being prepared by Almotriptan with less purity is not meeting with the pharmaceutically acceptable quality. There is therefore an unfulfilled need to provide industrially feasible process for the preparation of pharmaceutically acceptable salts of Almotriptan from impure Almotriptan without column chromatography purification as described in the prior art.

To overcome the problem inventors have tried to prepare Almotriptan pharmaceutically acceptable salts through Almotriptan acid addition salts from Almotriptan irrespective of its purity.

It is surprisingly found by the inventors that when the impure Almotriptan is reacted with hydroxy benzoic acids such as 2-Hydroxy benzoic acid (Salicylic acid) and 4-hydroxy benzoic acid, it selectively forms the corresponding acid addition salt, leaving behind the other related substances and impurities which are otherwise difficult to remove by the conventional methods. The hydroxy benzoic acid salts of Almotriptan are further converted to Almotriptan pharmaceutically acceptable salts with acceptable purity.

Summary of the invention:

The main object of the present invention is to provide an improved process for the preparation of Almotriptan and/or its pharmaceutically acceptable salts.

Another object of the invention is to provide a process for preparation of Almotriptan and/or its pharmaceutically acceptable salts using hydroxybenzoic acid salts of Almotriptan.

Accordingly in the present invention Almotriptan and its pharmaceutically acceptable salts are prepared by i) converting impure Almotriptan to its hydroxybenzoic acid salts

ii) *neutralizing* hydroxybenzoic acid salts and isolating Almotriptan and iii) converting Almotriptan to its pharmaceutically acceptable salts

Detailed description of the invention:

Thus in accordance with the present invention preparation of Almotriptan, its pharmaceutically acceptable salts comprise the following steps;

i. Methylation of 3-[5-(1-Pyrrolidinyl sulfonyl methyl) 1H-indol-yl] ethane amine with formaldehyde and sodium borohydride yields crude Almotriptan
ii. Treating crude Almotriptan with a hydroxy benzoic acid yields hydroxy benzoic acid addition salt of Almotriptan
iii. Converting *Almotriptan hydroxy benzoic acid addition salt to* Almotriptan
iv. Saltification of Almotriptan to its pharmaceutically acceptable salts

In a specific embodiment, the present invention provides a process for the preparation of Almotriptan and its pharmaceutically acceptable salts, which involves,

i. Dissolution of 3-[5-(1-Pyrrolidinyl sulfonyl methyl) 1H-indol-yl] ethane amine in methanol,
ii. Simultaneous slow addition of formaldehyde solution in methanol followed by aqueous sodium borohydride solution at temperature of 0 to 15°C preferably at 5 to 10°C, over a period of 1 hr to 6 hrs preferably over 2 to 4 hrs
iii. Acidification of the reaction mass with hydrochloric acid
iv. Neutralizing with alkali carbonates, alkali bicarbonates such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, preferably with sodium carbonate,
v. Removing methanol below 60°C under vacuum,
vi. Washing the reaction mass with ethyl acetate,
vii. Adjusting the pH to 9.0 to 12.0 with alkali carbonate preferably potassium carbonate,
viii. Separating the layers and the organic layer is concentrated under reduced pressure to get the crude residue of Almotriptan

Further reacting the resultant crude residue of Almotriptan with hydroxy benzoic acid by

i. Dissolving the residue in a short chain alcohol such as methanol, ethanol, propanol or mixture thereof,
ii. Adding hydroxy benzoic acid directly or as a solution in short chain alcohol,
iii. Maintaining the reaction mixture at 35°C to reflux temperature of the solvent for about 30 min to 2 hrs
iv. Cooling the reaction mixture to 10 to 35°C
v. Isolating the precipitated product and dying the product at 40 to 90°C, preferably at 50 to 75°C, affords the pure Almotriptan as an acid addition salt of hydroxy benzoic acid.

The prepared Almotriptan hydroxy benzoic acid addition salts (both 2-hydroxy benzoic acid and 4-hydroxy benzoic acid) are novel, identified and characterized by chemical analysis, IR, NMR & Mass spectral data. Almotriptan hydroxy benzoic acid addition salt is further converted to Almotriptan by

i. Neutralizing Almotriptan hydroxy benzoic acid with a base such as organic amines, alkali hydroxides, alkali carbonates, alkali bicarbonates and ammonia, in a mixture of water and water immiscible solvent
ii. Separating the layers,
iii. Washing the organic layer with water,
iv. Concentrating the organic layer under vacuum affords Almotriptan

The obtained Almotriptan is further converted to Pharmaceutically acceptable salts of Almotriptan by

i. Dissolving Almotriptan in an alcohol such as methanol, ethanol and propanol
ii. Treating with activated carbon,
iii. Saltification with a pharmaceutically acceptable organic acid, such as maleic acid, DL-malic acid and Tartaric acid,
iv. Isolating the precipitated salt by conventional methods,

v. Drying the product at 40°C to 100°C, preferably at 50 to 80°C affords the corresponding Almotriptan acid addition salts in pure form.

The required 3-[5-(1-Pyrrolidinyl sulfonyl methyl) 1H-indol-yl] ethane amine can be prepared by the prior art processes.

The invention is further illustrated with a few non-limiting examples

Example-1: *Preparation Almotriptan malate (Prepared from Almotriptan crude)*
Almotriptan crude (10gms, purity 87.39%) is dissolved in Ethanol (50ml) at room temperature. Reaction mass is stirred for 15 min for the complete dissolution. Malic Acid solution (4.6 gms in 21 ml Ethanol) is added to the above solution over 30 min at room temperature. Reaction mass temperature is raised to reflux and maintained for about 1 hr at that temperature. Slowly cooled the reaction mass to room temperature and maintained for about 2.0 hrs. The precipitated material is filtered and washed with 15 ml of Ethanol.
Dried the material at 70-75° C under vacuum till constant weight.
Dry Weight: 9.2 gms: Purity 97.34% (by HPLC)

Example-2: *Preparation of Almotriptan oxalate*
Almotriptan crude (10 gms, purity 92.5%) is dissolved in Ethanol (60ml) at room temperature. Reaction mass is stirred for 15 min for the complete dissolution. Oxalic Acid solution (4.0 gms in 15 ml Ethanol) is added to the above solution over 30 min at room temperature. Reaction mass temperature is raised to reflux and maintained for about 6 hrs. Slowly cooled the reaction mass to 0°C and maintained for about 1 hr at 0 ± 3°C. The precipitated material is filtered and washed with 15 ml of Ethanol.
Dried the product at 70-75° C under vacuum till constant weight.
Dry Weight: 5.0 gms: Purity 93.05% (by HPLC)

Example-3: *Preparation Almotriptan malate from Almotriptan oxalate*
Almotriptan oxalate (10gms) is suspended in dissolved in ethyl acetate (250 ml). Aqueous ammonia solution (100 ml) is added over a period of 30 min. The mass is maintained for 30 min and allowed to settle. Layers are separated and the aqueous layer is extracted with ethyl acetate (100 ml). Combined the organic layer and

washed with water (100 ml). The organic layer is dried over sodium sulphate and distilled off under vacuum at temperature below 50°C. Methanol (40 ml) is added to the mass, stirred at room temp for clear solution. DL-Malic acid solution (3.6 gms in 20 ml methanol) is added slowly over 30 min. Reaction mass temperature is raised to reflux and maintained for I hr. Cooled the reaction mass to room temperature and maintained at 25 – 35°C for 3 hrs. Precipitated product is filtered and washed with methanol (20 ml). The product is dried at temperature of 70 – 75°C till constant weight.

Dry weight of Almotriptan malate: 4.4 gms Purity: 94.08% (by HPLC)

Example-4: *Preparation of Almotriptan 2-Hydroxy benzoate (salicylate)*

Almotriptan crude (10gms, purity 87.39%) is dissolved in Ethanol (50ml) at room temperature. Reaction mass is stirred for 15 min for the complete dissolution. Salicylic acid solution (5.3 gms in 20 ml Ethanol) is added to the above solution over 30 min at room temperature. Reaction mass temperature is raised to reflux and maintained for about 1 hr at that temperature. Slowly cooled the reaction mass to room temperature and maintained for about 2.0 hrs. The precipitated material is filtered and washed with 20 ml of Ethanol.

Dried the material at 70-75° C under vacuum till constant weight.

Dry Weight: 11.5 gms Purity 99.22% (by HPLC)

Example - 5: *Preparation Almotriptan malate from Almotriptan 2-Hydroxy benzoate (salicylate)*

Almotriptan salicylate (10gms) is suspended in a mixture of water (100 ml) and ethyl acetate (100 ml) at a temperature of 25 – 30°C. Aqueous ammonia solution (25 ml) is added to the suspension over a period of 30 min. The mass is maintained for 30 min and allowed to settle. Layers are separated and the aqueous layer is extracted with ethyl acetate (2 x 50 ml). Combined the organic layer and washed with water (2 x 50 ml) and ethyl acetate is distilled off under vacuum at temperature below 50°C. The crude product is dissolved in Methanol (20 ml), stirred at room temp for clear solution. The organic layer is treated with activated charcoal (1 gms) for 30 min at 25 – 30°C and filtered the mass through hyflow bed. The hyflow bed is washed methanol (5 ml). To the clear filtrate Malic acid solution (3.2 gms in 15 ml)

is added slowly over 30 min and maintained the mass at reflux for 1hr. Slowly cooled the reaction mass to room temperature and maintained at 25 – 35°C for 3 hrs. Precipitated product is filtered and washed with chilled methanol (60 ml). The product is dried at temperature of 70 – 75°C till constant weight.

Dry weight of Almotriptan malate is 9.0 gms Purity: 99.81%(by HPLC)

We claim:

1. A process for the preparation of Almotriptan, its pharmaceutically acceptable acid addition salts comprises of the following steps,

   i. Methylation of 3-[5-(1-Pyrrolidinyl sulfonyl methyl) 1H-indol-yl] ethane amine with formaldehyde and sodium borohydride yields crude Almotriptan
   ii. Treating crude Almotriptan with a hydroxy benzoic acid yields hydroxy benzoic acid addition salt of Almotriptan
   iii. Converting Almotriptan hydroxy benzoic acid addition salt to Almotriptan
   iv. Saltification of Almotriptan to its pharmaceutically acceptable salts

2. The process as claimed in claim 1, wherein methylation is being carried out by formaldehyde and sodium borohydride

1. The process as claimed in claim 1, wherein the hydroxy benzoic acid is 2-hydroxy benzoic acid, 4-hydroxy benzoic acid or mixture thereof

2. The process as claimed in claim 1, wherein Almotriptan pharmaceutically acceptable salts are malate, maleate or tartarate

3. The process as claimed in claim 4, wherein Almotriptan pharmaceutically acceptable salts is Almotriptan malate

4. Almotriptan 2-Hydroxy benzoate salt

5. Almotriptan 4-Hydroxy benzoate salt

8. A process for the preparation of Almotriptan, its pharmaceutically acceptable acid addition salts comprises of the following steps,

   i. Treating crude Almotriptan with a hydroxy benzoic acid yields hydroxy benzoic acid addition salt of Almotriptan
   ii. Converting Almotriptan hydroxy benzoic acid addition salt to Almotriptan
   iii. Saltification of Almotriptan to its pharmaceutically acceptable salts

9. The process as claimed in claim 8, wherein crude Almotriptan is obtained from the acid addition salts of Almotriptan

10. The process as claimed in claim 9, wherein hydroxy benzoic acid is 2-hydroxy benzoic acid, 4-hydroxy benzoic acid or mixture thereof

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2006/000262

A. CLASSIFICATION OF SUBJECT MATTER
IPC[8]: ***C07D 401/12*** (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)
IPC[8]: 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)
EPOQUE: WPI, EPODOC, XPRD, XPESP, CAS-databases

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ES 2084560 A1 (ALMIRALL LAB) 1 May 1996 (01.05.1996) *claim 1*	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search	Date of mailing of the international search report
	21 December 2006 (21.12.2006)
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN 2006/000262

Patent document cited in search report	Publication date	Patent family member(s)	Publication date