International Application Published Under the Patent Cooperation Treaty (PCT)

Title: An Improved Process for the Preparation of Pure Palonosetron Hydrochloride

Abstract: The present invention relates to an improved and industrially viable process for the preparation of high purity >99.8% chemical and >99.8% chiral of palonosetron hydrochloride of formula-I ((3as)-2[(3s)-1-azabicyclo[2.2.2] oct-3-yl]-2,3,3a,4,5,6-hexahydro-IH-benzo[de]isouquinoline-1-one monohydrochloride) obtained from reduction of 2-[(S)-1-azabicyclo[2.2.2] oct-3-yl]-2,4,5, 6-tetrahydro-IH-benz[e]isoquinolin-1-one hydrochloride of formula-VI. In the prior art compound of formula-VI or its base are used in the catalytic hydrogenation. But the selection of solvents like acetic acid or THF rendered them commercially not viable due to low yield and low purity of palonosetron hydrochloride. In the present process simple solvent like methanol and readily available palladium-on-carbon were used to increase the yield and purity of palonosetron hydrochloride. Palonosetron Hydrochloride is useful as an anti-emetic agent during the chemotherapy of treatment of cancer patients and is marketed under the brand names ‘Aloxi’ and ‘Onicit’.
AN IMPROVED PROCESS FOR THE PREPARATION OF PURE PALONOSETRON HYDROCHLORIDE

FIELD OF INVENTION:
The present invention relates to an improved process for the preparation of pure Palonosetron Hydrochloride which is (3as)-2[(3s)-l-azabicyclo[2.2.2] Oct-3-yl]-2,3,3a,4,5,6-hexahydro-lH-benz[de]isoquinoline-l-one monohydrochloride of formula-I.

![Chemical Structure](image)

Palonosetron Hydrochloride is useful as anti-emetic agent during the chemotherapy treatment of cancer patients. It is marketed under the brand name ‘Aloxi’ and ‘Onicit’.

BACKGROUND OF INVENTION:
Palonosetron Hydrochloride is introduced for the first time by SYNTAX INC., a U.S. based company. Palonosetron Hydrochloride is a tricyclic 5-HT3 receptor antagonist containing a bridged bicyclic amine substituent.

Serotonin, a neurotransmitter with mixed and complex pharmacological characteristics, was first discovered in 1948 and subsequently has been the subject of the substantial research. Serotonin also referred to as 5-hydroxytryptamine (5-HT), acts both centrally and peripherally on discrete 5-HT receptors.

5-HT receptors are presently delineated into three major subclasifications-5HT1, 5-HT2 and 5-HT3 each of which may also be heterogenous. Receptors of the 5-HT3 subclass pervade autonomic neurons and appear to regulate the release of a variety of neurotransmitters in the gastrointestinal, cardiovascular and central nervous systems.

5-HT3 receptors are located in high densities on neurons associated with the emetic reflex and drugs which block the interactions of serotonin at the 5-HT3 receptor level, i.e., 5-
HT$_3$ receptor antagonists possess potent anti-emetic properties. Such antagonists demonstrate utility for counteracting the emetic effects of cancer chemotherapy and radiotherapy.

Process for the preparation of Palonosetron Hydrochloride is described in EP 0430190A$_2$ (1991) and US 5202333 (1993) patents. The process comprises of coupling reaction of 5,6,7,8-tetrahydro-l-naphthoyl chloride of formula-II,

\[
\text{II} \quad \text{Cl} \quad \text{H} \quad \text{H} \\
\text{N} \quad \text{H}_2
\]

with (S)-3-amino-l-azabicyclo[2.2.2]octane of formula-III

\[
\text{III} \quad \text{H}_2 \quad \text{N} \quad \text{H} \\
\text{H} \quad \text{H} \quad \text{N} \quad \text{H}
\]

to yield (S)-3-amino-l-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-l-naphthalenecarboxamide of formula-IV,

\[
\text{IV} \quad \text{H} \quad \text{H} \quad \text{N} \quad \text{H} \quad \text{N} \quad \text{H} \\
\text{Cl} \quad \text{H} \quad \text{H} \quad \text{N} \quad \text{H}
\]

Formylation of compound of formula-IV with N, N-dimethylformamide in the presence of n-Buli (1.6M solution in n-hexane) in inert solvents (like Tetrahydrofuran) followed by dehydration affords (S)-2[1-azabicyclo[2.2.2]oct-3-yl]-2,4,5,6-tetrahydro-lH-benz[de]iso-quinoline-l-one of formula-V, and is isolated as monohydrochloride salt of formula-VI.
The compound of formula-V as free base is hydrogenated in the presence of acetic acid, containing few drops of 70% perchloric acid, 20% palladium hydroxide-on-carbon at 85°C for 24 hours. The catalyst is removed by filtration and the filtrate is concentrated under reduced pressure. The residue is dissolved in water, basified with ammonium hydroxide solution and extracted with ethyl acetate. The solvent is evaporated to yield Palonosetron free base, which is recrystallized in ethanolic HCl, isopropyl alcohol, and ether to get Palonosetron HCl of formula-I.

The process disclosed in EP 0430190A2 and US 5202333 suffer from the following disadvantages, particularly at the final catalytic hydrogenation stage:

1. Usage of corrosive chemicals like acetic acid and perchloric acid.
2. Elevated temperature requirement (85°C) for long hours (24 hours)
3. Usage of expensive catalyst (20%) palladium hydroxide-on-carbon) in hydrogenation.
4. Purity of the product obtained is not mentioned.

The same process for catalytic hydrogenation of compound of formula-V to get compound of formula-I is published in J. Med. Chem. 1993, 36, 2645-2657.

The PCT application WO 96/01824 and the publication Synthesis, 1996, 7, 816-818 deals with alternative procedures to carry out the same conversion by hydrogenation process. In this process tetrahydrofuran (THF) is used as solvent and the reaction is carried out for more than 5 days at room temperature. Finally the compound of formula-I is obtained in a purity of 97% after treating with aqueous hydrochloric acid and isopropyl alcohol.
Reported optical rotation of the product is $[\alpha]_D^{25} -90.4^\circ$ (C=1.4, CHCl$_3$). This process also is beset with the disadvantages like very long reaction times of the order of six days and use of expensive solvent like tetrahydrofuran.

When the experimental procedures of US 5202333 (1993) and PCT application WO 96/01824 patents are repeated in our laboratory difficulties are encountered in getting desired product in reproducible yields and purity. The reaction is never complete and the unreacted starting material of formula-V is always present to the extent of 7-10%.

The unreacted compound of formula-V is difficult to remove by crystallization techniques, as the solubility properties of this compound and Palonosetron HCl are very close. Palonosetron HCl produced by this method being only 90-93% pure, is not suitable for pharmaceutical applications.

**SUMMARY OF THE INVENTION:**

Keeping in view of the difficulties at the hydrogenation step, we aimed to develop an improved process for the catalytic hydrogenation of compound of formula-V to generate pharmaceutical grade Palonosetron HCl of high purity.

Accordingly, the main objective of the present invention is to provide an improved process for catalytic hydrogenation of compound of formula-V, which is simple to adopt on commercial scale.

Another objective of the present invention is to provide an improved process for catalytic hydrogenation of compound of formula-V avoiding elevated temperatures.

Still another objective of the present invention is to provide an improved process for catalytic hydrogenation of compound of formula-V, which involves shorter reaction time.

Yet another objective of the present invention is to provide improved process for the catalytic hydrogenation of compound of formula-V avoiding the usage of hazardous chemicals like perchloric acid.
Still another objective of the present invention is to provide an improved process for catalytic hydrogenation by using compound of formula-VI, as starting material.

Still another objective of the present invention is to produce palonosetron HCl of high purity (>99.8% by HPLC) suitable for pharmaceutical applications.

Thus the process of the present invention is simple, reproducible, cost effective and non-hazardous and hence can be well suited for large scale manufacturing operations.

**DESCRIPTION OF INVENTION:**

The present invention is related to an improved process for the preparation of palonosetron HCl of formula-I,

\[ \text{I} \]

Which comprises:

(i) dissolving (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one hydrochloride salt of formula-VI

\[ \text{VI} \]

in an aliphatic alcohol solvent;

(ii) adding palladium catalyst to the reaction mass;

(iii) hydrogenating the reaction mass at 50 PSI at 25-75°C for 24 hours;

(iv) filtering the catalyst and evaporating the solvent from filtrate under reduced pressure to yield residue of palonosetron hydrochloride salt;
(v) leaching the residue of palonosetron hydrochloride obtained from step-(iv) with aqueous lower aliphatic alcohol at room temperature;
(vi) purifying the leached product by recrystallizing in suitable solvent or solvent mixture;
(vii) isolating the pure pharmaceutical grade palonosetron hydrochloride by filtration.

The solvent used as reaction medium in step (i) selected from lower aliphatic alcohols such as methanol, ethanol, isopropanol, n-butanol etc., preferably methanol.

The palladium catalyst used in step (ii) for hydrogenation is selected from 5% Pd/C, 10% Pd/C, 20% Palladium hydroxide on carbon etc., preferably 10% Pd/C. Temperature of reaction mass in step (iii) is range of 25-75°C, more preferably 25-35°C. The solvent used in step (v) for leaching the palonosetron hydrochloride salt is selected from aqueous lower aliphatic alcohols such as aqueous methanol, aqueous ethanol, aqueous isopropanol, preferably aqueous isopropanol.

The solvent used in step (vi) for the recrystallization of palonosetron hydrochloride salt is selected from lower aliphatic alcohols such as methanol, ethanol, isopropanol, n-butanol, etc.; esters such as ethyl acetate, methyl acetate; ketones such as acetone; ethers such as diethyl ether, isopropyl ether, tert-butylmethyl ether and hydrocarbons such as hexane, heptane, toluene, xylene or combination thereof. Preferred alcoholic solvent is methanol and the ether solvent is tert-butyl methyl ether or a combination of methanol/tert-butyl methyl ether. The temperature of reaction mass in step (vi) is 0-35°C preferably 10-35°C, more preferably 25-35°C.

Crystalline form of the Palonosetron HCl of the present invention is having chemical purity of >99.8% by HPLC, optical purity of >99% and optical rotation ($\alpha$)$_{D}^{25}$ = (−)1° to (−)105° (c = 0.4 in H$_2$O).

Thus by employing a salt of formula-VI as starting material instead of its base of formula-V in hydrogenation step, high purity (>99.8%) of Palonosetron HCl is generated by simple crystallization techniques.
The present invention is illustrated by the following example, which is not intended to limit the effective scope of the invention.

**Example**

**Process for the preparation of** (3as)-2[(3s)-1-Azabicyclo[2.2.2]Oct-3-yl]-2,3,3a,4,5,6-hexahydro-lH-benz[de]isoquinoline-1-one monohydrochloride [Palonosetron.HCl] (S)-2[1-Azabicyclo[2.2.2]Oct-3-yl]-2,4,5,6-tetrahydro-lH-benz[de]isoquinoline-1-one monohydrochloride (25.0 g) of formula-VI is dissolved in methanol (250 ml) and 10% Pd/C (25 g) is added to the solution. The reaction mass is hydrogenated at 50 psi at room temperature for 24 hours. Progress of the reaction is monitored by TLC. Upon completion of reaction the catalyst is filtered and the filtrate is evaporated in vacuo to get Palonosetron.HCl as residue.

To the above residue, isopropanol (180 ml) is added, stirred for 20 min at room temperature and water (6.0 ml) is added. The resulting suspension is stirred at room temperature for 2 hours. The product is filtered of and dried for 2 hours at 65-70°C. The resulting white solid is dissolved in methanol (64 ml) at 60-65°C and charcoal (2.0 g) is added to the solution. The reaction mass is stirred at 60-65°C for 45 minutes and charcoal is filtered on hyflo bed and washed with methanol (10 ml).

The filtrate is cooled to room temperature, stirred for 30 minutes. tert-Butyl methyl ether (74 ml) is added and stirred for 2 hours. The resulting white crystalline solid of Palonosetron monohydrochloride is filtered off under suction and the product is dried at 65-70°C for 6 hours under vacuum (25mm Hg).

Weight of the product = 8.3 g

HPLC purity (chemical): ≥ 99.80%. Chiral purity: > 99%.

(αD)25 = -102.19° (c=0.4 in H2O).

**ADVANTAGES OF PRESENT INVENTION:**

1. Present process provides simple, improved catalytic hydrogenation process.
2. Avoiding the usage of corrosive and hazardous chemicals like perchloric acid.
3. Avoiding the high temperature reactions.
4. Avoiding longer hours reaction time.
5. Present process provides simple isolation techniques, which avoids lengthy work-up process involving acidification or basification, extraction, distillation etc.
6. Present process produces high purity of palonosetron hydrochloride, which is suitable directly for pharmaceutical applications.
WE CLAIM:

1. Improved process for the preparation of Palonosetron hydrochloride of the formula-I,

\[
\text{I}
\]

which comprises

(i) dissolving (S)-2-[1-Azabicyclo[2.2.2]Oct-3-yl]-2,4,5,6-tetrahydro-1H-benz[de] isoquinolin-1-one monohydrochloride of formula-VI in an aliphatic alcohol;

\[
\text{VI}
\]

(ii) adding palladium catalyst to the reaction mass;

(iii) hydrogenating the reaction mass at 50 PSI at 25-75°C for 24 hours;

(iv) filtering the catalyst and evaporating the solvent from filtrate under reduced pressure to yield residue of palonosetron hydrochloride salt;

(v) leaching the residue of palonosetron hydrochloride obtained from step-(iv) with aqueous lower aliphatic alcohol at room temperature;

(vi) purifying the leached product by recrystalizing in suitable solvent or solvent mixture;

(vii) isolating the pure pharmaceutical grade palonosetron hydrochloride by filtration.

2. The process according to claim 1, wherein the solvent used as reaction medium in step (i) selected from lower aliphatic alcohols such as methanol, ethanol, isopropanol, n-butanol etc. preferably methanol.
3. The process according to claims 1 and 2, wherein the palladium catalyst used in step (ii) for hydrogenation is selected from 5%Pd/C, 10%Pd/C, 20% Palladium hydroxide on carbon etc., preferably 10% Pd/C.

4. The process according to claims 1-3, wherein the temperature of reaction mass in step (iii) is range of 25-75°C, more preferably 25-35°C.

5. The process according to claims 1-4, wherein the solvent used in step-(v) for leaching the Palonosetron hydrochloride is selected from aqueous lower aliphatic alcohols such as aqueous methanol, aqueous ethanol, aqueous isopropanol etc. preferably aqueous isopropanol.

6. The process according to claims 1-5, wherein the solvent used in step (vi) for the recrystallization of palonosetron hydrochloride salt is selected from lower aliphatic alcohols such as methanol, ethanol, isopropanol, n-butanol etc., and esters such as ethyl acetate, methyl acetate etc., ketones such as acetone and ethers such as diethyl ether, isopropyl ether, tert-butyl methyl ether and hydrocarbons such as hexane, heptane, toluene, xylene or combination thereof, more preferably methanol or methanol:tert-butyl methyl ether.

7. The process according to claims 1-6 wherein the temperature of reaction mass in step (vi) is 0-35°C, preferably 10-35°C, more preferably 25-35°C.

8. Purity of Palonosetron hydrochloride obtained according to the process of present invention is >99.8% (HPLC), chiral purity >99%, (α)25D = (-)l θl to (-)105° (c = 0.4 in H2O).
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D453/02 A61K31/439 A61P1/08

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 A61K A61P

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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.

See patent family annex

Date of the actual completion of the international search
20 November 2008

Date of mailing of the international search report
27/11/2008

Name and mailing address of the ISA/
European Patent Office, P.B. 5618 Patentlaan 2 NL - 2280 HW Rijswijk Tel: (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer

Bourghida, E
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

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Fees: PCT/ISA/210 (patent family annex) (April 2005)