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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 November 2009 (12.11.2009)

PCT

(10) International Publication Number
WO 2009/136405 A1

(51) International Patent Classification:
C07D 453/02 (2006.01)

(21) International Application Number:
PCT/IN2008/000285

(22) International Filing Date:
5 May 2008 (05.05.2008)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

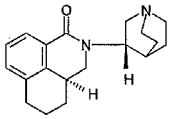
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2009/136405 A1

(54) **Title**: HIGH PURITY PALONOSETRON BASE AND ITS SOLID STATE CHARACTERISTICS



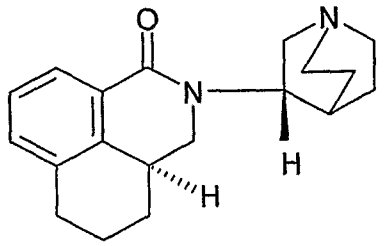
(I)

(57) **Abstract**: The present invention describes the process for the preparation of pure enantiomeric form of palonosetron base of formula (I), and its solid-state characteristics of said compound.

HIGH PURITY PALONOSETRON BASE AND ITS SOLID STATE CHARACTERISTICS

FIELD OF INVENTION:

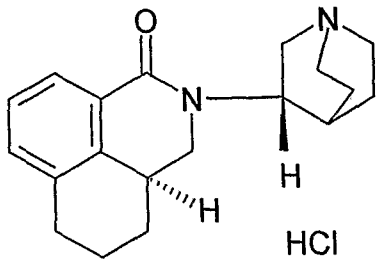
The present invention relates to an improved process for the preparation of high purity (> 99.8% chemical and >99.9% chiral by HPLC) crystalline palonosetron base. The present invention also describes the solid-state characteristics of palonosetron base. Palonosetron base is (3as)-2[(3s)-1-azabicyclo[2.2.2] oct-3-yl]-2,3,3a, 4,5,6-hexahydro-1H-benz [de] isoquinoline-1-one of formula-I,



I

BACKGROUND OF THE INVENTION:

Palonosetron hydrochloride, the active pharmaceutical ingredient is introduced for the first time by **Syntex Inc.** a U.S based company. Palonosetron Hydrochloride is useful as anti-emetic agent during the chemotherapy of treatment of cancer patients. It is marketed globally under the brand names 'Aloxi' and 'Onicit'. Pure enantiomeric form of Palonosetron hydrochloride is (3as)-2[(3s)-1-Azabicyclo [2.2.2] oct-3-yl]-2,3,3a, 4,5,6-hexahydro-1H-benz [de] isoquinoline-1-one monohydrochloride of formula-II



II

Palonosetron Hydrochloride is tricyclic 5-HT_3 receptor antagonist containing a bridged bicyclic amine substituent.

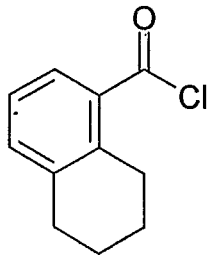
Serotonin, a neurotransmitter with mixed and complex pharmacological characteristics, was first discovered in 1948 and subsequently has been the subject of the substantial research. Serotonin also referred to as 5-hydroxy tryptamine (5-HT), acts both centrally and peripherally on discrete 5-HT receptors.

5-HT receptors are presently delineated into three major subclasifications-$5HT_1$, 5-HT_2 and 5-HT_3 each of which may also be heterogenous. Receptors of the 5-HT_3 subclass pervade autonomic neurons and appear to regulate the release of a variety of neurotransmitters in the gastrointestinal, cardiovascular and central nervous systems.

5-HT_3 receptors are located in high densities on neurons associated with the emetic reflex and drugs which block the interactions of serotonin at the 5-HT_3 receptor level, i.e. 5-HT_3 receptor antagonists posses potent anti-emetic properties. Such antagonists demonstrate utility for counteracting the emetic effects of cancer chemotherapy and radiotherapy.

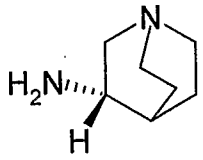
Neither the process for the preparation of palonosetron base nor its solid-state characteristic properties have been reported till date in the literature.

The process for the preparation of palonosetron hydrochloride is disclosed in the patents **EP 0430190 A_2 (1991)** and **US 5202333 (1993).** The process comprises of coupling reaction of 5,6,7,8-tetrahydro-1-naphthoyl chloride of formula-III,



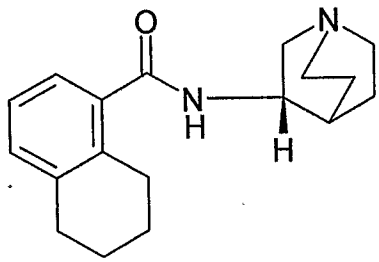
III

with (S)-3-amino-1-azabicyclo[2.2.2]octane of formula-IV,



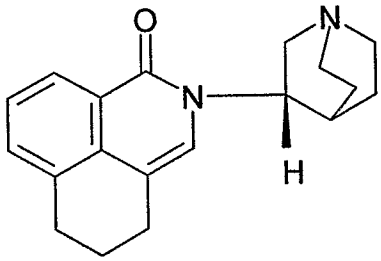
IV

to yield (S)-3-amino-1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalene carboxamide of formula-V,

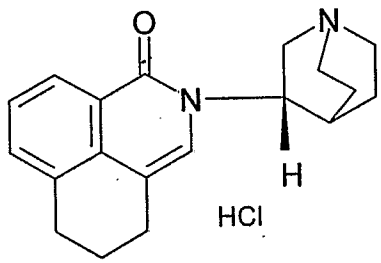


V

Formylation of compound of formula-V with N,N-dimethyl formamide in the presence of n-Buli (1.6M solution in n-Hexane) in inert solvents (like Tetrahydrofuran) followed by dehydration afforded (S)-2[1-Azabicyclo[2.2.2]Oct-3-yl]-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one of formula-VI, and is isolated as monohydrochloride salt of formula-VII,



VI



VII

The compound of formula-VI as free base is hydrogenated in the presence of acetic acid, containing a 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 a

residue, which is recrystallized from ethanolic hydrochloric acid, isopropyl alcohol and ether to get Palonosetron HCl of formula-II.

The same process for catalytic hydrogenation of compound of formula-VI to get palonosetron hydrochloride of compound of formula-II is published in **J. Med. Chem. 1993, 36, 2645-2657.**

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

1. Usage of corrosive chemicals likes 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.
4. Purity of the product is not mentioned.

The patent **WO 96/01824** and the publication **synthesis, 1996,7,816-818** deal with alternative procedure to carryout the same hydrogenation process. In this process compound of formula-VI is dissolved in tetrahydrofuran (THF), and the reaction is carried out in the presence of 10% palladium on charcoal catalyst for more than 5 days at room temperature. After hydrogenation has been completed, the catalyst is filtered off and the solvent is evaporated under reduced pressure to yield a residue. The resulting residue is treated with isopropyl alcohol and conc. hydrochloric acid to afford palonosetron hydrochloride of formula-II in a purity of 97%.

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** 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 (Formula-VI) is always present to the extent of 7-10%.

The unreacted compound of formula-VI 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 unsuitable for pharmaceutical applications.

A need is felt therefore, to investigate methods leading to the synthesis of palonosetron base of formula-I of high purity to enable its conversion to pharmaceutical grade Palonosetron.HCl of formula-II.

SUMMARY OF THE INVENTION:

Main objective of the present invention is to provide an improved process for the preparation of high chemical and enantiomeric purity palonosetron base of formula-I.

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

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

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

Yet another objective of the present invention is to provide an improved process for the catalytic hydrogenation of compound of formula-VII avoiding the usage of hazardous chemicals like perchloric acid.

Still another aspect of the present invention there is provided a process to isolate pure palonosetron base (I) in crystalline form by adapting simple crystallization techniques.

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.

According to yet another aspect of the present invention the crystalline form of pure enantiomeric form of palonosetron base is characterized by:

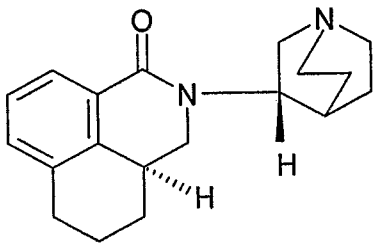
(i) Powder x-ray diffraction pattern (XRD) having peaks expressed as 2θ values at 10.54, 11.07, 11.88, 12.93, 13.77, 14.86, 15.48, 16.36, 16.91, 17.24,20.46, 20.99, 21.33, 21.77, 23.08, and 23.73 degrees.

(ii) Differential scanning calorimetric data (DSC): Peak 97.95°C

(iii) Absorption bands in the IR spectrum (KBr): 562, 694, 757, 976, 1054, 1190, 1322, 1425, 1589, 1639, 2868, 2938, and 3495 cm^{-1}.

DESCRIPTION OF INVENTION:

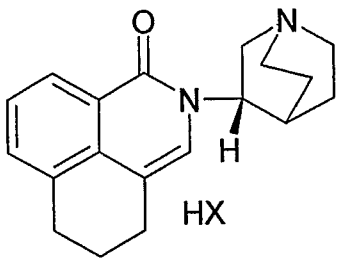
Accordingly, present invention provides an improved process for the preparation of more than 99.8% chemical and > 99.9% enantiomeric purity palonosetron base of formula-I,



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 acid addition salt of formula-VII (a),



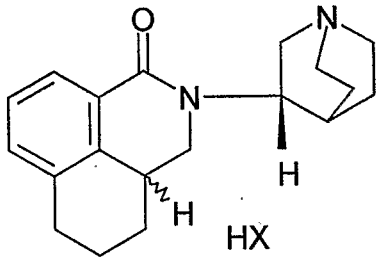
VII (a)

Wherein X= Cl, Br, oxalate, tartrate, or p-toluene sulfonate

in lower aliphatic alcohol at room temperature;

(ii) hydrogenating this solution in the presence of palladium catalyst at 25-75°C for 24 hours;

(iii) filtering the catalyst and evaporating the solvent under reduced pressure to get the residue of racemic mixture of palonosetron acid addition salt of formula-II(a),



II (a)

Wherein, X= Cl, Br, oxalate, tartrate, or p-toluene sulfonate

(iv) leaching the residue of racemic mixture of palonosetron acid addition salt obtained from step (iii) with aqueous C_1-C_4 aliphatic alcohol at ambient temperature;

(v) recrystallizing the palonosetron acid addition salt from step (iv) in a suitable solvent or a solvent mixture;

(vi) isolating the pure palonosetron acid addition salt by filtration;

(vii) treating the pure palonosetron acid addition salt with a base and extracting the base into an organic solvent;

(viii) distilling of solvent under reduced pressure to get palonosetron base;

(ix) purifying palonosetron base from a solvent to get chemically and enantiomerically pure palonosetron base.

The starting material used in step (i) is (S)-2[1-azabicyclo[2.2.2]oct-3-yl]-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one hydrochloride salt, hydro bromide salt, oxalate salt, tartarate salt, p-toluenesulphonate salt, preferably hydrochloride salt. The solvent used as reaction medium in step (i) selected from lower aliphatic alcohols such as methanol, ethanol, isopropanol, n-butanol, 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, preferably 10% Pd/C. The temperature of reaction mass in step (ii) is in the range of 25-75°C, more preferably 25-35°C. The solvent used in step (iv) for leaching the palonosetron acid addition salt is selected from aqueous lower aliphatic alcohols such as aqueous methanol, aqueous ethanol, aqueous isopropanol, preferably aqueous isopropanol.

The solvent used in step (v) for the crystallization of palonosetron acid addition 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 (v) is 0-35°C preferably 10-35°C, more preferably 25-35°C. The base used for treating pure palonosetron acid addition salt in step (vii) is selected from hydroxides and carbonates of alkali metals or alkali earth metals. Preferable hydroxides of alkali metals, more preferably sodium hydroxide. The organic solvent used for the extraction of liberated pure palonosetron base is selected from esters such as ethyl acetate, methyl acetate, isopropyl acetate or chlorinated solvents such as chloroform, dichloromethane, carbon tetra chloride, preferable ester solvent more preferably ethyl acetate.

Method selected for purification of palonosetron base is triturating with a solvent and/or crystallization from a solvent. The solvent used for leaching is selected from lower aliphatic ethers and saturated aliphatic hydrocarbons, preferably lower aliphatic ethers such as diethyl ether, diethyl ether, diisopropyl ether, dipropyl ether, tert-butyl methyl ether, more preferably tert-butyl methyl ether.

The solvent used for crystallization is selected from lower aliphatic ethers and saturated aliphatic hydrocarbons, preferably lower aliphatic ethers such as diethyl ether, diethyl ether, diisopropyl ether, dipropyl ether, tert-butyl methyl ether, more preferably tert-butyl methyl ether. The isolation temperature of palonosetron base in step (viii) is 0-35°C, preferably 25-30°C.

The process of present invention provides enantiomerically pure palonosetron base having a chiral purity of > 99.9% and $(\alpha)^{25}_{D}$ of -133.27° (c=0.5 in chloroform).

BRIEF DESCRIPTION OF DRAWINGS:

Figure 1 is X-ray Powder Diffraction pattern (XRPD) of racemic (S, S: R, S in 54:46 ratio) mixture of palonosetron base prepared according to the present invention.

Figure 2 is a Differential Scanning Calorimetric thermogram (DSC) of racemic (S,S : R,S in 54:46 ratio) mixture of palonosetron base prepared according to the present invention.

Figure 3 is an Infrared absorption spectrum (IR) of racemic (S,S : R,S in 54:46 ratio) mixture palonosetron base prepared according to the present invention.

Figure 4 is X-ray powder Diffraction Pattern (XRPD) of pure enantiomeric form of Palonosetron base prepared according to the present invention.

Figure 5 is a Differential Scanning Calorimetric thermogram (DSC) of pure enantiomeric form of palonosetron base prepared according to the present invention.

Figure 6 is an infrared absorption spectrum (IR) of pure enantiomeric form of palonosetron base prepared according to the present invention.

X-ray powdered diffraction pattern was measured on a Siemens D-5000 X-ray diffractometer having a copper –K alpha radiation. (1.5406A).

Differential scanning calorimetric data was measured on METTLER TOLEDO, MODEL: 823^e

The absorption bands of IR spectrometry were measured on PERKIN ELMER, MODEL: PARAGON 1000.

The details of the invention are given in the Examples given below which are provided to illustrate the invention only and therefore should not be construed to limit the scope of the present invention.

Example1

Preparation of racemic mixture of palonosetron base of formula-I (a)

(S)-2[1-Azabicyclo [2.2.2] Oct-3-yl]-2,4,5,6-tetrahydro-1H-benz [de] isoquinoline-1-one monohydrochloride (25.0 g) of formula-VII is dissolved in methanol (250 ml) and added 10% Pd/C (25 g) to the solution. The reaction mass is hydrogenated at 50 psi at room temperature for 24 hours. Progress of the reaction is followed by TLC. The catalyst is filtered of and the solvent is distilled of from the filtrate to get 25 g of palonosetron hydrochloride.

The above salt is treated with 25 ml of 25% aq. sodium hydroxide solution and extracted with ethyl acetate (3x100ml). Organic layer is separated, dried over anhydrous sodium sulphate and distilled of solvent under reduced pressure to yield 19 g of palonosetron base. The residue is crystallized from a mixture of ethyl acetate/hexane to get off white solid. The solid is dried at 50-55°C to afford pure palonosetron base (7.60 g).

Purity by HPLC = 99.61%. Chiral purity (by HPLC): 54: 46

$(\alpha)_D^{25}$ = -42.72° (c= 0.5% in chloroform)

Crystalline form of pure racemic mixture of palonosetron base is characterized by

(i) Powder x-ray diffraction pattern (XRD) having peaks expressed as 2θ values at 6.92, 10.67, 11.22, 12.86, 13.50, 14.85, 15.39, 16.11, 16.64, 16.99, 17.43, 17.77, 20.34, 21.54, 22.05, and 22.39 degrees.

(ii) Differential scanning calorimetric data (DSC): Peak at 84.55°C

(iii) Absorption bands in the IR spectrum (KBr): 553, 762, 980, 1056, 1154, 1328, 1428, 1588, 1637, 2872, 2939, 3313, and 3458cm^{-1}

Powder XRD: Showed in **figure 1.**

DSC thermogram: Showed in **figure 2.**

IR absorption bands: Showed in **figure 3.**

EXAMPLE 2

Preparation of pure enantiomeric form of palonosetron base of formula-I

(S)-2[1-Azabicyclo [2.2.2] Oct-3-yl]-2,4,5,6-tetrahydro-1H-benz [de] isoquinoline-1-one monohydrochloride (25.0 g) of formula-VI is dissolved in methanol (250 ml) and 10% Pd/C (25.0 g) is added to the above solution. The reaction mass is hydrogenated at 50 psi at room temperature for 24 hours. TLC is checked for completion of reaction and the catalyst is filtered of. The filtrate is evaporated in vacuum to get crude Palonosetron HCl.

IPA (180 ml) is added to the above crude palonosetron hydrochloride and stirred for 20 min at room temperature. Water (6 ml) is added to the reaction mass. The resulting suspension is stirred at room temperature for 2 hours. The reaction mass is filtered of and dried for 2 hours at 65-70°C. The Resulting white coloured solid is dissolved in methanol (64 ml) at 60-65°C and charcoal (2.0 g) is added to the above solution. The reaction mass is stirred at 60-65°C for 45 minutes and filtered on hyflo bed and the bed washed with methanol (10 ml). The filtrate is cooled to room temperature, stirred for 30 minutes, and 74 ml of tert-butyl methyl ether (TBME) is added. The reaction mass is stirred for 2 hours. The reaction mass containing white crystalline palonosetron

monohydrochloride is filtered off under suction and the product is dried at 65-70°C for 4 hours to yield pure palonosetron hydrochloride (6.7 g)

Above residue is treated with 6.7 ml of 25% aq. sodium hydroxide solution and extracted with ethyl acetate (3x15ml). Organic layer is separated, dried over anhydrous sodium sulphate and solvent is evaporated under reduced pressure to yield 6.0 g of palonosetron base. The resulting base is crystallized from tert-butyl methyl ether at room temperature. The white colored solid is filtered of and dried at 50-55°C under high vacuum (25mm) to afford pure enantiomeric form of palonosetron base (3.2g).

HPLC purity (chemical) ≥ 99.80%, Chiral purity: 100%, $(\alpha)_D^{25}$ = -133.27 (C=0.5 in chloroform).

Crystalline form of pure enantiomeric form of palonosetron base is characterized by
(i) Powder x-ray diffraction pattern (XRD) having peaks expressed as 2θ values at 10.54, 11.07, 11.88, 12.93, 13.77, 14.86, 15.48, 16.36, 16.91, 17.24,20.46, 20.99, 21.33, 21.77, 23.08, and 23.73 degrees.
(ii) Differential scanning calorimetric data (DSC): Peak 97.95°C
(iii) Absorption bands in the IR spectrum (KBr): 562, 694, 757, 976, 1054, 1190, 1322, 1425, 1589, 1639, 2868, 2938, and 3495 cm^{-1}
Powder XRD: Showed in **figure 4.**
DSC thermogram: Showed in **figure 5.**
IR absorption bands: Showed in **figure 6.**

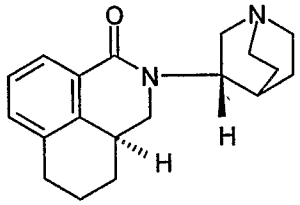
ADVANTAGES OF PRESENT INVENTION:

1. Present process provides simple, improved catalytic hydrogenation process.
2. Avoids the usage of corrosive and hazardous chemicals like perchloric acid.
3. Avoids high temperature reactions.
4. Avoids longer reaction time.
5. Present process produces crystalline racemic mixture and also pure enantiomeric form of palonosetron base in > 99.8 % purity by HPLC

6. The present invention provides the solid-state characteristics of racemic mixture and enantiomerically pure palonosetron base.

WE CLAIM:

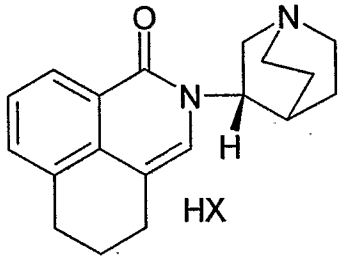
1. Improved process for the preparation of high purity (chemically > 99.8 % and enantiomerically > 99.9%) palonosetron base ((3as)-2[(3s)-1-azabicyclo[2.2.2] oct-3-yl]-2,3,3a,4,5,6-hexahydro-1H-benz [de] isoquinoline-1-one) of formula-I,



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 acid addition salt of formula-VII (a),



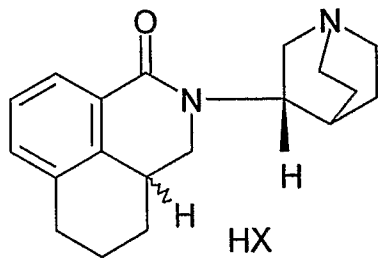
VII (a)

Wherein X= Cl, Br, oxalate, tartrate, or p-toluene sulfonate

in lower aliphatic alcohol at room temperature;

(ii) hydrogenating this solution in the presence of palladium catalyst at 25-75°C for 24 hours;

(iii) filtering the catalyst and evaporating the solvent under reduced pressure to get the racemic mixture of palonosetron acid addition salt of formula-II (a),



II (a)

Wherein, X= Cl, Br, oxalate, tartrate, or p-toluene sulfonate

(iv) leaching the residue of racemic mixture of palonosetron acid addition salt obtained from step (iii) with aqueous C_1-C_4 aliphatic alcohol at ambient temperature;

(v) recrystallizing the palonosetron acid addition salt from step (iv) in a suitable solvent or a solvent mixture;

(vi) isolating the pure palonosetron acid addition salt by filtration;

(vii) treating the pure palonosetron acid addition salt with a base and extracting the base into an organic solvent;

(viii) distilling of solvent under reduced pressure to get palonosetron base;

(ix) purifying palonosetron base from a solvent to get chemically and enantiomerically pure palonosetron base.

2. The process according to claim 1, wherein the starting material used in step (i) is (S)-2[1-azabicyclo[2.2.2]oct-3-yl]-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one hydrochloride salt, hydro bromide salt, oxalate salt, tartarate salt, p-toluenesulphonate salt, preferably hydrochloride salt.

3. The process according to claims 1 and 2, wherein the solvent used as reaction medium in step (i) selected from lower aliphatic alcohols such as methanol, ethanol, isopropanol, n-butanol, preferably methanol.

4. The process according to claims 1-3, wherein the palladium catalyst used in step (ii) for hydrogenation is selected from 5% Pd/C, 10% Pd/C, 20% Palladium hydroxide-on-carbon, preferably 10% Pd/C.

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

6. The process according to claims 1-5, wherein the solvent used in step (iv) for leaching the palonosetron acid addition salt is selected from aqueous lower aliphatic alcohols such as aqueous methanol, aqueous ethanol, aqueous isopropanol, preferably aqueous isopropanol.

7. The process according to claims 1-6, wherein the solvent used in step (v) for the crystallization of palonosetron acid addition 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. More preferably methanol or methanol/tert butyl methyl ether.

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

9. The process according to claims 1-8, wherein the base used for treating pure palonosetron acid addition salt in step (vii) is selected from hydroxides and carbonates of alkali metals or alkali earth metals. Preferable hydroxides of alkali metals, more preferably sodium hydroxide.

10. The process according to claims 1-9, wherein the organic solvent used in step (vii) for the extraction of liberated pure palonosetron base is selected from esters such as ethyl acetate, methyl acetate, isopropyl acetate or chlorinated solvents such as chloroform, dichloromethane, carbon tetra chloride, preferable ester solvent more preferably ethyl acetate.

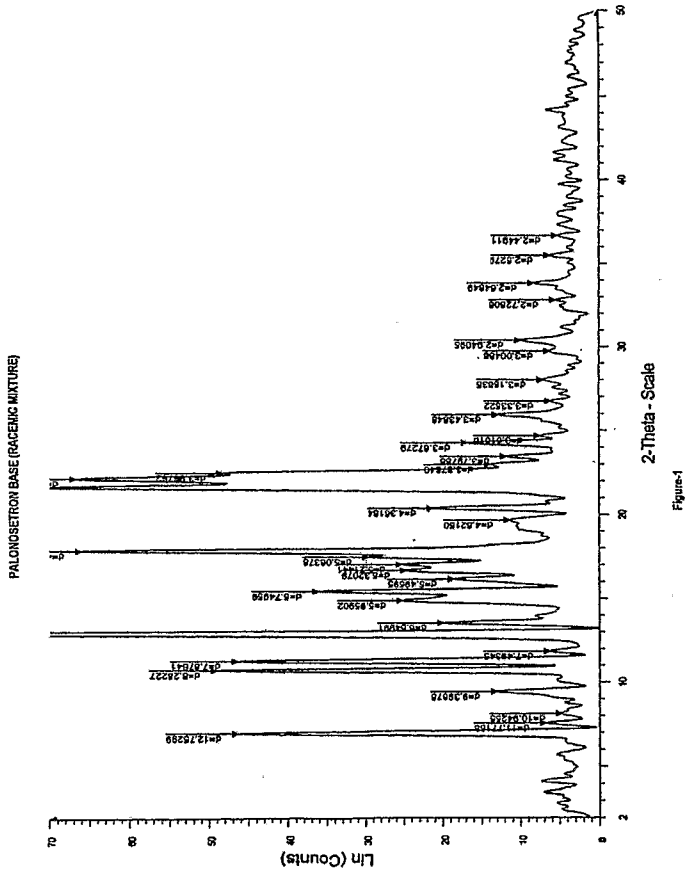
11. The process according to claims 1-10, wherein the purification method selected in step (ix) for purification of palonosetron base is triturating with a solvent and/or crystallization from a solvent.

12. The process according to claim 11, wherein the solvent used for triturating is selected from lower aliphatic ethers and saturated aliphatic hydrocarbons, preferably lower aliphatic ethers such as diethyl ether, diethyl ether, diisopropyl ether, dipropyl ether, tert-butyl methyl ether, more preferably tert-butyl methyl ether.

13. The process according to claims 11 and 12 wherein the solvent used for crystallization is selected from lower aliphatic ethers and saturated aliphatic hydrocarbons, preferably lower aliphatic ethers such as diethyl ether, diethyl ether, diisopropyl ether, dipropyl ether, tert-butyl methyl ether, more preferably tert-butyl methyl ether.

14. The process as claimed in claims 1-13 for the preparation of enantiomerically pure palonosetron base having a chiral purity of > 99.9% and $(\alpha)^{25}_{D}$ of -133.27° (c=0.5 in chloroform).

Angle 2-Theta °	d value Angstrom	Intensity %
6.926	12.75299	47.3
7.504	11.77188	6.7
8.073	10.94255	4.7
9.402	9.39878	13.2
10.673	8.28227	50.1
11.225	7.87641	47.4
11.800	7.49345	6.2
12.866	6.87538	100.0
13.508	6.54991	20.2
14.854	5.95902	25.6
15.399	5.74959	36.9
16.114	5.49595	18.9
16.648	5.32079	25.1
16.990	5.21441	25.7
17.430	5.08378	30.2
17.777	4.98523	67.5
19.618	4.52150	11.5
20.344	4.36184	21.5
21.544	4.12134	72.6
22.052	4.02755	68.3
22.390	3.96762	49.3
22.924	3.87640	14.0
23.404	3.79788	11.9
24.213	3.67279	17.1
24.640	3.61016	7.5
25.891	3.43848	13.0
26.707	3.33522	6.1
27.980	3.18635	7.1
29.707	3.00488	6.2
30.368	2.94095	10.0
32.802	2.72806	5.4
33.817	2.64849	8.2
35.483	2.52790	6.1
36.664	2.44911	5.1



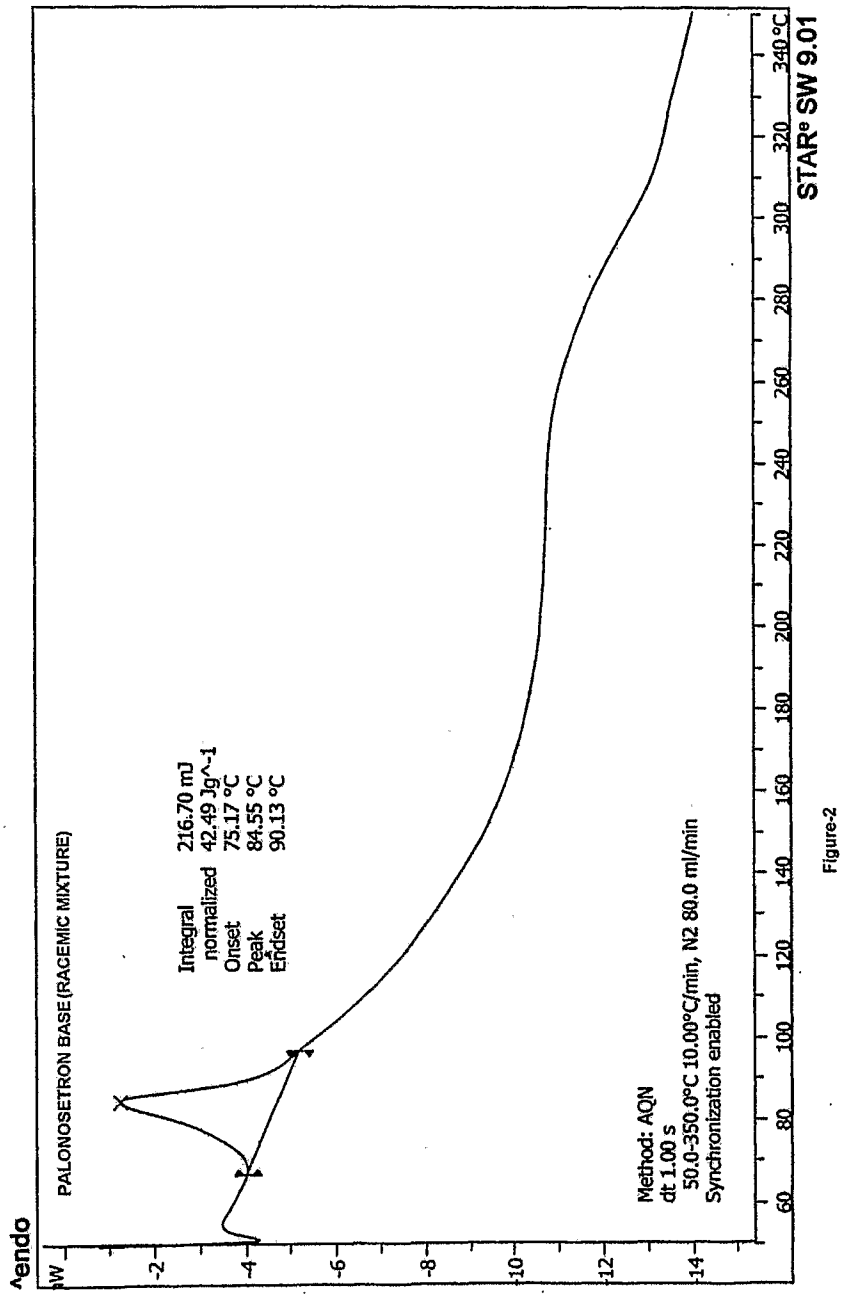

^endo
mW
PALONOSETRON BASE (RACEMIC MIXTURE)
Integral 216.70 mJ
normalized 42.49 Jg^-1
Onset 75.17 °C
Peak 84.55 °C
Endset 90.13 °C
Method: AQN
dt 1.00 s
50.0-350.0°C 10.00°C/min, N2 80.0 ml/min
Synchronization enabled
-2
-4
-6
-8
-10
-12
-14
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340 °C
STARe SW 9.01

Figure-2

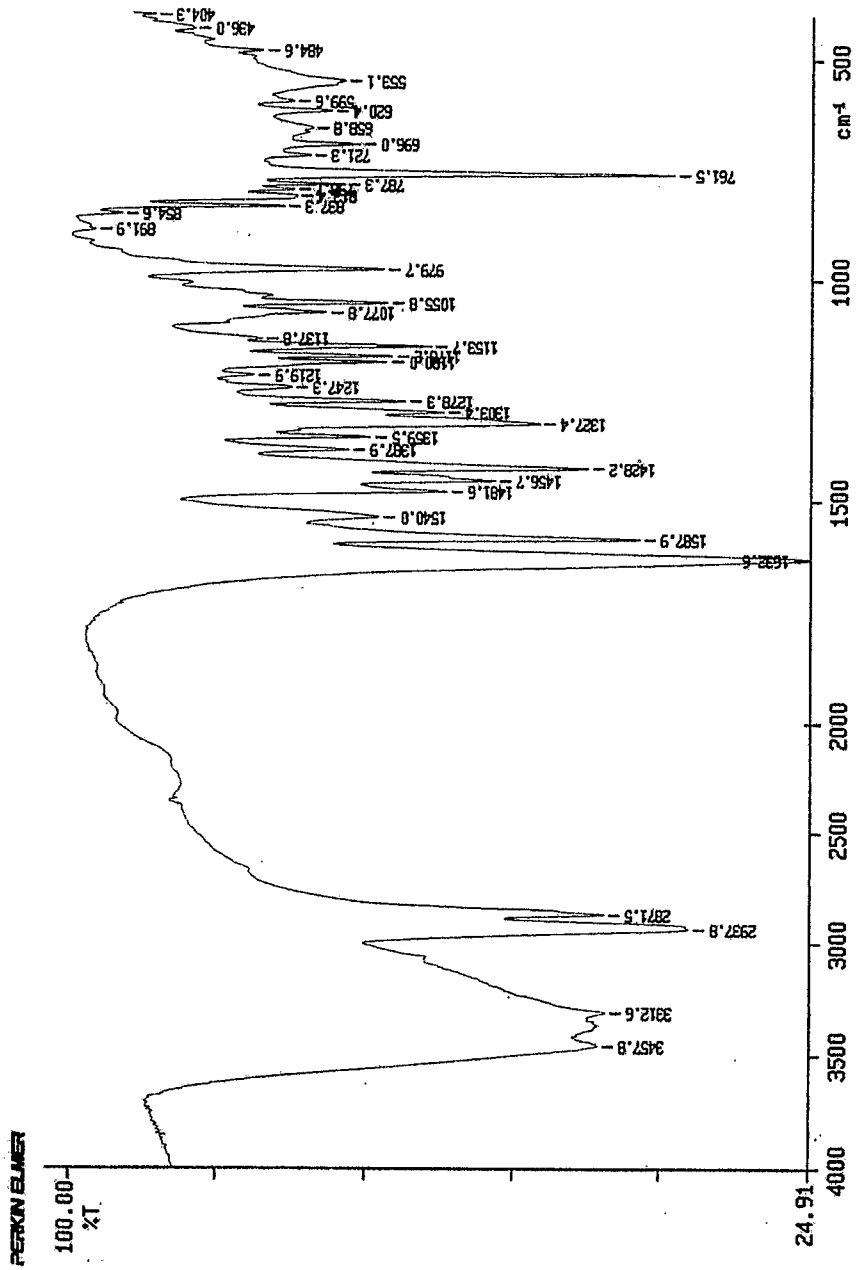


Figure-3

X: 1 scan, 4.0cm-1, flat, abex
PALONOSETRON BASE(RACEMIC MIXTURE)[KBr]

PALONOSETRON BASE(ENANTIOMER)

Angle 2-Theta °	d value Angstrom	Intensity % %
7.617	11.59684	9.1
8.398	10.52003	10.6
9.452	9.34905	4.5
10.543	8.38439	25.7
11.074	7.98351	42.2
11.888	7.43816	100.0
12.939	6.83643	26.2
13.777	6.42250	6.8
14.867	5.95382	41.6
15.485	5.71777	55.8
16.361	5.41363	18.7
16.913	5.23794	18.4
17.248	5.13703	46.7
17.798	4.97960	10.3
18.964	4.67597	7.0
19.396	4.57267	7.4
19.778	4.48520	6.8
20.460	4.33736	18.4
20.993	4.22836	26.2
21.334	4.16152	44.3
21.776	4.07811	30.3
22.370	3.97109	16.0
23.082	3.85018	41.2
23.733	3.74601	25.2
24.964	3.56395	9.2
25.655	3.46951	6.7
27.882	3.19731	4.8
29.788	2.99687	4.0
31.711	2.81945	6.3

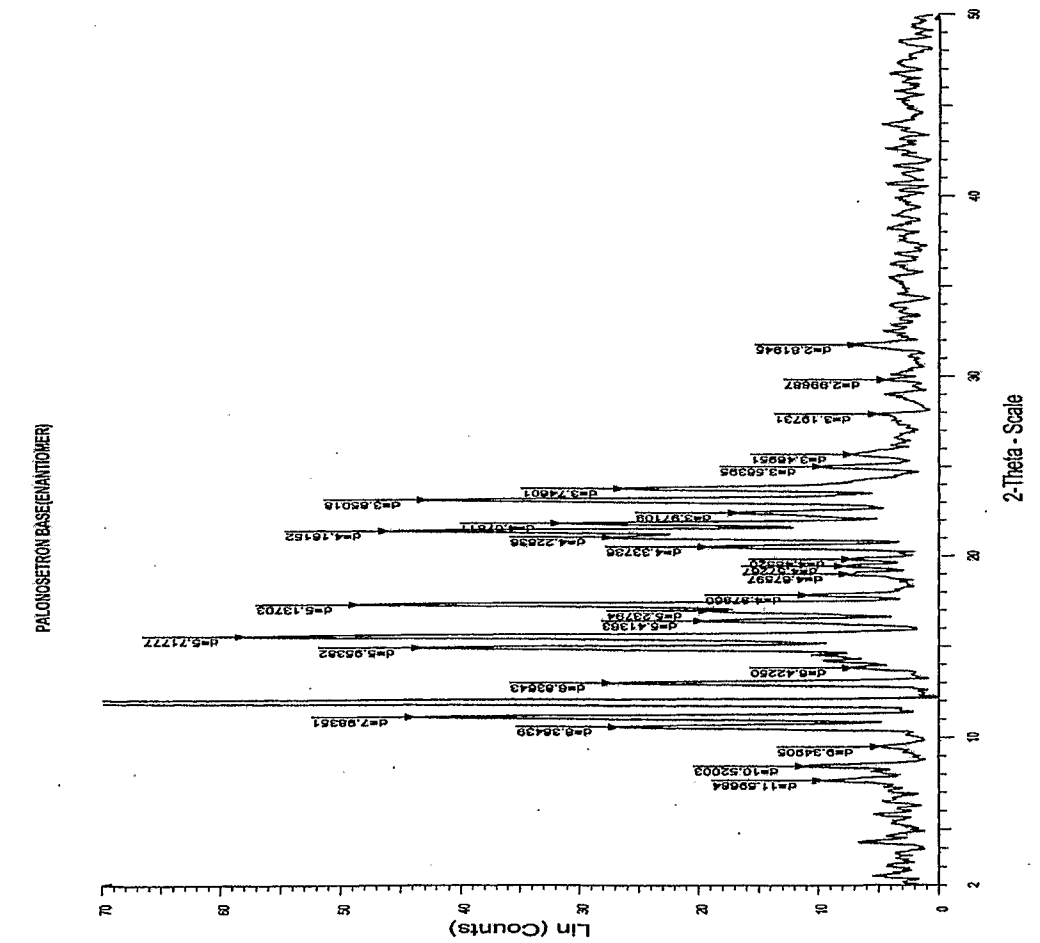


Figure-4

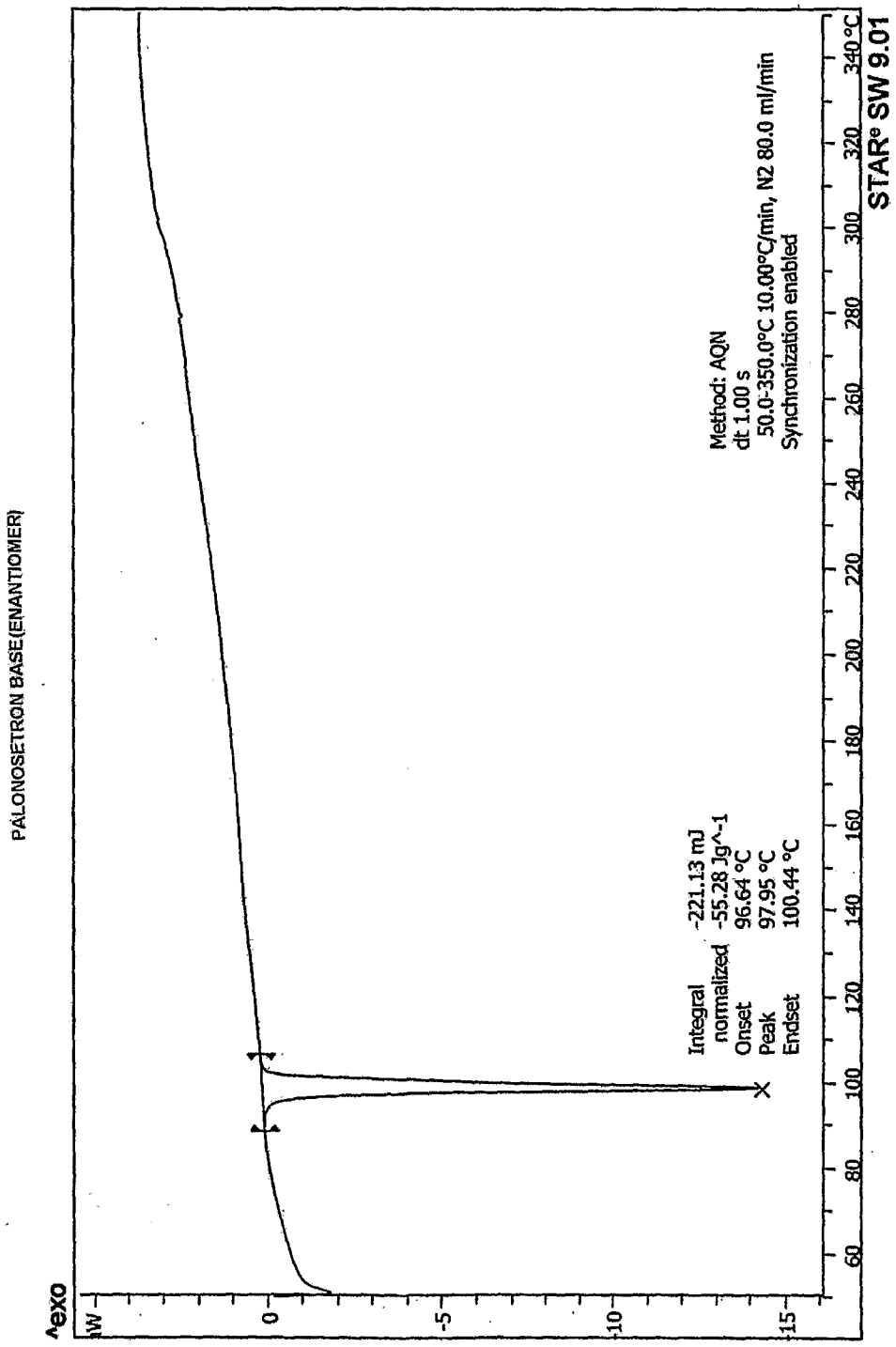
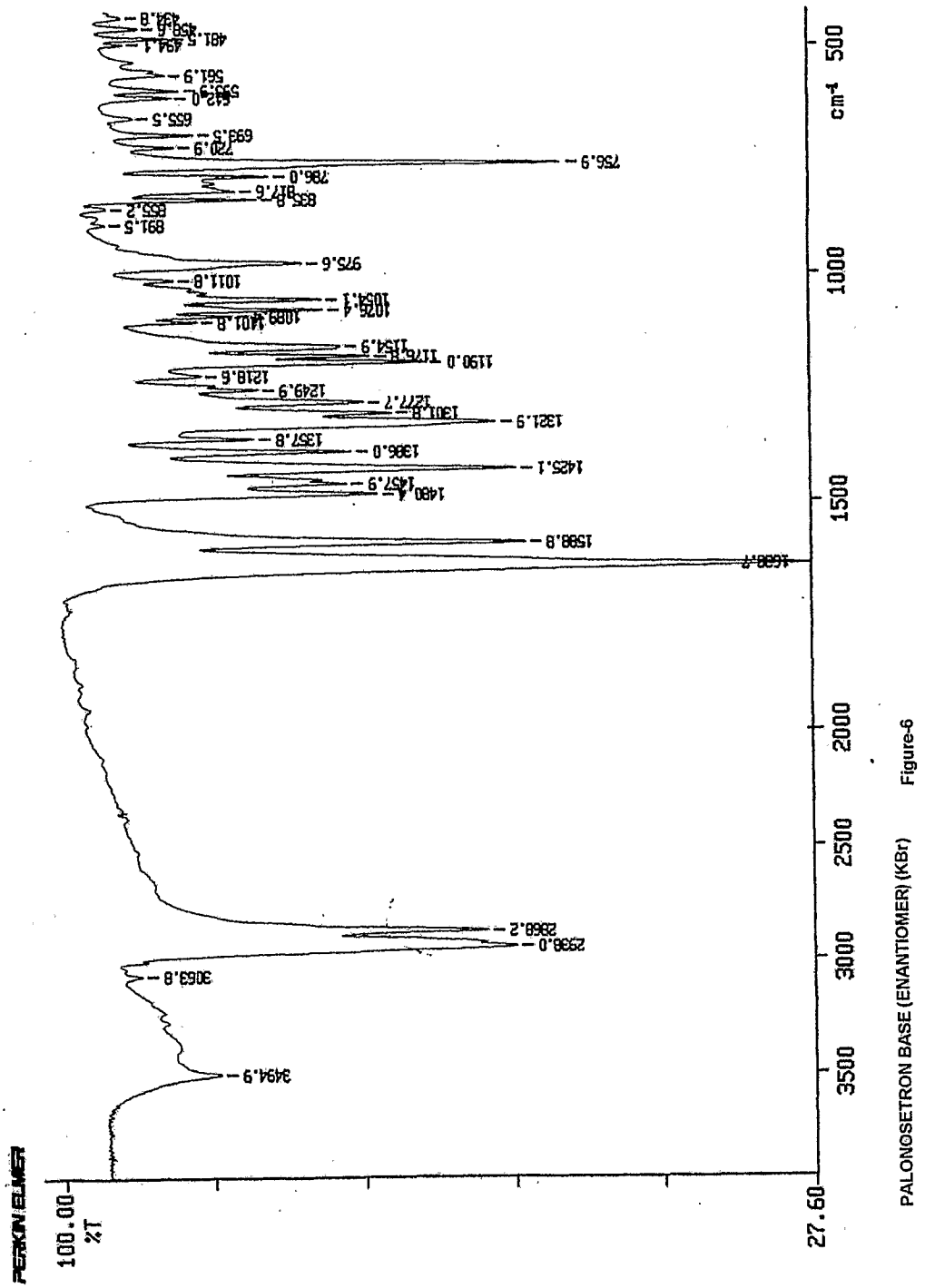

PALONOSETRON BASE(ENANTIOMER)
exo
mW
0
-5
-10
-15
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340 °C
Integral -221.13 mJ
normalized -55.28 Jg^-1
Onset 96.64 °C
Peak 97.95 °C
Endset 100.44 °C
Method: AQN
dt 1.00 s
50.0-350.0°C 10.00°C/min, N2 80.0 ml/min
Synchronization enabled
STARe SW 9.01

Figure-5



PALONOSETRON BASE (ENANTIOMER) (KBr) Figure-6

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2008/000285

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D453/02

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

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

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 430 190 A (SYNTEX INC [US]) 5 June 1991 (1991-06-05) cited in the application See Reactio scheme 1, page 14 and examples 7 and 9, pages 24-25.	1-14
Y	WO 2008/051539 A (SICOR INC [US]; ROSSETTO PIERLUIGI [CH]; MACDONALD PETER LINDSAY [CH];) 2 May 2008 (2008-05-02) See examples 5-10, pages 29-31.	1-14
Y	B. A. KOWALCZYK: "HYDROGENATION OF CHIRAL 1H-BENZ[DE]ISOQUINOLIN-1-ONE AND AN EQUILIBRATION USING PALLADIUM CATALYST" ORGANIC PROCESS RESEARCH & DEVELOPMENT, vol. 1, no. 2, 1997, pages 117-120, XP002506673 See tables 1-2, page 118.	1-14

-/--

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

[X] See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"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)

"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
15 January 2009	28/01/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Menchaca, Roberto

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2008/000285

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96/01824 A (HOFFMANN LA ROCHE [CH]; DVORAK CHARLES ALOIS [US]; KOWALCZYK BRUCE AND) 25 January 1996 (1996-01-25) cited in the application See lines 20-32, page 14. Example 7, pages 33-34.	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2008/000285

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