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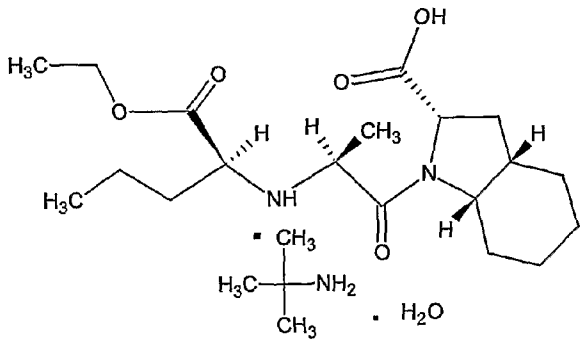
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(54) **Title:** PREPARATION OF NOVEL CRYSTALLINE FORM OF PERINDOPRIL ERBUMINE MONOHYDRATE



(III)

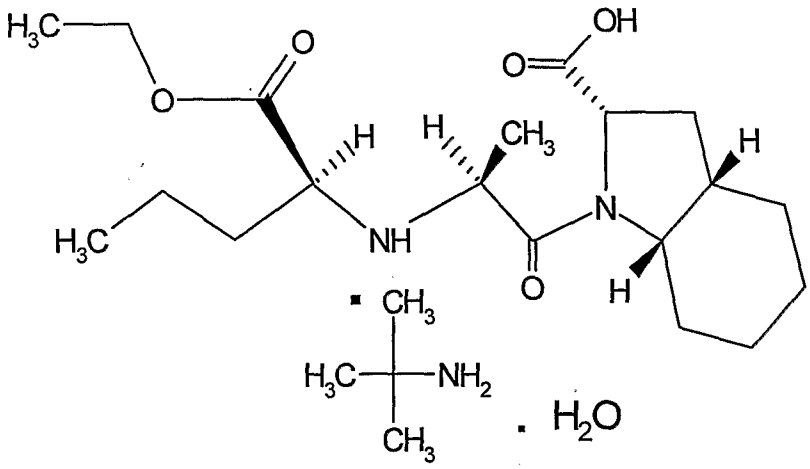
(57) **Abstract:** A novel crystalline form of Perindopril erbumine monohydrate of Formula (III) of characteristic 2θ values 8.87, 9.43, 9.60, 15.36, 15.96, 16.02, 19.97, 21.00, 21.13, 21.5, 22.14, 24.13, and 26.48. More particularly the present invention relates to a process for the preparation of the novel crystalline form of Perindopril erbumine monohydrate of Formula (III).

WO 2007/017893 A2

PREPARATION OF A NOVEL CRYSTALLINE FORM OF PERINDOPRIL ERBUMINE MONOHYDRATE

Field Of Invention

The present invention relates to a novel crystalline form of Perindopril erbumine monohydrate of Formula (III). More particularly the present invention relates to a process for the preparation of the novel crystalline form of Perindopril erbumine monohydrate of Formula (III).

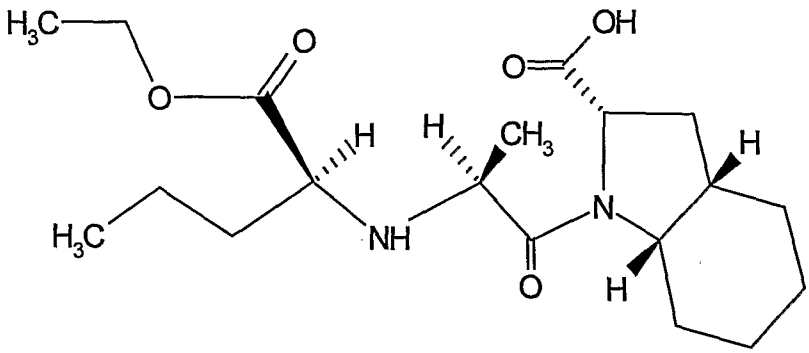


Perindopril Erbumine Monohydrate

Formula (III)

Background Of The Invention

The chemical species, (2S)-2-[(1S)-1-Carboethoxybutylamino]-1-oxopropyl-(2S, 3aS, 7aS) -octahydroindole-2-carboxylic acid of the formula (I) is generically known as Perindopril.

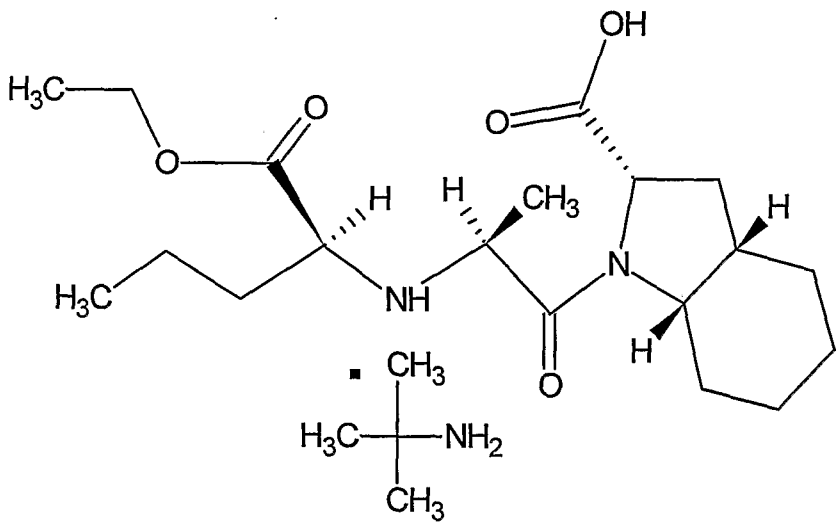


Perindopril
Formula (I)

Perindopril is disclosed in US Patent 4508729. Preparative processes described in this US patent are carried out in alcoholic medium, and in the presence of neutral dehydrating agent and an organic or inorganic cyanoborohydride. Deprotection processes can be carried out where necessary, for example with reference to hydrolysis and/or hydrogenolysis.

US Patent 4914214 discloses the process for preparation of perindopril and its t-butylamine salt. The process comprises condensation of protected ester of (2S, 3aS, 7aS)-2-carboxyperhydroindole with the (S, S) diastereoisomer of N-[(S)-1-carbethoxybutyl]-(S)-alanine, followed by deprotection employing charcoal containing 5% palladium and water, t-butylamine is then added to yield t-butyl amine salt of perindopril.

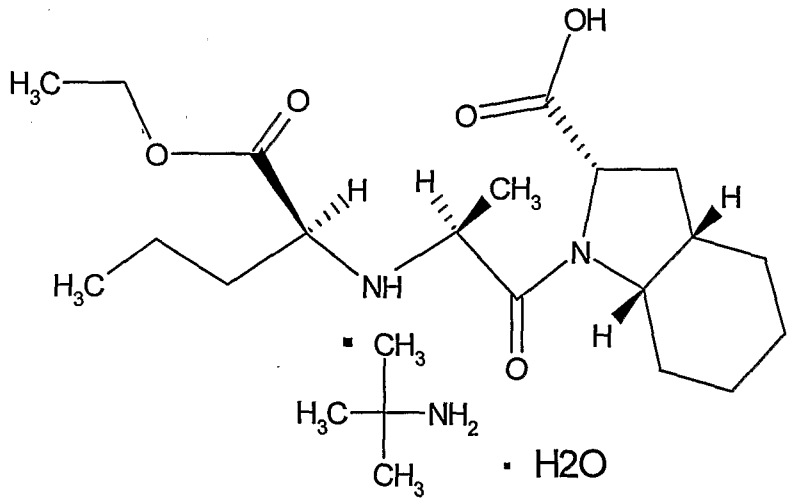
Perindopril erbumine and its pharmaceutically acceptable salts are active as angiotensin converting enzyme (ACE) inhibitors and thus are commercially valuable antihypertensive agents. Its pharmaceutically acceptable salts, especially t-butylamine / erbumine salt is represented by Formula (II).



Perindopril Erbumine

Formula (II)

Perindopril t-butylamine / erbumine monohydrate is represented by Formula (III).



Perindopril Erbumine Monohydrate

Formula (III)

GB2395195 discloses different XRD patterns of Perindopril erbumine monohydrate. It further teaches different methods for preparation of Perindopril erbumine monohydrate as follows:

a. Perindopril erbumine is suspended in acetone to which a calculated amount of water is added. The contents are heated to dissolve the solid and cooled to 10°C. Solid is separated by filtration and then dried.
b. Perindopril erbumine is suspended in ethyl acetate to which an appropriate quantity of water is added and the contents are heated to dissolve the solid and cooled to 10°C. Solid is separated by filtration and then dried.
c. Perindopril erbumine is suspended in acetonitrile to which known quantity of water is added and the contents are heated to dissolve and cooled. Solid is obtained by filtration and then dried.
d. Perindopril erbumine is suspended in ethyl acetate. The contents are heated to dissolve and then cooled to 10°C. Solid is obtained by filtration and air dried.

WO2005068425 discloses the new crystalline form of Perindopril, Where purification of obtained crude perindopril is done by filtration through the column. Columns are prepared with silica gel and is eluted with methylene dichloride / ethanol (94/6 v/v). Amorphous Perindopril so obtained is then dissolved in ethyl ether and crystallized first at room temperature followed by cooling to get new crystalline form having the melting range of 110-114°C.

WO2005037788 discloses a process for preparation of crystalline perindopril erbumine. The process comprises reacting a solution of perindopril in a solvent selected from N, N-dimethylformamide or dimethyl acetals of lower aliphatic aldehydes and ketones with tertiary butylamine and crystallization of the erbumine salt thus obtained by heating the reaction mixture to reflux, filtering hot, cooling gradually to 20°C to 30°C, and further cooling to 0°C to 15°C for 30 minutes to 1 hour and finally filtering off and drying the crystals.

The processes disclosed in prior art for the preparation of a crystalline form of Perindopril erbumine monohydrate does not describe any process as

such for removal of the undesirable associated pharmacopoeial impurities. Therefore, there is a long felt need for an improved process for preparing crystalline form of Perindopril erbumine monohydrate giving high purity.

The present invention has addressed the difficulties faced by the processes disclosed in prior art and have developed an excellent process for the purification of Perindopril erbumine monohydrate from (99%) pure material resulting into high purity (99.8%) and exhibiting characteristic 2θ values.

Object Of Invention

The object of the present invention is to provide a novel process for the preparation of a novel crystalline form of Perindopril erbumine monohydrate, which results in removal of undesirable impurities giving highly pure product.

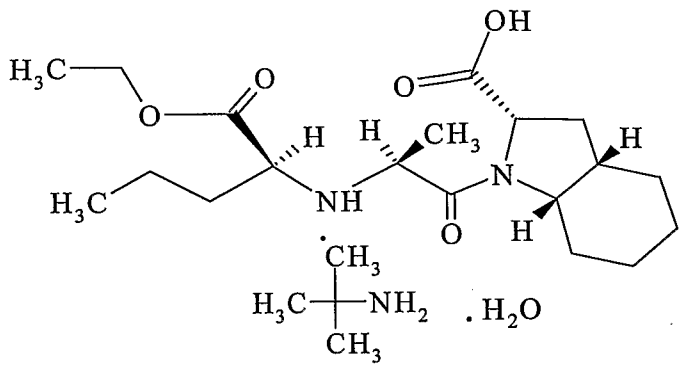
It is further object of the present invention to provide a novel crystalline form of Perindopril erbumine monohydrate exhibiting characteristic 2θ values, where the 2θ values are 8.87, 9.43, 9.60, 15.36, 15.96, 16.02, 19.97, 21.00, 21.13, 21.5, 22.14, 24.13, and 26.48.

Another object of the present invention is to provide a novel process for the purification of Perindopril erbumine which is of 99.8% purity.

Yet another object of the present invention is to provide a novel process for making Perindopril erbumine free from the described impurities.

Summary Of Invention

Thus according to an aspect of the present invention, there is provided a novel crystalline form of Perindopril erbumine monohydrate represented by Formula (III).



Perindopril Erbumine Monohydrate
Formula (III)

Wherein the novel polymorph of Perindopril erbumine monohydrate exhibits the characteristic 2θ as under: 8.87, 9.43, 9.60, 15.36, 15.96, 16.02, 19.97, 21.00, 21.13, 21.5, 22.14, 24.13 and 26.48.

According to another aspect of the present invention there is also provided a process for the preparation of the novel crystalline form of Perindopril erbumine monohydrate of Formula (III).

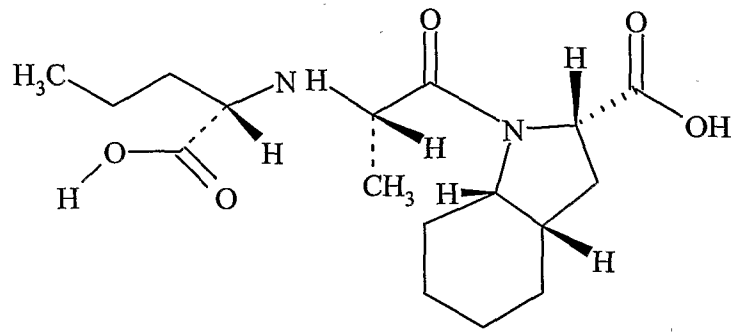
Detailed Description

According to the present invention, the novel process for preparing a novel crystalline form of Perindopril erbumine monohydrate is advantageous in terms of better removal of undesirable impurities and has a better solubility profile so as to achieve a highly pure product with characteristic 2θ values.

The powder X-ray diffraction spectrum of novel crystalline form of Perindopril erbumine monohydrate was measured under the following experimental conditions: where instrument used was analytical "X" pertpro, MPD system/multipurpose diffractometer, Holland. MPD system/multipurpose diffractometer, Holland. Measurement Temperature was 25 °C, Anode material used was Cu and Generator setting was 30mA, 40 kV. The Measurement range of (°2θ) was 4 to 49.98°, and Step size (°2θ) was 0.0170, the PSD mode was scanning and scan type is continuous.

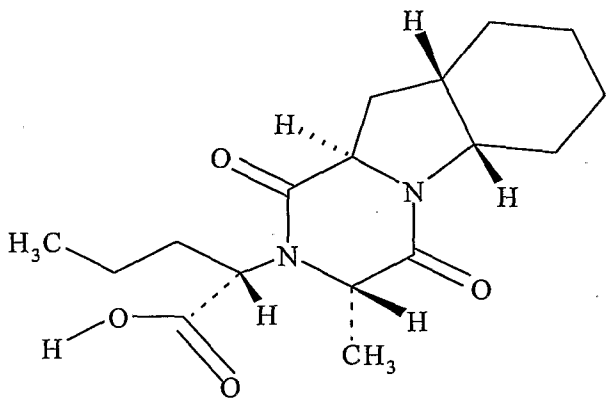
The present invention as disclosed herein relates to a novel and improved process for preparing a novel crystalline form of Perindopril erbumine monohydrate of Formula(III) and to make the process disclosed in prior art free from impurities as well as cost effective. However, while working it was found that Perindopril erbumine obtained by process disclosed in prior art remains associated with pharmacopoeial (EP-5) specified impurities viz. B, D and F shown by the structures given below and some unknown non-polar impurities.

PERINDOPRIL ERBUMINE IMPURITY B:



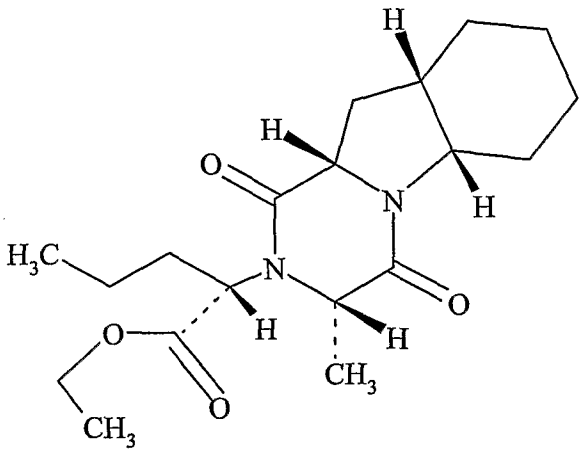
(2S,3aS,7aS)-1-[(2S)-2-[[(1S)-1-carboxybutyl]amino] propanoyl]octahydro-1H- indole-2- carboxylic acid

PERINDOPRIL ERBUMINE IMPURITY D:



(2S)-2-[(3S,5aS,9aS,10aS)-3-methyl-1,4-dioxodeca hydropyrazino[1,2-a]indol-2(1H)-yl]pentanoic acid

PERINDOPRI LERBUMINE IMPURITY F:



Ethyl (2S)-2-[(3A,5aS,9aS,10aS)-3-methyl-1,4-dioxidedecahydropyrazino[1,2-a]-2(1H)Pentanoate

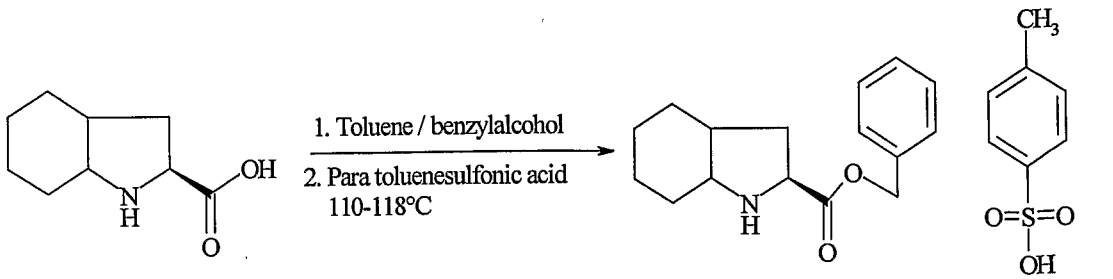
It was observed that impurities associated with Perindopril erbumine have different nature towards water. Hence, after the use of water during the

processing, it was found that impurity B is highly water soluble while impurity F is insoluble in water.

Perindopril Erbumine is prepared as per the process disclosed in the prior art. The process is reproduced as follows:

1) Preparation of (2S, 3aS, 7aS)-octahydroindole-2-benzyloxy carbonyl tosylate:

(2S, 3aS, 7aS)-Octahydroindole-2-benzyloxycarbonyl tosylate an important intermediate required for the purpose is made by reacting octahydrohydro indole-2-carboxylic acid, para toluene sulphonic acid and benzyl alcohol using aromatic hydrocarbon as solvent, wherein preferred solvent is selected from toluene, xylene and most preferred solvent used is toluene followed by heating the contents at 85-125°C preferably at 100-118°C. Reflux is continued till water is completely removed. Reaction mass is cooled to -5 to 15°C preferably at 0-5°C followed by addition of hexane and cooling is continued for 3-5 hours preferably 2-3 hours. Product is collected by filtration and is vacuum dried at 35-65°C preferably at 40-45°C. Crude so obtained is purified using isopropanol resulting into purity of (NLT 98%) with yield of 85-95% with respect to octahydro indole-2-carboxylic acid.

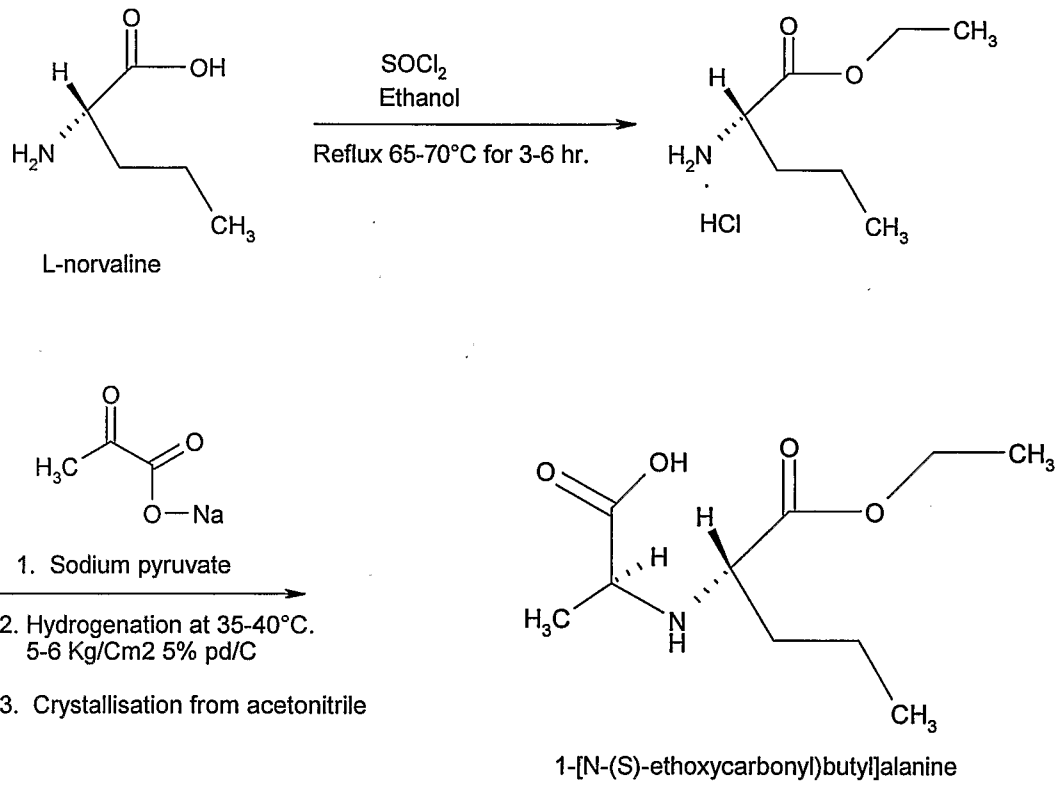


(2S,3aS,7aS)-octahydroindole-2-carboxylic acid (2S,3aS,7aS)-octahydroindole-2-benzoyloxycarbonyl tosylate

2) Preparation of Intermediate 1-[N (1-(S)-carboethoxy) butyl] alanine:

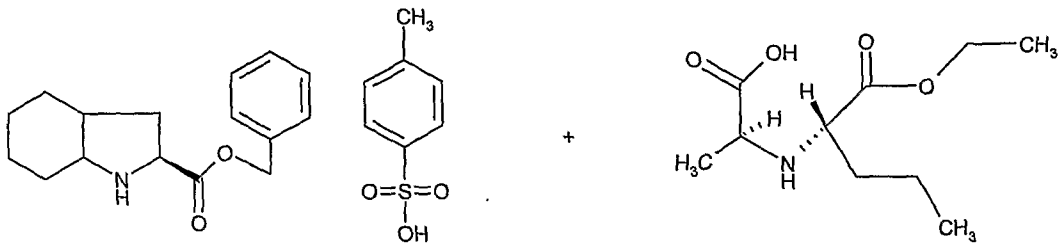
Insitu preparation of 1-[N (1-(S)-carboethoxy) butyl]-alanine required for the purpose is prepared by reaction between ethyl-L-norvalinate and

sodium pyruvate in acidic conditions. Ethyl-L-norvalinate for the purpose is prepared by adding thionyl chloride into mixture of L-norvaline and ethyl alcohol preferably pre-saturated with hydrogen chloride and heating the contents at 55-85°C preferably at 65-70°C for 2-7 hours preferably 3-6 hours. Solvent is removed under the reduced pressure followed by stripping of toluene and also with cyclohexane to remove the excess of thionyl chloride followed by addition of water. Aqueous layer is separated and reacted with sodium pyruvate in acidic condition. Contents so obtained are subjected for hydrogenation using 5%Pd/C at 25-50°C preferably at 35-40°C for 3-7 hours preferably 5-6 hours preferably after the reaction mixture is charcoalised to avoid the poisoning of catalyst due to the inorganic impurities coming from thionyl chloride. After completion of hydrogenation, catalyst is filtered off and sent for the recovery. Water is removed from the contents under the reduced pressure & crude so obtained is finally purified by using acetonitrile resulting into 98% purity. Product so obtained remains associated with water in the range 7-9% thus providing monohydrate of the product.



3) Preparation of (2a, 3aS, 7aS)-1-[N-[1(S)-carboethoxybutyl]-alanyl]-2 [benzyloxy) carbonyl-octahydro indole]:

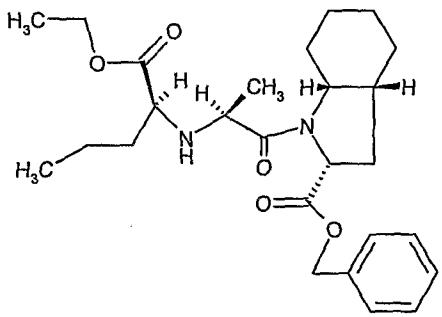
(2a, 3aS, 7aS)-1-[N-[1(S)-carboethoxybutyl]-alanyl]-2-[benzyloxy) carbonyl-octahydro indole is obtained by the procedure which comprises of condensation of N-[(S)-1-carboethoxybutyl]-(S)-alanine (98%) and (2S, 3aS, 7aS)-octahydroindole-2-benzyloxycarbonyl tosylate (98%) using 1-hydroxybenzotriazole, dicyclhexylcarbodiimide, triethylamine and ethyl acetate as solvent. After the completion of reaction organic layer is washed with water followed by its concentration under reduced pressure to get crude benzyl ester i.e. (2S,3aS,7aS)-1-[N-[1(s)-carboethoxybutyl]-alanyl-2[(benzyloxy)carbonyl octahydro indole] which is further purified by making its hydrochloride using acetone as solvent to get final purity of 98% HPLC.



(2S,3aS,7aS)-octahydroindole-2-benzoyloxycarbonyl tosylate

1-[N-(S)-ethoxycarbonyl)butyl]alanine

1. 1-hydroxybenzotriazole
   N,N-dicyclohexylcarbodiimide
   Triethylamine
   Ethyl acetate
   -5 to 30°C
2. Purification with HCl/Acetone

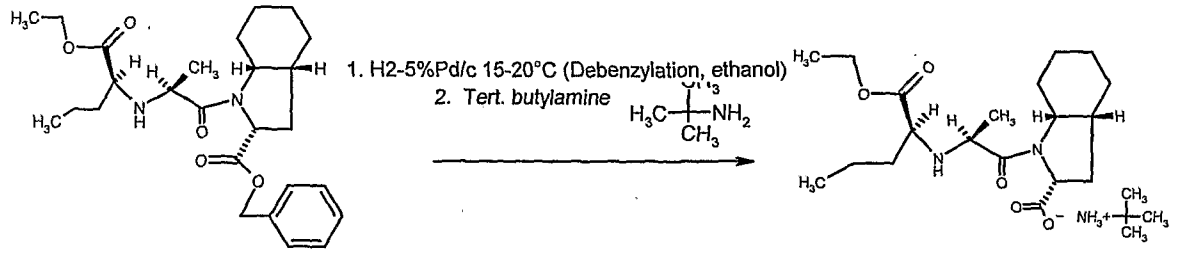


(2S,3aS,7aS)-1[N[1-(S)-carboethoxybutyl]-alanyl]-2-[(benzoyloxy)carbonyl octahydro indole]

Preparation of perindopril erbumine:

Perindopril erbumine i.e. (2S,3aS,7aS)-1-[N-[1(s)-carboethoxybutyl]-alanyl]-octahydro indole]-2-carboxylic acid tertiary butylamine salt of (98%) purity is obtained by process comprising of debenzylation of (2S,3aS,7aS)-1-[N-[1(s)-carboethoxybutyl]-alanyl-2[(benzyloxy)carbonyl octahydro indole] using Pd/C as catalyst and ethanol as solvent at 5-30°C preferably 10-20°C for 1-4 hours preferably 1.5-2.5 hours. Reaction mass is then taken for the recovery of solvent under reduced pressure keeping temperature is the range of 15-35°C preferably 20-30°C more preferably at 25-28°C is resulting into Perindopril base which is then converted Insitu into Perindopril erbumine of 98% purity by adding tert.butyl amine in to it

using ethylacetate as solvent. Salt thus obtained is further purified from ethyl acetate to get purity of 99%.



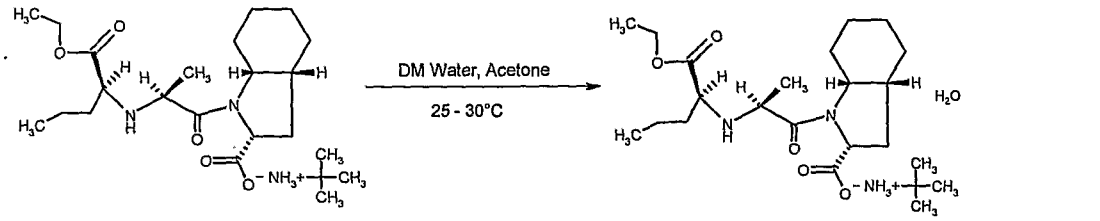
(2S,3aS,7aS)-1[N[1-(S)-carboethoxybutyl]-alanyl]-2-[(benzoyloxy)carbonyl octahydro indole]

(2S,3aS,7aS)-1[N[1-(S)-carboethoxybutyl]-amino]-1-oxopropyl] octahydro -1H-indole-2-carboxylic acid tertiary bytul amine

The inventive process for preparation and purification of Perindopril erbumine monohydrate is described in Reaction scheme as follows:

Preparation of Perindopril erbumine monohydrate:

Perindopril erbumine monohydrate of high purity and exhibiting novel crystalline form of Perindopril erbumine is prepared by dissolving Perindopril erbumine obtained by process described above having~99% purity in water. Aqueous layer containing product is then taken for recovery of water till water content reaches to 10-20% in the reaction mass which is further reduced using polar solvent like water soluble ketone , where most preferred solvent is acetone as co-solvent keeping the temperature at 25-55°C preferably at 35-45°C, till the water content reaches to 5-7% preferably of 5.0%. Solid thus obtained is slurried in acetone, cooled at 2-20°C preferably at 5 to 15° C and then filtered off. Solid is then dried at a temperature 25-75°C preferably at 45 to 50°C more preferably 30-35°C under vacuum till constant weight is achieved. Moisture content (NMT 4%), HPLC purity (~99.8%)Differential scanning calorimetry (167-170°C).



(2S,3aS,7aS)-1[N[1-(S)-carboethoxybutyl]-amino]-1-oxopropyl] octahydro -1H-indole-2-carboxylic acid tertiary bytul amine

(2S,3aS,7aS)-1[N[1-(S)-carboethoxybutyl]-amino]-1-oxopropyl] octahydro -1H-indole-2-carboxylic acid tertiary butyl amine monohydrate

The novel polymorph of perindopril erbumine monohydrate thus obtained exhibits characteristic XRD pattern as under:

8.87, 9.43, 9.60, 15.36, 15.96, 16.02, 19.97, 21.00, 21.13, 21.5, 22.14, 24.13, 26.48.

The most preferred volatile solvent according to present invention is acetone.

A novel process for purification of Perindoprl erbumine of the present invention resulted in HPLC purity of about ~ 99%.

A novel crystalline form of Perindopril erbumine monohydrate as obtained by the purification of the present invention is highly pure with HPLC purity of **~99.8%.**

The details of the invention, its objects and advantages are explained hereunder in greater detail in relation to the non-limiting exemplary illustrations.

Examples:

Example 1:

Preparation of (2S, 3aS, 7aS) octahydroindole-2-benzyloxycarbonyl tosylate:

Place toluene(4.4L) & octahydro-indole-2-carboxylic acid (0.5kg,2.95mol,), p-toluene sulfonic acid (0.7kg, 3.68 mol) and benzyl alcohol (0.535kg,4.95mol) into a 20 L four neck flask well equipped with azeotropic unit and thermopocket under stirring and heat all the content to react at the temperature about 100-118°C. Refluxion is continued till the water is removed completely & cooled at room temperature. Hexane is then added to the above contents and then cooled to temperature at 0-5°C for 2 hours. Filter off the product and dry it at 40-45°C under vacuum. Yield (1.3) Kg. Crude so obtained is further purified from isopropyl

alcohol to get purified product (1.2kg, 2.78-mol), M.P.140-145°C, and (purity of 98%).

Example 2:

Insitu preparation of N-[(S)-1-carboethoxybutyl]-(S)-alanine with high purity:

To the mixture of Alcohol (20lt) and L-Norvaline (1.5 kg, 12.8mol) presaturated with hydrogen chloride, thionyl chloride (1.1 L, 15.15mol) is charged slowly keeping the temperature in the range of 15-20°C. Contents are then heated to reflux at 65-70°C for 3-6 hours. Ethyl alcohol is completely evaporated, reaction mass is then added with fresh toluene (2X1.5lt) and removed under reduced pressure to remove the excess of thionyl chloride. The obtained residue is then taken into cyclohexane (3.5 L) .Cyclohexane is then partially distilled off, and to this (6 L) of water is charged under stirring. Collect the aqueous layer to which 25% solution of sodium pyruvate (0.775g, 7.0 mol) is then added under stirring. Reaction mass before hydrogenation is charcoalised using 0.25kg activated charcoal to remove impurities coming from thionyl chloride which are responsible for poisoning of the catalyst.

Content obtained after filtration are then taken for hydrogenation using 5% Pd/C (0.25kg) at 38-40°C and 5-6 Kg/Cm^2 till no more hydrogen is consumed (4-5 hours). Reaction mass is filtered off and filtrate is concentrated under reduced pressure. Treat the solid with ethanol, remove insoluble content if any. Ethanol is then removed under reduced pressure and finally is crystallized from acetonitrile (3.75 L) resulting into (1.3kg) of 98% purity which is used as such. Product so obtained remains associated with water in the range 7-9% thus providing monohydrate of the product.

Example 3:

Preparation of Benzyl ester of (2S, 3aS, 7aS)-1-{2-[1-(ethoxycarbonyl)-(S)-butylamino]-(S)-propionyl} Octahydroindole-2-carboxylic acid:

Charge (2S, 3aS, 7aS) octahydroindole-2-benzyloxycarbonyl tosylate (2kg, 4.63 mol) of (purity 98%) into a reactor containing ethyl acetate (28 L) under stirring and triethylamine (0.6kg, 5.94mol) is then added slowly to the contents at

temperature of -5 to10°C. To the resulting mass is then added with N-[(S)-1-carboethoxybutyl]-(S)alanine (1.05kg,4.8mol) of 98% purity and hydroxyl benzotriazole (0.92 kg,6.76mol) at temperature around -5 to 10°C and then solution of N,N-dicyclohexyl carbodiimide (1.12 kg, 5.43mol)diluted in (14 L) ethyl acetate is added slowly into the above contents in about one – two hours. Reaction mass then slowly brought to temperature of 25-30°C for about half an hour till the reaction gets over. Chill the reaction mass to a temperature 0-5°C and remove the salt by filteration. Filtrate so obtained is washed with water. Organic phase then concentrated under reduced pressure to get crude of (2kg) (88% HPLC).

Purification of benzyl ester of (2S, 3aS, 7aS)-1-{2[1-(ethoxycarbonyl)-(S)-butylamino]-(S)-propionyl} octahydroindole-2-carboxylic acid by making its hydrochloride:

Crude 2.0kg (88%) so obtained need purification for which it is dissolved in (11L) of acetone and insolubles are removed by the filteration. Hydrochloric acid is added to adjust the pH from 0.1 to 1.0 and acetone is distilled off. Hydrochloride so obtained is then dissolved into (9.6L) water to get clear solution. Washing of an organic solvent like toluene is given to remove the organic impurities. pH of aqueous layer is adjusted to 9 and then extracted with methylene dichloride till product is completely extracted. Methylene dichloride is removed under reduced pressure at ambient temperature to get thick oil (1.85kg) having the purity (HPLC 98%).

Example 4:

Preparation of perindopril erbumine:

Benzyl ester of (2S,3aS,7aS)-1-{2[1-(ethoxycarbonyl)-(S)-butylamino]-(S)-propionyl}octahydroindole-2-carboxylic acid (1.6kg) of 98% purity obtained by the process as described under above example was taken into ethyl alcohol(6.4L) and subjected for hydrogenation using 5%Pd/C (160g)at a pressure of 3-5kg/cm^2 for 1-2 hours at a temperature range of 10-15°C as high

temperature reduces the purity of the Perindopril erbumine formed. After the completion of reaction catalyst was removed by filteration and filtrate was concentrated to get a thick oil at a temperature of 30-35°C. Thick oil so obtained was then dissolved in ethyl acetate (14L) to which was then added tert. butyl amine (256g) to get perindopril erbumine (1.3kg) with not less than 98% HPLC purity which was further purified using ethyl acetate to get the purity of 99%.

Example 5:

Preparation of perindopril erbumine monohydrate:

Example A

Perindopril erbumine (150 g) of 99% purity as obtained in the above example is dissolved in DM water (0.450L) which was then extracted with (0.023 L) of toluene. Aqueous layer was collected and water was removed from the contents under the reduced pressure till water content reaches to 10-20% in the reaction mass which is further reduced using acetone as co-solvent keeping the temperature in the range of 20-45°C preferably at 25-30°C, till the moisture content is reached to the required (5-7%). Finally product so obtained was slurried in acetone (0.75L) and contents were cooled to 5-15°C and filtered off. Product was dried under vacuum at 25-35°C till required water content was reached. Dry weight of perindopril erbumine monohydrate (135g) with HPLC purity 99.8%, Moisture content NMT 4%, Differential scanning calorimetry (167-170°C),characteristic 2θ values as 8.87, 9.43, 9.60, 15.36, 15.96, 16.02, 19.97, 21.00, 21.13, 21.5, 22.14, 24.13, 26.48.

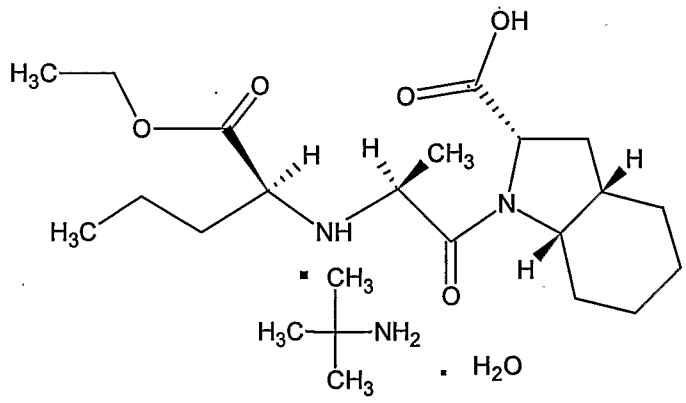
Example B

Perindopril erbumine (6.75kg) of 99% purity was dissolved in DM water (16.9L) which was then extracted with (0.68L) toluene. Aqueous layer was separated and aqueous layer was collected and water was removed from the contents under reduced pressure till water content reaches to 10-20% in the reaction mass which is further reduced using acetone as co-solvent in the range of 20-45°C preferably at 25-30°C, till the moisture content reached to the required (5-7%). Finally product so obtained was slurried in acetone (0.75L) and contents

were cooled to 5-15°C and filtered off. Product was dried under vacuum at 25-35°C till required water content was reached. Dry weight of perindopril erbumine monohydrate (6.1kg) with HPLC purity 99.8%, Moisture content NMT 4%, Differential scanning calorimetry (167-170°C), characteristic 2θ values as: 8.87, 9.43, 9.60, 15.36, 15.96, 16.02, 19.97, 21.00, 21.13, 21.5, 22.14, 24.13, 26.48.

Claims

1. A novel crystalline form of Perindopril erbumine monohydrate of Formula III.



Perindopril Erbumine Monohydrate

Formula (III)

2. The novel crystalline form according to claim 1 comprising the characteristic 2θ values of 8.87, 9.43, 9.60, 15.36, 15.96, 16.02, 19.97, 21.00, 21.13, 21.5, 22.14, 24.13, and 26.48.

3. The novel crystalline form according to claim 2, having a purity of not less than 99.8%

4. A process for the preparation of novel crystalline form of Perindopril erbumine monohydrate of Formula III comprising the following steps:
   - i) Dissolving Compound of Formula II in water.
   - ii) Further extracting the above solution with solvent selected from like toluene, xylene
   - iii) Water is removed from the aqueous layer obtained from step ii
   - iv) Polar solvent is then added to the mass obtained from step ii, at the temperature range of 20-45°C
   - v) Filtering off the solid obtained in step (iv) of formula (III)

5. The process according to claim 4, wherein the said aromatic hydrocarbon is selected from toluene and xylene.

6. The process according to claim 5, wherein preferred aromatic hydrocarbon is toluene.

7. The process according to claim 4, wherein the said polar solvent is selected from water soluble ketone

8. The process according to claim 7, wherein preferred ketone is Acetone.

9. The process according to claim 4, wherein temperature range is preferably at 25-30°C

10. The process according to claim 4, wherein the said crystalline form of Perindopril erbumine monohydrate of Formula III is of purity not less than 99.8%