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(71) Applicant (for all designated States except US): **HETERO DRUGS LIMITED** [IN/IN]; Hetero House, 8-3-166/7/1, Erragadda, Hyderabad, Andhrapradesh., 500 018 Hyderabad (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only):  
**PARTHASARADHI REDDY, bandi** [IN/IN]; Hetero House, 8-3-166/7/1, Erragadda, Hyderabad, Andhrapradesh., 500 018 Hyderabad (IN).  
**RATHNAKAR REDDY, kura** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad, Andhrapradesh., 500 018 Hyderabad (IN).  
**RAJI REDDY, rapolu** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad, Andhrapradesh., 500 018 Hyderabad (IN).  
**MURALIDHARA REDDY, dasari** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad, Andhrapradesh., 500 018 Hyderabad (IN).  
**RAMAKRISHNA REDDY, matta** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad, Andhrapradesh., 500 018 Hyderabad (IN).

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**Declarations under Rule 4.17:**

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR PURE PERINDOPRIL TERT-BUTYLAMINE SALT

(57) Abstract: Pure perindopril tert-butylamine salt is obtained by extracting an aqueous solution of perindopril or its salt contaminated with impurities with a suitable organic solvent such as methylenedichloride at a pH of 4.0 to 6.5, separating the organic layer, isolating perindopril from the organic layer and converting it into tert-butylamine salt.



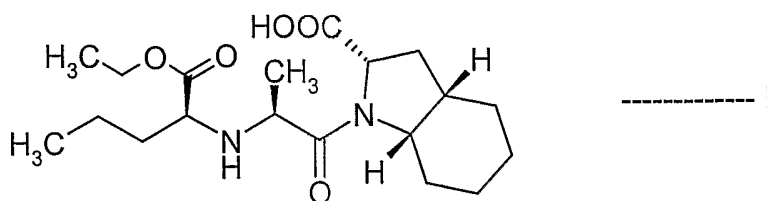
WO 2005/019173 A1

**PROCESS FOR PURE PERINDOPRIL tert-BUTYLAMINE SALT****FIELD OF THE INVENTION**

The present invention relates to a process for obtaining pure perindopril  
 5 tert-butylamine salt.

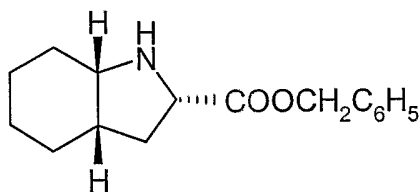
**BACKGROUND OF THE INVENTION**

Perindopril of formula I

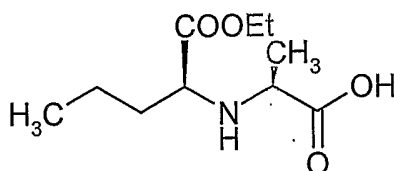


10 Or (2S,3aS,7aS)-1-[(2S)-2-[[[(1S)-1-(ethoxycarbonyl)butyl]amino]-1-oxopropyl] octahydro-1H-indole-2-carboxylic acid and its tert-butylamine salt are angiotensin-converting enzyme inhibitors. The therapeutic uses of perindopril and related compounds and their preparations are disclosed in US 4,508,729 and US 4,914,214.

15 US 4,914,214 describes an industrial process for preparation of perindopril and perindopril tert-butylamine salt. According to US 4,914,214 benzyl ester of formula

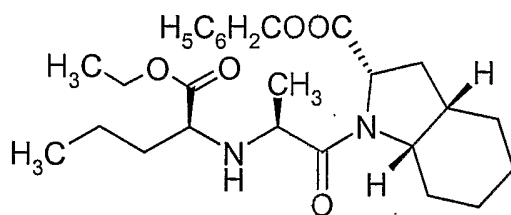


is condensed with the compound of formula



20

to give perindopril benzyl ester of formula

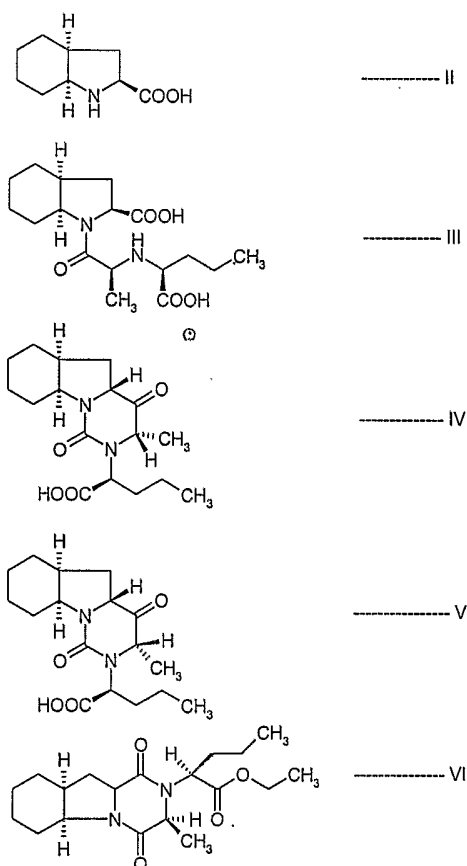


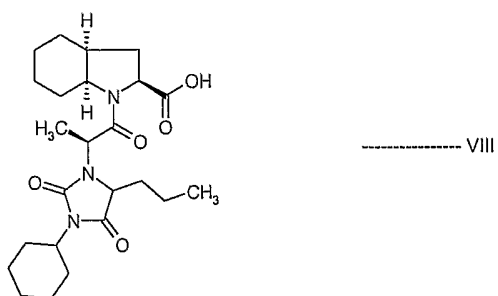
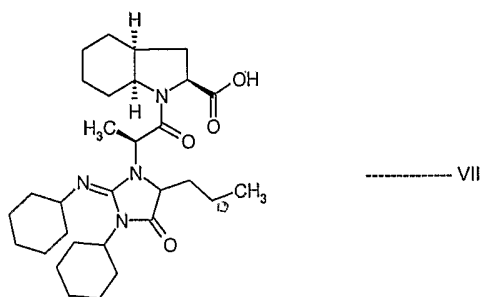
which is then subjected to hydrogenation in the presence of Pd/C to give perindopril, which is then dissolved in ethylacetate, tert-butylamine is added and  
5 finally crystallized to obtain perindopril tert-butylamine salt.

The process described in US 4,914,214 is not satisfactory from purity point of view and there is a need for a process for obtaining pure perindopril tert-butylamine salt that can be used in pharmaceutical preparation.

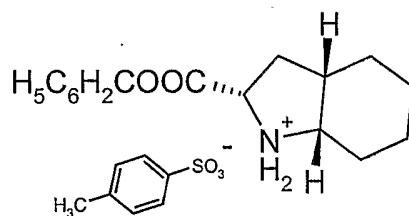
Impurities that are commonly associated with perindopril are:

10

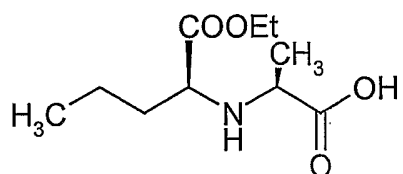




WO 0158868 describes a process for preparation of perindopril and perindopril tert-butylamine salt. According to WO 0158868 toluenesulfonate of  
 5 compound of formula



is condensed with the compound of formula



to give perindopril benzyl ester, which is hydrogenated and converted into perindopril tert-butylamine salt. The process controls the formation of the impurities of formula VII and VIII.

This process also suffers from drawbacks since the process requires  
 5 strict control of quantities of reactants and is unable to remove other common impurities such as those of formula II to VI.

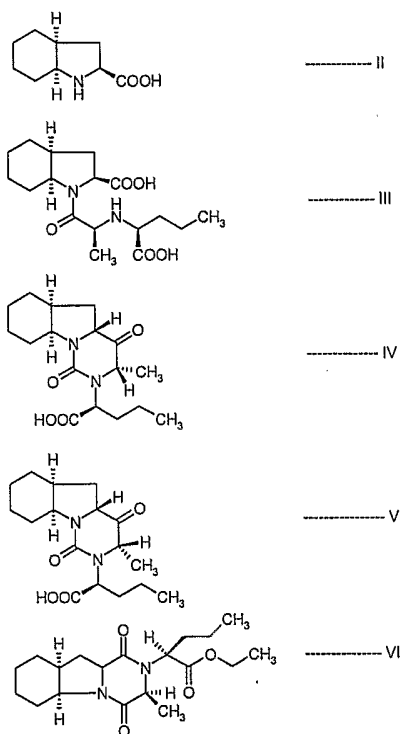
We have found that impurities can be isolated from perindopril by extracting an aqueous solution of perindopril or its salt contaminated with impurities with a suitable organic solvent under suitable conditions. The  
 10 impurities remain in the aqueous phase and perindopril extracted into the organic phase is then converted to pure perindopril tert-butylamine salt. The novel method provides a simple and economical process for obtaining pure perindopril tert-butylamine salt and since perindopril tert-butylamine salt obtained is with high purity, the product can be used in pharmaceutical  
 15 preparations.

#### SUMMARY OF THE INVENTION

The present invention provides a simple process for obtaining substantially pure perindopril tert-butylamine.

Impurities that are commonly associated with perindopril are:

20



In accordance with the present invention, there is provided a process for obtaining substantially pure perindopril tert-butylamine salt, which comprises the steps of:

- a) extracting an aqueous solution of impure perindopril or an impure perindopril salt with an organic solvent selected from methylenedichloride, chloroform, ethylenedichloride, toluene, heptane and a mixture thereof at pH 4.0 to 6.5;
- b) separating and concentrating the organic layer obtained in step (a);
- c) dissolving the concentrate obtained in step (b) in a solvent selected from ethylacetate, methanol, ethanol, isopropyl alcohol, acetonitrile, dioxane and a mixture thereof;
- d) mixing tert-butylamine to the solution obtained in step (c); and
- e) precipitating perindopril tert-butylamine salt from the solution obtained in step (d).

An aqueous solution of impure perindopril or a perindopril salt can be prepared, for example, by dissolving perindopril or a perindopril salt such as perindopril tert-butylamine salt contaminated with known or unknown impurities in water or water mixed with any other solvent.

Perindopril or a salt thereof prepared in an aqueous media may also be used in step (a).

The pH of the solution is adjusted to 4.0 to 6.5, preferably to 4.5 to 6.0 with an acid such as hydrochloric acid or sulfuric acid or a base such as sodium hydroxide, sodium or potassium carbonate, sodium or potassium bicarbonate or ammonia as required.

The aqueous solution of perindopril is extracted with a solvent selected from methylenedichloride, which is preferable, chloroform, ethylenedichloride, toluene, heptane and a mixture thereof.

Precipitation in step (e) may be initiated by a method usually known in the art such as cooling, seeding, partial removal of the solvent from the solution or a combination thereof.

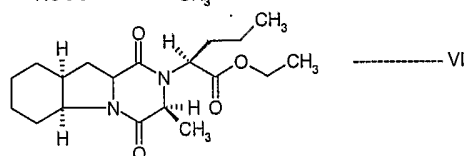
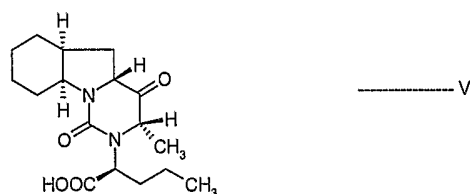
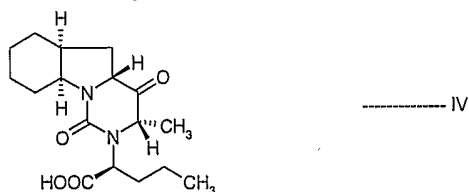
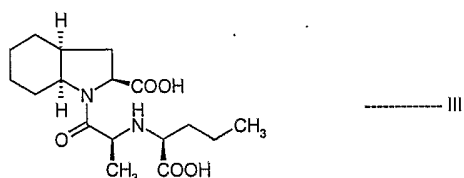
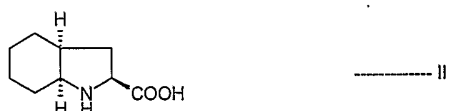
"Impure perindopril (or impure perindopril salt)" refers throughout the specification to perindopril (or perindopril salt) with total impurity content (by weight) of about 3.0% or above.

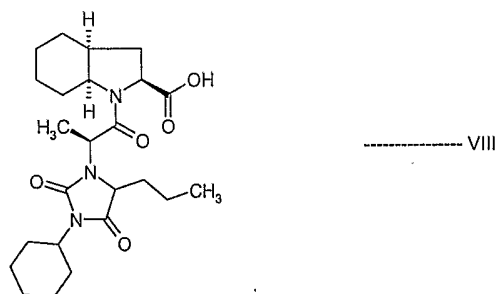
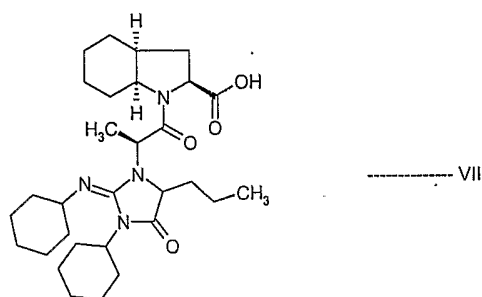
"Substantially pure" perindopril tert-butylamine refers to perindopril tert-butylamine having chromatographic purity of not less than 97%, preferably not less than 99% and more preferably not less than 99.5%.

### DETAILED DESCRIPTION OF THE INVENTION

5 In accordance with the present invention, there is provided a process for obtaining substantially pure perindopril tert-butylamine.

Perindopril salts such as tert-butyl amine salt produced by the prior art methods are contaminated with known and/or unknown impurities in significant amounts. The commonest among the impurities are:





Impure perindopril or an impure perindopril salt such as perindopril tert-butylamine salt is dissolved in water or water mixed with any other solvent.

5 "Impure perindopril (or impure perindopril salt)" refers to perindopril (or perindopril salt) with total impurity content (by weight) of about 3.0% or above.

An aqueous solution obtained as a part of preparing perindopril or a salt thereof may also be used in the novel process for obtaining a substantially pure perindopril salt. The pH of the solution varies with the method of preparation, the salt used etc.

10 The pH of the solution is then adjusted to 4.0 to 6.5, preferably to 4.5 to 6.0 with an acid such as hydrochloric acid or sulfuric acid or a base such as sodium hydroxide, sodium or potassium carbonate, sodium or potassium bicarbonate or ammonia as required.

15 The aqueous solution after pH adjustment is extracted with an organic solvent selected from methylenedichloride, chloroform, ethylenedichloride, toluene, heptane and a mixture thereof. Perindopril is extracted into the organic phase and the impurities remain in the aqueous phase thereby effectively isolating perindopril from the impurities.

20 The aqueous solution of perindopril is preferably extracted with methylenedichloride.

The pH adjustment may also be done after mixing impure perindopril or its salt, the solvent for extraction and water.

The phases are separated and the organic layer is concentrated by distilling off the solvent.

5       The concentrate is dissolved in a solvent selected from ethylacetate, which is preferred, methanol, ethanol, isopropyl alcohol, acetonitrile, dioxane and a mixture thereof. The solution is optionally filtered.

Tert-butylamine is added to the solution. The amount of tert-butylamine to perindopril present in the solution is not critical but at least one mole of tert-  
10       butylamine per mole of perindopril is preferably used for good yield.

After the addition of tert-butylamine, if necessary, the contents may be heated.

Substantially pure perindopril tert-butylamine salt is precipitated from the solution. The precipitation may be initiated by a commonly known method in the  
15       art such as cooling, seeding, partial removal of the solvent from the solution or a combination thereof.

Some or whole of the steps of the process may be repeated for obtaining perindopril tert-butylamine with desired purity, but by suitable choice of the conditions and solvents a single run may be enough for obtaining substantially  
20       pure perindopril tert-butylamine.

"Substantially pure" perindopril tert-butylamine refers to perindopril tert-butylamine having chromatographic purity of not less than 97%, preferably not less than 99% and more preferably not less than 99.5%.

25       The invention will now be further described by the following example, which is illustrative rather than limiting.

#### Example 1

Perindopril tert-butylamine salt ( 15 gm, purity: 92.4%) is added to water  
30       (100 ml) and methylenedichloride (100 ml) and the pH of the mass is adjusted to 5.4 by using 20% dilute hydrochloric acid. The phases are separated and the aqueous layer is washed with methylenedichloride (2 x 75 ml). The methylenedichloride layer and washings are combined and the combined organic phase is washed with water (50 ml) and then with 10% aq.sodium

chloride (50 ml). The organic layer is dried over sodium sulphate and concentrated to give a residue (99.3% purity).

Ethyl acetate (255 ml) is added to the residue (15 gm) and stirred for 10 min to obtain a clear solution. tert-Butyl amine is added drop wise to the solution at 30°C and stirred for 1 hour at the same temperature. The reaction mass is then heated to reflux, passed over hiflo rapidly at reflux temperature and washed with hot ethyl acetate (30 ml). Then the reaction mass is stirred for 2 hours at about 30°C, cooled to 0°C and stirred for further 2 hours at 0°C to 5°C. The separated solid is filtered, washed with ethylacetate (15 ml) and dried to give 12 gm of 99.77% pure perindopril tert-butylamine salt.

### Example 2

Ethylacetate (1800 ml) is added to (2S,3aS,7aS)- octahydro-1H-indole-2-carboxylic acid benzyl ester (300 gm) at 25°C and stirred for 30 min. The reaction mass is cooled to 10°C, triethylamine (172.5 gm) is added and stirred for 5 minutes to form a clear solution. Hydroxybenzotriazole monohydrate (105 gm), dicyclohexylcarbodiimide (150 gm) are added to the reaction mass at 25°C under stirring. Then N-[(S)-1-carbethoxybutyl]-(S)-alanine (150 gm) is added to the reaction mass and stirred for 5 hours. The contents are filtered, the filtrate is washed with water (700 ml), 5% sodium bicarbonate solution (700 ml), water (700 ml) and finally with sodium chloride (700 ml). Organic layer is dried and concentrated under vacuum.

The concentrate is taken in cyclohexane (500 ml), filtered the unwanted salts over hiflo and washed with cyclohexane (100 ml). The filtrate is concentrated under vacuum at 60°C to give 300 gm of (2S,3aS,7aS)-1-[(2S)-2-[[[(1S)-1-(ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro-1H-indole-2-carboxylic acid benzyl ester.

### Example 3

The mixture of (2S,3aS,7aS)-1-[(2S)-2-[[[(1S)-1-(ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro-1H-indole-2-carboxylic acid benzyl ester (300 gm, obtained in example 2), cyclohexane (750 ml), water (1050 ml) and 5% palladium-charcoal (60 gm) is taken in a hydrogenation flask and subjected to hydrogenation under a hydrogen pressure of 2 bars for 10 hours. The reaction mass is filtered over hiflo and washed with DM water (200 ml). The layers are

separated and the aqueous layer is washed with cyclohexane (900 ml) and the pH of the aqueous layer is adjusted to 5.7 by using aqueous ammonia. Then the aqueous layer is extracted with methylenedichloride (3000 ml), collected the organic layer and washed with water (500 ml). The organic layer is dried over sodium sulphate and concentrated under vacuum at 50°C to give 225 gm of (2S,3aS,7aS)-1-[(2S)-2-[[[(1S)-1-(ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro-1H-indole-2-carboxylic acid.

#### Example 4

(2S,3aS,7aS)-1-[(2S)-2-[[[(1S)-1-(ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro-1H-indole-2-carboxylic acid (225 gm) (concentrate obtained in example 3) is dissolved in ethyl acetate (3800 ml), tert-butylamine (56 gm) is added drop wise at about 30°C for 30 minutes and stirred for 1 hour at the same temperature. Then the temperature of the reaction mass is raised to about 70°C to form a clear solution, passed over hiflo bed while hot and the filtrate is cooled to 25°C. The reaction mass is stirred for 4 hour at 25°C, cooled to 0°C to 5°C and stirred for 2 hours at the same temperature. The mass is filtered, washed the solid collected with ethyl acetate (100 ml) and dried at 50°C to give 180 gm of 99.8 % pure perindopril tert-butylamine salt.

#### Comparative example 1

Example 3 is repeated except that after hydrogenation, layer separation and washing the aqueous layer with cyclohexane, (2S,3aS,7aS)-1-[(2S)-2-[[[(1S)-1-(ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro-1H-indole-2-carboxylic acid is collected by freeze-drying. Example 4 is repeated using the product thus obtained to give perindopril tert-butylamine with 95.5% purity.

We claim:

- 1) A process for obtaining substantially pure perindopril tert-butylamine, which comprises the steps of:
  - 5 a) extracting an aqueous solution of impure perindopril or an impure perindopril salt with an organic solvent selected from methylenedichloride, chloroform, ethylenedichloride, toluene, heptane and a mixture thereof at pH 4.0 to 6.5;
  - b) separating and concentrating the organic layer obtained in step (a);
  - c) dissolving the concentrate obtained in step (b) in a solvent selected from  
10 ethylacetate, methanol, ethanol, isopropyl alcohol, acetonitrile, dioxane and a mixture thereof;
  - d) mixing tert-butylamine to the solution obtained in step (c ); and
  - e) precipitating perindopril tert-butylamine salt from the solution obtained in step (d );
- 15 wherein "substantially pure perindopril tert-butylamine" refers to perindopril tert-butylamine having chromatographic purity of not less than 97%.
- 2) A process according to claim 1, wherein chromatographic purity of perindopril tert-butylamine obtained is not less than 99%.
- 3) A process according to claim 1, wherein chromatographic purity of  
20 perindopril tert-butylamine obtained is not less than 99.5%.
- 4) A process according to claim 1, wherein the organic solvent in step (a) is methylenedichloride.
- 5) A process according to claim 1, wherein the aqueous solution of impure perindopril or the impure perindopril salt is prepared by dissolving impure  
25 perindopril or an impure perindopril salt in water.
- 6) A process according to claim 5, wherein the perindopril salt is perindopril tert-butylamine salt.
- 7) A process according to claim 1, wherein the pH of the solution in step (a) is adjusted to 4.5 to 6.0.
- 30 8) A process according to claim 1, wherein the pH adjustment in step (a) is effected with an acid or a base.
- 9) A process according to claim 8, wherein the acid is hydrochloric acid or sulfuric acid.

- 10) A process according to claim 8, wherein the base is selected from sodium hydroxide, sodium or potassium carbonate, sodium or potassium bicarbonate or ammonia.
- 11) A process according to claim 9, wherein the acid is hydrochloric acid.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IN 03/00276-0

## CLASSIFICATION OF SUBJECT MATTER

IPC<sup>7</sup>: C07D 209/42

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<sup>7</sup>: C07D 209/00

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: EPODOC, WPI, TXT-databases

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages                  | Relevant to claim No. |
|----------|-----------------------------------------------------------------------------------------------------|-----------------------|
| X        | EP 1279665 A2 (ADIR) 29 January 2003 (29.01.2003)<br><i>pages 7,8.</i>                              | 1-11                  |
| A        | WO 2001/083439 A2 (ADIR ET CAMPAGNIE)<br>8 November 2001 (08.11.2001)<br><i>the whole document.</i> | 1                     |
|          | ----                                                                                                |                       |

☐ 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

27 April 2004 (27.04.2004)

Date of mailing of the international search report

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Name and mailing address of the ISA/AT

Austrian Patent Office

Dresdner Straße 87, A-1200 Vienna

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Authorized officer

SLABY S.

Telephone No. 1/53424/348

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/IN 03/00276-0

| Patent document cited<br>in search report |   |          | Publication<br>date | Patent family<br>member(s) |   |          | Publication<br>date |
|-------------------------------------------|---|----------|---------------------|----------------------------|---|----------|---------------------|
| EP                                        | A | 1279665  | 2003-01-29          | HU                         | A | 0202414  | 2003-02-28          |
|                                           |   |          |                     | PL                         | A | 355161   | 2003-01-13          |
|                                           |   |          |                     | WO                         | A | 03010142 | 2003-02-06          |
| WO                                        | A | 20010834 |                     | none                       |   |          |                     |
|                                           |   | 39       |                     |                            |   |          |                     |