Title: 3,3-DIARYLPROPAMINE DERIVATIVES AND PROCESSES FOR ISOLATION THEREOF

Abstract: The invention relates to 3,3-diarylpipramines derivatives and processes for producing them. More particularly, it relates to the preparation of pure tolterodine or a pharmaceutically acceptable salt thereof and pharmaceutical compositions that include the pure tolterodine or a pharmaceutically acceptable salt thereof. It also relates to a novel 3,3-diarylpipramine derivative, referred to as tolterodine dimer. Chemicly, tolterodine dimer is N,N-di-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]isopropylamine and has structural Formula (I). The invention also relates to use of pure tolterodine or tolterodine dimer as reference standards or reference markers for checking the purity of tolterodine.
3,3-DIARYLPROPYLAMINE DERIVATIVES AND PROCESSES FOR ISOLATION THEREOF

Field of the Invention

The field of the invention relates to 3,3-diarylpropylamines derivatives and processes for producing them. More particularly, it relates to the preparation of pure tolterodine or a pharmaceutically acceptable salt thereof and pharmaceutical compositions that include the pure tolterodine or a pharmaceutically acceptable salt thereof. It also relates to a novel 3,3-diarylpropylamine derivative, referred to as tolterodine dimer.

Chemically, tolterodine dimer is N,N-di-[3-[2-hydroxy-5-methylphenyl]-3-phenylpropyl]isopropylamine and has structural Formula I,

![Formula I](image)

The invention also relates to use of pure tolterodine or a pharmaceutically acceptable salt thereof or tolterodine dimer as reference standards or reference markers for checking the purity of tolterodine.

Background of the Invention

Tolterodine is a new potent and competitive muscarinic receptor antagonist intended for the treatment of urinary urge incontinence and other symptoms of bladder over activity.

Chemically, tolterodine tartrate is L-(+)-tartrate salt of (+)-R-3(2-hydroxy-5-methylphenyl), N, N-diisopropyl-3-phenylpropyl amine and has structural Formula II.
FORMULA II

In order to secure marketing approval for a new drug product, a drug manufacturer must submit detailed evidence to the appropriate regulatory authorities to show that the product is suitable for release on to the market. The regulatory authorities must be satisfied, inter alia that the active agent is acceptable for administration to humans and that the particular formulation which is to be marketed is free from impurities at the time of release and has an appropriate shelf-life.

Submissions made to regulatory authorities therefore typically include analytical records, which demonstrate:

(a) that impurities are absent from the drug at the time of manufacture, or are present only at negligible level, and

(b) that the storage stability i.e., shelf-life of the drug is acceptable.

These details are usually obtained by testing the drug against an external standard, or reference marker, which is a pure sample of a potential impurity or a potential degradation product. Tolterodine dimer has a possibility of being used as a reference marker compound in identifying the purity of the tolterodine or a pharmaceutically acceptable salt thereof.

Potential impurities in pharmaceutically active agents and formulations containing them include residual amounts of synthetic precursors to the active agent, by-products which arise during synthesis of the active agent, residual solvents, isomers of active agent, excipients used in the preparation of the pharmaceutical formulation, and unidentified adventitious substances. Other impurities which may appear on storage include substances resulting from degradation of the active agent, for instance by oxidation or hydrolysis.
Tolterodine easily forms dimer. However, there is no reference of the tolterodine dimer in the literature.

**Summary of the Invention**

In one general aspect there is provided a novel 3,3-diarylpropylamines derivative, which is chemically N,N-di-[3-[2-hydroxy-5-methylphenyl]-3-phenylpropyl]isopropylamine of Formula I (hereinafter referred to as tolterodine dimer).

In another general aspect there is provided use of tolterodine dimer as a reference standard for determination of the purity of tolterodine or a pharmaceutically acceptable salt thereof.

In another general aspect there is provided a process for the isolation of tolterodine dimer.

In another general aspect there is provided a pure tolterodine or a pharmaceutically acceptable salt thereof containing less than 0.5% tolterodine dimer.

In another aspect there is provide a pure tolterodine or a pharmaceutically acceptable salt thereof containing less than 0.05% tolterodine dimer.

In another aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of pure tolterodine or a pharmaceutically acceptable salt thereof containing less than 0.5% tolterodine dimer; and one or more pharmaceutically acceptable carriers, excipients or diluents.

In another aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of pure tolterodine or a pharmaceutically acceptable salt thereof containing less than 0.05% tolterodine dimer; and one or more pharmaceutically acceptable carriers, excipients or diluents.

In another aspect there is provided a process of depletion of tolterodine dimer impurity from tolterodine or a pharmaceutically acceptable salt thereof. The process includes obtaining a solution of crude tolterodine or a pharmaceutically acceptable salt thereof in one or more solvents; and recovering the pure tolterodine or a pharmaceutically acceptable salt thereof by the removal of the solvent.
The solvent may be one or more of lower alkanol, ketone, polar aprotic solvent, or mixtures thereof. The lower alkanol may include one or more of primary, secondary and tertiary alcohol having from one to six carbon atoms. The lower alkanol may include one or more of methanol, ethanol, denatured spirit, n-propanol, isopropanol, n-butanol, isobutanol and t-butanol.

The ketone may include one or more of acetone, 2-butanone, and 4-methylpentan-2-one. The polar aprotic solvent may include one or more of tetrahydrofuran, acetonitrile, 1,4-dioxane and N-methylpyrrolidone. Removing the solvent may include one or more of distillation, distillation under vacuum, filtration, filtration under vacuum, decantation and centrifugation.

The process may include further drying of the product obtained.

In one general aspect, the solution of crude tolterodine may be obtained by heating the solvent containing crude tolterodine. It may be heated from about 30°C to about reflux temperature of the solvent used, for example from about 30°C to about 100°C. In particular, it may be heated from about 40°C to about 60°C. It may be heated from about 15 minutes to about 10 hours. More particularly, it may be heated for about 2-3 hours.

In one general aspect the solution containing the crude tolterodine may be treated with charcoal before removing the solvent. The charcoal treatment may be carried out under heating conditions or it may be carried out at a lower temperature.

In another general aspect additional/another solvent may be added to residue obtained after removal of the solvent and it may be cooled before filtration to obtain better yields of the pure tolterodine.

The process may produce the pure tolterodine or a pharmaceutically acceptable salt thereof containing less than 0.5% tolterodine dimer. In particular, it may produce the pure tolterodine or a pharmaceutically acceptable salt thereof containing less than 0.05% tolterodine dimer.

In another aspect there is provided a method of treating urinary urge incontinence and other symptoms of bladder over activity using therapeutically effective amount of the pure tolterodine or a pharmaceutically acceptable salt thereof containing less than 0.5%
tolterodine dimer.

In another aspect there is provided a method of treating urinary urge incontinence and other symptoms of bladder over activity using therapeutically effective amount of the pure tolterodine or a pharmaceutically acceptable salt thereof containing less than 0.05% tolterodine dimer.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

The inventors have identified that the tolterodine dimer is formed as an impurity during the synthesis of tolterodine or a pharmaceutically acceptable salt thereof. The inventors have isolated tolterodine dimer which can be used as a reference standard for determination of the purity of tolterodine or a pharmaceutically acceptable salt thereof.

The process involves

\[ \text{a) heating } N,N\text{-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine of Formula III with aqueous hydrobromic acid in the presence of acetic acid to get crude tolterodine hydrobromide,} \]

\[
\text{FORMULA III}
\]

\[ \text{b) subjecting the crude tolterodine hydrobromide to preparative HPLC and eluting with a gradient mobile phase to get eluent containing tolterodine dimer, and} \]

\[ \text{c) isolating the pure tolterodine dimer from the eluent.} \]
N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine may be heated at reflux temperature for 10-12 hours with hydrobromic acid in the presence of acetic acid. The reaction mass may be cooled to ambient temperature and the precipitated product may be isolated by conventional means and dried. The crude product so obtained may be repeatedly loaded on YMC-Pack ODS-A (500 x 30 mm I. D.) column. Mobile phase used may be a gradient of phosphate buffer (2gm KH2PO4 / lit of distilled water) and acetonitrile in 8:2 to 2:8 v/v ratio. The fractions containing the dimer impurity may be further combined and concentrated to dryness. The pure tolterodine dimer can then be further purified by crystallization or column chromatography.

The inventors also have developed a process of depletion of tolterodine dimer impurity from tolterodine or a pharmaceutically acceptable salt thereof, by obtaining a solution of crude tolterodine or a pharmaceutically acceptable salt thereof in one or more solvents; and recovering the pure tolterodine or a pharmaceutically acceptable salt thereof by the removal of the solvent. The inventors also have developed pharmaceutical compositions that contain the pure tolterodine or a pharmaceutically acceptable salt thereof containing less than 0.5% tolterodine dimer, for example, less than 0.05% tolterodine dimer, in admixture with one or more solid or liquid pharmaceutical diluents, carriers, and/or excipients. These pharmaceutical compositions may be used for treating a patient in need of a treatment for urinary urge incontinence and other symptoms of bladder over activity.

The tolterodine or a pharmaceutically acceptable salt thereof may be prepared by the methods known in the literature. In particular, it may be prepared using the reactions and techniques described in our PCT patent application WO 03/014060 which is incorporated herein as reference.

In general, the solution of crude tolterodine may be obtained by dissolving crude tolterodine in a suitable solvent. Alternatively, such a solution may be obtained directly from a reaction in which tolterodine is formed. The solvent containing crude tolterodine may be heated to obtain a solution. It can be heated from about 30°C to about reflux temperature of the solvent used, for example from about 30°C to about 100°C. In particular, it can be heated from about 40°C to about 60°C. It can be heated from about 15 minutes to about 10 hours. More particularly, it can be heated for about 2-3 hours. The product may be isolated from the solution by a technique which includes, for example,
distillation, distillation under vacuum, filtration, filtration under vacuum, decantation, and centrifugation.

The term “suitable solvent” includes any solvent or solvent mixture in which crude tolterodine is soluble, including, for example, lower alkanol, ketone, polar aprotic solvent and mixtures thereof. Examples of alkanol include those primary, secondary and tertiary alcohols having from one to six carbon atoms. Suitable lower alkanol solvents include methanol, ethanol, denatured spirit, n-propanol, isopropanol, n-butanol, isobutanol and t-butanol.

A suitable ketone includes one or more of acetone, 2-butanone, and 4-methylpentan-2-one. Examples of polar aprotic solvents include solvents such as tetrahydrofuran, acetonitrile, 1,4-dioxane and N-methylpyrrolidone. Mixtures of all of these solvents are also contemplated.

In one aspect, the solution containing crude tolterodine can be treated with activated carbon and filtered while hot.

In another aspect, additional or another solvent can be added to the clear solution to precipitate the pure tolterodine or a pharmaceutically acceptable salt thereof.

The product obtained may be further or additionally dried to achieve the desired moisture values. For example, the product may be further or additionally dried in a tray drier, dried under vacuum and/or in a Fluid Bed Drier.

Methods known in the art may be used with the process of this invention to enhance any aspect of this invention. For example, the solution containing the crude tolterodine may be heated for dissolution, or may be cooled to separate out the product or the slurry may further be cooled prior to filtration or the solution may be seeded with seed crystals of the product to enhance precipitation of the product.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and are not intended to limit the scope of the invention. Although the examples are directed to the tolterodine hydrobromide and tolterodine tartrate, the principles described in these examples can be applied to other salts of tolterodine.
Example 1

Preparation of tolterodine hydrobromide

N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine (HPLC Purity, 97.41%) (225 g, 0.663 mol) was heated with aqueous hydrobromic acid (500 ml) and acetic acid (300 ml) to a reflux temperature (110-115°C) for 10-12 hours. The reaction mixture was cooled to room temperature, maintained for 1 hour and then filtered. The product so obtained was washed with water and dried under vacuum to yield the titled product. (234 g) in 86% yield;

Purity (by HPLC): 97.52%.

Dimeric Impurity: 1.29%,

The crude product was repeatedly loaded on YMC-Pack ODS-A (500 x 30 mm I. D.) column. Mobile phase used was gradient of phosphate buffer (2gm KH2PO4 / lit of distilled water) and acetonitrile 8:2 to 2:8. The fractions containing the dimer impurity were combined and concentrated to dryness. The spectral data of the isolated tolterodine dimer are as follows:

\(^1\)H-NMR (300 MHz) in DMSO-\textsubscript{D}_6, \(\delta\)ppm: 0.85 (d, 3H, -CH-CH\textsubscript{3}); 1.1 (d, 3H, -CH-CH\textsubscript{3}); 2.06-2.37 (m, 10H, 2x -CH\textsubscript{2}, 2x -CH\textsubscript{3}); 2.73-3.17 (m, 5H, 2x -CH\textsubscript{2}, -CH-CH\textsubscript{3}); 4.27 (m, 2H, 2x Ar-CH-Ar); 6.64 (d, 2H, 2x -C\textsubscript{3'} H); 6.70 (d, 2H, 2x -C\textsubscript{4'} H); 6.75 (s, 2H, 2x -C\textsubscript{6'} H); 7.20 (m, 10H, Ar)

MASS: 508.1 (M\textsuperscript{+})

MS/MS: 466.0, 284.1, 197.1, 147.0, and 121.0

Example 2

Preparation of tolterodine hydrobromide

N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine 225 g (HPLC Purity : 98.57%) was heated with aqueous hydrobromic acid (500 ml) and acetic acid to reflux temperature (110-115°C) for 10-12 hours. The reaction mixture was cooled to room temperature, maintained for 1 hour and then filtered. The product obtained was
washed with water and dried under vacuum to yield the product 237.35 g.

HPLC Purity: 98.37%.

Dimeric Impurity: 0.75%

Example 3

Preparation of tolterodine hydrobromide

N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine 225 g (HPLC Purity: 96.31) was heated with aqueous hydrobromic acid (500 ml) and acetic acid to reflux temperature (110 -115°C) for 10 -12 hours. The reaction mixture was cooled to room temperature, maintained for 1 hour and then filtered. The product obtained was washed with water and dried under vacuum to yield the product 233 g.

HPLC Purity: 95.92%

Dimeric Impurity: 2.86%

Example 4

Preparation of tolterodine tartrate

Tolterodine hydrobromide (230 g) from Example 1 (HPLC Purity: 97.52%), methylene chloride and water were mixed. The pH was adjusted to about 10 – 11 while adding sodium hydroxide (50%, 21 g in 42 ml) and sodium carbonate (26.45 g). After stirring for about 15 minutes, two clear homogeneous phases were formed. The organic layer was separated and washed with water twice (2 x 1150 ml), and was concentrated under reduced pressure. The concentrate was dissolved in acetone (1150 ml) and warmed to 50°C. The L-tartaric acid solution (126.5 g) dissolved in 575 ml methanol was added over about 30 minutes, followed by refluxing the slurry for 1 hour and was gradually cooled to 20 – 25°C. The mixture was filtered and washed with acetone (460 ml) and dried under reduced pressure to give crude tolterodine tartrate.

Yield (w/w): 118 g
HPLC Purity (%): 99.48

Dimeric Impurity (%): 0.33

The crude tolterodine tartrate (110 g) and methanol (1270 ml) were heated to reflux for 30 minutes. Charcoal was added to the solution and stirred for 1 hour at reflux temperature. The solution was filtered, and the mixture was concentrated to 1100 ml. Acetone (2.2 lit.) was added at reflux temperature and gradually cooled to 20 – 25°C. The solid was filtered and washed with acetone (440 ml) and dried under reduced pressure to give pure (R) tolterodine-L-tartrate.

Yield (w/w): 80.5 g

HPLC Purity (%): 99.90

Dimeric Impurity (%): 0.06

Example 5

Preparation of tolterodine tartrate

Tolterodine hydrobromide (230 g) from Example 2 (HPLC Purity: 98.37%), methylene chloride and water were mixed. The pH was adjusted to about 10 – 11 while adding sodium hydroxide (50%, 21 g in 42 ml) and sodium carbonate (26.45 g). After stirring for 15 minutes, two clear homogeneous phases were formed. The organic layer was separated and washed with water twice (2 x 1150 ml), and concentrated under reduced pressure. The concentrate was dissolved in acetone (1150 ml) and warmed to 50°C. The L-tartaric acid solution (126.5 g) dissolved in 575 ml methanol was added over about 30 minutes followed by refluxing the slurry for 1 hour and was gradually cooled to 20 – 25°C. The mixture was filtered and washed with acetone (460 ml) and dried under reduced pressure to give crude tolterodine tartrate.

Yield (w/w): 120 g

HPLC Purity (%): 99.66

Dimeric Impurity (%): 0.18

The crude tolterodine tartrate (110 g) and methanol (1270 ml) were heated to
reflux for 30 minutes. Charcoal was added to the solution and stirred for 1 hour at reflux temperature. The solution was filtered, and the mixture concentrated to 1100 ml. Acetone (2.2 l.) was added at reflux temperature and gradually cooled to 20 – 25°C. The solid was filtered and washed with acetone (440 ml) and dried under reduced pressure to pure (R) tolterodine-L-tartrate.

Yield (w/w): 81 g

HPLC Purity (%): 99.903

Dimeric Impurity (%): 0.035

Example 6

Preparation of tolterodine tartrate

Tolterodine hydrobromide (230 g) from Example 3 (HPLC Purity: 95.92%), methylene chloride and water were mixed. The pH was adjusted to about 10 – 11 while adding sodium hydroxide (50%, 21 g in 42 ml) and sodium carbonate (26.45 g). After stirring for 15 minutes, two clear homogeneous phases were formed. The organic layer was separated and washed with water twice (2 x 1150 ml), and concentrated under reduced pressure. The concentrate was dissolved in acetone (1150 ml) and warmed to 50°C. The L-tartaric acid solution (126.5 g) dissolved in 575 ml methanol was added over about 30 minutes followed by refluxing the slurry for 1 hour and was gradually cooled to 20 – 25°C. The mixture was filtered and washed with acetone (460 ml) and dried under reduced pressure to give crude tolterodine tartrate.

Yield (w/w): 115 g

HPLC Purity (%): 99.21

Dimeric Impurity (%): 0.60

The crude tolterodine tartrate (110 g) and methanol (1270 ml) were heated to reflux for 30 minutes. Charcoal was added to the solution and stirred for 1 hour at reflux temperature. The solution was filtered, and the mixture concentrated to 1100 ml. The acetone (2.2 l.) was added at reflux temperature and was gradually cooled to 20 – 25°C. The solid was filtered and washed with acetone (440 ml) and dried under reduced pressure
to pure (R) tolterodine-L-tartrate.

Yield (w/w): 82.5 g

HPLC Purity (%): 99.819

Dimeric Impurity (%): 0.10

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.
We claim:

1. Tolterodine dimer, N,N-di-[3-[2-hydroxy-5-methylphenyl]-3-phenylpropyl]isopropylamine of Formula I

```
               OH
         N     HO
       H3C - -CH3
    
```

**FORMULA I**

2. A method of determining purity of tolterodine or a pharmaceutically acceptable salt thereof or a pharmaceutical composition containing the same, which comprises use of tolterodine dimer of Formula I as a reference standard compound.

3. A process for the isolation of tolterodine dimer, the process comprising

   a) heating N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine of Formula III with aqueous hydrobromic acid in the presence of acetic acid to get crude tolterodine hydrobromide,

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               O
         H3C - -N
               
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**FORMULA III**

b) subjecting the crude tolterodine hydrobromide to preparative HPLC and eluting with a gradient mobile phase to get eluent containing tolterodine dimer, and

c) isolating the pure tolterodine dimer from the eluent.
4. The process of claim 3, wherein the crude tolterodine hydrobromide is repeatedly loaded on YMC-Pack ODS-A (500 x 30 mm I. D.) HPLC column and eluted using gradient mobile phase of phosphate buffer and acetonitrile.

5. A process of depletion of tolterodine dimer impurity from tolterodine or a pharmaceutically acceptable salt thereof, the process comprising obtaining a solution of crude tolterodine or a pharmaceutically acceptable salt thereof in one or more solvent; and recovering the pure tolterodine or a pharmaceutically acceptable salt thereof by the removal of the solvent.

6. The process of claim 5, wherein the solution of crude tolterodine is obtained by heating the solvent.

7. The process of claim 6, wherein the heating temperature ranges from about 30°C to about 100°C.

8. The process of claim 7, wherein the heating temperature ranges from about 40°C to about 60°C.

9. The process of claim 5, wherein the solvent comprises one or more of lower alkanol, ketone, polar aprotic solvent, or mixtures thereof.

10. The process of claim 9, wherein the lower alkanol comprises one or more of primary, secondary and tertiary alcohols having from one to six carbon atoms.

11. The process of claim 10, wherein the lower alkanol comprises one or more of methanol, ethanol, denatured spirit, n-propanol, isopropanol, n-butanol, isobutanol, and t-butanol.

12. The process of claim 9, wherein the ketone comprises one or more of acetone, 2-butanone, and 4-methylpentan-2-one.

13. The process of claim 9, wherein the polar aprotic solvent comprises one or more of tetrahydrofuran, acetonitrile, 1,4-dioxane and N-methylpyrrolidone.
14. The process of claim 5, wherein removing the solvent comprises one or more of distillation, distillation under vacuum, filtration, filtration under vacuum, decantation, and centrifugation.

15. The process of claim 5, further comprising additional drying of the product obtained.

16. The process of claim 5, further comprising forming the product obtained into a finished dosage form.

17. A method of treating urinary urge incontinence or other symptoms of bladder over activity, the method comprising providing a dosage form that includes pure tolterodine or a pharmaceutically acceptable salt thereof prepared by the process of claim 5.

18. Tolterodine or a pharmaceutically acceptable salt thereof containing less than 0.5% tolterodine dimer impurity when determined by HPLC.

19. Tolterodine or a pharmaceutically acceptable salt thereof containing less than 0.05% tolterodine dimer impurity when determined by HPLC.

20. A pharmaceutical composition comprising a therapeutically effective amount of pure tolterodine or a pharmaceutically acceptable salt thereof containing less than 0.5% tolterodine dimer; and one or more pharmaceutically acceptable carriers, excipients or diluents.

21. A pharmaceutical composition comprising a therapeutically effective amount of pure tolterodine or a pharmaceutically acceptable salt thereof containing less than 0.05% tolterodine dimer; and one or more pharmaceutically acceptable carriers, excipients or diluents.

22. A method of treating urinary urge incontinence or other symptoms of bladder over activity, the method comprising providing a dosage form that includes pure tolterodine or a pharmaceutically acceptable salt thereof containing less than 0.5% tolterodine dimer.
23. A method of treating urinary urge incontinence or other symptoms of bladder over activity, the method comprising providing a dosage form that includes pure tolterodine or a pharmaceutically acceptable salt thereof containing less than 0.05% tolterodine dimer.
## A. CLASSIFICATION OF SUBJECT MATTER

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<th>C07C213/08</th>
<th>C07C213/02</th>
<th>C07C215/54</th>
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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)

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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, PAJ, CHEM ABS Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>Y</td>
<td><em>column 1, last paragraph; column 2, lines 1-14; column 4, lines 40-67; columns 6 and column 7, lines 1-20</em></td>
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<td>5-11, 14-23</td>
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<td>WO 03/014060 A (NEELA PRAVEEN KUMAR; KUMAR YATENDRA (IN); PRASAD MOHAN (IN); RANBAXY) 20 February 2003 (2003-02-20) <em>page 1, lines 7-11; page 3, lines 17-22; page 8, lines 24-26 and page 10, step e</em></td>
<td>17-23</td>
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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:
  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "B" earlier document but published on or after the international filing date
  - "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 actual completion of the international search: 28 June 2004

Date of mailing of the international search report: 14/07/2004

Name and mailing address of the ISA:
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Fax: (+31 -70) 340-3016

Authorized officer:
Lorenzo Varela, M.J.
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<td>Y</td>
<td><em>pages 287 and 288</em></td>
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INTERNATIONAL SEARCH REPORT

Box II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. X Claims Nos.:  
   because they relate to subject matter not required to be searched by this Authority, namely:  
   Although claims 17, 22 and 23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. □ Claims Nos.:  
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. □ Claims Nos.:  
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. □ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. □ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:  

4. □ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  

Remark on Protest  
□ The additional search fees were accompanied by the applicant's protest.  
□ No protest accompanied the payment of additional search fees.
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