PROCESSSES FOR THE PREPARATION OF PIOGLITAZONE OR SALTS THEREOF

The present invention provides processes for the preparation of highly pure pioglitazone or a salt thereof. In addition, the present invention provides pioglitazone or a salt thereof having about 0.1% or less of dehydropioglitazone impurity.
PROCESSES FOR THE PREPARATION OF PIOGLITAZONE OR SALTS THEREOF

Field of the Invention

The present invention provides processes for the preparation of highly pure pioglitazone or a salt thereof. In addition, the present invention provides pioglitazone or a salt thereof having about 0.1% or less of dehydropioglitazone impurity.

Background of the Invention

Pioglitazone (hereinafter referred to as "PGL") of Formula I is chemically, [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-]thiazolidinedione, used as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes (non-insulin-dependent diabetes mellitus or "NIDDM"). Pioglitazone may be used alone or in combination with one or more of sulphonylureas, metformin or insulin when diet and exercise plus a single agent does not result in adequate glycemic control. The commercially available form of pioglitazone is its monohydrochloride salt.

![Chemical Structure of Pioglitazone](image)

**FORMULA I**

Several processes are known in the literature for making PGL or a salt thereof, for example, U.S. Patent Nos. 4,687,777; 5,585,495; 4,812,570; 5,554,758; 5,952,509 and 6,100,403; U.S. Patent Applications U.S. 2002/0106762 and U.S. 2002/0050563; PCT Applications WO 03/53367; WO 03/80056; WO 04/07490; WO 04/024059; WO04/101560 and WO 04/101561.

Dehydropioglitazone (hereinafter referred to as "DHP" or "DHP of Formula II") is known as an intermediate in the synthesis of pioglitazone or salts thereof.
In addition, DHP is also present as a process impurity or degradation product in PGL or salts thereof. Several reasons are attributed for the generation of DHP in PGL. Some factors linked to the generation of this impurity include the incomplete reduction of DHP and the oxidation of PGL during isolation or while on stability.

No toxicity data on DHP is available in the literature; therefore the presence of this compound in measurable quantities in the final PGL compound is not acceptable by regulatory agencies across the world. It was reported in Chemical & Pharmaceutical Bulletin 39(6), 1440-1445, 1991 that DHP has potent hypoglycemic and hypolipidemic activities, when compared to PGL; however no toxicity data on DHP has been reported in the literature.

Several approaches are used to control the levels of the DHP impurity in the pioglitazone active substance. For example, reducing the product with a suitable noble metal catalyst in the presence of hydrogen is a commonly applied approach. However, the cost of this type of reductive process is very high. Therefore, there exists a need for a simple, cost effective process for reducing or eliminating the DHP impurity in the pioglitazone active substance.

### Summary of the Invention

In one general aspect there is provided a process for the preparation of pioglitazone or salt thereof, the process comprising:

a) reacting a pioglitazone amino ether of Formula III,

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

### FORMULA III

with an alkyl acrylate of Formula IV, wherein R is a C$_{1-4}$ alkyl
FORMULA IV

in the presence of sodium nitrite, cuprous salt and hydrobromic acid to form a reaction mass;

b) optionally washing the reaction mass with one or more chelating agents to remove copper;

c) condensing the product obtained, pioglitazone bromo ether of Formula V,

![FORMULA V](image)

with thiourea to obtain a pioglitazone imino ether of Formula VI; and

![FORMULA VI](image)

d) optionally washing the reaction mass with one or more chelating agents to remove copper; and

e) hydrolyzing the pioglitazone imino ether of Formula VI to form pioglitazone or a salt thereof,

f) wherein at least one of the optional washings of steps b) and d) occurs.

Embodiments of the process may include one or more of the following features. For example, the alkyl acrylate may be methyl acrylate. The one or more chelating agents may be ethylenediaminetetraacetic acid (EDTA) or a salt thereof. The hydrolysis may be carried out in aqueous hydrochloric acid. The pioglitazone or a salt thereof obtained may
include less than 0.1% w/w of the impurity DHP. The washing of step b) and/or step d) may occur.

In another general aspect there is provided pioglitazone or a salt thereof that contains less than about 0.1% w/w of the impurity DHP. Embodiments may include one or more of the following features. For example, the pioglitazone may be incorporated into a pharmaceutical composition further including one or more pharmaceutically acceptable excipients, wherein the pioglitazone comprises less than about 0.1% w/w of the impurity DHP. The pioglitazone or salt thereof may comprise less than about 0.05% w/w of the impurity DHP. The one or more pharmaceutically acceptable excipients may be one or more of disintegrants, binders, lubricants, glidants, colorants, or other pharmaceutically inert excipients.

In another general aspect there is provided a method of improving glycemic control in patients with non-insulin-dependent diabetes mellitus. The method includes administering a pharmaceutical composition of pioglitazone or salt thereof and one or more pharmaceutically acceptable excipients, wherein the pioglitazone comprises less than about 0.1% w/w of the impurity DHP.

Embodiments of the method may include one or more of the following features. For example, the pioglitazone or salt thereof may comprise less than about 0.05% w/w of the impurity DHP. The one or more pharmaceutically acceptable excipients may be one or more of disintegrants, binders, lubricants, glidants, colorants, or other pharmaceutically inert excipients.

In another general aspect there is provided a step in a process for preparing PGL or salt thereof having less than 0.1% w/w DHP as impurity, comprising the step(s) of:

(a) washing a solution of PGL bromo ether of Formula V in organic solvent with a solution of chelating agent; and/or

![FORMULA V]
(b) washing a solution of PGL imino ether of Formula VI in organic solvent with a solution of chelating agent.

![Formula VI](attachment:formula.png)

**FORMULA VI**

5 Embodiments may include one or more of the following features. For example, the one or more chelating agents may be ethylenediaminetetraacetic acid (EDTA) or a salt thereof.

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 present inventors have found that while following the prior art when preparing PGL or salt thereof, the finished product obtained had more than 0.2% w/w of DHP when measured by HPLC. In our studies, we observed that during the hydrolysis step of pioglitazone imino ether in alcohol and concentrated hydrochloric acid, a blackish shiny mirror-like substance was deposited on the inner walls of the reaction vessel. This was observed irrespective of the nitrogen atmosphere under which the reaction was performed. The formation of metallic copper indicated a redox reaction wherein an undesired oxidation of pioglitazone to dehydropioglitazone occurred.

Thus, it was noticed that the carry over of copper from one step in the process to another was responsible for the oxidative degradation of PGL to form DHP. In order to confirm this finding, the present inventors have refluxed pure PGL having 0.17% w/w of DHP with a small quantity of cuprous bromide in ethanol for a few hours. The product obtained has about 0.96% w/w of DHP as an impurity. Thus in the presence of copper about a seven six fold increase in DHP impurity was observed.

Simply washing the organic layer containing crude pioglitazone bromo ether was not effective in removing all traces of copper salts. Therefore, it was reasoned that the use
of one or more copper chelating agents that bind to copper salts would be effective in removing them more effectively.

In order to prevent the carry over of copper the reaction mass is washed with one or more chelating agents for the removal of copper by complex formation. The PGL obtained as a product has less than about 0.1% w/w of DHP as impurity when measured by HPLC.

Therefore, a first aspect of the present invention provides a process for preparation of PGL or salt thereof. The process includes the steps of;

a) reacting the PGL amino ether of Formula III,

\[ \text{H}_2\text{N} \\begin{array}{c} \text{O} \\ \text{O} \end{array} \text{NR} \]

FORMULA III

with an alkyl acrylate of Formula IV, wherein R is C\(_{1-4}\) alkyl group

\[ \text{\text{O}} \text{R} \]

FORMULA IV

in the presence of sodium nitrite, cuprous salt and hydrobromic acid;

b) washing the reaction mass with one or more chelating agents to remove copper;

c) condensing the product, PGL bromo ether of Formula V;

\[ \text{R} \text{O} \text{O} \text{Br} \]

FORMULA V

with a thiourea to get a PGL imino ether of Formula VI; and
d) hydrolyzing a PGL imino ether of Formula VI to a PGL or salt thereof.

The PGL amino ether of Formula III is dissolved in a mixture of organic solvents such as ketones and alkanol and under cooling, aqueous hydrobromic acid is added. The mixture is further cooled and to it is added a solution of sodium nitrite in water followed by the addition of an alkyl acrylate, such as methyl acrylate, in one lot under cooling. The temperature is raised to about 35°C and cuprous oxide is added in small portions. After completion of the reaction the solvent is recovered under a vacuum and the residue is extracted with a chlorinated hydrocarbon or an aromatic hydrocarbon solvent and washed with water. The organic layer is washed with a solution of one or more chelating agents, and then washed with water. The organic layer is then subjected to evaporation to get crude PGL bromo ether of Formula V.

Suitable chelating agents are known to a person of ordinary skills in the art and may include one or more of ethylenediaminetetraacetic acid (EDTA) or salts thereof, bidentate, tridentate ligands and mixtures thereof.

The crude PGL bromo ether of Formula V is refluxed with a thiourea in the presence of an alkanol and sodium acetate. After completion of reaction the solvent is evaporated and the residue is triturated with a second organic which may include one or more of diethyl ether, diisopropyl ether, cyclohexane, methyl t-butyl ether and mixtures thereof to precipitate the PGL imino ether of Formula VI which can be further slurried with a second organic solvent and dried.

PGL imino ether is then hydrolyzed in the presence of an aqueous acid, optionally under a nitrogen atmosphere, in presence of an alkanol. After completion of the reaction, the reaction mass is neutralized using a base and chilled to precipitate PGL. The PGL may be subsequently converted to its salt by treating it with an acid or base as per the processes
known in the art. The HPLC analysis of this crude PGL shows less than 0.1% w/w of DHP impurity.

A second aspect of the present invention provides a process for preparation of PGL or salt thereof. The process includes the step of:

5  a) reacting a PGL amino ether of Formula III,

\[
\text{H}_2\text{N} - \text{O} - \text{C}_6\text{H}_4\text{N} - \text{O} - \text{C}_6\text{H}_4\text{N} - \text{CH}_2\text{CH}_2\text{OH}
\]

**FORMULA III**

with an alkyl acrylate of Formula IV, wherein R is C\textsubscript{1-4} alkyl group

\[
\text{CH}_2\text{CH}_2\text{O} - \text{R}
\]

**FORMULA IV**

in the presence of sodium nitrite, cuprous salt and hydrobromic acid;

b) condensing the product PGL bromo ether of Formula V;

\[
\text{R}_1\text{O} - \text{CO} - \text{Br}
\]

**FORMULA V**

15 with a thiourea to get PGL imino ether of Formula VI;

\[
\text{N} = \text{S} - \text{HN} - \text{C} - \text{H}
\]

**FORMULA VI**

c) washing the reaction mass with one more chelating agents to remove copper; and

d) hydrolyzing the PGL imino ether of Formula VI to obtain PGL or salt thereof.
The process of this aspect is similar to the process of the first aspect except that instead of washing the solution PGL bromo ether in organic solvent with one or more chelating agents, in this aspect the solution of PGL imino ether in organic solvent is washed with one or more suitable chelating agents. HPLC analysis of the PGL obtained as per this aspect of the invention shows less than about 0.1% w/w of DHP impurity.

A third aspect of the present invention provides PGL or salt thereof having less than about 0.1% w/w DHP as an impurity. For example, the PGL or salt thereof of the present invention may have less than about 0.05% w/w DHP as impurity.

A fourth aspect of the present invention provides PGL bromo ether of Formula V and PGL imino ether of Formula VI having less than about 20 ppm of copper content when determined by ICP-MS technique. It was observed that when the solution of compound of either Formula V or VI is washed with a chelating agent the residual copper content was reduced to less than about 20 ppm when determined by ICP-MS (Inductively Coupled Plasma – Mass Spectroscopy) technique. It was also observed that when such a low content of copper is present in these intermediates the resulting PGL obtained has less than 0.1% w/w of DHP as impurity.

A fifth aspect of the present invention provides for pharmaceutical compositions that include PGL or salt thereof having less than about 0.1% w/w DHP as an impurity and one or more pharmaceutically acceptable excipients. For example, the PGL or salt thereof of the present invention may have less than about 0.05% w/w DHP as impurity.

Suitable pharmaceutically acceptable excipients include one or more of disintegrants, binders, lubricants, glidants, colorants, or any other pharmaceutically inert excipient.

The following examples are provided to exemplify various aspect of the invention and should not be construed as limiting the invention.

**REFERENCE EXAMPLE**

PGL PREPARED AS PER THE EXAMPLE 1 OF U.S. 4,687,777

a) **Preparation of PGL bromo ether:** Pioglitazone amino ether (60 g) was dissolved in a mixture of acetone (150 ml) and methanol (60 ml). After cooling to about 10°C, aqueous hydrobromic acid (120 ml) was added over the course of 30 minutes during
which time a temperature rise from 10°C to 30°C was noticed. The mixture was cooled to 0°C-5°C and a solution of sodium nitrite (20 g in 48 ml water) was added over 30 minutes. To the resultant mass methyl acrylate (135 ml) was added in one lot. The temperature was then increased to 35°C and cuprous oxide (2.4 g) was added in small portions over 15 minutes while maintaining a temperature of between 35°C and 40°C. After stirring the mixture at 35°C-42°C for 2 hours, the solvent was recovered under a vacuum and dichloromethane (240 ml) and water (240 ml) was added to the residue. The resulting biphasic mixture was stirred and allowed to settle. After separating the layers, the aqueous layer was extracted with dichloromethane (120 ml). The organic layers containing PGL bromo ether were combined and washed with water (2 x 180 ml). The dichloromethane layer was completely concentrated under a vacuum to get crude PGL bromo ether.

Yield: 87 g.

Copper Content: 14000 ppm by ICP-MS (Inductively Coupled Plasma – Mass Spectroscopy)

b) **Preparation of PGL imino ether:** The crude PGL bromo ether (87 g) was dissolved in denatured spirit (315 ml) and sodium acetate trihydrate (63 g) and thiourea (19 g) was added at a temperature of between 30°C-32°C. The mixture was then refluxed at 80°C for 3-4 hours. After completion of the reaction the solvent was recovered under a vacuum and the residue was triturated with diisopropyl ether and water, neutralized and filtered. The solid was slurry washed with diisopropyl ether and then dried in air at 30°C for 18 hours to get crude PGL imino ether.

Yield: 70 g.

Copper Content: 10950 ppm by ICP-MS (Inductively Coupled Plasma – Mass Spectroscopy)

c) **Preparation of PGL:** The crude PGL imino ether (70 g) was taken in denatured spirit (500 ml) and concentrated hydrochloric acid (51 ml) was added to it while stirring under a nitrogen atmosphere. The mixture obtained was stirred at 79°C-80°C for 18 hours. After completion of reaction the mass was cooled to 30°C and neutralized using triethylamine (56 ml) at 10°C and stirred for 1 hour at 5°C-10°C. The product was filtered cold, slurry washed and dried at 45°C-50°C for 6 hours to get crude PGL.
Yield: 38 g

DHP impurity: 0.32% w/w by HPLC analysis.

Copper Content: 4400 ppm by ICP-MS (Inductively Coupled Plasma – Mass Spectroscopy)

5

EXAMPLE 1

PREPARATION OF PGL HAVING LESS THAN 0.1% W/W DHP IMPURITY

a) Preparation of PGL bromo ether: Pioglitazone amino ether (60 g) was dissolved in a mixture of acetone (150 ml) and methanol (60 ml). After cooling to about 10°C, aqueous hydrobromic acid (120 ml) was added over 30 minutes and a rise in temperature from 10°C to 30°C was observed. The mixture was cooled to 0°C-5°C and a solution of sodium nitrite (20 g in 48 ml water) was added over 30 minutes. To the resultant mass was added methyl acrylate (135 ml) in one lot. The temperature was increased to 35°C and cuprous oxide (2.4 g) was added in small portions over 15 minutes while the temperature was maintained at between 35°C and 40°C. After stirring the mixture at 35°C-42°C for 2 hours, the solvent was recovered under vacuum and dichloromethane (240 ml) and water (240 ml) were added to the residue. The biphasic mixture was stirred and then allowed to settle. After separating the layers, the aqueous layer was extracted with dichloromethane (120 ml). The organic layers containing PGL bromo ether were combined and washed with water (2 x 180 ml). The dichloromethane layer was further washed with a dilute solution of ethylenediamine-tetra-acetic acid disodium salt (2 x 240 ml of 2% aqueous solution) followed by water (180 ml). The organic layer was concentrated under a vacuum to provide crude pioglitazone bromo ether.

Yield: 87 g.

Copper Content: Less than 20 ppm by ICP-MS (Inductively Coupled Plasma – Mass Spectroscopy)

b) Preparation of PGL imino ether: The crude PGL bromo ether (87 g) was dissolved in denatured spirit (315 ml), and sodium acetate trihydrate (63 g) and thiourea (19 g) were added at a temperature of 30°C-32°C. The mixture was then refluxed at 80°C for 3-4 hours. After completion of the reaction the solvent was recovered under a vacuum and the residue was triturated with diisopropyl ether and water, neutralized and filtered.
The solid was slurry washed with diisopropyl ether and then dried in air at 30°C for 18 hours to get crude PGL imino ether.

Yield: 70 g.

Copper Content: Less than 20 ppm by ICP-MS (Inductively Coupled Plasma – Mass Spectroscopy)

c) **Preparation of PGL:** The crude PGL imino ether (70 g) was taken in denatured spirit (500 ml) and concentrated hydrochloric acid (51 ml) was added to it while stirring under nitrogen atmosphere. The mixture obtained was stirred at a temperature of between 79°C-80°C for 18 hours. After completion of the reaction the mass was cooled to 30°C and neutralized using triethylamine (56 ml) at 10°C and allowed to stir for 1 hour at a temperature of between about 5°C -10 °C. The product was filtered cold, slurry washed and dried at a temperature of between about 45°C-50°C for 6 hours to get crude PGL.

Yield: 38 g

DHP impurity: 0.04% w/w by HPLC analysis.

Copper Content: Less than 20 ppm by ICP-MS (Inductively Coupled Plasma – Mass Spectroscopy)

**EXAMPLE 2**

**PREPARATION OF PGL HAVING LESS THAN 0.1% W/W DHP IMPURITY**

a) **Preparation of PGL bromo ether:** Pioglitazone amino ether (60 g) was dissolved in a mixture of acetone (150 ml) and methanol (60 ml). After cooling to about 10°C, aqueous hydrobromic acid (120 ml) was added over 30 minutes during which a rise in temperature from 10°C to 30°C was observed. The mixture was cooled to a temperature of between 0°C-5°C and a solution of sodium nitrite (20 g in 48 ml water) was added over 30 minutes. To the resultant mass methyl acrylate (135 ml) in one lot was added. The temperature was increased to 35°C and cuprous oxide (2.4 g) was added in small portions over 15 minutes keeping the temperature between 35°C and 40°C. After stirring the mixture at 35°C-42°C for 2 hours, the solvent was recovered under a vacuum and to the residue dichloromethane (240 ml) and water (240 ml) were added. The biphase mixture was stirred and then allowed to settle. After separating the layers, the aqueous layer was
extracted with dichloromethane (120 ml). The organic layers containing PGL bromo ether were combined and washed with water (2 x 180 ml). The dichloromethane layer was concentrated completely under vacuum to get crude PGL bromo ether.

Yield: 87 g.

b) **Preparation of PGL imino ether:** The crude PGL bromo ether (87 g) was dissolved in denatured spirit (315 ml) and sodium acetate trihydrate (63 g) and thiourea (19 g) were added at a temperature of 30°C-32°C. The mixture was then refluxed at 80°C for 3-4 hours. After completion of reaction the solvent was recovered under a vacuum and the residue was triturated with diisopropyl ether and water, neutralized and filtered. The solid was slurry washed with diisopropyl ether and then dried in air at 30°C for 18 hours to get crude PGL imino ether. The crude product obtained was dissolved in dichloromethane (240 ml) and the organic layer was washed with a dilute solution of ethylenediamine-tetra-acetic acid disodium salt (2 x 240 ml of 2% aqueous solution) followed by water (180 ml). The organic layer was concentrated under a vacuum to provide crude pioglitazone imino ether.

Yield: 70 g.

Copper Content: Less than 20 ppm by ICP-MS (Inductively Coupled Plasma – Mass Spectroscopy)

c) **Preparation of PGL:** The crude PGL imino ether (70 g) is taken in denatured spirit (500 ml) and concentrated hydrochloric acid (51 ml) was added to it while stirring under nitrogen atmosphere. The mixture obtained was stirred at a temperature of between 79°C-80°C for 18 hours. After completion of the reaction the mass was cooled to 30°C and neutralized using triethylamine (56 ml) at 10°C and allowed to stir for 1 hour at a temperature of between 5°C-10°C. The product was filtered cold, slurry washed and dried at a temperature of between 45°C-50°C for 6 hours to get crude PGL.

Yield: 38 g

DHP impurity: 0.087% w/w by HPLC analysis.

Copper Content: Less than 20 ppm by ICP-MS (Inductively Coupled Plasma – Mass Spectroscopy)
EXAMPLE 3

PREPARATION OF PGL HAVING LESS THAN 0.1% W/W DHP IMPURITY

a) Preparation of PGL bromo ether: Pioglitazone amino ether (60 g) was dissolved in a mixture of acetone (150 ml) and methanol (60 ml). After cooling to about 10°C, aqueous hydrobromic acid (120 ml) was added in 30 minutes during which process a rise in temperature from 10 to 30°C was noticed. The mixture was cooled to 0-5°C and a solution of sodium nitrite (20 g in 48 ml water) was added over 30 minutes. To the resultant mass was added methyl acrylate (135 ml) in one lot. The temperature was increased to 35°C and cuprous oxide (2.4 g) was added in small portions over 15 minutes keeping the temperature between 35 and 40°C. After stirring the mixture at 35-42°C for 2 hours, the solvent was recovered under vacuum and to the residue was added dichloromethane (240 ml) and water (240 ml) and the biphasic mixture was stirred and then allowed to settle. After separating the layers, the aqueous layer was extracted with dichloromethane (120 ml). The organic layers containing PGL bromo ether were combined and washed with water (2 x 180 ml). The dichloromethane layer was concentrated completely under vacuum to get crude PGL bromo ether.

Yield: 87 g.

b) Preparation of PGL imino ether: The crude PGL bromo ether (87 g) was dissolved in denatured spirit (315 ml) and sodium acetate trihydrate (63 g) and thiourea (19 g) was added at 30-32°C. The mixture was then refluxed at 80°C for 3-4 hours. After completion of the reaction the solvent was recovered under vacuum and the residue was triturated with diisopropyl ether and water, neutralized and filtered. The solid was slurry washed with diisopropyl ether and further washed with dilute solution of ethylenediamine-tetra-acetic acid disodium salt (3 x 240 ml of 2% aqueous solution) at a temperature of 40-42°C for 30 minutes each. The product was dried at 30-35°C for 18-20 hours.

Yield: 75-80 g

Copper Content: Less than 20 ppm by ICP-MS (Inductively Coupled Plasma – Mass Spectroscopy)

c) Preparation of PGL: The crude PGL imino ether (70 g) was taken in denatured spirit (500 ml) and concentrated hydrochloric acid (51 ml) was added to it while stirring under
nitrogen atmosphere. The mixture thus obtained was stirred at 79-80°C for 18 hours.
After completion of the reaction the mass was cooled to 30°C and neutralized using
triethylamine (56 ml) at 10°C and allowed to stir for 1 hour at 5-10°C. The product was
filtered cold, slurry washed and dried at 45-50°C for 6 hours to get crude PGL.

Yield: 54-56 g

DHP impurity: 0.08 % w/w by HPLC analysis.
Copper Content: Less than 20 ppm by ICP-MS (Inductively Coupled Plasma – Mass
Spectroscopy)

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 included within the scope of the present invention. For example, the
pioglitazone synthesized herein may be incorporated into a pharmaceutical composition
with one or more pharmaceutically acceptable excipients and used in the treatment of
diabetes.
We Claim:

1. A process for preparation of pioglitazone or salt thereof, the process comprising:
   a) reacting a pioglitazone amino ether of Formula III,

   ![Formula III](image)

   FORMULA III

   with an alkyl acrylate of Formula IV, wherein R is a C₁-₄ alkyl

   ![Formula IV](image)

   FORMULA IV

   in the presence of sodium nitrite, cuprous salt and hydrobromic acid to
   form a reaction mass;

   b) optionally washing the reaction mass with one or more chelating agents to
   remove copper;

   c) condensing the product obtained, pioglitazone bromo ether of Formula V,

   ![Formula V](image)

   FORMULA V

   with thiourea to obtain a pioglitazone imino ether of Formula VI; and

   ![Formula VI](image)

   FORMULA VI

   d) optionally washing the reaction mass with one or more chelating agents to
   remove copper; and
20 e) hydrolyzing the pioglitazone imino ether of Formula VI to form
21 pioglitazone or a salt thereof, wherein at least one of the optional washings
22 of steps b) and d) occurs.

1 2. The process according to claim 1, wherein the alkyl acrylate is methyl acrylate.
1 3. The process according to claim 1, wherein the one or more chelating agents is
2 ethylenediaminetetraacetic acid (EDTA) or a salt thereof.
1 4. The process according to claim 1, wherein the hydrolysis is carried out in aqueous
2 hydrochloric acid.
1 5. The process according to claim 1, wherein the pioglitazone or a salt thereof
2 obtained comprises less than 0.1% w/w of the impurity DHP.
1 6. The process according to claim 1, wherein the washing of step b) occurs.
1 7. The process according to claim 1, wherein the washing of step d) occurs.
1 8. Pioglitazone or a salt thereof comprising less than about 0.1% w/w of the impurity
2 DHP.
1 9. The pioglitazone or salt thereof of claim 8, wherein the pioglitazone or salt thereof
2 is incorporated into a pharmaceutical composition further comprising one or more
3 pharmaceutically acceptable excipients, wherein the pioglitazone or salt thereof
4 comprises less than about 0.1% w/w of the impurity DHP.
1 10. The pioglitazone of claim 9, wherein the pioglitazone or salt thereof comprises
2 less than about 0.05% w/w of the impurity DHP.
1 11. The pioglitazone of claim 9, wherein the one or more pharmaceutically acceptable
2 excipients comprises one or more of disintegrants, binders, lubricants, glidants,
3 colorants, or other pharmaceutically inert excipient.
2 diabetes mellitus, the method comprising administering a pharmaceutical
3 composition of comprising pioglitazone or salt thereof and one or more
4 pharmaceutically acceptable excipients, wherein the pioglitazone comprises less
5 than about 0.1% w/w of the impurity DHP.
13. The method of claim 12, wherein the pioglitazone or salt thereof comprises less
than about 0.05% w/w of the impurity DHP.

14. The method of claim 12, wherein the one or more pharmaceutically acceptable
excipients comprise one or more of disintegrants, binders, lubricants, glidants,
colorants, or other pharmaceutically inert excipients.

15. A step in a process for preparing PGL or salt thereof having less than 0.1% w/w
DHP as impurity, the process comprising the step(s) of:
(a) washing a solution of PGL bromo ether of Formula V in organic solvent
    with a solution of chelating agent; and/or

\[
\begin{align*}
\text{FORMULA V} \\
\text{R} & \quad \text{O} \\
\text{O} & \quad \text{Br} \\
\end{align*}
\]

(b) washing a solution of PGL imino ether of Formula VI in organic solvent
    with a solution of chelating agent.

\[
\begin{align*}
\text{FORMULA VI} \\
\text{H} & \quad \text{N} \\
\text{N} & \quad \text{S} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

16. The process according to claim 15, wherein the one or more chelating agents
comprises ethylenediaminetetraacetic acid (EDTA) or a salt thereof.
## INTERNATIONAL SEARCH REPORT

**International application No**

PCT/IB2006/001134

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**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D417/12

According to International Patent Classification (IPC) or to both national classification and IPC

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**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

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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
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<th>Category</th>
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<td>US 4 687 777 A (MEGURO ET AL) 18 August 1987 (1987-08-18) cited in the application column 6, line 11 - line 60; claims 2,3,5</td>
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<td>WO 2004/024059 A (THEMIS LABORATORIES PRIVATE LIMITED.; LALA RAJENDRA, GHANSHAMLAL; GADK) 25 March 2004 (2004-03-25) cited in the application page 11, line 12 - line 26; claim 1; examples 3-5</td>
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**Further documents are listed in the continuation of Box C.**

**See patent family annex.**

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**Date of the actual completion of the international search**

12 September 2006

**Date of mailing of the international search report**

27/09/2006

**Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016**

**Authorized officer**

MORIGGI, J
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### 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 12-14 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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