**Title:** AN IMPROVED PROCESS FOR PREPARING LOSARTAN POTASSIUM

**Abstract:** The present invention relates to an improved process for preparing Losartan Potassium of formula (I).
Title of Invention: AN IMPROVED PROCESS FOR PREPARING LOSARTAN POTASSIUM

Field of the invention

The present invention relates to an improved process for preparing Losartan Potassium of formula (I)

\[
\text{C}_{22}\text{H}_{23}\text{ClN}_{6}\text{O}
\]

Background of the invention

The chemical name of Losartan is 2-Butyl-4-chloro-l-[2'-(lH-tetrazol-5-yl)[1,l'-biphenyl]-4-yl]methyl]-lH-imidazole-5-methanol and formula is \(\text{C}_{22}\text{H}_{23}\text{ClN}_{6}\text{O}\) and molecular weight is 422.91. The drug is used in its potassium salt. The current pharmaceutical product containing this drug is being sold by Merck using the tradename Cozaar, in the form of tablets.

Losartan is used as Antihypertensive. It is non-peptide angiotensin II receptor antagonist. It is used in the treatment of hypertension. It is also used in the treatment of diabetic nephropathy with an elevated serumcreatinine and proteinuria in patients with type 2 diabetes and a history of hypertension. It may be administered with other antihypertensive agents.

US patent 5138069 describes a process for the preparation of Losartan Potassium which is shown in the scheme-I.
The process involves alkylating 4′bromomethyl-2-cyanobiphenyl with 2-n-butyl-4-chloro-5-[(hydroxymethyl)imidazol in the presence of sodium methoxide and DMF to give 2-n-butyl-4-chloro-1-[2′-cyanobiphenyl-4-ylmethyl]-5-(hydroxymethyl)imidazol which is converted to losartan by reaction with sodium azide in the presence of sodium chloride and DMF. Losartan is converted to its potassium salt using 87% KOH solution.

WO2007020654 describes a process for the preparation of Losartan Potassium which is shown in the scheme-II.
The process involves alkylating 4'bromomethyl-2-cyanobiphenyl with 2-n-butyl-4-chloro-5-formyl imidazol in the presence of sodium hydroxide, DMF and phase transfer catalyst (PTC) to give 2-n-butyl-4-chloro-l- [2'-cyanobiphenyl - 4-ylmethyl] -5-formylimidazol which is reduced with sodium borohydride to give 2-n-butyl-4-chloro-l- [2'-cyanobiphenyl -4-ylmethyl] -5-(hydroxymethyl)imidazol which is further converted to losartan by reaction of sodium azide in the presence of triethylamine HCl in polar solvent. Losartan is converted to its potassium salt using KOH solution.

In the above processes, alkylation of 4'bromomethyl-2-cyanobiphenyl with 2-n-butyl-4-chloro-5-formyl imidazol in the solvent as mentioned hereinabove, gives an isomer which is reduced in next step to give isomeric alcohol along with the desired product. This unwanted isomeric alcohol is having the structural formula as shown below.
This impurity of unwanted isomeric alcohol is difficult to remove by conventional purification methods. Moreover the use of PTC makes the process economically unviable as it increases the raw material cost.

It is therefore, there exists a need to develop an easy to operate, industrially feasible and yet cost effective process for preparing Losartan potassium. Further, this process should ensure the formation of isomeric impurity to a minimum desirable level. The present invention addresses these needs.

Present inventors have directed their research work towards developing a process for the preparation of Losartan Potassium which is devoid of the above disadvantages. The present inventors used l-methyl-2-pyrrolidonone (NMP) as solvent as well as base in the reaction. Serendipitously, it was observed that the formation of an isomeric impurity is substantially reduced by the use of NMP instead of the use of other solvents as mentioned in prior art processes. This helps in the increasing the purity of desired product i.e. 2-n-butyl-4-chloro-l- [2'-cyanobiphenyl-4-ylmethyl] -5-formylimidazol which in turn increase the yield and purity of losartan.

Summary of the invention

Accordingly, it is an object of the present invention to provide an improved process for the preparation of Losartan Potassium.

Another object of the present invention is to provide a process which gives Losartan Potassium with high purity.

Yet another object of the present invention is to provide a process which gives
2-n-butyl-4-chloro-1-[2'-cyanobiphenyl-4-ylmethyl]-5-formylimidazole with minimum formation of unwanted isomeric alcohol impurity.

Another object of the present invention is to provide a process which is operationally simple and cost effective.

Accordingly, present invention provides an improved process for the preparation of Losartan Potassium (I) comprising a step of reacting 4'-bromomethyl-2-cyanobiphenyl (IV) with 2-butyl-4-chloro-5-formylimidazole (III)

in the presence of 1-Methyl-2-pyrrolidinone (NMP) and base to give an intermediate.
which is further reacted with sodium borohydride to give compound of formula (IV);

![Chemical structure of compound (IV)]

Accordingly, present invention provides an improved process for the preparation of Losartan Potassium (I)

![Chemical structure of compound (I)]

comprising steps of:

(i) reacting 4'-bromomethyl-2-cyanobiphenyl (II)

![Chemical structure of compound (II)]

with 2-butyl-4-chloro-5-formylimidazole (III)
in the presence of 1-Methyl-2-pyrrolidinone (NMP) and base to give an intermediate which is further reacted with sodium borohydride to give compound of formula (IV);

(ii) reacting the compound of formula (IV) obtained in step (i) with sodium azide in the presence of triethylamine hydrochloride (TEA-HCl) and 1-Methyl-2-pyrrolidinone (NMP) to give losartan (V);

(iii) reacting Losartan (V) with potassium hydroxide in methanol to give Losartan potassium (I)
Detailed description of the invention

[76] The present invention provides an improved process for the preparation of Losartan Potassium (I)

[77] \[
\begin{align*}
\text{H}_3\text{C} & \quad \text{Cl} \\
\text{N} & \\
\text{OH} & \\
\text{phenyl} & \\
\text{phenyl} & \\
\text{NH} & \\
\text{K} & \\
\end{align*}
\]

(I)

[78] comprising steps of:

[80] (i) reacting 4'-bromomethyl-2-cyanobiphenyl (II)

[81]

[82] \[
\begin{align*}
\text{Br} & \\
\text{phenyl} & \\
\text{CN} & \\
\end{align*}
\]

(II)

[83] with 2-butyl-4-chloro-5-formylimidazole (III)

[84]

[85]

[86] \[
\begin{align*}
\text{H}_3\text{C} & \quad \text{Cl} \\
\text{N} & \\
\text{CHO} & \\
\end{align*}
\]

(III)

[87] in the presence of 1-Methyl-2-pyrrolidinone (NMP) and base to give an intermediate which is further reacted with sodium borohydride to give compound of formula (IV);
(ii) reacting the compound of formula (IV) obtained in step (i) with sodium azide in the presence of triethylamine hydrochloride (TEA-HCl) and 1-Methyl-2-pyrrolidinone (NMP) to give losartan (V);

(iii) reacting Losartan (V) with potassium hydroxide in methanol to give Losartan potassium (I)

The synthetic reaction scheme of the present invention is shown in the scheme-III.
In the process of present invention, a mixture of 4'-Bromomethyl -2-cyanobiphenyl (II), 1-Methyl-2-pyrrolidinone (NMP), base and 2-Butyl-4-chloro-5-formylimidazole (III) is heated at 70°C to 75°C for about 4-5 hrs. The base is selected from \( \text{K}_2\text{CO}_3 \), \( \text{Na}_2\text{CO}_3 \), \( \text{NaHCO}_3 \), \( \text{KHCO}_3 \), \( \text{NaOH} \), \( \text{KOH} \), \( \text{LiOH} \) or mixtures thereof. The preferred base is anhydrous \( \text{K}_2\text{CO}_3 \). Sodium borohydride is charged to the reaction mixture at 30°C. Water and isopropanol are added to the wet cake and heated at about 75°C to about 80°C for 1.5 hours. The reaction mixture is cooled at room temperature and filtered. The solid is sucked dried and dried in oven to give 2-n-Butyl-4-chloro-l-\(\text{[2'-(cyanobiphenyl-4-yl)methyl]}\) -5-(hydroxymethyl)-imidazole (IV).

A mixture of 2-n-Butyl-4-chloro-l-\(\text{[2'-(cyanobiphenyl-4-yl)]methyl}\) -5-(hydroxymethyl)-imidazole (IV), sodium azide, triethylamine hydrochloride (TEA-HCl), 1-Methyl-2-pyrrolidinone (NMP) and toluene are heated at 110°C for 30-35 hours. Caustic solution is added to it and the layers are separated. Acetic acid is added to the aqueous layer and pH is adjusted to 4 to 4.5. The product is filtered and solid is washed with water. The solid is purified by triturating it with acetone to give pure Losartan (V).
85% Potassium hydroxide solution is added to a mixture of Losartan (V) in methanol. The reaction mixture is heated to get clear solution. Activated charcoal is added to the reaction mixture and stirred well. The mixture is filtered through Hyflow bed to remove charcoal. The filtrate is distilled to evaporate the solvent completely. Acetone is added to it and stirred. The resulting precipitates are filtered, washed with acetone and sucked dry. The solid is dried in oven to give Losartan potassium (I).

The Losartan potassium obtained by above process is having polymorphic Form-I.

The major advantage of this process is that the isomeric impurity formation is minimum in the first step. The percentage of isomer formation is very less compare to prior art process. Using other solvents, unwanted isomer is formed in 15-20%, whereas using NMP only 4-5% unwanted isomer is formed. The advantage of the present invention can be understand from the following data depicted in Table-1

<table>
<thead>
<tr>
<th></th>
<th>Prior art process (using other solvent)</th>
<th>Present invention (using NMP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPLC purity</td>
<td>70-80%</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>% of unwanted Isomer formed</td>
<td>10-15%</td>
<td>&lt; 4%</td>
</tr>
<tr>
<td>Yield</td>
<td>90%</td>
<td>90%</td>
</tr>
</tbody>
</table>

The following examples illustrate the invention further. It should be understood, however, that the invention is not confined to the specific limitations set forth in the individual examples but rather to the scope of the appended claims.

**Example-1**

**Preparation of** 2-n-Butyl-4-chloro-1-[2'-(cyanobiphenyl-4-yl)methyl]-5-(hydroxymethyl)-imidazole (IV)

A mixture of 4'-Bromomethyl-2-cyanobiphenyl (II) (125.0 g), 1-Methyl-2-pyrrolidinone (NMP) (375.0 ml), anhydrous potassium carbonate (76.0 g)
and 2-Butyl-4-chloro-5-formylimidazole (III) (90.0 g) was heated at 70°C to 75°C for about 4-5 hrs. Sodium borohydride (18.0 g) was charged to the reaction mixture at 30°C. Water (1875.0 ml) was added to it and isopropanol (562.5 ml) was added to the wet cake and heated at 75-80°C for 1.5 hours. The reaction mixture was cooled at room temperature and filtered. The solid was sucked dried and dried in oven to give the title compound (153.0 g).

Yield: 88.0%
Purity (By HPLC): 99.1%

**Example-2**

**Preparation of Losartan (V)**

A mixture of 2-n-Butyl-4-chloro-1-[2'-(cyanobiphenyl-4-yl)methyl]-5-(hydroxymethyl)-imidazole (IV) (125.0 g), sodium azide (85.6 g), triethyl amine hydrochloride (TEA-HCl) (181.0 g), 1-Methyl-2-pyrrolidinone (NMP) (125.0 ml) and toluene (500.0 ml) were heated at 110°C for 30-35 hours. Caustic solution (19.75g in 300ml water) was added to it and the layers were separated. Acetic acid was added to the aqueous layer and pH was adjusted to 4 to 4.5. The product was filtered and solid washed with water. The solid was triturated with Acetone (500.0 ml) to give pure Losartan (V) (105.0 g).

Yield: 75.0%
Purity (By HPLC): 99.25%

**Example-3**

**Preparation of Losartan potassium (I)**

85% Potassium hydroxide (15.02 g) solution was added to a mixture of Losartan (V) (100.0 g) in methanol (300.0 ml). The reaction mixture was heated to get clear solution. Activated charcoal was added to the reaction mixture and stirred well. The mixture was filtered through hyflow bed to remove charcoal. The filtrate was distilled to evaporate the solvent completely. Acetone (300.0 ml) was added to it and stirred. The resulting precipitates were filtered and washed with acetone (100.0 ml) and suck dried. The solid was dried in oven to give Losartan potassium (I) (98.0 g).

Yield: 90.0%
Purity (By HPLC): 99.85%
Claims

[Claim 1] 1. A process for preparation of Losartan Potassium (I)

\[
\begin{align*}
\text{(I)} & \\
\text{(II)} & \\
\text{(III)} & \\
\text{(IV)} & 
\end{align*}
\]

comprising a steps of reacting 4'-bromomethyl-2-cyanobiphenyl (II)

with 2-butyl-4-chloro-5-formylimidazole (III)

in the presence of l-Methyl-2-pyrrolidinone (NMP) and base to give an intermediate which is further reacted with sodium borohydride to give compound of formula (IV);
[Claim 2] 2. A process for preparation of Losartan Potassium (I)

![Chemical Structure of Losartan Potassium (I)]

comprising steps of:

(i) reacting 4'-bromomethyl-2-cyanobiphenyl (II)

![Chemical Structure of 4'-bromomethyl-2-cyanobiphenyl (II)]

with 2-butyl-4-chloro-5-formylimidazole (III)

![Chemical Structure of 2-butyl-4-chloro-5-formylimidazole (III)]

in the presence of 1-Methyl-2-pyrrolidinone (NMP) and base to give an intermediate which is further reacted with sodium borohydride to give compound of formula (IV):

![Chemical Structure of Compound (IV)]
(ii) reacting the compound of formula (IV) obtained in step (i) with sodium azide in the presence of triethylamine hydrochloride (TEA-HCl) and 1-Methyl-2-pyrrolidinone (NMP) to give losartan (V);

(iii) reacting Losartan (V) with potassium hydroxide in methanol to give Losartan potassium (I)

[Claim 3] 3. The process as claimed in claim 1 or 2, wherein the base is selected from $\text{K}_2\text{CO}_3$, $\text{Na}_2\text{CO}_3$, $\text{NaHCO}_3$, $\text{KHCO}_3$, NaOH, KOH, LiOH or mixtures thereof.