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Title: PROCESS FOR THE PREPARATION OF ALISKIREN

Abstract: The present invention relates to an improved process for the preparation of Aliskiren and its pharmaceutically acceptable salts comprising reducing the compound of Formula-Z in presence of catalyst and ammonia. The present invention further relates to Aliskiren hemifumarate having diastereomeric impurity less than 0.2%(F) H3C CH3 NH2 H3C 0 H3C CH3 Formula-Z.
This application claims priority to this Indian patent application numbers 173/CHE/2012 filed on March 28, 2012 and 1876/CHE/2012 filed on May 11, 2012.

FIELD OF THE INVENTION:

The present invention relates to an improved process for the preparation of renin inhibitor Aliskiren and its pharmaceutically acceptable salts.

BACKGROUND OF THE INVENTION:

Aliskiren, (2S, 4S, 5S, 7S)-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl] octanamide having the Formula-I, a new antihypertensive has been developed which interferes with the renin-angiotensin system at the beginning of angiotensin II biosynthesis.

Aliskiren is marketed by Novartis as TEKTURNA® in the form of its hemifumarate salt in a once-daily formulation.

US 5,559,111 discloses Aliskiren and related compounds along with the synthesis of Aliskiren. Aliskiren hemifumarate is having 4 chiral carbon atoms; hence the synthesis for the pure Aliskiren hemifumarate substantially free of diastereomeric impurities is quite difficult and demanding.
Further US 7132569, US 7009078, US 6730798 and US 6800769 claims novel intermediates used in the preparation of Aliskiren and process for the preparation of Aliskiren, which are incorporated here for reference.

In prior art US 7009078 the reduction of Azide compound (Formula-Z) is carried out in presence of ethanol amine. After completion of reaction the reaction mixture is filtered and the catalyst is washed with tert-butyl methyl ether. The filtrate is washed with sodium hydroxide and brine. To remove the ethanol amine repeated washing with water/aq. NaOH is required. The aqueous phases are extracted with tert-butyl methyl ether. The aqueous work-up decreases the yield of the final product. To overcome this problem the present inventors surprisingly found that usage of ammonia will increase the yield and purity of Aliskiren.

The present invention provides an improved process for the preparation of Aliskiren and its pharmaceutically acceptable salts thereof. Present invention further provides, Aliskiren hemifumarate having substantially free of diastereomeric impurities and process for the preparation of the same.

OBJECT AND SUMMARY OF THE INVENTION:

Principle object of the present invention is to provide an improved process for the preparation of Aliskiren and its pharmaceutically acceptable salts thereof.

One aspect of the present invention provides, an improved process for the preparation of Aliskiren and its pharmaceutically acceptable salts comprising reducing the compound of Formula-Z in presence of catalyst and ammonia.

![Formula-Z](attachment://formula_z.png)
Another object of the present invention is to provide pure Aliskiren hemifumarate having substantially free of diastereomeric impurities.

One aspect of the present invention is to provide a process for the preparation of Aliskiren hemifumarate having substantially free of diastereomeric impurities.

Another aspect of the present invention provides Aliskiren hemifumarate of the following structure:

![Chemical Structure](image)

having diastereomeric impurity of less than 0.2%, as measured by area percentage HPLC.

**DETAILED DESCRIPTION OF THE INVENTION:**

The present invention relates to an improved process for the preparation of renin inhibitors like Aliskiren and its pharmaceutically acceptable salts.

The main aspect of the present invention provides an improved process for the preparation of Aliskiren and its pharmaceutically acceptable salts comprising reducing the compound of Formula-Z in presence of catalyst and ammonia.
In prior art US 7009078 the reduction of compound of Formula-Z is carried out in presence of ethanol amine. After completion of reaction the reaction mixture is filtered and the catalyst is washed with tert-butyl methyl ether. The filtrate is washed with sodium hydroxide and brine. To remove the ethanol amine repeated washing with water/aq. NaOH is required. The aqueous phases are extracted with tert-butyl methyl ether. The aqueous work-up decreases the yield of the final product. To overcome this problem the present inventors surprisingly found that usage of ammonia will increase the yield and purity of Aliskiren.

Accordingly, present invention provides an improved process for the preparation of Aliskiren and its pharmaceutically acceptable salts comprising reducing the compound of Formula-Z in presence of catalyst and ammonia in an alcoholic solvent.

In one embodiment, the catalyst used in the reduction of compound of Formula-Z is selected from Pd/C, Raney nickel or Pd(OH)$_2$ in presence of H$_2$ gas.

In another embodiment, the ammonia used is in the form of non-aqueous ammonia such as alcoholic ammonia. The alcoholic ammonia is selected from ethanolic ammonia and methanolic ammonia, preferably ethanolic ammonia.

In one more embodiment, the reduction is carried out in presence of alcoholic solvent like ethanol, methanol, isopropanol and n-propanol; preferably ethanol.

In one more embodiment, the compound of Formula-Z is prepared by the conventional processes disclosed in prior art for example as disclosed in US 7009078 or in our co pending patent application IN 3087/CHE/2010.

As per the present invention, the compound of Formula-Z is hydrogenated in the presence of 10% Pd/C and ethanolic ammonia solution in alcoholic solvent like ethanol. To the obtained compound, fumaric acid is added to get Aliskiren Hemifumarate.
The present invention also relates to Aliskiren hemifumarate having substantially free of diastereomeric impurities. The present invention further relates to a process for the preparation of Aliskiren hemifumarate having substantially free of diastereomeric impurities.

Another aspect of the present invention is to provide Aliskiren hemifumarate of the following structure:

![Structural formula](image)

having diastereomeric impurity less than 0.2%, as measured by area percentage HPLC.

One embodiment of the present invention is to provide Aliskiren hemifumarate having diastereomeric impurity less than 0.18%, as measured by area percentage HPLC.

One more embodiment of the present invention is to provide Aliskiren hemifumarate having diastereomeric impurity less than 0.15%, as measured by area percentage HPLC.

One more aspect of the present invention provides, Aliskiren hemifumarate diastereomeric impurity of the following structure ALK-I.

The present inventors analyzed the TEKTURNA® tablet purity by HPLC. HPLC conditions are as follows
Instrumentation:

Waters HPLC system having alliance 2695 model pump and 2487 (UV) detector with Empower chromatography software or its equivalent.

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<th>S. No</th>
<th>Reagents/Solvents</th>
<th>Grade</th>
<th>Make</th>
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<tr>
<td>1</td>
<td>Ortho phosphoric acid</td>
<td>AR</td>
<td>Rankem or its equivalent.</td>
</tr>
<tr>
<td>2</td>
<td>Tetrabutyl ammonium hydrogen sulphate</td>
<td>Pure</td>
<td>Spectrochem</td>
</tr>
<tr>
<td>3</td>
<td>Acetonitrile</td>
<td>HPLC</td>
<td>Rankem or its equivalent.</td>
</tr>
<tr>
<td>4</td>
<td>Methanol</td>
<td>HPLC</td>
<td>Rankem or its equivalent.</td>
</tr>
<tr>
<td>5</td>
<td>Water (Milli Q)</td>
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</tr>
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</table>

Chromatographic parameters:
Column: YMC Pro C18, 250 x 4.6 mm, 5.0 µm
Detector: UV at 230 nm
Flow rate: 1.0 mL / min.
Injection volume: 10 µL
Column oven temp.: 27 °C
Run time: 65 minutes
Diluent: Acetonitrile and water in the ratio 1:1 v/v

Mobile Phase-A:
Weight and transfer about 1.0 g of Tetrabutyl ammonium hydrogen sulphate in 1000 mL of water and add 0.5 mL of Ortho phosphoric acid. Filter through 0.45 µm or finer porosity membrane and degas.

Mobile Phase-B:
Prepare a degassed mixture of Acetonitrile: Methanol 55:45 v/v.

Gradient program:

<table>
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<th>Time (minutes)</th>
<th>Mobile Phase-A (% v/v)</th>
<th>Mobile Phase-B (% v/v)</th>
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<tr>
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<td>65</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
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Standard solution
Weigh and transfer about 25.0 mg of each of standard into a 25 mL volumetric flask, dissolve in and dilute to volume with diluent.
Sample solution

Weigh and transfer about 25.0 mg of each of sample into a 25 mL volumetric flask, dissolve in and dilute to volume with diluent.

Procedure:

Inject sample solution into the chromatograph and record the chromatograms. Disregard the peaks due to blank and peak responses which are 0.05% and below apart from known impurities. Typical retention time and relative retention time are as follows (for information). It was found that Aliskiren in TKETURNA tablet (Batch No: 1205809U12TA) is having purity 99.76 at RT 19.51 and diastereomeric impurity of Formula ALK-I is 0.24% at RT 18.64.

Our co-pending Indian patent application IN 3087/CHE/2010 discloses novel process for the preparation of Aliskiren as disclosed in scheme-I.

The intermediate compound of Formula-Y obtained by the above process is in oil form.
The intermediate compounds play a vital role in the preparation of Aliskiren and its pharmaceutically acceptable salts thereof. Considering the lengthy synthesis of Aliskiren which involves almost all the intermediates as oil, it is highly beneficial if any of the intermediate could be obtained as a crystallisable solid which can give the intermediate of good purity as well as Aliskiren of good purity. To avoid that problem and to improve the purity of Aliskiren, the present inventors tried to open the lactone compound (Formula-X) with 3-amino-2,2-dimethyl-propionitrile and not only succeeded in getting fruitful aminolysis reaction, but also isolating the corresponding amide compound of Formula-Y as pure crystalline compound of chromatographic purity greater than or equal to 99%, which is substantially free of its corresponding diastereomer. This results increase in the purity of Aliskiren.

Thus another aspect of the present invention provides process for the preparation of Aliskiren substantially free of diastereomeric impurity comprising the steps of:

a) converting the cyano group of solid compound of Formula-Y into amide group to give compound of Formula-Z;
b) reducing the azide group of compound of Formula-Z with suitable reducing agent to give Aliskiren; and
c) optionally converting Aliskiren into Aliskiren hemifumarate.

In one embodiment, the solid compound of Formula-Y is prepared by reacting compound-X with 3-Amino-2,2-dimethyl-propionitrile, characterized in that after completion of the reaction, reaction mixture containing compound of Formula-Y in water immiscible solvent selected from hydrocarbons such as toluene, xylene, pentane, hexane, preferably toluene; is washed with aqueous base such as sodium bicarbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, preferably sodium bicarbonate to give solid compound of Formula-Y.

In another embodiment, cyano group of solid compound of Formula-Y is converted into compound of Formula-Z in the known manner as disclosed in co-pending Indian patent application IN 3087/CHE/2010.
In one more embodiment, reduction of compound of Formula-Z is carried out in the known manner as disclosed in co-pending Indian patent application IN 3087/CHE/2010.

According to the present invention, the compound of Formula-Y is prepared by reacting compound of Formula-X with 3-amino-2,2-dimethyl-propionitrile in presence of a base like organic or inorganic base, preferably organic base such as Triethylamine, Tripropylamine, diisopropylethylamine, etc., more preferably Triethylamine and a catalyst like 2-hydroxypyridine. After completion of the reaction the reaction mass is diluted with hydrocarbon solvent such as toluene, Xylene and chlorobenzene, preferably toluene and stirred with alkali solution to remove catalyst as an alkali salt. 3-amino-2,2-dimethyl-propionitrile and Triethylamine are extracted from hydrocarbon solvent layer using an organic acid like acetic acid. The hydrocarbon solvent layer is stirred with 1-10% aqueous base solution like sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, preferably 3-5% sodium bicarbonate solution to crystallize compound of Formula-Y. The obtained product is filtered and dried under vacuum to get the compound of Formula-Y as white solid.

All patents, patent applications, and non-patent publications cited herein by reference should be considered in their entirety. The following examples are provided to illustrate the process of the present invention. They, however, are not intended to limiting the scope of the present invention in any way and several variants of these examples would be evident to person ordinarily skilled in the art.
Experimental procedure:

Example-1: Process for the preparation of compound-Y

A mixture of compound-X (100 g), 3-Amino-2,2-dimethyl-propionitrile (74.5 g), and 2-hydroxypyridine (22.5 g) in triethylamine was stirred for about 24 hours at 60-70°C. The progress of the reaction was monitored by HPLC analysis. After completion of the reaction the reaction mass was diluted with toluene and stirred with aq NaOH solution to precipitate and remove 2-hydroxypyridine as sodium salt. The organic layer was washed with aqueous acetic acid. The organic layer was stirred with aqueous sodium bicarbonate solution to crystallize out the desired product. The product was filtered, washed with DM water followed by prechilled toluene and dried under vacuum to yield compound of Formula-Y as white solid. HPLC purity: >99%. Melting point: 62 °C.

Example-2: Process for the preparation of compound-Z

To a mixture of Compound-Y (13g) and ethanol (65 ml) aqueous NaOH (5g dissolved in 45 ml of DM water) and 35% Hydrogen peroxide (20 ml) was added at room temperature and stirred the at 30°- 40 °C for 2-4h. The progress of the reaction was monitored by
HPLC analysis. After completion of the reaction the peroxides were quenched by stirring with sodium bisulfite solution. Thereafter product was extracted in toluene. The toluene extract was washed with ethanolamine and water. The solvent was distilled off completely under vacuum to obtain compound Z.

Example-3: Process for the preparation of Aliskiren Hemifumarate

The compound of Formula-Z (50g) was hydrogenated for 5-6 hours in the presence of 10% Pd/C (5 g) and ethanolic ammonia solution (10% w/w ammonia in ethanol ~29.4g) in ethanol (400 ml) at ambient temperature and 7 Kg/cm² pressure. The reaction mixture was filtered and the catalyst was washed with ethanol (50 ml) and distilled to get residue. The obtained residue was co-distilled with acetonitrile (50 ml) and re-dissolved in ethanol and acetonitrile at 35-40°C. To this fumaric acid (4.5g) was added and stirred to get clear solution and filtered at 35-40°C to remove any insoluble particles. Acetonitrile (150 ml) was added to the above clear filtrate at 35-40°C and inoculated with 200mg of Aliskiren hemifumarate and agitated for 3 hours to get precipitation of the product. To the above slurry acetonitrile was added and agitated for 17 hours at ambient temperature. The suspension was cooled to 0°C and filtered off by suction after 2 hours. The product cake was washed with acetonitrile and then dried under vacuum at 35°C to yield 47g of Aliskiren hemifumarate as white crystals.
We claim:

1. A process for the preparation of Aliskiren or its pharmaceutically acceptable salts comprises reducing the compound of Formula-Z in presence of catalyst and ammonia.

![Formula-Z](formula.png)

2. The process according to claim 1, wherein the catalyst is selected from Pd/C, Raney nickel or Pd(OH)$_2$.

3. The process according to claim 1, wherein the ammonia is in the form of non-aqueous ammonia.

4. The process according to claim 1, wherein the ammonia is in the form of alcoholic ammonia.

5. The process according to claim 4, wherein alcoholic ammonia is selected from ethanolic ammonia and methanolic ammonia.

6. The process according to claim 1, wherein the reaction is carried out in presence of an alcoholic solvent.

7. The process according to claim 6, wherein alcoholic solvent is selected from ethanol, methanol, isopropanol and n-propanol.

8. The process according to claim 1, wherein pharmaceutically acceptable salt is Fumarate salt.
9. Aliskiren hemifumarate having diastereomeric impurity less than 0.2%.

10. Aliskiren hemifumarate according to claim 9, wherein diastereomeric impurity is less than 0.15%.
### A. CLASSIFICATION OF SUBJECT MATTER

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<th>INV.</th>
<th>C07C209/42</th>
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### ADD.

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

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C

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)

EPO-Internal, WPI Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<td>EP 2 062 874 Al (KRKA TOVARNA ZDRAVIL D D NOVO [SI]) 27 May 2009 (2009-05-27)</td>
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
  * "A" document defining the general state of the art which is not considered to be of particular relevance
  * "E" earlier application or patent 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

* "I" 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

* "A" document member of the same patent family

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

3 September 2013

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

13/09/2013

**Name and mailing address of the ISA**

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Fax: (+31-70) 340-3016

**Authorized officer**

Sen, Alina
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<td>wo 2011/148392 Al (MSN LAB LTD [IN]; SATYANARAYANA REDDY MANNE [IN]; THI RUMALAI RAJAN SRI) 1 December 2011 (2011-12-01) page 6, lines 14-17; page 16, lines 3-6; page 18, lines 5-9; page 43, Formula 1-13 to Formula 1-1; page 54, Example 17; pages 55-56, Example 19</td>
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