ORIGINAL

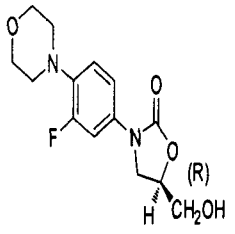
IMPROVED PROCESS FOR THE PREPARATION OF LINEZOLID

Abstract of the invention

The invention relates to a substantially pure linezolid hydroxide having R-isomer content more than about 99.9% relative to its S-isomer. Further aspect of invention provides the ambient moisture condition, which is critical for enantiomeric pure linezolid hydroxide. The obtained substantially enantiomerically pure linezolid hydroxide compound of formula-II can be subsequently converted into the linezolid compound of formula-I, having S-isomer content more than 99.9% relative to R-isomer.

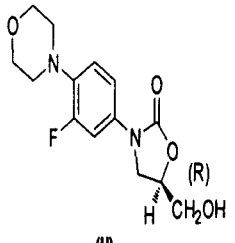
We claim:

1) Substantially enantiomerically pure linezolid hydroxide compound of formula II



(II)

2) The compound of formula-II, according to claim 1, wherein R-isomer content is more than about 99.9% relative to its S-isomer.
3) The compound of formula-II, according to claim 1, wherein R-isomer content is more than about 99.93% relative to its S-isomer.
4) The compound of formula-II, according to claim 1, wherein R-isomer content is more than about 99.95% relative to its S-isomer.
5) The compound according to claim 1, further comprises converting linezolid hydroxide to linezolid compound of formula-I.
6) A process for preparation of enantiomerically pure linezolid hydroxide compound of formula-II comprising the steps of:



(II)

(a) contacting linezolid hydroxide compound of formula-II and an ester solvent.

(b) optionally adjusting the moisture content of the solution of step (a) in between 0.2 to 0.6 w/w %.

(c) optionally adding anti solvent.

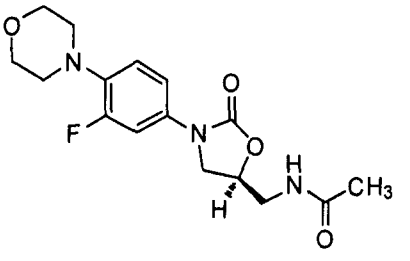
(d) isolating linezolid hydroxide.

7) The process according to claim 6, wherein an ester solvent is selected from the group consisting methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate and n-butyl acetate.

8) The process according to claim 6, wherein solvent is ethyl acetate.

9) The process according to claim 6, wherein antisolvent is selected from the group comprising pentane, hexane, cyclohexane, heptane, octane, methylcyclohexane, chloronaphthalene, orthodichlorbenzene, toluene, ethylbenzene, isopropylbenzene and diethylbenzene

10) The process according to claim 6, further comprising converting the enantiomerically linezolid hydroxide to linezolid compound of formula-I.



(I)

11) The compound of formula-I, according to claim 10, wherein S-isomer content is more than about 99.9% relative to its R-isomer.

12) The compound of formula-I, according to claim 10, wherein S-isomer content is more than about 99.93% relative to its R-isomer.

13) The compound of formula-I, according to claim 10, wherein S-isomer content is more than about 99.95% relative to its R-isomer.

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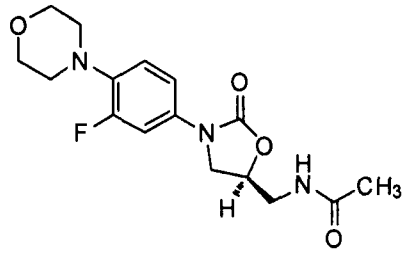
Field of the Invention

The present invention relates to the improved processes for the enantiomerically pure linezolid compound of formula-I. In particular, the present invention is directed to a novel process for enantiomeric pure linezolid hydroxide compound of formula-II, which provides enantiomeric purity more than 99.9% of R-isomer relative to its S-isomer. In the further aspect of present invention also provides conversion linezolid hydroxide to linezolid, having S-isomer content more than 99.9% relative to R-isomer.

Moreover, the present invention relates to an substantially enantiomerically pure R-isomer linezolid hydroxide compound of formula-II in a very high degree of enantiomeric purity as relative to its S-isomer and its use in subsequent conversion into linezolid compound of formula-I.

Background of the Invention

Linezolid, (S)-N-[[3-(3-fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methyl] acetamide compound of formula-I is an antimicrobial agent. Linezolid is an oxazolidinone, having the empirical formula $C_{16}H_{20}FN_3O_4$

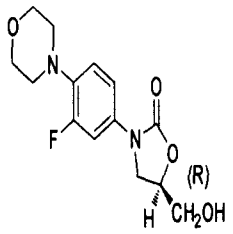


(I)

US 5,688,792 describe the linezolid and its use for the treatment of microbial infections. Various processes for preparation of linezolid are described in US 5,688,792; US 7,291,614; Tetrahedron Lett 40(26), 4855, 1999.

The preparations of linezolid are described in several patents and patent applications. The key constraint in the prior art process is to achieve the pharmaceutically acceptable enantiomeric

pure linezolid. The rational of the drawback is lack of enantiomeric purity in the advanced intermediates of linezolid such as linezolid hydroxide of formula-II.



(II)

Hence, there is a need to have enantiomerically pure intermediate to prepare enantiomeric pure linezolid of formula-I.

[(R)-N-[[3-(3-Fluoro-4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methanol] i.e. Linezolid hydroxide of formula-II is an intermediate used in the synthesis of linezolid. Linezolid hydroxide is an advanced key intermediate for the synthesis of linezolid. There are a number of methods for preparing linezolid hydroxide described in the prior art. US 5,688,792 describes crystallization from a mixture of ethyl acetate and hexane. International Patent Application No. WO 97/37980 ('980 application) describes crystallization from mixture ethyl acetate, heptane and water. The '980 application also discloses a method of crystallization of linezolid by means of dissolving in hot ethyl acetate and addition of heptane.

International Patent Application No. WO 2009/032294 ('294 application) describes substantially pure linezolid hydroxide and its purification from the solvent selected from the alcohol and ketone solvents. The '294 application discloses the significance of enantiomeric purity of linezolid hydroxide, which is used as an advanced key intermediate for the process of preparation of linezolid of formula-I. International Patent Application No. WO 2010/084514 describes the process of purification linezolid hydroxide from the ethyl acetate and water. However the purity of linezolid hydroxide obtained by all said prior art are from 98% to 99.8%, which reflects the enantiomeric purity of linezolid active pharmaceutical ingredient itself. Thus, therefore remains a need to obtain highly pure linezolid hydroxide and its subsequent conversion to pure linezolid.

Summary of the Invention

The present invention seeks to overcome the prior art limitations and to provide a cost effective and industrially favorable advanced intermediate of linezolid formula I, in the form of substantially pure linezolid hydroxide formula II, wherein the linezolid hydroxide compound having a R-isomer content is more than about 99.9% relative to its S-isomer, while avoiding cumbersome purification process such as chromatography or repeated crystallization.

The present invention also encompasses a process for the enantiomeric pure linezolid hydroxide compound of formula-II. The process for enantiomeric pure linezolid hydroxide comprises the steps of:

(a) contacting linezolid hydroxide compound of formula-II and an ester solvent.

(b) optionally adjusting the moisture content of the solution of step (a) in between 0.2 to 0.6 w/w %.

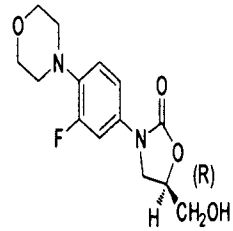
(c) optionally adding anti solvent.

(d) isolating linezolid hydroxide.

The present invention also encompasses substantially enantiomerically pure linezolid hydroxide compound of formula-II, which is subsequently converted into linezolid formula-I.

Detailed Description of the Invention

The present invention provides a substantially enantiomerically pure linezolid hydroxide formula II.



(II)

wherein the compound of formula II, having a R-isomer content more than about 99.9% relative to its S-isomer, while avoiding cumbersome purification process such as chromatography or repeated crystallization.

Further, the process of present invention involves the process for enantiomerically pure linezolid hydroxide, wherein linezolid hydroxide is directly isolated from the reaction mixture without isolating any separate purification step.

For purposes of the present invention, "substantially enantiomeric pure" means linezolid hydroxide having enantiomeric purity more than 99.9% of R-isomer relative to its S-isomer. Preferably, the R-isomer linezolid hydroxide having more than 99.93 % and more preferably more than 99.95 %, as measured by HPLC methods.

For purposes of the present invention, "substantially enantiomeric pure" means linezolid having enantiomeric purity more than 99.9% of S-isomer relative to its R-isomer. Preferably, the S-isomer linezolid hydroxide having more than 99.93 % and more preferably more than 99.95 %, as measured by HPLC methods.

In one embodiment of the present invention also encompasses a process for the enantiomeric pure linezolid hydroxide compound of formula-II. The process for enantiomeric pure linezolid hydroxide comprises the steps of

(a) contacting linezolid hydroxide compound of formula-II and an ester solvent.

(b) optionally adjusting the moisture content of the solution of step (a) in between 0.2 to 0.6 w/w %.

(c) optionally adding anti solvent.

(d) isolating linezolid hydroxide.

One another embodiment of the present invention relates to conversion of substantially pure linezolid hydroxide to linezolid by any means known in the art. Linezolid produced can be used in the preparation of a medicament.

[(R)-N-[[3-(3-Fluoro-4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methanol] (Linezolid hydroxide) is an intermediate used in the synthesis of linezolid. Linezolid hydroxide can be prepared by any method known in the prior art.

The moisture content of solvent may be maintained by means of adding required quantity of water or removing the excess water from the solution.

The moisture content of solution is maintained in between 0.2 – 0.6 *w/w* %. Preferably, 0.25 – 0.55 *w/w* %.

Linezolid hydroxide obtained from the reaction mixture can be directly used upon removal of solvents. Alternatively, the solution of linezolid hydroxide is prepared by dissolving linezolid hydroxide in the solvent, for example by heating or by stirring for a sufficient period of time to dissolve the Linezolid hydroxide.

The ester solvent is selected from the group comprising of methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate and mixtures thereof. Preferably, the solvent is ethyl acetate.

The antisolvent may be selected form a group comprising of cyclic and non-cyclic linear or branched chain hydrocarbon. Preferably, pentane, hexane, heptane, octane, cyclohexane, methylcyclohexane, chloronaphthalene, orthodichlorbenzene, toluene, ethylbenzene, isopropylbenzene, diethylbenzene and mixtures thereof. Preferably, the antisolvent is hexane or cyclohexane or heptane.

Once enantiomerically pure linezolid hydroxide is obtained, it can be isolated by any means known in the art.

In another embodiment present invention includes the repetition of the process for purification of linezolid hydroxide to further increase the content of the R-isomer. The repetition is dependent of the enantiomeric purity of linezolid hydroxide.

The weight to volume ratio [g/mL] of linezolid hydroxide to solvent is preferably from about 1:6 to about 1:12, preferably from about 1:8 to about 1:10.

The invention relates to enantiomerically pure linezolid hydroxide, obtained by process of present invention, having enantiomeric purity more than 99.9% of R-isomer relative to its S-isomer. Preferably, the R-isomer linezolid hydroxide having more than 99.93 % and more preferably, more than 99.95 %, as measured by HPLC methods.

Linezolid hydroxide may be obtained from the any process in the art or the process described in co-pending application WO2011/114210.

The resulting substantially pure linezolid hydroxide can be subsequently converted to linezolid by any means known in the art as well as by the process described in co-pending application WO2011/114210. Linezolid produced can then be used in the preparation of a medicament.

The process for preparation of linezolid hydroxide according to the present invention can be carried out by isolating the intermediate or one-pot reaction or without isolating the intermediate compounds, starting from steps: (a) condensation of 3,4-difluoronitrobenzene with morpholine to obtain 3-fluoro-4-morpholinyl nitrobenzene; (b) reduction of obtained compound in step 'a' to 3-fluoro-4-morpholinyl aniline; (c) carbamoylation of amino group of obtained compound in step 'b' to generate carbamate derivative like ethyl or benzyl carbamate and the like; (d) N-alkylation of obtained ethyl carbamate derivative or benzyl carbamate derivative in step (c) with (R)-glycidyl butyrate followed by cyclization to obtain (R)-N-[3-(3-fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methanol.

In another aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of linezolid or salts thereof according to the process of the present invention and one or more pharmaceutically acceptable carriers, excipients or diluents.

In yet another aspect there is provided a use of a pharmaceutical composition that includes a therapeutically effective amount of linezolid or salts thereof according to the process of the present invention and one or more pharmaceutically acceptable carriers, excipients or diluents to treat conditions in a subject, in need thereof such as antibacterial agent.

The present invention is further illustrated by the following examples, which are provided merely to be exemplary of the invention and do not limit the scope of the invention. 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.

Examples

Example-1:

To a stirred solution of benzyl (3-fluoro-4-morpholinyl)carbamate (100 g, 0.303 moles) in THF (800 mL) at -78°C was added n-butyl lithium solution (1.6 M in hexanes, 208 mL, 0.337 moles) in 30 min followed by stirring for 2 hr. The solution of R-glycidyl butyrate (53 g, 0.368 moles) in THF (100 mL) was then added in 30 min and the mixture was stirred at -78 °C for 2 hr. The reaction mass was then stirred at room temperature for 12 hr, followed by quenched with ammonium chloride solution (90 g, 0.84 moles in 300 mL demineralised water) followed by addition of demineralised water (50 mL). The reaction mixture was stirred at room temperature for 30 min. The aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (2x250 mL). The combined ethyl acetate layer was recovered under vacuum at 50-55°C and the main organic layer was charged to the residue and recovered under vacuum at 50-55°C. The obtained residue was stirred in ethyl acetate (700 mL) at 50°C, cooled to 40°C. The residue was filtered through hyflo and washed with ethyl acetate (200 mL). The combined ethyl acetate layer was cooled to 30°C. n-Hexane (300 mL) was added to the ethyl acetate solution at 25-30°C. The resulting mixture was stirred for 12 hr and then filtered.

Enantiomeric Purity: S-isomer 0.58%.

Examples-2:

To a stirred solution of benzyl (3-fluoro-4-morpholinyl)carbamate (100 g, 0.303 moles) in THF (800 mL) at -78°C was added n-butyl lithium solution (1.6 M in hexanes, 208.5 mL, 0.337 moles) in 30 min followed by stirring for 2 hr. The solution of R-glycidyl butyrate (53.0 g, 0.368 moles) in THF (100 mL) was added in 30 min and continued stirring at -78 °C for next 2 hr. The reaction mass was then stirred at room temperature for 12 hr. The solution of ammonium chloride (90.0 g, 0.84 moles in 300 mL demineralised water) was added followed by addition of

demineralized water (50 mL). The reaction mixture was stirred at room temperature 30 min. The aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (2x250 mL). The combined ethyl acetate layer was recovered under vacuum at 50-55°C and the main organic layer was charged to the residue and recovered under vacuum at 50-55°C. The obtained residue was stirred in ethyl acetate (700 mL) at 50°C, cooled to 40°C. The residue was filtered through hyflo and washed with ethyl acetate (200 mL). The moisture content of the combined ethyl acetate layer was adjusted to 1.03% by means of adding demineralised water (6 mL) and then cooled to 30°C. n-Hexane (600 mL) was added to the above ethyl acetate solution at 25-30°C and stirred for 2 hr and a small sample was filtered and analyzed.

Enantiomeric Purity: S-isomer 0.50%.

Examples-3:

To a suspension of benzyl (3-fluoro-4-morpholinyl)carbamate (50.g, 0.152 moles) in THF (400 mL) at -78°C was added n-butyl lithium solution (1.6 M in hexanes, 104 mL, 0.167 moles) in 30 min followed by stirring for 2 hr. The solution of R-glycidyl butyrate (26.2 g, 0.182 moles) in THF (50 mL) was then added in 30 min and continued stirring at -78 °C for 2 hr. The reaction mixture was stirred at room temperature for 12 hr and quenched by ammonium chloride solution (45.0 g, 0.84 moles in 150 mL demineralised water) followed by addition of demineralised water (25 mL). The reaction mixture was stirred for 30 min. The both aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (2x125 mL). The combined ethyl acetate layer was recovered under vacuum at 50-55°C and then main organic layer was charged to the residue and recovered under vacuum at 50-55°C. The obtained residue was stirred in ethyl acetate (350 mL) at 50°C, cooled to 40°C and filtered through hyflo and washed with ethyl acetate (100 mL). The moisture content of the combined ethyl acetate layer was adjusted to 0.28% by means of adding demineralised water (1.5 mL) and cooled to 30°C. n-Hexane (300 mL) was added to the ethyl acetate solution at 25-30°C and stirred for 12 hr, filtered the solid and dried at 50-55°C for 18 hr. The mother liquor was concentrated to dryness under vacuum at 50°C and crystallized from a mixture of ethyl acetate (150 mL) and n-hexane (150 mL) to get the 2nd crop of (R)-[N-3-(3- fluoro-4-morpholinyl phenyl)-2-oxo-5-oxazolidinyl]methanol, which matches with the 1st crop in all respect to provide 28.7 g material in a combined.

Enantiomeric Purity: S-isomer 0.02%.

Percentage Yield: 64%

Examples-4

To a stirred solution of benzyl (3-fluoro-4-morpholinyl)carbamate (50 g, 0.152 moles) in THF (400 mL) at -78°C was added n-butyl lithium solution (1.6 M in hexanes, 104 mL, 0.167 moles) in 30 min followed by stirring for 2 hr. The solution of R-glycidyl butyrate (26.2 g, 0.182 moles) in THF (50 mL) was added in 30 min and continued stirring at -78°C for 2 hr. The reaction mass was then stirred at room temperature for 12 hr and quenched with ammonium solution (45.0 g, 0.84 moles in 150 mL demineralised water) followed by addition of demineralised water (25 mL). The reaction mixture was stirred for 30 min. The both aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (2x125 mL). The combined ethyl acetate layer was recovered under vacuum at 50-55°C and the main organic layer was charged to the residue and recovered under vacuum at 50-55°C. The obtained residue was stirred in ethyl acetate (350 mL) at 50°C, cooled to 40°C and filtered through hyflo and washed with ethyl acetate (100 mL). The moisture content in the combined ethyl acetate layer was adjusted to 0.28% by adding demineralised water (1.5 mL) and then cooled to 30°C. Cyclohexane (225 mL) was charged to the above ethyl acetate solution at 25-30°C and stirred for 5 hr, filtered the solid and dried at 50-55°C for 18 hr. The mother liquor was concentrated to dryness under vacuum at 50°C and crystallized from a mixture of ethyl acetate (150 mL) and cyclohexane (150 mL) to get the 2nd crop of (R)-[N-3-(3-fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methanol which matches with the 1st crop in all respect to provide 34 g material with a combined 76% yield.

Enantiomeric Purity: S-isomer 0.05%.

Percentage Yield: 76%

Examples-5:

To a stirred solution of benzyl (3-fluoro-4-morpholinyl)carbamate (100 g, 0.303 moles) in THF (800 mL) at -78°C was added n-butyl lithium solution (1.6 M in hexanes, 208.5 mL, 0.337 moles) in 30 min followed by stirring for 2 hr. The solution of R-glycidyl butyrate (53 g, 0.368 moles) in THF (100 mL) was then added in 30 min and continued stirring at -78°C for next 2 hr. The reaction mass was stirred at room temperature for 12 hr and quenched by ammonium chloride solution (90 g, 0.84 moles in 300 mL demineralised water) followed by addition of

demineralised water (50 mL). The reaction mixture was stirred at room temperature for 30 min. The both aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (2x250 mL). The combined ethyl acetate layer was recovered under vacuum at 50-55°C and the main organic layer was charged to the residue and recovered under vacuum at 50-55°C. The obtained residue was dissolved in ethyl acetate (700 mL) at 50°C, cooled to 40°C and filtered through hyflo and washed with ethyl acetate (200 mL). The moisture content of the combined ethyl acetate layer was adjusted to 0.42% by adding demineralised water (1.0 mL) and then cooled to 30°C. Cyclohexane (600 mL) was added to the above ethyl acetate solution at 2530°C and stirred for 12 hr, filtered the solid and dried at 50-55°C for 18 hr. The mother liquor was concentrated under vacuum at 50°C and crystallized from a mixture of ethyl acetate (300mL) and cyclohexane (300 mL) to get the 2nd crop of (R)-[N-3-(3-fluoro-4-morpholinylphenyl)-2oxo-5-oxazolidinyl]methanol which matches with the 1st crop in all respect and to provide 65 g combined material.

Enantiomeric Purity: S-isomer 0.05%.

Percentage Yield: 73%

Examples-6:

To a stirred solution of benzyl (3-fluoro-4-morpholinyl)carbamate (20 g, 0.0606 moles) in THF (160 mL) at -78°C was added n-butyl lithium solution (1.6 M in hexanes, 41.7 mL, 0.0674 moles) in 30 min followed by stirring for 2 hr. The solution of R-glycidyl butyrate (having 2.3% S-isomer) (10.6 g, 0.0736 moles) in THF (20 mL) was then added in 30 min and continued stirring at -78°C for next 2 hr. The reaction mass was stirred at room temperature for 12 hr and quenched by ammonium chloride solution (18 g, 0.168 moles in 60 mL demineralised water) followed by addition of demineralised water (10 mL). The reaction mixture was stirred at room temperature for 30 min. The both aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (2x50 mL). The combined ethyl acetate layer was recovered under vacuum at 50-55°C and the main organic layer was charged to the residue and recovered under vacuum at 50-55°C. The obtained residue was dissolved in ethyl acetate (140 mL) at 50°C, cooled to 40°C and filtered through hyflo and washed with ethyl acetate (40 mL). The moisture content of the combined ethyl acetate layer was adjusted to 0.37% by adding demineralised water (0.75 mL) and then cooled to 30°C. Cyclohexane (120 mL) was added to the above ethyl

acetate solution at 25-30°C and stirred for 12 hr, filtered the solid and dried at 50-55°C for 16 hr. The mother liquor was concentrated under vacuum at 50°C and crystallized from a mixture of ethyl acetate (60 mL) and cycloexane (60 mL) to get the 2nd crop of (R)-[N-3-(3-fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methanol which matches with the 1st crop in all respect and to provide 12.8 g combined material.

Enantiomeric Purity: S-isomer 0.05%.

HPLC Purity: 99.69%

Percentage Yield: 73%