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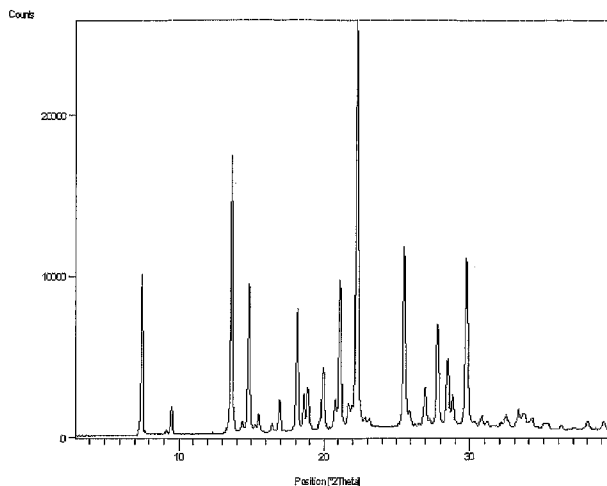
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- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

[Continued on next page]

(54) Title: PROCESS FOR PREPARATION OF (S) (N-[[3-[3-FLUORO-4-(4-MORPHOLINYL) HEN L -2-OXO-5-OXAZO-LIDIN L METHYL]ACETAMIDE

Figure 1



(57) Abstract: The present invention provides novel process for preparation of (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl] -acetamide which comprises combining (R)-N-[3-[3-fluoro-4-morpholinyl phenyl]-2-oxo-5-oxazolidinyl]methylazide in suitable solvent, acetylating agent and acid in presence of a catalyst.

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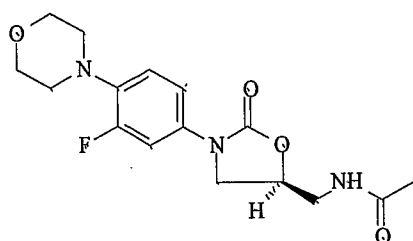
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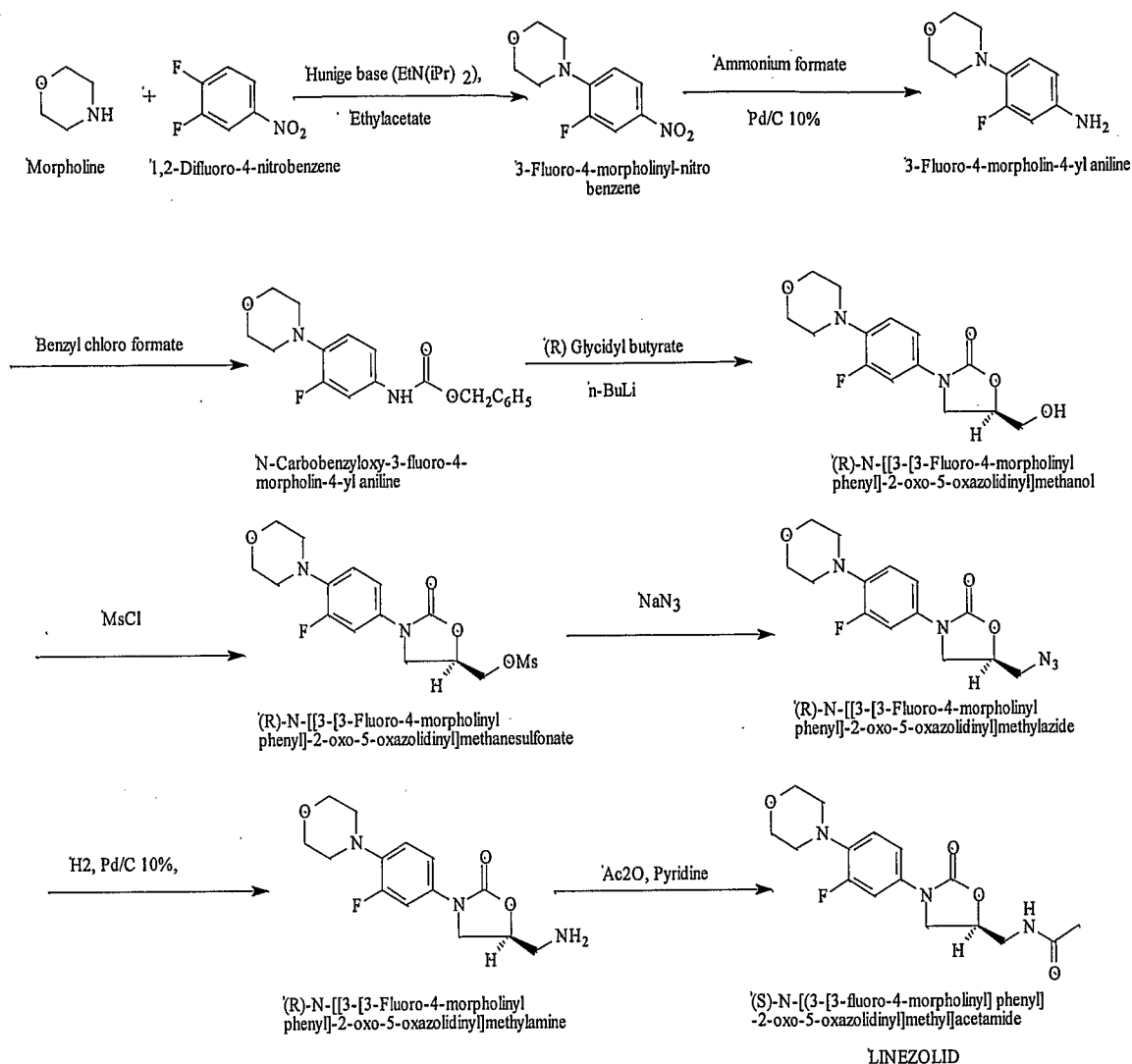
The present invention relates to process for preparation of (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide, also known as Linezolid (formula I).

**(I)****Background of invention:**

Linezolid is a synthetic antibacterial agent of the oxazolidinone class. Linezolid is useful in the treatment of infections caused by aerobic gram positive bacteria. Linezolid is marketed in United States of America by Pfizer Inc as an injection, tablets and oral suspension under the name Zyvox.

US5688792 discloses process for preparation of Linezolid comprising reducing (R)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]azide in ethyl acetate using 10% palladium/carbon. The reaction mixture was stirred for 17 hours. After a period of additional 5 hours stirring, pyridine and acetic anhydride were added and stirred for additional 2.5 hours, the mixture was filtered over diatomaceous earth, washing the pad with ethyl acetate, and the filtrate was concentrated in vacuo to give a brown gummy solid. The obtained residue was purified by chromatography on a 5.5 cmx25 cm 40-63 μm silica gel column, eluting with a gradient of 2-10% methanol/ethyl acetate (v/v). The combined proper fractions were triturated with ethyl acetate to get Linezolid. The reaction is represented in the following scheme I

Scheme I



The disadvantage of this process is that column chromatography was performed to get the pure compound which requires high quantity of solvent thus it is tedious, expensive and time consuming process. Another disadvantage is the use of pyridine in acylation of (R)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]azide which leads to numerous aqueous washing steps to remove the traces of pyridine from the product. This increases the work up steps which results in low yield (not reported) and purity of the product.

US 7291614 discloses process for preparation of Linezolid which involves (a) combining R-N-(4-morpholinyl-3-fluorophenyl)-2-oxo-5-oxazolidinyl-methyl azide with an organic

solvent other than ethyl acetate and chlorinated aromatic hydrocarbons to obtain a mixture and (b) inducing catalytic hydrogenation of the said azide mixture in the presence of any form of ammonium, including aqueous and gaseous form to obtain S-N-(4-morpholinyl-3-fluorophenyl)-2-oxo-5-oxazolidinyl-methyl amine and (c) converting the amine compound to Linezolid using acetic anhydride. Following the process disclosed in US 7291614, Linezolid obtained with a yield of 66.6% w/w and purity of 99.7%.

Thus, there is need to develop a simple, safe, robust and commercially as well as economically feasible process for preparation Linezolid with high yield and purity.

Objects of the invention:

An object of the present invention is to provide one pot process for preparation of (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide, formula (I) from the intermediate (R)-N-[[3-[3-Fluoro-4-morpholinylphenyl]-2-oxo-5-oxazolidinyl]methylazide (II).

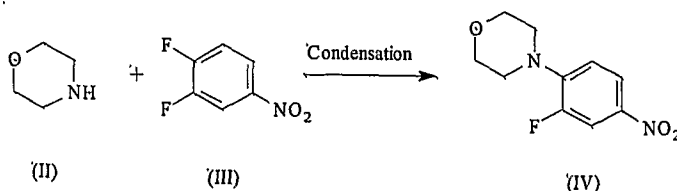
Another object of the present invention is to provide a cost effective, simple, scalable and robust process for preparation of Linezolid with good yield and high purity.

Yet another object of the present invention is to provide process for preparation of Linezolid in high yield avoiding column chromatography.

Summary of the invention:

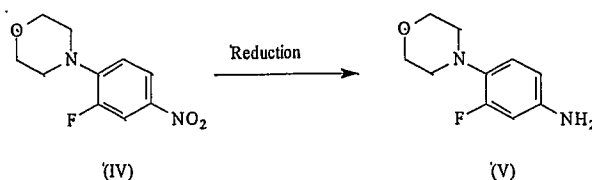
The present invention provides a process for the preparation of highly pure (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide which comprises the steps of;

- a) condensing 3,4-difluoronitrobenzene (III) with morpholine (II) to get 3-fluoro-4-morpholinyl nitrobenzene (IV);

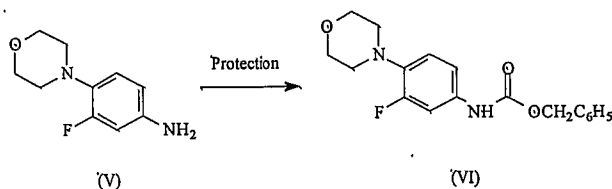


- b) reducing the nitro derivative (IV) to get amino compound (V);

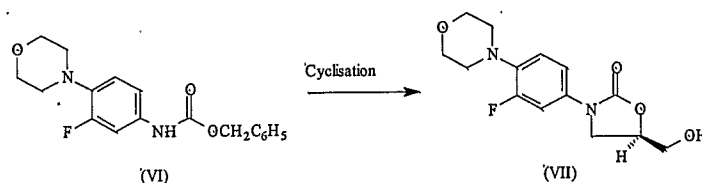
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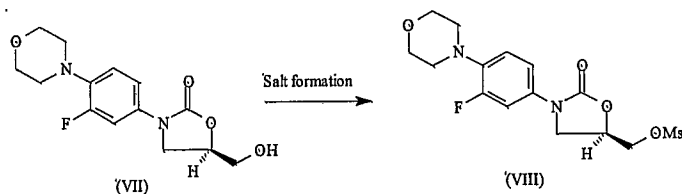
- c) reacting amino compound (V) with benzyl chloroformate to get amino carbamate derivative (VI);



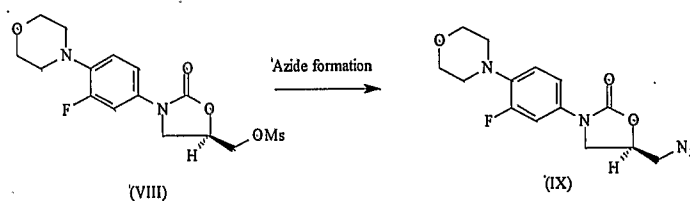
- d) condensing amino carbamate derivative (VI) with (R)-glycidyl butyrate to get (R)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methanol (VII);



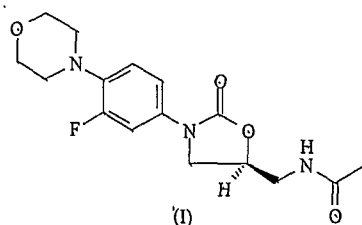
- e) treating methanol derivative (VII) with methanesulfonyl chloride to yield (R)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methane sulfonate (VIII);



- f) reacting methane sulfonate salt (VIII) with sodium azide to get (R)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methylazide (IX).

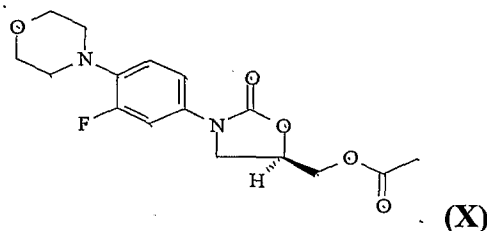


- g) combining the obtained compound (IX) with suitable solvent, acetylating agent, and acid in the presence of reducing catalyst and isolating compound (I);
- h) optionally purifying compound (I).



In accordance with another aspect of the present invention, there is provided purification process to get pure Linezolid (I).

In accordance with another aspect of the present invention, there is provided pure Linezolid with about 0.25% of (R)-[3-(3-fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methylacetate (X) preferably less than 0.15% weight of Linezolid.



In accordance with another aspect of the present invention, a pharmaceutical composition is provided comprising a therapeutically effective amount of Linezolid having a XRD pattern substantially in accordance with FIG. 1 and pharmaceutically acceptable carriers and/or excipients.

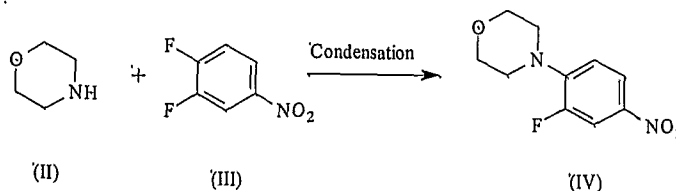
Brief description of figure:

FIG. 1 is a characteristic X-ray Powder diffraction pattern of Linezolid(I).

Detailed description of the invention:

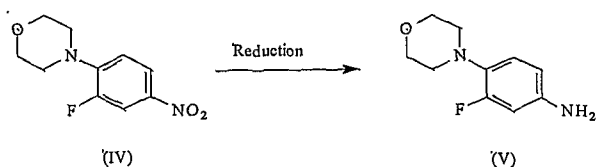
The present invention provides process for the preparation of Linezolid (I) which comprises the following steps:

- a) condensing 3,4-difluoronitrobenzene (III) with morpholine (II) in organic solvent in presence of base to get 3-fluoro-4-morpholinyl -nitrobenzene (IV).

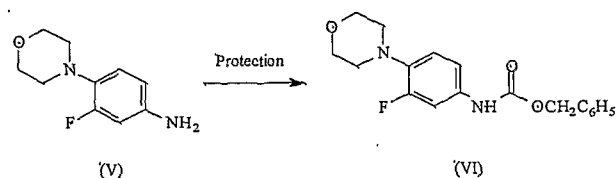


- b) reducing the nitro derivative (IV) in suitable solvent in presence of formate salt

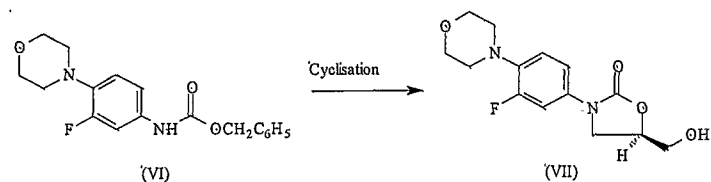
and reducing catalyst to get amino compound (V).



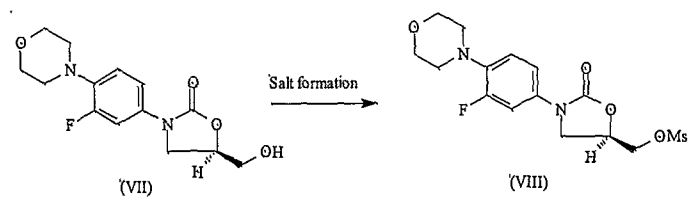
c) reacting amino compound (V) with benzyl chloroformate in organic solvent in presence of a base to yield amino carbamate derivative (VI).



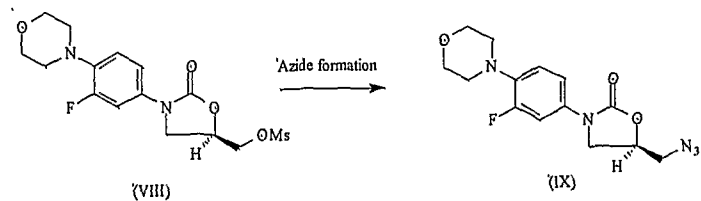
d) condensing amino carbamate derivative (VI) with (R)-glycidyl butyrate in suitable solvent in presence of base to get (R)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methanol (VII).



e) treating methanol derivative (VII) with methanesulfonyl chloride in organic solvent in presence of base to yield (R)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methane sulfonate (VIII).



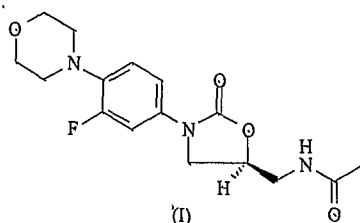
f) reacting methane sulfonate salt (VIII) with sodium azide in organic solvent to provide (R)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methylazide (IX).



g) combining the obtained compound (IX) in a suitable solvent, acetylating agent and

suitable acid in presence of a reducing catalyst and isolating the compound of formula (I);

h) optionally purifying the compound (I) to get pure Linezolid.



(I)

The organic solvent used in step (a) is selected from methyl acetate, ethyl acetate, butyl acetate, isobutyl acetate, preferably ethyl acetate. The base is selected from triethyl amine, piperidine or diisopropylethylamine preferably diisopropylethylamine.

The suitable solvent used in step (b) is selected from methanol or ethanol or tetrahydrofuran, the formate salt used is ammonium formate and the reducing catalyst is selected from palladium on carbon or platinum on carbon.

The base used in step (c) is selected from sodium bicarbonate, sodium carbonate or potassium carbonate and the solvent used is selected from acetone or acetonitrile.

The base used in step (d) is selected from n-butyl lithium, sec-butyl lithium or LDA. The suitable solvent used in step (d) is tetrahydrofuran.

The organic solvent used in step (e) is selected from chloroform or methylene dichloride. The base used is selected from diisopropylethylamine, piperidine or triethyl amine.

The solvent used in the step f) is dimethyl formamide.

In step g) the solvent used is selected from methyl acetate, ethyl acetate, butyl acetate, isobutyl acetate, preferably ethyl acetate. The suitable acid used is selected from acetic acid or formic acid the like. The acetylating reagent used is selected from acetic anhydride or acetyl chloride, preferably acetic anhydride. The catalyst used is selected from palladium on carbon, platinum on carbon, platinum oxide and Raney nickel, preferably palladium on carbon.

The preferred embodiments of the present invention are described in detail below.

In step (a) 3,4-difluoronitrobenzene and diisopropylethylamine in ethyl acetate is added to a solution of morpholine and heated at reflux under nitrogen for 4 hr. The reaction mixture is then allowed to cool to room temperature overnight and to the reaction mass ethyl acetate, methylene chloride and water is added and the separated aqueous layer is extracted with methylene chloride and ethyl acetate. The organic layers are combined together and concentrated to yield compound (IV).

In step (b) 3-fluoro-4-morpholinyl-nitrobenzene (IV) is suspended in ammonium formate in THF and methanol under nitrogen and condensed in presence of 10% palladium/carbon for 3 hrs. After the completion of reaction, the reaction mixture is filtered and obtained filtrate is concentrated and water is added to it followed by extraction with ethyl acetate. The organic layer is concentrated to get the compound (V).

In step (c) benzyl chloroformate is added to a solution of 3-fluoro-4-morpholinyl-aniline (V) and sodium bicarbonate in acetone and water at 0°C and stirred for 1.5 hr. The reaction mixture is then poured onto ice and water mixture and the precipitated solid is collected by filtration, washed with water and dried in a vacuum oven at 75°C to give compound (VI).

In step (d) N-carbobenzyloxy-3-fluoro-4-morpholinyl aniline (VI) is dissolved in tetrahydrofuran followed by addition of n-butyl lithium/hexane at -78°C under nitrogen over 30 min. Further (R)-glycidyl butyrate in tetrahydrofuran is added over 30 min to the above reaction mixture followed by stirring for 1 hr at the same temperature. The reaction mass is then allowed to come to ambient temperature. After stirring the mixture overnight saturated aqueous ammonium chloride is added followed by addition of water. The aqueous layer is extracted with ethyl acetate and concentrating the organic layer to get compound (VII).

In step (e) methanesulfonyl chloride is added to a solution of (R)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methanol (VII) in presence of triethylamine in methylene dichloride at 0°C under nitrogen. The reaction mixture is then stirred at 0°C

for 30 min and allowed to warm to ambient temperature. The precipitated solid is taken in water, methylene dichloride and ethyl acetate mixture and stirred for 30 min. The obtained reaction mass is filtered and then dried at 60 to 70°C to get compound (VIII)

In step (f) sodium azide is added to a solution (R)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methane sulfonate (VIII) in dimethyl formamide and heated the reaction mixture at 85°C overnight. After the completion of reaction, the mixture is cooled and poured into water and ethyl acetate mixture. The aqueous layer is extracted with ethyl acetate and the combined organic layers are concentrated to get compound (IX).

In step (g) (R)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methylazide is suspended in ethyl acetate, acetic acid and acetic anhydride mixture in presence of 10% Pd/C (50% moist) catalyst. The obtained reaction mixture is then hydrogenated in hydrogen gas at 30 psi at temperature of 25 to 35° C for 3 hr. After the completion of the reaction, 5% sodium carbonate solution is added to the mixture and stirred for 10 min and the catalyst is filtered off. The separated aqueous layer is washed with ethyl acetate and the combined ethyl acetate layers are evaporated under reduced pressure at temperature of 50 to 55° C to get the residue. Further the residue is stirred in 1,4-dioxane and reaction mass is cooled to 10 to 15° C followed by addition of diisopropyl ether (pre-cooled) at the same temperature to isolate crude Linezolid or the residue obtained is stirred in ethyl acetate and reaction mass is cooled to 10 to 15° C to isolate crude Linezolid.

The product obtained in above steps may be used directly in the next step, or it can be isolated and/or purified from the reaction mixture and used in the next step. In a preferred embodiment of the present invention, a one pot process is provided wherein the amine (II) is not precipitated from the reduction reaction mixture but rather is converted directly in the solution to Linezolid by acetylation. The present invention thus provides Linezolid with high purity and yield.

According to another embodiment of the present invention, crude Linezolid is purified from suitable solvent. The purification is carried out at temperature range of 40 to 70°C

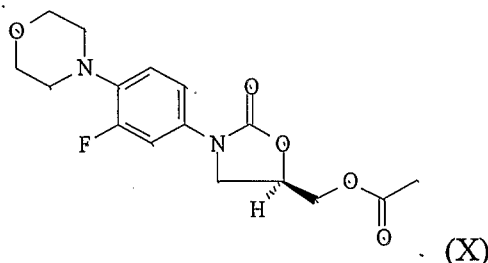
preferably at temperature 45-55°C followed by cooling at temperature range of about 10 to 15°C and further adding another suitable solvent under stirring and isolating the solid by filtration and further dried to get pure Linezolid of purity greater than 99.9% .

The suitable organic solvent used for purification of Linezolid is selected from the group consisting of a polar aprotic solvents such as tetrahydrofuran, 1,4-dioxane, 1,2-diethoxy ethane, 1,2-methoxy ethane, diethyl ether, diisopropyl ether, methyl tertiary butylether (MTBE) or mixture thereof, preferably 1,4-dioxane and diisopropyl ether.

According to another embodiment, crude Linezolid is purified by dissolving in suitable solvent at 70-75°C filtering the clear solution to remove any suspended solid. The clear hot solution is then subjected to rapid cooling at -5 to 5°C under stirring at same temperature for 2 hr to separate out pure Linezolid.

The suitable solvent used is an ester selected from the group consisting of methyl acetate, ethyl acetate, butyl acetate, isobutyl acetate, preferably ethyl acetate.

Linezolid obtained according to the process of the present invention has about 0.25% of (R)-[3-(3-fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methylacetate (X) which is further reduced to less than 0.15% weight of Linezolid by purification.



The particles size (d_{90}) of Linezolid is less than 200 μ preferably less than 100 μ .

The XRPD of Linezolid (I) is as shown in Figure 1 and exhibits the following peaks,

Pos. [$^{\circ}$ 2Theta]	Rel. Int. [%]
7.51	39.56
9.51	6.78
13.65	68.21
14.38	2.74
14.87	36.26
15.49	4.47
16.43	2.01
16.99	7.79
18.15	29.67

18.58	9.33
18.86	10.85
19.97	15.55
20.81	7.87
21.17	35.53
21.73	6.69
22.33	100.00
23.17	2.64
25.53	45.66
25.93	4.74
26.95	10.67
27.80	26.15
28.46	17.52
28.79	8.64
29.78	42.50
30.78	3.39
32.43	3.46
33.28	5.02
33.70	3.83
34.25	2.41
35.03	1.45
36.21	1.04
38.01	1.46
39.13	1.01
39.56	1.11

According to the present invention, there is provided an efficient and industrially feasible process for preparation of Linezolid which involves one pot process for conversion of (R)-N-[3-[3-fluoro-4-morpholinyl phenyl]-2-oxo-5-oxazolidinyl]methylazide to Linezolid (I).

According to another embodiment of the present invention there is provided process for preparation of Linezolid which comprises the steps of;

1. combining (R)-N-[3-[3-fluoro-4-morpholinyl phenyl]-2-oxo-5-oxazolidinyl]methylazide with suitable solvent, organic acid and acetylating agent in presence of reducing catalyst;
2. isolating pure Linezolid (I).

The solvent used is selected from methyl acetate, ethyl acetate, butyl acetate, isobutyl acetate, preferably ethyl acetate. The acid used is selected from acetic acid or formic acid the like. The acetylating reagent used is selected from acetic anhydride or acetyl chloride, preferably acetic anhydride. The catalyst used is selected from palladium on carbon, platinum on carbon, platinum oxide and Raney nickel, preferably palladium on carbon.

The isolation of step b) comprising neutralizing the obtained reaction mixture from step a) with base; separating and concentrating the organic layer to get a residue; c) treating and the obtained residue with suitable solvent to get Linezolid.

The base is selected from the group comprising sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, preferably sodium carbonate or liquid ammonia. The solvent is selected from tetrahydrofuran, 1,4-dioxane, 1,2-diethoxy ethane, 1,2-methoxy ethane, diethyl ether, diisopropyl ether, methyl tertiary butylether (MTBE), methyl acetate, ethyl acetate, butyl acetate, isobutyl acetate or mixture thereof.

According to another embodiment of the present invention there is provided process for preparation of Linezolid which comprises combining (R)-N-[3-[3-fluoro-4-morpholinyl phenyl]-2-oxo-5-oxazolidinyl]methylazide with suitable solvent, an acid and acetylating agent in presence of reducing catalyst to get Linezolid in high yield and purity.

According to a preferred embodiment of the present invention, (R)-N-[3-[3-fluoro-4-morpholinyl phenyl]-2-oxo-5-oxazolidinyl]methylazide of formula (II) is suspended in suitable solvent, suitable acid, acetylating agent in presence of reducing catalyst. The obtained reaction mixture is hydrogenated in presence of hydrogen gas at pressure range of 20 to 60 psi at a temperature range of 20 to 40^o C over a period of 1 to 6 hrs, preferably at hydrogen pressure of 30 psi at temperature 25 to 35^o C for 3 hrs.

After the completion of the reaction, the reaction mixture is basified and extracted in suitable solvent. The solvent is evaporated or concentrated to get a residue, which is further stirred with suitable solvent to yield crude Linezolid in high yield and high purity of greater than 99.5%. The suitable solvent used is selected from tetrahydrofuran, 1,4-dioxane, 1,2-diethoxy ethane, 1,2-methoxy ethane, diethyl ether, diisopropyl ether, methyl tertiary butylether (MTBE), methyl acetate, ethyl acetate, butyl acetate, isobutyl acetate or mixture thereof.

The azide compound is known and can be prepared by known methods such as those described in US 5,688,792.

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. The examples are provided to illustrate particular aspects of the disclosure and do not limit the scope of the present invention.

Examples

Example 1:

3-Fluoro-4-morpholinyl-nitrobenzene (IV)

To a solution of 199 gm of morpholine, 287 g of 3,4-difluoronitrobenzene and 148 g of diisopropylethylamine in 1 L of ethyl acetate was heated at reflux under nitrogen for 4 hr. The mixture was allowed to cool to room temperature overnight and 1 L of ethyl acetate, 1.5 L methylene chloride and 1.5 L of water were added to it. The aqueous layer was extracted with 2 x 500 ml of methylene chloride and 500 ml of ethyl acetate. The combined organic layer was concentrated to give a yellow solid. Yield: 390 g.; Percentage: 195% w/w

Example 2

3-Fluoro-4-morpholinyl-aniline (V)

To a suspension of 365.6 g of 3-fluoro-4-morpholinyl-nitrobenzene and 488.4 g of ammonium formate in 1 L of tetrahydrofuran and 4.40 L of methanol under nitrogen was added 5.24 g of 10% palladium/carbon. After stirring the mixture for 3 hrs, the mixture was filtered. The obtained filtrate was concentrated and 2 L of water was added to the obtained reaction mass and was extracted with 3.50 L of ethyl acetate. The organic layer was concentrated to give a brown solid. Yield: 295 g.; Percentage: 82.59% w/w

Example 3

N-Carbobenzyloxy-3-fluoro-4-morpholinyl aniline (VI)

To a solution of 289.1 g of 3-fluoro-4-morpholinyl-aniline and 278.8 g of sodium bicarbonate in 5L of acetone and 2.50 L of water at 0°C was added 286.8 g of benzyl chloroformate. After stirring the mixture for 1.5 hr, the mixture was poured onto ice and water mixture. The precipitated solid was collected by filtration and washed with 3 x 2.50 L of water and then dried in a vacuum oven at 75°C to give a gray purple solid.

Yield: 480 g.; Percentage: 166% w/w

Example 4

(R)-N-[[3-[3-Fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methanol (VII)

To a solution of 390 g of N-carbobenzyloxy-3-fluoro-4-morpholinyl aniline in 5.50 L of tetrahydrofuran at -78°C under nitrogen was added 770ml of 1.6M n-butyl lithium/hexane over 30 min. Further 183.2 g of (R)-glycidyl butyrate in 300 ml of tetrahydrofuran was added to the obtained reaction mixture over 30 min followed by stirring for 1 hr at -78°C . After the completion of reaction, the reaction mass was allowed to come to ambient temperature gradually. After stirring the mixture overnight, 200 ml of saturated aqueous ammonium chloride was added, followed by 5 L of water. The aqueous layer was extracted with ethyl acetate (4 x 3.0 L) and the combined organic layer was concentrated to get a light purple solid. Yield: 249.6 g.; Percentage: 64% w/w

Example 5

(R)-N-[[3-[3-Fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methanesulfonate (VIII)

To a solution of 132.8 g of (R)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methanol and 87.1 g of triethylamine in 1L of methylene dichloride at 0°C under nitrogen was added 74 gm of methanesulfonyl chloride. The reaction mixture was allowed to stir at 0°C for 30 min, then allowed to warm to ambient temperature. A white solid was precipitated. 1.75 L water, 6.50 L methylene dichloride and 1L ethyl acetate mixture were added followed by stirring for 30 min. The reaction mass was filtered to get a white solid. Yield: 140 g.; Percentage: 105.42% w/w

Example 6

(R)-N-[[3-[3-Fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methyl] azide (IX)

To a solution (R)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methane sulfonate (90 g) in 2L of dimethyl formamide was added 63.67 g of sodium azide and the mixture was heated at 85°C overnight. The mixture was then cooled and poured into 5L water and 1.50 L of ethyl acetate. The aqueous layer was extracted with 2 x 750 ml of ethyl acetate and the combined organic layer was concentrated to get brown oil.

Yield: 88 g.; Percentage: 97.23% w/w

Example 7

(S)(N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl]acetamide (Linezolid) (I):

80 g (R)-N-[[3-[3-fluoro-4-morpholinylphenyl]-2-oxo-5-oxazolidinyl]methylazide and 6 g 10% Pd/C (50% moist) was suspended in 1.6 L ethyl acetate, 24 ml acetic acid and 56 ml acetic anhydride mixture. The mixture was then hydrogenated in hydrogen gas at 30 psi at temperature of 25 to 35^o C for 3 hr. After the completion of the reaction, 1L of 5% sodium carbonate solution was added to the mixture and stirred for 10 min. The catalyst was then filtered off. The separated aqueous layer was washed with 1L ethyl acetate and the combined ethyl acetate layer was evaporated under reduced pressure at temperature of 50 to 55^o C to get the residue. The obtained residue was stirred in 640 ml 1,4-dioxane and the reaction mixture was cooled to 10 to 15^o C. 640 ml diisopropyl ether (precooled) was added to the above reaction mixture at temperature 10 to 15^oC and filtered. The solid obtained was washed with 200 ml diisopropyl ether and dried at 60 to 70^o C to get Linezolid crude. Yield: 65.5 g ; Percentage: 78% Purity: > 99.5%

Example 8

Preparation of (S)-4-[3-(2-dimethylaminoethyl)-1H-indol-5-ylmethyl]-1,3-oxazolidin-2-one (Linezolid)

(R)-N-[[3-[3-Fluoro-4-morpholinylphenyl]-2-oxo-5-oxazolidinyl]methylazide 10.0 g and 0.75 g 10% Pd/C (50% moist) were suspended in 200 ml ethyl acetate, 3 ml acetic acid and 7 ml acetic anhydride mixture. The mixture was then hydrogenated in hydrogen gas at 30 psi at 25-35^o C for 5 hr. After the completion of the reaction, 100 ml of 5% sodium bicarbonate solution was added to the mixture and stirred for 10 min. The catalyst was then filtered off, ethyl acetate layer was separated. The aqueous layer was washed with 100 ml ethyl acetate and the combined ethyl acetate layers were removed under reduced pressure at 50-55^o C. The obtained residue was stirred in 25 ml ethyl acetate, filtered, washed with 20 ml ethyl acetate and the product was dried at 60-70^o C. Yield: 7.35 g; 70% Purity: 99.5 ++

Example 9

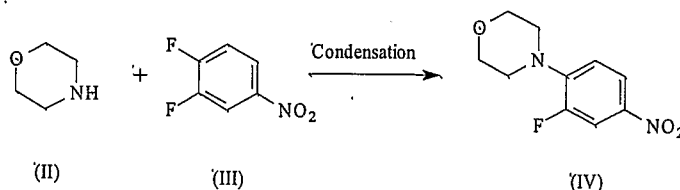
60 g of Linezolid obtained from Example 7 was suspended in 1.20 L 1,4-dioxane. The obtained reaction mass was warmed at 45 to 55°C and filtered at 45 to 55°C. The filtrate was cooled to 10 to 15°C, diisopropyl ether (1.20 L, previously cooled) was added to this at temperature 10 to 15°C and stirred for 1 hour. The solid obtained was filtered, washed with 250 ml diisopropyl ether and dried at 100°C for 2 hrs and then at 140°C for 3 to 4 hr to get pure Linezolid. Yield: 55.8 g.; Percentage: 93% Purity: > 99.9%

Example 10

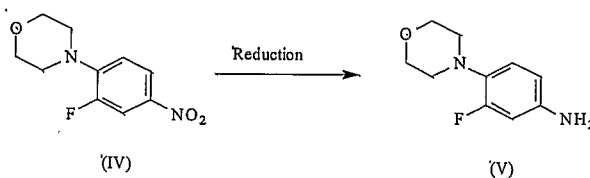
50 g Linezolid was dissolved in 2L ethyl acetate at 70-75°C. The clear solution was filtered to remove any suspended solid. The obtained clear hot solution was subjected to rapid cooling at -5 to 5°C and stirred at same temperature for 2 hr. The separated solid was filtered and dried at 70-80°C. Yield: 43 g.; Percentage: 86% Purity: > 99.9%

We claim,

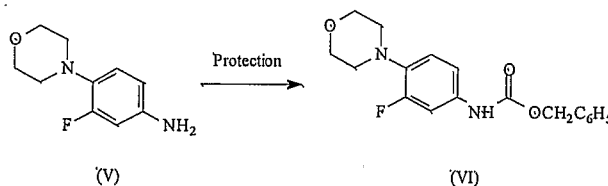
1. A process for the preparation of Linezolid (I) comprising the steps of;
 a) condensing 3,4-difluoronitrobenzene (III) with morpholine (II) to get 3-fluoro-4-morpholinyl -nitrobenzene (IV).



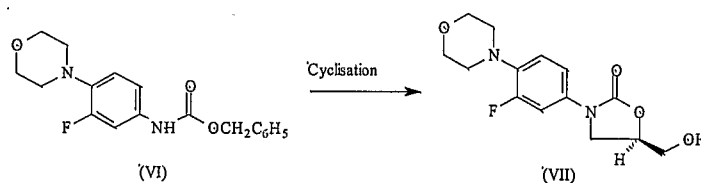
- b) reducing the nitro derivative (IV) to get amino compound (V).



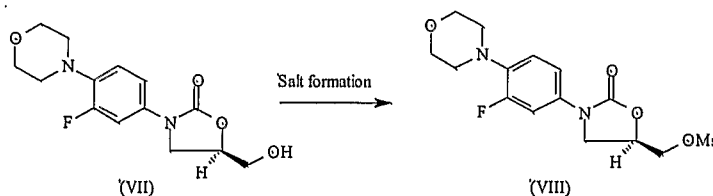
- c) reacting amino compound (V) with benzyl chloroformate to get amino carbamate derivative (VI).



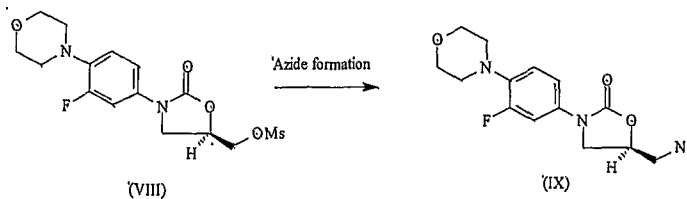
- d) condensing amino carbamate derivative (VI) with (R)-glycidyl butyrate to get (R)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methanol (VII).



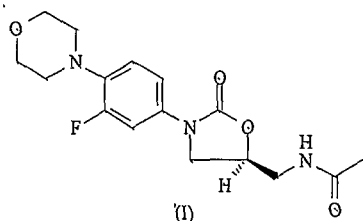
- e) treating methanol derivative (VII) with methanesulfonyl chloride to yield (R)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methane sulfonate (VIII).



- f) reacting methane sulfonate salt (VIII) with sodium azide to get (R)-N-[[3-[3-fluoro-4-morpholinylphenyl]-2-oxo-5-oxazolidinyl] methylazide (IX).



- g) combining the obtained compound (IX) with a suitable solvent, acetylating agent, and suitable acid in presence of reducing catalyst
- h) isolating compound (I);
- i) optionally purifying compound (I) to get pure Linezolid.



2. A process for preparation of Linezolid comprising the steps of;
 - a) combining (R)-N-[[3-[3-fluoro-4-morpholinyl phenyl]-2-oxo-5-oxazolidinyl]methylazide (IX) with suitable solvent, acetylating agent and an acid in presence of reducing catalyst;
 - b) isolating the compound (I);
 - c) optionally purifying the compound (I).
3. The process as claimed in claim 1 or 2 wherein said reducing catalyst used is selected from palladium on carbon or platinum on carbon and said solvent used is selected from methyl acetate, ethyl acetate, butyl acetate or isobutyl acetate.
4. The process as claimed in claim 1 or 2 wherein said acetylating agent is selected from acetic anhydride or acetyl chloride and said acid is selected from acetic acid or formic acid.
5. A process for preparation of Linezolid comprises combining (R)-N-[[3-[3-fluoro-4-morpholinyl phenyl]-2-oxo-5-oxazolidinyl]methylazide with a suitable solvent, reducing catalyst, acetylating agent and an acid.

6. The process as claimed in claim 1 or 2 wherein said isolation step comprises
 - a) neutralizing the reaction mixture with base;
 - b) separating and concentrating the organic layer to get a residue;
 - c) treating the obtained residue with suitable solvent to get Linezolid.
7. The process as claimed in claim 6 wherein said solvent is selected from tetrahydrofuran, 1,4-dioxane, 1,2-diethoxy ethane, 1,2-methoxy ethane, diethyl ether, diisopropyl ether, methyl tertiary butylether (MTBE), methyl acetate, ethyl acetate, butyl acetate, isobutyl acetate or mixture thereof.
8. A process for purification of Linezolid comprising the steps of;
 - a) suspending Linezolid in first solvent to form a mixture;
 - b) adding second solvent to the obtained mixture;.
 - d) isolating pure Linezolid.
9. The process as claimed in claim 7 wherein said first and second solvent used is selected from tetrahydrofuran, 1,4-dioxane, 1,2-diethoxy ethane, 1,2-methoxy ethane, diethyl ether, diisopropyl ether, methyl tertiary butylether (MTBE), methyl acetate, ethyl acetate, butyl acetate, isobutyl acetate or mixture thereof.
10. A process for purification of Linezolid comprising the steps of;
 - a) treating Linezolid with suitable solvent;
 - b) isolating pure Linezolid.

Figure 1

