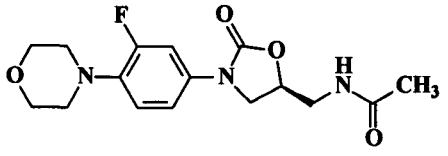
ABSTRACT

TITLE: "AN IMPROVED PROCESSES FOR PREPARING LINEZOLID"

The present invention provides simple, environmental friendly improved process for the preparation of Linezolid. The present invention also provides an alternate improved process for preparing Linezolid with good yield.

Claims:

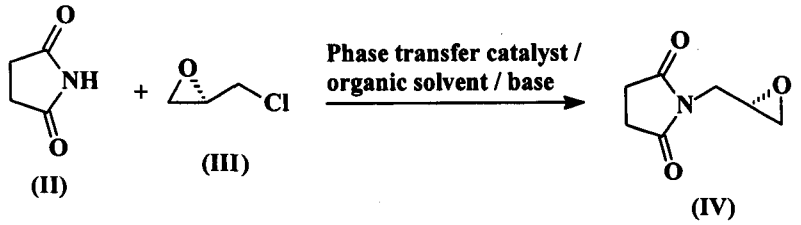
1. A process for the preparation of N-({(5S)-3-[3-fluoro-4-(morpholin-4-yl)phenyl]-2-oxo-1,3- oxazolidin-5-yl}methyl)acetamide (Linezolid) of formula (I).



Linezolid (I)

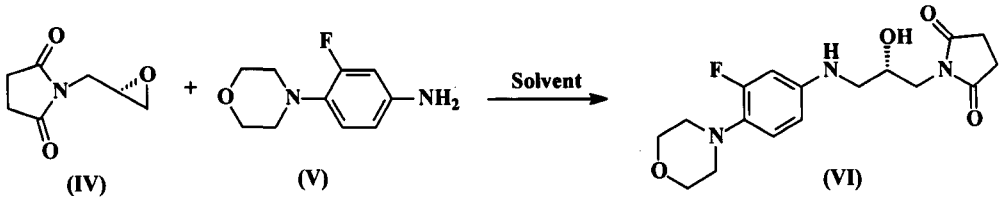
the process comprises the following steps:

a) pyrrolidine-2,5-dione (II) reacted with ((*S*)-2-(chloromethyl) oxirane) (III) in presence of phase transfer catalyst in organic solvent and a base (*S*)-1-(oxiran-2-ylmethyl)pyrrolidine-2,5-dione (IV)



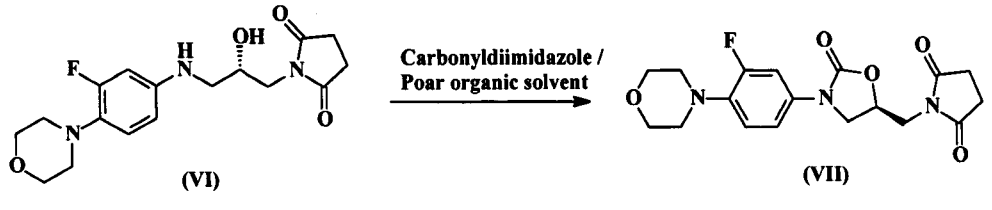
(II) (III) (IV)

b) (*S*)-1-(oxiran-2-ylmethyl)pyrrolidine-2,5-dione (IV) is reacted with 3-fluoro-4-morpholinoaniline (V) in presence of a polar solvent to give (*S*)-1-(3-((3-fluoro-4-morpholinophenyl)amino)-2-hydroxypropyl)pyrrolidine-2,5-dione (VI)



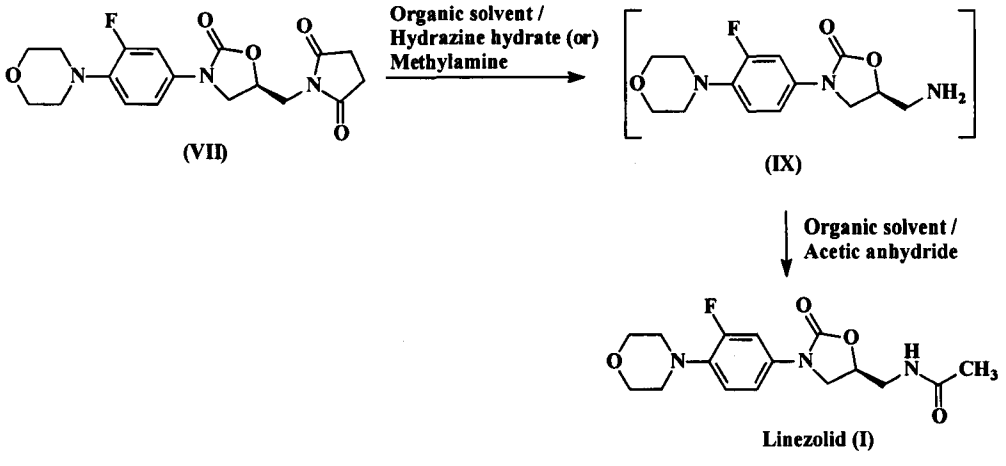
(IV) (V) (VI)

c) (*S*)-1-(3-((3-fluoro-4-morpholinophenyl) amino)-2-hydroxypropyl)pyrrolidine-2,5-dione (VI) is reacted with carbonyl diimidazole in presence of polar organic solvent to produce (*S*)-1-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl) pyrrolidine -2,5-dione (VII)



(VI) (VII)

d) (*S*)-1-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl) pyrrolidine -2,5-dione (VII) in organic solvent is reacted with hydrazine hydrate or methylamine to provide (5*S*)-5-(aminomethyl)-3-[3-fluoro-4-(morpholin-4-yl) phenyl]-1,3-oxazolidin-2-one (IX), which is not isolated and *in-situ* treated with acetic anhydride in presence of organic solvent to produce N-({(5*S*)-3-[3-fluoro-4-(morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl) acetamide (Linezolid)



(VII) (IX) Linezolid (I)

2. The process according to claim 1, the organic solvent used in step-a) is selected from the group comprising of alcohols having C_1-C_4 carbon atoms, preferably isopropanol.

3. The process according to claim 1, the phase transfer catalyst used in step-a) is selected from the group comprising of benzyl trimethyl ammonium chloride, tetra butyl ammonium bromide, tetra butyl ammonium chloride, preferably benzyl trimethyl ammonium chloride.

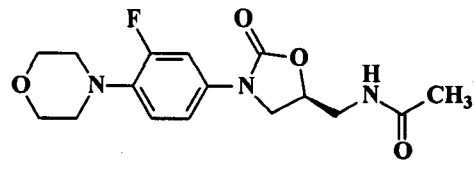
4. The process according to claim 1, the base used in step-a) is selected from the group comprising of alkali alkoxides such as potassium tertiary butoxide, sodium methoxide, sodium ethoxide, preferably potassium tertiary butoxide.

5. The process according to claim 1, the step-b) is carried out in presence of a polar solvent is selected from methanol, ethanol, isopropanol, water or mixtures thereof.

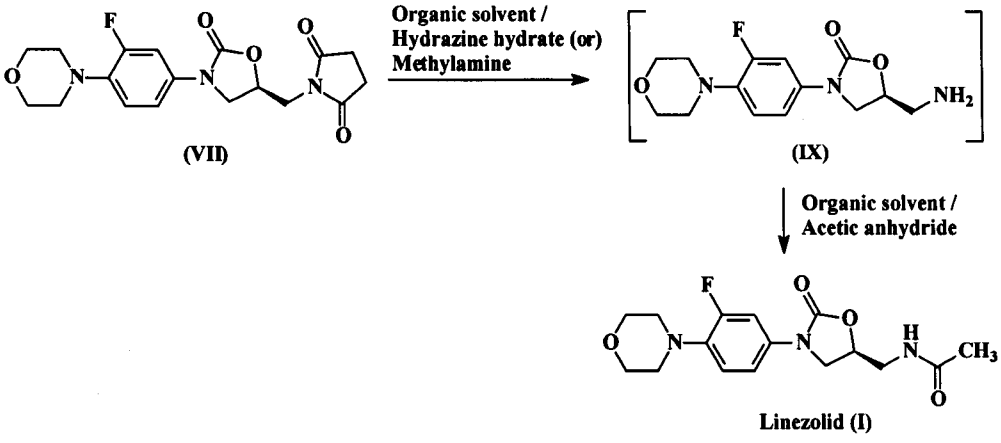
6. The process according to claim 1, the step-c) is carried out in presence of polar organic solvents selected from the group comprising of methylene dichloride, ethyl acetate, acetonitrile, alcohols having C_1-C_4 carbon atoms, dimethyl formamide, dimethyl sulfoxide, N-methyl pyrrolidine, tetrahydrofuran, preferably methylene dichloride.

7. The process according to claim 1, the step-d) is carried out in presence of organic solvent selected from the group comprising of methylene dichloride, ethyl acetate, acetonitrile, alcohols having C_1-C_4 carbon atoms, dimethyl formamide, dimethyl sulfoxide, N-methyl pyrrolidine, tetrahydrofuran, hydrocarbons selected from benzene, toluene, cyclohexane, preferably methylene dichloride.

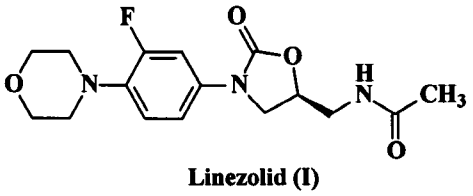
8. A process for the preparation of N-({(5S)-3-[3-fluoro-4-(morpholin-4-yl)phenyl]-2-oxo-1,3- oxazolidin-5-yl}methyl)acetamide (Linezolid) of formula (I)



comprising (*S*)-1-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl) pyrrolidine -2,5-dione (VII) in organic solvent is reacted with hydrazine hydrate or methylamine to provide (5*S*)-5-(aminomethyl)-3-[3-fluoro-4-(morpholin-4-yl) phenyl]-1,3-oxazolidin-2-one (IX), which is not isolated and *in-situ* treated with acetic anhydride in presence of organic solvent to produce N-({(5*S*)-3-[3-fluoro-4-(morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl) acetamide (Linezolid) (I)

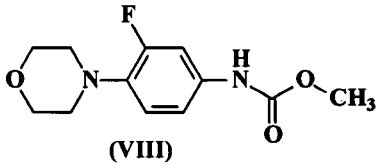


9. A process for the preparation of N-({(5*S*)-3-[3-fluoro-4-(morpholin-4-yl)phenyl]-2-oxo-1,3- oxazolidin-5-yl}methyl)acetamide (Linezolid) of formula (I)



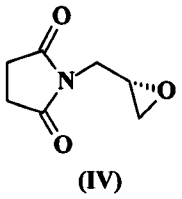
Linezolid (I)

comprising reacting methyl (3-fluoro-4-morpholinophenyl)carbamate (VIII) with alkyl alkali metal compound in inert solvent or alkali alkoxide in presence of polar solvent



(VIII)

and (*S*)-1-(oxiran-2-ylmethyl)pyrrolidine-2,5-dione (IV)



(IV)

10. A process according to claim 9, wherein the alkyl alkali metal compound is selected from the group comprising of C_1-C_4 alkyl sodium or lithium compound, preferably butyl lithium compound; inert solvent is selected the group comprising of hydrocarbon solvents such as hexane, heptane, benzene, toluene, xylene etc., preferably hexane solvent; alkali alkoxide is selected from the group comprising of sodium methoxide, sodium ethoxide, lithium tert-butoxide, potassium tert-butoxide etc., preferably lithium *tert*-butoxide; polar solvent is selected from the group comprising of

tetrahydrofuran, C_1-C_4 alcohol, ethyl acetate, methylene dichloride, acetonitrile or mixtures thereof, preferably tetrahydrofuran.

Dated this 4th day of September, 2013,

For Optimus Drugs Pvt. Ltd.

Srinivas Reddy Desi Reddy,

Managing Director

AN IMPROVED PROCESSES FOR PREPARING LINEZOLID

This application claims priority to this Indian patent application numbers 3963/CHE/2013 filed on September 4, 2013.

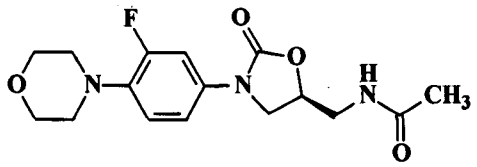
FIELD OF THE INVENTION

The present invention provides an improved process for preparing Linezolid and the present is also provides Linezolid with substantially free of impurities.

BACKGROUND OF THE INVENTION

Linezolid is a synthetic antibiotic used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to several other antibiotics. Linezolid is a synthetic antibiotic, the first of the oxazolidinone class, used for the treatment of infections caused by multi-resistant bacteria including streptococcus and methicillin-resistant Staphylococcus aureus (MRSA).

Chemically, Linezolid is (*S*)-N-[[3-(3-fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methyl] acetamide. The empirical formula is $C_{16}H_{20}FN_3O_4$. Its molecular weight is 337.35, and its chemical structure is represented below:



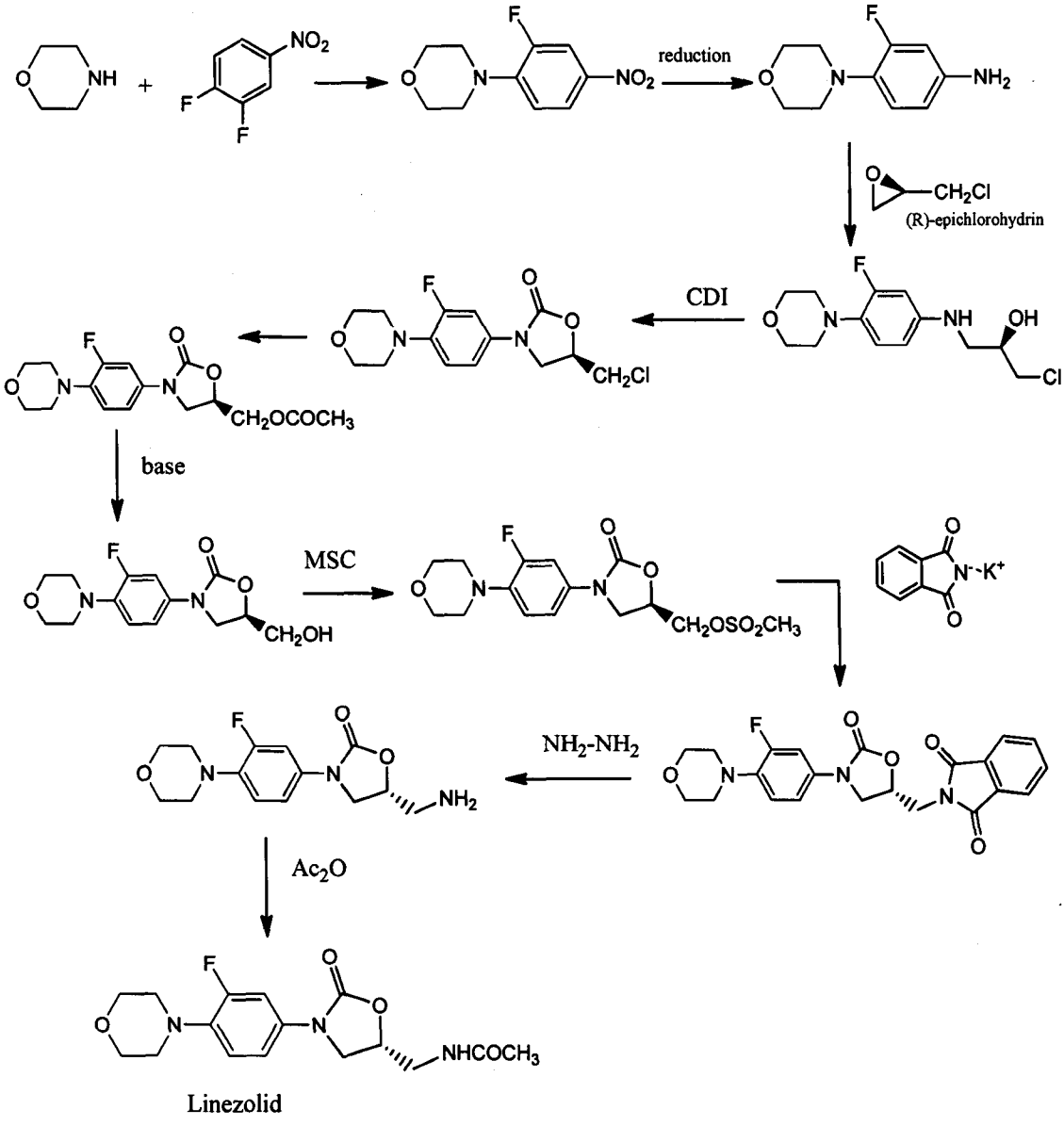
(I)

Linezolid is marketed by Pfizer under the trade names Zyvox (in the United States, United Kingdom, Australia and several other countries), Zyvoxid (in Europe), and Zyvoxam (in Canada and Mexico).

Linezolid is first discloses in US 5688792 (Barbachyn et al, 1997) and the process of US '792 patent describes the usage of *R* –glycidylbutyrate which results in the formation of (*R*) - N-

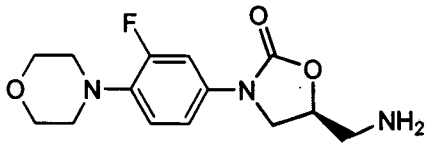
[[3-[3-fluoro-4-morpholinyl] phenyl]-2-oxo-5-oxazolidinyl] methanol which in the subsequent stages has to be converted to various intermediary compounds to finally form Linezolid. The said process also encompasses intermediary azide compound, which is difficult and harmful to handle at an industrial level.

WO 2012/114355 (Alla, Raghu Mitra et al, 2010), discloses a process for preparing Linezolid as described in the following scheme:

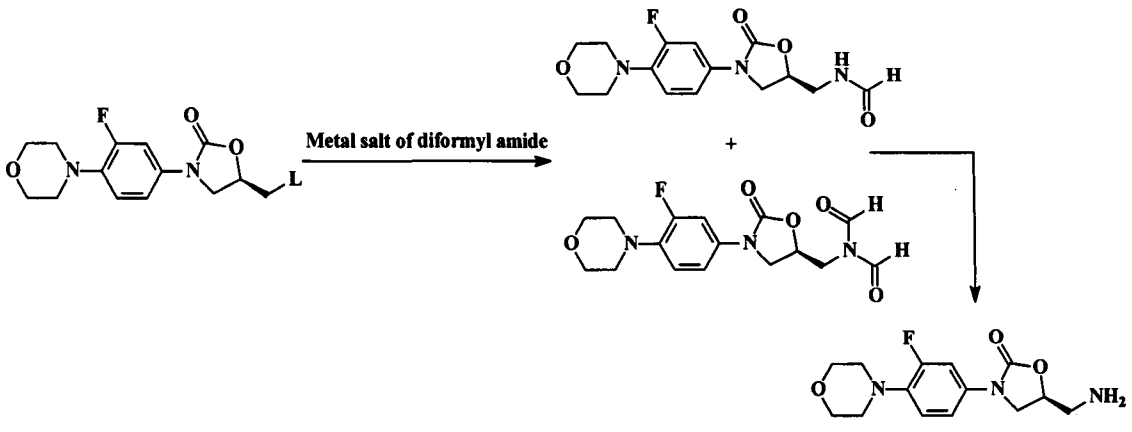


The disadvantages of the process covered under WO '355 are that it is a cumbersome process that may not be cost effective and being a lengthy process, the productivity will be affected.

WO 2012/019632 (Bartos Petr, et al, 2010) appears to cover a process for preparing 3-(3-fluoro-4-(morpholin-4-yl)phenyl)-2-oxo oxazolidin-5(*S*)-yl methyl)amine and/or an acid addition salt,

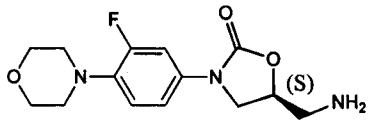


an intermediate used in the preparation of Linezolid, as shown below

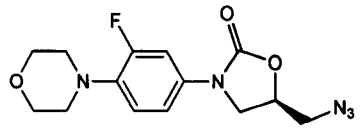


The drawbacks of WO '632 are the use of metal salt of diformylamide, which is commercially unavailable and therefore increases the cost of API. Also, the disadvantages of using metal salt of diformylamide, is that it is sensitive to water and it may require special storage conditions like dehumidifier.

US 20070021417 (Serguei Fine et al, 2005) appears to cover a process for preparation of *S*-N-(4-morpholinyl-3-fluorophenyl)-2-oxo-5-oxazolidinyl-methyl amine



from R-N-(4-morpholinyl-3-fluorophenyl)-2-oxo-5-oxazolidinyl-methyl azide (III)



by catalytic hydrogenation comprising combining R-N-(4-morpholinyl-3-fluorophenyl)-2-oxo-5-oxazolidinyl-methyl azide (III) with an organic solvent other than ethyl acetate.

In the above described process, the drawbacks are the use of azide intermediate which is industrially not preferred, catalytic hydrogenation requires special facility which increases the project cost and is environmentally hazardous. The use of catalyst can increase the analysis cost for heavy metal.

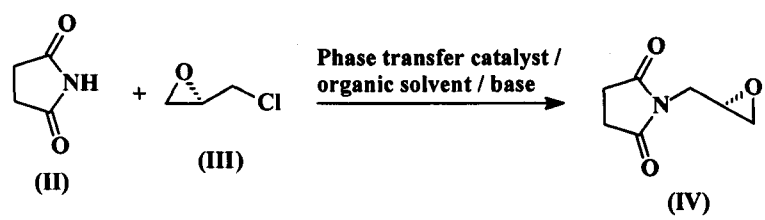
The inventors of the present invention have developed cost-effective, simple and environmental friendly processes for the preparation of Linezolid. The inventors have worked towards providing an operational friendly and cost effective process, wherein the formation of impurities is minimized and the yields are good.

The inventors have developed improved processes for preparing Linezolid using raw materials that are commercially available and it don't require special storage conditions or any special equipments like autoclave.

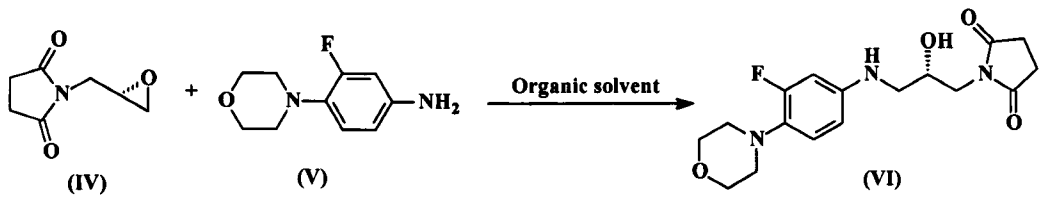
SUMMARY OF THE INVENTION

In one aspect of the present invention, a process for the preparation of N-({(5S)-3-[3-fluoro-4-(morpholin-4-yl) phenyl]-2-oxo-1, 3-oxazolidin-5-yl}methyl)acetamide (Linezolid) of formula (I), comprises the following steps:

a) pyrrolidine-2,5-dione (II) reacted with ((*S*)-2-(chloromethyl) oxirane) (III) in presence of phase transfer catalyst in organic solvent and a base (*S*)-1-(oxiran-2-ylmethyl)pyrrolidine-2,5-dione (IV)



b) (*S*)-1-(oxiran-2-ylmethyl)pyrrolidine-2,5-dione (IV) is reacted with 3-fluoro-4-morpholinoaniline (V) in presence of polar solvent to give (*S*)-1-(3-((3-fluoro-4-morpholinophenyl)amino)-2-hydroxypropyl)pyrrolidine-2,5-dione (VI)

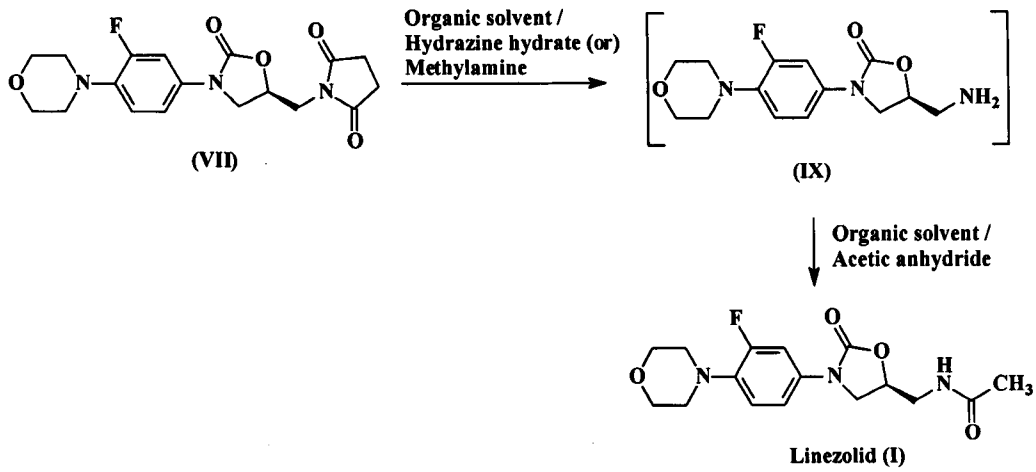


(IV) (V) (VI)

c) (*S*)-1-(3-((3-fluoro-4-morpholinophenyl) amino)-2-hydroxypropyl)pyrrolidine-2,5-dione (VI) is reacted with carbonyl diimidazole in presence of polar organic solvent to produce (*S*)-1-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl) pyrrolidine -2,5-dione (VII)

(VI) (VII)

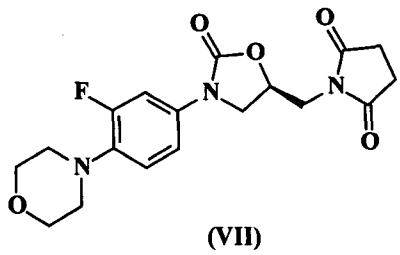
d) (*S*)-1-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl) pyrrolidine -2,5-dione (VI) in organic solvent is reacted with hydrazine hydrate or methylamine to provide (5*S*)-5-(aminomethyl)-3-[3-fluoro-4-(morpholin-4-yl) phenyl]-1,3-oxazolidin-2-one (VII), which is not isolated and *in-situ* treated with acetic anhydride in presence of organic solvent to produce N-({(5*S*)-3-[3-fluoro-4-(morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl) acetamide (Linezolid) of formula I)



(VII) (IX)

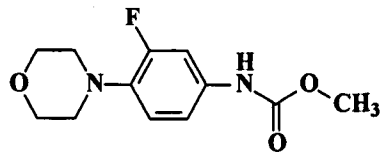
Linezolid (I)

In another aspect of the present invention provides a process for the preparation of (*S*)-1-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl) pyrrolidine-2, 5-dione (VII).



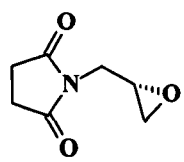
(VII)

comprises reacting methyl (3-fluoro-4-morpholinophenyl)carbamate of formula (VIII)



(VIII)

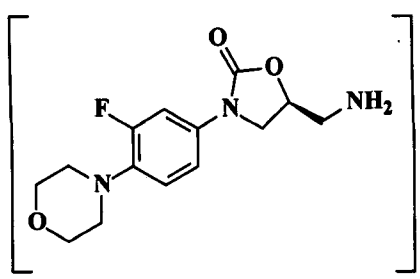
with (*S*)-1-(oxiran-2-ylmethyl) pyrrolidine-2,5-dione (IV)



(IV)

with alkyl alkali metal compound in inert solvent or alkali alkoxide in presence of polar solvent.

In yet another aspect of the present invention, (*S*)-1-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)pyrrolidine-2,5-dione (VII) in organic solvent reacted with hydrazine hydrate or methylamine to give (5S)-5-(aminomethyl)-3-[3-fluoro-4-(morpholin-4-yl) phenyl]-1,3-oxazolidin-2-one (IX), which is not isolated.



(IX)

(5*S*)-5-(aminomethyl)-3-[3-fluoro-4-(morpholin-4-yl) phenyl]-1,3-oxazolidin-2-one (IX) is treated with acetic anhydride in presence of organic solvent to give N-({(5*S*)-3-[3-fluoro-4-

(morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (Linezolid) of formula I.

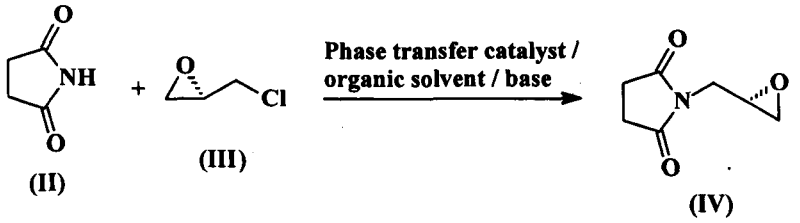
DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a simple, improved, operational and environmental friendly process for the preparation of pure crystalline form of Linezolid.

The present invention relates to an improved process for the preparation of Linezolid using raw materials that are commercially available and it does not require special storage conditions or any special equipment like autoclave.

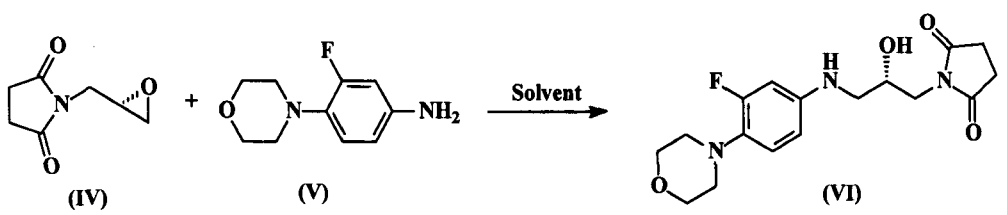
In one embodiment of the present invention, a process for the preparation of Linezolid of formula (I) involves the following steps:

a) pyrrolidine-2,5-dione (II) reacted with ((*S*)-2-(chloromethyl) oxirane) (III) in presence of phase transfer catalyst in organic solvent and a base (*S*)-1-(oxiran-2-ylmethyl)pyrrolidine-2,5-dione (IV)



(II) (III) (IV)

b) (*S*)-1-(oxiran-2-ylmethyl)pyrrolidine-2,5-dione (IV) is reacted with 3-fluoro-4-morpholinoaniline (V) in presence of polar solvent to give (*S*)-1-(3-((3-fluoro-4-morpholinophenyl)amino)-2-hydroxypropyl)pyrrolidine-2,5-dione (VI)

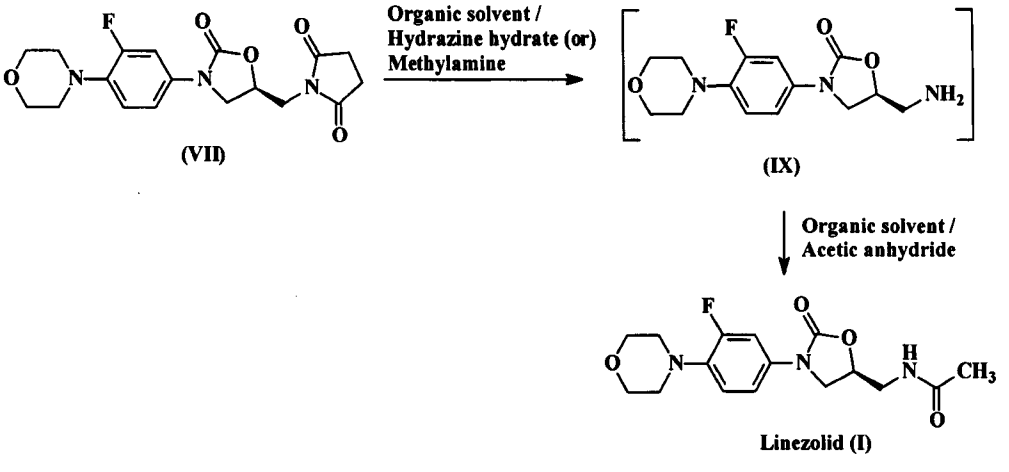


(IV) (V) (VI)

c) (*S*)-1-(3-((3-fluoro-4-morpholinophenyl) amino)-2-hydroxypropyl)pyrrolidine-2,5-dione (VI) is reacted with carbonyl diimidazole in presence of polar organic solvent to produce (*S*)-1-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl) pyrrolidine -2,5-dione (VII)

(VI) (VII)

d) (*S*)-1-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl) pyrrolidine -2,5-dione (VI) in organic solvent is reacted with hydrazine hydrate or methylamine to provide (5*S*)-5-(aminomethyl)-3-[3-fluoro-4-(morpholin-4-yl) phenyl]-1,3-oxazolidin-2-one (VII), which is not isolated and *in-situ* treated with acetic anhydride in presence of organic solvent to produce N-({(5*S*)-3-[3-fluoro-4-(morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl) acetamide (Linezolid) of formula (I)



(VII) (IX)

Linezolid (I)

In step-a) a phase transfer catalyst that are useful in the reaction including but are not limited to comprising of benzyl trimethyl ammonium chloride, tetra butyl ammonium bromide, tetra butyl ammonium chloride, preferably benzyl trimethyl ammonium chloride. Organic solvent that are useful in the reaction including but are not limited to selected from the group comprising of alcohols, such as methanol, ethanol, isopropyl alcohol, and n-propanol; halogenated hydrocarbons, such as dichloromethane, 1,2-dichloroethane, chloroform, and carbon tetrachloride; ketones, such as acetone, ethyl methyl ketone, and methyl isobutyl ketone; ethers, such as diethyl ether, dimethyl ether, diisopropyl ether, methyl tertiary-butyl ether, tetrahydrofuran, and 1 ,4-dioxane; hydrocarbons, such as n-heptane, cyclohexane, and n-hexane; aromatic solvents,

benzene, toluene, xylene, chlorobenzene, and methoxybenzene; aprotic solvents such as acetonitrile, propionithle and dimethylsulfoxide (DMSO) etc., preferably isopropanol.

Bases that are useful in the reaction including and are not limited to: inorganic bases, such as alkoxides, alkali metal or alkaline earth metal carbonates, hydrogen carbonates, hydroxides, oxides, carboxylates e.g., potassium t-butoxide, sodium t-butoxide, sodium methoxide, sodium carbonate, sodium hydrogen carbonate, potassium carbonate, cesium carbonate, sodium hydroxide, potassium hydroxide, potassium carbonate, calcium oxide, sodium acetate, and the like; or any mixtures thereof.

The reaction may be carried out for desired time periods to achieve the desired product yield and purity. The reaction times vary from about 1 hour to about 4 hours, or longer. The reaction may be conducted at temperatures ranging from about 10^0C to about 40^0C, more preferably 15°C to 20°C.

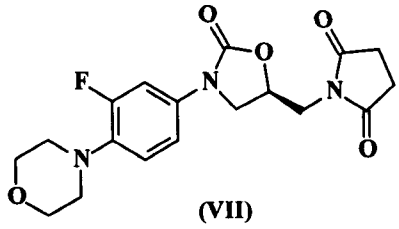
In step-b) the polar solvent was selected from the group comprising of methanol, ethanol, isopropanol, water or mixtures thereof, preferably ethanol and water.

After completion of the reaction, the product was obtained as a thick residue compound and this product can be recrystallized from the solvent such as alcohol having C_1-C_4 carbon atoms, more preferably ethanol solvent to achieve the pure white solid compound.

In step-c) polar organic solvent selected from the group comprising of methylene dichloride, ethyl acetate, acetonitrile, alcohols having C_1-C_4 carbon atoms, dimethyl formamide, dimethyl sulfoxide, N-methyl pyrrolidine, tetrahydrofuran, preferably methylene dichloride.

In step-d) the organic solvent used in this step is same as the organic solvent used in step-a).

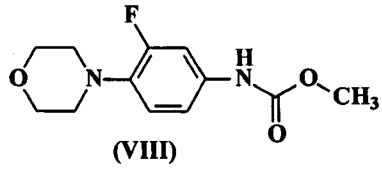
In another embodiment of the present invention, (*S*)-1-(3-((3-fluoro-4-morpholinophenyl)amino)-2-hydroxypropyl)pyrrolidine-2,5-dione (VI) is reacted with carbonyl diimidazole in presence of polar organic solvent to give (*S*)-1-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)pyrrolidine-2,5-dione (VII).



(VII)

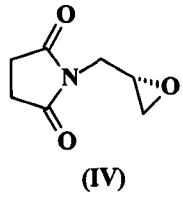
Wherein, the polar organic solvent is selected from the group comprising of alkyl halides: such as dichloromethane, chloro methane etc; esters: such as ethyl acetate, methyl acetate, propyl acetate etc.; alcohols: such as methanol, ethanol, propanol, isopropanol, t-butyl alcohol etc; nitriles: such as acetonitrile etc.; tetrahydrofuran, dimethyl formamide, dimethyl sulfoxide, N-methyl pyrrolidone (NMP) or mixtures thereof.

In yet another embodiment of the present invention, (*S*)-1-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)pyrrolidine-2,5-dione (VII) is prepared by reacting methyl (3-fluoro-4-morpholinophenyl)carbamate (VIII)



(VIII)

and (*S*)-1-(oxiran-2-ylmethyl)pyrrolidine-2,5-dione (IV)



(IV)

with alkyl alkali metal compound in inert solvent or alkali alkoxide in presence of polar solvent.

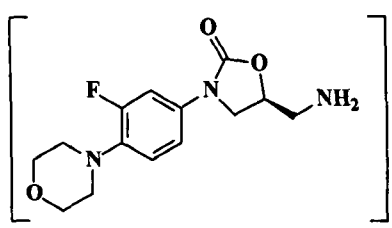
Alkyl alkali metal compound is selected from the group comprising of C_1-C_4 alkyl sodium or lithium compound, preferably butyl lithium compound.

Inert solvent is selected the group comprising of hydrocarbon solvents such as hexane, heptane, benzene, toluene, xylene etc., preferably hexane solvent.

Alkali alkoxide is selected from the group comprising of sodium methoxide, sodium ethoxide, lithium tert-butoxide etc., preferably lithium *tert*-butoxide.

Polar solvent is selected from the group comprising of tetrahydrofuran, C_1-C_4 alcohol, ethyl acetate, methylene dichloride, acetonitrile or mixtures thereof, preferably tetrahydrofuran.

In yet another embodiment of the present invention, (*S*)-1-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)pyrrolidine-2,5-dione (VII) in organic solvent such as methanol, water and mixtures thereof is reacted with hydrazine hydrate or methylamine at 70-90 °C, preferably 70-85 °C to give (5*S*)-5-(aminomethyl)-3-[3-fluoro-4-(morpholin-4-yl) phenyl]-1,3-oxazolidin-2-one (IX), which is not isolated.

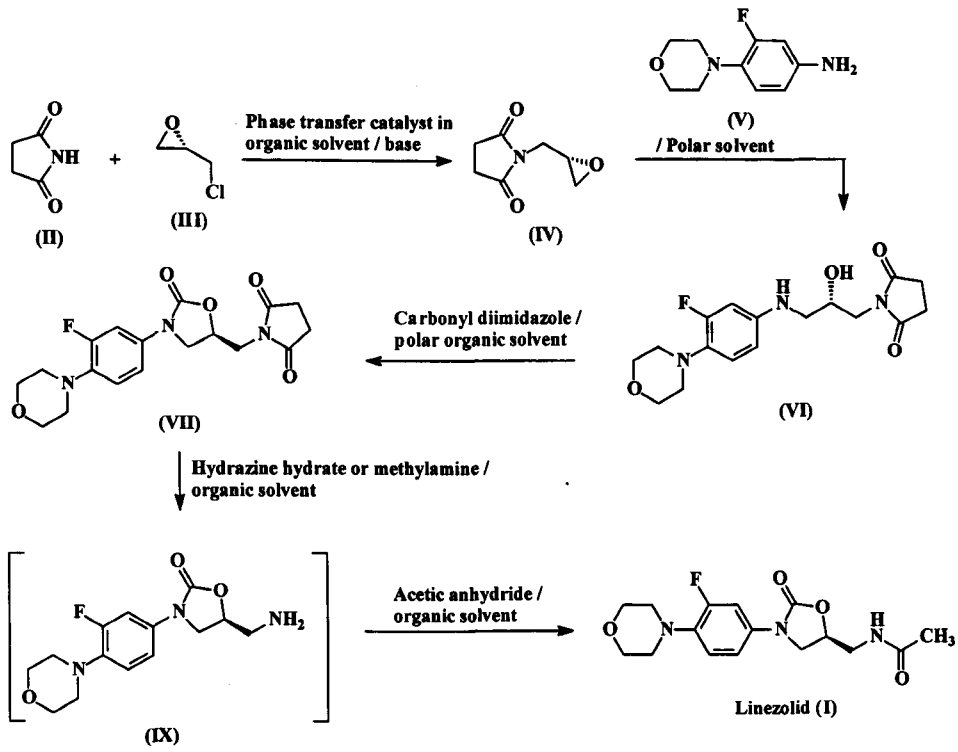


(IX)

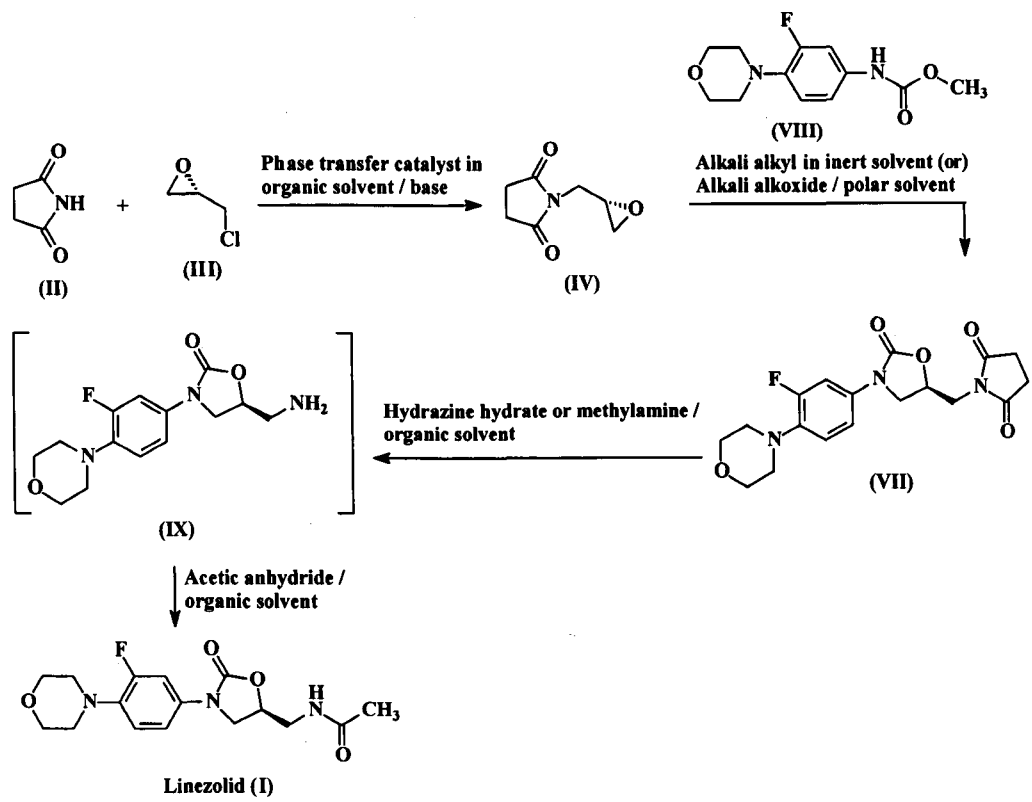
The residue of (5S)-5-(aminomethyl)-3-[3-fluoro-4-(morpholin-4-yl) phenyl]-1,3-oxazolidin-2-one (IX) is treated with acetic anhydride in presence of organic solvents such as dichloromethane, ethyl acetate, preferably dichloromethane to give N-({(5*S*)-3-[3-fluoro-4-(morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (Linezolid), which is crystallized from non polar solvents such as cyclohexane, hexane, diethyl ether, preferably cyclohexane.

The following improved processes for the preparation of Linezolid is depicted in Schemes A and B.

Scheme A:



Scheme B:



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 intended to be included within the scope of the present invention. The invention is illustrated below with reference to inventive and comparative examples and should not be construed to limit the scope of the invention.

EXAMPLES

Example 1: Preparation of (*S*)-1-(oxiran-2-ylmethyl)pyrrolidine-2,5-dione

S-Epichlorohydrin (((*S*)-2-(chloromethyl) oxirane)) (33.6 g, 0.36 moles) was added to a suspension of succinimide (pyrrolidine-2,5-dione) (20 g, 0.2 moles) and benzyl trimethyl ammonium chloride (3.75 g, 0.02 moles) in isopropanol (160 ml) and the mixture was heated to 40°C and maintained for 20 h at the same temperature. Potassium tertiary butoxide (25 g, 0.23 moles) was added portion wise at 15-20°C and the reaction mass was stirred for 2 h at the same temperature. After completion of the reaction, water (200 ml) and ethyl acetate (150 ml) were added, stirred for10 min and the layers were separated. The aqueous layer was extracted with ethyl acetate (100 ml x 2). The combined organic layers were washed with 100 ml water and brine solution (100 ml), the organic layer was concentrated to get title compound. Weight: 25 g (85%)

Example-2: Preparation of (*S*)-1-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)pyrrolidine-2,5-dione

95 ml (0.15moles) of ~15%w/w n-Butyl lithium in hexanes was added to a solution of 38.1g (0.15moles) of methyl (3-fluoro-4-morpholinophenyl)carbamate in tetrahydrofuran (380 ml) over a period of 30-40 min at 0 to -10°C. The solution was stirred for 30min at 0 to -10°C. 29.3 g (0.19 moles) of (*S*)-1-(oxiran-2-ylmethyl)pyrrolidine-2,5-dione was added to the reaction mass for over 30-40 min at 0 to -10°C, stirred continuously and the temperature was slowly raised to 50-55°C. The reaction was continued (~4 hrs) at 50-55°C till the conversion was about 75%. The solvent was removed by distillation under reduced pressure to obtain a thick residue. The residue was dissolved in methylene chloride (500ml) and washed with water (300 ml x 2). The methylene chloride layer was concentrated to get an oily residue. Isopropanol (100ml) was added to the residue and stirred for 15min at 50-55°C. The resulting

slurry was stirred for 30min. The product was filtered and the wet cake was washed with pre-cooled isopropanol (25ml), dried at 40-45°C to obtain crude 1-({(5*S*)-3-[3-fluoro-4-(morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)pyrrolidine-2,5-dione. The pure sample was obtained by re-crystallization from isopropanol. Yield 47 g (84%)

Example-3: Preparation of (*S*)-1-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)pyrrolidine-2,5-dione

To a solution of 19 g (0.075moles) of methyl (3-fluoro-4-morpholinophenyl)carbamate in tetrahydrofuran (190 ml), 6.73 g of lithium tertiary butoxide was added at 0 -5°C. The solution was stirred for 30min. at 0-5°C. 14.72 g (0.095 moles) of (*S*)-1-(Oxiran-2-ylmethyl)pyrrolidine-2,5-dione was added to the reaction solution over 30-40 min. at 0 -5°C. The stirring was continued and the temperature was slowly raised to 25-30°C. The reaction was continued for 20 hrs at 25-30°C. After completion of the reaction, the reaction mass was quenched with saturated ammonium chloride solution (500 ml) and extracted with ethyl acetate (500 ml x 3). The combined organic layer was washed with 200 ml water and 200 ml brine solution. The solvent was evaporated under reduced pressure below 55°C to get residue. The residue was crystallized using methanol to obtain title compound as white solid. Yield 24 g (85%)

Example-4: Preparation of (*S*)-1-(3-((3-fluoro-4-morpholinophenyl)amino)-2-hydroxypropyl)pyrrolidine-2,5-dione

(*S*)-1-(oxiran-2-ylmethyl)pyrrolidine-2,5-dione (8 g, 0.05 moles) was added to the solution of 3-fluoro-4-morpholinoaniline (10 g , 0.05 moles) in ethanol (90 ml) and water (10 ml) and refluxed for 24 h. After completion of the reaction, the solvent was evaporated under reduced pressure to get title compound as a thick residue. The residue was crystallized from ethanol to get title compound as a white solid. Wt: 10 g (94.7%)

Example-5: Preparation of (*S*)-1-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)pyrrolidine-2,5-dione

To a solution of (*S*)-1-(3-((3-fluoro-4-morpholinophenyl)amino)-2-hydroxypropyl) pyrrolidine-2,5-dione (10 g, 0.028 moles) in methylene dichloride (100 ml), was added

carbonyl diimidazole (6.8 g, 0.042 moles) and the reaction mass was stirred till completion. After completion of the reaction, water (50 ml) was added and the layers were separated. The organic layer was distilled off under reduced pressure to yield a title compound as a white compound.

Example-6: Preparation of (S)-1-((3-(3-fluoro-4-morpholinophenyl)-2-oxo oxazolidin-5-yl)methyl)pyrrolidine-2,5-dione

Carbonyl diimidazole (13.6 g, 0.084 moles) was added to a solution of (*S*)-1-(3-((3-fluoro-4-morpholinophenyl)amino)-2-hydroxypropyl) pyrrolidine-2,5-dione (20 g, 0.056 moles) in ethyl acetate (200 ml) and the reaction mass was stirred. After completion of the reaction, water (100 ml) was added and the layers were separated. The organic layer was distilled off under reduced pressure to yield a title compound as a white compound.

Example 7: Preparation of N-({(5S)-3-[3-fluoro-4-(morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (Linezolid)

Methanol (100 ml) was charged into the glass flask. DM water (400 ml) was added into the glass flask at ambient temperature. (*S*)-1-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)pyrrolidine-2,5-dione (100 g) was added to the aqueous methanol at 25-30°C. Methyl amine solution (47 g) was added to the reaction mixture at 25-30°C, stirred. The temperature of the reaction mixture was slowly raised to 80-85°C and stirred for 2-3 hours at 80-85°C. The reaction mixture was cooled to 25-30°C and dichloromethane (500 ml) was added, stirred for 15 min and the two layers were separated. MDC was distilled out by atmospheric pressure completely to get the residual product, (5*S*)-5-(aminomethyl)-3-[3-fluoro-4-(morpholin-4-yl) phenyl]-1,3-oxazolidin-2-one. Dichloromethane (400 ml) was added to the residue and acetic anhydride (25 g) was slowly added at 25-30°C over a period of 60 min. The reaction mixture was stirred for 60 min at 25-30°C. 5% aqueous sodium bicarbonate solution was slowly added to the reaction mixture, stirred for 15 min and the two layers were separated. The dichloromethane layer was washed with D M water (200 ml). The dichloromethane layer was filtered through hiflo and dichloromethane was distilled out completely under vacuum below 40°C. Cyclohexane (500 ml) was added to the residue and heated to 45-50°C. The slurry obtained was cooled to 20-25°C, stirred for 60 min, filtered, washed with cyclohexane (200 ml) and the solid obtained was dried at 45-55°C to furnish pure crystalline form of N-({(5S)-3-[3-fluoro-4-(morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (Linezolid) (53 g).

Example 8: Preparation of N-({(5S)-3-[3-fluoro-4-(morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (Linezolid)

Methanol (250 ml) was charged into the glass flask and DM water (250 ml) was added to it at ambient temperature. (*S*)-1-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)pyrrolidine-2,5-dione (50 g) was added to the aqueous methanol at 25-30°C. Hydrazine hydrate (47 g) was added to the reaction mixture at 25-30°C and stirred. The temperature was slowly raised to 70-75°C and stirred for 2-3 hours at 70-75°C. The reaction mixture was cooled to 25-30°C and dichloromethane (250 ml) was added, stirred the reaction mixture for 15 min and the two layers were separated. MDC layer was distilled out by atmospheric pressure completely to get the residual product (5*S*)-5-(aminomethyl)-3-[3-fluoro-4-(morpholin-4-yl) phenyl]-1,3-oxazolidin-2-one. Dichloromethane (200 ml) was added to the residue and acetic anhydride (13 g) was slowly added at 25-30°C over a period of 60 min. The reaction mixture was stirred for 60 min at 25-30°C.After completion of the reaction, 5% aqueous sodium bicarbonate solution was slowly added to the reaction mixture, stirred for 15 min and the two layers were separated. The dichloromethane layer was washed with water (100 ml). The dichloromethane layer was filtered through hiflo and dichloromethane was distilled out completely under vacuum below 40°C. Cyclohexane (250 ml) was added to the residue and heated to 45-50°C. The slurry obtained was cooled to 20-25°C, stirred for 60 min, filtered, washed with cyclohexane (100 ml) and the solid obtained was dried at 45-55°C to furnish pure crystalline form of N-({(5S)-3-[3-fluoro-4-(morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (Linezolid) (26 g).