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**Szellemi Tulajdon Nemzeti Hivatala**

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(54) **Új eljárás linezolid és új közbenső termékei előállítására**

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(54) **NOVEL PROCESS FOR PREPARATION OF LINEZOLID AND ITS NOVEL INTERMEDIATES**

NEUES VERFAHREN ZUR HERSTELLUNG VON LINEZOLID UND IHREN NEUEN ZWISCHENPRODUKTEN.

PROCÉDÉ NOUVEAU POUR LA PRÉPARATION DU LINEZOLID ET SON INTÉRMEDIAIRES NOUVEAUX.

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**WO-A1-2011/137222**
**US-A- 5 688 792**
**US-A- 5 837 870**
**US-A1- 2007 032 472**

- **S. ROEHRIG ET. AL.: "Discovery of the Novel Antithrombotic Agent 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxomorphol in-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl )thiophene2-carboxamide (BAY-59-7939): An Oral, Direct Factor Xa Inhibitor.", JOURNAL OF MEDICINAL CHEMISTRY, vol. 48, no. 19, 18 August 2009 (2009-08-18), pages 5900-5908, XP002680548,**

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification



EP 2 595 968 B1

## Description

### Field of invention

**[0001]** The present invention relates to a novel process for the preparation of oxazolidinone antibacterial agent Linezolid and their key intermediates.

### Background of the invention

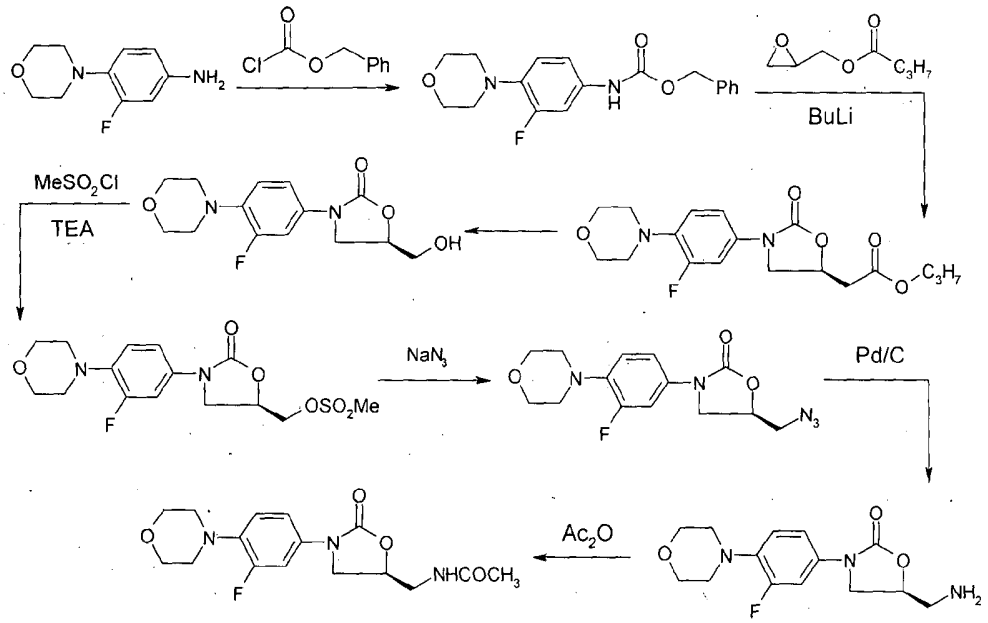
**[0002]** The oxazolidinone antibacterial agents are a novel synthetic class of antimicrobials with potent activity against a number of human and veterinary pathogens, including gram- positive aerobic bacteria such as multiply- resistant staphylococci and streptococci, anaerobic organisms such as bacteroides and clostridia species & acid-fast organisms such as mycobacterium tuberculosis & mycobacterium avium.

**[0003]** Among lower antibacterial agents, Linezolid is a recent synthetic class of antimicrobial active against a number of pathogenic microorganisms. Linezolid [(S)- N- [[3-[3-fluoro-4- (4-morpholinyl) phenyl]-2-oxo-5-oxazolidinyl] methyl] acetamide] is disclosed in US 5,688,792. It is marketed in US by Pfizer Inc having the brand name Zyvox®.

**[0004]** We have discovered and developed a novel intermediate and novel process, which is useful to prepare Linezolid. The process has the potential to lower the cost of commercial production of Linezolid. We also discovered novel key intermediates, which are more useful in the currently known process.

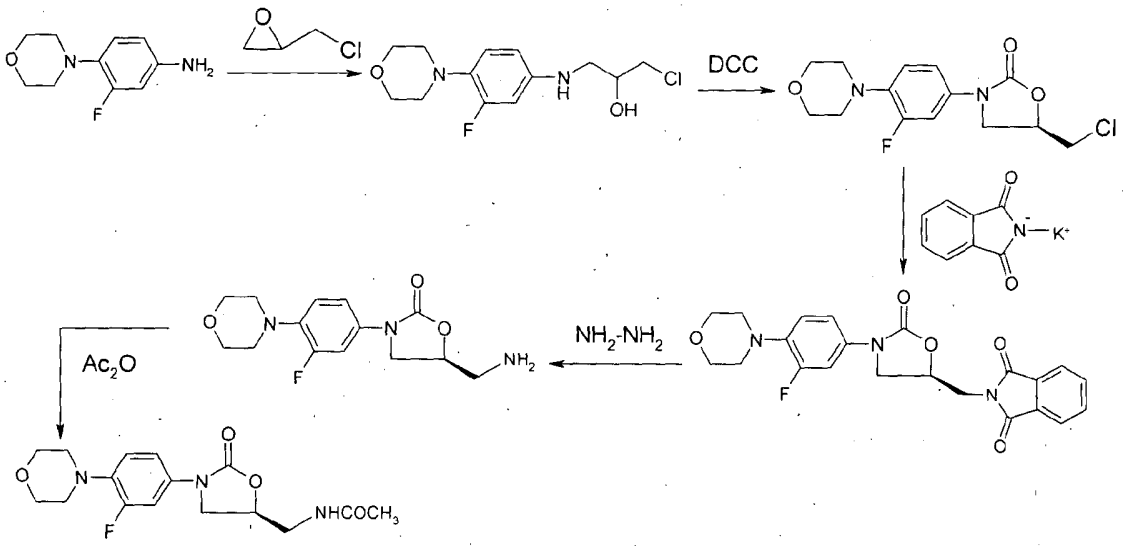
**[0005]** It has been found that US pat No: 5, 688, 792 described the process for the preparation of Linezolid as described in scheme.

**Scheme-1:**




**[0006]** Further is US 2007/0032472 A1 discloses two processes for the preparation of Linezolid in a different route as described in the following scheme.

**Scheme-2:**




**[0007]** The above mentioned base patent describes the preparation of hydroxy derivative by using hazardous chemical like n-BuLi at the temperature of -78 °C with reported very low yield. This process is not commercially viable and very difficult to handle BuLi as well as the very lower temperature.

**[0008]** In other mentioned patent process other unwanted isomer as well as unspecified impurities forms more, which are very difficult to remove and these impurities are continue to be present in the final drug Linezolid, and during the removal process yield becomes very low.

**[0009]** This has prompted and necessitated further research in an attempt to develop a novel route to avoid the formation of the impurity and to maximize the yield. We have discovered and developed a novel process for the preparation of novel intermediates, which are useful for the preparation of antimicrobial Linezolid. Another objective of the present invention is to provide improved method for the preparation of Linezolid avoiding the drawbacks of the hitherto known process. This process has the potential to significantly lower the cost of commercial production of Linezolid.

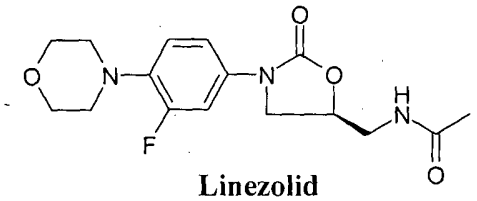
**Object of the invention**

**[0010]** Primary object of the invention is to provide a novel process for preparation of oxazolidinone antibacterial agent Linezolid.

**[0011]** Another object of the invention is to provide a novel process for preparation of key intermediates for preparing Linezolid.

**Summary of the invention**

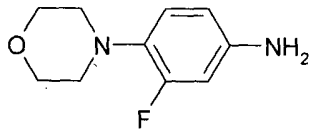
**[0012]** The present invention provides a process to prepare Linezolid




**Linezolid**

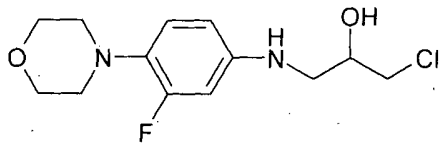
Which comprises;

Step (a): Reacting [3-fluoro-4-morpholinyl aniline] of formula IX with R-epichlorohydrin



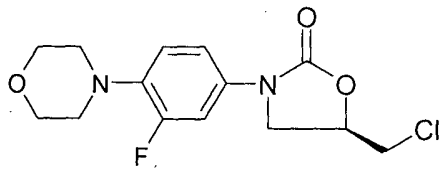
(IX)

Step (b): Carbonylation of compound structure VIII



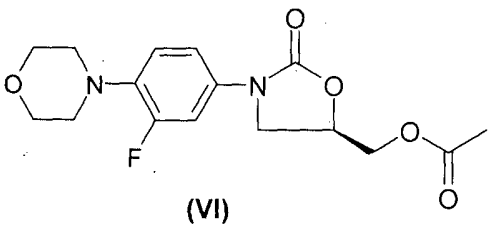
(VIII)

Step (C): Acetylation of compound structure VII



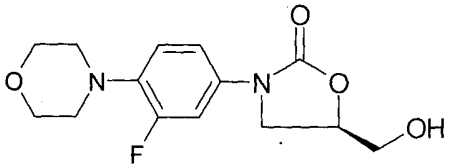
(VII)

Step (d): Hydrolysis of compound structure (VI)



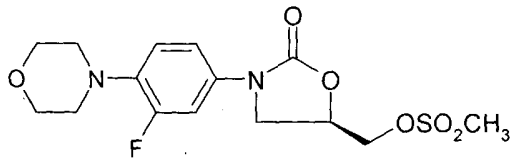
(VI)

Step (e): Mesylation of compound structure (V)



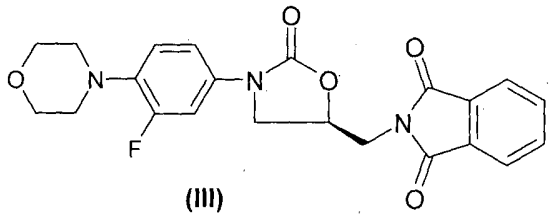
(V)

Step (f): Imidation of compound structure (IV)



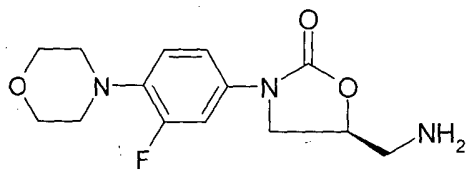
(IV)

Step (g): Hydrolysis of compound structure (III)



(III)

Step (h): Acetylation of compound structure (II)

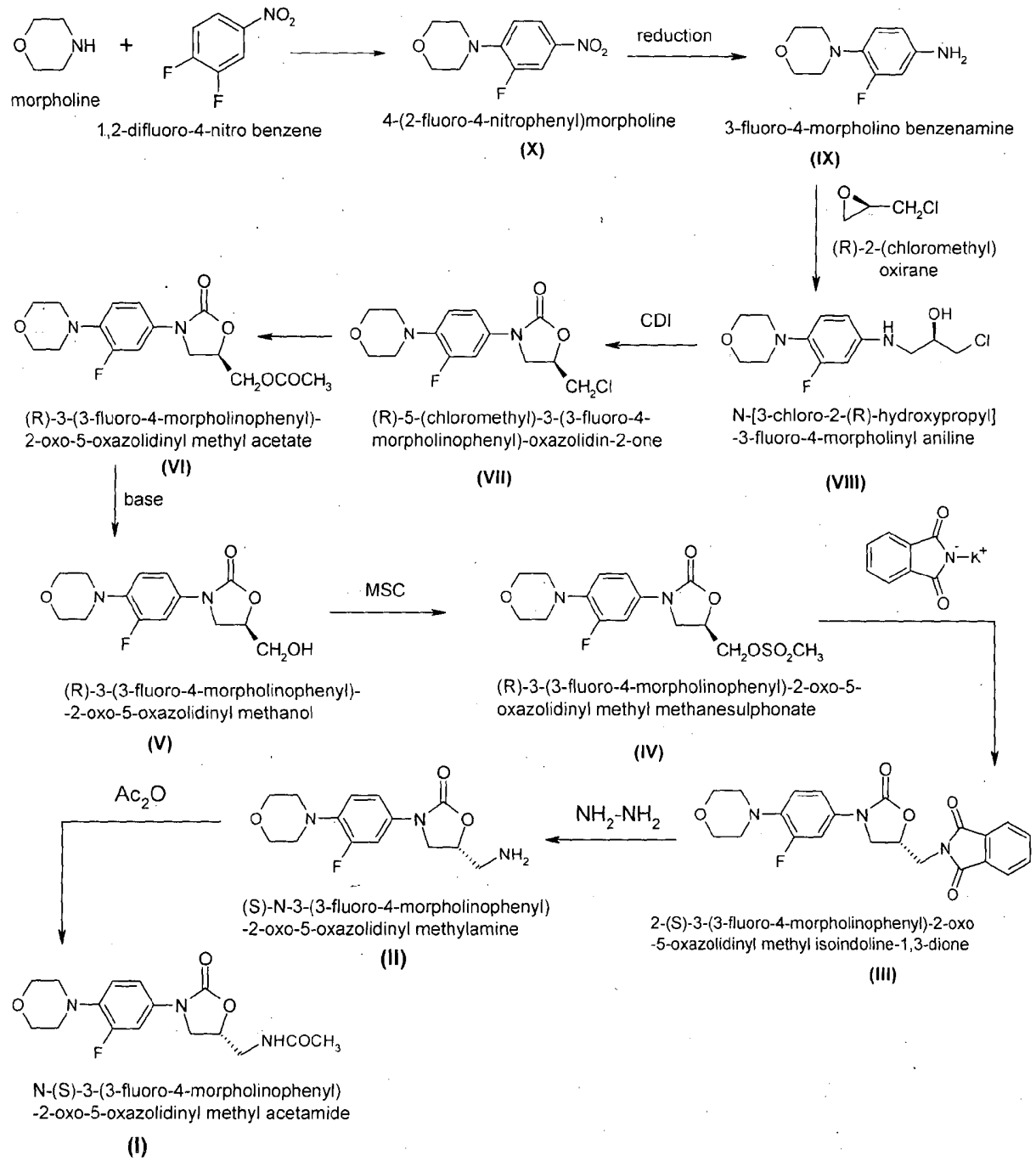


(II)

**Detailed description of the invention**

**[0013]** The process of the present invention is illustrated in scheme-3:

**Scheme-3:**




**[0014]** The present invention provides a process for the preparation of novel intermediate of the formula useful for the preparation of Linezolid of formula (I), which comprises;

**(i) Reacting the compound 1, 2-difluoro-4-nitrobenzene with morpholine** in presence of an organic base and solvent at a temperature in the range of 70-80°C to form the known intermediate of the formula X.

**[0015]** The base such as triethylamine, diisopropylamine, and pyridine, most preferably triethylamine may be used in step (i). Condensation can be carried out by known methods such as those described in US 5, 688, 792.

**(ii) Reduction of the compound of the formula X** in presence of catalyst and solvent at a temperature in the range of 25-60 °C to form a known intermediate of the formula IX.

**[0016]** The catalyst such as Hydrose, palladium, Raney Nickel, Zinc can be used. Preferably, palladium/Carbon, most preferably Raney Nickel may be used in step (ii). The solvents used may be selected from methanol, water, isopropyl alcohol, ethanol, and ethylacetate. Most preferably, methanol can be used as a solvent. There reaction temperature may preferably between 25-60 °C and most preferably between 40-45 °C. Raney Nickel can be used 10-30 %, preferably 20% catalyst, most preferably 15 %catalyst can be used. The hydrogen gas pressure can apply in the range of 4.0-6.0 $kg/cm^{-2}$; most preferably 4.0-4.5 $kg/cm^{-2}$ can be applied.

**(iii) Reaction of compound of formula IX with R-epichlorohydrin** in presence of alcohol to produce known intermediate of formula VIII.

**[0017]** The solvent such as DMF, DMAc, acetonitrile, sec. butanol, IPA, tert. butanol. Most preferably tert. butanol is used. The quantity of epichlorohydrin is a critical, but for better yield and highest enantiomeric purity. 1.25 molar equivalents are used with respect to 3-fluoro-4-morpholinyl aniline and for reaction completion purpose. The reaction is carried out at boiling temperature for about 16 hrs is required for reaction completion.

**(iv) The Carbonylation reaction of compound of formula VIII** with dicarbonylimidazolyl by known methods to produce intermediate of formula VII.

**[0018]** The solvent is selected for isolation/crystallization of formula VII from n-butyl acetate, sec. butyl acetate, ethyl acetate, and methyl acetate. Preferably solvent can be ethyl acetate, most preferably solvent can be n-butyl acetate to produce better quality of this intermediate.

**(v) The acetylation reaction of compound of formula VII** in presence of aprotic solvent to form novel intermediate of formula VI.

**[0019]** The acetylating agents such as sodium acetate (anhydrous), Sodium acetate (mono hydrate), sodium acetate (trihydrate) & potassium acetate can be used. Most preferably, sodium acetate anhydrous can be used in the molar equivalents of 1.0-2.5 equivalents. Most preferably, sodium acetate anhydrous 2.0 molar equivalents can be used.

**[0020]** The solvent selected from aprotic solvents such as dimethyl formamide, dimethyl sulphoxide, and dimethyl acetamide, most preferably dimethyl formamide. The reaction temperature may preferably between 90-130 °C and most preferably 120°C. The reaction time for completion may preferably between 8-12 hrs, most preferably between 8-10 hrs.

**(vi) Hydrolysis reaction of compound formula VI** in presence of non-polar solvents and in presence of base to produce novel compound of formula V.

**[0021]** Non-polar solvent is selected from tetrahydrofuran, toluene, hexane, most preferable solvent can be tetrahydrofuran. The basic hydrolysis inorganic base is selected from NaOH, $Na_2CO_3$, $NaHCO_3$, sodium tert. butoxide, potassium tert. butoxide. Most preferably sodium tert. butoxide can be used in the 1.0-1.5 molar equivalents. The reaction temperature may preferably between 0-15 °C, most preferably 10-15 °C.

**(vii) Mesylation reaction of compound of formula V** with methane sulphonyl chloride in presence of methylene dichloride can be carried out by known methods as described in US 5, 688, 792.

**(viii) Reaction of compound of formula IV** with potassium phthalimide in presence of dimethyl formamide to produce known intermediate of formula III by known methods.

**[0022]** The reaction temperature is between 80-140 °C and most preferably the reaction temperature is 120 °C.

**(ix) Reaction of compound of formula III** with hydrazine hydrate or aqueous methylamine to produce compound of formula II. These methods of deprotection are known and described in US 5,688, 792.

**(x) (S)-N-3- (3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methylamine** is reacted with acetic anhydride to produce compound of formula I (Linezolid).

**[0023]** The present invention is more particularly described and explained in the following examples.

**Examples:**

**(S)-N-3- (3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methyl acetamide**

**Step (1): 3-fluoro-4-morpholinyl nitrobenzene**

**[0024]** 3, 4-difluoro nitrobenzene (100 gr) is slowly added to a mixture of morpholine (76.6 gr), triethylamine (23 ml) and in presence of acetonitrile solvent (115 ml) at 40-50 °C. Reaction mass is heated for 6 hrs at reflux temperature, cooled to 25-30 °C. Then water (600 ml) is added slowly to the reaction mass and then cooled to 0-5°C. The reaction mixture is stirred for 1 hr. The solid is filtered to give 134 gr of 3-fluoro-4-morpholinyl nitrobenzene.

**Step (2): 3-fluoro-4-morpholinyl aniline**

**[0025]** Methanol (1. 35 Lt) and 3-fluoro-4-morpholinyl nitrobenzene (134 gr) are added into autoclave and followed by Raney Nickel (20.5 gr). The system was flushed with nitrogen and hydrogen gas. The pressure of hydrogen was set to 4.0 $kg/cm^{-2}$. The reaction mixture was stirred at 45-50 °C under $H_2$ pressure for 8 hrs & the reaction followed by TLC until completion. The reaction mixture was filtered through celite and the filtrate is distilled off / evaporate solvent completely U/ vaccum at < 50 °C temperature. Reaction mass is cooled to 25-30 °C. To this DM water (400 ml) is added. Stirred for 1 hr at 25-30 °C. The solid is filtered to give 105 gr of 3-fluoro-4-morpholinyl aniline.

**Step (3): N- [3-chloro-2-(R)- hydroxy propyl]-3-fluoro-4-morpholinyl aniline**

**[0026]** 3-fluoro-4-morpholinyl aniline (100 gr) is mixed with R-epichlorohydrin (59 gr) tert- butanol (500 ml) is added and heated for 16 hrs at reflux temperature. The solvent is distilled to give 156 gr of N- [3-chloro-2-(R)- hydroxy propyl]-3-fluoro-4-morpholinyl aniline.

**Step (4): (5R)-5-(chloromethyl)-3-(3-fluoro-4-morpholinophenyl)-oxazolidin-2-one**

**[0027]** N- [3-chloro-2-(R)- hydroxypropyl]-3-fluoro-4-morpholinyl aniline (156 gr) is dissolved in methylene dichloride (1.5 Lt), diimidazolyl carbonyl (87.4 gr) is added at room temperature, stirred for 24 hrs at 25-30 °C. Then washed thrice with water (750 ml×3). Dry over $Na_2SO_4$. Distilled methylene dichloride to give 156 gr of crude (5R)-5-(chloromethyl)-3-[3-fluoro-4-[4-morpholinyl] phenyl]-2-oxazolidinone, which is further isolated and crystallized from n-butyl acetate (100 ml) to give 83 gr of (5R)-5-(chloromethyl)-3-(3-fluoro-4-morpholinophenyl)-oxazolidin-2-one.

**Step (5): (R)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methyl acetate**

**[0028]** (5R)-5-(chloromethyl)-3-(3-fluoro-4-morpholinophenyl)-oxazolidin-2-one (83 gr) is mixed with sodium acetate (43 gr) and dimethyl formamide (320 ml) is added. Reaction mass is heated to 120 °C and stirred for 8-10 hrs. It is then cooled to 25-30 °C. Filter the inorganic salts and washed with DMF (10 ml). DM water (1.0 Lt) is added to round bottom flask. Slowly add above said reaction mass to water at 20-05 °C for a period of 60 min and stirred for 30 min at 20-25 °C. Filtered the precipitated solid, dried the material for 5-6 hrs at 50 °C to give 65 gr of (R)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methyl acetate.

**Step (6): (R)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methanol**

**[0029]** (R)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methyl acetate (62 gr) is mixed with tetrahydrofuran (300 ml), cooled to 0-5 °C. Slowly added sodium tert-butoxide (17.5 gr) at 0-5 °C and followed by slow addition of DM water (620 ml) at 10-15 °C. The reaction mass is stirred for 30 min at 10-15 °C. After completion of the reaction, methylene dichloride is added (300 ml), further extracted with methylene dichloride (120 ml). Solvent is evaporated completely U/vaccum. The precipitated solid is crystallized from hexane (150 ml). Isolated solid is filtered and washed with hexane. Dried the material at 50-55 °C to give 50 gr of (R)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methanol.

**Step (7): (R)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methyl methanesulphonate**

**[0030]** (R)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methanol (50 gr) and triethylamine (42.6 gr) in methylene dichloride (250 ml) was cooled in ice-bath and treated with methane sulphonyl chloride (38.2 gr). The mixture was stirred for 30 min at 0-5 °C. The precipitated product is filtered and washed with chilled DM water (250 ml). Dried the material at 50-55 °C to give 40 gr of (R)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methyl methanesulpho-

nate.

**Step (8): (S)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methyl phthalimide**

**[0031]** The mixture of (R)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methyl methanesulphonate (30 gr), potassium phthalimide (19.4 gr) and dimethyl formamide (180 ml) is heated for 2 hrs at 120 °C temperature. The reaction mixture is cooled to 0-5 °C, slowly added 360 ml of DM water and filtered the solid to give 27 gr of (S)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methyl phthalimide.

**Step (9): (S)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methyl amine**

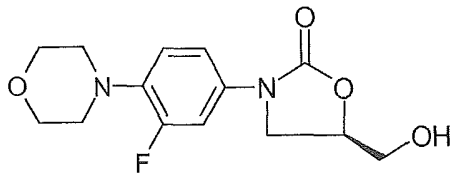
**[0032]** Methanol (150 ml) and hydrazine hydrate (16.2 gr) are added to flask containing (S)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methyl phthalimide (25 gr), heated for 1 hr at reflux temperature and cooled to room temperature. Distill off solvent completely U/vaccum at 45 °C. Then water (125 ml) is added to the reaction mass and extracted with methylene dichloride (62 ml×2). The combined extractions were washed with water (62 ml) and the solvent is distilled to give 15 gr of (S)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methylamine.

**Step (10): (S)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methyl acetamide**

**[0033]** (S)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methylamine (15 gr) is dissolved in ethylacetate (150 ml); acetic anhydride (15 gr) is added dropwise at ambient temperature and stirred for 1 hr. The reaction mixture is then cooled to 0-5 °C. Filtered the solid to give 12 gr of (S)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methyl acetamide.

## Claims

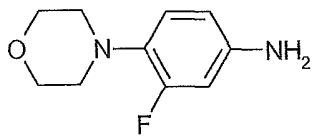
**1.** A process for preparing (R)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methanol




(V)

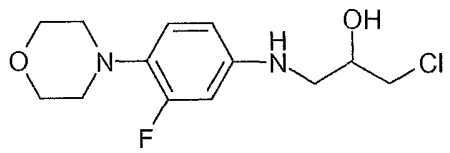
which comprises:

a) reacting a compound of formula IX



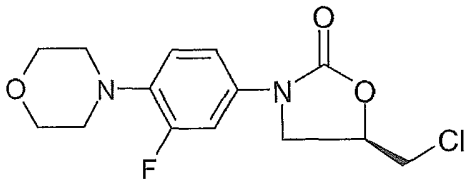

(IX)

with R-epichlorohydrin to produce a compound of formula VIII



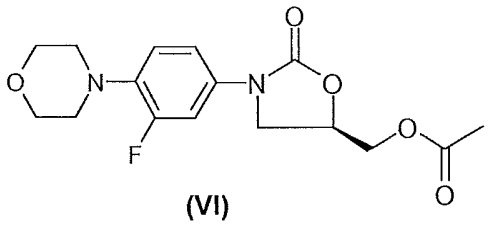
(VIII)

which is further converted to the chloromethyl oxazolidinone compound of formula VII



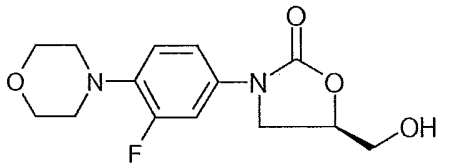
(VII) ,

b) reacting a compound of formula VII with sodium acetate to produce a compound of formula VI



(VI) ,

c) hydrolyzing the product of step (b) to form the hydroxymethyl oxazolidinone compound of formula V



(V) .

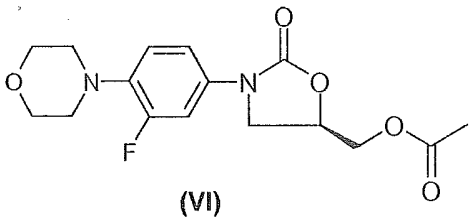
2. The process according to claim 1, wherein the quantity of epichlorohydrin is at least 1.25 molar equivalent per equivalent of formula IX.

3. The process according to claim 1, wherein the reaction in step (a) is carried out with use of a solvent and at 70-80 °C.

4. The process according to claim 3, wherein the solvent is tertiary butanol.

5. The process according to claim 1, wherein chloromethyl oxazolidinone is crystallized from an organic solvent selected from ethylacetate, n-butyl acetate.

6. The process according to claim 1, wherein the chloromethyl oxazolidinone compound of formula VII is converted in the step (b) to the acetyl derivative of compound of formula VI as defined in claim 1, which comprises reacting the said chloromethyl oxazolidinone with anhydrous sodium acetate to give the acetyl compound of formula VI



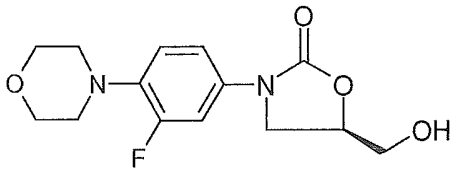
(VI)

7. The process according to claim 6, wherein the quantity of sodium acetate is at least 2.0 molar equivalents to compound of formula VII.

8. The process according to claim 6, wherein the reaction solvent is selected from aprotic solvent, preferably, wherein the reaction solvent is DMF.

9. The process according to claim 6, wherein the reaction is carried out at a temperature of 120 °C.

10. The process according to claim 1, wherein acetyl oxazolidinone compound of formula VI is hydrolyzed in the step (c) to hydroxy derivative of compound of formula V as defined in claim 1, which comprises reacting the said acetyl oxazolidinone with a base in presence of solvent or mixture of solvents to give hydroxy compound of formula V



(V)

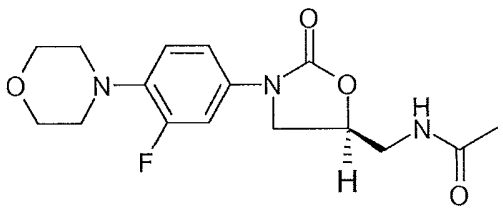
11. The process according to claim 10, wherein the base is sodium tert.-butoxide.

12. The process according to claim 10, wherein the reaction solvent mixture is THF and water.

13. The process according to claim 11, wherein the quantity of sodium tert.-butoxide is at least one molar equivalent to compound of formula VI.

14. The process according to claim 10, wherein the reaction temperature is 10-15 °C.

15. A process for the preparation of Linezolid of formula

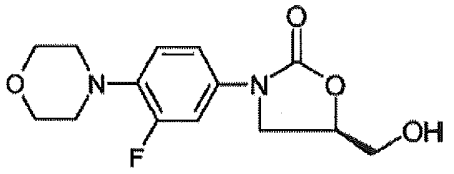


which comprises:

(a) reacting 3-fluoro-4-morpholinyl aniline with R-epichlorohydrin to give N-[3- chloro-2-(R)-hydroxypropyl]-3-fluoro-4-morpholinyl aniline;
(b) carbonylating N- [3-chloro-2-(R)-hydroxypropyl]-3-fluoro-4-morpholinyl aniline to produce (5R)-5-(chloromethyl)-3-(3-fluoro-4-morpholinophenyl)-oxazolidin-2-one;
(c) acetylating (5R)-5-(chloromethyl)-3-(3-fluoro-4-morpholinophenyl)-oxazolidin-2-one with sodium acetate to produce (R)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methyl acetate;
(d) hydrolizing (R)-3-(3-fluoro-4- morpholinophenyl)-2-oxo-5-oxazolidinyl methyl acetate with sodium tert.-butoxide to provide (R)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methanol;
(e) mesylating (R)-3-(3-fluoro-4- morpholinophenyl)-2-oxo-5-oxazolidinyl methanol to provide (R)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methyl methanesulphonate;
(f) reacting of (R)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methyl methanesulphonate with potassium phthalimide to give (S)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methyl phthalimide;
(g) deprotecting (S)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methyl phthalimide with hydrazine hydrate to provide (S)-3-(3-fluoro-4-morpholinophenyl) - 2-oxo-5-oxazolidinyl methyl amine; and
(h) acetylating (S)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl methylamine with acetic anhydride to give Linezolid in high yield and high enantiomeric purity.

**Patentansprüche**

**1.** Verfahren zur Herstellung von (R)-3-(3-Fluor-4-morpholinophenyl)-2-oxo-5-oxazolidinylmethanol:

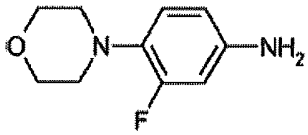



**(V)**

,

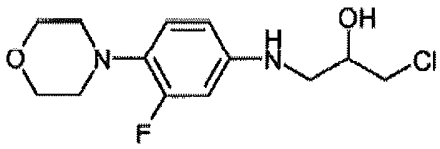
umfassend:

a) Umsetzen einer Verbindung der Formel IX




**(IX)**

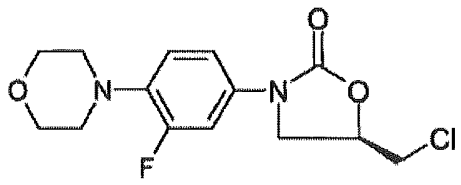
mit R-Epichlorhydrin unter Bildung einer Verbindung der Formel VIII




**(VIII)**

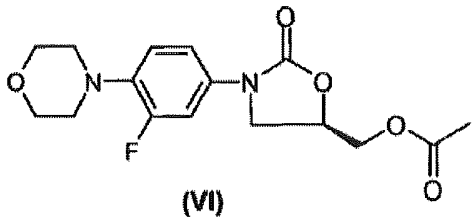
,

die weiter zu der Chlormethyloxazolidinon-Verbindung der Formel VII



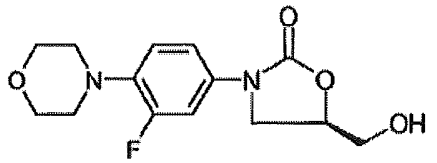
(VII)

umgewandelt wird;
b) Umsetzen einer Verbindung der Formel VII mit Natriumacetat unter Bildung einer Verbindung der Formel VI



(VI) ;

c) Hydrolysieren des Produkts von Schritt (b) unter Bildung der Hydroxymethyloxazolidinon-Verbindung der Formel V:



(V) .

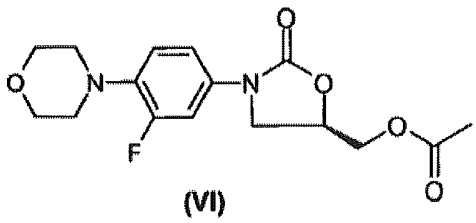
2. Verfahren gemäß Anspruch 1, wobei die Menge des Epichlorhydrins wenigstens 1,25 Moläquivalent pro Äquivalent der Formel IX beträgt.

3. Verfahren gemäß Anspruch 1, wobei die Reaktion in Schritt (a) unter Verwendung eines Lösungsmittels und bei 70-80 °C durchgeführt wird.

4. Verfahren gemäß Anspruch 3, wobei es sich bei dem Lösungsmittel um tertiär-Butanol handelt.

5. Verfahren gemäß Anspruch 1, wobei Chlormethyloxazolidinon aus einem organischen Lösungsmittel, das aus Ethylacetat und n-Butylacetat ausgewählt ist, kristallisiert wird.

6. Verfahren gemäß Anspruch 1, wobei die Chlormethyloxazolidinon-Verbindung der Formel VII in Schritt (b) in das Acetylderivat der Verbindung der Formel VI, wie sie in Anspruch 1 definiert ist, umgewandelt wird, was das Umsetzen des Chlormethyloxazolidinons mit wasserfreiem Natriumacetat unter Bildung der Acetylverbindung der Formel VI umfasst:



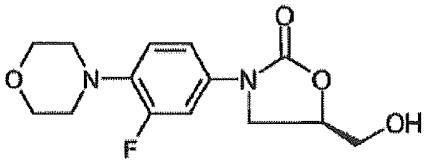
(VI)

7. Verfahren gemäß Anspruch 6, wobei die Menge des Natriumacetats wenigstens 2,0 Moläquivalent zur Verbindung der Formel VII beträgt.

8. Verfahren gemäß Anspruch 6, wobei das Reaktionslösungsmittel aus einem aprotischen Lösungsmittel ausgewählt ist, wobei es sich bei dem Reaktionslösungsmittel vorzugsweise um DMF handelt.

9. Verfahren gemäß Anspruch 6, wobei die Reaktion bei einer Temperatur von 120 °C durchgeführt wird.

10. Verfahren gemäß Anspruch 1, wobei die Acetyloxazolidinon-Verbindung der Formel VI in Schritt (c) zum Hydroxyderivat der Verbindung der Formel V, wie sie in Anspruch 1 definiert ist, hydrolysiert wird, was das Umsetzen des Acetyloxazolidinons mit einer Base in Gegenwart eines Lösungsmittels oder Lösungsmittelgemischs unter Bildung der Hydroxyverbindung der Formel V umfasst:



(V)

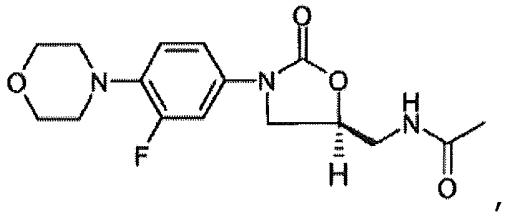
11. Verfahren gemäß Anspruch 10, wobei es sich bei der Base um Natrium-tert-butoxid handelt.

12. Verfahren gemäß Anspruch 10, wobei es sich bei dem Reaktionslösungsmittelgemisch um THF und Wasser handelt.

13. Verfahren gemäß Anspruch 11, wobei die Menge des Natrium-tert-butoxids wenigstens ein Moläquivalent zur Verbindung der Formel VI beträgt.

14. Verfahren gemäß Anspruch 10, wobei die Reaktionstemperatur 10-15 °C beträgt.

15. Verfahren zur Herstellung von Linezolid der Formel



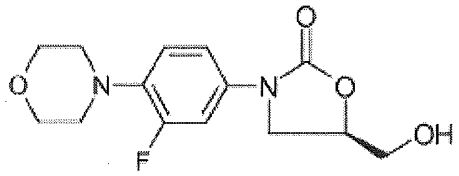
umfassend:

(a) Umsetzen von 3-Fluor-4-morpholinylanilin mit R-Epichlorhydrin unter Bildung von N-[3-Chlor-2-(R)-hydro-

xypropyl]-3-fluor-4-morpholinylanilin;
(b) Carbonylieren von N-[3-Chlor-2-(R)-hydroxypropyl]-3-fluor-4-morpholinylanilin unter Bildung von (5R)-5-(Chlormethyl)-3-(3-fluor-4-morpholinophenyl)oxazolidin-2-on;
(c) Acetylieren von (5R)-5-(Chlormethyl)-3-(3-fluor-4-morpholinophenyl)oxazolidin-2-on mit Natriumacetat unter Bildung von (R)-3-(3-Fluor-4-morpholinophenyl)-2-oxo-5-oxazolidinylmethylacetat;
(d) Hydrolysieren von (R)-3-(3-Fluor-4-morpholinophenyl)-2-oxo-5-oxazolidinylmethylacetat mit Natrium-tert-butoxid, was (R)-3-(3-Fluor-4-morpholinophenyl)-2-oxo-5-oxazolidinylmethanol ergibt;
(e) Mesylieren von (R)-3-(3-Fluor-4-morpholinophenyl)-2-oxo-5-oxazolidinylmethanol, was (R)-3-(3-Fluor-4-morpholinophenyl)-2-oxo-5-oxazolidinylmethylmethansulfonat ergibt;
(f) Umsetzen von (R)-3-(3-Fluor-4-morpholinophenyl)-2-oxo-5-oxazolidinylmethylmethansulfonat mit Kaliumphthalimid unter Bildung von (S)-3-(3-Fluor-4-morpholinophenyl)-2-oxo-5-oxazolidinylmethylphthalimid;
(g) Entfernen der Schutzgruppe von (S)-3-(3-Fluor-4-morpholinophenyl)-2-oxo-5-oxazolidinylmethylphthalimid mit Hydrazinhydrat, was (S)-3-(3-Fluor-4-morpholinophenyl)-2-oxo-5-oxazolidinylmethylamin ergibt; und
(h) Acetylieren von (S)-3-(3-Fluor-4-morpholinophenyl)-2-oxo-5-oxazolidinylmethylamin mit Essigsäureanhydrid unter Bildung von Linezolid in hoher Ausbeute und mit hoher Enantiomerenreinheit.

## Revendications

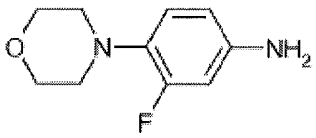
1. Procédé de préparation du (R)-3-(3-fluoro-4-morpholinophényl)-2-oxo-5-oxazolidinylméthanol



(V)

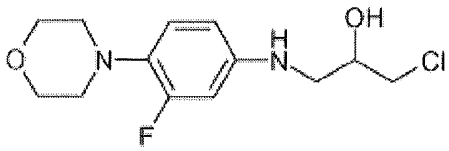
qui comprend:

a) la réaction d'un composé de formule IX



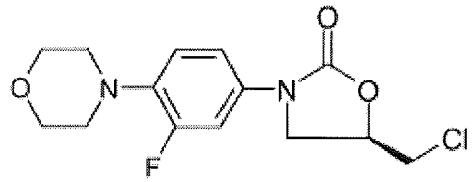
(IX)

avec de la R-épichlorhydrine pour produire un composé de formule VIII



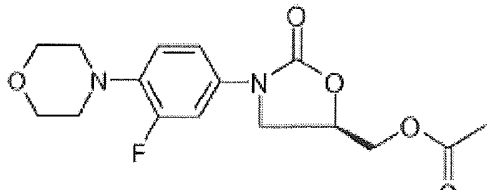
(VIII)

qui est en outre converti en composé chlorométhyloxazolidinone de formule VII



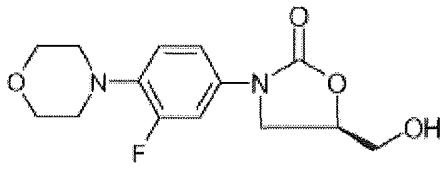
(VII)

b) la réaction d'un composé de formule VII avec de l'acétate de sodium pour produire un composé de formule VI



(VI)

c) l'hydrolyse du produit de l'étape (b) pour former le composé hydroxyméthyloxazolidinone de formule V



(V)

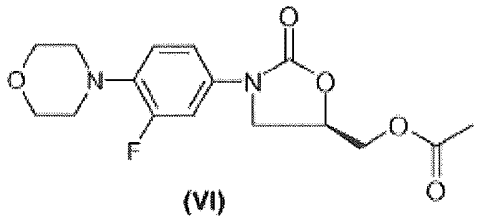
2. Procédé selon la revendication 1, dans lequel la quantité d'épichlorhydrine est d'au moins 1,25 équivalent molaire par équivalent de formule IX.

3. Procédé selon la revendication 1, dans lequel la réaction de l'étape (a) est réalisée en présence d'un solvant et à 70-80°C.

4. Procédé selon la revendication 3, dans lequel le solvant est du butanol tertiaire.

5. Procédé selon la revendication 1, dans lequel la chlorométhyloxazolidinone est cristallisée à partir d'un solvant organique choisi parmi l'acétate d'éthyle, l'acétate de n-butyle.

6. Procédé selon la revendication 1, dans lequel le composé chlorométhyloxazolidinone de formule VII est converti dans l'étape (b) en dérivé acétyle du composé de formule VI tel que défini dans la revendication 1, qui comprend la réaction de ladite chlorométhyloxazolidinone avec de l'acétate de sodium anhydre pour donner le composé acétyle de formule VI



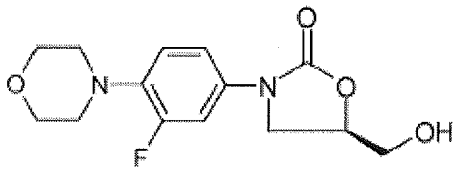
(VI)

7. Procédé selon la revendication 6, dans lequel la quantité d'acétate de sodium est d'au moins 2,0 équivalents molaires par rapport au composé de formule VII.

8. Procédé selon la revendication 6, dans lequel le solvant réactionnel est choisi parmi un solvant aprotique, de préférence, dans lequel le solvant réactionnel est le DMF.

9. Procédé selon la revendication 6, dans lequel la réaction est réalisée à une température de 120°C.

10. Procédé selon la revendication 1, dans lequel le composé acétyloxazolidinone de formule VI est hydrolysé dans l'étape (c) en dérivé hydroxylé du composé de formule V tel que défini dans la revendication 1, qui comprend la réaction de ladite acétyloxazolidinone avec une base en présence d'un solvant ou d'un mélange de solvants pour donner le composé hydroxylé de formule V



(V)

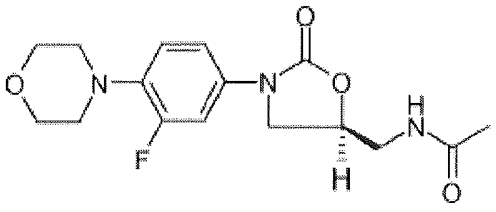
11. Procédé selon la revendication 10, dans lequel la base est le tert-butylate de sodium.

12. Procédé selon la revendication 10, dans lequel le mélange de solvants réactionnels est constitué de THF et d'eau.

13. Procédé selon la revendication 11, dans lequel la quantité de tert-butylate de sodium est d'au moins un équivalent molaire par rapport au composé de formule VI.

14. Procédé selon la revendication 10, dans lequel la température réactionnelle est de 10-15°C.

15. Procédé pour la préparation du Linézolide de formule



qui comprend:

(a) la réaction de la 3-fluoro-4-morpholinylaniline avec la R-épichlorhydrine pour donner la N-[3-chloro-2-(R)-hy-

droxypropyl]-3-fluoro-4-morpholinylaniline;
(b) la carbonylation de la N-[3-chloro-2-(R)-hydroxypropyl]-3-fluoro-4-morpholinylaniline pour produire la (5R)-5-(chlorométhyl)-3-(3-fluoro-4-morpholinophényl)oxazolidin-2-one;
(c) l'acétylation de la (5R)-5-(chlorométhyl)-3-(3-fluoro-4-morpholinophényl)oxazolidin-2-one avec de l'acétate de sodium pour produire l'acétate de (R)-3-(3-fluoro-4-morpholinophényl)-2-oxo-5-oxazolidinylméthyle;
(d) l'hydrolyse de l'acétate de (R)-3-(3-fluoro-4-morpholinophényl)-2-oxo-5-oxazolidinylméthyle avec du tert-butylate de sodium pour obtenir le (R)-3-(3-fluoro-4-morpholinophényl)-2-oxo-5-oxazolidinylméthanol;
(e) la mésylation du (R)-3-(3-fluoro-4-morpholinophényl)-2-oxo-5-oxazolidinylméthanol pour obtenir le méthanesulfonate de (R)-3-(3-fluoro-4-morpholinophényl)-2-oxo-5-oxazolidinylméthyle;
(f) la réaction du méthanesulfonate de (R)-3-(3-fluoro-4-morpholinophényl)-2-oxo-5-oxazolidinylméthyle avec du phtalimide de potassium pour donner le (S)-3-(3-fluoro-4-morpholinophényl)-2-oxo-5-oxazolidinylméthylphtalimide;
(g) la déprotection du (S)-3-(3-fluoro-4-morpholinophényl)-2-oxo-5-oxazolidinylméthylphtalimide avec de l'hydrate d'hydrazine pour obtenir la (S)-3-(3-fluoro-4-morpholinophényl)-2-oxo-5-oxazolidinyl-méthylamine; et
(h) l'acétylation de la (S)-3-(3-fluoro-4-morpholinophényl)-2-oxo-5-oxazolidinyl-méthylamine avec de l'anhydride acétique pour donner le Linézolide avec un rendement élevé et une grande pureté énantiomérique.

## REFERENCES CITED IN THE DESCRIPTION

*This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.*

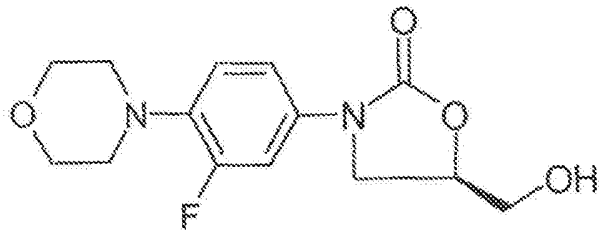
### Patent documents cited in the description


- US 5688792 A **[0003] [0005] [0015] [0021] [0022]**
- US 20070032472 A1 **[0006]**

# Új eljárás linezolid és új közbenső termékei előállítására

## Szabadalmi igénypontok

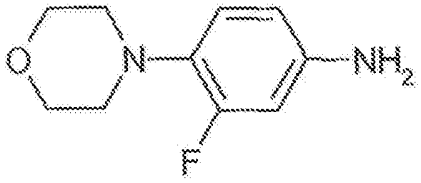
1. Eljárás (R)-3-(3-fluor-4-morfolino-fenil)-2-oxo-5-oxazolidinil-metanol előállítására



(V)

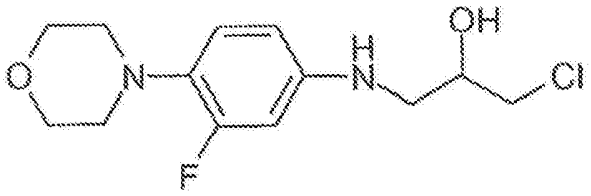
amelynek során

a) a IX képletű vegyületet



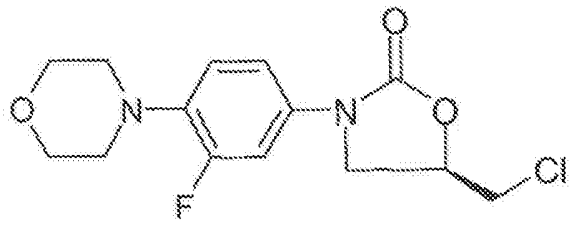
(IX)

R-epiklórhidrinnel reagáltatjuk a VIII képletű vegyület előállítására



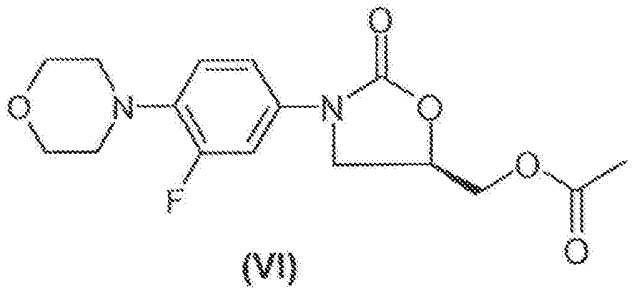
(VIII)

amelyet a VII képletű klór-metil-oxazolidinon vegyületté alakítunk tovább



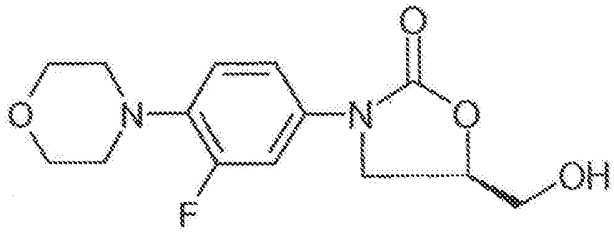
(VII)

b) a VII képletű vegyületet nátrium-acetáttal reagáltatjuk a VI képletű vegyület előállítására



(VI)

c) a b) lépés termékét hidrolizáljuk az V képletű hidroxi-metil-oxazolidinon vegyületté



(V)

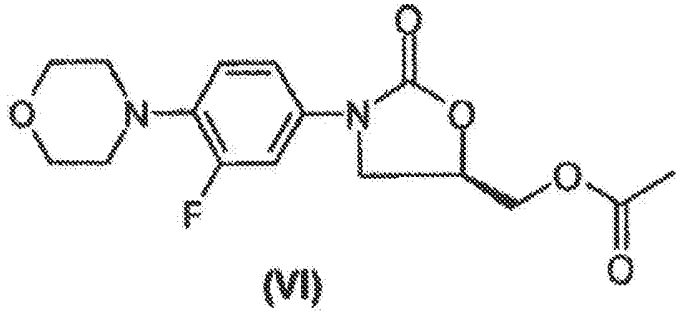
2. Az 1. igénypont szerinti eljárás, ahol az epiklórhidrin mennyisége legalább 1,25 mólekvivalens per ekvivalens mennyiségű IX képletű vegyület.

3. Az 1. igénypont szerinti eljárás, ahol az a) lépésben a reakciót oldószer alkalmazásával 70-80 °C-on vitelezzük ki.

4. A 3. igénypont szerinti eljárás, ahol az oldószer tercier-butanol.

5. Az 1. igénypont szerinti eljárás, ahol a klór-metil-oxazolidinont az etil-acetát, n-butil-acetát közül választott szerves oldószerből kristályosítjuk.

6. Az 1. igénypont szerinti eljárás, ahol a VII képletű klór-metil-oxazolidinon vegyületet a b) lépésben a VI képletű acetil származékká alakítjuk át az 1. igénypontban megadottak szerint, amelynek során a klór-metil-oxazolidinont vízmentes nátrium-acetáttal reagáltatjuk a VI képletű acetil vegyület előállítására



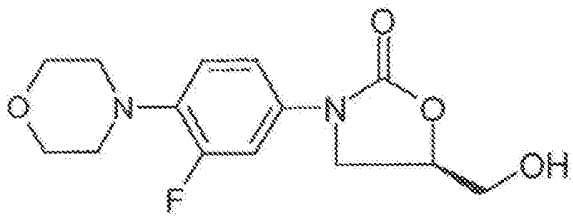
(VI)

7. A 6. igénypont szerinti eljárás, ahol a nátrium-acetát mennyisége legalább 2,0 mólekvivalens a VII képletű vegyületre vonatkoztatva.

8. A 6. igénypont szerinti eljárás, ahol a reakció oldószerét az aprotikus oldószerek közül választjuk ki, előnyösen ahol a reakció oldószere DMF.

9. A 6. igénypont szerinti eljárás, ahol a reakciót 120 °C hőmérsékleten folytatjuk le.

10. Az 1. igénypont szerinti eljárás, ahol a VI képletű acetil-oxazolidinon vegyületet a c) lépésben az V képletű hidroxi-származékká hidrolizáljuk az 1. igénypontban megadottak szerint, amelynek során az acetil-oxazolidinont bázissal reagáltatjuk oldószer vagy oldószerek elegye jelenlétében az V képletű hidroxi vegyület előállítására



(V)

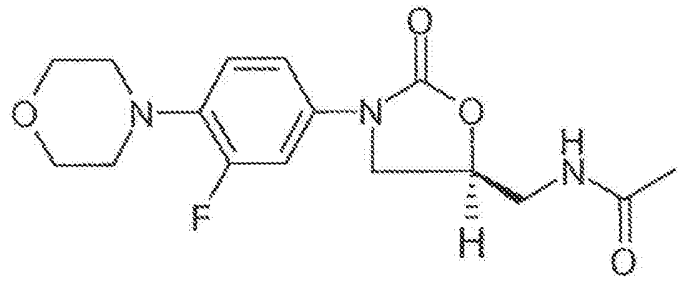
11. A 10. igénypont szerinti eljárás, ahol a bázis nátrium-terc.-butoxid.

12. A 10. igénypont szerinti eljárás, ahol a reakció oldószerelegye tetrahidrofurán és víz elegye.

13. A 11. igénypont szerinti eljárás, ahol a nátrium-terc.-butoxid mennyisége legalább egy mólekvivalens a VI képletű vegyületre vonatkoztatva.

14. A 10. igénypont szerinti eljárás, ahol a reakcióhőmérséklet 10-15 °C.

15. Eljárás az alábbi képletű Linezolid előállítására



amelynek során

(a) 3-fluor-4-morfolinil-anilint R-epiklórhidrinnel reagáltatunk N-[3-klór-2-(R)-hidroxi-propil]-3-fluor-4-morfolinil-anilin előállítására;

(b) N-[3-klór-2-(R)-hidroxi-propil]-3-fluor-4-morfolinil-anilint karbonilezünk (5R)-5-(klór-metil)-3-(3-fluor-4-morfolino-fenil)-oxazolidin-2-on előállítására;

(c) (5R)-5-(klór-metil)-3-(3-fluor-4-morfolino-fenil)-oxazolidin-2-on vegyületet nátrium-acetáttal acetilezünk (R)-3-(3-fluor-4-morfolino-fenil)-2-oxo-5-oxazolidinil-metil-acetát előállítására;

(d) (R)-3-(3-fluor-4-morfolino-fenil)-2-oxo-5-oxazolidinil-metil-acetátot nátrium-terc.-butoxiddal hidrolizálunk (R)-3-(3-fluor-4-morfolino-fenil)-2-oxo-5-oxazolidinil-metanol előállítására;

(e) (R)-3-(3-fluor-4-morfolino-fenil)-2-oxo-5-oxazolidinil-metanolt mezilezünk (R)-3-(3-fluor-4-morfolino-fenil)-2-oxo-5-oxazolidinil-metil-metán-szulfonát előállítására;

(f) (R)-3-(3-fluor-4-morfolino-fenil)-2-oxo-5-oxazolidinil-metil-metán-szulfonátot kálium-ftálimiddel reagáltatunk (S)-3-(3-fluor-4-morfolino-fenil)-2-oxo-5-oxazolidinil-metil-ftálimid előállítására;

(g) (S)-3-(3-fluor-4-morfolino-fenil)-2-oxo-5-oxazolidinil-metil-ftálimid védőcsoportját hidrazin-hidráttal eltávolítjuk (S)-3-(3-fluor-4-morfolino-fenil)-2-oxo-5-oxazolidinil-metil-amin előállítására; és

(h) (S)-3-(3-fluor-4-morfolino-fenil)-2-oxo-5-oxazolidinil-metil-amint ecetsav-anhidriddel reagáltatunk a linezolid jó termeléssel és nagy enantiomer tisztasággal történő előállítására.