(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 February 2007 (08.02.2007)

PCT

(10) International Publication Number
WO 2007/015265 A2

(51) International Patent Classification:
C07H 17/08 (2006.01)

(21) International Application Number:
PCT/IN2006/000180

(22) International Filing Date: 24 May 2006 (24.05.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
627/MUM/2005 24 May 2005 (24.05.2005) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** A PROCESS FOR PREPARING 6,9-IMINO ETHER

(57) **Abstract:** A process for preparing 6,9-Imino ether from Erythromycin thiocyanate without isolating Erythromycin base and Erythromycin oxime and Beckmann's rearrangement of erythromycin oxime is carried in the presence biphasic solvent system comprising methylene chloride and water in the presence of triethylamine along with sodium bicarbonate to obtain 87-96 % pure 6,9-Imino ether. Further the 6,9-Imino ether is hydrogenated to 9-Deoxo-9a-aza-9a-homoerythromycin A followed by reductive methylation to obtain Azithromycin dihydrate.

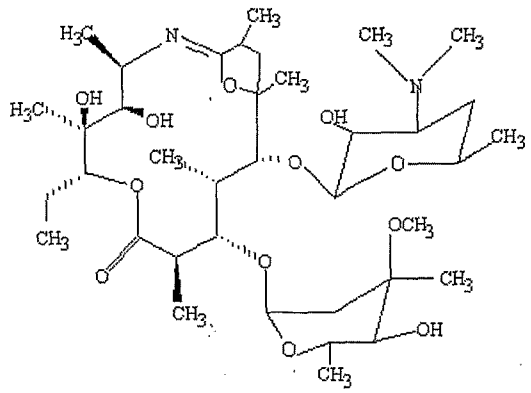
WO 2007/015265 A2

TITLE OF THE INVENTION

A process for preparing 6,9-Imino ether

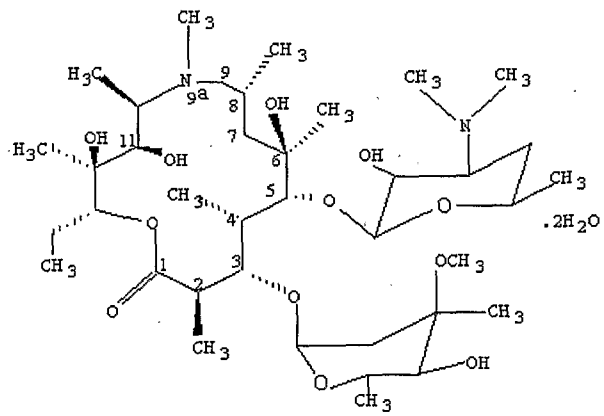
FIELD OF THE INVENTION

The invention relates to a process for preparing 6,9-Imino ether of formula I.



Formula I

The invention also relates to a process for preparing Azithromycin dihydrate of Formula V.



Formula V

BACKGROUND OF THE INVENTION

Azithromycin is a semi-synthetic macrolide antibiotic chemically related to Erythromycin. Azithromycin is a broad-spectrum bactericide and effective against a wide variety of microorganisms, such as Hemophilus influenzae, Streptococcus pneumoniae, Mycoplasma pneumoniae, Staphylococcus aureus, and Mycobacterium avium, and many others.

The transformation of Erythromycin A into Azithromycin comprises the conversion of Erythromycin base into its oxime; Beckmann's rearrangement of the Erythromycin oxime into 6,9-Imino ether; hydrogenation of the 6,9-Imino ether to 9-deoxo-9a-aza-9a-homoerythromycin A and further reductive methylation to obtain Azithromycin.

Erythromycin Oxime is prepared by treating Erythromycin base with hydroxylamine hydrochloride in methanol in presence of base. Erythromycin Oxime (either in the form of base or salt) is further subjected to Beckmann's rearrangement by treating it with p–Toluene sulfonyl chloride in aqueous acetone to produce 6,9-Imino ether, which is reported in WO 00/26,758, EP 0,503,932, EP 0,137,132 and US 4,328,334. In the reported process, the Beckmann's rearrangement of Erythromycin Oxime, the impurities including p-toluene sulfonic acid and unreacted Erythromycin oxime are present along with desired product, 6,9-Imino ether, in aqueous acetone. Hence, 6,9-Imino ether needs to be isolated by evaporation of acetone from aqueous acetone reaction mixture followed by solvent extraction at different pH, which is in the range of 5.5 to 8.

In the prior art, p-toluene sulfonyl chloride added directly to aqueous acetone. This may leads to decomposition of p-toluene sulfonyl chloride to corresponding acid. Thus, excess quantity of p-toluene sulfonyl chloride is needed to get satisfactory yield. Further acetone can not be recovered and recycled from the reaction phase, as it forms azeotrope with water. As stated earlier, after the completion of reaction, water-acetone reaction mixture comprises impurities including unreacted Erythromycin oxime and p-toluene sulfonic acid has to be disposed off as effluent. The p-toluene sulfonic acid is corrosive in nature, so effluent needs further treatment before disposing off the same.

WO 00/27,856 reports the stable hydrate form of 6,9-Imino ether and its process of preparation. During the preparation of Azithromycin dihydrate, 6,9-Imino ether is further hydrogenated to 9-Deoxo-9a-aza-9a-homoerythromycin A. Use of 6,9-Imino ether in its hydrated form for hydrogenation to 9-Deoxo-9a-aza-9a-homoerythromycin A, may hampers the hydrogenation due to its water content, which results in reduction of the yield.

US 6,528,492 describes preparation of 6,9-Imino ether by treating Erythromycin A with O-mesitylene sulfonyl hydroxylamine in acetone to form the mesitylene sulfonyl oxime in-situ which on further treatment with aqueous base (sodium carbonate) at 0° C gives 6,9-Imino ether. In this process, O-mesitylene sulfonyl hydroxylamine needs to be prepared as per the literature Tetrahedron Lett., 40, 4133-35, 1972.

US 5,680,587 describes the preparation of 6,9-Imino ether by treating oxime free base with p-toluene sulfonyl chloride in presence of pyridine and ether at - 45° C. This process gives 6,9-Imino ether along with 9,11-Imino ether, which needs to be separated chromatographically. Further, ether as a solvent is not user friendly.

The hydrogenation of 6,9-Imino ether to a secondary amine, 9-Deoxo-9a-aza-9a-homoerythromycin A, is carried out by using sodium borohydride in Methanol which is disclosed in J. Chem. Soc. Perkin Trans. 1, 1986, 1881; J. Org. Chem. 1997, 62, 7479-7481; US 4,328,334; US 5,869,629; International publications WO 01/00640; WO 03/082889 and WO 03/102009; or
by catalytic hydrogenation in the presence of platinum dioxide and acetic acid as solvent, which is disclosed in Tetrahedron lett. 1994, 35, 3025; International publications WO 94/26758 and WO 03/102009; or by catalytic hydrogenation in the presence of platinum over carbon (Pt /C) or rhodium over carbon (Rh /C) at 3-10 atm in solvent consisting of water-acetic acid-methanol mixture, which is disclosed in US 4,328,334; US 5,869,629; and EP 0,879,823. International publication WO 03/102009 describes hydrogenation of 6,9-Imino ether with platinum / carbon in water as solvent to which acid is added to adjust the pH till 4 followed by crystallization to obtain 9-Deoxo-9a-aza-9a-homoerythromycin A in crystalline form.

Reductive methylation of the secondary Amine is carried out to obtain Azithromycin. This process is described in US 4,517,359 and J. chem. Res. 1998, 132, which consists basically of the Escheweiler-Clarke reaction and uses formaldehyde in acetic acid or formaldehyde, and formic acid in carbon tetrachloride or chloroform for methylation.

Further EP 0,879,823 discloses preparation of Azithromycin from 6,9-Imino ether by carrying out the reduction and reductive methylation sequentially with the noble catalyst and hydrogen in the presence of formaldehyde. In this patent, the preferred catalyst is 5 % rhodium over carbon but platinum, palladium or rhuthenium, can also be used.
Further the product isolated in the prior art is Azithromycin in either monohydrate form or Azithromycin crude which has to be converted into its dihydrate form by crystallization, which is pharmaceutically acceptable form.

OBJECTS OF THE INVENTION

An object of the invention is to provide simple, efficient and economical alternative to known methods, to prepare 6,9-Imino ether from Erythromycin thiocyante.

Another object of the invention is to provide the simple, efficient and economical process for preparing 87 to 96 % pure 6,9-Imino ether from Erythromycin thiocyanate without isolating and purifying Erythromycin base and Erythromycin oxime.

Yet another object of the invention is to provide the simple, efficient and economical process for preparation of 6,9-Imino ether where reaction is carried out in biphasic system, where 6,9-Imino ether need not be further purified.

Yet another object of the invention is to provide the simple, efficient and economical process for preparation of 6,9-Imino ether where p-toluene sulfonyl chloride is employed in the form of solution in methylene chloride, which avoids decomposition of p-toluene sulfonyl chloride.

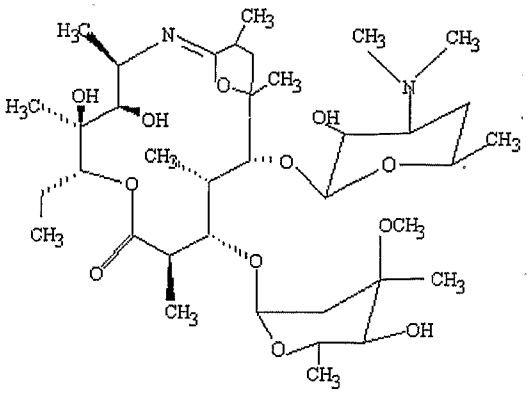
Yet another object of the invention is to provide the simple, efficient and economical process for preparation of 6,9-Imino ether where triethylamine, which is used in oximation of erythromycin base, is carried forward in the next step of Beckmann's rearrangement and used along with sodium carbonate as base, which increase the rate of the reaction.

Yet another object of the present invention is to provide the simple, efficient and economical process for preparation of 6,9-Imnio ether, where organic solvent can be recycled.

Yet another object of the present invention is to provide 87 to 96 % pure 6,9-Imino ether.

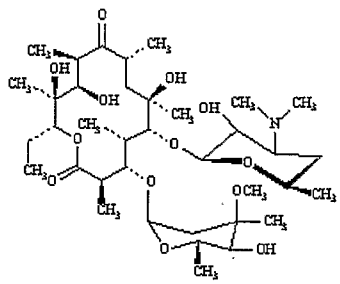
Detailed description of invention

According to the present invention there is provided a process for preparation of 6,9-Imino ether of formula (I);



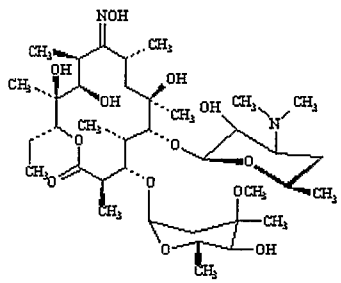
Formula I

without isolating Erythromycin base of formula (II);



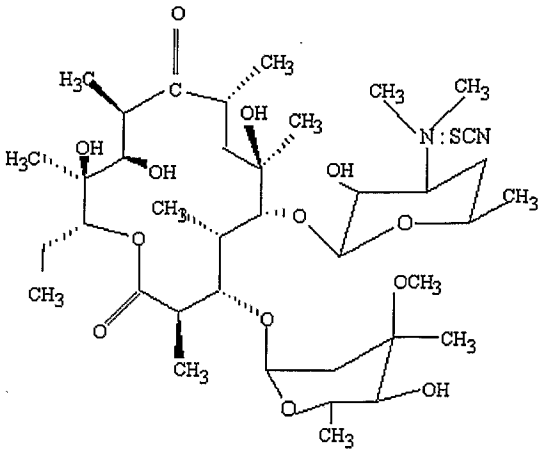
Formula II

and Erythromycin oxime of formula (IV);



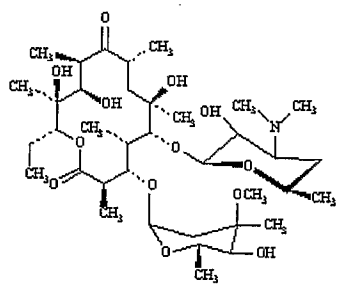
Formula IV

comprising dissolving Erythromycin thiocyanate of formula (III);



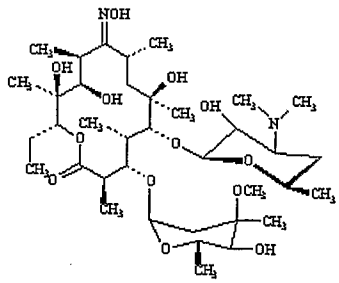
Formula III

in methylene chloride as a solvent by adding liquid ammonia as base with stirring to obtain clear solution; separating the organic layer from the solution, distilling out the solvent from the organic layer to obtain residue comprising Erythromycin base of formula (II);



Formula (II)

dissolving the residue in methanol followed by treatment with hydroxylamine hydrochloride in presence of triethylamine as base at reflux temperature; distilling out the methanol from the reaction mixture to obtain residue comprising Erythromycin oxime of formula (IV);



Formula (IV)

and triethylamine;

dissolving the residue comprising Erythromycin oxime and triethylamine in methylene chloride as a solvent adding liquid ammonia as a base with stirring to adjust the pH in the range of 9 to 10; separating the organic layer followed by washing the organic layer with water, cooling the organic layer to 0°-3° C, adding 1.24 % chilled aqueous sodium carbonate solution followed by adding 50 % solution of p-toluene sulfonyl chloride in methylene chloride to the organic layer, stirring the reaction mixture for 2-3 hours at 0°-3° C, adjusting the pH of the mixture to 5.4 to 5.5 by adding acetic acid, separating the aqueous layer from the mixture; adjusting pH of the aqueous layer to 12-13 by adding sodium hydroxide at temperature in the range of 25° to 30° C, filtering 6,9-Imino ether followed by washing with water and drying at 50°-60° C to obtain 87 to 96 % pure 6,9-Imino ether.

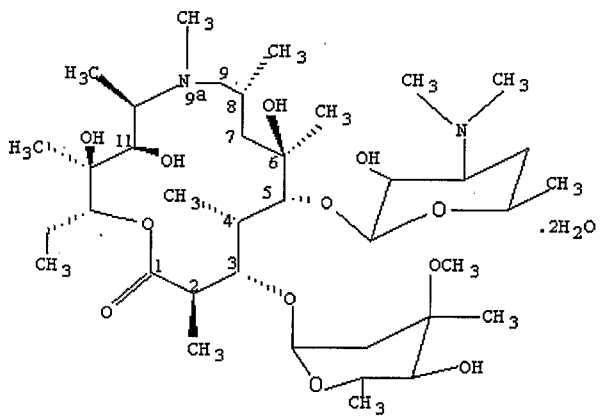
The ratio of methylene chloride to water used in preparation of 6,9-Imino ether from Erythromycin oxime is 0.41: 1.1 v/v.

The preferred ratio of methylene chloride to water used in preparation of 6,9-Imino ether from Erythromycin oxime is 0.46: 1 v/v.

The amount of triethylamine added is in the range of 30 to 35 % v/w with respect to Erythromycin thiocyanate.

The preferred amount of triethylamine added is 32 % v/w with respect to Erythromycin thiocyanate.

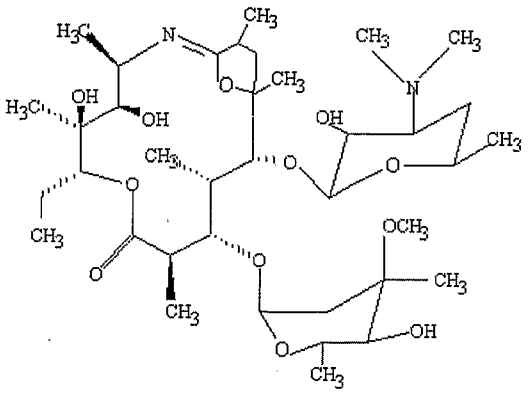
According to the present invention there is also provided a process for preparing Azithromycin dihydrate of formula (V);



Formula V

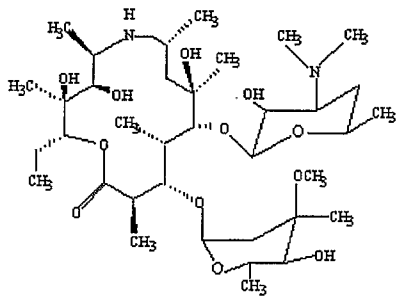
comprising

a) hydrogenating 6,9-Imino ether of formula (I);



Formula I

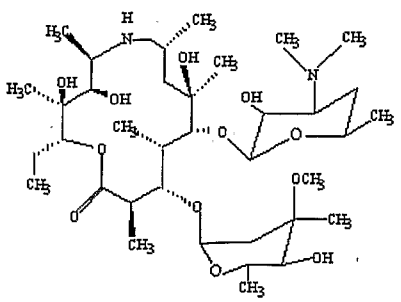
obtained according to the invention, in the presence of methanol as a solvent, to which 70 % perchloric acid is added to adjust the pH to 5.5 in presence 20 % by wt of Pt/C catalyst with respect to 6,9-Imino ether at temperature in the range of 30°-50° C and pressure in the range of 10-14 kg/cm^2 to achieve atleast 85 % conversion of 6,9-Imino ether to 9-Deoxo-9a-aza-9a-homoerythromycin A of formula (VI);



Formula VI

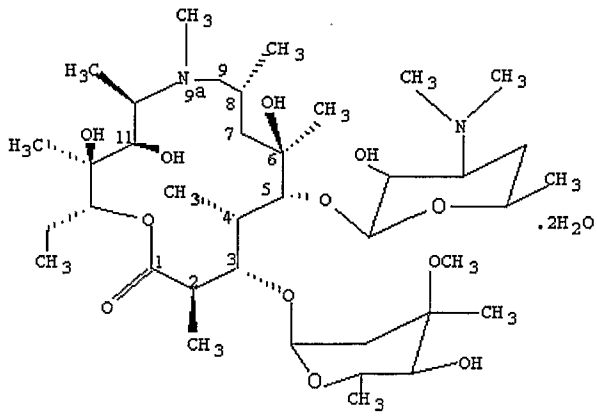
within 2-3 hours;

b) methylating the 9-Deoxo-9a-aza-9a-homoerythromycin A of formula (VI);



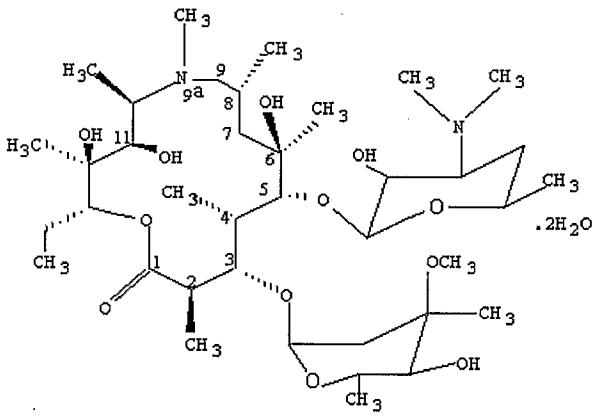
Formula VI

with formaldehyde and formic acid in presence of acetone or lower chain alcohol comprising methanol, ethanol or isopropanol as a solvent to obtain Azithromycin dihydrate of formula (V);



Formula V

c) isolating the Azithromycin dihydrate of formula (V);



Formula (V)

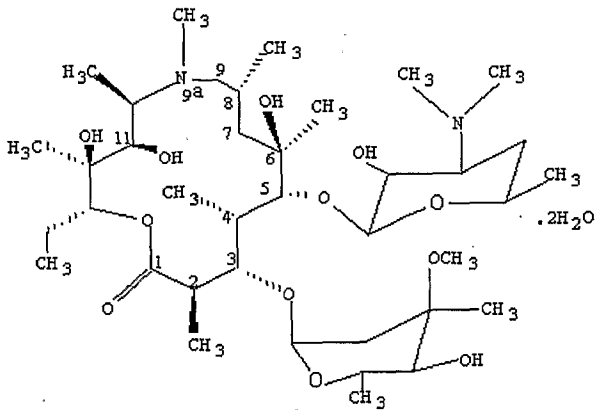
from methylation of 9-Deoxo-9a-aza-9a-homoerythromycin A mixture, and

d) purifying the Azithromycin dihydrate.

The hydrogenation of 6,9-Imino ether of step (a) is carried out preferably at temperature in the range of 40° -45° C and pressure in the range of 13 to 14 kg/cm^2.

The Azithromycin dihydrate is isolated in step (c) by separating acetone/ lower chain alcohol layer from the methylation of 9-Deoxo-9a-aza-9a-homoerythromycin A mixture, followed by adding water to the

acetone / alcohol layer within 12 hour while stirring, further stirring the mixture at 20° C for 12 hours, filtering the Azithromycin dihydrate of formula (V)



Formula V

washing the Azithromycin dihydrate with water and drying the Azithromycin dihydrate at 65° C.

The alcohol / acetone to water ratio used to isolate Azithromycin dihydrate is atleast 1:2.3 v/v.

The Azithromycin dihydrate is purified in step (d) by dissolving Azithromycin dihydrate in a solvent like acetone or lower chain alcohol comprising methanol, ethanol or isopropanol with stirring, adding charcoal to the solution with stirring, filtering the solution to obtain filtrate, adding water to filtrate at 50-55°C, cooling aqueous filtrate to room temperature, chilling the aqueous filtrate to 0° to 5° C, filtering Azithromycin dihydrate from the aqueous filtrate, washing the Azithromycin dihydrate with chilled water and drying Azithromycin dihydrate at 65° C.

The alcohol / acetone to water ratio used to purify the Azithromycin dihydrate is at least 1:6 v/v.

Thus, the invention provides a process for preparing 87-96 % pure 6,9-Imino ether from erythromycin thiocyanate without isolating and purifying Erythromycin base and Erythromycin oxime, thus minimizing steps. Further the present process for preparing 6,9-Imino ether is carried out in biphasic system (i.e. methylene chloride and water). p-toluene sulfonic acid formed during the process goes into methylene chloride along with the other impurities formed during the reaction and thus isolated 6,9-Imino ether need not to be further purified. In the invention, p-toluene sulfonyl chloride is employed in the form of solution in methylene chloride, which avoids decomposition and hence it is not required in excess amount. Triethylamine used in the preparation of Erythromycin oxime is carried forward in the next step of 6,9-Imino ether formation, which can react with hydrochloric acid released during 6,9-Imino ether preparation and triethylamine hydrochloride is formed. This is further neutralized with

sodium bicarbonate and triethylamine is again free to react with hydrochloric acid. This increases the rate of reaction and results in good yield. Thus, the process for preparing 6,9-Imino ether of the invention is simple, efficient and economical.

The invention is further illustrated by the following examples, which should not construe the effective scope of the claims.

Example 1A

Preparation of 6,9-Imino ether

To 100 gm of Erythromycin thiocynate, 450 ml of methylene chloride was added at 25°C. To this, 100 ml of Liquid ammonia was added and reaction mixture was stirred till it gets cleared solution. Once the reaction mixture was cleared, the layers were separated and organic layer was collected. Methylene chloride of organic layer was completely distilled off to obtain residue. To the residue, 100 ml of methanol was added followed by addition of 32 ml of triethylamine and 43.7 gm of hydroxyl amine hydrochloride. Reaction mixture was stirred at room temperature for 10 minutes and then the reaction mixture was refluxed for 25 hours. The reaction mixture was cooled to 55°C and the solvent was distilled off from the reaction mixture. The reaction mixture was further cooled to room temperature and 460 ml of methylene chloride was added to it. pH of the reaction mixture was adjusted to 9.8 to 10.0 by adding ammonia. Organic layer was separated from the reaction mixture and washed the organic layer with water. The organic layer was cooled to 0° to 3°C. Chilled Sodium bicarbonate solution (1.24 % w/v) was added to the reaction mixture followed by addition of p-toluene sulfonyl chloride solution (50 gm of p-toluene sulfonyl chloride + 100 ml methylene chloride) at 0° to 3°C and then reaction mixture was stirred for 2 hours at the same temperature. The pH of the reaction mixture was adjusted to 5.4 to 5.5 by adding acetic acid. Organic layer was separated from the reaction mixture. The pH of aqueous layer of the reaction mixture was adjusted to 12 to 13 by adding Sodium hydroxide solution at 30° C. 6,9-Imino ether was filtered from the reaction mixture. The 6,9-Imino ether was washed with water and dried at 50° to 60°C. The yield and purity of 6,9-Imino ether was 90% and 95 %.

6,9- Imino ether was characterized by IR (Refer Figure 1 of the Accompanying drawing).

Example 1 AA

(6,9-Imino ether is prepared by isolation of oxime as a free base)

100 gm of Erythromycin oxime which was prepared by known methods and solution of p-toluene sulfonyl chloride in methylene chloride (46 gm p-toluene sulfonyl chloride and 200 ml methylene chloride), was added to the solution of 1000 ml of water and 12.5 gm of sodium bicarbonate which was cooled to 0°-5°C while stirring. The reaction mixture was stirred for three hours. The reaction was monitored by TLC. After the completion of reaction, pH of the reaction mixture was adjusted to 5.3 to 5.5 by adding acetic acid and then again stirred for 15 minutes. Organic layer was separated from the aqueous reaction mixture. The pH of aqueous reaction mixture was adjusted to 8.5 to 9.0 by adding 12% Sodium hydroxide. Aqueous layer was concentrated and again pH was adjusted to 12 to 12.5 by adding 10% Sodium hydroxide solution. The aqueous layer was concentrated to give 6,9-Imino ether. The yield and purity of 6,9-Imino ether was 70% and 65%

Example 1B

Hydrogenation of 6,9-Imino ether to 9-Deoxo-9a-aza-9a-homoerythromycin A

To the 650 ml of methanol, 100 gm of 6,9-Imino ether (prepared according to example 1A) was added. The methanolic solution of 6,9-Imino ether was filtered after Charcoal treatment. The filtrate was chilled to 5° to 6°C. To this mixture, 70% perchloric acid solution was added to adjust the pH of the reaction mixture to 5.5. 20 gm of Pt/C catalyst was added to the reaction mixture. The reaction mixture was flushed with N_2 and then with H_2. The hydrogenation was carried out at temperature of 42° C and pressure of 14 kg/cm^2 with stirring for 3 hours. The reaction was monitored by HPLC. The spent catalyst was filtered from the reaction mixture. Methanol was distilled out from the reaction mixture to obtain residue. 700 ml of water was added to the residue. The pH of the residue was adjusted with 5 % aqueous sodium hydroxide solution to 12-12.5. The precipitated 9-Deoxo-9a-aza-9a-homoerythromycin A was filtered and washed with water. The product thus obtained was dried at 65° C. The yield and purity of 9-Deoxo-9a-aza-9a-homoerythromycin A was 91.5 % and 91%.
The Pt/C catalyst comprised reactivated Pt/C catalyst along with fresh Pt/C catalyst in the ratio of 98:2.

Example 1C

Preparation of Azithromycin dihydrate

To the 300 ml of acetone, 100 gm 9-Deoxo-9a-aza-9a-homoerythromycin A (prepared according to Example 1B) was added. The mixture of 17.49 ml of formic acid and 17.49 ml of formaldehyde was

prepared. This mixture was added to 9-Deoxo-9a-aza-9a-homoerythromycin A solution within 5 to 6 hours at 40° C. The reaction was monitored for 2 hours at 40° to 45° C. The pH of the reaction mixture was adjusted to 11 to 11.5 by adding sodium hydroxide solution. The charcoal treatment was given to reaction mixture. The acetone layer was separated from the reaction mixture. To the acetone layer, 650 ml water was added within 12 hour while stirring. The mixture was stirred at 20° C for 12 hours. After the completion of reaction, Azithromycin dihydrate was filtered and washed with water. Azithromycin dihydrate was dried at 65° C. The yield and purity of the Azithromycin dihydrate was 87 % and 98 %.

Example 1 D

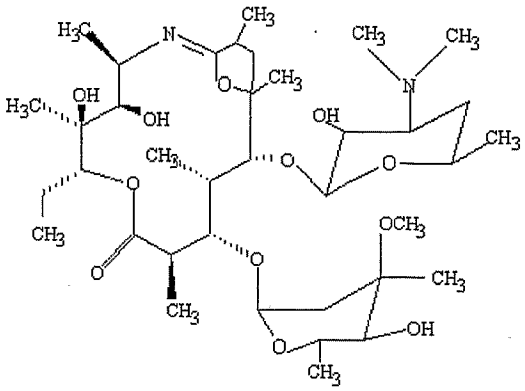
Purification of Azithromycin dihydrate

To 10 gm of Azithromycin dihydrate, 30 ml acetone was added for 30 minutes with stirring till the clear solution obtained. 0.3 gm charcoal was added to this solution and the mixture was stirred for 30 minutes and subsequently filtered. To the filtrate, 180 ml of water was added at 50° to 55° C within 12 hour. The aqueous filtrate was cooled to room temperature and then chilled to 0° to 5° C. Azithromycin dihydrate was filtered from the aqueous filtrate and washed with chilled water (0° to 5° C). Azithromycin dihydrate was dried at 65° C. The yield and purity of Azithromycin dihydrate was 95 % and 100 %.

Azithormycin dihydrate was characterized by IR (Refer Figure 2 of the Accompanying drawing).

CLAIMS

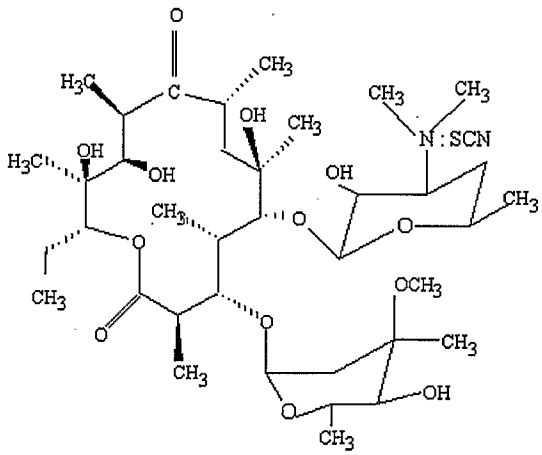
1. A process for preparation of 6,9-Imino ether of formula (I);



Formula (I)

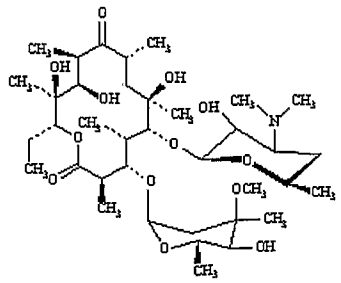
the process comprising

dissolving Erythromycin thiocyanate of formula (III);



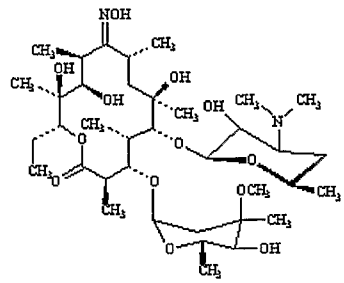
Formula III

in methylene chloride as a solvent by adding liquid ammonia as base with stirring to obtain clear solution; separating the organic layer from the solution, distilling out the solvent from the organic layer to obtain residue comprising Erythromycin base of formula (II);



Formula (II)

dissolving the residue in methanol followed by treatment with hydroxylamine hydrochloride in presence of triethylamine as base at reflux temperature; distilling out the methanol from the reaction mixture to obtain residue comprising Erythromycin oxime of formula (IV);



Formula (IV)

and triethylamine;

and

dissolving the residue comprising Erythromycin oxime and triethylamine in methylene chloride as a solvent adding liquid ammonia as a base to adjust the pH in the range of 9 to 10; separating the organic layer followed by washing with water, cooling the organic layer to 0-3° C, adding 1.24 % chilled aqueous sodium carbonate solution followed by adding solution of 50 % p-toluene sulfonyl chloride in methylene chloride to the organic layer, stirring the reaction mixture for 2-3 hours at 0-3° C, adjusting the pH of the mixture to 5.4 to 5.5 by adding acetic acid, separating the aqueous layer from the mixture; adjusting pH of the aqueous layer to 12-13 by adding sodium hydroxide at temperature in the range of 25 to 30° C, filtering 6,9-Imino ether followed by washing with water and drying at 50-60° C to obtain pure 6,9-Imino ether.

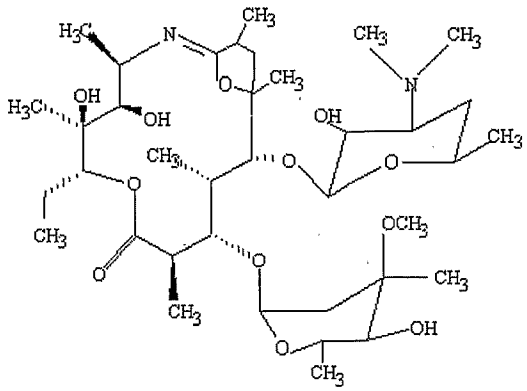
2. The process as claimed in claim 1, wherein the ratio of methylene chloride to water used in preparation of 6,9-Imino ether from Erythromycin oxime is 0.41 : 1.1 v/v.

3. The process as claimed in claim 2, wherein the preferred ratio of methylene chloride to water used in preparation of 6,9-Imino ether from Erythromycin oxime is 4.6 : 1 v/v .

4. The process as claimed in claim 1, wherein the amount of triethylamine added is in the range of 30 to 35 % v/w with respect to Erythromycin thiocyanate.

5. The process as claimed in claim 1, wherein the preferred amount of triethylamine added is 32 % v/w with respect to Erythromycin thiocyanate.

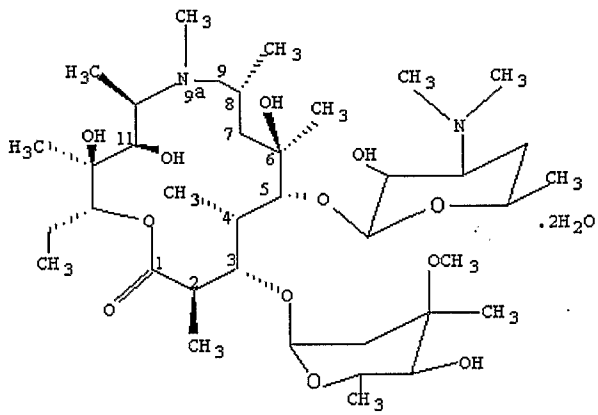
6. A 6,9-Imino ether of formula (I)



Formula I

prepared by the process as claimed in any one of the claim 1 to 5.

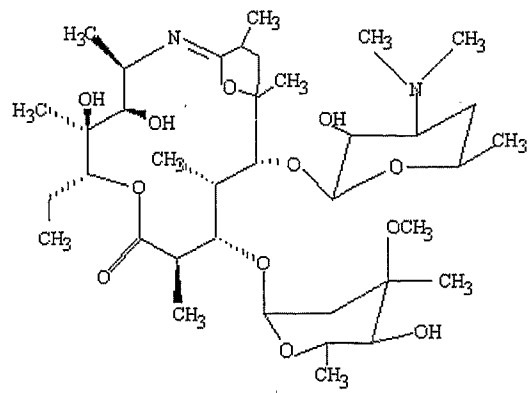
7. A process for preparing Azithromycin dihydrate of formula (V);



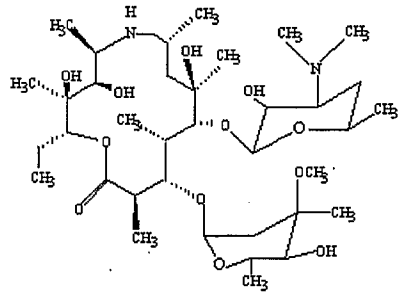
Formula (V)

comprising

a) hydrogenating 6,9-Imino ether of formula (I);



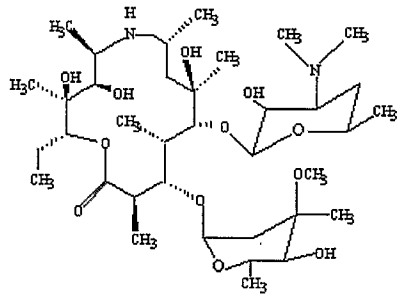
prepared according to any one of claim 1 to 6, in the presence of methanol as a solvent, to which 70 % perchloric acid is added to adjust the pH to 5.5 in presence 20 % by wt of Pt/C catalyst with respect to 6,9-Imino ether at temperature in the range of 30°-50° C and pressure in the range of 10-14 kg/cm^2 to achieve atleast 85 % conversion of 6,9-Imino ether to 9-Deoxo-9a-aza-9a-homoerythromycin A of formula (VI);



Formula (VI)

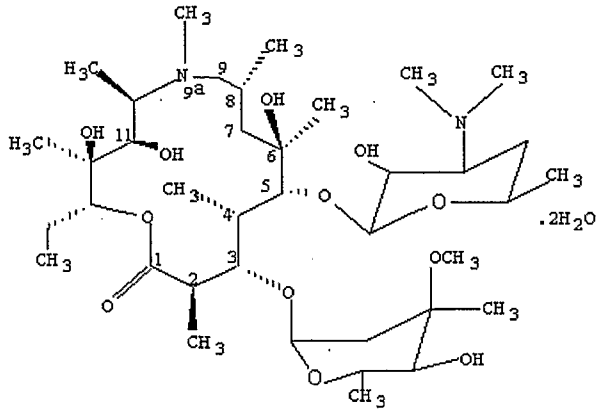
within 2-3 hours ;

b) methylating the 9-Deoxo-9a-aza-9a-homoerythromycin A of formula (VI);



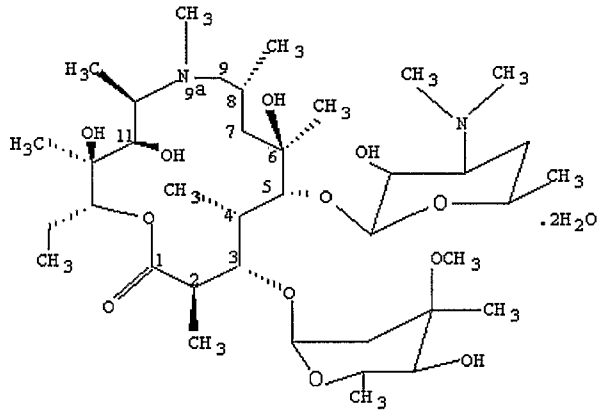
Formula VI

with formaldehyde and formic acid in presence of acetone or lower chain alcohol comprising methanol, ethanol or isopropanol as a solvent to obtain Azithromycin dihydrate of formula (V);



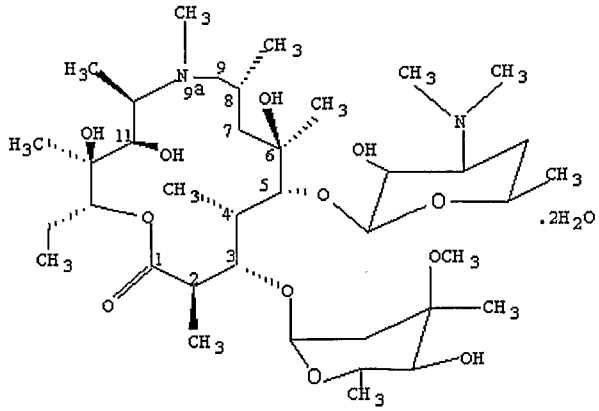
Formula V

c) isolating the Azithromycin dihydrate of formula (V);



Formula V

from methylation of 9-Deoxo-9a-aza-9a-homoerythromycin A mixture by separating acetone/ lower chain alcohol layer from the methylation of 9-Deoxo-9a-aza-9a-homoerythromycin A mixture, followed by adding water to the acetone / alcohol layer within 12 hour while stirring, further stirring the mixture at 20° C for 12 hours; filtering the Azithromycin dihydrate of formula (V);



Formula V

washing the Azithromycin dihydrate with water and drying the Azithromycin dihydrate at 65° C;

d) purifying Azithromycin dihydrate obtained in step (c) by dissolving Azithromycin dihydrate in a solvent like acetone or lower chain alcohol comprising methanol, ethanol or isopropanol with stirring, adding charcoal to the solution with stirring, filtering the solution to obtain filtrate, adding water to filtrate at 50°-55°C, cooling aqueous filtrate to room temperature, chilling the aqueous filtrate to 0° to 5° C, filtering Azithromycin dihydrate from the aqueous filtrate; washing the Azithromycin dihydrate with chilled water and drying Azithromycin dihydrate at 65° C.

8. The process as claimed in claim 7, wherein the hydrogenation of 6,9-Imino ether of step is carried out preferably at temperature in the range of 40-45° C and pressure in the range of 13 to 14 kg/cm^2.

9. The process as claimed in claim 7, wherein the alcohol / acetone to water ratio used to isolate Azithromycin dihydrate in step (C) is 1:2.3 atleast v/v.

10. The process as claimed in claim 7, wherein the alcohol / acetone to water ratio used to purify the Azithromycin dihydrate in step (d) is at least 1:6 v/v.