

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-062881-00003-0000

SECRETARIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
DE PATENTES Y MARCAS
FOLIO 2

Ref: Expediente No. 07-062.881

Solicitud de patente titulada: "MACROLIDOS BASADOS EN ERITROMICINA,
SU PREPARACION, INTERMEDIARIOS Y COMPOSICIONES PARA TRATAR
INFECCIONES BACTERIANAS".

Solicitante: PFIZER PRODUCTS INC.

Nuestra Ref.: P2007/000098

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 596

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina. Adjunto recibo por el monto de \$210.000 pesos para cubrir la tasa correspondiente, según la Resolución 44372 del año 2007.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por \$210.000 pesos

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

SECRETARIA DE INDUSTRIA Y COMERCIO



No. 07 062881-00003-0000

DEPARTAMENTO DE INDUSTRIA Y COMERCIO
SECRETARIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
CALLE 100 No. 8A-37, Piso 10, Bogotá D.C., Colombia
Tel: 57 1 601-7700, Fax: 57 1 601-7799, office@olarteraisbeck.com, www.olarteraisbeck.com

Ref: Expediente No. 07-062.881

Solicitud de patente titulada: "MACROLIDOS BASADOS EN ERITROMICINA,
SU PREPARACION, INTERMEDIARIOS Y COMPOSICIONES PARA TRATAR
INFECCIONES BACTERIANAS".

Solicitante: PFIZER PRODUCTS INC.

Nuestra Ref.: P2007/000098

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 596

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina. Adjunto recibo por el monto de \$210.000 pesos para cubrir la tasa correspondiente, según la Resolución 44372 del año 2007.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por \$210.000 pesos

2



No. 07-062881-00003-0000

Dep. 2020 NUL CREACIONE
 Dep. 2020 NUL CREACIONE
 Dep. 2020 NUL CREACIONE

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 89,264
 FECHA : NOVIEMBRE 13 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	81235490	12/11/2008	4,818,000.00

***** C O N C E P T O *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILID	210,000.00
	TOTAL :	\$ 210,000.00

SON: DOSCIENTOS DIEZ MIL PESOS

RESPONSABLE : 

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-62881

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **596** DE

FECHA **30 DE SEPTIEMBRE DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR

LA LEY EXPIRA EL **30 DE DICIEMBRE DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X



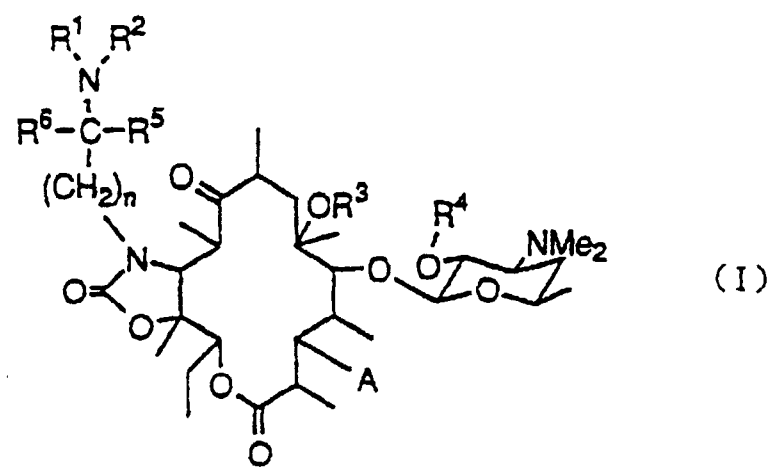
(12) **EUROPEAN PATENT APPLICATION**
 published in accordance with Art. 158(3) EPC

- | | |
|--|--|
| (43) Date of publication:
29.09.1999 Bulletin 1999/39 | (51) Int. Cl. ⁶ : C07H 17/08 |
| (21) Application number: 97943199.6 | (86) International application number:
PCT/JP97/03687 |
| (22) Date of filing: 14.10.1997 | (87) International publication number:
WO 98/23628 (04.06.1998 Gazette 1998/22) |

(84) Designated Contracting States: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE (30) Priority: 27.11.1996 JP 31580596 (71) Applicant: TAISHO PHARMACEUTICAL CO. LTD Tokyo 171 (JP) (72) Inventors: • ASAKA, Toshifumi Saitama 365 (JP) • KASHIMURA, Masato 702-12, Shimacho, Omiya-shi, Saitama 330 (JP)	• MATSUURA, Akiko Tokorozawa-shi, Saitama 359 (JP) • SUGIMOTO, Tomohiro Omiya-shi, Saitama 330 (JP) • TANIKAWA, Tetsuya Fuchu-shi, Tokyo 183 (JP) • ISHII, Takaaki Saitama 336 (JP) (74) Representative: Weisert, Annekäte, Dipl.-Ing. Dr.-Ing. Patentanwälte Kraus Weisert & Partner Thomas-Wimmer-Ring 15 80539 München (DE)
---	--

(54) **ERYTHROMYCIN A DERIVATIVES**

(57) An erythromycin A derivative represented by Formula (I):



[wherein n is an integer of from 1 to 4, R¹ is a group represented by the formula:

Description

Technical Field

[0001] The present invention relates to novel derivatives of antibiotic erythromycin A.

Background Art

[0002] Erythromycin A is an antibiotic clinically widely used as an agent for treating infectious diseases caused by Gram-positive bacteria, mycoplasmas, etc. However, erythromycin A is decomposed by the gastric acid due to instability to acids, and thus have a drawback of no constancy of movement in the body. Hitherto many erythromycin A derivatives have been prepared for the purpose of the improvement of the biological or pharmacological properties. For example, it is reported that 6-O-methylerythromycin A derivatives have an improved stability to acids and have a superior in vivo antibacterial activity in comparison with erythromycin A when administered orally (U.S. Patent No. 4331803). There are also recent reports relating to 11,12-cyclic carbamate derivatives prepared from 6-O-methylerythromycin A as a starting material with the aim of expansion of antibacterial spectrum as well as a stability to acids (EP. patent No. 487411 and U.S. Patent No. 4742049). In addition, the present inventors refer to the antibacterial activity of the ester derivatives at the 3-position (EP. Patent No. 619320).

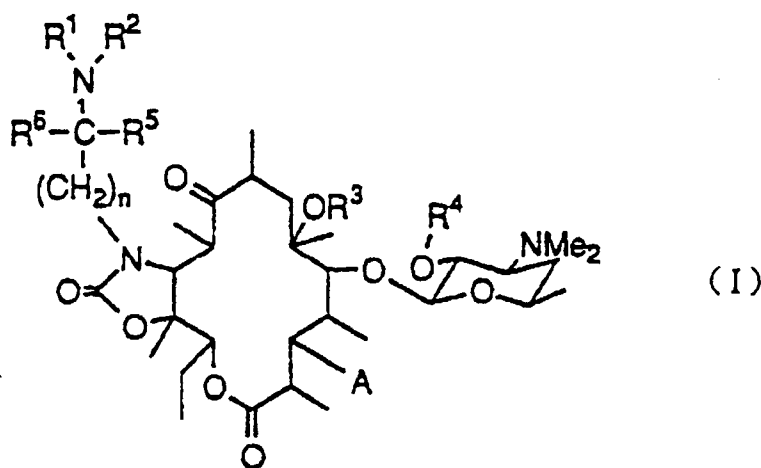
[0003] An object of the present invention is to provide a novel antibiotic erythromycin A derivative or a salt thereof having a strong antibacterial activity against not only known erythromycin-sensitive bacteria but also erythromycin-resistant bacteria which recently are showing a tendency to increase, and a composition comprising the same as an effective component.

[0004] Other objects of the present invention are to provide a method for the treatment of a bacterially infectious disease which comprises administering a pharmaceutically effective amount of the above-mentioned erythromycin A derivative or a salt thereof to patients, and use of the above-mentioned erythromycin A derivative or a salt thereof for the treatment of a bacterially infectious disease.

Disclosure of the Invention

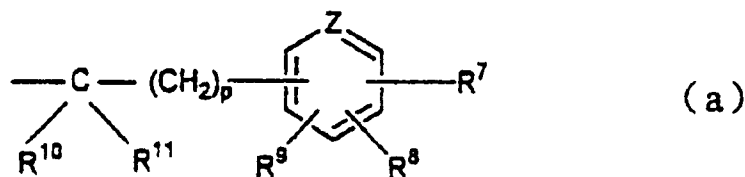
[0005] As a result of various researches on the antibacterial activity of erythromycin A derivatives, the present inventors have found that, among 6-O-methylerythromycin A 11,12-cyclic carbamate derivatives, in particular, the derivatives which are substituted by a substituted aminoalkyl group on the nitrogen atom forming the cyclic carbamate ring and converted into an ester at the 3-position have a strong antibacterial activity against erythromycin-resistant bacteria, and have further studied about analog compounds thereof, whereby the present invention has been accomplished.

[0006] The present invention relates to an erythromycin A derivative represented by Formula (I):

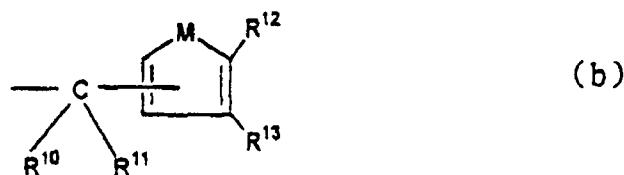


[wherein n is an integer of from 1 to 4,

R¹ is a group represented by the formula:

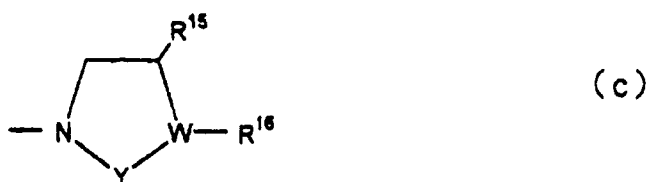


10 (wherein p is 0 or 1, Z is a nitrogen atom or CH; R⁷, R⁸ and R⁹ are each a hydrogen atom, a halogen atom, an alkyl group having 1 to 5 carbon atoms, a nitro group, an amino group, an acetylamino group, an amino group substituted by 1 or 2 alkyl groups having 1 to 3 carbon atoms, a hydroxyl group, a cyano group, an alkyl group having 1 to 3 carbon atoms substituted by 1 to 3 halogen atoms, an alkoxy group having 1 to 5 carbon atoms or a phenyl group, or R⁷ and R⁸ are attached to the carbon atoms which are attached side by side, and together form a methylenedioxy group, or R⁷ and R⁸ are attached to the carbon atoms which are attached side by side, and together with the carbon atoms to which they are attached form a benzene ring, R¹⁰ and R¹¹ are each a hydrogen atom, or R¹⁰ and R¹¹ together form an oxo group), a group represented by the formula:



25 (wherein R¹⁰ and R¹¹ are as defined above, M is an oxygen atom, a sulfur atom, -NCH₃ or -NH, or R¹² and R¹³ are each a hydrogen atom, or R¹² and R¹³ together with the carbon atoms to which they are attached form a benzene ring), a pyridylacetyl group, a cycloalkylmethyl group having 4 to 8 carbon atoms or a 1,2-bis(ethoxycarbonyl)vinyl group,

30 R² is the same group as defined for R¹, a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkanoyl group having 2 to 6 carbon atoms or an alkoxy carbonyl group having 2 to 6 carbon atoms, R¹ and R² together form a group of the formula: =CH-R¹⁴ (wherein R¹⁴ is a phenyl group, a phenyl group substituted by nitro group(s), cyano group(s) or alkyl group(s) having 1 to 3 carbon atoms substituted by 1 to 3 halogen atoms, or an imidazolyl group), or R¹ and R² together with the nitrogen atom to which they are attached form a group represented by the formula:

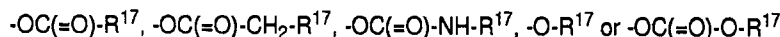


45 (wherein W is CH, a carbon atom or a nitrogen atom, Y is a group of -C(=O)- or -(CH₂)_m- (wherein m is 1 or 2), R¹⁵ and R¹⁶ are each a hydrogen atom or when W is a carbon atom, R¹⁵ and R¹⁶ together with the carbon atoms to which they are attached form a benzene ring or a naphthalene ring,

R³ is a hydrogen atom, an alkyl group having 1 to 5 carbon atoms or a cinnamyl group,

R⁴ is a hydrogen atom, an acetyl group, an ethylsuccinyl group or a nicotinoyl group,

50 A is a group represented by the formula:



55 (wherein R¹⁷ is a phenyl group, a pyridyl group, a quinolyl group, or those groups which are each substituted by 1 to 3 members selected by the group consisting of an alkyl group having 1 to 5 carbon atoms, a nitro group, an alkoxy group having 1 to 5 carbon atoms and a halogen atom), and

R⁵ and R⁶ are each a hydrogen atom or an alkyl group having 1 to 5 carbon atoms] or a pharmaceutically acceptable salt thereof.

[0007] In the present invention, the alkyl group having 1 to 5 carbon atoms refers to a straight or branched chain alkyl group, for example, a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, a tert-butyl group or a pentyl group. The alkoxy group having 1 to 5 carbon atoms refers to a straight or branched chain alkoxy group, preferably a methoxy group or an ethoxy group. The halogen atom refers to a fluorine atom, a chlorine atom, a bromine atom or an iodine atom. Examples of the 6-membered ring and the condensed ring in the group represented by Formula (a) are a benzene ring, a naphthalene ring, a pyridine ring, a quinoline ring and an isoquinoline ring. Examples of the 5-membered ring and the condensed ring in the group represented by Formula (b) are a furan ring, a thiophene ring, a pyrrole ring, a benzofuran ring, a benzothiophene ring and an indole ring. Examples of the 5-membered ring, the 6-membered ring and the condensed ring in the group represented by Formula (c) are a pyrrolidine ring, a piperidine ring, an imidazolidine ring, an isoindoline ring, a 1,2,3,4-tetrahydroisoquinoline ring and a 2-oxoisoindoline ring.

[0008] The amino group substituted by 1 or 2 alkyl groups having 1 to 3 carbon atoms as defined for R^7 , R^8 and R^9 is preferably an amino group substituted by methyl group(s), more preferably a dimethylamino group.

[0009] The alkyl group having 1 to 3 carbon atoms substituted by 1 to 3 halogen atoms as defined for R^7 , R^8 , R^9 and R^{14} is preferably an alkyl group substituted by fluorine atom(s), more preferably a methyl group substituted by fluorine atom(s), and most preferably a trifluoromethyl group.

[0010] The pharmaceutically acceptable salt refers to a salt used in chemotherapy or prophylaxis of bacterially infectious diseases, for example, a salt with acetic acid, propionic acid, butyric acid, formic acid, trifluoroacetic acid, maleic acid, tartaric acid, citric acid, stearic acid, succinic acid, ethylsuccinic acid, lactobionic acid, gluconic acid, glucoheptonic acid, benzoic acid, methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, laurylsulfuric acid, malic acid, aspartic acid, glutaminic acid, adipic acid, cysteine, N-acetylcysteine, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, hydroiodic acid, nicotinic acid, oxalic acid, picric acid, thiocyanic acid, undecanic acid, polyacrylate or carboxyvinyl polymer.

[0011] The compounds of the present invention can be prepared, for example, by the following methods, but not limited thereto.

the present invention against various experimental bacteria was measured using sensitive disc media (produced by Eiken Chemical Co.) according to the MIC measuring method specified by the Japan Society of Chemotherapy. Clarithromycin was used as a comparative drug. The results are expressed as MIC value (Minimum Inhibitory Concentration, $\mu\text{g/ml}$), and shown in Table 1. The compound obtained in Example 4 shows to have a strong antibacterial activity not only against erythromycin-sensitive bacteria but also erythromycin-resistant bacteria.

[Table 1]

In Vitro Antibacterial Activity: MIC ($\mu\text{g/ml}$)

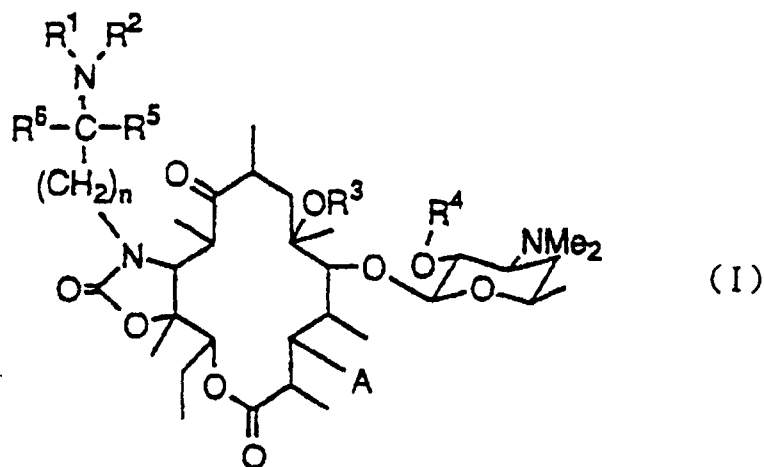
Microorganism \ Compound	Compound of Example 4	Comparative drug
<u>S. aureus</u> 209P-JC	0.10	0.10
<u>S. aureus</u> Smith	0.20	0.20
<u>S. aureus</u> J-109	>100	>100
<u>S. aureus</u> B1	0.39	>100
<u>S. pneumoniae</u> IID 553	0.10	0.10
<u>S. pneumoniae</u> BM 210	0.39	1.56
<u>S. pneumoniae</u> BM 205	0.39	>100

Industrial Applicability

[0099] The compounds of the present invention have an antibacterial activity against not only erythromycin-sensitive bacteria but also erythromycin-resistant bacteria. Therefore, the compounds of the present invention are useful as antibacterial agents for the treatment of bacterially infectious diseases in human beings and animals (including farm animals).

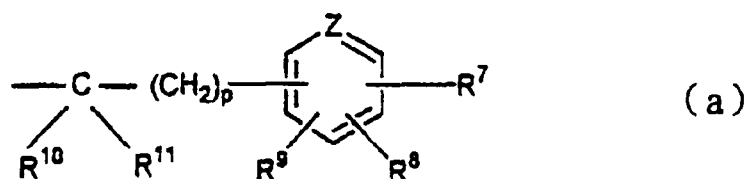
Claims

1. An erythromycin A derivative represented by Formula (I):

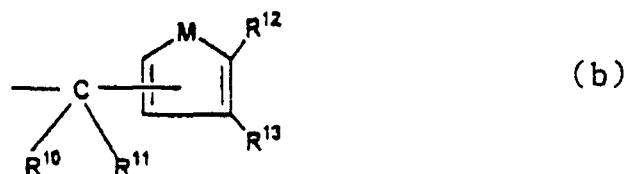


[wherein n is an integer of from 1 to 4,

R¹ is a group represented by the formula:

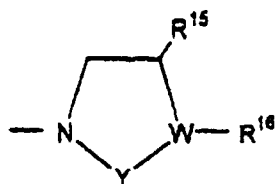


(wherein p is 0 or 1, Z is a nitrogen atom or CH; R⁷, R⁸ and R⁹ are each a hydrogen atom, a halogen atom, an alkyl group having 1 to 5 carbon atoms, a nitro group, an amino group, an acetylamino group, an amino group substituted by 1 or 2 alkyl groups having 1 to 3 carbon atoms, a hydroxyl group, a cyano group, an alkyl group having 1 to 3 carbon atoms substituted by 1 to 3 halogen atoms, an alkoxy group having 1 to 5 carbon atoms or a phenyl group, or R⁷ and R⁸ are attached to the carbon atoms which are attached side by side, and together form a methylenedioxy group, or R⁷ and R⁸ are attached to the carbon atoms which are attached side by side, and together with the carbon atoms to which they attached form a benzene ring, R¹⁰ and R¹¹ are each a hydrogen atom, or R¹⁰ and R¹¹ together form an oxo group), a group represented by the formula:



(wherein R¹⁰ and R¹¹ are as defined above, M is an oxygen atom, a sulfur atom, -NCH₃ or -NH, or R¹² and R¹³ are each a hydrogen atom, or R¹² and R¹³ together with the carbon atoms to which they are attached form a benzene ring), a pyridylacetyl group, a cycloalkylmethyl group having 4 to 8 carbon atoms or a 1,2-bis(ethoxycarbonyl)vinyl group,

R² is the same group as defined for R¹, a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkanoyl group having 2 to 6 carbon atoms or an alkoxy carbonyl group having 2 to 6 carbon atoms, R¹ and R² together form a group of the formula: =CH-R¹⁴ (wherein R¹⁴ is a phenyl group, a phenyl group substituted by nitro group(s), cyano group(s) or alkyl group(s) having 1 to 3 carbon atoms substituted by 1 to 3 halogen atoms, or an imidazolyl group), or R¹ and R² together with the nitrogen atom to which they are attached form a group represented by the formula:

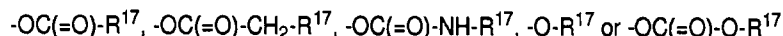


(wherein W is CH, a carbon atom or a nitrogen atom, Y is a group of $-C(=O)-$ or $-(CH_2)_m-$ (wherein m is 1 or 2), R^{15} and R^{16} are each a hydrogen atom or when W is a carbon atom, R^{15} and R^{16} together with the carbon atoms to which they are attached form a benzene ring or a naphthalene ring,

R^3 is a hydrogen atom, an alkyl group having 1 to 5 carbon atoms or a cinnamyl group,

R^4 is a hydrogen atom, an acetyl group, an ethylsuccinyl group or a nicotinoyl group,

A is a group represented by the formula:



(wherein R^{17} is a phenyl group, a pyridyl group, a quinolyl group, or those groups which are each substituted by 1 to 3 members selected by the group consisting of an alkyl group having 1 to 5 carbon atoms, a nitro group, an alkoxy group having 1 to 5 carbon atoms and a halogen atom), and

R^5 and R^6 are each a hydrogen atom or an alkyl group having 1 to 5 carbon atoms] or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising an effective amount of the erythromycin A derivative or a pharmaceutically acceptable salt thereof according to Claim 1.
3. An antibacterial preparation comprising the erythromycin A derivative or the pharmaceutically acceptable salt thereof according to Claim 1 as an effective component.
4. A method for the treatment of a bacterially infectious disease which comprises administering a pharmaceutically effective amount of the erythromycin A derivative or a pharmaceutically acceptable salt thereof according to Claim 1 to a patient.
5. Use of the erythromycin A derivative or a pharmaceutically acceptable salt thereof according to Claim 1 for the treatment of a bacterially infectious disease.