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MEDICINAL COMPOSITION AS A REMEDY FOR NON-SMALL CELL LUNG CANCER

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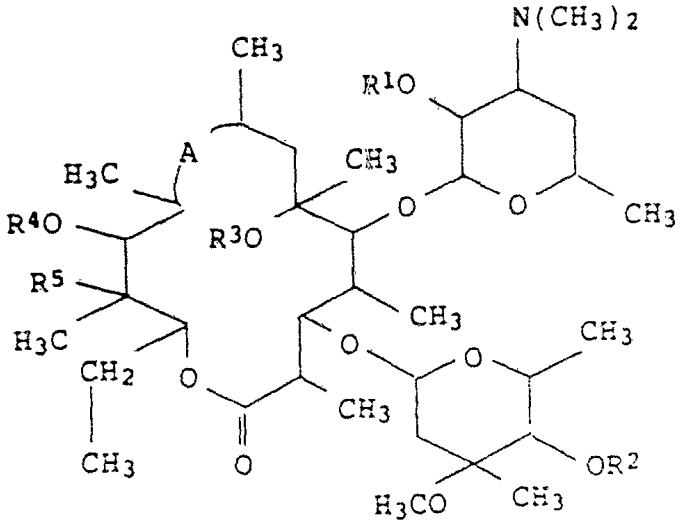
(57) Claim

1. A method for the treatment of non-small cell lung cancer in a human including administering to the human an effective amount of a compound represented by the formula:



(I)

[wherein R^1, R^2, R^3 and R^4 are each a hydrogen atom, an optionally substituted alkyl group or an acyl group, R^5 is a hydrogen atom or $-OR^6$ (wherein R^6 is a hydrogen atom, an optionally substituted alkyl group or an acyl group, or R^4 and R^6 together form $>C=O$), and

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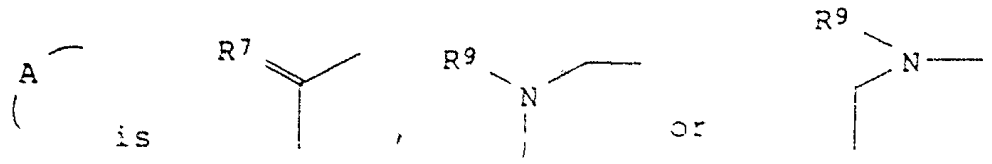

(wherein R^{7} is an oxygen atom or =N-O-(CH$_2$)$_n$-X-R^{8} (wherein n is an integer of 1 to 6, X is an oxygen atom, a sulphur atom or -NY- (wherein Y is a hydrogen atom or an optionally substituted hydrocarbon group), and R^{8} is an optionally substituted hydrocarbon group) and R^{9} is a hydrogen atom or an optionally substituted hydrocarbon group)] or a pharmaceutically acceptable salt thereof.

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(54) Title : MEDICINAL COMPOSITION AS A REMEDY FOR ~~NONSMALL~~ non-small CELL LUNG CANCER

(54) 発明の名称 非小細胞肺癌の治療のための医薬組成物

(57) Abstract

Fourteen- and fifteen-membered macrolide compounds such as clarithromycin and erythromycin B have a potent antitumor effect against nonsmall cell lung cancer which has been believed to be one of the tumors that are most difficult to subject to surgical operation and chemotherapy, and are hence useful as a practical remedy therefor.

（５７）要約

クラリスロマイシン、エリスロマイシンＢなどの１４又は１５員環のマクロライド系化合物は、手術が困難で化学療法が最も難しい腫瘍の一つとされてきた非小細胞肺癌に対して大きな抗腫瘍効果を発揮し、実用的な非小細胞肺癌の治療剤として有用である。

DESCRIPTION

PHARMACEUTICAL COMPOSITION FOR TREATMENT OF NON-SMALL CELL LUNG CANCER

Technical Field

The present invention relates to a pharmaceutical composition effective as an anticancer agent for non-small cell lung cancer comprising a 14- or 15-membered-ring macrolide compound as an effective ingredient.

Background Art

In many countries including Japan, Europe and America, the number of patients with lung cancer is fairly large and further increasing year after year with deterioration of atmospheric environment on the earth, contrary to the number of patients with gastric cancer which is reducing year after year. Lung cancers can be histologically classified into non-small cell lung cancers (e.g. squamous cell carcinoma, adeno carcinoma, large cell carcinoma, etc.) and small cell lung cancer. Non-small cell lung cancer has very largely different biological properties and responses to chemotherapeutics from those of small cell lung cancer. Thus, chemotherapeutic formulas are different between these two types of lung cancer.

It is reported that non-small cell lung cancers are the tumors of which chemotherapy is the most difficult, and any useful therapies for advanced inoperable cancers have not been established (Journal of Clinical Oncology, vol. 10, pp. 829 - 838 (1992)). The combination therapy of cisplatin and interferon is reported (European Journal of Cancer, vol. 30A, No. 1, pp. 11 - 15 (1994)). However, this remedy can not be widely acceptable because of insufficient therapeutic effect and harmful side effects.

Japanese Patent Kokai 5-163293 refers to some specified antibiotics of 16-membered-ring macrolides as a drug delivery carrier capable of transporting anthoracycline-type anticancer drugs into the lungs for the treatment of lung cancers. However, the macrolide antibiotics specified herein are disclosed to be only a drug carrier, and there is no reference to the therapeutic use of macrolides against non-small cell lung cancers.

WO 93/18652 refers to the effectiveness of the specified 16-membered-ring macrolides such as bafilomycin, etc. in treating non-small cell lung cancers, but they have not yet been clinically practicable.

Pharmacology, vol. 41, pp. 177 - 183 (1990) describes that a long-term use of erythromycin increases productions of interleukins 1, 2 and 4, all of which contribute to host immune responses, but there is

no reference to the effect of this drug on non-small cell lung cancers.

Tetragenesis, Carcinogenesis, and Mutagenesis, vol. 10, pp. 477 - 501 (1990) describes that some of antimicrobial drugs can be used as an anticancer agent, but does not refer to their application to non-small cell lung cancers.

In addition, interleukins are known to have an antitumor effect, but have not been reported to be effective against non-small cell lung cancers.

Any 14 - or 15-membered-ring macrolides have not been reported to be effective against non-small cell lung cancers.

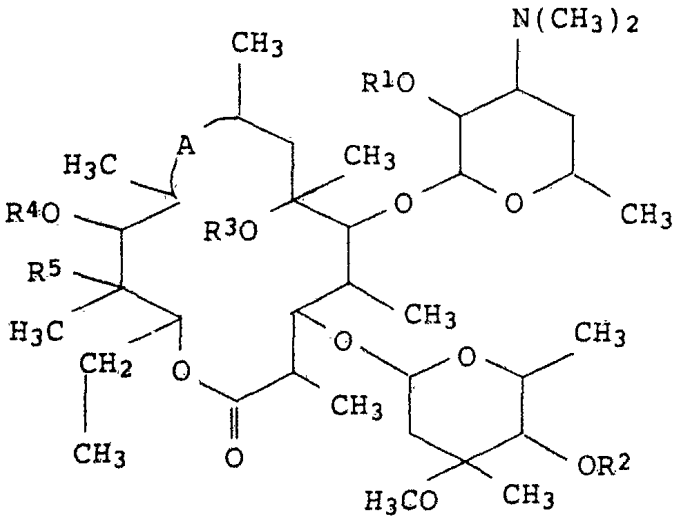
As stated above, at present, there is no disclosure about practical chemotherapeutic drugs of non-small cell lung cancer, and any chemotherapeutic drugs clinically available are not practicable for the treatment of non-small cell lung cancer. Accordingly, apart from the conventional concept of anticancer chemotherapy, there is a strong need for the development of therapeutic drugs practicably effective for the treatment of non-small cell lung cancers.

Disclosure of the Invention

As a result of extensive research of antitumor activity of various compounds in order to solve the above problem, unexpectedly, the present inventors have found that certain 14- or 15-membered-ring macrolide

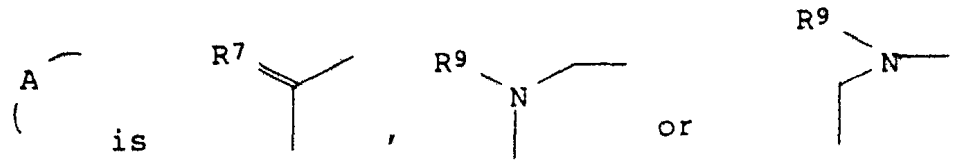
compounds have the ability to inhibit the growth and metastasis of non-small cell lung cancers, a useful effect on the malignant tumor which distantly metastasized to other organs and an excellent treatment effect in patients with advanced inoperable non-small cell lung cancers, and improve the quality of life of the patients. Based on these findings, the present invention has been accomplished.

The present invention is a pharmaceutical composition for the treatment of non-small cell lung cancers comprising as an effective ingredient a compound represented by Formula (I):



(I)

[wherein R^1, R^2, R^3 and R^4 are each a hydrogen atom, an optionally substituted alkyl group or an acyl group, R^5 is a hydrogen atom or $-OR^6$ (wherein R^6 is a hydrogen atom, an optionally substituted alkyl group or an acyl group, or R^4 and R^6 together form $>C=O$), and



(wherein R^7 is an oxygen atom or $=N-O-(CH_2)_n-X-R^8$ (wherein n is an integer of 1 to 6, X is an oxygen atom, a sulfur atom or -NY- (wherein Y is a hydrogen atom or an optionally substituted hydrocarbon group), and R^8 is an optionally substituted hydrocarbon group) and R^9 is a hydrogen atom or an optionally substituted hydrocarbon group)] or a pharmaceutically acceptable salt thereof.

Further, the present invention is a method for the treatment of non-small cell lung cancer ~~comprising~~ including administering an effective amount of the compound of Formula (I) or a pharmaceutically acceptable salt thereof to humans.

Furthermore, the present invention is use of the compound of Formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of the pharmaceutical composition for the treatment of non-small cell lung cancer.

In Formula (I), the alkyl group of the optionally substituted alkyl group as defined for R^1, R^2, R^3, R^4 and R^6 is, for example, a C_{1-6} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, t-butyl, etc.), preferably a C_{1-4} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, etc.), and particularly preferably a methyl group because of a stronger antitumor activity.

Examples of the substituent of the optionally substituted alkyl group are hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, ethylcarbonyloxy, etc.), halogen (fluorine, bromine, chlorine, iodine), etc. The alkyl group may optionally have 1 to 3 of these substituents at any available positions, and when there are two or more substituents, they may be the same or different.

The acyl group as defined for R^1, R^2, R^3, R^4 and R^6 in Formula (I) is, for example, a carboxylic acid acyl group or a sulfonic acid acyl group, and preferably a carboxylic acid acyl group because of a stronger antitumor activity.

The carboxylic acid acyl group is, for example, an acyl group derived from a carboxylic acid, and specifically $-CO-R^a$ (wherein R^a is a hydrogen atom or an optionally substituted hydrocarbon group).

The sulfonic acid acyl group is, for example, an acyl group derived from a sulfonic acid, and specifically $-SO_2-R^b$ (wherein R^b is an optionally substituted hydrocarbon group).

The optionally substituted hydrocarbon group for R^a and R^b is the same as the optionally substituted hydrocarbon group defined below.

Preferred examples of the acyl group are a carboxylic acid acyl group such as a formyl group, a C_{1-6} alkyl-carbonyl group (e.g. acetyl, propionyl, etc.), a C_{2-6} alkenyl-carbonyl group (e.g. acryloyl, methacryloyl, etc.) and a C_{6-14} aryl-carbonyl group (e.g. benzoyl, etc.); and a sulfonic acid acyl group such as a C_{1-6} alkylsulfonyl group (e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, etc.) and the like. The acyl group may optionally have 1 to 3 substituents in any available positions, and examples of the substituent are halogen (fluorine, chlorine, bromine, iodine), hydroxyl, C_{1-4} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), amino, cyano, etc. When there are two or more substituents, they may be the same or different.

Examples of the optionally substituted hydrocarbon group as defined for Y, R^8 and R^9 in Formula (I) are those shown in the following (1) to (5).

(1) a C_{1-6} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, etc.) optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propionyloxy, etc.) and halogen (fluorine, chlorine, bromine, iodine),

(2) a C_{2-6} alkenyl group (e.g. vinyl, allyl, isopropenyl, etc.) optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propionyloxy, etc.) and halogen (fluorine, chlorine, bromine, iodine),

(3) a C_{2-6} alkinyl group (e.g. ethinyl, 2-propinyl, 2-butinyl, etc.) optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propionyloxy, etc.) and halogen (fluorine, chlorine, bromine, iodine),

(4) a C_{6-14} aryl group (e.g. phenyl, etc.) optionally having 1 to 5 substituents selected from (a) a C_{1-6} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, etc.) optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propionyloxy, etc.) and halogen (fluorine,

chlorine, bromine, iodine), (b) mono- or di-C_{1-6} alkylamino (e.g. methylamino, ethylamino, dimethylamino, diethylamino, etc.), (c) C_{1-6} alkyl-carbonylamino (e.g. acetylamino, etc.), (d) hydroxyl, (e) carboxyl, (f) nitro, (g) cyano, (h) C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), (i) C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propionyloxy, etc.) and (j) halogen (fluorine, chlorine, bromine, iodine), and

(5) a C_{7-16} aralkyl group (e.g. benzyl, etc.) optionally having 1 to 5 substituents selected from (a) a C_{1-6} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, etc.) optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propionyloxy, etc.) and halogen (fluorine, chlorine, bromine, iodine), (b) mono- or di-C_{1-6} alkylamino (e.g. methylamino, ethylamino, dimethylamino, diethylamino, etc.), (c) C_{1-6} alkyl-carbonylamino (e.g. acetylamino, etc.), (d) hydroxyl, (e) carboxyl, (f) nitro, (g) cyano, (h) C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), (i) C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propionyloxy, etc.) and (j) halogen (fluorine, chlorine, bromine, iodine).

The optionally substituted hydrocarbon group is preferably a C_{1-6} alkyl group (e.g. methyl, ethyl,

propyl, isopropyl, etc.) optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propionyloxy, etc.) and halogen (fluorine, chlorine, bromine, iodine).

The C_{1-6} alkyl group, the C_{2-6} alkenyl group, the C_{2-6} alkinyl group, the C_{6-14} aryl group and the C_{7-16} aralkyl group as exemplified above for the optionally substituted hydrocarbon group are those optionally having substituents at any available positions, and when there are two or more substituents, they may be the same or different.

R^1, R^2, R^3 and R^4 are preferably each a hydrogen atom or a C_{1-4} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, etc.), and more preferably each a hydrogen atom or a methyl group because of a stronger antitumor activity.

R^5 is preferably a hydrogen atom or $-OR^6$ (wherein R^6 is a hydrogen atom or a C_{1-4} alkyl group such as methyl, ethyl, propyl, isopropyl, etc.), and more preferably a hydrogen atom, a hydroxyl group or a methoxy group because of a stronger antitumor activity.

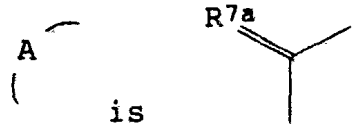
Preferably, R^7 is an oxygen atom or $=N-O-(CH_2)_n-X-R^8$ [wherein X is an oxygen atom or $-NY^a-$ (wherein Y^a is a C_{1-4} alkyl group such as methyl, ethyl,

propyl, isopropyl, etc.), and R^8 is a C_{1-4} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, etc.), a C_{1-4} alkoxy-C_{1-4} alkyl group (e.g. methoxymethyl, methoxyethyl, ethoxymethyl, ethoxyethyl, etc.), and n is an integer of 1 to 4] because of a stronger antitumor activity.

R^9 is preferably a hydrogen atom, a C_{1-4} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, etc.), or the C_{2-4} alkenyl group (e.g. vinyl, allyl, isopropenyl, etc.), and more preferably a C_{1-4} alkyl group (e.g. methyl, etc.) because of a stronger antitumor activity.

Examples of the compound of Formula (I) or salt thereof having a good therapeutic effect on non-small cell lung cancer are the following two Compounds A) and B).

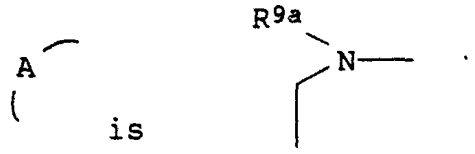
Compound A) : A compound of Formula (I) wherein R^1, R^2, R^3 and R^4 are each a hydrogen atom or a C_{1-4} alkyl group, R^5 is a hydrogen atom or $-OR^{6a}$ (wherein R^{6a} is a hydrogen atom or a C_{1-4} alkyl group), and



[wherein R^{7a} is an oxygen atom or $=N-O-(CH_2)_m-O-R^{8a}$ (wherein m is an integer of 1 to 4, and R^{8a} is a C_{1-4} alkoxy-C_{1-4} alkyl group)] or a salt thereof.

Compound B) : A compound of Formula (I) wherein R^1, R^2, R^3 and R^4 are each a hydrogen atom or a

C_{1-4} alkyl group, R^5 is a hydrogen atom or $-OR^{6a}$ (wherein R^{6a} is a hydrogen atom or a C_{1-4} alkyl group), and



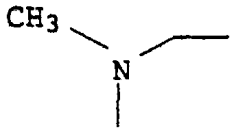
(wherein R^{9a} is a hydrogen atom, a C_{1-4} alkyl or a C_{2-4} alkenyl group) or a salt thereof.

In Compounds A) and B), the C_{1-4} alkyl group as defined for R^1, R^2, R^3, R^4 and R^6 is preferably a methyl, the C_{1-4} alkoxy-C_{1-4} alkyl group as defined for R^{8a} is preferably a methoxymethyl group, and the C_{2-4} alkenyl group as defined for R^{9a} is preferably a vinyl group.

The compounds of Formula (I) or salts thereof contain isomers thereof, but preferably natural-type because of a stronger antitumor activity.

Preferable compounds of the present invention are, for example, erythromycin A (R^1, R^2, R^3 and R^4 are each a hydrogen atom, R^5 is a hydroxyl group and -A- is >C=O in Formula (I)), erythromycin B (R^1, R^2, R^3, R^4 and R^5 are each a hydrogen atom, and -A- is >C=O in Formula (I)), clarithromycin (R^1, R^2 and R^4 are each a hydrogen atom, R^3 is a methyl group, R^5 is a hydroxyl group, and -A- is >C=O in Formula (I)), roxithromycin (R^1, R^2, R^3 are R^4 are each a hydrogen atom, R^5 is a hydroxyl group, and -A- is $>=N-OCH_2OCH_2CH_2OCH_3$ in Formula (I)) and azithromycin (R^1, R^2, R^3 and R^4 are each a hydrogen

atom, R^5 is a hydroxyl group, and -A- is



in Formula (I)), and erythromycin A and clarithromycin are more preferable because of establishing clinically therapeutic effect on non-small cell lung cancer in the present invention.

Examples of the pharmaceutically acceptable salt of the compound of the present invention are salts with inorganic acids (e.g. hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, nitrate, etc.) and salts with organic acids (e.g. acetate, malate, maleate, fumarate, tartrate, succinate, citrate, butyrate, methanesulfonate, p-toluenesulfonate, palmitate, salicylate, lactobionate, stearate, etc.) without, however, being limited thereby.

The compounds of the present invention or pharmaceutically acceptable salts thereof can be prepared, for example, by the methods described in U.S. Patents Nos. 2,823,203, 4,331,803, 4,349,545 and 4,517,359, Tetrahedron Lett., vol. 34, No. 31, pp. 4913 - 4916 (1993), Journal of Synthetic Organic Chemistry, vol. 38, No. 4, pp. 395 - 414 (1980) or modifications thereof.

The compounds of the present invention and pharmaceutically acceptable salts thereof have the

therapeutic effect on intractable solid cancers such as non-small cell lung cancer in humans and other mammals (e.g. rats, mice, rabbits, dogs, cats, cows, pigs, etc.), and can be used as their bulks because of low toxicity, but usually as dosage forms for the treatment of non-small cell cancer prepared by using pharmaceutically acceptable carriers in the same manner as other antibiotics are prepared. The pharmaceutically acceptable carriers to be used are appropriately chosen from excipients (e.g. calcium carbonate, kaolin, sodium bicarbonate, lactose, starches, crystalline cellulose, talc, granulated sugar, porous materials, etc.), binders (e.g. dextrin, gums, α-starch, gelatin, hydroxypropylcellulose, hydroxypropylmethylcellulose, pullulan, etc.), disintegrators (e.g. carboxymethylcellulose calcium, croscarmellose sodium, crospovidone, low substituted hydroxypropylcellulose, starch partially in the α-form, etc.), lubricants (e.g. magnesium stearate, calcium stearate, talc, starch, sodium benzoate, etc.), coloring agents (e.g. tar color, caramel, iron sesquioxide, titanium oxide, riboflavins, etc.), corrigents (e.g. sweetening agents, flavoring agents, etc.), stabilizers (e.g. sodium sulfite, etc.) and preservatives (e.g. parabens, sorbic acid, etc.).

The pharmaceutical composition of the present invention contains the compound of Formula (I) or a salt thereof in the same amount as it is used as an antibacterial agent. Usually, the amount of the compound of

Formula (I) or a salt thereof is 0.1 to 100 % by weight based on the total weight of the composition, specifically 20 to 100 % by weight in case of the solid form such as capsules, tablets, granules, etc., and 5 to 30 % by weight in case of the liquid form such as injections, etc. because of stability of the preparations. Examples of the dosage form are tablets (including sugar-coated tablets, film-coated tablets, etc.), pills, capsules, granules, fine granules, powders, syrups, emulsions, suspensions, injections, etc. These preparations can be prepared by conventional methods such as the methods described in Japanese Pharmacopoeia, etc. Specifically, tablets can be prepared by granulating a homogeneous mixture of the compound of the present invention with an excipient, a binder, a disintegrator or other appropriate additives, adding a lubricant and the like, and compressing the mixture for shaping. Alternatively, tablets can directly be prepared by compressing the compound of the present invention as it is or a homogeneous mixture of it with an excipient, a binder, a disintegrator, suitable additives and the like. If desired, the tablets can contain a coloring agent, a corrigent and the like. The tablets can be also coated with an appropriate coating agent. Injection can be prepared by charging a container with a suitable amount of a solution, a suspension or an emulsion of a suitable amount of the compound of the present invention in an aqueous solvent (e.g. water for injection, physiological

saline, Ringer's solution, etc.) or in non-aqueous solvent(e.g. vegetable oils, etc.), or a suitable amount of the compound of the present invention, and then sealing the container.

Examples of the carrier for oral compositions are conventional materials in pharmaceutical preparations such as starch, mannitol, crystalline cellulose and sodium carboxymethylcellulose, etc. Examples of the carrier for injections are distilled water, physiological saline, glucose solution and transfusion solutions such as sugar solution, electrolyte solution, amino acid solution, albumin, etc. Furthermore, other additives usually used in pharmaceutical preparations can appropriately be also added.

The above-mentioned preparations can appropriately contain suitable amounts of other anticancers (e.g. ifosfmide, mitomycin C, vindesine, cisplatin, vinblastine, procarbazine, vincristine, adriamycin, etc.) or antibiotics (e.g. penicillin G, takesulin, pansporin, amphotericin B, miconazol, sulfamethaxasole, trimethoprim, josamycin, etc.).

The dose of the pharmaceutical composition of the present invention depends on the patient's age, body weight, severity of the disease, administration route, administration frequency and the like, but for example, it is 0.1 to 100 mg/kg, preferably 0.5 to 10 mg/kg per day of the compound (I) or a salt thereof for an adult patient with non-small cell lung cancer, and more

preferably each 200 mg twice per day for an adult person weighing 60 kg. The administration route may be oral or parenteral.

Best Mode for Carrying out the Invention

The present invention is illustrated in more detail by the following experiments and examples without, however, being limited thereby.

Experiment 1 Antitumor effect on mouse Ehrlich ascites carcinoma EAC

Mouse Ehrlich ascites carcinoma EAC cells (5 x 10^6) were subcutaneously transplanted to ddy mice (weeks old). After 7 days, a control group received 0.9 % ethanol orally every day during the survival time. An administration group received erythromycin A dissolved in the same vehicle similarly. For comparison, an untreated group was also ~~inquired~~ investigated. Each group consists of 10 mice. 30 Days after the transplantation, the survival rate (%) of mice as well as the mean survival time (MST) were determined, and the results are together shown in Table 1.

Experiment 2 Antitumor effect on mouse leukemia P388

Mouse leukemia P388 cells (10^6) were abdominally transplanted to CDF1 mice (7 weeks old). The administration of erythromycin A was started on the next day. The test was carried out in the same manner

as that of Experiment 1, and the results are shown in Table 1.

Table 1

Antitumor effect on mouse Ehrlich ascites carcinoma EAC and mouse leukemia P388

	Antitumor Activity			
Dose of erythromycin	EAC (ddy mice) Survival rate (%)	MST	P388 (CDF1 mice) Survival rate(%)	MST
(mg/kg)	30 days	(day)	30 days	(day)
1	43*	38.2	57*	36.2
5	63**	42.7	77**	43.6
10	30*	30.8	33*	36.8
Vehicle-control	0	23.6	0	11.9
Untreated	0	24.2	0	12.3

*<0.5, **<0.05

As shown in Table 1, in case of the vehicle-control group, the survival rate after 30 days is 0 %, and the mean survival time is short (23.6 days). On the contrary, in case of the erythromycin A (5 mg/kg) administration group, the survival rate after 30 days is 63 %, and the mean survival time is long (42.7 days). Furthermore, in case of the untreated group, the survival rate after 30 days is 0 %, and the mean survival time is also short (24.2 days).

It is found from these results that erythromycin A has a prolonged survival effect against EAC-

and P388-transplanting mice, and an inhibitory effect on the growth of the cancer cells.

Experiment 3 Clinical effect in patients with primary multiple non-small cell lung cancer

A man, 70 years old, 163 cm in high, weighing 55 kg, with primary multiple non-small cell lung cancer was administered orally with erythromycin A every day, and there was no recurrence for 5 years after the therapy.

Experiment 4 Clinical effect in patients with primary multiple non-small cell lung cancer

Fifty patients, 41 to 82 years old, with III to IV stages of primary non-small cell lung cancers regarded as inoperable (43 patients with non-small cell lung cancer and 7 patients with small cell lung cancer) were randomly divided into an clarithromycin (CAM) administration group, which was orally administered with 200 mg of CAM twice every day, and a non-administration group. The survival time after the therapy of the patients of both groups was observed, and a survival curve was drawn according to the method of Kaplan-Maier, and thereby giving the 50 % survival time. Results are shown in Table 2.

Table 2

Comparison of therapeutic effect in patients with non-small cell lung cancer

Group	case	50 % survival time
CAM administration group	22	930 days
CAM non-administration group	21	299 days

Comparison of therapeutic effect in patients with small cell lung cancer

Group	case	50 % survival time
CAM administration group	3	246 days
CAM non-administration group	4	251 days

As shown in Table 2, in case of the patients with non-small cell lung cancer, the 50 % survival time is 930 days in the CAM administration group, contrary to 299 days in the CAM non-administration group. It is established from the results that the survival time of the CAM administration patients is prolonged much longer than that of the CAM non-administration patients. On the other hand, there is confirmed no difference between both groups in case of the patients with small cell lung cancer. It is found from the fact that CAM has an excellent therapeutic effect in patients with non-small lung cell cancer only.

It is also observed that the CAM administration patients are good in terms of appetite, general

conditions and the activity of daily living (ADL), show sluggish progress of disease, and improve the quality of life (QOL) by administration of CAM. In addition, the safety of a long-term administration of CAM to humans is already demonstrated (Chemotherapy, vol. 42, pp. 430 - 435 (1994)), and the side effects were not found in the above clinical experiments.

Example 1 Preparation of Coated tablets

Composition (per coated tablet)

(1) Erythromycin A	20.0 mg
(2) Lactose	80.0 mg
(3) Corn Starch	45.0 mg
(4) Gelatin	3.0 mg
(5) Magnesium stearate	2.0 mg

A mixture of 20.0 mg of erythromycin A, 80.0 mg of lactose and 45.0 mg of corn starch was granulated using 0.03 ml of 10 % aqueous gelatin solution (containing 3.0 mg of gelatin), sifted through a 1 mm-mesh sieve, dried at 40°C, and sifted again. The thus-obtained granules were mixed with 2.0 mg of magnesium stearate and compressed. The resulting core tablet was sugar-coated with an aqueous solution of sucrose, titanium oxide, talc and gum arabic, and polished with yellow bees wax to give a coated tablet.

Example 2 Preparation of Tablet

Composition (per tablet)

(1) Clarithromycin	20.0 mg
(2) Lactose	70.0 mg
(3) Corn Starch	50.0 mg
(4) Soluble starch	7.0 mg
(5) Magnesium stearate	3.0 mg

20.0 mg of clarithromycin and an 3.0 mg of magnesium stearate were granulated using 0.07 ml of 10 % aqueous solution of soluble starch (containing 7.0 mg of gelatin), dried and mixed with 70.0 mg of lactose and 50.0 mg of corn starch. The mixture was compressed to give a tablet.

Example 3 Preparation of Injection solution

Composition (per ampule)

(1) Erythromycin A	5.0 mg
(2) Lactobionic acid	2.5 mg
(3) Sodium chloride	20.0 mg
(4) Distilled water	ad 2 ml.

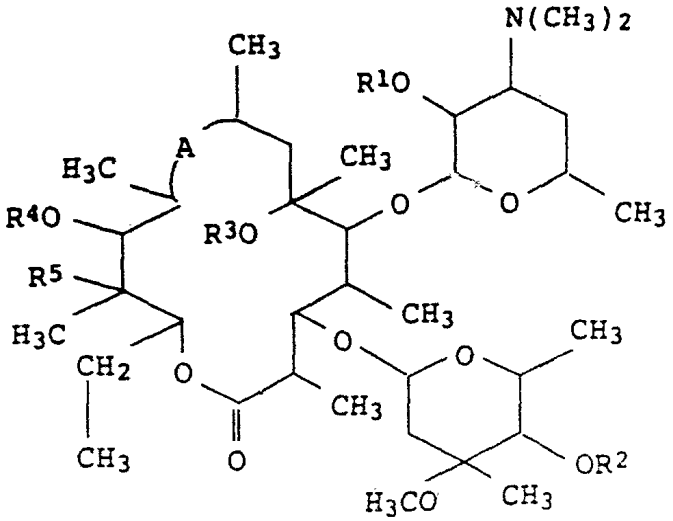
5.0 mg of erythromycin A, 2.5 mg of lactobionic acid, 20.0 mg of sodium chloride were mixed to distilled water to a total volume of 2.0 ml. The solution was filtered and charged into a 2 ml-ampule under aseptic conditions. The ampule was sterilized and sealed to obtain an injection solution.

Industrial Utilizability

The pharmaceutical composition comprising the compound of Formula (I) or a pharmaceutically acceptable salt thereof of the present invention has a great effect against non-small cell lung cancers which have been considered the most difficult tumors to be subjected to surgical operation and chemotherapy, and is useful as a practical therapeutic agent of non-small cell lung cancers. In addition, it can be used safely without side effects which induce serious conditions unlike the previously used anticancer agents.

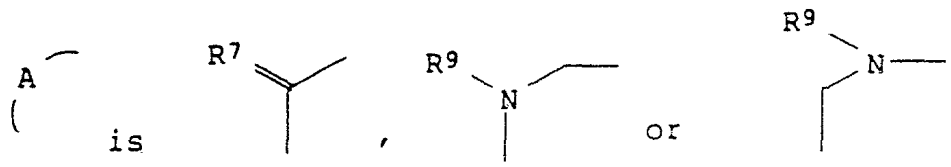
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for the treatment of non-small cell lung cancer in a human including administering to the human an effective amount of a compound represented by the formula:



(I)

[wherein R^1, R^2, R^3 and R^4 are each a hydrogen atom, an optionally substituted alkyl group or an acyl group, R^5 is a hydrogen atom or $-OR^6$ (wherein R^6 is a hydrogen atom, an optionally substituted alkyl group or an acyl group, or R^4 and R^6 together form >C=O), and



(wherein R^7 is an oxygen atom or $=N\text{-}O\text{-}(CH_2)_n\text{-}X\text{-}R^8$ (wherein n is an integer of 1 to 6, X is an oxygen atom, a sulphur atom or -NY- (wherein Y is a hydrogen atom or an optionally substituted hydrocarbon group), and R^8 is an optionally substituted hydrocarbon group) and R^9 is a hydrogen atom or an optionally substituted hydrocarbon group)] or a pharmaceutically acceptable salt thereof.

2. A method according to Claim 1, wherein the optionally substituted alkyl group for R^1, R^2, R^3, R^4, and R^6 is a C_{1-6} alkyl group optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, C_{1-6} alkyl-carbonyloxy and halogen.

3. A method according to Claim 1, wherein the acyl group for R^1, R^2, R^3, R^4, and R^6 is a formyl group; or a alkyl-carbonyl group, a C_{2-6} alkenyl-carbonyl group, a C_{6-14} aryl-carbonyl group or a C_{1-6} alkyl-sulfonyl group, each of which may optionally have 1 to 3 substituents selected from halogen, hydroxyl, C_{1-6} alkoxy, amino and cyano.

4. A method according to Claim 1, wherein the optionally substituted hydrocarbon group for Y, R^8 and R^9 is

(1) a C_{1-6} alkyl group optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy, mono- C_{1-6} alkylamino, di-C_{1-6} alkylamino, C_{1-6} alkyl-carbonyloxy and halogen.

(2) a C_{2-6} alkenyl group optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy, mono- C_{1-6} alkylamino, di- C_{1-6} alkylamino, C_{1-6} alkyl-carbonyloxy and halogen

(3) a C_{2-6} alkinyl group optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy, mono- C_{1-6} alkylamino, di- C_{1-6} alkylamino, C_{1-6} alkyl-carbonloxy and halogen,

(4) a C_{6-14} aryl group optionally having 1 to 5 substituents selected from (a) a C_{1-6} alkyl group optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, mono- C_{1-6} alkylamino, di- C_{1-6} alkylamino, C_{1-6} alkyl-carbonyloxy and halogen, (b) mono- or di- C_{1-6} alkylamino, (c) C_{1-6} alkyl-carbonylamino, (d) hydroxyl, (e) carboxyl, (f) nitro, (g) C_{1-6} alkoxy, (h) C_{1-6} alkyl-carbonyloxy and (i) halogen, or

(5) A C_{7-16} aralkyl group optionally having 1 to 5 substituents selected from (a) a C_{1-6} alkyl group optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, mono- C_{1-6} alkylamino, di- C_{1-6} alkylamino, C_{1-6} alkyl-carbonloxy and halogen, (b) mono- or di-C_{1-6} alkylamino, (c) C_{1-6} alkyl-carbonylamino, (d) hydroxyl, (e) carboxyl, (f) nitro, (g) C_{1-6} alkoxy, (h) C_{1-6} alkyl-carbonyloxy and (i) halogen.

5. The method according to Claim 1, wherein the optionally substituted hydrocarbon group for Y, R^8, and R^9 is a C_{1-6} alkyl group optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy, mono- C_{1-6} alkylamino, di- C_{1-6} alkylamino, C_{1-6} alkyl-carbonyloxy and halogen.

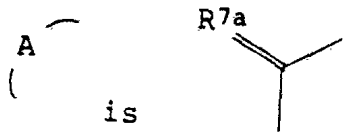
6. The method according to Claim 1, wherein R^1, R^2, R^3 and R^4 are each a hydrogen atom or a C_{1-4} alkyl group.

7. A method according to Claim 1, wherein R^5 is a hydrogen atom, a hydroxyl group or a methoxy group.

8. A method according to Claim 1, wherein R^7 is an oxygen atom or =N-O-$(CH_2)_n$-X-R^8 (wherein X is an oxygen atom or -NY^a-(wherein Y^a is a C_{1-4} alkyl group), and R^8 is a C_{1-4} alkyl group or a C_{1-4} alkoxy- C_{1-4} alkyl group, and n is an integer of 1 to 4.

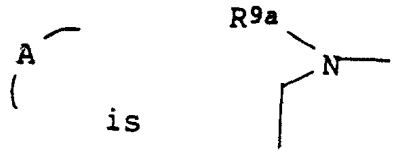
9. A method according to Claim 1, wherein R^9 is a hydrogen atom, a C_{1-4} alkyl group or a C_{2-4} alkenyl group.

10. A method according to Claim 1, wherein R^1, R^2, R^3 and R^4 are each a hydrogen atom or a C_{1-4} alkyl group, R^5 is a hydrogen atom or -OR^{6a} (wherein R^{6a} is a hydrogen atom or a C_{1-4} alkyl group), and



[wherein R^{7a} is an oxygen atom or =N-O-$(CH_2)_m$-O-R^{8a} (wherein m is an integer of 1 to 4, R^{8a} is a C_{1-4} alkoxy- C_{1-4} alkyl group)].

11. A method according to Claim 1, wherein R^1, R^2, R^3 and R^4 are each a hydrogen atom or a C_{1-4} alkyl group, R^5 is a hydrogen atom or $-OR^{6a}$ (wherein R^{6a} is a hydrogen atom or a C_{1-4} alkyl group), and



[wherein R^{9a} is a hydrogen atom, a C_{1-4} alkyl group or a C_{1-4} alkenyl group).

12. A method according to any one of Claims 1 to 11, wherein erythromycin A is coadministered in an effective amount.

13. A method according to any one of Claims 1 to 11, wherein erythromycin B is as an effective ingredient.

14. A method according to any one of Claims 1 to 11 wherein clarithromycin is coadministered in an effective amount.

15. A method according to any one of Claims 1 to 11 wherein roxithromycin is coadministered in an effective amount.

16. A method according to any one of Claims 1 to 11 wherein azithromycin is coadministered in an effective amount.

ABSTRACT

14- or 15-membered-ring macrolide compounds such as clarithromycin, erythromycin B, etc. have a potent antitumor effect on non-small cell lung cancers which are considered the most difficult tumors to be be subjected to surgical operation and chemotherapy, and are useful as a practical therapeutic agent of non-small cell lung cancer.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP95/00819

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl^6 A61K31/70, A61K31/71, C07H17/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl^6 A61K31/70, A61K31/71, C07H17/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chem. abstr., Vol. 96, (1982), (Columbus, OH, USA), the abstracts No. 1869 GOLDIN, B.R. "Effect of antibiotics on incidence of rat intestinal tumors induced by 1, 2-dimethylhydrazine dihydrochloride", JNCI, J. Natl. Cancer Inst.(1981), 67(4), p. 877-880 (Eng)	1 - 18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search	Date of mailing of the international search report
June 23, 1995 (23. 06. 95)	July 18, 1995 (18. 07. 95)
Name and mailing address of the ISA/ Japanese Patent Office	**Authorized officer**
Facsimile No.	**Telephone No.**

Form PCT/ISA/210 (second sheet) (July 1992)

国 際 調 査 報 告

国際出願番号 PCT/JP 95/00819

A. 発明の属する分野の分類（国際特許分類（IPC））

Int. Cl⁶ A61K31/70, A61K31/71, C07H17/08

B. 調査を行った分野

調査を行った最小限資料（国際特許分類（IPC））

Int. Cl⁶ A61K31/70, A61K31/71, C07H17/08

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

CAS ONLINE

C. 関連すると認められる文献

引用文献のカテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
A	Chem. abstr., Vol 96, (1982), (Columbus, OH, USA), the abstracts No 1869 GOLDIN, B.R. 「Effect of antibiotics on incidence of rat intestinal tumors induced by 1,2-dimethylhydrazine dihydrochloride」, JNCI, J. Natl. Cancer Inst. (1981), 67〔4〕, p.877-880 (Eng)	1-18

☐ C欄の続きにも文献が列挙されている。

☐ パテントファミリーに関する別紙を参照。

* 引用文献のカテゴリー
「A」特に関連のある文献ではなく、一般的技術水準を示すもの
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「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリー文献

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23. 06. 95

国際調査報告の発送日
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日本国特許庁(ISA/JP)
郵便番号100
東京都千代田区霞が関三丁目4番3号

特許庁審査官（権限のある職員）
内藤伸一 ㊞ 4C 8615

電話番号 03-3581-1101 内線 3452

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