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EP-A- 0 456 474 **JP-A- 4 018 087**

- **Biochemistry, Vol. 30, No. 37 (1991), pages 8936 to 8944.**
- **J. Am. Chem. Soc., Vol. 101, No. 12 (1979), pages 3402 to 3404.**

EP 0 670 317 B9

Description

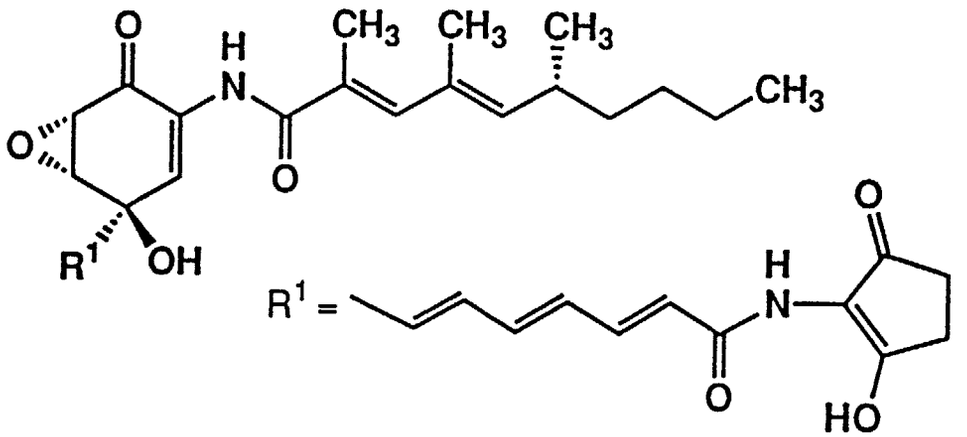
Technical Field

[0001] The present invention relates to an epoxycyclohexenedione derivative having antimicrobial activity and antitumor activity or a pharmaceutically acceptable salt thereof.

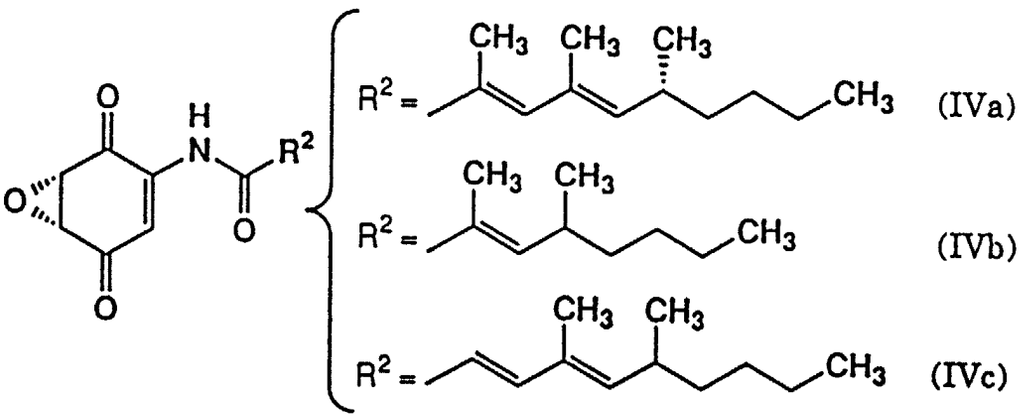
Background Art

[0002] Ras oncogene undergoes point mutation in many tumor tissues in humans and is detected as an activated form capable of transforming normal cells. It is essential for the expression of transforming activity of the ras oncogene product that the 12th, 13th or 61st amino acid should undergo point mutation and, additionally, the cysteine residue at the C terminal region should be farnesylated for the membrane association of the ras oncogene product. The reaction is catalyzed by farnesyltransferase (hereinafter referred to as "FTase"). Accordingly, an FTase inhibitor is expected to inhibit the function of the ras oncogene product and thereby to have antitumor activity.

[0003] Compounds represented by the following formulae are known as epoxycyclohexene derivatives having FTase inhibitory activity.



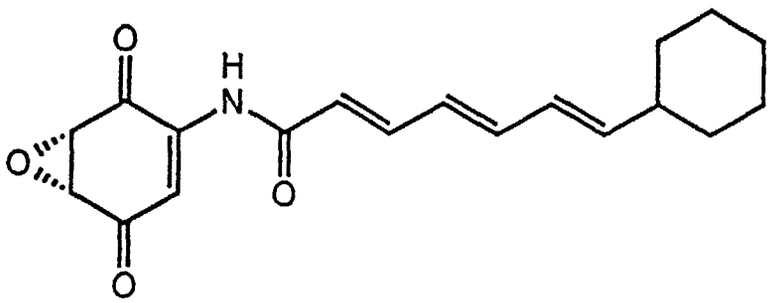
Manumycin [Proc. Natl. Acad. Sci. USA, 90, 2281 (1993)]. It is reported that IC_{50} against FTase of yeast origin is 5 μmol when ras protein of yeast origin is used as a substrate.



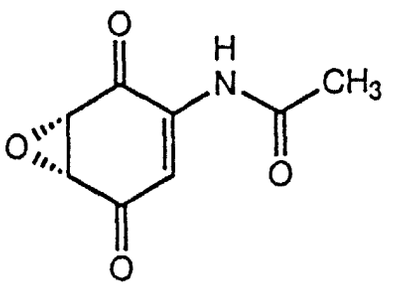
Manumycin derivatives (compounds IVa, IVb, and IVc) [Proc. Natl. Acad. Sci. USA, 90, 2281 (1993); Tetrahedron Letters, 4995 (1973); J. Antibiotics, 40, 1530 and 1549 (1987); Japanese Published Unexamined Patent Application

No. 221377/1992 (US-A-5 106 868)]. It is reported that the activity of these compounds can be detected, and that the activity is not numerically described, except for JP-A-221 377/1992.

[0004] Epoxycyclohexenedione derivatives represented by the following formulae are known, but FTase inhibitory activity of these compounds is not reported:



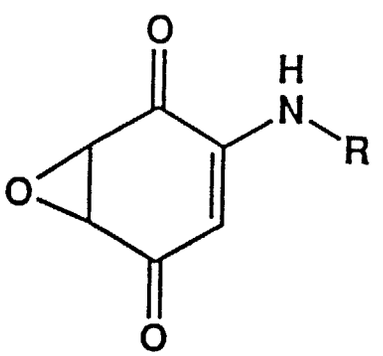
Askamycin derivative [J.Am. Chem. Soc., 101, 3402 (1979)].



LL-C10037 α derivative [J. Am. Chem. Soc., 111, 7932 (1989), J. Org. Chem., 59, 3518 (1994)].

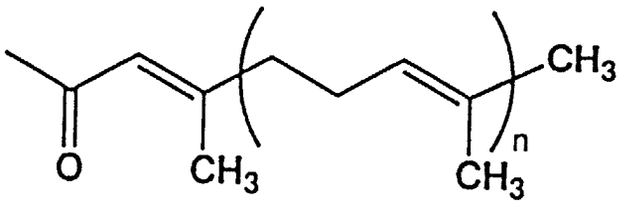
Disclosure of the Invention

[0005] The present invention relates to an epoxycyclohexenedione derivative represented by formula (I):



(I)

wherein R is a straight-chain or branched alkanoyl group having 10 to 25 carbon atoms, a straight-chain alkenoyl group having 16 to 25 carbon atoms, or a group represented by formula (A):



(A)

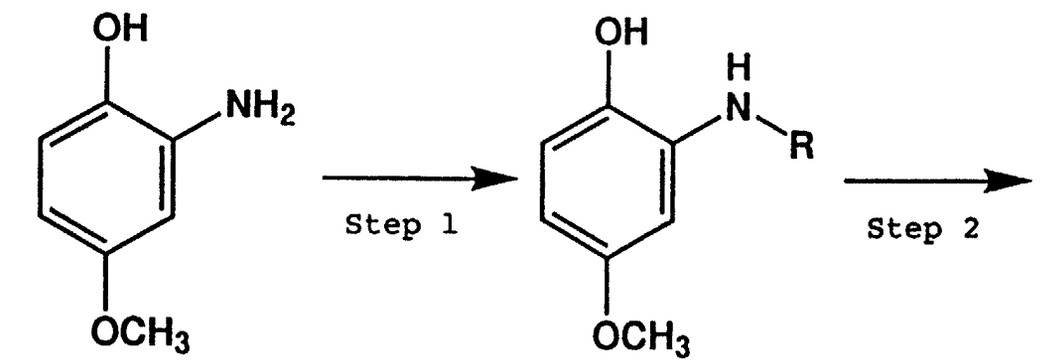
wherein n is an integer of 1 to 4;
or a pharmaceutically acceptable salt thereof.

[0006] Hereinafter the compound represented by formula (I) is referred to as Compound I. The same applies to the compounds of other formula numbers.

[0007] In the definition of each group in Compound I; the straight-chain or branched alkanoyl group having 10 to 25 carbon atoms includes lauroyl, myristoyl, palmitoyl, stearoyl, 3,7,11-trimethyllauroyl, and 3,7,11,15-tetramethylpalmitoyl; the straight-chain alkenoyl group having 16 to 25 carbon atoms includes palmitoleoyl, linoleoyl, and linolenoyl; and the group represented by formula (A) means geranoyl, farnesoyl, geranylgeranoyl or geranylfarnesoyl.

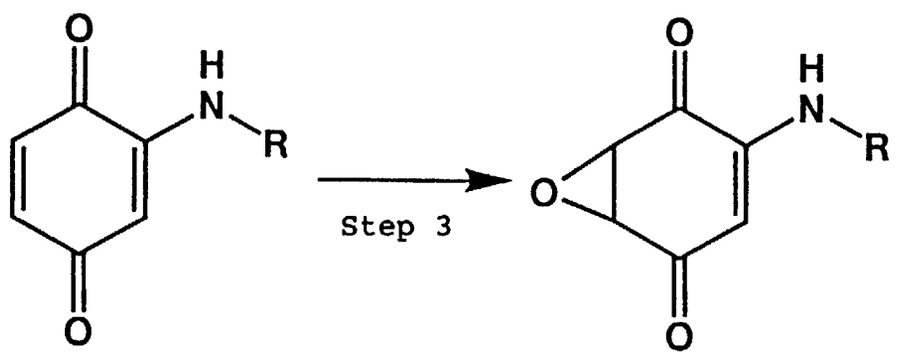
[0008] The pharmaceutically acceptable salts of Compound I include pharmaceutically acceptable acid addition salts, for instance, inorganic acid salts such as hydrochloride, sulfate and phosphate; and organic acid salts such as acetate, maleate, fumarate, tartrate and citrate.

[0009] The process for producing Compound I is explained below. Compound I can be prepared by the following steps: acylation of 2-amino-4-methoxyphenol (Step 1), oxidation to quinone (Step 2), and epoxidation (Step 3) as illustrated by the following reaction scheme.



2-amino-4-methoxyphenol

(II)



(III)

(I)

wherein R has the same meaning as defined above.

Step 1:

[0010] Compound II can be obtained by reacting 2-amino-4-methoxyphenol with 1 to 2 equivalents of an acyl halide, an acid anhydride or a mixed acid anhydride having a desired acyl group in the presence of an appropriate base, such as pyridine, N,N-dimethylaniline and N,N-diethylaniline, in a solvent, such as dimethylformamide, dimethylsulfoxide, chloroform, dichloromethane and toluene, or in a solvent such as an appropriate base. The reaction temperature is 0 to 50°C, preferably 20 to 30°C. The reaction period is usually 1 to 48 hours, which is varied with the reaction conditions. The reaction is carried out until the starting material is no longer detectable by thin layer chromatography.

Step 2:

[0011] Compound III can be obtained by oxidizing Compound II in the presence of 1 to 2 equivalents of an oxidizing agent, such as lead tetraacetate, ammonium cerium (IV) nitrate and [bis(trifluoroacetoxy)iodo]benzene, in a solvent such as tetrahydrofuran, diethyl ether, dioxane, acetonitrile, chloroform, acetic acid, water and a mixture thereof. The reaction temperature is 0 to 50°C, preferably 20 to 30°C. The reaction period is usually 10 to 120 minutes, which is varied with the reaction conditions. The reaction is carried out until the starting material is no longer detectable by thin layer chromatography.

Step 3:

[0012] Compound I can be obtained by oxidizing Compound III in the presence of 1 to 2 equivalents of a hypochlorite such as sodium hypochlorite and calcium hypochlorite, in a solvent, such as tetrahydrofuran and dioxane. The reaction temperature is preferably -10 to 20°C. The reaction period is usually 10 to 60 minutes, which is varied with the reaction conditions. The reaction is carried out until the starting material is no longer detectable by thin layer chromatography.

[0013] The product obtained by the above mentioned processes can be isolated and purified by an appropriate combination of the conventional methods employed in organic synthesis, for instance, filtration, extraction, washing, drying, concentration, crystallization, various kinds of chromatography. The intermediate product may be used for the subsequent reaction without purification.

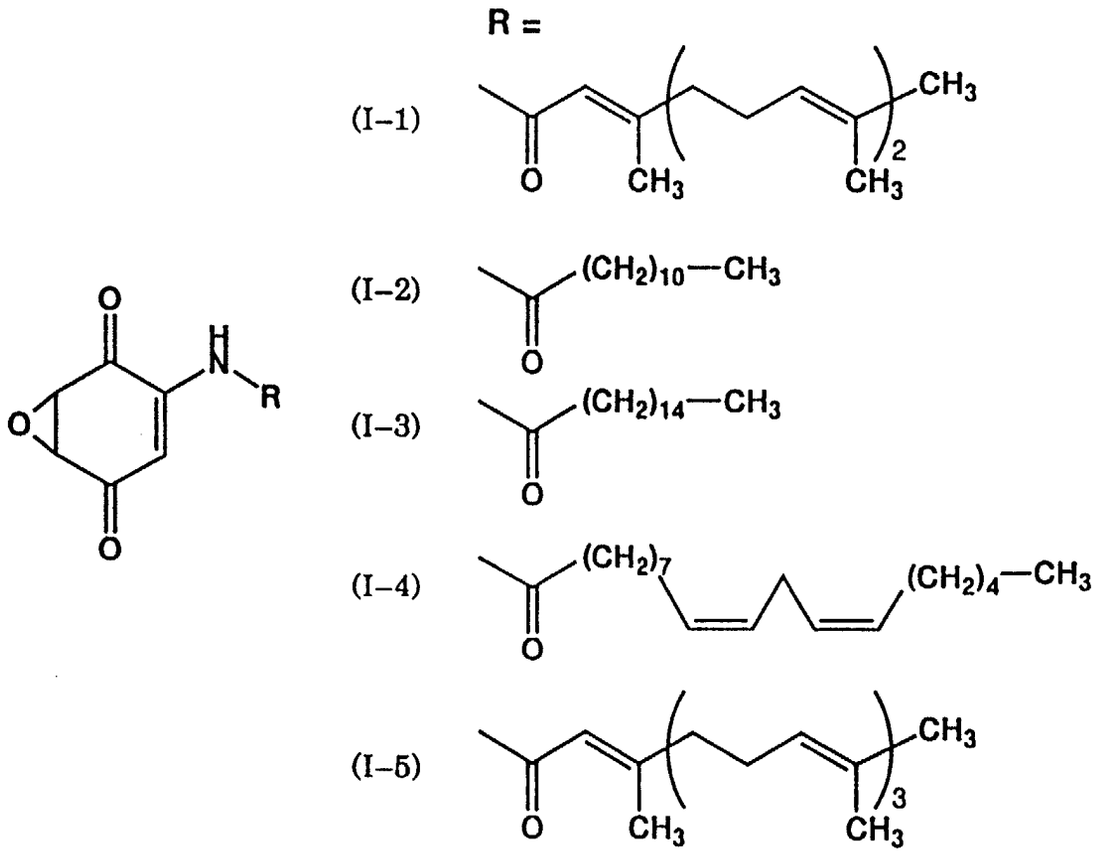
[0014] The compound obtained by the above-mentioned process is usually a mixture of stereoisomers with respect to the configuration of the epoxy group. These isomers can be separated by conventional methods for separation, such as fractional crystallization of a diastereomer, an optically active compound addition salt, or high performance liquid chromatography (HPLC) using an optically active column.

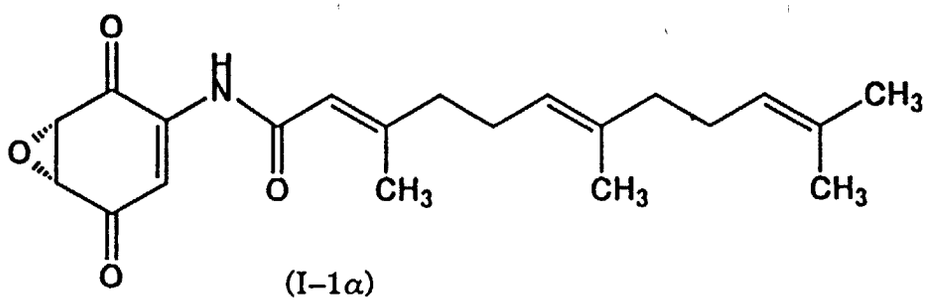
[0015] Compounds I includes stereoisomers, such as geometrical isomers and optical isomers. Mixtures of any possible isomers at any mixing ratio are embraced in the scope of the present invention.

[0016] Where a salt of Compound I is desired, a salt of Compound I as produced is purified, or a free compound as obtained is dissolved or suspended in an appropriate solvent, followed by addition of an acid to form a desired salt.

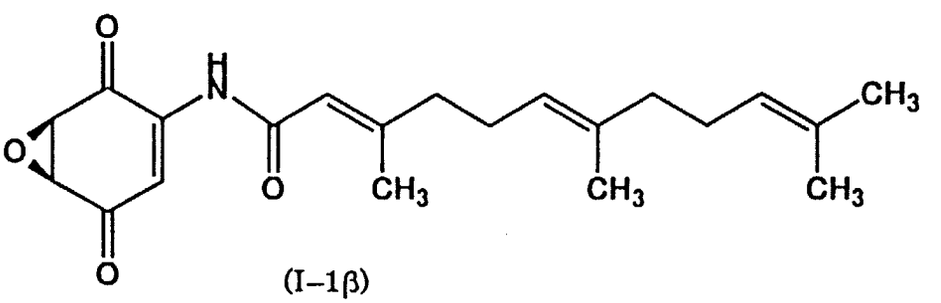
[0017] Compounds I or pharmaceutically acceptable salts thereof may exist in the form of an adduct with water or various solvents. These adducts are also included in the present invention.

[0018] Examples of Compound I are shown below.





(I–1α)



(I–1β)

[0019] The pharmacological activities of Compound I are explained in the following Test Examples.

Test Example 1

FTase Inhibitory Activity

[0020] The FTase used for the assay was obtained from rat brain as follows. An extract of minced brain of a male rat was salted out using ammonium sulfate. The fraction obtained at 50% saturation was dissolved in a buffer solution (20 mM Tris-HCl, pH 7.5, 1 mM dithiothreitol (DTT), 20 μM $ZnCl_2$) and further fractionated by column chromatography using a Mono Q 10/10 column. The column was eluted by gradient elution with 0.3 to 0.4M NaCl. The active fraction eluted at near 0.35M NaCl, was used as a partially purified preparation. Measurement of the activity was carried out by using the thus prepared enzyme and v-Ki-ras p21 as a substrate. The v-Ki-ras p21, used as a substrate, was obtained by high expression using Escherichia coli, followed by purification according to the method of Tamaoki, et al. [Biochem. Biophys. Res. Commun., 132, 126 (1985)]. [^{3}H]-FPP transferred into v-Ki-ras p21 was determined with a liquid scintillation counter according to the method of Reiss, Y. et al. [Cell, 62, 81 (1990)]. The enzyme inhibitory activity was measured as inhibition of the test compound on farnesylation of the C-terminal of v-ki-ras p21 in the above-mentioned reaction system. The concentration of the test compound inhibiting 50% of the farnesylation (IC_{50}) was calculated by comparing the enzyme inhibitory activity of a non-treated group and that of a group treated with the test compound of a known concentration.

[0021] The results are shown in Table 1.

Table 1

Experiment 1	
Compound No.	IC_{50} (μM)
I-1	18
Manumycin	76
Experiment 2	
Compound No.	IC_{50} (μM)
IVa	60
Manumycin	35

[0022] According to the result in Table 1 Compound I-1 shows a manifest inhibitory activity against FTase. The inhibitory activity of Compound I-1 is significantly strong as compared with those of manumycin and compound IVa which have been reported as FTase inhibitors.

Test Example 2

FTase Inhibitory Activity

[0023] An extract of minced bovine brain was subjected to column chromatography on DEAE-Sephacel (Pharmacia). The active fraction was concentrated by ultrafiltration and dialyzed against a mixture of 20 mM Tris-HCl (pH 8.0), 50 mM NaCl, 20 mM $ZnCl_2$, 1 mM DTT, 0.2 mM phenylmethylsulfonyl fluoride (PMSF). The resulting dialysate was used as a crude enzyme solution. Measurement of activity was carried out by using the enzyme obtained by the above-mentioned method and an FTase [^{3}H]SPA enzyme assay kit (Amersham). Enzyme inhibitory activity was measured as inhibition of farnesylation of the C-terminal peptide of lamin B by the test compound in the above-mentioned reaction system. The enzyme inhibitory activity of a group treated with a test compound of a known concentration was compared with that of a non-treated group to calculate the concentration of the test compound for 50% inhibition of farnesylation (IC_{50}).

[0024] The results are shown in Table 2.

Table 2

Compound No.	IC_{50} (μM)
I-1	21
I-2	21

Table 2 (continued)

Compound No.	IC_{50} (μM)
I-4	19
I-5	23

[0025] According to the results in Table 2, Compounds I-1, 2, 4 and 5 show manifest inhibitory activity against FTase.

Test Example 3

Inhibitory Activity on Cell Growth

[0026] The antitumor activity was measured by using NIH 3T3 fibroblasts transformed by oncogene EJ-ras (hereinafter referred to as "NIH 3T3/EJ-ras").

[0027] NIH 3T3/EJ-ras cells were suspended in a DME medium (Nissui KK) containing 10% fetal bovine serum, penicillin (100 U/ml) and streptomycin (100 μg/ml) (hereinafter referred to as medium A) in a cell concentration of 1.0×10^4 cells/ml. Each well of a 24-well microtiter plate was inoculated with 0.1 ml of the cell suspension, and the system was monolayer cultured by incubation in a carbon dioxide incubator at 37°C for 24 hours. To each well was added 0.1 ml of a test compound appropriately diluted with medium A, followed by incubation in the carbon dioxide incubator at 37°C for 72 hours. The cells were recovered by trypsinization, and the number of the cells was counted with a cell counter. A concentration of the test compound for 50% inhibition of cell growth (IC_{50}) was calculated.

[0028] The result is shown in Table 3.

Table 3

Compound No.	IC_{50} (μM)
I-1	4.3

[0029] According to the result in Table 3, Compound I-1 has a manifest inhibitory activity on growth of the NIH 3T3 fibroblasts transformed by oncogene EJ-ras and is useful as an anticancer agent.

Test Example 4

Antimicrobial Activity

[0030] Antimicrobial activity was measured by an agar dilution method using a culture medium (pH 7) prepared by dissolving 3g of Bacto-tryptone (Difco), 3g of meat extract, 1g of yeast extract, 1g of glucose, and 16g of agar in 1ℓ of water. The antimicrobial activity was expressed in terms of minimum growth inhibitory concentration (MIC).

[0031] The results are shown in Table 4.

Table 4

Compound No.	MIC (μg/ml)		
	SA	EH	BS
I-1	0.91	0.46	0.46
I-2	>100	0.04	0.08
I-4	>100	0.33	0.65
I-5	>100	0.65	0.65

SA: *Staphylococcus aureus* ATCC 6538P
EH: *Enterococcus hirae* ATCC 10541
BS: *Bacillus subtilis* No. 10707

[0032] According to the results in Table 4, Compounds I-1, 2, 4 and 5 have a remarkable antimicrobial activity and are useful as an antimicrobial agent.

[0033] Compound I or a pharmaceutically acceptable salt thereof can be administered orally or parenterally either as such or in various dosage forms, such as tablets, pills, powders, granules, capsules, suppositories, injections and infusions.

[0034] The pharmaceutical compositions in the form of the above-mentioned dosage forms can be prepared in a conventional manner. For example, the compositions may contain various vehicles, lubricants, binders, disintegrators, suspending agents, isotonic agents, emulsifiers, and absorption accelerators.

[0035] Examples of carriers which can be used in the pharmaceutical compositions are water, injectable distilled water, physiological saline, glucose, fructose, sucrose, mannitol, lactose, starch, corn starch, cellulose, methyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, alginic acid, talc, sodium citrate, calcium carbonate, calcium hydrogen phosphate, magnesium stearate, urea, silicone resins, sorbitan fatty acid esters and glycerin fatty acid esters. These carriers are properly selected depending on the dosage form.

[0036] The administration schedule of the compound of the present invention is usually 0.01 to 2 mg/kg a day for an injection, infusion, rectal administration using suppositories or application to the skin, depending on the aimed therapeutic effect, the administration route, the period of administration, the age and body weight of a patient, and the like.

[0037] Hereinafter, embodiments of the present invention are described by means of Examples and Reference Examples.

Example 1

4,5-Epoxy-1-farnesoylamino-3,6-dioxocyclohexene (Compound I-1)

[0038] To a solution of 61.0 mg of farnesic acid in toluene was added 0.04 ml of oxalyl chloride, followed by stirring at room temperature for 3 hours. The solvent was removed by evaporation to give farnesoyl chloride as a crude product.

[0039] In 2 ml of pyridine was dissolved 31.6 mg of 2-amino-4-methoxyphenol obtained in Reference Example 2, and the farnesoyl chloride obtained above was added dropwise to the mixture, followed by stirring at room temperature for 4 hours. The reaction mixture was diluted with ethyl acetate and 2M hydrochloric acid. The organic layer was washed successively with water and an aqueous saturated solution of sodium hydrogen carbonate, and dried over sodium sulfate. The solvent was removed by evaporation, and the residue was purified by silica gel chromatography (5/95 ethyl acetate/toluene) to give 46.0 mg (57%) of 2-farnesoylamino-4-methoxyphenol.

Rf 0.38 (ethyl acetate/toluene = 1/9)

^{1}HNMR ($CDCl_3$) δ; 1.60 (s, 3H), 1.62 (s, 3H), 1.68 (d, 3H, J=0.76 Hz), 1.99 - 2.23 (m, 8H), 2.24 (d, 3H, J=0.84 Hz), 3.74 (s, 3H), 5.11 (m, 2H), 5.78 (bs, 1H), 6.59 (d, 1H, J=2.9 Hz), 6.69 (dd, 1H, J=2.9, 8.9 Hz), 6.94 (d, 1H, J=8.9 Hz), 7.33 (bs, 1H).

FAB-MS (M/Z); 358 $(M+1)^+$

[0040] In a mixed solvent of 2 ml of tetrahydrofuran and 2 ml of water was dissolved 46.0 mg of 2-farnesoylamino-4-methoxyphenol obtained above, and 69 mg of lead tetraacetate was added to the solution, followed by stirring at room temperature for 30 minutes. The reaction mixture was diluted with ethyl ether and an aqueous saturated solution of sodium hydrogen carbonate. The organic layer was washed with an aqueous saturated solution of sodium chloride and dried over sodium sulfate. The solvent was removed by evaporation and the residue was purified by silica gel chromatography (ethyl acetate/toluene=5/95) to give 15.7 mg (36%) of 2-farnesoylamino-1,4-benzoquinone.

Rf 0.56 (ethyl acetate/toluene=1/9)

^{1}HNMR ($CDCl_3$) δ; 1.60 (s, 3H), 1.62 (d, 3H, J=1.1 Hz), 1.68 (d, 3H, J=1.1 Hz), 1.98 - 2.21 (m, 8H), 2.22 (d, 3H, J=1.2 Hz), 5.06 - 5.11 (m, 2H), 5.75 (d, 1H, J=1.1 Hz), 6.72 (dd, 1H, J=2.3, 10.1 Hz), 6.76 (d, 1H, J=10.1 Hz), 7.64 (d, 1H, J=2.3 Hz), 7.92 (br s, 1H).

FAB-MS (M/Z); 344 $(M+3)^+$

[0041] To a solution of 15.0 mg of 2-farnesoylamino-1,4-benzoquinone in 0.05 ml of dioxane was added dropwise 0.045 ml of an aqueous solution of sodium hypochlorite under cooling with water, followed by stirring at room temperature for 30 minutes. A phosphate buffer (pH 7) was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and dried over sodium sulfate. The solvent was removed by evaporation, and the residue was purified by silica gel chromatography (ethyl acetate/n-hexane=1/7-dichloromethane/toluene=4/3) to give 1.7 mg (11%) of Compound I-1.

Rf 0.29 (ethyl acetate/n-hexane=2/8)

^{1}HNMR ($CDCl_3$) δ; 1.59 (s, 3H), 1.61 (d, 3H, J=0.9 Hz), 1.67 (d, 3H, J=1.0 Hz), 1.96 - 2.11 (m, 4H), 2.21 (s, 3H), 2.18 - 2.24 (m, 4H), 3.81 (dd, 1H, J=2.2, 3.7 Hz), 3.90 (d, 1H, J=3.7 Hz), 5.08 (m, 2H), 5.70 (d, 1H, J=1.0 Hz), 7.59 (d, 1H, J=2.2 Hz), 7.73 (bs, 1H).

FAB-MS (M/Z); 358 $(M+1)^+$

[0042] Compound I-1 (racemate) was fractionated by HPLC using a column for optically active compound, CHIRACEL OD (1ø × 25 cm), and hexane-isopropyl alcohol (15:1) as an eluent at a flow rate of 4 ml/min. The peaks at

retention times of 24 minutes and 26.2 minutes were collected.

Compound I-1β (5S, 6R-form):

[0043] HPLC retention time: 24 minutes. The CD spectrum showed a negative Cotton effect at 367 nm and 317 nm.

Compound I-1α (5R, 6S-form):

[0044] HPLC retention time: 26.2 minutes. The CD spectrum showed a positive Cotton effect at 366 nm and 317 nm.

[0045] The compounds of Examples 2 to 5 described hereinafter were synthesized in a manner similar to that in Example 1 except for using a corresponding acid chloride or anhydride in place of farnesoyl chloride.

Example 2

4,5-Epoxy-1-lauroylamino-3,6-dioxocyclohexene (Compound I-2)

[0046] Rf 0.45 (ethyl acetate/hexane=1/4)
^{1}HNMR ($CDCl_3$) δ; 0.88 (t, 3H, J=6.9 Hz), 1.2 - 1.4 (m, 16H), 1.67 (quintet, 2H, J=7.5 Hz), 2.40 (t, 2H, J=7.5 Hz), 3.82 (dd, 1H, J=2.2, 3.7 Hz), 3.90 (d, 1H, J=3.7 Hz), 7.54 (d, 1H, J=2.2 Hz), 7.80 (bs, 1H).
FAB-MS (M/Z); 322 $(M+1)^+$

Example 3

4,5-Epoxy-1-palmitoylamino-3,6-dioxocyclohexene (Compound I-3)

[0047] Rf 0.20 (ethyl acetate/hexane=1/4)
^{1}HNMR ($CDCl_3$) δ; 0.88 (t, 3H, J=7.0 Hz), 1.2 - 1.4 (m, 24H), 1.67 (quintet, 2H, J=7.5 Hz), 2.40 (t, 2H, J=7.5 Hz), 3.82 (dd, 1H, J=2.3, 3.7 Hz), 3.91 (d, 1H, J=3.7 Hz), 7.54 (d, 1H, J=2.3 Hz), 7.80 (bs, 1H).
FAB-MS (M/Z); 378 $(M+1)^+$

Example 4

4,5-Epoxy-1-linoleoylamino-3,6-dioxocyclohexene (Compound I-4)

[0048] Rf 0.30 (ethyl acetate/hexane=1/4)
^{1}HNMR ($CDCl_3$) δ; 0.89 (t, 3H, J=6.8 Hz), 1.2 - 1.4 (m, 14H), 1.67 (quintet, 2H, J=7.0 Hz), 2.05 (q, 4H, J=7.0 Hz), 2.40 (t, 2H, J=7.5 Hz), 2.77 (t, 2H, J=6.8 Hz), 3.82 (dd, 1H, J=2.3, 3.7 Hz), 3.90 (d, 1H, J=3.7 Hz), 5.29 - 5.41 (m, 4H), 7.54 (d, 1H, J=2.3 Hz), 7.80 (bs, 1H).
FAB-MS (M/Z) ; 402 $(M+1)^+$

Example 5

4,5-Epoxy-1-geranylgeranoylamino-3,6-dioxocyclohexene (Compound I-5)

[0049] Rf 0.30 (ethyl acetate/hexane=1/4)
^{1}HNMR ($CDCl_3$) δ; 1.59 (d, 3H, J=0.7 Hz), 1.60 (bs, 3H), 1.62 (bs, 3H), 1.68 (d, 3H, J=1.1 Hz), 1.98 (quintet, 2H, J=7.5 Hz), 2.07 (quintet, 2H, J=7.5 Hz), 2.19 - 2.21 (m, 7H), 3.81 (dd, 1H, J=2.3, 3.7 Hz), 3.90 (d, 1H, J=3.7 Hz), 5.07 - 5.11 (m, 3H), 5.70 (bs, 1H), 7.54 (d, 1H, J=2.2 Hz), 7.59 (d, 1H, J=2.3 Hz), 7.73 (bs, 1H).
FAB-MS (M/Z); 426 $(M+1)^+$

Reference Example 1

4-Methoxy-2-nitrophenol

[0050] To a stirred solution of 124 mg of 4-methoxyphenol in dichloromethane were added 1g of silica gel and 0.077 ml of concentrated nitric acid at room temperature. After the completion of the reaction was detected by thin layer chromatography, the reaction mixture was filtered using Celite® 535 (NACALAI TESQUE, INC.). The filtrate was evaporated, and the residue was purified by silica gel chromatography (dichloromethane) to give 98.5 mg (58%) of 4-meth-

oxy-2-nitrophenol.
Rf 0.65 (ethyl acetate/toluene=1/9)
^{1}HNMR ($CDCl_3$) δ; 3.83 (s, 3H), 7.08 (d, 1H, J=9.3 Hz), 7.24 (dd, 1H, J=2.9, 9.3 Hz), 7.51 (d, 1H, J=2.9 Hz), 10.33 (s, 1H).
FAB-MS (M/Z); 168 $(M-1)^-$

Reference Example 2

2-Amino-4-methoxyphenol

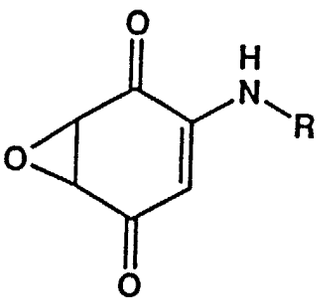
[0051] In 2.4 ml of ethyl acetate was dissolved 120 mg of 4-methoxy-2-nitrophenol obtained in Reference Example 1, and 12 mg of platinum oxide was added to the mixture, followed by stirring in a hydrogen stream at room temperature for 1 hour. The reaction mixture was filtered using Celite® 535 (NACALAI TESQUE, INC.) and a solution of hydrogen chloride in ethyl acetate was added to the filtrate. The resulting precipitate was collected by filtration and dried to give 111 mg (89%) of 2-amino-4-methoxyphenol.
Rf 0.47 (chloroform/methanol=1/9)
^{1}HNMR ($CDCl_3$) δ; 3.75 (s, 3H), 6.90 (m, 3H).

Effect of the Invention

[0052] The present invention provides an epoxycyclohexenedione derivative having antimicrobial activity and anti-tumor activity or a pharmaceutically acceptable salt thereof.

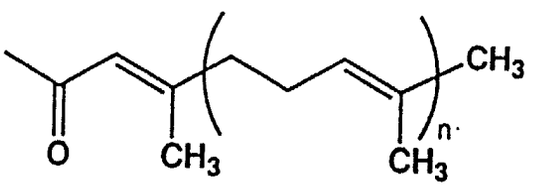
Claims

1. An epoxycyclohexenedione derivative represented by formula (I):



(I)

wherein R is a straight-chain or branched alkanoyl group having 10 to 25 carbon atoms, a straight-chain alkenoyl group having 16 to 25 carbon atoms, or a group represented by formula (A):



(A)

wherein n is an integer of 1 to 4; or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1 which is selected from the group consisting of 4,5-epoxy-1-farnesoylamino-3,6-dioxocyclohexene, 4,5-epoxy-1-lauroylamino-3,6-dioxocyclohexene, 4,5-epoxy-1-palmitoylamino-3,6-dioxocyclohexene, 4,5-epoxy-1-linoleoylamino-3,6-dioxocyclohexene, 4,5-epoxy-1-geranylgeranoylamino-3,6-dioxocyclohexene, and a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the epoxycyclohexenedione derivative or a pharmaceutically acceptable salt thereof according to Claim 1 or 2.

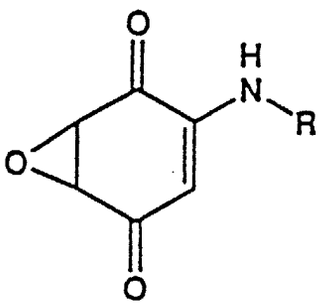
4. A compound according to claim 1 or 2 for use as a medicament.

5. Pharmaceutical composition for use as a medicament comprising one or more compounds according to claim 1 or 2 as the active ingredient and a pharmaceutically acceptable support.

6. Use of one or more compounds according to claim 1 or 2 or of the composition of claim 3 for the manufacture of a medicament having an antimicrobial and/or antitumor activity.

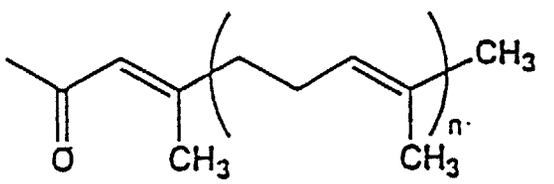
Patentansprüche

1. Epoxycyclohexendionderivat der Formel (I):



(I)

in der R ein geradkettiger oder verzweigter Alkanoylrest mit 10 bis 25 Kohlenstoffatomen ein geradkettiger Alkenoylrest mit 16 bis 25 Kohlenstoffatomen oder ein Rest der Formel (A), ist:



(A)

in der n eine ganze Zahl von 1 bis 4 ist; oder ein pharmazeutisch verträgliches Salz davon.

2. Verbindung nach Anspruch 1, ausgewählt aus 4,5-Epoxy-1-farnesoylamino-3,6-dioxocyclohexen, 4,5-Epoxy-1-lauroylamino-3,6-dioxocyclohexen, 4,5-Epoxy-1-palmitoylamino-3,6-dioxocyclohexen, 4,5-Epoxy-1-linoleoylamino-3,6-dioxocyclohexen, 4,5-Epoxy-1-geranylgeranoylamino-3,6-dioxocyclohexen und einem pharmazeutisch verträglichen Salz davon.

3. Arzneimittel, umfassend einen pharmazeutisch verträglichen Träger und das Epoxycyclohexendionderivat oder ein pharmazeutisch verträgliches Salz davon nach Anspruch 1 oder 2.

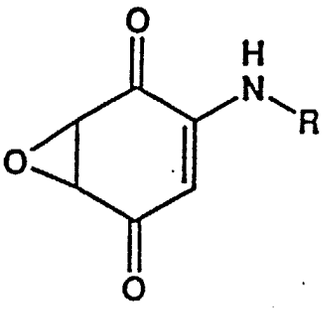
4. Verbindung nach Anspruch 1 oder 2 zur Verwendung als Medikament.

5. Arzneimittel zur Verwendung als Medikament, umfassend eine oder mehrere Verbindungen nach Anspruch 1 oder 2 als Wirkstoff und ein pharmazeutisch verträgliches Trägermaterial.

6. Verwendung einer oder mehrerer Verbindungen nach Anspruch 1 oder 2 oder des Mittels nach Anspruch 3 zur Herstellung eines Medikaments mit antimikrobieller und/oder Antitumor-Wirksamkeit.

Revendications

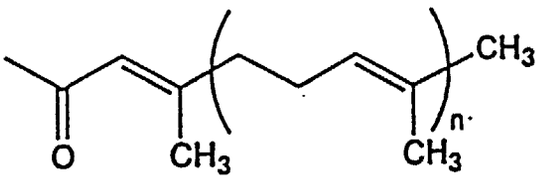
1. Dérivé d'épicyclohexènedione, représenté par la formule (I):



(I)

dans laquelle R représente :

un groupe alcanoyle à chaîne droite ou ramifiée, comportant de 10 à 25 atomes de carbone,
un groupe alcénoyle à chaîne droite ou ramifiée, comportant de 16 à 25 atomes de carbone,
ou un groupe représenté par la formule (A) :



(A)

où n représente un nombre entier valant de 1 à 4 ;
ou sel admissible en pharmacie d'un tel dérivé.

2. Composé conforme à la revendication 1, choisi dans l'ensemble que constituent :

le 4,5-époxy-1-farnésoylamino-3,6-dioxocyclohexène,
le 4,5-époxy-1-lauroylamino-3,6-dioxocyclohexène,
le 4,5-époxy-1-palmitoylamino-3,6-dioxocyclohexène,
le 4,5-époxy-1-linoléoylamino-3,6-dioxocyclohexène,
et le 4,5-époxy-1-géranylgéranoylamino-3,6-dioxocyclohexène, ainsi que leurs sels admissibles en pharmacie.

3. Composition pharmaceutique comprenant un véhicule admissible en pharmacie et un dérivé d'époxycyclohexènedione, ou un sel admissible en pharmacie d'un tel composé, conforme à la revendication 1 ou 2.

4. Composé conforme à la revendication 1 ou 2, destiné à être employé en tant que médicament.

5. Composition pharmaceutique destinée à être employée en tant que médicament, comprenant un ingrédient actif constitué d'un ou de plusieurs composés conformes à la revendication 1 ou 2, ainsi qu'un véhicule admissible en pharmacie.

6. Emploi d'un ou de plusieurs composés conformes à la revendication 1 ou 2, ou d'une composition conforme à la revendication 3, en vue de préparer un médicament possédant une activité anti-microbienne et/ou une activité antitumorale.