EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent: 24.01.2007 Bulletin 2007/04

(21) Application number: 01908199.1

(22) Date of filing: 01.03.2001

(51) Int CI.: C07D 493/10 (2006.01) A61K 31/357 (2006.01) A61P 33/06 (2006.01)

(86) International application number: PCT/JP2001/001568


(54) NOVEL TRIOXA TRICYCLIC COMPOUNDS HAVING ANTIMALARIAL ACTIVITY
NEUE TRIOXA-TRIZYKLISCHE-VERBINDUNGEN MIT ANTI-MALARIA-AKTIVITÄT
NOUVEAUX COMPOSÉS TRIOXA TRICYCLIQUES DOTES D’UNE ACTIVITE ANTIPALUDIQUE

(84) Designated Contracting States: CH FR GB LI

(30) Priority: 03.03.2000 JP 2000058736

(43) Date of publication of application: 04.12.2002 Bulletin 2002/49

(73) Proprietor: Japan Science and Technology Agency
Kawaguchi-shi
Saitama (JP)

(72) Inventors:
• IHARA, Masataka
Sendai-shi
Miyagi 982-0021 (JP)
• TAKASU, Kiyosei
Sendai-shi
Miyagi 982-0012 (JP)
• WATAYA, Yusuke
Okayama-shi
Okayama 703-8275 (JP)
• KIM, Hye-Sook
Okayama-shi, Okayama 700-0089 (JP)

(74) Representative: Harding, Charles Thomas
D Young & Co
120 Holborn
London EC1N 2DY (GB)

(56) References cited:
WO-A-93/14756
WO-A-00/04025


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The present invention relates to a novel compound having antimalarial activity and an antimalarial agent containing the novel compound as an active component.

Malaria is spread from person to person by the bite of a mosquito, Anopheles spp. A malaria parasite, being injected into a human body as a sporozoite together with saliva of a mosquito, enters into a hepatocyte and multiplies as an exoerythrocytic form (tissue form) parasite, and 10 to 14 days later, the parasite becomes a schizont. A schizont, which corresponds to a seed of a plant, is produced in a mature schizont, and this schizont (merozoite) spills and enters into another erythrocyte, and then repeats its asexual reproduction. Although some of the schizonts become male or female gametocytes without asexual reproduction, schizonts cannot proliferate further in a human body, and schizonts do not become male or female gametes and mate for sexual reproduction until they enter into the body of a mosquito. After several stages, such gamete matures and becomes a sporozoite which has numerous sporozoites inside, and when a mosquito sucks the blood of human, such sporozoites are transfused into the human body together with saliva of the mosquito. There are four kinds of malaria parasites that infect human: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale and Plasmodium malariae, and it is estimated that 200 to 300 million people are infected with malaria in the world, and that two to three million people die from malaria every year. In recent years, there emerge insecticide-resistant mosquitoes and chloroquine-resistant malaria parasites, and it is becoming difficult to deal with these organisms.

As an antimalarial agent or an antimalarial compound, the following are conventionally known: a novel compound of ortho-condensation system containing two heterocycles as described in Japanese Laid-Open Patent Application No. 2000-7673; an antimalarial agent containing a compound having ICAM-1 expression suppressing activity as an active component as described in Japanese Laid-Open Patent Application No. 11-228446; an antimalarial agent containing a nucleoside derivative and the like such as 5’-o-sulfamoyl-2-chloroadenosine or the like as an active component as described in Japanese Laid-Open Patent Application No. 11-228422; an antimalarial agent containing tricothecenes and the like as an active component as described in Japanese Laid-Open Patent Application No. 11-228408; an antimalarial agent containing cycloprodigiosin and the like as an active component as described in Japanese Laid-Open Patent Application No. 10-265382; a drug for preventing or treating malaria containing riminophenazone as an active component as described in Japanese Laid-Open Patent Application No. 8-231401; an agent for overcoming antimalarial drug resistance containing a quinoline derivative and the like as an active component as described in Japanese Laid-Open Patent Application No. 8-73355; an antimalarial agent containing 5-fluoroorotic acid and sulfamonomethoxyn as an active component as described in Japanese Laid-Open Patent Application No. 8-59471; an antimalarial agent containing Astragalus membranaceus, Cinnamomum cassia, Rehmanniae Radix, Paeonia lactiflora, Cnidii Rhizoma, Astragalus Radix, Angelicae Radix, Panax ginseng, Poria cocos, Glycyrrhizae Radix, Rehmanniae Radix, Paeonia lactiflora, Cnidii Rhizoma, Astragalus Radix, Angelicae Radix, Panax ginseng, Poria cocos, Glycyrrhizae Radix, or extracts thereof as an active component as described in Japanese Laid-Open Patent Application No. 7-82165; an antimalarial agent containing a tetrapyrrole derivative and the like as an active component as described in Japanese Laid-Open Patent Application No. 6-157308; an antimalarial agent containing 15-deoxyxperguin is the like as an active component as described in Japanese Laid-Open Patent Application No. 5-97665.

Malaria is a serious infection. 200 to 300 million people are infected with malaria and two to three million people die from malaria every year. Further, the emergence of a malaria parasite resistant to chloroquine, which is a drug heavily used as a panacea of malaria, has become a serious problem, and therefore, there is an urgent need to develop an effective remedy. Artemisinin, which is isolated from plants that belong to Asteraceae and has a trioxa structure, is effective to chloroquine-resistant malaria parasites, and this nature derived compound is currently used as a remedy. However, a malaria parasite which shows resistance also to artemisinin has already emerged as well, and it is causing a more serious problem. An object of the present invention is to provide a novel compound having antimalarial activity and an antimalarial agent containing the novel compound as an active component.

The inventors of the present invention have conducted intensive study as to synthesis of artemisinin analogues in order to attain the above-mentioned object, and found that found that 12-hydroxy-2-(1-methoxycarbonyl)-5-oxo-10,11,13-trioxatricyclo[7.2.0.1^5]tridecane synthesized by using photoreduction reaction, from bicyclic olefin synthesized by intramolecular Diels-Alder reaction, shows extremely high antimalarial activity and selective toxicity, and the
The present invention relates to a compound represented by a following general formula (I) wherein $R^1$ represents a hydrogen atom or an optionally branched C1-C6 alkyl group, $R^2$ represents an optionally branched C1-C6 alkyl group and $R^3$ represents an oxygen atom (claim 1), and the compound according to claim 1, wherein the compound represented by the general formula (I) is 12-hydroxy-2-(1-methoxycarbonylmethyl)-5-oxo-10,11,13-trioxatricyclo[7.2.0.0^1,6]tridecane represented by a following formula (II) (claim 2).

The present invention further relates to an antimalarial agent containing a compound represented by a following general formula (I) wherein $R^1$ represents a hydrogen atom or an optionally branched C1-C6 alkyl group, $R^2$ represents an optionally branched C1-C6 alkyl group and $R^3$ represents an oxygen atom; as an active component (claim 3), and the antimalarial agent according to claim 3, wherein the compound represented by the general formula (I) is 12-hydroxy-2-(1-methoxycarbonylmethyl)-5-oxo-10,11,13-trioxatricyclo[7.2.0.0^1,6]tridecane represented by a following formula (II) (claim 4).
BEST MODE TO CARRY OUT THE INVENTION

[0008] In the compound represented by the general formula (I) according to the present invention, R\(^1\) represents a hydrogen atom or an optionally branched C1-C6 alkyl group, and specific examples of such optionally branched C1-C6 alkyl group include a methyl group, an ethyl group, an isopropyl group and a t-butyl group. R\(^2\) represents an optionally branched C1-C6 alkyl group, and specific examples of such optionally branched C1-C6 alkyl group include a methyl group, an ethyl group, an isopropyl group and a t-butyl group.

[0009] Further, in the compound represented by the general formula (I) according to the present invention, R\(^3\) represents an oxygen atom.

[0010] Among these compounds represented by the general formula (I), 12-hydroxy-2-(1-methoxycarbonyl-ethoxy)-5-oxo-10,11,13-trioxatricyclo[7.2.0.0\(^{1,6}\)]tridecane represented by the formula (II) having excellent antimalarial activity is preferable in view of antimalarial activity and selective toxicity.

[0011] A method of producing the compound represented by the general formula (I) according to the present invention and 12-hydroxy-2-(1-methoxycarbonyl-ethoxy)-5-oxo-10,11,13-trioxatricyclo[7.2.0.0\(^{1,6}\)]tridecane represented by the formula (II) is not particularly limited. For example, said compounds can be obtained as a peroxide moiety by a method comprising the steps of: triene is synthesized from 1,4-butanediol derivative by several steps of known synthetic reaction; the synthesized triene is stereoselectively transformed into cis-decalone through Dess-Martin oxidation followed by intramolecular Diels-Alder reaction; the cis-decalone is subjected to base treatment and then to singlet oxygen oxidation-air oxidation (Roth’s method).

[0012] When the compound according to the present invention is used for prevention, inhibition and treatment of infection caused by malaria parasites, any of oral administration, subcutaneous injection, intravenous injection, local administration or the like can be used as an administration route. As examples of drugs, drugs for oral administration such as powders, tablets, sublingual tablets, pills, capsules, granules or the like and those for parenteral administration such as instillations, injectable solutions, suppositories or the like, both formulated by using pharmaceutically acceptable carriers, excipients and other additives, are usually exemplified. Examples of pharmaceutically acceptable carriers, excipients and other additives include glucose, lactose, gelatin, mannitol, starch paste, magnesium trisilicate, corn starch, keratin, colloidal silica, and it may further contain adjuvants such as a stabilizer, an expander, a colorant and an aromatic substance. Each of these drugs can be produced by methods conventionally known to person skilled in the art. In addition, though the dose per day depends on symptom, weight, age, sex and the like of patients and cannot be determined uniformly, it is usually preferable to administer 0.1 to 1000 mg, more preferably 1 to 600 mg, of the compound according to the present invention per day to adult patients.

[0013] The present invention is explained below with reference to examples, but the technical scope of the present invention is not limited to these examples.

Example 1 [Production of 12-hydroxy-2-(1-methoxycarbonyl-ethoxy)-5-oxo-10,11,13-trioxatricyclo[7.2.0.0\(^{1,6}\)]tridecane]

[0014] 12-hydroxy-2-(1-methoxycarbonyl-ethoxy)-5-oxo-10,11,13-trioxatricyclo[7.2.0.0\(^{1,6}\)]tridecane was synthesized by using (4E)-7-methyl-1-tetrahydropyranoxy-4,7-octadien-6-ol as a starting material. The starting material represented by a following formula (I), (4E)-7-methyl-1-tetrahydropyranoxy-4,7-octadien-6-ol was synthesized according to the method as previously described (the Journal of Organic Chemistry, Vol. 51, 4023-4028, 1986).
Example 1-1 [Synthesis of a novel substance, (4E)-7-methyl-6-propanoyloxy-1-tetrahydropyroxy-4,7-octadiene]

[0015] 7.26 g of (4E)-7-methyl-1-tetrahydropropyloxy-4,7-octadien-6-ol (1) and 7.4 ml of pyridine were put in methylene chloride solution (65 ml). 3.1 ml of propionyl chloride was added dropwise to the solution at 0°C, and the resulting mixture was stirred for 30 minutes. Subsequently, the mixture was added with water and subjected to diethyl ether extraction, and its organic layer was washed with 10% of aqueous potassium hydrogen sulfate and saturated saline, then dried over anhydrous magnesium sulfate. Residues obtained by refluxing a solvent under reduced pressure were subjected to silica gel column chromatography, and 7.74 g of achromatic oily substance was obtained at 86% yield from a hexane-ethyl acetate (10:1 v/v) eluting section. Physical property of the obtained substance is as follows, and a structural formula of a compound based on the physical property is shown in a formula (2).

IR (neat) cm⁻¹: 1740.¹H-NMR (300 MHz, CDCl₃) δ :1.15 (3H, t, J = 7.5 Hz), 1.47-1.76 (8H, m), 1.72 (3H, s), 2.10-2.20 (2H, m), 2.36 (2H, q, J = 7.5 Hz), 3.32-3.54 (4H, m), 3.68-3.90 (4H, m), 4.53-4.60 (1H, m), 4.88 (1H, s), 4.98 (1H, s), 5.45 (1H, dd, J = 14.5, 7.0 Hz), 5.57 (1H, d, J = 7.0 Hz), 5.75 (1H, dd, J = 14.5, 7.0 Hz). MS m/z: 295 (M⁺-1). Elemental analysis Calcd for C₁₇H₂₈O₄: C, 68.87; H, 9.52. Found : C, 69.02; H, 9.39.

Example 1-2 [Synthesis of a novel substance, methyl(2S*, 3R*, 4E)-2,6-dimethyl-3-[3'-(tetrahydropropyloxy)propyl]-hepta-4,6-dienoate]

[0016] 5.1 ml of butyllithium in hexan solution (1.54 M) was added dropwise to THF solution (50 ml) containing 1.51 ml of disopropylamine at 0°C, and then the resulting solution was stirred for 30 minutes at 0°C and for 1 hour at -78°C. 1.0 g of the obtained compound (2) above in tetrahydrofuran solution (5 ml) was added dropwise to the above solution in 1 hour and then the resulting mixture was stirred for 1 hour at -78°C. After that, the mixture was added with 1.03 ml of chlorotrimethylsilane and stirred for 1 hour, and gradually warmed to room temperature and stirred for 2 hours. After the reaction was completed, the mixture was added with 2 ml of methanol and stirred for 30 minutes. Residues obtained by refluxing a solvent were basified by aqueous sodium bicarbonate and subjected to back extraction. The obtained water layer was acidified by 10% of potassium hydrogen sulfate, followed by extraction with ethyl acetate. Its organic layer was washed with saturated saline, then dried over anhydrous magnesium sulfate. Residues obtained by refluxing a solvent under reduced pressure were added with ether (3 ml), then added dropwise with an excessive amount of diazomethane in diethyl ether solution at 0°C, and the resulting mixture was stirred for 1 hour. Residues obtained by refluxing a solvent under reduced pressure were subjected to silica gel column chromatography, and 0.76 g of light yellow oily substance was obtained at 72% yield from a hexan-ethyl acetate (9:1 v/v) eluting section. Physical property of the obtained substance is as follows, and a structural formula of a compound based on the physical property is shown in a formula (3).
Example 1-3 [Synthesis of a novel substance, methyl(2S*, 3R*, 4E)-3-(3'-hydroxypropyl)-2,6-dimethylhepta-4,6-dienoate]

0.11 g of the obtained compound (3) above in methanol solution (6 ml) was added with 34 mg of toluenesulfonic acid monohydrate at room temperature, and the resulting solution was stirred for 1 hour. Subsequently, residues obtained by refluxing a solvent under reduced pressure were added with saturated aqueous sodium bicarbonate, followed by extraction with ethyl acetate. The obtained organic layer was washed with saturated saline, then dried over anhydrous magnesium sulfate. Residues obtained by refluxing a solvent under reduced pressure were subjected to silica gel column chromatography, and 75.0 mg of achromatic oily substance was obtained at 94% yield from a hexan-ethyl acetate (2:1 v/v) eluting section. Physical property of the obtained substance is as follows, and a structural formula of a compound based on the physical property is shown in a formula (4).

IR (neat) cm⁻¹: 3400, 1740, 1610. ¹H-NMR (300 MHz, CDCl₃) δ: 1.08 (3H, d, J = 6.7 Hz), 1.08-1.10 (3H, dd, J = 15.7, 9.3 Hz), 2.24-2.45 (2H, m), 3.59-3.70 (2H, m), 3.62-3.80 (2H, m), 4.89 (2H, s), 5.27 (1H, dd, J = 15.7, 9.3 Hz), 6.10 (1H, dd, J = 15.7 Hz). MS m/z: 226 (M⁺). Elemental analysis Calcd for C₁₃H₂₂O₃: C, 71.39; H, 9.59. Found: C, 71.12; H, 9.75.

Example 1-4 [Synthesis of a novel substance, methyl(2S*, 3R*, 4E)-3-(3'-hydroxy-4-pentenyl)-2,6-dimethylhepta-4,6-dienoate]

253 mg of the obtained compound (4) above in methylene chloride solution (4 ml) was sequentially added with 631 mg of pyridinium bichromate and 0.7 g of powdery 4 Å of molecular sieve at room temperature, and the resulting mixture was stirred for 1.5 hour. The mixture was diluted with diethyl ether and added with 1 g of Frolisil, then stirred for 10 minutes, followed by celite filtration. By refluxing a filtrate under reduced pressure, crude aldehyde was obtained as a yellow oily substance. This crude substance was put in tetrahydrofuran solution (3 ml), and added dropwise with 1.1 ml of vinyl magnesium bromide-tetrahydrofuran solution (1.0 M) at -78°C, and then the resulting solution was stirred for 20 minutes. Subsequently, saturated aqueous ammonium chloride was added to the solution at 0°C, then diethyl ether...
extraction was conducted. Its organic layer was washed with saturated saline, then dried over anhydrous magnesium sulfate. Residues obtained by refluxing a solvent under reduced pressure were subjected to silica gel column chromatography, and 0.18 g of achromatic oily substance was obtained at 65% yield from a hexan-ethyl acetate (4:1 v/v) eluting section. Physical property of the obtained substance is as follows, and a structural formula of a compound based on the physical property is shown in a formula (5).

**Example 1-5 [Synthesis of a novel substance, (1R*, 2R*, 6R*, 1'S*)-2-(1'-methoxycarbonylethyl)-9-methylbicyclo[4.4.0]decane-9-ene-5-one]**

The obtained compound (5) above (12.1 mg) in methylene chloride solution (0.5 ml) was added to Dess-Martin reagent (32.8 mg) in methylene chloride solution (1.0 ml) at 0°C, and then the resulting mixture was stirred for 2 hours at room temperature. Then, the mixture was poured into saturated aqueous sodium bicarbonate-2% of aqueous sodium thiosulfate (1:7 v/v), followed by diethyl ether extraction. Its organic layer was washed with water and saturated saline, then dried over anhydrous magnesium sulfate. Residues obtained by refluxing a solvent under reduced pressure were subjected to silica gel column chromatography, and 9.4 mg of light yellow oily substance was obtained at 78% yield from a hexan-ethyl acetate (6:1 v/v) eluting section. Physical property of the obtained substance is as follows, and a structural formula of a compound based on the physical property is shown in a formula (6).

**Example 1-6 [Synthesis of a novel substance, (1R*, 2R*, 6S*)-2-(1'-methoxycarbonyl ethyl)-9-methylbicyclo[4.4.0]decane-9-ene-5-one]**

91 mg of the obtained compound (6) above in tetrahydrofuran solution (3 ml) was added with 73 mg of sodium hydride (60% of mineral oil suspension) at 0°C, and the mixture was stirred for 3 hours at room temperature. Subsequently, water was added to the mixture and diethyl ether extraction was conducted. The obtained organic layer was washed
with saturated saline, then dried over anhydrous magnesium sulfate. Residues obtained by refluxing a solvent under reduced pressure were subjected to silica gel chromatography, and 90 mg of a mixture of said compound represented by the formula (6) and a compound represented by a formula (7) mentioned below was obtained as achromatic oily substance [compound (6):compound (7)=1:1.2] from a hexan-ethyl acetate (5:1 v/v) eluting section. Production was then stopped, and the product was used for next reaction.

Example 1-7 [Synthesis of a novel substance of the present invention, 12-hydroxy-2-(1-methoxycarbonylethyl)-5-oxo-10,11,13-trioxatricyclo[7.2.0.0^{1,6}]tridecane]

[0022] Solution wherein 30 mg of the obtained mixture [of compound (6) and compound (7)] above was put in acetone solution (20 ml) was added with 0.9 mg of methylene blue, then irradiated by light of 100 W tungsten lamp for 24 hours at room temperature in oxygen air stream. After that, a solvent was refluxed under reduced pressure, and methylene blue was removed by filtration after diethyl ether was added to, and the filtrate was refluxed under reduced pressure. The obtained light yellow oily substance was suspended in petroleum ether (6 ml), and trifluoroacetic acid (0.01 ml) was added to the suspension, and the suspension was left for 24 hours at room temperature in air atmosphere. Subsequently, the petroleum ether dissolution was refluxed under reduced pressure, and the obtained residues were subjected to silica gel chromatography, and 1.8 mg of achromatic oily substance was obtained at 5% yield from a hexan-ethyl acetate (6:1 v/v) eluting section. Physical property of the obtained substance is as follows, and a structural formula of a compound based on the physical property was the one shown in the formula (II).

Example 2 [Measurement of antimalarial activity and selective toxicity]

[0024] Antimalarial activity and selective toxicity of the compound according to the present invention, 12-hydroxy-2-(1-methoxycarbonylethyl)-5-oxo-10,11,13-trioxatricyclo[7.2.0.0^{1,6}]tridecane, represented by the formula (II) as obtained in Example 1 was measured. Antimalarial activity was evaluated by measuring 50% inhibitory concentration, and selective toxicity was evaluated by calculating chemotherapeutic coefficient (selective toxicity).

Example 2-1 [Culture of Plasmodium falciparum]

[0025] P. Falciparum FCR-3 strain (ATCC30932) and R Falciparum Honduras-1 strain (ATCC30935), both of which are Plasmodium falciparum, were used as test malaria parasites for measuring antimalarial activity. A filter-sterilized RPMI1640 medium was adjusted to be pH 7.4 and added with human serum such that the serum made up 10% of the medium, and used as a test medium. The above-mentioned P. falciparum were cultured in O₂ at a concentration of 5%, CO₂ at a concentration of 5% and N₂ at a concentration of 90%, at a temperature of 36.5 °C. Hematocrit value (ratio of volume of erythrocytes in erythrocyte suspension) was used to be 5%. Initial infection rate of P. falciparum at the beginning of culture was adjusted to be 0.1%. A 24-well plate was used for culture and a medium was replaced everyday, and cultures were transferred at infection rate of 4%. A thin-layer smear was constructed and subjected to Giems staining which had been originally developed for malarial test, or Diff-Qick staining, and followed by measurement.
Infection rate of malarial parasite (%) = \frac{\text{number of infected erythrocytes}}{\text{total number of erythrocytes}} \times 100

Example 2-2 [Growth inhibition test of \textit{P. falciparum}]

[0026] Cultured erythrocytes infected with \textit{P. falciparum} were gathered by centrifugation and washed with a medium containing serum, then noninfected erythrocytes were added, and a culture liquid for \textit{P. falciparum} at initial infection rate of 0.3% was prepared. Hematocrit value in this case was adjusted to be 3%. The compound according to the present invention used for a test and represented by the formula (II) and three kinds of positive control drug (quinine, artemisinin, artesunate, mefloquine) were dissolved into sterilized water, N,N-dimethylformamide (DMF) or dimethylsulfoxide (DMSO), and a sample solution at prescribed concentration was prepared. 5 to 10 μl of the sample solution was added to each well of a 24-well plate. The sample solution was duplicated or triplicated. For control, sterilized water, DMF or DMSO was added by 10 μl per well. Next, the above-mentioned culture liquid for \textit{P. falciparum} prepared to be at initial infection rate of 0.3% was added by 990 to 995 μl each, and uniformly suspended in media by pipetting gently. After cultured for 72 hours in a CO₂-O₂-N₂ (5%, 5%, 90%) incubator, a thin-layer smear was constructed for each well of the culture plate, Giemsa staining or Diff-Qick staining was conducted, followed by measurement under a microscope (oil immersion, 1000x), and then infection rates of \textit{P. falciparum} in a group supplemented with a test liquid and in controls were calculated. The growth inhibition rate was calculated according to a formula mentioned below based on the infection rate of \textit{P. falciparum} as calculated above, and 50% growth inhibitory concentration (EC₅₀) was calculated.

\[
\text{Growth inhibition rate (\%)} = \frac{1-(b-a)}{(c-a)} \times 100
\]

a: initial infection rate  
b: infection rate of a sample solution after 72 hours  
c: infection rate of a control after 72 hours

Example 2-3 [Growth inhibition test of mouse FM3A cells]

[0027] An F28-7 strain, a wild-type strain of mouse breast cancer-derived FM3A cells was used. Immobilized fetal bovine serum was added to an ES medium such that the serum made up 2% of the medium, and culture was conducted in CO₂ at a concentration of 5%, and at 37°C. Doubling time of the F28-7 strain of FM3A cells under this condition was about 12 hours. Cells which had been precultured and entered to logarithmic growth phase were diluted to be 5x10⁴ cells/ml in the medium. The same sample solution as in the above-mentioned Example 2-2 was used. 5 to 10 μl of the sample solution was added to each well of a 24-well plate (when medium and the like were added, the final concentration became 1x10⁻⁴ ~ 1x10⁻⁵ M). The sample solution was duplicated or triplicated, and wells added with 10 μl of sterilized water, DMF or DMSO were prepared at the same time as controls. Next, a prepared suspension of cultured cells was added by 990 to 995 μl each, and uniformly suspended in media by pipetting gently. After cultured for 48 hours, the number of cells in each well was counted by a cell counter (CC-108; Toa. Medical Electrics), and growth rate was calculated by a formula mentioned below and 50% growth inhibitory rate (IC₅₀) was calculated. The cell proliferation inhibiting activity was calculated according to the number of cells in wells supplemented with the sample solution and in controls. Based on this, cell toxicity of the sample was evaluated.

\[
\text{Growth rate (\%)} = \frac{(C-A)}{(B-A)} \times 100
\]

A: the number of cells at the beginning  
B: the number of cells in a control after 2 days
C: the number of cells 2 days after supplementation of a sample

Example 2-4 [Assessment of drug efficacy]

[0028] Antimalarial activity of a sample was evaluated based on EC$_{50}$ and IC$_{50}$ values of the sample of P. falciparum and mouse FM3A cells. Chemotherapeutic coefficient used as an index of selective toxicity against P. falciparum was calculated by a formula mentioned below and drug efficacy was assessed.

Chemotherapeutic coefficient = $\frac{IC_{50} \text{ value of the sample of mouse FM3A cells}}{EC_{50} \text{ value of the sample of P. falciparum}}$

[0029] With regard to the compound according to the present invention and positive control drugs, EC$_{50}$ and IC$_{50}$ values and chemotherapeutic coefficients of samples of P. falciparum and mouse FM3A cells are shown in Table 1. Judging from the results shown in Table 1, the compound according to the present invention is revealed to have low toxicity and extremely excellent growth inhibition activity against malaria parasites.

<table>
<thead>
<tr>
<th>Compound</th>
<th>50% growth inhibitory concentration (M)</th>
<th>Chemotherapeutic coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EC$_{50}$</td>
<td>IC$_{50}$</td>
</tr>
<tr>
<td>Compound of the present invention</td>
<td>$3.9 \times 10^{-8}$</td>
<td>$2.4 \times 10^{-5}$</td>
</tr>
<tr>
<td>Quinine</td>
<td>$1.1 \times 10^{-7}$</td>
<td>$1.0 \times 10^{-4}$</td>
</tr>
<tr>
<td>Artemisinin</td>
<td>$7.9 \times 10^{-9}$</td>
<td>$1.0 \times 10^{-5}$</td>
</tr>
<tr>
<td>Artesunate</td>
<td>$1.7 \times 10^{-8}$</td>
<td>$3.0 \times 10^{-6}$</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>$3.2 \times 10^{-8}$</td>
<td>$2.9 \times 10^{-6}$</td>
</tr>
</tbody>
</table>

INDUSTRIAL APPLICABILITY

[0030] The novel compound having antimalarial activity according to the present invention inhibits the growth of drug-resistant P. falciparum at a mol concentration of $3.9 \times 10^{-8}$, and its selective toxicity against P. falciparum is more than 1,000 times as strong as that against mouse FA3A cells, and therefore, is extremely useful as an antimalarial agent.

Claims

1. A compound represented by a following general formula (I):

$$\text{R}^1\text{OH} \quad \text{R}^2\text{COOR}^2$$

(II)
EP 1 262 482 B1

wherein R¹ represents a hydrogen atom or an optionally branched C1-C6 alkyl group, R² represents an optionally branched C1-C6 alkyl group and R³ represents an oxygen atom.

2. The compound according to claim 1, wherein the compound represented by the general formula (I) is 12-hydroxy-2-(1-methoxycarbonylethyl)-5-oxo-10,11,13-trioxatricyclo[7.2.0.0₁,₆]tridecane represented by a following formula (II).

3. An antimalarial agent containing a compound represented by the general formula (I) as defined in claim 1.

4. An antimalarial agent containing the compound 12-hydroxy-2-(1-methoxycarbonylethyl)-5-oxo-10,11,13-trioxatricyclo[7.2.0.0₁,₆]tridecane represented by the formula (II) as defined in claim 2.

Patentansprüche

1. Verbindung, repräsentiert durch die folgende allgemeine Formel (I):

wobei R¹ ein Wasserstoffatom oder eine optional verzweigte C1-C6-Alkylgruppe repräsentiert, R² eine optional verzweigte C1-C6-Alkylgruppe repräsentiert und R³ ein Sauerstoffatom repräsentiert.

2. Verbindung nach Anspruch 1, wobei die durch die allgemeine Formel (I) repräsentierte Verbindung 12-Hydroxy-2-(1-methoxycarbonylethyl)-5-oxo-10,11,13-trioxatricyclo[7.2.0.0₁,₆]tridecane ist, repräsentiert durch die nachfolgende Formel (II):
3. Anti-Malariamittel, enthaltend eine Verbindung, repräsentiert durch die allgemeine Formel (I), wie sie in Anspruch 1 definiert ist.

4. Anti-Malariamittel, enthaltend die Verbindung 12-Hydroxy-2-(1-methoxycarbonylethyl)-5-oxo-10,11,13-trioxatri
cyclo[7.2.0.0^{1,6}]tridecan, repräsentiert durch die Formel (II), wie sie in Anspruch 2 definiert ist.

**Revendications**

1. Composé représenté par la formule générale (I) suivante :

   
   \[
   \text{dans laquelle } R^1 \text{ représente un atome d'hydrogène ou un groupe alkyle en C}_1 \text{ à C}_6 \text{ facultativement ramifié, } R^2 \text{ représente un groupe alkyle en C}_1 \text{ à C}_6 \text{ facultativement ramifié et } R^3 \text{ représente un atome d'oxygène.}
   \]

2. Composé selon la revendication 1, dans lequel le composé représenté par la formule générale (I) est le 12-hydroxy-
   2-(1-méthoxycarbonyléthyl)-5-oxo-10,11,13-trioxatricyclo[7.2.0.0^{1,6}]tridécan représenté par la formule (II) suivan-
   te
3. Agent antipaludéen contenant un composé représenté par la formule générale (I) telle que définie dans la revendication 1.

4. Agent antipaludéen contenant le composé 12-hydroxy-2-(1-méthoxycarbonyléthyl)-5-oxo-10,11,13-trioxatricyclo [7.2.0.0\(^{1,6}\)] tridécane représenté par la formule (II) telle que définie dans la revendication 2.