(54) Title: NOVEL ARTEMISININ OR DEOXOARTEMISININ GLYCOLIPID HYBRID DERIVATIVES AND ANTIANGIOGENIC USE THEREOF

(57) Abstract: The present invention relates to a novel artemisinin or deoxoartemisinin-glycolipid hybrid derivatives and antiangiogenic use thereof. The artemisinin or deoxoartemisinin-glycolipid hybrid derivatives of the present invention exhibit two or more times stronger activity than the existing drugs and little or no cellular toxicity to address safety to human body.
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NOVEL ARTEMISININ OR DEOXOARTEMISININ-GLYCOLIPID HYBRID DERIVATIVES AND ANTIANGIOGENIC USE THEREOF

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to a novel artemisinin or deoxoartemisinin-glycolipid hybrid derivatives and antiangiogenic use thereof.

DESCRIPTION OF THE RELATED ART

Angiogenesis is a physical process in which new blood vessels are formed from pre-existing vessels. The blockade of vascular endothelial growth factor results in regression of the disease and prolongation of survival when used for anti-cancer therapy. Discovery of new antiangiogenic agents based on small molecules is an attractive approach for the treatment of cancer.

Artemisinin, a sesquiterpene endoperoxide isolated from Artemisia annua L

Artemisinin and its derivatives have been reported as potential antitumor agents, and also been known to have antiangiogenic activity. In a previous report, we described the potent antiangiogenic effects of artemisinin derivatives. Non acetal-type derivates at C-12 of artemisinin and their dimers including a fullerene conjugate were synthesized and some of them showed potent in vivo antiangiogenic activity on the chorioallantoic membrane that was higher than or comparable to those of fumagillin and thalidomide. Furthermore, novel amide derivatives of a C-12 non acetal deoxoartemisinin trimer were synthesized and showed potent in vivo antiangiogenic activity according to the results of mouse matrigel plug assays.

Recently, some studies have reported the antiangiogenic activity of glycolipids.
Daumone, originally isolated from Caenorhabditis elegans, was identified by our laboratory and its total synthesis was presented. Daumone is represented by the following chemical formula:

\[
\text{HO}\stackrel{\text{O}}{\cdots}\text{HO} \quad \text{HO} \quad \text{OH}
\]

In a continuation of the investigation, we studied the anticancer activity of daumone against human cell lines. Daumone and tri-deoxyrhamnose derivatives containing amide side chains were the most potent anticancer compounds that we surveyed, with effective concentrations in the nanomolar range, which is comparable to that of doxorubicin.

Although various antiangiogenic agents have been developed, adverse side effects and limitations associated with antitumor therapies have recently become apparent. Cancer is a complex disease. In order to improve the activity of anticancer agents, treatment using hybrid dnjgs, an approach that incorporates two drugs in a single molecule, has been developed. The use of hybrid drugs can impact multiple targets simultaneously.

Throughout this application, several patents and publications are referenced and citations are provided in parentheses. The disclosure of these patents and publications is incorporated into this application in order to more fully describe this invention and the state of the art to which this invention pertains.

**SUMMARY OF THE INVENTION**

The present inventors have made intensive research to develop a novel compound having excellent antiangiogenic and anticancer activity. As a result, the inventors have synthesized various artemisinin or deoxoartemisinin-glycolipid hybrid derivatives which exhibit two or more times stronger activity than that of the existing drugs, thus completed the present invention.
Accordingly, it is an object of this invention to provide a novel artemisinin or deoxoartemisinin-glycolipid hybrid derivative.

It is another object of this invention to provide a pharmaceutical composition for preventing or treating an angiogenic disease.

It is still another object of this invention to provide a method for preventing or treating an angiogenic disease.

Other objects and advantages of the present invention will become apparent from the detailed description to follow taken in conjunction with the appended claims and drawings.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Fig. 1 represents the method of synthesizing compound 3i, one of the chemical compounds prepared in Example, by coupling reaction of deoxoartemisinin and glycolipid.

Fig. 2 represents the chemical structure of the deoxoartemisinin-glycolipid hybrid derivative of the present invention prepared in Example.

Fig. 3 is an image showing the antiangiogenic activity of artemisinin or deoxoartemisinin-glycolipid hybrid derivatives to the CAM (chick chorioallantoic membrane), (a) an image of control CAM, (b) an image of CAM treated with the artemisinin or deoxoartemisinin-glycolipid hybrid derivative of the present invention at a concentration of 2.5 nmol/egg.

**DETAILED DESCRIPTION OF THIS INVENTION**

In one aspect of the present invention, there is provided an artemisinin or deoxoartemisinin-glycolipid hybrid derivative represented by the Chemical Formula selected from the group consisting of the following Chemical Formulas 1-3:
wherein each $R_1$ and $R_2$ is independently hydrogen, halogen, $\text{C}_1-\text{C}_{10}$ alkyl, $\text{C}_1-\text{C}_{10}$ alkenyl, $\text{C}_1-\text{C}_{10}$ alkynyl, $\text{Q}-\text{Q}_0$ aryl, $\text{Q}-\text{Q}_0$ alkylaryl, $\text{Q}-\text{Q}_0$ aryalkyl, or $\text{Q}-\text{Q}_0$ heteroaryl;

each of $R_3$-$R_6$ is independently hydrogen, hydroxyl, alkoxy, carboxyl, halogen, nitro, $\text{C}_1-\text{C}_{10}$ alkyl, $\text{C}_1-\text{C}_{10}$ alkenyl, $\text{C}_5-\text{C}_{10}$ aryl, $\text{C}_6-\text{C}_{10}$ alkylaryl, $\text{Q}-\text{Q}_0$ aryalkyl, or $\text{Q}-\text{Q}_0$ heteroaryl;

$X$ and $Y$ are each independently substituted or unsubstituted linear or branched $\text{Q}-\text{Q}_0$ alkylene, or substituted or unsubstituted linear or branched $\text{Q}-\text{Q}_0$ alkenylene; and
each of m, n and k is independently 0 or 1.

The present inventors have made intensive research to develop a novel compound having excellent antiangiogenic and anticancer activity. As a result, the inventors have synthesized various artemisinin or deoxoartemisinin-glycolipid hybrid derivatives which exhibit two or more times stronger activity than that of the existing drugs, thus completed the present invention.

The artemisinin or deoxoartemisinin-glycolipid hybrid derivatives of the present invention may be synthesized by reacting various artemisinin or deoxoartemisinin derivatives with various glycoprotein derivatives. Deoxoartemisinin means a form of artemisinin in which an oxygen connected to a carbon at position 12 by a double bond is missed. If the hybrid of the present invention is synthesized from a deoxoartemisinin, the hybrid gets to have a nonacetal form at the 12^b carbon position.

One of the distinctive features of the deoxoartemisinin-glycolipid hybrid derivatives is to have a nonacetal form at the 12^a carbon position. The C-12 nonacetal-type artemisinin-glycolipid hybrids show more excellent antiangiogenic activity than the C-12 acetal-type artemisinin-glycolipid hybrids.

In the Chemical Formulas 1-3, the substituent indicated as R1 or R2 which is bound to the oxygen is each independently hydrogen, halogen, C1-C10 alkyl, C1-C10 alkenyl, Q-C10 alkynyl, C6-C9 aryl, Q-Q0 alkaryl, Q-Q0 arylalkyl, or Q-Q0 heteroaryl; preferably hydrogen, substituted or unsubstituted linear or branched C1-C3 alkyl, or benzyl.

The term "Q-Q0 alkyl" as used herein in conjunction with R group of the Formulas, means linear or branched monovalent saturated hydrocarbon having 1-10 carbon atoms, which includes methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyi, or various isomers thereof, but not limited to.

The term "Q-Q0 alkenyl" as used herein refers to branched or unbranched unsaturated hydrocarbon having 1-10 carbon atoms and one or more carbon-carbon double bonds. Alkenyl may comprise two or more carbon-carbon double bonds, and the double bonds may be conjugated or nonconjugated with each other. Alkenyl includes vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, petadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-
butene)-pentenyl, heptenyl, octenyl, nonenyi, decenyl, or isomers thereof, but not limited to.

The term "Q-Qo alkynyl" as used herein refers to randomly substituted \textit{e.g.}, substituted one or more) hydrocarbon radical (monovalent hydrocarbon) comprising 1 to 10 carbon atoms and one or more carbon-carbon triple bond.

The term "C_{5}-C_{0} aryl" as used herein refers to wholly or partially substituted or unsubstituted monocyclic or polycyclic carbon ring having 6-60 carbon atoms, which satisfies the law of Hückel. Aryl \textit{e.g.}, phenyl may be substituted at various positions by various substituent, for example by halo, hydroxy, nitro, cyano, substituted or unsubstituted linear or branched Q-Q alkyl, or linear or branched Q-Q alkoxy, but not limited to.

The term "aryalkyl \textit{e.g.}, benzyl" means alkyl group which is substituted by one or more aryl groups. The term "alkylaryl (alkaryl)" means aryl group which is substituted by one or more alkyl groups.

The term "heteroaryl" means heterocyclic aromatic group containing heteroatoms such as N, O and S. Heteroaryl may be substituted at various positions by various substituent, for example by halo, hydroxyl, nitro, cyano, substituted or unsubstituted linear or branched Q-Q alkyl, or linear or branched Q-Q alkoxy, but not limited to.

In the Chemical Formulas 1-3, the substituent indicated as the one of R_{1}-R_{e} which is directly bound to the ring carbon is independently hydrogen, hydroxyl, alkoxy, carboxyl, halogen, nitro, Q-Q_{0} alkyl, Q-Q_{0} alkenyl, Q-Q_{0} alkynyl, Q-Q_{0} aryl, Q-Q_{0} alkylaryl, Q-Q_{0} arylalkyl, or Q-Q_{0} heteroaryl; preferably hydrogen, hydroxyl, alkoxy, carboxyl, or substituted or unsubstituted linear or branched Q-Q alkyl.

In the Chemical Formulas 1-3, X and Y are each independently substituted or unsubstituted linear or branched Q-Q_{0} alkenylene, or substituted or unsubstituted linear or branched Q-Q_{0} alkenylene; preferably substituted or unsubstituted linear or branched Q-Q_{0} alkenylene.

The term "Q-Q_{0} alkenylene" as used herein refers to linear or branched divalent alkyl radical having 1-10 carbon atoms, which includes but not limited to methylene, ethylene, isopropylene, butylene, sec-butylene, pentylene, 1-methyl pentylene, 5-methyl pentylene, hexylene, heptylene, octylene, nonylene, decylene, or isomers thereof.

The term "Q-Q_{0} alkenylene" refers to linear or branched divalent unsaturated alkyl
radical having 1-10 carbon atoms and one or more carbon-carbon double bonds. Alkenylene
may comprise two or more carbon-carbon double bonds, and the double bonds may be
conjugated or nonconjugated with each other.

In the Chemical Formulas 1-3, each of m, n and k is independently 0 or 1. The
artemisinin or deoxoartemisinin-glycolipid hybrid derivatives of the present invention may be
synthesized by coupling various artemisinin or deoxoartemisinin derivatives with diverse
glycolipid derivatives. If the carboxyl acid or ester of the artemisinin or deoxoartemisinin
derivative reacts with the hydroxyl or alkoxy of the glycolipid derivative to form the one of the
hybrids of the present invention, n is 1. On the other hand, if the hydroxyl or alkoxy of the
artemisinin or deoxoartemisinin derivative reacts with the carboxyl acid or ester of the
glycolipid derivative to form the one of the hybrids of the present invention, n is 0.

If the m is 1 in the Chemical Formulas 1-3, the hybrid of the present invention is C-12
acetal-type artemisinin-glycolipid hybrid. If the m is 0 and the k is 1, the hybrid of the present
invention is C-12 nonacetal-type artemisinin-glycolipid hybrid. Even though the m is 0, the
hybrid of the present invention is C-12 acetal-type artemisinin-glycolipid hybrid if the k and the
n are both 0.

The artemisinin or deoxoartemisinin-glycolipid hybrids of the present invention may
comprise 12 or more chiral centers and the various stereoisomers of the hybrids are intended
to be included within the scope of the invention.

In an preferred embodiment, the artemisinin or deoxoartemisinin-glycolipid hybrid
derivative of the present invention may be represented by the one of the following Chemical
Formulas 4-12:
The compounds represented by the chemical formulas 1-12 are novel chemical compounds and exhibit still more excellent antiangiogenic activity than existing drugs.

In another aspect of the present invention, there is provided a method of synthesizing the artemisinin or deoxoartemisinin-glycolipid hybrid derivative of claim 1 or 2, which comprises: coupling the compound of the following Chemical Formula 13 with the compound of the following Chemical Formula 14; or coupling the compound of the following Chemical Formula 15 with the compound of the following Chemical Formula 16:
wherein each of $R_1$, $R_2$, $R'$ and $R''$ is independently hydrogen, halogen, $Q$-$Q_0$alkyl, $Q$-$C_{10}$alkenyl, $Q$-$Q_0$alkynyl, $Q$-$Q_0$aryl, $Q$-$Q_0$alkylaryl, $Q$-$Q_0$arylalkyl, or $Q$-$Q_0$ heteroaryl;

each of $R_3$-$R_5$ is independently hydrogen, hydroxyl, alkoxy, carboxyl, halogen, nitro, $Q$-$C_{10}$alkenyl, $Q$-$Q_0$alkynyl, $Q$-$Q_0$aryl, $Q$-$Q_0$alkylaryl, $Q$-$Q_0$arylalkyl, or $Q$-$Q_0$ heteroaryl;

$X$ and $Y$ are each independently substituted or unsubstituted linear or branched $Q$-$Q_0$ alkenylene, or substituted or unsubstituted linear or branched $Q$-$Cl_0$alkylene; and
each m and k is independently 0 or 1.

In a preferred embodiment, the coupling is earned out by a transesterification reaction. The carboxyl acid or ester of the artemisinin or deoxyartemisinin derivative may react with the hydroxyl or alkoxy of the glycolipid derivative to form the one of the hybrids of the present invention, or the hydroxyl or alkoxy of the artemisinin or deoxyartemisinin derivative may react with the carboxyl add or ester of the glycolipid derivative to form the one of the hybrids of the present invention. For example, one of the artemisinin or deoxyartemisinin-glycolipid hybrid derivatives of the present invention may be synthesized by the coupling reaction depicted in Figure 1.

In still another aspect of the present invention, there is provided a pharmaceutical composition for preventing or treating an angiogenic disease comprising (a) a pharmaceutically effective amount of the artemisinin or deoxyartemisinin-glycolipid hybrid derivative; and (b) a pharmaceutically acceptable carrier.

In a further aspect of the present invention, there is provided a method for preventing or treating an angiogenic disease, comprising administering to a subject in need thereof a pharmaceutical composition comprising (a) a pharmaceutically effective amount of the artemisinin or deoxyartemisinin-glycolipid hybrid derivative; and (b) a pharmaceutically acceptable carrier.

The term "pharmaceutically effective amount" refers to an amount enough to show and accomplish efficacies and activities of the compound of this invention for preventing or treating an angiogenic disease. The pharmaceutical composition of this invention comprises a pharmaceutically acceptable carrier besides the active ingredient compound.

The pharmaceutically acceptable carrier contained in the pharmaceutical composition of the present invention, which is commonly used in pharmaceutical formulations, but is not limited to, includes lactose, dextrose, sucrose, sorbitol, mannitol, starch, rubber arable, potassium phosphate, arginate, gelatin, potassium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrups, methylcellulose, methylhydroxy benzoate, propylhydroxy benzoate, talc, magnesium stearate, and mineral oils. The pharmaceutical
composition according to the present invention may further include a lubricant, a humectant, a
sweetener, a flavoring agent, an emulsifier, a suspending agent, and a preservative. Details of
suitable pharmaceutically acceptable carriers and formulations can be found in Remingtons'

The pharmaceutical composition of this invention may be administered orally or
parenterally. For non-oral administration, intravenous injection, subcutaneous injection,
intramuscular injection, intraperitoneal injection or transdermal administration may be
employed.

A suitable dose of the pharmaceutical composition of the present invention may vary
depending on pharmaceutical formulation methods, administration methods, the patient's age,
body weight, sex, severity of diseases, diet, administration time, administration route, an
excretion rate and sensitivity for a used pharmaceutical composition. Physicians of ordinary skill
in the art can determine an effective amount of the pharmaceutical composition for desired
treatment. Preferably, the pharmaceutical composition of the present invention is administered
with a daily dose of 0.001-1000 mg/kg (body weight).

According to the conventional techniques known to those skilled in the art, the
pharmaceutical composition according to the present invention may be formulated with
pharmaceutically acceptable carrier and/or vehicle as described above, finally providing several
forms including a unit dose form and a multi-dose form. Non-limiting examples of the
formulations include, but not limited to, a solution, a suspension or an emulsion in oil or
aqueous medium, an elixir, a powder, a granule, a tablet and a capsule, and may further
comprise a dispersion agent or a stabilizer.

According to a preferred embodiment, the pharmaceutical composition is used to
prevent or treat an angiogenic disease, for example cancer, hemangiomai, diabetic
retinopathy, retinopathy of prematurity, rejection after corneal transplant, angiogenic
glaucoma, erythromelanosis follicularis faciei et colli, proliferative retinopathy, psoriasis,
hemophilic arthritis, plaque angiogenesis in atherosclerosis, keloid, granulation tissue in wound,
blood vessel adhesion, rheumatoid arthritis, osteoarthritis, autoimmune disease, Crohn's
disease, recurrent stenosis, atherosclerosis, enteroadhesion, cat scratch disease, ulcer, liver
cirrhosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic
microangiopathy, rejection after organ transplant, glomerulonephritis, diabetes, or inflammation.

The artemisinin or deoxoartemisinin-glycolipid hybrid derivative which is an active ingredient in the pharmaceutical composition of the present invention is preferably represented by the one of the above Chemical Formulas 7-10, most preferably by the Chemical Formula 10. The compound of the Chemical Formula 10 shows no cytotoxicity, even though it has especially strong inhibiting activity to angiogenesis.

The pharmaceutical composition of the present invention may be used to treat an angiogenic disease including cancer, preferably, breast cancer, lung cancer, or oral cancer, most preferably oral cancer. The chemical compound represented by the one of the above Chemical Formulas 7-10 has an excellent antiangiogenic activity so that it can effectively treat breast cancer, lung cancer, or oral cancer.

The present invention will now be described in further detail by examples. It would be obvious to those skilled in the art that these examples are intended to be more concretely illustrative and the scope of the present invention as set forth in the appended claims is not limited to or by the examples.

**EXAMPLES**

**Example 1: Preparation of Artemisinin or Deoxoartemisinin-glycolipid Hybrid Derivatives**

The various derivatives of Artemisinin (dihydroartemisinin (Ia), hydroxyethyl deoxoartemisinin (Ib), hydroxypropyl deoxoartemisinin (Ic), and carboxymethyl deoxoartemisinin (Id)) were prepared according to the previously-described procedures.\(^{10}\) Glycolipid (daumone) and its derivatives (dibenzoyl daumone (2a) and daumone alcohol (2b)) were synthesized according to the previously-reported procedures.\(^ {7,8}\) Then, a short series of artemisinin-glycolipid hybrids (3a-3k) covalently linked were prepared by efficient coupling reactions and their structures were confirmed by spectral analysis as follows:

1. Preparation of Compound 3a
A stirred solution of dihydroartemisinin (DHA) (20.6 mg, 0.072 mmol), EDC (139.0 mg, 0.72 mmol, Sigma Aldrich, Korea) and DMAP (88.0 mg, 0.72 mmol, Sigma Aldrich, Korea) in DMF (2 ml) was combined with daumone 2 (20.0 mg, 0.072 mmol) at room temperature during 12 hours. The reaction mixture was quenched with slow addition of saturated citric acid (2 ml), extracted with ethyl acetate (3x5 ml) and washed with NaHCO₃ (5 ml) and brine (5 ml). The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The mixture was purified by flash column chromatography on silica gel with ethyl acetate as eluant to give compound 3a (28.8 mg, 0.053 mmol, 733 % yield).

To confirm the chemical structure of the artemisinin-glycolipid hybrid synthesized, NMR spectra were obtained on Bruker AC250 spectrometer using Me4Si as an internal standard and 13C NMR spectra (100 MHz) were measured on the same instrument. The GC-MS and direct mass were operated on an HP 5980ITGC-HP 5988 and JMS-700 Mstation spectrometer in FAB mode. Infrared spectra were taken on a Nicolet Impact 400 spectrometer. Anhydrous solvents were either obtained from commercial sources or dried and distilled immediately prior to use under a constant flow of dry nitrogen. All other reagents were used as received from Sigma Aldrich, TO, or Hsher.

The spectra data obtained were as follows:

H NMR (250 MHz, CDCl3) δ ppm 0.84 (d, J=6.95 Hz, 3H), 0.96 (d, J=5.69 Hz, 3H), 1.12 (d, J=6.00 Hz, 3H), 1.28 (d, J=6.00 Hz, 3H), 1.43 (s, 3H), 1.48-1.95 (m, 17H), 1.98-2.14 (m, 1H), 2.30-2.38 (m, 1H), 2.42 (dd, J=7.58 Hz, 2H), 2.50-2.64 (m, 1H), 3.53-3.86 (m, 4H), 4.70 (s, 1H), 5.44 (s, 1H), 5.76 (s, 0.5H), 5.80 (s, 0.5H). 13C NMR (63 MHz, CDCl3) δ ppm 12.10, 17.70, 18.85, 20.19, 21.03, 21.96, 24.57, 25.06, 25.92, 31.77, 34.07, 34.16, 35.21, 36.20, 36.69, 37.22, 45.22, 51.55, 68.07, 69.28, 69.86, 70.92, 80.12, 91.47, 91.78, 95.80, 104.44, 172.54.

IR (KBr, cm⁻¹) v max 3431, 2928, 2878, 2361, 2337, 1747, 1455, 1376, 1234, 1203, 1131, 1098, 1031; HRMS (FAB) calcd for C₃₆H₄₆NaO₁₀ [M + Na]+ m/z 565.2989, found 565.2970.
2. Preparation of Compound 3b

A stirred solution of hydroxyethyldeoxoartemisinin (22.6 mg, 0.072 mmol), EDC (139.0 mg, 0.72 mmol) and DMAP (88.0 mg, 0.72 mmol) in DMF (2 ml) was combined with daumone (20.0 mg, 0.072 mmol) at room temperature during 12 hours. The reaction mixture was quenched with slow addition of saturated citric acid (2 ml), extracted with ethyl acetate (3x5 ml) and washed with NaHCO₃ (5 ml) and brine (5 ml). The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The mixture was purified by flash column chromatography on silica gel with ethyl acetate as eluant to give compound 3b (24.4 mg, 0.043 mmol, 59.1 % yield).

To confirm the chemical structure of the artemisinin-glycolipid hybrid synthesized, the spectra data were obtained in the same manner as described above, and the resulting data were as follows:

\(^1\)H NMR (250 MHz, CDCl₃) ppm 0.87 (d, J=7.27 Hz, 3H), 0.96 (d, J=4.74 Hz, 3H), 1.12 (d, J=6.00 Hz, 3H), 1.28 (d, J=5.69 Hz, 3H), 1.41 (s, 3H), 1.53-2.15 (m, 19H), 2.24-2.42 (m, 3H), 2.58-2.79 (m, 1H), 3.49-3.92 (m, 4H), 4.06-4.38 (m, 3H), 4.70 (s, 1H), 5.30 (s, 1H).

\(^1\)C NMR (63 MHz, CDCl₃) ppm 12.91, 17.70, 18.90, 20.16, 24.70, 24.77, 24.89, 25.19, 26.05, 29.69, 34.00, 34.26, 34.43, 35.21, 36.53, 36.76, 37.47, 44.26, 52.30, 62.46, 68.11, 69.34, 69.88, 70.97, 71.76, 81.06, 88.96, 95.82, 103.23, 173.78. IR (KBr, cm⁻¹) v max 3450, 2928, 2878, 2361, 2337, 1734, 1455, 1376, 1130, 1100, 1044.: HRMS (FAB) calcd for C₃₆H₅₂O₁₀ [M] + m/z 593.3302, found 593.3382.

3. Preparation of Compound 3c
A stirred solution of hydroxypropyldeoxoartemisinin (23.6 mg, 0.072 mmol), EDC (139.0 mg, 0.72 mmol) and DMAP (88.0 mg, 0.72 mmol) in DMF (2 ml) was combined with daumone (20.0 mg, 0.072 mmol) at room temperature during 12 hours. The reaction mixture was quenched with slow addition of saturated citric acid (2 ml), extracted with ethyl acetate (3x5 ml) and washed with NaHCO₃ (5 ml) and brine (5 ml). The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The mixture was purified by flash column chromatography on silica gel with ethyl acetate as eluant to give compound 3c (10.0 mg, 0.017 mmol, 23.6% yield).

To confirm the chemical structure of the artemisinin-glycolipid hybrid synthesized, the spectra data were obtained in the same manner as described above, and the resulting data were as follows:

$^1$H NMR (250 MHz, CDCl₃) δ ppm 0.86 (d, J=7.27 Hz, 3H), 0.96 (d, J=5.37 Hz, 3H), 1.13 (d, J=6.00 Hz, 3H), 1.28 (d, J=6.00 Hz, 3H), 1.42 (s, 3H), 1.55-2.17 (m, 25H), 2.24-2.41 (m, 3H), 2.60-2.74 (m, 1H) 3.48-3.88 (m, 4H), 4.11 (t, J=6.32 Hz, 2H), 4.16 (m, 1H), 4.71 (s, 1H), 5.30 (s, 1H). $^13$C NMR (63 MHz, CDCl₃) δ ppm 12.87, 17.72, 18.90, 20.16, 24.73, 24.91, 24.97, 25.20, 25.98, 26.68, 30.28, 31.21, 34.27, 34.43, 35.21, 36.57, 36.78, 37.48, 44.25, 52.26, 62.76, 68.07, 69.32, 69.85, 70.89, 74.74, 81.12, 89.15, 95.78, 103.14, 173.88.

IR (KBr, cm⁻¹) v max 3440, 2928, 2873, 2364, 2342, 1732, 1455, 1376, 1175, 1138, 1102, 1043. : HRMS (FAB) calcd for C₂₉H₄₆NaO₁₀ [M + Na]$^+$ m/z 607.3458, found 607.3436.

4. Preparation of Compound 3d
A stirred solution of D dihydroartemisinin (DHA) (11.2 mg, 0.039 mmol), EDC (75.0 mg, 0.39 mmol) and DMAP (47.9 mg, 0.39 mmol) in DMF (2 ml) was combined with dibenzoyl daumone (19.0 mg, 0.039 mmol) at room temperature during 12 hours. The reaction mixture was quenched with slow addition of saturated citric acid (2 ml), extracted with ethyl acetate (3x5 ml) and washed with NaHCO₃ (5 ml) and brine (5 ml). The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The mixture was purified by flash column chromatography on silica gel with ethyl acetate as eluant to give compound 3d (18.4 mg, 0.025 mmol, 62.5% yield).

To confirm the chemical structure of the artemisinin-glycolipid hybrid synthesized, the spectra data were obtained in the same manner as described above, and the resulting data were as follows:

$^1$H NMR (250 MHz, CDCl₃) δ ppm 0.84 (d, J=7.27 Hz, 3H), 0.96 (d, J=6.00 Hz, 3H), 1.19 (d, J=6.00 Hz, 3H), 1.29 (d, J=6.00 Hz, 3H), 1.43 (s, 3H), 1.48-2.70 (m, 17H), 3.82-3.91 (m, 1H), 3.92 (d, J=6.00 Hz, 3H), 4.13 (s, 1H), 4.95 (s, 1H), 5.40 (s, 1H), 5.78 (s, 0.5H), 5.82 (s, 0.5H), 7.40-7.55 (m, 4H), 7.59 (t, J=7.27 Hz, 2H), 8.01-8.16 (m, 4H). $^{13}$C NMR (63 MHz, CDCl₃) δ ppm 12.12, 17.88, 19.06, 20.16, 21.93, 24.55, 24.65, 25.19, 25.93, 29.69, 31.78, 34.04, 34.26, 36.20, 36.77, 37.18, 45.20, 51.53, 66.97, 70.66, 71.20, 72.28, 80.08, 91.45, 91.70, 93.69, 104.39, 128.40, 128.44, 129.53, 129.64, 129.83, 129.99, 133.14, 133.18, 165.65, 165.74, 172.28. IR (KBr, cm⁻¹) v max 2930, 2873, 2364, 2337, 1721, 1451, 1368, 1310, 1266, 1107, 1025. HRMS (FAB) calcd for C₉₂H₅₆NaO₁₂ [M + Na]^+ m/z 773.3513, found 773.3510.

5. Preparation of Compound 3e
A stirred solution of hydroxyemyldeoxoartemisinin (11.0 mg, 0.035 mmol), EDC (67.3 mg, 0.35 mmol) and DMAP (42.9 mg, 0.35 mmol) in DMF (2 ml) was combined with dibenzoyl daumone (17.0 mg, 0.035 mmol) at room temperature during 12 hours. The reaction mixture was quenched with slow addition of saturated citric acid (2 ml), extracted with ethyl acetate (3x5 ml) and washed with NaHCO₃ (5 ml) and brine (5 ml). The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The mixture was purified by flash column chromatography on silica gel with ethyl acetate as eluant to give compound 3e (14.0 mg, 0.018 mmol, 51.2 % yield).

To confirm the chemical structure of the artemisinin-glycolipid hybrid synthesized, the spectra data were obtained in the same manner as described above, and the resulting data were as follows:

$^1$H NMR (250 MHz, CDCl₃) δ ppm 0.86 (d, $J$=721 Hz, 3H), 0.95 (d, $J$=5.37 Hz, 3H), 1.19 (d, $J$=6.00 Hz, 3H), 1.28 (d, $J$=6.32 Hz, 3H), 1.40 (s, 3H), 1.52-2.30 (m, 20H), 2.24-2.58 (m, 3H), 2.58-2.82 (m, 1H), 3.78-3.95 (m, 1H), 4.04-4.17 (m, 1H), 4.17-4.46 (m, 3H), 4.95 (s, 1H), 5.08-5.25 (m, 2H), 5.30 (s, 1H), 7.47 (t, $J$=7.42 Hz, 4H), 7.59 (t, $J$=7.27 Hz, 2H), 8.09 (dd, $J$=14.06, 7.42 Hz, 4H).: IR (KBr, cm⁻¹) v max 2934, 2873, 2360, 2342, 1722, 1452, 1381, 1310, 1267, 1175, 1104, 1068, 1025.: HRMS (FAB) calcd for C₄₄H₈₀NaO₁₂ [M + Na]⁺ m/z 801.3826, found 801.3862.

6. Preparation of Compound 3f
A stirred solution of hydroxyprapyldeoxoartemisinin (11.5 mg, 0.035 mmol), EDC (67.3 mg, 0.35 mmol) and DMAP (42.9 mg, 0.35 mmol) in DMF (2 ml) was combined with dibenzoyl daumone (17.0 mg, 0.035 mmol) at room temperature during 12 hours. The reaction mixture was quenched with slow addition of saturated citric acid (2 ml), extracted with ethyl acetate (3x5 ml) and washed with NaHCl (5 ml) and brine (5 ml). The organic layer was dried over MgSO_4, filtered and concentrated in vacuo. The mixture was purified by flash column chromatography on silica gel with ethyl acetate as eluant to give compound 3f (13.4 mg, 0.017 mmol, 48.2% yield).

To confirm the chemical structure of the artemisinin-glycolipid hybrid synthesized, the spectra data were obtained in the same manner as described above, and the resulting data were as follows:

$^1$H NMR (250 MHz, CDCl_3) ppm: 0.85 (d, J=7.58 Hz, 3H), 0.94 (d, J=5.05 Hz, 3H), 1.20 (d, J=6.32 Hz, 3H), 1.26 (d, J=4.42 Hz, 3H), 1.41 (s, 3H), 1.44–2.34 (m, 22H), 2.34–2.56 (m, 3H), 2.65 (dd, J=13.58, 6.63 Hz, 1H), 3.79–3.93 (m, 1H), 4.04–4.26 (m, 4H), 4.95 (s, 1H), 5.10–5.26 (m, 2H), 5.29 (s, 1H), 7.47 (t, J=7.27 Hz, 4H), 7.59 (t, J=7.11 Hz, 2H), 8.09 (dd, J=14.22, 7.27 Hz, 4H).

IR (KBr, cm$^{-1}$) v max 2929, 2864, 2355, 2337, 1722, 1451, 1377, 1310, 1266, 1176, 1151, 1106, 1068, 1025. HRMS (FAB) calcd for C_{45}H_{66}O_{12} [M + Na]$^+$ m/z 815.3982, found 815.3953.

7. Preparation of Compounds 3g and 3h
A stirred solution of cartjxymethyldeoxoartemisinin (15.0 mg, 0.046 mmol), EDC (88.0 mg, 0.46 mmol) and DMAP (56.1 mg, 0.46 mmol) in DMF (2 ml) was combined with olefinic daumone (15.0 mg, 0.046 mmol) at room temperature during 12 hours. The reaction mixture was quenched with slow addition of saturated citric acid (2 ml), extracted with ethyl acetate (3x5 ml) and washed with NaHCO₃ (5 ml) and brine (5 ml). The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The mixture was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (1:1 v/v) as eluant to give compound 3g (2.0 mg, 0.004 mmol, 7.7 % yield) and Compound 3h (4.1 mg, 0.007 mmol, 15.7 % yield).

To confirm the chemical structures of the artemisinin-glycolipid hybrids synthesized, the spectra data were obtained in the same manner as described above, and the resulting data were as follows:

**Compound 3g:** ¹H NMR (250 MHz, CDCl₃) ppm 0.87 (d, J=7.58 Hz, 3H), 0.97 (d, J=5.69 Hz, 3H), 1.11 (d, J=6.00 Hz, 3H), 1.16-1.27 (m, 4H), 1.28 (d, J=5.69 Hz, 3H), 1.41 (s, 3H), 1.49-2.23 (m, 17H), 2.25-2.49 (m, 2H), 2.61-2.83 (m, 1H), 3.58-3.85 (m, 3H), 3.63-3.71 (m, 1H), 4.70-4.82 (m, 1H), 4.73 (s, 1H), 4.91 (br. s., 1H), 4.94 (d, J=10.19 Hz, 1H), 5.00 (d, J=16.98 Hz, 1H), 5.34 (s, 1H), 5.70-5.93 (tdd, J=16.98, 10.19, 6.63, 6.63 Hz, 1H). IR (KBr, cm⁻¹) v max 2924, 2851, 2369, 2337, 1734, 1456, 1368. HRMS (FAB) calcld for C₃₀H₅₄O₆ [M + H]⁺ m/z 567.9899, found 567.9833

**Compound 3h:** ¹H NMR (250 MHz, CDCl₃) ppm 0.87 (d, J=7.58 Hz, 3H), 0.96 (d, J=5.37, 3H), 1.07-1.24 (m, 4H), 1.12 (d, J=6.32 Hz, 3H), 1.21 (d, J=6.00 Hz, 3H), 1.40 (s, 3H), 1.48-2.23 (m, 17H), 2.24-2.56 (m, 2H), 2.60-2.84 (m, 2H), 3.72-3.85 (m, 2H), 3.89 (m, 1H), 4.67-4.82 (m, 1H), 4.71 (s, 1H), 4.83-4.92 (m, 1H), 4.95 (d, J=10.23 Hz, 1H), 5.00 (d,
8. Preparation of Compounds 3i and 3j

A stirred solution of carboxymethyldeoxygenartemisinin (24.8 mg, 0.076 mmol), EDC (146.0 mg, 0.76 mmol) and DMAP (93.0 mg, 0.76 mmol) in DMF (2 ml) was combined with daumone alcohol (24.8 mg, 0.076 mmol) at room temperature during 12 hours. The reaction mixture was quenched with slow addition of saturated citric acid (2 ml), extracted with ethyl acetate (3x5 ml) and washed with NaHCO₃ (5 ml) and brine (5 ml). The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The mixture was purified by flash column chromatography on silica gel with ethyl acetate as eluant to give compound 3i (13.0 mg, 0.023 mmol, 29.9 % yield) and compound 3j (2.9 mg, 0.005 mmol, 6.7 % yield).

To confirm the chemical structures of the artemisinin-glycolipid hybrids synthesized, the spectra data were obtained in the same manner as described above, and the resulting data were as follows:

Compound 3i: ¹H NMR (250 MHz, CDCl₃) ppm 0.87 (d, \(J=7.58\) Hz, 3H), 0.96 (d, \(J=5.37\) Hz, 3H), 1.11 (d, \(J=4.42\) Hz, 3H), 1.27 (d, \(J=6.46\) Hz, 3H), 1.42 (s, 3H), 1.55-2.57 (m, 21H), 2.57-2.83 (m, 2H), 3.59-3.95 (m, 4H), 4.06-4.20 (m, \(J=5.37\) Hz, 3H), 4.67-8.4 (m, 1H), 4.84-4.98 (m, 1H), 5.32 (s, 1H). IR (KBr, cm⁻¹) v max 3497, 2927, 2873, 1736, 1452, 1376, 1315, 1234, 1268, 1176, 1105, 1054, 1014.: HRMS (FAB) calcd for C₃₆H₃₀NaO₉ \([M + Na]^+\) m/z 570.3404, found 570.3430

Compound 3j: ¹H NMR (400 MHz, CDCl₃) ppm 0.87 (d, \(J=7.52\) Hz, 3H), 0.97 (d, \(J=5.78\) Hz, 3H), 1.04-1.55 (m, 8H), 1.12 (d, \(J=5.91\) Hz, 3H), 1.27 (d, \(J=6.42\) Hz, 3H), 1.40 (s,
9. Preparation of Compound 3k

A stirred solution of carboxymethyldeoxoartemisinin (13.9 mg, 0.043 mmol), EDC (81.0 mg, 0.43 mmol) and DMAP (51.9 mg, 0.43 mmol) in DMF (2 ml) was combined with dibenzoyldaumone aldehyde (20.0 mg, 0.043 mmol) at room temperature during 12 hours. The reaction mixture was quenched with slow addition of saturated citric acid (2 ml), extracted with ethyl acetate (3x5 ml) and washed with NaHCO₃ (5 ml) and brine (5 ml). The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The mixture was purified by flash column chromatography on silica gel with ethyl acetate as eluant to give compound 3k (9.8 mg, 0.013 mmol, 29.6 % yield).

To confirm the chemical structures of the artemisinin-glycolipid hybrids synthesized, the spectra data were obtained in the same manner as described above, and the resulting data were as follows:

1H NMR (250 MHz, CDCl₃) ppm 0.86 (d, J=7.58 Hz, 3H), 1.20 (d, J=6.00 Hz, 3H), 1.29 (d, J=6.32 Hz, 3H), 1.41 (s, 3H), 1.48-2.35 (m, 20H), 2.36-2.57 (m, 2H), 2.57-2.86 (m, 2H), 3.78-3.96 (m, IH), 4.02-4.24 (m, 3H), 4.74-4.89 (m, 3H), 4.95 (s, IH), 5.10-5.27 (m, 2H), 5.32 (s, IH), 7.47 (t, J=7.27 Hz, 4H), 7.59 (t, J=6.79 Hz, 2H), 8.08 (dd, J=16.27, 7.11 Hz, 4H). 13C NMR (63 MHz, CDCl₃) ppm 13.02, 17.89, 19.17, 20.13, 24.65, 24.70, 25.43, 25.95, 25.98, 28.66, 29.73, 34.42, 36.04, 36.51, 37.01, 37.45, 44.23, 52.26, 67.02, 70.66, 71.27, 71.43, 71.62, 72.63, 80.84, 89.05, 89.14, 93.82, 103.21, 128.43, 129.62, 129.85, 129.88, 130.01, 133.15, 133.21, 165.67, 165.78, 171.66: IR (KBr, cm⁻¹) ν max 3062, 2936, 2859, 1610, 1452, 1376, 1315, 1267, 1177, 1151, 1106, 1068, 1025.: HRMS (FAB) calcd
Example 2: Evaluation of Antiangiogenic Activity

The in vivo antiangiogenic activity of the various hybrid compounds was evaluated using the CAM (chick chorioallantoic membrane) vessel development assay as previously described.\(^{5,11}\)

Briefly, fertilized eggs (Pulmuone Co., Kyungki-do, Korea) were incubated at 37 °C with 80-90% relative humidity. At day 3, a window was opened after the removal of 2 ml albumin in the eggs (Figure 3).

At day 5 of incubation, test samples loaded on a quarter size Thermanox coverslip (Nunc, Roskilde, Denmark) was applied to the CAM of each individual embryo at a concentration of 2.5 nmol/egg. After 2 incubation days, a 20% fat emulsion was injected into the CAM for observation of the inhibition avascular zone. If an avascular zone of about 3-6 mm diameter, as indicated with an arrow in Figure 4, was observed, then it was considered to represent effective inhibition on neovascularization. The results of these experiments are listed in Table 1. The standard drugs used for comparison were (-)-fumagillin and (-)-thalidomide.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Positive eggs (\text{/ eggs tested})</th>
<th>Inhibition effect(^*)</th>
<th>Inhibition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemisinin</td>
<td>3/10</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>Daumone</td>
<td>7/10</td>
<td>++</td>
<td>70</td>
</tr>
<tr>
<td>3a</td>
<td>5/10 (1) (^{b})</td>
<td>+</td>
<td>50</td>
</tr>
<tr>
<td>3b</td>
<td>6/10 (2) (^{b})</td>
<td>+</td>
<td>60</td>
</tr>
<tr>
<td>3c</td>
<td>6/10 (2) (^{b})</td>
<td>+</td>
<td>60</td>
</tr>
<tr>
<td>3d</td>
<td>1/10 (2) (^{b})</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>3e</td>
<td>6/10 (2) (^{b})</td>
<td>+</td>
<td>60</td>
</tr>
<tr>
<td>3f</td>
<td>8/10</td>
<td>+++</td>
<td>80</td>
</tr>
<tr>
<td>3g</td>
<td>7/10 (2) (^{b})</td>
<td>++</td>
<td>70</td>
</tr>
<tr>
<td>3h</td>
<td>5/10 (5) (^{b}) Low toxic</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>3i</td>
<td>10/10</td>
<td>+++</td>
<td>100</td>
</tr>
<tr>
<td>3j</td>
<td>5/10</td>
<td>+</td>
<td>50</td>
</tr>
<tr>
<td>3k</td>
<td>5/10 (2) (^{b})</td>
<td>+</td>
<td>50</td>
</tr>
<tr>
<td>(-)-Fumagillin</td>
<td>4/10 (1) (^{b})</td>
<td>-</td>
<td>40</td>
</tr>
<tr>
<td>(-)-Thalidomide</td>
<td>4/10 (4) (^{b}) Low toxic</td>
<td></td>
<td>40</td>
</tr>
<tr>
<td>Control</td>
<td>0/10</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>
inhibition effect; Antiangiogenic effect of plus (+) is similar to thalidomide or fumagillin, double plus (+++) is stronger and triple plus (+++) is the strongest. Number in parentheses describes eggs in which the embryo died. Control; solvent only (chloroform) to embryo.

As shown in Table 1, it is interesting to note that most hybrids exhibited twice the antiangiogenic activity at a concentration of 2.5 nmol/egg than that of fumagillin or thalidomide as the standard drug.

Artemisinin showed a weak inhibitory effect at the given concentration, while glycolipid (daumone) remained stronger than standard drugs. Generally hybrids showed higher antiangiogenic activity than artemisinin and comparable to that of glycolipid (daumone).

However, C-12 acetal-type artemisinin-glycolipid hybrids (3a and 3d) exhibited weaker activity than non-acetal type hybrids. A benzoyl protected hybrid (3d) with acetal function at C-12 of artemisinin displayed the weakest inhibitory activity, while a hybrid (3i) with free hydroxyl groups of glycolipid with non-acetal function of artemisinin showed complete (100%) inhibition of angiogenesis.

Interestingly, terminal olefin of the aliphatic side chain of a compound (3h) that has a good antitumor activity displayed dramatically increased toxicity, and 50% of tested chicken embryos died at the given concentration.

The regioisomers (3h, 3j) showed only comparable antiangiogenic activity, thus suggesting the coupling position of the C-12 side function of artemisinin should link with the terminal carboxylic acids of glycolipids.

It is noteworthy that the hybrid compound (3i) that does not exhibit cytotoxicity has the most potent antiangiogenic activity in this assay. The requirement for the presence of the peroxide bond for antiangiogenesis needs to be determined by preparation and in vivo screening of desoxy derivatives of artemisinin.

In summary, hybrids of nonacetal and acetal types of artemisinin and glycolipid were synthesized in one-step reactions and most showed one to two times more potent in vivo antiangiogenic activity than standard drugs. Among the 11 synthetic compounds tested, hybrids 3f, 3g and 3i showed the most potent antiangiogenic activity, twice as much potency as fumagillin and thalidomide, known as antiangiogenic agents. In particular, hybrid 3i showed
complete inhibition at 2.5 nm/egg with no toxicity. Compounds 3a and 3h showed similar activity to that of fumagillin. Evidence that acetal-type analogs at C-12 of artemisinin are more neurotoxic in animal studies than non acetal-type analogs is also emerging,\textsuperscript{12} and may thus lead to the future abandonment of the currently clinically used acetal-type potential anticancer drug candidates. Therefore, nonacetal \textsuperscript{12}\textbeta\textsuperscript{b} (C-C)-type derivatives of artemisinin-glycolipid hybrids deserve further evaluation as possible anticancer drug candidates because of their high acid stability,\textsuperscript{3b} low toxicity and high in vivo antiangiogenesis.

**Example 3: Evaluation of Anticancer Activity**

The anticancer activity of the artemisinin or deoxoartemisinin-glycolipid hybrids synthesized in Example 1 was evaluated using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay according to the previously described procedure (Carmichel, J. et al., Evaluation of a Tetrazolium-based Semiautomated Colorimetric Assay: Assessment of Chemosensitivity testing, \textit{Cancer Res.}, 47:936-42(1987)). The \textit{in vitro} cytotoxicity (IC\textsubscript{50}) of the artemisinin or deoxoartemisinin-glycolipid hybrid derivatives to cancer cell was measured and the results are represented in Table 2.

**Table 2**

<table>
<thead>
<tr>
<th>No.</th>
<th>Symbol or name</th>
<th>Chemical Structure</th>
<th>MDA-MB-231</th>
<th>MCF-7</th>
<th>A549</th>
<th>HSC-2</th>
<th>Ca.9-22</th>
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<tbody>
<tr>
<td>1</td>
<td>3b</td>
<td><img src="image" alt="Artmisinin Derivative 3b" /></td>
<td>&gt;100μM</td>
<td>&gt;100μM</td>
<td>&gt;100μM</td>
<td>&gt;100μM</td>
<td>&gt;100μM</td>
</tr>
<tr>
<td>2</td>
<td>3g</td>
<td><img src="image" alt="Deoxoartemisinin Derivative 3g" /></td>
<td>37.71μM</td>
<td>&gt;100μM</td>
<td>&gt;100μM</td>
<td>19.1 μM</td>
<td>19.4 μM</td>
</tr>
<tr>
<td>Compound</td>
<td>Description</td>
<td>IC50 (μM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>----------</td>
<td>-------------</td>
<td>-----------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3h</td>
<td>46.63, &gt;100, 29.68, 15.7, 15.1</td>
<td></td>
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<tr>
<td>4</td>
<td>artemisinin</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>5</td>
<td>daumone</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

MDA-MB-231 (Korean Cell Line Bank, Seoul, Korea): metastatic breast cancer cells (estrogen receptor-negative)

MCF7 (Korean Cell Line Bank, Seoul, Korea): estrogen receptor-positive breast cancer cells

A549 (Korean Cell Line Bank, Seoul, Korea): lung cancer cells

HSC-2 (Japanese Collection of Research Bioresources (JCRB), Japan): oral squamous carcinoma cells (gingiva origin)

Ca.9.22 (Japanese Collection of Research Bioresources (JCRB), Japan): oral squamous carcinoma cell (mouth origin)

As shown in Table 2, the artemisinin or deoxyartemisinin-glycolipid hybrids of the present invention were found to have an anticancer activity to the various cancer cells, and showed especially excellent efficacy to oral cancer cell. In the actual experiment, compound 3b also exhibited more excellent anticancer activity to all the cancer cell lines than artemisinin or
daumone alone.

Having described a preferred embodiment of the present invention, it is to be understood that variants and modifications thereof falling within the spirit of the invention may become apparent to those skilled in this art, and the scope of this invention is to be determined by appended claims and their equivalents.

References


What is claimed is:

1. An artemisinin or deoxoartemisinin-glycolipid hybrid derivative represented by the Chemical Formula selected from the group consisting of the following Chemical Formulas 1-3:

![Chemical Structures](image)

wherein each $R_4$ and $R_2$ is independently hydrogen, halogen, $\text{C}_1-\text{C}_{10}$ alkyl, $\text{C}_1-\text{C}_{10}$ alkenyl, $\text{C}_1-\text{C}_{10}$ alkynyl, $\text{Q}-\text{Q}_0$ aryl, $\text{Q}-\text{Q}_0$ aralkyl, $\text{Q}_0-\text{Q}_0$ heteroaryl;

each of $R_3$-$R_5$ is independently hydrogen, hydroxyl, alkoxy, carboxyl, halogen, nitro, $\text{Q}$-$\text{Q}_0$ alkyl, $\text{Q}_0-\text{Q}_0$ alkenyl, $\text{Q}_0-\text{Q}_0$ alkynyl, $\text{Q}_0-\text{Q}_0$ aryl, $\text{Q}_0-\text{Q}_0$ aralkyl, $\text{Q}_0-\text{Q}_0$ heteroaryl, or $\text{Q}_0-\text{Q}_0$.
heteroaryl;

X and Y are each independently substituted or unsubstituted linear or branched \( \text{C}_1-\text{C}_6 \) alkylene, or substituted or unsubstituted linear or branched \( \text{C}_1-\text{C}_6 \) alkenylene; and

each of \( m, n \) and \( k \) is independently 0 or 1.

2. The artemisinin or deoxoartemisinin-glycolipid hybrid derivative according to claim 1,

wherein each \( R_1 \) and \( R_2 \) is independently hydrogen, substituted or unsubstituted linear or branched \( \text{C}_1-\text{Q alkyl}, \) or benzyl;

each of \( R_3-R_6 \) is independently hydrogen, hydroxyl, alkoxy, carboxyl, or substituted or unsubstituted linear or branched \( \text{C}_1-\text{C}_6 \) alkyl;

\( X \) and the \( Y \) are each independently substituted or unsubstituted linear or branched \( \text{C}_1-\text{C}_6 \) alkylene; and

each of \( m, n \) and \( k \) is independently 0 or 1.

3. The artemisinin or deoxoartemisinin-glycolipid hybrid derivative according to claim 1,

wherein the artemisinin or deoxoartemisinin-glycolipid hybrid derivative is represented by the Chemical Formula selected from the group consisting of the following Chemical Formulas 4-12:

(4)

(5)
4. A method of synthesizing the artemisinin or deoxoartemisinin-glycolipid hybrid derivative of daim 1 or 2, which comprises:

   coupling the compound of the following Chemical Formula 13 with the compound of
   the following Chemical Formula 14; or

   coupling the compound of the following Chemical Formula 15 with the compound of
   the following Chemical Formula 16:
wherein each of \( R_1, R_2, R' \) and \( R'' \) is independently hydrogen, halogen, \( \text{C}_i\text{-}\text{C}_1\text{ alkyl}, \text{C}_i\text{-}\text{C}_1\text{ alkenyl}, \text{C}_i\text{-}\text{C}_1\text{ alkynyl}, \text{C}_i\text{-}\text{C}_1\text{ aryl}, \text{C}_i\text{-}\text{C}_1\text{ alkylaryl}, \text{C}_i\text{-}\text{C}_1\text{ arylalkyl}, \text{C}_i\text{-}\text{C}_1\text{ heteroaryl}; \\
\text{each of } R_3 \text{-} R_6 \text{ is independently hydrogen, hydroxyl, alkoxy, carboxyl, halogen, nitro, } \text{C}_i\text{-}\text{C}_1\text{ alkyl}, \text{C}_i\text{-}\text{C}_1\text{ alkenyl}, \text{C}_i\text{-}\text{C}_1\text{ alkynyl}, \text{C}_i\text{-}\text{C}_1\text{ aryl}, \text{C}_i\text{-}\text{C}_1\text{ alkyaryl}, \text{C}_i\text{-}\text{C}_1\text{ arylalkyl}, \text{C}_i\text{-}\text{C}_1\text{ heteroaryl; } \\
\text{X and Y are each independently substituted or unsubstituted linear or branched } \text{C}_i\text{-}\text{C}_1\text{ alkenylene, or substituted or unsubstituted linear or branched } Q\text{-}\text{C}_i\text{ alkenylene; and } \\
\text{each } m \text{ and } k \text{ is independently 0 or 1.}

5. The method according to claim 4, wherein the coupling is carried out by a transesterification reaction.

6. A pharmaceutical composition for preventing or treating an angiogenic disease comprising 
(a) a pharmaceutically effective amount of the artemisinin or deoxoartemisinin-glycolipid 
hybrid derivative as defined in any of claims 1-3; and (b) a pharmaceutically acceptable 
carrier.

7. The composition according to claim 6, wherein the angiogenic disease is selected from the 
group consisting of cancer, hemangiomas, diabetic retinopathy, retinopathy of prematurity,
rejection after corneal transplant, angiogenic glaucoma, erythromelanosis follicularis faciei et coli, proliferative retinopathy, psoriasis, hemophilic arthritis, plaque angiogenesis in atherosclerosis, keloid, granulation tissue in wound, blood vessel adhesion, rheumatoid arthritis, osteoarthritis, autoimmune disease, Crohn's disease, recurrent stenosis, atherosclerosis, enteroadhesion, cat scratch disease, ulcer, liver cirrhosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy, rejection after organ transplant, glomerulonephritis, diabetes, and inflammation.

8. The composition according to claim 6, wherein the artemisinin or deoxoartemisinin-glycolipid hybrid derivative is represented by the Chemical Formula selected from the group consisting of the following Chemical Formulas 7-10:

![Chemical Formula 7](image7)

![Chemical Formula 8](image8)

![Chemical Formula 9](image9)
9. The composition according to claim 7, wherein the angiogenic disease is breast cancer, lung cancer, or oral cancer.

10. The composition according to claim 9, wherein the artesiminin or deoxyartesiminin-glycolipid hybrid derivative is represented by the Chemical Formula selected from the group consisting of the following Chemical Formulas 7-10:
11. A method for preventing or treating an angiogenic disease, comprising administering to a subject in need thereof a pharmaceutical composition comprising (a) a pharmaceutically effective amount of the artemisinin or deoxoartemisinin-glycolipid hybrid derivative as defined in any one of claims 1-3; and (b) a pharmaceutically acceptable carrier.

12. The method according to claim 11, wherein the angiogenic disease is selected from the group consisting of cancer, hemangiomas, diabetic retinopathy, retinopathy of prematurity, rejection after corneal transplant, angiogenic glaucoma, erythromelanosia folliculare faciei et coli, proliferative retinopathy, psoriasis, hemophilic arthritis, plaque angiogenesis in atherosclerosis, keloid, granulation tissue in wound, blood vessel adhesion, rheumatoid arthritis, osteoarthritis, autoimmune disease, Crohn's disease, recurrent stenosis, atherosclerosis, enteroadhesion, cat scratch disease, ulcer, liver cirrhosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy, rejection after organ transplant, glomerulonephritis, diabetes, and inflammation.

13. The method according to claim 11, wherein the artemisinin or deoxoartemisinin-glycolipid hybrid derivative is represented by the Chemical Formula selected from the group
consisting of the following Chemical Formulas 7-10:

14. The method according to claim 12, wherein the angiogenic disease is breast cancer, lung cancer, or oral cancer.
15. The method according to claim 13, wherein the artemisinin or deoxoartemisinin-glycolipid hybrid derivative is represented by the Chemical Formula selected from the group consisting of the following Chemical Formulas 7-10:
Fig. 1

Deoxoartemisinin derivative + Glycolipid derivative

EDC/DMAP, DMF, r.t. 12h.

Deoxoartemisinin-glycolipid hybrid derivative
Fig. 3
### A. CLASSIFICATION OF SUBJECT MATTER

*C07D 493/18(2006.01)*, *C07H 13/06(2006.01)*, *A61K 31/335(2006.01)*, *A61P 35/00(2006.01)*

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)

*C07D 493/18; C07D 493/12; A61K 31/335*

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) & Keywords: artemisinin, deoxoartemisinin, glycolipid, hybrid, anticancer, angiogenesis.

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>MAGGS, JAMES L. et al., &quot;miliary metastases of b-artenether in rats: biotra nsformations of an antimalarial endoperoxide&quot;, Drug Metabolism and Disposition 2000, Vol. 28, No. 2, 209-217. See Tables 1-3; Figures 6 &amp; 8.</td>
<td>1-10</td>
</tr>
<tr>
<td>A</td>
<td>BATTY, KEVIN T. et al., &quot;Assessment of the effect of malaria infection on hepatic clearance of dihydroartemisinin using rat liver perfusions and microso mes&quot;, British Journal of Pharmacology 1998, Vol. 125, No. 1, 159-167. See Figure 1.</td>
<td>1-10</td>
</tr>
</tbody>
</table>

☐ 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
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search: 23 NOVEMBER 2011 (23.11.2011)

Date of mailing of the international search report: 23 NOVEMBER 2011 (23.11.2011)

Name and mailing address of the ISA/KR

Korean Intellectual Property Office

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Telephone No. 82-42-481-8647

Form PCT/ISA/210 (second sheet) (May 2009)
### Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **Claims Nos.: 11-15**
   - because they relate to subject matter not required to be searched by this Authority, namely:
     - Claims 11-15 relate to a method for treatment of the human body, which is a subject matter this International Searching Authority is not required to search under PCT Article 17(2)(a) and Rule 39.1(iv).

2. **Claims Nos.:**
   - because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. **Claims Nos.:**
   - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. **As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.**

2. **As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.**

3. **As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:**

4. **No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:**

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
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<tr>
<td>US 2008-0103 192 A1</td>
<td>01.05.2008</td>
<td>US 7692030 B2</td>
<td>06.04.2010</td>
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<td></td>
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<td>WO 2008-046 109 A3</td>
<td>29.05.2008</td>
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