

D E S C R I P T I O N

NOVEL SULFONATED SUGAR COMPOUND
AND USE THEREOF AS MEDICINE

5

Technical Field

The present invention relates to a novel sulfonated sugar compound and a drug containing the same.

10

Background Art

At present, in Japan, malignant tumor, cardiac disease, and cerebrovascular disease are responsible for about 60 percent of cause of death. Among them, malignant tumors have the top ranking of cause of death, and tends to increase. Surgical therapy, chemotherapy, and radiation therapy are known as three major therapies for treating malignant tumors.

15

In recent years, the quality of life (QOL) of a patient has been emphasized, and much attention is being paid to radiation therapy.

20

In common radiation therapy, halogenated pyrimidine and hypoxic cell sensitizers are known as chemical or pharmaceutical substances administered simultaneously with radiation thereby enhancing its therapeutic effect, more specifically, as clinically applicable radiosensitizers (for example, see Radiobiology for the Radiologist (Fourth Edition), Eric J. Hall et al, J. B. Lippincott Company

25

("Houshasennkainotameno Hoshasenseibutsugaku",
translated by Muneyasu Urano, Shinoharashinsha. Inc.).

Examples of known halogenated pyrimidines include 5-
iododeoxyuridine. Examples of known hypoxic cell
5 sensitizers include misonidazole. However, these known
radiosensitizers are scarcely in actual use, because
they produce side effects such as gastrointestinal
disorders, peripheral neurotoxicity, and involve other
outstanding problems.

10 On the other hand, in order to provide novel
radiosensitizers, radiosensitizers composed of
sulfopyranosylacylglycerol or salts thereof are applied
for a patent (Jpn. Pat. Appln. KOKAI Publication
No. 2004-374445). However, in
15 sulfopyranosylacylglycerol, the 2-position carbon atom
in the glycerol moiety is an asymmetric carbon, so that
the stereostructure cannot be controlled by a
relatively inexpensive and simple synthesis process as
described in Jpn. Pat. Appln. KOKAI Publication
20 No. 2004-374445, in which the terminal double bond of
an allyl group is dihydroxylated to form a glycerol
skeleton. Therefore, R/S diastereomers are generated
at a ratio of about 1:1. In order to solve the
problem, respective diastereomers can be independently
25 synthesized, but such process requires bonding of a
glycerol compound having a definite stereostructure to
a sugar compound during synthesis, which results in

further problems, the complication of the synthesis process and an enormous increase of the cost.

5 In addition, a sulfopyranosylacylglycerol compound generates an R/S diastereomer at the 2-position of the glycerol moiety, as well as several percents of a structural isomer (2-acyl isomer) wherein the acyl group at the 1-position of glycerol has been transferred to the 2-position between and/or within the molecules. These 2-acyl isomers are generated during
10 synthesis and storage in a solution. Therefore, even if the respective diastereomers are independently prepared, it is very difficult to provide a high purity sulfopyranosylacylglycerol compound.

15 Although a sulfopyranosylacylglycerol compound exhibits a noticeable radiosensitization effect, its development as a drug will entail very difficult situations due to problems with synthesis and physical properties.

Disclosure of Invention

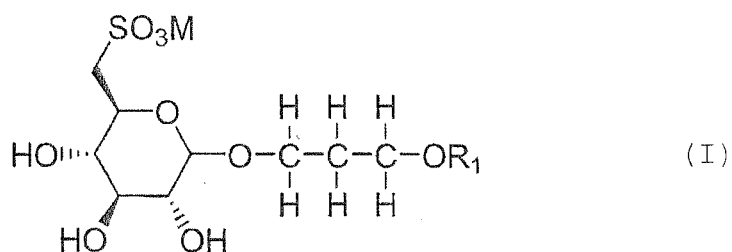
20 The present invention was achieved in view of the above problems. An object of the present invention is to provide a practicable novel sulfonated sugar compound and a drug including the same, and specifically to provide a practicable novel sulfonated
25 sugar compound obtainable at high purity by a simple synthesis method, and a drug including the same.

As a result of dedicated research by the

inventors, means for solving the above problems was found. More specifically:

(1) a sulfoquinovosylacetyl propanediol compound represented by the general formula (I):

5 [Chemical Formula 2]



wherein R₁ is an acyl residue of a fatty acid, and M represents a hydrogen or a metal ion or pharmaceutically acceptable salts thereof;

10

(2) a drug including as an active ingredient at least one selected from the group consisting of the sulfoquinovosylacetyl propanediol compound according to (1) represented by the general formula (I) and pharmaceutically acceptable salts thereof; and

15

(3) the drug according to (2), which is a radiosensitizer.

The present invention provides a practicable novel sulfonated sugar compound and a drug including the same. Specifically, the present invention provides a novel sulfonated sugar compound obtainable at high purity by a simple synthesis method, and a drug including the same.

20

A benefit of the present invention will be

described in the following description, and will be partially defined by the description or an embodiment of the present invention. A benefit of the present invention will be understood and achieved through drawings and below-described combinations.

Brief Description of Drawings

Figure 1 is a chromatogram showing the result of analysis of α SQAP C18:0.

Figure 2 is a chromatogram showing the result of analysis of α SQMG C18:0.

Figure 3 is a graph showing the effect of a test substance on the increase of tumor volume.

Figure 4 is a graph showing the effect of a test substance on the increase of tumor volume.

Figure 5 is a graph showing the effect of a test substance on the increase of tumor volume.

Figure 6 is a graph showing the effect of a test substance on the increase of tumor volume.

Figure 7 is a graph showing the effect of a test substance on the increase of tumor volume.

Figure 8 is a graph showing the effect of a test substance on the increase of tumor volume.

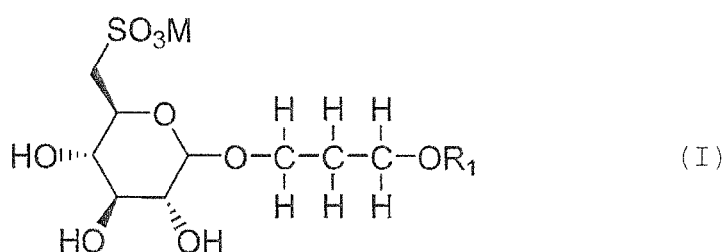
Figure 9 is a graph showing the effect of a test substance on the increase of tumor volume.

Figure 10 is a graph showing the effect of a test substance on the tube formation.

Best Mode for Carrying Out the Invention

According to an aspect of the present invention,
the sulfoquinovosylacyl propanediol compound expressed
by the formula (I) and pharmaceutically acceptable
5 salts thereof are provided;

[Chemical Formula 3]



wherein R_1 is an acyl residue of a fatty acid,
10 and M represents a hydrogen ion or a metal ion.

In the present invention, when the " R_1 " is an acyl
residue of a fatty acid, the number of carbons
contained therein is 26 or less and 1 or more, and
preferably 22 or less. The fatty acid for providing
15 the acyl residue of a fatty acid according to the
present invention may be a linear or branched,
saturated or unsaturated fatty acid.

The quinovose ring contained in the
sulfoquinovosylacyl propanediol compound according to
20 the present invention may exist in a boat form, a chair
form, or a mixed form, but typically exists in a chair
form because it is usually stable. The steric
configuration of the propanediol site in the quinovose
ring may be an α anomer, a β anomer, or a mixture

thereof.

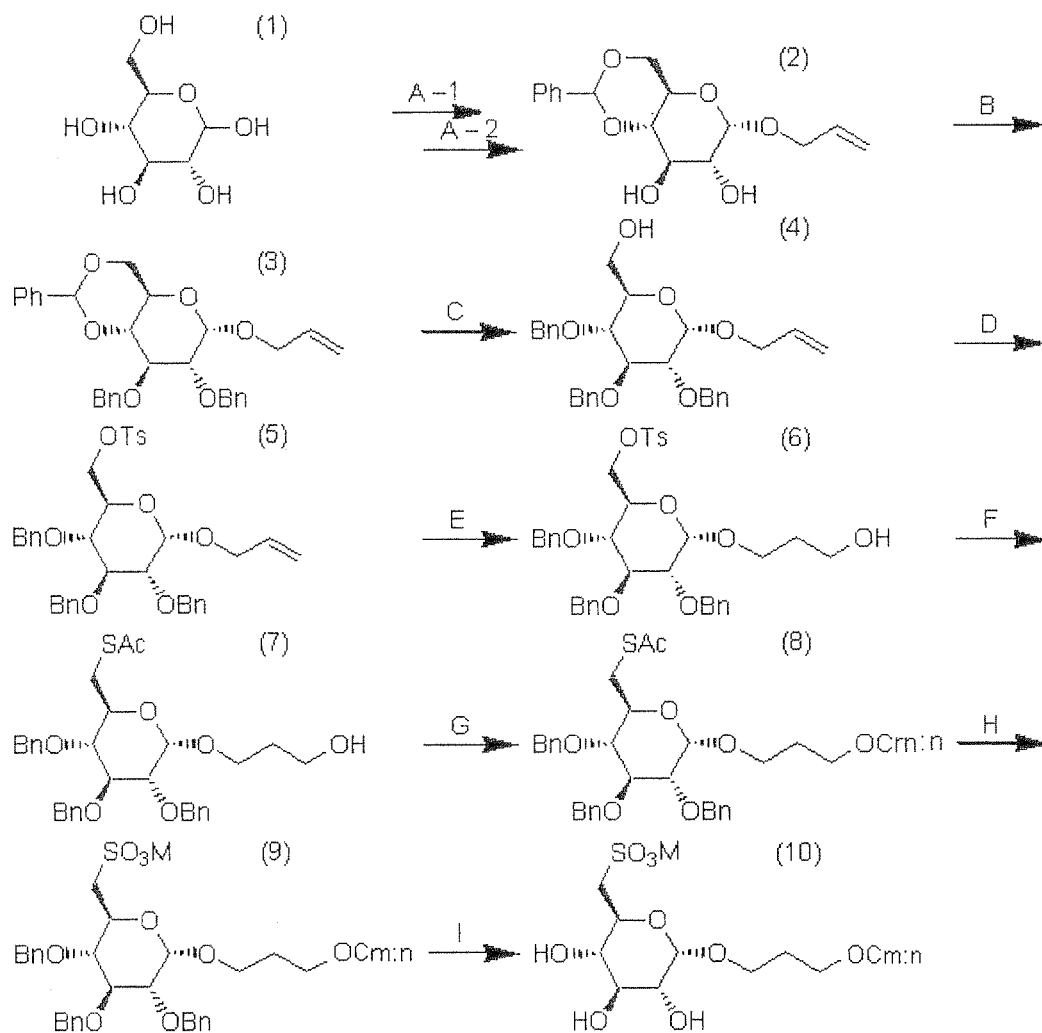
The sulfoquinovosylacyl propanediol compound according to the present invention may be hereinafter referred to as "SQAP" or "SQAP compound". In a term
5 "αSQAP Cm:n", "α" represents an α anomer, and "Cm:n" represents that the number of carbon atoms contained in the R₁ group of SQAP is "m", and the number of double bond(s) is "n", wherein "m" is an integer of 1 or more, and "n" is an integer of 0 or more. Accordingly, for
10 example, "αSQAP C18:0" represents an α anomer of sulfoquinovosylacyl propanediol wherein the number of carbon atoms contained in the acyl residue of the fatty acid is 18, and the number of double bond is 0.

The method for preparing the sulfoquinovosylacyl
15 propanediol compound according to the present invention may be, but not limited to, the following method. Since the sulfoquinovosylacyl propanediol compound according to the present invention will not generate new asymmetric carbon during the synthesis process, the
20 compound can be prepared easily, simply, and at high purity. In addition, the compound can be stored in a structurally stable state, because there is no hydroxy group, which readily causes transfer, present near the R₁ group.

25 "Ph" represents a phenyl group, "Bn" represents a benzyl group, "Ts" represents a tosyl group, "SAc" represents an acetylthio group, and "M" represents a

hydrogen ion or a metal ion.

[Chemical Formula 4]



5 A) A-1. allyl alcohol, trifluoromethanesulfonic acid, 80°C, 48 hours;

A-2. benzaldehyde dimethyl acetal, p-toluenesulfonic acid monohydrate, acetonitrile, 40°C, 4 hours;

10 B) benzyl bromide, sodium hydroxide, N,N-dimethylformamide, room temperature, 24 hours;

C) lithium hydride aluminum, aluminum chloride,

dichloromethane, diethyl ether, heating under reflux,
4 hours;

D) p-toluenesulfonyl chloride, 4-
dimethylaminopyridine, pyridine, room temperature;

5 E) 9-borabicyclononane, tetrahydrofuran, room
temperature, 10 hours; water, sodium hydroxide,
hydrogen peroxide water, room temperature, 12 hours;

F) potassium thioacetate, N,N-dimethylformamide,
90°C, 3 hours;

10 G) fatty acid derivative, pyridine,
dichloromethane, room temperature, 2 hours;

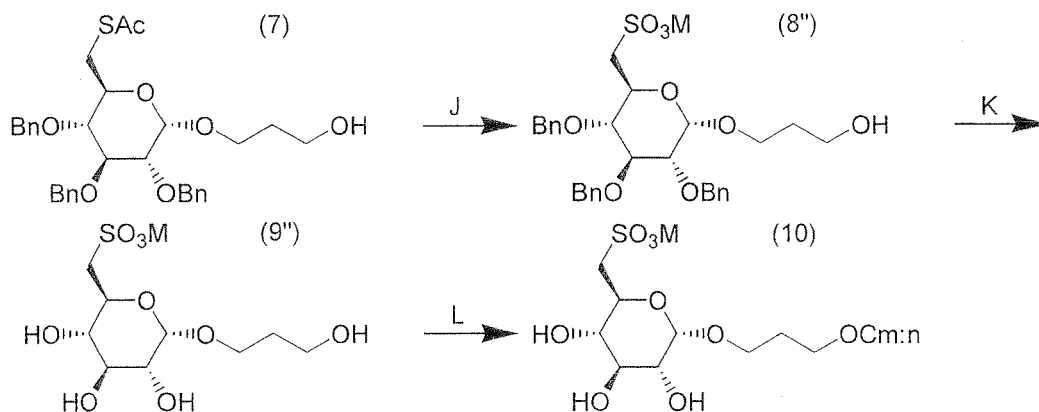
H) Oxon, acetic acid, potassium acetate, room
temperature, 48 hours; and

I) palladium activated carbon, hydrogen gas,
15 ethanol, dichloromethane, room temperature, 48 hours.

Alternatively, after the compound (7) is prepared
via the route including the steps A to F, the intended
compound (10) may be obtained via the following steps:

[Formula 1]

20



J) Oxon, acetic acid, potassium acetate, room
temperature, 48 hours;

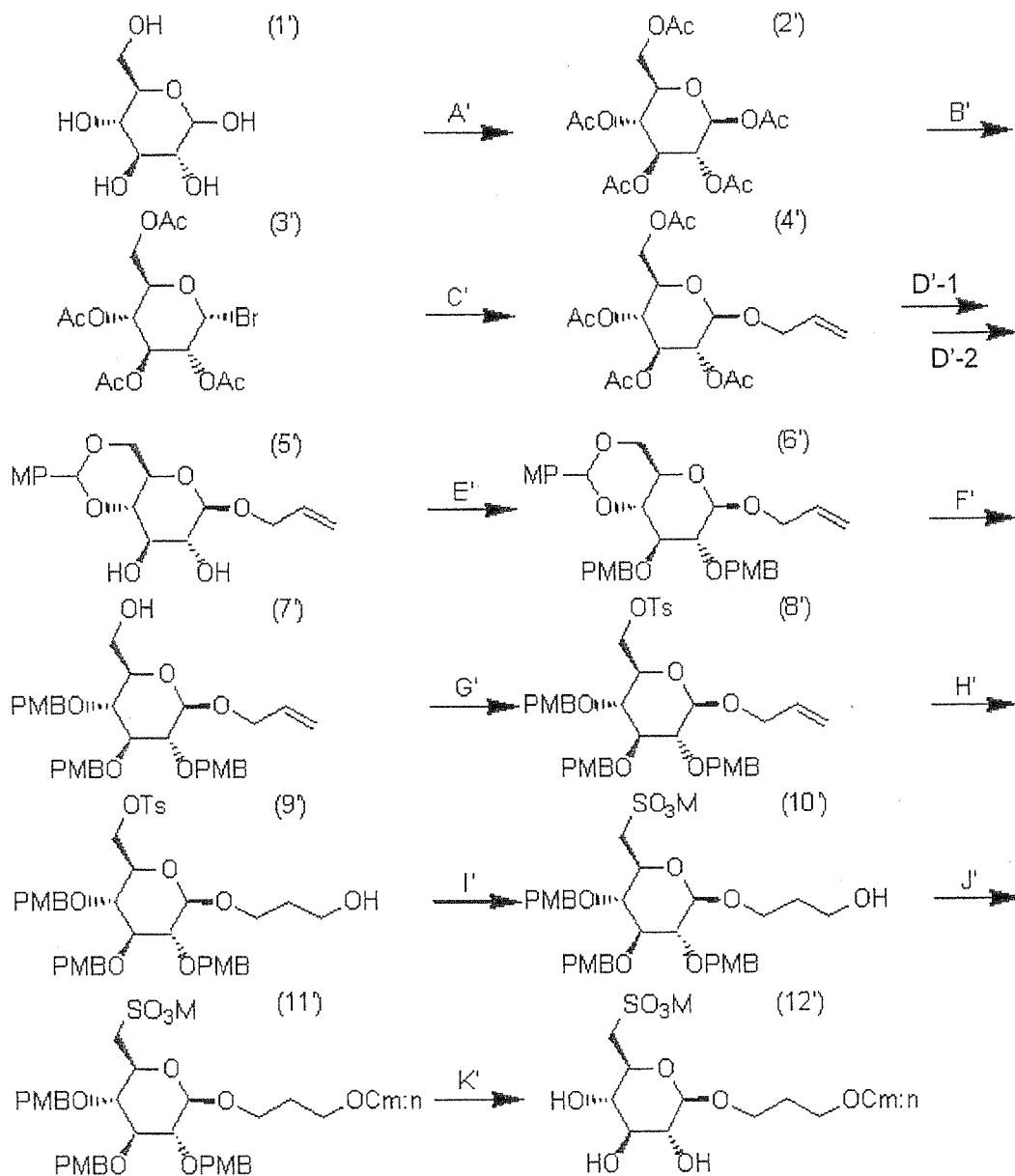
K) palladium activated carbon, hydrogen gas, methanol, dichloromethane, room temperature, 16 hours; and

L) fatty acid, 1-ethyl-3-(3-
5 dimethylaminopropyl)carbodiimide hydrochloride, 4-
dimethylaminopyridine, N,N-dimethylformamide, from 0 (C
to room temperature, 18 hours.

The method for preparing the sulfoquinovosylacyl
propanediol compound according to the present invention
10 is not limited to the above-given specific example and
the following additional method may be used.

"Ac" represents an acetyl group, "MP" represents a
p-methoxyphenyl group, "PMB" represents a p-
methoxybenzyl group, "Ts" represents a tosyl group,
15 "SAC" represents an acetylthio group, and "M"
represents a hydrogen ion or a metal ion.

[Chemical Formula 5]



A') acetic anhydride, sodium acetate, heating and boiling;

B') hydrobromic acid-acetic acid solution, dichloromethane, room temperature, 6 hours;

C') allyl alcohol, cyanide mercury, dichloromethane, room temperature, 16 hours;

D') D'-1. sodium methoxide, methanol, room

temperature, 4 hours;

D'-2. p-anisaldehyde dimethyl acetal, p-toluenesulfonic acid monohydrate, acetonitrile, 40°C, 16 hours;

5 E') p-methoxybenzyl chloride, sodium hydroxide, N,N-dimethylformamide, room temperature, 16 hours;

F') lithium hydride aluminum, aluminum chloride, dichloromethane, diethyl ether, 0°C, 1 hour;

10 G') p-toluenesulfonyl chloride, 4-dimethylaminopyridine, pyridine, room temperature, 16 hours;

H') 9-borabicyclo nonane, tetrahydrofuran, room temperature, 16 hours; water, sodium hydroxide, hydrogen peroxide water, room temperature, 4 hours;

15 I') sodium sulfite, ethanol, water, heating under reflux, 72 hours;

J') fatty acid derivative, 4-dimethylaminopyridine, pyridine, dichloromethane, heating under reflux, 16 hours; and

20 K') 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, dichloromethane, methanol, water, room temperature, 4 hours.

Alternatively, any procedures known to those skilled in the art may be combined thereby preparing
25 the sulfoquinovosylacyl propanediol compound and pharmaceutically acceptable salts thereof according to an aspect of the present invention. These preparation

methods are also included in the scope of the present invention.

Examples of the sulfoquinovosylacyl propanediol compound expressed by the general formula (I) and
5 pharmaceutically acceptable salts thereof according to the present invention include, but are not limited to, salts of monovalent cations such as sodium and potassium, and salts of divalent cations such as calcium and magnesium.

10 The salts according to the present invention may be prepared by the above-described synthesis method, or a modification of the synthesis method. Alternatively, the product synthesized by the above-described method may be subjected to a known ion exchange treatment to
15 obtain the desired salt. These methods for synthesizing the salts according to the present invention are also included within the scope of the present invention.

The sulfoquinovosylacyl propanediol compound and
20 pharmaceutically acceptable salts thereof according to the present invention have notable pharmacological effects such as radiation sensitizing effect and antineoplastic effect.

Therefore, according to another aspect of the
25 present invention, the sulfoquinovosylacyl propanediol compound and pharmaceutically acceptable salts thereof may be provided as drugs utilizing their

pharmacological effects.

Thus according to another aspect of the present invention, the sulfoquinovosylacyl propanediol compound and pharmaceutically acceptable salts thereof have
5 sensitizing effect as the first pharmacological effect. Accordingly, the sulfoquinovosylacyl propanediol compound and pharmaceutically acceptable salts thereof may be provided as radiosensitizers.

The radiosensitizer according to the present
10 invention may be used for treating malignant neoplasm. Examples of malignant neoplasm include, but are not limited to: neurogenic tumor such as cerebral tumor; squamous cell carcinoma and adenocarcinoma such as head and neck cancer, skin cancer, esophagus cancer, thyroid
15 cancer, stomach cancer, lung cancer, gallbladder cancer, biliary tract cancer, pancreas cancer, liver cancer, prostate cancer, uterus cancer, ovarian cancer, breast cancer, kidney cancer, bladder cancer, and colon cancer; and melanoma, osteoma, soft tissue tumor, and
20 lymphoma, leukemia, and myeloma. The term "treatment" used herein refers to the reduction, destruction, and/or inhibition of enhancement growth of the above-described malignant neoplasm.

The radiosensitizer according to the present
25 invention may contain, as an active ingredient, an effective dose of at least one compound selected from the group consisting of the sulfoquinovosylacyl

propanediol compound expressed by the general formula (I) and pharmaceutically acceptable salts thereof. The radiosensitizer may contain more than one kind of compounds having different substituents R_1 in the general formula (I). In addition, the radiosensitizer may be combined with other radiosensitizer(s), an antitumor agent(s), or other substance(s) having pharmacological activity and/or pharmaceutical activity without affecting its activity.

Hereinafter, the compounds consisting of the sulfoquinovosylacyl propanediol compound represented by the general formula (I) and pharmaceutically acceptable salts thereof according to the present invention may be referred to as "radiosensitizing substance of the present invention".

The radiosensitizing substance of the present invention may be given by, for example, oral administration or parenteral administration. According to these administration routes, the radiosensitizing substance of the present invention may be combined with an appropriate pharmaceutically acceptable drug additive such as an excipient or diluent thereby making a pharmaceutical preparation. The radiosensitizer according to the present invention shall contain an effective dose of the radiosensitizing substance of the present invention, and may be provided as a pharmaceutical preparation as described above.

Examples of dosage forms suitable for oral administration include solid, semi-solid, liquid, and gas forms, and specific examples of thereof include, but not limited to, tablets, capsules, powders, granules, solutions, suspending agents, syrups, elixirs, and aerosols.

When the radiosensitizing substance of the present invention is parenterally administered, it may be given by, for example, injection, transdermal administration, rectal administration, or ocular administration.

Administration by injection may be conducted through, for example, hypodermic, intradermal, intravenous, or intramuscular injection.

The conditions for administering the radiosensitizing substance of the present invention (for example, dose, frequency of administration, and interval of administration) may be appropriately established and adjusted according to the dosage form, administration route, disease to be treated, for example, state of malignant neoplasm (for example, type, location, and stage), conditions such as the drug to be combined (for example, presence or absence of combined drug, type, dose, frequency, and timing of administration of combined drug, and sequence of administration of the combined drug and the radiosensitizing substance of the present invention), the manner of combination with radiation (for example,

the timing of combination and the order of the administration of the radiosensitizing substance of the present invention), and the conditions of the subject to be treated (for example, body weight, sex, and age).

5 For example, the dose of the radiosensitizing substance may be, but is not limited to, from 0.001 to 100 mg/kg body weight per day via oral administration, 0.001 to 50 mg/kg body weight per day via injection, from 0.001 to 100 mg/kg body weight per day via transdermal
10 administration, 0.001 to 50 mg/kg body weight per day via rectal administration, or instillation of an about 0.001 to 3wt% solution several times a day via ocular administration.

 In the radiotherapy treatment, the type, dose, and
15 frequency of radiation may follow the conditions for conventional radiotherapy treatment. Specifically, conventional radiotherapy treatment for human is conducted through, for example, exposure to medical radiation such as an X ray, γ ray, electron ray, β ray, or other particle
20 beams such as π -meson, neutron, or heavy particle beams with an irradiation dose of about 0.1 to 100 Gy per time over a period of one week to 6 months to give a total irradiation dose of about 10 to 500 Gy. Typical example of human radiotherapy is conducted by, not limited to, X ray
25 irradiation with a dose of 2 Gy per time for five times thereby giving a total dose of 60 Gy over a period of about 6 weeks.

For example, the dose and frequency of irradiation may be reduced. Other examples of the radiotherapy method include conformation radiotherapy, stereotactic irradiation wherein the focus of malignant neoplasm is shot with pinpoint precision, or intensity modulated radiotherapy. In addition, irradiation with encapsulated sealed radioactive source, γ -ray teletherapy, or irradiation with particle beams also may be used. The irradiation dose per time may be increased, and the irradiation period may be reduced through internal irradiation.

Radiation therapy and administration of the radiosensitizer of the present invention may be conducted concurrently or sequentially. In this case, the radiosensitizer of the present invention is expected to serve as an antineoplastic agent to be combined with radiation therapy. Accordingly, according to another aspect of the present invention, the novel sulfoquinovosylacyl propanediol compound or pharmaceutically acceptable salts thereof according to the present invention may be provided as an antineoplastic agent to be combined with radiation therapy.

As known to those skilled in the field of radiotherapy treatment, the conditions of radiation therapy and administration of the radiosensitizer of the present invention may be appropriately selected by

health professionals or other specialist depending on,
for example: the type of radiation source, irradiation
method, site and period of irradiation; type of
sensitizer, route and timing of administration; type
5 and seriousness of the disease to be treated; and age,
body weight, health condition, and medical history of
the subject to be exposed to radiation.

In addition, according to yet another aspect of
the present invention, provided is a therapy for
10 treating a disease against which radiation therapy is
effective, including administration of an effective
dose of the radiosensitizing substance to the subject
in need of the substance. The term "a disease against
which radiation therapy is effective" refers to a
15 disease which is effectively treated by, for example,
radiation therapy on the above-described malignant
neoplasm. Details about the radiosensitizing substance
and method and conditions of its administration may be
as described above.

20 The therapy according to the present invention may
include administration of an effective dose of the
radiosensitizing substance to the subject in need of
the substance, concurrently with radiation therapy, or
before or after the radiation therapy.

25 According to yet another aspect of the present
invention, the sulfoquinovosylacetyl propanediol compound
and pharmaceutically acceptable salts thereof have

antineoplastic effect as a second pharmacological effect. More specifically, they synergistically accelerate the radiation effect, and can suppress malignant neoplasm when used alone. Accordingly, the
5 sulfoquinovosylacyl propanediol compound and pharmaceutically acceptable salts thereof may be provided as an antineoplastic agent.

When the sulfoquinovosylacyl propanediol compound and pharmaceutically acceptable salts thereof are used
10 as an antineoplastic agent, for example, they may be used in the same manner as the above-described radiosensitizer, except that they are not combined with radiation therapy.

In this case, the conditions for administering the
15 sulfoquinovosylacyl propanediol compound (for example, dose, frequency of administration, and interval of administration) may be appropriately established and adjusted according to the dosage form, administration route, disease to be treated, for example, state of
20 malignant neoplasm (for example, type, location, and stage), conditions such as the drug to be combined (for example, presence or absence of combined drug, type, dose, frequency, and timing of administration of combined drug, and sequence of administration of the
25 combined drug and the radiosensitizing substance of the present invention), and the conditions of the subject to be treated (for example, body weight, sex, and age).

Examples

Examples of the present invention are described below, but the present invention is not limited thereto.

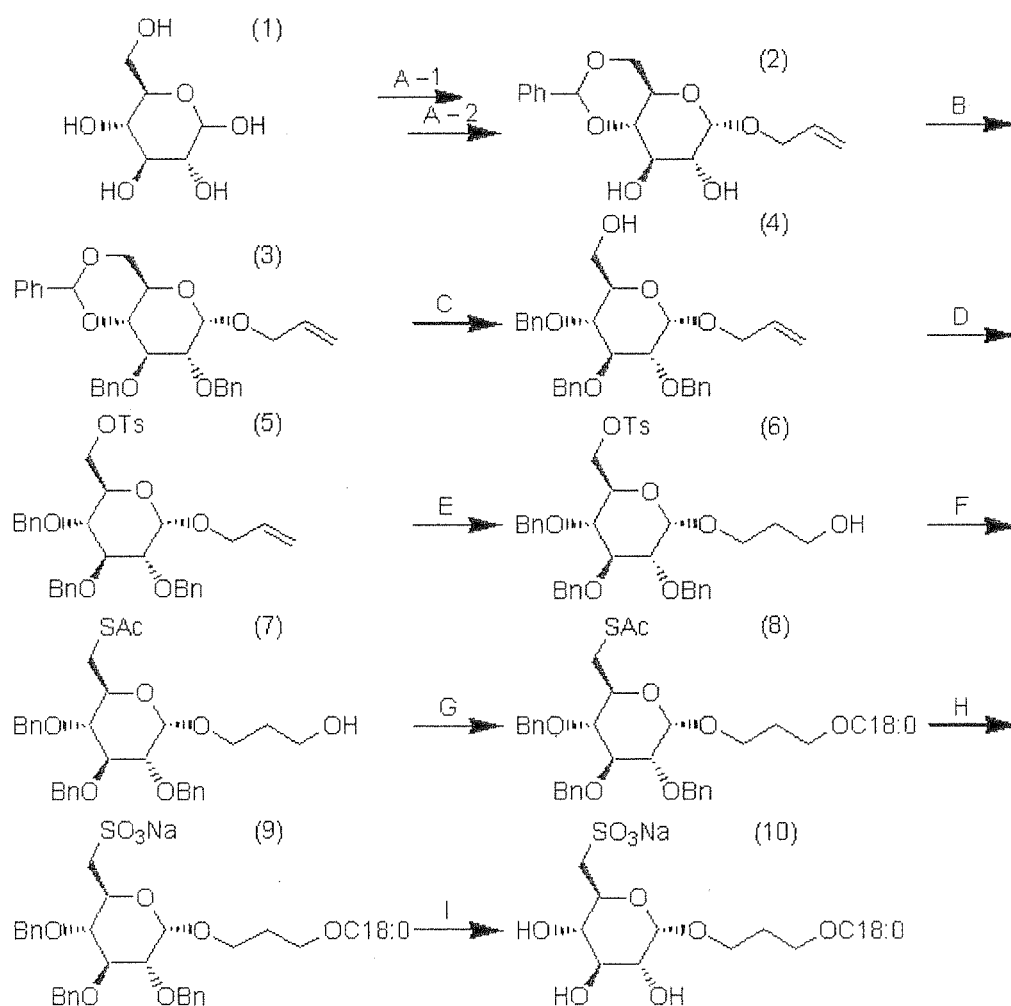
5 <Synthesis examples>

[Example I]

The steps for preparing the sulfoquinovosylacyl propanediol compound according to the present invention are described below taking, as an example, a sodium

10 salt of α -sulfoquinovosyl stearoyl propanediol.

[Chemical Formula 6]



A) A-1. allyl alcohol, trifluoromethanesulfonic acid, 80°C, 48 hours;

A-2. benzaldehyde dimethyl acetal, p-toluene sulfonic acid monohydrate, acetonitrile, 40°C, 4 hours,
5 20.2%;

B) benzyl bromide, sodium hydroxide, N,N-dimethylformamide, room temperature, 24 hours, 84.4%;

C) lithium hydride aluminum, aluminum chloride, dichloromethane, diethyl ether, heating under reflux,
10 4 hours, 90.2%;

D) p-toluenesulfonyl chloride, 4-dimethylaminopyridine, pyridine, room temperature, 16 hours, 87.9%;

E) 9-borabicyclononane, tetrahydrofuran, room
15 temperature, 10 hours; water, sodium hydroxide, hydrogen peroxide water, room temperature, 12 hours, 94.4%;

F) potassium thioacetate, N,N-dimethylformamide, 90°C, 3 hours, 90.8%;

G) stearoyl chloride, pyridine, dichloromethane, room temperature, 2 hours, 97.4%;

H) Oxon, acetic acid, potassium acetate, room temperature, 48 hours, 88.6%; and

I) palladium activated carbon, hydrogen gas, ethanol, dichloromethane, room temperature, 48 hours,
25 79.4%.

The procedure for obtaining, as the end product, a

sodium salt of α -sulfoquinovosyl stearoyl propanediol according to an aspect of the present invention was conducted via the routes A to I in the above-described scheme.

5 Example I-1

Step A: 1-O-allyl-4,6-O-benzylidene- α -D-glucopyranoside (2)

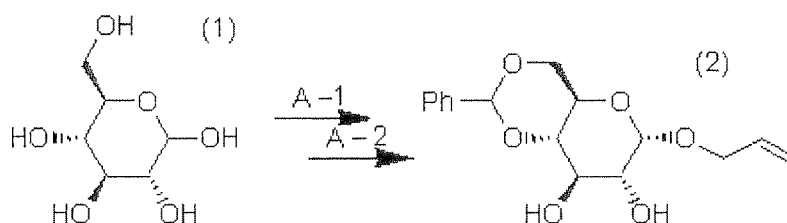
The compound (1) (100 g, 555 mmol) as the starting substance was suspended in allyl alcohol (500 ml), to which trifluoromethanesulfonic acid (1.00 ml) was added at 0°C, and the reaction liquid was vigorously stirred at 80°C for 48 hours. After the sufficient progress of the reaction was confirmed, triethylamine (3 ml) was added to stop the reaction, and the reaction liquid was concentrated under reduced pressure. Subsequently, the residue was suspended in anhydrous acetonitrile (500 ml), to which benzaldehyde dimethyl acetal (127 g, 1.5 equivalent) and p-toluenesulfonic acid monohydrate (5.28 g, 0.05 equivalent) were added. The reaction liquid was stirred at 40°C for 4 hours, to which triethylamine (10 ml) was added to stop the reaction, and the reaction liquid was concentrated under reduced pressure. The residue was poured to hexane (2000 ml) and water (500 ml), and the mixed liquid was vigorously stirred. The generated precipitate was collected by filtration, and rinsed with water and hexane. The precipitate was crystallized from heated ethanol twice

to obtain the title compound (2) in the form of colorless needle crystals {34.5 g (112 mmol), 20.2%}. $[\alpha]^{23}_D +97.5^\circ$ (c1.00 CH₃OH), LRMS 331m/z (M+Na)⁺, mp 139-141°C

¹H NMR (400 MHz, CD₃OD); δ 7.51-7.47 (m, 2H, ArH), 7.37-7.32 (m, 3H, ArH), 5.99 (dddd, 1H, J=17.2, 10.5, 6.08, 5.32 Hz, H2), 5.56 (s, 1H, PhCH), 5.36 (dq, 1H, J=17.3, 1.68 Hz, H3a), 5.20 (ddt, 1H, J=10.4, 1.80, 1.28 Hz, H3b), 4.88 (d, 1H, J=3.86 Hz, H1'), 4.25-4.18 (m, 2H, H1a & H6'a), 4.07 (ddt, 1H, J=13.0, 6.10, 1.36 Hz, H1b), 3.85 (t, 1H, J=9.38 Hz, H3'), 3.81-3.71 (m, 2H, H5' & H6'b), 3.52 (dd, 1H, J=9.38, 3.86 Hz, H2'), 3.45 (t, 1H, J=9.24 Hz, H4').

¹³C NMR (100 MHz, CD₃OD); δ 139.1 (Ar-ipso), 135.4 (C2), 129.9 (Ar), 129.0 (Ar), 127.5 (Ar), 117.8 (C3), 103.0 (PhCH), 100.0 (C1'), 82.9 (C4'), 74.0 (C2'), 72.0 (C3'), 69.9 (C6'), 69.7 (C1), 64.1 (C5).

[Chemical Formula 7]



Example I-2

Step B; 1-O-allyl-2,3-di-O-benzyl-4,6-O-benzylidene- α -D-glucopyranoside (3)

To a solution of the compound (2) (30.0 g, 97.3 mmol) in anhydrous N,N-dimethylformamide (DMF,

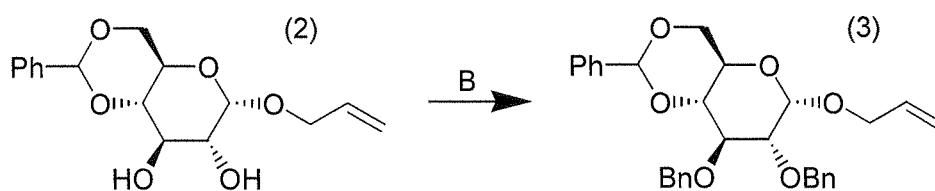
300 ml), added are benzyl bromide (41.6 g, 2.5 equivalents) and sodium hydroxide (11.7 g, 3.0 equivalents), and the reaction liquid was vigorously stirred at room temperature for 24 hours. After the sufficient progress of the reaction was confirmed, the reaction liquid was poured to chilled water (900 ml), and extracted with ethyl acetate (3 × 300 ml). The organic layers were combined and washed with saturated saline (2 × 100 ml), dried with sodium sulfate, filtered, concentrated under reduced pressure. The obtained residue was crystallized twice from heated ethanol to obtain the title compound (3) in the form of colorless needle crystals (33.5 g). The filtrate was concentrated, purified with silica gel chromatography (hexane-ethyl acetate, 15:1 → 10:1 → 8:1), crystallized from heated ethanol to obtain the compound (3) (6.63 g) {40.1 g (82.1 mmol) in total, 84.4%}. $[\alpha]^{26}_D -1.46^\circ (c1.03 \text{ CHCl}_3)$, LRMS m/z 511 ($M+Na$)⁺, mp 86-87°C.

¹H NMR (400 MHz, CDCl₃); δ 7.50-7.47 (m, 2H, ArH), 7.40-7.24 (m, 13H, ArH), 5.94 (dddd, 1H, $J=17.0, 10.4, 6.70, 5.24$ Hz, H2), 5.56 (s, 1H, PhCH), 5.33 (dq, 1H, $J=17.2, 1.56$ Hz, H3a), 5.24 (ddt, 1H, $J=10.3, 1.56, 1.12$ Hz, H3b), 4.92 (d, 1H, $J=11.2$ Hz, ArCH₂), 4.84 (d, 1H, $J=11.2$ Hz, ArCH₂), 4.83 (d, 1H, $J=12.1$ Hz, ArCH₂), 4.80 (d, 1H, $J=3.76$ Hz, H1'), 4.68 (d, 1H, $J=12.1$ Hz, ArCH₂), 4.26 (dd, 1H, $J=10.2, 4.84$ Hz, H6'a), 4.18

(ddt, 1H, $J=12.9$, 5.18, 1.40 Hz, H1a), 4.79 (t, 1H, $J=9.30$ Hz, H3'), 4.03 (ddt, 1H, $J=12.9$, 6.68, 1.20 Hz, H1b), 3.89 (dt, 1H, $J=9.96$, 4.80 Hz, H5'), 3.70 (t, 1H, $J=10.3$ Hz, H6'b), 3.61 (t, 1H, $J=9.44$ Hz, H4'), 3.57 (dd, 1H, $J=8.72$, 3.80 Hz, H2').

^{13}C NMR (100 MHz, CDCl_3); δ 138.7 (Ar-ipso), 138.1 (Ar-ipso), 137.3 (Ar-ipso), 133.5 (C2), 128.9–127.5 (m, Ar), 126.0 (Ar), 118.4 (C3), 101.2 (PhCH), 96.7 (C1'), 82.1 (C3'), 79.1 (C2'), 78.6 (C4'), 75.3 (ArCH₂), 73.6 (ArCH₂), 69.0 (C6'), 68.4 (C1), 62.5 (C5').

[Chemical Formula 8]



Example I-3

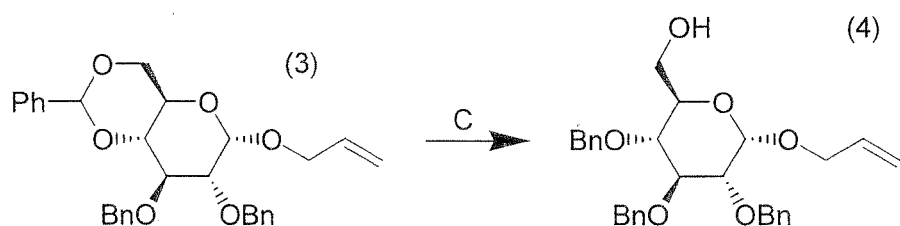
Step C; 1-O-allyl-2,3,4-tri-O-benzyl-α-D-glucopyranoside (4)

Aluminum lithium hydride (2.02 g, 1.3 equivalents) is suspended in a mixed solution of anhydrous dichloromethane (100 ml) and anhydrous diethyl ether (100 ml), to which the compound (3) (20.0 g, 40.9 mmol) was added. Subsequently, to the reaction liquid, added was 200 ml of an aluminum chloride (7.09 g, 1.3 equivalents) solution in anhydrous diethyl ether, and the mixture was stirred for 4 hours under heating and reflux. After the sufficient progress of the reaction was confirmed, water (10 ml) was slowly added dropwise, the precipitate was collected by filtration after

a standing overnight, and then the precipitate was rinsed with diethyl ether. The filtrate was washed with water (2 × 100 ml), the aqueous layers were combined, and extracted with diethyl ether (2 × 100 ml). The organic layers were
5 combined and washed with saturated saline (2 × 200 ml), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The obtained residue was purified with silica gel chromatography (hexane-ethyl acetate, 5:1 → 4:1 → 3:1 → 2:1) to obtain the title compound (4) in the form
10 of a colorless oily substance {18.1 g (36.9 mmol), 90.2%}. $[\alpha]_D^{22} +45.0^\circ$ (c1.21 CHCl₃), LRMS m/z 513 (M+Na)⁺.
¹H NMR (400 MHz, CDCl₃); δ 7.37–7.26 (m, 15H, ArH), 5.92 (dddd, 1H, J=17.1, 10.4, 6.66, 5.24 Hz, H2), 5.31 (dq, 1H, J=17.2, 1.52 Hz, H3a), 5.22 (ddt, 1H, J=10.3, 1.46,
15 1.10 Hz, H3b), 5.00 (d, 1H, J=10.9 Hz, ArCH₂), 4.89 (d, 1H, J=11.0 Hz, ArCH₂), 4.84 (d, 1H, J=10.9 Hz, ArCH₂), 4.77 (d, 1H, J=12.0 Hz, ArCH₂), 4.77 (d, 1H, J=3.60 Hz, H1'), 4.65 (d, 1H, J=12.1 Hz, ArCH₂), 4.64 (d, 1H, J=11.0 Hz, ArCH₂), 4.14 (ddt, 1H, J=12.9, 5.22, 1.34 Hz, H1a), 4.04 (t, 1H, J=9.36 Hz, H3'), 3.99 (ddt, 1H, J=12.9, 6.64, 1.08 Hz,
20 H1b), 3.79–3.66 (m, 3H, H5' & H6'a & H6'b), 3.54 (t, 1H, J=9.28 Hz, H4'), 3.51 (dd, 1H, J=9.60, 3.64 Hz, H2'), 1.69 (t, 1H, J=12.0 Hz, 6'-OH).
¹³C NMR (100 MHz, CDCl₃); δ 138.7 (Ar-ipso), 138.1

(Ar-ipso), 138.1 (Ar-ipso), 133.6 (C2), 128.4-127.6 (m, Ar), 118.3 (C3), 95.6 (C1'), 81.9 (C3'), 79.9 (C2'), 77.3 (C4'), 75.7 (ArCH₂), 75.0 (ArCH₂), 73.2 (ArCH₂), 70.8 (C5'), 68.2 (C1), 61.7 (C6').

5 [Chemical Formula 9]



Example I-4

Step D; 1-O-allyl-2,3,4-tri-O-benzyl-6-O-tosyl- α -D-glucopyranoside (5)

To a solution of the compound (4) (25.1 g, 51.2 mmol) in anhydrous pyridine (250 ml), added were p-toluenesulfonyl chloride (14.6 g, 1.5 equivalents) and 4-dimethylaminopyridine (626 mg, 0.1 equivalents), and the reaction liquid was stirred at room temperature for 16 hours. After the sufficient progress of the reaction was confirmed, water (10 ml) was added to stop the reaction, and the reaction liquid was concentrated under reduced pressure. The residue was suspended in a minor amount of ethyl acetate, poured to 0.5 M hydrochloric acid (200 ml), and extracted with ethyl acetate (3 $\times$ 200 ml). The organic layers were combined, washed with a saturated sodium hydrogen carbonate solution (2 $\times$ 100 ml) and saturated saline (2 $\times$ 100 ml), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The obtained

residue was crystallized twice from heated ethanol to obtain the title compound (5) in the form of colorless needle crystals (25.0 g). The filtrate was concentrated, purified with silica gel chromatography (hexane-ethyl acetate, 5:1 $\rightarrow$ 4:1 $\rightarrow$ 3:1) to obtain the compound (5) (4.00 g). (29.0 g (45.0 mmol) in total, 87.9%).

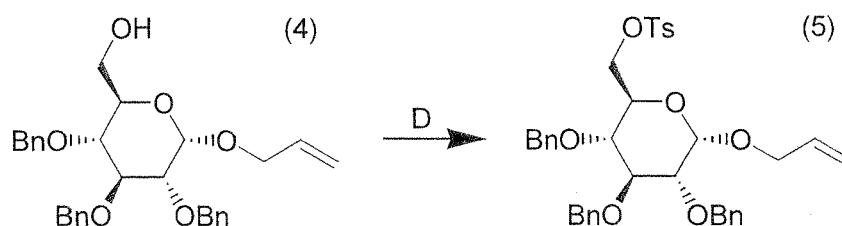
$[\alpha]_D^{25} +32.1^\circ$ (c1.02 CHCl₃), LRMS m/z 667 (M+Na)⁺, mp 86-87°C.

¹H NMR (400 MHz, CDCl₃); δ 7.76 (ddd, 2H, J=8.32, 1.96, 1.76 Hz, ArH), 7.35-7.26 (m, 15H, ArH), 7.17-7.12 (m, 2H, ArH), 5.88 (dddd, 1H, J=17.2, 10.3, 6.62, 5.24 Hz, H₂), 5.28 (dq, 1H, J=17.2, 1.56 Hz, H_{3a}), 5.20 (ddt, 1H, J=10.3, 1.60, 1.12 Hz, H_{3b}), 4.99 (d, 1H, J=10.9 Hz, ArCH₂), 4.82 (d, 1H, J=10.6 Hz, ArCH₂), 4.78 (d, 1H, J=10.8 Hz, ArCH₂), 4.74 (d, 1H, J=12.1 Hz, ArCH₂), 4.72 (d, 1H, J=3.58 Hz, H_{1'}), 4.62 (d, 1H, J=12.1 Hz, ArCH₂), 4.42 (d, 1H, J=10.6 Hz, ArCH₂), 4.22 (dd, 1H, J=10.5, 4.20 Hz, H_{6'a}), 4.16 (dd, 1H, J=10.5, 2.12 Hz, H_{6'b}), 4.07 (ddt, 1H, J=12.9, 5.24, 1.40 Hz, H_{1a}), 3.98 (t, 1H, J=9.24 Hz, H_{3'}), 3.93 (ddt, 1H, J=12.9, 6.64, 1.16 Hz, H_{1b}), 3.81 (ddd, 1H, J=10.1, 4.12, 2.04 Hz, H_{5'}), 3.48 (dd, 1H, J=9.62, 3.58 Hz, H_{2'}), 3.45 (dd, 1H, J=10.0, 8.90 Hz, H_{4'}), 2.39 (s, 3H, Ts-Me).

¹³C NMR (100 MHz, CDCl₃); δ 144.8 (Ar-ipso), 138.5 (Ar-ipso), 137.9 (Ar-ipso), 137.7 (Ar-ipso), 133.4 (C₂),

132.8 (Ar-ipso), 129.8 (Ar), 128.4-127.6 (m, Ar), 118.4 (C3), 95.4 (C1'), 81.8 (C3'), 79.6 (C2'), 76.9 (C4'), 75.7 (ArCH₂), 75.0 (ArCH₂), 73.2 (ArCH₂), 68.6 (C5'), 68.5 (C6'), 68.3 (C1), 21.6 (Ts-Me).

5 [Chemical Formula 10]



Example I-5

Step E; 1-O-(2,3,4-tri-O-benzyl-6-O-tosyl- α -D-glucopyranosyl)-propane-1,3-diol (6)

To a solution of the compound (5) (29.0 g, 45.0 mmol) in anhydrous tetrahydrofuran (THF, 150 ml), added was a solution of 0.5 M 9-borabicyclo[3,3,1]nonane (9-BBN) in tetrahydrofuran (180 ml, 90.0 mmol) at 0°C in an argon atmosphere. After a lapse of 1 hour, the reaction liquid was returned to room temperature, and continuously stirred for 10 hours. The reaction liquid was cooled again to 0°C, to which water (20 ml) was added firstly, and then 3 M sodium hydroxide solution (70 ml) and 35% hydrogen peroxide solution (70 ml) were added sequentially. After a lapse of 1 hour, the reaction liquid was returned to room temperature, and stirred for 12 hours. After the sufficient progress of the reaction was confirmed, the solution was extracted with ethyl

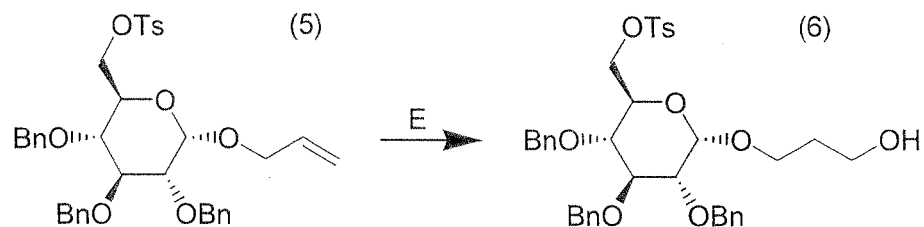
acetate (3 × 100 ml), the organic layers were combined and washed with saturated saline (2 × 100 ml), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The obtained residue was purified with silica gel chromatography (hexane-ethyl acetate, 3:2 → 1:1 → 2:3) to obtain the title compound (6) in the form of a colorless oily substance {28.2 g (42.5 mmol), 94.4%}.

$[\alpha]^{24}_{\text{D}} +26.6^\circ$ (c1.02 CHCl₃), LRMS m/z 685 (M+Na)⁺.

¹H NMR (400 MHz, CDCl₃); δ 7.76-7.74 (m, 2H, ArH), 7.35-7.26 (m, 15H, ArH), 7.16-7.12 (m, 2H, ArH), 4.94 (d, 1H, J=10.9 Hz, ArCH₂), 4.82 (d, 1H, J=10.7 Hz, ArCH₂), 4.77 (d, 1H, J=10.9 Hz, ArCH₂), 4.75 (d, 1H, J=12.0 Hz, ArCH₂), 4.61 (d, 1H, J=12.0 Hz, ArCH₂), 4.61 (d, 1H, J=3.64 Hz, H1'), 4.43 (d, 1H, J=10.7 Hz, ArCH₂), 4.20-4.13 (m, 2H, H6'a & H6'b), 3.92 (t, 1H, J=9.24 Hz, H3'), 3.84-3.74 (m, 4H, H1a & H3a & H3b & H5'), 3.48-3.40 (m, 3H, H1b & H2' & H4'), 2.52 (t, 1H, J=4.74 Hz, 3-OH), 2.39 (s, 3H, Ts-Me), 1.88-1.75 (m, 2H, H2a & H2b).

¹³C NMR (100 MHz, CDCl₃); δ 144.8 (Ar-ipso), 138.4 (Ar-ipso), 137.9 (Ar-ipso), 137.6 (Ar-ipso), 132.7 (Ar-ipso), 129.8 (Ar), 128.5-127.6 (m, Ar), 97.1 (C1'), 81.8 (C3'), 79.5 (C2'), 76.8 (C4'), 75.6 (ArCH₂), 75.0 (ArCH₂), 73.4 (ArCH₂), 68.7 (C5'), 68.6 (C6'), 67.5 (C1), 61.5 (C3), 31.5 (C2), 21.6 (Ts-Me).

[Chemical Formula 11]



Example I-6

5 Step F; 1-O-(2,3,4-tri-O-benzyl-6-thioacetyl- α -D-quinovopyranosyl)-propane-1,3-diol (7)

To a solution of the compound (6) (28.2 g, 42.5 mmol) in anhydrous DMF (300 ml), added was potassium thioacetate (7.28 g, 1.5 equivalents), and the mixture was stirred at 90°C for 3 hours. After the sufficient progress of the reaction was confirmed, the reaction liquid was poured to chilled water (900 ml), extracted with ethyl acetate (3 $\times$ 300 ml). The organic layers were combined and washed with saturated saline (2 $\times$ 200 ml), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The obtained residue was purified with silica gel chromatography (hexane-ethyl acetate, 2:1 $\rightarrow$ 3:2 $\rightarrow$ 1:1 $\rightarrow$ 2:3) to obtain the title compound (7) in the form of light brown oily substance {21.9 g (38.6 mmol), 90.8%}.

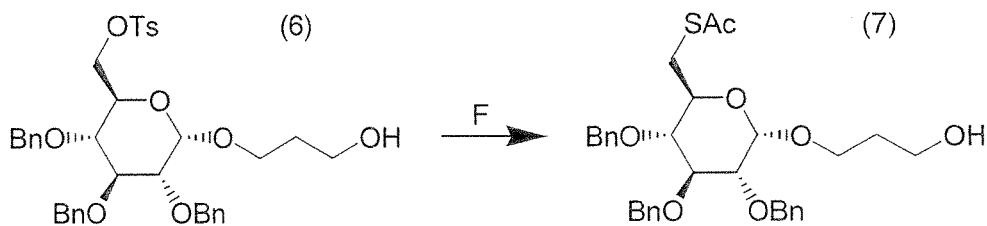
[α] $^{23}_D$ +33.0°(c1.02 CHCl₃), LRMS m/z 584 (M+Na)⁺.

¹H NMR (400 MHz, CDCl₃); δ 7.37-7.24 (m, 15H, ArH), 4.95 (d, 1H, J=10.8 Hz, ArCH₂), 4.89 (d, 1H, J=10.6 Hz, ArCH₂), 4.80 (d, 1H, J=10.8 Hz, ArCH₂), 4.77 (d, 1H, J=12.1 Hz, ArCH₂), 4.63 (d, 1H, J=12.0 Hz, ArCH₂), 4.63

(d, 1H, $J=3.52$ Hz, H1'), 4.61 (d, 1H, $J=10.7$ Hz, ArCH₂), 3.94 (t, 1H, $J=9.22$ Hz, H3'), 3.88 (ddd, 1H, $J=9.86, 6.10, 4.88$ Hz, H1a), 3.83-3.73 (m, 3H, H3a & H3b & H5'), 3.50 (dd, 1H, $J=9.60, 3.64$ Hz, H2'), 3.45 (ddd, 1H, $J=9.92, 5.24, 2.28$ Hz, H1b), 3.41 (dd, 1H, $J=13.6, 3.00$ Hz, H6'a), 3.30 (dd, 1H, $J=9.54, 9.06$ Hz, H4'), 3.02 (dd, 1H, $J=13.7, 7.64$ Hz, H6'b), 2.67 (br, 1H, 3-OH), 2.32 (s, 3H, SAc-Me), 1.92-1.78 (m, 2H, H2a & H2b).

¹³C NMR (100 MHz, CDCl₃); δ 195.0 (SAC-C=O), 138.5 (Ar-
ipso), 137.9 (Ar-ipso), 137.8 (Ar-ipso), 128.5-127.6 (m, Ar), 96.9 (C1'), 81.8 (C3'), 80.4 (C4'), 79.8 (C2'), 75.7 (ArCH₂), 75.2 (ArCH₂), 73.4 (ArCH₂), 69.5 (C5'), 67.2 (C1), 61.5 (C3), 31.5 (C2), 30.8 (C6'), 30.5 (SAc-Me).

[Chemical Formula 12]



Example I-7

Step G; 3-O-(2,3,4-tri-O-benzyl-6-thioacetyl- α -D-quinovopyranosyl)-1-O-stearoyl-propane-1,3-diol (8)

To a solution of the compound (7) (21.9 g, 38.6 mmol) in anhydrous dichloromethane (200 ml), added were stearoyl chloride (15.2 g, 1.3 equivalents) and anhydrous pyridine (5 ml), and the mixture was stirred at room temperature for 2 hours. After the sufficient

progress of the reaction was confirmed, methanol (5 ml) was added to stop the reaction, and the mixture was concentrated under reduced pressure. The residue was suspended in a minor amount of ethyl acetate, poured to water (200 ml), and extracted with ethyl acetate (3 × 100 ml). The organic layers were combined and washed with saturated saline (2 × 100 ml), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The obtained residue was purified with silica gel chromatography (hexane-ethyl acetate, 10:1 → 8:1 → 6:1) to obtain the title compound (8) in the form of a colorless oily substance {31.3 g (37.6 mmol), 97.4%}.

$[\alpha]_D^{23} +29.5^\circ$ (c1.01 CHCl₃), LRMS 855 m/z (M+Na)⁺.

¹H NMR (400 MHz, CDCl₃); δ 7.35–7.25 (m, 15H, ArH), 4.98 (d, 1H, J=10.8 Hz, ArCH₂), 4.89 (d, 1H, J=10.6 Hz, ArCH₂), 4.80 (d, 1H, J=10.8 Hz, ArCH₂), 4.76 (d, 1H, J=12.0 Hz, ArCH₂), 4.66 (d, 1H, J=3.60 Hz, H1'), 4.63 (d, 1H, J=12.1 Hz, ArCH₂), 4.62 (d, 1H, J=10.7 Hz, ArCH₂), 4.23–4.14 (m, 2H, H1a & H1b), 3.96 (t, 1H, J=9.20 Hz, H3'), 3.78 (ddd, 1H, J=9.68, 7.56, 2.92 Hz, H5'), 3.72 (dt, 1H, J=10.0, 6.40 Hz, H3a), 3.50 (dd, 1H, J=9.64, 3.60 Hz, H2'), 3.43 (dt, 1H, J=9.72, 6.36 Hz, H3b), 3.41 (dd, 1H, J=13.6, 2.96 Hz, H6'a), 3.31 (t, 1H, J=9.24 Hz, H4'), 3.05 (dd, 1H, J=13.6, 7.56 Hz, H6'b), 2.33 (s, 3H, SAc-Me), 2.29 (t, 2H, J=7.68 Hz, COCH₂), 1.95 (f, 2H, J=6.40 Hz, H2a & H2b),

1.61 (f, 2H, J=7.24 Hz, COCH₂CH₂), 1.25 (br,

28H, -CH₂-), 0.88 (t, 3H, J=6.84 Hz, Me).

¹³C NMR (100 MHz, CDCl₃); δ 194.8 (SAc-C=O), 173.8

(C=O), 138.6 (Ar-ipso), 138.1 (Ar-ipso), 137.8 (Ar-

5 ipso), 128.4-127.6 (m, Ar), 96.8 (C1'), 81.7 (C3'),

80.4 (C4'), 80.1 (C2'), 75.7 (ArCH₂), 75.2 (ArCH₂),

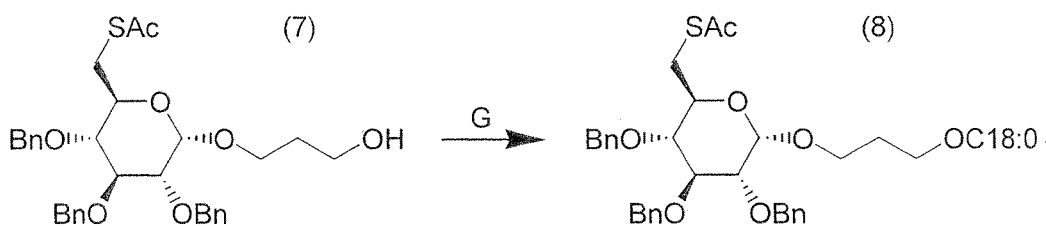
73.2 (ArCH₂), 69.4 (C5'), 64.6 (C3), 61.2 (C1), 34.3

(COCH₂), 31.9 (-CH₂-), 30.9 (C6'), 30.5 (SAc-Me), 29.7-

29.2 (m, -CH₂-), 28.7 (C2), 25.0 (COCH₂CH₂), 22.7

10 (-CH₂-), 14.1 (Me).

[Chemical Formula 13]



Example I-8

15 Step H; 3-O-(2,3,4-tri-O-benzyl-6-sulfo- α -D-quinovopyranosyl)-1-O-stearoyl-propane-1,3-diol sodium salt (9)

To a solution of the compound (8) (31.3 g, 37.6 mmol) in acetic acid (450 ml) were added Oxon (46.2 g) and potassium acetate (11.3 g), and the mixture was vigorously stirred at room temperature 48 hours. After the sufficient progress of the reaction was confirmed, the reaction liquid was poured to a chilled 7.5 M sodium hydroxide solution (1000 ml), and extracted with ethyl acetate (4 $\times$ 200 ml). The organic layers were combined, washed with saturated

sodium hydrogen carbonate solution (2 × 200 ml) and saturated saline (2 × 200 ml), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The obtained residue was purified with silica gel chromatography (dichloromethane-methanol, 15:1 → 10:1 → 8:1) to obtain the title compound (9) in the form of a colorless waxy substance {28.7 g (33.3 mmol), 88.6%}.

$[\alpha]^{23}_D +29.0^\circ$ (c1.16 CHCl₃), LRMS m/z 837 (M-Na)⁻.

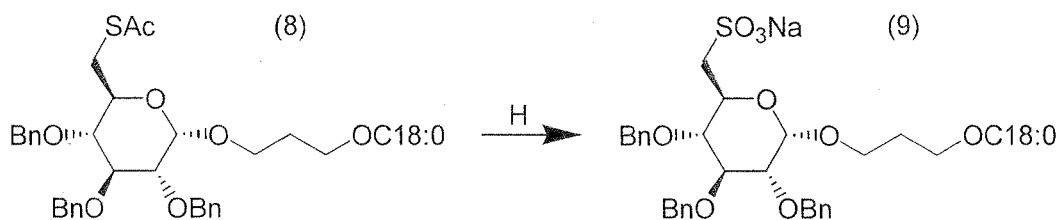
¹H NMR (400 MHz, DMSO-d₆); δ 7.36-7.22 (m, 15H, ArH), 4.85 (d, 1H, J=11.2 Hz, ArCH₂), 4.81 (d, 1H, J=3.72 Hz, H1'), 4.79 (d, 1H, J=11.4 Hz, ArCH₂), 4.69 (d, 1H, J=11.2 Hz, ArCH₂), 4.65 (d, 1H, J=12.0 Hz, ArCH₂), 4.61 (d, 1H, J=12.0 Hz, ArCH₂), 4.58 (d, 1H, J=11.4 Hz, ArCH₂), 4.19-4.10 (m, 2H, H1a & H1b), 4.05-3.96 (m, 2H, H3a & H5'), 3.79 (t, 1H, J=9.14 Hz, H3'), 3.47 (dd, 1H, J=9.56, 3.60 Hz, H2'), 3.38 (dt, 1H, J=10.1, 6.20 Hz, H3b), 3.20 (dd, 1H, J=9.80, 9.00 Hz, H4'), 2.94 (dd, 1H, J=13.9, 1.16 Hz, H6'a), 2.63 (dd, 1H, J=14.0, 9.06 Hz, H6'b), 2.29 (t, 2H, J=7.38 Hz, COCH₂), 1.86 (f, 2H, J=6.36 Hz, H2a & H2b), 1.52 (f, 2H, J=7.12 Hz, COCH₂CH₂), 1.23 (br, 28H, -CH₂-), 0.85 (t, 3H, J=6.84 Hz, Me).

¹³C NMR (100 MHz, DMSO-d₆); δ 172.9 (C=O), 138.9 (Ar-*ipso*), 138.6 (Ar-*ipso*), 138.6 (Ar-*ipso*), 128.2-127.3 (m, Ar), 95.0 (C1'), 81.4 (C3'), 80.5 (C4'), 80.0 (C2'), 74.4 (ArCH₂), 73.7 (ArCH₂), 71.4 (ArCH₂), 67.3

(C5'), 63.4 (C3), 61.5 (C1), 52.8 (C6'), 33.6 (COCH₂),
 31.3 (-CH₂-), 29.0-28.4 (m, C2 & -CH₂-), 24.5
 (COCH₂CH₂), 22.1 (-CH₂-), 13.9 (Me).

[Chemical Formula 14]

5



Example I-9

Step I; 3-O-(6-sulfo- α -D-quinovopyranosyl)-1-O-stearoyl-propane-1,3-diol sodium salt (10)

10 To a solution of the compound (9) (28.7 g, 33.3 mmol) in ethanol (400 ml) and dichloromethane (150 ml) was added 10% palladium activated carbon (7.00 g), and the mixture was stirred at room temperature for 48 hours in a hydrogen gas atmosphere.

15 After the sufficient progress of the reaction was confirmed, palladium activated carbon was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified with silica gel chromatography (dichloromethane-

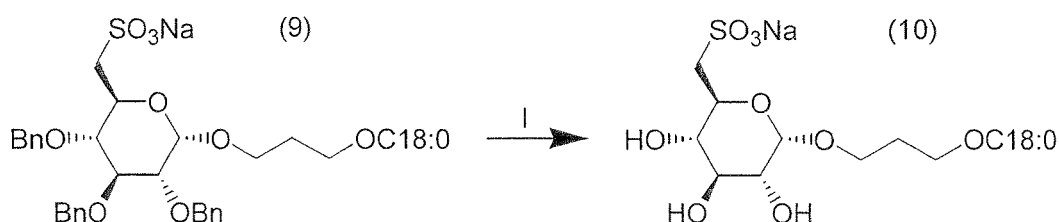
20 methanol, 10:1 $\rightarrow$ 5:1 $\rightarrow$ 3:1 $\rightarrow$ 2:1 $\rightarrow$ 1:1), and precipitated from 98% heated ethanol to obtain the title compound (10) in the form of a colorless powder {15.6 g (26.4 mmol), 79.4%}.

25 $[\alpha]^{22}_D +49.6^\circ$ (c1.00 H₂O), LRMS m/z 567 (M-Na)⁻, HRMS calcd for C₂₇H₅₁O₁₀S (M-Na)⁻ 567.3208, found 567.3210. ¹H NMR (400 MHz, DMSO-d₆); δ 5.40 (d, 1H, J=3.48Hz,

4'-OH), 4.58 (d, 1H, J=4.64 Hz, 3'-OH), 4.56 (d, 1H, J=3.72 Hz, H1'), 4.45 (d, 1H, J=6.52 Hz, 2'-OH), 4.15-4.06 (m, 2H, H1a & H1b), 3.84-3.78 (m, 2H, H3a & H5'), 3.42-3.34 (m, 2H, H3b & H3'), 3.19 (ddd, 1H, J=9.62, 6.50, 3.76 Hz, H2'), 2.98-2.91 (m, 2H, H4' & H6'a), 2.63 (dd, 1H, J=14.0, 6.00 Hz, H6'b), 2.28 (t, 2H, J=7.40 Hz, COCH₂), 1.86-1.80 (m, 2H, H2a & H2b), 1.55-1.48 (m, 2H, COCH₂CH₂), 1.24 (br, 28H, -CH₂-), 0.86 (t, 3H, J=6.84Hz, Me).

¹³C NMR (100 MHz, DMSO-d₆); δ 172.8 (C=O), 98.2 (C1'), 74.7 (C4'), 73.1 (C3'), 71.8 (C2'), 68.2 (C5'), 63.4 (C3), 61.2 (C1), 55.1 (C6'), 33.4 (COCH₂), 31.2 (-CH₂-), 28.9-28.4 (m, C2 & -CH₂-), 24.4 (COCH₂CH₂), 22.0 (-CH₂-), 13.8 (Me).

[Chemical Formula 15]



2.15 g of 3-O-(6-sulfo-α-D-quinovopyranosyl)-1-O-stearoyl-propane-1,3-diol sodium salt was dissolved in 60 ml of water, adsorbed to a WAKOGEL 100C18 (manufactured by Wako Pure Chemical Industries, Ltd.) column, and 500 ml of 1% calcium chloride solution was poured into the column for substitution, and washed with 500 ml of distilled water. Thereafter, elution was performed with 200 ml each of 50%, 80%, and 100% methanol, and reprecipitated from 98% heated ethanol to

obtain 1.47 g of 3-O-(6-sulfo- α -D-quinovopyranosyl)-1-O-stearoyl-propane-1,3-diol calcium salt.

Although not shown in Examples, with the same column treatment, a magnesium or potassium salt can be obtained
5 through substitution with a magnesium chloride or potassium chloride solution.

[Example II]

As other examples of α -sulfoquinovosylacyl propanediol compound, described below are α anomer compounds having 22,
10 14, 10, 6, 2 and 1 carbon atoms within the acyl residue of the fatty acid.

Example II-1

3-O-(6-sulfo- α -D-quinovopyranosyl)-1-O-decanoyl-propane-1,3-diol sodium salt

15 The title compound was synthesized in the same manner as Example I, except that decanoyl chloride was used as the fatty acid derivative in the step G.

$[\alpha]^{22}_D +57.9^\circ$ (c 0.76, H₂O), LRMS m/z 455 (M-Na)⁻, HRMS calcd for C₁₉H₃₅O₁₀S (M-Na)⁻ 455.1956, found 455.1954.

20 ¹H NMR (400 MHz, DMSO-d₆) ; δ 5.40 (d, 1H, J=3.1 Hz, 4'-OH), 4.65 (d, 1H, J=4.7 Hz, 3'-OH), 4.56 (d, 1H, J=3.7 Hz, H1'), 4.52 (d, 1H, J=6.48 Hz, 2'-OH), 4.14-4.08 (m, 2H, H1a & H1b), 3.84-3.78 (m, 2H, H3a & H5'), 3.41-3.33 (m, 2H, H3b & H3'), 3.21-3.16 (m, 1H, H2'), 2.97-2.92 (m, 2H, H4' &
25 H6'a), 2.61 (dd, 1H, J=14.0, 6.2 Hz, H6'b), 2.29 (t, 2H, J=7.4 Hz, COCH₂), 1.84-1.81 (m, 2H, H2a & H2b), 1.53-1.50 (m, 2H, COCH₂CH₂), 1.25 (br, 12H, -CH₂-), 0.86 (t, 3H,

$J=6.8$ Hz, Me).

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$); δ 173.1 (C=O), 98.4 (C1'), 74.8 (C4'), 73.2 (C3'), 71.9 (C2'), 68.4 (C5'), 63.5 (C3), 61.4 (C1), 55.2 (C6'), 33.6 (COCH₂), 31.4 (-CH₂-), 29.0-28.6 (m, C2 & -CH₂-), 24.6 (COCH₂CH₂), 22.2 (-CH₂-), 14.1 (Me)

Example II-2

3-O-(6-sulfo- α -D-quinovopyranosyl)-1-O-myristoyl-propane-1,3-diol sodium salt

The title compound was synthesized in the same manner as Example I, except that myristoyl chloride was used as the fatty acid derivative in the step G.

$[\alpha]^{23}_{\text{D}} +49.7^\circ$ (c 0.67, H₂O), LRMS m/z 511 (M-Na)⁻, HRMS calcd for C₂₃H₄₃O₁₀S (M-Na)⁻ 511.2582, found 511.2596.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) ; δ 5.41(br, 1H, 4'-OH), 4.63-4.61(m, 1H, 3'-OH), 4.55 (d, 1H, $J=3.7$ Hz, H1'), 4.50-4.48 (m, 1H, 2'-OH), 4.13-4.07 (m, 2H, H1a & H1b), 3.83-3.77 (m, 2H, H3a & H5'), 3.41-3.33 (m, 2H, H3b & H3'), 3.20-3.15 (m, 1H, H2'), 2.98-2.91 (m, 2H, H4' & H6'a), 2.64-2.59 (m, 1H, H6'b), 2.28 (t, 2H, $J=7.4$ Hz, COCH₂), 1.86-1.79 (m, 2H, H2a & H2b), 1.53-1.49 (m, 2H, COCH₂CH₂), 1.24 (br, 20H, -CH₂-), 0.85 (t, 3H, $J=6.8$ Hz, Me).

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$); δ 173.0 (C=O), 98.4 (C1'), 74.8 (C4'), 73.2 (C3'), 71.9 (C2'), 68.4 (C5'), 63.5 (C3), 61.4 (C1), 55.3 (C6'), 33.6 (COCH₂), 31.4 (-CH₂-), 29.1-28.6 (m, C2 & -CH₂-), 24.6 (COCH₂CH₂), 22.2 (-CH₂-), 14.0 (Me).

Example II-3

3-O-(6-sulfo- α -D-quinovopyranosyl)-1-O-behenoyl-

propane-1,3-diol sodium salt

The title compound was synthesized in the same manner as Example I, except that behenoyl chloride was used as the fatty acid derivative in the step G.

5 $[\alpha]^{23}_D +46.3^\circ$ (c 0.51, $\text{CHCl}_3:\text{MeOH}:\text{H}_2\text{O}=30:15:2$), LRMS m/z 623 $(\text{M}-\text{Na})^-$, HRMS calcd for $\text{C}_{21}\text{H}_{59}\text{O}_{10}\text{S}$ $(\text{M}-\text{Na})^-$ 623.3834, found 623.3835.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) ; δ 5.38-5.37 (m, 1H, 4'-OH), 4.78-4.77 (m, 1H, 3'-OH), 4.63 (d, 1H, $J=6.52$ Hz, 2'-OH), 10 4.56 (d, 1H, $J=3.72$ Hz, H1'), 4.14-4.07 (m, 2H, H1a & H1b), 3.86-3.78 (m, 2H, H3a & H5'), 3.43-3.32 (m, 2H, H3b & H3'), 3.22-3.17 (m, 1H, H2'), 2.98-2.90 (m, 2H, H4' & H6'a), 2.60 (dd, 1H, $J=14.0, 6.7$ Hz, H6'b), 2.28 (t, 2H, $J=7.22$ Hz, COCH_2), 1.86-1.79 (m, 2H, H2a & H2b), 1.52-1.49 (m, 2H, 15 COCH_2CH_2), 1.23 (br, 36H, $-\text{CH}_2-$), 0.85 (t, 3H, $J=6.1$ Hz, Me).

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$); δ 173.4 (C=O), 98.5 (C1'), 74.7 (C4'), 73.4 (C3'), 72.2 (C2'), 68.6 (C5'), 63.6 (C3), 61.8 (C1), 55.0 (C6'), 33.9 (COCH_2), 31.7 ($-\text{CH}_2-$), 29.4-28.8 (m, 20 C2 & $-\text{CH}_2-$), 24.9 (COCH_2CH_2), 22.5 ($-\text{CH}_2-$), 14.3 (Me).

Example II-4

3-O-(6-sulfo- α -D-quinovopyranosyl)-1-O-hexanoyl-propane-1,3-diol calcium salt (10)

A sodium salt was synthesized in the same manner as Example I, except that hexanoyl chloride was used as the fatty acid derivative in the step G.

LRMS m/z 399 $(M-Na)^+$

5 1H NMR (400 MHz, DMSO- d_6) ; δ 5.34 (br, 1H, 4'-OH),
4.56 (d, 1H, $J=4.0$ Hz, H1'), 4.53 (br, 1H, 3'-OH), 4.41
(d, 1H, $J=6.4$ Hz, 2'-OH), 4.10 (t, 2H, $J=6.6$ Hz,
H1a & H1b), 3.83-3.77 (m, 2H, H3a & H5'), 3.41-3.33 (m,
2H, H3b & H3'), 3.21-3.16 (m, 1H, H2'), 2.98-2.92 (m,
10 2H, H4' & H6'a), 2.63 (dd, 1H, $J=14.0, 6.0$ Hz, H6'b),
2.27 (t, 2H, $J=7.2$ Hz, COCH₂), 1.82 (tt, $J=6.4, 6.4$ Hz,
2H, H2a & H2b), 1.52 (tt, $J=7.2, 6.8$ Hz, 2H, COCH₂CH₂),
1.30-1.26 (m, 4H, -CH₂-), 0.85 (t, 3H, $J=6.6$ Hz, Me).
 ^{13}C NMR (100 MHz, DMSO- d_6); δ 173.0 (C=O), 98.3 (C1'),
15 74.7 (C4'), 73.2 (C3'), 71.9 (C2'), 68.3 (C5'), 63.5
(C3), 61.3 (C1), 55.2 (C6'), 33.5 (COCH₂), 30.7
(-CH₂-), 28.6 (C2), 24.1 (COCH₂CH₂), 21.7 (-CH₂-), 13.7
(Me).

20 The sodium salt was further subjected to ion
exchange treatment to obtain the title compound.

Example II-5

3-O-(6-sulfo- α -D-quinovopyranosyl)-1-O-acetyl-
propane-1,3-diol calcium salt

25 A sodium salt was synthesized in the same manner
as Example I, except that acetyl chloride was used as
the fatty acid derivative in the step G.

LRMS m/z 343 (M-Na)⁻

¹H NMR (400 MHz, DMSO-d₆) ; δ 5.47-5.46 (m, 1H, 4'-OH),
 4.57 (d, 1H, J=3.6 Hz, H1'), 4.50-4.49 (br, 1H, 3'-
 OH), 4.39-4.38 (br, 1H, 2'-OH), 4.10 (t, 2H, J=6.8 Hz,
 5 H1), 3.83-3.76 (m, 2H, H3a & H5'), 3.42-3.34 (m, 2H,
 H3b & H3'), 3.20-3.16 (m, 1H, H2'), 2.98 (ddd, 1H,
 J=9.0, 9.0, 3.2 Hz, H4'), 2.88 (dd, 1H, J=13.6,
 5.6 Hz, H6'a), 2.62 (dd, 1H, J=14.0, 5.6 Hz, H6'b),
 2.00 (s, 3H, Me), 1.835 (tt, 1H, J=6.4, 6.4 Hz, H2).
 10 ¹³C NMR (100 MHz, DMSO-d₆); δ 170.4 (C=O), 98.3 (C1'),
 74.6 (C4'), 73.2 (C3'), 71.9 (C2'), 68.3 (C5'), 63.5
 (C3), 61.5 (C1), 55.0 (C6'), 28.5 (C2), 20.7 (Me).

The sodium salt was further subjected to ion
 exchange treatment to obtain the title compound.

15 Example II-6

3-O-(6-sulfo-α-D-quinovopyranosyl)-1-O-formyloxy-
 propane-1,3-diol sodium salt (10)

The title compound was obtained through the steps
 A-1 to F of Example I, followed by the following steps
 20 J to L.

Step J; 3-O-(2,3,4-tri-O-benzyl-6-sulfo-α-D-
 quinovopyranosyl)-propane-1,3-diol sodium salt (8'')

To a solution of the compound (7) (542 mg,
 956 μmol) in acetic acid (5.5 g), added were Oxon
 25 (1.8 g) and potassium acetate (68 mg), and the mixture
 was vigorously stirred at room temperature for
 48 hours. After the sufficient progress of the

reaction was confirmed, the reaction liquid was poured to a chilled 7.5 M sodium hydroxide (13 ml) solution, and extracted with ethyl acetate (3 × 10 ml). The organic layers were combined, washed with saturated sodium hydrogen carbonate solution (2 × 10 ml) and saturated saline (2 × 10 ml), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The concentrated residue was purified with silica gel chromatography (chloroform-methanol, 10:1 → 8:1 → 6:1 → 4:1 → 2:1 → 1:1) to obtain the title compound 8" in the form of a colorless waxy substance [401 mg (675 μmol), 70.7%].

LRMS m/z 571 (M-Na)⁻

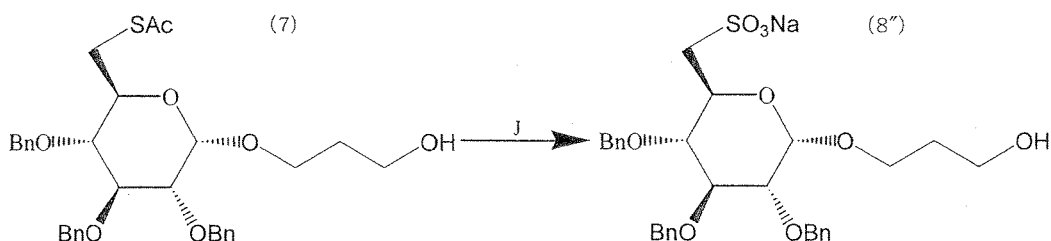
¹H NMR (400 MHz, CD₃OD+CDCl₃) ; δ 7.37-7.26 (m, 15H, ArH), 4.96(d, 1H, J=11.2 Hz, ArCH₂), 4.89(d, 1H, J=11.2 Hz, ArCH₂), 4.80(d, 1H, J=3.6 Hz, H1'), 4.78(d, 1H, J=10.4 Hz, ArCH₂), 4.75(d, 1H, J=11.6 Hz, ArCH₂), 4.66(d, 1H, J=11.6 Hz, ArCH₂), 4.62(d, 1H, J=11.2 Hz, ArCH₂), 4.24-4.19 (m, 1H, 5'), 4.09 (ddd, 1H, J=9.6, 8.4, 5.2 Hz, H1a), 3.97 (dd, 1H, J=9.2, 9.2 Hz, H3'), 3.80 (ddd, 1H, J=11.3, 8.0, 4.0 Hz, H3a), 3.68-3.62 (m, 1H, H3b), 3.56 (dd, 1H, J=9.6, 3.6 Hz, H2'), 3.46 (ddd, 1H, J=9.8, 5.4, 5.4 Hz, H1b), 3.32-3.23 (m, 2H, H6'a & H4'), 2.93 (dd, 1H, J=14.0, 9.8 Hz, H6'b), 1.98-1.81 (m, 2H, H2a & H2b).

¹³C NMR (100 MHz, CD₃OD+CDCl₃); δ 139.0 (Ar-ipso), 138.5 (Ar-ipso), 138.4 (Ar-ipso), 128.9-128.1 (m, Ar),

96.8 (C1'), 82.4 (C3'), 81.0 (C4'), 80.6 (C2'), 76.1 (ArCH₂), 75.5 (ArCH₂), 73.6 (ArCH₂), 67.9 (C5'), 65.5 (C1), 59.6 (C3), 52.8 (C6'), 32.6 (C2).

[Formula 2]

5

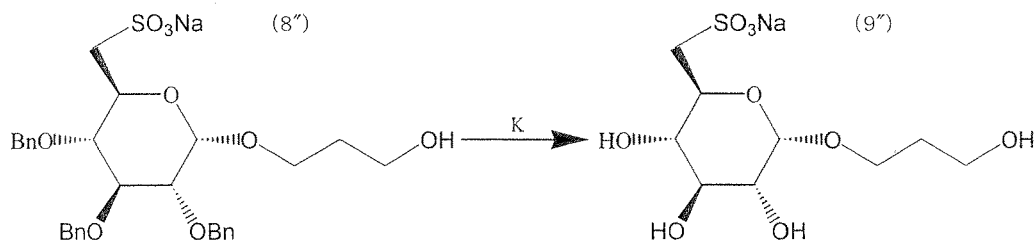


Step K; 3-O-(6-sulfo- α -D-quinovopyranosyl)-propane-1,3-diol sodium salt (9'')

To a solution of the compound (8'') (534 mg, 898 μ mol) in methanol (20 ml) and chloroform (5.0 ml), added was 10% palladium activated carbon (135 mg), and the mixture was stirred at room temperature for 16 hours in a hydrogen gas atmosphere. After the sufficient progress of the reaction was confirmed, palladium activated carbon was collected by filtration, and the filtrate was concentrated under reduced pressure. To the obtained residue, added were methanol (20 ml) and toluene (20 ml), the mixture was vigorously stirred, and the solvent was removed by evaporation under reduced pressure to obtain a mixture in the form of a colorless liquid (320 mg). The presence of the title compound in the mixture was confirmed by LRMS. The mixture containing the title compound (9'') was then subjected to the subsequent reaction.

LRMS m/z 301 (M-Na)

[Formula 3]



5 Step L; 3-O-(6-sulfo- α -D-quinovopyranosyl)-1-O-formyloxy-propane-1,3-diol sodium salt (10)

A mixture containing the compound (9'') (70 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI·HCl) (93 mg, 487 μmol), and 4-
 10 dimethylaminopyridine (12 mg, 97 μmol) were dissolved in anhydrous N,N-dimethylformamide (DMF, 10 ml), formic acid (14 mg, 259 μmol) was added dropwise to the solution under cooling with ice, and allowed to react at room temperature for 18 hours. After the sufficient
 15 progress of the reaction was confirmed, water (1.0 ml) was poured to the reaction liquid to stop the reaction, and then the solution was concentrated under reduced pressure. The obtained residue was purified with silica gel chromatography (chloroform-methanol-water,
 20 3:1:0.1 $\rightarrow$ 2:1:0.1 $\rightarrow$ 1:1:0.1) to obtain the title compound 10 in the form of a colorless oily substance [12 mg (33 μmol), 16.7%].

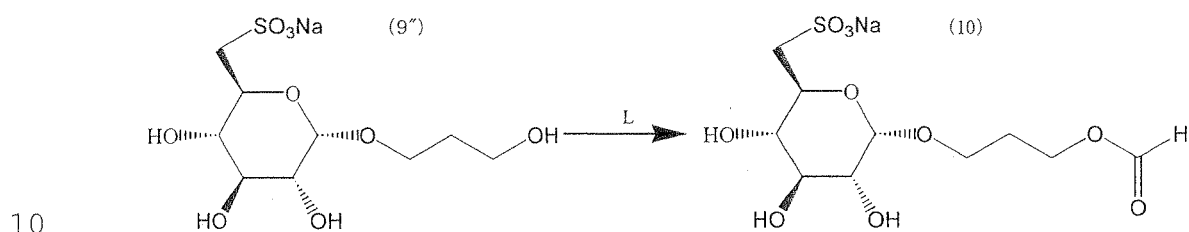
LRMS m/z 329 (M-Na)⁻

¹H NMR (400 MHz, DMSO-d₆) ; δ 8.18 (s, 1H, O=CH), 4.56
 25 (d, 1H, J=3.6Hz, H1'), 4.20 (t, 2H, J=6.8 Hz,

H1a & H1b), 3.86-3.78 (m, 2H, H3a & H5'), 3.41-3.31 (m, 2H, H3b & H3'), 3.18 (dd, 1H, J=9.6, 4.0 Hz, H2'), 3.03-2.90 (m, 2H, H4' & H6'a), 2.63-2.58 (m, 1H, H6'b), 1.86 (tt, J=6.4, 6.4 Hz, 2H, H2a & H2b)

¹³C NMR (100 MHz, DMSO-d₆); δ 162.2 (C=O), 98.4 (C1'), 74.7 (C4'), 73.2 (C3'), 71.9 (C2'), 68.4 (C5'), 63.3 (C3), 61.2 (C1), 55.1 (C6'), 26.1 (C2).

[Formula 4]



[Example III]

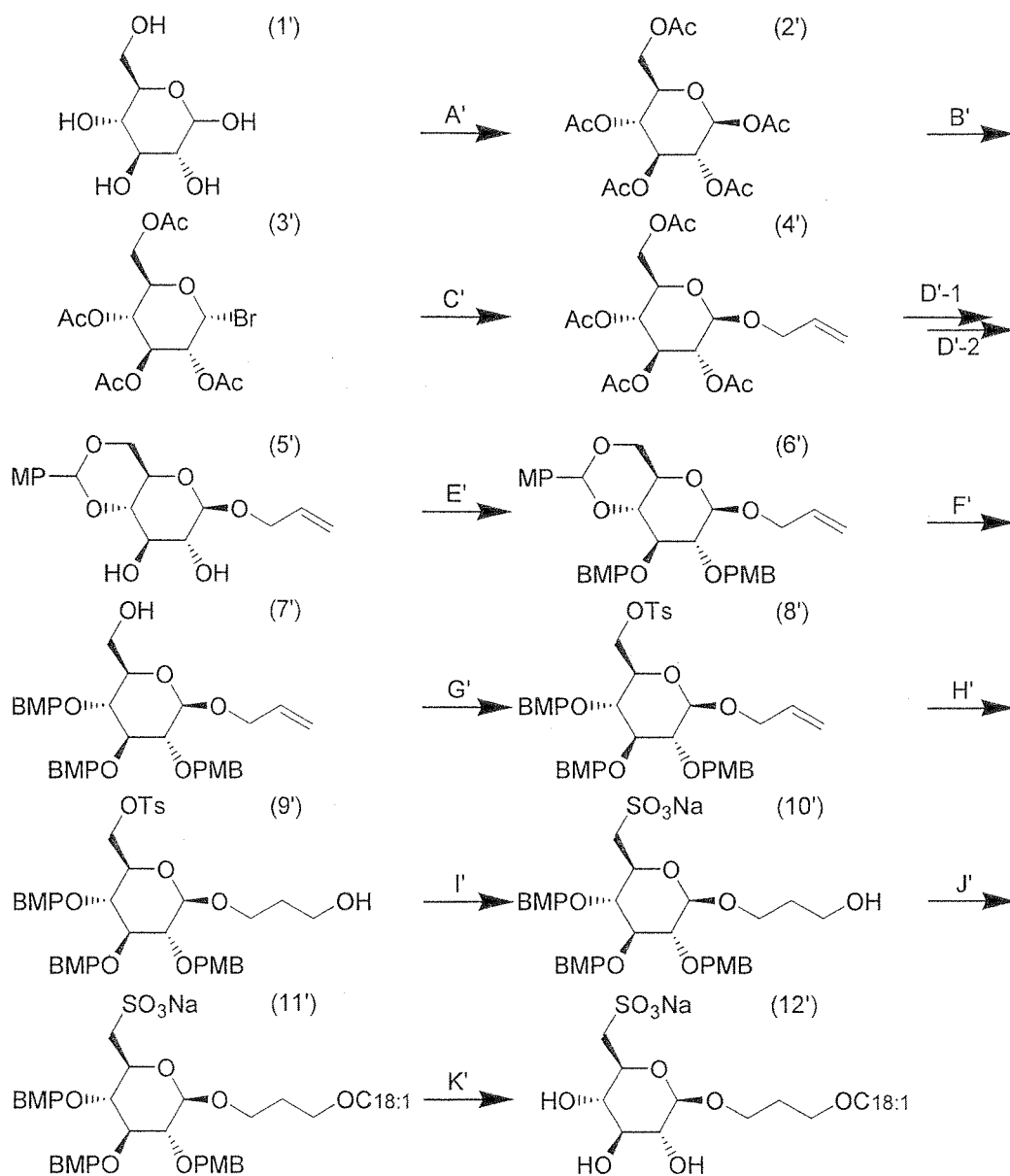
Another example of the process for preparing the β-sulfoquinovosylacyl propane-1,3-diol compound according to the present invention is described below.

15 Example III-1

3-O-(6-sulfo-β-D-quinovopyranosyl)-1-O-oleoyl-propane-1,3-diol sodium salt

The title compound was synthesized through the procedure according to the following scheme.

[Chemical Formula 16]



A') acetic anhydride, sodium acetate, heating and
 5 boiling, 55.3%;

B') hydrobromic acid-acetic acid solution,
 dichloromethane, room temperature, 6 hours, 58.5%;

C') allyl alcohol, cyanide mercury,
 dichloromethane, room temperature, 16 hours, 64.4%;

10 D') D'-1. sodium methoxide, methanol, room

temperature, 4 hours;

D'-2. p-anisaldehyde dimethyl acetal, p-toluenesulfonic acid monohydrate, acetonitrile, 40°C, 16 hours, 95.3%;

5 E') p-methoxybenzyl chloride, sodium hydroxide, N,N-dimethylformamide, room temperature, 16 hours, 92.0%;

F') aluminum lithium hydride, aluminum chloride, dichloromethane, diethyl ether, 0°C, 1 hour, 73.3%;

10 G') p-toluenesulfonyl chloride, 4-dimethylaminopyridine, pyridine, room temperature, 16 hours, 85.9%;

H') 9-borabicyclononane, tetrahydrofuran, room temperature, 16 hours; water, sodium hydroxide, 15 hydrogen peroxide water, room temperature, 4 hours, 93.5%;

I') sodium sulfite, ethanol, water, heating under reflux, 72 hours, 90.2%;

20 J') oleic acid anhydride, 4-dimethylaminopyridine, pyridine, dichloromethane, heating under reflux, 16 hours, 67.6%; and

K') 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, dichloromethane, methanol, water, room temperature, 4 hours, 55.9%.

25 $[\alpha]_D^{21} -3.1^\circ$ (c1.00 CH₃OH), LRMS m/z 565 (M-Na)⁻, HRMS calcd for C₂₇H₄₉O₁₀S (M-Na)⁻ 565.3051, found 565.3059. ¹H NMR (400 MHz, CD₃OD); δ 5.37-5.30 (m, 2H, -CH=CH-),

4.27 (d, 1H, $J=7.84$ Hz, H1'), 4.23-4.13 (m, 2H, H1a & H1b), 4.01-3.96 (m, 1H, H3a), 3.72 (ddd, 1H, $J=9.64, 8.62, 2.20$ Hz, H5'), 3.68-3.62 (m, 1H, H3b), 3.38 (dd, 1H, $J=14.4, 2.20$ Hz, H6'a), 3.36 (t, 1H, $J=9.08$ Hz, H3'), 3.19 (dd, 1H, $J=9.20, 7.88$ Hz, H2'), 3.13 (t, 1H, $J=9.28$ Hz, H4'), 2.98 (dd, 1H, $J=14.4, 8.62$ Hz, H6'b), 2.31 (t, 2H, $J=7.46$ Hz, COCH₂), 2.04-2.00 (m, 4H, -CH₂CH=CHCH₂-), 1.97-1.90 (m, 2H, H2a & H2b), 1.62-1.56 (m, 2H, COCH₂CH₂), 1.31-1.29 (br, 20H, -CH₂-), 0.89 (t, 3H, $J=6.84$ Hz, Me).

¹³C NMR (100 MHz, CD₃OD); δ 175.7 (C=O), 130.9 (-CH=CH-), 130.8 (-CH=CH-), 104.2 (C1'), 77.9 (C3'), 75.1 (C2'), 74.7 (C4'), 73.7 (C5'), 67.3 (C3), 62.8 (C1), 54.3 (C6'), 35.1 (COCH₂), 33.1 (-CH₂-), 30.8-30.1 (m, C2 & -CH₂-), 28.1 (-CH₂CH=CHCH₂-), 26.1 (COCH₂CH₂), 23.8 (-CH₂-), 14.5 (Me).

Example III-2

3-O-(6-sulfo- β -D-quinovopyranosyl)-1-O-stearoyl-propene-1,3-diol sodium salt

The title compound was synthesized in the same manner as Example III-1, except that stearoyl chloride was used in place of oleic acid anhydride.

$[\alpha]^{22}_D -4.7^\circ$ (c1.00 H₂O), LRMS m/z 567 (M-Na)⁻, HRMS calcd for C₂₇H₅₁O₁₀S (M-Na)⁻ 567.3208, found 567.3211.

¹H NMR (400 MHz, DMSO-d₆); δ 5.56 (d, 1H, $J=3.16$ Hz, 4'-OH), 4.81 (d, 1H, $J=4.92$ Hz, 2'-OH), 4.74 (d, 1H, $J=4.64$ Hz, 3'-OH), 4.09 (d, 1H, $J=7.76$ Hz, H1'), 4.07

(t, 2H, J=6.60 Hz, H1a & H1b), 3.77 (dt, 1H, J=10.2, 6.27 Hz, H3a), 3.54-3.45 (m, 2H, H3b & H5'), 3.13 (dt, 1H, J=8.80, 4.68 Hz, H3'), 2.99 (dt, 1H, J=9.14, 3.08 Hz, H4'), 2.97-2.91 (m, 2H, H2' & H6'a), 2.68 (dd, 1H, J=13.9, 5.24 Hz, H6'b), 2.27 (t, 2H, J=7.40 Hz, COCH₂), 1.86-1.78 (m, 2H, H2a & H2b), 1.54-1.47 (m, 2H, COCH₂CH₂), 1.24 (br, 28H, -CH₂-), 0.86 (t, 3H, J=6.88 Hz, Me).

¹³C NMR (100 MHz, DMSO-d₆); δ 172.9 (C=O), 102.8 (C1'), 76.1 (C3'), 74.6 (C4'), 73.4 (C2'), 72.5 (C5'), 65.2 (C3), 61.2 (C1), 55.6 (C6'), 33.6 (COCH₂), 31.3 (C2), 29.0-28.5 (m, -CH₂-), 24.5 (COCH₂CH₂), 22.1 (-CH₂-), 13.9 (Me).

<Analysis>

[Example IV]

Example IV-1. Analysis with high performance liquid chromatography and mass spectrometry

The 3-O-(6-sulfo- α -D-quinovopyranosyl)-1-O-stearoyl-propane-1,3-diol sodium salt and 3-O-(6-sulfo- α -D-quinovopyranosyl)-1-O-stearoyl-glycerol sodium salt were separated and detected by high performance liquid chromatography and electrospray mass spectrometry.

The test substance was dissolved in 5% acetonitrile in 5 mmol/l ammonium acetate aqueous solution, diluted with the solvent to an intended concentration, and then analyzed by high performance liquid chromatography equipped with CapCellPak C18MG

(column size; 2.0 × 50 mm, manufactured by Shiseido Co., Ltd.). The separation conditions were as follows: the column temperature was 40°C, the flow rate was 0.2 ml per minute, and elution was conducted over a period of 20 minutes with a linear concentration gradient of 50% to 70% of acetonitrile with reference to the above-described solvent.

The eluted test substance was detected with a Bruker Esquire 3000 plus ion mass spectrometer, and the detection ion mode was total ion chromatography (TIC), and the detection mass range was $m/z = 100$ to 1000.

Figures 1 and 2 show the chromatograms of the test substance.

The analysis result indicates that, as shown in Figure 1, the 3-O-(6-sulfo- α -D-quinovopyranosyl)-1-O-stearoyl-propane-1,3-diol sodium salt exhibited a single peak, while the 3-O-(6-sulfo- α -D-quinovopyranosyl)-1-O-stearoyl-glycerol sodium salt shown in Figure 2 exhibited minor peaks representing a structural isomer at 6.8 min (peak No. 1) and 7.3 minutes (peak No. 2), which suggests acyl transfer from the 1-position to 2-position in the glycerol moiety, and major peaks representing a diastereomer α SQMG C18:0 at 7.6 minutes (peak No. 3) and 7.8 minutes (peak No. 4).

These results indicate that the 3-O-(6-sulfo- α -D-quinovopyranosyl)-1-O-stearoyl-propane-1,3-diol sodium

salt according to an aspect of the present invention has very high purity in comparison with a known compound, 3-O-(6-sulfo- α -D-quinovopyranosyl)-1-O-stearoyl-glycerol sodium salt.

5 Example IV-2. Solubility measurement

1 g each of the sodium salt and calcium salt of 3-O-(6-sulfo- α -D-quinovopyranosyl)-1-O-stearoyl-propane-1,3-diol was placed in 5 ml of distilled water for injection (manufactured by Otsuka Pharmaceutical Co., Ltd.), strongly shaken at 25°C; they were immediately dissolved. This fact suggests that the substance is evaluated as "readily soluble" by the criteria described in the general rules Japanese Pharmacopeia.

These results indicate that α SQAP has very high solubility. In addition, although not shown herein, SQAP series according to the present invention other than the salts of 3-O-(6-sulfo- α -D-quinovopyranosyl)-1-O-stearoyl-propane-1,3-diol also have high solubility. Such high solubility facilitates dissolution of a necessary amount of the substance in a small amount of a solvent. As a result of this, for example, an injection to be administered to a subject can be readily prepared. In addition, such high water solubility is advantageous in preparation of injections, as well as other various formulations such as oral agents.

<Pharmacological test>

The pharmacological activity of the sulfoquinovosylacetyl propanediol compound according to the present invention was examined.

5 [Example V]

Radiosensitizing effect test

The radiosensitizing effect was examined through tumor-bearing mouse experiment.

10 Examples V-1. Human esophageal squamous cell carcinoma (No. 1)

Human esophageal squamous cell carcinoma cells TE-8 were transplanted into the right femoral region of KSN nude mice in a ratio of 1×10^6 cells per individual. Subsequently, the mice were bred for about 14 days to form a tumor mass of about 150 mm^3 in each individual. Thereafter, four mice were assigned to each of the following groups (1) to (4):

- (1) non-administered, unirradiated group (in Figure 3, indicated with white squares);
- 20 (2) non-administered, radiotherapy treated group (in Figure 3, indicated with white triangles);
- (3) α SQAP C18:0-administered, unirradiated group (in Figure 3, indicated with black circles); and
- (4) α SQAP C18:0-administered, radiotherapy-treated group (in Figure 3, indicated with black rhombuses).
- 25

The drug was administered from Day 1 to Day 5, 2 mg/kg once a day. The subjects were exposed to

radiation emitted from an X-ray generator (HS-225, manufactured by Shimadzu Co., Ltd.) at a dose of 2 Gy on Day 1 and Day 4. The tumor volume was calculated according to the calculation formula: (minor axis)² × major axis ×

5 0.5. The results are shown in Figure 3.

In all the groups, the tumor volume steadily increased from the start to end of the test. However, from about Day 10, the increment of the tumor volume in the groups (2) to (4) fell below that in the (1) non-administered, un-
10 irradiated group. In addition, suppression of the increase of the tumor volume in the (2) non-administered, radiotherapy-treated group and (3) αSQAP C18:0-administered, un-irradiated group was at the same level. The increase of the tumor volume was most suppressed in the
15 (4) αSQMG C18:0-administered, radiotherapy-treated group in comparison with other groups.

Example V-2. Human esophageal squamous cell carcinoma (No. 2)

Experiment was conducted in the same manner as Example
20 V-1, except that the drug dose administered from Day 1 to Day 5 was 1 mg/kg once a day, and the radiation dose was 4 Gy, and the tumor volume was measured. The results are shown in Figure 4.

Details about the groups are as follows:

25 (1) non-administered, un-irradiated group (in Figure 4, indicated with black rhombuses);

(2) non-administered, radiotherapy-treated group
(in Figure 4, indicated with black squares);

(3) α SQAP C18:0-administered, un-irradiated group
(in Figure 4, indicated with white rhombuses); and

5 (4) α SQAP C18:0-administered, radiotherapy-treated
group (in Figure 4, indicated with white squares).

The results indicate that, in all the groups, the
tumor volume increased with the lapse of time. The
increment in the tumor volume in the groups (2) to (4)
10 was smaller than that in the (1) non-administered, un-
irradiated group. In addition, the increase of the
tumor volume was most strongly suppressed in the (4)
 α SQAP C18:0-administered, radiotherapy-treated group in
comparison with other groups.

15 Example V-3. Human colonic adenocarcinoma

human colonic adenocarcinoma cells SW480 were
transplanted into the right femoral region of KSN nude
mice in a ratio of 1×10^6 cells per individual.
Subsequently, the mice were bred for about 14 days to
20 form a tumor mass of about 150 mm^3 in each individual.

Thereafter, four mice were assigned to each of the
three groups (1) to (3):

(1) non-administered, un-irradiated group (in
Figure 5, indicated with white rhombuses);

25 (2) non-administered, radiotherapy-treated group
(in Figure 5, indicated with black squares); and

(3) α SQAP C18:0-administered, radiotherapy-treated

group (in Figure 5, indicated with black triangles).

The drug was administered from Day 1 to Day 5, 2 mg/kg once a day. The subjects were exposed to radiation emitted from an X-ray generator (HS-225, manufactured by Shimadzu Co., Ltd.) at a dose of 2 Gy on Day 1 and Day 4. The tumor volume was calculated according to the calculation formula: (minor axis)² × major axis × 0.5. The results are shown in Figure 5.

The results indicate that, in all the groups, the tumor volume increased with the lapse of time. However, the increase of the tumor volume in the (1) non-administered, un-irradiated group and (2) non-administered, radiotherapy-treated group was alike, but the increase of the tumor volume in the (3) αSQAP C18:0-administered, radiotherapy-treated group was suppressed from the initial stage of the experiment, and the increase of the tumor volume was markedly suppressed in general.

The following Examples V-4, 5, 6, and Examples VI to VIII used an SQAP compound which had been calcium salt-substituted through ion exchange treatment.

Example V-4. Human colonic adenocarcinoma

Human colonic adenocarcinoma cells SW480 were transplanted into the right femoral region of KSN nude mice in a ratio of 2×10^6 cells per individual. After a tumor mass of about 50 mm³ was formed in each

individual, four mice were assigned to each of the four groups (1) to (4):

(1) non-administered, un-irradiated group (in Figure 6, indicated with black circles);

5 (2) non-administered, radiotherapy-treated group (in Figure 6, indicated with black squares);

(3) α SQAP C18:0-administered, un-irradiated group (in Figure 6, indicated with white triangles); and

10 (4) α SQAP C18:0-administered, radiotherapy-treated group (in Figure 6, indicated with white squares).

The drug was administered from the tail vein from Day 1 to Day 5, 1 mg/kg once a day. The subjects were exposed to radiation emitted from an X-ray generator (HS-225, manufactured by Shimadzu Co., Ltd.) at a dose
15 of 2 Gy on Day 1 and Day 4.

The results are shown in Figure 6, indicating that the tumor volume increased with time in all the groups. However, the increase of the tumor volume was most suppressed in the (4) α SQAP C18:0-administered,
20 radiotherapy-treated group in comparison with other groups.

Example V-5. Human esophageal squamous cell carcinoma

Human esophageal squamous cell carcinoma cells TE-
25 8 were transplanted into the right femoral region of KSN nude mice in a ratio of 1×10^6 cells per individual. After a tumor mass of about 50 mm^3 was

formed in each individual, four mice were assigned to each of the four groups (1) to (4):

(1) non-administered, un-irradiated group (in Figure 7, indicated with black rhombuses);

5 (2) non-administered, radiotherapy-treated group (in Figure 7, indicated with black circles);

(3) α SQAP C10:0-administered, un-irradiated group (in Figure 7, indicated with white triangles); and

(4) α SQAP C10:0-administered, radiotherapy-treated group (in Figure 7, indicated with white squares).

10 The drug was administered intraperitoneally from Day 1 to Day 5, 1 mg/kg once a day. The subjects were exposed to radiation emitted from an X-ray generator (HS-225, manufactured by Shimadzu Co., Ltd.) at a dose
15 of 4 Gy on Day 1 and Day 4.

The results are shown in Figure 7, indicating that the tumor volume increased with time in all the groups. However, the increase of the tumor volume was most suppressed in the (4) α SQAP C10:0-administered,
20 radiotherapy-treated group in comparison with other groups.

Example V-6. Human esophageal squamous cell carcinoma

Human esophageal squamous cell carcinoma cells TE-
25 8 were transplanted into the right femoral region of KSN nude mice in a ratio of 1×10^6 cells per individual. After a tumor mass of about 50 mm^3 was

formed in each individual, four mice were assigned to each of the four groups (1) to (4):

(1) non-administered, un-irradiated group (in Figure 8, indicated with black rhombuses);

5 (2) non-administered, radiotherapy-treated group (in Figure 8, indicated with black squares);

(3) α SQAP C18:0-administered, unirradiated group (in Figure 8, indicated with white squares); and

(4) α SQAP C18:0-administered, radiotherapy-treated group (in Figure 8, indicated with white circles).

The drug was administered intraperitoneally from Day 1 to Day 5, 1 mg/kg once a day. The subjects were exposed to radiation emitted from an X-ray generator (HS-225, manufactured by Shimadzu Co., Ltd.) at a dose of 4 Gy on Day 1 and Day 4.

The results are shown in Figure 8, indicating that the tumor volume increased with time in all the groups. However, the increase of the tumor volume was most suppressed in the (4) α SQAP C18:0-administered, radiotherapy-treated group in comparison with other groups.

[Example VI]

Antineoplastic effect test

Human colonic adenocarcinoma cells SW480 were transplanted into the right femoral region of KSN nude mice in a ratio of 2×10^6 cells per individual. After a tumor mass of about 50 mm³ was formed in each

individual, four mice were assigned to each of the two groups (1) and (2):

(1) non-administered (in Figure 9, indicated with white squares); and

5 (2) α SQAP C18:0-administered (in Figure 9, indicated with black squares).

The drug was administered intraperitoneally from Day 1 to Day 14, 20 mg/kg once a day.

The results are shown in Figure 9, indicating that
10 the increase of the tumor volume was markedly suppressed in the α SQAP C18:0-administered group in comparison with the non-administered group.

[Example VII]

Tube formation inhibition test using vascular
15 endothelial cell-fibrocyte cocultivation system

Using an angiogenesis kit (KZ-1000) manufactured by Kurabo Industries Ltd., which is a cocultivation system for human vascular endothelial cells and human fibrocytes, the effects of α SQAP C10:0, α SQAP C14:0,
20 α SQAP C18:0, α SQAP C22:0, β SQAP C18:0, and β SQAP C18:1 on tube formation were examined. Cultivation for tube formation using the kit was conducted according to the manufacturer's instruction manual.

Using a medium containing a final concentration of
25 10 ng/ml of VEGF-A and being designed specifically for angiogenesis, the respective SQAP compounds were prepared to have intended concentrations. On Day 1 of

the cell cultivation, special media each containing SQAP compounds at the respective concentrations and DMSO (negative control) were added to the cultivation systems. The systems were cultivated for 30 minutes, and irradiated with 2 Gy of cobalt 60. Thereafter, on Day 4, 7, and 10 of the cultivation, the media were replaced with newly prepared special media containing SQAP or DMSO. The media were removed on Day 11 of the cultivation, fixed with 70% ethanol, and the formed tubes were stained with anti-human CD31 antibody. The stained figures were photographed under an optical microscope, and the quantity of tube formation was calculated by the image analysis. The angiogenesis index was calculated according to the manufacturer's instruction manual.

The results are shown in Figure 10. In comparison with the control group not treated with the SQAP compound and/or radiation therapy, the groups subjected to radiation alone (2 Gy) and/or the SQAP compounds exhibited lower angiogenesis indexes. In Figure 10, "RT" is an abbreviation of radiation therapy. Further, those treated with the SQAP compounds exhibited lower indexes than the group treated with 2 Gy radiation alone. When combined with 2 Gy radiation, α SQAP C10:0 at final concentrations of 5, 10, and 20 μ M, α SQAP C14:0 at final concentrations of 5, 10, and 20 μ M, α SQAP C18:0 at final concentrations of 5, 10, and

20 μM , $\alpha\text{SQAP C22:0}$ at final concentrations of 5, 10,
and 20 μM , and $\beta\text{SQAP C18:0}$ at final concentrations of 5
and 10 μM , and $\beta\text{SQAP C18:1}$ at final concentrations of 5
and 10 μM inhibited tube formation in a concentration-
5 dependent manner.

[Example VIII]

Toxicity test

VIII-1. Ames test

A reverse mutation assay (Ames test) was conducted
10 using $\alpha\text{SQAP C18:0}$.

Five strains composed of two strains of *Salmonella*
typhimurium, which are base pair substitution mutants,
and one strain of *Escherichia coli*, and two strains of
Salmonella typhimurium, which are frameshift mutants
15 were used as indicator bacterial strains. These
strains were precultivated in the presence of αSQAP
 C18:0 , and transferred to agar plates and cultivated
thereon for 48 hours, and then the number of revertant
colonies on the plate was counted. The amounts of
20 $\alpha\text{SQAP C18:0}$ added to the respective plates were 2 μg ,
7 μg , 21 μg , 62 μg , 185 μg , 556 μg , 1667 μg , and
5000 μg . Regardless of the presence or absence of S9
mix added during the precultivation (wherein S9 mix is
a solution prepared by adding cofactor-1 to a
25 supernatant fraction of a liver homogenate prepared
from the liver of a male rat pretreated with
phenobarbital and 5,6-benzoflavone), for all the

strains, the number of revertant colonies did not increase. From the fact, mutagenicity of the substance was evaluated as negative.

VIII-2. Micronucleus test

5 Micronucleus test was conducted by rat intravenous administration using the α SQAP C18:0 calcium salt.

Five male SD rats were assigned to each of the six groups (1) to (6):

- (1) non-administered group;
- 10 (2) 25 mg/kg α SQAP C18:0-administered group;
- (3) 50 mg/kg α SQAP C18:0-administered group;
- (4) 100 mg/kg α SQAP C18:0-administered group;
- (5) 200 mg/kg α SQAP C18:0-administered group; and
- 15 (6) positive control group (2 mg/kg mitomycin C-administered group).

The test solutions for (1) to (5) contained a normal saline solution containing 10% CREMOPHOR EL as the solvents, and the above-described doses were administered to the rats twice in total for two consecutive days. To the positive control group, the above-described dose was administered once.

About 24 hours after the administration, bone marrow smears were prepared. Two thousands of immature erythrocytes were counted for each individual, and the incidence of immature erythrocytes having a micronucleus was calculated. As the index of marrow proliferation suppression, the proportion of immature

erythrocytes contained in 1000 erythrocytes was calculated. The result indicates that no significant increase was found in the incidence of micronuclei in the test substance-administered group in comparison with the non-administered group. In addition, no influence was found on the marrow proliferation suppression in the test substance-administered group. From these facts, the substance was evaluated as inducing no chromosomal aberration in bone marrow cells.

VIII-3. Single dose toxicity test

Using α SQAP C18:0, acute toxicity test was conducted on rats. Five female and five male SD rats of 5 to 6 weeks old were assigned to each of the groups (1) to (7):

- (1) non-administered group;
- (2) 25 mg/kg α SQAP C18:0-administered group;
- (3) 50 mg/kg α SQAP C18:0-administered group;
- (4) 100 mg/kg α SQAP C18:0-administered group;
- (5) 200 mg/kg α SQAP C18:0-administered group;
- (6) 400 mg/kg α SQAP C18:0-administered group; and
- (7) 800 mg/kg α SQAP C18:0-administered group.

The test solution for (1) and (4) to (7) contained a normal saline solution containing 10% CREMOPHOR EL, (2) contained a normal saline solution containing 2.5% CREMOPHOR EL, and (3) contained a normal saline solution containing 5% CREMOPHOR EL as the solvents.

These test solutions were administered via the rat tail vein, and the clinical signs were observed for two days including the date of administration. No individual died during the test period, and the lethal
5 dose was estimated to be higher than 800 mg/kg.

Other benefits and modifications would be readily understood by those skilled in the art. Accordingly, it is evident that the present invention in its broader aspect is not limited to the specific details and
10 representative embodiments shown and described herein. Accordingly, various modifications may be made without departing from the spirit or scope of the general inventive concept as defined by the appended claims and their equivalents.

15 The compound of the present invention is a novel substance, and, as described above, has remarkable radiosensitizing effect and antineoplastic effect. The compound of the present invention is obtainable at high purity by a simple synthesis method. Further, the
20 compound of the present invention is structurally stable, and highly soluble in water. Accordingly, the compound is advantageous in its manufacture and formulation when used as a drug, and is also advantageous in the use after storage as a compound and
25 a drug. In addition, the compound features low toxicity. Accordingly, the compound is very advantageous as a drug to be administered to human and

other animals over a short or long period.

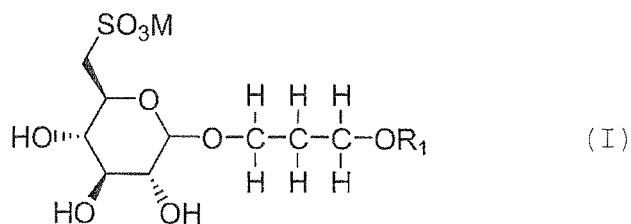
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C L A I M S

1. A sulfoquinovosylacyl propanediol compound represented by the general formula (I):

[Chemical Formula 1]

5



wherein R₁ is an acyl residue of a fatty acid, and M represents a hydrogen ion or a metal ion or pharmaceutically acceptable salts thereof.

10 2. A drug including as an active ingredient at least one selected from the group consisting of the sulfoquinovosylacyl propanediol compound according to claim 1 represented by the general formula (I) and pharmaceutically acceptable salts thereof.

15 3. The drug according to claim 2, which is a radiosensitizer.

4. The drug according to claim 2, which is an antineoplastic agent.