

【DESCRIPTION】

【Invention Title】

NOVEL USE OF 3-(4-(BENZYLOXY)PHENYL)HEX-4-INOIC ACID DERIVATIVE

5 【Technical Field】

The present invention relates to a novel use of a 3-(4-(benzyloxy)phenyl)hex-4-inoic acid derivative. Specifically, the present invention relates to a use of a 3-(4-(benzyloxy)phenyl)hex-4-inoic acid derivative for treating pancreatic beta cells and for treating type II diabetes in a patient of which the blood glucose is not regulated in a normal manner by using an agent for promoting insulin secretion.

10 【Background Art】

Sulfonylurea, which is used for type II diabetes, binds to the ATP-sensitive K^+ channel or SUR-1 receptor of a pancreatic beta cell membrane to depolarize the cell membrane, thereby increasing Ca^{2+} influx, and promotes insulin secretion due to the increased cytoplasmic Ca^{2+} .

However, an agent for promoting insulin secretion, such as sulfonylurea shows side effects during long-term administration. Since sulfonylurea secretes insulin regardless of blood glucose concentration, pancreatic beta cells are damaged by hyperexcitation of beta cells, and apoptosis of beta cells is induced through excitotoxic reactions. Ultimately, a decrease in the number of beta cells results in reduced insulin secretion, leading to impaired blood glucose regulation.

Such secondary failure of sulfonylurea-based drugs has become a major clinical challenge in the treatment of diabetes, and therefore there is a need for

development of a new drug capable of glucose-dependent insulin secretion with a low risk of such side effects.

Recently, it has been revealed that free fatty acid receptor 1 (FFAR1)/G-protein coupled receptor (GPR40) can improve blood glucose regulation by glucose-stimulated insulin secretion (GSIS) in pancreatic beta cells. In this regard, the present applicant has conducted studies on activators for GPR40, and revealed that a 3-(4-(benzyloxy)phenyl)hex-4-inoic acid derivative, a pharmaceutically acceptable salt thereof, or an optical isomer thereof increases intracellular calcium concentration through activity on GPR40, and exhibits an excellent hypoglycemic effect (Patent Document 1: 10-2014-0126248 A).

【Disclosure】

【Technical Problem】

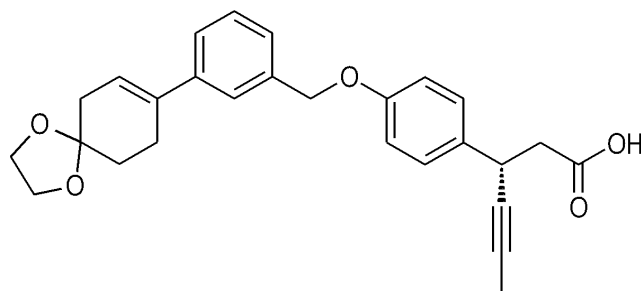
The present invention provides a use of a 3-(4-(benzyloxy)phenyl)hex-4-inoic acid derivative for protecting pancreatic beta cells and for treating type II diabetes in a patient of which the blood glucose is not regulated in a normal manner by using an agent for promoting insulin secretion.

【Technical Solution】

In the process of studies for the clinical trial of the 3-(4-(benzyloxy)phenyl)hex-4-ionic acid derivative, the present inventors found that the material exhibited not only a hypoglycemic effect, but also an excellent pancreatic beta cell protection effect, thereby completing the present invention.

The 3-(4-(benzyloxy)phenyl)hex-4-ionic acid derivative according to the present invention refers to a compound of the following Formula 1, an optical isomer thereof, or a pharmaceutically acceptable salt thereof.

[Formula 1]



The compound name of Formula 1 is (3S)-3-(4-(3-(1,4-dioxaspiro[4,5]des-7-en-8-yl)benzyloxy)phenyl)hex-4-ynoic acid.

5 The compound of Formula 1 of the present invention may be used in the form of a pharmaceutically acceptable salt.

For example, a pharmaceutically acceptable salt may be made using a base. An alkali metal or alkaline earth metal salt is obtained by, for example, dissolving the compound in an excess alkali metal hydroxide or alkaline earth metal hydroxide solution, filtering the non-soluble compound salt, evaporating the filtrate, and drying the resulting product. In this case, preparing a sodium, potassium or calcium salt as
10 the metal salt is pharmaceutically suitable. Further, a salt corresponding to this is obtained by reacting the alkali metal or alkaline earth metal salt with a suitable silver salt (for example, silver nitrate).

15 Furthermore, a pharmaceutically acceptable salt may be prepared using an amino acid with an amino group attached to an organic acid, and as the amino acid salt, it is pharmaceutically suitable to prepare a natural amino acid such as, for example, glycine, alanine, phenylalanine, valine, lysine, and glutamic acid, and most preferably, it is pharmaceutically suitable to prepare L-lysine.

Further, the compound according to the present invention includes not only the compound of Formula 1 and a pharmaceutically acceptable salt thereof, but also a solvate, an optical isomer, a hydrate and the like that can be prepared therefrom.

The present invention provides a use of a compound of Formula 1, an optical
5 isomer thereof, or a pharmaceutically acceptable salt thereof for protecting pancreatic beta cells, and a use of a compound of Formula 1, an optical isomer thereof, or a pharmaceutically acceptable salt thereof for treating type II diabetes in a patient of which the blood glucose is not regulated in a normal manner by using an agent for promoting insulin secretion.

10 Through the following examples, the present inventors confirmed that first, by *in vitro* experiments, the compound of Formula 1 is a drug that has excellent action activity on human GPR40, and is excellent in insulin secretion ability by glucose stimulation (Example 1). In addition, an oral glucose tolerance test (OGTT) and a glucose-stimulated insulin secretion (GSIS) test were performed on
15 Goto-Kakizaki (GK) rats, which are a type II diabetes model having a secondary failure and cell death of pancreatic beta cells (Examples 2 and 3). As a result, it was confirmed that a compound of Formula 1 has an excellent pancreatic beta cell protection effect by confirming that the compound of Formula 1 maintained an excellent ability to regulate blood glucose and ability to regulate insulin secretion
20 even after long-term repeated administration by protecting pancreatic beta cells even in GK rats with the already damaged pancreas, whereas a sulfonylurea-based drug glimepiride, which often causes a secondary failure in the treatment of diabetes, had deteriorated beta cell functions (reduction in insulin secretion ability), and these effects were confirmed again by the immunohistochemical staining results of rat
25 pancreatic tissues (Example 4).

In view of the fact that the GK rat is an animal model in which the pancreas is already damaged, repeated administration of the compound of Formula 1 according to the present invention cannot increase the amount of already damaged pancreatic beta cells, which suggests that pancreatic islets are preserved and the functionality of pancreatic beta cells is enhanced by preventing additional damage to pancreatic islets.

The present inventors evaluated the ability to regulate insulin secretion using TAK-875 as a positive control so as to confirm that the excellent pancreatic beta cell protection effect of the compound of Formula 1 exhibits the same pattern even as in TAK-875 (Patent Document 2: WO2008-001931) known as a GPR40 activator from Takeda Pharmaceutical Company Limited (Example 6). As a result, the compound of Formula 1 had an excellent ability to regulate insulin secretion compared to TAK-875 which is the same GPR40 activator, even though the compound of Formula 1 was administered at a low dose. The abnormality of the ability to regulate insulin secretion is manifested by damaged pancreatic beta cells, this result shows that even the GPR 40 activator causes damage to pancreatic beta cells by repeated administration, that is, a secondary failure, and the ability to protect pancreatic beta cells exhibited by the compound of Formula 1 of the present invention means an unexpectedly advantageous effect exhibited by only the compound of the present invention.

Based on the previous experimental results for GK rats with an already damaged pancreas, the present inventors intended to confirm that the excellent pancreatic beta cell protection effect of the compound of Formula 1 could prevent additional damage to pancreatic beta cells of a patient already administered a therapeutic agent for diabetes such as glimepiride, which causes a secondary failure, and restore the functionality of pancreatic beta cells.

Thus, the effects of protecting pancreatic beta cells after repeated administration of a drug to Wistar diet-induced obesity (DIO) rats were evaluated (Examples 7 and 8), and as a result, it was confirmed that even in a test group in which a test drug was changed to the compound of Formula 1 and additionally and
5 repeatedly administered after 4 weeks of repeated administration of glimepiride, pancreatic beta cells could be protected from additional damage, and furthermore, the ability of pancreatic beta cells to regulate insulin secretion could be restored.

The ability of the compound of Formula 1 to protect pancreatic beta cells prevents damage to pancreatic beta cells, which is a side effect appearing in patients
10 with type II diabetes, who are taking a therapeutic agent for diabetes for a long period of time to stimulate insulin secretion, that is, a secondary failure, and allows pancreatic beta cells to exhibit their functions properly. Therefore, when the compound of Formula 1 is used as a primary therapeutic agent for type II diabetes, it is possible to provide a sustained and excellent hypoglycemic effect and the ability to
15 regulate insulin secretion without any damage to pancreatic beta cells.

Further, when the compound of Formula 1 is administered to a patient with type II diabetes, in which a secondary failure is caused by already taking a therapeutic agent for type II diabetes, the compound of Formula 1 may be usefully used particularly for treatment of type II diabetes in a patient of which the blood
20 glucose is not regulated in a normal manner by using an agent for promoting insulin secretion because the compound of Formula 1 not only prevents additional damage to pancreatic beta cells, but also restores the insulin secretory function of pancreatic beta cells.

Therefore, the present invention provides a pharmaceutical composition for
25 protecting pancreatic beta cells, including a compound of Formula 1, an optical

isomer thereof, or a pharmaceutically acceptable salt thereof as an active ingredient, a use of a compound of Formula 1, an optical isomer thereof, or a pharmaceutically acceptable salt thereof for preparing a pharmaceutical composition for protecting pancreatic beta cells, and a method for protecting pancreatic beta cells, the method
5 including administering a therapeutically effective amount of a compound of Formula 1, an optical isomer thereof, or a pharmaceutically acceptable salt thereof to a subject.

In an exemplary embodiment, the present invention provides a pharmaceutical composition for protecting pancreatic beta cells in a patient with type
10 II diabetes, including a compound of Formula 1, an optical isomer thereof, or a pharmaceutically acceptable salt thereof as an active ingredient. In the present exemplary embodiment, patients with type II diabetes include all patients with or at risk of damage to pancreatic beta cells.

In another exemplary embodiment, the composition for protecting pancreatic
15 beta cells according to the present invention may be administered either alone or in combination with other drugs for treating type II diabetes. That is, the pharmaceutical composition for protecting pancreatic beta cells according to the present invention may be used as a single therapeutic agent, but can also be used when administered in combination with other types of therapeutic agents for type II
20 diabetes. The types of drugs that can be co-administered are not particularly limited, and all drugs used as known therapeutic agents for type II diabetes can be examples thereof. Examples of the known therapeutic agents for type II diabetes include an oral hypoglycemic agent, for example, a biguanide-based drug such as metformin, buformin, phenformin, or derivatives thereof, or an alpha-glucosidase inhibitor such
25 as acarbose and voglibose, a sulfonylurea-based drug and a meglitinide-based drug

which act as an agent for promoting insulin secretion, and the like. The co-administration includes both sequential and simultaneous administration. In exemplary embodiments of the present invention, the ability to protect pancreatic cells is confirmed even in a type II diabetes therapeutic agent administration group in which a secondary failure is already caused, so it is expected that it is possible to prevent damage to pancreatic beta cells caused by therapeutic agents for type II diabetes to be co-administered.

In another exemplary embodiment, the present invention provides a pharmaceutical composition for protecting pancreatic beta cells in a patient with type II diabetes having damaged pancreatic beta cells, the composition containing a compound of Formula 1, an optical isomer thereof, or a pharmaceutically acceptable salt thereof as an active ingredient.

The cause or degree of damage to the pancreatic beta cells of the “patient with type II diabetes having damaged pancreatic beta cells” is not particularly limited. When insulin is specifically lower than the normal level despite high blood glucose, it becomes impossible to regulate blood glucose, which means that the pancreatic beta cells responsible for insulin secretion do not play their role properly, which will be determined as damage to beta cells. Therefore, it may be verified whether beta cells are damaged by confirming the function of pancreatic beta cells using a method of confirming insulin secretion (for example, GSIS, ASIS, and the like), or a method of confirming insulin synthesis (for example, a method of confirming the content of insulin in the pancreas, and the like).

Damage to pancreatic beta cells is accelerated by the progression of type II diabetes, and the use of therapeutic agents for diabetes, which indiscriminately promote insulin secretion regardless of glucose concentration may be a major cause

of damage to pancreatic beta cells. Examples of an agent for promoting insulin secretion, which has an action mechanism of promoting insulin secretion in pancreatic beta cells include a sulfonylurea-based drug and a meglitinide-based drug, and the like. Representative examples of the sulfonylurea-based drug include
5 glimepiride, gliclazide, glibenclamide, glipizide, and the like, and examples of the meglitinide-based drug include nateglinide, repaglinide, and the like.

In an exemplary embodiment of the present invention, a patient with type II diabetes having damaged pancreatic beta cells may be a patient who has been administered an agent for promoting insulin secretion, for example, a sulfonylurea-
10 based drug and/or a meglitinide-based drug.

Further, the present invention provides a pharmaceutical composition for treating type II diabetes in a patient of which the blood glucose is not regulated in a normal manner by using an agent for promoting insulin secretion, which includes a compound of Formula 1, an optical isomer thereof, or a pharmaceutically acceptable
15 salt thereof as an active ingredient, a use of a compound of Formula 1, an optical isomer thereof, or a pharmaceutically acceptable salt thereof for preparing a pharmaceutical composition for treating type II diabetes in a patient of which the blood glucose is not regulated in a normal manner by using an agent for promoting insulin secretion, and a method for treating type II diabetes, the method including
20 administering a therapeutically effective amount of a compound of Formula 1, an optical isomer thereof, or a pharmaceutically acceptable salt thereof to a patient of which the blood glucose is not regulated in a normal manner by using an agent for promoting insulin secretion.

The patient of which the blood glucose is not regulated in a normal manner
25 by using an agent for promoting insulin secretion may be a patient who has been

administered an agent for promoting insulin secretion. As described above, the patient who has been administered an agent for promoting insulin secretion may suffer from pancreatic beta cell damage during long-term administration.

5 In addition, the patient of which the blood glucose is not regulated in a normal manner by using an agent for promoting insulin secretion may also be a patient who has been co-administered an agent for promoting insulin secretion and other hypoglycemic agents.

Clinically, patients with type II diabetes are administered a biguanide-based drug as a primary selective agent and if their blood glucose is not appropriately regulated by the biaguanide-based drug, the patients may be administered an agent for promoting insulin secretion, or co-administered an agent for promoting insulin secretion and a biguanide-based drug in many cases. Whether an agent for promoting insulin secretion is administered alone or an agent for promoting insulin secretion and a biaguanide-based drug are co-administered, patients who have been administered the agent for promoting insulin secretion are highly likely to become patients of which the blood glucose is not regulated in a normal manner due to pancreatic beta cell damage during long-term administration.

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In an exemplary embodiment, the agent for promoting insulin secretion may be a sulfonylurea-based drug and/or a meglitinide-based drug.

20 Further, the hypoglycemic agent which is administered in combination with the agent for promoting insulin secretion may be a biguanide-based drug.

A pharmaceutical composition according to the present invention, including a compound of Formula 1, an optical isomer thereof, or a pharmaceutically acceptable salt thereof may be administered alone or administered in combination with other drugs for treating type II diabetes. That is, the pharmaceutical composition

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according to the present invention may be used as a single therapeutic agent according to the present invention, but can also be used when administered in combination with other types of therapeutic agents for type II diabetes. The types of drugs that can be co-administered are not particularly limited, and all drugs used
5 as known therapeutic agents for type II diabetes can be examples thereof. Examples of the known therapeutic agents for type II diabetes include an oral hypoglycemic agent, for example, a biguanide-based drug such as metformin, buformin, phenformin, or derivatives thereof, or an alpha-glucosidase inhibitor such as acarbose and voglibose, a sulfonylurea-based drug and a meglitinide-based drug
10 which act as an agent for promoting insulin secretion, and the like. The co-administration includes both sequential and simultaneous administration.

In particular, the pharmaceutical composition according to the present invention may be administered in combination with a biguanide-based drug.

For example, in a patient with type II diabetes, who is taking a biguanide-
15 based drug as a first agent and a sulfonylurea-based drug as a second agent, when the second drug needs to be changed due to a reduction in the ability to regulate blood glucose, type II diabetes may be treated in a patient of which the blood glucose is not regulated in a normal manner by using an agent for promoting insulin secretion, by administering the pharmaceutical composition according to the present invention in
20 combination with a biguanide-based drug.

The pharmaceutical composition of the present invention may include a pharmaceutically acceptable carrier in addition to an active ingredient. In this case, the pharmaceutically acceptable carrier is typically used during formulation, and includes lactose, dextrose, sucrose, sorbitol, mannitol, starch, gum acacia, calcium
25 phosphate, alginate, gelatin, calcium silicate, microcrystalline cellulose,

polyvinylpyrrolidinone, cellulose, water, syrup, methylcellulose, methyl hydroxybenzoate, propyl hydroxybenzoate, talc, magnesium stearate, mineral oil, and the like, but is not limited thereto. Furthermore, the pharmaceutically acceptable carrier may further comprise a lubricant, a wetting agent, a sweetening agent, a flavoring agent, an emulsifying agent, a suspending agent, a preservative, and the like in addition to the above ingredients.

The dosage form of the pharmaceutical composition and the pharmaceutically acceptable carrier may be appropriately selected according to techniques known in the art, and for example, the following documents may be referenced: [Urquhart et al., Lancet, 16:367, 1980]; [Lieberman et al., PHARMACEUTICAL DOSAGE FORMS-DISPERSE SYSTEMS, 2nd ed., vol. 3, 1998]; [Ansel et al., PHARMACEUTICAL DOSAGE FORMS & DRUG DELIVERY SYSTEMS, 7th ed., 2000]; [Martindale, THE EXTRA PHARMACOPEIA, 31st ed.]; [Remington's PHARMACEUTICAL SCIENCES, 16th-20th editions]; [THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, Goodman and Gilman, eds., 9th ed., 1996]; [Wilson and Gisvolds' TEXTBOOK OF ORGANIC MEDICINAL AND PHARMACEUTICAL CHEMISTRY, Delgado and Remers, eds., 10th ed., 1998]. Further, for example, the following documents [Platt, Clin Lab Med, 7:289-99, 1987]; [Aulton, PHARMACEUTICS: THE SCIENCE OF DOSAGE FORM DESIGN, Churchill Livingstone, NY, 1988]; [EXTEMPORANEOUS ORAL LIQUID DOSAGE PREPARATIONS, CSHP, 1998], ["Drug Dosage," J Kans Med Soc, 70(1):30-32, 1969] and the like may be referenced for the principle of formulating the pharmaceutical composition.

The pharmaceutical composition of the present invention may be orally administered or may be parenterally administered (for example, applied

intravenously, subcutaneously, intraperitoneally, or locally) according to the target method, and the administration dose may vary depending on a patient's condition and body weight, severity of disease, drug form, and administration route and period, but the administration dose may be appropriately selected by the person skilled in the art.

5 An effective amount of the active ingredient of the pharmaceutical composition according to the present invention generally refers to an amount required to treat a disease. In the present invention, since the use of the compound of Formula 1 is for protection of pancreatic beta cells or the treatment of type II diabetes in a patient of which the blood glucose is not regulated in a normal manner
10 by using an agent for promoting insulin secretion, as used herein, an effective amount of the active ingredient of the pharmaceutical composition of the present invention refers to an amount required to protect pancreatic beta cells, or an amount required to regulate blood glucose to a normal range in a patient of which the blood glucose is not regulated in a normal manner by using an agent for promoting insulin
15 secretion. An effective dose level may be determined according to factors including types of diseases of patients, the severity of disease, the activity of drugs, sensitivity to drugs, administration time, administration route, excretion rate, treatment period, and simultaneously used drugs, and other factors well known in the medical field. The pharmaceutical composition according to the present invention may be
20 administered as an individual therapeutic agent or in combination with other therapeutic agents, may be administered sequentially or simultaneously with therapeutic agents in the related art, and may be administered in a single dose or multiple doses. It is important to administer the composition in a minimum amount that can obtain the maximum effect without any side effects, in consideration of all

the aforementioned factors, and this amount may be easily determined by the person skilled in the art.

Specifically, the effective amount of the pharmaceutical composition of the present invention may vary depending on the age, gender, condition, and body weight of the patient, absorption of the active ingredient in the body, inactivation rate, excretion rate, type of disease, and drug used in combination, and although the amount is not generally limited to the following numerical range, the compound of Formula 1 may be administered in an amount of 0.001 mg to 200 mg, preferably 0.01 mg to 100 mg, and more preferably 0.2 mg to 50 mg per 1 kg of the body weight when administered once to several times daily. However, since the effective amount may be increased or decreased depending on the administration route, the severity of obesity, gender, body weight, age, and the like, the dosage is not intended to limit the scope of the present invention in any way.

As used herein, the "subject" refers to a subject in need of treatment for a disease, and more specifically, refers to a mammal such as a human or a non-human primate, a mouse, a dog, a cat, a horse, and a cow.

【Advantageous Effects】

A 3-(4-(benzyloxy)phenyl)hex-4-inoic acid derivative according to the present invention addresses a side effect in which conventionally developed agents for treating diabetes induce apoptosis of pancreatic beta cells through excitotoxic reactions, thereby causing a secondary failure in which an insulin secretory function is not regulated. The 3-(4-(benzyloxy)phenyl)hex-4-inoic acid derivative according to the present invention promotes insulin secretion only when glucose concentration is increased, thereby protecting the pancreatic beta cells from apoptosis and restoring the insulin secretory function of the pancreatic beta cells. Therefore, according to

the present invention, the 3-(4-(benzyloxy)phenyl)hex-4-ynoic acid derivative: exhibits an excellent pancreatic beta cell protection effect, when administered as a primary selective agent for diabetes and also when administered to a patient suffering from pancreatic beta cell damage by the use of other drugs, which are primary selection agents for diabetes and cause a secondary failure; and restores the insulin secretory function of pancreatic beta cells, thereby being useful for treating type II diabetes in a patient of which the blood glucose is not regulated in a normal manner by using an agent for promoting insulin secretion.

【Description of Drawings】

FIG. 1A illustrates the results of measuring the action of *in vitro* activity of Compound A on human GPR40.

FIG. 1B illustrates the results of confirming the glucose-stimulated insulin secretion (GSIS) of Compound A.

FIGS. 2A and 2B illustrate the results of the oral glucose tolerance test (OGTT) on day 1 after administration, and FIGS. 2C and 2D illustrate the results of the oral glucose tolerance test (OGTT) at week 12 after administration. FIGS. 2A and 2C and FIGS. 2B and 2D illustrate glucose levels and reduction levels of glucose AUC, respectively.

FIGS. 3A, 3B, and 3C illustrate the results of the oral glucose tolerance test (OGTT) and blood insulin concentration measurement on day 1 after administration, and FIGS. 3D, 3E, and 3F illustrate the results of the oral glucose tolerance test (OGTT) and the results of measuring the blood insulin concentrations at week 4 after administration. FIGS. 3A and 3D illustrate glucose levels, FIGS. 3B and 3E illustrate reduction levels of glucose AUC, and FIGS. 3C and 3F illustrate the insulin secretion index (SI).

FIG. 4A illustrates pancreatic islet morphology immunostained with an anti-insulin antibody in 12-week-old GK rats after 4 weeks of repeated administration, and FIG 4B illustrates pancreatic islet morphology immunostained with an anti-insulin antibody in 40-week-old GK rats after 14 weeks of repeated administration.

5 FIG. 5 is a graph illustrating the insulin secretion index (SI) of the test material compound A and the control material TAK-875 administration groups in terms of ratio compared to the vehicle administration group.

FIG. 6 illustrates the results of measuring the ability to regulate insulin secretion in a fasting state after repeated drug administration in GK rats.

10 FIG. 7 is a graph illustrating the reduction levels of glucose AUC as a result of the oral glucose tolerance test (OGTT) in the 4-week administration group.

FIG. 8 is a graph illustrating the reduction levels of glucose AUC as a result of the oral glucose tolerance test (OGTT) in the 8-week administration group.

15 FIGS. 9 and 10 are graphs illustrating the insulin secretion index (SI) as the results of the glucose-stimulated insulin secretion (GSIS) experiment of the 4-week administration group and the 8-week administration group, respectively.

FIG. 11 illustrates pancreatic islet morphology immunostained with an anti-insulin antibody in Wistar rats after 4 weeks of repeated administration of a test material.

20 FIG. 12 illustrates pancreatic islet morphology immunostained with an anti-insulin antibody in Wistar rats after 10 weeks of repeated administration of a test material.

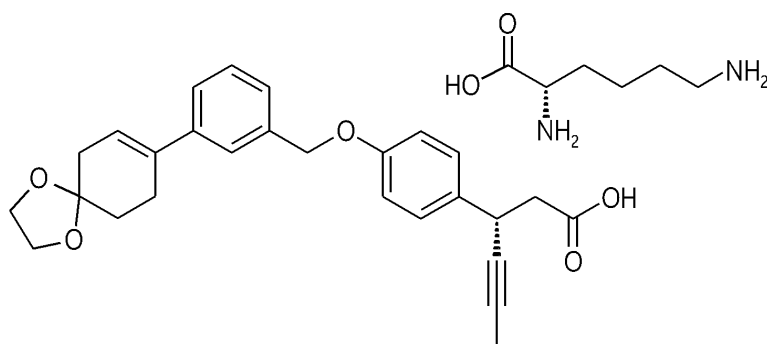
【Modes of the Invention】

25 The benefits and features of the present invention, and the methods of achieving the benefits and features will become apparent with reference to exemplary

embodiments to be described below in detail. However, the present invention is not limited to the exemplary embodiments to be disclosed below, but may be implemented in various other forms, and the present exemplary embodiments are only provided for rendering the disclosure of the present invention complete and for fully representing the scope of the invention to a person with ordinary skill in the technical field to which the present invention pertains, and the present invention will be defined only by the scope of the claims.

[Examples]

The test material used below as an example of the compound of Formula 1 according to the present invention is as follows.



Compound A: (3S)-3-(4-(3-(1,4-dioxaspiro[4,5]des-7-en-8-yl)benzyloxy)phenyl)hex-4-ynoic acid L-lysine salt

Example 1. Pharmacological activity test of Compound A

Example 1-1. Action activity test of Compound A on human GPR40

CHO cells stably expressing human GPR40 were cultured overnight at 37°C and under 5% CO₂. Then, the cells were cultured at 37°C in a loading buffer (50 ml Ham's F-12 (containing 1% FBS) + 50 ml Fluo-4 solution (Invitrogen, F10471)) for 2

hours. After various concentrations of Compound A were added to the cells, the increase in intracellular calcium ion concentration was monitored by FlexStation3 (Molecular Devices) for 100 seconds.

The action activity of Compound A on human GPR40 was expressed by the following equation.

$$(A/B) \times 100 \text{ (increased intracellular Ca}^{2+} \text{ concentration)}$$

A: Compound A-added cells, B: Vehicle-added cells

As a result, as illustrated in FIG. 1A, the action of *in vitro* activity of Compound A on human GPR40 was very excellent ($EC_{50}=15\text{nM}$).

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Example 1-2. Confirmation of glucose-stimulated insulin secretion (GSIS) of Compound A

For the insulin secretion ability test, INS-1 pancreatic cells were placed in a 24-well plate at 5×10^5 cells/well. After 48 hours, the cells were washed twice with a 1 mM glucose-KRB buffer (118 mM NaCl, 4.7 mM KCl, 1.2 mM KH_2P_4 , 1.16 mM MgCl_2 , 10 mM HEPES, 2.5 mM CaCl_2 , 25.5 mM NaHCO_3 , 0.2% BSA, pH 7.4), and cultured with a 1 mM glucose-KRB buffer for starvation for 2 hours. After starvation, the cells were washed twice with a 1 mM glucose-KRB buffer, and cultured with Compound A at a desired concentration in a 3 mM or 16 mM glucose-KRB buffer for 1 hour. The supernatant was collected and purified by centrifugation, and the insulin value was measured using an insulin ELISA kit (Millipore, EZRMI-13K) (* $p < 0.05$: Student t-test).

As a result, as illustrated in FIG. 1B, the secretion of insulin stimulated by glucose in INS-1 pancreatic beta cells was promoted in a concentration-dependent manner.

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Example 2. Confirmation of pancreatic beta cell protection effect of Compound A in 26-week-old Goto - Kakizaki (GK) rats

In order to confirm the pancreatic beta cell protection effect of Compound A,
5 Compound A was repeatedly administered to 26-week-old GK rats, and then the efficacy thereof was evaluated.

As experimental animals, GK rats, which are a non-obese animal and have characteristics of type II diabetes, such as hyperglycemia, hypoinsulinemia, and normal blood lipid concentration from 2 weeks after birth, were used. GK rats are
10 known to be a type II diabetes model having a secondary failure and cell death of pancreatic beta cells. Five-week-old male GK rats were purchased, bred *ad libitum* until they were 26 weeks old (old), and used in the experiment after causing a weight loss in the pancreas. Using only individuals in which diabetes induction was confirmed by a randomized complete block design according to the body weight and
15 blood glucose, eight rats per group were classified as an untreated group (GK rats, Vehicle), a glimepiride administration group (Glimepiride, 10 mg/kg), and Compound A administration groups (1, 3, and 10 mg/kg), a group in which Wistar rats (26-week-old males) were administered a vehicle was used as a normal group (WT), and the total 6 groups were orally administered each test material at 5 ml/kg
20 for 12 weeks. The solvent used for the vehicle and Compound A was a 0.5% CMC solution, and a solvent in which 1% PEG and 1% Tween 80 were contained in 0.25% CMC was used for the glimepiride administration group. An oral glucose tolerance test (OGTT) was performed after fasting for 16 to 18 hours on day 1 and at week 12 after administration. 60 minutes after the administration of the sample, glucose (4
25 g/kg) was orally administered at a dose of 5 ml/kg. Using a blood glucose meter

(G-doctor AGM-4000), fasting blood glucose and blood glucose levels were measured by puncturing the tail veins 0, 20, 40, 60, and 120 minutes after administration of glucose. After blood glucose levels during the oral glucose tolerance test (OGTT) were subjected to one-way ANOVA using the PRISM
5 statistical program, the significance among the average blood glucose levels of each experimental group was verified by performing the Dunnett's test based on the untreated group, and the width of decrease in blood glucose per group was converted into a percentage based on the area under the curve (AUC) value of the untreated group. The statistical significance compared to the vehicle treatment was expressed
10 as * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

FIGS. 2A and 2B illustrate the results of the oral glucose tolerance test (OGTT) on day 1 after administration, and FIGS. 2C and 2D illustrate the results of the oral glucose tolerance test (OGTT) at week 12 after administration. FIGS. 2A and 2C and FIGS. 2B and 2D illustrate glucose levels and reduction levels of glucose
15 AUC, respectively.

As a result of the experiment, when Compound A and glimepiride were repeatedly administered to 26-week-old GK rats for 12 weeks, the glimepiride administration group showed a tendency to attenuate the hypoglycemic effect, but Compound A did not. Since the GK rat is a type II diabetes model having a
20 secondary failure and cell death of pancreatic beta cells, these experimental results suggest that Compound A maintains the ability to regulate blood glucose even after long-term repeated administration through protection of pancreatic beta cells even in GK rats with an already damaged pancreas.

Example 3. Confirmation of pancreatic beta cell protection effect of Compound A in 8-week-old GK rats

In order to evaluate the pancreatic beta cell protection effect of Compound A, Compound A was repeatedly administered to 8-week-old rats, and then the efficacy thereof was evaluated.

Six-week-old male GK rats were purchased and bred *ad libitum* until they were 8 weeks old (young). Using only individuals in which diabetes induction was confirmed by a randomized complete block design according to the body weight and blood glucose, eight rats per group were classified as an untreated group (GK rats, Vehicle, Veh.), a glimepiride administration group (Glimepiride, 10 mg/kg), and Compound A administration groups (3 and 10 mg/kg), a group in which Wistar rats (8-week-old males) were administered a vehicle was used as a normal group (WT), and the total 5 groups were orally administered each test material at 5 ml/kg for 4 weeks. The solvent used for the vehicle and Compound A was a 0.5% carboxymethyl cellulose (CMC) solution, and a solvent in which 1% polyethylene glycol (PEG) and 1% Tween 80 were contained in 0.25% CMC was used for the glimepiride administration group. An oral glucose tolerance test (OGTT) and a blood insulin concentration measurement were performed after fasting for 16 to 18 hours on day 1 and at week 4 after administration. 60 minutes after the administration of the sample, glucose (4 g/kg) was orally administered at a dose of 5 ml/kg. Using a blood glucose meter (G-doctor AGM-4000), fasting blood glucose and blood glucose levels were measured by collecting blood from the tail veins 0, 30, 60, and 120 minutes after administration of glucose. After blood glucose levels during the oral glucose tolerance test (OGTT) were subjected to one-way ANOVA using the PRISM statistical program, the significance among the average blood

glucose levels of each experimental group was verified by performing the Dunnett's test based on the untreated group, and the width of decrease in blood glucose per group was converted into a percentage based on the area under the curve (AUC) value of the untreated group. The statistical significance compared to the vehicle treatment was expressed as * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. Meanwhile, in order to measure the blood insulin concentration, about 60 μ l of blood was collected by orbital vein blood sampling from the GK rats in the fasting state and 30 minutes after administration of glucose. Serum was separated by centrifuging the collected blood at 3,000 rpm (4°C) for 10 minutes, and a Rat/mouse Insulin ELISA kit (Millipore Merck) was used. An insulin secretion index (SI) was obtained by dividing the concentration of insulin 30 minutes after administration of glucose by the concentration of insulin in the fasting state. (Secretion index(SI) = insulin at 30 min / fasting insulin)

FIGS. 3A, 3B, and 3C illustrate the results of the oral glucose tolerance test (OGTT) on day 1 after administration, and FIGS. 3D, 3E, and 3F illustrate the results of the oral glucose tolerance test (OGTT) at week 4 after administration. FIGS. 3A and 3D illustrate glucose levels, FIGS. 3B and 3E illustrate reduction levels of glucose AUC, and FIGS. 3C and 3F illustrate the insulin secretion index (SI).

As a result of the experiments, after 4 weeks of repeated administration, the glimepiride administration group showed a hypoglycemic effect and a tendency to lower the beta cell function (decrease in insulin secretion ability), whereas Compound A increased the blood insulin concentration and maintained the ability to regulate blood glucose. This suggests that Compound A has a pancreatic beta cell protection effect.

25

Example 4. Confirmation of pancreatic beta cell protection effect of Compound A (Immunohistochemical staining results in GK rat pancreatic tissue)

In order to evaluate the pancreatic beta cell protection effect of Compound A, the pancreatic tissues were removed from each test group of the GK rats used in Examples 2 and 3, placed in a tissue cassette, and fixed in a 10% neutral formalin solution. After the tissues were allowed to become transparent by putting the tissues in an automatic tissue processor, a block was produced by allowing paraffin to penetrate into the tissue in a tissue embedding device, the block was sliced into a thickness of 5 μm using an automatic rotary microtome and attached to a slide, and then the slide was subjected to anti-insulin antibody immunostaining, and observed under an optical microscope.

FIG. 4A illustrates pancreatic islet morphology immunostained with an anti-insulin antibody in the rats used in Example 3, that is, 12-week-old GK rats after 4 weeks of repeated administration, and FIG. 4B illustrates pancreatic islet morphology immunostained with an anti-insulin antibody in 40-week-old GK rats after a total 14 weeks of repeated administration by administration to the GK rats used in Example 2 for a further 2 weeks.

As can be seen from FIG. 4, wild-type rat islets maintain their morphology, but GK rats generally show morphological damage. The relative amount of beta cells in the GK rats shows no significant difference between 4- and 14-week repeated administration of each drug. This suggests that the effect of Compound A on the regulation of blood glucose is due to the difference in beta cell function according to the beta cell protection, rather than the effect on the mass of beta cells.

25

The results of Examples 1 to 4 can be summarized as follows. Compound A had excellent activity *in vitro* and increased glucose-stimulated insulin secretion (GSIS) in INS-1 pancreatic beta cells. Administration of Compound A and glimepiride to young GK rats improved blood glucose regulation and insulin secretion, but chronic administration of glimepiride induced a loss of blood glucose regulation efficacy, whereas compound A did not induce a loss of blood glucose regulation efficacy. After the chronic administration, the glimepiride administration group had lower blood glucose regulation and insulin secretion during the oral glucose tolerance test (OGTT) than the Compound A administration group. When Compound A and glimepiride were administered to older GK rats, the Compound A administration group continued to maintain the ability to regulate blood glucose, but the glimepiride administration group did not continue to maintain the ability to regulate blood glucose.

Therefore, repeated administration of Compound A has the effect of preserving pancreatic islet cells and improving beta cell function.

Example 5. Evaluation of insulin secretion ability of Compound A

After 7-week-old male Sprague Dawley (SD) rats were purchased, a glucose-stimulated insulin secretion (GSIS) test was performed using only healthy individuals after a 1-week acclimatization period. After fasting for 12 to 16 hours, the rats were randomly separated into groups, and then orally administered a vehicle (0.5% CMC) or a test material Compound A and a control material TAK-875 at a dose of 10mg/kg, respectively.

60 minutes after administration of a vehicle or a test material, glucose (2 g/kg) was intraperitoneally administered. After 20 minutes, the tail veins were

punctured, whole blood was collected with a capillary tube, and then blood plasma was separated and measured using a Morinaga Ultra Sensitive Mouse/Rat Insulin ELISA Kit (MIoBS). The insulin secretion index (SI) was obtained by the following equation.

5 Secretion Index (SI) = insulin at 20 min/insulin at 0 min

The test results were expressed as the mean value and standard error (Mean $\pm$ SE), the significance of the difference between the control and the experimental group was verified by the one-way ANOVA (Dunnett's test) of the 'GraphPad Prism 4' software (GraphPad Co., La Jolla, CA, USA), and *** $p < 0.001$ vs. vehicle was
10 determined to be statistically significant.

FIG. 5 is a graph illustrating the insulin secretion index of the test material compound A and the control material TAK-875 administration groups in terms of ratio compared to the vehicle administration group.

As can be seen in FIG. 5, the insulin secretion ability of Compound A was
15 better than the control material TAK-875 in a glucose-stimulated insulin secretion (GSIS) test using SD rats.

Example 6. Evaluation of ability of Compound A to regulate insulin secretion

20 A vehicle (0.5% CMC) or a test material Compound A (1, 3 mg/kg) and a control material TAK-875 (10 mg/kg) were administered to 20-week-old male GK rats for 4 weeks. After the rats were allowed to fast 12 to 16 hours before insulin measurement, the tail veins were punctured and whole blood was collected with a capillary tube. Blood plasma was separated and insulin was measured using a
25 Morinaga Ultra Sensitive Mouse/Rat Insulin ELISA Kit (MIoBS).

The test results were expressed as the mean value and standard error (Mean $\pm$ SE), the significance of the difference between the control and the experimental group was verified by the t-tests and one-way ANOVA (Dunnett's test) of the 'GraphPad Prism 4' software (GraphPad Co., La Jolla, CA, USA), and # $p < 0.05$ vs. WT or * $p < 0.05$ vs. vehicle was determined to be statistically significant.

FIG. 6 illustrates the results of measuring the ability to regulate insulin secretion in a fasting state after repeated drug administration in GK rats. Many therapeutic agents for diabetes show an insulin secretion regulation disorder that excessively secretes insulin regardless of glucose concentration during repeated administration. As a result of the experiment, Compound A had an excellent ability to regulate insulin secretion compared to TAK-875 which is the same GPR40 activator, even though Compound A was administered at a low dose. Since the abnormality in the ability to regulate insulin secretion appears due to the damage to pancreatic beta cells, it can be determined that Compound A has an excellent ability to protect pancreatic beta cells.

Example 7. Confirmation of pancreatic beta cell protection effect of Compound A Wistar DIO rats

As experimental animals, 4-week-old female Wistar diet-induced obesity (DIO) rats were purchased, fed *ad libitum* with a high fat diet (Research Diets, D12492) for 37 weeks, and then used for the test. By a randomized complete block design according to the body weight and blood glucose, the animals were classified into the groups in the following Table 1.

[Table 1]

4-Week	Normal group (Wistar rats, Lean)
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administration group	Untreated group (Wistar DIO rats, Vehicle)
	Glimepiride administration group (Glimepiride, 10 mg/kg)
	Compound A administration group (1 mg/kg)
8-Week administration group	Normal group (Wistar rats, Lean)
	Untreated group (Wistar DIO rats, Vehicle)
	Glimepiride administration group (Glimepiride, 10 mg/kg)
	Compound A single administration group (1 mg/kg)
	4-week administration group of Compound (1 mg/kg) A after 4-week administration of glimepiride (10 mg/kg)

The 4-week administration group was classified into a normal group (Wistar rats, Lean), an untreated group (Wistar DIO rats, Vehicle), a glimepiride administration group (Glimepiride, 10 mg/kg), and Compound A administration group (1 mg/kg), and orally administered each material at 5 ml/kg for 4 weeks.

The 8-week administration group was classified into a normal group (Wistar rats, Lean), an untreated group (DIO rats, Vehicle), a glimepiride administration group (Glimepiride, 10 mg/kg), a Compound A single administration group (1 mg/kg), and a 4-week administration group of Compound A (1 mg/kg) after a 4-week administration of glimepiride (10 mg/kg), and orally administered each material at 5 ml/kg for 8 weeks.

The solvent used for the vehicle and Compound A was a 0.5% CMC solution, and a solvent in which 1% PEG and 1% Tween 80 were contained in 0.25% CMC was used for the glimepiride administration group.

An oral glucose tolerance test (OGTT) and a glucose-stimulated insulin secretion (GSIS) test were performed after 4 and 8 weeks of administration.

In the case of the 4-week oral glucose tolerance test (OGTT), 60 minutes after administration of the sample, glucose (4 g/kg) was orally administered at a dose of 5 ml/kg. Using a blood glucose meter (ACCU-CHEK active strip, Roche), fasting blood glucose and blood glucose levels were measured in blood collected

from the orbital veins 0, 30, 60, and 120 minutes after administration of glucose. After blood glucose levels during the oral glucose tolerance test (OGTT) were subjected to one-way ANOVA using the PRISM statistical program, the significance among the average blood glucose levels of each experimental group was verified by performing the Dunnett's test or t-test based on the untreated group, and the width of decrease in blood glucose per group was converted into a percentage based on the area under the curve (AUC) value of the untreated group.

In the case of the 8-week oral glucose tolerance test (OGTT), 60 minutes after administration of the sample, glucose (4 g/kg) was orally administered at a dose of 5 ml/kg. Using a blood glucose meter (ACCU-CHEK active strip, Roche), fasting blood and blood glucose levels were measured by punching the tail veins 0, 20, 40, 60, and 120 minutes after administration of glucose. After blood glucose levels during the oral glucose tolerance test (OGTT) were subjected to one-way ANOVA using the PRISM statistical program, the significance among the average blood glucose levels of each experimental group was verified by performing the Dunnett's test or t-test based on the untreated group, and the width of decrease in blood glucose per group was converted into a percentage based on the area under the curve (AUC) value of the untreated group.

In the case of the glucose-stimulated insulin secretion (GSIS) test, in a fasting state and 0, 30, and 120 minutes after administration of glucose, about 60 μ l of blood was collected by collecting blood from the orbital veins in the DIO rats. Serum was separated by centrifuging the collected blood at 3,000 rpm (4°C) for 10 minutes to measure the concentration of blood insulin, and a Rat/mouse Insulin ELISA kit (Millipore Merck) was used. An insulin secretion index (SI) was obtained by dividing the concentration of insulin 30 minutes after administration of glucose by

the concentration of insulin in the fasting state. ('Secretion Index(SI) = insulin at 30 min/fasting insulin')

FIG. 7 is a graph illustrating the reduction levels of glucose AUC as a result of the oral glucose tolerance test (OGTT) in the 4-week administration group.

5 It can be confirmed that after repeated administration for 4 weeks, a secondary failure was caused in the glimepiride administration group and the ability to regulate blood glucose deteriorated, whereas the Compound A administration group had an excellent ability to regulate blood glucose. Since the induction of the secondary failure indicates damage to pancreatic beta cells, conversely, this suggests
10 that Compound A exhibits an excellent ability to regulate blood glucose without damaging pancreatic beta cells.

Meanwhile, FIG. 8 is a graph illustrating the reduction levels of glucose AUC as a result of the oral glucose tolerance test (OGTT) in the 8-week administration group.

15 Similar to the results of the 4-week repeated administration, it could be confirmed that in the glimepiride administration group, a secondary failure was caused due to deterioration in the ability to regulate blood glucose. In contrast, the Compound A single administration group exhibited the best ability to regulate blood glucose. The 4-week administration group of Compound A (1 mg/kg) after the 4-
20 week administration of glimepiride (10 mg/kg) exhibited an ability to regulate blood glucose, which is lower than the Compound A single administration group, but is excellent, suggesting that when Compound A is administered to a patient suffering from pancreatic beta cell damage due to long-term administration of a sulfonylurea-based drug such as glimepiride, the pancreatic beta cells may be protected from
25 additional damage, and furthermore, the insulin secretory function of pancreatic beta

cells may be restored. This was additionally confirmed even in the following glucose-stimulated insulin secretion (GSIS) data and immunohistochemical staining results.

FIGS. 9 and 10 are graphs illustrating the insulin secretion index (SI) as the results of the glucose-stimulated insulin secretion (GSIS) experiment of the 4-week administration group and the 8-week administration group, respectively. The Compound A administration group had an excellent ability to regulate insulin, whereas the glimepiride administration group exhibited a result that the ability to regulate insulin deteriorated. However, it can be confirmed that in the 4-week administration group of Compound A (1 mg/kg) after the 4-week administration of glimepiride (10 mg/kg), the ability to regulate insulin is restored to a level similar to that of the Compound A administration group. This is a result confirming that when Compound A is administered to a patient suffering from pancreatic beta cell damage due to long-term administration of a sulfonylurea-based drug, the pancreatic beta cells may be protected from additional damage, and furthermore, the insulin secretory function of pancreatic beta cells may be restored.

Example 8. Confirmation of pancreatic beta cell protection effect of Compound A (Immunohistochemical staining results in Wistar DIO rat pancreatic tissue)

The rats belonging to the 4-week administration group tested in Example 4 were sacrificed after completion of the test, and the pancreatic tissue was isolated for each test group. The pancreatic tissue was placed in a tissue cassette, and fixed in a 10% neutral formalin solution. After the tissues were allowed to become transparent by putting the tissues in an automatic tissue processor, a block was

produced by allowing paraffin to penetrate into the tissue in a tissue embedding device, the block was sliced into a thickness of 5 μ m using an automatic rotary microtome and attached to a slide, and then the slide was subjected to anti-insulin antibody immunostaining, and the stained slide was scanned with Axio Scan.Z1 [Carl Zeiss, Germany]. Results were shown at 2.5x using ZEN Imaging Software.

Meanwhile, the sample was further administered to the rats belonging to the 8-week administered group tested in Example 6 under the same conditions for 2 weeks, and after completion of administration for a total of 10 weeks, immunostaining was performed by the same method.

FIG. 11 illustrates pancreatic islet morphology immunostained with an anti-insulin antibody in Wistar rats after 4 weeks of repeated administration of a test material. Wild-type Wistar rat (Lean) pancreatic islet cells maintain their morphology, but DIO rat (vehicle) pancreatic islet cells show some morphological damage. The glimepiride administration group shows general morphological damage, suggesting that a secondary failure is caused. The Compound A administration group does not show a significant difference even after the 4-week repeated administration.

FIG. 12 illustrates pancreatic islet morphology immunostained with an anti-insulin antibody in Wistar rats after 10 weeks of repeated administration of a test material. The Compound A administration group did not show a morphological change even after the 10-week repeated administration. When Compound A and glimepiride were each administered to the DIO rats, in which a secondary failure was caused by 4 weeks of administration of glimepiride, for 6 weeks, the glimepiride administration group (group to which glimepiride was administered for 10 weeks) had severe morphological damage whereas the degree of damage was suppressed in

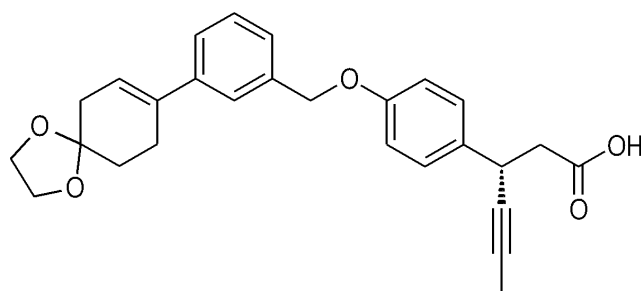
the Compound A administration group (Glimepiride 10 mg/kg pre-treatment (4w) + Compound A, 1 mg/kg (6w)). This is a result confirming that when Compound A is administered to a patient suffering from pancreatic beta cell damage due to long-term administration of a sulfonylurea-based drug, the pancreatic beta cells may be
5 protected from additional damage, and furthermore, the insulin secretory function of pancreatic beta cells may be restored.

【CLAIMS】

【Claim 1】

A pharmaceutical composition for protecting pancreatic beta cells,
comprising a compound of Formula 1, an optical isomer thereof, or a
5 pharmaceutically acceptable salt thereof as an active ingredient.

[Formula 1]



【Claim 2】

The pharmaceutical composition of claim 1, wherein the pharmaceutical
10 composition is for protecting pancreatic beta cells in a patient with type II diabetes.

【Claim 3】

The pharmaceutical composition of claim 1, wherein the pharmaceutical
composition is administered either alone or in combination with other drugs for
treating type II diabetes.

15 【Claim 4】

The pharmaceutical composition of claim 1, wherein the pharmaceutical
composition is for protecting pancreatic beta cells in a patient with type II diabetes
having damaged pancreatic beta cells.

【Claim 5】

The pharmaceutical composition of claim 4, wherein the patient with type II diabetes having damaged pancreatic beta cells is a patient who has been administered an agent for promoting insulin secretion.

5 **【Claim 6】**

The pharmaceutical composition of claim 4, wherein the patient with type II diabetes having damaged pancreatic beta cells is a patient who has been co-administered an agent for promoting insulin secretion and other hypoglycemic agents.

10 **【Claim 7】**

The pharmaceutical composition of claim 5, wherein the agent for promoting insulin secretion is a sulfonylurea-based drug, and/or a meglitinide-based drug.

【Claim 8】

15 The pharmaceutical composition of claim 6, wherein the hypoglycemic agent is a biguanide-based drug.

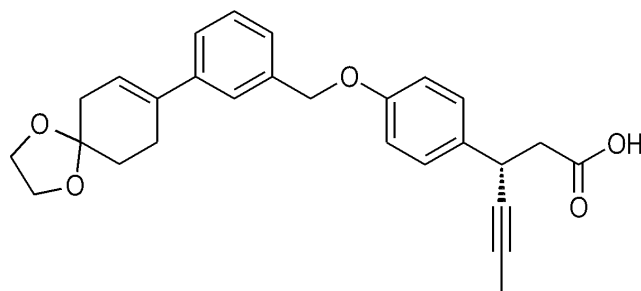
【Claim 9】

The pharmaceutical composition of any one of claims 1 to 8, wherein the pharmaceutically acceptable salt of the compound of Formula 1 is (3S)-3-(4-(3-(1,4-dioxaspiro[4,5]des-7-en-8-yl)benzyloxy)phenyl)hex-4-ionic acid L-lysine salt.

20 **【Claim 10】**

A pharmaceutical composition for treating type II diabetes in a patient of which the blood glucose is not regulated in a normal manner by using an agent for promoting insulin secretion, comprising a compound of Formula 1, an optical isomer thereof, or a pharmaceutically acceptable salt thereof as an active ingredient.

[Formula 1]



【Claim 11】

The pharmaceutical composition of claim 10, wherein the patient of which
5 the blood glucose is not regulated in a normal manner by using an agent for
promoting insulin secretion is a patient who has been administered an agent for
promoting insulin secretion.

【Claim 12】

The pharmaceutical composition of claim 10, wherein the patient of which
10 the blood glucose is not regulated in a normal manner by using an agent for
promoting insulin secretion is a patient who has been co-administered an agent for
promoting insulin secretion and other hypoglycemic agents.

【Claim 13】

The pharmaceutical composition of claim 10, wherein the agent for
15 promoting insulin secretion is a sulfonylurea-based drug, and/or a meglitinide-based
drug.

【Claim 14】

The pharmaceutical composition of claim 12, wherein the hypoglycemic
agent is a biguanide-based drug.

【Claim 15】

The pharmaceutical composition of claim 10, wherein the pharmaceutical composition is administered either alone or in combination with other drugs for treating type II diabetes.

5 **【Claim 16】**

The pharmaceutical composition of claim 10, wherein the pharmaceutical composition is administered in combination with a biguanide-based drug.