[Non-Patent Document 12] Lancet *359*, 2072-2077
[Non-Patent Document 13] JAMA *290*, 486-494
[Non-Patent Document 14] N Engl J Med *362*, 1463-1476
[Non-Patent Document 15] N Engl J Med *369*, 1317-1326
[Non-Patent Document 16] N Engl J Med *369*, 1327-1335
[Non-Patent Document 17] Circulation *122*, 406-441
[Non-Patent Document 18] Eat Weight Disord *14*, e56-65
[Non-Patent Document 19] Biochimica et Biophysica Acta - Bioenergetics 1817, S123
[Non-Patent Document 20] Bioorganic Medicinal Chemistry, vol.15, 2007, 1533-1538
[Non-Patent Document 21] ~~Tetrahydron~~ Tetrahedron Letters, *53*, 2012, 59-63

Summary of the Invention

Problems to be Solved by the Invention

[0008]

An object of the present invention is therefore to provide a compound which stimulates the citric acid cycle activity and/or improves hyperglycemia with less side effects, and excellent safety, and is useful for treating and/or preventing diseases or disorders on which citric acid cycle activation and/or improvement of hyperglycemia has a prophylactic and/or therapeutic effect, for example, diabetes, impaired glucose tolerance, insulin resistance, diabetic complications, obesity, dyslipidemia, hepatic steatosis, atherosclerosis and/or cardiovascular disease, as well as diseases or disorders that would benefit from stimulating energy expenditure.

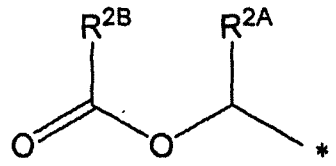
Means of Solving the Problems

[0009]

The present inventors intensively conducted studies with the view to attaining the aforementioned object. As a result, they found that a cyanotriazole compound represented by the general formula (1) below and a salt thereof stimulates the citric acid cycle activity and/or improves hyperglycemia with less side effects, and excellent safety, and is useful for

(A30) a benzoxazolediyl group,
(A31) a [1,3,4]thiadiazolediyl group,
(A32) a styrenediyl group,
(A33) -CO-phenylene-,
(~~A24~~A34) a cycloalkanediyl group,
(A35) a higher alkylene group,
(A36) a 2-oxo-1,2-dihydroquinolinediyl group,
(A37) a benzimidazolediyl group,
(A38) a 2,3-dihydro[1,4]benzodioxinediyl group,
(A39) a fluorenediyl group,
(A40) a bicyclo[2,2,1]hept-2-enediyl group,
(A41) a thieno[3,2-b]pyridinediyl group,
(A42) an imidazo[1,2-a]benzimidazolediyl group,
(A43) a 3,4-dihydro-2H-[1,4]benzoxazinediyl group,
(A44) a 3,4-dihydro-2H-benzo[b][1,4]dioxepinediyl group, and
(A45) -NH-,
each of (A1) to (A45) is optionally substituted with one or more members selected from the group consisting of
a halogen atom;
a lower alkyl group optionally substituted with one or more halogen atoms;
a lower alkenyl group;
a hydroxy group;
a lower alkoxy group optionally substituted with one or more halogen atoms;
a lower alkenyloxy group;
a lower alkynyloxy group;
a cyano group;
an amino group optionally mono- or di-substituted with members selected from the group consisting of a lower alkyl group, a lower alkyl-carbonyl group, a lower alkoxy-carbonyl group, and a lower alkylsulfonyl group;
a N,N-di-lower alkylamino lower alkyl group;
a N,N-di-lower alkylamino lower alkoxy group;
a cycloalkyl group optionally substituted with one or more

more halogen atoms,
(2-2) a 2-oxo-1,3-dioxolanyl group, and
(2-3) a group represented by the formula:
[0034]



[0035]
wherein
* is a bonding site;
R^{2A} is one of the following (2A-1) to (2A-2):
(2A-1) a hydrogen atom, ~~or~~and
(2A-2) a lower alkyl group; and
R^{2B} is one of the following (2B-1) to (2B-6):
(2B-1) a lower alkoxy group optionally substituted with one or more members selected from the group consisting of a lower alkoxy group; a carboxy group; a lower alkoxy-carbonyl group; a hydroxy group; a phenyl lower alkoxy-carbonyl group; a lower alkenyloxy-carbonyl group; a morpholinyl group; a benzyloxycarbonyl group; and a tetrahydropyran-2-yloxy group,
(2B-2) a lower alkyl group;
(2B-3) a lower alkylamino group optionally substituted with one or more lower alkoxy-carbonyl groups;
(2B-4) a cycloalkyl group;
(2B-5) a cycloalkoxy group; and
(2B-6) a phenyl group;
or a salt thereof (hereinafter to be referred to as Compound (1bb)).
[0036]
As preferable embodiment, the cyanotriazole compound or salt is a compound represented by the formula (1bbA):
[0037]

tetradecamethylene, hexadecamethylene, octadecamethylene and the like.

[0098]

Examples of the "lower alkenylene" include linear or branched ones that have 1 to 3 double bonds such as vinylene, 1-methylvinylene, 2-methylvinylene, 1,2-dimethylvinylene, 1-propenylene, 1-methyl-1-propenylene, 2-methyl-1-propenylene, 2-propenylene, 2-butenylene, 1-butenylene, 3-butenylene, 2-pentenylene, 1-pentenylene, 3-pentenylene, 4-pentenylene, 1,3-butadienylene, 1,3-pentadienylene, 2-penten-4-ynylene, 2-hexenylene, 1-hexenylene, 5-hexenylene, 3-hexenylene, 4-hexenylene, 3,3-dimethyl-1-propenylene, 2-ethyl-1-propenylene, 1,3,5-hexatrienylene, 1,3-hexadienylene, 1,4-hexadienylene and the like.

Examples of the "phenylene" include 1,2-phenylene, 1,3-phenylene and 1,4-phenylene.

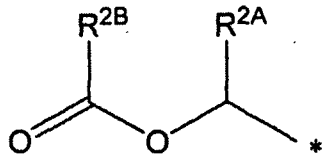
[0099]

Examples of "heterocyclyl" include saturated or unsaturated monocyclic or polycyclic heterocyclyl containing at least one hetero atom selected from the group consisting of oxygen, sulfur and nitrogen. Examples of preferable heterocyclyl include the following (a) to (n):

(a) unsaturated 3 to 8-membered, preferably 5 or 6-membered heteromonocyclyl containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, and its N-oxide, tetrahydropyridyl (e.g., 1,2,3,6-tetrahydropyridyl), pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), dihydrotriazinyl (e.g., 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), dihydropyrimidinyl (e.g., 1,6-dihydrodihydropyrimidinyl), tetrahydropyrimidinyl (e.g., 1,2,3,6-tetrahydropyrimidiny) etc.;

(b) saturated 3 to 8-membered, preferably 5 ~~or~~ to 7-

[0122]



[0123]

wherein

* is a bonding site;

R^{2A} is one of the following (2A-1) to (2A-2):

(2A-1) a hydrogen atom, ~~or~~and

(2A-2) a lower alkyl group; and

R^{2B} is one of the following (2B-1) to (2B-6):

(2B-1) a lower alkoxy group optionally substituted with one or more members selected from the group consisting of a lower alkoxy group; a carboxy group; a lower alkoxy-carbonyl group; a hydroxy group; a phenyl lower alkoxy-carbonyl group; a lower alkenyloxy-carbonyl group; a morpholinyl group; a benzyloxycarbonyl group; and a tetrahydropyran-2-yloxy group,

(2B-2) a lower alkyl group;

(2B-3) a lower alkylamino group optionally substituted with one or more lower alkoxy-carbonyl groups;

(2B-4) a cycloalkyl group;

(2B-5) a cycloalkoxy group; and

(2B-6) a phenyl group, ~~and~~

(2-4) a hydrogen atom.

[0124]

R^2 is more preferably one of the following groups:

a hydrogen atom;

a 1-(((2-carboxy-2,2-dimethylethoxy)carbonyl)oxy)ethyl group;

a 1-(((2-carboxy-1,1-dimethylethoxy)carbonyl)oxy)ethyl group;

a 1-(((2-hydroxyethoxy)carbonyl)oxy)ethyl group;

a 1-(butyryloxy)ethyl group;

a 1-(isobutyryloxy)ethyl group;

an acetoxymethyl group; and

group, an allyl group, a *tert*-butyl group, etc.

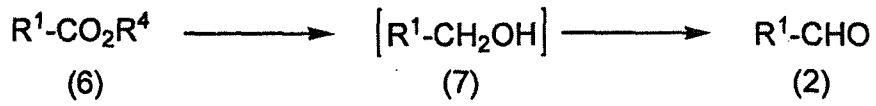
Examples of the hydroxy-protecting group include a tetrahydropyran-2-yl group, etc.

[0139]

Compound (2) can be produced according to one of the following non-limiting Reaction Schemes 3 to 7, or the like.

[0140]

Reaction Scheme 3



[0141]

wherein R^1 is as defined above; and R^4 is a hydrogen atom, an alkyl group, an aryl group or an acyl group.

The reaction for producing Compound (2) or Compound (7) from Compound (6) can be carried out in a suitable solvent, in the presence of a suitable reducing agent.

Examples of the solvent include diethyl ether, dimethoxyethane, dioxane, methanol, ethanol, tetrahydrofuran, hexane, toluene, dichloromethane, 1,2-dichloroethane, mixed solvents thereof, etc.

Examples of the reducing agent include hydride reducing agents such as borane, sodium borohydride, lithium aluminium hydride, diisobutylaluminum hydride, sodium bis(2-methoxyethoxy)aluminum hydride, etc.

The reducing agent is usually used in an amount of at least 0.25 to 10 mol, preferably about 1 to 5 mol, per 1 mol of Compound (6).

The reaction is usually carried out at about -78 to 100°C, preferably about -78 to 70°C. The reaction is usually finished in about 1 to about 12 hours.

The reaction for producing Compound (2) from Compound (7) can be carried out in a suitable solvent, in the presence of an oxidizing agent.

Examples of the solvent include *N*,*N*-dimethylformamide,

dimethyl sulfoxide, ethyl acetate, dioxane, acetonitrile, acetone, dichloromethane, 1,2-dichloroethane, chloroform, mixed solvents thereof, etc.

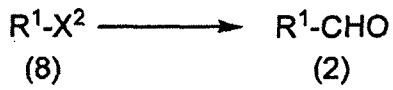
Examples of the oxidizing agent include pyridinium dichlorochlomate, mangange(IV) oxide, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) - oxidizing agents (sodium hypochlorite - potassium bromide, bromine, iodine, sodium nitrite, oxygen, etc.), 2-iodoxybenzoic acid, Dess-Martin reagent, dimethylsulfoxide (Swern oxidation, etc.), etc.

The oxidizing agent is usually used in an amount of at least 1 mol, preferably about 1 to 2 mol, per 1 mol of Compound (7).

The reaction is usually carried out at about -100 to 100°C, preferably about -80 to 70°C. The reaction is usually finished in about 1 to about 12 hours.

[0142]

Reaction Scheme 4



(8) (2)

[0143]

wherein R^1 is as defined above; and X^2 is a halogen atom.

The reaction for producing Compound (2) from Compound (8) can be carried out by subjecting Compound (8) to a formylation reaction.

This formylation reaction can be carried out in a suitable solvent, in the presence of an organometal reagent and a formylating reagent.

Examples of the solvent include diethyl ether, tetrahydrofuran, toluene, hexane, pentane, mixed solvents thereof, etc.

Examples of the organometal reagent include organolithium reagents (n-butyllithium, etc), organo magnesium reagents (ethymagnesium bromide, isopropylmagnesium chloride, etc.), etc.

Examples of the formylating reagent include *N,N*-

and the preparation can be administered by a route suitable for the form of the preparation, the patient's age and sex, the conditions of the disease, and other conditions.

For example, tablets, pills, solutions, suspensions, emulsions, granules and capsules are administered orally.

[0168]

Injections are intravenously administered singly or as mixed with general injection transfusions such as glucose solutions, amino acid solutions or the like, or singly administered intramuscularly, intracutaneously, subcutaneously or intraperitoneally, as required. Suppositories are administered intrarectally.

[0169]

The dosage of the pharmaceutical preparation is suitably selected according to the method of use, the patient's age and sex, the severity of the disease, and other conditions, and is typically about 0.001 to about 100 mg/kg body weight/day, preferably 0.001 to 50 mg/kg body weight/day, in single or divided doses.

[0170]

Hydrophobic penetrating cations, e.g. triphenylphosphonium derivatives and rodamine 123 derivatives, are known as carriers which lead various molecules toward mitochondria (non-patent documents: Trends Biotechnol 15, 326-330; PLoS One 8, e61902). Because the citric cycle exists within the mitochondria, the citric acid cycle activators are likely to be more potent by means of binding covalently to the hydrophobic penetrating cation or mixing with it.

Examples

[0171]

Working examples of compounds used in the invention are shown below, being followed by the Pharmacological Test results of these compounds.

The following compounds of Reference Examples and Examples are shown as one tautomer, which are not limited, and

R^{2A} is one of the following (2A-1) to (2A-2):

(2A-1) a hydrogen atom, ~~or~~and

(2A-2) a lower alkyl group; and

R^{2B} is one of the following (2B-1) to (2B-6):

(2B-1) a lower alkoxy group optionally substituted with one or more members selected from the group consisting of a lower alkoxy group; a carboxy group; a lower alkoxy-carbonyl group; a hydroxy group; a phenyl lower alkoxy-carbonyl group; a lower alkenyloxy-carbonyl group; a morpholinyl group; a benzyloxycarbonyl group; and a tetrahydropyran-2-yloxy group,

(2B-2) a lower alkyl group;

(2B-3) a lower alkylamino group optionally substituted with one or more lower alkoxy-carbonyl groups;

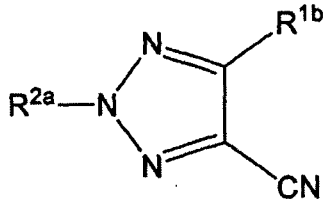
(2B-4) a cycloalkyl group;

(2B-5) a cycloalkoxy group; and

(2B-6) a phenyl group;

or a salt thereof.

11. The cyanotriazole compound or salt according to claim 10, which is a compound represented by the formula (1bbA):



(1bbA)

wherein each symbol is as defined in claim 10,

or a salt thereof.

12. The cyanotriazole compound or salt according to claim 10 or 11, wherein

R^{1b} is one of the following (1-1) to (1-5):

(1-1) a phenyl group optionally substituted with one or more members selected from:

(1-1-1) a lower alkyl group optionally substituted with one

cycle activation and/or improvement of hyperglycemia has a prophylactic and/or therapeutic effect is selected from the group consisting of diabetes, impaired glucose tolerance, insulin resistance, diabetic complications, obesity, dyslipidemia, hepatic steatosis, athrosclerosis and cardiovascular disease.

16. The cyanotriazole compound or salt according to claim 1 for use as a prophylactic and/or therapeutic agent for a disease or a disorder on which citric acid cycle activation and/or improvement of hyperglycemia has a prophylactic and/or therapeutic effect.

17. Use of the cyanotriazole compound or salt according to claim 1 for manufacturing a prophylactic and/or therapeutic agent for a disease or a disorder on which citric acid cycle activation and/or improvement of hyperglycemia has a prophylactic and/or therapeutic effect.

~~18. A method for preventing and/or treating a disease or a disorder on which citric acid cycle activation and/or improvement of hyperglycemia has a prophylactic and/or therapeutic effect, comprising administering an effective amount of the cyanotriazole compound or salt according to claim 1 to a patient.~~