[Patent Document 7] International Publication No. 2010/128163

[Summary of ~~Invention~~the Disclosure]

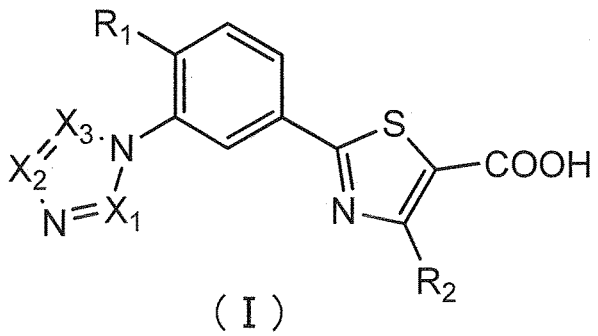
[Problems to be Solved by the Invention]

An object of the present ~~invention~~ disclosure is to provide a novel compound having a xanthine oxidase inhibitory activity. Further, an object of the present invention is to provide a compound having an excellent uric acid lowering effect. In addition, an object of the present ~~invention~~ disclosure is to provide a compound useful as a therapeutic agent or a preventive agent for diseases associated with xanthine oxidase such as gout, hyperuricemia, tumor lysis syndrome, urinary calculi, hypertension, dyslipidemia, diabetes, cardiovascular diseases such as arteriosclerosis or heart failure, kidney diseases such as diabetic nephropathy, respiratory diseases such as chronic obstructive pulmonary diseases, inflammatory bowel diseases or autoimmune diseases.

[Means for Solving the Problems]

As a result of earnest studies on compounds having a xanthine oxidase inhibitory activity, the present inventors have found that a compound represented by the following formula (I):

[Chemical Formula 1]



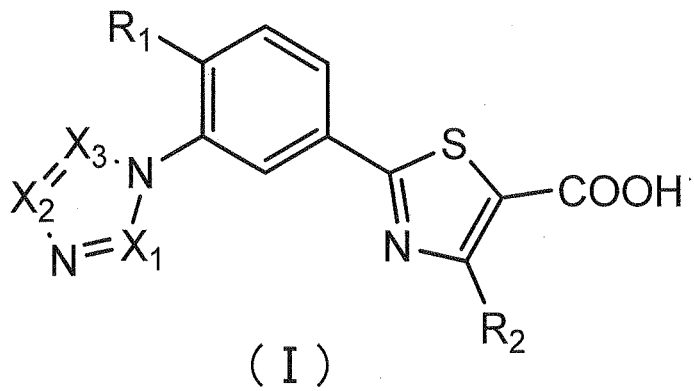
(I)

which is a benzene structure having 3 substituents and a azole benzene derivative

having a 2-thiazole ring at a position 1 and a 1,3-nitrogen-containing azole ring at a position 3 has a xanthine oxidase inhibitory activity, further a xanthine oxidase inhibitory activity accompanied by an excellent uric acid lowering effect, and further a sustained xanthine oxidase inhibitory activity capable of providing an especially excellent uric acid lowering effect over a long period of time, and completed the present ~~invention~~disclosure. In addition, the present inventors have found that the azole benzene derivative may serve as a favorable therapeutic or preventive agent for gout, hyperuricemia, tumor lysis syndrome, urinary calculi, hypertension, dyslipidemia, diabetes, cardiovascular diseases such as arteriosclerosis or heart failure, kidney diseases such as diabetic nephropathy, respiratory diseases such as chronic obstructive pulmonary diseases, inflammatory bowel diseases or autoimmune diseases and completed the present disclosure~~invention~~.

The present ~~invention~~ disclosure relates to a compound represented by the following formula (I) or a pharmaceutically acceptable salt thereof:

[Chemical Formula 2]



(I)

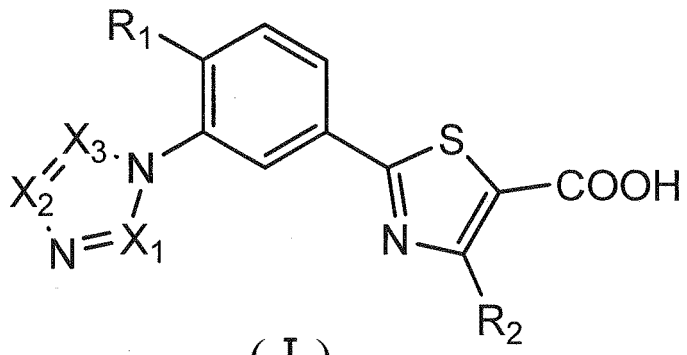
[wherein R_1 represents OR, NRR' which may form a ring or SR, in which R and R' independently represent a hydrogen atom, an alkyl group having 1 to 8 carbon atoms optionally substituted with one or a plurality of alkoxy groups having 1 to 8 carbon

atoms, halogen atoms or hydroxyl groups, an aryl group optionally substituted with one or a plurality of alkyl groups having 1 to 8 carbon atoms, alkoxy groups having 1 to 8 carbon atoms or halogen atoms, or a heteroaryl group optionally substituted with one or a plurality of alkyl groups having 1 to 8 carbon atoms, alkoxy groups having 1 to 8 carbon atoms or halogen atoms.

R_2 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms.

X_1, X_2 and X_3 are independently CR_3 or a nitrogen atom, or X_1 is CR_3 or a nitrogen atom, and X_2 and X_3 together form a benzene ring, in which R_3 is a hydrogen atom or an alkyl group having 1 to 8 carbon atoms.]

The present disclosure relates to a compound represented by the formula (I) or a pharmaceutically acceptable salt thereof:



(I)

[wherein R_1 represents OR, NRR' which may form a ring or SR, in which the term "NRR' forms a ring" means that R and R' together with the nitrogen atom to which they are attached, to form a saturated nitrogen-containing ring, and in which R and R' independently represent a hydrogen atom, an alkyl group having 1 to 8 carbon atoms optionally substituted with one or a plurality of alkoxy groups having 1 to 8 carbon atoms, halogen atoms or hydroxyl groups, an aryl group optionally substituted with one or a plurality of alkyl groups having 1 to 8 carbon atoms, alkoxy groups having 1

to 8 carbon atoms or halogen atoms, or a heteroaryl group optionally substituted with one or a plurality of alkyl groups having 1 to 8 carbon atoms, an alkoxy groups having 1 to 8 carbon atoms or a halogen atom,

R_2 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms, and

X_1, X_2 and X_3 are independently CR_3 or a nitrogen atom, or X_1 is CR_3 or a nitrogen atom, and X_2 and X_3 together form a benzene ring, in which R_3 is a hydrogen atom or an alkyl group having 1 to 8 carbon atoms.

In addition, the present ~~invention~~ disclosure relates to a pharmaceutical composition containing a compound represented by the above formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

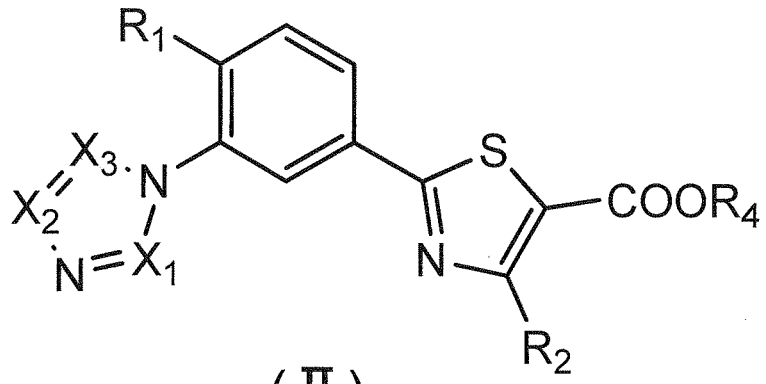
Further, the present ~~invention~~ disclosure relates to a xanthine oxidase inhibitor containing a compound represented by the above formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient.

In addition, the present ~~invention~~ disclosure relates to a therapeutic agent or a preventive agent for diseases associated with xanthine oxidase such as gout, hyperuricemia, tumor lysis syndrome, urinary calculi, hypertension, dyslipidemia, diabetes, cardiovascular diseases such as arteriosclerosis or heart failure, kidney diseases such as diabetic nephropathy, respiratory diseases such as chronic obstructive pulmonary diseases, inflammatory bowel diseases or autoimmune diseases, which contains a compound represented by the above formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient.

Further, the present ~~invention~~ disclosure relates to a compound represented by the

following formula (II), which may be used as a manufacturing intermediate of a compound represented by the above formula (I):

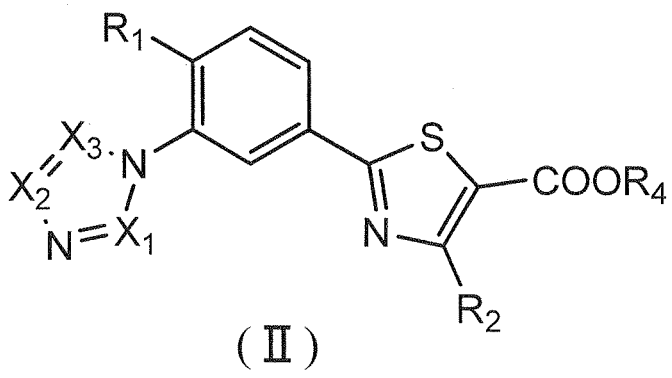
[Chemical Formula 3]



(Ⅱ)

[wherein R_1 represents OR, NRR' which may form a ring, or SR, in which R and R' independently represent a hydrogen atom, an alkyl group having 1 to 8 carbon atoms optionally substituted with one or a plurality of alkoxy groups having 1 to 8 carbon atoms, halogen atoms or hydroxyl groups, an aryl group optionally substituted with one or a plurality of alkyl groups having 1 to 8 carbon atoms, an alkoxy groups having 1 to 8 carbon atoms or a halogen atom, or a heteroaryl group optionally substituted with one or a plurality of alkyl groups having 1 to 8 carbon atoms, an alkoxy groups having 1 to 8 carbon atoms or a halogen atom.

The present disclosure relates to compound represented by the formula (II):



(Ⅱ)

[wherein R_1 represents OR, NRR' which may form a ring, or SR, in which the term "NRR' forms a ring" means that R and R' together with the nitrogen atom to which they are attached, to form a saturated nitrogen-containing ring, and in which R and R' independently represent a hydrogen atom, an alkyl group having 1 to 8 carbon atoms optionally substituted with a one or a plurality of alkoxy groups having 1 to 8 carbon atoms, halogen atoms or hydroxyl groups, an aryl group optionally substituted with one or a plurality of alkyl groups having 1 to 8 carbon atoms, alkoxy groups having 1 to 8 carbon atoms or halogen atoms, or a heteroaryl group optionally substituted with one or a plurality of alkyl groups having 1 to 8 carbon atoms, an alkoxy groups having 1 to 8 carbon atoms or a halogen atom,

R_2 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms,

X_1, X_2 and X_3 are independently CR_3 or a nitrogen atom, or X_1 is CR_3 or a nitrogen atom, and X_2 and X_3 together form a benzene ring, in which R_3 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms, and

R_4 represents a protective group of a carboxyl group selected from the group consisting of methyl group, ethyl group, isopropyl group, heptyl group, t-butyl group, methoxymethyl group, methylthiomethyl group, methoxyethoxymethyl group, methoxyethyl group, and benzyl group.

R_2 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms.

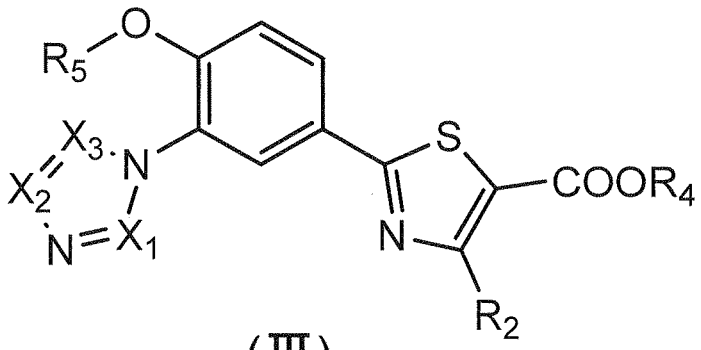
X_1, X_2 and X_3 are independently CR_3 or a nitrogen atom, or X_1 is CR_3 or a nitrogen atom, and X_2 and X_3 together form a benzene ring, in which R_3 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms.]

R_4 represents a protective group of a carboxyl group.

Further, the present ~~invention~~ disclosure relates to a compound represented by the following formula (III), which may be used as a manufacturing intermediate of a

compound represented by the above formula (I):

[Chemical Formula 4]



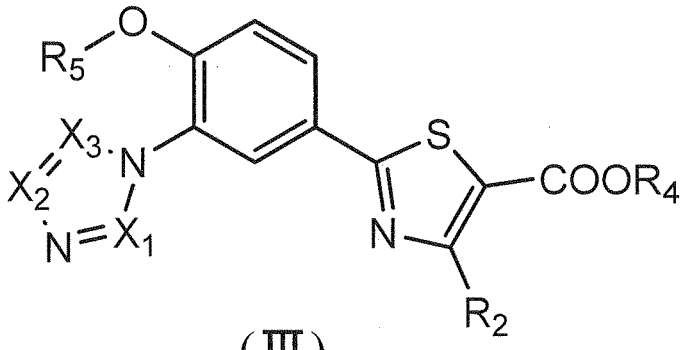
(Ⅲ)

[wherein R_2 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms. X_1, X_2 and X_3 are independently CR_3 or a nitrogen atom, or X_1 is CR_3 or a nitrogen atom, and X_2 and X_3 together form a benzene ring, in which R_3 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms.

R_4 represents a protective group of a carboxyl group.

R_5 represents a protective group of a phenolic hydroxyl group.]

The present disclosure relates to a compound represented by the formula (III):



(Ⅲ)

[wherein R_2 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms, X_1, X_2 and X_3 are independently CR_3 or a nitrogen atom, or X_1 is CR_3 or a nitrogen atom, and X_2 and X_3 together form a benzene ring, in which R_3 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms.

R_4 represents a protective group of a carboxyl group selected from the group consisting of methyl group, ethyl group, isopropyl group, heptyl group, t-butyl group, methoxymethyl group, methylthiomethyl group, methoxyethoxymethyl group, methoxyethyl group, and benzyl group, and

R_5 represents a protective group of a phenolic hydroxyl group selected from the group consisting of methyl group, isopropyl group, allyl group, t-butyl group, methoxymethyl group, methylthiomethyl group, methoxyethoxymethyl group, 1-ethoxyethyl group, benzyl group, 4-methoxybenzyl group, acetyl group, trimethylsilyl group, and t-butyldimethylsilyl group.].

[Advantages of the Invention]

The present ~~invention~~ disclosure provides a novel compound having a high xanthine oxidase inhibitory activity and a method for manufacturing the same. In addition, a product of the present ~~invention~~ disclosure is useful as a therapeutic agent or a preventive agent for diseases associated with xanthine oxidase such as gout, hyperuricemia, tumor lysis syndrome, urinary calculi, hypertension, dyslipidemia, diabetes, cardiovascular diseases such as arteriosclerosis or heart failure, kidney diseases such as diabetic nephropathy, respiratory diseases such as chronic obstructive pulmonary diseases, inflammatory bowel diseases or autoimmune diseases.

[Description of Embodiments]

XO or XOR activity of the test compound-administered animal) ×100/ XO or XOR activity of the control animal.

Liver and kidney XO activities and plasma XO activity 27 hours after compound 17, 25 and 26 administration are shown in the table below.

[Table 14]

% inhibition of tissue and Plasma XO activity
(27 hours after administration)

% of inhibition (vs. vehicle)

compound	17		25		26	
Dose (mg/kg)	1	10	1	10	1	10
Liver	≧80%	≧890%	≧80%	≧890%	≧80%	≧890%
Kidney	≧60%	≧780%	≧60%	≧780%	≧60%	≧780%
Plasma	≧25%	≧40%	≧25%	≧40%	≧25%	≧40%

Intestine, adipose tissue and vessel XOR activities 24 hours after compound 25 administration are shown in the table below.

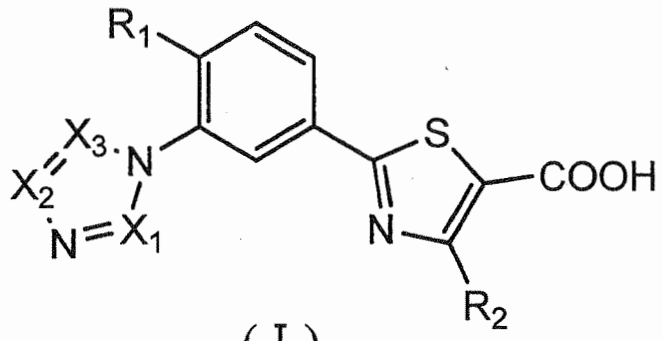
[Table 15]

[Title of the Document] Claims for the Patent

[Claim 1]

A compound represented by the formula (I) or a pharmaceutically acceptable salt thereof:

[Chemical Formula 1]



(I)

[wherein R_1 represents OR, NRR' which may form a ring or SR, in which R and R' independently represent a hydrogen atom, an alkyl group having 1 to 8 carbon atoms optionally substituted with one or a plurality of alkoxy groups having 1 to 8 carbon atoms, halogen atoms or hydroxyl groups, an aryl group optionally substituted with one or a plurality of alkyl groups having 1 to 8 carbon atoms, alkoxy groups having 1 to 8 carbon atoms or halogen atoms, or a heteroaryl group optionally substituted with one or a plurality of alkyl groups having 1 to 8 carbon atoms, an alkoxy groups having 1 to 8 carbon atoms or a halogen atom,

R_2 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms, and

X_1, X_2 and X_3 are independently CR_3 or a nitrogen atom, or X_1 is CR_3 or a nitrogen atom, and X_2 and X_3 together form a benzene ring, in which R_3 is a hydrogen atom or an alkyl group having 1 to 8 carbon atoms.]

[Claim 2]

The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein R_1 is OR.

[Claim 3]

The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein R_1 is SR.

[Claim 4]

The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein R_1 is NRR' which may form a ring.

[Claim 5]

The compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, wherein R and R' are independently an alkyl group having 1 to 8 carbon atoms optionally substituted with one or a plurality of alkoxy groups having 1 to 8 carbon atoms, halogen atoms or hydroxyl groups, or an aryl group optionally substituted with one or a plurality of alkyl groups having 1 to 8 carbon atoms, alkoxy groups having 1 to 8 carbon atoms or halogen atoms.

[Claim 6]

The compound according to claim 5 or a pharmaceutically acceptable salt thereof, wherein R and R' are independently an alkyl group having 1 to 8 carbon atoms optionally substituted with one or a plurality of alkoxy groups having 1 to 8 carbon atoms or halogen atoms or hydroxyl groups.

[Claim 7]

The compound according to claim 6 or a pharmaceutically acceptable salt thereof, wherein R_1 is OR or SR and R is an isopropyl group, a isobutyl group or a neopentyl group.

[Claim 8]

The compound according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof, wherein R_2 is a hydrogen atom or an alkyl group having 1 to 3 carbon atoms.

[Claim 9]

The compound according to claim 8 or a pharmaceutically acceptable salt thereof, wherein R_2 is a methyl group.

[Claim 10]

The compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof, wherein X_1, X_2 and X_3 are independently CR_3 or a nitrogen atom.

[Claim 11]

The compound according to claim 10 or a pharmaceutically acceptable salt thereof, wherein X_1 is a nitrogen atom, X_2 is CR_3 or nitrogen atom and X_3 is CR_3.

[Claim 12]

The compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof, wherein R_3 is a hydrogen atom.

[Claim 13]

Any one of compounds selected from the following (1) to (53) or a pharmaceutically acceptable salt thereof:

(1) 2-[3-(1H-imidazol-1-yl)-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(2) 2-[4-(2,2-dimethylpropoxy)-3-(1H-imidazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(3) 2-[4-(cyclobutylmethoxy)-3-(1H-imidazol-1-yl)phenyl]- 4-methyl-1,3-thiazole-5-carboxylic acid

(4) 2-[4-(cyclopentylmethoxy)-3-(1H-imidazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(5) 2-[4-(cyclopentyloxy)-3-(1H-imidazol-1-yl)phenyl]- 4-methyl-1,3-thiazole-5-carboxylic acid

(6) 2-[4-(cyclohexyloxy)-3-(1H-imidazol-1-yl)phenyl]- 4-methyl-1,3-thiazole-5-carboxylic acid

(7) 2-[3-(1H-imidazol-1-yl)-4-phenoxyphenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(8) 2-[4-(2-fluorophenoxy)-3-(1H-imidazol-1-yl)phenyl]- 4-methyl-1,3-thiazole-5-carboxylic acid

(9) 4-methyl-2-[3-(2-methyl-1H-imidazol-1-yl)-4-(2-methylpropoxy)phenyl]-1,3-thiazole-5-carboxylic acid

(10) 4-methyl-2-[3-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-4-(2-methylpropoxy)phenyl]-1,3-thiazole-5-carboxylic acid

(11) 2-[3-(1H-1,3-benzodiazol-1-yl)-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(12) 4-methyl-2-[3-(3-methyl-1H-1,2,4-triazol-1-yl)-4-(2-methylpropoxy)phenyl]-1,3-thiazole-5-carboxylic acid

(13) 4-methyl-2-[4-(2-methylpropoxy)-3-(1H-1,2,4-triazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid

(14) 4-methyl-2-[3-(5-methyl-1H-1,2,4-triazol-1-yl)-4-(2-methylpropoxy)phenyl]-1,3-thiazole-5-carboxylic acid

(15) 4-methyl-2-[4-phenoxy-3-(1H-1,2,4-triazol-1-yl)phenyl]- 1,3-thiazole-5-carboxylic acid

(16) 4-methyl-2-[4-(propan-2-yloxy)-3-(1H-1,2,3-triazol-1-yl)phenyl]- 1,3-thiazole-5-carboxylic acid

(17) 4-methyl-2-[4-(2-methylpropoxy)-3-(1H-1,2,3-triazol-1-yl)phenyl]- 1,3-thiazole-5-carboxylic acid

(18) 2-[4-(2,2-dimethylpropoxy)-3-(1H-1,2,3-triazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(19) 2-[4-(cyclobutylmethoxy)-3-(1H-1,2,3-triazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(20) 2-[4-(propan-2-yloxy)-3-(1H-1,2,3-triazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid

(21) 2-[4-(2-methylpropoxy)-3-(1H-1,2,3-triazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid

(22) 4-methyl-2-[4-phenoxy-3-(1H-1,2,3-triazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid

(23) 2-[4-(2-fluorophenoxy)-3-(1H-1,2,3-triazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(24) 4-methyl-2-[4-(propan-2-yloxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid

(25) 4-methyl-2-[4-(2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid

(26) 2-[4-(2,2-dimethylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(27) 2-[4-(cyclobutylmethoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(28) 2-[4-(cyclopentyloxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(29) 2-[4-(3-hydroxy-2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(30) 2-[4-(2-hydroxy-2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(31) 2-[4-(propan-2-yloxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid

(32) 2-[4-(2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid

(33) 4-methyl-2-[4-phenoxy-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid

(34) 2-[4-(2-fluorophenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(35) 2-[4-(2-methoxyphenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(36) 2-[4-(2,6-difluorophenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(37) 2-[4-(3-fluorophenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(38) 2-[4-(3-methylphenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(39) 2-[4-(2-chlorophenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(40) 2-[4-(4-fluoro-3-methylphenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(41) 2-[4-(4-fluoro-2-methylphenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(42) 2-[4-(2,4-difluorophenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(43) 2-[4-(2-fluoro-6-methoxyphenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(44) 2-[4-(2-methylphenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(45) 2-[4-(4-methylphenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(46) 2-[4-(3-fluoro-5-methylphenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(47) 2-[4-(2,5-difluorophenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-

carboxylic acid

(48) 2-[4-(2-fluoro-5-methylphenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(49) 4-methyl-2-{4-[(2-methylpropyl)sulfanyl]-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl}-1,3-thiazole-5-carboxylic acid

(50) 4-methyl-2-[4-(propan-2-ylsulfanyl)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid

(51) 4-methyl-2-{4-[(4-methylphenyl)sulfanyl]-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl}-1,3-thiazole-5-carboxylic acid

(52) 2-[4-(N,N-diethylamino)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(53) 4-methyl-2-[4-(pyrrolidine-1-yl)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole 5-carboxylic acid

[Claim 14]

A pharmaceutical composition containing a compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[Claim 15]

A xanthine oxidase inhibitor containing a compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof as an active ingredient.

[Claim 16]

A therapeutic agent or a preventive agent comprising a compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof as an active ingredient for gout, hyperuricemia, tumor lysis syndrome, urinary calculi, hypertension, dyslipidemia, diabetes, cardiovascular diseases, kidney diseases, respiratory diseases, inflammatory bowel diseases or

autoimmune diseases.

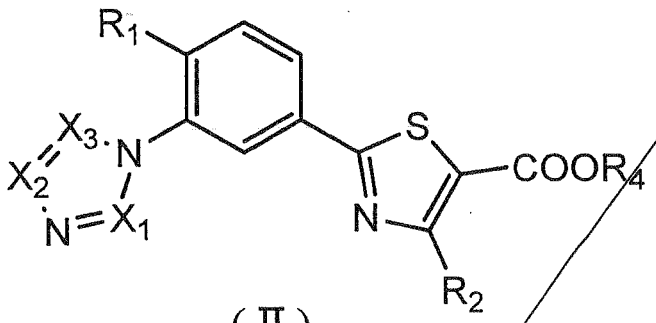
[Claim 17]

A therapeutic agent or a preventive agent for gout or hyperuricemia, which contains a compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof as an active ingredient.

[Claim 18]

A compound represented by the formula (II):

[Chemical Formula 2]



(II)

[wherein R_1 represents OR, NRR' which may form a ring, or SR, in which R and R' independently represent a hydrogen atom, an alkyl group having 1 to 8 carbon atoms optionally substituted with a one or a plurality of alkoxy groups having 1 to 8 carbon atoms, halogen atoms or hydroxyl groups, an aryl group optionally substituted with one or a plurality of alkyl groups having 1 to 8 carbon atoms, alkoxy groups having 1 to 8 carbon atoms or halogen atoms, or a heteroaryl group optionally substituted with one or a plurality of alkyl groups having 1 to 8 carbon atoms, an alkoxy groups having 1 to 8 carbon atoms or a halogen atom,

R_2 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms,

X_1, X_2 and X_3 are independently CR_3 or a nitrogen atom, or X_1 is CR_3 or a nitrogen atom, and X_2 and X_3 together form a benzene ring, in which R_3 represents a hydrogen atom or an alkyl group

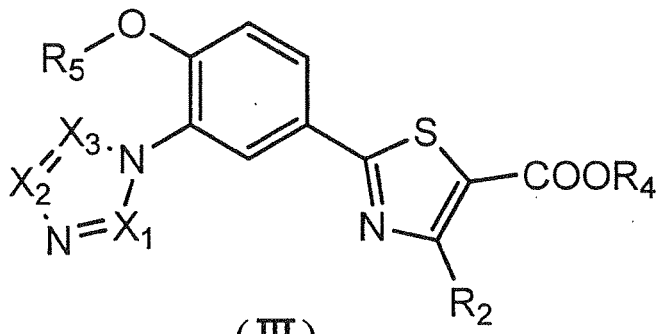
having 1 to 8 carbon atoms, and

R_4 represents a protective group of a carboxyl group.]

[Claim 19]

A compound represented by the formula (III):

[Chemical Formula 3]



(III)

[wherein R_2 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms,

X_1, X_2 and X_3 are independently CR_3 or a nitrogen atom, or X_1 is CR_3 or a nitrogen atom, and X_2 and X_3 together form a benzene ring, in which R_3 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms,

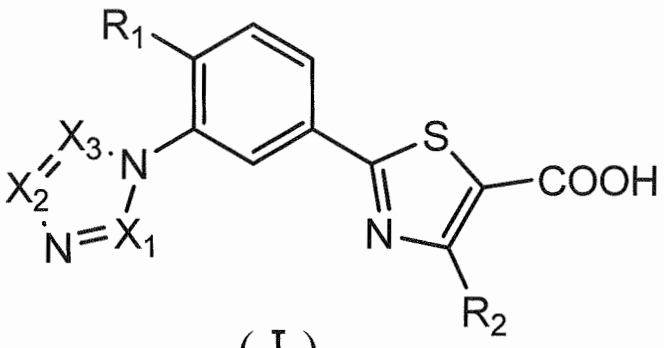
R_4 represents a protective group of a carboxyl group, and

R_5 represents a protective group of a phenolic hydroxyl group.]

[Title of the Document] Claims for the Patent

[Claim 1]

1. A compound represented by the formula (I) or a pharmaceutically acceptable salt thereof:



(I)

[wherein R_1 represents OR, NRR' which may form a ring or SR, in which the term "NRR' forms a ring" means that R and R' together with the nitrogen atom to which they are attached, to form a saturated nitrogen-containing ring, and in which R and R' independently represent a hydrogen atom, an alkyl group having 1 to 8 carbon atoms optionally substituted with one or a plurality of alkoxy groups having 1 to 8 carbon atoms, halogen atoms or hydroxyl groups, an aryl group optionally substituted with one or a plurality of alkyl groups having 1 to 8 carbon atoms, alkoxy groups having 1 to 8 carbon atoms or halogen atoms, or a heteroaryl group optionally substituted with one or a plurality of alkyl groups having 1 to 8 carbon atoms, an alkoxy groups having 1 to 8 carbon atoms or a halogen atom,

R_2 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms, and

X_1, X_2 and X_3 are independently CR_3 or a nitrogen atom, or X_1 is CR_3 or a nitrogen atom, and X_2 and X_3 together form a benzene ring, in which R_3 is a hydrogen atom or an alkyl group having 1 to 8 carbon atoms.].

2. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein R_1 is OR.

3. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein R_1 is SR.

4. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein R_1 is NRR' which may form a ring in which the term "NRR' forms a ring" means that R and R' together with the nitrogen atom to which they are attached, to form a saturated nitrogen-containing ring.

5. The compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, wherein R and R' are independently an alkyl group having 1 to 8 carbon atoms optionally substituted with one or a plurality of alkoxy groups having 1 to 8 carbon atoms, halogen atoms or hydroxyl groups, or an aryl group optionally substituted with one or a plurality of alkyl groups having 1 to 8 carbon atoms, alkoxy groups having 1 to 8 carbon atoms or halogen atoms.

6. The compound according to claim 5 or a pharmaceutically acceptable salt thereof, wherein R and R' are independently an alkyl group having 1 to 8 carbon atoms optionally substituted with one or a plurality of alkoxy groups having 1 to 8 carbon atoms or halogen atoms or hydroxyl groups.

7. The compound according to claim 6 or a pharmaceutically acceptable salt thereof, wherein R_1 is OR or SR and R is an isopropyl group, a isobutyl group or a neopentyl group.

8. The compound according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof, wherein R_2 is a hydrogen atom or an alkyl group having 1 to 3 carbon atoms.

9. The compound according to claim 8 or a pharmaceutically acceptable salt thereof, wherein R_2 is a methyl group.

10. The compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof, wherein X_1, X_2 and X_3 are independently CR_3 or a nitrogen atom.

11. The compound according to claim 10 or a pharmaceutically acceptable salt thereof, wherein X_1 is a nitrogen atom, X_2 is CR_3 or nitrogen atom and X_3 is CR_3.

12. The compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof, wherein R_3 is a hydrogen atom.

13. Any one of compounds selected from the following (1) to (53) or a pharmaceutically acceptable salt thereof:

(1) 2-[3-(1H-imidazol-1-yl)-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(2) 2-[4-(2,2-dimethylpropoxy)-3-(1H-imidazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(3) 2-[4-(cyclobutylmethoxy)-3-(1H-imidazol-1-yl)phenyl]- 4-methyl-1,3-thiazole-5-carboxylic acid

(4) 2-[4-(cyclopentylmethoxy)-3-(1H-imidazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(5) 2-[4-(cyclopentyloxy)-3-(1H-imidazol-1-yl)phenyl]- 4-methyl-1,3-thiazole-5-carboxylic acid

(6) 2-[4-(cyclohexyloxy)-3-(1H-imidazol-1-yl)phenyl]- 4-methyl-1,3-thiazole-5-carboxylic acid

(7) 2-[3-(1H-imidazol-1-yl)-4-phenoxyphenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(8) 2-[4-(2-fluorophenoxy)-3-(1H-imidazol-1-yl)phenyl]- 4-methyl-1,3-thiazole-5-carboxylic acid

(9) 4-methyl-2-[3-(2-methyl-1H-imidazol-1-yl)-4-(2-methylpropoxy)phenyl]-1,3-thiazole-5- carboxylic acid

(10) 4-methyl-2-[3-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-4-(2-methylpropoxy)phenyl]-1,3-thiazole-5-carboxylic acid

(11) 2-[3-(1H-1,3-benzodiazol-1-yl)-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5- carboxylic acid

(12) 4-methyl-2-[3-(3-methyl-1H-1,2,4-triazol-1-yl)-4-(2-methylpropoxy)phenyl]-1,3-

thiazole-5- carboxylic acid

(13) 4-methyl-2-[4-(2-methylpropoxy)-3-(1H-1,2,4-triazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid

(14) 4-methyl-2-[3-(5-methyl-1H-1,2,4-triazol-1-yl)-4-(2-methylpropoxy)phenyl]-1,3-thiazole-5- carboxylic acid

(15) 4-methyl-2-[4-phenoxy-3-(1H-1,2,4-triazol-1-yl)phenyl]- 1,3-thiazole-5-carboxylic acid

(16) 4-methyl-2-[4-(propan-2-yloxy)-3-(1H-1,2,3-triazol-1-yl)phenyl]- 1,3-thiazole-5-carboxylic acid

(17) 4-methyl-2-[4-(2-methylpropoxy)-3-(1H-1,2,3-triazol-1-yl)phenyl]- 1,3-thiazole-5-carboxylic acid

(18) 2-[4-(2,2-dimethylpropoxy)-3-(1H-1,2,3-triazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5- carboxylic acid

(19) 2-[4-(cyclobutylmethoxy)-3-(1H-1,2,3-triazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(20) 2-[4-(propan-2-yloxy)-3-(1H-1,2,3-triazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid

(21) 2-[4-(2-methylpropoxy)-3-(1H-1,2,3-triazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid

(22) 4-methyl-2-[4-phenoxy-3-(1H-1,2,3-triazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid

(23) 2-[4-(2-fluorophenoxy)-3-(1H-1,2,3-triazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(24) 4-methyl-2-[4-(propan-2-yloxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid

(25) 4-methyl-2-[4-(2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5- carboxylic acid

(26) 2-[4-(2,2-dimethylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5- carboxylic acid

(27) 2-[4-(cyclobutylmethoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5- carboxylic acid

(28) 2-[4-(cyclopentyloxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(29) 2-[4-(3-hydroxy-2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3- thiazole-5-carboxylic acid

(30) 2-[4-(2-hydroxy-2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3- thiazole-5-carboxylic acid

(31) 2-[4-(propan-2-yloxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid

(32) 2-[4-(2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid

(33) 4-methyl-2-[4-phenoxy-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid

(34) 2-[4-(2-fluorophenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(35) 2-[4-(2-methoxyphenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5- carboxylic acid

(36) 2-[4-(2,6-difluorophenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5- carboxylic acid

(37) 2-[4-(3-fluorophenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(38) 2-[4-(3-methylphenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5- carboxylic acid

(39) 2-[4-(2-chlorophenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5- carboxylic acid

(40) 2-[4-(4-fluoro-3-methylphenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(41) 2-[4-(4-fluoro-2-methylphenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(42) 2-[4-(2,4-difluorophenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5- carboxylic acid

(43) 2-[4-(2-fluoro-6-methoxyphenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-

1,3- thiazole-5-carboxylic acid

(44) 2-[4-(2-methylphenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5- carboxylic acid

(45) 2-[4-(4-methylphenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5- carboxylic acid

(46) 2-[4-(3-fluoro-5-methylphenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(47) 2-[4-(2,5-difluorophenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5- carboxylic acid

(48) 2-[4-(2-fluoro-5-methylphenoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

(49) 4-methyl-2-{4-[(2-methylpropyl)sulfanyl]-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl}-1,3-thiazole-5-carboxylic acid

(50) 4-methyl-2-[4-(propan-2-ylsulfanyl)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5- carboxylic acid

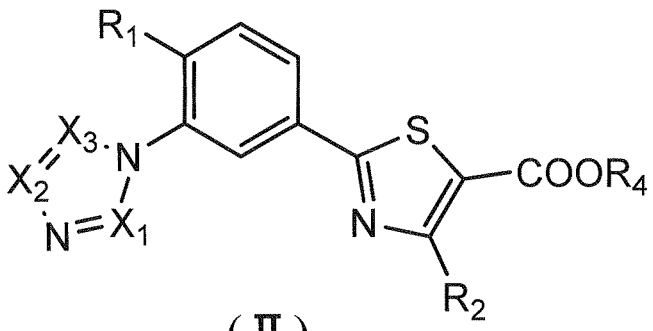
(51) 4-methyl-2-{4-[(4-methylphenyl)sulfanyl]-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl}-1,3-thiazole-5-carboxylic acid

(52) 2-[4-(N,N-diethylamino)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-4-methyl-1,3- thiazole-5-carboxylic acid

(53) 4-methyl-2-[4-(pyrrolidine-1-yl)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole 5-carboxylic acid.

14. A pharmaceutical composition containing a compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

15. A compound represented by the formula (II):



(Ⅱ)

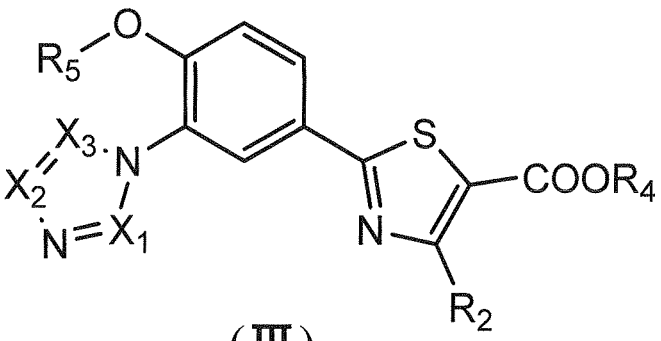
[wherein R_1 represents OR, NRR' which may form a ring, or SR, in which the term "NRR' forms a ring" means that R and R' together with the nitrogen atom to which they are attached, to form a saturated nitrogen-containing ring, and in which R and R' independently represent a hydrogen atom, an alkyl group having 1 to 8 carbon atoms optionally substituted with a one or a plurality of alkoxy groups having 1 to 8 carbon atoms, halogen atoms or hydroxyl groups, an aryl group optionally substituted with one or a plurality of alkyl groups having 1 to 8 carbon atoms, alkoxy groups having 1 to 8 carbon atoms or halogen atoms, or a heteroaryl group optionally substituted with one or a plurality of alkyl groups having 1 to 8 carbon atoms, an alkoxy groups having 1 to 8 carbon atoms or a halogen atom,

R_2 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms,

X_1, X_2 and X_3 are independently CR_3 or a nitrogen atom, or X_1 is CR_3 or a nitrogen atom, and X_2 and X_3 together form a benzene ring, in which R_3 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms, and

R_4 represents a protective group of a carboxyl group selected from the group consisting of methyl group, ethyl group, isopropyl group, heptyl group, t-butyl group, methoxymethyl group, methylthiomethyl group, methoxyethoxymethyl group, methoxyethyl group, and benzyl group.].

16. A compound represented by the formula (III):



(Ⅲ)

[wherein R_2 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms, X_1, X_2 and X_3 are independently CR_3 or a nitrogen atom, or X_1 is CR_3 or a nitrogen atom, and X_2 and X_3 together form a benzene ring, in which R_3 represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms,

R_4 represents a protective group of a carboxyl group selected from the group consisting of methyl group, ethyl group, isopropyl group, heptyl group, t-butyl group, methoxymethyl group, methylthiomethyl group, methoxyethoxymethyl group, methoxyethyl group, and benzyl group, and

R_5 represents a protective group of a phenolic hydroxyl group selected from the group consisting of methyl group, isopropyl group, allyl group, t-butyl group, methoxymethyl group, methylthiomethyl group, methoxyethoxymethyl group, 1-ethoxyethyl group, benzyl group, 4-methoxybenzyl group, acetyl group, trimethylsilyl group, and t-butyldimethylsilyl group.].