

[Prior Art Literatures]

[Patent Literature]

[0010]

[Patent Literature 1] International Publication WO00/75113

[Patent Literature 2] JP Patent Publication (Kokai) No. 2008-013499 A

[Patent Literature 3] International Publication WO07/120980

[Patent Literature 4] International Publication WO07/124221

[Patent Literature 5] International Publication WO09/026107

[Patent Literature 6] International Publication WO09/131687

[Patent Literature 7] International Publication WO09/136995

[Patent Literature 8] International Publication WO09/145856

[Non Patent Literature]

[0011]

[Non Patent Literature 1] The Journal of Biological Chemistry, Vol. 266, pp. 15790-15796, 1991

[Non Patent Literature 2] International Journal of Hematology, Vol. 75, No. 4, pp. 357-362, 2002

[Non Patent Literature 3] The Journal of Biological Chemistry, Vol. 270, pp. 16189-16197, 1995

[Non Patent Literature 4] The Journal of Immunology, Vol. 167, No. 11, pp. 6292-6302, 2001

[Non Patent Literature 5] Expert Opinion on Investigational Drugs, Vol. 13, No. 7, pp. 743-762, 2004

[Non Patent Literature 6] Expert Opinion on Therapeutic Targets, Vol. 9, No. 5, pp. 901-921, 2005

[Non Patent Literature 7] IDrugs, Vol. 12, No. 3, pp. 174-185, 2009

~~[Summary of Invention]~~

~~[Problem to be solved by the Invention]~~

[0012]

To date, various Syk inhibitors have been reported, but they have not been placed on the market yet. It has been desired to develop a compound and a pharmaceutical composition, which have excellent Syk-inhibitory activity.

[Means for Solution to Problem]

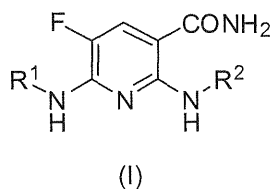
[0013]

As a result of intensive studies directed towards achieving the

aforementioned object, the present inventors have found that a nicotinamide derivative having a specific structure or a salt thereof has excellent Syk-inhibitory activity, thereby completing the present ~~invention~~disclosure.

Specifically, the nicotinamide derivative of the present ~~invention~~disclosure or a pharmaceutically acceptable salt thereof is characterized in that it is represented by the following formula (I):

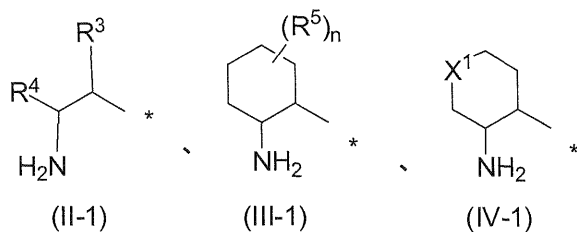
[Formula 1]



wherein

R¹ is a substituent represented by the following formula (II-1), (III-1), or (IV-1):

[Formula 2]



(wherein

R³ represents a hydrogen atom or a C₁₋₆ alkyl, C₃₋₈ cycloalkyl, phenyl, pyridyl, or thienyl group, each of which optionally has at least one substituent,

R⁴ represents a hydrogen atom, a C₁₋₆ alkyl group, or a C₃₋₈ cycloalkyl group,

R⁵ represents a hydroxy group, a halogen atom, or a C₁₋₆ alkyl or C₁₋₆ alkoxy group, each of which optionally has at least one substituent,

n is an integer of 0-2,

R⁵ may be the same or different, and two R⁵s may, together with the carbon atom to which they bind, form a C₃₋₈ cycloalkane ring when n is 2,

X¹ represents an oxygen atom or -N(R⁶)- (wherein R⁶ represents a hydrogen atom or an acyl group),

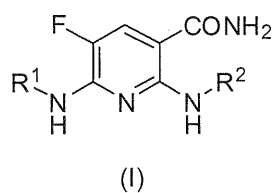
"*" represents a binding site), and

R² represents a pyridyl, indazolyl, phenyl, pyrazolopyridyl, benzisoxazolyl, pyrimidinyl, or quinolyl group, each of which optionally has at least one substituent.

[0014]

In one aspect, there is provided a nicotinamide derivative represented by the following formula (I) or a salt thereof:

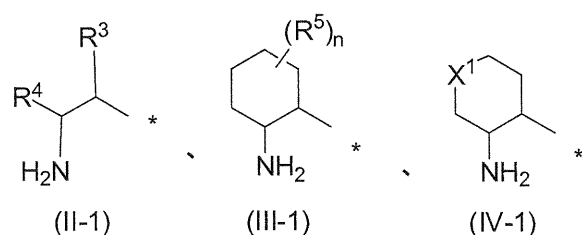
[Formula 1]



wherein

R¹ is a substituent represented by the following formula (II-1), (III-1), or (IV-1):

[Formula 2]



(wherein

R³ represents a hydrogen atom, or a C₁₋₆ alkyl, C₃₋₈ cycloalkyl, phenyl, pyridyl or thienyl group, each of which optionally has at least one substituent,

R⁴ represents a hydrogen atom, C₁₋₆ alkyl group, or C₃₋₈ cycloalkyl group,

R⁵ represents a hydroxy group, a halogen atom, or a C₁₋₆ alkyl or C₁₋₆ alkoxy group, each of which optionally has at least one substituent,

n represents an integer of 0-2,

when n is 2, R⁵ may be the same or different, and two R⁵s may, together with a carbon atom to which they bind, form a C₃₋₈ cycloalkane ring,

X¹ represents an oxygen atom or -N(R⁶)- (wherein R⁶ represents a hydrogen atom or acyl group, and

"*" represents a binding site)), and

R² represents a pyridyl, indazolyl, phenyl, pyrazolopyridyl, benzisoxazolyl, pyrimidinyl, or quinolyl group, each of which optionally has at least one substituent.

[0014a]

~~In addition, the present invention provides~~ In another aspect, there is provided a pharmaceutical composition comprising the ~~above-described~~ nicotinamide derivative or a salt thereof, ~~particularly, as defined above.~~ In another aspect, there is provided a pharmaceutical composition for use in the ~~as defined above, which is used for treatment of a Syk-related diseases, which comprises the above-described nicotinamide derivative or a salt thereof, and.~~ In another aspect, there is provided a pharmaceutical composition as defined above, which is used for use in the treatment of a disease selected from the group consisting of rheumatoid arthritis and idiopathic thrombocytopenic purpura, ~~which comprises the above-described nicotinamide derivative or a salt thereof.~~

[0015]

From a further viewpoint, the present ~~invention~~ disclosure provides: use of the above-described nicotinamide derivative or a salt thereof for production of the above-described pharmaceutical composition; a method for treating a Syk-related disease, which comprises a step of administering a therapeutically effective amount of the above-described nicotinamide derivative or a salt thereof to mammals including a human; and a method for treating a disease selected from the group consisting of rheumatoid arthritis and idiopathic thrombocytopenic purpura, which comprises a step of administering a therapeutically effective amount of the above-described nicotinamide derivative or a salt thereof to mammals including a human.

[Advantageous Effects of Invention]

[0016]

The nicotinamide derivative of the present ~~invention~~ disclosure or a salt thereof has excellent Syk-inhibitory activity, and it is useful as a pharmaceutical composition for use in the treatment of a Syk-related disease.

[Description of Embodiments]

[0017]

Hereinafter, the compound of the present invention will be described in detail.

It is to be noted that the following definitions are applied in the present specification, unless otherwise specified.

The term "halogen atom" is used herein to mean a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

The term "C₁₋₃ alkyl group" is used herein to mean a methyl, ethyl, propyl, or isopropyl group.

The term "C₁₋₄ alkyl group" is used herein to mean a methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, or tert-butyl group.