including Janus kinase 1, referred to as JAK1 hereinafter, JAK2, JAK3, and tyrosine kinase 2, referred to as Tyk2 hereinafter, and it is believed that a JAK1 inhibitor and a Tyk2 inhibitor are also useful for the prevention or treatment of varieties of diseases similar to a JAK3 inhibitor.

DISCLOSURE OF INVENTION

PROBLEMS TO BE RESOLVED BY THE INVENTION

According to extensive studies for the purpose of developing a novel therapeutic or preventive agent for organ transplant rejection, graft versus host reaction after transplantation, autoimmune disease and allergic disease alternative to conventional one, the inventors have found novel nitrogen-containing spiro-ring compounds with JAK3 inhibitory effect and achieved the present invention.

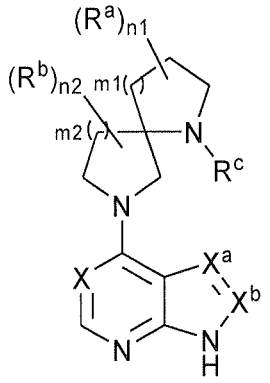
The present inventors have also found novel nitrogen-containing spiro-ring compounds with JAK2 inhibitory effect and achieved the present invention.

MEANS OF SOLVING THE PROBLEMS

Specifically, the present invention is as follows.

[1] A compound of the following general formula [I]:

~~[Chemical Formula 1]~~



[I] ,

wherein R^a is the same or different and each:

(1) C_{1-6} alkyl, or

(2) halogen atom,

n1 is an integer selected from 0 to 4,

R^b is the same or different and each:

(1) C_{1-6} alkyl, or

(2) halogen atom,

n2 is an integer selected from 0 to 4,

m1 is an integer selected from 0 to 3,

m2 is an integer selected from 1 to 4,

X^a=X^b is:

(1) CH=CH,

(2) N=CH, or

(3) CH=N,

X is:

(1) nitrogen atom, or

(2) C-R^d wherein R^d is hydrogen atom or halogen atom,

R^c is a group selected from the following (1) to (6):

(1) hydrogen atom,

(2) C_{1-6} alkyl optionally substituted by the same or different 1 to 5 substituents selected from the following Group A,

(3) -C(=O)-R^{c1},

(4) -C(=O)-O-R^{c2},

(5) -C(=O)-N$R^{c3}R^{c4}$

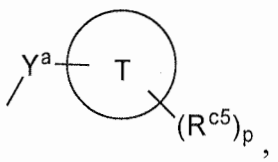
in which R^{c1}, R^{c2}, R^{c3} and R^{c4} are the same or different and each:

(i) hydrogen atom, or

(ii) C_{1-6} alkyl optionally substituted by the same or different 1 to 5 substituents selected from the following Group A, or

(6) a group of formula:

~~[Chemical Formula 2]~~



,

in which Y^a is a group selected from the following (i) to (iii):

(i) C_{1-6} alkylene,

(ii) -C(=O)-, or

(iii) -C(=O)-O-,

Ring T is:

(i) C_{6-10} aryl,

(ii) C_{3-10} cycloalkyl, or

(iii) saturated monoheterocyclyl wherein the saturated monoheterocyclyl comprises 1 to 4 heteroatoms selected from nitrogen atom, oxygen atom or sulfur atom as well as carbon atoms and the number of the constituent ring atoms is 3 to 7,

R^{c5} is the same or different and each:

(i) cyano, or

(ii) nitro,

p is an integer selected from 0 to 4,

Group A is the group consisting of:

(a) hydroxyl,

(b) C_{1-6} alkoxy,

(c) cyano,

(d) C_{1-6} alkoxycarbonyl,

(e) C_{1-6} alkylcarbonyloxy, and

(f) C_{2-6} alkenyloxy, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[2] The compound of [1], wherein, in the general formula [I], n1 is an integer selected from 0 to 2,

n2 is an integer selected from 0 to 2,

m1 is an integer selected from 0 to 3,

m2 is an integer selected from 1 to 3,

X is:

(1) nitrogen atom, or

(2) C-R^d wherein R^d is halogen atom,

R^c is a group selected from the following (1) to (6):

(1) hydrogen atom,

(2) C_{1-6} alkyl substituted by one substituent selected from the following Group A,

(3) -C(=O)-R^{c1},

(4) -C(=O)-O-R^{c2},

(5) -C(=O)-N$R^{c3}R^{c4}$

in which R^{c1} is C_{1-6} alkyl optionally substituted by one substituent selected from the following Group A,

R^{c2} is C_{1-6} alkyl,

R^{c3} is C_{1-6} alkyl optionally substituted by one substituent selected from the following Group A,

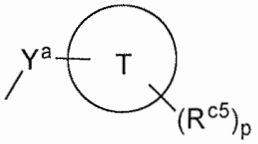
R^{c4} is

(i) hydrogen atom, or

(ii) C_{1-6} alkyl, or

(6) a group of formula:

~~[Chemical Formula 3]~~



in which Y^a is a group selected from the following (i) to (iii):

(i) C_{1-6} alkylene,

(ii) -C(=O)-, or

(iii) -C(=O)-O-,

Ring T is:

(i) phenyl,

(ii) C_{3-6} cycloalkyl, or

(iii) pyrrolidinyl,

R^{c5} is

(i) cyano, or

(ii) nitro,

p is an integer selected from 0 or 1,

Group A is the group consisting of:

(a) hydroxyl,

(b) C_{1-6} alkoxy,

(c) cyano,

(d) C_{1-6} alkoxycarbonyl,

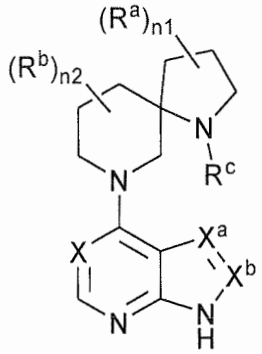
(e) C_{1-6} alkylcarbonyloxy, and

(f) C_{2-6} alkenyloxy, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[3] The compound of either one of [1] or [2], wherein m1 is an integer of 0 or 1 and m2 is an integer of 1 or 2, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[4] The compound of [3], wherein a combination of (m1,m2) is (1,2), which is a compound of the general formula [II]:

~~[Chemical Formula 4]~~



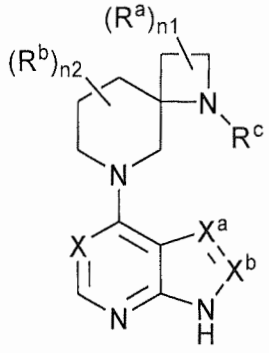
[II]

,

wherein each symbol has the same meaning as defined in [1], or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[5] The compound of [3], wherein a combination of (m1,m2) is (0,2), which is a compound of the general formula [III]:

~~[Chemical Formula 5]~~



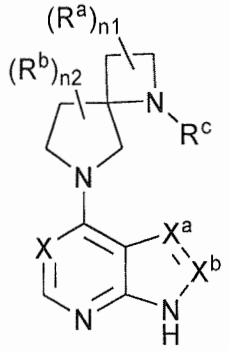
[III]

,

wherein each symbol has the same meaning as defined in [1], or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[6] The compound of [3], wherein a combination of (m1,m2) is (0,1), which is a compound of the general formula [IV]:

~~[Chemical Formula 6]~~



[IV]

,

wherein each symbol has the same meaning as defined in [1], or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[7] The compound of either one of [1] or [2], wherein a combination of (m1,m2) is selected from (0,3), (2,1), (2,2) or (3,2), or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[8] The compound of any one of [1] to [7], wherein X^a=X^b is CH=CH and X is nitrogen atom, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[9] The compound of either one of [1] or [2], wherein a combination of (n1,n2) is (0,0), or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[10] The compound of either one of [1] or [2], wherein a combination of (n1,n2) is (1,0), or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[11] The compound of either one of [1] or [2], wherein a combination of (n1,n2) is (0,1), or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[12] The compound of either one of [1] or [2], wherein a combination of (n1,n2) is (2,0), or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[13] The compound of either one of [1] or [2], wherein a combination of (n1,n2) is (0,2), or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[14] The compound of either one of [10] or [12], wherein R^a is methyl or fluorine atom, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[15] The compound of any one of [1] to [14], wherein R^c is -C(=O)-R^{c1}, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

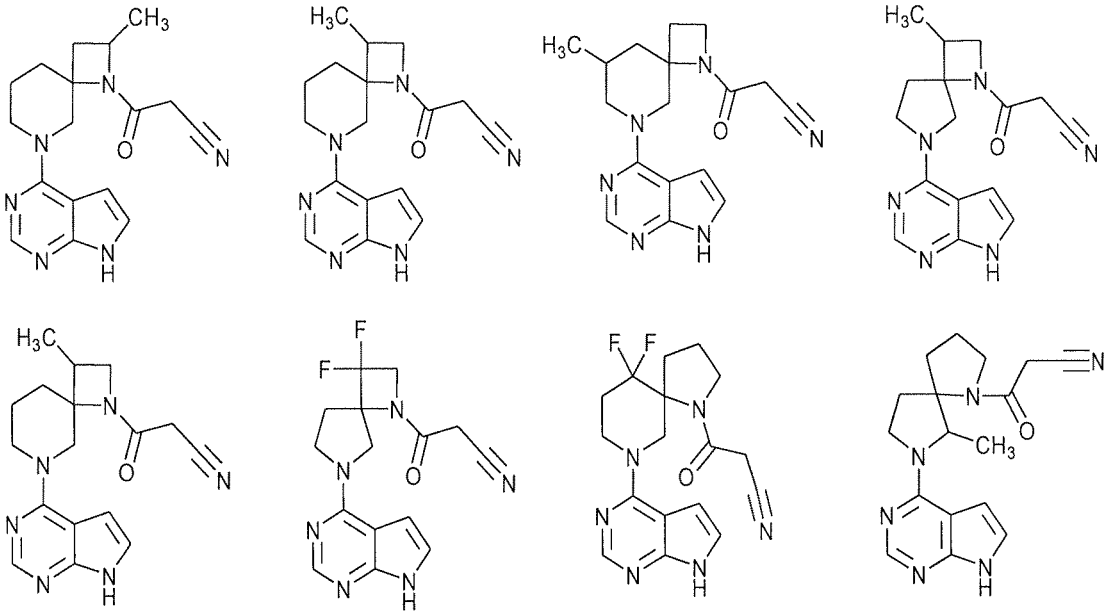
[16] The compound of [15], wherein R^{c1} is C_{1-6} alkyl substituted by one hydroxyl or cyano group, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[17] The compound of any one of [1] to [14], wherein R^c is -C(=O)-$NR^{c3}R^{c4}$, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

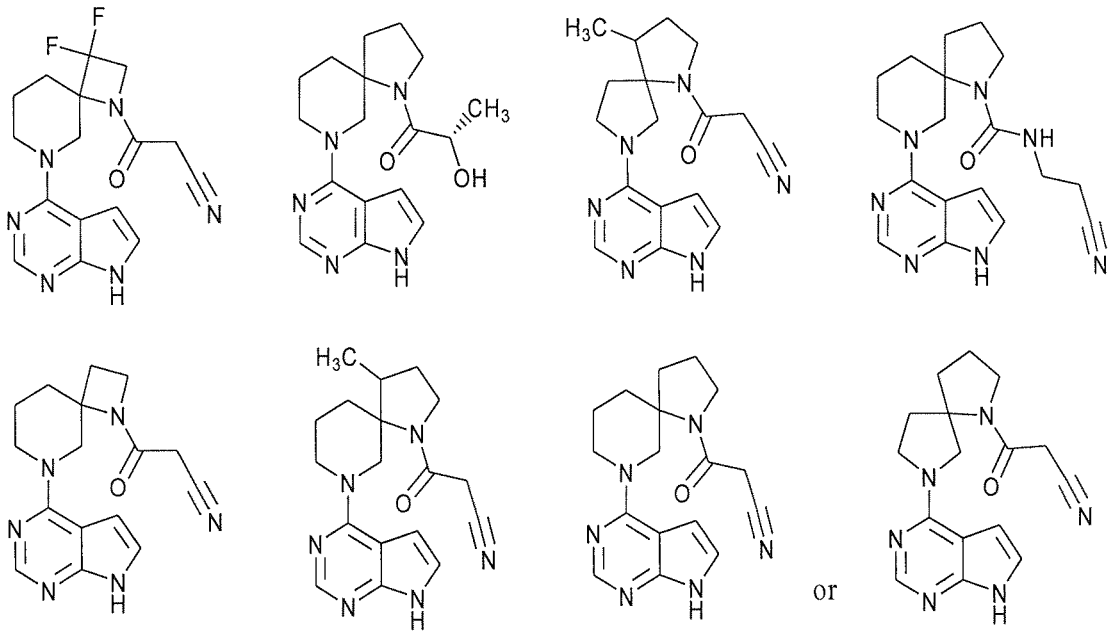
[18] The compound of [17], wherein R^{c3} is C_{1-6} alkyl substituted by one cyano group, and R^{c4} is hydrogen, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[19] The compound of [1] selected from the following chemical structural formula:

~~[Chemical Formula 7]~~

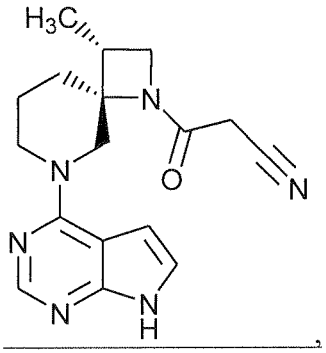


~~[Chemical Formula 8]~~



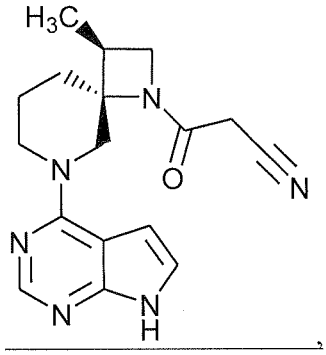
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[20] The compound of [1] represented by~~selected from~~ the following chemical structural formula:



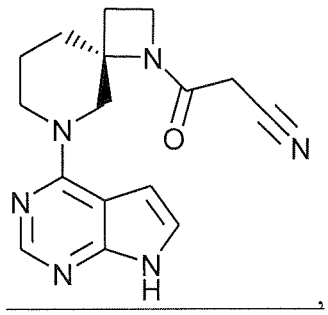
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[21] The compound of [1] represented by the following chemical structural formula:



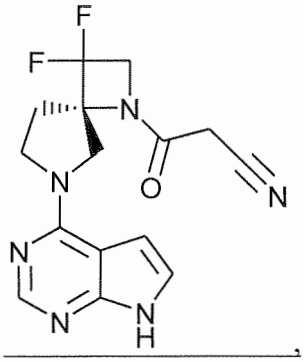
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[22] The compound of [1] represented by the following chemical structural formula:



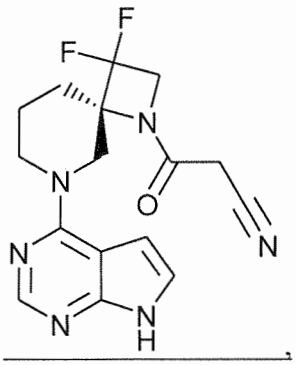
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[23] The compound of [1] represented by the following chemical structural formula:



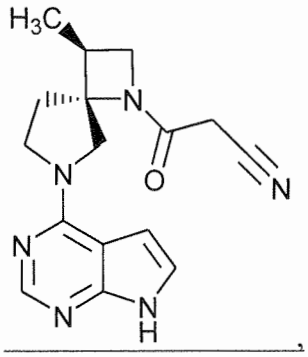
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[24] The compound of [1] represented by the following chemical structural formula:



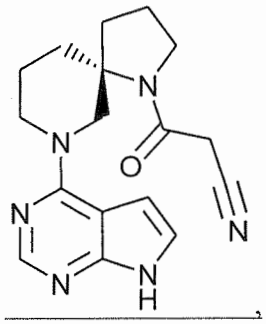
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[25] The compound of [1] represented by the following chemical structural formula:



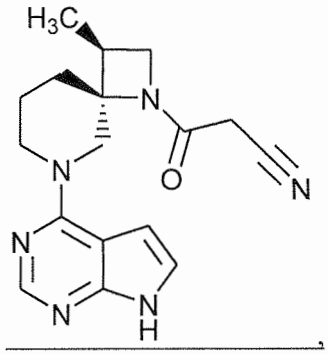
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[26] The compound of [1] represented by the following chemical structural formula:



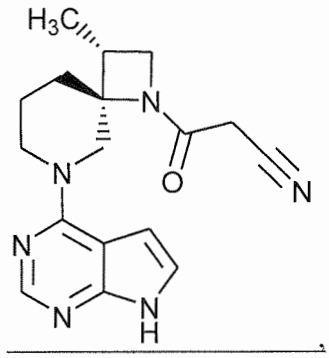
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[27] The compound of [1] represented by the following chemical structural formula:



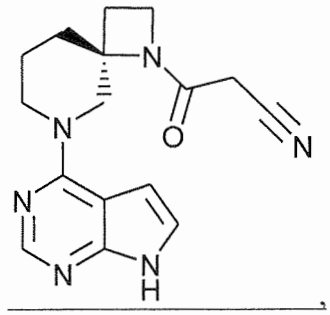
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[28] The compound of [1] represented by the following chemical structural formula:



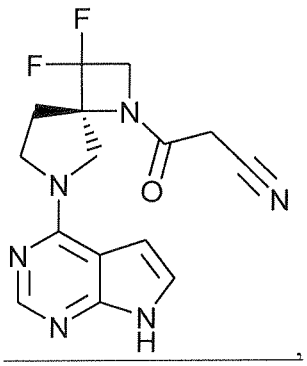
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[29] The compound of [1] represented by the following chemical structural formula:



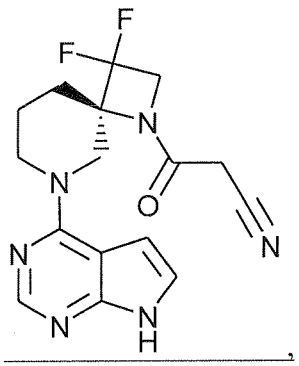
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[30] The compound of [1] represented by the following chemical structural formula:



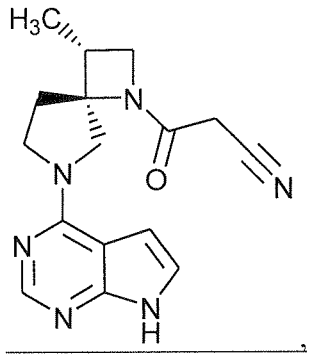
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[31] The compound of [1] represented by the following chemical structural formula:



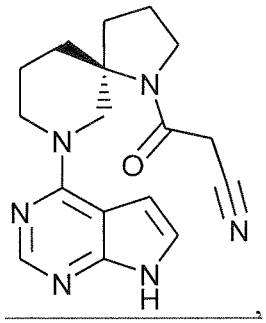
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[32] The compound of [1] represented by the following chemical structural formula:



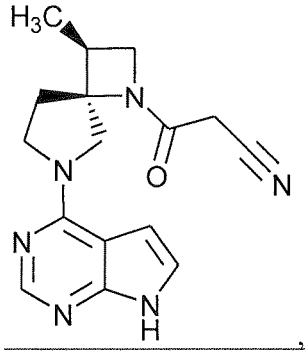
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[33] The compound of [1] represented by the following chemical structural formula:



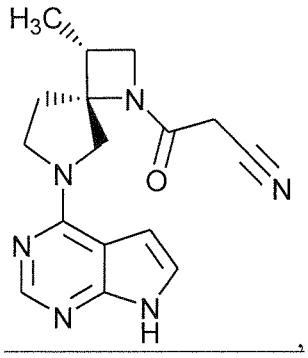
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[34] The compound of [1] represented by the following chemical structural formula:



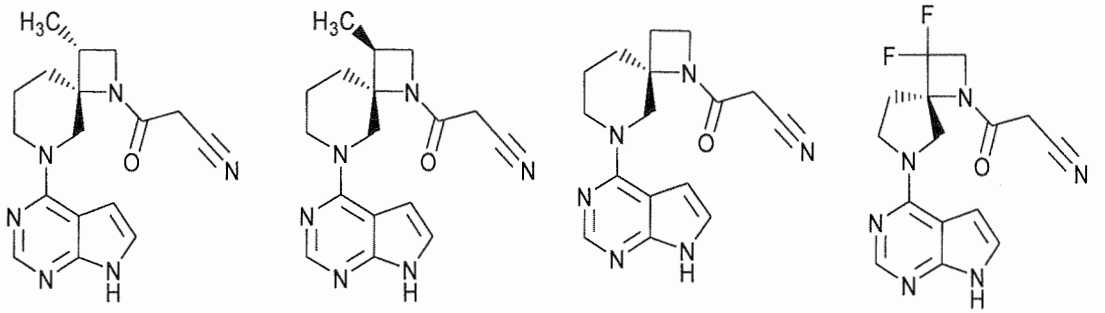
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

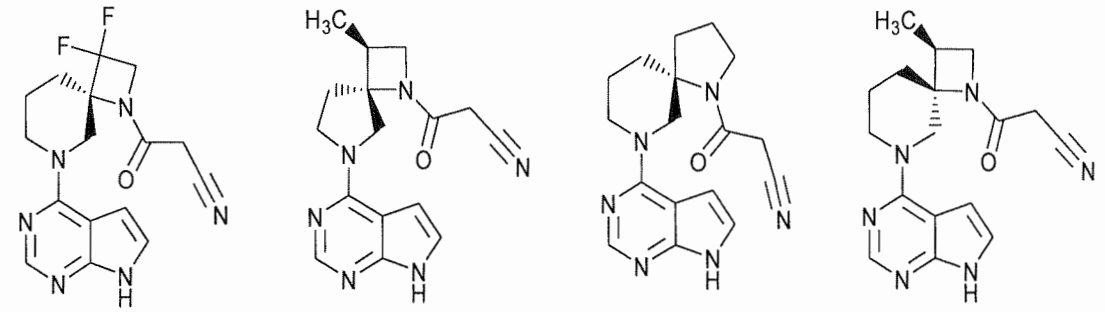
[35] The compound of [1] represented by the following chemical structural formula:



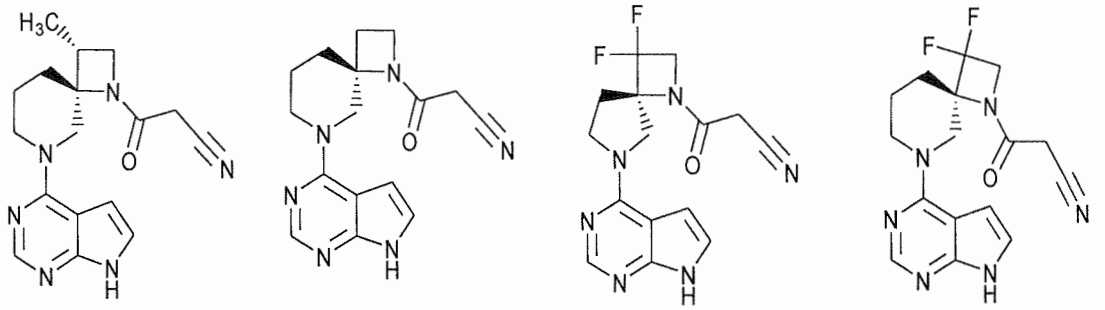
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

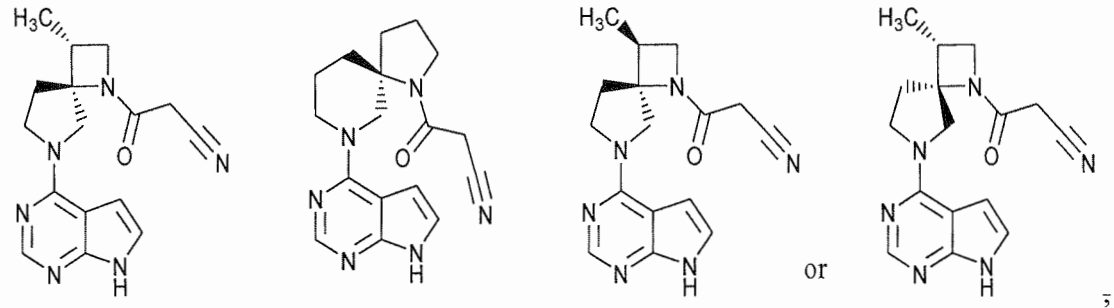
~~[Chemical Formula 9]~~





~~[Chemical Formula 10]~~




or

~~or a pharmaceutically acceptable salt thereof, or a solvate thereof.~~

[36~~21~~] A pharmaceutical composition, comprising the compound of any one of [1] to [35~~20~~] or a pharmaceutically acceptable salt thereof, or a solvate thereof, and a pharmaceutically acceptable carrier.

[37~~22~~] A Janus kinase inhibitor, comprising the compound of any one of [1] to [35~~20~~] or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[38~~23~~] The Janus kinase inhibitor of [37~~22~~], wherein the Janus kinase is Janus kinase 3.

[39~~24~~] The Janus kinase inhibitor of [37~~22~~], wherein the Janus kinase is Janus kinase 2.

[40~~25~~] A therapeutic or preventive agent for a disease selected from the group consisting of organ transplant rejection, graft versus host reaction after transplantation, autoimmune disease, allergic disease and chronic myeloproliferative disease, comprising the compound of any one of [1] to [35~~20~~] or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[41~~26~~] A therapeutic or preventive agent for rheumatoid arthritis, comprising the compound of any one of [1] to [35~~20~~] or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[42~~27~~] A therapeutic or preventive agent for psoriasis, comprising the compound of any one of [1] to [35~~20~~] or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[43] A therapeutic or preventive agent for dry eye, comprising the compound of any one of [1] to [35] or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[44] A therapeutic or preventive agent for atopic dermatitis, comprising the compound of any one of [1] to [35] or a pharmaceutically acceptable salt thereof, or a solvate thereof.

~~[28] A method for inhibiting Janus kinase, comprising administering to a mammal a pharmaceutically effective amount of the compound of any one of [1] to [20] or a pharmaceutically acceptable salt thereof, or a solvate thereof.~~

~~[29] The method of [28], wherein the Janus kinase is Janus kinase 3.~~

~~[30] The method of [28], wherein the Janus kinase is Janus kinase 2.~~

~~[31] A method for treating or preventing a disease selected from the group consisting of organ transplant rejection, graft versus host reaction after transplantation, autoimmune disease, allergic diseases and chronic myeloproliferative disease, comprising administering to a mammal a pharmaceutically effective amount of the compound of any one of [1] to [20] or a pharmaceutically acceptable salt thereof, or a solvate thereof.~~

~~[32] A method for treating or preventing rheumatoid arthritis, comprising administering to a mammal a pharmaceutically effective amount of the compound of any one of [1] to [20] or a pharmaceutically acceptable salt thereof, or a solvate thereof.~~

~~[33] A method for treating or preventing psoriasis, comprising administering to a mammal a pharmaceutically effective amount of the compound of any one of [1] to [20] or a pharmaceutically acceptable salt thereof, or a solvate thereof.~~

[45~~34~~] Use of the compound of any one of [1] to [35~~20~~] or a pharmaceutically acceptable salt thereof, or a solvate thereof in the manufacture of a Janus kinase inhibitor.

[46~~35~~] The use of [45~~34~~], wherein the Janus kinase is Janus kinase 3.

[47~~36~~] The use of [45~~34~~], wherein the Janus kinase is Janus kinase 2.

[48~~37~~] Use of the compound of any one of [1] to [35~~20~~] or a pharmaceutically acceptable salt thereof, or a solvate thereof in the manufacture of a medicament for treating or preventing a disease selected from the group consisting of organ transplant rejection, graft versus host reaction after transplantation, autoimmune disease, allergic diseases and chronic myeloproliferative disease.

[49~~38~~] Use of the compound of any one of [1] to [35~~20~~] or a pharmaceutically acceptable salt thereof, or a solvate thereof in the manufacture of a medicament for treating or preventing rheumatoid arthritis.

[50~~39~~] Use of the compound of any one of [1] to [35~~20~~] or a pharmaceutically acceptable salt thereof, or a solvate thereof in the manufacture of a medicament for treating or preventing psoriasis.

[51] Use of the compound of any one of [1] to [35] or a pharmaceutically acceptable salt thereof, or a solvate thereof in the manufacture of a medicament for treating or preventing dry eye.

[52] Use of the compound of any one of [1] to [35] or a pharmaceutically acceptable salt thereof, or a solvate thereof in the manufacture of a medicament for treating or preventing atopic dermatitis.

~~[40] A commercial kit, comprising (a) a pharmaceutical composition comprising as the active ingredient the compound of any one of [1] to [20] or a pharmaceutically acceptable salt thereof, or a solvate thereof; and (b) a drug package insert of the pharmaceutical composition which indicates that the pharmaceutical composition may be used or should be used for the treatment or prevention of rheumatoid arthritis or psoriasis.~~

~~[41] A commercial package, comprising (a) a pharmaceutical composition comprising as the active ingredient the compound of any one of [1] to [20] or a pharmaceutically acceptable salt thereof, or a solvate thereof; and (b) a drug package insert of the pharmaceutical composition which indicates that the pharmaceutical composition may be used or should be used for the treatment or prevention of rheumatoid arthritis or psoriasis.~~

EFFECT OF INVENTION

The inventive nitrogen-containing spiro-ring compound of the present application is effective as a therapeutic or preventive agent for organ transplant rejection, graft versus host reaction after transplantation, autoimmune disease and allergic disease, etc. due to its JAK3 activity-inhibition effect.

Moreover, the inventive nitrogen-containing spiro-ring compound of the present application is effective as a therapeutic or preventive agent for chronic myeloproliferative disease due to its JAK2 activity-inhibition effect.

BEST MODE FOR CARRYING OUT THE INVENTION

Terms and phrases used herein are defined as below.

The phrase "optionally substituted" includes both cases that substitutable positions are substituted and are not substituted (unsubstituted) in the subject group. The term "unsubstituted" refers to such a case that all substitutable positions are substituted by hydrogen atom in the subject group.

For example, "C_{1-6} alkyl optionally substituted by the same or different 1 to 5 substituents selected from Group A" includes both cases that substitutable positions of C_{1-6} alkyl are substituted by the same or different 1 to 5 substituents selected from Group A and not substituted (unsubstituted).

The phrase "halogen atom" includes fluorine atom, chlorine atom, bromine atom or iodine atom, preferably fluorine atom or chlorine atom.

The phrase "C_{1-6} alkyl" refers to C_{1-6} straight- or branched-chain saturated hydrocarbon, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, preferably methyl, ethyl, propyl, isopropyl, etc..

The phrase "C_{2-6} alkenyl" refers to C_{2-6} straight- or branched-chain unsaturated hydrocarbon containing one or more double bonds, e.g. vinyl, 1-methylvinyl, 1-propenyl, allyl, methylpropenyl (including 1-methyl-1-propenyl, 2-methyl-1-propenyl, etc.), 1-butenyl, 2-butenyl, 3-butenyl, methylbutenyl (including 1-methyl-1-butenyl, 2-methyl-1-butenyl, 3-methyl-1-butenyl, etc.), pentenyl, methylpentenyl, hexenyl, preferably vinyl, 1-methylvinyl, 1-propenyl, methylpropenyl, etc..

The phrase "C_{1-6} alkylene" refers to a divalent group derived from straight-chain C_{1-6} alkyl as defined above, e.g. methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, preferably methylene, ethylene, etc..

The phrase "C_{6-10} aryl" refers to C_{6-10} aromatic hydrocarbon, e.g. phenyl, 1-naphthyl, 2-naphthyl, preferably phenyl.

The phrase "C_{3-10} cycloalkyl" refers to C_{3-10} monocyclic saturated hydrocarbon, e.g.