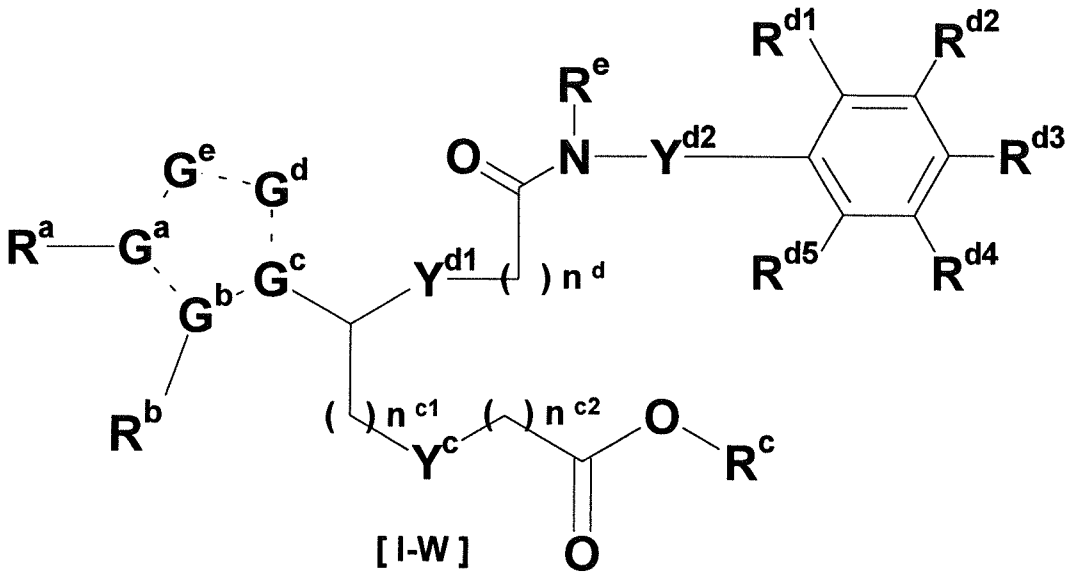
is to provide medicaments of preventing or treating autoimmune disease such as rheumatoid arthritis, psoriasis, inflammatory bowel disease such as Crohn's disease and ulcerative colitis, multiple sclerosis, systemic lupus erythematosus, ankylosing spondylitis, uveitis, polymyalgia rheumatica, and type I diabetes; allergic disease such as asthma; dry eye; fibrosis such as pulmonary fibrosis and primary biliary cirrhosis; and metabolic disease such as diabetes.

(Solution to Problem)

The present inventors have found amide compounds which are RORγ antagonists, thereby have completed the present invention.

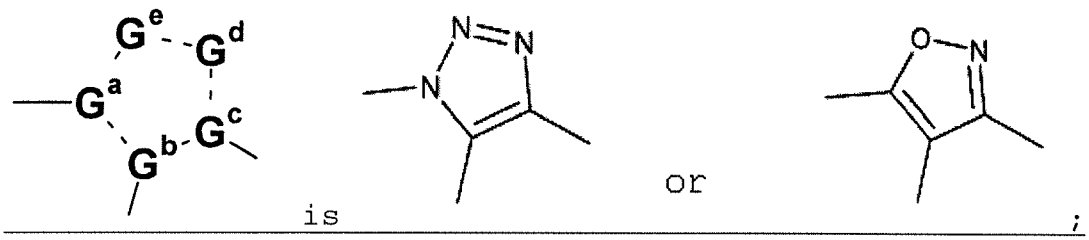
That is, the present invention provides the following aspects.

[1] A compound of formula [I-W]:



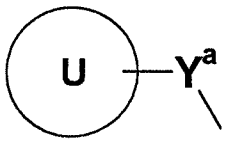
[I-W]

wherein



is ; R^a is

(1) C_{5-12} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A, or



(2) wherein

Y^a is

(i) single bond, or

(ii) C_{1-6} alkylene group,

cyclic moiety U is

(i) C_{3-7} cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(ii) C_{5-11} spirocyclic cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A, or

(iii) C_{6-10} aryl group which may be substituted with the same or different 1 to 5 substituents selected from Group A;

R^b is a group selected from the following (1) to (3):

(1) C_{1-3} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(2) C_{2-3} alkenyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(3) C_{3-7} cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A;

R^c is

(1) hydrogen atom, or

(2) C_{1-6} alkyl group;

Y^c is a group selected from the following (1) to (7):

(1) single bond,

(2) C_{1-6} alkylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(3) $-NR^{C1}-$ wherein R^{C1} is hydrogen atom or C_{1-6} alkyl group,

(4) -O-,

(5) C_{3-10} cycloalkylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(6) C_{6-10} arylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(7) thiazolylene group which may be substituted with 1 substituent selected from Group A;

Y^{d1} is

(1) single bond, or

(2) C_{1-6} alkylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A; or alternatively

both Y^{c} and Y^{d1} may be methine and be linked each other directly or via C_{1-4} alkylene group to form C_{3-7} cycloalkyl ring;

Y^{d2} is

(1) single bond, or

(2) C_{1-6} alkylene group;

R^{d1}, R^{d2}, R^{d3}, R^{d4}, and R^{d5} are the same or different group selected from the following (1) to (7):

(1) hydrogen atom

(2) halogen atom,

(3) C_{1-6} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(4) $-OR^{d10}$ wherein R^{d10} is hydrogen atom or C_{1-6} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(5) $-COOR^{d11}$ wherein R^{d11} is hydrogen atom or C_{1-6} alkyl group,

(6) C_{3-7} cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(7) cyano group, or alternatively

R^{d1} and R^{d2}, or R^{d2} and R^{d3} can be taken together to form a C_{6-10} aryl ring fused to the benzene ring to which they are all attached wherein the C_{6-10} aryl ring may be substituted with the same or different 1 to 4 substituents selected from Group A;

R^e is

(1) hydrogen atom, or

(2) C_{1-3} alkyl group, or alternatively

R^e and R^{d1}, or R^e and R^{d5} can be taken together to form C_{1-4} alkylene;

n^{c1} is an integer selected from 0 or 1 to 4,

n^{c2} is an integer selected from 0 or 1 to 3,

n^d is an integer selected from 0 or 1 to 3,

Group A is

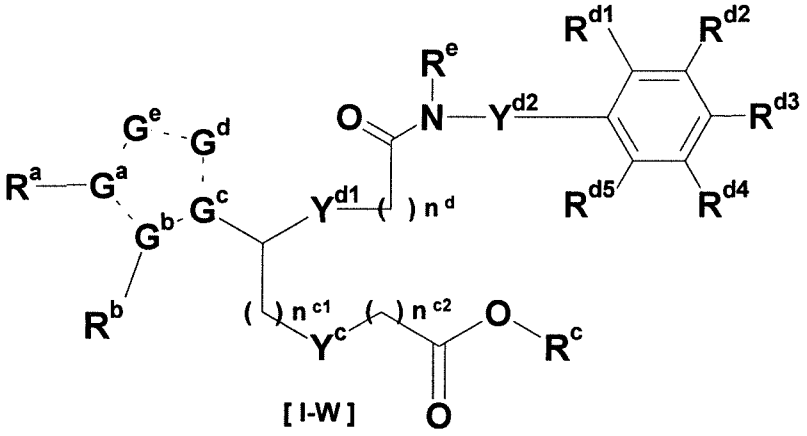
(a) C_{1-6} alkyl group,

(b) halogen atom, and

(c) $-OR^{A1}$ wherein R^{A1} is hydrogen atom or C_{1-6} alkyl group,

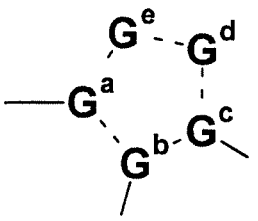
or a pharmaceutically acceptable salt thereof.

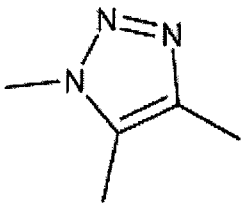
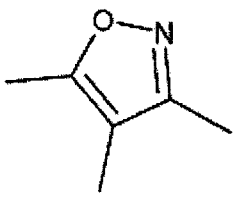
[2] The compound of formula [I-W] according to [1]:



[I-W]

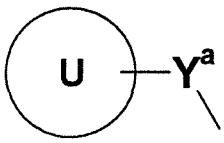
wherein



is  or ;

R^a is

(1) C_{5-12} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A, or

(2)  wherein

Y^a is

(i) single bond, or

(ii) C_{1-6} alkylene group,

cyclic moiety U is

(i) C_{3-7} cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A, or

(ii) C_{5-11} spirocyclic cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A;

R^b is a group selected from the following (1) to (3):

(1) C_{1-3} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(2) C_{2-3} alkenyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(3) C_{3-7} cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A;

R^c is

(1) hydrogen atom, or

(2) C_{1-6} alkyl group;

Y^c is a group selected from the following (1) to (7):

(1) single bond,

(2) C_{1-6} alkylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(3) $-NR^{c1}-$ wherein R^{c1} is hydrogen atom or C_{1-6} alkyl group,

(4) -O-,

(5) C_{3-10} cycloalkylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(6) C_{6-10} arylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(7) thiazolylene group which may be substituted with 1 substituent selected from Group A;

Y^{d1} is

(1) single bond, or

(2) C_{1-6} alkylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A;

Y^{d2} is

(1) single bond, or

(2) C_{1-6} alkylene group;

R^{d1}, R^{d2}, R^{d3}, R^{d4}, and R^{d5} are the same or different group selected from the following (1) to (4):

(1) hydrogen atom

(2) halogen atom,

(3) C_{1-6} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(4) $-OR^{d10}$ wherein R^{d10} is hydrogen atom or C_{1-6} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A, or alternatively

R^{d1} and R^{d2}, or R^{d2} and R^{d3} can be taken together to form a C_{6-10} aryl ring fused to the benzene ring to which they are all attached wherein the C_{6-10} aryl ring may be substituted with the same or different 1 to 4 substituents selected from Group A;

n^{c1} is an integer selected from 0 or 1 to 3,

n^{c2} is an integer selected from 0 or 1 to 3,

n^{d} is an integer selected from 0 or 1 to 3,

R^{e} is hydrogen atom,

Group A is

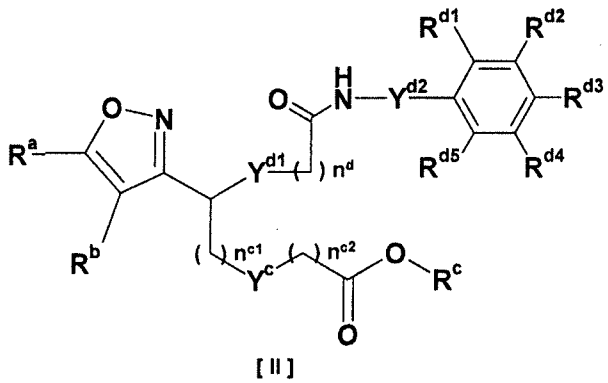
(a) C_{1-6} alkyl group,

(b) halogen atom, and

(c) $-OR^{A1}$ wherein R^{A1} is hydrogen atom or C_{1-6} alkyl group,

or a pharmaceutically acceptable salt thereof.

[3] The compound of formula [II] according to [1]:

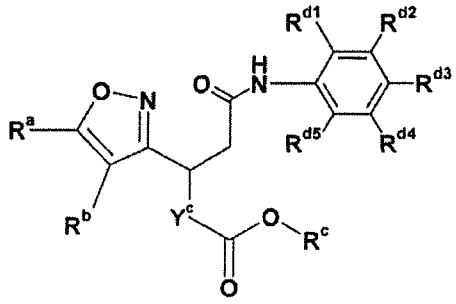


[II]

wherein each symbol is as defined in [1],

or a pharmaceutically acceptable salt thereof.

[4] The compound of formula [III] according to [3]:

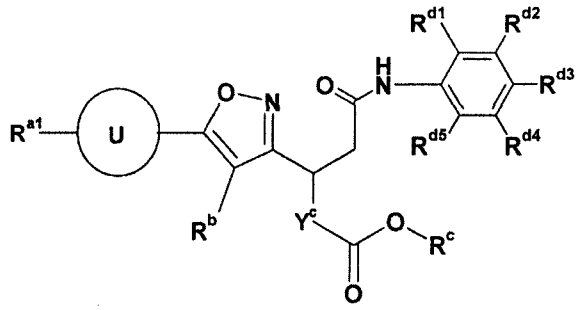


[III]

wherein each symbol is as defined in [1],

or a pharmaceutically acceptable salt thereof.

[5] The compound of formula [IV] according to [4]:

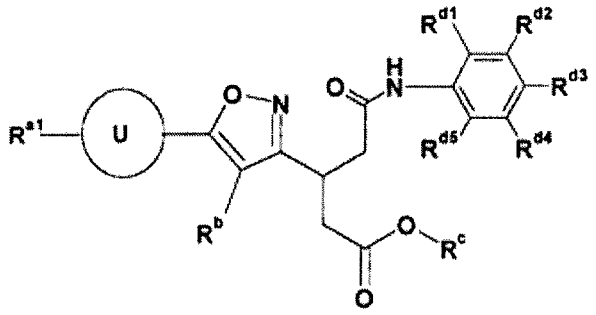


[IV]

wherein R^{a1} is C_{1-6} alkyl group, and the other symbols are as defined in [1],

or a pharmaceutically acceptable salt thereof.

[6] The compound of formula [IV-D1] according to [5]:

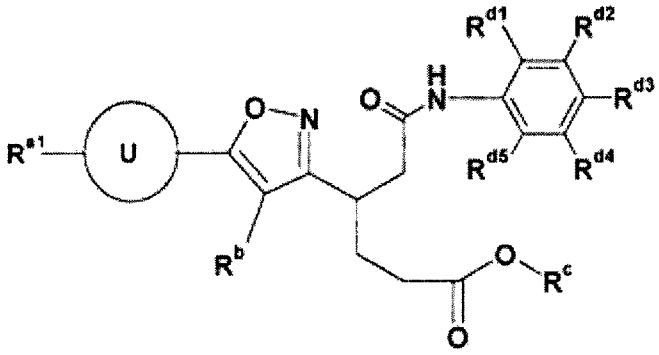


[IV-D1]

wherein R^{a1} is C_{1-6} alkyl group, and the other symbols are as defined in [1],

or a pharmaceutically acceptable salt thereof.

[7] The compound of formula [IV-D2] according to [5]:

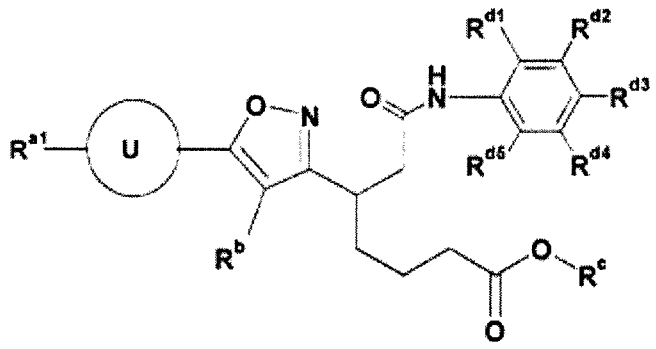


[IV-D2]

wherein R^{a1} is C_{1-6} alkyl group, and the other symbols are as defined in [1],

or a pharmaceutically acceptable salt thereof.

[8] The compound of formula [IV-D3] according to [5]:

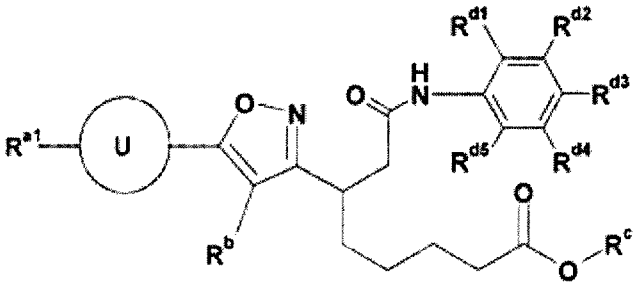


[IV-D3]

wherein R^{a1} is C_{1-6} alkyl group, and the other symbols are as defined in [1],

or a pharmaceutically acceptable salt thereof.

[9] The compound of formula [IV-D4] according to [5]:

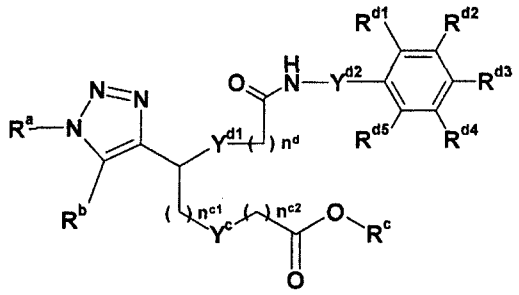


[IV-D4]

wherein R^{a1} is C_{1-6} alkyl group, and the other symbols are as defined in [1],

or a pharmaceutically acceptable salt thereof.

[10] The compound of formula [V] according to [1]:



[V]

wherein each symbol is as defined in [1],

or a pharmaceutically acceptable salt thereof.

[11] The compound according to any one of [1] to [10] wherein:

R^b is C_{3-7} cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

or a pharmaceutically acceptable salt thereof.

[12] The compound according to any one of [1] to [11] wherein:

R^b is cyclopropyl group,

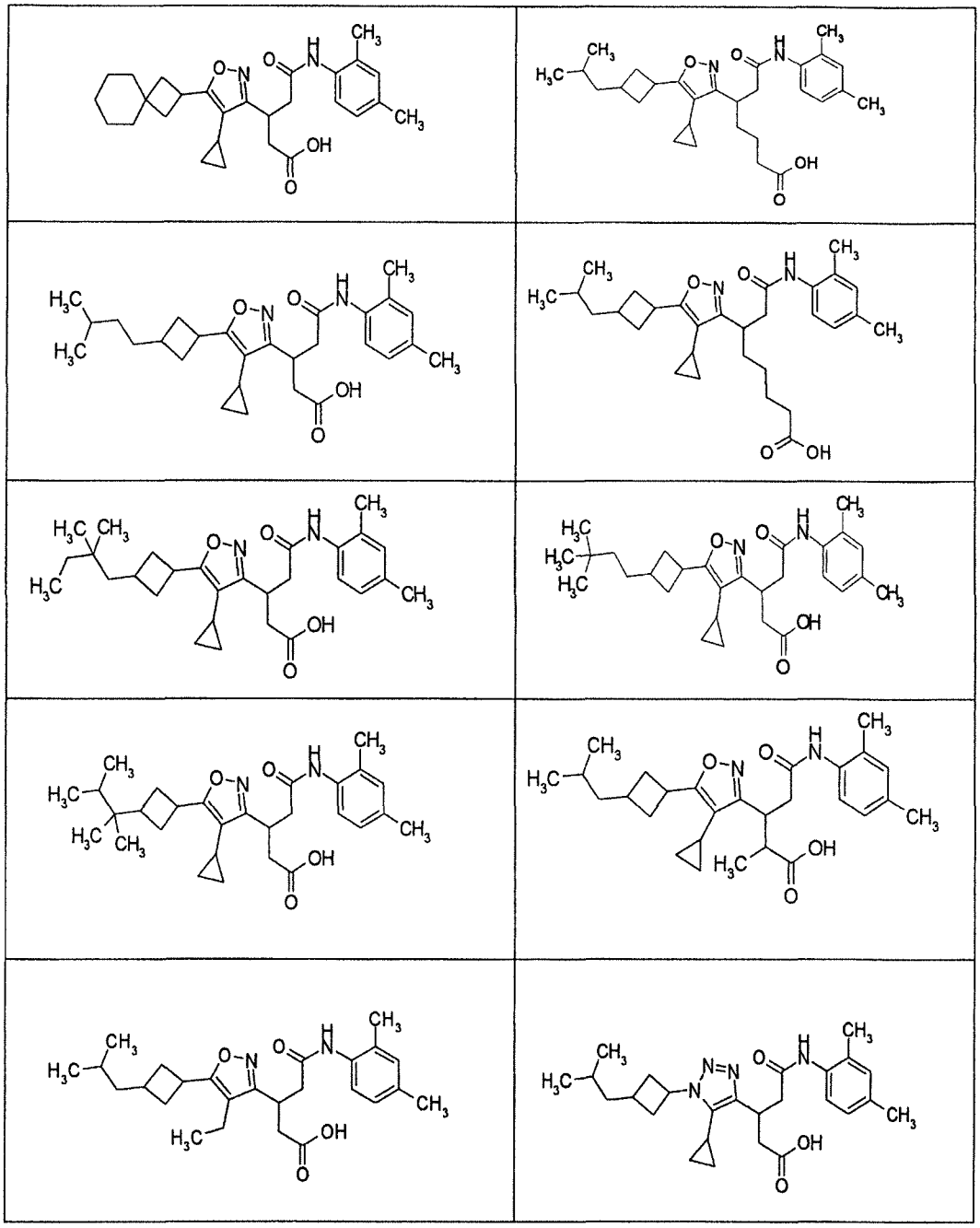
or a pharmaceutically acceptable salt thereof.

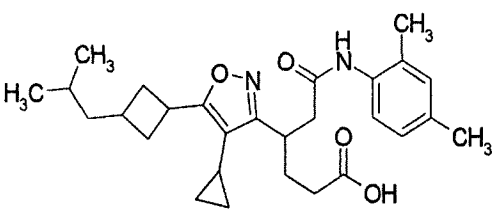
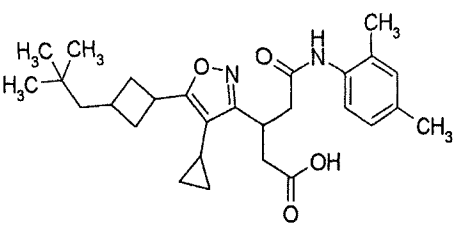
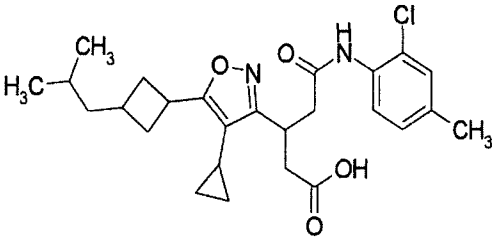
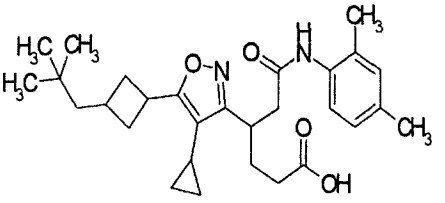
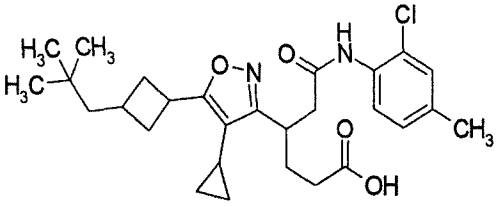
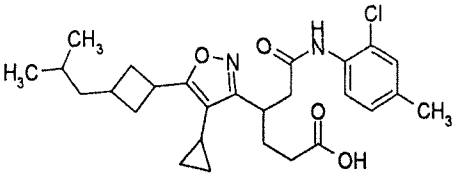
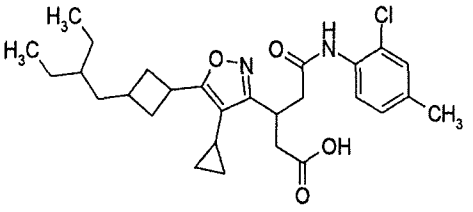
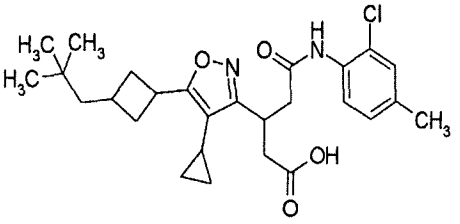
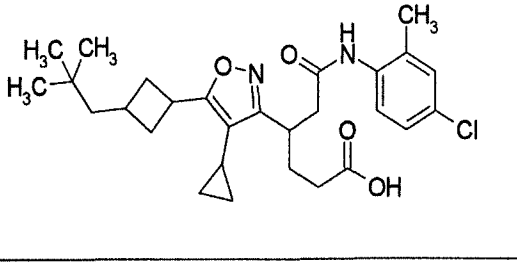
[13] The compound according to any one of [1] to [12] wherein:

the cyclic moiety U is C_{3-7} cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,
or a pharmaceutically acceptable salt thereof.

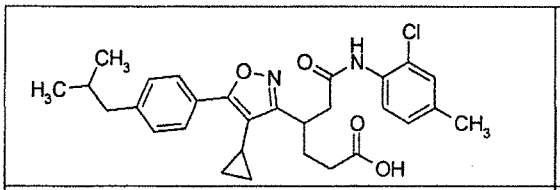
[14] The compound according to any one of [1] to [13] wherein:
the cyclic moiety U is cyclobutyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,
or a pharmaceutically acceptable salt thereof.

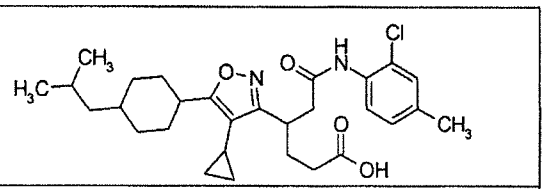
[15] The compound according to [1] or [2] which is selected from the group consisting of the following formulas, or a pharmaceutically acceptable salt thereof:

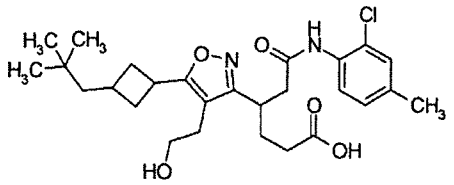


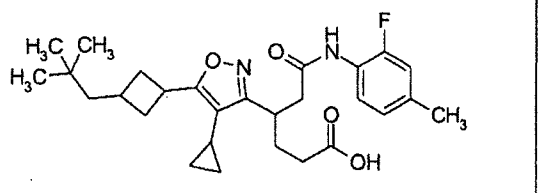
	
	
	
	
	

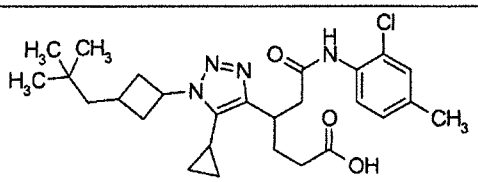
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H3C CH3 H3C O-N H N O CH3 CH3 OH O
H3C CH3 H3C O-N H N O Cl CH3 OH O
H3C CH3 H3C O-N H N O CH3 CH3 O OH
H3C CH3 H3C O-N H N O Cl CH3 O OH
H3C CH3 O-N H N O Cl CH3 O OH
H3C CH3 H3C O-N H N O Cl CH3 OH O
H3C CH3 H3C O-N H N O CH3 Cl O OH
H3C CH3 O-N H N O Cl CH3 OH O

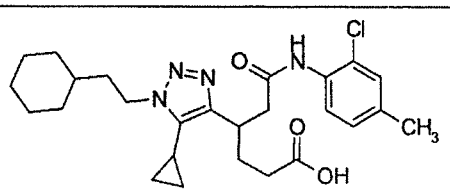


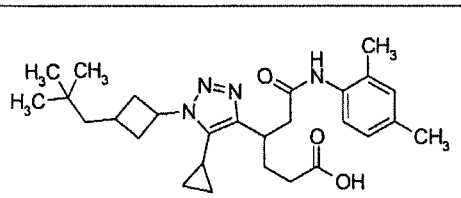


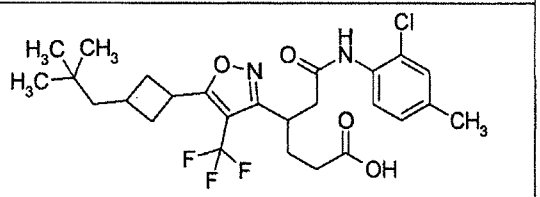


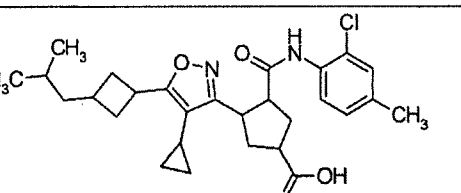


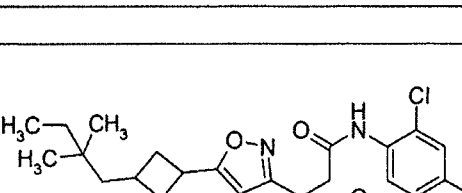


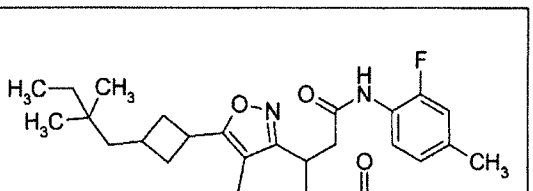


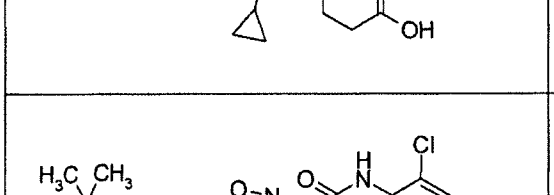




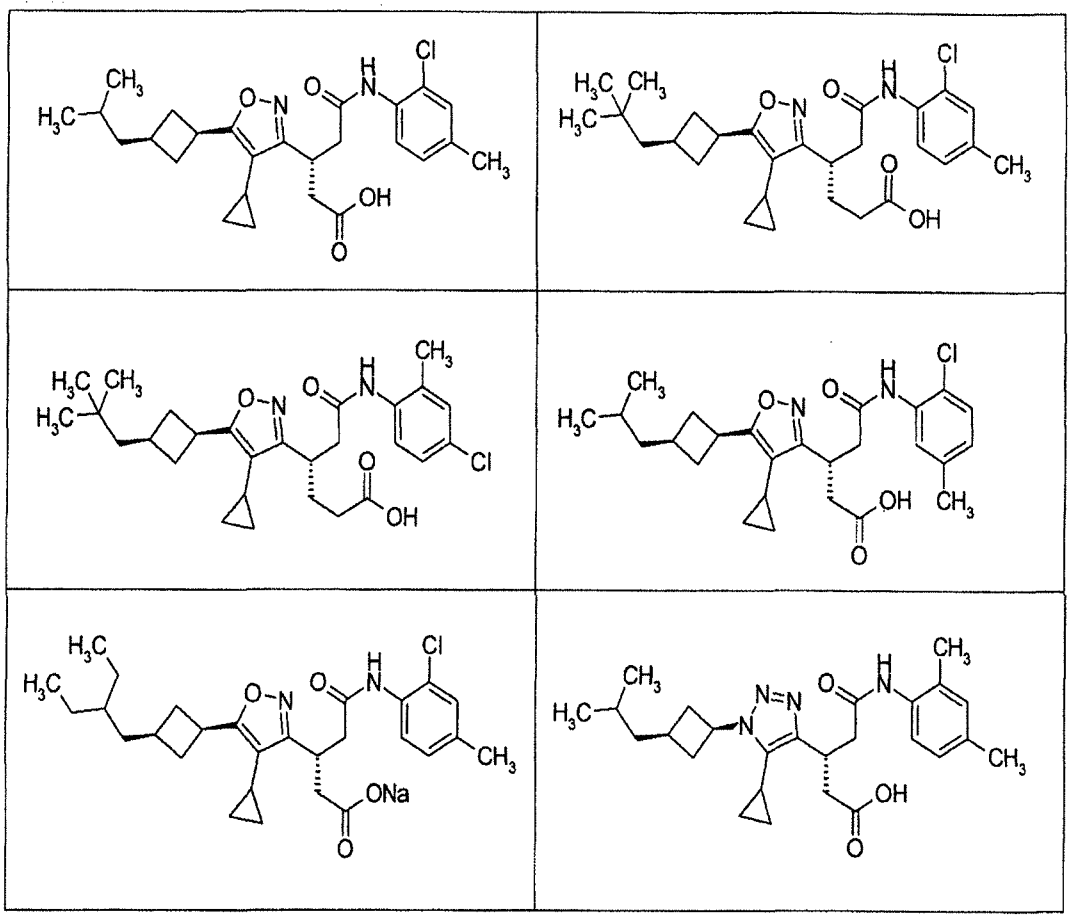




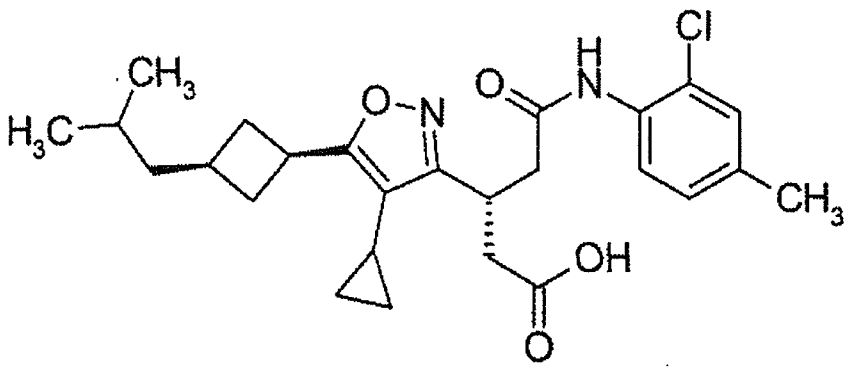




[16] The compound according to [1] or [2] which is selected from the group consisting of the following formulas, or a pharmaceutically acceptable salt thereof:

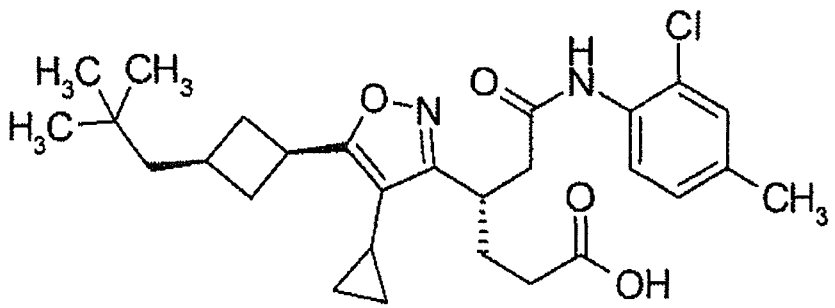


[17] The compound according to [1] or [2], which is



or a pharmaceutically acceptable salt thereof.

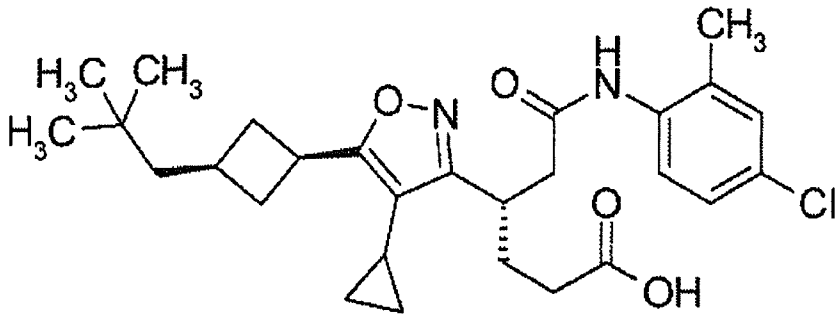
[18] The compound according to [1] or [2], which is



,

or a pharmaceutically acceptable salt thereof.

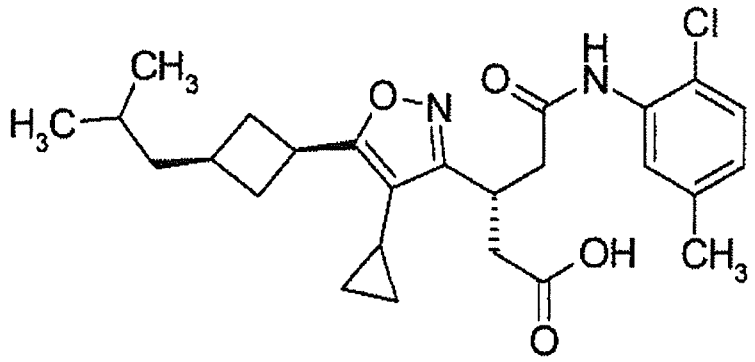
[19] The compound according to [1] or [2], which is



,

or a pharmaceutically acceptable salt thereof.

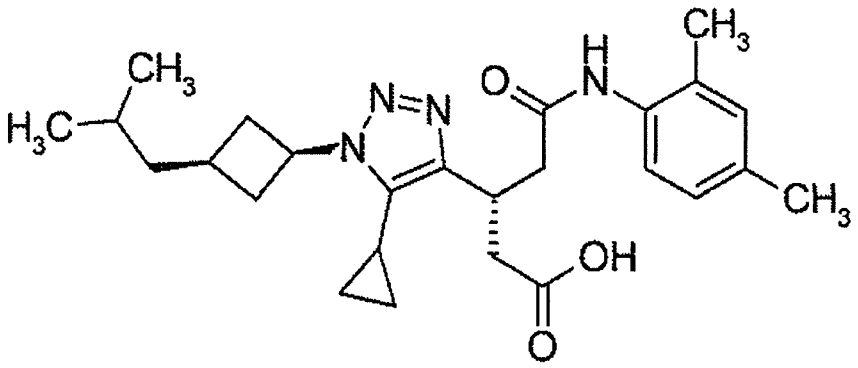
[20] The compound according to [1] or [2], which is



,

or a pharmaceutically acceptable salt thereof.

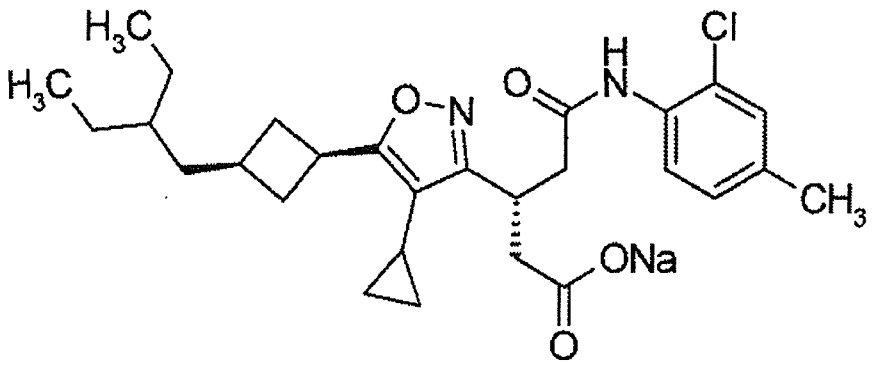
[21] The compound according to [1] or [2], which is



,

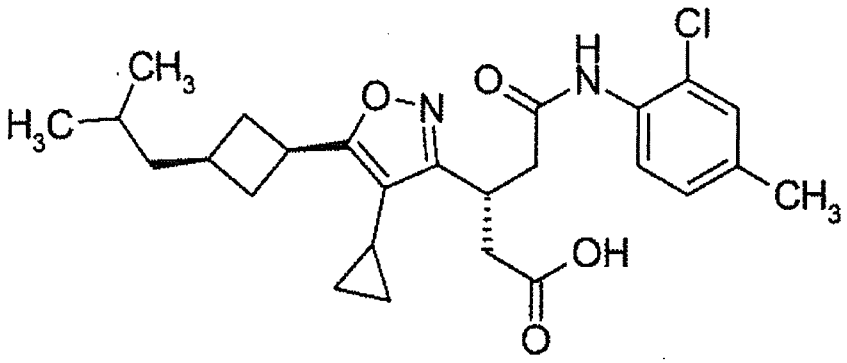
or a pharmaceutically acceptable salt thereof.

[22] The compound according to [1] or [2], which is



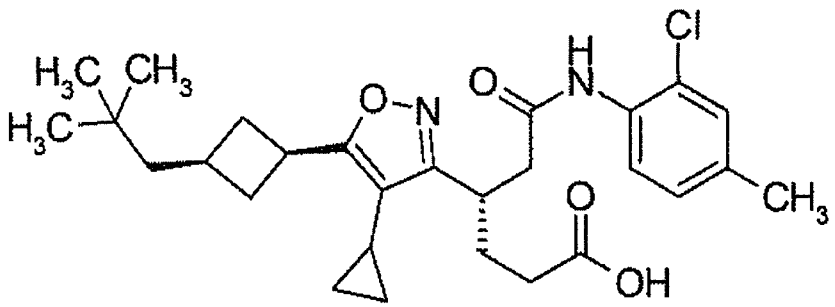
.

[23] The compound according to [1] or [2], which is



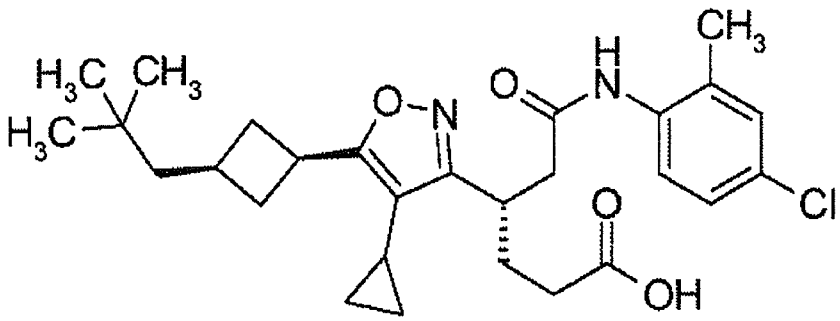
.

[24] The compound according to [1] or [2], which is



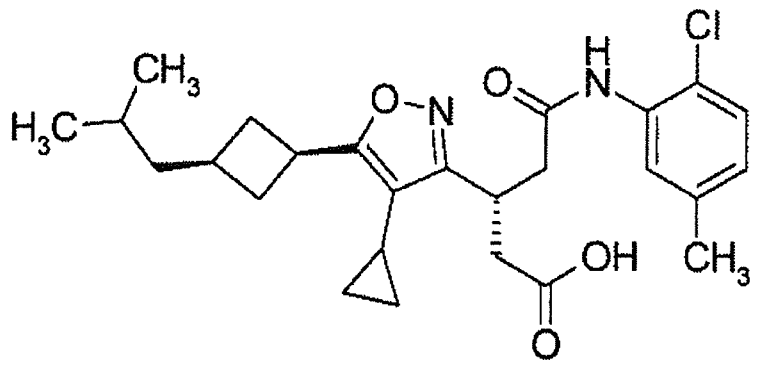
.

[25] The compound according to [1] or [2], which is



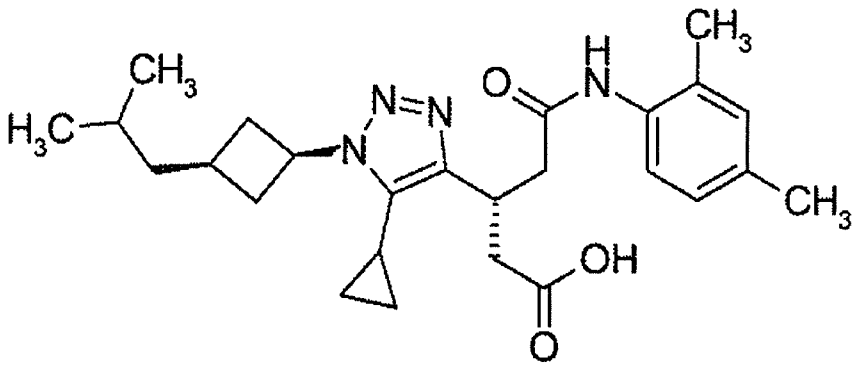
.

[26] The compound according to [1] or [2], which is



.

[27] The compound according to [1] or [2], which is



.

[28] A pharmaceutical composition comprising the compound according to any one of [1] to [27], or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[29] A RORγ antagonist comprising the compound according to any one of [1] to [27], or a pharmaceutically acceptable salt thereof.

[30] A medicament for use in treating or preventing a disease selected from the group consisting of autoimmune disease, allergic disease, dry eye, fibrosis, and metabolic disease, comprising the compound according to any one of [1] to [27], or a pharmaceutically acceptable salt thereof.

[31] The medicament for use according to [30], wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, psoriasis, inflammatory bowel disease, multiple sclerosis, systemic lupus erythematosus, ankylosing spondylitis, uveitis, polymyalgia rheumatica, and type I diabetes.

[32] The medicament for use according to [31], wherein the inflammatory bowel disease is Crohn's disease or ulcerative colitis.

[33] The medicament for use according to [30], wherein the allergic disease is asthma.

[34] The medicament for use according to [30], wherein the fibrosis is pulmonary fibrosis or primary biliary cirrhosis.

[35] The medicament for use according to [30], wherein the metabolic disease is diabetes.

[36] The medicament for use according to [35], wherein the diabetes is type I diabetes or type II diabetes.

[37] A compound, or a pharmaceutically acceptable salt thereof, according to any one of [1] to [27] for use in inhibiting RORγ in a mammal.

[38] A compound, or a pharmaceutically acceptable salt thereof, according to any one of [1] to [27] for use in treating or preventing a disease in a mammal selected from the group consisting of autoimmune disease, allergic disease, dry eye, fibrosis, and metabolic disease.

[39] The compound or the pharmaceutically acceptable salt thereof, for use according to [38], wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, psoriasis, inflammatory bowel disease, multiple sclerosis, systemic lupus erythematosus, ankylosing spondylitis, uveitis, polymyalgia rheumatica, and type I diabetes.

[40] The compound or the pharmaceutically acceptable salt thereof, for use according to [39], wherein the inflammatory bowel disease is Crohn's disease or ulcerative colitis.

[41] The compound or the pharmaceutically acceptable salt thereof, for use according to [38], wherein the allergic disease is asthma.

[42] The compound or the pharmaceutically acceptable salt thereof, for use according to [38], wherein the fibrosis is pulmonary fibrosis or primary biliary cirrhosis.

[43] The compound or the pharmaceutically acceptable salt thereof, for use according to [38], wherein the metabolic disease is diabetes.

[44] The compound or the pharmaceutically acceptable salt thereof, for use according to [43], wherein the diabetes is type I diabetes or type II diabetes.

[45] Use of the compound according to any one of [1] to [27], or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a disease selected from the group consisting of autoimmune

disease, allergic disease, dry eye, fibrosis, and metabolic disease.

[46] The use according to [45], wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, psoriasis, inflammatory bowel disease, multiple sclerosis, systemic lupus erythematosus, ankylosing spondylitis, uveitis, polymyalgia rheumatica, and type I diabetes.

[47] The use according to [46], wherein the inflammatory bowel disease is Crohn's disease or ulcerative colitis.

[48] The use according to [45], wherein the allergic disease is asthma.

[49] The use according to [45], wherein the fibrosis is pulmonary fibrosis or primary biliary cirrhosis.

[50] The use according to [45], wherein the metabolic disease is diabetes.

[51] The use according to [50], wherein the diabetes is type I diabetes or type II diabetes.

[52] Use of a compound, or a pharmaceutically acceptable salt thereof, according to any one of [1] to [27] in the manufacture of a medicament for inhibiting RORγ in a mammal.

[53] Use of a compound, or a pharmaceutically acceptable salt thereof, according to any one of [1] to [27] in the manufacture of a medicament for treating or preventing a disease in a mammal selected from the group consisting of autoimmune disease, allergic disease, dry eye, fibrosis, and metabolic disease.

[54] The use according to [53], wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, psoriasis, inflammatory bowel disease, multiple sclerosis, systemic lupus erythematosus, ankylosing spondylitis, uveitis, polymyalgia rheumatica, and type I diabetes.

[55] The use according to [54], wherein the inflammatory bowel disease is Crohn's disease or ulcerative colitis.

[56] The use according to [53], wherein the allergic disease is asthma.

[57] The use according to [53], wherein the fibrosis is pulmonary fibrosis or primary biliary cirrhosis.

[58] The use according to [53], wherein the metabolic disease is diabetes.

[59] The use according to [58], wherein the diabetes is type I diabetes or type II diabetes.

Effects of The Invention

The amide compound of the present invention can inhibit the RORγ activity, thereby the compound is effective as a medicament for treating or preventing a disease such as autoimmune disease such as rheumatoid arthritis, psoriasis, inflammatory bowel disease such as Crohn's disease and ulcerative colitis, multiple sclerosis, and systemic lupus erythematosus; allergic disease; metabolic disease; dry eye; and fibrosis.

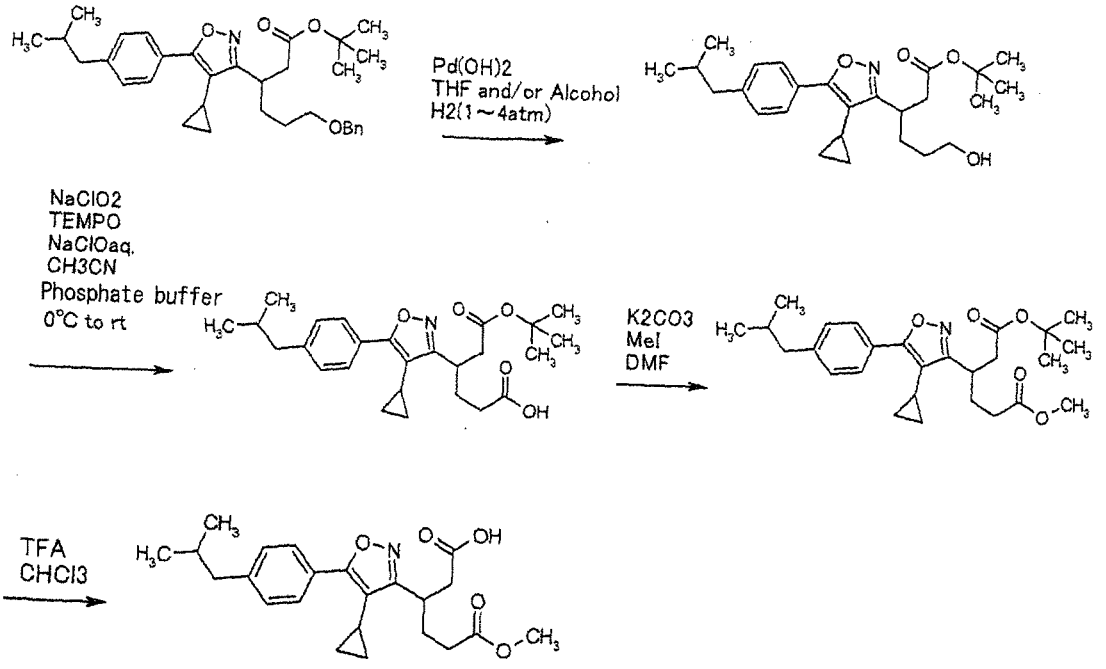
Brief Description of Drawings

[Figure 1] Structures, NMR results and the like of Examples A-1 to A-4.

[Figure 2] Structures, NMR results and the like of Examples A-5 to A-8.

Example A-6 was prepared by using L-homoserine as a material without using any chiral auxiliary reagent (AUX-H) according to the preparation methods of A-6 as described below.

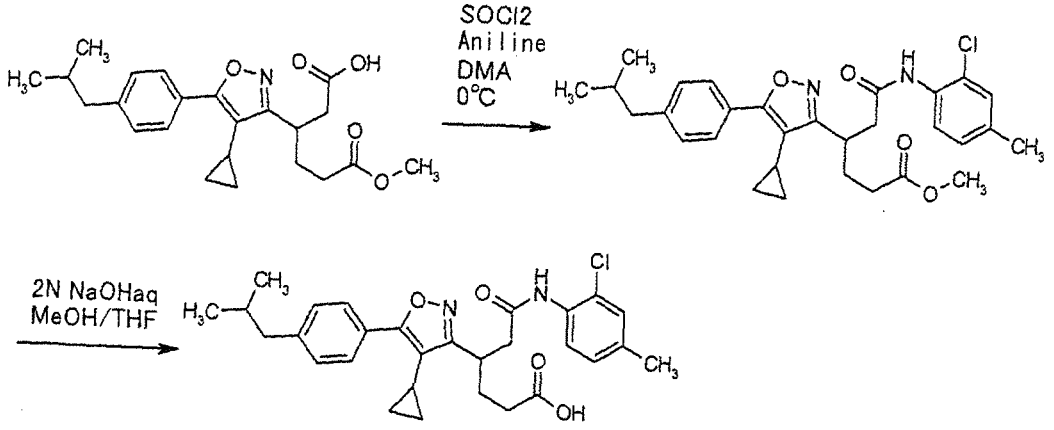
Example A-8 was prepared by using L(-)-malic acid as a material without using any chiral auxiliary reagent (AUX-H) according to the preparation methods of A-8 as described



[0344]

Example C-1

~~[化187]~~



[0345]

Example C-2

is to provide medicaments of preventing or treating autoimmune disease such as rheumatoid arthritis, psoriasis, inflammatory bowel disease such as Crohn's disease and ulcerative colitis, multiple sclerosis, systemic lupus erythematosus, ankylosing spondylitis, uveitis, polymyalgia rheumatica, and type I diabetes; allergic disease such as asthma; dry eye; fibrosis such as pulmonary fibrosis and primary biliary cirrhosis; and metabolic disease such as diabetes.

(Solution to Problem)

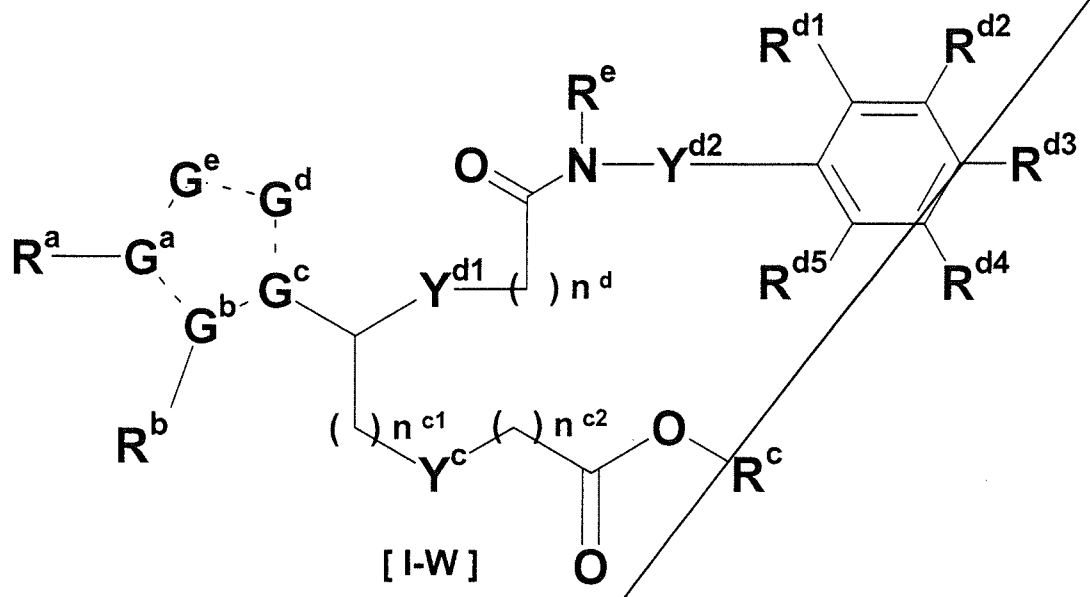
[0004]

The present inventors have found amide compounds which are RORγ antagonists, thereby have completed the present invention.

That is, the present invention provides the following aspects.

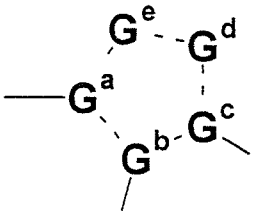
[0005]

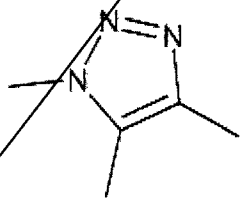
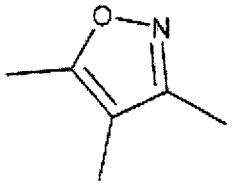
[01] A compound of formula [I-W]:



[I-W]

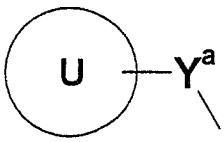
wherein



is  or ;

R^a is

(1) C_{5-12} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A, or

(2)  wherein

Y^a is

(i) single bond, or

(ii) C_{1-6} alkylene group,

cyclic moiety U is

(i) C_{3-7} cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(ii) C_{5-11} spirocyclic cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A, or

(iii) C_{6-10} aryl group which may be substituted with the same or different 1 to 5 substituents selected from Group A;

R^b is a group selected from the following (1) to (3):

(1) C_{1-3} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(2) C_{2-3} alkenyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(3) C_{3-7} cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A;

R^c is

(1) hydrogen atom, or

(2) C_{1-6} alkyl group;

Y^c is a group selected from the following (1) to (7):

(1) single bond,

(2) C_{1-6} alkylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(3) $-NR^{C1}-$ wherein R^{C1} is hydrogen atom or C_{1-6} alkyl group,

(4) -O-,

(5) C_{3-10} cycloalkylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(6) C_{6-10} arylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(7) monocyclic heteroaromatic group which may be substituted with the same or different 1 to 5 substituents selected from Group A wherein the monocyclic heteroaromatic ring consists of carbon atoms and the same or different 1 to 4 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, and is 3 to 7-membered;

Y^{d1} is

(1) single bond, or

(2) C_{1-6} alkylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A; or alternatively

both Y^{c} and Y^{d1} may be methine and be linked each other directly or via C_{1-4} alkylene group to form C_{3-7} cycloalkyl ring;

Y^{d2} is

(1) single bond, or

(2) C_{1-6} alkylene group;

R^{d1}, R^{d2}, R^{d3}, R^{d4}, and R^{d5} are the same or different

group selected from the following (1) to (7):

(1) hydrogen atom

(2) halogen atom,

(3) C_{1-6} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(4) $-OR^{d10}$ wherein R^{d10} is hydrogen atom or C_{1-6} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(5) $-COOR^{d11}$ wherein R^{d11} is hydrogen atom or C_{1-6} alkyl group,

(6) C_{3-7} cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(7) cyano group, or alternatively

R^{d1} and R^{d2}, or R^{d2} and R^{d3} can be taken together to form a C_{6-10} aryl ring fused to the benzene ring to which they are all attached wherein the C_{6-10} aryl ring may be substituted with the same or different 1 to 4 substituents selected from Group A;

R^e is

(1) hydrogen atom, or

(2) C_{1-3} alkyl group, or alternatively

R^e and R^{d1}, or R^e and R^{d5} can be taken together to form C_{1-4} alkylene;

n^{c1} is an integer selected from 0 or 1 to 4,

n^{c2} is an integer selected from 0 or 1 to 3,

n^d is an integer selected from 0 or 1 to 3,

Group A is

(a) C_{1-6} alkyl group,

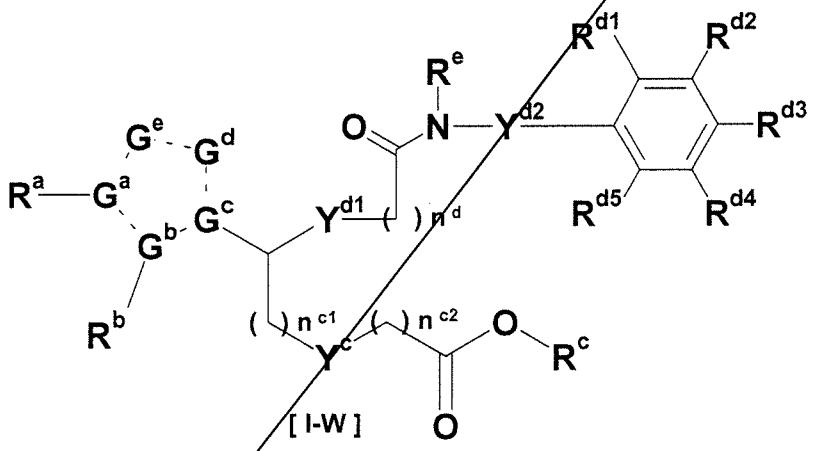
(b) halogen atom, and

(c) $-OR^{A1}$ wherein R^{A1} is hydrogen atom or C_{1-6} alkyl group,

or a pharmaceutically acceptable salt thereof.

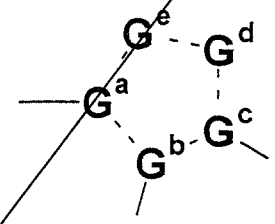
[0006]

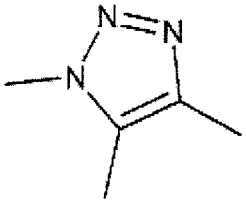
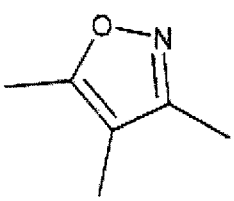
[02] The compound of formula [I-W] according to [01]:



[I-W]

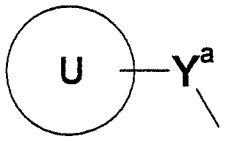
wherein



is  or ;

R^a is

(1) C_{5-12} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A, or

(2)  wherein

Y^a is

(i) single bond, or

(ii) C_{1-6} alkylene group,

cyclic moiety U is

(i) C_{3-7} cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A, or

(ii) C_{5-11} spirocyclic cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A;

R^b is a group selected from the following (1) to (3):

(1) C_{1-3} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(2) C_{2-3} alkenyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(3) C_{3-7} cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A;

R^c is

(1) hydrogen atom, or

(2) C_{1-6} alkyl group;

Y^c is a group selected from the following (1) to (7):

(1) single bond,

(2) C_{1-6} alkylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(3) $-NR^{C1}-$ wherein R^{C1} is hydrogen atom or C_{1-6} alkyl group,

(4) -O-,

(5) C_{3-10} cycloalkylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(6) C_{6-10} arylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(7) monocyclic heteroaromatic group which may be substituted with the same or different 1 to 5 substituents selected from Group A wherein the monocyclic heteroaromatic ring consists of carbon atoms and the same or different 1 to 4 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, and is 3 to 7-membered;

Y^{d1} is

(1) single bond, or

(2) C_{1-6} alkylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A;

Y^{d2} is

(1) single bond, or

(2) C_{1-6} alkylene group;

R^{d1}, R^{d2}, R^{d3}, R^{d4}, and R^{d5} are the same or different

group selected from the following (1) to (4):

(1) hydrogen atom

(2) halogen atom,

(3) C_{1-6} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(4) $-OR^{d10}$ wherein R^{d10} is hydrogen atom or C_{1-6} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A, or alternatively

R^{d1} and R^{d2}, or R^{d2} and R^{d3} can be taken together to form a C_{6-10} aryl ring fused to the benzene ring to which they are all attached wherein the C_{6-10} aryl ring may be substituted with the same or different 1 to 4 substituents selected from Group A,

n^{c1} is an integer selected from 0 or 1 to 3,

n^{c2} is an integer selected from 0 or 1 to 3,

n^{d} is an integer selected from 0 or 1 to 3,

R^{e} is hydrogen atom,

Group A is

(a) C_{1-6} alkyl group,

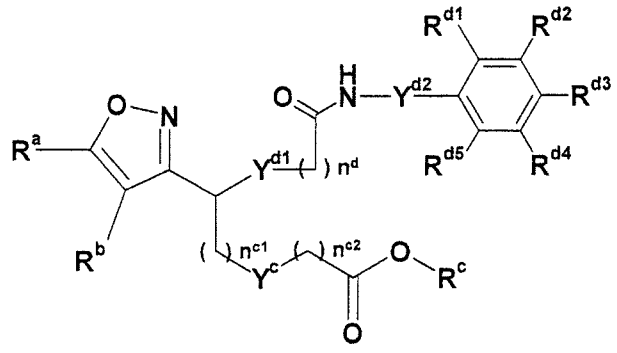
(b) halogen atom, and

(c) $-OR^{A1}$ wherein R^{A1} is hydrogen atom or C_{1-6} alkyl group,

or a pharmaceutically acceptable salt thereof.

[0007]

[03] The compound of formula [II] according to [01]:



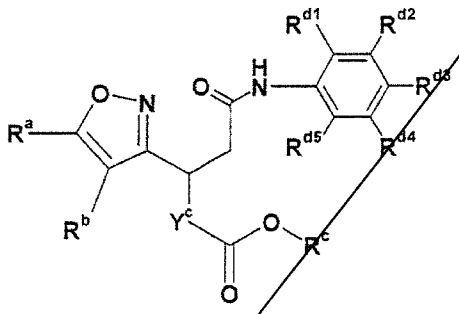
[II]

wherein each symbol is as defined in [01],

or a pharmaceutically acceptable salt thereof.

[0008]

[04] The compound of formula [III] according to [03]:



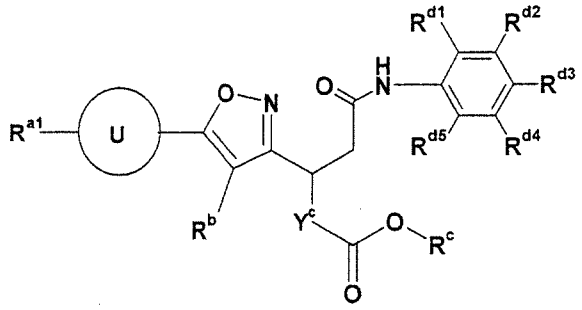
[III]

wherein each symbol is as defined in [01],

or a pharmaceutically acceptable salt thereof.

[0009]

[05] The compound of formula [IV] according to [04]:



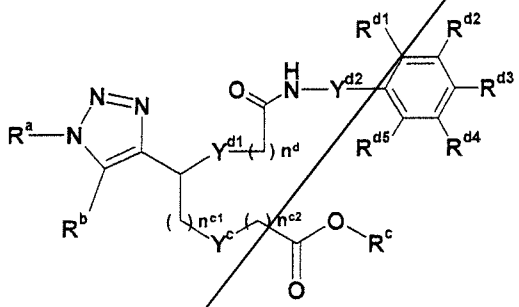
[IV]

wherein R^{a1} is C_{1-6} alkyl group, and the other symbols are as defined in [01],

or a pharmaceutically acceptable salt thereof.

[0010]

[06] The compound of formula [V] according to [01]:



[V]

wherein each symbol is as defined in [01],

or a pharmaceutically acceptable salt thereof.

[0011]

[07] The compound according to any one of [01] to [06] wherein:

R^b is C_{3-7} cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

or a pharmaceutically acceptable salt thereof.

[0012]

[08] The compound according to any one of [01] to [07] wherein:

R^b is cyclopropyl group,

or a pharmaceutically acceptable salt thereof.

[0013]

[09] The compound according to any one of [01] to [08]

wherein:

the cyclic moiety U is C_{3-7} cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

or a pharmaceutically acceptable salt thereof.

[0014]

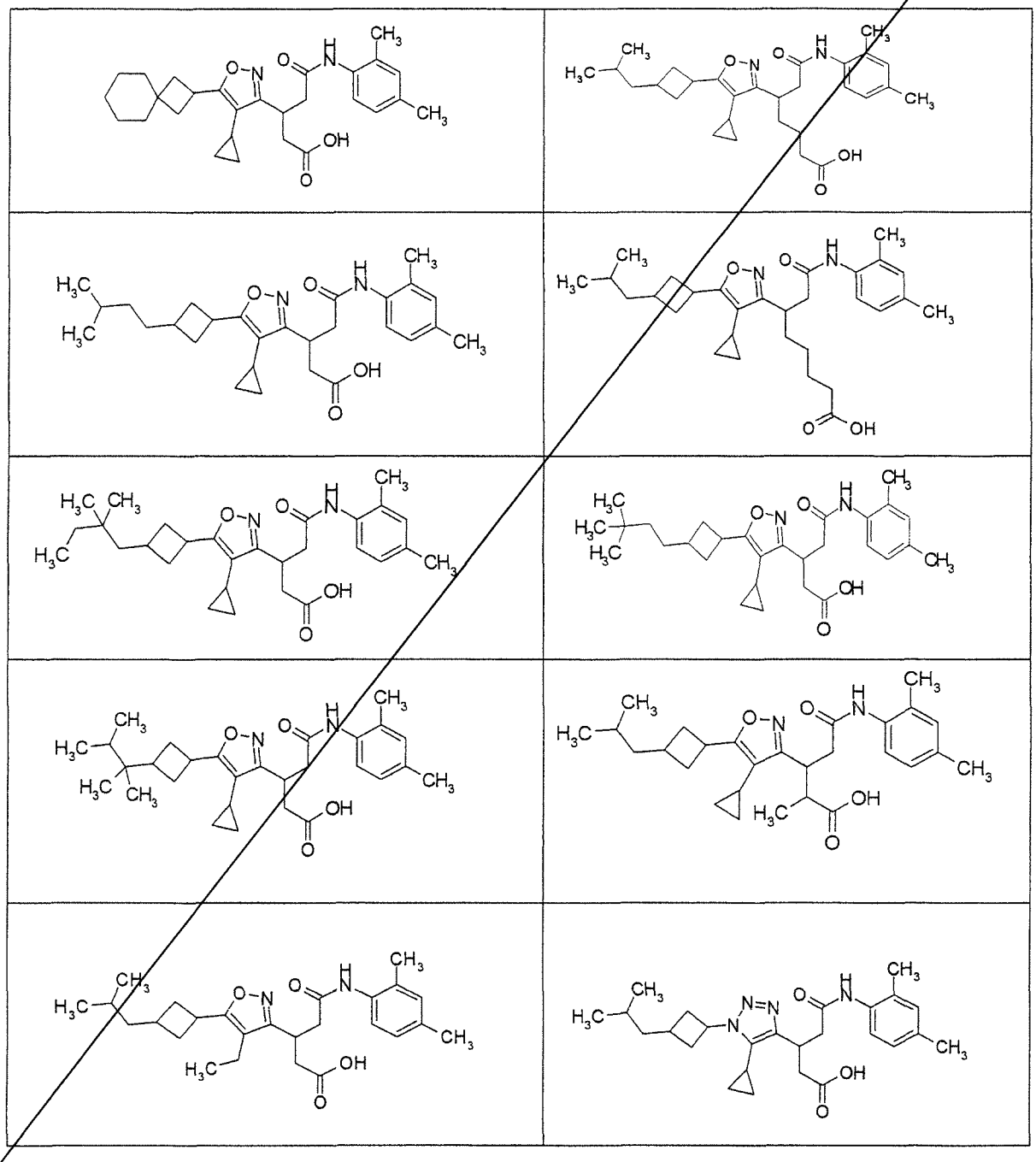
[10] The compound according to any one of [01] to [09] wherein:

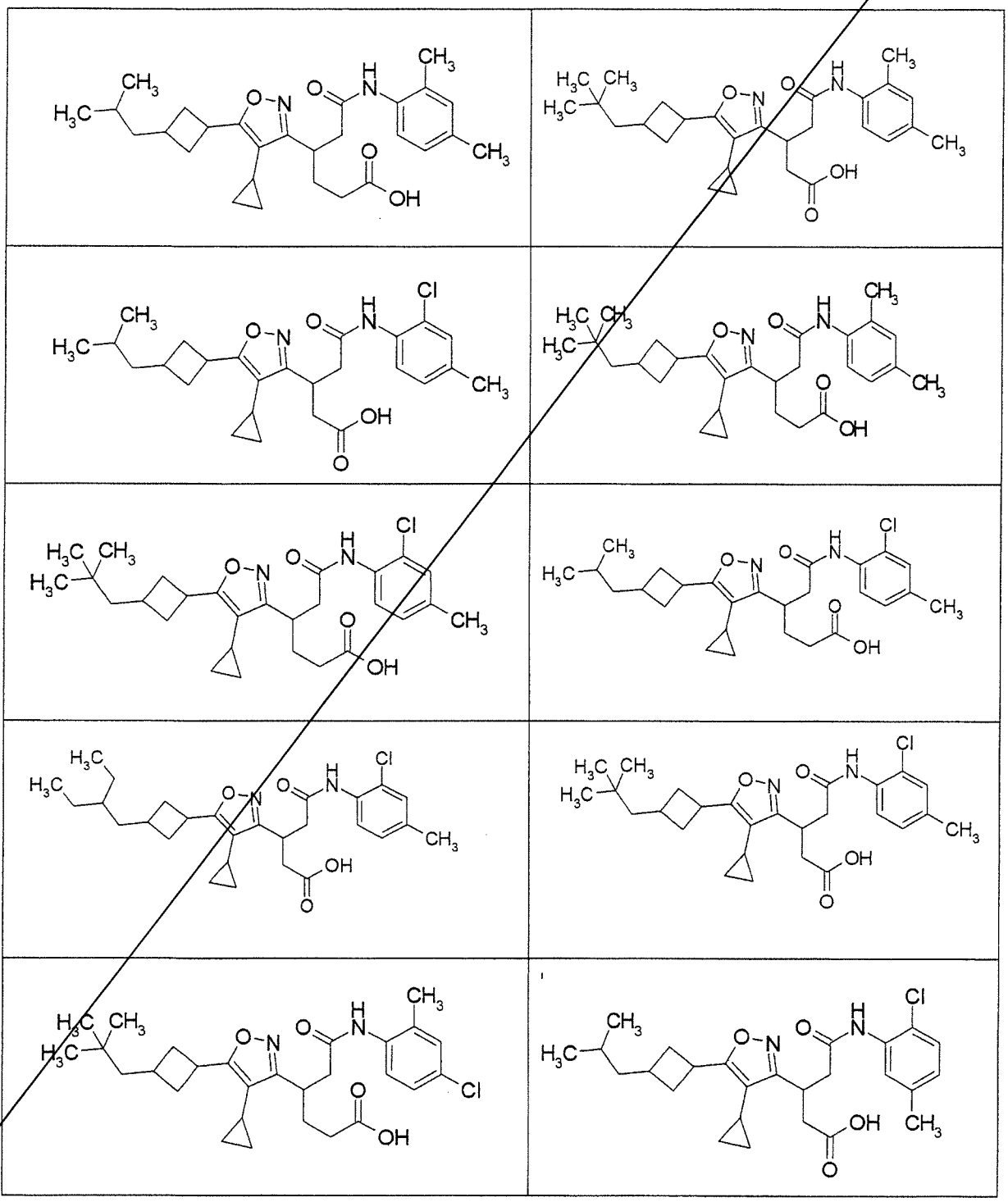
the cyclic moiety U is cyclobutyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

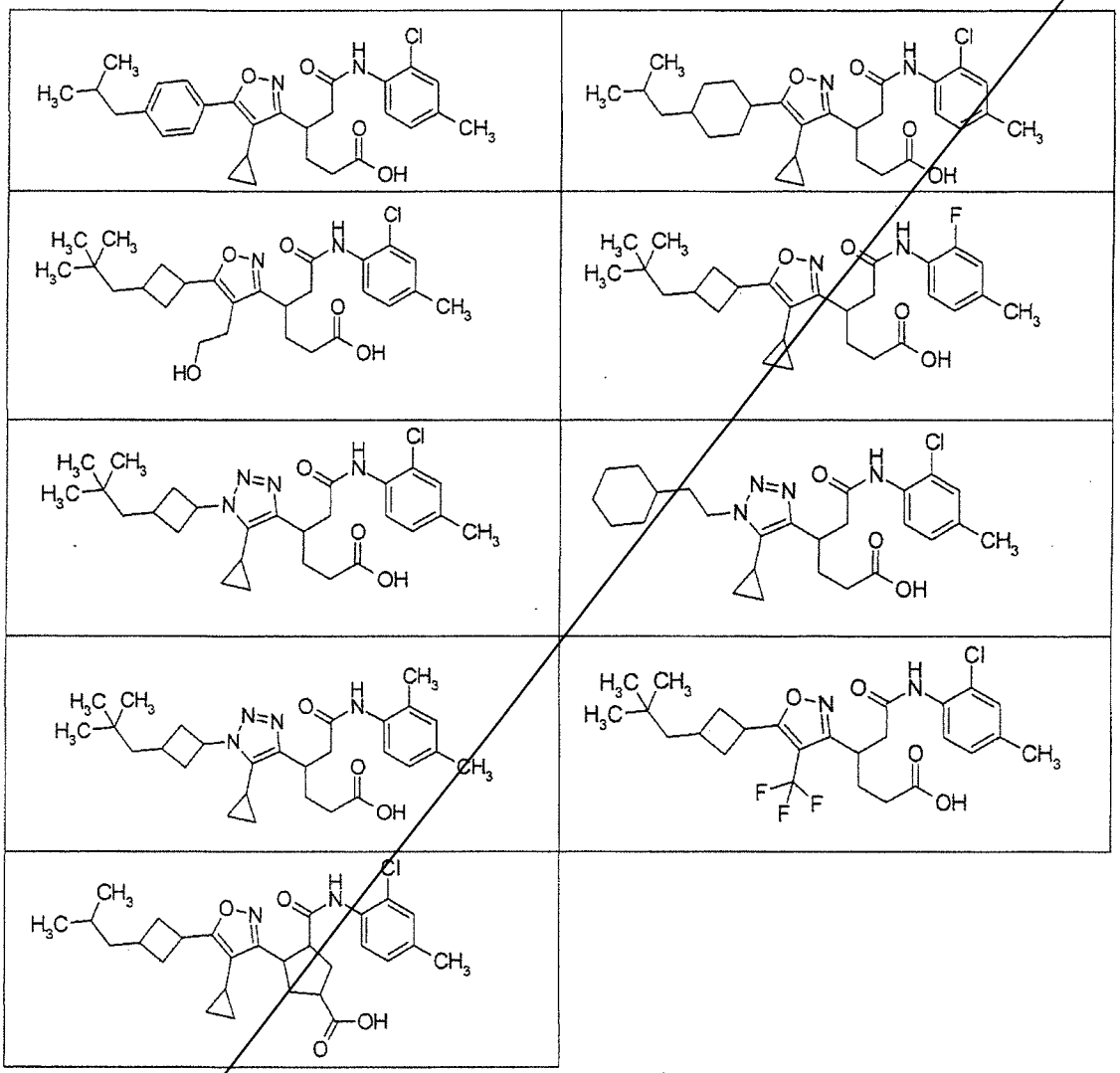
or a pharmaceutically acceptable salt thereof.

[0015]

[11] The compound according to [01] or [02] which is selected from the group consisting of the following formulas or a pharmaceutically acceptable salt thereof:

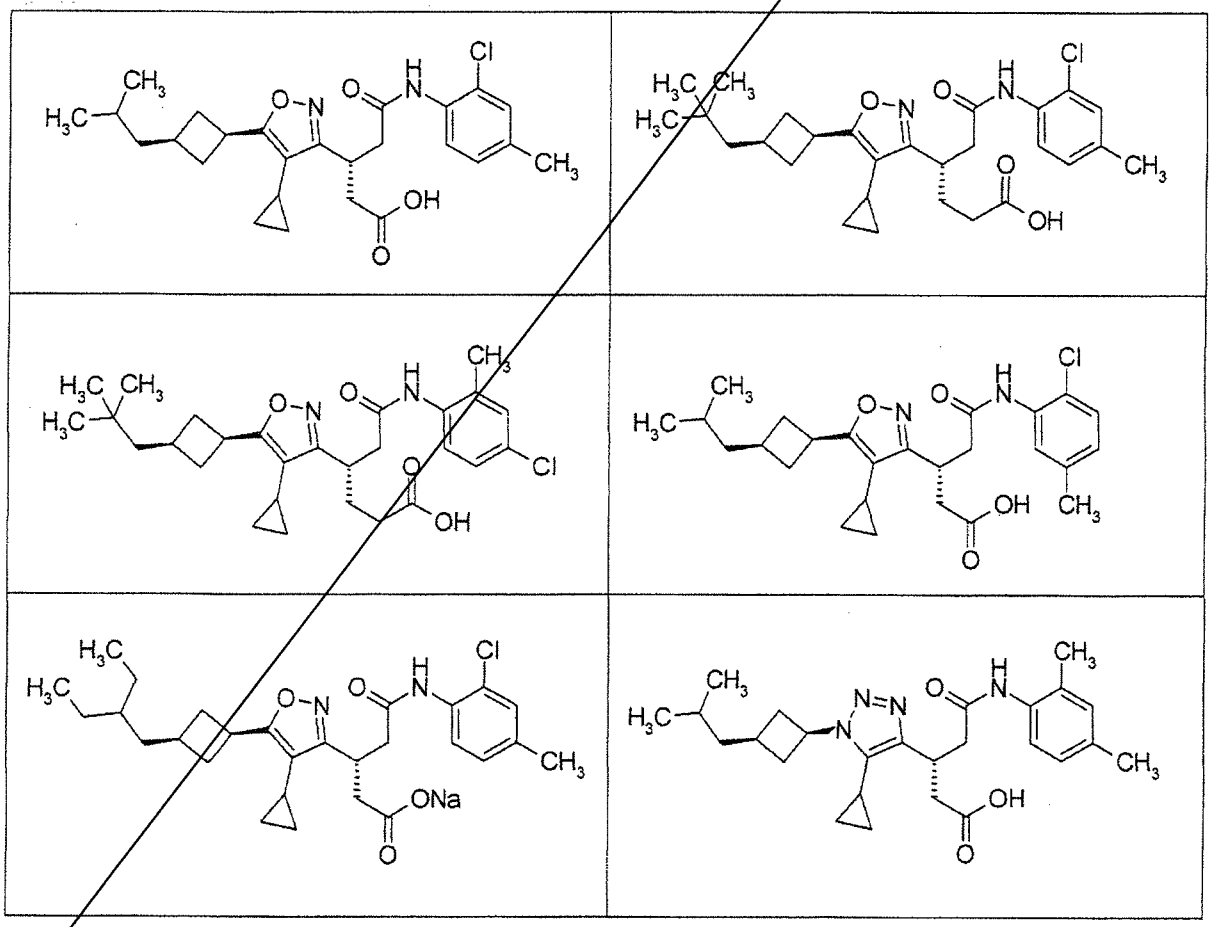






[0016]

[12] The compound according to [01] or [02] which is selected from the group consisting of the following formulas or a pharmaceutically acceptable salt thereof:



[0017]

[13] A pharmaceutical composition comprising the compound according to any one of [01] to [12] or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0018]

[14] A RORγ antagonist comprising the compound according to any one of [01] to [12] or a pharmaceutically acceptable salt thereof.

[0019]

[15] A medicament for treating or preventing a disease selected from the group consisting of autoimmune disease, allergic disease, and metabolic disease, comprising the compound according to any one of [01] to [12] or a pharmaceutically acceptable salt thereof.

[0020]

[16] A medicament for treating or preventing a disease selected from the group consisting of autoimmune disease and allergic disease, comprising the compound according to any one of [01] to [12] or a pharmaceutically acceptable salt thereof.

[0021]

[17] The medicament according to [15] or [16] wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, psoriasis, inflammatory bowel disease, multiple sclerosis, systemic lupus erythematosus, ankylosing spondylitis, uveitis, polymyalgia rheumatica, and type I diabetes.

[0022]

[18] The medicament according to [15] wherein the

metabolic disease is diabetes.

[0023]

[19] A method of inhibiting RORγ in a mammal, comprising administering to said mammal a therapeutically effective amount of the compound according to any one of [01] to [12] or a pharmaceutically acceptable salt thereof.

[0024]

[20] A method of treating or preventing a disease in a mammal selected from the group consisting of autoimmune disease, allergic disease, and metabolic disease, comprising administering to said mammal a therapeutically effective amount of the compound according to any one of [01] to [12] or a pharmaceutically acceptable salt thereof.

[0025]

[21] A method of treating or preventing a disease in a mammal selected from the group consisting of autoimmune disease and allergic disease, comprising administering to said mammal a therapeutically effective amount of the compound according to any one of [01] to [12] or a pharmaceutically acceptable salt thereof.

[0026]

[22] The method according to [20] or [21] wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, psoriasis, inflammatory bowel disease, multiple sclerosis, systemic lupus

erythematosus, ankylosing spondylitis, uveitis, polymyalgia rheumatica, and type I diabetes.

[0027]

[23] The method according to [20] wherein the metabolic disease is diabetes.

[0028]

[24] A pharmaceutical composition for treating or preventing a disease selected from the group consisting of autoimmune disease, allergic disease, and metabolic disease, which comprises:

(a) the compound according to any one of [01] to [12] or a pharmaceutically acceptable salt thereof, and

(b) at least one additional medicament for treating or preventing a disease selected from the group consisting of autoimmune disease, allergic disease, and metabolic disease.

[0029]

[25] A combination drug comprising:

(a) the compound according to any one of [01] to [12] or a pharmaceutically acceptable salt thereof, and

(b) at least one additional medicament for treating or preventing a disease selected from the group consisting of autoimmune disease, allergic disease and metabolic disease,

wherein the compound of (a) and the additional

medicament of (b) may be administered simultaneously, separately or consecutively.

[0030]

[26] Use of the compound according to any one of [01] to [12] or a pharmaceutically acceptable salt thereof in the manufacture of a RORγ antagonist.

[0031]

[27] Use of the compound according to any one of [01] to [12] or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a disease selected from the group consisting of autoimmune disease, allergic disease, and metabolic disease.

[0032]

[28] The use according to [27] wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, psoriasis, inflammatory bowel disease such as Crohn's disease and ulcerative colitis, multiple sclerosis, systemic lupus erythematosus, ankylosing spondylitis, uveitis, polymyalgia rheumatica, and type I diabetes.

[0033]

[29] The use according to [27] wherein the metabolic disease is diabetes.

[0034]

[30] The compound according to any one of [01] to

[12] or a pharmaceutically acceptable salt thereof for use in treating or preventing a disease selected from the group consisting of autoimmune disease, allergic disease, and metabolic disease.

[0035]

[31] A commercial package comprising the medicament according to [15], and instructions which explain that the medicament can be used to treat and / or prevent a disease selected from the group consisting of autoimmune disease, allergic disease, and metabolic disease.

[0036]

[32] The commercial package comprising the combination drug according to [25], and instructions which explain that the combination drug can be used to treat and / or prevent a disease selected from the group consisting of autoimmune disease, allergic disease, and metabolic disease.

[0037]

[33] A medicament for treating or preventing a disease selected from the group consisting of autoimmune disease such as rheumatoid arthritis, psoriasis, inflammatory bowel disease such as Crohn's disease and ulcerative colitis, multiple sclerosis, systemic lupus erythematosus, ankylosing spondylitis, uveitis, polymyalgia rheumatica, and type I diabetes; allergic disease such as

asthma; dry eye; fibrosis such as pulmonary fibrosis and primary biliary cirrhosis; and metabolic disease such as diabetes, comprising the compound according to any one of [01] to [12] or a pharmaceutically acceptable salt thereof.

[0038]

[34] A pharmaceutical composition for treating or preventing a disease selected from the group consisting of: autoimmune disease such as rheumatoid arthritis, psoriasis, inflammatory bowel disease such as Crohn's disease and ulcerative colitis, multiple sclerosis, systemic lupus erythematosus, ankylosing spondylitis, uveitis, polymyalgia rheumatica, and type I diabetes; allergic disease such as asthma; dry eye; fibrosis such as pulmonary fibrosis and primary biliary cirrhosis; and metabolic disease such as diabetes, comprising:

(a) the compound according to any one of [01] to [12] or a pharmaceutically acceptable salt thereof, and

(b) at least one additional medicament for treating or preventing a disease selected from the group consisting of autoimmune disease such as rheumatoid arthritis, psoriasis, inflammatory bowel disease such as Crohn's disease and ulcerative colitis, multiple sclerosis, systemic lupus erythematosus, ankylosing spondylitis, uveitis, polymyalgia rheumatica, and type I diabetes; allergic disease such as asthma; dry eye; fibrosis such as

pulmonary fibrosis and primary biliary cirrhosis; and metabolic disease such as diabetes.

[0039]

[35] A combination drug comprising:

(a) the compound according to any one of [01] to [12] or a pharmaceutically acceptable salt thereof, and

(b) at least one an additional medicament for treating or preventing a disease selected from the group consisting of autoimmune disease such as rheumatoid arthritis, psoriasis, inflammatory bowel disease such as Crohn's disease and ulcerative colitis, multiple sclerosis, systemic lupus erythematosus, ankylosing spondylitis, uveitis, polymyalgia rheumatica, and type I diabetes; allergic disease such as asthma; dry eye; fibrosis such as pulmonary fibrosis and primary biliary cirrhosis; and metabolic disease such as diabetes,

wherein the compound of (a) and the additional medicament of (b) may be administered simultaneously, separately or consecutively.

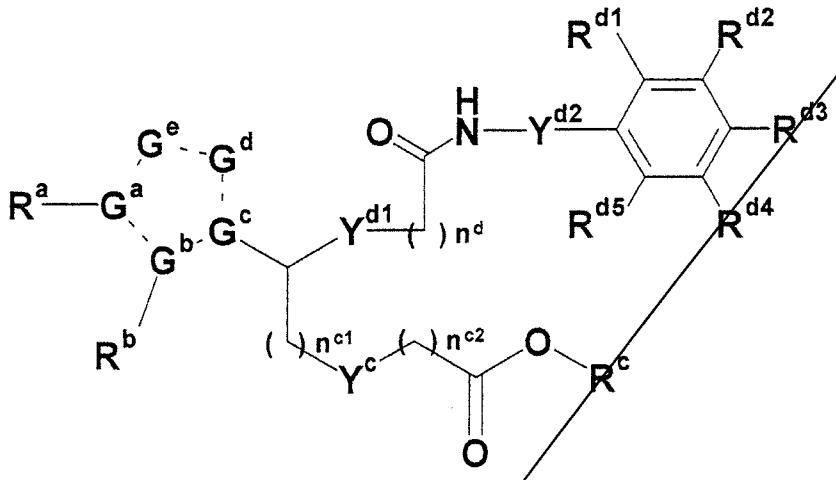
[0040]

Each symbol of the formulas described in the following [102] to [122] has the same meaning as defined in the formula [I] in the following [101].

In particular, R^a; Y^c and Y^{d1}; R^{d1}, R^{d2}, R^{d3}, R^{d4}, and R^{d5} of the formulas described in [102] to [122] have the same

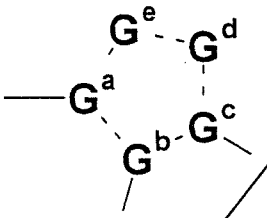
meaning as defined in the formula [I] described in [101].

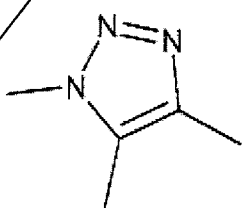
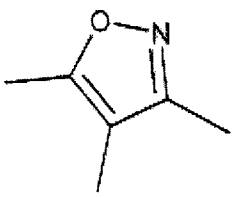
[101] A compound of formula [I]:



[I]

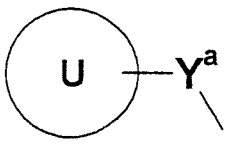
wherein



is  or ;

R^a is

(1) C_{6-12} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A, or

(2)  wherein

Y^a is

(i) single bond, or

(ii) C_{1-6} alkylene group,

cyclic moiety U is

(i) C_{3-7} cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A, or

(ii) C_{5-11} spirocyclic cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A;

R^b is a group selected from the following (1) to (3):

(1) C_{1-3} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(2) C_{2-3} alkenyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(3) C_{3-7} cycloalkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A;

R^c is

(1) hydrogen atom, or

(2) C_{1-6} alkyl group;

Y^c is a group selected from the following (1) to (7):

(1) single bond,

(2) C_{1-6} alkylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(3) $-NR^{C1}-$ wherein R^{C1} is hydrogen atom or C_{1-6} alkyl group,

(4) -O-,

(5) C_{3-10} cycloalkylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(6) C_{6-10} arylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(7) monocyclic heteroaromatic group which may be substituted with the same or different 1 to 5 substituents selected from Group A wherein the monocyclic heteroaromatic ring consists of carbon atoms and the same or different 1 to 4 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, and is 3 to 7-membered;

Y^{d1} is

(1) single bond, or

(2) C_{1-6} alkylene group which may be substituted with the same or different 1 to 5 substituents selected from Group A;

Y^{d2} is

(1) single bond, or

(2) C_{1-6} alkylene group;

R^{d1}, R^{d2}, R^{d3}, R^{d4}, and , R^{d5} are the same or different group selected from the following (1) to (4):

(1) hydrogen atom

(2) halogen atom,

(3) C_{1-6} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A,

(4) $-OR^{d10}$ wherein R^{d10} is hydrogen atom or C_{1-6} alkyl group which may be substituted with the same or different 1 to 5 substituents selected from Group A, or alternatively

R^{d1} and R^{d2}, or R^{d2} and R^{d3} can be taken together to form a C_{6-10} aryl ring fused to the benzene ring to which they are all attached wherein the C_{6-10} aryl ring may be substituted with the same or different 1 to 4 substituents selected from Group A;

n^{c1} is an integer selected from 0 or 1 to 3,

n^{c2} is an integer selected from 0 or 1 to 3,

n^{d} is an integer selected from 0 or 1 to 3,

Group A is

(a) C_{1-6} alkyl group,

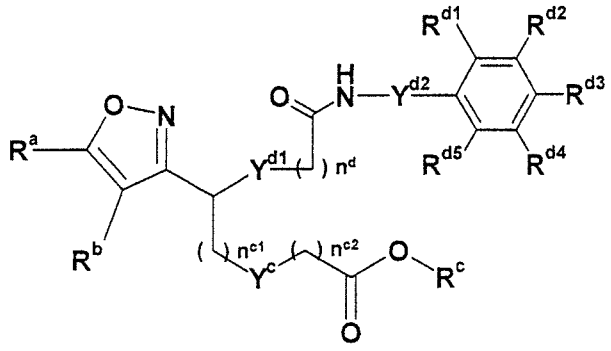
(b) halogen atom, and

(c) $-OR^{A1}$ wherein R^{A1} is hydrogen atom or C_{1-6} alkyl group,

or a pharmaceutically acceptable salt thereof.

[0041]

[102] The compound of formula [II] according to [101]:



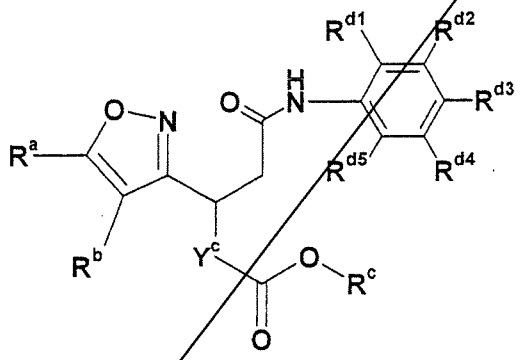
[II]

wherein each symbol is as defined in [101],

or a pharmaceutically acceptable salt thereof.

[0042]

[103] The compound of formula [III] according to [101] or [102]:



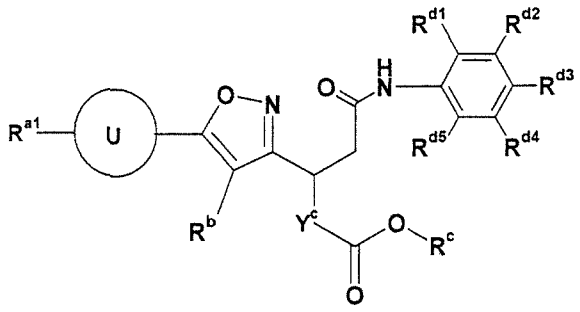
[III]

wherein each symbol is as defined in [101],

or a pharmaceutically acceptable salt thereof.

[0043]

[104] The compound of formula [IV] according to [101]:



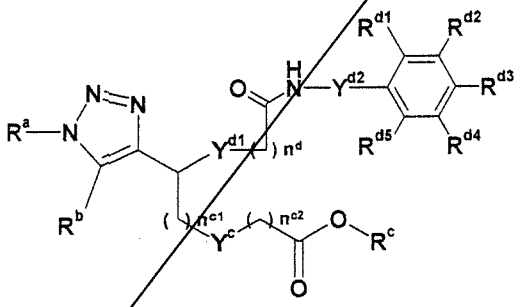
[IV]

wherein R^{a1} is C_{1-6} alkyl group, and the other symbols are defined in [101],

or a pharmaceutically acceptable salt thereof.

[0044]

[105] The compound of formula [V] according to [101]:



[V]

wherein each symbol is as defined in [101],

or a pharmaceutically acceptable salt thereof.

[106] The compound according to any one of [101] to [105] wherein:

R^b is cyclopropyl group,

or a pharmaceutically acceptable salt thereof.

[107] The compound according to any one of [101] to [106] werein

the cyclic moiety U is cyclobutyl group,

or a pharmaceutically acceptable salt thereof.

[0045]

[108] A pharmaceutical composition comprising the compound according to any one of [101] to [107] or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[109] A RORγ antagonist comprising the compound according to any one of [101] to [107] or a pharmaceutically acceptable salt thereof.

[110] A medicament for treating or preventing a disease selected from the group consisting of autoimmune disease and allergic disease, comprising the compound according to any one of [101] to [107] or a pharmaceutically acceptable salt thereof.

[111] The medicament according to [110] wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, psoriasis, inflammatory

bowel disease, multiple sclerosis, and systemic lupus erythematosus.

[0046]

[112] A pharmaceutical composition for treating or preventing a disease selected from the group consisting of autoimmune disease and allergic disease, comprising

(a) the compound according to any one of [101] to [107] or a pharmaceutically acceptable salt thereof, and

(b) at least one additional medicament for treating or preventing a disease selected from the group consisting of autoimmune disease and allergic disease.

[0047]

[113] A combination drug comprising:

(a) the compound according to any one of [101] to [107] or a pharmaceutically acceptable salt thereof, and

(b) at least one an additional medicament for treating or preventing a disease selected from the group consisting of autoimmune disease and allergic disease,

wherein the compound of (a) and the additional medicament of (b) may be administered simultaneously, separately or consecutively.

[0048]

[114] A method of inhibiting RORγ in a mammal, comprising administering to said mammal a therapeutically effective amount of the compound according to any one of [101] to [107] or a pharmaceutically acceptable salt thereof.

[115] A method of treating or preventing a disease in a mammal selected from the group consisting of autoimmune disease and allergic disease, comprising administering to said mammal a therapeutically effective amount of the compound according to any one of [101] to [107] or a pharmaceutically acceptable salt thereof.

[116] The method according to [115] wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, psoriasis, inflammatory bowel disease, multiple sclerosis, and systemic lupus erythematosus.

[0049]

[117] Use of the compound according to any one of [101] to [107] or a pharmaceutically acceptable salt thereof in the manufacture of a RORγ antagonist.

[118] Use of the compound according to any one of [101] to [107] or a pharmaceutically acceptable salt

thereof in the manufacture of a medicament for treating or preventing a disease selected from the group consisting of autoimmune disease and allergic disease.

[119] The use according to [118] wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, psoriasis, inflammatory bowel disease, multiple sclerosis, and systemic lupus erythematosus.

[120] The compound according to any one of [101] to [107] or a pharmaceutically acceptable salt thereof for use in treating or preventing a disease selected from the group consisting of autoimmune disease and allergic disease.

[0050]

[121] A commercial package comprising the medicament according to [110], and instructions which explain that the medicament can be used to treat and / or prevent a disease selected from the group consisting of autoimmune disease and allergic disease.

[122] A commercial package comprising the combination drug according to [113], and instructions which explain that the combination drug can be used to treat and / or prevent a disease selected from the group consisting

of autoimmune disease and allergic disease.

Effects of The Invention

[0051]

The amide compound of the present invention can inhibit the RORγ activity, thereby the compound is effective as a medicament for treating or preventing a disease such as autoimmune disease such as rheumatoid arthritis, psoriasis, inflammatory bowel disease such as Crohn's disease and ulcerative colitis, multiple sclerosis, and systemic lupus erythematosus; allergic disease; metabolic disease; dry eye; and fibrosis.

Brief Description of Drawings

[0052]

[Figure 1] Structures, NMR results and the like of Examples A-1 to A-4.

[Figure 2] Structures, NMR results and the like of Examples A-5 to A-8.

Example A-6 was prepared by using L-homoserine as a material without using any chiral auxiliary reagent (AUX-H) according to the preparation methods of A-6 as described below.

Example A-8 was prepared by using L(-)-malic acid as a material without using any chiral auxiliary reagent (AUX-H) according to the preparation methods of A-8 as described