

DESCRIPTION

Title of the Invention: PYRIDONE COMPOUND

Technical Field

5 [0001]

The present invention relates to a pyridone compound or a pharmaceutically acceptable salt thereof useful as an agent for the prophylaxis and/or treatment of skin diseases, and the like.

10 Background Art

[0002]

Chemokine is a series of families of small inflammatory cytokines having a strong chemotactic activity and being composed of about 70 - 120 amino acids, and is a chemotactic
15 cytokine released from a wide variety of cells in order to lead various cells such as monocyte, macrophage, T cell, eosinophil, basophil, neutrophil and the like to the inflammatory site. The chemokine family was originally defined by 4 conserved cysteine residues in an amino acid sequence,
20 namely, classified into two subfamilies of CXC-chemokine family and CC-chemokine family based on the configuration of the first cysteine pair (two residues) on the N terminal side. In the CXC-chemokine family including CXCL1, Mig, CX3CL1, IL-8, Gro- α , NAP-2, IP-10 and the like, these two cysteine residues
25 are separated by one of the amino acid residues other than cysteine; on the other hand, in the CC-chemokine family including RANTES(CCL5), MCP-1(CCL2), MCP-2(CCL8), MCP-3(CCL7), MCP-4(CCL13), MIP-1 α (CCL3), MIP-1 β (CCL4), Eotaxin(CCL11), Eotaxin-2(CCL24), Eotaxin-3(CCL26), PARC(CCL18), TARC(CCL17),
30 MDC(CCL22), LARC(CCL20), ELC(CCL19), SLC(CCL21), I-309(CCL1), TECK(CCL25), CTACK(CCL27), MEC(CCL28) and the like, these two cysteine residues are contiguous. Thereafter, the C chemokine family having, of the four cysteine residues originally present, only two cysteine residues corresponding to the
35 second and the fourth residues from the N terminal side, and

the CX3C chemokine family having a sequence having three amino acid residues different from cysteine between the first two cysteine residues on the N terminal side were found.

[0003]

5 Ten kinds of receptors have been reported as the chemokine receptor that CC-chemokine family binds to. That is, CCR1 (alias, CKR1 or CC-CKR-1) bindable with MIP-1 α , MIP-1 β , MCP-3, RANTES and the like, CCR2A (alias, CKR2A or CC-CKR-2A) and CCR2B (alias, CKR2B or CC-CKR-2B) bindable with MCP-1,
10 MCP-2, MCP-3, MCP-4 and the like, CCR3 (alias, CKR-3 or CC-CKR-3) bindable with Eotaxin, Eotaxin-2, RANTES, MCP-2, MCP-3 and the like, CCR4 (alias, CKR4 or CC-CKR-4) bindable with TARC, MDC and the like, CCR5 (alias, CKR-5 or CC-CKR-5) bindable with MIP-1 α , RANTES, MIP-1 β and the like, CCR6 (alias,
15 GPRCY4) bindable with LARC and the like, CCR7 (alias, EBI-1) bindable with ELC, SLC and the like, CCR8 bindable with I-309 and the like, CCR9 (alias, GPR9-6) bindable with TECK and the like, and CCR10 bindable with CTACK, MEC and the like are known [Nature Reviews Immunology, 2002, vol. 2, page 106].

20 [0004]

Chemokine receptors have different expression cells depending on the kind of the receptor. For example, CCR1 is expressed in various cells such as monocyte, T cell, mast cell, eosinophil, basophil and the like, and CCR2 is expressed in
25 various cells such as dendritic cell, B cell, basophil, eosinophil, vascular endothelial cell, fibroblast, platelet, T cell and the like. On the other hand, some receptors are expressed only in some cells such as CCR3 expressed in eosinophils and basophil, and CCR9 expressed in T cells.

30 [0005]

Since involvement of chemokine receptor in various diseases has been reported, a medicament modulating a chemokine receptor activity is expected to be a therapeutic drug for various diseases [Expert Opinion on Investigational
35 Drugs, 2010, vol. 19, page 345]. Heretofore, plural chemokine

receptor activity modulators have been used as therapeutic drugs. For example, it has been clarified that, when CD4+T cells are infected with HIV, HIV invades into the cells via CCR5, and therefore, CCR5 antagonist is used as a therapeutic
5 drug for HIV infection. Also, as a medicament for mobilization of stem cells in autologous stem cell transplantation in patients with non-Hodgkin lymphoma and multiple myeloma, a combined use of an antagonist of CXCR4 which is a receptor of CXC-chemokine family with G-CSF has been approved. Besides
10 these, CCR3 antagonist, CCR9 antagonist, antibody to CCR4 and the like are under clinical tests [Expert Opinion on Investigational Drugs, 2010, vol. 19, page 345].

[0006]

As diseases involving a chemokine receptor, inflammatory
15 diseases such as asthma, rhinitis, dermatitis, allergic disease and the like, immunoregulatory disorders and diseases, autoimmune diseases such as rheumatoid arthritis, lupus erythematosus, generalized scleroderma, Sjogren's syndrome, Celiac disease and the like, and the like are known [Current
20 Opinion in Immunology, 2001, vol. 13, page 670]. Involvement of chemokine receptors such as CCR1; CCR2A; CCR2B; CCR3; CCR4; CCR5; CCR6; CCR7; CCR8; CCR9; CCR10; CXCR3 and CXCR4 which are receptors of CXC-chemokine family; and the like in the onset of these diseases has been reported. Among these, as a disease
25 involving CCR4, CCR8, CCR9, CCR10 and the like, skin diseases and the like are known [Journal of Investigative Dermatology, 2009, vol. 129, page 2552].

[0007]

As skin diseases involving a chemokine receptor, acne
30 vulgaris, drug eruption, contact dermatitis, pollen dermatitis, urticaria, psoriasis, atopic dermatitis, Candida dermatitis, seborrheic dermatitis, eczema, Stevens-Johnson syndrome, toxic epidermal necrosis, erythema multiforme, pityriasis rosea, lichen planus, lichen pilaris (keratosis pilaris), herpes
35 simplex, lupus erythematosus, keloid, scabies, generalized

scleroderma and dermatitis as a side effect of anti-cancer agents and the like are known. In these skin diseases, various chemokines are highly expressed in the skin. For example, it is known that, in psoriasis, expression of chemokines such as MCP-1, RANTES, TARC, MDC, CTACK, CXCL1, Gro- α , IL-8, Mig, IP-10, CX3CL1 and the like increases in the dermatitis site and T cells and neutrophils infiltrate into the skin via CCR4; CCR6; CCR10; and CXCR1, CXCR2 and CXCR3, which are receptors of CXC chemokine family; and the like (non-patent document 1), in atopic dermatitis, expression of chemokine such as I-309, MCP-1, MIP-1 α , MIP-1 β , RANTES, Eotaxin, MCP-4, PARC, LARC, MDC, Eotaxin-3, CTACK and the like increases in the dermatitis site and T cells, monocyte, eosinophils infiltrate into the skin via CCR1; CCR2A; CCR2B; CCR3; CCR4; CCR5; CCR6; CCR8; CCR10; CX3CR1 which is the receptor of CX3C chemokine family; and the like (non-patent document 2) and the like. Also, it has been reported that anti-CTACK antibody suppresses dermatitis in various dermatitis models and the like (for example, non-patent documents 3, 4, 5, 6 and the like). As a medicament that modulates chemokine receptor activity in skin diseases and the like in which these chemokine receptors are involved, pyrazolopyrimidine derivatives are known (patent document 12). [0008]

CCR10 is a chemokine receptor belonging to the C-C chemokine family [Genomics, 1994, vol. 23, page 609], and mainly expressed in the cells localized in the skin such as Cutaneous lymphocyte-associated antigen (CLA) positive skin-homing T cells, skin vascular endothelial cell, skin fibroblast, skin keratinocyte and the like. As a chemokine whose receptor is CCR10, two kinds of Cutaneous T-cell attracting chemokine (CTACK: alias CCL27) and Mucosae-associated epithelial chemokine (MEC: alias CCL28) are known. CCR10 and ligand thereof are said to be involved in the immunity of epithelial cells [Protein & Cell, 2012, vol. 3, page 571].

[0009]

In recent years, involvement of CCR10 in atopic dermatitis has been reported. CTACK is selectively expressed in skin keratinocytes, and skin-homing CCR10 positive cells
5 selectively migrate into CTACK. In patients with atopic dermatitis, expression of CTACK in the lesion skin is promoted, and in atopic dermatitis patients, the blood level of CTACK shows a positive correlation with the severity of dermatitis (non-patent document 7). Also, in the lesion skin of atopic
10 dermatitis patients, localization of CCR10 positive T cells is found, and the CCR10 mRNA expression level of peripheral blood CD4 positive T cells of atopic dermatitis patients is higher than that of healthy adult (non-patent document 8).
Furthermore, IL-22 is highly expressed in the skin lesion of
15 atopic dermatitis patients, suppresses filaggrin production of the skin and is involved in the destruction of skin barrier. CCR10 is selectively expressed in Th22 cells that highly produce IL-22 (non-patent documents 9 and 10).

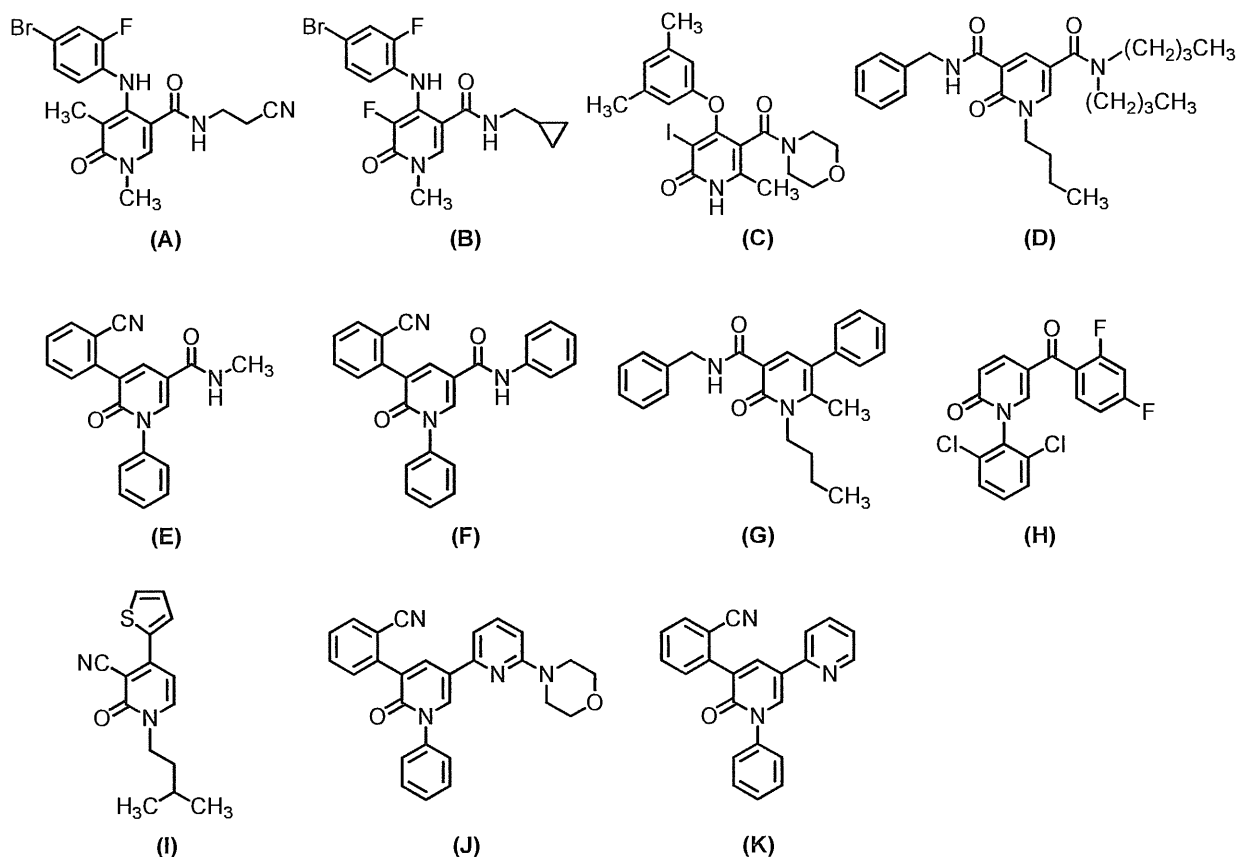
[0010]

20 The role of CTACK and CCR10 in dermatitis has been studied by using mouse dermatitis model. When chronic contact dermatitis involving type 2 helper T cell is developed in keratinocyte selective CTACK highly expressing mouse, infiltration of CCR10 positive T cells in the skin tissue and
25 skin tumouria significantly increase as compared to wild-type mouse (non-patent document 11).

On the other hand, as pyridone compounds, compounds represented by the following formulas (A), (B) (patent documents 1, 2) and the like are known as compounds having
30 arylamino at the 4-position and monoalkylcarbamoyl at the 5-position, a compound represented by the following formula (C) (patent document 3) and the like are known as a compound having aryloxy at the 4-position and aliphatic heterocyclic carbonyl at the 5-position, a compound represented by the
35 following formula (D) (patent document 4) and the like are

known as a compound having dialkylcarbamoyl at the 5-position,
a compound represented by the following formula (E) (patent
document 5) and the like are known as a compound having
monoalkylcarbamoyl at the 5-position, and a compound
5 represented by the following formula (F) (patent document 6)
and the like are known as a compound having monoarylcarbamoyl
at the 5-position. Besides these, for example, various
pyridone compounds represented by the following formulas (G) -
(K) and the like are known (patent documents 7 - 11).

10 [0011]



Prior Arts Documents

patent documents

[0012]

- 15 patent document 1: WO 05/051301
patent document 2: WO 06/056427
patent document 3: WO 02/024650
patent document 4: WO 03/070277
patent document 5: WO 01/096308
20 patent document 6: WO 03/047577

patent document 7: WO 02/053543
patent document 8: WO 05/105743
patent document 9: WO 06/030032
patent document 10: WO 06/107860
5 patent document 11: WO 06/109876
patent document 12: WO 13/031931
non-patent documents
[0013]
non-patent document 1: "Clinical Dermatology", 2008, vol. 26,
10 page 539
non-patent document 2: "Journal of Allergy and Clinical
Immunology", 2006, vol. 118, page 178
non-patent document 3: "Nature Medicine", 2002, vol. 8, page
157-165
15 non-patent document 4: "International Immunology", 2006, vol.
18, page 1233-1242
non-patent document 5: "European Journal of Immunology", 2008,
vol. 38, page 647-657
non-patent document 6: "Experimental Dermatology", 2007, vol.
20 17, page 30-34
non-patent document 7: "Journal of Allergy and Clinical
Immunology", 2004, vol. 113, page 334
non-patent document 8: "Journal of Investigative Dermatology",
2005, vol. 125, page 1149
25 non-patent document 9: "Nature Immunology", 2009, vol. 10,
page 857
non-patent document 10: "Nature Immunology", 2009, vol. 10,
page 864
non-patent document 11: "European Journal of Immunology", 2008,
30 vol. 38, page 647

Summary of the Invention

Problems to be Solved by the Invention

[0014]

35 An object of the present invention is to provide a

pyridone compound or a pharmaceutically acceptable salt thereof, which is useful as an agent for the prophylaxis and/or treatment of skin diseases, and the like.

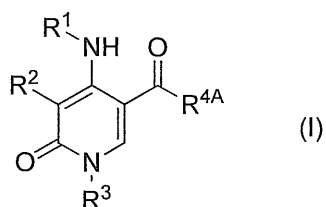
5 Means of Solving the Problems

[0015]

The present invention relates to the following (1) - (33).

(1) A pyridone compound represented by the formula (I)

[0016]



10

[0017]

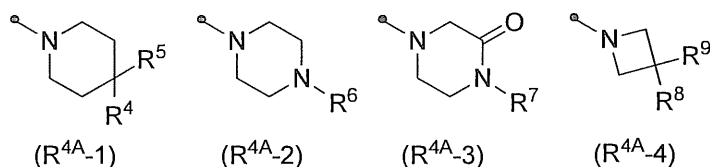
[wherein, R¹ represents cycloalkyl optionally having substituent(s), aryl optionally having substituent(s), an aromatic heterocyclic group optionally having substituent(s),
15 an aliphatic heterocyclic group optionally having substituent(s), aralkyl optionally having substituent(s), or heterocyclic alkyl optionally having substituent(s),
R² represents a hydrogen atom, cyano, nitro, halogen, lower alkyl optionally having substituent(s), or -NR^{1a}R^{1b} (wherein, R^{1a}
20 and R^{1b} are the same or different and each represents a hydrogen atom, lower alkanoyl optionally having substituent(s), or lower alkylcarbamoyl optionally having substituent(s)),
R³ represents hydroxy, lower alkyl optionally having substituent(s), lower alkenyl optionally having substituent(s),
25 lower alkynyl optionally having substituent(s), lower alkoxy optionally having substituent(s), cycloalkyl optionally having substituent(s), heterocyclic alkyl optionally having substituent(s), or -NR^{3a}R^{3b} (wherein, R^{3a} and R^{3b} are the same or different and each represents a hydrogen atom, lower alkyl
30 optionally having substituent(s), cycloalkyl optionally having substituent(s), aryl optionally having substituent(s), or aralkyl optionally having substituent(s), or R^{3a} and R^{3b} form,

together with the adjacent nitrogen atom, a nitrogen-containing heterocyclic group optionally having substituent(s)),

R^{4A} represents any one of the groups represented by the

5 following formulas (R^{4A-1}), (R^{4A-2}), (R^{4A-3}) or (R^{4A-4})

[0018]



[0019]

(wherein, R^4 and R^5 are the same or different and each
10 represents a hydrogen atom, aryl optionally having substituent(s), or lower alkoxy optionally having substituent(s), or R^4 and R^5 form, together with the adjacent carbon atom, an aliphatic heterocyclic group optionally having substituent(s), R^6 and R^7 represent aryl optionally having
15 substituent(s), R^8 and R^9 are the same or different and each represents a hydrogen atom, aryl optionally having substituent(s), or lower alkoxy optionally having substituent(s), or R^8 and R^9 form, together with the adjacent carbon atom, an aliphatic heterocyclic group optionally having
20 substituent(s))), or a pharmaceutically acceptable salt thereof.

(2) The pyridone compound or the pharmaceutically acceptable salt thereof according to (1), wherein R^1 is aryl optionally having substituent(s), an aromatic heterocyclic group
25 optionally having substituent(s), or an aliphatic heterocyclic group optionally having substituent(s).

(3) The pyridone compound or the pharmaceutically acceptable salt thereof according to (1), wherein R^1 is aryl optionally having substituent(s).

30 (4) The pyridone compound or the pharmaceutically acceptable salt thereof according to (1), wherein R^1 is a phenyl optionally having substituent(s).

(5) The pyridone compound or the pharmaceutically acceptable salt thereof according to (1), wherein R^1 is an aromatic heterocyclic group optionally having substituent(s).

(6) The pyridone compound or the pharmaceutically acceptable salt thereof according to (1), wherein R^1 is an aliphatic heterocyclic group optionally having substituent(s).

[0020]

(7) The pyridone compound or the pharmaceutically acceptable salt thereof according to any of (1) - (6), wherein R^2 is a hydrogen atom, halogen or lower alkyl optionally having substituent(s).

(8) The pyridone compound or the pharmaceutically acceptable salt thereof according to any of (1) - (6), wherein R^2 is lower alkyl optionally having substituent(s).

(9) The pyridone compound or the pharmaceutically acceptable salt thereof according to any of (1) - (6), wherein R^2 is halogen.

(10) The pyridone compound or the pharmaceutically acceptable salt thereof according to any of (1) - (9), wherein R^3 is lower alkyl optionally having substituent(s), lower alkoxy optionally having substituent(s), or $-NR^{3a}R^{3b}$ (wherein, R^{3a} and R^{3b} are each as defined above).

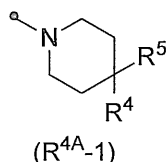
(11) The pyridone compound or the pharmaceutically acceptable salt thereof according to any of (1) - (9), wherein R^3 is lower alkyl optionally having substituent(s).

(12) The pyridone compound or the pharmaceutically acceptable salt thereof according to any of (1) - (9), wherein R^3 is lower alkoxy optionally having substituent(s).

(13) The pyridone compound or the pharmaceutically acceptable salt thereof according to any of (1) - (9), wherein R^3 is $-NR^{3a}R^{3b}$ (wherein, R^{3a} and R^{3b} are each as defined above).

(14) The pyridone compound or the pharmaceutically acceptable salt thereof according to any of (1) - (13), wherein R^{4A} is the following formula ($R^{4A}-1$)

[0021]



[0022]

(wherein, R⁴ and R⁵ are each as defined above).

(15) The pyridone compound or the pharmaceutically acceptable
5 salt thereof according to (14), wherein R⁴ and R⁵ are the same
or different and each is a hydrogen atom, or aryl optionally
having substituent(s).

(16) The pyridone compound or the pharmaceutically acceptable
salt thereof according to (14), wherein R⁴ and R⁵ are the same
10 or different and each is a hydrogen atom, or phenyl optionally
having substituent(s).

[0023]

(17) A medicament comprising, as an active ingredient, the
pyridone compound or the pharmaceutically acceptable salt
15 thereof described in any of (1) - (16).

(18) A CCR10 receptor antagonist comprising, as an active
ingredient, the pyridone compound or the pharmaceutically
acceptable salt thereof described in any of (1) - (16).

(19) An agent for the prophylaxis and/or treatment of a skin
20 disease comprising, as an active ingredient, the pyridone
compound or the pharmaceutically acceptable salt thereof
described in any of (1) - (16).

(20) The agent for the prophylaxis and/or treatment of a skin
disease according to (19), wherein the skin disease is a skin
25 disease selected from acne vulgaris, drug eruption, contact
dermatitis, dermatitis due to venomous moth, pollen dermatitis,
urticaria, psoriasis, atopic dermatitis, Candida dermatitis,
seborrheic dermatitis, eczema, Stevens-Johnson syndrome, toxic
epidermal necrosis, erythema multiforme, erythema nodosum,
30 granuloma annulare, pityriasis rosea, rosacea, lichen planus,
lichen pilaris (keratosis pilaris), photosensitivity, solar
dermatitis, miliaria, herpes simplex, Kaposi's varicelliform

eruption, impetigo contagiosa, staphylococcal scalded skin syndrome, erysipelas, slap cheek, lupus erythematosus, keloid, Hailey-Hailey disease, scabies and linear dermatitis.

(21) The agent for the prophylaxis and/or treatment of a skin
5 disease according to (19), wherein the skin disease is a skin
disease selected from contact dermatitis and atopic dermatitis.
[0024]

(22) A method of inhibiting a CCR10 receptor, comprising a
step of administering an effective amount of the pyridone
10 compound or the pharmaceutically acceptable salt thereof
described in any of (1) - (16).

(23) A method for the prophylaxis and/or treatment of a skin
disease, comprising a step of administering an effective
amount of the pyridone compound or the pharmaceutically
15 acceptable salt thereof described in any of (1) - (16).

(24) The method according to (23), wherein the skin disease is
a skin disease selected from acne vulgaris, drug eruption,
contact dermatitis, dermatitis due to venomous moth, pollen
dermatitis, urticaria, psoriasis, atopic dermatitis, Candida
20 dermatitis, seborrheic dermatitis, eczema, Stevens-Johnson
syndrome, toxic epidermal necrosis, erythema multiforme,
erythema nodosum, granuloma annulare, pityriasis rosea,
rosacea, lichen planus, lichen pilaris (keratosis pilaris),
photosensitivity, solar dermatitis, miliaria, herpes simplex,
25 Kaposi's varicelliform eruption, impetigo contagiosa,
staphylococcal scalded skin syndrome, erysipelas, slap cheek,
lupus erythematosus, keloid, Hailey-Hailey disease, scabies
and linear dermatitis.

(25) The method according to (23), wherein the skin disease is
30 a skin disease selected from contact dermatitis and atopic
dermatitis.

[0025]

(26) The pyridone compound or the pharmaceutically acceptable
salt thereof described in any of (1) - (16), for use in
35 inhibition of a CCR10 receptor.

(27) The pyridone compound or the pharmaceutically acceptable salt thereof described in any of (1) - (16), for use in the prophylaxis and/or treatment of a skin disease.

(28) The pyridone compound or the pharmaceutically acceptable salt thereof according to (27), wherein the skin disease is a skin disease selected from acne vulgaris, drug eruption, contact dermatitis, dermatitis due to venomous moth, pollen dermatitis, urticaria, psoriasis, atopic dermatitis, Candidal dermatitis, seborrheic dermatitis, eczema, Stevens-Johnson syndrome, toxic epidermal necrosis, erythema multiforme, erythema nodosum, granuloma annulare, pityriasis rosea, rosacea, lichen planus, lichen pilaris (keratosis pilaris), photosensitivity, solar dermatitis, miliaria, herpes simplex, Kaposi's varicelliform eruption, impetigo contagiosa, staphylococcal scalded skin syndrome, erysipelas, slap cheek, lupus erythematosus, keloid, Hailey-Hailey disease, scabies and linear dermatitis.

(29) The pyridone compound or the pharmaceutically acceptable salt thereof according to (27), wherein the skin disease is a skin disease selected from contact dermatitis and atopic dermatitis.

[0026]

(30) Use of the pyridone compound or the pharmaceutically acceptable salt thereof described in any of (1) - (16), for the manufacture of a CCR10 receptor antagonist.

(31) Use of the pyridone compound or the pharmaceutically acceptable salt thereof described in any of (1) - (16), for the manufacture of an agent for the prophylaxis and/or treatment of a skin disease.

(32) The use according to (31), wherein the skin disease is a skin disease selected from acne vulgaris, drug eruption, contact dermatitis, dermatitis due to venomous moth, pollen dermatitis, urticaria, psoriasis, atopic dermatitis, Candida dermatitis, seborrheic dermatitis, eczema, Stevens-Johnson syndrome, toxic epidermal necrosis, erythema multiforme,

erythema nodosum, granuloma annulare, pityriasis rosea, rosacea, lichen planus, lichen pilaris (keratosis pilaris), photosensitivity, solar dermatitis, miliaria, herpes simplex, Kaposi's varicelliform eruption, impetigo contagiosa,
5 staphylococcal scalded skin syndrome, erysipelas, slap cheek, lupus erythematosus, keloid, Hailey-Hailey disease, scabies and linear dermatitis.

(33) The use according to (31), wherein the skin disease is a skin disease selected from contact dermatitis and atopic
10 dermatitis.

Effect of the Invention

[0027]

The pyridone compound or the pharmaceutically acceptable
15 salt thereof of the present invention is useful as, for example, a prophylactic and/or therapeutic agent for skin diseases and the like.

According to the present invention, a pyridone compound or a pharmaceutically acceptable salt thereof useful as a
20 prophylactic and/or therapeutic agent for skin diseases, and the like are provided.

Mode for Carrying out the Invention

[0028]

25 Hereinafter a compound represented by the general formula (I) is referred to as compound (I). Compounds having the other formula numbers are referred to in the same manner.

In a definition of each group in the general formula (I), examples of the lower alkyl, and the lower alkyl moiety
30 of the lower alkoxy, the lower alkanoyl and the lower alkylcarbamoyl include linear or branched alkyl having 1 - 10 carbon atoms, and more specific examples thereof include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl,
35 nonyl, decyl and the like.

[0029]

Examples of the lower alkenyl include linear or branched alkenyl having 2 - 10 carbon atoms, and more specific examples thereof include vinyl, allyl, 1-propenyl, butenyl, pentenyl,
5 hexenyl, heptenyl, octenyl, nonenyl, decenyl and the like.

Examples of the lower alkynyl include linear or branched alkynyl having 2 - 10 carbon atoms, and more specific examples thereof include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl and the like.

10 [0030]

Examples of the cycloalkyl include cycloalkyl having 3 - 8 carbon atoms, and more specific examples thereof include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

15 Examples of the aralkyl include aralkyl having 7 - 16 carbon atoms, and more specific examples thereof include benzyl, phenethyl, phenylpropyl, phenylbutyl, phenylpentyl, phenylhexyl, phenylheptyl, phenyloctyl, phenylnonyl, phenyldecyl, naphthylmethyl, naphthylethyl, naphthylpropyl,
20 naphthylbutyl, naphthylpentyl, naphthylhexyl, anthrylmethyl, anthrylethyl and the like.

[0031]

Examples of aryl include aryl having 6 - 14 carbon atoms, and more specific examples thereof include phenyl, naphthyl,
25 azulenyl, anthryl and the like.

Examples of the aliphatic heterocyclic group, and the aliphatic heterocyclic group formed together with the adjacent carbon atom include a 3- to 7-membered monocyclic aliphatic heterocyclic group containing at least one atom selected from
30 a nitrogen atom, an oxygen atom and a sulfur atom, a bicyclic or tricyclic fused aliphatic heterocyclic group, in which 3- to 8-membered rings are fused, and which contains at least one atom selected from a nitrogen atom, an oxygen atom and a sulfur atom, and the like, and more specific examples thereof
35 include aziridinyl, azetidiny, pyrrolidinyl, piperidino,

piperidinyl, azepanyl, 1,2,5,6-tetrahydropyridyl,
imidazolidinyl, pyrazolidinyl, piperazinyl, homopiperazinyl,
pyrazolinyl, oxiranyl, tetrahydrofuranyl, tetrahydro-2H-
pyranyl, 5,6-dihydro-2H-pyranyl, oxazolidinyl, morpholino,
5 morpholinyl, thioxazolidinyl, thiomorpholinyl, 2H-oxazolyl,
2H-thioxazolyl, dihydroindolyl, dihydroisoindolyl,
dihydrobenzofuranyl, benzimidazolidinyl, dihydrobenzooxazolyl,
dihydrobenzothioxazolyl, benzodioxolinyl, tetrahydroquinolyl,
tetrahydroisoquinolyl, dihydro-2H-chromanyl, dihydro-1H-
10 chromanyl, dihydro-2H-thiochromanyl, dihydro-1H-thiochromanyl,
tetrahydroquinoxalinyl, tetrahydroquinazolinyl,
dihydrobenzodioxanyl, dihydrooxadiazolyl, isoindolinyl,
dihydrobenzodioxinyl, dihydrobenzodioxepinyl,
dihydroisobenzofuranyl, and the like.

15 [0032]

Examples of the aromatic heterocyclic group include a 5-
or 6-membered monocyclic aromatic heterocyclic group
containing at least one atom selected from a nitrogen atom, an
oxygen atom and a sulfur atom, a bicyclic or tricyclic fused
20 aromatic heterocyclic group, in which 3- to 8-membered rings
are fused, and which contains at least one atom selected from
a nitrogen atom, an oxygen atom and a sulfur atom, and the
like, and more specific examples thereof include furyl,
thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl,
25 oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, triazolyl,
tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl,
triazinyl, benzofuranyl, benzothiophenyl, benzoxazolyl,
benzothiazolyl, isoindolyl, indolyl, indazolyl, benzimidazolyl,
benzotriazolyl, oxazolopyrimidinyl, thiazolopyrimidinyl,
30 pyrrolopyridinyl, pyrrolopyrimidinyl, imidazopyridinyl,
purinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl,
quinazolinyl, quinoxalinyl, naphthyridinyl, benzooxadiazolyl,
dioxobenzothiophenyl and the like.

[0033]

35 Examples of the nitrogen-containing heterocyclic group,

which is formed together with the adjacent nitrogen atom include a 5-or 6-membered monocyclic heterocyclic group (said the monocyclic heterocyclic group may contain other nitrogen atom(s), oxygen atom(s) or sulfur atom(s)), a bicyclic or
5 tricyclic fused heterocyclic group, in which 3- to 8-membered rings are fused, and which contains at least one nitrogen atom (said the fused heterocyclic group may contain other nitrogen atom(s), oxygen atom(s) or sulfur atom(s)), and the like, and more specific examples thereof include aziridinyl, azetidiny, pyrrolidinyl, piperidino, azepanyl, pyrrolyl, imidazolidinyl, imidazolyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, piperazinyl, homopiperazinyl, oxazolidinyl, 2H-oxazolyl, thioxazolidinyl, 2H-thioxazolyl, morpholino, thiomorpholinyl, dihydroindolyl, dihydroisoindolyl, indolyl, isoindolyl, tetrahydroquinolyl,
15 tetrahydroisoquinolyl, dihydrobenzooxazolyl, dihydrobenzothioxazolyl, benzimidazolidinyl, benzimidazolyl, dihydroindazolyl, indazolyl, benzotriazolyl, pyrrolopyridinyl, pyrrolopyrimidinyl, imidazopyridinyl, purinyl, dihydroisobenzofuranyl and the like.

20 [0034]

Examples of the heterocyclic group moiety in the heterocyclic alkyl include the groups recited in the definitions of the aforementioned aliphatic heterocyclic group and the aforementioned aromatic heterocyclic group and the
25 like.

Examples of the alkylene moiety in the heterocyclic alkyl include the groups recited as examples of the aforementioned lower alkyl from which one hydrogen atom has been removed, and more specific examples thereof include methylene, ethylene,
30 propylene and the like.

[0035]

Halogen means each atom of fluorine, chlorine, bromine or iodine.

Examples of the substituent in the lower alkyl optionally
35 having substituent(s), the lower alkoxy optionally having

substituent(s), the lower alkenyl optionally having
substituent(s), the lower alkynyl optionally having
substituent(s), the lower alkanoyl optionally having
substituent(s), and the lower alkylcarbamoyl optionally having
5 substituent(s), which may be the same or different and in
number of 1 to 3, include substituents selected from the group
comprising halogen, hydroxy, mercapto, nitro, cyano, carboxy,
hydroxyimino, carbamoyl optionally having substituent(s)
(examples of the substituent in the substituted carbamoyl
10 include 1 to 2 substituents selected from cyano, C₁₋₁₀ alkyl, C₁₋₁₀
alkylsulfonyl and the like), C₃₋₈ cycloalkyl, C₁₋₁₀ alkoxy, C₃₋₈
cycloalkoxy, C₆₋₁₄ aryloxy, C₇₋₁₆ aralkyloxy, C₂₋₁₁ alkanoyloxy,
C₇₋₁₅ aroyloxy, C₁₋₁₀ alkylthio, -NR^XR^Y (wherein R^X and R^Y are the
same or different and each represents a hydrogen atom, C₁₋₁₀
15 alkyl, C₃₋₈ cycloalkyl, C₆₋₁₄ aryl, aromatic heterocyclic group,
C₇₋₁₆ aralkyl, C₂₋₁₁ alkanoyl, C₇₋₁₅ aroyl, C₁₋₁₀ alkoxy-carbonyl, C₇₋₁₆
aralkyloxy-carbonyl and the like), C₂₋₁₁ alkanoyl, C₇₋₁₅ aroyl,
C₁₋₁₀ alkoxy-carbonyl, C₆₋₁₄ aryloxy-carbonyl, aliphatic
heterocyclic carbonyl optionally having substituent(s)
20 (examples of the substituent in the substituted aliphatic
heterocyclic carbonyl include 1 to 3 substituents selected
from cyano and the like) and the like.

[0036]

Examples of the substituent in the aryl optionally having
25 substituent(s), the phenyl optionally having substituent(s),
the aromatic heterocyclic group optionally having
substituent(s), and the aralkyl optionally having
substituent(s), which may be the same or different and in
number of 1 to 3, include substituents selected from the group
30 comprising halogen, hydroxy, mercapto, nitro, cyano, carboxy,
carbamoyl, C₁₋₁₀ alkyl, trifluoromethyl, C₃₋₈ cycloalkyl, C₆₋₁₄
aryl, an aliphatic heterocyclic group, an aromatic
heterocyclic group, C₁₋₁₀ alkoxy optionally having
substituent(s) (examples of the substituent in the substituted
35 C₁₋₁₀ alkoxy include 1 - 3 substituents selected from halogen

aroyl, C₁₋₁₀ alkoxy carbonyl, C₇₋₁₆ aralkyloxy carbonyl or the like), C₂₋₁₁ alkanoyl, C₇₋₁₅ aroyl, C₁₋₁₀ alkoxy carbonyl, C₆₋₁₄ aryloxy carbonyl, C₁₋₁₀ alkyl carbamoyl, di-C₁₋₁₀ alkyl carbamoyl and the like.

5 [0038]

Examples of the C₁₋₁₀ alkyl shown herein and the C₁₋₁₀ alkyl moiety in the C₁₋₁₀ alkoxy, the C₂₋₁₁ alkanoyloxy, the C₁₋₁₀ alkylthio, the C₁₋₁₀ alkylsulfonyl, the C₂₋₁₁ alkanoyl, the C₁₋₁₀ alkoxy carbonyl, the C₁₋₁₀ alkyl carbamoyl, and the di-C₁₋₁₀ alkyl carbamoyl shown herein include the groups recited as examples of the aforementioned lower alkyl. The two C₁₋₁₀ alkyl moieties in the di-C₁₋₁₀ alkyl carbamoyl may be the same or different.

[0039]

15 Examples of the C₃₋₈ cycloalkyl and the cycloalkyl moiety in the C₃₋₈ cycloalkoxy include the groups recited as examples of the aforementioned cycloalkyl. Examples of the C₅₋₈ cycloalkyl include cycloalkyl having 5 - 8 carbon atoms, and more specific examples thereof include cyclopentyl, cyclohexyl, 20 cycloheptyl, cyclooctyl and the like.

Examples of the C₆₋₁₄ aryl and the aryl moiety in the C₆₋₁₄ aryloxy, the C₇₋₁₅ aroyl, the C₇₋₁₅ aryloxy and the C₆₋₁₄ aryloxy carbonyl include the groups recited as examples of the aforementioned aryl.

25 [0040]

Examples of the C₇₋₁₆ aralkyl and the aralkyl moiety in the C₇₋₁₆ aralkyloxy and the C₇₋₁₆ aralkyloxy carbonyl include the groups recited as examples of the aforementioned aralkyl.

Examples of the aliphatic heterocyclic group and the 30 aliphatic heterocyclic group moiety in the aliphatic heterocyclic carbonyl include the groups recited as examples of the aforementioned aliphatic heterocyclic group.

The aromatic heterocyclic group and the halogen are as defined for the aforementioned aromatic heterocyclic group and 35 the aforementioned halogen, respectively.

[0041]

In each group of compound (I),
as R¹, phenyl optionally having substituent(s), an aromatic
heterocyclic group optionally having substituent(s), or an
5 aliphatic heterocyclic group optionally having substituent(s)
is preferable, and more preferably, phenyl optionally having
substituent(s) is selected, and as the substituent in the
phenyl optionally having substituent(s), C₁₋₁₀ alkyl or halogen
is preferable, and the number thereof is preferably 1 or 2.
10 Also, R¹ is more preferably an aromatic heterocyclic group.

[0042]

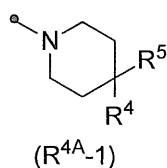
As R², a hydrogen atom, halogen or C₁₋₁₀ alkyl optionally
having substituent(s) is preferable, and more preferably,
halogen or C₁₋₁₀ alkyl is selected, and more preferably, halogen
15 is selected.

As R³, C₁₋₁₀ alkyl optionally having substituent(s), C₁₋₁₀
alkoxy optionally having substituent(s), or -NR^{3a}R^{3b} (wherein R^{3a}
and R^{3b} are each as defined above) is preferable, and more
preferably, C₁₋₁₀ alkyl optionally having substituent(s) is
20 selected, and as the substituent in the C₁₋₁₀ alkyl optionally
having substituent(s), halogen, cyano, hydroxy or C₁₋₁₀ alkoxy
is preferable, and the number thereof is preferably 0 or 1.
Also, R³ is more preferably C₁₋₁₀ alkoxy optionally having
substituent(s), and as the substituent in the C₁₋₁₀ alkoxy
25 optionally having substituent(s), halogen, hydroxy or C₁₋₁₀
alkoxy is preferable, and the number thereof is preferably 0
or 1.

[0043]

When R^{4A} is the following formula (R^{4A}-1),

30 [0044]



[0045]

as R⁴, a hydrogen atom is preferable.

As R⁵, a phenyl optionally having substituent(s) is preferable, and as the substituent in the phenyl optionally having substituent(s), halogen is preferable, and the number
5 thereof is preferably 0 or 1.

As compound (I), a compound wherein one or more of the above-mentioned preferable substituents are respectively combined is preferable. Furthermore, compounds obtained by limiting compounds (I) described in (2) - (16) in "Means of
10 Solving the Problems" with preferable substituents shown above are preferable. Compounds obtained by limiting compounds (I) described in (2) - (16) in "Means of Solving the Problems" with a combination of two or more preferable substituents shown above are more preferable.

15 [0046]

The pharmaceutically acceptable salt of compound (I) comprises, for example, pharmaceutically acceptable acid addition salts, metal salts, ammonium salts, organic amine addition salts, amino acid addition salts and the like.
20 Examples of the pharmaceutically acceptable acid addition salt of compound (I) include, but are not limited to, inorganic acid salts such as hydrochloride, hydrobromide, nitrate, sulfate, phosphate and the like, organic acid salts such as acetate, oxalate, maleate, fumarate, citrate, benzoate,
25 methanesulfonate and the like, and the like. Examples of the pharmaceutically acceptable metal salt include, but are not limited to, sodium salt, potassium salt, magnesium salt, calcium salt, aluminum salt, zinc salt and the like. Examples of the pharmaceutically acceptable ammonium salt include, but
30 are not limited to, salts such as ammonium salt, tetramethylammonium salt and the like. Examples of the pharmaceutically acceptable organic amine addition salt include, but are not limited to, addition salts of morpholine, piperidine and the like. Examples of the pharmaceutically
35 acceptable amino acid addition salt include, but are not

limited to, addition salts of lysine, glycine, phenylalanine, aspartic acid, glutamic acid and the like.

[0047]

Also, the pharmaceutically acceptable salt of compound
5 (I) comprises quaternary ammonium salt. The quaternary ammonium salt is a compound wherein a nitrogen atom is quaternized by Rx (Rx is, for example, lower alkyl or aralkyl and the like, wherein lower alkyl and aralkyl are as defined above).

10 Further, the pharmaceutically acceptable salt of compound (I) includes N-oxide form. The N-oxide form is a compound wherein a nitrogen atom is oxidized. An N-oxide form of compound (I) can be obtained from compound (I) wherein it is not N-oxide by any oxidation method and using an oxidation
15 reagent such as m-chloroperbenzoic acid, air oxidation, liver extract and the like.

[0048]

The skin disease in the present invention refers to a disease with a lesion appearing on the skin. Specific examples
20 include acne vulgaris, drug eruption, contact dermatitis, dermatitis due to venomous moth, pollen dermatitis, urticaria, psoriasis, atopic dermatitis, Candida dermatitis, seborrheic dermatitis, eczema, Stevens-Johnson syndrome, toxic epidermal necrosis, erythema multiforme, erythema nodosum, granuloma
25 annulare, pityriasis rosea, rosacea, lichen planus, lichen pilaris (keratosis pilaris), photosensitivity, solar dermatitis, miliaria, herpes simplex, Kaposi's varicelliform eruption, impetigo contagiosa, staphylococcal scalded skin syndrome, erysipelas, slap cheek, lupus erythematosus, keloid,
30 Hailey-Hailey disease, scabies, linear dermatitis and the like. However, the skin diseases in the present invention are not limited to these.

[0049]

The treatment in the present invention refers to
35 conversion, mitigation or inhibition of the progression of the

disease or condition to be applied, or one or more symptoms of such disease or condition. It further includes application for inhibition of the progression of symptoms before remission of the disease, or when they are mild. In skin diseases,
5 aggravation and remission may repeat periodically and chronically. The therapeutic agent and/or prophylactic agent of the present invention are/is also used for prolongation of the remission period or prevention of aggravation. The prophylactic agent is also used for the prevention of the
10 onset of the disease.

[0050]

The aggravation used in the present specification refers to exacerbation of the symptoms of a disease.

The remission used in the present specification refers to
15 temporary or permanent mitigation or disappearance of the symptoms of a disease. Time of remission refers to a remission state, and remission length means a period when the state of remission continues.

The present invention also comprises prodrugs of compound
20 (I). The prodrug of compound (I) is a compound converted to compound (I) as a result of a reaction with an enzyme, gastric acid and the like in the body. As prodrug, many kinds of prodrugs are known, and a suitable prodrug can be selected from a known document (for example, Development of
25 Pharmaceutical Product, Hirokawa Publishing INC., 1990, vol. 7, page 163) and synthesized by a known method. Examples of the prodrug of compound (I) when compound (I) has amino include a compound wherein the amino is acylated, alkylated or phosphorylated; examples thereof when compound (I) has hydroxy
30 include a compound wherein the hydroxy is acylated, alkylated, phosphorylated or borated; and examples thereof when compound (I) has carboxy include a compound wherein the carboxy is esterified or amidated and the like. Also, the prodrug of compound (I) may be any of hydrate, non-hydrate and solvate
35 and, like compound (I), may form a salt with a

pharmaceutically acceptable acid or base.

[0051]

A preferable compound used in the present specification is a compound having not only pharmacological activity but
5 also desirable properties in one or more items from various evaluation items requested for pharmaceutical products such as a prophylactic and/or therapeutic agent for skin diseases and the like, such as physical stability, stability under physiological conditions, safety for living organisms and the
10 like.

Compound (I) or a pharmaceutically acceptable salt thereof of the present invention sometimes shows an unpreferable action on living organisms. Even in such case, it can exhibit usefulness as a prophylactic and/or therapeutic
15 agent for skin diseases or as a pharmaceutical product, by employing an appropriate dose and administration method, while reducing the unpreferable action.

[0052]

Among compound (I) of the present invention,
20 stereoisomers such as geometric isomer, optical isomer and the like, tautomer and the like may exist. The present invention comprises all possible isomers and mixtures thereof including them, and the mixing ratio thereof may be any value.

Compound (I) or a pharmaceutically acceptable salt
25 thereof of the present invention is sometimes present as an adduct with water or various solvents, and such adduct is also comprised in the present invention.

[0053]

A part or all of the respective atoms in compound (I) may
30 be replaced by corresponding isotope atom(s), respectively, and the present invention also comprises such compounds replaced by such isotope atom(s). For example, a part or all of hydrogen atoms in compound (I) may be a hydrogen atom having an atomic weight of 2 (deuterium atom). A compound
35 incorporating a radioisotope such as ^3H (tritium) or ^{14}C from

among the isotopes is useful for examining the tissue distribution of a compound and screening for an agent for the prophylaxis and/or treatment of skin diseases.

[0054]

5 For example, a compound wherein a part or all of the respective atoms in compound (I) is/are replaced by corresponding isotope atom(s), respectively, can be produced by using a commercially available building block and in the same manner as in each of the production methods described in
10 the following. Also, a compound wherein a part or all of the hydrogen atoms in compound (I) is/are replaced by deuterium atom(s) can be synthesized by, for example, 1) a method using deuterium peroxide, to deuterate carboxylic acid and the like under basic conditions (US Patent No. 3849458), 2) a method
15 using an iridium complex as a catalyst, to deuterate alcohol, carboxylic acid and the like by using deuterium oxide as a deuterium source [J. Am. Chem. Soc., Vol. 124, No. 10, 2092 (2002)], 3) a method using palladium carbon as a catalyst, to deuterate fatty acid by using only a deuterium gas as a
20 deuterium source [LIPIDS, Vol. 9, No. 11, 913(1974)], 4) a method using a metal such as platinum, palladium, rhodium, ruthenium, iridium and the like as catalysts, to deuterate acrylic acid, methyl acrylate, methacrylic acid, methyl methacrylate and the like by using deuterium oxide, or
25 deuterium oxide and deuterium gas, as a deuterium source (JP-B-5-19536, JP-A-61-277648 and JP-A-61-275241), 5) a method using a catalyst such as palladium, nickel, copper or chromite copper and the like, to deuterate acrylic acid, methyl methacrylate and the like by using deuterium oxide as
30 deuterium source (JP-A-63-198638) and the like.

[0055]

 The isotope atom used in the present specification refers to an atom having an atom value or mass number different from the atom value or mass number generally found in nature.
35 Examples of the isotope atom in the compound of the present

invention include ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl and the like.

Next, production methods of compound (I) are explained.

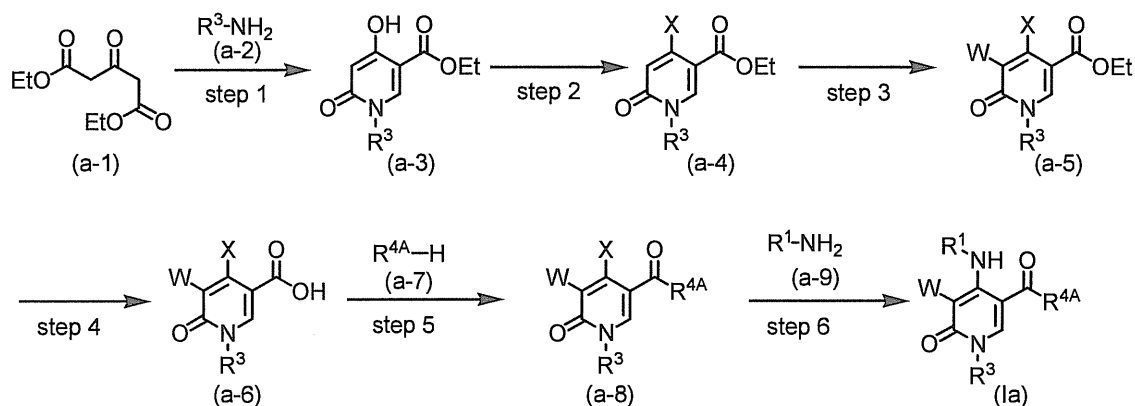
[0056]

Incidentally, in the production methods shown below, when a defined group changes under the conditions of the production methods or is inappropriate for performing the production methods, the desired compound can be produced by using the methods for introducing and removing a protecting group conventionally used in the synthetic organic chemistry (for example, methods described in Protective Groups in Organic Synthesis, third edition, T.W. Greene, John Wiley & Sons Inc., 1999 and the like) and the like. Also, if necessary, the order of the reaction steps such as substituent introduction and the like, can be changed.

Production method 1

Among compounds (I), compound (Ia) wherein R^2 is halogen can be produced according to, for example, the following steps.

[0057]



[0058]

[wherein R^1 , R^3 and $\text{R}^{4\text{A}}$ are each as defined above, W represents halogen, Et represents ethyl, X represents halogen or a leaving group such as sulfonate (for example, methanesulfonyloxy, p-toluenesulfonyloxy, trifluoromethanesulfonyloxy or the like) or the like]

step 1

Compound (a-3) can be produced by reacting commercially available diethyl 3-oxopentanedioate (a-1) in the presence of 1 - 5 equivalents of trialkyl orthoformate and 1 - 10
5 equivalents of acetic anhydride at a temperature between 80°C and 150°C for 5 min to 72 hr, concentrating same under reduced pressure, adding a solvent and 1 - 10 equivalents of compound (a-2), and reacting the mixture at a temperature between -20°C and 100°C for 5 min to 72 hr.

10 [0059]

Examples of the trialkyl orthoformate include trimethyl orthoformate, triethyl orthoformate and the like.

Examples of the solvent include acetonitrile, tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), methanol,
15 ethanol, N,N-dimethylformamide (DMF), water and the like, and these are used singly or in a mixture.

[0060]

Compound (a-2) can be obtained as a commercially available product, or can be obtained by a known method [for
20 example, Jikken Kagaku Kouza, 5th ed., vol. 14, p.351, Maruzen Company, Limited (2005) and the like] or a method analogous thereto.

Incidentally, depending on the kind of compound (a-2), the reactivity is poor and the reaction up to compound (a-3) may
25 not be completed. In such a case, the compound can be produced by once isolating the reaction intermediate, adding a solvent and, if necessary, preferably 1 equivalent to a large excess amount of an additive, and reacting the mixture for 5 min to 72 hr at a temperature between -20°C and the boiling point of
30 the solvent to be used.

[0061]

Examples of the additive include pyridine, triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and the like.

35 Examples of the solvent include dichloromethane,

chloroform, 1,2-dichloroethane, acetonitrile, toluene, diethyl ether, THF, DME, dioxane, DMF, N,N-dimethylacetamide (DMA), N-methylpyrrolidone (NMP) and the like, and these are used singly or in a mixture.

5 step 2

When X is halogen, compound (a-4) can be produced by reacting compound (a-3) in a solvent or without solvent in the presence of 1 equivalent to a large excess amount of a halogenating agent and, if necessary, a catalytic amount to 1
10 equivalent of an additive, at a temperature between -20°C and 150°C for 5 min to 72 hr.

[0062]

Examples of the halogenating agent include phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride,
15 thionyl chloride, phosphorus oxybromide, phosphorus tribromide and the like.

Examples of the additive include DMF, pyridine, diisopropylethylamine and the like.

Examples of the solvent include dichloromethane,
20 chloroform, 1,2-dichloroethane, acetonitrile, toluene, diethyl ether, THF, DME, dioxane, DMF, DMA, NMP, pyridine and the like, and these are used singly or in a mixture.

[0063]

When X is sulfonate, compound (a-4) can be produced by
25 reacting compound (a-3) in a solvent or without solvent in the presence of 1 - 10 equivalents of a sulfonylating agent and 1 - 10 equivalents of an additive at a temperature between -78°C and 150°C for 5 min to 72 hr.

Examples of the sulfonylating agent include
30 methanesulfonyl chloride, p-toluenesulfonyl chloride, trifluoromethanesulfonic anhydride and the like.

Examples of the additive include pyridine, triethylamine, diisopropylethylamine, DBU and the like.

[0064]

35 Examples of the solvent include dichloromethane,

chloroform, 1,2-dichloroethane, acetonitrile, toluene, diethyl ether, THF, DME, dioxane, DMF, DMA, NMP and the like, and these are used singly or in a mixture.

step 3

5 Compound (a-5) can be produced by reacting compound (a-4) in a solvent or without solvent in the presence of 1 - 5 equivalents of a halogenating agent, at a temperature between -30°C and 150°C for 5 min to 72 hr.

[0065]

10 Examples of the halogenating agent include chlorine, bromine, iodine, N,N,N,N-tetra-n-butylammonium tribromide, N-chlorosuccinimide, N-bromosuccinimide, N-iodosuccinimide, 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane-bis(tetrafluoroborate) and the like.

15 Examples of the solvent include acetone, 1,4-dioxane, acetonitrile, chloroform, dichloromethane, THF, DME, ethyl acetate, methanol, ethanol, DMF, acetic acid, water and the like, and these are used singly or in a mixture.

step 4

20 Compound (a-6) can be produced by treating compound (a-5) with 1 equivalent to a large excess amount of a base in a solvent for 5 min to 72 hr at a temperature between 0°C and the boiling point of the solvent to be used.

[0066]

25 Examples of the base include potassium carbonate, lithium hydroxide, potassium hydroxide, sodium hydroxide, sodium methoxide and the like.

 Examples of the solvent include solvents including water, and examples of the solvent include methanol, ethanol,
30 dichloromethane, chloroform, 1,2-dichloroethane, toluene, ethyl acetate, acetonitrile, diethyl ether, THF, DME, dioxane, DMF, DMA, NMP, pyridine and the like. These are used by mixing with water, or by mixing them and adding water thereto.

step 5

35 Compound (a-8) can be produced by reacting compound (a-6)

and 1 - 5 equivalents of compound (a-7) in a solvent in the presence of 1 - 5 equivalents of a condensing agent and, if necessary, 1 - 5 equivalents of an additive, for 5 min to 72 hr at a temperature between -20°C and the boiling point of the solvent to be used.

[0067]

Examples of the condensing agent include 1,3-dicyclohexanecarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC), carbonyldiimidazole (CDI), 2-chloro-1-methylpyridinium iodide, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HATU) and the like.

Examples of the additive include 1-hydroxybenzotriazole monohydrate (HOBt), N,N-diisopropylamine and the like.

[0068]

Examples of the solvent include methanol, ethanol, dichloromethane, chloroform, 1,2-dichloroethane, toluene, ethyl acetate, acetonitrile, diethyl ether, THF, DME, dioxane, DMF, DMA, NMP, pyridine, water and the like, and these are used singly or in a mixture.

Compound (a-7) is obtained as a commercially available product, or can be obtained by a known method [for example, Jikken Kagaku Kouza, 5th ed., vol. 14, p. 537, Maruzen Company, Limited (2005) and the like] or a method analogous thereto.

step 6

Compound (Ia) can be produced by reacting compound (a-8) and 1 equivalent to a large excess amount of compound (a-9) in a solvent, preferably in the presence of 1 equivalent to a large excess amount of a base at a temperature between -78°C and 150°C for 5 min to 72 hr.

[0069]

Examples of the base include n-butyllithium, sec-butyllithium, tert-butyllithium, phenyllithium, lithiumdiisopropylamide, hexamethyldisilasilithium, potassium tert-butoxide, potassium carbonate, sodium hydride

and the like.

Examples of the solvent include dichloromethane, chloroform, 1,2-dichloroethane, toluene, diethyl ether, THF, DME, dioxane, hexane and the like, and these are used singly
5 or in a mixture.

[0070]

As an alternative method, compound (Ia) can also be produced by reacting compound (a-8) and 1 equivalent to a large excess amount of compound (a-9) in a solvent, preferably
10 in the presence of 0.1 equivalent - 10 equivalents of an acid for 5 min to 72 hr at a temperature between 20°C and the boiling point of the solvent to be used.

Examples of the acid include hydrochloric acid, sulfuric acid, formic acid, acetic acid, trifluoroacetic acid, p-
15 toluenesulfonic acid, methanesulfonic acid and the like, and these are used singly or in a mixture.

[0071]

Examples of the solvent include methanol, ethanol, dichloromethane, chloroform, 1,2-dichloroethane, toluene,
20 ethyl acetate, acetonitrile, diethyl ether, THF, DME, dioxane, DMF, DMA, NMP and the like, and these are used singly or in a mixture.

Also, as an alternative method, compound (Ia) can be produced by reacting compound (a-8) and preferably 1 - 10
25 equivalents of compound (a-9) in a solvent, preferably in the presence of 0.1 - 10 equivalents of a base and preferably 0.001 - 1 equivalent of a palladium catalyst, and 0.001 - 1 equivalent of a phosphine compound, if necessary, for 5 min to 72 hr at a temperature between -20°C and the boiling point of
30 the solvent to be used.

[0072]

Examples of the base include potassium carbonate, cesium carbonate, potassium phosphate, potassium tert-butoxide, sodium tert-butoxide, sodium disilazide and the like.

35 Examples of the palladium catalyst include palladium

acetate, palladium trifluoroacetate,
tris(dibenzylideneacetone)dipalladium and a chloroform adduct
thereof, tetrakis(triphenylphosphine)palladium, 1,1'-
bis(diphenylphosphino)ferrocenedichloropalladium
5 dichloromethane 1:1 adduct and the like.

[0073]

Examples of the phosphine compound include 2,2'-
bis(diphenylphosphino)-1,1'-binaphthyl, o-tolylphosphine,
tributylphosphine, di-tert-butylidiphenylphosphine, 2-(di-tert-
10 butylphosphino)biphenyl, 2-(dicyclohexylphosphino)biphenyl and
the like.

Examples of the solvent include toluene, xylene, ethyl
acetate, acetonitrile, diethyl ether, THF, DME, dioxane and
the like, and these are used singly or in a mixture.

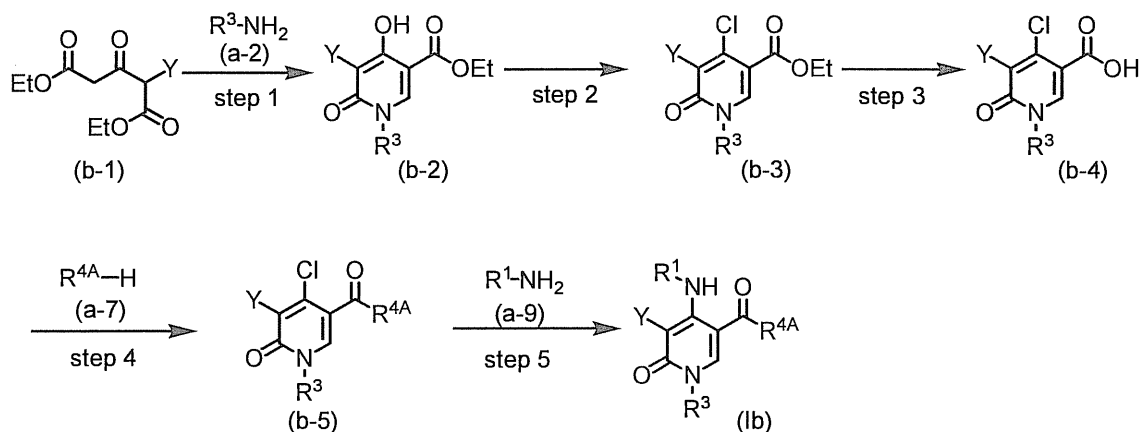
15 [0074]

Compound (a-9) can be obtained as a commercially
available product, or can be obtained by a known method [for
example, Jikken Kagaku Kouza, 5th ed., vol. 14, p. 351,
Maruzen Company, Limited (2005) and the like] or a method
20 analogous thereto.

Production method 2

Among compounds (I), compound (Ib) wherein R^2 is a
hydrogen atom, cyano or lower alkyl optionally having
25 substituent(s) can be produced according to the following
steps.

[0075]



[0076]

(wherein R^1 , R^3 , R^{4A} and Et are each as defined above, Y
 5 represents a hydrogen atom, cyano or lower alkyl optionally
 having substituent(s))

step 1

Compound (b-2) can be produced using compound (b-1) and
 compound (a-2) by a method similar to that of Production
 10 method 1, step 1.

[0077]

Compound (b-1) is obtained as a commercially available
 product, or can be obtained by a known method [for example,
 the method described in Journal of the Chemical Society, vol.
 15 85, p. 1760 (1904), the method described in Australian J. of
 Chemistry, vol. 52, p. 1013 (1999), and the like] or a method
 analogous thereto.

step 2

Compound (b-3) can be produced using compound (b-2) by a
 20 method similar to that of Production method 1, step 2.

step 3

Compound (b-4) can be produced using compound (b-3) by a
 method similar to that of Production method 1, step 4.

step 4

25 Compound (b-5) can be produced using compound (b-4) and
 compound (a-7) by a method similar to that of Production
 method 1, step 5.

step 5

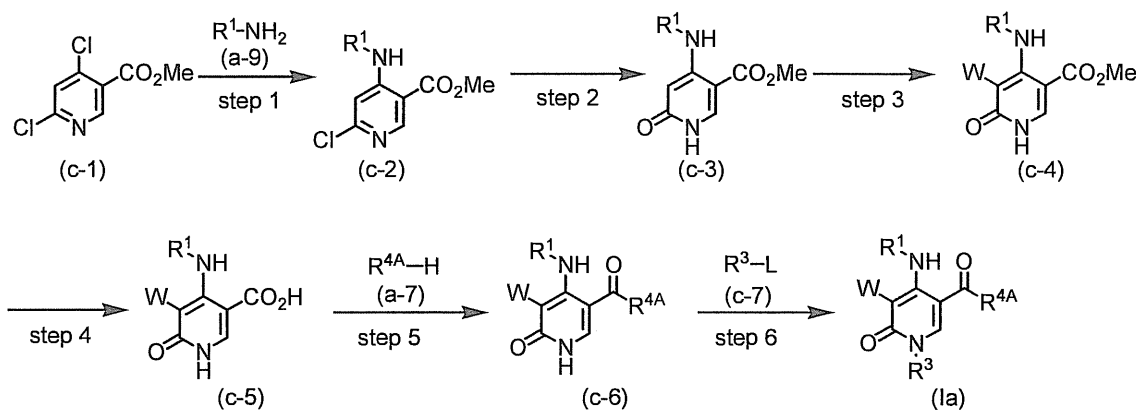
Compound (Ib) can be produced using compound (b-5) and compound (a-9) by a method similar to that of Production method 1, step 6.

5

Production method 3

Among compounds (I), compound (Ia) wherein R^2 is halogen can also be produced according to the following steps.

[0078]



10

[0079]

[wherein R^1 , R^3 , R^{4A} and W are each as defined above, L represents halogen, or a leaving group such as sulfonate (for example, methanesulfonyloxy, p-toluenesulfonyloxy, trifluoromethanesulfonyloxy or the like) or the like, and Me represents methyl]

step 1

Compound (c-2) can be produced using commercially available methyl 4,6-dichloronicotinate (c-1) and compound (a-9) by a method similar to that of Production method 1, step 6.

Compound (c-3) can be produced by treating compound (c-2) with 1 - 10 equivalents of an additive, if necessary, in a solvent for 5 min to 100 hr at a temperature between 0°C and the boiling point of the solvent to be used.

[0080]

Examples of the additive include ammonium acetate, sodium

methoxide and the like.

As the solvent, water, or a mixed solution of water and organic solvent is used. Examples of the organic solvent include acetic acid, methanol and the like, and these are used
5 singly or in a mixture.

As an alternative method, compound (c-3) can also be produced by treating compound (c-2) in a solvent with 1 equivalent to a large excess amount of a base for 5 min to 72 hr at a temperature between 0°C and the boiling point of the
10 solvent to be used.

[0081]

Examples of the base include potassium carbonate, lithium hydroxide, potassium hydroxide, sodium hydroxide, sodium methoxide and the like.

15 Examples of the solvent include solvents including water, and examples of the solvent include methanol, ethanol, dichloromethane, chloroform, 1,2-dichloroethane, toluene, ethyl acetate, acetonitrile, diethyl ether, THF, DME, dioxane, DMF, DMA, NMP, pyridine and the like. These are used by mixing
20 with water, or by mixing them and adding water thereto.

step 3

Compound (c-4) can be produced using compound (c-3) by a method similar to that of Production method 1, step 3.

step 4

25 Compound (c-5) can be produced using compound (c-4) by a method similar to that of Production method 1, step 4.

step 5

Compound (c-6) can be produced using compound (c-5) and compound (a-7) by a method similar to that of Production
30 method 1, step 5.

step 6

Compound (Ia) can be produced by reacting compound (c-6) and 1 equivalent to a large excess amount of compound (c-7) in a solvent in the presence of 1 equivalent to a large excess
35 amount of a base at a temperature between -78°C and 150°C for 5

min to 72 hr.

[0082]

Examples of the base include n-butyllithium, sec-butyllithium, tert-butyllithium, phenyllithium,
5 lithiumdiisopropylamide, hexamethyldisilasilithium, potassium tert-butoxide, potassium carbonate, sodium hydride and the like.

Examples of the solvent include dichloromethane, chloroform, 1,2-dichloroethane, toluene, diethyl ether, THF,
10 DME, dioxane, hexane and the like, and these are used singly or in a mixture.

[0083]

Also, as an alternative method, compound (Ia) can be produced by reacting compound (c-6) and 1 equivalent to a
15 large excess amount of compound (c-7) in a solvent in the presence of 0.1 - 10 equivalents of an acid, if necessary, for 5 min to 72 hr at a temperature between 20°C and the boiling point of the solvent to be used.

Examples of the acid include hydrochloric acid, sulfuric
20 acid, formic acid, acetic acid, trifluoroacetic acid, p-toluenesulfonic acid, methanesulfonic acid and the like, and these are used singly or in a mixture.

[0084]

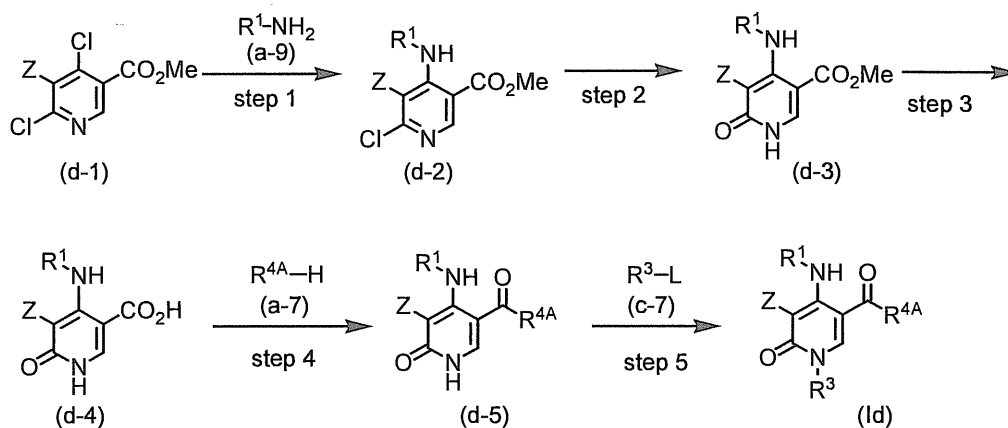
Examples of the solvent include methanol, ethanol,
25 dichloromethane, chloroform, 1,2-dichloroethane, toluene, ethyl acetate, acetonitrile, diethyl ether, THF, DME, dioxane, DMF, DMA, NMP and the like, and these are used singly or in a mixture.

Compound (c-7) can be obtained as a commercially
30 available product, or can be obtained by a known method [for example, Jikken Kagaku Kouza, 5th ed., vol. 14, p. 351, Maruzen Company, Limited (2005) and the like] or a method analogous thereto.

35 Production method 4

Among compounds (I), compound (Id) wherein R² is a hydrogen atom or fluorine atom can be produced according to the following steps.

[0085]



[0086]

(wherein R¹, R³, R⁴, R⁵, Me and L are each as defined above, and Z represents a hydrogen atom or a fluorine atom)

10 step 1

Compound (d-2) can be produced using compound (d-1) and compound (a-9) by a method similar to that of Production method 1, step 6.

[0087]

15 Compound (d-1) can be obtained as a commercially available product, or can be obtained by a known method [for example, Jikken Kagaku Kouza, 5th ed., vol. 16, p. 35, Maruzen Company, Limited (2005) and the like] or a method analogous thereto.

20 step 2

Compound (d-3) can be produced using compound (d-2) by a method similar to that of Production method 3, step 2.

step 3

Compound (d-4) can be produced using compound (d-3) by a method similar to that of Production method 1, step 4.

step 4

Compound (d-5) can be produced using compound (d-4) and compound (a-7) by a method similar to that of Production

method 1, step 5.

step 5

Compound (Id) can be produced using compound (d-5) by a method similar to that of Production method 3, step 6.

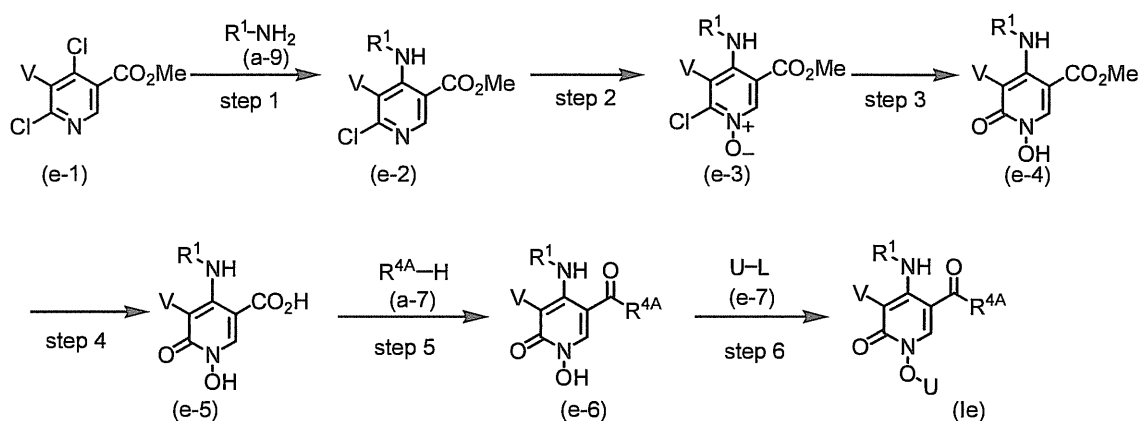
5

Production method 5

Among compounds (I), compound (Ie) wherein R³ is a hydrogen atom or halogen, and R³ is lower alkoxy optionally having substituent(s) can be produced according to the following steps.

10

[0088]



[0089]

15 (wherein R¹, R⁴, R⁵, Me and L are each as defined above, U represents the lower alkyl moiety optionally having substituent(s) of the lower alkoxy optionally having substituent(s) for R³, and V represents a hydrogen atom or halogen)

20 step 1

Compound (e-2) can be produced using compound (e-1) and compound (a-9) by a method similar to that of Production method 1, step 6.

[0090]

25 Compound (e-1) is obtained as a commercially available product, or can be obtained by a known method [for example, the method described in Jikken Kagaku Kouza, 5th ed., vol. 16, p. 35, Maruzen Company, Limited (2005) and the like] or a

method analogous thereto.

step 2

Compound (e-3) can be produced by treating compound (e-2) with 1 equivalent to a large excess amount of an oxidant, and
5 if necessary, 1 equivalent to a large excess amount of an additive, in a solvent or without solvent at a temperature between 0°C and 100°C for 5 min to 72 hr.

[0091]

Examples of the oxidant include metachlorobenzoic acid
10 (mCPBA), urea hydrogen peroxide (UHP), hydrogen peroxide and the like, and these are used singly or in a mixture.

Examples of the additive include phthalic anhydride, trifluoroacetic anhydride (TFAA), sulfuric acid, acetic acid and the like, and these are used singly or in a mixture.

15 Examples of the solvent include dichloromethane, chloroform, acetonitrile, THF, methanol, ethanol, water and the like, and these are used singly or in a mixture.

step 3

Compound (e-4) can be produced by treating compound (e-3)
20 with 1 equivalent to a large excess amount of an additive in a solvent or without solvent at a temperature between 0°C and 100°C for 5 min to 72 hr.

[0092]

Examples of the additive include potassium hydroxide,
25 sodium hydroxide, TFAA, acetic anhydride, acetic acid and the like, and these are used singly or in a mixture.

Examples of the solvent include 1,4-dioxane, THF, methanol, ethanol, water and the like, and these are used singly or in a mixture.

30 step 4

Compound (e-5) can be produced using compound (e-4) by a method similar to that of Production method 1, step 4.

step 5

Compound (e-6) can be produced using compound (e-5) and
35 compound (a-7) by a method similar to that of Production

method 1, step 5.

step 6

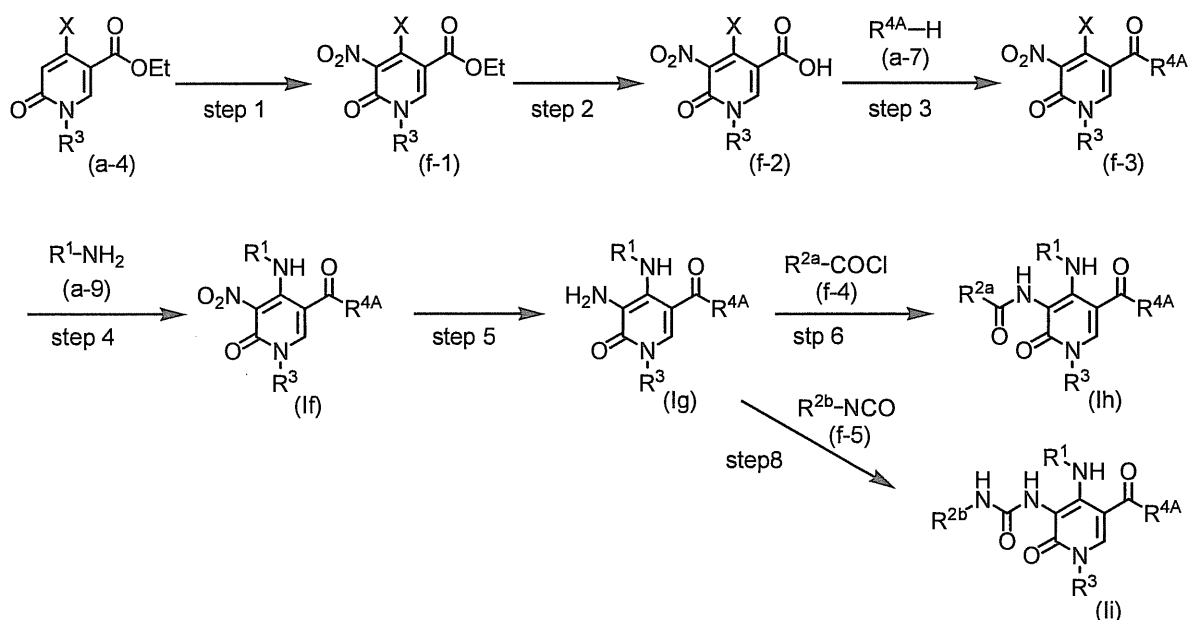
Compound (Ie) can be produced using compound (e-6) and compound (e-7) by a method similar to that of Production
5 method 3, step 6.

[0093]

Compound (e-7) is obtained as a commercially available product, or can be obtained by a known method [for example, Jikken Kagaku Kouza, 5th ed., vol. 14, p. 351, Maruzen Company,
10 Limited (2005) and the like] or a method analogous thereto.
production method 6

Among compounds (I), compound (If) wherein R^2 is nitro, and compounds (Ig) - (Ii) wherein R^2 is $-NR^{1a}R^{1b}$ (wherein R^{1a} and R^{1b} are each as defined above) can be produced according to the
15 following steps.

[0094]



[0095]

(wherein R^1 , R^3 , R^{4A} , X and Et are each as defined above, R^{2a}
20 represents the lower alkyl moiety optionally having
substituent(s) of the lower alkanoyl optionally having
substituent(s) when R^{1a} or R^{1b} is lower alkanoyl optionally
having substituent(s), and R^{2b} is the lower alkyl moiety
optionally having substituent(s) of the lower alkylcarbamoyl

optionally having substituent(s) when R^{1a} or R^{1b} is lower alkylcarbamoyl optionally having substituent(s))

step 1

Compound (f-1) can be produced by treating compound (a-4)
5 with 1 - 10 equivalents of a nitric acid compound and, where necessary, 1 equivalent to a large excess amount of an additive, without solvent or in a solvent, for 5 min - 72 hr at a temperature between -20°C and the boiling point of the solvent to be used.

10 [0096]

Examples of the nitric acid compound include concentrated nitric acid, fuming nitric acid, sodium nitrate, potassium nitrate and the like.

Examples of the additive include concentrated sulfuric
15 acid, concentrated hydrochloric acid, acetic acid and the like.

Examples of the solvent include dichloromethane, chloroform, 1,2-dichloroethane, nitromethane, nitroethane, water and the like, and these are used singly or in a mixture.
step 2

20 Compound (f-2) can be produced using compound (f-1) by a method similar to that of Production method 1, step 4.

step 3

Compound (f-3) can be produced using compound (f-2) and compound (a-7) by a method similar to that of Production
25 method 1, step 5.

step 4

Compound (If) can be produced using compound (f-3) and compound (a-9) by a method similar to that of Production method 1, step 6.

30 step 5

Compound (Ig) can be produced by treating compound (If) in a solvent under a hydrogen atmosphere or in the presence of 2 equivalents to a large excess amount of a hydrogen source, in the presence of 0.01 - 50 wt% of a catalyst, at a
35 temperature between -20°C and the boiling point of the solvent

to be used, under normal pressure or pressurization for 5 min to 72 hr.

[0097]

Examples of the catalyst include palladium carbon,
5 palladium, palladium hydroxide, palladium acetate, palladium black and the like.

Examples of the hydrogen source include formic acid, ammonium formate, sodium formate, cyclohexadiene, hydrazine and the like.

10 Examples of the solvent include methanol, ethanol, toluene, ethyl acetate, acetonitrile, diethyl ether, THF, DME, dioxane, DMF, DMA, NMP, water and the like, and these are used singly or in a mixture.

step 6

15 Compound (Ih) can be produced by reacting compound (Ig) and 1 - 10 equivalents of compound (f-4) in a solvent in the presence of 1 - 10 equivalents of a base for 5 min to 72 hr at a temperature between -20°C and the boiling point of the solvent to be used.

20 [0098]

Examples of the base include sodium carbonate, potassium carbonate, pyridine, triethylamine, diisopropylethylamine, DBU and the like.

Examples of the solvent include dichloromethane,
25 chloroform, 1,2-dichloroethane, acetonitrile, toluene, diethyl ether, THF, DME, dioxane, DMF, DMA, NMP and the like, and these are used singly or in a mixture.

[0099]

Compound (f-4) can be obtained as a commercially
30 available product or by a known method [for example, Jikken Kagaku Kouza, 5th ed., vol. 16, p.98, Maruzen Company, Limited (2005) and the like] or a method analogous thereto.

step 7

Compound (Ii) can be produced by reacting compound (Ig)
35 and 1 - 10 equivalents of compound (f-5) in a solvent in the

presence of 1 - 10 equivalents of a base, for 5 min to 72 hr at a temperature between -20°C and the boiling point of the solvent to be used.

[0100]

5 Examples of the base include sodium carbonate, potassium carbonate, pyridine, triethylamine, diisopropylethylamine, DBU and the like.

 Examples of the solvent include dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, toluene, diethyl
10 ether, THF, DME, dioxane, DMF, DMA, NMP and the like, and these are used singly or in a mixture.

[0101]

 Compound (f-5) is obtained as a commercially available product, or can be obtained by a known method [for example,
15 Jikken Kagaku Kouza, 5th ed., vol. 14, p. 537, Maruzen Company, Limited (2005) and the like] or a method analogous thereto.

 Conversion of a functional group contained in R¹, R², R³, R^{4A} and the like in compound (I) and each intermediate in the above-mentioned Production methods can also be performed by a
20 known method (e.g., the method described in Comprehensive Organic Transformations 2nd edition, R.C. Larock, Vch Verlagsgesellschaft MbH, 1999 and the like) or a method analogous thereto.

[0102]

25 The intermediates and the desired compounds in the above-mentioned production methods can be isolated and purified by applying separation and purification methods usually used in the synthetic organic chemistry such as filtration, extraction, washing, drying, concentration, recrystallization, various
30 chromatographies and the like. Also, intermediates can also be subjected to a next reaction without particular purification.

 To obtain a salt of compound (I), when compound (I) is obtained in a form of a salt, it can be directly purified. Or when compound (I) is obtained in a free form, it may be
35 dissolved or suspended in a suitable solvent, and an acid or a

base is added thereto to form a salt, and then the salt may be isolated and purified.

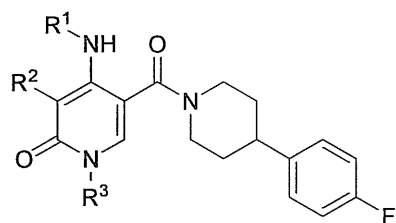
[0103]

Specific examples of compound (I) of the present
5 invention are shown in Table 1 to Table 21. However, the
compounds of the present invention are not limited to them.

[0104]

[Table 1]

Table 1

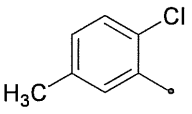
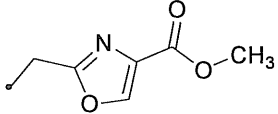
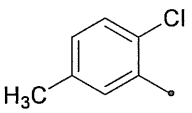
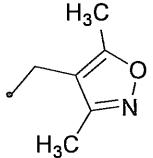
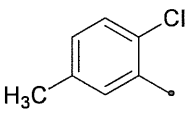
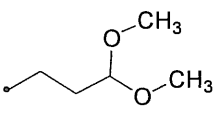
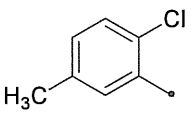
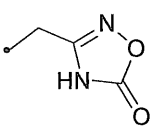
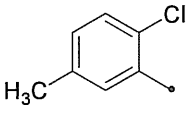
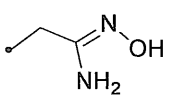
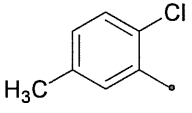
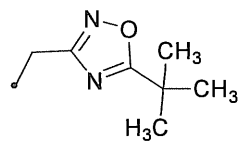
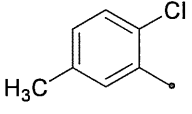
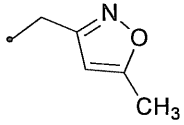
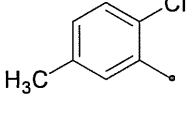
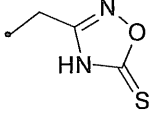
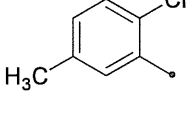
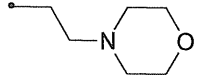
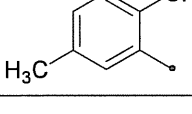
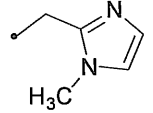


compound No.	R ¹	R ²	R ³
1		H	
2		H	
3		H	
4		H	
5		H	
6		H	
7		H	
8		H	

[0105]

[Table 2]

Table 2 (continued from Table 1)

compound No.	R ¹	R ²	R ³
9		H	
10		H	
11		H	
12		H	
13		H	
14		H	
15		H	
16		H	
17		H	
18		H	

[0106]

[Table 3]

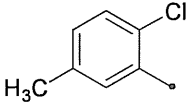
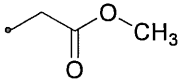
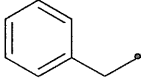
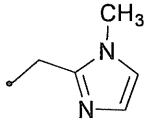
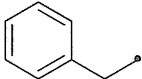
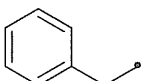
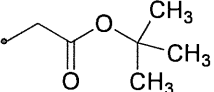
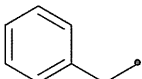
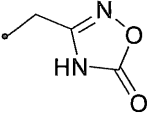
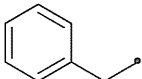
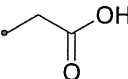
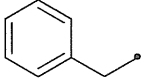
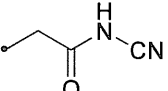
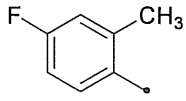
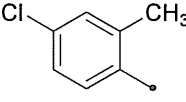
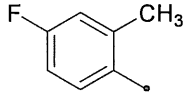
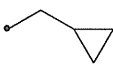
Table 3 (continued from Table 1)

compound No.	R ¹	R ²	R ³
19		H	
20		H	
21		Cl	
22		H	
23		H	
24		H	
25		H	
26		H	
27		H	
28		H	

[0107]

[Table 4]

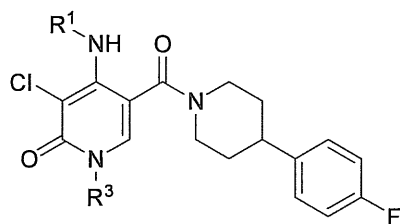
Table 4 (continued from Table 1)

compound No.	R ¹	R ²	R ³
29		H	
30		H	
31		H	
32		H	
33		H	
34		H	
35		H	
36		H	CH ₃
37		H	CH ₃
38		F	

[0108]

[Table 5]

Table 5

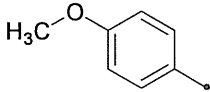
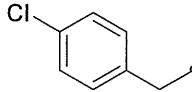
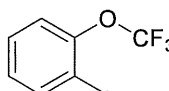
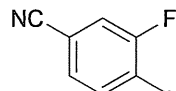
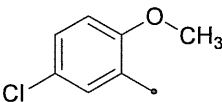
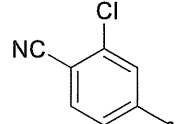
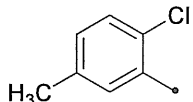
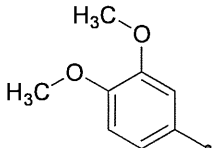
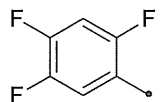
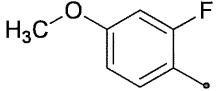
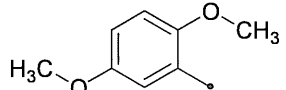
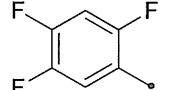
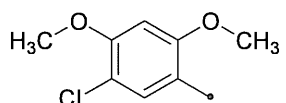
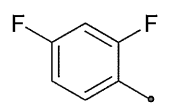
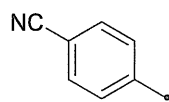
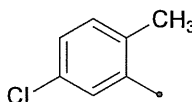
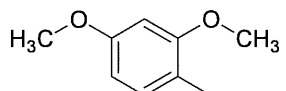
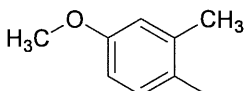
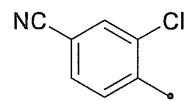
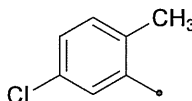


compound No.	R ¹	R ³	compound No.	R ¹	R ³
39		CH ₃	47		CH ₃
40		CH ₃	48		CH ₃
41		CH ₃	49		CH ₃
42		CH ₃	50		
43		CH ₃	51		CH ₃
44		CH ₃	52		CH ₃
45		CH ₃	53		
46		CH ₃	54		CH ₃

[0109]

[Table 6]

Table 6 (continued from Table 5)

compound No.	R ¹	R ³	compound No.	R ¹	R ³
55			65		CH ₃
56		CH ₃	66		CH ₃
57		CH ₃	67		CH ₃
58			68		CH ₃
59		CH ₃	69		CH ₃
60			70		
61		CH ₃	71		
62		CH ₃	72		
63		CH ₃	73		
64		CH ₃	74		CH ₃

[0110]

[Table 7]

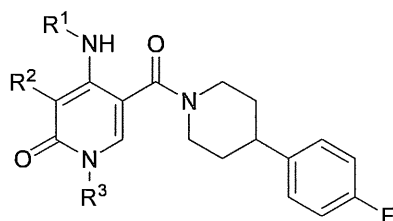
Table 7 (continued from Table 5)

compound No.	R ¹	R ³	compound No.	R ¹	R ³
75		CH ₃	84		
76		CH ₃	85		
77		CH ₃	86		CH ₃
78		CH ₃	87		CH ₃
79		CH ₃	88		CH ₃
80		CH ₃	89		CH ₃
81		CH ₃	90		CH ₃
82		CH ₃	91		CH ₃
83		CH ₃	92		CH ₃

[0111]

[Table 8]

Table 8

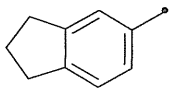
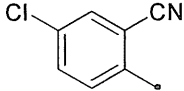
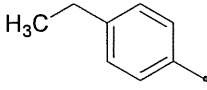
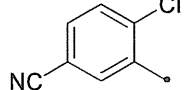
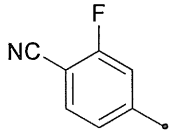
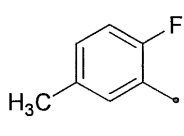
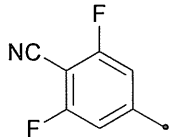
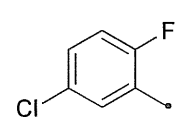
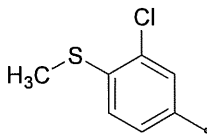
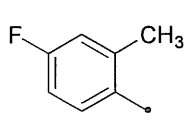
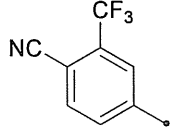
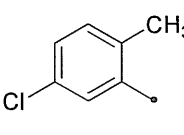
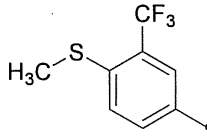
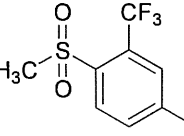
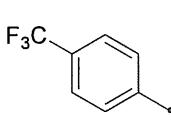
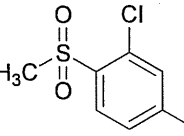
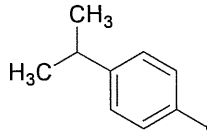
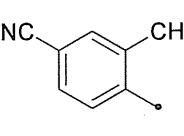


compound No.	R ¹	R ²	R ³	compound No.	R ¹	R ²	R ³
93		Cl	CH ₃	100		Cl	CH ₃
94		Br		101		Cl	CH ₃
95		Cl	CH ₃	102		Cl	CH ₃
96		Cl	CH ₃	103		Cl	CH ₃
97		Cl	CH ₃	104		Cl	CH ₃
98		Cl	CH ₃	105		Cl	CH ₃
99		Cl	CH ₃	106		Cl	CH ₃

[0112]

[Table 9]

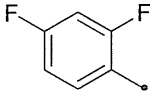
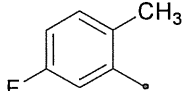
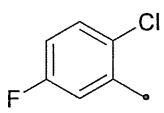
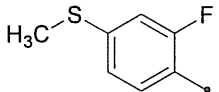
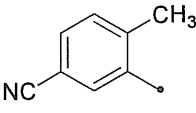
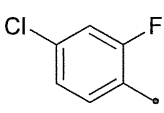
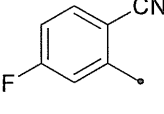
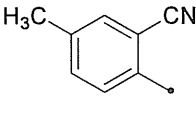
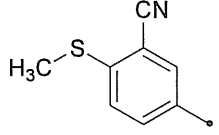
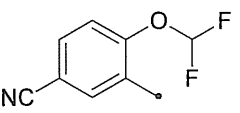
Table 9 (continued from Table 8)

compound No.	R ¹	R ²	R ³	compound No.	R ¹	R ²	R ³
107		Cl	CH ₃	116		Cl	CH ₃
108		Cl	CH ₃	117		Cl	CH ₃
109		Cl	CH ₃	118		Cl	CH ₃
110		Cl	CH ₃	119		Cl	CH ₃
111		Cl	CH ₃	120		CH ₃	CH ₃
112		Cl	CH ₃	121		CH ₃	CH ₃
113		Cl	CH ₃	122		Cl	CH ₃
114		Cl	CH ₃	123		Cl	CH ₃
115		Cl	CH ₃	124		CH ₃	CH ₃

[0113]

[Table 10]

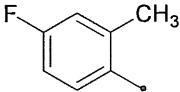
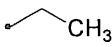
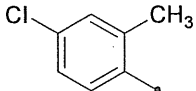
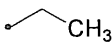
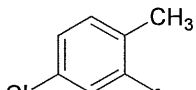
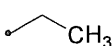
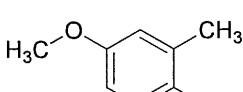
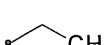
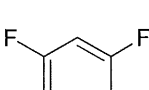
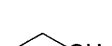
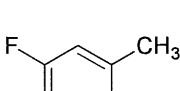
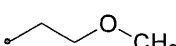
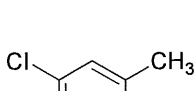
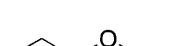
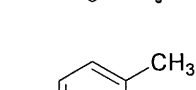
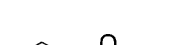
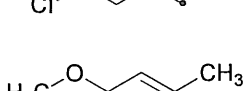
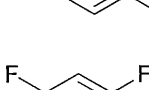
Table 10 (continued from Table 8)

compound No.	R ¹	R ²	R ³
125		CH ₃	CH ₃
126		Cl	CH ₃
127		Cl	CH ₃
128		Cl	CH ₃
129		Cl	CH ₃
130		Cl	CH ₃
131		Cl	CH ₃
132		Cl	CH ₃
133		Cl	CH ₃
134		Cl	CH ₃

[0114]

[Table 11]

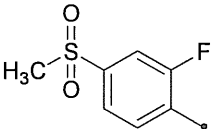
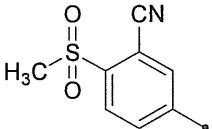
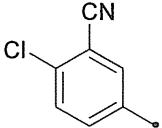
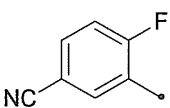
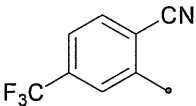
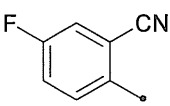
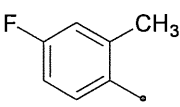
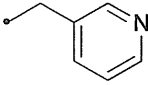
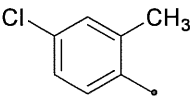
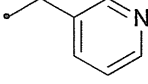
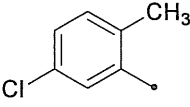
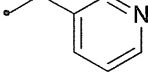
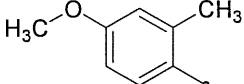
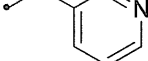
Table 11 (continued from Table 8)

compound No.	R ¹	R ²	R ³
135		Cl	
136		Cl	
137		Cl	
138		Cl	
139		Cl	
140		Cl	
141		Cl	
142		Cl	
143		Cl	
144		Cl	

[0115]

[Table 12]

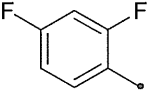
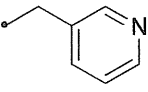
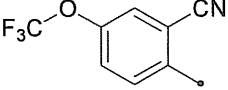
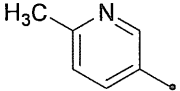
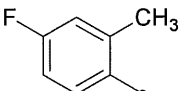
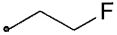
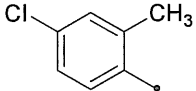
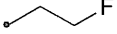
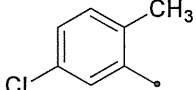
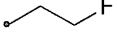
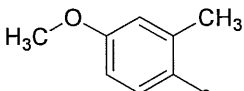
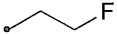
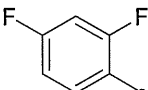
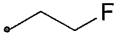
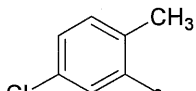
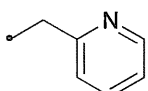
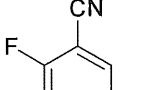
Table 12 (continued from Table 8)

compound No.	R ¹	R ²	R ³
145		Cl	CH ₃
146		Cl	CH ₃
147		Cl	CH ₃
148		Cl	CH ₃
149		Cl	CH ₃
150		Cl	CH ₃
151		Cl	
152		Cl	
153		Cl	
154		Cl	

[0116]

[Table 13]

Table 13 (continued from Table 8)

compound No.	R ¹	R ²	R ³
155		Cl	
156		Cl	CH ₃
157		Cl	CH ₃
158		Cl	
159		Cl	
160		Cl	
161		Cl	
162		Cl	
163		Cl	
164		Cl	CH ₃

[0117]

[Table 14]

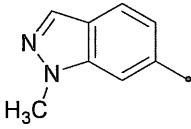
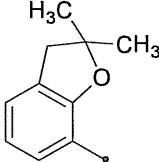
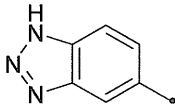
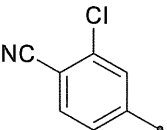
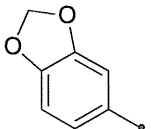
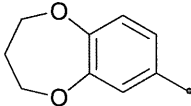
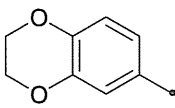
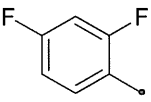
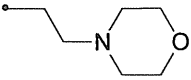
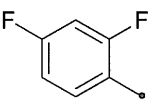
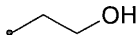
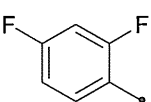
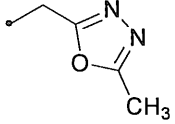
Table 14 (continued from Table 8)

compound No.	R ¹	R ²	R ³
165		Cl	CH ₃
166		Cl	
167		Cl	
168		Cl	
169		Cl	
170		Cl	
171		Cl	CH ₃
172		Cl	
173		Cl	CH ₃
174		Cl	CH ₃

[0118]

[Table 15]

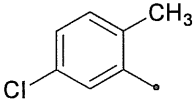
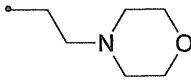
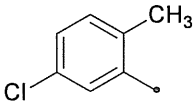
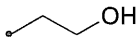
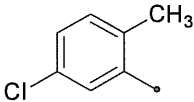
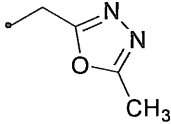
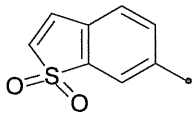
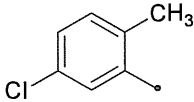
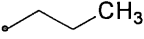
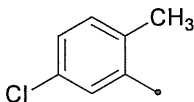
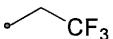
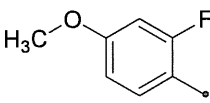
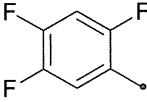
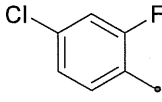
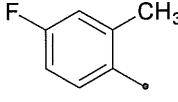
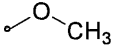
Table 15 (continued from Table 8)

compound No.	R ¹	R ²	R ³
175		Cl	CH ₃
176		Cl	CH ₃
177		Cl	CH ₃
178		CH ₃	CH ₃
179		Cl	CH ₃
180		Cl	CH ₃
181		Cl	CH ₃
182		Cl	
183		Cl	
184		Cl	

[0119]

[Table 16]

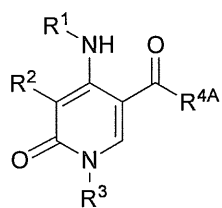
Table 16 (continued from Table 8)

compound No.	R ¹	R ²	R ³
185		Cl	
186		Cl	
187		Cl	
188		Cl	CH ₃
189		Cl	
190		Cl	
191		CH ₃	CH ₃
192		CH ₃	CH ₃
193		CH ₃	CH ₃
194		Cl	

[0120]

[Table 17]

Table 17

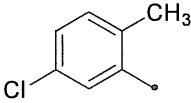
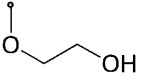
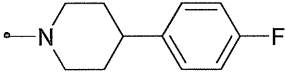
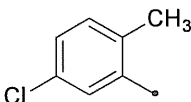
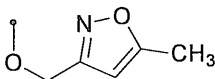
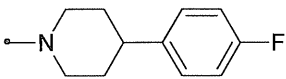
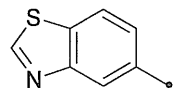
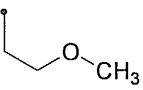
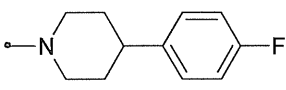
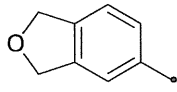
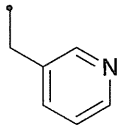
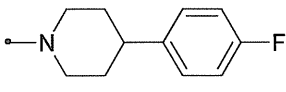
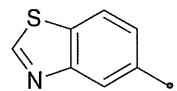
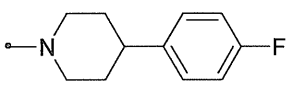
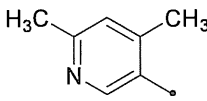
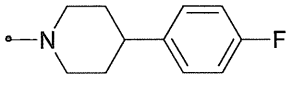
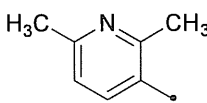
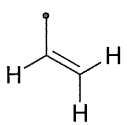
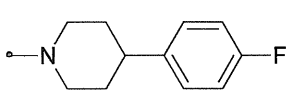
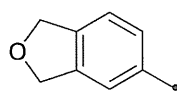
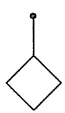
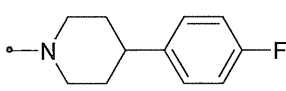
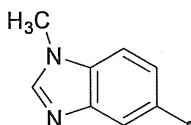
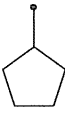
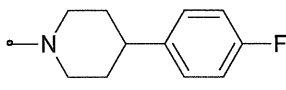
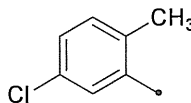
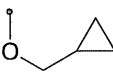
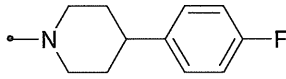


compound No.	R ¹	R ²	R ³	R ^{4A}
195				
196				
197				
198				
199		<td></td> <td></td>		
200				
201				
202				
203				

[0121]

[Table 18]

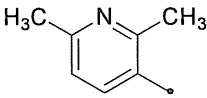
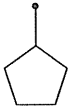
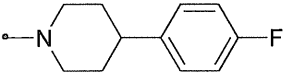
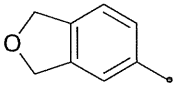
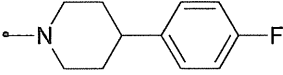
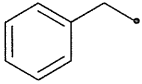
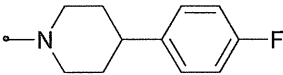
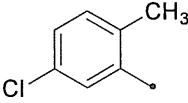
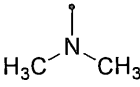
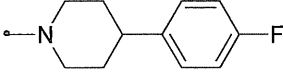
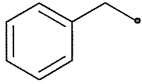
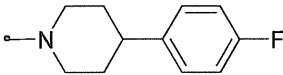
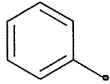
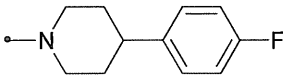
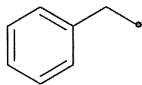
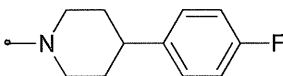
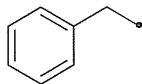
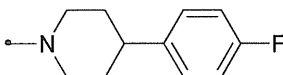
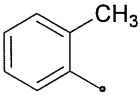
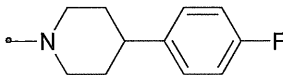
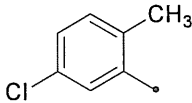
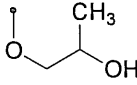
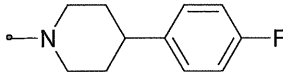
Table 18 (continued from Table 17)

compound No.	R ¹	R ²	R ³	R ^{4A}
204				
205				
206				
207				
208				
209				
210				
211				
212				
213				

[0122]

[Table 19]

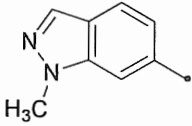
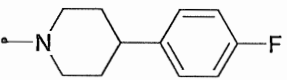
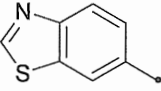
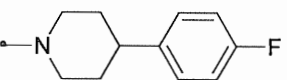
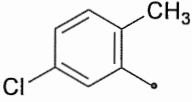
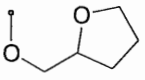
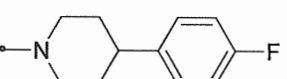
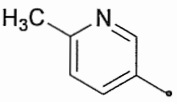
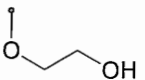
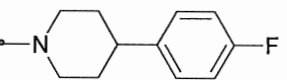
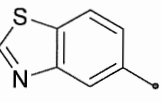
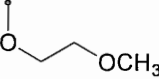
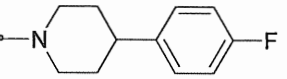
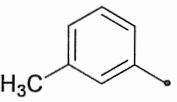
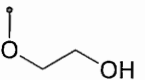
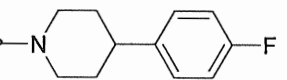
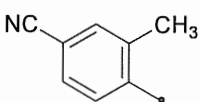
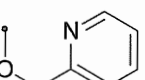
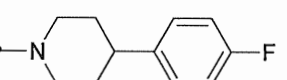
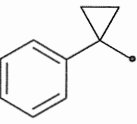
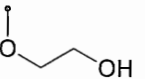
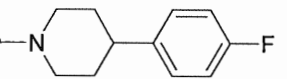
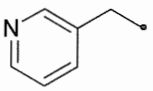
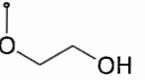
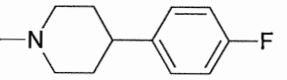
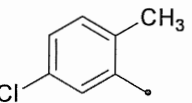
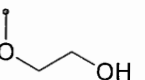
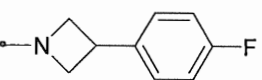
Table 19 (continued from Table 17)

compound No.	R ¹	R ²	R ³	R ^{4A}
214				
215				
216				
217				
218				
219				
220				
221				
222				
223				

[0123]

[Table 20]

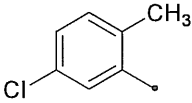
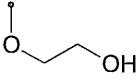
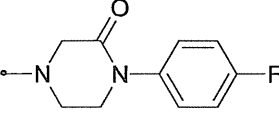
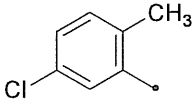
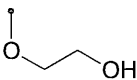
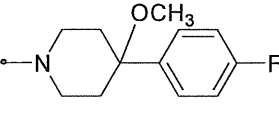
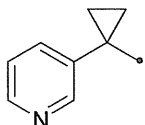
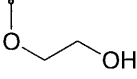
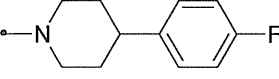
Table 20 (continued from Table 17)

compound No.	R ¹	R ²	R ³	R ^{4A}
224				
225				
226				
227				
228				
229				
230				
231				
232				
233				

[0124]

[Table 21]

Table 21 (continued from Table 17)

compound No.	R ¹	R ²	R ³	R ^{4A}
234				
235				
236				

5 [0125]

Next, pharmacological effects of a representative compound (I) are specifically explained by Experimental Examples.

[Experimental Example 1] CCR10 antagonistic effect

10 (1) Preparation of human CCR10-inducible expression plasmid

A CCR10-inducible expression plasmid was prepared according to a known method [Analytical Biochemistry, 2006, vol. 400, page 163]. A DNA encoding human CCR10 was obtained by PCR. Using human chromosome DNA (100 ng; manufactured by
15 Clontech) as a template, synthetic DNA having the sequences depicted in SEQ ID NOs: 1 and 2 as a human CCR10 cDNA specific primer, and Pyrobest DNA Polymerase (manufactured by TAKARA SHUZO CO. LTD.) as an enzyme, a DNA encoding human CCR10 was obtained by PCR. As a buffer for PCR, the buffer attached to
20 the enzyme to be used, which was diluted 10-fold with deionized water, was used. Using Thermal Cycler DNA Engine (manufactured by MJ Research), PCR was performed by 35 cycles of reactions composed of an incubation at 94°C for 30 sec, at an anneal temperature of 58°C for 30 sec, and at 72°C for 1 min
25 after treating at 90°C for 2 min.

[0126]

The amplified PCR fragment was cleaved with HindIII and NotI, then a human CCR10 DNA fragment was recovered by the agarose gel electrophoresis method. The fragment was
5 incorporated between the corresponding restriction enzyme sites (HindIII-NotI) of an inducible expression vector to construct a human CCR10-inducible expression plasmid.

Using a primer specific to the sequence of plasmid (synthetic DNA having the sequences shown in SEQ ID NOs: 3 and
10 4), the sequence of human CCR10 DNA region was determined. For the determination of the base sequence, DNA Sequencer 377 (manufactured by Perkin Elmer. Co.) and a reaction kit (ABI Prism (registered trade mark) BigDye (registered trade mark) Terminator Cycle Sequencing Ready Reaction kit: manufactured
15 by Applied Biosystems) were used. The sequence of human CCR10 DNA was identical with the sequence (NM_016602) registered in GenBank.

[0127]

(2) Preparation of human CCR10 expressing cell for calcium
20 assay

Cells for detecting signals from human CCR10 in calcium assay were prepared. According to a known method [Analytical Biochemistry (Analy Biochem), 2006, vol. 400, page 163], human CCR10-inducible expressing cells whose host cell is KJMGER8
25 cell (Namalwa cell-derived cell line) were prepared. Human CCR10-inducible expression plasmid produced above and Gα16 expression plasmid were co-transfected into the KJMGER8 cells by the electroporation method [Cytotechnology, 1990, vol. 3, page 133], whereby the signals from human CCR10 could be
30 detected by calcium assay (hereinafter to be referred to as hCCR10G16 cell). A Gα16 expression plasmid was produced by incorporating human Gα16 DNA into expression vector pAMoh (WO 03/087366). Expression of human CCR10 was induced by
35 cultivating hCCR10G16 cells in the presence of 10 nmol/L β-estradiol (manufactured by Sigma Ltd.) for 24 hr.

[0128]

(3) Calcium assay of human CCR10

Cells expressing human CCR10 induced by the above-mentioned method were suspended in RPMI1640 medium
5 (manufactured by Invitrogen), and adjusted to a cell density of 2×10^6 cells/mL. The cells were blended with an equivalent volume of a loading buffer prepared according to the attached protocol of Fluo-3 calcium assay kit (manufactured by Molecular Devices Corporation), and incubated at 37°C for
10 several dozen minutes. This mixture was dispensed to a 384 well clear-bottom plate (manufactured by Corning Incorporated) at 40 μ L/well. To this plate was added a solution of the test compound in dimethyl sulfoxide (DMSO), which was diluted 37-fold with RPMI1640 medium, at 5 μ L/well, and the mixture was
15 incubated at 37°C for 30 min. 300 nmol/L human recombinant CTACK (manufactured by R&D Systems, Inc.) diluted with RPMI1640 medium containing 1 w/v% bovine serum albumin (manufactured by Sigma Ltd.) was added at 5 μ L/well and, variation of intracellular calcium ion concentration for about
20 5 min after the addition was measured by a screening apparatus (FDSS; manufactured by Hamamatsu Photonics K.K.). The difference between the maximum fluorescence intensity and the minimum fluorescence intensity measured in the 5 minutes was calculated and taken as the measured value (maximum
25 fluorescence intensity - minimum fluorescence intensity).

[0129]

The inhibition rate of the test compound against increase of calcium ion concentration was calculated by the following formula.

30 [0130]

$$\begin{array}{l} \text{inhibition rate against increase} \\ \text{of calcium ion concentration} \end{array} (\%) = \left[1 - \frac{\text{test compound addition group} - \text{blank}}{\text{control} - \text{blank}} \right] \times 100$$

35 [0131]

test compound addition group: average measurement value of variation of intracellular calcium ion concentration of the test compound addition group

control: average measurement value as measured by adding,
5 instead of a solution of the test compound, DMSO 37-fold diluted with RPMI1640 medium, adding 300 nmol/L CTACK diluted with RPMI1640 medium containing 1 w/v% bovine serum albumin, and measuring variation of intracellular calcium ion concentration

10 blank: average measurement value as measured by adding, instead of a solution of the test compound, DMSO 37-fold diluted with RPMI1640 medium, adding, instead of a medium containing CTACK, RPMI1640 medium containing 1 w/v% bovine serum albumin, and measuring variation of intracellular
15 calcium ion concentration

A concentration-reaction curve was drawn from the inhibition rate against increase of calcium ion concentration when treated with not less than 5 concentrations of the test compound at 3- to 10-fold common ratio, and IC₅₀ value was
20 calculated.

[0132]

Compounds 1 - 3, 5 - 33, 35 - 44, 46, 47, 49 - 51, 53 - 55, 57 - 133, 135 - 145, 147 - 236 inhibited an increase in the calcium ion concentration by not less than 50% at a
25 concentration of not more than 1000 nmol/L. Compound (I) or a pharmaceutically acceptable salt thereof was considered to have a CCR10 antagonistic action, and to be useful as a prophylactic and/or therapeutic agent for the diseases involving CCR10.

30 Therefore, compound (I) or a pharmaceutically acceptable salt thereof was considered to be useful as a prophylactic and/or therapeutic agent for the diseases involving CCR10, for example, skin diseases [for example, acne vulgaris, drug eruption, contact dermatitis, dermatitis due to venomous moth,
35 pollen dermatitis, urticaria, psoriasis, atopic dermatitis,

Candida dermatitis, seborrheic dermatitis, eczema, Stevens-Johnson syndrome, toxic epidermal necrosis, erythema multiforme, erythema nodosum, granuloma annulare, pityriasis rosea, rosacea, lichen planus, lichen pilaris (keratosis pilaris), photosensitivity, solar dermatitis, miliaria, herpes simplex, Kaposi's varicelliform eruption, impetigo contagiosa, staphylococcal scalded skin syndrome, erysipelas, slap cheek, lupus erythematosus, keloid, Hailey-Hailey disease, scabies, linear dermatitis and the like] and the like.

10 [0133]

[Experimental Example 2] Suppressive action on dinitrofluorobenzene-induced auricle edema reaction in mouse BALB/c mice (female, supplied by CHARLES RIVER LABORATORIES JAPAN, INC.) were purchased at the age of 5 weeks. After quarantine and acclimation, mice showing smooth body weight increase and free of abnormality in appearance were used and the test was started at the age of 7 weeks. The mice were housed in a breeding room at room temperature 19 - 25°C, humidity 30 - 70%, 12 hr lighting per day (7 a.m. - 7 p.m.) with 3 mice in each plastic gauge, and bred on with free ingestion of a commercially available solid feed and water.

[0134]

Two days before the test, the abdomen of the BALB/c mice was shaved, and the mice were immunized by applying 100 μ L of a solution {concentration 0.5% [weight (w)/volume (v)%]} of dinitrofluorobenzene (manufactured by Nacalai Tesque) in acetone (manufactured by Wako Pure Chemical Industries, Ltd.) to the shaved part. The reaction was induced by applying dinitrofluorobenzene-acetone solution [concentration 0.2% (w/v%)] to the front and the back of auricle (10 μ L to each, total 20 μ L) on day 5 after the immunization. A test compound dissolved in acetone at concentration of 1% (w/v%) was administered by applying same to the front and the back of auricle (10 μ L to each, total 20 μ L) 1 hr before and 3 hr after induction of the reaction. After application, the

applied part was air-dried with a dryer.

[0135]

The group applying administered with the test compound was taken as a test compound administration group, and the group applying administered with acetone as a solvent instead of the test compound was taken as a solvent administration group. Also, the group free of immunization and reaction induction but applying administered with acetone instead of the test compound was taken as a normal group. The thickness of auricle was measured using a dial thickness gauge (G-1A manufactured by OZAKI MFG. CO., LTD.) immediately before and 24 hr after induction of the reaction, and the difference thereof was taken as auricle edema. The suppression rate (%) of auricle edema was calculated according to the following formula. The results are shown in Table 22.

[0136]

$$\text{auricle edema suppression rate (\%)} = \frac{\text{value of solvent administration group} - \text{value of test compound administration group}}{\text{value of solvent administration group} - \text{value of normal group}} \times 100$$

[0137]

[Table 22]

Table 22

compound No.	auricle edema suppression rate (%)
100	53
125	47
144	32
204	41
206	30

20

[0138]

Compounds 100, 125, 145, 204 and 206 showed a suppressive action on auricle edema response, and compound (I) or a pharmaceutically acceptable salt thereof was considered to be

useful as a prophylactic and/or therapeutic agent for contact dermatitis or atopic dermatitis.

While compound (I) or a pharmaceutically acceptable salt thereof used in the present invention can be directly
5 administered singly, it is generally desirable to provide as various pharmaceutical preparations. Also, such pharmaceutical preparations are used for animals or human.
[0139]

The pharmaceutical preparation of the present invention
10 can contain, as an active ingredient, compound (I) or a pharmaceutically acceptable salt thereof singly or in a mixture with any other active ingredient for the treatment. Also, such pharmaceutical preparation is produced by any method known in the technical field of formulation study, by
15 mixing the active ingredient with one or more kinds of pharmaceutically acceptable carriers (for example, diluent, solvent, excipient and the like).
[0140]

As the administration route, it is desirable to use a
20 route the most effective for the treatment and, for oral, or, parenteral routes such as intravenous, external or the like can be mentioned.

Examples of the administration form include tablet, injection, ointment or the like.

25 For example, tablet and the like suitable for oral administration can be produced using excipient such as lactose and the like, disintegrant such as starch and the like, lubricant such as magnesium stearate and the like, binder such as hydroxypropylcellulose and the like, and the like.
30 [0141]

For example, injection and the like suitable for intravenous administration can be produced using diluent or solvent such as salt solution, glucose solution or a mixture of salt water and glucose solution and the like, and the like.

35 For example, ointment suitable for external preparation

can be produced using a base material such as petrolatum and the like, and an additive such as stearyl alcohol and the like.

While the dose and administration frequency of compound (I) or a pharmaceutically acceptable salt thereof used in the present invention vary depending on the administration form, age and body weight of patients, nature or severity of the symptoms to be treated, and the like, it is generally 0.01 - 1000 mg, preferably 0.05 - 100 mg, by oral administration to an adult, which is administered in one to several portions per day. For intravenous administration, external use and the like, 0.001 - 1000 mg, preferably 0.01 - 100 mg, is administered to an adult in one to several portions per day. However, such dose and administration frequency vary depending on the aforementioned various conditions.

[0142]

The present invention is explained in more detail in the following by referring to Examples and Reference Examples. The scope of the present invention is not limited by these Examples and Reference Examples.

The proton nuclear magnetic resonance spectrum (^1H NMR) used in the Examples were measured at 270 MHz, 300 MHz or 400 MHz, and exchanging proton may not be observed clearly depending on the compound and measurement conditions. The indication of the multiplicity of the signals is conventional, where br means an apparently broad signal. For nomenclature of each synthesized compound, ChemBioDraw Ultra version 11.0.1 was used where necessary.

Example 1

[0143]

3-{4-(2-chloro-5-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}propionic acid (compound 3)

(step 1) Methyl 4,6-dichloronicotinate (8.0 g, 39 mmol) was dissolved in ethanol (150 mL), 2-chloro-5-methylaniline (6.05 g, 42.7 mmol) and concentrated hydrochloric acid (0.12 mL,

3.88 mmol) were added, and the mixture was stirred with heating under reflux for 16 hr. The reaction mixture was cooled to room temperature, and the precipitated solid was collected by filtration to give methyl 6-chloro-4-(2-chloro-5-methylphenylamino)nicotinate (3.68 g, 31%).

ESIMS m/z : 311 ($M + H$)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 2.36 (s, 3H), 3.95 (s, 3H), 6.76 (s, 1H), 7.03–7.06 (m, 1H), 7.21–7.22 (m, 1H), 7.38–7.40 (m, 1H), 8.80 (s, 1H), 9.83 (br s, 1H).

(step 2) Methyl 6-chloro-4-(2-chloro-5-methylphenylamino)nicotinate (3.69 g, 11.8 mmol) obtained in step 1 was dissolved in acetic acid (139 mL) and water (46 mL), and the mixture was stirred with heating under reflux for 3 days. The reaction mixture was cooled to room temperature, and the precipitated solid was collected by filtration to give methyl 4-(2-chloro-5-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (1.14 g, 33%).

ESIMS m/z : 293 ($M + H$)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 2.34 (s, 3H), 3.90 (s, 3H), 5.83 (s, 1H), 6.96–7.00 (m, 1H), 7.27–7.28 (m, 1H), 7.34–7.37 (m, 1H), 8.17 (s, 1H), 9.60 (br s, 1H).

[0144]

(step 3) Methyl 4-(2-chloro-5-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (0.42 g, 1.50 mmol) obtained in step 2 was dissolved in 10 mol/L aqueous potassium hydroxide solution (6.0 mL), and the mixture was stirred with heating under reflux for 1 hr. The reaction mixture was cooled to room temperature, concentrated hydrochloric acid was added to pH=1, and the precipitated solid was collected by filtration to give 4-(2-chloro-5-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (0.42 g, quantitative).

ESIMS m/z : 279 ($M + H$)⁺; ¹H NMR (400 MHz, DMSO- d_6 , δ): 2.33 (s, 3H), 5.41 (s, 1H), 7.06–7.08 (m, 1H), 7.37 (s, 1H), 7.45–7.47 (m, 1H), 8.07 (s, 1H), 9.60 (br s, 1H), 11.45 (br s, 1H).

(step 4) 4-(2-Chloro-5-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (1.12 g, 4.02 mmol) obtained in step 3 was dissolved in DMF (20 mL), HATU (3.06 g, 8.04

mmol), 4-(4-fluorophenyl)piperidine hydrochloride (1.73 g, 8.04 mmol) and N,N-diisopropylamine (3.42 mL, 20.1 mmol) were added, and the mixture was stirred at room temperature for 3 hr. To the reaction mixture was added 5% aqueous citric acid solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=100/0-20/70) to give 4-(2-chloro-5-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (1.63 g, 92%).

ESIMS m/z: 440 (M + H)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 1.60-1.71 (m, 2H), 1.93-2.08 (m, 2H), 2.32 (s, 3H), 2.77-2.86 (m, 1H), 3.04-3.13 (m, 2H), 4.46-4.49 (m, 2H), 6.07 (s, 1H), 6.90-6.92 (m, 1H), 6.99-7.03 (m, 3H), 7.14-7.17 (m, 2H), 7.28-7.38 (m, 2H), 8.37 (s, 1H).

[0145]

(step 5) 4-(2-Chloro-5-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (80 mg, 0.182 mmol) obtained in step 4 was dissolved in DMF (1.5 mL), potassium carbonate (75 mg, 0.546 mmol) and methyl acrylate (0.049 mL, 0.546 mmol) were added, and the mixture was stirred at 80°C for 1 hr. To the reaction mixture was added 10% aqueous citric acid solution (5 mL), and the precipitated solid was collected by filtration to give methyl 3-{4-(2-chloro-5-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}propionate (82 mg, 86%).

ESIMS m/z: 526 (M + H)⁺; ¹H NMR (270 MHz, DMSO-d₆, δ): 1.63-1.73 (m, 2H), 1.81-1.85 (m, 2H), 2.31 (s, 3H), 2.75 (t, J = 6.9 Hz, 2H), 2.81-2.94 (m, 1H), 3.01-3.11 (m, 2H), 3.58 (s, 3H), 4.03 (t, J = 6.9 Hz, 2H), 4.26-4.30 (m, 2H), 5.40 (s, 1H), 7.03-7.16 (m, 3H), 7.26-7.36 (m, 3H), 7.44 (d, J = 7.9 Hz, 1H), 7.78 (s, 1H), 8.26 (s, 1H).

(step 6) Methyl 3-{4-(2-chloro-5-methylphenylamino)-5-[4-(4-

fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}propionate (80 mg, 0.152 mmol) obtained in step 5 was dissolved in methanol (3 mL), 1 mol/L aqueous sodium hydroxide solution (2 mL) was added, and the mixture was stirred at room
5 temperature for 1 hr. The solvent of the reaction mixture was evaporated under reduced pressure. To the residue were added water (1 mL) and 2 mol/L hydrochloric acid (1.5 mL), and the precipitated solid was collected by filtration to give compound 3 (65 mg, 83%).
10 ESIMS m/z : 512 ($M + H$)⁺; ¹H NMR (300 MHz, DMSO- d_6 , δ): 1.64–1.67 (m, 2H), 1.81–1.84 (m, 2H), 2.31 (s, 3H), 2.66 (t, $J = 6.9$ Hz, 2H), 2.81–2.86 (m, 1H), 3.01–3.08 (m, 2H), 3.99 (t, $J = 6.9$ Hz, 2H), 4.26–4.31 (m, 2H), 5.43 (s, 1H), 7.02–7.15 (m, 3H), 7.26–7.33 (m, 3H), 7.42 (d, $J = 7.9$ Hz, 1H), 7.79 (s, 1H), 8.29 (s,
15 1H).

Example 2

[0146]

1-(benzyloxy)-3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one
20 (compound 21)
(step 1) To diethyl 3-oxopentanedioate (5.0 mL, 27.4 mmol) were added triethyl orthoformate (4.57 mL, 27.4 mmol) and acetic anhydride (5.18 mL, 54.8 mmol), and the mixture was stirred at 135°C for 2 hr. The reaction mixture was cooled to
25 room temperature, and concentrated under reduced pressure. The residue (6.84 g from 7.84 g) was dissolved in DMF (50 mL), a solution (70 mL) of O-benzylhydroxylamine hydrochloride (4.20 g, 26.3 mmol) in DMF was added at 0°C, and the mixture was stirred at room temperature for 1 hr. To the reaction mixture
30 was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in toluene (100 mL), DBU (7.20 mL, 47.8 mmol) was
35 added, and the mixture was stirred with heating under reflux

for 30 min. The reaction mixture was cooled to room temperature, 0.1 mol/L hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (heptane/ethyl acetate=80/20-50/50) to give ethyl 1-(benzyloxy)-4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylate (2.54 g, 3 steps 37%).

ESIMS m/z : 290 ($M + H$)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 1.30 (t, $J = 7.0$ Hz, 3H), 4.24 (q, $J = 7.0$ Hz, 2H), 5.28 (s, 2H), 6.01 (s, 1H), 7.33-7.43 (m, 5H), 7.80 (s, 1H), 10.60 (s, 1H).

(step 2) Ethyl 1-(benzyloxy)-4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylate (65.0 mg, 0.225 mmol) obtained in step 1 was dissolved in dichloromethane (2.0 mL), trifluoromethanesulfonic acid anhydride (0.057 mL, 0.337 mmol) and triethylamine (0.063 mL, 0.449 mmol) were added at 0°C and the mixture was stirred for 30 min. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (heptane/ethyl acetate=85/15-55/45) to give ethyl 1-(benzyloxy)-6-oxo-4-(trifluoromethylsulfonyloxy)-1,6-dihydropyridine-3-carboxylate (45.5 mg, 48%).

ESIMS m/z : 422 ($M + H$)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.32 (t, $J = 6.8$ Hz, 3H), 4.24 (q, $J = 6.8$ Hz, 2H), 5.31 (s, 2H), 6.54 (s, 1H), 7.33-7.44 (m, 5H), 8.06 (s, 1H).

[0147]

(step 3) Ethyl 1-(benzyloxy)-6-oxo-4-(trifluoromethylsulfonyloxy)-1,6-dihydropyridine-3-carboxylate (793 mg, 1.88 mmol) obtained in step 2, 5-chloro-2-methylaniline (400 mg, 2.82 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (352 mg, 0.565 mmol) and

cesium carbonate (1.23 g, 3.76 mmol) were suspended in toluene (10 mL), palladium(II) acetate (85.0 mg, 0.376 mmol) was added, and the mixture was stirred at 100°C for 90 min. The reaction mixture was cooled to room temperature, saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (heptane/ethyl acetate=90/10-60/40) to give ethyl 1-(benzyloxy)-4-(5-chloro-2-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (650 mg, 84%).
ESIMS m/z: 413 (M + H)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 1.30 (t, J = 7.2 Hz, 3H), 2.20 (s, 3H), 4.23 (q, J = 7.2 Hz, 2H), 5.28 (s, 2H), 5.62 (s, 1H), 7.12-7.29 (m, 3H), 7.36-7.48 (m, 5H), 7.91 (s, 1H).

(step 4) Using ethyl 1-(benzyloxy)-4-(5-chloro-2-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (593 mg, 1.44 mmol) obtained in step 3, and in the same manner as in Example 21, step 3, ethyl 1-(benzyloxy)-5-chloro-4-(5-chloro-2-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (481 mg, 75%) was obtained.

ESIMS m/z: 447 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.29 (t, J = 6.8 Hz, 3H), 2.26 (s, 3H), 4.23 (q, J = 6.8 Hz, 2H), 5.34 (s, 2H), 6.81 (d, J = 2.0 Hz, 1H), 7.03 (dd, J = 2.0, 7.8 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 7.39-7.51 (m, 5H), 7.97 (s, 1H), 9.26 (s, 1H).

[0148]

(step 5) Using ethyl 1-(benzyloxy)-5-chloro-4-(5-chloro-2-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (480 mg, 1.07 mmol) obtained in step 4, and in the same manner as in Example 1, step 6, 1-(benzyloxy)-5-chloro-4-(5-chloro-2-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (412 mg, 92%) was obtained.

ESIMS m/z: 419 (M + H)⁺; ¹H NMR (400 MHz, DMSO-d₆, δ): 2.21 (s,

3H), 5.27 (s, 2H), 6.90 (d, J = 2.0 Hz, 1H), 7.09 (dd, J = 2.0, 8.8 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 7.41-7.47 (m, 3H), 7.52-7.58 (m, 2H), 8.51 (s, 1H), 9.58 (s, 1H).

(step 6) Using 1-(benzyloxy)-5-chloro-4-(5-chloro-2-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (303 mg, 0.723 mmol) obtained in step 5, and in the same manner as in Example 1, step 4, compound 21 (423 mg, quantitative) was obtained.

ESIMS m/z: 580 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.18-1.33 (m, 2H), 1.64-1.73 (m, 2H), 2.27 (s, 3H), 2.42-2.65 (m, 3H), 3.41-3.99 (m, 2H), 5.35 (s, 2H), 6.58 (br s, 1H), 6.82 (d, J = 2.0 Hz, 1H), 6.98-7.15 (m, 7H), 7.33-7.45 (m, 5H).

Example 3

[0149]

4-(benzylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-[(1-methyl-1H-imidazol-2-yl)methyl]pyridin-2(1H)-one (compound 30)

(step 1) Using methyl 4,6-dichloronicotinate (3.00 g, 14.6 mmol) and benzylamine (2.34 g, 21.8 mmol), and in the same manner as in Example 1, step 1, methyl 4-(benzylamino)-6-chloronicotinate (3.63 g, 90%) was obtained.

ESIMS m/z: 277 (M + H)⁺

(step 2) Using methyl 4-(benzylamino)-6-chloronicotinate (1.63 g, 5.89 mmol) obtained in step 1, and in the same manner as in Example 1, step 2, methyl 4-(benzylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (0.52 g, 34%) was obtained.

ESIMS m/z: 259 (M + H)⁺

(step 3) Using methyl 4-(benzylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (0.52 g, 2.0 mmol) obtained in step 2, and in the same manner as in Example 1, step 3, 4-(benzylamino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (0.49 g, quantitative) was obtained.

ESIMS m/z: 245 (M + H)⁺

[0150]

(step 4) Using 4-(benzylamino)-6-oxo-1,6-dihydropyridine-3-

carboxylic acid (0.49 g, 2.0 mmol) obtained in step 3, and in the same manner as in Example 1, step 4, 4-(benzylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (0.82 g, quantitative) was obtained.

5 ESIMS m/z: 406 (M + H)⁺

(step 5) 4-(Benzylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (0.20 g, 0.49 mmol) obtained in step 4 was dissolved in DMF (2.5 mL), potassium carbonate (0.14 g, 0.99 mmol) and 2-(chloromethyl)-1-methyl-1H-imidazole
10 (0.064 g, 0.49 mmol) were added, and the mixture was stirred at room temperature for 3 hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated
15 under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol=100/0-70/30) to give compound 30 (0.18 g, 72%).

ESIMS m/z: 500 (M + H)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 1.61-1.68 (m, 2H), 1.86-1.89 (m, 2H), 2.72-2.78 (m, 1H), 2.95-3.01 (m, 2H),
20 3.75 (s, 3H), 4.27-4.33 (m, 4H), 5.17 (s, 2H), 5.56 (s, 1H), 6.43-6.46 (m, 1H), 6.83 (s, 1H), 6.92 (s, 1H), 6.99-7.03 (m, 2H), 7.15-7.18 (m, 2H), 7.28-7.36 (m, 5H), 7.60 (s, 1H).

Example 4

[0151]

25 3-chloro-4-(4-fluoro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methoxypyridin-2(1H)-one (compound 194)

(step 1) Using ethyl 1-(benzyloxy)-6-oxo-4-(trifluoromethylsulfonyloxy)-1,6-dihydropyridine-3-carboxylate
30 (105 mg, 0.249 mmol) obtained in Example 2, step 2, and 4-fluoro-2-methylaniline (0.042 mL, 0.374 mmol), and in the same manner as in Example 2, step 3, ethyl 1-(benzyloxy)-4-(4-fluoro-2-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (76.4 mg, 77%) was obtained.

35 ESIMS m/z: 397 (M + H)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 1.30 (t, J =

6.9 Hz, 3H), 2.22 (s, 3H), 4.24 (q, J = 6.9 Hz, 2H), 5.26 (s, 2H), 5.42 (s, 1H), 6.88-7.02 (m, 2H), 7.14-7.20 (m, 1H), 7.38-7.47 (m, 5H), 7.91 (s, 1H), 8.99 (s, 1H).

(step 2) Using ethyl 1-(benzyloxy)-4-(4-fluoro-2-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (75.2 mg, 0.190 mmol) obtained in step 1, and in the same manner as in Example 2, step 4, ethyl 1-(benzyloxy)-5-chloro-4-(4-fluoro-2-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (79.2 mg, 97%) was obtained.

ESIMS m/z: 431 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.30 (t, J = 6.8 Hz, 3H), 2.26 (s, 3H), 4.24 (q, J = 6.8 Hz, 2H), 5.31 (s, 2H), 6.79-6.92 (m, 3H), 7.40-7.50 (m, 5H), 7.97 (s, 1H), 9.30 (s, 1H).

[0152]

(step 3) Ethyl 1-(benzyloxy)-5-chloro-4-(4-fluoro-2-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (76.8 mg, 0.178 mmol) obtained in step 2 was dissolved in ethyl acetate (5.0 mL), 5% palladium-carbon (7.7 mg) was added, and the mixture was stirred under a hydrogen atmosphere at room temperature for 20 min. The reaction mixture was filtered through celite (registered trade mark). The solvent was evaporated under reduced pressure to give a crude product of ethyl 5-chloro-4-(4-fluoro-2-methylphenylamino)-1-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylate, which was used for the next step without purification.

(step 4) A crude product of ethyl 5-chloro-4-(4-fluoro-2-methylphenylamino)-1-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylate obtained in step 3 was dissolved in DMF (20 mL), methyl p-toluenesulfonate (0.040 mL, 0.267 mmol) and potassium carbonate (73.8 mg, 0.534 mmol) were added, and the mixture was stirred at room temperature for 2 hr. To the reaction mixture was added saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated

under reduced pressure. The residue was purified by silica gel column chromatography (heptane/ethyl acetate=60/40-30/70) to give ethyl 5-chloro-4-(4-fluoro-2-methylphenylamino)-1-methoxy-6-oxo-1,6-dihydropyridine-3-carboxylate (56.6 mg, 2 steps 90%).

ESIMS m/z: 355 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.39 (t, J = 6.8 Hz, 3H), 2.28 (s, 3H), 4.14 (s, 3H), 4.34 (q, J = 6.8 Hz, 2H), 6.79-6.93 (m, 3H), 8.40 (s, 1H), 9.34 (s, 1H).

(step 5) Using ethyl 5-chloro-4-(4-fluoro-2-methylphenylamino)-1-methoxy-6-oxo-1,6-dihydropyridine-3-carboxylate (55.3 mg, 0.156 mmol) obtained in step 4, and in the same manner as in Example 1, step 6, 5-chloro-4-(4-fluoro-2-methylphenylamino)-1-methoxy-6-oxo-1,6-dihydropyridine-3-carboxylic acid (45.1 mg, 89%) was obtained.

ESIMS m/z: 327 (M + H)⁺; ¹H NMR (400 MHz, DMSO-d₆, δ): 2.22 (s, 3H), 4.00 (s, 3H), 6.95-7.11 (m, 3H), 8.68 (s, 1H), 9.57 (br s, 1H).

[0153]

(step 6) Using 5-chloro-4-(4-fluoro-2-methylphenylamino)-1-methoxy-6-oxo-1,6-dihydropyridine-3-carboxylic acid (40.2 mg, 0.123 mmol) obtained in step 5, and in the same manner as in Example 1, step 4, compound 194 (52.6 mg, 88%) was obtained.

ESIMS m/z: 488 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.33-1.48 (m, 2H), 1.74-1.83 (m, 2H), 2.33 (s, 3H), 2.47-2.68 (m, 3H), 3.92-4.09 (m, 2H), 4.12 (s, 3H), 6.43 (br s, 1H), 6.83-6.89 (m, 1H), 6.94-7.02 (m, 4H), 7.07-7.11 (m, 2H) 7.46 (s, 1H).

Example 5

[0154]

3-chloro-4-(4-fluoro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (compound 39)

Using 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (120 mg, 0.31 mmol) obtained in Example 12, step 5, and 4-fluoro-2-methylaniline (118 mg, 0.94 mmol), and in the same manner as in Example 12,

step 6, compound 39 (28 mg, 19%) was obtained.

ESIMS m/z: 472 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.38–1.40 (m, 2H), 1.76–1.79 (m, 2H), 2.32 (s, 3H), 2.58–2.68 (m, 1H), 3.60 (s, 3H), 3.79–4.03 (m, 2H), 4.31–4.34 (m, 2H), 6.43 (s, 1H),
5 6.83–6.88 (m, 1H), 6.94–7.01 (m, 4H), 7.07–7.10 (m, 2H), 7.30 (s, 1H).

Example 6

[0155]

3-chloro-4-(4-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
10 (compound 40)

Using 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (120 mg, 0.31 mmol) obtained in Example 12, step 5, and 4-chloro-2-methylaniline
15 (133 mg, 0.94 mmol), and in the same manner as in Example 12, step 6, compound 40 (14 mg, 8.8%) was obtained.

ESIMS m/z: 488 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.36–1.46 (m, 2H), 1.76–1.80 (m, 2H), 2.32 (s, 3H), 2.59–2.69 (m, 1H), 3.61 (s, 3H), 3.79–4.03 (m, 2H), 4.31–4.33 (m, 2H), 6.48 (s, 1H),
20 6.92–6.94 (m, 1H), 6.97–7.01 (m, 2H), 7.07–7.15 (m, 2H), 7.23–7.26 (m, 2H), 7.36 (s, 1H).

Example 7

[0156]

4-(benzylamino)-3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (compound 42)
25

Using 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (200 mg, 0.52 mmol) obtained in Example 12, step 5, and benzylamine (168 mg, 1.57 mmol), and in the same manner as in Example 12, step 6,
30 compound 42 (5.1 mg, 2.2%) was obtained.

ESIMS m/z: 454 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.20–1.35 (m, 2H), 1.75–1.95 (m, 2H), 2.60–2.95 (m, 2H), 2.64–2.76 (m, 1H), 3.54 (s, 3H), 4.00–4.69 (m, 4H), 6.50–7.04 (m, 3H), 7.07–7.20 (m, 3H), 7.28–7.30 (m, 1H), 7.31–7.42 (m, 4H).

35 Example 8

[0157]

3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-(4-methoxy-2-methylphenylamino)-1-methylpyridin-2(1H)-one
(compound 43)

5 Using 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (200 mg, 0.52 mmol) obtained in Example 12, step 5, and 4-methoxy-2-methylaniline (215 mg, 1.57 mmol), and in the same manner as in Example 12, step 6, compound 43 (5.0 mg, 1.9%) was obtained.

10 ESIMS m/z: 484 (M + H)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 1.10-1.30 (m, 2H), 1.60-1.75 (m, 2H), 2.09 (s, 3H), 2.45-2.60 (m, 1H), 2.51 (s, 3H), 2.60-2.70 (m, 2H), 3.76-3.83 (m, 2H), 3.81 (s, 3H), 6.62-6.66 (m, 1H), 6.75-6.85 (m, 4H), 6.95-6.97 (m, 2H), 7.04-7.06 (m, 1H), 7.28 (s, 1H).

15 Example 9

[0158]

3-chloro-1-cyclopropyl-4-(4-fluoro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one
(compound 50)

20 (step 1) Using diethyl 3-oxopentanedioate (5.55 g, 27.4 mmol) and cyclopropylamine (3.92 g, 68.6 mmol), and in the same manner as in Example 12, steps 1, 2, 3 and 4, 4,5-dichloro-1-cyclopropyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid (2.52 g, 37%) was obtained.

25 ESIMS m/z: 247 (M + H)⁺

(step 2) Using 4,5-dichloro-1-cyclopropyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid (2.00 g, 8.06 mmol) obtained in step 1, and in the same manner as in Example 1, step 4, 3,4-dichloro-1-cyclopropyl-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (1.15 g, 35%) was obtained.

30 ESIMS m/z: 409 (M + H)⁺

[0159]

(step 3) Using 3,4-dichloro-1-cyclopropyl-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (100 mg, 0.24 mmol) obtained in step 2, and 4-fluoro-2-methylaniline

(46 mg, 0.38 mmol), and in the same manner as in Example 12, step 6, compound 50 (70 mg, 57%) was obtained.

ESIMS m/z: 498 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 0.80–0.97 (m, 2H), 1.05–1.20 (m, 2H), 1.23–1.48 (m, 2H), 1.51–1.67 (m, 2H),
5 2.33 (s, 3H), 2.53–2.70 (m, 1H), 3.28–3.32 (m, 1H), 3.68–4.14 (m, 2H), 4.31–4.33 (m, 2H), 6.41 (s, 1H), 6.80–6.88 (m, 1H), 6.97–7.02 (m, 4H), 7.06–7.14 (m, 2H), 7.26 (s, 1H).

Example 10

[0160]

10 3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (compound 74)

Using 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (80 mg, 0.21 mmol)
15 obtained in Example 12, step 5, and 5-chloro-2-methylaniline (133 mg, 0.94 mmol), and in the same manner as in Example 12, step 6, compound 74 (67 mg, 65%) was obtained.
ESIMS m/z: 488 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.30–1.60 (m, 2H), 1.73–1.86 (m, 2H), 2.31 (s, 3H), 2.55–2.70 (m, 1H), 3.60
20 (s, 3H), 3.85–4.15 (m, 2H), 4.31–4.33 (m, 2H), 6.51 (s, 1H), 6.94–7.02 (m, 3H), 7.03–7.12 (m, 3H), 7.16 (d, J = 8.8 Hz, 1H), 7.33 (s, 1H).

Example 11

[0161]

25 3-chloro-4-(cyclohexylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (compound 81)

Using 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (70 mg, 0.18 mmol)
obtained in Example 12, step 5, and cyclohexylamine (54 mg,
30 0.55 mmol), and in the same manner as in Example 12, step 6, compound 81 (12 mg, 15%) was obtained.
ESIMS m/z: 446 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.17–1.32 (m, 6H), 1.60–1.62 (m, 3H), 1.72–1.78 (m, 2H), 1.92–1.95 (m, 3H), 2.74–2.80 (m, 1H), 2.90–3.37 (m, 3H), 3.55 (s, 3H), 4.10–4.29
35 (m, 2H), 6.99–7.04 (m, 2H), 7.13–7.16 (m, 2H), 7.18–7.24 (m,

1H), 7.27(s, 1H).

Example 12

[0162]

4-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-
5 methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-3-
methylbenzonitrile (compound 100)

(step 1) To diethyl 3-oxopentanedioate (10 mL, 55 mmol) were
added triethyl orthoformate (9.1 mL, 55 mmol) and acetic
anhydride (10.4 mL, 110 mmol), and the mixture was stirred at
10 135°C for 1 hr. The reaction mixture was cooled to room
temperature, and concentrated under reduced pressure. To the
residue were added water (55 mL) and methylamine (9.87 mL, 137
mmol), and the mixture was stirred at room temperature
overnight. The reaction mixture was extracted with ethyl
15 acetate, and the aqueous layer was neutralized with
hydrochloric acid and extracted with ethyl acetate. The
solvent of the combined organic layer was evaporated under
reduced pressure to give ethyl 4-hydroxy-1-methyl-6-oxo-1,6-
dihydropyridine-3-carboxylate (9.2 g, 85%).

20 ESIMS m/z: 198 (M + H)⁺

(step 2) To ethyl 4-hydroxy-1-methyl-6-oxo-1,6-
dihydropyridine-3-carboxylate (9.2 g, 47 mmol) obtained in
step 1 were added phosphorus oxychloride (26.1 mL, 280 mmol)
and triethylamine (6.5 mL, 47 mmol), and the mixture was
25 stirred at 50°C for 3 hr. The reaction mixture was cooled to
room temperature, and the solvent was evaporated under reduced
pressure. To the residue was added saturated aqueous sodium
hydrogen carbonate solution (100 mL), and the mixture was
extracted with ethyl acetate. The solvent of the organic layer
30 was evaporated under reduced pressure to give ethyl 4-chloro-
1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (6.0 g, 60%).

ESIMS m/z: 216 (M + H)⁺

[0163]

(step 3) To ethyl 4-chloro-1-methyl-6-oxo-1,6-dihydropyridine-
35 3-carboxylate (6.0 g, 28 mmol) obtained in step 2 were added

N-chlorosuccinimide (4.1 g, 31 mmol) and DMF (130 mL), and the mixture was stirred at room temperature for 1 hr. To the reaction mixture was added water (200 mL), and the mixture was extracted with ethyl acetate. The organic layer was washed
5 with hydrochloric acid, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol=100/0-70/30) to give ethyl 4,5-dichloro-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (5.5 g, 79%).
10 ESIMS m/z: 250 (M + H)⁺
(step 4) To ethyl 4,5-dichloro-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (5.5 g, 22 mmol) obtained in step 3 were added 1 mol/L aqueous lithium hydroxide solution (66 mL, 66 mmol), THF (35 mL) and methanol (8.8 mL), and the
15 mixture was stirred at room temperature for 1 hr. To the reaction mixture was added hydrochloric acid to pH=1, and the precipitated solid was collected by filtration to give 4,5-dichloro-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid (4.9 g, quantitative).
20 ESIMS m/z: 222 (M + H)⁺
[0164]
(step 5) Using 4,5-dichloro-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid (0.52 g, 2.3 mmol) obtained in step 4, and in the same manner as in Example 1, step 4,
25 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (0.41 g, 46%) was obtained.
ESIMS m/z: 383 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.51-1.62 (m, 2H), 1.90-1.93 (m, 2H), 2.72-2.78 (m, 1H), 2.89-2.96 (m, 2H), 3.62 (s, 3H), 4.31-4.34 (m, 2H), 6.96-7.02 (m, 2H), 7.11-7.14
30 (m, 2H), 7.41 (s, 1H).
(step 6) 4-Amino-3-methylbenzonitrile (41 mg, 0.31 mmol) was dissolved in THF (1.0 mL), sodium hydride (33 mg, 0.84 mmol, 60% in oil) was added, and the mixture was stirred at room temperature for 1 hr. To the reaction mixture was added 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-

methylpyridin-2(1H)-one (80 mg, 0.21 mmol) obtained in step 5, and the mixture was stirred with heating under reflux for 4 hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed
5 with water, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol=100/0-70/30) to give compound 100 (77 mg, 77%).

10 ESIMS m/z: 479 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.15-1.50 (m, 2H), 1.60-1.89 (m, 2H), 2.39 (s, 3H), 2.60-2.70 (m, 1H), 3.07-3.13 (m, 2H), 3.63 (s, 3H), 3.85-4.25 (m, 2H), 6.88-6.92 (m, 2H), 6.96-7.01 (m, 2H), 7.03-7.04 (m, 2H), 7.42-7.50 (m, 2H), 7.51 (s, 1H).

15 Example 13

[0165]

4-chloro-2-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}benzonitrile (compound 103)

20 Using 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (80 mg, 0.21 mmol) obtained in Example 12, step 5, and 2-amino-4-chlorobenzonitrile (48 mg, 0.31 mmol), and in the same manner as in Example 12, step 6, compound 103 (55 mg, 53%) was
25 obtained.

ESIMS m/z: 499 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.20-1.90 (m, 4H), 2.60-2.75 (m, 1H), 3.65 (s, 3H), 3.85-4.10 (m, 2H), 4.30-4.35 (m, 2H), 6.92-7.05 (m, 3H), 7.05-7.22 (m, 4H), 7.49-7.62 (m, 2H).

30 Example 14

[0166]

3-chloro-4-[3-chloro-4-(methylthio)phenylamino]-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (compound 111)

35 Using 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-

carbonyl]-1-methylpyridin-2(1H)-one (120 mg, 0.31 mmol)
obtained in Example 12, step 5, and 3-chloro-4-
(methylthio)aniline (82 mg, 0.47 mmol), and in the same manner
as in Example 12, step 6, compound 111 (74 mg, 45%) was
5 obtained.

ESIMS m/z: 520 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.25-1.59 (m,
2H), 1.70-1.82 (m, 2H), 2.47 (s, 3H), 2.55-2.68 (m, 1H), 3.61
(s, 3H), 3.70-4.10 (m, 2H), 4.22-4.31 (m, 2H), 6.70 (s, 1H),
6.93-7.04 (m, 3H), 7.05-7.18 (m, 4H), 7.44 (s, 1H).

10 Example 15

[0167]

4-(2,4-difluorophenylamino)-5-[4-(4-fluorophenyl)piperidine-1-
carbonyl]-1,3-dimethylpyridin-2(1H)-one (compound 125)

(step 1) Using 4-chloro-1,5-dimethyl-6-oxo-1,6-
15 dihydropyridine-3-carboxylic acid (8.56 g, 42.5 mmol) obtained
by the method described in a document (Journal of Medicinal
Chemistry, 2006, vol. 9, p 441), and in the same manner as in
Example 1, step 4, 4-chloro-5-[4-(4-fluorophenyl)piperidine-1-
carbonyl]-1,3-dimethylpyridin-2(1H)-one (15.4 g, quantitative)
20 was obtained.

ESIMS m/z: 363 (M + H)⁺

(step 2) Using 4-chloro-5-[4-(4-fluorophenyl)piperidine-1-
carbonyl]-1,3-dimethylpyridin-2(1H)-one (80 mg, 0.22 mmol)
obtained in step 1, and 2,4-difluoroaniline (43 mg, 0.33 mmol),
25 and in the same manner as in Example 12, step 6, compound 125
(64 mg, 64%) was obtained.

ESIMS m/z: 456 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.30-1.55 (m,
2H), 1.70-1.90 (m, 2H), 1.98 (s, 3H), 2.57 (s, 3H), 2.57-2.73
(m, 1H), 3.90-4.35 (m, 4H), 6.23 (br s, 1H), 6.70-6.85 (m, 2H),
30 6.85-6.93 (m, 1H), 6.93-7.02 (m, 2H), 7.02-7.12 (m, 2H), 7.34
(s, 1H).

Example 16

[0168]

3-chloro-4-(4-chloro-2-fluorophenylamino)-5-[4-(4-
35 fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one

(compound 130)

Using 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (80 mg, 0.21 mmol) obtained in Example 12, step 5, and 4-chloro-2-fluoroaniline
5 (46 mg, 0.31 mmol), and in the same manner as in Example 12, step 6, compound 130 (85 mg, 83%) was obtained.
ESIMS m/z: 492 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.25-1.55 (m, 2H), 1.60-1.80 (m, 2H), 2.57-2.69 (m, 1H), 3.61 (s, 3H), 3.75-4.10 (m, 2H), 4.28-4.33 (m, 2H), 6.50 (br s, 1H), 6.95-7.12 (m,
10 6H), 7.15-7.21 (m, 1H), 7.44 (s, 1H).

Example 17

[0169]

3-chloro-4-(2,4-difluorophenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-methoxyethyl)pyridin-
15 2(1H)-one (compound 144)

Using diethyl 3-oxopentandioate (0.19 mL, 1.09 mmol), 2-methoxyethanamine and 2,4-difluoroaniline, and in the same manner as in Example 9, steps 1, 2 and 3, compound 144 (34 mg, 6.0%) was obtained.
20 ESIMS m/z: 520 (M + H)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 1.35-1.70 (m, 2H), 1.72-1.88 (m, 2H), 2.40-3.00 (m, 3H), 3.30 (s, 3H), 3.67 (t, J = 4.8 Hz, 2H), 3.90-4.25 (m, 4H), 6.60 (s, 1H), 6.80-7.40 (m, 7H), 7.61 (s, 1H).

Example 18

25 [0170]

3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-(4-methoxy-2-methylphenylamino)-1-(pyridin-3-ylmethyl)pyridin-
2(1H)-one (compound 154)

Using diethyl 3-oxopentandioate (0.43 mL, 2.38 mmol),
30 pyridin-3-ylmethanamine and 4-methoxy-2-methylaniline, and in the same manner as in Example 9, steps 1, 2 and 3, compound 154 (20 mg, 1.5%) was obtained.
ESIMS m/z: 561 (M + H)⁺; ¹H NMR (300 MHz, DMSO-d₆, δ): 1.25-1.75 (m, 4H), 2.17 (s, 3H), 2.60-3.10 (m, 3H), 3.70-4.30 (m, 2H),
35 3.72 (s, 3H), 5.13 (s, 2H), 6.68-6.82 (m, 2H), 6.93 (d, J =

6.0 Hz, 1H), 7.10–7.35 (m, 4H), 7.40–7.60 (m, 1H), 7.76 (s, 1H), 7.82 (d, $J = 6.0$ Hz, 1H), 8.50–8.58 (m, 1H), 8.61 (s, 1H).

Example 19

[0171]

5 3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-4-(6-methylpyridin-3-ylamino)pyridin-2(1H)-one (compound 157)

Using 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (80 mg, 0.21 mmol) obtained in Example 12, step 5, and 6-methylpyridin-3-ylamine
10 (34 mg, 0.31 mmol), and in the same manner as in Example 12, step 6, compound 157 (54 mg, 57%) was obtained.
ESIMS m/z : 455 ($M + H$)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.25–1.55 (m, 2H), 1.60–1.80 (m, 2H), 2.10–3.00 (m, 3H), 2.54 (s, 3H), 3.60 (s, 3H), 3.65–4.10 (m, 2H), 6.65 (br s, 1H), 6.96–7.00 (m, 2H),
15 7.09–7.14 (m, 3H), 7.30 (dd, $J = 8.3, 2.4$ Hz, 1H), 7.39 (s, 1H), 8.33 (s, 1H).

Example 20

[0172]

3-chloro-4-(5-chloro-2-methylphenylamino)-1-(2-fluoroethyl)-5-
20 [4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound 160)

Using diethyl 3-oxopentandioate (0.065 mL, 0.36 mmol), 2-fluoroethylamine and 5-chloro-2-methylaniline, and in the same manner as in Example 9, steps 1, 2 and 3, compound 160 (59 mg,
25 32%) was obtained.

ESIMS m/z : 520 ($M + H$)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 1.40–1.60 (m, 2H), 1.78–1.92 (m, 2H), 2.32 (s, 3H), 2.40–3.15 (m, 3H), 3.90–4.50 (m, 4H), 4.66 (t, $J = 4.0$ Hz, 1H), 4.82 (t, $J = 4.0$ Hz, 1H), 6.68 (s, 1H), 6.90–7.65 (m, 8H).

30 Example 21

[0173]

1-allyl-3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound 166)

35 (step 1) Using methyl 4,6-dichloronicotinate (8.00 g, 38.8

mmol) and 5-chloro-2-methylaniline (8.25 g, 58.2 mmol), and in the same manner as in Example 1, step 1, methyl 6-chloro-4-(5-chloro-2-methylphenylamino)nicotinate (6.68 g, 55%) was obtained.

5 ESIMS m/z: 311 (M + H)⁺

(step 2) Using methyl 6-chloro-4-(5-chloro-2-methylphenylamino)nicotinate (5.20 g, 16.7 mmol) obtained in step 1, and in the same manner as in Example 1, step 2, methyl 4-(5-chloro-2-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (3.78 g, 77%) was obtained.

ESIMS m/z: 293 (M + H)⁺

(step 3) Methyl 4-(5-chloro-2-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (2.0 g, 6.8 mmol) obtained in step 2 was dissolved in DMF (68 mL), N-chlorosuccinimide (1.0 g, 7.5 mmol) was added, and the mixture was stirred at room temperature for 3 hr. To the reaction mixture was added water, and the precipitated solid was collected by filtration to give methyl 5-chloro-4-(5-chloro-2-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (1.79 g, 80%).

20 ESIMS m/z: 327 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 2.28 (s, 3H), 3.87 (s, 3H), 6.89 (d, J = 2.0 Hz, 1H), 7.06 (dd, J = 8.8, 2.0 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 8.22 (s, 1H), 9.51 (s, 1H). [0174]

(step 4) Using methyl 5-chloro-4-(5-chloro-2-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (1.80 g, 5.50 mmol) obtained in step 3, and in the same manner as in Example 1, step 3, 5-chloro-4-(5-chloro-2-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (1.55 g, 90%) was obtained.

30 ESIMS m/z: 313 (M + H)⁺

(step 5) Using 5-chloro-4-(5-chloro-2-methylphenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (1.32 g, 4.22 mmol) obtained in step 4, and in the same manner as in Example 1, step 4, 3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (0.72 g,

36%) was obtained.

ESIMS m/z: 474 (M + H)⁺

(step 6) Using 3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (50 mg, 0.11 mmol) obtained in step 5, and allylbromide (0.011 mL, 0.13 mmol), and in the same manner as in Example 3, step 5, compound 166 (49 mg, 89%) was obtained.

ESIMS m/z: 514 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.37-1.46 (m, 2H), 1.78-1.82 (m, 2H), 2.31 (s, 3H), 2.59-2.75 (m, 3H), 3.95-4.10 (m, 2H), 4.61 (d, J = 5.9 Hz, 2H), 5.28-5.34 (m, 2H), 5.92-6.01 (m, 1H), 6.58 (s, 1H), 6.94-7.01 (m, 3H), 7.05-7.11 (m, 3H), 7.16 (d, J = 7.8 Hz, 1H), 7.26 (s, 1H).

Example 22

[0175]

2-{3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridine-1(2H)-yl}acetonitrile (compound 168)

Using 3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (177 mg, 0.373 mmol) obtained in Example 21, step 5, and bromoacetonitrile (0.039 mL, 0.56 mmol), and in the same manner as in Example 1, step 5, compound 168 (150 mg, 78%) was obtained.

ESIMS m/z: 513 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.42-1.55 (m, 2H), 1.81-1.84 (m, 2H), 2.31 (s, 3H), 2.63-2.69 (m, 1H), 2.95-3.00 (m, 2H), 3.95-4.05 (m, 2H), 4.96 (s, 2H), 6.83 (s, 1H), 6.97-7.01 (m, 3H), 7.11-7.20 (m, 4H), 7.47 (s, 1H).

Example 23

[0176]

3-({3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}methyl)-1,2,4-oxadiazol-5(4H)-one (compound 169)

Compound 168 (51 mg, 0.099 mmol) was dissolved in DMSO (1.0 mL), 50% hydroxylamine solution (0.12 mL, 2.0 mmol) was added, and the mixture was stirred at room temperature for 4

hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was dissolved in 1,4-dioxane (1.0 mL), CDI (24 mg, 0.15 mmol) and DBU (0.022 mL, 0.15 mmol) were added, and the mixture was stirred at 80°C for 2 hr. To the reaction mixture was added 5% aqueous citric acid solution (2.0 mL), and the mixture was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC (XBridge™ Prep C18 OBD Column, 5 µm, 19 x 150 mm, manufactured by Waters) (MeCN/0.05% aqueous TFA solution) to give compound 169 (40 mg, 70%).

ESIMS m/z: 572 (M + H)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 1.42–1.51 (m, 2H), 1.81–1.85 (m, 2H), 2.30 (s, 3H), 2.63–2.70 (m, 3H), 3.97–4.05 (m, 2H), 5.02 (s, 2H), 6.83 (s, 1H), 6.96–7.02 (m, 3H), 7.10–7.19 (m, 4H), 7.38 (s, 1H).

Example 24

[0177]

1-[(1H-tetrazol-5-yl)methyl]-3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound 170)

Compound 168 (32 mg, 0.062 mmol) was dissolved in toluene (2.0 mL), trimethylsilylazide (0.083 mL, 0.62 mmol) and dibutyltin oxide (7.7 mg, 0.031 mmol) were added, and the mixture was stirred at 110°C for 6 hr. To the reaction mixture was added methanol (1.0 mL), and the mixture was stirred at room temperature for 1 hr. To the reaction mixture was added water (2.0 mL), and the mixture was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol=99/1-90/10) to give compound 170 (16 mg, 46%) was obtained.

ESIMS m/z: 556 (M + H)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 1.48–1.58 (m, 2H), 1.82–1.86 (m, 2H), 2.30 (s, 3H), 2.45–2.71 (m, 3H), 3.95–4.15 (m, 2H), 5.46 (s, 2H), 6.78 (s, 1H), 6.94 (d, J = 1.8 Hz, 1H), 6.97–7.03 (m, 2H), 7.11–7.20 (m, 4H), 7.62 (s, 1H).

5 Example 25

[0178]

4-(benzo[d]thiazol-6-ylamino)-3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (compound 173)

10 Using 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (80 mg, 0.21 mmol) obtained in Example 12, step 5, and benzo[d]thiazol-6-ylamine (47 mg, 0.31 mmol), and in the same manner as in Example 12, step 6, compound 173 (60 mg, 58%) was obtained.

15 ESIMS m/z: 497 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.20–1.50 (m, 2H), 1.50–1.85 (m, 2H), 2.30–2.80 (m, 3H), 3.63 (s, 3H), 3.66–3.90 (m, 2H), 6.86 (br s, 1H), 6.91–7.10 (m, 4H), 7.20–7.30 (m, 1H), 7.48 (s, 1H), 7.64 (br s, 1H), 8.09 (d, J = 8.8 Hz, 1H), 8.95 (s, 1H).

20 Example 26

[0179]

3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-4-(1-methyl-1H-indazol-6-ylamino)pyridin-2(1H)-one (compound 175)

25 Using 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (80 mg, 0.21 mmol) obtained in Example 12, step 5, and 1-methyl-1H-indazol-6-amine (46 mg, 0.31 mmol), and in the same manner as in Example 12, step 6, compound 175 (94 mg, 91%) was obtained.

30 ESIMS m/z: 494 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.20–1.50 (m, 2H), 1.80–2.15 (m, 2H), 2.30–3.20 (m, 3H), 3.45–3.90 (m, 2H), 3.63 (s, 3H), 4.03 (s, 3H), 6.85–7.10 (m, 7H), 7.50 (s, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.92 (s, 1H).

Example 27

35 [0180]

4-(1H-benzo[d][1,2,3]triazol-6-ylamino)-3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (compound 177)

Using 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (80 mg, 0.21 mmol) obtained in Example 12, step 5, and 1H-benzo[d][1,2,3]triazol-6-ylamine (42 mg, 0.31 mmol), and in the same manner as in Example 12, step 6, compound 177 (8.0 mg, 8.9%) was obtained. ESIMS m/z: 481 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.10-1.90 (m, 4H), 2.50-2.65 (m, 1H), 2.65-3.40 (m, 2H), 3.50-3.90 (m, 2H), 3.78 (s, 3H), 6.98 (br s, 1H), 6.90-7.10 (m, 4H), 7.18 (d, J = 8.8 Hz, 1H), 7.36 (br s, 1H), 7.95 (br s, 1H), 8.04 (d, J = 7.8 Hz, 1H).

Example 28

[0181]

2-chloro-4-{5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1,3-dimethyl-2-oxo-1,2-dihydropyridin-4-ylamino}benzonitrile (compound 178)

Using 4-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1,3-dimethylpyridin-2(1H)-one (80 mg, 0.22 mmol) obtained in Example 15, step 1, and 4-amino-2-chlorobenzonitrile (50 mg, 0.33 mmol), and in the same manner as in Example 12, step 6, compound 178 (41 mg, 39%) was obtained. ESIMS m/z: 479 (M + H)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 1.30-1.50 (m, 2H), 1.80-1.90 (m, 2H), 1.94 (s, 3H), 2.65-2.80 (m, 1H), 2.80-3.10 (m, 1H), 3.59 (s, 3H), 4.15-4.50 (m, 2H), 6.59-6.67 (m, 1H), 6.70-6.80 (m, 1H), 6.90-7.05 (m, 4H), 7.34 (br s, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.51 (br s, 1H).

Example 29

[0182]

4-(benzo[d][1,3]dioxol-5-ylamino)-3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (compound 179)

Using 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-

carbonyl]-1-methylpyridin-2(1H)-one (80 mg, 0.21 mmol) obtained in Example 12, step 5, and benzo[d][1,3]dioxol-5-ylamine (43 mg, 0.31 mmol), and in the same manner as in Example 12, step 6, compound 179 (90 mg, 89%) was obtained.

5 ESIMS m/z: 484 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.30–1.50 (m, 2H), 1.70–1.95 (m, 2H), 2.30–2.90 (m, 3H), 3.40–4.10 (m, 2H), 3.58 (s, 3H), 5.97 (s, 2H), 6.50–6.60 (m, 2H), 6.60–6.65 (m, 1H), 6.75 (d, J = 8.8 Hz, 1H), 6.95–7.05 (m, 2H), 7.06–7.18 (m, 2H), 7.39 (br s, 1H).

10 Example 30
[0183]
3-chloro-4-(2,4-difluorophenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-hydroxyethyl)pyridin-2(1H)-one (compound 183)

15 (step 1) Using methyl 4,6-dichloronicotinate (19.5 g, 95.5 mmol) and 2,4-difluoroaniline (12.3 g, 95.5 mmol), and in the same manner as in Example 1, steps 1, 2 and 3, 4-(2,4-difluorophenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (8.5 g, 33%) was obtained.

20 ESIMS m/z: 267 (M + H)⁺
(step 2) Using 4-(2,4-difluorophenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (8.5 g, 32 mmol) obtained in step 1, and in the same manner as in Example 21, step 3, 5-chloro-4-(2,4-difluorophenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (5.0 g, 52%) was obtained.

25 ESIMS m/z: 301 (M + H)⁺
(step 3) Using 5-chloro-4-(2,4-difluorophenylamino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (0.17 g, 0.57 mmol) obtained in step 2, and 2-bromoethanol, and in the same manner as in

30 Example 1, step 4 and Example 3, step 5, compound 183 (55 mg, 19%) was obtained.

ESIMS m/z: 506 (M + H)⁺; ¹H NMR (300 MHz, DMSO-d₆, δ): 1.37–1.80 (m, 4H), 1.85–2.50 (m, 1H), 2.65–3.10 (m, 2H), 3.55–3.70 (m, 2H), 3.70–4.20 (m, 4H), 4.90 (br s, 1H), 6.95–7.40 (m, 7H),

35 7.49 (s, 1H), 8.00 (s, 1H).

Example 31

[0184]

3-chloro-4-(2,4-difluorophenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]pyridin-2(1H)-one (compound 184)

Using methyl 4,6-dichloronicotinate (0.43 g, 2.15 mmol), 2,4-difluoroaniline and 2-(chloromethyl)-5-methyl-1,3,4-oxadiazole, and in the same manner as in Example 30, steps 1, 2 and 3, compound 184 (96 mg, 8.0%) was obtained.

ESIMS m/z: 558 (M + H)⁺; ¹H NMR (300 MHz, DMSO-d₆, δ): 1.15–1.80 (m, 4H), 1.95–2.30 (m, 1H), 2.48 (s, 3H), 2.65–3.10 (m, 2H), 3.85–4.20 (m, 2H), 5.34 (s, 2H), 7.05–7.40 (m, 7H), 7.80 (s, 1H), 8.20 (s, 1H).

Example 32

[0185]

3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-hydroxyethyl)pyridin-2(1H)-one (compound 186)

Using methyl 4,6-dichloronicotinate (0.32 g, 1.57 mmol), 5-chloro-2-methylaniline and 2-bromoethanol, and in the same manner as in Example 30, steps 1, 2 and 3, compound 186 (114 mg, 14%) was obtained.

ESIMS m/z: 518 (M + H)⁺; ¹H NMR (300 MHz, DMSO-d₆, δ): 1.15–1.90 (m, 4H), 1.90–2.30 (m, 1H), 2.19 (s, 3H), 2.60–3.20 (m, 2H), 3.55–3.75 (m, 2H), 3.97 (br s, 4H), 4.90 (br s, 1H), 6.94 (s, 1H), 7.05–7.40 (m, 6H), 7.53 (s, 1H), 7.76 (s, 1H).

Example 33

[0186]

3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]pyridin-2(1H)-one (compound 187)

Using methyl 4,6-dichloronicotinate (0.33 g, 1.62 mmol), 5-chloro-2-methylaniline and 2-(chloromethyl)-5-methyl-1,3,4-oxadiazole and in the same manner as in Example 30, steps 1, 2 and 3, compound 187 (83 mg, 9.0%) was obtained.

ESIMS m/z: 570 (M + H)⁺; ¹H NMR (300 MHz, DMSO-d₆, δ): 1.15–1.85 (m, 4H), 1.90–2.30 (m, 1H), 2.20 (s, 3H), 2.48 (s, 3H), 2.60–3.20 (m, 2H), 3.96 (br s, 2H), 5.35 (s, 2H), 7.05–7.40 (m, 7H), 7.80 (s, 1H), 7.99 (s, 1H).

5 Example 34

[0187]

3-chloro-4-(1,1-dioxobenzo[b]thiophen-6-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (compound 188)

10 Using 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (80 mg, 0.21 mmol) obtained in Example 12, step 5, and 6-amino-1,1-dioxobenzo[b]thiophene (57 mg, 0.31 mmol), and in the same manner as in Example 12, step 6, compound 188 (57 mg, 52%) was
15 obtained.

ESIMS m/z: 528 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.38–1.47 (m, 2H), 1.79–1.82 (m, 2H), 2.60–2.80 (m, 3H), 3.63 (s, 3H), 3.89–3.98 (m, 2H), 6.69 (d, J = 6.9 Hz, 1H), 6.96–7.04 (m, 3H), 7.08–7.14 (m, 3H), 7.19 (d, J = 6.9 Hz, 1H), 7.29–7.33 (m, 2H),
20 7.46 (s, 1H).

Example 35

[0188]

3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-propylpyridin-2(1H)-one
25 (compound 189)

Using 3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (40 mg, 0.084 mmol) obtained in Example 21, step 5, and 1-bromopropane (0.0090 mL, 0.10 mmol), and in the same manner as in Example 3,
30 step 5, compound 189 (27 mg, 61%) was obtained.

ESIMS m/z: 516 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 0.98 (t, J = 7.3 Hz, 3H), 1.38–1.46 (m, 2H), 1.79–1.85 (m, 4H), 2.31 (s, 3H), 2.55–2.72 (m, 3H), 3.93 (t, J = 6.8 Hz, 2H), 3.97–4.08 (m, 2H), 6.54 (s, 1H), 6.95–7.01 (m, 3H), 7.05–7.17 (m, 4H), 7.27
35 (s, 1H).

Example 36

[0189]

3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2,2,2-trifluoroethyl)pyridin-2(1H)-one (compound 190)

Using 3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (40 mg, 0.084 mmol) obtained in Example 21, step 5, and 2,2,2-trifluoroethyl trifluoromethanesulfonate (23 mg, 0.10 mmol), and in the same manner as in Example 3, step 5, compound 190 (32 mg, 68%) was obtained.

ESIMS m/z: 556 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.40-1.50 (m, 2H), 1.83-1.86 (m, 2H), 2.32 (s, 3H), 2.64-2.71 (m, 3H), 4.00-4.15 (m, 2H), 4.65 (s, 2H), 6.67 (s, 1H), 6.97-7.02 (m, 3H), 7.11-7.14 (m, 3H), 7.18 (d, J = 8.8 Hz, 1H), 7.23 (s, 1H).

Example 37

[0190]

4-(2-fluoro-4-methoxyphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1,3-dimethylpyridin-2(1H)-one (compound 191)

Using 4-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1,3-dimethylpyridin-2(1H)-one (80 mg, 0.22 mmol) obtained in Example 15, step 1, and 2-fluoro-4-methoxyaniline (47 mg, 0.33 mmol), and in the same manner as in Example 12, step 6, compound 191 (53 mg, 51%) was obtained.

ESIMS m/z: 468 (M + H)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 1.39-1.50 (m, 2H), 1.77-1.81 (m, 2H), 2.00 (s, 3H), 2.62-2.70 (m, 1H), 2.70-2.91 (m, 2H), 3.55 (s, 3H), 3.77 (s, 3H), 4.09-4.16 (m, 2H), 6.02 (br s, 1H), 6.57-6.60 (m, 1H), 6.67-6.72 (m, 1H), 6.81-6.87 (m, 1H), 6.94-7.00 (m, 2H), 7.05-7.09 (m, 2H), 7.31 (s, 1H).

Example 38

[0191]

5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1,3-dimethyl-4-(2,4,5-trifluorophenylamino)pyridin-2(1H)-one (compound 192)

Using 4-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1,3-dimethylpyridin-2(1H)-one (80 mg, 0.22 mmol) obtained in Example 15, step 1, and 2,4,5-trifluoroaniline (49 mg, 0.33 mmol), and in the same manner as in Example 12, step 5 6, compound 192 (70 mg, 67%) was obtained.
ESIMS m/z: 474 (M + H)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 1.41-1.52 (m, 2H), 1.84-1.87 (m, 2H), 1.97 (s, 3H), 2.68-2.74 (m, 1H), 2.82-2.98 (m, 2H), 3.58 (s, 3H), 4.17-4.30 (m, 2H), 6.52-6.57 (m, 2H), 6.95-7.02 (m, 3H), 7.05-7.08 (m, 2H), 7.34 (s, 1H).

10 [Example 39]
[0192]
4-(benzo[d]thiazol-6-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-3-nitropyridin-2(1H)-one (compound 195) (step 1) Using ethyl 4-hydroxy-1-methyl-6-oxo-1,6-
15 dihydropyridine-3-carboxylate (2 g, 10.1 mmol) obtained in Example 12, step 1, and in the same manner as in Example 12, step 4, 4-hydroxy-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid (1.63 g, 95%) was obtained.
ESIMS m/z: 170 (M + H)⁺
20 (step 2) Using 4-hydroxy-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid (500 mg, 2.96 mmol) obtained in step 1, and in the same manner as in Example 1, step 4, 5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-hydroxy-1-methylpyridin-2(1H)-one (860 mg, 88%) was obtained.
25 ESIMS m/z: 331 (M + H)⁺
(step 3) 5-[4-(4-Fluorophenyl)piperidine-1-carbonyl]-4-hydroxy-1-methylpyridin-2(1H)-one (800 mg, 2.42 mmol) obtained in step 2 was dissolved in acetic acid (4 mL) and water (1 mL), concentrated nitric acid (0.43 mL, 9.69 mmol) was added at -
30 10°C, and the mixture was stirred for 1 hr while gradually raising the temperature from -10°C to room temperature. The reaction mixture was added dropwise to ice water, and the precipitated solid was collected by filtration to give 5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-hydroxy-1-methyl-3-
35 nitropyridin-2(1H)-one (755 mg, 83%).

ESIMS m/z: 376 (M + H)⁺

[0193]

(step 4) Using 5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-hydroxy-1-methyl-3-nitropyridin-2(1H)-one (500 mg, 1.33 mmol) obtained in step 3, and in the same manner as in Example 12, step 2, 4-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-3-nitropyridin-2(1H)-one (314 mg, 60%) was obtained. ESIMS m/z: 394 (M + H)⁺

(step 5) Using 4-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-3-nitropyridin-2(1H)-one (145 mg, 0.368 mmol), and benzo[d]thiazol-6-amine (111 mg, 0.736 mmol) obtained in step 4, and in the same manner as in Example 12, step 6, compound 195 (152 mg, 81%) was obtained. ESIMS m/z: 508 (M + H)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 1.21-1.43 (m, 2H), 1.65-1.78 (m, 2H), 2.50-2.63 (m, 1H), 2.75-3.00 (m, 2H), 3.59 (s, 3H), 3.65-3.78 (m, 2H), 6.91-7.07 (m, 4H), 7.33 (dd, J = 8.6, 2.0 Hz, 1H), 7.59 (s, 1H), 7.75 (d, J = 2.0 Hz, 1H), 8.13 (d, J = 8.6 Hz, 1H), 9.01 (s, 1H), 10.1 (s, 1H).

Example 40

[0194]

4-(benzo[d]oxazol-5-ylamino)-3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (compound 196)

Using 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (80 mg, 0.21 mmol) obtained in Example 12, step 5, and benzo[d]oxazol-5-amine (42 mg, 0.313 mmol), and in the same manner as in Example 12, step 6, compound 196 (9 mg, 9%) was obtained.

ESIMS m/z: 481 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.20-1.50 (m, 2H), 1.60-1.80 (m, 2H), 2.30-2.85 (m, 3H), 3.61 (s, 3H), 3.70-3.90 (m, 2H), 6.80 (s, 1H), 6.94-7.01 (m, 2H), 7.02-7.09 (m, 2H), 7.14 (dd, J = 8.8, 2.0 Hz, 1H), 7.42 (s, 1H), 7.50-7.58 (m, 2H), 8.12 (s, 1H).

Example 41

[0195]

3-amino-4-(benzo[d]thiazol-6-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (compound 197)

Compound 195 (140 mg, 0.276 mmol) was dissolved in
5 ethanol (3 mL), 10% palladium carbon (15 mg, 0.141 mmol) was added, and the mixture was stirred under a hydrogen atmosphere at room temperature for 5 hr. The reaction mixture was filtered through celite, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel
10 column chromatography (chloroform/methanol=99/1-95/5) to give compound 197 (120 mg, 91%).

ESIMS m/z: 478 (M + H)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 1.20-1.35 (m, 2H), 1.52-1.73 (m, 2H), 2.50-2.63 (m, 1H), 2.70-2.98 (m, 2H), 3.63 (s, 3H), 4.15-4.50 (m, 2H), 6.47 (s, 1H), 6.60-6.72 (m, 2H), 6.78-6.85 (m, 3H), 6.97 (dd, J = 8.8, 2.2 Hz, 1H), 7.06
15 (d, J = 2.2 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 8.77 (s, 1H).

Example 42

[0196]

N-{4-(benzo[d]thiazol-6-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide (compound 199)

Compound 197 (30 mg, 0.063 mmol) was dissolved in dichloromethane (1 mL), triethylamine (0.010 mL, 0.075 mmol) and acetyl chloride (0.006 mL, 0.075 mmol) were added, and the
25 mixture was stirred at room temperature for 15 hr. To the reaction mixture was added saturated aqueous ammonium chloride solution, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure, and the
30 residue was purified by silica gel column chromatography (chloroform/methanol=90/10) to give compound 199 (26.1 mg, 80%).

ESIMS m/z: 520 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.40-1.80 (m, 4H), 2.29 (s, 3H), 2.43-2.56 (m, 1H), 2.75-3.00 (m, 2H), 3.62
35 (s, 3H), 3.70-3.90 (m, 2H), 6.92-7.00 (m, 2H), 7.00-7.07 (m,

2H), 7.10 (dd, J = 8.8, 2.0 Hz, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.54 (s, 1H), 7.99 (d, J = 8.8 Hz, 1H), 8.11 (s, 1H), 8.28 (s, 1H), 8.82 (s, 1H).

Example 43

5 [0197]

1-{4-(benzo[d]thiazol-6-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-3-yl}-3-ethylurea (compound 200)

Compound 197 (30 mg, 0.063 mmol) was dissolved in
10 dichloromethane (1 mL), triethylamine (0.010 mL, 0.075 mmol) and ethyl isocyanate (0.006 mL, 0.075 mmol) were added, and the mixture was stirred at room temperature for 15 hr. To the reaction mixture was added saturated aqueous ammonium chloride solution, and the mixture was extracted with chloroform. The
15 organic layer was dried over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform/methanol=99/1-95/5) to give compound 200 (34 mg, 99%).

20 ESIMS m/z: 549 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.19 (t, J = 7.3 Hz, 3H), 1.50-1.90 (m, 4H), 2.47-2.55 (m, 1H), 2.75-2.95 (m, 2H), 3.28-3.37 (m, 2H), 3.62 (s, 3H), 3.73-3.88 (m, 2H), 6.22 (s, 1H), 6.88-7.12 (m, 5H), 7.39 (s, 1H), 7.50 (s, 1H), 7.92 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 8.80 (s, 1H), 8.99 (br.
25 s, 1H).

Example 44

[0198]

3-chloro-1-(2-fluoroethyl)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-(1-methyl-1H-indazol-6-ylamino)pyridin-2(1H)-one
30 (compound 203)

(step 1) In the same manner as in Example 12, step 1, and using 2-fluoroethylamine hydrochloride (16.4 g, 165 mmol) instead of methylamine, ethyl 1-(2-fluoroethyl)-4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylate (13.5 g, 54%) was
35 obtained.

ESIMS m/z: 230 (M + H)⁺

(step 2) Using ethyl 1-(2-fluoroethyl)-4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylate (13.5 g, 58.9 mmol) obtained in step 1, and in the same manner as in Example 12, step 2, ethyl
5 4-chloro-1-(2-fluoroethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (3.62 g, 25%) was obtained.

ESIMS m/z: 248 (M + H)⁺

(step 3) Using ethyl 4-chloro-1-(2-fluoroethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (1.0 g, 4.04 mmol) obtained in
10 step 2, and in the same manner as in Example 12, step 3, ethyl 4,5-dichloro-1-(2-fluoroethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (1.1 g, quantitative) was obtained.

ESIMS m/z: 282 (M + H)⁺

[0199]

15 (step 4) Using ethyl 4,5-dichloro-1-(2-fluoroethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (1.09 g, 3.86 mmol) obtained in step 3, and in the same manner as in Example 12, step 4, 4,5-dichloro-1-(2-fluoroethyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (0.82 g, 83%) was obtained.

20 ESIMS m/z: 254 (M + H)⁺

(step 5) Using 4,5-dichloro-1-(2-fluoroethyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (0.76 g, 3.0 mmol) obtained in step 4, and in the same manner as in Example 1, step 4, 3,4-dichloro-1-(2-fluoroethyl)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (1.25 g, quantitative) was obtained.

ESIMS m/z: 415

(step 6) Using 3,4-dichloro-1-(2-fluoroethyl)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (80 mg, 0.19 mmol) obtained in step 5, and 1-methyl-1H-indazol-6-amine (43 mg, 0.289 mmol), and in the same manner as in Example 12, step 6, compound 203 (33 mg, 33%) was obtained.

ESIMS m/z: 526 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.10-1.45 (m, 2H), 1.50-1.73 (m, 2H), 2.15-2.90 (m, 3H), 3.68-3.85 (m, 2H),
35 4.03 (s, 3H), 4.20-4.30 (m, 1H), 4.30-4.40 (m, 1H), 4.68 (t, J

= 4.4 Hz, 1H), 4.84 (t, J = 4.4 Hz, 1H), 6.88 (dd, J = 8.4, 1.8 Hz, 1H), 6.91-7.05 (m, 5H), 7.06 (br s, 1H), 7.46 (s, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.91 (s, 1H).

Example 45

5 [0200]

3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-hydroxyethoxy)pyridin-2(1H)-one (compound 204)

(step 1) Using compound 21 (369 mg, 0.636 mmol), and in the
10 same manner as in Example 4, step 3, a crude product (312 mg) of 3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-hydroxypyridin-2(1H)-one was obtained, which was used for the next step without purification.

15 (step 2) Using a crude product (20.5 mg from 312 mg) of 3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-hydroxypyridin-2(1H)-one obtained in step 1, and 2-bromoethanol (0.0059 mL, 0.084 mmol), and in the same manner as in Example 4, step 4, compound 204
20 (16.4 mg, 2 steps 73%) was obtained.

ESIMS m/z: 534 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.37-1.50 (m, 2H), 1.78-1.88 (m, 2H), 2.31 (s, 3H), 2.51-2.80 (m, 3H), 3.77-3.85 (m, 2H), 3.93-4.13 (m, 2H), 4.28-4.40 (m, 3H), 6.60 (br s, 1H), 6.94-7.03 (m, 3H), 7.08-7.15 (m, 3H), 7.18 (d, J = 8.8 Hz, 1H), 7.54 (s, 1H).
25

Example 46

[0201]

4-(benzo[d]thiazol-5-ylamino)-3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-methoxyethyl)pyridin-
30 2(1H)-one (compound 206)

(step 1) Using 2-methoxyethylamine (14.3 mL, 137 mmol) instead of methylamine used in Example 12, step 1, and in the same manner as in Example 12, step 1, ethyl 4-hydroxy-1-(2-methoxyethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (13 g, 49%) was obtained.
35

ESIMS m/z: 242 (M + H)⁺

(step 2) Using ethyl 4-hydroxy-1-(2-methoxyethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (13 g, 53.9 mmol) obtained in step 1, and in the same manner as in Example 12, step 2, ethyl
5 4-chloro-1-(2-methoxyethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (8.2 g, 59%) was obtained.

ESIMS m/z: 260 (M + H)⁺

(step 3) Using ethyl 4-chloro-1-(2-methoxyethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (14 g, 48.5 mmol) obtained in
10 step 2, and in the same manner as in Example 12, step 3, ethyl 4,5-dichloro-1-(2-methoxyethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (5.8 g, 39%) was obtained.

ESIMS m/z: 294 (M + H)⁺

[0202]

15 (step 4) Using ethyl 4,5-dichloro-1-(2-methoxyethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (1.6 g, 5.4 mmol) obtained in step 3, and in the same manner as in Example 12, step 4, 4,5-dichloro-1-(2-methoxyethyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (1.2 g, 86%) was obtained.

20 ESIMS m/z: 266 (M + H)⁺

(step 5) Using 4,5-dichloro-1-(2-methoxyethyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (0.8 g, 3.0 mmol) obtained in step 4, and in the same manner as in Example 1, step 4, 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-methoxyethyl)pyridin-2(1H)-one (1.25 g, 98%) was obtained.
25

ESIMS m/z: 427

(step 6) Using 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-methoxyethyl)pyridin-2(1H)-one (70 mg, 0.16 mmol) obtained in step 5, and benzo[d]thiazol-5-amine (37 mg,
30 0.246 mmol), and in the same manner as in Example 12, step 6, compound 206 (58 mg, 66%) was obtained.

ESIMS m/z: 541 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.20-1.55 (m, 2H), 1.60-1.80 (m, 2H), 2.20-2.90 (m, 3H), 3.32 (s, 3H), 3.65-3.75 (m, 2H), 3.90-4.05 (m, 2H), 4.10-4.30 (m, 2H), 6.93-7.00
35 (m, 2H), 7.02-7.12 (m, 3H), 7.23 (d, J = 6.8 Hz, 1H), 7.42 (s,

1H), 7.76 (s, 1H), 7.89 (d, J = 7.8 Hz, 1H), 9.01 (s, 1H).

Example 47

[0203]

4-(benzo[d]thiazol-5-ylamino)-5-[4-(4-fluorophenyl)piperidine-
5 1-carbonyl]-1,3-dimethylpyridin-2(1H)-one (compound 208)

Using 4-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1,3-dimethylpyridin-2(1H)-one (80 mg, 0.22 mmol) obtained in Example 15, step 1, and benzo[d]thiazol-5-amine (50 mg, 0.33 mmol), and in the same manner as in Example 12,
10 step 6, compound 208 (3.5 mg, 3%) was obtained.
ESIMS m/z: 477 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.20-1.45 (m, 2H), 1.65-1.80 (m, 2H), 2.00 (s, 3H), 2.55-2.67 (m, 1H), 2.70-2.90 (m, 2H), 3.59 (s, 3H), 4.14-4.35 (m, 2H), 6.65-6.95 (m, 5H), 6.99-7.04 (m, 1H), 7.33 (s, 1H), 7.49 (s, 1H), 7.81 (d, J
15 = 8.8 Hz, 1H), 8.98 (s, 1H).

Example 48

[0204]

3-chloro-4-(4,6-dimethylpyridin-3-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
20 (compound 209)

Using 3,4-dichloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (80 mg, 0.21 mmol) obtained in Example 12, step 5, and 4,6-dimethylpyridin-3-amine (38 mg, 0.313 mmol), and in the same manner as in
25 Example 12, step 6, compound 209 (55 mg, 56%) was obtained.
ESIMS m/z: 469 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.30-1.60 (m, 2H), 1.70-1.90 (m, 2H), 2.29 (s, 3H), 2.50 (s, 3H), 2.51-2.95 (m, 2H), 2.60-2.70 (m, 1H), 3.57 (s, 3H), 3.85-4.15 (m, 2H), 6.39 (s, 1H), 6.95-7.06 (m, 3H), 7.10-7.20 (m, 3H), 8.12 (s,
30 1H).

Example 49

[0205]

3-chloro-4-(5-chloro-2-methylphenylamino)-1-(dimethylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one
35 (compound 217)

(step 1) To diethyl 3-oxopentandioate (5.0 mL, 27.4 mmol) were added triethyl orthoformate (4.57 mL, 27.4 mmol) and acetic anhydride (5.18 mL, 54.8 mmol), and the mixture was stirred at 135°C for 2 hr. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The residue (6.90 g from 7.86 g) was dissolved in THF (100 mL), N,N-dimethylhydrazine (2.2 mL, 28.9 mmol) was added, and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure, and the residue was dissolved in toluene (100 mL). DBU (10.9 mL, 72.3 mmol) was added, and the mixture was stirred at 50°C for 30 min. The reaction mixture was cooled to room temperature, and the mixture was extracted with 0.1 mol/L hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was neutralized with 1 mol/L aqueous sodium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (heptane/ethyl acetate=60/40-30/70) to give ethyl 1-(dimethylamino)-4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylate (3.41 g, 63%).

ESIMS m/z: 227 (M + H)⁺

(step 2) Using ethyl 1-(dimethylamino)-4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylate (1.03 g, 4.55 mmol) obtained in step 1, and in the same manner as in Example 2, step 2, ethyl 1-(dimethylamino)-6-oxo-4-(trifluoromethylsulfonyloxy)-1,6-dihydropyridine-3-carboxylate (45.5 mg, 48%) was obtained.

ESIMS m/z: 359 (M + H)⁺

[0206]

(step 3) Using ethyl 1-(dimethylamino)-6-oxo-4-(trifluoromethylsulfonyloxy)-1,6-dihydropyridine-3-carboxylate (173 mg, 0.483 mmol) obtained in step 2, and in the same manner as in Example 2, step 3, ethyl 4-(5-chloro-2-methylphenylamino)-1-(dimethylamino)-6-oxo-1,6-

dihydropyridine-3-carboxylate (125 mg, 74%) was obtained.

ESIMS m/z: 350 (M + H)⁺

(step 4) Using ethyl 4-(5-chloro-2-methylphenylamino)-1-(dimethylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (123
5 mg, 0.352 mmol) obtained in step 3, and in the same manner as in Example 1, step 6, 4-(5-chloro-2-methylphenylamino)-1-(dimethylamino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (104 mg, 92%) was obtained.

ESIMS m/z: 322 (M + H)⁺

10 (step 5) Using 4-(5-chloro-2-methylphenylamino)-1-(dimethylamino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (100 mg, 0.311 mmol) obtained in step 4, and in the same manner as in Example 1, step 4 and Example 21, step 3, compound 217 (115 mg, 72%) was obtained.

15 ESIMS m/z: 517 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.41-1.60 (m, 2H), 1.78-1.90 (m, 2H), 2.31 (s, 3H), 2.58-2.86 (m, 3H), 3.08 (s, 6H), 4.01-4.19 (m, 2H), 6.57 (br s, 1H), 6.92 (d, J = 2.0 Hz, 1H), 6.96-7.03 (m, 2H), 7.06 (d, J = 7.8 Hz, 1H), 7.09-7.18 (m, 3H), 7.43 (s, 1H).

20 Example 50

[0207]

4-(benzylamino)-3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methoxypyridin-2(1H)-one (compound 220)

(step 1) Ethyl 1-(benzyloxy)-6-oxo-4-(trifluoromethylsulfonyloxy)-1,6-dihydropyridine-3-carboxylate
25 (635 mg, 1.51 mmol) obtained in Example 2, step 2, benzylamine (0.198 mL, 1.81 mmol), and N,N-diisopropylethylamine (0.526 mL, 3.01 mmol) were dissolved in acetonitrile (10 mL), and the mixture was stirred at 60°C for 2 hr. The reaction mixture was
30 cooled to room temperature, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (heptane/ethyl acetate=75/25-45/55) to give ethyl 4-(benzylamino)-1-(benzyloxy)-6-oxo-1,6-dihydropyridine-3-carboxylate (560 mg, 98%).

35 ESIMS m/z: 379 (M + H)⁺

(step 2) Using ethyl 4-(benzylamino)-1-(benzyloxy)-6-oxo-1,6-dihydropyridine-3-carboxylate (300 mg, 0.793 mmol) obtained in step 1, and in the same manner as in Example 21, step 3, ethyl 4-(benzylamino)-1-(benzyloxy)-5-chloro-6-oxo-1,6-dihydropyridine-3-carboxylate (329 mg, quantitative) was obtained.

ESIMS m/z: 413 (M + H)⁺

[0208]

(step 3) Using ethyl 4-(benzylamino)-1-(benzyloxy)-5-chloro-6-oxo-1,6-dihydropyridine-3-carboxylate (325 mg, 0.787 mmol) obtained in step 2, and in the same manner as in Example 1, step 6, 4-(benzylamino)-1-(benzyloxy)-5-chloro-6-oxo-1,6-dihydropyridine-3-carboxylic acid (257, 85%) was obtained.

ESIMS m/z: 385 (M + H)⁺

(step 4) Using 4-(benzylamino)-1-(benzyloxy)-5-chloro-6-oxo-1,6-dihydropyridine-3-carboxylic acid (250 mg, 0.650 mmol) obtained in step 3, and in the same manner as in Example 1, step 4, 4-(benzylamino)-1-(benzyloxy)-3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (359 mg, quantitative) was obtained.

ESIMS m/z: 546 (M + H)⁺

(step 5) Using 4-(benzylamino)-1-(benzyloxy)-3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (26.4 mg, 0.048 mmol) obtained in step 4, and in the same manner as in Example 4, steps 3 and 4, compound 220 (11.0 mg, 49%) was obtained.

ESIMS m/z: 470 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃, δ): 1.43-1.63 (m, 2H), 1.81-1.93 (m, 2H), 2.58-2.94 (m, 3H), 4.09 (s, 3H), 4.44-4.56 (m, 2H), 5.27-5.37 (m, 2H), 6.96-7.41 (m, 10H), 7.44 (s, 1H).

Example 51

[0209]

4-(benzylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (compound 221)

(step 1) Using ethyl 4-chloro-1-methyl-6-oxo-1,6-

dihydropyridine-3-carboxylate (250 mg, 1.16 mmol) obtained in Example 12, step 2, and benzylamine (0.19 mL, 1.74 mmol), and in the same manner as in Example 12, step 6, ethyl 4-(benzylamino)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (279 mg, 84%) was obtained.

ESIMS m/z: 287 (M + H)⁺

(step 2) To DMF (3 mL) was added phosphorus oxychloride (765 mL, 8.21 mmol) at 0°C, and the mixture was stirred at 0°C for 1 hr. Ethyl 4-(benzylamino)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (470 mg, 1.64 mmol) obtained in step 1 was added, and the mixture was stirred at room temperature for 3 hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to give ethyl 4-(benzylamino)-5-formyl-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (516 mg, quantitative).

ESIMS m/z: 315 (M + H)⁺

[0210]

(step 3) To ethyl 4-(benzylamino)-5-formyl-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (124 mg, 0.394 mmol) obtained in step 2 were added acetic acid (3 mL) and 50% aqueous hydroxylamine solution (0.076 mL, 0.592 mmol), and the mixture was stirred at 120°C for 4 hr. The reaction mixture was cooled to room temperature, saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to give ethyl 4-(benzylamino)-5-cyano-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (110 mg, 90%).

ESIMS m/z: 312 (M + H)⁺

(step 4) Using ethyl 4-(benzylamino)-5-cyano-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (110 mg, 0.353 mmol) obtained in step 3, and in the same manner as in Example 12,

step 4, 4-(benzylamino)-5-cyano-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid (78 mg, 78%) was obtained.

ESIMS m/z: 284 (M + H)⁺

(step 5) Using 4-(benzylamino)-5-cyano-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid (78 mg, 0.251 mmol) obtained in step 4, and in the same manner as in Example 1, step 4, compound 221 (99 mg, 89%) was obtained.

ESIMS m/z: 445 (M + H)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 1.44-1.60 (m, 2H), 1.86-1.96 (m, 2H), 2.70-2.80 (m, 1H), 2.92-3.04 (m, 2H), 3.47 (s, 3H), 4.23-4.33 (m, 2H), 4.93 (d, J = 5.5 Hz, 2H), 6.82-6.88 (m, 1H), 6.95-7.03 (m, 2H), 7.06-7.11 (m, 2H), 7.29 (s, 1H), 7.31-7.41 (m, 5H).

Example 52

[0211]

3-fluoro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-4-(1-methyl-1H-indazol-6-ylamino)pyridin-2(1H)-one (compound 224)

(step 1) 4-Chloro-5,6-difluoropyridine-3-carboxylic acid (3 g, 15.5 mmol), and 1-methyl-1H-indazol-6-amine (2.39 g, 15.8 mmol) were dissolved in THF (80 mL), 1.0 mol/L lithiumbis(trimethylsilyl)amide/THF solution (37.5 mL, 37.5 mmol) was added dropwise at -78°C, and the mixture was stirred at -78°C for 1 hr. The solvent of the reaction mixture was evaporated under reduced pressure, and the residue was adjusted to pH=3 by adding 4.0 mol/L aqueous hydrochloric acid solution. The precipitated solid was collected by filtration to give 5,6-difluoro-4-(1-methyl-1H-indazol-6-ylamino)nicotinic acid (2.98 g, 63%).

ESIMS m/z: 305 (M + H)⁺

(step 2) 5,6-Difluoro-4-(1-methyl-1H-indazol-6-ylamino)nicotinic acid (2.98 g, 9.79 mmol) obtained in step 1 was dissolved in methanol (50 mL) and THF (5 mL), trimethylsilyldiazomethane (24.5 mL, 49 mmol) was added dropwise at 0°C, and the mixture was stirred at room temperature for 4 hr. To the reaction mixture was added acetic

acid, and the precipitated solid was collected by filtration to give methyl 5,6-difluoro-4-(1-methyl-1H-indazol-6-ylamino)nicotinate (3.12 g, quantitative).

ESIMS m/z: 319 (M + H)⁺

5 [0212]

(step 3) Using methyl 5,6-difluoro-4-(1-methyl-1H-indazol-6-ylamino)nicotinate (3.12 g, 9.8 mmol) obtained in step 2, and in the same manner as in Example 1, step 2, methyl 5-fluoro-4-(1-methyl-1H-indazol-6-ylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (1.31 g, 42%) was obtained.

ESIMS m/z: 317 (M + H)⁺

(step 4) Using methyl 5-fluoro-4-(1-methyl-1H-indazol-6-ylamino)-6-oxo-1,6-dihydropyridine-3-carboxylate (1.11 g, 3.51 mmol) obtained in step 3, and in the same manner as in Example 1, step 3, 5-fluoro-4-(1-methyl-1H-indazol-6-ylamino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (1.06 g, quantitative) was obtained.

ESIMS m/z: 303 (M + H)⁺

(step 5) Using 5-fluoro-4-(1-methyl-1H-indazol-6-ylamino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (1.06 g, 3.51 mmol) obtained in step 4, and in the same manner as in Example 1, step 4, 3-fluoro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-(1-methyl-1H-indazol-6-ylamino)pyridin-2(1H)-one (500 mg, 31%) was obtained.

25 ESIMS m/z: 464 (M + H)⁺

[0213]

(step 6) 3-Fluoro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-(1-methyl-1H-indazol-6-ylamino)pyridin-2(1H)-one (250 mg, 0.54 mmol) obtained in step 5 was dissolved in DMF (3 mL), dimethyl sulfate (0.19 mL, 2.7 mmol) and cesium carbonate (352 mg, 1.08 mmol) were added, and the mixture was stirred at 90°C for 3 hr. The solvent of the reaction mixture was evaporated under reduced pressure, and the residue was subjected to preparative HPLC (XBridgeTM manufactured by Waters) (MeCN/10 mmol/L aqueous ammonium hydrogen carbonate solution) to give

compound 224 (39.6 mg, 15%).

ESIMS m/z: 478 (M + H)⁺; ¹H NMR (300 MHz, DMSO-d₆, δ): 1.12–1.70 (m, 4H), 2.20–2.55 (m, 1H), 2.56–2.97 (m, 2H), 3.49 (s, 3H), 3.89–4.12 (m, 5H), 6.87–6.89 (m, 1H), 6.99–7.15 (m, 5H), 7.57–
5 7.62 (m, 2H), 7.90 (s, 1H), 8.52 (s, 1H).

Example 53

[0214]

4-(benzo[d]thiazol-6-ylamino)-3-fluoro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
10 (compound 225)

(step 1) Using 4-chloro-5,6-difluoropyridine-3-carboxylic acid (3 g, 15.5 mmol), and benzo[d]thiazol-6-amine (2.45 g, 16.3 mmol), and in the same manner as in Example 12, step 6, 4-(benzo[d]thiazol-6-ylamino)-5,6-difluoronicotinic acid (4.4 g,
15 92%) was obtained.

ESIMS m/z: 308 (M + H)⁺

(step 2) Using 4-(benzo[d]thiazol-6-ylamino)-5,6-difluoronicotinic acid (4.4 g, 14.3 mmol) obtained in step 1, and in the same manner as in Example 52, step 2, methyl 4-(benzo[d]thiazol-6-ylamino)-5-fluoro-6-methoxynicotinate (2.42
20 g, 51%) was obtained.

ESIMS m/z: 334 (M + H)⁺

(step 3) Methyl 4-(benzo[d]thiazol-6-ylamino)-5-fluoro-6-methoxynicotinate (2.42 g, 7.26 mmol) obtained in step 2 was
25 dissolved in 1,4-dioxane (30 mL), concentrated hydrochloric acid (30 mL), and the mixture was stirred at 100°C for 18 hr. The solvent of the reaction mixture was evaporated under reduced pressure and the precipitated solid was collected by filtration to give 4-(benzo[d]thiazol-6-ylamino)-5-fluoro-6-
30 oxo-1,6-dihydropyridine-3-carboxylic acid (2.18 g, 98%).

ESIMS m/z: 306 (M + H)⁺

[0215]

(step 4) Using 4-(benzo[d]thiazol-6-ylamino)-5-fluoro-6-oxo-1,6-dihydropyridine-3-carboxylic acid (1.88 g, 6.16 mmol)
35 obtained in step 3, and in the same manner as in Example 1,

step 4, 4-(benzo[d]thiazol-6-ylamino)-3-fluoro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (820 mg, 29%) was obtained.

ESIMS m/z: 467 (M + H)⁺

5 (step 5) Using 4-(benzo[d]thiazol-6-ylamino)-3-fluoro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (100 mg, 0.21 mmol) obtained in step 4, and in the same manner as in Example 52, step 6, compound 225 (71 mg, 69%) was obtained.
ESIMS m/z: 481 (M + H)⁺; ¹H NMR (300 MHz, DMSO-d₆, δ): 1.08-1.49
10 (m, 2H), 1.58-1.62 (m, 2H), 2.18-2.49 (m, 1H), 2.56-2.75 (m, 1H), 2.76-3.31 (m, 1H), 3.49 (s, 3H), 3.71-4.29 (m, 2H), 7.02-7.22 (m, 5H), 7.61 (s, 1H), 7.71 (s, 1H), 7.94 (d, J = 8.7 Hz, 1H), 8.56 (s, 1H), 9.18 (s, 1H).

Example 54

15 [0216]

4-(benzo[d]thiazol-5-ylamino)-3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-methoxyethoxy)pyridin-2(1H)-one (compound 228)

(step 1) Using ethyl 1-(benzyloxy)-6-oxo-4-(trifluoromethylsulfonyloxy)-1,6-dihydropyridine-3-carboxylate
20 (300 mg, 0.712 mmol) obtained in Example 2, step 2, and benzo[d]thiazol-5-amine (160 mg, 1.07 mmol), and in the same manner as in Example 2, step 3, ethyl 4-(benzo[d]thiazol-5-ylamino)-1-(benzyloxy)-6-oxo-1,6-dihydropyridine-3-carboxylate
25 (285 mg, 95%) was obtained.

ESIMS m/z: 422 (M + H)⁺

(step 2) Using ethyl 4-(benzo[d]thiazol-5-ylamino)-1-(benzyloxy)-6-oxo-1,6-dihydropyridine-3-carboxylate (260 mg, 0.617 mmol) obtained in step 1, and in the same manner as in
30 Example 12, step 4, 4-(benzo[d]thiazol-5-ylamino)-1-(benzyloxy)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (226 mg, 93%) was obtained.

ESIMS m/z: 394 (M + H)⁺

(step 3) Using 4-(benzo[d]thiazol-5-ylamino)-1-(benzyloxy)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (220 mg, 0.559 mmol)
35

obtained in step 2, and in the same manner as in Example 1, step 4, 4-(benzo[d]thiazol-5-ylamino)-1-(benzyloxy)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (310 mg, quantitative) was obtained.

5 ESIMS m/z: 555 (M + H)⁺

[0217]

(step 4) 4-(Benzo[d]thiazol-5-ylamino)-1-(benzyloxy)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (270 mg, 0.487 mmol) obtained in step 3 was dissolved in acetic acid (2
10 mL) and concentrated hydrochloric acid (2 mL), and the mixture was stirred at 70°C for 8 hr. The reaction mixture was cooled to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium
15 sulfate. The solvent was evaporated under reduced pressure to give 4-(benzo[d]thiazol-5-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-hydroxypyridin-2(1H)-one (126 mg, 56%).

ESIMS m/z: 465 (M + H)⁺

20 (step 5) Using 4-(benzo[d]thiazol-5-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-hydroxypyridin-2(1H)-one (16 mg, 0.034 mmol) obtained in step 4, and 1-bromo-2-methoxyethane (0.0065 mL, 0.069 mmol), and in the same manner as in Example 3, step 5, 4-(benzo[d]thiazol-5-ylamino)-5-[4-
25 (4-fluorophenyl)piperidine-1-carbonyl]-1-(2-methoxyethoxy)pyridin-2(1H)-one (13.5 mg, 75%) was obtained.

ESIMS m/z: 523 (M + H)⁺

(step 6) Using 4-(benzo[d]thiazol-5-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-
30 methoxyethoxy)pyridin-2(1H)-one (13.5 mg, 0.026 mmol) obtained in step 5, and in the same manner as in Example 21, step 3, compound 228 (6 mg, 42%) was obtained.

ESIMS m/z: 557 (M + H)⁺; ¹H NMR (300 MHz, CDCl₃, δ): 1.25-1.35 (m, 2H), 1.60-1.75 (m, 4H), 2.50-2.59 (m, 1H), 3.41 (s, 3H), 3.71
35 (t, J = 4.4 Hz, 2H), 3.82-3.94 (m, 2H), 4.51 (t, J = 4.4 Hz,

2H), 6.91-7.06 (m, 5H), 7.22 (dd, J = 8.8, 2.2 Hz, 1H), 7.69 (s, 1H), 7.79 (d, J = 2.2 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 9.03 (s, 1H).

Example 55

5 [0218]

5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-hydroxyethoxy)-3-methyl-4-(m-tolylamino)pyridin-2(1H)-one (compound 229)

(step 1) To diethyl 2-methyl-3-oxopentanedioate (100 g, 462 mmol) were added triethyl orthoformate (75.4 g, 509 mmol) and acetic anhydride (70.8 g, 694 mmol), and the mixture was stirred at 130°C for 3 hr. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The residue was dissolved in DMF (100 mL), O-benzylhydroxylamine (109.8 g, 695 mmol) and triethylamine (70.2 g, 695 mmol) were added at 0°C, and the mixture was stirred at room temperature for 1 hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. 25 g from 70 g of the obtained residue was dissolved in toluene (200 mL), DBU (16.3 g, 107 mmol) was added, and the mixture was heated under reflux for 1 hr. The reaction mixture was cooled to room temperature, 0.1 mol/L hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give ethyl 1-(benzyloxy)-4-hydroxy-5-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (20 g, 40%).

ESIMS m/z: 304 (M + H)⁺

(step 2) Using ethyl 1-(benzyloxy)-4-hydroxy-5-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (30 g, 98.9 mmol) obtained in step 1, and in the same manner as in Example 1, step 6, 1-(benzyloxy)-4-hydroxy-5-methyl-6-oxo-1,6-dihydropyridine-3-

carboxylic acid (20 g, quantitative) was obtained.

ESIMS m/z: 276 (M + H)⁺

[0219]

(step 3) Using 1-(benzyloxy)-4-hydroxy-5-methyl-6-oxo-1,6-
5 dihydropyridine-3-carboxylic acid (20 g, 98.9 mmol) obtained
in step 2, and in the same manner as in Example 1, step 4, 1-
(benzyloxy)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-
hydroxy-3-methylpyridin-2(1H)-one (25 g, 79%) was obtained.

ESIMS m/z: 437 (M + H)⁺

10 (step 4) Using 1-(benzyloxy)-5-[4-(4-fluorophenyl)piperidine-
1-carbonyl]-4-hydroxy-3-methylpyridin-2(1H)-one (27 g, 61.9
mmol) obtained in step 3, and in the same manner as in Example
2, step 2, 1-(benzyloxy)-5-[4-(4-fluorophenyl)piperidine-1-
carbonyl]-3-methyl-2-oxo-1,2-dihydropyridin-4-yl

15 trifluoromethanesulfonate (22 g, 63%) was obtained.

ESIMS m/z: 569 (M + H)⁺

(step 5) Using 1-(benzyloxy)-5-[4-(4-fluorophenyl)piperidine-
1-carbonyl]-3-methyl-2-oxo-1,2-dihydropyridin-4-yl
trifluoromethanesulfonate (1.5 g, 2.64 mmol) obtained in step
20 4, and 3-methylaniline (0.394 g, 3.68 mmol), and in the same
manner as in Example 2, step 3, 1-(benzyloxy)-5-[4-(4-
fluorophenyl)piperidine-1-carbonyl]-3-methyl-4-(m-
tolylamino)pyridin-2(1H)-one (0.18 g, 13%) was obtained.

ESIMS m/z: 526 (M + H)⁺

25 [0220]

(step 6) Using 1-(benzyloxy)-5-[4-(4-fluorophenyl)piperidine-
1-carbonyl]-3-methyl-4-(m-tolylamino)pyridin-2(1H)-one (0.35 g,
0.67 mmol) obtained in step 5, and in the same manner as in
Example 4, step 3, 5-[4-(4-fluorophenyl)piperidine-1-
30 carbonyl]-1-hydroxy-3-methyl-4-(m-tolylamino)pyridin-2(1H)-one
(0.16 g, 55%) was obtained.

ESIMS m/z: 436 (M + H)⁺

(step 7) Using 5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-
hydroxy-3-methyl-4-(m-tolylamino)pyridin-2(1H)-one (80 mg,
35 0.18 mmol) obtained in step 6, and 2-bromoethan-1-ol (46 mg,

0.37 mmol), and in the same manner as in Example 4, step 4, 5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-hydroxyethoxy)-3-methyl-4-(m-tolylamino)pyridin-2(1H)-one (25 mg, 29%) was obtained.

5 ESIMS m/z: 480 (M + H)⁺; ¹H NMR (300 MHz, DMSO-d₆, δ): 1.21-1.48 (m, 2H), 1.53-1.66 (m, 2H), 1.89 (s, 3H), 2.22 (s, 3H), 2.55-3.23 (m, 3H), 3.54-4.30 (m, 6H), 4.92-5.11 (m, 1H), 6.57-6.72 (m, 3H), 7.01-7.20 (m, 5H), 7.78 (s, 1H), 7.89 (s, 1H).

Example 56

10 [0221]

The following compounds were synthesized based on Example 3.

2-{4-(2,5-dichlorophenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}-N-(ethylsulfonyl)acetamide (compound 1); ESIMS m/z: 609 (M + H)⁺

15 2-{4-(2-chloro-5-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}-N-(ethylsulfonyl)acetamide (compound 2); ESIMS m/z: 589 (M + H)⁺
4-(2-chloro-5-methylphenylamino)-1-(difluoromethyl)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound 4); ESIMS m/z: 490 (M + H)⁺

2-{4-(2-chloro-5-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}acetonitrile (compound 5); ESIMS m/z: 479 (M + H)⁺
25 4-(2-chloro-5-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(3-methoxypropyl)pyridin-2(1H)-one (compound 6); ESIMS m/z: 512 (M + H)⁺

4-(2-chloro-5-methylphenylamino)-1-(cyclopropylmethyl)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound 7); ESIMS m/z: 494 (M + H)⁺

4-(2-chloro-5-methylphenylamino)-1-(cyclobutylmethyl)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound 8); ESIMS m/z: 508 (M + H)⁺

35 methyl 2-({4-(2-chloro-5-methylphenylamino)-5-[4-(4-

fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl)methyl)oxazole-4-carboxylate (compound 9); ESIMS m/z: 579 (M + H)⁺

4-(2-chloro-5-methylphenylamino)-1-[(3,5-dimethylisoxazol-4-yl)methyl]-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound 10); ESIMS m/z: 549 (M + H)⁺

4-(2-chloro-5-methylphenylamino)-1-(3,3-dimethoxypropyl)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound 11); ESIMS m/z: 542 (M + H)⁺

3-({4-(2-chloro-5-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl)methyl}-1,2,4-oxadiazol-5(4H)-one (compound 12); ESIMS m/z: 538 (M + H)⁺

[0222]

(Z)-2-{4-(2-chloro-5-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}-N'-hydroxyacetimidamide (compound 13); ESIMS m/z: 512 (M + H)⁺

1-[(5-tert-butyl-1,2,4-oxadiazol-3-yl)methyl]-4-(2-chloro-5-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound 14); ESIMS m/z: 578 (M + H)⁺

4-(2-chloro-5-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-[(5-methylisoxazol-3-yl)methyl]pyridin-2(1H)-one (compound 15); ESIMS m/z: 535 (M + H)⁺

4-(2-chloro-5-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-[(5-thioxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)methyl]pyridin-2(1H)-one (compound 16); ESIMS m/z: 554 (M + H)⁺

4-(2-chloro-5-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-morpholinoethyl)pyridin-2(1H)-one (compound 17); ESIMS m/z: 553 (M + H)⁺

4-(2-chloro-5-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-[(1-methyl-1H-imidazol-

2-yl)methyl]pyridin-2(1H)-one (compound 18); ESIMS m/z: 534 (M + H)⁺

4-{4-(2-chloro-5-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}butanenitrile (compound 19); ESIMS m/z: 507 (M + H)⁺

1- (2-{4-(2-chloro-5-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}acetyl)pyrrolidine-2-carbonitrile (compound 20); ESIMS m/z: 576 (M + H)⁺

10 4-(2-chloro-5-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-[(tetrahydro-2H-pyran-4-yl)methyl]pyridin-2(1H)-one (compound 22); ESIMS m/z: 538 (M + H)⁺

2-{4-(4-fluoro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}acetonitrile (compound 23); ESIMS m/z: 463 (M + H)⁺

3-({4-(4-fluoro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl)methyl)-1,2,4-oxadiazol-5(4H)-one (compound 24); ESIMS m/z: 522 (M + H)⁺

20 [0223]

methyl 2-{4-(4-fluoro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}acetate (compound 25); ESIMS m/z: 496 (M + H)⁺

25 2-{4-(4-fluoro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}acetic acid (compound 26); ESIMS m/z: 482 (M + H)⁺

4-(4-fluoro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-[(1-methyl-1H-imidazol-2-yl)methyl]pyridin-2(1H)-one (compound 27); ESIMS m/z: 518 (M + H)⁺

30 4-{4-(4-fluoro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}butanenitrile (compound 28); ESIMS m/z: 491 (M + H)⁺

35 methyl 2-{4-(2-chloro-5-methylphenylamino)-5-[4-(4-

fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}acetate (compound 29); ESIMS m/z: 512 (M + H)⁺

2-{4-(benzylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}acetonitrile (compound 31);

5 ESIMS m/z: 445 (M + H)⁺

tert-butyl 2-{4-(benzylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}acetate (compound 32); ESIMS m/z: 520 (M + H)⁺

3-({4-(benzylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}methyl)-1,2,4-oxadiazole-5(4H)-one (compound 33); ESIMS m/z: 504 (M + H)⁺

10 2-{4-(benzylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}acetic acid (compound 34); ESIMS m/z: 464 (M + H)⁺

15 2-{4-(benzylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-oxopyridin-1(2H)-yl}-N-cyanoacetamide (compound 35); ESIMS m/z: 488 (M + H)⁺

Example 57

[0224]

20 The following compounds were synthesized based on Example 4.

3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(pyridin-3-ylmethoxy)pyridin-2(1H)-one (compound 198); ESIMS m/z: 581 (M

25 + H)⁺

3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-[(5-methylisoxazol-3-yl)methoxy]pyridin-2(1H)-one (compound 205); ESIMS m/z: 585 (M + H)⁺

30 3-chloro-4-(5-chloro-2-methylphenylamino)-1-(cyclopropylmethoxy)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound 213); ESIMS m/z: 544 (M + H)⁺

35 3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-

hydroxypropoxy)pyridin-2(1H)-one (compound 223); ESIMS m/z:
 548 (M + H)⁺
 3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-
 fluorophenyl)piperidine-1-carbonyl]-1-[(tetrahydrofuran-2-
 5 yl)methoxy]pyridin-2(1H)-one (compound 226); ESIMS m/z: 574 (M
 + H)⁺
 3-chloro-4-(5-chloro-2-methylphenylamino)-5-[3-(4-
 fluorophenyl)azetidine-1-carbonyl]-1-(2-hydroxyethoxy)pyridin-
 2(1H)-one (compound 233); ESIMS m/z: 506 (M + H)⁺
 10 4-[5-chloro-4-(5-chloro-2-methylphenylamino)-1-(2-
 hydroxyethoxy)-6-oxo-1,6-dihydropyridine-3-carbonyl]-1-(4-
 fluorophenyl)piperazin-2-one (compound 234); ESIMS m/z: 549 (M
 + H)⁺
 3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-
 15 fluorophenyl)-4-methoxypiperidine-1-carbonyl]-1-(2-
 hydroxyethoxy)pyridin-2(1H)-one (compound 235); ESIMS m/z: 564
 (M + H)⁺

Example 58

[0225]

20 The following compounds were synthesized based on Example
 12.

4-(4-fluoro-2-methylphenylamino)-5-[4-(4-
 fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 (compound 36); ESIMS m/z: 438 (M + H)⁺
 25 4-(4-chloro-2-methylphenylamino)-5-[4-(4-
 fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 (compound 37); ESIMS m/z: 454 (M + H)⁺
 1-(cyclopropylmethyl)-3-fluoro-4-(4-fluoro-2-
 methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-
 30 carbonyl]pyridin-2(1H)-one (compound 38); ESIMS m/z: 496 (M +
 H)⁺
 3-chloro-4-(2-chloro-4-fluoro-5-methylphenylamino)-5-[4-(4-
 fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 (compound 41); ESIMS m/z: 506 (M + H)⁺
 35 3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-(4-

methoxyphenylamino)-1-methylpyridin-2(1H)-one (compound 44);
 ESIMS m/z: 470 (M + H)⁺

3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-
 4-(pyridin-4-ylamino)pyridin-2(1H)-one (compound 45); ESIMS
 5 m/z: 441 (M + H)⁺

3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-(3-
 methoxyphenylamino)-1-methylpyridin-2(1H)-one (compound 46);
 ESIMS m/z: 470 (M + H)⁺

3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-(2-
 10 methoxyphenylamino)-1-methylpyridin-2(1H)-one (compound 47);
 ESIMS m/z: 470 (M + H)⁺

3-chloro-4-(cyclopropylamino)-5-[4-(4-fluorophenyl)piperidine-
 1-carbonyl]-1-methylpyridin-2(1H)-one (compound 48); ESIMS
 m/z: 404 (M + H)⁺

15 3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-
 4-[4-(trifluoromethoxy)phenylamino]pyridin-2(1H)-one (compound
 49); ESIMS m/z: 524 (M + H)⁺

3-chloro-4-(2,5-dimethoxyphenylamino)-5-[4-(4-
 fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 20 (compound 51); ESIMS m/z: 500 (M + H)⁺

3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-
 4-(pyridin-3-ylamino)pyridin-2(1H)-one (compound 52); ESIMS
 m/z: 441 (M + H)⁺

3-chloro-4-(4-chloro-2-methylphenylamino)-1-cyclopropyl-5-[4-
 25 (4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one
 (compound 53); ESIMS m/z: 514 (M + H)⁺

3-chloro-4-(2,4-difluorophenylamino)-5-[4-(4-
 fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 (compound 54); ESIMS m/z: 476 (M + H)⁺

30 3-chloro-1-cyclopropyl-5-[4-(4-fluorophenyl)piperidine-1-
 carbonyl]-4-(4-methoxyphenylamino)pyridin-2(1H)-one (compound
 55); ESIMS m/z: 496 (M + H)⁺

[0226]

3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-
 35 4-[2-(trifluoromethoxy)phenylamino]pyridin-2(1H)-one (compound

56); ESIMS m/z: 524 (M + H)⁺
 3-chloro-4-(5-chloro-2-methoxyphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 (compound 57); ESIMS m/z: 504 (M + H)⁺
 5 3-chloro-4-(2-chloro-5-methylphenylamino)-1-cyclopropyl-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one
 (compound 58); ESIMS m/z: 514 (M + H)⁺
 3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-4-(2,4,5-trifluorophenylamino)pyridin-2(1H)-one (compound 59);
 10 ESIMS m/z: 494 (M + H)⁺
 3-chloro-1-cyclopropyl-4-(2,5-dimethoxyphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound 60); ESIMS m/z: 526 (M + H)⁺
 3-chloro-4-(5-chloro-2,4-dimethoxyphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 15 (compound 61); ESIMS m/z: 534 (M + H)⁺
 4-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}benzonitrile
 (compound 62); ESIMS m/z: 465 (M + H)⁺
 20 3-chloro-4-(2,4-dimethoxyphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 (compound 63); ESIMS m/z: 500 (M + H)⁺
 3-chloro-4-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}benzonitrile (compound 64); ESIMS m/z: 499 (M + H)⁺
 25 3-chloro-4-(4-chlorobenzylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 (compound 65); ESIMS m/z: 488 (M + H)⁺
 4-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-3-fluorobenzonitrile (compound 66); ESIMS m/z: 483 (M + H)⁺
 30 2-chloro-4-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}benzonitrile (compound 67); ESIMS m/z: 499 (M + H)⁺
 35 3-chloro-4-(3,4-dimethoxyphenylamino)-5-[4-(4-

fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
(compound 68); ESIMS m/z: 500 (M + H)⁺
[0227]

3-chloro-4-(2-fluoro-4-methoxyphenylamino)-5-[4-(4-
5 fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
(compound 69); ESIMS m/z: 488 (M + H)⁺

3-chloro-1-cyclopropyl-5-[4-(4-fluorophenyl)piperidine-1-
carbonyl]-4-(2,4,5-trifluorophenylamino)pyridin-2(1H)-one
(compound 70); ESIMS m/z: 520 (M + H)⁺

10 3-chloro-1-cyclopropyl-4-(2,4-difluorophenylamino)-5-[4-(4-
fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound
71); ESIMS m/z: 502 (M + H)⁺

3-chloro-4-(5-chloro-2-methylphenylamino)-1-cyclopropyl-5-[4-
(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one
15 (compound 72); ESIMS m/z: 514 (M + H)⁺

3-chloro-1-cyclopropyl-5-[4-(4-fluorophenyl)piperidine-1-
carbonyl]-4-(4-methoxy-2-methylphenylamino)pyridin-2(1H)-one
(compound 73); ESIMS m/z: 510 (M + H)⁺

3-chloro-4-(4-fluoro-3-methylphenylamino)-5-[4-(4-
20 fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
(compound 75); ESIMS m/z: 472 (M + H)⁺

3-chloro-4-(2,5-dimethylphenylamino)-5-[4-(4-
fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
(compound 76); ESIMS m/z: 468 (M + H)⁺

25 3-chloro-4-[4-(difluoromethoxy)phenylamino]-5-[4-(4-
fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
(compound 77); ESIMS m/z: 506 (M + H)⁺

3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-(4-
isopropoxyphenylamino)-1-methylpyridin-2(1H)-one (compound
30 78); ESIMS m/z: 498 (M + H)⁺

3-chloro-4-(4-ethoxyphenylamino)-5-[4-(4-
fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
(compound 79); ESIMS m/z: 484 (M + H)⁺

3-chloro-4-(2,4-dimethylphenylamino)-5-[4-(4-
35 fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one

(compound 80); ESIMS m/z: 468 (M + H)⁺
 3-chloro-4-(2,5-difluorophenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 (compound 82); ESIMS m/z: 476 (M + H)⁺
 5 3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-(5-methoxy-2-methylphenylamino)-1-methylpyridin-2(1H)-one
 (compound 83); ESIMS m/z: 484 (M + H)⁺
 [0228]
 3-chloro-4-(4-chloro-3-methoxyphenylamino)-1-
 10 (cyclopropylmethyl)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound 84); ESIMS m/z: 544 (M + H)⁺
 3-chloro-1-(cyclopropylmethyl)-4-(4-fluoro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-
 15 carbonyl]pyridin-2(1H)-one (compound 85); ESIMS m/z: 512 (M + H)⁺
 3-chloro-4-(3,4-difluorophenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 (compound 86); ESIMS m/z: 476 (M + H)⁺
 20 3-chloro-4-(3,4-dimethylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 (compound 87); ESIMS m/z: 468 (M + H)⁺
 3-chloro-4-(4-chloro-3-methoxyphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 25 (compound 88); ESIMS m/z: 504 (M + H)⁺
 3-chloro-4-(4-fluoro-3-methoxyphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 (compound 89); ESIMS m/z: 488 (M + H)⁺
 3-chloro-4-(2,3-difluorophenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 30 (compound 90); ESIMS m/z: 476 (M + H)⁺
 3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-4-[4-(methylthio)phenylamino]pyridin-2(1H)-one (compound 91);
 ESIMS m/z: 486 (M + H)⁺
 35 3-chloro-4-(3-fluoro-4-methoxyphenylamino)-5-[4-(4-

fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
(compound 92); ESIMS m/z: 488 (M + H)⁺

3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-(4-methoxy-3-methylphenylamino)-1-methylpyridin-2(1H)-one
5 (compound 93); ESIMS m/z: 484 (M + H)⁺

3-bromo-1-cyclopropyl-4-(4-fluoro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one
(compound 94); ESIMS m/z: 542 (M + H)⁺

3-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}benzonitrile
10 (compound 95); ESIMS m/z: 465 (M + H)⁺

4-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}phthalonitrile
(compound 96); ESIMS m/z: 490 (M + H)⁺

15 [0229]

4-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-2,5-difluorobenzonitrile (compound 97); ESIMS m/z: 501 (M + H)⁺

5-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-2-methylbenzonitrile (compound 98); ESIMS m/z: 479 (M + H)⁺

20 2-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}benzonitrile
(compound 99); ESIMS m/z: 465 (M + H)⁺

25 4-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-3-ethylbenzonitrile
(compound 101); ESIMS m/z: 493 (M + H)⁺

3-chloro-4-(2-fluoro-4-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
30 (compound 102); ESIMS m/z: 472 (M + H)⁺

2-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-4-methylbenzonitrile (compound 104); ESIMS m/z: 479 (M + H)⁺

3-chloro-4-(2,3-dimethylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
35

(compound 105); ESIMS m/z: 468 (M + H)⁺
 3-chloro-4-(2,2-difluorobenzo[d][1,3]dioxol-5-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (compound 106); ESIMS m/z: 520 (M + H)⁺
 5 3-chloro-4-(2,3-dihydro-1H-inden-5-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (compound 107); ESIMS m/z: 480 (M + H)⁺
 3-chloro-4-(4-ethylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 10 (compound 108); ESIMS m/z: 468 (M + H)⁺
 4-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-2-fluorobenzonitrile (compound 109); ESIMS m/z: 483 (M + H)⁺
 4-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-2,6-
 15 difluorobenzonitrile (compound 110); ESIMS m/z: 501 (M + H)⁺
 [0230]
 4-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-2-
 20 (trifluoromethyl)benzonitrile (compound 112); ESIMS m/z: 533 (M + H)⁺
 3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-4-[4-(methylthio)-3-(trifluoromethyl)phenylamino]pyridin-2(1H)-one (compound 113); ESIMS m/z: 554 (M + H)⁺
 25 3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-4-[4-(trifluoromethyl)phenylamino]pyridin-2(1H)-one (compound 114); ESIMS m/z: 508 (M + H)⁺
 3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-(4-isopropylphenylamino)-1-methylpyridin-2(1H)-one (compound
 30 115); ESIMS m/z: 482 (M + H)⁺
 5-chloro-2-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}benzonitrile (compound 116); ESIMS m/z: 499 (M + H)⁺
 4-chloro-3-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-
 35

ylamino}benzonitrile (compound 117); ESIMS m/z: 499 (M + H)⁺
 3-chloro-4-(2-fluoro-5-methylphenylamino)-5-[4-(4-
 fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 (compound 118); ESIMS m/z: 472 (M + H)⁺
 5 3-chloro-4-(5-chloro-2-fluorophenylamino)-5-[4-(4-
 fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 (compound 119); ESIMS m/z: 492 (M + H)⁺
 3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-
 4-[4-(methylsulfonyl)-3-(trifluoromethyl)phenylamino]pyridin-
 10 2(1H)-one (compound 122); ESIMS m/z: 586 (M + H)⁺
 3-chloro-4-[3-chloro-4-(methylsulfonyl)phenylamino]-5-[4-(4-
 fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 (compound 123); ESIMS m/z: 552 (M + H)⁺
 3-chloro-4-(5-fluoro-2-methylphenylamino)-5-[4-(4-
 15 fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 (compound 126); ESIMS m/z: 472 (M + H)⁺
 3-chloro-4-(2-chloro-5-fluorophenylamino)-5-[4-(4-
 fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 (compound 127); ESIMS m/z: 492 (M + H)⁺
 20 3-chloro-4-[2-fluoro-4-(methylthio)phenylamino]-5-[4-(4-
 fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 (compound 128); ESIMS m/z: 504 (M + H)⁺
 [0231]
 3-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-
 25 methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-4-
 methylbenzonitrile (compound 129); ESIMS m/z: 479 (M + H)⁺
 2-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-
 methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-4-
 fluorobenzonitrile (compound 131); ESIMS m/z: 483 (M + H)⁺
 30 2-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-
 methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-5-
 methylbenzonitrile (compound 132); ESIMS m/z: 479 (M + H)⁺
 5-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-
 methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-2-
 35 (methylthio)benzonitrile (compound 133); ESIMS m/z: 511 (M +

H)⁺
 3-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-4-(difluoromethoxy)benzonitrile (compound 134); ESIMS m/z: 531
 5 (M + H)⁺
 3-chloro-1-ethyl-4-(4-fluoro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound 135); ESIMS m/z: 486 (M + H)⁺
 3-chloro-4-(4-chloro-2-methylphenylamino)-1-ethyl-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound
 10 136); ESIMS m/z: 502 (M + H)⁺
 3-chloro-4-(5-chloro-2-methylphenylamino)-1-ethyl-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound 137); ESIMS m/z: 502 (M + H)⁺
 15 3-chloro-1-ethyl-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-(4-methoxy-2-methylphenylamino)pyridin-2(1H)-one (compound 138); ESIMS m/z: 498 (M + H)⁺
 3-chloro-4-(2,4-difluorophenylamino)-1-ethyl-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound
 20 139); ESIMS m/z: 490 (M + H)⁺
 3-chloro-4-(4-fluoro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-methoxyethyl)pyridin-2(1H)-one (compound 140); ESIMS m/z: 516 (M + H)⁺
 3-chloro-4-(4-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-methoxyethyl)pyridin-2(1H)-one (compound 141); ESIMS m/z: 532 (M + H)⁺
 25 [0232]
 3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-methoxyethyl)pyridin-2(1H)-one (compound 142); ESIMS m/z: 532 (M + H)⁺
 30 3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-(4-methoxy-2-methylphenylamino)-1-(2-methoxyethyl)pyridin-2(1H)-one (compound 143); ESIMS m/z: 528 (M + H)⁺
 3-chloro-4-[2-fluoro-4-(methylsulfonyl)phenylamino]-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one
 35

(compound 145); ESIMS m/z: 536 (M + H)⁺
 5-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-2-(methylsulfonyl)benzonitrile (compound 146); ESIMS m/z: 543 (M + H)⁺
 2-chloro-5-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}benzonitrile (compound 147); ESIMS m/z: 499 (M + H)⁺
 3-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-4-fluorobenzonitrile (compound 148); ESIMS m/z: 483 (M + H)⁺
 2-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-4-(trifluoromethyl)benzonitrile (compound 149); ESIMS m/z: 533 (M + H)⁺
 2-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-5-fluorobenzonitrile (compound 150); ESIMS m/z: 483 (M + H)⁺
 3-chloro-4-(4-fluoro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one (compound 151); ESIMS m/z: 549 (M + H)⁺
 3-chloro-4-(4-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one (compound 152); ESIMS m/z: 565 (M + H)⁺
 3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one (compound 153); ESIMS m/z: 565 (M + H)⁺
 [0233]
 3-chloro-4-(2,4-difluorophenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one (compound 155); ESIMS m/z: 553 (M + H)⁺

2-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-5-(trifluoromethoxy)benzonitrile (compound 156); ESIMS m/z: 549 (M + H)⁺

5 3-chloro-4-(4-fluoro-2-methylphenylamino)-1-(2-fluoroethyl)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound 158); ESIMS m/z: 504 (M + H)⁺

3-chloro-4-(4-chloro-2-methylphenylamino)-1-(2-fluoroethyl)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one
 10 (compound 159); ESIMS m/z: 520 (M + H)⁺

3-chloro-1-(2-fluoroethyl)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-4-(4-methoxy-2-methylphenylamino)pyridin-2(1H)-one (compound 161); ESIMS m/z: 516 (M + H)⁺

3-chloro-4-(2,4-difluorophenylamino)-1-(2-fluoroethyl)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one
 15 (compound 162); ESIMS m/z: 508 (M + H)⁺

3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(pyridin-2-ylmethyl)pyridin-2(1H)-one (compound 163); ESIMS m/z: 565 (M +
 20 H)⁺

5-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-2-fluorobenzonitrile (compound 164); ESIMS m/z: 483 (M + H)⁺

2-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-5-(trifluoromethyl)benzonitrile (compound 165); ESIMS m/z: 533 (M + H)⁺

5-{3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-2-oxo-1,2-dihydropyridin-4-ylamino}-2-methylisoindoline-1,3-dione (compound 171); ESIMS m/z: 523 (M + H)⁺

3-chloro-4-(2,4-difluorophenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(pyridin-2-ylmethyl)pyridin-2(1H)-one (compound 172); ESIMS m/z: 553 (M +
 35 H)⁺

[0234]

- 4-(benzo[c][1,2,5]oxadiazol-4-ylamino)-3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (compound 174); ESIMS m/z: 482 (M + H)⁺
- 5 3-chloro-4-(2,2-dimethyl-2,3-dihydrobenzofuran-7-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (compound 176); ESIMS m/z: 510 (M + H)⁺
- 3-chloro-4-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-
- 10 2(1H)-one (compound 180); ESIMS m/z: 512 (M + H)⁺
- 3-chloro-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (compound 181); ESIMS m/z: 498 (M + H)⁺
- 3-chloro-4-(5-chloro-2-methylphenylamino)-1-methyl-5-[3H-
- 15 spiro(isobenzofuran-1,4'-piperidine)-1'-ylcarbonyl]pyridin-2(1H)-one (compound 201); ESIMS m/z: 498 (M + H)⁺
- 3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(2-chlorophenyl)piperazine-1-carbonyl]-1-methylpyridin-2(1H)-one (compound 202); ESIMS m/z: 505 (M + H)⁺
- 20 3-chloro-4-(2,6-dimethylpyridin-3-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-vinylpyridin-2(1H)-one (compound 210); ESIMS m/z: 481 (M + H)⁺
- 3-chloro-1-cyclopentyl-4-(2,6-dimethylpyridin-3-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one
- 25 (compound 214); ESIMS m/z: 523 (M + H)⁺
- 3-chloro-1-cyclopropyl-4-(1,3-dihydroisobenzofuran-5-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]pyridin-2(1H)-one (compound 215); ESIMS m/z: 508 (M + H)⁺

Example 59

30 [0235]

The following compounds were synthesized based on Example 15.

- 4-(4-fluoro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1,3-dimethylpyridin-2(1H)-
- 35 one (compound 120); ESIMS m/z: 452 (M + H)⁺

4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1,3-dimethylpyridin-2(1H)-one (compound 121); ESIMS m/z: 468 (M + H)⁺

4-{5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1,3-dimethyl-2-oxo-1,2-dihydropyridin-4-ylamino}-3-methylbenzonitrile (compound 124); ESIMS m/z: 459 (M + H)⁺

4-(4-chloro-2-fluorophenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1,3-dimethylpyridin-2(1H)-one (compound 193); ESIMS m/z: 472 (M + H)⁺

4-(1,3-dihydroisobenzofuran-5-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-3-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one (compound 207); ESIMS m/z: 539 (M + H)⁺

1-cyclobutyl-4-(1,3-dihydroisobenzofuran-5-ylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-3-methylpyridin-2(1H)-one (compound 211); ESIMS m/z: 502 (M + H)⁺

1-cyclopentyl-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-3-methyl-4-(1-methyl-1H-indazol-5-ylamino)pyridin-2(1H)-one (compound 212); ESIMS m/z: 528 (M + H)⁺

Example 60

[0236]

The following compounds were synthesized based on Example 21.

3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-propynyl)pyridin-2(1H)-one (compound 167); ESIMS m/z: 512 (M + H)⁺

3-chloro-4-(2,4-difluorophenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-morpholinoethyl)pyridin-2(1H)-one (compound 182); ESIMS m/z: 575 (M + H)⁺

3-chloro-4-(5-chloro-2-methylphenylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-morpholinoethyl)pyridin-2(1H)-one (compound 185); ESIMS m/z: 587 (M + H)⁺

Example 61

[0237]

The following compounds were synthesized based on Example 39.

4-(benzylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-3-nitropyridin-2(1H)-one (compound 216); ESIMS m/z: 465 (M + H)⁺

5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-3-nitro-4-(o-tolylamino)pyridin-2(1H)-one (compound 222); ESIMS m/z: 465 (M + H)⁺

10 Example 62

[0238]

The following compounds were synthesized based on Example 41.

3-amino-4-(benzylamino)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methylpyridin-2(1H)-one (compound 218); ESIMS m/z: 435 (M + H)⁺

3-amino-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-methyl-4-(phenylamino)pyridin-2(1H)-one (compound 219); ESIMS m/z: 421 (M + H)⁺

20 Example 63

[0239]

The following compounds were synthesized based on Example 50.

3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-hydroxyethoxy)-4-(1-phenylcyclopropylamino)pyridin-2(1H)-one (compound 231); ESIMS m/z: 526 (M + H)⁺

3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-hydroxyethoxy)-4-(pyridin-3-ylmethylamino)pyridin-2(1H)-one (compound 232); ESIMS m/z: 501 (M + H)⁺

30 3-chloro-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-hydroxyethoxy)-4-[1-(pyridin-2-yl)cyclopropylamino]pyridin-2(1H)-one (compound 236); ESIMS m/z: 527 (M + H)⁺

Example 64

[0240]

35 The following compounds were synthesized based on Example

55.

5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-1-(2-hydroxyethoxy)-3-methyl-4-(6-methylpyridin-3-ylamino)-pyridin-2(1H)-one (compound 227); ESIMS m/z: 481 (M + H)⁺

5 4-{5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-3-methyl-2-oxo-1-(pyridin-2-ylmethoxy)-1,2-dihydropyridin-4-ylamino}-3-methylbenzonitrile (compound 230); ESIMS m/z: 552 (M + H)⁺

Industrial Applicability

10 [0241]

The pyridone compound or the pharmaceutically acceptable salt thereof of the present invention is useful as, for example, a prophylactic and/or therapeutic agent for skin diseases and the like.

15 According to the present invention, a pyridone compound or a pharmaceutically acceptable salt thereof, which is useful as, for example, a prophylactic and/or therapeutic agent for skin diseases and the like are provided.

Sequence Listing Free Text

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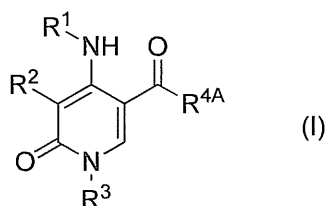
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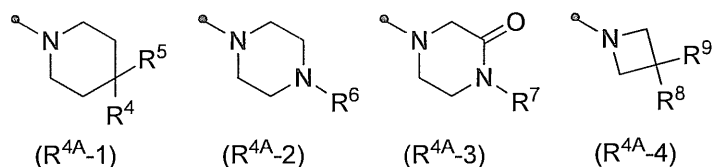
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Claims

1. A pyridone compound represented by the formula (I)



5 [wherein, R¹ represents cycloalkyl optionally having
 substituent(s), aryl optionally having substituent(s), an
 aromatic heterocyclic group optionally having substituent(s),
 an aliphatic heterocyclic group optionally having
 substituent(s), aralkyl optionally having substituent(s), or
 10 heterocyclic alkyl optionally having substituent(s),
 R² represents a hydrogen atom, cyano, nitro, halogen, lower
 alkyl optionally having substituent(s), or -NR^{1a}R^{1b} (wherein, R^{1a}
 and R^{1b} are the same or different and each represents a
 hydrogen atom, lower alkanoyl optionally having substituent(s),
 15 or lower alkylcarbamoyl optionally having substituent(s)),
 R³ represents hydroxy, lower alkyl optionally having
 substituent(s), lower alkenyl optionally having substituent(s),
 lower alkynyl optionally having substituent(s), lower alkoxy
 optionally having substituent(s), cycloalkyl optionally having
 20 substituent(s), heterocyclic alkyl optionally having
 substituent(s), or -NR^{3a}R^{3b} (wherein, R^{3a} and R^{3b} are the same or
 different and each represents a hydrogen atom, lower alkyl
 optionally having substituent(s), cycloalkyl optionally having
 substituent(s), aryl optionally having substituent(s), or
 25 aralkyl optionally having substituent(s), or R^{3a} and R^{3b} form,
 together with the adjacent nitrogen atom, a nitrogen-
 containing heterocyclic group optionally having
 substituent(s)),
 R^{4A} represents any one of the groups represented by the
 30 following formulas (R^{4A}-1), (R^{4A}-2), (R^{4A}-3) or (R^{4A}-4)



(wherein, R⁴ and R⁵ are the same or different and each represents a hydrogen atom, aryl optionally having substituent(s), or lower alkoxy optionally having substituent(s), or R⁴ and R⁵ form, together with the adjacent carbon atom, an aliphatic heterocyclic group optionally having substituent(s), R⁶ and R⁷ represent aryl optionally having substituent(s), R⁸ and R⁹ are the same or different and each represents a hydrogen atom, aryl optionally having substituent(s), or lower alkoxy optionally having substituent(s), or R⁸ and R⁹ form, together with the adjacent carbon atom, an aliphatic heterocyclic group optionally having substituent(s))), or a pharmaceutically acceptable salt thereof.

15

2. The pyridone compound or the pharmaceutically acceptable salt thereof according to claim 1, wherein R¹ is aryl optionally having substituent(s), an aromatic heterocyclic group optionally having substituent(s), or an aliphatic heterocyclic group optionally having substituent(s).

3. The pyridone compound or the pharmaceutically acceptable salt thereof according to claim 1, wherein R¹ is aryl optionally having substituent(s).

25

4. The pyridone compound or the pharmaceutically acceptable salt thereof according to claim 1, wherein R¹ is an aromatic heterocyclic group optionally having substituent(s).

5. The pyridone compound or the pharmaceutically acceptable salt thereof according to any of claims 1 to 4, wherein R² is a hydrogen atom, halogen or lower alkyl optionally having

substituent(s).

6. The pyridone compound or the pharmaceutically acceptable salt thereof according to any of claims 1 to 4, wherein R² is
5 lower alkyl optionally having substituent(s).

7. The pyridone compound or the pharmaceutically acceptable salt thereof according to any of claims 1 to 4, wherein R² is halogen.

10

8. The pyridone compound or the pharmaceutically acceptable salt thereof according to any of claims 1 to 7, wherein R³ is lower alkyl optionally having substituent(s), lower alkoxy optionally having substituent(s), or -NR^{3a}R^{3b} (wherein, R^{3a} and
15 R^{3b} are each as defined above).

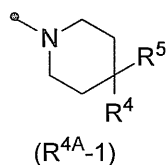
9. The pyridone compound or the pharmaceutically acceptable salt thereof according to any of claims 1 to 7, wherein R³ is lower alkyl optionally having substituent(s).

20

10. The pyridone compound or the pharmaceutically acceptable salt thereof according to any of claims 1 to 7, wherein R³ is lower alkoxy optionally having substituent(s).

25 11. The pyridone compound or the pharmaceutically acceptable salt thereof according to any of claims 1 to 7, wherein R³ is -NR^{3a}R^{3b} (wherein, R^{3a} and R^{3b} are each as defined above).

12. The pyridone compound or the pharmaceutically acceptable
30 salt thereof according to any of claims 1 to 11, wherein R^{4A} is the following formula (R^{4A}-1)



(wherein, R⁴ and R⁵ are each as defined above).

13. The pyridone compound or the pharmaceutically acceptable
5 salt thereof according to claim 12, wherein R⁴ and R⁵ are the
same or different and each is a hydrogen atom, or aryl
optionally having substituent(s).

14. A medicament comprising, as an active ingredient, the
10 pyridone compound or the pharmaceutically acceptable salt
thereof described in any of claims 1 to 13.

15. A CCR10 receptor antagonist comprising, as an active
ingredient, the pyridone compound or the pharmaceutically
15 acceptable salt thereof described in any of claims 1 to 13.

16. An agent for the prophylaxis and/or treatment of a skin
disease comprising, as an active ingredient, the pyridone
compound or the pharmaceutically acceptable salt thereof
20 described in any of claims 1 to 13.

17. The agent for the prophylaxis and/or treatment of a skin
disease according to claim 16, wherein the skin disease is a
skin disease selected from acne vulgaris, drug eruption,
25 contact dermatitis, dermatitis due to venomous moth, pollen
dermatitis, urticaria, psoriasis, atopic dermatitis, Candida
dermatitis, seborrheic dermatitis, eczema, Stevens-Johnson
syndrome, toxic epidermal necrosis, erythema multiforme,
erythema nodosum, granuloma annulare, pityriasis rosea,
30 rosacea, lichen planus, lichen pilaris (keratosis pilaris),
photosensitivity, solar dermatitis, miliaria, herpes simplex,
Kaposi's varicelliform eruption, impetigo contagiosa,

staphylococcal scalded skin syndrome, erysipelas, slap cheek, lupus erythematosus, keloid, Hailey-Hailey disease, scabies and linear dermatitis.

5 18. The agent for the prophylaxis and/or treatment of a skin disease according to claim 16, wherein the skin disease is a skin disease selected from contact dermatitis and atopic dermatitis.

10 19. A method of inhibiting a CCR10 receptor, comprising a step of administering an effective amount of the pyridone compound or the pharmaceutically acceptable salt thereof described in any of claims 1 to 13.

15 20. A method for the prophylaxis and/or treatment of a skin disease, comprising a step of administering an effective amount of the pyridone compound or the pharmaceutically acceptable salt thereof described in any of claims 1 to 13.

20 21. The method according to claim 20, wherein the skin disease is a skin disease selected from acne vulgaris, drug eruption, contact dermatitis, dermatitis due to venomous moth, pollen dermatitis, urticaria, psoriasis, atopic dermatitis, Candida dermatitis, seborrheic dermatitis, eczema, Stevens-Johnson
25 syndrome, toxic epidermal necrosis, erythema multiforme, erythema nodosum, granuloma annulare, pityriasis rosea, rosacea, lichen planus, lichen pilaris (keratosis pilaris), photosensitivity, solar dermatitis, miliaria, herpes simplex, Kaposi's varicelliform eruption, impetigo contagiosa,
30 staphylococcal scalded skin syndrome, erysipelas, slap cheek, lupus erythematosus, keloid, Hailey-Hailey disease, scabies and linear dermatitis.

22. The method according to claim 20, wherein the skin disease
35 is a skin disease selected from contact dermatitis and atopic

dermatitis.

23. The pyridone compound or the pharmaceutically acceptable salt thereof described in any of claims 1 to 13, for use in
5 inhibition of a CCR10 receptor.

24. The pyridone compound or the pharmaceutically acceptable salt thereof described in any of claims 1 to 13, for use in the prophylaxis and/or treatment of a skin disease.

10

25. The pyridone compound or the pharmaceutically acceptable salt thereof according to claim 24, wherein the skin disease is a skin disease selected from acne vulgaris, drug eruption, contact dermatitis, dermatitis due to venomous moth, pollen
15 dermatitis, urticaria, psoriasis, atopic dermatitis, Candidal dermatitis, seborrheic dermatitis, eczema, Stevens-Johnson syndrome, toxic epidermal necrosis, erythema multiforme, erythema nodosum, granuloma annulare, pityriasis rosea, rosacea, lichen planus, lichen pilaris (keratosis pilaris),
20 photosensitivity, solar dermatitis, miliaria, herpes simplex, Kaposi's varicelliform eruption, impetigo contagiosa, staphylococcal scalded skin syndrome, erysipelas, slap cheek, lupus erythematosus, keloid, Hailey-Hailey disease, scabies and linear dermatitis.

25

26. The pyridone compound or the pharmaceutically acceptable salt thereof according to claim 24, wherein the skin disease is a skin disease selected from contact dermatitis and atopic dermatitis.

30

27. Use of the pyridone compound or the pharmaceutically acceptable salt thereof described in any of claims 1 to 13, for the manufacture of a CCR10 receptor antagonist.

35 28. Use of the pyridone compound or the pharmaceutically

acceptable salt thereof described in any of claims 1 to 13,
for the manufacture of an agent for the prophylaxis and/or
treatment of a skin disease.

5 29. The use according to claim 28, wherein the skin disease is
a skin disease selected from acne vulgaris, drug eruption,
contact dermatitis, dermatitis due to venomous moth, pollen
dermatitis, urticaria, psoriasis, atopic dermatitis, Candida
dermatitis, seborrheic dermatitis, eczema, Stevens-Johnson
10 syndrome, toxic epidermal necrosis, erythema multiforme,
erythema nodosum, granuloma annulare, pityriasis rosea,
rosacea, lichen planus, lichen pilaris (keratosis pilaris),
photosensitivity, solar dermatitis, miliaria, herpes simplex,
Kaposi's varicelliform eruption, impetigo contagiosa,
15 staphylococcal scalded skin syndrome, erysipelas, slap cheek,
lupus erythematosus, keloid, Hailey-Hailey disease, scabies
and linear dermatitis.

30. The use according to claim 28, wherein the skin disease is
20 a skin disease selected from contact dermatitis and atopic
dermatitis.

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