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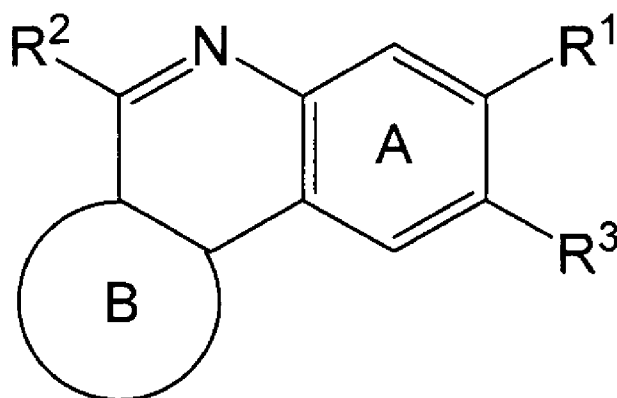
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(54) Title: HETEROCYCLIC COMPOUNDS



(I)

(57) Abstract: The present invention provides a compound represented by the formula (I) wherein each symbol is as defined in the specification, or a salt thereof has an BET family protein inhibitory action, and is useful as an agent for the prophylaxis or treatment of autoimmune diseases and/or inflammatory diseases (e.g., rheumatoid arthritis, multiple sclerosis, idiopathic pulmonary fibrosis, psoriasis, atopic dermatitis, inflammatory bowel disease, Sjogren's syndrome, Behcet's disease, systemic lupus erythematosus etc.), cancer and the like.



DESCRIPTION
HETEROCYCLIC COMPOUNDS

Technical Field

5 [0001]

The present invention relates to a novel heterocyclic compound having an inhibitory action on binding of bromodomain and extra-terminal domain family protein (hereinafter sometime to be referred to as "BET family protein") to protein having
10 acetylated lysine, and useful an agent for the prophylaxis or treatment of autoimmune diseases and/or inflammatory diseases (e.g., rheumatoid arthritis, multiple sclerosis, idiopathic pulmonary fibrosis, psoriasis, atopic dermatitis, inflammatory bowel disease, Sjogren's syndrome, Behcet's disease, systemic
15 lupus erythematosus etc.), cancer and the like, and a composition containing the compound, and the like.

[0002]

(Background of the Invention)

Bromodomain and extra-terminal domain (BET) protein
20 family is a family consisting of BRD2, BRD3, BRD4 and BRDT. These proteins recognize acetylated lysine residue via bromodomain, and bind to acetylated histone or the other acetylated protein. The interaction plays an important role in various gene expressions including cytokine production.
25 Cytokine is a protein secreted by the cells of immune system, and signals specific cells. There are a large variety of cytokines, and they almost involve immunity and inflammation, and also involve cellular growth, cellular differentiation, cellular death, wound healing and the like (non-Patent
30 Document 1).

BET protein family usually plays a role in inflammatory/immune response via gene expression such as IL-6 and TNF α , however, the excessive interaction thereof involves many immune-related diseases such as infection, rheumatoid
35 arthritis, multiple sclerosis, idiopathic pulmonary fibrosis

and the like, and cancer (non-Patent Document 2).

Tocilizumab which is an anti-IL-6 receptor antibody has been approved as a IL-6 signal blocker, and etanercept, infliximab, adalimumab and the like, which are therapeutic agents for chronic rheumatoid arthritis and the like, have been approved as a TNF α signal blocker. From the foregoing, BET family protein inhibitor can be a therapeutic agent for autoimmune diseases and/or inflammatory diseases (e.g., rheumatoid arthritis, multiple sclerosis, idiopathic pulmonary fibrosis, psoriasis, atopic dermatitis, inflammatory bowel disease, Sjogren's syndrome, Behcet's disease, systemic lupus erythematosus etc.), cancer and the like, which are cytokine-mediated diseases.

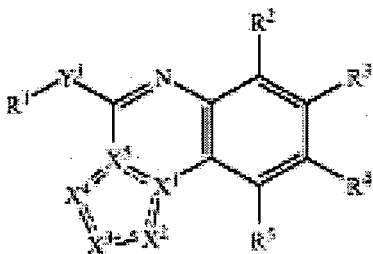
[0003]

Examples of the compound having a structure similar to the compound described in the present specification include the following compounds.

[0004]

(1) Patent document 1 describes a compound represented by the formula:

[0005]



[0006]

wherein

X² is [C(R⁶)(R⁷)]_n or the like,

R⁶ and R⁷ are each alkyl, arylalkyl, heteroarylalkyl or the like, and

R³ is heteroaryl or the like,

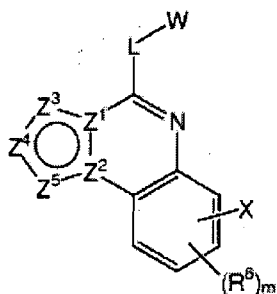
as an H1/H4 receptor inhibitor, and is useful as an agent for the prophylaxis or treatment of pruritus, eczema, atopic

dermatitis and the like.

[0007]

(2) Patent document 2 describes a compound represented by the formula:

5 [0008]



[0009]

wherein

Z¹ and Z² are both C, or one of Z¹ and Z² is N and the other is
10 C,

X is a polar substituent,

R⁶ is C₅₋₁₂ heteroaryl or the like,

Z⁵ is N, NR⁵, CR⁵ or the like, and

R⁵ is hydrogen, C₆₋₁₂ heteroarylalkyl or the like,

15 as a Pirn, Fit and/or CK2 kinases inhibitor, and is useful as an agent for the prophylaxis or treatment of psoriasis and the like.

Document List

Patent Document

20 [0010]

[Patent Document 1] US 2011/0257137

[Patent Document 2] WO 2010/135571

Non-Patent Document

[0011]

25 [Non-Patent Document 1] Curr Opin Cell Biol. 1991 Apr;3(2):171-5

[Non-Patent Document 2] Mol Cell. 2014 Jun 5;54(5):728-736

Summary of the Invention

Problems to be Solved by the Invention

30 [0012]

The present invention aims to provide a novel heterocyclic compound having an inhibitory action on binding of BET family protein to protein having acetylated lysine (hereinafter sometime to be referred to as "BET family protein inhibitory action"), and useful an agent for the prophylaxis or treatment of autoimmune diseases and/or inflammatory diseases (e.g., rheumatoid arthritis, multiple sclerosis, idiopathic pulmonary fibrosis, psoriasis, atopic dermatitis, inflammatory bowel disease, Sjogren's syndrome, Behcet's disease, systemic lupus erythematosus etc.), cancer and the like.

Means of Solving the Problems

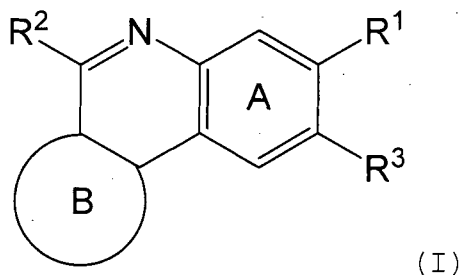
[0013]

The present inventors have conducted intensive studies, and have found that a compound represented by the below-mentioned formula (1) unexpectedly has an BET family protein inhibitory action, and therefore, is useful as an agent for the prophylaxis or treatment of autoimmune diseases and/or inflammatory diseases (e.g., rheumatoid arthritis, multiple sclerosis, idiopathic pulmonary fibrosis, psoriasis, atopic dermatitis, inflammatory bowel disease, Sjogren's syndrome, Behcet's disease, systemic lupus erythematosus etc.), cancer and the like, and completed the present invention based on these findings.

Accordingly, the present invention provides the following.

[1] A compound represented by the formula (I):

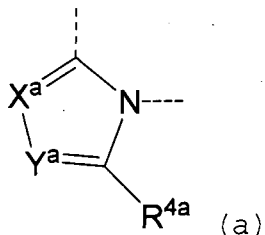
[0014]



[0015]

wherein

R^1 is an optionally substituted 5-membered aromatic heterocyclic group;
 ring A is an optionally further substituted benzene ring;
 R^2 and R^3 are each independently a hydrogen atom or a
 5 substituent; and
 ring B is
 a ring represented by the formula:
 [0016]



10 [0017]

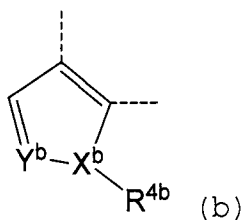
wherein

X^a and Y^a are each independently a nitrogen atom or a carbon atom, and

R^{4a} is a substituent, and

15 wherein said ring optionally further substituted,
 a ring represented by the formula:

[0018]



[0019]

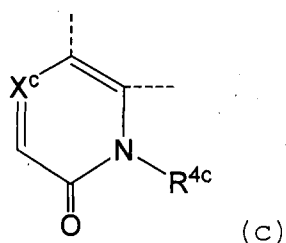
20 wherein

X^b and Y^b are each independently a nitrogen atom or a carbon atom, and

R^{4b} is a hydrogen atom or a substituent, and

wherein said ring is optionally further substituted, or
 25 a ring represented by the formula:

[0020]



[0021]

wherein

X^c is a nitrogen atom or a carbon atom, and

5 R^{4c} is a hydrogen atom or a substituent, and

wherein said ring is optionally further substituted;

or a salt thereof.

[0022]

[2] The compound or salt of the above-mentioned [1], wherein

10 R^1 is an optionally substituted isoxazolyl or an optionally substituted pyrazolyl;

R^2 and R^3 are each independently

(1) a hydrogen atom,

(2) a halogen atom,

15 (3) a cyano group,

(4) an optionally substituted C_{3-10} cycloalkyl group,

(5) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group,

(6) an optionally substituted 5- to 14-membered aromatic

20 heterocyclic group,

(7) an amino group optionally having 1 or 2 C_{1-6} alkyl groups optionally having 1 to 3 substituents selected from the following substituent group A,

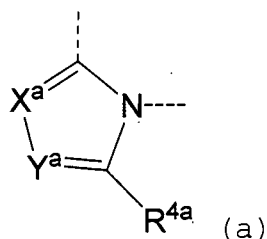
(8) a hydroxy group optionally having a C_{1-6} alkyl group, or

25 (9) a sulfanyl group optionally having a C_{1-6} alkyl group; and

Ring B is

a ring represented by the formula:

[0023]



[0024]

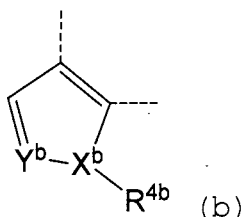
wherein

 X^a is a nitrogen atom;5 Y^a is a nitrogen atom; and R^{4a} is

- (1) an optionally substituted C_{1-6} alkyl group,
- (2) an optionally substituted C_{3-10} cycloalkyl group,
- (3) an optionally substituted C_{6-10} aryl group,
- 10 (4) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group, or
- (5) an amino group optionally having 1 or 2 C_{6-10} aryl groups optionally having 1 to 3 substituents selected from the following substituent group A,

15 a ring represented by the formula:

[0025]



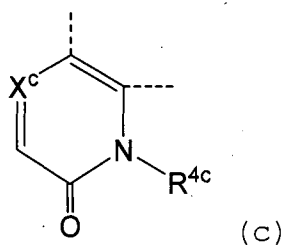
[0026]

wherein

20 X^b is a nitrogen atom; Y^b is a nitrogen atom; and R^{4b} is

- (1) an optionally substituted C_{1-6} alkyl group, or
 - (2) an optionally substituted C_{6-10} aryl group, or
- 25 a ring represented by the formula:

[0027]



[0028]

wherein

 X^c is a nitrogen atom; and5 R^{4c} is an optionally substituted C_{1-6} alkyl group,

[substituent group A]

- (1) a halogen atom,
- (2) a nitro group,
- (3) a cyano group,
- 10 (4) an oxo group,
- (5) a hydroxy group,
- (6) an optionally halogenated C_{1-6} alkoxy group,
- (7) a C_{6-14} aryloxy group,
- (8) a C_{7-16} aralkyloxy group,
- 15 (9) a 5- to 14-membered aromatic heterocyclyloxy group,
- (10) a 3- to 14-membered non-aromatic heterocyclyloxy group,
- (11) a C_{1-6} alkyl-carbonyloxy group,
- (12) a C_{6-14} aryl-carbonyloxy group,
- (13) a C_{1-6} alkoxy-carbonyloxy group,
- 20 (14) a mono- or di- C_{1-6} alkyl-carbamoyloxy group,
- (15) a C_{6-14} aryl-carbamoyloxy group,
- (16) a 5- to 14-membered aromatic heterocyclylcarbonyloxy group,
- (17) a 3- to 14-membered non-aromatic heterocyclylcarbonyloxy group,
- 25 (18) an optionally halogenated C_{1-6} alkylsulfonyloxy group,
- (19) a C_{6-14} arylsulfonyloxy group optionally substituted by a C_{1-6} alkyl group,
- (20) an optionally halogenated C_{1-6} alkylthio group,
- 30 (21) a 5- to 14-membered aromatic heterocyclic group,
- (22) a 3- to 14-membered non-aromatic heterocyclic group,

- (23) a formyl group,
- (24) a carboxy group,
- (25) an optionally halogenated C₁₋₆ alkyl-carbonyl group,
- (26) a C₆₋₁₄ aryl-carbonyl group,
- 5 (27) a 5- to 14-membered aromatic heterocyclylcarbonyl group,
- (28) a 3- to 14-membered non-aromatic heterocyclylcarbonyl group,
- (29) a C₁₋₆ alkoxy-carbonyl group,
- (30) a C₆₋₁₄ aryloxy-carbonyl group,
- 10 (31) a C₇₋₁₆ aralkyloxy-carbonyl group,
- (32) a carbamoyl group,
- (33) a thiocarbamoyl group,
- (34) a mono- or di-C₁₋₆ alkyl-carbamoyl group,
- (35) a C₆₋₁₄ aryl-carbamoyl group,
- 15 (36) a 5- to 14-membered aromatic heterocyclylcarbamoyl group,
- (37) a 3- to 14-membered non-aromatic heterocyclylcarbamoyl group,
- (38) an optionally halogenated C₁₋₆ alkylsulfonyl group,
- (39) a C₆₋₁₄ arylsulfonyl group,
- 20 (40) a 5- to 14-membered aromatic heterocyclylsulfonyl group,
- (41) an optionally halogenated C₁₋₆ alkylsulfinyl group,
- (42) a C₆₋₁₄ arylsulfinyl group,
- (43) a 5- to 14-membered aromatic heterocyclylsulfinyl group,
- (44) an amino group,
- 25 (45) a mono- or di-C₁₋₆ alkylamino group,
- (46) a mono- or di-C₆₋₁₄ arylamino group,
- (47) a 5- to 14-membered aromatic heterocyclylamino group,
- (48) a C₇₋₁₆ aralkylamino group,
- (49) a formylamino group,
- 30 (50) a C₁₋₆ alkyl-carbonylamino group,
- (51) a (C₁₋₆ alkyl)(C₁₋₆ alkyl-carbonyl)amino group,
- (52) a C₆₋₁₄ aryl-carbonylamino group,
- (53) a C₁₋₆ alkoxy-carbonylamino group,
- (54) a C₇₋₁₆ aralkyloxy-carbonylamino group,
- 35 (55) a C₁₋₆ alkylsulfonylamino group,

- (56) a C₆₋₁₄ arylsulfonylamino group optionally substituted by a C₁₋₆ alkyl group,
(57) an optionally halogenated C₁₋₆ alkyl group,
(58) a C₂₋₆ alkenyl group,
5 (59) a C₂₋₆ alkynyl group,
(60) a C₃₋₁₀ cycloalkyl group,
(61) a C₃₋₁₀ cycloalkenyl group and
(62) a C₆₋₁₄ aryl group.

[0029]

- 10 [3] 7-(3,5-dimethylisoxazol-4-yl)-8-methoxy-N-methyl-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4-amine or a salt thereof.

[4] 4-[8-methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole or a salt thereof.

- 15 [5] 7-(3,5-dimethylisoxazol-4-yl)-8-methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4-amine or a salt thereof.

[0030]

- [6] A medicament comprising the compound or salt of the above-
20 mentioned [1].

[7] The medicament of the above-mentioned [6], which is bromodomain and extra terminal domain family protein inhibitor.

- [8] The medicament of the above-mentioned [6], which is an agent for the prophylaxis or treatment of autoimmune diseases
25 and/or inflammatory diseases.

[9] The medicament of the above-mentioned [6], which is an agent for the prophylaxis or treatment of psoriasis or atopic dermatitis.

[0031]

- 30 [10] The compound or salt of the above-mentioned [1] for use in the prophylaxis or treatment of autoimmune diseases and/or inflammatory diseases.

- [11] The compound or salt of the above-mentioned [1] for use in the prophylaxis or treatment of psoriasis or atopic
35 dermatitis.

[0032]

[12] A method of inhibiting bromodomain and extra terminal domain family protein in a mammal, which comprises administering an effective amount of the compound or salt of the above-mentioned [1] to the mammal.

[13] A method for the prophylaxis or treatment of autoimmune diseases and/or inflammatory diseases in a mammal, which comprises administering an effective amount of the compound or salt of the above-mentioned [1] to the mammal.

[14] A method for the prophylaxis or treatment of psoriasis or atopic dermatitis in a mammal, which comprises administering an effective amount of the compound or salt of the above-mentioned [1] to the mammal.

[0033]

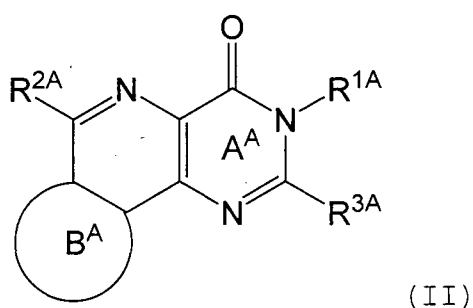
[15] Use of the compound or salt of the above-mentioned [1] for the production of an agent for the prophylaxis or treatment of autoimmune diseases and/or inflammatory diseases.

[16] Use of the compound or salt of the above-mentioned [1] for the production of an agent for the prophylaxis or treatment of psoriasis or atopic dermatitis.

[0034]

[17] A compound represented by the formula (II):

[0035]



[0036]

wherein

R^{1A} is an optionally substituted 5-membered aromatic heterocyclic group;

ring A^A is an optionally further substituted benzene ring;

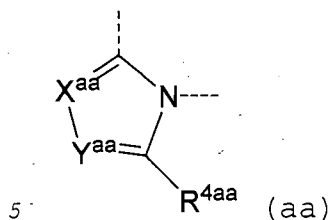
R^{2A} and R^{3A} are each independently a hydrogen atom or a

substituent; and

ring B^A is

a ring represented by the formula:

[0037]



[0038]

wherein

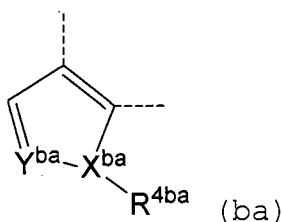
X^{aa} and Y^{aa} are each independently a nitrogen atom or a carbon atom, and

10 R^{4aa} is a substituent, and

wherein said ring is optionally further substituted,

a ring represented by the formula:

[0039]



15 [0040]

wherein

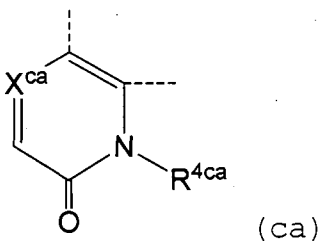
X^{ba} and Y^{ba} are each independently a nitrogen atom or a carbon atom, and

R^{4ba} is a hydrogen atom or a substituent, and

20 wherein said ring is optionally further substituted, or

a ring represented by the formula:

[0041]



[0042]

wherein

X^{ca} is a nitrogen atom or a carbon atom, and

R^{4ca} is a hydrogen atom or a substituent, and

5 wherein said ring is optionally further substituted;
or a salt thereof.

Effect of the Invention

[0043]

Compound (I) has a superior BET family protein inhibitory
10 action, and is useful as an agent for the prophylaxis or
treatment of autoimmune diseases and/or inflammatory diseases
(e.g., rheumatoid arthritis, multiple sclerosis, idiopathic
pulmonary fibrosis, psoriasis, atopic dermatitis, inflammatory
bowel disease, Sjogren's syndrome, Behcet's disease, systemic
15 lupus erythematosus etc.), cancer and the like.

Brief Description of the Drawings

[0044]

Figure 1 shows effect of the compounds of Example 4.7 and
Example 9.6 on ear thickness in Imiquimod induced-mouse model
20 of psoriasis.

Figure 2 shows effect of the compounds of Example 9.9 and
Example 9.10 on ear thickness in Imiquimod induced-mouse model
of psoriasis.

Figure 3 shows effect of the compound of Example 4.7 on
25 ear thickness in Imiquimod induced-mouse model of psoriasis.

[0045]

[Detailed Description of the Invention]

The definition of each substituent used in the present
specification is described in detail in the following. Unless
30 otherwise specified, each substituent has the following
definition.

In the present specification, examples of the "halogen
atom" include fluorine, chlorine, bromine and iodine.

In the present specification, examples of the "C₁₋₆ alkyl
35 group" include methyl, ethyl, propyl, isopropyl, butyl,

isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl and 2-ethylbutyl.

In the present specification, examples of the "optionally halogenated C₁₋₆ alkyl group" include a C₁₋₆ alkyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, tetrafluoroethyl, pentafluoroethyl, propyl, 2,2-difluoropropyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl and 6,6,6-trifluorohexyl.

In the present specification, examples of the "C₂₋₆ alkenyl group" include ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl and 5-hexenyl.

In the present specification, examples of the "C₂₋₆ alkynyl group" include ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexyne, 2-hexyne, 3-hexyne, 4-hexyne, 5-hexyne and 4-methyl-2-pentyne.

In the present specification, examples of the "C₃₋₁₀ cycloalkyl group" include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl and adamantyl.

In the present specification, examples of the "optionally halogenated C₃₋₁₀ cycloalkyl group" include a C₃₋₁₀ cycloalkyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include cyclopropyl, 2,2-difluorocyclopropyl, 2,3-difluorocyclopropyl, cyclobutyl, difluorocyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

In the present specification, examples of the "C₃₋₁₀

cycloalkenyl group" include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

In the present specification, examples of the "C₆₋₁₄ aryl group" include phenyl, 1-naphthyl, 2-naphthyl, 1-anthryl, 2-anthryl and 9-anthryl.

In the present specification, examples of the "C₇₋₁₆ aralkyl group" include benzyl, phenethyl, naphthylmethyl and phenylpropyl.

[0046]

In the present specification, examples of the "C₁₋₆ alkoxy group" include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy and hexyloxy.

In the present specification, examples of the "optionally halogenated C₁₋₆ alkoxy group" include a C₁₋₆ alkoxy group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy and hexyloxy.

In the present specification, examples of the "C₃₋₁₀ cycloalkyloxy group" include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and cyclooctyloxy.

In the present specification, examples of the "C₁₋₆ alkylthio group" include methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, pentylthio and hexylthio.

In the present specification, examples of the "optionally halogenated C₁₋₆ alkylthio group" include a C₁₋₆ alkylthio group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio and hexylthio.

In the present specification, examples of the "C₁₋₆ alkyl-

carbonyl group" include acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 3-methylbutanoyl, 2-methylbutanoyl, 2,2-dimethylpropanoyl, hexanoyl and heptanoyl.

In the present specification, examples of the "optionally
5 halogenated C₁₋₆ alkyl-carbonyl group" include a C₁₋₆ alkyl-carbonyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include acetyl, chloroacetyl, trifluoroacetyl, trichloroacetyl, propanoyl, butanoyl, pentanoyl and hexanoyl.

10 In the present specification, examples of the "C₁₋₆ alkoxy-carbonyl group" include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl and hexyloxycarbonyl.

15 In the present specification, examples of the "C₆₋₁₄ aryl-carbonyl group" include benzoyl, 1-naphthoyl and 2-naphthoyl.

In the present specification, examples of the "C₇₋₁₆ aralkyl-carbonyl group" include phenylacetyl and phenylpropionyl.

20 In the present specification, examples of the "5- to 14-membered aromatic heterocyclylcarbonyl group" include nicotinoyl, isonicotinoyl, thenoyl and furoyl.

In the present specification, examples of the "3- to 14-membered non-aromatic heterocyclylcarbonyl group" include
25 morpholinylcarbonyl, piperidinylcarbonyl and pyrrolidinylcarbonyl.

In the present specification, examples of the "mono- or di-C₁₋₆ alkyl-carbamoyl group" include methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl and N-
30 ethyl-N-methylcarbamoyl.

In the present specification, examples of the "mono- or di-C₇₋₁₆ aralkyl-carbamoyl group" include benzylcarbamoyl and phenethylcarbamoyl.

In the present specification, examples of the "C₁₋₆
35 alkylsulfonyl group" include methylsulfonyl, ethylsulfonyl,

propylsulfonyl, isopropylsulfonyl, butylsulfonyl, sec-butylsulfonyl and tert-butylsulfonyl.

In the present specification, examples of the "optionally halogenated C₁₋₆ alkylsulfonyl group" include a C₁₋₆ alkylsulfonyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include methylsulfonyl, difluoromethylsulfonyl, trifluoromethylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, 4,4,4-trifluorobutylsulfonyl, pentylsulfonyl and hexylsulfonyl.

In the present specification, examples of the "C₆₋₁₄ arylsulfonyl group" include phenylsulfonyl, 1-naphthylsulfonyl and 2-naphthylsulfonyl.

[0047]

In the present specification, examples of the "substituent" include a halogen atom, a cyano group, a nitro group, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an acyl group, an optionally substituted amino group, an optionally substituted carbamoyl group, an optionally substituted thiocarbamoyl group, an optionally substituted sulfamoyl group, an optionally substituted hydroxy group, an optionally substituted sulfanyl (SH) group and an optionally substituted silyl group.

In the present specification, examples of the "hydrocarbon group" (including "hydrocarbon group" of "optionally substituted hydrocarbon group") include a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₃₋₁₀ cycloalkyl group, a C₃₋₁₀ cycloalkenyl group, a C₆₋₁₄ aryl group and a C₇₋₁₆ aralkyl group.

[0048]

In the present specification, examples of the "optionally substituted hydrocarbon group" include a hydrocarbon group optionally having substituent(s) selected from the following substituent group A.

[substituent group A]

- (1) a halogen atom,
- (2) a nitro group,
- (3) a cyano group,
- (4) an oxo group,
- 5 (5) a hydroxy group,
- (6) an optionally halogenated C₁₋₆ alkoxy group,
- (7) a C₆₋₁₄ aryloxy group (e.g., phenoxy, naphthoxy),
- (8) a C₇₋₁₆ aralkyloxy group (e.g., benzyloxy),
- (9) a 5- to 14-membered aromatic heterocyclyloxy group (e.g.,
- 10 pyridyloxy),
- (10) a 3- to 14-membered non-aromatic heterocyclyloxy group (e.g., morpholinylloxy, piperidinylloxy),
- (11) a C₁₋₆ alkyl-carbonyloxy group (e.g., acetoxy, propanoyloxy),
- 15 (12) a C₆₋₁₄ aryl-carbonyloxy group (e.g., benzoyloxy, 1-naphthoyloxy, 2-naphthoyloxy),
- (13) a C₁₋₆ alkoxy-carbonyloxy group (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy),
- (14) a mono- or di-C₁₋₆ alkyl-carbamoyloxy group (e.g.,
- 20 methylcarbamoyloxy, ethylcarbamoyloxy, dimethylcarbamoyloxy, diethylcarbamoyloxy),
- (15) a C₆₋₁₄ aryl-carbamoyloxy group (e.g., phenylcarbamoyloxy, naphthylcarbamoyloxy),
- (16) a 5- to 14-membered aromatic heterocyclylcarbonyloxy
- 25 group (e.g., nicotinoyloxy),
- (17) a 3- to 14-membered non-aromatic heterocyclylcarbonyloxy group (e.g., morpholinylcarbonyloxy, piperidinylcarbonyloxy),
- (18) an optionally halogenated C₁₋₆ alkylsulfonyloxy group (e.g., methylsulfonyloxy, trifluoromethylsulfonyloxy),
- 30 (19) a C₆₋₁₄ arylsulfonyloxy group optionally substituted by a C₁₋₆ alkyl group (e.g., phenylsulfonyloxy, toluenesulfonyloxy),
- (20) an optionally halogenated C₁₋₆ alkylthio group,
- (21) a 5- to 14-membered aromatic heterocyclic group,
- (22) a 3- to 14-membered non-aromatic heterocyclic group,
- 35 (23) a formyl group,

- (24) a carboxy group,
- (25) an optionally halogenated C₁₋₆ alkyl-carbonyl group,
- (26) a C₆₋₁₄ aryl-carbonyl group,
- (27) a 5- to 14-membered aromatic heterocyclylcarbonyl group,
- 5 (28) a 3- to 14-membered non-aromatic heterocyclylcarbonyl group,
- (29) a C₁₋₆ alkoxy-carbonyl group,
- (30) a C₆₋₁₄ aryloxy-carbonyl group (e.g., phenyloxycarbonyl, 1-naphthyloxycarbonyl, 2-naphthyloxycarbonyl),
- 10 (31) a C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, phenethyloxycarbonyl),
- (32) a carbamoyl group,
- (33) a thiocarbamoyl group,
- (34) a mono- or di-C₁₋₆ alkyl-carbamoyl group,
- 15 (35) a C₆₋₁₄ aryl-carbamoyl group (e.g., phenylcarbamoyl),
- (36) a 5- to 14-membered aromatic heterocyclylcarbamoyl group (e.g., pyridylcarbamoyl, thienylcarbamoyl),
- (37) a 3- to 14-membered non-aromatic heterocyclylcarbamoyl group (e.g., morpholinylcarbamoyl, piperidinylcarbamoyl),
- 20 (38) an optionally halogenated C₁₋₆ alkylsulfonyl group,
- (39) a C₆₋₁₄ arylsulfonyl group,
- (40) a 5- to 14-membered aromatic heterocyclylsulfonyl group (e.g., pyridylsulfonyl, thienylsulfonyl),
- (41) an optionally halogenated C₁₋₆ alkylsulfinyl group,
- 25 (42) a C₆₋₁₄ arylsulfinyl group (e.g., phenylsulfinyl, 1-naphthylsulfinyl, 2-naphthylsulfinyl),
- (43) a 5- to 14-membered aromatic heterocyclylsulfinyl group (e.g., pyridylsulfinyl, thienylsulfinyl),
- (44) an amino group,
- 30 (45) a mono- or di-C₁₋₆ alkylamino group (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, N-ethyl-N-methylamino),
- (46) a mono- or di-C₆₋₁₄ arylamino group (e.g., phenylamino),
- 35 (47) a 5- to 14-membered aromatic heterocyclylamino group

- (e.g., pyridylamino),
(48) a C₇₋₁₆ aralkylamino group (e.g., benzylamino),
(49) a formylamino group,
(50) a C₁₋₆ alkyl-carbonylamino group (e.g., acetylamino,
5 propanoylamino, butanoylamino),
(51) a (C₁₋₆ alkyl)(C₁₋₆ alkyl-carbonyl)amino group (e.g., N-acetyl-N-methylamino),
(52) a C₆₋₁₄ aryl-carbonylamino group (e.g., phenylcarbonylamino, naphthylcarbonylamino),
10 (53) a C₁₋₆ alkoxy-carbonylamino group (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, tert-butoxycarbonylamino),
(54) a C₇₋₁₆ aralkyloxy-carbonylamino group (e.g.,
15 benzyloxycarbonylamino),
(55) a C₁₋₆ alkylsulfonylamino group (e.g., methylsulfonylamino, ethylsulfonylamino),
(56) a C₆₋₁₄ arylsulfonylamino group optionally substituted by a C₁₋₆ alkyl group (e.g., phenylsulfonylamino,
20 toluenesulfonylamino),
(57) an optionally halogenated C₁₋₆ alkyl group,
(58) a C₂₋₆ alkenyl group,
(59) a C₂₋₆ alkynyl group,
(60) a C₃₋₁₀ cycloalkyl group,
25 (61) a C₃₋₁₀ cycloalkenyl group and
(62) a C₆₋₁₄ aryl group.
[0049]

The number of the above-mentioned substituents in the "optionally substituted hydrocarbon group" is, for example, 1
30 to 5, preferably 1 to 3. When the number of the substituents is two or more, the respective substituents may be the same or different.

In the present specification, examples of the "heterocyclic group" (including "heterocyclic group" of
35 "optionally substituted heterocyclic group") include (i) an

aromatic heterocyclic group, (ii) a non-aromatic heterocyclic group and (iii) a 7- to 10-membered bridged heterocyclic group, each containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

[0050]

In the present specification, examples of the "aromatic heterocyclic group" (including "5- to 14-membered aromatic heterocyclic group") include a 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

Preferable examples of the "aromatic heterocyclic group" include 5- or 6-membered monocyclic aromatic heterocyclic groups such as thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, triazolyl, tetrazolyl, triazinyl and the like; and 8- to 14-membered fused polycyclic (preferably bi or tricyclic) aromatic heterocyclic groups such as benzothiophenyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzotriazolyl, imidazopyridinyl, thienopyridinyl, furopyridinyl, pyrrolopyridinyl, pyrazolopyridinyl, oxazolopyridinyl, thiazolopyridinyl, imidazopyrazinyl, imidazopyrimidinyl, thienopyrimidinyl, fuopyrimidinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, oxazolopyrimidinyl, thiazolopyrimidinyl, pyrazolotriazinyl, naphtho[2,3-b]thienyl, phenoxathiinyl, indolyl, isoindolyl, 1H-indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl and the like.

[0051]

In the present specification, examples of the "non-aromatic heterocyclic group" (including "3- to 14-membered non-aromatic heterocyclic group") include a 3- to 14-membered
5 (preferably 4- to 10-membered) non-aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

Preferable examples of the "non-aromatic heterocyclic
10 group" include 3- to 8-membered monocyclic non-aromatic heterocyclic groups such as aziridinyl, oxiranyl, thiiranyl, azetidiny, oxetanyl, thietanyl, tetrahydrothienyl, tetrahydrofuranly, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, oxazolinyl, oxazolidinyl, pyrazolinyl,
15 pyrazolidinyl, thiazolinyl, thiazolidinyl, tetrahydroisothiazolyl, tetrahydrooxazolyl, tetrahydroisooxazolyl, piperidinyl, piperazinyl, tetrahydropyridinyl, dihydropyridinyl, dihydrothiopyranyl, tetrahydropyrimidinyl, tetrahydropyridazinyl, dihydropyranyl,
20 tetrahydropyranyl, tetrahydrothiopyranyl, morpholinyl, thiomorpholinyl, azepanyl, diazepanyl, azepinyl, oxepanyl, azocanyl, diazocanyl and the like; and 9- to 14-membered fused polycyclic (preferably bi or tricyclic) non-aromatic heterocyclic groups such as
25 dihydrobenzofuranly, dihydrobenzimidazolyl, dihydrobenzoxazolyl, dihydrobenzothiazolyl, dihydrobenzisothiazolyl, dihydronaphtho[2,3-b]thienyl, tetrahydroisoquinolyl, tetrahydroquinolyl, 4H-quinoliziny, indolinyl, isoindolinyl, tetrahydrothieno[2,3-c]pyridinyl,
30 tetrahydrobenzazepinyl, tetrahydroquinoxalinyl, tetrahydrophenanthridinyl, hexahydrophenothiazinyl, hexahydrophenoxazinyl, tetrahydrophthalazinyl, tetrahydronaphthyridinyl, tetrahydroquinazolinyl, tetrahydrocinnolinyl, tetrahydrocarbazolyl, tetrahydro- β -
35 carbolinyl, tetrahydroacrydinyl, tetrahydrophenazinyl,

tetrahydrothioxanthenyl, octahydroisoquinolyl and the like.
[0052]

In the present specification, preferable examples of the "7- to 10-membered bridged heterocyclic group" include quinuclidinyl and 7-azabicyclo[2.2.1]heptanyl.

In the present specification, examples of the "nitrogen-containing heterocyclic group" include a "heterocyclic group" containing at least one nitrogen atom as a ring-constituting atom.

In the present specification, examples of the "optionally substituted heterocyclic group" include a heterocyclic group optionally having substituent(s) selected from the aforementioned substituent group A.

The number of the substituents in the "optionally substituted heterocyclic group" is, for example, 1 to 3. When the number of the substituents is two or more, the respective substituents may be the same or different.
[0053]

In the present specification, examples of the "acyl group" include a formyl group, a carboxy group, a carbamoyl group, a thiocarbamoyl group, a sulfinoyl group, a sulfo group, a sulfamoyl group and a phosphono group, each optionally having "1 or 2 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₃₋₁₀ cycloalkenyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a 5- to 14-membered aromatic heterocyclic group and a 3- to 14-membered non-aromatic heterocyclic group, each of which optionally has 1 to 3 substituents selected from a halogen atom, an optionally halogenated C₁₋₆ alkoxy group, a hydroxy group, a nitro group, a cyano group, an amino group and a carbamoyl group".

Examples of the "acyl group" also include a hydrocarbon-sulfonyl group, a heterocyclylsulfonyl group, a hydrocarbon-sulfinyl group and a heterocyclylsulfinyl group.

Here, the hydrocarbon-sulfonyl group means a hydrocarbon

group-bonded sulfonyl group, the heterocyclylsulfonyl group means a heterocyclic group-bonded sulfonyl group, the hydrocarbon-sulfinyl group means a hydrocarbon group-bonded sulfinyl group and the heterocyclylsulfinyl group means a
5 heterocyclic group-bonded sulfinyl group.

Preferable examples of the "acyl group" include a formyl group, a carboxy group, a C₁₋₆ alkyl-carbonyl group, a C₂₋₆ alkenyl-carbonyl group (e.g., crotonoyl), a C₃₋₁₀ cycloalkyl-carbonyl group (e.g., cyclobutanecarbonyl,
10 cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl), a C₃₋₁₀ cycloalkenyl-carbonyl group (e.g., 2-cyclohexenecarbonyl), a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic
15 heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a C₆₋₁₄ aryloxy-carbonyl group (e.g., phenyloxycarbonyl, naphthyloxycarbonyl), a C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, phenethyloxycarbonyl), a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₂₋₆
20 alkenyl-carbamoyl group (e.g., diallylcarbamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-carbamoyl group (e.g., cyclopropylcarbamoyl), a mono- or di-C₆₋₁₄ aryl-carbamoyl group (e.g., phenylcarbamoyl), a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a 5- to 14-membered aromatic heterocyclylcarbamoyl group (e.g., pyridylcarbamoyl),
25 a thiocarbamoyl group, a mono- or di-C₁₋₆ alkyl-thiocarbamoyl group (e.g., methylthiocarbamoyl, N-ethyl-N-methylthiocarbamoyl), a mono- or di-C₂₋₆ alkenyl-thiocarbamoyl group (e.g., diallylthiocarbamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-thiocarbamoyl group (e.g., cyclopropylthiocarbamoyl,
30 cyclohexylthiocarbamoyl), a mono- or di-C₆₋₁₄ aryl-thiocarbamoyl group (e.g., phenylthiocarbamoyl), a mono- or di-C₇₋₁₆ aralkyl-thiocarbamoyl group (e.g., benzylthiocarbamoyl, phenethylthiocarbamoyl), a 5- to 14-membered aromatic heterocyclylthiocarbamoyl group (e.g., pyridylthiocarbamoyl),
35 a sulfinio group, a C₁₋₆ alkylsulfinyl group (e.g.,

methylsulfinyl, ethylsulfinyl), a sulfo group, a C₁₋₆ alkylsulfonyl group, a C₆₋₁₄ arylsulfonyl group, a phosphono group and a mono- or di-C₁₋₆ alkylphosphono group (e.g., dimethylphosphono, diethylphosphono, diisopropylphosphono, dibutylphosphono).

[0054]

In the present specification, examples of the "optionally substituted amino group" include an amino group optionally having "1 or 2 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a C₁₋₆ alkylsulfonyl group and a C₆₋₁₄ arylsulfonyl group, each of which optionally has 1 to 3 substituents selected from substituent group A".

Preferable examples of the optionally substituted amino group include an amino group, a mono- or di-(optionally halogenated C₁₋₆ alkyl)amino group (e.g., methylamino, trifluoromethylamino, dimethylamino, ethylamino, diethylamino, propylamino, dibutylamino), a mono- or di-C₂₋₆ alkenylamino group (e.g., diallylamino), a mono- or di-C₃₋₁₀ cycloalkylamino group (e.g., cyclopropylamino, cyclohexylamino), a mono- or di-C₆₋₁₄ arylamino group (e.g., phenylamino), a mono- or di-C₇₋₁₆ aralkylamino group (e.g., benzylamino, dibenzylamino), a mono- or di-(optionally halogenated C₁₋₆ alkyl)-carbonylamino group (e.g., acetylamino, propionylamino), a mono- or di-C₆₋₁₄ aryl-carbonylamino group (e.g., benzoylamino), a mono- or di-C₇₋₁₆ aralkyl-carbonylamino group (e.g., benzylcarbonylamino), a mono- or di-5- to 14-membered aromatic heterocyclylcarbonylamino group (e.g., nicotinoylamino,

isonicotinoylamino), a mono- or di-3- to 14-membered non-aromatic heterocyclylcarbonylamino group (e.g., piperidinylcarbonylamino), a mono- or di-C₁₋₆ alkoxy-carbonylamino group (e.g., tert-butoxycarbonylamino), a 5- to 14-membered aromatic heterocyclylamino group (e.g., pyridylamino), a carbamoylamino group, a (mono- or di-C₁₋₆ alkyl-carbamoyl)amino group (e.g., methylcarbamoylamino), a (mono- or di-C₇₋₁₆ aralkyl-carbamoyl)amino group (e.g., benzylcarbamoylamino), a C₁₋₆ alkylsulfonylamino group (e.g., methylsulfonylamino, ethylsulfonylamino), a C₆₋₁₄ arylsulfonylamino group (e.g., phenylsulfonylamino), a (C₁₋₆ alkyl)(C₁₋₆ alkyl-carbonyl)amino group (e.g., N-acetyl-N-methylamino) and a (C₁₋₆ alkyl)(C₆₋₁₄ aryl-carbonyl)amino group (e.g., N-benzoyl-N-methylamino).

[0055]

In the present specification, examples of the "optionally substituted carbamoyl group" include a carbamoyl group optionally having "1 or 2 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group and a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, each of which optionally has 1 to 3 substituents selected from substituent group A".

Preferable examples of the optionally substituted carbamoyl group include a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₂₋₆ alkenyl-carbamoyl group (e.g., diallylcarbamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-carbamoyl group (e.g., cyclopropylcarbamoyl, cyclohexylcarbamoyl), a mono- or di-C₆₋₁₄ aryl-carbamoyl group (e.g., phenylcarbamoyl), a mono- or di-C₇₋₁₆ aralkyl-carbamoyl

group, a mono- or di-C₁₋₆ alkyl-carbonyl-carbamoyl group (e.g., acetylcarbamoyl, propionylcarbamoyl), a mono- or di-C₆₋₁₄ aryl-carbonyl-carbamoyl group (e.g., benzoylcarbamoyl) and a 5- to 14-membered aromatic heterocyclylcarbamoyl group (e.g., pyridylcarbamoyl).

[0056]

In the present specification, examples of the "optionally substituted thiocarbamoyl group" include a thiocarbamoyl group optionally having "1 or 2 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group and a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, each of which optionally has 1 to 3 substituents selected from substituent group A".

Preferable examples of the optionally substituted thiocarbamoyl group include a thiocarbamoyl group, a mono- or di-C₁₋₆ alkyl-thiocarbamoyl group (e.g., methylthiocarbamoyl, ethylthiocarbamoyl, dimethylthiocarbamoyl, diethylthiocarbamoyl, N-ethyl-N-methylthiocarbamoyl), a mono- or di-C₂₋₆ alkenyl-thiocarbamoyl group (e.g., diallylthiocarbamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-thiocarbamoyl group (e.g., cyclopropylthiocarbamoyl, cyclohexylthiocarbamoyl), a mono- or di-C₆₋₁₄ aryl-thiocarbamoyl group (e.g., phenylthiocarbamoyl), a mono- or di-C₇₋₁₆ aralkyl-thiocarbamoyl group (e.g., benzylthiocarbamoyl, phenethylthiocarbamoyl), a mono- or di-C₁₋₆ alkyl-carbonyl-thiocarbamoyl group (e.g., acetylthiocarbamoyl, propionylthiocarbamoyl), a mono- or di-C₆₋₁₄ aryl-carbonyl-thiocarbamoyl group (e.g., benzoylthiocarbamoyl) and a 5- to 14-membered aromatic heterocyclylthiocarbamoyl group (e.g.,

pyridylthiocarbamoyl).

[0057]

In the present specification, examples of the "optionally substituted sulfamoyl group" include a sulfamoyl group
5 optionally having "1 or 2 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to
10 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group and a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, each of which optionally has 1 to 3 substituents selected from
15 substituent group A".

Preferable examples of the optionally substituted sulfamoyl group include a sulfamoyl group, a mono- or di-C₁₋₆ alkyl-sulfamoyl group (e.g., methylsulfamoyl, ethylsulfamoyl, dimethylsulfamoyl, diethylsulfamoyl, N-ethyl-N-
20 methylsulfamoyl), a mono- or di-C₂₋₆ alkenyl-sulfamoyl group (e.g., diallylsulfamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-sulfamoyl group (e.g., cyclopropylsulfamoyl, cyclohexylsulfamoyl), a mono- or di-C₆₋₁₄ aryl-sulfamoyl group (e.g., phenylsulfamoyl), a mono- or di-C₇₋₁₆ aralkyl-sulfamoyl
25 group (e.g., benzylsulfamoyl, phenethylsulfamoyl), a mono- or di-C₁₋₆ alkyl-carbonyl-sulfamoyl group (e.g., acetylsulfamoyl, propionylsulfamoyl), a mono- or di-C₆₋₁₄ aryl-carbonyl-sulfamoyl group (e.g., benzoylsulfamoyl) and a 5- to 14-membered aromatic heterocyclylsulfamoyl group (e.g., pyridylsulfamoyl).

30 [0058]

In the present specification, examples of the "optionally substituted hydroxy group" include a hydroxy group optionally having "a substituent selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-

carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a C₁₋₆ alkylsulfonyl group and a C₆₋₁₄ arylsulfonyl group, each of which optionally has 1 to 3 substituents selected from substituent group A".

Preferable examples of the optionally substituted hydroxy group include a hydroxy group, a C₁₋₆ alkoxy group, a C₂₋₆ alkenyloxy group (e.g., allyloxy, 2-butenyloxy, 2-pentenylloxy, 3-hexenyloxy), a C₃₋₁₀ cycloalkyloxy group (e.g., cyclohexyloxy), a C₆₋₁₄ aryloxy group (e.g., phenoxy, naphthyloxy), a C₇₋₁₆ aralkyloxy group (e.g., benzyloxy, phenethyloxy), a C₁₋₆ alkyl-carbonyloxy group (e.g., acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, pivaloyloxy), a C₆₋₁₄ aryl-carbonyloxy group (e.g., benzoyloxy), a C₇₋₁₆ aralkyl-carbonyloxy group (e.g., benzylcarbonyloxy), a 5- to 14-membered aromatic heterocyclylcarbonyloxy group (e.g., nicotinoyloxy), a 3- to 14-membered non-aromatic heterocyclylcarbonyloxy group (e.g., piperidinylcarbonyloxy), a C₁₋₆ alkoxy-carbonyloxy group (e.g., tert-butoxycarbonyloxy), a 5- to 14-membered aromatic heterocyclyloxy group (e.g., pyridyloxy), a carbamoyloxy group, a C₁₋₆ alkyl-carbamoyloxy group (e.g., methylcarbamoyloxy), a C₇₋₁₆ aralkyl-carbamoyloxy group (e.g., benzylcarbamoyloxy), a C₁₋₆ alkylsulfonyloxy group (e.g., methylsulfonyloxy, ethylsulfonyloxy) and a C₆₋₁₄ arylsulfonyloxy group (e.g., phenylsulfonyloxy).

[0059]

In the present specification, examples of the "optionally substituted sulfanyl group" include a sulfanyl group optionally having "a substituent selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a

C₆₋₁₄ aryl-carbonyl group and a 5- to 14-membered aromatic heterocyclic group, each of which optionally has 1 to 3 substituents selected from substituent group A" and a halogenated sulfanyl group.

5 Preferable examples of the optionally substituted sulfanyl group include a sulfanyl (-SH) group, a C₁₋₆ alkylthio group, a C₂₋₆ alkenylthio group (e.g., allylthio, 2-butenylthio, 2-pentenylthio, 3-hexenylthio), a C₃₋₁₀ cycloalkylthio group (e.g., cyclohexylthio), a C₆₋₁₄ arylthio group (e.g., phenylthio, 10 naphthylthio), a C₇₋₁₆ aralkylthio group (e.g., benzylthio, phenethylthio), a C₁₋₆ alkyl-carbonylthio group (e.g., acetylthio, propionylthio, butyrylthio, isobutyrylthio, pivaloylthio), a C₆₋₁₄ aryl-carbonylthio group (e.g., benzoylthio), a 5- to 14-membered aromatic heterocyclylthio 15 group (e.g., pyridylthio) and a halogenated thio group (e.g., pentafluorothio).

[0060]

In the present specification, examples of the "optionally substituted silyl group" include a silyl group optionally 20 having "1 to 3 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group and a C₇₋₁₆ aralkyl group, each of which optionally has 1 to 3 substituents selected from substituent group A".

Preferable examples of the optionally substituted silyl 25 group include a tri-C₁₋₆ alkylsilyl group (e.g., trimethylsilyl, tert-butyl(dimethyl)silyl).

[0061]

In the present specification, examples of the "hydrocarbon ring" include a C₆₋₁₄ aromatic hydrocarbon ring, C_{3- 30 10} cycloalkane and C₃₋₁₀ cycloalkene.

In the present specification, examples of the "C₆₋₁₄ aromatic hydrocarbon ring" include benzene and naphthalene.

In the present specification, examples of the "C₃₋₁₀ cycloalkane" include cyclopropane, cyclobutane, cyclopentane, 35 cyclohexane, cycloheptane and cyclooctane.

In the present specification, examples of the "C₃₋₁₀ cycloalkene" include cyclopropene, cyclobutene, cyclopentene, cyclohexene, cycloheptene and cyclooctene.

In the present specification, examples of the
5 "heterocycle" include an aromatic heterocycle and a non-aromatic heterocycle, each containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

[0062]

10 In the present specification, examples of the "aromatic heterocycle" include a 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen
15 atom. Preferable examples of the "aromatic heterocycle" include 5- or 6-membered monocyclic aromatic heterocycles such as thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,2,4-oxadiazole, 1,3,4-oxadiazole,
20 1,2,4-thiadiazole, 1,3,4-thiadiazole, triazole, tetrazole, triazine and the like; and 8- to 14-membered fused polycyclic (preferably bi or tricyclic) aromatic heterocycles such as benzothiophene, benzofuran, benzimidazole, benzoxazole, benzisoxazole,
25 benzothiazole, benzisothiazole, benzotriazole, imidazopyridine, thienopyridine, furopyridine, pyrrolopyridine, pyrazolopyridine, oxazolopyridine, thiazolopyridine, imidazopyrazine, imidazopyrimidine, thienopyrimidine, furopyrimidine, pyrrolopyrimidine, pyrazolopyrimidine,
30 oxazolopyrimidine, thiazolopyrimidine, pyrazolopyrimidine, pyrazolotriazine, naphtho[2,3-b]thiophene, phenoxathiine, indole, isoindole, 1H-indazole, purine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, carbazole, β -carboline, phenanthridine,
35 acridine, phenazine, phenothiazine, phenoxathiine and the like.

[0063]

In the present specification, examples of the "non-aromatic heterocycle" include a 3- to 14-membered (preferably 4- to 10-membered) non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom. Preferable examples of the "non-aromatic heterocycle" include 3- to 8-membered monocyclic non-aromatic heterocycles such as aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrothiophene, tetrahydrofuran, pyrroline, pyrrolidine, imidazoline, imidazolidine, oxazoline, oxazolidine, pyrazoline, pyrazolidine, thiazoline, thiazolidine, tetrahydroisothiazole, tetrahydrooxazole, tetrahydroisoxazole, piperidine, piperazine, tetrahydropyridine, dihydropyridine, dihydrothiopyran, tetrahydropyrimidine, tetrahydropyridazine, dihydropyran, tetrahydropyran, tetrahydrothiopyran, morpholine, thiomorpholine, azepanine, diazepane, azepine, azocane, diazocane, oxepane and the like; and 9- to 14-membered fused polycyclic (preferably bi or tricyclic) non-aromatic heterocycles such as dihydrobenzofuran, dihydrobenzimidazole, dihydrobenzoxazole, dihydrobenzothiazole, dihydrobenzisoctiazole, dihydronaphtho[2,3-b]thiophene, tetrahydroisoquinoline, tetrahydroquinoline, 4H-quinolizine, indoline, isoindoline, tetrahydrothieno[2,3-c]pyridine, tetrahydrobenzazepine, tetrahydroquinoxaline, tetrahydrophenanthridine, hexahydrophenothiazine, hexahydrophenoxazine, tetrahydrophthalazine, tetrahydronaphthyridine, tetrahydroquinazoline, tetrahydrocinnoline, tetrahydrocarbazole, tetrahydro- β -carboline, tetrahydroacridine, tetrahydrophenazine, tetrahydrothioxanthene, octahydroisoquinoline and the like.

In the present specification, examples of the "nitrogen-containing heterocycle" include a "heterocycle" containing at least one nitrogen atom as a ring-constituting atom.

[0064]

The definition of each symbol in the formula (I) is explained in detail in the following.

[0065]

5 R^1 is an optionally substituted 5-membered aromatic heterocyclic group.

[0066]

In the present specification, examples of the "5-membered aromatic heterocyclic group" of the "optionally substituted 5-membered aromatic heterocyclic group" for R^1 include thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, triazolyl, tetrazolyl and the like.

15 [0067]

The "5-membered aromatic heterocyclic group" of the "optionally substituted 5-membered aromatic heterocyclic group" for R^1 optionally has 1 to 3 substituents at substitutable position(s). Examples of the substituent include substituents selected from the aforementioned substituent group A. When the number of the substituents is plural, the respective substituents may be the same or different.

[0068]

R^1 is preferably an optionally substituted isoxazolyl or an optionally substituted pyrazolyl.

[0069]

R^1 is more preferably isoxazolyl or pyrazolyl, each of which is optionally substituted by 1 to 3 C_{1-6} alkyl groups (e.g., methyl).

30 [0070]

In another embodiment, R^1 is more preferably isoxazolyl optionally substituted by 1 to 3 C_{1-6} alkyl groups (e.g., methyl).

[0071]

35 Ring A is an optionally further substituted benzene ring.

[0072]

The "benzene ring" of the "optionally further substituted benzene ring" for ring A optionally has 1 or 2 substituents, in addition to R^1 and R^3 . Examples of the substituent include
5 substituents selected from the aforementioned substituent group A. When the number of the substituents is plural, the respective substituents may be the same or different.

[0073]

Ring A is preferably a benzene ring having no substituent,
10 in addition to R^1 and R^3 .

[0074]

R^2 and R^3 are each independently a hydrogen atom or a substituent.

[0075]

15 R^2 and R^3 are preferably each independently

- (1) a hydrogen atom,
- (2) a halogen atom,
- (3) a cyano group,
- (4) an optionally substituted hydrocarbon group (preferably an
20 optionally substituted C_{3-10} cycloalkyl group, more preferably an optionally substituted C_{3-6} cycloalkyl group),
- (5) an optionally substituted heterocyclic group [preferably an optionally substituted 3- to 14-membered (preferably 4- to 10-membered) non-aromatic heterocyclic group (preferably an
25 optionally substituted 3- to 8-membered (preferably 4- to 6-membered) monocyclic non-aromatic heterocyclic group), and an optionally substituted 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocyclic group (preferably an optionally substituted 5- or 6-membered monocyclic aromatic
30 heterocyclic group)],
- (6) an optionally substituted amino group (preferably an amino group optionally having 1 or 2 C_{1-6} alkyl groups optionally having 1 to 3 substituents selected from substituent group A),
or
- 35 (7) an optionally substituted hydroxy group (preferably a

hydroxy group optionally having a C₁₋₆ alkyl group optionally having 1 to 3 substituents selected from substituent group A), or

(8) an optionally substituted sulfanyl group (preferably a sulfanyl group optionally having a C₁₋₆ alkyl group optionally having 1 to 3 substituents selected from substituent group A).
[0076]

R² and R³ are more preferably each independently

- (1) a hydrogen atom,
- 10 (2) a halogen atom (e.g., a chlorine atom),
- (3) a cyano group,
- (4) an optionally substituted C₃₋₁₀ cycloalkyl group (preferably an optionally substituted C₃₋₆ cycloalkyl group (e.g., cyclopropyl)),
- 15 (5) an optionally substituted 3- to 14-membered (preferably 4- to 10-membered) non-aromatic heterocyclic group (preferably an optionally substituted 3- to 8-membered (preferably 4- to 6-membered) monocyclic non-aromatic heterocyclic group, more preferably an optionally substituted 3- to 8-membered
- 20 (preferably 4- to 6-membered) nitrogen-containing monocyclic non-aromatic heterocyclic group (e.g., azetidiny, pyrrolidinyl)),
- (6) an optionally substituted 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocyclic group (preferably an
- 25 optionally substituted 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., isoxazolyl)),
- (7) an amino group optionally having 1 or 2 C₁₋₆ alkyl groups (e.g., methyl, ethyl) optionally having 1 to 3 substituents selected from substituent group A (preferably hydroxy),
- 30 (8) a hydroxy group optionally having a C₁₋₆ alkyl group (e.g., methyl, ethyl), or
- (9) a sulfanyl group optionally having a C₁₋₆ alkyl group (e.g., methyl).

[0077]

35 R² and R³ are further more preferably each independently

- (1) a hydrogen atom,
- (2) a halogen atom (e.g., a chlorine atom),
- (3) a cyano group,
- (4) a C₃₋₁₀ cycloalkyl group (preferably a C₃₋₆ cycloalkyl group
5 (e.g., cyclopropyl)),
- (5) a 3- to 8-membered (preferably 4- to 6-membered)
monocyclic non-aromatic heterocyclic group (preferably a 3- to
8-membered (preferably 4- to 6-membered) nitrogen-containing
monocyclic non-aromatic heterocyclic group (e.g., azetidinyl,
10 pyrrolidinyl)),
- (6) a 5- or 6-membered monocyclic aromatic heterocyclic group
(e.g., isoxazolyl) optionally having 1 or 2 C₁₋₆ alkyl groups
(e.g., methyl),
- (7) an amino group optionally having 1 or 2 C₁₋₆ alkyl groups
15 (e.g., methyl, ethyl) optionally having 1 to 3 hydroxy groups,
- (8) a hydroxy group,
- (9) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy), or
- (10) a C₁₋₆ alkylthio group (e.g., methylthio).

[0078]

20 Still more preferably,

R² is

- (1) a hydrogen atom,
- (2) a halogen atom (e.g., a chlorine atom),
- (3) a cyano group,
- 25 (4) a C₃₋₁₀ cycloalkyl group (preferably a C₃₋₆ cycloalkyl group
(e.g., cyclopropyl)),
- (5) a 3- to 8-membered (preferably 4- to 6-membered)
monocyclic non-aromatic heterocyclic group (preferably a 3- to
8-membered (preferably 4- to 6-membered) nitrogen-containing
30 monocyclic non-aromatic heterocyclic group (e.g., azetidinyl,
pyrrolidinyl)),
- (6) a 5- or 6-membered monocyclic aromatic heterocyclic group
(e.g., isoxazolyl) optionally having 1 or 2 C₁₋₆ alkyl groups
(e.g., methyl),
- 35 (7) an amino group optionally having 1 or 2 C₁₋₆ alkyl groups

(e.g., methyl, ethyl) optionally having 1 to 3 hydroxy groups,
(8) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy), or
(9) a C₁₋₆ alkylthio group (e.g., methylthio), and
R³ is

- 5 (1) a hydrogen atom,
(2) a hydroxy group, or
(3) a C₁₋₆ alkoxy group (e.g., methoxy).

[0079]

In another embodiment, R² and R³ are further more
10 preferably each independently

- (1) a hydrogen atom,
(2) a halogen atom (e.g., a chlorine atom),
(3) a cyano group,
(4) a C₃₋₁₀ cycloalkyl group (preferably a C₃₋₆ cycloalkyl group
15 (e.g., cyclopropyl)),
(5) a 3- to 8-membered (preferably 4- to 6-membered)
monocyclic non-aromatic heterocyclic group (preferably a 3- to
8-membered (preferably 4- to 6-membered) nitrogen-containing
monocyclic non-aromatic heterocyclic group (e.g., azetidiny)),
20 (6) a 5- or 6-membered monocyclic aromatic heterocyclic group
(e.g., isoxazolyl) optionally having 1 or 2 C₁₋₆ alkyl groups
(e.g., methyl),
(7) an amino group optionally having 1 or 2 C₁₋₆ alkyl groups
(e.g., methyl, ethyl),
25 (8) a hydroxy group,
(9) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy), or
(10) a C₁₋₆ alkylthio group (e.g., methylthio).

[0080]

Still more preferably,
30 R² is

- (1) a hydrogen atom,
(2) a halogen atom (e.g., a chlorine atom),
(3) a cyano group,
(4) a C₃₋₁₀ cycloalkyl group (preferably a C₃₋₆ cycloalkyl group
35 (e.g., cyclopropyl)),

- (5) a 3- to 8-membered (preferably 4- to 6-membered) monocyclic non-aromatic heterocyclic group (preferably a 3- to 8-membered (preferably 4- to 6-membered) nitrogen-containing monocyclic non-aromatic heterocyclic group (e.g., azetidiny)),
- 5 (6) a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., isoxazolyl) optionally having 1 or 2 C₁₋₆ alkyl groups (e.g., methyl),
- (7) an amino group optionally having 1 or 2 C₁₋₆ alkyl groups (e.g., methyl, ethyl),
- 10 (8) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy), or
- (9) a C₁₋₆ alkylthio group (e.g., methylthio), and
- R³ is
- (1) a hydrogen atom,
- (2) a hydroxy group, or
- 15 (3) a C₁₋₆ alkoxy group (e.g., methoxy).
- [0081]

In another embodiment, R² and R³ are further more preferably each independently

- (1) a hydrogen atom,
- 20 (2) a halogen atom (e.g., a chlorine atom),
- (3) a cyano group,
- (4) a 3- to 8-membered (preferably 4- to 6-membered) monocyclic non-aromatic heterocyclic group (preferably a 3- to 8-membered (preferably 4- to 6-membered) nitrogen-containing
- 25 monocyclic non-aromatic heterocyclic group (e.g., azetidiny, pyrrolidiny)),
- (5) an amino group optionally having 1 or 2 C₁₋₆ alkyl groups (e.g., methyl, ethyl) optionally having 1 to 3 hydroxy groups, or
- 30 (6) a C₁₋₆ alkoxy group (e.g., methoxy).
- [0082]

Still more preferably,

R² is

- (1) a hydrogen atom,
- 35 (2) a halogen atom (e.g., a chlorine atom),

- (3) a cyano group,
 (4) a 3- to 8-membered (preferably 4- to 6-membered) monocyclic non-aromatic heterocyclic group (preferably a 3- to 8-membered (preferably 4- to 6-membered) nitrogen-containing
 5 monocyclic non-aromatic heterocyclic group (e.g., azetidiny, pyrrolidinyl)), or
 (5) an amino group optionally having 1 or 2 C₁₋₆ alkyl groups (e.g., methyl, ethyl) optionally having 1 to 3 hydroxy groups, and

10 R³ is

- (1) a C₁₋₆ alkoxy group (e.g., methoxy).

[0083]

In another embodiment, R² and R³ are further more preferably each independently

- 15 (1) a hydrogen atom, or
 (2) a C₁₋₆ alkoxy group (e.g., methoxy).

[0084]

Still more preferably,

R² is

- 20 (1) a hydrogen atom, and

R³ is

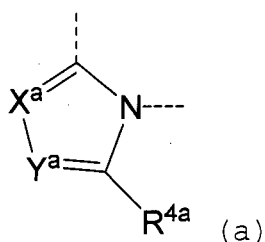
- (1) a C₁₋₆ alkoxy group (e.g., methoxy).

[0085]

Ring B is

- 25 a ring represented by the formula:

[0086]



[0087]

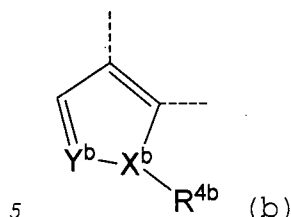
wherein

- 30 X^a and Y^a are each independently a nitrogen atom or a carbon atom, and

R^{4a} is a substituent, and

wherein said ring is optionally further substituted,
a ring represented by the formula:

[0088]



[0089]

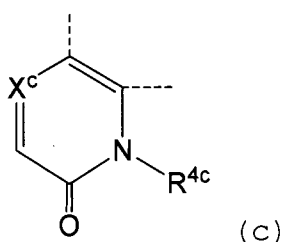
wherein

X^b and Y^b are each independently a nitrogen atom or a carbon atom, and

10 R^{4b} is a hydrogen atom or a substituent, and

wherein said ring is optionally further substituted, or
a ring represented by the formula:

[0090]



15 [0091]

wherein

X^c is a nitrogen atom or a carbon atom, and

R^{4c} is a hydrogen atom or a substituent, and

wherein said ring is optionally further substituted.

20 [0092]

X^a is preferably a nitrogen atom.

Y^a is preferably a nitrogen atom.

[0093]

R^{4a} is preferably

25 (1) an optionally substituted hydrocarbon group (preferably an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{3-10} cycloalkyl group, an optionally substituted C_6-

10 aryl group),

- (2) an optionally substituted heterocyclic group (preferably an optionally substituted 3- to 14-membered (preferably 4- to 10-membered) non-aromatic heterocyclic group, more preferably
5 an optionally substituted 3- to 8-membered (preferably 5- or 6-membered) monocyclic non-aromatic heterocyclic group), or
(3) an optionally substituted amino group (preferably an amino group optionally having 1 or 2 C₆₋₁₀ aryl groups optionally having 1 to 3 substituents selected from substituent group A).

10 [0094]

R^{4a} is more preferably

- (1) an optionally substituted C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl),
(2) an optionally substituted C₃₋₁₀ cycloalkyl group (preferably
15 an optionally substituted C₃₋₆ cycloalkyl group (e.g., cyclopropyl)),
(3) an optionally substituted C₆₋₁₀ aryl group (e.g., phenyl),
(4) an optionally substituted 3- to 14-membered (preferably 4- to 10-membered) non-aromatic heterocyclic group (preferably an
20 optionally substituted 3- to 8-membered (preferably 5- or 6-membered) monocyclic non-aromatic heterocyclic group (e.g., tetrahydropyranyl)), or
(5) an amino group optionally having 1 or 2 C₆₋₁₀ aryl groups (e.g., phenyl) optionally having 1 to 3 substituents selected
25 from substituent group A (preferably a halogen atom (e.g., a fluorine atom, a chlorine atom), a cyano group, a C₁₋₆ alkoxy group (e.g., methoxy)).

[0095]

R^{4a} is further more preferably

- 30 (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl) optionally substituted by 1 to 3 substituents selected from

(a) a C₆₋₁₀ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from

- 35 (i) a halogen atom (e.g., a fluorine atom, a chlorine

- atom),
- (ii) a cyano group,
- (iii) a carboxy group,
- (iv) a C₁₋₆ alkyl group (e.g., methyl) optionally
- 5 substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (v) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- 10 (vi) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl),
- (vii) a C₆₋₁₀ aryl group (e.g., phenyl),
- (viii) a C₆₋₁₀ aryloxy group (e.g., phenoxy), and
- (ix) a C₁₋₃ alkylenedioxy group (e.g., methylenedioxy),
- (b) a C₃₋₁₀ cycloalkyl group (e.g., cyclopentyl),
- 15 (c) a 3- to 14-membered (preferably 4- to 10-membered) non-aromatic heterocyclic group (preferably a 3- to 8-membered (preferably 5- or 6-membered) monocyclic non-aromatic heterocyclic group (e.g., tetrahydropyranyl), and
- (d) a 5- to 14-membered (preferably 5- or 10-membered)
- 20 aromatic heterocyclic group (e.g., thienyl, thiazoyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, quinolyl) optionally substituted by 1 to 3 substituents selected from
- (i) a C₁₋₆ alkyl group (e.g., methyl), and
- (ii) a C₁₋₆ alkoxy group (e.g., methoxy),
- 25 (2) a C₃₋₁₀ cycloalkyl group (preferably a C₃₋₆ cycloalkyl group (e.g., cyclopropyl)) optionally substituted by 1 to 3 substituents selected from
- (a) a C₆₋₁₀ aryl group (e.g., phenyl), and
- (b) a 5- to 14-membered (preferably 5- or 10-membered)
- 30 aromatic heterocyclic group (preferably a 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl)),
- (3) a C₆₋₁₀ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (4) a 3- to 8-membered (preferably 5- or 6-membered)
- 35 monocyclic non-aromatic heterocyclic group (e.g.,

tetrahydropyranyl)), or

(5) an amino group optionally having 1 or 2 C₆₋₁₀ aryl groups (e.g., phenyl) optionally having 1 to 3 substituents selected from

- 5 (a) a halogen atom (e.g., a fluorine atom, a chlorine atom),
(b) a cyano group, and
(c) a C₁₋₆ alkoxy group (e.g., methoxy)).

[0096]

X^b is preferably a nitrogen atom.

10 Y^b is preferably a nitrogen atom.

[0097]

R^{4b} is preferably an optionally substituted hydrocarbon group (preferably an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₆₋₁₀ aryl group).

15 [0098]

R^{4b} is more preferably

- (1) an optionally substituted C₁₋₆ alkyl group (e.g., methyl, ethyl, isobutyl), or
(2) an optionally substituted C₆₋₁₀ aryl group (e.g., phenyl).

20 [0099]

R^{4b} is further more preferably

- (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl, isobutyl) optionally substituted by 1 to 3 substituents selected from

25 (a) a C₆₋₁₀ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from

(i) a halogen atom (e.g., a fluorine atom, a chlorine atom),

30 (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and

(iii) a C₁₋₆ alkoxy group (e.g., methoxy),

(b) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclohexyl), and

35 (c) a 5- to 14-membered (preferably 5- or 10-membered) aromatic heterocyclic group (preferably a 5- or 6-membered

monocyclic aromatic heterocyclic group (e.g., pyridyl, pyrazolyl)) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), or

(2) a C₆₋₁₀ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom (e.g., a fluorine atom), and

(b) a C₁₋₆ alkoxy group (e.g., methoxy) optionally

substituted by 1 to 3 halogen atoms (e.g., a fluorine atom).

[0100]

X^c is preferably a nitrogen atom.

[0101]

R^{4c} is preferably an optionally substituted hydrocarbon group (preferably an optionally substituted C₁₋₆ alkyl group).

[0102]

R^{4c} is more preferably an optionally substituted C₁₋₆ alkyl group (e.g., methyl, ethyl).

[0103]

R^{4c} is further more preferably a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from

(a) a C₆₋₁₀ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from

(i) a halogen atom (e.g., a fluorine atom), and

(ii) a C₁₋₆ alkoxy group (e.g., methoxy) optionally

substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),

(b) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclohexyl), and

(c) a 5- to 14-membered (preferably 5- or 10-membered)

aromatic heterocyclic group (preferably a 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl)).

[0104]

The ring represented by the formula (a) optionally has 1 or 2 substituents at substitutable position(s), in addition to R^{4a}. Examples of the substituent include substituents selected

from the aforementioned substituent group A. When the number of the substituents is plural, the respective substituents may be the same or different.

[0105]

5 The rings represented by the formula (a) preferably have no substituent, in addition to R^{4a} .

[0106]

 The ring represented by the formula (b) optionally has 1 or 2 substituents at substitutable position(s), in addition to
10 R^{4b} . Examples of the substituent include substituents selected from the aforementioned substituent group A. When the number of the substituents is plural, the respective substituents may be the same or different.

[0107]

15 The rings represented by the formula (b) preferably have no substituent, in addition to R^{4b} .

[0108]

 The ring represented by the formula (c) optionally has 1 or 2 substituents at substitutable position(s), in addition to
20 R^{4c} . Examples of the substituent include substituents selected from the aforementioned substituent group A. When the number of the substituents is plural, the respective substituents may be the same or different.

[0109]

25 The rings represented by the formula (c) preferably have no substituent, in addition to R^{4c} .

[0110]

 Preferable examples of compound (I) include the following compounds.

30 [0111]

[Compound A]

 Compound (I) wherein

R^1 is an optionally substituted isoxazolyl or an optionally substituted pyrazolyl;

35 Ring A is an optionally further substituted benzene ring;

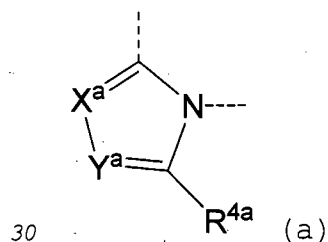
R^2 and R^3 are each independently

- (1) a hydrogen atom,
- (2) a halogen atom (e.g., a chlorine atom),
- (3) a cyano group,
- 5 (4) an optionally substituted C_{3-10} cycloalkyl group (preferably an optionally substituted C_{3-6} cycloalkyl group (e.g., cyclopropyl)),
- (5) an optionally substituted 3- to 14-membered (preferably 4- to 10-membered) non-aromatic heterocyclic group (preferably an
- 10 optionally substituted 3- to 8-membered (preferably 4- to 6-membered) monocyclic non-aromatic heterocyclic group, more preferably an optionally substituted 3- to 8-membered (preferably 4- to 6-membered) nitrogen-containing monocyclic non-aromatic heterocyclic group (e.g., azetidiny, pyrrolidinyl)),
- 15 (6) an optionally substituted 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocyclic group (preferably an optionally substituted 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., isoxazolyl)),
- 20 (7) an amino group optionally having 1 or 2 C_{1-6} alkyl groups (e.g., methyl, ethyl) optionally having 1 to 3 substituents selected from substituent group A (preferably hydroxy),
- (8) a hydroxy group optionally having a C_{1-6} alkyl group (e.g., methyl, ethyl), or
- 25 (9) a sulfanyl group optionally having a C_{1-6} alkyl group (e.g., methyl); and

Ring B is

a ring represented by the formula:

[0112]



[0113]

wherein

X^a is a nitrogen atom;

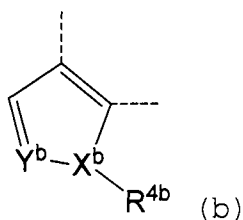
Y^a is a nitrogen atom; and

R^{4a} is

- 5 (1) an optionally substituted C_{1-6} alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl),
- (2) an optionally substituted C_{3-10} cycloalkyl group (preferably an optionally substituted C_{3-6} cycloalkyl group (e.g., cyclopropyl)),
- 10 (3) an optionally substituted C_{6-10} aryl group (e.g., phenyl),
- (4) an optionally substituted 3- to 14-membered (preferably 4- to 10-membered) non-aromatic heterocyclic group (preferably an optionally substituted 3- to 8-membered (preferably 5- or 6-membered) monocyclic non-aromatic
- 15 heterocyclic group (e.g., tetrahydropyranyl)), or
- (5) an amino group optionally having 1 or 2 C_{6-10} aryl groups (e.g., phenyl) optionally having 1 to 3 substituents selected from substituent group A (preferably a halogen atom (e.g., a fluorine atom, a chlorine atom), a cyano
- 20 group, a C_{1-6} alkoxy group (e.g., methoxy)),

a ring represented by the formula:

[0114]



[0115]

25 wherein

X^b is a nitrogen atom;

Y^b is a nitrogen atom; and

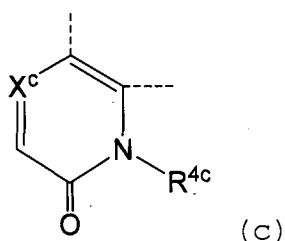
R^{4b} is

- 30 (1) an optionally substituted C_{1-6} alkyl group (e.g., methyl, ethyl, isobutyl), or
- (2) an optionally substituted C_{6-10} aryl group (e.g., phenyl),

or

a ring represented by the formula:

[0116]



5 [0117]

wherein

X^c is a nitrogen atom; and

R^{4c} is an optionally substituted C_{1-6} alkyl group (e.g., methyl, ethyl),

10 or a salt thereof.

[0118]

[Compound B]

Compound (I) wherein

R^1 is isoxazolyl or pyrazolyl, each of which is optionally
15 substituted by 1 to 3 C_{1-6} alkyl groups (e.g., methyl);

Ring A is a benzene ring having no substituent, in addition to R^1 and R^3 ;

R^2 and R^3 are each independently

- (1) a hydrogen atom,
- 20 (2) a halogen atom (e.g., a chlorine atom),
- (3) a cyano group,
- (4) a C_{3-10} cycloalkyl group (preferably a C_{3-6} cycloalkyl group (e.g., cyclopropyl)),
- (5) a 3- to 8-membered (preferably 4- to 6-membered)
- 25 monocyclic non-aromatic heterocyclic group (preferably a 3- to 8-membered (preferably 4- to 6-membered) nitrogen-containing monocyclic non-aromatic heterocyclic group (e.g., azetidiny, pyrrolidinyl)),
- (6) a 5- or 6-membered monocyclic aromatic heterocyclic group
- 30 (e.g., isoxazolyl) optionally having 1 or 2 C_{1-6} alkyl groups (e.g., methyl),

- (7) an amino group optionally having 1 or 2 C₁₋₆ alkyl groups
(e.g., methyl, ethyl) optionally having 1 to 3 hydroxy groups,
(8) a hydroxy group,
(9) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy), or
5 (10) a C₁₋₆ alkylthio group (e.g., methylthio)

[preferably

R² is

- (1) a hydrogen atom,
(2) a halogen atom (e.g., a chlorine atom),
10 (3) a cyano group,
(4) a C₃₋₁₀ cycloalkyl group (preferably a C₃₋₆ cycloalkyl group
(e.g., cyclopropyl)),
(5) a 3- to 8-membered (preferably 4- to 6-membered)
monocyclic non-aromatic heterocyclic group (preferably a 3- to
15 8-membered (preferably 4- to 6-membered) nitrogen-containing
monocyclic non-aromatic heterocyclic group (e.g., azetidiny, pyrrolidinyl)),
(6) a 5- or 6-membered monocyclic aromatic heterocyclic group
(e.g., isoxazolyl) optionally having 1 or 2 C₁₋₆ alkyl groups
20 (e.g., methyl),
(7) an amino group optionally having 1 or 2 C₁₋₆ alkyl groups
(e.g., methyl, ethyl) optionally having 1 to 3 hydroxy groups,
(8) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy), or
(9) a C₁₋₆ alkylthio group (e.g., methylthio), and

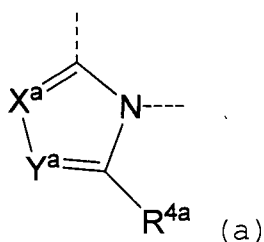
25 R³ is

- (1) a hydrogen atom,
(2) a hydroxy group, or
(3) a C₁₋₆ alkoxy group (e.g., methoxy)]; and

Ring B is

30 a ring represented by the formula:

[0119]



[0120]

wherein

 X^a is a nitrogen atom;5 Y^a is a nitrogen atom; and R^{4a} is

(1) a C_{1-6} alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl) optionally substituted by 1 to 3 substituents selected from

- 10 (a) a C_{6-10} aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
 - (ii) a cyano group,
 - 15 (iii) a carboxy group,
 - (iv) a C_{1-6} alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
 - (v) a C_{1-6} alkoxy group (e.g., methoxy) optionally
 - 20 substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
 - (vi) a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl),
 - (vii) a C_{6-10} aryl group (e.g., phenyl),
 - (viii) a C_{6-10} aryloxy group (e.g., phenoxy), and
 - 25 (ix) a C_{1-3} alkylenedioxy group (e.g., methylenedioxy),
 - (b) a C_{3-10} cycloalkyl group (e.g., cyclopentyl),
 - (c) a 3- to 14-membered (preferably 4- to 10-membered) non-aromatic heterocyclic group (preferably a 3- to 8-membered (preferably 5- or 6-membered) monocyclic non-
 - 30 aromatic heterocyclic group (e.g., tetrahydropyranyl),
- and

(d) a 5- to 14-membered (preferably 5- or 10-membered) aromatic heterocyclic group (e.g., thienyl, thiazoyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, quinolyl) optionally substituted by 1 to 3 substituents selected from

(i) a C₁₋₆ alkyl group (e.g., methyl), and

(ii) a C₁₋₆ alkoxy group (e.g., methoxy),

(2) a C₃₋₁₀ cycloalkyl group (preferably a C₃₋₆ cycloalkyl group (e.g., cyclopropyl)) optionally substituted by 1 to 3 substituents selected from

(a) a C₆₋₁₀ aryl group (e.g., phenyl), and

(b) a 5- to 14-membered (preferably 5- or 10-membered) aromatic heterocyclic group (preferably a 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl)),

(3) a C₆₋₁₀ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),

(4) a 3- to 8-membered (preferably 5- or 6-membered) monocyclic non-aromatic heterocyclic group (e.g., tetrahydropyranyl)), or

(5) an amino group optionally having 1 or 2 C₆₋₁₀ aryl groups (e.g., phenyl) optionally having 1 to 3 substituents selected from

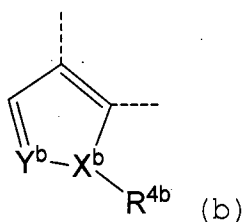
(a) a halogen atom (e.g., a fluorine atom, a chlorine atom),

(b) a cyano group, and

(c) a C₁₋₆ alkoxy group (e.g., methoxy)),

a ring represented by the formula:

[0121]



[0122]

wherein

X^b is a nitrogen atom;

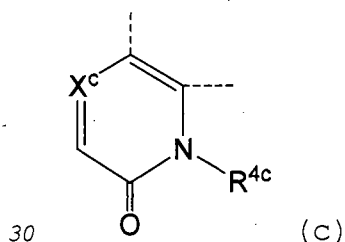
Y^b is a nitrogen atom; and

R^{4b} is

- 5 (1) a C_{1-6} alkyl group (e.g., methyl, ethyl, isobutyl) optionally substituted by 1 to 3 substituents selected from
 - (a) a C_{6-10} aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from
 - 10 (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
 - (ii) a C_{1-6} alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
 - (iii) a C_{1-6} alkoxy group (e.g., methoxy),
 - 15 (b) a C_{3-10} cycloalkyl group (e.g., cyclopropyl, cyclohexyl), and
 - (c) a 5- to 14-membered (preferably 5- or 10-membered) aromatic heterocyclic group (preferably a 5- or 6-membered monocyclic aromatic heterocyclic group (e.g.,
 - 20 pyridyl, pyrazolyl)) optionally substituted by 1 to 3 C_{1-6} alkyl groups (e.g., methyl), or
 - (2) a C_{6-10} aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from
 - (a) a halogen atom (e.g., a fluorine atom), and
 - 25 (b) a C_{1-6} alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), or

a ring represented by the formula:

[0123]



[0124]

wherein

X^c is a nitrogen atom; and

R^{4c} is a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from

- 5 (a) a C₆₋₁₀ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom), and
 - (ii) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine
- 10 atom),
- (b) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclohexyl), and
 - (c) a 5- to 14-membered (preferably 5- or 10-membered) aromatic heterocyclic group (preferably a 5- or 6-
- 15 membered monocyclic aromatic heterocyclic group (e.g., pyridyl)),

or a salt thereof.

[0125]

[Compound B-a]

20 Compound (I) wherein

R¹ is isoxazolyl or pyrazolyl, each of which is optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl);

Ring A is a benzene ring having no substituent, in addition to R¹ and R³;

25 R² and R³ are each independently

- (1) a hydrogen atom,
 - (2) a halogen atom (e.g., a chlorine atom),
 - (3) a cyano group,
 - (4) a C₃₋₁₀ cycloalkyl group (preferably a C₃₋₆ cycloalkyl group
- 30 (e.g., cyclopropyl)),
- (5) a 3- to 8-membered (preferably 4- to 6-membered) monocyclic non-aromatic heterocyclic group (preferably a 3- to 8-membered (preferably 4- to 6-membered) nitrogen-containing monocyclic non-aromatic heterocyclic group (e.g., azetidyl)),
- 35 (6) a 5- or 6-membered monocyclic aromatic heterocyclic group

(e.g., isoxazolyl) optionally having 1 or 2 C₁₋₆ alkyl groups
(e.g., methyl),

(7) an amino group optionally having 1 or 2 C₁₋₆ alkyl groups
(e.g., methyl, ethyl),

5 (8) a hydroxy group,

(9) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy), or

(10) a C₁₋₆ alkylthio group (e.g., methylthio)

[preferably

R² is

10 (1) a hydrogen atom,

(2) a halogen atom (e.g., a chlorine atom),

(3) a cyano group,

(4) a C₃₋₁₀ cycloalkyl group (preferably a C₃₋₆ cycloalkyl group
(e.g., cyclopropyl)),

15 (5) a 3- to 8-membered (preferably 4- to 6-membered)

monocyclic non-aromatic heterocyclic group (preferably a 3- to
8-membered (preferably 4- to 6-membered) nitrogen-containing
monocyclic non-aromatic heterocyclic group (e.g., azetidyl)),

(6) a 5- to 6-membered monocyclic aromatic heterocyclic group

20 (e.g., isoxazolyl) optionally having 1 or 2 C₁₋₆ alkyl groups
(e.g., methyl),

(7) an amino group optionally having 1 or 2 C₁₋₆ alkyl groups
(e.g., methyl, ethyl),

(8) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy), or

25 (9) a C₁₋₆ alkylthio group (e.g., methylthio), and

R³ is

(1) a hydrogen atom,

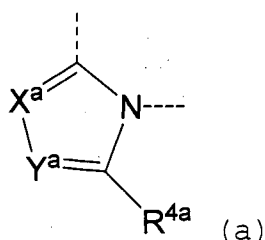
(2) a hydroxy group, or

(3) a C₁₋₆ alkoxy group (e.g., methoxy)]; and

30 Ring B is

a ring represented by the formula:

[0126]



[0127]

wherein

 X^a is a nitrogen atom;5 Y^a is a nitrogen atom; and R^{4a} is

(1) a C_{1-6} alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl) optionally substituted by 1 to 3 substituents selected from

- 10 (a) a C_{6-10} aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
 - (ii) a cyano group,
 - 15 (iii) a carboxy group,
 - (iv) a C_{1-6} alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
 - (v) a C_{1-6} alkoxy group (e.g., methoxy) optionally
 - 20 substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
 - (vi) a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl),
 - (vii) a C_{6-10} aryl group (e.g., phenyl),
 - (viii) a C_{6-10} aryloxy group (e.g., phenoxy), and
 - 25 (ix) a C_{1-3} alkylenedioxy group (e.g., methylenedioxy),
 - (b) a C_{3-10} cycloalkyl group (e.g., cyclopentyl),
 - (c) a 3- to 14-membered (preferably 4- to 10-membered) non-aromatic heterocyclic group (preferably a 3- to 8-membered (preferably 5- or 6-membered) monocyclic non-
 - 30 aromatic heterocyclic group (e.g., tetrahydropyranyl),
- and

- (d) a 5- to 14-membered (preferably 5- or 10-membered) aromatic heterocyclic group (e.g., thienyl, thiazoyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, quinolyl) optionally substituted by 1 to 3 substituents selected from
- 5 (i) a C₁₋₆ alkyl group (e.g., methyl), and
(ii) a C₁₋₆ alkoxy group (e.g., methoxy),
(2) a C₃₋₁₀ cycloalkyl group (preferably a C₃₋₆ cycloalkyl group (e.g., cyclopropyl)) optionally substituted by 1 to 3 substituents selected from
- 10 (a) a C₆₋₁₀ aryl group (e.g., phenyl), and
(b) a 5- to 14-membered (preferably 5- or 10-membered) aromatic heterocyclic group (preferably a 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl)),
- 15 (3) a C₆₋₁₀ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
(4) a 3- to 8-membered (preferably 5- or 6-membered) monocyclic non-aromatic heterocyclic group (e.g., tetrahydropyranyl)), or
- 20 (5) an amino group optionally having 1 or 2 C₆₋₁₀ aryl groups (e.g., phenyl) optionally having 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom, a chlorine atom),
- 25 (b) a cyano group, and
(c) a C₁₋₆ alkoxy group (e.g., methoxy))
or a salt thereof.

[0128]

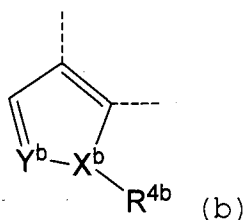
30 [Compound B-b]

Compound (I) wherein

R¹ is isoxazolyl optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl);

Ring A is a benzene ring having no substituent, in addition to
35 R¹ and R³;

- R^2 and R^3 are each independently
- (1) a hydrogen atom,
 - (2) a halogen atom (e.g., a chlorine atom),
 - (3) a cyano group,
 - 5 (4) a 3- to 8-membered (preferably 4- to 6-membered) monocyclic non-aromatic heterocyclic group (preferably a 3- to 8-membered (preferably 4- to 6-membered) nitrogen-containing monocyclic non-aromatic heterocyclic group (e.g., azetidiny, pyrrolidinyl)),
 - 10 (5) an amino group optionally having 1 or 2 C_{1-6} alkyl groups (e.g., methyl, ethyl) optionally having 1 to 3 hydroxy groups, or
 - (6) a C_{1-6} alkoxy group (e.g., methoxy) [preferably
 - 15 R^2 is
 - (1) a hydrogen atom,
 - (2) a halogen atom (e.g., a chlorine atom),
 - (3) a cyano group,
 - (4) a 3- to 8-membered (preferably 4- to 6-membered)
 - 20 monocyclic non-aromatic heterocyclic group (preferably a 3- to 8-membered (preferably 4- to 6-membered) nitrogen-containing monocyclic non-aromatic heterocyclic group (e.g., azetidiny, pyrrolidinyl)), or
 - (5) an amino group optionally having 1 or 2 C_{1-6} alkyl groups
 - 25 (e.g., methyl, ethyl) optionally having 1 to 3 hydroxy groups, and
 - R^3 is
 - (1) a C_{1-6} alkoxy group (e.g., methoxy)]; and
 - Ring B is
 - 30 a ring represented by the formula:
 - [0129]



[0130]

wherein

X^b is a nitrogen atom;

5 Y^b is a nitrogen atom; and

R^{4b} is

(1) a C_{1-6} alkyl group (e.g., methyl, ethyl, isobutyl)

optionally substituted by 1 to 3 substituents selected from

(a) a C_{6-10} aryl group (e.g., phenyl) optionally

10 substituted by 1 to 3 substituents selected from

(i) a halogen atom (e.g., a fluorine atom, a chlorine atom),

(ii) a C_{1-6} alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine

15 atom), and

(iii) a C_{1-6} alkoxy group (e.g., methoxy),

(b) a C_{3-10} cycloalkyl group (e.g., cyclopropyl, cyclohexyl), and

(c) a 5- to 14-membered (preferably 5- or 10-membered)

20 aromatic heterocyclic group (preferably a 5- or 6-

membered monocyclic aromatic heterocyclic group (e.g.,

pyridyl, pyrazolyl)) optionally substituted by 1 to 3 C_{1-6} alkyl groups (e.g., methyl), or

(2) a C_{6-10} aryl group (e.g., phenyl) optionally substituted
25 by 1 to 3 substituents selected from

(a) a halogen atom (e.g., a fluorine atom), and

(b) a C_{1-6} alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),

30 or a salt thereof.

[0131]

[Compound B-c]

Compound (I) wherein

R^1 is isoxazolyl optionally substituted by 1 to 3 C_{1-6} alkyl groups (e.g., methyl);

5 Ring A is a benzene ring having no substituent, in addition to R^1 and R^3 ;

R^2 and R^3 are each independently

(1) a hydrogen atom, or

(2) a C_{1-6} alkoxy group (e.g., methoxy)

10 [preferably

R^2 is

(1) a hydrogen atom, and

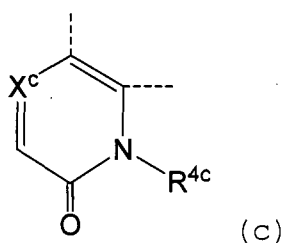
R^3 is

(1) a C_{1-6} alkoxy group (e.g., methoxy)]; and

15 Ring B is

a ring represented by the formula:

[0132]



[0133]

20 wherein

X^c is a nitrogen atom; and

R^{4c} is a C_{1-6} alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from

(a) a C_{6-10} aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from

25 (i) a halogen atom (e.g., a fluorine atom), and

(ii) a C_{1-6} alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),

30 (b) a C_{3-10} cycloalkyl group (e.g., cyclopropyl, cyclohexyl), and

(c) a 5- to 14-membered (preferably 5- or 10-membered) aromatic heterocyclic group (preferably a 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl)),
5 or a salt thereof.

[0134]

When compound (I) is in a form of a salt, examples thereof include metal salts, an ammonium salt, salts with organic base, salts with inorganic acid, salts with organic
10 acid, salts with basic or acidic amino acid, and the like. Preferable examples of the metal salt include alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt, barium salt and the like; an aluminum salt, and the like.
15 Preferable examples of the salt with organic base include salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like. Preferable examples of
20 the salt with inorganic acid include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like. Preferable examples of the salt with organic acid include salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid,
25 tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like. Preferable examples of the salt with basic amino acid include salts with arginine, lysine, ornithine and the like. Preferable examples of the salt with
30 acidic amino acid include salts with aspartic acid, glutamic acid and the like.

Among them, a pharmaceutically acceptable salt is preferable. For example, when a compound has an acidic functional group, examples thereof include inorganic salts
35 such as alkali metal salts (e.g., sodium salt, potassium salt

etc.), alkaline earth metal salts (e.g., calcium salt, magnesium salt etc.) and the like, ammonium salt etc., and when a compound has a basic functional group, examples thereof include salts with inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like, and salts with organic acid such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

10 [0135]

Compound (I) may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes are provided as one embodiment of the invention, and are illustrated by the following representative process.

15 Necessary starting materials may be obtained by standard procedure of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process and within the following examples. Alternatively, necessary starting materials are

20 obtained by a method known per se or a method analogous thereto.

[0136]

The starting material and/or the production intermediate for the compound (I) may form a salt. While the salt is not particularly limited as long as the reaction can be performed, examples thereof include those similar to the salts of compound (I) and the like.

[0137]

When the starting material has an amino group, a carboxyl group, a hydroxy group or a heterocyclic group, these groups may be protected by a protecting group generally used in peptide chemistry and the like. By removing the protecting group as necessary after the reaction, the objective compound can be obtained. The protection and deprotection can be

30 performed according to a method known per se, for example, the

method described in "Protective Groups in Organic Synthesis, 3rd Ed", John Wiley and Sons, Inc. (1999) (Theodora W. Greene, Peter G. M. Wuts). Preferable examples of the protecting group include a tert-butylcarbamate group, a benzylcarbamate group, a benzyl group, a methyl group, an ethyl group, a tert-butyl and the like.

[0138]

The compound obtained in each step can be used directly as the reaction mixture or as a crude product for the next reaction. It can also be isolated from a reaction mixture by a conventional method, and can be easily purified by a separation means such as recrystallization, distillation, chromatography and the like. When the compound in the formula is commercially available, a commercially available product can also be used directly.

[0139]

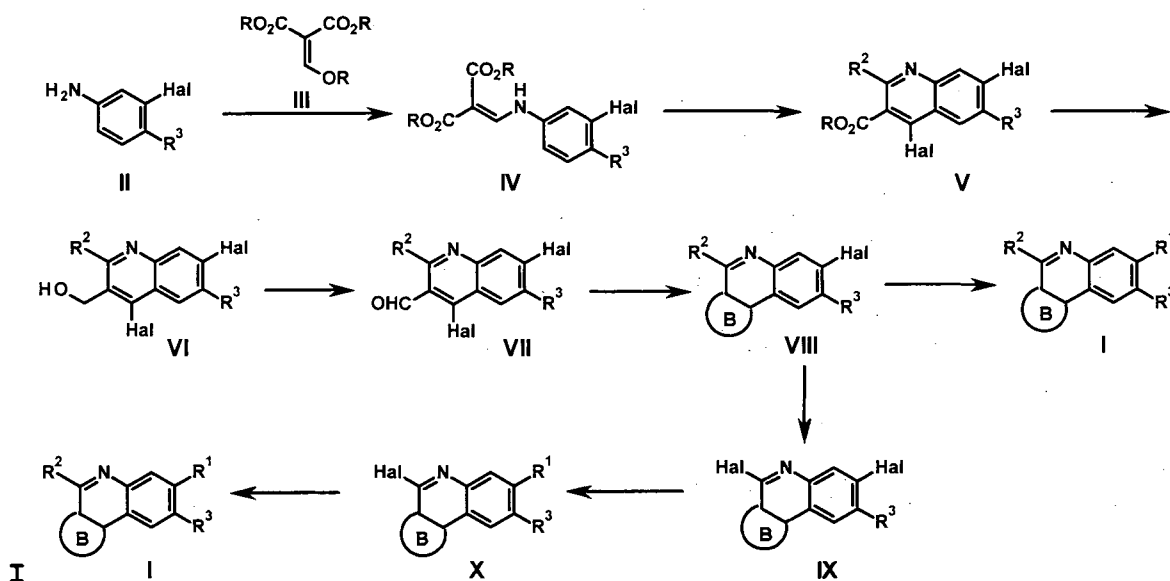
Unless otherwise specified, each symbol in the general formulas in the schemes is as defined above.

[0140]

Compound (I) is prepared as outlined in Schemes below:

[0141]

Scheme-I (Schemes-1 and 2 in Example)

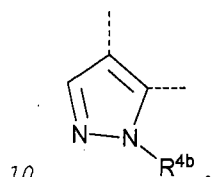


[0142]

wherein Hal is halogen, and R is C₁₋₆ alkyl.

Compound of formula (II) can be reacted with compound of formula (III) to provide compound of formula (IV), which can be cyclized to provide compound of formula (V) wherein R^2 is hydrogen. Compound of formula (V) can be reduced to provide
 5 compound of formula (VI), which can be oxidized to provide compound of formula (VII). Compound of formula (VII) can be cyclized to provide compound of formula (VIII) wherein ring B is

[0143]

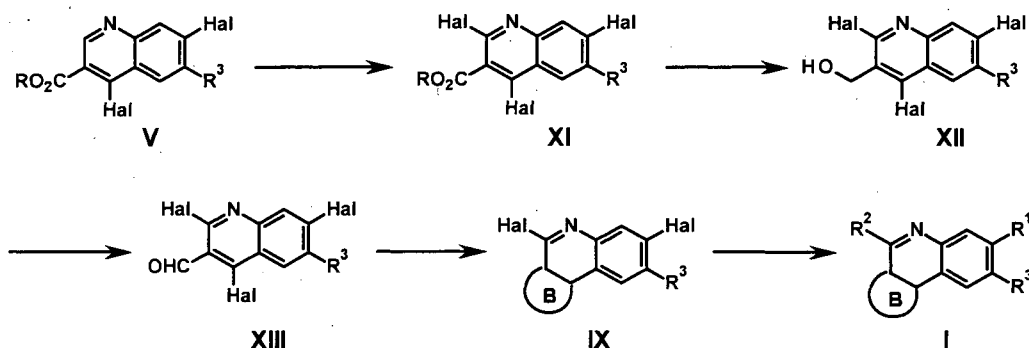


[0144]

Compound of formula (VIII) can be reacted with R^1 -LG wherein LG is a leaving group to provide compound of formula (I) wherein R^2 is hydrogen and the other symbols are as defined
 15 above. Alternatively, compound of formula (VIII) can be halogenated to provide compound of formula (IX), which can be selectively converted to compound of formula (X). Compound of formula (X) can be reacted with nucleophile R^2 -Y (e.g., R^2 -NH₂, R^2 -OH, Zn(CN)₂ etc.) to provide compound of formula (I) wherein
 20 R^2 is other than hydrogen and the other symbols are as defined above. In this method, compound (II) and compound (III) used as starting materials may be a commercially available product, or can also be produced according to a method known per se or a method analogous thereto.

25 [0145]

Scheme-II (Scheme-3 in Example)

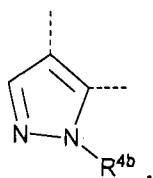


[0146]

wherein Hal is halogen, and R is C₁₋₆ alkyl.

Compound of formula (V) as obtained in Scheme I can be
 5 halogenated to provide compound of formula (XI), which can be
 reduced to provide compound of formula (XII). Compound of
 formula (XII) can be oxidized to provide compound of formula
 (XIII). Compound of formula (XIII) can be cyclized to provide
 compound of formula (IX) wherein ring B is

10 [0147]

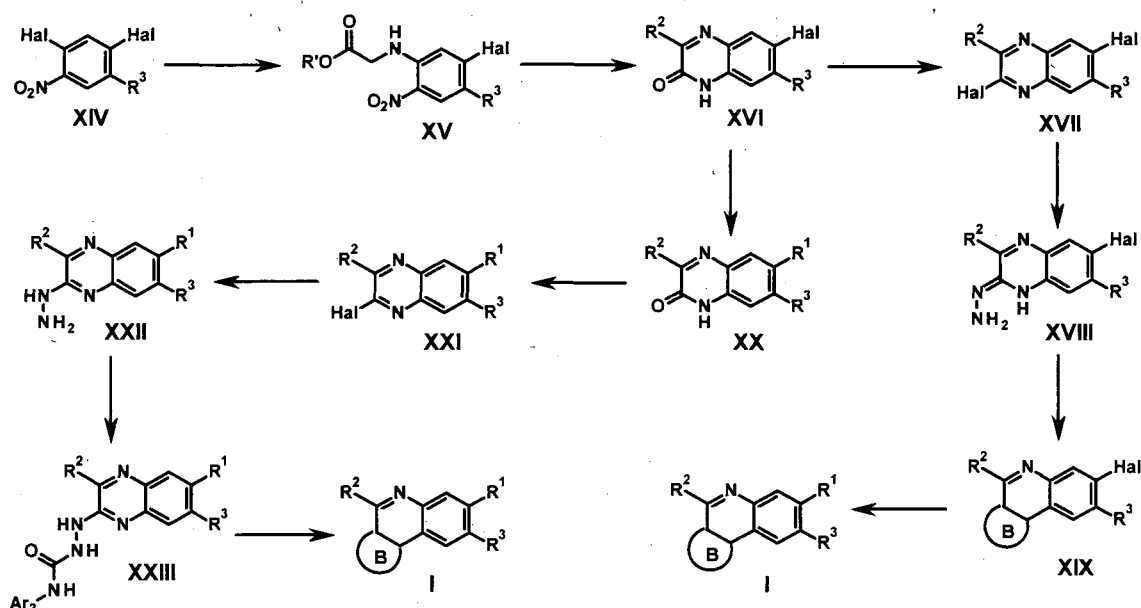


[0148]

Compound of formula (IX) can be reacted with R¹-LG
 wherein LG is as defined above, and reacted with R²-Y to
 15 provide compound of formula (I) wherein R² is other than
 hydrogen and the other symbols are as defined above.

[0149]

Scheme-III (Schemes-4, 6, 7 and 8 in Example)

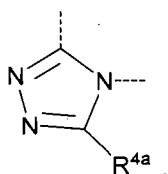


[0150]

wherein Hal is halogen, and R' is C₁₋₆ alkyl.

Compound of formula (XIV) can be reacted with glycine
 5 ester to provide compound of formula (XV), which can be
 cyclized to provide compound of formula (XVI) wherein R² is
 hydrogen. Compound of formula (XVI) can be halogenated to
 provide compound of formula (XVII), which can be converted to
 compound of formula (XVIII). Compound of formula (XVIII) can
 10 be cyclized to provide compound of formula (XIX) wherein ring
 B is

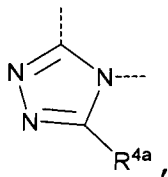
[0151]



[0152]

15 Compound of formula (XIX) can be reacted with R¹-LG
 wherein LG is as defined above to provide compound of formula
 (I) wherein R² is hydrogen and the other symbols are as defined
 above. Alternatively, compound of formula (XVI) can be reacted
 with R¹-LG wherein LG is as defined above to provide compound
 20 of formula (XX), which can be halogenated to provide compound
 of formula (XXI). Compound of formula (XXI) can be converted

to compound of formula (XXII). Compound of formula (XXII) can be converted to compound of formula (XXIII), which can be cyclized to provide compound of formula (I) wherein ring B is

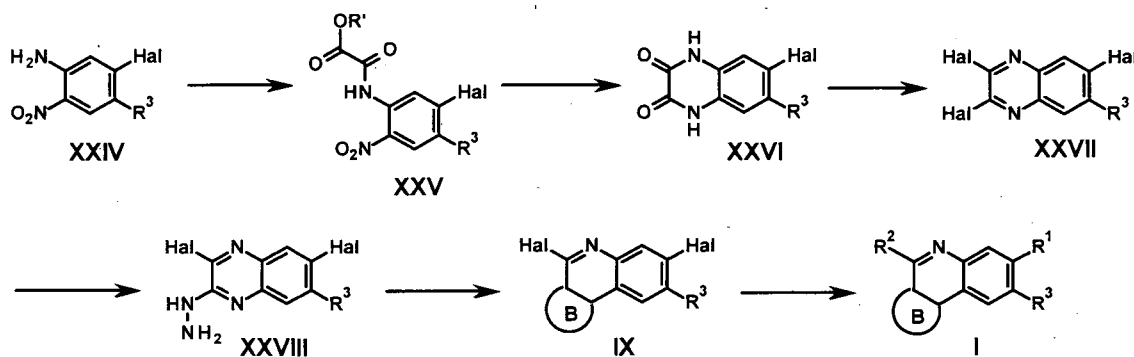


[0154]

R² is hydrogen and the other symbols are as defined above.

[0155]

Scheme-IV (Scheme-9 in Example)

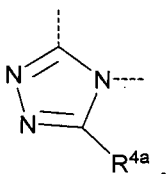


[0156]

wherein Hal is halogen, and R' is C₁₋₆ alkyl.

Compound of formula (XXIV) can be reacted with alkyl oxalyl chloride to provide compound of formula (XXV), which can be cyclized to provide compound of formula (XXVI). Compound of formula (XXVI) can be halogenated to provide compound of formula (XXVII), which can be converted to compound of formula (XXVIII). Compound of formula (XXVIII) can be cyclized to provide compound of formula (IX) wherein ring B is

[0157]

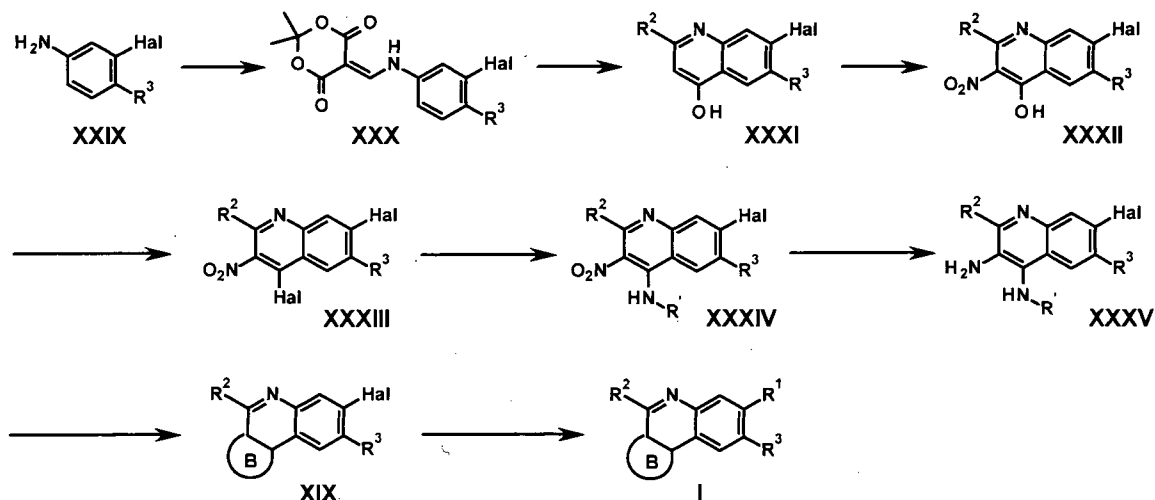


[0158]

Compound of formula (IX) can be reacted with R^1 -LG wherein LG is as defined above, and reacted with R^2 -Y to provide compound of formula (I) wherein R^2 is other than hydrogen and the other symbols are as defined above.

5 [0159]

Scheme-V (Scheme-10 in Example)

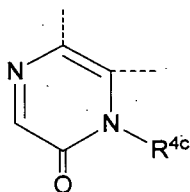


[0160]

wherein Hal is halogen.

10 Compound of formula (XXIX) can be reacted with Meldrums acid to provide compound of formula (XXX), which is cyclized to provide compound of formula (XXXI) wherein R^2 is hydrogen and the other symbols are as defined above. Compound of formula (XXXI) can be nitrated to provide compound of formula
 15 (XXXII), which can be halogenated to provide compound of formula (XXXIII). Compound of formula (XXXIII) can be reacted with amine $R'NH_2$ to provide compound of formula (XXXIV), which can be reduced to provide compound of formula (XXXV). Compound of formula (XXXV) can be cyclized to provide compound of
 20 formula (XIX) wherein ring B is

[0161]



[0162]

Compound of formula (XIX) can be reacted with R^1 -Y wherein Y is as defined above to provide compound of formula (I) wherein R^2 is hydrogen and the other symbols are as defined above.

[0163]

5 Compound (I) contains a stereoisomer depending on the kind of a substituent, and each stereoisomer and a mixture thereof are encompassed in the present invention.

Compound (I) may be a hydrate or a non-hydrate.

When desired, compound (I) can be synthesized by
10 performing deprotection reaction, acylation reaction, alkylation reaction, hydrogenation reaction, oxidation reaction, reduction reaction, reaction of carbon chain extension, substituent exchange reaction singly or two or more thereof in combination.

15 When the objective product is obtained as a free form by the above-mentioned reaction, it can be converted to a salt according to a conventional method, or when the objective product is obtained as a salt, it can be converted to a free form or other salt according to a conventional method. The
20 thus-obtained compound (I) can also be isolated and purified from a reaction mixture according to a known method such as phase transfer, concentration, solvent extraction, distillation, crystallization, recrystallization, chromatography and the like.

25 When compound (I) contains a configurational isomer, a diastereomer, a conformer and the like, each can be isolated according to the above-mentioned separation and purification methods, if desired. In addition, when compound (I) is racemic, d-form and l-form can be isolated according to a conventional
30 optical resolution.

[0164]

In each of the above-mentioned reactions, when the compound has a functional group such as an amino group, a hydroxy group or a carboxyl group, the reaction can be carried
35 out after a protecting group generally used in peptide

chemistry and the like is introduced into these groups. By removing the protecting group as necessary after the reaction, the objective compound can be obtained.

Examples of the protecting group include formyl, C₁₋₆ alkyl-carbonyl (e.g., acetyl, propionyl etc.), phenylcarbonyl, C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl etc.), phenyloxycarbonyl, C₇₋₁₀ aralkyloxy-carbonyl (e.g., benzyloxycarbonyl etc.), trityl, phthaloyl and the like, each of which is optionally substituted. Examples of the substituent include a halogen atom (e.g., fluorine, chlorine, bromine, iodine etc.), C₁₋₆ alkyl-carbonyl (e.g., acetyl, propionyl, valeryl etc.), nitro and the like. The number of substituents is, for example, 1 to 3.

The removal method of the protecting group can be carried out according to a method known per se, and for example, a method using acid, base, ultraviolet rays, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate and the like, a reduction method, and the like can be employed.

[0165]

The thus-obtained compound (I), other reaction intermediate therefor and starting materials thereof can be isolated and purified from a reaction mixture according to a method known per se, for example, extraction, concentration, neutralization, filtration, distillation, recrystallization, column chromatography, thin layer chromatography, preparative high performance liquid chromatography (preparative HPLC), moderate-pressure preparative liquid chromatography (moderate-pressure preparative LC) and the like.

[0166]

A salt of compound (I) can be produced according to a method known per se. For example, when compound (I) is a basic compound, it can be produced by adding an inorganic acid or organic acid, or when compound (I) is an acidic compound, by adding an organic base or inorganic base.

When compound (I) contains an optical isomer, each optical isomer and a mixture thereof are encompassed in the scope of the present invention, and these isomers can be subjected to optical resolution or can be produced
5 respectively, according to a method known per se, if desired.

When compound (I) contains a configurational isomer, a diastereomer, a conformer and the like, each can be isolated according to the above-mentioned separation and purification methods, if desired. In addition, when compound (I) is racemic,
10 S-form and R-form can be isolated according to a conventional optical resolution.

When compound (I) contains a stereoisomer, each isomer and a mixture thereof are encompassed in the present invention.
[0167]

15 Compound (I) may be a prodrug, and the prodrug of compound (I) refers to a compound which is converted to compound (I) as a result of a reaction with an enzyme, gastric acid, etc. under physiological conditions *in vivo*, thus a compound that undergoes enzymatic oxidation, reduction,
20 hydrolysis etc. to convert to compound (I) and a compound that undergoes hydrolysis and the like by gastric acid, etc. to convert to compound (I).

[0168]

Examples of the prodrug for compound (I) include
25 (1) a compound obtained by subjecting an amino group in compound (I) to acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting an amino group in compound (I) to eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation,
30 tetrahydrofurylation, pyrrolidylmethylation, pivaloyloxymethylation, tert-butylation, ethoxycarbonylation, tert-butoxycarbonylation, acetylation, cyclopropylcarbonylation and the like);

(2) a compound obtained by subjecting a hydroxy group in
35 compound (I) to acylation, alkylation, phosphorylation or

boration (e.g., a compound obtained by subjecting a hydroxy group in compound (I) to acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation or dimethylaminomethylcarbonylation and the like);

5 (3) a compound obtained by subjecting a carboxyl group in compound (I) to esterification or amidation (e.g., a compound obtained by subjecting a carboxyl group in compound (I) to ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification,

10 pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification or methylamidation and the like) and the like. Any of these compounds can be

15 produced from compound (I) according to a method known *per se*. [0169]

A prodrug of compound (I) may also be one which is converted to compound (I) under physiological conditions as described in "IYAKUHIN no KAIHATSU (Development of

20 Pharmaceuticals)", Vol. 7, Design of Molecules, p. 163-198, Published by HIROKAWA SHOTEN (1990). [0170]

In the present specification, compound (I) and a prodrug thereof are sometimes collectively abbreviated as "the

25 compound of the present invention". [0171]

When compound (I) has isomers such as optical isomer, stereoisomer, positional isomer, rotamer and the like, such isomers and a mixture thereof are also encompassed in compound

30 (I). For example, when compound (I) has optical isomers, an optical isomer resolved from this compound is also encompassed in compound (I). These isomers can be obtained as a single product according to synthesis methods or separation methods known *per se* (e.g., concentration, solvent extraction, column

35 chromatography, recrystallization, etc.).

[0172]

Compound (I) may be a crystal, and a single crystal form and a mixture of crystal forms are both encompassed in compound (I). The crystal can be produced by crystallizing
5 according to a crystallization method known *per se*.

Compound (I) may be a hydrate, a non-hydrate, a solvate or a non-solvate.

Compound (I) may be labeled with an isotope (e.g., ^3H , ^{11}C , ^{14}C , ^{18}F , ^{35}S , ^{125}I etc.) and the like.

10 Compound (I) also encompasses a deuterium conversion form wherein ^1H is converted to $^2\text{H}(\text{D})$.

Compound (I) may be a pharmaceutically acceptable cocrystal or a salt thereof. The cocrystal or a salt thereof means a crystalline substance constituted with two or more
15 special solids at room temperature, each having different physical properties (e.g., structure, melting point, melting heat, hygroscopicity, solubility and stability etc.). The cocrystal or a salt thereof can be produced according to a cocrystallization method known *per se*.

20 Compound (I) may also be used as a PET tracer.

[0173]

The compound of the present invention has low toxicity, and can be used as it is or in the form of a pharmaceutical composition by mixing with a pharmacologically acceptable
25 carrier etc. to mammals (e.g., human, mouse, rat, rabbit, dog, cat, bovine, horse, swine, monkey) as an agent for the prophylaxis or treatment of various diseases mentioned below.

[0174]

As pharmacologically acceptable carriers, various organic
30 or inorganic carrier substances conventionally used as preparation materials can be used. These are incorporated as excipient, lubricant, binder and disintegrant for solid preparations, or solvent, solubilizing agent, suspending agent, isotonicity agent, buffer and soothing agent for liquid
35 preparations, and the like, and preparation additives such as

preservative, antioxidant, colorant, sweetening agent and the like can be added as necessary.

[0175]

When the compound of the present invention is used as an ointment, the ointment is prepared by mixing the compound of the present invention with a general ointment base so that the concentration is adjusted to about 0.001 to 3% (W/W), preferably about 0.01 to 1% (W/W). The preparation of ointment preferably comprises a powderization step of the compound of the present invention, and a sterilization step of the formulation. The ointment is administered once to four times a day depending on condition of the patient.

[0176]

Examples of the ointment base include purified lanolin, white vaseline, macrogol, plastibase, liquid paraffin and the like.

[0177]

Preferable examples of the excipient include lactose, sucrose, D-mannitol, D-sorbitol, starch, gelatinated starch, dextrin, crystalline cellulose, low-substituted hydroxypropylcellulose, sodium carboxymethylcellulose, gum arabic, pullulan, light anhydrous silicic acid, synthesis aluminum silicate and magnesium alumino metasilicate.

[0178]

Preferable examples of the lubricant include magnesium stearate, calcium stearate, talc and colloidal silica.

[0179]

Preferable examples of the binder include gelatinated starch, sucrose, gelatin, gum arabic, methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, crystalline cellulose, sucrose, D-mannitol, trehalose, dextrin, pullulan, hydroxypropylcellulose, hydroxypropylmethylcellulose and polyvinylpyrrolidone.

[0180]

Preferable examples of the disintegrant include lactose,

sucrose, starch, carboxymethylcellulose, calcium carboxymethylcellulose, croscarmellose sodium, sodium carboxymethyl starch, light anhydrous silicic acid and low-substituted hydroxypropylcellulose.

5 [0181]

Preferable examples of the solvent include water for injection, physiological brine, Ringer's solution, alcohol, propylene glycol, polyethylene glycol, sesame oil, corn oil, olive oil and cottonseed oil.

10 [0182]

Preferable examples of the solubilizing agents include polyethylene glycol, propylene glycol, D-mannitol, trehalose, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, sodium

15 salicylate and sodium acetate.

[0183]

Preferable examples of the suspending agent include surfactants such as stearyltriethanolamine, sodium lauryl sulfate, lauryl aminopropionate, lecithin, benzalkonium

20 chloride, benzethonium chloride, glycerol monostearate and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, sodium carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the like; polysorbates, and

25 polyoxyethylene hydrogenated castor oil.

[0184]

Preferable examples of the isotonicity agent include sodium chloride, glycerol, D-mannitol, D-sorbitol and glucose.

[0185]

30 Preferable examples of the buffer include buffers such as phosphate, acetate, carbonate, citrate and the like.

Preferable examples of the soothing agent include benzyl alcohol.

[0186]

35 Preferable examples of the preservative include p-

oxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

Preferable examples of the antioxidant include sulfite and ascorbate.

5 [0187]

Preferable examples of the colorant include aqueous water-soluble food tar colors (e.g., food colors such as Food Color Red Nos. 2 and 3, Food Color Yellow Nos. 4 and 5, Food Color Blue Nos. 1 and 2 and the like), water insoluble lake
10 dyes (e.g., aluminum salt of the above-mentioned water-soluble food tar color) and natural dyes (e.g., β -carotene, chlorophyll, ferric oxide red).

[0188]

Preferable examples of the sweetening agent include
15 saccharin sodium, dipotassium glycyrrhizinate, aspartame and stevia.

[0189]

Examples of the dosage form of the pharmaceutical composition include oral preparations such as tablet
20 (including sugar-coated tablet, film-coated tablet, sublingual tablet, orally disintegrating tablet), capsules (including soft capsule, microcapsule), granule, powder, troche, syrup, emulsion, suspension, films (e.g., orally disintegrable films) and the like; and parenteral agents such as injection (e.g.,
25 subcutaneous injection, intravenous injection, intramuscular injection, intraperitoneal injection, drip infusion), external preparations (e.g., dermal preparation, ointment), suppository (e.g., rectal suppository, vaginal suppository), pellet, nasal preparation, pulmonary preparation (inhalant), eye drop and
30 the like.

These can be respectively safely administered orally or parenterally (e.g., topically, rectally, intravenously administered).

[0190]

35 These preparations may be a release control preparation

(e.g., sustained-release microcapsule) such as an immediate-release preparation, a sustained-release preparation and the like.

[0191]

5 The pharmaceutical composition can be produced according to a method conventionally used in the field of pharmaceutical formulation, for example, the method described in the Japanese Pharmacopoeia, and the like.

[0192]

10 While the content of the compound of the present invention in the pharmaceutical composition varies depending on the dosage form, dose of the compound of the present invention and the like, it is for example, about 0.1 to 100 wt%.

15 [0193]

During production of an oral preparation, coating may be applied as necessary for the purpose of masking of taste, enteric property or durability.

[0194]

20 Examples of the coating base to be used for coating include sugar coating base, water-soluble film coating base, enteric film coating base and sustained-release film coating base.

[0195]

25 As the sugar coating base, sucrose is used. Moreover, one or more kinds selected from talc, precipitated calcium carbonate, gelatin, gum arabic, pullulan, carnauba wax and the like may be used in combination.

[0196]

30 Examples of the water-soluble film coating base include cellulose polymers such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, methylhydroxyethyl cellulose etc.; synthetic polymers such as polyvinylacetal diethylaminoacetate, aminoalkyl methacrylate
35 copolymer E [Eudragit E (trade name)], polyvinylpyrrolidone

etc.; and polysaccharides such as pullulan etc.

[0197]

Examples of the enteric film coating base include cellulose polymers such as hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, carboxymethylethyl cellulose, cellulose acetate phthalate etc.; acrylic polymers such as methacrylic acid copolymer L [Eudragit L (trade name)], methacrylic acid copolymer LD [Eudragit L-30D55 (trade name)], methacrylic acid copolymer S [Eudragit S (trade name)] etc.; and naturally occurring substances such as shellac etc.

[0198]

Examples of the sustained-release film coating base include cellulose polymers such as ethyl cellulose etc.; and acrylic polymers such as aminoalkyl methacrylate copolymer RS [Eudragit RS (trade name)], ethyl acrylate-methyl methacrylate copolymer suspension [Eudragit NE (trade name)] etc.

[0199]

The above-mentioned coating bases may be used after mixing with two or more kinds thereof at appropriate ratios. For coating, for example, a light shielding agent such as titanium oxide, red ferric oxide and the like can be used.

[0200]

The compound of the present invention shows low toxicity (e.g., acute toxicity, chronic toxicity, genetic toxicity, reproductive toxicity, cardiotoxicity, carcinogenicity) and a few side effects. Therefore, it can be used as an agent for the prophylaxis or treatment or a diagnostic of various diseases in a mammal (e.g., human, bovine, horse, dog, cat, monkey, mouse, rat).

[0201]

Since the compound of the present invention have superior BET family protein inhibitory action, they are also useful as safe medicaments based on such action.

For example, the medicament of the present invention

containing the compound of the present invention can be used for a mammal (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey, human etc.) as an agent for the prophylaxis or treatment of autoimmune diseases and/or
5 inflammatory diseases, specifically, the diseases described in (1) - (6) below.

[0202]

(1) inflammatory diseases (e.g., acute pancreatitis, chronic pancreatitis, asthma, adult respiratory distress syndrome,
10 chronic obstructive pulmonary disease (COPD), inflammatory bone disease, inflammatory pulmonary disease, inflammatory bowel disease, celiac disease, hepatitis, systemic inflammatory response syndrome (SIRS), postoperative or posttraumatic inflammation, pneumonia, nephritis, meningitis,
15 cystitis, pharyngolaryngitis, gastric mucosal injury, meningitis, spondylitis, arthritis, dermatitis, chronic pneumonia, bronchitis, pulmonary infarction, silicosis, pulmonary sarcoidosis etc.);

(2) autoimmune diseases (e.g., psoriasis, rheumatoid arthritis,
20 inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis etc.), Sjogren's syndrome, Behcet's disease, multiple sclerosis, systemic lupus erythematosus, ankylopoietic spondylarthritis, polymyositis, dermatomyositis (DM), polyarteritis nodosa (PN), mixed connective tissue disease
25 (MCTD), scleroderma, profundus lupus erythematosus, chronic thyroiditis, Graves' disease, autoimmune gastritis, type I and type II diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, graft versus host disease,
30 Addison's disease, abnormal immunoresponse, arthritis, dermatitis, radiodermatitis, pulmonary fibrosis (e.g., idiopathic pulmonary fibrosis etc.) etc.) (especially, psoriasis, rheumatoid arthritis, inflammatory bowel disease, Sjogren's syndrome, Behcet's disease, multiple sclerosis,
35 systemic lupus erythematosus, graft versus host disease,

pulmonary fibrosis etc.);

(3) osteoarticular degenerative diseases (e.g., rheumatoid arthritis, osteoporosis, osteoarthritis etc.);

(4) neoplastic diseases [e.g., malignant tumor, angiogenesis
5 glaucoma, infantile hemangioma, multiple myeloma, acute
myeloblastic leukemia, chronic sarcoma, multiple myeloma,
chronic myelogenous leukemia, metastasis melanoma, Kaposi's
sacroma, vascular proliferation, cachexia, metastasis of the
breast cancer, cancer (e.g., colorectal cancer (e.g., familial
10 colorectal cancer, hereditary nonpolyposis colorectal cancer,
gastrointestinal stromal tumor etc.), lung cancer (e.g., non-
small cell lung cancer, small cell lung cancer, malignant
mesothelioma etc.), mesothelioma, pancreatic cancer (e.g.,
pancreatic duct cancer etc.), gastric cancer (e.g., mucinous
15 adenocarcinoma, adenosquamous carcinoma etc.), papillary
adenocarcinoma, breast cancer (e.g., invasive ductal carcinoma,
ductal carcinoma in situ, inflammatory breast cancer etc.),
ovarian cancer (e.g., ovarian epithelial carcinoma,
extragonadal germ cell tumor, ovarian germ cell tumor, ovarian
20 low malignant potential tumor etc.), prostate cancer (e.g.,
hormone-dependent prostate cancer, non-hormone dependent
prostate cancer etc.), liver cancer (e.g., primary liver
cancer, extrahepatic bile duct cancer etc.), thyroid cancer
(e.g., medullary thyroid carcinoma etc.), kidney cancer (e.g.,
25 renal cell carcinoma, transitional cell carcinoma in kidney
and urinary duct etc.), uterine cancer, brain tumor (e.g.,
pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma,
anaplastic astrocytoma etc.), melanoma, sarcoma, urinary
bladder cancer, hematologic cancer and the like including
30 multiple myeloma, hypophyseal adenoma, glioma, acoustic
neurinoma, retinoblastoma, pharyngeal cancer, laryngeal cancer,
cancer of the tongue, thymoma, esophagus cancer, duodenal
cancer, colorectal cancer, rectal cancer, hepatoma, pancreatic
endocrine tumor, bile duct cancer, gallbladder cancer, penile
35 cancer, urinary duct cancer, testis tumor, vulvar cancer,

cervix cancer, endometrial cancer, uterus sarcoma, cholelithiasis, cholelithic disease, vaginal cancer, skin cancer, fungoid mycosis, basal cell tumor, soft tissue sarcoma, malignant lymphoma, Hodgkin's disease, myelodysplastic syndrome, acute lymphocytic leukemia, 5 chronic lymphocytic leukemia, adult T cell leukemia, chronic bone marrow proliferative disease, pancreatic endocrine tumor, fibrous histiocytoma, leiomyosarcoma, rhabdomyosarcoma, cancer of unknown primary etc.);

(5) cardiovascular diseases (e.g., heart disease (e.g., 10 cardiac hypertrophy, acute heart failure and chronic heart failure including congestive, cardiomyopathy, angina pectoris, myocarditis, arrhythmia, tachycardia, myocardial infarction etc.), myocardial ischemia, venous insufficiency, heart failure after myocardial infarction, hypertension, cor 15 pulmonale, arteriosclerosis including atherosclerosis (e.g., aortic aneurysm (e.g., thoracoabdominal aortic aneurysm etc.), coronary atherosclerosis, cerebral atherosclerosis, peripheral arterial disease, arteriosclerosis obliterans, chronic arterial occlusion etc.), intervention (e.g., percutaneous 20 transluminal coronary angioplasty, stent placement, coronary angiography, intravascular ultrasound, thrombolysis therapy etc.), vascular hypertrophy or vascular occlusion and organ dysfunction after heart transplant, vascular reocclusion and restenosis after bypass surgery etc.);

(6) hormone-dependent diseases (e.g., sex hormone-dependent 25 cancers (e.g., prostate cancer, uterine cancer, breast cancer, pituitary tumor etc.), prostatic hyperplasia, endometriosis, uterine fibroid, precocious puberty, dysmenorrhea, amenorrhea, premenstrual syndrome, polycystic ovary syndrome etc.).

30 [0203]

The medicament of the present invention can be preferably used as an agent for the prophylaxis or treatment of rheumatoid arthritis, multiple sclerosis, idiopathic pulmonary fibrosis, psoriasis, atopic dermatitis, inflammatory bowel 35 disease, Sjogren's syndrome, Behcet's disease, systemic lupus

erythematosus, cancer and the like.

[0204]

Here, the above-mentioned "prophylaxis" of a disease means, for example, administration of a medicament containing
5 the compound of the present invention to patients who are expected to have a high risk of the onset due to some factor relating to the disease but have not developed the disease or patients who have developed the disease but do not have a subjective symptom, or administration of a medicament
10 containing the compound of the present invention to patients who are feared to show recurrence of the disease after treatment of the disease.
and the like.

[0205]

15 The dose of the compound of the present invention varies depending on the administration subject, route of administration, target disease, symptoms, etc. For example, when it is administered orally to an adult patient (body weight 60 kg), its dose is about 0.01 to 100 mg/kg body weight
20 per dose, preferably 0.05 to 30 mg/kg body weight per dose, more preferably 0.1 to 10 mg/kg body weight per dose and this amount is desirably administered in 1 to 3 portions daily.

[0206]

For the prophylaxis or treatment of various diseases, the
25 compound of the present invention can also be used together with other drugs. In the following, a medicament to be used when the compound of the present invention is used together with other drug is referred to as "the combination agent of the present invention".

30 For example, when the compound of the present invention is used as a BET family protein inhibitor, it can be used in combination with the following drugs.

[0207]

(1) non-steroidal anti-inflammatory drug (NSAIDs)

35 (i) Classical NSAIDs

- alcofenac, aceclofenac, sulindac, tolmetin, etodolac,
fenoprofen, thiaprofenic acid, meclofenamic acid, meloxicam,
tenoxicam, lornoxicam, nabumeton, acetaminophen, phenacetin,
ethenzamide, sulpyrine, antipyrine, migrenin, aspirin,
5 mefenamic acid, flufenamic acid, diclofenac sodium, loxoprofen
sodium, phenylbutazone, indomethacin, ibuprofen, ketoprofen,
naproxen, oxaprozin, flurbiprofen, fenbufen, pranoprofen,
flocatafenine, piroxicam, epirizole, tiaramide hydrochloride,
zaltoprofen, gabexate mesylate, camostat mesylate, ulinastatin,
10 colchicine, probenecid, sulfinpyrazone, benzbromarone,
allopurinol, sodium aurothiomalate, hyaluronate sodium, sodium
salicylate, morphine hydrochloride, salicylic acid, atropine,
scopolamine, morphine, pethidine, levorphanol, oxymorphone or
a salt thereof and the like.
- 15 (ii) cyclooxygenase inhibitor (COX-1 selective inhibitor, COX-
2 selective inhibitor etc.)

salicylic acid derivatives (e.g., celecoxib, aspirin),
etoricoxib, valdecoxib, diclofenac, indomethacin, loxoprofen
and the like.

- 20 (iii) nitric oxide-releasing NSAIDs

(iv) JAK inhibitor

tofacitinib, ruxolitinib and the like.

[0208]

(2) disease-modifying anti-rheumatic drugs (DMARDs)

- 25 (i) Gold preparation

auranofin and the like.

(ii) penicillamine

D-penicillamine and the like.

(iii) aminosalicyclic acid preparation

- 30 sulfasalazine, mesalazine, olsalazine, balsalazide and
the like.

(iv) antimalarial drug

chloroquine and the like.

(v) pyrimidine synthesis inhibitor

- 35 leflunomide and the like.

- (vi) prograf
[0209]
(3) anti-cytokine drug
(I) protein drug
- 5 (i) TNF inhibitor
etanercept, infliximab, adalimumab, certolizumab pegol, golimumab, PASSTNF- α , soluble TNF- α receptor, TNF- α binding protein, anti-TNF- α antibody and the like.
(ii) interleukin-1 inhibitor
10 anakinra (interleukin-1 receptor antagonist), soluble interleukin-1 receptor and the like.
(iii) interleukin-6 inhibitor
tocilizumab (anti-interleukin-6 receptor antibody), anti-interleukin-6 antibody and the like.
- 15 (iv) interleukin-10 drug
interleukin-10 and the like.
(v) interleukin-12/23 inhibitor
ustekinumab, briakinumab (anti-interleukin-12/23 antibody) and the like.
- 20 (II) non-protein drug
(i) MAPK inhibitor
BMS-582949 and the like.
(ii) gene modulator
inhibitor of molecule involved in signal transduction,
25 such as NF- κ , NF- κ B, IKK-1, IKK-2, AP-1 and the like, and the like.
(iii) cytokine production inhibitor
iguratimod, tetomilast and the like.
(iv) TNF- α converting enzyme inhibitor
30 (v) interleukin-1 β converting enzyme inhibitor
VX-765 and the like.
(vi) interleukin-6 antagonist
HMPL-004 and the like.
(vii) interleukin-8 inhibitor
35 IL-8 antagonist, CXCR1 & CXCR2 antagonist, reparixin and

the like.

(viii) chemokine antagonist

CCR9 antagonist (CCX-282, CCX-025), MCP-1 antagonist and the like.

5 (ix) interleukin-2 receptor antagonist

denileukin, diftix and the like.

(x) therapeutic vaccines

TNF- α vaccine and the like.

(xi) gene therapy drug

10 gene therapy drugs aiming at promoting the expression of gene having an anti-inflammatory action such as interleukin-4, interleukin-10, soluble interleukin-1 receptor, soluble TNF- α receptor and the like.

(xii) antisense compound

15 ISIS 104838 and the like.

[0210]

(4) integrin inhibitor

natalizumab, vedolizumab, AJM300, TRK-170, E-6007 and the like.

20 (5) immunomodulator (immunosuppressant)

methotrexate, cyclophosphamide, MX-68, atiprimod dihydrochloride, BMS-188667, CKD-461, rimexolone, cyclosporine, tacrolimus, gusperimus, azathiopurine, antilymphocyte serum, freeze-dried sulfonated normal immunoglobulin, erythropoietin,
25 colony stimulating factor, interleukin, interferon and the like.

(6) steroid

dexamethasone, hexestrol, methimazole, betamethasone, triamcinolone, triamcinolone acetonide, fluocinonide,
30 fluocinolone acetonide, predonisolone, methylpredonisolone, cortisone acetate, hydrocortisone, fluorometholone, beclomethasone dipropionate, estriol and the like.

(7) angiotensin converting enzyme inhibitor

enalapril, captopril, ramipril, lisinopril, cilazapril,
35 perindopril and the like.

[0211]

(8) angiotensin II receptor antagonist

candesartan, candesartan cilexetil, azilsartan,
azilsartan medoxomil, valsartan, irbesartan, olmesartan,
5 eprosartan and the like.

(9) diuretic drug

hydrochlorothiazide, spironolactone, furosemide,
indapamide, bendrofluazide, cyclopenthiazide and the like.

(10) cardiotonic drug

10 digoxin, dobutamine and the like.

(11) β receptor antagonist

carvedilol, metoprolol, atenolol and the like.

(12) Ca sensitizer

MCC-135 and the like.

15 (13) Ca channel antagonist

nifedipine, diltiazem, verapamil and the like.

(14) anti-platelet drug, anticoagulator

heparin, aspirin, warfarin and the like.

(15) HMG-CoA reductase inhibitor

20 atorvastatin, simvastatin and the like.

[0212]

(16) contraceptive

(i) sex hormone or derivatives thereof

gestagen or a derivative thereof (progesterone, 17 α -
25 hydroxy progesterone, medroxyprogesterone, medroxyprogesterone
acetate, norethisterone, norethisterone enanthate,
norethindrone, norethindrone acetate, norethynodrel,
levonorgestrel, norgestrel, ethynodiol diacetate, desogestrel,
norgestimate, gestodene, progestin, etonogestrel, drospirenone,
30 dienogest, trimegestone, nestorone, chlormadinone acetate,
mifepristone, nomegestrol acetate, Org-30659, TX-525, EMM-
310525) or a combination agent of a gestagen or a derivative
thereof and an estrogen or a derivative thereof (estradiol,
estradiol benzoate, estradiol cypionate, estradiol
35 dipropionate, estradiol enanthate, estradiol hexahydrobenzoate,

estradiol phenylpropionate, estradiol undecanoate, estradiol valerate, estrone, ethinylestradiol, mestranol) and the like.

(ii) antiestrogen

ormeloxifene, mifepristone, Org-33628 and the like.

5 (iii) spermatocide

usher cell and the like.

[0213]

(17) antibacterial agent

(i) sulfa drug

10 sulfamethizole, sulfisoxazole, sulfamonomethoxine, sulfamethizole, salazosulfapyridine, silver sulfadiazine and the like.

(ii) quinolone antibacterial agent

nalidixic acid, piperimidic acid trihydrate, enoxacin,
15 norfloxacin, ofloxacin, tosufloxacin tosylate, ciprofloxacin hydrochloride, lomefloxacin hydrochloride, sparfloxacin, fleroxacin and the like.

(iii) antituberculous

isoniazid, ethambutol (ethambutol hydrochloride), p-
20 aminosalicyclic acid (calcium p-aminosalicylate), pyrazinamide, ethionamide, prothionamide, rifampicin, streptomycin sulfate, kanamycin sulfate, cycloserine and the like.

(iv) antiacidfast bacterium drug

diaphenylsulfone, rifampicin and the like.

25 (v) antiviral drug

idoxuridine, acyclovir, vidarabine, gancyclovir and the like.

(vi) anti-HIV agent

zidovudine, didanosine, zalcitabine, indinavir sulfate
30 ethanolate, ritonavir and the like.

(vii) antispirochete

(viii) antibiotic

tetracycline hydrochloride, ampicillin, piperacillin, gentamicin, dibekacin, kanamycin, lividomycin, tobramycin,
35 amikacin, fradiomycin, sisomicin, tetracycline,

oxytetracycline, rolitetracycline, doxycycline, ampicillin,
piperacillin, ticarcillin, cephalothin, cephalirin,
cephaloridine, cefaclor, cephalixin, cefroxadine, cefadroxil,
cefamandole, cefotoam, cefuroxime, cefotiam, cefotiam hexetil,
5 cefuroxime axetil, cefdinir, cefditoren pivoxil, ceftazidime,
cefpiramide, cefsulodin, cefmenoxime, cefpodoxime proxetil,
cefpirome, ceftazopran, cefepime, cefsulodin, cefmenoxime,
cefmetazole, cefminox, cefoxitin, cefbuperazone, latamoxef,
flomoxef, cefazolin, cefotaxime, cefoperazone, ceftizoxime,
10 moxalactam, thienamycin, sulfazecin, aztreonam or a salt a
salt thereof, griseofulvin, lankacidin-group [Journal of
Antibiotics (J. Antibiotics), 38, 877-885(1985)], azole
compound [2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-
methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-(2,2,3,3-
15 tetrafluoropropoxy)phenyl]-3(2H,4H)-1,2,4-triazolone,
fluconazole, itraconazole and the like] and the like.

[0214]

(18) antifungal agent

(i) polyethylene antibiotic

20 amphotericin B, nystatin, trichomycin and the like.

(ii) griseofulvin, pyrrolnitrin and the like.

(iii) cytosine metabolism antagonist

flucytosine and the like.

(iv) imidazole derivative

25 econazole, clotrimazole, miconazole nitrate, bifonazole,
croconazole and the like.

(v) triazole derivative

fluconazole, itraconazole and the like.

(vi) thiocarbamic acid derivative

30 trinaphthol and the like.

(19) antiprotozoal agent

metronidazole, tinidazole, diethylcarbamazine citrate,
quinine hydrochloride, quinine sulfate and the like.

[0215]

35 (20) antitussive and expectorant drug

ephedrine hydrochloride, noscapine hydrochloride, codeine phosphate, dihydrocodeine phosphate, isoproterenol hydrochloride, ephedrine hydrochloride, methylephedrine hydrochloride, noscapine hydrochloride, alloclamide,
5 chlophedianol, picoperidamine, cloperastine, protokylol, isoproterenol, salbutamol, terbutaline, oxymetebanol, morphine hydrochloride, dextromethorfan hydrobromide, oxycodone hydrochloride, dimemorphan phosphate, tipepidine hibenzate, pentoxyverine citrate, clofedanol hydrochloride, benzonatate,
10 guaifenesin, bromhexine hydrochloride, ambroxol hydrochloride, acetylcysteine, ethyl cysteine hydrochloride, carbocysteine and the like.

(21) sedative

chlorpromazine hydrochloride, atropine sulfate,
15 phenobarbital, barbital, amobarbital, pentobarbital, thiopental sodium, thiamylal sodium, nitrazepam, estazolam, flurazepam, haloxazolam, triazolam, flunitrazepam, bromovalerylurea, chloral hydrate, triclofos sodium and the like.

20 [0216]

(22) anesthetic

(I) local anesthetic

cocaine hydrochloride, procaine hydrochloride, lidocaine, dibucaine hydrochloride, tetracaine hydrochloride, mepivacaine
25 hydrochloride, bupivacaine hydrochloride, oxybuprocaine hydrochloride, ethyl aminobenzoate, oxethazaine and the like.

(II) general anesthetic

(i) inhalation anesthetic

ether, halothane, nitrous oxide, isoflurane, enflurane
30 and the like.

(ii) intravenous anesthetic

ketamine hydrochloride, droperidol, thiopental sodium, thiamylal sodium, pentobarbital and the like.

(23) antiulcer drug

35 histidine hydrochloride, lansoprazole, metoclopramide,

pirenzepine, cimetidine, ranitidine, famotidine, urogastrone, oxethazaine, proglumide, omeprazole, sucralfate, sulpiride, cetraxate, gefarnate, aldioxa, teprenone, prostaglandin and the like.

5 (24) antiarrhythmic agent

(i) sodium channel blocker

quinidine, procainamide, disopyramide, ajmaline, lidocaine, mexiletine, phenytoin and the like.

(ii) β -blocker

10 propranolol, alprenolol, bufetolol hydrochloride, oxprenolol, atenolol, acebutolol, metoprolol, bisoprolol, pindolol, carteolol, arotinolol hydrochloride and the like.

(iii) potassium channel blocker

amiodarone and the like.

15 (iv) calcium channel blocker

verapamil, diltiazem and the like.

[0217]

(25) hypotensive diuretic drug

hexanethonium bromide, clonidine hydrochloride,
20 hydrochlorothiazide, trichlormethiazide, furosemide, ethacrynic acid, bumetanide, mefruside, azosemide, spironolactone, potassium canrenoate, triamterene, amiloride, acetazolamide, D-mannitol, isosorbide, aminophylline and the like.

25 (26) anticoagulant

heparin sodium, sodium citrate, activated protein C, tissue factor pathway inhibitor, antithrombin III, dalteparin sodium, warfarin potassium, argatroban, gabexate, sodium citrate, ozagrel sodium, ethyl icosapentate, beraprost sodium,
30 alprostadil, ticlopidine hydrochloride, pentoxifylline, dipyridamole, tisokinase, urokinase, streptokinase and the like.

(27) tranquilizer

diazepam, lorazepam, oxazepam, chlordiazepoxide,
35 medazepam, oxazolam, cloxazolam, clotiazepam, bromazepam,

etizolam, fludiazepam, hydroxyzine and the like.

(28) antipsychotic

chlorpromazine hydrochloride, prochlorperazine,
trifluoperazine, thioridazine hydrochloride, perphenazine
5 maleate, fluphenazine enanthate, prochlorperazine maleate,
levomepromazine maleate, promethazine hydrochloride,
haloperidol, bromperidol, spiperone, reserpine, clocapramine
hydrochloride, sulpiride, zotepine and the like.

[0218]

10 (29) antitumor drug

6-O-(N-chloroacetylcarbamoyl)fumagillol, bleomycin,
methotrexate, actinomycin D, mitomycin C, daunorubicin,
adriamycin, neocarzinostatin, cytosine arabinoside,
fluorouracil, tetrahydrofuryl-5-fluorouracil, picibanil,
15 lentinan, levamisole, bestatin, azimexon, glycyrrhizin,
doxorubicin hydrochloride, aclarubicin hydrochloride,
bleomycin hydrochloride, peplomycin sulfate, vincristine
sulfate, vinblastine sulfate, irinotecan hydrochloride,
cyclophosphamide, melphalan, busulfan, thiotepa, procarbazine
20 hydrochloride, cisplatin, azathioprine, mercaptopurine,
tegafur, carmofur, cytarabine, methyltestosterone,
testosterone propionate, testosterone enanthate, mepitiostane,
fosfestrol, chlormadinone acetate, leuprorelin acetate,
buserelin acetate and the like.

25 (30) hypolipidemic drug

clofibrate, ethyl 2-chloro-3-[4-(2-methyl-2-
phenylpropoxy)phenyl]propionate [Chemical and Pharmaceutical
Bulletin (Chem. Pharm. Bull), 38, 2792-2796 (1990)],
pravastatin, simvastatin, probucol, bezafibrate, clinofibrate,
30 nicomol, cholestyramine, dextran sulfate sodium and the like.

(31) muscle relaxant

pridinol, tubocurarine, pancuronium, tolperisone
hydrochloride, chlorphenesin carbamate, baclofen,
chlormezanone, mephenesin, chlorzoxazone, eperisone,
35 tizanidine and the like.

(32) antiepileptic drug

phenytoin, ethosuximide, acetazolamide, chlordiazepoxide,
trimethadione, carbamazepine, phenobarbital, primidone,
sulthiame, sodium valproate, clonazepam, diazepam, nitrazepam
5 and the like.

[0219]

(33) antidepressant

imipramine, clomipramine, noxiptiline, phenelzine,
amitriptyline hydrochloride, nortriptyline hydrochloride,
10 amoxapine, mianserin hydrochloride, maprotiline hydrochloride,
sulpiride, fluvoxamine maleate, trazodone hydrochloride and
the like.

(34) antiallergic drug

diphenhydramine, chlorpheniramine, tripeleennamine,
15 metodilamine, clemizole, diphenylpyraline, methoxyphenamine,
sodium cromoglicate, tranilast, repirinast, amlexanox,
ibudilast, ketotifen, terfenadine, mequitazine, azelastine
hydrochloride, epinastine, ozagrel hydrochloride, pranlukast
hydrate, seratrodast and the like.

20 (35) cardiac stimulants

trans- π -oxocamphor, terephyllol, aminophylline,
etilefrine, dopamine, dobutamine, denopamine, aminophylline,
vesnarinone, amrinone, pimobendan, ubidecarenone, digitoxin,
digoxin, methyl digoxin, lanatoside C, G-strophanthin and the
25 like.

(36) vasodilator

oxyfedrine, diltiazem, tolazoline, hexobendine, bamethan,
clonidine, methyl dopa, guanabenz and the like.

(37) vasoconstrictor

30 dopamine, dobutamine denopamine and the like.

(38) hypotensive diuretic

hexanethonium bromide, pentolinium, mecamlamine,
ecarazine, clonidine, diltiazem, nifedipine and the like.

(39) therapeutic drug for diabetes

35 tolbutamide, chlorpropamide, acetohexamide, glibenclamide,

tolazamide, acarbose, epalrestat, troglitazone, glucagon, glymidine, glipizide, phenformin, buformin, metformin and the like.

[0220]

5 (40) antinarcotic

levallorphan, nalorphine, naloxone or a salt thereof and the like.

(41) liposoluble vitamins

(i) vitamin A

10 vitamin A₁, vitamin A₂ and retinol palmitate

(ii) vitamin D

vitamin D₁, D₂, D₃, D₄ and D₅

(iii) vitamin E

α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocophero dl-
15 α-tocopherol nicotinate and the like.

(iv) vitamin K

vitamin K₁, K₂, K₃ and K₄

(v) folic acid

vitamin M and the like.

20 (42) vitamin derivative

various derivatives of vitamins, for example, vitamin D₃ derivatives such as 5,6-trans-cholecalciferol, 2,5-hydroxycholecalciferol, 1-α-hydroxycholecalciferol and the like, vitamin D₂ derivatives such as 5,6-trans-ergocalciferol
25 and the like, and the like.

(43) antiasthmatic

isoprenaline hydrochloride, salbutamol sulfate, procaterol hydrochloride, terbutaline sulfate, trimetoquinol hydrochloride, tulobuterol hydrochloride, orciprenaline
30 sulfate, fenoterol hydrobromide, ephedrine hydrochloride, ipratropium bromide, oxitropium bromide, flutropium bromide, theophylline, aminophylline, sodium cromoglicate, tranilast, repirinast, amlexanox, ibudilast, ketotifen, terfenadine, mequitazine, azelastine, epinastine, ozagrel hydrochloride,
35 pranlkast hydrate, seratrodast, dexamethasone, prednisolone,

- hydrocortisone, hydrocortisone sodium succinate, beclometasone dipropionate and the like.
- (44) therapeutic agent for pollakisuria/anischuria
flavoxate hydrochloride and the like.
- 5 (45) therapeutic agent for atopic dermatitis
sodium cromoglicate and the like.
- (46) therapeutic agent for allergic rhinitis
sodium cromoglicate, chlorpheniramine maleate,
alimemazine tartrate, clemastine fumarate, homochlorcyclizine
10 hydrochloride, fexofenadine, mequitazine and the like.
- (47) hypertensor
dopamine, dobutamine, denopamine, digitoxin, digoxin,
methyldigoxin, lanatoside C, G-strophanthin and the like.
[0221]
- 15 (48) others
- (i) T cell inhibitors
- (ii) inosine monophosphate dehydrogenase (IMPDH) inhibitor
mycophenolate mofetil and the like.
- (iii) adhesion molecule inhibitor
- 20 ISIS-2302, selectin inhibitor, ELAM-1, VCAM-1, ICAM-1 and
the like.
- (iv) thalidomide
- (v) cathepsin inhibitor
- (vi) matrix metalloprotease (MMPs) inhibitor
- 25 V-85546 and the like.
- (vii) glucose-6-phosphate dehydrogenase inhibitor
- (viii) Dihydroorotate dehydrogenase (DHODH) inhibitor (ix)
phosphodiesterase IV (PDE IV) inhibitor
roflumilast, CG-1088 and the like.
- 30 (x) phospholipase A₂ inhibitor
- (xi) iNOS inhibitor
VAS-203 and the like.
- (xii) microtubule stimulating drug
paclitaxel and the like.
- 35 (xiii) microtubule inhibitor

- reumacon and the like.
- (xiv) MHC class II antagonist
- (xv) prostacyclin agonist
iloprost and the like.
- 5 (xvi) CD4 antagonist
zanolimumab and the like.
- (xvii) CD23 antagonist
- (xviii) LTB4 receptor antagonist
DW-1305 and the like.
- 10 (xix) 5-lipoxygenase inhibitor
zileuton and the like.
- (xx) cholinesterase inhibitor
galanthamine and the like.
- (xxi) tyrosine kinase inhibitor
- 15 Tyk2 inhibitor (the compounds described in WO
2010/142752) and the like.
- (xxii) cathepsin B inhibitor
- (xxiii) adenosine deaminase inhibitor
pentostatin and the like.
- 20 (xxiv) osteogenesis stimulator
- (xxv) dipeptidylpeptidase inhibitor
- (xxvi) collagen agonist
- (xxvii) capsaicin cream
- (xxviii) hyaluronic acid derivative
- 25 synvisc (hylan G-F 20), orthovisc and the like.
- (xxix) glucosamine sulfate
- (xxx) amiprilose
- (xxxi) CD-20 inhibitor
rituximab, ibritumomab, tositumomab, ofatumumab and the
30 like.
- (xxxii) BAFF inhibitor
belimumab, tabalumab, atacicept, A-623 and the like.
- (xxxiii) CD52 inhibitor
alemtuzumab and the like.
- 35 (xxxiv) IL-17 inhibitor

secukinumab (AIN-457), LY-2439821, AMG827 and the like.
(xxxv) hydroxycam, diacerein, megestrol acetate, nicergoline,
prostaglandins and the like.

[0222]

5 For combined use, the administration time of the compound
of the present invention and the concomitant drug is not
restricted, and the compound of the present invention or the
concomitant drug can be administered to an administration
subject simultaneously, or may be administered at different
10 times. The dosage of the concomitant drug may be determined
according to the dose clinically used, and can be
appropriately selected depending on an administration subject,
administration route, disease, combination and the like.

The administration form of the combined use is not
15 particularly limited, and the compound of the present
invention and a concomitant drug only need to be combined on
administration. Examples of such administration mode include
the following:

(1) administration of a single preparation obtained by
20 simultaneously processing the compound of the present
invention and the concomitant drug, (2) simultaneous
administration of two kinds of preparations of the compound of
the present invention and the concomitant drug, which have
been separately produced, by the same administration route,
25 (3) administration of two kinds of preparations of the
compound of the present invention and the concomitant drug,
which have been separately produced, by the same
administration route in a staggered manner, (4) simultaneous
administration of two kinds of preparations of the compound of
30 the present invention and the concomitant drug, which have
been separately produced, by different administration routes,
(5) administration of two kinds of preparations of the
compound of the present invention and the concomitant drug,
which have been separately produced, by different
35 administration routes in a staggered manner (e.g.,

administration in the order of the compound of the present invention and the concomitant drug, or in the reverse order) and the like.

The mixing ratio of the compound of the present invention and a concomitant drug in the combination agent of the present invention can be appropriately selected based on the subject of administration, administration route, disease and the like.

For example, while the content of the compound of the present invention in the combination agent of the present invention varies depending on the preparation form, it is generally about 0.01 - 100 wt%, preferably about 0.1 - 50 wt%, more preferably about 0.5 - 20 wt%, of the whole preparation. [0223]

The content of the concomitant drug in the combination agent of the present invention varies depending on the preparation form, and generally about 0.01 to 100% by weight, preferably about 0.1 to 50% by weight, further preferably about 0.5 to 20% by weight, of the entire preparation.

While the content of the additive such as a carrier and the like in the combination agent of the present invention varies depending on the form of a preparation, it is generally about 1 to 99.99% by weight, preferably about 10 to 90% by weight, based on the preparation.

When the compound of the present invention and the concomitant drug are separately prepared, the same content may be adopted.

The dose of the combination agent varies depending on the kind of the compound of the present invention, administration route, symptom, age of patients and the like. For example, for oral administration to patients (body weight about 60 kg) with inflammatory bowel disease (IBD), about 0.1 mg/kg body weight - about 30 mg/kg body weight, preferably about 1 mg/kg body weight - 20 mg/kg body weight, of compound (I) can be administered once to several portions per day.

The dose of the pharmaceutical composition of the present

invention as a sustained-release preparation varies depending on the kind and content of compound (I), dosage form, period of sustained drug release, subject animal of administration (e.g., mammals such as mouse, rat, hamster, guinea pig, rabbit, 5 cat, dog, bovine, horse, swine, sheep, monkey, human etc.), and administration object. For example, for application by parenteral administration, about 0.1 to about 100 mg of compound (I) needs to be released from the administered preparation per 1 week.

10 [0224]

Any amount of the concomitant drug can be adopted as long as the side effects do not cause a problem. The daily dosage in terms of the concomitant drug varies depending on the severity, age, sex, body weight, sensitivity difference of the 15 subject, administration period, interval, and nature, pharmacology, kind of the pharmaceutical preparation, kind of effective ingredient, and the like, and not particularly restricted, and the amount of a drug is, in the case of oral administration for example, generally about 0.001 to 2000 mg, 20 preferably about 0.01 to 500 mg, further preferably about 0.1 to 100 mg, per 1 kg of a mammal and this is generally administered once to 4-times, divided in a day.

When the combination agent of the present invention is administered, the compound of the present invention and the 25 concomitant drug can be administered simultaneously, or may be administered in a staggered manner. When administered at a time interval, the interval varies depending on the effective ingredient, dosage form and administration method, and, for example, when the concomitant drug is administered first, a 30 method in which the compound of the present invention is administered within time range of from 1 minute to 3 days, preferably from 10 minutes to 1 day, more preferably from 15 minutes to 1 hour, after administration of the concomitant drug is an example. When the compound of the present invention 35 is administered first, a method in which the concomitant drug

is administered within time range of from 1 minute to 1 day, preferably from 10 minutes to 6 hours, more preferably from 15 minutes to 1 hour after administration of the compound of the present invention is an example.

5 Examples

[0225]

The present invention is explained in detail in the following by referring to Preparations, Examples, Experimental Examples and Formulation Examples, which are not to be
10 construed as limitative, and the invention may be changed within the scope of the present invention.

[0226]

In the following Examples, the "room temperature" generally means about 10°C to about 35°C. The ratios indicated
15 for mixed solvents are volume mixing ratios, unless otherwise specified. % means wt%, unless otherwise specified.

[0227]

In silica gel column chromatography, basic silica gel means use of aminopropylsilane-bound silica gel. In HPLC (high
20 performance liquid chromatography), C18 means use of octadecyl-bound silica gel. The ratios of elution solvents are volume mixing ratios, unless otherwise specified.

[0228]

¹H NMR (proton nuclear magnetic resonance spectrum) was
25 measured by Fourier-transform type NMR. For the analysis, ACD/SpecManager (trade name) and the like were used. Peaks with very mild protons such as a hydroxy group, an amino group and the like are not described.

[0229]

30 MS (mass spectrum) was measured by LC/MS (liquid chromatography mass spectrometer). As ionization method, ESI (Electro Spray Ionization) method or APCI (Atmospheric Pressure Chemical Ionization) method was used. The data indicates those found. Generally, a molecular ion peak is
35 observed. In the case of a salt, a molecular ion peak or

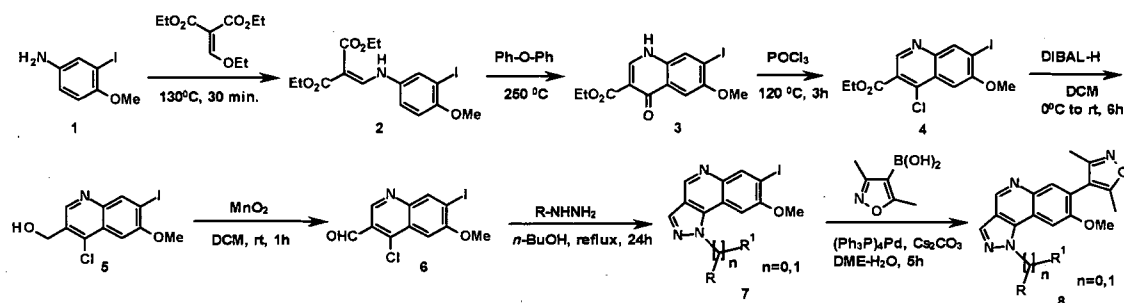
fragment ion peak of free form is generally observed.

[0230]

Experimental Procedure

[0231]

5 Scheme 1



[0232]

Diethyl 2-[(3-iodo-4-methoxy-anilino)methylene]propanedioate (2)

10 Compound **1** (2.5 g, 10 mmol) and diethyl ethoxymethylenemalonate (2.1 ml, 10.5 mmol) were mixed together, and the mixture was heated to 130°C for 30 minutes. The liberated ethanol was evaporated under reduced pressure. The reaction mixture was poured into diisopropyl ether (20 ml),
15 and the resulted precipitate was collected by filtration and then dried to give the title compound **2** (3.39 g, 80%).
¹HNMR (400 MHz, DMSO-*d*₆) δ: 10.58 (d, *J* = 14 Hz, 1H), 8.24 (d, *J* = 14.4 Hz, 1H), 7.82 (s, 1H), 7.38 (dd, *J* = 2.8, 8.8 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 4.19-4.14 (m, 2H), 4.12-4.06 (m, 2H),
20 3.79 (s, 3H), 1.25-1.19 (m, 6H).

[0233]

Ethyl 7-iodo-6-methoxy-4-oxo-1H-quinoline-3-carboxylate (3)

Compound **2** (3.9 g, 9.3 mmol) was added to preheated diphenyl ether at 260°C in portion wise for 10 minutes. The
25 reaction mixture was stirred at 260°C for 10 minutes. The black solution was cooled to room temperature, hexane was added to this reaction mixture, and the resulted precipitate was collected by filtration, washed with hexane and dried to give the title compound **3** (1.98 g, 57%).
30 ¹HNMR (400 MHz, DMSO-*d*₆) δ: 12.22 (brs, 1H), 8.50 (s, 1H), 8.11

(s, 1H), 7.51 (s, 1H), 4.21 (q, $J = 6.8$, 2H) 3.89 (s, 3H), 1.28 (t, $J = 6.8$ Hz, 3H).

[0234]

Ethyl 4-chloro-7-iodo-6-methoxy-quinoline-3-carboxylate (4)

5 Compound **3** (5.3 mmol) was dissolved in POCl₃ (5 ml), the solution was heated at 120°C for 3 hours, allowed to cool to room temperature and poured into crushed ice, and then the mixture was slowly quenched with addition of solid NaHCO₃ upto pH = 8. The mixture was extracted with ethyl acetate (3 X 50
10 ml), and the combined organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate-hexane as eluent to give the title compound **4** (85%).

¹HNMR (400 MHz, DMSO-*d*₆) δ : 8.97 (s, 1H), 8.63 (s, 1H), 7.51 (s, 1H), 3.43 (q, $J = 7.2$, 2H), 4.05 (s, 3H), 1.38 (t, $J = 7.2$ Hz, 3H).

[0235]

(4-Chloro-7-iodo-6-methoxy-3-quinolyl)methanol (5)

Compound **4** (2 g, 5.1 mmol) was dissolved in
20 dichloromethane, and then DIBAL-H (15.5 ml, 15.3 mmol) was added slowly thereto at 0°C. The reaction mixture was allowed to stir at room temperature for 6 h, quenched with a little crushed ice and stirred for 30 minutes. The solid was filtered off and washed with 5% methanol in dichloromethane (150 ml).
25 The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to give the title compound **5** (1.2 g, 67%).

¹HNMR (400 MHz, DMSO-*d*₆) δ : 8.82 (s, 1H), 8.56 (s, 1H), 7.40 (s, 1H), 5.66 (t, $J = 5.6$ Hz, 1H), 4.79 (d, $J = 5.6$ Hz, 2H), 4.02 (s, 3H).

[0236]

4-Chloro-7-iodo-6-methoxy-quinoline-3-carbaldehyde (6)

Activated manganese dioxide (6 g, 68.9 mmol) was added to
35 a stirred solution of compound **5** (1.2 g, 3.4 mmol) in

dichloromethane (150 ml). After 1 h, the reaction mixture was filtered through celite, and the filtrate was washed with 2% methanol in dichloromethane and concentrated under reduced pressure to give the title compound **6** (0.9 g, 75%).

5 ¹HNMR (400 MHz, CDCl₃) δ: 10.68 (s, 1H), 9.11 (s, 1H), 8.69 (s, 1H), 7.47 (s, 1H), 4.09 (s, 3H).

[0237]

Compound 7: General method for synthesis of pyrazole derivatives

10 A mixture of compound **6** (60 mg, 0.17 mmol) and appropriate hydrazine derivative (0.26 mmol) in *t*-BuOH was stirred in RT for 1 h and refluxed for 24 hour. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (20 ml). The organic layer was washed with water and
15 brine, dried over sodium sulfate and concentrated. The residue was purified on silica-gel column to give the title compound **7** (40-50%).

[0238]

Compound 8: General method for Suzuki coupling

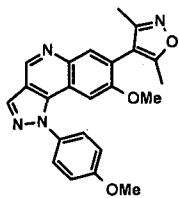
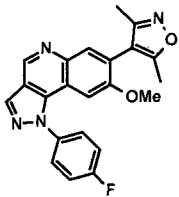
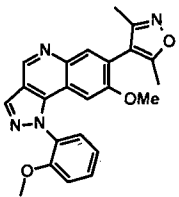
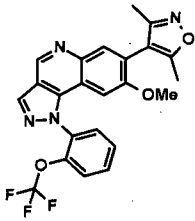
20 A mixture of compound **7** (0.10 mmol), 3,5-dimethylisoxazole-4-boronic acid (27 mg, 0.2 mmol) and cesium carbonate (125 mg, 0.4 mmol) in dimethoxyethane:water (4:1) was degassed with argon for 10 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.025 mmol) was
25 added thereto, and the reaction mixture was heated 5 h at 90°C. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (20 ml). The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified on silica-gel column to give the
30 title compound **8** (40-50%).

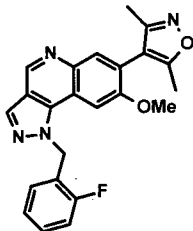
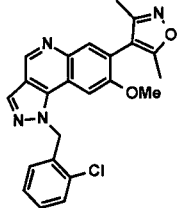
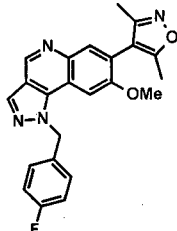
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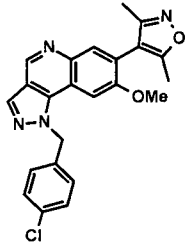
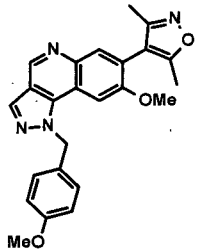
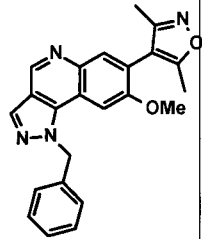
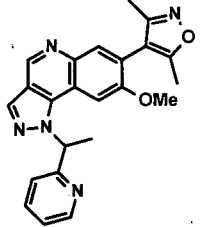
The following compounds of Examples were synthesized according to Scheme 1:

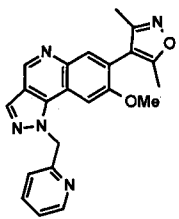
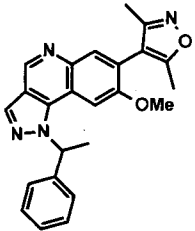
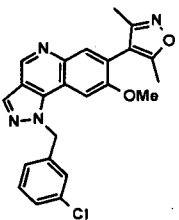
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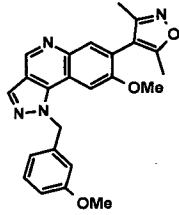
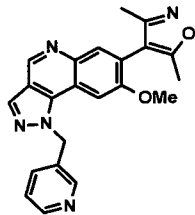
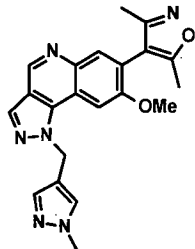
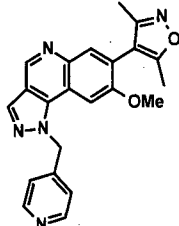
35 **Table 1**

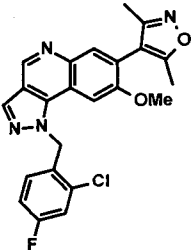
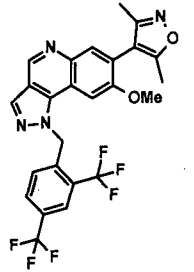
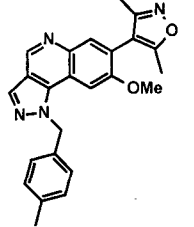
Example	Structure	IUPAC Name	¹ H NMR (400 MHz)
1.1		4-[8-methoxy-1-(4-methoxyphenyl)pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.17 (s, 1H), 8.36 (s, 1H), 7.99 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 7.00 (s, 1H), 3.94 (s, 3H), 3.52 (s, 3H), 2.34 (s, 3H), 2.18 (s, 3H)
1.2		4-[1-(4-fluorophenyl)-8-methoxy-pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.19 (s, 1H), 8.38 (s, 1H), 8.01 (s, 1H), 7.70-7.67 (m, 2H), 7.38-7.34 (m, 2H), 6.95 (s, 1H), 3.54 (s, 3H), 2.34 (s, 3H), 2.18 (s, 3H)
1.3		4-[8-methoxy-1-(2-methoxyphenyl)pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.19 (s, 1H), 8.41 (s, 1H), 7.99 (s, 1H), 7.58-7.63 (m, 2H), 7.19-7.26 (m, 2H), 6.81 (s, 1H), 3.73 (s, 3H), 3.43 (s, 3H), 2.33 (s, 3H), 2.17 (s, 3H)
1.4		4-[8-methoxy-1-(2-(trifluoromethoxy)phenyl)pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.18 (s, 1H), 8.57 (s, 1H), 8.02-8.05 (m, 1H), 7.99 (s, 1H), 7.92 (s, 1H), 7.55-7.58 (m, 3H), 4.01 (s, 3H), 2.38 (s, 3H), 2.24 (s, 3H)

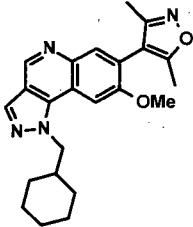
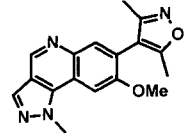
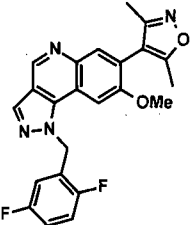
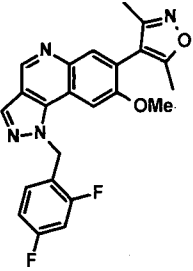
		isoxazole	
1.5		4-[1-[(2-fluorophenyl)methyl]-8-methoxy-3,5-dimethyl-1H-pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethyl-1H-isoxazole	(CDCl ₃): δ 9.15 (s, 1H), 8.32 (s, 1H), 7.98 (s, 1H), 7.42 (s, 1H), 7.26-7.31 (m, 1H), 7.18 (t, J = 8 Hz, 1H), 7.02 (t, J = 8 Hz, 1H), 6.78 (t, J = 8 Hz, 1H), 6.15 (s, 2H), 3.76 (s, 3H), 2.33 (s, 3H), 2.18 (s, 3H)
1.6		4-[1-[(2-chlorophenyl)methyl]-8-methoxy-3,5-dimethyl-1H-pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethyl-1H-isoxazole	(CDCl ₃): δ 9.16 (s, 1H), 8.33 (s, 1H), 7.98 (s, 1H), 7.51 (d, J = 8 Hz, 1H), 7.27 (s, 1H), 7.17 (s, 1H), 7.10 (t, J = 8 Hz, 1H), 6.48 (d, J = 8 Hz, 1H), 6.17 (s, 2H), 3.66 (s, 3H), 2.32 (s, 3H), 2.16 (s, 3H)
1.7		4-[1-[(4-fluorophenyl)methyl]-8-methoxy-3,5-dimethyl-1H-pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethyl-1H-isoxazole	(CDCl ₃): δ 9.15 (s, 1H), 8.30 (s, 1H), 7.99 (s, 1H), 7.37 (s, 1H), 7.11-7.13 (m, 2H), 7.05 (t, J = 8 Hz, 2H), 6.07 (s, 2H), 6.07 (s, 2H), 3.70 (s, 3H), 2.33 (s, 3H), 2.18 (s, 3H)

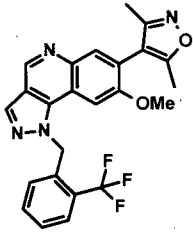
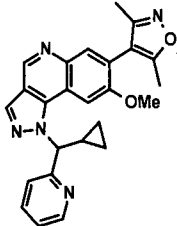
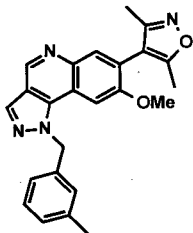
1.8		4-[1-[(4-chlorophenyl)methyl]-8-methoxy-pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethyl-isoxazole	(CDCl ₃): δ 9.16 (s, 1H), 8.31 (s, 1H), 7.99 (s, 1H), 7.35 (s, 2H), 7.32 (s, 1H), 7.09 (d, <i>J</i> = 8 Hz, 2H), 6.07 (s, 2H), 3.71 (s, 3H), 2.34 (s, 3H), 2.19 (s, 3H)
1.9		4-[8-methoxy-1-[(4-methoxyphenyl)methyl]pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethyl-isoxazole	(CDCl ₃): δ 9.14 (s, 1H), 8.29 (s, 1H), 7.98 (s, 1H), 7.45 (s, 1H), 7.09 (d, <i>J</i> = 8 Hz, 2H), 6.87 (d, <i>J</i> = 8 Hz, 2H), 6.03 (s, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 2.33 (s, 3H), 2.18 (s, 3H)
1.10		4-(1-benzyl-8-methoxy-pyrazolo[4,3-c]quinolin-7-yl)-3,5-dimethyl-isoxazole	(CDCl ₃): δ 9.16 (s, 1H), 8.32 (s, 1H), 7.98 (s, 1H), 7.38-7.32 (m, 5H), 7.16 (d, <i>J</i> = 7.6 Hz, 1H), 6.11 (s, 2H), 3.65 (s, 3H), 2.33 (s, 3H), 2.18 (s, 3H)
1.11		4-[8-methoxy-1-[1-(2-pyridyl)ethyl]pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethyl-isoxazole	(CDCl ₃) δ 9.12 (s, 1H), 8.62 (d, <i>J</i> = 4.4 Hz, 1H), 8.34 (s, 1H), 7.96 (s, 1H), 7.85 (brs, 1H), 7.58 (t, <i>J</i> = 7.6 Hz, 1H), 7.21 (t, <i>J</i> = 7.6 Hz, 1H), 6.90 (d, <i>J</i> = 4.4 Hz, 1H), 6.47-6.45

			(m, 1H), 3.92 (s, 3H), 2.33 (s, 3H), 2.23 (d, $J = 7.6$ Hz, 3H), 2.18 (s, 3H)
1.12		4-[8-methoxy-1-(2-pyridylmethyl)pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.13 (s, 1H), 8.64 (d, $J = 4.8$ Hz, 1H), 8.31 (s, 1H), 7.97 (s, 1H), 7.75 (s, 1H), 7.61 (d, $J = 7.2$ Hz, 1H), 7.26-7.24 (m, 1H), 6.98 (d, $J = 8.0$ Hz, 1H), 6.19 (s, 2H), 3.86 (s, 3H), 2.33 (s, 3H)
1.13		4-[8-methoxy-1-(1-phenylethyl)pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.15 (s, 1H), 8.34 (s, 1H), 7.97 (s, 1H), 7.47 (s, 1H), 7.35-7.26 (m, 3H), 7.17-7.15 (m, 2H), 6.36-6.34 (m, 1H), 3.74 (s, 3H), 2.32 (s, 3H), 2.21-2.19 (m, 3H), 2.17 (s, 3H)
1.14		4-[1-[(3-chlorophenyl)methyl]-8-methoxy-pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.15 (s, 1H), 8.31 (s, 1H), 7.99 (s, 1H), 7.35 (s, 1H), 7.31-7.3 (m, 2H), 7.20 (s, 1H), 7.03 (d, $J = 0.64$ Hz, 1H), 6.06 (s, 2H), 3.71 (s, 3H), 2.33 (s, 3H), 2.18 (s, 3H)

1.15		4-[8-methoxy-1-[(3-methoxyphenyl)methyl]pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃) δ: 9.14 (s, 1H), 8.29 (s, 1H), 7.97 (s, 1H), 7.41 (s, 1H), 7.29-7.26 (m, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.78 (d, J = 7.2 Hz, 1H), 6.65 (s, 1H), 6.05 (s, 2H), 3.71 (s, 3H), 3.69 (s, 3H), 2.32 (s, 3H), 2.17 (s, 3H)
1.16		4-[8-methoxy-1-(pyridylmethyl)pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.16 (s, 1H), 8.64 (s, 1H), 8.58 (d, J = 4 Hz, 1H), 8.32 (s, 1H), 8.00 (s, 1H), 7.36-7.39 (m, 2H), 7.26-7.28 (m, 1H), 6.13 (s, 2H), 3.74 (s, 3H), 2.33 (s, 3H), 2.18 (s, 3H)
1.17		4-[8-methoxy-1-(1-methylpyrazol-4-yl)methylpyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.13 (s, 1H), 8.24 (s, 1H), 8.02 (s, 1H), 7.62 (s, 1H), 7.52 (s, 1H), 7.13 (s, 1H), 5.96 (s, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 2.36 (s, 3H), 2.22 (s, 3H)
1.18		4-[8-methoxy-1-(4-pyridylmethyl)pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.17 (s, 1H), 8.60 (s, 2H), 8.33 (s, 1H), 8.01 (s, 1H), 7.22 (s, 1H), 7.05 (s, 2H),

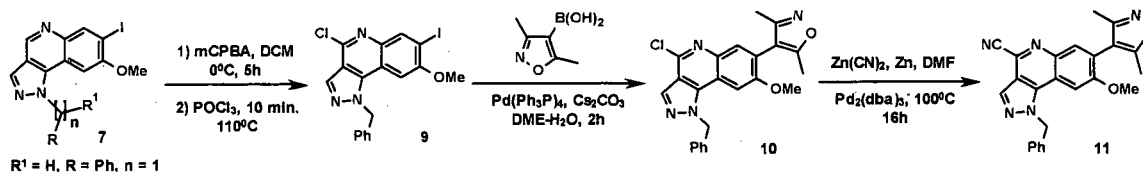
		yl]-3,5-dimethyl-isoxazole	6.10 (s, 2H), 3.65 (s, 3H), 2.33 (s, 3H), 2.17 (s, 3H)
1.19		4-[1-[(2-chloro-4-fluorophenyl)methyl]-8-methoxy-pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethyl-isoxazole	(CDCl ₃): δ 9.17 (s, 1H), 8.34 (s, 1H), 8.0 (s, 1H), 7.29 (s, 1H), 7.18 (s, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.46 (d, J = 7.6 Hz, 1H), 6.13 (s, 2H), 3.72 (s, 3H), 2.33 (s, 3H), 2.18 (s, 3H)
1.20		4-[1-[[2,4-bis(trifluoromethyl)phenyl]methyl]-8-methoxy-pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethyl-isoxazole	(CDCl ₃): δ 9.20 (s, 1H), 8.38 (s, 1H), 8.07 (brs, 1H), 8.03 (s, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.12 (s, 1H), 6.56 (d, J = 8.4 Hz, 1H), 6.39 (s, 2H), 3.58 (s, 3H), 2.23 (s, 3H), 2.17 (s, 3H)
1.21		4-[8-methoxy-1-(p-tolylmethyl)pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethyl-isoxazole	(CDCl ₃): δ 9.15 (s, 1H), 8.30 (s, 1H), 7.98 (s, 1H), 7.43 (s, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 6.06 (s, 2H), 3.69 (s, 3H), 2.33 (s, 3H), 2.32 (s, 3H), 2.18 (s, 3H)

1.22		4-[1-(cyclohexylmethyl)-8-methoxy-pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethyl-isoxazole	(CDCl ₃): δ 9.11 (s, 1H), 8.17 (s, 1H), 8.04 (s, 1H), 7.65 (s, 1H), 4.96 (d, <i>J</i> = 7.2 Hz, 1H), 4.00 (s, 3H), 2.39 (s, 3H), 2.25 (s, 3H), 1.79-1.71 (m, 6H), 1.24-1.22 (m, 6H)
1.23		4-(8-methoxy-1-methyl-pyrazolo[4,3-c]quinolin-7-yl)-3,5-dimethyl-isoxazole	(CDCl ₃): δ 9.10 (s, 1H), 8.17 (s, 1H), 8.04 (s, 1H), 7.80 (s, 1H), 4.60 (s, 3H), 4.02 (s, 3H), 2.38 (s, 3H), 2.24 (s, 3H)
1.24		4-[1-[(2,5-difluorophenyl)methyl]-8-methoxy-pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethyl-isoxazole	(CDCl ₃): δ 9.15 (s, 1H), 8.32 (s, 1H), 8.00 (s, 1H), 7.40 (s, 1H), 7.16 (dt, <i>J</i> = 9.2, 4.4 Hz, 1H), 7.00-6.96 (m, 1H), 6.50-6.46 (m, 1H), 6.11 (s, 2H), 3.79 (s, 3H), 2.34 (s, 3H), 2.19 (s, 3H)
1.25		4-[1-[(2,4-difluorophenyl)methyl]-8-methoxy-pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethyl-isoxazole	(DMSO- <i>d</i> ₆): δ 9.23 (s, 1H), 8.49 (s, 1H), 8.01 (s, 1H), 7.62 (s, 1H), 7.37-7.43 (m, 1H), 6.98-7.02 (m, 1H), 6.83-6.89 (m, 1H), 6.24 (s, 2H), 3.85 (s, 3H), 2.30 (s, 3H), 2.10

			(s, 3H)
1.26		4-[8-methoxy-1-[[2-(trifluoromethyl)phenyl]methyl]pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(DMSO- <i>d</i> ₆): δ 9.23 (s, 1H), 8.57 (s, 1H), 8.02 (s, 1H), 7.92 (d, <i>J</i> = 7.6 Hz, 1H), 7.47-7.56 (m, 2H), 7.26 (s, 1H), 6.38 (s, 3H), 3.56 (s, 3H), 2.28 (s, 3H), 2.07 (s, 3H)
1.27		4-[1-[cyclopropyl(2-pyridyl)methyl]-8-methoxy-pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.11 (s, 1H), 8.59 (d, <i>J</i> = 4.4 Hz, 1H), 8.37 (s, 1H), 7.95 (m, 2H), 7.63 (t, <i>J</i> = 8.0 Hz, 1H), 7.26-7.21 (m, 2H), 5.45 (d, <i>J</i> = 8.8 Hz, 1H), 3.97 (s, 3H), 2.33 (s, 3H), 2.24-2.18 (m, 1H), 2.18 (s, 3H), 0.84 (m, 4H)
1.28		4-[8-methoxy-1-(m-tolylmethyl)pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(DMSO- <i>d</i> ₆): δ 9.16 (s, 1H), 8.50 (s, 1H), 7.96 (s, 1H), 7.58 (s, 1H), 7.20-7.24 (m, 1H), 7.06-7.10 (m, 2H), 6.91 (d, <i>J</i> = 8.0 Hz, 1H), 6.18 (s, 2H), 3.79 (s, 3H), 2.28 (s, 3H), 2.22 (s, 3H), 2.08 (s, 3H)

1.29		4-[8-methoxy-1-[2-methyl-1-(2-pyridyl)propyl]pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(DMSO- <i>d</i> ₆): δ 9.09 (s, 1H), 8.53-8.58 (m, 2H), 8.42 (s, 1H), 7.95 (s, 1H), 7.78 (t, <i>J</i> = 6.4 Hz, 1H), 7.43 (d, <i>J</i> = 8.0 Hz, 1H), 7.30 (t, <i>J</i> = 6.8 Hz, 1H), 5.95 (d, <i>J</i> = 9.6 Hz, 1H), 4.16 (s, 3H), 3.14-3.18 (m, 1H), 2.29 (s, 3H), 2.10 (s, 3H), 0.83-0.93 (m, 6H)
1.30		4-[8-methoxy-1-[(6-methyl-2-pyridyl)methyl]pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.13 (s, 1H), 8.30 (s, 1H), 7.97 (s, 1H), 7.69 (s, 1H), 7.46 (t, <i>J</i> = 7.6 Hz, 1H), 7.10 (d, <i>J</i> = 7.6 Hz, 1H), 6.69 (d, <i>J</i> = 7.6 Hz, 1H), 6.15 (s, 2H), 3.83 (s, 3H), 2.59 (s, 3H), 2.33 (s, 3H), 2.18 (s, 3H)

[0241]

Scheme 2

5 [0242]

1-Benzyl-4-chloro-7-iodo-8-methoxy-pyrazolo[4,3-c]quinoline (9)

Solid mCPBA (1.04 mmol) was added to the solution of

compound **7** (0.87 mmol) in dichloromethane at 0°C, and the solution was stirred at room temperature for 5 hours. The reaction mixture was quenched with saturated NaHCO₃ solution and stirred for 30 minutes. The reaction mixture was diluted
5 with dichloromethane, and the organic layer was separated, washed with brine, dried over sodium sulfate and concentrated to give the crude corresponding *N*-oxide. The crude *N*-oxide was dissolved in POCl₃ (1.0 ml), and then the solution was heated for 10 min at 110°C. The reaction mixture was poured into cold
10 saturated NaHCO₃ solution. The organic layer was separated, washed with brine, dried over sodium sulfate and concentrated. The residue was purified on silica-gel column to give the title compound **9** (100 mg).

¹HNMR (400 MHz, CDCl₃) δ: 8.58 (s, 1H), 8.28 (s, 1H), 7.33-7.29
15 (m, 3H), 7.14 (s, 1H), 7.09-7.07 (m, 2H), 6.06 (s, 2H), 3.96 (s, 3H).

[0243]

Example 2.1: 4-(1-Benzyl-4-chloro-8-methoxy-pyrazolo[4,3-c]quinolin-7-yl)-3,5-dimethyl-isoxazole (10)

20 A mixture of compound **9** (40 mg, 0.09 mmol), 3,5-dimethylisoxazole-4-boronic acid (27 mg, 0.1 mmol) and cesium carbonate (65 mg, 0.2 mmol) in dimethoxyethane:water (4:1) was degassed with argon for 5 minutes.

Tetrakis(triphenylphosphine)palladium(0) (0.01 mmol) was added
25 thereto, and the reaction mixture was heated 2 h at 90°C. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (20 ml). The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified on preparative TLC to give the title compound **10**
30 (40%).

¹HNMR (400 MHz, CDCl₃) δ: 8.32 (s, 1H), 7.89 (s, 1H), 7.38-7.32 (m, 4H), 7.16-7.14 (m, 2H), 6.09 (s, 2H), 3.64 (s, 3H), 2.31 (s, 3H), 2.16 (s, 3H).

[0244]

35 **Example 2.2: 1-Benzyl-7-(3,5-dimethylisoxazol-4-yl)-8-methoxy-**

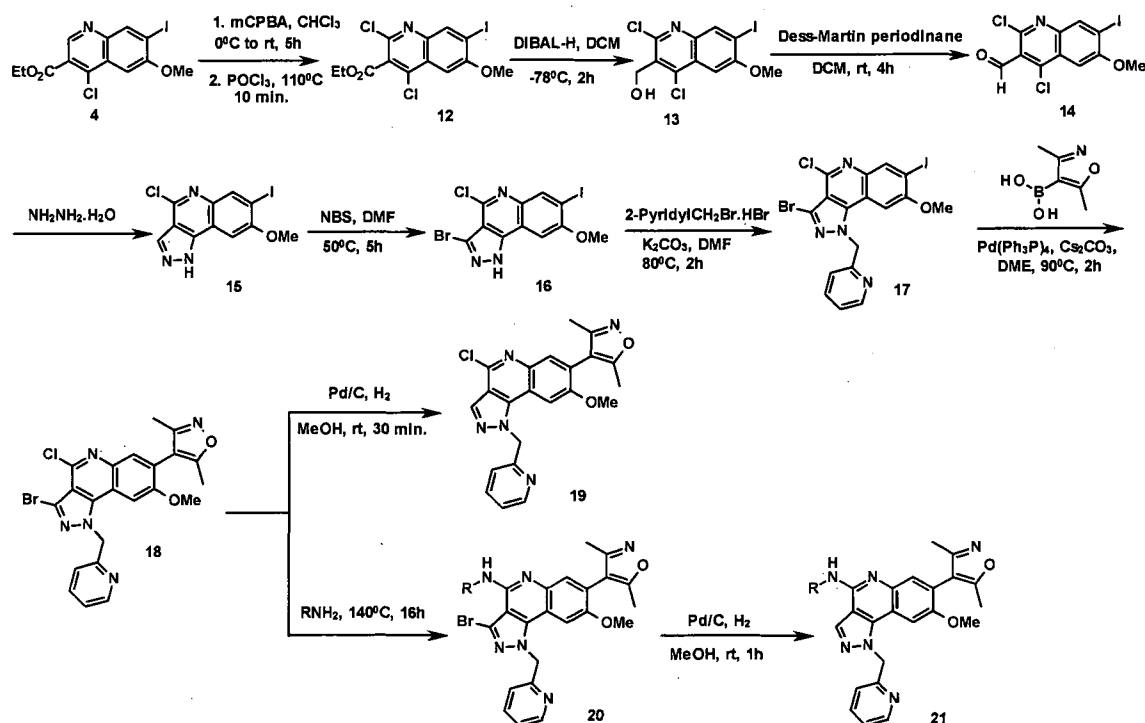
pyrazolo[4,3-c]quinoline-4-carbonitrile (11)

A mixture of compound **10** (0.12 mmol), zinc cyanide (0.24 mmol), dppf (0.02 mmol) and Zn powder (0.08 mmol) in DMF was degassed with argon for 5 minutes.

5 Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (0.01 mmol) was added thereto, and the reaction mixture was heated 16 h at 100°C. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (20 ml). The organic layer was washed with water and brine, dried over
 10 sodium sulfate and concentrated. The residue was purified on preparative TLC to give the title compound **11** (40%).

¹HNMR (400 MHz, CDCl₃) δ: 8.47 (s, 1H), 8.04 (s, 1H), 7.38-7.34 (m, 4H), 7.14-7.12 (m, 2H), 6.13 (s, 2H), 3.68 (s, 3H), 2.32 (s, 3H), 2.16 (s, 3H).

15 [0245]

Scheme 3

[0246]

Ethyl 2,4-dichloro-7-iodo-6-methoxyquinoline-3-carboxylate (12)

20

Solid mCPBA (4.0 mmol) was added to the solution of compound **4** (2.65 mmol) in chloroform at 0°C, and then the

mixture was stirred at room temperature for 5 hours. The reaction mixture was quenched with saturated NaHCO₃ solution and stirred for further 30 minutes. The organic layer was separated, washed water and brine, dried over sodium sulfate and concentrated to give crude product. This product was purified by passing through a short silica-gel column by using ethyl acetate-hexane to give the pure corresponding N-oxide. The N-oxide thus obtained was dissolved in POCl₃ (5.0 ml), and the solution was heated for 10 min at 110°C. The reaction mixture was poured into ice-NaHCO₃ mixture. The organic layer was separated, washed with water and brine, dried over sodium sulfate and concentrated. The residue was purified on silica-gel column to give the title compound **12** (60%).

¹HNMR (400 MHz, CDCl₃) δ: 8.56 (s, 1H), 7.32 (s, 1H), 4.54 (q, J = 7.2 Hz, 2H), 4.06 (s, 3H), 4.54 (t, J = 7.2 Hz, 3H).

[0247]

(2,4-Dichloro-7-iodo-6-methoxy-3-quinolyl)methanol (13)

A solution of compound **12** (600 mg, 1.45 mmol) in dichloromethane was cooled at -78°C, and 3.0 ml of DIBAL-H (1M solution in toluene) was added dropwise thereto. The reaction mixture was stirred for 2 h and then quenched with few drops of methanol and 0.2 ml of water. The reaction mixture was diluted with dichloromethane, stirred for 30 min and filtered through celite. The filtrate was concentrated, and the residue was purified on silica-gel column to give the title compound **13** (400 mg).

¹HNMR (400 MHz, CDCl₃) δ: 8.50 (s, 1H), 7.40 (s, 1H), 5.46-5.44 (m, 1H), 4.86-4.85 (m, 2H), 4.04 (m, 3H).

[0248]

2,4-Dichloro-7-iodo-6-methoxy-quinoline-3-carbaldehyde (14)

A mixture of compound **13** (400 mg) and Dess Martin periodinane (600 mg) in dichloromethane was stirred for 4 h at room temperature. The reaction mixture was quenched with saturated NaHCO₃ solution and diluted with dichloromethane. The organic layer was separated, washed with brine, dried over

sodium sulfate and concentrated. The residue was purified on silica-gel column to give the title compound **14** (260 mg).

¹HNMR (400 MHz, CDCl₃) δ: 10.46 (s, 1H), 8.59 (s, 1H), 7.52 (s, 1H), 4.06-4.04 (m, 3H).

5 [0249]

4-Chloro-7-iodo-8-methoxy-1H-pyrazolo[4,3-c]quinoline (15)

A mixture of compound **14** (250 mg) and hydrazine monohydrate in dioxane was stirred at room temperature for 1 h and then heated 6 h at 60°C. The reaction mixture was diluted
10 with ethyl acetate, washed with saturated NaHCO₃ solution and brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and the obtained residue was purified on silica-gel column to give the title compound **15** (150 mg).

[0250]

15 **3-Bromo-4-chloro-7-iodo-8-methoxy-1H-pyrazolo[4,3-c]quinoline (16)**

N-Bromosuccinimide (1.48 g, 8.35 mmol) was added to a solution of compound **15** (2.0 g, 5.57 mmol) in DMF (30 mL) at room temperature. After complete addition, the resulting
20 mixture was heated to 50°C. After 5 hour, water and ice were added to the reaction, and resulting solid was collected by filtration, washed with water and dried to give the title compound **16** (2.0 g, 82%).

¹HNMR (400 MHz, CDCl₃) δ: 14.98 (s, 1H), 8.48 (s, 1H), 7.84 (s,
25 1H), 4.00-3.99 (m, 3H).

[0251]

3-Bromo-4-chloro-7-iodo-8-methoxy-1-(2-pyridylmethyl)pyrazolo[4,3-c]quinoline (17)

A mixture of compound **16** (0.31 mmol), K₂CO₃ (0.62 mmol)
30 and 2-(Bromomethyl)pyridine hydrobromide (0.62 mmol) was heated in anhydrous N,N-dimethylformamide (2 ml) at 80°C. The reaction mixture was stirred for 2 hour, cooled to room temperature and diluted with ethyl acetate (20 ml). The organic layer was washed with brine, and dried over sodium
35 sulfate. The solvent was evaporated under reduced pressure,

and the residue was purified to give the title compound **17**.

¹HNMR (400 MHz, CDCl₃) δ: 8.49-8.45 (m, 2H), 7.80 (dt, *J* = 2, 7.6Hz, 1H), 7.58 (s, 1H), 7.34-7.29 (m, 2H), 6.28 (m, 2H), 3.82 (m, 3H).

5 [0252]

4-[3-Bromo-4-chloro-8-methoxy-1-(2-pyridylmethyl)pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethyl-isoxazole (18)

The preparation of compound **18** from compound **17** was carried out in a manner similar to that described for the
10 preparation of compound **10**.

¹HNMR (400 MHz, CDCl₃) δ: 8.52 (d, *J* = 4.4 Hz, 1H), 7.95 (s, 1H), 7.82 (dt, *J* = 1.2, 7.2 Hz, 1H), 7.73 (s, 1H), 7.36-7.32 (m, 2H), 6.30 (m, 2H), 3.79 (m, 3H), 2.29 (s, 3H), 2.08 (s, 3H)

15 [0253]

4-[4-Chloro-8-methoxy-1-(2-pyridylmethyl)pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethyl-isoxazole (19)

To a solution of compound **18** (1.0 eq.) in MeOH was added Pd/C (10% w/w). The reaction was stirred under H₂ atmosphere
20 by using hydrogen balloon for 30 minutes and filtered through celite. The celite was washed with MeOH, and the combined filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC to give the title compound **19** (50%).

25 [0254]

Compound 20: General method for amine coupling

A mixture of compound **18** (1.0 eq.) and amine (5.0 eq.) in *n*-butanol was heated at 140°C for 16 h. The reaction mixture was concentrated in vacuo, and the residue was purified to
30 give the title compound **20** (50-60%).

[0255]

Compound 21: General method for debromination

To compound **20** (1.0 eq.) in MeOH was added Pd/C (10% w/w). The reaction was stirred under H₂ atmosphere by using H₂
35 balloon for 1 h and then filtered through celite. The celite

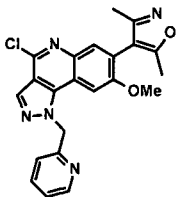
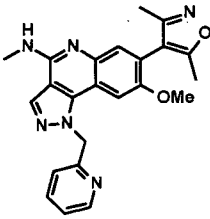
was washed with MeOH (200 mL), and the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC to give the title compound **21** (30-40%).

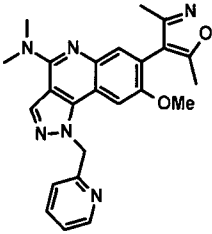
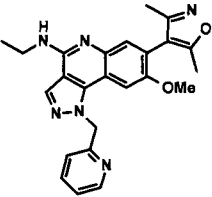
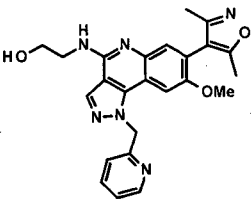
[0256]

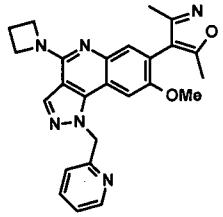
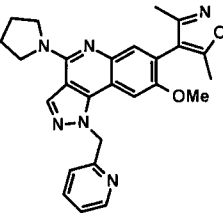
5 The following compounds of Examples were synthesized according to Scheme 3:

[0257]

Table 2

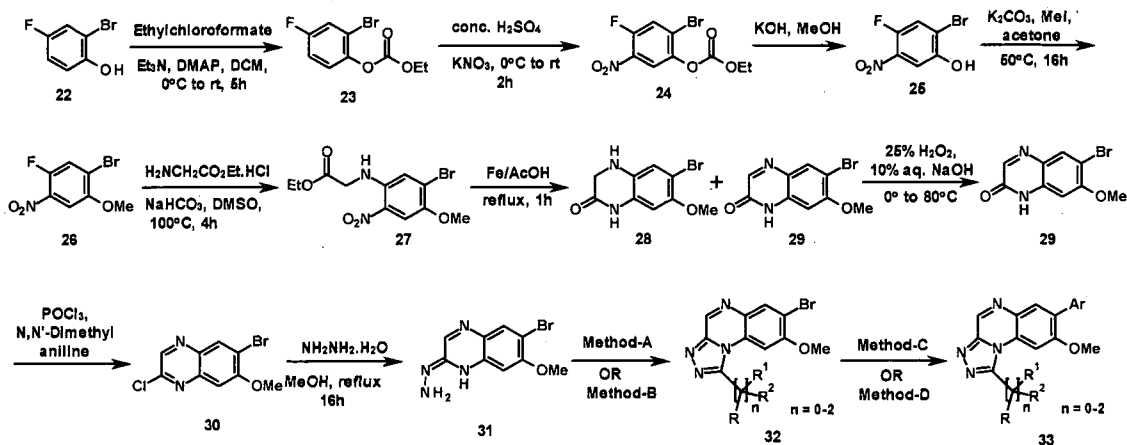
Example	Structure	IUPAC Name	¹ H NMR (400 MHz)
3.1		4-[4-chloro-8-methoxy-1-(2-pyridylmethyl)pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 8.63 (d, <i>J</i> = 4.4 Hz, 1H), 8.31 (s, 1H), 7.87 (s, 1H), 7.78 (s, 1H), 7.26 (s, 1H), 7.63 (t, <i>J</i> = 7.6 Hz, 1H), 7.02 (d, <i>J</i> = 8.0 Hz, 1H), 6.16 (s, 2H), 3.87 (s, 3H), 2.32 (s, 3H), 2.17 (s, 3H)
3.2		7-(3,5-dimethylisoxazol-1-yl)-8-methoxy-N-methyl-1-(2-pyridylmethyl)pyrazolo[4,3-c]quinolin-4-amine	(DMSO- <i>d</i> ₆): δ 8.56 (d, <i>J</i> = 4.0 Hz, 1H), 8.37 (s, 1H), 7.74 (t, <i>J</i> = 8.0 Hz, 1H), 7.51 (s, 1H), 7.42 (s, 2H), 7.32 (t, <i>J</i> = 8.0 Hz, 1H), 6.98 (d, <i>J</i> = 8.0 Hz, 1H), 6.14 (s, 2H), 3.68 (s, 3H), 3.01 (d, <i>J</i> = 4.0 Hz, 3H), 2.25 (s, 3H), 2.05 (s, 3H)

3.3		7-(3,5-dimethylisoxazol-1-yl)-8-methoxy-N,N-dimethyl-1-(2-pyridylmethyl)pyrazolo[4,3-c]quinolin-4-amine	(DMSO- <i>d</i> ₆): δ 8.57 (d, <i>J</i> = 4.0 Hz, 1H), 8.49 (s, 1H), 7.75 (dt, <i>J</i> = 8.0, 4.0 Hz, 1H), 7.55 (s, 1H), 7.41 (s, 1H), 7.32 (t, 4 Hz, 1H), 7.01 (d, <i>J</i> = 4.0 Hz, 1H), 6.18 (s, 2H), 3.68 (s, 3H), 3.37 (s, 6H), 2.25 (s, 3H), 2.05 (s, 3H)
3.4		7-(3,5-dimethylisoxazol-1-yl)-N-ethyl-8-methoxy-1-(2-pyridylmethyl)pyrazolo[4,3-c]quinolin-4-amine	(DMSO- <i>d</i> ₆): δ 8.56 (d, <i>J</i> = 4.0 Hz, 1H), 8.43 (brs, 1H), 7.74 (t, <i>J</i> = 8.0 Hz, 1H), 7.51 (s, 1H), 7.30-7.39 (m, 3H), 6.99 (s, 1H), 6.14 (s, 2H), 3.68 (s, 3H), 3.54-3.57 (m, 2H), 2.26 (s, 3H), 2.05 (s, 3H), 1.26 (t, <i>J</i> = 8.0 Hz, 3H)
3.5		2-[[7-(3,5-dimethylisoxazol-1-yl)-8-methoxy-1-(2-pyridylmethyl)pyrazolo[4,3-c]quinolin-4-yl]amino]ethanol	(DMSO- <i>d</i> ₆): δ 8.56 (d, <i>J</i> = 4.4 Hz, 1H), 8.46 (s, 1H), 7.71-7.76 (m, 1H), 7.51 (s, 1H), 7.46 (brs, 1H), 7.38 (s, 1H), 7.32 (t, <i>J</i> = 7.2 Hz, 1H), 6.98 (d, <i>J</i> = 8.0 Hz, 1H), 6.14 (s, 2H), 4.90 (brs, 1H), 3.60-3.68 (m, 7H), 2.25 (s, 3H), 2.08 (s, 3H)

3.6		4-[4-(azetidin-1-yl)-8-methoxy-1-(2-pyridylmethyl)pyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(DMSO- <i>d</i> ₆): δ 8.56 (d, <i>J</i> = 4.8 Hz, 1H), 8.27 (s, 1H), 7.73-7.78 (m, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 7.32 (dd, <i>J</i> = 5.2, 6.8 Hz, 1H), 7.01 (d, <i>J</i> = 8.0 Hz, 1H), 6.18 (s, 2H), 4.34 (t, <i>J</i> = 7.6 Hz, 4H), 3.69 (s, 3H), 2.40-2.50 (m, 2H), 2.25 (s, 3H), 2.05 (s, 3H)
3.7		4-[8-methoxy-1-(2-pyridylmethyl)-4-pyrrolidin-1-ylpyrazolo[4,3-c]quinolin-7-yl]-3,5-dimethylisoxazole	(DMSO- <i>d</i> ₆): δ 8.57 (d, <i>J</i> = 4.4 Hz, 1H), 8.45 (s, 1H), 7.74 (t, <i>J</i> = 2.0 Hz, 1H), 7.53 (s, 1H), 7.38 (s, 1H), 7.32-7.35 (dd, <i>J</i> = 2.0, 6.8 Hz, 1H), 6.98 (d, <i>J</i> = 8.4 Hz, 1H), 6.18 (s, 2H), 3.82 (brs, 4H), 3.68 (s, 3H), 2.25 (s, 3H), 2.05 (s, 3H), 2.01-2.03 (m, 4H)

[0258]

Scheme 4



[0259]

(2-Bromo-4-fluorophenyl) ethyl carbonate (23)

A solution of compound **22** (7.0 g, 36.6 mmol), DMAP (224
5 mg, 1.83 mmol) and triethylamine (10 ml, 73.30 mmol) in DCM
(70 ml) was cooled to 0°C, then treated with ethyl
chloroformate (7 ml, 73.30 mmol) dropwise, allowed to warm to
room temperature and stirred for 5 h. The reaction mixture was
quenched with sat. NaHCO₃ solution, and washed with brine (1 X
10 100 ml). The organic layer was dried over anhydrous Na₂SO₄,
filtered and concentrated to give the title crude compound **23**
(8.25 g, 85%).

¹HNMR (400 MHz, CDCl₃) δ: 7.35 (dd, *J* = 2.4, 3.2 Hz, 1H), 7.20
(dd, *J* = 4.8, 5.2 Hz, 1H), 7.08-7.03 (m, 1H), 4.35 (q, *J* = 7.6
15 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H).

[0260]

(2-Bromo-4-fluoro-5-nitrophenyl) ethyl carbonate (24)

Compound **23** (8.25 g, 31.36 mmol) was added portion wise
to conc. H₂SO₄ (45 ml) to give a colorless homogeneous solution.
20 This solution was then cooled to 0°C, and KNO₃ (3.48 g, 34.48
mmol) was added thereto portion wise over a period of 15 min
maintaining the internal temperature below 5°C. The reaction
was stirred for 2 h at RT and poured on ice water, and the
aqueous layer was extracted with DCM (3 X 50 ml). The combined
25 organic layer was washed with saturated NaHCO₃, water and brine.
The organic layer was dried over anhydrous Na₂SO₄, filtered and
concentrated to give the title compound **24** (8.8 g, 91%).

¹HNMR (400 MHz, CDCl₃) δ: 8.02 (d, *J* = 6.8 Hz, 1H), 7.62 (d, *J* = 10.0 Hz, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H).

[0261]

5 **2-Bromo-4-fluoro-5-nitro-phenol (25)**

To a solution of compound **24** (8.5 g, 27.6 mmol) in dry methanol (100 ml) was added KOH (3.86 g, 69 mmol) portion wise at 0°C. After the addition was complete, the reaction mixture was allowed to warm at room temperature and stirred for 2 h.

10 The reaction mixture was acidified with 1N HCl. The solvent was evaporated, and water was added thereto. The aqueous layer was extracted with DCM (2 X 50 ml). The combined organic layer was washed with brine (1 X 100 ml), dried over anhydrous Na₂SO₄, filtered and concentrated to give the title compound **25** (6.42 g, 99%).

¹HNMR (400 MHz, CDCl₃) δ: 7.72 (d, *J* = 6.4 Hz, 1H), 7.49 (d, *J* = 9.2 Hz, 1H), 5.99 (brs, 1H).

[0262]

1-Bromo-5-fluoro-2-methoxy-4-nitro-benzene (26)

20 To a solution of compound **25** (6.4 g, 27.1 mmol) in dry acetone (65 ml) was added K₂CO₃ (7.48 g, 54.2 mmol) at 0°C. Methyl Iodide (2.0 eq.) was added dropwise thereto, and after complete addition, the reaction mixture was warmed to 50°C and stirred for 16 h. The reaction mixture was cool to room temperature, diluted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to give the title compound **26** (6.6 g, 97%).

¹HNMR (400 MHz, CDCl₃) δ: 7.57-7.54 (m, 2H), 3.97 (s, 3H).

[0263]

30 **Ethyl 2-(5-bromo-4-methoxy-2-nitro-anilino)acetate (27)**

A mixture of compound **26** (40.0 mmol), glycine ethyl ester hydrochloride (5.58 g, 80.0 mmol) and NaHCO₃ (200 mmol) in dry DMSO (150 ml) was stirred 4 h at 100°C. The reaction was then cooled to room temperature and quenched with water. The solid was collected by filtration, washed thoroughly with water and

dried under vacuum to give the title compound **27** (9.0 g, 67%).
[0264]

Mixture of 6-Bromo-7-methoxy-3,4-dihydro-1H-quinoxalin-2-one (28) and 6-bromo-7-methoxy-1H-quinoxalin-2-one (29)

5 To a stirred solution of compound **27** (9 g, 27 mmol) in acetic acid (100 ml) was added iron powder (5.3 g, 94 mmol), and the mixture was stirred at 120°C for one hour. The reaction mixture was cooled to room temperature and filtered through celite. The filtrate was washed with ethyl acetate,
10 and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, and the solution was washed with sat. NaHCO₃, water and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a mixture of the title compounds **28** and **29** (6 g).

15 [0265]

6-Bromo-7-methoxy-1H-quinoxalin-2-one (29)

25% H₂O₂ (20 ml) was added slowly to a suspension of the mixture of compounds **28** and **29** (6 g) obtained in the previous step in 10% aqueous NaOH solution (30 ml) at 0°C. The reaction
20 mixture was stirred at 0°C for 1 hour and then allowed to stir at room temperature for 2 hours (till clear solution was formed). Once the clear solution was formed, it was heated at 80°C and stirred for half an hour, and then AcOH was added thereto slowly till pH =7 at 0°C. The solid was filtered and
25 dried to give the title compound **29** (4.2 g).

[0266]

6-Bromo-2-chloro-7-methoxy-quinoxaline (30)

Compound **29** (673 mg, 2.66 mmol) was added to cold phosphorous oxychloride (4 mL) in portions to give a slurry.
30 To the resulting slurry was added N,N-dimethylaniline (0.4 ml, 2.93 mmol) dropwise below 15°C. The brick red mixture was refluxed for 15 min, and the resulting dark brown clear solution was then cooled to ambient temperature. The mixture was poured into ice cold water (40 ml) and basified slowly
35 with 40% aq. NaOH to pH 8. The solid was collected by

filtration, washed with water (2x10) and dried to give the title compound **30**. (511 mg).

¹HNMR (400 MHz, DMSO-*d*₆): δ 8.85 (s, 1H), 8.43 (s, 1H), 7.57 (s, 1H), 4.05 (s, 3H).

5 [0267]

6-Bromo-7-methoxy-1H-quinoxalin-2-one hydrazone (31)

Hydrazine monohydrate (13.3 ml, 267.3 mmol) was added dropwise to a stirred suspension of compound **30** (29 g, 106.9 mmol) in methanol (290 ml), and the resulting mixture was
10 refluxed 16 h. The reaction mixture was cooled to room temperature, and the solid was collected by filtration, washed with methanol, and dried under vacuum to give the title compound **31**. (24 g, 84%).

¹HNMR (400 MHz, DMSO-*d*₆) δ: 8.77 (brs, 1H), 8.21 (s, 1H), 7.96
15 (s, 1H), 7.09 (s, 1H), 4.5 (brs, 2H), 3.94 (s, 3H).

[0268]

Compound 32: General method for triazole cyclization

Method-A: A mixture of compound **31** (0.37 mmol) and appropriate carboxylic acid (0.41 mmol) was refluxed in POCl₃ (2 ml) for 1
20 hours. The reaction mixture was cooled to room temperature and poured into crushed ice. The solid was collected by filtration and dried under vacuum to give the title compound **32** (50-60%).

[0269]

Method-B: To a stirred solution of compound **31** (1.85 mmol) and
25 appropriate carboxylic acid (2.04 mmol) in DMF (5 ml) were added DIPEA (2.78 mmol) and HATU (2.78 mmol) at 0°C, and the resulting mixture was stirred at room temperature for 16h. The reaction mixture was poured into ice water and extracted with EtOAc. The combined organic layers were washed with water and
30 brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was triturated in methanol, and the solid was collected by filtration to give the corresponding amide intermediate (1.34 mmol), which was mixed with N,O-bis(trimethylsilyl)acetamide (9.4 mmol) and
35 hexamethyl disilazane (33.5 mmol), and the mixture was stirred

at 120°C for 16 h. The reaction mixture was cooled to room temperature and carefully quenched with methanol and water. The solid was collected by filtration through Buchner funnel, washed with hexane and dried in vacuum to give the title
5 compound **32** (70-75%).

[0270]

Compound 33: General method for Suzuki coupling

Method C: To a solution of compound **32** (0.12 mmol) and aryl boronic acid (0.38 mmol) in DME (2 ml) was added Cs₂CO₃ (0.38
10 mmol) in water (0.5 ml). The mixture was degassed with N₂ for 30 minutes, tetrakis(triphenylphosphine)palladium(0) (0.006 mmol) was added thereto, and the resulting mixture was heated at 105°C for 2 h. The mixture was cooled to room temperature, poured into water and extracted with DCM. The organic layer
15 was washed with water and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound **33** (50-60%).

[0271]

Method D: To a solution of compound **32** (0.12 mmol) and aryl
20 boronic acid (0.38 mmol) in 1,4-Dioxane (2 ml) was added K₂CO₃ (0.38 mmol) in water (0.5 ml). The mixture was degassed with N₂ for 30 minutes, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.012 mmol) was added thereto, and the resulting mixture was heated
25 at 100°C for 16 h. The mixture was cooled to room temperature, poured into water and extracted with DCM. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound **33** (50-60%).

30 [0272]

4-[8-methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole:

To a stirred solution of compound **31** (2.8 g, 10.36 mmol) and 2-pyridylacetic acid (2.0 g, 11.52 mmol) in DMF (20 ml)
35 were added DIPEA (3 ml, 17.28 mmol) and HATU (6.5 g, 17.28

mmol) at 0°C, and the resulting mixture was stirred at room temperature for 16h. The reaction mixture was poured into ice water and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered
5 and concentrated under reduced pressure. The residue was triturated in methanol, and the solid was collected by filtration to give N-[(Z)-(6-bromo-7-methoxy-1H-quinoxalin-2-ylidene)amino]-2-(2-pyridyl)acetamide (2.3 g, 52%), which was mixed with N,O-bis(trimethylsilyl)acetamide (10.2 ml, 41.4
10 mmol) and hexamethyl disilazane (31.4 ml, 148.2 mmol), and the mixture was stirred at 120°C for 16 h. The reaction mixture was cooled to room temperature and carefully quenched with methanol and water. The solid was collected by filtration, washed with hexane and dried in vacuum to give 7-bromo-8-
15 methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxaline **(32)** (2.0 g, 91%).

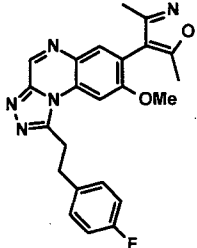
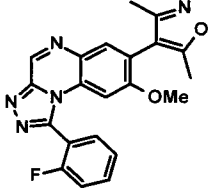
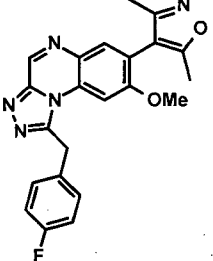
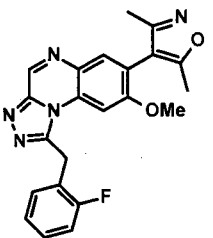
To a solution of compound **32** (2.0 g, 5.42 mmol) and 3,5-dimethylisoxazole-4-boronic acid (2.3 g, 16.2 mmol) in 1,4-Dioxane (16 ml) was added K₂CO₃ (1.49 g, 10.84 mmol) in water
20 (4 ml). The mixture was degassed with N₂ for 30 minutes, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.22 g, 0.27 mmol) was added thereto, and the resulting mixture was heated at 100°C for 16 h. The mixture was cooled to room temperature, poured into water and extracted with DCM.
25 The organic layer was washed with water and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound 4-[8-methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole **(33)** (1.6 g, 76%).

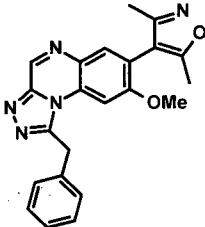
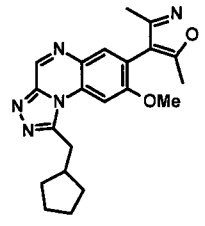
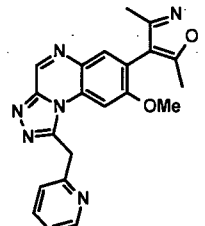
30 [0273]

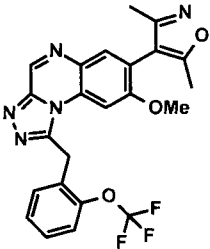
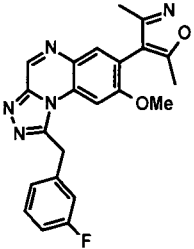
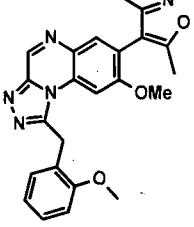
The following compounds of Examples were synthesized according to Scheme 4:

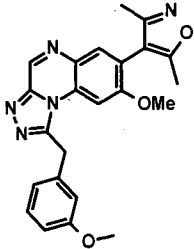
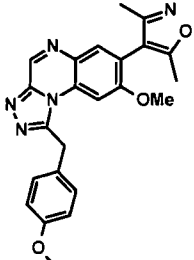
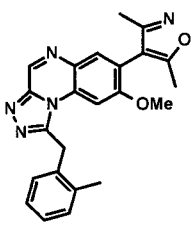
[0274]

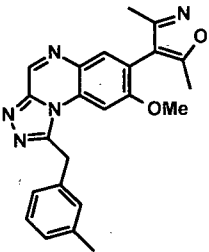
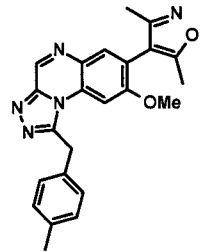
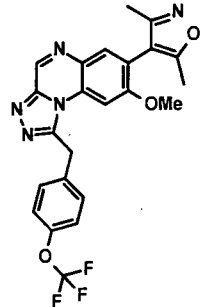
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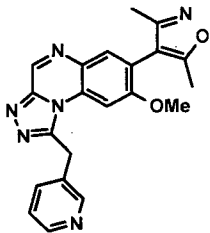
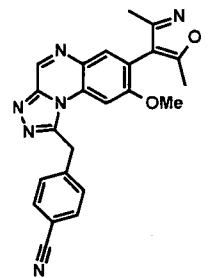
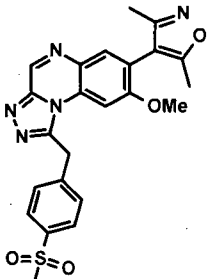
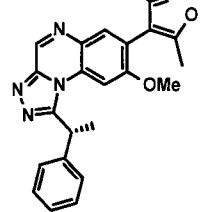
Example	Structure	IUPAC Name	¹ H NMR (400 MHz)
4.1		4-[1-[2-(4-fluorophenyl)ethyl]-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.21 (s, 1H), 8.02 (s, 1H), 7.78 (s, 1H), 7.43-7.40 (m, 2H), 7.14-7.10 (m, 2H), 4.01-3.98 (m, 4H), 3.33 (s, 3H), 2.33 (s, 3H), 2.13 (s, 3H)
4.2		4-[1-(2-fluorophenyl)-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(DMSO-d ₆): δ 9.39 (s, 1H), 8.06 (s, 1H), 7.94-7.83 (m, 2H), 7.67-7.58 (m, 2H), 6.87 (s, 1H), 3.41 (s, 3H), 2.28 (s, 3H), 2.08 (s, 3H)
4.3		4-[1-[(4-fluorophenyl)methyl]-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(DMSO-d ₆): δ 9.26 (s, 1H), 7.99 (s, 1H), 7.45 (s, 1H), 7.30-7.26 (m, 2H), 7.19 (t, J = 8.8 Hz, 2H), 5.09 (s, 2H), 3.73 (s, 3H), 2.27 (s, 3H), 2.07 (s, 3H)
4.4		4-[1-[(2-fluorophenyl)methyl]-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(DMSO-d ₆): δ 9.26 (s, 1H), 8.01 (s, 1H), 7.53 (s, 1H), 7.41-7.30 (m, 2H), 7.16-7.07 (m, 2H), 5.10

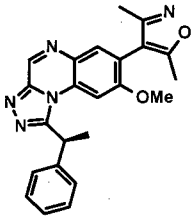
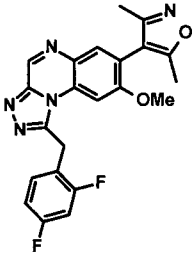
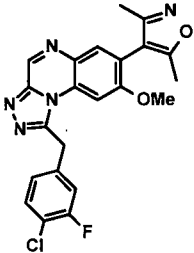
		a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole	(s, 2H), 3.79 (s, 3H), 2.95 (s, 3H), 2.09 (s, 3H)
4.5		4-(1-benzyl-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl)-3,5-dimethyl-isoxazole	(DMSO-d ₆): δ 9.26 (s, 1H), 7.97 (s, 1H), 7.43 (s, 1H), 7.37-7.33 (m, 2H), 7.30-7.26 (m, 1H), 7.22 (d, J = 7.2 Hz, 2H), 5.11 (s, 2H), 3.66 (s, 3H), 2.26 (s, 3H), 2.06 (s, 3H)
4.6		4-[1-(cyclopentylmethyl)-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole	(DMSO-d ₆): δ 9.20 (s, 1H), 8.01 (s, 1H), 7.78 (s, 1H), 4.05 (s, 3H), 3.60 (d, J = 7.2 Hz, 2H), 2.64-2.61 (m, 1H), 2.33 (s, 3H), 2.13 (s, 3H), 1.87-1.81 (m, 2H), 1.71-1.68 (m, 2H), 1.58-1.55 (m, 2H), 1.46-1.39 (m, 2H)
4.7		4-[8-methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole	(DMSO-d ₆): δ 9.16 (s, 1H), 8.56 (d, J = 4.8 Hz, 1H), 8.04 (s, 1H), 7.86 (s, 1H), 7.66 (dt, J = 5.6, 1.6 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.24-7.23 (m, 1H), 5.15 (s, 2H), 3.96 (s, 3H), 2.32

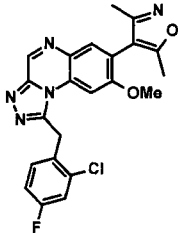
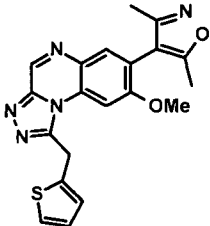
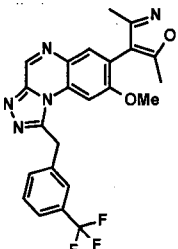
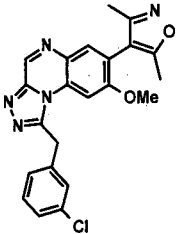
			(s, 3H), 2.16 (s, 3H).
4.8		4-[8-methoxy-1-[[2-(trifluoromethoxy)phenyl]methyl]-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.21 (s, 1H), 7.88 (s, 1H), 7.40-7.39 (m, 2H), 7.26-7.18 (m, 1H), 7.15 (s, 1H), 6.85 (d, <i>J</i> = 7.6 Hz, 1H), 5.05 (s, 2H), 3.61 (s, 3H), 2.30 (s, 3H), 2.14 (s, 3H)
4.9		4-[1-[(3-fluorophenyl)methyl]-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.21 (s, 1H), 7.88 (s, 1H), 7.37-7.32 (m, 1H), 7.26 (s, 1H), 7.04-6.99 (m, 2H), 6.89 (d, <i>J</i> = 9.2 Hz, 1H), 5.01 (s, 2H), 3.62 (s, 3H), 2.30 (s, 3H), 2.14 (s, 3H)
4.10		4-[8-methoxy-1-[(2-methoxyphenyl)methyl]-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.20 (s, 1H), 7.86 (s, 1H), 7.33-7.26 (s, 1H), 7.23 (s, 1H), 7.99 (d, <i>J</i> = 8.0 Hz, 1H), 6.84 (t, <i>J</i> = 7.6 Hz, 1H), 6.67 (d, <i>J</i> = 7.6 Hz, 1H), 4.94 (s, 2H), 3.94 (s, 3H), 3.54 (s, 3H), 2.30 (s, 3H), 2.14 (s, 3H)

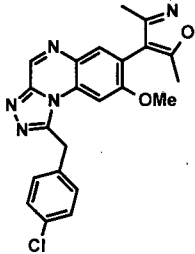
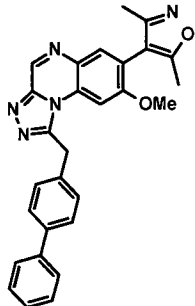
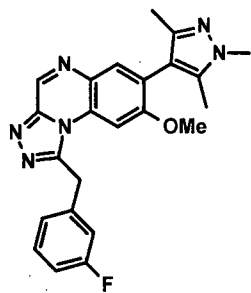
4.11		4-[8-methoxy-1-[(3-methoxyphenyl)methyl]-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.19 (s, 1H), 7.86 (s, 1H), 7.33 (s, 1H), 7.30-7.26 (m, 1H), 6.84-6.78 (m, 2H), 6.69 (s, 1H), 4.97 (s, 2H), 3.73 (s, 3H), 3.61 (s, 3H), 2.30 (s, 3H), 2.14 (s, 3H)
4.12		4-[8-methoxy-1-[(4-methoxyphenyl)methyl]-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.19 (s, 1H), 7.86 (s, 1H), 7.36 (s, 1H), 7.09 (d, <i>J</i> = 8.8 Hz, 2H), 6.88 (d, <i>J</i> = 8.8 Hz, 2H), 4.94 (s, 2H), 3.77 (s, 3H), 3.63 (s, 3H), 2.30 (s, 3H), 2.14 (s, 3H)
4.13		4-[8-methoxy-1-[(o-tolyl)methyl]-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.22 (s, 1H), 7.87 (s, 1H), 7.32 (d, <i>J</i> = 7.6 Hz, 1H), 7.26-7.21 (m, 1H), 7.08-7.04 (m, 2H), 6.58 (d, <i>J</i> = 8.0 Hz, 1H), 4.89 (s, 2H), 3.56 (s, 3H), 2.53 (s, 3H), 2.29 (s, 3H), 2.13 (s, 3H)

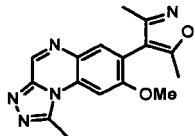
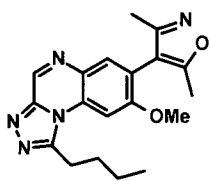
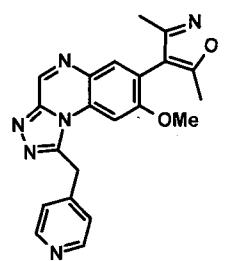
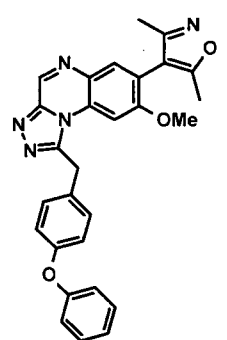
4.14		4-[8-methoxy-1-(m-tolylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.20 (s, 1H), 7.86 (s, 1H), 7.33 (s, 1H), 7.26-7.22 (m, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.00-6.98 (m, 2H), 4.96 (s, 2H), 3.60 (s, 3H), 2.30 (s, 3H), 2.28 (s, 3H), 2.14 (s, 3H)
4.15		4-[8-methoxy-1-(p-tolylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.19 (s, 1H), 7.86 (s, 1H), 7.34 (s, 1H), 7.15 (d, J = 7.6 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 4.96 (s, 2H), 3.60 (s, 3H), 2.32 (s, 3H), 2.30 (s, 3H), 2.14 (s, 3H)
4.16		4-[8-methoxy-1-[[4-(trifluoromethoxy)phenyl]methyl]-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.17 (s, 1H), 7.95 (s, 1H), 7.43 (s, 1H), 7.35 (d, J = 8.8, 2H), 7.29 (d, J = 8.8 Hz, 2H), 5.15 (s, 2H), 3.69 (s, 3H), 2.29 (s, 3H), 2.10 (s, 3H)

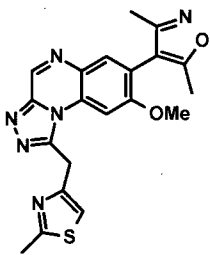
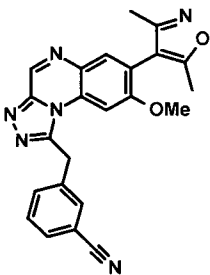
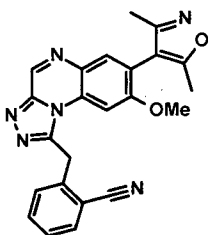
4.17		4-[8-methoxy-1- (3- pyridylmethyl)- [1,2,4]triazolo[4,3- a]quinoxalin-7- yl]-3,5- dimethyl- isoxazole	(CDCl ₃): δ 9.21 (s, 1H), 8.66 (s, 1H), 8.59 (d, <i>J</i> = 4.4 Hz, 1H), 7.47-7.45 (m, 2H), 7.31-7.29 (m, 2H), 5.03 (s, 2H), 3.69 (s, 3H), 2.30 (s, 3H), 2.14 (s, 3H)
4.18		4-[[7-(3,5- dimethylisoxazol -4-yl)-8- methoxy- [1,2,4]triazolo[4,3- a]quinoxalin-1- yl]methyl]benzon itrile	(CDCl ₃): δ 9.22 (s, 1H), 7.92 (s, 1H), 7.69 (d, <i>J</i> = 8.0 Hz, 2H), 7.35 (d, <i>J</i> = 8.0 Hz, 2H), 7.20 (s, 1H), 5.08 (s, 2H), 3.65 (s, 3H), 2.31 (s, 3H), 2.15 (s, 3H)
4.19		4-[8-methoxy-1- [(4- methylsulfonylph enyl)methyl]- [1,2,4]triazolo[4,3- a]quinoxalin-7- yl]-3,5- dimethyl- isoxazole	(CDCl ₃): δ 9.22 (s, 1H), 7.96 (d, <i>J</i> = 8.4, 2H), 7.91 (s, 1H), 7.44 (d, <i>J</i> = 8.4 Hz, 2H), 7.22 (s, 1H), 5.10 (s, 2H), 3.66 (s, 3H), 3.07 (s, 3H), 2.31 (s, 3H), 2.15 (s, 3H)
4.20		4-[8-methoxy-1- [(1R)-1- phenylethyl]- [1,2,4]triazolo[4,3- a]quinoxalin-7- yl]-3,5-	(CDCl ₃): δ 9.21 (s, 1H), 7.84 (s, 1H), 7.35-7.26 (m, 4H), 7.17 (d, <i>J</i> = 7.2 Hz, 2H), 5.01-4.99 (m, 1H), 3.63 (s, 3H), 2.28 (s, 3H), 2.12

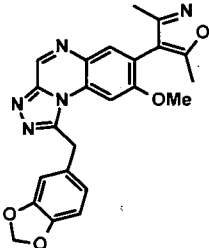
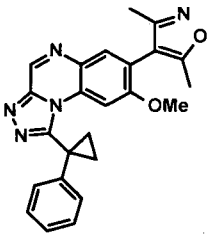
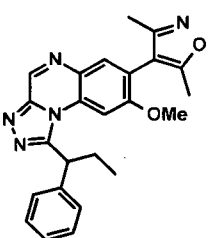
		dimethyl- isoxazole	(s, 3H), 2.11 (d, J = 6.8 Hz, 3H)
4.21		4-[8-methoxy-1- [(1S)-1- phenylethyl]- [1,2,4]triazolo[4,3- a]quinoxalin-7- yl]-3,5- dimethyl- isoxazole	(CDCl ₃): δ 9.21 (s, 1H), 7.84 (s, 1H), 7.35-7.26 (m, 4H), 7.17 (d, J = 7.2 Hz, 2H), 5.01-4.99 (m, 1H), 3.63 (s, 3H), 2.28 (s, 3H), 2.12 (s, 3H), 2.11 (d, J = 6.8 Hz, 3H)
4.22		4-[1-[(2,4- difluorophenyl)m ethyl]-8- methoxy- [1,2,4]triazolo[4,3- a]quinoxalin-7- yl]-3,5- dimethyl- isoxazole	(CDCl ₃): δ 9.20 (s, 1H), 7.90 (s, 1H), 7.31 (s, 1H), 6.99-6.80 (m, 3H), 4.95 (s, 2H), 3.78 (s, 3H), 2.31 (s, 3H), 2.16 (s, 3H)
4.23		4-[1-[(4-chloro- 3-fluoro- phenyl)methyl]- 8-methoxy- [1,2,4]triazolo[4,3- a]quinoxalin-7- yl]-3,5- dimethyl- isoxazole	(CDCl ₃): δ 9.21 (s, 1H), 7.90 (s, 1H), 7.32-7.29 (m, 2H), 7.17-7.07 (m, 2H), 4.95 (s, 2H), 3.72 (s, 3H), 2.31 (s, 3H), 2.16 (s, 3H)

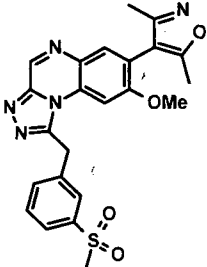
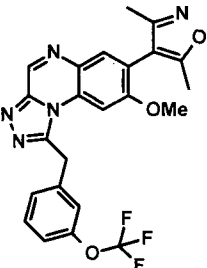
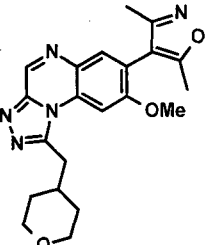
4.24		4-[1-[(2-chloro-4-fluoro-phenyl)methyl]-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.22 (s, 1H), 7.90 (s, 1H), 7.32 (dd, <i>J</i> = 8.0, 2.4 Hz, 1H), 7.10 (s, 1H), 6.90 (dt, <i>J</i> = 8.4, 2.4 Hz, 1H), 6.37-6.69 (m, 1H), 5.02 (s, 2H), 3.67 (s, 3H), 2.31 (s, 3H), 2.15 (s, 3H)
4.25		4-[8-methoxy-1-(2-thienylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.20 (s, 1H), 7.89 (s, 1H), 7.42 (s, 1H), 7.28-7.26 (m, 1H), 6.98-6.96 (m, 1H), 6.75 (d, <i>J</i> = 2.4 Hz, 1H), 5.13 (s, 2H), 3.71 (s, 3H), 2.32 (s, 3H), 2.16 (s, 3H)
4.26		4-[8-methoxy-1-[[3-(trifluoromethyl)phenyl]methyl]-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.22 (s, 1H), 7.89 (s, 1H), 7.63-7.60 (m, 2H), 7.49 (t, <i>J</i> = 8.0 Hz, 1H), 7.30 (d, <i>J</i> = 7.6 Hz, 1H), 7.26-7.24 (m, 1H), 5.07 (s, 2H), 3.61 (s, 3H), 2.30 (s, 3H), 2.14 (s, 3H)
4.27		4-[1-[(3-chlorophenyl)methyl]-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.21 (s, 1H), 7.89 (s, 1H), 7.31-7.26 (m, 4H), 7.04 (m, 1H), 4.98 (s, 2H), 3.66 (s,

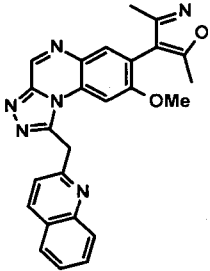
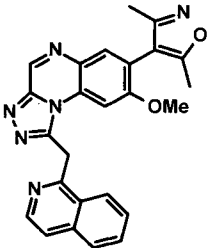
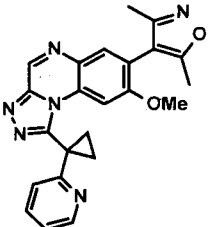
		a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole	3H), 2.30 (s, 3H), 2.15 (s, 3H)
4.28		4-[1-[(4-chlorophenyl)methyl]-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole	(CDCl ₃): δ 9.20 (s, 1H), 7.88 (s, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.27 (s, 1H), 7.13 (d, J = 8.4 Hz, 2H), 4.98 (s, 2H), 3.64 (s, 3H), 2.30 (s, 3H), 2.15 (s, 3H)
4.29		4-[8-methoxy-1-[(4-phenylphenyl)methyl]-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole	(CDCl ₃): δ 9.22 (s, 1H), 7.88 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 7.6 Hz, 2H), 7.43 (t, J = 6.8 Hz, 2H), 7.37-7.36 (m, 2H), 7.27-7.25 (m, 2H), 5.05 (s, 2H), 3.61 (s, 3H), 2.29 (s, 3H), 2.13 (s, 3H)
4.30		1-[(3-fluorophenyl)methyl]-8-methoxy-7-(1,3,5-trimethylpyrazol-4-yl)-[1,2,4]triazolo[4,3-a]quinoxaline	(CDCl ₃): δ 9.19 (s, 1H), 7.86 (s, 1H), 7.35-7.31 (m, 1H), 7.25 (s, 1H), 7.03-6.91 (m, 1H), 6.90 (d, J = 5.2 Hz, 2H), 5.01 (s, 2H), 3.79 (s, 3H), 3.62 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H)

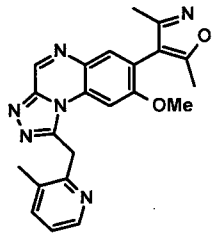
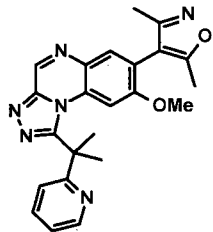
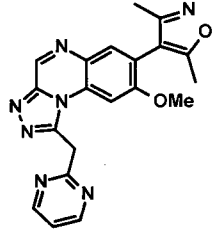
4.31		4-(8-methoxy-1-methyl-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl)-3,5-dimethyl-isoxazole	(CDCl ₃): δ 9.14 (s, 1H), 7.93 (s, 1H), 7.73 (s, 1H), 4.02 (s, 3H), 3.26 (s, 3H), 2.36 (s, 3H), 2.21 (s, 3H)
4.32		4-(1-butyl-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl)-3,5-dimethyl-isoxazole	(DMSO-d ₆): δ 9.15 (s, 1H), 7.93 (s, 1H), 7.64 (s, 1H), 4.01 (s, 3H), 3.53 (t, J = 7.6 Hz, 2H), 2.37 (s, 3H), 2.21 (s, 3H), 2.12-2.08 (m, 2H), 1.66-1.59 (m, 2H), 1.06 (t, J = 7.6 Hz, 3H)
4.33		4-[8-methoxy-1-(4-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole	(CDCl ₃): δ 9.22 (s, 1H), 8.62 (d, J = 6.4 Hz, 2H), 7.91 (s, 1H), 7.16-7.14 (m, 3H), 5.02 (s, 2H), 3.62 (s, 3H), 3.30 (s, 3H), 2.14 (s, 3H)
4.34		4-[8-methoxy-1-((4-phenoxyphenyl)methyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole	(DMSO-d ₆): δ 9.26 (s, 1H), 7.99 (s, 1H), 7.48 (s, 1H), 7.35 (t, J = 8.4 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 7.13-7.09 (m, 1H), 7.00 (d, J = 8.4 Hz, 2H), 6.95

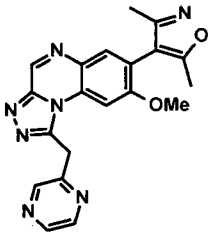
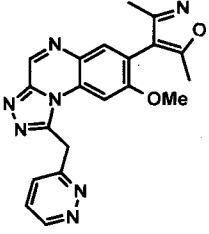
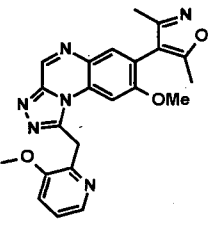
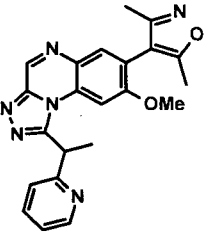
		dimethyl- isoxazole	(d, $J = 7.6$ Hz, 2H), 5.09 (s, 2H), 3.74 (s, 3H), 2.29 (s, 3H), 2.09 (s, 3H)
4.35		4-[8-methoxy-1- [(2- methylthiazol-4- yl)methyl]- [1,2,4]triazolo[4,3- a]quinoxalin-7- yl]-3,5- dimethyl- isoxazole	(CDCl ₃): δ 9.18 (s, 1H), 7.89 (s, 1H), 7.65 (s, 1H), 6.80 (s, 1H), 5.09 (s, 2H), 3.90 (s, 3H), 2.72 (s, 3H), 2.34 (s, 3H), 2.18 (s, 3H)
4.36		3-[[7-(3,5- dimethylisoxazol -4-yl)-8- methoxy- [1,2,4]triazolo[4,3- a]quinoxalin-1- yl]methyl]benzon itrile	(CDCl ₃): δ 9.23 (d, J = 0.8 Hz, 1H), 7.92 (s, 1H), 7.65 (d, J = 0.8 Hz, 1H), 7.55- 7.48 (m, 3H), 7.65 (s, 1H), 5.05 (s, 2H), 3.67 (s, 3H), 2.31 (d, $J = 0.8$ Hz, 3H), 2.15 (d, $J =$ 0.8 Hz, 3H)
4.37		2-[[7-(3,5- dimethylisoxazol -4-yl)-8- methoxy- [1,2,4]triazolo[4,3- a]quinoxalin-1- yl]methyl]benzon itrile	(CDCl ₃): δ 9.23 (s, 1H), 7.92 (s, 1H), 7.83 (dd, $J = 7.6$, 1.2 Hz, 1H), 7.55 (dt, $J = 7.6$, 1.6 Hz, 1H), 7.48 (t, J = 6.4 Hz, 1H), 7.20 (s, 1H), 7.02 (d, J = 8.0 Hz, 1H), 5.23 (s, 2H), 3.74 (s, 3H), 2.31 (s, 3H),

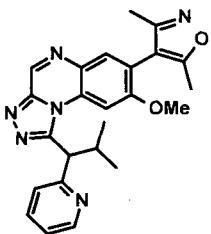
			2.15 (s, 3H)
4.38		4-[1-(1,3-benzodioxol-5-ylmethyl)-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.19 (s, 1H), 7.87 (s, 1H), 7.39 (s, 1H), 6.78 (d, <i>J</i> = 8.0 Hz, 1H), 6.66 (dd, <i>J</i> = 7.6, 1.6 Hz, 1H), 6.62 (d, <i>J</i> = 2.0 Hz, 1H), 6.94 (s, 2H), 4.90 (s, 2H), 3.69 (s, 3H), 2.31 (s, 3H), 2.15 (s, 3H)
4.39		4-[8-methoxy-1-(1-phenylcyclopropyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.21 (s, 1H), 7.86 (s, 1H), 7.70 (s, 1H), 7.30-7.22 (m, 3H), 6.94-6.92 (m, 2H), 3.46 (s, 3H), 2.29 (s, 3H), 2.14 (s, 3H), 1.07 (m, 4H)
4.40		4-[8-methoxy-1-(1-phenylpropyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(DMSO- <i>d</i> ₆): δ 9.25 (s, 1H), 7.94 (s, 1H), 7.53 (s, 1H), 7.35-7.32 (m, 2H), 7.27-7.22 (m, 3H), 5.16-5.15 (m, 1H), 3.83 (s, 3H), 2.57-2.54 (m, 1H), 2.55 (s, 3H), 2.24-2.23 (m, 1H), 2.05 (s, 3H), 1.07 (t, <i>J</i> = 7.2 Hz, 3H)

4.41		4-[8-methoxy-1-[[3-methylsulfonylphenyl)methyl]-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(DMSO- <i>d</i> ₆): δ 9.27 (s, 1H), 8.00 (s, 1H), 7.99 (s, 1H), 7.88 (d, <i>J</i> = 8.0 Hz, 1H), 7.63 (t, <i>J</i> = 7.6 Hz, 1H), 7.54 (d, <i>J</i> = 7.6 Hz, 1H), 7.49 (s, 1H) 5.25 (s, 2H), 3.76 (s, 3H), 3.20 (s, 3H), 2.81 (s, 3H), 2.07 (s, 3H)
4.42		4-[8-methoxy-1-[[3-(trifluoromethoxy)phenyl)methyl]-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(DMSO- <i>d</i> ₆): δ 9.26 (s, 1H), 7.99 (s, 1H), 7.48 (t, <i>J</i> = 8.0 Hz, 1H), 7.44 (s, 1H), 7.31 (m, 2H), 7.23 (d, <i>J</i> = 8.4 Hz, 1H), 5.19 (s, 2H), 3.70 (s, 3H), 2.27 (s, 3H), 2.07 (s, 3H)
4.43		4-[8-methoxy-1-[(3,4-dihydro-2H-pyran-4-yl)methyl]-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(DMSO- <i>d</i> ₆): δ 9.20 (s, 1H), 8.02 (s, 1H), 7.73 (s, 1H), 4.05 (s, 3H), 3.87-3.84 (m, 2H), 3.56 (d, <i>J</i> = 8.4 Hz, 2H), 3.32 (t, <i>J</i> = 10 Hz, 2H), 2.33 (s, 4H), 2.14 (s, 3H), 1.72-1.70 (m, 2H), 1.49-1.45 (m, 2H).

4.44		4-[8-methoxy-1-(2-quinolylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(DMSO- <i>d</i> ₆): δ 9.27 (s, 1H), 8.37 (d, <i>J</i> = 8.8 Hz, 1H), 7.98 – 7.96 (m, 2H), 7.84–7.82 (m, 2H), 7.75–7.71 (m, 1H), 7.59 (t, <i>J</i> = 7.2 Hz, 1H), 7.52 (d, <i>J</i> = 8.4 Hz, 1H), 5.43 (s, 2H), 3.81 (s, 3H), 2.23 (s, 3H), 2.03 (s, 3H)
4.45		4-[1-(1-isoquinolylmethyl)-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.15 (s, 1H), 8.83–8.80 (m, 1H), 8.35 (d, <i>J</i> = 5.6 Hz, 1H), 8.22 (s, 1H), 7.88–7.86 (m, 1H), 7.84 (s, 1H), 7.76–7.74 (m, 2H), 7.63 (d, <i>J</i> = 7.6 Hz, 1H), 5.63 (s, 2H), 3.66 (s, 3H), 2.30 (s, 3H), 2.15 (s, 3H)
4.46		4-[8-methoxy-1-(1-(2-pyridyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.20 (s, 1H), 8.55–8.54 (m, 1H), 7.88 (s, 1H), 7.85 (s, 1H), 7.51–7.46 (m, 1H), 7.16–7.13 (m, 1H), 6.88 (d, <i>J</i> = 7.6 Hz, 1H), 3.63 (s, 3H), 2.58 (brs, 1H), 2.49 (brs, 1H), 2.30 (s, 3H), 2.14 (s, 3H),

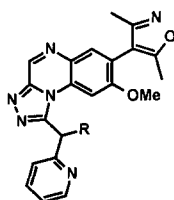
			1.78 (brs, 1H), 1.41 (brs, 1H)
4.47		4-[8-methoxy-1-[(3-methyl-2-pyridyl)methyl]-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.16 (s, 1H), 8.27-8.25 (m, 1H), 8.05 (s, 1H), 7.87 (s, 1H), 7.56 (d, J = 7.2 Hz, 1H), 7.17-7.14 (m, 1H), 5.11 (s, 2H), 3.79 (s, 3H), 2.56 (s, 3H), 2.33 (s, 3H), 2.17 (s, 3H)
4.48		4-[8-methoxy-1-[1-methyl-1-(2-pyridyl)ethyl]-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.22 (s, 1H), 8.64-8.62 (m, 1H), 7.82 (s, 1H), 7.61-7.57 (m, 1H), 7.24-7.21 (m, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.80 (s, 1H), 3.42 (s, 3H), 2.27 (s, 3H), 2.16 (s, 6H), 2.11 (s, 3H)
4.49		4-[8-methoxy-1-(pyrimidin-2-ylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(DMSO-d ₆): δ 9.27 (s, 1H), 8.78 (d, J = 5.2 Hz, 2H), 7.98 (s, 1H), 7.53 (s, 1H), 7.45 (d, J = 5.2 Hz, 1H), 5.41 (s, 2H), 3.71 (s, 3H), 2.27 (s, 3H), 2.07 (s, 3H)

4.50		4-[8-methoxy-1-(pyrazin-2-ylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(DMSO- <i>d</i> ₆): δ 9.26 (s, 1H), 8.82 (d, <i>J</i> = 1.2 Hz, 1H), 8.59 (d, <i>J</i> = 2.8 Hz, 1H), 8.54 (dd, <i>J</i> = 1.6, 2.4 Hz, 1H), 8.0 (s, 1H), 7.61 (s, 1H), 5.38 (s, 2H), 3.77 (s, 3H), 2.29 (s, 3H), 2.08 (s, 3H)
4.51		4-[8-methoxy-1-(pyridazin-3-ylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.15-9.14 (m, 2H), 8.28 (s, 1H), 7.87 (s, 1H), 7.65-7.62 (m, 1H), 7.49-7.46 (m, 1H), 5.35 (s, 2H), 4.15 (s, 3H), 2.32 (s, 3H), 2.17 (s, 3H)
4.52		4-[8-methoxy-1-[(3-methoxy-2-pyridyl)methyl]-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(DMSO- <i>d</i> ₆): δ 9.31 (s, 1H), 7.97 (s, 1H), 7.88 (d, <i>J</i> = 4.8 Hz, 1H), 7.55 (d, <i>J</i> = 8.4 Hz, 1H), 7.30-7.34 (m, 1H), 7.28 (s, 1H), 5.13 (s, 2H), 3.92 (s, 3H), 3.53 (s, 3H), 2.27 (s, 3H), 2.06 (s, 3H)
4.53		4-[8-methoxy-1-[1-(2-pyridyl)ethyl]-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.17 (s, 1H), 8.60 (d, <i>J</i> = 4.4 Hz, 1H), 7.97 (s, 1H), 7.84 (s, 1H), 7.65-7.61 (m,

		a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole	1H), 7.24-7.21 (m, 1H), 7.15 (d, J = 7.6 Hz, 1H), 5.25-5.24 (m, 1H), 3.98 (s, 3H), 2.30 (s, 3H), 2.15 (s, 3H), 2.14 (d, J = 4.0 Hz, 3H)
4.54		4-[8-methoxy-1-[2-methyl-1-(2-pyridyl)propyl]-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole	(CDCl ₃): δ 9.13 (s, 1H), 8.54 (d, J = 4.4 Hz, 1H), 8.47 (s, 1H), 7.84 (s, 1H), 7.66-7.61 (m, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.18 (m, 1H), 4.65 (d, J = 10 Hz, 1H), 4.19 (s, 3H), 3.26-3.24 (m, 1H), 2.32 (s, 3H), 2.18 (s, 3H), 1.14 (d, J = 6.4 Hz, 3H), 0.89 (d, J = 7.2 Hz, 3H)

[0275]

Following racemic compounds were separated using Chiral HPLC



5 [0276]

R = methyl:

4.53.1: First enantiomer ¹HNMR (400 MHz, CDCl₃) δ : 9.17 (s, 1H), 8.60 (d, J = 4.4 Hz, 1H), 7.97 (s, 1H), 7.84 (s, 1H), 7.65-7.61 (m, 1H), 7.24-7.21 (m, 1H), 7.15 (d, J = 7.6 Hz, 1H),

5.25 -5.24 (m, 1H), 3.98 (s, 3H), 2.30 (s, 3H), 2.15 (s, 3H),
2.14 (d, $J = 4.0$ Hz, 3H).

4.53.2: Second enantiomer ^1H NMR (400 MHz, CDCl_3) δ : 9.17 (s, 1H), 8.60 (d, $J = 4.4$ Hz, 1H), 7.97 (s, 1H), 7.84 (s, 1H),
5 7.65-7.61 (m, 1H), 7.24-7.21 (m, 1H), 7.15 (d, $J = 7.6$ Hz, 1H),
5.25 -5.24 (m, 1H), 3.98 (s, 3H), 2.30 (s, 3H), 2.15 (s, 3H),
2.14 (d, $J = 4.0$ Hz, 3H).

[0277]

R = isopropyl:

10 **4.54.1: First enantiomer** ^1H NMR (400 MHz, CDCl_3) δ : 9.13 (s, 1H),
8.54 (d, $J = 4.4$ Hz, 1H), 8.47 (s, 1H), 7.84 (s, 1H), 7.66-
7.61 (m, 1H), 7.43 (d, $J = 7.6$ Hz, 1H), 7.18 (m, 1H), 4.65 (d,
 $J = 10$ Hz, 1H), 4.19 (s, 3H), 3.26-3.24 (m, 1H), 2.32 (s, 3H),
2.18 (s, 3H), 1.14 (d, $J = 6.4$ Hz, 3H), 0.89 (d, $J = 7.2$ Hz,
15 3H).

4.54.2: Second enantiomer ^1H NMR (400 MHz, CDCl_3) δ : 9.13 (s, 1H), 8.54 (d, $J = 4.4$ Hz, 1H), 8.47 (s, 1H), 7.84 (s, 1H),
7.66-7.61 (m, 1H), 7.43 (d, $J = 7.6$ Hz, 1H), 7.18 (m, 1H),
4.65 (d, $J = 10$ Hz, 1H), 4.19 (s, 3H), 3.26-3.24 (m, 1H), 2.32
20 (s, 3H), 2.18 (s, 3H), 1.14 (d, $J = 6.4$ Hz, 3H), 0.89 (d, $J =$
7.2 Hz, 3H).

[0278]

R = ethyl:

4.55.1: First enantiomer ^1H NMR (400 MHz, CDCl_3) δ : 9.15 (s, 1H),
25 8.58 (d, $J = 2.0$ Hz, 1H), 8.18 (s, 1H), 7.84 (s, 1H), 7.62 (t,
 $J = 1.8$ Hz, 1H), 7.24-7.19 (m, 2H), 4.96 -4.93 (m, 1H), 4.08
(s, 3H), 2.60 (m, 1H), 2.49 (m, 1H), 2.31 (s, 3H), 2.16 (s,
3H), 1.13 (t, $J = 7.6$ Hz, 3H).

4.55.2: Second enantiomer ^1H NMR (400 MHz, CDCl_3) δ : 9.15 (s, 1H), 8.58 (d, $J = 2.0$ Hz, 1H), 8.18 (s, 1H), 7.84 (s, 1H),
30 7.62 (t, $J = 1.8$ Hz, 1H), 7.24-7.19 (m, 2H), 4.96 -4.93 (m,
1H), 4.08 (s, 3H), 2.60 (m, 1H), 2.49 (m, 1H), 2.31 (s, 3H),
2.16 (s, 3H), 1.13 (t, $J = 7.6$ Hz, 3H).

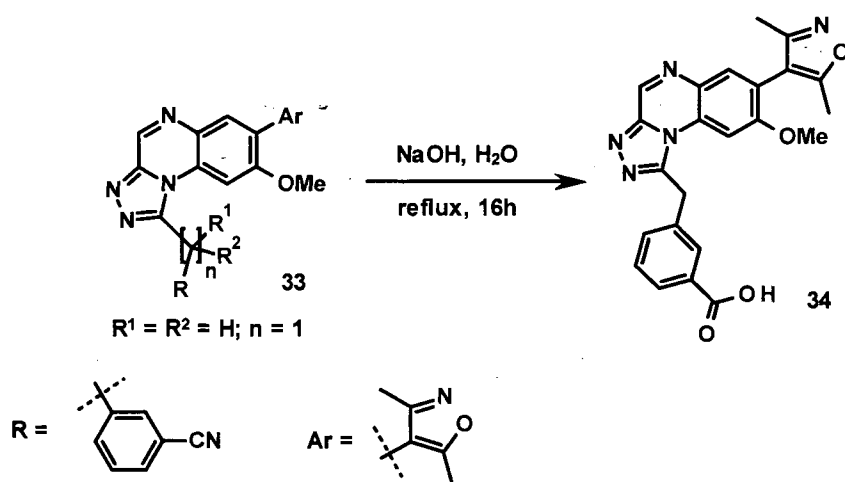
[0279]

35 R = cyclopropyl:

4.56.1: First enantiomer ^1H NMR (400 MHz, CDCl_3) δ : 9.17 (s, 1H), 8.55 (d, $J = 4.4$ Hz, 1H), 8.01 (brs, 1H), 7.83 (s, 1H), 7.63-7.67 (m, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 7.24-7.21 (m, 1H), 4.25 (s, 1H), 4.05 (s, 3H), 2.30 (s, 3H), 2.17 (s, 1H), 2.04 (s, 3H), 0.89-0.63 (m, 3H), 0.40-0.37 (m, 1H).

4.56.2: Second enantiomer ^1H NMR (400 MHz, CDCl_3) δ : 9.17 (s, 1H), 8.55 (d, $J = 4.4$ Hz, 1H), 8.01 (brs, 1H), 7.83 (s, 1H), 7.63-7.67 (m, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 7.24-7.21 (m, 1H), 4.25 (s, 1H), 4.05 (s, 3H), 2.30 (s, 3H), 2.17 (s, 1H), 2.04 (s, 3H), 0.89-0.63 (m, 3H), 0.40-0.37 (m, 1H).

[0280]

Scheme-5

[0281]

Example 5.1: 3-[[7-(3,5-dimethylisoxazol-4-yl)-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxalin-1-yl]methyl]benzoic acid (34)

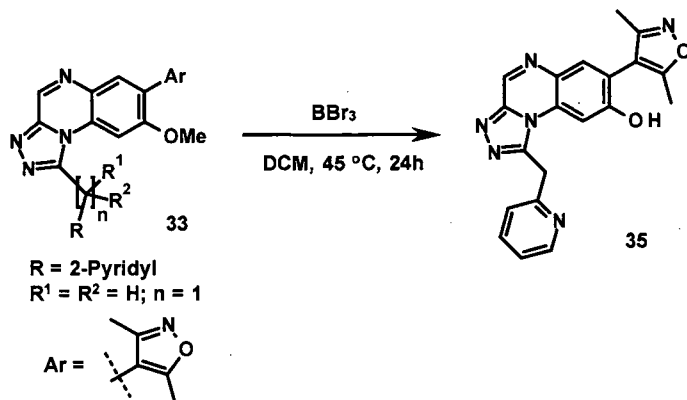
A solution of compound **33** (50 mg, 0.138 mmol) and NaOH (27.6 mg, 0.69 mmol) in water (2 ml) was stirred at reflux for 16 h. The reaction mixture was cooled to 0°C , acidified with 2M HCl and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure, and the residue was triturated in ethyl acetate to give the title compound **34** (60%).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 13.0 (brs, 1H) 9.26 (s, 1H), 7.98 (s, 1H), 7.94 (s, 1H), 7.87-7.85 (m, 1H), 7.51 (s, 1H), 7.48-

7.68 (m, 2H), 5.19 (s, 2H), 3.77 (s, 3H), 2.27 (s, 3H), 2.06 (s, 3H).

[0282]

Scheme-6



5

[0283]

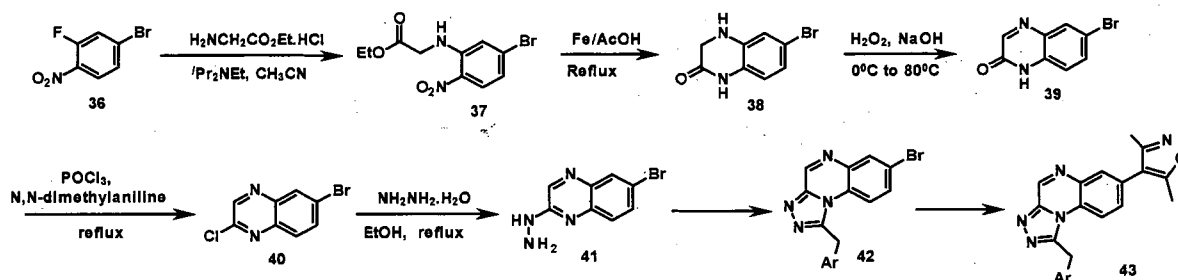
Example 6.1: 7-(3,5-Dimethylisoxazol-4-yl)-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-8-ol (35)

BBr₃ (0.5 ml) was added to a solution of compound **33** (100 mg) in DCM (20 ml) at room temperature, and the reaction mixture was stirred at 45°C for 24 h. The reaction mixture was poured into cold saturated NaHCO₃ solution and stirred for 10 min. The organic layer was separated, washed with water and brine and concentrated. The residue was purified on preparative TLC to give the title compound **35**.

¹HNMR (400 MHz, CDCl₃) δ: 10.95 (brs, 1H), 9.14 (s, 1H), 8.40 (d, *J* = 4.8 Hz, 1H), 7.90 (s, 1H), 7.80 (dt, 1.6, 7.6 Hz, 1H), 7.70 (s, 1H), 7.27 (dd, *J* = 5.6, 7.2 Hz, 1H), 5.06 (s, 2H), 2.30 (s, 3H), 2.13 (s, 3H).

20 [0284]

Scheme 7



[0285]

Ethyl 2-(5-bromo-2-nitro-anilino)acetate (37)

A solution of compound **36** (1 g, 4.5 mmol), glycine ethyl ester hydrochloride (0.7 g, 5 mmol) and diisopropylethylamine (0.9 g, 6.8 mmol) in acetonitrile (20 ml) was refluxed for 2 h. This reaction mixture was diluted with water and extracted (2x75 ml) with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the title compound **37** (80%).

¹HNMR (400 MHz, CDCl₃) δ: 8.45 (brs, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 6.86-6.83 (m, 2H), 4.32 (q, *J* = 6.8 Hz, 2H), 4.06 (d, *J* = 4.0 Hz, 2H), 1.33 (t, *J* = 8.0 Hz, 3H).

[0286]

6-Bromo-3,4-dihydro-1H-quinoxalin-2-one (38)

To the solution of compound **37** (1.2 g, 4 mmol) in acetic acid (15 ml) was added slowly iron powder (850 mg, 16 mmol), and then the mixture was stirred at reflux for 1 h. The reaction mixture was poured into crushed ice and then quenched with solid NaHCO₃ at 0°C. The solid was filtered off through celite, and the celite pad was washed with water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the title compound **38** (70%).

¹HNMR (400 MHz, DMSO-*d*₆) δ: 10.40 (s, 1H), 6.79 (s, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.26 (br s, 1H), 3.74 (s, 2H).

[0287]

6-Bromo-1H-quinoxalin-2-one (39)

A suspension of compound **38** (850 mg) in 10 % aqueous NaOH (10 ml) was slowly added 25 % H₂O₂ (5 ml) at 0°C while stirring. The reaction mixture was stirred at 0°C for 1h and then allowed to stir at room temperature for 2 h (till clear solution was formed). Once the clear solution was formed, it was stirred at

80°C for half an hour. The mixture was cooled to 0°C, and then AcOH was added slowly thereto till pH 7. The solid was collected by filtration and dried under vacuum to give the title compound **39** (600 mg, 70%).

5 ¹HNMR (400 MHz, DMSO-*d*₆) δ: 12.46 (brs, 1H), 8.20 (s, 1H), 7.98 (d, *J* = 2.4 Hz, 1H), 7.70 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H).

[0288]

6-Bromo-2-chloro-quinoxaline (40)

10 Compound **39** (600 mg, 2.66 mmol) was added to cold phosphorous oxychloride (4 mL) in portions wise to give a slurry. To the resulting slurry was added drop wise *N,N*-dimethylaniline (0.4 mL, 2.93 mmol) below 15°C. The brick red mixture was refluxed for 15 min, and the resulting dark brown
15 clear solution was then cooled to ambient temperature. It was added to ice cold water (40 mL), and the mixture was basified slowly with 40% aq. NaOH to pH 8. The solid was collected by filtration, washed with water (2x10 mL) and dried to give the title compound **40** (70%).

20 [0289]

(6-Bromoquinoxalin-2-yl)hydrazine (41)

To a solution of compound **40** (420 mg, 1.73 mmol) in ethanol (5 mL) was added excess hydrazine monohydrate (1.5 mL), and the resulting mixture was stirred at reflux for 16 h. The
25 reaction mixture was concentrated under reduced pressure, and the solid residue was washed with diethyl ether, and dried in vacuo to give the title compound **41** (80%).

[0290]

Compound 42: General method for triazole cyclization

30 The preparation of compound **42** from compound **41** was carried out in a manner similar to that described for the preparation of compound **32** according to Method-A (50-60%).

[0291]

Compound 43: General method for Suzuki coupling

35 The preparation of compound **43** from compound **42** was

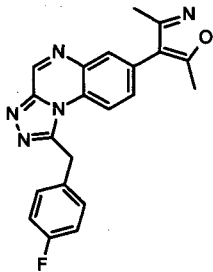
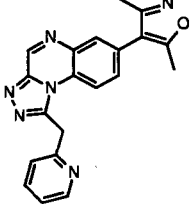
carried out in a manner similar to that described for the preparation of compound **33** according to Method-C (50-60% yield).

[0292]

- 5 The following compounds of Examples were synthesized according to Scheme 7:

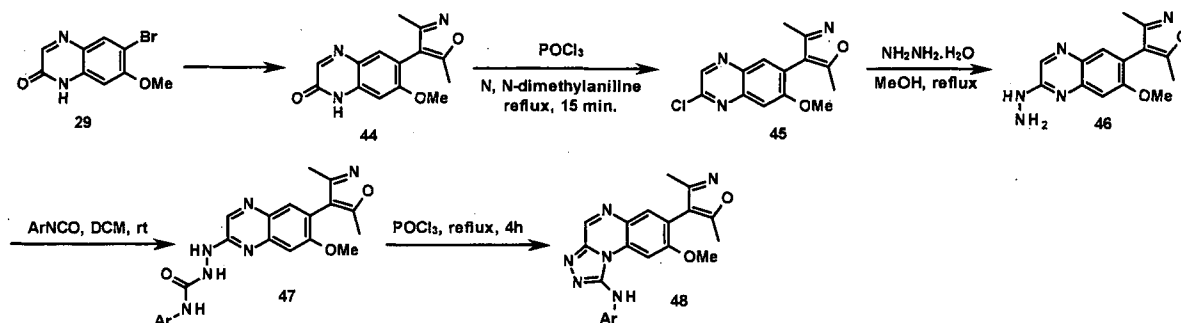
[0293]

Table 4

Example	Structure	IUPAC Name	¹ H NMR (400 MHz)
7.1		4-[1-[(4-fluorophenyl)methyl]-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 9.33 (s, 1H), 8.04 (s, 1H), 7.99 (d, <i>J</i> = 8.0 Hz, 1H), 7.46 (d, <i>J</i> = 8.0 Hz, 1H), 7.18-7.26 (m, 2H), 7.03 (t, <i>J</i> = 8.0 Hz, 2H), 4.92 (s, 2H), 2.46 (s, 3H), 2.31 (s, 3H)
7.2		3,5-dimethyl-4-[1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]isoxazole	(CDCl ₃): δ 9.31 (s, 1H), 8.57 (d, <i>J</i> = 4.0 Hz, 1H), 8.42 (d, <i>J</i> = 8.0 Hz, 1H), 8.02 (s, 1H), 7.65 (t, <i>J</i> = 8.0 Hz, 1H), 7.50 (d, <i>J</i> = 8.0 Hz, 1H), 7.28 (s, 1H), 7.20-7.23 (m, 1H), 5.13 (s, 2H), 2.46 (s, 3H), 2.31 (s, 3H)

10 [0294]

Scheme 8



[0295]

6-(3,5-Dimethylisoxazol-4-yl)-7-methoxy-1H-quinoxalin-2-one (44)

5 The preparation of compound **44** from compound **29** was carried out in a manner similar to that described for the preparation of compound **33** according to Method C (60% yield).

[0296]

4-(2-Chloro-7-methoxy-quinoxalin-6-yl)-3,5-dimethyl-isoxazole (45)

To a mixture of compound **44** (4.42 mmol) and POCl₃ (91.50 mmol) was added N,N-dimethylaniline (0.22 mmol). The resulting mixture was refluxed for 15 minutes. The mixture was cooled to room temperature, and POCl₃ was evaporated under reduced
 15 pressure. The residual POCl₃ was quenched with H₂O, and the aqueous layer was extracted with DCM (3 times). The combined organic layers were washed with water, brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give the title compound **45** (80%).

20 [0297]

[6-(3,5-Dimethylisoxazol-4-yl)-7-methoxy-quinoxalin-2-yl]hydrazine (46)

Hydrazine hydrate (17.30 mmol) was added to a solution of compound **45** (3.46 mmol) in methanol at room temperature. The
 25 resulting solution was refluxed for 12 h. The solid was collected by filtration, washed with methanol and dried to give the title compound **46** (80%).

[0298]

Compound 47: General method for coupling with isocyanate

To a stirred solution of compound **46** (1.0 eq.) in DCM was added appropriate isocyanate (1.0 eq). The resulting mixture was stirred at room temperature for overnight. The solid was collected by filtration, washed with EtOAc and dried to give the title compound **47** (60-70%).

[0299]

Compound 48: General method for triazole cyclization

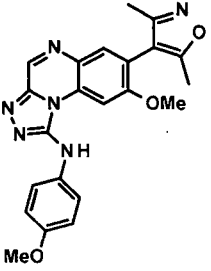
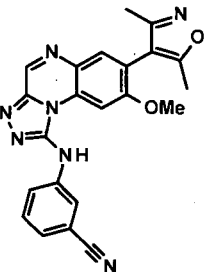
A heterogeneous mixture of compound **47** (1.0 eq.) in phosphorous oxychloride (10 eq.) was refluxed for 4h. The homogenous solution was allowed to cool to room temperature. Excess POCl₃ was evaporated in vacuo, and resulting residue was quenched with saturated sodium bicarbonate solution. The solid was collected by filtration and washed with water and DCM to give the title compound **48** (40-50%).

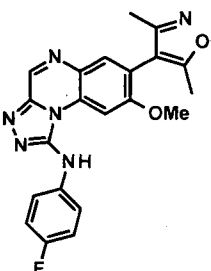
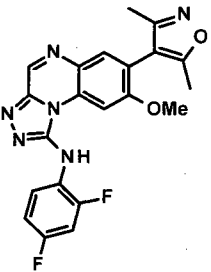
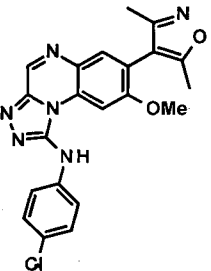
[0300]

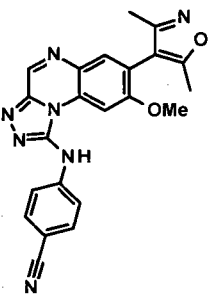
The following compounds of Examples were synthesized according to Scheme 8:

[0301]

Table 5

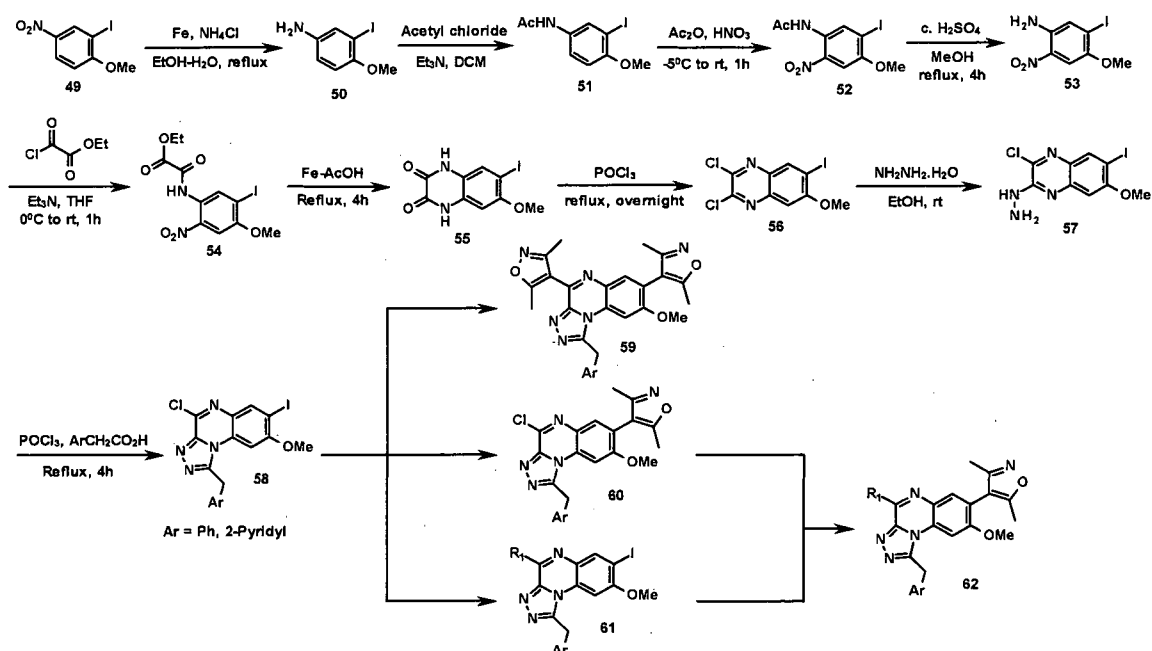
Example	Structure	IUPAC Name	¹ H NMR (400 MHz)
8.1		7-(3,5-dimethylisoxazol-4-yl)-8-methoxy-N-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]quinoxalin-1-amine	(DMSO-d ₆): δ 9.07 (s, 1H), 7.91 (s, 1H), 7.87 (s, 1H), 6.99 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 3.68 (s, 3H), 3.66 (s, 3H), 2.27 (s, 3H), 2.07 (s, 3H)
8.2		3-[[7-(3,5-dimethylisoxazol-4-yl)-8-methoxy-[1,2,4]triazolo[4,3-	(DMSO-d ₆): δ 9.87 (brs, 1H), 9.17 (s, 1H), 7.98 (s, 1H), 7.91 (s, 1H), 7.44-7.51 (m, 3H), 7.36-7.38 (m, 1H), 3.70

		a]quinoxalin-1-yl]amino]benzoni- trile	(s, 3H), 2.30 (s, 3H), 2.10 (s, 3H)
8.3		7-(3,5-dimethylisoxazol-4-yl)-N-(4-fluorophenyl)-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxalin-1-amine	(DMSO-d ₆): δ 9.49 (brs, 1H), 9.13 (s, 1H), 7.94 (s, 1H), 7.90 (s, 1H), 7.07-7.15 (m, 4H), 3.69 (s, 3H), 2.29 (s, 3H), 2.09 (s, 3H)
8.4		N-(2,4-difluorophenyl)-7-(3,5-dimethylisoxazol-4-yl)-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxalin-1-amine	(DMSO-d ₆): δ 9.07 (s, 1H), 8.28 (brs, 1H), 7.91 (s, 1H), 7.40-7.48 (m, 1H), 7.30-7.38 (m, 1H), 6.98-7.02 (m, 1H), 3.83 (s, 3H), 2.31 (s, 3H), 2.11 (s, 3H)
8.5		N-(4-chlorophenyl)-7-(3,5-dimethylisoxazol-4-yl)-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxalin-1-amine	(DMSO-d ₆): δ 9.56 (brs, 1H), 9.15 (s, 1H), 7.95 (s, 1H), 7.92 (s, 1H), 7.31 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H), 3.70 (s, 3H), 2.29 (s, 3H), 2.09 (s, 3H)

8.6		4-[[7-(3,5-dimethylisoxazol-4-yl)-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxalin-1-yl]amino]benzonitrile	(DMSO- <i>d</i> ₆): δ 10.13 (brs, 1H), 9.19 (s, 1H), 7.98 (s, 1H), 7.89 (s, 1H), 7.71 (d, <i>J</i> = 9.2 Hz, 2H), 7.20 (d, <i>J</i> = 8.4 Hz, 2H), 3.69 (s, 3H), 2.29 (s, 3H), 2.09 (s, 3H)
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[0302]

Scheme 9



5 [0303]

3-Iodo-4-methoxy-aniline (50)

NH₄Cl (38.3 g, 716.8 mmol) dissolved in H₂O (~100 ml) was added to a solution of compound **49** (50g, 179.2 mmol) in ethanol (600 mmol). Iron powder (40.15 g, 716.8) was added to this mixture, and the mixture was refluxed for 5 h. The reaction mixture was cooled to room temperature, and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, and the solution was washed with water and brine, dried over Na₂SO₄, filtered and concentrated

under reduced pressure to give the title compound **50**. (42 g, 93%).

¹HNMR (400 MHz, DMSO-*d*₆) δ: 7.02 (d, *J* = 2.4 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 6.55 (dd, *J* = 2.8, 8.8 Hz, 1H), 4.81 (brs, 2H), 3.66 (s, 3H).

[0304]

N-(3-Iodo-4-methoxy-phenyl)-acetamide (51)

Acetyl chloride (18.4 ml, 259 mmol) was added drop wise to a stirred solution of compound **50** (43.0 g, 172.6 mmol) and triethylamine (73 ml, 518 mmol) in DCM at 0°C. After complete addition, the reaction mixture was stirred at room temperature for 1h. The reaction mixture was quenched with water, and the organic layer was separated, washed with water and brine and dried over Na₂SO₄. The solvent was evaporated under reduced pressure to give the title compound **51** (39 g, 67%).

¹HNMR (400 MHz, DMSO-*d*₆) δ: 9.84 (brs, 1H), 8.06 (d, *J* = 2.8 Hz, 1H), 7.48 (dd, *J* = 2.8, 8.8 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 3.77 (s, 3H), 2.0 (s, 3H).

[0305]

N-(5-Iodo-4-methoxy-2-nitro-phenyl)-acetamide (52)

Concentrated nitric acid (78 ml) was added to acetic anhydride (390 ml) cooled to -10°C (internal temp). To this solution was added compound **51** (39 g, 134 mmol) portion wise at a rate which maintained an internal temperature below -5°C. The solution was stirred for 1h while warming to room temperature. The solution was then poured into an ice-water mixture, and the mixture was extracted several times with ethyl acetate. The combined extracts were washed with 10% NaHCO₃, water and brine, dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was triturated in methanol to give the title compound **52**. (36 g, 80%).

¹HNMR (400 MHz, DMSO-*d*₆) δ: 10.06 (brs, 1H), 8.02 (s, 1H), 7.45 (s, 1H), 3.90 (s, 3H), 2.02 (s, 3H).

[0306]

5-Iodo-4-methoxy-2-nitro-aniline (53)

Concentrated H₂SO₄ (60 ml) was added drop wise to a stirred suspension of compound **52** (36 g, 107.1 mmol) in methanol (1.3 lit), and the mixture was refluxed for 4h. The solvent was evaporated under reduced pressure, and the residue
5 was dissolved in ethyl acetate and water. The organic layer was separated, washed with sat.NaHCO₃ solution and brine, dried over Na₂SO₄, filtered and concentrated under vacuum to give the title compound **53** (31g, 98%).

¹HNMR (400 MHz, DMSO-*d*₆) δ: 7.63 (s, 1H), 7.33 (s, 1H), 7.20
10 (brs, 1H), 3.77 (s, 3H).

[0307]

Ethyl 2-(5-iodo-4-methoxy-2-nitro-anilino)-2-oxo-acetate (54)

Ethyl oxalyl chloride (17.7 ml, 158.1 mmol) was added dropwise at 0°C to a stirred solution of compound **53** (31.0 g,
15 105.4 mmol) and triethylamine (29.6 ml, 210.8 mmol) in THF (160 ml). After complete addition, the reaction mixture was stirred at room temperature for 1h. The mixture was quenched with water and extracted with ethyl acetate, and the combined extracts were washed with water and brine and dried over Na₂SO₄.
20 The solvent was evaporated under reduced pressure to give the title compound **54** (40 g, 96%).

¹HNMR (400 MHz, DMSO-*d*₆) δ: 8.40 (s, 1H), 7.58 (s, 1H), 4.33 (q, *J* = 6.8 Hz, 2H), 1.32 (t, *J* = 6.8 Hz, 3H).

[0308]

6-Iodo-7-methoxy-1,4-dihydroquinoxaline-2,3-dione (55)

Iron powder (28.4 g, 507.6 mmol) was added to a stirred solution of compound **54** (40g, 101.5 mmol) in acetic acid (250 ml), and the resulting mixture was heated to reflux. After 4h, the acetic acid was evaporated under reduced pressure, and the
30 residue was filtered through Buchner funnel and washed with MeOH:DCM (1:9). The solvent was evaporated under reduced pressure to give the title compound **55** (Crude amount 50 g contains inorganic material).

[0309]

2,3-Dichloro-6-iodo-7-methoxy-quinoxaline (56)

POCl₃ (1 L) was added slowly to the crude compound **55** (104 g, 183.6 mmol) obtained from the previous step. After complete addition, the resulting mixture was heated to reflux for overnight. The reaction mixture was cooled to room temperature and poured into crushed ice. The solid was collected by filtration and dried under vacuum to give the title compound **56** (46.6 g).

¹HNMR (400 MHz, DMSO-d₆) δ: 8.59 (s, 1H), 7.49 (s, 1H), 4.03 (s, 3H).

[0310]

(3-Chloro-6-iodo-7-methoxy-quinoxalin-2-yl)-hydrazine (57)

Hydrazine monohydrate (14 ml, 289.6 mmol) was added drop wise to a stirred suspension of compound **56** (46.6 g, 131.6 mmol) in ethanol (900 ml), and the mixture was stirred at room temperature for overnight. The solid was collected by filtration, washed with ethanol and dried under vacuum to give the title compound **57** (45 g, 98%).

¹HNMR (400 MHz, DMSO-d₆) δ: 8.94 (brs, 1H), 8.15 (s, 1H), 7.08 (s, 1H), 4.63 (brs, 2H), 3.93 (s, 3H).

[0311]

Compound 58: General method for triazole cyclization

Compound **57** (40 g, 114.2 mmol) and appropriate carboxylic acid were refluxed in POCl₃ for 4 hours. The reaction mixture was cooled to room temperature and poured into crushed ice. The solid was collected by filtration, washed with water and dried under vacuum to give the title compound **58** (60-70%).

[0312]

Compound 59: General method for Suzuki coupling

The preparation of compound **59** from compound **58** was carried out in a manner similar to that described in the preparation of compound **33** according to Method D (60%).

[0313]

Compound 60: General method for Suzuki coupling

The preparation of compound **60** from compound **58** was carried out in a manner similar to that described in the

preparation of compound **33** according to Method C (50-60%).

[0314]

Compound 62: General method for Cl-replacement reaction in compound 60

5 **7-(3,5-Dimethylisoxazol-4-yl)-8-methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxaline-4-carbonitrile (R₁ = CN, Ar = 2-pyridyl)**

A mixture of compound **60** (0.28 mmol) and zinc cyanide (0.85 mmol) in DMF (6 ml) was degassed with N₂ for 10 min, and
10 then Pd(PPh₃)₄ (0.028 mmol) was added thereto. The resulting mixture was heated at 120°C for 16h. The reaction mixture was cooled to room temperature, poured into water and extracted with ethyl acetate. The combined organic layers were washed with water and brine and dried over Na₂SO₄. The solvent was
15 evaporated, and the residue was purified by column chromatography to give the title compound (23%).

[0315]

**7-(3,5-Dimethylisoxazol-4-yl)-1-[(3-fluorophenyl)methyl]-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline-4-carbonitrile (R₁ =
20 CN, Ar = 3-fluorophenyl)**

A mixture of compound **60** (0.22 mmol) and zinc cyanide (0.68 mmol) in DMF (6 ml) was degassed with N₂ for 10 min, and then Pd(PPh₃)₄ (0.022 mmol) was added thereto, and the mixture was placed in oil bath and heated it at 120°C for 16 hours.
25 The reaction mixture was cooled to room temperature, poured into water and extracted with ethyl acetate. The combined extracts were washed with water and brine and dried over Na₂SO₄. The residue was purified by column chromatography using 230-400 mesh silica and methanol in DCM (0-5%) as eluent. The
30 solvent was evaporated under reduced pressure to give the title compound (25%).

[0316]

4-[4,8-Dimethoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole (R₁ = OMe, Ar = 2-pyridyl)
35

A mixture of compound **60** (0.095 mmol) in 3 ml of ammonia in methanol (2.0 M) was stirred in screw cap vial at room temperature for 16 h. The solvent was evaporated under reduced pressure, and the residue was purified using preparative TLC to give the title compound (50%).

[0317]

4-[4-Cyclopropyl-8-methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole (R₁ = Cyclopropyl, Ar = 2-pyridyl)

A mixture of compound **60** (0.095 mmol), cyclopropylboronic acid (0.47 mmol), K₃PO₄ (0.47 mmol) and tricyclohexylphosphine (0.019 mmol) in dry toluene (2 ml) and water (0.4 ml) was degassed with N₂ for 30 min, and then Pd(OAc)₂ (0.004 mmol) was added thereto. The resulting mixture was heated at 100°C for 16 h. The reaction mixture was cooled to room temperature and diluted with EtOAc, and the organic layer was separated, washed with water and brine and dried over Na₂SO₄. The solvent was evaporated, and the residue was purified by preparative TLC to give the title compound (35%).

[0318]

4-[4-Ethoxy-8-methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole (R₁ = OEt, Ar = 2-pyridyl)

Sodium ethoxide (0.14) was added to a stirred solution of compound **60** (0.071 mmol) in ethanol (2 ml). The resulting mixture was stirred at room temperature for overnight. The mixture was quenched with sat. NH₄Cl solution and extracted with ethyl acetate. The combined extracts were washed with water and brine and dried over Na₂SO₄. The solvent was evaporated, and the residue was purified by preparative TLC to give the title compound (65%).

[0319]

7-(3,5-Dimethylisoxazol-4-yl)-8-methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4-amine (R₁ = NH₂, Ar = 2-pyridyl)

Compound **57** (40 g, 114.2 mmol) and 2-pyridylacetic acid (21.8 g, 125.7 mmol) were refluxed in POCl₃ (400 ml) for 4 hours. The reaction mixture was cooled to room temperature and poured into crushed ice. The solid was collected by filtration, washed with water and dried under vacuum to give the title compound **58** (34 g, 66%).

To a solution of compound **58** (29 g, 64.3 mmol) and 3,5-dimethylisoxazole-4-boronic acid (27.3 g, 192.9 mmol) in DME (360 ml) was added Cs₂CO₃ (62.8 g, 192.9 mmol) in water (90 ml). The mixture was degassed with N₂ for 30 minutes, tetrakis(triphenylphosphine)palladium(0) (3.71 g, 3.2 mmol) was added thereto, and the resulting mixture was heated at 105°C for 2 h. The mixture was cooled to room temperature, poured into water and extracted with DCM. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **60** (6.3 g, 23%).

Liq. NH₃ was purged into a solution of compound **60** (0.095 mmol) in 1,4-dioxane (2 ml) at 0-5°C in a sealed tube. The resulting mixture was stirred at 100°C for 24 h. The solvent was evaporated under reduced pressure, and the residue was purified using preparative HPLC to give the title compound (45%).

[0320]

4-[4-(Azetidin-1-yl)-8-methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole (R₁ = Azetidin-1-yl, Ar = 2-pyridyl)

A mixture of compound **60** (0.095 mmol), azetidine hydrochloride (0.14 mmol) and K₂CO₃ (0.28 mmol) in DMF was stirred at 80°C for 16 h. The reaction mixture was cooled to room temperature, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over Na₂SO₄. The solvent was evaporated, and the residue was purified using preparative HPLC to give the title compound (40%).

[0321]

7-(3,5-Dimethylisoxazol-4-yl)-8-methoxy-N,N-dimethyl-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4-amine ($R_1 = \text{NMe}_2$, Ar = 2-pyridyl)

5 A mixture of compound **60** (0.095 mmol) and dimethylamine (2.0 M in methanol) (1.5 ml) was stirred at 80°C in sealed tube for 16 h. The solvent was evaporated under reduced pressure, and the residue was purified by preparative TLC to give the title compound (40%).

10 [0322]

7-(3,5-Dimethylisoxazol-4-yl)-N-ethyl-8-methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4-amine ($R_1 = \text{NEt}$, Ar = 2-pyridyl)

A mixture of compound **60** (0.095 mmol) and ethylamine (2.0 M in THF) (1.5 ml) was stirred at 80°C in sealed tube for 16 h. The solvent was evaporated under reduced pressure, and the residue was purified by preparative TLC to give the title compound (30%).

[0323]

20 **Compound 61: General method for Cl-replacement reaction in compound 58**

7-Iodo-8-methoxy-N-methyl-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4-amine ($R_1 = \text{NMe}$, Ar = 2-pyridyl)

25 Compound **57** (40 g, 114.2 mmol) and 2-pyridylacetic acid (21.8 g, 125.7 mmol) were refluxed in POCl_3 (400 ml) for 4 hours. The reaction mixture was cooled to room temperature and poured into crushed ice. The solid was collected by filtration, washed with water and dried under vacuum to give the title compound **58** (34 g, 66%).

A mixture of compound **58** (0.095 mmol) and methylamine (2 mL, 2.0 M in THF) was stirred at 80°C in sealed tube for 16 h. The reaction mixture was cooled to room temperature, and the residue was triturated in DCM. The solid was collected by
35 filtration, again triturated in water and collected by

filtration. The solid was washed with hexane and dried in vacuum to give the title compound (53%).

¹HNMR (400 MHz, DMSO-*d*₆) δ : 8.45 (brs d, *J* = 4.8 Hz, 1H), 8.05 (d, *J* = 5.2 Hz, 1H), 7.79 (dt, *J* = 7.2, 2.0 Hz, 1H), 7.43 (s, 2H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.31-7.28 (m, 1H), 5.16 (s, 2H), 3.60 (s, 3H), 3.03 (d, *J* = 4.4 Hz, 3H), 2.24 (s, 3H), 2.04 (s, 3H).

[0324]

7-Iodo-8-methoxy-4-methylsulfanyl-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxaline (R₁ = SMe, Ar = 2-pyridyl)

A mixture of compound **58** (100 mg, 0.22 mmol) and sodium thiomethoxide (15 mg, 0.26 mmol) in DMF was heated at 60°C for 15 h. The reaction mixture was diluted with 5% methanol in DCM. The organic layer was separated, washed with water and brine and dried over Na₂SO₄. The solvent was evaporated under reduced pressure, and the crude residue was purified to give the title compound (59%) as a yellow solid.

[0325]

Compound 62: General method for Suzuki coupling

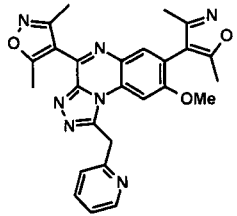
The preparation of the compound **62** from compound **61** was carried out in a manner similar to that described in the preparation of compound **33** according to Method D (50-60%).

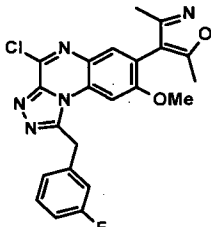
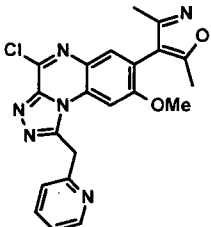
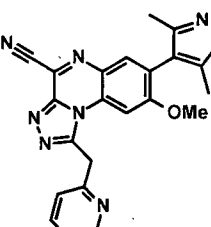
[0326]

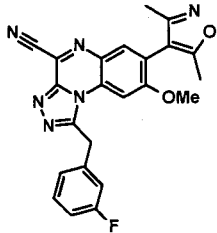
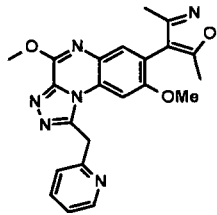
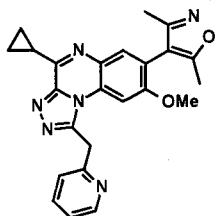
The following according to Examples were synthesized according to Scheme 9:

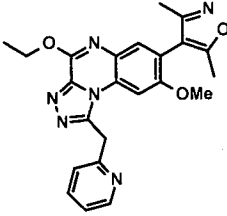
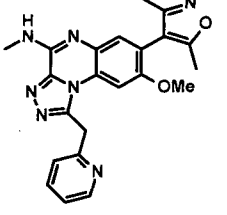
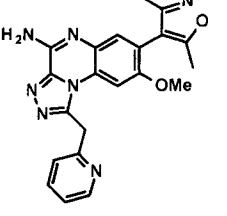
[0327]

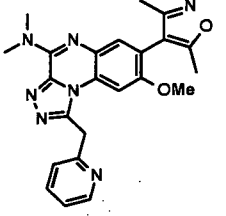
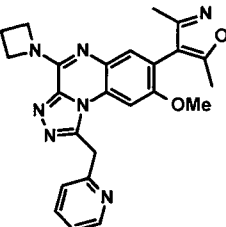
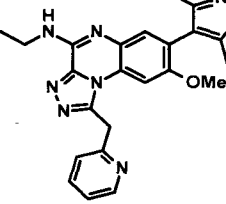
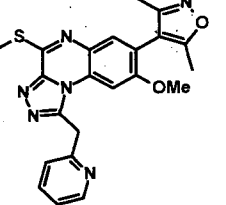
Table 6

Example	Structure	IUPAC Name	¹ H NMR (400 MHz)
9.1		4-[4-(3,5-dimethylisoxazol-1-yl)-8-methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-	(DMSO- <i>d</i> ₆): δ 8.48 (d, <i>J</i> = 6.0 Hz, 1H), 7.97 (s, 1H), 7.82 (dt, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.27 (s, 1H), 7.45 (d, <i>J</i> = 8.0 Hz, 1H), 7.32 (m, 1H), 5.23 (s, 2H), 3.75 (s,

		a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole	3H), 2.62 (s, 3H), 2.41 (s, 3H), 2.28 (s, 3H), 2.07 (s, 3H)
9.2		4-[4-chloro-1-[(3-fluorophenyl)methyl]-8-methoxy-1,2,4-triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(DMSO-d ₆): δ 7.96 (s, 1H), 7.41-7.38 (m, 2H), 7.15-7.10 (m, 3H), 5.15 (s, 2H), 3.69 (s, 3H), 2.26 (s, 3H), 2.06 (s, 3H)
9.3		4-[4-chloro-8-methoxy-1-(2-pyridylmethyl)-1,2,4-triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(CDCl ₃): δ 8.55 (d, J = 4.0 Hz, 1H), 8.06 (s, 1H), 7.78 (s, 1H), 7.67 (dt, J = 8.0, 1.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.26-7.23 (m, 1H), 5.15 (s, 2H), 3.97 (s, 3H), 2.31 (s, 3H), 2.16 (s, 3H)
9.4		7-(3,5-dimethylisoxazol-4-yl)-8-methoxy-1-(2-pyridylmethyl)-1,2,4-triazolo[4,3-a]quinoxaline-4-carbonitrile	(DMSO-d ₆): δ 8.48 (d, J = 4.4 Hz, 1H), 8.15 (s, 1H), 7.82 (dt, J = 7.2, 1.6 Hz, 1H), 7.77 (s, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.32 (m, 1H), 5.30 (s, 2H), 3.82 (s, 3H), 2.28 (s, 3H), 2.08 (s, 3H)

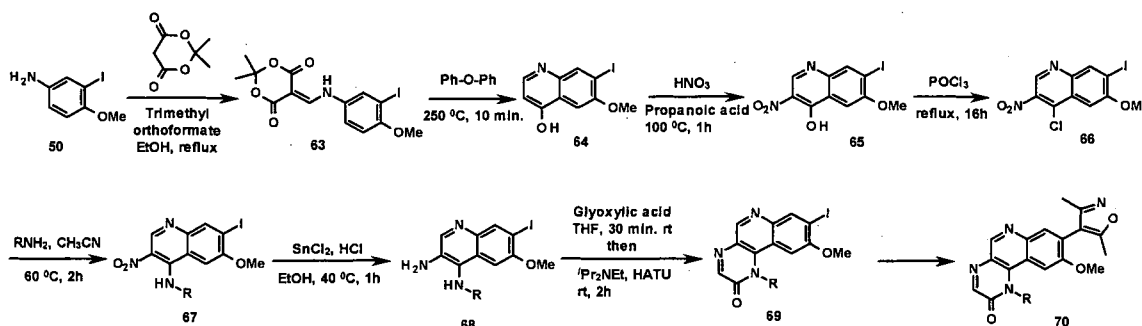
9.5		7-(3,5-dimethylisoxazolo-1-yl)-1-[(3-fluorophenyl)methyl]-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline-4-carbonitrile	(DMSO- <i>d</i> ₆): δ 8.17 (s, 1H), 7.43 (s, 1H), 7.42-7.38 (m, 1H), 7.15-7.06 (m, 3H), 5.19 (s, 2H), 3.75 (s, 3H), 2.27 (s, 3H), 2.07 (s, 3H)
9.6		4-[4,8-dimethoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(DMSO- <i>d</i> ₆): δ 8.45 (d, <i>J</i> = 4.0 Hz, 1H), 7.80 (dt, <i>J</i> = 8.0, 1.2 Hz, 1H), 7.66 (s, 1H), 7.56 (s, 1H), 7.40 (d, <i>J</i> = 8.0 Hz, 1H), 7.30 (m, 1H), 5.24 (s, 2H), 4.16 (s, 3H), 3.67 (s, 3H), 2.25 (s, 3H), 2.05 (s, 3H)
9.7		4-[4-cyclopropyl-8-methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(DMSO- <i>d</i> ₆): δ 8.45 (d, <i>J</i> = 4.0 Hz, 1H), 7.80 (dt, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.45 (s, 1H), 7.57 (s, 1H), 7.42 (d, <i>J</i> = 8.0 Hz, 1H), 7.30 (m, 1H), 5.24 (s, 2H), 3.68 (s, 3H), 2.96 (m, 1H), 2.25 (s, 3H), 2.04 (s, 3H), 1.33 (m, 2H), 1.23 (m, 2H)

9.8		4-[4-ethoxy-8-methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(DMSO- <i>d</i> ₆): δ 8.45 (d, J = 4.8 Hz, 1H), 7.08 (dt, J = 7.6, 1.6 Hz, 1H), 7.63 (s, 1H), 7.56 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.32-7.29 (m, 1H), 5.21 (s, 2H), 4.64 (d, J = 7.2 Hz, 2H), 3.67 (s, 3H), 2.26 (s, 3H), 2.05 (s, 3H), 1.48 (d, J = 7.2 Hz, 3H)
9.9		7-(3,5-dimethylisoxazol-1-yl)-8-methoxy-N-methyl-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4-amine	(DMSO- <i>d</i> ₆): δ 8.45 (d, J = 4.8 Hz, 1H), 8.05 (d, J = 5.2 Hz, 1H), 7.79 (dt, J = 7.2, 2.0 Hz, 1H), 7.43 (s, 2H), 7.39 (d, J = 7.6 Hz, 1H), 7.31-7.28 (m, 1H), 5.16 (s, 2H), 3.60 (s, 3H), 3.03 (d, J = 4.4 Hz, 3H), 2.24 (s, 3H), 2.04 (s, 3H)
9.10		7-(3,5-dimethylisoxazol-1-yl)-8-methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4-amine	(DMSO- <i>d</i> ₆): δ 8.45 (d, J = 4.8 Hz, 1H), 7.80 (dt, J = 7.6, 1.6 Hz, 1H), 7.44-7.39 (m, 4H), 7.36 (s, 1H), 7.31-7.28 (m, 1H), 5.16 (s, 2H), 3.60 (s, 3H), 2.24 (s, 3H), 2.04 (s, 3H)

9.11		7-(3,5-dimethylisoxazol-1-yl)-8-methoxy-N,N-dimethyl-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4-amine	(DMSO- <i>d</i> ₆): δ 8.45 (d, J = 4.4 Hz, 1H), 7.79 (dt, J = 7.2, 2.0 Hz, 1H), 7.45 (s, 1H), 7.40-7.38 (m, 2H), 7.31-7.28 (m, 1H), 5.18 (s, 2H), 3.59 (s, 3H), 3.55 (s, 6H), 2.24 (s, 3H), 2.03 (s, 3H)
9.12		4-[4-(azetidin-1-yl)-8-methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(DMSO- <i>d</i> ₆): δ 8.45 (d, J = 3.6 Hz, 1H), 7.79 (dt, J = 7.6, 2.0 Hz, 1H), 7.43 (s, 1H), 7.40 (s, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.29 (m, 1H), 5.20 (s, 2H), 4.50 (brs, 4H), 3.59 (s, 3H), 2.46 (m, 2H), 2.23 (s, 3H), 2.03 (s, 3H)
9.13		7-(3,5-dimethylisoxazol-1-yl)-N-ethyl-8-methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4-amine	(DMSO- <i>d</i> ₆): δ 8.46 (d, J = 4.8 Hz, 1H), 8.03 (t, J = 5.6 Hz, 1H), 7.79 (dt, J = 8.0, 2.0 Hz, 1H), 7.41 (m, 3H), 7.30 (m, 1H), 5.16 (s, 2H), 3.58 (m, 5H), 2.24 (s, 3H), 2.04 (s, 3H), 1.23 (d, J = 2.0 Hz, 3H)
9.14		4-[8-methoxy-4-methylsulfanyl-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-7-yl]-3,5-dimethylisoxazole	(DMSO- <i>d</i> ₆) δ : 8.45 (d, J = 4.4 Hz, 1H), 7.83-7.78 (m, 2H), 7.56 (s, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.30 (dd, J =

		[4,3-a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole	4.8, 7.2 Hz, 1H), 5.23 (s, 2H), 3.69 (s, 3H), 2.71 (s, 3H), 2.27 (s, 3H), 2.06 (s, 3H)
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[0328]

Scheme 10

5 [0329]

5-[(3-Iodo-4-methoxy-anilino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (63)

To a solution of compound **50** (22.0 g, 883 mmol) in ethanol (120 ml) were added trimethyl orthoformate (10.6 ml, 97.1 mmol) and Meldrums acid (15.2 g, 106 mmol). The resulting mixture was heated to reflux for 2 h, cooled to room temperature and filtered. The filtrate was washed with ethanol and dried under vacuum to give the title compound **63** (29.0 g, 80%).

15 ¹HNMR (400 MHz, DMSO-*d*₆) δ: 11.15 (d, *J* = 14.8 Hz, 1H), 8.42 (d, *J* = 14.4 Hz, 1H), 8.01 (d, *J* = 2.8 Hz, 1H), 7.56 (dd, *J* = 6.0, 8.8 Hz, 1H), 7.01 (d, *J* = 9.2 Hz, 1H), 3.81 (s, 3H), 1.64 (s, 6H).

[0330]

20 **7-Iodo-6-methoxy-quinolin-4-ol (64)**

Compound **63** (29.0 g, 71.9 mmol) was added in portion wise to boiling diphenyl ether (180 ml). 10 minutes after completion of addition, the reaction mixture was cooled to room temperature, diluted with diethyl ether and ethyl acetate

(5:1), and filtered. The obtained solid was washed with ethyl acetate and dried under vacuum to give the title compound **64** (76%).

¹HNMR (400 MHz, DMSO-*d*₆) δ: 11.67 (brs, 1H), 8.04 (s, 1H), 7.86 (t, *J* = 6.8 Hz, 1H), 7.44 (s, 1H), 6.01 (d, *J* = 7.2 Hz, 1H), 3.89 (s, 3H).

[0331]

7-Iodo-6-methoxy-3-nitro-quinolin-4-ol (65)

Nitric acid (7 ml) was added slowly to a solution of compound **64** (19.0 g, 63.1 mmol) in propanoic acid (220 ml) at room temperature, followed by heating to 100°C for 1 h. After cooling with an ice bath, the precipitate was collected by filtration, and washed with pentane to give the title compound **65** (14 g, 65%) as a yellow solid.

¹HNMR (400 MHz, DMSO-*d*₆) δ: 12.92 (brs, 1H), 9.15 (s, 1H), 8.19 (s, 1H), 7.58 (s, 1H), 3.95 (s, 3H).

[0332]

4-Chloro-7-iodo-6-methoxy-3-nitro-quinoline (66)

A suspension of compound **65** (12.0 g, 34.6 mmol) in POCl₃ (50 ml) was refluxed for 16 h. After cooling, the solvent was evaporated in vacuum. The resulting residue was poured into saturated aqueous NaHCO₃, and the mixture was extracted with DCM, washed with water, and dried over Na₂SO₄. The solvent was evaporated under reduced pressure to give title the compound **66** (80%).

¹HNMR (400 MHz, DMSO-*d*₆) δ: 9.23 (s, 1H), 8.73 (s, 1H), 7.56 (s, 1H), 4.08 (s, 3H).

[0333]

Compound 67: General method for amine coupling

A mixture of compound **66** (0.96 mmol) and amine (1.92 mmol) in acetonitrile (5 ml) was heated to 60°C for 2 h. The mixture was cooled to room temperature and extracted with DCM. The organic layer was washed with saturated aqueous NaHCO₃, water and brine and dried over Na₂SO₄. The solvent was evaporated under reduced pressure to give the title compound

67 (yield 60-70%).

[0334]

Compound 68: General method for nitro reduction

To a solution of compound **67** (1.06 mmol) in a mixture of
5 ethanol (5 ml) and HCl (1 ml) was added SnCl₂ · 2H₂O (2.12 mmol).
The reaction mixture was heated to 40°C for 1 h. 1N NaOH was
added thereto, and the mixture was extracted with DCM. The
organic layer was washed with water and brine, dried over
Na₂SO₄ and concentrated. The residue was purified by flash
10 chromatography on silica gel (DCM/MeOH, 95:5) to give the
title compound **68** (50-60%).

[0335]

Compound 69: General method for cyclization

Glyoxilic acid (0.21 mmol) was added to a suspension of
15 compound **68** (0.21 mmol) in THF (2 ml), and the mixture was
stirred under argon atmosphere for 30 minutes at room
temperature. Diisopropylethylamine (0.42 mmol) and HATU (0.23
mmol) were added thereto and the mixture was stirred continued
another 2 h at room temperature. The reaction mixture was
20 concentrated under reduced pressure, and the residue was
dissolved in ethyl acetate, and the solution was washed with
water and brine, dried over Na₂SO₄, filtered and concentrated.
The solvent was evaporated under reduced pressure to give the
title compound **69** (30-50%).

25 [0336]

Compound 70: General method for Suzuki coupling

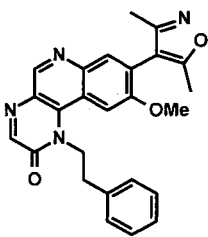
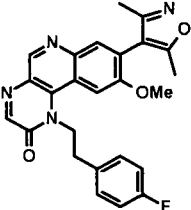
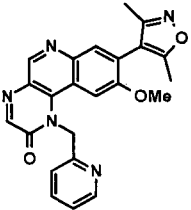
The preparation of the compound **70** from compound **69** was
carried out in a manner similar to that described in the
preparation of compound **33** according to Method C (50-60%).

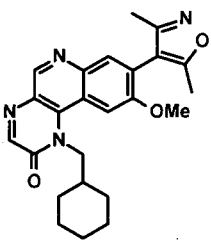
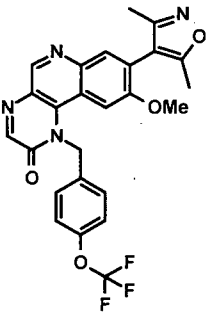
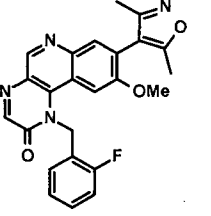
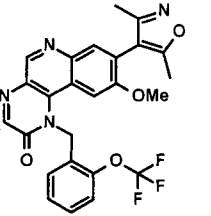
30 [0337]

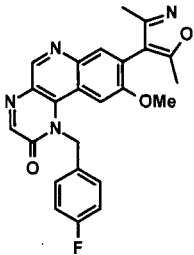
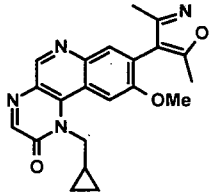
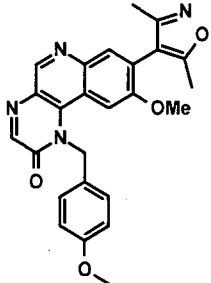
The following compounds of Examples were synthesized
according to Scheme 10:

[0338]

Table 7

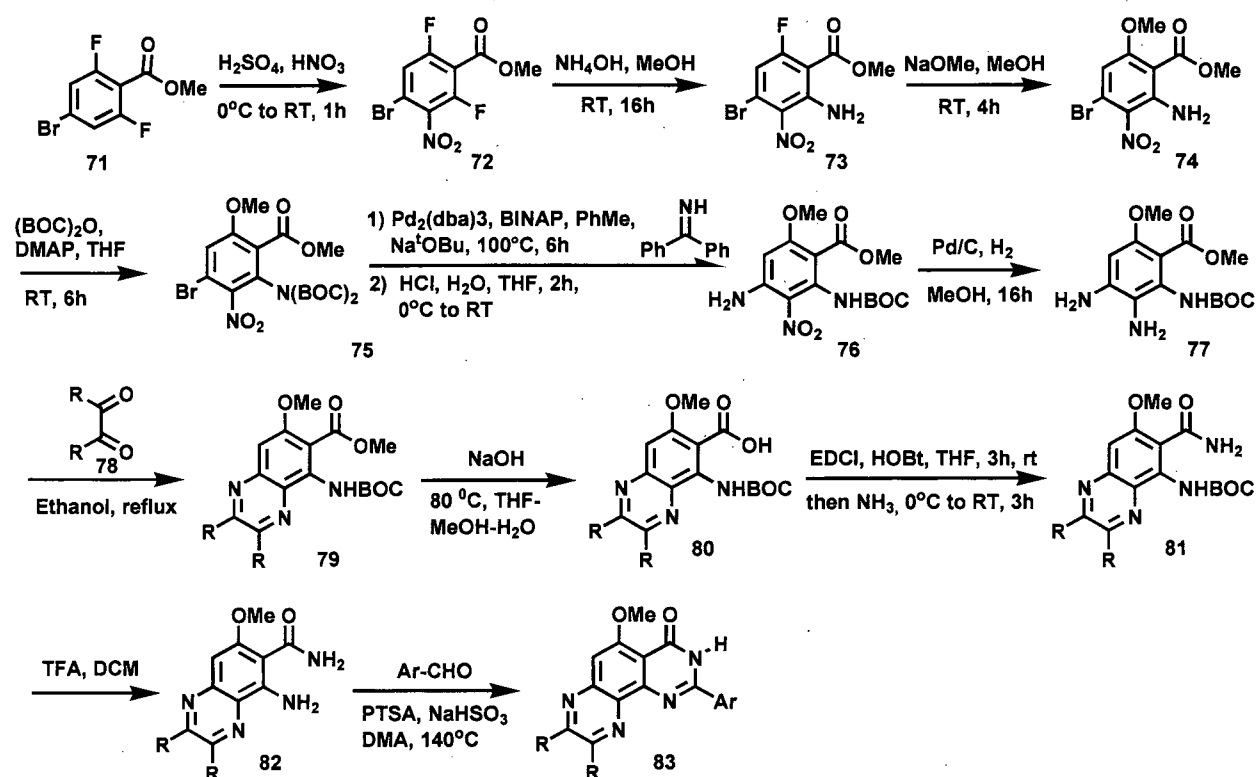
Example	Structure	IUPAC Name	¹ H NMR (400 MHz)
10.1		8-(3,5-dimethylisoxazol-4-yl)-9-methoxy-1-phenethyl-pyrazino[2,3-c]quinolin-2-one	(CDCl ₃): δ 9.13 (s, 1H), 8.43 (s, 1H), 8.00 (s, 1H), 7.79 (s, 1H), 7.37-7.26 (m, 5H), 5.02 (t, <i>J</i> = 8.0 Hz, 2H), 3.67 (s, 3H), 3.51 (t, <i>J</i> = 8.8 Hz, 2H), 2.38 (s, 3H), 2.29 (s, 3H)
10.2		8-(3,5-dimethylisoxazol-4-yl)-1-[2-(4-fluorophenyl)ethyl]-9-methoxy-pyrazino[2,3-c]quinolin-2-one	(CDCl ₃): δ 9.13 (s, 1H), 8.43 (s, 1H), 8.01 (s, 1H), 7.77 (s, 1H), 7.28-7.24 (m, 2H), 7.04 (t, <i>J</i> = 8.8 Hz, 2H), 4.98 (t, <i>J</i> = 8.8 Hz, 2H), 3.73 (s, 3H), 3.46 (t, <i>J</i> = 8.4 Hz, 2H), 2.39 (s, 3H), 2.23 (s, 3H)
10.3		8-(3,5-dimethylisoxazol-4-yl)-9-methoxy-1-(2-pyridylmethyl)pyrazino[2,3-c]quinolin-2-one	(DMSO- <i>d</i> ₆): δ 9.09 (s, 1H), 8.59 (d, <i>J</i> = 4.0 Hz, 1H), 8.52 (s, 1H), 8.00 (s, 1H), 7.88 (dt, <i>J</i> = 7.6, 1.6 Hz, 1H), 7.65 (d, <i>J</i> = 8.0 Hz, 1H), 7.54 (s, 1H), 7.39 (t, <i>J</i> = 6.8 Hz, 1H), 5.86 (s, 2H), 3.25 (s, 3H), 2.30 (s, 3H), 2.09 (s, 3H)

10.4		1-(cyclohexylmethyl)-8-(3,5-dimethylisoxazol-4-yl)-9-methoxy-pyrazino[2,3-c]quinolin-2-one	(CDCl ₃): δ 9.13 (s, 1H), 8.43 (s, 1H), 8.00 (s, 1H), 7.85 (s, 1H), 4.79 (brs, 2H), 3.98 (s, 3H), 2.41 (s, 3H), 2.25 (s, 3H), 1.75-1.73 (m, 2H), 1.64-1.58 (s, 3H), 1.25-1.10 (m, 6H)
10.5		8-(3,5-dimethylisoxazol-4-yl)-9-methoxy-1-[[4-(trifluoromethoxy)phenyl]methyl]pyrazino[2,3-c]quinolin-2-one	(CDCl ₃): δ 9.19 (s, 1H), 8.52 (s, 1H), 7.96 (s, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.38 (s, 1H), 7.34 (d, J = 8.4 Hz, 2H), 5.80 (brs, 2H), 3.17 (s, 3H), 2.33 (s, 3H), 2.17 (s, 3H)
10.6		8-(3,5-dimethylisoxazol-4-yl)-1-[(2-fluorophenyl)methyl]-9-methoxy-pyrazino[2,3-c]quinolin-2-one	(CDCl ₃): δ 9.19 (s, 1H), 8.53 (s, 1H), 7.96 (s, 1H), 7.43-7.39 (m, 2H), 7.26-7.16 (m, 3H), 5.82 (s, 2H), 3.26 (s, 3H), 2.33 (s, 3H), 2.17 (s, 3H)
10.7		8-(3,5-dimethylisoxazol-4-yl)-9-methoxy-1-[[2-(trifluoromethoxy)phenyl]methyl]pyrazino[2,3-c]quinolin-2-one	(CDCl ₃): δ 9.19 (s, 1H), 8.51 (s, 1H), 7.96 (s, 1H), 7.47-7.42 (m, 3H), 7.37-7.26 (m, 2H), 5.81 (s, 2H), 3.20 (s, 3H), 2.33 (s, 3H), 2.17 (s, 3H)

10.8		8-(3,5-dimethylisoxazol-4-yl)-1-[(4-fluorophenyl)methyl]-9-methoxy-pyrazino[2,3-c]quinolin-2-one	(CDCl ₃): δ 9.18 (s, 1H), 8.51 (s, 1H), 7.96 (s, 1H), 7.49 (s, 1H), 7.36-7.33 (m, 2H), 7.16 (t, <i>J</i> = 8.4 Hz, 2H), 5.79 (brs, 2H), 3.23 (s, 3H), 2.33 (s, 3H), 2.17 (s, 3H)
10.9		1-(cyclopropylmethyl)-8-(3,5-dimethylisoxazol-4-yl)-9-methoxy-pyrazino[2,3-c]quinolin-2-one	(CDCl ₃): δ 9.14 (s, 1H), 8.44 (s, 1H), 8.27 (s, 1H), 8.01 (s, 1H), 4.70 (d, <i>J</i> = 5.2 Hz, 2H), 4.03 (s, 3H), 2.41 (s, 3H), 2.26 (s, 3H), 1.48-1.45 (m, 1H), 0.78-0.76 (m, 4H)
10.10		8-(3,5-dimethylisoxazol-4-yl)-9-methoxy-1-[(4-methoxyphenyl)methyl]pyrazino[2,3-c]quinolin-2-one	(CDCl ₃): δ 9.02 (s, 1H), 8.69 (s, 1H), 8.20 (s, 1H), 7.85 (s, 1H), 7.27 (d, <i>J</i> = 8.8 Hz, 2H), 6.85 (d, <i>J</i> = 8.8 Hz, 2H), 5.61 (s, 2H), 4.04 (s, 3H), 3.76 (s, 3H), 2.35 (s, 3H), 2.20 (s, 3H)

[0339]

Scheme 11



[0340]

Methyl 4-bromo-2,6-difluoro-3-nitrobenzoate (72)

Concentrated sulfuric acid (26.52 mL, 498 mmol) was added drop wise to fuming nitric acid (15.0 mL, 318.7 mmol) at 0°C . After stirring for 5 min at 0°C , methyl 4-bromo-2,6-difluorobenzoate **71** (25.0 g, 99.6 mmol) was added portion wise thereto. The ice bath was removed, and the reaction mixture was stirred for 1 h at ambient temperature. The mixture was poured into ice-water, and the resulting precipitate was collected by filtration, washed with water, and dried in vacuo to give the title compound **72** (29.0 g, 99% yield) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.10 (dd, $J = 2.0$ Hz, 2.4 Hz, 1H), 3.92 (s, 3H).

[0341]

Methyl 2-amino-4-bromo-6-fluoro-3-nitrobenzoate (73)

To a solution of compound **72** (29.0 g, 97.98 mmol) in methanol (70.0 mL) was added 29% aqueous solution of ammonium hydroxide (15 mL, 91.22 mmol). After stirring for 16 h at ambient temperature, the reaction mixture was concentrated in

vacuo. The solid was triturated with methanol and collected by filtration, and dried in vacuo to give the title compound **73** (22 g, 76% yield) as a light yellow solid.

¹HNMR(400 MHz, DMSO-*d*₆): δ 7.12 (brs, 2H), 7.04 (d, *J* = 10 Hz, 1H), 3.3.86 (s, 3H).

[0342]

Methyl 2-amino-4-bromo-6-methoxy-3-nitro-benzoate (74)

To a solution of sodium methoxide (5.50 g, 102 mmol) in methanol (100 mL) was added compound **73** (22.0 g, 75.0 mmol) at 0°C. After complete addition, ice bath was removed, and the reaction mixture was stirred at ambient temperature for 4 h and then quenched with 1N aqueous hydrochloric acid. The resulting precipitate was collected by filtration, washed with water, and dried in vacuo to give the title compound **74** (18.0 g, 78% yield) as a yellow solid.

¹HNMR(400 MHz, DMSO-*d*₆): δ 6.74 (brs, 1H), 6.30 (brs, 2H) 3.81 (s, 3H), 3.79 (s, 3H).

[0343]

Methyl 2-[bis(tert-butoxycarbonyl)amino]-4-bromo-6-methoxy-3-nitro-benzoate (75)

DMAP (14.4 g, 118 mmol) was added to a solution of compound **74** (18.0 g, 59.0 mmol) in tetrahydrofuran (170 mL) followed by drop wise addition of di-tert-butyl dicarbonate (27.1 g, 118 mmol) in tetrahydrofuran (70 mL) at room temperature. The resulting mixture was stirred for 6h and quenched with water followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the crude material was purified on silica gel column to give the title compound **75** (24.0 g, 80%).

¹HNMR (400 MHz, DMSO-*d*₆): δ 7.89 (s, 1H), 3.95 (s, 3H), 3.78 (s, 3H), 1.31 (s, 18H).

[0344]

Methyl 4-amino-2-(tert-butoxycarbonyl)amino-6-methoxy-3-nitro-benzoate (76)

A dry three-neck round bottle flask, equipped with a magnetic stirrer bar, septum, and a condenser with a nitrogen inlet-outlet, was charged with compound **75** (5.0 g, 9.9 mmol), benzophenone imine (2.6 g, 11.8 mmol), Pd₂(dba)₃ (1.0 g, 0.99 mmol), ((±)-BINAP (1.23 g, 1.98 mmol) and the sodium tert-butoxide (1.5 g, 15.6 mmol). Dry toluene (50 mL) was added, and the resulting mixture was heated to 100°C for 6 h. The reaction mixture was cooled to room temperature, quenched with water (50 mL) and extracted with ethyl acetate (3x100 mL). The combined organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated. The crude imine adduct was dissolved in THF, and 1.0 N HCl (32 mL) was added thereto at 0°C. The resulting mixture was stirring at room temperature for 2h. The reaction mixture was neutralized with NaHCO₃ solution and extracted with ethyl acetate. The organic extract was washed with brine and dried over sodium sulfate. The solvent was removed, and the crude material was purified on silica gel column to give the title compound **76** (2.1 g, 63%)

[0345]

Methyl 3,4-diamino-2-(tert-butoxycarbonyl)amino-6-methoxybenzoate (77)

10% Palladium on activated carbon (0.8 g) was added to a solution of compound **76** (2.5 g, 5.0 mmol) in methanol, and the mixture was hydrogenated under hydrogen atmosphere for 16 h. The reaction mixture was filtered through celite pad and washed thoroughly with methanol-dichloromethane. The filtrate was concentrated to give the crude title compound **77** (2.0 g) which was directly used in the next step.

[0346]

Compound 79: Pyrazine ring formation

General procedure: Dicarbonyl compound **78** (4.8 mmol) was added to a solution of compound **77** (2.4 mmol) in ethanol, and the resulting mixture was refluxed for 3 h, cooled to room temperature and concentrated. The obtained residue was

dissolved in ethyl acetate, and the solution was washed with water and brine and dried over sodium sulfate. The organic layer was concentrated, and the crude material was purified on silica-gel column chromatography to give the title compound **79**.

5 [0347]

Methyl 5-(tert-butoxycarbonylamino)-7-methoxy-quinoxaline-6-carboxylate (R = H)

This compound was synthesized by the general procedure as describe above for compound **79** (45%).

10 ¹HNMR (400 MHz, DMSO-*d*₆): δ 9.15 (s, 1H), 8.98 (s, 1H), 8.82 (s, 1H), 7.38 (s, 1H), 3.96 (s, 3H), 3.79 (s, 3H), 1.42 (s, 9H)

[0348]

Methyl 5-(tert-butoxycarbonylamino)-7-methoxy-2,3-dimethyl-quinoxaline-6-carboxylate (R = Me)

15 This compound was synthesized by the general procedure as describe above for compound **79** (40%).

¹HNMR (400 MHz, CDCl₃): δ 8.57 (brs, 1H), 7.05 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 2.70 (s, 6H), 1.42 (s, 9H)

[0349]

20 **Compound 80: Hydrolysis of ester**

General procedure: Compound **79** (1.5 mmol) was dissolved in THF-methanol, and a solution of sodium hydroxide (6.0 mmol) in water was added thereto. The resulting mixture was heated at 80°C for 16h, cooled to room temperature and concentrated. The
25 residue was diluted with 5 ml of water, and the mixture was extracted with diethyl ether. The aqueous layer was carefully acidified with dilute HCl to pH ~6 and extracted with 5% methanol in dichloromethane. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated.
30 to give the title compound **80** which was directly used in next step.

[0350]

5-(tert-Butoxycarbonylamino)-7-methoxy-quinoxaline-6-carboxylic acid (R = H)

This compound was synthesized by the general procedure as describe above for compound **80**

[0351]

**5-(tert-Butoxycarbonylamino)-7-methoxy-2,3-dimethyl-
5 quinoxaline-6-carboxylic acid (R = Me)**

This compound was synthesized by the general procedure as describe above for compound **80**

[0352]

Compound 81: Amide formation

10 General procedure: Compound **80** (1.2 mmol) was dissolved in THF (6 mL), and to the solution were added HOBt (3.0 mmol), EDCI (3.0 mmol) and NMM (6.0 mmol). The resulting mixture was stirred at room temperature for 3 h and then cooled at 0°C. NH₃ gas was purged for 10 min to the reaction mixture, and the
15 mixture was stirred for 3 h. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, and dried over sodium sulfate. The solvent was removed, and the crude residue was purified by silica gel chromatography to give the title compound **81**.

20 [0353]

**tert-Butyl N-(6-carbamoyl-7-methoxy-quinoxalin-5-yl)carbamate
(R = H)**

This compound was synthesized by the general procedure as describe above for compound **81**.

25 ¹HNMR (400 MHz, DMSO-d₆): δ 8.88 (d, J = 1.6 Hz, 1H), 8.81 (d, J = 1.6 Hz, 1H), 8.62 (s, 1H), 7.63 (s, 1H), 7.43 (s, 1H), 7.40 (s, 1H), 3.96 (s, 3H), 1.39 (s, 9H).

[0354]

**tert-Butyl N-(6-carbamoyl-7-methoxy-2,3-dimethyl-quinoxalin-5-
30 yl)carbamate (R = Me)**

This compound was synthesized by the general procedure as describe above for compound **81**.

¹HNMR (400 MHz, DMSO-d₆): δ 8.42 (s, 1H), 7.56 (s, 1H), 7.39 (s, 1H), 7.30 (s, 1H), 3.90 (s, 3H), 2.65 (s, 3H), 2.62 (s, 3H),
35 1.40 (s, 9H).

[0355]

Compound 82: BOC-deprotection

General procedure: Trifluoroacetic acid (1 ml) was added to a solution of compound **81** (0.6 mmol) in dichloromethane (5 ml) at 0°C. After stirring for 6 h at room temperature, the reaction mixture was concentrated. The residue was dissolved in dichloromethane, and the solution was washed with saturated NaHCO₃ solution. The organic layer was separated, washed with brine, dried over sodium sulfate and concentrated. The crude material was purified on silica-gel column to give the title compound **82**.

[0356]

5-amino-7-methoxy-quinoxaline-6-carboxamide (R = H)

The compound was synthesized by the general procedure as describe above for compound **82**.

¹HNMR (400 MHz, DMSO-*d*₆): δ 8.83 (d, *J* = 1.6 Hz, 1H), 8.60 (d, *J* = 1.6 Hz, 1H), 7.74 (brs, 1H), 7.57 (s, 1H), 7.51 (brs, 2H), 6.63 (s, 1H), 3.95 (s, 3H).

[0357]

5-amino-7-methoxy-2,3-dimethyl-quinoxaline-6-carboxamide (R = Me)

This compound was synthesized by the general procedure as describe above for compound **82**.

[0358]

Compound 83: Quinazolinone ring formation

General procedure: A mixture of compound **82** (0.16 mmol), substituted benzaldehyde (0.24 mmol), *p*-toluenesulfonic acid (15 mg) and sodium hydrogen sulfite (0.24 mmol) in *N,N*-dimethyl acetamide (4 mL) was heated with stirring at 140°C for 16h. After cooling to room temperature, the reaction mixture was poured into aqueous NaHCO₃ solution and extracted three times with 5% MeOH in ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated. The crude material was purified on silica gel column to give the title compound **83** (30 - 50%).

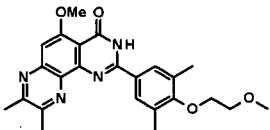
[0359]

The following compounds of Examples were synthesized according to Scheme 11:

[0360]

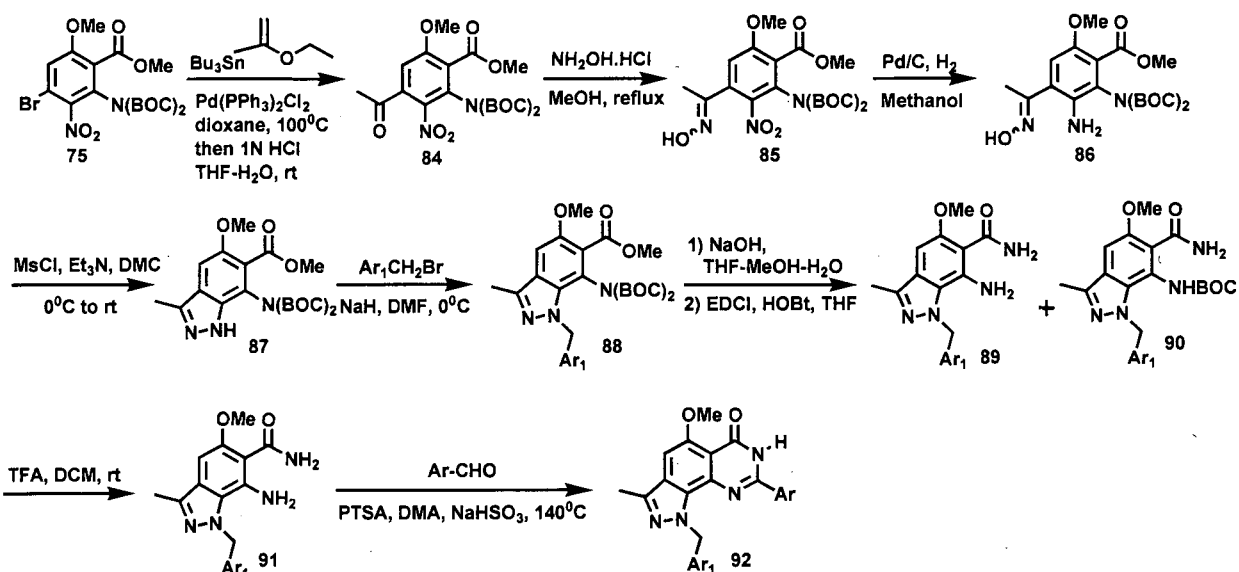
5 **Table 8**

Example	Structure	IUPAC Name	¹ HNMR (400 MHz)
11.1		2-[4-(2-hydroxyethoxy)-3,5-dimethylphenyl]-5-methoxy-3H-pyrazino[2,3-h]quinazolin-4-one	(DMSO-d ₆): δ 12.64 (brs, 1H), 9.00 (d, <i>J</i> = 1.2 Hz, 1H), 8.97 (d, <i>J</i> = 2.0 Hz, 1H), 8.06 (s, 2H), 7.33 (s, 1H), 4.91 (t, <i>J</i> = 6.0 Hz, 1H), 4.04 (s, 3H), 3.88-3.86 (m, 2H), 3.76-3.72 (m, 2H), 2.33 (s, 6H)
11.2		5-methoxy-2-[4-(2-methoxyethoxy)-3,5-dimethylphenyl]-3H-pyrazino[2,3-h]quinazolin-4-one	(DMSO-d ₆): δ 12.69 (brs, 1H), 8.99 (d, <i>J</i> = 2.0 Hz, 1H), 8.95 (d, <i>J</i> = 2.0 Hz, 1H), 8.06 (s, 2H), 7.30 (s, 1H), 4.03 (s, 3H), 3.99-3.97 (m, 2H), 3.68-3.66 (m, 2H), 3.35 (s, 3H), 2.34-2.32 (m, 6H)
11.3		2-[4-(2-ethoxyethoxy)-3,5-dimethylphenyl]-5-methoxy-3H-pyrazino[2,3-h]quinazolin-4-one	(DMSO-d ₆): δ 12.72 (brs, 1H), 9.0 (s, 1H), 8.97 (s, 1H), 8.06 (s, 2H), 7.32 (s, 1H), 4.04 (s, 3H), 3.99-3.97 (m, 2H), 3.71-3.69 (m, 2H), 3.56-3.51 (m, 2H), 2.35 (s, 6H), 1.16 (t,

			$J = 6.8 \text{ Hz, 3H}$
11.4		5-methoxy-2-[4-(2-methoxyethoxy)-3,5-dimethylphenyl]-8,9-dimethyl-3H-pyrazino[2,3-h]quinazolin-4-one	(DMSO- d_6): δ 12.55 (brs, 1H), 8.03 (s, 2H), 7.23 (s, 1H), 3.98-3.96 (m, 5H), 3.68-3.65 (m, 2H), 3.35 (s, 3H), 2.74 (s, 3H), 2.70 (s, 3H), 2.34 (s, 6H)

[0361]

Scheme 12



[0362]

5 **Methyl 4-acetyl-2-[bis(tert-butoxycarbonyl)amino]-6-methoxy-3-nitro-benzoate (84)**

A solution of compound **75** (2.0 g, 3.94 mmol), 1-ethoxyvinyltributyltin (1.5 g, 4.73 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (500 mg, 0.71 mmol) in 50 ml of 1,4-dioxane was refluxed for 5 h under argon atmosphere. The dark brown reaction mixture was filtered, and the filtrate was concentrated in vacuo. The crude material was dissolved in tetrahydrofuran (50 ml), and 1N HCl (1.0 mL) was added thereto. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was

diluted with ethyl acetate and washed with saturated solution of NaHCO₃. The organic layer was separated, washed with brine and dried over sodium sulfate. The solvent was removed, and the crude material was purified on silica-gel column to give
5 the title compound **84** (1.3 g 70%).

¹HNMR (400 MHz, DMSO-*d*₆): δ 7.65 (s, 1H), 4.01 (s, 3H), 3.8 (s, 3H), 2.67 (s, 3H), 1.25 (s, 18H).

[0363]

**Methyl 2-[bis(tert-butoxycarbonyl)amino]-4-[N-hydroxy-C-
10 methyl-carbonimidoyl]-6-methoxy-3-nitro-benzoate (85)**

A mixture of compound **84** (1.3 g, 2.76 mmol) and NH₂OH HCl (229 mg, 3.3 mmol) in 20 ml of MeOH was refluxed for 5h. After cooling to room temperature, the reaction mixture was concentrated in vacuo, and the residue was dissolved in ethyl
15 acetate. The solution was washed with brine, dried over sodium sulfate and concentrated to give the crude title compound **85** (1.1 g) which was used in the next step without purification.

[0364]

**Methyl 3-amino-2-[bis(tert-butoxycarbonyl)amino]-4-[N-hydroxy-
20 C-methyl-carbonimidoyl]-6-methoxy-benzoate (86)**

Compound **85** (1.1 g) was dissolved in methanol, and 500 mg of Pd/C (10% w/w) was added thereto. The reaction mixture was stirred under H₂ atmosphere for 8 h, filtered through a celite pad and washed with MeOH. The combined filtrate was
25 concentrated under reduced pressure to give the title compound **86** (800 mg) which was used in the next step without purification.

[0365]

**Methyl 7-[bis(tert-butoxycarbonyl)amino]-5-methoxy-3-methyl-
30 1H-indazole-6-carboxylate (87)**

Compound **86** (800 mg, 1.77 mmol) was dissolved in dichloromethane, and triethylamine (0.8 ml, 7.1 mmol) was added thereto. The reaction mixture was cooled to 0°C, and methanesulfonyl chloride (0.163 mL, 2.12 mmol) was added
35 dropwise thereto. The resulting reaction mixture was stirred

for 20 min, quenched with saturated NaHCO₃ solution and diluted with dichloromethane. The organic layer was separated, washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified on silica-gel column to give the title compound **87** (500 mg).
¹HNMR (400 MHz, DMSO-*d*₆): δ 12.99 (s, 1H), 7.27 (s, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 2.47 (s, 3H), 1.25 (s, 18H).
[0366]

Compound 88: Alkylation

General procedure: NaH (50 mg, 1.4 mmol, 60% mineral oil) was added to a solution of compound **87** (0.92 mmol) in anhydrous N,N-dimethylformamide (5 ml) at 0°C. After stirring for 30 min, the corresponding Ar₁CH₂Br (Ar₁ = benzyl, 2-pyridyl, 1.4 mmol) was added thereto, and the mixture was stirred for 1 h at room temperature. The reaction was quenched with saturated NH₄Cl solution and diluted with ethyl acetate (20 ml). The organic layer was washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified on silica gel column to give the title compound **88**.
[0367]

Methyl 1-benzyl-7-[bis(tert-butoxycarbonyl)amino]-5-methoxy-3-methyl-indazole-6-carboxylate (Ar₁ = phenyl)

This compound was synthesized by the general procedure as describe above for compound **88** (50%).
¹HNMR (400 MHz, DMSO-*d*₆): δ 7.39 (s, 1H), 7.29 – 7.22 (m, 3H), 6.95 – 6.93 (m, 2H), 5.42 (s, 2H), 3.86 (s, 3H), 3.74 (s, 3H), 2.49 (s, 3H), 1.25 (s, 18H).
[0368]

Methyl 7-[bis(tert-butoxycarbonyl)amino]-5-methoxy-3-methyl-1-(2-pyridylmethyl)indazole-6-carboxylate (Ar₁ = 2-pyridyl)

This compound was synthesized by the general procedure as describe above for compound **88** (45%).
¹HNMR (400 MHz, DMSO-*d*₆) δ: 8.47 (d, *J* = 4.0 Hz, 1H), 7.68 – 7.64 (m, 1H), 7.42 (s, 1H), 7.25 – 7.22 (m, 1H), 6.48 (d, *J* =

7.6 Hz, 1H), 5.51 (s, 2H), 3.87 (s, 3H), 3.73 (s, 3H), 2.52 (s, 3H), 1.25 (s, 18 H).

[0369]

Compounds 89 and 90:

5 General procedure: Compound **88** (0.6 mmol) was dissolved in THF-methanol (1:1, 6 ml), and a solution of sodium hydroxide (1.8 mmol) in water (2 ml) was added thereto. The resulting mixture was heated at 80°C for 16h. After cooling to room temperature, the reaction mixture was concentrated, and the
10 residue was diluted with 3 ml of water, and the mixture was extracted with diethyl ether. The aqueous layer was carefully acidified with dilute HCl to pH ~6 and extracted with 5% methanol in dichloromethane (three times). The combined organic layer was washed with brine, and dried over sodium
15 sulfate. The solvent was removed, and the crude material was dissolved in tetrahydrofuran (6 mL) followed by addition of HOBt (1.2 mmol), EDCI (1.2 mmol) and NMM (4.0 mmol) respectively. The resulting mixture was stirred at room temperature for 3h and then cooled at 0°C. NH₃ gas was purged
20 for 10 min, and the mixture was stirred for 3h at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was separated, washed with brine and dried over sodium sulfate. The solvent was removed, and the crude residue was purified by silica gel
25 column chromatography to give a mixture of compounds **89** and **90**.
[0370]

Compound 91:

General procedure: Trifluoroacetic acid (1 ml) was added to the mixture of compounds **89** and **90** (200 mg) in dichloromethane
30 (5 ml) at 0°C. After stirring for 6h at room temperature, the reaction mixture was concentrated. The residue was dissolved in dichloromethane, and the solution was washed with saturated NaHCO₃ solution and brine, dried over sodium sulfate, and concentrated. The crude material was purified on silica-gel
35 column to give the title compound **91**.

[0371]

7-Amino-1-benzyl-5-methoxy-3-methyl-indazole-6-carboxamide (Ar₁ = phenyl)

This compound was synthesized by the general procedure as describe above for compound **91**.

¹HNMR (400 MHz, DMSO-d₆): δ 7.60 (brs, 1H), 7.39 (brs, 1H), 7.25 – 7.19 (m, 3H), 7.02 – 7.01 (m, 2H), 6.44 (s, 1H), 6.22 (s, 2H), 5.72 (s, 2H), 3.79 (s, 3H), 2.38 (s, 3H).

[0372]

7-Amino-5-methoxy-3-methyl-1-(2-pyridylmethyl)indazole-6-carboxamide (Ar₁ = 2-pyridyl)

This compound was synthesized by the general procedure as describe above for compound **91**.

¹HNMR (400 MHz, DMSO-d₆): δ 8.52 (d, *J* = 5.2 Hz, 1H), 7.78 – 7.74 (m, 1H), 7.60 (brs, 1H), 7.39 (brs, 1H), 7.32 – 7.28 (m, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.68 (brs, 2H), 6.42 (s, 1H), 5.73 (s, 2H), 3.76 (s, 3H), 2.34 (s, 3H).

[0373]

Compound 92: Quinazolinone ring formation

The preparation of compound **92** from compound **91** was carried out in a similar manner to that described for the preparation of compound **83** (30%-50%).

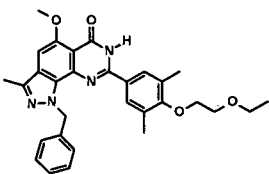
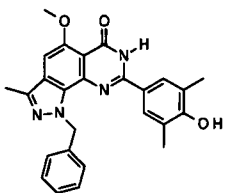
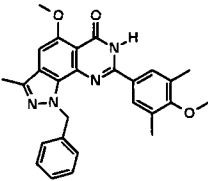
[0374]

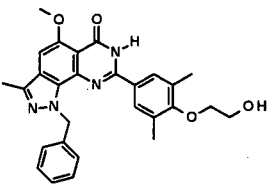
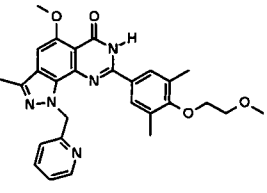
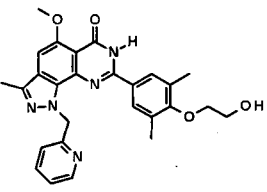
The following compounds of Examples were synthesized according to Scheme 12:

[0375]

Table 9

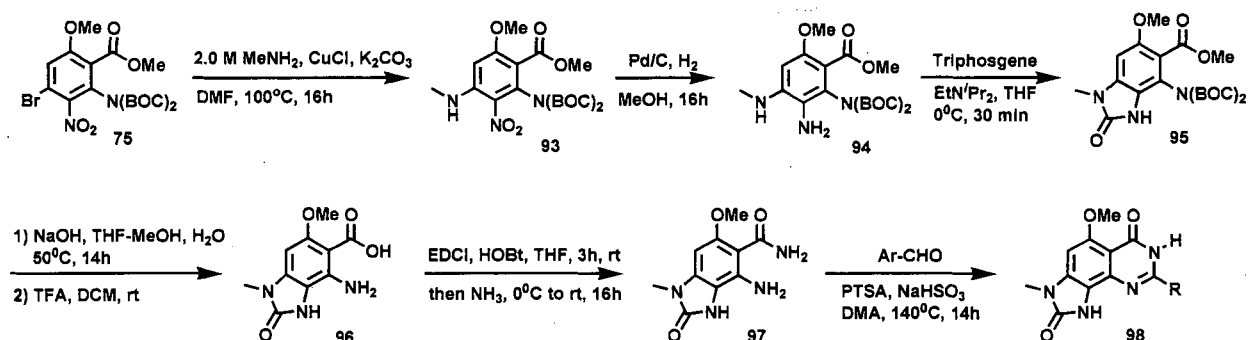
Example	Structure	IUPAC Name	¹ HNMR (400 MHz)
12.1		1-benzyl-5-methoxy-8-[4-(2-methoxyethoxy)-3,5-dimethylphenyl]-3-phenyl-	(DMSO-d ₆): δ 12.25 (brs, 1H), 7.79 (s, 2H), 7.26-7.19 (m, 3H), 7.14 (s, 1H), 7.10 (d, <i>J</i> = 7.6 Hz, 2H), 6.22 (s, 2H), 3.95-3.93 (m, 2H),

		methyl-7H-pyrazolo[4,3-h]quinazolin-6-one	3.89 (s, 3H), 3.64-3.62 (m, 2H), 3.33 (s, 3H), 2.25 (s, 3H), 2.24 (s, 6H)
12.2		1-benzyl-8-[4-(2-ethoxyethoxy)-3,5-dimethylphenyl]-5-methoxy-3-methyl-7H-pyrazolo[4,3-h]quinazolin-6-one	(DMSO-d ₆): δ 12.38 (brs, 1H), 7.79 (s, 2H), 7.28-7.19 (m, 3H), 7.14 (s, 1H), 7.11-7.09 (m, 2H), 6.22 (s, 2H), 3.92-3.88 (m, 2H), 3.89 (s, 3H), 3.68-3.65 (m, 2H), 3.54-3.49 (m, 2H), 2.52 (m, 3H), 2.24 (s, 6H), 1.15 (t, J = 6.8 Hz, 3H)
12.3		1-benzyl-8-(4-hydroxy-3,5-dimethylphenyl)-5-methoxy-3-methyl-7H-pyrazolo[4,3-h]quinazolin-6-one	(CD ₃ OD): δ 7.57 (s, 2H), 7.23-7.10 (m, 5H), 7.02 (s, 1H), 6.25 (s, 2H), 3.96 (s, 3H), 2.55 (s, 3H), 2.21 (s, 6H)
12.4		1-benzyl-5-methoxy-8-(4-methoxy-3,5-dimethylphenyl)-3-methyl-7H-pyrazolo[4,3-h]quinazolin-6-one	(DMSO-d ₆): δ 12.38 (brs, 1H), 7.79 (s, 2H), 7.27-7.19 (m, 3H), 7.14 (s, 1H), 7.11 (d, J = 7.6 Hz, 2H), 6.23 (s, 2H), 3.89 (s, 3H), 3.70 (s, 3H), 2.52 (s,

		6-one	3H), 2.23 (s, 6H)
12.5		1-benzyl-8-[4-(2-hydroxyethoxy)-3,5-dimethylphenyl]-5-methoxy-3-methyl-7H-pyrazolo[4,3-h]quinazolin-6-one	(DMSO-d ₆): δ 12.15 (brs, 1H), 7.79 (s, 2H), 7.28-7.19 (m, 3H), 7.12-7.10 (m, 3H), 6.29 (s, 2H), 4.90 (s, 1H), 3.89 (s, 3H), 3.84-3.81 (m, 2H), 3.72-3.70 (m, 2H), 2.52 (s, 3H), 2.25 (s, 6H)
12.6		5-methoxy-8-[4-(2-methoxyethoxy)-3,5-dimethylphenyl]-3-methyl-1-(2-pyridylmethyl)-7H-pyrazolo[4,3-h]quinazolin-6-one	(DMSO-d ₆): δ 12.15 (brs, 1H), 8.56 (d, <i>J</i> = 5.2 Hz, 1H), 7.78 (s, 2H), 7.62 (t, <i>J</i> = 8 Hz, 1H), 7.24-7.21 (m, 1H), 7.16 (s, 2H), 6.59 (d, <i>J</i> = 8.0 Hz, 2H), 3.94-3.93 (m, 2H), 3.90 (s, 3H), 3.65-3.63 (m, 2H), 3.45 (s, 3H), 2.56 (s, 3H), 2.22 (s, 6H)
12.7		8-[4-(2-hydroxyethoxy)-3,5-dimethylphenyl]-5-methoxy-3-methyl-1-(2-pyridylmethyl)-7H-pyrazolo[4,3-h]quinazolin-6-one	(DMSO-d ₆): δ 12.20 (brs, 1H), 8.55 (d, <i>J</i> = 4.8 Hz, 1H), 7.77 (s, 2H), 7.62 (dt, <i>J</i> = 7.6, 1.6 Hz, 1H), 7.23-7.59 (m, 1H), 7.14 (brs, 1H), 6.59 (d, <i>J</i> = 8.0 Hz, 1H), 6.29 (s, 2H), 4.89 (t, <i>J</i> = 5.2 Hz, 1H),

		h]quinazolin-6-one	3.90 (s, 3H), 3.82 (t, $J = 4.8$ Hz, 2H), 3.71 (q, $J = 4.8$ Hz, 2H), 2.55 (s, 3H), 2.26 (s, 6H)
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[0376]

Scheme 13

5 [0377]

Methyl 2-[bis(tert-butoxycarbonyl)amino]-6-methoxy-4-(methylamino)-3-nitrobenzoate (93)

Potassium carbonate (2.73 g, 19.80 mmol) and cuprous chloride (1.56 g, 15.84 mmol) were added to compound **75** (10.0 g, 19.80 mmol) in dry N,N-dimethylformamide (100 mL) in sealed tube. After stirring for 5-10 min, methyl amine (9.90 mL, 2.0M in tetrahydrofuran, 19.80 mmol) was added drop-wise thereto. The resultant solution was stirred for 16h at 100°C and then poured into ice water. The solid was filtered, washed with water and dried in vacuo to give the title compound **93** (5.0 g, 55% yield) as a yellow solid.

^1H NMR(400 MHz, DMSO- d_6): δ 7.80 (d, $J = 4.8$ Hz, 1H), 6.37 (s, 1H), 3.91 (s, 3H), 3.69 (s, 3H), 2.96 (d, $J = 4.8$ Hz, 3H), 1.30 (s, 18H).

20 [0378]

Methyl 3-amino-2-[bis(tert-butoxycarbonyl)amino]-6-methoxy-4-(methylamino)benzoate (94)

A mixture of compound **93** (5.0 g, 10.98 mmol) and 10% Pd/C (500 mg) in methanol (50 mL) was stirred under hydrogen

atmosphere at room temperature for 16h. The catalyst was then removed by filtration using celite. The filtrate was concentrated in vacuo, and the crude residue was purified by flash column chromatography to give the title compound **94** (4.0 g, 85%).

¹HNMR (400 MHz, DMSO-*d*₆): δ 6.10 (s, 1H), 5.40 (d, *J* = 5.2Hz, 1H), 3.95 (s, 2H), 3.70 (s, 3H), 3.60 (s, 3H), 2.78 (d, *J* = 5.2 Hz, 3H), 1.32 (s, 18H).

[0379]

10 Methyl 4-[bis(tert-butoxycarbonyl)amino]-6-methoxy-1-methyl-2-oxo-3H-benzimidazole-5-carboxylate (95)

Triphosgene (3.63 g, 12.23 mmol) was added to a mixture of compound **94** (4.0 g, 9.41 mmol) and DIPEA (3.28 mL, 18.82 mmol) in tetrahydrofuran (75 mL) at 0°C. After complete addition, the resulting mixture was stirred at same temperature for 30 min, quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give the title compound **95** (3.75 g, 88%).

¹HNMR (400 MHz, DMSO-*d*₆): δ 11.18 (br s, 1H), 6.96 (s, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 4.43 (br s, 3H), 1.30 (s, 18H).

[0380]

25 4-Amino-6-methoxy-1-methyl-2-oxo-3H-benzimidazole-5-carboxylic acid (96)

To a solution of compound **95** (1.0 g, 2.21 mmol) in tetrahydrofuran (10 mL) was added NaOH (117 mg, 4.43 mmol) in water (2 mL) and methanol (3 mL). The mixture was warmed to 50°C and stirred for 14h. After cooling to room temperature, the reaction mixture was concentrated, the residue was diluted with 5 ml of water, and the mixture was extracted with diethyl ether. The aqueous layer was carefully acidified with dilute HCl to pH ~6 and extracted with 5% methanol in dichloromethane (three times). The combined organic layer was washed with brine, and dried over sodium sulfate. The crude material (470

mg) was dissolved in dichloromethane (6 mL), and TFA (2 mL) was added thereto. The reaction was stirred at room temperature for overnight. The solvent was removed under vacuo to give the title compound **96** (400 mg, 98%).

¹HNMR (400 MHz, DMSO-*d*₆): δ 12.21 (brs, 2H), 10.21 (brs, 2H), 6.26 (s, 1H), 3.82 (s, 3H), 3.23 (s, 3H).

[0381]

4-Amino-6-methoxy-1-methyl-2-oxo-3H-benzimidazole-5-carboxamide (97)

The preparation of compound **97** from compound **96** was carried out in a similar manner to that described for the preparation of compound **81** (75%).

¹HNMR (400 MHz, DMSO-*d*₆): δ 10.15 (brs, 1H), 7.55 (brs, 1H), 7.18 (brs, 1H), 6.46 (brs, 2H), 6.20 (s, 1H), 3.82 (s, 3H), 3.23 (s, 3H).

[0382]

Compound 98: Quinazolinone ring formation

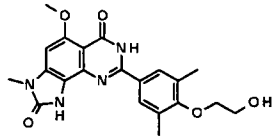
The preparation of compound **98** from compound **97** was carried out in a similar manner to that described for the preparation of compound **83** (30%-50%).

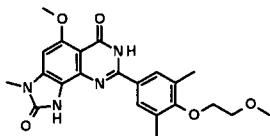
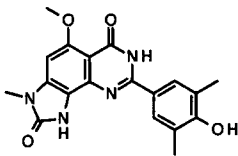
[0383]

The following compounds of Examples were synthesized according to Scheme 13:

[0384]

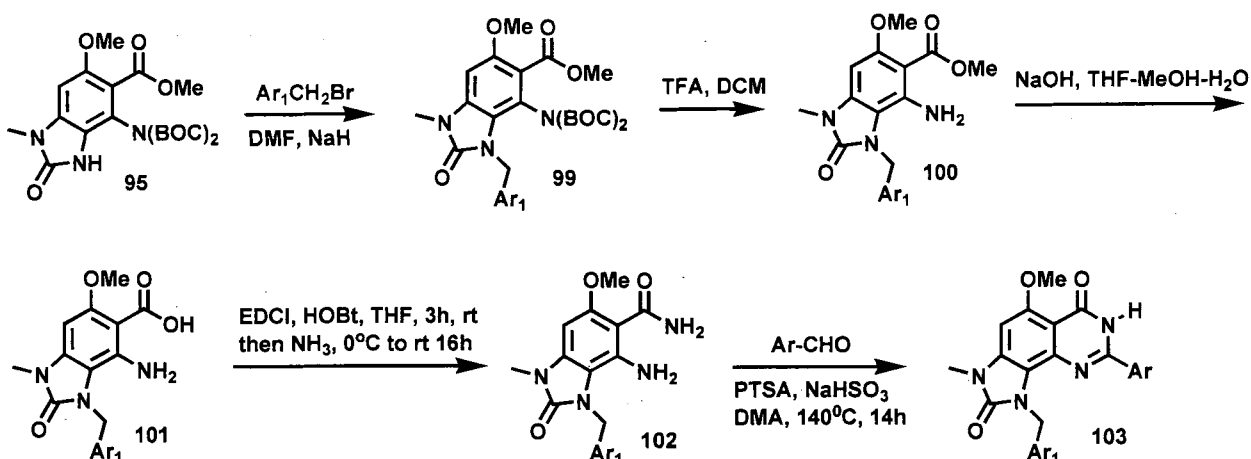
Table 10

Example	Structure	IUPAC Name	¹ HNMR (400 MHz)
13.1		8-[4-(2-hydroxyethoxy)-3,5-dimethylphenyl]-5-methoxy-3-methyl-1,7-dihydroimidazo[4,5-	(DMSO- <i>d</i> ₆): δ 11.65 (brs, 1H), 11.40 (brs, 1H), 8.14 (s, 2H), 6.90 (s, 1H), 4.91-4.89 (m, 1H), 3.89 (s, 3H), 3.86-3.83 (m, 2H), 3.74-3.72 (m, 2H), 3.37 (s, 3H), 2.31 (m, 6H)

		h]quinazoline -2,6-dione	
13.2		5-methoxy-8- [4-(2- methoxyethoxy) -3,5- dimethyl- phenyl]-3- methyl-1,7- dihydroimidaz o[4,5- h]quinazoline -2,6-dione	(DMSO- <i>d</i> ₆): δ 11.81 (brs, 1H), 11.42 (brs, 1H), 7.91 (s, 2H), 6.90 (s, 1H), 3.90- 3.87 (m, 2H), 3.88 (s, 3H), 3.65-3.62 (m, 2H), 3.37 (s, 3H), 3.34 (s, 3H), 2.30 (s, 6H)
13.3		8-(4-hydroxy- 3,5-dimethyl- phenyl)-5- methoxy-3- methyl-1,7- dihydroimidaz o[4,5- h]quinazoline -2,6-dione	(DMSO- <i>d</i> ₆): δ 11.56 (brs, 1H), 11.34 (s, 1H), 8.92 (brs, 1H), 8.09 (s, 2H), 6.86 (s, 1H), 3.88 (s, 3H), 3.36 (s, 3H), 2.24 (m, 6H)

[0385]

Scheme 14



5 [0386]

Compound 99: Alkylation

General procedure: NaH (8.86 mmol) was added at 0°C to a solution of compound **95** (4.43 mmol) in dry N,N-dimethylformamide followed by dropwise addition of
5 corresponding Ar₁CH₂Br (Ar₁ = benzyl, 2-pyridyl, 4.87 mmol). The resulting mixture was stirred for 30 min at room temperature and then poured into ice water. The solid was filtered and dried to give the title compound **99**.

[0387]

10 **Methyl 3-benzyl-4-[bis(tert-butoxycarbonyl)amino]-6-methoxy-1-methyl-2-oxo-benzimidazole-5-carboxylate (Ar₁ = phenyl)**

The compound was synthesized by the general procedure as describe above for compound **99**.

¹HNMR (400 MHz, DMSO-*d*₆): δ 7.30-7.26 (m, 3H), 7.23-7.21 (m,
15 1H), 7.14 (s, 1H), 7.03 (d, *J* = 7.2Hz, 1H), 4.95 (s, 2H), 3.85 (s, 3H), 3.45 (s, 3H), 3.34 (s, 3H), 1.17 (s, 18H).

[0388]

20 **Methyl 4-[bis(tert-butoxycarbonyl)amino]-6-methoxy-1-methyl-2-oxo-3-(2-pyridylmethyl)benzimidazole-5-carboxylate (Ar₁ = 2-pyridyl)**

The compound was synthesized by the general procedure as describe above for compound **99**.

¹HNMR (400 MHz, DMSO-*d*₆): δ 8.44 (d, *J* = 5.2Hz, 1H), 7.70 (dt, *J* = 8.0, 2.0Hz, 1H), 7.24-7.21 (m, 1H), 7.15 (s, 1H), 6.95 (d,
25 *J* = 7.6Hz, 1H), 5.05 (s, 2H), 3.85 (s, 3H), 3.65 (s, 3H), 3.44 (s, 3H), 1.17 (s, 18H).

[0389]

Compound 100: BOC deprotection

General procedure: The preparation of compound **100** from
30 compound **99** was carried out in a similar manner to that described for the preparation of compound **82**.

[0390]

Methyl 4-amino-3-benzyl-6-methoxy-1-methyl-2-oxo-benzimidazole-5-carboxylate (Ar₁ = phenyl)

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.32-7.28 (m, 2H), 7.25-7.23 (m, 1H), 7.17 (d, *J* = 7.2 Hz, 2H), 6.36 (s, 1H), 5.26 (s, 2H), 5.17 (s, 2H), 3.74 (s, 3H), 3.72 (s, 3H), 3.18 (s, 3H).

[0391]

5 **Methyl 4-amino-6-methoxy-1-methyl-2-oxo-3-(2-pyridylmethyl)benzimidazole-5-carboxylate (Ar₁ = 2-pyridyl)**

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.53 (d, *J* = 4.4 Hz, 1H), 7.83 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.37-7.33 (m, 2H), 6.34 (s, 1H), 5.83 (s, 2H), 5.25 (s, 2H), 3.74 (s, 6H), 3.30 (s, 3H).

10 [0392]

Compound 101: Ester hydrolysis

General procedure: The preparation of compound **101** from compound **100** was carried out in a similar manner to that described for the preparation of compound **80**.

15 [0393]

4-Amino-3-benzyl-6-methoxy-1-methyl-2-oxo-benzimidazole-5-carboxylic acid (Ar₁ = phenyl)

¹H NMR (400 MHz, DMSO-*d*₆): δ 12.50 (br s, 1H), 7.31-7.28 (m, 3H), 7.24-7.23 (m, 1H), 7.18-7.16 (m, 1H), 6.32 (s, 1H), 5.97 (s, 2H), 5.25 (s, 2H), 3.81 (s, 3H), 3.31 (s, 3H).

20 [0394]

4-Amino-6-methoxy-1-methyl-2-oxo-3-(2-pyridylmethyl)benzimidazole-5-carboxylic acid (Ar₁ = 2-pyridyl)

¹H NMR (400 MHz, DMSO-*d*₆): δ 12.2 (br s, 1H), 8.53 (d, *J* = 4.0 Hz, 1H), 7.82 (dt, *J* = 8.0, 2.0 Hz, 2H), 7.37-7.32 (m, 2H), 6.35 (s, 1H), 6.29 (br s, 1H), 5.26 (s, 2H), 3.80 (s, 3H), 3.30 (s, 3H).

25 [0395]

Compound 102: Amide formation

General procedure: The preparation of compound **102** from compound **101** was carried out in a similar manner to that described for the preparation of compound **81**.

30 [0396]

4-Amino-3-benzyl-6-methoxy-1-methyl-2-oxo-benzimidazole-5-carboxamide (Ar₁ = phenyl)

¹HNMR (400 MHz, DMSO-*d*₆): δ 7.51 (br s, 1H), 7.31-7.28 (m, 3H), 7.24-7.23 (m, 1H), 7.18-7.16 (m, 2H), 6.32 (s, 1H), 5.97 (s, 2H), 5.25 (s, 2H), 3.81 (s, 3H), 3.31 (s, 3H).

[0397]

5 **4-Amino-6-methoxy-1-methyl-2-oxo-3-(2-pyridylmethyl)benzimidazole-5-carboxamide (Ar₁ = 2-pyridyl)**

¹HNMR (400 MHz, DMSO-*d*₆): δ 8.53 (d, *J* = 4.8 Hz, 1H), 7.8 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.52 (br s, 1H), 7.35-7.32 (m, 3H), 6.55 (br s, 2H), 6.31 (s, 1H), 5.26 (s, 2H), 3.81 (s, 3H), 3.30 (s, 3H).

[0398]

Compound 103: Quinazolinone ring formation

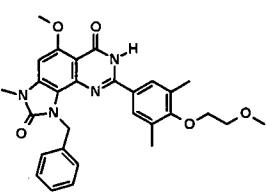
The preparation of compound **103** from compound **102** (Ar₁ = phenyl, 2-pyridyl) was carried out in a similar manner to that described for the preparation of compound **83**.

[0399]

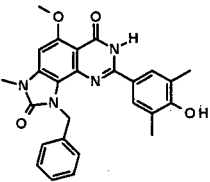
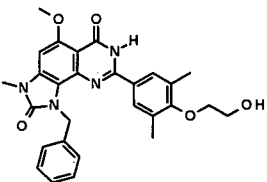
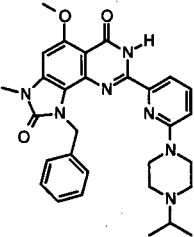
The following compounds of Examples were synthesized according to Scheme 14:

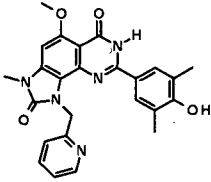
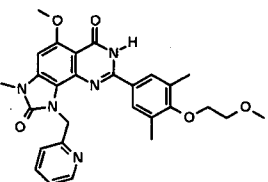
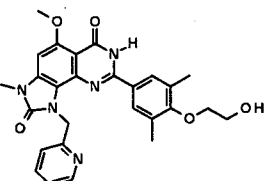
[0400]

20 **Table 11**

Example	Structure	IUPAC Name	¹ HNMR (400 MHz)
14.1		1-benzyl-5-methoxy-8-[4-(2-methoxyethoxy)-3,5-dimethylphenyl]-3-methyl-7H-imidazo[4,5-h]quinazolin-2,6-dione	(DMSO- <i>d</i> ₆): δ 11.95 (brs, 1H), 7.62 (s, 2H), 7.26-7.30 (m, 2H), 7.23-7.19 (m, 3H), 7.02 (s, 1H), 5.66 (s, 2H), 3.91-3.89 (m, 5H), 3.62 (t, <i>J</i> = 4.4 Hz, 2H), 3.46 (s, 3H), 3.30 (s, 3H), 2.23 (s, 6H)

14.2		1-benzyl-5-methoxy-8-(4-methoxy-3,5-dimethylphenyl)-3-methyl-7H-imidazo[4,5-h]quinazoline-2,6-dione	(DMSO- <i>d</i> ₆): δ 11.95 (brs, 1H), 7.62 (s, 2H), 7.30-7.26 (m, 2H), 7.23-7.19 (m, 3H), 7.02 (s, 1H), 5.66 (s, 2H), 3.92 (s, 3H), 3.67 (s, 3H), 3.46 (s, 3H), 2.19 (s, 6H)
14.3		1-benzyl-5-methoxy-3-methyl-8-(5-methyl-3-oxo-4H-1,4-benzoxazin-7-yl)-7H-imidazo[4,5-h]quinazoline-2,6-dione	(DMSO- <i>d</i> ₆): δ 11.95 (brs, 1H), 10.55 (brs, 1H), 7.52 (s, 1H), 7.45 (s, 1H), 7.26-7.18 (m, 5H), 7.01 (s, 1H), 5.56 (s, 2H), 4.57 (s, 2H), 3.91 (s, 3H), 3.45 (s, 3H), 2.19 (s, 3H)
14.4		1-benzyl-8-[4-(2-ethoxyethoxy)-3,5-dimethylphenyl]-5-methoxy-3-methyl-7H-imidazo[4,5-h]quinazoline-2,6-dione	(DMSO- <i>d</i> ₆): δ 11.95 (brs, 1H), 7.63 (s, 2H), 7.29-7.19 (m, 5H), 7.01 (s, 1H), 5.67 (s, 2H), 3.91-3.89 (m, 5H), 3.65 (t, <i>J</i> = 4.4 Hz, 2H), 3.50 (q, <i>J</i> = 7.2 Hz, 2H), 3.48 (s, 3H), 2.20 (s, 6H), 1.14 (t, <i>J</i> = 7.2 Hz, 3H)
14.5		1-benzyl-5-methoxy-8-[3-(2-methoxyethyl)-2-oxo-1,3-benzoxazin-4-yl]-7H-imidazo[4,5-h]quinazoline-2,6-dione	(DMSO- <i>d</i> ₆): δ 12.00 (brs, 1H), 7.93 (d, <i>J</i> = 8.8 Hz, 1H), 7.86 (s, 1H), 7.33 (d, <i>J</i> = 8.4 Hz, 1H), 7.27-

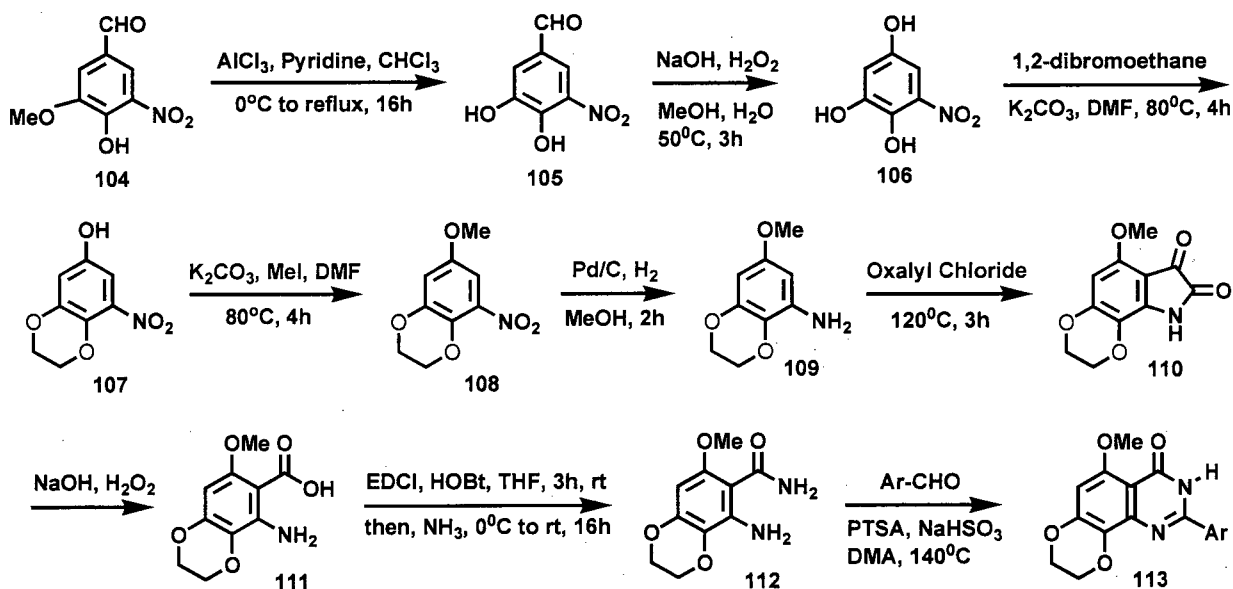
		benzoxazol-6-yl]-3-methyl-7H-imidazo[4,5-h]quinazoline-2,6-dione	7.18 (m, 5H), 6.94 (s, 1H), 5.69 (s, 2H), 4.02 (t, $J = 8.8$ Hz, 2H), 3.90 (s, 3H), 3.64 (t, $J = 8.8$ Hz, 2H), 3.44 (s, 3H), 3.24 (s, 3H)
14.6		1-benzyl-8-(4-hydroxy-3,5-dimethylphenyl)-5-methoxy-3-methyl-7H-imidazo[4,5-h]quinazoline-2,6-dione	(DMSO- d_6): 7.59 (s, 2H), 7.29-7.19 (m, 5H), 7.98 (s, 1H), 5.68 (s, 2H), 3.91 (s, 3H), 3.45 (s, 3H), 2.13 (s, 6H)
14.7		1-benzyl-8-[4-(2-hydroxyethoxy)-3,5-dimethylphenyl]-5-methoxy-3-methyl-7H-imidazo[4,5-h]quinazoline-2,6-dione	(DMSO- d_6): δ 11.8 (brs, 1H), 7.62 (s, 2H), 7.28-7.20 (m, 5H), 7.02 (s, 1H), 5.66 (s, 2H), 4.89-4.87 (m, 1H), 3.92 (s, 3H), 3.81-3.78 (m, 2H), 3.71-3.68 (m, 2H), 3.46 (s, 3H), 2.11 (s, 6H)
14.8		1-benzyl-8-[6-(4-isopropylpiperazin-1-yl)-2-pyridyl]-5-methoxy-3-methyl-7H-imidazo[4,5-h]quinazoline-2,6-dione	(DMSO- d_6): δ 7.57 (d, $J = 7.2$ Hz, 2H), 7.33-7.27 (m, 3H), 7.22-7.71 (m, 3H), 6.93 (d, $J = 8.0$ Hz, 1H), 6.89 (s, 1H), 5.69 (s, 2H), 3.99 (s, 3H), 3.66-3.63

		h]quinazoline -2,6-dione	(m, 4H), 3.5 (s, 3H), 2.76-2.69 (m, 5H), 1.15 (d, $J = 6.8$ Hz, 6H)
14.9		8-(4-hydroxy-3,5-dimethylphenyl)-5-methoxy-3-methyl-1-(2-pyridylmethyl)-7H-imidazo[4,5-h]quinazoline-2,6-dione	(DMSO- d_6): δ 11.5 (brs, 1H), 8.52 (d, $J = 4.0$ Hz, 1H), 7.65 (t, $J = 7.6$ Hz, 1H), 7.56 (s, 2H), 7.20 (dd, $J = 5.2, 7.6$ Hz, 1H), 7.02 (d, $J = 8.4$ Hz, 1H), 6.98 (s, 1H), 5.72 (s, 2H), 3.91 (s, 3H), 3.48 (m, 3H), 2.15 (s, 6H)
14.10		5-methoxy-8-[4-(2-methoxyethoxy)-3,5-dimethylphenyl]-3-methyl-1-(2-pyridylmethyl)-7H-imidazo[4,5-h]quinazoline-2,6-dione	(DMSO- d_6): δ 11.33 (brs, 1H), 8.53 (d, $J = 4.4$ Hz, 1H), 7.67 (dt, $J = 1.6, 7.6$ Hz, 1H), 7.59 (s, 2H), 7.22 (dd, $J = 5.2, 7.6$ Hz, 1H), 7.04-7.03 (m, 2H), 5.70 (s, 2H), 3.93 (s, 3H), 3.92-3.90 (m, 2H), 3.64-3.62 (m, 2H), 3.49 (m, 3H), 3.33 (s, 3H), 2.22 (s, 6H)
14.11		8-[4-(2-hydroxyethoxy)-3,5-dimethylphenyl]-5-methoxy-3-methyl-1-(2-pyridylmethyl)-7H-imidazo[4,5-h]quinazoline-2,6-dione	(DMSO- d_6): δ 11.7 (brs, 1H), 8.51 (d, $J = 4.0$ Hz, 1H), 7.65-7.63 (dd, $J = 1.6, 6.0$ Hz, 1H), 7.56 (s, 2H), 7.22 (t, $J = 5.2$

		methyl-1-(2-pyridylmethyl)-7H-imidazo[4,5-h]quinazoline-2,6-dione	Hz, 1H), 7.02 (d, J = 8.4 Hz, 2H), 5.70 (s, 2H), 4.89 (brs, 1H), 3.92 (s, 3H), 3.81-3.79 (m, 2H), 3.72-3.70 (m, 2H), 3.48 (s, 3H), 2.15 (s, 6H)
14.12		1-benzyl-5-methoxy-8-[5-methoxy-6-(4-methylsulfinylphenyl)-2-pyridyl]-3-methyl-7H-imidazo[4,5-h]quinazoline-2,6-dione	(DMSO- d_6): δ 11.60 (brs, 1H), 8.28 (d, J = 8.4 Hz, 2H), 8.04 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 9.2 Hz, 1H), 7.33-7.19 (m, 5H), 7.05 (s, 1H), 5.65 (s, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.46 (s, 3H), 2.80 (s, 3H)

[0401]

Scheme 15



5 [0402]

3,4-Dihydroxy-5-nitro-benzaldehyde (105)

Compound **104** (10 g, 50.76 mmol) was added to a stirred suspension of AlCl_3 (7.44 g, 55.83 mmol) in dry chloroform (150 mL) at 0°C. Pyridine (18.0 mL, 223.35 mmol) was dropwise added to the resulting mixture, and the mixture was refluxed for 16h. The mixture was cooled to room temperature and poured into ice water. The solid was filtered, and the residue was purified by silica gel column chromatography to give the title compound **105** (8.0 g, 86%).

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 10.91 (br s, 2H), 9.81 (s, 1H), 7.98 (d, $J = 2.0$ Hz, 1H), 7.46 (d, $J = 2.0$ Hz, 1H).
[0403]

6-Nitrobenzene-1,2,4-triol (106)

1N NaOH (21.85 mL, 21.85 mmol) was added to a solution of compound **105** (8.0 g, 43.71 mmol) in mixture of MeOH- H_2O (1:2, 225 mL) at room temperature. 30% H_2O_2 (24.6 mL) was added to the resulting mixture slowly, and after complete addition, the mixture was stirred at 60°C for 3h. The mixture was cooled to room temperature and concentrated to one-third volume. The residue was cooled to 0°C. The solid was collected by vacuum filtration, washed with H_2O and dried to give the title compound **106** (5.0 g, 75%).

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 10.00 (br s, 1H), 9.45 (br s, 2H), 6.69 (d, $J = 2.8$ Hz, 1H), 6.62 (d, $J = 3.2$ Hz, 1H).
[0404]

5-Nitro-2,3-dihydro-1,4-benzodioxin-7-ol (107)

1,2-Dibromoethane (2.23 mL, 25.80 mmol) was added dropwise to a mixture of compound **106** (5.0 g, 32.25 mmol) and potassium carbonate (8.90 g, 64.51 mmol) in dry N,N-dimethylformamide at room temperature. The reaction mixture was heated at 80°C for 4h. On completion, the reaction mixture was filtered, and the filtrate was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and the crude material was

purified over column chromatography to give the title compound **107** (3.5 g, 55%).

¹HNMR (400 MHz, DMSO-*d*₆): δ 9.80 (s, 1H), 6.85 (d, *J* = 2.8 Hz, 1H), 6.62 (d, *J* = 3.2 Hz, 1H), 4.31-4.28 (m, 4H).

5 [0405]

7-Methoxy-5-nitro-2,3-dihydro-1,4-benzodioxine (108)

Methyl iodide (2.21 mL, 35.53 mmol) was added at room temperature to a mixture of compound **107** (3.5 g, 17.76 mmol) and potassium carbonate (4.90 g, 35.53 mmol) in dry N,N-dimethylformamide. The resulting mixture was heated at 80°C for 4 h. On completion, the reaction mixture was filtered, and the filtrate was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure to give the title compound **108** (3.6 g, 96%).

¹HNMR (400 MHz, DMSO-*d*₆): δ 7.05 (d, *J* = 2.8 Hz, 1H), 6.85 (d, *J* = 2.8 Hz, 1H), 4.35-4.32 (m, 4H), 3.74 (s, 3H).

[0406]

7-Methoxy-2,3-dihydro-1,4-benzodioxin-5-amine (109)

10% Pd/C (400 mg) was added to a solution of compound **108** (3.6 g, 17.06 mmol) in methanol (30 mL). The resulting mixture was stirred under hydrogen atmosphere for 2h. The catalyst was then removed by filtration using celite pad and washed with methanol (100 mL). The filtrate was concentrated, and the residue was purified by flash column chromatography to give the title compound **109** (3.0 g, 99%).

¹HNMR (400 MHz, DMSO-*d*₆): δ 5.83 (d, *J* = 3.2 Hz, 1H), 5.66 (d, *J* = 2.8 Hz, 1H), 4.70 (br s, 2H), 4.16-4.13 (m, 4H), 3.58 (s, 3H).

30 [0407]

6-Methoxy-3,9-dihydro-2H-[1,4]dioxino[2,3-*g*]indole-7,8-dione (110)

Oxallyl chloride (30 mL) was added to compound **109** (3.0 g, 17.06 mmol), and the resulting mixture was heated at 120°C for 3h. The mixture was cooled to room temperature and

concentrated under reduced pressure. The residue was triturated with methanol. The solid was filtered and washed with H₂O. The crude material was purified by silica gel column chromatography to give the title compound **110** (2.6 g, 67%).

5 ¹HNMR (400 MHz, DMSO-*d*₆): δ 11.88 (s, 1H), 6.85 (s, 1H), 4.48-4.40 (m, 2H), 4.28-4.26 (m, 2H), 3.77 (s, 3H).

[0408]

5-Amino-7-methoxy-2,3-dihydro-1,4-benzodioxine-6-carboxylic acid (111)

10 30% Aqueous hydrogen peroxide (15 mL) was added drop-wise to a stirred suspension of compound **110** (2.6 g, 11.06 mmol) in 10% aqueous sodium hydroxide (15 mL) at 0°C. The reaction mixture was stirred at 50°C for 30 min and then allowed to reach room temperature. The mixture was filtered, and the
15 filtrate was acidified to pH ~4 with aqueous 1N hydrochloric acid. The solid was collected by filtration, washed thoroughly with cold water and dried under vacuum to give the title compound **111** (1.2 g, 50%).

¹HNMR (400 MHz, DMSO-*d*₆): δ 9.72 (br s, 1H), 6.56 (s, 1H),
20 4.30-4.16 (m, 4H), 3.69 (s, 3H), 3.39 (s, 2H).

[0409]

5-Amino-7-methoxy-2,3-dihydro-1,4-benzodioxine-6-carboxamide (112)

The preparation of compound **112** from compound **111** was
25 carried out in a similar manner to that described for the preparation of compound **81** (400 mg, 40%) was obtained.

¹HNMR (400 MHz, DMSO-*d*₆): δ 7.60 (br s, 2H), 7.38 (s, 1H),
6.25-6.18 (m, 2H), 3.82-3.80 (m, 5H), 3.60 (s, 2H).

[0410]

30 **Compound 113: Quinazolinone ring formation**

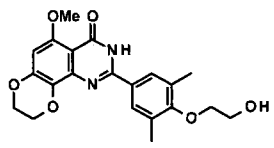
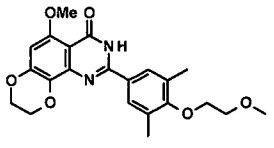
The preparation of compound **113** from compound **112** was carried out in a similar manner to that described for the preparation of compound **83**.

[0411]

The following compounds of Examples were synthesized according to Scheme 15:

[0412]

Table 12

Example	Structure	IUPAC Name	¹ HNMR (400 MHz)
15.1		2-[4-(2-hydroxyethoxy)-3,5-dimethylphenyl]-5-methoxy-8,9-dihydro-3H-[1,4]dioxino[2,3-h]quinazolin-4-one	(DMSO- <i>d</i> ₆): δ 11.84 (brs, 1H), 7.86 (s, 2H), 6.53 (s, 1H), 4.89 (d, <i>J</i> = 5.6Hz, 1H), 4.36-4.32 (m, 4H), 3.83 (t, <i>J</i> = 4.8 Hz, 2H), 3.77 (s, 3H), 3.72 (t, <i>J</i> = 5.2 Hz, 2H), 2.30 (s, 6H)
15.2		5-methoxy-2-[4-(2-methoxyethoxy)-3,5-dimethylphenyl]-8,9-dihydro-3H-[1,4]dioxino[2,3-h]quinazolin-4-one	(DMSO- <i>d</i> ₆): δ 11.83 (brs, 1H), 7.87 (s, 2H), 6.53 (s, 1H), 4.37-4.31 (m, 4H), 3.94 (t, <i>J</i> = 4.4 Hz, 2H), 3.77 (s, 3H), 3.65 (t, <i>J</i> = 4.4 Hz, 2H), 3.34 (s, 3H), 2.32 (s, 6H)

5

[0413]

Formulation Example 1 (production of capsule)

1) compound of Example 1	30 mg
2) fine powder cellulose	10 mg
10 3) lactose	19 mg
4) magnesium stearate	1 mg
Total	60 mg

1), 2), 3) and 4) are mixed and filled in a gelatin capsule.

[0414]

Formulation Example 2 (production of tablet)

5	1) compound of Example 1	30 g
	2) lactose	50 g
	3) cornstarch	15 g
	4) calcium carboxymethylcellulose	44 g
	5) magnesium stearate	1 g
10	1000 tablets total	140 g

The total amount of 1), 2) and 3) and 4) (30 g) is kneaded with water, vacuum dried, and sieved. The sieved powder is mixed with 4) (14 g) and 5) (1 g), and the mixture is punched by a tableting machine, whereby 1000 tablets
15 containing 30 mg of the compound of Example 1 per tablet are obtained.

[0415]

Formulation Example 3 (production of ointment)

	1) compound of Example 1	0.5 g
20	2) liquid paraffin	1 g
	3) white vaseline	98.5 g
	Total	100 g

1) and 2) are mixed well in a mortar, and 3) is added gradually thereto with kneading to make the total weight 100 g.
25 The obtained kneaded product is filled into tubes in parts to give an ointment.

[0416]

Experimental Example 1

Time Resolved Fluorescence Resonance Energy Transfer (TR-FRET)

30 Assays:

The binding of compounds to Bromodomain/s BRD4-BD(N) was assessed using TR-FRET assay that measures the binding of tetra-acetylated histone H4 peptide to the bromodomain.

[0417]

35 BRD4-BD(N) Bromodomain protein:

Recombinant Human Bromodomains BRD4-BD(N) (A.A 49-170) was expressed in *E-coli* cells (from pET28a vector) with a six-His tag at the N-terminal. The his-tagged BRD4-BD(N) was purified from E-coli cells by sonication followed by nickel
 5 affinity column (HisTrap HP, GE 17-5247-01) purification. The purified protein (>90% pure) was quantified by protein estimation by BCA protein estimation method. The purified protein was used for bromodomain - peptide binding assay as follows.

10 [0418]

Assay Protocol:

All assay components were dissolved in assay buffer composition of 50mM HEPES, pH7.5, 50mM NaCl, 0.5mM CHAPS. Compounds were pre-incubated with 100nM His-tagged BRD4-BD(N)
 15 for 15 minutes followed by addition of 200nM tetra-Acetylated histone H4 peptide coupled to biotin (Millipore, cat 12-379). The bromodomain protein and peptide interaction was detected by addition of 2nM Europium cryptate labelled streptavidin (Cisbio610SAKLA) and 10nM XL-665-labelled anti-6His antibody
 20 (Cisbio 61HisXLA) in assay buffer containing 0.05% (v/v) BSA and 400mM KF. Following incubation for 60 minutes, TR- FRET was measured (excitation 320nm, emission 615 nm and 665nm).
 [0419]

Table 13-1

Example No.	BRD4-BD (N) % Inhibition at 1 μ M
1.1	51.000
1.2	50.000
1.3	100.00
1.4	45.00
1.5	100.000
1.6	96.200
1.7	88.900
1.8	93.000

1.9	87.100
1.10	100.000
1.11	93.500
1.12	97.000
1.13	92.700
1.14	99.000
1.15	100.000
1.16	95.100
1.17	85.500
1.18	89.000
1.19	93.400
1.20	30.000
1.21	96.800
1.22	97.500
1.23	48.000
1.24	95.700
1.25	97.700
1.26	72.000
1.27	96.800
1.28	96.400
1.29	96.600
1.30	82.300
2.1	100.000
2.2	100.000
3.1	95.300
3.2	95.700
3.3	93.600
3.4	98.100
3.5	96.400
3.6	91.200
3.7	59.400
4.1	43.500

4.2	28.100
4.3	91.500
4.4	85.700
4.5	97.600
4.6	71.500
4.7	81.000
4.8	73.000
4.9	95.500
4.10	97.800
4.11	82.300
4.12	59.700
4.13	99.400
4.14	93.800
4.15	95.100
4.16	39.700
4.17	63.600
4.18	50.900
4.19	56.00
4.20	70.600
4.21	100.000
4.22	72.000
4.23	89.900
4.24	85.800
4.25	90.100
4.26	72.700
4.27	93.000
4.28	92.600
4.29	28.000
4.30	9.800
4.31	8.000
4.32	45.000
4.33	30.200

4.34	18.000
4.35	64.600
4.36	72.600
4.37	64.200
4.38	58.500
4.39	100.000
4.40	100.000
4.41	56.100
4.42	62.400
4.43	35.800
4.44	54.500
4.45	50.500
4.46	100.000
4.47	78.500
4.48	90.600
4.49	53.000
4.50	52.100
4.51	21.500
4.52	57.500
4.53	100.000
4.53.1	40.700
4.53.2	100.000
4.54	94.900
4.54.1	31.600
4.54.2	97.000
4.55.1	23.500
4.55.2	93.000
4.56.1	44.500
4.56.2	89.500
5.1	36.500
6.1	37.000
7.1	51.600

7.2	30.700
8.1	63.900
8.2	51.700
8.3	100.000
8.4	96.000
8.5	100.000
8.6	64.800
9.1	18.300
9.2	97.900
9.3	81.800
9.4	28.800
9.5	51.800
9.6	72.900
9.7	75.500
9.8	96.500
9.9	90.300
9.10	95.900
9.11	80.600
9.12	93.700
9.13	95.600
9.14	82.500
10.1	30.000
10.2	26.000
10.3	20.000
10.4	94.000
10.5	11.500
10.6	35.000
10.7	27.000
10.8	43.000
10.9	72.000
10.10	45.500

[0420]

Table 13-2

Example No.	BRD4-BD (C)
	% Inhibition at 1 μ M
11.1	16.8
11.2	14.8
11.3	18.5
11.4	20.2
12.1	4
12.2	19
12.3	43
12.4	20.5
12.5	64.5
12.6	51.9
12.7	46.6
13.1	29
13.2	19.4
13.3	27.5
14.1	41
14.2	49.7
14.3	25
14.4	24.5
14.5	37.5
14.6	30.8
14.7	55.1
14.8	28.3
14.9	68.2
14.10	50.5
14.11	44.9
14.12	19.9
15.1	35.5
15.2	38.5

[0421]

Experimental Example 2

Effect of BET inhibitors in Imiquimod induced-psoriasis model in BALB/c Mice

5 Objective:

To study effect of BET inhibitors (Compounds of Example 4.7, Example 9.6, Example 9.9 and Example 9.10) in Imiquimod (IMQ) induced-psoriasis model in BALB/c mice

Protocol:

10 Male BALB/c mice (8-10 weeks old) weighing 22-25 g were used in this study. Commercially available hair remover cream (Veet) was applied on the back of each animal on Day 0. From Day 1 onwards Imiquimod cream (~ 130 mg) was applied topically on the back of mice and ~ 5 mg on both ears daily till the end
15 of the study (Day 14). Animals were treated by topically applying test compounds from Day 1 to Day 14.

Following were the treatment groups:

- Naïve (Vaseline application)
- Vehicle, Cream Base, QD+IMQ
- 20 ▪ Compound of Example 4.7, 1% and 5% w/w cream, QD+IMQ
- Compound of Example 9.6, 5% w/w cream, QD+IMQ
- Compound of Example 9.9, 5% w/w cream, QD+IMQ
- Compound of Example 9.10, 5% w/w cream, QD+IMQ
- Betamethasone cream: 0.05% cream, 50 mg QD+IMQ

25 In the sepfication, QD (quaque die) means once-daily dosing.

Ear thickness was measured (twice a week) by a micrometer as a parameter of inflammation. The study was terminated on Day 14 and animals were sacrificed.

30 Satellite Group for pharmacokinetic/pharmacodynamics
(n=3/mice/time point)

- Compound of Example 4.7, 50 mg, (5%w/w cream), QD+IMQ

Skin and plasma were collected on Day 1 and Day 14 at 1, 6 and 24 hr post compound application. Three animals were
35 sacrificed at each time point.

Results: Effect on Ear thickness (shown in Figures 1 and 2)

- Vehicle treated group showed significant increase in ear thickness compared to naïve group starting Day 4 onwards.
- Compound of Example 4.7 at 1 and 5% cream showed 21 and 25% reduction (significant) in ear thickness starting Day 8 onwards compared to vehicle group at the end of study.
- Compound of Example 9.6 at 5% cream showed ~15% reduction (significant) in ear thickness on Day 14 compared to vehicle.
- Betamethasone 0.05% cream showed ~35-40% reduction in ear thickness starting Day 8 onwards compared to vehicle group.
- Compounds of Example 9.9 and Example 9.10 at 5% cream showed ~21% reduction (significant) in ear thickness starting Day 8/11 onwards till the end of treatment period compared to vehicle.

[0422]

No adverse effect or abnormal clinical signs were observed in any of the treatment group compared to vehicle at the end of study period.

[0423]

Experimental Example 3

Effect of BET inhibitor in Imiquimod induced-psoriasis model in BALB/c Mice (Dose response study)

Objective:

To study effect of BET inhibitor (Compound of Example 4.7) topical application in Imiquimod induced-psoriasis model in BALB/c mice

Protocol:

Male BALB/c mice (8-10 weeks old) weighing 22-25 g were used in this study. Commercially available hair remover cream (Veet) was applied on the back of each animal on Day 0. From Day 1 onwards Imiquimod cream (~ 130 mg) was applied topically on the back of mice and ~ 5 mg on both ears daily till the end of the study (Day 14). Animals were treated by topically applying test compounds from Day 1 to Day 14.

Following were the treatment groups:

- Naïve (Vaseline application)
 - Vehicle: Cream Base, QD+IMQ
 - Compound of Example 4.7, 50 mg, (1%, 2.5% and 5%w/w cream), QD+IMQ
- 5 ▪ Betamethasone cream: 0.05% cream, 50 mg QD+IMQ

Ear thickness was measured (twice a week) by a micrometer as a parameter of inflammation and study was terminated on Day 15 and animals were sacrificed

Satellite Group for pharmacokinetic/pharmacodynamics

10 (n=3/mice/time point)

- Compound of Example 4.7, 50 mg, (2.5% and 5%w/w cream), QD+IMQ

Skin and plasma was collected on Day 1 and Day 15 post 1, 6 and 24 hr post compound application. Three animals were
15 sacrificed at each time point.

Results: Effect on Ear thickness (shown in Figure 3)

- Vehicle treated group showed significant increase in ear thickness compared to naïve group starting day 4 onwards.
- Compound of Example 4.7 at 1, 2.5 and 5% cream showed ~48,
20 70 and 64% reduction in ear thickness respectively at the end of treatment period compared to vehicle group at the end of study.

Plasma concentration Efficacy treatment group is shown in Table 14, and plasma concentration Satellite pharmacokinetic
25 group 2.5% and 5% treatment group is shown in Tables 15 and 16.
[0424]

Table 14: Plasma and Skin concentration (μM) from efficacy treatment group on Day 15

Dose groups (cream)	Plasma conc. at 2 hr Mean $\pm$ SEM	Skin conc. at 2 hr Mean $\pm$ SEM
1%	1.88 $\pm$ 0.29	15.6 $\pm$ 0.59
2.5%	5.49 $\pm$ 0.47	43.4 $\pm$ 3.3
5%	6.79 $\pm$ 1.04	40.2 $\pm$ 2.7

[0425]

Table 15: Plasma and skin conc. from Imiquimod induced-psoriasis study in BALB/c mice (Compound of Example 4.7)
(Satellite arm- 2.5% cream; n=3/time point)

Time (hr)	Concentrations (μM)			
	Plasma		Skin	
	Day 1	Day 15	Day 1	Day 15
1	2.34 ± 0.06	4.43 ± 1.2	21.5 ± 1.6	18.8 ± 2.1
6	2.41 ± 0.94	2.44 ± 0.68	12.5 ± 2.8	12.6 ± 1.8
24	2.92 ± 0.20	0.41 ± 0.25	$22.5 \pm 5.1a$	3.87 ± 0.81
AUClast ($\mu\text{M}\cdot\text{hr}$)	61.0	45.1	411.1	236.4
AUC ratio Day 15/ day 1	NA	0.73	NA	0.57
Skin /Plasma AUC ratio	NA	NA	6.7	5.2

5

[0426]

Table 16: Plasma and skin conc. from Imiquimod induced-psoriasis study in BALB/c mice (Compound of Example 4.7)
(Satellite arm- 5% cream; n=3/time point)

Time (hr)	Concentrations (μM)			
	Plasma		Skin	
	Day 1	Day 15	Day 1	Day 15
1	2.98 ± 1.6	4.86 ± 0.61	33.9 ± 4.7	20.0 ± 4.26
6	1.01 ± 0.26	2.15 ± 0.46	19.7 ± 5.7	18.4 ± 3.4
24	5.0 ± 0.53	0.46 ± 0.25	20.6 ± 5.5	3.5 ± 1.3
AUClast ($\mu\text{M}\cdot\text{hr}$)	65.3	43.5	514.5	303.5
AUC ratio Day 15/ day 1	NA	0.66	NA	0.58
Skin /Plasma AUC ratio	NA	NA	7.8	6.9

10

[0427]

No adverse effect or abnormal clinical signs was observed in any of the treatment group compared to vehicle at the end of study period.

Industrial Applicability

5 [0428]

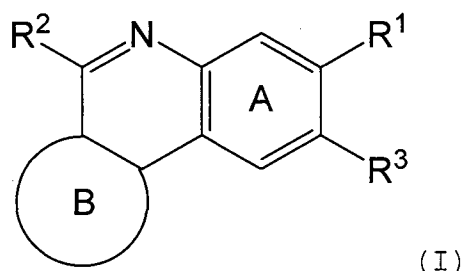
Compound (I) has a superior BET family protein inhibitory action, and is useful as an agent for the prophylaxis or treatment of autoimmune diseases and/or inflammatory diseases (e.g., rheumatoid arthritis, multiple sclerosis, idiopathic
10 pulmonary fibrosis, psoriasis, atopic dermatitis, inflammatory bowel disease, Sjogren's syndrome, Behcet's disease, systemic lupus erythematosus etc.), cancer and the like.

[0429]

This application is based on patent application No.
15 1750/DEL/2015 filed on June 11, 2015 in India, the contents of which are encompassed in full herein.

CLAIMS

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



5 wherein

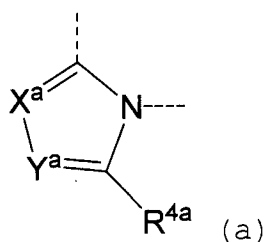
R¹ is an optionally substituted 5-membered aromatic heterocyclic group;

ring A is an optionally further substituted benzene ring;

R² and R³ are each independently a hydrogen atom or a
10 substituent; and

ring B is

a ring represented by the formula:

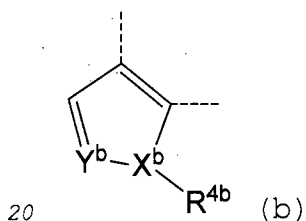


wherein

15 Xᵃ and Yᵃ are each independently a nitrogen atom or a carbon atom, and

R⁴ᵃ is a substituent, and

wherein said ring is optionally further substituted,
a ring represented by the formula:



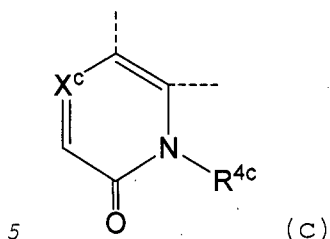
wherein

Xᵇ and Yᵇ are each independently a nitrogen atom or a carbon

atom, and

R^{4b} is a hydrogen atom or a substituent, and

wherein said ring is optionally further substituted, or
a ring represented by the formula:



wherein

X^c is a nitrogen atom or a carbon atom, and

R^{4c} is a hydrogen atom or a substituent, and

wherein said ring is optionally further substituted;

10 or a salt thereof.

2. The compound or salt of claim 1, wherein

R^1 is an optionally substituted isoxazolyl or an optionally
substituted pyrazolyl;

15 R^2 and R^3 are each independently

(1) a hydrogen atom,

(2) a halogen atom,

(3) a cyano group,

(4) an optionally substituted C_{3-10} cycloalkyl group,

20 (5) an optionally substituted 3- to 14-membered non-aromatic
heterocyclic group,

(6) an optionally substituted 5- to 14-membered aromatic
heterocyclic group,

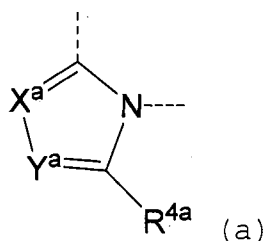
(7) an amino group optionally having 1 or 2 C_{1-6} alkyl groups
25 optionally having 1 to 3 substituents selected from the
following substituent group A,

(8) a hydroxy group optionally having a C_{1-6} alkyl group, or

(9) a sulfanyl group optionally having a C_{1-6} alkyl group; and

Ring B is

30 a ring represented by the formula:



wherein

X^a is a nitrogen atom;

Y^a is a nitrogen atom; and

5 R^{4a} is

(1) an optionally substituted C_{1-6} alkyl group,

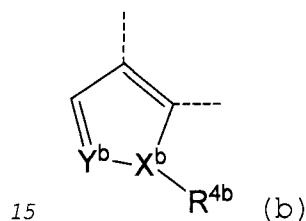
(2) an optionally substituted C_{3-10} cycloalkyl group,

(3) an optionally substituted C_{6-10} aryl group,

(4) an optionally substituted 3- to 14-membered non-
10 aromatic heterocyclic group, or

(5) an amino group optionally having 1 or 2 C_{6-10} aryl groups
optionally having 1 to 3 substituents selected from the
following substituent group A,

a ring represented by the formula:



wherein

X^b is a nitrogen atom;

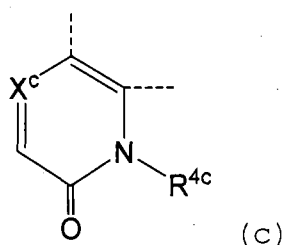
Y^b is a nitrogen atom; and

R^{4b} is

20 (1) an optionally substituted C_{1-6} alkyl group, or

(2) an optionally substituted C_{6-10} aryl group, or

a ring represented by the formula:



wherein

X^c is a nitrogen atom; and

R^{4c} is an optionally substituted C₁₋₆ alkyl group,

[substituent group A]

- 5 (1) a halogen atom,
- (2) a nitro group,
- (3) a cyano group,
- (4) an oxo group,
- (5) a hydroxy group,
- 10 (6) an optionally halogenated C₁₋₆ alkoxy group,
- (7) a C₆₋₁₄ aryloxy group,
- (8) a C₇₋₁₆ aralkyloxy group,
- (9) a 5- to 14-membered aromatic heterocyclyloxy group,
- (10) a 3- to 14-membered non-aromatic heterocyclyloxy group,
- 15 (11) a C₁₋₆ alkyl-carbonyloxy group,
- (12) a C₆₋₁₄ aryl-carbonyloxy group,
- (13) a C₁₋₆ alkoxy-carbonyloxy group,
- (14) a mono- or di-C₁₋₆ alkyl-carbamoyloxy group,
- (15) a C₆₋₁₄ aryl-carbamoyloxy group,
- 20 (16) a 5- to 14-membered aromatic heterocyclylcarbonyloxy group,
- (17) a 3- to 14-membered non-aromatic heterocyclylcarbonyloxy group,
- (18) an optionally halogenated C₁₋₆ alkylsulfonyloxy group,
- 25 (19) a C₆₋₁₄ arylsulfonyloxy group optionally substituted by a C₁₋₆ alkyl group,
- (20) an optionally halogenated C₁₋₆ alkylthio group,
- (21) a 5- to 14-membered aromatic heterocyclic group,
- (22) a 3- to 14-membered non-aromatic heterocyclic group,
- 30 (23) a formyl group,
- (24) a carboxy group,
- (25) an optionally halogenated C₁₋₆ alkyl-carbonyl group,
- (26) a C₆₋₁₄ aryl-carbonyl group,
- (27) a 5- to 14-membered aromatic heterocyclylcarbonyl group,
- 35 (28) a 3- to 14-membered non-aromatic heterocyclylcarbonyl

- group,
- (29) a C₁₋₆ alkoxy-carbonyl group,
- (30) a C₆₋₁₄ aryloxy-carbonyl group,
- (31) a C₇₋₁₆ aralkyloxy-carbonyl group,
- 5 (32) a carbamoyl group,
- (33) a thiocarbamoyl group,
- (34) a mono- or di-C₁₋₆ alkyl-carbamoyl group,
- (35) a C₆₋₁₄ aryl-carbamoyl group,
- (36) a 5- to 14-membered aromatic heterocyclylcarbamoyl group,
- 10 (37) a 3- to 14-membered non-aromatic heterocyclylcarbamoyl group,
- (38) an optionally halogenated C₁₋₆ alkylsulfonyl group,
- (39) a C₆₋₁₄ arylsulfonyl group,
- (40) a 5- to 14-membered aromatic heterocyclylsulfonyl group,
- 15 (41) an optionally halogenated C₁₋₆ alkylsulfinyl group,
- (42) a C₆₋₁₄ arylsulfinyl group,
- (43) a 5- to 14-membered aromatic heterocyclylsulfinyl group,
- (44) an amino group,
- (45) a mono- or di-C₁₋₆ alkylamino group,
- 20 (46) a mono- or di-C₆₋₁₄ arylamino group,
- (47) a 5- to 14-membered aromatic heterocyclylamino group,
- (48) a C₇₋₁₆ aralkylamino group,
- (49) a formylamino group,
- (50) a C₁₋₆ alkyl-carbonylamino group,
- 25 (51) a (C₁₋₆ alkyl) (C₁₋₆ alkyl-carbonyl) amino group,
- (52) a C₆₋₁₄ aryl-carbonylamino group,
- (53) a C₁₋₆ alkoxy-carbonylamino group,
- (54) a C₇₋₁₆ aralkyloxy-carbonylamino group,
- (55) a C₁₋₆ alkylsulfonylamino group,
- 30 (56) a C₆₋₁₄ arylsulfonylamino group optionally substituted by a C₁₋₆ alkyl group,
- (57) an optionally halogenated C₁₋₆ alkyl group,
- (58) a C₂₋₆ alkenyl group,
- (59) a C₂₋₆ alkynyl group,
- 35 (60) a C₃₋₁₀ cycloalkyl group,

(61) a C₃₋₁₀ cycloalkenyl group and

(62) a C₆₋₁₄ aryl group.

3. 7-(3,5-dimethylisoxazol-4-yl)-8-methoxy-N-methyl-1-(2-
5 pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4-amine or a
salt thereof.

4. 4-[8-methoxy-1-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-
a]quinoxalin-7-yl]-3,5-dimethyl-isoxazole or a salt thereof.

10

5. 7-(3,5-dimethylisoxazol-4-yl)-8-methoxy-1-(2-
pyridylmethyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4-amine or a
salt thereof.

15 6. A medicament comprising the compound or salt of claim 1.

7. The medicament of claim 6, which is bromodomain and extra
terminal domain family protein inhibitor.

20 8. The medicament of claim 6, which is an agent for the
prophylaxis or treatment of autoimmune diseases and/or
inflammatory diseases.

9. The medicament of claim 6, which is an agent for the
25 prophylaxis or treatment of psoriasis or atopic dermatitis.

10. The compound or salt of claim 1 for use in the prophylaxis
or treatment of autoimmune diseases and/or inflammatory
diseases.

30

11. The compound or salt of claim 1 for use in the prophylaxis
or treatment of psoriasis or atopic dermatitis.

12. A method of inhibiting bromodomain and extra terminal
35 domain family protein in a mammal, which comprises

administering an effective amount of the compound or salt of claim 1 to the mammal.

13. A method for the prophylaxis or treatment of autoimmune
5 diseases and/or inflammatory diseases in a mammal, which
comprises administering an effective amount of the compound or
salt of claim 1 to the mammal.

14. A method for the prophylaxis or treatment of psoriasis or
10 atopic dermatitis in a mammal, which comprises administering
an effective amount of the compound or salt of claim 1 to the
mammal.

15. Use of the compound or salt of claim 1 for the production
15 of an agent for the prophylaxis or treatment of autoimmune
diseases and/or inflammatory diseases.

16. Use of the compound or salt of claim 1 for the production
of an agent for the prophylaxis or treatment of psoriasis or
20 atopic dermatitis.

Figure 1

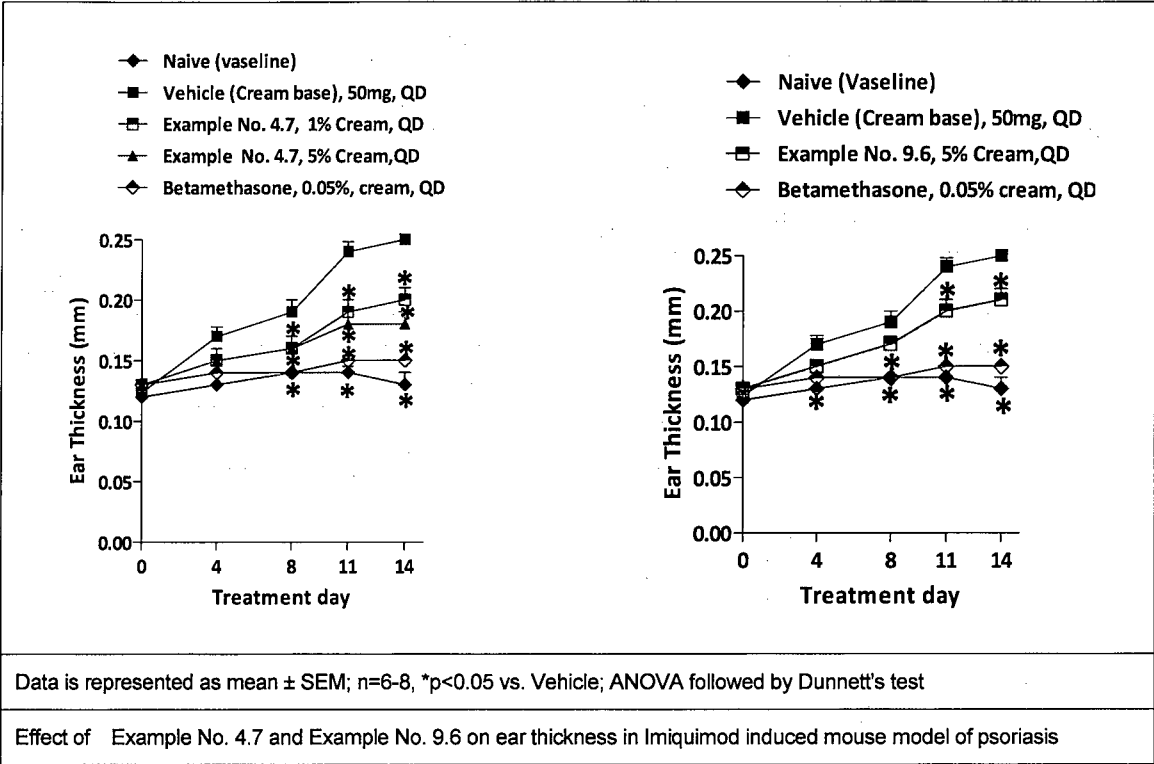


Figure 2

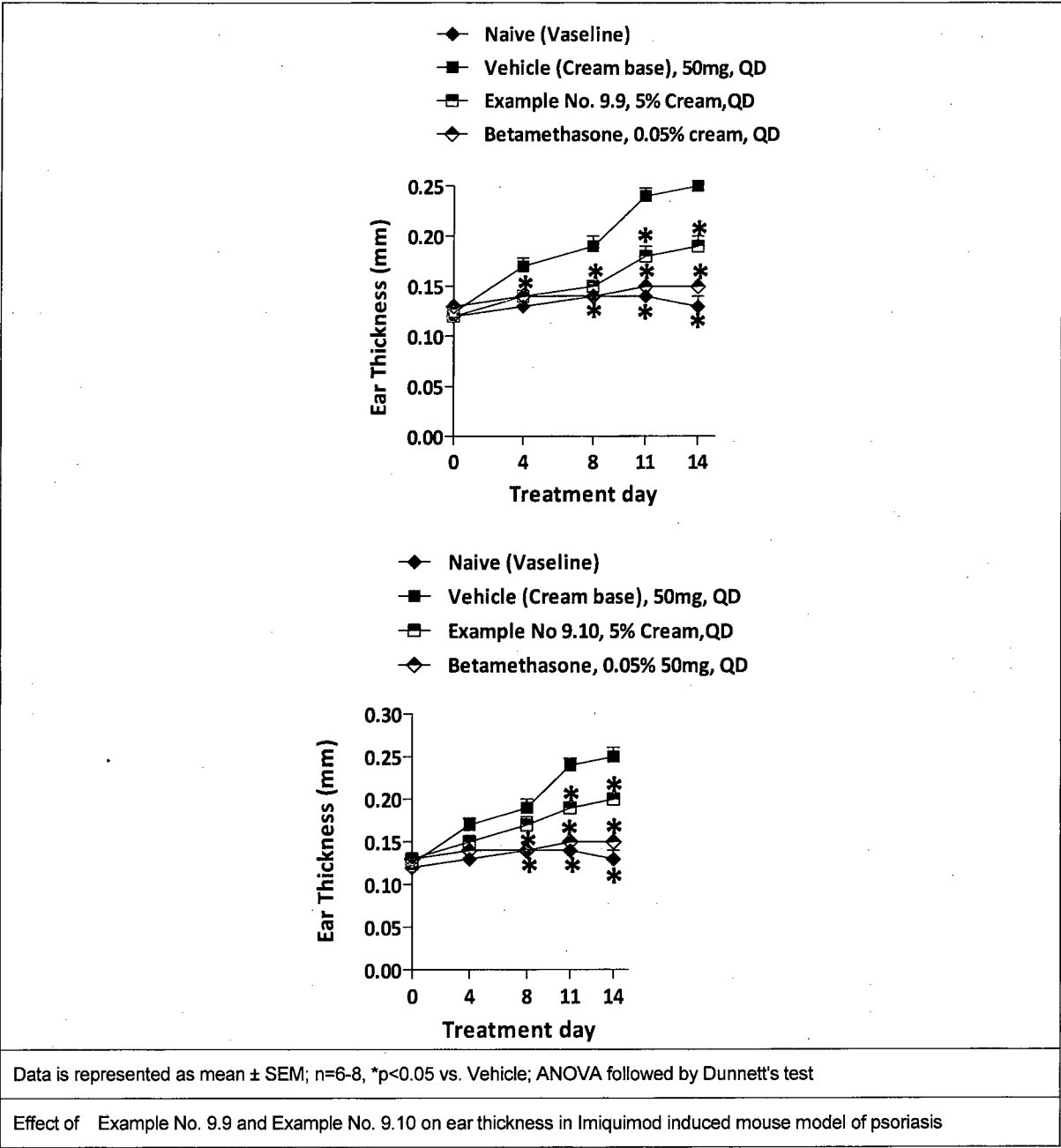
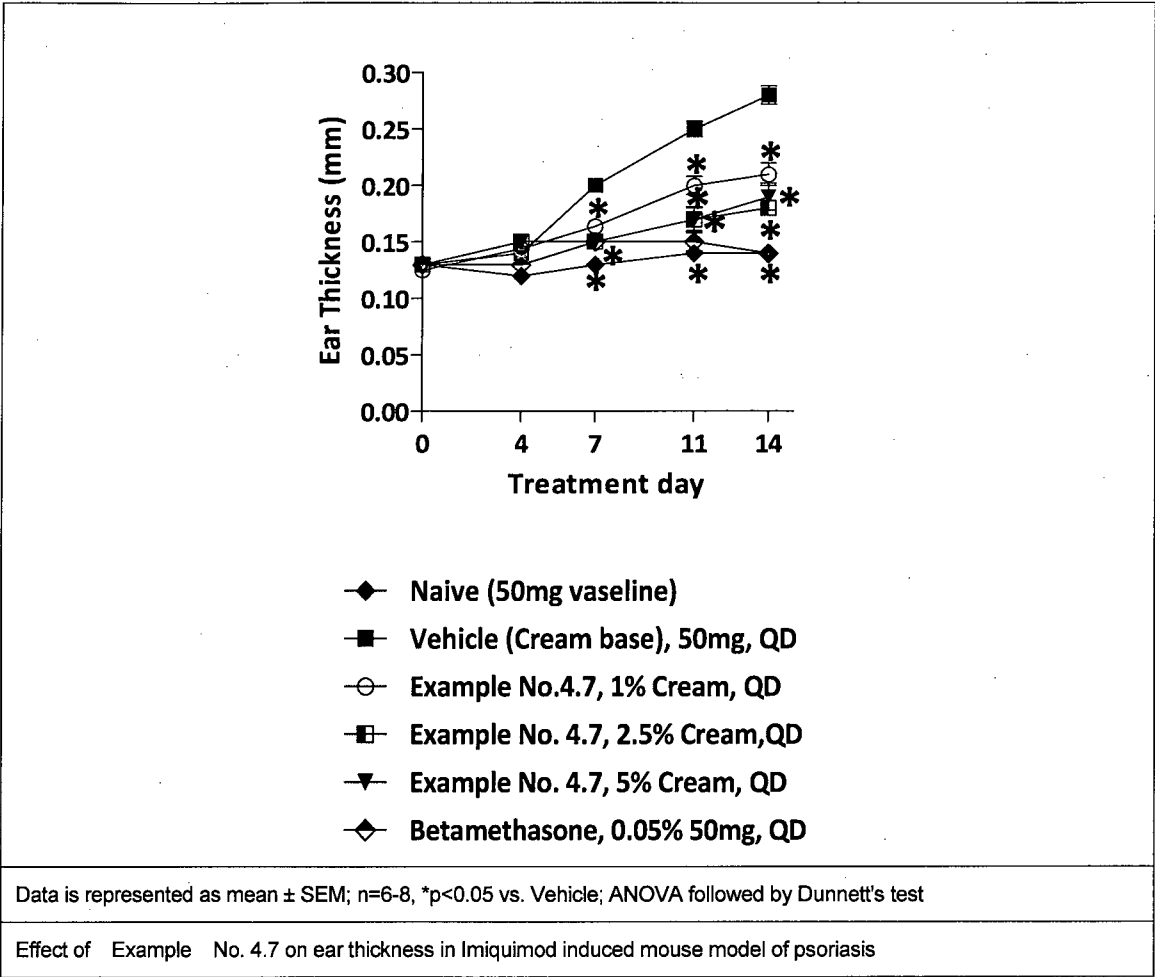


Figure 3



INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER INV. C07D471/04 C07D487/04 C07D491/056 A61K31/437 A61K31/4375 A61K31/4985 A61K31/519 A61P17/06 A61P29/00 A61P37/00 ADD. According to International Patent Classification (IPC) or to both national classification and IPC											
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data, CHEM ABS Data											
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>WO 2011/112731 A2 (KALYPSYS INC [US]; BORCHARDT ALLEN [US]; DAVIS ROBERT [US]; BEAUREGARD) 15 September 2011 (2011-09-15) claims 46, 56, 57 and examples in page 404 (first and 4th rows) -----</td> <td>1,6-16</td> </tr> <tr> <td>X</td> <td>WO 2010/135571 A1 (CYLENE PHARMACEUTICALS INC [US]; PIERRE FABRICE [US]; HADDACH MUSTAPHA) 25 November 2010 (2010-11-25) cited in the application claim 1, par. [0016] and [0168] and e.g. 1st and 3rd compound in p. 72, compounds in p. 73-74 and 76, last compound in p. 75, 1st compound in p. 77, last in p. 82, 2nd and 4th compounds in p. 101, compounds in p. 102-103 etc. ----- -/-</td> <td>1,6-16</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	WO 2011/112731 A2 (KALYPSYS INC [US]; BORCHARDT ALLEN [US]; DAVIS ROBERT [US]; BEAUREGARD) 15 September 2011 (2011-09-15) claims 46, 56, 57 and examples in page 404 (first and 4th rows) -----	1,6-16	X	WO 2010/135571 A1 (CYLENE PHARMACEUTICALS INC [US]; PIERRE FABRICE [US]; HADDACH MUSTAPHA) 25 November 2010 (2010-11-25) cited in the application claim 1, par. [0016] and [0168] and e.g. 1st and 3rd compound in p. 72, compounds in p. 73-74 and 76, last compound in p. 75, 1st compound in p. 77, last in p. 82, 2nd and 4th compounds in p. 101, compounds in p. 102-103 etc. ----- -/-	1,6-16
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.									
X	WO 2011/112731 A2 (KALYPSYS INC [US]; BORCHARDT ALLEN [US]; DAVIS ROBERT [US]; BEAUREGARD) 15 September 2011 (2011-09-15) claims 46, 56, 57 and examples in page 404 (first and 4th rows) -----	1,6-16									
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☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.											
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family											
Date of the actual completion of the international search 8 September 2016		Date of mailing of the international search report 19/09/2016									
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Sahagún Krause, H									

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International application No

PCT/JP2016/068023

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2008, DESPLAT, VANESSA ET AL: "Synthesis of New Pyrrolo[1,2-a]quinoxaline Derivatives as Potential Inhibitors of Akt Kinase", XP002761598, retrieved from STN Database accession no. 2008:1165843 compound with RN number 1074761-63-9 & DESPLAT, VANESSA ET AL: "Synthesis of New Pyrrolo[1,2-a]quinoxaline Derivatives as Potential Inhibitors of Akt Kinase", JOURNAL OF ENZYME INHIBITION AND MEDICINAL CHEMISTRY, 23(5), 648-658 CODEN: JEIMAZ; ISSN: 1475-6366, 2008, DOI: 10.1080/14756360802205448 10.1080/14756360802205448	1
X	----- EP 2 103 613 A1 (ASKA PHARM CO LTD [JP]) 23 September 2009 (2009-09-23) claim 1, par. [0003], EXAMPLES 146-147, 152-153	1,2,6,8, 10,13,15
X	----- JUNYA OHMORI ET AL: "8-(1H-Imidazol-1-yl)-7-nitro-4(5H)-imidaz o[1,2-a]quinoxalinone and Related Compounds: Synthesis and Structure-Activity Relationships for the AMPA-type Non-NMDA Receptor", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 40, no. 13, 1 January 1997 (1997-01-01), pages 2053-2063, XP002475040, ISSN: 0022-2623, DOI: 10.1021/JM960664C compound 18	1
X	----- WO 94/26746 A1 (NOVO NORDISK AS [DK]) 24 November 1994 (1994-11-24) CLAIM 1 AND EXAMPLES 1-3	1
X	----- WO 93/20077 A1 (YAMANOUCHI PHARMA CO LTD [JP]; SAKAMOTO SHUICHI [JP]; OHMORI JUN YA [J]) 14 October 1993 (1993-10-14) example 17 in p. 54	1
Y	----- WO 2013/024104 A1 (GLAXOSMITHKLINE LLC [US]; DEMONT EMMANUEL HUBERT [GB]; JONES KATHERINE) 21 February 2013 (2013-02-21)	1,2,6-16
A	claims and page 2, l. 15-18 ----- -/--	3-5

INTERNATIONAL SEARCH REPORT

International application No

PCT/JP2016/068023

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2011/054843 A1 (GLAXOSMITHKLINE LLC [US]; CHUNG CHUN-WA [GB]; NICODEME EDWIGE [FR]) 12 May 2011 (2011-05-12)	1,2,6-16
A	claims and examples 3-4 -----	3-5
Y	WO 2011/054846 A1 (GLAXOSMITHKLINE LLC [US]; BOUILLOT ANNE MARIE JEANNE [FR]; DONCHE FRED) 12 May 2011 (2011-05-12)	1,2,6-16
A	claims and examples 1-226 -----	3-5

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/JP2016/068023

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011112731 A2	15-09-2011	TW 201204727 A US 2011257137 A1 UY 33272 A WO 2011112731 A2	01-02-2012 20-10-2011 31-10-2011 15-09-2011
WO 2010135571 A1	25-11-2010	US 2010298302 A1 WO 2010135571 A1	25-11-2010 25-11-2010
EP 2103613 A1	23-09-2009	AU 2007332440 A1 CA 2671980 A1 CN 101553491 A EP 2103613 A1 EP 2489667 A1 EP 2848620 A1 ES 2536906 T3 ES 2566774 T3 JP 5578786 B2 JP 5744288 B2 JP 2014205686 A KR 20090097919 A KR 20140139631 A US 2010048556 A1 US 2013225572 A1 US 2014336197 A1 WO 2008072779 A1	19-06-2008 19-06-2008 07-10-2009 23-09-2009 22-08-2012 18-03-2015 29-05-2015 15-04-2016 27-08-2014 08-07-2015 30-10-2014 16-09-2009 05-12-2014 25-02-2010 29-08-2013 13-11-2014 19-06-2008
WO 9426746 A1	24-11-1994	AT 148120 T AU 683062 B2 AU 6720094 A CA 2162023 A1 CN 1125446 A DE 69401583 D1 DE 69401583 T2 DK 0698024 T3 EP 0698024 A1 ES 2097652 T3 FI 955304 A GR 3023001 T3 IL 109530 A JP H08509747 A NO 954402 A NZ 266127 A US 5532236 A WO 9426746 A1	15-02-1997 30-10-1997 12-12-1994 24-11-1994 26-06-1996 06-03-1997 12-06-1997 28-07-1997 28-02-1996 01-04-1997 06-11-1995 30-07-1997 10-01-1997 15-10-1996 05-01-1996 24-11-1997 02-07-1996 24-11-1994
WO 9320077 A1	14-10-1993	AU 3767793 A WO 9320077 A1	08-11-1993 14-10-1993
WO 2013024104 A1	21-02-2013	AR 087545 A1 AU 2012296914 A1 CA 2843537 A1 CL 2014000365 A1 CN 103889984 A CO 6862151 A2 CR 20140076 A DO P2014000031 A EA 201490200 A1 EP 2744809 A1	03-04-2014 13-02-2014 21-02-2013 11-07-2014 25-06-2014 10-02-2014 19-03-2014 01-06-2014 30-07-2014 25-06-2014

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/JP2016/068023

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
		JP 2014521735 A	28-08-2014	
		KR 20140064878 A	28-05-2014	
		NZ 620263 A	29-04-2016	
		PE 14062014 A1	25-10-2014	
		TW 201323424 A	16-06-2013	
		UA 110838 C2	25-02-2016	
		US 2014171462 A1	19-06-2014	
		US 2015315184 A1	05-11-2015	
		UY 34264 A	05-04-2013	
		WO 2013024104 A1	21-02-2013	

WO 2011054843	A1	12-05-2011	EP 2496235 A1	12-09-2012
			JP 2013510121 A	21-03-2013
			US 2012208800 A1	16-08-2012
			US 2015133436 A1	14-05-2015
			WO 2011054843 A1	12-05-2011

WO 2011054846	A1	12-05-2011	EP 2496576 A1	12-09-2012
			ES 2446358 T3	07-03-2014
			JP 5766708 B2	19-08-2015
			JP 2013510124 A	21-03-2013
			US 2012232074 A1	13-09-2012
			WO 2011054846 A1	12-05-2011
