

## DESCRIPTION

Title of the Invention: AGENT FOR PREVENTING AND/OR TREATING  
AMYOTROPHIC LATERAL SCLEROSIS

[Technical Field]

5 [0001]

The present invention relates to a prophylactic and/or therapeutic agent for amyotrophic lateral sclerosis.

[Background Art]

[0002]

10 Amyotrophic lateral sclerosis (hereinafter, ALS) is a motor neuron disease of poor prognosis, which develops at middle ages and thereafter and causes progressive paralysis of skeletal muscles. It is designated as a disease in the project for investigation and research into specific diseases sponsored  
15 by the Ministry of Health, Labor and Welfare of Japan. More than about 90% of cases of ALS are sporadic and the cause is unknown. As a component of ubiquitin-positive inclusion bodies found in the lower motor neuron of sporadic ALS patients, a 43-kDa TAR DNA-binding protein (TDP-43) has been identified in  
20 recent years, and is attracting attention as an etiology gene (non-patent document 1). On the other hand, the remaining 10% are familial cases, and point mutation of genes such as Cu/Zn superoxide dismutase (SOD1) gene, TDP-43 gene and the like has been reported. In this case, the gain-of-toxic function theory  
25 is likely wherein motor neuron death is caused by the cytotoxicity newly gained by mutated SOD1 (non-patent document 2).

[0003]

The only currently commercially available therapeutic  
30 drug for ALS is riluzole (Rilutek<sup>TM</sup>, Aventis), a glutamate receptor antagonist possessing glutamate suppressing action (patent document 1).

[0004]

On the other hand, it is considered that the pathology  
35 can be reproduced in vitro by establishing an induced

pluripotent stem cell (iPS cell) obtained from cells derived from a patient by using a reprogramming technique and inducing differentiation from this iPS cell into a pathogenic cell. The present inventors have demonstrated using atorvastatin known to  
5 have an anti-ALS action that a candidate substance of a therapeutic drug for ALS can be screened for by inducing differentiation of an iPS cell established from fibroblasts derived from ALS patients having a mutation in the SOD1 gene into astrocyte, and using, as an index, a decrease in the  
10 expression level of SOD1 in the obtained astrocyte (patent document 2). Furthermore, they have identified sorafenib, which is a multikinase inhibitor and used as a therapeutic drug for progressive renal cell carcinoma, as a candidate substance of a therapeutic drug for ALS, by using the screening system  
15 (patent document 3). Also, they have shown that a candidate substance of a therapeutic drug for ALS can be screened for by inducing differentiation of iPS cell, established from ALS patients having a mutation in TDP-43 gene, into motor neuron (MN), and screening using a decrease in the expression level of  
20 TDP-43 in the obtained motor neuron, improvement of fragility to stress, recovery of neurite length and the like as indices (patent document 4, non-patent document 3). Furthermore, they have shown that a motor neuron that reproduces pathology of patients well can be promptly and synchronically prepared by  
25 introducing 3 kinds of nerve cell lineage specific transcription factors into pluripotent stem cells (patent document 5).

Thus, while a screening and efficacy evaluation system of a therapeutic drug for ALS using nerve cell derived from iPS  
30 cell is being developed, and a promising candidate substance (therapeutic drug seeds) is being found, a considerable amount of way is still expected until practicalization as a pharmaceutical product.

[0005]

35 Incidentally, as a method for overcoming the deadlock

seen recently in the development and research of a new drug a  
new research concept called drug repositioning (DR) has become  
the subject of discussion. It aims to find a new medicinal  
effect from existing drugs showing safety and pharmacokinetics  
5 in human, which have already been confirmed from actual results,  
and achieve practicalization thereof. Since many existing data  
can be used, it is further advantageous in that the development  
cost can be suppressed low, accumulated know-how and materials  
(surrounding compounds and the like) exist and the like. As  
10 mentioned above, the present inventors have already found that  
sorafenib, which is used as a therapeutic drug for cancer, has  
an ALS treatment activity as novel efficacy.

[Document List]

[Patent documents]

15 [0006]

patent document 1: AU 666150 B2

patent document 2: WO 2011/074690

patent document 3: WO 2012/029994

patent document 4: WO 2013/108926

20 patent document 5: WO 2014/148646

[non-patent documents]

[0007]

non-patent document 1: Neumann M, et al., Science. 2006, 314:  
130-3.

25 non-patent document 2: Bruijn, L.I., et al., 2004. Annu. Rev.  
Neurosci. 27, 723-749.

non-patent document 3: Egawa N, et al., Sci. Transl. Med. 2012,  
4: 145ra104

[SUMMARY OF THE INVENTION]

30 [Problems to be Solved by the Invention]

[0008]

An object of the present invention is to provide a novel  
medicament candidate having a prophylactic and/or therapeutic  
activity for ALS, as well as accelerate the development of a  
35 prophylactic and/or therapeutic agent for ALS as a realistic

pharmaceutical product.

[Means of Solving the Problems]

[0009]

In an attempt to solve the above-mentioned problem, the  
5 present inventors induced differentiation of iPS cell  
established from ALS patients having a mutation in SOD1 gene  
into motor neuron and, using the survival of the motor neuron  
as an index, screened for a compound having an anti-ALS  
activity from a library of known compounds including  
10 medicaments already on the market as pharmaceutical products.  
As a result, they have found that epithelial cell growth factor  
receptor (EGFR) inhibitor, fibroblast growth factor receptor  
(FGFR) inhibitor, Aurorakinase inhibitor, protein kinase A  
(PKA) inhibitor, protein kinase C (PKC) inhibitor, MEK  
15 inhibitor, Met inhibitor, JNK inhibitor, Syk inhibitor, JAK  
inhibitor, prostaglandin analogue, 3-hydroxybutyric acid and  
estrogen receptor antagonist remarkably improve survival of ALS  
motor neuron. In addition, compounds having an anti-ALS  
activity including Bosutinib, which is a drug in the market,  
20 were also found even from the compounds not belonging to the  
above-mentioned category.

Furthermore, 6 kinds of drug in the market (including  
Tivozanib which was not approved after filing request for  
approval and examination thereof was completed) confirmed to  
25 have an anti-ALS activity against mutated SOD1 ALS were  
subjected to comparison of the anti-ALS effects thereof by  
using ALS motor neurons derived from iPS cells established from  
patients having SOD1 mutation, patients having TDP-43 mutation,  
patients having C9orf72 mutation, and sporadic ALS patients,  
30 and improvement in the cell survival rate as an index. As a  
result, they showed varying anti-ALS activity spectra depending  
on the medicaments.

From the above results, the present inventors have found  
that any of the above-mentioned kinase inhibitor or other  
35 medicament is useful for the prophylaxis and/or treatment of

ALS, and further that effective prophylaxis and/or treatment of ALS, which is suitable for individual patients or a preliminary group thereof, can be available by properly according to the causative gene of ALS, which resulted in the completion of the present invention.

Therefore, the present invention provides the following.

[1] A prophylactic and/or therapeutic agent for amyotrophic lateral sclerosis (ALS), which comprises one or more kinase inhibitors selected from the group consisting of an epithelial cell growth factor receptor (EGFR) inhibitor, a fibroblast growth factor receptor (FGFR) inhibitor, an Aurorakinase inhibitor, a protein kinase A (PKA) inhibitor, a protein kinase C (PKC) inhibitor, an MEK inhibitor, an Met inhibitor, a JNK inhibitor, a Syk inhibitor and a JAK inhibitor, and/or a prostaglandin analogue and/or an estrogen receptor antagonist.

[2] The agent of [1], wherein the aforementioned EGFR inhibitor is a PDGF Receptor Tyrosine Kinase Inhibitor III or BPIQ-I.

[3] The agent of [1], wherein the aforementioned FGFR inhibitor is Pazopanib or an analog thereof or PDGF Receptor Tyrosine Kinase Inhibitor III.

[4] The agent of [1], wherein the aforementioned Aurorakinase inhibitor is ZM-447439, VX-680, Aurora Kinase Inhibitor II, CYC116, KW2449, or AT9283.

[5] The agent of [1], wherein the aforementioned PKA inhibitor is PDGF Receptor Tyrosine Kinase Inhibitor III.

[6] The agent of [1], wherein the aforementioned PKC inhibitor is PDGF Receptor Tyrosine Kinase inhibitor III or Enzastaurin.

[7] The agent of [1], wherein the aforementioned MEK inhibitor is U0126-EtOH.

[8] The agent of [1], wherein the aforementioned Met inhibitor is MGCD-265, PF-2341066 (Crizotinib) or an analog thereof or BMS 777607.

[9] The agent of [1], wherein the aforementioned JNK inhibitor is SP600125.

[10] The agent of [1], wherein the aforementioned Syk inhibitor

is a Syk Inhibitor.

[11] The agent of [1], wherein the aforementioned JAK inhibitor is JAK Inhibitor I or AT9283.

[12] The agent of [1], wherein the aforementioned prostaglandin  
5 analogue is Bimatoprost.

[13] The agent of [1], wherein the aforementioned estrogen receptor antagonist is Raloxifene.

[14] A prophylactic and/or therapeutic agent for ALS,  
comprising one or more compounds selected from the group  
10 consisting of Tivozanib and an analog thereof, SB 216763, Cdk2  
Inhibitor II, BUDESONIDE, RIBOFLAVIN, alpha-TOCHOPHEROL,  
AMODIAQUINE, SU9516, Sunitinib and an analog thereof, GSK-3  
Inhibitor XIII, Bisindolylmaleimide I, HYDROQUINONE,  
FLUNISOLIDE, MGCD-265, Indirubin-3'-monoxime, HYDRASTINE (1R,  
15 9S), PIPERINE, BUTAMBEN, Axitinib and an analog thereof,  
APOMORPHINE, FENBUFEN, Bosutinib (SKI-606) and an analog  
thereof, Wee1 Inhibitor, Cdk2 Inhibitor IV, NU6140, 3-  
hydroxybutyric acid, Imatinib, Nilotinib, Rebastinib, and  
Bafetinib.

20 [15] A method for the prophylaxis and/or treatment of ALS,  
comprising administering an effective amount of one or more  
kinase inhibitors selected from the group consisting of an EGFR  
inhibitor, an FGFR inhibitor, an Aurorakinase inhibitor, a PKA  
inhibitor, a PKC inhibitor, an MEK inhibitor, an Met inhibitor,  
25 a JNK inhibitor, a Syk inhibitor and a JAK inhibitor, and/or a  
prostaglandin analogue and/or an estrogen receptor antagonist.

[16] A method for the prophylaxis and/or treatment of ALS,  
comprising administering an effective amount of one or more  
kinase inhibitors selected from the group consisting of  
30 Tivozanib and an analog thereof, SB 216763, Cdk2 Inhibitor II,  
BUDESONIDE, RIBOFLAVIN, alpha-TOCHOPHEROL, AMODIAQUINE, SU9516,  
Sunitinib and an analog thereof, GSK-3 Inhibitor XIII,  
Bisindolylmaleimide I, HYDROQUINONE, FLUNISOLIDE, MGCD-265,  
Indirubin-3'-monoxime, HYDRASTINE (1R,9S), PIPERINE, BUTAMBEN,  
35 Axitinib and an analog thereof, APOMORPHINE, FENBUFEN,

Bosutinib (SKI-606) and an analog thereof, a Wee1 Inhibitor, Cdk2 Inhibitor IV, NU6140, 3-hydroxybutyric acid, Imatinib, Nilotinib, Rebastinib, and Bafetinib.

[17] One or more kinase inhibitors selected from the group  
5 consisting of an EGFR inhibitor, an FGFR inhibitor, an Aurorakinase inhibitor, a PKA inhibitor, a PKC inhibitor, an MEK inhibitor, an Met inhibitor, a JNK inhibitor, a Syk inhibitor and a JAK inhibitor, and/or a prostaglandin analogue and/or an estrogen receptor for the prophylaxis and/or  
10 treatment of ALS.

[18] One or more kinase inhibitors selected from the group consisting of Tivozanib and an analog thereof, SB 216763, Cdk2 Inhibitor II, BUDESONIDE, RIBOFLAVIN, alpha-TOCHOPHEROL, AMODIAQUINE, SU9516, Sunitinib and an analog thereof, GSK-3  
15 Inhibitor XIII, Bisindolylmaleimide I, HYDROQUINONE, FLUNISOLIDE, MGCD-265, Indirubin-3'-monoxime, HYDRASTINE (1R,9S), PIPERINE, BUTAMBEN, Axitinib and an analog thereof, APOMORPHINE, FENBUFEN, Bosutinib (SKI-606) and an analog thereof, a Wee1 Inhibitor, Cdk2 Inhibitor IV, NU6140, 3-  
20 hydroxybutyric acid, Imatinib, Nilotinib, Rebastinib, and Bafetinib for the prophylaxis and/or treatment of ALS.

[Effect of the Invention]

[0010]

Various kinase inhibitors of the present invention and  
25 other compound having an anti-ALS activity are useful for the prophylaxis and/or treatment of ALS. In addition, an effective prophylaxis and/or treatment of ALS, which is suitable for individual patients or a preliminary group thereof, can be available by properly using the kinase inhibitor of the present  
30 invention according to the causative gene of ALS.

[Brief Description of the Drawings]

[0011]

In Fig. 1, Fig. 1A shows immunostained images showing accumulation of misfolded SOD1 in motoneuron cell established  
35 iPS cell derived from ALS patients having SOD1 mutation (SOD1-

L144FVX mutation) (SOD1 ALS). Control shows motoneuron cell established from iPS cell derived from healthy subject. The right panel shows the results of triple staining with  $\beta$ III-tubulin and DAPI. Fig. 1B shows immunostained images showing fragility (decrease in the number of surviving cells) of motoneuron cell derived from SOD1 mutation. The right graph shows the survival rate, at 14 days after the start of differentiation induction, of motoneuron cell. \*:p<0.05

Fig. 2 is a graph showing that Tivozanib, Bosutinib, Sunitinib, Crizotinib, Axitinib and Pazopanib improve survival rate of motoneuron cells having SOD1 mutation in a dose-dependent manner.

Fig. 3 shows that Tivozanib, Bosutinib and Sunitinib inhibit phosphorylation of Erk and c-abl in motoneuron cell having SOD1 mutation. Fig. 3A shows Western blot images using anti-Erk antibody and anti-phosphorylated Erk antibody, and anti-c-abl antibody and anti-phosphorylated c-abl antibody, Fig. 3B and C each show phosphorylated Erk/Erk (p-Erk/Erk) ratio and phosphorylated c-abl/c-abl (p-Abl/Abl) ratio obtained by image analysis of the band intensity.

Fig. 4 shows the survival rate, at 14 days after the start of induction, of motoneuron cell induced from iPS cell, derived from ALS patients having various gene mutations and sporadic ALS patients.

Fig. 5 shows a dose-dependent protection effect of Tivozanib, Bosutinib, Sunitinib, Crizotinib, Axitinib and Pazopanib on the survival of motoneuron cell induced from iPS cell derived from ALS patients having various gene mutations and sporadic ALS patients. In the Figure, SALS means sporadic ALS. The bar graph of the column of each motoneuron cell shows no addition (0  $\mu$ M), 0.1  $\mu$ M addition, 1  $\mu$ M addition of medicament from the left.

Fig. 6 is a graph showing that Bimatoprost, Edaravone, 3-hydroxybutyric acid and Raloxifene improve survival rate of motoneuron cells having SOD1 mutation in a dose-dependent

manner.

Fig. 7 is a drawing showing that Imatinib, Nilotinib, Rebastinib, AT9283 and Bafetinibin improve survival rate of familial ALS (mSOD1 ALS) motoneuron cells in a dose-dependent  
5 manner.

Fig. 8 is a drawing showing that Bosutinib decreases misfolded TDP43 even in familial ALS having TDP-43 mutation and sporadic ALS.

[Description of Embodiments]

10 [0012]

The present invention provides a prophylactic and/or therapeutic agent for amyotrophic lateral sclerosis (ALS) (hereinafter to be also referred to as an agent for the prophylaxis or treatment of ALS) containing one or more kinase  
15 inhibitors selected from the group consisting of an epithelial cell growth factor receptor (EGFR) inhibitor, a fibroblast growth factor receptor (FGFR) inhibitor, an Aurorakinase inhibitor, a protein kinase A (PKA) inhibitor, a protein kinase C (PKC) inhibitor, an MEK inhibitor, an Met inhibitor, a JNK  
20 inhibitor, a Syk inhibitor and a JAK inhibitor, and/or, one or more compounds selected from the group consisting of a prostaglandin analogue, 3-hydroxybutyric acid, an estrogen receptor antagonist, Tivozanib and an analog thereof, SB 216763, Cdk2 Inhibitor II, BUDESONIDE, RIBOFLAVIN, alpha-TOCHOPHEROL,  
25 AMODIAQUINE, SU9516, Sunitinib and an analog thereof, GSK-3 Inhibitor XIII, Bisindolylmaleimide I, HYDROQUINONE, FLUNISOLIDE, MGCD-265, Indirubin-3'-monoxime, HYDRASTINE (1R, 9S), PIPERINE, BUTAMBEN, Axitinib and an analog thereof, APOMORPHINE, FENBUFEN, Bosutinib (SKI-606) and an analog  
30 thereof, a Weel Inhibitor, Cdk2 Inhibitor IV, NU6140, AT9283, Imatinib, Nilotinib, Rebastinib, and Bafetinib.

[0013]

In the present invention, the amyotrophic lateral sclerosis (ALS) to be treated includes both sporadic and  
35 familial amyotrophic lateral sclerosis (ALS). In the case of

familial ALS, the causative gene is not particularly limited, and may be any known causative gene such as SOD1, TDP-43, C9orf72, alsin, SETX, FUS/TLS, VAPB, ANG, FIG4, OPTN, ATXN2, DAO, UBQLN2, PFN1, DCTN1, CHPM2B, VCP and the like. In one  
5 embodiment, in the case of familial ALS having SOD1 mutation, examples of the SOD1 gene mutation include, but are not limited to, a mutation in which the 144th Leu of SOD1 protein is substituted by Phe-Val-Xaa (Xaa is any amino acid) (SOD1-L144FVX), a mutation in which the 93rd Gly is substituted by  
10 Ser (SOD1-G93S), a mutation in which the 106th Leu is substituted by Val and the like. In another embodiment, in the case of familial ALS having TDP-43 mutation, examples of the TDP-43 gene mutation include, but are not limited to, a mutation in which the 337th Met of TDP-43 protein is  
15 substituted by Val (TDP-43-M337V). In still another embodiment, in the case of familial ALS having C9orf72 mutation, examples of the C9orf72 SOD1 gene mutation include, but are not limited to, (GGGGCC)n repeats of abnormal elongation in intron 1.  
[0014]

20 An EGFR inhibitor as an active ingredient of the prophylactic or therapeutic agent for ALS in the present invention includes all of naturally-occurring substances derived from microorganism etc., semi-synthetic substances derived therefrom, and fully synthetic compounds. Examples  
25 thereof include, but are not limited to, PDGF Receptor Tyrosine Kinase Inhibitor III, BPIQ-I (see Table 4 for the above), gefitinib, erlotinib, afatinib, lapatinib, cetuximab, panitumumab, icotinib/BPI-2009-H, dacomitinib/PF-00299804, AZD8931, AC480/BMS-599626, varlitinib/ARRY-334543, JNJ-26483327,  
30 CUDC-101, TAK-285, ARRY-380, AZD4769, HKI-357, S-222611, canertinib/CI-1033/ PD-183805, pelitinib/EKB-569, AV-412, HM61713, HM781-36B, CO-1686, CP-724714, AP26113, PR610, AZD9291, AEE788/NVP-AEE788, epitinib/HMPL-813, theliatinib/HMPL-309, XL647/KD019, poziotinib/HM781-36B, neratinib/PF-05208767/HKI-  
35 272, mubritinib/TAK-165, ASP8273 and the like. Preferably, it

may be PDGF Receptor Tyrosine Kinase Inhibitor III or BPIQ-I.  
In another embodiment, the EGFR inhibitor can be an EGFR  
selective inhibitor. Examples of the EGFR selective inhibitor  
include BPIQ-I.

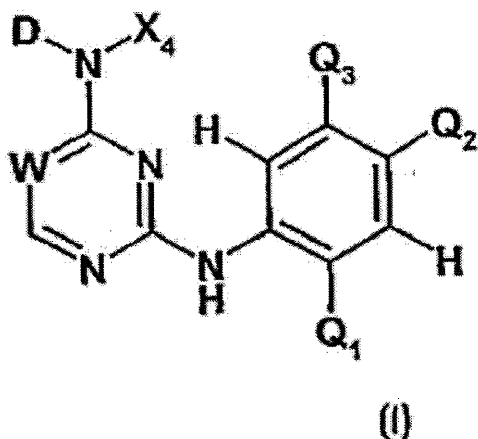
5 [0015]

An EGFR inhibitor as an active ingredient of the  
prophylaxis or therapeutic agent for ALS in the present  
invention includes all of naturally-occurring substance derived  
from microorganism etc., a semi-synthetic substance derived  
10 therefrom, and fully synthetic compounds. Examples thereof  
include, but are not limited to, Pazopanib or an analog thereof,  
PDGF Receptor Tyrosine Kinase Inhibitor III (see Table 4 for  
the above), lenvatinib, AZD4547, NVP-BGJ398, brivanib/BMS-  
582664, LY2874455, lucitanib/E-3810, CP-547632, masitinib/AB-  
15 1010, nintedanib/BIBF1120, sulfatinib/HMPL-012,  
dovitinib/TKI258/CHIR-258, XL228, orantinib/SU6668/TSU-68,  
ENMD-2076, S49076, JNJ-42756493, BAY 1163877,  
Debio1347/CH5183284 and the like. Preferably, it may be  
Pazopanib or an analog thereof, or PDGF Receptor Tyrosine  
20 Kinase Inhibitor III. In another embodiment, the EGFR  
inhibitor may be an EGFR selective inhibitor.

[0016]

Here, the "analog of Pazopanib" is, for example, a  
compound represented by the following formula (I):

25 [0017]

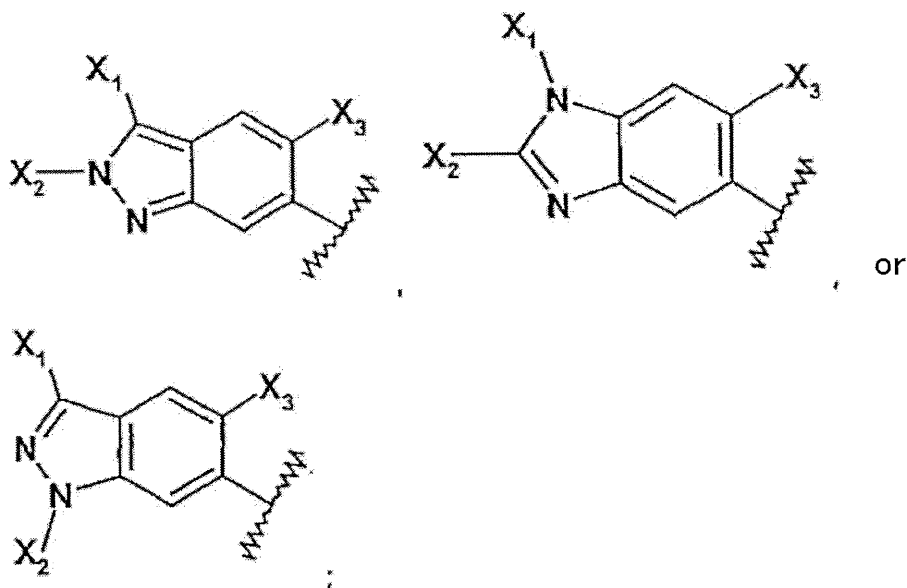


[0018]

wherein

D is

[0019]



5 [0020]

X<sub>1</sub> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl;

X<sub>2</sub> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C(O)R<sup>1</sup>, or aralkyl;

X<sub>3</sub> is hydrogen or halogen;

10 X<sub>4</sub> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, heteroaralkyl, cyanoalkyl, -(CH<sub>2</sub>)<sub>p</sub>C=CH(CH<sub>2</sub>)<sub>t</sub>H, -(CH<sub>2</sub>)<sub>p</sub>C≡C(CH<sub>2</sub>)<sub>t</sub>H, or C<sub>3</sub>-C<sub>7</sub> cycloalkyl;

p is 1, 2, or 3;

t is 0 or 1;

15 W is N or C-R (wherein R is hydrogen, halogen or cyano);

Q<sub>1</sub> is hydrogen, halogen, C<sub>1</sub>-C<sub>2</sub> haloalkyl, C<sub>1</sub>-C<sub>2</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> alkoxy, or C<sub>1</sub>-C<sub>2</sub> haloalkoxy;

Q<sub>2</sub> is A<sup>1</sup> or A<sup>2</sup>;

Q<sub>3</sub> is A<sup>1</sup> when Q<sub>2</sub> is A<sup>2</sup>, and A<sup>2</sup> when Q<sub>2</sub> is A<sup>1</sup>; wherein

20 A<sup>1</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> haloalkyl, or -OR<sup>1</sup>;

A<sup>2</sup> is a group defined by -(Z)<sub>m</sub>-(Z<sup>1</sup>)-(Z<sup>2</sup>) (wherein

Z is CH<sub>2</sub>, m is 0, 1, 2, or 3, or

Z is NR<sup>2</sup>, m is 0 or 1, or

Z is oxygen, m is 0 or 1, or

Z is  $\text{CH}_2\text{NR}^2$ , m is 0 or 1;

$\text{Z}^1$  is  $\text{S}(\text{O})_2$ ,  $\text{S}(\text{O})$ , or  $\text{C}(\text{O})$ ;

$\text{Z}^2$  is  $\text{C}_1\text{-C}_4$  alkyl,  $\text{NR}^3\text{R}^4$ , aryl, arylamino, aralkyl, aralkoxy, or heteroaryl;

5  $\text{R}^1$  is  $\text{C}_1\text{-C}_4$  alkyl;

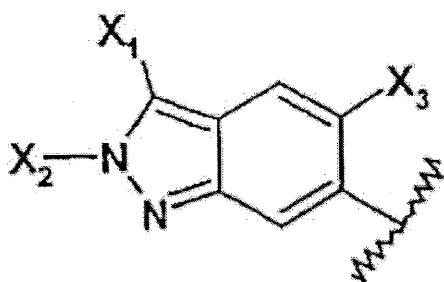
$\text{R}^2$ ,  $\text{R}^3$ , and  $\text{R}^4$  are each independently selected from hydrogen,  $\text{C}_1\text{-C}_4$  alkyl,  $\text{C}_3\text{-C}_7$  cycloalkyl,  $-\text{S}(\text{O})_2\text{R}^5$ , and  $-\text{C}(\text{O})\text{R}^5$ ;

$\text{R}^5$  is  $\text{C}_1\text{-C}_4$  alkyl, or  $\text{C}_3\text{-C}_7$  cycloalkyl; and

when Z is an oxygen,  $\text{Z}^1$  is  $\text{S}(\text{O})_2$ ; and

10 when D is

[0021]



[0022]

$\text{X}_2$  is  $\text{C}_1\text{-C}_4$  alkyl,  $\text{C}_1\text{-C}_4$  haloalkyl,  $\text{C}(\text{O})\text{R}^1$ , or aralkyl.

15 [0023]

The terms " $\text{C}_1\text{-C}_4$  alkyl", " $\text{C}_1\text{-C}_4$  haloalkyl", " $\text{C}_1\text{-C}_4$  hydroxyalkyl", "aralkyl", "halogen", "heteroaralkyl", "cyanoalkyl", " $\text{C}_3\text{-C}_7$  cycloalkyl", " $\text{C}_1\text{-C}_2$  haloalkyl", " $\text{C}_1\text{-C}_2$  alkyl", " $\text{C}_1\text{-C}_2$  alkoxy", " $\text{C}_1\text{-C}_2$  haloalkoxy", " $\text{C}_1\text{-C}_3$  alkyl", " $\text{C}_1\text{-C}_3$  haloalkyl", "aryl", "arylamino", "aralkoxy", and "heteroaryl" in the above-mentioned formula (I) are as defined in WO 2002/059110 (National Publication of International Patent Application No. 2004-517925).

[0024]

25 Specific examples of the analog of Pazopanib include the following.

$\text{N}^2$ -[5-(ethylsulfonyl)-2-methoxyphenyl]-5-fluoro- $\text{N}^4$ -methyl- $\text{N}^4$ -(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine;

3-(5-fluoro-4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-pyrimidinyl)amino)-4-methoxy-N-methylbenzenesulfonamide;

30

5-fluoro-N<sup>4</sup>-methyl-N<sup>4</sup>-(3-methyl-1H-indazol-6-yl)-N<sup>2</sup>-{3-  
 [(methylsulfonyl)methyl]phenyl}-2,4-pyrimidinediamine;  
 3-({5-fluoro-4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
 pyrimidinyl}amino)-N-isopropylbenzenesulfonamide;  
 5 5-fluoro-N<sup>2</sup>-[5-(isopropylsulfonyl)-2-methoxyphenyl]-N<sup>4</sup>-methyl-  
 N<sup>4</sup>-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine;  
 N-[5-({5-fluoro-4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
 pyrimidinyl}amino)-2-methylphenyl]methanesulfonamide;  
 5-fluoro-N<sup>4</sup>-methyl-N<sup>4</sup>-(3-methyl-1H-indazol-6-yl)-N<sup>2</sup>-[4-  
 10 (methylsulfonyl)phenyl]-2,4-pyrimidinediamine;  
 N<sup>4</sup>-(3-ethyl-1H-indazol-6-yl)-5-fluoro-N<sup>4</sup>-methyl-N<sup>2</sup>-{3-  
 [(methylsulfonyl)methyl]phenyl}-2,4-pyrimidinediamine;  
 4-({5-fluoro-4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
 pyrimidinyl}amino)benzenesulfonamide;  
 15 N<sup>4</sup>-ethyl-5-fluoro-N<sup>2</sup>-[2-methoxy-5-(methylsulfonyl)phenyl]-N<sup>4</sup>-(3-  
 methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine;  
 [4-({5-fluoro-4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
 pyrimidinyl}amino)phenyl]-N-methylmethanesulfonamide; 5-fluoro-  
 N<sup>2</sup>-{3-[(isopropylsulfonyl)methyl]phenyl}-N<sup>4</sup>-methyl-N<sup>4</sup>-(3-methyl-  
 20 1H-indazol-6-yl)-2,4-pyrimidinediamine;  
 3-({5-fluoro-4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
 pyrimidinyl}amino)-4-methoxybenzamide;  
 4-({5-fluoro-4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
 pyrimidinyl}amino)-3-methoxybenzenesulfonamide;  
 25 N<sup>2</sup>-(3-methyl-1H-indazol-6-yl)-N<sup>4</sup>-{3-  
 [(methylsulfonyl)methyl]phenyl}-1,3,5-triazine-2,4-  
 diaminetrifluoroacetic acid;  
 N<sup>2</sup>-methyl-N<sup>2</sup>-(3-methyl-1H-indazol-6-yl)-N<sup>4</sup>-{3-  
 [(methylsulfonyl)methyl]phenyl}-1,3,5-triazine-2,4-diamine;  
 30 N<sup>2</sup>-[5-(ethylsulfonyl)-2-methoxyphenyl]-N<sup>4</sup>-methyl-N<sup>4</sup>-(3-methyl-  
 1H-indazol-6-yl)-1,3,5-triazine-2,4-diamine;  
 N-[2-methyl-5-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-  
 1,3,5-triazin-2-yl}amino)phenyl]methanesulfonamide;  
 N<sup>2</sup>-methyl-N<sup>2</sup>-(3-methyl-1H-indazol-6-yl)-N<sup>4</sup>-[3-  
 35 (methylsulfonyl)phenyl]-1,3,5-triazine-2,4-diamine;

N-[4-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-1,3,5-triazin-2-yl}amino)phenyl]acetamide;  
 3-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-pyrimidinyl}amino)benzenesulfonamide;  
 5 N<sup>2</sup>-[5-(ethylsulfonyl)-2-methoxyphenyl]-N<sup>4</sup>-methyl-N<sup>4</sup>-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine;  
 N<sup>4</sup>-methyl-N<sup>4</sup>-(3-methyl-1H-indazol-6-yl)-N<sup>2</sup>-{3-[(methylsulfonyl)methyl]phenyl}-2,4-pyrimidinediamine;  
 N-isopropyl-3-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-pyrimidinyl}amino)benzenesulfonamide;  
 10 N-cyclopropyl-3-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-pyrimidinyl}amino)benzenesulfonamide;  
 N<sup>4</sup>-ethyl-N<sup>2</sup>-[5-(ethylsulfonyl)-2-methoxyphenyl]-N<sup>4</sup>-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine;  
 15 N-[3-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-pyrimidinyl}amino)phenyl]methanesulfonamide;  
 N<sup>2</sup>-{3-[(isopropylsulfonyl)methyl]phenyl}-N<sup>4</sup>-methyl-N<sup>4</sup>-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine;  
 N<sup>2</sup>-{4-[(isopropylsulfonyl)methyl]phenyl}-N<sup>4</sup>-methyl-N<sup>4</sup>-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine;  
 20 N<sup>2</sup>-[5-(isobutylsulfonyl)-2-methoxyphenyl]-N<sup>4</sup>-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine;  
 N-[3-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-pyrimidinyl}amino)phenyl]acetamide;  
 25 N-[3-({4-[ethyl(3-methyl-1H-indazol-6-yl)amino]-2-pyrimidinyl}amino)phenyl]acetamide;  
 N<sup>2</sup>-(2-methoxy-5-{{(5-methyl-3-isoxazolyl)methyl}sulfonyl}phenyl)-N<sup>4</sup>-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine;  
 30 4-methoxy-3-({4-[(3-methyl-1H-indazol-6-yl)amino]-2-pyrimidinyl}amino)benzenesulfonamide;  
 N<sup>2</sup>-[5-(isopropylsulfonyl)-2-methoxyphenyl]-N<sup>4</sup>-methyl-N<sup>4</sup>-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine;  
 N<sup>2</sup>-[5-(ethylsulfonyl)-2-methoxyphenyl]-N<sup>4</sup>-isopropyl-N<sup>4</sup>-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine;  
 35

$N^4$ -(1H-indazol-6-yl)- $N^4$ -methyl- $N^2$ -{3-  
 [(methylsulfonyl)methyl]phenyl}-2,4-pyrimidinediamine;  
 $N^4$ -(1,3-dimethyl-1H-indazol-6-yl)- $N^4$ -methyl- $N^2$ -{3-  
 [(methylsulfonyl)methyl]phenyl}-2,4-pyrimidinediamine;  
 5  $N^4$ -(2,3-dimethyl-2H-indazol-6-yl)- $N^4$ -methyl- $N^2$ -{3-  
 [(methylsulfonyl)methyl]phenyl}-2,4-pyrimidinediamine;  
 $N^4$ -(2,3-dimethyl-2H-indazol-6-yl)- $N^2$ -[5-(ethylsulfonyl)-2-  
 methoxyphenyl]- $N^4$ -methyl-2,4-pyrimidinediamine;  
 1-[4-methoxy-3-({4-[(3-methyl-1H-indazol-6-yl)amino]-2-  
 10 pyrimidinyl}amino)phenyl]-1-propanone;  
 4-methoxy-N-[3-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
 pyrimidinyl}amino)phenyl]benzenesulfonamide;  
 4-methoxy-N-methyl-3-({4-[(3-methyl-1H-indazol-6-yl)amino]-2-  
 pyrimidinyl}amino)benzenesulfonamide;  
 15 [(3-methyl-1H-indazol-6-yl)(2-{4-  
 [(methylsulfonyl)methyl]anilino}-4-  
 pyrimidinyl)amino]acetonitrile;  
 [{2-[5-(ethylsulfonyl)-2-methoxyanilino]-4-pyrimidinyl}(3-  
 methyl-1H-indazol-6-yl)amino]acetonitrile;  
 20 [(3-methyl-1H-indazol-6-yl)(2-{3-  
 [(methylsulfonyl)methyl]anilino}-4-  
 pyrimidinyl)amino]acetonitrile;  
 4-methoxy-N-methyl-3-({4-[methyl(3-methyl-1H-indazol-6-  
 yl)amino]-2-pyrimidinyl}amino)benzenesulfonamide;  
 25 4-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
 pyrimidinyl}amino)benzamide;  
 3-methoxy-4-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
 pyrimidinyl}amino)benzenesulfonamide;  
 $N^4$ -ethynyl- $N^4$ -(3-methyl-1H-indazol-6-yl)- $N^2$ -{3-  
 30 [(methylsulfonyl)methyl]phenyl}-2,4-pyrimidinediamine;  
 3-({4-[(3-methyl-1H-indazol-6-yl)(2-propynyl)amino]-2-  
 pyrimidinyl}amino)benzenesulfonamide;  
 4-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
 pyrimidinyl}amino)benzenesulfonamide;  
 35  $N^4$ -methyl- $N^4$ -(3-methyl-1H-indazol-6-yl)- $N^2$ -[3-

(methylsulfonyl)phenyl]-2,4-pyrimidinediamine;  
4-methoxy-3-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
pyrimidinyl}amino)benzenesulfonamide;  
N<sup>2</sup>-[5-(ethylsulfonyl)-2-methoxyphenyl]-N<sup>4</sup>-(3-methyl-1H-indazol-  
5 6-yl)-2,4-pyrimidinediamine;  
3-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
pyrimidinyl}amino)benzamide;  
N<sup>2</sup>-[4-(ethylsulfonyl)phenyl]-N<sup>4</sup>-methyl-N<sup>4</sup>-(3-methyl-1H-indazol-  
6-yl)-2,4-pyrimidinediamine;  
10 N-[4-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
pyrimidinyl}amino)benzyl]ethanesulfonamide;  
N-[3-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
pyrimidinyl}amino)benzyl]methanesulfonamide;  
2-chloro-5-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
15 pyrimidinyl}amino)benzenesulfonamide;  
2-chloro-4-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
pyrimidinyl}amino)benzenesulfonamide;  
4-chloro-3-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
pyrimidinyl}amino)benzenesulfonamide;  
20 3-methyl-4-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
pyrimidinyl}amino)benzenesulfonamide;  
2-methyl-5-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
pyrimidinyl}amino)benzenesulfonamide;  
4-methyl-3-({4-[methyl(3-methyl-1H-indazol-6-yl)amino]-2-  
25 pyrimidinyl}amino)benzenesulfonamide;  
N<sup>4</sup>-methyl-N<sup>4</sup>-(3-methyl-1H-indazol-6-yl)-N<sup>2</sup>-[3-  
(methylsulfinyl)phenyl]-2,4-pyrimidinediamine;  
N<sup>2</sup>-[2-fluoro-5-(methylsulfonyl)phenyl]-N<sup>4</sup>-methyl-N<sup>4</sup>-(3-methyl-  
1H-indazol-6-yl)-2,4-pyrimidinediamine;  
30 N<sup>2</sup>-[2-methoxy-5-(methylsulfonyl)phenyl]-N<sup>4</sup>-methyl-N<sup>4</sup>-(3-methyl-  
1H-indazol-6-yl)-2,4-pyrimidinediamine;  
3-({4-[(2,3-dimethyl-2H-indazol-6-yl)(methyl)amino]pyrimidin-2-  
yl}amino)benzenesulfonamide;  
2-[4-({4-[(2,3-dimethyl-2H-indazol-6-  
35 yl)(methyl)amino]pyrimidin-2-yl}amino)phenyl]ethanesulfonamide;

$N^4$ -(2,3-dimethyl-2H-indazol-6-yl)- $N^4$ -methyl- $N^2$ -(4-  
 [(methylsulfonyl)methyl]phenyl}pyrimidine-2,4-diamine;  
 3-({4-[[3-(hydroxymethyl)-2-methyl-2H-indazol-6-  
 yl](methyl)amino]pyrimidin-2-yl}amino)benzenesulfonamide;  
 5 3-({4-[(1,2-dimethyl-1H-benzimidazol-5-  
 yl)(methyl)amino]pyrimidin-2-yl}amino)benzenesulfonamide;  
 3-({4-[(2-benzyl-1-methyl-1H-benzimidazol-5-  
 yl)(methyl)amino]pyrimidin-2-yl}amino)benzenesulfonamide;  
 3-({4-[(2-ethyl-3-methyl-2H-indazol-6-  
 10 yl)(methyl)amino]pyrimidin-2-yl}amino)benzenesulfonamide;  
 3-({4-[[2-(3-chlorobenzyl)-3-methyl-2H-indazol-6-  
 yl](methyl)amino]pyrimidin-2-yl}amino)benzenesulfonamide;  
 3-({4-[(2,3-dimethyl-2H-indazol-6-yl)(methyl)amino]-1,3,5-  
 triazin-2-yl}amino)benzenesulfonamide; and  
 15 5-({4-[(2,3-dimethyl-2H-indazol-6-yl)(methyl)amino]-1,3,5-  
 triazin-2-yl}amino)-2-methylbenzenesulfonamide  
 [0025]

An Aurorakinase inhibitor as an active ingredient of the  
 prophylactic or therapeutic agent for of ALS in the present  
 20 invention includes all of naturally-occurring substances  
 derived from microorganism etc., semi-synthetic substances  
 derived therefrom, and fully synthetic compounds. Examples  
 thereof include, but are not limited to, ZM-447439, VX-680  
 (tozasertib/MK-0457), Aurora Kinase Inhibitor II, CYC116,  
 25 KW2449 (see Table 4 for the above), AT9283 (see Table 8),  
 danusertib/PHA-739358, alisertib/MLN8237, ENMD-2076, PF-3814735,  
 cenisertib/R763/AS703569, BI811283, AMG900, TTP607, GSK1070916A,  
 AZD1152, TAK-901, MK5108/VX-689, BI 847325 and the like.  
 Preferably, it may be ZM-447439, VX-680, Aurora Kinase  
 30 Inhibitor II, CYC116, KW2449 or AT9283. In another embodiment,  
 the Aurorakinase inhibitor may be an Aurorakinase selective  
 inhibitor. Examples of the Aurorakinase selective inhibitor  
 include ZM-447439, VX-680, Aurora Kinase Inhibitor II, CYC116  
 and the like.  
 35 [0026]

A PKA inhibitor as an active ingredient of the prophylactic or therapeutic agent for ALS in the present invention includes all of naturally-occurring substances derived from microorganism etc., semi-synthetic substances  
5 derived therefrom, and fully synthetic compounds. Examples thereof include, but are not limited to, PDGF Receptor Tyrosine Kinase Inhibitor III (see Table 4), H89, KT5720 and the like. Preferably, it may be PDGF Receptor Tyrosine Kinase Inhibitor III. In another embodiment, the PKA inhibitor may be a PKA  
10 selective inhibitor.

[0027]

A PKC inhibitor as an active ingredient of the prophylactic or therapeutic agent for ALS in the present invention includes all of naturally-occurring substances  
15 derived from microorganism etc., semi-synthetic substances derived therefrom, and fully synthetic compounds. Examples thereof include, but are not limited to, PDGF Receptor Tyrosine Kinase Inhibitor III, Enzastaurin (see Table 4 for the above), bryostatin 1, UCN-01, AEB071/sotrastaurin acetate, safinol,   
20 midostaurin/PKC<sub>4</sub> 12, sophoretin/quercetin and the like. Preferably, it may be PDGF Receptor Tyrosine Kinase Inhibitor III, Enzastaurin. In another embodiment, the PKC inhibitor may be a PKC selective inhibitor. Examples of the PKC selective inhibitor include Enzastaurin and the like.

25 [0028]

An MEK inhibitor as an active ingredient of the prophylactic or therapeutic agent for ALS in the present invention includes all of naturally-occurring substances derived from microorganism etc., semi-synthetic substances  
30 derived therefrom, and fully synthetic compounds. Examples thereof include, but are not limited to, U0126-EtOH (see Table 4), selumetinib/AZD6244/ARRY-142886, refametinib/RDEA119/BAY869766, pimasertib/MSK1936369/AS703026, MEK162/ARRY-162, AZD8330/ARRY-424704, cobimetinib/GDC-  
35 0973/RG7420, GDC-0623/RG7421/XL518, CIF/RG7167/RO4987655,

CKI27/RG7304/RO5126766/CH5126766, E6201, TAK-733, PD-0325901, AS703988/MS2 015103B, WX-554, BVD-523, MK-8353/SCH9000353, BI 847325, CI-1040/PD184352 and the like. Preferably, it may be U0126-EtOH. In another embodiment, the MEK inhibitor may be an  
5 MEK selective inhibitor. Examples of the MEK selective inhibitor include U0126-EtOH.

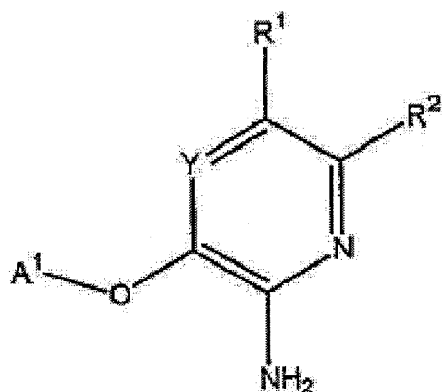
[0029]

An Met inhibitor as an active ingredient of the prophylactic or therapeutic agent for ALS in the present  
10 invention includes all of naturally-occurring substances derived from microorganism etc., semi-synthetic substances derived therefrom, and fully synthetic compounds. Examples thereof include, but are not limited to, MGCD-265, PF-2341066 (Crizotinib) or an analog thereof, BMS 777607 (see Table 4 for  
15 the above), INC2 80/INCB-028060, foretinib/GSK1363089/XL880, tivantinib/ARQ197, EMD-94283, MS2 156119J/EMD1214063, golvatinib/E7050, JNJ-38877605, MK-2461, MK-8033, PF-4217903, AMG208, AMG 337, SAR125844, cabozantinib/BMS-907351/XL184, LY2801653, TAS-115, volitinib/HMPL-504, amuvatinib/MP-470/HPK-  
20 56, S49076 and the like. Preferably, it may be MGCD-265, PF-2341066 (Crizotinib) or an analog thereof, BMS 777607. In another embodiment, Met inhibitor may be a Met selective inhibitor. Examples of the Met selective inhibitor include PF-2341066 (Crizotinib) or an analog thereof, BMS 777607 and the  
25 like.

[0030]

Here, the analog of "PF-2341066 (Crizotinib)" is, for example, a compound represented by the following formula (II):

[0031]



(I I)

[0032]

wherein

Y is N or CR<sup>12</sup>;

5 R<sup>1</sup> is selected from C<sub>6-12</sub> aryl, 5 - 12-membered heteroaryl, C<sub>3-12</sub> cycloalkyl, 3 - 12-membered heteroalicyclic, -O(CR<sup>6</sup>R<sup>7</sup>)<sub>n</sub>R<sup>4</sup>, -C(O)R<sup>4</sup>, -C(O)OR<sup>4</sup>, -CN, -NO<sub>2</sub>, -S(O)<sub>m</sub>R<sup>4</sup>, -SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>, -C(O)NR<sup>4</sup>R<sup>5</sup>, -NR<sup>4</sup>C(O)R<sup>5</sup>, -C(=NR<sup>6</sup>)NR<sup>4</sup>R<sup>5</sup>, C<sub>1-8</sub> alkyl, C<sub>2-8</sub> alkenyl, and C<sub>2-8</sub> alkynyl, each hydrogen in R<sup>1</sup> is optionally substituted by one or more R<sup>3</sup> groups;

10 R<sup>2</sup> is hydrogen, halogen, C<sub>1-12</sub> alkyl, C<sub>2-12</sub> alkenyl, C<sub>2-12</sub> alkynyl, C<sub>3-12</sub> cycloalkyl, C<sub>6-12</sub> aryl, 3 - 12-membered heteroalicyclic, 5 - 12-membered heteroaryl, -S(O)<sub>m</sub>R<sup>4</sup>, -SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>, -S(O)<sub>2</sub>OR<sup>4</sup>, -NO<sub>2</sub>, -NR<sup>4</sup>R<sup>5</sup>, -(CR<sup>6</sup>R<sup>7</sup>)<sub>n</sub>OR<sup>4</sup>, -CN, -C(O)R<sup>4</sup>, -OC(O)R<sup>4</sup>, -O(CR<sup>6</sup>R<sup>7</sup>)<sub>n</sub>R<sup>4</sup>, -NR<sup>4</sup>C(O)R<sup>5</sup>, -(CR<sup>6</sup>R<sup>7</sup>)<sub>n</sub>C(O)OR<sup>4</sup>, -(CR<sup>6</sup>R<sup>7</sup>)<sub>n</sub>NCR<sup>4</sup>R<sup>5</sup>, -C(=NR<sup>6</sup>)NR<sup>4</sup>R<sup>5</sup>, -NR<sup>4</sup>C(O)NR<sup>5</sup>R<sup>6</sup>, -NR<sup>4</sup>S(O)<sub>p</sub>R<sup>5</sup>, or -C(O)NR<sup>4</sup>R<sup>5</sup>, each hydrogen in R<sup>2</sup> is optionally substituted by one or more R<sup>8</sup> groups;

15 R<sup>3</sup> is halogen, C<sub>1-12</sub> alkyl, C<sub>2-12</sub> alkenyl, C<sub>2-12</sub> alkynyl, C<sub>3-12</sub> cycloalkyl, C<sub>6-12</sub> aryl, 3 - 12-membered heteroalicyclic, 5 - 12-membered heteroaryl, -S(O)<sub>m</sub>R<sup>4</sup>, -SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>, -S(O)<sub>2</sub>OR<sup>4</sup>, -NO<sub>2</sub>, -NR<sup>4</sup>R<sup>5</sup>, -(CR<sup>6</sup>R<sup>7</sup>)<sub>n</sub>OR<sup>4</sup>, -CN, -C(O)R<sup>4</sup>, -OC(O)R<sup>4</sup>, -O(CR<sup>6</sup>R<sup>7</sup>)<sub>n</sub>R<sup>4</sup>, -NR<sup>4</sup>C(O)R<sup>5</sup>, -(CR<sup>6</sup>R<sup>7</sup>)<sub>n</sub>C(O)OR<sup>4</sup>, -(CR<sup>6</sup>R<sup>7</sup>)<sub>n</sub>NCR<sup>4</sup>R<sup>5</sup>, -C(=NR<sup>6</sup>)NR<sup>4</sup>R<sup>5</sup>, -NR<sup>4</sup>C(O)NR<sup>5</sup>R<sup>6</sup>, -NR<sup>4</sup>S(O)<sub>p</sub>R<sup>5</sup>, or -C(O)NR<sup>4</sup>R<sup>5</sup>, each hydrogen in R<sup>3</sup> is optionally substituted by one or more R<sup>8</sup> groups, and R<sup>3</sup> groups on the adjacent atoms may be joined to form C<sub>6-12</sub> aryl, 5 - 12-membered heteroaryl, C<sub>3-12</sub> cycloalkyl, or 3 - 12-membered heteroalicyclic group;

20 R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are each independently hydrogen, halogen, C<sub>1-12</sub>

alkyl, C<sub>2-12</sub> alkenyl, C<sub>2-12</sub> alkynyl, C<sub>3-12</sub> cycloalkyl, C<sub>6-12</sub> aryl, 3 - 12-membered heteroalicyclic, or 5 - 12-membered heteroaryl, or any two of R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> bonded to the same nitrogen atom may be joined with the nitrogen bonded thereto to form 3 - 12-membered heteroalicyclic or 5 - 12-membered heteroaryl group containing 1 - 3 additional hetero atoms selected from N, O, and S; or any two of R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> bonded to the same carbon atom may be joined to form C<sub>3-12</sub> cycloalkyl, C<sub>6-12</sub> aryl, 3 - 12-membered heteroalicyclic, or 5 - 12-membered heteroaryl group; and each hydrogen in R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> is optionally substituted by one or more R<sup>8</sup> groups; one or more R<sup>8</sup> are each independently halogen, C<sub>1-12</sub> alkyl, C<sub>2-12</sub> alkenyl, C<sub>2-12</sub> alkynyl, C<sub>3-12</sub> cycloalkyl, C<sub>6-12</sub> aryl, 3 - 12-membered heteroalicyclic, 5 - 12-membered heteroaryl, -CN, -O-C<sub>1-12</sub> alkyl, -O-(CH<sub>2</sub>)<sub>n</sub>C<sub>3-12</sub> cycloalkyl, -O-(CH<sub>2</sub>)<sub>n</sub>C<sub>6-12</sub> aryl, -O-(CH<sub>2</sub>)<sub>n</sub>(3 - 12-membered heteroalicyclic) or -O-(CH<sub>2</sub>)<sub>n</sub>(5 - 12-membered heteroaryl); each hydrogen in R<sup>8</sup> is optionally substituted by one or more R<sup>11</sup> groups; A<sup>1</sup> is -(CR<sup>9</sup>R<sup>10</sup>)<sub>n</sub>-A<sup>2</sup> {provided:

(i) when Y is N, and R<sup>1</sup> is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, A<sup>1</sup> is -(CR<sup>9</sup>R<sup>10</sup>)<sub>n</sub>-A<sup>2</sup>, and n is not 0; and

(ii) when Y is N, R<sup>2</sup> is H, and A<sup>1</sup> is m-chlorobenzyl, R<sup>1</sup> is not unsubstituted piperazine};

R<sup>9</sup> and R<sup>10</sup> are each independently hydrogen, halogen, C<sub>1-12</sub> alkyl, C<sub>3-12</sub> cycloalkyl, C<sub>6-12</sub> aryl, 3 - 12-membered heteroalicyclic, 5 - 12-membered heteroaryl, -S(O)<sub>m</sub>R<sup>4</sup>, -SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>, -S(O)<sub>2</sub>OR<sup>4</sup>, -NO<sub>2</sub>, -NR<sup>4</sup>R<sup>5</sup>, -(CR<sup>6</sup>R<sup>7</sup>)<sub>n</sub>OR<sup>4</sup>, -CN, -C(O)R<sup>4</sup>, -OC(O)R<sup>4</sup>, -NR<sup>4</sup>C(O)R<sup>5</sup>, -(CR<sup>6</sup>R<sup>7</sup>)<sub>n</sub>C(O)OR<sup>4</sup>, -(CR<sup>6</sup>R<sup>7</sup>)<sub>n</sub>NCR<sup>4</sup>R<sup>5</sup>, -NR<sup>4</sup>C(O)NR<sup>5</sup>R<sup>6</sup>, -NR<sup>4</sup>S(O)<sub>p</sub>R<sup>5</sup>, or -C(O)NR<sup>4</sup>R<sup>5</sup>; R<sup>9</sup> and R<sup>10</sup> may be joined to form C<sub>3-12</sub> cycloalkyl, 3 - 12-membered heteroalicyclic, C<sub>6-12</sub> aryl, or 5 - 12-membered heteroaryl ring; each hydrogen in R<sup>9</sup> and R<sup>10</sup> is optionally substituted by one or more R<sup>3</sup> groups; A<sup>2</sup> is C<sub>6-12</sub> aryl, 5 - 12-membered heteroaryl, C<sub>3-12</sub> cycloalkyl, or 3 - 12-membered heteroalicyclic, A<sup>2</sup> is optionally substituted by

one or more  $R^3$  groups;  
 one or more  $R^{11}$  are each independently halogen,  $C_{1-12}$  alkyl,  $C_{1-12}$  alkoxy,  $C_{3-12}$  cycloalkyl,  $C_{6-12}$  aryl, 3 - 12-membered heteroalicyclic, 5 - 12-membered heteroaryl, -O- $C_{1-12}$  alkyl, -O-  
 5  $(CH_2)_n C_{3-12}$  cycloalkyl, -O- $(CH_2)_n C_{6-12}$  aryl, -O- $(CH_2)_n$  (3 - 12-membered heteroalicyclic), -O- $(CH_2)_n$  (5 - 12-membered heteroaryl), or-CN, each hydrogen in  $R^{11}$  is optionally substituted by one or more groups selected from halogen, -OH, -CN, - $C_{1-12}$  alkyl optionally halogenated partly or completely, -  
 10 O- $C_{1-12}$  alkyl optionally halogenated partly or completely, -CO, -SO, and -SO<sub>2</sub>;  
 $R^{12}$  is hydrogen, halogen,  $C_{1-12}$  alkyl,  $C_{2-12}$  alkenyl,  $C_{2-12}$  alkynyl,  $C_{3-12}$  cycloalkyl,  $C_{6-12}$  aryl, 3 - 12-membered heteroalicyclic, 5 - 12-membered heteroaryl, -S(O)<sub>m</sub>R<sup>4</sup>, -SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>, -S(O)<sub>2</sub>OR<sup>4</sup>, -NO<sub>2</sub>, -  
 15 NR<sup>4</sup>R<sup>5</sup>, -(CR<sup>6</sup>R<sup>7</sup>)<sub>n</sub>OR<sup>4</sup>, -CN, -C(O)R<sup>4</sup>, -OC(O)R<sup>4</sup>, -O(CR<sup>6</sup>R<sup>7</sup>)<sub>n</sub>R<sup>4</sup>, -NR<sup>4</sup>C(O)R<sup>5</sup>, -(CR<sup>6</sup>R<sup>7</sup>)<sub>n</sub>C(O)OR<sup>4</sup>, -(CR<sup>6</sup>R<sup>7</sup>)<sub>n</sub>NCR<sup>4</sup>R<sup>5</sup>, -C(=NR<sup>6</sup>)NR<sup>4</sup>R<sup>5</sup>, -NR<sup>4</sup>C(O)NR<sup>5</sup>R<sup>6</sup>, -NR<sup>4</sup>S(O)<sub>p</sub>R<sup>5</sup>, or -C(O)NR<sup>4</sup>R<sup>5</sup>, each hydrogen in  $R^{12}$  is optionally substituted by one or more  $R^3$  groups;  
 $R^1$  and  $R^2$ , or  $R^1$  and  $R^{12}$  may be joined to form  $C_{6-12}$  aryl, 5 - 12-  
 20 membered heteroaryl,  $C_{3-12}$  cycloalkyl, or 3 - 12-membered heteroalicyclic group;  
 m is 0, 1 or 2;  
 n is 0, 1, 2, 3 or 4; and  
 p is 1 or 2.

25 [0033]

Each term described as higher concept in the explanation of each group in the above-mentioned formula (II) (e.g., " $C_{6-12}$  aryl", "5 - 12-membered heteroaryl", " $C_{3-12}$  cycloalkyl", "3 - 12-membered heteroalicyclic", " $C_{1-8}$  alkyl", " $C_{2-8}$  alkenyl", " $C_{2-8}$  alkynyl" etc. for  $R^1$ ) is as defined in WO 2004/076412 (National  
 30 Publication of International Patent Application No. 2006-519232).

[0034]

Specific examples of the analog of PF-2341066  
 35 (Crizotinib) include the following.

4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenol;  
 3-(2,6-dichloro-benzyloxy)-5-[4-(2-morpholin-4-yl-ethoxy)-  
 phenyl]-pyridin-2-ylamine;  
 3-(2,6-dichloro-benzyloxy)-5-[3-(2-morpholin-4-yl-ethoxy)-  
 5 phenyl]-pyridin-2-ylamine;  
 3-(2,6-dichloro-benzyloxy)-5-(1H-indol-4-yl)-pyridin-2-ylamine;  
 3-[2-chloro-6-(1H-indol-4-yl)-benzyloxy]-5-(1H-indol-4-yl)-  
 pyridin-2-ylamine;  
 2-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-pyrrole-1-  
 10 carboxylic acid tert-butyl ester;  
 3-(2,6-dichloro-benzyloxy)-5-(1H-pyrrol-2-yl)-pyridin-2-  
 ylamine;  
 3-(2,6-dichloro-benzyloxy)-5-(4-fluoro-phenyl)-pyridin-2-  
 ylamine;  
 15 3-(2,6-dichloro-benzyloxy)-5-phenyl-pyridin-2-ylamine;  
 3-(2,6-dichloro-benzyloxy)-5-(2-fluoro-phenyl)-pyridin-2-  
 ylamine;  
 3-(2,6-dichloro-benzyloxy)-5-(3-fluoro-phenyl)-pyridin-2-  
 ylamine;  
 20 5-(4-amino-phenyl)-3-(2,6-dichloro-benzyloxy)-pyridin-2-  
 ylamine;  
 N-{4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-  
 methanesulfonamide;  
 N-{4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-  
 25 acetamide;  
 3-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenol;  
 3-(2,6-dichloro-benzyloxy)-5-(4-methoxy-phenyl)-pyridin-2-  
 ylamine;  
 5-(3-amino-phenyl)-3-(2,6-dichloro-benzyloxy)-pyridin-2-  
 30 ylamine;  
 3-(2,6-dichloro-benzyloxy)-5-(3-trifluoromethoxy-phenyl)-  
 pyridin-2-ylamine;  
 2-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenol;  
 3-(2,6-dichloro-benzyloxy)-5-(2-phenoxy-phenyl)-pyridin-2-  
 35 ylamine;

3-(2,6-dichloro-benzyloxy)-5-(3,4-difluoro-phenyl)-pyridin-2-ylamine;  
 3-(2,6-dichloro-benzyloxy)-5-(3-isopropyl-phenyl)-pyridin-2-ylamine;  
 5 3-(2,6-dichloro-benzyloxy)-5-(2-trifluoromethyl-phenyl)-pyridin-2-ylamine;  
 3-(2,6-dichloro-benzyloxy)-5-(2-methoxy-phenyl)-pyridin-2-ylamine;  
 3-(2,6-dichloro-benzyloxy)-5-(4-trifluoromethyl-phenyl)-pyridin-2-ylamine;  
 10 N-{2-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-methanesulfonamide;  
 {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-methanol;  
 15 5-benzo[1,3]dioxol-5-yl-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine;  
 3-(2,6-dichloro-benzyloxy)-5-(2-trifluoromethoxy-phenyl)-pyridin-2-ylamine;  
 3-(2,6-dichloro-benzyloxy)-5-(4-methyl-thiophen-2-yl)-pyridin-2-ylamine;  
 20 5-(2-benzyloxy-phenyl)-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine;  
 3-(2,6-dichloro-benzyloxy)-5-(3-methoxy-phenyl)-pyridin-2-ylamine;  
 25 3-(2,6-dichloro-benzyloxy)-5-(1H-indol-2-yl)-pyridin-2-ylamine;  
 5-(4-benzyloxy-3-fluoro-phenyl)-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine;  
 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-benzoic acid;  
 30 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-N-(2-diethylamino-ethyl)-benzamide;  
 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-N-(3-diethylamino-propyl)-benzamide;  
 {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;  
 35

{4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-  
 [(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-  
 [(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 5 {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-  
 (4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-  
 [4-(2-hydroxy-ethyl)-piperidin-1-yl]-methanone;  
 {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-  
 10 [(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-  
 [(3R)-3-dimethylamino-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-  
 [(3S)-3-cyclopropylaminomethyl-piperidin-1-yl]-methanone;  
 15 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-N-(2-  
 hydroxy-3-pyrrolidin-1-yl-propyl)-benzamide;  
 {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-  
 [(2S)-2-(3-fluoro-piperidin-1-ylmethyl)-pyrrolidin-1-yl]-  
 methanone;  
 20 {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-  
 (4-cyclopropyl-piperazin-1-yl)-methanone;  
 {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-  
 {(2R)-2-[(cyclopropylmethyl-amino)-methyl]-pyrrolidin-1-yl}-  
 methanone;  
 25 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-N-  
 cyclopropylmethyl-N-(2R)-pyrrolidin-2-ylmethyl-benzamide;  
 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-N-(2-  
 hydroxy-3-pyrrolidin-1-yl-propyl)-N-methyl-benzamide;  
 {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-  
 30 {(2S)-2-[(3R)-3-hydroxy-pyrrolidin-1-ylmethyl]-pyrrolidin-1-  
 yl}-methanone;  
 3-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-benzoic  
 acid;  
 {3-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-  
 35 [(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;

{4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenoxy}-  
 acetic acid;  
 2-{4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-  
 phenoxy}-1-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-  
 5 ethanone;  
 2-{4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-  
 phenoxy}-1-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-  
 ethanone;  
 3-(2,6-dichloro-benzyloxy)-5-(1H-indol-5-yl)-pyridin-2-ylamine;  
 10 3-(2,6-dichloro-benzyloxy)-5-[3-(1-methyl-1,2,3,6-tetrahydro-  
 pyridin-4-yl)-1H-indol-5-yl]-pyridin-2-ylamine;  
 3-(2,6-dichloro-benzyloxy)-5-[3-(1-methyl-piperidin-4-yl)-1H-  
 indol-5-yl]-pyridin-2-ylamine;  
 3-(2,6-dichloro-benzyloxy)-5-(3-morpholin-4-ylmethyl-1H-indol-  
 15 5-yl)-pyridin-2-ylamine;  
 3-(2,6-dichloro-benzyloxy)-5-(3-piperidin-1-ylmethyl-1H-indol-  
 5-yl)-pyridin-2-ylamine;  
 3-(2,6-dichloro-benzyloxy)-5-(3-pyrrolidin-1-ylmethyl-1H-indol-  
 5-yl)-pyridin-2-ylamine;  
 20 3-(2,6-dichloro-benzyloxy)-5-(3-diethylaminomethyl-1H-indol-5-  
 yl)-pyridin-2-ylamine;  
 (1-{5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-  
 indol-3-ylmethyl}-(3R)-pyrrolidin-3-yl)-carbamic acid tert-  
 butyl ester;  
 25 3-(2,6-dichloro-benzyloxy)-5-{3-(2,6-dimethyl-morpholin-4-  
 ylmethyl)-1H-indol-5-yl}-pyridin-2-ylamine;  
 N-(1-{5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-  
 indol-3-ylmethyl}-(3R)-pyrrolidin-3-yl)-acetamide;  
 1-(4-{5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-  
 30 indol-3-ylmethyl}-piperazin-1-yl)-ethanone;  
 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(1H-indole-5-yl)-pyridin-  
 2-ylamine;  
 1-(4-{5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-  
 yl]-1H-indol-3-ylmethyl}-piperazin-1-yl)-ethanone;  
 35 3-(2-chloro-3,6-difluoro-benzyloxy)-5-[3-(2,6-dimethyl-

morpholin-4-ylmethyl)-1H-indol-5-yl]-pyridin-2-ylamine;  
 N-(1-{5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-1H-indol-3-ylmethyl}-(3S)-pyrrolidin-3-yl)-acetamide;  
 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(3-piperidin-1-ylmethyl-  
 5 1H-indol-5-yl)-pyridin-2-ylamine;  
 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(3-morpholin-4-ylmethyl-1H-indol-5-yl)-pyridin-2-ylamine;  
 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(3-pyrrolidin-1-ylmethyl-1H-indol-5-yl)-pyridin-2-ylamine;  
 10 5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-2-carboxylic acid ethyl ester;  
 5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-2-carboxylic acid;  
 {5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indol-  
 15 2-yl}-(4-methyl-piperazin-1-yl)-methanone;  
 {5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indol-2-yl}-[(3R)-3-dimethylamino-pyrrolidin-1-yl]-methanone;  
 {5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indol-2-yl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 20 5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-2-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide;  
 5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-2-carboxylic acid (2-morpholin-4-yl-ethyl)-amide;  
 (1-{5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-  
 25 indole-2-carbonyl}-(3S)-pyrrolidin-3-yl)-carbamic acid tert-butyl ester;  
 {5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indol-2-yl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone;  
 5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-  
 30 2-carboxylic acid (2-hydroxy-3-pyrrolidin-1-yl-propyl)-amide;  
 4-(6-amino-5-benzyloxy-pyridin-3-yl)-phenol;  
 3-benzyloxy-5-phenyl-pyridin-2-ylamine;  
 3-(3-methoxy-benzyloxy)-5-phenyl-pyridin-2-ylamine;  
 3-(2-chloro-4-fluoro-benzyloxy)-5-phenyl-pyridin-2-ylamine;  
 35 3-(2-chloro-benzyloxy)-5-phenyl-pyridin-2-ylamine;

3-(2,5-dichloro-benzyloxy)-5-phenyl-pyridin-2-ylamine;  
 3-(2-chloro-5-trifluoromethyl-benzyloxy)-5-phenyl-pyridin-2-ylamine;  
 3-(2,4-dichloro-5-fluoro-benzyloxy)-5-phenyl-pyridin-2-ylamine;  
 5 3-(2-chloro-3-trifluoromethyl-benzyloxy)-5-phenyl-pyridin-2-ylamine;  
 3-(2-chloro-3,6-difluoro-benzyloxy)-5-phenyl-pyridin-2-ylamine;  
 3-(3,4-dichloro-benzyloxy)-5-phenyl-pyridin-2-ylamine;  
 2-(2-amino-5-phenyl-pyridin-3-yloxymethyl)-benzonitrile;  
 10 3-(2-chloro-6-fluoro-3-methyl-benzyloxy)-5-phenyl-pyridin-2-ylamine;  
 5-phenyl-3-(2,3,6-trifluoro-benzyloxy)-pyridin-2-ylamine;  
 3-(2,6-difluoro-benzyloxy)-5-phenyl-pyridin-2-ylamine;  
 3-(2,6-difluoro-3-methyl-benzyloxy)-5-phenyl-pyridin-2-ylamine;  
 15 3-(3-chloro-2,6-difluoro-benzyloxy)-5-phenyl-pyridin-2-ylamine;  
 3-(2-chloro-6-fluoro-benzyloxy)-5-phenyl-pyridin-2-ylamine;  
 3-(3-fluoro-4-methoxy-benzyloxy)-5-phenyl-pyridin-2-ylamine;  
 N-[3-(2-amino-5-phenyl-pyridin-3-yloxymethyl)-phenyl]-methanesulfonamide;  
 20 5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-3-(3-nitro-benzyloxy)-pyridin-2-ylamine;  
 5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-3-(naphthalen-1-ylmethoxy)-pyridin-2-ylamine;  
 3-(2-chloro-3,6-difluoro-benzyloxy)-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine;  
 25 2-{2-amino-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-3-yloxy}-N-(4-isopropyl-phenyl)-2-phenyl-acetamide;  
 3-(5-chloro-benzo[b]thiophen-3-ylmethoxy)-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine;  
 30 {4-[6-amino-5-(4-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(2-fluoro-6-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 35

{4-[6-amino-5-(5-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 (4-{6-amino-5-[1-(2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 5 {4-[6-amino-5-(2-bromo-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 10 {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenol};  
 15 4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenol;  
 3-(2,6-difluoro-benzyloxy)-5-(1H-indol-4-yl)-pyridin-2-ylamine;  
 3-(2,6-difluoro-benzyloxy)-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine;  
 4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid;  
 20 {4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 25 {4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy}-acetic acid ester;  
 {4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy}-acetic acid;  
 2-{4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy}-1-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-ethanone;  
 30 2-{4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy}-1-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-ethanone;  
 35 4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-

phenol;  
 4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-  
 phenol;  
 4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenol;  
 5 2-[2-amino-5-(4-hydroxy-phenyl)-pyridin-3-yloxymethyl]-  
 benzonitrile;  
 4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-  
 phenol;  
 4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenol;  
 10 4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-phenol;  
 N-{4-[6-amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-phenyl}-  
 methanesulfonamide;  
 2-[2-amino-5-(4-methanesulfonylamino-phenyl)-pyridin-3-  
 yloxymethyl]-benzamide;  
 15 2-[2-amino-5-(4-methanesulfonylamino-phenyl)-pyridin-3-  
 yloxymethyl]-benzoic acid;  
 N-(4-{6-amino-5-[2-(4-methyl-piperazine-1-carbonyl)-benzyloxy]-  
 pyridin-3-yl}-phenyl)-methanesulfonamide;  
 2-[2-amino-5-(4-methanesulfonylamino-phenyl)-pyridin-3-  
 20 yloxymethyl]-N-(2-hydroxy-ethyl)-benzamide;  
 2-[2-amino-5-(4-methanesulfonylamino-phenyl)-pyridin-3-  
 yloxymethyl]-N-isobutyl-benzamide;  
 4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-  
 benzoic acid;  
 25 {4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-  
 phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-  
 methanone;  
 {4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-  
 phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-  
 30 methanone;  
 {4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-  
 phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-  
 phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone;  
 35 {4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-

phenyl)-(4-methyl-piperazin-1-yl)-methanone;  
 1-(4-{4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-benzoyl}-piperazin-1-yl)-ethanone;  
 4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-N-(2-  
 5 morpholin-4-yl-ethyl)-benzamide;  
 4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide; 4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-benzoic acid;  
 {4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-  
 10 2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone;  
 15 {4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 {4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-  
 20 methyl-piperazin-1-yl)-methanone;  
 1-(4-{4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-benzoyl}-piperazin-1-yl)-ethanone;  
 4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide;  
 25 4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide;  
 4-[6-amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-benzoic acid;  
 2-{2-amino-5-[4-((2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzonitrile;  
 30 2-{2-amino-5-[4-((2S)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzonitrile;  
 2-{2-amino-5-[4-((3S)-3-dimethylamino-pyrrolidine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzonitrile;  
 2-{2-amino-5-[4-((3S)-3-amino-pyrrolidine-1-carbonyl)-phenyl]-  
 35 pyridin-3-yloxymethyl}-benzonitrile;

2-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxy-methyl}-benzonitrile;  
 2-{2-amino-5-[4-(4-methyl-piperazine-1-carbonyl)-phenyl]-pyridin-3-yloxy-methyl}-benzonitrile;  
 5 2-{5-[4-(4-acetyl-piperazine-1-carbonyl)-phenyl]-2-amino-pyridin-3-yloxy-methyl}-benzonitrile;  
 4-[6-amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide;  
 4-[6-amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-10 4-yl-ethyl)-benzamide;  
 4-[6-amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide;  
 4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-benzoic acid;  
 15 {4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-20 [(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 25 {4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;  
 1-(4-{4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-benzoyl}-piperazin-1-yl)-ethanone;  
 4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-N-(1-30 methyl-piperidin-4-yl)-benzamide;  
 4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide;  
 4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide;  
 35 4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-

benzoic acid;

{4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;

5 {4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;

{4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone;

10 [(3S)-3-amino-pyrrolidin-1-yl]-{4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-methanone;

{4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;

{4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;

15 1-(4-{4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-benzoyl}-piperazin-1-yl)-ethanone;

4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide;

20 4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-ylethyl)-benzamide;

4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide;

4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-benzoic acid;

25 {4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;

{4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;

30 {4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(3R)-3-dimethylamino-pyrrolidin-1-yl]-methanone;

{4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;

1-(4-{4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-benzoyl}-piperazin-1-yl)-ethanone;

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4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide;  
 4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide;  
 5 4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide;  
 4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-benzoic acid;  
 {4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 10 {4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 15 {4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;  
 20 1-(4-{4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-benzoyl}-piperazin-1-yl)-ethanone;  
 4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide;  
 25 4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide;  
 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid;  
 {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;  
 30 {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-amino-piperidin-1-yl)-methanone;  
 35 {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-

phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone;  
 {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-  
 phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-  
 methanone;

5 {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-  
 phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-  
 phenyl}-[(3R)-3-amino-pyrrolidin-1-yl]-methanone;  
 {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-  
 10 phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone;  
 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-  
 (1-methyl-piperidin-4-yl)-benzamide;  
 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-  
 (2-pyrrolidin-1-yl-ethyl)-benzamide;

15 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-  
 (3-pyrrolidin-1-yl-propyl)-benzamide;  
 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-  
 (2-morpholin-4-yl-ethyl)-benzamide;  
 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-  
 20 (3-morpholin-4-yl-propyl)-benzamide;  
 3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-  
 benzoic acid;  
 {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-  
 phenyl}-(4-methyl-piperazin-1-yl)-methanone;

25 {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-  
 phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-  
 phenyl}-(4-amino-piperidin-1-yl)-methanone;  
 {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-  
 30 phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone;  
 {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-  
 phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-  
 methanone;  
 {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-  
 35 phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone;

{3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3R)-3-amino-pyrrolidin-1-yl]-methanone;  
 {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone;  
 5 3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide;  
 3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;  
 3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-  
 10 (3-pyrrolidin-1-yl-propyl)-benzamide;  
 3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide;  
 3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide;  
 15 N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzamide;  
 3-(2-chloro-3,6-difluoro-benzyloxy)-5-[4-(1,1-dioxo-1 $\lambda$ <sup>6</sup>-isothiazolidine-2-yl)-phenyl]-pyridin-2-ylamine;  
 3-(2,6-dichloro-benzyloxy)-5-[4-(1,1-dioxo-1 $\lambda$ <sup>6</sup>-  
 20 isothiazolidine-2-yl)-phenyl]-pyridin-2-ylamine;  
 5-[4-(1,1-dioxo-1 $\lambda$ <sup>6</sup>-isothiazolidine-2-yl)-phenyl]-3-(2-fluoro-6-trifluoromethyl-benzyloxy)-pyridin-2-ylamine;  
 2-diethylamino-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;  
 25 2-cyclopropylamino-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;  
 2-pyrrolidin-1-yl-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide  
 ; 2-(4-hydroxy-piperidin-1-yl)-ethanesulfonic acid {4-[6-amino-  
 30 5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;  
 2-morpholin-4-yl-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;  
 2-piperidin-1-yl-ethanesulfonic acid {4-[6-amino-5-(2-chloro-  
 35 3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;

2-dimethylamino-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;

2-(4-acetyl-piperazin-1-yl)-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;

5 2-(cyclopropylmethyl-amino)-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;

2-[(3R)-3-hydroxy-pyrrolidin-1-yl]-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;

10 2-[(2S)-2-hydroxymethyl-pyrrolidin-1-yl]-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;

2-[4-(2-hydroxy-acetyl)-piperazin-1-yl]-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;

15 2-(4-acetyl-piperazin-1-yl)-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;

2-pyrrolidin-1-yl-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;

20 2-morpholin-4-yl-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;

2-diethylamino-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;

2-dimethylamino-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;

25 2-piperidin-1-yl-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;

2-[(3R)-3-hydroxymethyl-pyrrolidin-1-yl]-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;

30 2-(4-hydroxy-piperidin-1-yl)-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;

2-[4-(2-hydroxy-acetyl)-piperazin-1-yl]-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;

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2-[(3R)-3-hydroxy-pyrrolidin-1-yl]-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;

2-(cyclopropylmethyl-amino)-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide;

5 2-cyclopropylamino-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(2-dimethylaminomethyl-phenyl)-pyridin-2-ylamine (compound with trifluoroacetic acid);

10 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(3-pyrrolidin-1-yl-phenyl)-pyridin-2-ylamine (compound with trifluoroacetic acid); N-{4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-methanesulfonamide (compound with trifluoroacetic acid);

15 5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophene-2-carboxylic acid;

{5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophen-2-yl}-(4-methyl-piperazin-1-yl)-methanone;

{5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophen-2-yl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]methanone;

20 5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophene-2-carboxylic acid (1-methyl-piperidin-4-yl)-amide;

{5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophen-2-yl}-(3,5-dimethyl-piperazin-1-yl)-methanone;

25 5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophene-2-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide;

{5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophen-2-yl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;

30 4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-benzoic acid;

{4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;

4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide;

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{4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone;  
 {4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(3-dimethylamino-pyrrolidin-1-yl)-methanone;  
 5 {4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide;  
 10 {4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;  
 N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]benzamide;  
 2-piperidin-1-yl-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide;  
 15 2-(4-hydroxy-piperidin-1-yl)-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide;  
 20 2-dimethylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide;  
 2-cyclopropylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide;  
 25 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 30 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide;  
 (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-[(3R)-3-amino-pyrrolidin-1-yl]-methanone;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-

methanone;

(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone;

(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone;

2-cyclopropylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide;

2-dimethylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide;

2-[(3R)-3-hydroxy-pyrrolidin-1-yl]-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide;

4-[5-amino-6-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]-phenol;

3-(2,6-dichloro-benzyloxy)-5-[4-(1,1-dioxo-1λ<sup>6</sup>-isothiazolidine-2-yl)-phenyl]-pyrazin-2-ylamine;

3-(2,6-dichloro-benzyloxy)-5-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrazin-2-ylamine;

3-(2,6-dichloro-benzyloxy)-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrazin-2-ylamine;

5-(4-amino-phenyl)-3-(2,6-dichloro-benzyloxy)-pyrazin-2-ylamine;

4-[5-amino-6-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]-benzoic acid;

{4-[5-amino-6-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;

{4-[5-amino-6-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;

2-morpholin-4-yl-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

2-piperidin-1-yl-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

2-(4-hydroxy-piperidin-1-yl)-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

2-pyrrolidin-1-yl-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

2-[(3R)-3-hydroxy-pyrrolidin-1-yl]-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

2-[(2S)-2-hydroxymethyl-pyrrolidin-1-yl]-ethanesulfonic acid  
5 {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

2-(cyclopropylmethyl-amino)-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

2-dimethylamino-ethanesulfonic acid {4-[5-amino-6-(2-chloro-  
10 3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

2-diethylamino-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

2-(4-acetyl-piperazin-1-yl)-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

15 2-[4-(2-hydroxy-acetyl)-piperazin-1-yl]-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

2-cyclopropylamino-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

20 2-[(3R)-3-hydroxymethyl-pyrrolidin-1-yl]-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

2-(4-hydroxy-piperidin-1-yl)-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

25 2-(4-acetyl-piperazin-1-yl)-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

2-piperidin-1-yl-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

2-diethylamino-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

30 2-morpholin-4-yl-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

2-pyrrolidin-1-yl-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;

35 2-dimethylamino-ethanesulfonic acid {3-[5-amino-6-(2-chloro-

3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;  
 2-[4-(2-hydroxy-acetyl)-piperazin-1-yl]-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;  
 5 2-(cyclopropylmethyl-amino)-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;  
 2-[(3R)-3-hydroxy-pyrrolidin-1-yl]-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;  
 10 2-cyclopropylamino-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide;  
 4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-benzoic acid;  
 {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 15 4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;  
 {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone;  
 20 N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-benzamide;  
 4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide;  
 25 {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone;  
 {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(3R)-3-dimethylamino-pyrrolidin-1-yl]-methanone;  
 {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone;  
 30 {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(3-morpholin-4-yl-propyl)-benzamide;  
 35 4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-

(1-methyl-piperidin-4-yl)-benzamide;  
 4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide;  
 {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;  
 3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-benzoic acid;  
 {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;  
 {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(3R)-3-amino-pyrrolidin-1-yl]-methanone;  
 {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone;  
 {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone;  
 3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(3-morpholin-4-yl-propyl)-benzamide;  
 {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone;  
 3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;  
 3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(1-methyl-piperidin-4-yl)-benzamide;  
 {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(2S)-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;  
 3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide;  
 N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-benzamide;  
 3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide;  
 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(1H-indol-5-yl)-pyrazin-2-ylamine;

3-(2-chloro-3,6-difluoro-benzyloxy)-5-(3-pyrrolidin-1-ylmethyl-1H-indol-5-yl)-pyrazin-2-ylamine;

3-(2-chloro-3,6-difluoro-benzyloxy)-5-(3-diethylaminomethyl-1H-indol-5-yl)-pyrazin-2-ylamine;

5 1-(4-{5-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-1H-indol-3-ylmethyl}-piperazin-1-yl)-ethanone;

3-(2-chloro-3,6-difluoro-benzyloxy)-5-[3-(2,6-dimethyl-morpholin-4-ylmethyl)-1H-indol-5-yl]-pyrazin-2-ylamine;

N-(1-{5-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-1H-indol-3-ylmethyl}-(3S)-pyrrolidin-3-yl)-acetamide;

10 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(3-piperidin-1-ylmethyl-1H-indol-5-yl)-pyrazin-2-ylamine;

3-(2-chloro-3,6-difluoro-benzyloxy)-5-(3-morpholin-4-ylmethyl-1H-indol-5-yl)-pyrazin-2-ylamine;

15 3-[1-(2-chloro-3,6-difluoro-phenyl)-2-methyl-propoxy]-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrazin-2-ylamine;

3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrazin-2-ylamine (compound with trifluoroacetic acid);

20 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrazin-2-ylamine (compound with trifluoroacetic acid);

N-(4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-methanesulfonamide;

25 2-pyrrolidin-1-yl-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide;

2-(4-hydroxy-piperidin-1-yl)-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide;

30 2-piperidin-1-yl-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide;

2-(cyclopropylmethyl-amino)-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-

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phenyl)-amide;

2-[(3R)-3-hydroxy-pyrrolidin-1-yl]-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide;

5 2-[(2S)-2-hydroxymethyl-pyrrolidin-1-yl]-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide;

2-dimethylamino-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide;

10 2-morpholin-4-yl-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide;

2-diethylamino-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide;

15 2-cyclopropylamino-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide;

3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid;

20 (3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-[(3S)-3-amino-pyrrolidin-1-yl]-methanone;

(3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-[(3R)-3-amino-pyrrolidin-1-yl]-methanone;

(3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;

25 N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzamide;

(3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone;

30 3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid;

3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide;

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3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-  
 2-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide;  
 (3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-  
 5 methanone;  
 4-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-  
 yl]-benzoic acid;  
 4-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-  
 yl]-N-(2-morpholin-4-yl-ethyl)-benzamide;  
 10 4-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-  
 yl]-N-(1-methyl-piperidin-4-yl)-benzamide;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone;  
 N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-4-{6-amino-5-[1-(2,6-  
 15 dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzamide;  
 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide;  
 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide;  
 20 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 25 pyridin-3-yl}-phenyl)-(4-amino-piperidin-1-yl)-methanone;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-((S)-3-hydroxy-pyrrolidin-1-yl)-  
 methanone;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 30 pyridin-3-yl}-phenyl)-((R)-3-hydroxy-pyrrolidin-1-yl)-  
 methanone;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-((R)-2-hydroxymethyl-pyrrolidin-1-yl)-  
 methanone;  
 35 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-

3-yl}-N-(2-diethylamino-ethyl)-benzamide;  
 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;  
 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 5 3-yl}-benzoic acid;  
 (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone;  
 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide;  
 10 (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-  
 1-yl)-methanone;  
 N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-3-{6-amino-5-[1-(2,6-  
 dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzamide;  
 15 (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone;  
 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 3-yl}-N-(3-morpholin-4-yl-propyl)-benzamide;  
 (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 20 pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-  
 1-yl)-methanone;  
 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;  
 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 25 3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide;  
 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide;  
 (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-  
 30 methanone;  
 2-diethylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-  
 dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide;  
 2-(4-hydroxy-piperidin-1-yl)-ethanesulfonic acid (4-{6-amino-5-  
 [1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-  
 35 phenyl)-amide;

2-piperidin-1-yl-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide;  
 2-(cyclopropylmethyl)-amino-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide;  
 5 2-(R)-3-hydroxy-pyrrolidin-1-yl)-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide;  
 2-cyclopropylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide;  
 10 2-diethylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide;  
 4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid;  
 15 4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide;  
 4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide;  
 20 (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone;  
 (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(R)-3-amino-pyrrolidin-1-yl)-methanone;  
 25 (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone;  
 4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide;  
 30 (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone;  
 (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone;  
 35 (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-

pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;

4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5 (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone;

3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid;

(3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone;

10 (3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone;

3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide;

15 (3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone;

3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide;

20 3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

(3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone;

3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide;

25 (3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone;

(3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone;

30 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine;

3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine;

35

3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-pyrrolidin-  
 1-yl-ethoxy)-phenyl]-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-{4-[2-(1-methyl-  
 pyrrolidin-2-yl)-ethoxy]-phenyl}-pyridin-2-ylamine;  
 5 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-morpholin-  
 4-yl-ethoxy)-phenyl]-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[3-(2-morpholin-  
 4-yl-ethoxy)-phenyl]-pyridin-2-ylamine;  
 1-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 10 pyridin-3-yl}-phenoxy)-3-morpholin-4-yl-propan-2-ol;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-  
 diethylamino-ethoxy)-phenyl]-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(1-methyl-  
 piperazin-3-ylmethoxy)-phenyl]-pyridin-2-ylamine;  
 15 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-  
 diisopropylamino-ethoxy)-phenyl]-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(1-methyl-  
 piperazin-4-yloxy)-phenyl]-pyridin-2-ylamine;  
 N-(4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 20 pyridin-3-yl}-phenyl)-methanesulfonamide;  
 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-[4-(1,1-dioxo-  
 1λ<sup>6</sup>-isothiazolidine-2-yl)-phenyl]-pyridin-2-ylamine;  
 N-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-methanesulfonamide;  
 25 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-phenyl-pyridin-2-  
 ylamine;  
 N-(4-{6-amino-5-[(R)-1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-methanesulfonamide;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-thiophen-3-yl-  
 30 pyridin-2-ylamine;  
 5-benzo[b]thiophen-2-yl-3-[1-(2,6-dichloro-3-fluoro-phenyl)-  
 ethoxy]-pyridin-2-ylamine;  
 4-methyl-piperazine-1-carboxylic acid (4-{6-amino-5-[1-(2,6-  
 dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide;  
 35 1-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-

pyridin-3-yl}-phenyl)-3-(2-pyrrolidin-1-yl-ethyl)-urea;  
 1-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-3-(2-hydroxy-ethyl)-urea;  
 1-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 5 pyridin-3-yl}-phenyl)-3-(2-morpholin-4-yl-ethyl)-urea;  
 (R)-3-amino-pyrrolidine-1-carboxylic acid (4-{6-amino-5-[1-  
 (2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-  
 amide;  
 (S)-3-amino-pyrrolidine-1-carboxylic acid (4-{6-amino-5-[1-  
 10 (2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-  
 amide;  
 1-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-3-(1-methyl-piperidin-4-yl)-urea;  
 1-(4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 15 pyridin-3-yl}-phenyl)-3-(1-methyl-piperidin-4-yl)-urea;  
 (R)-3-amino-pyrrolidine-1-carboxylic acid (4-{6-amino-5-[1-(2-  
 chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-  
 amide;  
 (S)-3-amino-pyrrolidine-1-carboxylic acid (4-{6-amino-5-[1-(2-  
 20 chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-  
 amide;  
 1-(4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-3-(2-hydroxy-ethyl)-urea;  
 4-methyl-piperazine-1-carboxylic acid (4-{6-amino-5-[1-(2-  
 25 chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-  
 amide;  
 1-(4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-3-(2-pyrrolidin-1-yl-ethyl)-urea;  
 1-(4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 30 pyridin-3-yl}-phenyl)-3-(2-morpholin-4-yl-ethyl)-urea;  
 (R)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid (4-  
 {6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-  
 yl}-phenyl)-amide;  
 3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-  
 35 benzoic acid;

(3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone;  
 (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 5 3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;  
 3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide;  
 (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone;  
 10 3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide;  
 N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-benzamide;  
 15 3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide;  
 (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone;  
 20 (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone;  
 (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone;  
 25 (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone;  
 4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid;  
 4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;  
 30 4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide;  
 (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone;  
 35 methanone;

4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide;  
 (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone;  
 5 N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-benzamide;  
 4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide;  
 (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone;  
 10 (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone;  
 (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone;  
 15 (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone;  
 20 (S)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-amide;  
 4-methyl-piperazine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-amide;  
 25 4-pyrrolidin-1-yl-piperidine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-amide;  
 (3R,5S)-3,5-dimethyl-piperazine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-amide;  
 30 1-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-3-(1-methyl-piperidin-4-yl)-urea;  
 1-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-3-(3-pyrrolidin-1-yl-propyl)-urea;  
 35

1-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-prop-2-ynyl)-3-(2-pyrrolidin-1-yl-ethyl)-urea;  
 1-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-prop-2-ynyl)-3-(2-morpholin-4-yl-ethyl)-urea;  
 5 1-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-prop-2-ynyl)-3-(3-morpholin-4-yl-propyl)-urea;  
 (R)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid (3-  
 {6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-  
 yl}-prop-2-ynyl)-amide;  
 10 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-dimethylamino-  
 prop-1-ynyl)-pyridin-2-ylamine;  
 (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-prop-2-ynyl)-urea;  
 N-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 15 pyridin-3-yl}-prop-2-ynyl)-2-piperidin-1-yl-acetamide;  
 N-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-prop-2-ynyl)-2-morpholin-4-yl-acetamide;  
 N-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-prop-2-ynyl)-2-pyrrolidin-1-yl-acetamide;  
 20 N-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-prop-2-ynyl)-2-((R)-3-hydroxy-pyrrolidin-1-yl)-  
 acetamide;  
 N-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-prop-2-ynyl)-2-(4-hydroxy-piperidin-1-yl)-  
 25 acetamide;  
 N-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-prop-2-ynyl)-2-dimethylamino-acetamide;  
 N-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-prop-2-ynyl)-2-diethylamino-acetamide;  
 30 2-(4-acetyl-piperazin-1-yl)-N-(3-{6-amino-5-[1-(2,6-dichloro-3-  
 fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-acetamide;  
 4-methyl-piperazine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-  
 dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-  
 prop-2-ynyl)-amide;  
 35 (3R,5S)-3,5-dimethyl-piperazine-1-carboxylic acid (3-{6-amino-

5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-prop-2-ynyl)-amide;  
 (R)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-prop-2-ynyl)-amide;  
 5 (S)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-prop-2-ynyl)-amide;  
 1-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-prop-2-ynyl)-3-(2-morpholin-4-yl-ethyl)-urea;  
 10 1-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-prop-2-ynyl)-3-(2-pyrrolidin-1-yl-ethyl)-urea;  
 15 4-pyrrolidin-1-yl-piperidine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-prop-2-ynyl)-amide;  
 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-propynoic acid cyclohexylamide;  
 20 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-propynoic acid isopropylamide;  
 4-(3-amino-3-methyl-but-1-ynyl)-2-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-phenylamine;  
 (4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone;  
 25 (4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 (4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone;  
 30 (4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone;  
 35 (4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-

pyridin-3-yl}-phenyl)-(R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-  
 1-yl)-methanone;  
 4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-  
 pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide;  
 5 4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-  
 pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;  
 4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-  
 pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide;  
 4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-  
 10 pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide;  
 4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-  
 pyridin-3-yl}-N-(3-morpholin-4-yl-propyl)-benzamide;  
 6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 nicotinonitrile;  
 15 6-amino-5-[1-(2,6-dichloro-3-cyano-phenyl)-ethoxy]-  
 nicotinonitrile;  
 5-aminomethyl-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-2-ylamine;  
 (R)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid {6-  
 20 amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-  
 ylmethyl}-amide;  
 N-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 3-ylmethyl}-methanesulfonamide;  
 N-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 25 3-ylmethyl}-acetamide;  
 N-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 3-ylmethyl}-4-methyl-benzenesulfonamide;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-vinyl-pyridin-2-  
 ylamine;  
 30 (S)-1-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-ethane-1,2-diol;  
 (R)-1-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-ethane-1,2-diol;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(1H-pyrazol-4-  
 35 yl)-pyridin-2-ylamine;

3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[1-(2-pyrrolidin-1-yl-ethyl)-1H-pyrazol-4-yl]-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[1-(2-diisopropylamino-ethyl)-1H-pyrazol-4-yl]-pyridin-2-ylamine;  
 5 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[1-(2-morpholin-4-yl-ethyl)-1H-pyrazol-4-yl]-pyridin-2-ylamine;  
 5-bromo-3-(3-fluoro-2-methoxy-benzyloxy)-pyridin-2-ylamine;  
 5-bromo-3-[1-(3-fluoro-2-methoxy-phenyl)-ethoxy]-pyridin-2-ylamine;  
 10 {4-[6-amino-5-(3-fluoro-2-methoxy-benzyloxy)-pyridin-3-yl]-phenyl}-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone;  
 (4-{6-amino-5-[1-(3-fluoro-2-methoxy-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone;  
 5-bromo-3-(3-fluoro-2-isopropoxy-benzyloxy)-pyridin-2-ylamine;  
 15 {4-[6-amino-5-(3-fluoro-2-isopropoxy-benzyloxy)-pyridin-3-yl]-phenyl}-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone;  
 5-(4-amino-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-acetic acid methyl ester;  
 20 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-acetic acid;  
 2-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-1-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-ethanone;  
 25 2-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-1-((R)-3-hydroxy-pyrrolidin-1-yl)-ethanone;  
 4-[2-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-acetyl]-piperazine-1-carboxylic acid  
 30 tert-butyl ester;  
 2-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-1-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-ethanone; 5-bromo-3-(3-fluoro-6,7,8,9-  
 35 tetrahydro-5H-benzocyclohepten-5-yloxy)-pyridin-2-ylamine;

{4-[6-amino-5-(3-fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yloxy)-pyridin-3-yl]-phenyl}-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone;  
 3-(3-fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yloxy)-5-  
 5 [4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyridin-2-ylamine;  
 N-{4-[6-amino-5-(3-fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yloxy)-pyridin-3-yl]-phenyl}-methanesulfonamide;  
 3-(3-fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yloxy)-5-  
 10 (1H-pyrazol-4-yl)-pyridin-2-ylamine;  
 5-bromo-3-[1-(2-chloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine;  
 3-[1-(2-chloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyridin-2-ylamine;  
 15 5'-benzyloxy-[2,3']bipyridinyl-6'-ylamine;  
 5-benzyloxy-[3,3']bipyridinyl-6-ylamine;  
 3-benzyloxy-5-pyrimidin-5-yl-pyridin-2-ylamine;  
 5-benzyloxy-[3,3']bipyridinyl-6,6'-diamine;  
 5'-(2-chloro-benzyloxy)-[2,3']bipyridinyl-6'-ylamine;  
 20 5-(2-chloro-benzyloxy)-[3,3']bipyridinyl-6-ylamine;  
 3-(2-chloro-benzyloxy)-5-pyrimidin-5-yl-pyridin-2-ylamine;  
 5-(2-chloro-benzyloxy)-[3,3']bipyridinyl-6,6'-diamine;  
 5'-(4-chloro-benzyloxy)-[2,3']bipyridinyl-6'-ylamine;  
 5-(4-chloro-benzyloxy)-[3,3']bipyridinyl-6-ylamine;  
 25 3-(4-chloro-benzyloxy)-5-pyrimidin-5-yl-pyridin-2-ylamine;  
 5-(4-chloro-benzyloxy)-[3,3']bipyridinyl-6,6'-diamine;  
 5'-(2-chloro-3,6-difluoro-benzyloxy)-[2,3']bipyridinyl-6'-ylamine;  
 5-(2-chloro-3,6-difluoro-benzyloxy)-[3,3']bipyridinyl-6-  
 30 ylamine;  
 5-(2-chloro-3,6-difluoro-benzyloxy)-[3,4']bipyridinyl-6-ylamine;  
 3-(2-chloro-3,6-difluoro-benzyloxy)-5-pyrimidin-5-yl-pyridin-2-ylamine;  
 35 5-(2-chloro-3,6-difluoro-benzyloxy)-[3,3']bipyridinyl-6,6'-

diamine;  
 5'-(2,6-dichloro-benzyloxy)-[2,3']bipyridinyl-6'-ylamine;  
 5-(2,6-dichloro-benzyloxy)-[3,3']bipyridinyl-6-ylamine;  
 5-(2,6-dichloro-benzyloxy)-[3,4']bipyridinyl-6-ylamine;  
 5 3-(2,6-dichloro-benzyloxy)-5-pyrimidin-5-yl-pyridin-2-ylamine;  
 5-(2,6-dichloro-benzyloxy)-[3,3']bipyridinyl-6,6'-diamine;  
 5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-  
 6,6'-diamine;  
 {6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 10 [2,3']bipyridinyl-4-yl}-(4-methyl-piperazin-1-yl)-methanone;  
 {6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 [2,3']bipyridinyl-6-yl}-(4-methyl-piperazin-1-yl)-methanone;  
 {6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 [3,3']bipyridinyl-5-yl}-(4-methyl-piperazin-1-yl)-methanone;  
 15 {6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 [3,3']bipyridinyl-6-yl}-(4-methyl-piperazin-1-yl)-methanone;  
 {6'-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 [3,4']bipyridinyl-2'-yl}-(4-methyl-piperazin-1-yl)-methanone;  
 5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-  
 20 6,6'-diamine;  
 {6'-amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 [2,3']bipyridinyl-5-yl}-(4-methyl-piperazin-1-yl)-methanone;  
 {6'-amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 [2,3']bipyridinyl-4-yl}-(4-methyl-piperazin-1-yl)-methanone;  
 25 {6'-amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 [2,3']bipyridinyl-6-yl}-(4-methyl-piperazin-1-yl)-methanone;  
 {6'-amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 [3,3']bipyridinyl-5-yl}-(4-methyl-piperazin-1-yl)-methanone;  
 {6'-amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 30 [3,3']bipyridinyl-6-yl}-(4-methyl-piperazin-1-yl)-methanone;  
 {6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 [3,4']bipyridinyl-2'-yl}-(4-methyl-piperazin-1-yl)-methanone;  
 5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-  
 6'-ylamine;  
 35 5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-

6'-ylamine;  
 5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-  
 6-ylamine;  
 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-pyrimidin-5-yl-  
 5 pyridin-2-ylamine;  
 {6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 [2,3']bipyridinyl-5-yl}-(4-methyl-piperazin-1-yl)-methanone;  
 5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[3,4']bipyridinyl-  
 6-ylamine;  
 10 5-benzyloxy-3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 pyridin-2-ylamine;  
 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-(2-ethyl-butoxy)-  
 pyridin-2-ylamine;  
 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-(3-methyl-  
 15 butoxy)-pyridin-2-ylamine;  
 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-butoxy -pyridin-  
 2-ylamine;  
 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-propoxy-pyridin-  
 2-ylamine;  
 20 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-  
 cyclohexylmethoxy-pyridin-2-ylamine;  
 6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-  
 ol;  
 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-(2-cyclohexyl-  
 25 ethoxy)-pyridin-2-ylamine;  
 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-isobutoxy-  
 pyridin-2-ylamine;  
 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-phenethyloxy-  
 pyridin-2-ylamine;  
 30 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-(pyridin-2-  
 ylmethoxy)-pyridin-2-ylamine;  
 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-(pyridin-4-  
 ylmethoxy)-pyridin-2-ylamine;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 35 pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-

methanone;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-( (3R,5S)-3,5-dimethyl-piperazin-1-yl) -  
 methanone;  
 5 5-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 3-yl}-2-fluoro-benzonitrile;  
 4-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-piperidin-4-ol;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 10 pyridin-3-yl}-phenyl)-piperidin-1-yl-methanone;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-pyrrolidin-1-yl-methanone;  
 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 3-yl}-3-methyl-benzoic acid methyl ester;  
 15 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(dimethyl-  
 piperazine-1-ylmethyl)-phenyl]-pyridin-2-ylamine;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-3,5-dimethoxy-phenyl)-(dimethyl-piperazin-1-yl)-  
 methanone;  
 20 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-2-fluoro-phenyl)-(dimethyl-piperazin-1-yl)-  
 methanone;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-3-fluoro-phenyl)-(dimethyl-piperazin-1-yl)-  
 25 methanone;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-3-methyl-phenyl)-(dimethyl-piperazin-1-yl)-  
 methanone;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 30 pyridin-3-yl}-phenyl)-(4-methyl-[1,4]diazepan-1-yl)-methanone;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-[1,4]diazepan-1-yl-methanone;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-piperazin-1-yl-methanone;  
 35 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-vinyl-pyridin-2-

ylamine;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-  
 methanone;  
 5 5-[(1-benzyl-pyrrolidin-3-ylamino)-methyl]-3-[1-(2,6-dichloro-  
 3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine;  
 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 3-yl}-N-azetidin-3-yl-benzamide;  
 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 10 3-yl}-N,N-dimethyl-benzenesulfonamide;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(6-methoxy-1H-  
 benzimidazol-2-yl)-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(6-methoxy-1-  
 methyl-1H-benzimidazol-2-yl)-pyridin-2-ylamine;  
 15 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(4-methyl-  
 [1,4]diazepane-1-sulfonyl)-phenyl]-pyridin-2-ylamine;  
 6-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 3-yl}-1-methyl-1H-indazole-3-carboxylic acid amide;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(1-methyl-1H-  
 20 pyrazol-4-yl)-pyridin-2-ylamine;  
 5-(3-chloro-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-  
 ethoxy]-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(4-fluoro-3-  
 methyl-phenyl)-pyridin-2-ylamine;  
 25 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-  
 trifluoromethyl-phenyl)-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-fluoro-  
 phenyl)-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-  
 30 trifluoromethoxy-phenyl)-pyridin-2-ylamine;  
 5-benzo[1,3]dioxol-5-yl-3-[1-(2,6-dichloro-3-fluoro-phenyl)-  
 ethoxy]-pyridin-2-ylamine;  
 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 3-yl}-phenol;  
 35 (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-

pyridin-3-yl}-phenyl)-methanol;  
 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 3-yl}-benzonitrile;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-methoxy-  
 5 phenyl)-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,5-dichloro-  
 phenyl)-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,5-dimethyl-  
 phenyl)-pyridin-2-ylamine;  
 10 5-(5-chloro-2-methoxy-phenyl)-3-[1-(2,6-dichloro-3-fluoro-  
 phenyl)-ethoxy]-pyridin-2-ylamine;  
 5-(3-chloro-4-fluoro-phenyl)-3-[1-(2,6-dichloro-3-fluoro-  
 phenyl)-ethoxy]-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(5-fluoro-2-  
 15 methoxy-phenyl)-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-isopropyl-  
 phenyl)-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,4-dichloro-  
 phenyl)-pyridin-2-ylamine;  
 20 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-  
 3-yl}-benzonitrile;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,4-difluoro-  
 phenyl)-pyridin-2-ylamine;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 25 pyridin-3-yl}-phenyl)-((2R,6S)-2,6-dimethyl-morpholin-4-yl)-  
 methanone;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-ethoxy-  
 phenyl)-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,5-dimethoxy-  
 30 phenyl)-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,4-dimethoxy-  
 phenyl)-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,6-dimethoxy-  
 phenyl)-pyridin-2-ylamine;  
 35 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-

trifluoromethyl-phenyl)-pyridin-2-ylamine;  
 5-(2-chloro-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-  
 ethoxy]-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-  
 5 trifluoromethoxy-phenyl)-pyridin-2-ylamine;  
 1-(2-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-ethanone;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-fluoro-  
 phenyl)-pyridin-2-ylamine; (2-{6-amino-5-[1-(2,6-dichloro-3-  
 10 fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanol;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-o-tolyl-pyridin-  
 2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-methoxy-  
 phenyl)-pyridin-2-ylamine;  
 15 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,6-dimethyl-  
 phenyl)-pyridin-2-ylamine;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-morpholin-4-yl-methanone;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 20 pyridin-3-yl}-2-chloro-phenyl)-((3R,5S)-dimethyl-piperazin-1-  
 yl)-methanone;  
 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-2-methyl-phenyl)-((3R,5S)-dimethyl-piperazin-1-  
 yl)-methanone;  
 25 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-((2R,6S)-2,6-  
 dimethyl-morpholin-4-ylmethyl)-phenyl]-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(4-morpholin-4-  
 ylmethyl-phenyl)-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,5-dimethyl-  
 30 phenyl)-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-m-tolyl-pyridin-  
 2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,4-dimethoxy-  
 phenyl)-pyridin-2-ylamine;  
 35 5-biphenyl-3-yl-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-

pyridin-2-ylamine;  
 5-(3,5-bis-trifluoromethyl-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,4-dichloro-phenyl)-pyridin-2-ylamine;  
 1-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-ethanone;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,5-difluoro-phenyl)-pyridin-2-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,5-dichloro-phenyl)-pyridin-2-ylamine;  
 (4-{6-amino-5-[1-(2,6-dichloro-4-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-ethoxy-phenyl)-pyridin-2-ylamine;  
 (4-{6-amino-5-[1-(2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone;  
 (4-{6-amino-5-[1-(3-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone;  
 7-[4-(3,5-dimethyl-piperazine-1-carbonyl)-phenyl]-2-phenyl-4H-pyrido[3,2-b][1,4]oxazin-3-one;  
 {4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone;  
 {4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone;  
 [4-(6-amino-5-benzyloxy-pyridin-3-yl)-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone;  
 (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-ethyl-piperazin-1-yl)-methanone;  
 [4-(6-amino-5-benzyloxy-pyridin-3-yl)-phenyl)-(4-ethyl-piperazin-1-yl)-methanone;  
 {4-[6-amino-5-(2-methyl-benzyloxy)-pyridin-3-yl]-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone;  
 3-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-

phenyl]-pyridin-3-yloxymethyl}-benzoic acid methyl ester;  
 3-{2-amino-5-[4-(3,5-dimethyl-piperazine-1-carbonyl)-phenyl]-  
 pyridin-3-yloxymethyl}-benzoic acid methyl ester;  
 {4-[6-amino-5-(2-methyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-  
 5 pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 [4-(6-amino-5-cyclohexylmethoxy-pyridin-3-yl)-phenyl]-(4-  
 pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 4-(1-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-  
 phenyl]-pyridin-3-yloxy}-ethyl)-[2-(3-hydroxy-phenyl)-ethyl]-  
 10 benzamide;  
 4-(1-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-  
 phenyl]-pyridin-3-yloxy}-ethyl)-[2-(2,6-dichloro-phenyl)-  
 ethyl]-benzamide;  
 4-(1-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-  
 15 phenyl]-pyridin-3-yloxy}-ethyl)-(1-benzyl-piperidin-4-yl)-  
 benzamide;  
 4-(1-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-  
 phenyl]-pyridin-3-yloxy}-ethyl)-[3-(2-oxo-pyrrolidin-1-yl)-  
 propyl]-benzamide;  
 20 (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-(4-ethyl-piperazin-1-yl)-methanone;  
 {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-  
 (3,5-dimethyl-piperazin-1-yl)-methanone;  
 (6-amino-3-aza-bicyclo[3.1.0]hex-3-yl)-(4-{6-amino-5-[1-(2,6-  
 25 dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-  
 methanone;  
 5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-6'-(2-morpholin-4-  
 yl-ethoxy)-[3,3']bipyridinyl-6-ylamine;  
 6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-1-(2-  
 30 pyrrolidin-1-yl-ethyl)-1H-[3,3']bipyridinyl-6-one;  
 5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-6'-(2-pyrrolidin-1-  
 yl-ethoxy)-[3,3']bipyridinyl-6-ylamine;  
 6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-1-[2-(1-  
 methyl-pyrrolidin-2-yl)-ethyl]-1H-[3,3']bipyridinyl-6-one;  
 35 (4-{6-amino-5-[1-(2,4,6-trimethyl-phenyl)-ethoxy]-pyridin-3-

yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 (4-{6-amino-5-[1-(2-chloro-6-fluoro-phenyl)-ethoxy]-pyridin-3-  
 yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(4-fluoro-  
 5 phenyl)-pyridin-2-ylamine;  
 6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-1H-  
 [3,3']bipyridinyl-6-one;  
 5'-bromo-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 [3,3']bipyridinyl-6-ylamine;  
 10 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(4-dimethylamino-  
 phenyl)-pyridin-2-ylamine;  
 5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-2'-methoxy-  
 [3,3']bipyridinyl-6-ylamine;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(1H-indol-5-yl)-  
 15 pyridin-2-ylamine;  
 (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-propoxy]-pyridin-3-yl}-  
 phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone;  
 [4-(6-amino-5-benzyloxy-pyridin-3-yl)-phenyl)-(4-pyrrolidin-1-  
 yl-piperidin-1-yl)-methanone;  
 20 3-(2,6-dichloro-3-fluoro-benzyloxy)-5-thiazol-2-yl-pyridin-2-  
 ylamine;  
 (4-{6-amino-5-[1-(2-fluoro-6-trifluoromethyl-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-  
 methanone;  
 25 3-(2,6-dichloro-3-fluoro-benzyloxy)-5-(1-methyl-1H-imidazol-2-  
 yl)-pyridin-2-ylamine;  
 {4-[6-amino-5-(2,4,6-trimethyl-benzyloxy)-pyridin-3-yl]-  
 phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 {4-[6-amino-5-(2,3,5,6-tetramethyl-benzyloxy)-pyridin-3-yl]-  
 30 phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 {4-[6-amino-5-(2,4,6-trifluoro-benzyloxy)-pyridin-3-yl]-  
 phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 (4-{6-amino-5-[1-(2-fluoro-6-trifluoromethyl-phenyl)-ethoxy]-  
 pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-  
 35 methanone;

6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-N-methyl-nicotinamidine;

6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-N-(2-morpholin-4-yl-ethyl)-nicotinamidine; (4-{6-amino-5-[1-(2,4,5-trifluoro-phenyl)-propoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;

(4-{6-amino-5-[1-(6-chloro-2-fluoro-3-methyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;

10 3-(1-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxy}-ethyl)-benzoic acid;

3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide;

3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide;

15 3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide;

3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

20 3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide;

N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzamide;

(3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone;

25 (3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-2-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;

(3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone;

30 (3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone;

35 (3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-

pyrazin-2-yl}-phenyl)-(R)-3-amino-pyrrolidin-1-yl)-methanone;  
 (3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-phenyl)-(S)-3-amino-pyrrolidin-1-yl)-methanone;  
 4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-  
 5 2-yl}-benzoic acid;  
 4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-  
 2-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide;  
 (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone;  
 10 (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-  
 methanone;  
 (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-  
 15 methanone;  
 (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-phenyl)-(S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-  
 1-yl)-methanone;  
 (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 20 pyrazin-2-yl}-phenyl)-(R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-  
 1-yl)-methanone;  
 (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-phenyl)-(R)-3-amino-pyrrolidin-1-yl)-methanone;  
 4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-  
 25 2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide;  
 4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-  
 2-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;  
 4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-  
 2-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide;  
 30 N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-4-{5-amino-6-[1-(2-  
 chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzamide;  
 2-[4-(2-hydroxy-acetyl)-piperazin-1-yl]-ethanesulfonic acid (4-  
 {5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-  
 yl}-phenyl)-amide;  
 35 3-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-

yl]-benzoic acid;  
 {3-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 3-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-N-{2-[ethyl-(2-methoxy-ethyl)-amino]-ethyl}-benzamide;  
 {3-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;  
 3-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide;  
 10 N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-3-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-benzamide;  
 {4-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 {4-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;  
 15 {4-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-phenyl}-(S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone;  
 (3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone;  
 20 (3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone;  
 3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide;  
 3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;  
 3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide;  
 30 3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-morpholin-4-yl-propyl)-benzamide;  
 (3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-cyclopropylamino-piperidin-1-yl)-methanone;  
 35 3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-

2-yl}-N-((S)-2-hydroxy-3-morpholin-4-yl-propyl)-benzamide;  
 3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-  
 2-yl}-N-((R)-2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzamide;  
 (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 5 pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-  
 methanone;  
 2-diethylamino-ethanesulfonic acid (4-{5-amino-6-[1-(2,6-  
 dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide;  
 2-(4-hydroxy-piperidin-1-yl)-ethanesulfonic acid (4-{5-amino-6-  
 10 [1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-  
 phenyl)-amide;  
 2-dimethylamino-ethanesulfonic acid (4-{5-amino-6-[1-(2,6-  
 dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide;  
 2-((R)-3-hydroxy-pyrrolidin-1-yl)-ethanesulfonic acid (4-{5-  
 15 amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-  
 yl}-phenyl)-amide;  
 2-pyrrolidin-1-ylethanesulfonic acid (4-{5-amino-6-[1-(2,6-  
 dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide;  
 4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-  
 20 2-yl}-benzoic acid;  
 4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-  
 2-yl}-N-((R)-2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzamide;  
 (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-phenyl)-(4-cyclopropylamino-piperidin-1-yl)-  
 25 methanone;  
 4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-  
 2-yl}-N-((S)-2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzamide;  
 4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-  
 2-yl}-N-((R)-2-hydroxy-3-morpholin-4-yl-propyl)-benzamide;  
 30 4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-  
 2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide;  
 (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-  
 1-yl)-methanone;  
 35 (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-

pyrazin-2-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-  
 methanone;  
 4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-  
 2-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide;  
 5 (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone;  
 (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-  
 methanone;  
 10 4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-  
 benzoic acid;  
 (4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-  
 phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-  
 15 (2-morpholin-4-yl-ethyl)-benzamide;  
 (4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-  
 phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone;  
 4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-  
 (1-methyl-piperidin-4-yl)-benzamide;  
 20 (4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-  
 phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-  
 methanone;  
 (4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-  
 phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-  
 25 methanone;  
 (4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-  
 phenyl)-(4-methyl-piperazin-1-yl)-methanone;  
 (4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-  
 phenyl)-((R)-3-aminopyrrolidin-1-yl)-methanone;  
 30 (4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-  
 phenyl)-((S)-3-aminopyrrolidin-1-yl)-methanone hydrochloride;  
 4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-  
 (2-pyrrolidin-1-yl-ethyl)-benzamide;  
 4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-  
 35 (3-pyrrolidin-1-yl-propyl)-benzamide;

3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-  
 benzoic acid;  
 3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-  
 (1-methyl-piperidin-4-yl)-benzamide;  
 5 3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-  
 (2-pyrrolidin-1-yl-ethyl)-benzamide;  
 (3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-  
 phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone;  
 3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-  
 10 (2-morpholin-4-yl-ethyl)-benzamide;  
 (3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-  
 phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-  
 methanone;  
 (3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-  
 15 phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-4-{5-amino-6-[1-(2,6-  
 dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-benzamide;  
 N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-3-{5-amino-6-[1-(2,6-  
 dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-benzamide;  
 20 (3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-  
 phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-  
 methanone;  
 3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-  
 (3-pyrrolidin-1-yl-propyl)-benzamide;  
 25 (3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-  
 phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone;  
 (3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-  
 phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone hydrochloride;  
 (3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-  
 30 phenyl)-(4-methyl-piperazin-1-yl)-methanone; 1-(4-{5-amino-6-  
 [1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-  
 phenyl)-3-(2-morpholin-4-yl-ethyl)-urea;  
 (R)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid (4-  
 {5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-  
 35 yl)-phenyl)-amide;

1-(4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-phenyl)-3-(2-pyrrolidin-1-yl-ethyl)-urea;  
 4-methyl-piperazine-1-carboxylic acid (4-{5-amino-6-[1-(2-  
 chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-  
 5 amide;  
 1-(4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-phenyl)-3-(2-hydroxy-ethyl)-urea;  
 (S)-3-amino-pyrrolidine-1-carboxylic acid (4-{5-amino-6-[1-(2-  
 chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-  
 10 amide;  
 1-(4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-phenyl)-3-(1-methyl-piperidin-4-yl)-urea;  
 4-methyl-piperazine-1-carboxylic acid (4-{5-amino-6-[1-(2,6-  
 dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide;  
 15 1-(4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-phenyl)-3-(2-hydroxy-ethyl)-urea;  
 (S)-3-amino-pyrrolidine-1-carboxylic acid (4-{5-amino-6-[1-  
 (2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-  
 amide;  
 20 1-(4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-phenyl)-3-(1-methyl-piperidin-4-yl)-urea;  
 5-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-  
 thiophene-2-carboxylic acid;  
 {5-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-  
 25 thiophen-2-yl}-(4-methyl-piperazin-1-yl)-methanone;  
 {5-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-  
 thiophen-2-yl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;  
 {5-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-  
 thiophen-2-yl}-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone;  
 30 {5-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-  
 thiophen-2-yl}-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-  
 methanone;  
 5-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-  
 thiophene-2-carboxylic acid (2-morpholin-4-yl-ethyl)-amide;  
 35 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-{5-[(4-

methylpiperazin-1-yl)carbonyl]pyridin-2-yl}pyrazine-2-amine·  
 trifluoroacetate;  
 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-pyridin-4-yl-  
 pyrazin-2-ylamine;  
 5 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(1H-pyrrol-2-yl)-  
 pyrazin-2-ylamine;  
 (6-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-pyridin-3-yl)-(4-methyl-piperazin-1-yl)-  
 methanone;  
 10 (2-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-pyridin-4-yl)-(4-methyl-piperazin-1-yl)-  
 methanone;  
 (6-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-pyridin-2-yl)-(4-methyl-piperazin-1-yl)-  
 15 methanone;  
 (5-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-pyridin-3-yl)-(4-methyl-piperazin-1-yl)-  
 methanone;  
 (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 20 pyrazin-2-yl}-pyridin-2-yl)-(4-methyl-piperazin-1-yl)-  
 methanone;  
 6-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-  
 2-yl}-N-(2-morpholin-4-yl-ethyl)-nicotinamide;  
 5-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-  
 25 2-yl}-N-(2-morpholin-4-yl-ethyl)-nicotinamide;  
 6-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-  
 2-yl}-N-(3-morpholin-4-yl-propyl)-nicotinamide;  
 5-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-  
 2-yl}-N-(3-morpholin-4-yl-propyl)-nicotinamide;  
 30 (6-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-  
 pyrazin-2-yl}-pyridin-3-yl)-(4-isopropyl-piperazin-1-yl)-  
 methanone  
 [0035]

A JNK inhibitor as an active ingredient of the  
 35 prophylaxis or therapeutic agent for ALS in the present

invention includes all of naturally-occurring substances derived from microorganism etc., a semi-synthetic substance derived therefrom, and fully synthetic compounds. Examples thereof include, but are not limited to, SP600125 (see Table 4),  
5 JNK-IN-8, JNK Inhibitor IX, AS-601245/JNK Inhibitor V and the like. Preferably, it may be SP600125. In another embodiment, JNK inhibitor may be a JNK selective inhibitor. Examples of the JNK selective inhibitor include SP600125.

[0036]

10 A Syk inhibitor as an active ingredient of the prophylactic or therapeutic agent for ALS in the present invention includes all of naturally-occurring substances derived from microorganism etc., a semi-synthetic substances induced therefrom, and fully synthetic compounds. Examples  
15 thereof include, but are not limited to, Syk Inhibitor (see Table 4), fostamatinib disodium/R935788/R788, PRT-062607, GS-9973, TAK-659 and the like. Preferably, it may be Syk Inhibitor. In another embodiment, Syk inhibitor may be a Syk selective inhibitor. Examples of the Syk selective inhibitor  
20 include Syk Inhibitor.

[0037]

A JAK inhibitor as an active ingredient of the prophylactic or therapeutic agent for ALS in the present invention includes all of naturally-occurring substances  
25 derived from microorganism etc., a semi-synthetic substances derived therefrom, and a fully synthetic compounds. Examples thereof include, but are not limited to, JAK Inhibitor I (see Table 1), AT9283 (see Table 8), fedratinib/SAR302503/TG101348, pacritinib/SB1518, LY2784544, momelotinib/CYT387, AZD1480, XL-  
30 019, BMS-911543, NS-018, INCB039110, INCB47986, AT9283, lestaurtinib/CEP-701 and the like. Preferably, it may be JAK Inhibitor I or AT9283. In another embodiment, JAK inhibitor may be a JAK selective inhibitor. Examples of the JAK selective inhibitor include JAK Inhibitor I.

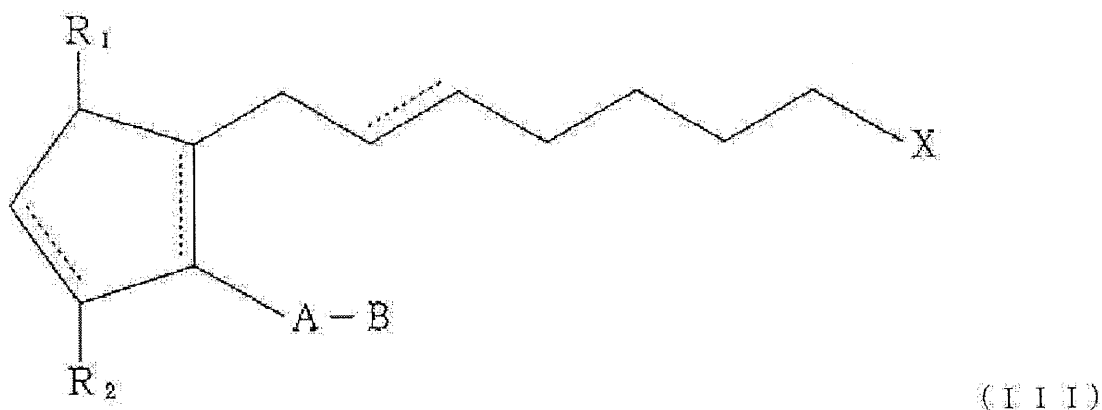
35 [0038]

A prostaglandin analogue as an active ingredient of the prophylaxis or therapeutic agent for ALS in the present invention includes all of naturally-occurring substances derived from mammal etc., a semi-synthetic substances derived therefrom, and fully synthetic compounds. Examples thereof include, but are not limited to, Bimatoprost or an analog thereof and the like.

[0039]

Here, the "analog of Bimatoprost" is, for example, a compound represented by the following formula (III):

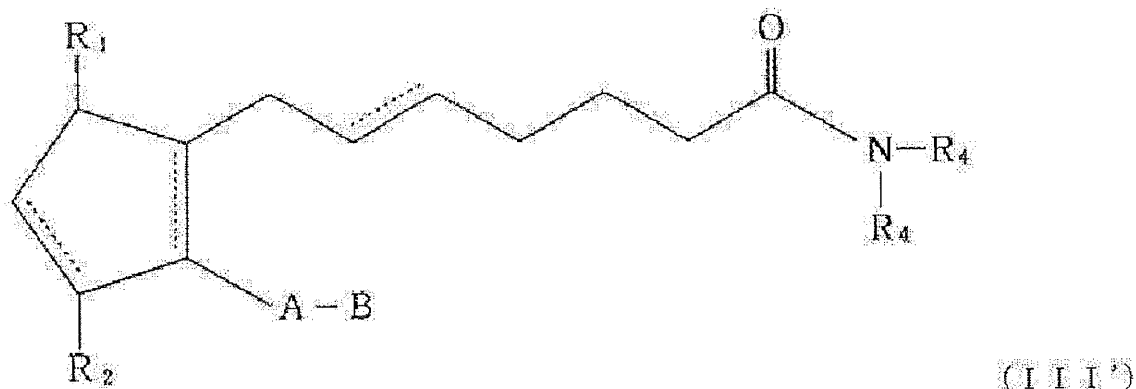
[0040]



[0041]

or the following formula (III'):

[0042]



[0043]

wherein

a bond with a dotted line is a single bond, or a double bond

possibly with a cis or trans configuration;

A is alkylene or an alkenylene group having 2 - 6 carbon atoms, and is optionally substituted by one or more hydroxy, oxo, alkyloxy or alkylcarboxy groups;

5 B is a cycloalkyl group having 3 - 7 carbon atoms, or an aryl group selected from the group consisting of hydrocarbylaryl and a heteroaryl group (hetero atom is selected from the group consisting of nitrogen, oxygen and sulfur atoms);

X is a group selected from the group consisting of halo, hydryl, 10 nitro, amino, azido, oxime, cyano, thiol, alkoxy and thioether groups;

one of  $R_1$  and  $R_2$  is  $=O$ ,  $-OH$  or  $-O(CO)R_6$ , and the other is  $-OH$  or  $-O(CO)R_6$ , or  $R_1$  is  $=O$  and  $R_2$  is  $H$ ;

$R_6$  is a saturated or unsaturated acyclic hydrocarbon group 15 having 1 - about 20 carbon atoms, or  $-(CH_2)_mR_7$ ;  
 $m$  is 0 - 10,  $R_7$  is a cycloalkyl group having 3 - 7 carbon atoms, or hydrocarbylaryl or a heteroaryl group (hetero atom is selected from the group consisting of nitrogen, oxygen and sulfur atoms); and

20 two  $R_4$  are the same or different and each is a hydrogen atom or a  $C_1 - C_3$  alkyl group.

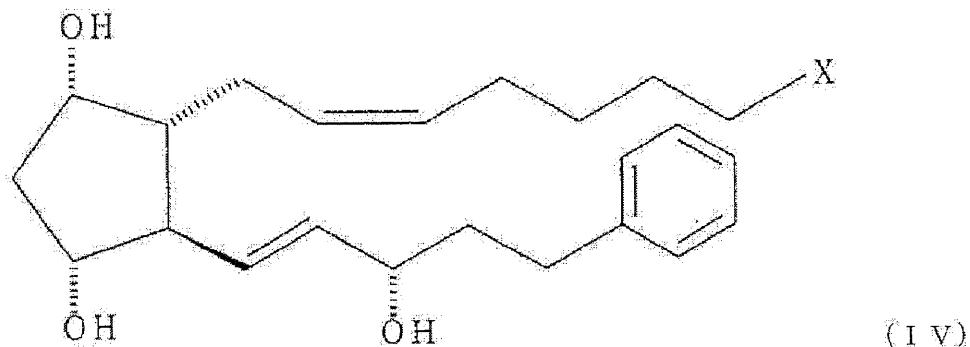
[0044]

Each term described as higher concept in the explanation of each group in the above-mentioned formulas (III) and (III') 25 (e.g., "alkylene or alkenylene group having 2 - 6 carbon atoms", "alkyloxy or alkylcarboxy group" for A, "cycloalkyl group having 3 - 7 carbon atoms", "hydrocarbylaryl group", "heteroaryl group" for B and  $R_7$ , "alkoxy group", "thioether group" for X, "saturated or unsaturated acyclic hydrocarbon group having 1 to about 20 carbon atoms" for  $R_6$ , " $C_1 - C_3$  alkyl group" for  $R_4$  etc.) is as defined in JP-A-2004-346080.

[0045]

Preferable examples of the analog of Bimatoprost include a compound represented by the following formula (IV):

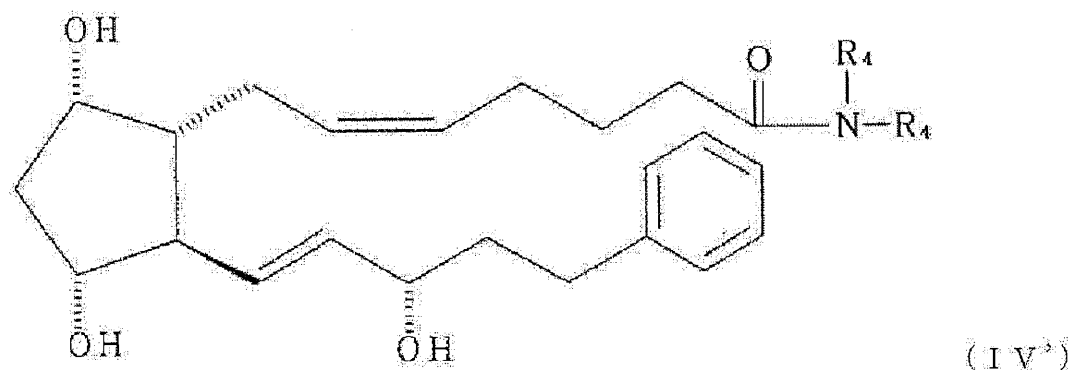
35 [0046]



[0047]

or the following formula (IV'):

5 [0048]



[0049]

wherein  $R_4$  is as defined above.

10 [0050]

Specific examples of the analog of Bimatoprost include the following compounds.

Cyclopentane heptenamide-5-cis-2-(3- $\alpha$ hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy,  $[1\alpha, 2\beta, 3\alpha, 5\alpha]$

15 Cyclopentane N,N-dimethylheptenamide-5-cis-2-(3- $\alpha$ hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy,  $[1\alpha, 2\beta, 3\alpha, 5\alpha]$

Cyclopentane heptenylmethoxide-5-cis-2-(3- $\alpha$ hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy,  $[1\alpha, 2\beta, 3\alpha, 5\alpha]$

20 Cyclopentane heptenylfluoride-5-cis-2-(3- $\alpha$ hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy,  $[1\alpha, 2\beta, 3\alpha, 5\alpha]$

Cyclopentane heptenylnitrate-5-cis-2-(3- $\alpha$ hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy,  $[1\alpha, 2\beta, 3\alpha, 5\alpha]$

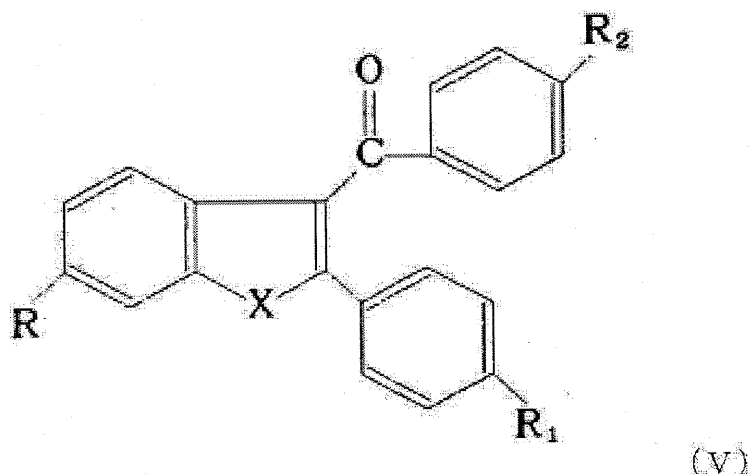
Cyclopentane heptenyliodide-5-cis-2-(3- $\alpha$ hydroxy-5-phenyl-1-

trans-pentenyl)-3,5-dihydroxy, [1 $\alpha$ ,2 $\beta$ ,3 $\alpha$ ,5 $\alpha$ ]  
 Cyclopentane hepteneamine-5-cis-2-(3- $\alpha$ hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, [1 $\alpha$ ,2 $\beta$ ,3 $\alpha$ ,5 $\alpha$ ]  
 Cyclopentane heptenecyanide-5-cis-2-(3- $\alpha$ hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, [1 $\alpha$ ,2 $\beta$ ,3 $\alpha$ ,5 $\alpha$ ]  
 Cyclopentane hepteneazide-5-cis-2-(3- $\alpha$ hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, [1 $\alpha$ ,2 $\beta$ ,3 $\alpha$ ,5 $\alpha$ ]  
 Cyclopentane heptene-5-cis-2-(3- $\alpha$ hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, [1 $\alpha$ ,2 $\beta$ ,3 $\alpha$ ,5 $\alpha$ ]  
 Cyclopentane N-isopropylheptenamide-5-cis-2-(3- $\alpha$ hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, [1 $\alpha$ ,2 $\beta$ ,3 $\alpha$ ,5 $\alpha$ ]  
 Cyclopentane N-methylheptenamide-5-cis-2-(3- $\alpha$ hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, [1 $\alpha$ ,2 $\beta$ ,3 $\alpha$ ,5 $\alpha$ ]  
 Cyclopentaneheptenamide-5-cis-2-(3- $\alpha$ hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3,5-dihydroxy, [1 $\alpha$ ,2 $\beta$ ,3 $\alpha$ ,5 $\alpha$ ]  
 [0051]

An estrogen receptor antagonist as an active ingredient of the prophylactic or therapeutic agent for ALS in the present invention includes all of naturally-occurring substances derived from microorganism etc., semi-synthetic substances derived therefrom, and fully synthetic compounds. Examples thereof include, but are not limited to, Raloxifene, an analog thereof and the like.  
 [0052]

Examples of the "analog of Raloxifene" include a compound represented by the following formula (V):

[0053]



[0054]

wherein

5 X is -S- or -S(O)-;

R is a hydrogen atom, a hydroxy group or a C<sub>1</sub>-C<sub>5</sub> alkoxy group;

R<sub>1</sub> is a hydrogen atom, a hydroxy group, a C<sub>1</sub>-C<sub>5</sub> alkoxy group, a  
C<sub>1</sub>-C<sub>5</sub> acyloxy group, a C<sub>1</sub>-C<sub>5</sub> alkoxy carbonyloxy group, a  
benzoyloxy group, adamantoyloxy group, a chlorine atom, a  
10 bromine atom, or -O(CH<sub>2</sub>)<sub>2</sub>N(R<sub>3</sub>)R<sub>4</sub>;

R<sub>2</sub> is a hydrogen atom, a hydroxy group, a C<sub>1</sub>-C<sub>5</sub> alkoxy group, or  
-O(CH<sub>2</sub>)<sub>2</sub>N(R<sub>3</sub>)R<sub>4</sub>; and

R<sub>3</sub> and R<sub>4</sub> are each independently a C<sub>1</sub>-C<sub>4</sub> alkyl group, or R<sub>3</sub> and  
R<sub>4</sub> are bonded to the adjacent nitrogen atom to form a hetero  
15 ring selected from pyrrolidino, piperidino, hexamethyleneimino  
and morpholino groups.

[0055]

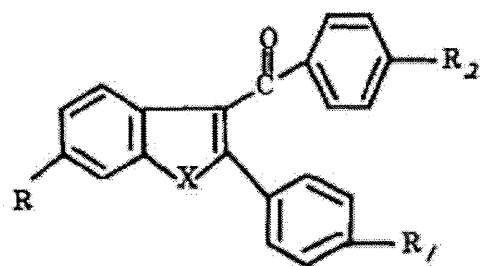
Each term described as higher concept in the explanation  
of each group in the above-mentioned formula (V) (e.g., "C<sub>1</sub>-C<sub>5</sub>  
20 alkoxy group" for R, R<sub>1</sub> and R<sub>2</sub>, "C<sub>1</sub>-C<sub>5</sub> acyloxy group", "C<sub>1</sub>-C<sub>5</sub>  
alkoxy carbonyloxy group" for R<sub>1</sub>, "C<sub>1</sub>-C<sub>4</sub> alkyl group" for R<sub>3</sub> and  
R<sub>4</sub> etc.) is as defined in JP-A-52-53851.

[0056]

Specific examples of the analog of Raloxifene include the  
25 compounds described in Table 1 (excerpt from the tables in JP-  
A-52-53851 with partial modification).

[0057]

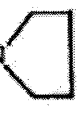
[Table 1-1]



| compound          |                                                                                                                        |                   |   |
|-------------------|------------------------------------------------------------------------------------------------------------------------|-------------------|---|
| R                 | R <sub>1</sub>                                                                                                         | R <sub>2</sub>    | X |
| -OH               | H                                                                                                                      | H                 | S |
| H                 | H                                                                                                                      | -OH               | S |
| -OCH <sub>3</sub> | H                                                                                                                      | -OCH <sub>3</sub> | S |
| -OH               | H                                                                                                                      | -OH               | S |
| -OH               | -OH                                                                                                                    | H                 | S |
| -OH               | -OH                                                                                                                    | -OCH <sub>3</sub> | S |
| H                 | -OC <sub>2</sub> H <sub>4</sub> -N  | -OCH <sub>3</sub> | S |

[0058]

[Table 1-2]

| compound        |                                                                                                                      |                                                                                                                      |   |
|-----------------|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|---|
| R               | R <sub>1</sub>                                                                                                       | R <sub>2</sub>                                                                                                       | X |
| H               | $-\text{OC}_2\text{H}_4\text{N}(\text{C}_2\text{H}_5)_2$                                                             | $-\text{OCH}_3$                                                                                                      | S |
| H               | $-\text{OC}_2\text{H}_4\text{N}$    | $-\text{OC}_2\text{H}_4\text{N}$    | S |
| H               | $-\text{OCH}_3$                                                                                                      | $-\text{OC}_2\text{H}_4\text{N}$    | S |
| H               | H                                                                                                                    | $-\text{OC}_2\text{H}_4\text{N}$   | S |
| H               | $-\text{OC}_2\text{H}_4\text{N}$  | $-\text{OCH}_3$                                                                                                      | S |
| H               | $-\text{OC}_2\text{H}_4\text{N}$  | $-\text{OCH}_3$                                                                                                      | S |
| $-\text{OCH}_3$ | $-\text{OCH}_3$                                                                                                      | $-\text{OC}_2\text{H}_4\text{N}$  | S |
| H               | $-\text{OH}$                                                                                                         | $-\text{OC}_2\text{H}_4\text{N}$  | S |
| H               | $-\text{O}-\text{CO}-\text{CH}_3$                                                                                    | $-\text{OC}_2\text{H}_4\text{N}$  | S |

[0059]

[Table 1-3]

| compound          |                                                                                            |                                                                                                                       |   |
|-------------------|--------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|---|
| R                 | R <sub>1</sub>                                                                             | R <sub>2</sub>                                                                                                        | X |
| -OCH <sub>3</sub> | H                                                                                          | -OC <sub>2</sub> H <sub>4</sub> N    | S |
| H                 | -OCH <sub>3</sub>                                                                          | -OC <sub>2</sub> H <sub>4</sub> N    | S |
| H                 | -OCH <sub>3</sub>                                                                          | -OC <sub>2</sub> H <sub>4</sub> N    | S |
| H                 | -OCH <sub>3</sub>                                                                          | -OC <sub>2</sub> H <sub>4</sub> N-<br>(CH(CH <sub>3</sub> )) <sub>2</sub> ) <sub>2</sub>                              | S |
| H                 | Cl                                                                                         | -OC <sub>2</sub> H <sub>4</sub> N  | S |
| H                 | -O-CO-CH <sub>2</sub> CH <sub>3</sub>                                                      | -OC <sub>2</sub> H <sub>4</sub> N  | S |
| H                 | -O-CO-O-CH <sub>2</sub> CH <sub>3</sub>                                                    | -OC <sub>2</sub> H <sub>4</sub> N  | S |
| H                 | -O-CO-(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>                                      | -OC <sub>2</sub> H <sub>4</sub> N  | S |
| H                 | -O-CO-  | -OC <sub>2</sub> H <sub>4</sub> N  | S |
| H                 | -O-CO-adamantyl                                                                            | -OC <sub>2</sub> H <sub>4</sub> N  | S |

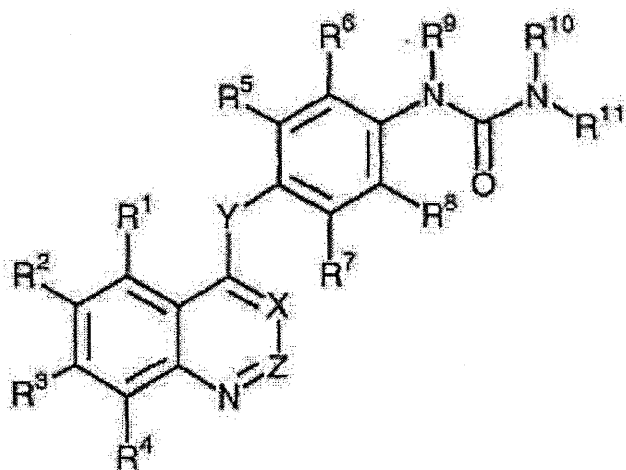
[0060]

As the active ingredient of the prophylactic or therapeutic agent for ALS of the present invention, which does not belong to any of the above-mentioned kinase inhibitor, prostaglandin analogue, and estrogen receptor antagonist, Tivozanib, SB 216763, Cdk2 Inhibitor II, BUDESONIDE, RIBOFLAVIN, alpha-TOCHOPHEROL, AMODIAQUINE, SU9516, Sunitinib, GSK-3 Inhibitor XIII, Bisindolylmaleimide I, HYDROQUINONE, FLUNISOLIDE, MGCD-265, Indirubin-3'-monoxime, HYDRASTINE (1R,9S), PIPERINE, BUTAMBEN, Axitinib, APOMORPHINE, FENBUFEN, Bosutinib (SKI-606), Weel Inhibitor and Cdk2 Inhibitor IV, NU6140 (see Tables 4-1 - 4-5), 3-hydroxybutyric acid (see Table 7), Imatinib, Nilotinib, Rebastinib, Bafetinib (see Table 8), and analogs of Tivozanib, analogs of Sunitinib, analogs of Axitinib and analogs of Bosutinib (SKI-606) can be mentioned.

[0061]

Here, the "analog of Tivozanib" is, for example, a compound represented by the following formula (VI):

[0062]



(VI)

[0063]

wherein

X and Z are each CH or N,

Y is O or S,

R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are each independently a hydrogen atom, a C<sub>1-6</sub> alkyl group, a C<sub>1-6</sub> alkoxy group, a C<sub>2-6</sub> alkenyl group, a C<sub>2-6</sub>

alkynyl group, a nitro group, or an amino group, wherein the C<sub>1-6</sub> alkyl group, C<sub>1-6</sub> alkoxy group, C<sub>2-6</sub> alkenyl group, and C<sub>2-6</sub> alkynyl group are optionally substituted by a halogen atom, a hydroxyl group, a C<sub>1-4</sub> alkyl group, a C<sub>1-4</sub> alkoxy carbonyl group, an amino group (1 or 2 hydrogen atoms of the amino group may be each substituted by a C<sub>1-4</sub> alkyl group (the C<sub>1-4</sub> alkyl group is optionally substituted by a hydroxyl group or a C<sub>1-4</sub> alkoxy group)), a group R<sup>12</sup>R<sup>13</sup>N-C(=O)-O- (R<sup>12</sup> and R<sup>13</sup> are each independently a hydrogen atom or a C<sub>1-4</sub> alkyl group (the C<sub>1-4</sub> alkyl group is optionally substituted by a hydroxyl group or a C<sub>1-4</sub> alkoxy group)), or group R<sup>14</sup>-(S)<sub>m</sub>- (R<sup>14</sup> is a saturated or unsaturated 3-7-membered carbon cyclic group or heterocyclic group optionally substituted by a C<sub>1-4</sub> alkyl group, m is 0 or 1), R<sup>4</sup> is a hydrogen atom,

R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are each independently a hydrogen atom, a halogen atom, a C<sub>1-4</sub> alkyl group, a C<sub>1-4</sub> alkoxy group, a C<sub>1-4</sub> alkylthio group, a trifluoromethyl group, a nitro group, or an amino group,

R<sup>9</sup> and R<sup>10</sup> are each independently a hydrogen atom, a C<sub>1-6</sub> alkyl group or a C<sub>1-4</sub> alkyl carbonyl group, wherein the alkyl moiety of the C<sub>1-6</sub> alkyl group or C<sub>1-4</sub> alkyl carbonyl group is optionally substituted by a halogen atom, a C<sub>1-4</sub> alkoxy group, an amino group (the amino group is optionally substituted by a C<sub>1-4</sub> alkyl group optionally substituted by a C<sub>1-4</sub> alkoxy group), or a saturated or unsaturated 3-7-membered carbon cyclic group or heterocyclic group,

R<sup>11</sup> is an azolyl group, one or more hydrogen atoms on the azolyl group are optionally substituted by a halogen atom, a C<sub>1-4</sub> alkyl group, a C<sub>1-4</sub> alkoxy group, a C<sub>1-4</sub> alkylthio group, a trifluoromethyl group, a nitro group, an amino group (1 or 2 hydrogen atoms on the amino group are each optionally substituted by a C<sub>1-4</sub> alkyl group), a C<sub>1-4</sub> alkoxy carbonyl C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkyl carbonyl, or C<sub>3-5</sub> cyclic alkyl group.

[0064]

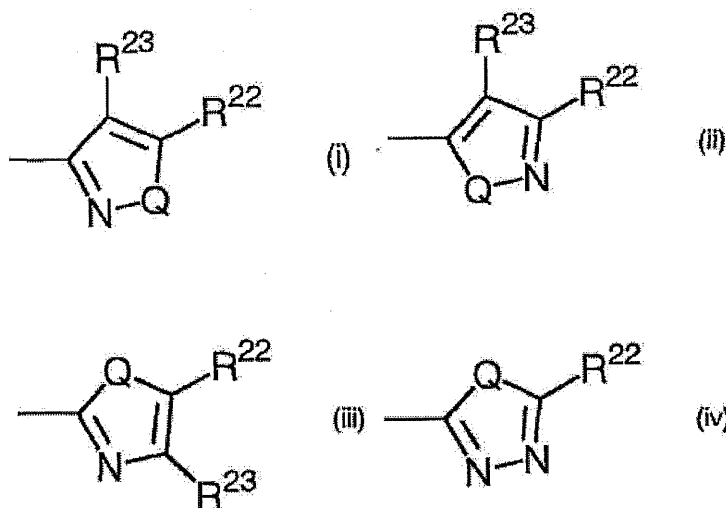
Each term described as higher concept in the explanation

of each group in the above-mentioned formula (VI) (e.g., "C<sub>1-6</sub> alkyl group", "C<sub>1-6</sub> alkoxy group", "C<sub>2-6</sub> alkenyl group", "C<sub>2-6</sub> alkynyl group", "C<sub>1-4</sub> alkyl group", "C<sub>1-4</sub> alkoxycarbonyl group", "C<sub>1-4</sub> alkoxy group", "saturated or unsaturated 3-7-membered  
5 carbon cyclic group or heterocyclic group" etc. for R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup>) is as defined in WO 02/088110.

[0065]

In the above-mentioned formula (VI), R<sup>11</sup> is preferably a group represented by the following formula (i)-(iv):

10 [0066]



[0067]

wherein

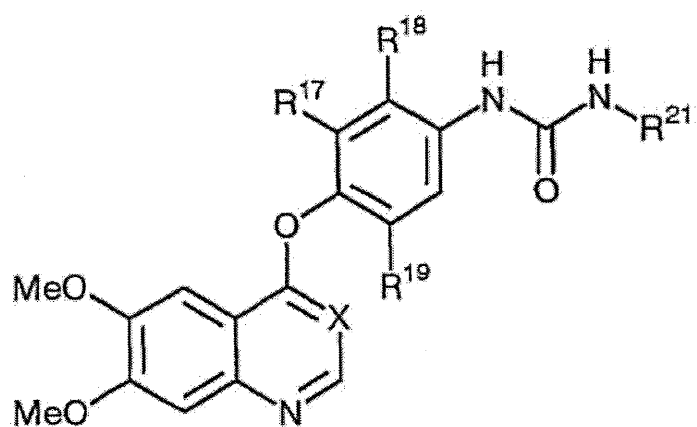
Q is O, S or NH,

15 R<sup>22</sup> and R<sup>23</sup> are each independently a hydrogen atom, a halogen atom, a C<sub>1-4</sub> alkyl group, a C<sub>1-4</sub> alkoxy group, a C<sub>1-4</sub> alkylthio group, a trifluoromethyl group, a nitro group, an amino group (1 or 2 hydrogen atoms on the amino group are each optionally substituted by a C<sub>1-4</sub> alkyl group), C<sub>1-4</sub> alkoxycarbonyl C<sub>1-4</sub> alkyl,  
20 C<sub>1-4</sub> alkylcarbonyl, or C<sub>3-5</sub> cyclic alkyl group.

[0068]

Specific examples of the analog of Tivozanib include the compounds shown by the following formula and Tables 2-1 - 2-3 (excerpt from Table 1 in WO 02/088110 with partial  
25 modification).

[0069]



[0070]

5 [Table 2-1]

| compound | X  | R <sup>17</sup> | R <sup>18</sup> | R <sup>19</sup> | R <sup>21</sup> | Q  | R <sup>22</sup> | R <sup>23</sup> |
|----------|----|-----------------|-----------------|-----------------|-----------------|----|-----------------|-----------------|
| 1        | CH | Cl              | H               | H               | (i)             | O  | H               | H               |
| 2        | CH | Cl              | H               | H               | (ii)            | O  | CH <sub>3</sub> | H               |
| 3        | CH | F               | H               | H               | (i)             | O  | H               | H               |
| 4        | CH | H               | Cl              | H               | (i)             | O  | CH <sub>3</sub> | H               |
| 5        | CH | H               | Cl              | H               | (ii)            | O  | CH <sub>3</sub> | H               |
| 6        | CH | H               | F               | H               | (ii)            | O  | CH <sub>3</sub> | H               |
| 7        | CH | F               | H               | H               | (ii)            | O  | CH <sub>3</sub> | H               |
| 8        | CH | F               | H               | H               | (i)             | O  | CH <sub>3</sub> | H               |
| 9        | CH | H               | F               | H               | (i)             | O  | CH <sub>3</sub> | H               |
| 10       | N  | H               | H               | H               | (i)             | O  | CH <sub>3</sub> | H               |
| 11       | N  | H               | H               | H               | (ii)            | O  | CH <sub>3</sub> | H               |
| 12       | N  | H               | Cl              | H               | (i)             | O  | CH <sub>3</sub> | H               |
| 13       | N  | H               | Cl              | H               | (ii)            | O  | CH <sub>3</sub> | H               |
| 14       | N  | Cl              | H               | H               | (i)             | O  | CH <sub>3</sub> | H               |
| 15       | N  | Cl              | H               | H               | (ii)            | O  | CH <sub>3</sub> | H               |
| 16       | N  | H               | H               | H               | (ii)            | S  | CH <sub>3</sub> | H               |
| 17       | N  | H               | Cl              | H               | (ii)            | S  | CH <sub>3</sub> | H               |
| 18       | N  | Cl              | H               | H               | (ii)            | S  | CH <sub>3</sub> | H               |
| 19       | CH | Cl              | H               | H               | (ii)            | NH | H               | H               |
| 20       | CH | H               | F               | H               | (ii)            | NH | H               | H               |
| 21       | CH | H               | F               | H               | (iii)           | S  | CH <sub>3</sub> | H               |
| 22       | CH | H               | Cl              | H               | (iii)           | S  | H               | CH <sub>3</sub> |
| 23       | CH | H               | F               | H               | (iii)           | S  | CH <sub>3</sub> | CH <sub>3</sub> |
| 24       | CH | H               | Cl              | H               | (iii)           | S  | CH <sub>3</sub> | CH <sub>3</sub> |
| 25       | CH | Cl              | H               | H               | (iii)           | S  | CH <sub>3</sub> | CH <sub>3</sub> |
| 26       | CH | H               | CF <sub>3</sub> | H               | (iii)           | S  | CH <sub>3</sub> | CH <sub>3</sub> |

[0071]

[Table 2-2]

|    |    |                 |                 |   |       |   |                 |                 |
|----|----|-----------------|-----------------|---|-------|---|-----------------|-----------------|
| 27 | CH | H               | F               | H | (iii) | S | H               | H               |
| 28 | CH | H               | F               | H | (iii) | S | H               | CH <sub>3</sub> |
| 29 | CH | H               | F               | H | (iii) | S | H               | A               |
| 30 | CH | H               | F               | H | (iii) | S | H               | tBu             |
| 31 | CH | H               | Cl              | H | (iii) | S | H               | A               |
| 32 | CH | H               | Cl              | H | (iii) | S | Br              | H               |
| 33 | CH | H               | Cl              | H | (iii) | S | H               | tBu             |
| 34 | CH | H               | Cl              | H | (iii) | S | Cl              | H               |
| 35 | CH | H               | F               | H | (iii) | S | Br              | H               |
| 36 | CH | H               | F               | H | (iii) | S | Ac              | CH <sub>3</sub> |
| 37 | CH | H               | F               | H | (iii) | S | Cl              | H               |
| 38 | N  | H               | Cl              | H | (iii) | S | H               | H               |
| 39 | N  | H               | Cl              | H | (iii) | S | CH <sub>3</sub> | H               |
| 40 | N  | H               | Cl              | H | (iii) | S | CH <sub>3</sub> | CH <sub>3</sub> |
| 41 | N  | H               | Cl              | H | (iii) | S | H               | CH <sub>3</sub> |
| 42 | N  | H               | H               | H | (iii) | S | H               | H               |
| 43 | N  | H               | H               | H | (iii) | S | CH <sub>3</sub> | H               |
| 44 | N  | H               | H               | H | (iii) | S | H               | CH <sub>3</sub> |
| 45 | N  | H               | H               | H | (iii) | S | CH <sub>3</sub> | CH <sub>3</sub> |
| 46 | N  | Cl              | H               | H | (iii) | S | H               | H               |
| 47 | N  | Cl              | H               | H | (iii) | S | CH <sub>3</sub> | H               |
| 48 | N  | Cl              | H               | H | (iii) | S | H               | CH <sub>3</sub> |
| 49 | N  | Cl              | H               | H | (iii) | S | CH <sub>3</sub> | CH <sub>3</sub> |
| 50 | CH | H               | H               | H | (iv)  | S | CF <sub>3</sub> | H               |
| 51 | CH | H               | F               | H | (iv)  | S | CF <sub>3</sub> | H               |
| 52 | CH | F               | H               | H | (iv)  | S | CF <sub>3</sub> | H               |
| 53 | CH | CH <sub>3</sub> | CH <sub>3</sub> | H | (iv)  | S | CF <sub>3</sub> | H               |

[0072]

[Table 2-3]

|    |    |                 |                 |                 |      |   |                 |   |
|----|----|-----------------|-----------------|-----------------|------|---|-----------------|---|
| 54 | CH | H               | H               | H               | (iv) | S | CH <sub>3</sub> | H |
| 55 | CH | H               | CH <sub>3</sub> | H               | (iv) | S | CH <sub>3</sub> | H |
| 56 | CH | CH <sub>3</sub> | H               | H               | (iv) | S | CH <sub>3</sub> | H |
| 57 | CH | CH <sub>3</sub> | CH <sub>3</sub> | H               | (iv) | S | CH <sub>3</sub> | H |
| 58 | CH | H               | F               | H               | (iv) | S | CH <sub>3</sub> | H |
| 59 | CH | H               | H               | H               | (iv) | S | Et              | H |
| 60 | CH | H               | CH <sub>3</sub> | H               | (iv) | S | Et              | H |
| 61 | CH | CH <sub>3</sub> | H               | H               | (iv) | S | Et              | H |
| 62 | CH | CH <sub>3</sub> | CH <sub>3</sub> | H               | (iv) | S | Et              | H |
| 63 | CH | H               | F               | H               | (iv) | S | Et              | H |
| 64 | CH | F               | H               | H               | (iv) | S | Et              | H |
| 65 | CH | H               | Cl              | H               | (iv) | S | Et              | H |
| 66 | CH | Cl              | H               | H               | (iv) | S | Et              | H |
| 67 | CH | H               | Cl              | H               | (iv) | S | cPr             | H |
| 68 | CH | Cl              | H               | H               | (iv) | S | cPr             | H |
| 69 | CH | H               | CH <sub>3</sub> | CH <sub>3</sub> | (iv) | S | cPr             | H |
| 70 | CH | H               | F               | H               | (iv) | S | EtS             | H |
| 71 | CH | CH <sub>3</sub> | CH <sub>3</sub> | H               | (iv) | S | EtS             | H |
| 72 | CH | H               | Cl              | H               | (iv) | S | CF <sub>3</sub> | H |
| 73 | CH | Cl              | H               | H               | (iv) | S | CF <sub>3</sub> | H |
| 74 | CH | H               | F               | H               | (iv) | S | tBu             | H |
| 75 | CH | CH <sub>3</sub> | CH <sub>3</sub> | H               | (iv) | S | tBu             | H |

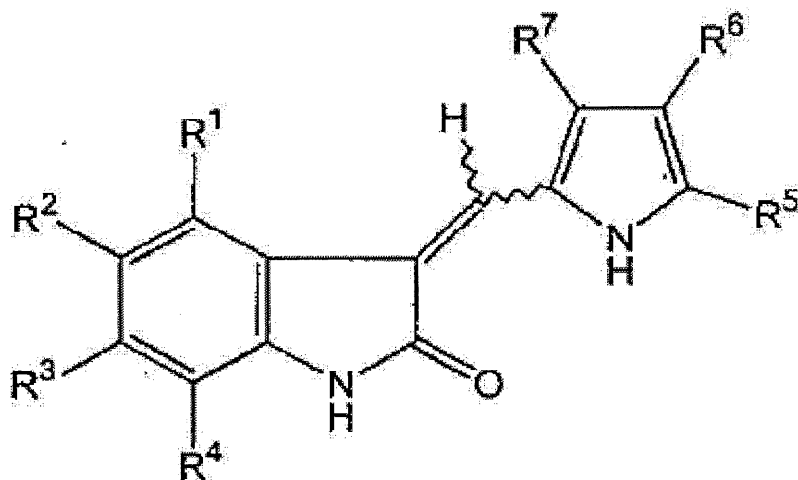
5 [0073]

In Tables 2-1 - 2-3, A is ethoxycarbonylmethyl, tBu is t-butyl, Ac is acetyl, Et is ethyl, cPr is cyclopropyl, and EtS is ethylthio, respectively.

[0074]

Examples of the analog of Pazopanib include a 3-pyrrole-substituted 2-indolinone compound represented by the following formula (VII):

5 [0075]



(VII)

[0076]

wherein

R<sup>1</sup> is selected from the group consisting of hydrogen, halo,  
10 alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy,  
alkoxy, -(CO)R<sup>15</sup>, -NR<sup>13</sup>R<sup>14</sup>, -(CH<sub>2</sub>)<sub>r</sub>R<sup>16</sup> and -C(O)NR<sup>8</sup>R<sup>9</sup>,

R<sup>2</sup> is selected from the group consisting of hydrogen, halo,  
alkyl, trihalomethyl, hydroxy, alkoxy, cyano, -NR<sup>13</sup>R<sup>14</sup>, -  
NR<sup>13</sup>C(O)R<sup>14</sup>, -C(O)R<sup>15</sup>, aryl, heteroaryl, -S(O)<sub>2</sub>NR<sup>13</sup>R<sup>14</sup> and -SO<sub>2</sub>R<sup>20</sup>  
15 (wherein R<sup>20</sup> is alkyl, aryl, aralkyl, heteroaryl or  
heteroaralkyl),

R<sup>3</sup> is hydrogen, halogen, alkyl, trihalomethyl, hydroxy, alkoxy,  
-(CO)R<sup>15</sup>, -NR<sup>13</sup>R<sup>14</sup>, aryl, heteroaryl, -NR<sup>13</sup>S(O)<sub>2</sub>R<sup>14</sup>, -S(O)<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>,  
-NR<sup>13</sup>C(O)R<sup>14</sup>, -NR<sup>13</sup>C(O)OR<sup>14</sup> and -SO<sub>2</sub>R<sup>20</sup> (wherein R<sup>20</sup> is selected  
20 from the group consisting of alkyl, aryl, aralkyl, heteroaryl  
and heteroaralkyl),

R<sup>4</sup> is selected from the group consisting of hydrogen, halogen,  
alkyl, hydroxy, alkoxy and -NR<sup>13</sup>R<sup>14</sup>,

R<sup>5</sup> is selected from the group consisting of hydrogen, alkyl and  
25 -C(O)R<sup>10</sup>,

R<sup>6</sup> is selected from the group consisting of hydrogen, alkyl and

$-C(O)R^{10}$ ,

$R^7$  is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl,  $-C(O)R^{17}$  and  $-C(O)R^{10}$ , or  $R^6$  and  $R^7$  may be joined to form a group selected from the group consisting of -

5  $(CH_2)_4-$ ,  $-(CH_2)_5-$  and  $-(CH_2)_6-$ ;

at least one of  $R^5$ ,  $R^6$  and  $R^7$  should be  $-C(O)R^{10}$ ;

$R^8$  and  $R^9$  are each independently selected from the group consisting of hydrogen, alkyl and aryl,

$R^{10}$  is selected from the group consisting of hydroxy, alkoxy, 10 aryloxy,  $-N(R^{11})(CH_2)_nR^{12}$  and  $-NR^{13}R^{14}$ ,

$R^{11}$  is selected from the group consisting of hydrogen and alkyl,

$R^{12}$  is selected from the group consisting of  $-NR^{13}R^{14}$ , hydroxy,  $-C(O)R^{15}$ , aryl, heteroaryl,  $-N^+(O^-)R^{13}R^{14}$ ,  $N(OH)R^{13}$ , and  $-NHC(O)R^a$  (wherein  $R^a$  is unsubstituted alkyl, haloalkyl, or aralkyl),

15  $R^{13}$  and  $R^{14}$  are each independently selected from the group consisting of hydrogen, alkyl, cyanoalkyl, cycloalkyl, aryl and heteroaryl, or  $R^{13}$  and  $R^{14}$  may be joined to form a heterocyclic group;

$R^{15}$  is selected from the group consisting of hydrogen, hydroxy, 20 alkoxy and aryloxy,

$R^{16}$  is selected from the group consisting of hydroxy,  $-C(O)R^{15}$ ,  $-NR^{13}R^{14}$  and  $-C(O)NR^{13}R^{14}$ ,

$R^{17}$  is selected from the group consisting of alkyl, cycloalkyl, aryl and heteroaryl,

25  $R^{20}$  is alkyl, aryl, aralkyl or heteroaryl; and

$n$  and  $r$  are each independently 1, 2, 3, or 4.

[0077]

In the above-mentioned formula (VII), preferably,

$R^1$  is selected from the group consisting of hydrogen, halo, 30 alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy,  $-C(O)R^{15}$ ,  $-NR^{13}R^{14}-(CH_2)_rR^{16}$  and  $-C(O)NR^8R^9$ ,

$R^2$  is selected from the group consisting of hydrogen, halo, alkyl, trihalomethyl, hydroxy, alkoxy,  $-NR^{13}R^{14}$ ,  $-NR^{13}C(O)R^{14}$ ,  $-C(O)R^{15}$ , aryl, heteroaryl, and  $-S(O)_2NR^{13}R^{14}$ ,

35  $R^3$  is selected from the group consisting of hydrogen, halogen,

alkyl, trihalomethyl, hydroxy, alkoxy,  $-(CO)R^{15}$ ,  $-NR^{13}R^{14}$ , aryl, heteroaryl,  $-NR^{13}S(O)_2R^{14}$ ,  $-S(O)_2NR^{13}R^{14}$ ,  $-NR^{13}C(O)R^{14}$ , and  $-NR^{13}C(O)OR^{14}$ ,

$R^4$  is selected from the group consisting of hydrogen, halogen,  
5 alkyl, hydroxy, alkoxy and  $-NR^{13}R^{14}$ ,

$R^5$  is selected from the group consisting of hydrogen, alkyl and  $-C(O)R^{10}$ ,

$R^6$  is selected from the group consisting of hydrogen, alkyl and  $-C(O)R^{10}$ ,

10  $R^7$  is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl,  $-C(O)R^{17}$  and  $-C(O)R^{10}$ ,

$R^6$  and  $R^7$  may be joined to form a group selected from the group consisting of  $-(CH_2)_4-$ ,  $-(CH_2)_5-$  and  $-(CH_2)_6-$ ;

at least one of  $R^5$ ,  $R^6$  and  $R^7$  should be  $-C(O)R^{10}$ ;

15  $R^8$  and  $R^9$  are each selected from the group consisting of independently hydrogen, alkyl and aryl,

$R^{10}$  is selected from the group consisting of hydroxy, alkoxy, aryloxy,  $-N(R^{11})(CH_2)_nR^{12}$  and  $-NR^{13}R^{14}$ ,

$R^{11}$  is selected from the group consisting of hydrogen and alkyl,

20  $R^{12}$  is selected from the group consisting of  $-NR^{13}R^{14}$ , hydroxy,  $-C(O)R^{15}$ , aryl and heteroaryl,

$R^{13}$  and  $R^{14}$  are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl and heteroaryl,

$R^{13}$  and  $R^{14}$  may be joined to form a group selected from the  
25 group consisting of  $-(CH_2)_4-$ ,  $-(CH_2)_5-$ ,  $-(CH_2)_2O(CH_2)_2-$ , and  $(CH_2)_2N(CH_3)(CH_2)_2-$ ;

$R^{15}$  is selected from the group consisting of hydrogen, hydroxy, alkoxy and aryloxy,

$R^{16}$  is selected from the group consisting of hydroxy,  $-C(O)R^{15}$ ,  
30  $-NR^{13}R^{14}$  and  $-C(O)NR^{13}R^{14}$ ,

$R^{17}$  is selected from the group consisting of alkyl, cycloalkyl, aryl and heteroaryl, and

$n$  and  $r$  are each independently 1, 2, 3, or 4.

[0078]

35 Each term described as higher concept in the explanation

of each group in the above-mentioned formula (VII) (e.g.,  
"halo", "alkyl", "cycloalkyl", "aryl", "heteroaryl",  
"heteroalicycle", "alkoxy" etc. for R<sup>1</sup>) is as defined in WO  
01/060814 (National Publication of International Patent  
5 Application No. 2003-523340).

[0079]

Specific examples of the analog of Sunitinib include the  
compounds shown by Tables 3-1 - 3-25 (excerpt from Tables 1 -  
25 in National Publication of International Patent Application  
10 No. 2003-523340 with partial modification).

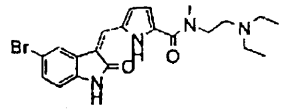
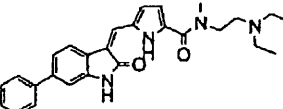
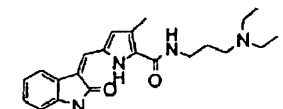
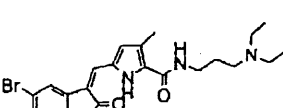
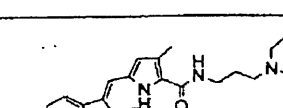
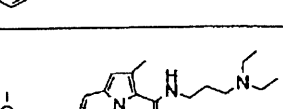
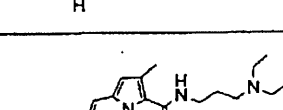
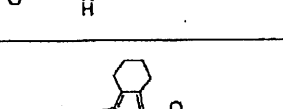
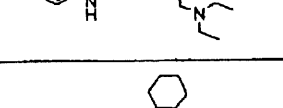
[0080]

[Table 3-1]

| compound | Structure | Name                                                                                                                    |
|----------|-----------|-------------------------------------------------------------------------------------------------------------------------|
| 1        |           | 4-Methyl-5-(2-oxo-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-2-carboxylic acid                                        |
| 2        |           | 4-Methyl-5-(1-methyl-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-2-carboxylic acid                               |
| 3        |           | 4-Methyl-5-(2-oxo-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-2-carboxylic acid methyl ester                           |
| 4        |           | 5-(5-Chloro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-4-methyl-1H-pyrrole-2-carboxylic acid ethyl ester                   |
| 5        |           | 5-(5-Chloro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-4-methyl-1H-pyrrole-2-carboxylic acid                               |
| 6        |           | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-4-methyl-1H-pyrrole-2-carboxylic acid (3-pyrrolidin-1-ylpropyl)amide |
| 7        |           | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-4-methyl-1H-pyrrole-2-carboxylic acid (3-diethylaminopropyl)amide    |
| 8        |           | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-2-carboxylic acid (2-diethylaminoethyl)amide              |
| 9        |           | 5-(2-Oxo-6-phenyl-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-2-carboxylic acid (2-diethylaminoethyl)amide             |

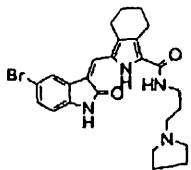
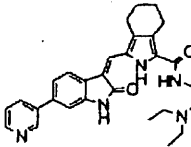
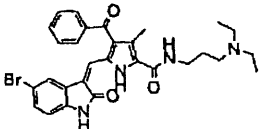
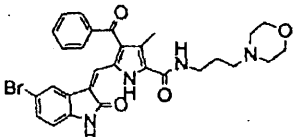
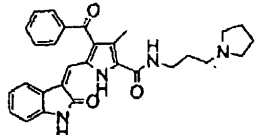
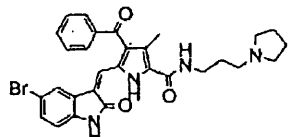
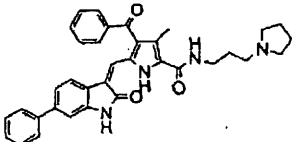
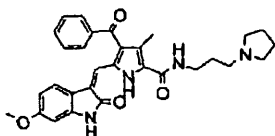
[0081]

[Table 3-2]

|    |                                                                                     |                                                                                                                                  |
|----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| 10 |    | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-2-carboxylic acid (2-diethylaminoethyl)methylamide                 |
| 11 |    | 5-(2-Oxo-6-phenyl-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-2-carboxylic acid (2-diethylaminoethyl)methylamide                |
| 12 |    | 3-Methyl-5-(2-oxo-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-2-carboxylic acid (3-diethylaminopropyl)amide                     |
| 13 |    | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-3-methyl-1H-pyrrole-2-carboxylic acid (3-diethylaminopropyl)amide             |
| 14 |   | 3-Methyl-5-(2-oxo-6-phenyl-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-2-carboxylic acid (3-diethylaminopropyl)amide            |
| 15 |  | 5-(5-Methoxy-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-3-methyl-1H-pyrrole-2-carboxylic acid (3-diethylaminopropyl)amide           |
| 16 |  | 5-(6-Methoxy-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-3-methyl-1H-pyrrole-2-carboxylic acid (3-diethylaminopropyl)amide           |
| 17 |  | 3-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid (2-diethylaminoethyl)amide  |
| 18 |  | 3-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid (3-diethylaminopropyl)amide |

[0082]

[Table 3-3]

|    |                                                                                     |                                                                                                                                        |
|----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| 19 |    | 3-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid (3-pyrrolidin-1-ylpropyl)amide    |
| 20 |    | 3-(2-Oxo-6-pyridin-3-yl-1,2-dihydroindol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid (2-diethylaminoethyl)amide |
| 21 |    | 4-Benzoyl-5-(5-bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-3-methyl-1H-pyrrole-2-carboxylic acid (3-diethylaminopropyl)amide         |
| 22 |   | 4-Benzoyl-5-(5-bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-3-methyl-1H-pyrrole-2-carboxylic acid (3-morpholin-4-ylpropyl)amide       |
| 23 |  | 4-Benzoyl-3-methyl-5-(2-oxo-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-2-carboxylic acid (3-pyrrolidin-1-ylpropyl)amide              |
| 24 |  | 4-Benzoyl-5-(5-bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-3-methyl-1H-pyrrole-2-carboxylic acid (3-pyrrolidin-1-ylpropyl)amide      |
| 25 |  | 4-Benzoyl-3-methyl-5-(2-oxo-6-phenyl-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-2-carboxylic acid (3-pyrrolidin-1-ylpropyl)amide     |
| 26 |  | 4-Benzoyl-5-(6-methoxy-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-3-methyl-1H-pyrrole-2-carboxylic acid (3-pyrrolidin-1-ylpropyl)amide    |

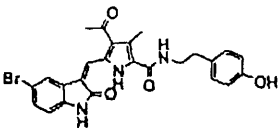
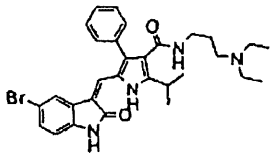
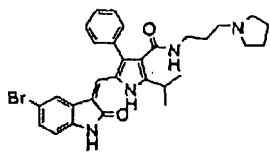
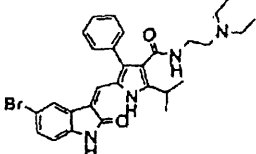
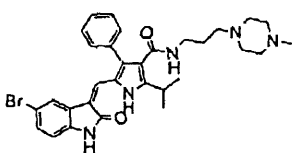
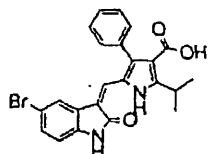
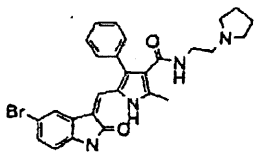
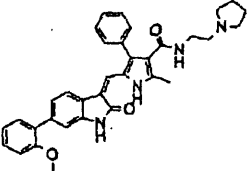
[0083]

[Table 3-4]

|    |  |                                                                                                                                     |
|----|--|-------------------------------------------------------------------------------------------------------------------------------------|
| 27 |  | 4-Benzoyl-5-(5-methoxy-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-3-methyl-1H-pyrrole-2-carboxylic acid (3-pyrrolidin-1-ylpropyl)amide |
| 28 |  | 4-Benzoyl-5-(5-fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-3-methyl-1H-pyrrole-2-carboxylic acid (3-pyrrolidin-1-ylpropyl)amide  |
| 29 |  | 4-Acetyl-5-(5-bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-3-methyl-1H-pyrrole-2-carboxylic acid (3-diethylaminopropyl)amide       |
| 30 |  | 4-Acetyl-5-(5-bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-3-methyl-1H-pyrrole-2-carboxylic acid (3-pyrrolidin-1-ylpropyl)amide    |
| 31 |  | 4-Acetyl-5-(5-bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-3-methyl-1H-pyrrole-2-carboxylic acid (3-morpholin-4-ylpropyl)amide     |
| 32 |  | 4-Acetyl-5-(5-bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-3-methyl-1H-pyrrole-2-carboxylic acid (3-hydroxy-propyl)amide           |
| 33 |  | 4-Acetyl-5-(5-bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-3-methyl-1H-pyrrole-2-carboxylic acid (2-hydroxy-ethyl)amide            |
| 34 |  | 4-Acetyl-5-(5-bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-3-methyl-1H-pyrrole-2-carboxylic acid (2-morpholin-4-yl-ethyl)amide     |
| 35 |  | 4-Acetyl-5-(5-bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-3-methyl-1H-pyrrole-2-carboxylic acid (2-pyrrolidin-1-yl-ethyl)amide    |

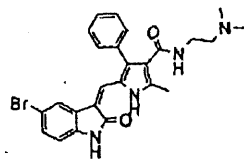
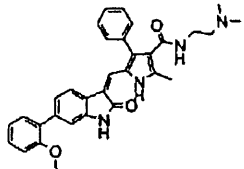
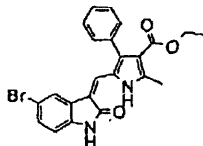
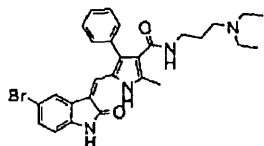
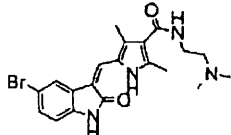
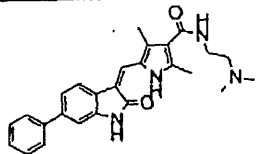
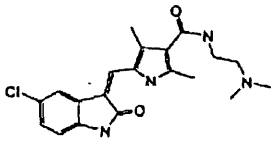
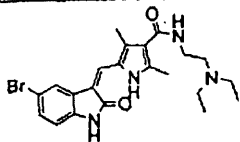
[0084]

[Table 3-5]

|    |                                                                                     |                                                                                                                                                |
|----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| 36 |    | 4-Acetyl-5-(5-bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-3-methyl-1H-pyrrole-2-carboxylic acid (2-(4-hydroxy-phenyl)-ethyl)amide            |
| 37 |    | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylic acid (3-diethylaminopropyl)amide               |
| 38 |    | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylic acid (3-pyrrolidin-1-ylpropyl)amide            |
| 39 |    | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide                |
| 40 |  | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylic acid (3-(4-methyl-piperazin-1-yl)-propyl)amide |
| 41 |  | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylic acid                                           |
| 42 |  | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2-methyl-4-phenyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)amide               |
| 43 |  | 5-[6-(2-Methoxy-phenyl)-2-oxo-1,2-dihydroindol-3-ylidenemethyl]-2-methyl-4-phenyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)amide  |

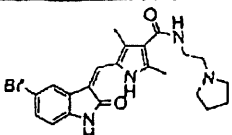
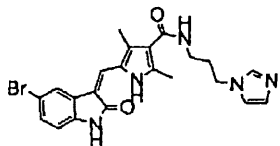
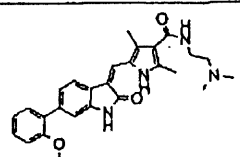
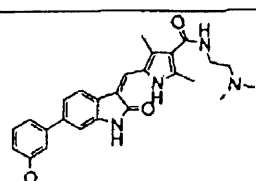
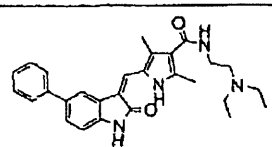
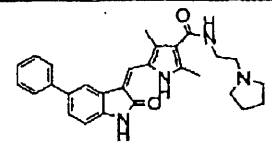
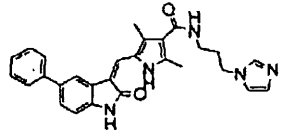
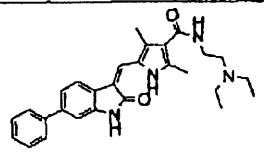
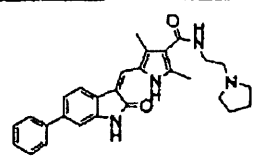
[0085]

[Table 3-6]

|    |                                                                                     |                                                                                                                                             |
|----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| 44 |    | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2-methyl-4-phenyl-1H-pyrrole-3-carboxylic acid (2-dimethylamino-ethyl)amide              |
| 45 |    | 5-[6-(2-Methoxy-phenyl)-2-oxo-1,2-dihydroindol-3-ylidenemethyl]-2-methyl-4-phenyl-1H-pyrrole-3-carboxylic acid (2-dimethylamino-ethyl)amide |
| 46 |    | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2-methyl-4-phenyl-1H-pyrrole-3-carboxylic acid ethyl ester                               |
| 47 |   | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2-methyl-4-phenyl-1H-pyrrole-3-carboxylic acid (3-diethylaminopropyl)amide               |
| 48 |  | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-dimethylamino-ethyl)amide                   |
| 49 |  | 2,4-Dimethyl-5-(2-oxo-6-phenyl-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-3-carboxylic acid (2-dimethylamino-ethyl)amide                  |
| 50 |  | 5-(5-Chloro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-dimethylamino-ethyl)amide                  |
| 51 |  | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide                     |

[0086]

[Table 3-7]

|    |                                                                                     |                                                                                                                                        |
|----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| 52 |    | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)amide            |
| 53 |    | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (3-imidazol-1-ylpropyl)amide              |
| 54 |    | 5-[6-(2-Methoxy-phenyl)-2-oxo-1,2-dihydroindol-3-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-dimethylamino-ethyl)amide |
| 55 |    | 5-[6-(3-Methoxy-phenyl)-2-oxo-1,2-dihydroindol-3-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-dimethylamino-ethyl)amide |
| 56 |   | 2,4-Dimethyl-5-(2-oxo-5-phenyl-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide               |
| 57 |  | 2,4-Dimethyl-5-(2-oxo-5-phenyl-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)amide           |
| 58 |  | 2,4-Dimethyl-5-(2-oxo-5-phenyl-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-3-carboxylic acid (3-imidazol-1-ylpropyl)amide             |
| 59 |  | 2,4-Dimethyl-5-(2-oxo-6-phenyl-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide               |
| 60 |  | 2,4-Dimethyl-5-(2-oxo-6-phenyl-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)amide           |

[0087]

[Table 3-8]

|    |  |                                                                                                                                         |
|----|--|-----------------------------------------------------------------------------------------------------------------------------------------|
| 61 |  | 2,4-Dimethyl-5-(2-oxo-6-phenyl-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-3-carboxylic acid (3-imidazol-1-ylpropyl)amide              |
| 62 |  | 5-[6-(3,5-Dichloro-phenyl)-2-oxo-1,2-dihydroindol-3-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide |
| 63 |  | 2,4-Dimethyl-5-(2-oxo-6-pyridin-3-yl-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide          |
| 64 |  | 2,4-Dimethyl-5-(2-oxo-6-pyridin-3-yl-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)amide      |
| 65 |  | 2,4-Dimethyl-5-(2-oxo-6-pyridin-3-yl-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-3-carboxylic acid (3-dimethylamino-propyl)amide       |
| 66 |  | 2,4-Dimethyl-5-(2-oxo-5-phenyl-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-3-carboxylic acid (3-dimethylamino-propyl)amide             |
| 67 |  | 2,4-Dimethyl-5-(2-oxo-5-phenyl-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-3-carboxylic acid (3-diethylaminopropyl)amide               |
| 68 |  | 2,4-Dimethyl-5-(2-oxo-6-phenyl-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrole-3-carboxylic acid (3-diethylaminopropyl)amide               |

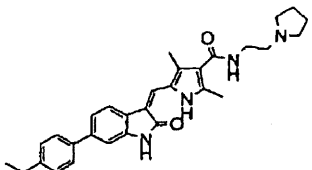
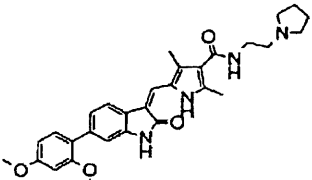
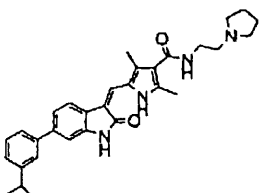
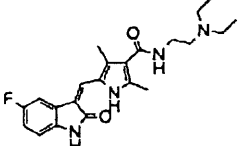
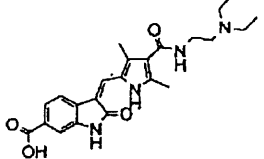
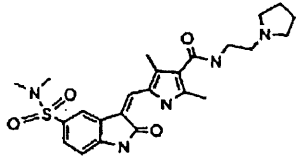
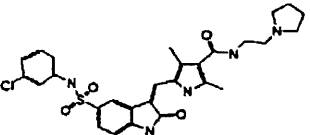
[0088]

[Table 3-9]

|    |  |                                                                                                                                                              |
|----|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 69 |  | 3-[4-(3-Diethylamino-propylcarbamoyl)-3,5-dimethyl-1H-pyrrol-2-yl(methylene)]-2-oxo-2,3-dihydro-1H-indole-4-carboxylic acid (3-chloro-4-methoxy-phenyl)amide |
| 70 |  | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (3-diethylaminopropyl)amide                                     |
| 71 |  | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-diisopropyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide                                   |
| 72 |  | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-diisopropyl-1H-pyrrole-3-carboxylic acid (3-diethylaminopropyl)amide                                  |
| 73 |  | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-diisopropyl-1H-pyrrole-3-carboxylic acid (3-pyrrolidin-1-ylpropyl)amide                               |
| 74 |  | 5-(5-Bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (pyridin-4-ylmethyl)amide                                       |
| 75 |  | 5-[6-(4-Butyl-phenyl)-2-oxo-1,2-dihydroindol-3-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)amide                       |
| 76 |  | 5-[6-(5-Isopropyl-2-methoxy-phenyl)-2-oxo-1,2-dihydroindol-3-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)amide         |

[0089]

[Table 3-10]

|    |                                                                                     |                                                                                                                                                  |
|----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| 77 |    | 5-[6-(4-Ethyl-phenyl)-2-oxo-1,2-dihydroindol-3-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)amide           |
| 78 |    | 5-[6-(2,4-Dimethoxy-phenyl)-2-oxo-1,2-dihydroindol-3-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)amide     |
| 79 |    | 5-[6-(3-Isopropyl-phenyl)-2-oxo-1,2-dihydroindol-3-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)amide       |
| 80 |  | 5-(5-Fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide                         |
| 81 |  | 3-[4-(2-diethylaminoethylcarbamoyl)-3,5-dimethyl-1H-pyrrol-2-ylmethylene]-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid                          |
| 82 |  | 5-(5-Dimethylsulfamoyl-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)amide          |
| 83 |  | 5-[5-(3-Chloro-phenylsulfamoyl)-2-oxo-1,2-dihydroindol-3-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)amide |

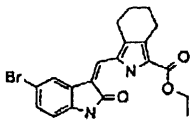
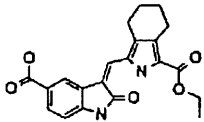
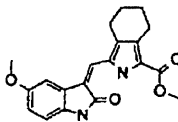
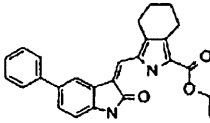
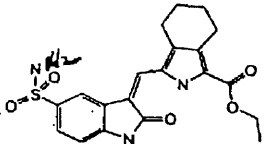
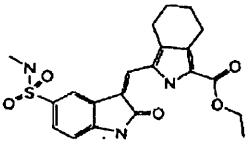
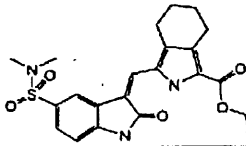
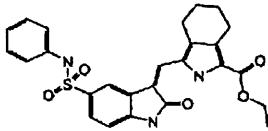
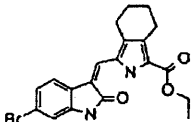
[0090]

[Table 3-11]

|    |  |                                                                                                                                               |
|----|--|-----------------------------------------------------------------------------------------------------------------------------------------------|
| 84 |  | 2,4-Dimethyl-5-[2-oxo-5-(pyridin-3-ylsulfamoyl)-1,2-dihydroindol-3-ylidenemethyl]-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)amide |
| 85 |  | 3-[3,5-Dimethyl-4-(4-methyl-piperazine-1-carbonyl)-1H-pyrrol-2-ylmethylene]-4-(2-hydroxy-ethyl)-1,3-dihydroindol-2-one                        |
| 86 |  | 3-[3,5-Dimethyl-4-(4-methyl-piperazine-1-carbonyl)-1H-pyrrol-2-ylmethylene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonic acid phenylamide           |
| 87 |  | 5-(5-Dimethylsulfamoyl-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide           |
| 88 |  | 5-[5-(3-Chloro-phenylsulfamoyl)-2-oxo-1,2-dihydroindol-3-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide  |
| 89 |  | 3-(5-Bromo-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid (2-dimethylamino-ethyl)-amide           |
| 90 |  | 3-(2-Oxo-1,2-dihydro-indol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid ethyl ester                                     |
| 91 |  | 3-(4-Methyl-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid ethyl ester                            |

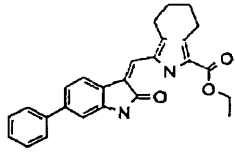
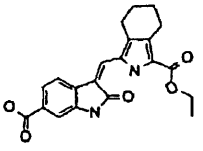
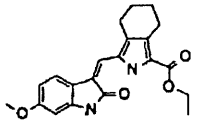
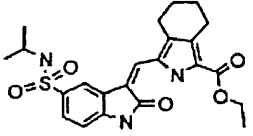
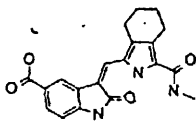
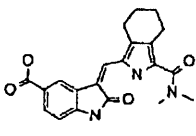
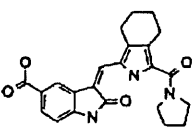
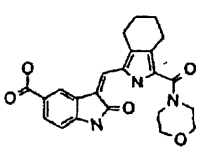
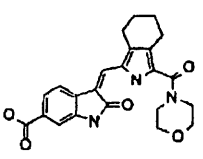
[0091]

[Table 3-12]

|     |                                                                                     |                                                                                                                               |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| 92  |    | 3-(5-Bromo-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid ethyl ester             |
| 93  |    | 3-(3-Ethoxycarbonyl-4,5,6,7-tetrahydro-2H-isoindol-1-ylmethylene)-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid               |
| 94  |    | 3-(5-Methoxy-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid ethyl ester           |
| 95  |    | 3-(2-Oxo-5-phenyl-1,2-dihydro-indol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid ethyl ester            |
| 96  |   | 3-(2-Oxo-5-sulfamoyl-1,2-dihydro-indol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid ethyl ester         |
| 97  |  | 3-(5-Methylsulfamoyl-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid ethyl ester   |
| 98  |  | 3-(5-Dimethylsulfamoyl-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid ethyl ester |
| 99  |  | 3-(2-Oxo-5-phenylsulfamoyl-1,2-dihydro-indol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid ethyl ester   |
| 100 |  | 3-(6-Bromo-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid ethyl ester             |

[0092]

[Table 3-13]

|     |                                                                                     |                                                                                                                                |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| 101 |    | 3-(2-Oxo-6-phenyl-1,2-dihydro-indol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid ethyl ester             |
| 102 |    | 3-(3-Ethoxycarbonyl-4,5,6,7-tetrahydro-2H-isoindol-1-ylmethylene)-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid                |
| 103 |    | 3-(6-Methoxy-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid ethyl ester            |
| 104 |    | 3-(5-Isopropylsulfamoyl-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid ethyl ester |
| 105 |   | 3-(3-Methylcarbamoyl-4,5,6,7-tetrahydro-2H-isoindol-1-ylmethylene)-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid               |
| 106 |  | 3-(3-Dimethylcarbamoyl-4,5,6,7-tetrahydro-2H-isoindol-1-ylmethylene)-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid             |
| 107 |  | 2-Oxo-3-[3-(pyrrolidine-1-carbonyl)-4,5,6,7-tetrahydro-2H-isoindol-1-ylmethylene]-2,3-dihydro-1H-indole-5-carboxylic acid      |
| 108 |  | 3-[3-(Morpholine-4-carbonyl)-4,5,6,7-tetrahydro-2H-isoindol-1-ylmethylene]-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid       |
| 109 |  | 3-[3-(Morpholine-4-carbonyl)-4,5,6,7-tetrahydro-2H-isoindol-1-ylmethylene]-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid       |

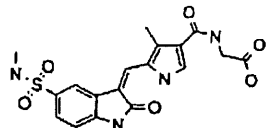
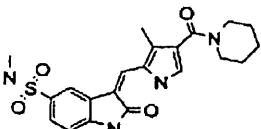
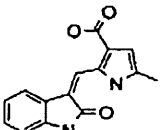
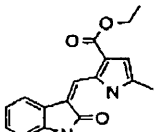
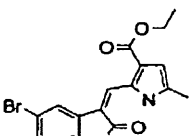
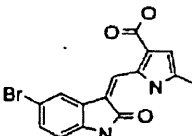
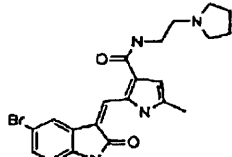
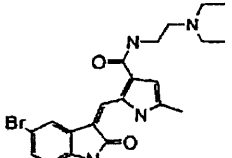
[0093]

[Table 3-14]

|     |  |                                                                                                                                         |
|-----|--|-----------------------------------------------------------------------------------------------------------------------------------------|
| 110 |  | 3-(5-Bromo-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid methylamide                       |
| 111 |  | 3-(5-Bromo-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid dimethylamide                     |
| 112 |  | 5-Bromo-3-[3-(pyrrolidine-1-carbonyl)-4,5,6,7-tetrahydro-2H-isoindol-1-ylmethylene]-1,3-dihydro-indol-2-one                             |
| 113 |  | 5-Bromo-3-[3-(morpholine-4-carbonyl)-4,5,6,7-tetrahydro-2H-isoindol-1-ylmethylene]-1,3-dihydro-indol-2-one                              |
| 114 |  | 3-[3-Dimethylcarbamoyl-4,5,6,7-tetrahydro-2H-isoindol-1-ylmethylene]-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid                      |
| 115 |  | 4-Methyl-5-(5-methylsulfamoyl-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrole-3-carboxylic acid                                     |
| 116 |  | [[4-Methyl-5-(4-methyl-5-methylsulfamoyl-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrole-3-carbonyl]-amino]-acetic acid ethyl ester |
| 117 |  | [[4-Methyl-5-(5-methylsulfamoyl-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrole-3-carbonyl]-amino]-acetic acid ethyl ester          |

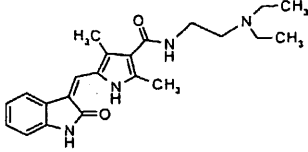
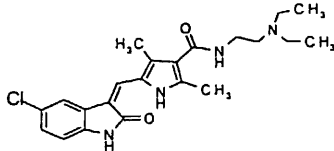
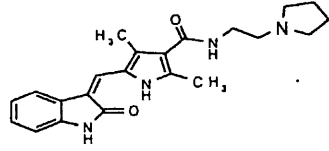
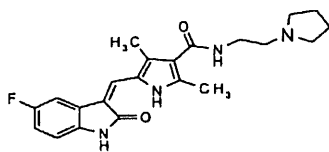
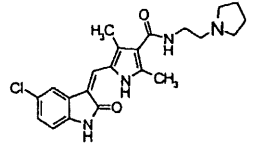
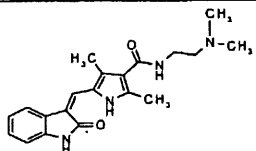
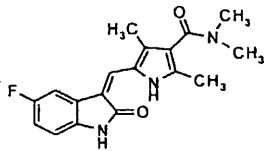
[0094]

[Table 3-15]

|     |                                                                                     |                                                                                                                           |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| 118 |    | [[4-Methyl-5-(5-methylsulfonyl-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrole-3-carbonyl]-amino]-acetic acid         |
| 119 |    | 3-[3-Methyl-4-(piperidine-1-carbonyl)-1H-pyrrol-2-ylmethylene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonic acid methylamide    |
| 120 |    | 5-Methyl-2-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrole-3-carboxylic acid                                         |
| 121 |    | 5-Methyl-2-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrole-3-carboxylic acid ethyl ester                             |
| 122 |  | 2-(5-Bromo-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-5-methyl-1H-pyrrole-3-carboxylic acid ethyl ester                     |
| 123 |  | 2-(5-Bromo-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-5-methyl-1H-pyrrole-3-carboxylic acid                                 |
| 124 |  | 2-(5-Bromo-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-5-methyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide |
| 125 |  | 2-(5-Bromo-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-5-methyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide    |

[0095]

[Table 3-16]

|     |                                                                                     |                                                                                                                                      |           |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 126 |    | 2,4-Dimethyl-5-[2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)-amide                 | 381 [M+1] |
| 127 |    | 5-[5-Chloro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)-amide        | 415 [M+1] |
| 128 |    | 2,4-Dimethyl-5-[2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-ylethyl)-amide | 379 [M+1] |
| 129 |    | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-ylethyl)-amide     | 397 [M+1] |
| 130 |  | 5-[5-Chloro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-ylethyl)-amide                  | 413 [M+1] |
| 131 |  | 2,4-Dimethyl-5-[2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-dimethylaminoethyl)-amide   | 353 [M+1] |
| 132 |  | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-dimethylaminoethyl)-amide       | 371 [M+1] |

[0096]

[Table 3-17]

|     |  |                                                                                                                                                          |                        |
|-----|--|----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 133 |  | 5-[5-Chloro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-acetylamino-ethyl)-amide                            | 399 [M-1]              |
| 134 |  | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-acetylamino-ethyl)-amide                            | 383 [M-1]              |
| 135 |  | 2,4-Dimethyl-5-[2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-1H-pyrrole-3-carboxylic acid (2-acetylamino-ethyl)-amide                                     | 365 [M-1]              |
| 136 |  | 5-[5-Bromo-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [3-(2-oxo-tetrahydropyrimidin-1-yl)-propyl]-amide       | 500 [M+1]<br>502 [M+1] |
| 137 |  | 5-[5-Chloro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [3-(2-oxo-tetrahydropyrimidin-1-yl)-propyl]-amide      | 454 [M-1]              |
| 138 |  | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [3-(2-oxo-tetrahydropyrimidin-1-yl)-propyl]-amide      | 438 [M-1]              |
| 139 |  | 2,4-Dimethyl-5-[2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-1H-pyrrole-3-carboxylic acid [3-(2-oxo-tetrahydropyrimidin-1-yl)-propyl]-amide               | 422 [M+1]              |
| 140 |  | 5-[5-Cyano-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [3-(2-oxo-tetrahydropyrimidin-1-yl)-propyl]-amide       | 447 [M+1]              |
| 141 |  | Trifluoro-acetate 4-{2-((5-[5-bromo-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl)-amino)-ethyl}-2-oxo-piperazin-1-ium; | 486 [M+1]<br>488 [M+1] |

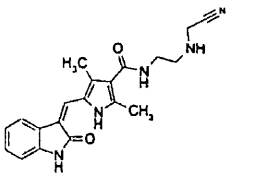
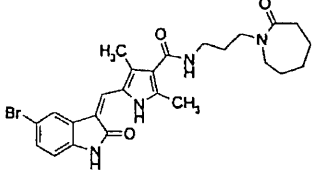
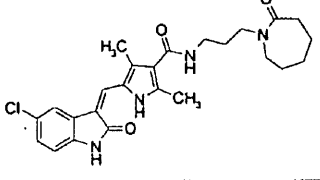
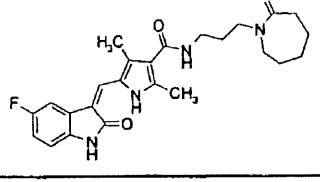
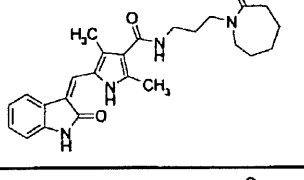
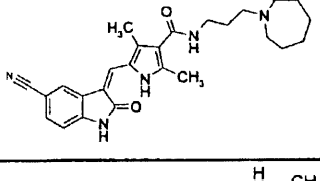
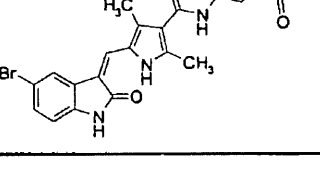
[0097]

[Table 3-18]

|     |  |                                                                                                                                                          |                        |
|-----|--|----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 142 |  | 5-[5-Cyano-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide                | 430 [M-1]              |
| 143 |  | 5-[5-Bromo-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-(2-oxo-imidazolidin-1-yl)-ethyl]-amide               | 470 [M-1]<br>472 [M-1] |
| 144 |  | 5-[5-Cyano-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-(2-oxo-imidazolidin-1-yl)-ethyl]-amide               | 428 [M+1]              |
| 145 |  | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-(2-oxo-imidazolidin-1-yl)-ethyl]-amide              | 412 [M+1]              |
| 146 |  | 2,4-Dimethyl-5-[2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-1H-pyrrole-3-carboxylic acid [2-(2-oxo-imidazolidin-1-yl)-ethyl]-amide                       | 392 [M-1]              |
| 147 |  | 5-[5-Cyano-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-(2-oxo-imidazolidin-1-yl)-ethyl]-amide               | 419 [M+1]              |
| 148 |  | {4-[2-({5-[5-Bromo-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}amino)-ethyl]-piperazin-1-yl}-acetic acid ethyl ester  | 558 [M+1]<br>560 [M+1] |
| 149 |  | {4-[2-({5-[5-Chloro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}amino)-ethyl]-piperazin-1-yl}-acetic acid ethyl ester | 514 [M+1]              |
| 150 |  | {4-[2-({5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}amino)-ethyl]-piperazin-1-yl}-acetic acid ethyl ester | 498 [M+1]              |

[0098]

[Table 3-19]

|     |                                                                                     |                                                                                                                                        |                        |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 153 |    | 2,4-Dimethyl-5-[2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-1H-pyrrole-3-carboxylic acid [2-(cyanomethyl-amino)-ethyl]-amide           | 362 [M-1]              |
| 154 |    | 5-[5-Bromo-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [3-(2-oxo-azepan-1-yl)-propyl]-amide  | 511 [M-1]<br>513 [M-1] |
| 155 |    | 5-[5-Chloro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [3-(2-oxo-azepan-1-yl)-propyl]-amide | 469 [M+1]              |
| 156 |   | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [3-(2-oxo-azepan-1-yl)-propyl]-amide | 453 [M+1]              |
| 157 |  | 2,4-Dimethyl-5-[2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-1H-pyrrole-3-carboxylic acid [3-(2-oxo-azepan-1-yl)-propyl]-amide          | 435 [M+1]              |
| 158 |  | 5-[5-Cyano-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [3-(2-oxo-azepan-1-yl)-propyl]-amide  | 460 [M+1]              |
| 159 |  | 5-[5-Bromo-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-acetyl-amino-ethyl)-amide          | 443 [M-1]<br>445 [M-1] |

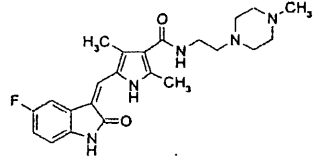
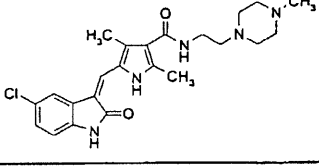
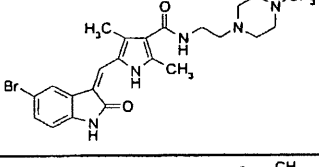
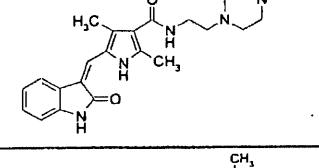
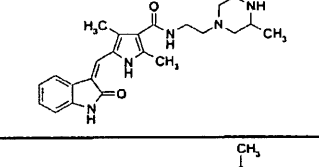
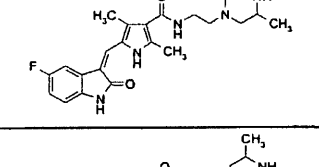
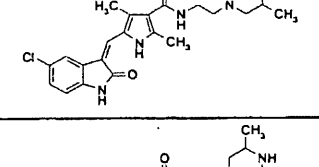
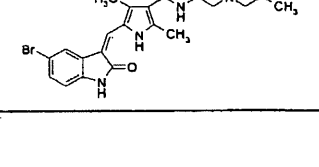
[0099]

[Table 3-20]

|     |  |                                                                                                                                                           |                        |
|-----|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 160 |  | Trifluoro-acetate 4-[2-((5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl)-amino)-ethyl]-2-oxo-piperazin-1-ium; | 426 [M+1]              |
| 161 |  | Trifluoro-acetate 4-[2-((2,4-dimethyl-5-[2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-1H-pyrrole-3-carbonyl)-amino)-ethyl]-2-oxo-piperazin-1-ium;          | 408 [M+1]              |
| 162 |  | Trifluoro-acetate 4-[2-((5-[5-cyano-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl)-amino)-ethyl]-2-oxo-piperazin-1-ium;  | 433 [M+1]              |
| 163 |  | 5-[5-Bromo-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-(2-cyano-ethylamino)-ethyl]-amide                     | 454 [M-1]<br>456 [M-1] |
| 164 |  | 5-[5-Chloro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-(2-cyano-ethylamino)-ethyl]-amide                    | 410 [M-1]              |
| 165 |  | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-(2-cyano-ethylamino)-ethyl]-amide                    | 394 [M-1]              |
| 166 |  | 2,4-Dimethyl-5-[2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-1H-pyrrole-3-carboxylic acid [2-(2-cyano-ethylamino)-ethyl]-amide                             | 376 [M-1]              |
| 167 |  | 5-[5-Cyano-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-(2-cyano-ethylamino)-ethyl]-amide                     | 401 [M-1]              |
| 168 |  | Trifluoro-acetate 4-[2-((5-[5-chloro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl)-amino)-ethyl]-2-oxo-piperazin-1-ium; | 440 [M-1]              |

[0100]

[Table 3-21]

|     |                                                                                     |                                                                                                                                                 |                        |  |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|--|
| 168 |    | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-(4-methyl-piperazin-1-yl)-ethyl]-amide     | 424 [M-1]              |  |
| 169 |    | 5-[5-Chloro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-(4-methyl-piperazin-1-yl)-ethyl]-amide     | 440 [M-1]              |  |
| 170 |    | 5-[5-Bromo-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-(4-methyl-piperazin-1-yl)-ethyl]-amide      | 484 [M-1]<br>486 [M-1] |  |
| 171 |   | 2,4-Dimethyl-5-[2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-1H-pyrrole-3-carboxylic acid [2-(4-methyl-piperazin-1-yl)-ethyl]-amide              | 406 [M-1]              |  |
| 172 |  | 2,4-Dimethyl-5-[2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-1H-pyrrole-3-carboxylic acid [2-(3,5-dimethyl-piperazin-1-yl)-ethyl]-amide          | 422 [M+1]              |  |
| 173 |  | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-(3,5-dimethyl-piperazin-1-yl)-ethyl]-amide | 438 [M-1]              |  |
| 174 |  | 5-[5-Chloro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-(3,5-dimethyl-piperazin-1-yl)-ethyl]-amide | 456 [M+1]              |  |
| 175 |  | 5-[5-Bromo-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-(3,5-dimethyl-piperazin-1-yl)-ethyl]-amide  | 498 [M-1]<br>500 [M-1] |  |

[0101]

[Table 3-22]

|     |  |                                                                                                                                              |                        |  |
|-----|--|----------------------------------------------------------------------------------------------------------------------------------------------|------------------------|--|
| 176 |  | 2,4-Dimethyl-5-[2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-1H-pyrrole-3-carboxylic acid [3-(4-methyl-piperazin-1-yl)-propyl]-amide          | 422 [M+1]              |  |
| 177 |  | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [3-(4-methyl-piperazin-1-yl)-propyl]-amide | 438 [M-1]              |  |
| 178 |  | 5-[5-Chloro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [3-(4-methyl-piperazin-1-yl)-propyl]-amide | 454 [M-1]              |  |
| 179 |  | 5-[5-Bromo-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [3-(4-methyl-piperazin-1-yl)-propyl]-amide  | 498 [M-1]<br>500 [M-1] |  |
| 180 |  | 2,4-Dimethyl-5-[2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-1H-pyrrole-3-carboxylic acid [2-(4-benzyl-piperazin-1-yl)-ethyl]-amide           | 482 [M-1]              |  |
| 181 |  | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-(4-benzyl-piperazin-1-yl)-ethyl]-amide  | 500 [M-1]              |  |
| 182 |  | 5-[5-Chloro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-(4-benzyl-piperazin-1-yl)-ethyl]-amide  | 517 [M-1]              |  |
| 183 |  | 5-[5-Bromo-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-(4-benzyl-piperazin-1-yl)-ethyl]-amide   | 560 [M-1]<br>562 [M-1] |  |

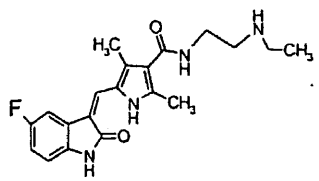
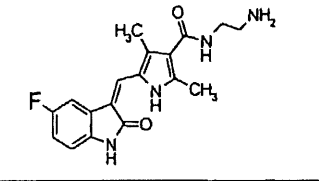
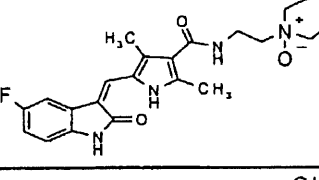
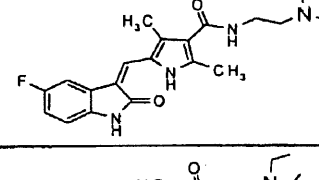
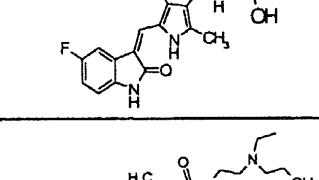
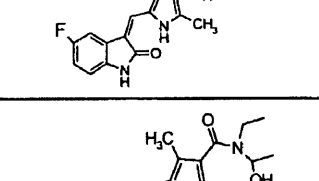
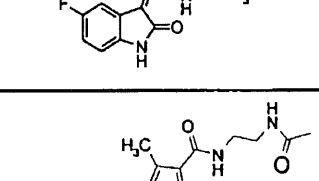
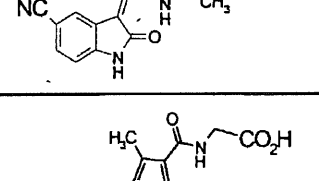
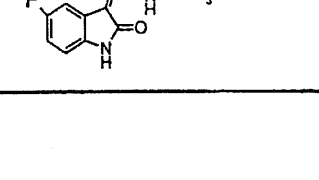
[0102]

[Table 3-23]

|     |  |                                                                                                                                                        |           |
|-----|--|--------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 184 |  | 5-[5-Chloro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (3-pyrrolidin-1yl-2-one)-amide                       | 480 [M+1] |
| 185 |  | Trifluoroacetate 4-[2-({5-[5-Chloro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}amino)-ethyl] 2-oxo-piperazin-1-ium | 440 [M-1] |
| 186 |  | 5-[5-Chloro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (3-pyrrolidin-1yl-2-one)-amide                       |           |
| 187 |  | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (3-pyrrolidin-1yl-2-one)-amide                       |           |
| 188 |  | 5-[2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (3-pyrrolidin-1yl-2-one)-amide                                |           |
| 189 |  | 5-[5-Chloro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyridin-2-ylethyl)-amide                          |           |
| 190 |  | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyridin-2-ylethyl)-amide trifluoroacetate salt    |           |
| 191 |  | 5-[2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyridin-2-ylethyl)-amide hydrochloride salt                |           |
| 192 |  | 5-[5-Bromo-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyridin-2-ylethyl)-amide trifluoroacetate salt     |           |

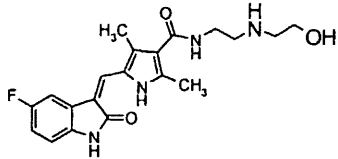
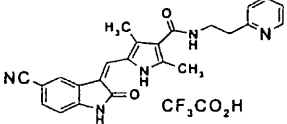
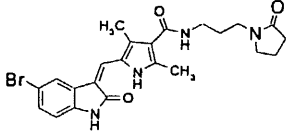
[0103]

[Table 3-24]

|     |                                                                                     |                                                                                                                                                  |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| 193 |    | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-ethylaminoethyl)-amide                      |
| 194 |    | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-aminoethyl)-amide                           |
| 195 |    | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethyl-N-oxoaminoethyl)-amide |
| 196 |   | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-ethyl-N-hydroxy-aminoethyl)-amide           |
| 197 |  | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-1H-pyrrole-3-carboxylic acid (2-diethylamino-2-hydroxyethyl)-amide                       |
| 198 |  | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-ethyl-2-(2-hydroxyethyl)aminoethyl]-amide   |
| 199 |  | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-ethyl-2-(1-hydroxyethyl)aminoethyl]-amide   |
| 200 |  | 5-[5-Cyano-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-N-acetylaminoethyl)-amide                    |
| 201 |  | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (carboxymethyl)-amide                          |

[0104]

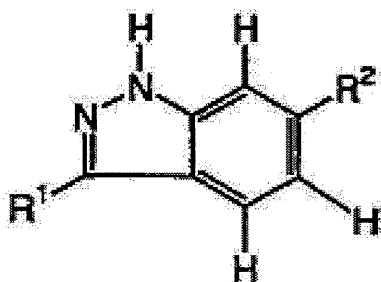
[Table 3-25]

|     |                                                                                   |                                                                                                                                            |
|-----|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| 202 |  | 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-1H-pyrrole-3-carboxylic acid [2-(2-hydroxyethylamino)ethyl]-amide                  |
| 203 |  | 5-[5-Cyano-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-1H-pyrrole-3-carboxylic acid (2-pyridin-2-ylethyl)-amide trifluoroacetate           |
| 204 |  | 5-[5-Bromo-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-1H-pyrrole-3-carboxylic acid (3-pyrrolidin-1-yl-2-onepropyl)-amide trifluoroacetate |

[0105]

5 Specific examples of the "analog of Axitinib" include a compound represented by the following formula (VIII):

[0106]



(VIII)

[0107]

10 wherein

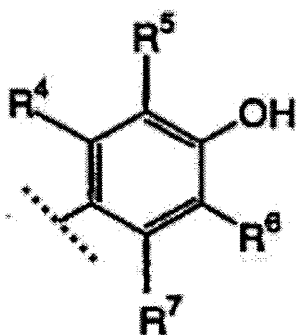
R<sup>1</sup> is a substituted or unsubstituted aryl group or heteroaryl group, or a group of the formula CH=CH-R<sup>3</sup> or CH=N-R<sup>3</sup> wherein R<sup>3</sup> is a substituted or unsubstituted alkyl group, alkenyl group, cycloalkyl group, heterocycloalkyl group, aryl group or

15 heteroaryl group;

R<sup>2</sup> is a substituted or unsubstituted aryl group or heteroaryl group, or a Y-X group wherein Y is O, S, C=CH<sub>2</sub>, C=O, S=O, SO<sub>2</sub>, an alkylidene group, NH or N-(C<sub>1</sub>-C<sub>8</sub> alkyl) group, X is substituted or unsubstituted Ar, heteroaryl group, NH-(alkyl)

group, NH-(cycloalkyl) group, NH-(heterocycloalkyl) group, NH(aryl) group, NH(heteroaryl group), NH-(alkoxyl) group or NH-(dialkylamide) group, Ar is substituted or unsubstituted aryl.  
[0108]

5 In the above-mentioned formula (VIII), when R<sup>2</sup> is a substituted aryl group, R<sup>2</sup> is preferably a group represented by the following formula:  
[0109]



10 [0110]

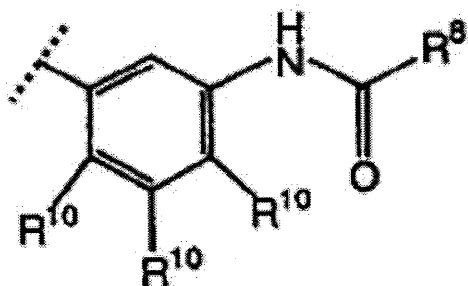
wherein

R<sup>4</sup> and R<sup>7</sup> are each independently hydrogen, OH, a halo group, a C<sub>1</sub>-C<sub>8</sub> alkyl group, a C<sub>1</sub>-C<sub>8</sub> alkoxy group, a C<sub>1</sub>-C<sub>8</sub> alkenyl group, an aryloxy group, a thioaryl group, CH<sub>2</sub>-OH, a CH<sub>2</sub>-O-(C<sub>1</sub>-C<sub>8</sub> alkyl) group, CH<sub>2</sub>-O-aryl, a CH<sub>2</sub>-S-(C<sub>1</sub>-C<sub>8</sub> alkyl) group, a CH<sub>2</sub>-S-aryl group;  
R<sup>5</sup> and R<sup>6</sup> are each independently hydrogen, OH, a halo group, a Z-alkyl group, a Z-aryl group, or Z-CH<sub>2</sub>CH=CH<sub>2</sub> wherein Z is O, S, NH or CH<sub>2</sub>, and alkyl group and aryl group of Z-alkyl group and Z-aryl group are each optionally substituted. In this case, more preferably, in the above-mentioned formula (V), R<sup>1</sup> is substituted or unsubstituted bicyclic heteroaryl, or a group of the formula CH=CH-R<sup>3</sup> wherein R<sup>3</sup> is a substituted or unsubstituted aryl group or heteroaryl group;  
25 R<sup>4</sup> and R<sup>7</sup> are each independently hydrogen or a C<sub>1</sub>-C<sub>8</sub> alkyl group;  
R<sup>5</sup> and R<sup>6</sup> are each independently a halo group, a Z-alkyl group or Z-CH<sub>2</sub>CH=CH<sub>2</sub> wherein Z is O or S.

[0111]

In another preferable embodiment, in the above-mentioned formula (VIII),  $R^2$  is Y-Ar (Y, Ar are as defined above), more preferably, Ar is a group represented by the following formula:

5 [0112]



[0113]

wherein

$R^8$  is a substituted or unsubstituted alkyl group, alkenyl group, cycloalkyl group, heterocycloalkyl group, aryl group, heteroaryl group, alkoxy group or aryloxy group;

$R^{10}$  is independently selected from hydrogen, halogen and a lower alkyl group. In this case, more preferably, in the above-mentioned formula (V),

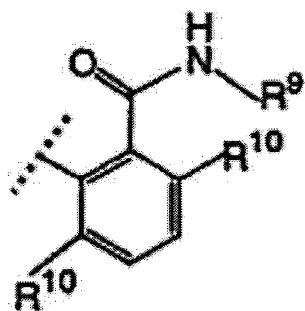
15  $R^1$  is a substituted or unsubstituted bicyclic heteroaryl group, or a group of the formula  $CH=CH-R^3$  wherein  $R^3$  is a substituted or unsubstituted aryl group or heteroaryl group; Y is O, S,  $C=CH_2$ ,  $C=O$ , NH or N-( $C_1$ - $C_8$  alkyl) group;

$R^8$  is a substituted or unsubstituted aryl group, heteroaryl group, alkyl group, alkenyl group, more preferably, a substituted or unsubstituted aryl group, heteroaryl group, and each  $R^{10}$  is independently hydrogen or halogen, more preferably, all hydrogen.

[0114]

25 In the above-mentioned formula (VIII), in another preferable embodiment wherein  $R^2$  is Y-Ar (Y, Ar are as defined above), Ar is a group represented by the following formula:

[0115]



[0116]

wherein

$R^9$  is a substituted or unsubstituted alkyl group, cycloalkyl  
 5 group, heterocycloalkyl group, aryl group, heteroaryl group,  
 alkoxy group, aryloxy group, cycloalkoxy group,  $NH-(C_1-C_8$   
 alkyl) group,  $NH-(aryl)$  group,  $NH-(heteroaryl)$  group,  $N=CH-$   
 (alkyl) group,  $NH(C=O)R^{11}$  group or  $NH_2$  wherein  $R^{11}$  is  
 independently selected from hydrogen, a substituted or  
 10 unsubstituted alkyl group, cycloalkyl group, heterocycloalkyl  
 group, aryl group and heteroaryl group);  
 $R^{10}$  is independently selected from hydrogen, halogen and a  
 lower alkyl group. In this case, more preferably, in the  
 above-mentioned formula (V),  
 15  $R^1$  is a group of the formula  $CH=CH-R^3$  wherein  $R^3$  is a  
 substituted or unsubstituted aryl group or heteroaryl group);  
 $Y$  is S or NH;  
 $R^9$  is a substituted or unsubstituted alkyl group, alkoxy group  
 or  $NH-(heteroaryl)$  group.

20 [0117]

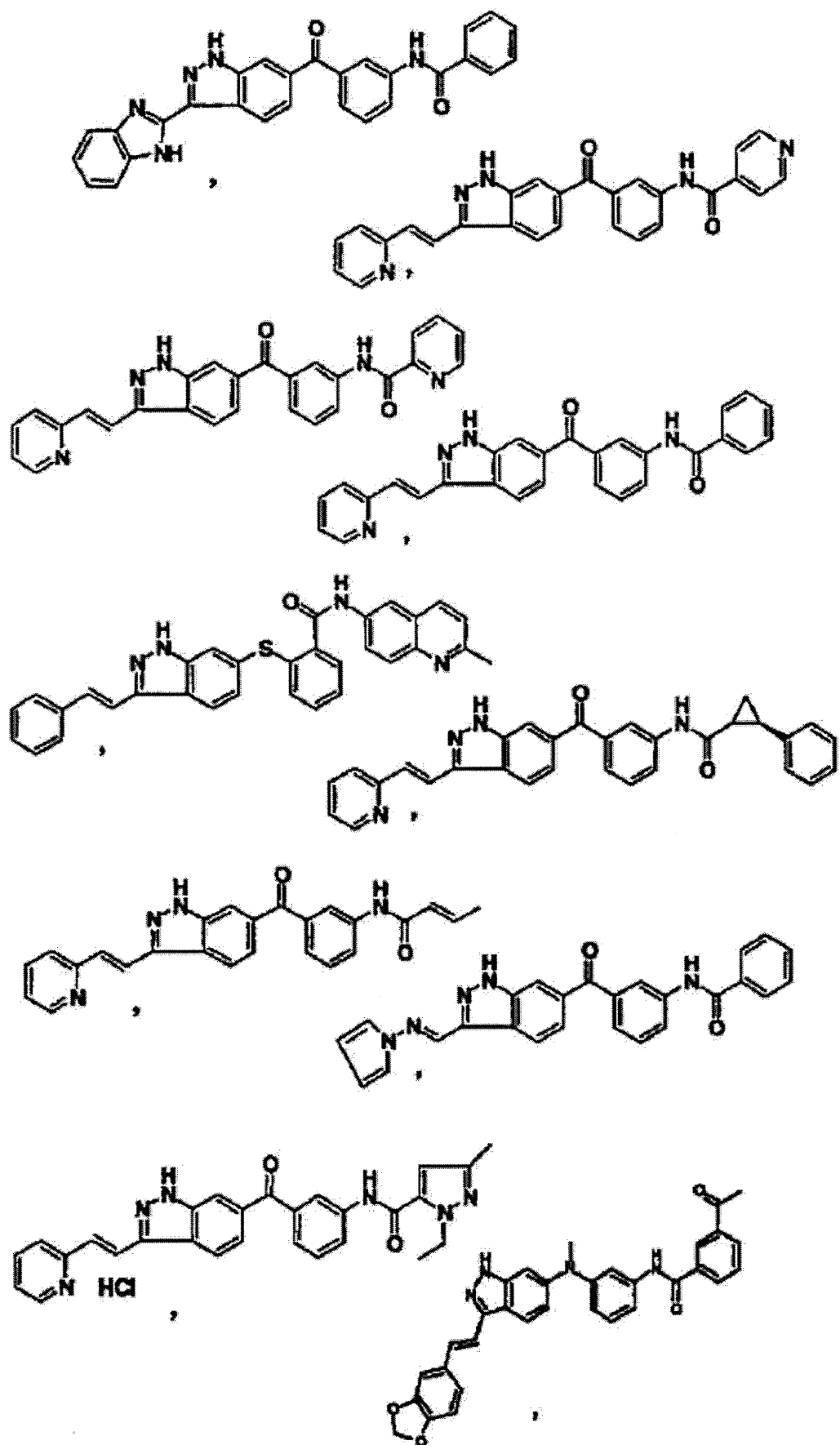
Each term described as higher concept in the explanation  
 of each group in the above-mentioned formula (VIII) (e.g.,  
 "substituted or unsubstituted aryl group", "substituted or  
 unsubstituted heteroaryl group", "substituted or unsubstituted  
 25 alkyl group", "substituted or unsubstituted alkenyl group",  
 "substituted or unsubstituted cycloalkyl group", "substituted  
 or unsubstituted heterocycloalkyl group", "substituted or  
 unsubstituted aryl group", "substituted or unsubstituted  
 heteroaryl group" etc. for  $R^1$ ) is as defined in WO 01/002369

(National Publication of International Patent Application No. 2003-503481).

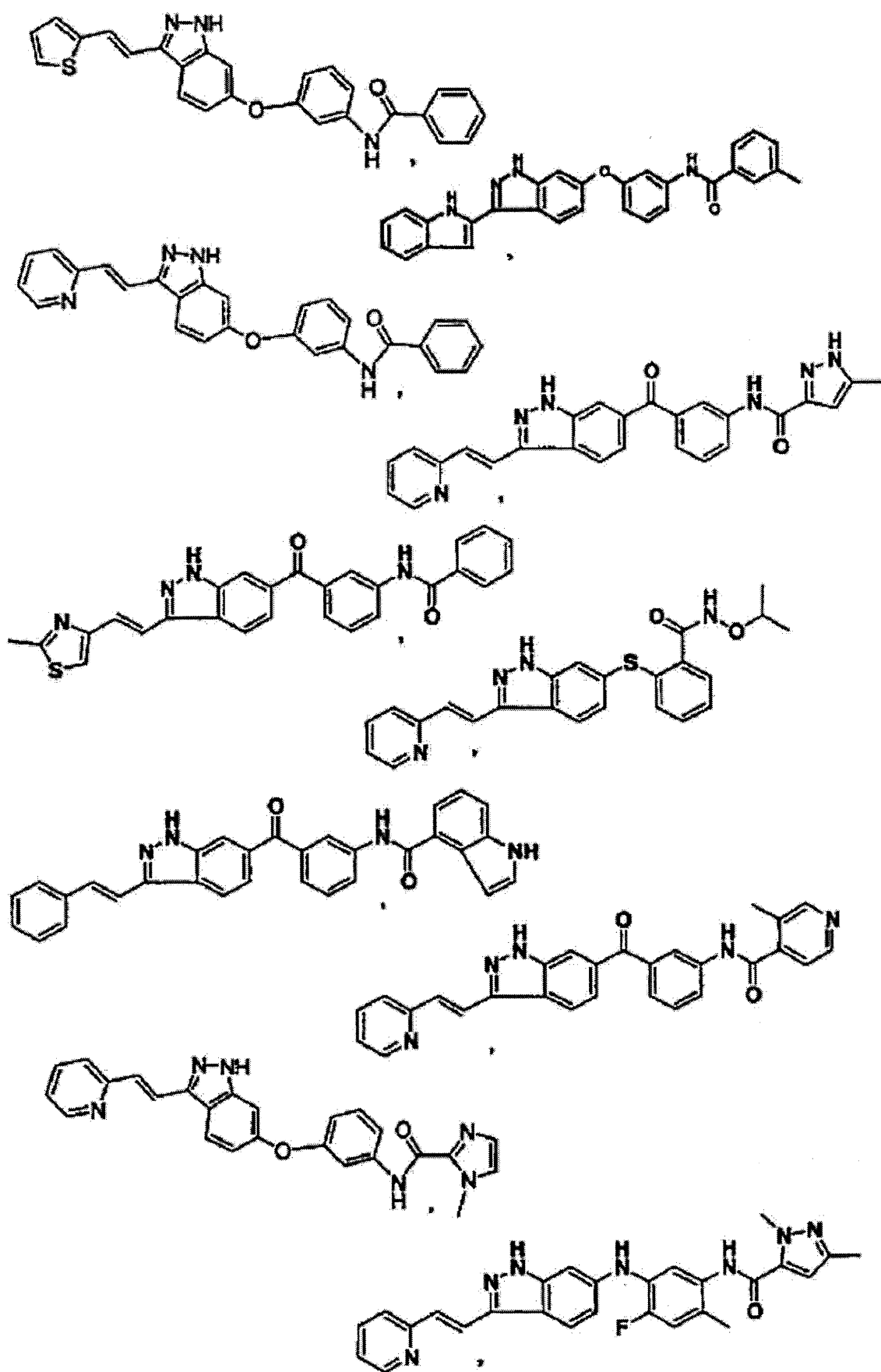
[0118]

Specific examples of the analog of Axitinib include the  
5 compounds represented by the following structural formulas.

[0119]



[0120]

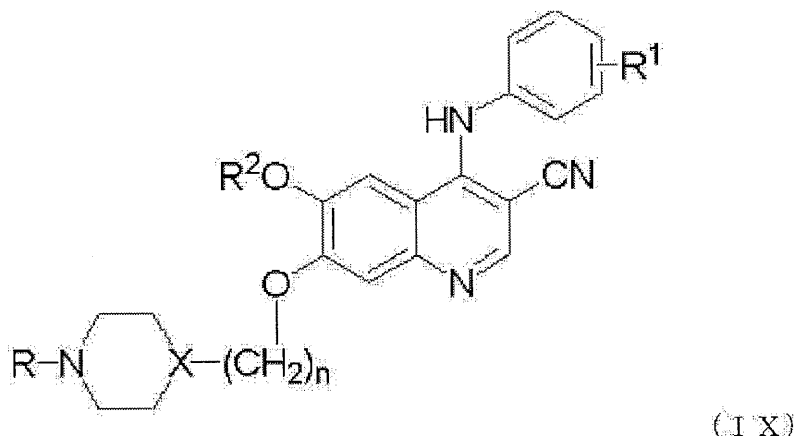




[0122]

Examples of the analog of the above-mentioned "Bosutinib (SKI-606)" include a compound represented by the following formula (IX):

5 [0123]



[0124]

wherein

n is an integer of 1-3;

10 X is N, CH, provided when X is N, then n is 2 or 3;

R is alkyl having 1 to 3 carbon atoms;

R¹ is 2,4-dichloro and 5-methoxy, 2,4-dichloro, 3,4,5-trimethoxy, 2-chloro and 5-methoxy, 2-methyl and 5-methoxy, 2,4-dimethyl, 2,4-dimethyl and 5-methoxy, or 2,4-dichloro and  
15 5-ethoxy;

R² is alkyl having 1 or 2 carbon atoms.

[0125]

Each term described as higher concept in the explanation of each group in the above-mentioned formula (IX) ("alkyl having 1 to 3 carbon atoms" for R, "alkyl having 1 or 2 carbon  
20 atoms" for R²) is as defined in WO 2005/046693 (National Publication of International Patent Application No. 2007-533655).

[0126]

25 Specific examples of the analog of "Bosutinib (SKI-606)" include the following compounds.

4-[(2,4-dichloro-5-methoxyphenyl)amino]-7-[3-(4-ethyl-1-

piperazinyl)propoxy]-6-methoxy-3-quinolinecarbonitrile;  
 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[2-(4-  
 methyl-1-piperazinyl)ethoxy]-3-quinolinecarbonitrile;  
 4-[(2,4-dichloro-5-methoxyphenyl)amino]-7-[2-(4-ethyl-1-  
 5 piperazinyl)ethoxy]-6-methoxy-3-quinolinecarbonitrile;  
 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[(1-  
 methylpiperidin-4-yl)methoxy]-3-quinolinecarbonitrile;  
 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[2-(1-  
 methylpiperidin-4-yl)ethoxy]-3-quinolinecarbonitrile;  
 10 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(1-  
 methylpiperidin-4-yl)propoxy]quinoline-3-carbonitrile;  
 4-[(2,4-dichloro-5-methoxyphenyl)amino]-7-[(1-ethylpiperidin-4-  
 yl)methoxy]-6-methoxyquinoline-3-carbonitrile;  
 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(4-  
 15 methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile;  
 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[(1-  
 methylpiperidin-4-yl)methoxy]quinoline-3-carbonitrile;  
 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(4-  
 ethylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile;  
 20 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(1-  
 methylpiperidin-4-yl)propoxy]quinoline-3-carbonitrile;  
 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[2-(4-  
 methyl-1-piperazinyl)ethoxy]quinoline-3-carbonitrile;  
 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[2-(1-  
 25 methylpiperidin-4-yl)ethoxy]quinoline-3-carbonitrile;  
 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-  
 propyl-1-piperazinyl)propoxy]-3-quinolinecarbonitrile;  
 4-[(2,4-dichlorophenyl)amino]-6-methoxy-7-[(1-methylpiperidin-  
 4-yl)methoxy]-3-quinolinecarbonitrile;  
 30 6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]-4-[(3,4,5-  
 trimethoxyphenyl)amino]quinoline-3-carbonitrile;  
 4-[(2-chloro-5-methoxyphenyl)amino]-6-methoxy-7-[(1-  
 methylpiperidin-4-yl)methoxy]quinoline-3-carbonitrile;  
 6-methoxy-4-[(5-methoxy-2-methylphenyl)amino]-7-[(1-  
 35 methylpiperidin-4-yl)methoxy]quinoline-3-carbonitrile;

4-[(2,4-dimethylphenyl)amino]-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinoline-3-carbonitrile;

6-methoxy-4-[(5-methoxy-2,4-dimethylphenyl)amino]-7-[(1-methylpiperidin-4-yl)methoxy]quinoline-3-carbonitrile;

5 4-[(2,4-dichloro-5-ethoxyphenyl)amino]-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinoline-3-carbonitrile

[0127]

In one embodiment, EGFR inhibitor, FGFR inhibitor, Aurorakinase inhibitor, PKA inhibitor, PKC inhibitor, MEK  
10 inhibitor, Met inhibitor, JNK inhibitor, Syk inhibitor and JAK inhibitor, prostaglandin analogue, estrogen receptor antagonist, and the above-mentioned compounds which do not belong to these medicaments (hereinafter sometimes to be referred comprehensively to as "the compound of the present invention")  
15 as the active ingredient of the prophylactic or therapeutic agent for ALS of the present invention do not belong to platelet-derived growth factor receptor (PDGFR) inhibitor, vascular endothelial cell growth factor receptor (VEGFR) inhibitor, c-Kit inhibitor, Flt3 inhibitor, Cdk1 inhibitor,  
20 Cdk2 inhibitor, GSK-3 $\beta$  inhibitor and Src inhibitor.

[0128]

As the compound of the present invention, a commercially available product may be used, or each compound can be produced by each method known per se.

25 For example, Pazopanib or an analog thereof can be produced according to the method described in, for example, WO 2002/059110 (National Publication of International Patent Application No. 2004-517925).

PF-2341066 (Crizotinib) or an analog thereof can be  
30 produced according to the method described in, for example, WO 2004/076412 (National Publication of International Patent Application No. 2006-519232).

Bimatoprost or an analog thereof can be produced according to the method described in, for example, US Patent No.  
35 5,607,978.

Raloxifene or an analog thereof can be produced according to the method described in, for example, JP-A-52-53851.

Tivozanib or an analog thereof can be produced according to the method described in, for example, WO 02/088110.

5 Sunitinib or an analog thereof can be produced according to the method described in, for example, WO 01/060814 (National Publication of International Patent Application No. 2003-523340).

Axitinib or an analog thereof can be produced according  
10 to the method described in, for example, WO 01/002369 (National Publication of International Patent Application No. 2003-503481).

Bosutinib (SKI-606) or an analog thereof can be produced according to the methods described in, for example, US Patent  
15 Nos. 6,002,008 and 6,780,996, or Boschelli, D.H. et al., J. Med. Chem., 44, 3965 (2001), Boschelli, D.H. et al., J Med. Chem., 44, 822 (2001), Boschelli, D.H. et al., Bioorg. Med. Chem. Lett., 13, 3797 (2003), Boschelli, D.H. et al., J. Med. Chem., 47, 1599 (2004), and Ye, F. et al., 221th National Meeting of  
20 the American Chemical Society, San diego, California (April, 2001).

[0129]

The compound of the present invention encompasses not only a free form but also a pharmacologically acceptable salt  
25 thereof. While the pharmacologically acceptable salt varies depending on the kind of the compound, examples thereof include base addition salts such as salts with inorganic base such as alkali metal salts (sodium salt, potassium salt etc.), alkaline earth metal salts (calcium salt, magnesium salt etc.), aluminum  
30 salt, ammonium salt and the like, and salts with organic base such as trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like and the like, and acid addition salts such as salts with  
35 inorganic acid such as hydrochloride, hydrobromide, sulfate,

hydroiodide, nitrate salt, phosphate and the like, and salts with organic acid such as citrate, oxalate, acetate, formate, propionate, benzoate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, paratoluenesulfonate and  
5 the like, and the like.

[0130]

When the compound of the present invention contains isomers such as an optical isomer, a stereoisomer, a regioisomer or a rotamer, any one of the isomers and mixtures  
10 are also encompassed in the compound of the present invention. For example, when the compound of the present invention contains an optical isomer, an optical isomer resolved from racemate is also encompassed in the compound of the present invention. For example, while 3-hydroxybutyric acid contains  
15 an optical isomer, D-3-hydroxybutyric acid is preferably used as a prophylactic or therapeutic agent for ALS.

These isomers can be obtained as single products by a synthesis method, a separation method (e.g., concentration, solvent extraction, column chromatography, recrystallization  
20 etc.), an optical resolution method (e.g., fractional recrystallization, chiral column method, diastereomer method etc.) and the like each known per se.

The compound of the present invention may be a crystal, and is included in the compound of the present invention  
25 whether it is in a single crystal form or a crystal mixture. The crystal can be produced by crystallizing by applying a crystallization method known per se.

The compound of the present invention may be a solvate (e.g., hydrate etc.) or a non-solvate (e.g., non-hydrate etc.),  
30 both of which are encompassed in the compound of the present invention.

In addition, a compound labeled with an isotope (e.g.,  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{35}\text{S}$ ,  $^{125}\text{I}$  etc.) is also encompassed in the compound of the present invention.

35 [0131]

Even when the compound of the present invention is any of the above-mentioned kinase inhibitors, or prostaglandin analogue, estrogen receptor antagonist, or any of the above-mentioned compounds not belonging to these, it can show  
5 efficacy for any ALS. For example, when the compound of the present invention is an Met inhibitor (e.g., Crizotinib), its anti-ALS activity may be higher on ALS having mutation in SOD1 gene.

When the compound of the present invention is an FGFR  
10 inhibitor (e.g., Pazopanib), its anti-ALS activity may be higher on ALS having mutation in TDP-43 gene and/or C9orf72 gene.

When the compound of the present invention is Tivozanib, its anti-ALS activity may be higher on ALS having mutation in  
15 SOD1 gene and/or TDP-43 gene and sporadic ALS.

When the compound of the present invention is Bosutinib or Sunitinib, its anti-ALS activity may be higher on ALS having mutation in SOD1 gene and/or C9orf72 gene and sporadic ALS.

When the compound of the present invention is Axitinib,  
20 its anti-ALS activity may be higher on ALS having mutation in C9orf72 gene.

Thus, since the compound of the present invention has different therapeutic activity spectrum for various familial or sporadic ALS depending on the kind thereof, a prophylactic or  
25 therapeutic agent for ALS, which contains a compound having higher anti-ALS activity as an active ingredient, can be appropriately selected and used according to the kind of ALS of the subject in need of the prophylaxis and/or treatment. Alternatively, a prophylactic or therapeutic agent for ALS,  
30 which has a high anti-ALS activity against any ALS, can also be provided by combining two or more compounds of the present invention having different therapeutic activity spectra. In this case, two or more compounds of the present invention may be each formulated singly or produced as a combination agent.  
35 In the former case, each preparation can be administered to the

same subject simultaneously or with time lag.

[0132]

The prophylactic and/or therapeutic agent for ALS of the present invention can be administered orally or parenterally in the form of the active ingredient the compound of the present invention as it is alone, or as a pharmaceutical composition in an appropriate dosage form blended with a pharmacologically acceptable carrier, excipient, diluent and the like.

[0133]

As the composition for oral administration, solid or liquid dosage forms, specifically tablets (including sugar-coated tablets and film-coated tablets), pills, granules, powders, capsules (including soft capsules), syrups, emulsions, suspensions and the like can be mentioned. Meanwhile, as examples of the composition for parenteral administration, injections, suppositories and the like are used; the injections may include dosage forms such as intravenous injections, subcutaneous injections, intracutaneous injections, intramuscular injections and drip infusion injections. These preparations are produced by a well-known method using additives, including excipients (e.g., organic excipients like sugar derivatives such as lactose, sucrose, glucose, mannitol, and sorbitol; starch derivatives such as cornstarch, potato starch,  $\alpha$  starch, and dextrin; cellulose derivatives such as crystalline cellulose; gum arabic; dextran; and pullulan; and inorganic excipients like silicate derivatives such as light anhydrous silicic acid, synthetic aluminum silicate, calcium silicate, and magnesium metasilicoaluminate; phosphates such as calcium hydrogen phosphate; carbonates such as calcium carbonate; and sulfates such as calcium sulfate), lubricants (e.g., stearic acid, stearic acid metal salts such as calcium stearate and magnesium stearate; talc; colloidal silica; waxes such as beeswax and spermaceti; boric acid; adipic acid; sulfates such as sodium sulfate; glycol; fumaric acid; sodium benzoate; DL leucine; lauryl sulfates such as sodium lauryl

sulfate and magnesium lauryl sulfate; silicates such as silicic anhydride and silicic hydrates; and the aforementioned starch derivatives), binders (e.g., hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, macrogol, and the same compounds as the aforementioned excipients), disintegrants (e.g., cellulose derivatives such as low-substitutional hydroxypropylcellulose, carboxymethylcellulose, carboxymethylcellulose calcium, and internally crosslinked carboxymethylcellulose sodium; chemically modified starches and cellulosides such as carboxymethylstarch, carboxymethylstarch sodium, and crosslinked polyvinylpyrrolidone), emulsifiers (e.g., colloidal clays such as bentonite and Veegum; metal hydroxides such as magnesium hydroxide and aluminum hydroxide; anionic surfactants such as sodium lauryl sulfate and calcium stearate; cationic surfactants such as benzalkonium chloride; and non-ionic surfactants such as polyoxyethylene alkyl ethers, polyoxyethylene sorbitan fatty acid ester of, and sucrose fatty acid ester), stabilizers (para-oxybenzoic acid esters such as methyl paraben and propyl paraben; alcohols such as chlorobutanol, benzyl alcohol, and phenylethyl alcohol; benzalkonium chloride; phenols such as phenol and cresol; thimerosal; dehydroacetic acid; and sorbic acid), taste/odor correctives (e.g., sweeteners, souring agents, and flavors in common use), and diluents.

[0134]

The dose of the compound of the present invention as an active ingredient of the prophylactic and/or therapeutic agent for ALS in the present invention is variable according to various conditions such as the kind of compound, the patient's symptoms, age, weight, drug receptivity and the like. For oral administration, at least 0.1 mg (suitably 0.5 mg) to at most 1000 mg (suitably 500 mg) per dose for oral administration, or at least 0.01 mg (suitably 0.05 mg) to at most 100 mg (suitably 50 mg) per dose for parenteral administration, can be administered to an adult 1 to 6 times a day. The dose may be

increased or reduced according to the symptoms. Particularly, when the compound of the present invention is already on the market as a pharmaceutical product for a disease other than ALS, an appropriately dose of each compound can be determined within  
5 the range confirmed to be safe.

[0135]

Furthermore, the prophylactic and/or therapeutic agent for ALS of the present invention may be used in combination with other drugs, for example, glutamic acid action  
10 suppressants (e.g., riluzole and the like), neurotrophic factors [e.g., insulin-like growth factor-1, 5-HT<sub>1A</sub> receptor agonists (e.g., xaliproden) and the like] and the like. The prophylactic and/or therapeutic agent for ALS of the present invention and these other drugs can be administered  
15 simultaneously, sequentially, or separately.

[0136]

The present invention is hereinafter described in further detail by means of the following Example, to which, however, the invention is never limited.

20 [Example 1]

[0137]

iPS cells were produced according to Okita K, et al, Nat Methods. 2011, 8:409-12, by introducing SOX2, KLF4, OCT4, L-MYC, LIN28 and small hairpin RNA for p53 into fibroblast isolated  
25 from ALS patients (SOD1-L144FVX mutation) by using episomal vectors. The obtained iPS cells were cultured on SNL cells in a primate embryonic stem cell medium (ReproCELL) added with 4 ng/ml basic FGF (Wako Chemicals) and penicillin/streptomycin.

[0138]

30 Motoneuron cells established from iPS cells derived from ALS patients related to SOD1 mutation (SOD1-L144FVX mutation) were immunostained, whereby accumulation of misfolded SOD1 (Fig. 1A) and fragility (decrease in the number of surviving cells) derived from mutation of SOD1 was confirmed (Fig. 1B).

35 Immunostaining was performed by preparing samples according to

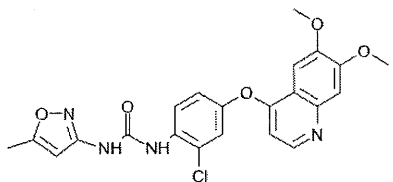
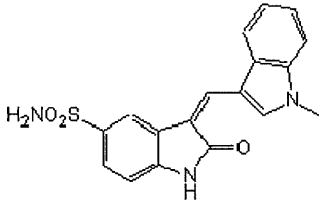
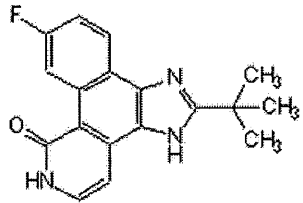
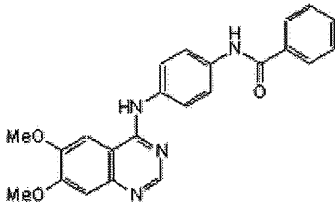
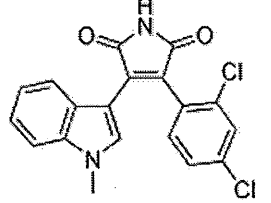
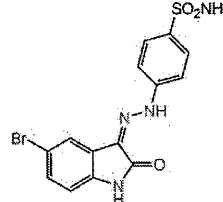
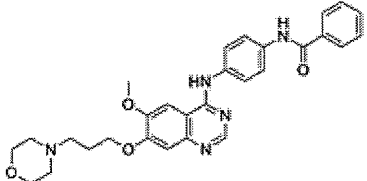
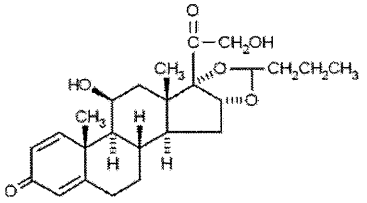
a conventional method, and staining same with  $\beta$ III tubulin (1:2000, Covance; 1:1000, abcam), HB9 (1:200, Developmental Studies Hybridoma Bank) and misfolded SOD1 (B8H10) (1:100, MEDIMABS). As the surviving cells, the cells stained with  $\beta$ III tubulin were counted using IN Cell Analyzer 2000 (GE Healthcare), IN Cell Analyzer 6000 and IN CELL Developer toolbox software 1.9 (GE Healthcare). Induction into motoneuron cells was performed by the method described in WO 2014/148646. In brief, 3 transcription factors of LIM homeobox protein 3 (Lhx3), neurogenin 2 (Ngn2) and ISL LIM homeobox 1 (Isl1) were introduced into iPS cells by using piggyBac transposon, and were polycistronically expressed by a tetracycline responsive promoter on a Matrigel-coated culture dish, whereby iPS cells were directly induced into motoneuron cells. At 7 days after addition of doxycycline, induction of motoneuron cell was completed. The cells were cultured in DMEM/F12 (Life Technologies) added with 100  $\mu$ g/ml apotransferrin (Sigma), 5  $\mu$ g/ml insulin (Sigma), 30 nM selenite (Sigma), 20 nM progesterone (Sigma), 100 nM putrescine (Sigma), 1  $\mu$ M RA, 1  $\mu$ M Shh, 10 ng/ml BDNF, 10 ng/ml GDNF, 10 ng/ml NT-3 and 1  $\mu$ g/ml doxycycline (Clontech). A known drug, riluzole, was added to the motoneuron cells derived from patients having SOD1-L144FVX mutation (at 7 days after addition of doxycycline), and the cells were cultured for 7 more days. Since the number of surviving cells was high, the motoneuron cell was confirmed to be useful for the evaluation of a therapeutic drug for ALS. [0139]

Subsequently, motoneuron cells derived from iPS cells having SOD1-L144FVX mutation, which were induced as mentioned above, were contacted with a medicament for 7 days, and a candidate therapeutic drug was screened for by using cell survival as an index. Screening was performed after calculating the Z factor from a 50  $\mu$ M Kenpaullone (Tocris) (Cell Stem Cell, 12, 1-14, 2013) administration group having a known effect (positive control) and a DMSO administration group

(negative control) (Zhang, J.H., et al., J. Biomol. Screen 4: 67-73, 1999), and confirming that the Z factor was not less than 0.5. The effect was studied with the libraries of 1760 compounds and medicaments considered to be effective for the treatment of ALS having an MN index (motoneuron cell survival number ratio as compared to negative control) of not less than 3SD were detected. The medicaments are shown in the following Tables 4-1 - 4-5. As the compound libraries, Microsource US Drugs (Microsource Discovery Systems), Microsource International Drugs (Microsource Discovery Systems), InhibitorSelect™ 96-Well Protein Kinase Inhibitor Library (EMD), InhibitorSelect™ 96-Well Protein Kinase Inhibitor Library II (EMD), InhibitorSelect™ 96-Well Protein Kinase Inhibitor Library III (EMD), Screen-Well(R) Kinase inhibitor library (ENZO) and Kinase Inhibitor Library (Selleck Chemicals LLC.) were used.

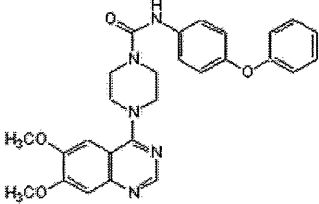
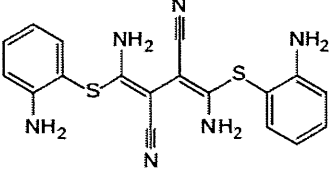
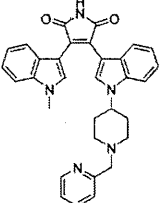
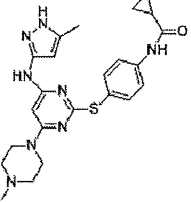
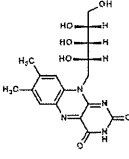
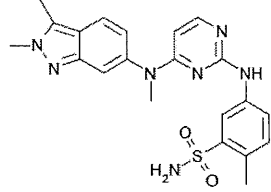
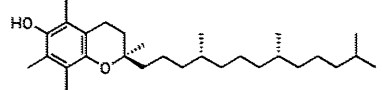
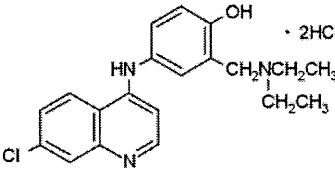
[0140]

[Table 4-1]

| drug                       | structural formula                                                                  | MN index | category                |
|----------------------------|-------------------------------------------------------------------------------------|----------|-------------------------|
| Tivozanib                  |   | 17.26    | none                    |
| Syk Inhibitor              |    | 16.14    | Syk inhibitor           |
| JAK Inhibitor I            |    | 12.59    | JAK inhibitor           |
| Aurora Kinase Inhibitor II |   | 11.77    | Aurora kinase inhibitor |
| SB 216763                  |  | 11.73    | none                    |
| Cdk2 Inhibitor II          |  | 10.93    | none                    |
| ZM-447439                  |  | 10.90    | Aurora kinase inhibitor |
| BUDESONIDE                 |  | 10.27    | none                    |

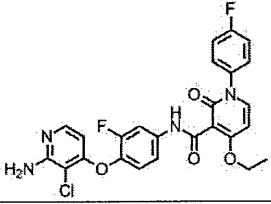
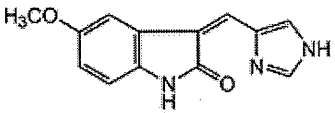
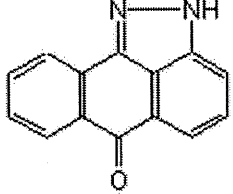
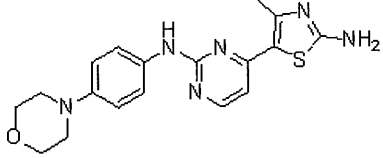
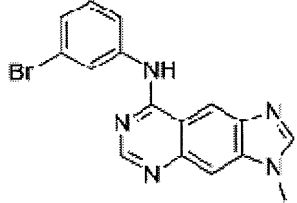
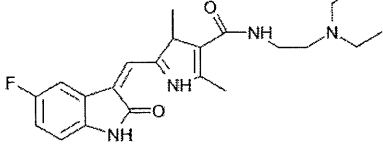
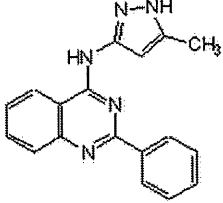
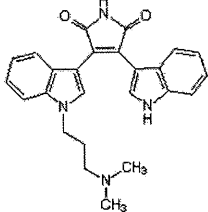
[0141]

[Table 4-2]

| drug                                              | structural formula                                                                  | MN index | category                                                                       |
|---------------------------------------------------|-------------------------------------------------------------------------------------|----------|--------------------------------------------------------------------------------|
| PDGF Receptor<br>Tyrosine Kinase<br>Inhibitor III |    | 10.15    | EGFR<br>inhibitor<br>FGFR<br>inhibitor<br>PKA<br>inhibitor<br>PKC<br>inhibitor |
| U0126-EtOH                                        |    | 10.13    | MEK<br>inhibitor                                                               |
| Enzastaurin                                       |    | 9.84     | PKC<br>inhibitor                                                               |
| VX-680                                            |  | 9.58     | Aurora<br>kinase<br>inhibitor                                                  |
| RIBOFLAVIN                                        |  | 9.55     | none                                                                           |
| Pazopanib<br>Hydrochloride                        |  | 9.53     | FGFR<br>inhibitor                                                              |
| alpha-TOCHOPHEROL                                 |  | 9.46     | none                                                                           |
| AMODIAQUINE<br>DIHYDROCHLORIDE                    |  | 8.98     | none                                                                           |

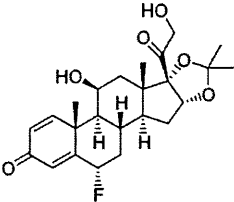
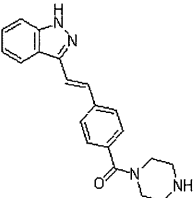
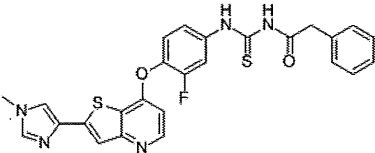
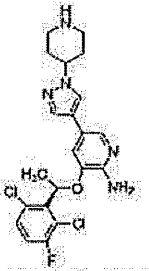
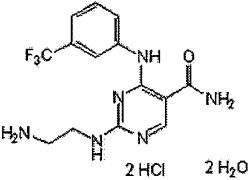
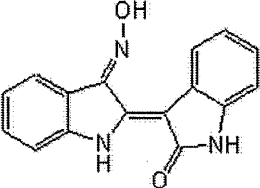
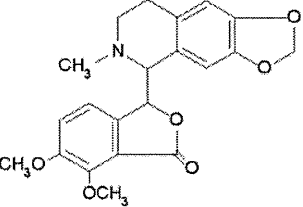
[0142]

[Table 4-3]

| drug                   | structural formula                                                                  | MN index | category                |
|------------------------|-------------------------------------------------------------------------------------|----------|-------------------------|
| BMS 777607             |    | 8.55     | Met inhibitor           |
| SU9516                 |    | 8.39     | none                    |
| SP600125               |    | 8.38     | JNK inhibitor           |
| CYC116                 |   | 8.14     | Aurora kinase inhibitor |
| BPIQ-I                 |  | 8.14     | FGFR inhibitor          |
| Sunitinib Malate       |  | 8.13     | none                    |
| GSK-3 Inhibitor XIII   |  | 8.13     | none                    |
| Bisindolyl-maleimide I |  | 7.96     | none                    |

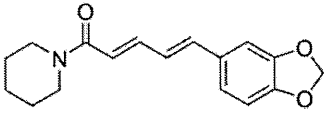
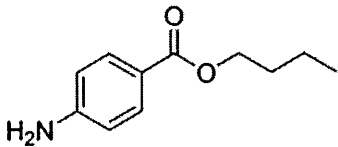
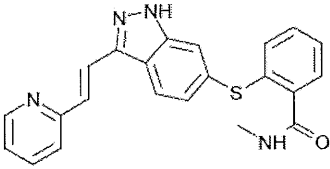
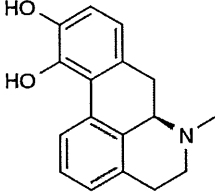
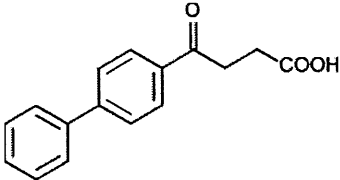
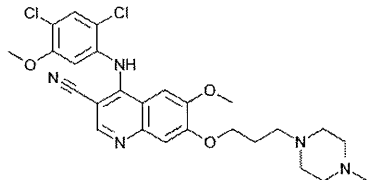
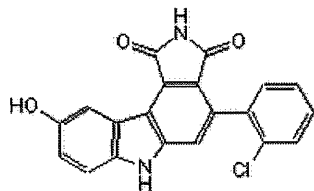
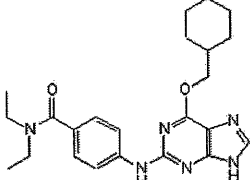
[0143]

[Table 4-4]

| drug                    | structural formula                                                                  | MN index | category                      |
|-------------------------|-------------------------------------------------------------------------------------|----------|-------------------------------|
| HYDROQUINONE            |    | 7.96     | none                          |
| FLUNISOLIDE             |    | 7.86     | none                          |
| KW 2449                 |    | 7.72     | Aurora<br>kinase<br>inhibitor |
| MGCD-265                |   | 7.62     | none                          |
| Crizotinib (PF-2341066) |  | 7.60     | Met<br>inhibitor              |
| Syk Inhibitor II        |  | 7.59     | Syk<br>inhibitor              |
| Indirubin-3'-monoxime   |  | 7.54     | none                          |
| HYDRASTINE (1R, 9S)     |  | 7.53     | none                          |

[0144]

[Table 4-5]

| drug                         | structural formula                                                                  | MN index | category |
|------------------------------|-------------------------------------------------------------------------------------|----------|----------|
| PIPERINE                     |    | 7.39     | none     |
| BUTAMBEN                     |    | 7.39     | none     |
| Axitinib                     |    | 7.35     | none     |
| APOMORPHINE<br>HYDROCHLORIDE |   | 7.26     | none     |
| FENBUFEN                     |  | 7.22     | none     |
| Bosutinib (SKI-606)          |  | 7.20     | none     |
| Wee1 Inhibitor               |  | 7.18     | none     |
| Cdk2 Inhibitor<br>IV, NU6140 |  | 7.08     | none     |

[Example 2]

[0145]

Bosutinib was purchased from Abcam, Sunitinib was purchased from SIGMA, Tivozanib and Crizotinib were purchased from LKT Laboratories, Axitinib was purchased from Selleck Chemicals LLC, and Pazopanib was purchased from AdooQ BioScience and used for this Example.

[0146]

Tivozanib, Bosutinib, Sunitinib, Crizotinib, Axitinib and Pazopanib obtained in Example 1 as candidate drugs for ALS were studied for the dose correlation in the protection effect on motoneuron cell having SOD1 mutation. As a result, all medicaments were confirmed to show an increase in the effect in a dose-dependent manner (Fig. 2).

[0147]

Tivozanib, Bosutinib and Sunitinib were studied for the effect on nerve cell derived from iPS cell having SOD1-L144FVX mutation. The nerve cells induced by 56 days of culture were subjected to a filter treatment with a 70  $\mu$ m mesh, transferred to a 96 well plate, 1  $\mu$ M of Tivozanib, Bosutinib, Sunitinib was added, the cells were cultured for 48 hr, and the length of neuritis was evaluated. As a result, elongation of neuritis was confirmed in the Tivozanib, Bosutinib and Sunitinib treatment groups. For induction of nerve cells, Wada, T. et al PLoS One, 4(8):e6722 2009, Chambers, S. M. et al Nat Biotechnol, 27(3):275-280, 2009 were used after modification. In detail, small clumps (diameter 40 - 100  $\mu$ m) of iPS cell colonies were subjected to a filter treatment with Cell Strainer (BD Falcon), and cultured for 10 days in N2B27 medium [DMEM/F12, Neurobasal, N2 supplement, B27 supplement, L-Gln] added with 100 ng/ml human recombinant Noggin (R&D systems) and 1  $\mu$ M SB431542 (Sigma) in a culture dish coated with poly-L-lysine (Sigma)/Laminin (BD Falcon) (PLL/LM). Then, the colonies were dissociated into small clumps with 200 U/ml collagenase added with  $\text{CaCl}_2$ , and transferred into a culture dish coated with

PLL/ECL (Millipore). After 7 days of culture, the cells were dissociated with Accutase (Innovative Cell Technologies), and cultured in a culture dish coated with PLL/ECL for 7 days (24d). Finally, the cells dissociated with Accutase and selected by a  
5 40  $\mu$ m cell strainer (BD Falcon) were counted, cultured for 31 days (56d) in N2B27 medium added with 10 ng/ml BDNF, GDNF, and NT-3 (R&D systems) in a culture dish coated with PLL/LM/Fibronectin (Millipore) to give nerve cells from the iPS cells.

10 [0148]

It is known that phosphorylation of Erk is promoted in nerve cells having mutation SOD1. To examine the mechanism of these candidate medicaments, phosphorylation of Erk was examined by Western blot method. The Western blot method  
15 included dissolving cells in RIPA buffer containing 0.1% SDS, 150 mM NaCl, 1% NP-40, 0.5% deoxycholate, 50 mM Tris-HCl (pH 8.0), protease inhibitor (Roche) and phosphatase inhibitor (Roche), centrifugation, measurement of protein concentration, addition of 20  $\mu$ g amount of protein to each lane, and  
20 electrophoresis in 10-20% polyacrylamide gel. After blotting to Immobilon-P membrane (Millipore), the cells were stained with antibodies against Erk, phosphorylated Erk, c-Abl and phosphorylated c-Abl and detected. As a result, it was confirmed that phosphorylation of Erk decreased by culturing  
25 nerve cells after addition of 1  $\mu$ M of Tivozanib, Bosutinib, Sunitinib. Similarly, it was confirmed that phosphorylation of c-abl also decreased by the treatment with the medicaments (Fig. 3). These results suggest that the medicaments suppress motoneuron cell death by inhibiting phosphorylation of Erk and  
30 c-abl.

[0149]

Lastly, the effect of candidate medicaments on the motoneuron cells derived from ALS patients was studied using iPS cells derived from ALS patients having other gene mutation  
35 (SOD1, TDP-43 and C9orf72) and iPS cells derived from sporadic

ALS patients. The iPS cells were prepared from fibroblast isolated from ALS patients (SOD1-L144FVX mutation, TDP-43-M337V mutation and abnormal elongation of (GGGGCC)<sub>n</sub> repeat number in gene locus intron 1 of C9orf72) by a method similar to the above-mentioned method. iPS cells were cultured on SNL cells in a primate embryonic stem cell medium (ReproCELL) added with 4 ng/ml basic FGF (Wako Chemicals) and penicillin/streptomycin. Sporadic ALS was acknowledged by post mortem pathological test and exomeanalysis of fibroblast of patients. The number of survived motoneuron cells (on day 14 from the start of induction) induced from iPS cells derived from these ALS patients was counted, whereby it was confirmed that the number survived decreased in any ALS (Fig. 4). On day 7 from the start of induction from iPS cells, Tivozanib, Bosutinib, Sunitinib, Crizotinib, Pazopanib and Axitinib were added and the cells were cultured, and further cultured for 7 days, and the survived motoneuron cells were counted on day 14. It was confirmed that each medicament specifically shows the effect on ALS having particular mutation (Fig. 5). Those having a significant difference in the cell survival rate improving effect are shown in Table 5. In addition, those showing 20% improvement in the cell survival rate are considered to have a marked effect, and the analysis results thereof are shown in Table 6.

[0150]

[Table 5]

|            | SOD1<br>mutation | TDP-43<br>mutation | C9orf72<br>mutation | sporadic |
|------------|------------------|--------------------|---------------------|----------|
| Tivozanib  | O                | O                  | O                   | O        |
| Bosutinib  | O                | O                  | O                   | O        |
| Sunitinib  | O                | O                  | O                   | O        |
| Crizotinib | O                | x                  | O                   | x        |
| Pazopanib  | O                | O                  | O                   | x        |
| Axitinib   | x                | x                  | O                   | x        |

O: significant difference (p<0.05)

x: no significant difference (p≥0.05)

[0151]

[Table 6]

|            | SOD1<br>mutation | TDP-43<br>mutation | C9orf72<br>mutation | sporadic |
|------------|------------------|--------------------|---------------------|----------|
| Tivozanib  | O                | O                  | x                   | O        |
| Bosutinib  | O                | x                  | O                   | O        |
| Sunitinib  | O                | x                  | O                   | O        |
| Crizotinib | O                | x                  | x                   | x        |
| Pazopanib  | x                | O                  | O                   | x        |
| Axitinib   | x                | x                  | O                   | x        |

O: cell survival rate improvement not less than 20%

x: cell survival rate improvement less than 20%

5

[0152]

From the above results, Tivozanib was confirmed to show higher efficacy for ALS having SOD1 mutation, ALS having TDP-43 mutation and sporadic ALS, Bosutinib was confirmed to show  
10 higher efficacy for ALS having SOD1 mutation, ALS having C9orf72 mutation and sporadic ALS, Sunitinib was confirmed to show higher efficacy for ALS having SOD1 mutation, ALS having C9orf72 mutation and sporadic ALS, Crizotinib was confirmed to show higher efficacy for ALS having SOD1 mutation, Pazopanib  
15 was confirmed to show higher efficacy for ALS having TDP-43 mutation and ALS having C9orf72 mutation, and Axitinib was confirmed to show higher efficacy for ALS having C9orf72 mutation.

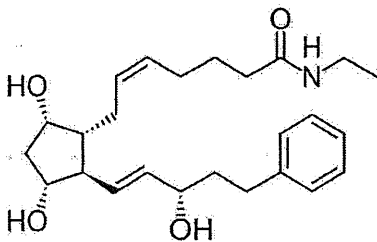
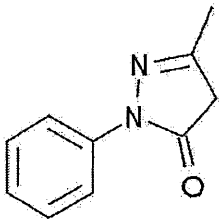
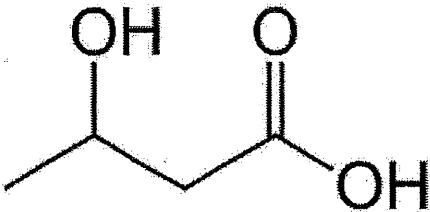
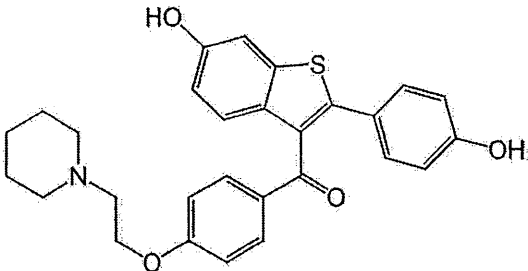
[Example 3]

20 [0153]

Bimatoprost was purchased from SIGMA, Edaravone was purchased from TOCRIS, (+-) 3-hydroxybutyric acid was purchased from SIGMA, and Raloxifene was purchased from TOCRIS and they were used for this Example. The structural formulas of these  
25 compounds are shown in Table 7.

[0154]

[Table 7]

| drug                  | structural formula                                                                   | category                     |
|-----------------------|--------------------------------------------------------------------------------------|------------------------------|
| Bimatoprost           |     | prostaglandin analogue       |
| Edaravone             |     |                              |
| 3-hydroxybutyric acid |    |                              |
| Raloxifene            |  | estrogen receptor antagonist |

5 [0155]

Bimatoprost, Edaravone, 3-hydroxybutyric acid and Raloxifene were studied for the dose correlation in the protection effect on motoneuron cell having the aforementioned SOD1-L144FVX mutation. As a result, all medicaments were confirmed to show an increase in the effect in a dose-dependent manner (Fig. 6). As described in Amyotroph Lateral Scler

Frontotemporal Degener. 15:610-617, 2014, Edaravone is shown to be effective for ALS, and it was demonstrated that the medicaments found by screening in this Example are effective for ALS.

5 [Example 4]

[0156]

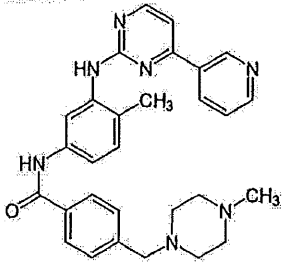
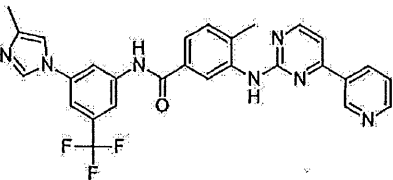
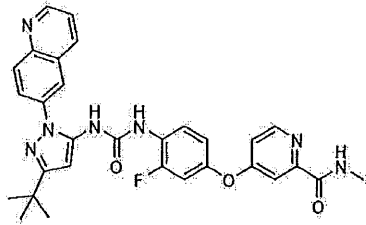
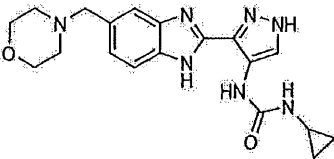
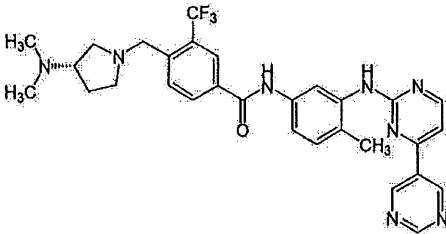
Method

1. Medicament screening using motor neuron derived from iPS cell

10 Imatinib, Nilotinib, Rebastinib, AT9283, Bafetinib were purchased from Selleck. Using 0, 0.01, 0.1, 1, 10  $\mu$ M of the above-mentioned reagents, screening was performed. The structural formulas of these compounds are shown in Table 8.

[0157]

[Table 8]

| drug       | structural formula                                                                  | category                                            |
|------------|-------------------------------------------------------------------------------------|-----------------------------------------------------|
| Imatinib   |    |                                                     |
| Nilotinib  |    |                                                     |
| Rebastinib |   |                                                     |
| AT9283     |  | <p>Aurora kinase inhibitor</p> <p>JAK inhibitor</p> |
| Bafetinib  |  |                                                     |

5 [0158]

The production method and screening method of motor neuron are similar to those in Example 1.

## 2. Western blotting

Vehicle (DMSO) or 1  $\mu$ M Bosutinib was added to the motor neuron on day 7 of culture, and the mixture was cultured for 72 hr. PBS washing was performed once, and the cells were recovered with a scraper and dissolved in RIPA buffer (0.1% SDS, 150 mM NaCl, 1% NP-40, 0.5% deoxycholate, 50 mM Tris-HCl (pH 8.0), protease inhibitor (Roche), phosphatase inhibitor (Roche)). After sonication, the cells were centrifuged at 13,000 g for 10 min, and the supernatant was separated. 10  $\mu$ g of a sample added with sample buffer (free of reducing agent, Nacalai) was electrophoresed on SDS-page, and blotted on Immobilon-P membrane (Millipore). The cells were blocked with 5% skim milk for 1 hr, primary antibody TDP-43 antibody (1:2000, protein tech) was added and the mixture was reacted at 4°C overnight. The secondary antibody Rb IgG-HRP (1:5000, GE healthcare) was reacted for 1 hr, ECL prime (GE healthcare) was added over 5 min, and the cells were detected by LAS4000 (GE healthcare).

[0159]

## 20 Results

### 1. Screening by familial ALS (mSOD1 ALS) motoneuron cells

Imatinib, Nilotinib, Rebastinib, AT9283, and Bafetinib increased survival of motor neuron (n=6, one-way ANOVA; p<0.05, post hoc test p<0.05) (Fig. 7).

### 25 2. Effect of Bosutinib on ALS other than mSOD1 ALS

In familial ALS having TDP-43 mutation and sporadic ALS, accumulation of 40-200 kD misfolded TDP-43 was found. Misfolded TDP43 decreased by the addition of Bosutinib (Fig. 8).  
[Industrial Applicability]

30 [0160]

The compound of the present invention is useful for the prophylaxis and/or treatment of ALS. Particularly, since clinical and nonclinical data of safety and the like of medicaments already on the market as pharmaceutical products for other diseases have been accumulated, and the libraries of

surrounding compounds already exist, it is expected that a pharmaceutical product capable of preventing and/or treating ALS can be developed rapidly at a low cost. In addition, an effective prophylaxis and/or treatment of ALS, which is  
5 suitable for individual patients or a preliminary group thereof, can be available by properly using the compound of the present invention according to the causative gene of ALS.

[0161]

All patents, patent specifications and all publications  
10 including scientific documents described herein are incorporated in their entireties by reference to the extent that they have been disclosed in the present specification.

[0162]

This application is based on patent application Nos.  
15 2015-004589 filed in Japan (filing date: January 13, 2015) and 2015-137909 filed in Japan (filing date: July 9, 2015), the contents of which are incorporated in full herein.

## Claims

- 5 1. Use of Bosutinib (SKI-606) in the manufacture of a prophylactic and/or therapeutic agent for amyotrophic lateral sclerosis (ALS) having mutation in SOD1 gene and/or C9orf72 gene and sporadic ALS.