

DESCRIPTION

Title of Invention: PHARMACEUTICAL COMPOSITION COMPRISING BICYCLIC
NITROGEN-CONTAINING AROMATIC HETEROCYCLIC AMIDE COMPOUND AS
5 ACTIVE INGREDIENT

Technical Field

[0001]

The present invention relates to a pharmaceutical composition for treating lung
10 cancer in which mitochondrial Complex I is involved, particularly non-small cell lung
cancer, comprising a bicyclic nitrogen-containing aromatic heterocyclic amide compound
or a pharmaceutically acceptable salt thereof as an active ingredient.

Background Art

15 [0002]

Lung cancer occurs by the disorganized proliferation of cells resulting from a loss
of normal function in cells of the trachea, bronchi, and alveoli. The number of lung
cancer deaths accounts for 17% of the total cancer deaths, which is the highest, and
approximately 1.3 million people in the world die each year due to lung cancer.

20 The treatment of lung cancer is roughly divided into surgery (surgical treatment),
anticancer agents (chemotherapy), and radiation (radiation therapy), but whether the
treatment will be effective or not changes according to histological types of lung cancer.
For example, a definitive diagnosis of lung cancer is performed by the cytopathologic
diagnosis of microscopic specimens by a pathologist, but small cell lung cancer accounting
25 for approximately 20% of lung cancers generally has high degree of malignancy, grows
and progresses very quickly, and often metastasizes to other organs, and therefore is often
an advanced cancer already when found. For this reason, chemotherapy and radiation
therapy are performed in many cases, but even with a relatively high sensitivity to these
therapies, relapse occurs, and therefore a prognosis is not good. Meanwhile, surgical
30 treatment is considered for non-small cell lung cancer accounting for the remainder of 80%
up to certain stages, but beyond those stages, surgery is unlikely to be applied, and
chemotherapy and radiation therapy become the main treatment. Accordingly, in all lung
cancers, chemotherapy is an important choice for the treatment.

Based on such background, metformin known as the primary drug of choice of an
35 agent for treating type II diabetes is attracting attention. It has been reported that in
epidemiological analysis, the lung cancer risk of metformin users is significantly lower
compared to that of non-metformin users (BMC Cancer 2012, 12: 410). In addition, it
has been reported that in non-clinical trials, metformin exhibits an anti-tumor effect on

various types of cancer including non-small cell lung cancer, and many clinical trials that should be applied for the treatment of lung cancer are being carried out (Expert Opin. Investig. Drugs. 2013, 22: 1401-1409).

[0003]

5 Regarding the anti-tumor mechanism of metformin, it has been well known that the activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK) inhibits the proliferation of cancer cells (Cancer Res. 2006, 66: 10269-10273, Trends Endocrinol. Metab. 2013, 24: 469-480). AMPK is a highly-preserved serine/threonine kinase, controls energy metabolism in various cells, and monitors changes in the AMP/ATP
10 ratio in the cells and responds to it (Annu. Rev. Biochem. 1998, 67: 821-855). The activation of AMPK by metformin is known to be based on the effect of inhibiting mitochondrial Complex I (Diabetes Metab. 2003, 29 (4 Pt 2): 6S88-94). Mitochondrial Complex I is a NADH dehydrogenase located in the mitochondrial inner membrane and is known as the "entry enzyme" for oxidative phosphorylation in the mitochondria. As ATP
15 levels in the cells decrease by the inhibition of mitochondrial Complex I, the AMP/ATP ratio increases, AMP allosterically binds to AMPK, threonine-172 of AMPK's α -subunit is phosphorylated by liver kinase B1 (LKB1, also known as STK11), and therefore AMPK is activated. The activated AMPK inhibits mammalian target of rapamycin (mTOR) signaling via phosphorylation of tuberous sclerosis complex 2 (TSC2) (Genes Cells. 2003,
20 8: 65-79). This is considered to be one of the reasons why metformin inhibits the proliferation of cancer cells including non-small cell lung cancer (Clin. Cancer Res. 2013, 19: 3508-3519).

[0004]

25 In addition, the phosphorylation of AMPK by LKB1 is important in the activation of AMPK as described above, but mutations/defects in LKB1 occur very frequently in non-small cell lung cancer (Fam. Cancer. 2011, 10: 447-453). It has been reported recently that in such cancer, by the inhibition of mitochondrial Complex I by phenformin that is a structural analog of metformin, reactive oxygen species (ROS) are excessively produced, which induces cell death (Cancer Cell. 2013, 23: 143-158). That is, it is considered that a
30 compound such as metformin having the effect of inhibiting mitochondrial Complex I induces cell death of non-small cell lung cancer cells by mainly inhibiting mitochondrial Complex I as a starting point.

[0005]

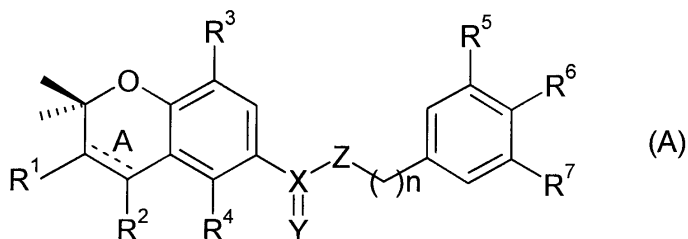
35 As a compound having the effect of inhibiting mitochondrial Complex I, regardless of whether they are natural or unnatural, many types of compounds such as rotenone, pyridaben, bullatacin, piericidin A, capsaicin, fenazaquin, and the like are known. In addition, for example, it has been reported that a compound of Formula (A)

below has the effect of inhibiting mitochondrial Complex I and inhibits the proliferation of various types of cancer cells including lung cancer cells (Patent Document 1).

[0006]

[Chem. 1]

5



(refer to the corresponding publication for the meaning of symbols in the formula)

[0007]

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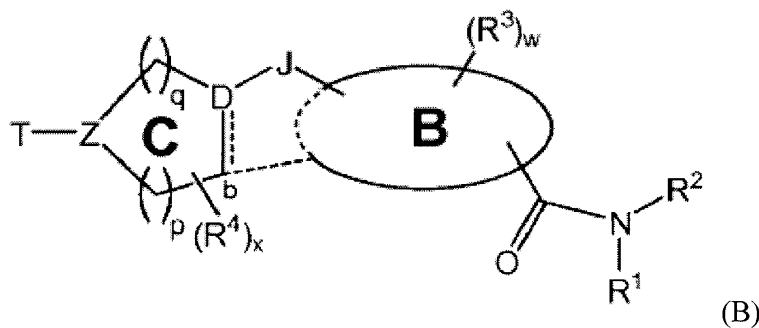
In addition, as a compound having the effect of activating AMPK, it has been reported that for example, compounds of Formulae (B) and (C) below have the effect of activating AMPK, and is useful for treating a metabolic disorder such as type II diabetes, atherosclerosis, cardiovascular disease, and the like (refer to Patent Document 2 and Patent Document 3, respectively). However, in the documents, there is no specific description

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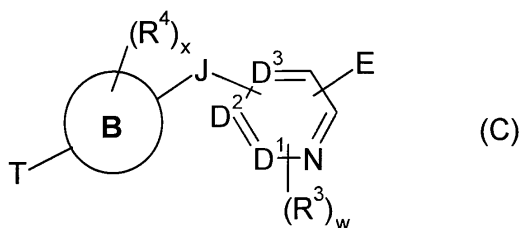
that teaches usefulness for treating cancer and the like.

[0008]

[Chem. 2]



20



(refer to the corresponding publication for the meaning of symbols in the formulas)

Related Art Document

Patent Document

[0009]

- 5 Patent Document 1: WO 02/20008
 Patent Document 2: WO 2009/132136
 Patent Document 3: WO 2012/016217

Summary of Invention

10 Problems to Be Solved by the Invention

[0010]

A pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved, particularly a pharmaceutical composition for treating non-small cell lung cancer is provided.

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Means for Solving the Problems

[0011]

- As a result of intensive examination for creating a pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved, particularly a
 20 pharmaceutical composition for treating non-small cell lung cancer, the inventors of the present invention have found that a bicyclic nitrogen-containing aromatic heterocyclic amide compound of the present invention or a pharmaceutically acceptable salt thereof exhibits an excellent effect of inhibiting mitochondrial Complex I (WO 2014/199933 internationally published by the applicant of the present application after the patent
 25 application that is the basis of the priority of the present application), and that this compound exhibits an anti-tumor effect on mice bearing tumors of non-small cell lung cancer-derived cells, and therefore have completed the present invention.

- That is, the present invention relates to a pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved, comprising a compound
 30 selected from (5-{1-[(6-methoxypyridin-3-yl)methyl]piperidin-4-yl}-1H-benzimidazol-2-yl){4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}methanone (hereinafter will be referred to as "Compound A"), (5-{1-[(5-methoxypyrazin-2-yl)methyl]piperidin-4-yl}-1H-benzimidazol-2-yl){4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}methanone (hereinafter will be referred to as "Compound B"), 4-({4-[(6-{1-[(5-ethoxypyrazin-2-yl)methyl]piperidin-4-yl}-1-methyl-1H-indol-2-yl)carbonyl]piperazin-1-yl}
 35 {1-[(5-methoxypyrazin-2-yl)methyl]piperidin-4-yl}-1-methyl-1H-indol-2-yl)carbonyl]piperazin-1-yl}methyl)benzonitrile (hereinafter will be referred to as "Compound C"), and 4-({4-[(5-{1-[(5-methoxypyrazin-2-yl)methyl]piperidin-4-yl}-1-methyl-1H-indol-2-yl)carbonyl]piperazin-1-yl}methyl)benzonitrile (hereinafter will be referred to as

“Compound D”), or a pharmaceutically acceptable salt thereof as an active ingredient, in another embodiment, a pharmaceutical composition for treating non-small cell lung cancer, in still another embodiment, a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved, in still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved.

[0012]

In addition, the present invention includes an agent for treating lung cancer in which mitochondrial Complex I is involved, comprising a compound selected from Compound A, Compound B, Compound C, and Compound D or a pharmaceutically acceptable salt thereof, in another embodiment, an agent for treating non-small cell lung cancer, in still another embodiment, an agent for treating non-small cell lung cancer in which mitochondrial Complex I is involved, in still further another embodiment, an agent for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in still further another embodiment, an agent for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved.

[0013]

In addition, the present invention relates to the use of a compound selected from Compound A, Compound B, Compound C, and Compound D or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved, in another embodiment, for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer, in still another embodiment, for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved, in still further another embodiment, for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in still further another embodiment, for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved; the use of a compound selected from Compound A, Compound B, Compound C, and Compound D or a pharmaceutically acceptable salt thereof for treating lung cancer in which mitochondrial Complex I is involved, in another embodiment, for treating non-small cell lung cancer, in still another embodiment, for treating non-small cell lung cancer in which mitochondrial Complex I is involved, in still further another embodiment, for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in still further another embodiment, for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial

Complex I is involved; a compound selected from Compound A, Compound B, Compound C, and Compound D or a pharmaceutically acceptable salt thereof for treating lung cancer in which mitochondrial Complex I is involved, in another embodiment, for treating non-small cell lung cancer, in still another embodiment, for treating non-small cell lung cancer in which mitochondrial Complex I is involved, in still further another embodiment, for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in still further another embodiment, for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved; and a method for treating lung cancer in which mitochondrial Complex I is involved by administering an effective amount of a compound selected from Compound A, Compound B, Compound C, and Compound D or a pharmaceutically acceptable salt thereof to a subject, in another embodiment, a method for treating non-small cell lung cancer, in still another embodiment, a method for treating non-small cell lung cancer in which mitochondrial Complex I is involved, in still further another embodiment, a method for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in still further another embodiment, a method for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved. The term "subject" refers to humans or any other animals in need of the treatment, and in another embodiment, refers to humans in need of the treatment.

20

Effects of the Invention

[0014]

A compound selected from Compound A, Compound B, Compound C, and Compound D or a pharmaceutically acceptable salt thereof, which are active ingredients of a pharmaceutical composition of the present invention, has the effect of inhibiting mitochondrial Complex I, exhibits an anti-tumor effect on mice bearing tumors of non-small cell lung cancer-derived cells, and can be used as an active ingredient of a pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved, in another embodiment, of a pharmaceutical composition for treating non-small cell lung cancer, in still another embodiment, of a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved, in still further another embodiment, of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in still further another embodiment, of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved.

35

Embodiments for Carrying Out the Invention

[0015]

Hereinafter, the present invention will be described in detail.

[0016]

In the present specification, examples of lung cancer in which mitochondrial Complex I is involved include lung cancer in which the electron transport system of the mitochondria is activated and thereby oxidative phosphorylation in the mitochondria is enhanced, in another embodiment, non-small cell lung cancer, and in still another embodiment, non-small cell lung cancer in which mitochondrial Complex I is involved. In addition, examples of non-small cell lung cancer having mutations and/or defects in LKB1 include non-small cell lung cancer in which phosphorylation of AMPK by LKB1 is suppressed, and in another embodiment, non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved.

[0017]

In the present specification, “a pharmaceutically acceptable salt of a compound selected from Compound A, Compound B, Compound C, and Compound D” means an acid addition salt of Compound A, Compound B, Compound C, or Compound D. Specific examples of the acid addition salt include the salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, mandelic acid, tartaric acid, dibenzoyltartaric acid, ditoluoyltartaric acid, citric acid, methanesulfonic acid (mesylic acid), ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid (tosylic acid), aspartic acid, glutamic acid, and the like.

Examples of “a compound selected from Compound A, Compound B, Compound C, and Compound D” include various solvates of Compound A, Compound B, Compound C, or Compound D, and specifically, include a hydrate or an ethanol solvate. Furthermore, “a pharmaceutically acceptable salt” includes an acid addition salt of these solvates.

In addition, examples of “a compound selected from Compound A, Compound B, Compound C, and Compound D or a pharmaceutically acceptable salt thereof” include freebase in which a salt is not formed, that is, Compound A, Compound B, Compound C, or Compound D in a certain embodiment, Compound A in another embodiment, Compound B in still another embodiment, and Compound C in still further another embodiment, and Compound D in still further another embodiment. Furthermore, a tosylate salt of Compound A, Compound B, Compound C, or Compound D is included in another embodiment, a ditosylate salt of Compound A in still another embodiment, a ditosylate salt of Compound B in still further another embodiment, a ditosylate salt of Compound C in still further another embodiment, and a ditosylate salt of Compound D in still further another embodiment.

[0018]

The embodiments of the present invention are presented as below.

(1-1) A pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved, comprising Compound A or a pharmaceutically acceptable salt thereof as an active ingredient. In another embodiment, a pharmaceutical composition for treating non-small cell lung cancer, comprising Compound A or a pharmaceutically acceptable salt thereof as an active ingredient. In still another embodiment, a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved, comprising Compound A or a pharmaceutically acceptable salt thereof as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, comprising Compound A or a pharmaceutically acceptable salt thereof as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved, comprising Compound A or a pharmaceutically acceptable salt thereof as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved, comprising a ditosylate salt of Compound A as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer, comprising a ditosylate salt of Compound A as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved, comprising a ditosylate salt of Compound A as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, comprising a ditosylate salt of Compound A as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved, comprising a ditosylate salt of Compound A as an active ingredient.

[0019]

(1-2) The use of Compound A or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved. In another embodiment, the use of Compound A or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer. In still another embodiment, the use of Compound A or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of Compound A or a

pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1. In still further another embodiment, the use of Compound A or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound A for the manufacture of a pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound A for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer. In still further another embodiment, the use of a ditosylate salt of Compound A for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound A for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1. In still further another embodiment, the use of a ditosylate salt of Compound A for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved.

[0020]

(1-3) The use of Compound A or a pharmaceutically acceptable salt thereof for treating lung cancer in which mitochondrial Complex I is involved. In another embodiment, the use of Compound A or a pharmaceutically acceptable salt thereof for treating non-small cell lung cancer. In still another embodiment, the use of Compound A or a pharmaceutically acceptable salt thereof for treating non-small cell lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of Compound A or a pharmaceutically acceptable salt thereof for treating non-small cell lung cancer having mutations and/or defects in LKB1. In still further another embodiment, the use of Compound A or a pharmaceutically acceptable salt thereof for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound A for treating lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound A for treating non-small cell lung cancer. In still further another embodiment, the use of a ditosylate salt of Compound A for treating non-small cell lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound A for treating non-small cell lung cancer having mutations and/or defects in LKB1. In still further another embodiment, the use of a ditosylate salt

of Compound A for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved.

[0021]

(1-4) Compound A or a pharmaceutically acceptable salt thereof for treating lung
5 cancer in which mitochondrial Complex I is involved. In another embodiment,
Compound A or a pharmaceutically acceptable salt thereof for treating non-small cell lung
cancer. In still another embodiment, Compound A or a pharmaceutically acceptable salt
thereof for treating non-small cell lung cancer in which mitochondrial Complex I is
involved. In still further another embodiment, Compound A or a pharmaceutically
10 acceptable salt thereof for treating non-small cell lung cancer having mutations and/or
defects in LKB1. In still further another embodiment, Compound A or a
pharmaceutically acceptable salt thereof for treating non-small cell lung cancer having
mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved. In
still further another embodiment, a ditosylate salt of Compound A for treating lung cancer
15 in which mitochondrial Complex I is involved. In still further another embodiment, a
ditosylate salt of Compound A for treating non-small cell lung cancer. In still further
another embodiment, a ditosylate salt of Compound A for treating non-small cell lung
cancer in which mitochondrial Complex I is involved. In still further another
embodiment, a ditosylate salt of Compound A for treating non-small cell lung cancer
20 having mutations and/or defects in LKB1. In still further another embodiment, a
ditosylate salt of Compound A for treating non-small cell lung cancer having mutations
and/or defects in LKB1, and in which mitochondrial Complex I is involved.

[0022]

(1-5) A method for treating lung cancer in which mitochondrial Complex I is
25 involved by administering an effective amount of Compound A or a pharmaceutically
acceptable salt thereof to a subject. In another embodiment, a method for treating non-
small cell lung cancer by administering an effective amount of Compound A or a
pharmaceutically acceptable salt thereof to a subject. In still another embodiment, a
method for treating non-small cell lung cancer in which mitochondrial Complex I is
30 involved by administering an effective amount of Compound A or a pharmaceutically
acceptable salt thereof to a subject. In still further another embodiment, a method for
treating non-small cell lung cancer having mutations and/or defects in LKB1 by
administering an effective amount of Compound A or a pharmaceutically acceptable salt
thereof to a subject. In still further another embodiment, a method for treating non-small
35 cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial
Complex I is involved by administering an effective amount of Compound A or a
pharmaceutically acceptable salt thereof to a subject. In still further another embodiment,
a method for treating cancer in which mitochondrial Complex I is involved by

administering an effective amount of a ditosylate salt of Compound A to a subject. In still further another embodiment, a method for treating non-small cell lung cancer by administering an effective amount of a ditosylate salt of Compound A to a subject. In still further another embodiment, a method for treating non-small cell lung cancer in which
5 mitochondrial Complex I is involved by administering an effective amount of a ditosylate salt of Compound A to a subject. In still further another embodiment, a method for treating non-small cell lung cancer having mutations and/or defects in LKB1 by administering an effective amount of a ditosylate salt of Compound A to a subject. In still further another embodiment, a method for treating non-small cell lung cancer having
10 mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved by administering an effective amount of a ditosylate salt of Compound A to a subject.

[0023]

(2-1) A pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved, comprising Compound B or a pharmaceutically
15 acceptable salt thereof as an active ingredient. In another embodiment, a pharmaceutical composition for treating non-small cell lung cancer, comprising Compound B or a pharmaceutically acceptable salt thereof as an active ingredient. In still another embodiment, a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved, comprising Compound B or a
20 pharmaceutically acceptable salt thereof as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, comprising Compound B or a pharmaceutically acceptable salt thereof as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer having mutations
25 and/or defects in LKB1, and in which mitochondrial Complex I is involved, comprising Compound B or a pharmaceutically acceptable salt thereof as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved, comprising a ditosylate salt of Compound B as an active ingredient. In still further another embodiment, a pharmaceutical
30 composition for treating non-small cell lung cancer, comprising a ditosylate salt of Compound B as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved, comprising a ditosylate salt of Compound B as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small
35 cell lung cancer having mutations and/or defects in LKB1, comprising a ditosylate salt of Compound B as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer having mutations

and/or defects in LKB1, and in which mitochondrial Complex I is involved, comprising a ditosylate salt of Compound B as an active ingredient.

[0024]

(2-2) The use of Compound B or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved. In another embodiment, the use of Compound B or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer. In still another embodiment, the use of Compound B or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of Compound B or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1. In still further another embodiment, the use of Compound B or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound B for the manufacture of a pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound B for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer. In still further another embodiment, the use of a ditosylate salt of Compound B for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound B for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1. In still further another embodiment, the use of a ditosylate salt of Compound B for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved.

[0025]

(2-3) The use of Compound B or a pharmaceutically acceptable salt thereof for treating lung cancer in which mitochondrial Complex I is involved. In another embodiment, the use of Compound B or a pharmaceutically acceptable salt thereof for treating non-small cell lung cancer. In still another embodiment, the use of Compound B or a pharmaceutically acceptable salt thereof for treating non-small cell lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of Compound B or a pharmaceutically acceptable salt thereof for treating non-small cell

lung cancer having mutations and/or defects in LKB1. In still further another embodiment, the use of Compound B or a pharmaceutically acceptable salt thereof for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved. In still further another embodiment, the use of a
5 ditosylate salt of Compound B for treating lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound B for treating non-small cell lung cancer. In still further another embodiment, the use of a ditosylate salt of Compound B for treating non-small cell lung cancer in which
10 mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound B for treating non-small cell lung cancer having mutations and/or defects in LKB1. In still further another embodiment, the use of a ditosylate salt of Compound B for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved.

[0026]

15 (2-4) Compound B or a pharmaceutically acceptable salt thereof for treating lung cancer in which mitochondrial Complex I is involved. In another embodiment, Compound B or a pharmaceutically acceptable salt thereof for treating non-small cell lung cancer. In still another embodiment, Compound B or a pharmaceutically acceptable salt thereof for treating non-small cell lung cancer in which mitochondrial Complex I is
20 involved. In still further another embodiment, Compound B or a pharmaceutically acceptable salt thereof for treating non-small cell lung cancer having mutations and/or defects in LKB1. In still further another embodiment, Compound B or a pharmaceutically acceptable salt thereof for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved. In
25 still further another embodiment, a ditosylate salt of Compound B for treating lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, a ditosylate salt of Compound B for treating non-small cell lung cancer. In still further another embodiment, a ditosylate salt of Compound B for treating non-small cell lung cancer in which mitochondrial Complex I is involved. In still further another
30 embodiment, a ditosylate salt of Compound B for treating non-small cell lung cancer having mutations and/or defects in LKB1. In still further another embodiment, a ditosylate salt of Compound B for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved.

[0027]

35 (2-5) A method for treating lung cancer in which mitochondrial Complex I is involved by administering an effective amount of Compound B or a pharmaceutically acceptable salt thereof to a subject. In another embodiment, a method for treating non-small cell lung cancer by administering an effective amount of Compound B or a

pharmaceutically acceptable salt thereof to a subject. In still another embodiment, a method for treating non-small cell lung cancer in which mitochondrial Complex I is involved by administering an effective amount of Compound B or a pharmaceutically acceptable salt thereof to a subject. In still further another embodiment, a method for treating non-small cell lung cancer having mutations and/or defects in LKB1 by administering an effective amount of Compound B or a pharmaceutically acceptable salt thereof to a subject. In still further another embodiment, a method for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved by administering an effective amount of Compound B or a pharmaceutically acceptable salt thereof to a subject. In still further another embodiment, a method for treating cancer in which mitochondrial Complex I is involved by administering an effective amount of a ditosylate salt of Compound B to a subject. In still further another embodiment, a method for treating non-small cell lung cancer by administering an effective amount of a ditosylate salt of Compound B to a subject. In still further another embodiment, a method for treating non-small cell lung cancer in which mitochondrial Complex I is involved by administering an effective amount of a ditosylate salt of Compound B to a subject. In still further another embodiment, a method for treating non-small cell lung cancer having mutations and/or defects in LKB1 by administering an effective amount of a ditosylate salt of Compound B to a subject. In still further another embodiment, a method for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved by administering an effective amount of a ditosylate salt of Compound B to a subject.

[0028]

(3-1) A pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved, comprising Compound C or a pharmaceutically acceptable salt thereof as an active ingredient. In another embodiment, a pharmaceutical composition for treating non-small cell lung cancer, comprising Compound C or a pharmaceutically acceptable salt thereof as an active ingredient. In still another embodiment, a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved, comprising Compound C or a pharmaceutically acceptable salt thereof as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, comprising Compound C or a pharmaceutically acceptable salt thereof as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved, comprising Compound C or a pharmaceutically acceptable salt thereof as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating lung cancer in

which mitochondrial Complex I is involved, comprising a ditosylate salt of Compound C as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer, comprising a ditosylate salt of Compound C as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved, comprising a ditosylate salt of Compound C as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, comprising a ditosylate salt of Compound C as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved, comprising a ditosylate salt of Compound C as an active ingredient.

[0029]

(3-2) The use of Compound C or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved. In another embodiment, the use of Compound C or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer. In still another embodiment, the use of Compound C or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of Compound C or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1. In still further another embodiment, the use of Compound C or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound C for the manufacture of a pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound C for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer. In still further another embodiment, the use of a ditosylate salt of Compound C for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound C for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1. In still further another embodiment, the use of a ditosylate salt of Compound C for the manufacture of a pharmaceutical composition for treating non-

small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved.

[0030]

(3-3) The use of Compound C or a pharmaceutically acceptable salt thereof for
5 treating lung cancer in which mitochondrial Complex I is involved. In another
embodiment, the use of Compound C or a pharmaceutically acceptable salt thereof for
treating non-small cell lung cancer. In still another embodiment, the use of Compound C
or a pharmaceutically acceptable salt thereof for treating non-small cell lung cancer in
which mitochondrial Complex I is involved. In still further another embodiment, the use
10 of Compound C or a pharmaceutically acceptable salt thereof for treating non-small cell
lung cancer having mutations and/or defects in LKB1. In still further another
embodiment, the use of Compound C or a pharmaceutically acceptable salt thereof for
treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which
mitochondrial Complex I is involved. In still further another embodiment, the use of a
15 ditosylate salt of Compound C for treating lung cancer in which mitochondrial Complex I
is involved. In still further another embodiment, the use of a ditosylate salt of Compound
C for treating non-small cell lung cancer. In still further another embodiment, the use of a
ditosylate salt of Compound C for treating non-small cell lung cancer in which
mitochondrial Complex I is involved. In still further another embodiment, the use of a
20 ditosylate salt of Compound C for treating non-small cell lung cancer having mutations
and/or defects in LKB1. In still further another embodiment, the use of a ditosylate salt
of Compound C for treating non-small cell lung cancer having mutations and/or defects in
LKB1, and in which mitochondrial Complex I is involved.

[0031]

(3-4) Compound C or a pharmaceutically acceptable salt thereof for treating lung
25 cancer in which mitochondrial Complex I is involved. In another embodiment,
Compound C or a pharmaceutically acceptable salt thereof for treating non-small cell lung
cancer. In still another embodiment, Compound C or a pharmaceutically acceptable salt
thereof for treating non-small cell lung cancer in which mitochondrial Complex I is
30 involved. In still further another embodiment, Compound C or a pharmaceutically
acceptable salt thereof for treating non-small cell lung cancer having mutations and/or
defects in LKB1. In still further another embodiment, Compound C or a
pharmaceutically acceptable salt thereof for treating non-small cell lung cancer having
mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved. In
35 still further another embodiment, a ditosylate salt of Compound C for treating lung cancer
in which mitochondrial Complex I is involved. In still further another embodiment, a
ditosylate salt of Compound C for treating non-small cell lung cancer. In still further
another embodiment, a ditosylate salt of Compound C for treating non-small cell lung

cancer in which mitochondrial Complex I is involved. In still further another embodiment, a ditosylate salt of Compound C for treating non-small cell lung cancer having mutations and/or defects in LKB1. In still further another embodiment, a ditosylate salt of Compound C for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved.

[0032]

(3-5) A method for treating lung cancer in which mitochondrial Complex I is involved by administering an effective amount of Compound C or a pharmaceutically acceptable salt thereof to a subject. In another embodiment, a method for treating non-small cell lung cancer by administering an effective amount of Compound C or a pharmaceutically acceptable salt thereof to a subject. In still another embodiment, a method for treating non-small cell lung cancer in which mitochondrial Complex I is involved by administering an effective amount of Compound C or a pharmaceutically acceptable salt thereof to a subject. In still further another embodiment, a method for treating non-small cell lung cancer having mutations and/or defects in LKB1 by administering an effective amount of Compound C or a pharmaceutically acceptable salt thereof to a subject. In still further another embodiment, a method for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved by administering an effective amount of Compound C or a pharmaceutically acceptable salt thereof to a subject. In still further another embodiment, a method for treating cancer in which mitochondrial Complex I is involved by administering an effective amount of a ditosylate salt of Compound C to a subject. In still further another embodiment, a method for treating non-small cell lung cancer by administering an effective amount of a ditosylate salt of Compound C to a subject. In still further another embodiment, a method for treating non-small cell lung cancer in which mitochondrial Complex I is involved by administering an effective amount of a ditosylate salt of Compound C to a subject. In still further another embodiment, a method for treating non-small cell lung cancer having mutations and/or defects in LKB1 by administering an effective amount of a ditosylate salt of Compound C to a subject. In still further another embodiment, a method for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved by administering an effective amount of a ditosylate salt of Compound C to a subject.

[0033]

(4-1) A pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved, comprising Compound D or a pharmaceutically acceptable salt thereof as an active ingredient. In another embodiment, a pharmaceutical composition for treating non-small cell lung cancer, comprising Compound D or a pharmaceutically acceptable salt thereof as an active ingredient. In still another

embodiment, a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved, comprising Compound D or a pharmaceutically acceptable salt thereof as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, comprising Compound D or a pharmaceutically acceptable salt thereof as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved, comprising Compound D or a pharmaceutically acceptable salt thereof as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved, comprising a ditosylate salt of Compound D as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer, comprising a ditosylate salt of Compound D as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved, comprising a ditosylate salt of Compound D as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, comprising a ditosylate salt of Compound D as an active ingredient. In still further another embodiment, a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved, comprising a ditosylate salt of Compound D as an active ingredient.

[0034]

(4-2) The use of Compound D or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved. In another embodiment, the use of Compound D or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer. In still another embodiment, the use of Compound D or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of Compound D or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1. In still further another embodiment, the use of Compound D or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound D for the manufacture of a

pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound D for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer. In still further another embodiment, the use of a ditosylate salt of Compound D for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound D for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1. In still further another embodiment, the use of a ditosylate salt of Compound D for the manufacture of a pharmaceutical composition for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved.

[0035]

(4-3) The use of Compound D or a pharmaceutically acceptable salt thereof for treating lung cancer in which mitochondrial Complex I is involved. In another embodiment, the use of Compound D or a pharmaceutically acceptable salt thereof for treating non-small cell lung cancer. In still another embodiment, the use of Compound D or a pharmaceutically acceptable salt thereof for treating non-small cell lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of Compound D or a pharmaceutically acceptable salt thereof for treating non-small cell lung cancer having mutations and/or defects in LKB1. In still further another embodiment, the use of Compound D or a pharmaceutically acceptable salt thereof for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound D for treating lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound D for treating non-small cell lung cancer. In still further another embodiment, the use of a ditosylate salt of Compound D for treating non-small cell lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, the use of a ditosylate salt of Compound D for treating non-small cell lung cancer having mutations and/or defects in LKB1. In still further another embodiment, the use of a ditosylate salt of Compound D for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved.

[0036]

(4-4) Compound D or a pharmaceutically acceptable salt thereof for treating lung cancer in which mitochondrial Complex I is involved. In another embodiment, Compound D or a pharmaceutically acceptable salt thereof for treating non-small cell lung cancer. In still another embodiment, Compound D or a pharmaceutically acceptable salt

thereof for treating non-small cell lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, Compound D or a pharmaceutically acceptable salt thereof for treating non-small cell lung cancer having mutations and/or defects in LKB1. In still further another embodiment, Compound D or a
5 pharmaceutically acceptable salt thereof for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved. In still further another embodiment, a ditosylate salt of Compound D for treating lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, a ditosylate salt of Compound D for treating non-small cell lung cancer. In still further
10 another embodiment, a ditosylate salt of Compound D for treating non-small cell lung cancer in which mitochondrial Complex I is involved. In still further another embodiment, a ditosylate salt of Compound D for treating non-small cell lung cancer having mutations and/or defects in LKB1. In still further another embodiment, a ditosylate salt of Compound D for treating non-small cell lung cancer having mutations
15 and/or defects in LKB1, and in which mitochondrial Complex I is involved.

[0037]

(4-5) A method for treating lung cancer in which mitochondrial Complex I is involved by administering an effective amount of Compound D or a pharmaceutically acceptable salt thereof to a subject. In another embodiment, a method for treating non-
20 small cell lung cancer by administering an effective amount of Compound D or a pharmaceutically acceptable salt thereof to a subject. In still another embodiment, a method for treating non-small cell lung cancer in which mitochondrial Complex I is involved by administering an effective amount of Compound D or a pharmaceutically acceptable salt thereof to a subject. In still further another embodiment, a method for
25 treating non-small cell lung cancer having mutations and/or defects in LKB1 by administering an effective amount of Compound D or a pharmaceutically acceptable salt thereof to a subject. In still further another embodiment, a method for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved by administering an effective amount of Compound D or a
30 pharmaceutically acceptable salt thereof to a subject. In still further another embodiment, a method for treating cancer in which mitochondrial Complex I is involved by administering an effective amount of a ditosylate salt of Compound D to a subject. In still further another embodiment, a method for treating non-small cell lung cancer by administering an effective amount of a ditosylate salt of Compound D to a subject. In
35 still further another embodiment, a method for treating non-small cell lung cancer in which mitochondrial Complex I is involved by administering an effective amount of a ditosylate salt of Compound D to a subject. In still further another embodiment, a method for treating non-small cell lung cancer having mutations and/or defects in LKB1 by

administering an effective amount of a ditosylate salt of Compound D to a subject. In still further another embodiment, a method for treating non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved by administering an effective amount of a ditosylate salt of Compound D to a subject.

5 [0038]

Pharmacological effects of a pharmaceutical composition of the present invention are confirmed by Test Examples below. In the Test Examples below, a ditosylate salt of Compound A (hereinafter will be referred to as Compound A1), a ditosylate salt of Compound B (hereinafter will be referred to as Compound B1), a ditosylate salt of
10 Compound C (hereinafter will be referred to as Compound C1), and a ditosylate salt of Compound D (hereinafter will be referred to as "Compound D1) were used as a test compound. In each Test Example, the concentration of Compounds A1, B1, C1, and D1 is described in terms of the concentration of each freebase.

[0039]

15 Test Example 1 Evaluation on Effect of Inhibiting Human Mitochondrial Complex I

Mitochondria were extracted from MDA-MB-453 tumor that is Human PIK3CA mutation-positive breast cancer, and the activity of inhibiting Complex I by Compounds A1, B1, C1, and D1 was evaluated.

20 PIK3CA mutation-positive breast cancer refers to breast cancer having mutations in PIK3CA, a gene name of p110 α which is the catalytic subunit of PI3K, among mutations in phosphatidylinositol 3-kinase (PI3K) pathway genes.

In addition, MDA-MB-453 cells used in this Test Example and the next Test Example 2 were obtained from the American Type Culture Collection (hereinafter will be
25 referred to as ATCC).

4-week-old male nude mice (Charles River Laboratories Japan, Inc.) were treated to bear the tumor of MDA-MB-453 cells derived from human PIK3CA mutation-positive breast cancer under their skin, and after MDA-MB-453 tumor reached a certain size, it was extracted. A solution for extraction of mitochondria (0.275 M Sucrose, 2.2 mM EDTA,
30 11 mM Tris/HCl, pH 7.5, Complete-EDTA-free (Roche Diagnostics)) was added thereto, by 9 times as much as the tumor weight, and then the tumor was crushed. The centrifugation was performed at 600 x g for 10 minutes at 4°C, the supernatant was obtained, and then the centrifugation was performed at 14,000 x g for 10 minutes at 4°C, and pellets were obtained. The pellets were suspended in 10 mM Tris/HCl pH 7.5 in the
35 amount of 5 times as much as the weight of the extracted tumor, and a suspension of human mitochondria was obtained.

Next, 25 or 50 μ l of the suspension of human mitochondria was added per 1 ml of a solution for measuring Complex I activity (25 mM potassium phosphate, pH 7.6, 0.35%

Bovine Serum Albumin (BSA), 60 μ M 2,6-dichlorophenol-indophenol, 70 μ M decylubiquinone, 1 μ M antimycin). After the solution was collected and added to a 96 or 384 well plate, a test compound was added to an arbitrary range from the final concentration of 10,000 nM to the final concentration of 0.3 nM. As a negative control, dimethylsulfoxide (DMSO) that is a solvent of the test compound was added to make a final concentration of 1%, and as a positive control, rotenone that is a Complex I inhibitor was added to make a final concentration of 1 μ M. Furthermore, NADH was added to each well to make a final concentration of 0.2 or 0.5 mM, and the change in absorbance at a wavelength of 600 nm was measured by using the SpectraMax (Molecular Devices, LLC.) set to 37°C in advance. Signal values in a DMSO treatment were set as the top value, and signal values in a rotenone 1 μ M treatment were set as the bottom value. Fluctuations in the signals were calculated within a range where the reaction was linear, and 50% inhibition values (IC_{50}) were calculated by a nonlinear regression analysis method using a Sigmoid Emax model. The result of Test Compounds A1, B1, C1, and D1 is shown in Table 1. Compounds A1 to D1 were produced by using a method described in Examples 1 to 4 described below (the same shall apply hereinafter).

[0040]

[Table 1]

Test Compound	IC_{50} (nM)
A1	41
B1	75
C1	22
D1	120

[0041]

Test Example 2 Evaluation on Effect of Activating AMPK

Phosphorylation of 79th serine (Ser79) of Acetyl-CoA Carboxylase (ACC) which is a substrate of AMPK was measured using Cell ELISA, and thereby the effect of activating AMPK by Compounds A1, B1, C1, and D1 was evaluated.

36 μ l each of MDA-MB-453 cells was seeded in Leibovitz's L-15 medium including 10% fetal bovine serum (Life Technologies Corporation) in a 384 well plate so that the cells became 15,000 cells per well, and the cells were cultured overnight at 37°C in the absence of CO₂. On the following day, Test Compounds A1, B1, C1, and D1, and DMSO which is a solvent for the test compounds as a negative control were diluted to a 10-fold concentration of a final concentration with a fresh medium, and 4 μ l of the resultant product was added to each well (the test compounds had 10 steps in a final concentration from 10,000 nM to 0.3 nM, and DMSO had a final concentration of 0.1%). After that, the cells were cultured at 37°C for 2 hours in the absence of CO₂. 20 μ l of a

40% glyoxal solution (Nacalai Tesque, INC.) was added to each well, and then the cells were left to stand at room temperature for 30 minutes to be fixed. Thereafter, the supernatant was removed by centrifuging the plate (at 800 rpm for 8 seconds by using the Ecospin of C.A.N. Hereinafter the centrifugation was performed under the same conditions unless otherwise specified), and 20 μ l of 0.1% Triton X-100-containing Phosphate-Buffered Saline (PBS) was added to each well, and then left to stand at room temperature for 10 minutes. The 0.1% Triton X-100-containing PBS was removed by centrifugation, and 20 μ l of a blocking solution (Odyssey Blocking Buffer manufactured by LI-COR Biosciences, Inc.) was added to each well, and then left to stand at room temperature for 1 hour. The blocking solution was removed by centrifugation, and 10 μ l of a blocking solution containing a phosphorylation antibody of ACC Ser79 (manufactured by Cell Signaling Technology, Inc.) as a primary antibody in the amount of 1/500 with respect to the undiluted solution was added to each well, and then left to stand at 4°C overnight. On the following day, the reaction solution was removed by centrifuging the plate, and 25 μ l of 0.05% Tween-20-containing Tris-Buffered Saline (TBS) (manufactured by Thermo Scientific; used in 1x by diluting 20xTBS Tween-20 with ion-exchange water) was added to each well, and then each well was washed by centrifugal removal. The washing was performed for a total of 3 times. After washing, 10 μ l of a blocking solution containing IRDye (registered trademark) 800CW Goat anti-Rabbit IgG (manufactured by LI-COR Biosciences, Inc.) as a secondary antibody in the amount of 1/1000 with respect to the undiluted solution was added to each well, and then left to stand at room temperature for 1 hour. The reaction solution was removed by centrifuging the plate, and then each well was washed for 3 times with 0.05% Tween-20-containing TBS in the same manner as after the primary antibody reaction. After the washing solution was removed, the plate was air-dried at room temperature for 3 hours or longer and signals were measured by Aeries (manufactured by LI-COR Biosciences, Inc.). Signal values in a DMSO treatment were set to a bottom value, and signal values when reaching a plateau were set to a top value, and 50% activation values (EC_{50}) were calculated by a nonlinear regression analysis method using a Sigmoid Emax model. The result of Test Compounds A1, B1, C1, and D1 is shown in Table 2.

[0042]

[Table 2]

Test Compound	EC_{50} (nM)
A1	24
B1	8.3
C1	1.8
D1	3.3

[0043]

Test Example 3 Anti-Tumor Test on Mice bearing Tumors of Non-Small Cell Lung Cancer-derived Cell (1)

5 A427 cells and NCI-H1395 cells which are LKB1 mutation-positive non-small cell lung cancer cell lines, and HARA cells and NCI-H1993 cells which are LKB1 wild-type non-small cell lung cancer cell lines, suspended in a mixed solution of PBS and Matrigel (registered trademark) in 1:1, were injected and implanted, 3×10^6 cells each, to 4- to 5-week-old male BALB/c nude mice (Charles River Laboratories Japan, Inc.) under the skin on the back. After that, administering of the test compounds was started after confirming
10 that the average tumor volume exceeded 100 mm^3 . The test was performed on each of the 4 to 5 mice in a solvent group and a compound administered group. By oral administration, 6% cyclodextrin aqueous solution for the solvent group, and 6% cyclodextrin aqueous solution in which the test compound was mixed by 8 mg/kg for the compound administered group were administered. The administration was performed
15 once a day for 14 days (NCI-H1993, HARA), 21 days (A427), or 35 days (NCI-H1395), and the body weight and the tumor diameter were measured twice a week. For calculation of the tumor volume, the formula below was used.

$$[\text{Tumor volume (mm}^3\text{)}] = [\text{major axis of tumor (mm)}] \times [\text{minor axis of tumor (mm)}]^2 \times 0.5$$

20 The inhibition rate of tumor growth and the rate of tumor regression were calculated from the average value of the tumor volume according to the formula below. The rate of tumor regression was calculated with respect to a group having an inhibition rate of tumor growth $> 100\%$.

25 Inhibition rate of tumor growth (%) = $(1 - \text{average of tumor volume growth in each group} / \text{average of tumor volume growth in control group}) \times 100$

Rate of tumor regression (%) = $(1 - \text{average tumor volume in each group on measuring day} / \text{average tumor volume in each group when dividing groups}) \times 100$

30 A427 cells, NCI-H1395 cells, NCI-H1993 cells, and HARA cells which are derived from non-small cell lung cancer can be purchased from ATCC, JCRB cell bank, or the like.

The anti-tumor effect of Test Compound A1 on the final measuring day is shown in Table 3.

[0044]

[Table 3]

Cell	Inhibition or regression rate
A427	41% regression
NCI-H1395	16% regression
HARA	32% inhibition
NCI-H1993	62% inhibition

[0045]

Test Example 4 Anti-Tumor Test on Mice bearing Tumors of Non-Small Cell Lung

5 Cancer-derived Cell (2)

A427 cells and NCI-H1395 cells which are LKB1 mutation-positive non-small cell lung cancer cell lines, and HARA cells and NCI-H1993 cells which are LKB1 wild-type non-small cell lung cancer cell lines, suspended in a mixed solution of PBS and Matrigel (registered trademark) in 1:1, were injected and implanted, 3×10^6 cells each (for A427 cells, 5×10^6), to 4- to 5-week-old male BALB/c nude mice (Charles River Laboratories Japan, Inc.) under the skin on the back. Dividing into groups was performed when the tumor volume reached 100 to 300 mm³, and administering of the test compounds was started. The test was performed on each of the 5 mice in the solvent group and the compound administered group. By oral administration, 6% cyclodextrin aqueous solution for the solvent group, and 6% cyclodextrin aqueous solution in which the test compound was mixed by the dosage shown in Table 4 for the compound administered group were administered. The administration was performed once a day for 14 days (HARA), 21 days (A427, NCI-H1993), or 35 days (NCI-H1395), and the body weight and the tumor diameter were measured twice a week. For calculation of the tumor volume, the formula below was used.

$$[\text{Tumor volume (mm}^3\text{)}] = [\text{major axis of tumor (mm)}] \times [\text{minor axis of tumor (mm)}]^2 \times 0.5$$

The inhibition rate of tumor growth and the rate of tumor regression were calculated from the average value of the tumor volume according to the formula below.

25 The rate of tumor regression was calculated with respect to a group having an inhibition rate of tumor growth > 100%.

Inhibition rate of tumor growth (%) = (1-average of tumor volume growth in each group/average of tumor volume growth in control group) x 100

30 Rate of tumor regression (%) = (1-average tumor volume in each group on measuring day/average tumor volume in each group when dividing groups) x 100

A427 cells, NCI-H1395 cells, and NCI-H1993 cells which are derived from non-small cell lung cancer can be purchased from ATCC, and HARA cells from JCRB cell bank, or the like.

The anti-tumor effect of Test Compounds A1, B1, C1, and D1 on the final measuring day is shown in Table 4.

[0046]

[Table 4]

Test Compound	Dosage (mg/kg)	Inhibition rate or regression rate A427	Inhibition rate NCI-H1395	Inhibition rate HARA	Inhibition rate NCI-H1993
A1	8	84% inhibition	61%	1.2%	47%
B1	8	99% inhibition	74%	14%	62%
C1	1	69% regression	75%	29%	50%
D1	1	96% inhibition	70%	31%	42%

5

[0047]

From the above results, it was confirmed that Compound A, Compound B, Compound C, and Compound D which are active ingredients of a pharmaceutical composition of the present invention inhibit mitochondrial Complex I and have the effect of activating AMPK. In addition, it was confirmed that the compounds have an anti-tumor effect with respect to mice bearing tumors of non-small cell lung cancer-derived cells. Furthermore, it was confirmed that the compounds have an anti-tumor effect with respect to mice bearing tumors of LKB1 mutation-positive non-small cell lung cancer-derived cells. It was confirmed that some of the test compounds exhibited a strong anti-tumor effect, that is, tumor regression, particularly on mice transplanted with LKB1 mutation-positive non-small cell lung cancer-derived cells.

15

[0048]

Accordingly, a compound selected from Compound A, Compound B, Compound C, and Compound D or a pharmaceutically acceptable salt thereof can be used for treating lung cancer in which mitochondrial Complex I is involved, in another embodiment, non-small cell lung cancer, in still another embodiment, non-small cell lung cancer in which mitochondrial Complex I is involved, in still further another embodiment, non-small cell lung cancer having mutations and/or defects in LKB1, and in still further another embodiment, non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved.

25

[0049]

A pharmaceutical composition comprising a compound selected from Compound A, Compound B, Compound C, and Compound D or a pharmaceutically acceptable salt thereof as an active ingredient may include excipients as an arbitrary additive, or can be

prepared by methods which are commonly used, using excipients commonly used in this field, that is, pharmaceutical excipients, pharmaceutical carrier, or the like.

Administration may be any form of oral administration by a tablet, a pill, a capsule, a granule, powder, a liquid, and the like, or parenteral administration by intra-articular, intravenous, intramuscular, and the like injections, a suppository, a transdermal solution, an ointment, a transdermal patch, a transmucosal solution, a transmucosal patch, an inhaler, and the like.

[0050]

As a solid composition for the oral administration, a tablet, powder, a granule, and the like is used. In such solid composition, one or two or more kinds of active ingredients are mixed with at least one inert excipient. The composition may contain an inert additive, for example, a lubricant, a disintegrant, a stabilizer, a solubilizer, and the like by commonly used methods. The tablet or the pill may be coated with a film of sugar or a stomach-soluble, or enteric-soluble substance, if necessary.

A liquid composition for the oral administration includes an emulsion, a solution preparation, a suspension, a syrup or an elixir, and the like which is pharmaceutically acceptable, and includes a generally used inert diluent, for example, purified water or ethanol. The liquid composition may contain adjuvants such as a solubilizing agent, a wetting agent, and a suspension, a sweetener, a flavor, an aromatic, or a preservative in addition to the inert diluent.

[0051]

The injection for the parenteral administration includes a sterile aqueous or non-aqueous solution preparation, a suspension or an emulsion. As the aqueous solvent, for example, distilled water for injection or physiological saline is included. As the non-aqueous solvent, for example, alcohols such as ethanol are included. Such a composition may further include a tonicity agent, a preservative, a wetting agent, an emulsifier, a dispersant, a stabilizer, or a solubilizer. These are sterilized by, for example, filtration through a bacteria-retaining filter, mixing of a germicide, or irradiation. In addition, these can also be used in a manner in which a sterile solid composition is prepared, and is dissolved or suspended in sterile water or a sterile solvent for injection before being used.

[0052]

As an external application, an ointment, a plaster, a cream, a jelly, a poultice, a spray, a lotion, and the like is included. A generally used ointment base, lotion base, aqueous or non-aqueous solution, suspension, emulsion, and the like is contained.

[0053]

The transmucosal agent such as an inhaler or a transnasal agent and the like is used in a solid, liquid, or semi-solid form, and can be prepared according to methods known in the related art. For example, a known excipient, a pH adjuster, a preservative, a

surfactant, a lubricant, a stabilizer, a thickener, and the like may be suitably added. In administration, it is possible to use an appropriate device for inhalation or insufflation. For example, by using a known device such as a metered dose inhaler device and the like, or a nebulizer, the administration can be performed as a powder of a compound alone or of a prescribed mixture, or as a solution or a suspension in combination with a carrier which is pharmaceutically acceptable. A dry powder inhaler and the like may be an inhaler for single or multiple administration, and it is possible to use dry powder or a powder-containing capsule. Alternatively, this may be in a form of a pressurized aerosol spray and the like that uses an appropriate propellant, for example, a suitable gas such as chlorofluoroalkane or carbon dioxide, and the like.

[0054]

In a case of normal oral administration, a daily dose is approximately 0.001 to 100 mg/kg of body weight, preferably 0.1 to 30 mg/kg, and more preferably 0.1 to 10 mg/kg, and this dose is administered at once or in 2 to 4 divided doses. In a case of an intravenous administration, approximately 0.0001 to 10 mg/kg of body weight is suitable for a daily dose, and this dose is administered at once or in multiple divided doses per day. In addition, as the transmucosal agent, approximately 0.001 to 100 mg/kg of body weight is administered at once or in multiple divided doses per day. The dose is appropriately determined according to individual cases in consideration of symptoms, age, gender, or the like.

[0055]

The amount differs depending on the type of administration route, dosage form, administration site, excipients, and additives, but the pharmaceutical composition of the present invention contains 0.01 to 100% by weight, and in a certain embodiment, 0.01 to 50% by weight of a compound selected from Compound A, Compound B, Compound C, and Compound D or a pharmaceutically acceptable salt thereof which are active ingredients.

[0056]

There is a possibility that the pharmaceutical composition of the present invention can be used together with various agents for treating diseases which are believed to exhibit effectiveness with respect to lung cancer, that is, lung cancer in which mitochondrial Complex I is involved, particularly non-small cell lung cancer. For use in combination, co-administration or separate administration in succession may be performed, or administration may be performed at a desired time interval. When performing the co-administration, these may be a combination agent or may be formulated separately.

Examples

[0057]

Hereinafter, preparation methods for Compound A, Compound B, Compound C, and Compound D will be described in detail based on examples. In addition, preparation methods for starting compounds thereof will be described in Preparation Examples. In addition, the preparation methods for Compound A, Compound B, Compound C, and
5 Compound D are not limited to the preparation methods in the specific examples shown below, and the compounds can also be prepared by using another combination of the preparation methods, or a method obvious to those skilled in the art.

[0058]

In the present specification, naming a software such as ACD/Name (registered
10 trademark, Advanced Chemistry Development, Inc.) or the like is used in naming of compounds in some cases.

[0059]

In addition, for the sake of convenience, a concentration mol/l is expressed by M. For example, a 1 M aqueous sodium hydroxide solution means a 1 mol/l aqueous sodium
15 hydroxide solution.

[0060]

The powder X-ray diffraction was measured using RINT-TTRII (RIGAKU Corporation) under the conditions of tube: Cu, tube current: 300 mA, tube voltage: 50 kV, sampling width: 0.020°, scanning speed: 4°/min, wavelength: 1.54056 Å, and measurement
20 diffraction angle range (2θ): 2.5° to 40°. Handling of a device including a data process was in accordance with the methods and procedures instructed on each device.

Each crystal was characterized by a powder X-ray diffraction pattern, respectively, but judging from the nature of data of the powder X-ray diffraction, the crystal lattice distance and the overall pattern are important in determining the identity of the crystal, and
25 the diffraction angle and diffraction intensity are not to be strictly interpreted since these may vary slightly in accordance with the direction of crystal growth, the particle size, and measurement conditions. The diffraction angle (2θ(°)) of powder X-ray diffraction patterns is interpreted in consideration of an error range that is generally acceptable in the measuring method, and the error range is ±0.2° in a certain embodiment.

30 [0061]

Preparation Example 1

N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (1.2 g) was added to a mixture of 5-bromo-1H-benzimidazol-2-carboxylic acid (1.0 g), 1-[4-(trifluoromethyl)benzyl]piperazine (1.0 g), 1H-benzotriazol-1-ol (840 mg), and N,N-dimethylformamide (10 ml: hereinafter, abbreviated as DMF), followed by stirring at room
35 temperature overnight. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, followed by stirring at room temperature for 1 hour, and the resulting solid was collected by filtration, followed by drying under reduced pressure.

The obtained solid was dissolved in a mixture of chloroform (100 ml) and ethanol (1 ml) while heating to reflux. The mixture was cooled to room temperature and then hexane (100 ml) was added thereto. The resulting solid was collected by filtration, followed by drying under reduced pressure, thereby obtaining (5-bromo-1H-benzimidazol-2-yl){4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}methanone (1.4 g) as a solid.

[0062]

Preparation Example 2

A mixture of (5-bromo-1H-benzimidazol-2-yl){4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}methanone (1.2 g), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.6 g), tetrakis(triphenylphosphine)palladium (590 mg), sodium carbonate (2.2 g), dioxane (40 ml), and water (10 ml) was stirred at 95°C for 24 hours in an argon atmosphere, and then cooled to room temperature. Water was added to the reaction mixture, and extraction was carried out using ethyl acetate. After the organic layer was dried over anhydrous sodium sulfate, the desiccant was removed, and then the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform-methanol), thereby obtaining tert-butyl 4-[2-({4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}carbonyl)-1H-benzimidazol-5-yl]-3,6-dihydropyridine-1(2H)-carboxylate (1.2 g) as an oily material.

[0063]

Preparation Example 3

To an ethanol (40 ml) solution of tert-butyl 4-[2-({4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}carbonyl)-1H-benzimidazol-5-yl]-3,6-dihydropyridine-1(2H)-carboxylate (1.4 g) was added 10% palladium-activated charcoal (approximately 50% water-containing product, 500 mg), followed by stirring at room temperature for 6 hours in a hydrogen atmosphere. The insoluble material was removed, and then the solvent was evaporated under reduced pressure. To an ethanol (40 ml) solution of the obtained residue was added 10% palladium-activated charcoal (approximately 50% water-containing product, 500 mg), followed by stirring at room temperature for 4 hours in a hydrogen atmosphere of 3.0 kgf/cm². The insoluble material was removed, and then the solvent was evaporated under reduced pressure. To a methanol (41 ml) solution of the obtained residue was added 20% palladium hydroxide-activated charcoal (approximately 50% water-containing product, 800 mg), followed by stirring at room temperature for 24 hours in a hydrogen atmosphere of 3.0 kgf/cm². The insoluble material was removed, and then the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform-methanol), thereby obtaining tert-butyl 4-[2-({4-[4-

(trifluoromethyl)benzyl]piperazin-1-yl}carbonyl)-1H-benzimidazol-5-yl]piperidine-1-carboxylate (1.1 g) as an oily material.

[0064]

Preparation Example 4

5 A 4 M hydrogen chloride/ethyl acetate solution (5 ml) was added to an ethyl acetate (30 ml) solution of tert-butyl 4-[2-({4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}carbonyl)-1H-benzimidazol-5-yl]piperidine-1-carboxylate (1.1 g), followed by stirring at room temperature for 6 hours, and being left to stand overnight. The solvent was evaporated under reduced pressure, and then ethyl acetate and hexane were added to the
10 obtained residue. The resulting solid was collected by filtration, followed by drying under reduced pressure, thereby obtaining hydrochloride of [5-(piperidin-4-yl)-1H-benzimidazol-2-yl]{4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}methanone (740 mg: a molar ratio to hydrogen chloride was undetermined) as a solid.

[0065]

15 Preparation Example 5

Trifluoroacetic acid (1 ml) was added to a dichloromethane (2 ml) solution of tert-butyl 4-[2-({4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}carbonyl)-1H-benzimidazol-5-yl]piperidine-1-carboxylate (270 mg), followed by stirring at room temperature for 30 minutes. A saturated aqueous sodium hydrogen carbonate solution was added to the
20 reaction mixture, and extraction was carried out using chloroform. The organic layer was washed with a saturated aqueous sodium chloride solution and then dried over anhydrous sodium sulfate. The desiccant was removed, and then the solvent was evaporated under reduced pressure. The obtained residue was purified by amino silica gel column chromatography (chloroform-methanol), thereby obtaining [5-(piperidin-4-yl)-1H-benzimidazol-2-yl]{4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}methanone (150 mg) as
25 an amorphous material.

[0066]

Preparation Example 6

A mixture of 6-bromo-1H-indole-2-carboxylate (1.0 g), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (1.1 g), 1H-benzotriazol-1-ol (770 mg), and dichloromethane (15 ml) was stirred at room temperature for 10 minutes.
30 To the reaction mixture were added 4-(piperazin-1-ylmethyl)benzonitrile dihydrochloride (1.2 g) and N,N-diisopropylethylamine (1.6 ml), followed by stirring at room temperature overnight. A saturated aqueous sodium hydrogen carbonate solution was added to the
35 reaction mixture, extraction was carried out using chloroform, and then extraction was carried out using chloroform-methanol. The organic layer was dried over anhydrous magnesium sulfate, the desiccant was removed, and then the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column

chromatography (chloroform-methanol), thereby obtaining 4-({4-[(6-bromo-1H-indol-2-yl)carbonyl]piperazin-1-yl}methyl)benzonitrile (1.1 g) as a solid.

[0067]

Preparation Example 7

5 A mixture of 4-({4-[(6-bromo-1H-indol-2-yl)carbonyl]piperazin-1-yl}methyl)benzonitrile (1.1 g), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.6 g), tetrakis(triphenylphosphine)palladium (480 mg), sodium carbonate (790 mg), dioxane (18 ml), and water (1.8 ml) was stirred at 100°C overnight in an argon atmosphere, and then cooled to room temperature. Water was
10 added to the reaction mixture, and extraction was carried out using chloroform. The organic layer was dried over anhydrous sodium sulfate, the desiccant was removed, and then the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform-methanol, and then hexane-ethyl acetate), and the obtained solid was washed with diisopropyl ether, thereby obtaining
15 tert-butyl 4-(2-{[4-(4-cyanobenzyl)piperazin-1-yl]carbonyl}-1H-indol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (470 mg) as a solid.

[0068]

Preparation Example 8

To a mixture of tert-butyl 4-(2-{[4-(4-cyanobenzyl)piperazin-1-yl]carbonyl}-1H-indol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (470 mg), tetrahydrofuran (hereinafter,
20 abbreviated as THF) (14 ml), and ethanol (3 ml) was added 10% palladium-activated charcoal (approximately 50% water-containing product, 230 mg), followed by stirring at room temperature for 2 hours in a hydrogen atmosphere. After the insoluble material was removed, the solvent was evaporated under reduced pressure, and 10% palladium-activated
25 charcoal (approximately 50% water-containing product, 230 mg) was added to a mixture of the obtained residue, THF (14 ml), and ethanol (3 ml), followed by stirring at room temperature overnight in a hydrogen atmosphere. After the insoluble material was removed, the solvent was evaporated under reduced pressure, and 20% palladium
hydroxide-activated charcoal (approximately 50% water-containing product, 230 mg) was
30 added to a mixture of the obtained residue, THF (14 ml), and ethanol (3 ml), followed by stirring at room temperature for 4 hours in a hydrogen atmosphere of 3.0 kgf/cm², and being left to stand for 3 days. The insoluble material was removed, and then the solvent was evaporated under reduced pressure. The obtained residue was purified by amino
35 silica gel column chromatography (chloroform-methanol), thereby obtaining tert-butyl 4-[2-(piperazin-1-ylcarbonyl)-1H-indol-6-yl]piperidine-1-carboxylate (360 mg) as an oily material.

[0069]

Preparation Example 9

Sodium triacetoxyborohydride (360 mg) was added to a mixture of tert-butyl 4-[2-(piperazin-1-ylcarbonyl)-1H-indol-6-yl]piperidine-1-carboxylate (350 mg), 4-formylbenzonitrile (140 mg), and dichloromethane (3 ml), followed by stirring at room temperature for 1.5 hours. A saturated aqueous sodium hydrogen carbonate solution and methanol were added to the reaction mixture, and extraction was carried out using chloroform. The organic layer was dried over anhydrous sodium sulfate, the desiccant was removed, and then the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform-methanol), thereby obtaining tert-butyl 4-(2-{[4-(4-cyanobenzyl)piperazin-1-yl]-carbonyl}-1H-indol-6-yl)piperidine-1-carboxylate (450 mg) as an oily material.

[0070]

Preparation Example 10

Sodium hydride (containing approximately 45% of a liquid paraffin, 40 mg) was added to a DMF (4 ml) solution of tert-butyl 4-(2-{[4-(4-cyanobenzyl)piperazin-1-yl]-carbonyl}-1H-indol-6-yl)piperidine-1-carboxylate (450 mg) under ice-cooling, followed by stirring at room temperature for 1 hour. Methyl iodide (58 μ l) was added to the reaction mixture at room temperature, followed by stirring at room temperature for 1 hour. A saturated aqueous ammonium chloride solution and water were added to the reaction mixture, and extraction was carried out using ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution in this order, and then dried over anhydrous sodium sulfate. The desiccant was removed, and then the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform-methanol), thereby obtaining tert-butyl 4-(2-{[4-(4-cyanobenzyl)piperazin-1-yl]carbonyl}-1-methyl-1H-indol-6-yl)piperidine-1-carboxylate (200 mg) as an oily material.

[0071]

Preparation Example 11

Trifluoroacetic acid (500 μ l) was added to a dichloromethane (1 ml) solution of tert-butyl 4-(2-{[4-(4-cyanobenzyl)piperazin-1-yl]carbonyl}-1-methyl-1H-indol-6-yl)piperidine-1-carboxylate (200 mg) at room temperature, followed by stirring at room temperature for 2 hours. The solvent was evaporated under reduced pressure, a saturated aqueous sodium hydrogen carbonate solution and water were added to the obtained residue, and then extraction was carried out using chloroform. The organic layer was dried over anhydrous sodium sulfate, the desiccant was removed, and then the solvent was evaporated under reduced pressure. The obtained residue was purified by amino silica gel column chromatography (chloroform-methanol), thereby obtaining 4-[(4-{[1-methyl-6-(piperidin-4-yl)-1H-indol-2-yl]carbonyl}piperazin-1-yl)methyl]benzonitrile (120 mg) as a solid.

[0072]

Preparation Example 12

Sodium borohydride (2.6 g) was added in portions plural times to a methanol (100 ml) solution of ethyl 5-ethoxypyrazine-2-carboxylate (4.5 g) under ice-cooling, followed by stirring at room temperature for 6 hours. 1 M hydrochloric acid was added to the reaction mixture so that pH became 4, followed by stirring at room temperature for 15 minutes. A 1 M aqueous sodium hydroxide solution was added to the mixture so that pH became 9, and then extraction was carried out using chloroform. The organic layer was dried over anhydrous sodium sulfate, the desiccant was removed, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane-ethyl acetate), thereby obtaining (5-ethoxypyrazin-2-yl)methanol (2.6 g) as an oily material.

[0073]

Preparation Example 13

Thionyl chloride (200 μ l) was added to a dichloromethane (3 ml) solution of (5-ethoxypyrazin-2-yl)methanol (150 mg) under ice-cooling, followed by stirring at room temperature for 30 minutes and concentration under reduced pressure, thereby obtaining 2-(chloromethyl)-5-ethoxypyrazine (160 mg) as an oily material.

[0074]

Preparation Example 14

A mixture of ethyl 5-bromo-1H-indole-2-carboxylate (5.2 g), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (13 g), tetrakis(triphenylphosphine)palladium (5.3 g), 2 M aqueous sodium carbonate solution (28 ml), and dioxane (110 ml) was stirred at 95°C for 17 hours in an argon atmosphere, and then cooled to room temperature. Water was added to the reaction mixture, and extraction was carried out using chloroform. The organic layer was dried over anhydrous sodium sulfate, the desiccant was removed, and then the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane-ethyl acetate, and then chloroform-methanol) and amino silica gel column chromatography (hexane-ethyl acetate). Hexane-diisopropyl ether was added to the obtained solid (6.5 g), and powderization was carried out. The solid was collected by filtration, followed by drying under reduced pressure, thereby obtaining ethyl 5-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole-2-carboxylate (5.0 g) as a solid.

[0075]

Preparation Example 15

To a mixture of ethyl 5-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole-2-carboxylate (5.0 g), ethanol (55 ml), and THF (55 ml) was added 20%

palladium hydroxide-activated charcoal (approximately 50% water-containing product, 1.0 g), followed by stirring at room temperature for 3 hours in a hydrogen atmosphere. The insoluble material was removed, and then the solvent was evaporated under reduced pressure. The obtained residue was purified by amino silica gel column chromatography (hexane-ethyl acetate), thereby obtaining ethyl 5-[1-(tert-butoxycarbonyl)piperidin-4-yl]-1H-indole-2-carboxylate (4.8 g) as a solid.

[0076]

Preparation Example 16

Dimethyl sulfate (1.8 ml) was added to a mixture of ethyl 5-[1-(tert-butoxycarbonyl)piperidin-4-yl]-1H-indole-2-carboxylate (4.8 g), cesium carbonate (7.0 g), and acetonitrile (70 ml), followed by stirring at 75°C for 2 hours, and then cooled to room temperature. After ethyl acetate was added to the reaction mixture, washing was performed with water and a saturated aqueous sodium chloride solution in this order. The organic layer was dried over anhydrous sodium sulfate, the desiccant was removed, and then the solvent was evaporated under reduced pressure, thereby obtaining ethyl 5-[1-(tert-butoxycarbonyl)piperidin-4-yl]-1-methyl-1H-indole-2-carboxylate (5.7 g) as an oily material.

[0077]

Preparation Example 17

A 1 M aqueous sodium hydroxide solution (23 ml) was added to a mixture of ethyl 5-[1-(tert-butoxycarbonyl)piperidin-4-yl]-1-methyl-1H-indole-2-carboxylate (5.7 g), dioxane (23 ml), and ethanol (23 ml), followed by stirring at 60°C overnight, and then cooled to room temperature. 1 M hydrochloric acid (23 ml) was added to the reaction mixture under ice-cooling, and extraction was carried out using chloroform. The organic layer was dried over anhydrous sodium sulfate, the desiccant was removed, and the solvent was evaporated under reduced pressure, thereby obtaining 5-[1-(tert-butoxycarbonyl)piperidin-4-yl]-1-methyl-1H-indole-2-carboxylate (4.8 g) as an amorphous material.

[0078]

Preparation Example 18

To a mixture of 5-[1-(tert-butoxycarbonyl)piperidin-4-yl]-1-methyl-1H-indole-2-carboxylate (4.8 g), 1H-benzotriazol-1-ol (1.9 g), N,N-diisopropylethylamine (6.8 ml), and dichloromethane (55 ml) were added 4-(piperazin-1-ylmethyl)benzonitrile dihydrochloride (4.0 g) and N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (3.1 g), followed by stirring at room temperature for 2 hours. A saturated aqueous sodium hydrogen carbonate solution and water were added to the reaction mixture, and extraction was carried out using chloroform. The organic layer was dried over anhydrous sodium sulfate, the desiccant was removed, and then the solvent was evaporated under reduced

pressure. The obtained residue was purified by silica gel column chromatography (hexane-ethyl acetate), thereby obtaining tert-butyl 4-(2-{[4-(4-cyanobenzyl)piperazin-1-yl]carbonyl}-1-methyl-1H-indol-5-yl)piperidine-1-carboxylate (6.8 g) as an amorphous material.

5 [0079]

Preparation Example 19

Trifluoroacetic acid (5 ml) was added to a dichloromethane (10 ml) solution of tert-butyl 4-(2-{[4-(4-cyanobenzyl)piperazin-1-yl]carbonyl}-1-methyl-1H-indol-5-yl)piperidine-1-carboxylate (6.8 g) at room temperature, followed by stirring at room
10 temperature for 2 hours. The solvent was evaporated under reduced pressure, a saturated aqueous sodium hydrogen carbonate solution was added to the obtained residue, and then extraction was carried out using chloroform. The organic layer was dried over anhydrous sodium sulfate, the desiccant was removed, and then the solvent was evaporated under reduced pressure, thereby obtaining 4-[(4-{[1-methyl-5-(piperidin-4-yl)-1H-indol-2-yl]carbonyl}piperazin-1-yl)methyl]benzonitrile (7.1 g) as an amorphous material.

15

[0080]

Example 1

A mixture of hydrochloride of [5-(piperidin-4-yl)-1H-benzimidazol-2-yl]{4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}methanone (200 mg), 6-methoxynicotinaldehyde
20 (100 mg), triethylamine (140 μ l), acetic acid (100 μ l), and dichloromethane (4 ml) was stirred at room temperature for 10 minutes. Sodium triacetoxyborohydride (580 mg) was added to the reaction mixture at room temperature, followed by stirring at room temperature for 2 hours, and being left to stand at room temperature overnight. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture,
25 and extraction was carried out using chloroform. The organic layer was dried over anhydrous sodium sulfate, the desiccant was removed, and then the solvent was evaporated under reduced pressure. The obtained crude product was purified by amino silica gel column chromatography (chloroform-methanol). Tosic acid monohydrate (69 mg) was added to an acetone solution of the obtained oily material (Compound A, 110 mg), and
30 then the solvent was evaporated under reduced pressure. Ethanol (3 ml) and diisopropyl ether (20 ml) were added to the obtained residue, followed by stirring at room temperature. The resulting solid was collected by filtration, and then dried under reduced pressure, thereby obtaining ditosylate salts of (5-{1-[(6-methoxypyridin-3-yl)methyl]piperidin-4-yl}-1H-benzimidazol-2-yl){4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}methanone
35 (Compound A) (180 mg) as an amorphous material. In addition, after stirring a mixture of Compound A (200 mg) prepared in the same manner as above and acetonitrile (10 ml) at 95°C for 30 minutes, tosic acid monohydrate (130 mg) was added thereto. The mixture was cooled to room temperature while stirring, and then stirred at room temperature for 7

days. The resulting solid was collected by filtration, and then dried under reduced pressure, thereby obtaining ditosylate salts of (5-{1-[(6-methoxypyridin-3-yl)methyl]piperidin-4-yl}-1H-benzimidazol-2-yl){4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}methanone (Compound A) (300 mg) as a crystal. The powder X-ray diffraction data of this crystal is shown in Table 10 described below.

[0081]

Example 2

To a mixture of [5-(piperidin-4-yl)-1H-benzimidazol-2-yl]{4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}methanone (47 mg), N,N-diisopropylethylamine (68 μ l), acetonitrile (1 ml), and DMF (1 ml) was added 2-(chloromethyl)-5-methoxypyrazine (16 mg), followed by stirring at room temperature for 5 days. Water was added to the reaction mixture, and extraction was carried out using ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, the desiccant was removed, and then the solvent was evaporated under reduced pressure. The obtained crude product was purified by silica gel column chromatography (chloroform-methanol). Tosic acid monohydrate (24 mg) and ethyl acetate (3 ml) were added to an acetone (2 ml) solution of the obtained oily material (Compound B, 38 mg), followed by stirring at room temperature overnight. The resulting solid was collected by filtration, and then dried under reduced pressure, thereby obtaining ditosylate salts of (5-{1-[(5-methoxypyrazin-2-yl)methyl]piperidin-4-yl}-1H-benzimidazol-2-yl){4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}methanone (Compound B) (53 mg) as a solid. In addition, after stirring a mixture of Compound B (200 mg), prepared in the same manner as above, acetone (18 ml), and acetonitrile (3 ml) at 80°C, tosic acid monohydrate (130 mg) was added thereto. The mixture was cooled to room temperature while stirring, and then stirred at room temperature for 72 hours. The resulting solid was collected by filtration, and then dried under reduced pressure, thereby obtaining ditosylate salts of (5-{1-[(5-methoxypyrazin-2-yl)methyl]piperidin-4-yl}-1H-benzimidazol-2-yl){4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}methanone (Compound B) (300 mg) as a crystal. The powder X-ray diffraction data of this crystal is shown in Table 10 described below.

[0082]

Example 3

An acetonitrile (500 μ l) solution of 2-(chloromethyl)-5-ethoxypyrazine (53 mg) was added to a mixture of 4-[(4-{[1-methyl-6-(piperidin-4-yl)-1H-indol-2-yl]carbonyl}piperazin-1-yl)methyl]benzonitrile (120 mg), N,N-diisopropylethylamine (160 μ l), and acetonitrile (1 ml), followed by stirring at room temperature overnight. After the solvent of the reaction mixture was evaporated under reduced pressure, the obtained residue was purified by silica gel column chromatography (chloroform-methanol) and DIOL silica gel column chromatography (hexane-ethyl acetate). After stirring a mixture

of the obtained solid (110 mg) and acetone (3 ml) at 80°C, tosic acid monohydrate (68 mg) was added thereto. The mixture was cooled to room temperature while stirring, and then stirred at room temperature overnight. The resulting solid was collected by filtration, and then dried under reduced pressure, thereby obtaining ditosylate salts of 4-({4-[(6-{1-[(5-ethoxypyrazin-2-yl)methyl]piperidin-4-yl}-1-methyl-1H-indol-2-yl)carbonyl]piperazin-1-yl}methyl)benzonitrile (Compound C) (130 mg) as a crystal. The powder X-ray diffraction data of this crystal is shown in Table 10 described below.

[0083]

Example 4

10 A dichloromethane (5 ml) solution of 2-(chloromethyl)-5-methoxypyrazine (760 mg) was added to a mixture of 4-[(4-{[1-methyl-5-(piperidin-4-yl)-1H-indol-2-yl]carbonyl}piperazin-1-yl)methyl]benzonitrile (2.0 g), N,N-diisopropylethylamine (2.7 ml), and acetonitrile (10 ml), followed by stirring at room temperature for 5 days. After the solvent of the reaction mixture was evaporated under reduced pressure, the obtained
15 residue was purified by silica gel column chromatography (chloroform-methanol) and amino silica gel column chromatography (hexane-ethyl acetate, and then chloroform-methanol), thereby obtaining amorphous material (1.4 g). After the obtained amorphous material (1.2 g) was purified by silica gel column chromatography (chloroform-methanol), a mixture of the obtained solid (760 mg) and acetone (100 ml) was heated and stirred at
20 80°C for 30 minutes, and then tosic acid monohydrate (510 mg) was added thereto. The mixture was cooled to room temperature while stirring, and then stirred at room temperature for 4 hours. The resulting solid was collected by filtration, and then dried under reduced pressure, thereby obtaining ditosylate salts of 4-({4-[(5-{1-[(5-methoxypyrazin-2-yl)methyl]piperidin-4-yl}-1-methyl-1H-indol-2-yl)carbonyl]piperazin-
25 1-yl}methyl)benzonitrile (Compound D) (1.1 g) as a crystal. The powder X-ray diffraction data of this crystal is shown in Table 10 described below.

The structure and physicochemical data of the compounds of the preparation examples and the compounds of examples are shown in Tables 5 to 10 described below.

[0084]

30 The following abbreviations may be used in Tables 5 to 10 described below.

Pre: Preparation Example No, Ex: Example No, Str: chemical structure formula, Dat: physicochemical data, ESI+: m/z value in mass spectrometry (ionization method ESI, $[M+H]^+$ unless otherwise specified), ESI-: m/z value in mass spectrometry (ionization method ESI, $[M-H]^-$ unless otherwise specified), APCI/ESI: APCI/ESI-MS (atmospheric pressure chemical ionization method APCI, APCI/ESI refers to the simultaneous measurement of APCI and ESI, and APCI/ESI+ is $[M+H]^+$), NMR1: δ (ppm) of peak in ^1H -NMR in CD_3OD , NMR2: δ (ppm) of peak in ^1H -NMR in $DMSO-d_6$, Me: methyl, Et: ethyl, Boc: tert-butoxycarbonyl, and $2\theta(^{\circ})$: diffraction angle of powder X-ray diffraction.

[0085]

Furthermore, in the chemical structure formulae, xHCl indicates that the compound is a hydrochloride, but the molar ratio to hydrogen chloride is undetermined, and 2TsOH indicates that the compound is a ditosylate salt, respectively.

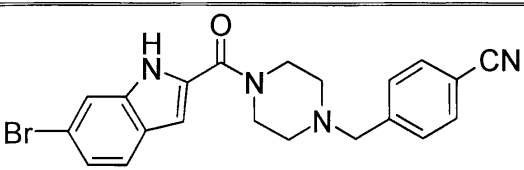
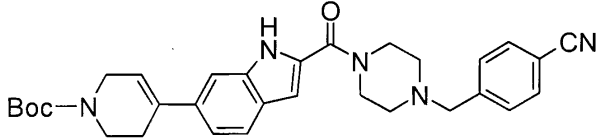
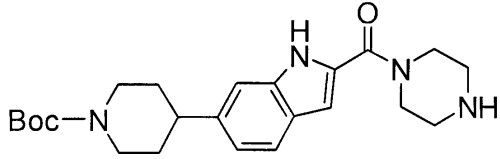
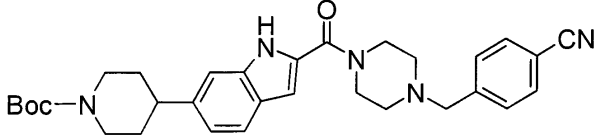
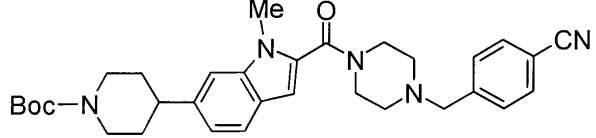
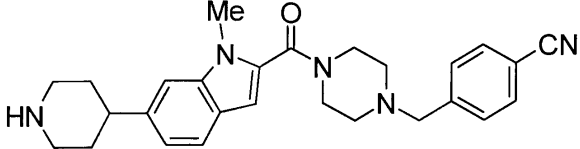
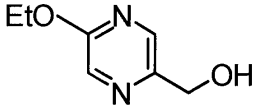
[0086]

[Table 5]

Pre	Str	Dat
1	 <chem>Brc1ccc2nc(=O)n(cnc2=O)C(=O)N3CCN(CC3)Cc4ccc(C(F)(F)F)cc4</chem>	ESI+: 467, 469
2	 <chem>CC(C)(C)OC(=O)N1CCc2ccc(cc2c3nc(=O)n(cnc3=O)C(=O)N4CCN(CC4)Cc5ccc(C(F)(F)F)cc5)cc1</chem>	ESI+: 570
3	 <chem>CC(C)(C)OC(=O)N1CCc2ccc(cc2c3nc(=O)n(cnc3=O)C(=O)N4CCN(CC4)Cc5ccc(C(F)(F)F)cc5)cc1</chem>	ESI+: 572
4	 <chem>C1CCNCC1c2ccc(cc2c3nc(=O)n(cnc3=O)C(=O)N4CCN(CC4)Cc5ccc(C(F)(F)F)cc5)cc1.Cl</chem> xHCl	ESI+: 472
5	 <chem>C1CCNCC1c2ccc(cc2c3nc(=O)n(cnc3=O)C(=O)N4CCN(CC4)Cc5ccc(C(F)(F)F)cc5)cc1</chem>	APCI/ESI+: 472

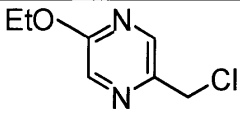
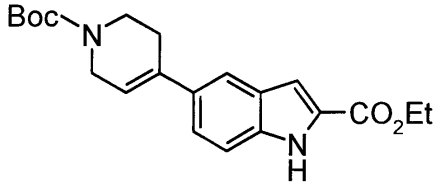
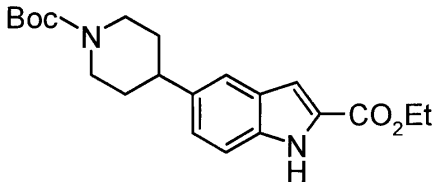
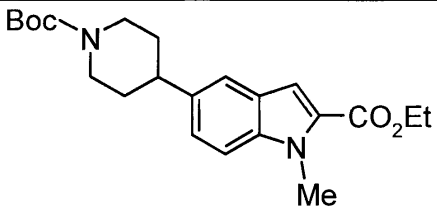
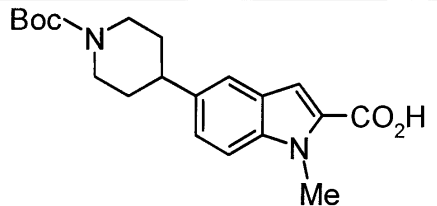
[0087]

[Table 6]

Pre	Str	Dat
6		ESI+: 423, 425
7		ESI+: 526
8		ESI-: 411
9		ESI-: 526
10		ESI+: 542
11		ESI+: 442
12		ESI+: 155

[0088]

[Table 7]

Pre	Str	Dat
13		ESI+: 173, 175
14		ESI-: 369
15		ESI+: 373
16		ESI+: 409 [M+Na] ⁺
17		ESI-: 357

[0089]

[Table 8]

Pre	Str	Dat
18	 <chem>Cc1c2c(c[nH]2C(=O)N3CCN(CC3Cc4ccc(C#N)cc4)CC)C5=CC=C(C=C5)C6CCN(CC6)C(=O)OC(=O)C7=CC=CC=C7</chem>	ESI+: 542
19	 <chem>Cc1c2c(c[nH]2C(=O)N3CCN(CC3Cc4ccc(C#N)cc4)CC)C5=CC=C(C=C5)C6CCN(CC6)C(=O)OC(=O)C7=CC=CC=C7</chem>	ESI+: 442

[0090]

[Table 9]

Ex	Str
1	 2TsOH
2	 2TsOH
3	 2TsOH
4	 2TsOH

[0091]

[Table 10]

Ex	Dat
1	ESI+: 593; NMR1: 1.98-2.21 (4H, m), 2.38 (6H, s), 2.99-3.09 (1H, m), 3.12-3.27 (2H, m), 3.27-3.58 (8H, m), 3.59-3.68 (2H, m), 3.95 (3H, s), 4.36 (2H, s), 4.39-4.51 (2H, m), 6.86-6.92 (1H, m), 7.19-7.24 (4H, m), 7.25-7.30 (1H, m), 7.54-7.65 (2H, m), 7.68-7.83 (8H, m), 7.85 (1H, dd, J = 2.8, 8.4 Hz), 8.31 (1H, d, J = 2.0 Hz); 2θ (°) = 6.5, 10.1, 15.2, 16.2, 18.6, 19.6, 20.1, 20.8, 23.3, 25.8
2	ESI+: 594; NMR1: 2.01-2.22 (4H, m), 2.35 (6H, s), 3.01-3.11 (1H, m), 3.20-3.80 (12H, m), 4.02 (3H, s), 4.47 (2H, s), 4.52 (2H, s), 7.18-7.25 (4H, m), 7.31 (1H, dd, J = 1.6, 8.6 Hz), 7.55-7.59 (1H, m), 7.64 (1H, d, J = 8.5 Hz), 7.67-7.73 (4H, m), 7.75-7.78 (2H, m), 7.78-7.84 (2H, m), 8.31-8.35 (2H, m); 2θ (°) = 6.2, 6.7, 13.3, 15.2, 16.4, 19.0, 20.5, 20.9, 22.6, 24.8
3	ESI+: 578 NMR2: 1.38 (3H, t, J = 7.0 Hz), 1.89-2.10 (4H, m), 2.29 (6H, s), 2.88-3.00 (1H, m), 3.02-3.69 (12H, m), 3.76 (3H, s), 4.26-4.63 (4H, m), 4.41 (2H, q, J = 7.1 Hz), 6.61-6.79 (1H, m), 6.96-7.03 (1H, m), 7.06-7.14 (4H, m), 7.32 (1H, s), 7.44-7.51 (4H, m), 7.57 (1H, d, J = 8.3 Hz), 7.62-7.81 (2H, m), 7.85-8.10 (2H, m), 8.39 (1H, d, J = 1.2 Hz), 8.42 (1H, d, J = 1.2 Hz), 9.67-9.81 (1H, m), 9.89-10.16 (1H, m); 2θ (°) = 3.6, 7.2, 10.9, 16.1, 16.7, 17.2, 19.2, 20.9, 22.8, 26.6
4	ESI+: 564 NMR2: 1.84-2.07 (4H, m), 2.29 (6H, s), 2.82-2.94 (1H, m), 3.08-3.68 (12H, m), 3.75 (3H, s), 3.97 (3H, s), 4.21-4.66 (4H, m), 6.57-6.80 (1H, m), 7.06-7.13 (4H, m), 7.12-7.19 (1H, m), 7.37-7.43 (1H, m), 7.44-7.54 (5H, m), 7.58-7.79 (2H, m), 7.84-8.10 (2H, m), 8.41 (1H, d, J = 1.2Hz), 8.46 (1H, d, J = 1.3Hz), 9.64-9.83 (1H, m), 9.87-10.16 (1H, m); 2θ (°) = 7.5, 9.8, 13.2, 14.7, 15.6, 16.9, 18.8, 19.5, 20.0, 22.6

Industrial Applicability

[0092]

A compound selected from Compound A, Compound B, Compound C, and Compound D or a pharmaceutically acceptable salt thereof, which are active ingredients of a pharmaceutical composition of the present invention, has the effect of inhibiting mitochondrial Complex I, exhibits an anti-tumor effect on mice bearing tumors of non-small cell lung cancer-derived cells, and can be used as an active ingredient of a pharmaceutical composition for treating lung cancer in which mitochondrial Complex I is involved, particularly non-small cell lung cancer.

10

Claims

[Claim 1] A pharmaceutical composition for treating non-small cell lung cancer, the composition comprising:

5 a compound selected from (5-{1-[(6-methoxypyridin-3-yl)methyl]piperidin-4-yl}-1H-benzimidazol-2-yl){4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}methanone, (5-{1-[(5-methoxypyrazin-2-yl)methyl]piperidin-4-yl}-1H-benzimidazol-2-yl){4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}methanone, 4-({4-[(6-{1-[(5-ethoxypyrazin-2-yl)methyl]piperidin-4-yl}-1-methyl-1H-indol-2-yl)carbonyl]piperazin-1-yl)methyl)benzonitrile, and 4-({4-[(5-{1-[(5-methoxypyrazin-2-yl)methyl]piperidin-4-yl}-1-methyl-1H-indol-2-yl)carbonyl]piperazin-1-yl)methyl)benzonitrile, or a
10 pharmaceutically acceptable salt thereof as an active ingredient.

[Claim 2] The pharmaceutical composition according to claim 1,
15 wherein the non-small cell lung cancer is a non-small cell lung cancer in which mitochondrial Complex I is involved.

[Claim 3] The pharmaceutical composition according to claim 1,
20 wherein the non-small cell lung cancer is a non-small cell lung cancer having mutations and/or defects in LKB1, and in which mitochondrial Complex I is involved.

[Claim 4] The pharmaceutical composition according to any one of claims 1 to 3, comprising:
25 (5-{1-[(6-methoxypyridin-3-yl)methyl]piperidin-4-yl}-1H-benzimidazol-2-yl){4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}methanone or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[Claim 5] The pharmaceutical composition according to any one of claims 1 to 3, comprising:
30 (5-{1-[(5-methoxypyrazin-2-yl)methyl]piperidin-4-yl}-1H-benzimidazol-2-yl){4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}methanone or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[Claim 6] The pharmaceutical composition according to any one of claims 1 to 3, comprising:
35 4-({4-[(6-{1-[(5-ethoxypyrazin-2-yl)methyl]piperidin-4-yl}-1-methyl-1H-indol-2-yl)carbonyl]piperazin-1-yl)methyl)benzonitrile or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[Claim 7] The pharmaceutical composition according to any one of claims 1 to 3, comprising:

4-({4-[(5-{1-[(5-methoxypyrazin-2-yl)methyl]piperidin-4-yl}-1-methyl-1H-indol-2-yl)carbonyl]piperazin-1-yl)methyl)benzonitrile or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[Claim 8] The pharmaceutical composition according to any one of claims 1 to 3, comprising:

(5-{1-[(6-methoxypyridin-3-yl)methyl]piperidin-4-yl}-1H-benzimidazol-2-yl){4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}methanone ditosylate, and a pharmaceutically acceptable excipient thereof.

[Claim 9] The pharmaceutical composition according to any one of claims 1 to 3, comprising:

(5-{1-[(5-methoxypyrazin-2-yl)methyl]piperidin-4-yl}-1H-benzimidazol-2-yl){4-[4-(trifluoromethyl)benzyl]piperazin-1-yl}methanone ditosylate, and a pharmaceutically acceptable excipient thereof.

[Claim 10] The pharmaceutical composition according to any one of claims 1 to 3, comprising:

4-({4-[(6-{1-[(5-ethoxypyrazin-2-yl)methyl]piperidin-4-yl}-1-methyl-1H-indol-2-yl)carbonyl]piperazin-1-yl)methyl)benzonitrile ditosylate, and a pharmaceutically acceptable excipient thereof.

[Claim 11] The pharmaceutical composition according to any one of claims 1 to 3, comprising:

4-({4-[(5-{1-[(5-methoxypyrazin-2-yl)methyl]piperidin-4-yl}-1-methyl-1H-indol-2-yl)carbonyl]piperazin-1-yl)methyl)benzonitrile ditosylate, and a pharmaceutically acceptable excipient thereof.