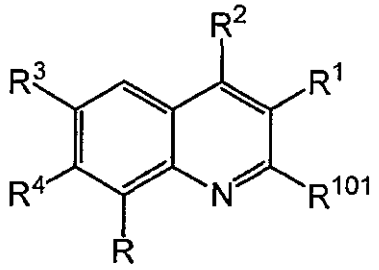
CLAIMS

1. A compound represented by the following formula or a pharmaceutically acceptable salt thereof:



(I)

wherein,

R^1 represents

a hydrogen atom,

a halogen,

a cyano,

an optionally substituted C_3-C_{10} cycloalkyl,

an optionally substituted aromatic heterocyclic group,

an optionally substituted C_1-C_6 alkylsulfinyl,

an optionally substituted C_1-C_6 alkylsulfonyl, or

-CO-R^5 [wherein,

R^5 is

an optionally substituted C_1-C_6 alkyl,

an optionally substituted aliphatic heterocyclic-(C_1-C_6 alkylenyl),

an optionally substituted C_3-C_{10} cycloalkyl,

an optionally substituted aryl,

an optionally substituted aromatic heterocyclic group,

a hydroxy,

an optionally substituted C_1-C_6 alkoxy, or

$-NR^8R^9$ (wherein,

R^8 and R^9 are the same or different and represent

a hydrogen atom,

an optionally substituted aryl,

an optionally substituted C_1-C_6 alkyl,

an optionally substituted C_3-C_{10} cycloalkyl,

an optionally substituted aromatic heterocyclic-(C_1-C_6 alkylenyl), or

an optionally substituted aliphatic heterocyclic-(C_1-C_6 alkylenyl))],

R^2 represents
a hydrogen atom,
a halogen,
a hydroxy,
a di(C_1-C_6 alkyl)amino-(C_1-C_6 alkylenyloxy),
an optionally substituted aryl,
an optionally substituted aromatic heterocyclic group,
an optionally substituted aliphatic heterocyclic group,
$-NR^6R^7$ [wherein,
R^6 and R^7 are the same or different and represent
a hydrogen atom,
an optionally substituted C_1-C_6 alkyl,
a C_1-C_6 aminoalkyl,
an optionally substituted C_1-C_6 alkylamino-(C_1-C_6 alkylenyl),
an optionally substituted di(C_1-C_6 alkyl)amino-(C_1-C_6 alkylenyl),
an optionally substituted C_2-C_7 alkanoylamino-(C_1-C_6 alkylenyl), or
$-(CH_2)_n-R^{10}$ (wherein,
n represents an integer of 0 to 6, and
R^{10} is
an optionally substituted C_3-C_{10} cycloalkyl,
an optionally substituted aryl,
an optionally substituted aromatic heterocyclic group, or
an optionally substituted aliphatic heterocyclic group), or
R^6 and R^7 form with an adjacent nitrogen atom an optionally substituted heterocyclic group],
R^3 represents
a hydrogen atom,
a halogen,
an optionally substituted C_1-C_6 alkyl,
an optionally substituted C_1-C_6 alkoxy,
an optionally substituted C_3-C_8 cycloalkenyl,
an optionally substituted aryl,
an optionally substituted aromatic heterocyclic group, or
an optionally substituted aliphatic heterocyclic group,
R^4 represents
a hydrogen atom,
a halogen

a cyano,
a C_1-C_6 alkyl which may have a halogen as a substituent, or
an optionally substituted C_1-C_6 alkoxy,
R represents
a hydrogen atom, or
a halogen, and
R^{101} represents
a hydrogen atom, or a C_1-C_6 alkyl.

2. The compound or a pharmaceutically acceptable salt thereof of claim 1, wherein R^4 is a hydrogen atom or a halogen and R^{101} is a hydrogen atom.

3. The compound or a pharmaceutically acceptable salt thereof of claim 2, wherein R^1 is R^{1A} [R^{1A} represents a cyano, a C_1-C_6 alkylsulfinyl, a C_1-C_6 alkylsulfonyl, or -CO-R^{5A} (wherein, R^{5A} represents a C_1-C_6 alkyl, or a C_3-C_{10} cycloalkyl)],

R^2 is R^{2A} {R^{2A} represents an optionally substituted aryl which may have a substituent group selected from Substituent Group C, an optionally substituted aromatic heterocyclic group which may have a substituent group selected from Substituent Group H, or -$NR^{6A}R^{7A}$ [wherein, R^{6A} represents a hydrogen atom, and R^{7A} represents -$(CH_2)_n$-R^{10A} (wherein, n represents an integer of 0 to 6, and R^{10A} represents an optionally substituted C_3-C_{10} cycloalkyl which may have a substituent group selected from Substituent Group D, an optionally substituted aryl which may have a substituent group selected from Substituent Group E, an aliphatic heterocyclic group which may be substituted with a C_1-C_6 alkyl, an aromatic heterocyclic group which may have a substituent group selected from Substituent Group I), or R^{6A} and R^{7A} form with an adjacent nitrogen atom an optionally substituted heterocyclic group which may have a substituent group selected from Substituent Group F]},

R^3 is R^{3A} (R^{3A} represents an optionally substituted aryl which may have a substituent group selected from Substituent Group G, or an optionally substituted aromatic heterocyclic group which may have a substituent group selected from Substituent Group H), and

R^4 is a hydrogen atom or a halogen, and

the above-mentioned Substituents C to I are one to three substituents each independently selected from the following Substituent Groups:

Substituent Group C: a halogen, a hydroxy, a C_1-C_6 alkoxy, and a di(C_1-C_6 alkyl) amino;

Substituent Group D: a hydroxy, a C_1-C_6 alkyl, a C_1-C_6 aminoalkyl, an aliphatic heterocyclic-(C_1-C_6 alkylenyl) (wherein, the aliphatic heterocyclic may have an amino, a

hydroxy, a C_1-C_6 hydroxyalkyl, a C_1-C_6 alkoxy, or a halogen as a substituent), a C_1-C_6 alkylamino-(C_1-C_6 alkylenyl), a di(C_1-C_6 alkyl)amino-(C_1-C_6 alkylenyl) (wherein, either one of C_1-C_6 alkyl may have a hydroxy or a cyano as a substituent, and wherein hydrogen atom of C_1-C_6 alkyl may be substituted with deuterium atom), an amino, a C_1-C_6 alkylamino, a di(C_1-C_6 alkyl)amino, a C_1-C_6 aminoalkylcarbonylamino, a di(C_1-C_6 alkyl)amino(C_1-C_6 alkylenyl)carbonylamino, an aliphatic heterocyclic group (wherein, the aliphatic heterocyclic group may have a C_1-C_6 alkoxy as a substituent), and an aliphatic heterocyclic-carbonylamino;

Substituent Group E: a halogen, a di(C_1-C_6 alkyl)amino-(C_1-C_6 alkylenyl) (wherein, the C_1-C_6 alkylenyl may have a hydroxy as a substituent), an amino, a C_2-C_7 alkanoylamino, a di(C_1-C_6 alkyl)amino, a C_1-C_6 aminoalkyl, and an aliphatic heterocyclic-(C_1-C_6 alkylenyl) (wherein, the aliphatic heterocyclic may have a C_1-C_6 alkyl as a substituent);

Substituent Group F: a carbamoyl, an amino, a C_1-C_6 aminoalkyl, a di(C_1-C_6 alkyl)amino-(C_1-C_6 alkylenyl), a C_1-C_6 alkylamino-(C_1-C_6 alkylenyl), an aliphatic heterocyclic-(C_1-C_6 alkylenyl), and an aliphatic heterocyclic group which may be substituted with a C_1-C_6 alkyl;

Substituent Group G: a halogen, a hydroxy, a cyano, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, a trifluoromethoxy, a C_1-C_6 aminoalkyl, a C_1-C_6 alkylamino-(C_1-C_6 alkylenyl), a di(C_1-C_6 alkyl)amino-(C_1-C_6 alkylenyl), an amino, a C_1-C_6 alkylsulfonylamino, a carbamoyl, a sulfamoyl, a (C_1-C_6 alkyl)ureide, a benzylureide, andan aliphatic heterocyclic group;

Substituent Group H: a halogen, a cyano, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, an amino, a carbamoyl, a dimethylaminopropylaminocarbonyl, and an aminocyclohexylaminocarbonyl;

Substituent Group I: an aliphatic heterocyclic group (wherein, the aliphatic heterocyclic group may have a C_1-C_6 alkyl, an amino group or a C_1-C_6 alkylamino as a substituent); an aliphatic heterocyclic-(C_1-C_6 alkylenyl); an aliphatic heterocyclic-amino (wherein, the aliphatic heterocyclic may have a C_1-C_6 alkyl or an amino as a substituent); a di(C_1-C_6 alkyl)amino-(C_1-C_6 alkylenyl); a C_1-C_6 aminoalkyloxy; a di(C_1-C_6 alkyl)amino-(C_1-C_6 alkylenyl)oxy; a di(C_1-C_6 alkyl)amino-(C_1-C_6 alkylenyl)amino; a cyclohexyl (wherein, the cyclohexyl may have an amino or a C_1-C_6 aminoalkyl as a substituent).

4. The compound or a pharmaceutically acceptable salt thereof of claim 2, wherein R^1 is -CO-R^{5A} (wherein, R^{5A} has the same meaning as described in claim 3).

5. The compound or a pharmaceutically acceptable salt thereof of claim 4, wherein R^{5A} is a C_1-C_6 alkyl or a C_3-C_{10} cycloalkyl.

6. The compound or a pharmaceutically acceptable salt thereof of claim 2, wherein R^1 is a cyano.

7. The compound or a pharmaceutically acceptable salt thereof of claim 2, wherein R^1 is a C_1-C_6 alkylsulfonyl.

8. The compound or a pharmaceutically acceptable salt thereof of claim 2, wherein R^1 is a methylsulfonyl.

9. The compound or a pharmaceutically acceptable salt thereof of claim 2, wherein R^2 is $-NR^{6A}R^{7A}$ (wherein, R^{6A} and R^{7A} have the same meaning as described in claim 3).

10. The compound or a pharmaceutically acceptable salt thereof of claim 9, wherein R^{6A} is a hydrogen atom, and R^{7A} is $-(CH_2)_n-R^{10A}$ (wherein, n and R^{10A} each have the same meaning as described in claim 3).

11. The compound or a pharmaceutically acceptable salt thereof of claim 9, wherein R^{6A} and R^{7A} form with an adjacent nitrogen atom an optionally substituted heterocyclic group which may have a substituent group selected from Substituent Group F described in claim 3.

12. The compound or a pharmaceutically acceptable salt thereof of claim 2, wherein R^2 is a piperidin-4-spiro-3'-pyrrolidin-1-yl, an optionally substituted piperidyl which may have a substituent group selected from Substituent Group F described in claim 3, or an optionally substituted 1-piperazinyl which may have a substituent group selected from Substituent Group F described in claim 3.

13. The compound or a pharmaceutically acceptable salt thereof of claim 2, wherein R^2 is an optionally substituted aryl which may have a substituent group selected from Substituent Group C described in claim 3.

14. The compound or a pharmaceutically acceptable salt thereof of claim 2, wherein R^2 is an optionally substituted phenyl which may have a substituent group selected from Substituent Group C described in claim 3.

15. The compound or a pharmaceutically acceptable salt thereof of claim 2, wherein R^3 is an optionally substituted aryl which may have a substituent group selected from Substituent Group C described in claim 3, or an optionally substituted aromatic heterocyclic group which may have a substituent group selected from Substituent Group H described in claim 3.

16. A pharmaceutical composition comprising as an active ingredient a compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 15.

17. An MELK inhibitor comprising as an active ingredient a compound or a pharmaceutically

acceptable salt thereof of any one of claims 1 to 15.

18. An MELK-expression modulating agent comprising as an active ingredient a compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 15.

19. An antitumor agent comprising as an active ingredient a compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 15.

20. A therapeutic and/or preventive agent for a disease that involves overexpression of MELK, comprising as an active ingredient a compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 15.

21. The therapeutic and/or preventive agent of claim 20, wherein the disease is cancer.

22. The therapeutic and/or preventive agent of claim 21, wherein the cancer is selected from the group consisting of breast cancer, lung cancer, bladder cancer, lymphoma, and uterine cancer.

23. A method for treating and/or preventing a disease that involves overexpression of MELK, wherein an effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 15 is administered to a subject in need thereof.

24. A compound or a pharmaceutically acceptable salt thereof any one of claims 1 to 15 for use in a treatment and/or prevention of a disease that involves overexpression of MELK.

25. Use of a compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 15 in the manufacture of a therapeutic and/or preventive agent for a disease that involves overexpression of MELK.

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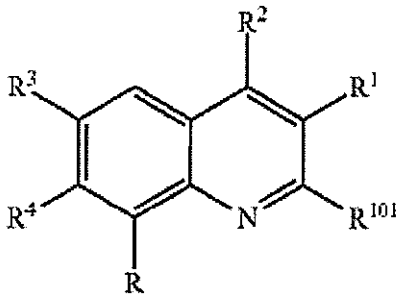
The invention claimed is:

1. A compound represented by the following formula or a pharmaceutically acceptable salt thereof:

(I)



wherein,

R^1 represents

a C_1-C_6 alkylsulfonyl, or

—CO—R^5 wherein,

R^5 is

a C_1-C_6 alkyl, or

a C_3-C_{10} cycloalkyl,

R^2 represents

an aryl which may have a substituent group selected from Substituent Group C, an aromatic heterocyclic group which may have a substituent group selected from Substituent Group H, or

—$NR^{6A}R^{7A}$;

wherein R^{6A} represents a hydrogen atom, and R^{7A} represents —$(CH_2)_n$—R^{10A} (wherein n represents an integer of 0 to 6, and R^{10A} represents a C_3-C_{10} cycloalkyl which may have a substituent group selected from Substituent Group D, an aryl which may have a substituent group selected from Substituent Group E, an aliphatic heterocyclic group

which may be substituted with a C_1-C_6 alkyl, an aromatic heterocyclic group which may have a substituent group selected from Substituent Group I), or R^{6A} and R^{7A} form with an adjacent nitrogen atom a heterocyclic group which may have a substituent group selected from Substituent Group F,

R^3 represents

an aryl which may have a substituent group selected from Substituent Group G, or an aromatic heterocyclic group which may have a substituent group selected from Substituent Group H;

R^4 represents

a hydrogen atom, or

a halogen

R represents

a hydrogen atom, or

a halogen, and

R^{101} represents

a hydrogen atom

wherein Substituent Groups C to I are one to three substituents each independently selected from the following Substituent Groups:

Substituent Group C: a halogen, a hydroxy, a C_1-C_6 alkoxy, and a di(C_1-C_6 alkyl) amino;

Substituent Group D: a hydroxy, a C_1-C_6 alkyl, a C_1-C_6 aminoalkyl, an aliphatic heterocyclic-(C_1-C_6 alkylenyl) (wherein, the aliphatic heterocyclic may have an amino, a hydroxy, a C_1-C_6 hydroxyalkyl, a C_1-C_6 alkoxy, or a halogen as a substituent), a C_1-C_6 alkylamino-(C_1-C_6 alkylenyl), a di(C_1-C_6 alkyl)amino-(C_1-C_6 alkylenyl) (wherein, either one of C_1-C_6 alkyl may have a hydroxy or a cyano as a substituent, and wherein hydrogen atom of C_1-C_6 alkyl may be substituted with deuterium atom), an amino, a C_1-C_6 alkylamino, a di(C_1-C_6 alkyl)amino, a C_1-C_6 aminoalkylcarbonylamino, a di(C_1-C_6 alkyl)amino(C_1-C_6 alkylenyl)carbonylamino, an aliphatic heterocyclic group (wherein, the aliphatic heterocyclic group may have a C_1-C_6 alkoxy as a substituent), and an aliphatic heterocyclic-carbonylamino;

Substituent Group E: a halogen, a di(C_1-C_6 alkyl)amino-(C_1-C_6 alkylenyl) (wherein, the C_1-C_6 alkylenyl may

have a hydroxy as a substituent), an amino, a C_2-C_7 alkanoylamino, a di(C_1-C_6 alkyl)amino, a C_1-C_6 aminoalkyl, and an aliphatic heterocyclic-(C_1-C_6 alkylenyl) (wherein, the aliphatic heterocyclic may have a C_1-C_6 alkyl as a substituent);

Substituent Group F: a carbamoyl, an amino, a C_1-C_6 aminoalkyl, a di(C_1-C_6 alkyl)amino-(C_1-C_6 alkylenyl), a C_1-C_6 alkylamino-(C_1-C_6 alkylenyl), an aliphatic heterocyclic-(C_1-C_6 alkylenyl), and an aliphatic heterocyclic group which may be substituted with a C_1-C_6 alkyl;

Substituent Group G: a halogen, a hydroxy, a cyano, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, a trifluoromethoxy, a C_1-C_6 aminoalkyl, a C_1-C_6 alkylamino-(C_1-C_6 alkylenyl), a di(C_1-C_6 alkyl)amino-(C_1-C_6 alkylenyl), an amino, a C_1-C_6 alkylsulfonylamino, a carbamoyl, a sulfamoyl, a (C_1-C_6 alkyl)ureide, a benzylureide, and an aliphatic heterocyclic group;

Substituent Group H: a halogen, a cyano, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, an amino, a carbamoyl, a dimethylaminopropylaminocarbonyl, and an aminocyclohexylaminocarbonyl;

Substituent Group I: an aliphatic heterocyclic group (wherein, the aliphatic heterocyclic group may have a C_1-C_6 alkyl, an amino group or a C_1-C_6 alkylamino as a substituent); an aliphatic heterocyclic-(C_1-C_6 alkylenyl); an aliphatic heterocyclic-amino (wherein, the aliphatic heterocyclic may have a C_1-C_6 alkyl or an amino as a substituent); a di(C_1-C_6 alkyl)amino-(C_1-C_6 alkylenyl); a C_1-C_6 aminoalkyloxy; a di(C_1-C_6 alkyl)amino-(C_1-C_6 alkylenyl)oxy; a di(C_1-C_6 alkyl) amino-(C_1-C_6 alkylenyl)amino; a cyclohexyl (wherein, the cyclohexyl may have an amino or a C_1-C_6 aminoalkyl as a substituent).

2. The compound or a pharmaceutically acceptable salt thereof of claim **1**, wherein R^1 is —CO—R^5.

3. The compound or a pharmaceutically acceptable salt thereof of claim **1**, wherein R^1 is a methylsulfonyl.

4. The compound or a pharmaceutically acceptable salt thereof of claim **1**, wherein R^2 is —$NR^{6A}R^{7A}$ (wherein, R^{6A} and R^{7A} have the same meaning as described in claim **1**).

5. The compound or a pharmaceutically acceptable salt thereof of claim **2**, wherein R^{6A} is a hydrogen atom, and R^{7A} is $—(CH_2)_n—R^{10A}$ (wherein, n and R^{10A} each have the same meaning as described in claim **1**).

6. The compound or a pharmaceutically acceptable salt thereof of claim **2**, wherein R^{6A} and R^{7A} form with an adjacent nitrogen atom a heterocyclic group which may have a substituent group selected from Substituent Group F described in claim **1**.

7. The compound or a pharmaceutically acceptable salt thereof of claim **1**, wherein R^2 is a piperidin-4-spiro-3'-pyrrolidin-1-yl, a piperidyl which may have a substituent group selected from Substituent Group F described in claim **1**, or a 1-piperazinyl which may have a substituent group selected from Substituent Group F described in claim **1**.

8. The compound or a pharmaceutically acceptable salt thereof of claim **1**, wherein R^2 is an aryl which may have a substituent group selected from Substituent Group C described in claim **1**.

9. The compound or a pharmaceutically acceptable salt thereof of claim **1**, wherein R^2 is a phenyl which may have a substituent group selected from Substituent Group C described in claim **1**.

10. The compound or a pharmaceutically acceptable salt thereof of claim **1**, wherein R^3 is an aryl which may have a substituent group selected from Substituent Group G described in claim **1**, or an optionally substituted aromatic heterocyclic group which may have a substituent group selected from Substituent Group H described in claim **1**.

11. A pharmaceutical composition comprising as an active ingredient a compound or a pharmaceutically acceptable salt thereof claim **1**.

12. An MELK inhibitor comprising as an active ingredient a compound or a pharmaceutically acceptable salt thereof of claim **1**.

13. An MELK-expression modulating agent comprising as an active ingredient a compound or a pharmaceutically acceptable salt thereof of claim **1**.

14. An antitumor agent comprising as an active ingredient a compound or a pharmaceutically acceptable salt thereof of claim **1**.

15. The compound or a pharmaceutically acceptable salt thereof of claim **1**, which is selected from

1-(6-(3-chloro-4-hydroxy-5-methoxyphenyl)-4-(1R,4R)-4-((dimethylamino)methyl)-cyclo-hexylamino)quinolin-3-yl)ethanone;

2,6-dichloro-4-(4-(1R,4R)-4-((dimethylamino)methyl) cyclohexylamino)-3-(methylsulfonyl)-quinolin-6-yl) phenol;

cyclopropyl(6-(3,5-dichloro-4-hydroxyphenyl)-4-((1s, 4s)-4-((dimethylamino)-methyl)cyclo-hexylamino) quinolin-3-yl)methanone;

1-(6-(3-chloro-4-hydroxy-5-methoxyphenyl)-4-(1R,4R)-4-((dimethylamino)-methyl)cyclo-hexylamino)quinolin-3-yl)propan-1-one;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((1R,4R)-4-((dimethylamino)methyl)-cyclohexyl)-amino)quinolin-3-yl)propan-1-one;

1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((trans)-4-((dimethylamino)methyl)-cyclo-hexylamino)quinolin-3-yl)ethanone;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((trans)-4-((dimethylamino)methyl)-cyclohexylamino)-quinolin-3-yl) ethanone;

cyclopropyl(6-(3,5-dichloro-4-hydroxyphenyl)-4-((trans)-4-((dimethylamino)-methyl)cyclo-hexylamino)quinolin-3-yl)methanone;

(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-quinolin-3-yl)(cyclopropyl)methanone;

(S)-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-quinolin-3-yl)(cyclopropyl)methanone;

(R)-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-quinolin-3-yl)(cyclopropyl)methanone;

1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3, 5-dichloro-4-hydroxyphenyl)-quinolin-3-yl)ethanone;

1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3, 5-dichloro-4-hydroxyphenyl)-quinolin-3-yl)propan-1-one; and

(S)-1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)quinolin-3-yl) propan-1-one;

and a pharmaceutically acceptable salt thereof.